Precision Therapy in CLL: Optimizing Sequencing Strategies beyond First-Line Treatment

Nitin Jain, MD

Professor, Department of Leukemia
Director, Leukemia CAR T Program
MD Anderson Cancer Center
Houston, Texas

LL&M great debates

Disclosures

Nitin Jain, MD: research funding—Pharmacyclics, AbbVie, Genentech, AstraZeneca, BeOne, Eli Lilly, BMS, ADC Therapeutics, Cellectis, Adaptive Biotechnologies, Kite/Gilead, Takeda, Newave, Carna Biosciences, Bioheng Therapeutics, Ubix Therapeutics, Ascentage; advisory board/honoraria—Pharmacyclics, Janssen, AbbVie, Genentech, AstraZeneca, BeOne, Eli Lilly, Nurix, BMS, SERB Pharma, Adaptive Biotechnologies, Kite/Gilead, Cellectis, Autolus

This CME activity includes brand names for participant clarity purposes only.
No product promotion or recommendation should be inferred.

LL&M great debates

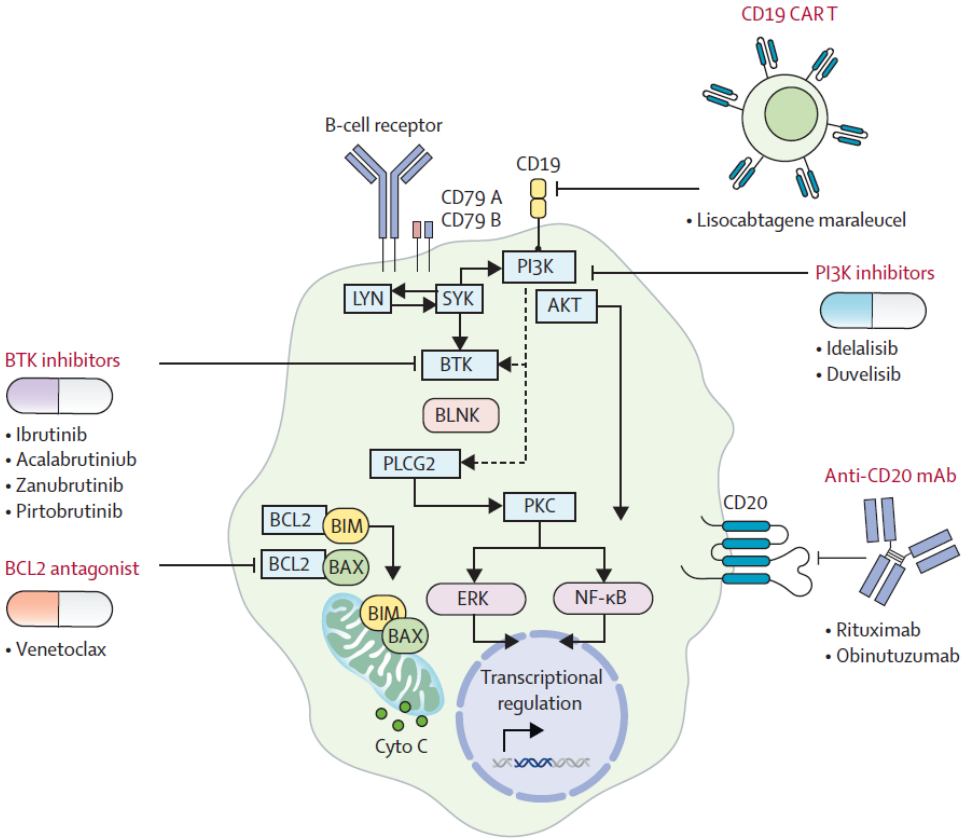
Learning Objectives

- Analyze the latest clinical trial and real-world evidence supporting BTK inhibitor and BCL2-based strategies in patients with CLL requiring therapy beyond the first line
- Implement evidence-based sequencing strategies to select appropriate targeted therapies for CLL following disease progression, resistance, or intolerance
- Incorporate MRD assessment and genomic risk factors into personalized treatment selection and duration decisions in relapsed or progressive CLL

CLL = chronic lymphocytic leukemia; MRD = measurable residual disease.

LL&M great debates

CLL Therapy Armamentarium



Jain N, et al. *Lancet*. 2024;404(10453):694-706.

Treatment Evolution in CLL

1960s

Alkylating agents
- Chlorambucil
- Cyclophosphamide

1970s

Purine nucleosides
- Fludarabine
- Pentostatin

1980s

1990s

Purine nucleosides and alkylators

2000s

Chemoimmunotherapy (FCR, BR)
Alemtuzumab
Lenalidomide

2014

BTK inhibitors (ibrutinib, acalabrutinib)
BCL-2 inhibitor (venetoclax)
Novel CD20 mAb (obinutuzumab)
PI3K inhibitors (idelalisib, duvelisib)

2023

BTK inhibitors (zanubrutinib, pirtobrutinib)

2024

CD19 CAR T (liso-cel)

2026+

BTK degraders, novel BCL2i, novel BTKi, CD20 bispecifics, etc.

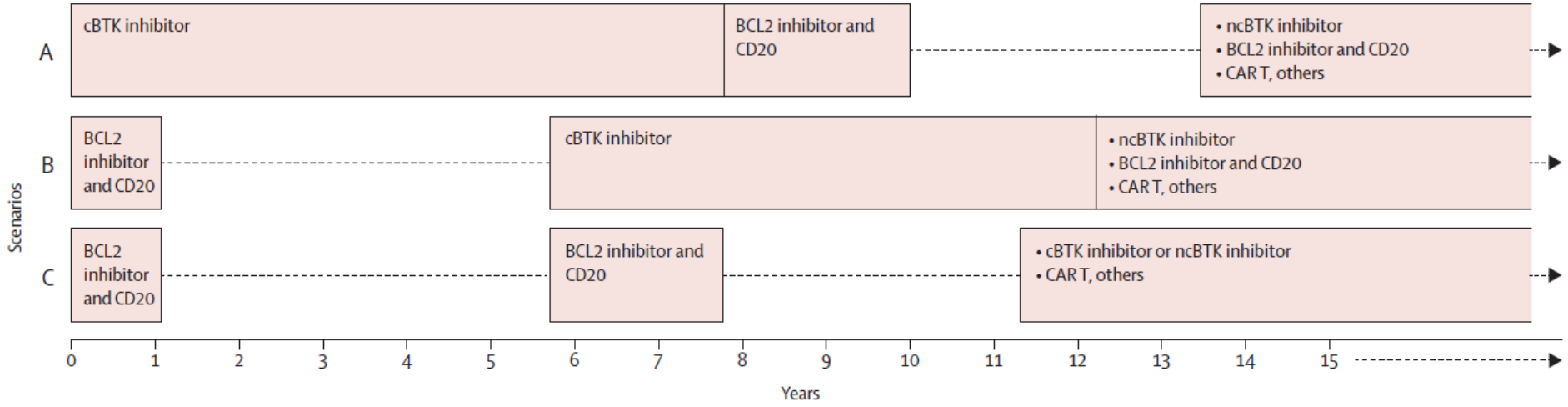
FCR = fludarabine, cyclophosphamide, rituximab; BR = bendamustine rituximab; mAb = monoclonal antibody.

LL&M great debates

R/R CLL

LL&M great debates

CLL Rx Sequencing Scenarios



R/R = relapsed/refractory; cBTK = covalent BTK; ncBTK = noncovalent BTK.
Jain N, et al. *Lancet*. 2024;404(10453):694-706.

LL&M great debates

Deciding on Therapy for R/R CLL

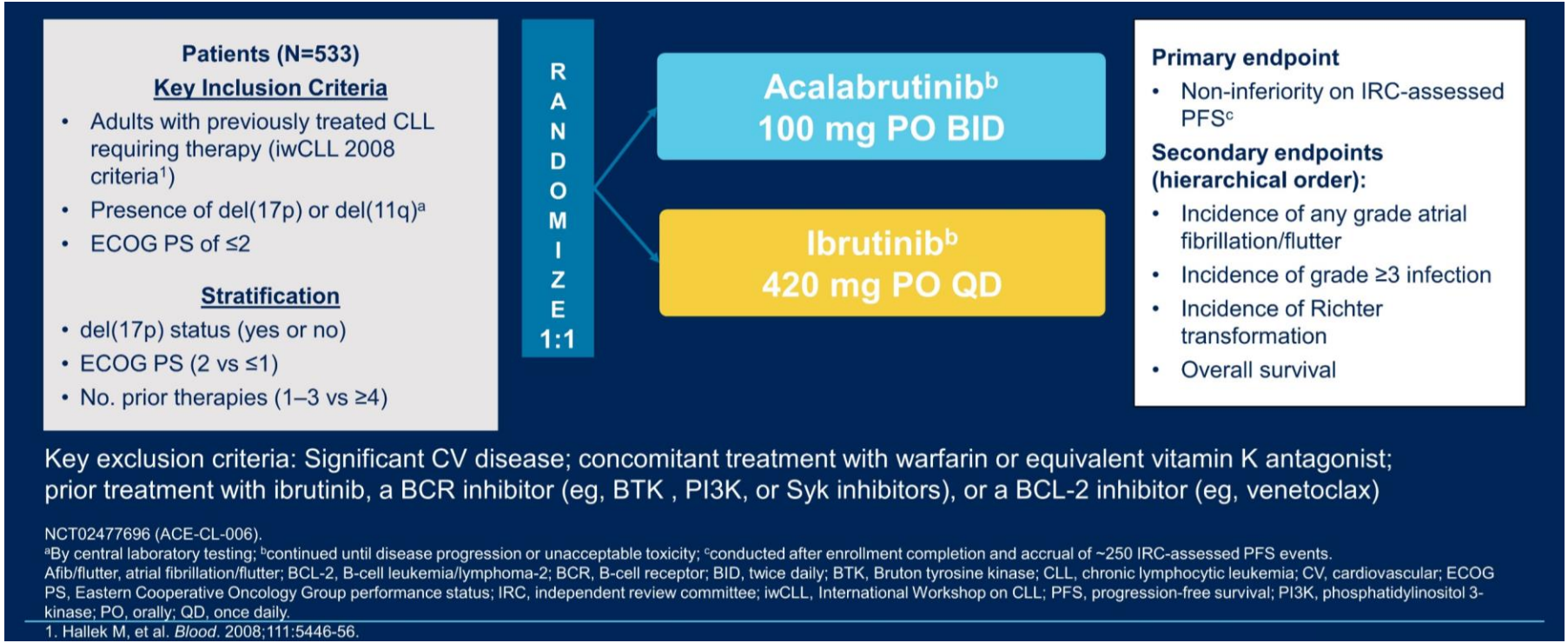
Most important factor is what prior therapies patient has received and response to prior therapies

- If patient only received CIT: BTKi and/or BCL2i
- If patient received BTKi
  - If intolerant—an alternative BTKi is an option
  - If relapsed after continuous cBTKi—BCL2i
  - If relapsed after time-limited BTKi (with BCL2i combo)—retreatment is a consideration
- If patient received BCL2i: retreatment vs cBTKi

CIT = chemoimmunotherapy; BTKi = BTK inhibitor; BCL2i = BCL2 inhibitor.

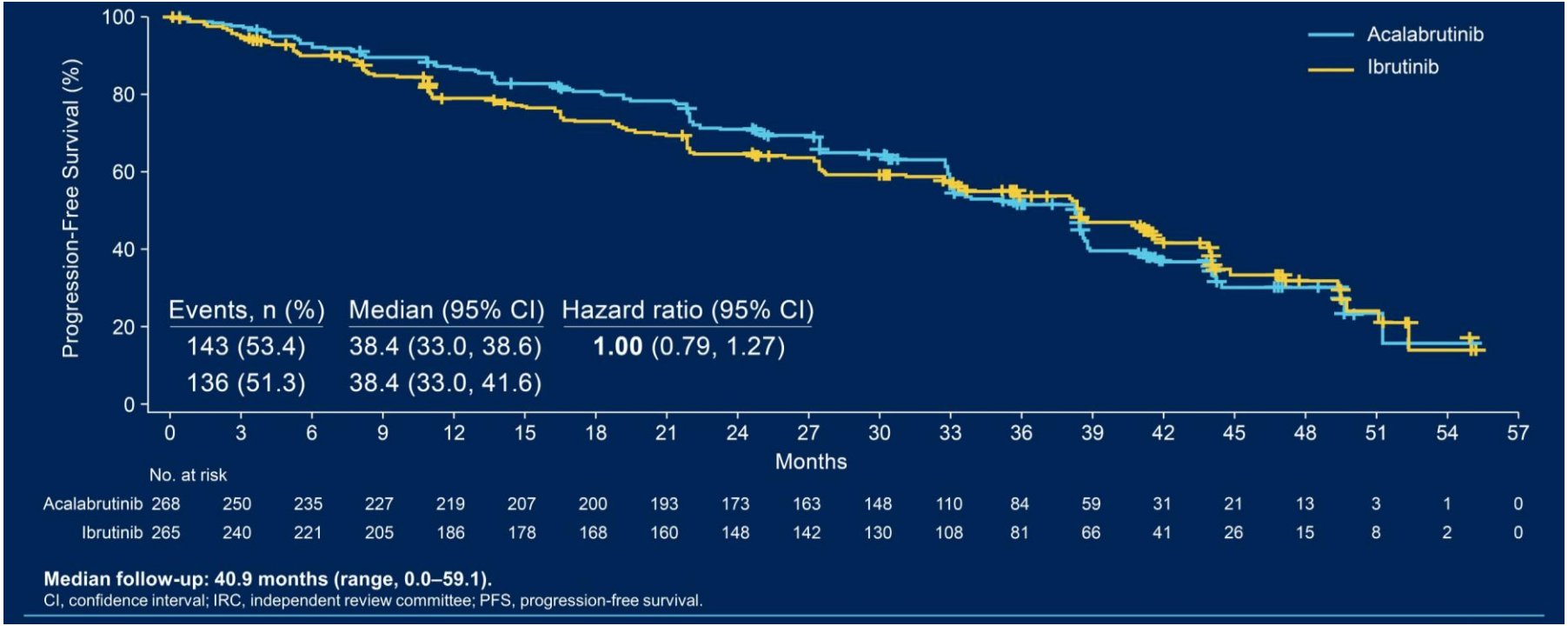
LL&M great debates

ELEVATE-RR: Phase 3 Randomized Non-Inferiority Open-Label Trial



Byrd JC, et al. Presented at: American Society of Clinical Oncology (ASCO) Annual Meeting; 2021.

Primary Endpoint: Non-Inferiority Met on IRC-Assessed PFS



Median follow-up: 40.9 months (range, 0.0–59.1).

CI, confidence interval; IRC, independent review committee; PFS, progression-free survival.

Byrd JC, et al. Presented at: ASCO Annual Meeting; 2021.

ALPINE Study Design (NCT03734016)

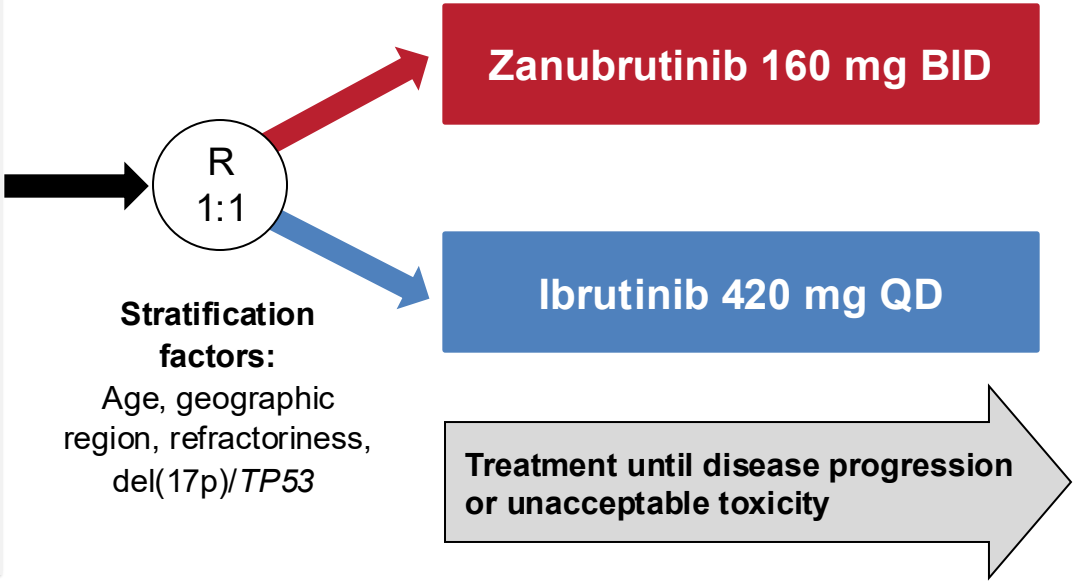
R/R CLL/SLL with ≥1 prior treatment
(N=652)

Key Inclusion Criteria

- R/R to ≥1 prior systemic therapy for CLL/SLL
- Measurable lymphadenopathy by CT or MRI
- Requires treatment per iwCLL

Key Exclusion Criteria

- Prior BTK inhibitor therapy
- Treatment with warfarin or other vitamin K antagonists

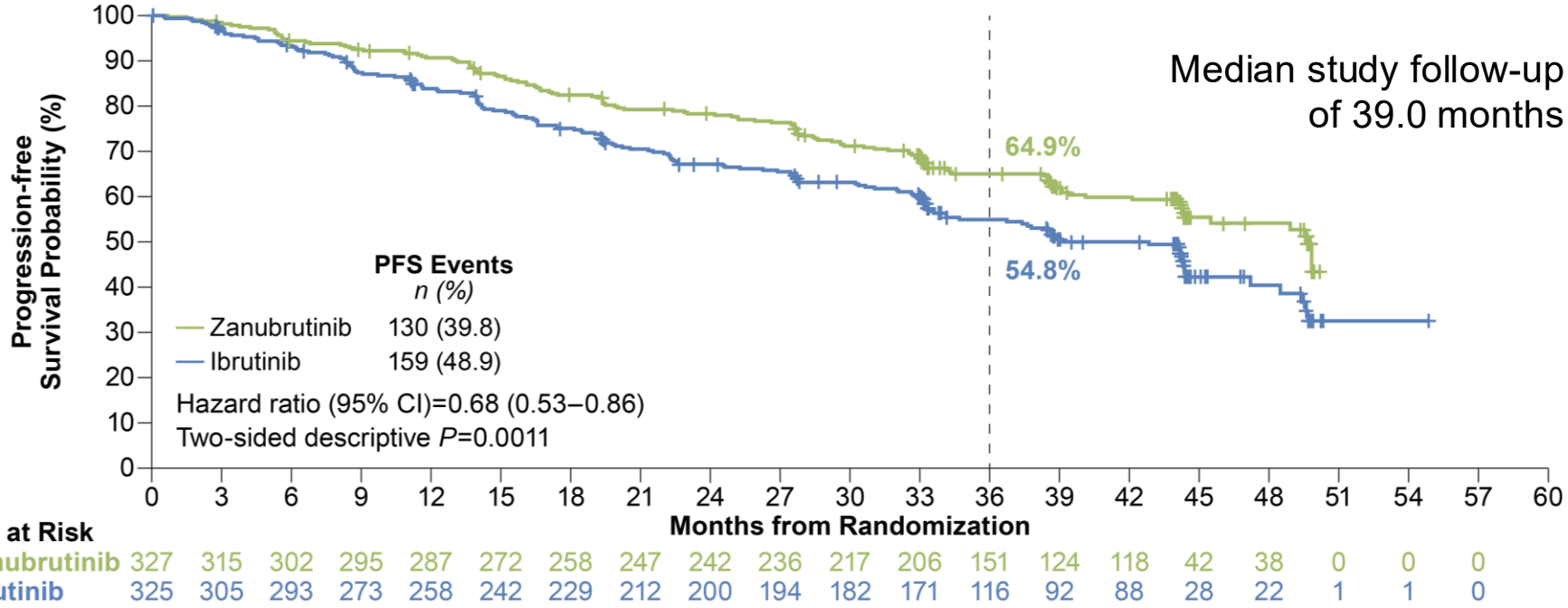


SLL = small lymphocytic lymphoma; CT = computed tomography; MRI = magnetic resonance imaging.

Brown JR, et al. *N Engl J Med*. 2023;388(4):319-332.

LL&M great debates

Zanubrutinib Sustains PFS Benefit over Ibrutinib at Extended Follow-Up



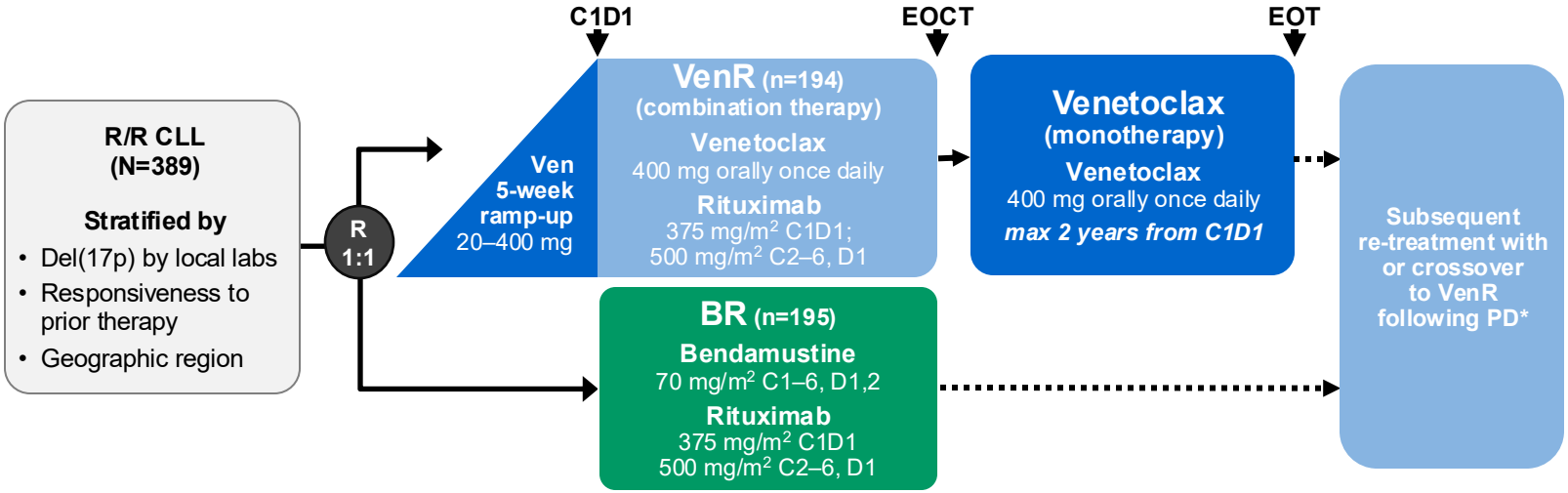
Data cutoff: September 15, 2023.

Brown JR, et al. *N Engl J Med*. 2023;388(4):319-332.

LL&M great debates

MURANO Study (NCT02005471)

Global, phase III, open-label, randomized study[1]



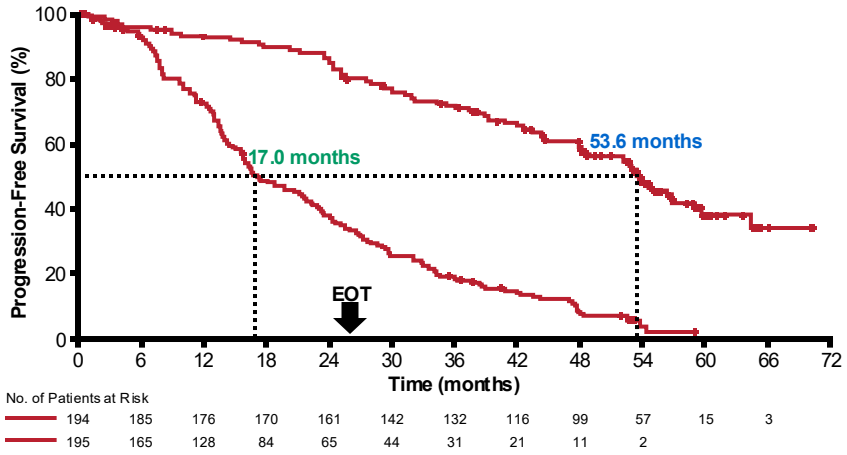
At 48 months of follow-up, deep responses with uMRD were associated with favorable PFS[2]

***Investigator-assessed PD according to (iwCLL) criteria.**
C = cycle; D = day; EOCT = end of combination treatment; EOT = end of treatment; R = randomization; (u)MRD = undetectable MRD; PD = progressive disease; VenR = venetoclax-rituximab; PD = progressive disease.
1. Seymour JF, et al. *N Engl J Med.* 2018;378(12):1107-1120. 2. Kater AP, et al. *J Clin Oncol.* 2020;38(34):4042-4054.

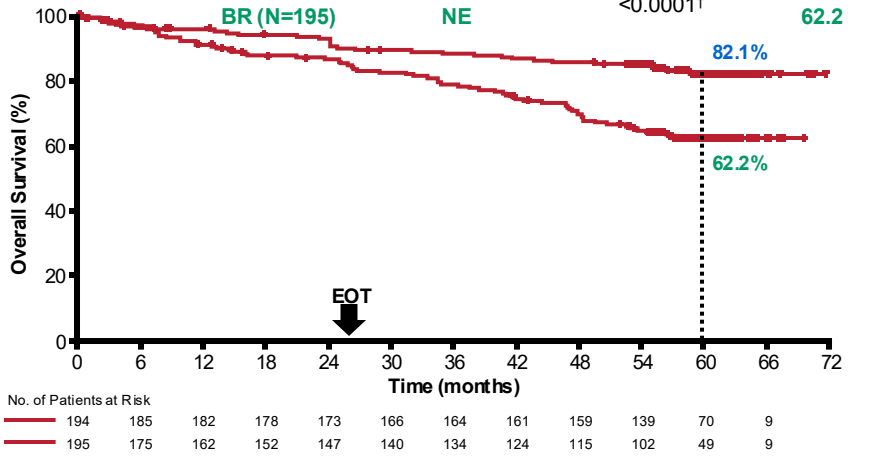
LL&M great debates

PFS and OS Benefits with VenR over BR Were Sustained 3 Years after EOT

	Median PFS (95% CI), months	HR* (95% CI)	5-yr PFS (%)
VenR (N=194)	53.6 (48.4, 57.0)	0.19 (0.15, 0.26) Stratified *P*-value <0.0001†	37.8
BR (N=195)	17.0 (15.5, 21.7)		NE



	Median OS (95% CI), months	HR‡ (95% CI)	5-yr OS (%)
VenR (N=194)	NE	0.40 (0.26, 0.62) Stratified *P*-value <0.0001†	82.1
BR (N=195)	NE		62.2



- With this 5-year update we can now accurately define the median PFS of VenR-treated patients
- No new safety signals were identified 3 years after EOT with longer follow-up and patients outside of the adverse event reporting window

***Unstratified HR=0.21. ‡Unstratified HR = 0.42. †P-values are descriptive only; +, censored.**
NE = not evaluable; OS = overall survival; yr = year.
Kater AP, et al. *J Clin Oncol*. 2020;38(34):4042-4054.

LL&M great debates

Unmet Medical Need

“Double-exposed” or “double-refractory” CLL

- Double-exposed
  - Prior use of BTKi and BCL2i (regardless of the reason for discontinuation)
- Double-refractory
  - PD on BTKi AND
  - PD on BCL2i OR PD within 12-24 mos after planned BCL2i discontinuation

Pirtobrutinib in Post-cBTKi CLL/SLL: ~30 Months Follow-Up and Subgroup Analysis with/without Prior BCL2i from the Phase 1/2 BRUIN Study

Jennifer A. Woyach[1], Jennifer R. Brown[2], Paolo Ghia[3], Lindsey E. Roeker[4], Krish Patel[5], Toby A. Eyre[6], Talha Munir[7], Ewa Lech-Maranda[8], Nicole Lamanna[9], Constantine S. Tam[10], John F. Seymour[11], Benoit Tessoulin[12], Nirav N. Shah[13], Chaitra Ujjani[14], Bita Fahkri[15], Catherine C. Coombs[16], Ian Flinn[17], Manish R. Patel[18], Sunita D. Nasta[19], Jonathon B. Cohen[20], Alvaro J. Alencar[21], Chan Y. Cheah[22], Shuo Ma[23], Joanna M. Rhodes[24], Deepa Jagadeesh[25], Pier Luigi Zinzani[26], Anders Osterborg[27], Koji Izutsu[28], Donald E. Tsai[29], Paolo Abada[29], Minna Balbas[29], Jian Li[29], Amy S. Ruppert[30], Wojciech Jurczak[31], William G. Wierda[32]

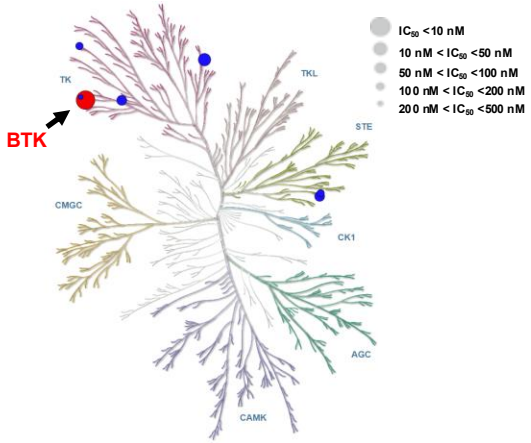
[1]The Ohio State University Comprehensive Cancer Center, Columbus, OH; [2]Dana-Farber Cancer Institute and Harvard Medical School, Boston, MA; [3]Università Vita-Salute San Raffaele and IRCCS Ospedale San Raffaele, Milano, Italy; [4]Memorial Sloan Kettering Cancer Center NY; [5]Swedish Cancer Institute, Seattle, WA; [6]Oxford University Hospitals NHS Foundation Trust, Churchill Cancer Center, UK; [7]Department of Haematology, St. James's University Hospital, Leeds, UK; [8]Institute of Hematology and Transfusion Medicine, Poland; [9]Herbert Irving Comprehensive Cancer Center, Columbia University, New York, NY; [10]Alfred Health and Monash University, Melbourne, Victoria, Australia; [11]Royal Melbourne Hospital, Peter MacCallum Cancer Centre and University of Melbourne, Victoria, Australia; [12]Haematology Department, University Hospital, Nantes, France; [13]Medical College of Wisconsin, Milwaukee, WI; [14]Fred Hutchinson Cancer Research Center, Seattle, WA; [15]Division of Hematology at Stanford University School of Medicine, Stanford, CA; [16]University of California Irvine, Irvine, CA; [17]Sarah Cannon Research Institute, Nashville, TN; [18]Florida Cancer Specialists/Sarah Cannon Research Institute, Sarasota, FL; [19]Abramson Cancer Center, University of Pennsylvania, Philadelphia, PA; [20]Winship Cancer Institute, Emory University, Atlanta, GA; [21]Sylvester Comprehensive Cancer, Miami, FL; [22]Linear Clinical Research and Sir Charles Gairdner Hospital, West Australia, Australia; [23]Robert H. Lurie Comprehensive Cancer Center of Northwestern University, Chicago, IL; [24]Rutgers Cancer Institute of New Jersey, New Brunswick, NJ; [25]Cleveland Clinic, Cleveland, OH; [26]Institute of Hematology "Seràgnoli" University of Bologna, Bologna, Italy; [27]Karolinska Institute and Karolinska University Hospital, Stockholm, SE; [28]National Cancer Center Hospital, JP; [29]Loxo@Lilly, Indianapolis, IN; [30]Eli Lilly and Company, Indianapolis, IN; [31]Maria Sklodowska-Curie National Research Institute of Oncology, Krakow, Poland; [32]MD Anderson Cancer Center, Houston, TX.

Woyach JA, et al. *Blood*. 2023;142(Suppl 1):325.

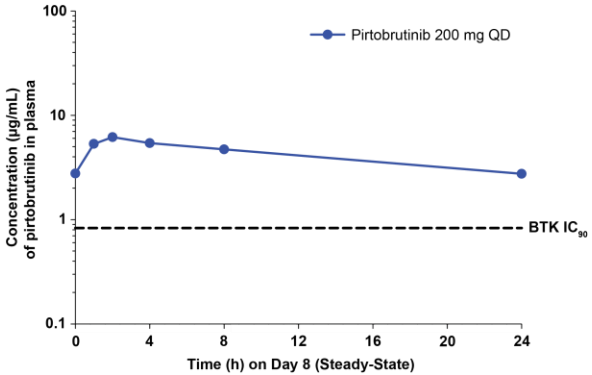
LL&M great debates

Pirtobrutinib Is a Highly Selective, Non-Covalent (Reversible) BTK Inhibitor

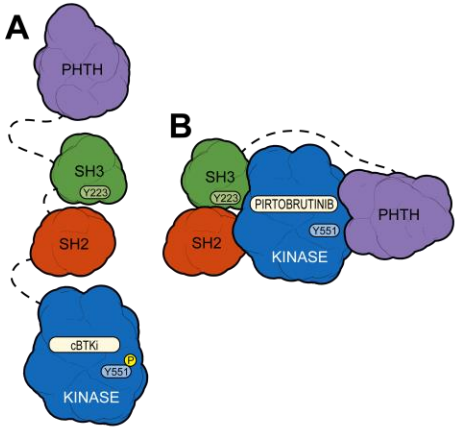
Highly selective for BTK[1,2]



Plasma exposures exceeded BTK IC_{90} throughout dosing interval



Pirtobrutinib may stabilize/maintain BTK in a closed inactive conformation[3]



- Inhibits both WT and C481-mutant BTK with equal low nM potency[3]
- Steady-state plasma exposure corresponding to 96% BTK target inhibition and a half-life of about 20 hours[3]
- In contrast to cBTKi (A), pirtobrutinib (B) appears to stabilize BTK in a closed, inactive conformation, blocking access to upstream kinases and phosphorylation of Y551, thus inhibiting scaffolding interactions that support kinase-independent BTK signaling[3]

IC = inhibitory concentration; WT = wild type.

[1]Mato AR, et al. *Lancet*. 2021;397(10277):892-901. [2]Brandhuber B, et al. *Clin Lymphoma Myeloma Leuk*. 2018;18(Suppl.1):S216. [3]Gomez EB, et al. *Blood*. 2023;142(1):62-72.

Baseline Characteristics of Patients with CLL/SLL Who Received Prior cBTKi

Characteristics	Prior cBTKi (n=282)	BCL2i-N (n=154)	BCL2i-E (n=128)
Median age, years (range)	69 (36-88)	69 (36-87)	68 (41-88)
Male, n (%)	192 (68)	106 (69)	86 (67)
Rai staging, n (%)			
0-II	147 (52)	94 (61)	53 (41)
III-IV	120 (43)	58 (38)	62 (48)
Missing	15 (5)	2 (1)	13 (10)
Bulky lymphadenopathy ≥5 cm, n (%)	88 (31)	42 (27)	46 (36)
ECOG PS, n (%)			
0	144 (51)	89 (58)	55 (43)
1	118 (42)	56 (36)	62 (48)
2	20 (7)	9 (6)	11 (9)
Median number of prior lines of systemic therapy, (range)	4 (1-11)	3 (1-9)	5 (1-11)
Prior therapy, n (%)			
BTK inhibitor	282 (100)	154 (100)	128 (100)
Anti-CD20 antibody	251 (89)	127 (83)	124 (97)
Chemotherapy	228 (81)	114 (74)	114 (89)
BCL2 inhibitor	128 (45)	0 (0)	128 (100)
PI3K inhibitor	71 (25)	17 (11)	54 (42)
CAR T	17 (6)	2 (1)	15 (12)
Allogeneic stem cell transplant	7 (3)	1 (1)	6 (5)

Characteristics	Prior cBTKi (n=282)	BCL2i-N (n=154)	BCL2i-E (n=128)
Median time from diagnosis to first dose, years (IQR)	11 (8-15)	11 (7-15)	12 (8-15)
Reason for any prior BTKi discontinuation[a], n (%)			
Progressive disease	217 (77)	110 (71)	107 (84)
Toxicity/other	64 (23)	43 (28)	21 (16)

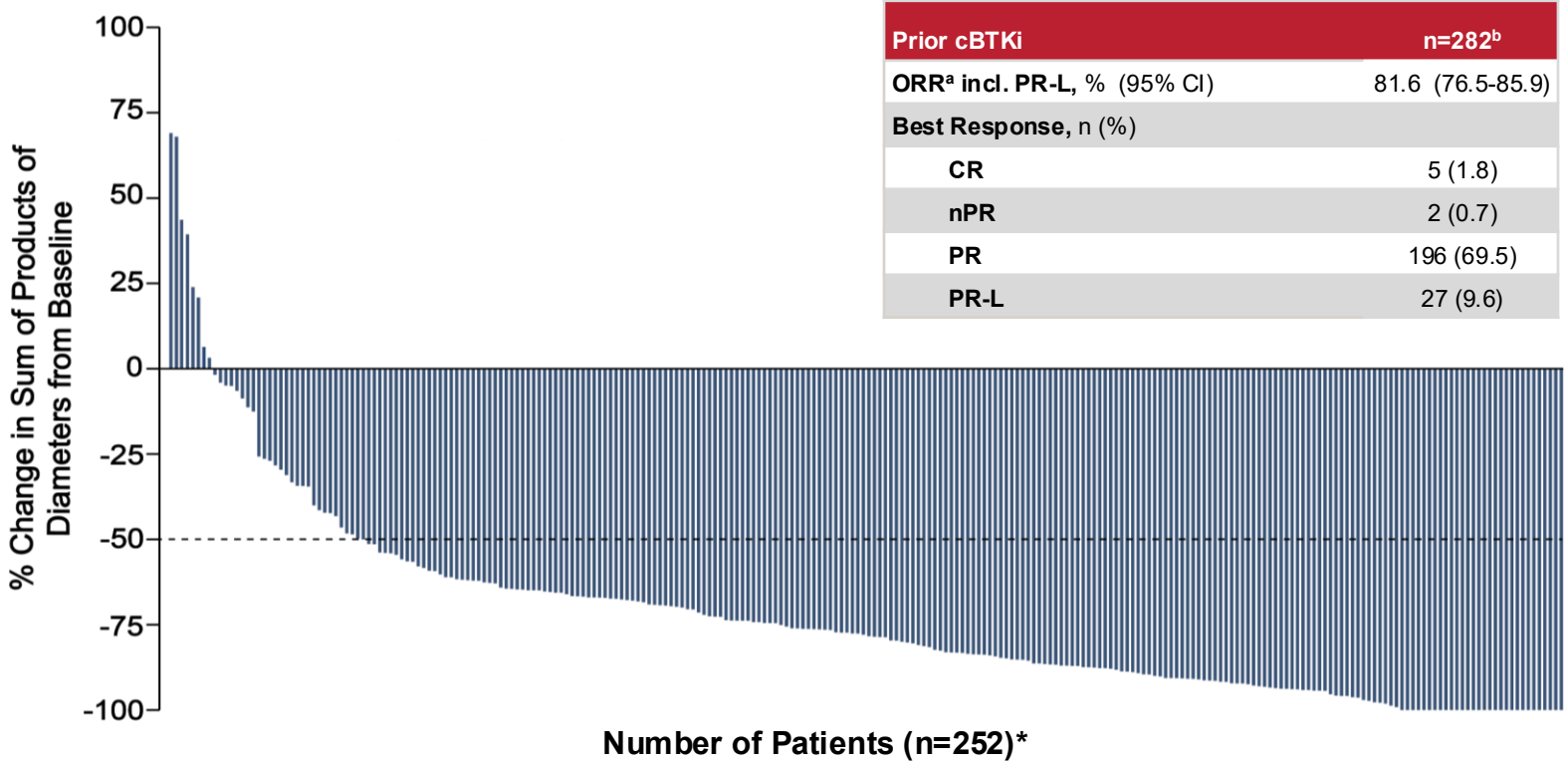
Baseline molecular characteristics[b]	Prior cBTKi (n=282)	BCL2i-N (n=154)	BCL2i-E (n=128)
Mutation status, n/n available (%)			
BCL2 mutated	19/246 (8)	0/133 (0)	19/113 (17)
BTK C481-mutant	96/245 (39)	57/138 (41)	39/107 (36)
PLCG2-mutant	18/245 (7)	10/138 (7)	8/107 (8)
High-risk molecular features, n/n available (%)			
17p deletion and/or TP53 mutation	104/217 (48)	57/123 (46)	47/94 (50)
IGHV unmutated	193/225 (86)	100/125 (80)	93/100 (93)
Complex karyotype	33/73 (45)	17/41 (42)	16/32 (50)
11q deletion	47/202 (23)	28/115 (24)	19/87 (22)

[a]In the event more than one reason was noted for discontinuation, disease progression took priority. [b]Molecular characteristics were determined centrally and are presented based on data availability, in those patients with sufficient sample to pass assay quality control.
ECOG PS = Eastern Cooperative Oncology Group performance status; IQR = interquartile range; IGHV = immunoglobulin heavy chain variable region.

Woyach JA, et al. *Blood*. 2023;142(Suppl 1):325.

Pirtobrutinib Efficacy in All Patients with CLL/SLL who Received Prior cBTKi

Prior cBTKi	n=282[b]
ORR[a] incl. PR-L, % (95% CI)	81.6 (76.5-85.9)
Best Response, n (%)	
CR	5 (1.8)
nPR	2 (0.7)
PR	196 (69.5)
PR-L	27 (9.6)

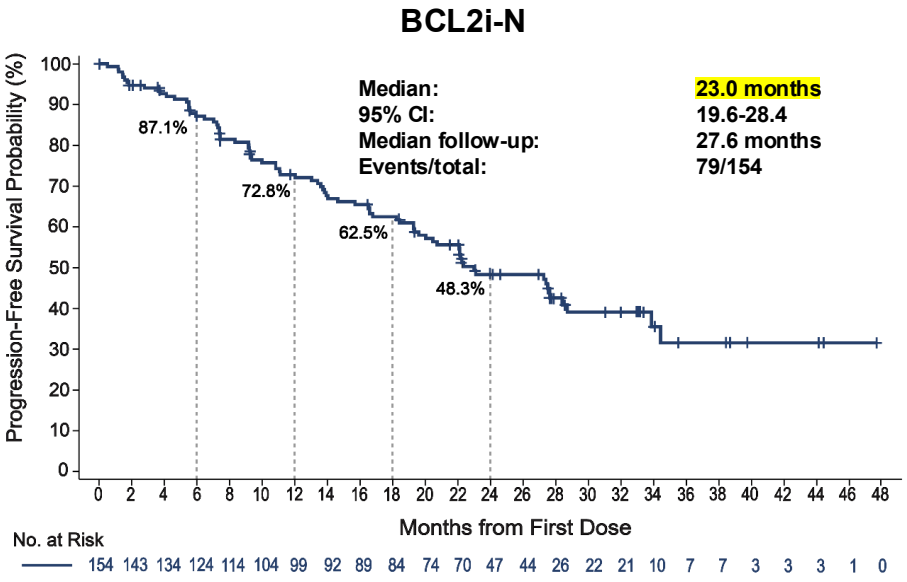


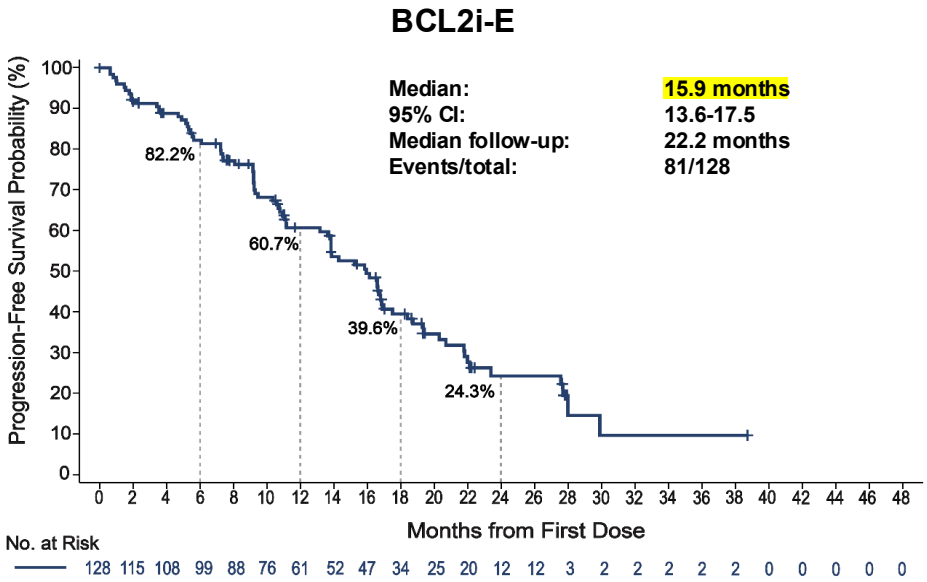
Data of patients with baseline and at least one evaluable post baseline tumor measurement. *Data for 30/282 patients are not shown in the waterfall plot due to no measurable target lesions identified by CT at baseline, discontinuation prior to first response assessment, or lack of adequate imaging in follow-up. aORR including PR-L is the number of patients with best response of PR-L or better divided by the total number of patients; 14 patients with a best response of not evaluable (NE) are included in the denominator. bPost-cBTKi patients included a subgroup of 19 patients with one prior line of cBTKi-containing therapy and second line therapy of pirtobrutinib, who had an ORR including PR-L of 89.5% (95% CI: 66.9-98.7). Response status per iwCLL 2018 based on IRC assessment. ORR = overall response rate; PR-L = partial response with lymphocytosis; CR = complete response; nPR = nodular PR.

Woyach JA, et al. *Blood*. 2023;142(Suppl 1):325.

LL&M great debates

Pirtobrutinib Progression-Free Survival with Prior cBTKi, with or without Prior BCL2i





Woyach JA, et al. *Blood*. 2023;142(Suppl 1):325.

BRUIN CLL-321: Randomized Phase III Trial of Pirtobrutinib versus Idelalisib plus Rituximab (IdelaR) or Bendamustine plus Rituximab (BR) in BTK Inhibitor Pretreated Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma

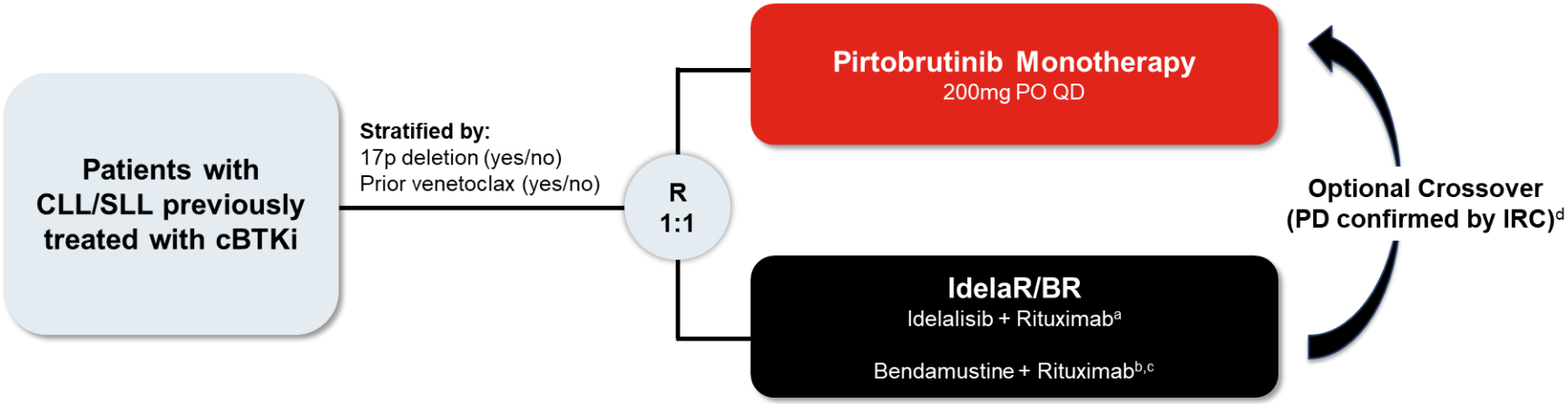
Jeff P. Sharman[1], Talha Munir[2], Sebastian Grosicki[3], Lindsey E Roeker[4], John M Burke[5], Christine Chen[6], Norbert Grzasko[7], George Follows[8], Zoltán Mátrai[9], Alessandro Sanna[10], Shuhua Yi[11], Ru Feng[12], Vu Minh Hua[13], Jadwiga Holodja[14], Wojciech Jurczak[15], Matthias Ritgen[16], Lugui Qiu[11], Francesc Bosch[17], Catherine C Coombs[18], Katherine Bao[19], Vishalkumar Patel[19], Bin Liu[19], Livia Compte[19], Ananya Guntur[19], Denise Y. Wang[19], Marisa Hill[19], Ching Ching Leow[19], Paolo Ghia[20], Paul M Barr[21]

[1] Willamette Valley Cancer Institute and Research Center, US Oncology Research, Eugene, OR, USA, [2] Department of Haematology, St. James's University Hospital, Leeds, UK, [3] Department of Hematology & Cancer Prevention, Silesian Medical University, Katowice, Poland, [4] Department of Medicine, Memorial Sloan Kettering Cancer Center New York, NY, USA, [5] Sarah Cannon Research Institute, Rocky Mountain Cancer Centers, Aurora, CO, USA, [6] Division of Medical Oncology & Hematology, Princess Margaret Cancer Centre, Toronto, ON, Canada, [7] Department of Experimental Hematooncology, Medical University of Lublin, Lublin, Poland, [8] Department of Haematology, Addenbrooke's Hospital NHS Trust, Cambridge, UK, [9] Central Hospital of Southern Pest, National Institute for Haematology and Infectology, Budapest, Hungary, [10] Department of Hematology, AOU Careggi - University of Florence, Firenze, Italy, [11] Institute of Hematology & Blood Diseases Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College, Tianjin 300020, China, [12] Department of Radiation Oncology, Nanfang Hospital, Southern Medical University, Guangzhou, Guangdong, China, [13] Haematology Department, Liverpool Hospital Sydney Australia, [14] Department of Hematology, City Hospital, Legnica, Poland, [15] Maria Sklodowska-Curie National Research Institute of Oncology, Krakow, Poland, [16] Universitätsklinik Schleswig-Holstein, Campus Kiel, Germany, [17] Department of Haematology, University Hospital Vall d'Hebron, Autonomous University, Barcelona, Spain, [18] University of California Irvine, Irvine, CA, USA, [19] Eli Lilly and Company, Indianapolis, IN, USA, [20] Università Vita-Salute San Raffaele and IRCCS Ospedale San Raffaele, Milano, Italy, [21] Wilmot Cancer Institute, University of Rochester Medical Center, Rochester, NY, USA.

Sharman JP, et al. *J Clin Oncol*. 2025;43(22):2538-2549.

LL&M great debates

BRUIN CLL-321 Study Design



Key Eligibility

- Age ≥18
- ECOG PS 0-2
- Confirmed CLL/SLL requiring treatment per iwCLL 2018
- **Prior cBTKi required**
- **No limit on prior lines of therapy**
- **Prior history of atrial fibrillation allowed**

Key Endpoints

- **Primary Endpoint: PFS assessed by IRC**
- PFS assessed by investigator
- Event-Free Survival
- Time to Next Treatment
- Overall survival
- Safety

Treatment was given in 28-day cycles. PFS assessed based on iwCLL2018. [a]Idelalisib dosed at 150 mg PO BID. Day 1 of cycle 1, first dose of rituximab at 375 mg/m2, next 4 infusions at 500 mg/m2 every 2 weeks, next 3 infusions at 500 mg/m2 every 4 weeks. [b]Bendamustine (70 mg/m2) administered IV D1, D2 of cycles 1-6. [c]Day 1 of cycle 1, first dose of rituximab at 375 mg/m2, next 5 infusions day 1 of cycle 2 through cycle 6 at 500 mg/m2. [d]Eligible patients receiving investigator's choice of IdelaR/BR could crossover to receive pirtobrutinib monotherapy upon confirmation of PD by IRC per protocol.
IdelaR = idelalisib, rituximab; IRC = independent review committee; PD = progressive disease.
Sharman JP, et al. *J Clin Oncol*. 2025;43(22):2538-2549.

LL&M great debates

Patient Characteristics at Baseline

Characteristics	Pirtobrutinib n=119	IdelaR/BR n=119
Median age, years (range)	66 (42-90)	68 (42-85)
Male, n (%)	83 (70)	83 (70)
Region, n (%)		
North America	24 (20)	39 (33)
Europe	76 (64)	63 (53)
Asia	14 (12)	15 (13)
Australia	5 (4)	2 (2)
Histology, n (%)		
CLL	109 (92)	108 (91)
SLL	10 (8)	11 (9)
ECOG PS, n (%)		
0-1	107 (90)	114 (96)
2	12 (10)	5 (4)
Rai stage[a], n (%)		
0-II	58 (49)	62 (52)
III-IV	56 (47)	54 (45)
High-risk molecular features (Central Lab), n/n available (%)		
17p deletion and/or *TP53* mutation	51/94 (54)	53/98 (54)
IGHV unmutated	90/97 (93)	74/93 (80)
Complex karyotype[b]	53/74 (72)	44/75 (59)
Molecular Characteristics, n/n available (%)		
BTK C481S	37/99 (37)	36/94 (38)
PLCγ2	15/99 (15)	11/94 (12)

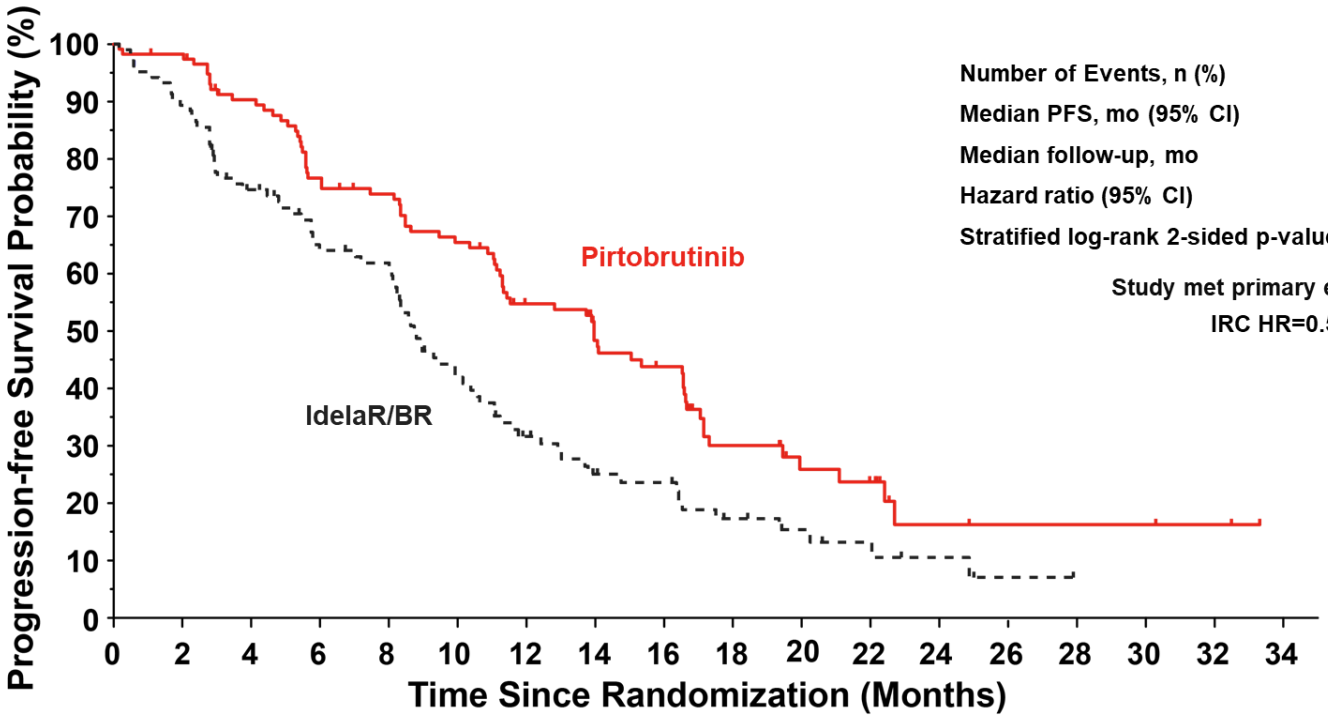
Characteristics	Pirtobrutinib n=119	IdelaR/BR n=119
Median lines of prior systemic therapy, n (range)	3 (1-13)	3 (1-11)
Prior therapy, n (%)		
cBTKi	119 (100)	119 (100)
Ibrutinib	100 (84)	106 (89)
Acalabrutinib	17 (14)	20 (17)
Zanubrutinib	10 (8)	7 (6)
Other[c]	5 (4)	3 (3)
>1 Prior cBTKi	17 (14)	18 (15)
BCL2 inhibitor[d]	60 (50)	62 (52)
Chemotherapy	81 (68)	83 (70)
Anti-CD20 Antibody	86 (72)	83 (70)
PI3K inhibitor	11 (9)	11 (9)
Immunomodulator	2 (2)	3 (3)
Autologous Stem Cell Transplant	1 (1)	0 (0)
Allogeneic Stem Cell Transplant	2 (2)	1 (1)
Reason for any prior cBTKi discontinuation[e], n (%)		
Disease progression	85 (71)	87 (73)
Toxicity	20 (17)	22 (18)
Other	14 (12)	8 (7)

Poor prognosis (eg, >50% del(17p) and/or *TP53 mutation* and complex karyotype) and heavily pre-treated population (eg, 33% received ≥4 prior lines of therapy, ~50% received prior BCL2i)

[a]Rai stage at study entry; excludes patients with missing stage. [b]≥3 abnormalities in same clonal population. [c]Other includes orelabrutinib, tirabrutinib, zebutinib, and AVL-292-003. [d]2 patients in the IdelaR/BR arm received an investigational BCL2i; all other patients received venetoclax. [e]In the event more than one reason was noted for discontinuation, disease progression was prioritized, then toxicity, then other reasons.

Sharman JP, et al. *J Clin Oncol*. 2025;43(22):2538-2549.

IRC-Assessed Progression-Free Survival



	Pirtobrutinib n=119	IdelaR/BR n=119
Number of Events, n (%)	74 (62)	79 (66)
Median PFS, mo (95% CI)	**14.0** (11.2-16.6)	**8.7** (8.1-10.4)
Median follow-up, mo	19.4	17.7
Hazard ratio (95% CI)	**0.54 (0.39-0.75)**	
Stratified log-rank 2-sided p-value	0.0002*	

Study met primary endpoint at earlier data cut (Aug 2023)
IRC HR=0.58 (95% CI 0.38-0.89); p=0.01

Pirtobrutinib reduced risk of progression or death by 46% according to IRC assessment

Number at Risk

Pirtobrutinib	119	113	100	84	79	69	54	44	36	19	12	10	4	3	3	3	2	0
IdelaR/BR	119	92	73	60	57	37	25	18	16	10	7	5	3	1	0	0	0	0

*nominal *P*-value.

Sharman JP, et al. *J Clin Oncol*. 2025;43(22):2538-2549.

LL&M great debates

Fixed-Duration Pirtobrutinib plus Venetoclax–Rituximab versus Venetoclax-Rituximab for Patients with Previously Treated CLL/SLL: A Phase 3, Randomized Trial (BRUIN CLL-322)

Matthew S. Davids[1], Toby A. Eyre[2] ,Jennifer A. Woyach[3], Lindsey E. Roeker[4], Alessandra Ferrajoli[5], Yucai Wang[4], Constantine S. Tam[6], Wojciech Jurczak[7], Pier Luigi Zinzani[8], Martin Šimkovič[9], Jian-Yong Li[10], Francesc Bosch[11], Damien Roos-Weil[12], Paula Cramer[13], Anders Osterborg[14], Prioty Islam[15], Ryan Jacobs[16], Alan Skarbnik[17], Seema A. Bhat[3], Suhyun Kang[18], Bastien Nguyen[18], Samuel C. McNeely[18], Karen Lee Chung[18], Joana M. Oliveira[18], Rodrigo Ito[18], Paolo Ghia[19,20] William G. Wierda[5]

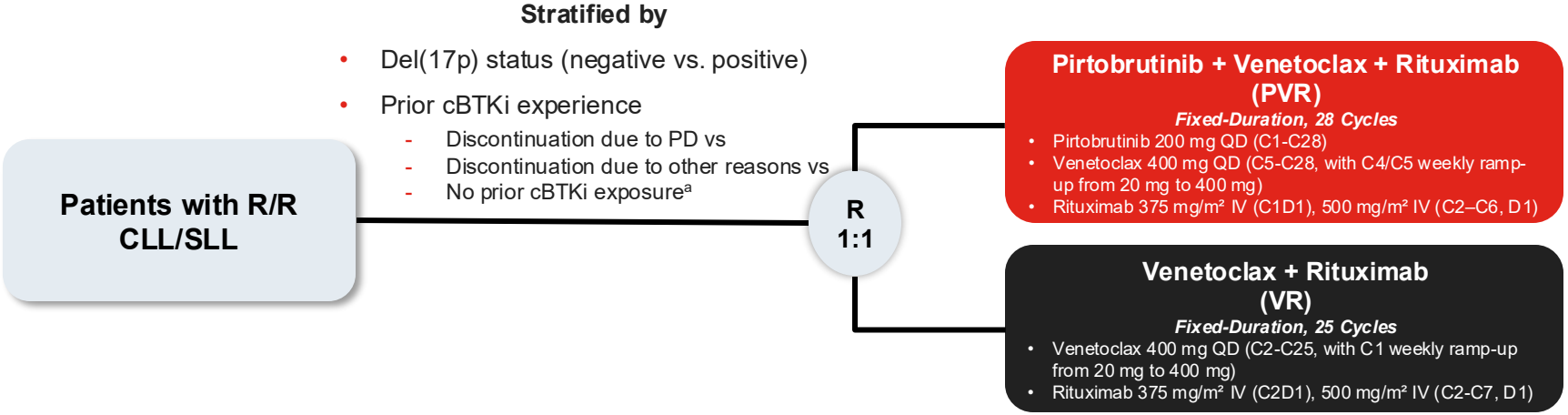
[1] Department of Medical Oncology, Dana-Farber Cancer Institute, Boston, MA, USA , [2] Department of Haematology, Oxford University Hospitals NHS Foundation Trust, Churchill Cancer Centre, Oxford, UK , [3] The Ohio State University Comprehensive Cancer Center, Columbus, OH, USA , [4] Division of Hematology, Mayo Clinic, Rochester, MN, USA , [5] Department of Leukemia, The University of Texas MD Anderson Cancer Center, Houston, TX, USA , [6] Alfred Hospital and Monash University, Melbourne, Australia, [7] Maria Sklodowska-Curie National Institute of Oncology, Krakow, Poland, [8] IRCCS Azienda Ospedaliero-Universitaria di Bologna; Istituto di Ematologia "Seràgnoli", Bologna, Italy, [9] 4th Department of Internal Medicine – Haematology, Faculty of Medicine in Hradec Králové, University Hospital and Charles University in Prague, Hradec Kralove, Czech Republic, [10] Department of Hematology, The First Affiliated Hospital of Nanjing Medical University, Jiangsu Province Hospital, Nanjing, China, [11] Department of Haematology, Vall d'Hebron University Hospital, Barcelona, Spain ,[12] Haematology Clinic, Hospital Pitié-Salpêtrière, Sorbonne Université, APHP, Paris, France , [13] Department of Internal Medicine, Faculty of Medicine and University Hospital of Cologne, Centre for Integrated Oncology Aachen Bonn Cologne Duesseldorf, German CLL Study Group, University of Cologne, Cologne, Germany, [14] Karolinska University Hospital and Karolinska Institute, Stockholm, Sweden, [15] Memorial Sloan Kettering Cancer Center, New York, NY, USA,[16] Atrium Health Levine Cancer Institute, Wake Forest University School of Medicine, Charlotte, NC, USA, [17] Novant Health Cancer Institute, Charlotte, NC, USA, [18] Eli Lilly and Company, Indianapolis, IN, USA, [19] Medical School, Università Vita-Salute San Raffaele, Milano, Italy, [20] Comprehensive Cancer Center, IRCCS Ospedale San Raffaele, Milano, Italy

Davids MS, et al. *Lancet*. 2026:S0140-6736(26)01204-3 [Epub ahead of print].

LL&M great debates

BRUIN CLL-322 Trial Design

Phase 3, Randomized, Open-Label, Global, Multicenter Trial | 22 Countries | NCT04965493



Key Eligibility Criteria

- Confirmed CLL/SLL requiring treatment (iwCLL 2018[1])
- Age ≥18 years
- R/R disease, ≥1 prior line (may include cBTKi)
- Known del(17p) status (FISH)
- ECOG PS ≤2
- No prior noncovalent BTKi or venetoclax/BCL2i

Primary Endpoint

- IRC-assessed PFS (iwCLL 2018[1])

Exploratory Endpoint

- MRD (peripheral blood, clonoSEQ®)

Secondary Endpoints

- OS
- INV-assessed PFS
- TTNT
- ORR (IRC)
- Safety

No crossover permitted.

Data cutoff: February 2, 2026.
[a]cBTKi-naïve enrollment capped at ~20% of total enrollment.
FISH = fluorescence in situ hybridization; INV = investigator; TTNT = time to next treatment; W = week.
Hallek M, et al. *Blood*. 2018;131(25):2745-2760. Davids MS, et al. *Lancet*. 2026:S0140-6736(26)01204-3 [Epub ahead of print].

LL&M great debates

Patient Demographics and Baseline Characteristics

ITT Population

Characteristics	PVR n=321	VR n=318
Median age, years (range)	68.0 (32, 85)	67.0 (37, 87)
Male, n (%)	216 (67.3)	223 (70.1)
Region, n (%)		
Europe	149 (46.4)	141 (44.3)
North America	104 (32.4)	110 (34.6)
Asia	55 (17.1)	50 (15.7)
Australia/New Zealand	8 (2.5)	9 (2.8)
Middle East	5 (1.6)	8 (2.5)
ECOG PS, n (%)		
0-1	300 (93.5)	301 (94.7)
2	20 (6.2)	16 (5.0)
Rai stage[a], n (%)		
0-II	188 (64.2)	180 (61.4)
III-IV	105 (35.8)	113 (38.6)
Median duration of disease, years (range)	8.6 (0.4, 33.7)	8.4 (0.2, 27.9)
Bulky disease[b], n (%)	116 (36.1)	107 (33.6)
High-risk features[c], n (%)		
IGHV unmutated	203 (63.2)	225 (70.8)
Complex karyotype (≥3 abnormalities)	84 (26.2)	117 (36.8)
Del(17p)	66 (20.6)	71 (22.3)
TP53 mutation	106 (33.0)	112 (35.2)
TP53 mutation and/or Del(17p), n (%)	126 (39.3)	132 (41.5)

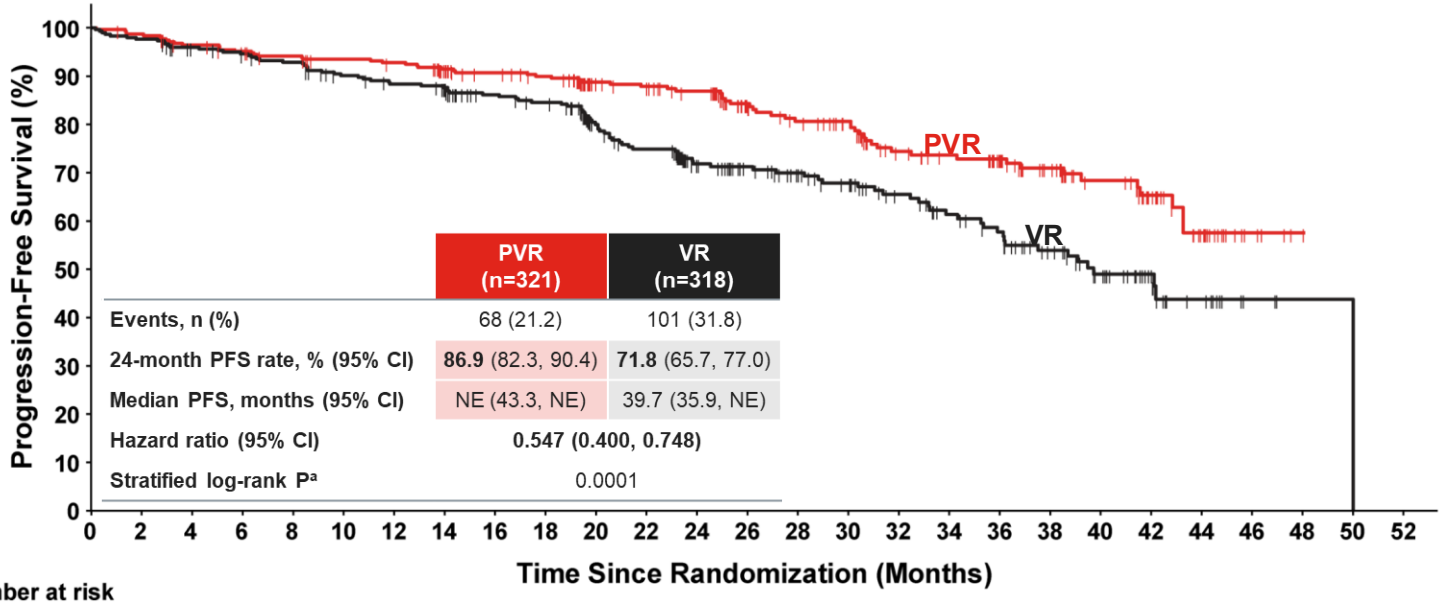
Characteristics	PVR n=321	VR n=318
Median lines of prior systemic therapy, n (range)	2 (1, 7)	2 (1, 9)
Prior lines of systemic therapy, n (%)		
1	135 (42.1)	143 (45.0)
2	90 (28.0)	88 (27.7)
≥3	96 (29.9)	87 (27.4)
Prior therapy, n (%)		
cBTKi	256 (79.8)	254 (79.9)
Ibrutinib	168 (65.6)	175 (68.9)
Acalabrutinib	64 (25.0)	57 (22.4)
Zanubrutinib	38 (14.8)	39 (15.4)
Other[d]	23 (9.0)	20 (7.9)
Anti-CD20 antibody	219 (68.2)	210 (66.0)
Chemotherapy	213 (66.4)	208 (65.4)
Other[e]	75 (23.4)	76 (23.9)
Prior cBTKi experience[f], n (%)		
Discontinued due to PD	181 (56.4)	181 (56.9)
Discontinued due to intolerance	44 (13.7)	35 (11.0)
Discontinued due to other reasons	31 (9.7)	38 (11.9)
No prior cBTKi	65 (20.2)	64 (20.1)

Baseline characteristics were balanced and representative of a contemporary R/R CLL population.
~80% of patients had received a prior cBTKi.

[a]Summarized for subjects with CLL (n=293, in both arms), and percentages use the number of subjects with CLL as the denominator. [b]≥5 cm—measurable target lesion (lymph node). Patients with no measurable target lesions (lymph node) at baseline: PVR, n=30 (9.3%); VR, n=19 (6.0%), and data were missing for 1 patient in PVR. [c]Central lab test. Missing data are due to the reasons samples not collected, received out of stability, inadequate, failed testing, etc. Patients with missing data for each category in PVR and VR, respectively: IGHV unmutated, 68 vs 57; complex karyotype, 116 vs 98; Del(17p), 20 vs 30; TP53 mutation, 65 vs 55; TP53 mutation and/or Del(17p), 65 vs 52. [d]Other cBTKi included investigational drugs and orelabrutinib. [e]Other prior therapies included: other systemic therapy (PVR, n=67; VR, n=72; PI3K agent, steroids, IMiD/immunomodulator, other immunotherapies excluding anti-CD20, other molecular pathways/small molecule inhibitors, clinical trial), stem cell transplant therapy (PVR, n=7; VR, n=3); other transplant: (PVR, n=1; VR, n=0); CAR T (PVR, n=0; VR, n=1). fPrior cBTKi experience as reported in the EDC.
EDC = electronic data capture; ITT = intent-to-treat; PVR = pirtobrutinib + venetoclax + rituximab; VR = venetoclax + rituximab; IMiD = immunomodulatory drug.
Davids MS, et al. *Lancet*. 2026:S0140-6736(26)01204-3 [Epub ahead of print].

LL&M great debates

Progression-Free Survival by IRC (ITT Population)



	PVR (n=321)	VR (n=318)
Events, n (%)	68 (21.2)	101 (31.8)
24-month PFS rate, % (95% CI)	**86.9** (82.3, 90.4)	**71.8** (65.7, 77.0)
Median PFS, months (95% CI)	NE (43.3, NE)	39.7 (35.9, NE)
Hazard ratio (95% CI)	**0.547 (0.400, 0.748)**	
Stratified log-rank P[a]	0.0001	

Number at risk

PVR	321	308	297	291	284	278	275	258	243	237	196	191	182	147	131	123	99	93	86	66	48	32	19	5	1	0	0
VR	318	293	282	276	269	256	249	245	221	215	175	161	127	114	104	94	80	70	63	49	36	21	11	3	1	1	0

16 events of Richter transformation occurred in the VR arm *vs* 8 events in the PVR arm

With a median follow-up of 27.3 months, PVR demonstrated superiority in IRC-assessed PFS compared with VR, reducing the risk of progression or death by 45%.

[a]Two-sided *P*-value based on the stratified log-rank test, stratified by prior cBTKi experience and Del(17p).
NE = not estimable.
Davids MS, et al. *Lancet*. 2026:S0140-6736(26)01204-3 [Epub ahead of print].

LL&M great debates

Adverse Events of Interest

Safety Population

Adverse Event, n (%)	PVR n=316		VR n=311	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Infections[a]	249 (78.8)	107 (33.9)	224 (72.0)	72 (23.2)
COVID-19	98 (31.0)	17 (5.4)	80 (25.7)	12 (3.9)
Upper respiratory tract infection	69 (21.8)	5 (1.6)	64 (20.6)	6 (1.9)
Pneumonia	56 (17.7)	35 (11.1)	46 (14.8)	23 (7.4)
Neutropenia[b]	194 (61.4)	159 (50.3)	168 (54.0)	136 (43.7)
Febrile neutropenia	8 (2.5)	7 (2.2)	11 (3.5)	11 (3.5)
Thrombocytopenia[c]	84 (26.6)	31 (9.8)	84 (27.0)	34 (10.9)
Bleeding	82 (25.9)	9 (2.8)	44 (14.1)	8 (2.6)
Hemorrhage[d]	45 (14.2)	9 (2.8)	33 (10.6)	8 (2.6)
Bruising[e]	40 (12.7)	0	16 (5.1)	0
Petechiae and purpura	12 (3.8)	0	1 (0.3)	0
Atrial fibrillation/flutter	11 (3.5)	6 (1.9)	8 (2.6)	3 (1.0)
Hypertension[f]	38 (12.0)	16 (5.1)	23 (7.4)	9 (2.9)
Tumor lysis syndrome	4 (1.3)	3 (0.9)	13 (4.2)	12 (3.9)

PVR preserved pirtobrutinib's favorable cardiovascular profile, with low rates of AF/flutter, hemorrhage, and hypertension, consistent with prior pirtobrutinib monotherapy data, and with reduction of TLS risk prior to venetoclax ramp-up.

[a]Includes all preferred terms indicating infection and including COVID-19 disease. [b]Includes neutropenia, neutrophil count decreased, febrile neutropenia, neutropenic infection, agranulocytosis, granulocytopenia, and neutropenic sepsis. [c]Includes thrombocytopenia and platelet count decreased. [d]Includes all preferred terms indicating hemorrhage and hematoma, epistaxis, hematuria, intermenstrual bleeding, hemarthrosis, hemoptysis, hematospermia, blood urine present, hematochezia, and bleeding varicose vein. [e]Includes contusion, ecchymosis, and increased tendency to bruise. [f]Includes hypertension, blood pressure increased, hypertensive crisis, and white coat hypertension.
TLS = tumor lysis syndrome.
Davids MS, et al. *Lancet*. 2026:S0140-6736(26)01204-3 [Epub ahead of print].

BTK Inhibitor Resistance Mutations

LL&M great debates

BTK/PLCG2 Mutations Common at Time of Resistance to Ibrutinib

Table 1. Characteristics of Six Patients with Resistance to Ibrutinib.

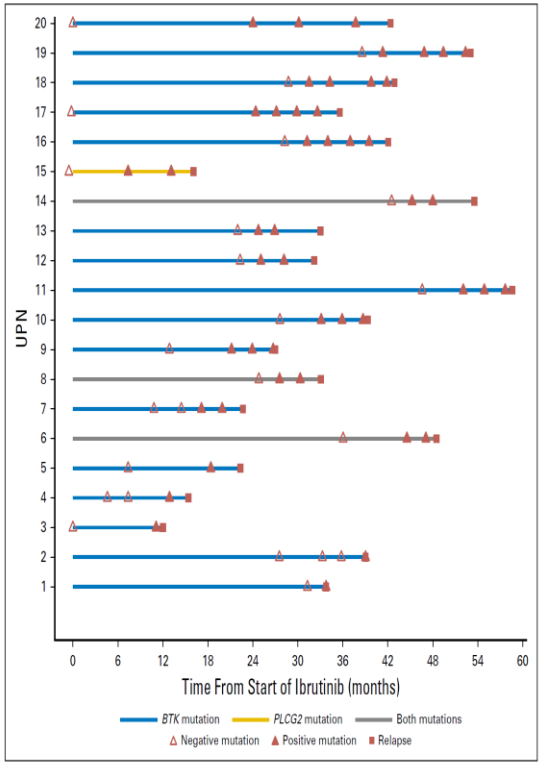
Patient No.	Age	Prior Therapies	Baseline Cytogenetic Features*	Study Treatment and Daily Dose†	Duration of Ibrutinib Treatment	Best Response	Time to First Response	Identified Mutations of Interest‡
	yr	*no.*			*days*		*days*	
1	59	5	del(17p13.1), trisomy 12	Ibrutinib, 560 mg	621	Partial	70	C481S mutation in BTK
2	59	3	del(11q22.3)	Bendamustine–rituximab for 6 cycles; ibrutinib, 420 mg	388	Complete	70	C481S mutation in BTK
3	51	2	complex karyotype	Ofatumumab for 24 wk; ibrutinib, 420 mg	674	Complete	85	C481S mutation in BTK
4	69	9	del(17p13.1), complex karyotype	Ibrutinib, 840 mg	868	Partial	133	C481S mutation in BTK
5	61	4	del(17p13.1), complex karyotype	Ofatumumab for 24 wk; ibrutinib, 420 mg	505	Partial	85	L845F, R665W, and S707Y mutations in PLCγ2 and C481S mutation in BTK
6	75	2	del(17p13.1), complex karyotype	Ibrutinib, 420 mg	673	Partial	159	R665W mutation in PLCγ2

* We used fluorescence in situ hybridization to detect del(17p13.1), del(11q22.3), centromere 12, and del(13q14.3) and metaphase analysis of stimulated G-banded cells to determine complexity.
† Doses are given for ibrutinib only.
‡ All functional mutations that were detected only at the time of relapse are listed in Table 1 in the Supplementary Appendix.

Woyach JA, et al. *N Engl J Med*. 2014;370(24):2286-2294.

BTK/PLCG2 Mutations Precede Clinical Relapse

- 46 pts CLL PD on ibrutinib
- 40 (87%) had BTK/PLCG2 mutation
  - 20 had serial testing prior to clinical relapse
  - All 20 had a mutation detected median 9.3 mos prior to clinical relapse



Woyach JA, et al. *J Clin Oncol*. 2017;35(13):1437-1443.

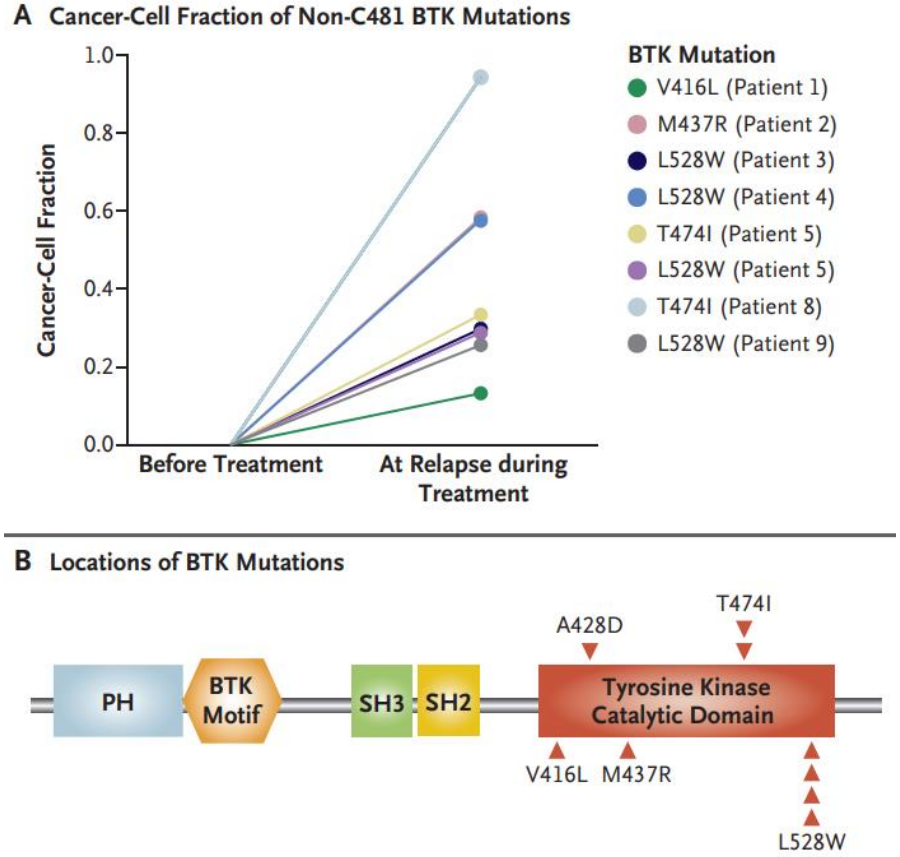
LL&M great debates

Pirtobrutinib Resistance

- Pre-/post-pirtobrutinib samples on 9 pts with CLL
  - All 9 patients had prior ibrutinib
  - At the time of relapse from pirtobrutinib
    - 6 CLL relapse
    - 3 Richter relapse
  - 7/9 patients acquired new non-C481 BTK mutations

Wang E, et al. *N Engl J Med*. 2022;386(8):735-743.

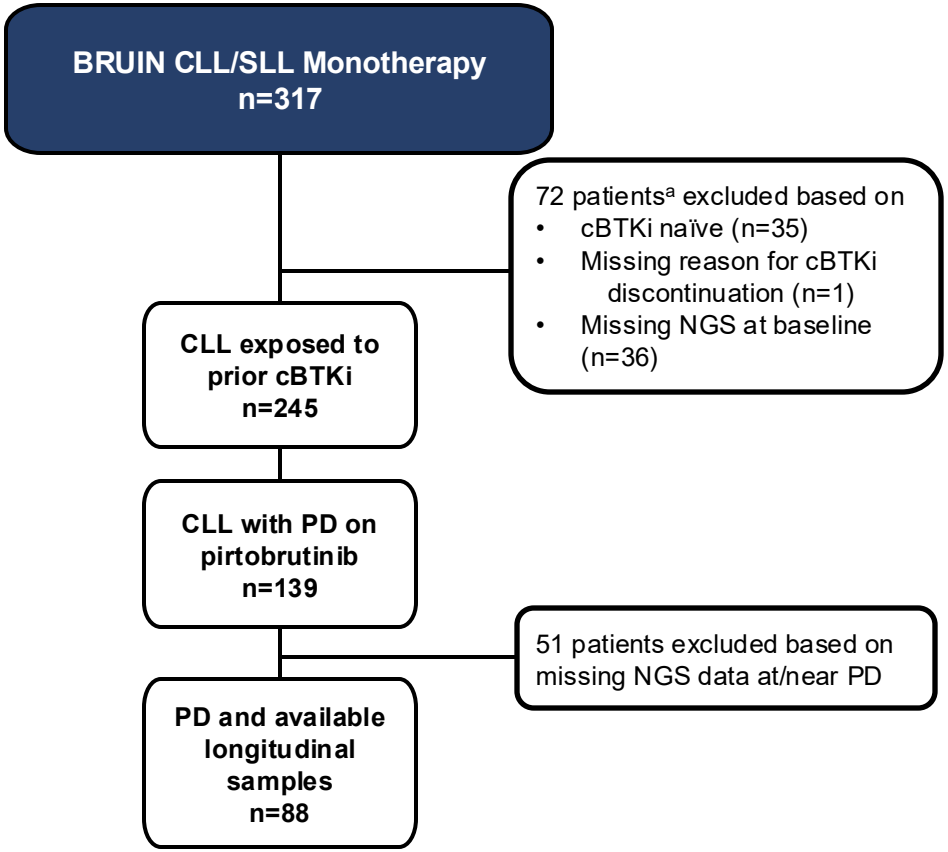
Pirtobrutinib Resistance



Wang E, et al. *N Engl J Med*. 2022;386(8):735-743.

LL&M great debates

Study Design and Methods

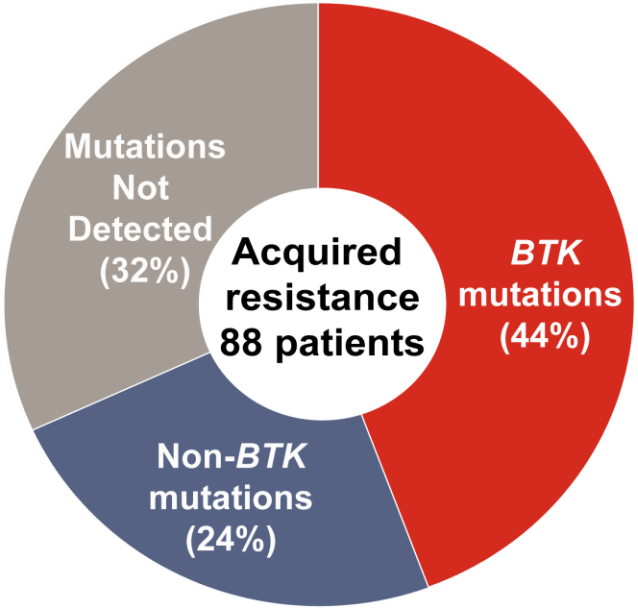


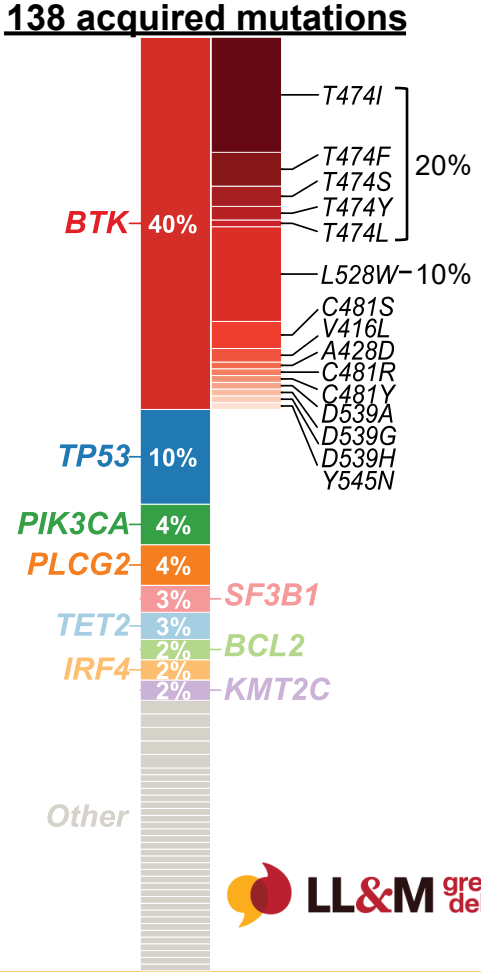
- Next-generation sequencing (NGS) of paired baseline and progression PBMC samples from 88 cBTKi pre-treated CLL patients who progressed on pirtobrutinib
- Targeted NGS (5% VAF limit of detection [LoD]) gene list (all exons, 74 genes):
  - ***BTK***, ***PLCG2***, ***TP53***, *ABL1, APC, ARID1A, ATM, BAP1, BCL2, BCL6, BRAF, BRD4, CARD11, CCND1, CCND3, CD79A, CD79B, CDK4, CDKN2A, CDKN2B, CREBBP, EP300, EPHA7, ERBB3, EZH2, FAS, FGFR1, FLT1, FOXP1, GNA13, GRIN2A, GSK3B, HRAS, IKZF1, IRF4, JAK1, JAK2, KDR, KIT, KLHL6, KMT2C, KMT2D, KRAS, MAP2K1, MED12, MEF2B, MTOR, MYC, MYD88, NFKBIA, NOTCH1, NOTCH2, NRAS, NTRK1, PDGFRA, PIK3CA, PIK3CG, PIK3R1, PIK3R2, PRDM1, PRKDC, PTEN, RAF1, RB1, ROS1, SF3B1, SMARCA4, SOCS1, STAT3, SYK, TET2, TNFAIP3, TNFRSF14, XPO1*
- 79 baseline PBMC samples were re-sequenced using a more sensitive assay (LoD ~0.5% VAF) to assess the presence of pre-existing *BTK* mutations

Data cutoff date of May 5, 2023 (NCT03740529). [a]Patients with SLL were excluded from the analysis with these criteria.
PBMC = peripheral blood mononuclear cell; VAF = variant allele frequency.

LL&M great debates

Acquired Mutations Were Detected at PD in 68% of Patients





- 68% (60/88) acquired mutations at PD
  - 44% (39/88) had at least one acquired *BTK* mutation at PD
    - 64% (25/39) who acquired a *BTK* mutation had a *BTK* mutation at baseline
- 56% (49/88) did not acquire a BTK mutation
  - The most frequently acquired non-BTK mutation was TP53
- 32% (28/88) had no acquired mutations detected at PD

LL&M great debates

But If I Use My Best Drugs Upfront, What Would I Do at the Time of Relapse?

- Important point is time-limited nature of doublet/triplet therapies
- CAPTIVATE trial
  - Patients who received 12-month combined ibr + ven fixed duration Rx
  - 29 patients had disease progression during follow-up
  - No patient among 25 with available samples developed BTK, PLCG2, or BCL2 mutation at the time of PD
  - Retreatment works
    - 19 patients required subsequent Rx (16 ibr alone; 3 ibr + ven)
      - 17 patients achieved PR or better

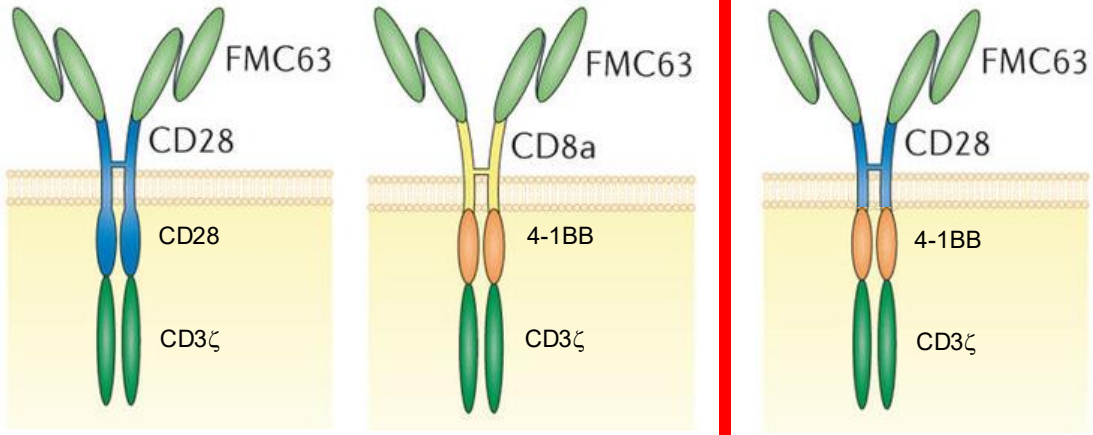
Rx = prescription.

Jain N, et al. *Clin Cancer Res*. 2024;30(3):498-505.

LL&M great debates

CD19 CAR T Products in Pivotal Trials in ALL and NHL

	NCI	U Penn	FHCRC/MSKCC
CD19 Ab	FMC63	FMC63	FMC63
Hinge Transmembrane	CD28	CD8a	CD28
Signal 2	CD28	4-1BB	4-1BB
Signal 1	CD3ζ	CD3ζ	CD3ζ
Gene transfer	Retrovirus	Lentivirus	Lentivirus
	KTE-C19 Axicabtagene (Yescarta®) KTE-X19 Brexucabtagene (Tecartus®)	CTL019 Tisagenlecleucel (Kymriah®)	JCAR017 Lisocabtagene (Breyanzi®)



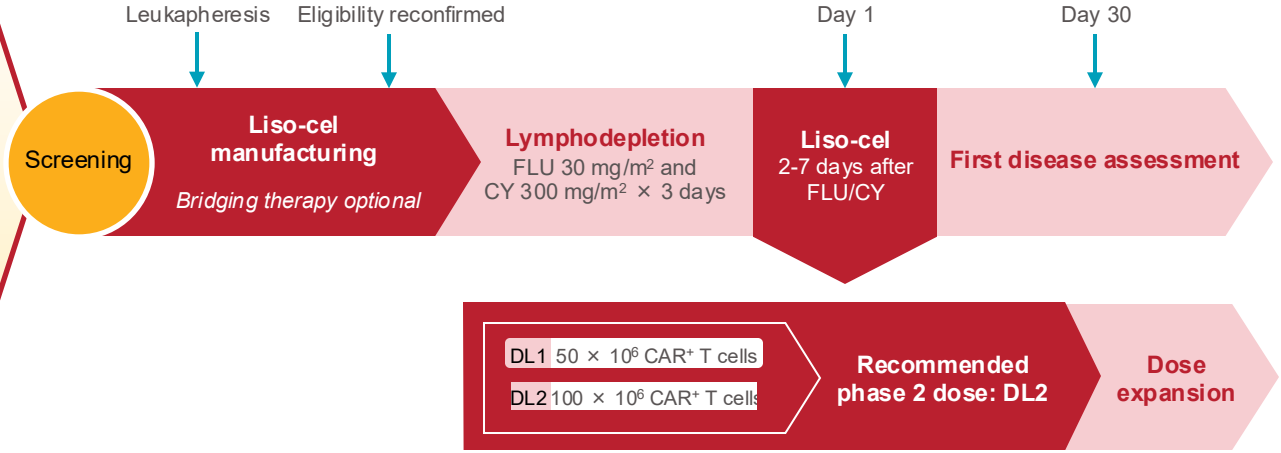
ALL = acute lymphocytic leukemia; NHL = non-Hodgkin lymphoma; Ab = antibody; NCI = National Cancer Institute; FHCRC = Fred Hutchinson Cancer Research Center; MSKCC = Memorial Sloan Kettering Cancer Center.
Slide courtesy of Neelapu S. Adapted from van der Stegen, et al. *Nat Rev Drug Discov*. 2015;14(7):499-509.

LL&M great debates

TRANSCEND CLL 004: Phase 1/2, Open-Label, Multicenter Study

Key eligibility criteria

- Age ≥ 18 years
- R/R CLL/SLL
- Previously failed or ineligible for BTKi
- Failure of ≥2 (high risk) or ≥3 (standard risk) lines of prior therapy
- ECOG PS ≤1
- Adequate bone marrow, organ, and cardiac function
- No Richter transformation nor active CNS involvement by malignancy



Follow-up

On-study: 24 or 48 months

Long-term (NCT03435796): up to 15 years after liso-cel infusion

Primary endpoint (PEAS at DL2)
CR/CRi rate per iwCLL 2018 by IRC assessment

Key secondary endpoints (PEAS at DL2)
ORR, uMRD rate in blood

Post-hoc analyses
Median time to next treatment

ClinicalTrials.gov: NCT03331198.
CY = cyclophosphamide; DL = dose level; FLU = fludarabine; CNS = central nervous system; PEAS = primary efficacy analysis set (prespecified subset of patients with BTKi progression and venetoclax failure); uMRD = undetectable minimal residual disease; CRi = CR with incomplete blood recovery.
Siddiqi T, et al. Presented at: 65th American Society of Hematology (ASH) Annual Meeting & Exposition; 2023. Abstract 330.

LL&M great debates

Demographics and Baseline Characteristics

	Full study population (n=118)	BTKi progression/venetoclax failure subset (n=71)
Median (range) age, y	65.0 (49-82)	66.0 (49-78)
Median (range) prior lines of systemic therapy	5 (2-14)	5 (2-14)
Bulky lymph nodes,[a] n (%)		
Yes	53 (45)	33 (46)
Unknown	9 (8)	8 (11)
High-risk cytogenetics,[b] n (%)	98 (83)	61 (86)
Prior BTKi, n (%)	118 (100)	71 (100)
BTKi refractory[c]	104 (88)	71 (100)
BTKi relapsed[d]	2 (2)	0
BTKi intolerant only	12 (10)	0
Prior venetoclax, n (%)	95 (81)	71 (100)
Venetoclax refractory	90 (76)	68 (96)
Venetoclax relapsed[d]	0	0
Venetoclax intolerant only	4 (3)	3 (4)
Prior BTKi and venetoclax, n (%)	95 (81)	71 (100)
BTKi progression/venetoclax failure,[e] n (%)	71 (60)	71 (100)
Received bridging therapy, n (%)	90 (76)	56 (79)

[a]Defined as ≥1 lesion with the longest diameter of ≥5 cm. [b]Includes del(17p), TP53 mutation, unmutated immunoglobulin heavy-chain variable region, and complex cytogenetics. [c]Defined as no response or progression ≤6 months from last dose of therapy. [d]Defined as disease progression in a patient who previously had CR/CRi or PR/nPR for ≥6 months. [e]Including patients who progressed on a BTKi and met one of the following: (1) discontinued venetoclax due to disease progression or intolerability and patient's disease met indications for further therapy per iwCLL 2018, or (2) failed to achieve an objective response ≤3 months of initiating therapy.

Siddiqi T, et al. Presented at: 65th ASH Annual Meeting & Exposition; 2023. Abstract 330.

Efficacy Outcomes: DL2 Only

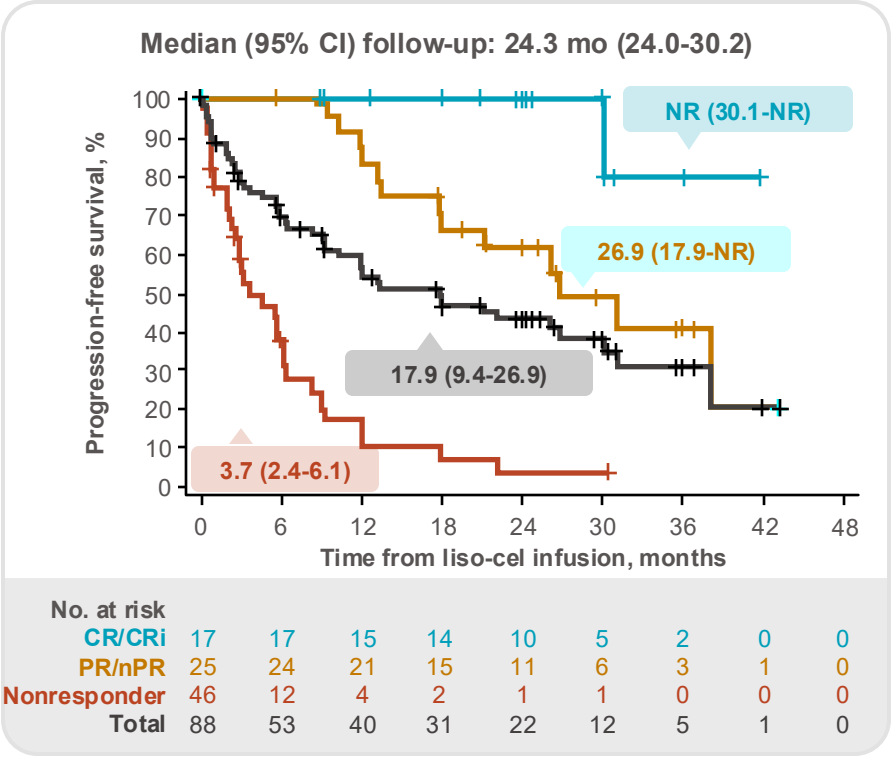
	Full study population at DL2 (n=88)	BTKi progression/venetoclax failure subset at DL2 (n=50)
Primary endpoint: IRC-assessed CR/CRi rate per iwCLL 2018, n (%) [95% CI]	17 (19) [12-29]	10 (20) [10-34]
Key secondary endpoints		
IRC-assessed ORR, n (%) [95% CI]	42 (48) [37-59]	22 (44) [30-59]
uMRD rate in blood, n (%) [95% CI]	58 (66) [55-76]	32 (64) [49-77]
Exploratory endpoint: uMRD rate in marrow, n (%) [95% CI]	53 (60) [49-71]	30 (60) [45-74]
Other secondary endpoints		
Best overall response, n (%)		
CR/CRi	17 (19)	10 (20)
PR/nPR	25 (28)	12 (24)
SD	34 (39)	21 (42)
PD	6 (7)	4 (8)
Not evaluable	6 (7)	3 (6)
Time to first response, months, median (range)	1.3 (0.8-17.4)	1.1 (0.8-17.4)
Time to first CR/CRi, months, median (range)	5.5 (0.8-18.0)	2.1 (0.8-18.0)

- **uMRD was achieved in MRD-evaluable patients in the full population at DL2 by**
  - **15/15 (100%) patients with CR/CRi in blood and 15[a]/16 (94%) in marrow**
  - 24/24 (100%) patients with PR/nPR in blood and 23/23 (100%) in marrow
  - 19/32 (59%) patients with SD in blood and 15/32 (47%) in marrow

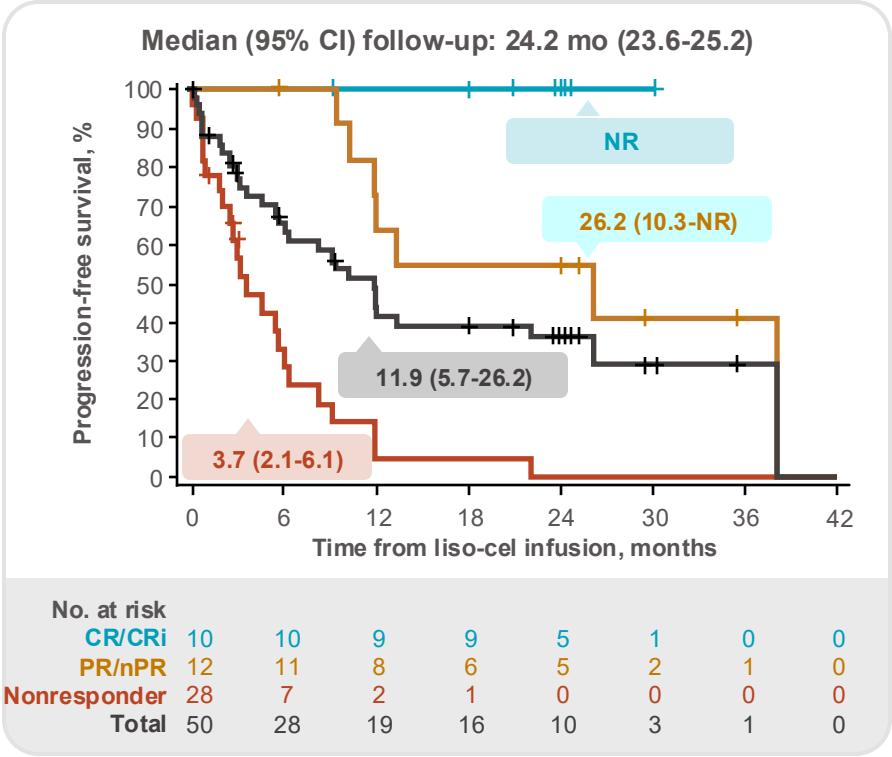
[a]One patient had an indeterminate status for MRD, which was considered positive as per FDA guidelines.
SD = stable disease; FDA = US Food and Drug Administration.
Siddiqi T, et al. Presented at: 65th ASH Annual Meeting & Exposition; 2023. Abstract 330.

Progression-Free Survival by Best Overall Response

(A) Full study population at DL2 (n=88)



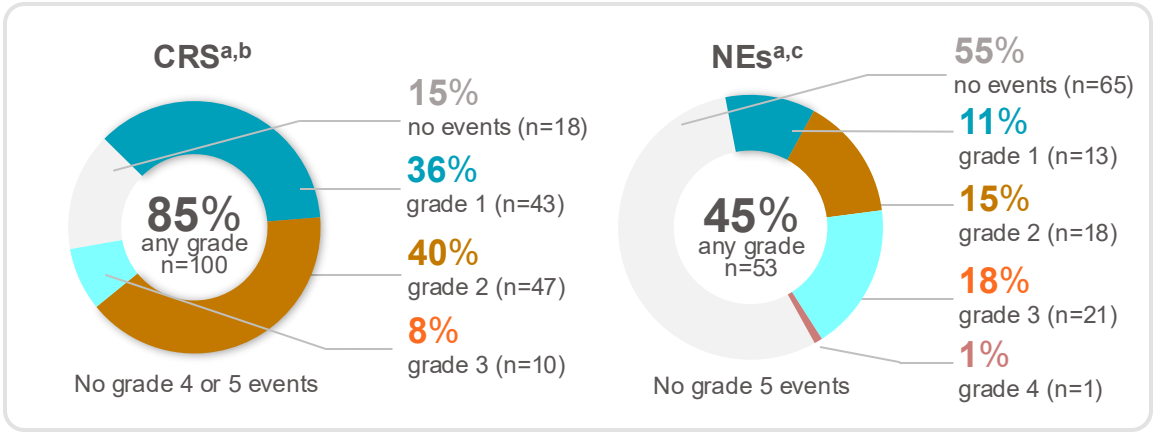
(B) PEAS (BTKi progression/venetoclax failure subset) at DL2 (n=50)



Data on KM curves are expressed as median (95% CI, if available).
NR = no response.
Siddiqi T, et al. Presented at: 65th ASH Annual Meeting & Exposition; 2023. Abstract 330.

LL&M great debates

Safety: Full Study Population (n=118)



	Total (n = 118)	
	CRS	NE
Patients with an event, n (%)	100 (85)	53 (45)
Median (range) time to onset, days	4 (1-18)	7 (1-21)
Median (range) time to resolution, days	6 (2-37)	7 (1-83)
Received tocilizumab and/or corticosteroids for CRS and/or NE	82 (69)	

Other AESIs, n (%)

- Prolonged cytopenias[d]: 64 (54%)
- Grade ≥3 infections[e]: 21 (18%)
- Hypogammaglobulinemia[f]: 18 (15%)
- Tumor lysis syndrome: 13 (11%)
- SPM[f]: 11 (9%)
- MAS: 4 (3%)

Deaths due to TEAEs, n=5 (4%)

- 4 (3%) considered unrelated to liso-cel by investigators (respiratory failure, sepsis, *Escherichia coli* infection, and invasive aspergillosis)
- 1 (1%) considered related to liso-cel by investigators (MAS)

[a]Summed percentages for grouped grades within each graph may not equal the any-grade percentage due to rounding. [b]CRS was graded based on the Lee 2014 criteria. [c]NEs were defined as investigator-identified neurological AEs related to liso-cel. [d]Defined as grade ≥3 laboratory abnormalities of neutropenia, anemia, or thrombocytopenia at day 30 after liso-cel infusion. [e]Includes grade ≥3 TEAEs from infections and infestations (system organ class) by AE high-level group term. [f]AEs from the 90-day treatment-emergent period, post-treatment-emergent period, and long-term follow-up were included.
AESI = adverse event of special interest; MAS = macrophage activation syndrome; NE = neurological event; SPM = second primary malignancy; TEAE = treatment-emergent adverse event; CRS = cytokine release syndrome.
Siddiqi T, et al. Presented at: 65th ASH Annual Meeting & Exposition; 2023. Abstract 330.

LL&M great debates

Lisocabtagene Maraleucel Combined with Ibrutinib for Patients with Relapsed or Refractory Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma: Primary Results from the Open-Label, Phase 1/2 TRANSCEND CLL 004 Study

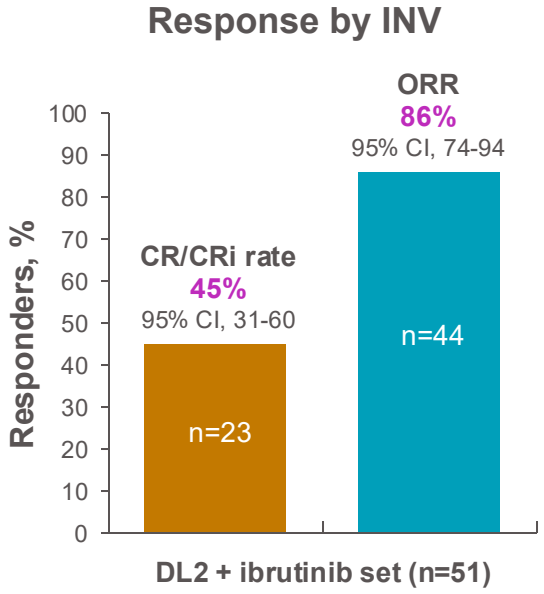
William G. Wierda, MD, PhD,[1] Kathleen Dorritie, MD,[2] Jordan Gauthier, MD, MSc,[3] Rajneesh Nath, MD,[4] Thomas Kipps, MD, PhD,[5] Peter A. Riedell, MD,[6] Herbert A. Eradat, MD,[7] Saad S. Kenderian, MB, ChB,[8] Mohamed A. Kharfan-Dabaja, MD, MBA,[9] Nirav N. Shah, MD,[10] Scott R. Solomon, MD,[11] Daniel A. Ermann, MD,[12] Jon Arnason, MD,[13] Abhinav Deol, MD,[14] Tatyana Feldman, MD,[15] Charalambos Andreadis, MD, MS,[16] Monalisa Ghosh, MD,[17] Shuo Ma, MD, PhD,[18] Stephen J. Schuster, MD,[19] Usama Gergis, MD, MBA,[20] Julie M. Vose, MD, MBA,[21] Jacob Soumerai, MD,[22] Koen van Besien, MD, PhD,[23]* Sherilyn A. Tuazon, MD,[24] Serena K. Perna, MD,[25] San-San Ou, MS,[24] Neha Rane, MD,[25] Eniko Papp, PhD,[24] Yizhe Chen, PhD,[25] Tanya Siddiqi, MD, MBBS[26]

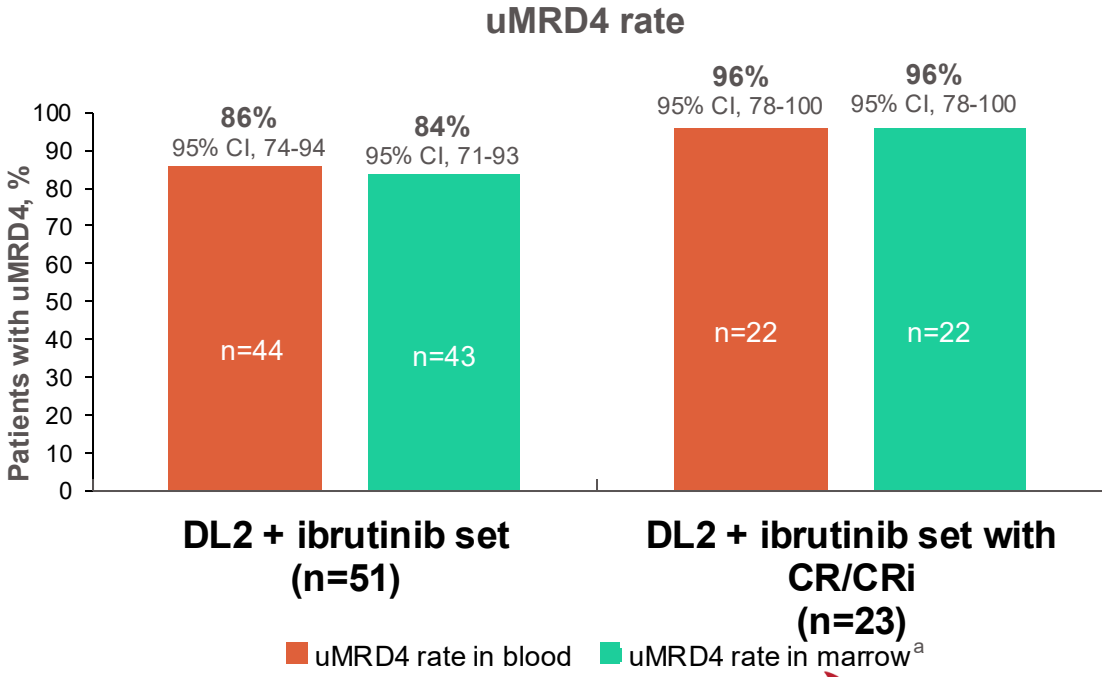
Wierda WG, et al. Presented at: 66th ASH Annual Meeting & Exposition; 2024. Abstract 887.

LL&M great debates

Efficacy Outcomes: Response by Investigator and uMRD4

- Median (IQR) on-study follow-up (including LTFU): 24.8 months (14.2-34.6)
- Median (range) time to first response: 1 month (0.9-6.0)
- Median (range) time to first CR/CRi: 3 months (0.9-12.1)

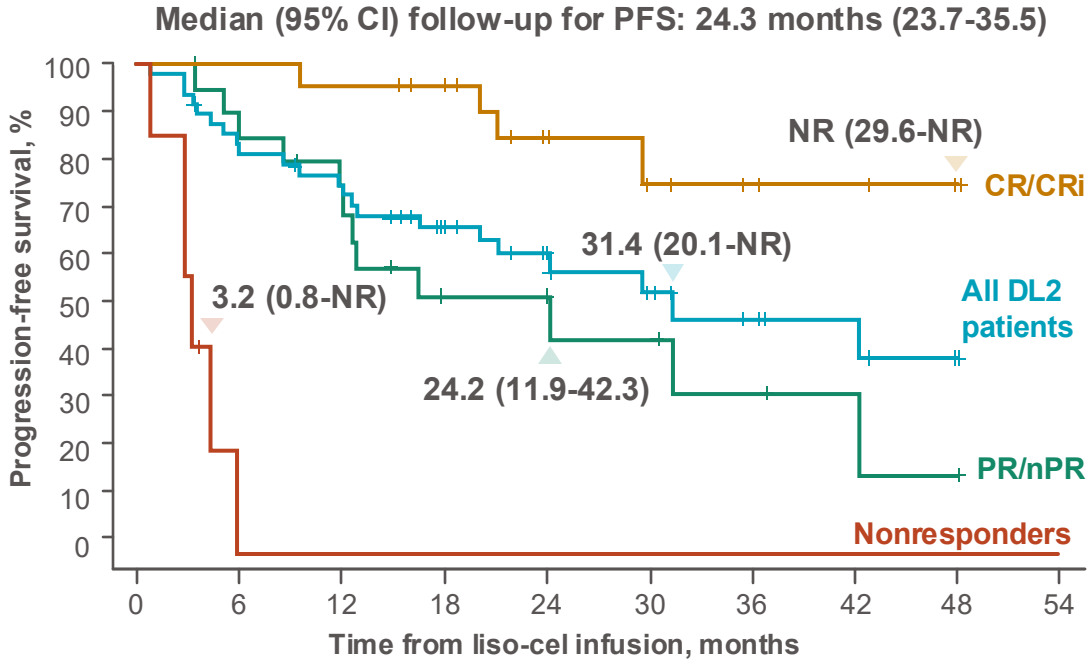




[a]Forty-nine patients (22 with CR/CRi) were evaluable for MRD in marrow.
LTFU = long-term follow-up.
Wierda WG, et al. Presented at: 66th ASH Annual Meeting & Exposition; 2024. Abstract 887.

LL&M great debates

Progression-Free Survival by Best Overall Response at DL2



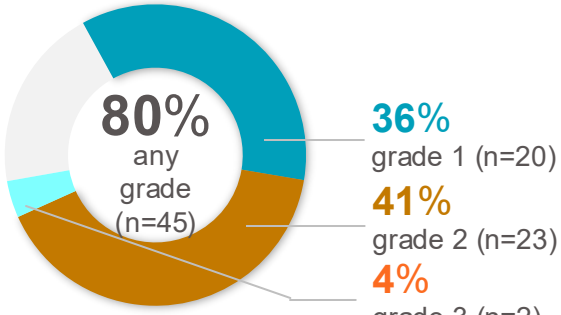
No. at risk										
CR/CRi	23	23	22	20	12	7	5	4	2	0
PR/nPR	21	17	14	7	6	5	3	2	1	0
Nonresponders	7	0	0	0	0	0	0	0	0	0
All DL2 patients	51	40	36	27	18	12	8	6	3	0

	% progression free (95% CI)	
	12 months	24 months
All DL2 patients (n=51)	76 (61-85)	62 (46-74)
Patients with CR/CRi (n=23)	96 (73-99)	85 (60-95)

Data on KM curves are expressed as median (95% CI). No formal landmarking analyses were conducted.
Wierda WG, et al. Presented at: 66th ASH Annual Meeting & Exposition; 2024. Abstract 887.

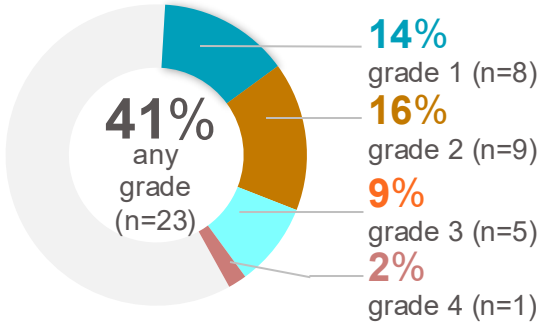
Safety: Incidence of CRS and NEs

CRS[a,b]



No grade 4 or 5 events

NEs[a,c]



No grade 5 events

	Total combination-treated set (n=56)
Median (range) days to CRS onset	7 (1-14)
Median (range) days to CRS resolution	5 (2-18)
Received tocilizumab and/or corticosteroids for CRS and/or NE, n (%)	33 (59)

	Total combination-treated set (n=56)
Median (range) days to NE onset	8 (1-15)
Median (range) days to NE resolution	8 (1-362)
Received tocilizumab and/or corticosteroids for CRS and/or NE, n (%)	33 (59)

[a]Summed percentages for grouped grades within each graph may not equal the any-grade percentage due to rounding. [b]CRS was graded based on Lee 2014 criteria. [c]NEs were defined as INV-identified neurological AEs related to liso-cel.

Wierda WG, et al. Presented at: 66th ASH Annual Meeting & Exposition; 2024. Abstract 887.

An emerging approach in clinical practice:

Start pirto as debulking Rx followed by CAR T

LL&M great debates

BTK Degraders

LL&M great debates

Tacabrutideg (BGB-16673), A Bruton Tyrosine Kinase Degrader, in Patients with Relapsed/Refractory Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma: A Phase 1 CaDAnCe-101 Study Update

Stephan Stilgenbauer,[1] Ricardo D. Parrondo,[2] Meghan C. Thompson,[3] Anna Maria Frustaci,[4] John N. Allan,[5] Paolo Ghia,[6,7] Irina Mocanu,[8] Damien Roos-Weil,[9] Constantine S. Tam,[10] Judith Trotman,[11] Inhye E. Ahn,[12] Lydia Scarfò,[6,7] Carlo Visco,[13] Michael Choi,[14] Yanan Zhang,[15] Linlin Xu,[15] Kunthel By,[15] Shannon Fabre,[15] Daniel Persky,[15] Shelonitda Rose,[15] John F. Seymour[16]

[1]Ulm University, Ulm, Germany; [2]Mayo Clinic - Jacksonville, Jacksonville, FL, USA; [3]Memorial Sloan Kettering Cancer Center, New York, NY, USA; [4]ASST Grande Ospedale Metropolitano Niguarda, Milano, Italy; [5]Weill Cornell Medicine, New York, NY, USA; [6]Università Vita-Salute San Raffaele, Milano, Italy; [7]Comprehensive Cancer Center, IRCCS Ospedale San Raffaele, Milano, Italy; [8]The Institute of Oncology, ARENSIA Exploratory Medicine, Chisinau, Moldova; [9]Pitié-Salpêtrière Hospital, Paris, France; [10]Alfred Hospital and Monash University, Melbourne, VIC, Australia; [11]Concord Repatriation General Hospital, University of Sydney, Concord, NSW, Australia; [12]Dana-Farber Cancer Institute, Boston, MA, USA; [13]Universita di Verona, Verona, Italy; [14]Moores Cancer Center, University of California San Diego, La Jolla, CA, USA; [15]BeOne Medicines, Ltd, San Carlos, CA, USA; [16]Peter MacCallum Cancer Centre, Royal Melbourne Hospital, and University of Melbourne, Melbourne, VIC, Australia

Stilgenbauer S, et al. Presented at: European Hematology Association (EHA) 2026 Congress; 2026. Abstract S152.

LL&M great debates

Baseline Patient Characteristics

Heavily pretreated, with high-risk CLL features

	Total (N=67)
Age, median (range), years	70 (47-91)
Male, n (%)	46 (68.7)
ECOG PS, n (%)	
0	38 (56.7)
1	28 (41.8)
2	1 (1.5)
CLL/SLL risk characteristics, n/N (%)	
Unmutated IGHV	43/56 (76.8)
del(17p) and/or *TP53* mutation	44/67 (65.7)
Complex karyotype (≥3 abnormalities)	23/43 (53.5)
Mutation status, n/N (%)	
BTK mutation present	25/66 (37.9)
PLCG2 mutation present	10/66 (15.2)
BTK and *PLCG2* mutation present	5/66 (7.6)

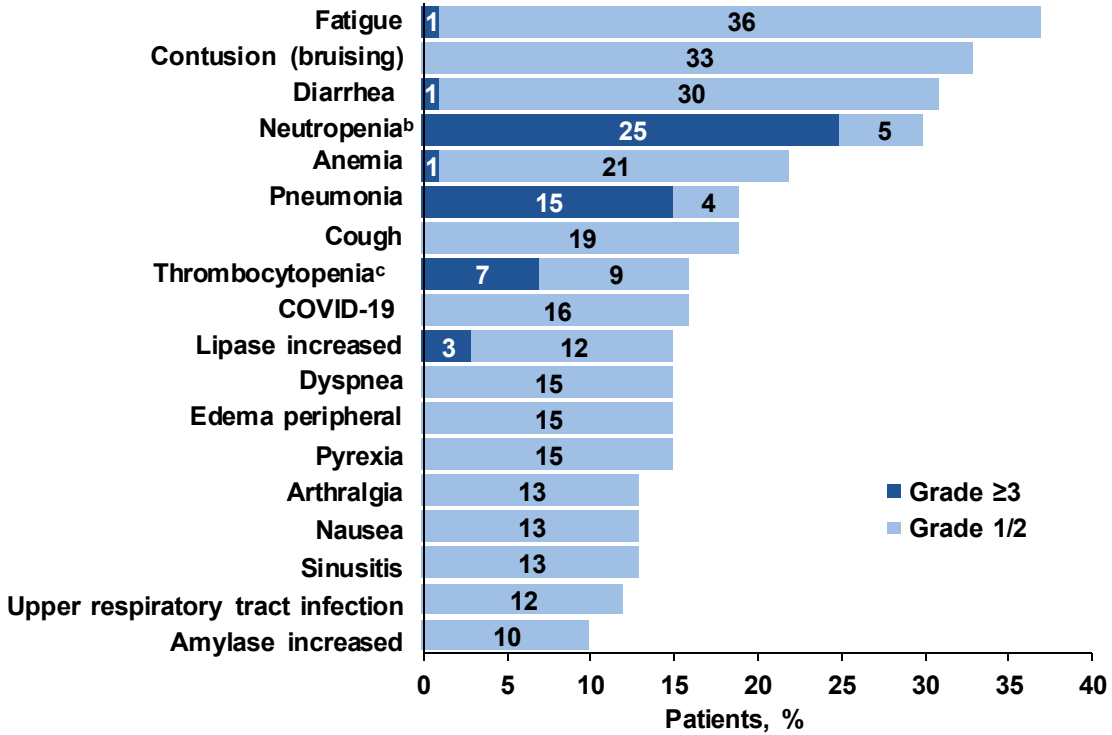
	Total (N=67)
No. of prior lines of therapy, median (range)	4 (2-10)
Prior therapy, n (%)	
Chemotherapy	48 (71.6)
cBTK inhibitor	63 (94.0)
ncBTK inhibitor	14 (20.9)
BCL2 inhibitor	55 (82.1)
cBTK + BCL2 inhibitors (no ncBTK inhibitor)	43 (64.2)
cBTK + ncBTK + BCL2 inhibitors	12 (17.9)
Refractory to last cBTK inhibitor + last BCL2 inhibitor[a]	37/41 (90.2)
Discontinued prior BTK inhibitor due to PD, n/N (%)[b]	56/63 (88.9)

Data cutoff: February 25, 2026. Median study follow-up: 25.4 (range, 0.3-40.1) months.
[a]Refractory status in 14/55 patients with prior cBTK inhibitor and BCL2 inhibitor is unknown. [b]The remaining seven patients discontinued prior BTK inhibitor due to toxicity (n=4) and other (n=3).
Stilgenbauer S, et al. Presented at: EHA2026 Congress; 2026. Abstract S152.

LL&M great debates

All-Grade TEAEs in ≥10% of All Patients

- Grade ≥3 neutropenia: n=17 (25.4%); 15 patients (22.4%) had grade ≥2 neutropenia at baseline
  - Febrile neutropenia: n=1
- Grade ≥3 infection: n=24 (35.8%)
- Atrial fibrillation: n=3 (grade 1 and 2)
- All transient (2 of them lasting 1 day and all in the context of infection and PD)
- Treatment-related major hemorrhagea: n=2 (one grade 3 subdural hematoma and one grade 3 post-procedural hematuria)
- No new cases of atrial fibrillation, major hemorrhage, and invasive fungal infections since the last data cutoff (August 22, 2025)

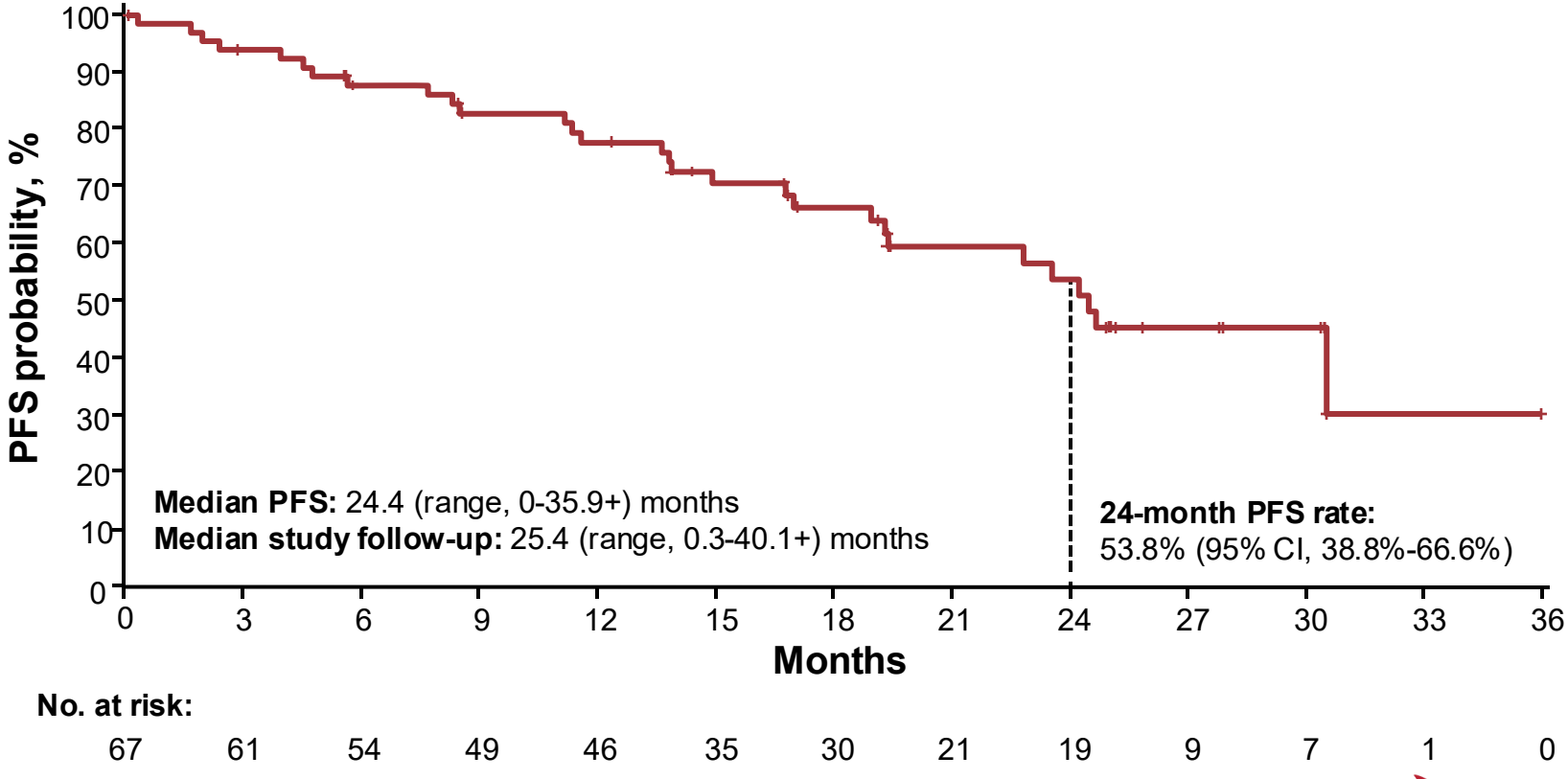


Data cutoff: February 25, 2026. Median duration of exposure: 18.2 (range, 0.2-36.4) months. The values of any-grade TEAEs have been calculated from individual grade 1/2 and grade ≥3 values rounded to the nearest whole number.
[a]Grade ≥3, serious, or any central nervous system bleeding. [b]Neutropenia combines preferred terms *neutropenia* and *neutrophil count decreased*. [c]Thrombocytopenia combines preferred terms *thrombocytopenia* and *platelet count decreased*.
Stilgenbauer S, et al. Presented at: EHA2026 Congress; 2026. Abstract S152.

LL&M great debates

Progression-Free Survival

Durable PFS in heavily-pretreated patients across all dose levels in phase 1



Data cutoff: February 25, 2026.

Stilgenbauer S, et al. Presented at: EHA2026 Congress; 2026. Abstract S152.

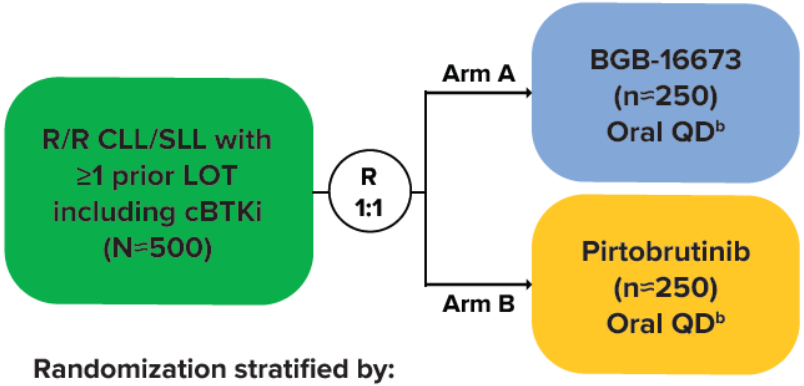
LL&M great debates

CaDAnCe-304 Trial

Key eligibility criteria

- Age ≥18 years
- Confirmed CLL/SLL (iwCLL 2018 criteria)[9]
- R/R to ≥1 LOT[a] including a cBTKi
- Measurable disease by CT/MRI (SLL)
- ECOG PS of 0-2
- Adequate organ function
- No prior BTK protein degraders or ncBTKi

Study design



Randomization stratified by:

- Prior BCL2i
- del(17p) and/or *TP53* mutated
- Refractory to last cBTKi treatment

Objectives

Primary

- PFS (IRC)[c]

Secondary

- OS
- PFS (INV)[c]
- ORR (IRC/INV)
- PR-L or better rate (IRC/INV)
- DOR (IRC/INV)
- Time to next treatment
- Safety/tolerability[d]
- PROs

LOT = line of therapy; DOR = duration of response; PRO = patient-reported outcome.
Stilgenbauer S, et al. Presented at: EHA2026 Congress; 2026. Abstract S152.

LL&M great debates

Updated Efficacy and Safety Data from an Ongoing Phase 1a/b Trial of the BTK Degrader Bexobrutideg (NX-5948) in Patients with CLL/SLL across Lines of Therapy

[1]Talha Munir, [2]Zulfa Omer, [3]Sebastian Grosicki, [4]Michal Kwiatek, [5]Alexey Danilov, [6]Nirav N. Shah, [7]Francesco Forconi, [8]Alvaro Alencar, [9,10]Mary Gleeson, [11]Laura Samples, [12]Graham P. Collins, [13]Jane Robertson, [14]Jonathon B. Cohen, [15]William Wierda, [16]Danielle Brander, [17]Shuo Ma, [18]Allison Winter, [19]Krzysztof Giannopoulos, [2]John C. Byrd, [20]Sarah Injac, [21]Wojciech Jurczak

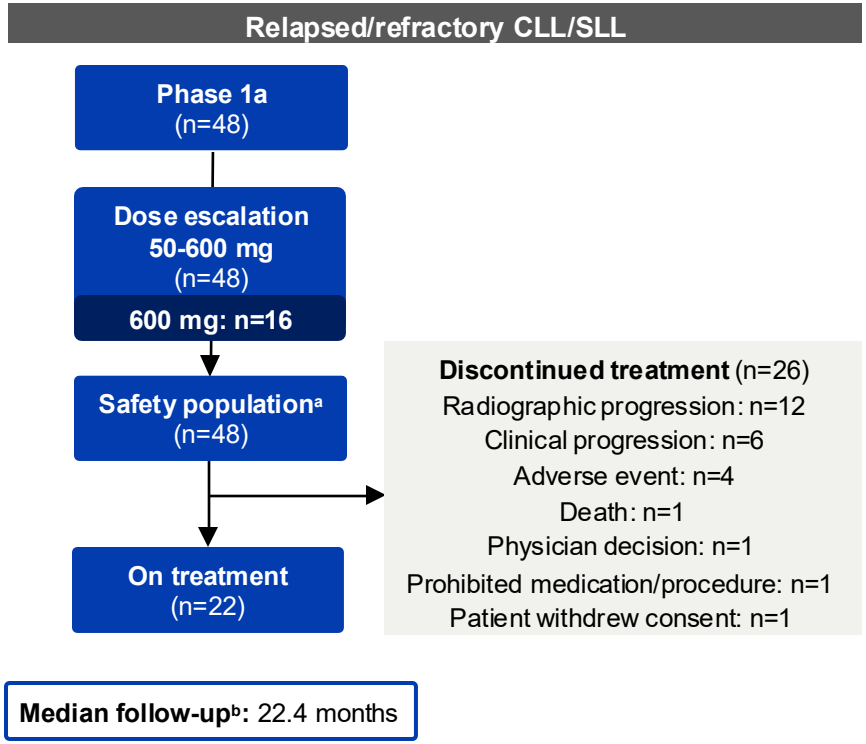
[1]St. James's Hospital, Leeds, UK; [2]University of Cincinnati, Cincinnati, OH, USA; [3]Medical University of Silesia, Katowice, Poland; [4]AidPort Hospital, Skórzewo (Poznan), Poland; [5]City of Hope National Medical Center, Duarte, CA, USA; [6]Medical College of Wisconsin, Milwaukee, WI, USA; [7]University Hospital Southampton NHS Trust, Southampton, UK; [8]Sylvester Comprehensive Cancer Center, University of Miami Miller School of Medicine, Miami, FL, USA; [9]Guy's and St Thomas' NHS Foundation Trust, London, UK; [10]Sarah Cannon Research Institute, London, UK; [11]Fred Hutchinson Cancer Center, Seattle, WA, USA; [12]Oxford Cancer and Haematology Centre, Churchill Hospital, Oxford, UK; [13]The Christie Hospital NHS Foundation Trust, Manchester, UK; [14]Emory University Winship Cancer Institute, Atlanta, GA, USA; [15]MD Anderson Cancer Center, Houston, TX, USA; [16]Duke Cancer Institute, Durham, NC, USA; [17]Feinberg School of Medicine, Northwestern University, Chicago, IL, USA; [18]Cleveland Clinic Foundation, Cleveland, OH, USA; [19]Medical University of Lublin, Lublin, Poland; [20]Nurix Therapeutics, Inc., Brisbane, CA, USA; [21]Maria Sklodowska-Curie National Research Institute of Oncology, Krakow, Poland

Munir T, et al. Presented at: EHA2026 Meeting; 2026.

LL&M great debates

Patient Disposition and Baseline Characteristics (Phase 1a)

Patients with relapsed/refractory CLL/SLL



Median follow-up[b]: 22.4 months

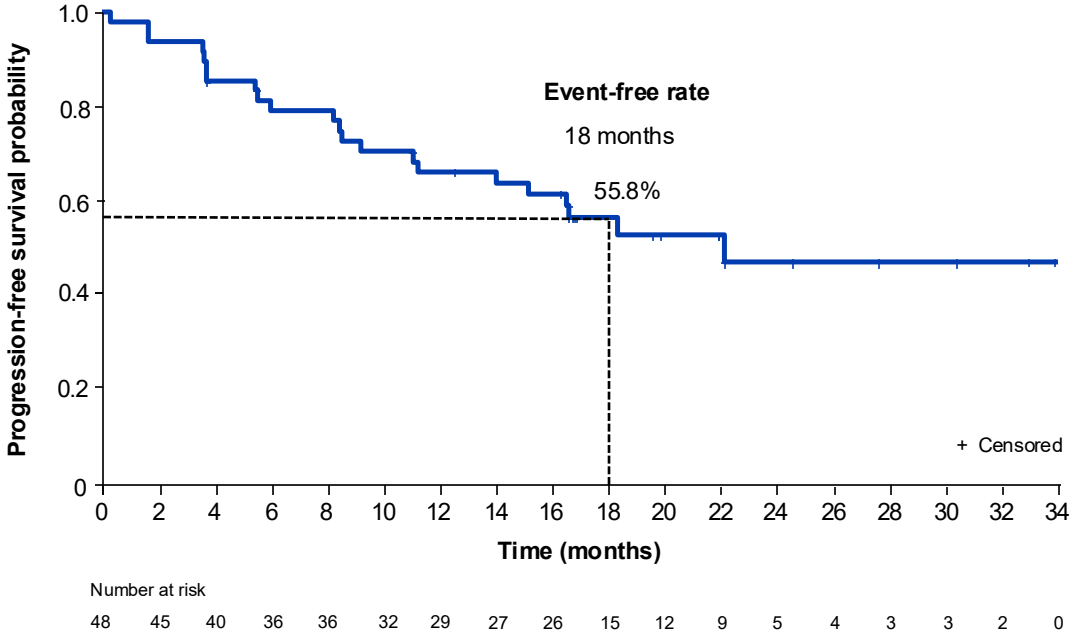
Characteristics	Relapsed/refractory CLL/SLL Phase 1a: Dose escalation 50–600 mg* (n=48)
Median age, years (range)	68.5 (35.0-88.0)
Male, n (%)	32 (66.7)
White, n (%)	42 (87.5)
ECOG PS 0/1, n (%)	19 (39.6)/29 (60.4)
CNS involvement, n (%)	5 (10.4)
Median prior lines of therapy, n (range)	4.0 (2-12)
Previous treatments,[c] n (%)	
BTKi	47 (97.9)
cBTKi / ncBTKi	47 (97.9) / 13 (27.1)
BCL2i	40 (83.3)
BTKi and BCL2i	39 (81.3)
cBTKi, ncBTKi and BCL2i	11 (22.9)
Chemo/chemo-immunotherapies	35 (72.9)
Mutation status,[d] n (%)	(n=47)
BTK	18 (38.3)
TP53	21 (44.7)
PLCG2	7 (14.9)
BCL2	6 (12.8)
IGHV (unmutated)	29 (85.3), n=34

Data cutoff: Jan 1, 2026
***Starting dose.**
[a]Safety and efficacy populations are identical. [b]Time from treatment start to data cutoff. [c]Patients could have received multiple prior treatments. [d]Patients could have multiple mutations (which are reported at VAF >5%).
Munir T, et al. Presented at: EHA2026 Meeting; 2026.

LL&M great debates

Bexobrutideg PFS and ORR in Relapsed/Refractory Patients (Phase 1a)

PFS remains durable with a median of 22.1 months



Relapsed/refractory CLL/SLL	
PFS summary	
	n=48
Median PFS[a], months (95% CI)	**22.1** (14.0-NR)
ORR summary	
	n=47[b]
ORR, % (95% CI)[c]	**83.0** (69.2-92.4)
CR	2 (4.3)
nPR	1 (2.1)
PR	36 (76.6)
SD	6 (12.8)
PD	2 (4.3)
Median follow-up,[d] months (range)	22.4 (16.9-35.7)

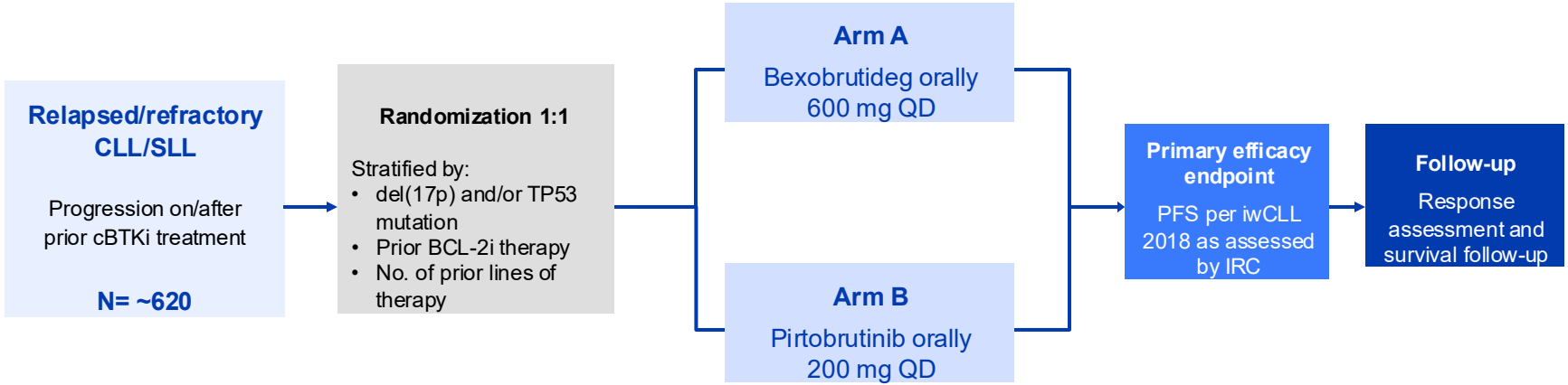
Data cutoff: Jan 1, 2026.

[a]Median for PFS by Kaplan-Meier method. [b]Excludes 1 patient who was not evaluable for response. [c]Objective response rate includes CR + nPR + PR + PR-L. [d]Time from treatment start to data cutoff.

Munir T, et al. Presented at: EHA2026 Meeting; 2026.

LL&M great debates

NX-5948-306 Phase 3



Munir T, et al. Presented at: EHA2026 Meeting; 2026.

LL&M great debates

Epcoritamab Monotherapy in Patients (Pts) with Relapsed or Refractory (R/R) Chronic Lymphocytic Leukemia (CLL): Results from CLL Expansion and Optimization Cohorts of EPCORE CLL-1

Alexey Danilov, MD, PhD,[1] Bita Fakhri, MD, MPH,[2] Farrukh Awan, MD,[3] Hans Herluf Bentzen, MD,[4] Herbert Eradat, MD,[5] Carsten Utoft Niemann, MD, PhD,[6] Fritz Offner, MD, PhD,[7] Christian Bjørn Poulsen, MD,[8] Thor Høyer, MD,[9] Mar Bellido, MD, PhD,[10] Damien Roos-Weil, MD, PhD,[11] Alessandra Ferrajoli, MD,[12] Meghan C. Thompson, MD,[13] Jacob Haaber Christensen, MD, PhD,[14] Ann Janssens, MD, PhD,[15] Tamar Tadmor, MD,[16] Mazyar Shadman, MD, MPH,[17] Pegah Jafarinasabian, MD, PhD,[18] Jimin Zhang, PhD,[19] Marcia Rios, MBA,[19] Alexandra Kuznetsova, PhD,[20] Rebecca Valentin, MD, PhD,[20] Arnon P. Kater, MD, PhD[21]

[1]City of Hope, Duarte, CA, USA; [2]Stanford Cancer Institute, Stanford University, Palo Alto, CA, USA; [3]The University of Texas Southwestern Medical Center, Dallas, TX, USA; [4]Aarhus University Hospital, Aarhus, Denmark; [5]David Geffen School of Medicine at UCLA, Los Angeles, CA, USA; [6]Rigshospitalet, Copenhagen University Hospital, Copenhagen, Denmark; [7]Universitair Ziekenhuis Gent, Ghent, Belgium; [8]Zealand University Hospital, Roskilde, Denmark; [9]Aalborg University Hospital, Aalborg, Denmark; [10]University Medical Center Groningen and University of Groningen, Groningen, Netherlands; [11]Sorbonne Université, Department of Clinical Haematology, APHP, Hôpital Pitié-Salpêtrière, Paris, France; [12]Department of Leukemia, The University of Texas MD Anderson Cancer Center, Houston, TX, USA; [13]Memorial Sloan Kettering Cancer Center, New York, NY, USA; [14]Odense University Hospital, Odense, Denmark; [15]University Hospitals Leuven, Leuven, Belgium; [16]Hematology Unit, Bnai Zion Medical Center, and The Ruth and Bruce Rappaport Faculty of Medicine, Technion, Haifa, Israel; [17]Fred Hutchinson Cancer Center, Seattle, WA, USA; [18]AbbVie, North Chicago, IL, USA; [19]Genmab, Plainsboro, NJ, USA; [20]Genmab, Copenhagen, Denmark; [21]Amsterdam UMC, Cancer Center Amsterdam, University of Amsterdam, Amsterdam, Netherlands

Danilov A, et al. Presented at: 66th ASH Annual Meeting; 2024.

LL&M great debates

Deep Responses across Subgroups

Response, n (%)	EXP mFU: 22.8 months					C1 OPT mFU: 2.9 months
	Full Analysis Set N=23	Response Evaluable n=21	*TP53* Aberration n=15	*IGHV* Unmutated n=16	Double Exposed[a] n=19	Response Evaluable n=10
Overall response[b]	**14 (61)**	**14 (67)**	**10 (67)**	**10 (63)**	**10 (53)**	**6 (60)**
Complete response	9 (39)	9 (43)	5 (33)	7 (44)	7 (37)	1 (10)
Partial response	5 (22)	5 (24)	5 (33)	3 (19)	3 (16)	5 (50)
Stable disease	4 (17)	4 (19)	2 (13)	3 (19)	4 (21)	2 (20)
Progressive disease	1 (4)	1 (5)	1 (7)	0	1 (5)	1 (10)

- With limited follow-up, the C1 OPT regimen does not appear to affect epcoritamab efficacy
- uMRD4 in PBMCs was observed in most responders, including all patients with CR who were tested for MRD

EXP MRD negativity, n/n (%)[c]	uMRD4	uMRD6[d]
Overall response[b]	9/12 (75)	8/12 (67)
Complete response	7/7 (100)	6/7 (86)
Partial response	2/5 (40)	2/5 (40)
Full analysis set	9/23 (39)	8/23 (35)

Four patients (TP53 aberration, n=2; IGHV unmutated, n=3; double exposed, n=4) in EXP and 1 in C1 OPT shown above were not evaluable or had no assessment, including 3 in EXP (TP53 aberration, n=2; IGHV unmutated, n=2; double exposed, n=3) and 1 in C1 OPT who died without post-baseline assessment. [a]Patients previously treated with both a BTK inhibitor and a BCL-2 inhibitor. [b]Response assessment according to iwCLL criteria. [c]Patients evaluated for MRD had at least 1 on-treatment MRD result and were not MRD-negative at baseline. MRD was only evaluated in patients with CR or PR. [d]Two of 3 evaluated patients had uMRD6 in bone marrow at or shortly after the first CR assessment.
mFU = median follow-up; EXP = expansion; OPT = optimization
Danilov A, et al. Presented at: 66th ASH Annual Meeting; 2024.

LL&M great debates

Key Learning Points

R/R CLL

- Acalabrutinib demonstrated noninferior progression-free survival with an improved safety profile compared with ibrutinib
- Zanubrutinib demonstrated improved PFS and safety profile compared to ibrutinib
- Ibrutinib added to CD19 CAR T improved outcomes
- BTK degraders and CD20 bispecifics—promising data in R/R CLL
- Venetoclax-based therapy following progression on a covalent BTK inhibitor in CLL
- Other agents in development
  - Novel BCL2 inhibitors (sonrotoclax, lisaftoclax)
  - Novel noncovalent BTKi (LP-168, AS-1763)
- Move into earlier lines of Rx, including first-line CLL

Thank You!

njain@mdanderson.org

@NitinJainMD

LL&M great debates