

(P 01) FEASIBILITY OF A QUANTITATIVE METHYLATION-BASED CTDNA ASSAY IN PATIENTS WITH ADVANCED SARCOMAS

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Objective: Circulating tumor DNA (ctDNA) is an emerging biomarker for monitoring treatment response, but its use across multiple cancer types, particularly in sarcoma, remains challenging. Northstar Response (NSR®) is a tissue-free, mutation-agnostic, pan-cancer therapy response monitoring assay that measures >500 cancer-specific methylated loci and precisely quantifies these loci with single-base-pair resolution. Quantification of these loci yields a tumor methylation score (TMS), which can be utilized as a surrogate of tumor burden. We evaluated the feasibility of using NSR in a real-world cohort of patients with advanced sarcomas to assess the detectability of ctDNA.

Methods: We performed a retrospective analysis of patients with advanced sarcomas who underwent NSR testing as part of routine care. All patients had at least one NSR test. For patients with serial testing, we performed correlations to radiographic or clinical response. Tumor methylation score (TMS) was expressed as Log10 values to normalize the skewed distribution.

Results: A total of 31 patients were analyzed. Among these patients, 19 (61%) had at least three ctDNA assays, and all had radiographic or clinical response assessments. The median age was 52 years (range, 19–82), with 54% of the participants being female. The breakdown of diagnoses was as follows: GIST (n = 6), SFT (n = 4), leiomyosarcoma (n = 4), and Other (n = 10). Baseline TMS-log10 showed statistically significant variation ($p = 0.047$) between these groups and was measurable in 28 patients (90%), with LMS having the highest ctDNA levels. Of the three patients with undetectable initial TMS, two developed detectable levels during their disease. Patients with progressive disease on their third assessment had rising TMS values more frequently, whereas decreases were more common in those with stable or responsive disease; however, this difference was not statistically significant ($p = 0.35$).

Conclusion: NSR testing was feasible in patients with advanced sarcoma and showed histology-specific variation. These findings support the potential of methylation-based circulating ctDNA for disease monitoring in sarcoma. Additional analyses of ctDNA dynamics and clinical outcomes are underway and will be presented.

(P 02) METHYLATION PROFILING AS A DIAGNOSTIC ADJUNCT FOR UNDIFFERENTIATED SARCOMAS: A REAL-WORLD EVALUATION

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Objective: Aberrant DNA methylation is a key epigenetic mechanism and hallmark of malignancy that offers diagnostic potential through tumor-specific methylation signatures. A

recently developed, publicly available sarcoma methylation classifier offers potential diagnostic improvement. We assessed its performance with two aims: (1) to evaluate concordance between methylation-based classification and expert pathology; and (2) to determine whether the classifier could provide refined subtyping.

Methods: DNA was extracted and processed per manufacturer protocol from formalin-fixed, paraffin-embedded (FFPE) sarcoma specimens and run in the Infinium MethylationEPIC v2.0 BeadChip. Methylation data were analyzed via Illumina GenomeStudio and classified using the Heidelberg Epignostix Sarcoma Classifier (v12.3). Classification scores were stratified as high (≥ 0.90), intermediate ($0.30\text{--}0.89$), or indeterminate (< 0.30). Methylation results were compared to prior expert pathology and discrepancies categorized as major (clinical impact) or minor (no expected consequence).

Results: Fifty-five sarcoma specimens (2012–2022) were included, predominantly undifferentiated/pleomorphic sarcomas ($n=33$; 60%) and high-grade (grade 2/3, $n=45$; 82%). Of 55 samples, 50 (91%) yielded usable methylation profiles (score ≥ 0.30). Among these, 42 (84%) had high-confidence classifications (≥ 0.90), and 8 (16%) were intermediate. In the intermediate group, 75% showed concordance with expert pathology; 2 cases had minor discrepancies. In the high-confidence group, 76% were concordant with 5 cases each of major and minor discrepancies.

Major discrepancies included reclassification of tumors initially diagnosed as undifferentiated sarcoma to alveolar rhabdomyosarcoma, schwannoma, or angiomatoid fibrous histiocytoma. In some cases, methylation profiling provided more specific subtypes (e.g., malignant peripheral nerve sheath tumor vs. undifferentiated sarcoma), while in others, expert pathology was more definitive (e.g., malignant PEComa labeled as undifferentiated by classifier).

Conclusion: Methylation profiling showed ~75% concordance with expert pathology and occasionally enabled diagnostic refinement. Compared to DNA/RNA sequencing, it is faster and more cost-effective. Limitations include inflammatory contamination and classifier immaturity in rare subtypes. A prospective study is planned to assess its integration into diagnostic workflows for ambiguous sarcomas.

Demographic summaries from included patients with sarcoma

Characteristics	
Sex	27 Female 26 Male 2 Unknown
Age	Median 65 (19-96)
Grade	39 G3 6 G2 4 Unknown 3 G1 3 Ungraded
Ethnicity	40 White 7 Black 3 American Indian 3 Unknown 2 Asian
Sarcoma subtype	33 Undifferentiated sarcoma/undifferentiated pleomorphic 4 Leiomyosarcoma 3 WDLPS/DDLPs 2 Pleomorphic dermal sarcoma 2 Pleomorphic rhabdomyosarcoma 2 Synovial sarcoma 2 Solitary fibrous tumor 2 DFSP/FS 1 Myxoid liposarcoma 1 Ewing 1 Undifferentiated round cell sarcoma 1 PECOMA
Primary location	42 Extremity 5 Pelvis/Inguinal 3 Unknown 1 Spine 4 Chest/abdominal wall

(P 03) CONGRUENCE OF CIRCULATING TUMOR DNA & RADIOGRAPHIC RESPONSE IN BONE AND SOFT TISSUE SARCOMA

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Objective: The prognostic value of tumor-informed ctDNA (Signatera, Natera Inc) in advanced sarcoma remains unclear. We evaluated whether ctDNA offers prognostic insight by analyzing its congruence with radiography in real-world conditions.

Methods: We assessed congruence between ctDNA and imaging at serial timepoints in advanced sarcoma patients with ≥ 2 ctDNA assessments taken ± 30 days of imaging. Congruence (true positive/negative) was determined by two methods (A) Discrete Pairings (DP): increasing/positive ctDNA vs progression/persistence or decreasing/negative ctDNA with clinical benefit; or (B) Positive Conversion (PC): surveillance patients with baseline negative ctDNA and no evidence of disease (NED) scans, with congruence determined at last follow-up by positive conversion with progression or persistent negativity with NED. DP includes patients on treatment.

Results: 32 patients (leiomyosarcoma-9, liposarcoma-5, Ewing-3, angiosarcoma-3, osteosarcoma-2, clear cell-2, spindle cell-2, other-6) from 5/2022-5/2025 met criteria (median follow-up 301 days, 5 ctDNA assessments). 15/32 received treatment, including chemotherapy (11), immunotherapy (6), radiation (3), and/or ablation (2). In DP (n=159), 87% (138/159) were congruent (69% sensitivity, 97% specificity, PPV 93%, NPV 84%) (Table 1). In PC, 17 patients (median follow-up 281 days) were analyzed: 10/17 remained NED (100% congruence (10/10)), 7 recurred (71% congruence (5/7)). Notably, 2/3 DP false positives progressed on follow-up scans; 14/18 false negatives became congruent with scans (median time to congruence: 5.7mo) while 4/18 became NED.

Conclusion: Tumor-informed ctDNA shows promise as a monitoring tool in sarcoma. While DP sensitivity was < 70%, most false negatives became congruent over time, indicating possible

ctDNA lag. Further studies are ongoing to assess tumor-type and treatment effects on ctDNA shedding.

ctDNA Congruency by Discrete Pairings and Positive Conversion

Discrete Pairings (n=159)		
	Progression/Persistence on Scans	NED/ Clinical Benefit on Scans
Increasing/Positive ctDNA	41 (25.79%)	3 (1.89%)
Decreasing/Negative ctDNA	18 (11.32%)	97 (61.01%)
69% sensitivity, 97% specificity, PPV 93%, NPV 84%		
Positive Conversion (n=17)		
	Disease Progression	NED
Positive ctDNA	5 (29.41%)	0 (0.00%)
Negative ctDNA	2 (11.76%)	10 (58.82%)
71% sensitivity, 100% specificity, PPV 100%, NPV 83%		

(P 04) EARLY ON-TREATMENT CIRCULATING TUMOR DNA DYNAMICS TO PREDICT RESPONSE IN PATIENTS WITH SARCOMA

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Objective: ctDNA (circulating tumor DNA) holds promise as an emerging biomarker for risk stratification and treatment response monitoring across multiple cancers. We explored early on-treatment ctDNA dynamics to predict response in patients (pts) with soft tissue and bone sarcomas receiving cytotoxic chemotherapy.

Methods: 22 pts with sarcoma undergoing chemotherapy at Wilmot Cancer Institute through 12/31/24 with serial tumor-informed ctDNA testing (SignateraTM, Natera, Inc.) were retrospectively evaluated; 4 had a second set of treatment (Tx). We additionally prospectively enrolled 12 patients for banked ctDNA analysis at early timepoints on chemotherapy and interrogated these with Natera; 6 met inclusion criteria for a total of 32 Tx. Clinical responders (CR) were classified as those achieving a complete or partial response on first follow up imaging. Pts with progressive disease were classified as non-responders (NR), and those with mixed response or stable disease were considered intermediate responders (IR). ctDNA clearance (ND) was approximated to 0.01 MTM/mL for log-fold calculations.

Results: Of the 32 Tx, 14 led to CR, 10 NR, and 8 IR. Early on-Tx ctDNA dynamics were highly associated with response, with CRs showing a statistically significant decrease in ctDNA levels compared to NRs (p=0.001). CRs achieved a median of -1.9 (ND to -0.02) and -2.6 (ND to -1.3)

log10 fold decrease in ctDNA levels by cycle 1 & 2, respectively. Conversely, NRs were associated with a median of -0.3 (-1.0 to 0.16) and -0.3 (-1.2 to 0.21) fold decrease by cycle 1 & 2, respectively. A value of -1.25 log fold fall in ctDNA by cycle 2 separated CR from NR. Of 13 pts with ctDNA clearance, none were in NR group (100% NPV).

Conclusion: Early ctDNA dynamics, particularly log-fold reduction of -1.25 or greater after 1-2 cycles predicts Tx response. ctDNA may offer clinical utility for interpreting equivocal scans, bony lesions or infiltrative subtypes such as angiosarcoma. Prospective validation in larger cohorts is warranted.

(P 05) CONCORDANCE OF GENOMIC ALTERATIONS WITH CIRCULATING TUMOR DNA: INITIAL FINDINGS FROM A PILOT STUDY

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Objective: The precise role of circulating tumor DNA (ctDNA) has yet to be investigated in sarcomas. This pilot study investigated the concordance between ctDNA and genomic alterations in archival tumor tissue in patients with sarcoma.

Methods: Patients with metastatic sarcoma and a high tumor burden harboring a genomic alteration in archival tumour tissue were included from the Department of Oncology at Herlev University Hospital. For ctDNA analysis, 40 ml of blood were collected in BCT STRECK tubes from each patient. Plasma was investigated using either digital droplet PCR (ddPCR) with the QX200 ddPCR system from Bio-Rad, employing patient-specific primers, or next-generation sequencing with the TruSight Oncology 500 ctDNA (TSO500 ctDNA) Illumina assay.

Results: In total, 20 patients were included, 14 (70%) were males, with a mean age of 55 years. Dedifferentiated liposarcoma (25%) and leiomyosarcoma (20%) were the most common subtypes. CtDNA was analyzed using TSO500 ctDNA in 14 patients and ddPCR in 10 patients. CtDNA was detected in 10 (71%) patients with TSO500 ctDNA and in five (50%) patients with ddPCR. The most common genomic alteration identified with ddPCR was an *MDM2* amplification (40%). Both analyses were used in four patients, with no ctDNA detected in two of them. In the remaining patients, an *EGFR* mutation was identified with ddPCR, and an *NRAS* mutation with TSO500 ctDNA. There was a concordance in five (45%) out of 14 patients between genomic alterations in archival tumor tissue and those found in plasma with TSO500 ctDNA. The following three mutations and three fusions were identified: *TP53*, *TERT*, *KDM5C*, *PAX3-CRB1*, *NAB2-STAT6* and *EWSR1-WT1*. Progressive disease was confirmed in 12 (60%) out of 20 patients at the time of blood sample collection with ctDNA detected in 11 (92%) of these.

Conclusion: CtDNA can be detected in patients with sarcoma using the TSO500 ctDNA assay and ddPCR. Additionally, patients with progressive disease are more likely to shed ctDNA.

(P 06) RAPID, POINT-OF-CARE DNA METHYLATION & MOLECULAR LANDSCAPE BASED SARCOMA CLASSIFICATION

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Objective: Sarcomas are a group of >200 types of cancer with mesenchymal differentiation. In up to 20% of patients, sarcoma cannot be conclusively classified. Identifying translocations and DNA methylation patterns can classify specific sarcoma sub-types. Oxford Nanopore DNA sequencing is a rapid, point-of-care method. Nanopore DNA sequencing detects DNA methylation, translocations, copy number alterations and point mutations. In this work we characterize which sarcoma sub-types are correctly classified using whole genome nanopore sequencing?

Methods: All patients signed an informed consent to participate in the study. Fresh tissue was flash frozen, and DNA extracted using Qiagen DNeasy blood and Tissue Kit; Whole genome sequencing was performed at low coverage of $\approx 0.1X$ using the Minion or at $\approx 10X$ high coverage using Promethion2 solo. We use NanoDx Methylation based classification to classify sarcomas. Using the NanoSV and Clair3 analysis tools single nucleotide and structural variant are identified.

Results: Using Nanopore low coverage whole genome DNA sequencing we examined 59 sarcoma samples from different subtypes. The NanoDx methylation classifier correctly diagnoses sarcomas such as all 8 Ewing's sarcoma and 3 desmoplastic small round blue cell sarcoma samples. In liposarcoma samples 3 of 10 samples are correctly classified using

NanoDx and MDM2 amplification is found in all samples. Using Nanopore high coverage whole genome DNA sequencing we examined five sarcoma and matched blood samples of synovial, Ewing's and desmoplastic small round blue cell sarcoma, the SYT and EWS translocations are identified correctly. A patient initially diagnosed with undifferentiated spindle cell sarcoma was reclassified. The NanoDx classified the sample as an Ewing's sarcoma and a FUS-ERG translocation verified the diagnosis. The tumor's DNA Methylation patterns and translocations can accurately identify certain types of sarcomas. A classifier incorporating clinical data, methylation data & molecular features could improve sarcoma classification. Additional testing of different sarcoma sub-types is needed to further evaluate the clinical utility of whole genome nanopore sequencing.

Conclusion: Whole genome nanopore sequencing can classify some sarcoma subtypes using low coverage sequencing and identify rare translocations using high coverage sequencing.

(P 07) A LIVING MULTI-OMICS BIOBANK OF PATIENT-DERIVED XENOGRRAFT MODELS FOR SARCOMA

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Objective: Sarcomas are rare and highly heterogeneous malignancies with poor prognosis and limited reliable preclinical models. Patient-derived xenograft (PDX) models provide an effective tool to study tumor biology and evaluate therapeutic strategies. We aimed to establish a large, clinically annotated sarcoma PDX biobank with integrated genomic and transcriptomic profiling to uncover key molecular characteristics.

Methods: Fresh tumor samples from sarcoma patients at Shanghai General Hospital were subcutaneously implanted into NOD scid gamma (NSG) mice to generate PDX models. Genomic and transcriptomic sequencing were performed on both PDXs and matched patient tumors. Histopathological and molecular concordance were evaluated, and actionable genomic alterations were annotated using the OncoKB knowledge base.

Results: Between 2014 and 2024, we successfully established 155 PDX models encompassing 11 sarcoma subtypes. Successful engraftment was associated with poorer prognosis, more aggressive clinical features, higher TP53 mutation rates, and elevated tumor mutational burden. PDXs preserved high morphological fidelity and demonstrated strong concordance with the corresponding patient tumors in gene expression, copy number alterations, and DNA methylation profiles. Compared with patient tumors, PDXs exhibited higher tumor purity but reduced stromal and immune cell components. Recurrent driver alterations, including TP53 mutations, MYC gain/amplification, and complex structural variants, were frequently observed, particularly in osteosarcoma. Canonical disease-specific fusion

genes (e.g., SS18–SSX in synovial sarcoma, EWSR1–FLI1 in Ewing sarcoma) were consistently identified in both PDXs and matched patient samples, whereas noncanonical fusions showed lower concordance. Multi-passage sequencing confirmed genomic stability across serial passages, and 52% of models harbored potentially actionable alterations within the cohort. Additionally, clonal evolution analysis indicated that most PDXs followed a linear evolutionary trajectory compared with their original patient tumors.

Conclusion: To our knowledge, this represents the largest multi-omics–annotated sarcoma PDX biobank derived from a Chinese population, faithfully recapitulating patient tumors at both histological and molecular levels. This resource provides a robust platform for translational research in sarcoma.

(P 08) BUILDING A MEDICAL DONATION NETWORK TO ENHANCE DEVELOPMENT OF PEDIATRIC TUMOR MODELS

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Objective: Survival outcomes for relapsed or metastatic pediatric solid tumors remain poor, and there is a critical need for preclinical models reflective of high-risk, relapsed/refractory disease. To address this, the Pediatric Research in Oncology Xenografting Consortium (PROXC) has developed an integrated medical donation network to enable autopsy-based patient-derived xenograft (PDX) model generation and tissue banking.

Methods: Tissue procurement protocols from each consortium site (Nationwide Children's Hospital, Texas Children's Hospital, St Jude Children's Research Hospital, Dana-Farber Cancer Institute and Memorial Sloan Kettering Cancer Center) were compiled to establish a comprehensive workflow and streamline coordination of tissue procurement between donating and receiving centers. Partnership with patient advocacy groups were established to raise awareness of the PROXC-coordinated medical donation workflow.

Results: We describe the establishment of 6 regional donation sites aimed at expediting the transport of autopsy tissue to a PROXC site for tissue banking and PDX model generation. We delineate the logistics of patient consent for autopsy tissue collection, information guide explaining the rationale for medical donation of tissue and FAQs around research medical donation for donating centers, material transfer documentation, and specification of tissue requirements to enable model generation and molecular characterization of collected tissue. Metrics have been established to evaluate the feasibility of autopsy tissue procurement and assess the impact on PDX model generation from autopsy cases. Partnerships with patient advocacy groups were established to enhance awareness of this medical donation workflow.

Conclusion: This PROXC initiative represents a collaborative effort to establish a nationwide workflow for medical donation in pediatric oncology to increase the development and access to

models of relapse/refractory disease for pediatric solid tumors. Development of these models will contribute to improved understanding of tumor evolution and therapy resistance. Through partnership with patient advocacy groups, this initiative aims to raise institutional awareness, reduce barriers for medical donations, and demonstrate the value of these contributions to both research and families.

(P 09) ESTABLISHMENT AND CHARACTERIZATION OF 18 SARCOMA CELL LINES: UNRAVELING THE MOLECULAR MECHANISMS OF DOXORUBICIN RESISTANCE IN SARCOMA CELL LINES

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Objective: Sarcomas, malignant tumors from mesenchymal tissues, exhibit poor prognosis despite advancements in treatment modalities such as surgery, radiotherapy, and chemotherapy, with doxorubicin being a cornerstone treatment. Resistance to doxorubicin remains a significant hurdle in therapy optimization. This study aims to dissect the molecular bases of doxorubicin resistance in sarcoma cell lines, which could guide the development of tailored therapeutic strategies.

Methods: Eighteen sarcoma cell lines from 14 patients were established under ethical approvals and classified into seven subtypes. Molecular, genomic, and transcriptomic analyses included whole-exome sequencing, RNA sequencing, drug sensitivity assays, and pathway enrichment studies to elucidate the resistance mechanisms.

Results: Variability in doxorubicin sensitivity was linked to specific genetic alterations, including mutations in TP53 and variations in the copy number of genomic loci like 11q24.2. Transcriptomic profiling divided cell lines into clusters by karyotype complexity, influencing drug responses. Additionally, pathway analyses highlighted the role of signaling pathways like WNT/BETA-CATENIN and HEDGEHOG in doxorubicin-resistant lines.

Conclusion: Comprehensive molecular profiling of sarcoma cell lines has revealed complex interplays of genetic and transcriptomic factors dictating doxorubicin resistance, underscoring the need for personalized medicine approaches in sarcoma treatment. Further investigations into these resistance mechanisms could facilitate the development of more effective, customized therapy regimens.

(P 10) COLLATERAL SENSITIVITIES EMERGE DURING THE EVOLUTION OF CHEMORESISTANCE TO MAP CHEMOTHERAPY IN OSTEOSARCOMA

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Objective: We aimed to model the evolution of chemoresistance to methotrexate, doxorubicin, and cisplatin (MAP) in vitro and to characterize collateral drug sensitivity and resistance patterns over time, potentially informing second-line treatment strategies in chemo resistant primary or recurrent disease.

Methods: Five evolutionary replicates of MG63.3 osteosarcoma cells were treated with six complete cycles of pulsed, clinically relevant doses of cisplatin and doxorubicin, alternating with methotrexate. Dose-response curves were performed after each chemotherapy cycle to assess resistance to MAP and collateral responses to 16 drugs and combinations. RNA sequencing and transcription factor activity inference were performed across treatment timepoints to temporally explore transcriptional correlates of drug response.

Results: Cells developed resistance to doxorubicin (1.49–2.59 fold) and methotrexate (0.92–2.87 fold) but remained sensitive to cisplatin. Collateral resistance emerged to etoposide, vincristine, and topotecan, while sensitivity increased to gemcitabine, cabozantinib, and palifosfamide. Collateral responses varied temporally, with some increasing linearly with evolution of MAP resistance, and some appearing transient or stochastic. Transcriptional profiling revealed increased activity of E2F and ERG and context-dependent roles for interferon signaling. Resistance phenotypes persisted after drug withdrawal and cryopreservation.

Conclusion: Our model reveals temporally dynamic, heterogeneous collateral responses during the development of chemoresistance to MAP in osteosarcoma. While cross-resistance to several agents emerged, collateral sensitivity to gemcitabine and cabozantinib supports a second line use for these agents. These data may inform rational sequencing of therapies to preempt or exploit resistance evolution.

(P 11) ESTABLISHMENT, CHARACTERIZATION AND RESEARCH APPLICATION OF EIGHT NOVEL PATIENT-DERIVED OSTEOSARCOMA CELL LINES

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Objective: There are no established effective targeted therapies to treat advanced/metastatic osteosarcoma. Access to reliable in vitro models, that accurately reflect the patient's original tumor, capture molecular disease heterogeneity and allow rapid pre-clinical testing, are critical to identify novel therapeutics. Previous attempts at developing patient-derived osteosarcoma cell cultures have had limited success. Here, we describe our program where we generated a new panel of fully molecularly- and clinically-annotated, patient-derived osteosarcoma cell lines (OZ-SBT), expanding the global resources available for research.

Methods: Osteosarcoma patient-derived xenograft (PDX) cells were cultured in up to 24 different conditions to determine optimal culture medium, supplementation and plate-coating. Cells were validated by comparing their Single Nucleotide Polymorphism (SNP) data to whole

genome sequencing profiles of original patient tumors. Tumor content was verified by immunohistochemistry. Cell lines were also transduced with CRISPR-Cas9, subjected to short- and long-term drug viability assays and injected in vivo, to determine potential research applications and allow early therapeutic testing.

Results: Our most successful culture protocol, with a success rate of 73%, allowed the in vitro expansion of eight unique osteosarcoma patient models while retaining the patients' original tumor characteristics: the OZ-SBT panel. These models capture diverse molecular profiles, and include samples taken at diagnosis, progression and relapse (including one patient with matched samples) (all expected survival < 30%). We successfully transduced all OZ-SBT cell lines with CRISPR-cas9 and subjected them to short- and long-term drug assays, revealing known and novel drug/gene dependencies. All tested OZ-SBT cells propagated in vivo.

Conclusion: We believe our new osteosarcoma OZ-SBT cell panel, which captures distinct molecular profiles and allows a variety of research techniques, to be an important addition for the global osteosarcoma research community to expedite research. Early data illustrate their potential for exploring osteosarcoma biology and identifying potential novel therapeutic avenues, which we are currently exploring in matched in vivo models.

(P 12) DNA REPLICATION STRESS AND DEFICIENT HOMOLOGOUS RECOMBINATION IN OSTEOSARCOMA RISK AND THERAPY

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Objective: For 40 years, osteosarcoma (OST) treatments have not improved children's survival, mainly due to the lack of patient stratification. OST is marked by high genomic instability linked to DNA double-strand breaks (DSBs). Two sources of DSB accumulation were explored: replication stress (RS) and homologous recombination deficiency (HRD). A cohort of 100 patients was used to assess their potential for new stratification strategies and targeted therapies.

Methods: We used complementary approaches to study replication stress (RS) and homologous recombination deficiency (HRD) in osteosarcoma (OST): The Illumina TruSight™ Oncology 500 HRD assay to assess genomic instability scores and detect mutations and amplifications in 523 genes, the Shallow whole genome sequencing (sWGS) to measure large-scale genomic alterations, RNA sequencing to analyze gene expression patterns related to RS and HRD, and Digital pathology on FFPE tissues to evaluate expression and activation of key pathway components, supporting biomarker development.

Results: We identified two distinct subgroups of OST patients based on genomic instability: one showing signs of replication stress (RS), including oncogene amplifications and chromothripsis-like profiles, and another resembling HRD ovarian cancer patients, marked by high genomic instability without chromothripsis. We then developed innovative biomarkers linked to each subgroup's survival mechanisms: ATR, which controls the replication checkpoint in RS-OST tumors, and DNA polymerase θ (Pol θ), a backup DSB repair factor in HRD-OST

tumors. These biomarkers were validated by immunohistochemical (IHC) staining in OST samples.

Conclusion: These results define potential novel molecular subtypes of osteosarcoma based on replication stress and DNA repair deficiency signatures. This stratification will open new therapeutic possibilities with already existing drugs, which target specifically compensatory mechanisms that limit excessive DSB and genomic instability: ATR inhibitors for RS OST and Polθ inhibitors for HRD OST.

(P 13) TRANSCRIPTIONAL DIVERSITY AND NICHE REMODELING AT THE METASTATIC BOTTLENECK IN OSTEOSARCOMA

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Objective: Metastasis in osteosarcoma is highly inefficient; although many tumor cells enter circulation, few succeed in colonizing the lung. Emerging evidence points to a subpopulation of “anchor cells” that establish paracrine signaling with the lung microenvironment, producing cytokines such as IL-6 and CXCL8 that recruit proliferative tumor cells. We aimed to characterize the transcriptional landscape of these anchor cells and define how they remodel the metastatic niche.

Methods: We performed single-cell RNA sequencing (scRNA-seq) on OS-17 lung metastases isolated at early and midpoint timepoints to define a transcriptional program of “anchorness.” We then performed scRNA-seq on lung stromal cells to identify the earliest changes in stromal phenotype and composition at the metastatic bottleneck.

Results: Tumor cells present at early metastatic timepoints were transcriptionally diverse and lacked a uniform anchor cell signature previously described in functional studies. Notably, early tumor–lung interactions rapidly induced persistent fibrogenic remodeling of the stroma: fibrogenic pathways were upregulated in macrophages and fibroblasts by day 14. These changes may help create a scar-like matrix that supports tumor cell survival and proliferation despite the metastatic bottleneck.

Conclusion: Heterogeneity in tumor cells is preserved even at early stages of lung colonization, and this heterogeneity contributes to niche remodeling. Our findings highlight the importance of shifting focus from purely tumor-intrinsic phenotypes to understanding how anchor cells condition the lung microenvironment. Identifying key mediators of tumor–matrix crosstalk could inform new therapeutic strategies to limit metastatic progression.

(P 14) EVALUATING THE COMBINATION OF DISULFIRAM AND ENZALUTAMIDE IN OSTEOSARCOMA

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Objective: Despite treatment advances in primary disease, survival rates for patients with metastatic osteosarcoma (OS) have remained dismal. Recent studies have suggested Targeting aldehyde dehydrogenase 1A1 (ALDH1A1) and androgen receptor (AR) as possible targets. Both targets have FDA-approved targeted agents available that can be repurposed for used in OS.

Methods: We evaluated disulfiram, enzalutamide, or combination across a range of concentrations in primary SaOS-2 and metastatic SaOS-LM2 OS cells in vitro using cytotoxic, clonogenic, migration, and proliferation assays. Tumor cell migration was evaluated using scratch assays while proliferation was established using the Incucyte cell imaging system.

Results: Both disulfiram and enzalutamide reduce tumor cell proliferation and survival although the effect was significantly larger in response to disulfiram. We observed a biphasic effect of disulfiram treatment where low concentrations have a profoundly higher efficacy than high concentrations. Similar results were observed across assays. While the low dose combination of disulfiram and enzalutamide displayed mild additive effects, we did not observe significant differences to disulfiram monotherapy. These effects were consistently observed across assays.

Conclusion: The combination of disulfiram and enzalutamide successfully targets OS cells across multiple assays; however, these responses are driven by disulfiram, suggesting that AR inhibition may not add a benefit that is of significant enough magnitude to warrant the side effects of Enzalutamide treatment. Nevertheless, our observations suggest an underlying mechanistic interaction between the pathways that may be exploited in the future.

(P 15) EZHIP: A NOVEL EPIGENETIC DRIVER OF OSTEOSARCOMA PATHOGENESIS

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Objective: Osteosarcoma (OS) is the most common malignant bone tumor. OS incidence rates peak during the pubertal growth spurt as mesenchymal progenitors expand and differentiate to form new bone, suggesting that OS is rooted in altered development. Comprehensive genomic studies did not improve clinical care in the past 30 years. Conversely, the OS epigenome remains largely uncharted. Given the pivotal role of epigenetics in orchestrating development, we sought to investigate epigenomic perturbations in Osteosarcomagenesis.

Methods: We evaluated the expression of cancer-driving histone mutations “oncohistones”, the oncohistone-mimic EZHIP and post-translational modifications in 2 independent cohorts (>75 patients) by immunohistochemistry. Next, we interrogated the functional consequences of EZHIP expression in patient-derived cells, mouse orthotopic models and human mesenchymal cells (hMSC). CUT&RUN and RNAseq were used to study the epigenome and transcriptome

and results were validated via functional assays including live-cell imaging and in-vitro differentiation. Finally, in-vitro and in-vivo assessment of FDA-approved drugs was performed.

Results: EZHIP is ectopically expressed in ~22% of OS resulting in the loss of H3K27me3. Importantly, acute H3K27me3 loss significantly correlated with poor response to neoadjuvant chemotherapy. At a cohort-level, relapsed tumors exhibited significantly lower H3K27me3 levels compared to primaries, highlighting its important role in OS progression. CRISPR/Cas9 knockout and lentiviral overexpression showed that EZHIP is a prominent oncogene required for in-vivo tumorigenesis in NSG mice. Transcriptomic and functional investigation revealed that EZHIP activates key oncogenic pathways in hMSC and OS cells. Moreover, EZHIP promotes the expansion of pre-osteoblastic osteo-CAR programs that lock hMSC in a stem-like pre-malignant state at the expense of normal differentiation which becomes blocked. Lastly, EZHIP expression imparts sensitivity to EZH2 inhibitors, including Tazemetostat, in orthotopic models.

Conclusion: EZHIP and H3K27me3 loss are novel mechanisms in osteosarcoma (OS) pathogenesis. While H3K27me3 loss is a poor prognostic marker, it also presents a therapeutic opportunity especially in chemoresistant OS, through the use of Tazemetostat and other EZH2 inhibitors. Further investigation combining Tazemetostat with current standards of care for patients with refractory tumors is warranted.

(P 16) MITOCHONDRIAL GENETIC VARIATION ORCHESTRATES COPZ1 TRANSCRIPT HETEROGENEITY AND REVEALS TELOMERE-MEDIATED VULNERABILITIES IN OSTEOSARCOMA

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Objective: While telomere biology has been implicated in osteosarcoma, potential connections with mitochondrial function remain unexplored. We investigated causal roles of telomere length and mtDNA copy number in osteosarcoma risk and characterized regulatory mechanisms potentially linking these cellular processes.

Methods: We performed Mendelian randomization using 94 telomere length and 113 mtDNA copy number variants against FinnGen osteosarcoma statistics. Analytical approaches included inverse variance weighted regression, MR-Egger, weighted median, and MR-PRESSO. sQTL analysis used GTEx v10 skeletal muscle data. Expression profiling used GTEx muscle and 212 osteosarcoma samples from Recount3.

Results: Mendelian randomization revealed longer telomeres confer significant osteosarcoma protection ($\beta=-0.5358$, 95% CI: -0.72 to -0.36, $p=0.0029$). mtDNA copy number showed no causal association ($\beta=0.2963$, $p=0.511$). Among mitochondrial variants, rs11451044 emerged as significant muscle-specific sQTL for COPZ1 (slope=-0.2714, $p<0.001$), predicted to alter splicing across 18 isoforms. Expression analysis identified ENST00000262061.7 as the dominant COPZ1 transcript (mean TPM=48.5). In osteosarcoma samples, this transcript

showed remarkable heterogeneity (range: 18,758-215,617). Length-normalized analysis revealed COPZ1 transcriptional activity 3.3-fold higher than COPZ2 (median: 50,080 vs 14,902 reads/kb).

Conclusion: Our findings establish telomere length as a protective factor against osteosarcoma risk through Mendelian randomization while revealing no causal role for mtDNA copy number. rs11451044 controlling COPZ1 transcript processing, combined with expression heterogeneity and COPZ1 dominance over COPZ2, suggests mitochondrial variation influences coatomer function through telomere-mitochondria crosstalk. COPZ1 variability may reflect tumor-specific stress buffering dependencies, with therapeutic potential arising from COPZ2 silencing in malignant cells creating selective vulnerability windows for targeted intervention.

(P 17) EXTRASKELETAL OSTEOSARCOMA: MICRORNA PATTERNS PROVIDE INSIGHTS INTO SIMILARITIES AND CONTRASTS WITH OTHER SARCOMAS

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Objective: Extraskeletal osteosarcoma (ESOSA) is a rare sarcoma histology. Despite its official classification as a soft tissue sarcoma, ESOSA shares similarities with conventional osteosarcoma (OSA), and the sarcoma literature lacks clear consensus on clinical treatment paradigms. Therefore, the objective of this study was to profile and compare the microRNA expression of tumor samples from patients with ESOSA, OSA, and common soft tissue sarcoma (STS) subtypes.

Methods: Final analysis included 33 tumor samples: 5 OSA, 12 ESOSA, and 16 STS. MicroRNA profiling was conducted using the MiRXES real-time RT-PCR assay (MiRXES, Singapore). Raw miRNA expression data underwent two-step normalization: global scaling to equalize sample means, followed by feature-wise Z-scoring to standardize miRNA expression distributions. Hierarchical clustering was performed using multiple linkage (ward, average, complete) and distance metrics (Euclidean, correlation, cosine). Chi-squared tests assessed associations between cluster assignments and tissue types. Statistical analysis included per-miRNA t-tests with FDR correction between tissue groups and calculation of three pairwise fold change ratios (OSA vs ESOSA, STS vs ESOSA, OSA vs STS).

Results: Preliminary analysis of average miRNA expression revealed a statistically significant difference between primary OSA and STS. In contrast, ESOSA samples did not exhibit materially different overall miRNA expression from STS, while they exhibited a trend for overall miRNA expression difference from primary OSA.

Conclusion: Our analysis to date suggests that ESOSA displays a miRNA expression pattern that appears to be closer to STS than to primary OSA. We also found that miRNA analysis can more clearly discriminate between primary OSA and STS, extending background knowledge about genomic differences between these histotypes. Comprehensive analysis is ongoing and will be presented at the conference. Our findings suggest that studies of larger cohorts are warranted to better elucidate the molecular similarities and differences between ESOSA,

primary OSA, and STS.

(P 18) ESTABLISHMENT AND CHARACTERIZATION OF A NOVEL PRIMARY CELL LINE FROM A BONE METASTASIS OF OSTEOSARCOMA

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Objective: Bone metastasis from osteosarcoma (OS) occurs in only 10% of patients as first relapse. Here, we report the case of a 62-year-old man, presenting a pelvic OS in 2022 followed by a metachronous scapular metastasis in 2024. We grab the opportunity to develop a preclinical model, which, to the best of our knowledge, is not available yet for bone metastasis from OS.

Methods: We enzymatically digested fresh tumour tissue to obtain a primary cell culture, namely OS-MET-R-092, which has now been cultured in vitro for over a year. We characterized OS-MET-R-092 cells in terms of growth and clonogenic potential, ability to form spheroids under 3D non-adherent culture conditions, migratory abilities and osteogenic differentiation.

Results: OS-MET-R-092 cells displayed a very slow proliferation ability and no clonogenic and osteogenic differentiative potentials. In relation to OS cell lines, OS-MET-R-092 displayed spheroid formation ability intermediate between Saos-2 and U2OS and migratory abilities comparable to Saos-2. Functionally, OS-MET-R-092 cells showed a multi-drug resistant phenotype when exposed to doxorubicin, cisplatin, gemcitabine and docetaxel (all included in the therapeutic regimen of the patient), with overexpression of ABCB1, a known chemoresistance marker in OS. As a surrogate measurement of in vivo tumorigenic ability, OS-MET-R-092 cells were seeded on the chick chorioallantoic membrane (CAM) and were allowed to grow for 7 days. Cells engrafted in 100% of CAMs, growing in bundles and forming a thick and opaque tissue, where it was possible to recognize OS cells, positive for SATB2 expression. In parallel, lively stocked tumour specimens were also engrafted on the CAM, which allowed their maintenance and growth as well as the spread of cells from the graft onto the CAM.

Conclusion: Altogether, OS-MET-R-092 could represent a useful tool for studying bone metastasis from bone sarcoma in diverse experimental settings and could be the first building block for more composite and translatable 3D models.

(P 19) SERUM EXOSOMES IDENTIFY AN ABERRANT PROTEOMIC SIGNATURE IN CANINE OSTEOSARCOMA PRECEDING METASTATIC PROGRESSION

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Objective: Osteosarcoma (OS) is an aggressive bone cancer affecting both dogs and humans, often associated with treatment resistance and metastasis. Exosomes, small extracellular vesicles, play a critical role in facilitating cellular interactions that drive key hallmarks of cancer, including therapy resistance, invasion, and metastasis. To determine how exosomal cargo evolves over the treatment course of OS, we characterized longitudinal changes in protein cargo from circulating exosomes collected from a cohort of canine OS patients who underwent amputation and received adjuvant chemotherapy preceding metastatic progression.

Methods: Exosomes were isolated from serum of 14 canine OS patients prior to and after amputation, prior to metastatic progression, and at the time of radiographic detection of pulmonary metastasis. Mass spectrometry proteomic analysis followed by pathway and protein-protein interaction (PPI) network analysis were performed to identify differentially abundant proteins and key pathways associated with proteomic signatures.

Results: The median disease-free interval between amputation and metastatic progression was 130 days (range: 56-933 days). A unique proteomic signature (97 DAPs) was identified in exosomes at the pre-metastatic time point, which ranged between 30-150 days prior to radiographic evidence of metastatic disease (median 120 days). Pathway analysis identified enrichment in fibrinolysis, coagulation, and complement systems. PPI analyses identified 13 hub proteins. Integration of biological pathways (WikiPathways) and the fold change of differential protein abundance at the pre-metastatic stage suggests a state of reduced complement and fibrinolysis activity and elevated kallikrein-kinin pathway activity preceding metastatic progression.

Conclusion: Circulating exosomal protein cargo from canine OS patients reveals systemic dysregulation of complement, fibrinolysis, and kallikrein-kinin systems that precedes metastatic progression in OS. These findings provide insight into how key biologic pathways evolve over time and may support metastatic progression in OS.

(P 20) IDENTIFICATION OF A PROGNOSTIC GENE SIGNATURE FOR OSTEOSARCOMA RELAPSE BASED ON RESIDUAL TUMOR DISEASE AND ITS MICROENVIRONMENT

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Objective: The prognosis of osteosarcoma (OS) patients is largely dependent on their response to chemotherapy, yet the evaluation method for this response is not optimal. We hypothesized that the residual tumor after chemotherapy could help identify a prognostic expression signature for relapse in OS.

Methods: To address this hypothesis, we mapped the heterogeneity of treatment responses in different regions of resected samples using single-nucleus RNA sequencing (snRNA-seq). We performed snRNA-seq on 9 samples from 7 patients (3 poor responders, 4 good responders). We identified microenvironment populations and residual tumor cells. For each subset of the population (TILs, osteoblast-like cells, myeloid cells, pericytes, CAFs, and endothelial cells), we selected the top 10 differentially expressed genes from each cluster. We evaluated prognostic genes for progression-free survival (PFS) using univariate Cox regression models from an original RNA-seq "bulk" cohort (n=75), annotated by an expert bone pathologist. We then computed centroids for each sample using a leave-one-out cross-validation approach to classify our cohort into two groups. The prognostic value of our signature was confirmed using Kaplan-Meier survival analysis for PFS. We validated our signature by performing survival analysis on the TARGET cohort (n=80) by transferring the centroid values to determine our groups.

Results: We identified a total of 12 genes with prognostic value for PFS using univariate Cox regression models. Our signature demonstrated a prognostic value for PFS ($p < 0.00055$) in our original cohort (n=75). This signature was validated in the TARGET cohort (n=80) and was prognostic for event-free survival ($p = 0.025$) and overall survival ($p = 0.019$).

Conclusion: Based on the analysis of residual disease, we generated a prognostic signature derived from the tumor microenvironment and residual tumor cells. This signature of treatment resistance, prognostic from the biopsy stage, could improve the therapeutic management of osteosarcoma.

(P 21) EXAMINING THE THERAPEUTIC EFFECT OF TBL1/ β -CATENIN TARGETED COMBINATION THERAPIES ON METASTATIC OSTEOSARCOMA

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Objective: Osteosarcoma (OS) is the most prevalent pediatric bone cancer and treatment outcomes and survival rates have not changed in decades. Patients with metastatic or relapsed/refractory disease face five-year survival rates below 30%, with no salvage therapies available after standard of care failure. Dysregulation of the Wnt signaling pathway, particularly through TBL1-mediated nuclear translocation of β -catenin and transcription of target genes promoting metastasis, correlates with poor prognosis in OS. Tegavivint, a novel first-in-class small molecule inhibitor targeting TBL1XR1, has shown promising antitumor activity in preclinical models and is currently in clinical trial. However, resistance to Tegavivint monotherapy necessitates identification of effective combination approaches.

Methods: A high-throughput drug screen was performed on high-risk patient-derived xenograft (PDX) OS cell lines using Tegavivint to identify synergistic agents. IC50 values were determined for Tegavivint and lead candidates, Ponatinib (multi-tyrosine kinase inhibitor) and Vorinostat (histone deacetylase inhibitor), both as monotherapies and in synergy assays. Cell viability was assessed in 2D and 3D culture systems. In vivo efficacy of Tegavivint was examined using two high MYC-expressing PDX models in immunodeficient NOD scid gamma (NSG) mice.

Results: Tegavivint and the candidate drugs demonstrated IC50 values below 1.5µM, indicating high sensitivity. Combination treatments exhibited additive and synergistic effects, reducing cell viability at lower Tegavivint concentrations. In 3D spheroids, Tegavivint treatment decreased ATP levels without visible spheroid size reduction. In vivo studies revealed decreased tumor volume in both high-MYC models treated with Tegavivint monotherapy, with one study showing complete inhibition of metastasis.

Conclusion: Targeting the TBL1/β-catenin axis with Tegavivint in combination with Ponatinib or Vorinostat may offer a more effective treatment strategy for high-risk OS. These combinations show promise in overcoming drug resistance and improving outcomes for patients with limited options.

(P 22) SINGLE CELL SEQUENCING ENABLES LINEAGE-INFORMED TARGETING OF OSTEOSARCOMA

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Objective: Osteosarcoma (OS) remains difficult to treat due to its genetic heterogeneity and lack of consistent targetable mutations. Notably, current OS treatment is not subtype-specific, and morphology alone does not reveal targets. Here, we demonstrate that single-cell transcriptomic profiling can resolve conserved differentiation states - or "archetypes" - with prognostic and pharmacologic relevance.

Methods: We used a non-negative matrix factorization-based framework to project bulk RNA-seq data from 16 OS cell lines and six matched primary-relapse patient-derived xenograft (PDX) tumor pairs onto a single-cell atlas of normal mesenchymal differentiation. To find archetype-selective compounds, we (1) compared transcriptional responses of two OS cell lines to 337 agents via PLATE-seq (a low-depth, multiplexed RNA-seq method), (2) correlated archetype scores with DepMap viabilities, and (3) prioritized clinically relevant drugs. We then tested 32 drugs across six OS cell lines in dose-response assays.

Results: We identified three dominant archetypes: a stem-like mesenchymal state, a committed chondrogenic state, and a transitional osteoblastic state. The stem-like state was enriched in relapsed PDX tumors and associated with poor survival in the TARGET-OS cohort, suggesting a role in therapeutic resistance. Archetype scores significantly correlated with drug responses ($p < 0.05$, Spearman rank test). Stem-like lines were differentially sensitive to refametinib (IC50 range: 1.37 - 66.0 µM), a MEK inhibitor, consistent with MAPK pathway dependence. Osteoblastic-like lines were more sensitive to belinostat (IC50 range: 0.30 -1.66 µM), an HDAC inhibitor, reflecting epigenetic plasticity in transitional states.

Conclusion: Our single-cell atlas offers a foundation for lineage-specific therapeutic targeting and disease monitoring. Expanded drug screening and larger-scale in vivo validation studies are needed to inform future precision strategies in OS.

(P 23) DEFINING THE NONENZYMATIC FUNCTIONS OF LSD1 IN EWING SARCOMA

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Objective: Ewing sarcoma (ES) is an aggressive malignancy and the second most frequent bone tumor afflicting the adolescent and young adult population. Despite knowing the oncologic driving event of ES for decades, outcomes and treatment options have not improved. A translocation between chromosome 11 and 22, fusing the EWSR1 gene to the FLI1 gene (EWS::FLI1), is the cause of 85% of ES cases. Due to the inability to therapeutically target EWS::FLI1, targeting critical co-regulators of EWS::FLI1 is a more promising therapeutic avenue. One such co-regulator, histone specific lysine demethylase 1 (LSD1), is overexpressed in ES, directly interacts with, colocalizes with EWS::FLI1. Multiple LSD1 inhibitors have been developed, but the efficacy of these inhibitors has been challenging to interpret. Enzymatic inhibition seems to have no impact on cells, but noncompetitive inhibition results in significant off target effects. We hypothesize that LSD1 regulates a distinct set of genes via its nonenzymatic functions in ES.

Methods: To pinpoint the nonenzymatic effects of LSD1, we have depleted LSD1 at the DNA level via CRISPR genome editing and the protein level with UM-171 in 3 ES cell lines. We rescued LSD1 with a wildtype construct or a construct with two key residues mutated, K661Q and A539E, rendering the protein enzymatically dead. We tested for proliferation and transformation capacity defects via Incucyte growth assays and soft agar transformation assays, then found differentially expressed transcripts with RNA-sequencing.

Results: Of note, only 4 genes are differentially expressed when cells enzymatic inhibited by OG-L002. With loss of the complete protein by CRISPR or degradation, hundreds of genes are differentially expressed. These genes are involved in axon development and neural differentiation pathways, correlating with known LSD1 functions.

Conclusion: Our results suggest the demethylase activity of LSD1 is dispensable, whereas the nonenzymatic functions have critical gene targets in ES. LSD1 likely serves a scaffolding or recruitment role, distinct from its demethylase activity, in larger chromatin regulatory complexes that significantly contributes to the ES genetic program.

(P 24) THE SIRTUIN SIRT5 SUPPORTS EWING SARCOMA SURVIVAL VIA REGULATION OF EWS-FLI1 STABILITY AND ACTIVITY

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Objective: Ewing sarcoma (EWS) is an aggressive tumor of bone or soft tissue that mainly affects children and young adults. With typical treatment modalities, patients with localized disease show favorable outcome; however, those with metastatic/recurrent diseases still have poor prognosis. Moreover, current EWS treatments have many adverse side effects. Therefore, there is an important need to develop improved therapeutic approaches that have fewer detrimental side effects, and that can effectively treat patients with recurrent/metastatic disease. Sirtuins are NAD⁺-dependent deacylases that regulate diverse cellular processes such as metabolic homeostasis and genomic integrity. Mammals possess seven sirtuin family members, SIRT1-SIRT7, that display diverse subcellular localization patterns, catalytic activities, protein targets, and biological functions. In the current study, we have tested the tumor promoter functions of the sirtuin SIRT5, a desuccinylase, in EWS.

Methods: EWS cell lines were evaluated for their survival dependency on SIRT5 in vitro and in xenograft models via shRNA and CRISPR mediated SIRT5 knockdown (KD). A variety of cutting-edge tools in addition to traditional techniques were employed to decipher the mechanism behind tumor promoting roles of SIRT5 in EWS. These include, immunoblotting, flow cytometry, RNA-Seq analysis, CHIP-Seq, qRT-PCR, site-directed mutagenesis, mass spectrometry-based metabolite analysis, metabolic profiling using the Agilent-Seahorse extracellular flux analyzer, biochemical assays, drug screening via thermostability assay, and crystallography, among others. GraphPad Prism was used to perform all statistical analysis.

Results: Depletion of SIRT5 resulted in reduced cell proliferation and impaired colony formation ability in 6/6 EWS cell lines tested in vitro. These results were further corroborated by the inability of SIRT5 knockdown (KD) EWS cells to form tumors in xenograft models. Loss of SIRT5 resulted in increased apoptosis, as evidenced by increased levels of cleaved PARP and cleaved caspase 3, and increased number of annexin V- and PI-positive cells. It has been reported that silencing the expression or activity of oncogenic driver EWS-FLI1 induces apoptosis and decreases viability as well as tumorigenicity in EWS cells, like the phenotypes that we observe upon SIRT5 loss. Interestingly, we find that EWS-FLI1 is hypersuccinylated, and its levels are reduced, in SIRT5-depleted EWS cells. Consistently, SIRT5 KD EWS cells display reduced chromatin occupancy of EWS-FLI1 and attenuated expression of its target genes. Based on these results, we speculate that SIRT5 regulates succinylation on the oncogenic driver EWS-FLI1 and modulates its stability and activity. Crucially, SIRT5-deficient mice, and normal cells depleted of SIRT5, show normal development and minimal phenotypes. Therefore, a great deal of interest exists in targeting SIRT5 pharmacologically. In this context, we have generated a novel small molecule inhibitor that can suppress SIRT5 activity both in vitro and in vivo. EWS cells treated with this inhibitor exhibited attenuated growth and other signature phenotypes of SIRT5 loss of function, suggesting that pharmacological SIRT5 inhibition may have therapeutic potential in EWS.

Conclusion: In conclusion, we have found that SIRT5 is crucial for the survival of EWS cells and represents an attractive therapeutic target in EWS. Mechanistically, SIRT5 regulates succinylation levels on the oncogenic driver EWS-FLI1 and promotes its stability and activity. SIRT5 depletion/inhibition causes hypersuccinylation on EWS-FLI1, resulting in its reduced levels and decreased chromatin binding, which in turn alters the expression of multiple genes including pro-survival genes that leads to EWS cell death.

(P 25) IDENTIFICATION AND VALIDATION OF NON-GENETICALLY ENCODED VULNERABILITIES IN EWING SARCOMA

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Objective: Prognosis for relapsed or metastatic Ewing sarcoma (EWS) remains poor with few actionable targets. We previously described a transcriptome-based systems biology approach, OncoTarget for identifying targetable Master Regulator (MR) proteins representing critical non-genetically encoded vulnerabilities from bulk RNA-seq across pediatric sarcomas. To better understand regulatory interactions and therapeutic vulnerabilities in EWS, we applied regulatory network-based analysis of EWS single-cell RNA-seq, hypothesizing that identifying and targeting cell state-specific MRs will prioritize effective and durable drug combinations.

Methods: A EWS-specific gene regulatory network was constructed from snRNA-seq of 6 EWS tumors, regulatory protein activity computed, and protein activity-based tumor cell states identified. OncoTarget analysis identified the cell state-specific activity of directly targetable MRs. Functional validation included ex vivo drug screens and in vivo testing in 2 EWS patient-derived xenograft (PDX) models (TP53 and STAG2 mutant). Anti-tumor activity and progression-free survival (PFS) were assessed.

Results: OncoTarget analysis identified histone deacetylases (HDACs), notably HDAC6, 9 and 3 (in rank order) as top significantly activated targets ($p < 10^{-5}$) across tumor cell states. Ex vivo screens showed synergistic activity of citarinostat (selective HDAC6 inhibitor) combined with vorinostat (pan-HDAC inhibitor). In vivo assessment of citarinostat with vorinostat in 2 EWS PDXs showed statistically significant differences in tumor volume ($p = 0.005$, EWS-83033; $p = 0.02$, EWS-83311) and PFS ($p = 0.02$, EWS-83033; $p = 0.04$, EWS-83311) compared to vehicle control. Combination therapy also showed improved efficacy in terms of best response to treatment compared to vehicle control in both models. ($p = 0.003$). No significant effect on tumor volume or PFS with HDAC inhibitor monotherapy was observed.

Conclusion: Single-cell regulatory network analysis identified HDACs as targetable vulnerabilities in EWS. These findings highlight this approach's ability to identify non-genetically encoded therapeutic targets in genomically "silent" tumors and provides rationale for combinatorial strategies targeting HDACs in EWS.

(P 26) DEVELOPING AN ORTHOTOPIC MODEL OF DESMOPLASTIC SMALL ROUND CELL TUMOR

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Objective: Desmoplastic Small Round Cell Tumor (DSRCT) is a rare and aggressive sarcoma of adolescent and young adults, characterized by high metastatic rates and poor prognosis. Current DSRCT patient-derived xenograft (PDX) models often exhibit slow growth and variable engraftment when implanted subcutaneously. Additionally, flank heterotopic models do not

recapitulate the native DSRCT microenvironment since these tumors predominantly arise in the abdominal cavity. To address the need for in vivo DSRCT models with more consistent growth kinetics that better resemble the original tumors, we evaluated the impact of orthotopic (intraperitoneal) modeling of DSRCT on tumor engraftment and growth relative to heterotopic (subcutaneous flank) implantation.

Methods: DSRCT BER cells were transduced with a lentiviral vector for stable expression of mCherry and luciferase, enabling selection of transduced cells and subsequent in vivo tumor monitoring. NSG mice were divided into two groups for intraperitoneal and subcutaneous flank injections, and tumor growth was monitored weekly via bioluminescence imaging. Formalin-fixed paraffin-embedded (FFPE) samples from primary tumors and metastatic sites were collected at tumor endpoints for histology and immunohistochemical (IHC) analyses.

Results: Our optimized transduction protocol enabled the establishment of an orthotopic DSRCT CDX model. Following injection of mCherry-luciferase-labeled BER DSRCT cells, engraftment was uniformly confirmed by week 2 in 6 out of 6 mice for both groups, followed by overlapping tumor growth rates with no statistically significant differences. Metastases were observed in 4 out of 6 mice from the orthotopic group, with lesions in the spleen, omentum, abdominal wall, visceral fat, and rectum, whereas no metastatic spread was detected in the heterotopic group.

Conclusion: Our study provides proof of concept that orthotopic DSRCT models can be successfully generated and will be applied to patient-derived DSRCT models in upcoming work. Our development of a DSRCT model that better recapitulates the clinical behavior of DSRCT and its key molecular features provides an important model system for improved preclinical evaluation of existing and emerging therapeutic strategies.

(P 27) MOLECULAR CHARACTERIZATION OF RESPONSE TO NEOADJUVANT CHEMORADIATION IN PATIENTS WITH LOCALLY ADVANCED SOFT TISSUE SARCOMAS

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Objective: Soft tissue sarcomas (STS) are a heterogeneous and complex group of neoplasms. STS remain a diagnostic and treatment challenge. A multidisciplinary approach to any single case is mandatory to define a tailored therapeutic plan through case-specific evaluation and to

decide which treatments should be applied. This study aimed to identify the molecular profile of STS to find new and more efficient therapeutic approaches.

Methods: We analysed core biopsy samples of 29 patients before treatment. Patients were treated preoperatively with 5×5 Gy radiotherapy combined with 3 cycles of doxorubicin-ifosfamide chemotherapy. For Next-Generation Sequencing, the TruSight Oncology 500 kit (Illumina) and FusionPlex Sarcoma v2 (Archer™) were used. The Genome Analysis Toolkit (GATK) package, Arriba, PureCN, and OpenCRAVAT software were used to analyze sequencing data. The response to neoadjuvant therapy was assessed using the European Organization for Research and Treatment of Cancer-Soft Tissue and Bone Sarcoma Group (EORTC-STBSG) recommendations.

Results: The most common gene fusions consist of genes related to cell proliferation – MAPK or PI3K-AKT-mTOR pathways (e.g., FGFR1, PIK3CA, ROS1, JAK2, AKT3) and genes related to the apoptosis pathway (FOXO1, BCL2, TP53, HGMA2). Additionally, three patients with detected ROS1-associated gene fusions showed a good pathological response to treatment. The most frequent amplification, with the highest level of amplification, was the MDM2 gene, found in 13.8% of patients with a poor pathological response to treatment. Amplifications of the FGF7 and RICTOR genes were detected in over 10% of cases. The most frequent deletion was loss of the PTEN gene, detected in four cases (in one case, loss of two copies of the gene). The most pathogenic point mutations were detected: three in the TP53 gene (c.733G>A, c.817C>T, c.814G>A), and one in the MET gene (c.2975C>T). Each of the patients with STS with these molecular alterations progressed to distant metastases and/or death.

Conclusion: Cell cycle, apoptosis and proliferation pathways are deregulated in STS. Some of the molecular changes involve the same genes, suggesting a possible link with the development of STS. The obtained results may indicate new therapeutic targets in the treatment of STS.

(P 28) ADVANCING PRECISION ONCOLOGY IN SOFT TISSUE SARCOMAS: THE ROLE OF ITRAC IN METASTATIC RISK STRATIFICATION AND TREATMENT PERSONALIZATION

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Objective: Soft Tissue Sarcomas (STS), known for their extensive Genomic instability (GIN), often result in poor clinical outcomes. grading systems, such as FNCLCC, have limited prognostic accuracy in stratifying metastatic risk for STS patients. We introduce transcription-associated GIN indice (iTRAC) to improve prognostic precision and guide treatment decisions.

Methods: This study analyzed 226 STS tumor samples using RNA sequencing (RNAseq) to assess breakpoint distribution from fusion transcripts as a surrogate for GIN. We calculated iTRAC to quantify transcription-associated GIN. Kaplan-Meier survival analysis were used to evaluate prognostic relevance in patients receiving or not chemotherapy. Multivariate analysis was performed to evaluate the iTRAC compared to FNCLCC and CINSARC for metastatic risk stratification.

Results: STS patients with medium iTRAC level had the poorest metastasis-free survival (MFS) compared to low and high iTRAC levels. Importantly, patients with low iTRAC have a poorer outcome when treated with chemotherapy than those untreated, but at the contrary patients with medium iTRAC and treated by chemotherapy have a better outcome, raising the question of the potential predictive value of iTRAC for adjuvant chemotherapy in STS patients. FNCLCC and CINSARC groups did not show significant difference in MFS between treated and not treated patients.

Conclusion: iTRAC is a novel biomarker for stratifying metastatic risk and guiding personalized treatment in STS. It outperforms molecular and histological prognosis systems like CINSARC and FNCLCC by revealing distinct MFS between patients receiving or not chemotherapy. This could enable better identification of patients who may benefit from chemotherapy and alternative options for those with poor responses. Prospective clinical trials are needed for validation and integration for patients care.

(P 29) ANTI-TUMOR ACTIVITY OF MICVOTABART PELIDOTIN IS ASSOCIATED WITH ENZYME GENE EXPRESSION IN PATIENT-DERIVED XENOGRFT SARCOMA MODELS

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Objective: Sarcomas comprise a variety of heterogeneous cancer subtypes which hinders development of effective therapies. Micvotabart pelidotin (micvo, formerly PYX-201), a first-in-concept antibody drug conjugate targeting extradomain-B of fibronectin (EDB+FN) in the tumor extracellular matrix, is in clinical development and preliminary data showed favorable activity in sarcomas. Micvo has a linker that is cleaved by extracellular proteases in the tumor microenvironment and releases the cytotoxic payload to kill tumor cells. Here, a pre-clinical study was conducted to elucidate mechanisms conferring sensitivity to micvo in patient derived xenograft (PDX) models of sarcoma.

Methods: For each model, mice were randomized into two groups and treated with micvo (3mg/kg Q4D×4) or a vehicle control. Tumor growth inhibition (%TGI) was calculated at study endpoint. Tumors were collected at baseline and study endpoint (when available) for histological analyses; baseline tumors were also analyzed for gene expression profiling by Nanostring.

Results: Micvo induced strong anti-tumor activity across PDX models. Immunohistochemistry analysis demonstrated robust EDB+FN expression in baseline tumors across subtypes, but no correlation was observed between EDB+FN expression and %TGI. To identify what other factor(s) besides target expression may confer sensitivity to micvo, genes expressed in baseline tumors between PDX models with very strong response (TGI>90%) and those which did not respond (TGI< 25%) were compared and revealed an enzyme gene signature, including proteases capable of cleaving micvo's linker, associated with response to micvo. Evaluation of on-study tumors treated with micvo is ongoing.

Conclusion: These results demonstrate anti-tumor activity of micvo across diverse PDX sarcoma subtypes and show EDB+FN is necessary but not sufficient for micvo sensitivity. Notably, an enzyme gene signature was elevated at baseline in models with very strong

response to micvo, suggesting the importance of enzymes in the mechanism of action of micvo. Broad activity in PDX models supports the ongoing clinical development of micvo for patients with sarcoma in Phase 1 monotherapy (NCT05720117) and Phase 1/2 combination with pembrolizumab (NCT06795412) trials.

(P 30) MYELOPEROXIDASE AS A POTENTIAL THERAPEUTIC TARGET IN SOFT TISSUE SARCOMA

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Objective: Soft tissue sarcoma (STS), although a rare malignancy, is one that presents unique challenges for patients given the lack of durable systemic treatment options currently available. Prior studies have documented the extensive infiltration of tumor-associated myeloid cells (TMCs) within the sarcoma tumor microenvironment. The goal of this study is to elucidate myeloperoxidase (MPO) as a novel therapeutic target in STS as our previous work has shown that MPO is present in approximately two-thirds of patient STS resection samples.

Methods: Using a preclinical STS murine model, MCA205, we assessed the efficacy of MPO inhibition in combination with immune checkpoint inhibition (ICI). Flow cytometry was employed to characterize alterations in the immune composition of the tumor microenvironment. Histological analysis quantified MPO expression in patient sarcoma tissue samples.

Results: In the MCA205 murine model, MPO inhibition enhanced ICI response, defined by an increased survival time and delayed tumor growth in those mice treated with the MPO inhibitor in addition to ICIC compared to the control group treated only with ICI. MPO inhibition significantly increased CD8+ T cells and B cells and decreased CD11b+Ly6G+ myeloid cells within the tumor microenvironment suggesting MPO inhibition enhanced anti-tumor immune infiltration and suppressed immunosuppressive TMCs.

Conclusion: MPO serves as a potential target where its inhibition has been shown to increase ICI responses with an overall anti-tumorigenic effect in sarcoma. Given the critical need to improve durable therapeutic options in patients with STS, particularly those with advanced disease, this study serves as a preclinical foundation supporting the incorporation of MPO-specific inhibitors as an effective adjunct to immunotherapy in medical management.

(P 31) TARGETING CANCER STEM CELLS BY TYROSINE PEPTIDE ANALOGUE IN REFRACTORY SARCOMA

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Objective: Disease recurrence in aggressive sarcomas following conventional therapies remains common among cancer patients and is often accompanied by tumor regrowth and metastatic spread. Cancer relapse is frequently linked to drug resistance, driven by small population of cancer stem cells (CSC). We have recently shown that a tyrosine peptide analogue (TPA), developed in our laboratory, specifically targets CSC's. The purpose of this study was to explore TPA's effect on tumor growth of human HT1080 fibrosarcoma, dedifferentiated chondrosarcoma with fibroblastic features cell line xenograft mouse model.

Methods: In our primary tumor growth model, luciferase-labeled human fibrosarcoma HT1080 cells were xenografted in the quadriceps of immunocompromised mice. Doxorubicin (DOX) was delivered intravenously while TPA systemically using osmotic minipumps transplanted subcutaneously. To generate a model for relapsed tumors, cells obtained from orthotopic tumors that had regrown after two rounds of DOX were isolated, expanded in vitro and reinjected in mice orthotopically. For the experimental metastasis model, luciferase-labeled HT1080 cells were injected intravenously.

Results: Our results show that TPA inhibits CSC growth by reducing drastically expression of the polycomb group protein enhancer of zester (EZH2) and its downstream cancer stem marker ALDH1A1, along with embryonic transcription factor NANOG. Moreover, TPA when dosed at 40 µg/ml and higher prevented spheroid formation. The combination of TPA and DOX led to a seven-fold decrease in primary tumor burden with 2-fold, and in experimental metastatic model 3-fold improvement in overall survival.

Conclusion: In combination with DOX, TPA significantly decreased tumor growth and extended overall survival in both primary and metastatic models. Future studies will shed light on the ability of TPA to prevent metastatic formation. Combining conventional chemotherapy drugs with CSC targeting agents is predicted to be more effective as it targets both CSC and non-CSC.

(P 32) EFFECTIVENESS OF LURBINECTEDIN PLUS IRINOTECAN IN PRECLINICAL MODEL OF DESMOPLASTIC SMALL ROUND CELL TUMOR

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Objective: Conventional multimodal treatments failed to improve outcome in desmoplastic small round cell tumor (DSRCT). We demonstrated the effectiveness of the combination trabectedin plus irinotecan in a PDX model of DSRCT. Here, we aimed at i) testing lurbinectedin instead of trabectedin; ii) analyzing effect of the combination in a different DSRCT preclinical model; and iii) investigating the effect of lurbinectedin plus irinotecan on the

EWS::WT1 translocation.

Methods: JN-DSRCT cells were exposed to increasing concentrations of lurbinectedin and SN38 (irinotecan's active metabolite), alone or in combination, for 24 hours to assess antiproliferative activity. Drug interactions were analyzed using a dose-response matrix, and synergy was evaluated with the Loewe additivity model via SynergyFinder software. Apoptosis was measured by TUNEL assay. Expression of the EWS–WT1 fusion protein was assessed by western blot. In vivo efficacy of the treatment combination (lurbinectedin 0.13 mg/kg, irinotecan 2.5 mg/kg) was tested in a DSRCT PDX model by monitoring tumor volume over time after treatment with single agents or their combination.

Results: JN-DSRCT cells showed high sensitivity to both agents, with IC_{50} values of 1 ± 0.06 nM for lurbinectedin and 5 ± 0.3 nM for SN38. Combination treatment produced a dose-dependent inhibition of cell proliferation, and the synergy analysis indicated a mildly synergistic activity of lurbinectedin and SN38. TUNEL assay revealed significantly increased apoptosis in the combination group compared to single-agent treatments. Western blot analysis demonstrated a reduction in EWS–WT1 expression after 24 hours of treatment with either each drug alone or in combination, relative to untreated JN-DSRCT cells. In vivo, treatment combination resulted in complete response lasting 38 days after treatment in all tumors, outperforming each drug alone.

Conclusion: Lurbinectedin and irinotecan exhibit potent antiproliferative activity in DSRCT models. These results lead to the design of a phase II study of lurbinectedin and irinotecan in adult and young adult patients with advanced DSRCT (EU 2024-519261-21-00). Further molecular studies on the effect of drugs on EWS::WT1 modulation both in vitro and in vivo are ongoing.

(P 33) THE NOVEL TRANSCRIPTIONAL INHIBITORS ECUBECTEDIN AND PM54 DEMONSTRATE ANTITUMOR ACTIVITY IN PATIENT-DERIVED XENOGRFT MODELS OF SOFT TISSUE SARCOMA

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Objective: We explored the antitumor activity of two novel transcription inhibitors, ecubectedin (ECU) and PM54, derivatives of lurbinectedin (LUR), under development by PharmaMar (Spain). ECU and PM54 inhibit oncogenic transcription by displacing transcription factors from gene promoters and inducing double strand breaks through DNA adduct formation, replicating the cytotoxic effects of natural ecteinascidins.

Methods: The experimental compounds were tested in 6 patient-derived xenograft (PDX) models of soft tissue sarcoma (STS): two leiomyosarcomas (UZLX-ST22_2 and STS111), two dedifferentiated liposarcomas (STS204 and STS112), one CIC-rearranged sarcoma (STS134) and one synovial sarcoma (STS336) model. Female NMRI nu/nu mice (n=52/experiment) were

transplanted subcutaneously bilaterally with respective PDX models. An additional 52 mice were transplanted with model STS336 to investigate a potential survival benefit after treatment had stopped. Xenografted mice were randomized to 6 treatment groups: 1) vehicle (VEH) (5% dextrose) 5 mL/kg once weekly (QW) intravenously (IV); 2) doxorubicin (DOX) 5mg/kg QW IV; 3) trabectedin (TRA) 0.15 mg/kg QW IV; 4) LUR 0.18 mg/kg QW IV; 5) ECU 1.2mg/kg QW IV; 6) PM54 1.2 mg/kg QW IV. Treatment lasted 16 days and antitumor activity was assessed by tumor volume (TV) and histopathology. The Mann-Whitney U test and the Wilcoxon test were used to compare the treatment effect to baseline values and between groups, respectively.

Results: ECU and PM54 caused tumor shrinkage ($p < 0.05$) in STS134 (Table 1), while other treatments led to tumor growth on day 16. ECU-treated tumors were statistically significantly smaller compared to VEH control in all other models except STS22_2 on day 16. PM54-treated tumors showed TV stabilization in all other models on day 16. In STS336 Both ECU- and PM54-treated tumors displayed prolonged TV stabilization up to 26 days after the last treatment. Histopathological analysis of collected tumor material showed the strongest antitumor effect with the novel drugs in all models as compared to other treatments.

Conclusion: The novel compounds ECU and PM54 consistently showed the strongest antitumor activity in the PDX models tested, achieving prolonged TV-stabilization in STS336 even after treatment cessation. In ongoing experiments we are now exploring the impact of the DNA repair capacity of the models on the antitumor effects observed with the drugs.

Tumor volume change on day 16 and comparison of mitotic and apoptotic activity of respective treatment groups compared to vehicle on day 16. ↓ decrease in activity, as compared to baseline. ↑ increase in activity. VEH: vehicle; DOX: doxorubicin; TRA: trabectedin; LUR; lurbinectedin; n/a: not applicable (* $p < 0.05$).

Subtypes Treatment	Relative tumor volume as compared to baseline						
	STS22_2	STS111	STS204	STS112	STS134	STS336 Day16	STS336 Day 41
VEH	349%	155%	205%	273%	387%	259%	463%
DOX	243%	170%	148%	154%	177%	161%	269%
TRA	254%	137%	172%	135%	230%	167%	414%
LUR	232%	126%	173%	175%	202%	169%	376%
ECU	181%	104%	143%	104%	41%	97%	101%
PM54	162%	113%	145%	125%	76%	100%	136%
Mitotic activity							
VEH	n/a	n/a	n/a	n/a	n/a	n/a	n/a
DOX	↓	↓	↓	↓*	↓*	↓	↓
TRA	↓	↓	↓	↓*	↓*	↓	↓
LUR	↓*	↓*	↓	↓*	↓*	↓*	↓
ECU	↓*	↓*	↓	↓*	↓*	↓*	↓*
PM54	↓*	↓*	↓*	↓*	↓*	↓*	↓*
Apoptotic activity							
VEH	n/a	n/a	n/a	n/a	n/a	n/a	n/a
DOX	↑*	↑*	↑	↑*	↑*	↑*	↓
TRA	↑*	↑*	↑*	↑*	↑*	↑*	↑*
LUR	↑*	↑*	↑*	↑*	↑*	↑*	↑
ECU	↑*	↑*	↑*	↑*	↑*	↑*	↑
PM54	↑*	↑*	↑*	↑*	↑*	↑*	↑

(P 34) **EXPRESSION OF ONCOFETAL ANTIGEN 5T4 IN SARCOMA SUBTYPES AND PRECLINICAL ACTIVITY OF TUB-030, A NOVEL 5T4-TARGETING ANTIBODY-DRUG CONJUGATE (ADC)**

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Objective: 5T4 is an oncofetal surface glycoprotein with restricted normal tissue expression, mainly limited to the developing placenta. 5T4 overexpression is observed in a variety of solid malignancies and functions in cell adhesion, epithelial-mesenchymal transition, and oncogenic signaling, making it an attractive target for therapeutic development. A previous study showed 5T4 expression in soft tissue sarcoma (STS) subtypes, including non-uterine leiomyosarcoma, undifferentiated pleomorphic sarcoma (UPS), myxofibrosarcoma, and rhabdomyosarcoma. TUB-030 is a novel 5T4-targeting ADC under clinical development with optimized biophysical properties, an effector function-silenced antibody, and the topoisomerase I inhibitor exatecan as payload.

Methods: To further define 5T4 expression in sarcoma subtypes, histological sections of human osteosarcoma, chondrosarcoma, uterine and non-uterine LMS, rhabdomyosarcoma, fibrosarcoma, and liposarcoma were stained with anti-5T4 antibody, imaged, and H-scores calculated based on the percentage of 5T4-positive tumor cells and their expression intensity (0 to 3+). Mice bearing PDX models with high 5T4 expression (Sarc10562 (5T4high), Sarc10642 (5T4high); UPS subtype) were treated with a single dose of TUB-030 and tumor growth was monitored until the humane endpoint or 60 days was reached.

Results: Strong 5T4 surface staining was observed in osteosarcoma and chondrosarcoma; of N=61 samples analyzed, 14% showed low expression (H-score < 100), 46% medium (100-250) and 39% high 5T4 expression (>250). Liposarcoma showed no 5T4 signal, while other STS subtypes (N=59) had 36% low, 41% medium, and 24% high expression. In PDX models, complete tumor regression and durable control were maintained for 60 days after a single i.v. dose of TUB-030. A phase I/IIa multi-center, first-in-human clinical trial (5-STAR 1-01) evaluating TUB-030 is underway in patients with advanced solid tumors, including selected soft tissue and bone sarcomas (NCT06657222).

Conclusion: 5T4 is broadly expressed in sarcoma subtypes and preclinical data provide rationale for further investigation of TUB-030 in patients with sarcomas.

(P 35) MECHANISTIC AND TRANSCRIPTOMIC ANALYSES REVEAL MUTATION-SPECIFIC THERAPEUTIC RESPONSES IN DESMOID TUMOR CELLS TREATED WITH SORAFENIB AND NIROGACESTAT

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Objective: Desmoid tumors are rare fibroblastic neoplasms characterized by mutations in the β -catenin (CTNNB1 gene), with T41A and S45F variants showing differential therapeutic responses. While niraparicestat recently received FDA approval for desmoid tumors, sorafenib remains an important treatment option. Despite the routine clinical use of these compounds, little is known about the biology which underpins response or resistance to treatment. This study aims to elucidate mutation-specific therapeutic vulnerabilities in desmoid by comparing sorafenib and niraparicestat responses in CTNNB1-mutant models through integrated mechanistic and transcriptomic analyses to advance personalized treatment strategies.

Methods: We conducted comprehensive analyses using HCM-BROD-0762-C49 (T41A mutant) and DES23 (S45F mutant) desmoid cell lines in response to sorafenib and niraparicestat. Viability assays were performed at 24-48 hours with varying concentrations of both drugs. RNA sequencing was conducted to evaluate transcriptomic changes, followed by differential expression and gene set enrichment analysis. Immunofluorescence microscopy assessed β -catenin and Notch1 localization patterns following treatment.

Results: BROD-0762-C49 (T41A) exhibited increased sensitivity to both sorafenib and niraparicestat relative to DES23 (S45F) cells, consistent with established mutation-specific therapeutic responses. RNA sequencing revealed distinct transcriptomic signatures for each treatment: niraparicestat primarily affected Notch pathway genes (HES1, HEY1) with significant β -catenin downregulation (6.26-fold inhibition), while sorafenib showed effects on PDGFR/c-Abl signaling pathways. Immunofluorescence confirmed niraparicestat-mediated reduction in nuclear cleaved Notch1 levels at both timepoints, while β -catenin localization remained largely unchanged in S45F cells but showed modest reduction in T41A cells at 24 hours.

Conclusion: To our knowledge this is the first study investigating niraparicestat and sorafenib treatment response in these novel preclinical models of desmoid tumor biology. The transcriptomic signatures identified represent promising targets for further translational strategies to overcome treatment resistance, specifically NOTCH, β -catenin and KRAS signaling. Moreover, this study demonstrates mutation-specific therapeutic vulnerabilities in desmoid tumors with potential implications for personalized treatment approaches in desmoid tumor management.

(P 36) MODULATION OF THE SARCOMA MICROENVIRONMENT THROUGH β -ADRENERGIC BLOCKADE

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Objective: β -adrenergic signaling has emerged as a key contributor to tumor progression across multiple cancer types, yet its immunosuppressive role in soft tissue sarcoma (STS) remains poorly defined. Propranolol, a non-selective β -blocker, has shown clinical efficacy in angiosarcoma, with an orphan drug designation by EMA. In this study, we explore the anti-tumor effects of propranolol in preclinical murine models of sarcoma.

Methods: We utilized murine models of sarcoma, melanoma, breast and colon cancer. Flow cytometry for characterizing immune cell infiltration. IHC on FFPE lung sections was performed.

Results: In the MCA205 fibrosarcoma model, propranolol significantly delayed tumor growth and prolonged survival and were associated with reduced tumor angiogenesis via VEGF pathway inhibition, decreased infiltration of immunosuppressive myeloid-derived suppressor cells (MDSCs), and enhanced CD4⁺ T cell recruitment. Intratumoral CD4⁺ T cells displayed an activated phenotype, marked by increased expression of CD137 and PD-1. The therapeutic benefit of propranolol was T cell-dependent. Combining propranolol and anti-CTLA-4 synergistically improved tumor responses and extended survival than either therapy alone. Given the high incidence of pulmonary involvement in metastatic sarcoma, we employed a preclinical model of sarcoma lung metastasis to evaluate therapeutic efficacy. Propranolol treatment reduced lung metastasis burden. Mechanistically, propranolol reduced recruitment of inflammatory monocytes to the lung and increased infiltration of CD4⁺ T cells. In models of melanoma, breast cancer, and colon cancer lung metastasis, propranolol similarly reduced lung metastases by reshaping the monocyte compartment and recruiting tumor reactive CD4⁺ T cells.

Conclusion: These findings highlight β -adrenergic blockade as a promising immunomodulatory strategy that reprograms the tumor microenvironment, enhances CD4⁺ T cell-mediated immunity, and sensitizes sarcomas to checkpoint inhibition

(P 37) DISSECTING THE TUMOR MICROENVIRONMENT OF UTERINE LEIOMYOSARCOMAS FOR TARGETED DRUG PREDICTIONS

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Objective: Uterine leiomyosarcomas (ULMS) are highly lethal, rare malignancies of the uterine myometrium. They typically affect young women and confer a dismal prognosis regardless of the stage at diagnosis. Current treatments for ULMS are limited in efficacy. The lack of effective treatment options for ULMS is in part due to the limited understanding of the pathophysiology of the disease. The overall purpose of this study is to investigate the transcriptomic landscape of ULMS to derive targeted therapies.

Methods: Fresh ULMS specimens were collected from consenting patients, which were then dissociated into single cells and underwent library preparation, followed by single cell RNA sequencing (scRNA-seq). Following read alignment, standard quality control metrics, and integration with scVI, the resulting clusters were manually annotated. Tumor cells were

identified using canonical markers and inferCNV. Broad cell types were then subsetted, re-integrated and clustered to identify subtypes. Tumor cell subtype markers were then leveraged for targeted drug predictions. FFPE blocks of the same tumors were used to study the spatial transcriptomic profiles of these tumors.

Results: ScRNA-seq was performed on 15 uterine sarcoma samples from 13 patients. All patients had a variety of pre-operative chemoradiation regimens. Initial annotation uncovered a complex tumor microenvironment (TME) with multiple cell types, including lymphocytes, myeloid cells, endothelial cells, and tumor cells. The subsetted tumor cells revealed notable heterogeneity with differing transcriptomic signatures, with five overarching subtypes. The five subtypes exhibited a spectrum of differentiation states and had differing drug sensitivities.

Conclusion: We present a single-cell transcriptomic atlas of ULMS, which reveals a rich TME and marked heterogeneity. The targeted drug predictions derived from the transcriptomic signatures of these tumors uncover novel therapeutic avenues for treating ULMS.

(P 38) VALIDATION OF THE SIGNIOS SEVEN-GENE SIGNATURE FOR PREDICTING ANTI-PD-1 INHIBITOR EFFICACY IN SARCOMA

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Objective: Immune checkpoint inhibitors (ICIs) show limited efficacy in sarcomas, primarily attributed to an immunologically "cold" tumor microenvironment. A previously identified 7-gene signature (CD86, CHI3L1, CXCL10, CXCL9, LAG3, NR4A1, VCAM1; designated SIGNIOS - SIGNature for Immuno-Oncology anti-PD-1 inhibitors in Sarcoma) predicted response to combined antiangiogenic/PD-1 inhibitor therapy in soft-tissue sarcoma (STS). This study aimed to externally validate SIGNIOS' predictive value for efficacy to ICI in an independent cohort of patients (pts) with advanced sarcomas.

Methods: Using transcriptomic data (RNA-Seq) from pre-treatment tumor samples from the SARC028 phase 2 trial (pembrolizumab for advanced sarcomas), we calculated the SIGNIOS score. Patients were stratified into low (score 0-4) and high (score 5-7) risk groups. Progression-free survival (PFS) and clinical benefit (complete response, partial response, or stable disease vs. progression of disease [PD]) were compared between groups.

Results: The validation cohort included 31 patients (median age: 33 years; 45.2% female). Key histologic subtypes included osteosarcoma (25.8%), Ewing sarcoma (19.4%), leiomyosarcoma (12.9%), synovial sarcoma (12.9%), and undifferentiated pleomorphic sarcoma (12.9%). The SIGNIOS score was significantly associated with PFS (median PFS of low-score vs high-score groups: 49 vs 170 days, Hazard Ratio = 0.71; p=0.007). The 7-gene-based signature was

unable to distinguish between patients who experienced clinical benefit from pembrolizumab and patients with PD ($p=0.15$).

Conclusion: This external validation in a pembrolizumab-treated cohort confirms the SIGNIOS 7-gene signature as a robust biomarker for predicting ICI efficacy in patients with advanced sarcomas. Prospective studies are warranted to refine its clinical utility across diverse sarcoma subtypes and explore applicability in other tumor types.

(P 39) BUB1 AN OVEREXPRESSED KINASE IN SARCOMA: FINDING NEW TARGET THERAPY FOR OSTEOSARCOMA, LIPOSARCOMA, SYNOVIAL SARCOMA AND LEIOMYOSARCOMA

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Objective: This study aimed to identify and validate common overexpressed kinases in osteosarcoma, liposarcoma, synovial sarcoma, and leiomyosarcoma, to establish novel therapeutic targets.

Methods: This work was developed in two steps: First, we performed a bioinformatics workflow utilizing several data mining methods through the R programming language (4.1.1), the Bioconductor environment (3.13), and gene expression data sets. To establish the differentially expressed (DE) kinase genes in each type of sarcoma, we employed the DESeq2 package. Then, we developed a comparative analysis using the VennDiagram R package to establish common kinases with overexpression between the four sarcomas analyzed. The transcriptional regulation of BUB1 kinase was investigated, first determining its interaction with gene expression regulatory molecules such as transcription factors, mRNA-interacting molecules, and non-coding RNAs (microRNAs and long non-coding RNAs). Later, BUB1 interactions with transcription factors, RNA binding proteins, and long noncoding RNAs were tested using RNAinter. The second step consisted of experimental validation. For that, the cell lines HTB-86 (U-2 OS), HTB-92 (SW-872), HTB-88 (SK-LMS-1), and HTB-93 (SW-982), derived from osteosarcoma, liposarcoma, leiomyosarcoma, and synovial sarcoma, respectively, were obtained from ATCC. Dental Pulp Stem Cells (DPSC) were used as non-tumoral mesenchymal cells. Total RNA and protein extracts were obtained from the cells to validate the BUB1 levels. To demonstrate functional inhibition of BUB1 kinase activity, the sarcoma cell lines were treated with the inhibitor 2OH-BNPP1. Phosphorylation levels of H2A and AKT (BUB1 targets previously reported) were evaluated. The biological implication of BUB1 activity was tested by colony formation and proliferation assays. Finally, an Overall Survival (OS) analysis was performed to explore the relation of BUB1 levels with the OS of sarcoma patients.

Results: In this work, we used gene expression databases and bioinformatic tools to identify the overexpressed kinases in the four most frequent types of sarcomas: osteosarcoma, synovial sarcoma, liposarcoma, and leiomyosarcoma. Then, over-expressed (OE) kinases shared in all analyzed sarcomas were determined. BUB1 kinase was identified as a key enzyme across all four types of sarcomas analyzed. The interaction network for BUB1 expression regulation was predicted and a gene set enrichment analysis was performed to determine biological implications. BUB1 interactions suggest a potential role in promoting cell proliferation and invasion. Signaling pathways that regulate malignancy and pro-gression of STS and BS were the most represented. Using sarcoma cell lines and non-tumoral mesenchymal cells, the gene expression and protein levels of BUB1 were measured. Pharmacological BUB1 inhibition assays showed an implication in cell pro-liferation of this kinase. Finally, a correlation between high levels of BUB1 and poor overall survival in patients of all analyzed sarcomas was determined.

Conclusion: This study highlights the overexpression of effector molecules such as kinases in the four most frequent types of sarcomas. Our analysis allowed us to identify a molecule that clearly could be a target of pharmacological inhibition in the treatment of both, bone and soft tissue sarcomas. This strengthens the idea of the use of target therapies focused on the inhibition of BUB1. As perspectives of this work remain the deep analysis of the molecular aspects that modulate the inhibition of this kinase and how it affects the biology of the assayed subtypes of sarcomas.

(P 40) PRECLINICAL EFFICACY OF A PH-SENSITIVE EXATECAN PEPTIDE-DRUG-CONJUGATE IN RHABDOMYOSARCOMA

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Objective: There is a pressing need for novel therapies in rhabdomyosarcoma (RMS). Peptide-drug conjugates offer a promising approach to deliver potent cytotoxic agents directly to tumor cells. Tumors exhibit a relatively acidic microenvironment (pH 6.0–7.1) due to the Warburg effect, which can be selectively targeted using pH-Low Insertion Peptides (pHLIPs®). Exatecan, a potent topoisomerase I inhibitor, shows strong anti-tumor activity but is limited by systemic toxicity. CBX-12 (alphalex™ exatecan) is a pHLIP-based conjugate that selectively delivers exatecan to tumors. In a completed Phase I study in adults with advanced solid tumors, CBX-12 allowed for higher exatecan doses with manageable myelosuppression and demonstrated single-agent activity, including complete responses. Here, we evaluated the preclinical activity of CBX-12 in RMS.

Methods: In vitro cell viability assays were performed using serial dilutions of free exatecan to determine IC₅₀ values in RH30, RH41 (both FOXO1-fusion positive) and RD (FOXO1-fusion negative) RMS cell lines. Orthotopic murine models were generated by injecting RMS cells into the hind legs of mice. Mice were treated with CBX-12 (20 mg/kg, I.P.) or vehicle on a 4-days-on/3-days-off schedule for three cycles. Tumor volumes were measured twice weekly. Study endpoints included tumor size (> 2000 mm³) or ≥20% weight loss. Overall survival was analyzed

using the Kaplan-Meier method, and treatment groups were compared using the log-rank test.

Results: RMS models exhibited exquisite sensitivity to exatecan in vitro with IC₅₀ values < 1 nM. In vivo, CBX 12 induced complete tumor regression and significantly extended median survival from 21 to 59 days ($p < 0.0001$). Treatment was well tolerated with no significant weight loss.

Conclusion: Preclinical data demonstrate CBX-12's potent activity in RMS models, with excellent tolerability. Combined with Phase I adult data showing tumor responses and manageable safety, these findings strongly support further clinical development in pediatric RMS.

(P 41) THE IMPACT OF PAZOPANIB AND EXTREMITY RADIOTHERAPY ON TRANSAMINASES

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Objective: Transaminase elevations are common adverse effects of pazopanib. In the PASART trials, approximately one-third of patients receiving concurrent pazopanib and radiotherapy experienced grade ≥ 3 transaminase elevations, substantially higher than expected. No clear explanation was identified. Although, alanine transaminases (ALT) and aspartate transaminase (AST) primarily originate from the liver, both are also present in muscle tissue. In patients with extremity soft tissue sarcomas (STS), where large muscle volumes are within the radiation field, radiation-induced muscle damage may contribute to these elevations. This study evaluated the impact of extremity radiotherapy, pazopanib, and their combination on the incidence and degree of ALT/AST elevations in STS patients.

Methods: A prospective cohort of patients treated with extremity radiotherapy alone was combined with retrospective cohorts treated with pazopanib or both (PASART). Patient characteristics, radiation and pazopanib details, and laboratory values (liver enzymes and muscle injury biomarkers) were collected. Descriptive analyses and logistic regression were conducted to evaluate the effect of radiotherapy and pazopanib on the incidence of grade ≥ 3 ALT/AST elevations. Binomial probability analysis assessed the likelihood of the observed events in PASART.

Results: Among 146 patients (10 radiotherapy, 100 pazopanib, 36 PASART), none of the radiotherapy group experienced grade ≥ 3 ALT/AST elevations. Post-irradiation ALT/AST, creatine kinase and myoglobin elevations were minimal. Grade ≥ 3 ALT/AST elevations occurred in 6% of pazopanib and 36% of PASART patients. ALT/AST typically normalized after discontinuing pazopanib. Grade ≥ 3 ALT/AST elevations were significantly associated with pazopanib use, but not with radiotherapy or pazopanib C_{trough} levels. The probability of ≥ 13 events (36%) in 36 patients, assuming a true event rate of 6% is < 1 in 13 million, indicating the PASART incidence exceeds the expected variability.

Conclusion: Extremity radiotherapy does not meaningfully contribute to transaminase

elevations. The higher observed incidence in PASART is unlikely due to chance or radiation-induced muscle damage. The cause of transaminase elevations in PASART remains unclear.

(P 42) PRECLINICAL VALIDATION OF M3554, A NOVEL ANTI-GD2 ANTIBODY-DRUG CONJUGATE, AND EPIGENETIC SENSITIZATION STRATEGIES IN SOFT TISSUE SARCOMAS

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Objective: GD2, a disialoganglioside is enriched in various malignancies and has recently emerged as a potential therapeutic target in select soft tissue sarcomas (STS). However, approved anti-GD2 antibodies are associated with adverse events, limiting broader applicability. M3554 is a novel anti-GD2 antibody-drug conjugate (ADC) with a β -glucuronide linker and exatecan payload that has shown strong antitumor activity in neuroblastoma PDX models. The Fc region of M3554 has been engineered to reduce pain associated with anti-GD2 antibodies. In this study, we evaluated the preclinical efficacy of M3554 in GD2-expressing STS models and explored the potential of EZH2 inhibition to upregulate GD2 expression as prior findings showed that EZH2 can silence ganglioside biosynthesis genes.

Methods: GD2 surface expression was assessed via flow cytometry in STS cell lines with or without the EZH2 inhibitor tazemetostat, followed by analysis of ganglioside biosynthetic enzyme expression. The in vitro cytotoxicity of M3554 was evaluated, and synergy between M3554 and tazemetostat was tested using combination treatment assays. In vivo, a dedifferentiated liposarcoma xenograft model was treated with either a single or fractionated dose of M3554, with tumor growth inhibition and toxicity monitored.

Results: GD2 was heterogeneously expressed across sarcoma subtypes. Tazemetostat upregulated GD2 expression across all tested cell lines, particularly in low-GD2-expressing models. M3554 exhibited potent in vitro cytotoxicity that correlated with the percentage of GD2-positive cells. Combination with tazemetostat showed signs of enhanced sensitivity to M3554 in select models tested. In vivo, M3554 significantly inhibited tumor growth without evidence of systemic toxicity.

Conclusion: M3554 is a promising anti-GD2 ADC with strong preclinical activity in GD2-expressing STS cell lines. Epigenetic modulation using EZH2 inhibition effectively upregulates GD2 expression, potentially enhancing therapeutic response and expanding the range of treatable tumors. These findings support the clinical development of M3554 in STS populations and provide a rationale for combining GD2-targeted therapies with epigenetic modulators. A first-in-human study of M3554 in patients with STS and IDH wildtype glioblastoma is ongoing (NCT06641908).

(P 43) OVERCOMING PROMISCUOUS TUMOR FORMATION: A CONTROLLED GENETICALLY ENGINEERED MOUSE MODEL OF CIC::DUX4 SARCOMA

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Objective: CIC::DUX4 sarcoma (CDS) is a rare and aggressive sub-type of sarcoma with no effective treatment options currently available. A significant barrier to identifying alternative therapeutic approaches is the lack of robust pre-clinical models. We previously generated 3 genetically engineered mouse models of CDS, however, all 3 models spontaneously formed tumors in the absence of Cre-recombinase. Accordingly, we developed a novel dual-recombinase FLEEx-switch model (dFLEEx CDS). In this study we show the dFLEEx CDS model is leak-proof, spatially and temporally controllable, and recapitulates human CDS.

Methods: The dFLEEx CDS allele features a stop cassette preceded by an inverted exon 1, and exon 2. Cre-mediated recombination inverts the first exon into frame and removes the upstream stop cassette while FLP-mediated recombination inverts exon 2 into frame. Both Cre and FLP-mediated recombination are required for CIC::DUX4 expression. To induce recombination, two approaches were used: (1) injection of Adeno-Cre-2A-FLP and (2) electroporation of pCAG-Cre and pCAG-FLPE plasmids. Additionally, dFLEEx CDS mice were crossed with R26-FlpO deleter or R26-Cre mice to remove 1 of the 2 FLEEx switches (sFLEEx CDS).

Results: Injection of AdCre-2A-FLP resulted in tumors within 60 days with 100% penetrance; however, tumor formation was not restricted to the injected hindlimb. Conversely, electroporation of separate pCAG-Cre and pCAG-FLPE plasmids resulted in spatially and temporally restricted tumors that express the CIC::DUX4 fusion and known CIC::DUX4 target genes. Interestingly, sFLEEx CDS mice were less viable and suffered from spontaneous tumor formation, similar to our previous CDS GEMMs.

Conclusion: dFLEEx CDS is the first temporally and spatially controllable mouse model that recapitulates human CDS tumors. sFLEEx CDS mice develop spontaneous tumors, further highlighting the potency of the CIC::DUX4 oncogene and need for multiple layers of recombination protection. The use of two FLEEx systems minimizes unintended tumor development, providing a reliable platform for mechanistic insight and robust preclinical drug testing for CDS.

(P 44) A SYSTEMATIC REVIEW OF FUSION-DRIVEN SARCOMAS

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Objective: Sarcomas are rare and complex malignancies, approximately 30% of which are defined by characteristic gene fusions that serve as diagnostic, prognostic, and therapeutic biomarkers. These fusions provide a powerful tool across various types of sarcomas, facilitating diagnosis and treatment precision approaches. In this review, we summarize current knowledge on major fusion-driven sarcoma categories and outline a proposed systematic review aimed at evaluating emerging diagnostic methodologies and targeted therapies. We also highlight how

fusion genes are influencing the future of sarcoma care.

Methods: We conducted a comprehensive review of published literature from 2015–2025 across PubMed, Web of Science, Cochrane, and ClinicalTrials.gov. We focused on research involving human fusion-positive sarcomas, molecular diagnostics, and targeted therapies. A systematic review protocol following PRISMA guidelines has been developed and screening is currently in progress.

Results: We found that sarcoma-related fusion genes fall into four major categories: 1. Transcription Factor Fusions such as EWSR1-FLI1, SS18-SSX, PAX3-FOXO1 which define tumor lineage but remain difficult to target directly. 2. Tyrosine Kinase Fusions including NTRK, ALK, and COL1A1-PDGFB are highly actionable with FDA-approved therapies like larotrectinib, imatinib, and others. 3. Chromatin Remodeling Fusions like BCOR- and NAB2- rearrangements highlight the potential for epigenetic targeting such as EZH2 inhibitors. 4. Rare and Novel Fusions including CIC-DUX4 and YAP1-TFE3, are increasingly identified through advances in RNA-based sequencing. RNA-based next generation sequencing (NGS) is revolutionizing fusion detection and improving diagnostic precision. Hi-C sequencing is an emerging DNA-based NGS that may detect cryptic fusions and potential therapeutic targets. Targeted therapies, including kinase inhibitors, epigenetic modulators, and emerging immunotherapies are under investigation preclinically and within clinical trials.

Conclusion: With the continued discovery of tumor-specific oncogenes, understanding fusion protein activity is essential for developing efficacious systemic therapies. Barriers in this path include the rarity of fusions, limited actionability, and lack of comprehensive fusion registries. Our proposed systematic review aims to assess the evolving clinical utility of fusion-targeted diagnostics and therapies. Multi-institutional/national collaborations are essential to advance fusion-targeted care of these rare tumors, particularly with discovery of novel genes using more sensitive technologies. Harnessing the clinically relevant fusion gene biology holds promise for improving outcomes in patients with these rare and often aggressive tumors.

(P 45) MONITORING EWSR1 FUSIONS IN SARCOMA PATIENTS USING PERSONALIZED LIQUID BIOPSY ASSAYS

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Objective: Sarcomas and sarcoma-like tumors harbor gene fusions involving the EWSR1 gene. Using liquid biopsies to analyze cell-free DNA (cfDNA) to detect these gene fusions could allow improved disease management without ionizing radiation. However, the structural complexity and individual intronic breakpoints poses challenges for the detection in patient plasma. We present a novel approach that involves mapping each patient's unique EWSR1

fusion breakpoint, designing personalized primers, developing a customized TaqMan assay, and using it to longitudinally track tumor burden in plasma cfDNA.

Methods: Patients with EWSR1 fusion positive sarcomas are identified through clinical RNA-based sequencing. Tumor DNA is sequenced to map the intronic DNA breakpoint and customized primers spanning the breakpoint are designed and validated for each patient, and subsequently Taqman assays are designed. Plasma timepoints are collected at regular intervals, and the tumor burden is quantified and correlated with clinical imaging studies.

Results: We consented 16 patients to participate in this study, with a total of 48 collected plasma timepoints. TaqMan assays were designed for 8 patients, and the remaining 8 patients are currently under analysis. One patient was followed over the period of three years with a total of 12 plasma timepoints. The patient started with a low number of EWSR1-FLI1 copies of < 1ng/ml plasma for 18 months while on vincristine, irinotecan, and temozolomide combination therapy. Due to complications, the patient was switched to a temozolomide monotherapy. The next plasma timepoint after 4 months still showed a low number of fusion copies < 1ng/ml plasma. Ten months after starting monotherapy, disease progression correlated with an increase of EWSR1-FLI1 fusion copies to 3ng/ml plasma. Despite different treatment approaches, the patient continued to progress, with an increase in fusion copies to 21ng/ml plasma.

Conclusion: Our pilot assay was able to detect ESWR1 fusions in cfDNA in plasma of sarcoma patients. In two patients who had serial testing, the level of ESWR1 fusion in cfDNA correlated with disease status. This exciting finding will need to be confirmed in future work with a larger number of homogenous patients to confirm if this biomarker could be an adjunct assay to imaging. Nevertheless, our approach using an individually tailored cfDNA TaqMan assay for each patient could provide a valuable monitoring tool to inform clinicians about tumor progression.

(P 46) INVESTIGATING THE IMPACT OF SARCOMA FUSION PROTEINS ON EPIGENETIC AND DNA-DEPENDENT PROCESSES THROUGH INTERACTOME PROFILING

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Objective: Around 30 % of sarcomas carry oncogenic fusions as primary drivers of tumorigenesis. The resulting chimeric proteins often lack proper regulatory domains, leading to inappropriate functional roles and disruption of cellular homeostasis. While these fusion proteins are studied for their role in cell signaling, their impact on epigenetic regulation and other DNA-dependent processes remains poorly explored.

Methods: Our study aims to elucidate how sarcoma fusion proteins interact with cellular machineries that govern chromatin organization, DNA replication, and repair in order to define biomarkers and potential sarcoma vulnerabilities. Patients' representative fusion genes (122 fusions recurrent for 20 sarcoma subtypes) have been designed and ectopically expressed in relevant cell models. Chimeric protein complexes, along with their interacting partners, are being identified using Tandem Affinity Purification/Mass Spectrometry (TAP/MS).

Results: Analysis of the interactomes of Ewing sarcoma fusions (9 fusions recurring in this subtype) showed that their interactomes are interconnected. The results show that Ewing fusions shared interactions with three transcription factors (TFs), ZEB1, BCL11A and TRPS1. As a proof of concept for the significance of these common TFs in the oncogenic activity of Ewing fusions, we analyzed survival of Ewing patients with high vs low mRNA expression of these TFs. High expression levels were associated with lower survival rates of patients. Further, to understand the underlying molecular mechanisms, we identified genes that are positively correlated with ZEB1, BCL11A and TRPS1 and subjected these factors to pathway enrichment analysis. This resulted in enrichment of PI3K/AKT and MAPK pathways. Moreover, to assess validity of these pathways in Ewing sarcoma, we analyzed publicly available drug screening data of Ewing sarcoma cell line (A673 with endogenous EWSR1-FLI1). A673 cells were significantly sensitive to PI3K and GSK3B inhibitors.

Conclusion: Future analyses will focus on identifying interactors across sarcoma subtypes and validating how these interactions modulate chromatin and DNA-dependent pathways to support tumor survival. Linking the oncogenic activity of chimeras to vulnerabilities in epigenetic regulation and genome maintenance could uncover new therapeutic opportunities in sarcoma.

(P 47) EWSR1::WT1 FUSION ONCOPROTEIN ACTIVITY SHAPES LINEAGE HETEROGENEITY IN DESMOPLASTIC SMALL ROUND CELL TUMORS

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Objective: Desmoplastic small round cell tumors (DSRCTs) are rare, aggressive sarcomas driven by the EWSR1::WT1 fusion oncoprotein (FP) and characterized by poor long-term survival. To uncover mechanisms underlying tumor plasticity and therapeutic resistance, we investigated how the FP may drive lineage through integrated multi-omic analyses.

Methods: We performed scMultiome on post-chemotherapy DSRCT specimens to assess gene expression and chromatin accessibility. Androgen receptor (AR) CUT&RUN after dihydrotestosterone (DHT) stimulation and HOMER motif analysis explored transcriptional regulation. Spatial heterogeneity and FP activity were evaluated using multiplex immunofluorescence and RNAScope.

Results: ScMultiome analysis revealed inter-tumoral heterogeneity, distinguishing tumors by epithelial and neural (NE) lineage signatures, with epithelial lineage co-expressing AR. We hypothesized that epigenetic regulation of the EWSR1::WT1 FP contributes to this lineage divergence. To explore FP activity, we found that neogenes (non-coding RNA FP targets) and known FP-regulated genes were more highly expressed in NE-lineage tumors, suggesting FP effects on lineage type. Spatial transcriptomic analysis revealed intratumoral heterogeneity,

with distinct clusters of epithelial (AR+, cytokeratin+) and non-epithelial tumor cells. Despite phenotypic differences, all tumor cells expressed neogenes, as confirmed by RNAScope. Epigenetic profiling showed enrichment of forkhead TFs (FOXA1/2). FOXA2 was associated with NE, and AR/GRHL2 were associated with epithelial lineages. CUT&RUN analysis of AR after DHT stimulation revealed co-occupancy of FOXA1/2 and WT1 at AR-bound regions, suggesting interaction between AR signaling, FP, and FOXA1/2. FP knockdown in DSRCT cell lines induced a shift toward an epithelial-like state, increased FOXA1, and decreased FOXA2 expression.

Conclusion: Tumor cells exhibit both inter- and intra-tumoral heterogeneity, adopting epithelial and NE phenotypes. We find that the high FP levels favor a NE-lineage state mediated by chromatin accessibility and transcriptional regulation. Spatial analyses revealed co-existing epithelial and non-epithelial tumor cells within the same nests, highlighting the pervasive role of the FP. Differences in cell states may influence chemosensitivity, and targeting cell state transitions may present a novel therapeutic approach. Our work also suggests that future FP-directed therapy will alter cell fate and phenotype.

(P 48) PRECLINICAL ACTIVITY OF MEK INHIBITION IN COMBINATION WITH CHEMOTHERAPY IN MALIGNANT PERIPHERAL NERVE SHEATH TUMOR

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Objective: Malignant peripheral nerve sheath tumor (MPNST) is an aggressive soft tissue sarcoma most commonly occurring in individuals with neurofibromatosis 1 (NF1) and associated with poor prognosis despite conventional therapy. MEK inhibitors have emerged as promising agents for NF1-associated tumors. Mirdametinib is a selective MEK1/2 inhibitor with improved potency and bioavailability compared to earlier MEK inhibitors and is FDA approved for NF1 plexiform neurofibromas in adults and children. We evaluated the preclinical activity of mirdametinib in combination with chemotherapy in MPNST patient-derived xenografts (PDXs).

Methods: Clinically relevant dosing of mirdametinib monotherapy (0.5 mg/kg PO BID x 21 days) and in combination with conventional soft tissue sarcoma-based chemotherapy (ifosfamide/doxorubicin) were administered to nude mice to assess tolerability. After confirmation of dose and schedule, an MPNST PDX model (NF1 null) was propagated and treated with vehicle, trametinib, or mirdametinib with each MEK inhibitor administered as monotherapy or in combination with chemotherapy. Differences in tumor volume and progression-free survival (PFS) were assessed across treatment arms.

Results: Administration of mirdametinib singly and in combination with chemotherapy were tolerated at clinically relevant dosing of each drug with no appreciable toxicity observed when given with supportive care (daily saline infusion and wet food). While significant tumor volume control is observed with mirdametinib monotherapy or chemotherapy (p=0.02 for both, AUC comparison) relative to vehicle control, the combination of mirdametinib with chemotherapy was significantly improved compared to mirdametinib alone (p=0.03) and chemotherapy alone (p=0.02). Mirdametinib with chemotherapy is superior to trametinib alone (p=0.04) and with a

trend to improved activity compared to trametinib with chemotherapy though not currently significant ($p=0.07$). Similarly, mirdametinib with chemotherapy improves PFS compared to chemotherapy alone ($p=0.008$, log-rank) but not significantly different when compared with trametinib with chemotherapy ($p=0.07$).

Conclusion: MEK inhibition in combination with chemotherapy results in superior tumor volume control and PFS in preclinical models of MPNST and supports future investigation of this combination strategy in patients with MPNST.

(P 49) GENETIC INTERACTION BETWEEN SPRED3 AND SMARCB1 CAUSES EXPLOSIVE MULTIFOCAL MALIGNANT PERIPHERAL NERVE SHEATH TUMORS

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Objective: Whole genome sequencing (WGS) can solve unexplained familial cancer patterns. Here we used WGS and functional studies to understand the genetic basis for an unfortunate family afflicted by highly penetrant and aggressive malignant peripheral nerve sheath tumors (MPNST).

Methods: A family with multiple members afflicted by aggressive, multifocal MPNST was identified as part of the International Sarcoma Kindred Study. One parent had a known SMARCB1 mutation causing a benign Schwannoma at age 30, while the second parent developed a glioblastoma multiforme at her 50s. Three children developed aggressive multifocal MPNST before 20 years, with all 3 succumbing by age 30. We applied WGS to the germlines of 4/5 family members, as well as more than 30 MPNST or atypical Schwannomas to identify genetic modifiers or de novo events which could explain the dramatic phenotype in the children. We then used cellular models to confirm the functional contribution of candidate genes, and to map the sequence of events leading to development of these cancers.

Results: We identified 15 genes carrying variants which could potentially explain the acceleration of phenotype in the children. Of these, we selected 6 for functional studies using the immortalized human neural progenitor ReN cell line. Using a variety of assays, including clonogenic expansion and differentiation, we show the novel gene, SPRED3, as the likely modifier. SPRED3 is a member of the Sprouty family of proteins that regulate growth factor-induced activation of the MAP kinase cascade. A related gene, SPRED1, is associated with Legius syndrome, sharing clinical features with Neurofibromatosis type 1. We then mapped the phylogenetic relationships between the MPNST within each individual to derive a probable sequence of events leading to tumor development, showing that the earliest events arose prior to day 15 in the embryo.

Conclusion: This study of a rare and tragic family has shed fundamental insight into the genetic basis of Schwannomas and MPNST.

(P 50) A NEW MURINE MODEL OF DEDIFFERENTIATED LIPOSARCOMA DEFINED BY HIGH PROLIFERATION AND METABOLIC ADAPTABILITY

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Objective: Dedifferentiated liposarcoma (DDLPS) is a high grade soft tissue sarcoma with limited treatment options. We derived two cell lines from autochthonous adipocyte-CreTrp53f/f;Ptenf/f (ACPP) tumors which develop orthotopic DDLPS tumors in WT C57BL/6 mice. These cell lines recapitulate histological and transcriptional alterations observed in DDLPS in patients. Our aim was to elucidate the phenotypic and molecular differences between the cell lines to enhance their utility as reliable preclinical models for studying DDLPS.

Methods: We used HoloMonitor M4, a digital holographic microscope, to track live cells' morphometric and optical features over time. We performed bulk RNA-seq and compared two ACPP-derived DDLPS cell lines, N1011 and N1018, by gene set enrichment (GSEA) Hallmark pathway analysis.

Results: Each DDLPS cell line exhibit distinct morphology, cell characteristics, and dynamics. In terms of morphology, N1018 shows greater heterogeneity in cell size, volume, optical density, and surface features, consistent with the metabolic plasticity required for rapid division and higher motility (28% higher than N1011). Hallmark GSEA revealed strong activation of the E2F, MYC-I/II, G2M-checkpoint, and mitotic-spindle programs in N1018, supporting the higher proliferation rate (65% above N1011). In addition, pathways tied to rRNA metabolism, 5.8 S-rRNA maturation, cytosolic and mitochondrial translation, and RHO-GTPase signaling were elevated in N1018, indicating enhanced ribosome biogenesis, actin remodeling, and metabolic flexibility. In contrast, N1011 displayed a more uniform, lower-intensity optical and morphometric values, stable surface features, and balanced internal organization.

Conclusion: These results suggest that the N1018 cell line could serve as a model for studying mechanisms underlying rapid proliferation, invasion, and potential treatment resistance in aggressive DDLPS, providing a valuable platform for preclinical therapeutic development.

(P 51) OVEREXPRESSION OF GLI2 IN DEDIFFERENTIATED LIPOSARCOMA TUMORS INDUCES MICROENVIRONMENT REMODELING

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Objective: Liposarcoma is the most common soft tissue sarcoma, comprised of various histological subtypes that influence clinical outcomes such as metastasis and survival, with dedifferentiated liposarcoma (DDLPS) tumors being more aggressive and resistant to treatment than their well-differentiated counterparts. We have previously shown that the Hedgehog (HH) signaling is elevated in DDLPS patient tumors. Thus, we sought to further expand upon the role of HH signaling in DDLPS using both in vitro and orthotopic models.

Methods: Gli2, a transcriptional regulator of HH, expression was found to be tumor cell specific

in scRNA-seq of patient tumors. We generated an SW872 DDLPS cell line overexpressing (OE) Gli2 to evaluate cellular proliferation, differentiation, and transcriptomics in vitro, as well as tumor formation and tumor-microenvironment interactions in vivo.

Results: Our results showed a marked increase in proliferation by the activation of Gli2, in addition to a noticeable loss of differentiation capacity in vitro. Upon orthotopic injection into athymic nude mice, we found that Gli2 OE resulted in larger tumor volume, collagen encapsulation of tumors, robustly increased macrophage infiltration, and a modest increase in fibroblast recruitment and PD-L1 expression. RNA sequencing of tumor cells indicated significant changes in cytokine expression which was then validated by ELISA and cytokine arrays.

Conclusion: We found that overexpression of Gli2 in DDLPS tumor cells yielded a profoundly oncogenic phenotype resulting in larger tumor growth and robust tumor microenvironment remodeling. Specifically, we found that Gli2 OE recruited robust amounts of macrophages in DDLPS, a phenotype that has been largely uncharacterized. DDLPS tumor cells overexpressing Gli2 yielded an altered cytokine and growth factor secretion profile that could implicate HH signaling as a driver of immune suppressive cell recruitment that has potential to impede therapeutic progress moving forward. This opens an avenue for exploring Gli2 or HH pathway inhibition as a combinatorial treatment for established therapies or improving response to immune checkpoint blockade in the future.

(P 52) VALIDATION OF SYNGENEIC MURINE DEDIFFERENTIATED LIPOSARCOMA MODELS FOR PRECLINICAL EVALUATION OF THERAPEUTIC SENSITIVITY

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Objective: Dedifferentiated liposarcoma (DDLPS) is a high-grade soft-tissue sarcoma with significant clinical challenges. Doxorubicin is the standard systemic therapy, yet fewer than 30% of patients respond effectively. This study examines chemotherapeutic sensitivity and transcriptional response in murine and human DDLPS models and assesses in vivo efficacy in an immune-competent mouse model to inform patient treatment strategies.

Methods: Adipocyte-CreTrp53f/f;Ptenf/f (ACPP)-derived DDLPS murine (N1011, N1018, N1343) and human (LPS141, DDLS8817) DDLPS cell lines, along with control murine mesenchymal stem cells (3T3), were tested with doxorubicin, selinexor, trabectedin, and dacarbazine to calculate IC₅₀ values using CyQUANT assays. Gene expression of p21 and Cdk4 in untreated and treated cells was assessed by qRT-PCR. For in vivo studies, N1011 cells were injected into C57BL/6 mice and treated with PBS, 1 mg/kg, or 4 mg/kg doxorubicin thrice weekly.

Results: Doxorubicin was consistently effective in all DDLPS lines (IC₅₀ ~230–460 nM), with 3T3 controls less sensitive. Selinexor demonstrated selective activity in N1011 (IC₅₀ = 400 nM), while trabectedin showed moderate efficacy (IC₅₀ = 500–750 nM), and dacarbazine was effective only in N1011. Doxorubicin reduced p21 and Cdk4 expression, notably in N1011 (40% p21 decrease). In vivo, 4 mg/kg doxorubicin significantly slowed tumor growth compared to control and 1 mg/kg.

Conclusion: Murine and human DDLPS cell lines show consistent doxorubicin sensitivity and transcriptional changes in cell cycle genes. N1011 cells were also uniquely sensitive to selinexor and dacarbazine, with moderate sensitivity to trabectedin observed in murine cell lines. The in vivo validation using a syngeneic murine model highlights its relevance for further mechanistic studies and the development of rational drug combination strategies in DDLPS.

(P 53) ESTABLISHMENT AND CHARACTERISATION OF LIPOSARCOMA-DERIVED CELLS AS RELEVANT PRE-CLINICAL MODELS FOR TARGET DISCOVERY

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Objective: Pre-clinical models that encompass disease heterogeneity are limited for liposarcoma research. We aim to establish and characterise matched liposarcoma-derived tumours and liposarcoma cells cultured in vitro. Subsequently, we aim to identify drug susceptibilities in these established liposarcoma (LPS) cells for target discovery.

Methods: Liposarcoma tumours and the corresponding patient-derived sarcoma cells (PDSC) established in vitro were profiled using single-cell RNA sequencing (scRNA-seq) at passages 0 and 4 and subsequently integrated with existing liposarcoma tumour dataset by Gruel et al. Findings were validated by whole genome sequencing, differentiation assays, immunofluorescence and fluorescence in-situ hybridisation (FISH). High throughput drug screening on established PDSCs was carried out on a panel of 3158 FDA-approved drugs and selective cytotoxicity assay testing of top hits was carried out on primary human mesenchymal stem cells and adipose stem cells.

Results: We have successfully established LPS PDSCs with a success rate of 80% using our optimised growth factor media. scRNAseq analyses reveal an enrichment of adipocyte stem and progenitor cell (ASPC) population in established PDSCs, with significant heterogeneity among subpopulations harbouring MDM2 and CDK4 amplifications. These findings corroborate with recent evidence identifying MDM2-amplified ASPCs as the potential cell-of-origin in liposarcomas, underscoring their relevance as a targetable cell type for therapeutic discovery.

Biological validation demonstrates ASPC marker expression CD55 and DPP4, MDM2 amplification, as well as adipogenic and osteogenic differentiation potential of PDSCs. Functional drug screening and selective cytotoxic profiling identify several therapeutic vulnerabilities, including susceptibility to proteasome inhibitors, epigenetic inhibitors and tyrosine kinase inhibitors.

Conclusion: We have identified, characterised and validated the ASPC population in our liposarcoma PDSC models. Our established models represent biologically relevant pre-clinical platforms for therapeutic target discovery, through which we have uncovered several candidate drug targets with potential utility in the treatment of liposarcomas.

(P 54) PRECLINICAL MODELS REVEALING MDM2-P53 INTERACTION AND DEPENDENCY FOR TUMOR CELL SURVIVAL IN WELL-DIFFERENTIATED (WD) AND DEDIFFERENTIATED (DD) LIPOSARCOMA (LPS).

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Objective: WD and DD LPS are characterized by the amplification (amp) of 12q13-15 chromosomal region, leading to the usage of MDM2 amp as a diagnostic marker. Though WD has low metastatic potential, 10-20% progress to the more aggressive DD. The mechanism underlying transition remains unclear.

Methods: We generated patient (pt) derived xenograft (PDX: 4 WD, 5 DD) and cell culture (PDC:10 WD, 6 DD) models from 105 surgical specimens. The models were characterized with H&E stain, WES, RNA sequencing (RS), FISH, and drug sensitivity assays. The validation was done compared to original pt tumors. The association between MDM2 amp levels and pt prognosis were analyzed. A comparative analysis between WD and DD tumors was done using Reverse-Phase Protein Array (RPPA).

Results: Clinical data showed WD with increased cellularity area had a shorter time to progression into DD and displayed intermediate survival prognosis between pure WD and DD, implying a transitional phenotype. DD tumors had higher MDM2 copy number (CN) compared to WD both within the same and across different pts, while serially resected tumors from the same pts showed no increase in MDM2 CN over time. Moreover, MDM2 CN decreased over serial passages in both PDXs and PDCs suggesting increased MDM2 amp is likely a consequence rather than a driver of DD. RPPA revealed upregulation of DNA repair and hypoxia-related pathways in DD compared to WD. An inverse correlation between MDM2 CN and PPARG RNA expression was found, supporting the association of MDM2 amp with higher grades. It is notable that MDM2 CN did not correlate with MDM2 RNA and protein expression, implying MDM2 amp in high-grade tumors may not directly impact MDM2 functional output. WES and RS of PDXs revealed reduced expression of anaphase-promoting complex: CCNA2 and UBE2C in tumors with higher MDM2 amp, implicating cell cycle dysregulation. Interestingly, analysis of aggressive DD tumors showed increased activation of the p53 pathway despite persistent MDM2 amp, suggesting stronger influence of genomic instability on p53 activation than its suppression by MDM2. Drug testing using models is ongoing.

Conclusion: We successfully developed both WD and DD PDX and PDC models. Chronological changes and functional response unveil complex interaction between MDM2-p53 axis central to understanding the transition between WD and DD and future therapeutic strategies.

(P 55) THE EFFECT OF STAT1 Y701 PHOSPHORYLATION ON GENE EXPRESSION IN UPS

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Objective: Investigating the signal transduction pathways related to immunotherapy could improve the survival rates for some sarcoma types. We previously found that a subset of Undifferentiated Pleomorphic Sarcoma (UPS) cases had tumor-infiltrating lymphocytes, high PD-L1 RNA expression, and improved clinical outcomes in comparison to those with low PD-L1 expression. Genes differentially expressed but unique to the PD-L1 high UPS cohort were significantly enriched in the Th1 pathway. We hypothesized that the expression of Th1-related genes such as STAT1, a transcription factor activated by IFN- γ , may be associated with an anti-tumor microenvironment. STAT1 can exist in a tyrosine 701-phosphorylated (pSTAT1) or unphosphorylated (uSTAT1) state. pSTAT1 is associated with anti-tumor and anti-proliferative functions, whereas uSTAT1 has been linked to increased DNA resistance gene expression programs. We aimed to investigate how STAT1 phosphorylation influenced gene expression in UPS.

Methods: STAT1 knockouts (STAT1KO) were generated from primary UPS cell lines. Lentiviral vectors encoding wildtype STAT1 or a Y701F phosphomutant were transfected into two UPS STAT1KO cell lines. RNA was extracted from cells overexpressing wildtype STAT1 (pSTAT1) or Y701F-mutant STAT1 (uSTAT1), along with empty vector controls (EV), and subjected to transcriptomic analysis. Differentially expressed genes (DEGs) associated with STAT1 Y701 phosphorylation were identified and subjected to pathway analyses.

Results: DEGs based on STAT1 Y701 phosphorylation status were identified. In pathway analyses from one case, all pathways were negatively enriched when comparing DEGs between the uSTAT1 and pSTAT1 cell lines. Further, when comparing uSTAT1 cells to the EV, all pathways—including type I IFN signalling—were negatively enriched. This may indicate an inhibitory role for uSTAT1 on other STATs or downstream effectors within these pathways.

Conclusion: In UPS, uSTAT1 was associated with a negative enrichment in multiple pathways, suggesting the Y701 residue is critical in IFN- γ signal transduction. The negative enrichment of pathways in uSTAT1 compared to the EV suggests that uSTAT1 may negatively regulate transcriptional programs mediated by other STAT family members. Together, these findings support that STAT1 phosphorylation status impacts expression programs and may influence UPS cell properties as well as the tumor microenvironment.

(P 56) COMPARISON OF PATHOGENIC AND LIKELY PATHOGENIC VARIANTS DISTINCT FROM SPECIFIC DRIVERS IN DIFFERENT SARCOMA GROUPS

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Objective: To comparatively describe pathogenic and likely pathogenic variants (PLPVs) distinct from specific drivers in sarcomas by relevant groups.

Methods: We retrospectively reviewed NGS reports of patients with sarcomas in our Center. Sarcomas were divided into three groups: translocation-related sarcomas (TRS), translocation-unrelated sarcomas with activating mutations (AM), or without them (WAM).

Results: Eighty-five patients with a median age of 38 years were included. In the TRS group, PLPVs different from the specific translocation were found in 8/27 (29.6%) of patients. STAG2 (5/27), TP53 (2/27), and APC (2/27) were the most commonly mutated genes. DDR, WNT, and Epigenetic regulation were the most commonly involved pathways. In the AM group, 7 secondary mutations were found in 13 patients (53.8%), all of them in 11 Gastrointestinal Stromal Tumor patients. The main pathway involved was the MYC, linked to MGA mutations. In the WAM group, in 9 patients with Desmoid fibromatosis a total of 10 PLPVs different from CTNNB1 or APC were identified across 7 patients. In the 36 other WAM sarcomas, the PLPVs were found in 50% of patients: being ATRX (8.3%) and TP53 (5.5%) the two most common. Epigenetic regulation, RTK-RAS, and DDR were the most commonly altered pathways.

Conclusion: In sarcomas with specific drivers, additional PLPVs are common. Some of them have a strong sarcoma-type specificity, while others are shared between sarcoma groups, as well as the main signaling pathways they alter. The effectiveness of therapeutic actionability on these alterations should be studied.

Comparison of pathogenic variants distinct from from the specific drivers in different

sarcoma types.

Feature	TRIS	AM	WAM-Desmoid	WAM-Others [†]
% with PLPVs	29.6% (8/27)	53.8% (7/13)	77.8% (7/9)	50% (10/20)
Top mutated genes	STAG2, TP53, APC	MGMT	TP53	ATRX, TP53
Main affected pathways	DDR, Wnt, Epigenetic	MYC (via MGMT), RTK-RAS	Wnt, Epigenetic, RTK-RAS, DDR	Epigenetic, RTK-RAS, DDR, Cell Cycle

(P 57) STUDYING HYPOXIA-INDUCED METASTASIS IN GENETICALLY ENGINEERED MOUSE MODELS OF UPS

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Objective: Undifferentiated pleomorphic sarcoma (UPS) is a common soft-tissue sarcoma subtype with a predilection for lung metastasis. Current therapies offer limited therapeutic benefits for metastatic UPS, demonstrating a critical need for identifying alternative therapeutic vulnerabilities. Our group previously identified hypoxia-related gene upregulation in lung metastases compared to matched primary tumors in a genetically engineered mouse model (GEMM) of UPS. Hypoxia also promotes the expansion of mesenchymal stem cells and myotubes, both candidate UPS cells of origin, suggesting an association between hypoxia and stemness. We proposed that hypoxia promotes a stem-like state that enhances metastatic potential in UPS.

Methods: We employed a novel spontaneous GEMM of UPS via intramuscular electroporation of plasmids encoding oncogenic KrasG12D, Cas9 and a single-guide RNA (sgRNA) targeting p53 (KP model). Animals exclusively develop tumors at the site of plasmid electroporation within 3-4 weeks of tumor induction, demonstrating high spatial and temporal control of tumor initiation in this model.

Results: Hypoxic tumor regions were confirmed upon administration of pimonidazole (PIMO), a permanent hypoxia label, with some inter-tumoral variability across animals, akin to heterogeneity observed in UPS patient samples following oral PIMO administration. To study the early stages of metastasis, tumor-bearing mice were treated with PIMO 2 hours prior to terminal blood collection for isolation of pre-metastatic circulating tumor cells (CTCs). We could detect upwards of 800 CTCs in this model, and a small fraction ~8-10% were pimonidazole

positive on flow cytometry analysis.

Conclusion: The KP model reliably generates spontaneous CTCs, providing a platform to interrogate the early stages of UPS metastasis. Despite robust CTC yields per animal, a minority were hypoxic. To test whether hypoxic CTCs possess enhanced metastatic capacity, we will perform competitive tail vein injections of hypoxic versus normoxic CTCs into syngeneic hosts and assess lung colonization. These studies will define hypoxia's functional role in metastasis and evaluate its potential as a therapeutic vulnerability in UPS.

(P 58) **PLK1 AS A VULNERABLE TARGET OF BAP1-DRIVEN UNDIFFERENTIATED PLEOMORPHIC SARCOMAS**

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Objective: Undifferentiated pleomorphic sarcoma (UPS) is one of the most common soft tissue sarcomas (STS) in adults, yet it remains lethal and understudied diseases. Additionally, UPS is genetically heterogenous and lacks recurrent oncogenic driver mutations, complicating efforts to develop broadly effective therapies. Consequently, a promising approach is to develop targeted therapies for UPS driven by specific tumor suppressor drivers. However, the molecular pathogenesis of UPS remains largely unknown, hindering the development of such therapies. Approximately 65% of UPS harbor TP53 mutations, but somatic mutation of Trp53 alone is insufficient to induce sarcomas in vivo. The role of other genes in facilitating Trp53-driven UPS is unknown. For instance, BAP1 deletion is dominantly associated with UPS among all STS. However, the role of BAP1 in UPS development is unexplored.

Methods: A tailored in vivo CRISPR/Cas9 screen of 35 tumor suppressor genes (TSG) commonly mutated in UPS, followed by individual gene validation in vivo, were conducted to identify TSG critical for UPS development. Additionally, total RNA sequencing, multiplex immunohistochemistry, flow cytometry, and preclinical trials using autochthonous mouse models of Bap1-driven UPS were utilized in the study.

Results: We discovered that Bap1 knockout cooperates with Trp53 knockout to induce metastatic UPS in vivo. We found that Bap1-driven UPS is poorly immunogenic, even at early stages. Additionally, a B cell signature may play a role in immune suppression caused by loss of Bap1. Moreover, we demonstrated that Polo-like Kinase 1 (Plk1) is critical for Bap1-driven sarcomagenesis. Finally, we demonstrated that a Plk1 inhibitor, volasertib, drastically inhibited tumor growth in an autochthonous mouse model of Bap1-driven UPS.

Conclusion: We determined that Bap1 is a potent tumor suppressor of UPS. Our findings pave the way for translating volasertib as a targeted therapy to treat patients with Bap1-driven UPS, a group currently lacking treatment option.

(P 59) TARGETING ADORA2B TO HALT METASTASIS IN UNDIFFERENTIATED PLEOMORPHIC SARCOMA: FROM MULTI-OMICS TO THERAPEUTIC INHIBITION

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Objective: Undifferentiated pleomorphic sarcoma (UPS) is an aggressive soft tissue sarcoma with poor prognosis, especially in metastatic cases. The biological mechanisms underlying metastasis remain poorly defined, hindering therapeutic progress. The aim of our study was to elucidate these mechanisms with the goal of use them for therapeutic purposes.

Methods: We employed a multi-omics approach to analyze matched primary and metastatic UPS tumor samples. Spatial transcriptomics, bulk RNA sequencing, and computational deconvolution analyses were used to explore molecular pathways and immune microenvironment alterations associated with UPS metastatic evolution. We identified interesting potential therapeutic targets and we performed functional validation, including CRISPR-Cas9-mediated gene knockouts in UPS cell lines and in vivo tumor models. To explore therapeutic relevance of one of the most interesting target we found, we tested a pharmacological inhibitor, currently in early-phase trials for advanced solid tumors.

Results: Transcriptomic profiling revealed enrichment of hypoxia, epithelial-mesenchymal transition (EMT), and immune-suppressive pathways in metastatic UPS. Among these, ADORA2B emerged as a key driver, with elevated expression correlating with shorter disease-free survival. Loss-of-function studies demonstrated that ADORA2B promotes cell proliferation, migration, invasion, and extracellular matrix remodeling via metalloprotease regulation. Pharmacological inhibition with M1069, a dual ADORA2A/ADORA2B inhibitor, recapitulated these effects in vitro, significantly reducing UPS cell proliferation, migration, and invasion. ADORA2B knockout also impaired tumor growth and metastasis in vivo. Ongoing in vivo experiments with M1069 will provide further insight into its translational potential and suitability for clinical evaluation in UPS.

Conclusion: Our findings identify ADORA2B as a central regulator of metastatic progression in UPS and support adenosine signaling as a viable therapeutic target. The efficacy of the dual ADORA2A/ADORA2B inhibitor M1069 reinforces its potential as a candidate for future clinical trials in UPS patients. Even more, our transcriptomic analyses provide a large database for further target identification.

(P 60) EXPLORING METABOLIC REWIRING IN CHORDOMA

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Objective: Chordoma is a rare, malignant bone tumor that arises from notochordal remnants within the axial skeleton. Primary tumors most commonly develop in the skull base or sacrum, and 30–40% metastasize to secondary sites such as the lungs or liver. In the United States, roughly 300 patients are diagnosed with chordoma every year (0.08 cases per 100,000 people). In these cases, individuals face a locally aggressive cancer that is extremely challenging to resect completely, prone to recurrence, and therapeutically resistant. These barriers to treatment, and the low 10-year survival rate (40%), highlight a drastic need for further research and development of new therapies to target chordoma. Metabolic reprogramming has been a fundamental area of cancer research in recent years, but chordoma metabolism is understudied and has not been fully utilized to aid in the development of novel therapies. Given the increasing interest in targeting cancer metabolism, understanding these metabolic alterations could reveal novel therapeutic targets not yet considered for treatment of chordoma.

Methods: Our lab has optimized an LC-MS/MS-based protocol for identifying 400 polar metabolites and 600 lipid species. We have used this protocol to determine the metabolic state of four different chordoma cell lines (U-CH2, UM-CHOR1, JHC7, and CH22) relative to two different fibroblast cell lines (LF and IMR90).

Results: Principal component analysis (PCA) of data obtained from our metabolomics panel demonstrated that chordoma cell lines possess a distinct metabolic profile compared to fibroblast controls. In addition to broad alterations across several key metabolic pathways, a subset of individual metabolites displayed statistically significant differences in abundance, further supporting a unique metabolic phenotype that may offer novel targets for therapeutic intervention.

Conclusion: We have identified several unique features in chordoma cell lines that warrant further investigation for their therapeutic capacity. Continued research into these differences will provide key insights into the biology of this malignancy and aid in therapy for those diagnosed.

(P 61) HER2 TARGETING IN CHORDOMA: PRECLINICAL INSIGHTS ON TRASTUZUMAB DERUXTECAN

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Objective: Chordomas are rare malignant tumors with limited therapeutic options, particularly in advanced disease. Although HER2 (human epidermal growth factor receptor 2) is a well-established target in several cancers, its expression and potential role in chordoma remain unexplored. Trastuzumab deruxtecan (T-DXd), a HER2-directed antibody-drug conjugate, has demonstrated efficacy across HER2-expressing tumors. In this study, we aim to investigate HER2 expression in chordoma and evaluate the therapeutic potential of trastuzumab deruxtecan in relevant cell models.

Methods: HER2 expression was analyzed by flow cytometry in three chordoma cell lines: CH-22, U-CH17 and U-CH14. The HER2-amplified breast cancer cell line SK-BR-3 was used as a positive control. T-DXd cytotoxicity was assessed by measuring cell viability via flow cytometry.

Results: Flow cytometry analysis revealed that all three chordoma cell lines were HER2-positive. Median fluorescence intensity (MFI) values were as follows: SK-BR-3 (MFI: 505261; SD: 56,546), CH-22 (MFI: 2379; SD: 327), U-CH17 (MFI: 1791; SD: 371), and U-CH14 (MFI: 1607; SD: 259). Treatment with trastuzumab deruxtecan (T-DXd) was performed on CH-22 and U-CH17 cells and significantly reduced cell viability in both lines. However, sensitivity to T-DXd varied, with CH-22 cells exhibiting greater susceptibility (IC₅₀: 7.2 µg/mL) compared to U-CH17 cells (IC₅₀: 55.3 µg/mL).

Conclusion: Chordoma cell lines exhibit measurable HER2 expression and treatment with trastuzumab deruxtecan significantly reduced cell viability, particularly in CH-22 cells. These findings suggest HER2 as a promising therapeutic target in chordoma and support further investigation of HER2-directed therapies in preclinical and clinical studies.

(P 62) INTRAOPERATIVE BONE AND SOFT TISSUE TUMOR MARGIN IDENTIFICATION WITH FLUORESCENCE LIFETIME (FLT) IMAGING

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Objective: Surgical margin status is a critical predictor of sarcoma outcomes, and despite optimal resections and thorough intraoperative pathologic assessment, residual positive margins can persist and complicate clinical management. Fluorescence-guided surgery using indocyanine green (ICG) is a promising tool to aid intraoperative margin assessment. However non-specific dye uptake is a major problem that reduces sensitivity and specificity. We evaluated the accuracy of FLT imaging to identify tumor margins in benign and malignant bone and soft tissue tumors.

Methods: Patients undergoing surgery of various sarcomas (n=43), including Leiomyosarcoma, chondrosarcoma, and chordoma received a preoperative injection with ICG a few hours prior to surgery, in doses of 0.5mg/kg (n=15), 1mg/kg (n=15) and 1.5mg/kg (n=13). Representative tumor samples were next analyzed using FLT microscopy and sensitivity and specificity were calculated against histology, using pixel-wise and specimen-wise analysis.

Results: The uptake and mean FLT of ICG strongly depended on the radiation status of the tumor, with necrotic/non-viable tumor regions showing either low ICG uptake or markedly shorter FLT (0.56ns) compared to viable tumor (0.65ns). In addition, normal muscles, adipose tissue and bone showed shorter FLT (0.57ns) than viable tumors. A preliminary specimen-level analysis (n = 33) suggests that FLT improves tumor delineation accuracy (70 - 90%) compared to fluorescence intensity (< 50%).

Conclusion: Our results show that FLT outperforms fluorescence intensity for identifying sarcoma margins in patients injected with ICG a few hours before surgery. While same day injections are clinically more feasible, longer injection intervals should significantly improve

accuracy. Ongoing work is focused on studying more detailed ICG dosage and timing dependence of FLT imaging accuracy, and on evaluating real-time intraoperative FLT imaging during sarcoma surgeries.

(P 63) EVALUATING SURGICAL MARGINS IN SARCOMA RESECTION WITH INDOCYANINE GREEN FLUORESCENCE IMAGING

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Objective: Extremity sarcomas are primarily managed surgically, and achieving negative resection margins remains critical for reducing local recurrence and potentially improving survival. While intraoperative indocyanine green (ICG) fluorescence imaging has shown promise in other cancers, its role in sarcoma margin assessment remains underexplored. This study aimed to evaluate ICG's efficacy as an intraoperative margin assessment tool in sarcoma surgery.

Methods: This was a prospective, non-randomized clinical trial for patients with confirmed or suspected extremity sarcomas. Patients received 2.0 mg/kg ICG intravenously three hours preoperatively. The tumor bed was imaged intraoperatively using a SPY-PHI camera, and signal-to-background ratio was calculated using the formula ($SBR = \text{tumor bed fluorescence} / \text{average background fluorescence}$). ICG-positive margins were defined as fluorescence intensity ≥ 1.67 times SBR. ICG results were compared to final pathology and surgeon's clinical impression.

Results: Among 51 participants with bone ($n = 11$) or soft tissue ($n = 40$) sarcomas, pathology reported 15 (29.4%) positive margins, whereas surgeons predicted 8 (15.7%). When compared to pathological findings, surgeons correctly identified 4 out of 15 positive margins (sensitivity: 26.7%) and 32 out of 36 negative margins (specificity: 88.9%). Using an SBR of 1.67, ICG correctly identified 14/15 positive margins (sensitivity: 93.3%).

Conclusion: ICG shows promise for intraoperative margin assessment in sarcoma surgery. As surgeons are very specific (88.9%) and ICG is very sensitive (93.3%), we posit that these strengths could be combined to decrease local recurrence rates to the benefit of sarcoma patients. As ICG imaging platforms are used by many institutions and surgical specialties, this research suggests an opportunity for a multi-institutional clinical trial.

(P 64) ATRX EXPRESSION CORRELATES WITH REDUCED IMMUNE CHECKPOINT EXPRESSION AND POOR SURVIVAL IN HIGH-RISK SOFT TISSUE SARCOMAS

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Objective: ATRX encodes the alpha-thalassemia mental retardation X-linked syndrome protein, which plays a key role in DNA damage response and is frequently altered in different tumors. ATRX alterations have been associated with significant changes in the tumor microenvironment (TME). In high-risk soft tissue sarcoma (HR-STS), the influence of ATRX expression on the TME and patient survival remains poorly understood.

Methods: ATRX protein expression was assessed in pre-treatment biopsies of patients with HR-STS undergoing curative-intent treatment. Its expression was correlated with clinicopathological parameters, including tumor-infiltrating lymphocyte (TIL) counts and the expression of immune checkpoint markers such as programmed cell death 1 (PD-1), programmed cell death-ligand 1 (PD-L1), and T cell immunoglobulin and mucin domain-containing protein 3 (TIM-3). The impact of ATRX expression on survival was evaluated.

Results: : ATRX expression was observed in 170 of 206 patients (83%). Its expression was significantly associated with lower tumor grade ($p=0.003$), smaller tumor size ($p=0.001$), and non-UPS histology ($p=0.002$). ATRX expression correlated with higher TIL counts ($p=0.010$), negative expression of PD-1 ($p=0.008$) and TIM-3 ($p=0.036$). In multivariate analysis, ATRX expression emerged as an independent predictor of poor overall survival (HR 2.484, $p=0.020$).

Conclusion: ATRX expression is linked to poor survival in HR-STS patients undergoing curative-intent treatment. Although ATRX expression is associated with increased immune infiltration, as reflected by higher TIL counts, the TME shows reduced expression of key immune checkpoint receptors. Further molecular profiling is required to elucidate alternative immune evasion mechanisms and the functional role of ATRX in HR-STS patients with immunohistochemical ATRX expression.

(P 65) INVESTIGATING MACROPHAGE POPULATIONS IN PRIMARY AND METASTATIC SARCOMA SAMPLES

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Objective: Sarcomas display high metastatic potential to the lung. Studies in other malignancies emphasize the tumor microenvironment in metastasis. Macrophages are

important in immunity and tumor progression. Here, we investigate the roles of M1 (tumoricidal) and M2 (tumor permissive) macrophages in primary and metastatic sarcoma samples.

Methods: This study utilized sets of 3 tissue arrays each for primary and metastatic tumor samples. 13 patients with primary tumors and 21 patients with metastatic tumors were used for analysis. 61 primary and 41 metastatic tumor samples were observed. Vectra Polaris microarrays were used to investigate macrophage subsets (CD68+/HLADR+/CD163- for M1, CD68+/HLADR-/CD163+ for M2). Cell counts per core and antibody were collected for bioinformatics analysis using R software. M2/M1 cell density ratios were calculated, and distinct groups were identified.

Results: The M2/M1 cell density ratios in the primary samples ranged from 5.8 to 237.1. The low (5.8-63.2), medium (73.7-124.7), and high (107.8-237.1) ratio groups were statistically significant from each other. The M2/M1 cell density ratios in the metastatic samples ranged from 0.0 to 37.5. The low (0.0-1.0), medium (1.0-5.0), and high (>5.0) ratio groups were statistically significant from each other. Patient outcomes were identified, and unique patient characteristics were noted for each ratio.

Conclusion: We demonstrate for the first time in primary and metastatic osteosarcoma samples that distinct macrophage populations arise and form unique tumor microenvironments. Importantly, we observe M2/M1 ratios that are several times higher than in the primary samples. This indicates a more pro-tumor environment in the primaries than the metastases.

(P 66) ARHGEF4 EXPRESSION IN SOFT TISSUE SARCOMA CORRELATES WITH LOCAL GROWTH PATTERN: WHOLE TRANSCRIPTOME SEQUENCING ON SPATIALLY SEPARATED REGIONS, PATIENT-DERIVED MODELS, AND ORTHOTOPIC IN VIVO ANALYSIS

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Objective: Soft tissue sarcoma (STS) is known to respect barriers to tumor spread, while its infiltrative and expanding growth patterns have not been studied at the molecular level. We hypothesized the presence of genes up- or down- regulated during local growth of STS. We explored the discovery of candidate genes involved in the growth pattern of STS and sought their correlation with clinical outcomes including local recurrence and metastasis. In addition, we investigated the role of ARHGEF4, which is mainly located in the cytoplasm and involved in the regulation of the actin cytoskeleton.

Methods: We collected tumor cells from central and peripheral areas separately and performed whole transcriptome sequencing (WTS) in 3 undifferentiated pleomorphic sarcoma (UPS) and one pleomorphic liposarcoma (P-LPS) tissues. Among the 58 selected candidate genes, ARHGEF4 showed higher expression in the peripheral than in the central areas of the tumors by real-time PCR. To investigate the role of ARHGEF4 in cell invasion, migration, and cell viability, Boyden chamber assay, wound healing assay, and MTT assay were performed using

patient-derived STS cell lines after knockdown of ARHGEF4 by short interfering RNA (siRNA). We also performed immunohistochemistry for ARHGEF4 expression in biopsy specimens from 66 patients with UPS and myxofibrosarcoma (MFS). Finally, we developed a patient-derived STS organoid system using sarcosphere and established an orthotopic mouse model by injecting luciferase-expressing STS organoid cells into Balb/c nude mice.

Results: Knockdown of ARHGEF4 by siRNA resulted in decreased cell invasion, migration, and cell viability in patient-derived STS cell lines. ARHGEF4 expression correlated with an infiltrative and expanding histological growth pattern ($p=0.023$). Increased ARHGEF4 expression was associated with a trend towards decreased local recurrence-free survival ($p=0.046$). Immunofluorescence staining with anti-ARHGEF4 antibodies showed significant reduction in Alexa Fluor 488 (green) signal in ARHGEF4 siRNA-treated cells compared to control siRNA. For in vivo validation, serial IVIS imaging on days 5, 7, 9 and 12 showed a significant suppression of tumor growth in ARHGEF4 siRNA group compared to controls.

Conclusion: The in vitro and in vivo results suggest that ARHGEF4 could serve as a biomarker and a therapeutic target of local growth patterns in STS.

(P 67) MULTIPLE MESENCHYMAL LINEAGES AS POTENTIAL CELL-OF-ORIGINS OF SMARCB1-DEFICIENT EPITHELIOID SARCOMA

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Objective: Epithelioid sarcoma (EPS) is an aggressive soft-tissue sarcoma with multiple histological variations, including classical and proximal types. While SMARCB1 deficiency is recognized as a primary driving event, the mechanisms initiating EPS remain largely unknown. Progress in understanding EPS biology is limited by the small number of available patient samples and limited disease models to study sarcomagenesis. To address this, we performed a systematic study to develop mouse models of EPS.

Methods: We deleted *Smarb1* in a site- or lineage-specific manner using the Cre-loxP system. Genetically engineered mice (GEMs) expressing CreERT2 under lineage-specific promoters were used, including *Pax7*, *Prrx1*, *Pdgfra*, or *Cdh5*, to target myogenic, mesenchymal, fibro-adipogenic, or endothelial lineages, respectively. GEMs carrying floxed *Smarb1* (S), floxed *p53* (P), or both alleles (SP) were used for Adeno-Cre and TAT-Cre injection to induce site-specific recombination or to generate CreERT2 mice carrying these alleles.

Results: Delivery of Adeno-Cre and TAT-Cre induced tumors in both S and SP mice, with higher incidence rates in SP mice. TAT-Cre induced earlier tumor onset, with a median latency of 68 days compared to 228 days with Adeno-Cre. Tumor formation was observed in all CreERT2 lines tested. Tumors in *Pax7* and *Pdgfra* lines were restricted to the 4OHT-injection site, whereas *Prrx1* and *Cdh5* lines frequently developed tumors at other sites, such as those on the face (*Prrx1*) and genital tract (*Cdh5*). Histological analysis revealed tumor cells with characteristic epithelioid morphology, occasional rhabdoid cells, and loss of *Smarb1* staining. Principal component analysis (PCA) of bulk tumor RNA-seq revealed several distinct tumor clusters, where tumors with myogenic and fibro-adipogenic signatures constituted two major clusters.

Conclusion: In this study, we developed highly efficient conditional mouse models of EPS, providing a robust platform for preclinical testing of novel therapeutic approaches. Our results support a model where multiple muscle-resident cell types can give rise to EPS following SMARCB1 loss, potentially explaining the tumor heterogeneity of EPS across patients.

(P 68) MULTI-OMIC INTRA- AND INTER-TUMOR HETEROGENEITY OF BENIGN SMOOTH MUSCLE TUMORS

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Objective: Uterine leiomyomas (LM) are benign tumors originating from the myometrium, commonly affecting women of reproductive age. Approximately half of patients present with multiple tumors, termed multifocal LM. LM are thought to be monoclonal proliferations, but it is unknown whether multifocal LM exhibit inter-tumor molecular heterogeneity, which may contribute to their variable response to hormone therapy. Anecdotal reports suggest that LM may occasionally progress into malignant metastasizing leiomyosarcoma (LMS). We hypothesized that better understanding of inter- and intra-tumor heterogeneity of LM may identify molecular processes that may contribute to oncogenic transformation.

Methods: We performed multi-omic profiling of 62 specimens from 21 LM patients (median of 3 tumors per patient, range: 2-8). We analyzed multiple regions of a single tumor, and multiple concurrent LM from patients with multifocal disease. We profiled DNA methylation (EPIC microarrays), point mutations (whole exome sequencing) and gene expression (RNA-seq) in these specimens.

Results: Multi-omic profiling showed a remarkable intra- and inter-tumor heterogeneity of genomic, epigenomic and transcriptomic patterns in LM. Through reconstruction of phylogenetic trees based on single nucleotide variants, we identified for the first time different MED12 mutations in co-existing nodules, and novel clonal and subclonal somatic mutations in LM. We also observed differential enrichment of oncogenic pathways between distinct regions within the same nodule and among co-existing nodules.

Conclusion: Molecular heterogeneity has been well-documented in malignant tumors, and we report it here for the first time in histologically bland, non-metastasizing LM. Our study reveals that in multifocal LM, distinct tumors can acquire unique molecular alterations, meaning that single-tumor analysis may not capture the full spectrum of molecular changes. This highlights the importance of considering molecular heterogeneity in diagnosis and evaluation of response to treatment in LM. Our results warrant further investigation into clonal evolution and localized activation of oncogenic pathways that may contribute to the rare transformation of benign LM into malignant LMS.

(P 69) EPIDEMIOLOGY AND POTENTIAL CLINICAL RELEVANCE OF TOP1 AND TOP2A TOPOISOMERASES EXPRESSION IN SOFT TISSUE SARCOMA

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Objective: Topoisomerases (TOPs) are essential, highly conserved enzymes that are required for genome stability. They are frequently overexpressed in rapidly dividing cancer cells, thus rendering them attractive treatment targets. The efficacy of TOP inhibitors has been shown to be positively correlated with the expression level of TOP. We aimed to conduct a comprehensive epidemiological evaluation of two TOPs (TOP1 and TOP2A) in soft tissue sarcoma (STS) and to establish their potential role as prognostic biomarkers.

Methods: Expression levels of TOP1 and TOP2A were evaluated using immunohistochemistry on tissue microarrays, constructed from tumor specimens collected from patients with leiomyosarcoma (LMS; n=134 samples), myxofibrosarcoma (MFS; n=130), synovial sarcoma (SynSa; n=105), angiosarcoma (AS; n=87), liposarcoma (LPS; n=80) and gastrointestinal stromal tumor (GIST; n=67). As previously described, TOP1 and TOP2A expression was scored as negative, low- and high. These categories were then utilized to establish the correlation with the progression-free survival (PFS) and overall survival (OS) of STS patients, employing the Kaplan-Meier estimates and the log-rank test. The statistical analysis was conducted using GraphPad software, with p-value < 0.05 being considered as statistically significant.

Results: Overall, TOP1 was expressed in 81.6% of STS specimens, with high and low expression detected in 51.1% and 30.5% samples, respectively. Most frequently the high expression was found in AS (82.8% of specimens) and MFS (79.2%), while only 22.4% of LMS samples demonstrated high TOP1 expression. Altogether almost 80% of STS specimens showed high TOP2A expression, with the high expression levels primarily observed in MFS (88.5% of samples), LMS (86.0%), and AS (84.5%), while it was less frequently detected in LPS (51.3%). High TOP1 expression was significantly associated with worse PFS and OS in LMS, while high TOP2A expression correlated with poorer PFS and OS in LPS.

Conclusion: The high level of TOP1 and TOP2A expression indicate its potential as prognostic biomarker in some STS subtypes. Our study supports the utilization of TOP1 inhibitors as payloads for antibody-drug conjugates in the treatment of STS patients. References: 1 Warmoes et al. Oncotarget. 2016;7(39):63537-48. 2 Cai et al. Transl Cancer Res. 2020;9(2):983-92.

(P 70) EPIDEMIOLOGY AND POTENTIAL CLINICAL RELEVANCE OF CONTACTIN-4 EXPRESSION IN SOFT TISSUE SARCOMA

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Objective: Contactin-4 (CNTN4) is a cell adhesion protein that functions as an immune checkpoint, by suppressing T-cell activation through its interaction with the amyloid precursor protein. High levels of CNTN4 expression has been observed in a number of human cancers (e.g. gallbladder, pancreatic, endometrial, and prostate tumors) and was also recently studied as a promising target for treatment with antibody-drug conjugates (ADC). We aimed to evaluate the epidemiology of CNTN4 expression in soft tissue sarcoma (STS) and to assess its potential as a prognostic biomarker.

Methods: The expression of CNTN4 was evaluated by immunohistochemistry (IHC) on tissue microarrays (TMA), constructed from tumor specimens collected from patients with leiomyosarcoma (LMS; n=128 samples), myxofibrosarcoma (MFS; n=121), angiosarcoma (AS; n=79), liposarcoma (LPS; n=60) and gastrointestinal stromal tumor (GIST; n=63). IHC results were quantified using the H-score (staining intensity * percentage of positive cells). The H-score distribution was used to define the threshold of 55, which was utilized to distinguish between low (H-score ≤ 55) and high (>55) CNTN4 expression. These categories were then used to correlate with patient's progression-free survival (PFS) and overall survival (OS) using Kaplan-Meier curve and log-rank test. GraphPad software was utilized for the statistical analysis, with p-value < 0.05 being considered as statistically significant.

Results: Overall the majority of STS samples analyzed exhibited positivity for CNTN4, with 55.0% and 28.6% of the samples demonstrating high and low immunopositivity, respectively. A high level of expression was detected in 63.3% of LMS, 58.7% of MFS, 58.2% of AS and 54.0% of GIST, while in LPS high expression was observed in only 26.7%. High CNTN4 expression was found to be significantly associated with worse prognosis (both PFS and OS) in the entire cohort of STS. In the subtype-specific analysis, high CNTN4 expression was significantly associated with shorter PFS in MFS and LPS patients, and with a worse OS in the latter only.

Conclusion: The high frequency and the high level of CNTN4 expression indicate its potential as both a prognostic biomarker and a novel therapeutic target. Our study also supports also the development of anti-CNTN4 therapies, including ADCs for the treatment of STS patients.

(P 71) GERMLINE POLYMORPHISMS IN THE VEGF PATHWAY AS PROGNOSTIC BIOMARKERS IN LOCALIZED HIGH-GRADE OSTEOSARCOMA: A STUDY BASED ON DATA FROM THE GEIS-33 PROTOCOL

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Spain, (11) Hospital Universitario Cruces, Bilbao, Pais Vasco, Spain, (12) Hospital Universitario Ramón y Cajal, Madrid, Madrid, Spain, (13) Complejo Hospitalario Universitario de Santiago, Santiago de Compostela, Galicia, Spain, (14) Hospital General Universitario Gregorio Marañón. Instituto de Investigación Sanitaria Gregorio Marañón, Madrid, Madrid, Spain, (15) Vall d'Hebron University Hospital, Barcelona, Catalonia, Spain, (16) Hospital Universitari Son Espases, Palma de Mallorca, Islas Baleares, Spain, (17) Hospital Universitario Central de Asturias, Oviedo, Asturias, Spain, (18) Institut de Recerca Sant Pau (IR Sant Pau), Barcelona, Catalonia, Spain

Objective: The VEGF pathway influences angiogenesis, which impacts tumor progression and patient outcomes. This study aimed to evaluate whether genetic polymorphisms in the vascular endothelial growth factor (VEGF) pathway are associated with relapse-free survival (RFS) and overall survival (OS) in patients with localised high-grade osteosarcoma.

Methods: 68 patients with localised high-grade osteosarcoma enrolled in the GEIS 33 protocol were included. All patients received two cycles of MAP (methotrexate, doxorubicin, cisplatin) chemotherapy followed by surgery, with adjuvant treatment tailored to histological response and P-glycoprotein expression. DNA was extracted from peripheral blood samples and genotyped for specific variants in the VEGFA, VEGFR1, and VEGFR2 genes. Clinical and genetic data were correlated with survival outcomes.

Results: median follow-up was 62.4 months. The 5-year RFS was 71%, and the 5-year OS was 72%. Among clinical factors, only surgical margins (wide/radical vs. marginal) were significantly associated with RFS ($P = 0.04$), while age, gender, tumor site, and histological response did not correlate with OS. For the VEGFR1 rs7993418 variant, the 5-year RFS was 89% for AA genotype carriers, 48% for heterozygotes, and 50% for GG genotype ($P = 0.03$). The 5-year OS was 79% for AA genotype, 68% for heterozygotes, and 33% for GG genotype ($P = 0.01$). For the VEGFR2 rs9582036 variant, AA genotype had a 5-year RFS of 92%, compared to 24% for carriers of the C allele ($P = 0.02$). The 5-year OS was 68% for AA genotype, 46% for C allele carriers ($P = 0.03$). In the multivariate Cox regression analysis conducted for each SNP, where surgical margins were included as covariate, these polymorphisms remained statistically significant.

Conclusion: Germline polymorphisms in the VEGF pathway may help predict RFS and OS in high grade localised osteosarcoma patients treated with chemotherapy. Their role as predictive/prognostic biomarkers in osteosarcoma patients treated with antiangiogenic drugs should be explored.

(P 72) COUNTY-LEVEL ASSOCIATIONS BETWEEN AIRBORNE TOXICANT EMISSIONS AND EWING SARCOMA DIAGNOSIS IN THE UNITED STATES

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Objective: Ewing sarcoma, a rare pediatric bone cancer with unclear origins, has been hypothesized to link with environmental factors like airborne toxins, though population evidence remains scarce. This study investigates associations between industrial airborne chemical emissions and Ewing sarcoma incidence across U.S. counties.

Methods: We conducted a cross-sectional ecological study using U.S. county-level data on Ewing sarcoma diagnoses the Surveillance, Epidemiology, and End Results (SEER) 2020 county population estimates derived from ZIP Code Tabulation Areas, and industrial airborne chemical emissions (EPA Toxics Release Inventory, 24 chemicals). Counties were categorized as “high” or “low” exposure for each chemical based on median emission thresholds. Ewing sarcoma incidence per 1,000,000 population was compared between groups using Mann-Whitney U tests.

Results: Of 3,229 total U.S. counties, 1,090 had Ewing sarcoma data, and 656 had complete data on case counts, population, and chemical exposure. 17 chemicals met inclusion criteria with ≥10 counties per exposure group. Xylene (12.95 vs 7.63, p=0.001), ethylbenzene (13.56 vs 9.33, p=0.007), toluene (12.88 vs 7.35, p=0.01), naphthalene (13.56 vs 10.65, p=0.016), nickel compounds, (11.75 vs 9.41, p=0.019) and benzo[g,h,i]perylene (13.13 vs 10.84, p=0.005) was determined to be statistically significant in counties with high exposure levels (Table 1).

Conclusion: In this national ecological analysis, xylene, ethylbenzene, toluene, naphthalene, nickel compounds, and benzo[g,h,i]perylene were associated with increased diagnosis rates of Ewing sarcoma at the county level. While causality cannot be inferred, these findings support further investigation of environmental risk factors in Ewing sarcoma, particularly in high-emission geographic clusters.

Table 1. Comparison of Ewing sarcoma incidence rates (per 1,000,000 population) between high and low exposure counties for significant chemicals.

Chemical	Median Rate/1M (High Exposure)	Median Rate/1M (Low Exposure)	Median Diff. Rate/1M	p-value
Xylene (Mixed Isomers)	12.95	7.63	5.32	0.001174
Ethylbenzene	13.56	9.33	4.23	0.007157
Toluene	12.88	7.35	5.53	0.010179
Naphthalene	13.56	10.65	2.91	0.015969
Nickel Compounds	11.75	9.41	2.34	0.018913
Benzo[g,h,i]perylene	13.13	10.84	2.29	0.028205

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Objective: Ewing sarcoma (EwS) is a bone and soft tissue cancer primarily driven by a FET::ETS fusion protein, most commonly EWS::FLI1. While localized tumors have a five-year survival rate of 70–80% with multimodal treatment, the prognosis for relapsed or metastatic disease remains dismal, with survival rates below 30%. Starting from a large, multi-institutional cohort of patient-derived transcriptomes, this study identified prognostic markers and therapeutic vulnerabilities associated with transcriptional subtypes of EwS.

Methods: To characterize the transcriptional diversity of EwS tumors, we applied RACCOON, an unsupervised hierarchical clustering approach, to define distinct transcriptional subtypes. We then used OTTER, a tumor classifier, to assign tumors from validation cohorts and preclinical models to these subtypes. Single-cell RNA sequencing and commonly used in vitro EwS cell lines were analyzed to assess transcriptional variability at single-cell resolution and in experimental systems. Clinical outcome stratification was evaluated using independent validation cohorts. Subtype-specific gene dependencies were inferred by integrating transcriptional subtype classifications with genome-wide CRISPR screening data from the DepMap project.

Results: Three distinct transcriptional subtypes of EwS were identified: EWS::FLI1-high, mesenchymal-like, and muscle-like. The muscle-like group was more distinct from the other subtypes, potentially due to myofiber infiltration. The remaining tumors exhibited a continuum of transcriptional states between EWS::FLI1-high and EWS::FLI1-low/mesenchymal-like subtypes. Transcriptional variability driven by fusion activity was further observed to differ across single-cell datasets and preclinical models. In the validation cohort, mesenchymal-like tumors were associated with the poorest prognosis (< 35% five-year overall survival) and the highest metastatic potential. In vivo studies in patient-derived xenografts supported these findings. Integration of CRISPR screening data from DepMap revealed subtype-specific gene dependencies – for instance, EWS::FLI1-high tumors showed sensitivity to disruption of the Fanconi anemia pathway.

Conclusion: We define three transcriptional subtypes of Ewing sarcoma – EWS::FLI1-high, mesenchymal-like, and muscle-like – with distinct gene dependencies, metastatic potential, and clinical outcomes. Our findings provide a foundation for new diagnostic approaches and molecular subtype-specific treatment strategies in EwS.

(P 74) TERTIARY LYMPHOID STRUCTURES PREDICT PROGNOSIS AND IMMUNE LANDSCAPE IN OSTEOSARCOMA: A MACHINE LEARNING-BASED TRANSCRIPTOMIC STUDY

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Objective: Osteosarcoma (OS) is a highly aggressive bone malignancy with poor prognosis in advanced cases. Tertiary lymphoid structures (TLS), ectopic lymphoid aggregates that

orchestrate anti-tumor immunity, have shown prognostic and therapeutic relevance in various solid tumors. However, their presence and function in OS remain unexplored.

Methods: We analyzed transcriptomic data from 286 primary OS samples across public databases and Peking University People's Hospital cohort to identify TLS-related gene expression patterns. A TLS prognostic index (TLSPI) was developed through the integration of 99 machine learning model combinations. TLS presence was validated by immunohistochemistry and multiplex immunofluorescence. Functional enrichment, immune landscape profiling, immunotherapy response prediction, and drug sensitivity analysis were performed using multi-omics bioinformatics tools. The immunoregulatory role of CXCL13 in TLS formation was further investigated through single-cell analysis and in vitro assays.

Results: The spatial structure of TLS was detected in OS specimens. The TLSPI signature (CXCL13, IL2RA, STAT5A) demonstrated superior prognostic performance compared to existing OS models. Low TLSPI was associated with immune-active tumor microenvironment (TME), enriched cytotoxic lymphocyte infiltration, higher expression of immune checkpoint genes, and enhanced predicted responsiveness to immune checkpoint blockade. Mechanistically, CXCL13 promoted B-cell migration, activation, and survival, suggesting its critical role in TLS formation within the OS microenvironment.

Conclusion: Our study provides the first evidence of TLS in OS and introduces a robust TLS-based prognostic model with strong clinical and immunological relevance. TLSPI holds promise for patient risk stratification, immunotherapy response prediction, and personalized treatment guidance. Targeting TLS-associated pathways, particularly CXCL13-mediated B-cell recruitment, may offer novel therapeutic avenues in OS.

(P 75) CD248 AS A PROGNOSTIC MARKER IN OSTEOSARCOMA

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Objective: Osteosarcoma is the most common primary malignant bone tumor in children and adolescents. However, patient prognosis still relies on the Enneking staging system and necrosis rate, with a lack of effective biomarkers. CD248 is primarily expressed in the stroma, particularly in tumor-associated fibroblasts and pericytes, and is also expressed in tumor cells of most sarcomas. The aim of this study was to evaluate the expression level of CD248 in osteosarcoma and its impact on patient prognosis.

Methods: Immunohistochemical analysis was performed on osteosarcoma tissue microarrays to detect CD248 expression in tumor tissues. Follow-up data were used to investigate the relationship between CD248 protein expression and osteosarcoma patients, with clinical data serving as evidence to confirm the significant role of CD248 in the progression of osteosarcoma. Survival analysis was conducted using Kaplan-Meier curves, with a p-value < 0.05 considered statistically significant.

Results: The study included 99 osteosarcoma patients, of whom 56 were CD248-positive and 43 were CD248-negative. The median follow-up time was 41 months (range: 0.5–118.4 months). A statistically significant difference in survival was observed between CD248-positive

and CD248-negative groups. The CD248-positive group (median survival: 48.2 months) had significantly worse survival than the CD248-negative group (median survival: 79.5 months).

Conclusion: CD248 expression has prognostic significance in osteosarcoma, with CD248-positive patients exhibiting poorer outcomes.

(P 76) CD47 BLOCKADE SYNERGIZES WITH CHEMOTHERAPY IN ENHANCING MACROPHAGE PHAGOCYTOSIS OF EWING SARCOMA CELLS

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Objective: Macrophages are known to harbor phagocytic activity against cancer cells, yet they fail to phagocytose Ewing sarcoma (ES) cells and confer a poor prognosis for ES patients. We previously found that ES cells utilize dual mechanisms, that is, up-regulation of CD47 “don’t eat me” signal and down-regulation of cell surface calreticulin (csCRT) “eat me” signal, to resist macrophage mediated phagocytosis. We demonstrated that enhancing csCRT by chemotherapy doxorubicin (DOX) and blocking CD47 by magrolimab (MAG) significantly enhanced macrophage phagocytosis of ES cells and had synergistic anti-tumor effects against ES xenograft tumors. However, the cumulative total lifetime dose of DOX is limited, and MAG is associated with side effects especially anemia due to CD47 expression on erythrocytes. To better translate the CD47 blockade and chemotherapy combinatorial therapy to the clinic, we sought to identify and evaluate alternative regimens in enhancing macrophage phagocytosis and anti-tumor activity against ES.

Methods: Macrophages were derived from human PBMC by M-CSF (100 ng/mL). Cyclophosphamide (CP), another common chemotherapy regimen for ES and was reported to enhance csCRT level on cancer cells, was utilized to enhance csCRT on ES cells (0-20 mg/mL for 24 hrs). Lemzoparlimab (LEM) (1 µg/mL), a next generation therapeutic CD47 blockade that does not produce substantial hematologic toxicity, was used to block CD47 signal. Flow cytometry based in vitro phagocytosis assay was performed to evaluate and compare macrophage phagocytosis of ES cells induced by CP+LEM and DOX+MAG.

Results: We found that csCRT levels on ES (A673, TC32, EWS502) cells were increased by CP in a dose-dependent manner with 20 mg/mL as the most effective dose (Fig.1A). CP or LEM alone significantly enhanced ($p < 0.01$), and the combination of the two further significantly enhanced ($p < 0.01$) macrophage phagocytosis of ES cells (Fig.1B). Furthermore, we found that CP and/or LEM induced comparable levels of increase in macrophage phagocytosis of ES cells as DOX and/or MAG (Fig.1C).

Conclusion: Our data demonstrates a synergistic effect of CP and LEM in increasing macrophage phagocytosis of ES cells that is comparable to the combination of DOX and MAG. This provides a rationale to move this combinatorial therapy to preclinical investigation.

(P 77) BARRIERS TO GUIDELINE CONCORDANT CARE IN AYA PATIENTS WITH BONE SARCOMAS

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Objective: Adolescents and young adults (AYA ages 15-39) with bone sarcomas (Ewing sarcoma and osteosarcoma) have worse survival when compared to children, but treatment with guideline concordant care (GCC) can improve survival. However, many AYAs with cancer do not receive GCC, especially older AYAs and those with limited resources. We therefore sought to elucidate the barriers to delivery of GCC to AYA patients with bone sarcomas through semi-structured interviews with healthcare providers caring for this patient population.

Methods: Semi-structured virtual interviews with 18 healthcare providers were conducted to elicit their experiences and to explore the complexities surrounding the multimodal and multidisciplinary care often required to effectively treat AYA patients with bone sarcomas. A purposive sample of participants were recruited based on type of institution, geographical location and specialty. Data were coded deductively and analyzed iteratively using qualitative thematic analysis with two trained qualitative researchers. Themes were identified by comparing both within transcripts and across transcripts using the CFIR 2.0 Framework.

Results: Semi-structured interviews were conducted with 8 pediatric oncologists, 4 medical oncologists, 2 orthopedic surgeons, 2 nurses and 2 social workers, providing over 500 minutes of data. Thirteen interviews were from National Cancer Institute (NCI) designated cancer centers and 5 were from NCI Community Oncology Research Program (NCORP) sites. Provider-reported patient-level barriers to delivery of GCC included comorbidities, treatment side effects, competing demands to treatment, financial strains, parenting young children, lack of parental/family support and mental health support. In addition, inadequate communication and coordination between patients and providers, and between providers across different treating institutions were reported as barriers. Suggested solutions to these barriers included placing patients on a clinical trial when possible, centralizing care at one institution when possible, integration of multidisciplinary oncology teams to include radiologists, pathologists, social workers and dietitians.

Conclusion: These interviews provide critical information, laying the foundation for development of cancer care delivery interventions to reduce survival disparities in AYAs with bone sarcomas.

(P 78) MENTAL HEALTH DISORDERS FOLLOWING PATHOLOGICAL FRACTURE: A RETROSPECTIVE COHORT STUDY

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Objective: Pathological fractures, resulting from underlying conditions such as metastatic cancer or metabolic bone disease, often signal advanced disease and are associated with

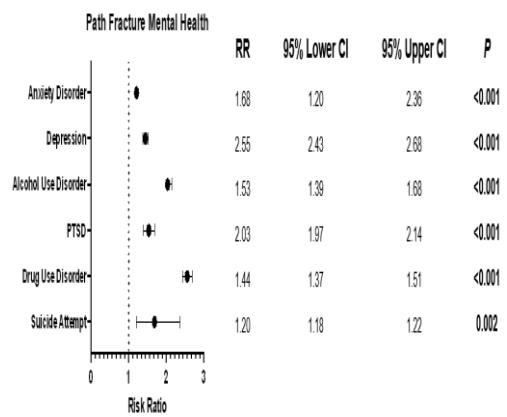
significant morbidity. These fractures can lead to loss of mobility, functional dependence, and prolonged recovery, compounding the emotional burden of the primary illness. Despite this, the mental health burden in patients sustaining pathological fractures remains underexplored. This study aimed to assess whether individuals with pathological fractures are at increased risk for subsequent mental health diagnoses compared to a broader orthopaedic population.

Methods: A retrospective cohort analysis was conducted using TriNetX research network. Patients with pathological fractures and no prior diagnosis of mental health disorders were identified using ICD-10 codes and compared to a matched global control cohort without pathological fractures. Propensity score matching was performed based on demographics and baseline comorbidities. Risk ratios (RR) with 95% confidence intervals (CI) were calculated for the development of specific mental health conditions within three years post index.

Results: A total of 7,829,222 patients were included, after successful matching there were 179,029 in both cohorts. Patients with pathological fractures demonstrated a significantly increased risk of subsequent mental health diagnoses. Specifically, pathological fracture was associated with higher rates of depression (RR 2.55; 95% CI 2.43–2.68; $p < 0.001$), post-traumatic stress disorder (RR 2.03; 95% CI 1.97–2.14; $p < 0.001$), anxiety disorder (RR 1.68; 95% CI 1.20–2.36; $p < 0.001$), alcohol use disorder (RR 1.53; 95% CI 1.39–1.68; $p < 0.001$), drug use disorder (RR 1.44; 95% CI 1.37–1.51; $p < 0.001$), and suicide attempt (RR 1.20; 95% CI 1.18–1.22; $p = 0.002$).

Conclusion: Patients sustaining a pathological fracture are at increased risk of developing a range of mental health conditions. These findings highlight the importance of proactive psychological screening and mental health support in the post-fracture period to optimize long-term outcomes.

Risk of mental health diagnosis following pathological fracture



(P 79) AGE-BASED TREATMENT PATTERNS AND OUTCOMES OF LOCALIZED HIGH-GRADE OSTEOSARCOMA FROM A NATIONWIDE DATABASE: WHAT IS THE OPTIMAL STRATEGY FOR PATIENTS OLDER THAN 40 YEARS?

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Objective: Standard treatment for osteosarcoma in pediatric and young adult patients typically includes surgery combined with neoadjuvant and adjuvant chemotherapy using methotrexate (MTX), doxorubicin, and cisplatin (CDDP). However, no consensus exists regarding optimal management in middle-aged and elderly patients. This study aimed to evaluate real-world treatment patterns and outcomes in patients aged >40 years using a nationwide registry in Japan.

Methods: Data were obtained from the Bone and Soft Tissue Tumor Registry by 89 JOA-certified hospitals. Patients with localized, high-grade osteosarcoma diagnosed between 2011 and 2020 were included. Clinical features, treatments, and outcomes were analyzed across three age groups: ≤40, 41–64, and ≥65 years.

Results: Among 886 patients, 622 (70%), 156 (18%), and 108 (12%) were aged ≤40, 41–64, and ≥65, respectively. Trunk tumors were more frequent in older patients (5% vs. 29% vs. 38%, $p < 0.001$). Definitive surgery was performed in 98%, 91%, and 85% ($p < 0.001$), and perioperative chemotherapy in 93%, 87%, and 41% ($p < 0.001$), respectively. Neoadjuvant chemotherapy was used in 96%, 80%, and 68% of chemotherapy cases. Use of MTX and CDDP declined with age: MTX (91%/41%/8%) and CDDP (94%/76%/42%) (≤40 / 41–64 / ≥65 years). Five-year DFS was 78.6%, 61.9%, and 48.0% ($p < 0.001$). Lack of definitive surgery was an independent poor prognostic factor for DSS in patients ≤65 years ($p < 0.001$). Among patients older than 40 years receiving perioperative chemotherapy, survival was similar between primary chemotherapy vs. upfront surgery groups.

Conclusion: This large-scale study shows that treatment patterns used in younger patients are also widely applied over age 40, while no consensus exists on optimal treatment for osteosarcoma in older patients. Given reduced histological response and increased toxicity in older patients, upfront surgery may be a non-inferior option. These findings prompt us to initiate preparations for prospective trials to define optimal strategies for the timing of surgery and chemotherapy in this age group through international collaboration.

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Methods: MOTOR is a tissue bank collecting fresh tumor tissue, blood, and clinical data from patients with musculoskeletal system malignancies such as sarcomas or bone metastasis. Specimens are processed into multiple formats, including cryopreserved, flash frozen, and OCT samples of tumor and normal tissue, as well as plasma and buffy coat that are processed and stored long term. The registry includes 43 distinct sarcoma subtypes. All samples are annotated with demographic and clinical information and continuously updated as new clinical information emerges.

Conclusion: MOTOR serves as a critical resource for musculoskeletal oncology research by addressing the shortage of high-quality, annotated rare cancer specimens. MOTOR has enabled numerous domestic and international collaborations, advancing sarcoma research

through publications, deeper insights into disease biology, and contributions to drug development and repurposing.

(P 81) ASSESSING PROGNOSTIC FACTORS OF CAUSE-SPECIFIC SURVIVAL IN PATIENTS WITH MALIGNANT GIANT CELL TUMORS: A POPULATION BASED STUDY FROM THE SEER DATABASE

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Objective: Malignant Giant Cell Tumors (MGCTs) are aggressive bone tumors typically managed with resection, while radiation and systemic therapies address advanced/recurrent disease. The impact of socioeconomic status (SES) on treatment access and survival remains unclear. We evaluated survival outcomes across SES groups in MGCT patients.

Methods: This retrospective cohort study analyzed 408 MGCT patients (2000–2021 SEER database). Variables included age, sex, income (above/below 2022 national median), rurality (urban/rural), and treatment modalities (surgery, chemotherapy, radiation). Time from diagnosis to treatment was compared across SES groups. Survival was assessed via Fine-Gray models.

Results: Patients were predominantly urban (89.2%) and higher-income (70.6%), with 47.1% aged >40 years and 50.1% male. Surgery was performed in 77.9% of patients, with 18.0% receiving chemotherapy and 17.8% radiation. There was no difference in frequency of treatment types or median time from diagnosis to treatment by income or rurality. Age >40 years (sub-hazard ratio [SHR]=4.78, 95%-CI:2.56–8.92), radiation (SHR=2.04, 95%-CI:1.21–3.43), and chemotherapy (SHR=3.25, 95%-CI:1.91–5.52) were associated with mortality risk. Surgery reduced mortality (SHR=0.55, 95%-CI:0.33–0.90). Income and rurality were not prognostic.

Conclusion: In this cohort of MGCT patients, income and rurality were not significant prognostic survival factors. However, survival outcomes were associated with age, surgery, radiation, and chemotherapy. Given that our measures of socioeconomic factors did not differ in the median time from diagnosis to treatment, further research is warranted to better understand the barriers contributing to survival disparities.

(P 82) DISPARITIES IN OSTEOSARCOMA BY SOCIOECONOMIC STATUS

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Objective: The influence of socioeconomic status on survival in osteosarcoma has been suggested by large registry studies; however, other studies have not found an association. These studies have relied on varying definitions of socioeconomic status and inclusion criteria. Additionally, they are limited to only variables included in the registries. The objective of this study was to examine the presentation, treatment, and outcomes of patients with osteosarcoma at a single-institution.

Methods: An institutional database identified 71 patients with osteosarcoma diagnosed between 2010-2023. Demographic data including the Area Deprivation Index (ADI) and treatment outcomes were collected from patient records. Patients were stratified by socioeconomic status using 75th percentile and greater representing increased social disadvantage. Survival was compared using Log-rank Test.

Results: Low utilization of outpatient clinics for initial evaluation was found in osteosarcoma (38%) cohorts with high ADI deprivation. Patients with osteosarcoma and high ADI scores had longer median symptoms duration prior to diagnosis compared to low deprivation scores [13.1 weeks (IQR: 6.7-19.2) vs 6.7 weeks (IQR: 4.0-11.3), $p < 0.01$]. High ADI deprivation patients with osteosarcoma needed more additional weeks to complete planned chemotherapy [7.9 (IQR: 6.3 to 11.7) versus the low ADI deprivation group [5.6 weeks (IQR: 3.9 to 9.0) ($p = 0.012$)]. 5-year overall survival ($p = 0.04$) and metastasis free survival ($p = 0.03$) were lower in osteosarcoma patients with ADI > 75th percentile

Conclusion: Measures of socioeconomic disadvantage are associated with presentation, treatment, and survival in pediatric osteosarcoma. Further study is needed to determine whether medical causes or social barriers lead to worse outcomes in this population.

(P 83) OUTCOMES OF MULTIMODAL PERIOPERATIVE TREATMENT IN OSTEOSARCOMAS OF THE JAW

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Objective: Osteosarcoma of the jaw (mandible and maxilla) is a rare subset of osteosarcoma that has typically been associated with a higher propensity for local recurrence, but lower risk of metastasis as compared to conventional high-grade OS of the extremity. We previously reported improvement in local control (LC) with postop RT; however, there is limited data regarding the role of perioperative chemotherapy and outcomes.

Methods: Patients with jaw OS were retrospectively identified within an institutional pathology database from 9/2020 to 11/2024. Patients were included if they underwent treatment at MD

Anderson Cancer Center, had surgical resection of the primary tumor, and had adequate follow up data available. Clinical and pathologic features were collected.

Results: As of submission, 83 patients with jaw osteosarcoma who underwent surgical resection were identified who met inclusion, with 81/84 (96.4%) presenting with localized disease. Initial treatment was resection alone (28/84, 33.3 %), resection with radiation (14/84, 16.7%), or perioperative chemotherapy with resection +/- radiation (42/84, 50%). Patients diagnosed more recently and with positive margins ($p=0.004$) were more likely to receive RT. First line chemotherapy regimens were heterogeneous, with doxorubicin/cisplatin as the most common regimen (21/42), which demonstrated variable tumor necrosis (36-86%). The median time to local recurrence was 12.7 months, which occurred in 23/84 pts. Patients with localized disease who received any RT vs no RT had a reduced local relapse rate (18.2 vs 30.6%), while chemotherapy vs no chemotherapy did not significantly affect local relapse rate ($p=0.32$). Patients who received chemotherapy had no significant difference in time to local recurrence, but further comparative analysis of chemotherapy response in more cases is ongoing.

Conclusion: This expanded series confirms the utility of RT in improved LC in patients with jaw osteosarcoma. Although chemotherapy did not significantly change local control rate, further detailed analysis is pending.

(P 84) A MULTICENTER COMPARISON OF REVERSE TOTAL SHOULDER ARTHROPLASTY VERSUS HEMIARTHROPLASTY FOR ENDOPROTHETIC RECONSTRUCTION FOLLOWING ONCOLOGIC RESECTION OF THE PROXIMAL HUMERUS

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Objective: The purpose of this study was to compare the complication rate and functional outcome of reverse total shoulder arthroplasty (rTSA) and hemiarthroplasty (HA) endoprosthetic reconstruction (EPR) in patients undergoing proximal humeral resection for primary or metastatic bone tumors.

Methods: Patients undergoing oncologic resection and proximal humerus EPR with rTSA or HA at six institutions between 2010 and 2024 were retrospectively reviewed. In total, 295

patients were included, with 154 (52%) HA and 141 (48%) rTSA. Eighty-six percent (n=121) rTSA were performed by orthopaedic oncologists without shoulder surgeon collaboration. Patient, tumor, and surgical details were collected. Complications and functional outcomes were compared with Fischer exact tests. Median final follow-up was 18.6 months (rTSA) and 12.2 months (HA) ($p=0.247$).

Results: At final follow up, the reoperation rate was 28% with rTSA and 8% with HA ($p < 0.0001$). Dislocation was the indication for first reoperation in 18 rTSA (46%) versus 3 HA (2%) ($p=0.0004$). Acute dislocation occurred in 24 rTSA (17%) and 3 HA (2%) ($p < 0.0001$), whereas 23 HA (15%) demonstrated chronic dislocation in the form of anterosuperior escape. Humeral aseptic loosening rate was 2% (3% rTSA, 1% HA); glenoid aseptic loosening in rTSA patients was 1%. Fifty-four rTSA (38%) had final forward elevation (FE) > 90 degrees, while only 10 HA (6%) did ($p < 0.0001$). Conversely, 91 HA (59%) had active FE < 45 degrees compared to only 22 rTSA (16%) ($p < 0.0001$).

Conclusion: Modular rTSA has significantly improved active FE when compared to HA, but with higher reoperation rates primarily driven by instability.

(P 85) MAKING NEGATIVE MARGIN MUSCULOSKELETAL TUMOR SURGERY A VIRTUAL REALITY USING 3D SPECIMEN SCANNING

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Objective: Surgical resection is the primary treatment for bone and soft tissue sarcoma. Negative margin status is associated with improved local control. Given the large volume and 3D anatomic complexity of many musculoskeletal tumors, communication of margin results between surgeons and pathologists can lack specificity based in a two-dimensional report. We sought to perform a feasibility study of ex vivo 3D scanning of bone and soft tissue tumor specimens to enhance communication between surgeons and pathologists.

Methods: Immediately after surgical resection, 3D scanning of the gross specimen was performed using the Einscan SP 3D scanner. During standard-of-care gross specimen processing, frozen and final margin sampling sites are annotated on the virtual 3D model. Then, using the 3D modeling software Blender, final margin distance to viable tumor was heat mapped onto 3D models for improved visualization.

Results: 3D scanning was performed in 19 cases (Table 1). This novel method of 3D margin mapping was found to be a feasible and reliable technique for communicating detailed information about margin status across a wide range of histopathological diagnoses and tumor

locations. As gross sectioning disrupts the original specimen’s structure, a scanned 3D virtual specimen can be kept indefinitely and used for communication and margin localization.

Conclusion: Virtual 3D scanning specimen mapping is feasible and allows for enhanced documentation and communication. This technology provides useful insight into anatomically complex musculoskeletal tumor specimens. Future studies should validate the utility of this method to assist in planning additional resections and adjuvant therapies.

Demographic and Surgical Characteristics of Included Patients

Age	Anatomic Region	Final Pathology	Positive Margins?	Largest Tumor Dimension (cm)	Closest Gross Margin (mm)
51	Chest	Undifferentiated Pleomorphic Sarcoma	No	8.3	9
69	Arm	Osteochondroma	No	5.8	N/A
27	Arm	Chondroblastoma	No	9.2	1
54	Thigh	Myxofibrosarcoma	No	14.5	10
52	Thigh	Myxoma	No	11.7	4
19	Leg	Osteochondroma	No	9	N/A
26	Wrist	Giant Cell Tumor of Bone	No	4.3	N/A
31	Thigh	Chondrosarcoma	No	6.6	0.9
57	Pelvis	Chondrosarcoma	No	8.8	0.9
35	Thigh	Myxofibrosarcoma	No	8.2	N/A
58	Leg	Epithelioid Sarcoma	Yes	8	N/A
71	Pelvis	Chordoma	No	14	1
48	Thigh	Leiomyosarcoma	No	17	0.9
80	Pelvis	Lipoma	No	13	3
52	Thigh	Renal	No	12	N/A
26	Thigh	Solitary Fibrous Tumor	No	8.1	N/A
63	Ankle	Melanoma	No	5	0.9
70	Thigh	Liposarcoma	No	13.7	4
35	Thigh	Ewing's Sarcoma	No	17	N/A

(P 86) CARBON FIBRE-REINFORCED PEEK IMPLANTS FOR TUMORS OF THE SPINE

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Objective: Carbon fibre-reinforced polyetheretherketone (CFR-PEEK) implants are a valuable option in spinal tumor surgery, offering structural integrity, minimizing interference with diagnostic and therapeutic interventions. We aimed to evaluate outcomes of CFR-PEEK implants, focusing on spinal stability, neurological recovery, pain relief and survival in patients with spinal tumors.

Methods: This retrospective analysis included 83 patients (52 males, mean age 59.9 years, range 18–88) treated between 2018 and 2024. 22 patients had primary and 61 secondary tumors, most commonly chordoma (6) and renal cell carcinoma (16). Surgical interventions involved the cervical (12), thoracic (42), and lumbar (29) spine. Mean surgery time was 207 minutes, with an average of 5 fusion levels. Pre- and postoperative outcomes (Frankel-, VAS Score), SINS-Score, and oncological follow-up were analysed using Wilcoxon and Mann-Whitney-U tests.

Results: Mean follow-up was 13 months (range 0–55). Postoperative mortality (34%) was associated with local recurrence in 10 patients (p = 0.008). Significant neurological (Frankel

Score from 40% to 62%, $p < 0.001$), and VAS improvements (mean of 3 points, SD 2.5, $p < 0.001$) were observed. SINS Score classified 26% as unstable, but without correlating with complications, neurological outcomes, or VAS improvement. Complications occurred in 19 patients, including 6 with wound healing disorders and 3 with implant loosening; 3 complications, including 2 dural tears, occurred intraoperatively.

Conclusion: CFR-PEEK implants demonstrate effective spinal stabilization, significant neurological and functional improvements, as well as manageable complication rates, supporting their use as a reliable option for spinal fusion in tumor surgery.

(P 87) ACUTE PATHOLOGICAL LONG BONE FRACTURES: WEEKEND VERSUS WEEKDAY VARIATIONS AND THEIR CLINICAL IMPACT

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Objective: Complete pathological fractures due to metastatic bone disease are time-sensitive emergencies in orthopedic oncology. Emerging evidence suggests the timing of hospital admission may influence outcomes. This study investigates the impact of weekday versus weekend admission on clinical outcomes in patients undergoing surgical management for acute pathological long bone fractures.

Methods: A retrospective cohort study was conducted using data from 1,642 patients who underwent surgery for metastatic long bone lesions from 1999 to 2023. Patients were categorized by admission day (weekend vs. weekday) and fracture type: complete pathologic fracture ($n=883$) or impending pathologic fracture ($n=759$). Outcomes included in-hospital complications, 30-day complications, and mortality. Logistic regression was used to adjust for age, sex, comorbidities, and fracture type.

Results: Weekend admissions ($n=186$) were more likely to present with complete pathologic fractures (71.0%) than weekday admissions (51.6%). In-hospital complications were higher for weekend admissions (47.3% vs. 27.1%, $P < 0.001$), particularly among patients with complete pathologic fractures. At 30 days, complication rates remained elevated for weekend patients (28.0% vs. 21.8%, $P=0.021$). One-year mortality was also higher (71.0% vs. 60.9%, $P=0.001$). Weekend admission was independently associated with increased odds of in-hospital complications for both complete pathologic fractures (OR 2.20, $P=0.001$) and impending pathologic fractures (OR 2.34, $P=0.001$).

Conclusion: Complete pathologic fractures were more prevalent on weekends, and these patients experienced higher complication rates regardless of admission day. These findings suggest that the observed “weekend effect” may result from differences in case mix rather than care quality. Accurate classification and adjusted analysis are essential for interpreting outcome variation by admission timing.

Table 1. Summary of Weekend vs Weekday Outcomes for Pathologic Long Bone

Fractures

Outcome	Weekend (n=186)	Weekday (n=1456)	P-value
Complete pathologic fracture (n=883)	71.0%	51.6%	0.001
Impending pathologic fracture (n=759)	29.0%	48.4%	
In-hospital complications	47.3%	27.1%	0.001
30-day complications	28.0%	21.8%	0.021
1-year mortality	71.0%	60.9%	0.001
OR (complete pathologic, weekend vs wkday)	2.20	Ref	0.001
OR (impending pathologic, weekend vs wkday)	2.34	Ref	0.001

(P 88) THE RAY CHALLENGE: HOW MANY RAY RESECTIONS CAN PATIENTS TOLERATE AND WHICH RAY RESECTIONS AFFECTS FUNCTIONAL OUTCOME THE MOST IN ORTHOPEDIC ONCOLOGY?

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Objective: Achieving complete resection with negative margins remains the primary objective in orthopedic oncology, with limb salvage becoming an increasingly important secondary goal. Treating foot sarcomas presents challenges due to anatomical constraints and limited reconstructive options, often leading to below-knee amputations (BKAs) which reliably achieve negative margins and acceptable function. However, limb salvage through ray resections can offer comparable survival and improved psychological outcomes when appropriately indicated.

Methods: This study retrospectively analyzed data from 39 patients who underwent single or multiple ray amputations for oncologic indications over the past 30 years. Patients were grouped into First Ray Amputation (1RA), Central Ray Amputation (CRA), Fifth Ray Amputation (5RA), and Multiple Ray Amputations (MRA). Functional outcomes, including pre- and post-operative TESS, MSTs87, and MSTs93 scores, were available for 25 patients and compared within subgroups and against a cohort of 25 BKA patients.

Results: Most patients (92.3%) achieved negative margins. Local recurrence occurred in 10.3% of cases, and wound dehiscence requiring debridement in 10.3% of patients. Functional scores improved postoperatively, with mean MSTs93 scores rising from 77.9 to 88.4 at five years. Mean MSTs93 scores for ray amputations and BKAs were 84.3 and 86.1, respectively,

with no significant difference ($p = 0.63$). Fifth ray resections showed better tolerance and outcomes, while multiple ray resections were associated with greater functional decline.

Conclusion: Ray resections provide a viable limb salvage option with functional results comparable to BKA, particularly when negative margins are achieved. Further research is needed to clarify long-term outcomes based on ray involvement.

(P 89) PATELLAR HEIGHT AND ITS INFLUENCE ON FUNCTIONAL OUTCOMES FOR MEGAPROSTHESES AROUND THE KNEE PERFORMED FOR ONCOLOGICAL INDICATIONS

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Objective: Distal femur and proximal tibia are the most common sites for osseous involvement in bone and soft tissue sarcomas. Endoprosthetic implants are widely used methods for reconstruction. The influence of patellar height is extensively studied in primary joint replacement literature. Its effect is somewhat less recognized in megaprosthesis reconstruction, given the extent and the multiplicity of associated factors. This study aimed to evaluate the impact of patellar height on patients who underwent distal femur and proximal tibia megaprosthesis reconstruction.

Methods: This retrospective study included 118 patients (93 distal femur and 25 proximal tibia reconstructions) who had bone and soft tissue tumors treated in a single institution. Data recorded included patient demographics, tissue diagnosis, history of radiotherapy, surgical approach, number of previous surgeries, polyethylene thickness, resection length, resection/total segment ratio, Insall-Salvati (IS) ratio, knee range of motion (ROM), extensor lag, and Musculoskeletal Tumor Society Score. Patients were followed up at least one year until their latest office visit or revision surgery due to failure.

Results: The mean age at surgery was higher for the distal femur group (37.8 ± 20.8 years) vs. the proximal tibia group (32.5 ± 18.9 years). Osteosarcoma was the most common diagnosis (53.8% and 64.0%, respectively). Number of prior surgeries was 0.67 ± 1.35 for distal femur and 1.16 ± 1.99 for proximal tibia. Postoperative patellar height, measured by IS ratio, was greater in the proximal tibia group (1.19 ± 0.53) than in the distal femur group (1.01 ± 0.24), with patella alta more common (52.0% vs. 12.9%). A higher IS ratio was significantly associated with improved postoperative ROM in both distal femur ($\beta = 0.002$, $p = 0.034$) and proximal tibia ($\beta = 0.009$, $p = 0.007$) groups. No significant associations were observed with extensor lag or MSTS score. In proximal tibia cases, resection proportion ($\beta = -9.332$, $p = 0.038$) and radiotherapy ($\beta = 1.325$, $p = 0.023$) were independently associated with IS ratio; no significant predictors were found for distal femur.

Conclusion: This study demonstrated that postoperative patellar height, as identified by IS ratio, is positively associated with knee ROM following both distal femur and proximal tibia

reconstructions. In proximal tibia cases, resection extent and radiotherapy influence IS ratio, highlighting the impact of surgical and adjuvant factors on functional alignment.

(P 90) MEGAPROSTHESIS CONVERSION FROM FAILED OSTEOARTICULAR ALLOGRAFT VERSUS PRIMARY RECONSTRUCTION FOR DISTAL FEMUR AND PROXIMAL TIBIA TUMORS: A PROPENSITY MATCHED-PAIR ANALYSIS

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Objective: Osteochondral allografts have been used to reconstruct osseous defects following periarticular tumor resection around the knee joint. Despite radiologically progressing into a Charcot-type joint, they provided biological solutions and good functional outcomes. However, high long-term failure rates have led to their decline as primary treatment options. When osteoarticular allografts fail, treatment options become limited and depend on the condition of the limb. The aim of this study is to compare failed allograft conversion into megaprosthesis with primary megaprosthesis for reconstruction following tumor resection.

Methods: This retrospective study included patients who underwent osteoarticular allograft reconstruction then conversion to megaprosthesis for tumors of the distal femur or proximal tibia. These patients were matched 1:2 with patients who received megaprosthesis as the primary reconstruction method after segmental resection using propensity scores based on age, gender, BMI, diagnosis, resected segment ratio and implant size. Outcomes assessed included MSTS scores, range of motion (ROM), extensor lag, complications, revisions, amputations, subsequent surgeries and implant survival.

Results: Twenty-three conversion patients were matched with 46 primary megaprosthesis patients. Revision rates were higher in the conversion group (31.8% vs. 19.5%, $p=0.43$), while amputation rates were similar (4.6% vs 5.0%, $p=1.0$). No significant differences were found in failure modes or implant survival ($p>0.7$). MSTS scores were higher in the primary group (25.3 vs 23.2, $p=0.079$). Time to revision was longer in the conversion group (10.36 vs 8.21 years, $p=0.537$), though they trended toward less ROM and extensor lag and a higher number of future surgeries.

Conclusion: While functional results were superior with primary reconstruction, megaprosthesis conversion from osteoarticular allograft provided comparable outcomes with reasonable complication rates and implant survival, proving its feasibility.

(P 91) A COMPARISON OF ACETABULAR AUGMENTATION AND PHOTODYNAMIC NAIL STABILIZATION FOR COMPLEX ONCOLOGIC TOTAL HIP ARTHROPLASTY

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Objective: Total hip arthroplasty (THA) is well-established for managing primary sarcoma or skeletal metastases in the hip; however, periacetabular disease complicates fixation due to poor bony substrate. Traditional strategies for overcoming acetabular bone loss include tantalum augments or protrusion cups. More recently, photodynamic nails (PDN) have emerged as a promising method for periacetabular disease because of their radiolucency and ability to accommodate screw fixation after polymerization. This study compared patients undergoing complex THA with acetabular augments versus photodynamic nails (PDNs), with Simple THAs included as a reference group.

Methods: A retrospective comparative study of patients undergoing THA for oncologic indications was conducted. Simple THA utilized only conventional implants; complex THA was defined as THA with additional pelvic fixation with PDNs (PDN+THA) or acetabular augments (Augment+THA). Demographic, surgical, and outcome data were collected. Primary outcomes were the cumulative incidence of reoperation or revision.

Results: Final analysis included 15 PDN+THA, 36 Augment+THA, and 80 simple THA. Acetabular cementation was more common for Augment+THA (89%) and Simple THA (40%) than PDN+THA (7%, $p < 0.001$). While PDN+THA required longer operative time, blood loss and length of stay were decreased compared to Augment+THA ($p < 0.001$). Simple THA showed significantly lower rates of reoperation at 12 months (9%) and 24 months (13.2%) follow-up ($p < 0.05$); 12- and 24-month reoperation rates in PDN+THA (29.4% and 40.6%) and Augment+THA (24.3% and 34.1%) were comparable ($p = 0.682$). Revision rates for Simple THA, PDN+THA, and Augment+THA were similar at 12 months (7.5% vs. 15.7% vs. 19.7%, $p > 0.05$) and 24 months (12% vs. 24.4% vs. 30.1%, $p > 0.05$).

Conclusion: PDN+THA showed comparable reoperation and revision rates compared to Augment+THA, with overall lower perioperative morbidity. As expected, PDN+THA and Augment+THA displayed worse outcomes compared to Simple THA, highlighting the challenge of THA in patients with poor periacetabular quality. Regardless, PDN+THA is a viable strategy for mitigating periacetabular bone destruction and improving durability of THA constructs.

(P 92) PRIMARY TUMOR SIZE AS AN INDEPENDENT PROGNOSTIC FACTOR IN OSTEOSARCOMA: PROPENSITY SCORE-MATCHED ANALYSIS DEMONSTRATES A CONTINUOUS DOSE-RESPONSE RELATIONSHIP

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Objective: Primary tumor size is an important prognostic factor in osteosarcoma; however, quantitative risk estimates remain poorly defined. We aimed to quantify the relationship between tumor size and survival using comprehensive analytical methods.

Methods: We conducted a retrospective cohort study of 2,467 osteosarcoma patients from the Surveillance, Epidemiology, and End Results (SEER) database (2000-2021). Cox proportional hazards models assessed both crude and treatment-adjusted effects of tumor size on survival. Systematic threshold analysis tested cutpoints from 40-150 mm with multiple testing corrections. Propensity score matching (1:1) compared large (>85 mm) versus small (≤85 mm) tumors, controlling for demographics, tumor characteristics, and treatment modalities. Bootstrap validation confirmed effect stability.

Results: Each 10 mm increase in tumor size was associated with a 6.4% increased hazard of death after adjusting for age, sex, tumor site, grade, surgery, radiation, and chemotherapy (Hazard ratio [HR]=1.064, p< 0.001; C-index=0.717). All tested thresholds demonstrated significant associations (HR range: 1.70-1.96), with no single optimal cutpoint identified (Table 1). Propensity score matching of 991 patient pairs confirmed the effect (HR=1.492, 95%-confidence interval: 1.297-1.717, p< 0.001).

Conclusion: Tumor size demonstrates a continuous dose-response relationship with survival in osteosarcoma, independent of treatment factors. These findings support integration of size-based risk assessment into clinical practice.

Table 1. Threshold analysis of primary tumor size with associated mortality risk

Analysis Type	Size Comparison	Hazard Ratio	95% CI	P Value
Threshold 40mm	>40mm vs ≤40mm	1.94	1.54-2.44	< 0.001
Threshold 50mm	>50mm vs ≤50mm	1.96	1.63-2.36	< 0.001
Threshold 60mm	>60mm vs ≤60mm	1.93	1.64-2.26	< 0.001
Threshold 75mm	>75mm vs ≤75mm	1.72	1.50-1.98	< 0.001
Threshold 85mm	>85mm vs ≤85mm	1.492	1.297-1.717	< 0.001
Threshold 100mm	>100mm vs ≤100mm	1.70	1.50-1.94	< 0.001
Threshold 125mm	>125mm vs ≤125mm	1.81	1.57-2.08	< 0.001
Threshold 150mm	>150mm vs ≤150mm	1.81	1.53-2.16	< 0.001

(P 93) INTERCALARY COMPRESSIVE OSSEOINTEGRATION OF DIAPHYSEAL TUMORS: A MULTI-INSTITUTIONAL CASE SERIES

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Objective: There is no consensus on treatment for diaphyseal reconstruction after significant bone loss. While intercalary allografts restore bone stock, they are associated with longer healing times, infection, and allograft fracture. Intercalary endoprostheses, by contrast, may offer immediate stability and early mobilization. We present a multi-institutional case series evaluating outcomes following reconstruction with Compress® Compliant Pre-Stress (CPS) spindle paired with the Orthopedic Salvage System for intercalary endoprostheses, with one spindle placed proximally and one distally. Our goal was to assess revision rates.

Methods: A retrospective review of 13 patients who underwent diaphyseal tumor resection and reconstruction using an intercalary endoprostheses between 2007-2024 at three tertiary sarcoma centers was performed. Median age was 28 years; median follow-up was 11 months. Diagnoses included primary bone sarcomas (n=11), primary intraosseous hemangioma (n=1), and metastatic melanoma (n=1). Chemotherapy was administered to 85% (n=11) and radiation therapy to 23% (n=3). Flap closure was required in 62% (n=8) of cases.

Results: There were no cases of periprosthetic infection. Five patients (39%) required reoperation: two for ingrowth failure (one converted to megaprosthesis), two for Morse taper dissociation (one revised with soft tissue reconstruction, one with a custom lap joint), and one for disease progression (amputation). There were no periprosthetic fractures.

Conclusion: Spindle complications following Compress® intercalary reconstruction were similar to those seen in megaprosthetic reconstructions. These findings support its use as a promising option for diaphyseal reconstruction; however, larger cohort studies are needed given the rarity of these reconstructions to better assess long-term outcomes and implant durability.

Patient demographics, tumor characteristics, treatment details, and outcomes following

Intercalary reconstruction

Patient	Age	Sex	BMI	Diagnosis	Location	Resection Length (cm)	Skin Closure	Chemotherapy	Radiation therapy	Follow-up (months)	Complication/Revision History
1	17	M	8	28. OSA	DT	22	Free flap	Neoadj.	None	109	Exchange of components – spindles retained
2	24	M	5	23. OSA	PH	14	Normal	Adj.	None	8	None
3	69	M	1	27. OSA	DF	19	Normal	Neoadj.	Neoadj.	7	Exchange of components – spindles retained – recurrent structural failure resulted in DFR
4	25	M	1	27. OSA	DF	23	Normal	Adj.	None	56	None
5	15	F	9	16. EWS	DF	18	Normal	Adj.	Adj.	11	Tumor progression – amputation
6	29	M	4	38. EWS	DT	18	Rotation	Neoadj.	Adj.	147	None
7	29	F	8	32. PBS	DT	14	Rotation	none	None	2	Morse-lapar dissociation – spindles retained – soft tissue revision
8	14	F	6	25. OSA	DF	17	Rotation	Neoadj.	None	1	None
9	50	F	23	20. OSA	PH	19	Normal	None	None	52	Morse-lapar dissociation – spindles retained – recurrent structural failure resulted in custom lap joint
10	8	F	1	20. OSA	DF	19	Rotation	Neoadj.	None	9	None
11	13	M	3	27. EWS	PT	15.5	Free flap	Neoadj.	None	6	None
12	33	M	5	28. OSA	PT	17	Free flap	Neoadj.	None	15	None
13	35	M	3	31. OSA	PT	15.5	Free flap	Neoadj.	Adj.	33	None

OSA = Osteosarcoma, M = Metastatic Melanoma, EWS = Ewing's Sarcoma, PBS = Primary Bone Sarcoma, PH = Primary Interosseous Hemangioma, DT = Distal Tibia, PH = Proximal Humerus, DF = Distal Femur, Neoadj = neoadjuvant, Adj = adjuvant

(P 94) EFFECT OF POSTOPERATIVE PHYSICAL THERAPY ON FUNCTIONAL OUTCOMES FOLLOWING MUSCULOSKELETAL TUMOR RESECTION

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Objective: Musculoskeletal tumor resections frequently lead to significant postoperative functional impairment. While physical therapy (PT) is widely implemented in general orthopedics, its use in orthopedic oncology remains inconsistent. This study evaluated whether postoperative PT referral improves longitudinal recovery in adults undergoing primary bone or soft tissue tumor resection using Patient Reported Outcomes Measurement Information System (PROMIS) domains.

Methods: We retrospectively reviewed patients (≥18 years) who underwent tumor resection from September 2022 to February 2024. PROMIS domains of Physical Function (PF), Global Physical Health (GPH), and Pain Interference (PI), were collected at baseline and at 1, 2, 6, and 12 months postoperatively. Outcomes were compared by PT referral status and tumor type (benign vs. malignant; bone vs. soft tissue).

Results: Of 264 patients (mean age 54.2 years, 53.1% female), 70.7% received PT referrals. PT patients started with significantly lower PF but demonstrated improvements over time. By one year, PF improved by +4.15 in PT vs. -1.28 in non-PT patients. PT was associated with greater gains in GPH and reductions in PI. In benign bone tumors, PT patients surpassed non-PT peers in PF at one year (53.9 vs. 40.8, pinteraction = 0.047). Pain and general health similarly improved in PT groups across subtypes, with the most changes between 2 and 6 months.

Conclusion: Postoperative PT significantly improved PROMIS outcomes across subgroups supporting its broader integration into musculoskeletal tumor care.

Table I. Mean PROM Scores by PT Referral Status

Outcome Measure	Baseline	1 Month	2 Months	6 Months	1 Year
PF (No PT)	49.82(12.09)	49.78(10.98)	51.26(11.86)	47.39(12.03)	48.54(12.34)
PF (PT)	40.62(10.61)	37.23(9.52)	38.47(9.74)	42.4(11.53)	44.77(12.31)
GPH (No PT)	50.61(9.13)	51.67(10.04)	50.97(9.98)	48.24(9.93)	50.29(12.73)
GPH (PT)	45.05(10.05)	44.64(9.27)	44.55(9.78)	46.75(10.89)	47.82(11.27)
PI (No PT)	50.59(10.52)	50.89(10.28)	50.01(9.74)	51.02(10.79)	52.09(11.26)
PI (PT)	58.28(9.98)	59.47(9.20)	57.70(9.30)	55.06(9.74)	54.10(10.14)

(P 95) COMPARATIVE OUTCOMES OF OPERATIVE AND NON-OPERATIVE TREATMENT FOR METASTATIC HUMERAL PATHOLOGIC FRACTURES

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Objective: To evaluate the survival and clinical outcomes of surgical and non-surgical management of pathologic humerus fractures secondary to metastatic cancer.

Methods: A retrospective review of 103 patients (63 surgical and 40 non-surgical) with pathologic humerus fractures due to metastatic cancer between 2010-2024. Patient demographics, cancer characteristics (including primary tumor type and oncologic treatments), surgical details, and clinical outcomes were collected. Univariable/multivariable comparisons, Kaplan-Meier, and Cox regression analyses assessed survival and clinical outcomes.

Results: The surgical cohort was older (mean 63.8 vs 61.5 years) with higher rates of renal cell carcinoma (27.0% vs 10.0%) and comorbidity burden (CCI $\geq$ 11: 30.2% vs 17.5%). Fracture healing was achieved in 73.0% of surgically treated patients. Postoperative complication rates were low, with infections, revisions, and implant failures occurring in 4.8%, 3.2%, and 6.3% of cases, respectively. Functional outcomes post-surgery revealed persistent pain in 52.4%, with 44.4% reporting functional decline. Overall mortality was comparable (55.6% vs. 57.5%; $p = 0.846$), but the surgical cohort had longer survival from fracture occurrence (mean 354 vs. 110 days, $p < 0.001$, Cohen's $d = 0.99$). Kaplan-Meier analysis showed no overall survival difference (log-rank $p = 0.174$), although the surgery group showed improved early survival (Breslow $p = 0.008$; median survival, 497 vs. 132 days). When controlling for confounding variables, Cox analysis demonstrated a 50% reduction in mortality risk with surgery (HR=0.496,

p=0.022).

Conclusion: Metastatic pathologic humeral fractures managed with surgical stabilization improve survival time, especially in the early to mid-time period, compared to non-surgical treatment. Implants outlast patient survival, but there is limited data, with only 4 reported failures.

(P 96) AMPUTATION FOLLOWING MEGAPROSTHESIS USE IN LIMB SALVAGE

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Objective: Megaprotheses, articulating implants that replace a portion of the diaphysis, are often employed during limb salvage for oncologic resection of primary or metastatic disease to avoid amputation. The purpose of this study was to determine the rate at which limb salvage procedures using megaprotheses ultimately required amputation.

Methods: The total joint registry from a single institution was queried for patients who underwent endoprosthesis placement for oncologic indications. Patients whose index procedure involved placement of an articulating, diaphyseal-replacing implant were included. These implants included proximal femoral replacements (PFR), distal femoral replacements (DFR), total femoral replacements (TFR), proximal tibial replacements (PTR), proximal humeral replacements (PHR), distal humeral replacements (DHR), total humeral replacements (THR), saddle endoprosthesis, and hemipelvic endoprosthesis. Patient demographics, implant type, oncologic characteristics, oncologic outcomes, complications, and reoperations, including amputation, were collected on eligible patients. Patients who received amputation of the operative limb following megaprosthesis were manually chart-reviewed to identify the reason for amputation.

Results: 607 implants in 598 patients were included for analysis. The underlying oncologic indication for surgery was metastatic disease in 312 patients and primary neoplasm in 296 patients. Mean age at surgery was 51 years. Implants placed during the index procedure consisted of PFR (n=222), DFR (n=163), TFR (n=31), PTR (n=34), PHR (n=124), DHR (n=7), THR (n=4), saddle (n=13) and hemipelvic (n=9) endoprotheses. Among all patients, the rate of reoperation was 39%. The rate of amputation following megaprosthesis placement was 2.6% (n=16). In 12 patients, amputation was the first and only reoperation following initial megaprosthesis implantation. The indication for amputation was local recurrence in 8 patients (50%), infection in 7 patients (44%), and recurrent instability in 1 patient (6%). Mean time to amputation was 44 ± 58 months for all indications, 81 ± 70 months for infection, and 14 ± 14 months for local recurrence. DFR and PTR were associated with significantly higher rates of amputation ($p < 0.001$).

Conclusion: Overall, the rate of amputation following megaprosthesis placement is low. However, proximal tibia and distal femoral replacements are associated with a higher risk of eventual amputation. Amputation for infection tended to occur as a late complication, whereas amputation for local recurrence typically occurred within the first few years of megaprosthesis implantation.

(P 97) RISK FACTORS ASSOCIATED WITH AMPUTATION VERSUS CONTINUED LIMB SALVAGE IN LOWER EXTREMITY ENDOPROSTHETIC RECONSTRUCTION

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Objective: Endoprosthetic reconstruction has become an increasingly common form of limb salvage in patients with primary or metastatic bone disease. However, up to 10 percent of endoprostheses will eventually fail. The purpose of this study was to identify the factors associated with amputation or continued limb salvage following removal of a lower extremity endoprosthesis.

Methods: A retrospective, single-center study of 78 patients with failure of a primary lower extremity endoprosthesis requiring implant removal between 2000-2022 was performed. Demographic, surgical, and endoprosthesis-related outcomes data were collected and compared between patients who resulted in limb salvage (n= 50) and amputation (n= 28).

Results: Smoking status (OR [95% CI]: 4.074 [1.278, 13.78], p=0.019) and a pre-existing diagnosis of diabetes mellitus (OR [95% CI]: 5.833 [1.539, 18.18], p=0.006) at the time of index endoprosthetic implantation were significantly associated with progression to amputation versus limb salvage. Indication for initial endoprosthetic reconstruction (OR [95% CI]: 1.103 [0.4327, 2.717], p>0.999), was not associated with progression to amputation versus limb salvage. Aseptic loosening as a mode of endoprosthetic failure was associated with limb salvage (10/50 (20.0%) vs. 0/28 (0.0%); p=0.012), while tumor recurrence or progression was associated with progression to amputation (OR [95% CI]: 9.600 [1.940, 46.57], p=0.003). In patients with a deep infection after a primary endoprosthesis, a polymicrobial infection, as compared to monomicrobial or culture negative infection, was not associated with progression to amputation (2/24 (8.3%) vs. 1/19 (5.3%); p=0.864).

Conclusion: Aseptic loosening following endoprosthesis implantation is associated with continued limb salvage. Smoking and diabetes mellitus at the time of endoprosthesis implantation, and tumor recurrence or progression following implantation are associated with progression to amputation. These risk factors may be useful in patient counseling.

(P 98) PERCUTANEOUS STABILIZATION OF METASTATIC BONE LESIONS WITH A PHOTODYNAMIC INTRAMEDULLARY SYSTEM: EXPERIENCE FROM A 15-PATIENT CASE SERIES

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Objective: Metastatic bone lesions are a common complication of advanced malignancy, often leading to fractures, pain, and impaired mobility. Conventional fixation methods, such as intramedullary nailing and endoprosthetic reconstruction, are invasive and may delay systemic

therapy. The IlluminOss® Photodynamic Bone Stabilization System is a minimally invasive alternative that may facilitate earlier recovery. This single-center case series describes our institution's experience using IlluminOss® for stabilization of metastatic bone lesions.

Methods: With Institutional Review Board approval, records of patients with metastatic bone lesions who underwent fixation with IlluminOss® (2023–2024) were retrospectively reviewed. Demographic, clinical, surgical, and patient-reported (PR) data were collected. PR data and clinical outcomes were analyzed with mixed linear model regression and ordinal logistic mixed regression.

Results: Fifteen patients (mean age 66.87 ± 8.65 years) underwent pelvic fixation with IlluminOss®. The average BMI was 27.41 ± 6.60 kg/m², ASA classification was 3 [3–3], and 53.3% of patients were active smokers. The mean operative time was 215.20 ± 144.86 minutes, with an average blood loss of 426.31 ± 776.91 mL. The average length of stay was 9.71 ± 9.30 days, and no postoperative complications were reported. VAS pain scores significantly decreased from baseline at all follow-up time points ($p < 0.05$): -21.66 at 2 days, -20.85 at 2 weeks, -20.53 at 6 weeks, -30.91 at 3 months, -38.14 at 6 months, and -30.94 at 1 year. Weight-bearing status showed a significant linear increase over time ($\beta = 2.41$, $p = 0.012$), progressing from 0% full weight-bearing preoperatively to 93% at 1 year. Assistive device use decreased from 80% to 33% at 1-year follow-up ($p = 0.017$).

Conclusion: IlluminOss® fixation for metastatic pelvic lesions was safe, well-tolerated, and associated with significant pain relief, early weight-bearing, and reduced reliance on assistive devices. Further research is needed to evaluate its comparative effectiveness, long-term outcomes, and integration into multidisciplinary oncologic care pathways.

(P 99) LIMB SALVAGE FOR PROXIMAL TIBIA TUMORS: OUTCOMES OF ALLOGRAFT-PROSTHESIS COMPOSITE AND ENDOPROSTHETIC RECONSTRUCTION

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Objective: The proximal tibia (PT), one of the most common sites for primary bone tumors, poses reconstruction challenges due to limited soft-tissue coverage and extensor mechanism repair. Reconstruction options include endoprosthetic (EP) and allograft-prosthesis composites (APC), with each method facing high failure rates. This study compares APC and EP outcomes, including failure characteristics, functional recovery, and predictors of failure.

Methods: With Institutional Review Board approval, records of patients who underwent proximal tibia reconstruction (2009–2024) were retrospectively reviewed. Demographic, clinical, radiographic, and surgical data were analyzed using Mann-Whitney U, Chi-square tests, Fisher's exact test, and univariate and multivariate logistic regression.

Results: Thirteen patients underwent APC (mean age: 32.3 ± 17.3) and 38 underwent EP

reconstruction (mean age: 37.6 ± 21.2). Prosthetic failure occurred in 6 (46.2%) APC patients and 18 (47.4%) EP patients ($p = 0.999$). Time and type of failure did not differ between groups (Table 1). Radiographic analysis showed no differences in zone of radiolucency (ZOR) or cortical expansion remodeling ($p > 0.05$). All patients with aseptic loosening had a ZOR ≥ 2 ($p=0.002$). Functional recovery was similar between groups ($p > 0.05$). ZOR (OR [95% CI] = 2.10 [1.26–3.50], $p = 0.005$), age at follow up (OR [95% CI] = 1.03 [1.00–1.06], $p = 0.026$) and length of follow up (OR [95% CI] = 1.13 [1.01–1.27], $p = 0.027$) to be associated with failure on univariate analysis. Multivariate regression showed no significant predictors of failure.

Conclusion: APC and EP showed comparable clinical outcomes and failure rates. Aseptic loosening was associated with ZOR ≥ 2 , and ZOR may predict prosthetic failure but could be confounded by age and follow-up duration. APC offers potential benefits in extensor mechanism reinforcement and bone stock restoration, while EP avoids allograft risks, allows soft-tissue closure, and enables immediate weight bearing. Larger multicenter studies and validated functional assessments (e.g., PROMIS, MSTs) are needed to inform individualized reconstruction strategies.

Table 1. Prosthetic Failure Characteristics

	APC (n=13)	EP (n=38)	P-Value
Failure	6 (46.2%)	18 (47.4%)	0.999
<i>Classification</i>			
Soft Tissue Failure	1 (16.7%)	5 (27.8%)	0.999
Aseptic Loosening	1 (16.7%)	6 (33.3%)	0.662
Structural Failure	4 (66.7%)	5 (27.8%)	0.208
Periprosthetic Infection	0 (0.0%)	5 (27.8%)	0.311
Time to Failure (years, mean $\pm$ SD)	2.78 $\pm$ 1.98	4.60 $\pm$ 5.77	0.999

(P 100) THE ROLE OF CANCER TYPE IN THE DEVELOPMENT OF PERIPROSTHETIC JOINT INFECTION IN DISTAL FEMORAL REPLACEMENT

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Objective: Periprosthetic joint infection (PJI) is the second most common and devastating complication following endoprosthetic reconstruction, often necessitating hardware explantation, cement mantle removal, prolonged antibiotics, and potential amputation. Oncologic patients are often presumed to be at elevated risk due to chemotherapy-induced immunosuppression and tumor-driven immune modulation. We hypothesized that primary oncologic diagnosis may influence PJI risk following distal femoral replacement (DFR).

Methods: We retrospectively reviewed 175 patients who underwent DFR at a single center between 1990 and 2022. PJI was defined according to Henderson failure mode of classification (Type IV). Demographic, oncologic, and surgical variables were extracted, including age, sex, primary oncologic diagnosis, chemotherapy exposure, radiation therapy, and prior revision surgery. Univariate analyses were performed using Fisher's exact tests for categorical variables and t-tests for continuous variables. Cox proportional hazards regression was used to model time to PJI, with follow-up time defined as time from surgery to PJI occurrence (for events) or last clinical follow-up (for censored observations). Variables with complete separation (zero events in certain categories) were noted in the analysis. The final multivariable Cox model included age, sex, cancer type, prior revision surgery, chemotherapy, and radiation therapy.

Results: Among 161 oncologic patients (mean age 30.6 years) who underwent distal femoral replacement (DFR), 8.7% developed periprosthetic joint infection (PJI) over a mean follow-up of 42.6 months. Over half (54.7%) received chemotherapy, and 11.3% had radiation therapy. PJI rates varied by tumor type, with the highest rates in Ewing sarcoma (40%) and chondrosarcoma (25%), followed by soft tissue sarcomas (16.7%) ($p=0.047$). Significant risk factors for PJI included older age, osteosarcoma, Ewing sarcoma, soft tissue sarcomas, and prior revision surgery (all with $p < 0.05$). Sex, chemotherapy, and radiation therapy were not significantly associated with PJI risk in the time-to-event analysis.

Conclusion: Prior revision surgery, age, osteosarcoma, Ewing sarcoma, and soft-tissue sarcomas were identified as factors associated with increased risk of PJI following DFR in time-to-event analysis. These findings suggest potential biological or malignant tumor characteristics that increase PJI susceptibility and underscore the need for future risk stratification in oncologic arthroplasty.

(P 101) METAL ION MONITORING AFTER CUSTOM 3D-PRINTED IMPLANTS IN BONE TUMOR SURGERY: COMPARISON WITH MODULAR SYSTEMS AND EARLY OBSERVATIONS

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Objective: To evaluate metal ion release following skeletal reconstruction using 3D-printed endoprostheses in bone tumor patients, compared to conventional modular tumor implants.

Methods: We prospectively monitored serum and drain concentrations of titanium (Ti), aluminum (Al), and vanadium (V) in 16 patients with custom 3D-printed Ti6Al4V implants and 3 patients with MUTARS® prostheses, all with ≥ 12 -month follow-up. Serial measurements were analyzed for early and late-phase ion trends.

Results: Both groups showed an early postoperative peak in drain fluid, followed by a serum peak at 2–3 months. The 3D group included reconstructions in the pelvis (n=6), lower limb (n=8), and upper limb (n=3), with 6 patients having prior implants. Mean peak Ti, Al, and V in the 3D group were 47.6, 225.0, and 1.99 µg/L, respectively, compared to 9.4, 176.7, and 0.84 µg/L in the MUTARS® group. Postoperative Ti elevation was higher in 3D patients (Δ Ti 37.6 vs. 9.8 µg/L), while Al and V were similar. A second ion peak was noted after 3 months in both groups, suggesting ongoing material interaction. Al levels did not correlate with Ti, but late Ti increases in the 3D group raise concerns about corrosion.

Conclusion: 3D-printed implants showed significantly higher Ti release compared to conventional systems, possibly due to surface roughness or lattice design. Late-phase re-elevation suggests potential long-term degradation. Al accumulation, a neurotoxic concern, was comparable between groups. Long-term surveillance and improved surface treatments are warranted.

(P 102) FACTORS RELATED TO ASEPTIC LOOSENING IN ENDOPROTHESIS RECONSTRUCTION OF THE PROXIMAL TIBIA

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Objective: Endoprosthetic reconstruction is frequently used after tumor resection in the proximal tibia. Among limb salvage procedures, proximal tibia replacement (PTR) is associated with the least favorable outcomes. However, data on factors related to aseptic loosening in modern PTR implants are lacking.

Methods: This was a retrospective review of patients who underwent PTR from 1998 to 2024. The primary endpoint was aseptic loosening. Ratios of the width of the medullary canal to the width of the implant stem at the tibial and femoral diaphysis and femoral metaphysis were measured on anteroposterior (AP) and lateral radiographs to assess fill of the canal by the implant stem. Linear regression was used to identify factors associated with aseptic loosening.

Results: Sixty patients treated with PTR were included. Revision-free survival was 60% at 5 years and 34% at 10 years. Nine patients had revision surgery for aseptic loosening (15%); of these, 7 (11.7%) had femoral loosening while 4 had tibial loosening (6.7%). Compared to patients with stable implants, patients with aseptic loosening had smaller femoral stem size (median 13.0 mm, range 11.0-17.0 vs median 16.0 mm, range 13.0-21.0, $p < 0.001$). On univariate analysis, tibial stem size 11 mm or larger (odds ratio (OR) 0.23, 95% confidence interval (CI) (0.05-0.99); $p = 0.048$) and femoral stem size 15 mm or larger (OR 0.03, 95% CI (0.00-0.19); $p < 0.001$) were associated with a lower risk of aseptic loosening. Higher femoral AP ratio (OR 34.5, 95% CI (3.59-630); $p = 0.001$), femoral metaphysis AP ratio (OR 17.3, 95% CI (3.57-165); $p < 0.001$), and femoral metaphysis lateral ratio (OR 5.73, 95% CI (1.04-40.3); $p = 0.045$) were associated with a higher risk of aseptic loosening. When controlling for confounding variables, femoral stem size less than 15 mm was associated with aseptic loosening (OR 14.7, 95% CI 2.19-145.28; $p = 0.005$).

Conclusion: These findings highlight the importance of careful implant selection in PTR,

particularly regarding femoral stem size. Femoral implant canal fill measured on AP and lateral radiographs may help clinicians select the optimal stem size to reduce loosening risk. Further studies are needed to explore strategies to improve implant longevity in this high-risk population.

Univariate Analysis of Factors Associated with Aseptic Loosening

Variable	Univariate analysis OR (95% CI)	P value
Age (years)	0.99 (0.95-1.02)	0.55
Sex (Male vs female)	0.74 (0.18-3.32)	0.68
BMI	0.96 (0.81-1.09)	0.51
Chemotherapy (Yes vs no)	3.33 (0.54-64.6)	0.22
Radiation therapy (Yes vs no)	0.58 (0.03-3.80)	0.61
Tibial bone resection length (cm)	1.22 (0.90-1.73)	0.20
Tibial prosthesis length (cm)	1.01 (0.80-1.26)	0.92
Vascular graft (Yes vs no)	0.63 (0.14-2.65)	0.52
Tibial stem size (mm)	0.63 (0.34-1.08)	0.10
Tibial stem size (mm) (≥11 vs < 11)	0.23 (0.05-0.99)	0.048
Tibial AP ratio	4.84 (0.23-107)	0.29
Tibial lateral ratio	5.52 (0.39-74.5)	0.20
Femoral stem size (mm)	0.27 (0.10-0.52)	< 0.001
Femoral stem size (mm) (≥15 vs < 15)	0.03 (0.00-0.19)	< 0.001
Femoral AP ratio	34.5 (3.59-630)	0.001
Femoral metaphysis AP ratio	17.3 (3.57-165)	< 0.001
Femoral lateral ratio	6.76 (0.91-66.2)	0.061
Femoral metaphysis lateral ratio	5.73 (1.04-40.3)	0.045

(P 103) EARLY OUTCOMES OF BONE PROSTHESIS COMPOSITE FOR RECONSTRUCTION IN LOWER LIMB TUMORS. A SINGLE INSTITUTION STUDY

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Objective: Reconstruction after long tumor resection are challenging due to limited options available. Augmenting residual bone length with either allograft or autograft to enhance prosthesis fixation after long segment resection, provides a good option for avoiding a total bone replacement.

Methods: In order to analyse the short-term outcomes with a view to judge the efficacy of this technique, we retrospectively analyzed 20 patients operated between 2005- June 2021 at our institution for graft union, time to weight bearing and associated complications. Patients in whom patient's own bone was used after sterilization (Extracorporeal radiotherapy/Cryotherapy), or an allograft was used to augment fixation were included in the study. In 15 out of 20 patients, more than 50% of implant stem was in the augmented bone. Fixation with plate was done in 10 out of these 15 cases to improve the stability. In remaining 4 of 5 cases, allograft was telescoped with the host bone to improve stability.

Results: Ten patients died of disease and 1 was lost to follow up. Among the 18 constructs

with known outcomes, 14 constructs were in-situ at a mean follow-up of 40 months (range: 6–116 months) while 4 underwent removal. Constructs were completely intact in 11, partially intact (during revision surgery) in 2 and in 1 patient with local recurrence who underwent amputation, stem-graft construct was retained. The overall graft survival was 88.5% at 2 years and 69% at 5 years. For constructs with $\geq 50\%$ stem incorporation, the 2-year and 5-year graft survival rates were 86.2% and 61.3%, respectively. In contrast, constructs with $< 50\%$ stem incorporation demonstrated 100% survival at both 2 and 5 years ($p=0.31$).

Conclusion: Bone prosthesis composite is an acceptable option for reconstruction after long segment resection in lower limb.

(P 104) 3D PRINTED CUTTING GUIDES FOR LONG BONE SARCOMA RESECTION AND INTERCALARY ALLOGRAFT RECONSTRUCTION: A CASE SERIES

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Objective: Metaphyseal Sarcomas are common. Historically, if limb preservation is possible, intra-articular resection sacrificing the joint with complex arthroplasty was performed. With the use of 3D printed cutting guides and intercalary allograft reconstruction, the joint can potentially be preserved with better functional outcomes. Two questions remain with this technique, allograft union and margins + local recurrence?. Historically, an unacceptably high rate of allograft non-union and positive margins have been reported. Computed digital images are sent to the engineer to prepare a plan for both the resection guide and allograft preparation. A 3D model is produced that helps place the guide on the bone in the appropriate position to achieve the planned outcome. Next the resection is performed with a 3D printed guide and the specimen removed and compared to the model. Once negative margins are achieved, the allograft is prepared on the back table using the guide to create an identical bone replacement. At the same time, internal fixation can be planned. An intercalary graft is placed in the patient with metal for rigid internal fixation and precise osteosynthesis using compression principles.

Methods: We performed a retrospective review of the first 9 patients treated at our institution with 3D printed technology with significant follow up. Histopathological and clinical data were reviewed with a focus on allograft union, margins, and local recurrence.

Results: All nine patients achieved negative margins with no local recurrences. Allograft union; 16/18 (89%) junctions. 7/9 (78%) grafts remain at most recent follow-up. One patient was revised to a modular oncology device due to non-union after irradiation for Ewing's sarcoma, a second osteosarcoma revised to modular oncology.

Conclusion: The use of 3D printed technology is very useful to preserve the joint around metaphyseal sarcoma. It not only helps achieve negative margins but a precise reconstruction with a high union rate.

(P 105) TREATMENT SUCCESS RATE AFTER SURGICAL MANAGEMENT OF PERIPROSTHETIC JOINT INFECTIONS IN ONCOLOGIC PROXIMAL TIBIA RECONSTRUCTION

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Objective: Periprosthetic joint infection (PJI) is a devastating complication following oncologic proximal tibia reconstruction (PTR), yet optimal management remains unclear. We aimed to assess treatment success and functional outcomes of different surgical strategies for PTR PJI.

Methods: We retrospectively reviewed patients with PTR PJI treated between 1995–2023 at two tertiary centers. Surgical approaches included DAIR (debridement, antibiotics, and implant retention), DAIR plus (with modular component exchange), and two-stage revision. Reinfection-free survival (RFS) and amputation-free survival were analyzed using Kaplan-Meier methods. Functional outcome (MSTS) and quality of life (EQ index) were assessed at last follow-up.

Results: Six-month RFS was 22% (DAIR), 67% (DAIR plus), and 83% (two-stage) ($p=0.002$). At two years, DAIR plus and two-stage had significantly higher RFS than DAIR ($p<0.001$), with no difference between DAIR plus and two-stage. Amputation-free survival at two years was 86% (two-stage), 58% (DAIR plus), and 44% (DAIR) ($p=0.36$). Median MSTS was 63%, with no significant difference across groups ($p=0.92$). Median EQ index was 68.4, also without significant differences ($p=0.69$).

Conclusion: DAIR plus achieved comparable infection control to two-stage revision and may be considered in selected patients with well-fixed stems. Functional outcomes following PTR PJI remain modest, underscoring the need for prospective data to assess the functional impact of different surgical strategies.

(P 106) REPAIR: A PRELIMINARY REPORT ON AN ONGOING MULTI-CENTER TRIAL FOR PATIENTS UNDERGOING SURGICAL STABILIZATION FOR METASTATIC BONE DISEASE OF THE FEMUR

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Objective: In patients with metastatic bone disease (MBD), metastases to the bone frequently lead to catastrophic pathologic fractures of the femur, which are associated with significant morbidity. Although prophylactic stabilization is considered the standard preventive intervention for those at risk of pathologic fractures, there have been no studies prospectively evaluating the outcomes of this intervention.

Methods: Ongoing prospective multicenter observational study of patients undergoing prophylactic stabilization for impending pathologic femur fractures. PROMIS Pain Interference (PI) and Physical Function (PF) scores were collected preoperatively and at 1, 2, 4, 6, 10 weeks; 3, 6 months; and 1, 2 years postoperatively.

Results: A total of 61 patients were enrolled across eight institutions, with an average age of 64.6 years (SD 11.2) and BMI of 27 at the time of surgery. The cohort was predominantly white (79%), non-Hispanic or Latino (83.6%), and male (50.8%). The most common diagnosis was metastatic carcinoma in 72.9% of patients, and the most common lesion location was the proximal femur (74.6%). Most patients had received systemic therapy (63.2%) and radiation (54.2%) prior to surgery. Patients reported immediate improvement in pain at one week postoperatively, which continued up to one year. However, physical function scores continued to decline up to one year postoperatively (Table 1). Data on postoperative complications were available for 55 patients. There were 2 incidences of wound dehiscence (3.6%), 2 implant failures (3.6%), and 3 reoperations (5.4%).

Conclusion: Prophylactic stabilization of the femur for patients with MBD results in improved pain for up to 1 year postoperatively, while physical function continues to decline. This information is crucial when counseling patients and serves as a baseline for future randomized trials aimed at elucidating the optimal surgical approach to MBD in the femur.

Table 1. Average PROMIS scores after Prophylactic Femur Stabilization

	n	Mean PROMIS Pain (+/- SD)	Mean PROMIS Physical Function (+/- SD)
Baseline	59	66 (6.9)	48 (9.6)
Week 1	60	65 (6.8)	50 (8.8)
Week 2	48	62 (8.9)	44 (10.6)
Week 4	38	59 (9.1)	42 (10.1)
Week 6	40	58 (10.1)	41 (10.6)
Week 10	37	56 (9.7)	39 (10.7)
Month 3	32	54 (10.2)	38 (10.1)
Month 6	25	51 (8.5)	36 (8.1)
Year 1	18	50 (8.7)	35 (9.2)
Year 2	12	47 (8.5)	31 (8.7)

(P 107) IS THERE A BETTER OPTION: INTRAMEDULLARY NAIL VERSUS PLATE OSTEOSYNTHESIS FOR PATHOLOGIC HUMERAL FRACTURES?

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Objective: Intramedullary nailing (IMN) and plate osteosynthesis (POS) are both used for fixation of pathologic humeral fractures. IMN is minimally invasive but disrupts the rotator cuff. POS spares the cuff but may delay systemic therapy due to open exposure. Data comparing outcomes between techniques are limited.

Methods: A retrospective review (2014–2024) of patients with pathologic humeral fractures treated with IMN or POS was performed. Outcomes were assessed using logistic regression and Wilcoxon rank-sum tests.

Results: 114 patients (56.1% female, mean age 63.1 ± 17.2) with 119 fractures were included. IMN was used in 54 (45.4%) fractures and POS in 65 (54.6%). There was no significant difference in time to failure (13.1 vs. 5.8 months, $p=0.56$) or revision rates (7.4% vs. 12.3%, $p=0.37$). Time to systemic therapy resumption was shorter with IMN (17 vs. 28 days, $p=0.09$). Shoulder ROM was similar in POS vs. IMN: forward flexion (122° vs. 118° , $p=0.77$), abduction (110° vs. 120° , $p=0.09$), and external rotation (64° vs. 58° , $p=0.75$). Prior radiation to the fracture site was associated with increased odds of failure (OR = 5.60, 95% CI: 1.53–20.44, $p = 0.009$); any radiation regardless of timing also predicted failure (OR = 3.98, 95% CI: 1.02–15.52, $p = 0.047$). Preoperative systemic therapy was not associated with failure (OR = 2.10, $p = 0.287$). Plate thickness, use of dual plates, number of proximal and distal screws, and nail diameter were not associated with revision or failure.

Conclusion: IMN and POS result in comparable functional and failure outcomes. IMN may facilitate earlier systemic therapy. Higher powered future studies will be needed to confirm these results.

(P 108) DISTANCE WEIGHTED MATCHING IN THE QUANTIFICATION OF EXCESS MORBIDITY IN EXTERNAL HEMIPELVECTOMY AND HIP DISARTICULATION

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Objective: Hemipelvectomy represents one of the most complex oncologic procedures; however, the actual excess morbidity compared to matched controls remains poorly quantified. We aimed to quantify the excess risk and resource utilization associated with hemipelvectomy and hip disarticulation using a distance-weighted methodology.

Methods: We conducted a retrospective cohort study using National Surgical Quality Improvement Program (NSQIP) data (2019-2023). Patients undergoing hemipelvectomy or hip disarticulation ($n=79$) were compared to composite controls created from patients undergoing pelvic tumor resection (CPT 27045, $n=89$) and radical pelvic resection (CPT 27049, $n=63$), totaling 152 patients. Composite controls were generated using distance-weighted matching based on 16 variables across four domains: patient demographics (age, sex, BMI), preoperative risk factors (ASA classification, functional status, diabetes, smoking, COPD, hypertension, steroid use), preoperative laboratory values (albumin, hematocrit, white blood cell

count, creatinine), and procedure complexity (operative time, work relative value units). Primary outcomes included length of stay, textbook outcome, and massive transfusion.

Results: Hemipelvectomy demonstrated significant excess morbidity compared to composite controls with 4.9 days longer length of stay (9.0 vs 4.1 days, $p < 0.001$), 48.3% lower textbook outcome rate (32.9% vs 81.2%, $p < 0.001$), and 25.3% excess massive transfusion risk (25.3% vs 0.0%, $p < 0.001$). Major morbidity occurred in 7.6% vs 0.0% of controls ($p = 0.013$), and major complications in 25.3% vs 8.9% ($p = 0.002$) (Table 1).

Conclusion: Hemipelvectomy and hip disarticulation carry substantial excess morbidity and resource utilization, with prolonged hospitalization, reduced textbook outcome probability, and significant transfusion requirements.

Table 1. Treatment Outcomes for Hemipelvectomy and Hip Disarticulation Patients Compared to Composite Controls

Outcome	Hemipelvectomy (n=79)	Composite Control (n=79)	Excess Risk	95% Confidence Interval	p-value
Primary Outcomes					
Length of Stay, days (median, IQR)	9.0 (5.0, 15.0)	4.1 (2.9, 8.6)	+4.9 days	3.5, 7.9	<0.001
Textbook Outcome, %	32.9	81.2	-48.3%	-58.5, -38.1	<0.001
Massive Transfusion (≥ 4 units), %	25.3	0.0	+25.3%	15.5, 35.1	<0.001
Secondary Outcomes (%)					
Major Morbidity Composite	7.6	0.0	+7.6%	1.6, 13.6	0.013
Any Major Complication	25.3	8.9	+16.4%	6.4, 26.5	0.002
30-Day Mortality	2.5	0.0	+2.5%	-1.0, 6.1	0.159
Multiple Readmissions	1.3	0.0	+1.3%	-1.3, 3.8	0.320
IQR: Interquartile Range					

(P 109) FINITE ELEMENT ANALYSIS FOR FIXATION EVALUATION OF PATIENT-SPECIFIC ORTHOPEDIC IMPLANTS

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Objective: Patient-specific 3D printed implants are valuable in selected pediatric and adult bone tumor patients when standard implants are not suitable, particularly for joint-sparing reconstructions. However, verification of these implants must account for anatomical variations, bone defects, and cortical bone quality for screw fixation. Conventional verification is often limited by tumor progression timelines. Finite element analysis (FEA) is an efficient alternative to mechanical testing, yet most previous models assume full bone-implant integration. This

study aimed to develop a patient-specific FEA approach to simulate various clinical scenarios including the non-osteointegration phase, to predict fixation stability in complex reconstructions.

Methods: We deliberately selected two patients who underwent reconstruction using customized 3D printed implants. Inclusion criteria were: (1) minimum 3-year follow-up, (2) complex implant geometry with sufficient volume, (3) favorable bone quality, and (4) occurrence of an adverse fixation-related event to verify FEA prediction power. CT-based models were generated, and clinical boundary conditions replicating surgical fixation steps were applied. Static load analyses simulated three conditions: (1) screw pull-out during the non-osteointegration phase, (2) screw failure under cyclic loading in the same phase, and (3) fixation post-osteointegration. A cumulative fatigue damage model predicted screw fracture timing under repetitive loading.

Results: The simulation accurately predicted screw pull-out and fracture observed clinically. The estimated timing of fatigue failure closely matched the actual clinical course.

Conclusion: This study highlights the importance of screw fixation stability prior to osteointegration. The proposed FEA approach enables effective preoperative evaluation and design refinement for patient-specific implants, reducing reliance on physical testing and supporting broader clinical use.

(P 110) DEFINITIVE RADIATION THERAPY IN "OPERABLE" EWING SARCOMA OF THE EXTREMITIES AND PELVIS

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Objective: Definitive radiation therapy (RT) has traditionally been reserved for inoperable or metastatic Ewing sarcoma, with limited data on its role in operable disease. However, a subset of patients showing excellent response to neoadjuvant chemotherapy with residual intraosseous disease may represent a favorable group where RT can offer effective local control while preserving function. This study evaluates oncological and functional outcomes in operable Ewing sarcoma treated with definitive RT.

Methods: A retrospective analysis was performed on patients with Ewing sarcoma of the extremities and pelvis treated with definitive RT at our institute between 2013 and 2022. Patients included had operable, non-metastatic disease but received RT alone for local control after demonstrating excellent response to neoadjuvant chemotherapy. Data regarding patient demographics, tumor location, radiation details (dose, timing, technique), and outcomes were collected. Endpoints included local control, systemic recurrence, and survival. Functional outcomes were assessed using the Musculoskeletal Tumor Society (MSTS) score and site-specific functional scales.

Results: contributed to favorable outcomes. Twenty-five patients were included, with 75% involving extremities and the rest pelvis or other skeletal sites. All had operable disease and responded well to chemotherapy. The local control rate with definitive RT was 90%, which compares favorably to published data on RT in Ewing sarcoma. Functional outcomes were encouraging, with high MSTS scores and satisfactory site-specific function. No major treatment-related morbidity affecting limb use was noted. Careful case selection and adherence to RT protocols were pivotal in achieving these outcomes.

Conclusion: Definitive RT provides an effective, function-preserving local control strategy in selected cases of operable Ewing sarcoma with excellent chemotherapy response and residual intraosseous disease. High local control rates and favorable functional outcomes support its use in appropriately chosen patients. Prospective validation of selection criteria, including clinical, radiological, and metabolic response markers, is warranted.

(P 111) DOES DOSE MATTER? POSTOPERATIVE RADIATION DOSE AND OUTCOMES FOLLOWING FIXATION OF METASTATIC EXTREMITY BONE LESIONS

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Objective: Pathologic and impending fractures are debilitating complications of bone metastases. Standard care involves surgical stabilization followed by post-operative radiation therapy (PORT), but optimal dosing and efficacy remain unclear. This study identified factors associated with local progression, hardware failure, and interventional survival (IS-time from surgery to death) in patients undergoing surgery and PORT for extremity fractures due to metastases.

Methods: A retrospective review was conducted of patients treated with surgery and PORT between 2000–2025. Data included demographics, tumor characteristics, and treatment details. Outcomes assessed were local progression-free survival (LPFS), IS (time from surgery to death), and hardware failure-free survival (HFFS), analyzed with Kaplan-Meier and Cox models. A subset analysis examined radioresistant (RR) tumors (RCC/sarcoma).

Results: 171 patients (190 sites) were included. Median age was 61 years; median follow-up was 34.1 months. Tumor types were adenocarcinoma (29%), RCC (19%), hematologic (15%), sarcoma (6%), squamous (3%), and others (28%). Patient, tumor, treatment characteristics, and outcomes for the non-RR and RR groups are summarized in Table 1. RR patients more often had visceral metastases (74% vs. 54%, $p=0.0008$). Two-year LPFS was lower in RR vs. non-RR tumors (78% vs. 94%, $p=0.02$).

On MVA, OS was worse with KPS < 80 ($p=0.0004$; HR 2.0) and better with multiple myeloma ($p=0.01$; HR 0.49). HFFS was worse with pathologic fractures ($p=0.002$; HR 9.8) and better in upper extremity metastases ($p=0.02$; HR 0.15). LPFS improved with bisphosphonates ($p=0.03$; HR 0.06) but worsened in RR tumors ($p=0.0006$; HR 7.8) and with 8 Gy x1 fraction ($p=0.01$; HR 11.0). IS was worse without systemic therapy ($p<0.0001$; HR 3.5), with PORT < 20 Gy ($p=0.046$; HR 1.7), and improved with RCC histology ($p=0.01$; HR 0.6).

In RR patients, reduced IS was linked to lack of systemic therapy ($p=0.002$; HR 3.8) and KPS < 80 ($p=0.04$; HR 2.0). PORT < 20 Gy trended toward decreased IS ($p=0.05$; HR 2.8).

Conclusion: Performance status, histology, systemic therapy, PORT dose, and bisphosphonates influenced outcomes. PORT < 20 Gy was linked to reduced IS, and 8 Gy x1 fraction to higher local progression, underscoring the need for individualized, multidisciplinary management in this high-risk population.

Table 1: Patient, Tumor, Treatment Characteristics, and Outcomes

Variable	Non-RR Histology (n=137)	RR Histology (n=53)	p-value
Age(Median)	61	61	>0.99
Current Smoker	11%	9%	>0.99
KPS ≥ 80	71%	62%	0.59
Oligometastatic at time of surgery ?	48%	41%	0.51
Disease Extent			0.0008
Bone-only	46%	27%	
Visceral	54%	73%	
Surgery Extent			0.11
Nail/Rod	78%	62%	
Curettage/arthroplasty	25%	38%	
Radiation			0.86
Dose/Fractionation			
8 Gy x 1		9%	
4 Gy x 5	11%	43%	
3 Gy x 10	33%	37%	
Other	49%	11%	
Bisphosphonates	31%	13%	0.02
Fracture			>0.99
Impending	61%	64%	
Pathologic	39%	36%	
Extremity Location			0.85
Upper	24%	25%	
Lower	76%	75%	
Bone Site			0.54
Proximal	80%	75%	
Distal	20%	25%	
Systemic therapy after surgery	75%	81%	0.44
2-year OS	65%	67%	0.99
2-year LPFS	94%	78%	< 0.0001
2-year IS	38%	49%	0.35
2-year HHFS	91%	90%	0.67

(P 112) PEDIATRIC GIANT CELL TUMOR OF BONE

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Objective: Giant cell tumor (GCT) of bone accounts for nearly 20% of benign tumors and mainly affects young adults, though it can rarely occur in children. In this population, limited data exist on the impact of physeal closure on local recurrence. This study aims to address this gap and characterize clinical features and outcomes in pediatric GCT cases.

Methods: We retrospectively reviewed patients ages 18 and younger with histologically confirmed GCT of bone surgically treated at three tertiary care academic centers between 1997 and 2022 with minimum one-year follow-up. Data on demographics, clinical and treatment characteristics, and oncologic outcomes was reviewed. Local recurrence-free survival (LRFS) was assessed using Kaplan-Meier analysis and differences between groups with log-rank tests.

Results: Forty-two patients were included. Median patient age and tumor size was 16 years (IQR: 14–17) and 5 cm (IQR: 3–7), respectively. Most tumors arose in long bones (n=32, 76%) versus flat bones (n=10, 24%). Median follow-up was 63 months (IQR: 27–94). Tumors were located in epiphyseal (n=2), metaphyseal (n=3), or epi-metaphyseal (n=27) regions. Adjacent physes were open in 11 (34%) and closed in 21 (66%) of patients (Table 1). Local recurrence occurred in 19 patients (45%) at a median of 7 months (IQR: 4.8–14), while metastasis was rare, occurring in only two patients (5%) at a median of 16 months (IQR: 3.1–28) (Table 2). LRFS for open physes was 73%, 55%, and 44% at 12, 24, and 60 months, respectively; for closed physes, 81%, 71%, and 60%, with no significant difference at any time point (p=0.62,

0.34, and 0.35, respectively) (Figure 1, Table 3).

Conclusion: In this multicenter cohort of pediatric patients with GCT, most tumors involved both the epiphysis and metaphysis. LRFS did not significantly differ between patients with open versus closed physes at any timepoint. These findings contrast with prior literature, which has reported significantly higher recurrence among patients with open physes and a greater proportion of metaphyseal-only tumors in skeletally immature patients. Our results suggest that while GCT in children often involves the metaphysis, physeal status alone may not predict recurrence risk. Differences across studies may reflect variability in sample size, follow-up duration, or surgical management. Larger studies are needed to confirm these findings and optimize risk stratification and surgical strategies in the pediatric population.

(P 113) ASSESSING TREATMENT OUTCOMES OF CHONDROMYXOID FIBROMA: A CASE SERIES

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Objective: Chondromyxoid fibroma (CMF) is a rare, benign, and locally aggressive bone tumor that presents diagnostic challenges due to its radiologic similarity to other lesions. While surgical intervention remains the primary treatment strategy, recurrence rates vary, and there is a lack of standardized treatment guidelines in the literature.

Methods: We conducted a retrospective review of patients diagnosed with CMF at our institution between 2010 and 2024. Eight patients met inclusion criteria, with treatment modalities including en-bloc resection (n=2), intralesional curettage with adjuvants (n=4), and conservative management with serial imaging (n=2). Demographic, clinical, and treatment-related data were collected, and outcomes were analyzed.

Results: The cohort consisted of three males and five females, with a mean age of 55.3 ± 11.8 years and an average follow-up of 41.7 ± 28.5 months. Lesions were located in the distal femur (n=3), pelvis (n=2), clavicle (n=1), great toe (n=1), and T3 vertebral body (n=1). All surgical patients remained free of tumor recurrence, regardless of treatment modality. Two patients treated with en-bloc resection experienced surgical complications requiring revision arthroplasty. Conservative management with serial imaging was successful in asymptomatic patients, with no evidence of disease progression.

Conclusion: This case series demonstrates that en-bloc resection, intralesional curettage with adjuvants, and conservative management with serial imaging are viable options for managing CMF, depending on patient specific factors. Notably, this is the first series to describe successful conservative management with serial imaging of CMF. Our results add to the limited literature on CMF and propose that serial imaging could be a potential management strategy in select patients with CMF.

(P 114) DENOSUMAB THERAPY AND MIRELS ADJUSTED ODDS OF PATHOLOGIC FRACTURE OR PROPHYLACTIC STABILIZATION IN APPENDICULAR SKELETAL METASTASES

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Objective: In metastatic disease to the skeleton, pathologic fracture is debilitating, and prophylactic fixation carries its own morbidity and cost. Denosumab may avert both events, yet evidence that accounts for lesion biomechanics is scarce. We analyzed whether denosumab lowers the combined risk of pathologic fracture or prophylactic fixation in the context of Mirels' score.

Methods: We performed a retrospective analysis of 535 radiographically confirmed long-bone metastases arising from five primary histologies (breast, lung, renal, thyroid, prostate) treated between 2015-2024 at a tertiary cancer center. Patients were categorized by denosumab exposure, and the primary composite endpoint was occurrence of pathologic fracture or prophylactic stabilization. Associations were examined with logistic regression, unadjusted and adjusted for Mirels' total score and reported as odds ratios (ORs) with 95% confidence intervals (CI).

Results: Among 535 patients, 202 (37.8%) received denosumab. Pathologic fracture or prophylactic surgery occurred in 24.8% of denosumab-treated versus 34.2% of untreated patients ($p = 0.026$). Unadjusted analysis showed a 37% reduction in odds of fracture or surgery with denosumab therapy (OR 0.63, 95% CI 0.43-0.93). After controlling for Mirels' score, this association lost statistical significance (OR 0.83, 0.52-1.33). Mirels' score remained the dominant predictor of event occurrence even after accounting for denosumab therapy, with each point increase more than tripling event odds (OR 3.13, 2.55-3.93).

Conclusion: Denosumab was associated with a reduction in the odds of fracturing or requiring prophylactic surgery. However, lesion severity remains the key driver of outcomes, highlighting the importance of Mirels' score for guiding treatment decisions.

(P 115) SINGLE-CENTER EXPERIENCE WITH TYROSIN KINASE INHIBITORS IN ADVANCED BONE SARCOMA: EFFICACY AND SAFETY OUTCOMES

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Objective: Tyrosine kinase inhibitors (TKIs) have emerged as potential therapeutic options for refractory osteosarcoma and Ewing sarcoma. However, clinical experience remains limited, and outcomes are variable.

Methods: We conducted a retrospective analysis of patients with primary advanced bone sarcomas treated with TKIs at our institution between December 2013 and March 2025. Primary endpoints included progression-free survival (PFS) with different TKIs and objective response rate (ORR).

Results: Twenty-eight patients were included (18 osteosarcoma, 4 Ewing sarcoma, 1 Ewing sarcoma-like, and 5 other sarcoma histologies). Median age was 28 years (range 13–55). Fifty-three percent of the patients were male. The majority of patients had received more than two prior lines of therapy (57.1%). TKIs used included sorafenib (n=17, 60.7%), cabozantinib (n=5, 17.9%), regorafenib (n=4, 14.3%), and pazopanib (n=2, 7.1%). Median progression-free survival (PFS) with all TKIs was 4 months (95% CI: 1.3–6.4), with better outcomes observed with cabozantinib (median PFS 4 months, 95% CI: 2.8–5.1) and pazopanib (median PFS 10 months, though only 2 patients). Cabozantinib achieved the highest ORR (66.7% stable disease [SD] and 33.3% partial responses [PR]), with a disease control rate of 100%. The observed toxicities were consistent with those reported in clinical trials.

Conclusion: Our experience confirms the modest activity of TKIs in refractory bone sarcomas, with similar PFS rates across all drugs. Cabozantinib appears to have the highest disease control rates and a more favorable toxicity profile, as reported in the literature.

(P 116) A DUAL-TARGETED SYSTEMIC THERAPEUTIC APPROACH FOR THE SELECTIVE ELIMINATION OF TUMOR CELLS IN PRIMARY AND METASTATIC SARCOMA.

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Objective: Osteosarcoma (OS), the most common primary bone cancer in children and adolescents, has a poor prognosis, especially in metastatic cases, with a 5-year survival rate of only ~20%. Around 20% of patients present with metastases at diagnosis, and most others are presumed to have micrometastases, with nearly half progressing to clinical metastasis. Despite aggressive treatment, outcomes have not improved since the 1970s, highlighting an urgent need for novel therapies targeting disseminated disease.

Methods: We propose a dual-targeted systemic therapy using a modified bacteriophage vector for intravenous delivery of therapeutic genes to primary and metastatic tumors. The non-pathogenic phage is engineered to bind tumor-specific receptors with minimal normal tissue interaction. It carries a gene for secreted TRAIL (sTRAIL), which selectively induces apoptosis in cancer cells, enabling targeted and localized treatment following systemic administration.

Results: We evaluated the efficacy of our sTRAIL-encoding gene delivery vector against osteosarcoma (OS) using both in vitro human tumor cell models and in vivo murine models following intravenous administration. Our initial analysis demonstrated that the majority of human OS cell lines and patient-derived specimens expressed the $\alpha\beta3$ integrin, the molecular target receptor of our delivery system. This receptor-mediated interaction enabled selective homing of the vector to both primary and metastatic tumor sites in mice after systemic administration. As a result, sTRAIL was effectively delivered and locally released at the tumor sites, while healthy tissues remained largely unaffected. Repeated systemic administrations of

the therapy were well tolerated, with no significant toxicity observed. Importantly, this approach led to the selective and efficient elimination of both primary tumors and metastatic lesions. These findings highlight the potential of this dual-targeted gene therapy as a safe and effective strategy for personalized treatment of osteosarcoma.

Conclusion: Our dual-targeted systemic therapy, using a bacteriophage vector to deliver sTRAIL to $\alpha\beta 3$ -expressing osteosarcoma cells, achieved selective tumor targeting and effective elimination of both primary and metastatic lesions with no observed toxicity. These results highlight its potential as a safe, personalized treatment for advanced osteosarcoma and warrant further preclinical and clinical development.

(P 117) THERAPEUTIC POTENTIAL OF DOXORUBICIN AND DASATINIB COMBINATION IN OSTEOSARCOMA

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Objective: Osteosarcoma is a rare, aggressive malignancy and the most common primary bone sarcoma affecting children, adolescents, and young adults. Despite advancements in treatment, survival rates have stagnated, underscoring the need for new therapeutic strategies. Although doxorubicin remains a cornerstone in osteosarcoma treatment, resistance often develops. Enhancing doxorubicin effectiveness against osteosarcoma cells through combination therapy may improve treatment efficacy. This study aimed to identify agents that synergize with doxorubicin in osteosarcoma.

Methods: A kinase inhibitor library was screened using MTT assays in KHOS and 143B osteosarcoma cell lines. Drug interactions were evaluated using the ZIP synergy model, where $ZIP < 0$ indicates antagonism, $0 \leq ZIP \leq 10$ is additive, and $ZIP > 10$ indicates synergy. Src and phosphorylated Src (p-Src) expression and subcellular localization were assessed using Western blotting and immunofluorescence, respectively. Expression of anti-apoptotic proteins and PARP cleavage were also evaluated by Western blot. The functional role of p-Src inhibition in enhancing doxorubicin effectiveness was further evaluated using flow cytometric apoptosis and clonogenic assays.

Results: MTT assays demonstrated that dasatinib exhibited the highest synergy with doxorubicin in both KHOS and 143B cells, with synergy scores of 10.575 and 13.968, respectively ($p < 0.05$). Immunofluorescence analysis showed that p-Src was predominantly localized in the cytoplasm. Western blot showed that the combination treatment significantly reduced p-Src and anti-apoptotic protein levels, while enhancing PARP cleavage compared to either agent alone. Flow cytometry analysis revealed increased apoptosis in the combination group, while clonogenic assays showed decreased colony-forming ability. These findings indicate dasatinib enhances doxorubicin effectiveness in osteosarcoma cells.

Conclusion: The combination of doxorubicin and dasatinib demonstrates synergistic anti-tumor effects in osteosarcoma. By reducing cell proliferation, downregulating p-Src and anti-apoptotic proteins, and enhancing apoptosis, this combination therapy offers a new and inspiring direction for osteosarcoma treatment. The data strongly support the potential of dasatinib to enhance doxorubicin effectiveness, making it a promising strategy for overcoming drug resistance in osteosarcoma. This inspiring finding motivates further exploration and clinical trials of this combination therapy.

(P 118) IMPACT OF TYROSINE KINASE INHIBITOR THERAPY ON BONE PROGRESSION IN PATIENTS WITH DRIVER-MUTATED METASTATIC NON-SMALL CELL LUNG CANCER WITH DE NOVO BONE METASTASES

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Objective: In non-small cell lung cancer (NSCLC), 45-60% of patients will develop bone metastases, leading to impaired mobility, increased pain, and reduced quality of life. Although tyrosine kinase inhibitors (TKI) are the standard first-line treatment for patients with metastatic NSCLC (mNSCLC) with EGFR, ALK, ROS, or RET driver mutations, their efficacy in preventing bone metastasis progression (BM-P) and skeletal-related events (SREs) remains unclear. This study assessed bone metastases progression-free-survival (BM-PFS) and the incidence of SREs in patients with driver-mutated mNSCLC with de novo bone metastases treated with first-line TKI.

Methods: We conducted a single-institution retrospective analysis of patients with driver-mutated mNSCLC treated with first-line TKI monotherapy between 01/2017-12/2024. We assessed BM-PFS and incidence of SREs, including pathological fractures requiring orthopedic surgery and/or radiotherapy, pain, spinal cord compression, and hypercalcemia.

Results: 105 patients were included with median follow-up of 34.2 months (Table 1). Progression occurred in 69 (65.7%) patients with PFS of 25.7 months (Figure 1). Twenty-two (21%) patients experienced BM-P, including oligoprogression. BM-PFS was 63.6 months; however, of the patients who experienced BM-P, median time-to-event was 9.4 months. Fifteen patients (14.2%) experienced >1 SRE, with a median time-to-event of 8.3 months. SRE was predictive of BM-P (HR 5.28, p=0.006). Three-year overall survival (OS) was 77%. BM-P was not predictive for OS.

Conclusion: TKIs appear to be protective against BM-P, but there remains a small subset of patients who experience BM-P early in their disease course, often preceded by SRE. Encouragingly, BM-P was not associated with decreased OS, as prior studies indicated. Understanding BM-P and SREs in response to targeted therapy is critical in guiding treatment to reduce the morbidity and mortality of mNSCLC.

(P 119) DEVELOPMENT OF AN EXTINCTION THERAPY APPROACH FOR OSTEOSARCOMA USING ECO-EVOLUTIONARY PRINCIPLES

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Objective: Patients with high-grade osteosarcoma (OS) face high recurrence rates and significant treatment-related toxicity, despite multiagent chemotherapy (MAP: methotrexate, adriamycin (doxorubicin), cisplatin). Tumor recurrence is in part driven by chemoresistance, which can develop after a maximally tolerated dose (MTD) approach. In contrast, “extinction therapy” (ET) is an emerging strategy that leverages eco-evolutionary principles to drive heterogeneous tumors to extinction through multi-strike delivery of sub-MTD therapies targeting unique subpopulations. This study aims to develop an ET regimen that offers a rational path to improved OS outcomes with reduced toxicity.

Methods: The first strike of ET uses standard doxorubicin and cisplatin to reduce tumor size and heterogeneity. Subsequent strikes use sequential second-line agents selected from established guidelines. Efficacy of ET versus standard therapy is assessed using cell growth and post-treatment cell viability. In vitro modelling uses a 143B OS cell line; ex vivo uses a pulmonary metastasis assay (PuMA). Statistical analysis uses one-way ANOVA.

Results: Compared to standard therapy, ET significantly inhibits OS cell growth and significantly reduces OS cell viability in in vitro testing. ET stabilizes OS metastatic tumor burden within the PuMA ex vivo model. In regards to overall toxicity, multiple in vitro drug concentrations in the ET regimen were significantly lower than reported in published pharmacokinetic studies.

Conclusion: Current agents used in OS demonstrate chemoresistance with repeat use, leading to a need to explore new therapies. ET demonstrates efficacy in preclinical models and represents a promising approach to minimize toxicity and chemoresistance in OS. Future work aims to optimize the current ET regimen by incorporating novel agents and validate ET across multiple in vitro, ex vivo, and in vivo OS models.

(P 120) SURVIVAL OUTCOMES AND ROLE OF CHEMOTHERAPY IN PATIENTS OLDER THAN 40 YEARS WITH OSTEOSARCOMA (OLD-SARC STUDY).

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Objective: Osteosarcoma predominantly affects adolescents and young adults, but a second incidence peak occurs in individuals >40 years. Older adults often have higher comorbidity burdens, lower chemotherapy tolerance, and limited representation in clinical trials, leading to

scarce evidence-based guidance. This study aims to describe clinical characteristics, treatment patterns, and outcomes of patients aged ≥40 years with osteosarcoma and assess chemotherapy’s safety and efficacy.

Methods: We conducted a single-center retrospective study of patients aged ≥40 with histologically confirmed osteosarcoma treated at McGill University Health Centre (MUHC) from 2014–2024. Data were sourced from the CanSaRCC and SaRC-Q registries. Endpoints included overall survival (OS), progression-free survival (PFS), and objective response rate (ORR) per RECIST 1.1. OS was analyzed via Kaplan-Meier and log-rank tests.

Results: We included 40 patients (median age 64 [range 40–101]; 55% male) (Table 1). Most tumors were appendicular (57.5%) and high-grade conventional osteosarcoma was the most frequent subtype (50%). At diagnosis, 67.5% had localized and 32.5% had metastatic disease. Among localized cases, 37% received neoadjuvant and 33.3% adjuvant chemotherapy. Doxorubicin plus cisplatin was the most used regimen. Among 15 evaluable metastatic patients treated with first-line chemotherapy, ORR was 13.3% (2 partial responses); 20% achieved stable disease; 60% had progression. Median OS was not reached for localized disease. Recurrence occurred in 7 patients (17.5%) locally, 4 (10%) metastatically, and 1 (2.5%) with both. Median OS in metastatic disease was 6.97 months (95% CI: 3.49–10.44). The 5-year OS was 51.1% (localized) vs. 4.0% (metastatic). Mean PFS with first-line chemotherapy was 4.39 months (range 1.41–44.38). Median number of lines was 1.5 (range 0–4). Of 16 patients treated, 25% had treatment interruptions and 50% required dose reductions.

Conclusion: Older patients with localized osteosarcoma benefit from multimodal therapy, though outcomes are inferior to younger counterparts. In metastatic disease, prognosis remains poor, with modest chemotherapy benefit and frequent dose modifications. These findings highlight the need for better systemic therapies and greater inclusion of older adults in sarcoma trials.

Table 1. Demographics and clinical characteristics

Characteristic	n (%)
Total Patients	40
Median Age at Diagnosis (range)	64 (40–101)
Gender	
Male	22 (55%)
Female	18 (45%)
Location	
Axial	18 (45%)
Appendicular	23 (57.5%)
Unknown	1 (2.5%)
Histology	
Conventional Osteosarcoma	20 (50%)
Extraskeletal	13 (32.5%)
Other*	7 (17.5%)
Disease Status at Diagnosis	
Localized	27 (67.5%)
Metastatic	13 (32.5%)
Systemic Therapy – Neoadjuvant	10
Doxorubicin + Cisplatin	8 (80%)
MAP	1 (10%)
Risofamide + Etoposide	1 (10%)
Systemic Therapy – Adjuvant	9
Doxorubicin + Cisplatin	7 (77.8%)
Risofamide + Etoposide	1 (11.1%)
Doxorubicin + Carboplatin	1 (11.1%)
Systemic Therapy – Palliative 1 st line	16
Doxorubicin + Cisplatin	7 (43.8%)
Liposomal Doxorubicin	5 (31.3%)
Doxorubicin monotherapy	2 (12.5%)
Risofamide + Etoposide	1 (6.3%)
Gemcitabine + Docetaxel	1 (6.3%)

(P 121) REAL-WORLD EXPERIENCE OF CABOZANTINIB MONOTHERAPY IN RELAPSED OR REFRACTORY OSTEOSARCOMA AND EWING SARCOMA: A SINGLE-CENTRE AUSTRALIAN STUDY

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Objective: Cabozantinib (CBZ) has demonstrated efficacy in advanced osteosarcoma and Ewing sarcoma (ES) per the CABONE study (Italiano et al, Lancet Oncol. 2020). This study aimed to evaluate the real-world efficacy and safety of CBZ in relapsed or refractory osteosarcoma and ES in the Australian context.

Methods: We conducted a retrospective single-centre study to assess the real-world outcomes of CBZ monotherapy in relapsed or refractory osteosarcoma or ES.

Results: Between November 2022 and June 2025, 14 patients (pts) received CBZ monotherapy, 13 osteosarcoma and 1 ES. Median age was 30 (range 18-56) years and 8 were male (57%). 8 (57%) pts had received ≥ 2 lines of prior systemic therapy. All pts commenced CBZ at 60mg. At analysis cutoff with a median follow-up of 8.4 months, 4 (29%) pts remained on CBZ, 10 (71%) pts had ceased due to disease progression. Median duration of treatment was 7 months (range 0.5-NR). Best overall response was 3 (21%) partial response, 5 (36%) stable disease (4 for ≥ 6 months), 6 (43%) progressive disease. Median progression-free survival (PFS) was 4.2 months (95% CI 2.2-7.2). 6-month PFS rate was 43%. One patient achieved a near complete metabolic response following 6 weeks of CBZ. Another patient maintained a durable partial response for 18 months. Median overall survival was 9.0 months (95% CI 4.1-NA). In the relapsed/refractory setting, first-line use of CBZ resulted in a median PFS of 7.1 months (n=6); second- and later-line use resulted in a median PFS of 2.6 months (n=8). Following progression (n=9), one patient received oral etoposide, one received palliative radiation therapy, the remainder (n=7) did not receive further anti-cancer therapy. Most common adverse events were nausea (50%, G1/2), mucositis (43%, G1), diarrhoea (36%, G1/2), hepatotoxicity (36%, G2) and fatigue (29%, G1). 5 (36%) pts required dose reduction to 40mg due to G2 hepatotoxicity and 4 (29%) pts due to multiple concurrent G1/2 toxicities (fatigue, mucositis, diarrhoea). There were no withdrawals or deaths due to toxicity.

Conclusion: Our real-world data showed that CBZ monotherapy has clinically meaningful activity in osteosarcoma and ES, with acceptable toxicities. Validation in larger cohorts is warranted.

(P 122) INTERVAL-COMPRESSED CHEMOTHERAPY FOR TREATMENT OF EWING SARCOMA IN ADULTS: A SINGLE INSTITUTION STUDY

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Objective: Ewing sarcoma is predominantly a pediatric malignancy, and its occurrence in adults (>18 years) is rare and associated with poorer outcomes. Given absence of adult-specific clinical trials, chemotherapy regimens in adults are derived from pediatric protocols. This study evaluates the impact of chemotherapy cycle number and interval on overall survival in adults with Ewing sarcoma.

Methods: We retrospectively reviewed adults with biopsy-confirmed Ewing sarcoma. Patients were stratified by age (≥ 40 as older, < 40 as younger). Chemotherapy was grouped by cycle count: >9 as prolonged, ≤ 9 as abbreviated. Outcome analysis included only those with localized disease.

Results: Of 95 patients, mean (range) was 36.9 (18-73) years at diagnosis. Overall, 44 (46.3%) patients were female and majority were White (55.8%). The most common primary Ewing sarcoma locations were abdomen/pelvis (67.3%) and extremities (38.5%). All were treated with chemotherapy: alternating vincristine-doxorubicin-cyclophosphamide and ifosfamide-etoposide cycles was the most common regimen (75.8%). Overall, 25 (26.3%) patients received surgery, 21 (22.1%) received radiation, and 47 (49.5%) received both. At presentation, 60 (63.2%) patients had localized disease. Median number of chemotherapy cycles received was 12: older patients received 8.5, while younger patients received 14. The 5-year overall survival (OS) rate was 75.0% and progression free survival (PFS) was 71.2%. There were no significant differences in OS or PFS with an age cutoff of 40 ($p = 0.63$, 0.59) nor number of chemotherapy cycles beyond 9 ($p = 0.99$, $p = 0.98$). There was a significant improvement in OS by use of every 2-week compared to 3-week chemotherapy (5-year OS 90% vs 66%, $p = 0.04$) but not for PFS (5-year PF 78% vs 66%, $p = 0.28$). On multivariate analysis including age, location, cycle count, and cycle frequency, only cycle frequency showed statistically significant effect on overall survival with every 3-week having worse outcomes (HR 6.3, $p = 0.02$) compared to 2-week chemotherapy.

Conclusion: In adult Ewing sarcoma patients, there was no difference in OS or PFS between patients who received more than 9 cycles of chemotherapy nor was there a difference in age >40 years. This suggests that adult Ewing's sarcoma patients may not need to complete all 14 cycles of standard chemotherapy.

(P 124) ISOLATED LIMB PERFUSION AS LIMB SALVAGING TREATMENT; A SINGLE CENTRE RETROSPECTIVE STUDY

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Objective: Isolated limb perfusion (ILP) is a limb-sparing treatment modality for patients with locally advanced extremity sarcomas. This retrospective study evaluates the clinical response rates to ILP over a 20-year period.

Methods: We reviewed a prospectively maintained database of Swedish patients who underwent ILP due to locally advanced extremity sarcomas. Clinical responses were categorized as complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD) based on post-treatment evaluations at three months.

Results: Between 2004 and 2024, 92 Swedish patients with locally advanced extremity sarcomas were identified. 14 patients were excluded (adjuvant treatments, non-perfused patients). A total of 78 patients (female $n=37$, male $n=41$) were response-rated, with a mean age of 59 years. All patients received Melphalan+TNF-alfa except one who was given only Melphalan. At follow up CR was observed in 17% ($n=13$), PR in 45% ($n=35$), SD in 28% ($n=22$), and PD in 10% ($n=8$).

Conclusion: ILP for locally advanced extremity sarcomas demonstrates high efficacy, with 62% overall response rate resulting in delayed or spared amputation. These findings support the continued use of ILP as a valuable therapeutic strategy in limb-sparing management of sarcoma.

(P 125) **TARGETING LCP1-MEDIATED METASTASIS IN CHONDROSARCOMA WITH OROXYLIN A**

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Objective: Chondrosarcoma, the second most common bone sarcoma, is chemo/radiotherapy-resistant. Standard treatment, en-bloc resection, is often ineffective for metastatic disease, highlighting an urgent need for new therapies. Our lab linked dysregulated actin-binding protein LCP1 to metastatic cell behavior. We aimed to validate LCP1 as a metastatic driver and assess LCP1 inhibition, specifically with oroxylin A, to suppress chondrosarcoma metastasis.

Methods: To confirm LCP1's role, two patient-derived high-grade metastatic chondrosarcoma cell lines (725 & 731) underwent CRISPR/Cas9 LCP1 knockout (KO), confirmed by western blot. LCP1 KO effects were assessed via in vitro assays (viability, wound healing, invasion). In vivo, metastatic mouse models compared lung tumor burden and bioluminescent signaling (14 weeks post-tail-vein injection) of luciferase-labeled wild-type (WT) vs. KO cells in immunodeficient mice. Pharmacologic inhibition with 50 μ M oroxylin A was assessed in WT cells via functional assays.

Results: In vitro, LCP1 KO significantly impaired chondrosarcoma cell migration and invasion without affecting viability. Scratch wound assays showed reduced motility (725: $p=0.0003$; 731: $p<0.0001$). Invasion assays showed reduced invasive potential (725: $p<0.001$; 731: $p<0.01$). In vivo, LCP1 KO tumors showed reduced bioluminescent signal ($p=0.0026$) and lower lung metastatic burden at 14 weeks. Oroxylin A similarly suppressed migration ($p<0.0001$) and invasion ($p<0.0001$) without affecting viability.

Conclusion: LCP1 is a key mediator of chondrosarcoma metastatic migration and invasion, in vitro and in vivo. Pharmacologic LCP1 inhibition with oroxylin A effectively mimicked LCP1 KO's anti-metastatic phenotype, crucially without impacting cell viability. LCP1 is a druggable driver of chondrosarcoma metastasis. Oroxylin A is a promising therapeutic candidate to prevent or delay metastatic disease progression.

(P 126) **SINGLE-CELL RNA SEQUENCING AND PROTEOMIC SPATIAL PROFILING REVEAL COMPLEX TUMOR MICROENVIRONMENT AND NOVEL IMMUNE INTERACTIONS IN CHONDROSARCOMA**

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Objective: Chondrosarcoma (CSA) is a primary bone malignancy with few therapeutic options. Discovery of new therapies is hampered by the paucity of data on the biology of CSA and its tumor microenvironment (TME). The TME significantly influences CSA progression, yet its cellular composition and critical intercellular interactions remain poorly understood. This study aimed to dissect the CSA TME using integrated single-cell and spatial approaches to identify novel interactions that could be leveraged for future therapeutic targets.

Methods: Fresh tumor tissues from 10 CSA patients (Grades 2, 3, dedifferentiated) underwent single-cell RNA sequencing (scRNA-seq). Computational analysis (including SCEVAN for tumor cell identification) defined cell populations. CellChat explored intercellular communication. Key findings were validated using PhenoCycler, a multiplexed spatial proteomics technique.

Results: scRNA-seq of CSA tumors revealed diverse tumor, cancer-associated fibroblast, and immune cell populations, plus osteoclast-like cells in dedifferentiated CSA. PhenoCycler spatial profiling validated these, visualizing Sox9+ tumor cells, T cells (CD4+, CD8+), dendritic cells, and monocyte/macrophages. Cell-cell interaction analysis inferred key tumor-immune interactions, including TNF signaling, MIF-CD74 axis, and SPP1-integrin signaling, pathways implicated in macrophage polarization, tumor progression, and immune evasion.

Conclusion: Chondrosarcomas exhibit a complex ecology of cellular phenotypes within their TME. Our combined single-cell and spatial proteomics approach provides an unprecedented atlas of the CSA cellular landscape and organization, detailing the tumor-immune interface. These findings, including the identification of specific intercellular signaling pathways, offer new insights into CSA pathobiology and identify specific cell populations and their interactions that could be exploited for novel therapeutic interventions.

(P 127) AN INTEGRATED CLINICAL GENOMIC AND TRANSCRIPTOMIC SUBGROUPING OF CENTRAL CHONDROSARCOMA

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Objective: Central conventional chondrosarcoma, a malignant cartilage-producing bone tumor, is the second most-common bone sarcoma. Chondrosarcomas are histologically graded, which

is so far the best predictor of survival. Early mutations in isocitrate dehydrogenase (IDH)-1 and -2 genes are frequent, leading to the production of the oncometabolite D-2-hydroxyglutarate, which affects DNA methylation, resulting in a preferred chondrogenic differentiation over osteogenic differentiation of mesenchymal stem cells, which are currently considered the precursor cells of chondrosarcoma. DNA methylation profiling has previously revealed distinct profiles between IDH mutant and wild-type chondrosarcomas, but the presence of further DNA methylation subgroups indicates that classification based solely on IDH status is too simplistic.

Methods: In this study, we aim to identify biological subgroups in a total of 116 chondrosarcomas by integrating clinical data, IDH mutation status, gene expression and genome wide loss of heterozygosity (gwLOH).

Results: Clinical associations were observed between several factors, including sex and histological grade, as well as tumor site and IDH mutation status. RNAseq and gwLOH confirmed the distinction between IDH wild-type and IDH mutant chondrosarcomas, where the number of chromosome arms affected by LOH was significantly higher in IDH wild-type tumors compared to IDH mutant tumors. However, no clear subgroups emerged within each IDH group. Further clustering on RNA expression of differentiation markers identified subgroups characterized by chondrogenic, osteogenic, resting chondrocyte, or dedifferentiated profiles. These different subgroups showed a specific clinical presentation and suggest different precursor cells.

Conclusion: Instead of a simple dichotomy between IDH mutant and IDH wild-type, our integrated approach highlight interconnected clinical, genomic, and transcriptomic patterns that offer a more nuanced view of chondrosarcoma biology and might potentially guide treatment stratification.

(P 128) ISOCITRATE DEHYDROGENASE 1 (IDH1) MUTATION TESTING IN THE PHASE 3 STUDY OF IVOSIDENIB VS PLACEBO IN IDH1-MUTANT CONVENTIONAL CHONDROSARCOMA (CHONQUER)

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Objective: Conventional chondrosarcoma (cCS) accounts for 85-90% of all CS cases. Mutations in isocitrate dehydrogenase 1 (IDH1) have been reported in approximately 50% of patients (pts) with cCS. Ivosidenib, an inhibitor of mutant IDH1 (mIDH1), demonstrated activity in a phase 1 trial that included pts with cCS. CHONQUER (NCT06127407) is an ongoing, phase 3, double-blind, randomized, placebo-controlled study to investigate the efficacy and safety of ivosidenib in pts with locally advanced or metastatic mIDH1 cCS. The frequency of mIDH1 in the first group of screened pts is reported here.

Methods: Key eligibility criteria include a histopathological diagnosis of cCS (all grades), locally-advanced or metastatic disease not eligible for curative resection; received 0 or 1 prior systemic treatment regimen; RECIST v1.1 progression/recurrence of disease; and mIDH1 confirmed by central testing with the Ion Torrent™ OncoPrint™ Dx Express Test. Eligible pts will be randomized to receive ivosidenib 500 mg once daily or placebo. The primary endpoint is progression-free survival.

Results: As of 17 June 2025, 105 pts had undergone mIDH1 central testing. 81 (77.1%) pts had an initial valid test result, of which 29 (35.8%) were positive for mIDH1 and 52 (64.2%) were IDH1 wildtype. 14 (58.3%) of the 24 pts with an initial invalid test underwent additional testing, of which 3 pts were positive for mIDH1 and 7 pts were IDH1 wildtype and 4 had repetitive invalid test result. Thus, 32/91 (35.2%) pts with a valid test result had a positive mIDH1 test result. Invalid test results were mainly due to insufficient DNA extraction from the sample which can be impacted by low cellularity or tissue amount, and improper fixation, decalcification or other tissue processing steps.

Conclusion: IDH1 testing has begun to identify pts with mIDH1 cCS for inclusion to CHONQUER. The frequency of mIDH1 in our cohort is lower than anticipated based on literature. Technical reasons, as well as a potential selection bias, may explain this discrepancy.

(P 129) HIJACKED FUEL: GLYCOGEN-DRIVEN METABOLIC SHIFTS IN IDH1-MUTANT CHONDROSARCOMA

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Objective: Conventional chondrosarcomas (CSA) remain therapeutically challenging. IDH1 mutations are common in CSA, but their metabolic consequences are not fully understood. This study investigates how alterations in glycogen metabolism and glycan biosynthesis relate to tumor grade, IDH status, metastasis, and survival.

Methods: We retrospectively reviewed 53 patients with primary CSA of bone (grades 2, 3, and dedifferentiated) diagnosed and treated at the University of Florida (2017–2024). Thirty-one cases with next-generation sequencing (NGS) data were analyzed using spatial metabolomics. Unstained slides from representative tumor blocks underwent MALDI mass spectrometry imaging. Glycogen and glycan levels were quantified and correlated with IDH1/2 status and clinical outcomes, including metastasis and survival.

Results: Distinct metabolic profiles emerged by tumor grade and IDH mutation status. Glycogen levels were highest in grade 3 and lowest in dedifferentiated CSA. Notably, IDH1-mutant tumors—unlike IDH2-mutant or wild-type tumors—exhibited elevated glycan levels despite reduced glycogen reserves, suggesting active glycogen utilization for glycan biosynthesis. The most striking metabolic divergence occurred between IDH1-mutant and wild-type tumors, driven by glycan enrichment in the former. Clinically, higher glycogen levels were associated with non-metastatic disease and survival, whereas lower glycogen and higher glycan levels were observed in patients with metastases or poor outcomes. These findings support a model in which glycogen is consumed to generate glycans that may promote dedifferentiation and progression in IDH1-mutant CSA.

Conclusion: IDH1-mutant CSA demonstrates a distinct metabolic phenotype marked by glycogen depletion and glycan accumulation. This reprogramming correlates with higher tumor grade, metastasis, and decreased survival. Spatial metabolomics may offer prognostic biomarkers and reveal metabolic vulnerabilities. This work lays the groundwork for future studies aimed at identifying targetable pathways within the glycogen-to-glycan axis, potentially opening new avenues for therapeutic intervention in CSA.

(P 130) INVESTIGATING LCP1-MEDIATED ONCOGENIC SIGNALING IN CHONDROSARCOMA METASTASIS

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Objective: Chondrosarcoma (CSA) is an aggressive malignancy of bone that lacks effective adjuvant therapies. There is an urgent need to identify mediators of metastasis for therapeutic targets. Prior work in our lab pinpointed lymphocyte cytosolic protein 1 (LCP1) as a driver of metastasis. While LCP1 is known for actin-bundling, some literature also suggests a role in oncogenic signaling, specifically JAK/STAT activation. This study aimed to investigate the role

of LCP1 in modulating JAK/STAT signaling in CSA cells.

Methods: To identify LCP1's key binding partners, a bio-proximity labeling assay was performed. A phospho-microarray assessed the dependence of LCP1 on the activation states of a panel of JAK/STAT proteins. Validation of STAT3 expression/activation in LCP1 wildtype and knockdown CSA cells was performed via ELISA with and without interleukin-6 (IL-6) stimulation. IL6-induced STAT3 nuclear localization in these cells was assessed via immunofluorescence. Statistical analysis was performed using GraphPad Prism software with ANOVA significance threshold set as $p \leq 0.05$.

Results: Bio-proximity labeling revealed that LCP1 interacts with key JAK/STAT signaling molecules—including STAT3 and IL6-associated receptor proteins. IL-6 induced STAT3 phosphorylation increased with reduced LCP1 ($p=0.02$). Immunofluorescence showed disrupted cytoskeletal architecture in the setting of LCP1 loss, with impaired IL-6 induced STAT3 nuclear localization.

Conclusion: This study demonstrated a novel role for LCP1 in oncogenic signal transduction. LCP1 interacts in close proximity to key components of interleukin mediated STAT activation—specifically, the absence of LCP1 disrupts cytoskeletal architecture and subcellular trafficking of STAT3. These findings further implicate LCP1 as a key regulator of oncogenic signaling, and highlight additional potential therapeutic targets for high grade CSA.

(P 131) GLUCOSE TRANSPORTER 1 (GLUT1) INHIBITION DECREASES THE GROWTH AND PROLIFERATION OF CHONDROSARCOMA

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Objective: The glucose transporter 1 (GLUT1) is upregulated in many cancer cells, facilitating increased glucose uptake and fueling rapid cell growth and proliferation, making it a potential therapeutic target. However, the expression and function of GLUT1 in chondrosarcoma remain unknown. We investigated the expression and function of GLUT1 in chondrosarcoma, with subsequent analysis of the therapeutic value of targeted GLUT1 in chondrosarcoma.

Methods: Immunohistochemistry was performed to evaluate GLUT1 expression on a chondrosarcoma tissue microarray. GLUT1 expression in three chondrosarcoma cell lines and patient tissues was evaluated by Western blot and immunofluorescence assay. GLUT1 siRNA and GLUT1 inhibitor BAY876 were applied to assess the effect of GLUT1 inhibition on chondrosarcoma cell growth, proliferation, and apoptosis. The effect of GLUT1 inhibition on clonogenicity and cell motility were examined using 2D clonogenic and wound healing migration assays. An ex vivo 3D cell culture model was performed to mimic the in vivo chondrosarcoma environment and to assess how GLUT1 inhibition affects the capacity of chondrosarcoma cells to form characteristic spheroids.

Results: Immunohistochemistry showed GLUT1 is expressed in both chondrosarcoma tumor tissues and cell lines. Silencing of GLUT1 with siRNA and reduction of GLUT1 signaling with the GLUT1 inhibitor BAY876 decreased chondrosarcoma cell growth and proliferation, while also inducing cell death in a time- and dose-dependent manner. Inhibition of GLUT1 makes chondrosarcoma cells more sensitive to doxorubicin. Targeting GLUT1 also reduced chondrosarcoma cell clonogenicity formation and spheroid growth.

Conclusion: Our study showed GLUT1 is expressed in chondrosarcoma, and, when inhibited, causes chondrosarcoma cell growth and proliferation to decrease. These results support GLUT1 as a potential target in chondrosarcoma therapy.

(P 132) MOLECULAR LANDSCAPE AND CLINICAL HETEROGENEITY OF BRAZILIAN CHONDROSARCOMAS: INSIGHTS FROM IDH, TERT, AND GENOME-WIDE ANALYSIS

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Objective: Chondrosarcomas (CS) account for ~30% of malignant bone tumors, with 90% being conventional subtype. Mutations in IDH1/IDH2 and the TERT promoter occur in ~50% and 23–60% of cases, respectively. These alterations have been linked to high-grade or metastatic tumors and poorer prognosis, though findings remain conflicting. Alone, they do not fully explain the clinical heterogeneity of CS. This study aims to characterize somatic genomic alterations associated with CS development and behavior.

Methods: We expect to include 100 Brazilian patients (pts) diagnosed with conventional CS between 2002–2024. Hotspot mutations in IDH1 (R132), IDH2 (R172), and TERT (c.-124C>T, c.-146C>T) were assessed via targeted next-generation sequencing (NGS). Associations between mutation status and clinical variables were evaluated using non-parametric tests, χ^2 or Fisher's exact test. Additionally, whole-exome sequencing (WES), methylation profiling, and optical genome mapping are underway in a subset of 30 pts with conventional or dedifferentiated CS showing extreme phenotypes (indolent vs. aggressive disease).

Results: This interim analysis includes 88 pts (54% male, 45% female), with median age 43 years (range: 11–81). Only 3.4% of patients had metastases at diagnosis, which increased to 20% during follow-up, and an additional 20% had local recurrences. IDH1 mutations were found in 33% of cases, IDH2 in 8%, and TERT in 32%. Co-occurring IDH+TERT mutations were seen in 19% and were significantly associated with higher tumor grade ($p=0.005$), older age ($p=0.002$; mean 55 vs. 45 years), and larger lesions ($p=0.008$; mean 14 vs. 9 cm). Somatic WES in 10 pts identified driver mutations in half of them, affecting genes such as TP53, PTCH1, KRAS, CDKN2A, CREBBP, and PBRM1. One case exhibited a high tumor mutational burden (40 mut/Mb).

Conclusion: One case exhibited a high tumor mutational burden (40 mut/Mb). Conclusion: Preliminary findings suggest lower frequencies of IDH1, IDH2, and TERT mutations in this Brazilian cohort compared to previous studies. Co-mutated IDH+TERT tumors were linked to features of poor prognosis. Continued analysis aims to refine the molecular landscape of CS

and identify therapeutic targets and prognostic biomarkers.

(P 133) INVESTIGATION OF COMBINING MDM2 INHIBITORS WITH DR5 AGONISTS FOR BONE SARCOMA TREATMENT

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Objective: Death Receptor 5 (DR5) is expressed on the surface of primary bone sarcoma cells. Enhanced activation of DR5 has been achieved with novel DR5 agonists (1). INBRX-109 is currently being investigated in a randomized, blinded, placebo-controlled, in patients with unresectable or metastatic conventional chondrosarcoma (ClinicalTrials.gov Identifier: NCT04950075), which is an area of unmet need (2). Combining agonists of DR5 with an MDM2 inhibitor (MDM2i) such as RG7388 could have enhanced effects. 1. Gamie Z, et al., Targeting Death Receptor 5 (DR5) for the imaging and treatment of primary bone and soft tissue tumors: an update of the literature. *Frontiers in molecular biosciences*. 2024;11:1384795. 2. Laitinen MK, et al., Enhancing surgical margins: A key to survival in pelvic chondrosarcoma. *European Journal of Surgical Oncology*. 2024:109491.

Methods: Western blotting for total protein (p53, p21, MDM2) and flow cytometry for surface DR5 expression after RG7388 exposure to the SJSA-1 osteosarcoma (known to have MDM2 amplification), SW1353 chondrosarcoma and HT1080 dedifferentiated chondrosarcoma cell lines. RT-PCR for DR5 transcript levels. Cytotoxicity assays following MDM2i +/- DR5 agonist application using Cell Counting Kit-8 (CCK-8) and Sulforhodamine B (SRB) assays.

Results: RG7388 increased DR5 mRNA transcript levels in the SJSA-1 osteosarcoma cell line. Total DR5 protein expression was enhanced in the SJSA-1 cell line. DR5 surface expression increased in all the cell lines. A dose-dependent cytotoxic effect was found in SJSA-1 and HT1080 cell lines, and increased caspase 3-7 for the SJSA-1 cell line.

Conclusion: RG7388 is cytotoxic and upregulates DR5 in bone sarcoma cell lines. Combining this agent with novel DR5 agonists may enhance cell killing and potentially survival outcomes. The phase 2 clinical trial of INBRX-109 in unresectable or metastatic conventional chondrosarcoma patients (ClinicalTrials.gov Identifier: NCT04950075) has an estimated primary completion date of September 2025. Depending on the result, it may be that characterisation of patients for tissue DR5 level of expression and combination therapy with an MDM2i is a potential line of investigation to be incorporated into further trials and help enhance the outcomes.

(P 134) INTEGRATIVE MICRORNA PROFILING IN CHONDROSARCOMA: TOWARD BIOMARKER DISCOVERY AND PROGNOSTIC SIGNATURE DEVELOPMENT

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Objective: Chondrosarcoma (ChSA) is an aggressive cartilaginous malignancy with poor response to conventional therapies and limited prognostic tools. MicroRNAs (miRNAs) are known regulators of gene expression in cancer, yet their role in ChSA remains poorly defined. This study aims to characterize global miRNA expression patterns in ChSA to uncover potential biomarkers and regulatory mechanisms linked to tumor progression.

Methods: Formalin-fixed paraffin-embedded (FFPE) tumor and adjacent normal tissues were collected from 40 ChSA patients. Total RNA was extracted, and small RNA sequencing was performed to profile miRNA expression. Differential expression analysis using DESeq2 identified significantly altered miRNAs ($|\log_2FC| > 1.5$, p-adjusted < 0.05). Bioinformatic tools, including TargetScan and miRTarBase, were applied for target gene prediction and pathway enrichment analysis. Future plans include expanding the cohort to 60 cases, stratifying by tumor grade, and integrating clinical outcome data.

Results: Distinct miRNA expression patterns differentiated tumors from normal cartilage. Dysregulation was prominent in the miR-7a-345 and miR-7a-100-122 networks. miR-4488 was among the most upregulated ($\log_2FC > 5$, $p < 0.05$). Over 50 miRNAs showed strong differential expression. Upregulated miRNAs included miR-100, miR-134, miR-140, miR-199, miR-214, miR-455, and miR-98, while miR-139, miR-142, miR-150, miR-183, miR-223, miR-486, and miR-744 were downregulated. Target gene analysis highlighted oncogenic pathways involving MYC, BCL2, NCOA3, and MTUS1.

Conclusion: This study provides the first comprehensive miRNA expression profile in ChSA, revealing dysregulated miRNA networks associated with tumor biology. These findings lay the groundwork for identifying clinically relevant miRNA biomarkers for diagnosis, prognosis, and therapeutic targeting in Chondrosarcoma.

(P 135) EXPLORING THE ROLE OF CLUSTER OF DIFFERENTIATION 44 IN CHONDROSARCOMA

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Objective: Chondrosarcoma is the most common type of primary bone sarcoma in adults with a high risk of local recurrence and metastasis. Most chondrosarcomas are resistant to chemotherapy and radiotherapy meaning surgery is the only effective treatment option for the majority of patients. Therefore, new therapeutic targets are required. Cluster of differentiation 44 (CD44) is a transmembrane protein and is the key receptor for hyaluronic acid. When hyaluronic acid binds to CD44, pathways are regulated which lead to increased cancer cell proliferation, migration and invasion. CD44 has also been shown to be overexpressed in several tumour types. The main objectives of this study were to examine the expression of CD44 across chondrosarcoma patient tissue and to determine the role that CD44 has in chondrosarcoma cell invasion.

Methods: Chondrosarcoma tissue from 46 patients was immunostained for CD44 and the H-score was measured. Survival analysis using Kaplan-Meier analysis and multivariate analysis using Cox regression was then undertaken to determine the effect that CD44 had on the overall survival (OS) and event-free survival (EFS) of the patients. Clustered regularly interspaced short palindromic repeats (CRISPR) – CRISPR associated protein 9 (Cas9) gene editing was used to knockout CD44 from HT1080 dedifferentiated chondrosarcoma cells. To assess the effect of the knockout on the invasion of the cells, a spheroid invasion assay was used. CD44 Wild type (WT) and knockout (KO) spheroids were encased in a collagen hydrogel or a collagen hydrogel with hyaluronic acid added for 72 hours.

Results: Staining of the patient tissue for CD44 showed that CD44 expression was increased in the grade 2 and 3 chondrosarcoma tissues compared to grade 1 ($p < 0.05$). Multivariate analysis using Cox regression showed that CD44 expression was significant ($p < 0.01$) in contributing to reduced OS and EFS of the patients. The results of the spheroid invasion assay showed that the CD44 KO cells invaded less than the WT cells when encased in collagen ($p < 0.001$) and collagen with hyaluronic acid added ($p < 0.0001$).

Conclusion: The results obtained in this study suggest that CD44 is key for the invasion and progression of chondrosarcoma and could therefore be a future therapeutic or theragnostic target.

(P 136) ESTROGEN HAS A PROTECTIVE EFFECT ON CHONDROSARCOMA GROWTH IN VITRO AND IN VIVO

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Objective: Chondrosarcoma, the most common primary bone malignancy in adults, accounts for approximately 25% of primary bone cancers. Surgical resection of localised tumours with adequate margins remains the primary treatment option, underscoring the need for novel therapeutic strategies. Chondrosarcoma affects men more than women (ratio 1.5:1) and recent clinical data suggests that women have improved survival compared to men of comparable age. This effect diminishes after the age associated with menopause suggesting that estrogen may have a protective effect in chondrosarcoma. Here, we present novel data that shows that estrogen is indeed protective in chondrosarcoma and that this effect is largely mediated via the G-protein coupled estrogen receptor (GPER).

Methods: We validated the expression of all three estrogen receptors: ER α , ER β , and GPER in both male (JJ012) and female (SW1353) chondrosarcoma cell lines via qPCR and western blotting. To understand which receptors predominantly mediate the protective effect of estrogen, we used selective ligands for each ER receptor subtype, and measured dose-dependent changes in cell proliferation. For the in vivo study, 7-week-old female NOD-scid gamma mice were subjected to ovariectomy (OVX), to mimic post-menopausal status, or sham-operated. One-week post-surgeries, mice were injected with 2.5e5 luciferase-expressing SW1353 cells subcutaneously and tumour burden monitored via bioluminescence imaging.

Results: GPER-selective ligand G1 inhibited cell proliferation of JJ012 (IC50 6.65e-7M) and SW1353 (IC50 3.54e-7M) cells over 72 hours compared to vehicle control. In contrast, propylpyrazoletriol (PPT; ER α -selective) and diarylpropionitrile (DPN; ER β -selective) had minimal effects. For the in vivo study, at day 31, higher tumour burden was observed in the OVX mice compared to the sham controls (1.53e6 vs 6.76e5; P< 0.0001). Further studies are required to validate if these effects are also mediated predominantly via GPER.

Conclusion: These preliminary data indicate that estrogen plays a protective role in the progression of chondrosarcoma and are consistent with the clinical findings, and that selectively targeting GPER may have therapeutic potential in chondrosarcoma.

(P 137) GENOMIC ALTERATIONS IN RARE CARTILAGINOUS TUMOR SYNDROMES ASSOCIATED WITH CHONDROSARCOMA DEVELOPMENT

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Objective: Chondrosarcomas (CS) may arise de novo or secondarily from benign cartilaginous lesions, frequently associated with syndromes such as Ollier disease (OD), Maffucci syndrome (MS), and hereditary multiple exostoses (HME). OD and MS are rare, non-hereditary tumor predisposition syndromes caused by post-zygotic somatic mutations, primarily in IDH1 and IDH2, and carry a high risk of malignant transformation to CS (40% and >50%, respectively). In contrast, HME is a rare autosomal dominant disorder caused by germline pathogenic variants in EXT1 or EXT2, with a lower risk of malignization (~3.9%). This study aimed to characterize germline and somatic alterations in patients (pts) with these syndromes, correlating molecular data with clinical phenotype and CS development.

Methods: A cohort of 168 CS cases from A.C.Camargo Cancer Center was analyzed. Clinical data were extracted from electronic records, and germline data for 23 pts were available from a previous study (Carvalho et al., 2023 – PMID: 37536918). Tumor samples (fresh or FFPE) were analyzed for IDH1 (R132) and IDH2 (R172) mutations via targeted next generation sequencing; negative cases proceeded to OncoPrint Comprehensive Assay Plus (517 genes) or whole-exome sequencing.

Results: Ten pts were identified with OD (n=3), MS (n=2), or HME (n=5). Median age of CS diagnosis was 41 years, 50% were female, 5/10 had disease recurrence, with 20% developing metastasis. Among HME cases, 3 had pathogenic EXT2 variants and 2 in EXT1, and 4/4 tested

tumors were negative for IDH mutations. IDH1 R132 was found in 2/3 OD cases (VAF 12% and 39%), and IDH2 R172 in one (VAF 5%). One MS patient had IDH1 R132 (VAF 5%), and one was negative. Extended genomic analysis is ongoing in IDH-negative cases.

Conclusion: Most patients showed somatic and/or germline alterations in genes known to drive these syndromes, reinforcing their role in tumor predisposition, mosaicism, and malignant transformation to CS. Our findings contribute to the genomic characterization of rare cartilaginous tumor syndromes and will help to expand our understanding of the molecular mechanisms underlying their development and malignant progression.

(P 138) A MULTI-INSTITUTIONAL ARCHIVE AND DEEP LEARNING PIPELINE FOR QUANTIFYING CHONDROSARCOMA COMPOSITION

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Objective: Chondrosarcomas are often resistant to chemotherapy and radiation, and survival in the setting of metastatic disease is poor. Histologic grade guides management, but clinical decisions are impacted by high interobserver variability among pathologists and the limited prognostic power of grade alone. To address this, we developed a deep-learning pipeline that quantitatively describes chondrosarcoma composition on whole-slide images (WSIs).

Methods: We conducted a multicenter, retrospective study that included tumors from 230 patients. Patient survival by tumor grade and dedifferentiation status was evaluated with Kaplan–Meier (KM) analysis. Our computational workflow comprised the following steps: (1) partitioning each WSI into 225×225-pixel tiles; (2) background removal; (3) stain normalization; (4) tile feature extraction; (5) K-means clustering to identify visual phenotypes; (6) training a random-forest classifier to recognize those phenotypes; and (7) quantifying phenotype frequencies in new WSIs. Pipeline development used an initial subset of 22 WSIs from unique patients, and pipeline evaluation used 10 WSIs withheld during development.

Results: On KM analysis histologic grade and dedifferentiation status were significantly associated with overall survival. K-means clustering identified 10 visual phenotypes, and the random-forest model classified each with over 93% accuracy. Clusters represented normal bone elements (cluster 0 – bone, and cluster 3 –marrow) as well as five distinct tumor clusters (clusters 2, 4, 7, 8, and 9). Withheld WSIs were processed, tiles were classified, and a map of feature percentages was generated. Clusters with the highest incidence and average representation within this subset (clusters 4, 7) were tumor features.

Conclusion: Our results show that automated deep-learning analysis of WSIs may be able to objectively characterize chondrosarcoma histology. Future work will involve assessing the accuracy of the system relative to manual annotation, scaling the approach to the full cohort, refining feature extraction, and assessing correlations between computational phenotypes and

clinical outcomes.

	Cluster (%)									
ID	0	1	2	3	4	5	6	7	8	9
1	12.0	0.6	0	2.8	0	0	7.5	4.8	72.3	0
2	8.5	2.4	0	0	49.1	0.5	36.5	3.0	0	0
3	6.1	0.4	0	0	52.9	0.0	34.4	6.2	0	0
4	0.6	0.1	0	0	6.0	1.1	92.2	0.1	0	0
5	9.2	0	20.6	16.5	0	53.6	0	0	0	0
6	18.8	41.5	0.1	0	22.7	0	15.4	0.9	0.7	0
7	0	0	0	0	0	0	2.2	97.8	0	0
8	2.6	3.1	48.0	0	0	45.3	0	0	0	1.1
9	30.7	10.8	0	0.1	51.7	0	4.5	0.3	2.0	0
10	0	0	6.7	0	0	86.7	0	0	0	6.6
Mean	8.9	5.9	7.5	1.9	18.2	18.7	19.3	11.3	7.5	0.8
St Dev	9.8	12.9	15.6	5.2	23.8	31.5	29.1	30.5	22.8	2.1

(P 139) IMMUNOGENOMIC PROFILING OF CHONDROSARCOMA REVEALS DISTINCT IMMUNE PHENOTYPES AND PROGNOSTIC MUTATIONS

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Objective: Chondrosarcomas (ChS) are considered “cold” tumors due to poor immunotherapy responses, and their immune and molecular characteristics remain poorly understood given the lack of effective therapies. We aimed to identify distinct immune phenotypes and key genetic alterations correlating with grade, outcomes, and potential therapeutic targets.

Methods: Ninety-nine ChS patients underwent immune (tumor microarray immunohistochemistry with 20 immune-cell and checkpoint markers) and genomic profiling (targeted sequencing of 409 genes for somatic mutations and tumor mutational burden). Unsupervised clustering and multivariate Cox analysis were used to define immune phenotypes

and prognostic factors.

Results: Clustering of immune markers revealed three phenotypes (“cold”, “hot”, “intermediate”) that differed by histologic grade ($p < 0.001$), with high-grade tumors shifting from “cold” to predominantly “hot” profiles. Molecular analysis showed low TMB (~2 mutations/Mb) and frequent mutations in IDH1/2 (~40%) and TP53 (~15%), enriched in high-grade tumors, and ARID1A (~12%) mutations predominantly in grade 2–3. High-grade tumors had greater genomic complexity. Despite increased immune infiltration, the hot phenotype was associated with worse survival; in multivariate analysis, hot (and intermediate) tumors had ~3-fold risk of death, with IDH1 mutation conferring a similar hazard. High intratumoral CD3+ T-cell density and PD-L1 expression were also linked to worse prognosis.

Conclusion: High-grade ChS harbor more mutations and immune infiltrates yet confer poorer survival, implying an immunosuppressive microenvironment. IDH1/2 mutations and a “hot” immune phenotype define a subset with poor prognosis. This supports exploration of combined IDH-targeted therapy with immune checkpoint blockade to improve outcomes.

(P 140) **REFINING PRE-SURGICAL ASSESSMENT OF LONG-BONE CHONDROSARCOMA THROUGH THE RADIOLOGIC AGGRESSIVENESS SCORE**

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Objective: An accurate pre-surgical diagnosis of resection-grade (grade 2, 3 and dedifferentiated) versus low-grade chondrosarcoma is crucial for treatment decision-making. Historically, biopsy was the gold standard for grading chondrosarcomas, but recent studies suggest radiologic methods may be more accurate. This study sought to externally validate the Radiologic Aggressiveness Score (RAS) in characterizing cartilage tumors and guiding treatment.

Methods: Seventy patients who underwent resection of primary intraosseous chondrosarcoma in long bones from 2000 to 2024 were reviewed in a retrospective analysis. Inclusion required the presence of preoperative X-rays and advanced imaging. Nine radiologic parameters for characterizing chondrosarcoma were analyzed, with the presence of each parameter earning one point. Resection-grade lesions were defined by a total RAS of $\geq 4/9$ points. Preoperative biopsy grade was also recorded. Final surgical pathology grades were compared to preoperative RAS and biopsy grades to determine each method’s accuracy in distinguishing low-grade from resection-grade tumors.

Results: A RAS of ≥ 4 was significantly more sensitive (92% vs. 57%; $p < 0.001$) and accurate (90% vs. 65%; $p = 0.002$) in determining resection-grade chondrosarcoma when compared to biopsy. Specificity did not differ significantly between groups. Six cases were inaccurately graded by biopsy but correctly by RAS, while none were inaccurately predicted by RAS but correctly by biopsy. Mean RAS scores were 1.6/9 for low-grade and 5.9/9 for resection-grade tumors ($p < 0.001$). When controlling for potentially confounding variables, the parameters most associated with prediction of resection-grade histology were complete cortical erosion,

periosteal reaction, and soft tissue extension ($p < 0.01$).

Conclusion: The RAS is a highly sensitive and accurate standardized tool for preoperatively grading long-bone chondrosarcomas. It outperforms biopsy in signaling tumors that are resection-grade, decreasing the potential for malignant tumors to be left untreated. Further studies should evaluate the potential for RAS use in non-long bone chondrosarcomas and whether certain parameters signal worse clinical outcomes.

(P 141) A RETROSPECTIVE ANALYSIS OF THE BIRMINGHAM ATYPICAL CARTILAGE TUMOUR IMAGING PROTOCOL (BACTIP) IN MANAGING CENTRAL CARTILAGE TUMORS OF THE LONG BONES

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Objective: Central cartilage tumors (CCT), which include enchondromas and chondrosarcomas, present a diagnostic and therapeutic challenge. It is critical for providers to accurately differentiate between aggressive versus benign tumors in deciding whether surgery or surveillance is necessary. Misclassification can lead to unnecessary or delayed treatment. This study sought to externally validate the Birmingham Atypical Cartilage Tumour Imaging Protocol (BACTIP) in advising treatment for CCTs.

Methods: This was a retrospective review of 94 patients presenting with CCT in the long bones between 2001 and 2024 at a tertiary cancer center. Inclusion required preoperative imaging and either surgical pathology, if resected, or a minimum of 3 years of follow-up imaging, if surveilled. CCTs were divided into classes of A, B and C for increasingly severe levels of endosteal scalloping, and into types I or II based on the length of tumor (< 4 cm or > 4 cm) or type III if there were any aggressive features (periosteal reaction, cortical destruction, soft tissue involvement or medullary expansion). BACTIP category was compared to surgical pathology or follow-up imaging to determine the efficacy of its guidelines for managing CCTs.

Results: Malignancy was present in 47 (50%) of CCTs. Applied to this cohort, BACTIP identified all malignant tumors with 100% sensitivity and 64% specificity for specialist referral. Only type III CCTs were found to be malignant. 47/54 (80%) of Class C tumors were found to be malignant, significantly greater than class B (13%) or A (8.3%) tumors ($p < 0.001$), with there being no significant difference between classes B and A. ROC analysis demonstrated that aggressive imaging features contributed significantly more to predicting malignancy than endosteal scalloping proportion (AUC 0.90 vs. 0.84, $p = 0.046$) or tumor length (AUC 0.90 vs. 0.73, $p < 0.001$).

Conclusion: BACTIP is a valid, highly sensitive tool for the characterization of CCT risk. The model's specified aggressive features more effectively predict malignancy compared to endosteal scalloping and tumor length, albeit combining all factors provides maximal accuracy.

(P 142) ARE THERE INDEPENDENT PREDICTORS OF DEDIFFERENTIATED CHONDROSARCOMA ON MAGNETIC RESONANCE IMAGING? A MULTIVARIATE ANALYSIS

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Objective: Dedifferentiated chondrosarcoma (DDCS) is an aggressive subtype of central cartilage tumor (CCT) requiring early, accurate diagnosis for effective surgical management. While radiologic protocols often differentiate benign from malignant CCTs, the ability of specific imaging features to reliably identify DDCS remains uncertain. This study aimed to identify independent imaging predictors of DDCS to enhance diagnostic accuracy and guide clinical decisions.

Methods: From 2001 to 2024, 69 patients who had preoperative imaging before CCT resection at a tertiary cancer center were retrospectively reviewed. Nine binary imaging features were assessed: pathologic fracture, endosteal scalloping of >2/3 circumference and length, medullary expansion, complete cortical breakage, periosteal reaction, cortical thickening, marrow edema, and soft tissue involvement. Surgical pathology confirmed the presence or absence of DDCS. Multivariate logistic regression evaluated each feature's independent prediction of DDCS, excluding complete cortical breakage due to collinearity with other cortical-integrity variables.

Results: Lesions included 23 DDCS, 44 conventional chondrosarcomas, one mesenchymal chondrosarcoma, and one enchondroma. No significant age or sex differences existed between DDCS and non-DDCS groups. Of the eight included variables, only bone marrow oedema significantly independently predicted the presence of DDCS. This held with (OR=7.3, p=0.019) or without (OR=9.3, p=0.007) the inclusion of complete cortical breakage in the multivariate regression. McFadden's pseudo-R² (0.399) showed the model explained substantial variability in DDCS presence. Bone marrow edema alone had an area under the ROC curve (AUC) of 0.78, while the full model achieved slightly better discrimination (AUC=0.88).

Conclusion: Marrow oedema identified on preoperative imaging is a strong independent predictor of dedifferentiated chondrosarcoma among central cartilage tumors, serving as a key differentiator for clinicians, with diagnostic accuracy further enhanced by incorporating additional imaging features.

(P 143) IMPACT OF SURGICAL MARGINS IN CHEST WALL CHONDROSARCOMAS: A CANSARCC STUDY

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Objective: Chest wall chondrosarcomas necessitate en bloc resection to achieve local control due to their inherent resistance to adjuvant therapies. The thoracic surgery literature commonly recommends a 5 cm surgical margin for these tumors, which exceeds the margins typically employed for chondrosarcomas of the extremities or pelvis. The association between margin width, local recurrence, and overall survival in chest wall chondrosarcoma remains poorly defined. We assessed the influence of surgical margin status on local recurrence and survival outcomes in patients undergoing resection of chest wall chondrosarcomas.

Methods: Patients undergoing surgical resection of chest wall chondrosarcomas between 2000-2024 from 9 institutions were reviewed. Demographic, tumor characteristics, surgical details, post-resection overall (OS) and disease-free survival (DFS) data were retrospectively collected from the CanSaRCC (Canadian Sarcoma Research and Clinical Collaboration) database. Overall and DFS were estimated using Kaplan-Meier curves and multivariable cox regressions were performed to evaluate predictors of survival and recurrence.

Results: 147 patients were included with 59 (40%) patients with low grade tumors and 82 (56%) had intermediate-high grade tumors. Negative margin surgery was achieved in 80% of cases, 12% had microscopic positive (R1) margins, and 2% had grossly (R2) positive margins. OS and DFS were 90% ($\pm 3.2\%$) and 81% ($\pm 4.1\%$) at 2 years and 77% ($\pm 4.8\%$) and 68% ($\pm 5.2\%$) at 5 years, respectively. Higher tumor grade and older age were independent predictors of worse overall survival while surgical margins did not impact survival. Higher grade tumors were predictive of local recurrence whereas overall margin and bony margin width did not predict local recurrence rates.

Conclusion: Contrary to conventional surgical principles advocating wider resections in the chest wall, wider margins did not independently influence overall survival or local recurrence rates. These findings suggest that aggressive attempts to achieve wider margins may not confer additional benefit and should be carefully weighed against the morbidity of more extensive resections in this anatomically complex region.

Patient Characteristics

Eligible Patients (n=147)	
Sex	
• Female	51
• Male	96
Age at diagnosis (SD)	53.5 (15)
Grade	
• I	59
• II	69
• III	13
• unknown	6
Tumor Size	
• < 5cm	52
• 5-10cm	67
• >10cm	24

(P 144) THE RISK OF PATHOLOGICAL FRACTURES AFTER INTRALESIONAL CURETTAGE IN ATYPICAL CARTILAGINOUS TUMOURS: A RETROSPECTIVE COHORT STUDY

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Objective: Atypical cartilaginous tumors (ACT) are locally aggressive, cartilage-producing neoplasms, traditionally classified as chondrosarcoma grade 1. They exist within the spectrum of cartilaginous tumors, between enchondroma and high-grade chondrosarcoma. The diagnosis of ACT remains challenging, with limited consensus on optimal treatment. Despite ongoing debate, intralesional curettage is commonly performed, though the risk of pathological fractures post-treatment remains a significant complication. This study aims to investigate the impact of cortical window design on fracture risk following curettage for ACT in the distal femur.

Methods: We compared two types of cortical windows: smooth oval (low stress riser) and windows with sharp or predrilled rounded corners (high stress riser). A retrospective cohort of 153 patients treated between 2000 and 2020 was included. Fracture occurrence was recorded, and logistic regression models were used to assess the relationship between surgical technique and fracture risk. We corrected for void filling and tumour size.

Results: Our findings revealed no significant difference in fracture risk between the two types of cortical windows (OR= 1.62, 95% CI:0.66-3.96). However, the use of cement as a void filler significantly increased fracture risk, with odds ratio (OR) approximately five times higher than those using bone chips (OR=5.00, 95% CI:1.81-13.88). Tumor size (cm) was also associated with fracture risk (OR 1.31, 95% CI:1.04-1.63).

Conclusion: The study highlights the importance of choosing appropriate void filling material, with bone chips offering a lower fracture risk compared to cement. These results suggest that optimizing surgical techniques, particularly the choice of filling material, may reduce post-curettage fracture risk in ACT treatment.

(P 145) PATHOLOGIC FRACTURE IN CHONDROSARCOMA OF LONG BONES: A RETROSPECTIVE COHORT STUDY

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Objective: Chondrosarcoma poses a unique challenge to treat, as this malignancy is characterized by resistance to both radiation and chemotherapy. In the extremities, cases of chondrosarcoma are prone to pathologic fractures, which can further complicate treatment. However, evidence is limited exploring the relationship between pathologic fractures and prognosis in long bone chondrosarcoma patients. This study investigates the impact of pathologic fractures on surgical complications, recurrence rates, and overall outcomes in patients with chondrosarcoma of long bones.

Methods: A retrospective review was performed of 82 cases from 1999 to 2024 with chondrosarcoma of long bones who had undergone surgical resection of their tumor. Long bone chondrosarcoma patients were excluded if they did not receive oncologic surgical intervention or if they were lost to follow-up within one year of surgery for an unknown reason. Univariate and multivariate comparisons were made between patients with and without pathologic fracture regarding surgical and oncologic outcomes.

Results: 15 patients sustained a pathologic fracture (18%). There was no statistical difference noted in patient characteristics between patients who did and did not have a pathologic fracture. Pathologic fracture was associated with higher grade and dedifferentiated histology. There was no difference in margin status at time of definitive resection between patients with and without fracture. Pathologic fracture was associated with a higher risk of any relapse ($p < 0.001$), local recurrence ($p < 0.001$) and metastasis ($p < 0.001$), even when controlling for low grade histology. Disease specific survival was significantly worse for patients with pathologic fracture (5-year survival 20% vs. 75%, $p < 0.001$). When controlling for potentially confounding variables, histologic grade was independently associated with risk of metastasis while pathologic fracture was independently associated with risk of local recurrence.

Conclusion: Pathologic fractures in chondrosarcoma of the long bones are associated with poorer oncologic outcomes and appear to be an independent predictor of local recurrence.

(P 146) LOCALISED CHONDROSARCOMA PERIOPERATIVE TREATMENT: REAL-WORLD OUTCOMES AND CHALLENGES ACROSS HISTOLOGIC SUBTYPES

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Objective: Surgical resection remains the cornerstone of chondrosarcoma (ChS) treatment; however, the role of chemotherapy (CHT) and radiotherapy (RT) is less well defined, particularly in high-grade and rare variants. We aimed to evaluate the impact of multimodal treatment (MDT) in a perioperative setting in marginally resectable chondrosarcoma (ChS); and describe perioperative complications of MDT treatment.

Methods: We retrospectively analysed patients(pts) with a confirmed diagnosis of localized ChS treated between 1998 and 2025. Median overall survival (mOS) and median relapse-free survival (mRFS) were calculated with Kaplan-Meier and prognostic factors were assessed with a log-rank test. Surgery complications were described with Clavien-Dindo scale (C-D).

Results: 27 ChS pts were enrolled in the study with dedifferentiated (DD)ChS in 9 pts (33.3%), mesenchymal (M)ChS in 8 (29.6%), and conventional (C)ChS in 8 (29.6%). Primary ChS tumors were most often located in lower extremity (n=13; 48.1%), and trunk (n=7; 25.9%). CHT was administered as neoadjuvant in 16 pts (59.3%), adjuvant - in 17 pts (63%). Neoadjuvant RT was administered in 6 pts (22.2%) and as adjuvant in 4 (14.8%). We performed surgery with reconstruction in 16 pts (59.3%), endoprosthesis implantation in 7 pts (25.9%), while in 11 pts (40.7%) limb amputation was necessary. R0 margins were achieved in 19 pts (70.4%), R1- in 7 (25.9%), and R2 in 1 (3.7%). In the entire cohort, mRFS was 10.6 months(mo) with the 3- and 5-year RFS rates of 36% and 22.5%, respectively. mOS was 40.8 mo (3-; 5-year OS: 50.4%, 40.8%). Only 4 pts (14.8%) had an uneventful postoperative course. We reported C-D complications of Grade I-II in 14 pts (51.9%) and ≥ Grade IIIA in 5 pts (18.5%).

Conclusion: Localised ChS remains a therapeutically challenging malignancy, with modest long-term survival and high relapse rates despite multimodal treatment. Achieving R0 surgical margins was feasible in the majority of pts and remains critical for disease control. Postoperative complications were frequent, with a significant proportion of pts experiencing moderate to severe surgical morbidity. There is an urgent need for optimised surgical strategies and the development of effective systemic therapies for ChS.

(P 147) CONVENTIONAL AND DEDIFFERENTIATED CHONDROSARCOMA; IS ENCHONDROMA THE PRECURSOR LESION?

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Objective: Chondrosarcoma is the second most common primary malignant bone tumor after osteosarcoma. It is subclassified into conventional, dedifferentiated, clear cell, and mesenchymal types. Most (85%) chondrosarcomas are conventional hyaline/myxoid variants and 10% are dedifferentiated. Traditionally, conventional chondrosarcoma has been considered to develop de novo except in rare instances. We analyzed the prevalence of enchondroma in patients with conventional and dedifferentiated chondrosarcoma to determine the relationship between these neoplasms.

Methods: We identified 72 cases of intramedullary conventional and dedifferentiated chondrosarcoma from patients who underwent resection from our archives between 2014-2025. The electronic medical records were evaluated for demographic data and imaging findings. The histopathologic materials were reviewed for the presence of underlying enchondroma within the chondrosarcoma.

Results: There were fifty-seven cases (79%) of conventional chondrosarcoma (including three cases designated atypical cartilaginous neoplasm), and fifteen (21%) dedifferentiated chondrosarcomas. There was a slight male predominance (M: F=1.1). Patient's ages ranged from 22 to 85 years (mean=58). Pelvic bones were the most frequently affected (27%) followed by the femur (20%), chest wall (rib/sternum 18%), humerus (16%), scapula (8%), tibia and fibula (5%), vertebrae (3%), and phalanx/metatarsal (3%). The size of the neoplasms ranges from 1.6 cm to 23 cm (median=6.9 cm). Thirty-three patients (46%) had a solitary enchondroma encompassed by chondrosarcoma. Among these, twenty-four (73%) were conventional and nine (27%) were dedifferentiated chondrosarcomas. The femur and humerus were the most common locations (36% and 24%, respectively) followed by pelvic bones (18%), and phalanx/metatarsal bones, tibia, scapula and vertebra (4% each). Three patients (4%) had enchondromatosis.

Conclusion: The prevalence of enchondroma in conventional and dedifferentiated chondrosarcoma is under-recognized in the literature. We demonstrate that nearly half of patients with conventional chondrosarcoma and dedifferentiated chondrosarcoma have an associated enchondroma. This observation is evidence that enchondroma is a precursor lesion that may undergo biological transformation into conventional and dedifferentiated chondrosarcoma.

(P 148) CHARACTERISTICS AND OUTCOMES OF CHONDROSARCOMA PATIENTS TREATED WITH PROTON THERAPY: A SYSTEMATIC REVIEW OF PUBLISHED SERIES

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Objective: Chondrosarcoma is a rare malignant cartilage tumor that typically arises in the appendicular skeleton and pelvis, but can also involve the spine and skull base. It is notably resistant to chemotherapy and conventional photon-based radiotherapy (RT). While surgery remains the mainstay of treatment, RT plays a key role when complete resection is not feasible or when margins are close or positive. Proton therapy (PT), with its superior dose conformity, allows for high-dose delivery while sparing adjacent critical structures and is increasingly used in this setting. The objective of this study is to systematically evaluate patient characteristics and clinical outcomes associated with proton therapy for chondrosarcoma, with the goal of informing optimal treatment strategies and guiding future research directions.

Methods: We conducted a review of published series reporting outcomes in chondrosarcoma patients treated with PT. Data on patient demographics, tumor site, histologic grade, radiation dose, toxicity profiles, and clinical outcomes were extracted and analyzed.

Results: Most cohorts included adults with skull base tumors, predominantly grade 1 or 2, treated postoperatively with PT at median doses of 66-74 Gy (RBE or CGE). For skull base chondrosarcoma, reported 3-year local control (LC) rates ranged from 86% to 100%, and 5-year LC rates varied from 75% to 94%. Five-year overall survival (OS) rates, where reported, ranged from 84% to 100%. Outcomes for spinal and sacral tumors are more variable and generally lower. Severe late toxicities are uncommon, with sensorineural hearing loss and temporal lobe necrosis being the most notable adverse events.

Conclusion: PT provides excellent LC and OS outcomes for chondrosarcoma, particularly in skull base tumors treated postoperatively. Its favorable toxicity profile supports its continued use as standard of care in anatomically challenging cases. Further studies are needed in non-skull base and pediatric populations.

(P 149) SURGICAL TEXTBOOK OUTCOMES IN PATIENTS DIAGNOSED WITH CHONDROSARCOMA

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Objective: To characterise clinicopathological features, surgical treatment patterns, and survival outcomes in patients(pts) diagnosed with chondrosarcoma(ChS), and to determine complications following primary ChS resection.

Methods: We retrospectively analysed ChS pts treated at reference centre over the last 25 years. Median relapse-free survival (mRFS) and median overall survival (mOS) were analysed. We used the Kaplan-Meier to calculate the median values of relapse-free survival (mRFS) and overall survival (mOS); the log-rank test was used to assess potential prognostic factors; and Clavien-Dindo scale - to classify surgical complications.

Results: 205 ChS pts were included (median age: 51.84 years; 114 male (55.6%), 91 female (44.4%)). Histological subtypes included: conventional (CChS; n=134, 65.4%), secondary peripheral (SChS; n=25, 12.2%), dedifferentiated (DDChS; n=21, 10.2%), mesenchymal (MCS; n=12, 5.9%). The histologic grades were: G1 (n=83, 40.5%), G2 (n=65, 31.7%), G3 (n=38, 18.5%) and Gx (n=13, 6.3%). R0 resection was achieved in 132 pts (64.4%), R1 in 45 pts (22%) and R2 in 19 pts (9.3%). Amputation was performed in 22 cases (10.7%) - mostly due to primary tumour volume (21/22). 110 pts (53.7%) underwent resection with reconstruction, while endoprosthesis was used in 57 pts (27.8%) and curettage in 13 pts (6.3%). Hemipelvectomy was performed in 37 pts (18%) and the Tikhoff-Lindberg procedure in 38 pts (18.5%). The entire cohort demonstrated mRFS of 41.8 months(mo; 5-year: 45.2%), and mOS of 103.6 mo

(5-year: 65.2%). Both values were significantly associated with histological grade (log-rank $p < 0.001$), with G3 and Gx subtypes demonstrating markedly poorer outcomes. No surgical complications were observed in 84 pts (41%), Grade II occurred in 58 pts (28.3%), IIIB in 27 pts (13.2%), and I in 26 pts (12.7%). A single grade V fatal event ($n=1$; 0.5%) was recorded.

Conclusion: ChS represents a high heterogeneity. Histopathological diagnosis, including grade significantly influences patients outcomes. Surgical complications have to be considered in clinical decision-making. These data reinforce the importance of referral to high-volume sarcoma centres capable of achieving wide margins and complex reconstructions.

(P 150) **LOCAL RECURRENCE OF CHONDROSARCOMA: IMPACT ON SURVIVAL AND RECURRENCE AT AN INCREASED GRADE**

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Objective: Chondrosarcoma grade has been established as a predictor of disease-specific survival (DSS). Impact of local recurrence (LR) on DSS, however, remains controversial. Increased tumor grade following LR has been reported in 10% of LRs, however no studies have compared outcomes based on increased grade. The aim of this study was to evaluate the impact of LR on DSS and report outcomes of chondrosarcoma that recur at an increased grade.

Methods: Three-hundred-and-nine patients with surgically treated chondrosarcoma between 1989 and 2022 were retrospectively reviewed. Demographic and treatment characteristics were collected, local recurrence free survival (LRFS) was calculated, and DSS was compared between those that recurred at a similar grade versus an increased grade.

Results: LRFS was 80% at 10 years. LR was associated with disease-specific mortality based on time-dependent binary covariate analysis (HR 9.38, 95% CI [5.40, 16.3], $p < 0.001$). Of those that recurred, 33 had pathology available (Table 1) for review. Recurrence occurred at an increased grade in 10 (30%), decreased grade in 1 (3%), and same grade in 22 (67%). Increased grade changes included: Grade 1 to 2 ($n=2$); Grade 1 to 4 ($n=1$); Grade 2 to 3 ($n=3$); Grade 2 to 4 ($n=4$). Ten-year DSS did not differ between groups based on similar or increased grade LR (68% vs. 21%, $p=0.3$).

Conclusion: LRFS in this cohort was 80% at 10 years, with LR a risk factor for worse DSS. Increased grade occurred in 30% of LR, three times higher than published in previous series. While no survival differences can be elucidated for increased LR in this study, increased grade trended toward worse DSS.

Table 1: Demographic and tumor features of patients with recurrent chondrosarcoma

Characteristic	Recur at same or lower grade	Recur at increased grade	Overall	P-value
Total n	23	10	33	
Low grade	16 (70%)	10 (100%)	26 (79%)	0.06
High grade	7 (30%)	0 (0%)	7 (21%)	
Age at surgery, yr	50±18	52±16	51±17	0.09
Male	16 (70%)	8 (80%)	24 (73%)	0.5
Secondary lesion	5 (22%)	1 (10%)	6 (18%)	0.4
Tumor size, cm	11±5	11±4	11±5	0.4
Soft tissue mass	14 (61%)	8 (80%)	22 (67%)	0.3
Central location	9 (39%)	6 (60%)	15 (45%)	0.3
Pathologic fracture	3 (13%)	3 (30%)	6 (18%)	0.2
Positive margin	12 (52%)	4 (40%)	16 (48%)	0.5
Follow up, yr	8±8	7±5	8±8	0.2

(P 151) SHOULD WE USE ADJUVANT CHEMOTHERAPY IN PATIENTS WITH LOCALIZED DEDIFFERENTIATED CHONDROSARCOMA (DDCS) OF THE PELVIS? AN ANALYSIS BY THE PELVIC DDCS STUDY GROUP

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Objective: Dedifferentiated chondrosarcoma (DDCS) accounts for up to 1-2% of all chondrosarcomas, it is associated with poor prognosis, and presents PDL1 positivity in 20 - 40% of the cases. 5-year survival rates range from 7% to 24% with worse outcomes in pelvic primary location. Recently, a consensus on the use of adjuvant chemotherapy in patients with DDCS was reached, while data are limited in the pelvis. Here we report an analysis on neoadjuvant or adjuvant chemotherapy (adj-CT) from the pelvic DDCS Study Group.

Methods: Multicenter retrospective cohort study from 35 orthopedics oncology centers. Period of study: 1985-2022. A subgroup analysis on 240/297 DDCS patients with localized disease was performed. Progression-free survival (PFS) and Overall survival (OS) were evaluated using Kaplan-Meier curves and Cox regression, stratified by the use of adj-CT.

Results: 86/240 (35%) of the patients underwent adj-CT and were younger than those who did not. Median PFS and OS were 10.7 and 20.1 months, respectively, with no significant difference by adj-CT use (median PFS adj-CT No 10.4 months, adj-CT Yes 11.1 months, p 0.67).

After multivariable analysis, separate Cox models showed that R1 and R2 positive margins were associated with worse PFS and OS. Male sex was associated with worse PFS in both models (aHR = 1.47, p = 0.01).

Conclusion: This retrospective review did not observe a statistically significant superiority of adj-CT in patients with pelvic DDCS. R1 and R2 margins and identification as male were associated with poorer PFS. Due to PDL1 expression, further studies evaluating adjuvant immune checkpoint, combined with radiotherapy (proton or other), and adj-CT, are warranted.

	Total (N=240)	adj-CT No (N=154)	Adj-CT Yes (N=86)	Q- value
Gender				
F	88 (36.7%)	53 (34.4%)	35 (40.7%)	1
M	152 (63.3%)	101 (65.6%)	51 (59.3%)	
Age				
Mean (SD)	54.2 (12.9)	56.8 (13.3)	49.6 (10.5)	< 0.001
Median [Q1, Q3]	54.0 [46.0, 63.0]	58.0 [48.0, 66.0]	49.0 [44.0, 56.0]	
Missing	2 (0.8%)	1 (0.6%)	1 (1.2%)	
Limb Sparing Surgery				
No	48 (20.0%)	35 (22.7%)	13 (15.1%)	1
Yes	192 (80.0%)	119 (77.3%)	73 (84.9%)	
Extraosseous extent				
No	17 (7.1%)	7 (4.5%)	10 (11.6%)	0.565
Yes	215 (89.6%)	144 (93.5%)	71 (82.6%)	
Missing	8 (3.3%)	3 (1.9%)	5 (5.8%)	
Margins (mm)				
Mean (SD)	4.0 (6.4)	4.1 (6.7)	3.9 (5.9)	1
Median [Q1, Q3]	1.0 [0.0, 5.0]	1.0 [0.0, 5.0]	2.0 [0.2, 4.0]	
Missing	93 (38.8%)	62 (40.3%)	31 (36.0%)	
Margins (R_class)				
R0	169 (70.4%)	105 (68.2%)	64 (74.4%)	1
R1	46 (19.2%)	32 (20.8%)	14 (16.3%)	
R2	22 (9.2%)	14 (9.1%)	8 (9.3%)	
Missing	3 (1.3%)	3 (1.9%)	0 (0%)	
Tumor Size (cm)				
Mean (SD)	11.8 (6.6)	12.5 (7.5)	10.4 (4.6)	0.407
Median [Q1, Q3]	10.0 [8.0, 15.0]	10.0 [8.0, 15.0]	10.0 [7.0, 13.0]	
Missing	14 (5.8%)	9 (5.8%)	5 (5.8%)	
Radiotherapy				
No	197 (82.1%)	134 (87.0%)	63 (73.3%)	0.301
Yes	42 (17.5%)	20 (13.0%)	22 (25.6%)	
Missing	1 (0.4%)	0 (0%)	1 (1.2%)	

(P 152) EFFICACY OF PALLIATIVE CHEMOTHERAPY AND LOCAL TREATMENTS IN ADVANCED CHONDROSARCOMA: A SUBTYPE-SPECIFIC RETROSPECTIVE ANALYSIS

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Objective: Chondrosarcoma (ChS) represents a heterogeneous group of malignant cartilaginous tumors characterized by variable clinical behavior and therapeutic response. Among these, MChS is a rare and aggressive variant often presenting in younger patients, yet some retrospective studies suggest it may be more chemosensitive compared to other subtypes. This study aimed to assess subtype-specific responses to palliative chemotherapy (CHT), progression-free survival (PFS), overall survival (OS), and the impact of adjunct local interventions in advanced ChS.

Methods: The retrospective analysis included patients (pts) with a confirmed diagnosis of unresectable or metastatic ChS, treated in our sarcoma clinic between 1998 and 2025. Median overall survival (mOS) and median progression-free Survival (mPFS) were calculated using Kaplan-Meier analysis with prognostic factors assessed with a log-rank test.

Results: 51 pts received palliative CHT (median age: 48 years) including pts with dedifferentiated (DDChS; n=9, 17.6%), mesenchymal (MChS; n=16, 31.4%) and high-grade conventional (CChS, n=26, 51%). For pts receiving first-line CHT (n=50) mOS was 14.9 months (mo), while mPFS 5 mo. MChS pts had longer mPFS - 8.77 mo, and mOS-18.33 mo than those with DDChS (mPFS: 7.1 mo; mOS: 8.21 mo) and CChS (mPFS: 3.48 mo; mOS: 9.79 mo). Objective Response Rate (ORR) was 19.6% for the entire cohort, including 25% for MChS; 15.4% for CChS, and 22.2% for DDChS. 17 pts received 2nd-line CHT with mPFS 5.39 mo and ORR of 23.5% for the entire cohort (MChS-37.5% ORR; CChS-16.7% ORR). Pts receiving local interventions (metastasectomy: n=15, 29.4%; palliative radiotherapy: n=13, 25.5%; both: n=6, 35.2%) exhibited a trend towards longer OS (p= 0.1): 18.3 mo with vs 12.7 mo.

Conclusion: These findings highlight the heterogeneity of chondrosarcoma subtypes and suggest that MChS may derive greater benefit from systemic therapy. Local interventions may improve survival and merit integration into multimodal treatment strategies. The role of local therapies in prolonging survival warrants further investigation.

(P 153) DOES THE QUANTITY OF DEDIFFERENTIATION MATTER IN THE CLINICAL OUTCOMES OF DEDIFFERENTIATED CHONDROSARCOMA? A 10-YEAR SINGLE TERTIARY INSTITUTIONAL EXPERIENCE OF A SERIES.

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Objective: Dedifferentiated chondrosarcoma (DD-CHS) is an aggressive primary bone sarcoma characterized by low-intermediate grade cartilage component with abrupt transition to a high-grade non-cartilaginous component. Though the dedifferentiated (DD) component is usually large, rarely it may be minimal (< 5%) and may be missed altogether on initial presentation. There is no precedent data addressing the relevance of the amount of dedifferentiation in the overall prognosis of DD-CS. Prompted by a recent case of metastatic DD-CHS to the heart (previously diagnosed as primary cardiac undifferentiated pleomorphic sarcoma) who had only a minute focus of dedifferentiated (missed on prior evaluation), we performed a retrospective analysis of DD-CHS in our institution over a 10-year period to determine the prevalence and the prognostic significance of the quantity of dedifferentiation in DD-CHS.

Methods: We performed a retrospective analysis of DD-CHS diagnosed between 2013 and 2023. The radiographic, clinicopathological, immunohistochemical, molecular features and follow up data were collected.

Results: A total of 21 patients were identified (15 males and 6 females). The mean age was 68.7 years with a male: female ratio of 2:1 (Table 1). The average tumor size was 11.1 cm (range 4.5 to 28.0 cm). 3 patients had minimal DD < 5% which were missed on initial evaluation, reported as intermediate grade conventional chondrosarcomas; and 18 had large DD (>5%). One case presented an undifferentiated pleomorphic sarcoma in the heart, suggesting a second primary but IDH1 mutation was positive and re-review showed < 5% DD. The second case presented with metastatic osteosarcoma, suggesting a second primary but re-review of the original pathology showed < 5% DD containing osteosarcoma. The third case presented as metastatic high grade spindle cell sarcoma in the acetabulum and re-review found < 5% DD in the sacrum. 7 locally recurred, 13 developed distant metastases, and 16 died of disease. (76%). Overall survival was slightly better in those with minimal DD than large DD, though not statistically significant ($p=0.5$). All three cases with minimal DD (< 5%) died from disease.

Conclusion: DD-CHS is a highly aggressive neoplasm with a high mortality rate. The presence of dedifferentiation regardless of amount is predictive of aggressive biology and adverse outcome. This underscores an imperative need for thorough gross and histopathologic examination.

Table showing cohort information

Age/sex	Site/ Size (cm) of tumor	Dediff component	Recurrence	Metastasis/Site	Survival	Treatment
58/M	R proximal femur/ 10.7	Osteosarcoma	No	No/NA	Alive	SR + chemo
84/M	L femur/ NA	Leiomyosarcoma	No	No/NA	DOD	RT
66/M	L humerus/ NA	HG spindle sarcoma	No	Yes/ Lung, T3	DOD	IT + chemo
62/M	R hemipelvis/ 13.5	Osteosarcoma	No	Yes/ Lung	DOD	RT + chemo
65/F	L femur/ 10.5	HG spindle sarcoma	No	No/ NA	DOD	SR + chemo + RT
66/M	L femur/ 9.4	HG epithelioid myxofibrosarcoma	No	Yes/ Brain	DOD	SR + chemo + RT + IT
78/F	L femur/ 9.6	HG spindle sarcoma	No	Yes/ Skin	Alive	SR
71/M	L hemipelvis/ 23.4	HG spindle sarcoma	No	Yes/ L inguinal node	DOD	SR
54/F	Sacrum*/ 6.6	HG spindle sarcoma	No	Yes/ Acetabulum	DOD	SR
65/M	Humerus*/ 7.8	HG spindle sarcoma	No	Yes/ Myocardium	DOD	SR + IT
60/F	R distal femur/ NA	HG spindle sarcoma	No	Yes/ Lung	Alive	SR + chemo + RT
74/M	R femoral neck/ NA	HG spindle sarcoma	No	Yes/ Lung	DOD	SR
72/M	R femur/ 4.5	Osteosarcoma	No	No/ NA	DOD	SR
62/M	Xiphoid/ 5.5	HG spindle sarcoma	No	Yes/ Lung	Alive	SR
68/M	R femur/ NA	HG spindle sarcoma	Yes	No/ NA	DOD	SR + chemo + RT
84/M	L distal femur/ 6.8	HG spindle sarcoma	Yes	No/ NA	Alive	SR
59/F	L knee/ 5.9	HG spindle sarcoma	Yes	Yes/ Knee	DOD	SR + chemo + RT + IT
81/M	L humerus/ 28.0	Osteosarcoma	Yes	No/ No	DOD	SR
77/F	L humerus/ 9.7	HG spindle sarcoma	Yes	Yes/ L arm, chest	DOD	SR
71/M	R femur/ 19.8	HG spindle sarcoma	Yes	No/ NA	DOD	SR + chemo + RT
66/M	R gluteal*/ 6.5	HG spindle cell sarcoma	Yes	Yes/ Lung	DOD	SR + chemo + RT

(P 154) BCOR-MUTATED CONVENTIONAL AND DEDIFFERENTIATED CHONDROSARCOMA: A CLINICOPATHOLOGIC STUDY

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Objective: Chondrosarcomas (CSAs) are a heterogeneous group of malignant neoplasms that arise within or on the surface of bone.

IDH1/2, COL2A1, and TP53 are the most commonly mutated genes in conventional chondrosarcomas (CCSA) and dedifferentiated chondrosarcomas (DCSA).

Mutations in BCOR are frequently acquired in other IDH-driven neoplasms, and it is unclear if they contribute to IDH inhibitor resistance and disease progression.

The significance of BCOR mutations in CCSA and DCSA has not yet been defined.

After identifying an index case of CCSA with unusually aggressive clinical evolution, we investigated a series of BCOR-mutated CCSA and DCSA to determine the biological significance of this genetic alteration in these sarcoma subtypes.

Methods: We interrogated the surgical pathology archives for CCSA and DCSA between 2019 and 2023 that underwent genomic analysis to identify those with BCOR mutations.

All cases were sequenced using a commercial NGS panel (CARIS Life Sciences, Irving, Texas).

Fifteen in-house cases with available NGS results, were used as the group control.

Frequentist statistics were performed to establish association between the presence of BCOR mutations and mean tumor size, presence of metastases at diagnosis, dedifferentiation, histological grade, axial vs appendicular involvement, and pT stage (simplified as T1, T2, T3 and T4).

Results: The overall prevalence of BCOR mutations in CCSA and DCSA was 5% (12/231). The mean size difference between the BCOR-mutated CSA group and the control group was 3.92 cm ($p=0.024$ CI=0.59-7.24), and the proportion difference for the presence of metastatic disease at the time of diagnosis was 0.42 ($p<0.001$). The proportion difference for having a pT stage3-4 vs 1-2 was 0.34 ($p=0.009$). There were no statistically significant differences for histological grades, dedifferentiation, or involvement of axial skeleton or pT stage as a continuous variable.

Conclusion: This is the first study to establish the biological significance of BCOR mutations in CCSA and DCSA.

BCOR mutations are infrequent and can occur as standalone mutations or, most commonly, as co-occurring with other driver mutations.

Missense and frameshift mutations of BCOR are the genetic alterations in CCSA and DCSA without internal tandem duplication or rearrangements as in other sarcoma types.

BCOR mutations in CCSA and DCSA are associated with a larger tumor size, presence of metastasis at diagnosis, and higher pT category.

Clinicopathological findings and relevant statistical analysis results

	BCOR mutant		BCOR WT	
	n	%	n	%
Number of cases	12	-	15	-
M/F ratio	3	-	0.44	-
Mean age	55	-	55	-
Histological Grade				
Grade I	-	-	2	13
Grade II	6	50	7	47
Grade III	1	8	1	7
Dedifferentiated	5	42	5	33
Location				
Pelvis	6	50	4	27
Extremities	3	25	6	40
Spine	1	8	1	6
Craniofacial	-	-	4	27
Scapula	1	8	-	-
Metastasis at presentation	7/9	78	4/15	27
pT stage				
T1	1	8	5	33
T2	3	25	5	33
T3	4	34	0	0
T4	1	8	2	14
TX	3	25	3	20

	Estimate	Lower	Upper	P
Tumor size	3.92	0.59	7.24	0.024 a
Metastasis	0.42	0.25	0.6	<0.001 b
Dedifferentiation	0.08	-0.28	0.44	0.652 b
Histological grade	0.32	-0.49	1.12	0.444 a
Axial/appendicular skeleton involvement	0.13	-0.23	0.49	0.489 b
pT stage	0.72	-0.16	1.62	0.126 a
pT stage (1&2 vs 3&4)	0.34	0.09	0.59	0.009 b

a Mean difference, b Proportion difference

(P 155) BRCA2-MUTATED CONVENTIONAL CHONDROSARCOMA RESPONDING TO PARP INHIBITION: A CASE REPORT

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Objective: Chondrosarcomas commonly harbor recurrent mutations in IDH1/2, as well as alterations such as CDKN2A and COL2A1 inactivation, while homologous recombination deficiency is rare. Here, we describe the case of a young adult diagnosed with a high-grade

conventional chondrosarcoma harboring a somatic BRCA2 pathogenic variant and highlight the observed radiological response to PARP inhibition.

Methods: We describe the clinical course of a 22-year-old female diagnosed in January 2021 with grade 3 chondrosarcoma of the proximal tibia. Following surgical resection and adjuvant surveillance, pulmonary metastases developed five months postoperatively. She received multiple lines of systemic therapy, including anthracycline-based chemotherapy and pazopanib. Tumor genomic profiling revealed a pathogenic somatic BRCA2 alteration (p.Trp1692Metfs*32; allele frequency: 95.7%). Based on this finding, treatment with the PARP inhibitor olaparib was initiated as fourth-line therapy in July 2024.

Results: Despite prior disease progression on three lines of systemic therapy, olaparib led to a partial radiological response per RECIST criteria, with up to a 50% reduction in pulmonary lesions at the first disease assessment, 2 months after treatment initiation. Interruptions due to grade 3 hepatitis, pneumonitis, and neutropenia required temporary dose reduction. However, the patient was able to resume the original dose without further adverse events and maintained prolonged disease stability, with ongoing therapeutic benefit at last follow-up in June 2025.

Conclusion: This case highlights the potential sensitivity of BRCA-mutated conventional chondrosarcomas to PARP inhibition. It reinforces the rationale for tumor-agnostic approaches in molecularly selected sarcoma patients and supports further investigation of homologous recombination deficiency as a therapeutic target in bone sarcomas. Evaluation of the patient's germline BRCA2 status is ongoing to better characterize the biological context of this response.

(P 156) **CHONDROSARCOMA INCIDENCE, SURVIVAL AND MANAGEMENT IN ENGLAND 2013-2022; AN ANALYSIS FROM THE NATIONAL DISEASE REGISTRATION SERVICE**

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Objective: Chondrosarcoma (CS) is an uncommon primary malignant bone tumour with histologically distinct subtypes, with differing management and outcomes. In England, all cancer diagnoses are registered with the National Disease Registration Service, providing an opportunity for this national population-based study that sought to describe the incidence, management and outcomes of patients registered with CS.

Methods: All patients diagnosed with CS, resident in England between 2013 and 2022, were included. Age-standardised incidence rates per 100,000 person-years (ASR) were calculated for all subtypes. Outcome was assessed by five-year relative survival (RS) and Cox proportional hazards modelling to determine impact of patient characteristics and treatment on outcome, including histological subtype, primary site and grade; age at diagnosis, gender, deprivation and treatment within 12 months of diagnosis.

Results: A total of 1,816 CS patients were included; 1,589 (84%) with conventional CS (CCS), 133 (7%) with dedifferentiated CS (DDCS) and 34 (2%) with mesenchymal CS (MC). Overall ASR was 0.34, ranging from 0.30 in CCS to 0.001 for malignant chondroblastoma. DDCS patients were older than CCS patients (median age 67 vs 54 years). Primary site varied; extremity was most common overall (58%) but more frequent in DDCS (72%) and CCS (57%) than MC (29%). Pelvic site was more common in DDCS (23%) than CCS (13%). At total of 1,319 CCS patients (83%), 109 DDCS patients (82%) and 25 MC patients (74%) had surgery. Systemic therapy use was rare in CCS (1.7%); more common in DDCS (22%) and MC (59%). Radiotherapy use was most frequent in MC (35%, of which 50% had proton beam therapy), less so in CCS and DDCS (6.6% and 5.3% respectively). Five-year RS was 96% (93-99) for low-grade CCS, 76% (71-81) for high-grade CCS, 18% (11-29) for DDCS and 74% (58-93) for MC. Older age, DDCS histology, male gender, high deprivation and pelvic or spinal primary site conferred higher risk of death in multivariate analysis of CS overall, but only older age was significant when modelling high-grade CCS alone. Older age, male gender and higher deprivation conferred lower survival in DDCS. In multivariate analysis there was no significant difference in outcome between DDCS patients treated with surgery and chemotherapy vs surgery alone (p = 0.49).

Conclusion: This large national population-based study provides valuable data to better understand the heterogeneity of CS and inform stakeholders on patient management.

Patient characteristics, incidence and 5-year relative survival (RS) for CS patients diagnosed in England 2013-2022.

Characteristic	Overall N=1,816 ^a	Conventional chondrosarcoma N=1,589	Dedifferentiated chondrosarcoma N=133	Mesenchymal chondrosarcoma N=34	Overall relative survival ^b N=1,816	Conventional chondrosarcoma N=1,589	Dedifferentiated chondrosarcoma N=133	Mesenchymal chondrosarcoma N=34	p-value ^{c,d}
Age-standardised incidence rate per 100,000 person-years (95% CI) ^e									
	0.341 (0.305-0.377)	0.298 (0.283-0.313)	0.529 (0.522-0.531)	0.006 (0.004-0.008)	0.303 (0.263-0.343)	0.303 (0.263-0.343)	0.003 (0.000-0.005)	0.003 (0.001-0.005)	-
Age at diagnosis									
Median (IQR)	55 (35-85)	54 (35-85)	67 (21-84)	51 (10-83)	48 (16-79)	55 (21-77)	55 (14-74)	55 (17-85)	0.001***
Gender									
Male	938 (51.7%)	805 (51.1%)	77 (58.7%)	17 (50.0%)	19 (39.6%)	8 (33.3%)	8 (57.7%)	2 (58.7%)	0.4
Female	880 (48.3%)	784 (48.9%)	56 (41.3%)	17 (50.0%)	9 (20.4%)	7 (27.8%)	6 (42.3%)	1 (29.3%)	
Primary site									
Extremity	1,047 (57.7%)	898 (56.5%)	56 (41.3%)	10 (29.4%)	19 (39.6%)	9 (64.3%)	1 (29.3%)	0 (0.0%)	0.001***
Pelvic	209 (11.5%)	145 (9.1%)	5 (3.8%)	4 (11.8%)	4 (27.1%)	4 (29.0%)	0 (0.0%)	0 (0.0%)	
Trunk and back	158 (8.7%)	140 (8.8%)	4 (3.0%)	2 (5.9%)	2 (13.0%)	2 (14.6%)	0 (0.0%)	0 (0.0%)	
Thorax	236 (13.0%)	200 (12.6%)	4 (3.0%)	1 (2.9%)	1 (6.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	
Spine	86 (4.7%)	86 (5.4%)	0 (0.0%)	0 (0.0%)	1 (6.1%)	0 (0.0%)	1 (7.5%)	0 (0.0%)	
Non-specified primary site	40 (2.2%)	40 (2.5%)	2 (1.5%)	1 (2.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	
Grade at diagnosis									
High grade	867 (47.8%)	860 (54.1%)	1 (0.8%)	10 (29.4%)	6 (48.0%)	10 (71.4%)	0 (0.0%)	0 (0.0%)	0.001***
Low grade	949 (52.2%)	729 (45.9%)	0 (0.0%)	1 (2.9%)	0 (0.0%)	2 (14.3%)	0 (0.0%)	0 (0.0%)	
L1	246 (13.5%)	204 (12.8%)	0 (0.0%)	15 (44.1%)	13 (66.0%)	9 (60.0%)	2 (14.3%)	3 (100%)	
Indices of multiple deprivation quintile									
1 - least deprived	809 (44.6%)	705 (44.3%)	26 (19.6%)	4 (11.8%)	2 (13.0%)	6 (42.9%)	2 (58.7%)	0 (0.0%)	0.001***
2	400 (22.0%)	352 (22.1%)	9 (6.8%)	2 (5.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	
3	312 (17.2%)	305 (19.2%)	27 (20.3%)	3 (8.8%)	4 (27.1%)	4 (29.0%)	0 (0.0%)	0 (0.0%)	
4	305 (16.8%)	288 (18.2%)	27 (20.3%)	3 (8.8%)	3 (20.0%)	1 (7.1%)	0 (0.0%)	0 (0.0%)	
5 - most deprived	390 (21.5%)	339 (21.3%)	20 (15.0%)	4 (11.8%)	4 (20.0%)	4 (28.6%)	1 (7.5%)	0 (0.0%)	
Treatment									
Chemotherapy	77 (4.2%)	27 (1.7%)	28 (21.1%)	0 (0.0%)	0 (0.0%)	1 (7.1%)	0 (0.0%)	0 (0.0%)	0.001***
Surgery	1,540 (84.8%)	1,318 (83.1%)	108 (80.7%)	25 (72.9%)	10 (64.3%)	13 (92.9%)	2 (58.7%)	0 (0.0%)	0.008
Radiotherapy	137 (7.5%)	109 (6.8%)	7 (5.3%)	12 (35.3%)	3 (17.6%)	6 (38.6%)	2 (14.3%)	0 (0.0%)	0.001***
Proton beam therapy	70 (3.8%)	64 (4.0%)	1 (0.8%)	0 (0.0%)	2 (11.6%)	1 (7.1%)	0 (0.0%)	0 (0.0%)	0.001***
5-year relative survival ^b (95% CI) ^e									
	76% (71-82)	84% (81-87)	14% (11-18)	74% (58-93)	-	-	-	-	-
T ₀ (%)									
*Adjusted Wald chi-squared test (continuous) or Pearson's Chi-squared test (factor)									
***p<0.001, **p<0.01, *p<0.05									
^a Only patients with 5 years of follow-up included, i.e. 2013-2019 diagnosis included.									

(P 157) INCOME IMPACTS OVERALL BUT NOT CAUSE-SPECIFIC SURVIVAL IN PATIENTS WITH CHONDROSARCOMA: A POPULATION BASED STUDY FROM THE SEER DATABASE

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Objective: Chondrosarcoma is a common primary bone tumor, yet the prognostic role of socioeconomic status (SES) is unclear. Prior studies have not accounted for competing causes of death, which may lead to overestimation of risk. This study evaluates the prognostic significance of income and rurality in patients with chondrosarcoma using both Cox Proportional Hazards and Fine-Gray competing risk models.

Methods: A retrospective cohort study was performed using the SEER database (1975–2021). Patients were stratified by income (low: <\$55,000; middle: \$55,000–\$70,000; high: >\$70,000) and rurality (urban vs. rural). Cox and Fine-Gray models were used to assess overall and cause-specific survival. Histologic subtype and tumor location were included as covariates.

Results: A total of 3,678 patients met inclusion criteria (mean age 53.3 ± 17.1 years): 72.5% were high-income, 18.3% middle-income, and 9.2% low-income. In Cox analysis, low income (HR = 1.43, 95% CI: 1.10–1.84, $p = 0.006$) and rural residence (HR = 0.71, 95% CI: 0.55–0.90, $p = 0.006$) were significant prognostic factors for mortality. These findings were attenuated in Fine-Gray analysis: low income (SHR = 1.36, 95% CI: 0.95–1.94, $p = 0.089$) and rurality (SHR = 0.76, 95% CI: 0.54–1.07, $p = 0.122$). Mesenchymal and dedifferentiated histologies and pelvic location were also associated with increased mortality in both models ($p < 0.001$).

Conclusion: SES influences chondrosarcoma survival, but its effect on cause-specific mortality decreases when competing risks are considered. Fine-gray modeling reveals critical nuances in survival analysis, stressing the need for appropriate statistical methods to interpret SES-related disparities.

(P 158) GLOBAL INEQUITIES IN CHONDROSARCOMA CLINICAL TRIALS: A COMPREHENSIVE ANALYSIS ACROSS THREE DECADES

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Objective: Chondrosarcoma (CS) is the second most common malignant bone tumor after osteosarcoma, accounting for 20–30% of all malignant bone tumors. Despite recent advances in molecular understanding and targeted therapies, clinical progress has been hampered by low trial activity and limited global representation. This study aims to evaluate the global landscape of chondrosarcoma clinical trials over the past three decades, identifying geographic, economic, and demographic disparities.

Methods: We conducted a systematic analysis of chondrosarcoma-related clinical trials registered on ClinicalTrials.gov between 1992 and 2025. Trials were identified using disease-specific search terms and manually screened for relevance. Extracted variables included study

type, phase, geographic location, World Bank income classification, sponsor, primary outcomes, and trial status. Descriptive statistics were used to summarize trial characteristics.

Results: Out of 123 studies, 17.9% were focused exclusively on chondrosarcoma. The USA was the most represented country, 88 studies (42.5%), followed by France (8.2%), the UK (6.3%), and Spain (5.8%). Alarming, only 4 (3.2%) were conducted in low and middle-income countries (LMICs) and only 7 (5.6%) studies in upper-middle-income countries. A total of 37 trials (30.1%) included all three age groups: children, adults, and older adults. Recruitment status varied, with 23 trials (18.7%) actively recruiting, 56 (45.5%) completed, and 10 (8.1%) terminated—predominantly due to challenges in participant accrual. Interventional trials accounted for 107 studies (87%) of the total, though most lacked randomization. Early-phase trials predominated, comprising 35 studies (28.5%) in phase 1 and phase 1/2, and 49 (39.8%) in phase 2. Late-phase and post-marketing studies were sparse, representing only 8 studies (6.5%) of the total. The majority of studies, 95 (77%), were academia-sponsored trials. The median sample size was 54 participants (IQR 26–130).

Conclusion: Chondrosarcoma clinical trials are predominantly sponsored by academic institutions and are heavily concentrated in high-income countries. Upper-middle-income and low- and lower-middle-income countries remain profoundly underrepresented, limiting global equity and generalizability. Expanding geographic diversity and fostering broader sponsorship—including industry and international partnerships—are critical to advancing research in this rare malignancy.

(P 159) **CHONDROSARCOMA IN JAPAN: A POPULATION-BASED ANALYSIS USING NATIONAL CANCER REGISTRY**

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Objective: Chondrosarcoma is a rare malignant bone tumor with diverse histological features. This study investigated epidemiological characteristics, clinical features, prognostic factors, and subtype differences of chondrosarcoma in Japan using National Cancer Registry data.

Methods: We analyzed chondrosarcoma cases diagnosed 2016-2019 from Japan's National Cancer Registry covering the entire population. Cases were identified using ICD-O-3 codes. We calculated age-adjusted incidence, estimated survival using Kaplan-Meier methods, and identified prognostic factors through multivariate Cox regression. Subtype characteristics were compared among conventional, dedifferentiated, mesenchymal, clear cell, and other variants.

Results: We identified 1,015 cases with age-adjusted incidence 0.159 per 100,000. The cohort comprised 558 men (55%) and 457 women (45%), 84% aged ≥40 years. Common locations were extremities (45.9%) and chest wall (23.8%). Conventional type was predominant (84.7%), followed by dedifferentiated (6.7%), mesenchymal (2.9%), and clear cell (2.5%). Overall 1-year and 3-year survival were 90% and 76.2%. Multivariate analysis revealed female sex (HR 0.531,

p=0.001), age 15-39 years (HR 0.163, p< 0.001), non-dedifferentiated subtypes, localized disease, and surgery as favorable factors. Subtype differences included younger age for mesenchymal and clear cell variants and higher metastases in dedifferentiated (18%) and mesenchymal (21%) types.

Conclusion: This first nationwide chondrosarcoma analysis in Japan provides comprehensive epidemiological data and identifies key prognostic factors. Findings demonstrate significant subtype heterogeneity and highlight individualized management importance. These data establish foundation for future clinical trial design and patient stratification in Japan.

(P 160) A COMPARATIVE ANALYSIS OF DEDIFFERENTIATED AND CONVENTIONAL CHONDROSARCOMA OUTCOMES

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Objective: Dedifferentiated chondrosarcoma (DDCS) is a rare cartilaginous malignancy characterized by aggressive behavior and resistance to chemotherapy and radiation. Although the lungs are a common site of metastasis of DDCS, the rate of metachronous metastasis remains unclear. This study compares the oncologic outcomes of DDCS patients to those of patients with conventional chondrosarcoma and investigates the nature of DDCS lung metastasis.

Methods: A retrospective review was performed on 166 chondrosarcoma patients who underwent surgical excision of their tumor from 1999 to 2024. Patients were excluded if they had metastasis on presentation, had a non-conventional chondrosarcoma (i.e., extraskeletal myxoid or mesenchymal), or were lost to follow-up within one year of surgery. Patients were categorized as DDCS (n = 27) or conventional chondrosarcoma (n = 139). Univariate and multivariate comparisons were made between patients with and without DDCS regarding surgical and oncologic outcomes.

Results: At a mean follow up of 5.4 years, 74% of DDCS patients died from disease compared to 28% of conventional cases. Disease relapse was observed in 70% of DDCS versus 32% of conventional cases. Disease-specific survival was significantly worse for patients with DDCS compared to conventional chondrosarcoma cases (5-year survival 23% vs 78%, p< 0.001). In addition, DDCS was associated with significantly worse disease-free survival compared to both conventional (HR $\approx$ 4.8, p< 0.001) and high-grade conventional chondrosarcoma (HR $\approx$ 3.8, p< 0.001). Lung metastases were significantly more common in DDCS than in conventional chondrosarcoma (52% vs 14%, p< 0.001), including when compared only to high-grade conventional tumors (52% vs 18%, p=0.0014). The rate at which DDCS metastasized to the lungs was also much faster than conventional chondrosarcoma (median 85 vs. 326 days, p = 0.0014).

Conclusion: Dedifferentiated chondrosarcoma is associated with significantly worse outcomes than conventional chondrosarcoma and notably spreads to the lungs at a higher and more rapid rate compared to conventional chondrosarcoma. These findings support the need for early

surveillance and aggressive treatment of DDCS.

(P 161) CLINICAL CHARACTERISTICS, PATTERNS OF CARE, AND TREATMENT OUTCOMES OF CHONDROSARCOMA: A SINGLE-INSTITUTIONAL EXPERIENCE

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Objective: Chondrosarcomas (CS) represent a spectrum of malignant connective tissue tumors whose management remains uncertain, with high-grade patients experiencing particularly poor outcomes.

Methods: We retrospectively reviewed CS patients evaluated at The Ohio State University between January 1, 2010 to March 7, 2022. Demographics, histologic subtypes, tumor characteristics, treatments, and survival outcomes were analyzed.

Results: Of 140 patients identified, 118 were evaluable with adequate follow-up. 91.5% were white and 50.8% were male. Median age at diagnosis was 57 (range: 21-84). 70.3% had Conventional CS, 13.5% Dedifferentiated CS, 3.4% Mesenchymal/Clear cell CS, and 12.7% Myxoid/Extraskeletal myxoid CS. At diagnosis, 47.5% had Grade I tumor, 29.7% Grade II tumor, and 18.6% Grade III tumor. 92.2% had localized disease at presentation and the median primary tumor size was 6.3 cm. The lower extremities were the most common primary site (36.4%), followed by thoracoabdominal (38.9%), skull base/head and neck (14.4%), and upper extremities (10.2%). 94.9% of patients received surgery, of whom R0 margins were achieved in 70.5%, R1 margins 17.0%, and R2 margins 0.1%, with the remainder undefined. 15.3% of patients (of whom 22.2% had localized disease and 77.8% metastatic disease) received systemic therapy, most frequently Pazopanib (55%). 10.2% of patients received radiation therapy, 41.7% with palliative intent and 58.3% with locally definitive intent. Median overall survival in the entire cohort was 90.6 months. The median survival time differed significantly by subtype: Conventional CS 104.6 months, Dedifferentiated CS 25.9 months, Mesenchymal/Clear cell CS 57.2 months, Myxoid/Extraskeletal myxoid CS 108.3 months (Chi-square $p < 0.001$). No association was seen between anatomic subsite and overall survival (upper extremities 202.80 months, lower extremities 85.30 months, and Pelvis/Retroperitoneal/Lower back & Chest/Abdomen Wall/Upper Back 82.3 months, $p=0.216$). Grade was associated with overall survival: Grade I median 202.80 months, Grade II 80.87 months, and Grade III 21.067 months ($p=0.000$).

Conclusion: CS remains a clinical challenge due to its rarity and limited treatment options. While surgical resection remains the primary treatment for localized disease, systemic therapy and radiation can have important roles in patients with locally recurrent, advanced, or metastatic disease. These findings highlight the need for subtype-specific strategies and prospective trials to refine CS care.

(P 162) CHONDROSARCOMA OUTCOMES IN YOUNG VERSUS ADULT POPULATIONS

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Objective: Chondrosarcoma is rare in patients under 25 years of age. While outcomes of chondrosarcoma in adults have been explored, there is limited data comparing outcomes between patients based on age. Thus, the purpose of this study was to compare presentation and outcomes of chondrosarcoma in patients older and younger than age 25.

Methods: We retrospectively reviewed all patients who were diagnosed with musculoskeletal chondrosarcoma at one institution from 1990-2022. Patients were grouped into cohorts based on age greater than 25 years (N=285) or less than 25 years (N=26) at the time of chondrosarcoma diagnosis. Average age at time of surgery was 19 years (range, 12-25) for the young group, and 55 years (range, 26-88) for the adult group. Average follow up was 10±7 years in the young group, and 6±15 years in the adult group (p=0.2)

Results: There were no differences in rates of neoadjuvant and adjuvant chemotherapy or radiation between groups (p>0.7). Eighteen (70%) patients presented with soft tissue masses in the young group compared to 190 (67%) in the adult group (p=1). At presentation, 3 (12%) patients in the young group had pathologic fractures compared to 44 (15%) patients in the adult group (p=0.8). There were no patients in the young group with metastatic disease at presentation, compared to 5 (2%) patients in the adult group (p=1). Adults had higher rates of dedifferentiated chondrosarcoma at diagnosis (p=0.03), while the young cohort had higher rates of low-grade disease (p=0.005). There was no difference in local recurrence-free survival (LRFS) between groups (p=0.4), with a 10-year local recurrence-free survival of 87% in the young cohort and 79% in the adult cohort. There were no differences in metastatic disease-free survival (MDFS), with rates of 96% at all timepoints in the young cohort compared to 82%, 79%, and 78% in the adult cohort at 2-, 5-, and 10-years (p=0.05). Grade adjusted disease-specific survival (DSS) at 2-, 5-, and 10-years was 95%, 95%, and 89% in the young cohort compared to 79%, 70%, and 62% in the adult cohort (p=0.5).

Conclusion: Young patients with chondrosarcoma demonstrated similar characteristics on presentation and treatment modalities as adults. LRFS was similar in young and adult patients, with MDFS and DSS trending toward improved survival in the young cohort.

(P 163) CHONDROSARCOMA IN THE AYA POPULATION

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Objective: Chondrosarcoma is the second most common primary bone malignancy; however, its incidence is low in the adolescent and young adult (AYA) population. We sought to review our experience with patients between the ages of 15 and 39 years of age to evaluate their demographics, treatment and oncologic outcomes.

Methods: A retrospective review of the tumor registry at a comprehensive cancer center for AYA patients treated between 1997 to 2023 was performed. Demographics, oncologic

information and treatment variables were evaluated. Primary outcome evaluated was overall survival.

Results: Out of 941 patients with a bone sarcoma, 42 had the diagnosis of chondrosarcoma. 56% were male and 84.1% were white. Mean age at diagnosis was 30.5 years (range 17-39). The majority were in the pelvis 16 (39%), followed by long bones 12 (29.2%). Three had the diagnosis of multiple hereditary exostoses. 87.8% were conventional chondrosarcoma, 4.8% juxtacortical, 4.8% dedifferentiated and 2.4% myxoid chondrosarcoma. 83% were intermediate and high-grade tumors. 8 (19%) presented with stage 4 disease. Forty (95%) patients underwent surgery for either primary resection or metastasectomy. For the 34 patients who presented with localized disease and underwent surgery, 91% had a resection, with 9 (26%) having surgery for a local recurrence, 1 (2.9%) had an amputation and 2 (6%) had an intralesional curetting. 14 (34%) of the cohort received radiation, most were either face/ skull or pelvis and one in a patient with stage 4 disease. Four (9.7%) patients received chemotherapy. Overall survival was 71%, mean survival was 140 months (range 4-599) from initial diagnosis. For the 22 patients with localized grade 2 and 3 disease, the overall survival was 63%, with mean survival of 140 months (range 22-505) from initial diagnosis. Overall survival of patients with metastatic disease was 43%, mean survival was 40.2 months.

Conclusion: Chondrosarcoma is not common in the adolescent and young adult population. The overall survival is comparable to reported survival in all patients. The distribution of site, age, gender and stage at presentation were also similar to the adult population. Further analysis of margin status, use of adjuvant therapies and management of metastatic disease is warranted.

(P 164) LONG TERM OUTCOMES IN PATIENTS DIAGNOSED WITH SECONDARY CHONDROSARCOMA

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Objective: Secondary chondrosarcoma (SChS), arising from pre-existing benign cartilaginous lesions such as osteochondromas, is a rare malignant tumour with limited evidence guiding optimal surgical management and prognostication. We aim to evaluate the clinical outcomes, prognostic factors, and surgical complication profile in patients with SChS, with a particular focus on the impact of resection margin status on relapse-free and overall survival.

Methods: Patients(pts) with a confirmed diagnosis of SChS were included in a retrospective analysis. Median relapse-free survival (mRFS) and median overall survival (mOS) were analysed using the Kaplan-Meier; log-rank test was used to assess potential prognostic factors; Clavien-Dindo scale - to classify surgical complications.

Results: The cohort included 31 pts, predominantly male (67.7%), with a median age of 35.7 years (range: 18.5–71.3). Predispositions included solitary osteochondroma (n=21, 67.7%), hereditary multiple osteochondromas (HMO; n=3, 9.7%), enchondroma (n=2, 6.5%), Ollier's

disease (n=1, 3.2%); in 4 pts (12.9%) no specific predisposition was diagnosed. Tumours were located predominantly in the lower extremities (n=19, 61.3%), followed by the trunk (n=10, 32.3%) and upper extremities (n=2, 6.5%). Subtypes included: peripheral (n=27, 87.1%) and central (n=4, 12.9%). Grades were: G1 (n=27, 87.1%) and G2 (n=4, 12.9%). All pts underwent primary SChS resection with endoprosthesis implantation (n=7, 22.6%), hemipelvectomy (n=3, 9.7%). Resection margins were R0 (n=18, 58.1%), R1 (n=9, 29%), and R2 (n=1, 3.2%). Surgical complications were recorded in 19 pts (61.3%), with Clavien-Dindo grade $\geq$ IIIA in 8 pts (25.8%). mRFS was 10.2 months (95% CI: 110.2–NA), with 5-year RFS and OS rates of 76.7% and 92.2%, respectively. mRFS was 10.2 months (95% CI: 110.2–NA), with 3- and 5-year RFS rates of 86.1% and 76.7%, respectively. mOS was 110.2 months (95% CI: 97.1–NA), with a 5-year OS rate of 92.2%. Pts with R0 resection showed improved mRFS and mOS compared to those with R1 or R2 resections.

Conclusion: Resection with negative margins (R0) remains the most important determinant of improved RFS and OS in SChS pts. Despite a high incidence of surgical complications, long-term prognosis is favourable and local control achieved in most pts with SChS.

(P 165) EVALUATING LARGE LANGUAGE MODELS AS DECISION SUPPORT TOOLS IN MULTIDISCIPLINARY TUMOR BOARDS FOR GASTROINTESTINAL STROMAL TUMORS

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Objective: To assess the concordance of treatment recommendations generated by two reasoning large language models (LLMs), OpenAI o1 and DeepSeek-R1, with decisions made by a multidisciplinary team (MDT) in real-world gastrointestinal stromal tumor (GIST) cases, and to evaluate the feasibility of using LLMs as evaluators in clinical oncology.

Methods: In a retrospective single-center study, 65 real-world GIST cases presented at a certified sarcoma MDT were selected from a total of 753 cases. Two advanced LLMs were prompted to simulate a tumor board discussion using a multi-role prompting strategy, supported by the German S3 sarcoma guidelines. Recommendations were independently rated by five clinical experts using a 5-point Likert scale. Additionally, Mistral AI served as an automated evaluator. Recommendations were assessed for concordance with MDT decisions and

alignment with guidelines.

Results: OpenAI o1 demonstrated higher concordance with MDT decisions (76.9% vs. 53.8%, $p < 0.001$) and more outputs aligned with MDT or guidelines (80.0% vs. 63.1%, $p = 0.005$) compared to DeepSeek-R1. Expert inter-rater reliability was excellent (ICC = 0.929). Mistral AI ratings moderately aligned with expert consensus ($\kappa = 0.588$). OpenAI o1 outputs were significantly more verbose (mean 1359 vs. 697 characters, $p < 0.001$), offering detailed justifications that may support documentation but present usability challenges. The LLM judge also detected more instances of hallucinations in DeepSeek-R1 outputs.

Conclusion: Reasoning LLMs, particularly OpenAI o1, show promising performance as decision support tools in complex GIST cases and demonstrate potential for partially automating clinical evaluation through LLM-as-a-judge frameworks. Their deployment should be supervised by experts to ensure reliability. One limitation of the study is that a large number of MTBs were evaluated, but only from a single center. Further multicenter studies and integration into real-time MDT workflows are warranted.

Case descriptions

Category	Subcategory	N (%)
Age range	21-30	2 (3.1%)
	31-40	1 (1.5%)
	41-50	10 (15.4%)
	51-60	16 (24.6%)
	61-70	22 (33.8%)
	71-80	11 (16.9%)
	81-90	3 (4.6%)
Sex	Male	34 (52.3%)
	Female	31 (47.7%)
Interval from first diagnosis to discussion	Median (range), months	12.0 (2.9–252.0)
Patient Status	Primary diagnosis	15 (23.1%)
	Postoperative care	28 (43.1%)
	Recurrent/metastatic disease	22 (33.8%)
	Liver	7 (10.7%)
Primary tumor site	Peritoneum	5 (7.7%)
	Multiple sites	10 (15.4%)
	Stomach	41 (63.1%)
	Duodenum	9 (9.2%)
	Jejunum/Ileum	12 (18.5%)
	Colorectal	3 (4.6%)
	unknown	3 (4.6%)

(P 166) LARGE LANGUAGE MODEL EXTRACTION OF STRUCTURED DATA IN UNSTRUCTURED SARCOMA PATHOLOGY NOTES: A PILOT STUDY

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Objective: Bone and soft-tissue sarcomas are rare, heterogeneous tumors with unique treatment challenges. This heterogeneity has led to difficulty with registry curation, as well as effective outcomes assessment. The purpose of this study was to assess the feasibility of LLMs in extracting key information from surgical pathology notes following surgical sarcoma excision.

Methods: Surgical pathology notes were retrospectively identified from 353 patients who received surgical intervention for a diagnosis of bone or soft tissue sarcoma at one institution from 2000-2024. Data points of interest included tumor diagnosis (osteosarcoma, Ewing's sarcoma, etc), greatest dimension (cm), closest margin (cm), and grade. All labeled pathology notes were then split into test and training sets in an 85/15 split (303 testing notes, 50 training notes). Each LLM data extraction pipeline for each data point was developed using Llama-3-8B-Instruct (Meta).

Results: All LLM-enabled data extraction pipelines demonstrated satisfactory accuracies on the testing set following iterative prompt modification. Diagnosis, greatest dimension, closest margin, and grade accuracies were 98%, 88%, 85%, and 94%, respectively. The mean time of data extraction for each data point was 4.1 seconds.

Conclusion: This pilot study demonstrates critical proof of concept for automated registry production utilizing LLM outputs of unstructured pathology note data.

(P 167) **LARGE LANGUAGE MODEL EXTRACTION OF STRUCTURED DATA FROM UNSTRUCTURED RADIATION ONCOLOGY NOTES: A PILOT STUDY**

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Objective: Reliable registry curation is essential for outcome assessment. Since bone and soft-tissue sarcomas are rare, heterogeneous tumors with unique treatment challenges can make it difficult for creation of reliable registries. Multidisciplinary management including radiation is essential for the management of sarcoma and follow-up notes often contain unstructured data, requiring manual data abstraction for data tracking or attempted registry creation. Large language models (LLM) have potential to extract structured results from unstructured inputs. The purpose of this study was to assess the feasibility of LLMs in extracting information from radiation oncology notes of patients with sarcoma.

Methods: Follow-up notes were retrospectively identified from 544 patients who received surgical intervention for a diagnosis of bone or soft tissue sarcoma at one institution from 2000-2024. Data points of interest included location (anatomic location), radiation dose (in Gray) and stop date. Three human observers manually annotated all notes for each metric of interest. All labeled pathology notes were then split into test and training sets in a 90/10 split (490 testing notes, 54 training notes). Data was extracted through customized pipelines built with Llama-3-8B-Instruct (Meta), with the optimal prompting approach (one-shot, few-shot, or chain of thought reasoning) selected for each data point. Prompts were iteratively fine-tuned to teach the LLM background information and data extraction methodologies. The accuracy of developed pipelines was evaluated by comparing the LLM predictions with the manual labels (ground truths) on the held-out testing notes.

Results: All LLM-enabled data extraction pipelines demonstrated excellent accuracy on the location and dose, and moderate accuracy on stop date. The following accuracies were achieved: location(92%), dose (92%), and stop date (85%). The mean time of data extraction for each data point was 3 seconds.

Conclusion: This pilot study demonstrates a critical proof-of-concept for automated registry production utilizing LLM outputs of unstructured radiation oncology note data. The data extraction pipeline utilized an open-source model (critical for medical data safety) to demonstrate satisfactory accuracy in extracting key data elements. This approach holds promise to augment the efficiency and accuracy of human data abstraction for registry production, which can be leveraged for optimal risk stratification and outcomes assessments in future endeavors.

(P 168) LEVERAGING LARGE LANGUAGE MODELS FOR STRUCTURED INFORMATION EXTRACTION FROM EWING SARCOMA PATHOLOGY REPORTS

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Objective: Risk stratification in Ewing sarcoma (EWS) is dependent on tumor stage and size, with new prognostic factors needed. We will address this knowledge gap by leveraging computational pathology and advances in machine learning (ML). For this report we address the labor-intensive and time-consuming task to build a case bank of structured data from pathology reports to allow ML based knowledge discovery.

Methods: We secured 1,018 digitized histology images at time of biopsy with institutional pathology reports, from 932 unique patients enrolled on 7 Children's Oncology Group EWS clinical trials (AEWS0031, AEWS1031, AEWS1221, B947, AEWS02B1, AEWS07B1 and APEC14B1). Pathology reports were converted to text files using optical character recognition and we performed exploratory studies for pathological attributes for study with large language models (LLM).

Results: We developed a potential critical variable and EWS variable list based on the College of American Pathologists protocol on pathology reporting in JavaScript object notation form. Attributes such as procedure, specimen, and tumor site as well as their sub-attributes present broadly in pathology reports, while lympho-vascular invasion and regional lymph node status were present in over 80% of the reports. Accurate data extraction challenges include variability in reporting structure and terms, as well as the risk of hallucinations (which are LLM generated content that appear plausible but are factually false). To address these risks and optimize accuracy and reliability we use multiple LLMs to estimate pathological attributes, then combine the outputs by using ensemble methods, such as majority vote. The extracted structured data will enrich the context for classification tasks with computational pathology for this rare disease.

Conclusion: We have successfully extracted pathology report variables using LLM from a rare sarcoma. We will now merge AI extracted histology features, and pathology report variables with known clinical outcomes to create an integrated risk stratification model for sarcoma

patients that will be testable in future prospective clinical trials.

(P 169) BENCHMARKING LARGE LANGUAGE MODELS VS MULTIDISCIPLINARY TUMOR BOARDS OF 21 SARCOMA CENTERS

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Objective: This study compares treatment recommendations of four leading large language models (LLMs) with those of 21 multidisciplinary tumor boards (MDTs) from certified sarcoma centers.

Methods: We simulated STS MTBs using four LLMs – Llama 3.2-vision: 90b, Claude 3.5 Sonnet, DeepSeek-R1, and OpenAI-o1 – based on five anonymized STS cases (inguinal dedifferentiated liposarcoma (G2), chest wall myxoid liposarcoma (G3), retroperitoneal dedifferentiated liposarcoma (G2), well-differentiated liposarcoma (G1), popliteal pleomorphic rhabdomyosarcoma (G3)). Each model was queried 21 times per case using standardized input, and the responses were compared with human MTBs for consistency within the model, agreement of treatment recommendations, and source citations. The presented cases had previously been discussed in a ring trial of sarcoma MDTs at certified German sarcoma centers.

Results: LLMs showed consistency between models in 20% of cases, and their recommendations were consistent with human consensus patterns in 20–60% of cases. The best model, Claude 3.5 Sonnet, agreed with the experts in 60% of cases. MTD recommendations were very heterogeneous, which contextualizes the variable performance of the LLMs (figure 1). Some common human recommendations were missing from the LLM outputs. LLMs used national and international guidelines as sources for recommendations (e.g., the German sarcoma guideline in 24.8% to 55.2% of responses).

Conclusion: Both the recommendation patterns in the sarcoma ring study and those of the AI tools show considerable heterogeneity in the recommendations for a specific sarcoma case. The main reason for this is that there are only a few randomized studies available for common treatment decisions and that the guidelines do not provide clear, unambiguous recommendations. The considerable disagreements highlight the current limitations in the training and evaluation of AI tools as well as the heterogeneity of clinical practice in various sarcoma centers.

Pattern of treatment recommendations for a 67-year-old female patient with a high grade myxoid liposarcoma of the chest wall for MTDs of 21 different sarcoma centers and 21 consecutive runs of various LLMs.

	Surgery alone	Surgery and Radiotherapy	Surgery and Chemotherapy	Surgery and Chemo- and Radiotherapy	Other
MDT sarcoma centers	3	8	4	5	1
Llama 3.2 90B	.	.	.	21	.
Claude 3.5 Sonnet	.	21	.	.	.
DeepSee-R1	1	13	4	3	.
OpenAI-o1	4	15	.	2	.

(P 170) GEMSARC: AN AI BASED PREDICTIVE GENE SIGNATURE FOR GEMCITABINE EFFICACY IN ADVANCED SOFT-TISSUE SARCOMAS

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Objective: Predictive biomarkers that guide rational selection of therapeutic agents represent an unmet clinical need in patients with advanced soft-tissue sarcomas (STS). Studies in other malignancies have generated predictive signatures which patients who may benefit from Gemcitabine therapy, however no such biomarker exists in patients with STS. Here, we present GemSarc: an AI based predictive transcriptomic-based signature for gemcitabine efficacy in STS.

Methods: Participants enrolled in the prospective Electronic Health Record (EHR)-Based Comprehensive Bone and Soft Tumor Registry (NCT02677961) at The Ohio State James Cancer Center who had received gemcitabine-based chemotherapy for the treatment of STS were eligible for this study. A total of 36 patients were identified who had received at least one cycle of gemcitabine-based chemotherapy and had transcriptomic data available, between January 1st, 2014, to December 31st, 2022. Transcriptomic data from 11 STS cell lines from the Cancer Cell Line Encyclopedia (CCLE) was also included. Random Forest Machine Learning was utilized to identify genes significantly associated with Gemcitabine duration of therapy in patients and Gemcitabine IC50 in cell lines. These genes were used as input to build a gene expression signature, using a multivariate Cox regression with a Lasso penalty. This model was validated using an independent cohort of 31 STS patients from the Oncology Research Information Exchange Network (ORIEN).

Results: An 18-gene predictive signature of gemcitabine efficacy was built. GemSarc included genes related to nuclear transport, nucleotide metabolism and cell cycle progression; all processes known to drive gemcitabine resistance. Patients in the high-risk gene signature group showed a significantly shorter time on gemcitabine therapy compared to patients in the low-risk group: [2 months (95% CI 1.7-2.2) vs. 11 months (95% CI 8-12.2), $p < 0.05$]. Specificity/sensitivity analysis for gemcitabine duration of therapy on an independent cohort of 31 STS patients from ORIEN demonstrated an AUC of 0.8801 (95% CI: 0.8256- 0.9124). GemSarc did not predict gemcitabine efficacy in ORIEN patients with other cancer types.

Conclusion: Our study is one of the first Gemcitabine signatures in STS. Utilizing AI tools, we identified a novel 18-gene-based signature that predicts gemcitabine duration of therapy specific in two STS patient cohorts. Furthermore GemSarc was specific to STS. Prospective validation of this predictive gene signature is warranted.

GemSarc Model Performance on Training and Validation Cohorts

	OSU Cohort (N=36)	ORIEN Cohort (N=31)
Mean Time to Gemcitabine Discontinuation GemSarc High vs Low Risk (p value, 95% CI)	2.67 months vs 11.39 months ($p < 0.05$, 95% CI 8-12.2)	1.83 months vs 7.98 months ($p < 0.01$, 95% CI 5.84-9.12)
Hazard Ratio (p value, 95% CI)	0.2341 ($p < 0.01$, 95% CI: 0.082-0.66)	0.2987 ($p < 0.01$, 95% CI: 0.128-0.694)
Area Under Curve (95% CI)		0.8801 (95% CI: 0.8241-0.9346)

(P 171) THREE-DIMENSIONAL DEEP LEARNING MODEL FOR PREDICTING PROXIMAL FEMORAL PATHOLOGIC FRACTURE USING OPPORTUNISTIC ABDOMINOPELVIC CT IN PATIENTS WITH ADVANCED CANCER: A PRELIMINARY REPORT

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Objective: Proactive surgical intervention for proximal femoral pathologic fractures in patients with advanced cancer is crucial, and opportunistic use of follow-up abdominopelvic CT scans can help predict them. This study aimed to develop and validate a 3D deep learning model to predict the fractures.

Methods: A total of 2,933 abdominopelvic CT scans of 540 patients were collected from four tertiary academic hospitals. Since patients with bilateral proximal femoral metastatic lesions contributed two different cases from a single CT scan, 3,621 cases were finally included. There were 1,956 and 1,665 scans from females and males, respectively, with a mean age of 63 ± 11 years. The scans were labeled into fracture (F) and non-fracture (N) groups based on fracture occurrence within 3 months post-CT. Images were clipped to a bone window, normalized, and converted to 3D volumes using anterior-inferior-iliac-spine-based segmentation. From this landmark, 32 consecutive axial slices were extracted to create three-dimensional input volumes. The training dataset, from a single institution, included 1,884 N- and 12 F-labelled scans, and the latter was augmented 20-fold through affine transformations. Internal validation used 472 N- and 12 augmented F-labelled scans. An external test set comprised 1,241 scans from the other institutions: 1,214 N- and 27 F-labelled scans. Performance of four 3D deep learning models (ResNet-18, ResNet-34, DenseNet-121, and Swin Transformer) was evaluated.

Results: DenseNet-121 apparently showed the highest external test performance, (accuracy 0.9315, sensitivity 0.8483, specificity 0.9703, precision 0.9315, F1 score 0.9315). ResNet-34 followed closely (accuracy 0.9242, sensitivity 0.7743, specificity 0.9942, precision 0.9242, F1 score 0.9242), showing better performance than ResNet-18 (accuracy 0.8782, sensitivity 0.8201, specificity 0.9053, precision 0.8782, F1 score 0.8782). Swin Transformer showed lower performance (accuracy 0.5244, sensitivity 0.3686, specificity 0.5972, precision 0.5244, F1 score 0.5244).

Conclusion: The three-dimensional deep learning model alone demonstrated promising performance. Evaluating how model-assisted predictions influence clinical decision-making is essential to establish the model's clinical utility. To improve the model's robustness and generalizability, an extensive dataset will be derived from the Clinical Data Warehouse.

(P 172) COMPARISON OF CELL SEGMENTATION METHODS IN SOFT TISSUE SARCOMA (STS) SPATIAL PROTEOMIC DATASETS

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Objective: Accurate cell segmentation in spatial proteomic images is essential for analyzing the heterogeneous STS immune microenvironment. Benchmarking segmentation algorithms remains challenging due to limited high-quality, hand annotated cell masks. Recently developed reference-free quality scores enable comparison of algorithms without ground-truth annotations.

Methods: Sequential immunofluorescence was performed on tissue microarrays (1mm cores) representing 4 common STS: dedifferentiated liposarcoma [DDLPS], soft tissue leiomyosarcoma [STLMS], undifferentiated pleomorphic sarcoma [UPS], and uterine leiomyosarcoma [ULMS], using a 20-plex antibody panel on the Lunaphore Comet™ platform. Cell segmentation was performed on the images (5358 × 5358 pixels) of 27 samples based on nuclear (DAPI) and CD45 staining using four pre-trained deep learning methods: StarDist, Cellpose, MEDIAR, and CellSAM. The resulting segmentation masks and corresponding images were partitioned into non-overlapping 512 × 512 pixel tiles. Segmentation quality was assessed using a reference-free scoring framework across tiles with ≥10 cells detected by all methods. For validation, we manually annotated cell boundaries in 9 tiles (256 × 256 pixels) as the ground truth and calculated mean average precision (mAP).

Results: Among 954 image tiles evaluated, CellSAM achieved the best overall segmentation quality with a median reference-free quality score of 3.94, outperforming StarDist (3.85), MEDIAR (3.81), and Cellpose (3.85) ($p < 0.001$). Segmentation quality varied by sarcoma subtype with STLMS having the highest median scores (4.02), followed by ULMS (3.94), UPS (3.86) and DDLPS (3.79). In the hand-annotated tiles, CellSAM again outperformed the other methods (median mAP 0.47 vs MEDIAR 0.40, Cellpose 0.33, and StarDist 0.24; $p = 0.008$).

Conclusion: Reference-free quality scoring framework revealed significant differences in performance across 4 cell segmentation methods applied to STS images. CellSAM demonstrated the highest median quality score. Segmentation quality varied by STS subtypes, highlighting tissue heterogeneity's impact on algorithm performance.

(P 173) DEVELOPMENT AND EXTERNAL VALIDATION OF A MACHINE LEARNING ALGORITHM TO PREDICT OVERALL SURVIVAL IN PATIENTS WITH PELVIC OR APPENDICULAR LIPOSARCOMA

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Objective: Liposarcoma accounts for approximately 20% of all soft tissue sarcomas, making it one of the most common subtypes. Despite this prevalence, predicting survival outcomes remains challenging due to significant heterogeneity across histologic subtypes, anatomical locations, and patient characteristics. Current prognostic approaches rely on limited clinical factors and lack the ability to integrate complex personalized data. Machine learning (ML) offers a promising solution to enhance predictive accuracy through pattern recognition in high-dimensional datasets. Thus, this study aimed to develop and validate an ML algorithm capable of predicting one-, two-, five-, and ten-year overall survival (OS) in liposarcoma patients, with adaptability to treatment type.

Methods: We included 6,643 patients with histologically confirmed liposarcoma from the SEER database for model training and internal validation, plus 200 patients from an institutional database for external validation. Patient data were converted into high-dimensional embeddings using a pre-trained language model. Multiple ML algorithms were developed and compared, with performance assessed using AUC, precision, recall, F1-scores, and Brier scores.

Results: Key predictors included histologic subtype, tumor size, anatomical location, age, metastatic status, and surgical margins. Our neural network demonstrated superior performance with internal validation AUCs of 0.82, 0.77, 0.68, and 0.6 and external validation AUCs of 0.93, 0.96, 0.95, and 0.95 for one-, two-, five-, and ten-year OS, respectively.

Conclusion: We successfully developed an ML algorithm that accurately predicts survival in liposarcoma patients, adaptable to treatment type. Additional multi-institutional external validation is recommended for broader clinical applicability.

Comparison of performance metrics for the internal validation and external validation of the neural network

Internal Validation				
Metric	1-year OS	2-year OS	5-year OS	10-year OS
AUC	0.759 (0.689-0.825)	0.742 (0.687-0.787)	0.714 (0.683-0.746)	0.854 (0.834-0.875)
Accuracy	0.959 (0.949-0.969)	0.898 (0.883-0.916)	0.764 (0.743-0.787)	0.780 (0.756-0.804)
Precision	0.959 (0.949-0.969)	0.898 (0.883-0.916)	0.760 (0.738-0.783)	0.605 (0.545-0.668)
Recall	1.000 (1.000-1.000)	1.000 (1.000-1.000)	0.989 (0.981-0.995)	0.463 (0.407-0.520)
F1 score	0.979 (0.974-0.984)	0.946 (0.938-0.956)	0.859 (0.844-0.874)	0.524 (0.472-0.574)
Brier	0.038 (0.029-0.047)	0.084 (0.072-0.096)	0.173 (0.163-0.184)	0.139 (0.130-0.148)
External Validation				
Metric	1-year OS	2-year OS	5-year OS	10-year OS
AUC	0.927 (0.864-0.977)	0.955 (0.913-0.988)	0.951 (0.909-0.980)	0.949 (0.903-0.985)
Accuracy	0.889 (0.838-0.925)	0.863 (0.808-0.904)	0.872 (0.819-0.911)	0.855 (0.800-0.897)
Precision	0.951 (0.912-0.973)	0.964 (0.928-0.982)	0.928 (0.884-0.956)	0.889 (0.838-0.925)
Recall	0.925 (0.880-0.954)	0.860 (0.805-0.901)	0.865 (0.811-0.906)	0.814 (0.754-0.862)
F1 score	0.938 (0.896-0.964)	0.909 (0.861-0.942)	0.895 (0.845-0.930)	0.850 (0.794-0.893)
Brier	0.070 (0.031-0.109)	0.086 (0.047-0.125)	0.095 (0.056-0.134)	0.089 (0.050-0.128)

(P 174) BIAS OR BEST FIT? A COMPARATIVE ANALYSIS OF SEER AND NCDB DATASETS IN SINGLE MODEL MACHINE LEARNING FOR PREDICTING OSTEOSARCOMA SURVIVAL OUTCOMES

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Objective: Machine learning models have been increasingly utilized in orthopaedic oncology to predict survival outcomes for osteosarcoma patients. Typically, these models are trained on a

single dataset, such as the Surveillance, Epidemiology, and End Results(SEER) or the National Cancer Database(NCDB). However, this approach may lead to biased predictions that mirror the characteristics of the training data. In this study, we aimed to determine which dataset performs better with a single-model machine learning(SMML) model.

Methods: We included a total of 4,049 patients from the NCDB dataset and 4,278 patients from the SEER dataset with confirmed osteosarcoma. We developed an SMML model for each dataset and compared the performance of these models. The primary outcomes to assess each SMML were accuracy, area under the receiver curve(AUC), Brier score, precision, and F1 score.

Results: SMML models trained and validated on the same dataset displayed excellent performance predicting 2-year and 5-year overall survival(OS). The NCDB-trained/validated model had an AUC of 0.927 at 2 years and 0.911 at 5 years, compared to 0.898 and 0.916 for the SEER-trained/validated model. The NCDB-trained and SEER-validated model had an AUC of 0.665 and 0.599 for 2-year and 5-year OS, respectively. The SEER-trained and NCDB-validated model had an AUC of 0.606 and 0.563 for 2-year and 5-year OS, respectively.

Conclusion: These results highlight the challenges in generalizing models across different datasets in medical machine learning development and prognosis prediction, suggesting significant differences between the NCDB and SEER datasets or potential overfitting to dataset-specific characteristics.

Comparison of performance metrics between single model same dataset training and validation and cross dataset validation

2-year OS						
Metric	NCDB trained - NCDB validated	SEER trained - SEER validated	P value	NCDB trained - SEER validated	SEER trained - NCDB validated	P value
AUC	0.927 (0.919- 0.935)	0.898 (0.889- 0.907)	< 0.05	0.665 (0.651-0.679)	0.606 (0.590-0.620)	< 0.001
Brier Score	0.078	0.120		0.226	0.238	
Precision	0.903 (0.894- 0.912)	0.869 (0.859- 0.879)	< 0.001	0.675 (0.661-0.689)	0.625 (0.611-0.639)	< 0.001
Recall	0.961 (0.955- 0.967)	0.863 (0.852- 0.873)	< 0.001	0.992 (0.989-0.994)	0.701 (0.687-0.715)	< 0.001
F1-score	0.931 (0.923- 0.938)	0.866 (0.856- 0.876)	< 0.001	0.803 (0.791-0.815)	0.661 (0.647-0.675)	< 0.001
5-year OS						
Metric	NCDB trained - NCDB validated	SEER trained - SEER validated	P value	NCDB trained - SEER validated	SEER trained - NCDB validated	P value
AUC	0.911 (0.902- 0.919)	0.916 (0.907- 0.924)	0.683	0.599 (0.583-0.615)	0.563 (0.548-0.578)	0.0013
Brier Score	0.118	0.114		0.266	0.253	
Precision	0.805 (0.793- 0.817)	0.787 (0.775- 0.799)	0.038	0.638 (0.610-0.666)	0.700 (0.686-0.714)	< 0.001
Recall	0.918 (0.909- 0.926)	0.865 (0.854- 0.875)	< 0.001	0.392 (0.369-0.413)	0.007 (0.005-0.010)	< 0.001
F1-score	0.858 (0.847- 0.868)	0.824 (0.812- 0.835)	< 0.001	0.486 (0.463-0.505)	0.013 (0.010-0.017)	< 0.001

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Objective: A subset of sarcomas is immunogenic and responsive to immunotherapy. Identification of sarcoma immune subtypes (SICs) has previously required transcriptomic profiling. We aimed to develop an interpretable, AI-driven pathology model to classify SICs directly from H&E-stained whole-slide images (WSIs), offering immune stratification based on histopathological features.

Methods: Using WSIs from The Cancer Genome Atlas (TCGA) with SICs annotated per Petitprez et al. (Nature 2020), we evaluated three embeddings and 5 aggregators in distinguishing SIC E (immunologically active) from non-E. Integrated Gradients (IG) analyses were performed to identify features contributing to SIC E classification.

Results: CONCHv1.5 with slide encoder achieved AUROC of 0.907 in distinguishing SIC E from non-E. Regions driving SIC E predictions had features such as high immune cell interconnectivity and tumor-immune proximity.

Conclusion: We developed a deep learning model capable of classifying SICs from H&E WSIs, offering scalable, sequencing-free identification of patients likely to benefit from immunotherapy.

Performance of models in distinguishing SIC E from non-E.

Model	MeanMIL			ABMIL			TransMIL			TEA-graph			Slide Encoder			
	U	C	P	U	C	P	U	C	P	U	C	P	Linear	Finetune		
Feature*	U	C	P	U	C	P	U	C	P	U	C	P	C	P	C	P
Accuracy	.743	.805	.657	.589	.650	.611	.739	.790	.689	.724	.797	.772	.775	.741	.846	.792
AUROC	.816	.864	.738	.691	.668	.724	.798	.830	.708	.816	.859	.790	.832	.730	.907	.814
F1 Score	.554	.652	.441	.349	.386	.364	.571	.625	.500	.552	.639	.526	.577	.514	.667	.640
Interpretability																
Features** (log FC)	Immune Cell Fraction						Graph Features (T: Tumor, I: Immune)									
	I-I Coreness						I-I Betweenness (normalized)			I-I Degrees			T-I Edge Length (mm)			
High IG / Background	1.185 (***)						0.241 (**)			0.292 (**)			0.278 (*)			
Low IG / Background	0.221 (n.s.)						-0.481 (***)			-0.248 (**)			-0.593 (***)			

*UN2 (U), CONCHv1.5 (C), ProVigra (P), **Interpretability features shown for the top model.

(P 176) DEEP LEARNING MODEL FOR DIFFERENTIATING BETWEEN NEOPLASTIC PATHOLOGIC FRACTURE AND NONPATHOLOGIC FRACTURE FROM PLAIN HIP RADIOGRAPHS

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Objective: Although radiographs are the first-line imaging modality, differentiating between neoplastic pathologic fractures and nonpathologic fractures on radiographs can sometimes be challenging. Misdiagnosing a neoplastic fracture as nonpathologic and providing standard fracture treatment may result in devastating outcomes, including limb amputation or death. This study aimed to develop and evaluate a deep learning model capable of distinguishing neoplastic pathologic fractures from nonpathologic fractures on hip radiographs to enhance diagnostic accuracy.

Methods: This retrospective, multicenter study analyzed anteroposterior hip radiographs from patients who visited the emergency department at four distinct institutions. The deep learning model was trained and tested on data from 338 patients at a single institution and externally validated on data from 488 patients across three additional institutions.

Results: The model achieved an overall accuracy of 88.0%, with a sensitivity of 88.2% and a specificity of 87.9% on the internal test set. It was then externally tested on 488 patients from institutions separate from where it was developed, including 67 cases of neoplastic pathologic fractures and 421 nonpathologic fractures. The model achieved an overall accuracy of 84.8%, sensitivity of 91.0%, and specificity of 78.6%. Its performance was comparable to that of general orthopedic surgeons.

Conclusion: Our deep learning model demonstrates robust performance in distinguishing neoplastic pathologic fractures from nonpathologic fractures on hip radiographs, offering a clinically meaningful diagnostic aid. By enabling early and accurate identification of neoplastic lesions, especially in resource-constrained settings, the tool has the potential to significantly reduce misdiagnosis-related morbidity. To enhance clinical accessibility and impact, the model is freely available at <https://pathfxdx.org>.

Performance of the model compared to experts

	F1 Score	Accuracy	Sensitivity	Specificity	PPV	NPV	P-value
Model	0.85	0.90	0.82	0.94	0.88	0.91	-
Expert1	0.63	0.74	0.65	0.79	0.61	0.81	0.08
Expert2	0.63	0.70	0.76	0.67	0.54	0.85	0.02
Expert3	0.75	0.84	0.71	0.91	0.80	0.86	0.27
Expert consensus	0.72	0.80	0.76	0.82	0.68	0.87	0.50

(P 177) DEEP LEARNING AND DIMENSIONALITY REDUCTION FOR SARCOMA SUBTYPING

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Objective: Synovial sarcoma (SS) and leiomyosarcoma (LMS) are distinct soft tissue sarcomas with overlapping histologic characteristics, complicating accurate diagnosis. Traditional diagnostic methods involving histopathologic evaluation, immunohistochemistry, and molecular testing are often time-consuming, subjective, and resource intensive. The objective of this study was to leverage convolutional neural networks (CNNs) and Uniform Manifold Approximation and Projection (UMAP) to improve diagnostic accuracy, reduce reliance on ancillary testing, and provide interpretable deep learning visualizations.

Methods: This computational study used six SS and seven LMS whole-slide images from The Cancer Genome Atlas. After background removal, slides were segmented into 225×225-pixel grayscale images, and a random sample of 5000 of these images (2500 SS, 2500 LMS) was drawn due to limitations in computing power. Data were partitioned into training (80%), validation (10%), and testing (10%) sets. We employed a pre-trained ResNet50 model and used transfer learning with data augmentation, dropout layers, Adam optimization, and early stopping to mitigate overfitting. UMAP was applied to visualize high-dimensional CNN embeddings. Generalized model performance will be validated on independent samples in the future.

Results: Preliminary results demonstrated that CNN-based classification effectively distinguished SS from LMS (accuracy: 97.4%) capturing morphological subtleties not readily discernible through conventional methods. UMAP visualization facilitated interpretability by illustrating distinct clustering of CNN-derived features for SS and LMS.

Conclusion: Integration of CNNs and UMAP offers a promising AI-driven approach to improve sarcoma classification accuracy, potentially reducing reliance on ancillary diagnostic testing. Future work will address validation with external datasets to further establish clinical utility and generalizability.

Table 1: Model Performance Metrics

Accuracy	0.9740
Precision	0.9793
Recall (Sensitivity)	0.9673
Specificity	0.9804
F1 Score	0.9733

(P 178) TREATMENT RESPONSE AND SURVIVAL OUTCOMES IN GASTROINTESTINAL STROMAL TUMORS FOLLOWING NEOADJUVANT THERAPY

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Objective: Gastrointestinal stromal tumors (GIST) are the most common mesenchymal tumors of the gastrointestinal tract. Neoadjuvant therapy may be used to improve resectability. However, the optimal treatment duration before surgery and role of mutation-specific treatment decisions remain unclear. This study evaluates treatment response and survival outcomes in patients receiving neoadjuvant imatinib.

Methods: This retrospective cohort study used data from a Provincial Cancer Registry for patients diagnosed with GIST between 2010 and 2022. Of 925 charts reviewed, 79 patients who received neoadjuvant therapy followed by curative-intent surgical resection were included. Data collected included demographics, tumor characteristics, mutational profile, treatment duration, surgical outcomes, recurrence, and survival.

Results: Of the 79 patients, 73.4% had gastric and 17.7% had small intestine tumors. The median baseline tumor size was 10.6 cm, which decreased by a median of 3.5 cm after neoadjuvant therapy. Notably, 50.6% of patients achieved partial response based on the

RECIST, 46.8% had stable tumor size, and 2.5% had tumor progression. The median duration of neoadjuvant therapy was 9.6 months. 53.2% of patients completed three years of combined neoadjuvant and adjuvant therapy. Mutational analysis was performed in 57% of patients (43/79 c-KIT, 2/79 PDGFRA mutations). Multivisceral resection was required in 49.4% of cases, with an R0 resection rate of 96.2%. Recurrence occurred in 36.7% of patients during follow-up. The 5-year overall and relapse-free survival rates were 84.7% and 62.3%, respectively. Multivariable Cox regression analysis revealed that non-gastric tumor site (hazard ratio [HR] 4.96, $p = 0.008$), R1 resection margins (HR 8.16, $p = 0.019$), and older age (HR 1.12 per year, $p = 0.001$) were associated with worse overall survival. A high mitotic rate ($> 5/50$ high-power fields; HR 3.37, $p = 0.005$) and increasing age (HR 1.05 per year, $p = 0.016$) were strong predictors of recurrence.

Conclusion: Neoadjuvant therapy in patients with large or locally advanced GISTs results in significant tumor response in most cases and is associated with favorable long-term recurrence and survival outcomes.

(P 179) NEOADJUVANT AVAPRITINIB IN PDGFRA-MUTANT GIST: NEAR COMPLETE PATHOLOGICAL RESPONSES AT THE COST OF HIGH ADVERSE EVENT RATES

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Objective: To evaluate the therapeutic response and safety profile of neoadjuvant avapritinib in patients with localized PDGFRA-mutant gastrointestinal stromal tumors (GIST).

Methods: A retrospective analysis was performed on six patients with biopsy-confirmed, localized PDGFRA-mutant gastric GIST treated with neoadjuvant avapritinib (300 mg daily) between 2020 and 2025. Tumor response was assessed by change in maximal tumor diameter between baseline and post-treatment CT scans according to radiology reports and independent review. In patients who underwent resection, surgical specimens were evaluated by board-certified pathologists for tumor viability, necrosis, and mitotic index in accordance with institutional protocols. Adverse events were graded according to CTCAE version 5.0.

Results: The median duration of avapritinib therapy was 2 months (range, < 1 to 6 months). Among all six patients, radiographic tumor shrinkage ranged from 2% to 49%, with greater regression associated with longer treatment duration. Three patients discontinued therapy early; all experienced grade ≥ 3 treatment-related adverse events, including one fatal intracranial hemorrhage. Of the three who underwent surgical resection with curative intent, complete (100%) or near-complete (98%) pathologic responses were achieved, highlighting discordance between radiographic and pathologic response in avapritinib-treated tumors.

Conclusion: Neoadjuvant avapritinib induced tumor regression in PDGFRA-mutant GIST; however, the high incidence of serious treatment-related toxicities, including a fatal adverse event, raises concern regarding its tolerability and real-world applications. These findings emphasize the necessity of cautious clinical consideration, with close attention to patient selection, risk-benefit balance, and alternative therapeutic approaches when prescribing

avapritinib in the neoadjuvant setting.

(P 180) COMPARATIVE EFFICACY OF GENERIC AND BRAND-NAME IMATINIB IN NEOADJUVANT TREATMENT OF KIT EXON 11 MUTANT GIST

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Objective: To compare the clinical and pathological efficacy of FDA-approved generic versus brand-name imatinib in patients with localized KIT exon 11–mutant gastrointestinal stromal tumors (GIST) treated with neoadjuvant intent.

Methods: A retrospective analysis was conducted on 70 patients with resectable KIT exon 11–mutant GIST (without co-mutations in other genes) treated with neoadjuvant imatinib between 2010 and 2025. Patients received either FDA-approved generic (n=53) or brand-name (n=17) formulations. Tumor response was defined as the percent change in maximum tumor diameter between pretreatment cross-sectional imaging and post-resection pathology; partial response (PR) was defined per RECIST criteria as $\geq 30\%$ tumor shrinkage. Histopathologic features including tumor viability, necrosis, and mitotic index were assessed by board-certified pathologists during routine surgical evaluation. Comparative analyses used nonparametric testing and multivariable linear regression.

Results: Clinicopathologic features were similar between groups. Median tumor reduction was -24% in the generic cohort and -22% in the brand-name group ($P = 0.79$), with comparable rates of partial response (34% vs 35%). No significant differences in tumor viability, necrosis, or mitotic index were observed between formulations. Notably, longer treatment duration, regardless of drug type, was associated with greater tumor shrinkage (Pearson's $r = -0.26$; $P = 0.032$).

Conclusion: In this single institution, retrospective cohort of patients with resectable KIT exon 11–mutant GIST, neoadjuvant treatment with FDA-approved generic and brand-name imatinib was associated with comparable radiographic and pathologic responses. These findings support the clinical equivalence of generic imatinib and its role as a viable alternative in curative-intent therapy.

Clinicopathologic Characteristics by Imatinib Formulation

Characteristic	Generic (n = 53)	Brand-Name (n = 17)	P Value
Age, median (IQR), y	63 (49–72)	72 (60–76)	.51
Female, No. (%)	23 (43%)	8 (47%)	
Male, No. (%)	30 (57%)	9 (53%)	
Tumor size reduction, % (median [IQR])	~24% [~38% to ~8%]	~22% [~40% to 5%]	.79
Treatment duration, mo (median [IQR])	9 [8–12]	5 [4–8]	.29
Tumor viability, % (median [IQR])	5 [0–40]	10 [5–90]	.92
Tumor necrosis, % (median [IQR])	0 [0–30]	0 [0–10]	.61
Mitotic index, (median [IQR] per 5 mm ²)	1 [0–3]	1 [0–2]	.63
Tumor site, No. (%)			.55
Gastric	38 (72%)	12 (70%)	
Small Bowel	12 (23%)	5 (30%)	
Rectum	3 (5%)	0 (0%)	
Mutation type, No. (%)			.77
In-frame Deletion	25 (47%)	10 (59%)	
Missense	18 (34%)	6 (35%)	
Del-Ins	6 (11%)	1 (6%)	
Insertion	2 (4%)	0 (0%)	
Other	2 (4%)	0 (0%)	

(P 182) USING IN VITRO MODELS TO PREDICT IMATINIB RESPONSES OF PDGFRA EXON 18-MUTANT GIST

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Objective: Gastrointestinal stromal tumor (GIST) is the most common sarcoma with 85% of cases driven by mutations in KIT or PDGFRA, which are treated with tyrosine kinase inhibitors (TKIs). First-line (1L) imatinib (IM), a type II TKI, is effective for KIT mutations but not for the most common PDGFRA driver mutation, exon 18 D842V. While D842V is resistant to all type II TKIs, avapritinib (AVA), a type I TKI, is FDA-approved for all exon 18 PDGFRA-mutant GIST. Outside the US, AVA is only available for D842V-mutant GIST or not at all, leaving some patients with no treatment. As some clinical evidence suggests the use of IM in some exon 18 cases, its usage is not well defined, therefore the use of predictive in vitro models define which exon 18 mutations could be treated with IM, a more accessible drug than AVA. We curated a cohort of 1019 patients with PDGFRA-exon 18 mutant GIST. ~67% had D842V, and ~33% had non-D842V point mutations or complex in/dels, and ~78% of all cases had mutations involving the 842 residue. We hypothesized that IM sensitivity could be predicted based on the nature of the amino acid in the 842-position.

Methods: We modeled all 20 amino acids at the 842 position in both point mutation and 4-residue deletion contexts, that were expressed in Ba/F3s or CHOs, and assessed TKI sensitivities with immunoblotting. In silico modeling was performed using PyMol.

Results: When in the 842-position, hydrophobic amino acids except for alanine were IM resistant, while all other amino acids in the polar, +/- charged, and special case classes were IM sensitive. 1L IM response data were concordant with these predictions, where the median

progression free survival for predicted IM-resistant mutations (n=80) was 4 months compared to 30 months for those with predicted IM-sensitive mutations (n=35) (HR 3.028, CI 2.011-4.561, $p < 0.0001$). In silico modeling showed that IM binding depends on the structure of the amino acid side chain at the 842 position.

Conclusion: Our models defined cases where 1L IM can be used to treat PDGFRA exon 18 mutant GIST while also defining those that require 1L AVA. We suggest that all patients with predicted IM-sensitive mutations should receive 1L IM, regardless of regulatory approvals in a country, as IM is more widely available and more cost-effective than AVA. Our work highlights a paradigm shifting approach in which clinical guidelines for the treatment of PDGFRA-mutant GIST should be based on specific patient mutations, allowing for the optimization of patient care.

(P 183) ACTIONABLE GENOMICS IN GASTROINTESTINAL STROMAL TUMORS LACKING KIT OR PDGFRA MUTATIONS.

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Objective: KIT or PDGFRA mutations are established drivers of GIST, targeted via tyrosine kinase inhibition. Less is understood of the pathogenesis of KIT/PDGFRA-wild type GIST, for which therapies are limited.

Methods: cBioPortal was queried for GIST without KIT/PDGFRA alteration (WT). Frequency of mutations (mut), copy number alterations including homologous deletions (homdel), and gene structural variants was described. Alterations (alt) were assessed for potential actionability (PA); marked "*", based on at least "compelling biological evidence" of an alteration's role as a predictive biomarker per OncoKB. Clinicopathologic characteristics were compared between WT and patients with KIT/PDGFRA-mutated (MUT) via chi square and Wilcoxon tests. Overall survival (OS) was compared via Kaplan-Meier.

Results: Of 499 cases, 68 (13.6%) were WT: 36 gastric (59.0%), 23 small bowel (37.7%), 1 colorectal and 1 esophageal (1.6%). Alt in 97 genes were identified, most commonly NF1 (31%), SDHA (22%), TP53 (10%), TERT (9%) and MAX (7%). PA alt were found in n=7/68 tumors (10.3%), most in primary (n=5/7; 71.4%) vs metastatic tissue (28.6%). Identified RTK/MAPK pathway alt included BRAF (n=2 mut* + 1 structural variant*, 4.4%), EGFR (n=2 mut, 2.9%), ROS1 (n=2 mut, 2.9%), FGFR1 (n=1 mut*, 1.5%), and RET (n=1 homdel, 1.5%). PI3K/AKT/mTOR pathway alt included AKT1 (n=3 homdel, 4.4%), MTOR (n=2 mut*, 2.9%), PIK3CD (n=2 homdel, 2.9%), TSC2 (n=1 homdel* + 1 mut, 2.9%), and TSC1 (n=1 mut, 1.5%). DNA damage repair pathway alt included PALB2 (n=1 mut, 1.5%), RAD51D (n=1 homdel, 1.5%), FANCC (n=1 mut, 1.5%), ATM (n=1 mut*, 1.5%), and CHEK2 (n=1 homdel, 1.5%). Patients with WT were younger (median age 48 vs 63; $p < 0.001$) and more often female (64.7% vs 44.1%, $p < 0.001$). OS between cohorts did not differ after controlling for stage (IV) and primary site (gastric), likely due to limited sample (log-rank $p=0.323$). However, median OS was 52.5 months in MUT and not reached in WT gastric, stage IV GIST.

Conclusion: Actionable somatic alterations may occur in ~10% of KIT/PDGFR- α -WT GIST. RTK/MAPK pathway and less commonly the PI3K/AKT/MTOR and homologous recombination repair pathways are affected.

(P 184) MTAP IN GASTROINTESTINAL STROMAL TUMOR (GIST): RATE OF MTAP LOSS AND CONCORDANCE BETWEEN GENOMIC SEQUENCING AND IMMUNOHISTOCHEMISTRY

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Objective: GIST harboring CDKN2A homozygous deletion (del) have poorer prognosis. In solid tumors with CDKN2A del, co-deletion of the neighboring gene MTAP is common and actionable with PRMT5 inhibitors (PRMT5i). This study evaluates the rate of MTAP loss in GIST and the concordance between targeted exome sequencing (TES) and IHC.

Methods: Two tissue microarrays (TMAs) containing both primary and metastatic (met) GIST surgical specimens were stained for MTAP (Abnova monoclonal antibody clone 2G4). To evaluate IHC and TES concordance, a separate cohort with available research TES (Oncopanel) showing MTAP del or CDKN2A del was formed and clinically annotated. MTAP status was recorded as wild type (WT), single copy loss (SCL), or del. MTAP IHC was performed on the profiled tissue and additional specimens, if available.

Results: The 2 TMAs included primary tumors and mets and revealed a similar rate of MTAP loss in primary tumors (12/58, 21%) and mets (4/16, 25%). MTAP loss was enriched in patients (pts) presenting with mets (6/11, 55%) vs localized disease (10/59, 17%; $p=0.02$). The TES cohort included 23 pts with 28 profiled specimens; 14 pts (61%) presented with mets and an additional 7 (91% total) developed mets during median follow-up of 7.8 years (range 2.0-23.3). 75% of profiled specimens were mets; 9 (32%) MTAP del, 12 (43%) SCL, and 7 (25%) WT. MTAP del always co-occurred with CDKN2A del. 19 specimens were available for paired IHC. All cases with MTAP del on TES showed MTAP loss by IHC, and all SCL or WT showed retained MTAP by IHC. All pts with MTAP del by TES had MTAP loss in the primary tumor (5/7 available). Seven pts had more than one specimen available for IHC, and MTAP status was consistent across specimens with 1 intriguing exception: a patient with a primary tumor showing MTAP loss had a met with MTAP WT, both confirmed by TES and IHC.

Conclusion: MTAP del is common in GIST and enriched in pts presenting with mets. We found 100% concordance between MTAP del by TES and MTAP loss by IHC in this small series. In MTAP del cases, all available primary tumors had MTAP loss, but further studies are needed to determine if the event is truncal or subclonal. These data provide fundamental information for

investigating PRMT5i in GIST with MTAP del.

(P 185) CANCER TESTIS ANTIGENS AS TARGETS IN KIT11-MUTATED, IMATINIB-RESISTANT GIST

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Objective: Treatment of gastrointestinal stromal tumors (GIST) involves tyrosine kinase inhibitors (TKIs) such as imatinib (IM) which are directed against KIT and PDGFRA. However, TKI-independent approaches are lacking. We sought to identify alternate therapeutic targets in IM-resistant (IM-res) tumors with KIT exon 11 mutations (KIT11-mut) using a bioinformatics approach.

Methods: As described by Vitiello et al (2019), samples from 75 patients with resected GIST underwent RNA sequencing. Counts were TPM-normalized, log-transformed, and correlated with clinicopathologic data. Differential gene expression (DGE) was performed using DESeq2. Genes of interest were defined as demonstrating log2 fold change (logFC) > 2, and adjusted p < 0.05. DGE analysis compared 1) KIT- vs. PDGFRA-mutated (mut) tumors, and 2) IM-untreated/sensitive (IM-u/s) vs. IM-res KIT11-mut tumors. Pathway analysis was performed using Cluster Profiler. R version 4.5.0 was used.

Results: A number of cancer testis antigens (CTAs) were among the most overexpressed genes in KIT-mut tumors (n=41) as compared with PDGFRA-mut tumors (n=24): MAGEA3 (logFC = 21), MAGEA6 (8.1), MAGEC2 (7.7), MAGEA1 (5.8), MAGEB17 (5.0), and MAGEC3 (2.6). PDGFRA-mut tumors were enriched in genes involved in regulation of membrane potential, chemotaxis, and ERK1/2 signaling. Subsequent DGE analysis revealed that among the most overexpressed genes in KIT11-mut IM-res (n=15) tumors, as compared with IM-u/s tumors (n=22), were MAGEA6 (logFC = 6.7), MAGEA3 (6.4), and MAGEA12 (4.8). 17/37 (45.9%) of KIT11-mut tumors expressed 1 or more MAGE gene. IM-res KIT11-mut tumors were enriched in genes involved in nuclear division, organelle fission, and cytoskeleton/intermediate filament organization.

Conclusion: CTAs are overexpressed in KIT-mut GIST as compared with PDGFRA-mut GIST, with nearly half expressing at least 1 MAGE gene and notable overexpression of MAGEA3. Both MAGEA3 and MAGEA6 were overexpressed in KIT11-mut IM-res tumors, which also demonstrated typical hallmarks of aggressiveness on pathway analysis. Given the recent success of T cell therapies directed against CTAs, and a lack of treatments for GIST beyond TKIs, further investigation is warranted to determine if CTA expression can be exploited in novel therapeutic approaches.

(P 186) BRAF V600E-MUTATED GASTROINTESTINAL STROMAL TUMORS: A CASE SERIES AND ANALYSIS OF IMMUNE TUMOR INFILTRATE

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Objective: BRAF V600E-mutated gastrointestinal stromal tumors (GISTs) represent a rare molecular subset, accounting for ~1% of all GISTs. Although BRAF/MEK inhibitors show clinical activity and have received tumor-agnostic regulatory approval, treatments beyond this remain undefined. The immune cell landscape and potential role for immune checkpoint inhibitors (ICIs) in this population are not well characterized.

Methods: We retrospectively identified patients with BRAF V600E mutant GIST at Memorial Sloan Kettering Cancer Center (2009–2024) who underwent next-generation sequencing. Clinical, demographic, genomic, and treatment data were extracted. Immunohistochemistry (IHC) for PD-L1, PD-1, LAG-3, CD3, CD8 and CD20 was performed on available tumor specimens from metastatic patients.

Results: Five patients (median age 48, 4M/1F) were identified; primary tumor locations included small bowel (n=4) and gastric (n=1). Four presented with localized disease (one had metastatic recurrence after 6m [patient A]); one patient (B) presented with metastatic disease at diagnosis. All patients were found to harbor the BRAF V600E mutation, with additional co-alterations identified: EP300, RB1, NF1, and TSC2 in one patient, FLT4 in one patient, and JAK3 in one patient. Both patients with advanced disease received BRAF+/- MEK inhibition in the first-line setting. Patient A received vemurafenib for 21 months achieving an initial response, followed by gradual progression. He subsequently received dabrafenib/trametinib for 8 months with stable disease initially followed by slow progression. Ipilimumab/nivolumab was initiated and achieved a durable complete response, remaining disease-free for 6.5 years off therapy. Patient B received binimetinib/encorafenib for 26 months showing an initial mixed response with regression of the primary tumor but progression of hepatic metastases. Patient A was managed subsequently by multiple surgical and liver-directed interventional procedures. IHC in both metastatic cases, on material from metastatic sites obtained prior to ICI treatment, showed infiltration by CD3+ and CD8+ T cells, notably more pronounced in the ICI responding patient. Both were negative for CD20, PD-L1, PD-1, and LAG-3.

Conclusion: BRAF mutant GISTs are rare with variable responses to BRAF/MEK inhibition. A durable complete response to ICI was observed in one patient. Preliminary immune profiling supports further investigation of immunotherapy in selected cases with immune-infiltrated microenvironments.

(P 187) THERAPEUTIC OUTCOMES IN NF1-ALTERED GIST TREATED WITH MEK INHIBITION: A SINGLE-CENTER EXPERIENCE

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Objective: Neurofibromatosis type 1 (NF1)-altered gastrointestinal stromal tumors (GIST) represent a rare molecular subtype, characterized by insensitivity to imatinib and limited systemic therapy options. These tumors can arise from germline (GI) NF1 alterations associated with NF1 syndrome or sporadic (Sp) alterations in the NF1 gene. MEK inhibition has emerged as a promising approach for NF1 related tumors. We aimed to review our institutional experience with NF1-altered GIST, focusing on clinical outcomes following MEK inhibition.

Methods: We performed a systematic retrospective analysis of GIST cases harboring NF1 alterations identified through MSK-IMPACT between 2010 and 2024. Clinical, demographic and therapeutic data were extracted from electronic medical records and reviewed.

Results: Twenty-three patients with NF1-altered GIST were identified: 13 with germline (GI) and 10 with sporadic (Sp) alterations. Median age was 48 years (range 34–70), with 17 females. Racial distribution: 20 White, 2 Asian, 1 other. Primary sites included small bowel (n=20) and stomach (n=3). Histology included spindle (n=17), mixed (n=3), epithelioid (n=1), and unknown (n=2). Multifocal tumors occurred exclusively in the germline NF1 group (9/13). Twenty-one patients presented with localized disease and underwent surgical resection; two presented with de novo metastatic disease. Among those resected, five experienced recurrence with a median disease-free survival of 170 months (95% CI: 88–not estimable). Six patients received MEK inhibitor-based therapy for advanced or recurrent disease. Five patients received imatinib combined with binimetinib (IB) as first-line therapy within a clinical trial. Two patients (both GI) achieved prolonged stable disease (30 and 47+ months), while three (1 GI, 2 Sp) progressed within 2.5 to 4.5 months. One additional patient (Sp) initially received imatinib alone with early progression, followed by disease control lasting 80 months on binimetinib and pexidartinib (pexidartinib discontinued after 38 months) as part of a clinical trial. This patient was later treated with IB for 7 months before disease progression.

Conclusion: NF1-altered GIST is characterized by unique clinical and molecular features and demonstrates variable response to MEK inhibitor-based regimens with some patients experiencing prolonged disease control.

(P 188) A CALCULATOR TO ESTIMATE EFFECTIVE IMATINIB CONCENTRATIONS IN GIST AFTER ADJUSTING FOR PROTEIN BINDING

Jerry W. Call, The Life Raft Group, Star Tannery, VA

Objective: Therapeutic drug monitoring (TDM) of imatinib in gastrointestinal stromal tumor (GIST) patients is typically based on total plasma levels, despite imatinib being >95% protein-bound. Only the unbound fraction enters target cells and drives efficacy. Binding to alpha-1-acid glycoprotein (AGP) can inflate total imatinib measurements and represents a potential pitfall in interpreting plasma levels, potentially misrepresenting effective exposure.

Methods: We adapted a published pharmacokinetic model to create a user-friendly calculator implemented as an Excel spreadsheet, which estimates the effective imatinib concentration adjusted for protein binding (Cadjusted) by using measured total imatinib (Ctot) and AGP levels. The calculator first estimates the unbound imatinib concentration (Cu), representing the concentration of pharmacologically active, free drug, before calculating the adjusted total concentration (Cadjusted). The model assumes non-linear, 1:1 binding with AGP (dissociation constant $K_d = 319 \text{ ng/mL}$) and applies a correction formula derived from Haouala et al., 2012 (Br J Clin Pharmacol). Cadjusted represents the total concentration normalized to a standard AGP level, improving interpretability of pharmacologically active drug exposure.

Results: Sample scenarios illustrate how AGP levels affect effective drug exposure. For example, at $C_{tot} = 1200 \text{ ng/mL}$ and $AGP = 1.5 \text{ g/L}$, Cadjusted is 808 ng/mL ; with $AGP = 0.9 \text{ g/L}$, Cadjusted increases to 1329 ng/mL . These shifts highlight the importance of accounting for protein binding when interpreting TDM results.

Conclusion: This calculator provides a practical tool for estimating protein-binding–adjusted imatinib exposure. By aiding in the understanding of AGP-related binding as a potential pitfall, it may help refine therapeutic drug monitoring and support more precise dosing in GIST patients.

Sample Outputs from Protein-Binding–Adjusted Imatinib Calculator

$C_{tot} (\text{ng/mL})$	$AGP (\text{g/L})$	$C_u (\text{ng/mL})$	$C_{adjusted} (\text{ng/mL})$
1200	1.5	22.9	808
1200	0.9	39.5	1329
800	1.1	20.6	729

(P 189) AN ALGORITHM TO PERSONALIZE IMATINIB PLASMA TESTING AND DOSE DECISIONS IN GIST PATIENTS

Jerry W. Call, The Life Raft Group, Star Tannery, VA

Objective: Therapeutic drug monitoring (TDM) of imatinib in GIST provides actionable information beyond standard dosing but must be interpreted cautiously. We sought to develop a clinical algorithm that incorporates plasma level testing without compromising patient safety, while identifying patients receiving subtherapeutic exposure.

Methods: We designed a stepwise decision algorithm for patients with imatinib-sensitive GIST (excluding resistant genotypes such as PDGFRA D842V). The algorithm respects three core principles: (1) maintain the standard 400 mg dose when tolerated, (2) avoid dose reduction based solely on plasma level, and (3) ensure plasma levels remain above a personalized therapeutic threshold in the absence of unacceptable side effects. Personalized thresholds (800–1100 ng/mL) were defined from trial data and real-world studies.

Results: The algorithm begins with standard 400 mg dosing of imatinib. If toxicity is tolerable and plasma levels fall below the personalized threshold, dose escalation is considered. Dose reductions occur only with clinically significant toxicity and are independent of plasma levels. Thresholds from 800 to 1100 ng/mL are chosen based on treatment timing, tolerance, and clinical judgment.

Conclusion: This algorithm offers a safe and practical method to integrate imatinib plasma level testing into clinical care. It balances evidence-based thresholds with individualized patient factors to optimize long-term response while reducing toxicity risk.

Setting a personalized therapeutic threshold

Threshold	Which patients might benefit / Comments
800 ng/mL	Later treatment (>20 days); experiencing more side effects; more comfort with lower-end threshold.
1100 ng/mL	Early treatment (e.g., day 29); fewer side effects; preference for higher assurance of therapeutic level.

(P 190) TEMPORAL DECLINE IN PROGRESSION-FREE SURVIVAL, TIME ON MEDICATION, AND OVERALL SURVIVAL IN ADVANCED GASTROINTESTINAL STROMAL TUMOR

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Objective: To investigate temporal trends in progression-free survival (PFS), time on medication (TOM), and overall survival (OS) in patients with advanced gastrointestinal stromal tumor (GIST) receiving first-line imatinib (IM).

Methods: We analyzed 1,490 patients with metastatic or inoperable GIST treated with first-line imatinib (IM) from the Life Raft Group Registry. PFS, TOM, and OS were calculated and stratified by year of treatment initiation: 2000–2010, 2011–2017, and 2018–2024. The 2000–2010 cohort was excluded due to limited access to later-line therapies. Kaplan-Meier survival analysis and Cox proportional hazards models were used to compare outcomes across time groups. Time strata were selected using the optimal cutoff method implemented in the survminer package in R. 2010 was identified as the inflection point for OS, and 2017 was the optimal threshold for both PFS and TOM.

Results: Patients who began IM between 2018–2024 experienced significantly shorter PFS and TOM. Median PFS was 40 months for the 2011–2017 group versus 24 months for the 2018–2024 group. The hazard ratio (HR) for PFS was 1.46 (95% CI: 1.16–1.85; $p < 0.005$), indicating a 46% higher risk of progression. TOM declined in parallel, with a median of 57 months in the 2011–2017 group versus 31 months in the 2018–2024 group (HR 1.80, 95% CI: 1.42–2.29; $p < 0.005$). Overall survival curves for KIT exon 11 patients also significantly diverged, with worse outcomes in the 2018–2024 group compared to 2010–2017 ($p = 0.03$). No significant OS differences were observed in other subgroups. Follow-up duration was shorter in the recent cohort, potentially impacting survival estimates.

Conclusion: This study shows a significant decline in PFS, TOM, and OS (KIT exon 11 only) for first-line IM starting in 2018, suggesting reduced treatment durability. Further comparative studies are needed to confirm these findings. Continued real-world monitoring is key to improving care and advancing research.

Temporal Trends in PFS, TOM, and OS for First-Line Imatinib in Advanced GIST

Time period	N	mPFS (mo)	HR (PFS)	mTOM (mo)	HR (TOM)
2011-2017	308	40	Ref	57	Ref
2018-2024	304	24	1.46†	31	1.80‡
OS in KIT exon 11					
2011-2017	162	154			Ref
2018-2024	195	NA			Worse ($p=0.03$)
†95% CI: 1.16-1.85; $p = 0.0015$					
‡95% CI: 1.42-2.29; $p < 0.00001$					

(P 191) EFFICACY OF SYSTEMIC PALLIATIVE THERAPIES IN PATIENTS WITH ADVANCED GASTROINTESTINAL STROMAL TUMORS (GIST) PREVIOUSLY TREATED WITH ADJUVANT IMATINIB - REAL-WORLD CLINICAL PRACTICE DATA

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Objective: Imatinib has revolutionized the management of patients (pts) with GIST, both in adjuvant and advanced settings; however, many patients treated with adjuvant imatinib ultimately relapse during or after completion of therapy. Data on efficacy of palliative systemic therapy in this group remain limited. This study aimed to evaluate the outcomes of palliative treatment in patients with GIST previously treated with adjuvant imatinib.

Methods: We conducted a retrospective analysis of pts with advanced GIST who received palliative treatment after adjuvant therapy at reference center between 2004 and 2025. Data included clinic-pathologic data, and survival outcomes: progression-free survival (PFS), overall survival (OS), objective response rate (ORR), and disease control rate (DCR).

Results: 54 pts were included; (46.3% female, median age 60.9 years). Primary tumors were mostly located in the small intestine (57.4%) or stomach (31.5%). KIT mutations were found in 85.2%; exon 11 in 78.7%, exon 9 in 19.1%. Median DFS on adjuvant imatinib was 46.3 months. Recurrence occurred during adjuvant treatment in 20.4% (11) and within one year of its completion in 46.3% (25). In 1st line, 88.9% pts received imatinib, and 11.1% sunitinib. Median PFS was 37.9 months (95%CI: 23.7-44.9), with ORR 27.8% and DCR 72.2%. No significant differences in PFS were observed between imatinib- and sunitinib-treated patients (36.4 vs 44.6 months; $p = 0.87$), imatinib dose, or between mutation subgroups. 2nd and 3rd line therapy were administered to 50% and 22.2% pts. Imatinib 800 mg was offered to 55.5%, while sunitinib to 29.6% pts in 2nd line. PFS in 2nd and 3rd line therapy was 8.7 (95%CI: 5.00-NR) and 9.0 (95%CI: 5.73-NR) months, respectively. In 2nd line 11.1% achieved ORR, while in later lines, SD remained the best observed response (57.1% in 3rd, 33.3% in 4th). Median OS on palliative treatment was 8.5 years (95%CI: 5.80-NR); 5-year OS was 39.8%.

Conclusion: Palliative treatment with imatinib and sunitinib remains effective in patients with recurrent GIST after adjuvant imatinib. Outcomes align with those in TKI-naïve populations. Patients who have disease recurrence after completion of adjuvant imatinib can be effectively treated with reinduction of imatinib.

(P 192) OPTIMAL DOSING SCHEDULE OF SUNITINIB BASED ON PLATELET COUNT IN AN OLDER PATIENT WITH GASTROINTESTINAL STROMAL TUMOR

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Objective: Sunitinib, a second-line treatment for gastrointestinal stromal tumors (GIST), is commonly associated with adverse events such as myelosuppression in older patients. However, an optimal dosing schedule has not been established. This study evaluated the therapeutic efficacy and toxicity management of sunitinib administration based on platelet count.

Methods: An 83-year-old man receiving imatinib for rectal GISTs was switched to sunitinib (initially 50 mg/day) due to imatinib failure. After 8 days of treatment, the patient developed grade 2 anorexia and nausea, prompting a dose reduction to 37.5 mg/day; however, these

adverse events persisted. Sunitinib was discontinued 15 days after the start of treatment and later resumed at 25 mg/day after symptoms improved. Thereafter, the sunitinib withdrawal period was adjusted based on neutrophil and platelet counts. Changes in these counts during each withdrawal period were predicted using a quadratic regression model and validated through leave-one-out cross-validation.

Results: The coefficient of determination (R^2) of the neutrophil count prediction model during the withdrawal period was 0.28, and the validated R^2 for each cycle ranged from -0.26 to -0.11. In contrast, the platelet count model yielded an R^2 value of 0.86, with validated R^2 values ranging from 0.42 to 0.88. Adjusting the sunitinib withdrawal period according to platelet count resulted in the only non-hematologic adverse event of grade 2 or higher of hypothyroidism, with no serious adverse events. The patient achieved a partial response according to Choi criteria but was switched to regorafenib after five cycles of sunitinib due to disease progression.

Conclusion: Low-dose sunitinib monotherapy, with dosing intervals based on platelet counts, may be an effective treatment option for managing toxicity in older patients with imatinib-resistant GIST.

(P 193) CLINICAL ANALYSIS OF RIPRETINIB DOSE ESCALATION IN ADVANCED GISTS AFTER STANDARD DOSE PROGRESSION

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Objective: This study explores the clinical outcomes of ripretinib dose escalation after standard-dose treatment across different treatment lines.

Methods: 16 advanced GIST patients who underwent ripretinib dose escalation after failure of ripretinib standard-dose (150mg qd) were retrospectively analyzed. All patients were treated at the First Affiliated Hospital of Sun Yat-sen University between June 2020 and April 2025. Progression free survival (PFS) was further classified to standard dose (PFS1) and dose escalation (PFS2) phases, respectively.

Results: Primary tumors were from small intestine in 12 patients (75.0%), metastases mainly in the liver (75.0%) and peritoneal cavity (68.6%), with 8 (50.0%) having multi-site metastases. Tumor size (Sum of lesions length diameter) were ≤ 5 cm in 5 (31.3%), 6-10 cm in 3 (18.8%), and 10-20 cm in 7 (43.8%). Nine (56.3%) received ripretinib as fourth-line treatment; others as second-line (n=3, 18.8%), third-line (n=1, 6.3%), or fifth-line and beyond (n=3, 18.8%). Primary KIT exon 11 mutations were in 12 (75.0%), and 13 (81.3%) had secondary mutations, including 11 (68.8%) with KIT exon 17 mutations and 5 (31.3%) with KIT exon 13 mutations. The median follow-up was 12.3 (2.7-39.0) months. Initial escalated dose was 150 mg bid, with 14 continuing. Two adjusted to 150 mg +100 mg QD/200 mg QD due to adverse reactions. Among three second-line ripretinib patients, no tumor regression was observed and 1 patient (PFS1 21.8m) had tumor progression only in 1.3 months. The other two patient early switched to sunitinib due to lack of response (dose-escalation ≤ 2 months). The single third-line patient had a PFS1 of 17.8 months, and stable disease for more than 8 months after dose-escalation. Among the 12 fourth-line and beyond patients, the best responses were partial response (PR) in 3 cases, stable disease (SD) in 6 cases, and progressive disease (PD) in 3 cases; the median PFS1

was 3.1 (95% CI: 2.1-8.7) months. After dose escalation, SD was observed in 9 cases and PD in 3 cases; the median PFS2 was 3.3 (95% CI: 2.6-3.5) months. During standard-dose therapy, 11 patients experienced grade 1-2 adverse reactions, and one had grade 3 palmar-plantar erythrodysesthesia. During dose escalation, two developed grade 3 palmar-plantar erythrodysesthesia.

Conclusion: Ripretinib dose escalation may offer additional survival benefits with highly individual diversity. The adverse reactions were tolerable, though patient characteristics predicting benefit require further investigation.

(P 194) UPDATED RESULTS FROM STRATEGIST 1: A PHASE 1/1B STUDY OF IDRX-42 (GSK6042981A) IN PATIENTS (PTS) WITH ADVANCED GASTROINTESTINAL STROMAL TUMORS (GIST)

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Objective: Most GIST are driven by mutations in KIT and resistance to approved KIT inhibitors is largely mediated by additional mutations in KIT exons 13 and 17. IDRX-42 is a novel, highly selective KIT tyrosine kinase inhibitor (TKI) with preclinical activity across clinically relevant activating and secondary resistance KIT mutations. We present updated results from a phase 1/1b study (StrateGIST 1) evaluating IDRX-42 in pts with advanced GIST.

Methods: Phase 1 enrolled previously treated pts at doses of 120 mg to 1200 mg daily. Phase 1b enrolled pts at the recommended phase 1b dose (RP1bD) of 300 mg QD (tablet) in 4 cohorts: 1st line, 2nd line, and two ≥3rd-line cohorts (prior approved TKIs +/- investigational TKIs). This pooled phase 1/1b data focuses on clinical activity in 2nd and later-line pts at the RP1bD.

Results: As of April 28, 2025, 167 pts across all cohorts received IDRX-42 at the RP1bD (or exposure-equivalent 400-mg capsules) for a median duration of 6.4 months. Median age was 58 years old; 5%, 26%, 11%, and 57% of pts received 0, 1, 2, and ≥3 prior lines of therapy for advanced GIST, respectively. All enrolled pts had GIST harboring any KIT or nonexon-18 PDGFRA mutation(s) at baseline. Table 1 presents investigator-assessed clinical activity in 2nd and later-line pts. At the RP1bD, the most common grade ≥3 treatment-emergent adverse events were anemia (16%), neutropenia (9%), vomiting (3%), and abdominal pain (3%).

Conclusion: IDRX-42 exhibits promising activity and safety in previously treated GIST, warranting further study in early-line pts.

Table 1: Clinical Activity per Modified RECIST v1.1

Clinical Activity per Modified RECIST v1.1 ^{a,b}					
	2nd line (N=45)	3rd line		≥4th line	
		All (N=19)	No prior bevacizumab (N=15)	All (N=94)	No prior regorafenib/bevacizumab/ NBO03/TH-302 (N=25)
Median follow-up, months	7.3	9.1	9.1	9.2	9.2
ORR, c ^c n (%)	16 (36)	5 (26)	5 (33)	16 (17)	9 (36)
Median PFS, months (95% confidence interval)	14.8 (9.2–NE)	8.5 (1.9–NE)	16.6 (1.9–NE)	5.5 (3.7–7.4)	11.0 (3.7–20.3)
^a NE, not estimable; ORR, objective response rate; PFS, progression-free survival; RECIST, Response Evaluation Criteria in Solid Tumors. ^b Efficacy-evaluable population (postbaseline scan or prior clinical progression/death). ^c At 300-mg QD tablet (or exposure-equivalent 400-mg QD capsule). ^d 35 confirmed responses, 2 awaiting confirmation.					

(P 195) **IMPACT OF EXPERT-LED EDUCATION PROGRAMS ON HEALTH CARE PROVIDER (HCP) KNOWLEDGE OF GASTROINTESTINAL STROMAL TUMOR (GIST)**

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Objective: GIST is a rare disease often treated in community oncology centers. The expanding GIST therapeutic landscape presents significant challenges for community-based HCPs to remain current with best practices, frequently relying on expert perspectives to guide treatment. Unmet educational needs exist in areas such as GIST biology, clinical guidelines, and emerging treatments. Committed to advancing GIST education, Deciphera supports evidence-based educational initiatives for HCPs to ultimately improve patient (pt) care. Here, we describe survey results collected after expert-led GIST education programs for the broader HCP community.

Methods: Nine expert-led programs were held in person/virtually in 2024. Attendees later provided pre- and post-program ratings on background GIST knowledge, understanding of drivers of resistance and progression, the importance of life-long tyrosine kinase inhibitor (TKI) therapy (per NCCN guidelines), and the importance of proactive pt management/setting treatment goals. Five-point responses ranged from “poor” to “excellent” or “not important” to “critically important.”

Results: Overall, 36 surveys from HCPs of various specialties were analyzed. After attendance, very good/excellent ratings were increased for background GIST knowledge (28% pre-program vs 72% post-program) and understanding of drivers of resistance and progression (22% vs 61%). Similarly, more HCPs provided very/critically important ratings for the importance of life-long TKI therapy in advanced GIST (39% pre-program vs 83% post-program) and the importance of proactive pt management/setting treatment goals (42% vs 92%). Similar improvements were observed after other independent programs, including a GIST education program where oncologists and gastroenterologists reported increased knowledge and confidence in treatment selection (Worst MA et al. J Clin Oncol. 2020; abs 837).

Conclusion: Expert-led GIST education programs had positive impacts on HCP self-rated knowledge and confidence in managing this complex sarcoma. The evolving landscape of GIST management necessitates ongoing HCP education to advance knowledge of the disease state and treatment paradigms. Recognizing the vital role of industry partnerships in supporting these efforts, Deciphera is committed to enhancing GIST education in the broader oncology setting.

(P 196) **SURVEILLANCE STRATEGIES AND LONG-TERM OUTCOMES IN LOW-RISK GASTRIC GASTROINTESTINAL STROMAL TUMORS (GGISTS)**

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Objective: Gastric gastrointestinal stromal tumors (gGISTs) may be stratified based on risk profile for recurrence. International guidelines vary widely in terms of intensity and modalities of recommended surveillance strategies. Given the lack of consensus to inform an optimal surveillance strategy, this study examines recurrence patterns and risk factors of gGISTs.

Methods: This retrospective, population-based study included patients diagnosed with gastric GISTs between 2015 and 2024. GISTs were identified via pathological data, and demographic, surgical, and surveillance data was collected via chart review. Patients were included if the gGIST was discovered incidentally, and patients were excluded if they were metastatic at initial presentation.

Results: Of 134 cases, the median age at diagnosis was 69 years (IQR 60-75), with a slight male predominance (n=74, 55%). Most cases were very low (n=74, 55%) or low risk (n=40, 30%), with a smaller amount of moderate (n=19, 14%) and high risk (n=2, 1%). The majority of patients had low grade tumors (n=122, 90%); median mitoses was 2, IQR 1-3. The majority were resected using minimally invasive techniques (n=115, 85%). gGISTs were typically resected via wedge resection (95%, n=127), with 5% receiving total gastrectomy. Intra-operative endoscopies were performed in 46% (n=63). The median size of the GISTs included in the study was 3.9 cm (IQR 3-5.7). Median follow-up time was 32.5 months (IQR 15, 54). Only 2 recurrences were identified on surveillance; one patient had a moderate risk tumor and the other had a high risk primary tumor. 5-year recurrence was 0.8%, and 8-year recurrence was 9.9%. Overall survival was 86.6% at 5 years and 77.0% at 8-years. There was a large variation in surveillance strategies, including endoscopy, cross-sectional imaging, and no surveillance.

Conclusion: Gastric GIST recurrence risk is low following resection. Larger cohort studies are required to identify specific risk factors for recurrence and determine if surveillance strategies are warranted.

(P 197) DIFFERENTIAL EFFECTS OF ANAGRELIDE IN GASTROINTESTINAL STROMAL TUMORS (GIST) IN VITRO

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Objective: GISTs are molecularly heterogeneous tumors that include KIT-mutant and succinate dehydrogenase deficient (SDH-def) subtypes. Unlike KIT-mutant GIST, SDH-def GIST are somewhat resistant to standard tyrosine kinase inhibitors. Phosphodiesterase 3A (PDE3) was previously identified as highly expressed in GIST, and together with its binding partner, Schlafen family member 12 (SLFN12), have been implicated in drug-induced apoptosis in GIST. This study evaluated PDE3A and SLFN12 expression, as well as the anti-tumor effects of the PDE3 inhibitor, anagrelide in KIT-mutant vs. SDH-def GIST in vitro models.

Methods: Models included KIT-mutant (GIST882: KIT K642E; GIST-T1: KIT V560_Y579del) and SDH-def [SD-437A (SDHA 1432_1432+1delGG); SD-435C (SDHC R133*)]. Expression of PDE3A and SLFN12 were analyzed in cell lines using bulk transcriptomics and expression was analyzed in 27 GIST using single-nucleus RNA-seq (snRNAseq). Cells treated with anagrelide were analyzed for drug sensitivity, mRNA/protein expression, apoptosis induction, and migration/invasion capacity.

Results: Bulk and snRNAseq revealed higher PDE3A expression in KIT-mutant tumor cells, while SLFN12 was low across these subtypes. Relative to GIST882, PDE3A protein was highly expressed in GIST-T1 (10.8-fold) followed by SD-437A (3.1-fold) and SD-435C (1.3-fold) cells. In contrast, SLFN12 was highly expressed in GIST882, but had < 50% expression ($p < 0.01$) in other lines. In GIST882, anagrelide induced cytotoxicity (IC_{50} 20 nM), with caspase-3 activation and PARP cleavage. However, SDH-def and GIST-T1 cells were resistant to anagrelide (IC_{50} >50 μ M) induced apoptosis. However, at sub-lethal doses (GIST882: 2 nM; GIST-T1: 2 μ M; SD-437A/SD-435C : 3 μ M), anagrelide significantly reduced migration/invasion in GIST-T1, SD-437A, and SD-435C cells by 30–45% vs. GIST882 (< 10%), $p < 0.05$.

Conclusion: Anagrelide shows context-dependent activity in GIST, with apoptosis induced in PDE3A(Low)-SLFN12(High) GIST882 cells, while exerting anti-migratory and anti-invasive effects in PDE3A(High)-SLFN12(Low) SDH-def and GIST-T1 cells despite lack of apoptosis. These findings support further exploration of PDE3A and SFLN12 signaling as a potential target for distinct GIST subtypes.

(P 198) **EXPLOITING METABOLIC DYSREGULATION IN SUCCINATE DEHYDROGENASE-DEFICIENT GASTROINTESTINAL STROMAL TUMOR**

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Objective: Gastrointestinal stromal tumor (GIST) is a common soft tissue sarcoma, with most tumors driven by oncogenic activation of a receptor tyrosine kinase (RTK). In contrast, approximately 10% of “wild-type” GISTs lack RTK mutations and are instead driven by loss of the succinate dehydrogenase (SDH) complex. Loss of SDH leads to succinate accumulation, though little is understood about how tumor cells adapt to this metabolic dysregulation or its effects on the global metabolic architecture critically necessary to support oncogenesis. The goal of this study is to determine how SDH-deficient GIST accommodates and depends upon metabolic dysregulation, and how this adaptation can be exploited therapeutically.

Methods: We profiled an annotated cohort of RTK and SDH-deficient GIST samples using transcriptional, metabolic, proteomic, and phosphoproteomic methods to characterize global changes in metabolic regulation. Findings were validated in engineered cell lines and patient-derived xenograft models of SDH-deficient GIST to show functional dependency.

Results: RTK and SDH-deficient GIST samples characterized by global proteomic and metabolomic methods clustered by oncogenic driver, with differences observed in enzymes and metabolites comprising the TCA cycle and other metabolic pathways. Phosphoproteomic evaluation identified differential and antagonistic enrichment of AMP-activated protein kinase and cyclin dependent kinases between tumor subtypes, and disruption of this balance led to

transcriptional and metabolic changes which inhibited growth in SDH-deficient models. We identified significant enrichment of protein succinylation arising from SDH-deficiency. Inhibition of enzymatic protein desuccinylation resulted in toxic hypersuccinylation in a subset of the proteome, which significantly reduced SDH-deficient GIST growth in preclinical models.

Conclusion: These results define global perturbations in metabolic and regulatory effectors in SDH-deficient GIST, improving our understanding of how tumor cells adapt to loss of the SDH complex, and how these accommodations can be targeted therapeutically.

(P 199) CHARACTERISTICS OF AN IMMUNOHISTOCHEMICAL AND MOLECULARLY DISCORDANT POPULATION OF GIST PATIENTS: A SINGLE CENTER RETROSPECTIVE REVIEW

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Objective: CD117, the immunohistochemistry (IHC) marker for protein expression of KIT or the c-KIT proto-oncogene, is expressed in greater than 90% of gastrointestinal stromal tumors (GIST), with platelet-derived growth factor receptor alpha (PDGFRA) mutations also showing variable CD117 expression. However, 10-27% of CD117-expressing GIST tumors do not have detectable KIT or PDGFRA mutations on molecular testing. There is limited data in the literature describing outcomes of patients (pts) with this discordance in IHC and molecular results. Our objective was to evaluate this population of patients with CD117 expression and negative KIT/PDGFRA mutations.

Methods: We performed a retrospective chart review of consecutive pts seen at the University of Virginia with a tissue diagnosis of GIST between 1/1/2018 and 6/1/2025 who also had molecular testing data available. We analyzed patient- and disease-related characteristics within this cohort. Descriptive statistics were used.

Results: Of 40 pts in our total cohort, 45% were male, median age was 68 years, 22.5% were stage IV, 30% originated in the small bowel, and 55% had a moderate to high risk of recurrence at the time of diagnosis. 10 pts (25%) had CD117 positivity but negative molecular testing for KIT/PDGFRA mutations. Within this discordant cohort, 50% were male, median age was 69.5 years, 10% were stage IV, 50% originated in the small bowel, and 30% had a moderate to high risk of recurrence at the time of diagnosis. Median overall survival (OS) was unable to be calculated as > 50% of pts are still living.

Conclusion: Higher representation of small bowel GIST (50 vs 30%), NF1 mutations (50 vs 15%), CDKN2A deletion (10 vs 7.5%) and FH mutations (10 vs 2.5%) were seen in our population of pts with discordant IHC and molecular testing compared to the concordant cohort. Overall survival remains high in this group despite potentially higher risks of recurrence. Larger studies are needed to further elucidate the outcomes of this population.

Molecular and Patient Data for our IHC/Molecular Testing Concordant and Discordant

Cohort

Total Cohort, n = 40	% of Concordant Population, n = 30	% of Discordant Population, n = 10
KIT	65	-
Exon 11	50	-
Exon 9	2.5	-
Exon 16	2.5	-
Other KIT	10	-
PDGFRA	15	-
Exon 11	2.5	-
Exon 16	2.5	-
Exon 18	2.5	-
Exon 26	2.5	-
Exon 32	2.5	-
NF1	15	50
CDKN2A	7.5	10
CHEK2	5	0
BRCA	2.5	0
FH	2.5	10
PD-L1	2.5	0
EXT2	2.5	10
Other Mutations (BAP1, DICER1, IRF2)	2.5	10
Underwent Surgical Resection	65	60
Received Systemic Treatment	87.5	70
Neoadjuvant	37.5	30
Only Adjuvant	50	40
Imatinib	87.5	80
Sunitinib	7.5	0
Currently Alive with Disease	30	20
Currently Alive with No Evidence of Disease	45	50
Dead of Disease	0	0

(P 200) DISSECTING INTRATUMORAL HETEROGENEITY IN GIST USING SPATIAL TRANSCRIPTOMICS

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Objective: Gastrointestinal stromal tumors (GISTs) are characterized by driver mutations, primarily in the KIT and PDGFRA genes, leading to the abnormal activation of these receptor tyrosine kinases. Approximately 40% of high-risk patients experience relapse after adjuvant imatinib therapy, emphasizing the importance of better understanding tumor biology and heterogeneity, and their influence on prognosis and resistance.

Methods: We have applied Visium 10x Genomics spatial transcriptomics technology on formalin-fixed paraffin-embedded (FFPE) samples from seven treatment-naïve GISTs. Our approach integrates deconvolution analysis to delineate distinct spatial transcriptomic niches, to identify specific cell types within the tumor and its microenvironment. Preliminary analyses focused on characterizing transcriptomic profiles within the tumor area and across patients, supplemented by inferred DNA copy number changes from gene expression data.

Results: The inclusion of normal tissue was essential for enhancing our analyses and defining cell types within the tumor microenvironments. Our findings revealed significant intratumoral heterogeneity, with distinct spatial domains displaying unique transcriptional landscapes. Despite the uniformity of KIT mutations among patients, we observed substantial variability in gene expression profiles, suggesting potential differences in the activation of downstream pathways. Additionally, areas of localized chromosome copy number changes were linked to signatures associated with aggressive disease behavior.

Conclusion: This study highlights the complex transcriptional and genomic heterogeneity in GISTs, which may have significant implications for patient stratification and the development of personalized therapeutic strategies. Future work will integrate single-cell RNA sequencing to

further dissect this heterogeneity and correlate it with clinical outcomes. A deeper understanding of the molecular mechanisms driving heterogeneity in GISTs will be crucial for enhancing targeted therapies and reducing the risk of relapse in high-risk patients.

(P 201) METASTATIC PATTERNS, TREATMENT MODALITIES, AND OVERALL SURVIVAL IN OLIGOMETASTATIC GIST: A SINGLE-CENTER RETROSPECTIVE STUDY

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Objective: Treatment of oligometastatic gastrointestinal stromal tumor (GIST), defined as fewer than five metastatic lesions, remains challenging. Metastatic site and patient factors guide management, limiting consensus on treatment and prognosis. We evaluated whether overall survival (OS) varies by metastatic site, ethnicity, and treatment.

Methods: We queried our prospectively maintained pan-sarcoma database for subjects with biopsy-proven GIST cases (Jan 2011–June 2025), collecting data on genomics, metastases, treatment, ethnicity, and OS. Associations between treatment and metastatic sites were assessed by Chi-square tests. OS for metastatic sites and treatments were estimated by Kaplan-Meier analysis and compared by log-rank test. The Mantel-Haenszel test was used to calculate hazard ratios (HR).

Results: Of 525 subjects, 96 (18.3%) had oligometastatic GIST (median age at diagnosis: 54 years; median OS: 13.9 years; 49/47 M/F). 91.6% were KIT-positive (exon 11: 66; exon 9: 15; exon 17: 7). No association was found between exon status and OS. The liver was the most frequent metastatic site (43), then peritoneum (38) and lymph nodes (4). There was no significant OS difference for liver vs peritoneal metastases or Hispanic vs non-Hispanic ethnicity. Notably, surgery plus systemic therapy (55/96) was significantly associated with longer median OS (14.67 years) vs systemic therapy alone (9.65 years), with a HR of 0.479 (95% CI 0.232–0.988, $p=0.04$). 21/55 underwent surgery for multifocal disease after response to systemic therapy (TKI), 18/55 for unifocal disease after TKI response, 13/55 for unifocal progression with poor TKI response, and 3/55 for bleeding or obstruction.

Conclusion: Surgery plus systemic therapy had longer median OS than systemic therapy alone. This highlights the need for prospective studies to define optimal treatment and develop standardized care strategies.

(P 202) **TRAVEL GRANT**

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Objective: Not applicable

Methods: Not applicable

Results: Not applicable

Conclusion: Not applicable

(P 203) **MINIMALLY INVASIVE RESECTION OF MULTIFOCAL DUODENO-JEJUNAL GISTS IN NEUROFIBROMATOSIS TYPE 1**

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Objective: To assess the feasibility, surgical technique, and early clinical outcomes of a minimally invasive, organ-sparing approach in resecting multiple synchronous duodeno-jejunal gastrointestinal stromal tumors (GISTs) in a patient with neurofibromatosis type 1 (NF1).

Methods: A 62-year-old male with NF1 was diagnosed with three GISTs (duodenal: 2.7 cm; jejunal: 1.0 and 1.2 cm) via EUS-guided biopsy and contrast-enhanced CT. A multidisciplinary tumor board recommended surgery due to documented lesion growth.

Results: A minimally invasive approach was adopted, beginning with the Hasson open technique for laparoscopic access. Three additional trocars (two 5 mm, one 10 mm) were placed for full abdominal exploration, which revealed the known lesions and multiple millimetric nodules along the jejunum. Complete duodeno-pancreatic mobilization was achieved via Kocher maneuver and division of the ligament of Treitz. Wedge resections were performed through a minilaparotomy with Alexis retractor assistance. All lesions were excised manually and closed using a double-layer Maxon 3/0 suture. Pathological examination confirmed R0 margins. The duodenal GIST had a mitotic index of 1/5 mm² (low-risk), and both jejunal GISTs had < 1/5 mm² mitoses (very low-risk). Postoperative recovery was uneventful, except for transient delayed gastric emptying, which resolved spontaneously.

Conclusion: Minimally invasive, organ-sparing resection is a feasible and safe strategy for managing multifocal duodeno-jejunal GISTs in NF1 patients. This approach enables complete tumor removal while preserving gastrointestinal function and offers a reproducible solution for such complex presentations.

(P 204) **ANALYSIS OF QUALITY INDICATORS OF SOFT TISSUE SARCOMA TREATMENT WITH CANCER REGISTRY DATA IN GERMANY 2015-2021**

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Objective: Empirical data show that soft tissue sarcoma (STS) treatment according to clinical guidelines and in sarcoma centers results in a survival benefit for patients. In 2021, the first comprehensive German STS guideline was published including the definition of quality indicators (QIs) of STS treatment. In the same time period, the German Cancer Society established an audit system for certified sarcoma centers in Germany. This article analyses the quality of STS care in Germany prior to the publication of the German STS guideline and before establishing certified sarcoma centers in Germany.

Methods: A comprehensive population-based cohort of 20,936 sarcoma patients diagnosed between 2015 and 2021 was extracted from cancer registry data using ICD-O-3 codes for topography and histological subtype. To identify trends over time, annual percentage changes (APCs) were calculated. The following QIs were suitable and thus selected for comparison: pre-treatment tumor board, R0 resection, hysterectomy without morcellation for sarcoma confined to the uterus, anthracycline-based first line systemic treatment (excluding GIST) and postoperative mortality for retroperitoneal sarcomas.

Results: A pre-treatment referral to a tumor board (initial diagnosis of STS)) was documented in 12% of all cases in 2015 and 28% in 2021. The mean R0 resection rate was 82% (81-83%). Hysterectomy without morcellation for sarcoma confined to the uterus were performed in 88% (83-91%). An anthracycline based first-line chemotherapy for STS was chosen in 80% (77%-82%) of all cases. The postoperative mortality for retroperitoneal sarcomas revealed was 1.4% (0-9.1%) in the years 2015-2021. For comparison, the median fraction of patients discussed in pre-treatment tumor boards and the rate of R0 resections at sarcoma patients treated at one of the 21 certified sarcoma centers in 2023 were 92% and 82%.

Conclusion: The evaluation of cancer registry data with regard to QIs is representative of the population as a whole. The possibility of filtering the data according to localization and ICD-O coding is a strength; limitations may lie in the completeness and correctness of the data. In the coming years, we expect that data from the cancer registries can also be used on a site-specific

basis and thus as a benchmark for the certified sarcoma centers.

(P 205) **CENTRALIZATION OF SARCOMA CARE IMPROVES OUTCOMES DESPITE POORER PRESENTATION: A SYSTEMATIC REVIEW AND META-ANALYSIS**

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Objective: Soft tissue sarcoma (STS) and bone sarcoma (BS) are rare, highly heterogeneous groups of malignancies of mesenchymal origin. With the recent emphasis on multidisciplinary approach to sarcoma treatment, centralization of treatment at high-volume centers (HVC) has been suggested to offer advantages over low-volume centers (LVC). The purpose of this systematic review was to report on the differences in tumor presentation, treatment, and outcomes of primary BS and STS patients treated at HVC and LVC.

Methods: PubMed and Embase databases were queried to conduct a systematic review of articles from inception to October 2024. A total of 16 studies were included: 4 BS, 12 STS. Study characteristics, HVC/LVC definition, tumor histology, primary anatomic location, tumor presentation (size, grade), treatment (surgery, amputation, chemotherapy, radiotherapy), margin status, and survival outcomes were analyzed.

Results: There was substantial heterogeneity in the definition of HVC and LVC applied in the included studies, generally left to the authors' arbitrary discretion. While presenting tumor histology and primary anatomic location were comparable between HVC and LVC, HVC patients had substantially higher grade and larger size tumors. HVC more frequently utilized radiotherapy and chemotherapy and achieved negative margins at surgery. Treatment at HVC was associated with a 17% reduction in mortality (HR, 0.83; 95% CI, 0.78 to 0.89; $p < 0.001$; $I^2 = 78.5\%$). Subgroup analyses demonstrated a consistent and significant reduction in mortality within both the BS and STS cohorts.

Conclusion: Despite presenting with poorer prognosis, both BS and STS patients experienced superior outcomes at HVC, highlighting the importance and efficacy of centralization of sarcoma care. Furthermore, the need for standardization of HVC and LVC definitions is emphasized.

(P 206) **IMPACT OF PROXIMITY TO HEALTH CENTER ON ADHERENCE TO NATIONAL COMPREHENSIVE CANCER NETWORK GUIDELINES IN PATIENTS WITH SOFT TISSUE SARCOMAS**

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Objective: Soft tissue sarcomas (STS) are a relatively rare malignancy, with approximately 13,590 cases diagnosed annually. Due to their infrequency and complexity, the National

Comprehensive Cancer Network (NCCN) provides evidence-based guidelines to guide the workup and treatment of STS. Adherence to these guidelines is crucial, as demonstrated by studies showing improved survival outcomes with compliance. However, factors influencing adherence, such as proximity to treatment centers, remain underexplored. This study aims to assess NCCN guideline adherence at a single academic institution in 2023 and identify factors affecting compliance.

Methods: We performed a retrospective review of patients diagnosed with or treated for soft tissue sarcomas at a single academic institution in 2023. In concordance with NCCN guidelines, based on tumor staging we reviewed whether patients received the proper workup and treatment including a history & physical, primary site imaging, core needle biopsy (CNB), chest/abdominal imaging, presentation to multidisciplinary team, wide resection surgery, radiation therapy, and chemotherapy.

Results: A total of 43 patients were included in the study. The most common diagnoses were spindle cell sarcoma and undifferentiated pleomorphic sarcoma (22.73% each). The most common TNM stage was IV (51.16%). All patients (100%) met workup compliance according to the NCCN guidelines. Thirty four patients (79.07%) completed their treatment course adhering to the NCCN guidelines to completion. Two (4.65%) underwent a complete workup but were seen as second opinions and returned to their previous provider to complete their care. Three (6.98%) were recommended for further treatment of either radiation therapy or chemotherapy but declined. These cases had travel distances of 1.5, 10.9, and 22.5 miles. Four (9.30%) passed away while undergoing treatment. Travel distance ranged from 1.5 to 201 miles, with a median distance of 31 miles and a median travel time of 55 minutes.

Conclusion: Our findings demonstrate a high rate of compliance with NCCN guidelines at a single academic institution. Contrary to expectations, proximity to the cancer center did not significantly affect adherence. Further studies are needed to explore additional factors influencing non-compliance, such as socioeconomic and healthcare system barriers.

(P 207) LONG-TERM FOLLOW-UP AND LATE EFFECTS MONITORING FOR UK BONE SARCOMA PATIENTS: A SERVICE MAPPING EXERCISE

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Objective: Treatment for bone sarcoma involves highly-toxic chemotherapy, intensive radiotherapy and, for many, life-altering surgery. Support to manage the lasting physical and psychological impacts of treatment is vital, yet the Bone Cancer Research Trust's community have voiced limited awareness and varying access to services and support. This service mapping exercise therefore seeks to provide a comprehensive overview of the long-term follow-up and late effects services available to UK bone sarcoma patients, and to identify any potential gaps in service provision.

Methods: This cross-sectional survey study is open to professionals working in cancer long-term follow-up services in the UK healthcare setting. A single online survey will gather key information relating to service access & eligibility and the frequency, duration and extent of

follow-up & monitoring. Extensive survey development was undertaken in close consultation with the project's Working Group of healthcare professionals & people affected by bone sarcoma. The survey opened in June 2025 and has been shared via BCRT's and the Working Group's UK-wide network of healthcare professionals. It will continue to gather responses until representation across all four nations is achieved.

Results: Full results are anticipated in late 2025 and will be used to develop a visual map and service directory which will, for the first time, provide a detailed overview of the services and support available to UK bone sarcoma survivors.

Conclusion: This vital research will take the first step towards understanding the provision of long-term follow-up care for UK bone sarcoma patients facing life-long challenges as a result of their treatment. Future steps will involve a UK-wide consultation with the bone sarcoma community, to understand how the needs of patients & families align with the services available to them.

(P 208) TRANSLATION, CROSS CULTURAL ADAPTATION AND VALIDATION OF TESS IN REGIONAL INDIAN LANGUAGES WITH ~500 MILLION GLOBAL DIASPORA

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Objective: The Toronto-Extremity-Salvage-Score (TESS), a patient-reported-outcome-measure in patients with surgery for an extremity tumor, has not been validated in regional Indian languages Hindi (600 million worldwide-speakers) and Marathi (100 million worldwide-speakers) with a global diaspora. We translated, culturally adapted and validated TESS for Indian patients in English, Hindi and Marathi to allow international comparison of results. We evaluate 1. Test-retest reliability 2. Internal-consistency 3. Construct-validity 4. External-validity with Musculoskeletal-Tumour-Society-Score (MSTS); for the translated versions.

Methods: We developed Hindi and Marathi versions of TESS using standard process of translation, synthesis, back-translation, expert review and appraisal. 400 patients were administered TESS twice, at day 0 and at 2 weeks (for test-retest reliability). After data attrition, responses were analysed in 387 (80 English, 198 Hindi and 109 Marathi). Reliability was measured using Intraclass-correlation-coefficient (ICC), internal-consistency using Cronbach's alpha (Ca), construct-validity using Kaiser's-criteria (Eigenvalue >1 rule), Scree-Plots for factor-analysis, external-validity against MSTS using Bland-Altman-plots and criterion-validity Spearman's-Rho.

Results: The reliability and consistency were excellent both for Hindi and Marathi (ICC 0.91 Upper-Extremity, 0.92 Lower-Extremity, Cronbach's-alpha 0.96 Upper-Extremity and 0.94 Lower-Extremity). Construct-validity was excellent with Kaiser-criteria of 0.8, Bartlett's-test ($p < 0.0001$), Scree-plot elbow of 3 domains. External-validity against MSTS was excellent with Bland-Altman-plot showing less than 5% disagreement and a Spearman's-Rho of 0.4 Hindi and 0.41 Marathi ($p < 0.0001$).

Conclusion: The Hindi, Marathi TESS-versions are reliable, consistent and valid in measuring

patient reported functional outcome for patients treated with surgery for an extremity tumor.

(P 209) SARCOMA PATIENT COMMUNITY DATA COLLABORATION TO ADVANCE RESEARCH

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Objective: Research and innovation in sarcoma has historically lagged behind more common malignancies. Among other contributing factors, including disparate funding support, there is lack of cohesive high-quality genetic and genomic data available to researchers that is representative of the heterogeneous nature of this group of diseases. To address this unmet need, Sarcoma Foundation of America has launched a sarcoma community data project as a collaboration among patient advocacy organizations and researchers.

Methods: Through this collaboration we will (1) retrospectively combine existing data from patients, patient organizations and care providers and (2) prospectively collect data from patients, patient organizations care providers into a centralized de-identified data repository. Further, this initiative will combine next-generation sequencing and molecular profiling studies with electronic medical records data to allow the community to learn about patient outcomes, natural history of disease, and off-label drug effectiveness. By pooling data from many patients across different institutions, we will improve the ability to achieve statistical power and derive meaningful conclusions from these data. This data source will be available to researchers interested in asking important questions about molecular predictors of metastatic disease, treatment failure and success, effective drug combinations and other correlative metrics.

Results: N/A

Conclusion: Currently, patients, providers, and advocacy organizations collect and deposit data in one of many commercially available or academically affiliated platforms, creating a fractured network of data that cannot be mined collectively to answer a scientific question. The sarcoma patient community data collaboration to advance research represents a patient-driven and outcomes-focused data initiative within the sarcoma advocacy community to facilitate ethical data sharing and research advancement.

(P 210) TOWARDS INTERNATIONALIZATION OF THE CLINICAL RESEARCH COORDINATOR ROLE: THE FIRST DROP OF THE NIAGARA FALLS PROJECT

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Objective: The Clinical Research Coordinator (CRC) role lacks global recognition, causing unclear job description and wide EU/non-EU variation. In Italy, CRCs handle mainly administrative tasks, while in Canada, they manage patient-centered activities. This highlights the need for unified CRC responsibilities worldwide.

Methods: A collaboration between the Istituto Nazionale dei Tumori (Milan), the Italian Sarcoma Group, and Mount Sinai Hospital (Toronto) developed a 36-question survey for CRCs in sarcoma care. The survey, hosted on REDCap, covers institutional support, patient interaction/data protection, and professional context. A pilot phase (June 2025, 6 CRCs: 3 Italian, 3 Canadian) tested usability; a second phase will include a larger cohort. Results will be analyzed separately to examine cross-national CRC role differences.

Results: The pilot group completed the survey in a median of 15 minutes, with no usability issues. Results show differences in CRC roles, especially in patient interaction. Informed consent process is managed by physicians (2 Italians), jointly by CRCs and physicians (1 Italian, 1 Canadian), by nurses (1 Canadian), or CRCs alone (1 Canadian). Patient visits are scheduled by multiple staff in 83%. Direct CRC–patient contact occurs in 50%; nurses manage interactions in 33%. Data protection takes >80% of tasks in 33%, 51–80% in 17%, < 25% in 50%. One reports patient association involvement in study protocols and informed consent development. Recognition of CRC is absent for 83%, both relative to other jobs and nationally, with 50% reporting job insecurity. Unstable roles are institution-, investigator-, or donor-funded. Career and salary prospects (67%) drive intentions to leave the role. Half report the presence of boards formally supporting the CRC role, though none affiliated, showing a poor CRC role recognition.

Conclusion: Combined with phase two results (expected July 2025), findings will identify challenges to harmonizing the CRC role. A third phase may include sarcoma centers in the US, Spain, France, and Australia. The survey aims to define CRC duties crucial for improving quality, ethics, and outcomes in sarcoma trials, supporting global alignment and enhancing patient care and trial outcomes.

(P 211) HEALTH-RELATED QUALITY OF LIFE IN IRISH SARCOMA PATIENTS

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Objective: Health-related quality of life (HRQoL) is a multi-dimensional patient-reported outcome (PRO) crucial for comprehensive patient (pt) care. Monitoring PROs reduces symptom burden and hospitalisations and improves treatment (tx) adherence and survival. We aim to evaluate HRQoL using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) in pts with sarcoma treated at Ireland's national referral centre.

Methods: Pts ≥ 18 years with a diagnosis of bone or soft tissue sarcoma (STS) treated at St

Vincent's Hospital Group completed the EORTC QLQ-C30 questionnaire (version 3) between October 2024 and May 2025. Demographic and clinical data was collected. Responses were scored as per EORTC guidelines. Descriptive statistics were performed, and group comparisons were conducted using the Mann-Whitney U test and Spearman's rank correlation.

Results: 101 pts were included for analysis with a median age of 56 [19-82]. The majority of pts were female (57%) with STS (82%), metastatic or unresectable disease (59%), and on active tx (61%). The median global health score (GHS) was 67. HRQoL domain scores were highest for emotional (83) and cognitive (83) functioning, followed by physical (73), role (67), and social (67). Pts with metastatic or unresectable disease reported significantly lower physical ($p=0.002$), role ($p=0.002$), and social functioning ($p=0.0002$). Female pts reported significantly lower emotional ($p=0.0045$) and cognitive functioning ($p=0.032$) compared with male pts. Pts on systemic tx reported lower social functioning than those not on tx ($p<0.0001$). There were no significant differences in GHS or functional domains based on age, grouped histology (bone vs STS), or tumour location (extremity vs non-extremity).

Conclusion: Irish pts with sarcoma report an impaired HRQoL, with a mean GHS consistent with previously published data. Pts with metastatic or unresectable disease report significantly worse function across multiple domains, female pts report poorer emotional and cognitive function, and pts on active tx report more impaired social functioning. There were no clear disease-specific predictors of HRQoL, including across grouped histological subtypes or primary tumour location. Given the prognostic value of HRQoL and the relative paucity of real-world data in sarcoma, ongoing longitudinal assessment of this cohort will help characterise HRQoL across the disease continuum and guide strategies to improve pt care and outcomes.

(P 212) MISINFORMATION IN SARCOMA CONTENT ON SOCIAL MEDIA PLATFORMS

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Objective: To evaluate the presence and characteristics of misinformation in sarcoma-related content and user comments on widely used social media platforms, given the increasing role of social media as a health information source and its potential impact on patient understanding and decision-making.

Methods: We evaluated sarcoma-related information on TikTok, Instagram, and YouTube by analyzing the first 30 posts retrieved with the keyword "sarcoma" on each platform without filters, all searched on the same day during May 2025. For each post, we recorded publication date, number of visualizations, narrative tone (educational, personal narrative, fear-arousing), author type (health professional, institution, patient, influencer), and the presence of misinformation in user comments. Three independent evaluators assessed post veracity (true, confounding, false) and noted misinformation in comments using predefined criteria, resolving discrepancies by consensus.

Results: A total of 51% of analyzed posts were published within the last two years. Total visualizations reached 86.8 million on Instagram, 10.0 million on TikTok, and 1.7 million on YouTube. Median visualizations per post were highest on TikTok (44,700), followed by Instagram (38,600) and YouTube (6,800). Narrative tones included educational (49%), personal narrative (33%), and fear-arousing (18%). Posts were rated as true in 69%, confounding in

23%, and false in 7%. Institutions posted exclusively true content, while influencers and patients had higher proportions of confounding or false content (influencers: 54% non-true; patients: 42% non-true). Notably, misinformation was present in comments under 47% of posts, including 32 posts (36%) that were rated as true.

Conclusion: While most sarcoma-related social media content was accurate, a substantial proportion was confounding or false, particularly among patient and influencer posts. Importantly, misinformation frequently appeared in user comments, even under accurate posts, underscoring a potential threat to patient education and decision-making.

(P 213) FINANCIAL TOXICITY IN IRISH SARCOMA CARE: A SINGLE-CENTRE ANALYSIS

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Objective: Financial toxicity (FT) is an under-recognized consequence for patients (pts) diagnosed with cancer. There is a paucity of data on FT in pts with sarcoma, which has implications for clinical outcomes, such as health-related quality of life (HRQOL) and survival. We aim to evaluate FT in Irish sarcoma pts using the validated patient-reported outcome measure, the Comprehensive Score for Financial Toxicity (COST) Functional Assessment of Chronic Illness Therapy (FACIT).

Methods: Pts ≥ 18 years with a diagnosis of bone or soft tissue sarcoma (STS) treated at St Vincent's Hospital Group (SVHG) completed the COST questionnaire (version 2) between October 2024 and May 2025. Demographic and clinical data were collected. FT was graded as Grade 0 (none, ≥ 26), G1 (mild, 14–25), G2 (moderate, 1–13), and G3 (severe, 0). Descriptive statistics were performed, and group comparisons were conducted using the Mann-Whitney U test and Spearman's rank correlation.

Results: 101 pts participated; 3 were excluded. 98 pts were included for analysis with a median age of 56 [range 19–82]. The majority of pts were female (57%) with STS (82%), metastatic or unresectable disease (59%), and on active treatment (61%) in the public hospital (64%). Financial toxicity was reported by 48% of pts (G1 n = 37, G2 n=8, G3 n=2). The median COST score was 26 [0–44]. Pts in the public system experienced greater FT than those in the private system ($p = 0.031$). No significant differences were observed between genders, disease states (metastatic or unresectable vs. non-metastatic), grouped histology (bone vs. soft tissue sarcoma), or treatment status (on or off systemic treatment). Younger age at the time of diagnosis ($p = 0.28$, $p = 0.006$) and at the time of completion ($p = 0.27$, $p = 0.008$) of COST was associated with higher FT.

Conclusion: FT is common among pts treated at Ireland's national referral centre for sarcoma. Younger pts and those treated in a public hospital reported higher levels of FT. Clinical features and treatment status were not associated with significant differences in FT. Ongoing research is exploring the effect of FT on HRQOL and other patient-reported outcomes. Systematic

assessment of and focused support for FT is essential to improve patient experience and clinical outcomes.

(P 214) FINANCIAL TOXICITY IN PATIENTS WITH A HISTORY OF EXTREMITY AND PELVIC SARCOMA TREATMENT

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Objective: Financial toxicity in oncology, defined as the economic burden and psychosocial distress of cancer care, has been associated with poor clinical outcomes. Despite high projected treatment costs, data on financial toxicity in patients with sarcoma remain limited. The objective of this study was to characterize financial toxicity in patients with sarcoma, to better inform screening practices in patients with rare cancers requiring complex, multidisciplinary treatment plans.

Methods: We conducted a survey of a retrospective cohort study of patients diagnosed with trunk or extremity sarcomas between 2016-2024. Patients were administered the Comprehensive Score for Financial Toxicity (COST), which has been validated in patients with cancer. Scores ranged from 0-44; financial toxicity was categorized into moderate-to-severe (< 26), and low-to-none (≥26) groups. Demographic and clinical variables were obtained from electronic medical records. Univariate logistic regression analyses were used to explore variables associated with financial toxicity.

Results: Among 205 participants, 77% reported moderate-to-severe financial toxicity. The odds of financial toxicity were similar across insurance types, race, ethnicity, employment status, income, and geography. Patients were less likely to report financial toxicity if they had soft tissue sarcomas (in comparison with bone sarcomas; OR 0.43 [95% CI 0.18 – 0.98]).

Conclusion: Financial toxicity is highly prevalent among patients with sarcoma. The widespread nature of this financial distress across different patient groups suggests that no specific population is disproportionately affected, underscoring the universal risk of financial toxicity. These findings support exploring universal financial toxicity screening in patients with sarcoma to facilitate timely interventions.

Univariate Logistic Regression Results: Demographic and Clinical Characteristics as

Associative Factors for Financial Toxicity

Variable	Odds Ratio (95% Confidence Interval)	p-value
Age at Diagnosis	1.02 (0.99 – 1.04)	0.06
Race/Ethnicity		
Non-Hispanic White	Reference	N/A
Minoritized	1.59 (0.78 – 3.25)	0.21
Education Level		
< High School	Reference	
> High School	0.89 (0.41 – 1.93)	0.76
Insurance Status		
Private	Reference	N/A
Medicaid	4.14 (0.90 – 19.05)	0.07
Medicare	2.01 (0.97 – 4.16)	0.06
Uninsured/Other	3.22 (0.68 – 15.11)	0.14
Income		
< \$60,000	Reference	N/A
> \$60,000	0.60 (0.29 – 1.24)	0.17
Area Deprivation Index (ADI)		
National ADI %ile	1.00 (0.98 – 1.02)	0.82
Distance from Treatment Center		
Miles to Treatment Center	1.00 (0.99 – 1.01)	0.28
Minutes to Treatment Center	1.00 (0.99–1.01)	0.30
Type of Sarcoma		
Bone Sarcoma	Reference	N/A
Soft Tissue Sarcoma	0.43 (0.18 – 0.98)	0.05*
Surgical Treatment		
Amputation	Reference	N/A
Limb Salvage	0.62 (0.50 – 3.91)	0.35
No Surgery	1.67 (0.20 – 14.37)	0.64
Chemotherapy Treatment		
None	Reference	N/A
Yes	0.89 (0.44 – 1.80)	0.75
Radiation Treatment		
None	Reference	N/A
Yes	0.80 (0.41 – 1.56)	0.51

(P 215) SHAPEHUB: A MULTICENTRE REAL-WORLD-TIME DATA PLATFORM WITH DIGITAL TWIN ENGINE FOR A LEARNING HEALTH SYSTEM IN SARCOMA

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Objective: To describe the design and early deployment of SHAPEHUB, a federated real-world-time (RWT) platform supporting value-based, data-driven sarcoma care. The platform integrates digital twin representations, automated quality indicators, and causal machine learning pipelines as foundational tools of a learning health system.

Methods: SHAPEHUB connects eight institutions within a hub-and-spoke model: one central sarcoma expertise hub and multiple affiliated centers. Structured data from electronic health records, pathology, imaging, genomics, PROMs, and administrative modules are harmonised using HL7-FHIR and OMOP standards. Real-time ingestion enables synchronized multidisciplinary tumour board (MDT) dashboards, shared longitudinal views, and metadata queries. A digital twin engine mirrors each patient's clinical journey and forms the substrate for causal counterfactual modelling. Automated algorithms for sarcoma-specific quality indicators (e.g. margin documentation, staging procedures, timely treatment) are embedded. Cost linkage pipelines are in development to enable real-time outcome-to-cost mapping.

Results: All centers are live with RWT data ingestion, dashboard functionality, and unified MDT participation. PROM capture and quality monitoring are operational; validation is ongoing. Digital twin timelines support exploratory queries and are being prepared for causal inference layers. Initial cost integration is active in one spoke center. The network operates in a fully federated architecture: institutional data custody is maintained while analytics occur across the shared environment.

Conclusion: SHAPEHUB establishes a scalable digital infrastructure for individualised, value-

based sarcoma care. By combining real-time data flow, digital twins, and causal analytics within a hub-and-spoke model, it enables dynamic quality assessment and personalised decision support, positioning SHAPEHUB's hub-and-spoke model as a blueprint for scalable learning health systems.

(P 216) VIRTUAL MULTIDISCIPLINARY MEETINGS IN THE CARE OF SARCOMA PATIENTS

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Objective: Sarcomas are a heterogeneous and rare group of malignancies with an increasing number of subtypes. The aim of virtual multidisciplinary team (MDT) meetings is to provide support from the reference center for oncologists in peripheral centers in the diagnosis and therapeutic decision-making for patients with soft tissue sarcomas.

Methods: Virtual MDTs are held biweekly via Zoom. Invitations are sent a week in advance. Patient cases, including imaging, are submitted securely. Following each meeting, a summary with recommendations is emailed to participants.

Results: The first meeting took place on October 7, 2022. To date, 311 cases have been discussed: 181 patients with soft tissue sarcomas, 43 with bone sarcomas, 34 with retroperitoneal sarcomas, 13 with uterine sarcomas, 11 with desmoid tumors, and 29 with benign soft tissue tumors or carcinomas. As a result of MDT discussions, 94 patients were referred for in-person consultation or initiated treatment at the National Institute; 97 received palliative chemotherapy locally; 55 underwent radical surgery or radiotherapy in their primary centers. In 65 cases, alternative decisions were made, such as further observation or repeat biopsy.

Conclusion: Interdisciplinary consultations across centers facilitate the management of rare tumors and often allow patients to receive treatment locally without referral. Simultaneously, MDT meetings enhance access to specialized care or clinical trials when needed.

(P 218) THE IMPACT OF BROADENED GENETIC COUNSELLING REFERRAL CRITERIA IN SARCOMA PATIENTS: A REFERENCE CENTRE'S EXPERIENCE

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Objective: Although most sarcomas are sporadic, up to 20% of patients meet criteria for suspected hereditary cancer predisposition, mainly TP53-related cancer syndrome. Germline pathogenic variants (PVs) are found up to 8-20% of analysed cases, including many who do not meet strict referral criteria, suggesting the need to expand referrals to Hereditary Cancer Counseling (HCC) unit. The objective of this study is to evaluate the impact on diagnostic and preventive clinical management following the implementation of broadened referral criteria at our center in 2023, which includes referring all patients with sarcoma under 45 years.

Methods: Retrospective observational study of a cohort of consecutive patients diagnosed with sarcoma and referred to HCC unit of a reference center between January 2007 and April 2025. Germline testing was performed according to clinical practice.

Results: Between 2007 and 2022, 22 patients diagnosed with sarcoma were referred to HCC unit. The median age was 46.5 years, and all met the established criteria for germline testing. PVs were identified in nine patients (40.9%). From January 2023 to April 2025, a total of 115 patients were referred to HCC unit. The median age was 37 years, with 71.3% of patients younger than 45 years. Women accounted for 54.8% of the referred individuals. Of these patients, 41 met the criteria for suspected hereditary cancer predisposition (85.4% were suspected of having TP53-related cancer syndrome). Germline testing was performed on 71 patients; 33 of them (46.5%) did not meet the strict criteria for suspicion. Germline PVs were found in 9.9% (seven patients): 13.2% of those who strictly met the criteria and 6% of those who did not. The PVs identified were: POT1 in one patient, TP53 in two patients, MUTYH in one patient, NF1 in one patient, RB in one patient and MSH6 in one patient. Of these seven patients, two (28.6%; both with TP53 PVs) did not strictly meet the criteria for germline testing.

Conclusion: The expansion of referral criteria to the Hereditary Cancer Counseling (HCC) unit to include all patients under 45 years of age has resulted in an increase in germline testing and PVs detection. This approach has significantly influenced clinical management and follow-up.

(P 219) RETROPERITONEAL SARCOMA: HEALTH SYSTEM BARRIERS AND THE RATIONALE FOR A SPECIALIZED SARCOMA UNIT

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Objective: Colombia's fragmented healthcare system, due to economic and geographic inequities, significantly impedes sarcoma patient care. We analyzed health system-dependent variables affecting retroperitoneal sarcoma patients, proposing a specialized sarcoma unit to address these challenges.

Methods: Descriptive retrospective analysis of patients surgically treated for retroperitoneal

sarcoma at Fundación Colombiana de Cancerología Clínica Vida, Medellín, Colombia (2016-2025). Descriptive statistics presented qualitative (frequencies) and quantitative variables (medians, interquartile ranges [IQR]). Wilcoxon test compared median follow-up and diagnosis-to-surgery days across health insurance regimens. Kruskal-Wallis test compared these medians across insurance companies. $p < 0.05$ significant.

Results: Seventy-four retroperitoneal sarcoma patients underwent surgery; 47 (63.5%) were women with a median age of 61 [IQR: 26-85] years. Most (75.6%) resided in the Medellín metropolitan area, and 22.9% had a subsidized health insurance regimen. Patients were from 5 different insurance companies and used a median of 3 [IQR: 2-4] imaging providers and 2 [IQR: 1-2] pathology providers. Of 69 patients, 24% lacked presurgical biopsy; 4% were by laparotomy and 1.3% by laparoscopy. Ten (13.5%) had prior non-oncological surgery at a non-oncological institution. Median days from diagnosis to oncological surgery were 65 [IQR: 9-189] higher in subsidized vs. contributory regimens and non-metropolitan vs. metropolitan residents. Median follow-up was 24 [IQR: 11-47] and it was shorter in subsidized vs. contributory regimens and non-metropolitan vs. metropolitan residents. Treatment and follow-up times varied according to insurance companies.

Conclusion: The fragmented healthcare system of Colombia, driven by insurer-led provider changes, causes significant sarcoma care barriers and delays. Establishing a specialized sarcoma unit in Medellín would consolidate diagnosis, treatment, and follow-up. The proposal aims to overcome fragmentation, ensure consistent expertise access, and improve outcomes for these rare tumors.

(P 220) THE IMPACT OF WOUND HEALING COMPLICATIONS ON PATIENT-REPORTED OUTCOMES FOLLOWING SOFT TISSUE SARCOMA SURGERY

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Objective: Surgical resection of soft tissue sarcoma (STS) carries a risk of wound healing complications (WHCs), which can delay recovery, increase healthcare utilization, and require additional surgical interventions. While prior studies have evaluated surgical and oncologic outcomes, fewer have assessed how WHCs affect the patient experience. This study aimed to use validated patient-reported outcome measures to assess the short-term impact of WHCs on physical and mental health.

Methods: We conducted a retrospective review of a prospectively collected, multi-institutional cohort of adults with extremity or trunk STS treated with limb-sparing surgery between 2017–2025. Only patients amenable to primary closure were included. WHCs were defined as seroma, infection, dehiscence, or return to the operating room. PROMIS Global Physical and Mental Health T-scores were collected at baseline, 3 months, and 6 months postoperatively.

Results: Among 76 patients, 45 (59%) experienced a WHC, and 16 (21%) required reoperation. Patients with WHCs had significantly lower mental health scores at 3 months (mean 50.0 vs. 55.5, $p = 0.036$), indicating early psychological impact, although scores equalized by 6 months. Physical function trended lower in WHC patients at 3 months but did

not reach statistical significance.

Patients who underwent reoperation experienced a more sustained decline in physical health. At 6 months, physical T-scores were significantly lower for reoperation patients (44.8 vs. 52.9, $p = 0.020$), with a trend toward worse mental health as well. Baseline scores were similar across groups.

Conclusion: WHCs are associated with transient declines in mental health during early recovery, while reoperations are associated with prolonged physical impairment. These findings highlight the need for proactive counseling and tailored postoperative care for patients at risk of complications following STS surgery.

PROMIS Scores Stratified by Reoperation Status

Timepoint	Domain	No Return to OR	Return to OR	p-value
Baseline	Physical	47.6 ± 11.0 (n = 58)	48.2 ± 10.7 (n = 16)	0.836
3 mo	Physical	49.4 ± 9.8 (n = 48)	43.7 ± 9.7 (n = 16)	0.078
6 mo	Physical	52.9 ± 10.2 (n = 44)	44.8 ± 9.7 (n = 12)	0.020
Baseline	Mental	52.2 ± 8.6 (n = 58)	52.5 ± 6.9 (n = 16)	0.895
3 mo	Mental	53.3 ± 9.4 (n = 48)	47.6 ± 13.2 (n = 16)	0.128
6 mo	Mental	55.4 ± 9.4 (n = 44)	49.2 ± 10.3 (n = 12)	0.079

(P 221) QUALITATIVE ANALYSIS OF THE PERIOPERATIVE EXPERIENCE OF YOUNG ADULT PATIENTS UNDERGOING EXTREMITY SARCOMA SURGERY

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Objective: Young adults (YAs) with extremity sarcoma experience unique challenges and poorer oncologic outcomes compared to other patient populations. This interview-based study of YAs with resectable extremity sarcoma sought to understand challenges faced in the perioperative period, factors impacting the patient experience, and perceived barriers and facilitators to recovery after sarcoma surgery.

Methods: YAs with extremity sarcoma treated with surgery at a single NCI-designated comprehensive cancer center between 2019-2024 were eligible. Semi-structured interviews were conducted with questions focusing on how YAs experienced their initial diagnosis, treatment decision-making, provider communication, hospital experience, surgical cosmesis, post-operative support, and long-term recovery. Inductive coding by 3 investigators was performed to identify themes related to these facets of care.

Results: Demographic, tumor, and treatment characteristics are detailed in Table 1. Participants reported feeling isolated as a result of being YAs at the time of their cancer diagnosis. Some reported their personal goals for functionality were more ambitious than their providers'. Ongoing medical debt, limited eligibility for financial assistance, and difficulty navigating health insurance were common among YAs. Fertility was another area in which additional support was desired.

Conclusion: Age-specific concerns affect the quality of life of YA patients during the perioperative period and survivorship. Peer support, YA-customized financial navigation, and conversations to align patients' goals with surgeon expectations provide opportunities for intervention to improve care in this underserved cohort.

Patient, tumor, and treatment characteristics.

Characteristic	N
Sex	
Female	9
Male	5
Age at time of surgery	
18-25	4
26-39	10
Sarcoma type	
Bone Sarcoma	4
Soft Tissue Sarcoma	10
AJCC 8th edition stage at time of surgery	
Primary Bone Sarcoma	
IIA	3
IIB	1
Soft Tissue Sarcoma	
IA	1
IB	1
II	2
IIIA	4
IIIB	1
IV	1
Treatment Modalities	
Surgery only	5
Surgery + Chemotherapy	4
Surgery + Radiation	1
Surgery + Chemoradiation	4
Type of Surgery	
Amputation	1
Rotationplasty	1
Limb-Salvage	
Without endoprosthesis or flap reconstruction	3
With flap reconstruction	8
With endoprosthesis	1

(P 222) DO WE ALL SEE IT THE SAME: AN INTER-RATER RELIABILITY ANALYSIS OF THE MUSCULOSKELETAL TUMOR REGISTRY DATA ELEMENTS

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Objective: The Musculoskeletal Tumor Registry (MsTR) is designed to understand clinical data and patient-reported outcomes following treatment for musculoskeletal malignancies. The initial Sarcoma Module affords a level of detail regarding the nature of the disease and treatment not previously seen outside of single-institutional databases. However, the utility of the MsTR in providing research-quality data depends upon ensuring reliable and accurate data entry. To assess data integrity, the current analysis aims to: 1) understand data elements for which MSTS members do not have consensus regarding how best to code into the registry, and 2) to develop a data dictionary to advise as to how registry coding should be performed.

Methods: A series of surveys were conducted of MsTR Steering Committee Members and MsTR users to identify data elements for which uncertainty may exist as to the optimal registry coding. Once these were compiled, a survey was completed by 60 MSTS members involving the data entry for 35 clinical vignettes related to the areas of question. Consensus was defined as at least 90% agreement. A modified Delphi method was utilized to establish a consensus on a data dictionary to inform guidance as to how registry elements should be coded in previously ambiguous clinical scenarios.

Results: The MsTR member survey highlighted areas of inconsistency or confusion, particularly for 1) the range of percent necrosis on histopathology, 2) defining the longitudinal location of the tumor along the compartment, and 3) the appropriate categorization of tumor depth when the tumor was situated along the superficial aspect of the fascia, without invasion deep to the fascia.

Conclusion: Through a series of surveys and a consensus meeting, the MsTR utilized a modified Delphi approach to identify data elements for which inter-rater reliability of data entry was a concern. This allowed for development of a data dictionary to promote coding consistency between institutions contributing to the registry. This effort, and similar ones in the future, aim to optimize the accuracy, reliability, and utility of the MsTR in providing reproducible, research-quality data for this highly complex patient population.

Areas Without Initial Consensus

1. Estimated Necrosis as a Range (eg 80-90% necrosis)

- Recommendation: Use the average of the range

2. Longitudinal Location within the Compartment

- Recommendation: Utilize AO definitions

3. Tumor Depth

- Recommendation: Fascia is considered "deep", superficial is defined as whatever is not deep.

4. Compartment Status

- Recommendation: Utilize Enneking's original definitions

5. Method of Biopsy if Presentation is After Unplanned Excision

- Recommendation: Add a category for "Unplanned Excision"

6. Final Margins are Wide, but only after Intraoperative Re-Excision for Positive Frozen Section

- Recommendation: Utilize surgeon and pathologist judgment

(P 223) OUTCOMES OF GERIATRIC PATIENTS WITH DE NOVO SARCOMA AND LUNG METASTASES: ROLE OF TUMOR CHARACTERISTICS AND TREATMENT STRATEGY

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Objective: This study aimed to assess the impact of clinicopathological characteristics and treatment strategies on survival in geriatric patients presenting sarcoma with lung metastases.

Methods: We retrospectively analyzed patients aged ≥ 80 years with de novo sarcoma diagnosis and lung metastasis in the Surveillance, Epidemiology, and End Results (SEER) database (2000-2020). Kaplan-Meier analysis and log-rank tests were used to assess differences in overall survival (OS). Cox regression analysis was used to assess prognostic factors for this group of patients.

Results: A total of 406 patients were included with median OS (mOS) of 3 mo (3-4 mo), reflecting the aggressive nature of metastatic sarcoma in this population. Sarcoma with higher grade ($P=0.0078$), bone metastasis ($P=0.036$), and distant lymph node metastases ($P=0.019$) were associated with a poorer prognosis of patients. Cox analysis further identified bone metastasis as an independent factor associated with a worse OS (HR 1.33, 95%CI 1.00-1.76, $P=0.049$), whereas female sex was associated with an improved OS (HR 0.075, 95%CI 0.60-0.95, $P=0.017$). Treatments of the primary disease with surgery (HR 0.47, 95%CI 0.36-0.61, $P<0.001$), RT (HR 0.54, 95%CI 0.42-0.70, $P<0.001$), or CT (HR 0.41, 95%CI 0.31-0.56, $P<0.001$) were each independently correlated to improved OS. Patients receiving multimodal therapy had better outcomes compared to those receiving monotherapy. Comparable prognoses were observed in patients with surgery plus RT/CT or triplet therapies. Radiotherapy timing relative to surgery did not significantly impact survival ($P=0.11$).

Conclusion: Among geriatric patients with de novo sarcoma and lung metastases, synchronous bone and lymph node involvement and high-grade histology are negative prognostic indicators. Multimodal treatments improved survival, despite of patients' advanced age. Personalized treatment plans incorporating surgery, chemotherapy or radiotherapy when feasible may offer survival benefit in this vulnerable population.

(P 224) PAN-SARCOMA DATABASE (PSDB): AN UPDATE ON MIAMI'S COLLABORATIVE MULTI-USER DATA PIPELINE OF SARCOMA DATA USING REDCAP AND R CODING

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Objective: Sarcomas are a rare group of mesenchymal malignancies arising soft tissue and bone, often requiring multidisciplinary care. Capturing the complexity of patients' sarcoma diagnoses, treatments, and progressions pose several logistical data challenges. The Pan-Sarcoma Database (PSDB) is an innovative open-source research application developed to efficiently collect and manage data on sarcoma patients to create a reliable research pipeline by funneling data from multiple sources.

Methods: The Model-View-Controller (MVC) framework is a software design pattern used by many modern applications. In this framework, "model" is the database, including the structure and metadata; "view" is the user interface software; "controller" is the coding language used to handle user input, update the model, and interact with the viewer. PSDB uses REDCap, shiny, and R, respectively. The database is comprised of over 400 data fields to capture demographics, survival, initial HPI, pathology, stage, grade, detailed location, detailed progression history, genetic testing, and all associated treatment data. Two developmental open-source R packages were written for these tasks: REDCapSync and RosyREDCap. REDCapSync uses the REDCap Application Program Interface (API) to maintain a feed of REDCap data. RosyREDCap uses the feed from REDCapSync to filter, visualize, and analyze the data from REDCap.

Results: We captured data from 31,253 candidate sarcoma patients from 2010 to present, including 4,303 confirmed cases, with 1,270 (30%) cases reviewed to date, merging data from multiple databases, pathology, and prior projects. Currently, 20% of our cases are metastatic at diagnosis; 51% are High grade; the median age at diagnosis is 52. By capturing key data and organizing an open-source code base in R mapped to our "model", we produced updating tables, statistics, time-to-endpoint analyses, and other modifiable outputs to identify outcome disparities that produce data for dozens of real-world data projects.

Conclusion: The PSDB successfully addresses the unique data challenges faced by sarcoma research groups, allowing for in-depth exploratory data analysis from refreshing data sources. The use of the MVC framework with REDCap, shiny, and R, enabled the creation of an application that is secure, user-friendly, and adaptable, supporting collaborative research efforts. We hope to share our pipeline methods with other institutions to increase collaborative research efforts and data sharing in sarcoma.

(P 225) GLOBAL REGISTRY OF SOLITARY FIBROUS TUMORS (SFT): INTEGRATING CLINICAL, MOLECULAR, AND ENVIRONMENTAL DATA- THE HOROWITZ SFT INITIATIVE (HSFTI)

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Objective: Solitary Fibrous Tumors (SFTs) are rare, accounting for ~2% of all sarcomas. While most are benign, 10–40% exhibit aggressive behavior, recurrence, or metastasis. Epidemiological and molecular research remains limited. Few studies address key features such as the most significant NAB2-STAT6 fusion or risk factors, and there is only one available cell line derived from a mouse PDX model. To address these gaps, the HSFTI was launched on April 12, 2023. Objectives: Primary: Establish a comprehensive biorepository of tumor and biological samples from patients with SFTs. Secondary: Collect survey data on risk factors and medical and family history to identify statistically significant associations; maintain clinical and pathological data to support molecular and translational research.

Methods: Single-site, longitudinal registry with adults (≥ 18 years) with confirmed SFT. The goal is to enroll 650 participants (500 nationally and 150 internationally) over a 10-year period. Approved by the University of Miami IRB, the protocol is being amended to support global expansion. Data collection components: Survey: A detailed, IRB-approved survey examining environmental, occupational, and lifestyle exposures that may correlate with SFT. Currently available in English, Spanish, and Haitian Creole, with additional languages to be added to support global participation. Biorepository and Medical Data: A linked biorepository will collect tumor tissue and blood samples. Medical records will be reviewed to obtain longitudinal clinical data and support translational research. Global accessibility: The registry is designed for international collaboration, with an interactive data-sharing platform hosted on the Sylvester Comprehensive Cancer Center website. The site will share global SFT research updates, including those from the Horowitz Initiative.

Results: The registry and website will be live and enrolling by CTOS. The use of recruitment materials such as flyers, mass communication to sarcoma oncologists, and direct communication with patients via existing SFT support groups on social media, should allow for rapid enrollment once site is activated. Enrollment and preliminary demographics updates will be presented at CTOS.

Conclusion: This first-of-its-kind global SFT registry will serve as a foundational resource to expand understanding of disease biology, evaluate environmental associations, and support the discovery of novel diagnostics and therapies, ultimately improving outcomes in this rare malignancy.

(P 226) REAL-WORLD MANAGEMENT OF SYMPTOMATIC VS ASYMPTOMATIC TGCT FROM AN OBSERVATIONAL REGISTRY

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Objective: Tenosynovial giant cell tumor (TGCT) is a rare neoplasm presenting with a wide range of clinical symptoms and severity. Treatment decisions should balance the possible curative nature of surgery with the benign, potentially indolent, nature of TGCT, the risk recurrence and the potential for surgery-related morbidity. This cross-sectional analysis of an ongoing registry compares management strategies for symptomatic versus asymptomatic

TGCT.

Methods: The TGCT Support Registry is an international, prospective database of longitudinal patient-reported demographic, clinical, and pathologic data. This analysis included adults with TGCT, classified as symptomatic or asymptomatic using pain inference and physical function derived from validated patient-reported outcomes tools (e.g., PROMIS-PF).

Results: In this analysis of 1,156 adult TGCT patients, most were female (72.1%, n=833), symptomatic at last entry (77.2%, n=893), with a median age of 44 years (18-85) and had diffuse TGCT (68.8%, n=795) of the knee (67.7%, n=339). Patients reported being treated by orthopedic surgeons (74.9%) and orthopedic oncologists (56.1%), with frequent involvement of community healthcare providers (54%, n=624). Symptomatic patients had more surgeries (2.8 vs 1.6; $p < 0.001$) and higher local recurrences rates (63.0% vs 36.6%; $p < 0.001$). Importantly, 37% of patients reported being symptomatic without recurrence (n=269). Asymptomatic patients were more likely to engage in active surveillance (58.9% vs 42.7%, $p < 0.01$), had fewer recurrences, and improved quality of life (QoL). Among patients on systemic therapies (n=222), 68.9% (n=153) reported improvement in QoL and greatest improvement was observed in asymptomatic patients (75.5% vs 39.3%, $p < 0.01$).

Conclusion: This real-world analysis underscores the need for timely diagnosis, early multidisciplinary care, tailored symptom-focused strategies, and integration of physical therapy, palliative care, and thoughtful treatment timing to reduce disease burden and prolong asymptomatic periods. Given the transient nature of symptom status and its influence by repeated interventions, it remains unclear whether sustained dysfunction is driven by TGCT itself or treatment-related sequela.

Table 1. Patient treatments and quality of life (QoL) improvement

	Symptomatic (n=893, 77.2%)	Asymptomatic (n=263, 22.8%)	Total (n=1156)
Number of surgeries, mean $\pm$ SD	2.8 $\pm$ 2.7	1.6 $\pm$ 1.2	2.2 $\pm$ 1.8
Systemic therapies, n (%)	173 (19.4)	49 (18.6)	222 (19.2)
Wait-and-see, n (%)	381 (42.7)	155 (58.9)	536 (46.4)
Those with prior surgery	(n=727)	(n=183)	(n=910)
LRR, n (%)	458 (63.0)	67 (36.6)	525 (57.7)
QoL Improvements on Systemic Therapies, n (%)	(n=173)	(n=49)	(n=222)
Significantly improved	68 (39.3)	37 (75.5)	105 (47.3)
Somewhat improved	39 (22.5)	9 (18.4)	48 (21.6)
Unsure	20 (11.6)	0 (0.0%)	20 (9.0)
Mostly not improved	28 (16.2)	0 (0.0%)	28 (12.6)
Not improved at all	18 (10.4)	3 (6.1)	21 (9.5)

(P 227) TREATMENT PATTERNS IN PATIENTS WITH TENOSYNOVIAL GIANT CELL TUMORS: ADDRESSING COMMUNICATION IN A NEW THERAPEUTIC LANDSCAPE

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Objective: Tenosynovial giant cell tumors (TGCTs) are benign neoplasms that can arise from synovial tissues and can be locally aggressive. TGCT treatment has primarily relied on surgical resection, but recent development of systemic therapies provides a non-surgical option. Indications for systemic therapy for TGCTs outside of clinical trials vary, requiring discourse between patients and their medical team providers. The purpose of this study is to identify patterns of multidisciplinary care of TGCTs at a large academic institution.

Methods: Patient and disease characteristics, treatment data, and referral patterns were extracted from the electronic medical record. Quantitative analysis was completed using summary statistics. Qualitative data was obtained through anonymous patient surveys to evaluate patient-provider communication and knowledge regarding TGCT management.

Results: Fifty-four patients were included in this study. Most underwent initial surgery (79.6%), and seventeen individuals (40%) underwent additional surgical procedures. Twelve patients received systemic therapy with pexidartinib or imatinib, and a majority (83.4%) experienced radiographic and/or symptomatic improvement after starting systemic therapy. Indications for systemic therapy ranged from recurrent/extensive disease to high-risk of morbidity associated with additional surgery. The most common referral pattern noted within our institution involved initial evaluation by orthopedic surgery or orthopedic oncology with subsequent surgery or discussion at a multidisciplinary tumor board.

Seventeen patients completed the survey. 14/17 reported good communication overall, but 6/17 were unfamiliar with or did not discuss any non-surgical treatment options. No knowledge question had greater than 50% correct responses.

Conclusion: Treatment of individuals with TGCT at our institution involved providers across various specialties and coordination with support services. With medical therapy emerging as both safe and effective, we propose a change to the historical referral pattern for patients specifically with recurrent TGCTs or external diagnoses to include an initial evaluation by both orthopedic and medical oncology, ideally at a multidisciplinary tumor board, to optimize patient understanding of all treatment options.

TGCT Treatment Characteristics

Covariate	Number (%)
Treatment Modality:	
Surgery	44 (81.5)
Radiation therapy	4 (7.4)
Systemic therapy	12 (22.2)
Surgery as Initial Treatment:	
Yes	43 (79.6)
No	11 (20.4)
Case Reviewed with Medical Oncology:	
Yes	40 (74.1)
No	14 (25.9)
Reasons for Use of Systemic Therapy:	
High risk surgical candidate	2 (16.7)
Morbidity associated with additional surgery	3 (25.0)
Recurrent/extensive disease	4 (33.3)
Delay need for additional procedure	1 (8.3)
Unknown	2 (16.7)
Support Services Utilized	
Physical therapy	25 (46.3)
Occupational therapy	2 (3.7)
Social work	5 (9.3)
Symptom management/palliative care	3 (5.6)

(P 228) FREQUENCY AND CLARITY OF SURGICAL GOALS FOR TUMOR RESECTION IN ADVANCED SARCOMA

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Objective: Tumor resection in advanced sarcoma is often non-curative, but may prolong life, preserve function, and provide palliation. Clearly stating how surgery may help patients live longer and/or improve their quality of life is essential in supporting informed decision-making, yet the frequency of this documentation is unknown. This study aimed to determine how often tumor resection is performed for advanced sarcoma and evaluate whether surgical goals were documented in preoperative clinic notes.

Methods: A retrospective cohort study was conducted among patients ≥ 18 years old who underwent tumor resection for any site of soft tissue sarcoma from March 2024 to February 2025 at two academic medical centers. Advanced sarcoma was defined as recurrent or metastatic disease. Preoperative notes were abstracted, categorizing patient-centered surgical goals to prolong life, relieve symptoms, prevent disability, or obtain diagnosis.

Results: Of 291 patients who had tumor resection for sarcoma, 102 (35.1%) had advanced disease (Table). Among these, 31 (30.4%) had a documented patient-centered surgical goal. An additional 27 (26.5%) referenced goals for cancer control, albeit without identifying a clear patient benefit. In 44 (43.1%) tumor resections for advanced sarcoma, no surgical goal was documented.

Conclusion: In this multisite cohort study, over one-third of sarcoma surgeries were for advanced disease, yet patient-centered surgical goals were documented in only 30% of these cases. Communicating and documenting how surgery aligns with patients' goals can better

counsel patients as they consider the value of surgery for advanced sarcoma.

Histologic Subtypes and Preoperative Documentation of Surgical Goals in Patients Undergoing Tumor Resection for Advanced Sarcoma

	All Sarcoma	Advanced Sarcoma ^a
Histology, n (%) ^b	N = 291	N = 102
Liposarcoma	64	26 (40.6)
Gastrointestinal stromal tumor	60	15 (25.0)
Leiomyosarcoma	41	19 (46.3)
Myxofibrosarcoma	19	6 (31.6)
Undifferentiated pleomorphic sarcoma	15	3 (20.0)
Spindle cell sarcoma	13	8 (61.5)
Angiosarcoma	11	4 (36.4)
Malignant peripheral nerve sheath tumor	8	4 (50.0)
Other histologies	60	17 (28.3)
Surgical Goal Documentation for Advanced Sarcoma		
Patient-Centered Surgical Goals, n (%) ^c		31 (30.4)
Prolong life		18 (17.6)
Relieve symptoms		7 (6.9)
Prevent disability		3 (2.9)
Obtain diagnosis		3 (2.9)
Cancer Control Surgical Goals, n (%) ^c		27 (26.5)
Remove visible or progressive sites of disease		15 (14.7)
Prolong time off systemic therapy		11 (10.8)
"Reset the clock"		2 (2.0)
No Goal Documentation		44 (43.1)

^a Advanced disease was defined as metastatic or recurrent sarcoma.

^b Percentage refers to the proportion of surgical operations for that histology which were performed for patients with advanced disease.

^c Percentage refers to the proportion of patients who underwent an operation for advanced sarcoma and had the surgical goal documented prior to surgery.

(P 229) DETERMINANTS OF DIAGNOSTIC INTERVAL IN EPITHELIOID HEMANGIOENDOTHELIOMA: A LINEAR AND QUANTILE REGRESSION ANALYSIS OF PATIENT-REPORTED DATA FROM THE SPAGN GLOBAL SARCOMA DIAGNOSIS PATHWAY SURVEY

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Objective: Delayed diagnosis is a major challenge in managing epithelioid hemangioendothelioma (EHE), a rare vascular sarcoma with nonspecific symptoms. This study assessed demographic and clinical factors associated with diagnostic interval length in EHE patients.

Methods: Data were derived from the SPAGN Global Sarcoma Diagnosis Pathway Survey, including adults with EHE. Outcome was the log-transformed diagnosis interval, defined as time in days from onset of symptoms to current diagnosis. Associations between clinical and demographic variables and diagnostic interval were explored, using linear regression and quantile regression at the 25th, 50th, and 75th percentiles to capture effects across the distribution. Variable selection was AIC-based; missing data were imputed using chained equations. Bootstrapped 95% confidence intervals (R = 500) were calculated; coefficients were exponentiated for interpretability.

Results: A total of 50 EHE patients were included. The median diagnostic interval was 349 days (IQR 28-1,542). While no associations were statistically significant, trends suggested potentially meaningful effects. For instance, longer diagnostic intervals were seen in females ($\exp(\beta)=1.89$, 95% CI: 0.88–4.06) and those with symptoms ($\exp(\beta)=1.72$, 95% CI: 0.88–3.35), while older age trended toward shorter intervals ($\exp(\beta)=0.98$ per year; 95% CI: 0.96–1.00). Quantile regression revealed longer delays in 75th percentile analysis if symptoms were reported ($\exp(\beta) = 2.09$; 95% CI: 1.12-3.92). Also, poor healthcare accessibility was significantly associated with shorter diagnostic intervals at the 50th ($\exp(\beta) = 0.43$; 95% CI: 0.22-0.82) and 75th percentiles ($\exp(\beta) = 0.45$; 95% CI: 0.25-0.83).

Conclusion: Delayed diagnosis in EHE remains substantial with a median diagnostic interval approaching 12 months. Although only a few variables reached statistical significance, the observed trends suggest an influence of various distribution-dependent factors. Quantile regression is important in uncovering associations masked in mean-based models, stressing the need for tailored diagnostics in ultra-rare cancers.

(P 230) CIRCULATING TUMOR DNA AS AN EARLY INDICATOR OF RESPONSE, PROGRESSION, AND RECURRENCE OF SARCOMAS

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Objective: Circulating tumor DNA (ctDNA) is an emerging tool for monitoring sarcomas alongside clinical exam and imaging. ctDNA has been shown to be an effective prognostic biomarker. As a convenient and minimally invasive liquid biopsy, ctDNA may serve as an early indicator to enable timely interventions.

Methods: In this retrospective study, we analyzed interval changes in ctDNA (Signatera mPCR-NGS) drawn every 6-12 weeks alongside clinical data for 73 sarcoma patients (618 plasma samples). For patients with at least one positive ctDNA result, treatment response, progression, and recurrence events were correlated with change in ctDNA. Patients with all negative ctDNA results were separately assessed for recurrence or residual disease.

Results: Among ctDNA positive patients (n=27), ctDNA decrease correlated with 93.3% of treatment responses. ctDNA increase correlated with 82.5% of progression events and preceded clinical and radiologic findings in 62.5%, by a median of 16 days (range: 2-55). Conversion from negative to positive ctDNA preceded 50% of recurrences by 31-64 days. Leiomyosarcoma (n=6) was the most common histology among ctDNA positive patients. Among ctDNA negative patients (n=46), 10 patients had recurrence or residual disease on imaging. Dedifferentiated liposarcoma (n=3) and undifferentiated pleomorphic sarcoma (n=3) subtypes were highest represented among patients with these false negatives.

Conclusion: Our study demonstrates ctDNA is an effective early indicator of treatment response, progression, and recurrence. ctDNA may prompt changes in management weeks or months before standard monitoring, benefiting high-grade sarcoma patients. However, clinically

aggressive subtypes carry higher false-negative risk, highlighting the need for more sensitive assays.

(P 231) INCREASED LIFETIME RISK (LTR) OF SOFT TISSUE SARCOMAS (STS) IN PATIENTS WITH LOW-RISK GASTROINTESTINAL STROMAL TUMORS (GIST): A RETROSPECTIVE ANALYSIS FROM THE ITALIAN SARCOMA GROUP (ISG)

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Objective: Several studies consistently showed an increased incidence of second primary neoplasms (SPNs) in patients with GIST. ISG previously reported that 25.4% of patients developed an SPN either before or after diagnosis. We investigated whether the LTR of developing an SPN was different across tumor types and exceeded that expected in the general population.

Methods: We included patients with histologically confirmed, surgically resected GIST, classified as low risk of relapse according to AFIP criteria, who were treated at ISG centers and did not receive neo/adjuvant imatinib. We analyzed the incidence and subtype distribution of SPNs, comparing observed rates with the expected LTR in the general population using data from the SEER database using Mantel-Haenszel odds ratios (ORs) with corresponding 95% confidence intervals (CIs).

Results: A total of 737 patients with low-risk GIST were included, with a median follow-up of 69.2 months. Among them, 187 patients (25.4%, 95% CI: 22.2–28.7%) were diagnosed with an SPNs (80 before, 51 synchronous with, and 56 after GIST diagnosis) (Table 1). Notably, 8 patients (1.1%; M/F 3/5) were diagnosed with STS: 1 before GIST, 4 synchronously, and 3 during follow-up. Histologic subtypes included solitary fibrous tumor (2), MDM2-amplified liposarcoma (2), soft tissue leiomyosarcoma (2), uterine leiomyosarcoma (1), and endometrial stromal sarcoma (1). When compared with SEER-based LTR data, the risk of developing STS was the only significantly increased in our cohort (OR 3.22, 95% CI: 1.48–6.97, $p=0.0031$). (Table 1)

Conclusion: Our findings showed increased risk of STS in patients with low-risk GIST compared to the general population. This observation is consistent with previous reports and supports the hypothesis that patients with GIST may share a common genetic predisposition to mesenchymal tumor development.

Table 1. Second Primary Neoplasms (SPNs) in Low-Risk GISTs and Odds Ratios (OR) for SEER Database Tumor-specific Lifetime Risk.

SPNs	Male	male %	Female	female %	tot	tot %	OR	95%CI
Breast	1	0.3%	31	8.6%	32	4.3%	0.59	0.41-0.86
Colon-rectum	13	3.4%	13	3.6%	26	3.5%	0.91	0.60-1.36
Melanoma	7	1.9%	13	3.6%	20	2.7%	0.88	0.56-1.40
Prostate	18	4.8%			18	2.4%	0.34	0.21-0.55
Other gastrointestinal tract	7	1.9%	7	1.9%	14	3.8%	NE	NE
Kidney	8	2.1%	3	0.8%	11	1.5%	0.83	0.45-1.53
Lung	4	1.1%	6	1.7%	10	1.4%	0.22	0.12-0.41
Non-Hodgkin lymphoma	6	1.6%	4	1.1%	10	1.4%	0.67	0.35-1.28
Urothelial	8	2.1%	1	0.3%	9	1.2%	0.48	0.25-0.94
Neuroendocrine	4	1.1%	4	1.1%	8	1.1%	0.6	0.29-1.22
Other hematologic malignancies	4	1.1%	4	1.1%	8	1.1%	NE	NE
STS	3	0.8%	5	1.4%	8	1.1%	3.22	1.48-6.97
Gynecological			7	1.9%	7	0.9%	NE	NE
Skin	2	0.5%	3	0.8%	5	0.7%	NE	NE
Pancreas	2	0.5%	2	0.6%	4	0.5%	0.33	0.12-0.88

(P 232) IS THERE A ROLE FOR POSITRON EMISSION TOMOGRAPHY IN THE STAGING OF LANGERHANS CELL HISTIOCYTOSIS?

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Objective: There is a lack of standardized staging imaging for Langerhans Cell Histiocytosis (LCH). Positron Emission Tomography (PET), bone scan, and skeletal survey are commonly used modalities to assess for systemic involvement. These differ substantially in radiation exposure with PET delivering significantly higher ionizing radiation. This study aimed to identify patient and disease factors associated with imaging selection and to determine whether PET improves systemic disease detection compared to other modalities.

Methods: A retrospective review (2001 – 2024) was conducted of patients with biopsy-proven LCH evaluated at a single institution. Age, sex, and presenting location at diagnosis were compared. Systemic disease detection was assessed across imaging groups.

Results: The cohort included 78 patients: 30 underwent PET, 11 bone scan, and 37 skeletal survey. Median age differed significantly by modality: PET (34 years [IQR 8–56]) vs. bone scan (13 [3–37]) vs. skeletal survey (7 [2–14])($p < 0.001$). Imaging modality differed significantly by location ($p=0.016$): 53% of bone lesions were assessed with skeletal survey, 28% with PET, and 19% with bone scan. Of skin lesions, 57% received skeletal survey, 36% PET, and 7% bone scan. All lung lesions were staged with PET. PET detected systemic disease in 30% of patients, significantly higher than bone scan (9.1%) and skeletal survey (8.1%)($p=0.049$).

Conclusion: In addition to age, the site of initial presentation affects the choice in selection of imaging modality. Further research is needed to determine whether increased systemic detection with PET translates to improved clinical outcomes, especially given its higher radiation burden.

(P 233) DNG64-CAR-V+ REGIMEN SHOWS CLINICAL BENEFIT IN PATIENTS WITH ADVANCED CCNG1 ONCOGENE EXPRESSING SARCOMAS (NCT04091295)

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Objective: Targeted gene delivery has long been considered the “Holy Grail” of cancer gene therapy. Off-the-shelf injectable DNG64-CAR-V, a tumor-targeted Chimeric Amphotropic RNA Vector encoding a CCNG1 inhibitor gene, induces apoptosis not only in cancer cells but also in tumor-associated endothelial cells and activated cancer-associated fibroblasts, thereby priming the tumor microenvironment for enhanced innate immune cell and/or drug entry. Expanded access DNG64-CAR-V is currently available for advanced sarcomas (NCT04091295).

Endpoints: Primary: Clinical benefit rate (CBR) defined as the percentage of patients achieving a confirmed or best response of CR, PR, or SD; Secondary: Overall response rate (ORR) and incidence of TRAEs; Collaborative: Correlation of CCNG1 expression level with CBR. The study will use a Simon 2-stage design with Type I error rate = 0.1 and power = 0.8; a CBR $\geq$ 30% would warrant opening a Phase II study.

Methods: The study site will treat 40 patients with DNG64-CAR-V (1.7 x 10¹⁰ RV copies i.v. 3x weekly, 3 weeks/month) plus FDA approved drugs ("DNG64-CAR-V+ regimen"). Archived tumor samples from all patients will undergo RNA sequencing to determine CCNG1 expression level. The study will use a Simon 2-stage design with Type I error rate = 0.1 and power = 0.8; a CBR $\geq$ 30% would warrant opening a Phase II study.

Results: Analysis of 6 evaluable patients (1 Extra-skeletal myxoid chondrosarcoma, 1 spindle cell sarcoma, 1 uterine leiomyosarcoma, 1 dedifferentiated liposarcoma, 1 osteosarcoma, 1 synovial sarcoma) treated with DNG64-CAR-V+ regimen demonstrated 83% CBR and 33% ORR (2 PR, 3 SD, 1 PD). All tumors showed enhanced CCNG1 expression. Stratified by CCNG1 expression level, high CCNG1 expressors (n=4) had a 75% CBR (1 PR, 2 SD, 1 PD), medium-high expressors (n=1) had a 100% CBR (1 PR), and medium-low expressors (n=1) had a 100% CBR (1 SD). No DNG64-CAR-V related adverse events were reported.

Conclusion: These data demonstrate 83% CBR and 33% ORR. Based on a CBR $\geq$ 30% for the entire cohort and for each subgroup stratified by CCNG1 expression level, all groups qualify for further studies of efficacy/safety in a Phase II study using the DNG64-CAR-V+ regimen.

(P 234) DOXORUBICIN PLUS BOTENSILIMAB, A NEXT GENERATION CTLA4 INHIBITOR, WITH OR WITHOUT BALSTILIMAB, A PD1 INHIBITOR, IN PATIENTS WITH ADVANCED SOFT TISSUE SARCOMAS

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Objective: Most soft tissue sarcomas (STSs) are immune cold and do not respond to immune checkpoint inhibitors (ICIs) blocking PD1 and CTLA4. Botensilimab (BOT) is an Fc-enhanced, next generation CTLA4 inhibitor engineered to improve T cell priming and activation. Treatment with BOT plus PD1 inhibitor balstilimab (BAL) induced responses in heavily pre-treated immune cold STS pts in a Phase 1 trial. We hypothesized that concurrent doxorubicin (DOX) would improve STS immunogenicity and boost efficacy of ICIs, including BOT with or without BAL.

Methods: We expanded a previously reported Phase 2 trial of DOX plus first-generation CTLA4 inhibitor zalifrelimab (ZAL) plus BAL (NCT04028063). Pts with no prior DOX/ICIs were enrolled to 1 of 3 dose levels: DOX 60 mg/m² every 3 weeks (q3w) plus BOT 75 mg IV every 6 weeks (q6w); DOX 75 mg/m² q3w plus BOT 75 mg q6w; or DOX 75 mg/m² q3w plus BOT 75 mg q6w and BAL 450 mg IV q3w. Primary endpoints were incidence of dose-limiting toxicities (DLTs) within the first 6 wks, using time to Bayesian optimal interval (TITE-BOIN) design and treatment-related adverse events (TRAEs). Secondary endpoints included progression-free

survival rate at 6 months (PFS6mo), objective response rate (ORR), disease control rate (DCR), overall survival (OS), and duration of response (DoR).

Results: 21 pts were evaluable for safety and 18 for efficacy. 20 pts (95%) experienced at least 1 TRAE. Most frequent TRAEs were GI (81% of pts), systemic fatigue or flu-like symptoms (62%), hematologic AEs (52%), rash (43%), mucositis (33%), and febrile neutropenia (29%); most were related to DOX. Immune-related TRAEs occurred in 14 pts (67%), with 8 (38%) requiring steroids/anti-TNF- α therapy. 6 pts had colitis (29%), including 1 with concurrent gastroparesis, and 2 other pts had diarrhea not requiring steroids. 3 pts had pneumonitis related to BAL (n=2) or BOT (n=1). Other immune AEs not requiring steroids included thyroid abnormalities (19%), pancreatitis (19%), unilateral hearing loss (DLT, n=1), and adrenal insufficiency (n=1). The ORR was 33.3% [95%CI 13-59], with median DoR of 20.9 wks [range 11-36], and DCR of 83% [59-96]. Median PFS was 25.4 wks [17.9-NA], with PFS6mo of 38.5% (13 evaluable). Median OS was 93.9 wks [68.3-NA].

Conclusion: DOX with BOT +/- BAL exhibits safety and efficacy consistent with prior experience of DOX/ZAL/BAL. Further investigation is needed to determine biomarkers of response/resistance and the optimal timing/sequence of DOX/ICIs to further improve outcomes.

(P 235) AGNOSTIC INDICATION OF IMMUNE CHECKPOINT INHIBITORS (ICI): PATTERNS OF RESPONSE OF SARCOMAS

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Objective: The ICI pembrolizumab is approved for solid tumors with high tumor mutational burden (TMB), mismatch repair deficient status (dMMR), and/or microsatellite stability-high status (MSI-H). Recent data indicate high response rates and prolonged response duration in carcinomas, but scant data exist for sarcomas with those features. This study describes our single-center experience with ICI in sarcomas characterized by high TMB, dMMR status and/or MSI-H.

Methods: A retrospective analysis of patients' charts was authorized by the Institutional Review Board. Eligible case criteria: age >18; any sarcoma subtype; tumor demonstrating at least one of the following by NGS: high TMB (>10 mutations/Mb), dMMR and/or MSI-H. Receipt of ICI was required. We retrieved the following data for analysis: date of initiation/termination of ICI treatment; best response observed per RECIST criteria; response duration.

Results: 11 patients (6 M/5 F) met the inclusion criteria. They were aged 34-73 at the time of diagnosis. The following histologies were represented: leiomyosarcoma (3), undifferentiated pleomorphic sarcoma (UPS) or unclassified high-grade sarcoma (2); malignant peripheral nerve sheath tumor (MPNST) (2), angiosarcoma (2); pleomorphic dermal sarcoma (PDS) (1), extra-skeletal osteosarcoma (ESO) (1). TMB ranged from 10.5 to 151 mutations/Mb. 2 patients have just started treatment with pembrolizumab. 9 patients for now are evaluable: 7 received single-agent pembrolizumab, 1 pembrolizumab/eribulin, and 1 ipilimumab/nivolumab. 3/9 (33%)

patients experienced objective response (1 CR cutaneous angiosarcoma, 1 CR PDS, 1 PR UPS). 2 patients experienced stable disease as their best outcome: 1 extra-skeletal osteosarcoma, 1 leiomyosarcoma. Finally, upfront progression was seen in the remaining 4 patients (2 leiomyosarcomas, 1 MPNST, 1 UPS). For the 3 responders, the duration of response ranged from 8 months (UPS) to 18 months (PDS), with 1 patient (cutaneous angiosarcoma) presently in CR at 6 months of on an ongoing treatment. Toxicity was consistent with previously published reports. Updated results will be presented at the conference.

Conclusion: Although high TMB, dMMR and MSI-H status are uncommon in sarcomas, this small series suggests these cases can benefit from ICI. However, the best responses were observed in subtypes known to benefit from ICI regardless of their biomarker status. A larger study is needed to evaluate the predictive value of high TMB, dMMR, and MSI-H status across sarcoma subtypes.

(P 236) EXCEPTIONAL RESPONSE TO COMBINATION IMMUNOTHERAPY WITH YH001 AND ENVAFOLIMAB IN METASTATIC SARCOMA.

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Objective: Single-agent immunotherapy has limited efficacy in sarcoma. Dual checkpoint inhibition targeting PD-(L)1 and CTLA-4 pathways show promise for improved clinical outcomes. Data from a group of patients at a single institution enrolled in a prematurely discontinued clinical trial are presented, focusing on one patient who showed an exceptional response.

Methods: This discontinued phase 1/2 open-label study was designed to investigate the combination of YH001 (recombinant humanized anti-CTLA-4 IgG1 monoclonal antibody) and envafolelimab (KN035, an anti-PD-L1 agent approved in China) in advanced sarcomas. YH001 was given intravenously every 3 weeks at an initial dose of 2 mg/kg for 4 doses, alongside KN035 at its recommended phase 2 dose of 600 mg subcutaneously every 3 weeks. We conducted a retrospective review of the four patients included in the trial at Northwestern University, all of whom were in phase 2.

Results: Synovial sarcoma, de-differentiated liposarcoma, leiomyosarcoma and fibrosarcoma (n=1, each) were represented. The median patient age was 47 years (range 32–64). One patient withdrew pre-treatment due to gastrointestinal bleeding. Of treated patients, 2 discontinued after RECIST progression at first imaging follow up. The patient with fibrosarcoma, widely metastatic to the lungs, achieved RECIST partial response with sustained stability at 7 months of follow up after 4 cycles of dual immunotherapy followed by 6 cycles of single-agent KN035. Subclinical hypothyroidism was diagnosed as an adverse event. After premature closing of trial, the patient with fibrosarcoma was transitioned to single agent nivolumab. Response occurred despite low tumor mutational burden (TMB) of 1.6 m/MB, negative PD-L1 staining (tumor proportion and combined positive scores < 1%), and primary failure to 3 preceding systemic regimens: AIM; trabectedin and pazopanib.

Conclusion: A sustained disease response was identified in a patient with metastatic

fibrosarcoma refractory to chemotherapy and TKI, after PD-L1/CTLA-4 treatment, underscoring potential for combined immunotherapeutics in sarcoma and the need for predictive biomarker identification beyond TMB and PD-L1.

(P 237) DEVELOPMENT OF EPHA2 CAR T CELL THERAPY FOR OSTEOSARCOMA

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Objective: Osteosarcoma (OS) is the most common malignant bone tumor in children and adolescents, with poor outcomes in metastatic or relapsed cases. EPHA2, a receptor tyrosine kinase minimally expressed in normal tissues but overexpressed in OS, non-small cell lung cancer (NSCLC), and glioblastoma, is associated with aggressive disease. Application of CAR T cell therapy in solid tumors has been hampered by antigen heterogeneity and an immunosuppressive tumor microenvironment. This study aims to preclinically validate EPHA2-targeted CAR T cells with improved tumor clearance and immune activation.

Methods: 24 fully human EPHA2-specific antibodies were selected based on strong binding to soluble and cell-surface EPHA2 (EC50 < 25 nM by ELISA). Second-generation CAR T cells were engineered and screened in vitro using luciferase-based cytotoxicity assays and live-cell imaging against OS (143B, SAOS2) and high EPHA2-expressing A549 NSCLC cell lines. The top 3 candidates were evaluated in vivo in metastatic 143B and A549 xenograft models in MHC DKO mice. Tumor burden by bioluminescence imaging and time to disease progression were assessed and compared across treatment groups.

Results: In cytotoxicity assays, 75% growth inhibition in A549 and 90% in 143B was seen with the lead CAR T construct (EP10) compared to 41% and 53% with a contemporaneous construct, 4H5, respectively (1:8 Effector:Target ratio). Significant reduction in tumor burden with EP10 was also observed in A549 ($p < 0.0001$, 2-way ANOVA) and 143B xenografts ($p < 0.005$) compared to 4H5 and a non-targeting control ($p < 0.0001$ in A549 and 143B). Significant progression free survival was also observed in EP10 treated A549 model (vs 4H5, $p < 0.0005$, median survival (MS) 115 days; vs control, $p < 0.0001$, MS 105 days) and aggressive 143B model (MS 54 days, vs 4H5, $p < 0.01$, MS 49 days; vs control, $p < 0.005$, MS 44 days) compared to 4H5 and control.

Conclusion: We describe initial development of a novel EPHA2-targeted CAR T cells with superior cytotoxicity, tumor control, and survival benefit over a contemporaneous product in OS and NSCLC models. Construct optimization with cytokine armoring is ongoing. Results from these studies will provide preclinical support for development of an investigator-initiated clinical trial in relapsed/metastatic OS.

(P 238) INVESTIGATING HOW MACROPHAGES INFILTRATE THE TUMOUR MICROENVIRONMENT AND INFLUENCE THE EFFICACY OF CAR T THERAPY IN A MURINE MODEL OF STS

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Objective: Soft tissue sarcomas (STS) are aggressive tumors of mesenchymal origin. Metastatic STS is resistant to systemic therapies and is in desperate need of new treatments. Chimeric antigen receptor (CAR) T therapy is a novel immunotherapy where a patient's T cells are engineered to recognize and kill malignant cells based on a target antigen. However, STS generally do not respond to this therapy despite expressing known CAR T target antigens. This is thought to be due to the immune suppressive tumor microenvironment (TME) characteristic of many STS, which diminishes CAR T cells infiltrating the TME. Additionally, studies suggest tumor associated macrophages (TAMs) are highly abundant in STS and may be driving immune suppression in the TME. Thus, targeting TAMs may alleviate the immune suppression in the TME and enhance the efficacy of CAR T therapy in STS.

Methods: We used a previously published murine model of STS developed by our laboratory. We engrafted STS into wild type C57Bl/6 mice and Ccr2^{-/-} mice, which have a deficiency in the classical monocyte recruitment pathway, which is essential for macrophages to infiltrate inflamed tissues. For CAR T therapy, we have generated a second generation CD28-CD3z mouse GD2 CAR using the 14G2a scFV currently being utilized in GD2 clinical trials. Mice bearing STS will undergo nonmyeloablative lymphodepletion with a single 200mg/kg dose of cyclophosphamide as standard part of CAR T cell therapy, followed by an intravenous delivery of GD2 CAR T cells.

Results: Ccr2^{-/-} mice bearing STS showed significantly smaller tumor size in comparison to C57Bl/6 mice. In assessing the TME, we found a significant reduction in the proportion of monocytes and TAMs, and an increased proportion CD3e⁺ and CD8⁺ T cells in the TME. Thus, reducing TAMs may provide an avenue to increase CAR T cell infiltration in the TME. Next, we administered CAR T cells to Ccr2^{-/-} mice and C57Bl/6 mice. Ccr2^{-/-} mice showed a trend to increased survival although this did not reach significance. We are repeating this experiment with a higher CAR T dose.

Conclusion: CCR2 deficiency provided both a significant reduction to TAMs and tumor size in this murine model of STS. Given the increased proportion of CD8 T cells, we believe this strategy may also improve the efficacy of CAR T therapy, which is under experimental assessment.

(P 239) **CHARACTERIZING THE ROLES OF T-CELLS IN THE CONTEXT OF TUMOR CLEARANCE AND MEMORY IN THE KP MODEL OF SARCOMA FOLLOWING STING THERAPY**

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Objective: Recent studies have shown that the stimulator of interferon genes (STING) agonist, E7766 can induce tumor clearance in the murine KP model of soft tissue sarcoma (STS). Following STING therapy with this translational STING agonist, tumor infiltrating lymphocyte frequencies increase. As lymphocytes are dominant mediators of tumor cell killing, we sought to investigate the contributions of CD4+ and CD8+ lymphocytes in the context of tumor clearance and subsequent protection against a model of STS recurrence.

Methods: C57BL/6 mice bearing STS tumors were treated intratumorally with a single dose of E7766 and were followed for survival in control and CD8+T-cell depleted states. Following survival studies, mice that showed evidence of STS eradication for over 90 days were re-challenged with an inoculation of STS cells in the contralateral limb. Re-challenged mice were allocated into control, anti-CD8+ and anti-CD4+ antibody depletion groups. Depletion was confirmed via flow cytometry.

Results: In a CD8+ depleted state, the therapeutic benefit of E7766 therapy was entirely negated, while non-depleted controls exhibit tumor clearance frequencies of 38%. Following contralateral limb re-challenge, 88% of E7766 surviving mice retained protection against STS. In a CD8+ T-cells depleted state, 100% of survivors continued to demonstrate immunity against STS re-challenge. However, in a CD4+ T-cell depleted state, 60% of mice developed STS tumors following re-challenge.

Conclusion: Following treatment with the translational STING agonist E7766, STS tumor clearance is primarily dependent on CD8+ T-cells. However, the adaptive immune protection conferred following STING therapy following re-challenge appears to be largely CD4+ T-cell dependent. Further characterization of the immunologic landscapes of relapsed tumors following re-challenge are ongoing. Ultimately, the characterization of the immunologic landscapes of STS tumors, particularly the lymphocyte populations will be critical for further understanding of responsiveness of tumors to therapy and long term protection against disease recurrence.

(P 240) NEW INSIGHTS FROM SPATIOTEMPORALLY DEFINED TUMOR INDUCTIONS IN A NOVEL MOUSE MODEL OF SYNOVIAL SARCOMA

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Objective: Synovial sarcomas (SS) are driven by the SS18::SSX fusion oncogene, generated by the pathognomonic t(X; 18) translocation. In genetically engineered Rosa26-LSL-SS18-SSX2 mice, conditional activation of the fusion oncogene leads to SS tumor formation in anatomic locations dictated by the spatial expression of Cre recombinase. However, limited control over the timing and site of Cre delivery in these models hampers detailed investigations of tumor evolution and therapeutic responses. Thus, we set out to generate a genetically engineered mouse model of SS that allows precise spatial and temporal control over tumor initiation.

Methods: We developed a novel SS mouse model where Cre protein is locally delivered via

intramuscular injection to simultaneously induce SS18::SSX expression, Pten deletion, and β -catenin activation. This strategy generates tumors at the injection site within three weeks with 100% penetrance. The resulting tumors—and cell lines derived from them—exhibit aggressive growth and faithfully recapitulate the histological and molecular features of human SS.

Results: Single-cell RNA sequencing, spatial transcriptomics, and comprehensive immune profiling of these tumors uncovered an unexpected role for B cells in SS pathogenesis. Mechanistic studies indicate that tumor-derived CXCL12 recruits B cells with immunosuppressive properties, which may suppress T cell activity within the tumor microenvironment (TME). While SS is typically 'immunologically cold' with limited lymphocyte infiltration, the recent FDA approval of engineered T cells for SS immunotherapy underscores the importance of understanding the mechanisms that regulate T cell function in this context.

Conclusion: Our novel mouse model provides a robust platform for dissecting SS tumor biology and testing new therapeutic approaches. The model also reveals new insights into the immune microenvironment of SS that can lead to new opportunities for immunotherapeutic intervention.

(P 241) **MACROPHAGE INHIBITION ENHANCES PERIPHERAL CAR T CELL EXPANSION AND TUMOR CONTROL IN A PATIENT-DERIVED HUMANIZED MODEL OF AUTOLOGOUS CAR T CELL EFFICACY IN PEDIATRIC OSTEOSARCOMA (OS)**

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Objective: CAR T cell therapy holds promise for treatment of refractory pediatric solid tumors, but early phase clinical trials have not realized preclinical promise, in part due to the lack of preclinical models that recapitulate T cell – immune interactions impacting CAR T cell efficacy. We report the first humanized mouse model derived from OS patient hematopoietic CD34+ stem cells (Hu-pHSC) and compare performance of autologous CAR T cells in Hu-pHSC versus nonhumanized immunodeficient mice.

Methods: CD34+ HSCs and autologous CD3+ T cells were obtained from patient bone marrow historically discarded during primary tumor resection. CD34+ cells were assessed for colony formation and in vivo engraftment. B7-H3 CAR T cells were generated by lentiviral transduction and assessed for phenotype and in vitro function. NSG-SGM3 mice were humanized by injection of patient HSCs after busulfan ablation and autologous CAR T cell efficacy was assessed against orthotopic LM7 OS tumors. Macrophage inhibition with the small molecule BLZ945 was assessed in combination with B7-H3 CAR T cells in Hu-pHSC and nonhumanized mice.

Results: CD34+ HSCs engrafted into NSG-SGM3 mice with mean peripheral human engraftment of 10% after 8 weeks. Autologous B7-H3 CAR T cells were equally potent in in vitro cytokine production and killing assays as standard healthy peripheral donor-derived pBMCs. In an orthotopic OS model, B7-H3 CAR T cells had minimal antitumor activity in Hu-pHSC compared to nonhumanized mice. CAR T cell performance was rescued in Hu-pHSC mice by combination with the macrophage inhibitor BLZ945, which also enhanced peripheral CAR T cell expansion and cytokine expression including IFN- γ , IL4, IL6, and IL10. On histology, treated tumors in Hu-pHSC mice contained fibrosis, activated histiocytes, and immune

infiltrates consistent with human patient treatment effects, while treated tumors in nonhumanized mice showed only bony remodeling.

Conclusion: Hu-pHSC mice developed from OS patient bone marrow products allow investigation of the effect of the patient's inhibitory immune environment on CAR T cell efficacy. In this model, CAR T cells had limited antitumor activity, as in early phase clinical trials, unless macrophages were depleted. This model improves on standard xenograft models and has the potential to serve as a reliable avatar for modeling immunotherapeutics for OS.

(P 242) IMMUNE PROFILING OF UNDIFFERENTIATED PLEOMORPHIC SARCOMAS REVEALS DISTINCT PROGNOSTIC SUBGROUPS

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Objective: UPS is a clinically aggressive and heterogeneous subtype of soft tissue sarcoma. The tumor microenvironment (TME) plays a critical role in UPS biology and likely influences prognosis and therapeutic response. However, detailed characterization of immune infiltration patterns and their clinical significance in UPS remains limited.

Methods: To investigate the immune landscape of UPS, we analyzed the TME of 74 primary UPS by H+E assessment for the presence of lymphoid aggregates (LA), immunohistochemistry (IHC) and RNA-sequencing (RNA-seq). IHC was performed for CD3, CD8, CD20, CD163, PD1, ICOS, OX40, and IDO1, and used to classify tumors into 3 distinct immune clusters: Immune High, Immune Intermediate, and Immune Low. MCP-counter was used to perform immune deconvolution using RNA-seq data to quantify the relative abundance of immune and stromal cell populations. We then evaluated the association between immune cluster defined by IHC, presence of LA, TME composition inferred by immune deconvolution, and patient survival. Kaplan-Meier survival analysis was used to assess the prognostic significance of the immune clusters.

Results: Distinct immune cell signatures were observed across the three immune clusters. The Immune High group showed greater infiltration of T cells, NK cells, cytotoxic markers, B cells, macrophages, and myeloid dendritic cells while the Immune Intermediate cluster demonstrated moderate levels of diverse immune populations and the Immune Low group exhibited sparse immune cell infiltration. These clusters also showed distinct patterns of LA, with LAs observed more frequently in Immune High tumors. Survival analysis revealed a significant difference in overall survival across immune clusters (log-rank $p = 0.0062$), with patients in the Immune High group exhibiting the most favorable outcomes and those in the Immune Low group having the worst prognosis.

Conclusion: Our findings highlight the prognostic importance of the TME in UPS. Integrated immune profiling using MCP-counter and IHC-based clustering reveals biologically distinct UPS

subgroups associated with LA and clinical outcomes, supporting their potential role in guiding patient stratification and therapeutic strategies.

(P 243) CLINICAL SIGNIFICANCE OF TUMOR-INFILTRATING IMMUNE CELL SUBSETS IN THE RETROPERITONEAL DEDIFFERENTIATED LIPOSARCOMAS AND LEIOMYOSARCOMAS

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Objective: Tumor-infiltrating immune cells play a fundamental role in shaping patient prognosis and therapeutic response across many cancers. A deeper understanding of the immune architecture in retroperitoneal dedifferentiated liposarcomas (DDLPS) and leiomyosarcomas (LMS) is warranted to identify novel predictive biomarkers and immunotherapeutic targets.

Methods: To gain novel insights into the immune landscape of retroperitoneal DDLPS and LMS, we explored the spatial organization, frequency, and proportions of CD8+ T cell (including activated, proliferating, and exhausted phenotypes), CD4+ T cell, and macrophage subsets in primary treatment-naïve retroperitoneal DDLPS (n = 22) and LMS tissues (n = 10) using multiplex immunohistochemistry. Immune cell distribution was assessed in the tumor area and invasive margin. These results were subsequently correlated with clinicopathological characteristics of the patients.

Results: When investigating the whole cohort, CD8+LAG-3+ T cells comprised the highest proportion of all analyzed CD8+ subsets. Their elevated density was associated with improved overall survival (OS). High proportions of CD8+LAG-3+ T cells emerged as an independent prognostic factor for OS. Moreover, proliferating CD8+ subsets demonstrated clinical relevance. High proportions of CD8+Ki-67+LAG-3+ T cells were linked to significantly prolonged metastasis-free survival (MFS), while both the density and proportion of CD8+Ki-67+PD-1+ T cells were independent prognostic factors for progression-free survival (PFS). Interestingly, an enhanced density of regulatory T cells correlated with favorable survival outcomes. The density and proportions of CD4+ and CD8+ subsets did not significantly differ between DDLPS and LMS. Macrophages were the predominant immune cell population within this cohort, and M2-

like macrophages (CD68+CD163+) accounted for 40.7% of the macrophage compartment. A lower density of M2-like macrophages was linked to better PFS and recurrence-free survival.

Conclusion: These findings highlight the clinical relevance of immune infiltration in retroperitoneal DDLPS and LMS. They support the rationale for further exploration of the immune architecture for prognostic biomarkers and development of targeted immunotherapeutic strategies to improve the clinical outcomes of these patients. Funding: AZV NU23J-08-00031, GA UK 94323

(P 244) INTRATUMORAL TIGIT BLOCKADE AUGMENTS ANTI-TUMOR RESPONSES AND BYPASSES HYPERFUNCTIONALITY OF PERIPHERAL TIGIT+ NK CELLS IN MOUSE AND HUMAN MODELS OF BONE AND SOFT TISSUE SARCOMA

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Objective: Although TIGIT has been shown to be a key exhaustion marker in NK cells, recent data have suggested that a subset of TIGIT expressing NK cells can be hyperfunctional. We hypothesized that TIGIT+ peripheral blood NK cells are hyperfunctional, limiting efficacy of systemic TIGIT blockade. We further hypothesized that intra-tumoral administration of TIGIT blockade would overcome limitations of systemic administration.

Methods: Human and murine NK cells were analyzed from human patients and mice with osteosarcoma (OSA) and soft tissue sarcoma (STS) using flow cytometry, immunohistochemistry, live cell imaging, and RNA sequencing. TIGIT blockade was delivered systemically and intratumorally in both orthotopic and flank models of OSA (K7M2) and STS (MCA-205). Clinical and genomic data were evaluated using CARIS codeAI™. CD155 expression on myeloid cells and tumor targets was evaluated as a rheostat of TIGIT hyperfunction/dysfunction, and recombinant CD155 was used to induce dysfunction on TIGIT expressing hyperfunctional NK cells.

Results: TIGIT+ NK cells from the periphery of tumor-bearing mice, STS, and OSA patients were hyperfunctional using degranulation and Incucyte killing assays. In contrast, TIGIT+ NK cells from the sarcoma TME were more dysfunctional than TIGIT- NK cells with upregulation of senescence and chemotaxis gene expression pathways. Intratumoral administration of TIGIT blockade significantly delayed tumor growth and prolonged survival in murine OSA with partial reversal of NK dysfunction in the TME. Clinical and genomic data demonstrated that NK cell infiltration in human STS was significantly more predictive of survival when CD155 expression was low, and exposure to CD155 induced dysfunction in human peripheral TIGIT+ NK cells.

Conclusion: We identified context dependent effects of TIGIT expression on NK cell phenotype and function with peripheral TIGIT+ NK cells showing hyperfunction and intratumoral TIGIT+ NK cells showing dysfunction. Intratumoral delivery of TIGIT blockade prolonged mouse survival, suggesting that this strategy may have impact for bone and soft tissue sarcomas.

(P 245) SUBTYPE SPECIFIC CHARACTERIZATION OF IMMUNE INFILTRATION IN SOFT TISSUE SARCOMAS

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Objective: Intratumoral natural killer (NK) cells have been linked with favorable outcomes in soft tissue sarcoma (STS) patients, but data assessing immune heterogeneity across the over 50 different STS histologic subtypes and associations with clinical outcomes are lacking.

Methods: We evaluated archived tumor tissue from 83 patients with resectable STS from 2007-2022. Immune markers were analyzed by immunohistochemistry, including tumor infiltrating lymphocyte (TIL) score (0-3) and H-scores (0-300) for CD3, CD8, and NKp46. Primary outcome variables were metastasis-free survival (MFS) and overall survival (OS). Multivariate analysis was performed using a Cox proportional hazards model, adjusting for age, sex, histologic type, and tumor size.

Results: Among our cohort, the mean age was 64 years and 57% were male. Mean tumor size was 12.5 cm and 88% were high grade, consistent with a high-risk population. 64% were located on the extremity, 20% retroperitoneal, and 16% trunk. Histologies included undifferentiated pleomorphic sarcoma (UPS) (25%), myxofibrosarcoma (25%), liposarcoma (24%), synovial sarcoma (9%), leiomyosarcoma (7%), and other (10%). 75% of the liposarcomas were dedifferentiated liposarcoma. Immune infiltrates were overall low across histologies with mean TIL score of 1.03 ± 0.83 . Synovial sarcoma had the lowest mean TIL score compared to myxofibrosarcoma, UPS, and dedifferentiated liposarcoma ($P < 0.05$). We observed the greatest expression of both CD3 and NKp46 in UPS (27.5 ± 7.4 and 8.8 ± 5.2 , respectively) as compared to the lowest CD3 in synovial sarcoma (3.3 ± 1.3 , $P < 0.05$) and lowest NKp46 in leiomyosarcoma (0 ± 0 , $P = 0.06$). On univariate analysis, CD3, CD8, and NKp46 expression were all positively associated with improved OS, but on multivariate analysis, only NKp46 expression was independently associated with significantly improved OS ($P = 0.04$) for all histologic subtypes.

Conclusion: Despite variability in extent of immune infiltration, NK cell infiltration is associated with improved survival across STS histologies. These data support intratumoral NK cells as a biomarker for both prognosis and improving immunotherapy approaches in STS.

(P 246) CTLA4 PATHWAY ACTIVATION IN RADIATION-INDUCED ANGIOSARCOMA: A TRANSCRIPTOMIC RATIONALE FOR IMMUNE CHECKPOINT BLOCKADE

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Objective: Radiation-induced breast angiosarcoma (RIBAS) is a rare but aggressive malignancy that arises as a late complication of radiotherapy, with limited effective treatment options. This study aimed to elucidate the molecular distinctions between RIBAS and primary breast angiosarcoma (PBA) and to identify potential therapeutic targets, with a particular focus on immune checkpoint pathways.

Methods: We analyzed gene expression profiles from the GSE49790 dataset, which includes 35 formalin-fixed paraffin-embedded (FFPE) breast angiosarcoma samples, including 10 from patients with PBA and 25 from those with RIBAS. Differential gene expression analysis was performed to identify key regulatory genes. Single-sample gene set enrichment analysis (ssGSEA) was used to assess immune signaling, DNA repair, and oncogenic pathway activity.

Results: CTLA4 was significantly upregulated in RIBAS compared to PBA, indicating heightened immune checkpoint activation. ssGSEA revealed that RIBAS is enriched for T cell and NK cell exhaustion signatures, suggesting a state of immune dysfunction closely associated with elevated CTLA4 expression. In parallel, pathways related to cell cycle progression and DNA damage repair, including PARP-associated and RNA editing/processing nuclease activity, were also upregulated, pointing to increased genomic instability. Together, these findings suggest that RIBAS exhibits a distinct transcriptional landscape characterized by immune exhaustion and active DNA damage response. The concurrent upregulation of CTLA4 and DNA repair pathways implies possible immune-DDR crosstalk, which may contribute to tumor immune evasion and therapeutic resistance, supporting CTLA4 as a rational target for immune checkpoint blockade in this setting.

Conclusion: RIBAS exhibits a distinct transcriptomic profile compared to PBA, with co-enrichment of CTLA4-mediated immunosuppression and DNA repair activity. These findings support CTLA4 as a promising therapeutic target in RIBAS and provide a molecular rationale for future investigation of immune checkpoint blockade in this challenging disease context.

(P 247) SINGLE-CELL RNA SEQUENCING OF AFAMITRESGENE AUTOLEUCEL INDICATES MECHANISMS OF PERSISTENCE AND ANTI-TUMOR ACTIVITY

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Objective: Afamitresgene autoleucel (afami-cel) is an engineered T-cell receptor (TCR) T-cell therapy targeting tumors expressing melanoma-associated antigen (MAGE) A4 and is the first such therapy with advanced FDA approval for a solid tumor. In the Phase 2 SPEARHEAD-1 trial in patients with advanced synovial sarcoma or myxoid (with/without round cell) liposarcoma, greater long-term afami-cel pharmacokinetic exposure was associated with clinical benefit (D'Angelo S, et al. Lancet 2024). We explored gene expression profiles and functional characteristics of afami-cel manufactured product (MP) associated with long-term persistence.

Methods: Afami-cel MP were flow sorted into transduced (t)CD4+ and tCD8+ subpopulations. Single-cell RNA sequencing was performed on afami-cel tCD4+ and tCD8+ MP subpopulations from 22 and 23 patients, respectively, using 10X Genomics single-cell 5' technology. In vitro cytotoxicity assays measured killing of a target HLA-A2/MAGE-A4-expressing tumor cell line over 125 hours co-culture with afami-cel MP subpopulations. qPCR specific to the engineered TCR measured afami-cel persistence in patient peripheral blood, with pharmacokinetic exposure calculated as area under the curve over 0–6 months after infusion.

Results: We saw distinct gene expression profiles associated with greater pharmacokinetic exposure in patients. In tCD8+ MP samples, this was characterized by an effector function and long-lived memory formation expression profile, whereas expression of genes involved in T-cell dysfunction was associated with lower pharmacokinetic exposure. In tCD4+ MP samples, higher exposure was associated with expression of T-cell activation genes and lower exposure was associated with pro-apoptotic, anti-proliferative gene expression. Afami-cel tCD8+ MP samples demonstrated strong cytotoxicity in vitro and sustained cytotoxic activity was associated with greater long-term pharmacokinetic exposure. Loss of initial cytotoxic activity was associated with a higher percentage of cells expressing a T-cell dysfunction-like gene profile. Greater in vitro cytotoxicity of afami-cel tCD4+ T-cells was associated with CD4+ T-cell activation and effector gene expression.

Conclusion: We hypothesize that MP with T-cell subsets poised for sustained effector function and long-lived memory formation are capable of longer post-infusion persistence, sustaining higher afami-cel pharmacokinetic exposure, and will discuss the gene expression programs underlying these different cellular potentials.

(P 248) AN EX VIVO ASSAY TO PREDICT IMMUNOTHERAPY RESPONSE IN SARCOMA

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Objective: Sarcomas are a heterogeneous group of mesenchymal tumors with limited response to current immunotherapies. Predictive tools to assess immune responsiveness are lacking. We developed a functional co-culture assay using our mRNA lipid particle aggregate (LPA) vaccine platform to evaluate immune-mediated tumor killing ex vivo, with potential application as a predictive platform for immunotherapy response.

Methods: Two sarcoma cell lines were studied: M3-9-M and K7M2. K7M2 was engineered to express a representative fusion oncoprotein. The cell lines were cultured into 3D spheroids. C57bl/6 and BALB/c mice were vaccinated with either total tumor or fusion-targeted mRNA-LPA

which were manufactured using our standard protocol. Post-vaccination splenocytes were harvested and co-cultured with tumor spheroids in a hydrogel matrix. Confocal time-lapse microscopy tracked immune-tumor interactions over 72 hours. Interferon-gamma (IFN- γ) levels were measured in supernatants via ELISA.

Results: mRNA vaccination induced robust immune activation, with splenocytes demonstrating directed migration and tumor spheroid infiltration. Time-lapse imaging revealed progressive tumor destruction in co-culture. IFN- γ levels were significantly elevated in the groups where splenocytes were collected from vaccinated mice indicating a strong Th1 immune response. These findings were consistent across biological replicates.

Conclusion: This co-culture assay models immune-tumor interactions in a controlled, quantifiable system and may serve as a functional tool to predict immunotherapy responsiveness in sarcoma. The use of mRNA vaccination provides proof-of-concept; the use of patient tumor samples and immune cells while correlating with clinical findings will further validate the tool.

(P 249) IN VITRO EXPANSION OF TUMOR-INFILTRATING GAMMA-DELTA T-CELLS FROM PATIENTS WITH SOFT TISSUE SARCOMAS

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Objective: The role of $\gamma\delta$ T-cells in anti-tumor immunity remains complex and not fully elucidated. Their MHC-independent target cell recognition distinguishes them from $\alpha\beta$ T-cells, positioning them as promising candidates for novel immunotherapies, including adoptive cell transfer. In this study, we aimed to expand tumor-infiltrating $\gamma\delta$ T-cells from sarcoma samples and conduct in vitro phenotypic and functional analyses.

Methods: Patients with detectable tumor-infiltrating $\gamma\delta$ T-cells were identified from our institutional biobank, which includes samples (e.g. in vitro expanded TILs) from patients who underwent surgery for primary or recurrent soft tissue sarcoma. TILs were expanded from fresh tumor tissue using IL-2-supplemented culture medium. TIL samples exhibiting a substantial proportion of $\gamma\delta$ T-cells (> 10%) were selected for this sub-study. Phenotypic and functional characterization was performed using flow cytometry.

Results: We identified nine samples containing a significant population of $\gamma\delta$ T-cells, originating from patients with undifferentiated pleomorphic sarcoma, leiomyosarcoma, myxoid liposarcoma, and pleomorphic liposarcoma. The median TIL expansion time was 29 days (range: 22-42 days). The proportion of $\gamma\delta$ T-cells within the total TIL product ranged from 10% to 60%, corresponding to an absolute number of 12-68 million cells. Phenotypic analysis

revealed that the majority of $\gamma\delta$ T-cells displayed a CD3+CD4-CD8- or CD3+CD8+CD4- phenotype. Notably, in one sample from a patient with undifferentiated pleomorphic sarcoma, a subset of $\gamma\delta$ T-cells demonstrated in vitro tumor recognition, as evidenced by IFN γ and/or TNF α production upon co-culture with autologous tumor cells.

Conclusion: Our findings demonstrate that some soft tissue sarcomas are infiltrated by tumor-reactive $\gamma\delta$ T-cells capable of in vitro expansion using clinically established methods. This suggests a role for $\gamma\delta$ T-cells in the anti-tumor immune response and highlights the potential relevance of $\gamma\delta$ T-cell-based immunotherapy for specific sarcoma subtypes.

(P 250) **OUTCOME OF INFANTS WITH RHABDOMYOSARCOMA: A REPORT FROM THE INTERNATIONAL SOFT TISSUE SARCOMA CONSORTIUM**

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Objective: Up to 11% of rhabdomyosarcoma (RMS) cases occur in infants ≤ 1 year. Due to its rarity, diverse treatment approaches, and limited sample sizes, published outcomes remain inconsistent. We conducted a pooled analysis of cooperative group trials (1991–2016) using the International Soft Tissue Sarcoma Consortium (INSTRuCT) database to evaluate survival outcomes and identify prognostic factors in infants with RMS.

Methods: Patients ≤ 1 year with newly diagnosed RMS included in the INSTRuCT database were eligible. Event-free survival (EFS) was defined from enrollment to progression/recurrence, second malignancy, or death; overall survival (OS) was defined from enrollment to death from any cause. Cox proportional hazards model was used to assess factors associated with survival.

Results: We included 389 infants treated on 15 trials from COG (n=95), CWS (n=83), MMT (n=74), ICG (n=24), and EpSSG (n=113). Genitourinary bladder/prostate was the common site (23%). Metastatic disease was present in 7% (n=26). In those with localized disease, 68% had Group III disease, 17% had Group II disease, and 8% had Group I disease. Histologically, 64% had embryonal/botryoid RMS, 26% alveolar RMS (ARMS) and 10% had spindle cell RMS. FOXO1 fusion status was known for 148; of these, 78% were fusion-negative, 17% had a PAX3-FOXO1 fusion, and 5% had a PAX7-FOXO1 fusion. The 5-year EFS and OS were 59.9%

(95% CI, 54.3%–65.5%) and 76.1% (95% CI, 71.3%–80.9%), and 15.4% (95% CI, 0.0%–31.4%) and 37.6% (95% CI, 15.6%–59.6%) for those with localized and metastatic disease, respectively. On multivariable analysis, among patients with localized disease, younger age (≤ 3 months), ARMS histology, and Group III disease were associated with inferior EFS, while younger age (≤ 3 months), ARMS histology, T2 tumor, and larger tumor (> 5 cm) were associated with worse OS. In those with metastatic RMS, only younger age (≤ 3 months) was associated with worse EFS and OS on univariable analysis.

Conclusion: In this largest pooled analysis of infants with RMS, survival outcomes remain suboptimal, particularly among those with metastatic disease. Younger age (≤ 3 months) predicts inferior survival among infants with both localized and metastatic disease.

(P 251) SPATIAL MULTI-OMIC ANALYSIS OF RHABDOMYOSARCOMA IDENTIFIES THERAPEUTIC VULNERABILITIES

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Objective: Rhabdomyosarcoma (RMS) has FOXO1 fusion positive (FP) and fusion negative (FN) subtypes showing distinct clinical behavior and treatment responses. The spatial biology and metabolic heterogeneity of RMS remain poorly understood. We aimed to characterize RMS using spatial multi-omics to identify phenotypes and lipid pathways that offer potential as therapeutic targets.

Methods: Patient samples, including metastatic FP RMS and TP53 mutated localized FN RMS, were analyzed using mass spectrometry imaging (MSI), H&E staining, and multiplex immunohistochemistry (mIHC). MALDI MSI was carried out using a Solarix XR 7T FTICR mass spectrometer according to our previously published protocols. SCiLS Lab multi-vendor software, ver. 2023c Pro was used for co-registration of imaging data with corresponding H&E and molecular biology data.

Results: Glycosphingolipids, cardiolipins, phosphatidylinositol, and ceramide-1-phosphates were identified within distinct tumor cells. Cellular accumulation of each lipid class was structure-dependent based on the fatty acid residue composition. All data were correlated to histopathology, mIHC and Ki67 proliferation index. MALDI MSI revealed heterogeneous lipid distributions within FP and FN RMS samples. We identified global lipid changes in proliferating tumor cells regardless of the molecular subtype. We also detected subtype specific alterations, with FP RMS displaying distinct biochemical clusters relative to FN RMS. Of interest, gangliosides contributed to subtype-specific spatial profiles, with localized high-intensity signals observed within tumor cell regions of FN RMS.

Conclusion: Spatial multi-omic analysis of RMS identified heterogeneous lipid landscapes in association with cellular phenotypes. The structure-specific accumulation of these lipids within distinct tumor cell populations provide novel insights into RMS biology and identify potential therapeutic routes for investigation.

(P 252) NUCLEAR AND GENOMIC ORGANIZATION OF CHEMOTHERAPY RESISTANT RHABDOMYOSARCOMA CELLS

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Objective: The pediatric tumor rhabdomyosarcoma has seen relatively modest improvement in survival rates in the past few decades, particularly in the case of metastatic and recurrent disease. Novel understanding of chemoresistance in these tumors could lead to novel approaches to manage such tumors and thereby improve survival. Organization of the genome and the manner in which chromatin is packed in space has been demonstrated to be related to chemoresistance in certain types of adult tumors, but is less understood in pediatric tumors. Our overall goal is to compare multiple aspects of the nuclear and genomic organization of rhabdomyosarcoma cells across a range of degrees of chemoresistance with the goal of finding novel therapeutic targets.

Methods: Publicly available rhabdomyosarcoma cell lines were serially exposed to increasing concentrations of chemotherapeutic agents in their media to generate progressively more chemoresistant cell lines. Quantitative assessment of chromatin packing for individual nuclei was performed using partial wave spectroscopic imaging of live cells. Nuclear size and morphology were assessed using the program Cellprofiler. Nuclear positioning of genomic loci were assessed using fluorescent in situ hybridization and analyzed with Cellprofiler.

Results: To date, our results demonstrate that exposure to even relatively low concentrations of a single chemotherapeutic agent cause significant changes in chromatin packing, as assessed by changes measured by partial wave spectroscopic imaging.

Conclusion: Changes in chromatin packing in response to chemotherapy drug exposure are largely sustained across a range of chemotherapy drug concentrations, suggesting that even small doses of chemotherapeutic agents can cause wide-scale changes in rhabdomyosarcoma chromatin packing, thereby potentially influencing the activity of numerous other genes.

(P 253) ELUCIDATING THE ROLE OF SIRT7 IN EWING SARCOMA

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Objective: SIRT7 is a member of the Sirtuin family, a group of NAD⁺-dependent deacetylases involved in the regulation of various cellular processes. Predominantly localized to the nucleolus, SIRT7 regulates RNA transcription, DNA repair, and chromatin remodeling. SIRT7 deacetylates H3K18 and H3K36, two epigenetic marks associated with tumorigenesis. Ewing Sarcoma (EWS) is a rare, aggressive tumor of the bone or soft tissue that predominantly affects children and young adults. Localized EWS has a 70–80% 5-year survival rate with standard treatment, but metastatic cases carry a poor prognosis, and current therapies often cause significant short- and long-term side effects that impact survivors' quality of life. In a preliminary analysis, we found that high SIRT7 expression in metastatic EWS patients correlates with poor

survival. This work aims to assess the response of EWS cells to SIRT7 depletion and elucidate the mechanisms by which SIRT7 promotes tumor growth in EWS.

Methods: We used short hairpin RNA (shRNA) and a SIRT7 enzymatic inhibitor to deplete or inhibit SIRT7 in Ewing Sarcoma (EWS) cell lines (A673, A4573, TC32). Cell proliferation and colony formation assays were performed to evaluate growth. Transcriptomic changes were assessed via RNA sequencing, while metabolic alterations were analyzed using LC-MS/MS-based metabolomics and Seahorse XF extracellular flux analysis. ATF4 expression was measured at the mRNA and protein levels by qRT-PCR and Western blotting, respectively.

Results: SIRT7 depletion or inhibition impaired the growth of EWS cell lines (A673, A4573, TC32) in vitro, as shown by proliferation and colony formation assays. RNA-seq analysis of SIRT7-depleted or SIRT7-inhibited EWS cells revealed that the most significantly affected pathways were related to metabolism. Consistently, we observed that the loss of SIRT7 altered metabolite levels and reduced both glycolytic rates and mitochondrial respiration in SIRT7-depleted EWS cells. Furthermore, loss of SIRT7 in EWS cells leads to a significant reduction in activating transcription factor 4 (ATF4) in both gene expression and protein levels.

Conclusion: We hypothesize that loss of SIRT7 may be regulating EWS cell survival by modulating ATF4 expression, either through direct regulation at the chromatin level or indirectly by disrupting stress response signaling. This dysregulation may, in turn, alter metabolic homeostasis, ultimately compromising EWS cell viability and leading to cell death.

(P 254) EOSINOPHILIC FASCIITIS (EF) AS A COMPLICATION OF NATURAL KILLER (NK) CELL-BASED IMMUNOTHERAPY IN A YOUNG ADULT WITH RECURRENT METASTATIC EWING SARCOMA

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Objective: EF is a rare inflammatory connective tissue disease characterized by painful edema, erythema, thickening of muscle fascia and surrounding tissues, and sclerosis with limited range of motion [1]. Definitive diagnosis is an ongoing area of study but is supported by key findings on physical exam, imaging, and histopathology [2]. While its etiology remains unknown it is frequently associated with immunomodulation and malignancy

Methods: n/a

Results: A 19 year-old male with metastatic Ewing Sarcoma of the right tibia presented with recurrence to the primary site and right humerus, a year off standard of care therapy per COG AEWS1221 protocol. He underwent four cycles of salvage Irinotecan/Temozolomide but discontinued due to intolerable side effects. He then enrolled in a trial investigating universal donor, TGF-B imprinted NK cell infusions with dual chemotherapy for recurrent sarcoma (NCT05634369). Initial infusions were well-tolerated, however during Cycle 4 he reported painful bilateral leg pitting edema, weight gain and orthopnea refractory to oral diuretics. By Cycle 10, symptoms had progressed with a skin-tightening sensation, limited knee flexion, and foot drop of the right leg, and induration of both legs with linear depressions following venous

tracks ('Groove sign'). He was referred to Dermatology where punch biopsy showed marked dermal fibrosis, patchy lymphocytic infiltrate, sclerotic collagen, and thick/hyalinized fibrous bands in subcutaneous tissue; combined exam and pathology findings all consistent with EF. Oral methylprednisolone was prescribed but declined due to the side effect profile. He continued to have stable disease on treatment but was unfortunately taken off study due to a Grade 3 anaphylactic event during NK cell infusion. Since being off treatment the patient's edema, discoloration and limb function have gradually improved without other interventions.

Conclusion: EF remains an uncommon but known adverse event reported with the use of immunomodulating agents. Most cases were described in patients receiving checkpoint inhibitors, especially PD-1 inhibitors such as nivolumab and pembrolizumab (3,4); to our knowledge, this is the first reported case of EF as a complication of NK cell adoptive immunotherapy for Ewing Sarcoma. With the rising trend of using established and novel immunomodulators in the treatment of various cancers (5), clinicians should remain vigilant in monitoring for complications of these therapies including atypical conditions like EF.

(P 255) AN OPEN-LABEL, TWO-COHORT, PHASE 1A/B STUDY OF WEEKLY IRINOTECAN HYDROCHLORIDE LIPOSOME INJECTION COMBINED WITH VINCRIStINE AND TEMOZOLOMIDE (NALIRI-VT) IN PATIENTS WITH ADVANCED EWING SARCOMA

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Objective: To determine the recommended phase II dose (RP2D), safety, and preliminary efficacy of weekly liposomal irinotecan combined with vincristine and temozolomide (NALIRI-VT) in relapsed/refractory Ewing sarcoma in both children and adults.

Methods: This was an open-label, non-randomized, two-cohort, 2-part phase Ia/b study enrolling patients with relapsed or refractory Ewing sarcoma. Children and adults were enrolled in two cohorts (Cohort A and Cohort B) respectively. A starting dose of 25mg/m² (level 1) NALIRI weekly infusion was initiated in the escalation phase, utilizing a 3+3 design with the following dose levels of 30mg/m², 35mg/m² and 40mg/m² (level 2-4). Vincristine (1.5 mg/m² Dmax 2mg D1 i.v.) and temozolomide (100 mg/m² D1-5 p.o.) were given every 21 days. Primary objectives were safety and tolerability.

Results: 24 children and 24 adults were enrolled from 2024.04.15 to 2024.12.30. 16 children and 19 adults were enrolled in phase 1a part. 8 more children and 5 more adults were enrolled in phase 1b part. Finally, 11 children and 11 adults were treated at RP2D dose. No dose-limiting toxicity (DLT) was found at level 1 and 2 in both cohorts. 0/3 and 1F/6 DLT was found at level 3 in each cohort respectively, while 2/6 and 2/6 DLTs were found at level 4. RP2D established at level 3 of 35 mg/m² NALIRI. For patients at RP2D dose, confirmed objective response (ORR) was 54.5% in both cohorts, while clinical benefit rate (CBR) was 81.8% in cohort A and 63.6% in cohort B. The median PFS was 3.6 (95% CI, 2.7-NA) months in total and OS was not matured. Duration of response (DOR) was 4.3 months. Grade 3/4 toxicities were found in hematologic toxicity (most common), anorexia, fatigue, nausea or vomiting, pain and diarrhea.

Conclusion: NALIRI-VT demonstrates manageable toxicity and promising activity in advanced Ewing sarcoma, warranting further investigation in phase II trials.

(P 256) THE SEAN KARL COHORT: A NATIONAL COLLABORATIVE SINGLE-CELL RNASEQ STUDY OF PAIRED PATIENT EWING SARCOMA SPECIMENS

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Objective: Ewing sarcoma (EwS) is a fusion oncoprotein-driven primary bone cancer that demonstrates vast intra- and inter-tumoral heterogeneity. Tumor cell subpopulations, tumor progression, and therapeutic vulnerabilities of cell subpopulations are poorly understood. Paired patient samples (primary and metastatic disease or relapse) are rare at any single institution and collaborative efforts are needed to address these pressing biologic questions. A national collaborative effort (the Sean Karl Cohort) has been established to conduct single-cell RNAseq analyses of retrospective paired tumor samples from patients with EwS and serial samples due to metastasis or relapse. Four analytic teams will utilize these data to understand therapeutic vulnerabilities of EwS cell subsets and discern immunobiologic dysfunction.

Methods: A national collaborative effort was established to acquire retrospective, paired patient EwS tumor samples. Individual cells were isolated from FFPE scrolls or slides and prepared for single-cell RNAseq using the GEM-X Flex Gene Expression reagents (10x Genomics). Alex's Lemonade Stand Foundation (ALSF) Data Lab established a common data processing and cell annotation workflow to create a harmonized dataset for downstream analysis.

Results: We have demonstrated the feasibility of generating quality, single-cell RNAseq data from retrospective FFPE tumor material at scale across institutions. We have generated data from 73 specimens, yielding more than 340,000 cells sequenced to date. Analytic teams are analyzing the processed data to assess tumor cell subpopulations, therapeutic vulnerabilities, immune cell subsets, and the tumor microenvironment as a whole. Processing and sequencing of additional samples is ongoing at the time of abstract submission.

Conclusion: To make progress toward improving outcomes for patients with aggressive EwS, a detailed understanding of heterogenous tumor cell subpopulations and therapeutic vulnerabilities is needed. We have established a multi-institution, collaborative, and multi-analytic approach to facilitate discovery as a first step towards improving outcomes for aggressive EwS.

(P 257) TARGETING LEUCINE-RICH REPEAT-CONTAINING PROTEIN 15 (LRRC15): SOT106 ANTIBODY-DRUG CONJUGATE FOR SOFT TISSUE SARCOMA AND OSTEOSARCOMA TREATMENT

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Objective: Soft tissue sarcomas (STS) and osteosarcoma (OS) are difficult to treat and associated with poor prognoses. Current therapies are limited to chemotherapy and surgery, with few effective targeted treatments. LRRC15, a protein overexpressed in many sarcomas, has emerged as a promising therapeutic target.

Methods: SOT106, a novel LRRC15-targeted antibody-drug conjugate (ADC) conjugated with monomethyl auristatin E (MMAE) via a beta-glucuronidase cleavable linker, was developed for targeted cytotoxic payload release. In vitro assays evaluated binding, internalization, and cytotoxicity. In vivo efficacy was assessed using multiple mouse and patient-derived xenograft (PDX) sarcoma models. Pharmacokinetics and toxicity profiles were examined in cynomolgus monkeys. A diagnostic antibody was also developed for patient selection in upcoming clinical trials.

Results: SOT106 showed potent, antigen-specific cytotoxicity in vitro with nanomolar activity and a robust bystander effect. In vivo, it achieved dose-dependent tumor regression, including complete responses at 1 mg/kg. It outperformed current benchmarks in both soft tissue sarcoma and osteosarcoma PDX models, even in tumors with low-to-medium LRRC15 expression and in orthotopic models of osteosarcoma. In non-human primates, SOT106 showed favorable pharmacokinetics (half-life of 4.5–6 days), no premature payload release, and a high therapeutic index. Dose-limiting toxicities aligned with known MMAE effects.

Conclusion: SOT106 is a highly effective and well-tolerated LRRC15-targeted ADC with significant promise for treating sarcomas and potentially other LRRC15-positive malignancies. Its preclinical profile supports further clinical development.

(P 258) INVESTIGATING THE ROLE OF ALVEOLAR PNEUMOCYTES IN THE LUNG MICROENVIRONMENT OF OSTEOSARCOMA METASTASES

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Objective: Pulmonary metastasis is the leading cause of mortality in human and canine osteosarcoma (OS) patients. However, the contribution of lung-resident epithelial cells—particularly surfactant protein C (SPC) expressing type II alveolar pneumocytes (TIIPs)—to metastatic progression remains undefined. This study investigates the transcriptional as well as spatial changes in pneumocytes in OS lung metastases and explores their interactions with tumor cells across human, canine, and murine models.

Methods: Firstly, spatial transcriptomics was used to determine alveolar TIIPs' abundance and location in the tumor microenvironment of human lung tissue of varying OS histological subtypes (n=7). Further, immunohistochemistry staining for SPC+ cells was carried out in both canine (n=14) and murine (n=18; orthotopic injection of K7M2 murine OS cell line) models of OS lung metastases. HALO quantitative image analysis was used to quantify SPC+ cells, and a paired t-test was performed for statistical analysis. To assess direct OS cell–pneumocyte crosstalk, primary in TIIPs alone compared to those co-cultured with OS cells.

Results: Spatial transcriptomics of human specimens showed an accumulation of TIIPs in the region immediately adjacent to the tumor. These findings were validated through observation of SPC+ staining of TIIPs surrounding OS metastases in murine and canine lung tissue. Quantification of SPC+ cells showed a significant increase of TIIPs located around the tumor margin versus the non-tumor associated lung in both canine and murine tissue. RNA sequencing revealed an increase in expression of MYC targets involved in cell proliferation and a decrease in inflammatory response gene signatures in TIIPs co-cultured with OS cells.

Conclusion: This multi-species investigation reveals that pneumocytes play an active role in the lung metastatic niche of OS. These findings highlight a previously under-recognized epithelial component of the metastatic microenvironment and identify new approaches for targeting host–tumor interactions to limit metastatic progression of OS in both human and canine patients.

(P 259) PRECLINICAL MODELING OF CHEMOTHERAPY RELEASE IDENTIFIES MITOCHONDRIAL ADAPTATIONS IN DOXORUBICIN TREATED OSTEOSARCOMA

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Objective: Osteosarcoma (OS), the most common bone tumor in children, is often associated with poor outcomes due to chemotherapy resistance. Studies of therapy-resistant OS have focused on mechanisms of resistance but have largely neglected the temporal dynamics of chemotherapy delivery and release that occur in real-world settings. To address this, we have developed models of chemotherapy-released OS to determine how cellular adaptations to the stress of chemotherapy may enhance fitness after chemotherapy exposure. Our preliminary data identified alterations in mitochondrial Complex I (CI) activity and transcriptional enrichment in mitochondrial genes supporting CI after long-term doxorubicin (DOX) exposure in OS cell lines. The objective of this study is to determine how mitochondrial function in OS is impacted after short-term DOX exposure with an overall goal to identify and target mechanisms of mitochondrial remodeling in chemotherapy-resistant OS.

Methods: DOX was administered to canine OS patient-derived organoids (PDOs) for 48 hours and then removed from the culture to begin DOX release. DOX-naïve and -released PDOs were rechallenged with DOX to assess phenotypic resistance and growth. Respiratory flux

assays and RNA sequencing were performed to explore adaptations in respiratory capacity and expression of mitochondrially-supporting genes.

Results: Canine OS PDOs demonstrate heterogeneity in cell viability in response to DOX and rate of growth, reflecting a biologically diverse cohort. After DOX-release, PDOs demonstrate increased DOX-resistance (Release/Naïve DOX IC50 fold change 1.5-72.8). Relative to DOX-naïve PDOs, DOX-treated PDOs demonstrate transcriptional enrichment in numerous mitochondrial and CI pathways and preserve or increase maximal respiratory capacity.

Conclusion: OS PDOs demonstrate enhancement in mitochondrial function and gene expression following DOX-exposure. Ongoing work aims to further characterize the mitochondrial stress response in OS after DOX treatment and release to determine how mitochondrial adaptations contribute to DOX-resistance and how to target mitochondrial remodeling during DOX-release.

(P 260) MECHANISM AND EFFICACY OF ANTHRACYCLINE MEDIATED EPIGENETIC DISRUPTION IN BONE SARCOMAS.

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Objective: Doxorubicin (Doxo) is a cornerstone therapy for osteosarcoma (OS) and Ewing sarcoma (EwS), but its use is limited by severe off-target toxicities. In addition to Topo II-mediated genotoxicity, Doxo disrupts chromatin through a Topo II-independent mechanism. Chemical modification of Doxo enables separation of chromatin-disrupting effects from DNA damage. Here, we investigate dimethyl-doxorubicin (DMD), a novel anthracycline analog that retains anti-tumor potency with reduced toxicity. We assess its preclinical efficacy, safety, and elucidate its epigenetic consequences in bone sarcoma models.

Methods: Doxo and DMD efficacy was assessed in EwS and OS cell lines, PDX models, and immunocompromised in vivo xenografts. Doxo-pretreated C57BL/6 mice were used to mimic DMD safety in the relapsed setting, with survival and toxicity monitored for 12 weeks. CUT&RUN assessed effects on targeted histone marks (H3K27ac, H3K4me3, H3K27me3, H3K4me1), transcription factors (EWS::FLI1, MYC), and RNA pol II. Multiplexed Assay for the Rational Modulation Of Transcription factors (MARMOT), a novel mass spectrometry-based assay, was used to comprehensively profile protein-chromatin interactions across the genome.

Results: DMD induced apoptosis comparable to Doxo in established and PDX-derived OS and EwS cell lines at nanomolar concentrations in vitro, without evidence of DNA damage. In vivo, DMD suppressed tumor growth equivalently to Doxo in an EwS xenograft model; OS PDX studies are ongoing. C57BL/6 mice with prior Doxo exposure showed improved tolerability to subsequent DMD treatment compared to repeated Doxo administration. CUT&RUN profiling revealed that both agents potently disrupted chromatin binding of H3K27ac, H3K4me3 key, EWS::FLI1, MYC, and RNA pol II, without altering total protein levels. Bulk RNA-seq studies are ongoing to assess downstream transcriptional consequence. Using the MARMOT platform we

found that anthracyclines globally perturb protein–chromatin interactions. Notably, a subset of ribosomal proteins was enriched following treatment, suggesting that co-targeting ribosome biogenesis may potentiate DMD efficacy.

Conclusion: Our studies show that DMD is a safe and potent anthracycline for bone sarcomas, inducing tumor cell death without significant DNA damage. It broadly disrupts protein–chromatin interactions and reveals ribosome biogenesis as a potential co-targetable vulnerability. These findings support further development of DMD as a therapeutic backbone for bone sarcomas.

(P 261) SUSTAINED RESPONSE WITH RIVOCERANIB AND DENOSUMAB IN RELAPSED OSTEOSARCOMA

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Objective: Osteosarcoma is a malignancy originating in the mesenchymal cells within the bones. Relapsed osteosarcoma typically has an abysmal prognosis with less than 20% overall survival at 5 years. Targeted therapies have made significant advancements in overall survival for oncology patients in the last two decades, but there have unfortunately been few advancements in treatment of relapsed osteosarcoma. Angiogenesis is an important means for tumor growth in osteosarcoma, and VEGF-2 is a main receptor in the angiogenesis pathway. VEGF overactivation is a poor prognostic indicator in relapsed osteosarcoma with lung metastasis. Rivoceranib is a medication which targets the vascular endothelial growth factor receptor 2 (VEGF-2). Rivocernib's mechanism of action would indicate it could be a possible targeted treatment option for relapsed osteosarcoma patients.

Methods: Our patient presented in 2015 with osteosarcoma of the left distal femur. She underwent conventional chemotherapy and resection at her original diagnosis. She subsequently relapsed a total of four times, and during this time she underwent five resections and systemic therapy. The patient decided she did not want to undergo conventional chemotherapy after her fourth relapse, and expanded access was obtained for Rivoceranib. The patient was started on Rivoceranib 700mg PO daily with monthly denosumab 120mg SQ injections. On repeat imaging her lesions have continued to show either complete response or partial response with stability in her lung lesions with gradually decreasing SUV.

Results: Imaging shows sustained partial response with Rivoceranib and denosumab therapy for over 1 year since the patient's fourth relapse. She has mucocutaneous side effects and hypothyroidism secondary to her Rivoceranib, but these have been managed by topical interventions for her rashes and levothyroxine replacement. This therapy was otherwise well tolerated.

Conclusion: Rivoceranib and denosumab combination therapy is a promising treatment option for relapsed osteosarcoma. Further research is needed in the use of Rivoceranib in patients with relapsed osteosarcoma.

(P 262) EVALUATING FRONT-LINE THERAPY ACCORDANCE WITH CURRENT SYNOVIAL SARCOMA GUIDELINES

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Objective: The standard treatment of synovial sarcoma (SS) consists of surgery with or without chemoradiotherapy and is stratified by tumor features and extent of surgery. Current pediatric practices are based on ARST0332 which utilized chemoradiotherapy for high grade localized disease >5 cm, while NCCN guidelines suggest only consideration of chemoradiotherapy for tumors >5 cm (T2 and higher) in adults. Given this variation, it is important to understand how this has been translated into practice. In this study, we assessed front-line therapy in the national SS Registry & Biospecimen Repository (SSRBR).

Methods: The SSRBR was established at the Children's Hospital of Philadelphia. Informed consent was completed and medical records were obtained from treating institutions with updates every 6 months. Treatment was evaluated across pediatric (< 18 years) and adult (≥18 years) populations. This analysis includes patients enrolled in the SSRBR in the first 14 months (cut-off July 31, 2024).

Results: Fifty-two patients were enrolled and 2 were excluded due to incorrect initial diagnosis. Of the 50 evaluable patients, 43 (86%) had localized disease and 7 (14%) had metastatic disease. Of the 43 patients with localized disease, all underwent surgical resection, 32 (71%) received chemotherapy, and 21 (47%) had radiotherapy. All patients with metastatic disease received chemotherapy, four (57%) underwent surgical resection and two (29%) received radiotherapy. Notably, there was a difference in chemoradiotherapy utilization for patients with tumors >5 cm across the pediatric and adult populations (Table 1).

Conclusion: Within the SSRBR, patients received care consistent with treatment guidelines. When stratified by age, there was an observed difference in the use of chemoradiotherapy for localized disease >5 cm, which may reflect the variation in pediatric and adult practice. Analysis of factors contributing to the difference in chemoradiotherapy use is ongoing.

Table 1. Front-Line Therapy Received in Patients with Localized Disease*

	Pediatric Patients, Tumor ≤5 cm	Pediatric Patients, Tumor >5 cm	Adult Patients, Tumor ≤5 cm	Adult Patients, Tumor >5 cm
Chemotherapy:				
Yes	3	8	1	19
No	3	0	2	5
Radiation:				
Yes	4	6	2	9
No	2	2	1	15
Surgery:				
Yes	6	8	3	24
No	0	0	0	0
Margin Status:				
R0	1	3	1	17
R1	3	3	1	3
R2	1	2	1	2
Unknown	1	0	0	2
*2 patients with unknown tumor size				

(P 263) DESCRIBING THE CHARACTERISTICS AND TREATMENT OF SYNOVIAL SARCOMA IN THE RECURRENT SETTING

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Objective: As synovial sarcoma (SS) is a rare disease, national and international efforts are crucial to expand understanding of the disease course and establish treatment options in different disease settings. This is particularly important for patients with recurrent/relapsed SS, for whom few effective therapies exist. Herein, we describe the characteristics of patients in the SS Registry & Biospecimen Repository (SSRBR) who experienced disease relapse and evaluate the treatments employed in the relapsed setting.

Methods: The SSRBR was established at the Children's Hospital of Philadelphia, with informed consent completed in person or remotely. Patients completed an intake survey at enrollment, and medical records were obtained from all treating institutions with updates requested every 6 months. Kaplan Meier method was utilized to evaluate post-relapse event-free survival. Data cutoff for this analysis was July 31, 2024.

Results: In the first 14 months, 52 patients were enrolled and two patients were excluded from analysis for incorrect initial diagnosis. Twenty-seven patients experienced recurrence with the majority (n=21, 78%) experiencing metastatic relapse. For treatment of first metastatic relapse, 14 (67%) of patients received chemotherapy, eight patients (38%) underwent surgery, and three patients (16%) received palliative radiotherapy. Patients experienced a median of three disease recurrences (range 1-10). Looking cumulatively at the treatment of all relapses, the most common systemic therapies were pazopanib (n=17), clinical trial regimens (n=15), and ifosfamide (n=7). Notably, of those receiving pazopanib, 23% (n=4) discontinued for reported

toxicity. Progression-free survival (PFS) was assessed for systemic therapies administered in the recurrent disease setting, with median PFS of 322 days for ifosfamide and 310 days for pazopanib.

Conclusion: The SSRBR provides the opportunity to characterize the clinical course of SS disease recurrence and describe the treatment options chosen by physicians and patients in the relapsed setting. Ongoing analysis as the registry population expands will allow for further assessments of time to recurrence in the relapsed setting.

(P 264) RARE CASE OF INFLAMMATORY MYOFIBROBLASTIC TUMOR (IMT) IN NEWBORN

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Objective: IMT is a rare mesenchymal tumor. Approximately half of cases harbor a fusion involving the anaplastic lymphoma kinase (ALK) gene. ALK is a transmembrane tyrosine kinase receptor vital for neuronal cell growth, division, and maturation. Activation of the ALK protein kinase domain results in overexpression, uncontrolled cell growth, constitutive dimerization, and tumorigenesis. Standard treatment for IMT is surgical resection with chemotherapy or targeted therapy for unresectable disease. We present a case of a newborn with IMT who demonstrated a marked clinical response to ALK inhibitor therapy highlighting personalized oncologic treatment in very young pediatric patients to achieve favorable outcomes with minimal adverse effects.

Methods: Right neck mass was diagnosed prenatally in a 36-week female infant. Imaging studies (CT neck, MR head/neck) showed a 7.1 x 6.5 x 5.8cm mass of the right neck with erosion/remodeling of adjacent bony structures. Biopsy demonstrated proliferation of spindle to stellate cells with mixed inflammatory infiltrate. Immunohistochemistry showed positivity for SMA, patchy positivity for ALK1, CAM5.2 and desmin, and was negative for myogenin, myoD1, S100, pancytokeratin, CD34, and MUC4. Metastatic work up was negative. Somatic disease germline comparator (SDGC) exome sequencing, RNA-sequencing, and RT-PCR demonstrated a LRRFIP1::ALK fusion.

Results: Given the inability to surgically resect the mass without substantial comorbidities, treatment was started with vinblastine/methotrexate. Lorlatinib was added after identification of the ALK fusion. Chemotherapy was discontinued after a total of six weeks and lorlatinib monotherapy continued for seven months. No major side effects were noted. Substantial reduction in tumor size allowing surgical removal. Resected tissue showed treatment-related

changes with no residual proliferative changes or ALK expression.

Conclusion: We present the case of an infant with a prenatally diagnosed, unresectable neck mass, confirmed IMT with LRRFIP1::ALK fusion. Only a limited number of IMT cases diagnosed in the prenatal period have been described in the literature. This case is further characterized by the infant's complete response to treatment, highlighting the feasibility and effectiveness of personalized, targeted therapy in very young patients.

(P 265) MULTI-SITE SINGLE CELL TRANSCRIPTOMICS REVEAL DISTINCT IMMUNE INFILTRATIVE PATTERNS IN DESMOPLASTIC SMALL ROUND CELL TUMOR

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Objective: Desmoplastic small round cell tumor (DSRCT) is a rare soft-tissue sarcoma, most often affecting adolescent and young adult males, with poor overall survival. DSRCT cells exist within nests of stromal cells, with varying degrees of immune infiltration. The interplay of these cell types in the tumor microenvironment (TME) has not been thoroughly interrogated. To this end, we performed multi-site single cell RNA sequencing on tumor samples from patients with DSRCT to better define the TME within and among patients.

Methods: Tumor samples from 2-3 sites from 4 patients with DSRCT, who had prior cytoreductive chemotherapy, were collected from the operating room. Samples were processed and submitted for 10X Genomics single cell RNA sequencing. Analysis of the resultant data was performed, with DSRCT cells identified in a similar manner to Henon et. al., 2024.

Results: CD45+ immune cells had varying TME contributions, with 15-41% of total cells in patient 1, 34-80% in patient 2, and wider ranges in patients 3 and 4. Within the immune compartment, samples were either lymphocyte or neutrophil predominant; patient 1 had on average 70% lymphocytes with minimal neutrophils, with the inverse pattern in patients 2 and 4. This correlated with patients' peripheral neutrophil-to-lymphocyte (NTL) ratio: 2.5 in patient 1, but 44 and 17 in patients 2 and 4, respectively. Interestingly, patient 3 had a neutrophil predominant pattern in sample 1 and a lymphocyte-predominant pattern in sample 2, with an NTL ratio of only 1.7. Finally, NK cells did not contribute significantly to any sample, despite low class I HLA transcripts in all DSRCT cells.

Conclusion: DSRCT remains a poorly understood and difficult to treat cancer. To better understand the DSRCT TME, we employed single cell transcriptomics on multi-site patient samples. We found that the intra-patient abundance of immune infiltrate remained consistent, with wide inter-patient variability. Samples had either lymphocyte or neutrophil predominance, correlating with peripheral blood NTL ratio, as seen in other cancers, though both patterns may be found within an individual patient. We also found no significant NK cell infiltration despite the low level of class I HLA transcript in all DSRCT cells, suggesting alternate mechanisms to allow surface expression. Analyses of the DSRCT transcriptome are underway to understand the mechanisms leading to these infiltration patterns, and to understand the functional status of infiltrating lymphocytes and neutrophils.

(P 266) TARGETING THE DNA DAMAGE RESPONSE TO ADVANCE PRECISION THERAPIES IN PAEDIATRIC SARCOMA

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Objective: Outcomes for children with sarcoma remain poor, and standard treatments are associated with significant toxicity. Targeted therapies are not routinely available. Early evidence suggests that inhibitors of the DNA damage response (DDR) may offer therapeutic benefit in sarcoma. To identify which patients are most likely to benefit from DDR inhibitors by characterising the DDR landscape in paediatric sarcoma and evaluating its association with drug sensitivity.

Methods: Comprehensive genomic profiling of DDR aberrations was performed in 130 paediatric sarcoma patients using whole-genome sequencing. Based on these data, seven DDR-targeting agents were selected for in vitro testing, both as monotherapies and in combinations. Drug efficacy was assessed via cell viability assays. Cell cycle effects were evaluated by flow cytometry, molecular changes in DDR mediators by western blotting, and mitotic entry via immunofluorescence microscopy. Gene set enrichment analysis (GSEA) was used to explore the link between genomic profiles and drug responses. A genome-wide CRISPR-Cas9 screen is underway to uncover determinants of drug sensitivity.

Results: Frequent DDR gene alterations were observed across the sarcoma cohort. Inhibition of ATR, CHK1, or WEE1 led to potent growth inhibition in multiple paediatric sarcoma cell lines, with particularly strong responses in Ewing sarcoma (ES) and fusion-positive rhabdomyosarcoma (FP-RMS). Dual inhibition of the ATR pathway resulted in synergistic responses at doses well below clinically achievable concentrations. Mechanistically, ATR, CHK1, and WEE1 inhibitors induced S-phase and G2/M arrest, increased DNA damage, and triggered apoptosis. Immunofluorescence microscopy revealed elevated premature mitotic entry, consistent with checkpoint failure as a mechanism of cell death. GSEA revealed G2/M checkpoint upregulation in sensitive models, particularly in fusion-driven sarcomas, implicating fusion proteins in checkpoint control. Nonetheless, resistance was observed in a subset of ES models, suggesting additional pathways or biomarkers modulate response.

Conclusion: DDR pathway alterations are common in paediatric sarcomas. Inhibiting ATR, CHK1, or WEE1 is a promising therapeutic approach, particularly in fusion-driven subtypes such as ES and FP-RMS. These findings support further exploration of DDR-targeted therapy and highlight the need for predictive biomarkers to guide patient selection.

(P 267) THE RAF/MEK INHIBITOR VS-6766 SHOWS EFFICACY IN RAS-MUTANT PEDIATRIC PRECLINICAL XENOGRAFT MODELS- A REPORT FROM THE PEDIATRIC PRECLINICAL IN VIVO TESTING CONSORTIUM

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Objective: VS-6766 is an allosteric MEK inhibitor that dually inhibits MEK and RAF. VS-6766 has shown benefit in tumors with mutant RAS and clinical trials are underway in adult cancers; however, activity in pediatric cancer has not been defined. Pediatric histologies such as acute leukemias (ALL) and rhabdomyosarcoma (RMS) have an appreciable frequency of RAS mutations. To evaluate the role of RAF/MEK inhibition in pediatric cancers, VS-6766 was tested against pediatric solid tumor and leukemia patient-derived xenografts (PDXs).

Methods: VS-6766 was provided by Verastem Oncology and given orally at 0.3 mg/kg daily. Tolerability testing was performed in 3 non-tumor bearing immunodeficient mice at 100%, 71%, 33%, and 24% of the recommended dose. To test efficacy, PDXs were dosed with VS-6766 and compared to control (see Table). To evaluate drug combinations, RMS PDXs were treated with VS-6766 in doublet with 14 other drugs targeting additional areas of the MAPK/ERK pathway along with untreated control, VS-6766 alone, and vincristine + irinotecan (standard of care) for a total of 17 treatment groups. Models were labeled with luciferase for weekly bioluminescent monitoring of tumor burden along with calipers.

Results: VS-6766 was well tolerated in mice. In ALL, 5/27 evaluable models achieved objective responses with 4/5 responders harboring a RAS mutation (2 KRAS, 2 NRAS). In MPNST, 3/4 models had stable disease with 2 of those harboring NF-1 mutations. In RMS, survival advantage was noted in 4/5 models tested for 4 weeks, and 7/9 models tested for 16 weeks. All 11 RMS responders had RAS mutations (4 HRAS, 2 KRAS, 5 NRAS). Of the 3 non-responder PDXs, 1 had HRAS and 2 were non-mutated. In combination testing, survival advantage was most notable when VS-6766 was combined with VS-4718 (FAK), everolimus (mTOR), copanlisib (PI3K δ/α), capivasertib (AKT), BBP-398 (SHP2) and LY3023414 (PI3K) compared to VS-6766 alone.

Conclusion: VS-6766 exhibited antitumor activity across several pediatric cancers. As single agent, there was activity in the majority of solid tumor models tested with prolongation of time on study and stabilization of disease. Solid tumor models harboring RAS mutations appear more likely to respond, although limited non-mutant models were tested. The response of VS-6766 in RMS was further enhanced when used in combination, and additional studies are needed across a broader panel of pediatric PDXs to prioritize the best combination for clinical development.

Preclinical Testing Details. SMT, single mouse trial (1 mouse/treatment group); Con,

conventional (6 mice/group); Twin Mouse (2 mice/group)

	Disease	Treatment Length (wks)	Type of Study	Total # Models	Non-Mutant	HRAS	KRAS	NRAS	NF-1
single agent testing	ALL	4	SMT	n=30	7		14	9	
	MPNST	4	Con	n=4	1				3
	RMS	4	Con	n=5	1	1	1	2	
	RMS	16	Con	n=9	1	4	1	3	
combination testing	RMS	12	Twin Mouse	n=2		1		1	

(P 268) **QUALITY OF LIFE OUTCOMES IN PEDIATRIC PATIENTS UNDERGOING SURGICAL INTERVENTION FOR LOWER EXTREMITY BONE SARCOMAS**

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Objective: Multiple surgical options are available for pediatric patients with lower extremity bone sarcomas, though the influence of these interventions on quality of life (QoL) outcomes is not well described. This study examines differences in QoL based on surgical intervention over time.

Methods: This is a prospective cohort study performed at a single institution. SF-36 health surveys were administered pre-operatively and throughout long-term follow up. The relationships between surgical intervention (rotationplasty, amputation, intercalary allograft, endoprosthetic reconstruction), reoperation, and QoL scores were assessed using mixed linear models and ANOVA tests.

Results: 84 patients met inclusion criteria. SF-36 General Health scores of patients with endoprosthetic reconstruction had a yearly average decrease of 1.18 (PEMT=0.036, 95% CL = [-2.27, -0.079]) controlling for the main effects of number of reoperations (PANOVA=0.26). SF-36 Pain scores for patients with intercalary allograft reconstruction had a linear relationship with time showing a decrease of 3.709 points per year (PEMT=0.0008, 95% CL = [-5.86, -1.56]), while controlling for the main effects of the number of reoperations (PANOVA=0.014). When all patient reported outcome time points are averaged, there is no significant difference between tumor location or surgical intervention after pairwise analysis (p>0.05).

Conclusion: Differences in the long-term patient reported QoL scores are multifactorial but

seem to be related to the need for revision surgery. These findings may help counsel patients regarding expected outcomes. Limitations include survey compliance, loss to follow-up, and sample size.

(P 269) **INCIDENCE OF MALIGNANCY IN BIOPSIED PEDIATRIC SOFT TISSUE MASSES**

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Objective: Pediatric soft tissue masses are common and most often benign. However, comprehensive studies on these tumors, including the incidence of sarcoma or neoplasms of uncertain behavior (NUB, as defined by the WHO), are lacking. Predictors of soft tissue sarcoma commonly cited in the adult literature include short duration of symptoms, size greater than 5 cm, and depth. It is unknown whether these descriptors accurately predict non-benign masses in pediatric patients.

Methods: CPT codes were used to identify all soft tissue masses of the trunk or extremities that were biopsied or resected in patients < 18-year-of-age between 2010-2024 throughout a state-wide health system. Patients with retroperitoneal, deep pelvic or intrathoracic masses were excluded. Symptom duration, tumor characteristics, patient demographics, and treatment were retrospectively collected from medical record

Results: : 990 soft tissue masses of the trunk and extremity undergoing resection or biopsy were identified. The overall incidence of soft tissue sarcoma was 6% (n=57). 4% (n=42) of soft tissue masses were neoplasms of uncertain behavior. < 1% (n=5) of soft tissue masses were other malignancies. The incidence of sarcoma, neoplasm of uncertain behavior, and benign masses varied by anatomical site ($p < 0.001$). Soft tissue sarcomas were significantly larger than neoplasm of uncertain behavior and benign lesions ($p=0.019$ and $p < 0.0001$ respectively, Fig 2).

Conclusion: Overall, 11% of pediatric soft tissue masses biopsied or resected in a 15-year period at our institution were non-benign lesions. The incidence of soft tissue sarcoma varies by anatomical site and has a higher incidence in the lower extremity.

Incidence of benign and non-benign pediatric soft tissue masses by location

	Benign	Non-benign
Arm/Forearm	84% (n=102)	16% (n=20, 8% sarcoma & 8% NUB)
Trunk	88% (n=292)	12% (n=36, 6% sarcoma & 5% NUB)
Wrist/Hand	97% (n=321)	3% (n=9, 8% sarcoma & 2% NUB)
Thigh/Leg	83% (n=139)	17% (n=29, 12% sarcoma & 4% NUB)
Ankle/Foot	89% (n=87)	11% (n=10, 5% sarcoma & 5% NUB)
NUB=Neoplasm of uncertain behavior		

(P 270) FEASIBILITY OF FERTILITY PRESERVATION IN CHILDREN, ADOLESCENTS AND YOUNG ADULTS WITH SARCOMAS - A PROSPECTIVE COHORT STUDY WITH LONG-TERM FOLLOW-UP

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Objective: To report the long-term experience with fertility preservation (FP) in patients with sarcomas and their reproductive outcomes.

Methods: The program for FP of Karolinska University Hospital, Stockholm, Sweden, is tax-funded, and it has included adolescents and young adults (AYAs) with cancers. Hereby we report on the patient diagnosed with sarcomas between 1999 to 2024, their clinical characteristics, treatment received, FP methods chosen, outcome of fertility preservation, and reproductive outcome in females.

Results: During the study period, 76 males and 75 females, 63% with bone sarcomas and 27% with soft tissue sarcomas, received counseling for FP. The mean age was 19 years at the time of cancer diagnosis and one third of the patients were pre-pubertal. In total, 89% of males underwent FP by semen banking (N=66) or testis biopsies (N=2), whereas 73% of females underwent oocyte/embryo (N=20) or ovarian tissue cryopreservation (N=35). Fourteen females that did not undergo FP at time of diagnosis and showed signs of maintained ovarian function at teenage, underwent FP and cryopreserved oocytes post-cancer treatment. Most survivors in the cohort are still young. Six adult women have attempted pregnancy and five have delivered children, one after transplantation of ovarian tissue, four after using of cryopreserved specimens in assisted reproductive treatment and one after natural conception.

Conclusion: Most patients in the cohort accessed FP directly after receiving their cancer

diagnosis, however, semen banking was easily planned and most males could access it, whereas the need of invasive methods, hormone treatment and interventions for female FP resulted in lower uptake of this methods early after diagnosis. However, adolescent girls presenting with signs of ovarian function could be offered FP afterwards, indicating the need of surveillance of gonadal function in these patients. Most patients in the cohort are still young, thus longer follow-up is warranted.

(P 271) SAFETY AND EFFICACY OF CABOZANTINIB IN PEDIATRIC PATIENTS WITH MALIGNANT SOLID TUMORS (CAMEL TRIAL/NCCH2106): A SINGLE-CENTRE PHASE I TRIAL

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Objective: Cabozantinib (CABO) has been reported to be effective for osteosarcoma (OS) and Ewing sarcoma. In the United States, a phase I trial of CABO in pediatric patients (ADVL1211 study) established 40 mg/m² as the recommended phase 2 dose (RP2D). However, safety data in Japanese pediatric patients were lacking; therefore, a phase I trial of CABO in Japanese children was conducted.

Methods: This open-label, single-center phase I trial evaluated the safety, efficacy, and RP2D of CABO in pediatric patients aged 3–19 years with relapsed or metastatic malignant solid tumors. CABO was administered orally once daily at a dose of 40 mg/m². In cohort 1, the incidence of adverse events (AEs) equivalent to dose-limiting toxicity (DLT) was evaluated in six patients. Once the RP2D was confirmed, additional patients were enrolled in cohort 2. The primary endpoint was the incidence of DLTs in cohort 1. Secondary endpoints included the incidence of AEs, pharmacokinetic parameters, overall response, and the 16-week disease control rate.

Results: Between April 2022 and the data cut-off date in April 2024, 12 pediatric patients, including 5 with OS, were enrolled. Among the six patients in cohort 1, one patient experienced a grade 3 elevation of alanine aminotransferase during the first cycle, which was considered a DLT. Based on this, 40 mg/m² was confirmed as the RP2D. No additional DLT-equivalent AEs were observed among the 12 patients. In the context of severe AEs, one patient died due to CABO-related upper gastrointestinal bleeding. Other common grade ≥3 CABO-related AEs were manageable hematologic toxicities. Noncompartmental analysis showed that the steady-state clearance (1.51 ± 1.34 L/h/m²) was consistent with previously reported data. In terms of efficacy, the 16-week disease control rate was 50.0% (3/6). Stable disease was achieved in 66.7% (2/3) of patients with OS, one of whom maintained long-term disease control for >1 year.

Conclusion: In this study, CABO at 40 mg/m²/day was tolerable in Japanese pediatric patients. The incidence of DLTs at this dose was lower compared to the ADVL1211 study. Although the number of enrolled patients was small, these findings suggest that CABO may be effective in Japanese pediatric patients with OS, consistent with results from overseas studies. Funding: This study was supported by Takeda Pharmaceutical Co., Ltd. Clinical Trial

Registration: jRCT2031210610

(P 272) **THE HAZARDS OF BIOPSY IN PEDIATRIC SOFT TISSUE SARCOMAS**

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Objective: Pediatric soft tissue sarcomas (STS) are encountered by many surgical specialties. Deviations from oncologic principles alters patient outlook, as shown for all ages in the classic 1982 and 1996 studies by Mankin, Simon, and the Musculoskeletal Tumor Society (MSTS) membership. A similar review specific to pediatric tumors is lacking.

Methods: We retrospectively identified 114 patients < 18 years of age treated for STS or neoplasms of uncertain behavior (NUB, as defined by the WHO) of the trunk and extremities between 2010-2024. Each case was reviewed by a panel of four fellowship trained orthopedic oncologists and one pediatric general surgeon using a standardized questionnaire (Fig.1).

Results: 67 STS and 47 NUB were identified. 30% (20/67) of pediatric STS underwent an unplanned excision. STS that underwent unplanned excision were smaller than those undergoing planned excision or biopsy ($p < 0.0001$, Fig. 2). 13% (9/67) of patients with STS had a materially altered outlook due to biopsy or pathologic inaccuracy. 45% (21/47) of NUB had an unplanned resection. 10% (5/47) of NUB patients had an altered outlook. There was no difference in size of unplanned and planned excisions of neoplasms of uncertain behavior.

Conclusion: Pediatric soft tissue masses are treated by a variety of subspecialists. Unplanned resections of pediatric soft tissue sarcomas and neoplasm of uncertain behavior is not infrequent and leads to morbidity. Unplanned excisions of soft tissue sarcomas are more commonly performed in small tumors in pediatric patients. Increased understanding of pediatric soft tissue masses is needed to decrease the incidence of unplanned excision.

Figure 1

Pediatric Soft Tissue Tumor Consensus Panel Questionnaire
Was the resection of sarcoma or NUB unplanned?
Did an inaccurate pathologic diagnosis change management?
Was "biopsy" or resection planned and performed optimally?
Did technical aspects change treatment?
Meaningful increase in amount of tissue resected?
Surgery changed from limb-sparing to amputation?
Local tissue rearrangement or flap, when otherwise not needed?
Post-operative radiation, when otherwise not needed?
Post-operative chemotherapy, when otherwise not needed?
Did pathologic inaccuracy or technical aspects materially alter patient outlook?

(P 273) RADIOMIC PREDICTORS OF SPONTANEOUS PNEUMOTHORAX DURING TYROSINE KINASE INHIBITOR THERAPY FOR LUNG METASTASES

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Objective: Tyrosine kinase inhibitors (TKIs) are increasingly used to treat pulmonary metastatic disease in osteosarcoma (OS) and synovial sarcoma (SS). However, TKIs have been associated with spontaneous pneumothorax (sPNX). This study aims to identify clinical and radiomic features associated with sPNX while on TKI therapy.

Methods: We performed a retrospective review of patients aged 15–39y with OS or SS lung metastases treated with TKI therapy between 2007–2023. Demographics, therapy and outcomes data were collected under IRB approval. The pretreatment chest CT was reviewed, and all lung lesions were segmented. Radiomic features were extracted from all segmented lung lesions using a well validated feature extraction package. The primary outcome was the occurrence of sPNX during TKI therapy and up to a month after. Univariate mixed-effects logistic regression was used to assess associations between individual features and sPNX, controlling the false discovery rate at 5%.

Results: A total of 58 patients were included (median age= 28; 64% male, 26 OS and 32 SS), of which, 43 (74%) patients had prior thoracic surgery. The median number of lesions per patient was 6 (range 1-207), and 51(88%) patients had lesions abutting the pleura. Seven patients (3 OS, 4 SS) experienced TKI related sPNX, including two with bilateral events, for a total of nine sPNX events. The number of lung lesions was significantly higher in patients with sPNX (median 17 vs. 5; p = 0.03). Other clinical factors including presence of pleural abutment

and history of thoracic surgery were not significantly associated with sPNX. The radiomics analysis included 963 features across 1121 lesions. Sixteen representative features were identified from the associated classes: Gray-Level Co-occurrence Matrix (GLCM), Gray-Tone Difference Matrix (GTDM), Grey Level Run Length (GLRL), Laplacian of Gaussian (LoG) and Intensity. Among these the GLRL class feature (OR 0.04, 95% CI: 0.01-0.34) had the strongest association suggesting a strong protective effect.

Conclusion: Our study identified clinical and radiomic features associated with sPTX during TKI therapy. These results suggest the potential for modeling risk based on pre-treatment cross-sectional imaging.

(P 274) RACIAL DISPARITIES IN INCIDENCE AND MORTALITY OVER 20 YEARS AMONG AYA PATIENTS WITH SARCOMA IN THE US: A SEER DATABASE ANALYSIS

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Objective: Despite a steady increase in the incidence of cancers in adolescent and young adult (AYAs), the trend of bone sarcoma (BS) and soft tissue sarcoma (STS) remains understudied. We conducted a Surveillance, Epidemiology, and End Results (SEER) database analysis to evaluate the effects of race/ethnicity on the incidence, trends, and mortality among AYA patients with BS and STS.

Methods: AYA cases (aged 15–39) with BS or STS diagnosed between 2000 and 2021 were identified using the SEER research plus data (22 Registries). SEER*Stat (v8.4.4) was used to calculate incidence rates per 100,000 individuals, mortality rates per 100,000 individuals, age-adjusted incidence rates (AAIR), annual percent change (APC), trends, incidence rate ratios (IRR), and survival outcomes compared among racial groups, including Non-Hispanic White (NHW), Non-Hispanic Black (NHB), Non-Hispanic Asian/Pacific Islander (NHAPI), Non-Hispanic American Indian/Alaska Native (NHAIAN) and Hispanic patients. R (v4.3.2) was utilized for survival analysis.

Results: A total of 5,389 and 16,097 new diagnoses of BS and STS were retrieved from the SEER database, with 10,589 (49.3%) patients being female. All BS and STS patients were categorized by race: NHW, NHB, NHAPI, NHAIAN, and Hispanic, comprising 10,601 (49.3%), 3,120 (14.5%), 1,941 (9.0%), 195 (0.9%), and 5,629 (26.3%) cases, respectively. The incidence of BS increased from 0.8 to 0.9 while STS decreased from 2.7 to 2.3 per 100,000 (from 2000 to 2021). NHW had a high incidence of BS and STS in both sexes compared to all other groups. Among NHWs, there were significant decreases in AAIR for STS (APC -3.6 (95% CI -5.6 to -1.5) for males and -5.4 (-8.1 to -2.6) for females), but no statistically significant changes were observed for BS in any racial group. NHBs had an increased mortality from BS (HR 1.31, 95% CI 1.12–1.53, $p = 0.006$). For STS, NHAIAN patients had higher mortality compared to NHWs (HR 1.37, 95% CI 1.05–1.78, $p = 0.02$).

Conclusion: We observed some interesting racial trends in AYA. AAIR for STS decreased over time for NHW. Mortality from BS in NHB patients and STS in NHAIAN patients was higher compared to NHW patients. Further studies are needed to understand the reasons behind disparate outcomes and address barriers to care.

Table 1 Racial/ethnic disparities in mortality among patients with bone and soft tissue sarcomas

	Bone sarcoma		Soft tissue sarcoma	
	HR	95% CI	HR	95% CI
NHW	1.00 (reference)		1.00 (reference)	
NHB	1.31	1.12-1.53	1.28	1.18-1.39
NHAPI	0.996	0.83-1.20	1.19	1.07-1.32
NHAIAN	1.33	0.80-2.21	1.37	1.05-1.78
Hispanic	1.18	1.05-1.32	1.16	1.08-1.24

(P 275) NEXT GENERATION SEQUENCING IN ADOLESCENT AND YOUNG ADULT (AYA) SARCOMAS: CLINICAL IMPACT, DIAGNOSTIC UTILITY, AND IMPLICATIONS

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Objective: To evaluate the clinical utility of next-generation sequencing (NGS) in adolescent and young adult (AYA) sarcomas, focusing on diagnostic refinement, identification of actionable alterations, germline mutation prevalence, and implications for treatment and clinical trial access.

Methods: We conducted a narrative review of five peer-reviewed studies and two conference abstracts encompassing approximately 360 AYA sarcoma patients (ages 15–39) who underwent comprehensive molecular profiling (CMP). Sequencing platforms included RNA sequencing, hybrid-capture NGS panels, and whole-genome sequencing. Key metrics assessed were the frequency of actionable alterations, diagnostic reclassification, germline mutation rates, turnaround time, and downstream clinical impact.

Results: About 48-81% of AYA patients with sarcoma received treatment recommendations from CMP findings. CMP and central pathology review also aided enrollment into clinical trials, reclassifying the diagnosis in multiple cases. On average, 3 genomic alterations were identified per tumor, with common mutations in TP53 (~25%), RB1, CDKN2A, LMNA-NTRK1, and EWSR1. Germline pathogenic variants were detected in 10–14% of patients, most frequently in TP53, BRCA2, and CHEK2, prompting changes in surveillance and family counseling. NGS findings expanded clinical trial eligibility in 20–30% of patients, particularly for mutation-driven

basket trials. The median turnaround time was 28–45 days, with >95% assay success rates and no major biopsy-related complications reported.

Conclusion: NGS is a feasible and impactful tool in the clinical management of AYA sarcomas. It enables identification of actionable genomic alterations, enhances diagnostic precision, and broadens access to targeted therapies and clinical trials. To fully realize the potential of precision oncology in this age group, expanded access to molecular profiling and inclusive trial designs are essential. Rapid turnaround time in AYA sarcomas is required to meet these goals and combat these aggressive malignancies.

(P 276) RADIATION-INDUCED SARCOMA (RIS): CLINICAL SPECTRUM AND ONCOLOGIC OUTCOMES FROM A TERTIARY INDIAN SARCOMA CLINIC

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Objective: Radiation-induced sarcoma (RIS) is a rare but highly aggressive late complication of therapeutic radiotherapy. Data on RIS in the Indian population are limited, and optimal treatment strategies remain undefined. This study aimed to evaluate the clinicopathological characteristics, treatment patterns, and outcomes of patients diagnosed with RIS at a tertiary sarcoma referral center.

Methods: A retrospective analysis was conducted of a prospectively maintained sarcoma database at the All India Institute of Medical Sciences (AIIMS), New Delhi. Patients diagnosed with biopsy-proven RIS between January 2015 and June 2025 were included. Clinical, pathological, and treatment data were extracted from institutional records. Survival outcomes, including overall survival (OS), were estimated using the Kaplan–Meier method. Group-wise comparisons (metastatic vs. non-metastatic) were performed using the log-rank test using SPSS V.30.

Results: A total of 23 patients (0.32% of 7,138 sarcoma cases evaluated) were diagnosed with radiation-induced sarcoma (RIS). The median age at RIS diagnosis was 51.1 years, and the median latency from radiotherapy was 13.25 years. Breast cancer (21.7%) was the most frequent primary malignancy. Soft tissue sarcomas were more common (60.9%), with undifferentiated pleomorphic sarcoma being the predominant histological subtype (34.8%). At diagnosis, 52.2% had metastatic disease, while 13.1% were locally unresectable. Most tumors were high-grade (87.0%) with a median size of 6.9 cm. Surgery was performed in 7 out of 8 patients with resectable disease, achieving R0 resection margins in 62.5% of cases. Re-irradiation was administered in 3 patients. A total of 16 patients (69.6%) received systemic therapy comprising heterogeneous regimens. The most commonly used regimen was single-agent doxorubicin (n = 5), followed by combination therapy including doxorubicin, ifosfamide, and platinum (n = 3), among others. For those who received systemic therapy, partial response

was observed in 12.5% of patients, while stable disease was achieved in 31.3%. Median follow-up was 68.2 months. The overall median survival was 50.9 months, with a non-significant survival difference between metastatic and non-metastatic patients (13.4 vs. 59.2 months, log-rank $p = 0.07$).

Conclusion: In this largest single-institution series of RIS from India, the majority of patients presented with large tumor size, high-grade, and metastatic or unresectable disease. Despite these unfavorable characteristics, curative-intent surgery was achieved in most non-metastatic cases, and systemic therapies were employed across various clinical settings. The higher median OS is encouraging, particularly within the context of LMIC, highlighting the value of centralized, multidisciplinary sarcoma care even in resource-constrained environments.

(P 277) THE ROLE OF RADIOTHERAPY IN THE MULTIDISCIPLINARY MANAGEMENT OF RADIATION-ASSOCIATED ANGIOSARCOMA OF THE BREAST: A REFERRAL CENTER EXPERIENCE

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Objective: Radiation-associated angiosarcoma (RAAS) of the breast is a rare and aggressive disease, occurring as a late complication of adjuvant radiotherapy (RT) for primary breast cancer (BC). To date, the role of RT in RAAS is unclear and controversial. In this retrospective study, we evaluated the role of RT within a multidisciplinary (MD) treatment of patients who underwent surgery at a referral center.

Methods: Cases of resectable histologically-proven RAAS, evaluated by a MD team were analysed. RT was given either preoperatively (Preop) +/- chemotherapy (CT) or postoperatively (Postop). RT treatment details and toxicity profiles according to CTCAE scale v5 were collected. Overall and disease-free survival (OS, DFS) data were analysed using Cox models and estimating Kaplan-Meier curves. Inverse probability weighting with propensity scores was used to account for groups' differences in baseline characteristics.

Results: From March 2010 and October 2023, 27 patients (median age 69.8 years) were identified. All of them had received postop RT for primary BC. The interval between prior breast RT and RAAS was 7.6 years (4.69; 11.17). Thirteen patients received Postop RT (dose 50-60Gy in 25-30 fractions). Fourteen patients received Preop RT (dose 44-50.4Gy in 22-28 fractions): 7 sequentially to CT and other 7 concurrent CT-RT. Median follow-up was 36.81 months. The adjusted 5-year OS were 73.04% and 53.6% for postop RT and preop RT, while 5-year DFS were 75.2% and 53.8%, respectively. Overall, 5 patients experienced a local recurrence with a 12, 24-month crude cumulative incidence of 3.7% and of 20.42%, respectively. Patients receiving preop RT appeared to have a higher risk of death and recurrence than postop RT group (hazard ratios: 2.17- $p=0.395$, and 2.71- $p=0.182$, respectively). In the postop RT group were observed significantly longer time interval to prior RT ($p=0.0198$) and higher rates of total mastectomies ($p=0.0001$). Regarding acute toxicities, 13 (48%) G2 skin, 1 (3.7%) G3 skin toxicity and 1 (3.7%) G2 pneumonitis were observed.

Three (11%) patients developed major wound complications, all of them in the preop RT group. As of late toxicities G1 pneumonitis in 2 (7.4%) patients, rib fracture in 1 (3.4%) patient and cardiac events in 2 (7.4%) patients were observed.

Conclusion: The findings of this study support that RT within a trimodality approach leads to improved local control without increased toxicity for RAAS.

(P 278) NEOADJUVANT HYPOFRACTIONATED RADIOTHERAPY AND CHEMOTHERAPY IN EXTREMITY SOFT TISSUE SARCOMAS

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Objective: To address the role of hypofractionated radiotherapy combined with chemotherapy in the neoadjuvant setting for extremity soft-tissue sarcomas, we report long-term results from a single-institution protocol.

Methods: Between 2015 and 2024, 23 patients with non-metastatic, histologically confirmed extremity soft-tissue sarcomas were treated with a protocol combining three neoadjuvant cycles of doxorubicin and ifosfamide, with hypofractionated radiotherapy (25 Gy in 5 fractions) delivered on day 1 of the second cycle. Primary endpoint was disease-free survival; secondary outcomes included pathologic response, wound complications, and morbidity.

Results: Median age was 54 years (range: 21–75), and median follow-up was 62 months (range: 6.7–93). At last follow-up, 17 patients (74%) were alive without local or systemic disease, three died from metastatic disease, and two (8.5%) experienced local recurrence. Common chemotherapy-related adverse events included grade 1–2 nausea, vomiting, fatigue, mucositis, and alopecia. Febrile neutropenia occurred in 17.5%, leading to the suspension of the final chemotherapy cycle in one patient. Acute skin toxicity was absent in 56.5%; grade 1 erythema occurred in 17.4%, and grade 2 or 3 reactions in 13% each. No grade 4 toxicity was reported. All patients completed radiotherapy, followed by surgery at a median of 7 weeks post-chemotherapy. Two patients (8.5%) had amputation as primary surgery. According to EORTC-STBSG scoring, eight patients (35%) had no residual viable tumor. Eight had 10–49% viable cells, and seven had ≥50%. Major wound complications occurred in nine patients (39%), all but one involving lower extremity lesions. Late toxicity included grade 1 fibrosis in 43.5%, grade 2 in 17.5%, and one case of femur fracture and necrosis with grade 4 joint stiffness. Nonetheless, 70% reported no joint stiffness or edema.

Conclusion: Despite elevated WC rates, this treatment approach is feasible, well-tolerated, and yields high rates of local control (91.5%), and pathologic complete response of 35%. Limitations include the small sample size and absence of correlation between pathologic findings and outcomes.

(P 279) IMPACT OF PREOPERATIVE 5-DAY HYPOFRACTIONATED RADIOTHERAPY (HFRT) FOR SOFT TISSUE SARCOMA (STS) ON BARRIERS TO TREATMENT AT A HIGH-VOLUME SARCOMA CENTER (HV-SC)

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Objective: Current guidelines for extremity/trunk STS recommend management by an experienced oncology team and preoperative radiotherapy (RT) (50Gy/25 fractions (fx), 5 wks) followed by limb sparing surgery. This study evaluated the feasibility of preoperative 5-Day HFRT (30Gy/5fx) at Holling Cancer Center (HCC), South Carolina's only HV-SC. An exploratory analysis was performed comparing the sociodemographic profile and travel distance to HCC between the trial cohort and a historical cohort to inform the hypothesis that HFRT decreased barriers to radiotherapy (RT) at a HV-SC.

Methods: The primary endpoint of feasibility was protocol uptake rate, defined as the proportion of eligible patients (pts) who elected to participate in the trial. The trial cohort was defined as those enrolled and treated with at least 1 fx of RT (N=15). The historical cohort (N=8) was defined as those meeting trial criteria and receiving conventionally fractionated RT within the preceding 3 years. The differences in Social Vulnerability Index (SVI) and the geographic distance to HCC were analyzed between the two cohorts using Wilcoxon Rank Sum tests.

Results: Preoperative HFRT was deemed feasible with only one candidate declining the trial, uptake rate of 0.94 (90% CI; 0.77, 1.00). Travel distance to HCC was higher in the trial cohort with a median (IQR) of 72.8 (34.6, 101.3) miles, compared to a median (IQR) of 13.2 (2.3, 24.8) miles in the historical cohort (p=0.008). SVI Theme 1 (higher score = more vulnerable) was higher in the historical cohort with a median (IQR) of 0.68 (0.56, 0.85) compared to a median of 0.38 (0.20, 0.46) in the trial cohort (p=0.04). Total SVI and SVI Themes 2-4 were not significantly different between the cohorts (p>0.15).

Conclusion: Preoperative HFRT as a trial treatment option was overwhelmingly accepted by the HCC STS population. The increased travel distance for the trial cohort suggests a shorter RT treatment option can decrease the geographic barriers to treatment at a HV-SC. The differences in the SVI Theme 1, which correlates with geocode, suggest the preoperative HFRT trial option diversified the sociodemographic profile of HCC STS population.

(P 280) PERSONALIZED ULTRA-FRACTIONATED STEREOTACTIC ADAPTIVE RADIOTHERAPY (PULSAR) FOR ADULT AND PEDIATRIC SARCOMAS

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Objective: Personalized Ultra-fractionated Stereotactic Adaptive Radiation Therapy (PULSAR) is a novel treatment which delivers high-dose pulses of radiation at extended intervals to allow treatment adaptation and optimize synergy with concurrent immuno- and other systemic therapies. Our institution has implemented PULSAR in a variety of clinical situations including oligo- metastatic or progressive disease and unresectable primaries in both pediatric and adult sarcoma patients. Here we report our initial clinical outcomes after PULSAR in sarcoma patients with a hypothesis that PULSAR provides excellent local tumor control with minimal toxicities.

Methods: This IRB-approved retrospective study evaluated pediatric and adult patients with primary or metastatic sarcomas treated with PULSAR at UT Southwestern from 2022-2025. We collected patient demographics, tumor characteristics, treatment details, toxicities, and clinical outcomes including local tumor control (LC), progression-free survival (PFS), and overall survival (OS). Kaplan-Meier analysis was used for survival outcomes.

Results: Among 58 irradiated sites in 31 patients, 38 sites in 20 patients had adequate follow-up imaging (median 8 months). 76% of irradiated sites were metastatic, while 24% were primary tumors. The most common histologies in adults were leiomyosarcoma and undifferentiated pleomorphic sarcomas, while in pediatrics were osteosarcoma, Ewing sarcoma, and rhabdomyosarcoma. Concurrent systemic therapy was administered in 92% of cases: immunotherapy (45%), chemotherapy (32%), targeted therapy (16%). The most common radiation dose 8 Gy/pulse given every 3 weeks x 5 total (cumulative 40 Gy). Overall, LC of irradiated sites was 90%. At 6-month follow-up, metastatic sites showed 90% LC, 71% distant control, and 65% PFS, while primary sites showed 88% LC, 63% distant control, and 56% PFS. Treatment-related toxicity occurred in 35% of patients, with radiation pneumonitis most common (20%) with all cases occurring with concurrent immunotherapy.

Conclusion: In primary and metastatic sarcomas, PULSAR offers excellent local control with limited toxicity despite high rates of concurrent systemic therapy integration (92%). These promising findings warrant further prospective study.

(P 281) LOCAL CONTROL WITH MODERATELY HYPOFRACTIONATED DEFINITIVE RADIOTHERAPY DELIVERED WITH A SIMULTANEOUS INTEGRATED BOOST TECHNIQUE TO NON-EXTREMITY SOFT TISSUE AND BONE SARCOMAS

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Objective: While surgery is the primary treatment for soft tissue sarcomas (STS) and primary bone sarcomas, a notable proportion of patients with non-extremity tumours do not undergo resection. Outcome data for definitive radiotherapy in this context are limited, as is evidence on the use of hypofractionation at non-extremity sites near sensitive organs at risk. We report our institutional experience delivering moderately hypofractionated definitive radiotherapy (MHDRT, 2.2-2.5 Gy per fraction) to patients with inoperable non-extremity STS and primary bone sarcomas including those who were unfit for, or declined, surgery.

Methods: 59 adult sarcoma patients received MHDRT to non-extremity disease between July 2021 and September 2024 in 60 treatment courses (Table 1). Radiotherapy was delivered over 28 fractions in 95% of patients, with a dose of 50.4 Gy to the low dose target volume and a simultaneous integrated boost (SIB) to the high dose target volume of 63 Gy for STS (equivalent dose in 2 Gy fractions, EQD2 65.3 Gy, $\alpha/\beta = 5$) and 70 Gy for bone sarcomas (EQD2 77.0 Gy, $\alpha/\beta = 3$).

Results: With a median follow-up of 17.7 months, local control at 1 year was 90.8% for STS (n=37), 100% for chordoma (n=14) and 55.6% for high-grade bone sarcomas (n=9). Progression-free survival and overall survival at 1 year were 59.9% and 94.4% for STS, 85.7% and 92.3% for chordoma, and 27.8 and 47.4% for high-grade bone sarcomas. Acute and late grade 3 toxicities were observed in 5 (8.3%) and 6 (10%) patients respectively.

Conclusion: These data indicate that MHDRT can be delivered to inoperable non-extremity sarcomas with acceptable toxicity and promising early local control rates, representing an important radical treatment option in this patient group.

Table 1. Baseline and treatment characteristics.

Characteristic	Number (%)
Age, years	
Median	60
Range	20-90
Site	
Sacrum / lumbar spine / coccyx	17 (28.3)
Intra-abdominal / intra-pelvic	30 (50.0)
Thorax	9 (15.0)
Head & neck	4 (6.7)
Context	
Primary tumour, definitive	34 (56.7)
Primary tumour, post operative residual	2 (3.3)
Recurrence	15 (25.0)
Metastasis	9 (15.0)
Metastases at time of radiotherapy	15 (25.0)
Soft tissue	7 (18.9)
Chordoma	2 (14.3)
High-grade bone	6 (66.7)
Modality	
Intensity-modulated radiotherapy	54 (90.0)
Proton beam therapy	6 (10.0)
Concurrent systemic anti-cancer therapy	12 (20.0)
Median follow-up for local control, months	17.7
Soft tissue	17.8
Chordoma	21.3
High-grade bone	9.5

(P 282) LOCAL FAILURE ANALYSIS OF SOFT TISSUE SARCOMA TREATED WITH PREOPERATIVE ULTRA-HYPOFRACTIONATED RADIATION: UPDATE

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Objective: While normo-fractionation using 50Gy applied in 25 fractions represents the historically most used and best-known conventional preoperative RT regimen, ultra-hypofractionated RT (uhRT) with 5 fractions is not (yet) accepted as a 'standard', however is based on a fast-increasing literature body derived from clinical results. There are no prospective randomized trials yet comparing normo- vs uhRT. This analysis focused on local recurrence in a single center cohort.

Methods: Between 03.2020-12.2024, 77 consecutive STS pats have been pre-operatively irradiated with 5x 5.0Gy/1w uhRT. PTVs/GTVs were defined according to the RTOG 0630 trial. Bolus material on skin was placed in 59/77 (77%). Induction chemotherapy was given in 2/77 patients (3%). The indication for RT was determined in all patients @ the weekly Swiss Sarcoma Network (SSN; swiss-sarcoma.net) multi-center sarcoma conference. The cohort was characterized by unfavourable features in >40%, Tab. 1.

Results: After a mean/median FU time of 31/29.5 months (2-62), 5/77 (6%) local recurrences were diagnosed 4/5/6/8 and 28 m. post treatment, Tab. 2, Fig. 1. 6/77 patients presented with synchronous distant metastases. 2y LC/OS/DFS and distant metastasis free survival were 94%/88%/61% and 68%, respectively. Early RT tolerance was excellent, allowing for timely surgery, Tab. 3. R0-resection was achieved in 92%.

Conclusion: We found a 2y local/final local control rate of 94%/96% in our single institution STS cohort treated with 25 Gy / 5f / 1w uhRT with omission of systemic therapy. The results are well comparable to published reports on results following normofractionated RT +/- systemic treatment. Treatment tolerance was excellent.

Table 1. Unfavourable features of the cohort

N patients	77
mean/median age	62/60 (28-91)
unfavourable features	
o G3	49 (63%)
o Whoops lesion	9 (12%)
o uhRT for local recurrence	10 (13%)
o retroperitoneal/abdominal	10 (13%)
o previous local surgery	18 (23%)
o previous local surgery+RT	4 (5%)

(P 283) **PALLIATIVE LATTICE RADIATION THERAPY IN SOFT TISSUE SARCOMA VERSUS CARCINOMA AND MELANOMA: OUTCOME COMPARISON**

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Objective: Presentation of single center results following Lattice Radiation, a Spatially Fractionated Radiation Therapy (SFRT) technique delivering highly inhomogeneous doses to very large tumors - with focus on the comparison of Soft Tissue Sarcoma lesions versus other histologies.

Methods: A total of 66 pats with 81 large lesions ≥ 7 cm were treated between 01.2022-05.2025. Histologies included carcinoma (n=34), sarcoma (n=31), and melanoma (n=16). Median gross tumor volume (GTV) was 415cc (range: 33–4027); sarcoma GTV measured mean 922cc (88-3704). At least one follow up (FU) imaging was available for volumetric analysis in 63/81 (71%) lesions. Previous palliative systemic therapy was given in 72%. Treatment consisted of 5x 4–5 Gy to the lesion with a simultaneous integrated boost (SIB) of 9–13 Gy to lattice vertices (n=55), or a single fraction of 20 Gy to vertices only (n=26). The combination of the two regimens was applied in 6 lesions. Focus was on diagnosis-related outcome comparison.

Results: The mean/median follow-up was 7.7/5 months (range: 0.4–38.2), 11.6/7.1 in 17 alive patients, respectively. 87% (32/37) of symptomatic patients reported immediate relief. Radiological response was found in 80%, with a mean/median tumor reduction of 51%/60%: Melanoma lesions showed less extent of tumor shrinkage (mean/median: 28/28%) compared to carcinoma (61/65%) and sarcoma (51/49%). The mean duration of volumetric response was 7.4 months. Early tolerance was excellent (Grade 0–1), with only 2 cases of Grade 2–3 dermatitis (skin affected by tumor); no late toxicity was stated so far.

Conclusion: Palliative Lattice RT was found highly effective in sarcoma regarding subjective benefit and volumetric response, and iso-effective as compared to carcinomatous lesions. This is -to our best knowledge- the first histology-related comparison of palliative Lattice RT outcome.

Diagnosis-related Volumetric Response to Lattice RT

PARAMETER	CARCINOMA	SARCOMA	MELANOMA	ALL LESIONS
FU imaging available	23/34	28/31	12/16	63/81
Volumetric response to LRT				
•PD (>10% of initial cc) in	3/34 * (9 %)	3/31 * (10 %)	1/16 * (6 %)	7/81 * (9 %)
•SD (+/-10% of initial cc) in	5/23 (22 %)	5/28 (18 %)	2/12 (17 %)	12/63 (19 %)
•Shrinkage (>10% of initial cc) in	17/23 (74 %)	23/28 (82 %)	10/12 (83 %)	50/63 (79 %)

(P 284) THE IMPACT OF SARCOMA SBRT ON THE IMMUNE SYSTEM: EARLY RESULTS FROM A PROSPECTIVE TRIAL

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Objective: We sought to prospectively evaluate the baseline immune profile of patients receiving SBRT for metastatic sarcoma and to determine if there is any correlation with survival.

Methods: Patients receive 5 fraction SBRT for metastatic sarcoma. Labs are collected prior to SBRT, after last fraction of SBRT, at 3 to 6 months, and at 1 year or time of progression. Labs consist of CBC, albumin, LDH, CRP, MDSCs and immune and inflammatory panels. High parameter flow analysis was performed. Data was analyzed using FlowJo to visualize clusters of cells at baseline by Uniform Manifold Approximation and Projection (UMAP), FlowSOM, and Marker Enrichment Modeling (MEM). Patients were assessed for local control and survival.

Results: Nine patients with a median age of 23 enrolled on our IRB approved prospective trial. 4 patients have died at a median of 3.25 months post SBRT. Five patients had 1 target treated with SBRT and 4 patients had 2. Targets included lung (6), soft tissue (3), bone (2), and kidney (1). Number of metastases at time of SBRT included 1 (n=2 patients), ≤5 (4), >5-10 (1), >10 (2). 5 patients received concurrent therapy. At time of this analysis, 1 patient had local recurrence, 3 had regional recurrence and 7 had distant failure. Five patients had a complete response to SBRT and 3 had a partial response. Patients that survived < 6 months had higher frequencies of monocytic MDSC (CD33+HLADR-CD14+) and large granular lymphocytes (CD56+CD16+) at baseline than those that survived >6 months. Patients that survived >6 months had higher frequencies of memory CD4+ T cells and CD57+ T cells at baseline than those that survived <

6 months. There was no significant difference in baseline NTLR, albumin, CRP, or LDH for these small patient groups.

Conclusion: On this trial, patients with metastatic sarcoma had early good responses to SBRT. Patients receiving SBRT for metastatic sarcoma may have different baseline MDSCs, large granular lymphocytes, and memory T cells that relate to survival post SBRT.

(P 285) MULTICENTER STUDY OF SPATIALLY FRACTIONATED RADIOTHERAPY (LATTICE) FOR LARGE-VOLUME RADIORESISTANT SARCOMAS

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Objective: The management of bulky unresectable sarcomas with limited therapeutic options is challenging. Radiotherapy in this setting also has limitations. Most sarcomas are radioresistant, and treatment toxicities are often prohibitive. Spatially fractionated radiotherapy, also known as GRID or lattice, may be a viable alternative. This technique involves the intentional delivery of a heterogeneous dose distribution, alternating high and low doses across the tumor. Literature data on lattice therapy for sarcomas are limited. This study aims to evaluate the outcomes of this technique in large, radioresistant sarcomas.

Methods: A retrospective, international, multicenter cohort study was conducted. Eligible participants had a histopathological diagnosis of radioresistant sarcoma, lesions larger than 4.5 cm, were refractory to systemic therapy, or were ineligible for surgery. Two lattice protocols were used. A single-fraction (peaks) dose of 15–22 Gy, followed by 3–16 fractions of 2.66–8 Gy (24–42.56 Gy in the valleys). The other treatment used five fractions on alternate day of 4–5 Gy (20–25 Gy in the valleys), with an integrated boost of 12–13.25 Gy (60–65.25 Gy at the peaks).

Results: The study included 30 patients with 42 lesions treated. At first follow-up none of the lesions evaluated showed progression, with 43% remaining stable and 45% exhibiting reduction. The median survival was 10.0 months, with 33% of patients still alive at the time of analysis. Most patients reported significant pain relief, with limited and manageable side effects.

Conclusion: Lattice therapy demonstrated a good response rate and tolerability. These findings are valuable and hypothesis-generating, justifying further research to compare this strategy with current radiotherapy protocols for sarcomas in the palliative setting.

(P 286) INTERSTITIAL BRACHYTHERAPY FOR ORGAN AND FUNCTION PRESERVATION IN SOFT TISSUE SARCOMAS: LONG TERM OUTCOMES

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Objective: To report the long-term outcomes with a combination of organ and function preserving surgery and perioperative interstitial brachytherapy (BT) for adults with soft tissue sarcomas treated at a tertiary cancer centre.

Methods: Between December 1986 and December 2024, 345 patients with non-metastatic soft tissue sarcomas were treated with combined modality approach at our institute. The median age of the patients was 42 years (IQR: 30.3- 57.8years) and the majority (62%) were males. Sixty-nine percent had primary lesions and lesions involving the extremities. Spindle cell sarcoma was the most common histology (22%) followed by pleomorphic sarcoma (16%) and synovial sarcoma (14%). The majority (69%) had grade III lesions. Treatment included wide local excision of the primary tumor followed by BT alone in 65% and a combination of BT with external beam radiotherapy (EBRT) in 35% of the patients. The majority (88%) underwent primary closure, while 12% required flaps. Close or positive margins were seen in 17%.

Results: After a median follow-up of 60 months (range: 2-187months), the 10-year local control (LC), disease-free survival (DFS), and overall survival (OS) for the entire cohort was 82%, 64%, and 81%, respectively. On multivariate analysis, deep tumors and a positive margin significantly predicted for a worse LC. Deep tumors, positive margin, Tumor size >5cm and high grade predicted a worse DFS. Deep tumors and tumor size >5cm predicted a worse OS. Acute wound complications were seen in 9.6% patients and were not higher in patients with flap (p=0.48) or patients receiving EBRT (p=0.32). Subcutaneous fibrosis (24%, n=84) was the most common late complication and strongly correlated with additional EBRT (p=0.001). The average Musculoskeletal Tumor Society (MSTS) function score was 28.

Conclusion: Interstitial BT with or without EBRT, as a part of function-preserving protocol results in excellent local control and functional outcomes in patients with STS. BT alone results in fewer complications compared with the combination of BT and EBRT.

(P 287) A PHASE 1 STUDY OF NEOADJUVANT CABOZANTINIB IN COMBINATION WITH RADIATION THERAPY FOR SARCOMAS OF THE EXTREMITIES

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Objective: Cabozantinib demonstrates promising activity in multiple soft tissue sarcoma (STS) subtypes, but use with concurrent radiation therapy (RT) has previously been limited by concern for risk of fistula or perforation. This phase 1 nonrandomized trial evaluated safety of concurrent cabozantinib and RT as neoadjuvant therapy in patients with extremity STS.

Methods: Adults with new diagnosis of localized extremity STS who were planned for neoadjuvant RT and surgical resection were eligible. Subjects received radiation per standard clinical care with 5000-5040 cGy with conventional fractionation. A 3+3 dose-finding design was used with starting doses of cabozantinib 40mg and 60mg daily. Patients were observed for dose-limiting toxicity (DLT) up to 28 days after completion of concurrent RT with cabozantinib. The primary endpoint was recommended phase 2 dose (RP2D) of cabozantinib for combination with RT, and secondary endpoints were treatment related adverse event (TRAE) rates, margin status, and objective response rates.

Results: Six patients were enrolled from 2020-2024, with histologic subtypes of undifferentiated pleomorphic sarcoma, myxofibrosarcoma, leiomyosarcoma, and myxoid liposarcoma. No DLT due to the combination of cabozantinib and radiation were observed, but 3/6 (50%) patients required dose-reduction due to TRAE of cabozantinib alone. No grade ≥ 3 toxicities were attributed to RT, with most common grade 1-2 RT-related TRAE of fatigue and dry skin. The maximum tolerated dose (MTD) was not reached, and RP2D for the combination was cabozantinib 60mg. 6/6 (100%) of patients demonstrated stable disease 12 weeks after initiating therapy, and 5/6 (83%) underwent R0 resection. Relapse-free survival at a median follow up of 24.1 months was 50% (3/6). 2/6 (33%) of patients developed metastatic recurrence and 1/6 (17%) of patients died of unrelated causes, with no local recurrences.

Conclusion: In this phase 1 trial, concurrent cabozantinib and RT was safe and feasible for patients with extremity STS.

Table 1. Patient Demographics and Baseline Characteristics for All Patients (n=6)

Patient Characteristics	n (%)
Age, median (range)	53 (42-61)
Sex	
Male	3 (50)
Female	3 (50)
ECOG PS	
0	3 (50)
1	3 (50)
Histology	
Undifferentiated pleomorphic sarcoma	2 (33)
Myxofibrosarcoma	2 (33)
Leiomyosarcoma	1 (17)
Myxoid liposarcoma	1 (17)
Minimum FNCLCC grade	
1	1 (17)
2	4 (67)
Not assessed	1 (17)
Baseline longest-axis tumor size (mm), median (range)	75 (27-126)
Tumor location	
Proximal LE	3 (50)
Distal LE	2 (33)
Proximal UE	1 (17)

Abbreviations: ECOG PS = Eastern Cooperative Oncology Group Performance Status; FNCLCC = Fédération Nationale des Centres de Lutte Contre le Cancer; LE = lower extremity; UE = upper extremity

(P 288) IDENTIFICATION OF A DNA REPAIR INHIBITOR FOR THE COMBINATION WITH LURBINECTEDIN AND RADIOTHERAPY IN SARCOMA CELL LINES

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Objective: Improved multimodal treatment could optimize therapeutic outcomes for sarcoma patients. We performed radiochemotherapy (RCT) by combining the chemotherapeutic agent lurbinectedin (LU) with radiotherapy (RT) in sarcoma cell lines. Moreover, our goal was to identify an inhibitor of the DNA damage response in order to improve the efficacy of RCT.

Methods: We treated four sarcoma cell lines, namely SW-684 (fibrosarcoma), SW-872 (liposarcoma), SW-982 (biphasic synovial sarcoma), and TE-671 (rhabdomyosarcoma) with 0.5 nM LU chemotherapy (CT) and a single dose of 2 Gy or 3 Gy or fractionated regimen with 2x 3 Gy or 3x 2 Gy ionizing radiation (IR). Furthermore, we combined RT and RCT with two ATM inhibitors (ATMi) (M4076, AZD1390) and two ATR inhibitors (ATRi) (BAY-1895344, VE-822). We determined cell death (Annexin V/7AAD) and cell cycle distribution (Hoechst) with flow cytometry and clonogenicity by the colony formation assay to find a useful triple combination.

Results: Initially, we examined the effect of the combined treatment of LU and IR. LU increased cell death ($p=0.029$) in three of four cell lines and intensified G2/M arrest ($p=0.029$) in all cell lines compared to control, but the combined treatment with IR had no further radiosensitizing effect. In contrast, clonogenicity was significantly reduced in the fractionated RCT compared to CT alone (TE-671, 3x 2 Gy, $p=0.028$; SW-982, 2x 3 Gy, $p=0.007$). Secondly, we investigated the impact of different ATMi and ATRi in combination with a single dose of 2 Gy IR on cell death and cell cycle distribution. 5 μ M M4076, 0.7 μ M AZD1390, 50 nM BAY-1895344, and 1.5 μ M VE-822 significantly ($p=0.029$) increased cell death compared to IR alone in at least two of four cell lines. Finally, we combined the ATMi and ATRi with 0.5 nM LU and 2 Gy IR to identify the most suitable inhibitor for a triple therapy. 1.5 μ M VE-822 increased the amount of dead cells at least by 7 % in SW-872 and up to 27 % in TE-671.

Conclusion: Our preclinical data suggest that the combination of LU with RT has no sensitizing effect compared to LU treatment alone in sarcoma cell lines. However, combining LU and IR with DNA repair inhibitors such as the ATRi VE-822 is a promising way to improve sarcoma treatment.

(P 289) SIX YEAR FOLLOW-UP ON CIVASHEET® USE FOR SOFT TISSUE SARCOMA: A SINGLE INSTITUTION EXPERIENCE

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Objective: CivaSheet® is a palladium-103, implantable, intraoperative radiation therapy device which emits unidirectional radiation that enables boost doses in patients who have otherwise received the maximum radiation dose. Here, we present six year follow-up experience with this technology.

Methods: A retrospective chart review of all patients with STS treated with surgical resection and CivaSheet® placement at a tertiary care center from January 2018 to June 2025 was performed. Adjuvant radiation was administered by a palladium-103 implant, which delivered an average of 47 Gy (35-55) to a depth of 5 mm.

Results: Nine patients underwent CivaSheet® placement from January 2018 until December 2019 for a total of 10 CivaSheets® placed and followed for a mean of 45 months (4-76 months). 5 patients were alive at present analysis for an overall survival rate of 50%. Four tumors were located in the retroperitoneum, two in the chest, two in the groin, and two within the lower extremity. At the time of tumor resection and CivaSheet® placement, tumor sizes ranged from 2.5 cm to 13.8 cm with an average of 7.6 cm. Seven patients' tumors recurred locally for a local recurrence rate of 70%. Three patients had modified accordion grade 4 complications necessitating additional surgery for CivaSheet® removal. Extremity tumors unanimously developed modified accordion grade 4 adverse events.

Conclusion: On follow-up, CivaSheet® continues to be an acceptable alternative treatment modality for recurrent, non-extremity tumors.

(P 290) CLINICAL OUTCOMES AFTER RADIOTHERAPY FOR PATIENTS WITH POORLY DIFFERENTIATED CHORDOMA

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Objective: Poorly differentiated chordoma (PDC) is an aggressive malignancy, often requiring intensive multimodal therapy, including surgery, radiotherapy (RT), and systemic therapy. Little is currently known about the optimal treatment regimen and outcomes after RT for this disease.

Methods: This was an Institutional Review Board-approved retrospective study for patients diagnosed with PDC and who received RT at Massachusetts General Hospital between 2007-2024. Clinical and treatment characteristics were recorded. Kaplan-Meier method was used to assess overall survival (OS), progression-free survival (PFS), and local recurrence-free survival (LRFS). Cox regression model was used for univariate analyses (UVA). Toxicity was graded

using CTCAE v5.

Results: We identified 22 patients with median age at diagnosis of 11.0 years (range: 2-34.1). Sixteen patients (72.7%) were female. Primary tumor location included clivus/craniocervical junction (n=10), cervical/thoracic spine (n=11), and sacrum (n=1). Seven patients had metastases at diagnosis. Seven patients received gross total/near-total resections, 9 had subtotal resections, and 6 had biopsy alone prior to RT. Sixteen patients received pre-RT chemotherapy with median of 6.5 cycles (range: 1-17). Two patients had a complete response to pre-RT chemotherapy at the primary site and 10 had a partial response. Two patients had pre-operative RT and all received post-operative RT. Median RT total dose was 74.6 Gy (range: 66.6-79.4). The median time from diagnosis to RT was 8.6 months (range: 1.4-42.2). With a median follow-up time from end of RT of 39.8 months (range: 0.5-144.6), 3-year OS, PFS and LRFS after RT was 69.8%, 25.6% and 63.5%, respectively. Three patients (13.6%) had acute and 2 patients (9.1%) had late grade ≥ 3 toxicity, respectively. On UVA, metastatic disease at diagnosis (HR: 4.55, 95% CI: 1.42-14.59, $p=0.011$) and biopsy alone (HR: 4.42, 95% CI: 1.02-19.16, $p=0.047$) was associated with progression post-RT.

Conclusion: Patients with PDC remain at high risk of metastatic and local recurrence despite multimodality treatment, including RT. Patients with metastatic disease and biopsy alone are at higher risk of relapse after RT. Future studies with larger cohorts and multivariable analyses remain needed to better characterize outcomes for patients with PDC.

(P 291) INTRA-ARTERIAL CHEMOTHERAPY WITH CONCOMITANT RADIATION THERAPY FOR UNRESECTABLE SARCOMA

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Objective: We have performed intra-arterial chemotherapy with concomitant radiation therapy (IACRT) for long-term local control and symptom palliation of bone and soft tissue sarcomas which are large and not resectable in our institution. The objective of this study is to clarify the outcomes of IACRT.

Methods: Fifty sarcoma patients with mean age of 59.3 years who received IACRT at single institution from 2002 to 2024 were enrolled. We have retrospectively collected the patient characteristics, treatment details, radiological findings and clinical outcomes, and analyzed availability and issues of IACRT.

Results: Twenty-one bone and 29 soft tissue sarcomas were included. The tumor locations were the pelvis, lower extremities and chest wall, in 32, 17 and 1 case, respectively. The mean tumor size was 13.0 cm. The median follow-up period was 23.5 months, and oncologic outcomes were AWD/NED in 12 and DOD/DOOD in 38 patients. Forty-two patients received cisplatin as the most common drug used in IACRT, with a mean administration number of 4.1 times. Twenty-eight and 22 patients received photon and proton beam radiotherapy, respectively, with a mean total dose of 62.7 Gy(E). The 2-years and 5-years overall survival was 51.0% and 17.9%, and the local control rate was 65.0% and 35.7%, respectively. Nausea,

anemia and diarrhea as acute complications, and enteritis/bleeding and peripheral neurological disturbance as delayed complications were observed. Most alive cases (77.8%) showed 0 to 1 of performance status at the final observation. Statistical analyses revealed the local control was significantly related to patients' survival ($p=0.041$), and the intra-arterial administration number was an important factor ($p=0.001$). All 6 patients who survived more than 5 years (6.4-17 years) were without distant metastasis before treatment, 3 or more times of intra-arterial cisplatin, more than cumulative 200 mg/m², and a dose of 66 Gy(E) or more with proton beam therapy.

Conclusion: This study suggests that IACRT may be a promising treatment for unresectable sarcomas. Further study is needed to establish the indication and protocols of IACRT according to the purpose, and to search for biomarkers to predict treatment efficacy.

(P 292) CRANIOVERTEBRAL EWINGS SARCOMA WITH MENINGEAL INFILTRATION - A CLINICAL OUTCOME ANALYSIS

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Objective: Cranial and vertebral bones are uncommon site for primary Ewing's sarcoma (ES) to occur as a primary. We report the outcomes and patterns of failure of cranio-vertebral ES (CVES) with meningeal infiltration (intracranial or intraspinal component).

Methods: We conducted a retrospective audit of patients of CVES treated across two institutes of Tata Memorial Centre, Mumbai from 2011 to 2024, approved by the Institutional Ethics Committee. The diagnosis of CVES – cranial or vertebral origin and histological confirmation, was ratified in a multi-disciplinary tumor board. All patients were radiologically evaluated with localized MR spine and PET-CT for staging. Patients treated with curative intent Ewing's sarcoma chemotherapy regimen (VAC/IE based), focal radiotherapy (RT) and/or decompressive surgery were included in this study.

Results: Thirty-eight patients were eligible for the study with a median age 12 years (IQR: 7-14), 20 patients (52.6%) being males. Majority had a vertebral primary (89.5%, n=34 patients). Neurological deficits (motor weakness, sensory loss, bowel/bladder retention or incontinence) were seen in 20 patients at presentation. All patients underwent local MRI and whole-body PET-CT. Five patients had systemic metastases at presentation (lungs – 4, lymph nodes – 1) at presentation. Definitive RT was delivered to the primary in all patients with a dose of 45-55.8Gy in conventional fractionation. Of the 20 patients who had neurological deficits at presentation, 14 patients had almost complete recovery, while the remaining four patients had only partial recovery. The most common pattern in the 18 patients who had a relapse was local recurrence (7) followed by systemic metastases (6), CNS dissemination (2) and combined (3: local

recurrence + systemic/ local recurrence + CNS dissemination). At the time of analysis, 22 patients were alive (including two with disease). The 5-year local control (LC), progression free survival (PFS) and overall survival (OS) were 69.1 + 9.5%, 50.2 + 9.4% and 65 + 9.2%, respectively.

Conclusion: CVES is a rare and high-risk presentation of Ewing's sarcoma with outcomes inferior to other primary sites. While local and systemic failures remain predominant, CNS dissemination—though less frequent—is a noteworthy pattern of relapse.

(P 293) CRYOABLATION FOR EXTRA-ABDOMINAL DESMOID TUMORS: A RETROSPECTIVE STUDY OF RADIOLOGIC AND CLINICAL OUTCOMES

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Objective: Desmoid tumors are locally aggressive soft tissue neoplasms with high local recurrence. Image-guided cryoablation has emerged as a minimally invasive treatment option. This study aimed to assess radiologic response, clinical success, and treatment-related complications of cryoablation for extra-abdominal desmoid tumors.

Methods: Patients with desmoid tumors treated between 2020 and 2024 were identified using the Alberta electronic medical record. Those who underwent image-guided cryoablation were included for analysis. The primary outcomes were radiologic response, clinical success, and complications. Radiologic response was assessed using volumetric measurements on contrast-enhanced MRI. Clinical success was defined as no disease progression, no need for additional treatment, and symptom improvement. Repeat cryoablations were allowed.

Results: Of 208 patients with desmoid tumors, 44 (20.7%) underwent cryoablation, and 38 had available data for analysis. A total of 92 cryoablation sessions were performed. Median tumor size was 6.9 cm (IQR 5.5–9.3), and median follow-up was 28.9 months (IQR 14.3–37.3). Among patients treated exclusively with cryoablation, radiologic response was complete in 27.3%, partial in 57.6%, stable in 12.1%, and progressive in 3.0%. Unplanned repeat cryoablations were performed in 26.3% of patients. The overall clinical success rate was 81.6%. Additional treatment modalities were required in 13.2% of cases following cryoablation. Complications occurred in 21.1% of patients, with 10.5% classified as Grade ≥3. These included two cases of severe pain, one hemorrhage and one skin necrosis requiring grafting.

Conclusion: Cryoablation is a safe and effective treatment option for selected patients with desmoid tumors, demonstrating favorable tumor control and high rates of symptom improvement. These findings support its role in the multidisciplinary management of desmoid tumors

(P 294) RISK FACTORS FOR RECURRENCE AND COMPLICATIONS OF CT-GUIDED RADIOFREQUENCY ABLATION FOR THE TREATMENT OF OSTEIOD OSTEOMA: A MULTI-INSTITUTIONAL ANALYSIS.

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Objective: Radiofrequency ablation (RFA) is the gold standard for treating symptomatic osteoid osteoma (OO), yet risk factors for recurrence and complications remain poorly understood. This study aimed to identify predictors of recurrence and local complications following RFA.

Methods: A retrospective cohort study of OO patients treated with RFA at two academic medical centers between 2010 and 2024 was conducted. Primary outcomes were recurrence—defined as the return of symptoms with radiological confirmation—and post-procedural complications. Secondary outcomes included clinical success (complete pain resolution) and technical success (procedure done according to protocol). Descriptive, univariable, multivariable, and survival analyses were performed, with a sub-analysis of anterior tibial lesions.

Results: A total of 272 patients were included. Median age was 20 years, and 69.5% of patients were male. The most common locations for OO were the femur (41.9%), tibia (26.5%), and foot (11.4%). The median tumor size was 7 mm. Recurrence occurred in 5.5% of cases, with spinal location as a risk factor (odds ratio [OR] = 6.22; $p = 0.048$). Complications were observed in 4% of patients, with increased risk in females (OR = 5.17; $p = 0.01$) and those with tibial lesions (OR = 13.23; $p = 0.02$). In tibial lesions, an anterior approach with the RFA probe was associated with a higher rate of wound infection (100% vs. 0%; $p = 0.03$).

Conclusion: RFA is a highly effective treatment for OO, with low rates of recurrence and complications. The identified risk factors underscore the need for tailored treatment plans. Furthermore, the anterior tibial approach should consistently incorporate a soft tissue buffer to minimize the risk of wound infection.

(P 295) FROM HISTORICAL REFERENCE TO MODERN PRACTICE: WOUND COMPLICATION RATES IN SOFT TISSUE SARCOMA TREATED WITH RADIOTHERAPY ACROSS ERAS

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Objective: Conventional preoperative radiotherapy for soft tissue sarcomas (STS) has historically been associated with a 35% wound complication rate, as reported in the Canadian SR-2 trial in 2002. However, over the past two decades, more recent studies with further advanced radiation techniques suggest a decrease in wound complications with this treatment approach. This study aims to investigate whether the incidence of major wound complications has changed in recent years.

Methods: Patients were included if they were treated with preoperative radiotherapy with a regimen of 25 x 2 Gy between May 2003 and September 2024 in a curative setting. Data was collected on major wound complications within 120 days post-surgery and factors potentially influencing these wound complications. To assess changes in the percentage of wound complications in recent years, patients were stratified into two groups based on treatment date: before 2015 and from 2015 onwards, reflecting the broader adoption of image guided radiotherapy and intensity modulated radiotherapy. To assess differences in wound complications between these time periods, a multivariable logistic regression model was estimated, to adjust for potential confounders. Statistical analyses were performed in SPSS (30.0.0.0).

Results: In total, 155 patients were included, 84 (54.2%) and 71 (45.8%) patients were treated before 2015 and after 2015 respectively. Overall, 41 Patients experienced a major wound complication. The complication rate was 28.6% in the group treated before 2015 and 23.9% from 2015 onwards. Adjusted odds ratio (OR) with 95% confidence interval (CI) for the period was not significant (OR: 1.59 (95% CI 0.62–4.09). Confounding incorporated in the model were sex, age, smoking status, hypertension, adiposity, diabetes mellitus, tumor grade and histology, tumor location and size, and the interval between the last fraction of radiotherapy and surgery.

Conclusion: Our results shows no significant difference in major wound complications following preoperative conventional radiotherapy for STS since 2015. More studies are now focusing on hypofractionation to assess oncological outcomes and treatment-related toxicities. To allow a more accurate comparison between conventional and hypofractionated radiotherapy in terms of wound complications, a head-to-head comparison in a randomized phase II trial is needed to clarify the impact of modern radiotherapy and surgical techniques on wound complication rates.

(P 296) PULMONARY CEMENT EMBOLISM ASSOCIATED WITH PERCUTANEOUS CEMENTOPLASTY FOR BONE METASTASIS: MECHANISMS AND PROTECTIVE FACTORS

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Objective: Minimally invasive percutaneous cement injection is a valuable palliative technique for managing symptomatic pelvic bone metastases in advanced cancer, offering significant pain relief. However, the risk of pulmonary cement embolism remains poorly understood. This study aimed to identify its mechanisms and potential protective factors to inform safer clinical practice.

Methods: We retrospectively analyzed data from 208 patients who underwent percutaneous cementoplasty for pelvic metastatic lesions between 2008 and 2024. After excluding 50 patients without perioperative computed tomography (CT), 158 were included. We reviewed preoperative factors related to tumor vascularity and intraosseous pressure during cement injection. From 2021 to 2023, a decompression needle was used to maintain intraosseous pressure below 10 kPa. Pulmonary cement embolism was assessed using pre- and postoperative CT imaging.

Results: Pulmonary cement embolism occurred in 20 patients (12.7%). Hypervascular tumors—hepatocellular carcinoma and thyroid cancer—were significantly associated with embolism ($p=0.05$). Pre-injection radiation therapy showed a protective effect ($p=0.02$). Intraosseous pressure and other variables were not significantly associated with cement embolism risk.

Conclusion: Pulmonary cement embolism appears to be more closely related to tumor vascularity than to intraosseous pressure during injection. Extra caution is needed when treating hypervascular tumors. Where feasible, radiation therapy prior to cementoplasty may reduce embolism risk and should be considered as a protective strategy.

(P 297) ANALYSIS OF CTDNA KINETICS IN PATIENTS WITH METASTATIC LEIOMYOSARCOMA UNDERGOING LOCOREGIONAL PROCEDURAL INTERVENTION

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Objective: In patients affected with metastatic leiomyosarcoma (LMS), locoregional interventions are often undertaken to maximize disease control and palliate symptoms. Circulating tumor DNA (ctDNA) in the blood are a promising non-invasive modality to assess changes in disease burden in real time. Data are needed to guide interpretation of ctDNA kinetics peri-intervention to assess their correlation with patient outcomes.

Methods: This retrospective study includes patients with metastatic LMS who underwent locoregional procedures (surgery, radiation, ablation, or embolization) at Stanford Sarcoma Center between October 2020 and June 2025. Blood samples were collected as part of routine clinical care, and ctDNA analysis was performed using a clinically validated, personalized, tumor-informed mPCR-NGS assay (Signatera, Natera, Inc). Progression was identified by routine imaging (CT or MRI). Patients who had ctDNA assessed within 8 weeks prior to locoregional procedure and a second ctDNA level within 8 weeks after the procedure were included in the analysis. If the same patient had multiple procedures with serial ctDNA collection, the earliest procedure was included to maximize follow-up.

Results: Forty-seven patients with metastatic LMS were included in the analysis, median age at diagnosis 55 (range 29 – 74 years), 89% female, 62% uterine. Nearly half underwent surgical metastasectomy/debulking (53%); the remaining underwent radiation (30%), ablation (9%), or embolization (6%). Patients underwent baseline ctDNA collection at median of 26 days (range 0 – 56) prior to procedure and follow-up ctDNA collection at median 25 days after the procedure (range 2 – 55 days). At median follow-up of 14.1 months (range 0.5 – 50.7 months), median progression-free survival (PFS) for the entire cohort from date of procedure was 5.6 months

(95% CI 4.4 – 10.2 months), and median overall survival (OS) from date of procedure was 50.7 months (95% CI 32.8 – not reached). Compared to patients who had decline or unchanged ctDNA level, patients who experienced any rise in ctDNA level (n = 15 or 32%) had worse PFS (ctDNA rise vs no rise: 3.6 months vs. 6.1 months, p = 0.03). Median OS was not statistically different between the two groups (ctDNA rise vs no rise: 50.7 months vs not reached, p = 0.3).

Conclusion: Our results suggest that rise in ctDNA in the blood within 8 weeks after locoregional intervention correlates with worse outcomes. Studies are underway to assess these findings in a prospective design.

(P 298) RESECTION OF PARA-RENAL INFERIOR VENA CAVA LEIOMYOSARCOMA WITH RIGHT NEPHRECTOMY AND LEFT RENAL VEIN LIGATION WITHOUT VENOUS RECONSTRUCTION.

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Objective: Leiomyosarcomas (LMS) of the inferior vena cava (IVC) often require segmental vascular resection. When both renal pedicles are involved in the tumour, enbloc right nephrectomy and left renal vein (LRV) ligation may be necessary to achieve negative margins. Whether LRV reconstruction is required in this context remains unclear. This study evaluates perioperative renal outcomes and safety following IVC resection, right nephrectomy, and LRV ligation without reconstruction in LMS.

Methods: A retrospective review of patients undergoing IVC LMS resection between 2010 – 2024 at a high-volume sarcoma unit.

Results: 46 patients underwent IVC resection for LMS; 20 (43 %) had IVC reconstruction with graft, 26 (57 %) had ligation of the IVC without reconstruction. Among them, 18 (39%) required both right nephrectomy and LRV ligation without reconstruction.

The overall complication rate (Clavien-Dindo ≥ 3) was 19% (9/46), with median length of stay (LOS) of 13 days. In the LRV ligation subgroup, complication rate was 33%, median LOS 13 days.

Of the 18 patients with LRV ligation, 14 (78%) had either no renal dysfunction n=4 (22%), or transient impairment managed conservatively n=10 (56%). In these 14 patients, serum creatinine peaked on postoperative day (POD) 2 (mean 169 $\mu\text{mol/L}$) and decreased significantly by POD10 (mean 122 $\mu\text{mol/L}$) consistent with recovery of renal function. 4 (22%) patients required short-term hemofiltration starting POD 1-3 with median duration of 7 days. Further improvement in renal function was seen at 1-month follow up confirming the reversible nature of the renal impairment. No patient required long-term dialysis (Table 1).

No significant difference in OS (p=0.349) and DFS (p=0.233) was found between patients with or without LRV reconstruction.

Conclusion: LRV ligation without reconstruction, even when combined with right nephrectomy, is safe and well-tolerated in patients undergoing IVC LMS resection. Most patients develop sufficient venous collaterals, and renal dysfunction is mild, reversible, and not associated with

adverse oncologic outcomes.

Mean serum creatinine (μmol/L) after surgery for LMS IVC with right nephrectomy and LVR ligation in patients with vs. without postoperative hemofiltration

Postoperative Day	Creatinine (μmol/L) (95%CI); No Hemofiltration (n=14)	Creatinine (μmol/L) (95%CI); Hemofiltration (n=4)
POD 1	139 (114-165)	236 (167-306)
POD 2	169 (129-209)	425 (282-568)
POD 3	162 (104-219)	464 (212-717)
POD 5	152 (93-210)	314 (16-612)
POD 7	129 (88-169)	233 (206-260)
POD 10	122 (76-167)	300 (90-509)
1-Month Follow-up	102.5 (88-116)	130 (65-195)

(P 300) FEATURES AND OUTCOMES OF PATIENTS WITH GASTROINTESTINAL LEIOMYOSARCOMA

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Objective: Gastrointestinal (GI) leiomyosarcomas (LMS) are aggressive spindle cell neoplasms from GI smooth muscle. The incidence is low and limited to a few case series. This study evaluated treatment (tx) and outcomes of patients (pts) with GI LMS.

Methods: We performed a chart review for pts aged 18 and above with GI LMS from 1/1/00 to 12/31/24 treated at Mayo Clinic.

Results: Twenty-nine pts had GI LMS. Ten (34.5%) were female, median age was 67 years (range 35 – 81 yrs). Twenty-one (72.4%) pts had symptoms: GI bleed (8/29, 27.6%), abdominal pain (8/29, 27.6%), and odynophagia (3/29, 10.3%). Most common site was small intestine (11/29, 37.9%) followed by stomach (8/29, 27.6%), colorectal (5/29, 17.2%), and esophagus (5/29, 17.2%). Median tumor size was 5.8 cm (0.7 – 25 cm).

Of pts with localized disease (n=25), 24 had surgery (sx). One pt had neoadjuvant chemotherapy (chemo); 1 had neoadjuvant radiation therapy (RT). One pt received adjuvant chemo. One pt with esophageal LMS had definitive RT with stable scans 6 yrs later.

Seven (28%) pts relapsed, median relapse-free survival was 7 months (range 5 – 20). Of these, 1 (14.2%) had local and 6 (85.7%) had distant recurrence, most commonly to liver. Six (85.7%)

pts received tx for recurrence, one pursued hospice. Three pts received chemo; 2 pts had sx, and 1 pt had RT followed by gastrectomy. Three pts died from recurrent LMS. Median overall survival (OS) for pts with localized disease was 40 months (range 3 – 290).

Four (13.8%) of 29 pts had metastatic disease at diagnosis (Table 1). Of these, 3 had chemo, 1 had RT, and 1 had sx. Median OS was 20 months (range 10 – 30).

Conclusion: In this cohort of GI LMS, pts with localized disease had favorable outcomes, and few relapsed within the first two years of surgery. Perioperative chemo or RT was uncommon. Outcomes for localized LMS originating in GI tract appear more favorable compared to other sites.

Table 1: Pts with metastasis at dx

Pt	Age	Sex	Primary site	Tumor size (cm)	Initial tx	Subsequent tx	OS (months)
1	74	F	Small intestine	10	Gemcitabine	Cyclophosphamide/topotecan	26
2	68	M	Esophagus	11	Dacarbazine/ifosfamide, RT	Doxorubicin/ifosfamide Pazopanib	14
3	50	M	Esophagus	10	Partial esophagogastrectomy, liver resection, doxorubicin/ifosfamide	Gemcitabine Temozolomide Trabectedin Pazopanib Eribulin	30
4	80	M	Small intestine	2	None		10

(P 300) RECURRENCES AFTER PRIMARY RPS SURGERY IN A HIGH-VOLUME SARCOMA CENTER: A RETROSPECTIVE ANALYSIS ON 402 PATIENTS

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Objective: The objective of this study was to evaluate the treatment strategies and outcomes for recurrences of primary retroperitoneal sarcomas (RPS) in a high-volume sarcoma center.

Methods: We conducted a retrospective review of all consecutive patients who underwent surgery for RPS at our tertiary care center between 1994 and 2024. Recurrences were defined as local if they occurred at the surgical site or within the peritoneum, and distant otherwise.

Survival outcomes were estimated using Kaplan-Meier methods from the date of diagnosis and compared using the log-rank test. A Cox proportional hazards model and competing risk analysis were also employed.

Results: A total of 402 patients were included, with a median age of 60 years at diagnosis. Histologic subtypes included 30% well-differentiated liposarcoma (WDLPS), 49% dedifferentiated liposarcoma (DDLPS), 16% leiomyosarcoma (LMS) and other (12% high-grade, 4% low-grade). Preoperative chemotherapy and radiotherapy were administered in 14% and 11% of patients, respectively. Postoperative chemotherapy and/or radiotherapy was given to 17% of patients. After a median follow-up of 90 [79–102] months, the median overall survival (OS) was 16 [11–not reached] years and the median disease-free survival (DFS) was 7,9 [7,25–9,25] years. In the competing risk analysis stratified by histologic subtype, LMS was associated with the highest risk of distant recurrence, and DDLPS with the highest risk of local recurrence. 184 patients (46%) experienced recurrence. Among the 137 patients with local recurrence, 30% underwent surgery, 48% received chemotherapy, 23% radiotherapy and the median OS was 32 [23–58] months. Among the 80 patients with distant recurrence 25% were treated surgically, 48% with chemotherapy, 31% with radiotherapy and the median OS was 29 [22–53] months.

Conclusion: This study provides one of the largest single-center analyses of recurrence after primary RPS surgery. While primary surgery achieves good initial disease control, both local and distant recurrences remain associated with poor survival outcomes.

(P 301) RETROPERITONEAL SARCOMA: SINGLE CENTER EXPERIENCE IN LATIN AMERICA. DO WE HAVE DIFFERENT SARCOMAS WHEN COMPARED TO THE REST OF THE WORLD?

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Objective: Retroperitoneal sarcomas are rare tumors and international collaborations have been the main instrument for understanding tumor biology and prognosis. In this study we aim to describe the characteristics of patients with retroperitoneal sarcomas at our institution and compare them to those reported around the globe.

Methods: This is an observational retrospective study of retroperitoneal sarcoma patients who were surgically treated at Fundación Colombiana de Cancerología Clínica Vida in Medellín, Colombia, from 2016 to 2025. Categorical variables: absolute/relative frequencies. Numerical variables: medians, interquartile ranges [IQR]. 5-year overall survival (OS) and relapse-free survival (RFS) estimated via Kaplan-Meier. Cox proportional hazards regression identified OS/RFS-associated factors. A nonsystematic review of the literature was performed, and data from around the globe was compared to the present data.

Results: Seventy-four patients were included: 63.5% women, median age 61 [IQR: 50.2–69] years. Median size is 15 [IQR: 11.7–20] cm. Most frequent histological subtypes:

dedifferentiated liposarcoma (37.8%), well-differentiated liposarcoma (36.5%), and leiomyosarcoma (12.2%). Histological grade I was 32.6%, grade II 18.3%, and grade III 48.9%. Median follow-up 24 [IQR: 11-47] months. 5-year OS: 54% (95% CI: 42–70); RFS: 44% (95% CI: 31–62). Histology other than well-differentiated liposarcoma and intraoperative blood transfusions were associated with worse OS and RFS.

Conclusion: When compared to The Transatlantic Australasian Retroperitoneal Sarcoma Working Group (TARPSWG) and other European and North American databases, we have more women with retroperitoneal sarcomas but a similar proportion when compared to a recently published report from Brazil. The histological distribution is similar to TARPSWG, but we have fewer leiomyosarcomas when compared to North America. We had a proportion of grade III sarcomas close to 50%, higher than TARPSWG and other European series but similar to Latin and North American reports. We have a lower median follow-up time compared to most series and lower OS when compared to TARPSWG but similar to the USA, UK, and Mexico.

(P 302) PREDICTORS AND OUTCOMES OF RECURRENT RETROPERITONEAL SARCOMA: A SINGLE-CENTER LATIN AMERICAN COHORT STUDY

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Objective: Retroperitoneal sarcomas (RPS) are rare mesenchymal tumours arising in the retroperitoneal space, accounting for approximately 15% of all soft-tissue sarcomas and characterised by diverse histologic subtypes and typically large tumour size. Tumour-specific factors—most notably high histologic grade, increasing tumour size, and specific subtypes such as leiomyosarcoma and dedifferentiated liposarcoma—have been consistently associated with an elevated risk of distant recurrence, which negatively impacts long-term survival. Despite advances in surgical technique, systemic recurrence rates remain substantial and portend a poor prognosis.

Methods: We performed a retrospective cohort analysis of 142 adult patients (mean age 51.7 ± 14.0 years; 54.2% male) with histologically confirmed primary (n = 103) or recurrent (n = 39) RPS who underwent curative-intent resection between January 2019 and December 2024 at a single high-volume tertiary referral centre in Latin America. Baseline data included demographics, histologic subtype, FNCLCC grade, maximum tumour diameter, margin status, and presence of histologically confirmed vascular invasion. Systemic recurrence-free survival (SRFS) and overall survival (OS) were estimated by Kaplan–Meier methods.

Results: Median follow-up was 39 months (IQR 22–63). Systemic recurrence occurred in 17 patients (12.0%) at a median interval of 40 months (IQR 28–62). In univariate analysis, FNCLCC grade III (vs I–II), recurrent presentation, and tumour size > 20 cm were associated with shorter SRFS. In multivariate analysis, only high histologic grade remained an independent predictor of systemic recurrence (hazard ratio [HR] 3.12, 95% CI 1.45–6.71; p = 0.003), with the highest recurrence rates observed in leiomyosarcoma (15.6%) and dedifferentiated liposarcoma (13.8%) subgroups. Histologic subtype per se was not predictive of systemic recurrence unless coupled with high grade, and organic invasion was not associated with recurrence risk in our cohort (p = 0.56). Five-year OS was 67%.

Conclusion: In this single-centre Latin American cohort, high histologic grade—but not histologic subtype alone—was the principal determinant of systemic recurrence in RPS, particularly in leiomyosarcoma and dedifferentiated liposarcoma. Histologically confirmed organic invasion did not predict recurrence.

(P 303) MULTIVISCERAL RESECTIONS AND URINARY TRACT RECONSTRUCTION TECHNIQUES IN THE SURGERY OF RETROPERITONEAL SARCOMAS: A CASE SERIES.

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Objective: Surgical management of retroperitoneal and pelvic soft tissue sarcomas aims for complete (R0) resection, often requiring complex multivisceral procedures. While nephrectomy - performed in more than 50% of cases - is among the most common organ resections during retroperitoneal sarcoma surgeries, en-bloc resection of the urinary tract structures, including the bladder, ureter, and prostate, is considerably rarer, occurring in less than 5% of cases. Owing to its rarity and the complex anatomical location, surgical strategies for urinary tract reconstruction are challenging and not yet standardized.

Methods: This case series aims to present various surgical reconstruction techniques following nephrectomy, partial cystectomy, and prostatectomy and autologous kidney transplantation during sarcoma resections. Five complex cases were analyzed from a total of 46 retroperitoneal and pelvic sarcoma surgeries performed at the Sarcoma Center Mannheim between December 2023 and January 2025.

Results: The analysis included three retroperitoneal dedifferentiated liposarcomas and two pelvic sarcomas—one leiomyosarcoma and one epithelioid sarcoma of the prostate (Table 1). Continence-preserving reconstruction was performed in all cases and kidney preservation were also achieved in all cases. One case required autologous kidney transplantation into the iliac fossa due to semicircumferential tumor contact with the ureter, despite no evidence of direct renal infiltration. In the remaining cases, ureteral involvement was managed using a psoas hitch procedure, and partial bladder resections with direct suturing reconstruction. For the prostatic sarcomas, a primary vesicourethral anastomosis was performed.

Conclusion: Resection of retroperitoneal and pelvic soft tissue sarcomas often necessitates nephrectomy or partial resection of the urinary tract. Reconstruction poses a surgical challenge and requires close collaboration between urologic and visceral surgery teams, utilizing a range

of established techniques—from direct suturing and psoas hitch procedures to autologous kidney transplantation.

Case summary

Tumor Location	Subtype, FNCLCC Grading	Sex	Age (years)	Neoadjuvant Therapy	Extent of Resection	Reconstruction	Postoperative Course
Retroperitoneum	Dedifferentiated Liposarcoma, G2	Male	46	Proton therapy (39 Gy)	Right nephrectomy + ureterectomy Right adrenalectomy Right hemicolectomy Spermatic cord resection Resection of the diaphragm muscle Abdominal wall resection Diaphragm resection	Autotransplantation of the ex vivo prepared kidney into the right iliac fossa Hemitransversostomy Diaphragm suture	No complications. 6 weeks after surgery: Good kidney function (creatinine 1.06 mg/dL), no urinary obstruction.
Retroperitoneum	Dedifferentiated Liposarcoma, G3	Male	72	Proton therapy (39 Gy)	Left distal ureterectomy Iliopsoas muscle resection Preserving femoral and obturator nerves Left hemicolectomy Partial resection of iliac vein	Psoas hitch procedure Transversorectostomy with protective ileostomy Iliac vein bypass using Vascuguard	Anastomotic leakage → transverse colectomy Recurrent urinary tract infections GJ stent occlusion with enterostomy → GJ replacement, ureteric catheter
Retroperitoneum	Dedifferentiated Liposarcoma, G2	Male	41	None	Resection of Gerota's fascia encircling the left kidney Long segment ureterectomy Partial bladder resection Left hemicolectomy Diaphragm resection	Simple closure by running suture Transversorectostomy Diaphragm suture	No complications. Cystogram on POD 7 without extravasation
Pelvis (Prostate)	Leiomyosarcoma, G2	Male	76	None	Radical prostatectomy Right seminal vesicle resection	Vesicourethral anastomosis	No complications. Cystogram on POD 7 without extravasation
Pelvis (Prostate)	Epithelioid Sarcoma, G3	Male	32	Chemotherapy (Doxorubicin/ Irinotecan, 6 cycles) Proton radiation (48 Gy)	Radical prostatectomy Seminal vesicle resection Resection of anterior rectal wall	Vesicourethral anastomosis Anterior rectal wall suture with protective ileostomy	No complications. Cystogram on POD 14 without extravasation.

(P 304) MANAGEMENT OF RECURRENT RETROPERITONEAL SARCOMAS: A RETROSPECTIVE STUDY FROM A TERTIARY CANCER CENTER.

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Objective: Retroperitoneal sarcoma (RPS) is a rare and complex malignancy, requiring specialized multidisciplinary care. While significant progress has been made in managing primary RPS, limited literature exists on the outcomes of recurrent RPS (Rec RPS). This study audits the oncological outcomes of Rec RPS at a leading sarcoma referral center in India, addressing gaps in the existing literature

Methods: A retrospective analysis was performed on patients with Rec RPS who underwent surgery between January 2011 and December 2024. . Surgical procedures included compartmental resections, en bloc resections, vascular resections, and tumor excisions. Histopathological assessment, organ invasion analysis, and adjuvant therapy utilization were recorded. Kaplan-Meier estimates evaluated overall survival (OS) and disease-free survival (DFS), with statistical significance assessed via log-rank test and Cox regression analysis.

Results: The study analyzed 288 patients, with 188 undergoing primary surgery at an oncological center and 100 previously operated elsewhere. Recurrence rates were significantly higher (93.9%) in patients who had inadequate surgery at non-oncological centers compared to those initially treated at specialized centers (39.1%). Histological subtypes included

dedifferentiated liposarcoma (DDLPS) (32.3%), well-differentiated liposarcoma (WDLPS) (23.9%), and leiomyosarcoma (LMS) (23.4%). Histopathologic organ invasion (HOI) was identified in 47% of recurrent cases, with colon, kidney, and small intestine being most affected. Median OS for primary RPS was 137.1 months, while Rec RPS had significantly reduced survival at 42.48 months ($p=0.002$). DFS was notably lower in recurrent cases, particularly in patients who had undergone prior inadequate surgery. Patterns of recurrence impacted survival outcomes, with distant recurrence and sarcomatosis associated with worse prognosis. On multivariate analysis, factors influencing recurrence included margin status, HOI, and receipt of adjuvant therapy.

Conclusion: Surgery for recurrent RPS remains a viable option, particularly in the early stages of recurrence. Inadequate initial resections lead to significantly higher recurrence rates and worse survival outcomes. The study underscores the importance of initial treatment at specialized centers, multidisciplinary management, and personalized surgical strategies in improving survival rates in Rec RPS

(P 305) COMPARISON OF GOAL-DIRECTED VERSUS EMPIRICAL TRANSFUSION MANAGEMENT IN PATIENTS WITH SEVERE HEMORRHAGE DURING RETROPERITONEAL TUMOR SURGERY

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Objective: Retroperitoneal tumor resection carries a high risk of severe hemorrhage and coagulopathy, necessitating optimal transfusion strategies. Conventional empirical transfusion protocols lack precision, potentially leading to over- or under-transfusion. This study evaluated the efficacy of goal-directed transfusion management guided by the Century Clot® coagulation and platelet function analyzer (CPA) compared to empirical transfusion in patients undergoing retroperitoneal tumor surgery with massive bleeding.

Methods: This retrospective cohort study included patients who underwent retroperitoneal tumor resection at Peking University International Hospital (January 2019–May 2024) with intraoperative blood loss exceeding 20% of total blood volume. Patients were divided into a goal-directed group ($n=127$), managed using CPA-guided thresholds for fresh frozen plasma (FFP), fibrinogen (FIB), prothrombin complex concentrate (PCC), and platelet (PLT) transfusions, and a control group ($n=254$), receiving empirical 1:1 RBC: FFP ratio transfusions. Outcomes included intraoperative blood product utilization, postoperative complications, and hospitalization duration.

Results: Baseline characteristics, operative duration, and blood loss were comparable between groups. The goal-directed group demonstrated significantly lower intraoperative use of FFP (median 400 vs. 600 mL, $P<0.05$), FIB (0 vs. 0–1 g, $P<0.001$), and PCC (0 vs. 0–550 IU, $P<0.001$), with no difference in RBC transfusion ($P>0.05$). Postoperative complication rates (acute kidney injury, deep vein thrombosis, Clavien-Dindo grade ≥ 3 , and mortality) were similar ($P>0.05$). However, the goal-directed group had shorter median postoperative (16 vs. 20 days,

P< 0.001) and total hospitalization (28 vs. 31 days, P< 0.001).

Conclusion: CPA-guided transfusion reduced FFP, FIB, and PCC utilization without increasing complications, while significantly shortening hospitalization. These findings support integrating viscoelastic testing into transfusion protocols for major surgeries with high bleeding risk. Prospective studies are needed to validate long-term outcomes and cost-effectiveness.

(P 306) PROGNOSTIC NUTRITIONAL INDEX PREDICTS MAJOR POSTOPERATIVE COMPLICATIONS IN RETROPERITONEAL SARCOMA: RESULTS FROM THE LATAMSARC COHORT

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Objective: Retroperitoneal sarcomas (RPS) are rare malignancies requiring complex, often multivisceral surgical resections. Despite curative-intent procedures, postoperative morbidity remains high. Identifying preoperative risk factors is crucial for enhancing patient selection and perioperative care. The Prognostic Nutritional Index (PNI) is a simple immunonutritional biomarker that is increasingly recognized in oncologic surgery; however, its utility in RPS has not been firmly established.

To assess whether preoperative PNI is associated with major postoperative complications and survival outcomes in patients undergoing surgery for RPS.

Methods: A multicenter retrospective analysis was conducted, including 71 patients with histologically confirmed primary or recurrent RPS who underwent surgical treatment between January 2022 and December 2024 at Latin American centers participating in the LATAMSARC consortium. The optimal PNI cutoff to predict major complications was defined by ROC analysis using Youden's index. Patients were stratified into two groups based on PNI: low (≤ 33.0) and high (> 33.0). Associations with significant postoperative complications (Clavien-Dindo grade $\geq$ III) were assessed using multivariable logistic regression. Kaplan–Meier estimates were used to evaluate survival.

Results: The cohort included 53.5% males, with a median age of 53 years. The most frequent histology was liposarcoma (74.6%). Most patients underwent extended resections (49.3%) and multivisceral surgery (median 3 organs resected). The optimal PNI cutoff was 33.0 (AUC 0.899, 95% CI: 0.802–0.996). Major complications occurred in 12.7% of patients. Those with low PNI had a significantly higher complication rate (16.0% vs. 5.4%, $p = 0.047$). In multivariable analysis, low PNI remained independently associated with significant complications (OR 3.45, 95% CI: 1.01–11.79, $p = 0.048$). The median disease-free survival was 38.0 months (95% CI: 28.7–47.3), and the mean overall survival was 36.9 months (95% CI: 33.7–40.0).

Conclusion: A preoperative PNI ≤ 33.0 was independently associated with a threefold increase in the risk of major postoperative complications. This finding has practical implications for the perioperative care of RPS patients. However, low PNI was not significantly associated with worse overall or disease-free survival. PNI may represent a valuable, accessible tool to guide perioperative decision-making and individualized optimization strategies in retroperitoneal sarcoma surgery.

Table 1. Demographic characteristics of the 71 patients included in the LATAMSARC cohort

Table 1. Demographic characteristics of the 71 patients included in the LATAMSARC cohort		
Variable	n	%
Mean age (years)	52.8 (SD 13.3)	
Male	38	53.5
Female	33	46.5
ECOG 0	32	45.1
ECOG 1	34	47.9
ECOG 2	5	7.0
No comorbidities	45	63.4
Diabetes Mellitus	7	9.9
Hypertension	13	18.3
Primary	58	81.7
Recurrent	13	18.3
Retroperitoneal location	54	76.1
Pelvic location	17	23.9
Liposarcoma	53	74.6
Leiomyosarcoma	11	15.5
Other histologic subtypes	7	9.9
Grade G1	27	38.0
Grade G2	5	7.0
Grade G3	38	53.5
R0/R1 margin	69	97.2
R2 margin	2	2.8
Vascular invasion	16	22.5
Neoadjuvant treatment (any)	14	19.7
Extended/compartamental resection	35	49.3
Median number of organs resected	3.0 (SD 2)	
Significant weight loss $\geq 10\%$	19	26.8
Major complications ($\geq$ Clavien-Dindo grade II)	9	12.7
ICU admission	28	39.4

(P 307) STRATEGIES FOR DATA QUALITY IN TARPSWG RETROPERITONEAL SARCOMA REGISTRY (RESAR)

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Objective: RESAR is a resource created by TARSPWG members for prospective data collection on patients with primary retroperitoneal sarcoma managed at referral centers (NCT03838718). Launched in 2017 with local prospective data collection, the registry then was

later centralized and, since 2023, data are entered directly online. As of 06/2025, 3,384 de-identified patient records are included. Data consistency and completeness, across >30 centers are supported by specific quality procedures, herein described.

Methods: The joint efforts of participating centers and IT teams built a comprehensive dataset. Whenever possible, predefined values list ensured consistency. Robust IT support enabled local data import into a centralized platform, facilitating data integration. Semiautomatic quality checks flagged disallowed values, temporal inconsistencies and outlier values to enhance data accuracy and integrity at entry.

Results: Data entry onto the RESAR platform is a collaborative process involving interdisciplinary teams and requires accurate interpretation of complex datasets. An Executive Committee keeps local PIs informed via newsletters and provides SOPs for data entry. Following the March 2025 review, we recognized the need to establish a core of mandatory data fields to define minimum criteria for patient evaluability, as established by the RESAR Governance Committee. We also introduced a three-month time limit between patient enrollment and data entry, to ensure prospectivity. Regular webinars will support data entry teams and promote adherence to these standards. The aim is to establish open communication among personnel involved in data entry across centers, to achieve a shared standard for data completeness, ultimately ensuring high data quality. Publication of a position statement on pathology specimen evaluation and standard reporting is also underway to ensure data consistency across centers. In addition, routine quality checks on incomplete or outdated follow-up will be sent to local PIs by the RESAR Clinical Research Coordinator.

Conclusion: A dedicated team for long-term data entry is key to RESAR's data quality and studies relevance. Data reliability is enhanced by ongoing self-training and interventions across the international network of collaborating institutions.

(P 308) **IMPACT OF PSOAS MUSCLE RESECTION ON OUTCOMES IN PRIMARY RETROPERITONEAL DEDIFFERENTIATED LIPOSARCOMA**

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Objective: Concomitant resection of the tumor with adjacent organs and structures decreases the risk of local recurrence, the predominant issue in retroperitoneal liposarcoma. Based on a recent translational study which demonstrated a direct crosstalk between liposarcoma cells and muscle tissue, we sought to study the specific impact of ipsilateral psoas muscle resection on clinical outcomes.

Methods: Data were reviewed for all patients with primary dedifferentiated retroperitoneal liposarcoma who underwent curative intent, complete resection at a high-volume referral center from 2002 to 2023. The type of concomitant organ/structure(s) resected in each case was scrutinized. Patients with intraabdominal or pelvic tumors were excluded. Overall survival (OS) was calculated and crude cumulative incidences of local recurrence (LR) and distant metastasis (DM) were estimated. Multivariable analyses (MVA) were performed to assess the association between specific clinicopathologic factors of interest with OS, LR and DM.

Results: In this study, 437 patients were stratified into 373 who had psoas muscle resection (Ps-Y) versus 48 who did not (Ps-N). A separate cohort of 16 patients with resection of a different muscle (diaphragm or parietal, e.g., abdominal wall, D/Par) was used as a comparator to further assess psoas-specificity. OS was highest ($p < 0.001$) and incidence of LR was lowest ($p = 0.005$) in the Ps-Y compared to Ps-N and D/Par cohorts. On MVA, psoas resection had a strong association with better OS ($p = 0.001$) and lower LR incidence ($p = 0.047$), whereas there was no association with greater number of (any) organs resected ($p = 0.088$, $p = 0.847$). A trend for higher incidence of DM was observed in the D/Par versus Ps-Y and Ps-N cohorts ($p = 0.115$); however, on MVA, there was no association between cohorts and DM ($p = 0.193$). FNCLCC grade 3 disease had the strongest association with DM ($p = 0.007$).

Conclusion: Psoas muscle resection specifically contributes to improved local control and overall survival. This clinical study provides intriguing proof-of-concept in support of recent translational work that warrants continued investigation. In addition to amelioration of a critical soft tissue margin around the tumor, we speculate that psoas resection may potentially have direct positive impact on the disease biology.

(P 309) RETROPERITONEAL LIPOMAS: MULTICENTER CLINICAL EXPERIENCE WITH AN EXTREMELY RARE DISEASE ENTITY

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Objective: The differential diagnosis for a large lipomatous mass in the retroperitoneum is predominantly liposarcoma. Retroperitoneal lipoma is an extremely rare benign entity with bland histomorphology and absence of MDM2 amplification. To date, the largest reported case series of these tumors included 19 patients. In this study, we sought to leverage multicenter collaboration through the Transatlantic Australasian Retroperitoneal Sarcoma Working Group (TARPSWG) to describe collective experience with retroperitoneal lipoma and inform clinical management.

Methods: Data were collected from participating TARPSWG centers for cases of pathology-verified retroperitoneal lipoma from 2010 to 2020. Patient demographics and clinicopathologic factors were summarized. Management algorithms were studied, and clinical outcomes were determined.

Results: 43 patients with retroperitoneal lipoma from 6 centers across Europe, North America, and Asia were included in the study. On initial presentation, 23 (54%) patients were symptomatic, and 20 (46%) were asymptomatic with incidentally found tumors. Among all study patients, needle biopsy was performed on 20 patients (46%), more frequently in those who were asymptomatic (15, 75%) versus those with symptoms (5, 25%, $p = 0.0004$, Fisher's exact test). In total, 19 (44%) patients underwent upfront surgery while 24 (56%) patients were initially observed. The presence of symptoms was the most common indication for upfront surgery. In the initially observed patients, this management approach continued for a median of 25.5 months (range: 1-116). In fact, 13 (54%) were continuously observed for 2 or more years. Ultimately, an additional 8 initially observed patients proceeded to surgery, most commonly due to continued growth in tumor size or development of symptoms. Among the total of 27 patients, concomitant organ resection was performed in 6 (22%). On the resection specimen, only 1 patient (4%) had a change in final diagnosis to well-differentiated liposarcoma. With a median follow-up of 49 months, 1 of 27 (4%) patients had local recurrence.

Conclusion: Retroperitoneal lipomas are benign tumors for which initial observation may be appropriate in select patients. Surgery can be offered for tumor growth or the development of symptoms. A deeper comparison of retroperitoneal lipoma versus well-differentiated liposarcoma is warranted to better understand differences in disease biology that likely underlie clinical behavior.

(P 310) ATYPICAL SPINDLE CELL PLEOMORPHIC LIPOMATOUS TUMORS OF THE RETROPERITONEUM ARE HETEROGENOUS: A REPORT OF FOUR DISPARATE CASES

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Objective: The vast majority of retroperitoneal fatty tumors are MDM2-amplified liposarcomas. Atypical spindle cell pleomorphic lipomatous tumors (ASPLT) have recently been described outside of the retroperitoneum, characterized by absence of MDM2 amplification, loss of Rb1, and CD34 positivity. The presentation and characteristics of these rare tumors have not been described in the retroperitoneum. Here, we present four cases of retroperitoneal ASPLT.

Methods: The Vanderbilt University Medical Center pathology database was queried for atypical lipomatous tumors of the retroperitoneum from 2010 to 2025. Clinical and pathologic data were extracted from the medical record.

Results: There were 3 males and 1 female, with a median age of 60 years (range 56-62). One patient presented with a 70cm left retroperitoneal fatty mass with extension into the inguinal canal. Two patients presented with bilateral but asymmetrically large (>40cm) retroperitoneal tumors. The final patient presented with three tumor foci: left retroperitoneum, diaphragm and in

the subcutaneous tissue of the back – all three lacked lipomatous signal characteristics on pre-operative imaging. Pre-operative biopsies were suspicious for well-differentiated liposarcoma despite the absence of MDM2 amplification. Margin-negative resections were performed in all cases. All four patients are without recurrence of resected tumors at a median follow-up of 18 months. Invasion of encased organs was not observed.

Conclusion: APSLTs are rare benign lipomatous MDM2-non-amplified tumors. These cases highlight their heterogeneity in the retroperitoneum, since they may be bilateral or multifocal, and even lack a fatty appearance on pre-operative imaging. Immunostains for Rb1 and CD34 on pre-operative biopsy could be diagnostic and potentially allow surveillance or organ-sparing resection, although the natural history of these tumors remains uncertain.

(P 311) A FOLLOW-UP STUDY ON THE NOVEL USE OF CONTRAST-ENHANCED SUSCEPTIBILITY-WEIGHTED IMAGING FOR EXTREMITY DESMOID FIBROMATOSIS RESPONSE ASSESSMENT

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Objective: The use of contrast-enhanced susceptibility-weighted imaging (CE-SWI) for characterizing desmoid tumors can enhance the separation between fibrous T2-hypointense and cellular T1-enhancing components. We aimed to evaluate the effectiveness of the CE-SWI signal, volumetric, and radiomics-derived features in assessing desmoid treatment response.

Methods: This IRB-approved study included 17 patients with single-lesion extremity desmoid fibromatosis who underwent standard-of-care MRI, including CE-SWI, from March 2021 to February 2024. Measurements of maximum diameter, volume, and the modified Choi (m-Choi) were computed based on CE-SWI and T2-STIR volumetric tumor segmentations. One hundred and seven radiomic features were calculated. Patient response was assessed using conventional RECIST as a reference standard and compared against T2-STIR and CE-SWI volumetric, m-Choi, and radiomics.

Results: • RECIST-progression (n=3): In two patients, CE-SWI volume detected progression 10 months earlier than T2-STIR-based RECIST. Only 33% were characterized as progression by the routine radiologic report (RRR). • RECIST-stability (n=14): 5% exhibited at least one expected first-order response/progression-related change in the mean, skewness, 10th percentile, or 90th percentile, with all four changes present in 33% of cases. • In RECIST-progression, CE-SWI showed an average of 15% more voxels at the 90th percentile than T2-STIR. • Volume and CE-SWI/T2-STIR shape-derived size dimensional features demonstrated the highest separation between progressive and responding patients.

Conclusion: CE-SWI demonstrated higher sensitivity than T2-WI in detecting the active/progressive enhancing component. Volume- and shape-derived, as well as to a lesser extent, textural radiomic features, and m-Choi effectively distinguish between progressive and responding cases, outperforming first-order radiomics, RRR, and RECIST. Notably, progression prediction using CE-SWI/T2-STIR Volume and response prediction using CE-SWI-m-Choi

outperform and precede RRR and RECIST.

(P 312) APOSTT: A PROSPECTIVE TRIAL TO EVALUATE ACUPUNCTURE AFTER SURGERY OF EXTREMITY SOFT TISSUE TUMORS

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Objective: There is little prospective data available on acute pain management after resection of soft tissue tumors (STT). Current pain management guidelines recommend pharmacological treatment but also highlight the importance of non-pharmacologic therapies. The primary aim of the APOSTT Trial was to investigate the effect of acupuncture on pain relief after STT surgery of the extremities (German Clinical Trials Register identifier DRKS00032703).

Methods: This prospective single-arm, single-centre study included 25 patients who underwent surgery of soft tissue tumors (STT) of the extremities. Standard pain management regimen consisted of orally administered dipyrone (metamizole, 4x1g) or acetaminophen (paracetamol, 4x1g) plus ibuprofen (4x400mg). Additional opioids were prescribed upon request. Acupuncture was performed on the first postoperative day (POD). We assessed feasibility of postoperative acupuncture, postoperative pain intensity via numeric pain scale, and extremity function and quality of life using validated questionnaires.

Results: Twenty-five patients (median age 68years) were included. Twenty-two of 25 (88%) tumors were malignant. Twenty-one of 25 (84%) tumors were located in the lower extremity. The median tumor size was 8.5 cm. Acupuncture was administered on POD 1 in all cases. In 8 of 25 (32%) patients, optimal acupuncture point selection was limited due to patient positioning and presence of surgical drainages or wound dressings. Postoperative pain was low (median NRS 3 on POD 1). The lowest pain scores were documented on POD 2. Opioid prescriptions declined over time. Six patients had wound complications; wound healing disorders were not related to acupuncture in any case.

Conclusion: In general, pain levels and opioid use after STT resection were rather low. Acupuncture was safe, and well accepted in the postoperative setting of STT resection. The ability to perform acupuncture at the optimal point is limited postoperatively by dressings and drains. Further randomized controlled trials are warranted to evaluate the efficacy of acupuncture in the context of STT resection.

Pain after soft tissue tumor resection

	Before Surgery	POD1, before acupuncture	POD1, 20min after acupuncture	POD2	POD3	At Discharge
n	25	25	25	17	13	23
Median pain score (0-10) median (range)	0 (0-6)	1 (0-3)	1 (0-4)	1 (0-3)	0 (0-1)	0 (0-2)
Patients with pain n (%)	8 (32%)	15 (60%)	14 (56%)	7 (30%)	4 (31%)	4 (17%)
Mean highest pain score within last 24h (0-10)	5 (3-7)	5 (1-9)		3 (1-7)	3 (1-8)	3 (1-8)
Average pain score within last 24h (0-10)		3 (2-6)		2 (0-3)	2 (1-4)	1 (0-2)

(P 313) SIGNIFICANCE OF LYMPH NODE PROCEDURES IN SOFT TISSUE SARCOMA PATIENTS

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Objective: Lymph node metastases in Soft Tissue Sarcomas (STS) are an infrequent clinical event. Although it is well established that lymphatic spread is associated with a poorer prognosis, there is limited data on evaluating the impact of Sentinel Lymph Node Biopsy (SLNB) and Lymph Node Dissection (LND) on treatment outcomes in these patients.

Methods: We performed a retrospective analysis of patients treated radically for sarcoma and undergoing SLNB, LND or both of these procedures at sarcoma clinic between 1998 and 2025. Relapse-free survival (RFS) and overall survival (OS) were estimated using the Kaplan–Meier method.

Results: 36 patients underwent SLNB: 21 (58%) patients had epithelioid sa, 12 (33%) – clear cell sa, 3 (8.4%) – other sarcoma. Pathologically confirmed nodal metastases were present in 15 (41.7%) cases. Patients with negative SLNB results exhibited a trend toward better long-term outcomes, with 65% (95% CI: 47.1 – 89.7) remaining relapse-free at 3 years since SLNB compared to 48.5% (95% CI: 27.8 – 84.5) among those with positive SLNB (p=0.12). 106 patients underwent LND, including 93 (88%) due to clinically overt metastases and 13 (12.3%) underwent completion LND due to positive SLNB. The most common subtypes in the first group were: epithelioid sa – in 7 (53.8%) patients and clear cell sa - 5 (38.5%) patients, while in the latter group: undifferentiated pleomorphic sa – 19 (20.4%) patients, epithelioid sa – 12 (12.9%) patients and rhabdomyosarcoma – 11 (11.8%) patients. Median RFS since LND was notably longer for patients undergoing LND due to positive SLNB—27.1 months; 95% CI: 7.1 to not

reached (NA)—compared to 10.2 months (95% CI: 7.3–20.4) than observed in the group with clinically suspected metastases. OS at 5 years since the LND was respectively: 75% (95% CI: 49.6 – 100) and 52.7% (95% CI: 40.7 – 68.5). The predominant pattern of relapse after LND was an occurrence of distant metastases.

Conclusion: Further investigation into the role of lymph node procedures in sarcoma patients including SLNB and LND is expected. The presence of lymph node metastases is associated with worse clinical outcomes.

(P 314) AN INTERNATIONAL, MULTI-CENTRE STUDY OF SURGICAL MARGINS IN INTERMEDIATE TO HIGH GRADE SARCOMA

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Objective: Surgical resection with a negative margin typically forms the cornerstone of curative management in sarcoma, with positive margins associated with increased local recurrence (LR). Most margins studies include all sarcoma subtypes as a single entity and fail to appreciate the diverse characteristics of various histological subtypes. This study aims to compare the influence of margins on outcome in different histological subtypes and define a 'close' pathological margin.

Methods: Patients treated for intermediate to high grade sarcomas at 5 centres from 3 countries between 01/01/2010 and 31/12/2015 were included. Visceral, retroperitoneal and intracranial tumours were excluded. Statistical analysis was performed using R Studio.

Results: 1510 patients were suitable for inclusion. Overall, the positive margin rate was 17.6% and the 5-year local recurrence (LR) was 12.6%; positive margin and LR rates varied greatly between subtypes, with no correlation. Overall, positive margins were associated with increased LR (HR=3.59, $p < 0.0001$) and decreased overall survival (OS) (HR=1.495, $p < 0.001$) as expected. When analysing histological subtypes independently, only myxofibrosarcoma, undifferentiated pleomorphic sarcoma (UPS), angiosarcoma, and spindle cell sarcoma (SCS) had increased LR with positive margins ($p=0.002 / < 0.0001 / 0.0067 / 0.0091$ respectively). In myxofibrosarcoma, UPS and SCS, a closest margin of ≤ 10 mm reduced the LR risk to $\leq 5\%$ ($p < 0.05$). In angiosarcoma, a closest margin ≤ 30 mm reduced the LR risk to 10% ($p=0.021$). Surprisingly, positive margins were only associated with decreased OS in angiosarcoma and myxoid liposarcoma ($p=0.042 / 0.0059$ respectively). A closest margin of > 2 mm in myxoid liposarcoma significantly improved OS ($p=0.022$).

Conclusion: This study is the first to truly demonstrate the varying importance of surgical margins in different histological subtypes. Dedifferentiated liposarcoma, leiomyosarcoma and synovial sarcoma have low margin risk (negative sufficient). Myxoid liposarcoma is medium risk (2mm or more recommended). Myxofibrosarcoma, UPS and SCS are high risk (10mm or

more). Angiosarcoma is very high risk (30mm/entire field).

(P 315) ANALYSIS OF CHANGES IN T2-WEIGHTED SIGNAL INTENSITY AND TUMOR VOLUME AND EXPOSURE-RESPONSE IN THE RINGSIDE PHASE 2 STUDY OF VAREGACESTAT FOR DESMOID TUMORS

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Objective: T2-weighted signal intensity (T2W) and tumor volume (TV) on MRI may be more sensitive than RECIST for assessing treatment effect in desmoid tumors (DT). On T2W images, hyperintense areas are associated with active fibroblast proliferation and hypointense areas with tumor cell loss and increased collagenous tissue. RINGSIDE Phase 2 (NCT04871282) showed safety and early and continued MRI changes in DTs with oral varegacestat (AL102). We report exploratory analyses of T2W, TV, and exposure-response (ER).

Methods: Adults with progressing DT and $\geq 10\%$ unidimensional growth in ≤ 18 mo or DT pain requiring non-opioid medication were randomized to 3 varegacestat doses: 1.2 mg once daily (n=14), 2 mg intermittent (n=14) or 4 mg intermittent (n=14) (intermittent=2 days on, 5 days off). In the open-label extension, active pts received 1.2 mg once daily. T2W, TV and RECIST sum of diameters (SOD) were evaluated at screening, Week 16 and every 12 weeks thereafter. Linear correlations were evaluated with Pearson correlation coefficient. ER modeling evaluated time course of drug effect on TV to support selection of 1.2 mg once daily for further study.

Results: As of Jan. 6, 2025, median time on treatment was 23.3 mo (range 0.7–38.8) and 12 (29%) pts were still on treatment. By Week 16, median % change was -39% for T2W, -24% for TV and -8% for SOD. Median best % change was -96% for T2W, -86% for TV and -48% for

SOD. Correlations were observed for best % changes in T2W vs SOD ($R=0.67$), TV vs SOD ($R=0.81$), and T2W vs TV ($R=0.93$). In 25 pts with PR/CR, median best % change was -99% for T2W, -91% for TV and -56% for SOD. In 10 pts with SD, median best % change was -82% for T2W, -39% for TV and -8% for SOD. Preliminary ER analysis predicted median time to 30% TV decrease of 3 mo with 1.2 mg once daily.

Conclusion: Substantial early and rapid reductions in T2W and TV preceded subsequent varenicline responses by RECIST in adults with DT, adding to evidence that T2W and TV may play a role in evaluating DT treatment response. © 2025 American Society of Clinical Oncology, Inc. Reused with permission. This abstract was accepted and previously presented at the 2025 ASCO Annual Meeting. All rights reserved.

(P 316) AREA DEPRIVATION INDEX (ADI) AND OUTCOMES IN LOCALIZED SOFT TISSUE SARCOMA: DO SOCIAL DETERMINANTS INFLUENCE SURVIVAL?

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Objective: The Area Deprivation Index (ADI) is a validated measure of neighborhood-level socioeconomic disadvantage. This study aimed to assess the association between ADI and five-year 1) disease-specific survival (DSS), 2) metastasis-free survival (MFS), and 3) recurrence-free survival (RFS) in patients with localized soft tissue sarcoma (STS).

Methods: This was a retrospective study of 286 patients who underwent resection of a localized STS from January 2010 to December 2021. Patients with American Joint Committee on Cancer (AJCC) stage 4 were excluded. The ADI is a range with higher values indicating greater deprivation. We categorized ADI into three groups (ADI1 = 0 to 33, ADI2 = 34 to 66, ADI3 = 67 to 100). A Kaplan-Meier analysis was used to estimate the five-year DSS, MFS, and RFS, with log-rank test and Cox proportional hazards models used to assess significance.

Results: Five-year DSS was worse for patients in ADI3 and ADI2 compared to ADI1 (66% vs. 77% vs. 93%, $p = 0.01$). When controlling for age and AJCC stage, ADI3 was associated with worse DSS compared to ADI1 [HR 4.98 (1.03-8.34), $p = 0.03$]. Although five-year MFS and RFS trends were similar to DSS, the findings were not statistically significant for ADI3 vs. ADI2 vs. ADI1, respectively [MFS: 53% vs. 64% vs. 76%, $p = 0.11$; RFS: 77% vs. 83% vs. 90%, $p = 0.30$]. However, when controlling for age and AJCC stage, ADI3 was associated with worse MFS compared to ADI1 [HR 2.26 (1.0-5.13), $p = 0.05$].

Conclusion: ADI was associated with significantly worse DSS in patients with localized STS, even after adjusting for clinical factors. These findings suggest that a patient's neighborhood location, which serves as a proxy for socioeconomic status, can directly impact cancer outcomes. Possible drivers include delayed diagnosis, reduced access to specialized care, and barriers to timely adjuvant therapy. Further efforts to improve sarcoma outcomes must address social determinants of health to ensure equity in cancer care.

Patient Demographics and Survival Outcomes

Variable	Level	ADI 1 (n = 50)	ADI 2 (n = 122)	ADI 3 (n = 114)	p-value
Age		66.0 [55.0;73.3]	62.5 [45.8;76.0]	63.0 [54.0;71.3]	
Sex	F	21 (42.0%)	51 (41.8%)	53 (46.5%)	
	M	29 (58.0%)	71 (58.2%)	61 (53.5%)	
Race	White	44 (88.0%)	110 (90.2%)	76 (66.7%)	
	Black	3 (6.0%)	5 (4.1%)	35 (30.7%)	
	Other	3 (6.0%)	7 (5.7%)	3 (2.6%)	
Histologic Grade	G1	15 (34.8%)	22 (19.5%)	13 (11.8%)	
	G2	5 (11.6%)	29 (25.7%)	34 (30.9%)	
	G3	9 (20.9%)	37 (32.7%)	27 (24.6%)	
	GX	14 (32.6%)	25 (22.1%)	36 (32.7%)	
AJCC Stage	1	26 (66.7%)	50 (48.5%)	59 (57.8%)	
	2	3 (7.7%)	36 (35.0%)	20 (19.6%)	
	3	10 (25.6%)	17 (16.5%)	23 (22.6%)	
5-year DSS		93%	77%	66%	0.01
5-year MFS		76%	64%	53%	0.11
5-year RFS		90%	83%	77%	0.30

(P 317) BUILDING A PRE-SURGICAL MULTIPARAMETRIC-MRI-BASED PREDICTIVE TREATMENT RESPONSE MODEL FOR UNDIFFERENTIATED PLEOMORPHIC SARCOMA TO REPLACE RECIST

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Objective: Undifferentiated pleomorphic sarcoma (UPS) is the largest subgroup of soft-tissue sarcomas. It demonstrates post-therapeutic hemosiderin deposition, granulation tissue formation, fibrosis, and calcification. We aimed to establish the multiparametric MRI (mp-MRI) value for predicting response to UPS treatment.

Methods: This IRB-approved retrospective study included 33 extremity UPS patients who underwent diffusion-weighted imaging, contrast-enhanced susceptibility-weighted imaging (CE-SWI), and perfusion-weighted imaging with dynamic contrast-enhancement (PWI/DCE), as well as surgical resection, from February 2021 to May 2023. Lesions were categorized into 6 CE-SWI and 6 PWI/DCE morphologic patterns. Time-intensity curves (TICs) were classified as types I-V. Patients were categorized into three groups based on the percentage of pathology-assessed treatment effect (PATE) in the surgical specimen: Responders (> 90% PATE, n = 16), partial responders (31-89% PATE, n = 10), and non-responders (< 30% PATE, n = 7).

Results: • At post-radiation therapy (PRT), a CE-SWI Complete-Ring pattern was observed in 71% of responders ($p=7.71 \times 10^{-6}$). On PWI/DCE images, 79% of responders displayed a Capsular pattern ($p=1.49 \times 10^{-7}$), and 100% demonstrated a TIC-type II ($p=8.32 \times 10^{-7}$). • ROC analysis comparing responders (n=14) vs. partial/non-responders (n=16) at PRT showed that the model combining PWI/DCE TIC-type II, PWI/DCE Capsular pattern, and CE-SWI Complete-Ring pattern yielded the highest classification performance (AUC=0.99), outperforming

PWI/DCE Capsular + TIC-type II (AUC=0.97), PWI/DCE Capsular (AUC=0.89), PWI/DCE TIC-type II (AUC=0.88), and CE-SWI Complete Ring (AUC=0.79). • RECIST demonstrated 100% stability at PRT and 100% pseudo-progression at PC in responders and partial/non-responders (AUC=0.47).

Conclusion: Mp-MRI-derived features are valuable in assessing UPS treatment response. A pre-operative model that combines PWI/DCE TIC-type II, PWI/DCE Capsular pattern, and CE-SWI Complete Ring pattern can reliably predict successfully treated UPS with $\geq 90\%$ PATE, outperforming RECIST.

(P 318) BURIED DE-EPITHELIALIZED FLAP RECONSTRUCTION AFTER WIDE EXCISION OF THIGH SARCOMAS: EARLY EXPERIENCE FROM A SPECIALIZED SARCOMA SURGERY UNIT

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Objective: Wound complications after wide excision of thigh soft tissue sarcomas (STS) may impair functional recovery and quality of life. Obliteration of dead space is essential to reduce this risk. This study reports early outcomes of buried de-epithelialized flap reconstruction in selected cases.

Methods: Since 2024, this technique has been adopted at IRCCS Humanitas Research Hospital (Rozzano, Milan, Italy). Five patients underwent wide excision for thigh STS followed by buried de-epithelialized flap reconstruction. All received psychiatric evaluation and post-discharge rehabilitation.

Results: Median age was 66 years (54–82). Histologies included Undifferentiated Pleomorphic Sarcoma (UPS, n=2), Myxofibrosarcoma (MFS, n=1), Leiomyosarcoma (LMS, n=1), and Solitary Fibrous Tumor (SFT, n=1). All were FNCLCC grade 3. Median tumor size was 14.0 cm (9.5–18.5). Three patients received neoadjuvant chemotherapy, including two with concurrent radiotherapy. Two patients, including an elderly and symptomatic case, received no preoperative treatment. All cases required en bloc resection of the involved muscle compartment and of the femoral periosteum. Median operative time was 212 minutes (172–254). One patient developed a superficial wound dehiscence, managed conservatively. No deep infections, seromas, bone exposure, or reoperations were observed. Median length of hospital stay (LOS) was 9 days (7–15). All patients regained ambulation with one or two crutches after rehabilitation. Patient data are summarized in Table 1.

Conclusion: Buried de-epithelialized flap is a reliable option in selected thigh sarcomas when other plastic reconstructions are excluded. In this series, it showed low morbidity and favorable functional outcomes.

Patient data

PT SEX AGE COMORBIDITY HISTOLOGY SIZE LOCATION NEOTX TIME COMPLICATION LOS

1	F	82	HBP	UPS, G3	14.0	Anterior	None	212	Superf. dehiscence	12
2	M	57	CVD	MFS, G3	14.5	Anterior	CT/RT	254	None	9
3	M	54	HBP, DMII	UPS, G3	14.0	Postero-medial	CT/RT	200	None	7
5	M	72	CVD	SFT	9.5	Antero-medial	None	215	None	9
4	F	66	DMII, Obesity	LMS, G3	18.5	Antero-lateral	CT	172	None	15

(P 319) CARDIOTOXICITY AND OVERALL SURVIVAL IN PATIENTS WITH SARCOMA TREATED WITH DOXORUBICIN, OLARATUMAB AND DEXRAZOXANE: A REAL-WORLD EXPERIENCE IN DENMARK

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Objective: Cardiotoxicity is a significant side effect of anthracycline-based chemotherapy. Dexrazoxane can reduce this risk, allowing for a higher cumulative dose and potentially improve overall survival (OS). This study examined the risk of cardiotoxicity and the OS in patients with soft tissue sarcoma (STS) treated with doxorubicin, olaratumab, and dexrazoxane.

Methods: A retrospective analysis was conducted including all patients with locally advanced or metastatic STS treated with doxorubicin, olaratumab, and dexrazoxane from 2015 to 2019 at Herlev University Hospital (HGH) and Århus University Hospital (AUH). Cardiotoxicity was evaluated using a multigated acquisition scan or echocardiography and defined as a decline in left ventricular ejection fraction (LVEF) by over 10 percentage points to below 50%. Early cardiotoxicity occurred within one year of doxorubicin initiation, while late occurred after one year. OS was measured from the start of doxorubicin to death from any cause.

Results: A total of 103 patients were included, 71 (69%) at HGH, 62 (60%) were males with a mean age of 58 years. The median cumulative dose of doxorubicin was 500 mg/m² at HGH and 450 mg/m² at AUH (p = 0.9). Dexrazoxane was administered in 86 (84%) patients, starting with the first cycle of doxorubicin at HGH and with the fourth cycle at AUH. Cardiotoxicity was observed in 6 (8%) out of 71 patients at HGH and in 5 (16%) out of 32 patients at AUH (p =

0.3), with a median LVEF of 44%. All patients experienced early cardiotoxicity and were referred for a cardiac evaluation, which confirmed the decline in LVEF. Median OS was 19.6 months at HGH and 15 months at AUH ($p = 0.3$).

Conclusion: Administering dexrazoxane with doxorubicin in the first treatment cycle showed no statistically significant reduction in cardiotoxicity and improvement in OS. Further data from a larger retrospective study are pending.

(P 320) CLINICAL CHARACTERISTICS AND RECURRENCE PATTERNS IN HISPANIC VS. NON-HISPANIC PATIENTS WITH LEIOMYOSARCOMA: FINDINGS FROM A RETROSPECTIVE SINGLE-CENTER COHORT STUDY

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Objective: Leiomyosarcoma (LMS), a rare and aggressive malignancy, commonly arises from the uterus, retroperitoneum, and extremities, carrying a poor prognosis. This study investigates differences in clinical characteristics, treatment patterns, outcomes, and genomic data from next-generation sequencing (NGS) between Hispanic and non-Hispanic patients with non-metastatic and metastatic LMS. The goal is to identify disparities that may inform personalized treatment strategies and improve outcomes for underrepresented populations.

Methods: This single-center retrospective cohort study, conducted under an IRB-approved protocol, evaluated 190 patients with biopsy-proven LMS, confirmed by sarcoma pathologists at the University of Miami Sylvester Cancer Center. NGS data were collected for patients tested between January 2009 and December 2024. Patient demographics, including sex, ethnicity, and age, along with clinical variables such as tumor location, size, grade, and recurrence, were gathered from electronic medical records and stored in REDCap. Kaplan-Meier and logistic regression models were used for survival analysis, adjusting for confounding variables. Patients with incomplete clinical histories were excluded.

Results: The dataset included 190 patients (154 females, 33 males) with a median age of 55.8 years. Of these, 55 were metastatic, and 132 were nonmetastatic. Among nonmetastatic patients, 81 were high grade, including 55 non-Hispanic and 26 Hispanic patients. In the nonmetastatic, high-grade LMS cohort, disparities were observed: 5-year overall survival (OS) was 87.7% for non-Hispanics compared to 76.2% for Hispanics ($p=0.045$; hazard ratio: 1.96). Median disease-free survival (DFS) was shorter for Hispanics (14.3 months) than for non-Hispanics (50.7 months), indicating earlier recurrence among Hispanics ($p=0.32$). At 24 months, DFS was 39.4% for Hispanics versus 72.2% for non-Hispanics. Initial therapies, including radiation, surgery, and systemic treatments, showed no significant differences in recurrence rates, though non-Hispanic patients were more likely to receive radiation.

Conclusion: These findings highlight survival disparities between Hispanics and non-Hispanics, potentially driven by earlier recurrence. NGS data from 38 patients' diagnostic tissue will be analyzed to identify potential drivers of these disparities and inform equitable treatment strategies.

Clinical Characteristics in Patients with High Grade, Nonmetastatic Leiomyosarcoma

Clinical Variable	Not Hispanic or Latino (N=55)	Hispanic or Latino (N=26)	Overall (N=81)
Age at Diagnosis (Mean)	53.3	56.7	54.4
Retroperitoneum	12.7%	11.5%	12.3%
Trunk/Extremity	23.6%	34.6%	27.2%
Uterine	63.6%	53.8%	60.5%
Tumor Size at Diagnosis			
< 5 cm	10.9%	19.2%	13.6%
5-10 cm	36.4%	42.3%	38.3%
10-15 cm	29.1%	15.4%	24.7%
> 15 cm	12.7%	7.7%	11.1%
Next-Generation Sequencing	76.4%	65.4%	72.8%
Disease Recurrence	61.8%	65.4%	63.0%
Initial Treatment Modality			
Systemic	18.2%	19.2%	18.5%
Radiation	3.6%	0%	2.5%
Surgery	76.4%	73.1%	75.3%

(P 321) COMPARATIVE ANALYSIS OF FIRST-LINE DOXORUBICIN-BASED COMBINATION REGIMENS IN METASTATIC LEIOMYOSARCOMA: IMPACT ON SURVIVAL AND DISEASE CONTROL

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Objective: First-line chemotherapy is crucial in the management of metastatic leiomyosarcoma; however, limited comparative data exist for approved combination regimens. This study examines progression-free survival (PFS), overall survival (OS), treatment sequencing, and safety profiles to determine optimal therapeutic strategies.

Methods: We retrospectively analyzed 73 metastatic leiomyosarcoma patients (2011–2024), assessing demographics, tumor features, treatments, and outcomes including response rates, PFS, PFS2, and OS using Kaplan-Meier analysis.

Results: The cohort (86% female, median age 54) included 42% uterine primaries and 50% metastatic cases. First-line regimens were mainly doxorubicin + dacarbazine (27%) and doxorubicin + trabectedin (24%). Doxorubicin + dacarbazine had the longest median PFS (12 months), followed by doxorubicin + trabectedin (8 months). PFS differences showed a non-significant trend (p=0.07), and median OS was similar across regimens (33 months, p=0.9).Doxorubicin + DTIC showed the highest disease control rate at 86.4%, indicating superior stabilization.

Second-line PFS is longer (12 months) in patients treated first with doxorubicin + trabectedin followed by gemcitabine + dacarbazine, compared to those starting with doxorubicin + dacarbazine followed by trabectedin (5 months).

Excluding uterine leiomyosarcomas, first-line PFS is longer with doxorubicin + trabectedin (18 months) than doxorubicin + dacarbazine (13 months), but not statistically significant (p=0.6).

Conclusion: Doxorubicin + dacarbazine showed the longest first-line PFS and highest disease control rate, though overall survival was similar across regimens.

Second-line PFS was longer when doxorubicin + trabectedin was used first.

Excluding uterine leiomyosarcomas, doxorubicin + trabectedin showed a non-significant PFS advantage over doxorubicin + dacarbazine

Descriptive analysis

Number of patients	73pts
Median age (range)	54years (19-84)
Gender distribution	85% female 15% male
Primary tumor lcoalitation	40% uterus 60% non uterus
Metastatic at diagnosis	50%
First line chemotherapy regimens	18% doxorubicin monotherapy 30% doxorubicin+ Dacarbazin 10% Epirubicin + ifosfamide 13% Doxorubicin+olaratumab 29% Doxorubicin+Trabectedin
Second-line chemotherapy regimens	20% gemcitabine+ dacarbazine 12% pazopanib 12% trabectedin

(P 322) DYNAMIC PET/MRI REVEALS METABOLIC-DIFFUSION INTERACTIONS IN SUSPECTED SOFT TISSUE SARCOMAS

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Objective: Hybrid imaging with PET/MRI provides a unique opportunity for real-time characterization of tumor tissue composition and biological behavior. Our study explores this field by examining the temporal interactions between functional imaging-derived biomarkers (primary tumor diffusion restriction, amino acid and glucose metabolism) in patients with a suspicion of soft tissue sarcoma using a dynamic PET/MRI data acquisition protocol after administration of both [18F]FET and [18F]FDG.

Methods: A single-site, explorative, prospective study including 19 patients (11f/8m, median age 61.5y [range: 36.6-82.2]) with newly diagnosed tumors and strong suspicion of soft tissue sarcoma (Table 1). At diagnosis, all patients underwent conventional imaging for primary tumor characterization and disease staging, as well as dynamic, regional [18F]FET and [18F]FDG PET/MRI (Siemens Biograph mMR®) of the primary tumor, with a maximum of 7 days between the examinations. Following i.v. administration of 4 MBq/kg radiotracer, continuous PET acquisition was performed 0-60 min post-injection. Within the same timeframe, MRI was performed according to standard tumor protocols, including DWI sequences. The primary tumor was delineated on MRI and the region of interest was transferred to the corresponding PET datasets. Voxel-to-voxel tumor analysis compared semiquantitative measures of diffusion restriction (ADC) with time-dependent amino acid (SUVFET) and glucose metabolism (SUVFDG) across six successive 10 min intervals to characterize primary tumor tissue.

Results: Despite being more time-consuming than standard soft tissue tumor imaging with PET/MRI, the proposed imaging protocol and subsequent analysis proved feasible, and all included patients were able to cooperate. Voxel-to-voxel comparison of semiquantitative parameters for tumor diffusion and glucose metabolism revealed distinct distribution patterns that varied according to histopathological tumor subtype and tumor grade, with correlation coefficients reflecting the heterogenic nature of soft tissue sarcomas/tumors. Furthermore, time-dependent accumulation patterns of both radiotracers demonstrated this biological complexity.

Conclusion: Given the rarity and heterogeneity of soft tissue sarcomas being as major clinical challenges, dynamic functional imaging with PET/MRI demonstrates correlations between tumor diffusion and metabolism, providing a platform for comprehensive imaging characterization of tumor tissue composition and biological behavior.

Clinical Characteristics of Included Patients. Abbreviations: Pt.: patient; M: male; F: female; y: years; gr.: FNCLCC tumor grade; Dediff.: dedifferentiated; Undiff.: undifferentiated; NOS: not otherwise specified; GCT: giant cell tumor; LE: lower extremity; UE: upper extremity. Histopathological extent of necrosis was determined according to the FNCLCC grading system. Tumor size was determined on MRI. The presence of metastatic disease at the time of diagnosis was determined on [18F]FDG

PET/CT.

Pt. #	Gender	Age (y)	Histopathology/FNCLCC Tumor Grade	Necrosis	Tumor Site	Tumor Size (cm)	Metastasis @ diagnosis
1	M	71.1	Leiomyosarcoma gr. II	< 50%	LE	4 x 6 x 7	No
2	F	43.5	Biphasic synovial sarcoma gr. III	> 50%	LE	7 x 13 x 9	No
3	M	70.6	Undiff. pleomorphic sarcoma gr. III	< 50%	LE	12 x 8 x 16	No
4	F	58.4	Pleomorphic sarcoma gr. III	> 50%	LE	10 x 9 x 17	Yes
5	M	36.6	Myxoid liposarcoma gr. I	No	LE	4 x 4 x 7	No
6	F	76.1	Leiomyosarcoma gr. III	> 50%	UE	10 x 6 x 6	No
7	F	70.9	Leiomyosarcoma gr. III	< 50%	LE	10 x 6 x 6	No
8	F	68.4	Dediff. liposarcoma gr. III	< 50%	LE	7 x 5 x 11	No
9	F	73.4	Undiff. pleomorphic sarcoma gr. III	> 50%	LE	5 x 5 x 11	No
10	F	82.2	Sarcoma NOS gr. III	> 50%	Trunk	5 x 2 x 3	No
11	M	52.1	Angiomatoid fibrous histiocytoma	No	LE	10 x 8 x 12	No
12	F	52.8	Undiff. sarcoma NOS gr. III	> 50%	UE	8 x 9 x 12	No
13	M	63.3	Undiff. pleomorphic sarcoma gr. III	< 50%	LE	6 x 6 x 12	No
14	F	61.5	Leiomyosarcoma gr. III	> 50%	LE	3 x 3 x 4	No
15	M	53.8	Myxoid liposarcoma gr. I	No	LE	8 x 7 x 13	No
16	F	65.5	Undiff. sarcoma NOS gr. III	< 50%	LE	4 x 5 x 12	No
17	F	42.1	Myxoid liposarcoma gr. I	No	LE	7 x 5 x 12	No
18	M	45.7	Monophasic synovial sarcoma gr. II	No	Neck	6 x 5 x 4	No
19	F	48.2	Tenosynovial-GCT extra-articular diffuse type	No	LE	9 x 8 x 9	No

(P 323) EVALUATION OF COSMIC MUTATIONAL SIGNATURES IN SOFT TISSUE SARCOMA

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Objective: Previously in our study, the comprehensive genomic analysis of alterations in undifferentiated pleomorphic sarcoma (UPS) and myxofibrosarcoma (MFS) tumors showed a significant number of genomic alterations, complex rearrangements and frequent genomic imbalances that affect the p53 and RB1-CDK4 pathways. Mutational signatures connect mutational patterns with biological and chemical processes that take place in cancers. Catalogue Of Somatic Mutations In Cancer (COSMIC) is a resource to explore the impact of these mutations on cancer development and progression. We aim to identify the mutational processes present in primary UPS/ MFS tumors, metastases, and tumor-derived cell lines using COSMIC's mutational signature analysis. We aim to compare the mutational signatures in eight primary tumors to their matched tumor-derived cell lines that were established for use as in-vitro soft tissue sarcoma (STS) models and compare the mutation signatures of the seven primary tumors to the matched metastatic tumors to identify metastasis specific signatures.

Methods: Mutational signature analyses were performed to identify patterns of somatic base substitutions (SBS) in 45 primary UPS/MFS, 8 matched primary-cell line and 7 matched primary-metastatic tumors that aligned with the COSMIC mutational signatures.

Results: Using the COSMIC mutational signatures database, we found that SBS1 was the predominant signature in primary tumors (93%). SBS1 is associated with the endogenous mutational process initiated by spontaneous or enzymatic deamination of 5-methylcytosine to thymine, that results in C to T substitutions and other studies suggest it is related to the age of the individual. SBS3 was present in half of the primary tumors and is associated with the failure

of double strand break repair. Interestingly, SSB1 in cell line samples remained the dominant signature, however, the total number of signatures represented in the cell lines were more than the primary tumors. This suggests that cell lines were comprised of more diverse COSMIC mutational signatures and represent a sub-clonal population of tumor cells that persisted in-vitro. Metastatic tumors also had SSB1 as the predominant signature, however overall, they had more signatures than their primary tumors, indicating changes in the underlying mutational processes during metastases.

Conclusion: A more comprehensive analysis of the COSMIC mutational signatures of our cohort can help elucidate tumor evolution, prognosis, and therapeutic strategies in STS.

(P 324) FULLY MATURE TERTIARY LYMPHOID STRUCTURES AS PREDICTORS OF LOCAL RECURRENCE IN SOFT TISSUE SARCOMAS

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Objective: Soft-tissue sarcomas (STS) are rare and heterogeneous malignancies with generally poor and unpredictable prognosis. Tertiary lymphoid structures (TLS) have been identified as favorable prognostic indicators in several cancer types, yet their specific role in STS remains poorly defined. This study investigates the prognostic relevance of TLS presence, maturity, location and semi-quantitative assessment of their density in resected primary STS.

Methods: We retrospectively analyzed 219 cases of primary STS surgically resected at the Bergonié Institute (Comprehensive Cancer Center of Bordeaux, France) between 1990 and 2020. TLS were assessed for presence, spatial distribution, semi-quantitative density and degree of maturity using CD20 and CD23 immunohistochemistry, categorizing tumors as fully mature TLS-positive (fmTLS⁺) or negative (fmTLS⁻). RNA sequencing was performed on 126 formalin-fixed paraffin-embedded samples to characterize immune microenvironment profiles. Survival outcomes—including overall survival (OS), time to locoregional progression (TTLRP), and time to distant progression (TTDP)—were analyzed using Kaplan-Meier estimates and Cox proportional hazards models.

Results: The presence of fmTLS was significantly associated with improved 5-year OS ($p=0.012$) and cause-specific survival ($p=0.006$). Unexpectedly, fmTLS⁺ tumors showed a higher rate of local recurrence (22.9% vs. 8.1%, $p=0.002$). On multivariate analysis, high-density fmTLS⁺ tumors conferred a 2.68-fold increased risk of locoregional progression (95% CI: 1.28-5.59, $p=0.009$). Transcriptomic profiling confirmed a significant correlation between fmTLS⁺ status and an high-immune phenotype ($\Phi=0.30$, $p<0.001$), supporting our pathological assessment.

Conclusion: The presence of fmTLS in STS are associated with favorable improved OS but paradoxically increased risk of local recurrence. These findings suggest that fmTLS could serve as a dual prognostic biomarker, highlighting the need for stratified surveillance and tailored adjuvant strategies in fmTLS⁺ patients.

(P 325) FUSION GENES IN SARCOMAS: DIAGNOSTIC APPROACHES AND EMERGING TARGETED THERAPIES

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Objective: Sarcomas are rare and complex mesenchymal malignancies, many of which are defined by characteristic gene fusions that serve as diagnostic, prognostic, and therapeutic biomarkers. These fusions provide a powerful tool across various types of sarcomas, facilitating diagnosis and treatment precision approaches. In this systematic review, we aim to explore the current knowledge on fusion genes in sarcoma, associated diagnostic methodologies, emerging targeted therapies. We also outline how fusion genes are shaping the future of sarcoma care.

Methods: Following PRISMA guidelines, we conducted a systematic review of published literature from 2015–2025 across PubMed, Web of Science, Cochrane, and ClinicalTrials.gov. We focused on research involving human fusion-positive sarcomas, molecular diagnostics, and targeted therapies.

Results: We found that sarcoma-related fusion genes fall into four major categories: 1. Transcription Factor Fusions such as EWSR1-FLI1, SS18-SSX, PAX3-FOXO1 which define tumor lineage but remain difficult to target directly. 2. Tyrosine Kinase Fusions, including NTRK, ALK, COL1A1-PDGFB, are highly actionable with FDA-approved therapies like larotrectinib and imatinib. 3. Chromatin Remodeling Fusions, like BCOR-CCNB3, NAB2-STAT6, highlight the potential for epigenetic drugs; such as EZH2 inhibitors. 4. Rare and Novel Fusions, including CIC-DUX4, YAP1-TFE3, are being uncovered with advances in RNA-based sequencing. RNA-based Next Generation Sequencing (NGS) is revolutionizing the detection of these fusions and is improving diagnostic precision. Targeted therapies, including kinase inhibitors, epigenetic modulators, and emerging immunotherapies are being explored in clinical trials.

Conclusion: Fusion genes are central to sarcoma diagnosis and treatment. They are a key to transforming and personalizing sarcoma management. Barriers in this path include the rarity of fusions, limited actionability, and lack of comprehensive fusion registries. Broader access to RNA diagnostics, AI integration, and multi-institutional collaborations are needed to advance fusion-targeted care.

(P 326) GERMLINE POT1 MUTATIONS IN ANGIOSARCOMA DIFFER FROM SOMATIC MUTATIONS

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Objective: Protection of Telomeres Protein 1, (POT1) protein, is a component of the shelterin telomere complex, which is involved in regulating telomere length. Genomic mutations in POT1 compromise chromosomal stability, leading to impaired cellular aging and apoptosis. POT1 tumor predisposition syndrome (POT1-TPD) is caused by point mutations in POT1, with the POT1/R117C mutation being the most well-recognized. This mutation results in abnormally long telomeres and is associated with an increased risk of familial cutaneous melanoma, angiosarcoma (AS), glioma and chronic lymphocytic leukemia. The prevalence of pathogenic POT1 mutations in AS ranges between 16-23%, although most patients do not exhibit a POT1-

TPD phenotype. In this study, we aimed to examine the landscape of pathogenic POT1 gene mutations in angiosarcoma

Methods: Genomic profiles of clinical AS specimens analyzed by Foundation Medicine (Foundation Medicine, Inc., Cambridge, MA) between 2012-2018 were retrieved using cBioPortal. A query for mutations in the POT1 gene identified 9/301 out of AS specimens (data sourced from MSKCC, Nat Commun 2022). Clinical data for all patients harboring pathogenic POT1 variants were extracted

Results: Pathogenic POT1 mutations were identified in 3% (9/301) of AS patients. Among these, only one mutation (I78T) was a germline mutation associated with familial melanoma, while the remaining eight were somatic splice-site mutations resulting in a truncated protein. The primary tumor sites included skin in four patients and parotid gland, spleen, and pleura in one patient each. The median age of patients was 62 years (range 46–81), and 7 of 9 patients were male. Co-mutations in TP53 were observed in 6/8 cases, while no significant associations with other genes were noted. Somatic truncating mutations in POT1 were the predominant finding.

Conclusion: Our findings show that somatic POT1 mutations are predominantly truncating, resulting in POT1 loss, while germline POT1 mutations are typically point mutations causing missense changes. We propose that germline truncating POT1 mutations are not compatible with life and, therefore, are not associated with POT1-TPD. This observation should be validated in a larger AS cohort and may facilitate the identification of inherited cases of AS

(P 327) INITIAL TREATMENT MODALITY AND RECURRENCE IN NON-METASTATIC LEIOMYOSARCOMA: A RETROSPECTIVE COHORT STUDY

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Objective: Leiomyosarcoma (LMS) is an aggressive malignancy comprising 10–20% of soft tissue sarcomas, with high recurrence rates in non-metastatic cases. While surgery remains the mainstay, systemic therapy and radiation are often used for large, high-grade, or locally advanced tumors. Guidelines recommend neoadjuvant or adjuvant therapy in select non-metastatic cases, but how initial treatment influences recurrence remains unclear. We aimed to evaluate recurrence patterns by first treatment by analyzing real world data.

Methods: We retrospectively reviewed non-metastatic LMS cases treated at the University of Miami. Patients were categorized by initial treatment: surgery, systemic therapy, or radiation. The primary outcome was recurrence (local or distant). Logistic regression was used to estimate odds of recurrence across treatment types. This project is part of an ongoing study that will further assess planned vs unplanned surgeries and high-risk features (e.g., high grade,

large size) in systemically treated non-metastatic patients.

Results: Among 151 patients, recurrence occurred in 58.1% of those receiving surgery first, 45.8% of those receiving systemic therapy first, and 50.0% of those receiving radiation first. Compared to the reference group, patients treated with systemic therapy first had significantly reduced odds of recurrence (OR 0.35, 95% CI 0.13–0.87, $p=0.03$). Although there was a trend toward higher recurrence odds with surgery first, the odds of recurrence were not statistically different in the surgery (OR 2.08, $p=0.08$) or radiation (OR 1.71, $p=0.54$) first groups.

Conclusion: Systemic therapy as the initial treatment was significantly associated with lower odds of recurrence for patients with non-metastatic LMS. These findings support further investigation into treatment sequencing and highlight the importance of tailoring therapy based on risk features. Using real world data we can design investigator initiated trials to further validate findings and improve care in LMS.

(P 328) INNOVATING SARCOMA EDUCATION: EARLY OUTCOMES OF THE ITALIAN SOCIETY OF SURGICAL ONCOLOGY (SICO) SARCOMA SOCIAL MULTI-PLATFORM JOURNAL CLUB INITIATIVE

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Objective: In 2025, the Sarcoma Oncoteam of the Italian Society of Surgical Oncology (SICO) launched “SICO Sarcoma Social”, a social media-based journal club aimed at enhancing education on sarcoma through monthly, evidence-based posts. This report summarizes the first three months of activity in terms of content, engagement, and audience reach.

Methods: Launched in March 2025, the initiative runs across Instagram, X, and LinkedIn. Each monthly cycle includes a clinical case, a key reference, an expert-led video, and a Q&A post. Content is curated by SICO sarcoma surgeons and researchers using concise formats including surgical images, videos, and commentary. Metrics collected included views, shares, comments, and follower growth.

Results: From March to May 2025, 12 educational posts were published across three thematic series: right-sided retroperitoneal sarcoma, left-sided approaches, and neoadjuvant treatments. Instagram was the most impactful platform, with >300% follower growth, 25,000+ total views, and nearly 7,200 unique accounts reached. The top reel exceeded 8,700 views. Median post views were 1,291 (range 203–8,714). The audience was mostly aged 25–34 (54.5%) and 60.8% female. Most were based in Italy (61.8%), followed by the USA (10.3%) and India (5.6%); Milan alone represented 28%, followed by Rome (4.3%). On LinkedIn, the page grew to over 200 followers, mostly senior professionals (46.8%) and fewer trainees (6.4%). Median impressions per post were 393 (range 36–1,229). The audience was again largely Italian (Milan 38.4%, Rome, Palermo, Catania), with international views from Europe (18%, notably Spain and the UK), Asia (7%), the Americas (4%), and Africa/Middle East (3%). X fostered professional engagement, especially with senior international surgeons and academic societies, often driven by congress-related content.

Conclusion: SICO Sarcoma Social demonstrates how structured, evidence-based content can drive engagement and international collaboration in rare cancer education through social media platforms.

(P 329) LAPAROSCOPY-ASSISTED PERCUTANEOUS CRYOABLATION FOR THE TREATMENT OF ABDOMINAL WALL DESMOID TUMORS

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Objective: Management of abdominal wall desmoid tumors (DT) has evolved over the last decade, with emphasis on conservative management based on guidelines from the Desmoid Tumor Working Group. However, symptoms associated with these tumors and the significant cost of medical therapy warrant exploring safer, more effective procedural options for DT. There is growing evidence for ablative therapies, including percutaneous cryoablation (PCA); however, complications associated with abdominal adhesions and the proximity of bowel to tumor limit the success of this approach. This study describes our approach to and early experience with laparoscopy-assisted PCA for abdominal wall DT.

Methods: Inclusion criteria: Patients with pathologically-confirmed abdominal wall DT were recruited consecutively at a high-volume referral center.

Procedure: Diagnostic laparoscopy (DL), lysis of adhesions (LOA), and PCA were performed in an interventional radiology suite under general anesthetic by a Surgical Oncologist and Interventional Radiologist. The abdomen was insufflated to 12-15 mmHg. LOA was performed to dissect viscera away from tumor. Saline hydrodissection was performed around the tumor, and PCA with standard freeze-thaw cycles was performed with intermittent CT imaging to confirm expanding ice ball in the rectus sheath. The abdomen was desufflated after a prolonged thaw.

Analysis: Data points, including demographics, tumor characteristics, and operative details, were collected. Primary outcomes were the change in total lesion volume (TLV), complications, and symptom resolution.

Results: Five patients had attempted laparoscopy-assisted PCA for abdominal wall DT; four were successful. One patient could not complete PCA after DL due to extensive adhesions. Demographic and tumor characteristics are summarized in Table 1. Median follow-up was 11.8

months (IQR 8.75 – 20). One patient experienced a severe adverse event within 30 days, requiring return to OR. Mean % change in TLV (Δcm^3) was -69.8%, and all patients presenting with symptoms had symptom resolution after PCA.

Conclusion: Laparoscopy-assisted PCA is effective for patients with abdominal wall DT, as indicated by a large decrease in TLV and symptom resolution. We noted one severe AE after PCA for a massive DT; for DT at extremes of size, staged interventions can be considered.

Table 1. Patient and tumor characteristics and outcomes after treatment with laparoscopy-assisted PCA.

#	Sex	Age	FAP	Symptoms	Prior therapy	Preop TLV (cm^3)	Postop TLV (cm^3)	% change in TLV (Δcm^3)	PCA success	30-day G3+ AE	90-day G3+ AE
1	F	53	Yes	Pain, PM	MTx	14.57	-	-	Aborted	-	-
2	F	33	No	Pain, PM	None	301.60	1.65	-99.45	Yes	Hematoma	None
3	F	42	No	Pain, PM	MTx	167.50	46.02	-72.52	Yes	None	None
4	M	42	No	No	None	1.68	1.56	-7.14	Yes	None	None
5	F	37	No	Pain, PM	None	4.23	0.00	-100.00	Yes	None	None

FAP - familial adenomatous polyposis, TLV - total lesion volume, PCA - percutaneous cryablation, G3+ - grade 3 or higher, AE - adverse event, PM - palpable mass, MTx - medical therapy

(P 330) LEIOMYOSARCOMA IN THE REAL WORLD: RETROSPECTIVE ANALYSIS OF CLINICAL CHARACTERISTICS AND TREATMENT PATTERNS IN PATIENTS AT A COMMUNITY ONCOLOGY CENTER IN SOUTH FLORIDA (MEMORIAL HEALTHCARE SYSTEM)

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Objective: Leiomyosarcoma (LMS) is a rare, aggressive soft tissue sarcoma with heterogeneous presentations and limited data from community oncology settings. We conducted a retrospective analysis of patients treated for LMS at a large community oncology center in South Florida to characterize real-world demographics, tumor characteristics, treatment patterns, and survival outcomes.

Methods: We reviewed electronic medical records of patients diagnosed with LMS at Memorial Healthcare System (MHS) over the past decade. Only patients who received all modalities of treatment within the MHS system were included; those who received part of their care at outside institutions were excluded. Demographic data, tumor site, grade, stage at diagnosis, and treatment modalities were collected. Descriptive statistics were used to summarize the

cohort. Kaplan-Meier methods were employed to estimate overall survival (OS).

Results: A total of 23 patients with histologically confirmed LMS were identified. The median age at diagnosis was 55 years (range: 34–78), with 60% female and 40% male. The racial distribution included 70% White, 20% Black, and 10% other races; 25% identified as Hispanic or Latino. The primary tumor site was uterine in 45% of cases, followed by extremities (30%), retroperitoneum (15%), and other locations (10%). Most tumors were high grade (80%), with the remainder being intermediate or low grade (20%). At diagnosis, 40% of patients presented with stage III disease, 35% with stage II, and 25% with stage IV. Treatment modalities varied: 85% underwent surgical resection, 50% received radiation therapy, and 60% were treated with systemic therapy. Notably, 40% received all three modalities, indicating a multimodal approach in a significant portion of patients. Survival data, available for all patients, revealed a median OS of 24 months. The 1-year survival rate was 70%, decreasing to 40% at 3 years. The survival curve demonstrated a gradual decline, highlighting the aggressive nature of LMS.

Conclusion: This single-institution, real-world analysis provides insights into the clinical and demographic characteristics of LMS patients treated in a community oncology setting. A high proportion of patients presented with advanced-stage, high-grade tumors and underwent multimodal treatment. Despite comprehensive management, outcomes remain poor, emphasizing the need for continued research into effective treatment strategies and earlier detection in community-based populations.

Patient demographics, Tumor characteristics, Treatment patterns and Survival outcomes

Category	Details
Median Age (years)	55 (range: 34–78)
Sex	Female: 60% (n=14) Male: 40% (n=9)
Race	White: 70% (n=16) Black: 20% (n=5) Other: 10% (n=2)
Ethnicity	Hispanic/Latino: 25% (n=6) Non-Hispanic: 75% (n=17)
Primary Tumor Site	Uterus: 45% (n=10) Extremities: 30% (n=7) Retroperitoneum: 15% (n=3) Other: 10% (n=2)
Tumor Grade	High grade (Grade 3): 80% (n=18) Intermediate/Low grade: 20% (n=5)
Stage at Diagnosis	Stage II: 35% (n=8) Stage III: 40% (n=9) Stage IV: 25% (n=6)
Treatment Modalities	Surgery: 85% (n=20) Radiation: 50% (n=11) Systemic therapy: 60% (n=14) All three modalities: 40% (n=9)
Median Overall Survival	24 months
Survival Rates	1-year: 70% 3-year: 40%

(P 331) **MAINTENANCE THERAPY (M-TP) WITH DACARBAZINE (DTIC) AFTER FIRST-LINE ANTHRACYCLINE-BASED DOUBLET IN ADVANCED LEIOMYOSARCOMA (LMS) PATIENTS (PTS): OUTCOMES OF A CASE SERIES IN A SINGLE REFERRAL CENTER**

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Objective: Doublet chemotherapy (ChT) with adriamycin and dacarbazine (ADM-DTIC) represents a first-line (1L) option for advanced LMS pts. Due to cumulative anthracycline toxicity, ChT is usually limited to six cycles (6c). The potential benefit of single-agent DTIC m-tp in pts achieving disease control after ADM-DTIC remains unclear. This study aims to explore the efficacy of adopting DTIC m-tp after ADM-DTIC on survival outcomes.

Methods: All consecutive metastatic LMS pts receiving ADM-DTIC as 1L tp from January 1st, 2015, at our institution, were retrieved. Pts with stable disease (SD) or partial response (PR) after ≥ 3 cycles ($\geq 3c$) were included in this analysis. On the evaluable pts, Overall Survival (OS) and Progression-Free Survival (PFS) were evaluated by using Kaplan Meier (KM) method. Time to event was calculated from the date of the ADM-DTIC treatment start. KM curves, stratified for the administration of DTIC m-tp were also constructed for both OS and PFS, and the median OS (mOS) and PFS (mPFS) were calculated. Cox model was used to estimate the effect of DTIC m-tp on OS and PFS and hazard ratios (HRs) were reported; pts on active surveillance (AS, i.e., not receiving DTIC m-tp), were considered the reference group.

Results: Of 52 metastatic LMS pts receiving ADM-DTIC as 1L tp, 28 were SD or PR after $\geq 3c$ and 24/28 were evaluable at the time of this analysis. Median age was 53 years, 18/24 were females, and the median follow-up was 38 months (mos); mOS and mPFS were 54 mos (IQR, 22 - 77) and 11 mos (10-21) respectively; mOS was 24 mos (19-77) for patients in DTIC m-tp and 54 mos (22-65) for pts in AS (HR: 1.26, $p=0.734$); mPFS was 11 mos (7-18) for patients in DTIC m-tp and 12 mos (10-28) for pts in AS (HR: 2.28, $p=0.107$).

Conclusion: In this retrospective single-center case series, DTIC m-tp following initial ADM-DTIC doublet did not show a survival benefit for advanced LMS pts both in terms of OS and PFS. However, results may reflect selection bias, as pts with higher tumor burden or symptomatic disease were likely favored for maintenance. Multicenter studies with standardized criteria are warranted to clarify DTIC maintenance benefits.

(P 332) MARGINAL EXCISION OF EXTREMITY DEDIFFERENTIATED LIPOSARCOMA WITHOUT RADIATION MAY BE SAFE IN SELECT PATIENTS

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Objective: Dedifferentiated liposarcoma (DDLPS) is a heterogeneous tumor comprising low-grade atypical lipomatous tumor (ALT) and high-grade sarcomatous components. This study evaluates local recurrence and metastasis rates in extremity DDLPS patients post-surgical resection, focusing on the impact of tumor grade at surgical margins and the role of adjuvant radiation therapy.

Methods: A retrospective analysis was conducted on 137 patients with pathologically confirmed extremity DDLPS who underwent surgical resection between 1995 and 2024. Outcomes assessed included local recurrence-free survival, metastasis-free survival, and overall survival. Statistical analyses utilized Chi-square tests for categorical variables, t-tests for continuous variables, and Kaplan–Meier methods for survival estimates.

Results: Among the 137 patients (mean age 67 years; mean tumor size 16 cm), 54.7% had negative surgical margins, while 45.3% had positive margins. Of those with positive margins, 48.3% involved only the ALT component. Notably, patients with positive margins confined to the ALT component who did not receive radiation therapy 40%(n=12) exhibited no local recurrences or metastases. From all of the patients in this study (n=137), those with negative margins treated without radiation therapy 28%(n=21), demonstrated low recurrence 4.7%(n=1) and metastasis 23%(n=5) rates.

Conclusion: In select extremity DDLPS cases where positive surgical margins are limited to the ALT component, marginal excision without adjuvant radiation therapy may be oncologically safe, offering comparable outcomes to those with negative margins. This approach can enhance functional preservation by avoiding unnecessary radiation exposure.

RESULTS

Margin Status	Treatment Modality	Patients (n)	Local Recurrence	Metastasis
Positive – ALT Component Only	Surgery Only	12	0 (0%)	0 (0%)
	Surgery + Radiation	18	1 (5.5%)	2 (11%)
Positive – Sarcomatous Component	Surgery Only	1	0 (0%)	1 (100%)
	Surgery + Radiation	31	3 (9.7%)	7 (22.6%)
Negative Margins	Surgery Only	21	1 (4.7%)	5 (23%)
	Surgery + Radiation	54	1 (1.8%)	6 (11%)
All Patients	Surgery Only	34	1 (2.9%)	6 (17.6%)

(P 333) **METABOLIC SYNDROME CORRELATION WITH LIPOSARCOMA INCIDENCE AND OUTCOMES: A RETROSPECTIVE ANALYSIS.**

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Objective: Metabolic syndrome (MS) has been linked to the development of various cancers, but its association with liposarcoma (LPS) remains unexplored.

Methods: We conducted an IRB-approved, retrospective study to investigate the influence of MS and its components in LPS patients at the Sylvester Comprehensive Cancer Center. Medical records of LPS patients between January 2015 and June 2024 were reviewed. MS was defined as either a documented history of MS or the presence of at least three of the following four components: diabetes mellitus (DM), hypertension (HTN), hyperlipidemia (HLD), or obesity. Demographic, MS components and LPS data was collected. The percentage of MS in LPS patients was compared to the incidence in general population. Logistic regression analysis was used to assess the odds ratio (OR) of disease progression with different components of MS. Additionally, Cox proportional hazard ratio (HR) was calculated to assess the impact of MS and BMI on survival outcomes.

Results: Of the 132 LPS patients, 58% were male, and 34.5% were Hispanic, with a mean age of 64.5 years (Standard Deviation (SD) = 13.79), with the majority being White (83.2%). Subtypes included 46.2% dedifferentiated, 19.3% well-differentiated, 13% pleomorphic, and the remaining cases were myxoid and round cell pathology. Most tumors were axial (63.6%), and 41.2% of cases were Stage 3. Disease progression despite treatment and distant metastasis were observed in around one-third of patients, 34.5% and 35.3%, respectively. The overall mortality rate was 21%. HTN, DM, and HLD were prevalent in the cohort at 62.2%, 22.7%, and 57%, respectively. MS was present in 61.3% cases. BMI greater than 25 in 75.6% of patients with a mean BMI of 29.1 (SD = 5.6; 95% Confidence Interval (95CI) = 28.1-30.2). A significant proportion of people used HLD and DM medications, including 51.3% on statins and 17.6% on metformin. The Relative Incidence of MS was 1.5 ($p < 0.001$) in LPS patients compared to the general population. DM was associated with progressive disease with OR of 3.01 (95CI= 1.5-7.4), while obesity was associated with decreased risk of adverse outcomes (Table). No specific genetic variant was observed in LPS patients with MS.

Conclusion: Our study raises concern that individuals with MS may be at a higher risk of LPS. DM's association with disease progression might be related to insulin resistance. Decreased mortality with obesity might be secondary to better treatment tolerance.

Impact of Metabolic Syndrome Components on Liposarcoma Progression and Survival

	Prevalence	LPS PROGRESSION		LPS SURVIVAL	
		OR	p	HR	p
BMI		0.95	0.13	0.94	0.16
Obesity	38.7%	0.38	0.03	0.38	0.02
HTN	62.2%	0.85	0.75	1.31	0.58
DM	22.7%	3.01	0.04	0.94	0.91
HLD	57.1%	0.37	0.25	0.21	0.12

(P 334) MRI VOLUMETRIC AND MODIFIED CHOI-BASED ASSESSMENT OF TREATMENT RESPONSE IN EXTREMITY DESMOID TUMORS TREATED WITH NIROGACESTAT OR SORAFENIB

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Objective: Desmoid fibromatosis patients are typically treated with active surveillance and with drugs on progression, particularly sorafenib and, most recently, with nirogacestat. This study aimed to determine the objective signal and volume changes under therapy and over time, comparing both drugs using volumetric and modified Choi (mChoi) measurements.

Methods: This study included 17 patients with single-lesion extremity desmoid fibromatosis with standard-of-care MRI from March 2021-February 2024. Volumetric tumor segmentations were created on T2-STIR images, and diameter, mChoi, and volume measurements were computed at four time points: Pre-treatment (Pre-Rx), post-treatment 1 (Rx1), post-treatment 2 (Rx2), and post-treatment 3 (Rx3). The percentage change in diameter (RECIST), mChoi, and volume across time were computed with respect to Rx1 and compared in nirogacestat vs. sorafenib patients.

Results: Nirogacestat group (8 patients): o mChoi detected two progressions not detected by RECIST or volume. o From Pre-Rx to Rx1, the average mChoi decreased by 62% over 14 months, representing its maximum slope. From Pre-Rx to Rx3, the mChoi decreased by 66% over a period of 20 months of observation (-3.3%/month). o From Pre-Rx to Rx1, the average volume decreased by 17% over 14 months (maximum slope), and from Pre-Rx to Rx3, the volume reduced by 49% over a period of observation of 20 months (-2.45%/month). o By volume and mChoi a sustained response was observed in an average of 3 time points following

Pre-Rx (20 months). Sorafenib group (9 patients): o mChoi detected one response not detected by RECIST or volume. o From Pre-Rx to Rx1, the average mChoi decreased by 79% over 23 months, and from Pre-Rx to Rx3, the mChoi decreased by 49% over a period of observation of 34 months (-1.44%/month). o From Pre-Rx to Rx1, the average volume decreased by 20% over 23 months (maximum slope), and from Pre-Rx to Rx3, the volume decreased by 4% over a period of observation of 34 months (-0.09%/month). o By volume and mChoi a sustained response was observed in an average of 1 time point following Pre-Rx (23 months).

Conclusion: Patients treated with nirogacestat displayed larger magnitude of volumetric and mChoi changes across treatment, with the fastest positive response (highest slope) and similar period of sustained positive treatment effects compared to patients treated with sorafenib, indicating the potential advantage of nirogacestat as an effective treatment in desmoid tumors.

(P 335) OUTCOMES OF TALIMOGENE LAHERPAREPVEC IN SOFT TISSUE SARCOMA

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Objective: Talimogene laherparepvec (TVEC), an intralesional therapy to illicit an immunogenic anti-tumor response, has a favorable safety profile in phase II trial and may be an effective second-line therapeutic in sarcoma; however, there is a paucity of data on its therapeutic efficacy. We present a case series of patients who received TVEC for sarcoma at a high-volume sarcoma center.

Methods: A retrospective review of an institutional database for sarcoma patients who received TVEC between January 2018 and January 2025 was performed. We assessed treatment response, adverse events, duration of therapy, and progression-free survival. Response Evaluation Criteria in Solid Tumors v1.1 was used to assess treatment response. A total of 2-4 ml of intra-tumoral TVEC at 100 million plaque-forming units/ml was administered every 2-3 weeks.

Results: A total of four patients who had prior progression of disease on immune checkpoint inhibitors (ICI) received a median of 9.5 (range, 4-15) doses of TVEC over 26.5 (range, 10-49) weeks. One patient with angiosarcoma had a partial response, with a 79% decrease in lesion size after four treatments (Image 1, Panel A: at initial TVEC injection, Panel B: after 9 weeks at fourth TVEC injection), before having distant disease progression at 10 weeks. One patient with alveolar soft part sarcoma had metastatic disease with a good response to ICI but persistent local disease treated with TVEC. The local disease remained stable during 36 weeks of neoadjuvant therapy, with no evidence of recurrence at 33 weeks post-surgery. Two patients, with undifferentiated pleomorphic sarcoma and dedifferentiated chondrosarcoma, had progression of disease at 8 weeks. Only one patient experienced toxicity, which presented as mild flu-like symptoms hours after an injection. Therapy was held in one patient to allow for healing of an open wound that formed due to tumor necrosis. All patients received ICI in combination with TVEC.

Conclusion: This case series of patients receiving TVEC for sarcoma adds to the literature of intralesional therapies for this rare disease. Our experience suggests that TVEC may be

administered safely and may provide local tumor control in select patients who have failed prior therapy with ICI.

(P 336) PEXIDARTINIB RISK EVALUATION AND MITIGATION STRATEGY PROGRAM: 5-YEAR RETROSPECTIVE HEPATIC SAFETY ASSESSMENT

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Objective: First-in-class TKI pexidartinib (pexi; TURALIO®) is conditionally approved by the US FDA for the treatment of adults with symptomatic tenosynovial giant cell tumor (TGCT) based on the development of the TURALIO® REMS (tREMS) Program. We report hepatic safety data of pexi in adult patients (pts) with TGCT from the retrospective 5-year evaluation of the tREMS Program.

Methods: Cumulative hepatic data were collected from Aug 2019 to Jun 2024 from healthcare practitioners, pts, pharmacies, and distributors who participated in the tREMS Program. Liver AE reporting forms captured data for pts who experienced a liver AE or serious or potentially fatal liver injury. For liver injury events of concern (LIEC), data were manually extracted in May 2025 from the global safety database and pts narratives. All data were summarized using descriptive statistics.

Results: 784 pts were enrolled in the tREMS Program; 735 received ≥ 1 dispense of pexi. There were 45 pts (6.1%) with a LIEC (Table). The median (Q1, Q3) time to event onset was 27 d (21, 48). Most pts (73.3%) were on the same daily dose at the time of event compared with their initial dose; 46.7% and 24.4% of pts were taking a daily dose of 800 mg or 500 mg, respectively, at the time of event onset, reflective of the dose-equivalent formulations: 200-mg tablet (empty stomach) and 125-mg tablet (low-fat meal). The median (Q1, Q3) time to event onset was similar for patients taking a daily dose of 800 mg (22.5 d [18.5, 27.5]) at event onset and for pts taking 500 mg (29 d [19, 44]). As of last follow-up (Feb 2025), 71.1% of pts recovered, 13.3% were recovering, 13.3% had not yet recovered, and 2.2% had an unknown status.

Conclusion: The results from this retrospective 5-year hepatic safety assessment of the tREMS Program show that careful monitoring of liver enzyme levels, along with early intervention, can mitigate the risk of potential hepatotoxicity associated with pexi treatment in adult pts with TGCT. The frequency, pattern, and timing of serious hepatic AEs was consistent with previous reports, and no new safety signals were observed.

n (%)	n=45
Initial dose (mg)	
125	1 (2.2)
200	2 (4.4)
250	0
400	4 (8.9)
500	13 (28.9)
600	2 (4.4)
800	20 (44.4)
Unknown	3 (6.7)
Dose (mg) at time of event	
125	0
200	1 (2.2)
250	3 (6.7)
400	3 (6.7)
500	11 (24.4)
600	3 (6.7)
800	21 (46.7)
Unknown	3 (6.7)

(P 337) POOLED ANALYSIS OF TRABECTEDIN EFFICACY IN MYXOID/ROUND CELL LIPOSARCOMA FROM THREE PROSPECTIVE CLINICAL TRIALS

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Objective: Trabectedin is a standard of care (SOC) chemotherapy for recurrent/metastatic liposarcomas (LPS). LPS include genetically distinct subtypes: well-differentiated/dedifferentiated, pleomorphic, and myxoid/round cell liposarcoma (MRCLS). Clinical trials often group subtypes, not typically reporting comprehensive outcomes for each. We performed a pooled analysis of trabectedin efficacy in MRCLS across multiple trials to serve as an SOC efficacy baseline.

Methods: The Yale University Open Data Access Project was queried for prospective trabectedin trials. Seven were identified; 4 excluded (3 had no means to reference MRCLS within the data, 1 was a neoadjuvant trial). Participant-level data on patients (pts) with locally unresectable/metastatic MRCLS who received ≥ 1 trabectedin dose (1.0–1.5 mg/m² 24 hrs continuous infusion every 3 wks) were extracted from 3 trials: ClinicalTrials.gov NCT00060944 (Phase 2), NCT00210665 (expanded access), and NCT01343277 (Phase 3). Primary outcome was overall response rate (ORR; complete response or partial response per RECIST v1.1). Secondary outcomes included disease control rate (DCR; ORR + stable disease [SD]), duration of response, overall survival (OS; time between first date of trabectedin treatment and death), and duration of SD for pts with available data. Responses were assessed using RECIST by investigators in NCT01343277 and by independent review in NCT00060944. In NCT00210665, tumor assessment followed institutional standards, so only OS was analyzed.

Results: Eligibility criteria required that pts were intolerant to or had relapsed/progressed after

previous SOC cytotoxic chemotherapy. Sixty-three pts (42 from NCT01343277, 13 from NCT00060944, 8 from NCT00210665) were included: 32% (20/63) female, median age 50 (range, 20–75) yrs, and 79% (50/63) White. ORR was analyzed for 49 pts: 37 from NCT01343277, 12 from NCT00060944 (Table). For 22 pts with duration of SD data, 18 had SD ≥ 12 wks, 4 had SD < 12 wks; median duration of SD was 6.41 (range, 0.03–15.74) mo. OS data were available for 63 pts: median OS was 22.51 mo (95% CI: 16.99–34.33).

Conclusion: This represents one of the largest populations to date of pts with advanced MRCLS treated with trabectedin in prospective clinical trials. It is limited by typical factors affecting pooled analyses including heterogeneity across studies. Nevertheless, the results provide a trabectedin efficacy baseline against which to compare other therapies for MRCLS.

Best Overall Responses in 49 Pts with Advanced MRCLS Receiving Trabectedin.

	n/N (%)	95% CI
ORR	8/49 (16.3)	7.3–29.7
DCR	38/49 (77.6)	63.4–88.2
Best overall response		
Partial response	8/49 (16.3)	
SD	30/49 (61.2)	
Progressive disease	11/49 (22.4)	

(P 338) POORLY DIFFERENTIATED SYNOVIAL SARCOMA: A HISTOLOGIC CHALLENGE OF AN AGGRESSIVE VARIANT

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Objective: Poorly differentiated synovial sarcoma (PDSS) is a more aggressive variant of synovial sarcoma (SS). Histologic features differ from that of conventional SS; leading to incorrect diagnosis. We aimed to study histologic and molecular features of PDSS and highlight their differences from conventional SS.

Methods: 47 patients diagnosed with PDSS were identified amongst a total of 300 synovial sarcomas from a period of 8 years (2018-2025). Retrospective analysis of histologic features was performed and compared to a subset of conventional SS. Immunohistochemistry and

molecular profiles were documented.

Results: Age range of 47 patients was 12 to 64 years, median being 39 years. Male: Female ratio was 1.2: 1. Commonest site of involvement was soft tissue of lower extremity (52%). Morphologically, 11% tumours contained exclusive round cell component. Other 15% showed partial areas of malignant round cells in combination of conventional spindle cell pattern. Only 2% tumours showed biphasic morphology. Necrosis was present in 60% of tumours. Brisk mitoses ($> 10/2\text{mm}^2$) were noted in 50%. Poor differentiation was seen in recurrent SS in 5 cases. 22% patients experienced distal metastasis. On immunohistochemistry (IHC), all PDSS were positive for TLE1, AE1/AE3 and EMA. Immunohistochemistry for SS18 was performed in 30 % of cases, all of which were positive. Molecular translocation for SS18-SXX was done in 10 % cases, all of which showed positive results

Conclusion: Poor differentiation is a poor prognostic parameter in SS. PDSS has morphologic deviation from the conventional variant, leading to diagnostic challenges. We could demonstrate round cell morphology in a significant proportion of tumours mimicking Ewing sarcoma, lymphoma and rhabdomyosarcoma. Presence of necrosis and brisk mitoses were not found in conventional SS, thus being important diagnostic parameters for PDSS. TLE1 and epithelial markers aided the diagnosis; however IHC for SS18 was far more specific and sensitive, negating the need for molecular testing in most cases. Thus recognition of PDSS is relatively easier if conventional morphology co-exists; otherwise high index of suspicion with use of SS18 IHC preferably with molecular testing is required.

(P 339) POSTERIOR APPROACH FOR RADICAL RESECTION OF SACROCOCYGEAL CHORDOMA: A SURGICAL PERSPECTIVE FROM A TERTIARY REFERRAL CENTER

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Objective: Sacrococcygeal chordoma (CH) is a rare malignancy with complex surgical management due to its infiltrative growth and proximity to vital neurovascular and visceral structures. While the SACRO trial has questioned the role of surgery in primary cases, resection remains a valid option in selected operable patients. This study presents the long-term experience of a high-volume center with the posterior-only approach for radical CH resection.

Methods: We retrospectively reviewed all patients who underwent surgery for sacrococcygeal CH at Humanitas Research Hospital (Rozzano, Milan, Italy) between 1998 and 2024. All procedures were performed using a standardized posterior approach with an arched incision, originally described in a series of 8 patients by Gennari, Azzarelli, and Quagliuolo in 1987. The strategy involves en-bloc resection of the sacrum and tumor via high sacral osteotomy, without anterior or combined approaches.

Results: The technique was used in 19 patients who underwent surgical resection for sacrococcygeal CH. All patients were operated through an upward-arched incision, which allowed optimal exposure and may have contributed to a lower wound complication rate

(26.3%) compared to the original series (37.4%) where a downward-arched incision was used in some cases. Tumor size in our cohort was smaller than the size reported in the historical series (range 2-15 vs 12–20 cm), reflecting modern selection strategies favoring non-operative treatment for larger and higher tumors. The rate of local recurrence was 52.6%, in line with the literature and improved compared to the 62.5% reported in the original series. Additional patient demographics, tumor characteristics, and treatment details are summarized in Table 1.

Conclusion: The role of surgery in sacral CH is evolving. While definitive radiotherapy (RT) has gained traction following the SACRO trial, our experience supports posterior radical resection as a safe and effective option in selected patients. This may be explained by a contemporary tendency to surgically treat more favorable tumors, leaving more advanced cases to high-dose RT protocols. Standardizing the posterior approach may help optimize outcomes where surgery remains indicated.

Table 1. Clinicopathologic patients' characteristics

	N 19 (%)
Median age, y (range)	59.0 (29-80)
Sex (M/F)	9 (47.4)/10 (52.6)
First Symptom	
- Pain	11 (57.9)
- Mass	6 (31.6)
- Sphincter problems	2 (10.5)
Localization	
- sacrum	17 (89.5)
- coccyx	2 (10.5)
Adjuvant RT	6 (31.6)
Median follow-up, months (range)	57 (6.5 – 208.0)

(P 340) PREDICTORS OF LATE RECURRENCE AFTER SARCOMA SURGICAL RESECTION

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Objective: The vast majority of sarcoma recurrences occur within the first 2 years after diagnosis and treatment. Only 10% of recurrences take place greater than five years after diagnosis. After this time, surveillance is often de-escalated. We aimed to identify patient and tumor risk factors associated with sarcoma recurrence five years or later after surgical resection.

Methods: A retrospective analysis of a prospectively maintained single-institution database was utilized. Adult who underwent surgical resection of a sarcoma, were on regular, standardized surveillance, and subsequently had a recurrence were included in the study.

Patient and tumor characteristics were compared between recurrences that took place prior to and after five years from surgery. Local and distant recurrences were both included.

Results: The study population included 1290 patients; all had a sarcoma recurrence after surgical resection. Of these, 1059 (82%) experienced a recurrence within 5 years of surgery (early recurrence), while 231 (18%) recurred greater than 5 years later (late recurrence). There were no differences between the early and late recurrence groups with respect to sex, smoking history, race, or margin status. Late recurrence was significantly more likely to occur in patients younger than age 55 ($p < 0.001$) and those with well-differentiated tumors ($p < 0.001$, 9.2% early recurrence versus 26% late recurrence). Early recurrences were significantly more likely to occur distantly when compared to late recurrences, which were more likely to be local recurrences ($p = 0.011$). On multivariable logistic regression adjusting for histologic subtype, older age (greater than 55) was associated with decreased likelihood of late recurrence (OR .49, $p < .05$) compared to younger age. Those with pathologic stage IV disease were less likely to have late recurrence than those with stage I (OR 0.4, $p = 0.02$). Those with poorly differentiated tumors were less likely to have late recurrence than those with well-differentiated disease (OR 0.47, $p < .001$).

Conclusion: Late as opposed to early recurrence of sarcoma after surgical resection is perhaps more common than widely believed. Patients who recurred more than 5 years after surgical resection were more likely to be younger and have well-differentiated tumors. Late recurrences also were more likely to occur locally rather than distantly. These data speak to the importance of long term surveillance and management of sarcoma patients beyond the traditional five years of follow up.

(P 341) PROGNOSTIC RELEVANCE OF CYCLOPHOSPHAMIDE DOSE FOR HIGH-RISK RHABDOMYOSARCOMA IN ADULT PATIENTS TREATED WITH VAC THERAPY

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Objective: Adult rhabdomyosarcoma (RMS) is often classified as high-risk and has a poor prognosis. Treatment strategies frequently follow pediatric protocols, such as vincristine, actinomycin D, and cyclophosphamide (VAC) regimen, despite concerns regarding toxicity in adults. Although higher doses of cyclophosphamide (CPA) may improve outcomes, the optimal dosing in adult patients remains unclear due to limited adult-specific data. In this study, we evaluated the association between the dose intensity of CPA and outcomes for high-risk RMS in adult patients.

Methods: We retrospectively reviewed patients with histologically confirmed RMS who received VAC therapy as initial chemotherapy at our institution between February 2014 and April 2024. High-risk was defined according to the Children's Oncology Group (COG) classification, and all patients had distant metastasis. We classified the patients as pediatric (≤ 19 years) and adults

(≥20 years). CPA dose was administered at initial dose into three groups (1.2, 1.5, or 2.2 g/m²); 2.2 g/m² was mainly used in adults, the dose was reduced after 4–7 cycles mainly due to hematologic tolerability concerns. Progression-free survival (PFS) and overall survival (OS) were analyzed using Kaplan–Meier method.

Results: During the study period, 40 patients with high-risk RMS received VAC therapy at our institution. Three patients were excluded (1 discontinued follow-up during VAC, 2 received VAC on an irregular schedule). Among the 37 patients analyzed, 13 were pediatric (median age, 14; range, 5-19) and 24 were adults (median age, 27; range, 20-60). Alveolar histology was noted in 25 patients (67.6%), all of whom were positive for FOXO1 fusion. The median PFS was 13 months in pediatric patients and 7 months in adults ($p = 0.0023$). The median OS was 37 months in pediatric patients and 12 months in adults ($p = 0.0022$). Among adult, 8 patients received CPA at a dose of 1.2 g/m², 1 received 1.5 g/m², and 15 received 2.2 g/m². No statistically significant differences were observed in PFS ($p = 0.77$) or OS ($p = 0.54$) between patients who received 1.2 g/m² and those who received 2.2 g/m².

Conclusion: In this retrospective analysis, a high starting dose of cyclophosphamide did not result in a statistically significant survival difference compared to a low-dose regimen in adult patients with high-risk RMS.

(P 342) PROGNOSTIC RELEVANCE OF TUMOR LOCATION IN MYXOID LIPOSARCOMA

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Objective: Myxoid liposarcoma (MLS) is a common extremity soft tissue sarcoma with favorable local control, likely due to its radiosensitivity and expansile growth pattern. The influence of anatomic presentation on outcomes remains unclear.

Methods: We retrospectively reviewed 112 patients with localized MLS who underwent surgical resection. Tumors were classified by MRI into four anatomic types: superficial (n=14), intramuscular (n=23), intermuscular (n=33), and extracompartmental (n=23). Radiation therapy was given in 52 patients with large or high-grade tumors.

Results: Median follow-up was 63 months. Five- and ten-year local recurrence-free survival (LRFS) rates were 85% and 83%, respectively. Intramuscular MLS showed no local recurrence, with progressively higher recurrence in superficial (7.1%), intermuscular (9.1%), and extracompartmental (44%) types. Metastasis-free survival (MFS) was 83% at 5 years and 78% at 10 years, with the lowest metastasis rate in intramuscular tumors (4.4%). Disease-specific survival (DSS) was 94% and 89% at 5 and 10 years. Anatomic presentation, margin status, and radiotherapy influenced LRFS; tumor size and grade influenced MFS and DSS.

Conclusion: Anatomic presentation significantly impacts local control in MLS. Intramuscular

MLS demonstrates excellent outcomes, suggesting that small, low-grade intramuscular tumors may not require radiotherapy. Anatomical classification may aid in individualizing treatment strategies.

Univariate Log-rank and multivariate Cox hazard analysis of prognostic factors.

Variable	n	Local recurrence-free survival			Metastasis-free survival			Disease-specific survival		
		Uni- variate	Multivariate			Uni- variate	Multivariate			Uni- variate
			Exp (B)	95% CI	p		Exp (B)	95% CI	p	
Age (year) ^a	112	0.12				0.25				0.08
Size ^b	107	0.48			0.001	6.93	1.90-25.3	0.003	0.02	19.74
FNCLCC grade ^c	90	0.82			<0.001	4.75	2.39-9.42	<0.001	11.5	3.20-41.4
Round cell percent (5%)	94	0.24			0.13				0.38	
Microscopic margins	108	<0.001	4.31	1.25-14.8	0.021	0.75			0.53	
Radiation therapy	112	0.007	0.215	0.057-0.804	0.022	0.60			0.29	
Anatomic presentation ^d	93	<0.001	9.84	2.46-39.5	0.001	0.14			0.042	1.32
Chemotherapy	112	0.14				0.16			0.17	

^a Age > 45 years;

^b Diameter > 10 cm;

^c FNCLCC grade 3 vs others;

^d Extrascompartmental vs others.

(P 343) PROGRESSION FREE SURVIVAL OF IMMUNE CHECKPOINT INHIBITORS IN THE FIRST-LINE TREATMENT OF METASTATIC SARCOMA: A SINGLE CENTER RETROSPECTIVE ANALYSIS.

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Objective: The role of immune checkpoint inhibitors (ICI) in the treatment of metastatic sarcoma remains off-label or investigational. Sarcomas are largely chemotherapy resistant, and there is an urgent need to explore alternative treatments in sarcoma to prolong survival.

Methods: Patients with metastatic sarcoma who received first-line ICI at our institution were identified via electronic medical records for retrospective analysis from May 2012 to July 2024. Patient (pts) and disease characteristics, including histology, PD-L1 tumor proportion score (TPS), and metastatic sites, were analyzed. PFS (date of metastasis diagnosis to disease progression or death due to any cause) was estimated using the Kaplan-Meier method, and Cox regression was used to assess the significance of covariates on PFS.

Results: Cohort had 94 patients with median age 63 years, 51% male, 49% undifferentiated sarcoma, 18% leiomyosarcoma, 31% other sarcomas. With regards to metastases, 63% had lung, 14% liver, and 15% bone. Of 94 patients, 61 patients had PD-L1 staining available. TPS were 0 for 46%, 1 for 3%, and 2 and 3 for 25% each. 94% received pembrolizumab, 4%

Nivolumab (3 with ipilimumab and 1 with relatlimab), and the remainder had trial enrolment. ICI monotherapy was employed in 85%, and in combination with other systemic treatments in 15%. Median PFS for all patients was 16.7 months. By histology, median PFS was 35.6 months for leiomyosarcoma, 9.2 months for undifferentiated sarcoma, and 18.5 months for other sarcomas. Patients receiving monotherapy had a median PFS of 17.5 months, compared to 15 months for combination therapy. The 6-, 1-, 2-, 3-, 4-, and 5-year PFS rates were 76%, 57%, 37%, 23%, 19%, and 15% respectively. The 3-year PFS rate for leiomyosarcoma was higher numerically than undifferentiated sarcoma (39% versus 23%), thereafter did not show any difference in survival. No patient or disease characteristics, including TPS, histology, or metastatic sites, were significantly associated with PFS.

Conclusion: We present a real-world retrospective study in patients with sarcoma treated with first-line checkpoint inhibitor immunotherapy. The PFS was encouraging at 16.7 months, with an intriguing revelation of better survival in leiomyosarcoma numerically. Our results could be biased due to patient selection, but it remains an area of study that should be promoted. Further studies should prospectively assess PFS in sarcoma in the first-line setting, given poor outcomes with chemotherapy.

(P 344) REAL-WORLD EXPERIENCE OF SORAFENIB IN DESMOID TUMOURS: A SINGLE-CENTRE AUSTRALIAN STUDY

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Objective: Sorafenib (SFN) has demonstrated clinical efficacy in desmoid tumours (DT) per Gounder et al (NEJM 2018). This study aimed to evaluate the real-world efficacy and safety of SFN in DT within the Australian context.

Methods: We conducted a retrospective single-centre study to assess the real-world outcomes of SFN in DT. Response was evaluated using RECIST 1.1. An exploratory imaging endpoint using MRI T2-weighted signal intensity (T2SI) was also investigated as a response measurement, with a change of at least 30% in T2SI over time arbitrarily defined as significant.

Results: Between Jan 2022 and Feb 2025, 13 patients (pts) received SFN. Median age was 35 (range 23-53) years and 12 (92%) were female. 11 (85%) pts received SFN as first line systemic therapy. All pts commenced SFN at 400mg. At analysis cutoff with a median follow-up of 11.8 months, 8 (62%) pts remained on SFN, 5 pts had ceased due to completion of 12-month treatment (15%), toxicities (15%) or disease progression (8%). Median duration of treatment was 8.9 months (range 3.1-NR). Best overall response as per RECIST was 1 (8%) partial response, 9 (69%) stable disease and 3 (23%) progressive disease. Median progression-free survival (PFS) was 17.7 months (95% CI 3.7-NA) and estimated 1-year PFS rate was 75% (95% CI 50-99%). Based on T2SI, 6 (46%) pts had a significant reduction by 32% (median, range 30-84%), 5 (38%) had a non-significant reduction by 27% (median, range 19-28%), 2 (15%) had a significant increase by 43% and 69% respectively in T2SI. Median PFS was 17.7 months (95% CI 3.7-NA) and estimated 1-year PFS rate was 84% (95% CI 63-100%). Most common adverse events were hand-foot syndrome (HFS, 54%, G1/2), mucositis (31%, G1/2), diarrhoea (31%, G1) and rash (31%, G1). Most common toxicities

resulting in dose reduction were HFS (15%, G2), rash (15%, G2) and hypertension (8%, G2). Treatment cessations were due to multiple concurrent toxicities (G1/2 rash, fatigue, diarrhoea).

Conclusion: Our real-world data showed that SFN has clinically meaningful activity in DT with acceptable toxicities, though ongoing follow-up is required to determine longer term survival. T2SI may be a complementary response measurement to RECIST, further evaluation and correlation with clinical symptoms in a larger cohort is warranted.

(P 345) **SARCOMA BIOPSY COMPARISON BETWEEN REFERRAL CENTERS AND TREATING CENTERS: THE MUSCULOSKELETAL TUMOR REGISTRY (MSTR) EXPERIENCE**

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Objective: Inappropriate pre-referral biopsy presents potential risks and complications. The Musculoskeletal Tumor Registry (MsTR) is a centralized record of patient, tumor, treatment, and outcomes data on musculoskeletal malignancies. This is the first report of patient data from the MsTR and aims to examine biopsy patterns for bone and soft tissue sarcoma, specifically how biopsies are performed at referring versus treating centers and the proportion of attempted excisions prior to referral.

Methods: This analysis includes all MsTR patients diagnosed with bone or soft tissue sarcoma and a completed "Disease and Treatment Summary" form including a known biopsy date. Study variables included demographic information, tumor characteristics, and biopsy details. Frequency distributions and bivariate analyses examined associations between patient, tumor, or biopsy characteristics and institution type. Separate analyses limited to excisional biopsies were performed. Pearson's chi-square test, Fisher's exact test, or independent two-sample t-tests assessed statistical significance at $p \leq 0.05$.

Results: Between 2016-2025, 889 patients at 7 centers were included, with 273 (30.7%) performed at the referring center. Of the biopsies performed at the referring center, 54.2% were incisional or excisional biopsies. Of 645 soft tissue sarcomas, 136 (21.1%) had incisional or excisional biopsy prior to referral. 85/94 (90.4%) of the excisional biopsies done prior to referral had positive margins or margins that were not possible to assess. Core needle biopsy was more commonly performed at treating centers (74.0% vs 44.7%, $p < 0.001$), whereas excisional biopsy was more commonly performed at referral centers (35.5% vs 9.6%, $p < 0.001$).

Conclusion: Inappropriate sarcoma excisions are known to impact patient care, resulting in diagnostic delays, increased need for additional interventions, and increased concern for local recurrence. Using the MsTR to compile comprehensive multi-institutional data and benchmarking, we found an overall rate of incisional biopsies or attempted excisions prior to referral to a sarcoma specialist of 4.9% in bone tumors and 21.1% in soft tissue tumors.

(P 346) **SURROGATE ENDPOINTS FOR OVERALL SURVIVAL IN ADVANCED SOFT TISSUE SARCOMA TRIALS: A SYSTEMATIC REVIEW AND META-ANALYSIS**

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Objective: Randomized controlled trials (RCTs) are the gold standard assessment of determining if a treatment has an effective outcome by prolonging overall survival (OS). The assessment of OS requires large patient numbers and prolonged follow-up. Given these challenges, alternate endpoints are used as a surrogate for OS to allow a more rapid measure of treatment efficacy. These include progression free survival (PFS), 3-month progression free survival (3moPFS), 6-month progression free survival (6moPFS) and overall response rates (ORR). However, the use of these surrogate endpoints remain controversial. In soft tissue sarcoma (STS) RCTs, intermediate endpoints are increasingly used as primary endpoint. Our objective is to perform a systemic review of RCTs in patients with advanced STS and complete a meta-analysis to evaluate the surrogacy of these alternate endpoints for OS.

Methods: A systemic search of Medline, Embase, Clarivate WoS and Cochrane Central Register of Controlled Trials for RCTs in adults with advanced STS, published between Jan 1946 to Dec 2024, was performed. Non-randomised and non-comparative trials, trials including bone/Kaposi sarcoma, GIST, reviews and meta-analyses were excluded. The relationship between surrogate endpoints and overall survival (OS) was evaluated using weighted linear regression, comparing the HR for OS with the HR for PFS and the odds ratio for ORR, 3moPFS, and 6moPFS. The coefficient of determination (R²) was used to measure the strength of the association, R² >0.8 signifies strong surrogacy. Surrogate endpoints were only included in the analysis if available. PFS was only included if the HR was available.

Results: Of 10,062 articles, 59 trials (comprising 12,471 patients) met the inclusion criteria. Of these, 42 trials included any STS and 17 included specific subtypes. Phase II design represented 29 trials, 27 Phase III trials and 3 were not documented. Trials the first line setting represented 29 trials.

Conclusion: Of all the surrogate endpoints utilized in STS RCT, PFS correlates best with OS. However, this trial level analysis showed weak correlation for all surrogate endpoints when compared to OS. Despite the limitations of relatively small number of studies and heterogenous population, OS should remain the primary endpoint in STS RCTs, especially in a registration/phase III trial setting. This study highlights the urgent need to identify a true surrogate endpoint for OS, if any, by examining patient level data of identified trials in this study.

Results

Surrogate end point	N available for Correlation analysis	Correlation coefficient with HR for OS	Coefficient of determination (R^2)	p-value
HR for PFS	34	0.60	0.36	<0.001
OR for RR	27	0.31	0.09	0.11
OR for 3moPFS	22	0.25	0.06	0.25
OR for 6moPFS	20	0.27	0.07	0.25

(P 347) SURVIVAL ANALYSIS AND PROGNOSTIC FACTORS OF SOFT TISSUE SARCOMAS OF THE TRUNK AND EXTREMITIES TREATED BETWEEN 2010 AND 2015: EXPERIENCE OF THE BRAZILIAN NATIONAL CANCER INSTITUTE

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Objective: To evaluate the fiveyear overall survival (OS) of patients with soft tissue sarcomas (STS) located in the trunk and extremities, who underwent surgical treatment at the National Cancer Institute (INCA).

Methods: A retrospective cohort study conducted between 2010 and 2015, analyzing survival rates and clinicopathological characteristics. The statistical tests log rank, Cox regression, and chisquare were applied.

Results: A total of 223 patients were included, of whom 106 (47.53%) were men and 117 (52.46%) were women. Patients with high grade tumors had a significantly lower five year OS compared to patients with low grade tumors (HR = 5.21; 95% CI: 3.11–8.73). Patients with tumors < 5 cm had better OS compared to those with tumors ≥ 5 cm (HR = 1.99; 95% CI: 1.12–3.54). Patients in stages III and IV had an OS at least four times lower. No significant differences were observed regarding other prognostic factors.

Conclusion: The five year OS data, along with the clinico pathological characteristics and followup details, helped to outline an epidemiological profile of patients with STS undergoing surgical treatment at INCA, with results comparable to those found in the biomedical literature.

(P 348) **SYNOVIAL SARCOMA INVOLVING NERVES: HIGH RATE OF MISIDENTIFICATION AS BENIGN TUMORS**

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Objective: Synovial sarcoma can present as a slow-growing mass in the extremities, frequently mimicking benign or less aggressive conditions. Its nonspecific clinical and radiographic features can lead to diagnostic confusion, particularly with peripheral nerve sheath tumors. Misidentification may result in delayed diagnosis and potential compromise of oncologic outcomes. This study aims to characterize cases of primary synovial sarcoma involving peripheral or central nerves, evaluate the clinical and radiologic features contributing to misdiagnosis, and assess the impact on treatment and outcomes.

Methods: A retrospective review was conducted of all patients diagnosed with synovial sarcoma of the extremities, pelvis, or trunk at a single institution between 1994 and 2022. Patients with synovial sarcomas involving or initially thought to arise from nerves were identified for subgroup analysis. For these patients, data regarding initial diagnosis, misdiagnosis, initial treatment approach, and time to definitive oncologic management were recorded.

Results: A total of 173 patients were diagnosed with synovial sarcoma of the extremities, pelvis, or trunk. Of these, 41 tumors (24%) involved a peripheral nerve (n=38) or a nerve root (n=3). The mean age of patients was 40 years at diagnosis. Most commonly, the tumor arose in the lower extremity (n=20, 49%). At the time of presentation, 15 (37%) were misdiagnosed as a benign tumor, most commonly a schwannoma (n=6). Thirteen of 15 patients were presumed to have a benign diagnosis based on imaging, and two patients had an initial needle biopsy diagnosis of a schwannoma and a desmoid tumor (Table 1). Among patients with nerve involvement, misdiagnosis was associated with a higher rate of non-oncologic excision (OR 13.3, 95% CI [2.80, 63.4], $p < 0.001$) but not disease-specific survival (DSS) ($p = 0.99$). Thirteen of the 15 patients (87%) required repeat wide local excision or amputation for oncologic margins. None of the misdiagnosed patients had a local recurrence. Among patients with nerve involvement, tumors that were misdiagnosed were more likely to be smaller than 5 cm (OR 0.13, 95% CI [0.03–0.58]) and were less frequently treated with chemotherapy (OR 0.19, 95% CI [0.04–0.86]).

Conclusion: A high proportion of patients with synovial sarcoma involving nerves were misdiagnosed as benign conditions, with a majority receiving subsequent non-oncologic surgical interventions that may compromise surgical margins and local control.

(P 349) **THE COST OF SURVEILLANCE IN CALIFORNIA: MRI UTILIZATION IN RECURRENT EXTREMITY SOFT TISSUE SARCOMA**

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Objective: To evaluate the 5-year cost of MRI surveillance for extremity soft tissue tumor (STS) patients following surgical resection in California, stratified by recurrence.

Methods: This retrospective cohort study analyzed the 2017–2024 Humana Pearl Diver M170 Ortho dataset for California patients who underwent extremity STS resection between 2010–

2018, using specific Current Procedural Terminology (CPT) codes for upper and lower extremities. MRI use over a five-year surveillance period was tracked via CPT codes. Recurrence was defined by CPT codes for subsequent tumor excision, radiation, or chemotherapy during the surveillance period. Financial burden was evaluated using insurer-reported reimbursement amounts. Key outcomes included number of MRIs, average cost per MRI, and total surveillance cost per patient.

Results: A total of 1,793 patients (765 upper extremity, 1,028 lower extremity) were identified (mean age 58.18 years; 53.5% female). Of these, 132 (7.36%) experienced recurrence, while 1,661 (92.6%) did not. Patients without recurrence underwent an average of 4.2 MRIs at a cost of \$865.30 each, resulting in a total of \$ 3,043.61 per patient for surveillance. Those with recurrence underwent an average of 6.7 MRIs at a cost of \$983.29 each, resulting in a total of \$5,240.95 per patient for surveillance. Stratification by extremity is detailed in Table 1.

Conclusion: Recurrent extremity STS patients required 59.5% more MRIs (6.7 vs. 4.2) and incurred 72% higher total surveillance costs (\$5,241 vs. \$3,044) over 5 years. The higher cost per-MRI in the recurrence group (\$983 vs \$865) further amplified this financial strain. These findings highlight the significant economic disparities in MRI surveillance for extremity STS, emphasizing the importance of risk stratification and tailored surveillance protocols to improve resource allocation, thereby balancing clinical benefits with economic sustainability in STS.

Table 1. Surveillance Metrics Stratified by Extremity and Recurrence Status

	Subgroup (n)	Age (SD)	Sex	# of MRIs	Cost per MRI	Total Surveillance Cost
Recurrence	UE (49)	57.78 (19)	22F/27M	7.85	\$927.98	\$5389.42
	LE (83)	56.93 (19)	35F/48M	5.45	\$1038.6	\$5092.48
	Combined (132)	57.36	57F/75M	6.65	\$983.29	\$5240.95
No Recurrence	UE (716)	59.21 (16.6)	385F/331M	3.97	\$793.33	\$2735.22
	LE (945)	58.78 (15.7)	518F/427M	4.32	\$937.27	\$3352
	Combined (1661)	58.99	903F/758M	4.15	\$865.30	\$3043.61

(P 350) THE PATTERN.ORG SARCOMA CONSORTIUM: BUILDING A MULTI-INSTITUTIONAL DATA RESOURCE FOR THE SARCOMA RESEARCH COMMUNITY

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Objective: Sarcomas are rare, heterogeneous cancers with poor outcomes. Molecularly focused research has led to breakthroughs, notably afami-cel in synovial sarcoma and nab-sirolimus in PEComa. To accelerate more advances, a comprehensive database that can accommodate detailed histological, clinical, and molecular characterization, with robust biobanking infrastructure, is needed. While many academic centers have internal registries, these are not multi-institutional and do not account for all types of translational data, limiting sample size and utility. Pattern.org, an initiative of the Rare Cancer Research Foundation (RCRF), has partnered with community and academic institutions and patients to provide fresh tissue collection, biobanking logistics, and specialized software for multi-omic clinico-molecular data collection, aggregation, and harmonization.

Methods: Sarcoma patients across the US were recruited and consented. The Pattern biologistics team arranged for fresh tissue transfer to research labs, while clinical records and molecular results were ingested directly into the RCRF research ecosystem by the Pattern team. Partnerships with the University of North Carolina (UNC) through an internal registry, and Parker Institute for Cancer Immunotherapy (PICI) through their AMADEUS trial, have added additional data.

Results: Pattern collected 110 fresh sarcoma tissue samples from 54 centers across the US and delivered them to partner research labs. 61% were female with an average age of 54, 22% had molecular sequencing and clinical records. The UNC cohort added 269 patients seen by sarcoma medical oncology in 2024. The average age was 56 years, 62.5% were female, and 42.8% had molecular sequencing. The PICI cohort added 9 sarcoma patients of various types treated with CTLA-4 + PD-1 with comprehensive longitudinal multi-omic data.

Conclusion: This pilot sarcoma data consortium project combined efforts from RCRF, UNC and PICI. These data offer some preliminary insights into the cohort, but we seek additional partners to facilitate a multi-institutional consortium around sarcoma sample and data collection and sharing. We plan to bring additional institutions in as we expand this resource in the coming year.

(P 351) THE ROLE OF SOCIOECONOMIC DISPARITIES ON SURVIVAL OUTCOMES IN MALIGNANT PERIPHERAL NERVE SHEATH TUMORS

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Objective: Malignant Peripheral Nerve Sheath Tumors (MPNST) are rare and aggressive sarcomas with poor prognosis. Factors influencing survival include status of neurofibromatosis type 1 (NF1), tumor size, and adequacy of resection margins. Emerging evidence indicates socioeconomic factors may also impact survival rates. This study aims to compare outcomes of MPNST patients (pts) treated at a tertiary center with national data, focusing on social determinants of health.

Methods: We conducted a retrospective study of pts with NF1-associated MPNST treated at MD Anderson Cancer Center (MDA) between 1980-2020. We collected data and assessed socioeconomic status using Center for Disease Control and Prevention's (CDC) Social Vulnerability Index (SVI), defining high vulnerability as SVI ≥ 0.5 . We compared our results to the Surveillance, Epidemiology, and End Results (SEER) program. Survival analysis was performed using Cox regression and Kaplan-Meier methods.

Results: Of ~900 pts with NF1, 174 developed MPNST. At presentation, 72% had localized disease and 28% had metastases, compared to 54% localized and 34% metastatic in the SEER population. There was no difference in overall survival (OS) when comparing MDA localized NF1-MPNST to SEER cases. The median SVI was 0.80 (interquartile range [IQR], 0.57-0.92) for MDA pts with NF1-MPNST, with 141 pts categorized as having a high SVI (≥ 0.5 -1.0) and 33 pts categorized as low SVI (< 0.5). A lower educational level was independently associated with poorer OS (hazard ratio 4.2, $P=0.008$). Additionally, the MDA NF1-MPNST cohort included a higher proportion of African American (19.5% vs. 10.6%) and Hispanic (23.6% vs. 17.8%) pts compared to the SEER population ($P=0.001$). Finally, we compared the actual OS (aOS) of the NF1-MPNST cohort to the predicted OS (pOS) from the Sarcuator and MONACO nomogram models. The aOS was found to be 35.8% (95% confidence interval 28.3% - 43.4%), significantly lower than the pOS of 69% (Sarcuator) and 51% (MONACO).

Conclusion: High SVI and low education were linked to worse OS, suggesting that socioeconomic barriers affect access to care. Actual survival was markedly lower than predicted, underscoring the need to address social determinants to improve outcomes and highlighting the need to incorporate social risk factors into the research and care of rare cancers.

(P 352) TIME TOXICITY AND EFFECT OF CHEMOTHERAPY FOR PATIENTS WITH METASTATIC SOFT TISSUE SARCOMA - A RETROSPECTIVE REAL-WORLD STUDY OF 244 PATIENTS

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Objective: Patients with metastatic soft tissue sarcoma (STS) often undergo multiple lines of chemotherapy. These treatments are associated with toxicity, not only due to adverse effects, but also in terms of time spent in hospital—so-called time toxicity. In this study, we analyzed overall survival, treatment efficacy, and hospital time burden in a cohort of patients with metastatic STS receiving one or more lines of chemotherapy.

Methods: We included all patients diagnosed with STS (ICD-10/ICD-11) who received at least one dose of doxorubicin as first-line therapy between 2017 and 2023 at the Department of

Oncology, Herlev Hospital, Denmark. Clinical data were extracted from electronic health records (Sundhedsplatformen, Epic). Statistical analyses were performed using RStudio (version 2024.12.1). Time to next treatment (TTNT) was used as a proxy for progression free survival. Time spend in hospital was defined as the number of days with at least one hospital contact (including outpatient visits, treatments, scans, blood draws, etc.) and expressed as a proportion of the patient's remaining lifetime.

Results: A total of 244 patients were included. Of these, 153 received doxorubicin with dexrazoxane, 47 received doxorubicin with olaratumab, and 44 received doxorubicin monotherapy. Median overall survival (OS) for the entire cohort was 21.7 months, with no statistically significant difference between treatment subgroups. Patients with leiomyosarcoma had the longest median OS at 32.2 months. TTNT following first-line doxorubicin was 5.4 months, while TTNT for subsequent lines ranged from 3.8 to 4.7 months. Median time spend in hospital was 20.3% out of the patients' remaining lifetime.

Conclusion: This study provides novel and comprehensive data on survival outcomes and treatment efficacy in patients with metastatic STS. Importantly, our findings underscore that a substantial proportion of patients' remaining lifespan is spent attending hospital, emphasizing the need to consider time toxicity in treatment decisions and shared clinical decision-making.

(P 353) TREATMENT OF ADVANCED EPITHELIOID SARCOMA WITH COMBINATION TAZEMETOSTAT AND PEMBROLIZUMAB

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Objective: Epithelioid sarcoma (ES) is an aggressive soft tissue sarcoma accounting for < 1% of soft tissue sarcomas. Tazemetostat, an oral selective inhibitor of EZH2, is a treatment option for advanced ES. Other treatment options include anthracycline-based or other cytotoxic chemotherapy and tyrosine kinase inhibitors with modest clinical benefit. Here we present data from two patients at a single institution treated with tazemetostat in combination with immune checkpoint inhibitor therapy.

Methods: We conducted a retrospective review of two patients with advanced ES treated with combination tazemetostat and pembrolizumab (PD-1 inhibitor) 200 mg every three weeks at our institution.

Results: Patient A, a 38-year-old man, presented with ES of the right hemipelvis, treated with neoadjuvant adriamycin/cisplatin, surgery, and adjuvant radiation (RT). Four years later found to have metastatic disease, treated with gemcitabine/paclitaxel, pazopanib, and targeted RT. On progression, tazemetostat yielded stable disease for 7 months and continued with RT to a right humerus lesion for 24 additional months. At progression, patient was initiated on combination tazemetostat and pembrolizumab with partial response for 27 months. Adverse events were Grade 2 nausea. Patient B, a 30-year-old man, presented with ES of the left wrist, treated with surgical resection and adjuvant RT. Two years later found to have metastatic disease, treated with vincristine/cyclophosphamide/ifosfamide/etoposide,

gemcitabine/docetaxel, pazopanib, and targeted RT. At progression, tazemetostat yielded stable disease for 20 months and continued with RT to bilateral femur lesions for 3 additional months. On progression, combination pembrolizumab was added to tazemetostat yielding stable disease for 10 months and continued with RT to a scalp lesion for an additional 9 months. Pembrolizumab was held at 19 months for Grade 3 autoimmune pancreatitis. The patient has recovered and continues tazemetostat while considering pembrolizumab resumption.

Conclusion: In both cases, pembrolizumab was added to tazemetostat at progression, yielding sustained and durable response for treatment of ES. This demonstrates the potential for combination epigenetic regulation and immunotherapy in sarcoma.

(P 354) UNEXPECTED RESPONSE TO ERIBULIN IN A REFRACTORY LEIOMYOSARCOMA PATIENT WITH HEREDITARY P53 MUTATION

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Objective: To describe an unexpectedly nice response to eribulin in a heavily pre-treated patient with leiomyosarcoma and germline p53 mutation

Methods: At the age of 57, a patient was complaining of upset stomach associated with nausea, abdominal pain and fatigue. In Feb 2023, CT imaging showed multiple bilateral pulmonary nodules, lytic lesion in the T9 vertebral body, multifocal hepatic masses, mild periportal adenopathy, several subcutaneous nodules, and a lytic lesion of medial right iliac bone. Liver mass biopsy done Feb 2023 showed leiomyosarcoma. NGS of the liver mass showed RB1 and TP53 mutations as well as BCL6 rearrangement. It was microsatellite-equivocal with low tumor mutational burden. PDL-1 0%. PET showed widely metastatic disease as well as a large left thigh leiomyosarcoma, not appreciated previously. Over the next year, she tried single-agent doxorubicin, combo of doxorubicin/dacarbazine, pazopanib, and trabectedin. She also had radiation to the left thigh mass. Due to ongoing progression, she was started on fifth-line therapy with eribulin late April 2024. Intriguingly, she found out her nephew died of leiomyosarcoma at the age of 24 and her nephew's daughter was found to have hereditary p53 mutation. Despite her age, due to this family history, we sent her to genetic counseling in Feb 2024; she was found to have a pathogenic germline p53 mutation to match that found in her tumor NGS.

Results: She has maintained on eribulin since, with latest CT May 2025 showing more or less stability (>1 year since starting). She is having more neuropathy and constipation the longer the drug is used, but certainly this drug has managed her disease a lot longer than expected.

Conclusion: Wozniak et al showed that p53 mutations were associated with significantly better response to eribulin in the sarcoma cohort studied in EORTC trial. In patients with tumors that harbor p53 mutations somatically or even the hereditary p53 mutations, should eribulin be a more standard drug tried alone or in combination with more targeted therapy?

(P 355) **CLASSIFYING WOUND HEALING COMPLICATIONS IN SURGICALLY TREATED EXTREMITY SOFT TISSUE SARCOMA**

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Objective: Wound healing complications occur in up to one-third of soft tissue sarcoma (STS) patients following limb-sparing resection and are a major source of morbidity. Despite their prevalence, no universally accepted classification system exists to characterize complication severity. We aimed to develop and apply a more comprehensive reporting system to enhance accuracy and clinical relevance.

Methods: We conducted a retrospective review of 186 adult patients with extremity or trunk STS treated surgically by orthopedic oncologists at a single institution (2013–2023). Data were imported to REDCap via extraction from the Electronic Medical Record. Exclusion criteria included intra-abdominal/retroperitoneal, intrathoracic, or head/neck tumors, or primary amputations. Wound healing complications were identified using previously reported terminology and a novel proposed scale (Types 1–4) reflecting level of intervention, OR return, and reconstructive demands. A senior investigator verified all complication classifications, and the primary complication was determined when multiple types were present.

Results: Of 186 patients, 62 (33.3%) had a wound complication: 52 (83.9%) lower extremity, 9 (14.5%) upper extremity, and 1 (1.6%) trunk. The most common complication was skin/tissue necrosis (41.9%), followed by seroma (24.2%), hematoma (12.9%), dehiscence (11.3%), and deep infection (6.5%). Time to complication ranged from 26–89 days, with necrosis presenting latest (mean 89 days). Reoperation was required in 75.8% of cases, including 88.5% of necrosis cases and 100% of deep infections. Multiple reoperations occurred in 37.1% of all complications, highest for deep infection (75%) and necrosis (52.1%). Preoperative radiation was received by 66.1% of those with complications. Refer to Table 1 for the proposed grading system and distribution of complication types.

Conclusion: Our proposed framework of reporting captures complication severity and resource utilization. These offer insight into the patient experience as well as demands on the healthcare system. Incorporating this system into STS literature going forward may improve comparability of future prospective investigations.

Proposed Classification System for Wound Healing Complications (n = 62)

Type	Definition	Examples / Criteria	n (%)
1 – Minor	No intervention required	Mild dehiscence, superficial infection, seroma observed only. No wound VAC or aspiration.	3 (4.8%)
2 – Moderate	Non-OR intervention or delayed wound healing	Seroma aspiration, wound VAC, packing/dressing changes >6 weeks.	9 (14.5%)
3 – Major	Requires return to OR	I&D, debridement, re-closure, hematoma evacuation.	30 (48.4%)
4 – Complex	Multiple OR trips, flap/graft, amputations.	2+ reoperations, use of flap/graft.	20 (32.3%)

(P 356) DESMOID TUMORS: A RETROSPECTIVE ANALYSIS FROM A REFERRAL CENTER

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Objective: Desmoid tumors (DT) are rare, locally aggressive neoplasms with no metastatic potential but high risk of recurrence. Their unpredictable behavior makes management challenging. We present a retrospective series from a national sarcoma referral center, aiming to describe clinical features, treatment approaches and outcomes, and to identify prognostic factors.

Methods: We conducted a retrospective cohort study of patients with histologically confirmed DT treated at our center between 2011 and 2024. Event-free survival (EFS) was defined as the time from diagnosis to progression, treatment change, or death. Cumulative event rates were estimated using Kaplan-Meier method. Prognostic factors were analyzed using Cox proportional hazards models

Results: 109 patients were included (56.9% female; median age 36.8 years). Most frequent tumor sites were extremities/chest wall (n=44, 40.4%) and intra-abdominal (n=40, 36.7%), followed by abdominal wall (n=17, 15.6%), and head and neck (n=8, 7.3%). First-line strategies included surgery (n=54, 49.5%), active surveillance (AS) (n=24, 22%), hormone therapy ± non-steroidal anti-inflammatory drugs (HT+/-NSAIDs) (n=20, 18.4%), systemic therapy (chemotherapy/tyrosine-kinase inhibitors) (n=6, 5.5%), cryoablation (CA) (n=4, 3.7%), and radiotherapy (n=1, 0.9%). Among patients undergoing upfront surgery, 35.8% experienced

relapse (median relapse-free survival 26.5 months). In those managed with AS at some point (n=36), 22.2% showed spontaneous regression and 52.8% disease stabilization. CA (n=12) achieved a 69.5% response rate, and all responses were maintained after a median follow-up of 10.5 months. Median follow-up for the total cohort was 41.5 months. Median EFS was 57 months. In multivariate analysis, R1/R2 surgical margins (HR=2.26; p=0.006) and initial conservative approaches (AS or HT+/-NSAID) (HR=5.36; p=0.001) were independently associated with worse EFS. Tumor size >5 cm showed a non-significant trend (HR=2.00; p=0.10); and tumor location (p=0.55) and CTNNB1 mutation did not influence EFS (presence vs absence p=0.10, type of mutation p=0.96).

Conclusion: Our findings support individualized, multidisciplinary management of DT. AS (with or without HT+/-NSAIDs) are suitable for many, yet active therapy is often required. Surgery showed high relapse rates, and margins had a significant impact. Emerging therapies such as CA showed encouraging activity. Given the chronic nature of DT and potential treatment morbidity, shared decision-making is essential.

(P 357) DEVELOPMENT OF AN ALGORITHM TO IDENTIFY PATIENTS (PT) WITH DESMOID TUMORS (DT) IN A UNITED STATES (US) CLAIMS DATASET

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Objective: International Classification of Disease (ICD) codes 238.1 (ICD-9) and D48.1 (ICD-10), which represent neoplasms of uncertain behavior of connective and other soft tissue, were generally used for DT before Oct 2023 with limited precision. We aimed to construct an algorithm to more accurately identify pt with DT in a US claims dataset.

Methods: Adult pt in the University of Utah Health network who may have DT were identified via ICD codes 238.1/D48.1 in claims data from Jan 1, 2011 to Jul 31, 2023. Clinical notes or pathology reports were reviewed to confirm a past diagnosis (dx) of DT. Pt with confirmed DT dx and >2 DT-related encounters served as cases; pt without confirmed DT dx served as controls. Cases and controls were randomly assigned to the model construction or validation dataset on a 1:1 split. Stepwise logistic regression was performed using the construction dataset. Demographics, ICD codes and Current Procedural Terminology (CPT) codes were independent variables; case/control status was the dependent variable. The optimal threshold to identify pt with DT was determined using the receiver operating characteristic curve. Model performance was assessed in the validation dataset.

Results: A total of 1,593 pt were identified based on ICD codes 238.1/D48.1, of which 146 (9%) were eligible to serve as cases for algorithm development and 1,314 (91%) pt were eligible to serve as controls. The final algorithm consisted of 12 variables (age, sex, ICD codes for neoplasms and CPT codes for biopsy and imaging procedures [Table 1]). Among pt with a confirmed DT dx, the algorithm correctly identified 83.6% (sensitivity) [84.0% for specificity].

Individuals identified as a patient with DT by the algorithm have a 36.8% probability of a confirmed DT dx verified by chart review (positive predictive value, PPV) [97.9% for negative predictive value, NPV].

Conclusion: The predictive algorithm developed more accurately identified pt with DT compared to using the non-specific DT ICD-10 codes alone. As a result, this may help to further improve the precision of identifying pt with DT from future longitudinal analyses of claims data before Oct 2023.

Table 1. Model Variables of Algorithm to Identify Pt with DT

	Odds ratio of being associated with DT diagnosis
Age (in years)	0.97
Sex (male vs female)	0.36
ICD: Benign neoplasm of small bowel	27.4
ICD: Neoplasm of uncertain/unknown behavior of retroperitoneum/peritoneum	9.6
ICD: Neoplasm of uncertain/unknown behavior of breast	62.8
ICD: Other fibromatoses, pseudosarcomatous fibromatosis	7.0
ICD: Other fibroblastic disorders	97.2
CPT: Muscle biopsy with percutaneous needle	13.0
CPT: MRI brain/brain stem without contrast	0.04
CPT: Diagnostic CT thorax without contrast	0.14
CPT: MRI chest +/- contrast	53.8
CPT: MRI abdomen +/- contrast	4.5
Constant	0.30
Optimal threshold	8.2%
Adjusted R ²	48.3%

(P 358) EFFECT OF A HIGH-FAT MEAL ON THE PHARMACOKINETICS (PK) OF VIMSELTINIB, AN ORAL INHIBITOR OF THE COLONY-STIMULATING FACTOR 1 RECEPTOR (CSF1R), IN HEALTHY PARTICIPANTS

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Objective: Vimseltinib is indicated for treatment of adult patients with symptomatic tenosynovial giant cell tumor for which surgical resection will potentially cause worsening functional limitation or severe morbidity. Per the US prescribing information, and consistent with the pivotal MOTION phase 3 trial (NCT05059262) design, vimseltinib can be taken with or without food. Here, we report results of a randomized crossover study that investigated the effect of a high-fat meal on vimseltinib PK in healthy participants.

Methods: Adult participants (N = 18) were randomized 1:1 to receive a single 30-mg dose of vimseltinib in a fed (high-fat meal) or fasted state, followed by a 2-wk washout period and crossover between states (fed vs fasted) with repeated dosing. Plasma PK samples were collected throughout each period, and parameters were obtained by noncompartmental analysis. The log-transformed maximum concentration (C_{max}), area under the curve (AUC) from first dose to last quantifiable concentration (AUC_{0-tlast}), and AUC extrapolated to infinity

(AUC₀–inf) for fed (test) vs fasted (reference) were analyzed using an analysis of variance model. Geometric mean ratios (GMRs) and 90% confidence intervals (CIs) of C_{max}, AUC₀–t_{last}, and AUC₀–inf were constructed. Adverse events (AEs) were monitored throughout the study.

Results: Median C_{max} of vimseltinib was 338 ng/mL in the fed state and 470 ng/mL in the fasted state (median time to C_{max}, 6 h and 1 h, respectively). The GMRs (90% CI) of vimseltinib AUC₀–t_{last} and AUC₀–inf were 105.88 (99.03–113.20) and 103.51 (98.20–109.12), respectively. Geometric mean observed terminal half-life of vimseltinib was similar in the fed vs fasted state (135 h vs 137 h). All treatment-emergent AEs were grade 1/2, except for 1 serious AE of grade 3 increased blood creatine phosphokinase (possibly related to vimseltinib), which is consistent with the known mechanism of action of CSF1R inhibitors.

Conclusion: The 90% CIs for the GMRs of vimseltinib AUC₀–t_{last} and AUC₀–inf fell within the equivalence limits of 80% to 125%, indicating that administration of vimseltinib with a high-fat meal did not affect vimseltinib PK. Vimseltinib was well tolerated, and safety was consistent with prior reports. These results provide the basis for the approved labeling instruction that vimseltinib may be taken with or without food.

(P 359) EVALUATION OF PREOPERATIVE MYXOFIBROSARCOMA GROWTH AND SURGICAL MORBIDITY AFTER NEOADJUVANT RADIATION USING SEMI-AUTOMATED VOLUMETRIC ANALYSIS

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Objective: Myxofibrosarcoma (MFS) is an aggressive and highly recurrent type of soft tissue sarcoma typically treated with adjuvant or neoadjuvant radiation therapy (NRT) and surgical resection. Grossly, MFS tumors are often irregularly shaped with significant edema and stranding that can obscure true tumor borders. Additionally, tumor size often increases during NRT which may result in increased surgical morbidity. According to RECIST criteria, tumor response is measured by change in the single greatest dimension of the tumor, which may not accurately measure the entire tumor. An accurate method of measuring tumor size and thus preoperative change is needed to assess growth and morbidity. We conducted a study using 3D-Slicer to evaluate volumetric tumor changes and compare tumor response based on RECIST guidelines.

Methods: Any MFS patient treated with NRT and resection at our institution from 2002-2021 were included. Tumor measurements were obtained from pre- and post-radiation MRIs based on RECIST guidelines and three-dimensional analysis via 3D-Slicer. Tumors were grouped by location: Upper extremity (UE), lower extremity (LE), and torso tumors.

Results: Seventeen patients met our inclusion criteria. Ten experienced tumor growth following NRT, and five experienced increased surgical morbidity as a result. According to RECIST criteria, 3/3 UE tumors, 8/8 LE tumors, and 4/6 torso tumors were classified as stable disease. 1/6 torso tumors were classified as partial response, and 1/6 as progressive disease. According to volumetric 3D Slicer measurements, all three UE tumors decreased in volume while three LE tumors decreased and five increased. Of the torso tumors, all four stable disease tumors increased volume, while the partial response tumor decreased, and the progressive disease tumor increased.

Conclusion: Comparing tumor response using RECIST vs 3D Slicer showed several discrepancies and suggests that RECIST criteria may over or underestimate actual changes in MFS tumor size. This is likely due to most MFS tumors having irregular borders or significant stranding and perilesional edema that can obscure true tumor borders on unidimensional imaging. More information is needed for generalizability of this study's results; however, this study raises questions about the accuracy of reporting MFS tumor size and response using unidimensional RECIST guidelines vs volumetric analysis particularly in larger and more irregularly shaped tumors.

(P 360) MRI SURVEILLANCE PRACTICES AND RECURRENCE DETECTION IN EXTREMITY SOFT TISSUE SARCOMA: A RETROSPECTIVE STUDY

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Objective: To analyze MRI surveillance and recurrence patterns in extremity soft-tissue sarcoma (STS) patients to optimize risk-stratified protocols and provide baseline metrics for alternative imaging modalities.

Methods: A retrospective review of 59 adults with extremity STS resected between 2010 and 2018, with a minimum follow-up of 5 years. Patient demographics, tumor characteristics, outcomes, and surveillance metrics were collected from their EMR. Univariate comparisons, logistic regression, Kaplan-Meier, and Cox models evaluated recurrence predictors and MRI surveillance patterns.

Results: The mean age was 59.9 ± 16.2 years with a mean tumor size of 9.7 ± 7.7 cm (range 0.5-30.0 cm). Histopathology showed 47.5% high-grade tumors and 10.2% R1 margins. The overall recurrence rate was 23.7% (14/59) at a median of 725 days (range 14-2,450 days). Patients underwent an average of 5.6 ± 3.8 MRIs (non-recurrence) and 7.1 ± 4.3 MRIs (recurrence) over a median follow-up of 6.2 years, with the first MRI occurring at 300 ± 273 days. Cox analysis revealed no association between MRI frequency and recurrence (HR = 1.003, $p = 0.97$). Tumor size independently predicted recurrence; every 1 cm increase in size increased odds by 24% (OR = 1.24, $p = 0.028$) and length of stay by 0.09 days ($p = 0.026$). Larger tumors were linked to shorter recurrence-free survival (log-rank, $p = 0.002$).

Conclusion: In this cohort, patients had an average of 6 MRIs over five years, with 23.7% experiencing recurrence at a mean of 2.5 years. This occurred in patients with larger tumors, longer hospital stay, and increased MRI utilization. Although MRI remains the gold standard, the lack of association between MRI frequency and outcomes challenges current imaging strategies. These findings support the implementation of risk-stratified surveillance protocols and the need for baseline imaging metrics to evaluate alternative imaging methods, like ultrasounds, which could reduce costs and improve access for underserved groups without sacrificing clinical effectiveness.

(P 361) PEXIDARTINIB FOR THE TREATMENT OF TENOSYNOVIAL GIANT CELL TUMORS: CLINICAL EXPERIENCE FROM FIVE CHINESE PATIENTS

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Objective: To describe long-term efficacy and safety of pexidartinib (pexi) in patients with diffuse-type tenosynovial giant cell tumors (D-TGCT) in China.

Methods: From 11/2020-5/2025, five Chinese patients with D-TGCT not amenable to surgery received pexi 400 mg BID at the Beijing Jishuitan Hospital, Peking University Cancer Hospital, and Fudan University Shanghai Cancer Center.

Results: Patient A: Female (62 years) with right knee D-TGCT received pexi for ~4.5 years. MRI evaluation showed a 16.7% reduction in tumor diameter (150 mm to 125 mm). Following treatment, the patient achieved disease control lasting >4 years. Patient B: Female (34 years) with right knee D-TGCT received pexi for ~4.5 years. Following treatment, MRI assessment showed a 19.1% reduction in tumor diameter (115 mm to 93 mm). The patient achieved disease control and improvement of joint mobility lasting >4 years. Patient C: Male (18 years) with right knee D-TGCT received pexi for 4 years. Following treatment, MRI evaluation showed a reduction in tumor diameter (141 mm to 80-90 mm); the range of joint motion was improved. Patient D: Female (29 years) with left hip D-TGCT received pexi for 4 years. After 3 months of treatment, a significant improvement in hip joint swelling was observed. Following treatment, MRI assessment showed a 64.1% reduction in tumor diameter (169.1 mm to 60.7 mm). Improvements in range of hip joint motion were observed, especially flexion and internal rotation. Patient E: Female (67 years) with dorsal foot D-TGCT received pexi for 4 years. The patient exhibited improvements in range of joint motion, and MRI assessment showed a reduction in tumor area from 23 × 10 mm to 16 × 11 mm. Overall, most treatment-related AEs (TRAEs) were grade 1-2 in severity. TRAEs reported by >1 patient included facial edema, GGT increased, blood AST increased, blood ALT increased, blood LDH increased, serum creatine kinase increased, and pruritus. Dose reductions occurred in 4 patients.

Conclusion: These real-world observations from five Chinese patients with D-TGCT who were treated with pexi for >4 years showed improvements in TGCT-related symptoms in all patients. Most patients achieved long-term improvements in range of motion and reductions in tumor diameter. Most TRAEs were grade 1-2 in severity and represented the known safety profile of pexi.

(P 362) SHOULD PAZOPANIB BE USED AS A MAINTENANCE THERAPY TO IMPROVE RECURRENCE-FREE SURVIVAL AND OVERALL SURVIVAL IN PATIENTS WHO RECEIVED MAI IN SOFT TISSUE SARCOMA?

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Objective: Mesna, doxorubicin, and ifosfamide (MAI) is a standard first-line regimen for advanced or high-grade soft tissue sarcoma (STS). While the combination improves response rates and progression-free survival (PFS), it has not shown a definitive overall survival (OS) benefit over doxorubicin alone. Pazopanib, an oral multikinase inhibitor, is approved for advanced non-adipocytic STS after prior chemotherapy, based on improved PFS versus placebo. Despite low response rates and no OS benefit, its tolerability makes it a potential maintenance option following induction chemotherapy. This study evaluates whether pazopanib, used as maintenance after MAI chemotherapy in advanced/aggressive STS, improves survival compared to observation alone.

Methods: A single-center retrospective cohort study was conducted under an IRB-approved protocol at the University of Miami Sylvester Comprehensive Cancer Center. From 2009 to 2025, 108 biopsy-confirmed sarcoma patients who received both MAI and pazopanib were identified. Demographic and clinical variables were extracted from medical records and stored in REDCap. A resident physician independently verified pazopanib was used as maintenance, defined as administration after completing MAI without radiographic progression. Patients with missing data were excluded. Kaplan-Meier methods estimated PFS and OS, with multivariable logistic regression to adjust for confounders.

Results: A total of 22 patients met inclusion criteria. Median age at diagnosis was 48.0 years (range 17–74); 63.6% were female, 36.4% Hispanic/Latino, and 31.8% Black. Synovial sarcoma was the most common subtype (31.8%), followed by leiomyosarcoma (13.6%). Most tumors were high-grade (72.7%), and 36.4% had metastatic disease at diagnosis. The median PFS was 19.1 months.

Conclusion: The median PFS was notably longer than historical benchmarks, including 7.4 months in the EORTC 62012 trial and 6.3 and 3.7 months for synovial and other STS subtypes, respectively, in pooled analyses. These findings suggest that maintenance pazopanib may prolong disease control in high-risk STS patients who respond to MAI. However, due to the retrospective design, small sample size, and lack of a comparator group, results should be interpreted with caution. A retrospective analysis of patients who received MAI alone is in progress to provide a comparative cohort. Ultimately, a prospective clinical trial is warranted to validate these findings and clarify the optimal role of pazopanib in this setting.

Demographic and Clinical Profile of Study Participants

	Overall (N=22)
Birth Sex	
Female	14 (63.6%)
Male	8 (36.4%)
Ethnicity	
Not Hispanic or Latino	14 (63.6%)
Hispanic or Latino	8 (36.4%)
Race	
Asian	2 (9.1%)
Black or African American	7 (31.8%)
White	13 (59.1%)
Age at Diagnosis	
Mean	45.3
Median (Min, Max)	48.0 (17.0, 74.0)
Sarcoma Type	
Osteosarcoma	1 (4.5%)
Rhabdomyosarcoma	1 (4.5%)
Synovial Sarcoma	7 (31.8%)
Malignant Peripheral Nerve Sheath Tumor	1 (4.5%)
Leiomyosarcoma	3 (13.6%)
Liposarcoma	1 (4.5%)
Fibrosarcoma	2 (9.1%)
Undifferentiated Pleomorphic Sarcoma	1 (4.5%)
Endometrial Stromal Sarcoma	2 (9.1%)
High-grade, poorly-differentiated spindle and round cell sarcoma	1 (4.5%)
Grade	
Low	1 (4.5%)
Intermediate	5 (22.7%)
High	16 (72.7%)
Metastatic at Diagnosis	
No	12 (54.5%)
Yes	8 (36.4%)
Primary Tumor Location	
Head/Neck	2 (9.1%)
Chest	3 (13.6%)
Abdomen	2 (9.1%)
Pelvis	6 (27.3%)
Extremity	8 (36.4%)
Initial Intervention	
Systemic	7 (31.8%)
Surgery	11 (50.0%)
Radiation	4 (18.2%)

(P 363) TEMPERATURE CHANGES IN THE IRRADIATED SKIN OF SOFT TISSUE SARCOMA PATIENTS

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Objective: Acute and late effects of radiation on the skin has been adequately documented, but the functional effect has received little attention. The purpose of this study was to document long-term effects of radiation on the skin temperature in soft tissue sarcoma patients.

Methods: Temperature changes in the irradiated skin of soft tissue sarcoma patients who had undergone surgery and external beam radiation were examined throughout the follow-up period starting at six weeks to 5 years after completion of radiation. Changes in skin temperature of irradiated and non-irradiated skin were measured 3 monthly in 1st year, 4 monthly in 2nd year and 6 monthly in 3rd to 5th year. 20 cases were included in this cohort study from 2020 to 2024 and only limb sarcoma cases included.

Results: The resting skin temperature of the irradiated region was significantly elevated compared to similar non-irradiated skin, while the rate of sweating was lower. The temperature difference varies from 1.2 to 1.6 degree Celsius with mean recording of 1.4 degree Celsius during first 5 years of follow up.

Conclusion: Present observations suggest that functional effects, such as the elevated skin temperature and reduced sweating ability of irradiated skin, persist beyond 5 years. Before starting external radiation soft tissue sarcoma patients must be informed about these late toxicities.

(P 364) TRENDS IN SURGICAL MANAGEMENT OF DESMOID TUMOR IN THE VETERANS AFFAIRS (VA) NATIONAL DATABASE

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Objective: Surgery is no longer recommended for the management of desmoid tumors (DT) in most clinical scenarios because it is associated with morbidity and high local recurrence rates. An evolving understanding of the natural history of DT has resulted in a shift to active surveillance for asymptomatic or minimally symptomatic, non-morbid or non-progressive DTs, while systemic treatment options, such as nirogacestat, should be considered first-line if treatment is warranted. The purpose of this study was to characterize the utilization and timing of surgical management for DT following initial diagnosis, using the national VA database.

Methods: Surgical pathology notes from 2003 to 2024 were searched to identify histopathologic diagnoses of DT and the earliest date of the core needle or excisional biopsy was used as the date of DT diagnosis. Charts were manually reviewed to determine time to subsequent operative management.

Results: 270 patients were identified who had DT confirmed by histopathology. Anatomic location varied: 29% abdominal wall; 34% chest wall; 19% extremities/ girdles; 27% head/ neck; and 21% intraabdominal. Sixty-five (24%) patients underwent surgery following the initial diagnosis. Among the group who underwent surgery for DT, 56 (86%) had one surgery, five (8%) had two, two (3%) had three, one (2%) had four, and one (2%) had six. For patients who received surgery, the median time from initial diagnosis to first surgery was 84 days (interquartile range 32-220) and greater than 75% of the surgeries happened within the first year of diagnosis.

Conclusion: The majority of patients who received surgery were operated on within three months of initial diagnosis. The early surgery suggests there may be a gap between guideline recommended active surveillance and real-world practice within the VA. Further analyses will focus on understanding how surgical practices may have changed over time, to reflect more recent guideline recommendations.

(P 365) UROLOGICAL RECONSTRUCTION DURING RETROPERITONEAL AND PELVIC SARCOMA SURGERY: EXPERIENCE FROM A HIGH-VOLUME SARCOMA CENTER

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Objective: The aim was to describe surgical characteristics, perioperative outcomes, and long-term results of patients undergoing urological reconstruction after retroperitoneal sarcoma (RPS) resection at a high-volume center.

Methods: We retrospectively reviewed all patients who underwent surgery for RPS or pelvic sarcomas at IRCCS Humanitas Research Hospital, Rozzano (Milan, Italy). Twelve patients requiring resection of urologic organs and urological reconstruction were included.

Results: Table 1 shows patients' and tumors' characteristics. The reconstructions were performed by urologists in 10 cases (83.3%). Uretero-ureteral termino-terminal anastomosis over monoJ or double J stents was performed in 3 cases (25.0%). Ureteral reimplantation in 4 patients (33.3%): 2 via a direct uretero-vesical anastomosis and 2 using the Gregoire technique. One patient (8.3%) underwent ureterocutaneostomy (UCS). Uretero-ileal anastomosis was adopted in 2 cases (16.7%): bilaterally in one patient and unilaterally in the other due to the en bloc resection of a kidney. Bladder direct suture was performed in 2 patients by the sarcoma surgeons themselves. Histological infiltration of urological organs (HOI) was observed in 10 patients (83.3%), involving the ureter (n=4), bladder (n=4), prostate (n=1), and seminal vesicles (n=2). Visceral resection margin (VRM) was positive in 1 patient (bladder). Median overall survival was 31.5 months (10–52). At last follow-up, 5 patients were alive with no evidence of disease, 2 were alive with disease, and 5 had died of sarcoma.

Conclusion: Urological reconstruction in sarcoma surgery is complex and demands a high level of multidisciplinary expertise. When performed in referral centers, these procedures are safe and effective, ensuring curative resection while preserving urinary function. Centralization remains key to achieving optimal long-term outcomes in this challenging setting.

Table 1: Patients' and tumors' characteristics

	N=12 (%)
Age (y), median (IQR)	59 (55-65)
Sex	
- Male	6 (50.0)
- Female	6 (50.0)
Presentation	
- Primary	10 (83.3)
- Local Recurrence	2 (16.7)
Localization	
- Retroperitoneum	2 (16.7)
- Pelvis	7 (58.3)
- Visceral	3 (25.0)
Histology	
- Leiomyosarcoma	3 (25.0)
- Ewing sarcoma	2 (16.7)
- PEComa	2 (16.7)
- Dedifferentiated Liposarcoma	2 (16.7)
- Undifferentiated Pleomorphic Sarcoma	2 (16.7)
- Solitary Fibrous Tumor	1 (8.3)
Size (cm), median (IQR)	8.8 (3.8-15.0)
Neoadjuvant treatment	
- Yes	7 (58.3)
- No	5 (41.7)
Number of resected organs, median (IQR)	2 (1.5-4.5)
Urological resected organs	
- Ureter	11 (91.7)
- Bladder	5 (41.7)
- Prostate	3 (25.0)
- Kidney	2 (16.7)
- Urethra	2 (16.7)
- Seminal vesicles	2 (16.7)
- Adrenal gland	1 (8.3)
- Vas deferens	1 (8.3)
Complications	
- Yes	5 (41.7)
- No	7 (58.3)
Severe complications >=3	2 (16.7)
LOS (d), median (IQR)	13 days (9-1)

(P 366) **WOUND COMPLICATIONS AFTER ULTRA-HYPOFRACTIONATED NEOADJUVANT RADIATION FOR SOFT TISSUE SARCOMA: WHAT IS OPTIMAL SURGICAL TIMING?**

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Objective: Ultra-hypofractionated radiation therapy (UHFR) for soft tissue sarcomas is an alternative to conventionally fractionated radiation therapy (CFR) and may be associated with higher rates of wound complications. Optimal timing between radiation and surgery is unknown. We compared rates of wound complications for patients who received CFR or UHFR and within UHFR, compared immediate surgery (UHFR-IS) to delayed surgery (UHFR-DS).

Methods: Patients with extremity and truncal soft tissue sarcoma who received neoadjuvant radiation and surgery between January 2016 and June 2025 were retrospectively identified. CFR was defined as 45-50 Gy in 25 fractions and UHFR radiation was defined as 30 Gy in 5 fractions. Patients who received UHFR were dichotomized as having undergone surgery within seven days (UHFR-IS) or greater than seven days (UHFR-DS) post-radiation. Wound complications (IV antibiotics, percutaneous drain placement, reoperation) were compared between groups.

Results: In total, 126 patients were identified. Of these, 94 received CFR (median 38 days between radiation and surgery), 22 received UHFR-IS (median one day between radiation and surgery), and 10 received UHFR-DS (median 35 days between radiation and surgery). Neither complication rates (CFR: 37.2%, 35/94; UHFR-IS: 40.9%, 9/22; UHFR-DS: 70%, 7/10, $p = 0.13$) nor the rate of complications requiring reoperation (CFR: 35.1%, 33/94; UHFR-IS: 31.8%, 7/22; UHFR-DS: 70%, 7/10, $p = 0.08$) differed between groups. Neither the rates of wound complication ($p=0.25$) nor complications requiring reoperation ($p=0.10$) above differed between UHFR-IS and UHFR-DS groups.

Conclusion: In our single-institution retrospective series, a strategy of neoadjuvant UHFR was not associated with higher rates of wound complications compared to CFR. Delaying surgery after UHFR did not change complication rates. Further research is needed to optimize neoadjuvant radiation strategies in this population.

Results of Neoadjuvant Conventional Radiation vs Ultra-hypofractionated Radiation

Therapy and Post-Operative Wound Complications

	CFR (45-50 Gy/25fx) N=94	UHFR-IS (30 Gy/5 fx) N=22	UHFR-DS (30 Gy/5 fx) N=10	P-value
Male sex (n (%))	51 (54.3)	15 (59.5)	9 (90.0)	0.06
Age (mean (SD))	59.6 (15.6)	68.4 (14.6)	71.6 (9.3)	< 0.01
BMI (mean (SD))	29.2 (6.8)	28.6 (5.5)	33.2 (4.7)	0.14
Location (n (%))				0.19
Upper extremity	13 (13.8)	7 (31.8)	2 (20.0)	
Lower extremity	78 (83.0)	15 (68.2)	7 (70.0)	
Trunk	3 (3.2)	0 (0.0)	1 (10.0)	
Histology (n (%))				0.11
UPS	36 (38.3)	5 (22.7)	5 (50.0)	
Myxofibrosarcoma	18 (19.1)	5 (44.7)	4 (40.0)	
Myxoid liposarcoma	13 (13.8)	1 (4.5)	1 (10.0)	
Other	27 (28.7)	11 (50.0)	0 (0.0)	
Closure (n (%))				0.21
Primary	76 (80.9)	18 (81.8)	7 (70.0)	
Flap based	10 (10.6)	4 (18.2)	3 (30.0)	
Other	8 (8.5)	0 (0.0)	0 (0.0)	
Radiation technique (n (%))				< 0.001
3D radiotherapy	28 (29.8)	3 (13.6)	0 (0.0)	
IMRT	66 (70.2)	8 (36.4)	8 (80.0)	
SBRT	0 (0.0)	11 (50.0)	2 (20.0)	
Any complication (n (%))	35 (37.2)	9 (40.9)	7 (70.0)	0.13
Required reoperation	33 (35.1)	7 (31.8)	7 (70.0)	0.08

(P 367) ADHERENCE TO GERMAN SARCOMA GUIDELINE FOR MRI SEQUENCING IN SOFT TISSUE SARCOMA: EVALUATION OF IMAGING PRACTICES AND COMPLIANCE

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Objective: An accurate diagnosis is crucial for treatment planning and prognostic assessment when a soft tissue sarcoma (STS) is suspected. Imaging is fundamental for tumor characterization and surgical planning and functional imaging techniques may also support accurate tumor grading. The German guideline “Adult Soft Tissue Sarcoma” advocates the use of contrast-enhanced magnetic resonance imaging (MRI) when STS is suspected. According to the guideline, at least five defined MRI sequences as well as diffusion-weighted imaging (DWI) should be performed. This study aims to assess the consistency between the MRI protocols recommended in the guideline and the actual MRI sequences performed at initial diagnosis.

Methods: This study is based on a cohort of sarcoma patients treated at the Sarcoma Center of University Medical Center Mannheim (UMM). Most sarcoma patients have already undergone MRI imaging, which is only repeated at the center if the anatomical image quality is inadequate. All MRI sequences performed were compared with those recommended in the German sarcoma guideline.

Results: We evaluated imaging studies in a total of 64 patients with STS of the extremities and trunk. Of these MRIs 62 were performed at external radiology centers, while 2 were done at

UMM. In 43/64 (67 %) of the cases, the referral form for radiology explicitly indicated the presence of a suspected mass. Pre-treatment contrast-enhanced MRI was available for 39/43 (91 %) with suspected tumor and for 12/21 (57 %) with incidental diagnosis. DWI was available for 12/64 (19 %) patients. In more than 80 % of all cases, not all MRI sequences recommended in the guideline text were performed.

Conclusion: The choice of the MRI protocol is primarily based on the clinical question. The analysis reveals that a significant proportion of the analyzed MRI examinations did not include the guideline-recommended sequences. Notably, DWI was frequently omitted. Possible explanations include a lack of familiarity with the guidelines, outpatient billing practices, the radiologist's preference for alternative sequences or a different initial suspected diagnosis. Prospective evaluation studies should be considered, particularly to assess tumor margins for resection planning and to improve functional imaging grading.

(P 368) ASSESSMENT OF PAIN DIAGNOSIS AND PAIN MEDICATION USE IN ADULTS TREATED WITH NIROGACESTAT: A UNITED STATES REAL-WORLD ANALYSIS

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Objective: Pain is among the most debilitating symptoms of desmoid tumors (DT). Nirogacestat (niro) demonstrated significant and clinically meaningful pain reduction in adults with progressing DT in the phase 3 DeFi trial. This analysis assessed the prevalence of pain diagnoses (dx) and pain medication use (PMU) in adult patients before and after initiating a niro prescription (Rx).

Methods: A US claims database (data window: 27AUG2023-31DEC2024) was used to identify the first-filled niro Rx date as the index date. Pain dx and PMU were assessed in a continuous enrollment (CE) period of 3- and 6-month pre- (baseline, BL) and 3- and 6-month post-index (follow-up, FU), with ≥ 2 filled niro Rxs as eligible for the analysis. Pain dx were identified using pain-specific ICD10 codes. PMU was assessed for patients who filled ≥ 1 Rx for opioids or non-steroidal anti-inflammatory drugs (NSAIDs). Subgroups included sex and age (≤ 30 vs > 30), excluding unknown. Opioid dose reduction in FU (relative to BL) was calculated as a decrease in total Morphine Milligram Equivalent (MME) dose ($\text{MME} = \text{strength per unit} \times \text{number of units} \times \text{MME conversion factor}$).

Results: In the 3-month BL and FU period, 155 patients were eligible for the pain dx analysis, of which 80 (52%) had a pain dx in BL. In FU, 36% (29/80) no longer had a pain dx [female: 32% (18/56) vs male: 45% (10/22); age ≤ 30 : 45% (5/11) vs age > 30 : 35% (24/69)]. Of 314 patients eligible for the PMU analysis, 125 (40%) filled ≥ 1 Rx for a pain medication in BL [opioids: n=86, NSAIDs: n=48]. In FU, 37% (32/86) did not fill an opioid Rx [female: 39% (22/57) vs male: 33% (9/27); age ≤ 30 : 43% (6/14) vs age > 30 : 36% (26/72)]. Of 52 patients with opioid use and data for MME in FU, 37% (19/52) had a dose reduction. Also, 58% (28/48) of patients did not fill an Rx for NSAIDs in FU. 6-month BL and FU data will be presented.

Conclusion: This analysis showed a clinically relevant reduction in pain dx for patients during 3 months of niro treatment. These results are consistent with the significant and clinically meaningful benefit of pain reduction associated with niro in DeFi. The reduction in opioid Rx

and dose during 3 months of niro treatment may help reduce the risk of chronic opioid use.

(P 369) **CLINICAL CHARACTERISTICS & TREATMENT OUTCOME PATTERNS OF SOLITARY FIBROUS TUMORS: A SINGLE-INSTITUTION RETROSPECTIVE ANALYSIS**

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Objective: Solitary Fibrous Tumors (SFT) are rare soft tissue neoplasms characterized by heterogeneous clinical behavior, making prognosis and treatment challenging. This retrospective study aims to evaluate clinical characteristics, treatment patterns, recurrence rates, and survival outcomes in patients diagnosed with SFT at a single institution.

Methods: We conducted a retrospective analysis of 107 patients diagnosed with SFT. Patient demographics (age, sex, ethnicity, race), tumor characteristics (location, grade, metastatic status at diagnosis), treatment modalities (surgery, radiation, systemic therapy), recurrence patterns, and survival outcomes were collected and analyzed using descriptive statistics.

Results: The cohort consisted predominantly of non-Hispanic (52.3%) patients, with a median age at diagnosis of 61 years (range 24–94). Primary tumor sites most frequently included chest (24.3%), head/neck (21.5%), and extremities (15.9%). Tumor grades were evenly split between high and low grade (12.1% each). At diagnosis, metastatic disease was present in 12.1% of patients, and recurrence occurred in 11.2% of patients. Surgical resection was the mainstay of treatment, with selected cases receiving radiation or systemic therapy. Descriptive trends indicated that recurrence occurred more commonly among patients without initial metastasis, possibly reflecting extended survival and prolonged surveillance.

Conclusion: This single-institution retrospective analysis highlights the clinical heterogeneity and challenges associated with managing SFT. Surgical resection remains central to treatment, complemented selectively by radiation or systemic therapies. The absence of association between initial metastatic status and recurrence underlines the complexity of SFT behavior and emphasizes the importance of long-term surveillance. Future studies focusing on detailed risk stratification and targeted therapies are necessary to further optimize patient outcomes.

Patient Demographics and Clinical Characteristics of the Solitary Fibrous Tumor Cohort

(Nf110)

Category	Overall (N=110)
Birth Sex	
Female	53 (53.0%)
Male	57 (56.9%)
Ethnicity	
Not Hispanic or Latino	55 (50.0%)
Hispanic or Latino	45 (41.8%)
Unknown / Not Reported	9 (8.2%)
Race	
American Indian/Alaska Native	1 (0.9%)
Asian	1 (0.9%)
Black or African American	7 (6.4%)
White	89 (80.9%)
More Than One Race	1 (0.9%)
Unknown / Not Reported	0 (0.0%)
Other	1 (0.9%)
Age at Diagnosis	
Mean (SD)	68.4 (16.4)
Median (Min, Max)	61.0 (24.0, 94.0)
Grade	
Low	13 (11.8%)
Intermediate	7 (6.4%)
High	13 (11.8%)
Metastatic at Diagnosis	
No	83 (75.5%)
Yes	13 (11.8%)
Primary Tumor Location	
Head/Neck	23 (20.9%)
Chest	26 (23.6%)
Abdomen	16 (14.5%)
Pelvis	14 (12.7%)
Extremity	17 (15.5%)
Other	3 (2.7%)
Had Recurrence	
No	95 (86.4%)
Yes	13 (11.8%)

(P 370) CLINICAL OUTCOMES OF CUTANEOUS UNDIFFERENTIATED PLEOMORPHIC SARCOMA AND SUBCUTANEOUS MYXOFIBROSARCOMA: A RETROSPECTIVE REVIEW

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Objective: Cutaneous undifferentiated pleomorphic sarcoma (UPS) and subcutaneous myxofibrosarcoma are rare soft tissue sarcomas with ill-defined clinical trajectory presenting challenges in treatment given limited prospective data to guide management. We reviewed the clinical course of patients with cutaneous UPS and myxofibrosarcoma at a single academic institution with a focus on patterns of metastasis and treatment outcomes in those who received immunotherapy.

Methods: We conducted a retrospective chart review of 117 patients diagnosed with cutaneous UPS or subcutaneous myxofibrosarcoma. Inclusion criteria were histologically confirmed diagnosis and available clinical follow-up. Demographic, pathologic, and treatment data were collected, including the use of immunotherapy. Clinical outcomes of interest included distant metastasis and survival. Patients were followed from date of diagnosis to last known follow-up or death.

Results: A total of 111 patients were included in the analysis: 32 with UPS and 79 with myxofibrosarcoma. The average age at diagnosis was 68.5 years for cutaneous UPS and 69.8 years for myxofibrosarcoma. Distant metastases occurred in 6 of 32 patients (18.8%) with UPS and 4 of 79 patients (5.1%) with myxofibrosarcoma. Among patients with metastatic disease, progression-free survival (PFS) for cutaneous UPS was three months. For metastatic myxofibrosarcoma, PFS was four months. A total of 14 patients in the cohort received immunotherapy, seven in each group. The median PFS for patients who received immunotherapy was over four months. Overall, mortality was low in both groups: eight patients with cutaneous UPS (25%) and 21 with myxofibrosarcoma (26.5%) died.

Conclusion: In this retrospective cohort study, both cutaneous UPS and subcutaneous myxofibrosarcoma showcased relatively low rates of distant metastases and mortality. However, cutaneous UPS may be somewhat different from subcutaneous myxofibrosarcoma given the increased risk of metastasis in its cohort. Although a small cohort, patients who received immunotherapy had evidence of a durable response. These findings highlight the need for further study of systemic treatment strategies in rare cutaneous and subcutaneous soft tissue sarcomas.

(P 371) CLINICAL PROFILE AND TREATMENT PATTERNS OF ANGIOSARCOMA IN THE REAL- WORLD SETTING: A SINGLE CENTER EXPERIENCE FROM 1991-2024.

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Objective: Angiosarcoma (AS) has high rates of metastasis and mortality. It is considered more sensitive to novel therapies in clinical trials, including immune checkpoint inhibitors (ICI) and oncolytic viruses (OV), but data for patients (pts) who are not clinical trial candidates is lacking.

Methods: AS pts were identified via electronic medical records for retrospective analysis from 1991 to December 2024. Pt and disease characteristics were analyzed. Kaplan-Meier method and Cox regression were used for survival analysis.

Results: Total of 129 pts were identified with median age 69 years, 51% male, 93% Caucasian, 39% ECOG PS 0, 33% PS 1, 16% PS 2, 15% radiation related, and 30% de-novo metastasis. Of 129, 117 (91%) had received at least 1 modality of treatment; 77% received at least 1 systemic therapy. Wound healing complications (WHC) were noted in 18 (19%) pts after local modality treatment. Of head/neck AS (n = 37), 42% who received (n = 26) and 9% who did not receive (n = 11) radiation had WHC. Of 90, 48% had 1-line, 23% 2-lines, 16% 3-lines, 9% 4-lines of systemic therapies. Of 90, 39 (43%) had ICI use at least once; with 67% in first-line, 26% in second, 3% in third and 5% in fourth line. Of 129, 71% died and 29% were censored at the time of analysis. Median OS was 24.3 months (95% CI 17.7–33.4). Median OS for nonmetastatic pts was 33.4 months (95% CI 23.1–61.2) and 12.8 months (95% CI 5.5–25.2) for metastatic pts with p = 0.0016. Median OS in pts who received ICI did not differ by metastatic status (30.9 vs 27.6 months, p = 0.67). Univariate cox regression showed age, ECOG PS, visceral AS, de novo metastasis, radiation or systemic therapy as first modality as significant predictors of inferior survival; multivariate model showed age and PS as significant predictor of inferior survival in pts without metastasis; PS and visceral AS primary for metastatic pts. Though early use of ICI (1st and 2nd line) did not show statistical significance, they numerically had lower hazard ratio (HR) (0.59 and 0.78, respectively). Six pts received an OV (4 non-metastatic and 2 metastatic); 3 in 1st, 2 in 3rd and 1 in 4th line. Median OS was 30.8 months in pts receiving OVs.

Conclusion: AS continues to have poor overall survival outcomes. Early ICI use resulted in improved HR, although sample size was small. New treatments for AS are urgently needed.

(P 372) CLINICOPATHOLOGICAL FEATURES AND OUTCOMES OF PATIENTS WITH KAPOSI SARCOMA: A SINGLE CENTER RETROSPECTIVE REAL WORLD ANALYSIS

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Objective: Kaposi sarcoma(KS) is a chronic, rare, multifocal angioproliferative neoplasm associated with immunodeficiency. Four clinical subtypes are recognized: classic KS(CKS), immunosuppression-associated KS, acquired immune deficiency syndrome(AIDS)-related KS, and endemic African KS. While often indolent and limited to the skin, KS can exhibit aggressive behavior. This study aims to characterize the clinicopathological features, treatment patterns, and outcomes of KS patients treated at the Instituto Português de Oncologia de Lisboa(IPOL) from 2004 to 2024.

Methods: We conducted a retrospective review of medical records from KS patients treated at IPOL between 2004 and 2024. Data collected included demographics, disease characteristics, treatment modalities, and clinical outcomes. Survival analyses were conducted using the Kaplan–Meier method.

Results: A total of 69 patients were included, of whom 88% were male. The median age at diagnosis was 69 years(range, 36–91), and 84% had an ECOG performance status of 0-1. The CKS subtype was the most common(81%) followed by AIDS-related KS(9%). At presentation, 46% had locally advanced or metastatic disease. Nodal and mucosal involvement were observed in 13% and 9% of cases, respectively. The lower limbs were the most frequently affected site(74%). Initial treatment modalities included surgery(64%), radiotherapy(30%), and chemotherapy(29%). Systemic treatment was administered to 45% of patients during their disease course, most commonly with pegylated liposomal doxorubicin(PLD, 78%), followed by paclitaxel(25%), and etoposide(25%). The median follow-up was 4.1 years. Median progression free survival was 2.3 years(95% CI,1.6-2.9), and median overall survival was 4.6 years(95% CI,0.2-21.3). Among 20 patients(29%) who received chemotherapy as first-line treatment, the objective response rate was 75%, including 3 complete and 12 partial responses. Systemic treatments were well tolerated, with only three reported cases of grade 3 toxicity(hematologic and neurologic).

Conclusion: This real-world, single-center study highlights the clinical heterogeneity of KS and the diversity of treatment approaches. Chemotherapeutic agents demonstrated encouraging efficacy and manageable toxicity profiles, particularly PLD. However, the disease often remains a chronic, relapsing disease requiring diverse treatment approaches. Given its rarity and complexity, optimal management benefits from a multidisciplinary approach to guide diagnosis, treatment, and long-term follow-up.

(P 373) COMPLETE RESPONSE TO FRONT-LINE PEXIDARTINIB IN SYMPTOMATIC TEMPOROMANDIBULAR JOINT TENOSYNOVIAL GIANT CELL TUMOR

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Objective: Tenosynovial giant cell tumor (TGCT) diffuse type is a rare (1.8-8 cases/million/year), locally destructive lesion arising from the synovium, with proliferation often driven by overproduction of colony-stimulating factor 1 receptor (CSF-1R). Surgical resection is standard of care, with high recurrence rates (60-70%) and often significant morbidity. Pexidartinib, a small molecule CSF-1R inhibitor, results in excellent overall response rates (>60%) and is increasingly utilized in the front-line to minimize surgical morbidity. Here we present a unique case in TGCT management, a 51 year old male patient who presented with 2 years of right temporomandibular joint (TMJ) pain and a 2.6cm expansile TMJ lesion on imaging. Biopsy was consistent with TGCT, and multidisciplinary case review determined surgical resection would require extensive reconstruction with the potential for reduced joint function, nerve injury, and persistent post-operative pain. Given critical location, pexidartinib was initiated as an alternative first line treatment modality.

Methods: Data collected retrospectively by manual chart review, including time to response (TTR) and patient reported outcomes such as symptomatic benefit and adverse effects (AEs). Patient received standard dose of 250mg pexidartinib twice daily and was monitored as per the TURALIO-REMs program requirements.

Results: The patient's pain improved within 1 month of pexidartinib initiation. TTR by RECIST was 5.8 months, including resolution of extension into critical surrounding structures. Complete response was noted by 17.8 months, with resolution of all associated symptoms. AEs included grade 1 fatigue and hair depigmentation; no grade 3-4 AEs observed. Given excellent response, pexidartinib was discontinued at 18.5 months. At time of submission, duration of response measured 20 months.

Conclusion: Here we present a unique case of TGCT of the TMJ where surgery would have meant catastrophic morbidity. Pexidartinib therapy represents a feasible, well-tolerated front-line management strategy in cases where surgical morbidity is high, offering symptom relief and the opportunity for tumor resolution.

(P 374) DISTINCT PATTERNS OF METASTATIC SPREAD IN LEIOMYOSARCOMA: A COMPARATIVE ANALYSIS OF TRUNCAL AND EXTREMITY TUMOURS

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Objective: Leiomyosarcoma (LMS) is a soft tissue sarcoma (STS) with a potentially distinct metastatic pattern compared to other sarcomas. This study evaluates the distribution and frequency of metastases in truncal and extremity LMS, hypothesizing a higher rate of extra-pulmonary spread relative to other STS.

Methods: A retrospective cohort analysis of patients undergoing truncal and extremity LMS resections from 1995–2022, compared to a cohort of non-LMS STS patients. Benign tumors and STS subtypes predisposed to extra-pulmonary metastases, including myxoid liposarcoma, were excluded. Baseline demographic and tumor variables, metastatic rates, and anatomical distribution were compared. Overall (OS) and disease-free survival (DFS) were assessed using Kaplan-Meier curves.

Results: There were 354 LMS and 1,141 non-LMS STS patients. Age and sex distributions were comparable, but LMS patients were more likely to present with low-grade ($p < 0.001$), superficial tumors ($p < 0.001$). The overall rate of metastases was similar (28% LMS vs. 26% non-LMS). However, LMS was associated with a significantly higher rate of extra-pulmonary metastases (29% vs. 15%, $p < 0.006$), with soft tissues, viscera, and lymph nodes being the most common sites. LMS patients exhibited superior 5-year DFS compared to non-LMS patients (72% vs. 66%, $p = 0.018$), while 5-year OS rates were similar (77% vs. 74%).

Conclusion: LMS demonstrates a distinct metastatic profile, with a higher incidence of extra-pulmonary metastases compared to other STS. These findings suggest the potential benefit of refined surveillance approaches to account for the unique metastatic behavior of LMS.

(P 375) DOES STAGED RESECTION WITH TEMPORIZING WOUND VACUUM INFLUENCE LOCAL RECURRENCE RISK? A MULTI-INSTITUTIONAL MATCHED COHORT ANALYSIS

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Objective: For soft tissue sarcomas (STS), margin status is a significant predictor of local recurrence (LR). Staged resection with a temporizing vacuum-assisted closure (VAC) delays soft tissue coverage until final margins return negative, a strategy typically employed for locally aggressive histologies and highly infiltrative tumors. The objective of this analysis is to compare LR between patients treated with single-stage versus staged resection.

Methods: A matched cohort, multi-institutional retrospective review (2018-2024) was performed of STS patients undergoing localized resection. Patients treated with staged resection at two institutions ($n = 185$) were matched by grade, depth, and radiation to patients treated with single-stage resection at a third institution ($n = 185$). Demographics, tumor information, and treatment variables were collected. The primary outcome was LR.

Results: There was no significant difference in depth, grade, and radiation use between staged and single-stage groups. VAC patients were more likely to have had a prior unplanned surgery and a myxofibrosarcoma histology ($p < 0.01$) while tumor size tended to be smaller (6.4 vs 7.7cm, $p = 0.008$). Initial margin status was more likely to be positive in the staged group (31 vs 18%, $p = 0.002$), while final margin status was more likely to be negative in the staged group (94 vs 83%, $p = 0.001$). However, the rate of LR was higher in the staged group (19.5% vs 5.5%, $p < 0.001$). When controlling for potential confounders, initial positive margins increased LR risk (OR 4.5, CI 2.0-10.4), while radiation was protective (OR 0.3, CI 0.14-0.63). Final margin status, grade, and depth were not associated with LR.

Conclusion: Staged resection did not reduce LR. Initial margin status was a strong predictor of

LR, indicating the first resection is the best opportunity for local control. Notably, higher LR rate in the staged group likely reflects a higher propensity for staging more locally aggressive tumors, such as myxofibrosarcoma. Further analysis is recommended to determine indications for staged resection for various histologies and tumor characteristics.

(P 376) EFFECT OF ITRACONAZOLE (ITZ) AND RABEPRAZOLE (RBP) ON THE PHARMACOKINETICS (PK) OF VIMSELINIB, AN ORAL INHIBITOR OF THE COLONY-STIMULATING FACTOR 1 RECEPTOR, IN HEALTHY PARTICIPANTS

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Objective: Vimseltinib is indicated for treatment of adult patients with symptomatic tenosynovial giant cell tumor for which surgical resection will potentially cause worsening functional limitation or severe morbidity. In preclinical studies, vimseltinib was both a P-glycoprotein (P-gp) substrate and inhibitor, which may inform drug-drug interactions (DDIs). Here, we report the results of a phase 1, open-label study investigating the effects of ITZ (P-gp inhibitor) and RBP (proton pump inhibitor [PPI] for gastric acid suppression) on the single-dose PK of vimseltinib in healthy participants.

Methods: Adult participants (N = 89) were randomized 1:1:1 to receive a single 30-mg vimseltinib dose on day 1 (arm 1; reference) or 1 h after ITZ/RBP on day 5 (arms 2/3; test). Participants in arm 2 received ITZ 200 mg once daily (QD) on days 1–24 and those in arm 3 received RBP 20 mg QD on days 1–5. Plasma PK samples were collected, and parameters were obtained by noncompartmental analysis. The log-transformed maximum concentration (C_{max}), area under the curve (AUC) from first dose to last quantifiable concentration (AUC_{0–tlast}), and AUC extrapolated to infinity (AUC_{0–inf}) of vimseltinib were analyzed using an analysis of variance model. Geometric mean ratios (GMRs) and 90% confidence intervals (CIs) of C_{max}, AUC_{0–tlast}, and AUC_{0–inf} were constructed. Adverse events (AEs) were monitored throughout the study.

Results: C_{max} was similar for vimseltinib alone vs with ITZ; the 90% CI for the GMR was within bioequivalence limits (Table). Total vimseltinib exposure (AUC_{0–tlast} and AUC_{0–inf}) was 17% and 22% higher, respectively, with ITZ vs alone. Vimseltinib C_{max}, AUC_{0–tlast}, and AUC_{0–inf} was 26%, 25%, and 21% lower, respectively, with RBP vs alone. All treatment-emergent AEs were grade 1/2.

Conclusion: P-gp inhibition with ITZ and gastric acid suppression with RBP had weak effects on total vimseltinib exposure and absorption, respectively. Neither treatment affected the safety profile. Overall, the DDI for vimseltinib with ITZ or with RBP was not considered clinically significant, providing basis for approved concomitant use of vimseltinib with P-gp inhibitors and PPIs.

Plasma PK Parameters of Vimseltinib by Treatment

Parameter	Vimseltinib Reference n = 29	Vimseltinib + ITZ Test n = 30	Vimseltinib + RBP Test n = 30
C_{max} , ng/mL	425 (38.1)	408 (33.9)	313 (61.8)
Participants, n	29	30	30
GMR (90% CI)		0.96 (0.83–1.12)	0.74 (0.60–0.91)
AUC_{0-12h} , h·ng/mL	51,200 (27.0)	60,100 (30.9)	38,600 (52.1)
Participants, n	29	30	30
GMR (90% CI)		1.17 (1.04–1.33)	0.75 (0.63–0.90)
AUC_{0-24h} , h·ng/mL	57,200 (26.1)	69,900 (30.8)	45,100 (50.3)
Participants, n	28	23	28
GMR (90% CI)		1.22 (1.07–1.39)	0.79 (0.67–0.94)

Data presented as geometric mean (% coefficient of variation) unless otherwise noted.

(P 377) GERMLINE RECQL4 VARIANT IN A PEDIATRIC PATIENT WITH EWING SARCOMA AND DESMOID FIBROMATOSIS

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Objective: RecQ helicases, including RECQL4, maintain genome stability and alterations that result in loss of function may predispose to malignancy.¹ However, malignancy risk in germline RECQL4 heterozygotes is inconclusive.²⁻³ Ewing sarcoma (ES) is a primary bone cancer driven by an EWSR1::FLI1 fusion. Genetic predisposition has not been strongly linked to development of ES.⁴ Desmoid fibromatosis (DF) is a benign but locally aggressive neoplasm typically associated with alteration of the WNT pathway, including alterations of CTNNB1 (somatic) or APC (germline or somatic). Risk factors for DF include abdominal trauma, preceding abdominal surgery, and high estrogen exposure.⁵

Methods: Literature search and retrospective chart review performed. Genetic sequencing performed and analyzed at the Institute of Genomic Medicine at Nationwide Children's Hospital.

Results: An 11-year-old male with biopsy-proven localized ES of the left distal femur was treated on AEWS1031 Regimen B. He underwent surgical resection with negative margins and achieved radiographic remission post-therapy sans radiation. A non-tender palpable abdominal mass was noted 6.5 years off-therapy. A biopsy verified DF in the pelvic region, followed by complete surgical resection with negative margins. Paired exome sequencing revealed a germline heterozygous frameshift variant in RECQL4. No additional somatic variants were found in the ES sample. A hotspot missense variant in CNNTB1 was observed in the DF sample, consistent with the histopathologic diagnosis. Due to recurrence of DF 2 years post-

resection, the gamma secretase inhibitor Nirogacestat was initiated with radiograph remission.

Conclusion: Biallelic pathogenic RECQL4 alterations are associated increased risk for malignancy. However, the relationship between heterozygous RECQL4 carriers and malignancy risk is understudied. Currently, there is no known association between RECQL4 and risk for ES or DF; however, this case underscores the value of comprehensive genetic testing for pediatric solid tumors in uncovering potential germline predisposition and enhancing patient care.

(P 378) HIGH DOSE RADIATION THERAPY PROMOTES IMMUNE SUPPRESSIVE MACROPHAGE PHENOTYPES, WHEREAS LOW DOSE RADIATION THERAPY PROMOTES IMMUNOGENIC MACROPHAGE PHENOTYPES IN A MURINE MODEL OF SOFT TISSUE SARCOMA

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Objective: Soft tissue sarcomas (STS) are aggressive tumours of mesenchymal origin, which are treated with neoadjuvant radiation therapy (RT) of 2Gy in 25 fractions and surgical resection. While RT is typically used to improve local control in combination with surgery, there is a growing body of evidence that RT modulates the immune compartment of tumours. Interestingly, there is evidence that macrophages are highly abundant in STS after RT and appear to express immune suppressive markers. These macrophage phenotypes have also been shown to inhibit anti-tumour T cells. Thus, macrophages may be dampening the potential of these immune cells. Herein, we assessed how RT influences both myeloid and T cell populations after RT.

Methods: Syngeneic, murine STS were engrafted in C57Bl/6 mice, then used for RT experiments when tumours were ~500-800mm³ in size. Tumours were treated with three RT regimens; 1) 6Gy x5 clinical RT, 2) 8Gy x3 high dose hypofractionated RT, and 3) 8Gy x1 low dose RT. A SmART+ (Precision X-ray) irradiator was used to deliver RT. A CT image was acquired prior to treatment, then image planning was completed to deliver RT to the entire tumour. Tumours were assessed 72hrs after RT by flow cytometry to evaluate macrophages and lymphocytes.

Results: We found that 6Gy x5 and 8Gy x3 increased the proportion of TGFB1+ immune suppressive macrophages, whereas the 8Gy x1 reduced CD206+ and TGFB1+ macrophages and increased CD80+ immunogenic macrophages. Interestingly, the 6Gy x5 and 8Gy x3 led to increased CD3e+ and CD8+ T cells, as well as increased activated CD8 T cells. In contrast, the 8Gy x1 did not increase T cells, but increased activated CD8 T cells.

Conclusion: High doses of RT induce an immune suppressive macrophage phenotype 72hrs after treatment, whereas low dose induces immunogenic macrophage phenotypes. However,

all doses exhibited increased activated T cells. We will assess various RT regimens in combination with anti-PD1 or CAR T immunotherapy.

(P 379) IMPACT OF EWSR1 GENE REARRANGEMENT TESTING ON DIAGNOSIS OF A WIDE RANGE OF SOLID TUMOURS

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Objective: EWSR1 gene rearrangement is seen in a wide variety of tumours, Ewing sarcoma (ES) being the commonest of all. It serves as a diagnostic tool in conjunction with clinical presentation, tumour morphology and immunohistochemistry (IHC). We present our data of 143 patients who have undergone testing for EWSR1 gene rearrangement with a focus on real impact of this molecular test on diagnostic process.

Methods: This is a retrospective observational study wherein we reviewed clinical features, tumour morphology and IHC along with results of EWSR1 gene rearrangement performed by fluorescent in-situ hybridization (FISH) technique of tumours from 143 patients. Clinical and demographic data was obtained from electronic medical records.

Results: 49% of all patients were diagnosed with ES based on tumour morphology and IHC. NKX2.2 was uniformly expressed in all ES on IHC. 92% of ES had EWSR1 gene rearrangement. 27% of tumours diagnosed histologically as undifferentiated round cell tumours (RCTs) and 25% of other high grade sarcomas, not otherwise specified (NOS) demonstrated EWSR1 gene rearrangement, hence were considered as ES after molecular testing. All 4 tumours with strong and diffuse positivity for BCOR IHC were negative for EWSR1 rearrangement. All 7 patients diagnosed with hylanising clear cell carcinoma of salivary gland showed EWSR1 gene rearrangement. 6 of 10 patients with EWSR1 gene rearrangement helped distinguish clear cell sarcoma from malignant melanoma. We also found EWSR1 rearrangement in one case each of sclerosing epithelioid fibrosarcoma (SEF) and angiomatoid fibrous histiocytoma (AFH) respectively.

Conclusion: ES is characterized by EWSR1 gene rearrangement. IHC for NKX2.2 is a robust tool for definitive diagnosis of ES as seen in our results. Similarly, tumours with strong BCOR positivity on IHC lacked EWSR1 gene rearrangement. Thus it may be concluded IHC is a strong surrogate for molecular testing in these cases. However, EWSR1 gene rearrangement seen in 25% of undifferentiated round cell sarcomas highlighting its significance and also limitations of IHC. EWSR1 testing had significant impact on distinction between malignant melanoma and clear cell sarcoma and diagnosis of rare tumours such as hylanising clear cell carcinoma of salivary glands, SEF and AFH. While distinction between ES and DSRCT was not possible based on EWSR1 status, it was helpful to differentiate ES from rhabdomyosarcoma.

(P 380) INVESTIGATING THE ROLE OF HISTONE DEACETYLASE-3 IN METASTATIC UNDIFFERENTIATED PLEOMORPHIC SARCOMA

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Objective: Undifferentiated Pleomorphic Sarcoma (UPS) is among the most commonly diagnosed soft tissue sarcoma in adults and carries a poor prognosis for patients with metastatic disease. There are no therapeutic options for metastatic UPS and robust heterogeneity within the primary tumors negatively impacts treatment efficacy. How the diverse populations contribute to tumor growth and metastasis is poorly understood. Previous literature identifies histone deacetylases as drivers of metastasis. My objective is to identify and elucidate the epigenetic mechanisms of histone deacetylase-3 (HDAC3) in metastatic UPS.

Methods: Our models utilize a localized cre-activation system, generating primary tumors that harbor an oncogenic KrasG12D mutation and p53 knockout. Investigation of clonal dynamics in UPS was achieved by incorporating CRISPR barcoding and fluorescent reporters into our models. Following tumor initiation, amputation of the tumor bearing limb is performed and metastasis is observed overtime. Subsequent in vitro assays and tumor studies utilize primary cell cultures harvested from these mouse models.

Results: Tumors generated in our models recapitulate the clonal heterogeneity, characteristic of UPS. Excitingly, lung metastasis was shown to arise from a single clone. This specific population, which can migrate and form lung tumors, we termed metastatic initiating cells (MCs). Comparative analysis of the MC and the non-metastatic initiating cells (nMCs) revealed distinct expression clusters despite insignificant differences in transcriptomic and mutational profiles. Investigating regulators of gene expression identified HDACs, specifically HDAC3, to play a key role in the ability of the MC population to successfully colonize the lung.

Conclusion: We have demonstrated the monoclonal origin of UPS metastasis using murine models. My data highlights a key regulatory role of HDAC3 in the metastatic potential of the MC population. Loss of Hdac3 in vivo significantly impaired migrative and invasive properties and delayed primary tumor growth. My findings have the potential to elucidate an ill-defined mechanism of UPS pathogenesis and propose a targeted approach for therapeutic intervention. Ongoing studies aim to understand the functional significance of Hdac3 in the MC population and the underlying mechanism through which Hdac3 regulates metastasis in UPS.

(P 381) KNOWLEDGE, ATTITUDES, AND BEHAVIOR OF HEALTHCARE PROVIDERS ENROLLED IN THE PEXIDARTINIB RISK MITIGATION AND EVALUATION PROGRAM

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Objective: Upon approval of TURALIO® (pexidartinib) in the United States, a Risk Evaluation and Mitigation Strategy (REMS) Program was required to ensure that benefits of its treatment outweigh its potential risk of serious and fatal liver injury. A core component of the TURALIO REMS (tREMS) assessment plan is the conduct of a knowledge, attitudes, and behavior (KAB) survey of healthcare providers (HCPs). This survey was conducted annually during 2019-2022 (waves 1-3), and every 2 years since then (wave 4). This survey assesses: (i) HCP knowledge of the risks associated with its use and of the requirements of the tREMS; (ii) the attitudes and behavior of HCPs regarding the key risk messages (KRM). The goal of KRMs is to ensure awareness that: TURALIO can cause serious and potentially fatal liver injury; monitoring of liver tests is required prior to and during treatment with TURALIO and HCPs must modify the dose based upon liver tests; HCPs must counsel patients on the risk of serious and potentially fatal liver injury, liver test monitoring prior to and during treatment with TURALIO, and to report any signs and/or symptoms of liver injury during therapy. The objective of this study is to retrospectively assess the results of the TURALIO HCP KAB surveys conducted during 2019-2024.

Methods: The survey was administered via internet, telephone, or paper. HCPs who had received tREMS training and were certified in the tREMS Program were targeted.

Results: 83.1-100% of the HCPs understood that TURALIO can cause serious and potentially fatal liver injury; 87.5-96.7% were aware that monitoring of liver tests is required prior to and during treatment and HCPs must modify the TURALIO dose based upon liver tests. All (100%) HCPs were aware that they must counsel patients on the risk of serious and potentially fatal liver injury, liver test monitoring prior to and during treatment with TURALIO, and to report any signs and/or symptoms of liver injury during therapy.

Conclusion: The tREMS Program is considered to be meeting its goal if the point estimates of all KRMs achieve a demonstrated understanding of $\geq 80\%$. The results from retrospective assessment of all survey waves indicate that this threshold was consistently exceeded since TURALIO approval. The HCPs demonstrated a solid understanding of all 3 KRMs. The tREMS is consistently meeting its goal to mitigate the potential risk of serious and fatal liver injury associated with TURALIO use.

(P 382) METHOD FOR VOLUMETRIC ASSESMENT OF TUMOR RESPONSE FOLLOWING NEOADJUVANT RADIATION IN PRIMARY MYXOFIBROSARCOMA

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Objective: Myxofibrosarcoma (MFS) is an aggressive subtype of soft tissue sarcoma typically treated with neoadjuvant radiotherapy (NRT) and surgical resection. Tumor response to NRT is defined by RECIST criteria which classify response based on changes in the greatest dimension of the tumor. MFS tumors are often irregularly shaped with perilesional stranding which may obscure measurements and complicate response assessment. Three-dimensional volumetric analysis has been used to measure other tumor types. We propose a volumetric method to assess MFS tumors and compare accuracy and reliability to unidimensional RECIST measurements.

Methods: Patients aged 18-100 years diagnosed with MFS and treated with NRT at KUMC from 2002-2021 were included. Pre- and post-NRT MRIs were measured in their greatest

dimension 3 times by 3 reviewers. Each MRI stack was uploaded to 3D-Slicer and 3 tumor models per reviewer created. Tumor size changes were compared pre- vs post-NRT. Tumors were grouped by location: upper extremity (UE), lower extremity (LE) and torso. Intra-rater and inter-rater reliability was assessed using interclass correlations. Paired t-tests and Pearson correlations were used to compare changes in tumor size between methods.

Results: Inter- and intra-rater reliability for both methods showed no statistically significant difference ($p=0.092$) and no significant correlation between methods ($r=0.199$). On average, volumetric measurements showed 24% shrink in UE, 29% growth in LE and 45% growth in torso tumors. Unidimensional measurements showed 21% shrink, 9% growth and 2% shrink, respectively. Individually, RECIST classified all UE and LE tumors, as well as 4/6 torso tumors as stable disease. Volumetrically, all UE tumors shrank while three LE tumors shrank and five grew. All “stable disease” torso tumors grew, while the “partial response” tumor shrank and the “progressive disease” tumor grew.

Conclusion: Volumetric analysis demonstrated similar reliability to RECIST but may provide more accurate classification of tumor response. Differences are likely due to more complete and sensitive inclusion of MFS tumor morphology. Further development of volumetric MFS analyses may be a valuable tool in evaluating treatment response.

(P 383) **MULTIDISCIPLINARY TREATMENT OF INGUINOSCROTAL SARCOMAS: ANALYSIS OF 39 CASES TREATED BY SURGICAL APPROACH**

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Objective: Inguinoscrotal sarcomas are a rare sarcoma subtype. Treatment of choice is radical inguinal orchiectomy with wide local resection of surrounding soft tissues. However, consensus regarding prognostic factors is lacking. We present our experience at a referral sarcoma centre regarding the management, oncologic results, and prognostic factors.

Methods: We conducted a retrospective analysis of patients who underwent surgery for inguinoscrotal sarcomas between 2005 and 2023 at a sarcoma referral hospital.

Results: The study included 39 patients. The most frequent histology was liposarcoma. Seven patients required surgical reconstruction with a microvascularized free flap. Four patients presented major postoperative complications. Mean follow-up was 46 months. Overall survival rates were 97.4%, 81.7% and 64.8% at one, three and five years. High-grade tumours were correlated with worse overall and disease-free survival.

Conclusion: The chance finding of a sarcoma in the inguinal region poses a diagnostic and therapeutic dilemma when considering options for treatment with curative intent. Vascular and muscle resection followed by vascular and/or free flap reconstruction may be necessary to

achieve complete surgical resections, therefore a multidisciplinary approach is needed. A preoperative biopsy should be performed to establish the histological grade, which may be a main prognostic factor.

(P 384) PELVIC LOCATION PREDICTS WORSE OUTCOMES IN ALVEOLAR RHABDOMYOSARCOMA: UNDERUSE OF RADIOTHERAPY AND MISSED SURVIVAL BENEFIT

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Objective: Alveolar rhabdomyosarcoma (ARMS) is a rare, aggressive soft-tissue tumor with a poor prognosis. Pelvic presentation poses diagnostic and therapeutic challenges due to proximity to critical structures. This study aims to assess the prognostic treatment factors associated with pelvic ARMS.

Methods: We conducted a retrospective cohort study using the Surveillance, Epidemiology, and End Results (SEER) database (2000-2021) that included patients with ARMS. Variables included demographics, socioeconomic factors, and treatment modalities. Logistic regression evaluated associations between tumor location and treatment receipt. Competing-risks outcomes were analyzed using the Fine-Gray model.

Results: The study included 325 ARMS patients (232 extremity vs 93 pelvic). Patients with pelvic tumors had significantly higher mortality risk (sub-hazard ratio [SHR]=1.68, 95%-confidence interval [95%-CI]: 1.18-2.39, p=0.004) and were less likely to undergo resection (56.0% vs 30.1%, p< 0.001). Propensity score matching analysis demonstrated radiation therapy was associated with improved survival in pelvic tumors, with a mean survival difference of 31.2 months (66 vs 34.8 months). Both radiation therapy (SHR=0.58, 95%-CI: 0.41-0.80, p=0.001) and surgery (SHR=0.58, 95%-CI: 0.41-0.82, p=0.002) were independently associated with decreased cancer-specific mortality (Table 1).

Conclusion: Radiation therapy demonstrated a significant survival benefit in pelvic ARMS, emphasizing the need for standardized treatment strategies in high-risk sites.

Table 1. Subgroup Analysis of Radiation Impact by Tumor Location

Analysis Group	Subdistribution Hazard Ratio for Radiation	95%-CI	p-value
Overall Cohort			
No Radiation (reference)	1.00		
Radiation	0.58	0.41-0.80	0.001
Pelvic Tumors			
No Radiation (reference)	1.00		
Radiation	0.51	0.30-0.88	0.016
Extremity Tumors			
No Radiation (reference)	1.00		
Radiation	0.63	0.41-0.97	0.036
Interaction Model			
Pelvic (vs. Extremity)	1.88	1.02-3.46	0.042
Radiation (vs. No Radiation)	0.62	0.41-0.94	0.023
Pelvic × Radiation Interaction	0.83	0.40-1.72	0.616
CI: Confidence Interval			

(P 385) PROGNOSTIC IMPACT OF PERIPHERAL BLOOD CELL RATIO VALUES IN PATIENTS WITH ADVANCED LEIOMYOSARCOMA: A REFERENCE CENTER EXPERIENCE.

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Objective: Peripheral blood cell ratio (PBCR) values, such as the neutrophil-to-lymphocyte ratio (NLR), the monocyte-to-lymphocyte ratio (MLR), and the platelet-to-lymphocyte ratio (PLR), have been associated with prognosis in many solid malignancies. However, their role in metastatic leiomyosarcoma (LMS) has not yet been established. The aim of this study is to evaluate the association between NLR, MLR, and PLR and prognosis in patients with metastatic LMS.

Methods: Retrospective study of a consecutive cohort of patients with metastatic LMS treated at a reference sarcoma center in Spain between 2009 and 2024. Clinical, treatment, and laboratory data were collected to calculate PBCR prior to first-, second, and third-line systemic therapies (NLR1/MLR1/PLR1 before first-line; NLR2/MLR2/PLR2 before second-line; and NLR3/MLR3/PLR3 before third-line). We evaluated the relationship between PBCR and survival outcomes (overall survival -OS-; progression free survival -PFS-) using Spearman's correlation. ROC curves identified optimal cut-off values, and its prognostic significance was analyzed through Kaplan–Meier curves and Cox regression models.

Results: A weak negative correlation was observed between NLR and survival, particularly between OS and NLR1 ($p = -0.293$; $p = 0.003$). For OS, the optimal cut-offs were 2.249 for NLR1 and 0.33 for MLR1 and for PFS were 2.249 for NLR1, 2.439 for NLR2, and 1.91 for NLR3. Using these cut-offs, a higher NLR1 was associated with worse OS (median: 14.4 vs. 46

months -m-; HR: 2.7; $p < 0.001$) and PFS1 (median: 5.6 vs. 11.9m; HR: 1.99; $p = 0.004$). Similarly, a higher NLR2 was associated with shorter PFS to second-line treatment (median: 4.9 vs. 11.3m; HR: 1.79; $p = 0.05$), while a higher NLR3 showed a trend toward worse PFS to third-line treatment (median: 7.4 vs. 14.5m; HR: 2.66; $p = 0.055$). MLR1 > 0.33 showed a non-significant trend toward worse OS (median: 18.8 vs. 37.3m; $p = 0.10$). No association was found between PLR values and survival outcomes.

Conclusion: Elevated NLR (NLR1 > 2.249 , NLR2 > 2.439 , NLR3 > 1.91) was associated with worse prognosis in advanced LMS, suggesting its potential as a prognostic biomarker. Prospective studies are needed to confirm these findings.

(P 386) RADIO-GUIDED SURGERY FOR NONPALPABLE SOFT-TISSUE SARCOMAS

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Objective: To evaluate the feasibility and results of a series of patients with soft tissue sarcomas resected using intraoperative radio-guided surgery.

Methods: This is a retrospective and descriptive study on a prospective database. All patients with nonpalpable soft tissue sarcomas treated between 2005 and 2025 who underwent radio-guided surgery were included. Technique: within 24 hours before surgery the patients were injected in the peritumoral area with 99mTc-labeled colloid via ultrasound guidance. During surgery, the tumor area was localized using a hand-held gamma probe in order to avoid direct visualization of the tumor. We evaluated tumor characteristics, location, history of previous treatments (surgery and/or radiotherapy), resection margins and recurrence.

Results: We performed a radio-guided surgery on 10 patients with localized soft tissue sarcomas. The female:male ratio was 8:3. The median age was 58 years (IQR 50-65 years). According to histology we observed 3 mixofibrosarcomas, 1 malignant peripheral nerve sheath tumor, 1 undifferentiated pleomorphic sarcoma, myxoid liposarcoma, 1 sinovial sarcoma, 1 solitary fibrous tumor, 1 leiomyosarcoma, 1 chondrosarcoma. All tumors were located in the lower extremities and were deep to the superficial fascia. Previous radiotherapy has been administered in 8 patients. The median tumor size was 2.7cms (IQR 2-3.5cms). Median operative time was 171min (IQR 155-180min). Intraoperative localization was successful in 100% of patients. Complete resection was achieved in 9 patients, 1 patient presented multiple nodules during surgery that were not detected by ultrasound at the moment of the injection. Local recurrence after radio-guided resection was observed in 2 patients (20%). There were no complications related to the 99mTc-labeled colloid use. There were 2 patients with grade ≤ 2 Clavien-Dindo postoperative complications (in both cases it was a wound infections treated with antibiotic).

Conclusion: In our experience, radio-guided tumor resection is a feasible and safe procedure than can be performed in patients with nonpalpable and deep sarcomas. The local control rate (80%) was similar to that obtained in conventional surgery.

(P 387) TREATMENT PATTERNS AND PROGNOSTIC FACTORS IN LOCALISED SYNOVIAL SARCOMA: A RETROSPECTIVE STUDY FROM A TERTIARY CANCER CENTRE IN INDIA

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Objective: Synovial sarcoma (SS) is an uncommon subtype of soft tissue sarcoma, predominantly affecting adolescents and young adults. Although chemo-sensitive histology, the optimal role and timing of chemotherapy remain unclear. This study aimed to analyze clinical characteristics, treatment outcomes, and prognostic factors in patients with localized SS treated at a tertiary care centre in India.

Methods: We retrospectively reviewed 111 patients with histologically confirmed, localized SS treated at Tata Memorial Hospital, Mumbai, India, between 2010 and 2019. Clinical, pathological, and treatment data were collected. Survival outcomes: overall survival (OS) and disease-free survival (DFS) were assessed using Kaplan-Meier analysis and log-rank tests. Prognostic factors were evaluated through univariate analysis.

Results: The median age was 31 years, with a slight male preponderance. The most common site was the lower extremity (55.8%), and monophasic histology predominated (46.8%). About 63% of tumors were more than 5 cm size. Surgery was performed on 88.3% of patients, with 56.7% received chemotherapy (either perioperative or adjuvant) and 63.9% received radiotherapy. The 5-year OS and DFS rates were 62.2% and 54.1%, respectively. Poorly differentiated histology, larger size and higher ECOG performance status were associated with worse outcomes. Adjuvant chemotherapy was associated with improved OS compared to perioperative chemotherapy (HR 0.494, $p = 0.043$). Radiotherapy was also associated with better OS (HR 1.736, $p = 0.033$).

Conclusion: Multimodality treatment achieves favorable long-term outcomes in localized synovial sarcoma. Tumor differentiation, gender, and use of adjuvant therapy significantly impact prognosis. The apparent benefit of adjuvant over perioperative chemotherapy in this cohort warrants further validation in prospective, multicenter studies.

(P 388) TRIAL IN PROGRESS: A PHASE 2 STUDY OF METRONOMIC TRABECTEDIN, GEMCITABINE, AND DACARBAZINE IN PREVIOUSLY TREATED ADVANCED SOFT TISSUE SARCOMA (NCT04535271)

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Objective: We hypothesize that metronomic dosing of trabectedin, gemcitabine, and dacarbazine will produce synergistic effects while limiting additive toxicities in advanced soft tissue sarcoma patients, potentially presenting a safer and more durable approach compared to standard chemotherapy regimens, which often cause unacceptable toxicity and chemoresistance.

Methods: This is a phase 2 open-label single-site study (NCT04535271) evaluating the safety and efficacy of metronomic trabectedin, gemcitabine, and dacarbazine, which we hypothesize will increase progression free survival in patients with advanced soft tissue sarcoma (STS). 80 previously treated adult patients with advanced STS will be treated with a 3-week cycle consisting of trabectedin 0.5mg/m² CIV over 24 hours, gemcitabine 200 mg/m² IV, and dacarbazine 200 mg/m² IV, on Days 1 and 8. Primary endpoint: Progression Free Survival (PFS). Secondary endpoints: Best overall response (BOR) and duration of response (DOR) by RECIST v1.1; PFS Rate and Overall survival (OS) Rate at 4, 6, and 12 months; and incidence of treatment-related adverse events (TRAEs). Analysis: The Intention-To-Treat (ITT) population, including all patients who received at least one dose of each study drug, will be analyzed for safety. The Modified Intention-To-Treat (MITT) population, including patients who completed the first 2 cycles and follow-up scans, will be used for efficacy analysis. Key inclusion criteria: pathologic diagnosis of locally advanced, unresectable or metastatic STS, previously treated patients with measurable disease by RECIST v1.1, ECOG ≤ 2, life expectancy of at least 3 months, acceptable liver and renal function, and acceptable hematological status. Key exclusion criteria: patients who have progressed with all three study drugs, known hypersensitivity to any of the three study drugs, currently receiving treatment or < 14 days since ending treatment with another investigational device/study drug, patients unwilling to use contraception, patients pregnant or breastfeeding or who have plans to become pregnant or breastfeed. The study has enrolled 13 of 80 patients and is actively recruiting.

Results: N/A

Conclusion: N/A

(P 389) UNRESECTABLE AND METASTATIC DEDIFFERENTIATED LIPOSARCOMA (DDLPS): INSIGHTS FROM A MULTICENTER REAL-WORLD COHORT (RWC)

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Objective: DDLPS is a high-grade soft tissue sarcoma characterized by aggressive behavior and poor prognosis. Systemic treatments (Tx), such as chemotherapy (CT), have shown limited efficacy. This study evaluates Tx outcomes for unresectable/metastatic (UM) DDLPS across a multicentric RWC.

Methods: This retrospective study enrolled adult patients (pts) included in the national registry of the Spanish Sarcoma Group (GEIS) who had started systemic Tx from 1/1/18 to 1/1/24 for a confirmed UM DDLPS. Demographics and clinical data were collected. Survival endpoints were evaluated using Kaplan–Meier and log-rank tests.

Results: 155 pts were included (67% male; median age 64; 48% T4, 38.7% G3, and 17.4% metastatic). Most tumors were retroperitoneal (66%), followed by trunk (17.4%) and extremities (11%). Neoadjuvant and adjuvant Tx were given in 15% and 23%, respectively. In advanced stages, 14.8% entered clinical trials and 40% were initially treated in non-referral centers. First line (1L) Tx were Doxorubicin (D) (46.5%), anthracycline-ifosfamide (AI) (21%), trabectedin (Tr) (10.3%) brigimadlin (Bg) (7.1%) and eribulin (Er) (6.5%). Toxicity $\geq$ G3 occurred in 40%, mainly hematological. Median 1L progression free survival (mPFS) was 4.2 months(m) (95% CI: 0.3–0.5). PFS and response rate (RR) were: AI (7.3m, 34%), Er (7.3m, 20%), Bg (5.6m, 18%), Tr (4.7m, 19%) and D (3.5m, 10.6%). Median overall survival (OS) was 2.2 years (95% CI: 1.7–4.5). Among regimens, AI and Bg had the highest OS at 3 years (55%, 64%, respectively), though no Tx sequence demonstrated statistical significance. Second line (2L) CT was given in 56% of pts: Tr (41.4% ; RR: 22%), DTIC-Gemcitabine DG (19.5%; RR: 5.9%), Er (16%; RR: 14%), and D (9.2%; RR: 14%), with mPFS of 3.9m. Third-line Tx (23.9% of pts) included Er (45%) and Tr (35%), with mPFS of 2.8m. About 39% received Tx beyond 2L , mostly Er (28.3%), Tr (28.3%), and DG (17%). In this latter setting, RR was minimal, with no significant differences in PFS/OS between Tx arms.

Conclusion: Tx patterns in UM DDLPS remain heterogeneous with modest outcomes. AI and Bg showed OS trends, though not statistically significant due to sample size. These data underscore the need for novel Tx strategies and randomized trials to improve care.

(P 390) USE OF DERMAL TEMPLATE FOR NERVE PROTECTION IN LIMB-SPARING SURGERY FOR SOFT TISSUE SARCOMAS: PRELIMINARY EXPERIENCE FROM INSTITUT BERGONIE

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Objective: In limb-sparing surgery for soft tissue sarcomas, large nerve exposure is common and poses risks of neuropathic pain and functional impairment. Optimizing reconstruction is a cornerstone of postoperative recovery.

Methods: Between 2023 and 2025, we conducted a retrospective and prospective analysis of 10 patients undergoing limb sarcoma resection at Institut Bergonié. A dermal regeneration matrix (Matriderm®) was applied to protect exposed peripheral nerves and assist in soft tissue reconstruction. Outcomes included DN4 questionnaire scores for neuropathic pain, analgesic consumption, and functional evaluation using the MSTs score.

Results: Preliminary results indicate effective nerve protection, a reduction in neuropathic pain (lower DN4 scores), decreased analgesic use, and favorable early functional outcomes. Few matrix-related complications were observed.

Conclusion: The use of dermal matrices in complex sarcoma surgery may improve both pain control and functional recovery. This approach warrants further investigation in a larger cohort, with stratification based on pre- or postoperative radiotherapy to assess its influence on integration and outcomes.

(P 391) ATRX LOSS BLOCKS THE DIFFERENTIATION OF MESENCHYMAL STEM CELLS AND ADVANCES UNDIFFERENTIATED SARCOMA DEVELOPMENT

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Objective: Undifferentiated sarcoma (US) accounts for over 20% of soft tissue sarcoma and is correlated with high tumor grade and poor prognosis. Recent genomic profiling in US has identified p53 and ATRX among the most frequently mutated or deleted genes. ATRX is a chromatin remodeling factor that functions in the deposition of histone variant H3.3. However, how ATRX loss contributes to US tumorigenesis and whether ATRX-deficient US can be therapeutically targeted remain largely unknown.

Methods: Genetic engineered mouse model was established to target Atrx and Tp53 deletion in mesenchymal cells. Survival and pathological analysis were conducted to assess tumor initiation/progression and subtypes. Bulk RNA-seq and scRNA-seq were conducted to characterize transcriptomic and tumor heterogeneity alterations associated with Atrx loss. MSC with ATRX deletion was generated to evaluate the impact of ATRX loss on the differentiation into multiple lineages. ATAC-seq, ChIP-seq, and CUT&RUN are performed to characterize ATRX-dependent epigenetic alterations during cell differentiation. Genome-wide Cpf1-mediated loss-of-function screens were conducted to identify genetic vulnerabilities in ATRX-deficient US cells.

Results: Deletion of *Atrx* in mouse MSCs, but not terminally differentiated cells, accelerated p53-loss-induced sarcoma development and significantly shortened the overall survival. *Atrx*-deficient tumors are highly reminiscent of human high-grade UPS pathologically and transcriptomically. *Atrx*-null tumor cells exhibit enhanced proliferation and enrichment of cell cycle-related pathways. ATRX loss in MSCs blocks the differentiation into multiple mesenchymal lineages and sustains stemness and proliferation. Epigenetic profiling identified RUNX1 as the potential master regulator for the transcriptional alterations associated with ATRX loss during MSC differentiation. Deletion of *Runx1* in MSCs reverses the differentiation defect in ATRX-deficient MSCs. Genome-wide Cpf1-mediated genetic screen in mouse UPS cells further identified *Cbfb*, the RUNX1-binding partner required for its transcriptional activity, as the top differentially essential gene in ATRX-deficient tumor cells compared to *Atrx*-wildtype ones. Treatment with RUNX1/CBFB inhibitor preferentially inhibits the tumorigenic activity of ATRX-deficient tumor cells.

Conclusion: ATRX deficiency contributes to UPS development by inhibiting MSC differentiation in RUNX1-dependent manner. RUNX1/CBFB may serve as a therapeutic target for ATRX-deficient UPS.

(P 392) CLASSIFICATION AND DIFFERENTIATION OF MYXOID LIPOSARCOMA AND MYXOMA WITH MACHINE LEARNING

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Objective: To develop and evaluate machine learning (ML) models for differentiating myxomas from myxoid liposarcomas (MLS) and for classifying MLS by histologic grade.

Methods: MR imaging data from 109 patients (71 MLS, 38 myxomas) across multiple institutions were manually segmented using 3D Slicer. Radiomic features were extracted from T1-weighted, T2-weighted, and post-contrast sequences using PyRadiomics. Supervised ML models, including support vector machines (SVM), random forest, and XGBoost, were trained on this dataset. Model performance was evaluated on an external validation cohort comprising 32 patients (16 MLS, 16 myxomas). Diagnostic performance was assessed using accuracy and area under the receiver operating characteristic curve (AUC) for both tumor type differentiation and MLS grade classification (low, intermediate, high, round cell). Performance was compared with that of a musculoskeletal (MSK) radiologist and a general radiologist with over 15 years of experience. The Delong test was utilized to assess the difference in model performance.

Results: The T1-based models outperformed T2 and contrast-enhanced models. For MLS vs. myxoma classification, the SVM achieved accuracy and AUC of 0.89/0.87 for training and 0.84/0.92 for validation. XGBoost and random forest performed better during training (accuracy/AUC: 0.86/0.94 and 0.86/0.93) but showed reduced generalizability (0.69/0.81 and

0.81/0.82 on validation). For MLS grading, SVM again showed consistent accuracy/AUC (0.61/0.91, 0.53/0.79 training and validation). XGBoost and random forest had stronger training results (0.74/0.94 and 0.79/0.94) but dropped on validation (0.50/0.74 and 0.59/0.76). Important predictive features included lesion size and uniformity for tumor type; gray-level texture and entropy for grading. Delong Test demonstrated p value < 0.01 for AUC between the different models. The MSK radiologist achieved 0.92/0.92 for differentiation but 0.60/0.69 for grading. The general radiologist scored 0.85/0.83 and 0.42/0.60, respectively.

Conclusion: The T1-based SVM model was the most robust and reliable AI approach. While a specialist radiologist was superior at differentiating between tumor types, the top-performing AI models were competitive with the specialist in the more challenging task of tumor grading and outperformed a general radiologist in both tasks. The significant statistical difference between the models (Delong Test, $p < 0.01$) confirms the varying reliability of the different AI approaches.

(P 392) DIFFERENTIATION OF MYXOMA AND MYXOID LIPOSARCOMA BASED ON RADIOMICS PHENOTYPES

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Objective: To investigate the utility of radiomics in phenotypically differentiating myxoma (Myx) from myxoid liposarcoma (MLS) and its subtypes using MRI, with the potential to obviate the need for biopsy.

Methods: MR imaging data from 139 patients (87 MLS, 54 Myx) were manually segmented using 3D Slicer. Radiomic features were extracted from T1-weighted, T2-weighted, and post-contrast sequences using PyRadiomics. Features assessed included T1 and T2 signal intensity, irregularity of shape (sphericity), uniformity of signal (first-order uniformity, first-order entropy), and coarseness of texture (GLCM Sum Entropy (GSE) and GLCM Sum of Squares (GSS)). Statistical analysis was performed using Mann-Whitney U and Kruskal-Wallis tests to differentiate tumor types and MLS classes.

Results: Specific radiomic features effectively differentiated Myx from MLS and various MLS grades. Myx exhibited lower median T1 intensity (19 vs. 24 for MLS, $p=0.0001$) and higher median T2 intensity (538 vs. 386 for MLS, $p=0.0059$). Myx also demonstrated greater sphericity (median 0.8 vs. 0.7 for MLS, $p=0.00000003$) and higher signal uniformity (median 0.2 vs. 0.1 for MLS, $p=0.000002$). Conversely, MLS showed higher entropy (median 3.9 vs. 3 for Myx, $p=0.000001$) and coarser textures, evidenced by higher median GSE (4.6 vs. 3.5 for Myx, $p=0.000001$) and GSS (20.1 vs. 4.4 for Myx, $p=0.000001$). Furthermore, varying grades of MLS displayed pronounced differences in signal heterogeneity, with round cell, high, and intermediate grades exhibiting greater complexity and coarser textures (higher GSS) compared to low-grade MLS.

Conclusion: Our study demonstrates that Myx and MLS can be reliably differentiated through specific radiomic features. MLS is characterized by higher T1 values (suggesting fat content), while Myx shows elevated T2 signal intensity (indicating water content). MLS also exhibits greater shape irregularity and increased signal heterogeneity (lower uniformity, higher entropy) and coarser texture compared to Myx. These findings suggest that radiomics holds significant potential as a noninvasive probe for tumor characterization, aiding in diagnosis, predicting tumor behavior, and assessing treatment response.

(P 393) DISTINCT SECONDARY MUTATIONAL LANDSCAPES ARE ASSOCIATED WITH NAB2-STAT6 FUSION BREAKPOINTS IN SOLITARY FIBROUS TUMORS

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Objective: Solitary fibrous tumor (SFT) is a mesenchymal neoplasm driven by a NAB2::STAT6 fusion and exhibits variable clinical behavior. Emerging evidence suggests that specific fusion breakpoints carry prognostic significance: the NAB2 exon 6::STAT6 exon 16 (ex6::ex16) fusion is linked to younger age, aggressive behavior, and extrapulmonary location, while NAB2 exon 4::STAT6 exon 2 (ex4::ex2) is associated with older age, indolent course, and pulmonary origin. However, fusion-specific patterns of secondary genomic alterations remain largely unexplored.

Methods: We sought to assess the genomics of a cohort of SFTs, to identify if there are any distinct mutational signatures based on fusion breakpoints. FFPE tissue from 471 clinically advanced SFT patient tumors underwent comprehensive genomic profiling by a next-generation sequencing based in vitro diagnostic test (clinical trial assay based on FoundationOne®Heme) to evaluate all classes of genomic alterations (GAs) and tumor mutational burden (TMB, mutations/Mb). Overall, 54% were male and median age was 62 years.

Results: Seven distinct NAB2::STAT6 exon fusion configurations were identified in over 10 patients each (Table 1). The most prevalent was NAB2 exon 6::STAT6 exon 16 (ex6::ex16; n = 202), followed by ex4::ex2 (n = 56) and ex7::ex2 (n = 37). Patients with ex6::ex16 fusion were significantly younger (median age 55 years) compared to those with ex4::ex2 (66 years, p = 5.3×10^{-9}) or ex7::ex2 (67 years, p = 7.6×10^{-8}). Compared to the ex6::ex16 fusion, both ex4::ex2 and ex7::ex2 fusion variants were more commonly associated with lung primaries. Ex4::ex2 cases demonstrated a higher frequency of TP53 mutations (46% vs. 24%, p = 0.0014), whereas ex7::ex2 cases were enriched for CDKN2A/B mutation (19% vs. 2%, p = 0.0001).

Conclusion: SFTs demonstrate distinct molecular profiles based on NAB2::STAT6 fusion breakpoints. Specifically, ex4::ex2 cases are enriched for TP53 mutations, while ex7::ex2 cases show a higher frequency of CDKN2A/B alterations. The ex6::ex16 fusion is associated with younger patient age and extrapulmonary tumor location, consistent with prior reports. These findings suggest that fusion subtype and genomic profiling may inform diagnosis, prognosis, and potentially treatment frameworks.

Table 1. Clinicogenomic characteristics of solitary fibrous tumor (SFT) stratified by NAB2::STAT6 fusion exon breakpoints.

	Total cohort	NAB2 ex6-STAT6 ex16	NAB2 ex4-STAT6 ex2	NAB2 ex7-STAT6 ex2	NAB2 ex6-STAT6 ex17	NAB2 ex4-STAT6 ex1	NAB2 ex7-STAT6 ex1	NAB2 ex5-STAT6 ex16
Number of patients	471	202	56	37	28	16	14	13
Median age (range, years)	62 (13-89)	55 (13-89)	66 (41-89)	67 (41-86)	61 (31-86)	67 (55-89)	71 (32-84)	53 (15-81)
% Male	54%	54%	59%	60%	50%	31%	57%	46%
Median TMB (Q1-Q3, mut/Mb)	1.6 (0.8-2.4)	0.8 (0.8-1.6)	1.6 (0.8-3.2)	2.0 (0.8-3.2)	1.6 (0.8-2.4)	2.0 (1.6-2.4)	1.2 (0.8-2.4)	1.2 (0.8-2.4)
% TP53 mutant	28.7%	23.8%	46.4%	27.0%	17.9%	31.3%	14.3%	15.4%
% RB1 mutant	7.9%	4.0%	10.7%	16.2%	14.3%	18.8%	0.0%	7.7%
% CDKN2A/B mutant	5.5%	1.5%	8.9%	18.9%	0.0%	6.3%	14.3%	0.0%

(P 394) DUAL OR TRIMODALITY THERAPY VERSUS SURGERY ALONE IN RADIATION-ASSOCIATED ANGIOSARCOMA OF THE BREAST

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Objective: Radiation-associated angiosarcoma (RAAS) in the breast is an aggressive malignancy with high local and distant recurrence rates. There are no consensus guidelines on treatment, and institutional case series suggest either dual modality therapy (DMT; surgery + chemo) or tri-modality therapy (TMT; surgery + chemo + radiation) may improve recurrence free survival (RFS) and overall survival (OS). We sought to compare outcomes from different multidisciplinary treatment regimens to confirm findings from smaller institutional series.

Methods: Our institutional data was queried for RAAS patients presenting with localized disease and treated with curative intent. Demographic, treatment plan, recurrence, and survival data were recorded. Kaplan Meier curves for RFS and OS were plotted. Cox proportional hazards models were created to assess for variables associated with improved RFS and OS.

Results: From 2004–2023, a total of 57 patients were identified with a median follow up of 41 months. The average latency period between radiation and development of RAAS was 8.0 years, and average tumor size was 5.5 cm. Patients had either stage 2 (n=22, 39%) or stage 3 (n=33, 57%) disease and were treated with surgery alone (n=22, 39%), DMT (n=22, 39%), or TMT (n=13, 22%). Paclitaxel was the most common chemo agent used (80%) and most (63%) received this in the neoadjuvant setting. Median RFS for the surgery only group was 19.6 months vs. 39.0 months for DMT and TMT patients (P=0.1). The median OS was not met for

any group by 60 months. For RFS (Table 1), Cox multivariate analysis showed age (HR 1.06, $P < 0.001$), size of primary tumor in cm (HR 1.10, $P = 0.026$), and treatment group (DMT vs surgery HR=0.27, TMT vs surgery HR=0.34, $P = 0.021$; DMT/TMT composite group vs surgery alone HR=0.30, $P = 0.006$) to be statistically significant. Multivariate analysis for OS (Table 1) showed age (HR=1.12, $P < 0.001$) and treatment group (DMT/TMT composite group vs surgery HR=0.28, $P = 0.025$) to be statistically significant, with a trend towards significance for individual treatment groups (DMT vs surgery HR=0.30, TMT vs surgery HR=0.25, $P = 0.078$).

Conclusion: Receiving dual modality or tri-modality therapy for RAAS significantly improved RFS and OS by 70% and 72%, respectively, over surgery alone. Our findings further validate prior reports that surgical resection alone results in inferior outcomes for RAAS. The added benefit of radiation in RAS was not observed in this study but warrants further investigation with larger sample sizes.

Cox Proportional Hazards Models for (a) Recurrence Free Survival and (b) Overall Survival

(a) Recurrence Free Survival			
Variable	HR	95% CI	P-value
Age at diagnosis	1.06	1.03, 1.10	< 0.001
Size of primary tumor	1.10	1.02, 1.20	0.026
Disease stage			0.7
2	—	—	
3	0.82	0.30, 2.20	
Treatment Group			0.021
Surgery Only	—	—	
Surgery + Chemo	0.27	0.10, 0.74	
Surgery + Chemo + Rad	0.34	0.12, 0.97	
Dual or Triple Therapy (vs surgery)	0.30	0.12, 0.72	0.006
Abbreviations: CI = Confidence Interval, HR = Hazard Ratio			
b) Overall Survival			
Variable	HR	95% CI	P-value
Age at diagnosis	1.12	1.05, 1.19	< 0.001
Size of primary tumor	1.05	0.95, 1.17	0.4
Disease stage			0.3
2	—	—	
3	2.09	0.58, 7.53	
Treatment Group			0.078
Surgery Only	—	—	
Surgery + Chemo	0.30	0.08, 1.09	
Surgery + Chemo + Rad	0.25	0.06, 1.04	
Dual or Triple Therapy (vs surgery)	0.28	0.09, 0.86	0.025
Abbreviations: CI = Confidence Interval, HR = Hazard Ratio			

(P 395) ERIBULIN IN RECURRENT PRETREATED METASTATIC SOFT TISSUE SARCOMA. A CANADIAN SARCOMA RESEARCH AND CLINICAL COLLABORATION (CANSARCC) REAL WORLD ANALYSIS

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Objective: Eribulin (E) has demonstrated overall survival (OS) benefit in a phase III trial, particularly in liposarcoma, though the findings had a low fragility index (Braik et al., 2025). We evaluated the real-world effectiveness of E in advanced soft tissue sarcoma (STS).

Methods: Adults (≥ 18 y) with advanced STS who received ≥ 1 dose of E between April 2014 and March 2023 were included. Clinical data, dose reductions (RE), delays, and $\geq G3$ adverse events (AE) were retrieved from the multi institutional CanSaRCC Database. Median progression-free survival (PFS) and OS were estimated according to RECIST v1.1 using the Kaplan-Meier and log-rank test. Uni-/multivariate analyses explored outcome predictors.

Results: A total of 168 pts were included. Demographic and clinical data are in Table 1. At a median follow-up of 6.9 months (mo), median OS and PFS were 7.8 (95%CI, 6.3–10.3) and 2 (95%CI, 1.9–2.4) mo, respectively. A breakdown of PFS and OS for the different subtypes are in Table 1. RE occurred in 43 (25.6%) pts while 10 pts (5.95%) had treatment discontinuation due to AE. The most common $\geq G3$ AEs were neutropenia (14.9%), anemia (8.9%), and leukopenia (3.6%). On univariate and multivariate analysis, RE and neutropenia were positively associated with PFS; worse ECOG status was associated with inferior OS.

Conclusion: E showed lower OS than previously reported, probably due to use in heavily pretreated pts, supporting real-world validation of trial findings. Toxicity was consistent with prior reports.

(P 396) EVALUATING THE SAFETY AND EFFICACY OF METRONOMIC GEMCITABINE, DOXORUBICIN, AND DOCETAXEL PLUS NIVOLUMAB IN PREVIOUSLY TREATED ADVANCED LEIOMYOSARCOMA AND LIPOSARCOMA: A PHASE 2 STUDY (NCT04535713)

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Objective: Standard chemotherapy doses often cause unacceptable toxicity in soft tissue sarcoma (STS) patients. To decrease toxicity, this phase 2 trial employs metronomic doses of gemcitabine, doxorubicin, and docetaxel, and adds PD-1 inhibitor nivolumab, for previously treated advanced leiomyosarcoma (LMS) or liposarcoma (LPS). Objectives: Primary: Determine progression-free survival (PFS); Secondary: Evaluate best overall response (BOR) and duration of response (DOR) by RECIST v1.1, Determine progression-free survival (PFS) and overall survival (OS) at 6 and 12 months

Methods: Schedule: 3-week cycle. Gemcitabine (600 mg/m²; max:1000 mg), doxorubicin (18 mg/m²; max: 32 mg), docetaxel (25 mg/m²; max:42 mg) on days 1 and 8, and nivolumab (240 mg) on day 1. Key eligibility criteria: ≥ 18 years, previously treated locally advanced unresectable or metastatic LMS/LPS, measurable disease by RECIST v1.1, acceptable hematologic/organ function

Results: Efficacy: 41 patients who received at least one dose of each agent were evaluated to determine: Median OS =16.1 months (95% CI: 7.4-20.1 months). 31 patients who completed at least 2 treatment cycles and follow-up imaging were used to determine: Median PFS = 8.6 (95% CI: 3.3-12.0) months; ORR = 22%; DCR = 87.5%; 6-month PFS rate = 58%; 6-month OS rate = 70.7%; 12-month PFS rate = 35.5%; 12-month OS rate = 59.1%; BOR = 7 PR, 21 SD, 4 PD. Safety: 28 of 41 patients (68%) experienced Grade 3/4 TRAEs: thrombocytopenia (n=12), lymphopenia (n=11), anemia (n=10), neutropenia (n=9), leukopenia (n=4), back pain (n=4), fatigue (n=2), dyspnea (n=2), hypocalcemia (n=1), muscle weakness (n=1), colitis (n=1), diarrhea (n=1), anorexia (n=1), abdominal pain (n=1), alkaline phosphatase increased (n=1), nausea (n=1), bone pain (n=1), peripheral sensory neuropathy (n=1), edema (n=1). No unexpected or Grade 5 adverse events were observed.

Conclusion: The combination of metronomic gemcitabine, doxorubicin, and docetaxel plus nivolumab may be a synergistic regimen and may be as effective as standard first-line therapy for advanced LMS and LPS with manageable toxicity.

(P 397) EXPLORING REAL WORLD DATA OF RECURRENCE IN NON-METASTATIC MYXOFIBROSAROMA: AN UPDATED RETROSPECTIVE COHORT STUDY

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Objective: Myxofibrosarcoma is a rare subtype of soft tissue sarcoma characterized by its locally infiltrative behavior and high recurrence rates. It accounts for approximately 5% of all

soft tissue sarcomas and typically affects older adults in their sixth or seventh decade. Local recurrence rates are as high as 50-60% especially in cases where positive margins are present. Many prior studies have reported an association between recurrence and prior radiation for other cancers, however there is a paucity of literature investigating the real world outcomes of recurrence.

Methods: Building upon a prior review, we conducted an IRB-approved retrospective cohort study of patients diagnosed with non-metastatic primary myxofibrosarcoma at the University of Miami from 2008 to 2024. Data on demographics, clinical characteristics, treatments, and outcomes were extracted from electronic medical records with attention to recurrence, local versus distant recurrence, and if local recurrence was within the prior radiation field. Detailed treatment timelines were collected including the original control method and the sequence of treatments. Kaplan-Meier curves and logistical regression models were used for survival analysis using the R statistical programming language.

Results: 99 patients with non-metastatic myxofibrosarcoma were identified with recurrence observed in 36 patients (36.4%). Of the patients who recurred, 10 patients had distant recurrence (45.5%), 5 had local recurrence without prior radiation (22.7%), and 7 had local recurrence within a prior radiation field 7 (31.8%). Patients treated with radiation first had significant increased odds of distant recurrence OR 11.85 ($p < 0.001$). Patients who received systemic therapy first had decreased odds of any recurrence, OR 0.38 ($p 0.03$). Patients who received surgery first had increased odds of local recurrence, OR 3.03 ($p 0.02$).

Conclusion: The findings suggest that having surgery first is a significant predictor of local recurrence in non-metastatic myxofibrosarcoma. Radiation therapy seems to prevent local recurrence at the site but in those patients there is an increased rate of distant recurrence. We are collaborating with additional sarcoma centers in Florida to expand our cohort for additional analysis. We hope to use this data to improve outcomes and prevent recurrence... We plan to use this preliminary data to further the study on effective management of sarcoma in a multidisciplinary context to improve patient outcomes.

(P 398) INVESTIGATING THE SAFETY AND EFFICACY OF LURBINECTEDIN WITH IPILIMUMAB AND NIVOLUMAB FOR ADVANCED SOFT TISSUE SARCOMA: LINNOVATE PHASE 1/2 STUDY (NCT05876715)

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Objective: Sarcoma cells exhibit heightened immunogenicity during the early stages of the disease. Therefore, immune checkpoint inhibitors (ICIs) such as ipilimumab and nivolumab, which enhance sustained T-cell activation by suppressing regulatory T cells, are most effective when administered as first-line therapy in combination with lurbinectedin—a synthetic analog of the marine alkaloid trabectedin—that not only induces apoptosis in cancer cells and exposes tumor neoantigens for immune recognition but also depletes tumor-associated macrophages, thereby restoring immune surveillance and potentially enhancing the efficacy of ICIs. This interim analysis presents the clinical outcomes of combining lurbinectedin with ipilimumab and nivolumab in patients with advanced soft tissue sarcoma (STS), encompassing both previously treated and untreated cohorts.

Methods: Inclusion criteria: Adult patients >18 years, confirmed pathologic diagnosis of advanced STS, measurable target lesion of 1 cm, previously treated in phase 1, previously untreated in phase 2. Endpoints: Clinical Benefit Rate (CBR) defined by confirmed or best response (CR, PR or SD) by RECIST v1.1 via CT or MRI; Progression-free survival (PFS) at 6-months. Up to 40 patients with advanced STS will be enrolled. A Simon 2-stage design with a Type I error rate = 0.1 and power = 0.8 will be used. Accordingly, a CBR $\geq$ 30% would warrant continuing the phase 2 part of the study.

Results: Safety analysis: 19 patients who received at least one dose of study drug were evaluated for safety. Eight of 19 (42%) experienced $\geq$ Grade 3 TRAEs: platelet count decreased (n= 1), white blood cell decreased (n=2), anemia (n=1), ANC decreased (n=1), lymphocyte count decreased (n=6), flu-like symptoms (n=1), and fatigue (n=1). Efficacy analysis (CBR): 11 patients who completed at least one treatment cycle and had a follow-up CT or MRI were evaluated. In Phase 1, there were 4/5 SD (80% CBR). In Phase 2, there was 1/6 CR, 1/6 PR and 4/6 SD with 28% BORR and 100% CBR.

Conclusion: The observed 28% BORR and 100% CBR support the continuation of the phase 2 portion of the study, with manageable toxicity.

(P 399) LATE LOCAL RECURRENCE (>5YEARS) OF SOFT TISSUE SARCOMA OF THE EXTREMITIES AND TRUNK WALL: PREDICTIVE FACTORS AND ONCOLOGIC OUTCOMES

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Objective: The primary objective of this study was to investigate the clinicopathologic characteristics, treatment patterns, and oncologic outcomes of patients who developed LLR in a Korean tertiary referral center. Specifically, we aimed to identify features that distinguish LLR from more typical recurrence patterns, evaluate the timing and progression of metastasis following LLR, and assess the implications of LLR on survival and recurrence-free intervals. By focusing on this under-recognized subset, we hope to inform risk-adapted follow-up strategies, refine the five-year surveillance threshold, and improve long-term care for STS survivors.

Methods: A retrospective cohort study was conducted involving 279 STS patients with local recurrence, treated at a tertiary referral center in Korea. Patients were grouped into ELR (< 5 years; n = 254) and LLR ($\geq$ 5 years; n = 25). Eighteen clinical, pathological, and treatment-related variables were analyzed using chi-square tests, t-tests, and Kaplan–Meier survival analysis.

Results: Among the 279 patients with local recurrence of STS, LLR represented 9% of all local recurrences. Compared to ELR, LLR cases were more frequently associated with low- or intermediate-grade tumors (p = 0.016), infiltrative tumor borders (p = 0.014), and clear surgical margins (80% vs. 65.7%; p = 0.26). After LLR, 11 patients (44%) developed distant metastases, of whom 9 died of disease. The post-LLR 5 year survival rate was 59%.

Conclusion: This study provides one of the few detailed examinations of LLR in soft tissue sarcoma, using a Korean cohort. Our findings reveal that LLR, though relatively uncommon, comprises a distinct subgroup characterized by delayed onset, association with low- to

intermediate-grade histology, clear surgical margins, and indolent histologic subtypes. Despite these features, LLR remains clinically significant due to its latent risk for distant metastasis and associated mortality.

In conclusion, late local recurrence in STS is not merely a delayed version of recurrence but may represent a distinct biological process. Future prospective studies are warranted to investigate the molecular underpinnings of LLR, assess surveillance cost-effectiveness, and explore tailored approaches to follow-up that balance patient burden with early detection benefits. Until then, clinicians should maintain a high index of suspicion for recurrence beyond five years and consider extending surveillance protocols for patients at elevated risk.

Variable	Category	Late Recurrence (n=25)	p-value
Age Group	≤ 40 years	3 (12)	0.018*
	41–60 years	13 (52)	
	> 60 years	9 (36)	
Sex	Male	16 (64)	0.66
	Female	9 (36)	
Presentation	Fresh	8 (32)	0.127
	Recurred	8 (32)	
	Unplanned Excision	9 (36)	
Depth	Superficial	4 (16)	0.126
	Deep	21 (84)	
Size (cm)	Mean ± SD / Median (IQR)	6.4 ± 5.5 5 (2.6–8.1)	0.24
FNCLCC Grade	Low	5 (20)	0.016*
	Intermediate	11 (44)	
	High	6 (24)	
Histopathologic Margin	N/A	3 (12)	0.26
	Clear	20 (80)	
	Positive	2 (8)	
Histopathologic Border	N/A	3 (12)	0.014*
	Infiltrative	9 (36)	
	Pushing/Expansile	1 (4)	
Anatomic Location	N/A	15 (60)	0.68
	Extremities	22 (88)	
Histologic Type	Trunk	3 (12)	
	Leiomyosarcoma	1(4)	
	MPNST	3(12)	
	Myxofibrosarcoma	3(12)	
	Myxoid Liposarcoma	4(16)	
	UPS	8(32)	
	Synovial Sarcoma	2(8)	
	Others	4(16)	
Radiation Therapy	Yes	7 (28)	0.262
	No	18 (72)	
Chemotherapy	Yes	4 (16)	0.277
	No	21 (84)	
Average Time to Local Recurrence	Mean ± SD / Median (IQR)	89 ± 31 76 (68–106)	
Metastasis Before Local Occurrence	No	25 (100)	0.96
Metastasis After Local Recurrence	Yes	11 (44)	< 0.001*
	No	14 (56)	
Average Time to Metastasis	Mean ± SD / Median (IQR)	63 ± 55 79 (7–101)	
Mortality	All-cause death	9 (36)	0.97

(P 400) LONGITUDINAL EPIGENETIC AND TRANSCRIPTOMIC REMODELING ACROSS PRIMARY, IRRADIATED, AND LOCALLY RELAPSED SOFT TISSUE SARCOMAS

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Objective: Radiotherapy is essential for local control of soft tissue sarcomas (STS), yet the mechanisms underlying relapse within the irradiated field remain unclear. While DNA methylation is a key regulator of gene expression, the epigenetic evolution of STS across treatment and relapse is poorly understood. We sought to characterize methylation and transcriptional changes induced by radiotherapy to uncover epigenetic mechanisms driving radiation resistance.

Methods: We profiled 160 undifferentiated pleomorphic sarcoma and myxofibrosarcoma samples including primary, irradiated, recurrent tumors, and matched normals from 37 patients using RRBS and RNA-seq. RRBS data were processed with Bismark, and DMLs were

identified with edgeR. RNA-seq data were quantified with Salmon and analyzed for differential expression using edgeR. HOMER was used to identify TF binding sites impacted by methylation changes. CNAs were inferred from exome sequencing using TitanCNA and integrated into PRISM to model subclonal methylation architecture.

Results: We identified over 130,000 DMLs across tumor progression. Primary and relapsed sarcomas showed predominant hypermethylation (~75%) in promoters, gene bodies, and intergenic regions, while irradiated tumors exhibited increased hypomethylation, suggesting therapy-induced disruption. In relapsed tumors, hypermethylation suppressed adhesion and transport pathways, whereas hypomethylation activated chromatin remodeling and ribosome biogenesis—supporting invasion, proliferation, and resistance. Integration with RNA-seq revealed silencing of tumor suppressors (e.g., CDKN2A) and activation of oncogenes (e.g., KIF5B, RRAS2). In irradiated tumors, hypomethylation-driven upregulation of CCND1 and DDB2 suggests enhanced DNA repair and cell-cycle bypass. Motif analysis implicated altered TF accessibility (e.g., SOX9, MAFB, PBX3), indicating regulatory rewiring. Subclonal analysis revealed increased epigenetic complexity and emergence of distinct methylation clones in relapse, consistent with clonal selection and resistance evolution.

Conclusion: These findings reveal the temporal and spatial dynamics of epigenetic remodeling in STS and nominate targets for relapse and radiation resistance. By uncovering methylation-driven regulatory changes and subclonal evolution, this work lays the groundwork for precision epigenetic therapies to overcome treatment resistance.

(P 401) LONG-TERM OUTCOMES OF IMATINIB-TREATED DERMATOFIBROSARCOMA PROTUBERANS: INSIGHTS FROM A SINGLE-INSTITUTION CASE SERIES

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Objective: Dermatofibrosarcoma protuberans (DFSP) is a rare, monoclonal cutaneous soft tissue sarcoma with an indolent growth pattern and an incidence of 4.1 cases per million. It is characterized by a fusion of COL1A1 and PDGFB, rendering the tumor susceptible to PDGFR inhibition with imatinib. Imatinib has demonstrated efficacy in both metastatic and localized disease, including DFSP with fibrosarcomatous transformation (DFSP-FS). It is often used neoadjuvantly to reduce tumor size, enabling resection with minimal cosmetic or functional compromise. Some patients remain disease-free following resection and discontinuation of therapy; however, resistance and adverse effects can limit long-term efficacy.

Methods: We present a case series illustrating the natural history of DFSP treated with imatinib, highlighting both the successes and challenges of therapy in real-world clinical settings outside of trial protocols.

Results: • Case 1: A patient with large, localized DFSP was started on neoadjuvant imatinib. The tumor has shown continuous reduction in size, with surgical resection planned once stability is achieved. • Case 2: A patient's treatment was complicated by prolonged non-adherence to imatinib. Despite reinitiation, the tumor progressed locally, necessitating resection. The surgery resulted in significant postoperative morbidity. • Case 3: A patient with DFSP-FS experienced prolonged remission on imatinib. After discontinuation due to adverse effects, she developed multiple distant recurrences, all resectable. Over 20 years post-diagnosis, her disease became clinically resistant to imatinib and is now managed as a high-

grade sarcoma.

Conclusion: Imatinib remains a valuable therapeutic option for both metastatic and locally advanced DFSP, offering the potential for durable disease control and facilitating surgical resection in select cases. However, these cases highlight critical real-world challenges, including treatment-limiting side effects, the consequences of non-adherence, and the emergence of resistance over time. Long-term management requires a multidisciplinary approach, patient education, and close monitoring to optimize outcomes. These findings underscore the need for prospective studies and real-world data registries to better define optimal treatment duration, identify predictors of response, and guide management of resistance in DFSP.

(P 402) LYMPH NODE METASTASES IN SOFT TISSUE SARCOMA: A DATABASE ANALYSIS

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Objective: Certain soft tissue sarcomas (STS) metastasize to regional lymph nodes (LN). Proper identification of these metastases is relevant for staging and prognosis, as these portend a worse prognosis, and lymphadenectomy is associated with improved survival. Recent database studies have called into question the traditionally considered most prevalent STS subtypes with LN metastases, specifically synovial sarcoma. We aimed to analyze the largest STS patient cohort currently available to understand 1) prevalence of regional LN metastasis in STS, 2) factors associated with LN metastasis, and 3) implication of LN metastasis on survival.

Methods: We used the Surveillance, Epidemiology, and End Results (SEER) and National Cancer Database (NCDB) databases to identify patients with histologically confirmed diagnosis of STS located in the extremities, trunk, or pelvis. Duplicate patients were identified based on year of diagnosis, age, sex, race, tumor location, size, and histology. Demographic and clinical variables were assessed using descriptive statistics and overall survival was evaluated with the Kaplan-Meier method.

Results: In total, 65,538 patients with STS were included. Overall prevalence of regional LN metastasis (N1) on presentation was 3,066/65,538 (4.7%). The histologic subtypes with the greatest prevalence of N1 disease: rhabdomyosarcoma (26.2%), clear cell sarcoma (22.0%), epithelioid sarcoma (16.7%), angiosarcoma (10.8%), alveolar soft part sarcoma (10.6%). Prevalence of N1 spread in synovial sarcoma was 4.0%. Several tumor characteristics such as tumor grade, tumor size, stratified by histologic subtype, correlate positively with regional LN metastasis. Overall survival was significantly worse with LN and with distant metastatic spread.

Conclusion: This is the largest cohort to date to determine factors associated with LN metastasis in STS, which portends a worse prognosis. Limitations: database study design.

Soft tissue sarcoma (STS) histologic subtypes with regional lymph node (LN) metastasis

STS <i>histologic subtype</i>	Regional LN metastasis %
Rhabdomyosarcoma	26.2
Clear cell sarcoma	22.0
Epithelioid sarcoma	16.7
Angiosarcoma	10.8
Alveolar soft part sarcoma	10.6
Sarcoma, NOS	8.0
Undifferentiated sarcoma	4.4
MPNST	4.1
UPS	4.0
Synovial sarcoma	4.0
Leiomyosarcoma	3.0
Liposarcoma	1.4
Fibromyxoid sarcoma	1.4
Myxofibrosarcoma	1.2

(P 403) MEDICAL MANAGEMENT OF TENOSYNOVIAL GIANT CELL TUMOR

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Objective: Tenosynovial giant cell tumor (TGCT) is a benign neoplasm of the synovia, bursae, and tendon sheaths. Guidelines recommend active surveillance for manageable symptoms. Symptomatic patients (pts) have been treated with surgery, but complete removal of tumors is not always feasible due to their diffuse nature and high risk of morbidity, with postsurgery recurrence rate of 20%-50%.

Multiple colony-stimulating factor 1 receptor inhibitors (CSF1Ris) have emerged for symptomatic pts, with pexidartinib (pexi) and vimseltinib (vim) approved. Here, we review phase 3 reports for pexi, vim, and pimicotinib (pimi).

Methods: PubMed was searched for publications associated with TGCT, CSF-1Ri, therapies for treatment of TGCT, and known guidelines, with a focus on phase 3 trials and postmarket analyses. Additional targeted searches for ongoing clinical trials were performed.

Results: Three phase 3 TGCT studies were identified (total N=337). The studies enrolled adults with histologically confirmed TGCT for which surgery was not recommended due to risk of dysfunction and morbidity. Pts had measurable disease per RECIST and moderate pain or stiffness. The primary endpoint for all studies was objective response rate (ORR) per RECIST v1.1 at Week 25. Key secondary endpoints were ORR by tumor volume score (TVS), range of motion (ROM), worst stiffness, Brief Pain Inventory (BPI) worst pain, and PROMIS physical function (PF) at Week 25.

Baseline characteristics were similar, with 59%-68% female, ROM of 62.5%-63.0%, PROMIS-PF of 37.5-39.0, and worst stiffness numeric rating of 5.1-5.9. Results are shown in Table 1.

Conclusion: CSF1Ris show efficacy in TGCT. Pts should be monitored for potential side effects that are different for each presented drug. Further research to understand long-term side effects and duration of response will be paramount to optimize therapeutic strategies for pts with TGCT. Efforts to increase awareness (eg, input from pt advocacy groups) are essential.

Table 1. Phase 3 Trials of CSF1Ris for TGCT

Efficacy (Wk 25)						
		Pexi (n=61)	PBO (n=59)	Vim (n=83)	PBO (n=40)	Pimi (n=63)
ORR (%)	RECIST	39	0	40	0	54
	TVS	56	0	67	0	63
PROs (Δ from index)	ROM	15.1	6.2	18.4	3.8	15.6
	Worst stiffness	-2.5	-0.3	-2.1	-0.3	-3.0
	PROMIS-PF	4.1	-0.9	4.6	1.3	5.6
	BPI worst pain					-2.3
PRO (%)	$\geq 30\%$ BPI improvement	31*	15	48	23	
Safety						
		Pexi (n=91)		Vim (n=83)		Pimi (n=63)
$\geq 5\%$ G3/4 AEs		†ALT: 10% †AST: 9% Hypertension: 8%		†Blood creatine kinase: 10% Hypertension: 5%		-
Mixed/hepatocholestatic hepatotoxicity (n)		3		0		0
AEs leading to... (%)	Discontinuation	13		6		2
	Dose reduction	38		42		8

*NS vs PBO.

PBO: placebo; PRO, patient-reported outcome; RECIST, Response Evaluation Criteria in Solid Tumors.

(P 404) OUTCOMES OF NEOADJUVANT THERAPY IN ANGIOSARCOMA PATIENTS: A KAPLAN-MEIER-RECONSTRUCTED INDIVIDUAL PATIENT-LEVEL META-ANALYSIS

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Objective: The benefit of neoadjuvant therapy (NAT) in angiosarcoma (AS) patients remains unclear due to limited available evidence and the rare nature of this disease. We evaluated the impact of NAT in an individual patient-level meta-analysis using reconstructed Kaplan-Meier data from over 1,000 AS patients.

Methods: We searched three databases for studies exploring NAT in primary/secondary AS.

Analyses included patients who did (NAT group) or did not (non-NAT group) receive NAT. We evaluated disease-free survival (DFS), distant metastasis-free survival (DMFS), and overall survival (OS) using Cox proportional hazards models, reporting hazard ratios (HRs) with 95% confidence intervals (CIs). The proportional hazards assumption was violated in all models (Grambsch-Therneau test, $p < 0.05$). Accordingly, we performed landmark analyses and restricted mean survival time (RMST). Analyses were conducted on R (v.4.2.2).

Results: Six studies met our eligibility criteria. Out of 1,112 AS patients included, 243 (21.9%) received NAT and 869 (78.1%) did not. Most NAT patients had primary cutaneous AS (84.4%), and breast was the most common site (40.7%). All but one study explored systemic NAT regimens. Taxane-based regimens were commonly administered (64%, $n=75/117$; three studies). Patients on NAT had a 24% (HR: 0.76, 95% CI 0.60-0.98, $p=0.03$) and 39% (HR: 0.61, 95% CI 0.45-0.81, $p=0.0001$) lower risk of disease recurrence and death, respectively, compared to non-NAT. The DMFS was nonsignificant (HR, 0.80, 95% CI 0.59-1.07, $p=0.13$). In the first 24 months (mos) after treatment, a significant DFS (HR: 0.70, 95% CI 0.52-0.94, $p=0.016$) and OS (HR: 0.27, 95% CI 0.13-0.55, $p=0.00001$) benefit were observed for NAT. The OS benefit was sustained in the following mos (landmark analysis up to 60 mos, HR, 0.48; 95% CI 0.35-0.67, $p < 0.0001$). The RMST analysis up to 60 mos revealed longer mean survival times in the NAT group compared to non-NAT across all three outcomes ($p < 0.03$, Table 1).

Conclusion: This study suggests a strong survival benefit of NAT compared to non-NAT in AS patients.

RMST up to 60 mos.

	NAT (mos)	NON-NAT (mos)	p value
DFS	36.9	30.7	0.009
DMFS	42.8	37.0	0.02
OS	48.6	38.0	$p < 0.0001$

(P 405) PAN-RAS INHIBITION AS A NOVEL THERAPEUTIC STRATEGY FOR RAS-DRIVEN RHABDOMYOSARCOMA

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Objective: Attempts to indirectly inhibit RAS and RAS-effector signaling have been unsuccessful in RAS-driven rhabdomyosarcoma. RMC-6236 and its tool compound RMC-7977 are novel state selective pan-RAS inhibitors that inhibit GTP-bound oncogenic and wild-type (WT) RAS, known as RAS(ON)i. RMC-6236 may prevent therapeutic resistance caused by activation of RTK-driven WT-RAS signaling and activation of bypass survival pathways such as PI3K-AKT. RMC-6236 has been active in RAS-mutant PDAC (RASolute 302- NCT06625320), NSCLC (NCT06881784), and other RAS-mutant solid tumors (NCT05379985). We have therefore considered it a high priority to evaluate the preclinical efficacy of RAS(ON)i in RAS-driven RMS tumor models.

Methods: We used genetic and functional approaches to define drug responses to RAS(ON)i in a genomically heterogeneous panel of RMS tumor models including patient-derived cell lines and xenografts (PDX) as well as isogenic systems representing the most commonly occurring HRAS, NRAS, and KRAS mutations.

Results: We found that RAS(ON)i decreased RAS-MEK-ERK signaling, prevented adaptive PI3K-AKT signaling, and decreased in vitro growth in RAS mutant and WT cell lines with RTK activation. RAS(ON)i led to tumor regression and reduced MEK-ERK signaling in RAS-mutant xenograft models. In RAS-driven FN-RMS, hyperactive ERK signaling promotes cell cycling and impairs myogenic differentiation. We found that RAS(ON)i effectively promoted myogenic differentiation, as measured by expression of the myogenic transcription factor MYOG in vitro and in vivo.

Conclusion: Our data demonstrate that RAS(ON)i decreases RAS-MEK-ERK signaling, prevents adaptive PI3K-AKT signaling, and decreases in vitro and in vivo tumor growth in RAS-driven RMS. These findings can rapidly translate into a clinical trial for patients with RAS-pathway-altered RMS using clinically available compounds in late-stage clinical development.

(P 406) PILOT STUDY: CAN A MULTIPARAMETRIC MRI-DERIVED MODEL OUTPERFORM RECIST PREDICTING PATHOLOGY RESPONSE IN RHABDOMYOSARCOMA?

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Objective: Rhabdomyosarcoma (RMS) is the most common soft-tissue sarcoma in the pediatric population, and it is an aggressive cancer that is subtyped as embryonal, alveolar, pleomorphic, or not otherwise specified. This pilot study aimed to provide initial evidence for developing a multiparametric MRI-feature-derived (mp-MRI) predictive response model to outperform RECIST.

Methods: An IRB-approved retrospective study of 11 extremity and pelvic RMS patients with presurgical mp-MRI, including diffusion-weighted imaging (DWI), contrast-enhanced

susceptibility-weighted imaging (CE-SWI), and perfusion-weighted imaging with dynamic-contrast-enhancement (PWI/DCE), with surgery 02/2021-06/2024. Lesions were categorized into 6 CE-SWI and 6 PWI/DCE morphologic patterns. Time-intensity curves (TICs) were classified as types I-V. Patients were categorized by the percentage of pathology-assessed treatment effect (PATE) in the surgical specimen as responders (>90%, n=3) and partial/non-responders (< 90%, n=8).

Results: • The ADC-mean for the 6 extremity RMS increased from $1,425 \pm 476 \times 10^{-6}$ mm²/s at baseline (BL) to $1,494 \pm 386 \times 10^{-6}$ mm²/s at the presurgical time point (PS). • The ADC-mean for the 5 pelvic RMS increased from $1,093 \pm 342 \times 10^{-6}$ mm²/s at BL to $1,677 \pm 313 \times 10^{-6}$ mm²/s at PS. • All responders and partial/non-responders presented presurgical RECIST, WHO, and volume stability. • At PS, 50% of responders displayed a CE-SWI Complete Ring pattern (P = 0.5578), a PWI/DCE Capsular pattern (P = 0.6065), and a TIC Type-2 (P = 0.6065). • The model based on the CE-SWI GLSZM Large-Area-High-Gray-Level-Emphasis yielded perfect classification performance (AUC=1.0) in responders vs. partial/non-responders, outperforming ADC-Maximum-2D-Diameter-Slice (AUC=0.83), CE-SWI Complete Ring (AUC=0.67), PWI/DCE Capsular (AUC=0.67), RECIST (AUC=0.67), and TIC type-2 (AUC=0.6).

Conclusion: Deriving from PS mp-MRI, a model using a single high-order CE-SWI GLSZM radiomic texture feature achieved perfect classification performance, indicating its potential in predicting RMS response, outperforming RECIST.

(P 407) PIMICOTINIB IN TENOSYNOVIAL GIANT CELL TUMOR (TGCT): LONG-TERM EFFICACY, SAFETY, AND PATIENT-REPORTED OUTCOMES FROM THE PHASE 3 MANEUVER STUDY

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Objective: TGCT is a rare, locally aggressive and often debilitating synovial tumor driven by overproduction of colony-stimulating factor-1 (CSF-1), highlighting the unmet need for effective systemic therapies. Pimicotinib (pimi) is an oral, highly selective, potent CSF-1 receptor inhibitor. MANEUVER (NCT05804045) is the first global Phase 3, randomized, placebo (pbo)-controlled trial evaluating efficacy and safety of pimi in patients (pts) with TGCT from Asia, Europe, and North America. The primary endpoint (objective response rate [ORR] by blinded independent review committee [BIRC] per RECIST v1.1) and all key secondary endpoints were met in Part 1 at Week 25 (Niu et al. ASCO 2025).

Methods: In Part 1 (double-blind), pts received pimi 50 mg once daily or pbo (2:1) for 24 weeks; at Week 25, pts continued or switched to pimi open-label for a further 24 weeks (Part 2), followed by an open-label extension phase. This analysis reports the extended efficacy (including clinical outcome assessments [COAs]) and safety outcomes at the end of Part 2.

Results: There were 94 pts randomized (pimi = 63; pbo = 31). Median age was 40 years (range: 18–69); 68% were female; 50% had disease in the knee. At the final analysis data cutoff (Mar 12, 2025; median follow-up: 62 weeks), when all pts had completed Part 2, ORR in pts randomized to pimi was 76.2% (95% confidence interval [CI] 63.8, 86.0) per RECIST v1.1 and 74.6% (95% CI 62.1, 84.7) per tumor volume score; all COAs, including EuroQol visual analog scale, had ongoing improvement (Table). Pts switching from pbo to pimi in Part 2 derived ORR and COA benefits. No new safety signals, or evidence of cholestatic hepatotoxicity or drug-induced liver injury, emerged. Treatment-emergent adverse events led to discontinuations in 4 (6.3%) pts randomized to pimi and 2 (6.5%) pts randomized to pbo who switched to pimi.

Conclusion: Sustained treatment with pimi in pts with TGCT demonstrated continued improvements in efficacy, enhanced patient outcomes, and an acceptable safety profile, reinforcing its potential for long-term use in eligible pts.

Clinical Outcome Assessments

Change from baseline, mean (SD)	Randomized to pimeciclinib	
	Week 25	Week 49
Active range of motion	n=55 14.28 (20.407)	n=44 16.44 (21.840)
Worst stiffness numeric rating scale ^a	n=56 -2.98 (2.116)	n=46 -3.70 (1.914)
Brief pain inventory worst pain ^a	n=56 -2.32 (1.746)	n=46 -2.56 (1.893)
PROMIS-PF ^a	n=56 5.59 (6.224)	n=49 6.55 (7.728)
EQ-VAS ^a	n=58 7.4 (10.58)	n=48 9.4 (10.88)

^aPatient-reported outcome.

EQ-VAS, EuroQol visual analogue scale; PROMIS-PF, Patient-Reported Outcomes Measurement Information System-Physical Function; SD, standard deviation.

(P 408) REAL-WORLD SINGLE-CENTER INSIGHTS INTO CT-DNA DYNAMICS ACROSS SOFT TISSUE SARCOMAS

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Objective: Soft Tissue Sarcomas (STS) are a heterogeneous group of tumors with few reliable biomarkers for real-time monitoring. Circulating tumor DNA (ctDNA) offers a minimally invasive approach to assess tumor burden and minimal residual disease (MRD), though its clinical utility in STS remains under investigation. Here we present ctDNA's promise as a real-time biomarker across diverse STS subtypes.

Methods: We retrospectively analyzed plasma-derived ctDNA from 45 patients with STS enrolled in the prospective EHR-Based Comprehensive Bone and Soft Tumor Registry (NCT02677961) at The Ohio State James Cancer Center. ctDNA was measured using Tempus (n=22) and Signatera (n=23) platforms. Serial ctDNA levels were compared with radiographic tumor volume, histologic grade, and stage. Tumor burden was quantified via volumetrics, and clinical response was categorized per RECIST or physician assessment.

Results: ctDNA was detected in >75% of patients overall. ctDNA levels significantly correlated with tumor volume in both the Signatera (Spearman $r=0.83$, $p=2.04 \times 10^{-9}$) and Tempus (Spearman $r=0.53$, $p=0.0187$) cohorts. ctDNA presence was associated with histological high-grade tumors ($p=.0217$), with Grade 3 tumors showing the highest proportion of detectable ctDNA. Surprisingly, ctDNA was not correlated with surgical stage ($p=0.666$). Serial monitoring in 13 patients showed ctDNA levels mirrored tumor burden changes during surgery, chemotherapy and radiation. Sensitivity of ctDNA in patients with radiographically evident disease was 77.1%; 5.27% of tests were ctDNA positive despite no evidence of disease radiographically. Long term follow up of these patients will be presented in a future study.

Conclusion: To our knowledge, this study is one of the first real-world evaluations of ctDNA dynamics across diverse STS subtypes. ctDNA levels from both Signatera and Tempus platforms correlated with tumor volume. Furthermore, ctDNA presence correlates with histologic grade and disease burden. These findings highlight ctDNA's potential as a real-time biomarker for disease monitoring and treatment response, supporting its integration into future sarcoma trials. Larger studies are needed to validate these results.

ctDNA Cohort Characteristics for by Testing Modality

	All Patients	Tempus Testing	Signatera Testing
Total Number of Patients	45	22	23
Median Age (Range)	59 (19-85)	57 (19-75)	67 (24-85)
Gender	Female 26 Male 19	Female 14 Male 8	Female 12 Male 11
Stage I-II	7	5	2
Stage III-IV	38	17	21
Patients with Serial Measurements with at least 1 detectable value	13	5	8
Spearman Correlation of ctDNA levels and Tumor Volume (p value)	0.76 ($p = 3.31 \times 10^{-23}$)	0.53 ($p = 0.0187$)	0.84 ($p = 1.25 \times 10^{-21}$)

(P 409) RETROSPECTIVE ANALYSIS OF PROGNOSTIC FACTORS INCLUDING HLA GENOTYPE IN MYXOID LIPOSARCOMA

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Objective: Myxoid liposarcomas (MLPS) can express HLA-A*02-restricted cancer-testis antigens (NY-ESO-1, MAGE-A4) that are targets for adoptive T cell therapy. However, the impact of HLA status on MLPS outcomes is unknown. We conducted a retrospective analysis of MLPS patients who underwent genomic profiling with Memorial Sloan Kettering Integrated Molecular Profiling of Actionable Cancer Targets (MSK-IMPACT) to evaluate associations

between clinical data and outcomes and to test the hypothesis that HLA status does not predict survival.

Methods: HLA genotype was inferred via MSK-IMPACT. Patients were considered HLA-A*02+ if they carried HLA-A*02:01, *02:05, or *02:06. Analyses were conducted separately in two cohorts: Cohort 1 (resectable disease) assessed overall survival (OS), metastatic free survival (MFS), and local recurrence free survival (LRFS); Cohort 2 (metastatic disease) assessed OS from metastasis and time to treatment failure on first-line therapy.

Results: Cohort 1 consisted of 70 patients (53% HLA-A*02+); HLA-A*02 status was not significantly associated OS, MFS, or LRFS. Increasing tumor size was associated with a shorter OS [HR = 1.08, p = 0.06] and MFS [HR = 1.08, p = < 0.001]. A round cell component $\geq 5\%$ was associated with shorter OS, [HR = 7.1, p = 0.06] while intraabdominal primary tumor location was associated with a shorter LRFS [HR = 8.1, p = < 0.001]. Female gender correlated with a significantly longer OS [HR 0.26, p = 0.04]. Cohort 2 consisted of 54 patients (46% HLA-A*02+); HLA-A*02 status was not significantly associated with OS or time to treatment failure. Female gender again predicted significantly longer OS [HR = 0.20, p = 0.04] and a round cell component $\geq 5\%$ was linked to worse OS [HR = 6.0, p = 0.02].

Conclusion: HLA-A*02 status was not significantly associated with clinical outcomes in either MLPS cohort. The known high-risk features of larger tumors and round cell component were linked to worse survival, and intraabdominal primary tumors had an increased risk of local recurrence. In contrast, female gender was associated with improved survival in both cohorts. Given the small sample size, further study is needed to clarify the prognostic impact of gender and tumor location to guide individualized treatment approaches.

(P 410) SUBGROUP ANALYSIS OF THE PHASE 2 PART OF THE RINGSIDE PHASE 2/3 TRIAL OF VAREGACESTAT FOR TREATMENT OF DESMOID TUMORS

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Objective: Gamma secretase inhibitors (GSIs) have shown antitumor activity against desmoid tumors (DT). The RINGSIDE Phase 2 study (NCT04871282) demonstrated safety and early and continued response to three dose regimens of varegacestat (AL102) in patients with DTs. We evaluated treatment response in key subgroups.

Methods: RINGSIDE Phase 2 is an open-label, dose-finding study in adults with progressing DT ($\geq 10\%$ unidimensional growth ≤ 18 months or DT-related pain requiring non-opioid medication). Pts were randomized to three dose regimens: 1.2 mg once daily (n=14), 2 mg intermittent (n=14) or 4 mg intermittent (n=14) (intermittent = 2 days on, 5 days off). In the open-label extension (OLE), active pts began receiving 1.2 mg once daily. We performed descriptive analyses of objective response rate (ORR) in the following subgroups with ≥ 5 participants: age (≤ 40 years vs > 40 years), tumor size (< 70 mm vs ≥ 70 mm), prior lines of therapy (0, 1, or 2+), tumor location (intra-abdominal vs extra-abdominal) and mutational biomarkers (APC vs CTNNB1). Subgroups were analyzed by pooling across dose regimens.

Results: RINGSIDE Phase 2 enrolled 42 pts, of whom 29 (69%) entered the OLE. As of Jan. 6, 2025, median time on treatment was 23.3 months (range 0.7–38.8) and 12 pts (29%) were still on treatment. Median age was 38.5 years (range 19–72), 74% were women, and 69% received prior systemic DT therapy. ORR ranged from 50% to 78% across age, tumor size, prior therapy, tumor location and mutation subgroups (Table 1).

Conclusion: Objective tumor responses to oral varegacestat were seen in all subgroups examined. These findings support continued evaluation of varegacestat for DTs in the ongoing, double-blind, randomized, placebo-controlled RINGSIDE Phase 3 study (NCT04871282).

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Table 1. Varegacestat Response in Subgroups

Subgroups	ORR n (%)
All MRI-evaluable patients (n=37)	24 (65)
Age	
≤40 years (n=22)	13 (59)
>40 years (n=15)	11 (73)
Tumor size	
< 70 mm (n=19)	10 (53)
≥70 mm (n=18)	14 (78)
Prior lines of therapy	
0 (n=11)	6 (55)
1 (n=13)	9 (69)
2+ (n=13)	9 (69)
Tumor location	
Intra-abdominal (n=10)	5 (50)
Extra-abdominal (n=27)	19 (70)
Mutation*	
APC (n=8)	4 (50)
CTNNB1 (n=19)	13 (68)

*Excludes 10 pts with APC & CTNNB1 "no" or "unknown"

(P 411) TFCEP2 FUSION-POSITIVE RHABDOMYOSARCOMAS: A REPORT OF 10 CASES AND A REVIEW OF THE LITERATURE

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Objective: The fusion of the TFCEP2 gene with either EWSR1 or FUS is associated with the spindle cell and/or epithelioid variant of rhabdomyosarcoma. This is an ultra-rare fusion associated sarcoma, only reported in case reports and small case series. Herein, we look to describe the clinical characteristics and treatment course of patients with TFCEP2 fusion sarcomas.

Methods: In this retrospective case series, we identified 10 patients in our hospital system with TFCEP2 fusion sarcomas. We also identified 43 reported cases in the literature. We assessed primary tumor characteristics, treatment regimens, and outcomes among all cases.

Results: In our institution's series of 10 patients, seven had FUS-TFCEP2 fusion and three had EWSR1-TFCEP2 fusion. We find that TFCEP2 fusion sarcomas most commonly occur in young adults (median age: 33 years) and arise in craniofacial bones (70%). The median overall survival in our cohort was 24.7 months. Four patients were treated with upfront surgery, and all developed recurrent disease with median time to recurrence being 2.1 months. Five patients received systemic therapy, and the median progression-free survival was 1.6 months. We reviewed 43 cases in the literature, again highlighting the predilection for craniofacial bones

(69.8%) and incidence in young adults (median age: 30 years). Median overall survival amongst all cases in the literature was 17 months. For the 17 patients with localized disease, the median recurrence-free survival was 4 months. For the 25 cases with metastatic disease, the median progression-free survival was 2 months. Concomitant ALK overexpression is nearly universal, and two of our patients were treated with ALK inhibitors; one patient had a near complete response before eventual progression after 6 months, while the other had progressive disease after 2 months. This pattern of limited response is mirrored amongst the 11 patients who have received ALK inhibitors in the literature.

Conclusion: TFCP2 fusion sarcomas are characterized by aggressive biology and have poor prognoses. The 43 patients previously reported in the literature had similar clinical characteristics as our cohort with most cases occurring in the craniofacial bones of young adults. ALK overexpression was again demonstrated in nearly all patients, however, there was not a clinically meaningful survival benefit seen with the use of ALK inhibitors for the few who received this therapy. Additional work is needed to find the optimal treatment course for these sarcomas.

(P 412) UNCOVERING HER2 OVEREXPRESSION IN SOFT TISSUE SARCOMAS (STS): INSIGHTS FROM THE CANCER GENOME ATLAS (TCGA)

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Objective: HER2 (ERBB2) is a transmembrane receptor belonging to the EGFR family, known to play a pivotal role in tumorigenesis. HER2 expression in STS, while less prevalent than in epithelial cancers, is a therapeutic target with the development of Antibody–Drug Conjugates (ADC). This is particularly true in select subtypes such as synovial sarcoma (SS). Multiple studies have demonstrated variable expression in SS, with some reports indicating overexpression in 30% of cases. Gene amplification is rare. Importantly, the relationship between HER2 mRNA and protein levels may be inconsistent, and membrane localization is not always detectable. These findings underscore the therapeutic potential of HER2-directed strategies in a defined subset of STS and support further clinical investigation. We evaluated HER2 mRNA expression in STS from TCGA data.

Methods: Amp defined by either CNV (Affymetrix single nucleotide polymorphism [SNP] 6.0 array data) or transcriptome (RNA-Seq_v2, log2-transformed RNA-Seq by expectation maximization [RSEM] normalized values) via cBioPortal. Query for amp of “ERBB2” gene was performed on 255 samples of STS from the TCGA Sarcoma PanCancer Atlas (Cohort 1) and on 34 samples from the ICGC TGCA Nature 2020 dataset (Cohort 2).

Results: Cohort 1 (255 patients) included undifferentiated pleomorphic sarcoma (UPS), myxofibrosarcoma (MFS), synovial sarcoma (SS), leiomyosarcoma (LMS), dedifferentiated liposarcoma (DDLPS), and malignant peripheral nerve sheath tumor (MPNST). HER-2 overexpression was observed in 5 out of 10 SS cases (50%), 1 out of 25 MFS cases (4%), 1 out of 100 LMS cases (1%), 1 out of 59 DDLPS cases (2%), 1 out of 50 UPS cases (2%), and in 4 out of 9 MPNST cases (44%). Cohort 2 included 34 STS samples, comprising 19 DDLPS and 15 LMS. No ERBB2 amplification or overexpression was detected in either subtype (0%).

Conclusion: Overexpression of HER2 has been identified in specific subtypes, such as SS and MPNST, suggesting its potential as a therapeutic target. Our findings emphasize the need for further investigation of HER2 in STS, including IHC analysis and clinical trials with ADCs such as Trastuzumab-deruxtecan, in pursuit of cutting-edge therapies to improve outcomes in STS.

(P 413) EFFICACY OF NIROGACESTAT IN PATIENTS WITH DESMOID TUMORS AND PRESENCE OR ABSENCE OF POOR PROGNOSTIC FACTORS: POST HOC ANALYSES OF THE PHASE 3 DEFI TRIAL

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Objective: Desmoid tumors (DT) are rare, locally aggressive, and invasive soft-tissue tumors, often associated with debilitating symptom burden. Nirogacestat (niro), a targeted gamma secretase inhibitor, is the only FDA-approved treatment for adults with progressing DT who require systemic treatment. In the global, multicenter, phase 3 DeFi trial (NCT03785964, data cutoff 07April2022), niro significantly improved progression-free survival (PFS; HR, 0.29 [95% CI, 0.15–0.55]; $P < .001$), objective response rate (ORR; 41% vs 8%; $P < .001$), and patient-reported outcomes (PROs; all $P \leq .01$) vs placebo (pbo). Factors associated with poor prognosis in DT include larger tumor size, age ≤ 30 , presence of S45F or T41A CTNNB1 tumor mutations, and presence of pain. This study assessed the efficacy of niro vs pbo in patient subgroups with or without a poor prognostic factor.

Methods: In DeFi, patients were randomized 1:1 to niro 150 mg BID (N=70) or pbo (N=72). Post hoc analyses of PFS, ORR, and PROs were conducted for subgroups with a poor prognostic factor (tumor size > 10 cm, age ≤ 30 years, presence of somatic S45F or T41A CTNNB1 mutation, or baseline pain by Average Pain Intensity [API >0] of the Brief Pain Inventory–Short Form) and those without (tumor size ≤ 10 cm, age > 30 years, and no baseline pain [API=0]). Other CTNNB1 mutations were not assessed due to small sample size. PROs were evaluated as change from baseline score.

Results: HRs for PFS ranged from 0.18–0.39 for subgroups of patients with poor prognostic factors, and 0.27–0.45 for those without (HRs < 1 favored niro over pbo). ORR group differences (niro–pbo) ranged from 18.1–56.0% for subgroups of patients with poor prognostic factors, and 31.1–45.8% for those groups without (values >0 favored niro over pbo). Overall, niro-treated patients reported greater improvement vs pbo from baseline through cycle 25 in PROs of pain, DT-specific symptom burden, physical and role functioning, and overall QoL, regardless of subgroup. PRO improvements were observed early and sustained on treatment with niro vs pbo.

Conclusion: Niro was associated with consistent improvement in PFS, ORR, and PROs vs pbo regardless of the presence or absence of DT poor prognostic factors.

(P 414) PATTERNS OF RELAPSE OF BORDERLINE AND MALIGNANT PHYLLODES TUMOUR- RESULTS FROM SARCOMA REFERENCE CENTRE (SRC)

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Objective: Phyllodes tumours (PT) are a rare fibroepithelial breast neoplasm. Borderline and malignant Phyllodes are considered more aggressive in nature. NCCN Guidelines recommend local surgical resection with at least a 1cm tumour-free margin as the mainstay of treatment, however this may not be achievable with breast conserving surgery and consider 5mm clearance with radiotherapy considered in selected cases. We present our 25 year experience.

Methods: Patients were retrospectively identified with a borderline and malignant PT diagnosis referred and discussed at a SRC between 2000 and 2024. Patient characteristics, surgical, pathological details, adjuvant treatment and patterns of relapse were analysed. Routine surveillance programme consisted of breast ultrasound and CXR 3-4 monthly Years 1-2, 6 monthly Years 3-5 and annually Years 6-10.

Results: 185 patients with a median follow up of 16.9 months received recommendations through a SRC. Nineteen patients (10%) previously presented with benign phyllodes. Demographic and treatment details are listed in Table1. The local recurrence rate was 15% and distant relapse rate at 14%. Median time to local recurrence occurred within 12 (2.9-49.4) months of first presentation. Nineteen patients (10%) developed local recurrence alone, 9 (5%) developed local and distant relapse and 17 (9%) patients developed metastatic disease alone. Median survival following presentation of metastatic disease is poor at 3.4 months, despite doxorubicin based chemotherapy.

Conclusion: Local control rates of 85-90% can be achieved with surgery with a minimum of 5mm clearance and/or addition of adjuvant radiotherapy. 14% develop distant metastases with poor outcomes, alternative novel systemic therapy options need to be considered to improve survival.

Summary of patient characteristics and treatments

N	185 patients		Patterns of relapse LR (local recurrence) 15% DR (distant recurrence) 14%
Age	50 years	22-84 years	
Ethnicity	White Other NA	67% 23% 10%	
Median size	57mm	12-300 mm	
Surgery	WLE WLE + Re-excision of margins Mastectomy for re-excision of margins NA	89 27 70 4	LR: 11% LR: 22% LR: 14% LR: 25%
Nodal status	NA	4	
	N1	1	
Adjuvant Radiotherapy	Yes: 36 No: 129 NA: 20	60 Gy/30F= 26 50 Gy/25F= 4 40 Gy/15F= 1 NA= 5	RT cohort: 6% recurrence rate LR: 3% LR and DR: 3% Non-RT cohort: 19% recurrence rate LR: 14% LR and DR: 5%
Adjuvant Chemotherapy	Yes: 4 No: 181		Chemo cohort: 100% distant relapse Non-Chemo Cohort: 12% distant relapse
Pathology review	Borderline Malignant	52 133	LR: 52% (10) LR: 14% (18)
Margin	Infiltrative 0- < 5mm 5- < 10mm 10mm or greater NA	52 102 21 50 12	19% (10) LR 16% (16) LR 10% (2) LR alone 5% (1) LR and DR synchronous 10% (5) LR (4) LR

(P 415) A PHASE 1/2 TRIAL OF FOG-001, A FIRST-IN-CLASS DIRECT β -CATENIN:TCF4 INHIBITOR: SAFETY AND PRELIMINARY ANTITUMOR ACTIVITY IN PATIENTS WITH DESMOID TUMORS (DT)

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Objective: Wnt pathway-activating mutations (WPAMs) are highly prevalent in DT, almost all of which harbor a WPAM in APC or CTNNB1. FOG-001 is a Helicon™ peptide that competitively inhibits the interaction between β -catenin and TCF transcription factors. Given the causal nature of WPAM mutations in desmoid tumors, targeting β -catenin offers a more direct and

disease-relevant approach than γ -secretase inhibitors, which inhibit Notch signaling. We describe a first-in-human, phase 1/2, multicenter clinical trial of FOG-001 in patients (pts) with WPAM+ solid tumors, including DT. Herein we report updated data from study pts with DT.

Methods: Eligibility for DT pts: histological confirmation of DT with WPAM; ≥ 1 prior systemic therapy or treatment naïve but deemed appropriate for participation. The primary objective is safety/tolerability of FOG-001. Secondary objectives include preliminary anti-tumor activity and PK.

Results: As of May 11, 2025, 6 DT pts have received FOG-001 at doses ranging from 72–480 mg/m². Median age was 34 years; 33.3% male. One pt with familial adenomatous polyposis had a DT with an APC mutation, while the remaining 5 pts had CTNNB1 mutations; 4 pts had prior treatment with niraparic acid and either progressed (n=3) or discontinued due to intolerability (n=1). FOG-001 demonstrated low PK variability and a dose-proportional increase in exposure. The most common (all-grade/grade ≥ 3) treatment-related adverse events were AST increase (5/1, reversible), ALT increases (4/0, reversible), alopecia (4/0; reversible), and fatigue (4/0). Median treatment duration was 28 weeks (range 2 – 81 weeks), with all pts still on study treatment at data cut-off. Three of 5 efficacy-evaluable pts, including 2 pts that had progressed on niraparic acid, achieved a partial response (PR: 60%). The remaining 2 pts had stable disease (20.4% and 15.6% tumor reduction), for a disease-control rate of 100%.

Conclusion: Preliminary data show that FOG-001 has acceptable tolerability in pts with DT. Tumor reductions were seen in all pts, including multiple PRs in pts who progressed on niraparic acid. Dose expansion in a DT-specific cohort is currently ongoing.

(P 416) A PHASE 2 MULTICENTER OPEN-LABEL BASKET STUDY OF TAZEMETOSTAT IN ADULT PATIENTS WITH INI1-NEGATIVE EPITHELIOID SARCOMA – FINAL ANALYSIS

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Objective: To report the clinical activity and safety of the EZH2 inhibitor tazemetostat (Taz) in patients (pts) with INI1-negative epithelioid sarcoma (INI1-neg ES) (NCT02601950).

Methods: Eligible pts with locally advanced or metastatic INI1-neg ES were enrolled into cohorts 5 (C5) or 6 (C6; plus paired tumor biopsies). Pts received oral Taz 800 mg BID in continuous 28-day cycles. Primary endpoint: investigator-assessed objective response rate (ORR) (RECIST v1.1). Secondary endpoints: duration of response (DOR), 32-week disease control rate (DCR), progression-free survival (PFS), overall survival (OS). Activity and safety were assessed in pts receiving ≥ 1 Taz dose.

Results: From 22 Dec 2015 to 30 Aug 2021, 131 enrolled pts received Taz (C5, n=62; C6, n=69). Median age, 37.0 (range 16–88) yrs; male, 63%; had progressive disease at study entry, 97%. Median exposure duration was 5.1 (range 0.1–69.0) mths (C5, 5.5 mths; C6, 4.2 mths). Clinical activity in C5 was previously published (Gounder M et al. 2020 The Lancet); C6 showed confirmatory outcomes (Table). Exposure–efficacy analyses indicated numerical trends of higher ORR and DCR and longer DOR with higher Taz exposure ($>$ median AUC of 3314 $\mu\text{g}\cdot\text{day/mL}$) vs lower than median exposure. Grade 3–4 treatment-related adverse events (TRAE) occurred in 12% of pts, grade 3–4 treatment-emergent adverse events (TEAEs) in 42%, serious TRAEs in 2%, and serious TEAEs in 34%. TEAEs led to dose reduction in 3% of pts, Taz withdrawal in 4%, and study discontinuation in 12%. Most common TRAEs were nausea, fatigue, diarrhea and decreased appetite. No new safety findings reported.

Conclusion: A notable proportion of pts with advanced/progressive INI-neg ES had durable responses to Taz, which was generally well tolerated (low TRAEs, dose reduction and discontinuation rates), and positive exposure–efficacy relationships were identified. These findings support further studies of Taz in pts with epithelioid sarcoma.

Clinical outcomes in C5 and C6

Clinical activity outcome	Tazemetostat 800 mg BID		
	Cohort 5 Epithelioid sarcoma (n = 62)	Cohort 6 Epithelioid sarcoma + paired tumor biopsy (n = 69)	Cohorts 5 and 6 Pooled epithelioid sarcoma (N = 131)
ORR – n (%)	10 (16.1)	11 (15.9)	21 (16.0)
DOR, months – median (95% CI)	20.2 (7.9–51.6)	22.1 (3.7–∞)	20.2 (9.2–51.6)
32-week DCR – n (%)	16 (25.8)	20 (29.0)	36 (27.5)
PFS, months – median (95% CI)	5.5 (3.4–5.9)	3.7 (1.9–3.8)	3.7 (3.5–5.5)
OS, months – median (95% CI)	19.0 (10.9–26.9)	25.6 (14.5–∞)	19.2 (14.5–31.4)

All outcomes other than OS were assessed by investigators per RECIST v1.1

BID, twice daily; CI, confidence interval; DCR, disease control rate; DOR, duration of response; ORR, objective response rate; OS, overall survival; PFS, progression-free survival.

(P 417) EFFICACY AND SAFETY OF LAROTRECTINIB (LARO) IN PATIENTS (PTS) WITH TRK FUSION SARCOMAS

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Objective: Laro is a first-in-class, highly selective TRK inhibitor approved for tumor-agnostic use in pts with TRK fusion cancer. We report efficacy and safety of laro in pts with TRK fusion sarcomas.

Methods: Pts enrolled in 3 laro clinical trials (NCT02122913, NCT02576431 [NAVIGATE], NCT02637687 [SCOUT]) were included. Responses were independent review committee-assessed per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1. Pts in SCOUT could pause laro in the absence of on-treatment progression (“wait-and-see”). Data cutoff was July 20, 2024.

Results: At cutoff, 129 pts (38 adult; 91 pediatric) were enrolled (49 [38%] infantile fibrosarcoma [IFS]; 72 [56%] non-IFS soft tissue sarcoma [STS]; 5 [4%] gastrointestinal stromal tumors [GIST]; 3 [2%] bone sarcoma). NTRK gene fusions were identified by next-generation sequencing (NGS) in 99 (77%) pts. In the metastatic/unresectable setting, 49 (38%) pts received no prior therapies; 39 (30%) received ≥2.

Overall response rate (ORR) was 78% (95% confidence interval [CI] 69–84); 58 (45%) pts had complete response (CR; including 15 pathological CR [pCR]), 42 (33%) had partial response (PR), 16 (12%) had stable disease (SD), and 10 (8%) had progressive disease. Response could not be assessed in 3 pts. Highest ORR was in pts with IFS (94% [95% CI 83–99]; 63% had CR/pCR). Other efficacy outcomes are reported in the Table. At cutoff, 50 pts (39%) remained on treatment.

Of 93 pts enrolled in SCOUT, 51 (20 non-IFS STS; 31 IFS) entered a first “wait-and-see” period of median duration 33 (range 1–72) months. Of these, 16 (31%) restarted treatment; 11 (69%) had an investigator-assessed response (6 CR, 5 PR), 4 had SD, and 1 could not be assessed. Twelve (24%) pts exited the period and were alive at cutoff. Grade 3/4 treatment-related adverse events occurred in 33 (26%) pts.

Conclusion: Laro shows durable long-term responses and manageable safety in pts with TRK fusion sarcomas. This supports the wider adoption of NGS panels including NTRK gene fusions.

Table. Response to treatment

	Non-IFS STS (n=72)	IFS (n=49)	GIST (n=5)	Bone sarcoma (n=3)	All sarcomas (N=129)
ORR, % (95% CI)	68 (56–79)	94 (83–99)	80 (28–99)	33 (1–91)	78 (69–84)
Median time to response, months (range)	1.8 (0.9–22.9)	1.8 (0.9–7.3)	1.9 (1.7–3.5)	1.6 (1.6–1.6)	1.8 (0.9–22.9)
Median DoR, months (95% CI)	55 (26–NE)	NE (23–NE)	17 (10–NE)	10 (NE–NE)	55 (27–NE)
Median follow-up for DoR, months	46	47	50	NE	47
5-year DoR rate, % (95% CI)	47 (29–66)	52 (33–70)	NE (NE–NE)	0	48 (36–61)
Median duration of treatment, months (range)	21 (0–100+)	41 (4–85+)	28 (11–53)	6 (1–13)	26 (0–100+)

CI, confidence interval; DoR, duration of response; NE, not estimable.

(P 418) INTEGRATING SARCULATOR AND PET RESPONSE TO GUIDE NEOADJUVANT TREATMENT DECISIONS IN HIGH-RISK SOFT TISSUE SARCOMA

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Objective: The benefit of perioperative chemotherapy in high-grade soft tissue sarcomas (STS) remains controversial. Meta-analyses and trials have shown improved progression-free survival (PFS), but overall survival (OS) benefits are inconsistent. The objective of this study was to determine how Positron Emission Tomography (PET) response to neoadjuvant chemotherapy outcomes compare to baseline risk estimates using SARCULATOR.

Methods: Sixty-nine patients with high-grade STS received preoperative pegylated liposomal doxorubicin and ifosfamide. PET scans were performed after cycles 1 and 4. Responders were defined as having $\geq 40\%$ reduction in SUVmax from baseline. PFS and OS were analyzed by PET response and compared to SARCULATOR-predicted risk. Number needed to treat (NNT) was calculated to estimate clinical impact.

Results: Of the 69 patients, 38 (55%) were PET responders at the completion of four cycles of neoadjuvant chemotherapy. The mean SARCULATOR-predicted 5-year OS was 70.1% in responders compared to 71.9% in non-responders; 10-year OS was 58.9% and 60.1%, respectively. In contrast, the observed 5-year OS was 87% (95% CI, 77–99) in responders versus 37% (95% CI, 21–64) in non-responders; observed 10-year OS was 81% vs. 37%. Predicted 5-year distant metastasis (DM) was 38.7% in responders versus 37.2% in non-responders; the 10-year DM was 42.8% and 41.2%. Observed PFS at 5 and 10 years was 72% and 69% in responders, respectively, versus 33% at both time points in non-responders. The absolute OS benefit (87% vs. 37% at 5 years and 81% vs. 37% at 10 years) corresponds to NNT of 2.0 and 2.3, respectively.

Conclusion: Metabolic response assessed by PET provides significantly stronger prognostic stratification than SARCULATOR alone. As predictive models evolve to incorporate dynamic, real-time data throughout the treatment course, PET response should be recognized as a critical factor. In this study, patients with a metabolic response had substantial improvements in long-term OS and PFS. In contrast, non-responders appeared to derive no benefit from chemotherapy, with outcomes comparable or worse than those expected with local therapy alone. Approximately 50% of patients benefited from chemotherapy. These findings support the use of neoadjuvant chemotherapy in high-risk STS and highlight PET response as a valuable tool to guide treatment stratification and future trial design—particularly for tailoring therapy in PET non-responders.

(P 419) PROSPECTIVE REAL-WORLD STUDY OF LAROTRECTINIB (LARO) IN PATIENTS (PTS) WITH TRK FUSION SOLID TUMORS: INTERIM ANALYSIS OF ON-TRK

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Objective: NTRK gene fusions are oncogenic drivers in various tumors including sarcomas. Laro is a highly selective, central nervous system (CNS)-active TRK inhibitor approved for tumor-agnostic use in pediatric and adult pts with TRK fusion cancer. ON-TRK aims to assess laro long-term safety and efficacy in pts with TRK fusion cancer treated in real-world settings. Here, we report interim results for sarcoma and other tumors.

Methods: ON-TRK (NCT04142437) is an ongoing, open-label, non-interventional, multi-cohort, prospective study enrolling pediatric and adult pts with locally advanced or metastatic TRK fusion cancer. Laro dosing is determined by the treating physician. The primary endpoint is safety while secondary endpoints assess efficacy.

Results: At data cutoff (December 19, 2024), 157 pts were enrolled, of whom 120 had ≥ 6 months of follow-up and were included in the interim analysis. Median age at enrollment was 47 years (range 0–81). There were 11 (9%) pts with infantile fibrosarcoma (IFS) and 22 (18%) pts with non-IFS soft tissue sarcoma. Safety data are reported in the Table. The efficacy analysis included 111 pts. Best overall response was available for 96 pts. For the 66 response-evaluable pts with non-primary CNS tumors and 30 pts with response-evaluable CNS primary tumors, objective response rate (%; 95% CI) was 61 (48–72) and 23 (10–42); 24-week disease control rate (%; 95% CI) was 77 (65–87) and 53 (34–72); and median progression-free survival (months [mo], 95% CI) was 20 (10–not estimable [NE]) and 4 (3–11), respectively. Median duration of response (mo, 95% CI) was not reached ([NR] 13–NE) in pts with non-primary CNS tumors and 4 (1–NE) in pts with CNS primary tumors. Median overall survival for 111 pts with survival data (mo, 95% CI) was NR (28–NE) and 12 (7–NE), respectively.

Conclusion: Laro demonstrated manageable safety and favorable response rates and survival in a prospective, real-world trial.

Table

	TEAE N=120	TRAE N=120
Any AE [†]	106 (88.3)	71 (59.2)
Not gradable	1 (0.8)	1 (0.8)
Grade 1/2	51 (42.5)	50 (41.7)
Grade 3/4	43 (35.8)	20 (16.7)
Grade 5	11 (9.2)	0 (0)
Serious AE	41 (34.2)	10 (8.3)
AE leading to dose modification [‡]	36 (30.0)	25 (20.8)
AE leading to dose interruption	30 (25.0)	19 (15.8)
AE leading to permanent discontinuation	14 (11.7)	5 (4.2)
All data are n (%).		
[†] Worst CTCAE grade. [‡] Including dose reductions, increases, and interruptions.		
AE, adverse event; CTCAE, Common Terminology Criteria for Adverse Events; TEAE, treatment-emergent adverse event; TRAE, treatment-related adverse event.		

(P 420) THE EFFECT OF CHEMOTHERAPY AND RADIOTHERAPY IN THE MULTIPARAMETRIC MRI-BASED ASSESSMENT OF TREATMENT RESPONSE IN EXTREMITY SOFT-TISSUE UNDIFFERENTIATED PLEOMORPHIC SARCOMA

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Objective: Undifferentiated pleomorphic sarcoma (UPS) is the largest subgroup of soft-tissue sarcomas. Before surgery, UPS patients are typically treated with either consecutive chemotherapy and radiotherapy (CT-RT) or RT alone. This study aimed to determine the impact of the treatment strategy on imaging and pathology in UPS response assessment based on multiparametric MRI (mp-MRI).

Methods: This retrospective study included 30 extremity UPS patients who underwent preoperative mp-MRI, including contrast-enhanced susceptibility-weighted imaging (CE-SWI) and perfusion-weighted imaging with dynamic contrast enhancement (PWI/DCE), and surgery from February 2021 to May 2023. Lesions were visually classified on CE-SWI into one of 6 morphology patterns. On PWI/DCE, lesions were classified into one of 6 patterns, and time-intensity curves (TICs) were classified as types I-V. Patients demonstrating $\geq 90\%$ pathology-assessed treatment effect (PATE) were labeled as responders (n=15), and those with $< 90\%$ PATE were labeled as partial/non-responders (n=15).

Results: • 19 patients were treated with presurgical consecutive CT-RT and 11 with RT alone. • CT-RT patients displayed a higher number of responders (53%). Responders are defined as a pathology assessed treatment effect (PATE) of 90% or higher. This group demonstrated a higher PATE average (78%) compared to the RT patients (45% responders, with a 63% PATE average). After CT-RT, 80% of responders displayed a CE-SWI complete ring pattern

($P=1.77 \times 10^{-5}$), 90% a PWI/DCE capsular pattern ($P=3.06 \times 10^{-6}$), and 100% a time intensity curve (TIC) type II ($P=4.54 \times 10^{-5}$). • In the RT group, 100% of responders displayed a TIC II ($P=0.0253$). • In patients with CT-RT, a model combining the TIC II, capsular, and complete ring pattern yielded the highest classification performance (AUC=0.98) discriminating responders vs. partial/non-responders, outperforming RECIST (AUC=0.49). In patients with RT, a perfect classification performance was only achieved by a model based on the TIC II (AUC=1.0).

Conclusion: Models based on PWI/DCE and CE-SWI-derived features can significantly outperform RECIST, regardless of the treatment strategy. Furthermore, classification models that best separate responders from partial/non-responders can vary not only by tumor type but also by treatment regimen.

(P 421) CHARACTERIZING THE IMMUNE RESPONSE TO INTRATUMORAL TIGILANOL TIGLATE (TT) IN PATIENTS WITH ADVANCED AND/OR METASTATIC SOFT TISSUE SARCOMA (STS) IN A PHASE IIA TRIAL (NCT05755113)

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Objective: TT is an epoxytigilane small molecule that induces tumor necrosis and vascular disruption via intratumoral injection. Here we report the exploratory outcomes of a completed phase Ila clinical trial.

Methods: Eleven patients with recurrent or metastatic STS were enrolled, with one replaced, in a single arm, open label phase Ila trial of intratumoral TT dosed at 28-day intervals. The primary endpoint was the ablation rate assessed via ultrasound 28 days post injection. Immunohistochemistry (IHC) and TCR β chain sequencing were performed on baseline and 2-week posttreatment biopsies. T cell exhaustion/activation and pan-leukocyte flow cytometry (FC) panels and TCR β chain sequencing on gDNA were performed on blood samples collected pretreatment and at 2-, 4-, and 12-weeks posttreatment.

Results: Ten patients, 3 with leiomyosarcoma, 3 with myxofibrosarcoma, and one each of myxoinflammatory fibroblastic sarcoma, extraskeletal osteosarcoma, angiosarcoma, and sarcoma NOS were evaluable for response. Eight of 10 patients had complete or partial ablation of the injected tumor. IHC and FC demonstrated a markedly immunosuppressed phenotype at baseline, with scant intratumoral immune infiltrate and 60-80% of peripheral CD4+ and CD8+ T cells expressing the exhaustion markers CD57 and TIM3 across all patients. TCR diversity was not significantly different between pre and posttreatment blood samples. However, TCR sequencing demonstrated posttreatment enrichment in the peripheral blood of specific TCR clones found in the pretreatment tumor biopsies in 8/8 patients with evaluable samples. In one patient with biopsied distant metastases, TCR clones from the injected tumor were enriched in the periphery and increased in frequency in a non-injected tumor posttreatment.

Conclusion: Despite patients with STS having a markedly exhausted immune phenotype at

baseline, intratumoral injection of TT was associated with systemic enrichment of TCR clones found in the injected tumors at baseline, suggesting a systemic immune response to intratumoral TT injection. This trial and translational research was funded by QBiotech Group Ltd.

(P 422) EFFICACY WITH VIMSELTINIB IN PATIENTS (PTS) WITH TENOSYNOVIAL GIANT CELL TUMOR (TGCT) AND PRIOR COLONY-STIMULATING FACTOR 1 (CSF1) INHIBITOR THERAPY: A PHASE 2 CASE SERIES

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Objective: Vimseltinib, an oral, switch-control inhibitor of the CSF1 receptor (CSF1R), is approved in the US for treatment of symptomatic TGCT not amenable to surgery. In the phase 2 expansion of a phase 1/2 study (NCT03069469), vimseltinib showed promising antitumor activity (best overall response [BOR] rate of 64% and 37% in pts with TGCT without [cohort A] and with [cohort B] prior anti-CSF1/CSF1R therapy, respectively), favorable safety, and clinically meaningful improvements in pt-reported outcomes regardless of prior therapy. Here, we report efficacy with vimseltinib in pts with prior pexidartinib or vimseltinib treatment.

Methods: Pts with symptomatic TGCT not amenable to surgery were enrolled in this multicenter, open-label, phase 1/2 trial. In cohort B of phase 2, pts with prior anti-CSF1/CSF1R therapy received vimseltinib 30 mg twice weekly (BIW) in 28-day cycles. Antitumor activity (by independent radiological review [IRR] or local assessment using RECIST v1.1) and treatment duration were assessed in pts who received prior pexidartinib or vimseltinib (data cutoff: Feb 22, 2025).

Results: Among 20 pts enrolled in cohort B, 16 received prior pexidartinib, and the BOR rate on vimseltinib was 40%. Median treatment duration was 10.0 months on pexidartinib and 21.8 months on vimseltinib. Reasons for pexidartinib discontinuation were not known for some pts. Two pts in cohort B had prior vimseltinib. One pt had vimseltinib 30 mg BIW in phase 1 of this study (3 cycles; BOR: stable disease [SD] by local assessment, no IRR available); ~2.5 yrs posttreatment, they received 38 cycles of vimseltinib in cohort B with a BOR of partial response by IRR. The second pt had vimseltinib in cohort A (9 cycles; BOR: SD by IRR), and ~1 yr posttreatment, had 9 cycles of vimseltinib in cohort B, achieving a BOR of SD by IRR. This pt discontinued vimseltinib and has maintained SD (last follow-up: wk 60). Most treatment-emergent adverse events were grade 1/2, with no evidence of cholestatic hepatotoxicity or drug-induced liver injury.

Conclusion: These results suggest that pts with TGCT not amenable to surgery can derive clinical benefit from resumption of anti-CSF1R therapy, even after discontinuing the same (vimseltinib) or a different inhibitor. Vimseltinib retreatment was well tolerated with a manageable safety profile, consistent with prior reports.

(P 423) ZIFTOMENIB IN COMBINATION WITH IMATINIB IN ADVANCED GASTROINTESTINAL STROMAL TUMORS (GIST) AFTER IMATINIB FAILURE: PHASE 1A/B STUDY OF SAFETY, PHARMACOKINETICS, AND ANTITUMOR ACTIVITY

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Objective: GIST, the most common digestive tract mesenchymal neoplasm, is mainly driven by KIT gain-of-function oncogenic mutations. Patients (pts) with GIST are typically treated with anti-KIT tyrosine kinase inhibitors (TKIs) like imatinib, but few achieve complete response and most eventually progress due to secondary KIT alterations that cause resistance. Other TKIs are approved in later lines with only moderate clinical outcomes and additional therapies are needed. The menin-KMT2A complex epigenetically upregulates KIT expression in GIST cells in preclinical studies. Ziftomenib is a potent and highly selective menin inhibitor that disrupts menin-KMT2A complex formation. Ziftomenib + imatinib has shown synergistic antitumor activity in imatinib-sensitive and -resistant GIST models, with reduced KIT protein levels and downstream oncogenic signaling observed in imatinib-resistant GIST pt-derived xenografts. Ziftomenib + imatinib may enhance KIT recycling while reducing KIT transcription.

Methods: KOMET-015 (NCT06655246) is a phase 1a/b, open-label study to determine safety, tolerability, recommended phase 2 dose (RP2D), and preliminary antitumor activity of ziftomenib + imatinib 400 mg in advanced/metastatic GIST. KOMET-015 includes dose escalation, RP2D-determination, and dose expansion parts. Eligible pts: ≥18 yrs, biopsy-proven diagnosis of advanced/metastatic KIT-mutant GIST (T670X excluded) that progressed on imatinib at any point (dose escalation, RP2D determination), ECOG PS ≤2, measurable disease (mRECIST). Dose escalation (i3 + 3 design) will evaluate safety and tolerability of up to 4 dose levels (DL) of ziftomenib combined with imatinib. Based on escalation, up to 2 DL will be compared to determine the RP2D. Dose expansion will examine toxicity and preliminary clinical activity of the RP2D: Cohort A: progressed on imatinib as immediate prior therapy; Cohort B: failed imatinib and received ≥2 lines of therapy; Cohort C: imatinib-naïve. Tumor response to be assessed (mRECIST). All adverse events to be recorded, monitored, and graded (CTCAE v5.0). This trial is open and actively recruiting in the United States.

Results: n/a

Conclusion: n/a

(P 424) AN OPEN-LABEL PHASE 1/2 STUDY OF DCC-3009 MONOTHERAPY IN PATIENTS (PTS) WITH ADVANCED GASTROINTESTINAL STROMAL TUMOR (GIST)

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Objective: KIT and platelet-derived growth factor receptor α (PDGFRA) mutations remain key oncogenic drivers in most pts with advanced GIST, and acquired secondary drug-resistant mutations contribute to the heterogeneity of the disease. The diversity of these mutations allows escape from standard-of-care tyrosine kinase inhibitor (TKI) therapy, creating an unmet need for novel therapies that inhibit all clinically relevant mutations. DCC-3009 is an investigational, highly potent, and selective switch-control KIT and PDGFRA inhibitor designed to act against known clinically relevant primary and secondary GIST-driving mutations while limiting off-target effects. In preclinical studies, DCC-3009 showed strong antitumor effects in xenograft models driven by resistant KIT mutations, optimized properties for oral administration, and low risk of cytochrome P450 inhibition. Here, we describe an ongoing study of DCC-3009.

Methods: This multicohort, open-label, phase 1/2 trial is evaluating the safety, tolerability, and efficacy of DCC-3009 in pts with advanced GIST (NCT06630234) using a modular approach. Each trial module is defined by the therapy (DCC-3009 alone or with other anticancer agents) and divided into dose escalation and dose expansion. For inclusion in the monotherapy dose escalation, adult pts must have histologically or cytologically confirmed advanced GIST with documented KIT or PDGFRA mutation, progression on or intolerance to ≥ 1 approved TKI regimen in the advanced setting (imatinib if KIT-mutant), ≥ 1 measurable lesion per modified Response Evaluation Criteria in Solid Tumors version 1.1 (mRECIST v1.1), and an Eastern Cooperative Oncology Group performance status of 0 or 1 at screening. Exclusion criteria include receiving systemic anticancer therapy within 14 days or < 5 half-lives, radiotherapy within 14 days prior to first dose of study drug, prior or concurrent malignancy requiring or expected to need treatment, known allergy or hypersensitivity to the study drug components or excipients, and impaired oral absorption or malabsorption syndrome. Pts enrolled in monotherapy dose escalation will receive oral DCC-3009 in 28-day cycles. The primary outcome measures include safety assessments. Secondary outcome measures include

objective response rate, duration of response, progression-free survival by mRECIST v1.1, overall survival, and pharmacokinetics. Abstract originally presented at ASCO 2025 in Chicago, IL, USA.

Results: N/A

Conclusion: N/A

(P 425) BEZUCLASTINIB EXPANDED ACCESS PROGRAM (EAP) FOR PATIENTS WITH GASTROINTESTINAL STROMAL TUMORS (GIST)

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Objective: Imatinib is the worldwide standard for first-line therapy of advanced KIT-mutant GIST. However, secondary resistance mutations in the KIT ATP-binding domain (exon 13/14), activation loop (exon 17/18), or both develop and result in loss of imatinib-sensitivity. Bezuclastinib is an oral, potent, selective type 1 tyrosine kinase inhibitor (TKI) targeting KIT mutations in exons 9, 11, 17, and 18. High selectivity of bezuclastinib allows it to be combined with sunitinib, which targets mutations in exons 9, 11, 13, and 14. Whereas no single TKI inhibits all KIT mutations, the combination of bezuclastinib + sunitinib provides activity against all primary and secondary KIT mutations relevant in GIST. In a Phase 1/2 study, patients with relapsed and/or refractory GIST treated with bezuclastinib + sunitinib (n=15) experienced clinical benefit and an acceptable safety profile. Bezuclastinib + sunitinib is being evaluated in a registrational Phase 3 study in patients with GIST (Peak, NCT05208047). Given that the clinical trial is fully enrolled, the GIST EAP (NCT06948955) is designed to provide access to investigational bezuclastinib outside of a clinical trial to patients with GIST who meet specific criteria and have no comparable or satisfactory alternative therapy to treat the disease.

Methods: Key eligibility criteria for the EAP include diagnosis of histologically confirmed, locally advanced, metastatic, and/or unresectable GIST; intolerant to imatinib or received prior imatinib therapy for treatment of advanced, metastatic, and/or unresectable GIST that resulted in disease progression; and acceptable laboratory parameters. Key exclusion criteria include prior or known intolerance to sunitinib; eligibility for and/or enrolled in an ongoing bezuclastinib clinical trial; or discontinuation of investigational bezuclastinib due to toxicity or withdrawal of consent. Patients will receive oral bezuclastinib 600 mg + sunitinib 37.5 mg (locally sourced). The treating physician will be responsible for standard of care patient assessments and reporting of any serious adverse events. In collaboration with interested sites, real-world data may be collected in the future. The duration of bezuclastinib treatment through the EAP will be determined by the treating physician but may continue until regulatory approval and commercial availability. The EAP is currently open to receive EAP requests from treating physicians for patients residing in the United States.

Results: N/A

Conclusion: N/A

(P 426) A PHASE I/II TRIAL USING RNA LIPID NANOPARTICLES FOR RECURRENT OSTEOSARCOMA: A REPORT FROM THE NATIONAL PEDIATRIC CANCER FOUNDATION

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Objective: Recurrent osteosarcoma (rOS) has few effective therapeutic options. We developed multi-lamellar RNA lipid nanoparticles (RNA-LP) incorporating autologous total tumor RNA as a personalized immunotherapeutic to reprogram the tumor microenvironment and target the tumor. Canine studies, including OS, provided preliminary data on safety and efficacy. We designed a first-in-pediatrics clinical trial testing the safety, feasibility, and efficacy of this approach for rOS (NCT05660408).

Methods: RNA Lipid Particles Targeting Pediatric Recurrent Intracranial Malignancies and Other systemic Solid Tumors (RNA PRIME) is a multi-institutional Phase I/II trial, funded by the National Pediatric Cancer Foundation, NCI, and the V Foundation, designed to test RNA-LP in recurrent pediatric brain tumors and rOS. Phase I follows a 3+3 dose escalation followed by a modified Simon Two-Stage Phase II at the recommended phase II dose. The primary phase I objective is to demonstrate manufacturing feasibility and safety, and the primary phase II objective is 12-month event-free survival for resectable pulmonary rOS and 4-month progression-free survival for unresectable rOS. Main eligibility criteria include: age 3-39 years, ability to undergo surgical resection or biopsy, adequate organ function, and Karnofsky/Lansky performance status $\geq 60\%$. The study consists of three parts: 1) biopsy/resection; 2) "off the shelf" pp65 (a CMV-associated viral peptide) RNA-LP administered biweekly, followed by contralateral thoracotomy when indicated; and 3) personalized pp65/tumor mRNA RNA-LP administered biweekly x3 then monthly for up to 1 year. Correlative studies examine peripheral blood and tumor immune monitoring. Accrual began in April 2025. The trial will enroll up to 18 subjects in phase I and up to 55 subjects in phase II. Patients with unilateral or bilateral resectable rOS will be analyzed together while patients with unresectable rOS will be analyzed separately.

Results: N/A

Conclusion: N/A

(P 427) PHASE 1/2 TRIAL TO EVALUATE THE SAFETY AND EFFICACY OF PEEL-224 IN COMBINATION WITH VINCRIStINE AND TEMOZOLOMIDE IN ADOLESCENTS AND YOUNG ADULTS WITH RELAPSED OR REFRACTORY SARCOMAS

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Objective: Adolescents and young adults with sarcomas, such as Ewing sarcoma (EWS), desmoplastic small round cell tumor (DSRCT), rhabdomyosarcoma (RMS) and osteosarcoma (OS), experience substantial morbidity and mortality. While topoisomerase 1 (TOP1) inhibitors have activity across these malignancies, they have multiple limitations. PEEL-224 represents a novel tetravalent, pegylated, pro-drug formulation of SN22, an advanced TOP1 inhibitor with enhanced pharmacological properties. PEEL-224 is water-soluble, does not require hepatic activation, and has a prolonged half-life, allowing for increased drug delivery to tumor and once weekly dosing. SN22 does not undergo glucuronidation and ABC transporter-mediated cellular export, thereby reducing acquired resistance. The lack of glucuronidation and anticholinergic activity reduces GI toxicity. Pre-clinical data in EWS, DSRCT and RMS demonstrate significantly improved efficacy over irinotecan.

Methods: This is a prospective, open-label, single-arm, non-randomized, phase 1/2 clinical trial conducted at Dana-Farber Cancer Institute and three external sites (NCT06709495). Patients 12-49 with relapsed or refractory sarcomas receive PEEL-224 (days 1,8) in 21-day cycles in combination with vincristine (days 1,8) and oral temozolomide [days 1-5; V(P)T]. The phase 1 portion of the trial is designed to determine the recommended phase 2 dose of PEEL-224 given in combination with vincristine and temozolomide. During phase 2, there are two dedicated cohorts for patients with relapsed or refractory EWS and DSRCT designed to determine the objective response rate to V(P)T. Patients will be required to have measurable disease in both cohorts. There is a cohort for patients with "other" sarcomas designed to determine progression-free survival in patients with evaluable or measurable disease treated with V(P)T. Correlative biology includes pharmacokinetics, and tissue and ctDNA sequencing. The trial is now open and enrolling.

Results: N/A

Conclusion: N/A

(P 428) MAINTENANCE PEGYLATED LIPOSOMAL DOXORUBICIN VERSUS ACTIVE SURVEILLANCE FOR ADVANCED SOFT TISSUE SARCOMA PATIENTS WHO HAD CONTROLLED DISEASE AFTER STANDARD ANTHRACYCLINE-BASED TREATMENT (MELODY)

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Objective: The progression-free survival (PFS) associated with first-line chemotherapy for advanced soft tissue sarcoma (STS) remains suboptimal. Maintenance therapy with an active agent may delay disease progression beyond initial treatment, however cumulative cardiotoxicity limits prolonged use of conventional anthracyclines. Pegylated liposomal doxorubicin (PLD) with a more favorable cardiac safety profile presents a viable option for extended treatment. MELODY is a multinational, randomized phase II trial designed to evaluate the clinical benefit of maintenance PLD versus active surveillance in pts with advanced STS who have achieved disease control following first-line anthracycline-based therapy. The trial incorporates patient-reported outcomes (PROs) to assess the impact of ongoing therapy on quality of life and translational endpoint to explore predictive biomarkers and support personalized treatment strategies.

Methods: Eligible criteria include advanced STS pts aged ≥ 18 years who had either CR, PR, or SD after first-line anthracycline-based therapy (at least five cycles). Pts will be randomized 2:1 to receive PLD (40 mg/m² every 28 days, up to 12 cycles) or active surveillance. Crossover is not permitted. The primary endpoint is progression-free survival (PFS) post randomization. Secondary endpoints include QoL by EORTC C30 questionnaire, OS, 12-month PFS rate, ORR by RECIST 1.1, and time to next treatment. Left ventricular ejection fraction (LVEF) change will be an interest of safety. Exploratory objectives include efficacy endpoints (PFS, OS, 12-month PFS rate) based on circulating tumor DNA (mandatory) and FDG PET/CT SUVmax (Optional). Based on our systematic review (currently under submission), the mPFS for the control arm is estimated to be 4 months. A clinically meaningful improvement is anticipated in the experimental arm, with a mPFS of 8 months. Assuming 80% power and an alpha level of 0.1, a total of 63 evaluable subjects are required. Accounting for an anticipated 20% drop-out rate, MELODY plans to enroll a total of 81 subjects.

Results: N/A

Conclusion: N/A

(P 429) SINGLE-ARM, OPEN-LABEL PHASE II TRIAL OF XL092 (ZANZALINTINIB) IN PATIENTS WITH ADVANCED LEIOMYOSARCOMA: TRIAL IN PROGRESS

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Objective: Advanced leiomyosarcoma (LMS) has limited effective systemic treatment options in the metastatic setting. Approved subsequent line agents such as trabectedin and pazopanib have demonstrated short-term improvements in progression-free survival (PFS). Other tyrosine kinase inhibitors (TKIs) targeting Vascular Endothelial Growth Factor Receptor (VEGFR), have shown activity in LMS. Their broader use is often limited by toxicity and the emergence of resistance. New active and tolerable agents are needed. XL092 is a next-generation, orally available, multi-targeted TKI that inhibits VEGFR2, MET, and TAM family kinases (e.g. AXL, and MER)—pathways implicated in LMS tumor growth. XL092 has a relatively short half-life (~21 hours), allowing for daily dosing and potentially more flexible management of side effects. Early clinical data report a favorable safety profile, with most common grade ≥3 treatment related adverse events being hypertension (13%), diarrhea (4%), fatigue (4%). This Phase II trial aims to assess the antitumor activity and tolerability of XL092 in patients with advanced LMS.

Methods: This is a single-center, phase II study of XL092 monotherapy in patients with advanced or metastatic LMS. Eligible patients must have histologically confirmed LMS, measurable disease per RECIST 1.1, and ≥2 prior lines of systemic therapy (≥ 2 previous TKIs allowed). XL092 is dosed at 100 mg orally once daily in 14-day cycles until progression or unacceptable toxicity. Dose reduction to 60 mg and 40 mg is allowed. The primary endpoint is 6-month PFS. Secondary endpoints include ORR, median PFS, OS, duration of response (DOR), and safety.

Results: Enrollment is ongoing. The first patient was screened in September 2024. As of June 2025, 12 have enrolled. A total of 29 patients will be enrolled to ensure 26 evaluable for primary analysis.

Conclusion: This trial will evaluate the clinical activity and tolerability of XL092 in heavily pretreated LMS. A 6-month PFS of ≥50% would strongly support further investigation of XL092 in this population. Protocol is being amended to include a second cohort of translocation-associated sarcomas

(P 430) A PH/2 STUDY OF THE RADIOPHARMACEUTICAL [AC-225]RTX-2358 IN THE TREATMENT OF RELAPSED / REFRACTORY (R/R) SOFT TISSUE SARCOMA (STS) THE ATLAS STUDY - ACTINIUM THERAPY FOR LATE-STAGE AGGRESSIVE SARCOMAS

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Objective: STUDY OVERVIEW ATLAS is a seamless Ph1/2 clinical study to evaluate safety, tolerability, dosimetry, biodistribution, PK and anti-tumor activity of [Ac-225]RTX-2358 in adult patients with R/R STS.

Methods: RATIONALE Fibroblast Activation Protein (FAP) is expressed on the surface of cancer-associated fibroblasts (CAFs) with minimal normal tissue expression and is involved in the formation, maintenance, and spread of tumors. Sarcomas frequently demonstrate high FAP expression on tumor cells themselves in contrast to other solid tumors, where it is mainly expressed on CAFs within the tumor stroma. Radioligand therapies utilizing alpha emitters, specifically Ac-225, have emerged as a treatment strategy in oncology. Ac-225 and its daughter radionuclides emit high-energy alpha particles capable of inducing double-stranded DNA breaks, leading to significant cytotoxic effects within cells. Clinical investigations of Ac-225-labeled compounds have shown promising outcomes, particularly in settings where traditional therapies have failed. STUDY MEDICATION [Ac-225]RTX-2358 (Ratio Therapeutics, Boston) has been designed to have high affinity to FAP, translating into extended tumor residence times. This enhanced binding characteristic may lead to increased therapeutic efficacy by sustained cytotoxic radiation delivery directly at the FAP expressing tumor cells. The selective binding to FAP results in low levels of [Ac-225]RTX-2358 binding to normal tissue. STUDY DESIGN Patients will be treated in 3 dose escalation cohorts (7.5, 11.25, 15 MBq) with up to 6 cycles of [Ac-225]RTX-2358 in a 3 x 3 dose escalation design (up to 26 patients) and subsequent Ph2 expansion cohort (up to 50 patients). Dose escalation / de-escalation decisions will be made by a Safety Review Committee. PATIENT POPULATION Patients over 18 yrs with a history of histologically confirmed R/R STS (measurable disease per RECIST v1.1) are eligible if they have a positive screening [Cu-64] FAP PET, with an SUV mean ≥ 2 in at least one tumor site, an ECOG 0 to 1, and adequate organ reserve and renal function.

Results: N/A

Conclusion: N/A

(P 431) INVOKE: A PHASE 1 STUDY OF OKN4395, A FIRST-IN-CLASS EP2/EP4/DP1 TRIPLE PROSTANOID RECEPTOR ANTAGONIST, IN PATIENTS WITH ADVANCED SOLID TUMORS, INCLUDING SARCOMAS

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Objective: The immunosuppressive pathway of prostaglandin E2 (PGE2), part of the cyclooxygenase (COX) pathway, is upregulated in certain cancers and has been implicated in tumor evasion of immune cells, allowing tumor growth and metastasis (Jin et al., 2023). COX2 inhibitors, aspirin and nonsteroidal anti-inflammatories (NSAIDs) have shown some survival benefit in patients with certain cancers (Cao et al., 2016; Lim et al., 2012; Huang et al., 2014; Takiuchi et al., 2018), however results are inconsistent, highlighting the need for more potent but selective COX pathway inhibitors. OKN4395 is a first-in-class, highly selective, equipotent inhibitor of EP2, EP4 and DP1, downstream receptors for PGE2, and PGD2, respectively. DP1 is described in immunosuppression and apoptosis inhibition, supporting the therapeutic rationale (Luo et al., 2024; Peinhaupt et al., 2017). OKN4395 is hypothesized to modulate the tumor microenvironment to allow an effective immune response, and to potentiate the effect of other immunotherapies, both evaluated in INVOKE.

Methods: INVOKE (OKN-4395-121; NCT06789172) is a Ph1a/1b, first-in-human study of OKN4395 (oral, BID) as monotherapy (mono) or in combination with pembrolizumab 200mg IV 3-weekly (combo), in patients with COX-associated immunosuppressed advanced tumors. Ph1a, a mono Bayesian dose escalation followed by combo dose confirmation, assesses safety and establishes the Ph1b dose. Using artificial intelligence (AI) drug-matching algorithms, Ph1b tumors were selected, and response will be assessed (n=20 each): select sarcomas (mono), pancreatic (mono), non-small cell lung (combo), colorectal (combo), head & neck squamous cell (combo). Key inclusion criteria include COX-active (Ph1a) or above-listed (Ph1b) tumors, performance status 0-1, biopsy-amenable lesions, and adequate organ function. Ph1b mono cohorts will explore the effect of food & gastric pH on OKN4395 pharmacokinetics. Trial data, paired pre- and on-treatment biopsies, and exploratory biomarkers will be used to enhance development using advanced agentic AI systems, including a synthetic digital twin control arm. Ph1a is currently recruiting in the US, UK, and Australia.

Results: N/A

Conclusion: N/A

(P 432) EXPANSION OF A PHASE 1 STUDY OF SON-1010 (IL12-FHAB) ADDING TRABECTEDIN IN SOFT TISSUE SARCOMA: TRIAL IN PROGRESS

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Objective: Interleukins have had limited success due to inefficient tumor targeting and short pharmacokinetics (PK), requiring frequent dosing leading to aberrant immunostimulation and toxicity. IL-12 potently activates NK, NKT, Th1, and cytotoxic CD8 T cells to produce IFN-gamma and efficiently kill tumor cells in mice, yet clinical studies of recombinant IL-12 at the maximum tolerated dose (MTD) of 500 ng/kg have failed to show adequate therapeutic benefit in humans. A novel platform technology was developed that delivers cytokine(s) linked to a fully-human albumin binding (FHAB®) scFv domain. Single-chain native IL 12 linked to the FHAB (SON-1010) provides enhanced targeting and retention through albumin binding to over-expressed FcRn, GP60, and SPARC in the tumor microenvironment (TME), with an improved PK profile, a dose-sparing effect that decreases the toxicity risk, and a broader therapeutic index. The safety of SON-1010 along with its PK and PD is being studied clinically as monotherapy (study SB101) in advanced solid tumors and the target MTD of 1200 ng/kg was recently achieved. Trabectedin (Yondelis®) is licensed for patients with metastatic soft tissue sarcoma (STS). While trabectedin is an alkylating drug, it also activates tumor macrophages toward a pro-inflammatory phenotype. SON-1010 may 'warm up' the TME to improve the effectiveness of trabectedin in these immunologically-active tumors.

Methods: SB101 is a Phase 1 dose-escalation study that assessed the safety, tolerability, PK, PD, and efficacy of SON-1010 dosed every 3 weeks to establish the MTD (NCT05352750). An expansion cohort adding alternating doses of trabectedin in 18 patients with STS was designed to show added benefit using a Simon 2-stage statistical approach. Enrollment of the expansion cohort is in progress and follow-up is ongoing. The combination of SON-1010 with trabectedin offers a unique opportunity to use this extended half-life version of IL-12 to augment the potential for tumor control in STS, which represents a significant unmet medical need.

Results: N/A

Conclusion: N/A

(P 433) PHASE I DOSE ESCALATION TRIAL OF STX-001, AN LNP SELF-REPLICATING MRNA EXPRESSING IL-12, IN PATIENTS WITH REFRACTORY TUMORS INCLUDING SARCOMAS

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Objective: STX-001 is a lipid nanoparticle-encapsulated self-replicating mRNA that activates innate immunity, promotes immunogenic cell death, and expresses IL-12. Preclinical models had significant immune modulation and antitumor activity.

Methods: Open-label phase 1 trial using Bayesian Optimal Interval design with 3 + 3 run-in dose escalation. Eligible patients (pts) had advanced solid tumors with ≥ 1 injectable lesion. STX-001 was administered intratumorally once every 3 weeks. Response was evaluated by RECIST 1.1. Cutoff dates were April 3, 2025 (safety/demographics), and May 1, 2025 (efficacy).

Results: 22 pts were enrolled across 5 doses (10 - 900 ug): 1 angiosarcoma, 16 melanoma, 5 others. Post-treatment biopsy of angiosarcoma pt (300 ug) with prior chemotherapy, tyrosine kinase inhibitor, and surgery showed complete pathological response with high CD4/CD8 and PD-L1 expression. 13 melanoma pts were efficacy evaluable; all refractory to anti-PD-1. Notable results are 1 RECIST complete response (100 ug; skin/lymph node metastases (mets); subcutaneous lesion injected), 2 RECIST partial response (30 ug; skin/lung/muscle mets; subcutaneous lesions injected, and 900 ug, lymph node mets, nodal lesion injected), and 1 with 100% target lesion reduction and inflammatory response across cutaneous/visceral lesions after initial progression (30 ug; skin/lymph node/lung mets; [sub]cutaneous lesions injected). Biopsies demonstrated robust increases in PD-L1 and CD4/CD8 in injected/non-injected lesions. Plasma IL-12 and IFN- γ were observed. Grade ≥ 3 treatment-related adverse events included transient neutropenia (4 pts; 18%), lymphopenia (3 pts; 14%), ALT increase (2 pts; 9.1%), and AST increase (2 pts; 9.1%). No drug-induced liver injury reported. One DLT (Grade 3 CRS and Grade 4 lymphopenia) in the 900 ug cohort; pt remained on study.

Conclusion: STX-001 shows preliminary efficacy, immune activation, and tolerability in refractory tumors, including sarcomas, supporting the continued development of STX-001 as monotherapy and in combination with immune checkpoint inhibitors. Dose optimization is ongoing. Clinical trial information: NCT06249048

(P 434) A FIRST-IN-HUMAN PHASE 1, MULTICENTER, OPEN-LABEL STUDY OF M3554, A NOVEL ANTI-GD2 ANTIBODY-DRUG CONJUGATE, IN PATIENTS WITH ADVANCED SOLID TUMORS

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Objective: GD2 is a glycosphingolipid with limited expression in normal tissues and overexpression in various cancers, particularly neuroblastoma, glioblastoma (GBM), and several sarcoma subtypes. GD2 is a clinically validated target in pediatric neuroblastoma, however, currently approved anti-GD2 antibodies (e.g., dinutuximab, naxitamab) are associated with severe pain adverse events (AEs), likely due to Fc γ receptor-mediated immune activation

via antibody dependent cellular cytotoxicity (ADCC) and complement dependent cytotoxicity (CDC). M3554 is a first-in-class, anti-GD2 antibody drug conjugate (drug-to-antibody ratio: 8) that uses a β -glucuronide linker-payload combination to selectively deliver the Top1 inhibitor, exatecan, to GD2-overexpressing tumor cells. M3554 uses a Fc-modified anti-GD2 antibody and IgG1.4 backbone designed to reduce ADCC and CDC, potentially reducing the incidence and severity of pain AEs. In preclinical studies, M3554 showed strong antitumor activity in patient-derived xenograft models of neuroblastoma, osteosarcoma, and GBM. It had a favorable PK and safety profile in animal studies. We present the design of the currently active, first-in-human study of M3554 accruing patients with soft tissue sarcomas (STS) and targeting a future cohort of IDH-wildtype GBM.

Methods: This is a multicenter, open label, dose escalation (Ph1a) and expansion (Ph1b) study to evaluate the safety, PK, and clinical activity of M3554. Eligible patients (≥ 18 years; ECOG PS ≤ 1) have histopathologically-confirmed metastatic and/or locally advanced STS or GBM (IDH-wildtype). Ph1a uses a Bayesian design, with separate dose escalations in patients with STS and GBM. The Ph1a primary endpoint is evaluating dose limiting toxicities and AEs to determine the maximum tolerated dose of M3554 (if reached), to support selection of the recommended dose for expansion. Secondary endpoints are PK, objective response, duration of response, progression-free survival, and ECG assessments. In the absence of archival tissue, fresh biopsies are collected for biomarker analysis (tertiary endpoint) in the STS dose escalation. The RDE(s) established in Ph1a will be used to evaluate the safety and preliminary antitumor activity of M3554 in Ph1b. The study is currently recruiting and aims to enroll 52 patients in the dose escalation phase and 110 patients in the dose expansion phase (STS, n=80; GBM, n=30) in Japan, Belgium, France, and US. Clinical trial information: NCT06641908.

Results: N/A

Conclusion: N/A

(P 435) A PHASE II STUDY OF HIGH DOSE IFOSFAMIDE IN METASTATIC/LOCALLY ADVANCED SYNOVIAL SARCOMA FROM A TERTIARY CARE CENTER IN INDIA

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Objective: There have been no prospective trials examining single agent ifosfamide at 11g/m² specifically in synovial sarcomas. In the relapsed setting, the treatment options are limited and it is important to maximize use of existing regimens. Being a chemosensitive disease, it is important to evaluate this chemotherapy regimen in a prospective study with diagnosis of synovial sarcoma confirmed by FISH. Others treatment options like Anlotinib and cellular therapies like afamitresgene autoleucel are either expensive or not suitable due to very low positivity of HLA-02 in Indian population As Indian and international data is lacking, we are doing this phase II study and analyse the effectiveness of this drug in this particular sarcoma type. Primary objective: • To study single agent ifosfamide in relapsed metastatic synovial sarcoma patients as determined by overall response rate (Complete response + Partial Response) Secondary objectives include overall survival, Toxicity profiles, Quality of life analysis and median progression free survival

Methods: Study design: Single arm, Phase II, Simon 2-stage clinical trial Study setting: The study will be conducted at Department of Medical Oncology, BRAIRCH, AIIMS, New Delhi. After screening and registering the patients who meet the inclusion criteria, the patients will be enrolled into the trial. Oncology nursing staff under supervision of medical oncologist will provide the chemotherapy. Treatment administered Inj Ifosfamide 11g/m² given over 4 days q 21 days for 4 cycles Inj MESNA 3g/m² d1- d4 G-CSF support for 5 days from d5 –d9/ peg-gcsf on D3 Radiological response assessment would be done using RECIST v1.1 after 4 cycles Patients having objective response will receive 2 more cycles as mentioned above and will have final response assessment post cycle 6 Patients will be kept under regular interval followup after treatment completion. This trial is registered under clinical trials registry of India CTRI/2024/03/063743 on 6th march 2024 Simon minimax two stage, one-sample, testing procedure is applied. Sample size of 25 is calculated The trial is currently in stage 2 after showing favourable response in stage 1 and accruing patients at the time of this abstract submission 21 patients have been recruited and response assessments have been done for 15 patients who completed atleast 4 cycles of chemotherapy showed objective response rate in 10 patients (66.6% response rate) final analysis will likely be completed in next 2 months

Results: N/A

Conclusion: N/A

(P 436) SAKK 57/24 FEASIBILITY OF TOTAL NEOADJUVANT TREATMENT WITH HYPERTHERMIA IN PATIENTS WITH HIGH-RISK EXTREMITY AND TRUNK SOFT TISSUE SARCOMA. A MULTICENTER, SINGLE ARM, OPEN LABEL, PHASE II TRIAL

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Objective: Despite optimal local treatment, 40-50% of patients affected by localized high-risk extremity and trunk soft tissue sarcoma (eSTS) die of metastatic disease. Two recent phase III randomized trials including neoadjuvant anthracyclin-based combination chemotherapy followed by surgery and radiotherapy showed an impressive survival outcome, which now has evolved as a potential new standard of care in high-risk eSTS. Based on the results of another phase III randomized EORTC trial the combination of hyperthermia with perioperative chemotherapy in STS might increase overall survival. Consequently, we are aiming at combining hyperthermia with neoadjuvant chemotherapy followed by radiotherapy and surgery

in a total neoadjuvant treatment (TNT) setting. If feasibility is proven and the study were to demonstrate promising efficacy data, the results could serve as the basis for conducting an international randomised study. Objective: Primary: To assess protocol feasibility when hyperthermia is added concomitantly to standard of care neoadjuvant chemotherapy. Secondary: To assess the safety and efficacy in terms of 3-years disease-free survival, 3-years overall survival and radiological/pathologic response rate.

Methods: In this national, multicenter, prospective, interventional, single-arm phase II trial (NCT06835049) conducted by 7 Swiss sarcoma centers and supported by SAKK (Swiss Group for Clinical Cancer Research) all patients suffering from localized, high-risk eSTS according to the prognostic Sarculator tool (10-year OS probability < 60%) will receive three cycles of neoadjuvant chemotherapy followed by radiotherapy and surgery. Chemotherapeutic treatment will consist of Doxorubicin/Ifosfamide in non-leiomyosarcoma-STs and Doxorubicin/Dacarbazine in leiomyosarcoma, respectively. As this new TNT approach has not yet been prospectively evaluated, feasibility is defined as primary endpoint, defined as percentage of patients who complete treatment according to protocol. 24 patients will be enrolled. The protocol feasibility rate will be estimated with a two-sided 90% Clopper-Pearson confidence interval. All time-to-event endpoints will be analyzed by the Kaplan-Meier method. Additionally, QoL will be assessed by the EORTC QLQ-C30. A central pathology and imaging review will be performed.

Results: N/A This abstract is submitted under Trials in Progress

Conclusion: N/A This abstract is submitted under Trials in Progress

(P 437) CLINICAL DATA CONFIRM GALENIC PRINCIPLE AND DEMONSTRATE THERAPEUTIC POTENTIAL OF THE001 (DPPG2-TSL-DOX) PLUS REGIONAL HYPERTHERMIA IN SOFT TISSUE SARCOMA

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Objective: Doxorubicin (DOX) remains standard therapy for soft tissue sarcoma (STS). However, clinical benefits are limited by systemic toxicity and low intratumoral drug levels. THE001 (DPPG2-TSL-DOX) is a thermosensitive liposomal DOX formulation designed for heat-triggered, intravascular release, enabling high local drug concentrations with systemic exposure comparable to conventional DOX. In preclinical models, THE001 + regional hyperthermia (RHT) achieved up to 15-fold higher intratumoral DOX. Complementary, in a neoadjuvant study in feline sarcoma, 3 of 4 animals treated with THE001 + RHT had < 10% vital tumor cells (pCR), compared to 0 of 4 with standard DOX + RHT.

Methods: Phase 1 dose-escalation trial [NCT05858710] in heavily (including DOX-) pretreated participants (pts) with advanced unresectable/metastatic STS. THE001 IV was administered q3w for up to 12 cycles. From cycle 2 onwards, RHT is applied. Primary objectives are safety and definition of Highest Tolerated Dose (HTD); responses are assessed per RECIST v1.1 and Choi. Pharmacokinetics (PK) evaluate heat-induced DOX release and systemic exposure of DOX and liposomal components.

Results: Seven pts were treated in DL1 (20mg/m²; n=4) and DL2 (40mg/m²; n=3). No dose-limiting toxicities occurred with low rate of grade ≥3 TRAEs for THE001 + RHT (3.4% of all AE), leading to determination of 40mg/m² as HTD for THE001 + RHT in this setting. In DL1, 3 pts achieved local tumor control in RHT-region with one stable disease (SD) per RECIST 1.1. In DL2, all pts achieved SD, with 2 of 3 meeting Choi response criteria. Two pts completed 12 cycles with one (epithelioid sarcoma) becoming eligible for resection with no vital tumor cells in resected target lesion. PK profiles showed near-complete DOX release upon heating. Systemic AUCinf was comparable to conventional DOX, while Cmax was substantially lower, suggesting reduced cardiotoxicity.

Conclusion: THE001 + RHT demonstrates clinical activity, proof of galenic principle, and a favorable safety profile in STS. Exploration in the neoadjuvant setting aims to enhance pathological responses (e.g., pCR rate) and immune induction. Orphan Drug Designation by EMA and FDA were granted for THE001 + RHT, validating the potential in STS.

(P 438) RANDOMIZED, OPEN-LABEL, PHASE III TRIAL OF ADJUVANT CHEMOTHERAPY VERSUS OBSERVATION IN NON-METASTATIC, HIGH-RISK SOFT TISSUE SARCOMAS (ACO-SARC TRIAL)

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Objective: Soft tissue sarcomas (STS) are rare and heterogeneous malignancies with variable outcomes. The benefit of adjuvant chemotherapy in STS remains controversial due to mixed evidence from prior studies. The SMAC meta-analysis found that certain patient groups benefit from chemotherapy based on age, sex, and tumor characteristics. The EORTC 62931 trial studied 351 patients but found no significant survival difference between chemotherapy and control groups. The EORTC trials showed that adjuvant chemotherapy did not significantly improve survival for most patients. Many studies on STS involve diverse patient groups, making it hard to identify effective treatments. The Sarcuator tool helps estimate the risk of relapse and survival in STS patients. Sarcuator uses patient age, tumour size, grade, and histology to predict outcomes. A 60% probability of overall survival is used to identify high-risk patients for chemotherapy. High-risk patients with specific characteristics may benefit from early adjuvant therapy. Early intervention in high-risk STS patients is crucial for improving outcomes. The proposed trial aims to determine the efficacy of adjuvant chemotherapy in improving 3-year

disease-free survival (DFS) in patients with high-risk, non-metastatic, chemo-sensitive STS of the extremity, limb girdle, or trunk wall.

Methods: This is a randomised, open-label, Phase III trial involving 270 adult patients with histologically confirmed, high-risk STS (as per Sarculator with < 60% 10-year pr-OS) and chemo-sensitive histologies (undifferentiated pleomorphic sarcoma, synovial sarcoma, myxoid liposarcoma, leiomyosarcoma, and malignant peripheral nerve sheath tumour). Patients with oligo-metastatic disease, other sarcoma subtypes, uncontrolled heart disease, or severe infections will be excluded from the study. After written informed consent, patients will be randomised 1:1 to receive either five cycles of doxorubicin/epirubicin and ifosfamide-based chemotherapy or observation. Stratification factors are tumour site, recurrence status, radiotherapy use, and age.

Results: N/A

Conclusion: N/A

(P 439) AN OPEN LABEL MULTICENTER PHASE 2 STUDY WITH SAFETY LEAD IN OF INTRATUMORAL VUSOLIMOGENE ODERPAREPVEC IN COMBINATION WITH PEMBROLIZUMAB IN PATIENTS WITH ANGIOSARCOMA

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Objective: Angiosarcoma is an aggressive soft tissue sarcoma of endothelial differentiation with a median overall survival of less than one year for metastatic disease. Standard treatments including paclitaxel or anthracycline based chemotherapies are associated with significant toxicities and tyrosine kinase inhibitors when used as single agents have limited response rates. Immune checkpoint inhibitors, either as monotherapy or in combination have demonstrated durable responses. Oncolytic virus (OV) immunotherapy when injected intratumorally can selectively replicate within cancer cells and lead to cell lysis thereby leading to an immune response. This ultimately leads to the elimination of the injected and non-injected distant tumors. Initial studies using OV and anti-PD1 combination have shown promising responses in immunotherapy naïve angiosarcoma patients. However, studies in patients progressing on anti-PD1 immunotherapy are lacking and are an unmet need. Vusolimogene Oderparepvec (VO) is a selective replication competent herpes simplex virus herpes engineered and genetically armed with a fusogenic protein (GALV-GP R-) and hGM-CSF. In Phase 1/2 IGNYTE study trial cohort with anti-PD(L)-1 failed non melanomatous skin cancer including angiosarcoma patients, treated with intratumoral VO and IV nivolumab demonstrated an overall response rate of 33.3%.

Methods: Patients aged ≥ 18 years with biopsy-proven cutaneous angiosarcoma that is either locally advanced and unresectable or metastatic, who have received and progressed on a first-line taxane- or anthracycline-based regimen and have received at least one prior immunotherapy-based regimen within 6 months prior to screening, are eligible for enrollment. Patients must have adequate organ function and at least two measurable lesions per RECIST 1.1 criteria. All patients must provide informed consent prior to participation. Patients will receive a first intratumoral injection of VO, followed 14 days later by 7 additional VO injections every 3 weeks, administered concurrently with intravenous pembrolizumab. Disease assessments will be conducted at baseline and every 8 weeks thereafter. This trial will begin with a safety lead-in of 6 patients, followed by a Phase 2 expansion cohort of up to 18 patients. The primary endpoint is overall response rate (ORR), with a follow-up period of 2 years. Tissue and blood samples will be collected for correlative studies aimed at identifying biomarkers of immune response. (NCT06898970).

Results: N/A

Conclusion: N/A

(P 440) CASE REPORT: COMPLETE CLINICAL AND MOLECULAR RESPONSE TO INTRATUMORAL STX-001, AN LNP-SELF REPLICATING MRNA EXPRESSING IL-12 IN A PATIENT WITH REFRACTORY ANGIOSARCOMA

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Objective: Angiosarcoma (AS) is a rare, aggressive malignancy affecting the vascular and lymphatic system with limited treatment options and poor prognosis. We report a patient with refractory AS who achieved complete clinical and molecular response following intratumoral (IT) injection of STX-001, a lipid nanoparticle (LNP) encapsulated self-replicating mRNA encoding interleukin-12 (IL-12). STX-001 has a unique mechanism of action: it induces LNP-triggered immunogenic cell death, while its self-replicating mRNA activates pattern-recognition receptors via nucleic acid sensing, and drives IT IL-12 to levels multiple logs higher, and with longer duration, than previous generations of IL-12-based therapeutics.

Methods: A 70-year-old female patient (pt) presented with AS on the left chest. Previous biopsy had high-grade atypical vascular proliferation with CD31, CD34, and MYC amplification, consistent with radiation-induced AS due to prior breast cancer treatment. Prior therapies for AS included surgical resection, pazopanib, paclitaxel, and gemcitabine+docetaxel. Pt was enrolled in the monotherapy STX-001 dose escalation clinical trial (NCT06249048), receiving 300 μ g of STX-001 once every 3 weeks.

Results: The pt had transient adverse events of grade 3 neutropenia and liver enzyme

elevation, and grade 1 cytokine release syndrome. Radiographic assessment demonstrated partial response by RECIST criteria on day 207 after initial STX-001 injection. Day 10 on-treatment biopsy revealed reduced cellularity with evidence of degeneration, necrosis, and immune infiltration, as well as a 3x rise in CD4 and 25x rise in CD8 T cells from baseline (quantified by immunohistochemistry). Biopsies on Days 56 and 190 demonstrated a complete pathological response, increased T cell infiltration, and PD-L1 expression. Baseline plasma ctDNA was at 0.82 MTM/ml and on day 230 was undetectable.

Conclusion: This case demonstrates preliminary activity of STX-001 in refractory AS with the potential to induce a T cell infiltrated tumor microenvironment. STX-001 may offer a promising strategy for sarcomas refractory to conventional treatments.

(P 441) COLOSARC-Q: A PROSPECTIVE MULTICENTER STUDY FOR EVALUATING SURGICAL STRATEGIES FOR COLORECTAL RESECTIONS AND POSTOPERATIVE QUALITY OF LIFE IN RETROPERITONEAL SARCOMA PATIENTS

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Objective: Retroperitoneal sarcomas (RPS) are rare malignancies frequently requiring extensive surgery including colorectal resections for complete tumor removal. Complication rates – including anastomotic leakage – are high, but surgical strategies for colorectal reconstruction remain poorly defined. The prospective COLOSARC-Q study investigates the impact of colorectal interventions during RPS surgery and the health-related quality of life (HRQoL), with the aim of optimizing surgical strategies and supporting shared decision-making.

Methods: COLOSARC-Q is a prospective, multicenter, non-interventional study that will enroll 120 patients with primary RPS undergoing colorectal resection as part of sarcoma surgery at specialized sarcoma centers in Germany or Switzerland. HRQoL will be assessed using validated questionnaires (EORTC QLQ-C30 and -CR29) and semi-structured interviews conducted in collaboration with psycho-oncology services and patient advocates. Clinical data will be collected through electronic case report forms and will include demographic, clinical, surgical, and outcome-related variables. The primary objective is to evaluate surgical approaches to colorectal resection and reconstruction. Secondary endpoints include postoperative complications, tumor characteristics, and patient-related factors.

Results: Abdominal symptoms as well as stoma formation can significantly impact the HRQoL of cancer patients. In colorectal cancer surgery, factors like age, malnutrition, neoadjuvant therapy, and blood loss influence complications like anastomotic leakage and mortality. The study results could offer insights into whether the same factors apply to sarcoma surgery; however, it is essential to ensure that these factors are integrated into the shared decision-making process for both surgical and multimodal treatment planning.

Conclusion: COLOSARC-Q aims to provide valuable insights into colorectal resections during surgery for retroperitoneal sarcomas, focusing on reducing complications, improving surgical strategies, and enhancing patient HRQoL.

(P 442) TRIAL IN PROGRESS: A SINGLE-ARM, OPEN-LABEL PHASE 4 TRIAL OF NIROGACESTAT IN ADULT PREMENOPAUSAL FEMALES WITH DESMOID TUMORS

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Objective: Nirogacestat (niro) is an oral, targeted, gamma secretase inhibitor (GSI) and the only FDA-approved treatment for adults with progressing desmoid tumors (DT) who require systemic treatment. In the DeFi trial, niro had clinically significant improvement vs placebo in progression-free survival, objective response rate, and patient-reported outcomes with a manageable safety profile. Also, 75% (27/36) of females of reproductive potential (FORP) on niro had ovarian toxicity (OT) events vs none for 37 FORP on placebo. OT was identified by investigators per abnormal reproductive hormone values, perimenopausal symptoms, or both. Off-treatment resolution of OT was reported by investigators in all (100%; 11/11) FORP who discontinued niro for any reason. Due to OT incidence with niro as a novel GSI drug class, this trial aims to further characterize the incidence and recovery rate of OT events in FORP with DT treated with niro.

Methods: In this single-arm, phase 4 clinical trial, eligible patients (pts) will be female, aged 18–40 years, and premenopausal (estradiol >30 pg/mL, follicle-stimulating hormone [FSH] < 40 IU/L, and regular menses for ≥3 menstrual cycles) at baseline, with histologically confirmed, symptomatic/progressive DT requiring systemic treatment and Eastern Cooperative Oncology Group performance status ≤2 at screening. Pts will receive niro, starting at 150 mg BID, for ≥12 to ≤24 cycles (28-day cycle). After last dose, pts reporting an OT event will be followed until OT resolution, new DT treatment is initiated, or ≤2 years, whichever occurs first. Primary endpoint is percentage of pts reporting an OT event who achieve ovarian function recovery, including recovery after niro discontinuation. OT is defined as new onset amenorrhea lasting ≥3 consecutive menstrual periods, FSH ≥30 mIU/mL, and a negative serum β-human chorionic gonadotropin pregnancy test. Ovarian function recovery is defined as resumption of menses and normalization of hormone values or a positive pregnancy test. Secondary endpoints include OT incidence, time to ovarian function recovery, and safety/tolerability.

Results: ~50 eligible pts with progressing DT will be enrolled. Trial is planned for Belgium,

Germany, Italy, Netherlands, Spain, and the UK. EudraCT number: 2024-515215-21-00.

Conclusion: N/A

**(P 443) FIRST-LINE PAZOPANIB IN PATIENTS WITH EPITHELIOID
HEMANGIOENDOTHELIOMA: A RETROSPECTIVE SINGLE-CENTER ANALYSIS**

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Objective: Epithelioid hemangioendothelioma (EHE) represents an ultra-rare, translocated vascular sarcoma with a heterogeneous course of disease. The optimal systemic treatment for patients with advanced EHE remains unclear. We sought to evaluate the value of pazopanib (PAZ) as a first-line treatment in metastatic EHE.

Methods: Thirteen patients with metastatic EHE and PAZ as a first-line treatment at our institution between 2012 und 2023 were reviewed and analyzed with regard to clinical outcomes.

Results: At a median follow-up of 51.4 months, the median progression-free survival (PFS) and overall survival (OS) were 35.1 and 53.8 months, respectively. In patients with documented prior tumor progression (n = 10), the median PFS and OS were 12.6 and 105 months, respectively. In patients with serosal effusion/ systemic symptoms (n = 4), the median PFS and OS were 6.1 and 10.3 months. The clinical benefit rate of the overall cohort was 62% with no complete or partial responses. Two of four patients experienced a reduction of symptoms (pain and ascites reduction/hemoptysis, respectively) under treatment with PAZ. Toxicity was mainly gastrointestinal and manageable with dose reductions. Permanent treatment interruption due to toxicity was necessary in one patient.

Conclusion: This is the first study to systematically report survival outcomes for PAZ as a first-line treatment in patients with metastatic EHE. PAZ is active and safe in patients with metastatic EHE and may be considered as an alternative to sirolimus for specific patient subgroups. RECIST criteria should be questioned for evaluation of treatment response in EHE.

(P 444) HEALTH-RELATED QUALITY OF LIFE (HRQOL) CHALLENGES IN PATIENTS WITH EPITHELIOID HEMANGIOENDOTHELIOMA (EHE): ANALYSIS OF AN ULTRA-RARE SARCOMA GROUP

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Objective: Patients diagnosed with Epithelioid Hemangioendothelioma (EHE) face significant challenges due to the ultra-rare nature of their disease. EHE is known for its heterogeneity, with some patients experiencing an indolent, asymptomatic course, while others face aggressive disease with pain and poor prognosis. Little is known about how their health-related quality of life (HRQoL) is affected by these challenges and the scarcity of information surrounding their condition. This study qualitatively explored EHE patients' HRQoL.

Methods: This is a secondary analysis from an EORTC QLQ project on health-related quality of life in solid rare cancers (003-2022). Thirty-one patients with EHE from twelve different countries completed one quality of life questionnaire (EORTC QLQ-C30) and were interviewed. Thematic analysis was performed using ATLAS.ti and core themes and sub-themes were identified via the biopsychosocial model. Descriptive basic analysis and questionnaire data were performed.

Results: The EORTC QLQ-C30 showed no floor or ceiling effects. The highest mean scores were related to pain. Interview analysis identified 25 themes across three domains: physical (e.g., fatigue, sleep disturbances, pain, respiratory issues, and functional limitations), mental (e.g., fear of recurrence, scanxiety, emotional distress, and cognitive changes), and social health (e.g., loss of independence, financial burden, lack of support, and impact on relationships). These themes illustrate the multifaceted burden of living with EHE.

Conclusion: Patients with EHE face challenges because of the rarity of their disease. HRQoL themes illustrate the multifaceted burden of living with a sarcoma, from uncertainty, isolation, and lack of understanding, to more shared physical complaints such as fatigue and pain. Further research is needed to further explore different disease courses and how it affects patients' quality of life. Beyond the need of personalised supportive care, results of this study will help create an item list to complement the EORTC QLQ-C30 questionnaire for use in trials among EHE patients.

(P 445) TEADES PH1/2 STUDY WITH ODM-212: PRELIMINARY RESULTS IN EHE PATIENTS

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Objective: The Hippo signalling pathway regulates organ size and cell proliferation via YAP and TAZ, coactivators that drive oncogenic gene expression by binding TEA domain (TEAD) transcription factors. Epithelioid hemangioendothelioma (EHE) is a rare sarcoma characterized by a WWTR1(TAZ)–CAMTA1 fusion in >90% of cases, which drives constitutive TAZ activation and aberrant TEAD-mediated transcription, making the YAP/TAZ–TEAD interaction an attractive therapeutic target. ODM-212 is a novel small molecule pan-TEAD inhibitor that has shown anti-tumour activity in non-clinical models in vitro and in vivo in solid tumours.

Methods: TEADES is a Phase 1/2 multi-site, open-label, first-in-human trial with two parts (dose escalation and dose expansion) with ODM-212. Phase 1 of the study will enrol subjects ≥18 years of age with various types of advanced, metastatic solid tumours known to harbour mutations affecting or interacting with the Hippo pathway, or where Hippo pathway has been indicated to be involved in tumour growth (basket-type approach). Phase 2 expansion including dose optimization is conducted in parallel cohorts in selected tumour types potentially responsive to TEAD inhibition based on data from Phase I or other scientific data. The primary endpoint of TEADES Phase 1/2 trial is to evaluate safety and tolerability of ODM-212 in human subjects. The trial is currently open and enrolling, with maximum 112 subjects in Phase I.

Results: Three patients with EHE have been treated with ODM-212. One patient achieved a confirmed partial response (PR, >30% tumour shrinkage) that is ongoing beyond 12 months, and two patients had tumour regression (< 30% shrinkage) with prolonged stable disease (all ongoing >6 months on therapy). ODM-212 has been well tolerated, with no dose-limiting toxicities observed to date. Results of RNA sequencing of paired tumour biopsies from the PR patient will be presented.

Conclusion: TEAD inhibition with ODM-212 has induced durable tumour regression in EHE, demonstrating proof-of-concept for this targeted approach in a TAZ-fusion driven sarcoma. ODM-212 showed encouraging anti-tumour activity and manageable safety, highlighting the potential of targeting the Hippo–YAP/TAZ–TEAD pathway in EHE.

(P 446) GDF-15 AS A PROGNOSTIC FACTOR IN PATIENTS WITH EPITHELIOID HEMANGIOENDOTHELIOMA

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Objective: GDF-15 (G) is a cytokine which is associated with cachexia. It is also released by epithelioid hemangioendothelioma (EHE) tumor cells. We herein report on its role in risk assessment of EHE patients (pts), as investigated within POEM, an international prospective observational study of EHE (NCT06680401).

Methods: All consecutive molecularly confirmed EHE pts seen at the Istituto Nazionale Tumori, Milan, Italy, and the Royal Marsden Hospital, London, UK, were enrolled in POEM starting from March 2021. Plasma G levels were measured at study entry and predefined study timepoints, using both Elisa and ElectroChemiluminescence ImmunoAssay (ECLIA) by Roche diagnostics tests, and classified as normal or high (i.e., >95th percentile of healthy controls). Overall survival (OS) and RECIST-based progression-free survival (PFS) were analyzed in relation to G levels and serosal effusion (SE), assessed by newly defined exploratory radiologic criteria called Response Evaluation by Serosal Changes and Outcomes Reporting (RESCORE). OS and PFS were estimated with the Kaplan-Meier method.

Results: G levels at study entry were available in 56 pts of 63. Comparison of Elisa and ECLIA tests showed comparable results; G levels were high in 15/56 (27%) and normal in 41/56 (73%). G levels were unrelated to number of metastatic sites, but were strongly linked to SE, which occurred in 8/15 pts with high G levels and only in 2/41 pts with normal G levels. High G levels correlated to worse outcomes (Table 1). Of 56 pts, 8 died of disease: 7 had high baseline G levels, while 1/8 had normal G level initially but it rose one month later. Combining G and SE improved prognostic discrimination, raising the hazard ratio for OS from 12 to 25.

Conclusion: Elevated plasma G levels identified EHE pts at higher risk of progression and death. Combining high G with SE (by RESCORE) at baseline and during follow-up improved the identification of aggressive cases. These preliminary findings support G being a potential biomarker of aggressiveness, warranting prospective external validation. G could be incorporated in treatment response assessment.

Outcomes According to GDF-15 and Serosal Effusion

GDF-15	2-year PFS % RECIST	2-year PFS % RESCORe	2-year OS %
Normal	82	77	91
Normal and no SE	81	79	94
High	42	30	44
High and/or SE	43	29	40

(P 447) PAIN ASSESSMENT CRITERIA (PAC) ANTICIPATE RECIST PROGRESSION AND CORRELATE WITH BLOOD LEVELS OF GROWTH DIFFERENTIATION FACTOR 15 (GDF15) IN EPITHELIOID HEMANGIOENDOTHELIOMA (EHE)

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Objective: To report on new criteria for disease-related pain evaluation (PAC) in patients (pts) with EHE, developed as part of POEM, an international prospective observational study of EHE (NCT06680401) launched in March 2021.

Methods: PAC were developed by Palliative Care Specialists (PCS), focusing on worst pain intensity (WPI) and analgesic use. After their implementation in 2025 PAC were retrospectively/prospectively evaluated by PCS in all pts enrolled in POEM and with WPI>4. PAC categorized pain response as partial response (PR), stable disease (SD), or progressive disease (PD). PAC results were compared to re-sponse evaluation by RECIST and matched to the serum levels of GDF15, a cytokine released by EHE tumor cells, measured at baseline and

predefined study timepoints, and categorized as normal or high (>95th percentile of healthy subjects). Linear regression of log1p-transformed oral morphine equivalent daily dose (OMEDD) on GDF15 serum sample assessed their association.

Results: Of 63 pts who entered POEM from March 2021, 15 reported EHE-related pain; 13/15 had WPI>4 and were evaluable by PAC. At analysis, 7/13 pts had died of disease (DoD), 6/13 were alive. GDF15 levels at study entry were high in 8/13 pts. PAC detected a PD in all DoD pts, while RECIST showed a PD in 4/7 only. PAC detected PD earlier than RECIST, with a median time from PD to death of 8.8 and 6.2 months by PAC and RECIST, respectively. In alive pts, 2/6 had a PAC PD without RECIST PD, followed by SD after start of siroli-mus. GDF15 was markedly elevated in all blood samples collected at the time of PAC-detected PD, including those with RECIST SD. Notably, the log-linear model showed that doubling serum GDF-15 corresponded to a 45 % increase in daily OMEDD ($p = 0.020$).

Conclusion: In this exploratory analysis, PAC were better than RECIST in detecting disease progression in EHE patients who died of disease. Elevated GDF15 blood levels were associated with PD by PAC and higher OMEDD. These preliminary findings underscore PAC's potential to guide therapeutic decision-making and assessment in EHE, and warrant its validation and correlation with GDF15 in prospective EHE trials.

(P 448) **OVERCOMING CHALLENGES IN ULTRA-RARE SARCOMAS: A CENTRALIZED BIOBANK FOR EPITHELIOID HEMANGIOENDOTHELIOMA AS A RESOURCE TO ACCELERATE DISCOVERY**

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Objective: Epithelioid Hemangioendothelioma (EHE) is an ultra-rare vascular sarcoma with an estimated incidence of less than 1 per million people.¹ The rarity and heterogeneity of EHE presents significant challenges in basic, translational, and clinical research with very limited access to tissue and fluid specimens. Development of EHE model systems is essential to advance therapeutic discovery. Presently, there remain too few disease models, and no published human cell lines. EHE model development is an urgent need that will result in better understanding of disease phenotypes, inform biomarker development, and identify therapeutic targets in EHE. To address this need, the EHE Foundation initiated the EHE Biobank, a central biorepository of specimens including fresh tumor tissue from surgeries, archived tumor tissue, serosal effusions, blood, and saliva, making samples available for ethical research and model development.

Methods: EHE patients were informed about the opportunity to donate biospecimens by the EHE Foundation. Patients provided electronic informed consent. The EHE Biobank facilitated specimen procurement requests with patients' medical institutions at the request of the patient. A minimal clinical dataset was maintained; specimens and data were de-identified. The Foundation sought partners for model development and drug discovery through its collaborative research network.

Results: Since initiation of the Biobank in 2021, 98 participants consented, 112 specimens have been collected. Of these, 83 are fresh, frozen, or paraffin-embedded tissue, 17 serosal fluids, and 15 blood samples. 5 participants donated EHE tumor tissue posthumously. To date, 21 specimens have been distributed to researchers and 4 models are in development.

Conclusion: Patient organizations are capable to initiate and conduct ethical research leveraging professional resources and partners. People diagnosed with EHE are uniquely positioned to work together within patient organizations to accelerate model and biomarker development by donating human specimens, making ultra-rare biospecimens readily available for research.

(P 449) UNDERSTANDING GAPS IN KNOWLEDGE AND PATIENT-REPORTED PAIN IN EPITHELIOID HEMANGIOENDOTHELIOMA: RESULTS FROM A GLOBAL PATIENT REGISTRY

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Objective: Epithelioid Hemangioendothelioma (EHE) is an ultra-rare vascular sarcoma with an incidence of < 1 per million. EHE can occur anywhere in the body with variable spread and aggressiveness, posing challenges to diagnosis and clinical management of symptoms. We aimed to investigate (1) patient awareness of their molecular mutation subtype and (2) pain burden. These insights identify gaps in molecular subtype classification and underscore unmet needs in symptom management, illustrating opportunities to improve care and advance therapeutic discovery.

Methods: People diagnosed with EHE were informed about opportunities to join the EHE Global Patient Registry by the EHE Foundation. Participants provided eConsent. Data was collected in surveys through a secure web-based application. PROMIS® Pain Intensity and Interference instruments were utilized. Categorical variables were represented using frequency distributions and compared using the Chi-square test. A p-value < 0.05 was considered significant.

Results: Of 209 respondents of the diagnosis survey, 25% had genomic testing, whereas 19% did not and 56% were unsure if genomic analysis was done. While 16% of respondents had the WWTR1 (TAZ)-CAMTA1 mutation and 0.5% had YAP1-TFE3, 83% did not know their genomic subtype. Of 160 respondents of the pain assessment survey, 36% reported moderate to severe worst pain and 23% reported moderate to severe average pain. Pain interfered moderately to severely with daily activities (25%), work at home (24%), social activities (24%), and household chores (26%). Compared to those with localized disease, a higher percent of participants with multi-organ EHE reported moderate to severe levels of worst pain (40% vs. 30%, p = 0.2) and average pain (25% vs. 19%, p = 0.4), though statistically insignificant.

Conclusion: These findings highlight suboptimal patient awareness of molecular diagnostic results and notable pain burden in EHE. Optimizing genomic test use and patient education can improve care planning and research participant identification. Pain characterization may inform care and serve as exploratory endpoint in drug development.

(P 450) OUTCOMES IN CLEAR CELL SARCOMA: UPDATED INSIGHTS FROM ELECTRONIC HEALTH RECORDS IN A PATIENT-LED REGISTRY

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Objective: Clear Cell Sarcoma (CCS) is a rare, aggressive soft tissue sarcoma driven by EWSR1-ATF1 gene fusion. It typically affects adolescents and young adults and is known for its resistance to conventional therapies and tendency to metastasize early. Clinical trial data are extremely limited due to its ultra-rare nature. To address this gap, we previously reported early findings from a patient-led registry utilizing de-identified electronic health records (EHRs) to help characterize the natural history of CCS. The objective of this study is to present updated analyses from this registry, reflecting expanded enrollment and additional real-world outcome data.

Methods: Patients or caregivers contributed de-identified EHRs through a secure data collection platform. Records were reviewed and curated by a trained medical data team. Extracted data included demographic information, tumor location and stage, treatment history (surgery, radiation, systemic therapy), progression events, and survival outcomes. Each included case had a confirmed Diagnosis of CCS with EWSR1-ATF1 gene fusion documented in the EHR. Descriptive statistics were used to summarize clinical characteristics and treatment patterns, with subgroup comparisons where applicable.

Results: As of June 2025, the registry includes 22 CCS patients, with ongoing data analysis underway. Preliminary trends in treatment patterns, disease progression, and clinical outcomes are being evaluated. Final results will be available at the time of presentation.

Conclusion: This expanded dataset reinforces the feasibility and value of patient-led EHR registries in rare cancers. Real-world data collection enables deeper insight into treatment patterns and outcomes, offering an essential bridge while prospective clinical trials remain limited in CCS. Ongoing updates will further inform clinical decision-making and research priorities.

(P 451) TREATMENT OUTCOMES OF GEMCITABINE AND DOCETAXEL IN PATIENTS WITH CLEAR CELL SARCOMA (CCS) OR GASTROINTESTINAL NEUROECTODERMAL TUMOR (GNET): A CASE SERIES

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Objective: CCS and GNET are rare, aggressive sarcomas characterized by EWSR1 fusions with poor response to conventional chemotherapy. However, the efficacy of gemcitabine and docetaxel (GD), a common sarcoma regimen, is not well known.

Methods: We reviewed a series of patients (pts) with CCS or GNET who received GD at MD Anderson Cancer Center. Clinical data, treatment, and outcomes were collected. Descriptive statistics was used to report BOR (best overall response), TTP (time to progression or last stable scan), and OS (time from diagnosis to death or last follow-up (f/u)).

Results: Of the 4 pts (ID 1,2,3 GNET of small bowel and ID 4 CCS of left ankle) with median age 38 yrs, 2 pts (ID 2, 3) had EWSR1-CREB while the other 2 had EWSR1-ATF fusion. All pts initially presented with localized disease and underwent curative-intent surgery before developing recurrence. Table 1 details pt characteristics, response to GD, and survival. At last f/u, all pts were alive.

Conclusion: Although CCS and GNET are generally believed to be chemo-resistant, our limited series shows efficacy with GD, suggesting that this regimen may offer clinical benefit in select pts. GD should be considered as a potential option and perhaps a comparator for newer therapies being tested in this subtype.

Table 1 Clinical Characteristics and Outcomes in Patients with CCS or GNET Treated with Gemcitabine/Docetaxel

ID	Age (yr)	Sex	Metastatic site	Systemic Rx (no. of cycles, stop reason)	BOR on GD	TTP (mo)	OS (mo)
1	34	M	Liver, Lung	1.GD (6, T) 2.AMG337 (1, PD) 3.GD (4, T) 4.Nivolumab (1, PD) 5.GD (8, PD) 6.Olaparib (3, PD) 7.Ivosidenib (6, PD) 8.Devimistat/hydroxychloroquine (NA, PD) 9.Liposomal Doxorubicin (6, PD)	1. PR 3. SD 5. SD	9.1* 3* 9.9	63.7
2	60	F	Liver	1.GD (4, PD) 2. AI (1, PD)	PD	2.7	15
3	35	M	Peritoneum	1. GD (6, pt choice)	SD	32.3*	125.7
4	23	F	Inguinal and external iliac nodes	1. GD (4, pt choice) 2. Cabozantinib (on going)	SD	3.5*	10.7

T: toxicity, AI: doxorubicin/ifosfamide, NA: not available

*Time to last stable scan on GD.

(P 452) EFFECTIVENESS OF ERIBULIN FOR MYXOID PLEOMORPHIC LIPOSARCOMA: INSIGHTS FROM A PATIENT-DERIVED MODEL AND CLINICAL TRANSLATION IN A PATIENT WITH ADVANCED DISEASE

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Objective: Myxoid pleomorphic liposarcoma (MPL) is an ultra-rare soft tissue sarcoma primarily affecting children and adolescents. This study investigates the effectiveness of systemic therapeutic options for MPL by correlating findings from a patient-derived model with observations in a patient with advanced, widespread metastatic disease.

Methods: A patient-derived xenograft (PDX) and a paired cell line was established from a primary MPL. Drug activity was quantified as maximum tumor volume inhibition percentage (max TVI%). We evaluated a patient with advanced MPL who had experienced disease progression despite multiple prior lines of systemic treatment and surgical interventions.

Results: Eribulin achieved complete tumor response (max TVI 100%) in all treated PDX models. While six tumors regrew approximately 50 days post-treatment, one tumor exhibited a complete histopathological response. Single-agent doxorubicin (max TVI 87%) and ifosfamide (max TVI 94%), as well as their combination (max TVI 97%) showed meaningful activity but tumor regrowth occurred in all mice. Trabectedin (max TVI 67%) and selinexor (max TVI 55%) exhibited limited effectiveness. The differences in tumor response to eribulin seems to rely on the ability of the drug to induce programmed cell death in terms of apoptosis and necroptosis, as observed at western blot and RNA-seq analysis. Based on these preclinical findings, the patient with progressive MPL, who had undergone extensive prior treatments, was initiated on eribulin. This patient achieved disease stability for 11 cycles (January-October 2024) with symptom improvement before disease progression was observed.

Conclusion: Eribulin emerged as the most effective treatment option in a patient-derived preclinical model of MPL. These preclinical results were successfully translated to a patient with advanced disease, who experienced a significant period of disease stability after multiple prior therapeutic lines.

(P 453) OUTCOMES OF PLEOMORPHIC LIPOSARCOMA PATIENTS FOLLOWING MULTI-DISCIPLINARY MANAGEMENT WITHIN A TERTIARY CANCER CENTER

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Objective: Given the ultra-rare incidence of pleomorphic liposarcoma (PLPS), management of this subtype of soft tissue sarcoma (STS) is based on small retrospective studies. Here we report our institutional series of outcomes for PLPS patients (pts).

Methods: Clinicodemographic and treatment-related information from all PLPS pts treated between 1/2015-4/2025 were extracted from our database. Time-to-event analyses (RFS/OS) were evaluated by Kaplan-Meier method.

Results: We identified 31 PLPS pts. The median age was 66 (26-97), and 51.6% were female. The median primary tumor size was 10 cm (1.7-37.3), with 23 (74%) arising from the extremities, and 28 (90%) FNCLCC grade 3. At presentation, 9 pts (29%) had stage II disease, 19 (61.3%) stage III, and 3 (9.7%) stage IV; 11 pts developed distant metastases on treatment. The most common sites were lungs (12/14 - 85.7%), liver (8/14 - 57%), bones (7/14 - 50%), and soft parts (6/14 - 43%). 28 pts were managed for stage II/III PLPS; 17 (60.7%) underwent neoadjuvant/adjuvant RT, 8 (28.6%) received chemotherapy, and 6 underwent resection alone. 2/28 (7.1%) were deemed inoperable. Of the 15 pts that underwent resection at our institution, all had R0/R1 margins. Median follow-up was 16 months (m). 4/26 (15.4%) and 11/26 (42.3%) pts developed local and distant relapses, respectively; 1 and 5-year distant RFS were 65.1% and 40.5%. The median OS of the entire population was 23.3 m, with 1 and estimated 5-year OS of 87.1% and 37.3%. Among 26 pts managed with curative intent, median OS was 51.9 m, with 5-year OS of 46.9%. 15 pts (45.1%) were managed for advanced disease and received at least one line of therapy. The 1st-line was doxorubicin (dox)-based in 7/15 pts (46.6%), with only two responses (13.3%). The median PFS on 1st-line was 2.9 m. Only half of the pts received a 2nd-line regimen, due to fast PD and PS deterioration. Four pts underwent anti-PD-1-based regimens, with no responses.

Conclusion: PLPS is an aggressive STS, with high metastatic potential and poor response to chemotherapy and immunotherapy. Surveillance scans may require comprehensive imaging, due to the common metastases beyond the lung in PLPS.

(P 454) TREATMENT PATTERNS AND OUTCOMES IN RADIATION-INDUCED SARCOMA: FIRST RESULTS OF THE TETRIS-PROJECT - A MULTIMODAL RETROSPECTIVE ANALYSIS FROM A TERTIARY CENTER

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Objective: This study presents the first results of the "TumorEcoSystems in Radiation-Induced Sarcoma (TETRIS)-project, funded by the DKFZ-Hector Foundation, which aims to establish an integrated clinical and translational research framework for radiation-induced sarcomas (RIS). RIS are rare, high-grade malignancies arising as a late complication of radiotherapy. Their management is clinically challenging due to prior treatment burden, anatomical constraints, and poor prognosis. This study aimed to characterize treatment strategies and assess outcomes in RIS patients treated at a certified sarcoma center.

Methods: We retrospectively analyzed RIS patients treated at the Sarcoma Center Mannheim, Germany. Patient records were reviewed for treatment modalities including across up to five therapy lines. Key data included intervention types, timing, and time to recurrence or progression. Response was quantified in months from therapy initiation to disease recurrence. Subgroup analyses were performed for patients treated at our certified sarcoma center.

Results: Notably, 92 % of patients were initially treated outside of certified centers. 60 RIS patients were analyzed, with 89.9% having a history of breast cancer. Radiation-induced angiosarcoma was the most common histological subtype (75.4%). The median latency was 9.2 years. Among RIS patients, initial surgical treatment was performed in 91.4% of cases. First-line chemotherapy was administered in 8.6% of patients, primarily with anthracycline-based regimens. Time to progression after first-line therapy ranged from 1 to 32 months (mean 8.1, SD 7.9). In the subgroup treated at our center (n = 29), 62% received neoadjuvant chemotherapy, while 38% underwent primary surgery. Second-line treatments included repeat resections and taxane-based chemotherapy. Mean response duration dropped to 5.3 months in second-line therapy. Only three durable remissions were observed beyond the second line.

Conclusion: Neoadjuvant chemotherapy combined with surgery showed more favorable outcomes in our center compared to surgery elsewhere. These results underscore the need for early referral to specialized centers and highlight that simple surgical excision in breast centers without sarcoma expertise and without initiation of multimodal therapy remains a major burden in RIS therapy. The TETRIS project aims to provide insights into molecular mechanisms of RIS, develop translational therapeutic approaches and includes patient participation in focus groups.

Initial Treatment Patterns Radiation-Induced Sarcoma

Initial Treatment	Total patients n = 60
Outside center	55 (92%)
Surgery	52 (95 %)
Multimodal therapy	3 (5 %)
Inside Center	5 (8%)
Surgery	2 (40%)
Multimodal therapy	3 (60 %)

(P 455) DEVELOPMENT OF PATIENT-CENTERED INFORMATION MATERIAL ON RADIATION-INDUCED SARCOMA: QUALITATIVE RESULTS FROM FOCUS GROUPS OF THE TETRIS-PROJECT

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Objective: Radiation-induced sarcoma (RIS) is a rare but serious late sequela of cancer radiotherapy. The disease is associated with uncertainty, limited treatment options, and poor prognosis. Currently, there is a significant lack of reliable German-language patient information. The InfoSiS sub-study, conducted within the multicenter “TumorEcosystems in Radiation-Induced Sarcoma (TETRIS)”- project, aims to systematically identify patients’ and relatives’ information needs to guide development of patient-centered materials that foster health literacy and shared decision-making.

Methods: The Cancer Information Service of the German Cancer Research Center used formative evaluation to conduct three online focus groups with 13 participants (9 RIS patients, 4 relatives). Discussions were guided by a semi-structured protocol. Standardized questionnaires captured sociodemographic, disease-related, and subjective health literacy data. Qualitative content analysis was performed on verbatim transcripts. Recruitment was supported by Sarcoma Center Mannheim and German Sarcoma Foundation.

Results: Focus groups revealed substantial information deficits. Participants frequently

reported inconsistent treatment recommendations, inadequate, often unempathetic medical communication, and difficulties obtaining reliable information. Some felt left alone with key therapy decisions. Participants agreed on the urgent need for trustworthy digital information, such as a website. Key content requirements included information on RIS, therapy options, and psycho-oncological support. Awareness of resources such as specialized sarcoma centers and the German Sarcoma Foundation was notably low.

Conclusion: There is a clear and urgent demand for reliable, patient-oriented informational material on rare cancer entities such as RIS, designed to strengthen health literacy and facilitate shared decision-making. Following the formative phase, the developed material will undergo summative evaluation by the target group before public release. Projects like InfoSiS and TETRIS are therefore highly relevant for providing the best possible support to affected patients and their families.

(P 456) **OUTCOMES OF FIRST-LINE CHEMOTHERAPY IN ADVANCED ADULT-TYPE RHABDOMYOSARCOMAS: POOLED ANALYSIS OF CLINICAL TRIALS FROM THE EORTC SOFT TISSUE AND BONE SARCOMA GROUP**

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Objective: Embryonal and alveolar rhabdomyosarcomas are uncommon in adults. Pleomorphic and spindle cell/sclerosing are the most frequent adult-type rhabdomyosarcomas (A-Rhab), both considered ultra-rare sarcomas. Data on chemosensitivity in A-Rhab remain scarce. We assessed outcomes of first-line chemotherapy (ChT) in A-Rhab patients (pts) enrolled in EORTC Soft Tissue and Bone Sarcoma Group trials.

Methods: Data from A-Rhab pts entered in prospective STS phase II/III trials after 1990 were pooled. Diagnosis was locally or centrally confirmed, and all pts had inoperable/metastatic disease at baseline. Response was assessed per RECIST 1.1. Progression-free survival (PFS) and overall survival (OS) were calculated from date of registration or randomization.

Results: Eight clinical trials were included, yielding a dataset of 35 pts with A-Rhab, of whom 19 (54.3%) were men. Median age at diagnosis was 38 years (range 18–71). Tumor grade was intermediate in 4 pts (11.4%), and high in 26 (74.3%). First-line ChT included anthracycline alone in 14 pts (40%), doxorubicin plus ifosfamide in 8 (22.8%), ifosfamide alone in 9 (25.7%), and other regimens in 4 (11.4%). Best response was 1 complete response (2.9%), 5 partial responses (14.3%), 12 stable disease (34.3%), and 14 progressive disease (40%). Median follow-up for pts alive (n=5) at the time of their respective study clinical cut-off dates was 7.2 m (IQR= 4.8 - 21.8). Global median PFS was 2.7 m (95% CI = 1.6–4.1); 3.4 m (95% CI: 0.8–5.0) for pts treated with anthracycline alone, 3.6 m (95% CI: 1.3–8.2) for those receiving doxorubicin plus ifosfamide, and 1.7 m (95% CI: 0.9–7.3) for those treated with ifosfamide alone. Global median OS was 8.5 m (95% CI = 6.2–12.3); 7.8 m (95% CI: 4.0–15.4) for anthracycline, 12.6 m (95% CI: 1.7–22) for combination of doxorubicin and ifosfamide, and 8.5 m (95% CI: 1.9–NE) for ifosfamide alone.

Conclusion: In this analysis, first-line ChT in A-Rhab pts yielded modest outcomes, with low response rates and limited PFS. Collaborative efforts are essential to better define treatment strategies and improve outcomes in these ultra-rare sarcoma subtypes.

(P 457) A RETROSPECTIVE REVIEW OF LOW-GRADE FIBROMYXOID SARCOMA: SURGICAL MANAGEMENT, RADIATION THERAPY, AND OUTCOMES

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Objective: Low-grade fibromyxoid sarcoma (LGFMS) is an ultra-rare soft tissue sarcoma with deceptively benign histologic features yet a potential for late recurrence and metastasis, necessitating lifelong surveillance despite its generally favorable prognosis. This study retrospectively evaluates the oncologic outcomes of LGFMS, examining how tumor location, surgical margin status, and use of neoadjuvant and adjuvant radiation therapy impact recurrence and survival.

Methods: We conducted a single institution retrospective analysis of 19 patients treated between 1998 and 2024 with histologically confirmed LGFMS and who met inclusion criteria for complete surgical, adjuvant, and follow-up data.

Results: Within the patient cohort, the median age at presentation was 40.0 years (IQR 24.0-56.8), and 58% were female. Tumors most commonly arose in the lower extremity (42%), followed by the upper extremity (21%) and trunk (21%). The majority were in deep (intramuscular) compartments (53%) with a median tumor size of 6.8 cm (IQR 4.5-8.7). Negative margins (R0) were achieved in 58% of cases, while 32% had microscopic residual margins (R1), and 11% had gross residual margins (R2). All patients underwent primary resection; two patients (11%) received pre-operative radiation, and three patients (16%) received post-operative radiation. Among patients who received radiation therapy, metastasis occurred in one patient with negative margins following pre-operative radiation. At a median and average follow-up of 4 and 6.5 years, respectively, 2 patients had recurrence after non-oncological resection. There were no recurrences after oncological resection.

Conclusion: In this retrospective review of 19 patients with LGFMS, recurrence was observed in over 10% (2/19) of cases despite surgical resection, while distant metastasis was rare (1/19). Additional studies are needed to confirm the role of radiation therapy in preventing disease progression. The recurrence patterns observed represent an important area for further exploration to better inform surgical decision-making and optimize long-term outcomes.

Clinical characteristics of the 19 patients with LGFMS

Characteristic	Value
Age at presentation, years	
Median (IQR)	40.0 (24.0-56.8)
Gender, n (%)	
Female	11 (57.9)
Male	8 (42.1)
Primary site, n (%)	
Lower extremity	8 (42.1)
Upper extremity	4 (21.1)
Trunk/Torso	4 (21.1)
Head/neck	1 (5.3)
Pelvis	2 (10.5)
Tumor compartment, n (%)	
Deep (intramuscular)	10 (52.6)
Superficial (subcutaneous)	7 (36.8)
Intermuscular	2 (10.5)
Tumor size, cm	
Median (IQR)	6.8 (4.5-8.7)
Surgical margin status, n (%)	
R0 (negative margins)	11 (57.9)
R1 (microscopic positive)	6 (31.6)
R2 (grossly positive)	2 (10.5)
Radiation therapy, n (%)	
Pre-operative	2 (10.5)
Post-operative	3 (15.8)
None	14 (73.7)

(P 458) BETWEEN LYMPHOMAS AND SARCOMAS: A RETROSPECTIVE, MULTI-INSTITUTIONAL STUDY FROM THE ITALIAN SARCOMA GROUP (ISG) ON HISTIOCYTIC AND DENDRITIC CELL NEOPLASMS (HDCN)

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Objective: HDCN are ultra-rare tumors with features of both lymphomas (L) and sarcomas (S), lacking standardized treatments.

Methods: We reviewed consecutive cases of histiocytic S (HS), Langerhans cell S (LS) interdigitating dendritic cell S (IDCS), indeterminate dendritic cell tumour (DCT), follicular

dendritic cell S (FDCS), fibroblastic reticular cell tumour (FRCT) diagnosed between 2000-2022 in 7 ISG centers. Response was assessed using RECIST1.1 threshold for complete, CR, or partial response, PR; stable disease, SD; progressive, PD. Survival curves were estimated using Kaplan-Meier.

Results: Sixty-three pts were included, 43 with local (LD) and 20 with metastatic disease (MD; table 1). The median (m-) follow up was 101 mos. The 5-yr OS was 88% in LD, 43% in MD ($p=0.002$). Systemic symptoms at diagnosis predicted a worse 5-yr OS (36% vs 91%, $p<0.001$). In LD, the 10-yr OS for FDCS and HS was 69% and 86%. Among IDCS, FRCT, LS none recurred. Two pts (LS, FDCS) managed with definitive anthracycline-based (Ab) chemo-(CT)/radiotherapy (RT) are progression-free (PF) at 5 and 3 yrs. All pts recurring locally did not receive adjuvant RT nor those who developed MD received adjuvant AbCT. In MD, high tumor burden correlated with worse OS (5-yr OS 34% vs 100%, $p=0.1$). The 2-yr OS in FDC-S was 17% vs 78% in HS. Among 28 pts treated with AbCT, 8 had CR (28%), 10 PR (36%), 5 (18%) SD, 4 (15%) PD. The ORR was 65% (HS:80%; FDCS:55%), the m-PFS 12 mos. Two HS pts, receiving definitive Ab CT/RT, had CR and are PF at 8 yrs; 1 pt with metastatic HS, treated with AbCT, had CR and is PF at 2 yrs.

Conclusion: In our series, the outcome in primary HDCN is favorable. Advanced FDCS is an unmet need with a m-OS< 12mos. Similarly to L, long lasting CR were seen in different HDCN types treated with definitive CT/RT, which can be an option for unresectable cases. AbCT was active with a higher ORR compared to S. These data suggest a role for definitive and perioperative CT and RT, especially in FDCS and HS, warranting prospective confirmation.

(P 459) EPIDEMIOLOGICAL TRENDS, TREATMENT PATTERNS, AND SURVIVAL DISPARITIES IN MALIGNANT PERIPHERAL NERVE SHEATH TUMORS: A SEER ANALYSIS, 2001-2020

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Objective: Malignant peripheral nerve sheath tumors (MPNST) are rare and aggressive soft tissue sarcomas with limited contemporary population-level data. We aim to (1) evaluate incidence trends over the past two decades, (2) characterize real-world treatment patterns, and (3) identify demographic, clinical, and pathologic factors associated with overall survival (OS) using a large national cancer registry.

Methods: We identified all first primary MPNST cases (ICD-O-3 code 9540/3) diagnosed from 2001 to 2020 within the SEER 17-registry database (~28% of the U.S. population), using SEER*Stat v9.0.2. Variables included year of diagnosis, age, sex, race/ethnicity, tumor size, site, stage (SEER Summary Stage 2000), and first-course treatments (surgery, radiation, chemotherapy). Age-adjusted incidence rates (AAIRs) were standardized to the 2000 U.S. census population; annual percent change (APC) was calculated using Joinpoint regression. OS was assessed via Kaplan–Meier methods and compared using log-rank tests. Multivariable Cox regression identified independent predictors of mortality.

Results: Among 2,914 MPNST cases, AAIR remained stable (APC = 0.3%, $p = 0.42$). Median age at diagnosis was 48 years (IQR 29–66); 55% were male, 67% non-Hispanic White, 16% Black, 11% Hispanic, and 6% Asian/Pacific Islander. At presentation, 24% had localized, 43%

regional, and 33% distant disease. Surgery was performed in 76%, radiation in 43%, and chemotherapy in 29%. 5-year OS was 54% overall- 77% for localized, 55% for regional, and 17% for distant disease (log-rank $p < 0.001$). On multivariable analysis, worse OS was independently associated with age ≥ 60 (HR 1.84), Black race (HR 1.25), tumor size >10 cm (HR 1.51), regional (HR 1.67) or distant (HR 3.58) stage, omission of surgery (HR 2.05), and axial location (HR 1.29). Radiation conferred a modest benefit in regional-stage disease (HR 0.88); chemotherapy showed no significant OS impact (HR 0.96).

Conclusion: In this largest contemporary population-based study of MPNST, incidence remained stable from 2001–2020, with limited improvements in survival. Complete surgical resection remains the cornerstone of curative therapy. Black race, older age, larger tumors, axial location and advanced stage were independently linked to inferior outcomes, underscoring the need for earlier diagnosis and improved access to high-volume sarcoma centers. Prospective, multi-institutional studies are needed to define the role of systemic therapy and address persistent survival disparities.

Variable	Value / Result
Total cases	2,914
Median age at diagnosis (IQR)	48 years (29–66)
Sex	55% Male
Race/Ethnicity	67% Non-Hispanic White 16% Black 11% Hispanic 6% Asian/Pacific Islander
Stage at Diagnosis	24% Localized 43% Regional 33% Distant
Treatment Patterns	76% Surgery 43% Radiation 29% Chemotherapy
5-Year Overall Survival (OS)	54% Overall 77% Localized 55% Regional 17% Distant
Multivariable Predictors of Worse OS	
- Age ≥ 60 years	HR 1.84 (95% CI 1.62–2.10)
- Black race	HR 1.25 (95% CI 1.08–1.46)
- Tumor size >10 cm	HR 1.51 (95% CI 1.32–1.72)
- Regional stage	HR 1.67 (95% CI 1.42–1.96)
- Distant stage	HR 3.58 (95% CI 3.12–4.11)
- Omission of surgery	HR 2.05 (95% CI 1.76–2.39)
- Axial site	HR 1.29 (95% CI 1.12–1.49)
Impact of Radiation (Regional stage)	HR 0.88 (95% CI 0.79–0.98)
Impact of Chemotherapy	HR 0.96 (95% CI 0.85–1.08); <i>not statistically significant</i>

(P 460) OUTCOMES OF LATER-LINES SYSTEMIC THERAPIES IN MALIGNANT PERIPHERAL NERVE SHEATH TUMORS (MPNST)

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Objective: MPNSTs are rare sarcomas known for high rates of recurrence and metastasis with limited systemic treatment (ST) options. While doxorubicin/ifosfamide (AI) is the most efficacious 1st line ST, there is little data about subsequent regimens. We sought to establish outcomes of ST in later line settings as a baseline for future studies.

Methods: Baseline characteristics, treatment data and outcomes were collected from locally advanced/metastatic neurofibromatosis type 1 (NF1)-related and sporadic (non-NF1) MPNST patients (pts) treated with ST at MD Anderson Cancer Center (n=154). Chi squared and Fisher's exact tests were used for comparisons between groups. Survival outcomes were estimated by Kaplan-Meier method and compared with log-rank test.

Results: Out of 112 NF1 and 42 non-NF1 MPNST pts, the median age at diagnosis was 30 and 52 years, respectively. Trunk was the most common location for both NF1 and non-NF1 (50% and 57.1%), followed by extremities (25% and 31%). Of the 130 pts with follow-up scans, the response rate (RR) and median PFS for 1st line treatment was 20% (19/93) and 3.1 mo (95%CI 2.5-5.8) in NF1 and 37.8% (14/37) and 5.9 (2.8-10) mo in non-NF1. Of these pts, 69, 26, 9, and 1 received 2nd, 3rd, 4th, and 5th line therapy, respectively. AI was the most common in the 1st line setting (46.2%) while gemcitabine/docetaxel (GT) was commonly used in ≥2nd line (22.8%). The RR of any ST in ≥ 2nd lines was lower (11.5%, 12/105); 5.6% (4/71) in NF1 and 23.5% (8/34) in non-NF1. The mPFS of ≥ 2nd line regimens was 1.9 mo (95%CI 1.6-2.4) in NF1 and 3.8 mo (2-6.5) in non-NF1 (p 0.0045). Median OS was 23.2 mo. (19.6-28.5) and 47.5 mo. (28.3-NR) in NF1 and non-NF1 (p 0.0017). The table lists the outcomes for regimens used in ≥ 5 pts in any line.

Conclusion: Significant attrition of pts occurs after 1st line therapy in this cohort, likely attributable to aggressive disease biology and lack of effective 2nd line therapy options. Non-NF1 showed better RR and PFS compared to NF-1 MPNST for each of the regimens.

	NF1		Non-NF1		All
	RR (%)	mPFS (mo) [95%CI]	RR	mPFS	
Any regimen 1 st L	19/93 (20.4)	3.1 [2.5-5.8]	14/37 (37.8)	5.9 [2.8-10]	4.4 [2.9-6.1]
Any regimen ≥ 2 nd L	4/71 (5.6)	1.9 [1.6-2.4]	8/34 (23.5)	3.8 [2.-6.5]	2.1 [1.8-2.9]
AI	12/46 (26.1)	5.2 [2.8-7.8]	11/21 (52.4)	8.4 [4.7-11.9]	5.9 [4.6-7.8]
ADIC	0/5 (0)	1.8 [1.77-]	1/5 (20)	2 [1.4-]	2 [1.4-4.8]
GT	1/29 (3.5)	1.7 [1.4-2.9]	2/11 (18.2)	2.8 [1.3-6.5]	1.7 [1.5-3]
IE	3/10 (30)	3 [1.5-1.1]	2/4 (50)	NR	6.3 [1.4-NR]
Single A	0/5 (0)	3 [1.4-]	2/4 (50)	3.7 [2.8-]	3.7 [1.4-]
Single I	1/10 (10)	2.5 [0.7-6.1]	0/2 (0)	1.2	2.5 [0.8-4.9]
Pazopanib-based	1/6 (16.7)	1.6 [0.9-]	1/11 (9.1)	2.6 [1.7-]	2.6 [1.6-3.5]
mTOR inh	0/6 (0)	2.3 [0.7-]			2.3 [0.7-]

(P 461) A RETROSPECTIVE ANALYSIS OF PATIENTS WITH CONVENTIONAL CHORDOMA TREATED WITH SYSTEMIC THERAPY

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Objective: Chordoma (CH) is a rare tumor arising along the axial skeleton, with ~ 350 cases per year in the U.S. Despite standard treatments, many patients experience locoregional relapse or metastasis with limited salvage options. No FDA-approved systemic therapies exist for metastatic or recurrent CH. This study investigates real-world systemic treatment patterns and associated outcomes in conventional CH.

Methods: A retrospective analysis was performed on patients treated for conventional chordoma, excluding those with poorly-differentiated or de-differentiated histology. Progression-free survival (PFS) was calculated for different systemic agents and lines of treatment. Progression was defined as primary tumor enlargement or new metastatic lesions.

Results: From December 1986 to March 2025, 202 patients were identified in our electronic medical record as receiving systemic therapy; 173 had conventional chordoma and were included in this analysis. The median age at diagnosis was 47 years (range, 1-87), with 80 (46%) females and 93 (54%) males. Ten patients had metastatic disease at diagnosis. Primary tumor locations included the base of skull (n=77), mobile spine (n=41), and sacrum (n=55). Surgical resection included gross total resection (GTR)/near total resection (NTR) (n=48), subtotal resection (STR) (n=98), and biopsy only (n=27). 162 patients received adjuvant radiotherapy, with a median total dose of 76 Gy (range, 30-88.4 Gy). 150 out of 173 had local recurrences or developed metastases. Sixty-nine of these patients were treated with tyrosine kinase inhibitors (TKI), immunotherapy, CDK4/6 inhibitors, and pemetrexed outside of clinical trials. Of these patients, we observed a median PFS of 6.5 months with first-line treatment (n=69), 6.0 months with second-line treatment (n=27), and 5.2 months with third-line treatment (n=18). Specific median PFS by agent class (any line of therapy) were: imatinib alone or combination (n=59, 6.3 months), epidermal growth factor receptor inhibitors (EGFRi) (n=17, 7.6 months), immunotherapy (n=16, 9.2 months), CDK4/6 inhibitors (n=11, 8.5 months), and pemetrexed (n=8, 7.3 months). At last follow-up, 111 patients had died from progressive CH, 10 from other causes, and 52 were alive.

Conclusion: This analysis provides valuable insights into historical and current systemic therapy patterns in conventional chordoma. The data underscore the need for further research and clinical trials to identify more effective systemic strategies for this rare disease.

(P 462) HDAC INHIBITORS AS POTENTIAL SFT THERAPIES

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Objective: Solitary fibrous tumor (SFT) is a rare mesenchymal neoplasm occurring with an incidence of 1 case/million people/year. Typically, slow growing and asymptomatic, SFT can occur in various anatomical locations. Intrachromosomal rearrangement results in the pathognomonic oncogenic fusion of NGFI-A-binding protein 2 (Nab2) and signal transducer and activator of transcription 6 (Stat6). Based on the different exons of the two genes involved, there are several fusion variants, with the most frequent being Nab2ex4-Stat6ex2 and Nab2ex6-Stat6ex16/ex17. No FDA approved treatments exist to manage SFT. Our study aims to identify potential new therapies to treat SFT and generate new insights into disease mechanisms.

Methods: To identify potential therapeutic vulnerabilities in SFT, we performed a small-molecule screen of 318 compounds inclusive of epigenetic and metabolic compounds in isogenic lung fibroblast cell lines with Nab2ex6-Stat6ex17 fusion (Lf-ns) and without fusion (Lf). LC-MS based targeted metabolomics was performed for mechanistic insights.

Results: The small molecule library screen yielded HDAC inhibitors (HDACi) as top potential candidates. Romidepsin, a prodrug activated by reduced glutathione (GSH) was found to be the most potent HDACi with a 5-fold lesser IC₅₀ in Lf-ns cells implicating increased sensitivity to HDACi. Metabolomics revealed increased levels of GSH in Lf-ns cells thus resulting in increased levels of oxidized glutathione (GSSG) after Romidepsin treatment. Therefore, altered metabolism could possibly explain increased sensitivity of N-S expressing cells to Romidepsin.

Conclusion: In conclusion, HDACi Romidepsin shows selective efficacy in Nab2-Stat6 expressing cells, potentially due to metabolic reprogramming. These findings highlight HDAC inhibition as a promising therapeutic strategy for SFT. Building on these findings, the ongoing work explores mechanisms of action and synergistic FDA-approved drug combinations, focused on proteasome inhibitors.

(P 463) **EXTRANODAL FOLLICULAR DENDRITIC CELL SARCOMAS AND THEIR OLIGORECURRENCES: TRIUMPHS, TRIALS AND LESSONS LEARNT AT A SINGLE TERTIARY CANCER REFERRAL CENTRE, INDIA.**

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Objective: Follicular Dendritic Cell Sarcoma (FDGS) is a rare and an aggressive malignant neoplasm, predominantly involving lymph nodes in the head and neck region. These tumors also occur at extra-nodal sites and designated as extranodal (ENFDGSs). Given their rarity, standardized treatment protocols remain elusive, making comprehensive research essential for a better understanding and management of patients harbouring these tumors.

Methods: Patients diagnosed with ENFDCs, who presented to the gastrointestinal oncology unit of a tertiary cancer center were included. Diagnostic confirmation involved positive immunostaining for antibody markers, namely CD21, CD23, and CD35. The treatment details and outcomes were analysed.

Results: Fourteen patients with ENFDCS, (9 males and 4 females), with a median age of 41 years, were included. The sites included the colon (n=6), retroperitoneum (n=3), rectum (n=2) and one tumor each, in the mesentery, liver and pelvis, respectively. Four (30.7%) tumors were initially misdiagnosed. The treatments offered included surgical resection and various chemotherapy regimens as neoadjuvant, adjuvant or for salvage. Among 13 patients, 7 developed recurrences (liver, rectovesical pouch, omentum, peritoneum), while 5 were free of disease.. At a median follow-up of 26 months (range, 7 to 153 months), 2 patients succumbed to the disease and 2 were lost to follow-up. Among 9 alive patients, 5 were disease-free, 4 were on systemic therapy with partial response, and one patient did not show improvement with alternative treatment options and was offered best supportive care. The median overall survival of the cohort was 26 months and the median disease-free survival was 10.5 months.

Conclusion: ENFDCS is an uncommon neoplasm that can be misdiagnosed. Surgery with chemotherapy appears to have a pivotal role, with a role of multimodality treatment in recurrences. .

(P 464) EFFICACY OUTCOMES AMONG PATIENTS WITH ADVANCED EPITHELIOID SARCOMAS OF PROXIMAL-TYPE AND DISTAL-TYPE TREATED WITH TAZ: POST HOC ANALYSIS OF STUDY EZH-202

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Objective: To report efficacy outcomes of patients (pts) with proximal-type epithelioid sarcoma (pES) and distal-type ES (dES) treated with tazemetostat (TAZ) in the Phase 2 study EZH-202 (NCT02601950), a multicenter, open-label, single-arm basket trial with results reported so far only for a single cohort (cohort 5).

Methods: This post-hoc unplanned analysis of ES pts in EZH-202 (Pooled Cohorts 5 and 6) stratified pts by ES subtypes. Analyses were descriptive; confidence intervals (CIs) were calculated but no comparisons or statistical tests were performed.

Results: Among 124 patients with documented ES subtype, 69 (56%) had pES and 55 (44%) had dES. Median age and sex distribution were similar for pES and dES. Stage IV disease at diagnosis was more common among pES (61%) than dES (53%). Normal performance status (ECOG 0) was more common in dES (67%) than pES (58%). Most pts exhibited progressive disease prior to study entry (pES: 99%; dES: 95%). Pts with pES exhibited larger recorded tumor bulk (median RECIST v1.1 sum of target lesion diameters; 7.0 cm) than dES (4.4 cm). Objective response rates (ORR) were similar among pES (16%, 95% CI: 9-27) and dES (13%, 95% CI: 6-25). Median progression-free survival (PFS) during TAZ was similar for both groups

(pES: 4.0 months (mos), dES: 4.1 mos). Disease control rate (DCR) was similar between groups at 32 weeks (pES: 29%; dES: 25%). Median duration of response was not met for pES and 22 mos for dES. Receipt of subsequent anticancer therapy post-TAZ was similar among pES (49%) and dES (51%). Median overall survival (OS) was slightly higher for pES (25 mos) than dES (20 mos). For all differences described, 95% CIs overlapped, indicating that results were not statistically different.

Conclusion: Baseline pt characteristics prior to EZH-202 enrollment showed a more severe clinical presentation in pES compared to dES, as expected. TAZ demonstrated anticancer efficacy both in pts with pES and dES. Despite small differences in the magnitude of anticancer efficacy, no conclusions can be drawn given small patient numbers and overlapping 95% CIs.

(P 465) JAK/STAT PATHWAY CO-OPERATES WITH CIC-FUSIONS TO DRIVE CIC-REARRANGED SARCOMAS

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Objective: CIC-rearranged sarcoma (CRS) is a rare disease driven by a specific fusion protein involving the CIC gene. Occurrence in the brain is 3% in all CRS patients and these tumors frequently metastasize to the brain. The most common rearrangement is with the double homeobox 4 (DUX4) transcription factor (CIC-DUX4), and others, such as CIC-NUTM1 fusions. However, the molecular mechanisms by which CIC-fusions drive CRS remain unknown. Preliminary data shows that CIC-DUX4/NUTM1 fusions activate JAK and its downstream effector STAT1/3.

Methods: CRS and fusion-negative sarcoma cell lines were treated with JAK1 inhibitors (Ruxolitinib, Solicitinib). STAT1/3 activation and ETV1/4/5 expression were assessed by Western blot and qPCR. Luciferase assays measured ETV5 promoter activity. ChIP was used to examine STAT1/3 binding and histone acetylation. CRS xenografts in mice were treated with Ruxolitinib to evaluate in vivo effects on tumor growth and target gene expression

Results: Patient-derived CRS cell lines showed elevated levels of JAK1/STAT1/3 activation compared to fusion-negative sarcoma lines. Inhibition of JAK1 using Ruxolitinib and Solicitinib reduced STAT1/3 phosphorylation, downregulated ETV1/4/5 expression at both mRNA and protein levels, and diminished ETV5 promoter activity, cell proliferation, and tumorigenicity. Although the mechanism by which CIC-fusions activate oncogenic targets is still under investigation, histone acetylation appears to play a central role. STAT1/3 interacts with p300/CBP to enhance transcription, and STAT1 is necessary for p300 acetyltransferase activity. Ruxolitinib significantly reduced histone acetylation at ETV1/4/5 promoters in hMSC cells expressing CIC-DUX4/NUTM1, as well as in CRS cell lines. Unlike the p300 inhibitor C646, which causes global hypoacetylation, Ruxolitinib's effects were promoter-specific, indicating its potential as a more targeted and less toxic therapeutic option. Importantly, we found that STAT1/3 binds to ETV1/4/5 promoters only in the presence of CIC-fusions. Luciferase assays confirmed that STAT1/3 alone cannot activate ETV5 transcription without CIC-fusions, revealing a novel cooperative mechanism. In vivo, Ruxolitinib treatment of CRS xenografts led to significant reductions in tumor volume, STAT1/3 activation, and ETV1/4/5 expression.

Conclusion: These findings support JAK1/STAT1/3 inhibition as a promising therapeutic strategy for CRS and warrant further preclinical investigation.

(P 466) PATHOGENESIS AND THERAPEUTIC TARGETS IN KERATIN-POSITIVE GIANT CELL-RICH TUMOR

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Objective: Keratin-positive giant cell-rich tumor (KPGCT) is an extremely rare, newly described tumor arising in bone and soft tissue. The tumor is characterized by keratin-positive cells, sometimes with abundant xanthogranulomatous infiltrate (“xanthogranulomatous epithelial tumor”), and harbors HMGA2::NCOR2 gene fusions. The identity of the cells harboring this translocation is unknown, and little is known about the tumorigenic mechanism of KPGCT. Our study aimed to elucidate the mechanisms by which these tumors develop, and identify possible therapeutic targets.

Methods: Using 10x Genomics single-nuclei sequencing (snRNA-seq) we analyzed 27675 nuclei from a total of five formalin-fixed paraffin-embedded (FFPE) KPGCT cases. snRNA-seq findings were validated using IHC and immunofluorescence on corresponding FFPE cases and independent cases from our archive.

Results: We show that KPGCT consists of a small amount of scattered keratin-positive neoplastic cells that co-express HMGA2 and CSF1. The bulk of the tumor consists of macrophages and osteoclast-like giant cells that express CSF1R. The cells with the HMGA2 translocation show upregulation of the hippo signaling pathway, a pathway that is known to directly regulate CSF1 expression.

Conclusion: While being distinct tumor types, many of the histologic features and pathophysiological mechanisms of KPGCT are similar to those of tenosynovial giant cell tumor (TGCT). One central mechanism is the CSF1-CSF1R axis which is likely stimulating the migration and proliferation of macrophages, as well as their differentiation into osteoclasts. This suggests that newly developed small-molecule CSF1R inhibitors that show high efficacy in TGCT may also be an effective therapy for KPGCT.

(P 467) TREATMENT OUTCOMES IN AGGRESSIVE ANGIOMYXOMA: A SINGLE INSTITUTION EXPERIENCE

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Objective: Aggressive angiomyxoma is a rare mesenchymal tumor arising predominantly in the pelvis and perineum, characterized by a high risk of local recurrence after surgery. Data on its natural history, treatment outcomes with systemic therapy, and genomic characteristics remain limited. In this retrospective study, we evaluated clinical outcomes following surgery and systemic treatments for patients with aggressive angiomyxoma.

Methods: We retrospectively reviewed records of patients with a histologic diagnosis of aggressive angiomyxoma treated at Memorial Sloan Kettering Cancer Center between January 1, 2000, and August 31, 2024. Patients with only a single visit were excluded. The data cutoff was March 18, 2025. Demographics, treatment history, and genomic profile were collected. Overall survival (OS), progression-free survival, and duration of treatment (DOT) were estimated using Kaplan-Meier methodology.

Results: A total of 40 patients were included. The median age at diagnosis was 42 years (range, 12–67), and 35 (87.5%) were female. At a median follow-up of 67 months (range, 6–220), OS data remained immature, with only 2 deaths (5%). The estimated 6-year OS rate was 95.8% (95% CI: 74–100%). Primary surgical resection was performed in 31 patients; 8 required a second surgery, and 1 underwent a third. Among the 9 patients who did not undergo surgery, 7 received systemic endocrine therapy and 2 were managed with surveillance, for durations of 6 and 66 months, respectively. Thirteen patients received first-line endocrine therapy: 8 with GnRH agonists, 2 with aromatase inhibitors, and 3 with combination therapy. Of these, 7 were treated for recurrent disease following prior surgery. The median DOT was 15 months (95% CI: 3 months – not reached). One patient received neoadjuvant endocrine therapy for 2 months prior to surgery. Radiation therapy was rarely used, administered in only 2 patients with recurrent disease. Molecular profiling was performed in a subset: 4 patients underwent next-generation sequencing with MSK-IMPACT, which revealed no pathogenic alterations. Archer fusion testing was performed in 3 patients, with one identifying an HMGA2::LOC105369898 fusion. Additional data on systemic therapy and surgical outcomes will be presented.

Conclusion: Surgical resection remains the cornerstone of treatment in aggressive angiomyxoma, though local recurrence is observed in a subset. Hormonal therapy represents an active and durable option for selected patients.

Characteristics	Patients (n = 40), n (%)
Median age at diagnosis (range), yr	42 (12-67)
Sex	
Male	5 (12.5)
Female	35 (87.5)
Tumor site	
Pelvis	16 (40)
Perineum	20 (50)
Extra-pelvic	4 (10)
Tumor size , cm	
0-5 cm	7 (17.5)
5-10 cm	10 (25)
10-20 cm	12 (30)
> 20cm	5 (12.5)
Unknown	6 (15)
Primary surgical resection	31 (77.5)
Systemic therapy	
GnRH agonist	8 (20)
Aromatase inhibitor	2 (5)
Combination*	3 (7.5)

(P 468) CLINICAL UTILITY OF TARGETED NEXT-GENERATION SEQUENCING IN GUIDING SARCOMA DIAGNOSIS AND PERSONALIZED MANAGEMENT: A SINGLE-CENTER STUDY FROM INDIA

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Objective: To determine the diagnostic and therapeutic impact of RNA-based targeted NGS in patients with complex or ambiguous sarcoma histology.

Methods: A prospective study was conducted using a sarcoma-specific RNA-based NGS panel at AIIMS, New Delhi (2020–2025). Multidisciplinary Tumor Board–guided patient selection was based on clinical ambiguity and therapeutic relevance. NGS results were integrated with histopathology and IHC for diagnostic and treatment decisions.

Results: NGS was advised for 70 patients (median age: 38.5 years); 68 were evaluable (2 excluded due to inadequate tissue). Soft tissue sarcomas predominated (77.1%) and 67.1% presented with advanced/metastatic disease. Initial histology identified 17 (24.2%) round cell sarcomas (RC), 19 (27.1%) undifferentiated sarcomas (US), and 34 (48.5%) heterogeneous subtypes. Of 16 evaluable RC cases, NGS identified diagnostic fusions in 14 (87.5%; 5 known, 9 novel), enabling reclassification in 11 (68.7%) and treatment changes in 3 (18.7%). Among 19 US cases, 4 (21.1%) harbored diagnostic fusions (2 known, 2 novel), all reclassified, with therapy modified in 3 (75%). In 33 other subtypes, diagnostic alterations were found in 16 (48.4%; 8 known, 8 novel), prompting reclassification in 13 (39.3%) and treatment changes in 7 (21.2%).

Non-diagnostic mutations (e.g., TP53, SLX4, NF1) were observed in 9 US cases (47.4%) and 6 of other subtypes (18.2%). Actionable variants (KIT, PIK3CA) were identified in 5.8% (4/68). Overall, NGS yielded clinically informative findings in 50% (34/68), enabled diagnostic refinement in 41.1% (28/68), and impacted treatment in 19.1% (16/68).

Conclusion: This first-of-its-kind study underscores the clinical utility of integrating targeted RNA-based NGS into multidisciplinary sarcoma management. Diagnostic reclassification was achieved in over 40% of cases, with the most pronounced impact observed in round cell sarcomas with atypical histomorphology. Both established and novel genomic alterations informed individualized treatment strategies, reinforcing NGS as a vital adjunct to enhance diagnostic accuracy and enable precision oncology in sarcoma care.

Impact of NGS on Sarcoma Diagnosis and Treatment

Category	Round Cell Sarcoma	Undifferentiated Sarcoma	Other Subtypes	Total (N=68)
Diagnostic Mutations	14	4	16	34 (50%)
Diagnosis Reclassified	11	4	13	28 (41.1%)
Known Mutations	5	2	8	16 (23.5%)
Novel/Ultra-Rare Mutations	9	2	8	19 (27.9%)
Treatment Plan Changed	3	3	7	13 (19.1%)
No Mutations	2	6	8	16 (23.5%)

(P 469) THE IMPACT OF PREOPERATIVE ANEMIA ON POSTOPERATIVE COMPLICATIONS AND SHORT-TERM PROGNOSIS IN RETROPERITONEAL TUMOR SURGERY PATIENTS.

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Objective: Investigate preoperative anemia's effect on postoperative complications and short-term prognosis in retroperitoneal tumor surgery patients, and pinpoint risk factors for severe complications.

Methods: A retrospective cohort study included 1,968 patients undergoing retroperitoneal tumor surgery at Peking University International Hospital (2015-2023). Patients were divided into anemia and non-anemia groups based on WHO hemoglobin criteria. Preoperative data were collected. Primary outcome: postoperative complication severity (Clavien-Dindo classification). Secondary outcomes: ICU stay, mechanical ventilation duration, hospital stays, and 24-hour/30-day mortality. Statistical analyses were conducted using R software.

Results: Among 1,968 patients (46.4% males, 53.6% females), 55.9% had preoperative anemia. Baseline characteristics differed significantly between groups ($P < 0.001$). The anemia group had a higher rate of severe complications (10.8% vs. 5.8%, $P < 0.001$), longer total (median: 31 vs. 26 days, $P < 0.001$) and postoperative (18 vs. 15 days, $P < 0.001$) hospital stays, extended mechanical ventilation ($P < 0.001$) and ICU stays ($P < 0.001$), and a higher 30-day mortality rate (1.5% vs. 0.5%, $P = 0.029$). Multivariate analysis identified sex (OR = 0.6, $P = 0.003$), age (OR = 1.014, $P = 0.025$), and preoperative anemia (OR = 1.9, $P < 0.001$) as independent risk factors for increased complication severity.

Conclusion: Preoperative anemia, sex, and age are independent risk factors for severe postoperative complications in retroperitoneal tumor surgery. Anemia is linked to longer hospital stays, extended ventilation, and increased ICU stays.

(P 470) OFF-LABEL TREATMENT AND ULTRARARE SARCOMAS - SINGLE INSTITUTION REPORT

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Objective: Off-label therapies have potential benefit of improving poor outcomes in advanced soft tissue and bone sarcomas with some evidence of activity in ultrarare subtypes.

Methods: Patients with locally advanced or metastatic sarcomas, after exhaustion of standard treatments, were retrospectively analyzed. Data on demographics, disease, treatments, and survival were collected. OS and EFS were calculated, with statistical analysis via log-rank tests. DCR and ORR were assessed.

Results: Seventy-four patients treated from September 2019 to April 2025 met criteria. Off-label therapies included: atezolizumab for 2025 met eligibility criteria. Off-label therapies included: atezolizumab for alveolar ASPS (n=11); ivosidenib and pazopanib for chondrosarcoma (n=11; 2 and 9); imatinib and pembrolizumab for chordoma (n=14; 5 and 9); sirolimus for epithelioid hemangioendothelioma EHE (n=8); cabozantinib for Ewing sarcoma ES (n=11); crizotinib and alectinib for inflammatory myofibroblastic tumor IMT (n=1 and 2);

sorafenib for osteosarcoma (n=7); pembrolizumab for sclerosing epithelioid sarcoma SEF (n=2). The cohort was 82% metastatic, median age 43, 53% female. Patients ≤30 years comprised 26%, ≥60 years 27%. Median follow-up was 16.8 months; 81 events (33 deaths). Grade 1–2 adverse events occurred in 23 patients; 4 ended treatment. At analysis, 31% continued O-LT, 57% ended due to progression or death. Patients ≤30 had worse mEFS (5 months) vs ≥60 (21.8; p=0.032). DCR was 61%, ORR 15%, only in ASPS (45%), EHE (13%), ES (18%), IMT (67%), SEF (50%). Patients with ≥4 prior lines had shorter OS (8.2 months) and EFS (3.8) vs 2–3 lines (OS 37.8, EFS 16.2; p=0.0016 and 0.0087). Immunotherapy significantly improved OS and EFS versus kinase inhibitors, with median OS not reached vs 9.2 months, and EFS 23.4 vs 4.6 months (p=0.0043 and 0.0069).

Conclusion: Off-label treatments can improve outcomes in ultrarare sarcoma subtypes: ASPS (atezolizumab), EHE (sirolimus), SEF (pembrolizumab). 3-year survival rates and median EFS surpass historical data. Younger patients show more aggressive disease with shorter EFS. Benefit diminishes after the third line, so O-LT should be considered earlier rather than only as a last therapy.

Summary of analysis - sarcoma type, treatment, results as DCR rates, ORR rates, 3-year OS for sarcoma types from M1/locally advanced diagnosis, median OS and median EFS for off-label treatment for sarcoma types.

diagnosis	treatment/drug	No total	% treated pts	DCR rate	DCR for drug	ORR rate	ORR for drug	3-yr OS from M1/locally advanced diagnosis in %pts	median OS in 5yr observation from M1/locally advanced diagnosis (months)	median OS on off-label (months)	median EFS on off-label (months)	95% CI
all off-label patients		74		61%		15%						
abovular soft part sarcoma (ASPS)	atezolizumab	11	15%	82%	82%	45%	82%	not reached	not reached	36.0	0.1163-0.619	
chondrosarcoma		11	15%	64%		0%	57%	not reached	8.55	4.5	0.1644-0.322	
	ixazumab	2	18%	0%		0%						
	paucapath	9	82%	70%		0%						
chondroma		14	19%	71%		0%	100%	53.4	not reached	7.4	0-1	
	ixazumab	5	36%	80%		0%						
	pembrolizumab	9	64%	67%		0%						
epithelioid haemangioendothelioma (EHE)		8	11%	88%		13%	60%	not reached	12.3	12.2	0.219-0.293	
	sirolimus	8	100%	88%		13%						
Ewing sarcoma		11	15%	27%		18%	36%	30.6	5.25	1.8	0.145-0.1864	
	cabozantinib	11	100%	27%		18%						
inflammatory myofibroblastic tumor (IMT)		3	4%	67%		67%	not reached	not reached	not reached	0.272-0.3		
	crizotinib	1	33%	0%		0%						
	alacitinib	2	67%	100%		100%						
osteosarcoma (plus undiff. pleomorphic w/ bone)		7	9%	43%		0%	57%	37.8	9.0	3.6	0.187-0.301	
	sorafenib	7	100%	43%		0%						
sclerosing epithelioid sarcoma (SEF)		2	3%	100%		50%	100%	not reached	9.6	not reached	0-1	
	pembrolizumab	2	100%	100%		50%						
other*		7		29%		0%	50%	33.6	5.25	3.0	0.24-0.2246	

*pleomorphic sarcoma, synovial sarcoma, myofibroblastic tumor, dedifferentiated liposarcoma, dermatofibrosarcoma protuberans, angiosarcoma, aggressive angiosarcoma

(P 471) COMBINATION CHEMOTHERAPY WITH GEMCITABINE AND PACLITAXEL: A HIGHLY EFFICACIOUS AND BETTER TOLERATED OPTION FOR ANGIOSARCOMA

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Objective: Angiosarcoma (AS) is an aggressive soft tissue sarcoma with limited treatment options and frequent recurrence/metastasis. Current guidelines recommend single-agent Paclitaxel or Gemcitabine-based regimens, but Gemcitabine/Docetaxel causes significant myelosuppression and QoL-impacting toxicities. This retrospective review explored whether Gemcitabine/Paclitaxel could improve clinical outcomes with decreased toxicity.

Methods: Four AS patients received Gemcitabine 900 mg/m² (D1, D8) and Paclitaxel 90 mg/m² (D1, D8) every 21 days.

Results: Pt A (37F, metastatic breast AS): This patient was diagnosed with AS 5 yrs ago and then had recurrence after lumpectomy and chemotherapy. Pt has had clinical response and has continued on this regimen for residual disease for the last 6 months with minimal toxicities after progressing on prior treatments with Pazopanib and Pembrolizumab. Pt B (49F, metastatic breast AS): Diagnosed with AS 3 years ago and has lung and bone mets and has had clinical response and continuing on treatments for residual disease for 7 months with minimal toxicities after progressing on Doxorubicin and Pembrolizumab. Pt C (46F, forearm epithelioid AS): Developed extensive AS in background of right arm lymphedema. Has a complete response with minimal toxicities for the last 2 years. Pt D (68M, bladder AS with intestinal mets): Achieved initial clinical complete response for 9 months, then resumed treatment upon recurrence, maintaining complete clinical response with minimal toxicities.

Conclusion: In all cases, Gemcitabine/Paclitaxel led to significant clinical responses and decreased toxicities compared to standard treatments (single-agent Paclitaxel, Anthracycline, other Gemcitabine regimens). Pts A and B have stable disease, and Pts C and D had complete responses. The favorable side effect profile improved QoL despite long-term use and prolonged chemotherapy durations. This provides promising evidence for Gemcitabine/Paclitaxel combination therapy in AS, requiring further studies.

(P 472) LANDSCAPE OF ULTRA-RARE SARCOMAS: A NATIONWIDE STUDY FOR EPIDEMIOLOGY AND PROGNOSIS

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Objective: The term "ultra-rare sarcoma" was introduced to highlight the unique clinical difficulties stemming from its extreme rarity. Due to the recency of this classification and the limited volume of existing data, this study sought to explore the epidemiological characteristics and survival outcomes of ultra-rare sarcomas.

Methods: We utilized data from the Bone and Soft Tissue Tumor Registry in Japan (2001–2019) to compare ultra-rare sarcomas with non-ultra-rare sarcomas. Survival outcomes were assessed using Kaplan–Meier estimates with propensity score matching. Additional analyses included multivariate modeling and random survival forest, a machine learning approach.

Results: Out of 22,821 registered cases, 18.9% were diagnosed with ultra-rare sarcomas. Patients with ultra-rare bone sarcomas were significantly older (average age: 57.6 vs. 39.2

years, $p < 0.001$), whereas those with ultra-rare soft tissue sarcomas were younger (mean age: 49.4 vs. 62.2 years, $p < 0.001$) than their non-ultra-rare counterparts. Among individuals over 80 years with bone sarcoma and those under 20 with soft tissue sarcoma, nearly half had ultra-rare types. Survival analyses revealed better outcomes for ultra-rare bone sarcoma cases ($p = 0.022$), but no overall survival difference in soft tissue sarcomas ($p = 0.052$). However, patients younger than 40 with ultra-rare soft tissue sarcomas exhibited significantly worse survival ($p < 0.001$). Multivariate analysis yielded hazard ratios of 0.73 for ultra-rare bone sarcomas and 1.25 for ultra-rare soft tissue sarcomas. In the random survival forest model, ultra-rare classification had lower prognostic relevance compared to other variables.

Conclusion: Ultra-rare sarcomas are more frequently observed in older patients with bone sarcomas and younger patients with soft tissue sarcomas. Notably, younger individuals with ultra-rare soft tissue sarcomas face significantly poorer prognoses. Although ultra-rare status plays a relatively minor role in overall prognostic modeling, its impact is age-dependent and clinically relevant in certain subgroups.