Optimizing Treatment for Patients with Relapsed/Refractory Chronic Lymphocytic Leukemia

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Disclosures

Consulting Agreements	AbbVie Inc, Adaptive Biotechnologies Corporation, Ascentage Pharma, AstraZeneca Pharmaceuticals LP, BeOne, Bristol Myers Squibb, Galapagos NV, Genentech, a member of the Roche Group, Genmab US Inc, Janssen Biotech Inc, Lilly, MEI Pharma Inc, Merck, Nuvalent, Schrödinger, Takeda Pharmaceuticals USA Inc
Contracted Research	Ascentage Pharma, AstraZeneca Pharmaceuticals LP, MEI Pharma Inc, Novartis
Nonrelevant Financial Relationships	UpToDate

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TO PRACTICE

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Miami, Florida

Key Datasets

- Thompson PA, Tam CS. **Pirtobrutinib**: A new hope for patients with **BTK inhibitor-refractory** lymphoproliferative disorders. *Blood* 2023 June 29;141(26):3137-42.
- Shah NN et al. **Pirtobrutinib monotherapy** in Bruton tyrosine kinase inhibitor-intolerant patients with B-cell malignancies: Results of the **phase I/II BRUIN trial**. *Haematologica* 2025 January 1;110(1):92-102.
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- Woyach J et al. **Pirtobrutinib vs ibrutinib in treatment-naïve and relapsed/refractory CLL/SLL**: Results from the first randomized **phase III study** comparing a non-covalent and covalent BTK inhibitor. ASH 2025;Abstract 683.
- Jurczak W et al. **Pirtobrutinib vs bendamustine plus rituximab (BR)** in patients with CLL/SLL: First results from a randomized **phase III study** examining a non-covalent BTK inhibitor in **untreated patients**. ASH 2025;Abstract LBA3.

RTP RESEARCH TO PRACTICE

Key Datasets

- Siddiqi T et al. **Lisocabtagene maraleucel** (liso-cel) in R/R CLL/SLL: **24-month median follow-up** of **TRANSCEND CLL 004**. ASH 2023;Abstract 330.
- Wierda WG et al. **Lisocabtagene maraleucel** (liso-cel) **combined with ibrutinib** (ibr) for patients (pts) with relapsed or refractory (R/R) chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL): **Primary results** from the open-label, **phase 1/2 Transcend CLL 004 study**. ASH 2024;Abstract 887.

Key Datasets

- Cassanello G et al**. Trial watch: Bispecific antibodies** for the treatment of relapsed or refractory large B-cell lymphoma. *Oncoimmunology* 2024 March 3;13(1):2321648.
- Danilov A et al. **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**. ASH 2024;Abstract 883.
- Ahn I et al. **Updated efficacy and safety results** of the Bruton tyrosine kinase **(BTK) degrader BGB-16673** in patients with relapsed/refractory chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) from the ongoing **phase 1 CaDAnCe-101 study**. ASH 2025;Abstract 85.
- Shah NN et al. **Efficacy and safety** of the Bruton's tyrosine kinase **(BTK) degrader NX-5948** in patients with relapsed/refractory (R/R) chronic lymphocytic leukemia (CLL): Updated results from an **ongoing phase 1a/b study**. ASH 2024;Abstract 884.
- Woyach JA et al. **First-in-human study** of the **reversible BTK inhibitor nemtabrutinib** in patients with relapsed/refractory chronic lymphocytic leukemia and B-cell non-Hodgkin lymphoma. *Cancer Discov* 2024;14(1):66-75.

RTP RESEARCH TO PRACTICE

Management of Double-Refractory CLL

Introduction: Sequencing of Treatment for CLL

Module 1: Clinician Survey Results

Module 2: Noncovalent BTK Inhibitor Pirtobrutinib

Module 3: Clinician Survey Results

Module 4: CAR T-Cell Therapy

Module 5: Clinician Survey Results

Module 6: Bispecific Antibodies and Promising Investigational Strategies

Management of Double-Refractory CLL

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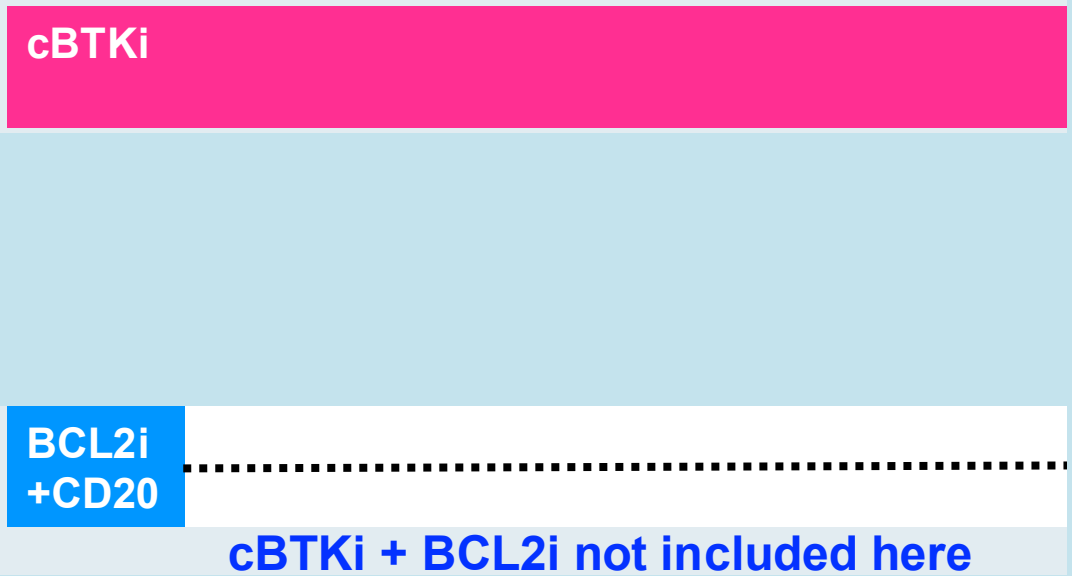
Targeted Therapy Sequencing for CLL



Factors affecting timelines:

- Age
- Del(17p) / *TP53*-m
- IGHV-MS / Del(11q)
- Complex karyotype

1	2	3	4	5	6	7	8	9	10	11	12	13	14

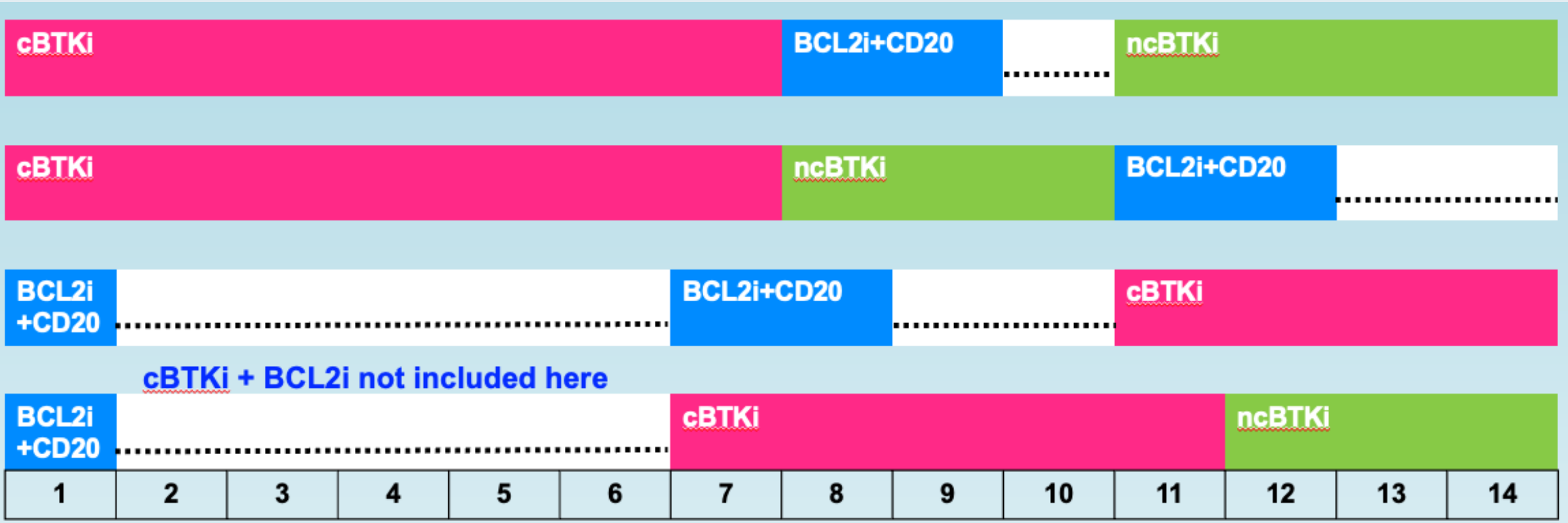
Years

Double Exposed *vs.* Double Refractory:

- Exposed ≠ Refractory
- Refractory=progression on treatment

Courtesy of William G Wierda, MD, PhD

Targeted Therapy Sequencing for CLL



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Courtesy of William G Wierda, MD, PhD

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RTP RESEARCH TO PRACTICE

75-year-old patient with relapsed CLL, no del(17p) or TP53 mutation: Covalent BTKi 6 years → PD → venetoclax/anti-CD20 antibody 2 years → 3 years observation → PD

 Dr Coombs	Venetoclax/anti-CD20 antibody
 Dr Davids	Venetoclax/anti-CD20 antibody
 Dr Fakhri	Pirtobrutinib
 Dr Lamanna	Venetoclax/anti-CD20 antibody
 Dr Sharman	Pirtobrutinib bridge to CAR-T
 Dr Wierda	Pirtobrutinib
 Dr Woyach	Venetoclax/anti-CD20 antibody

BTKi = Bruton tyrosine kinase inhibitor; PD = disease progression; CAR-T = chimeric antigen receptor T-cell therapy

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In general, what is the minimum duration of remission after second-line venetoclax/ anti-CD20 antibody before you would consider retreatment as third-line therapy?

 Dr Coombs	12 months
 Dr Davids	12 months
 Dr Fakhri	24 months
 Dr Lamanna	>24 months
 Dr Sharman	24-36 months
 Dr Wierda	24 months
 Dr Woyach	36 months

RTP RESEARCH TO PRACTICE

75-year-old patient with relapsed CLL, no del(17p) or TP53 mutation:
Covalent BTKi 6 years → PD → venetoclax/anti-CD20 antibody 2 years → 1 year observation → PD

 Dr Coombs	Pirtobrutinib
 Dr Davids	Pirtobrutinib
 Dr Fakhri	Pirtobrutinib
 Dr Lamanna	Pirtobrutinib
 Dr Sharman	Pirtobrutinib bridge to CAR-T
 Dr Wierda	Pirtobrutinib bridge to CAR-T
 Dr Woyach	Pirtobrutinib

75-year-old patient with relapsed CLL, no del(17p) or TP53 mutation:
Venetoclax/anti-CD20 antibody 1 year → 2 years observation → PD → covalent BTKi 4 years → PD

 Dr Coombs	Pirtobrutinib
 Dr Davids	Venetoclax/anti-CD20 antibody
 Dr Fakhri	Pirtobrutinib or rechallenge with venetoclax
 Dr Lamanna	Pirtobrutinib
 Dr Sharman	Venetoclax/anti-CD20 antibody
 Dr Wierda	Pirtobrutinib
 Dr Woyach	Pirtobrutinib

RTP RESEARCH TO PRACTICE

75-year-old patient with relapsed CLL, no del(17p) or TP53 mutation:
Venetoclax/anti-CD20 antibody 1 year → 4 years observation → PD → covalent BTKi 4 years → PD

 Dr Coombs	Venetoclax/anti-CD20 antibody
 Dr Davids	Venetoclax/anti-CD20 antibody
 Dr Fakhri	Pirtobrutinib or rechallenge with venetoclax
 Dr Lamanna	Venetoclax/anti-CD20 antibody
 Dr Sharman	Venetoclax/anti-CD20 antibody
 Dr Wierda	Pirtobrutinib
 Dr Woyach	Pirtobrutinib

RTP RESEARCH TO PRACTICE

75-year-old patient with relapsed CLL, no del(17p) or TP53 mutation:
Covalent BTKi 2 years → responds but stops due to subdural hematoma → 3 years observation → PD → venetoclax/anti-CD20 antibody 2 years → 6 months observation → PD

 Dr Coombs	Pirtobrutinib
 Dr Davids	Venetoclax monotherapy
 Dr Fakhri	CAR T-cell therapy or epcoritamab on clinical trial
 Dr Lamanna	Venetoclax monotherapy
 Dr Sharman	Pirtobrutinib or CAR-T
 Dr Wierda	Pirtobrutinib
 Dr Woyach	Pirtobrutinib or CAR-T

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Key Differences Between Available Covalent and Reversible Bruton Tyrosine Kinase (BTK) Inhibitors

	Ibrutinib	Acalabrutinib	Zanubrutinib	Pirtobrutinib
BTK binding	Covalent C481	Covalent C481	Covalent C481	Reversible ATP pocket Distant from C481
Half-life	6 hours	1 hour	4 hours	20 hours >90% BTK inhibition
BTK Y223 autophosphorylation	Inhibited	Inhibited	Inhibited	Inhibited
BTK Y551 phosphorylation	No effect	No effect	No effect	Inhibited (maintenance of closed conformation)
BTK C481S mutation	Common	Reported	Reported	Not described Effective against C481S
Kinase-dead mutations	Uncommon and restricted to C481* (active against HCK)	Not reported to date	Reported: L528W > C481Y	Reported: L528W > V416L, A428D, C481R, M477I, and M437R
T474I/T474L gatekeeper mutation	Uncommon*; active against T474I and T474L	Reported	Not reported to date	Reported
Off-target hits†	BLK BMX BRK EGFR HER2 HER4 ITK JAK3 RLK TEC	HER4	BLK BMX BRK EGFR HER4 RLK	HER4 BRK

Thompson PA, Tam CS. *Blood* 2023;141(26):3137-42.

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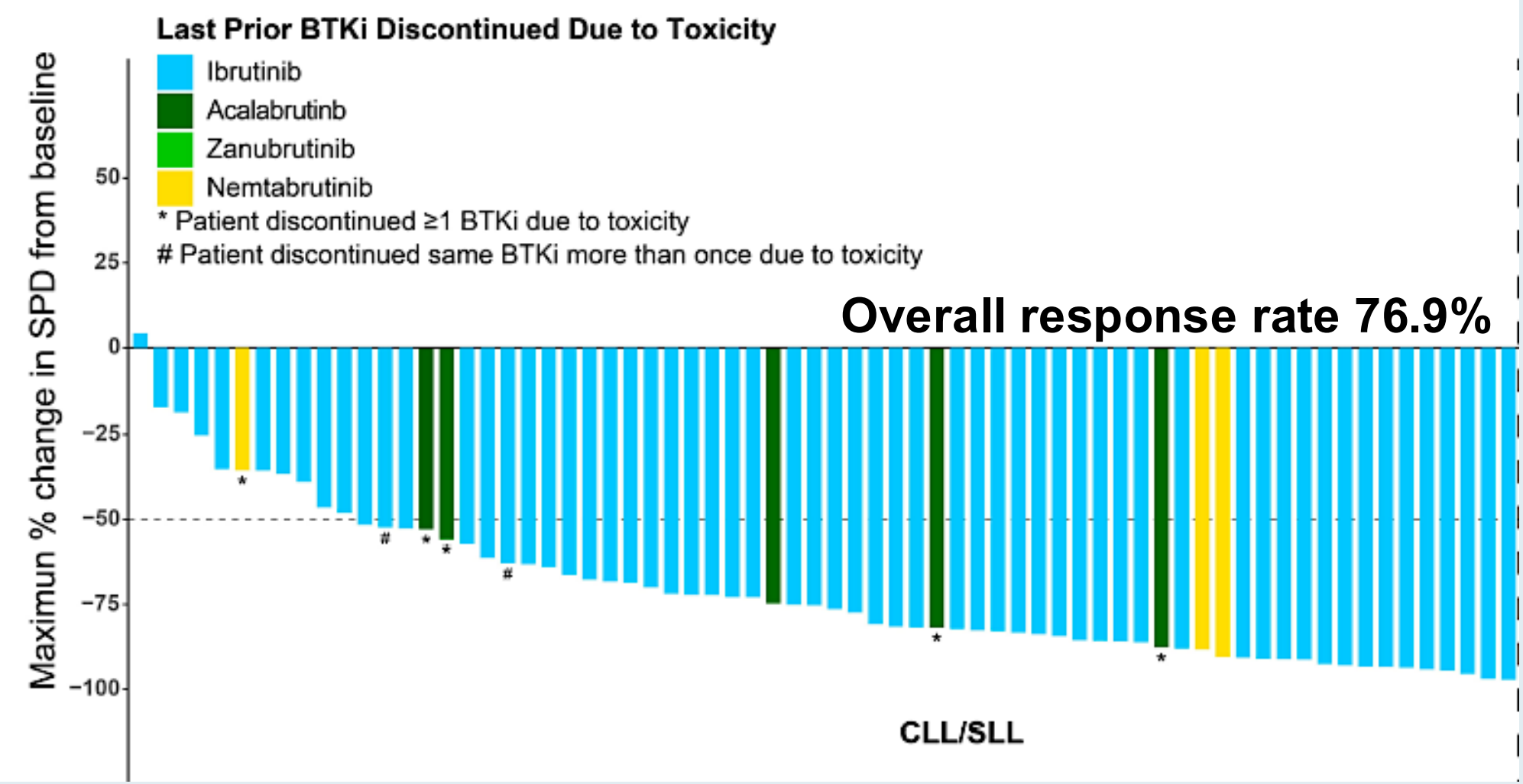
haematologica
Journal of the Ferrata Storti Foundation

Pirtobrutinib monotherapy in Bruton tyrosine kinase inhibitor-intolerant patients with B-cell malignancies: results of the phase I/II BRUIN trial

by Nirav N. Shah, Michael Wang, Lindsey E. Roeker, Krish Patel, Jennifer A. Woyach, William G. Wierda, Chaitra S. Ujjani, Toby A. Eyre, Pier Luigi Zinzani, Alvaro J. Alencar, Paolo Ghia, Nicole Lamanna, Marc S. Hoffmann, Manish R. Patel, Ian Flinn, James N. Gerson, Shuo Ma, Catherine C. Coombs, Chan Y. Cheah, Ewa Lech-Maranda, Bita Fakhri, Won Seog Kim, Minal A. Barve, Jonathon B. Cohen, Wojciech Jurczak, Talha Munir, Meghan C. Thompson, Donald E. Tsai, Katherine Bao, Nicholas A. Cangemi, Jennifer F. Kherani, Richard A. Walgren, Hongmei Han, Amy S. Ruppert, and Jennifer R. Brown

Haematologica **2025;110(1):92-102.**

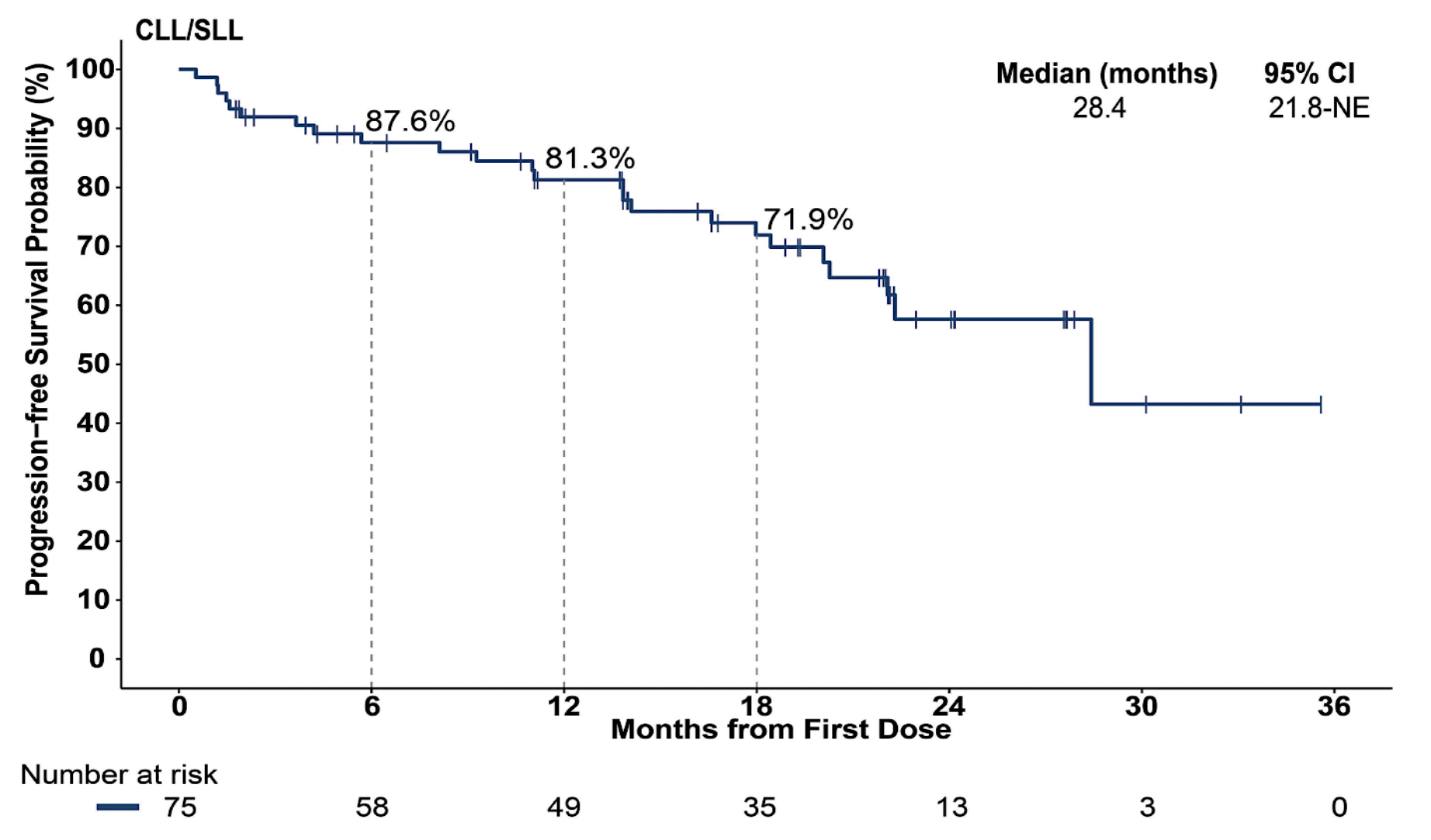
BRUIN: Pirtobrutinib Efficacy in Patients with CLL or SLL Who Received Prior BTK Inhibitor (BTKi) Treatment



SPD = sum of product diameters

Shah NN et al. *Haematologica* 2025;110(1):92-102.

BRUIN: Median Progression-Free Survival for Patients with CLL/SLL



Shah NN et al. *Haematologica* 2025;110(1):92-102.

BRUIN: Pirtobrutinib Safety Profile in the Overall Population

	BTKi-intolerant (n=127)			
	All cause AEs, %		Treatment-related AEs, %	
AE	**Any Grade**	**Grade ≥3**	**Any Grade**	**Grade ≥3**
Fatigue	39.4	3.9	9.4	1.6
Neutropenia[a]	37.0	31.5	21.3	17.3
Diarrhea	29.9	1.6	12.6	0.8
Contusion	29.1	0.0	22.0	0.0
Cough	26.8	0.0	4.7	0.0
Headache	25.2	0.8	7.1	0.8
COVID-19	22.8	4.7	0.0	0.0
Abdominal pain	22.0	2.4	4.7	0.8
Dyspnea	22.0	2.4	5.5	0.0
Nausea	20.5	0.0	4.7	0.0
AEs of Interest[b]	**Any Grade**	**Grade ≥3**	**Any Grade**	**Grade ≥3**
Infections[c]	68.5	24.4	14.2	5.5
Infections (excluding COVID-19)	59.8	17.3	14.2	5.5
Bruising[d]	36.2	0.0	26.8	0.0
Rash[e]	22.8	0.8	8.7	0.8
Arthralgia	21.3	0.8	4.7	0.0
Hemorrhage/hematoma[f]	14.2	3.1	4.7	0.8
Hypertension	7.9	0.8	3.1	0.0
Atrial fibrillation/flutter[g]	4.7	1.6	0.8	0.0

Shah NN et al. *Haematologica* 2025;110(1):92-102.

FDA Grants Traditional Approval to Pirtobrutinib for Chronic Lymphocytic Leukemia and Small Lymphocytic Lymphoma

Press Release: December 3, 2025

"... the Food and Drug Administration granted traditional approval to pirtobrutinib for adults with relapsed or refractory chronic lymphocytic leukemia or small lymphocytic lymphoma (CLL/SLL) who have previously been treated with a covalent BTK inhibitor.

Efficacy was evaluated in BRUIN-CLL-321 (NCT 04666038), a randomized, open-label, active-controlled trial. The trial randomized 238 patients who were previously treated for CLL/SLL, including a covalent BTK inhibitor. Patients previously treated with a non-covalent BTK inhibitor were not permitted. Patients were randomized (1:1) to receive either pirtobrutinib or investigator's choice of idelalisib plus a rituximab product (IR) or bendamustine plus a rituximab product (BR).

Median PFS was 11.2 months (95% CI: 9.5, 11.4) in the pirtobrutinib arm and 8.7 months (95% CI: 7.2, 10.2) in the investigator's choice of IR/BR arm (Hazard ratio 0.58 [95% CI: 0.38, 0.89]; p-value 0.0105). Of the 119 patients in the investigator's choice arm, 50 crossed over to receive pirtobrutinib therapy. At an updated analysis with a median follow-up time of 19.8 months, the HR for overall survival (OS) was 1.09 (95% CI: 0.68, 1.75)."

https://www.fda.gov/drugs/resources-information-approved-drugs/fda-grants-traditional-approval-pirtobrutinib-chronic-lymphocytic-leukemia-and-small-lymphocytic

RTP RESEARCH TO PRACTICE

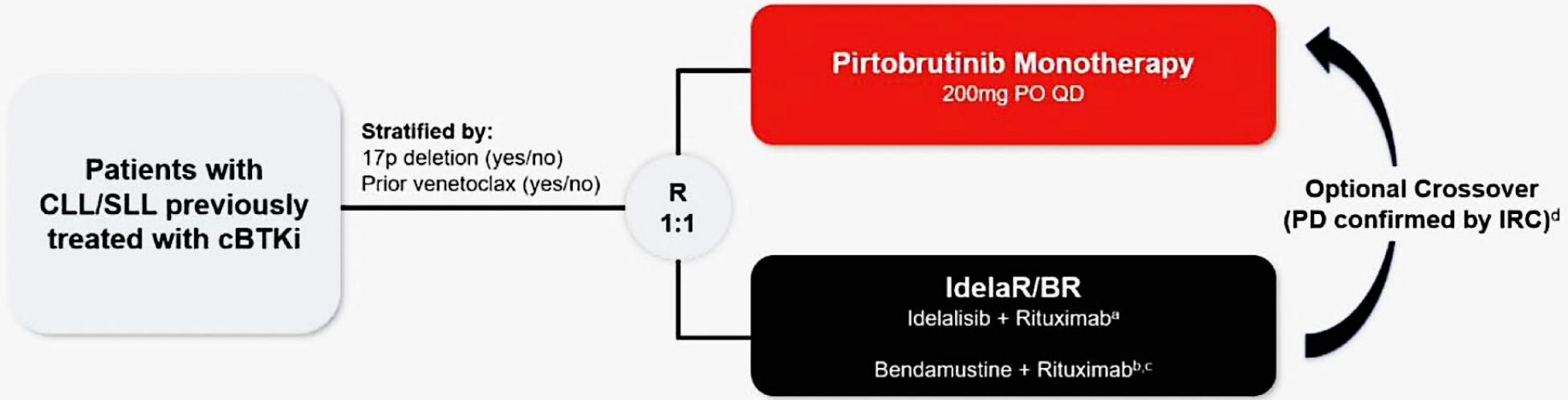
Original Reports | Hematologic Malignancy

Phase III Trial of Pirtobrutinib Versus Idelalisib/Rituximab or Bendamustine/Rituximab in Covalent Bruton Tyrosine Kinase Inhibitor–Pretreated Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma (BRUIN CLL-321)

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

J Clin Oncol 2025;43:2538-49.

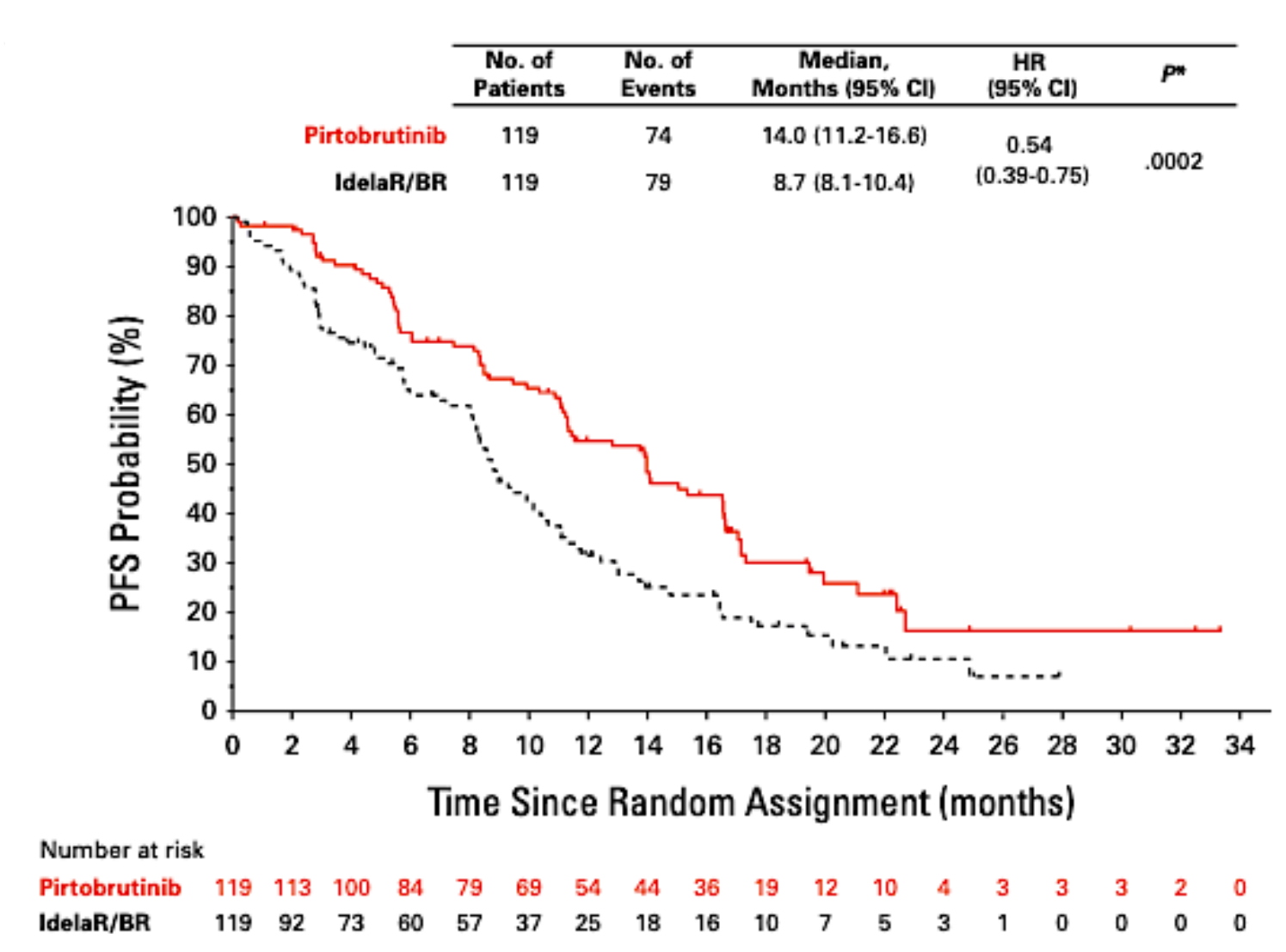
BRUIN CLL-321: A Phase III Trial of Pirtobrutinib Monotherapy for Relapsed/Refractory CLL



Treatment was given in 28-day cycles. PFS assessed based on iwCLL2018. [a]Idelalisib dosed at 150mg 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. Abbreviations: BID, twice daily; BR, bendamustine + rituximab; cBTKi, covalent Bruton tyrosine kinase inhibitor; CLL, chronic lymphocytic leukemia; ECOG PS, Eastern Cooperative Oncology Group Performance Status; IdelaR, idelalisib + rituximab; IRC, Independent Review Committee; iwCLL, international workshop on chronic lymphocytic leukemia; mg, milligram; PD, progressive disease; PFS, progression-free survival; PO, by mouth; QD, once daily; R, randomized; SLL, small lymphocytic lymphoma.

Sharman JP et al. ASH 2024;Abstract 886.

BRUIN CLL-321: IRC-Assessed Progression-Free Survival (PFS)

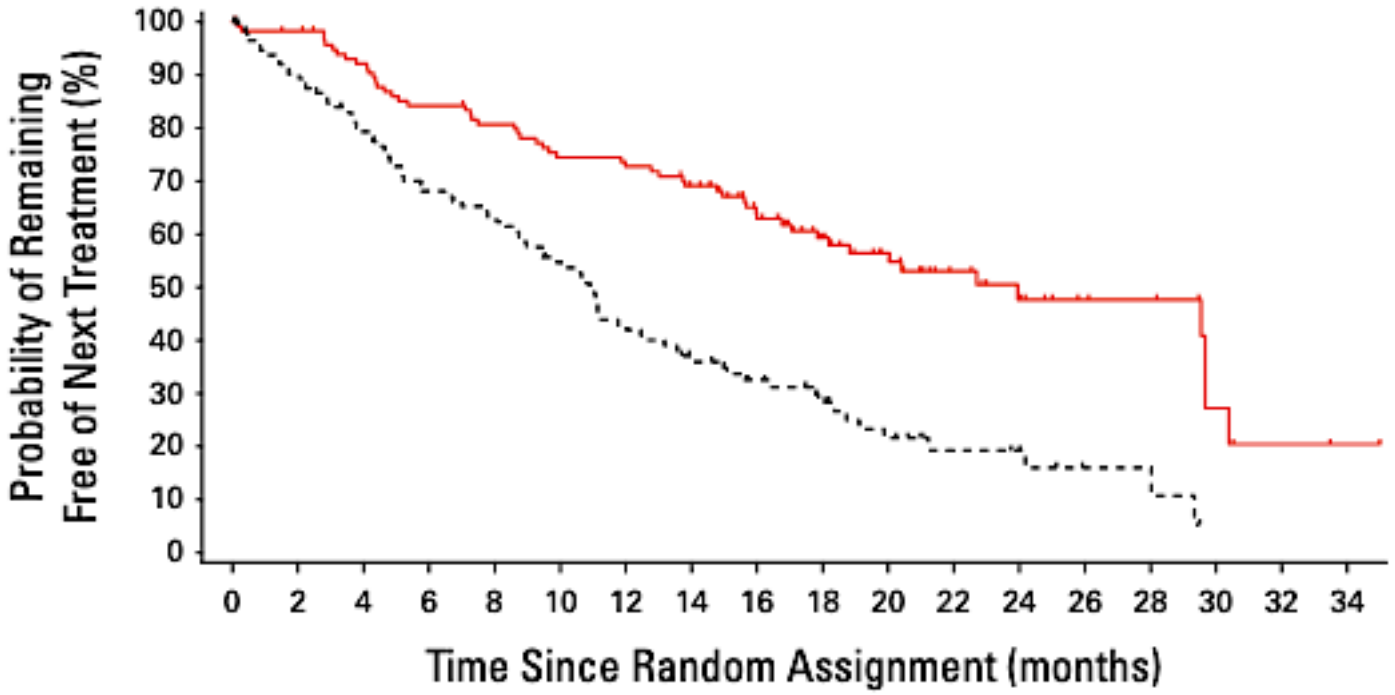


IRC = independent review committee

Sharman JP et al. *J Clin Oncol* 2025;43:2538-49.

BRUIN CLL-321: Time to Next Treatment

	No. of Patients	No. of Events	Median, Months (95% CI)	HR (95% CI)	P*
Pirtobrutinib	119	54	24.0 (17.8-29.7)	0.37 (0.25-0.52)	<.0001
IdelaR/BR	119	82	10.9 (8.7-12.5)		



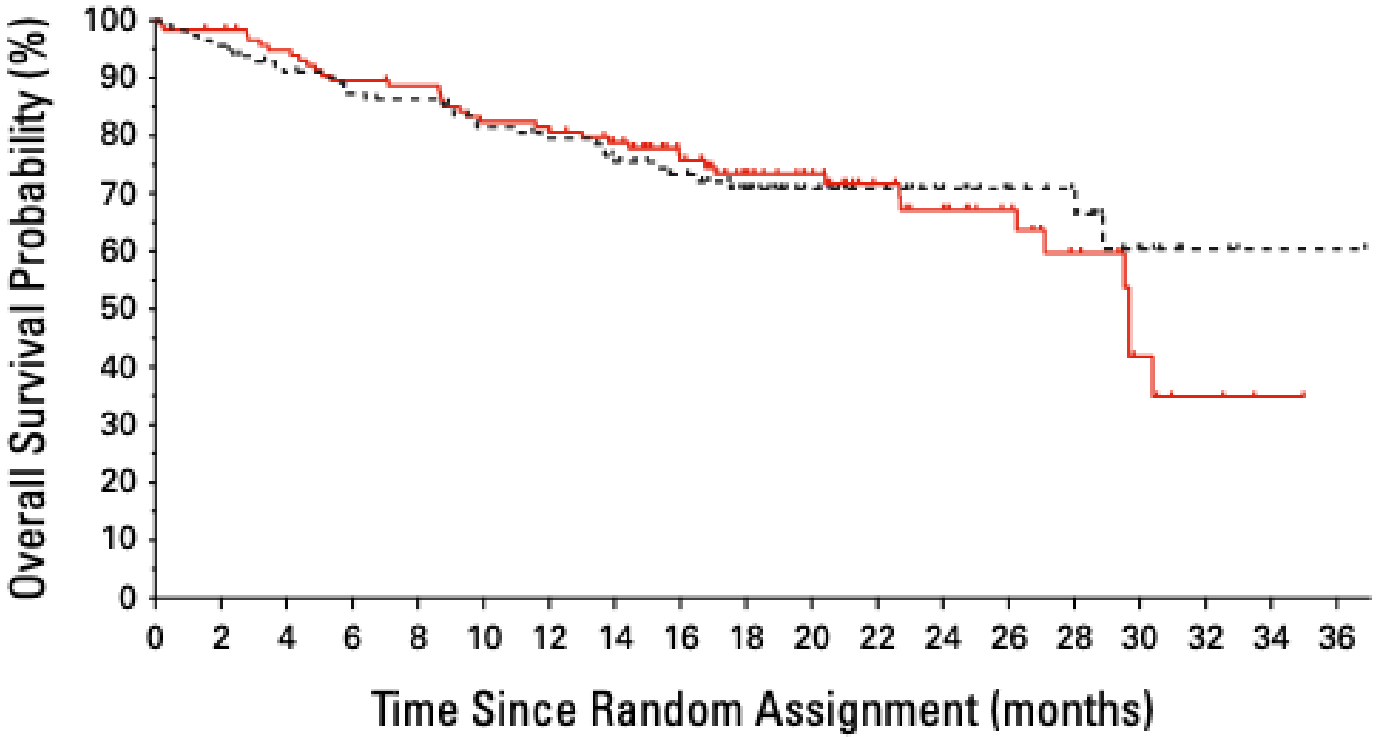
Number at risk:

Pirtobrutinib	119	114	105	96	91	84	81	74	60	45	34	23	17	10	9	4	2	1
IdelaR/BR	119	101	86	72	66	56	44	33	26	19	13	8	7	3	3	0	0	0

Sharman JP et al. *J Clin Oncol* 2025;43:2538-49.

BRUIN CLL-321: Overall Survival

	No. of Patients	No. of Events	Median, Months (95% CI)	HR (95% CI)	*P*
Pirtobrutinib	119	38	29.7 (27.1-NE)	1.09 (0.68-1.75)	.7202
IdelaR/BR	119	32	NR (28.9-NE)		



Number at risk

Pirtobrutinib	119	114	108	102	100	93	90	84	70	56	45	34	28	20	14	6	3	1	0
IdelaR/BR	119	107	99	93	91	83	80	71	64	54	40	32	27	21	16	8	3	1	1

Sharman JP et al. *J Clin Oncol* 2025;43:2538-49.

BRUIN CLL-321: Safety Profile

TEAE	Pirtobrutinib (n = 116), IR[a]	IdelaR or BR (n = 109), IR[a]	IRR (95% CI)[b]	P[c]
Infections[d]	94.5	125.5	0.75 (0.53 to 1.07)	.11
Pneumonia[e]	20.4	19.5	1.04 (0.54 to 2.03)	.90
COVID-19	11.1	33.4	0.33 (0.17 to 0.65)	.001
Anemia	18.5	30.3	0.61 (0.33 to 1.12)	.11
Neutropenia[f]	26.4	66.5	0.40 (0.25 to 0.64)	<.001
Cough	14.3	30.8	0.47 (0.25 to 0.88)	.02
Diarrhea	15.3	63.7	0.24 (0.14 to 0.42)	<.001
Pyrexia	11.1	52.4	0.21 (0.11 to 0.40)	<.001
Fatigue	9.5	34.2	0.28 (0.14 to 0.55)	<.001
Nausea	9.8	38.3	0.26 (0.13 to 0.51)	<.001
Vomiting	5.8	29.6	0.19 (0.08 to 0.44)	<.001
ALT increased	2.8	33.6	0.08 (0.03 to 0.25)	<.001
Weight decreased	2.8	28.5	0.10 (0.03 to 0.29)	<.001

TEAE = treatment-emergent adverse event; IR = incidence rate; IRR = IR ratio

Sharman JP et al. *J Clin Oncol* 2025;43:2538-49.

Incidence and Management Recommendations for Select BTK Inhibitor-Associated Cardiologic Adverse Events and Bleeding

Adverse event	BTK inhibitor	Incidence Any grade, Grade ≥3 %	Management
Atrial fibrillation	Ibrutinib	16, 2-5	**A**void stroke; anticoagulation **B**etter symptom control: rate vs rhythm **C**ardiovascular and other comorbidity management
	Acalabrutinib	6-9, 1-5	
	Zanubrutinib	3-6, ≤1	
	Pirtobrutinib	2.8, 1.2	
Hypertension	Ibrutinib	16-23, 8-12	Correct predisposing factors Antihypertensive therapy
	Acalabrutinib	7-9, 3-4	
	Zanubrutinib	14-17, 6-15	
	Pirtobrutinib	9.2, 2.3	
Bleeding	Ibrutinib	36-51, 3-4	Minor bleeding: no intervention Major bleeding: • Consider treatment discontinuation • Platelet transfusions regardless of platelet counts
	Acalabrutinib	36-51, 3	
	Zanubrutinib	36-45, 3	
	Pirtobrutinib	—	

Galitzia A et al. *Cancers* 2024;16:1996; Jurczak W et al. EHA 2023;Abstract P618.

Incidence and Management Recommendations for Select BTK Inhibitor-Associated Noncardiovascular Adverse Events

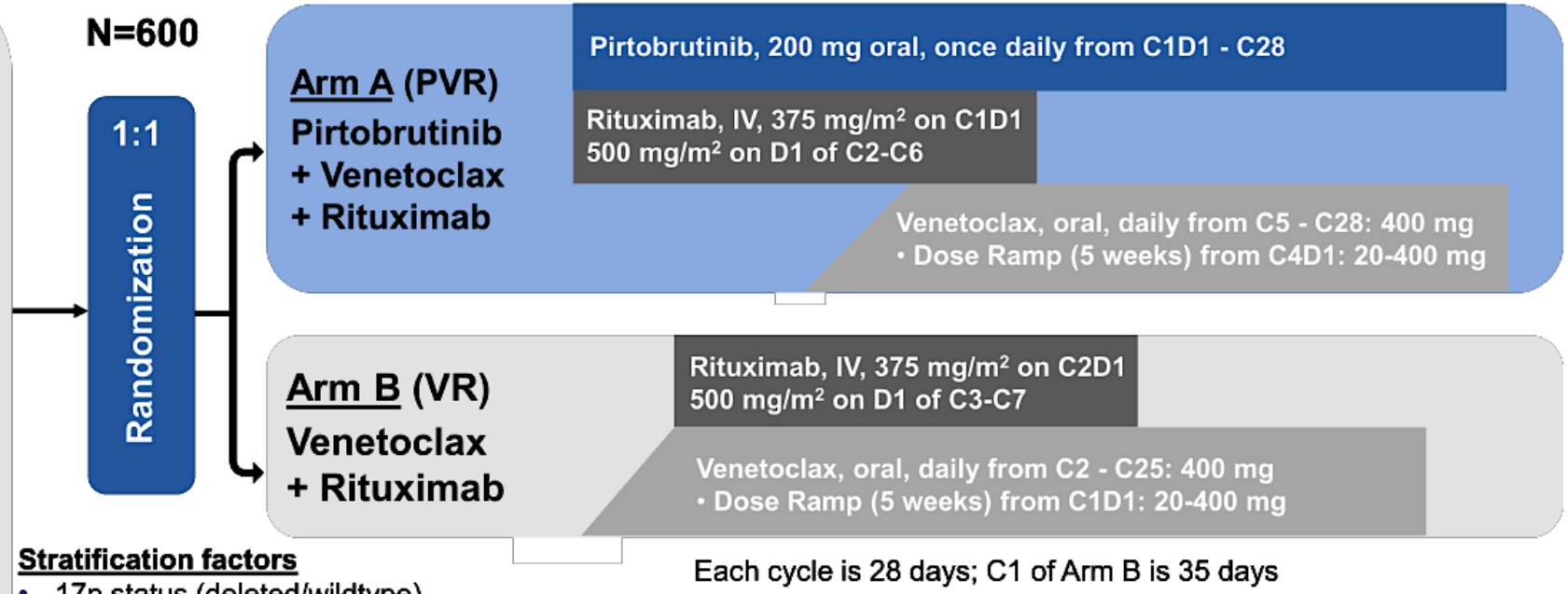
Adverse event	BTK inhibitor	Incidence Any grade, Grade ≥3 %	Management
Neutropenia	Ibrutinib	25-39, 13-31	Growth factor support
	Acalabrutinib	21-23, 13-19	
	Zanubrutinib	37-34, 15-19	
	Pirtobrutinib	25, 20.3	
Diarrhea	Ibrutinib	22-59, <1-4	Symptomatic treatments and dose adjustments Dietary modifications, hydration, anti-diarrheal medications Probiotics
	Acalabrutinib	18-39, 1-5	
	Zanubrutinib	14-18, <1-2	
	Pirtobrutinib	24.2, 0-9	
Headache	Ibrutinib	14-18, 1-2	Moderate dose of caffeine or acetaminophen
	Acalabrutinib	22-39, <1	
	Zanubrutinib	11-12, 0-1	
	Pirtobrutinib	13.1, 0.5	

Galitzia A et al. *Cancers* 2024;16:1996; Jurczak W et al. EHA 2023;Abstract P618.

BRUIN CLL-322: An Ongoing Phase III Trial of Pirtobrutinib and Venetoclax/Rituximab for Relapsed/Refractory CLL

Key Inclusion Criteria

- Confirmed CLL/SLL per iwCLL 2018[3]
- Previously treated CLL/SLL (including a covalent BTKi or covalent BTKi naïve [limited to 20% of total enrollment])
- Known 17p status
  - If 17p status is unknown, local or central FISH test results during screening can be used
- No prior venetoclax
- ≥18 years of age and ECOG 0-2



Stratification factors

- 17p status (deleted/wildtype)
- Prior experience of BTKi (discontinuation due to PD or other vs no prior BTKi)

Primary endpoint: Progression-free survival per iwCLL 2018 by IRC

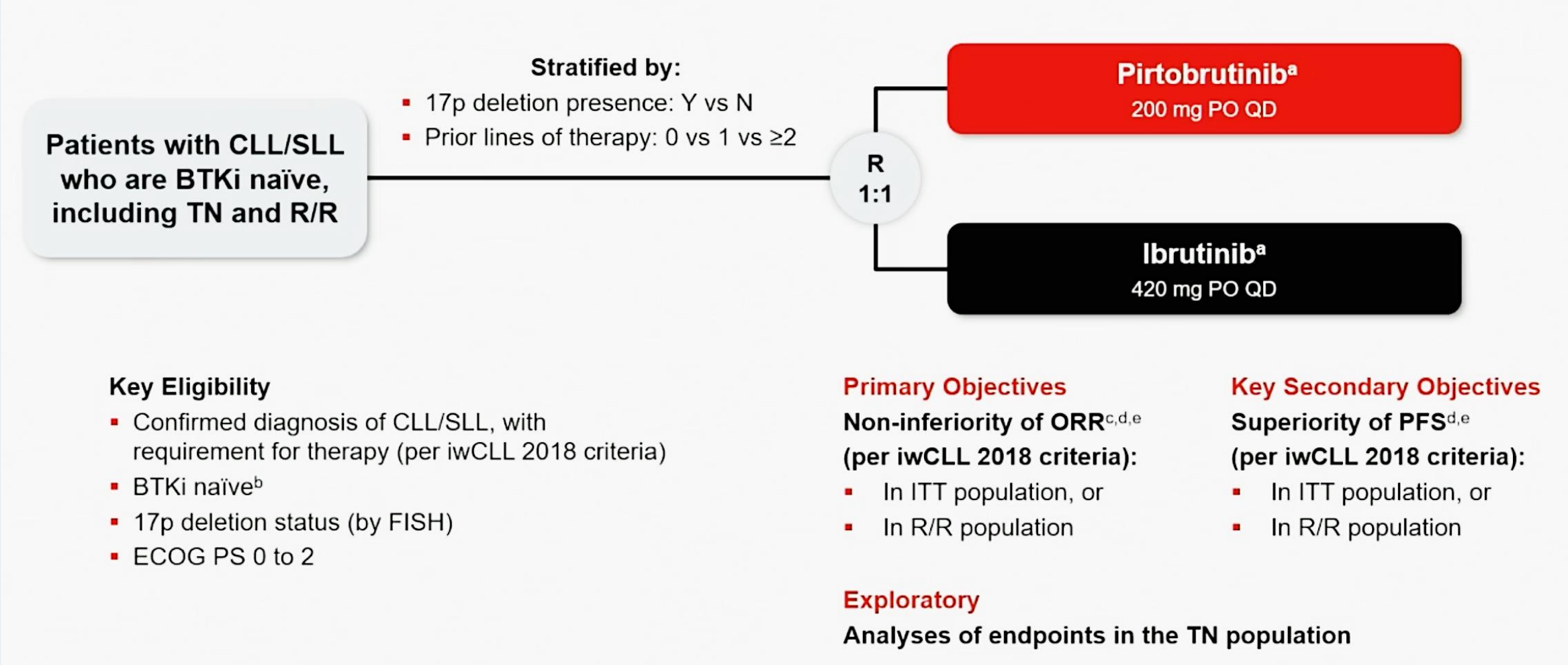
Eyre TA et al. ASCO 2023;Abstract TPS7583. Wierda WG et al. SOHO 2022;Abstract CLL-322.

Pirtobrutinib vs Ibrutinib in Treatment-Naïve and Relapsed/Refractory CLL/SLL: Results From the First Randomized Phase III Study Comparing a Non-covalent and Covalent BTK Inhibitor

Jennifer A. Woyach[1], Lugui Qiu[2], Sebastian Grosicki[3], Tomasz Wrobel[4], Marcelo Capra[5], Jaroslaw Czyz[6], Shuhua Yi[2], Ki Seong Eom[7], Anna Panovská[8], Wojciech Jurczak[9], Kamel Laribi[10], Lutz Jacobasch[11], Ross Baker[12], Richy Agajanian[13], Alejandro Berkovits[14], Muhit Özcan[15], Stéphane Lepretre[16], Catherine C. Coombs[17], Paula Cramer[18], Katharine L. Lewis[19,20], Marisa Hill[21], Katherine Bao[21], Yuanyuan Bian[21], Amy S. Ruppert[21], Ching Ching Leow[21], William G. Wierda[22]

ASH 2025;Abstract 683.

BRUIN CLL-314 Study Design



TN = treatment naïve

Woyach J et al. ASH 2025;Abstract 683; Woyach JA et al. *J Clin Oncol* 2025 December 7;[Online ahead of print].

BRUIN CLL-314: Response Data

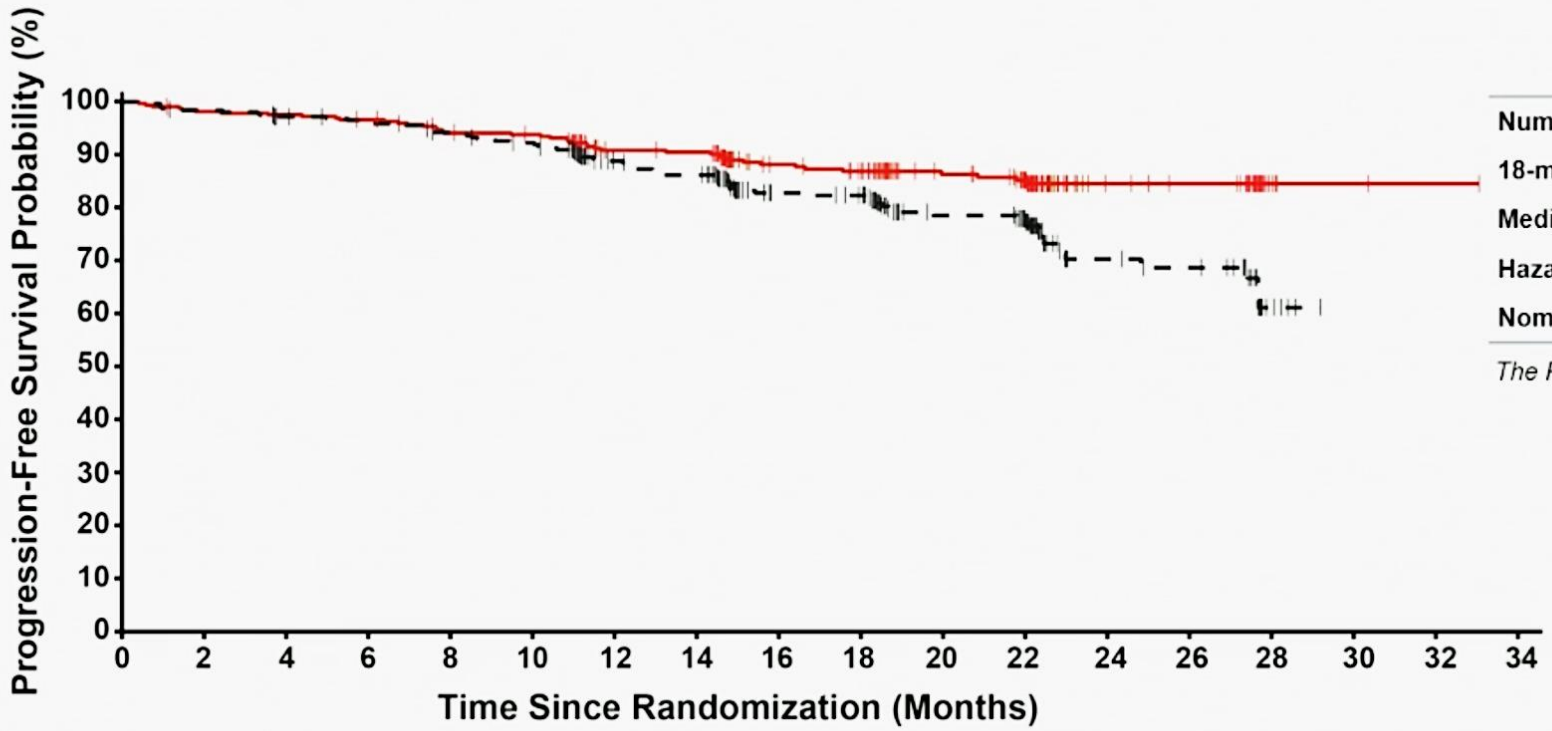
	ITT Population		TN Population		R/R Population	
	Pirtobrutinib n=331	Ibrutinib n=331	Pirtobrutinib n=112	Ibrutinib n=113	Pirtobrutinib n=219	Ibrutinib n=218
ORR[a] (PR or better)						
%	**87.0**	**78.5**	**92.9**	**85.8**	**84.0**	**74.8**
95% CI[b]	82.90, 90.44	73.73, 82.85	86.41, 96.87	78.03, 91.68	78.48, 88.61	68.46, 80.39
Nominal p-value[c]	0.0035		0.0886		0.0175	
ORR[a] ratio						
ORR ratio (95% CI)	1.1080 (1.034, 1.187)		1.0797 (0.989, 1.179)		1.1233 (1.020, 1.237)	
p-value for NI[d]	<0.0001		-		<0.0001	
Best Overall Response[e], %						
CR or CRi	4.8	2.4	7.1	3.5	3.7	1.8
PR or nPR	82.2	76.1	85.7	82.3	80.4	72.9
PR-L	2.4	3.9	0.9	2.7	3.2	4.6
SD	5.4	10.9	2.7	4.4	6.8	14.2
PD	1.5	1.2	0	0	2.3	1.8
ORR including PR-L						
%	89.4	82.5	93.8	88.5	87.2	79.4
95% CI[b]	85.60, 92.52	77.95, 86.42	87.55, 97.45	81.13, 93.73	82.05, 91.33	73.37, 84.53
Nominal p-value[c]	0.0093		0.1692		0.0286	

ORR results presented are IRC-assessed

ORR = overall response rate; NI = noninferiority; PR-L = partial remission with lymphocytosis

Woyach J et al. ASH 2025;Abstract 683; Woyach JA et al. *J Clin Oncol* 2025 December 7;[Online ahead of print].

BRUIN CLL-314: PFS in ITT Population



Number at risk

Pirtobrutinib	331	319	315	311	301	298	257	255	205	198	154	140	48	45	7	3	1	0
Ibrutinib	331	310	303	297	288	280	235	227	177	173	129	118	44	41	6	0	0	0

	Pirtobrutinib (n=331)	Ibrutinib (n=331)
Number of events, n (%)	43 (13.0)	69 (20.8)
18-month PFS rate (95% CI)	**86.9** (82.4, 90.3)	**82.3** (77.3, 86.3)
Median follow-up, mo	22.0	19.7
Hazard ratio (95% CI)	**0.569 (0.388, 0.834)**	
Nominal p-value[a]	0.0034	

The PFS results presented are INV-assessed

Pirtobrutinib reduced the risk of progression or death by 43%, with ibrutinib outcomes consistent with historical data

ITT = intent to treat

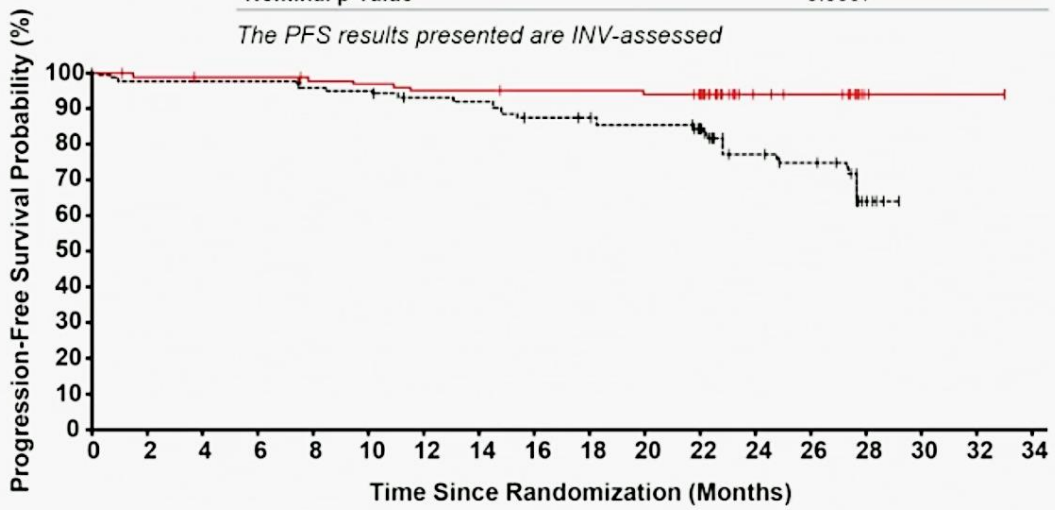
Woyach J et al. ASH 2025;Abstract 683; Woyach JA et al. *J Clin Oncol* 2025 December 7;[Online ahead of print].

BRUIN CLL-314: PFS by Prior Treatment Status

TN population

	Pirtobrutinib (n=112)	Ibrutinib (n=113)
Number of events, n (%)	6 (5.4)	24 (21.2)
18-month PFS rates (95% CI)	**95.3** (89.1, 98.0)	**87.6** (79.7, 92.6)
Median follow-up, mo	22.5	22.4
Hazard ratio (95% CI)	**0.239 (0.098, 0.586)**	
Nominal p-value[a]	0.0007	

The PFS results presented are INV-assessed



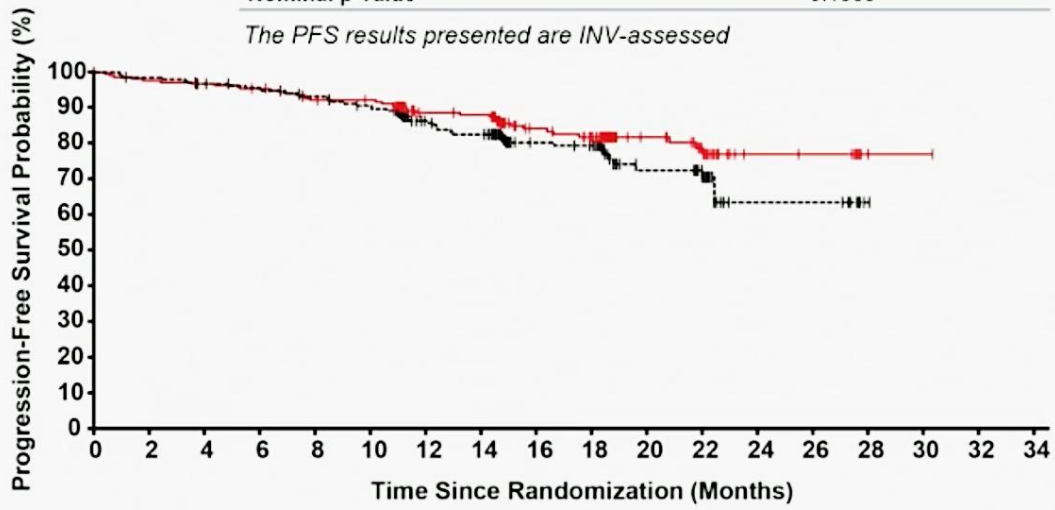
Number at risk

Pirtobrutinib	112	107	106	106	104	103	100	100	99	99	98	94	35	33	4	1	1	0
Ibrutinib	113	105	105	105	102	101	97	96	90	89	86	81	32	29	5	0	0	0

R/R population

	Pirtobrutinib (n=219)	Ibrutinib (n=218)
Number of events, n (%)	37 (16.9)	45 (20.6)
18-month PFS rate (95% CI)	**81.7** (75.1, 86.7)	**79.2** (72.3, 84.6)
Median follow-up, mo	18.4	15.8
Hazard ratio (95% CI)	**0.729 (0.471, 1.128)**	
Nominal p-value[a]	0.1563	

The PFS results presented are INV-assessed



Number at risk

Pirtobrutinib	219	212	209	205	197	195	157	155	106	99	56	46	13	12	3	2	0	0
Ibrutinib	218	205	198	192	186	179	138	131	87	84	43	37	12	12	1	0	0	0

Pirtobrutinib reduced the risk of progression or death by 76% in the TN population, the subgroup with the longest follow-up

Woyach J et al. ASH 2025;Abstract 683; Woyach JA et al. *J Clin Oncol* 2025 December 7;[Online ahead of print].

BRUIN CLL-314: Safety Profile

Preferred Term ≥10% of Participants in Either Arm	Pirtobrutinib n=330		Ibrutinib n=325	
	Any Grade n (%)	Grade ≥3 n (%)	Any Grade n (%)	Grade ≥3 n (%)
Subjects with ≥1 TEAE	320 (97.0)	181 (54.8)	318 (97.8)	174 (53.5)
Neutropenia	75 (22.7)	57 (17.3)	58 (17.8)	43 (13.2)
Upper respiratory tract infection	59 (17.9)	2 (0.6)	63 (19.4)	0 (0)
Anemia	50 (15.2)	19 (5.8)	46 (14.2)	12 (3.7)
Pneumonia	45 (13.6)	21 (6.4)	49 (15.1)	28 (8.6)
Diarrhea	44 (13.3)	1 (0.3)	62 (19.1)	4 (1.2)
COVID-19	40 (12.1)	4 (1.2)	33 (10.2)	5 (1.5)
Hypertension	35 (10.6)	11 (3.3)	49 (15.1)	16 (4.9)
Contusion	33 (10.0)	0 (0)	30 (9.2)	0 (0)
Arthralgia	26 (7.9)	0 (0)	41 (12.6)	0 (0)
Thrombocytopenia	26 (7.9)	9 (2.7)	37 (11.4)	10 (3.1)
Urinary tract infection	26 (7.9)	3 (0.9)	40 (12.3)	3 (0.9)
Atrial fibrillation	8 (2.4)	3 (0.9)	41 (12.6)	12 (3.7)
Dose modifications due to TEAEs				
Reductions	26 (7.9)		59 (18.2)	
Discontinuations	31 (9.4)		35 (10.8)	

Median time on treatment was 20.5 months with pirtobrutinib and 19.3 months with ibrutinib;
1 patient developed Richter Transformation (RT) on pirtobrutinib; 4 patients developed RT on ibrutinib

Pirtobrutinib was well-tolerated with fewer dose reductions and discontinuations due to TEAEs than ibrutinib

RTP RESEARCH TO PRACTICE

Woyach J et al. ASH 2025;Abstract 683; Woyach JA et al. *J Clin Oncol* 2025 December 7;[Online ahead of print].

BRUIN CLL-314: Adverse Events of Special Interest (AESI)

≥10% of Participants in Either Arm	Pirtobrutinib n=330		Ibrutinib n=325	
	Any Grade n (%)	Grade ≥3 n (%)	Any Grade n (%)	Grade ≥3 n (%)
Subjects with ≥1 AESI	288 (87.3)	127 (38.5)	288 (88.6)	117 (36.0)
Infections[a]	226 (68.5)	56 (17.0)	241 (74.2)	54 (16.6)
Infection without COVID-19	214 (64.8)	53 (16.1)	234 (72.0)	49 (15.1)
Bleeding	115 (34.8)	11 (3.3)	118 (36.3)	9 (2.8)
Hemorrhage[b]	78 (23.6)	11 (3.3)	81 (24.9)	9 (2.8)
Bruising[c]	45 (13.6)	0 (0)	39 (12.0)	0 (0)
Petechiae and purpura	17 (5.2)	0 (0)	25 (7.7)	0 (0)
Neutropenia[d]	103 (31.2)	83 (25.2)	76 (23.4)	57 (17.5)
Anemia[e]	51 (15.5)	20 (6.1)	51 (15.7)	12 (3.7)
Thrombocytopenia[f]	39 (11.8)	12 (3.6)	57 (17.5)	13 (4.0)
Atrial fibrillation and atrial flutter	8 (2.4)	3 (0.9)	44 (13.5)	13 (4.0)
≥75 years old[g]	3 (4.5)	1 (1.5)	15 (21.4)	5 (7.1)

AEs were mostly low-grade and consistent with prior pirtobrutinib studies

Incidence of atrial fibrillation/flutter was substantially lower with pirtobrutinib vs ibrutinib, particularly among older patients

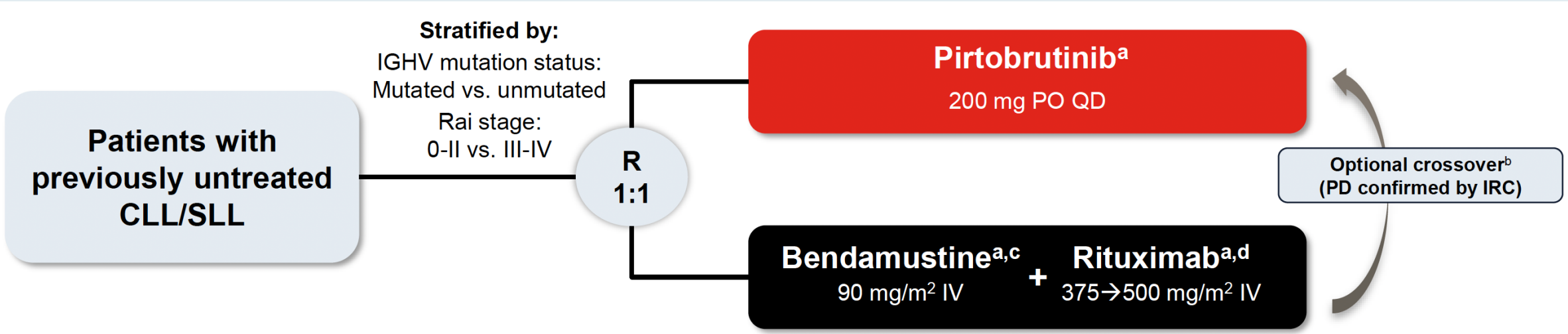
Woyach J et al. ASH 2025;Abstract 683; Woyach JA et al. *J Clin Oncol* 2025 December 7;[Online ahead of print].

Pirtobrutinib vs Bendamustine Plus Rituximab (BendaR) in Patients With CLL/SLL: First Results From a Randomized Phase III Study Examining a Non-Covalent BTK Inhibitor in Untreated Patients

Wojciech Jurczak[1], Michal Kwiatek[2], Jaroslaw Czyz[3], Ederson Roberto de Mattos[4], Ki-Seong Eom[5], Alexander Egle[6], Anna Panovská[7], Zhanet Grudeva-Popova[8], Hsuan-Jen Shih[9], Luis Felipe Casado Montero[10], Paolo Sportoletti[11], Vu Minh Hua[12], James T. D'Olimpio[13], Shinsuke Iida[14], Rodrigo Ito[15], Katherine Bao[15], Anne Fink[15], Weiji Su[15], Amy S. Ruppert[15], Alejandro Levy[15], Tomasz Wrobel[16]

ASH 2025;Abstract LBA3.

BRUIN CLL-313 Study Design



Key Eligibility Criteria

- Confirmed diagnosis of CLL/SLL, with requirement for therapy (per iwCLL 2018 criteria)
- ECOG PS 0 to 2
- Naïve to systemic therapy for CLL/SLL
- No 17p deletion
- Platelets ≥75 × 10^9/L (≥50 × 10^9/L for patients with evidence of bone marrow infiltrate)
- Hemoglobin ≥8 g/dL
- Absolute neutrophil count ≥0.75 × 10^9/L

Endpoints

Primary
- PFS[e,f] (per iwCLL 2018 criteria)

Key secondary
- OS[f]

Secondary
- ORR[g] (per iwCLL 2018 criteria)
- Safety measures

Jurczak W et al. ASH 2025;Abstract LBA3; *J Clin Oncol* 2025 December 9;[Online ahead of print].

BRUIN CLL-313: Response Data

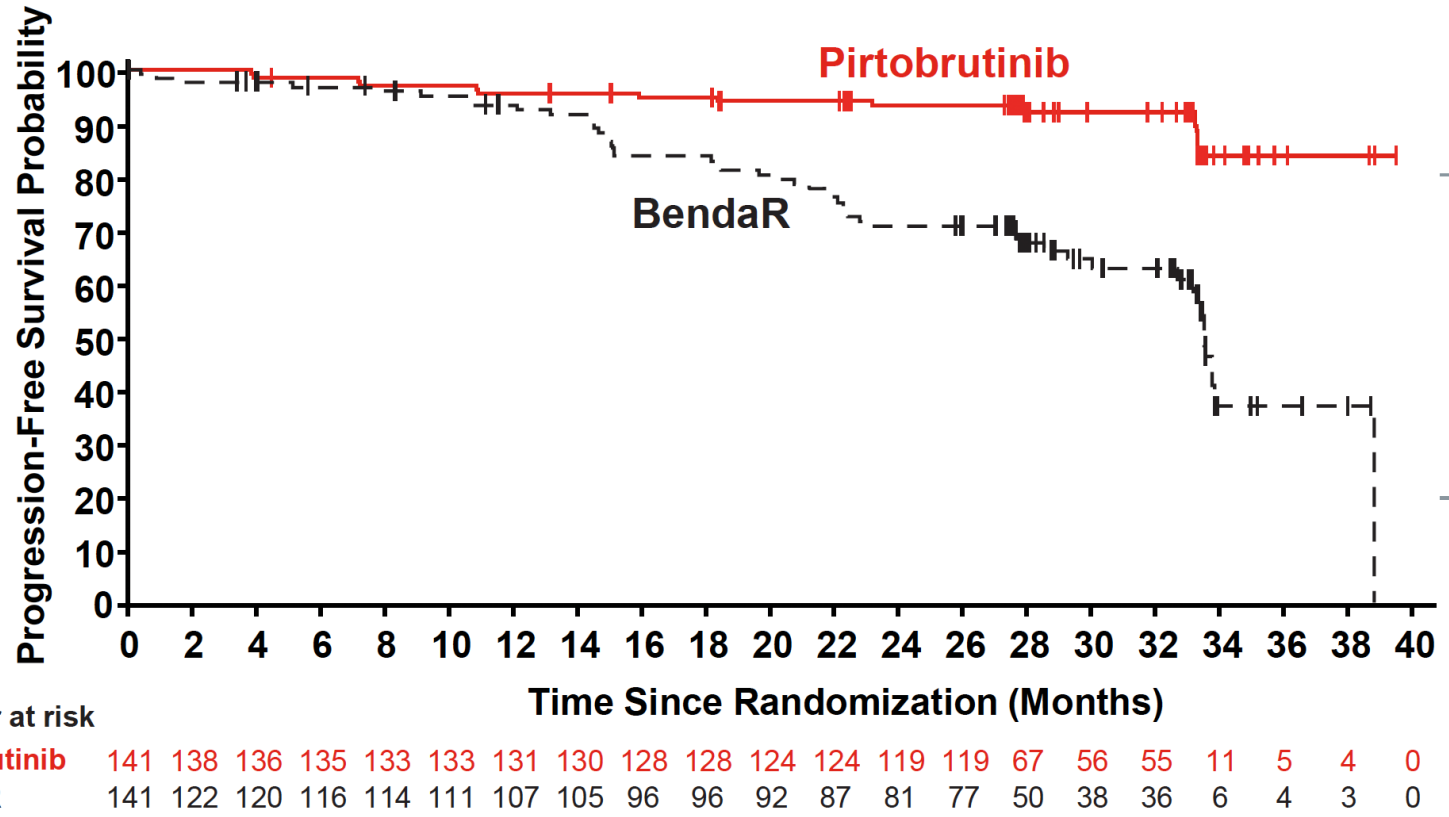
	IRC-Assessed ORR		INV-Assessed ORR	
	Pirtobrutinib (n=141)	BendaR (n=141)	Pirtobrutinib (n=141)	BendaR (n=141)
ORR[a] (PR or better)				
n (%)	133 (**94.3**)	114 (**80.9**)	133 (**94.3**)	116 (**82.3**)
95% CI[b]	89.1, 97.5	73.4, 87.0	89.1, 97.5	75.0, 88.2
Best overall response[c], n (%)				
CR or CRi	19 (13.5)	29 (20.6)	8 (5.7)	29 (20.6)
PR or nPR	114 (80.9)	85 (60.3)	125 (88.7)	87 (61.7)
PR-L	0	0	2 (1.4)	0
SD	3 (2.1)	10 (7.1)	1 (0.7)	6 (4.3)
PD	2 (1.4)	1 (0.7)	2 (1.4)	3 (2.1)
Unknown/not applicable[d]	3 (2.1)	16 (11.3)	3 (2.1)	16 (11.3)

ORR with pirtobrutinib was >90% by both IRC and INV, and higher than with BendaR

ORR = overall response rate; PR = partial response

Jurczak W et al. ASH 2025;Abstract LBA3; *J Clin Oncol* 2025 December 9;[Online ahead of print].

BRUIN CLL-313: PFS Outcomes



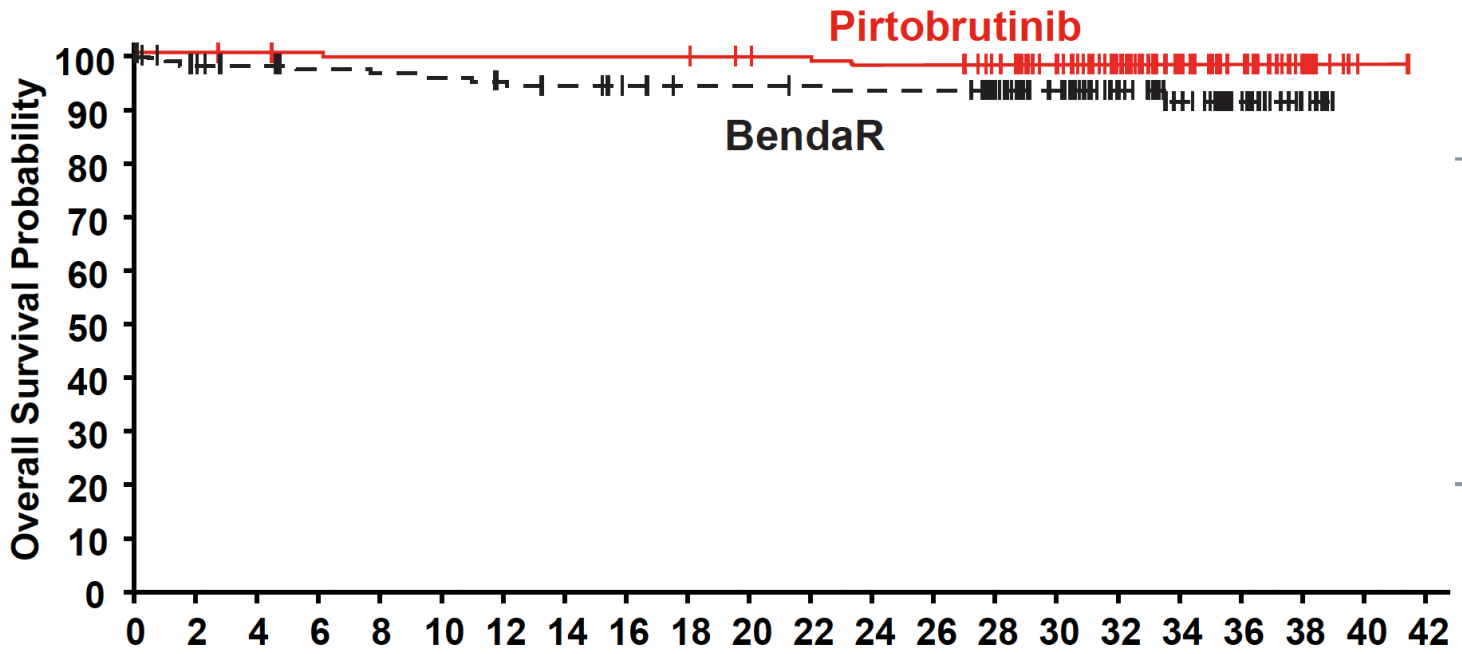
	Pirtobrutinib (n=141)	BendaR (n=141)
Number of events, n (%)	13 (9.2)	48 (34.0)
24-month PFS rate, (95% CI)	**93.4** (87.6, 96.5)	**70.7** (61.5, 78.1)
Median follow-up, months	28.1	28.3
Hazard ratio (95% CI)	**0.20 (0.11, 0.37)**	
p-value[a]	<0.0001[a]	

The PFS results presented are IRC assessed

Pirtobrutinib demonstrated a statistically significant and clinically meaningful PFS improvement, with an 80% reduction in risk of PD or death compared with BendaR

Jurczak W et al. ASH 2025;Abstract LBA3; *J Clin Oncol* 2025 December 9;[Online ahead of print].

BRUIN CLL-313: OS Outcomes



Number at risk

Pirtobrutinib	141	140	139	138	137	137	137	137	137	137	135	134	132	132	125	106	80	52	39	15	1	0
BendaR	141	130	127	124	123	122	119	117	114	113	113	112	111	111	100	82	61	40	23	9	0	0

	Pirtobrutinib n=141	BendaR n=141
Number of events, n (%)	3 (2.1)	10 (7.1)
24-month OS rate, (95% CI)	**97.8** (93.3, 99.3)	**93.0** (87.0, 96.3)
Median follow-up, months	32.7	31.7
Hazard ratio (95% CI)	**0.26 (0.07, 0.93)**	
p-value	0.0261[a]	

Effective crossover rate[b]:

52.9% (18/34)

OS data were immature, but trended in favor of pirtobrutinib, despite a high effective crossover rate

Jurczak W et al. ASH 2025;Abstract LBA3; *J Clin Oncol* 2025 December 9;[Online ahead of print].

BRUIN CLL-313: Safety Profile

Preferred Term ≥15% of Participants in Either Arm	Pirtobrutinib (n=140)		BendaR (n=132)		EAIR per 100 Person-Years		
	Any Grade n (%)	Grade ≥3 n (%)	Any Grade n (%)	Grade ≥3 n (%)	Pirtobrutinib Any Grade EAIR[a]	BendaR Any Grade EAIR[a]	EAIR Ratio (95% CI)[b]
Patients with ≥1 TEAE	131 (93.6)	56 (40.0)	117 (88.6)	89 (67.4)	196.7	844.6	0.23 (0.18, 0.30)
Neutropenia	17 (12.1)	10 (7.1)	51 (38.6)	46 (34.8)	5.2	110.0	0.05 (0.03, 0.08)
COVID-19	30 (21.4)	1 (0.7)	12 (9.1)	2 (1.5)	9.9	20.9	0.47 (0.24, 0.92)
Pyrexia	12 (8.6)	0	25 (18.9)	0	3.5	49.1	0.07 (0.04, 0.14)
Upper respiratory tract infection	25 (17.9)	1 (0.7)	9 (6.8)	0	7.7	15.7	0.49 (0.23, 1.05)
Anemia	13 (9.3)	6 (4.3)	21 (15.9)	10 (7.6)	3.8	37.7	0.10 (0.05, 0.20)
Nausea	3 (2.1)	0	31 (23.5)	1 (0.8)	0.8	65.1	0.01 (0.00, 0.04)
Infusion-related reaction	0	0	20 (15.2)	4 (3.0)	0	39.0	NA

Median time on pirtobrutinib treatment was 32.3 months and on BendaR treatment was 5.6 months

Richter's transformation occurred in 1 patient treated with BendaR

Exposure adjusted TEAEs were lower with pirtobrutinib

Discontinuation due to TEAE, including deaths, occurred less frequently with pirtobrutinib (4.3%) vs. BendaR (15.4%)

Dose reduction due to TEAE also occurred less frequently with pirtobrutinib than BendaR (3.6% vs. 31.1%)

EAIR = exposure-adjusted incidence rate

Jurczak W et al. ASH 2025;Abstract LBA3; *J Clin Oncol* 2025 December 9;[Online ahead of print].

BRUIN CLL-313: AEs of Special Interest

	Pirtobrutinib (n=140)		BendaR (n=132)		EAIR per 100 Person-Years		
	Any Grade n (%)	Grade ≥3 n (%)	Any Grade n (%)	Grade ≥3 n (%)	Pirtobrutinib Any Grade EAIR[g]	BendaR Any Grade EAIR[g]	EAIR Ratio (95% CI)[h]
Infection[a]	80 (57.1)	19 (13.6)	44 (33.3)	11 (8.3)	38.3	89.7	0.43 (0.30, 0.62)
Infection without COVID-19	72 (51.4)	19 (13.6)	38 (28.8)	9 (6.8)	30.9	74.9	0.41 (0.28, 0.61)
Bleeding[b]	36 (25.7)	1 (0.7)	2 (1.5)	0 (0)	12.5	3.3	3.73 (0.90, 15.50)
Hemorrhage	17 (12.1)	1 (0.7)	2 (1.5)	0 (0)	5.2	3.3	1.55 (0.36, 6.69)
Bruising	16 (11.4)	0 (0)	0 (0)	0 (0)	4.8	0	NE
Petechiae and purpura	8 (5.7)	0 (0)	0 (0)	0 (0)	2.3	0	NE
Neutropenia[c]	21 (15.0)	13 (9.3)	68 (51.5)	60 (45.5)	6.5	169.5	0.04 (0.02, 0.06)
Anemia[d]	14 (10.0)	6 (4.3)	21 (15.9)	10 (7.6)	4.1	37.7	0.11 (0.06, 0.21)
Thrombocytopenia[e]	12 (8.6)	4 (2.9)	23 (17.4)	9 (6.8)	3.5	43.1	0.08 (0.04, 0.16)
Atrial fibrillation and atrial flutter	2 (1.4)	1 (0.7)	2 (1.5)	1 (0.8)	0.5	3.3	0.17 (0.02, 1.17)
≥75 years old[f]	1 (5.0)	0	1 (4.3)	0	2.2	10.0	0.22 (0.01, 3.46)
Hypertension	11 (7.9)	4 (2.9)	6 (4.5)	4 (3.0)	3.2	10.2	0.31 (0.11, 0.84)

Incidence of atrial fibrillation/flutter remains low in older patients aged ≥75 years (5.0% with pirtobrutinib and 4.3% with BendaR)

Jurczak W et al. ASH 2025;Abstract LBA3; *J Clin Oncol* 2025 December 9;[Online ahead of print].

Management of Double-Refractory CLL

Introduction: Sequencing of Treatment for CLL

Module 1: Clinician Survey Results

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Module 3: Clinician Survey Results

Module 4: CAR T-Cell Therapy

Module 5: Clinician Survey Results

Module 6: Bispecific Antibodies and Promising Investigational Strategies

Based on current clinical trial data and your personal experience, how would you compare the global efficacy and tolerability/toxicity of pirtobrutinib to that of ibrutinib, acalabrutinib and zanubrutinib for patients with relapsed/refractory CLL?

	Efficacy	Tolerability/toxicity
 Dr Coombs	There are not enough available data at this time	Pirtobrutinib has the least toxicity
 Dr Davids	About the same	Pirtobrutinib has the least toxicity
 Dr Fakhri	There are not enough available data at this time	Pirtobrutinib has the least toxicity
 Dr Lamanna	About the same	Pirtobrutinib has the least toxicity
 Dr Sharman	There are not enough available data at this time	Pirtobrutinib has the least toxicity
 Dr Wierda	There are not enough available data at this time	Pirtobrutinib has the least toxicity
 Dr Woyach	There are not enough available data at this time	Pirtobrutinib has the least toxicity

An older patient with newly diagnosed CLL and a significant history of atrial fibrillation has come to you for a second opinion after the recommendation of first-line treatment with pirtobrutinib. How would you respond?

 Dr Coombs	I do not agree with the recommendation, but it is a valid option
 Dr Davids	I do not agree with the recommendation, but it is a valid option
 Dr Fakhri	I do not agree with the recommendation, but it is a valid option
 Dr Lamanna	I do not agree with this recommendation
 Dr Sharman	I do not agree with this recommendation
 Dr Wierda	I do not agree with this recommendation
 Dr Woyach	I agree with this recommendation

RTP RESEARCH TO PRACTICE

Management of Double-Refractory CLL

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Module 3: Clinician Survey Results

Module 4: CAR T-Cell Therapy

Module 5: Clinician Survey Results

Module 6: Bispecific Antibodies and Promising Investigational Strategies

Key Datasets

- Siddiqi T et al. **Lisocabtagene maraleucel** (liso-cel) in R/R CLL/SLL: **24-month median follow-up** of **TRANSCEND CLL 004**. ASH 2023;Abstract 330.
- Wierda WG et al. **Lisocabtagene maraleucel** (liso-cel) **combined with ibrutinib** (ibr) for patients (pts) with relapsed or refractory (R/R) chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL): **Primary results** from the open-label, **phase 1/2 Transcend CLL 004 study**. ASH 2024;Abstract 887.

Lisocabtagene Maraleucel in Relapsed or Refractory Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma: 24-Month Median Follow-up of TRANSCEND CLL 004

Tanya Siddiqi,[1] David G. Maloney,[2] Saad S. Kenderian,[3] Danielle M. Brander,[4] Kathleen Dorritie,[5] Jacob Soumerai,[6] Peter A. Riedell,[7] Nirav N. Shah,[8] Rajneesh Nath,[9] Bita Fakhri,[10] Deborah M. Stephens,[11] Shuo Ma,[12] Tatyana Feldman,[13] Scott R. Solomon,[14] Stephen J. Schuster,[15] Serena K. Perna,[16] Sherilyn A. Tuazon,[17] San-San Ou,[17] Neha Rane,[16] William G. Wierda[18]

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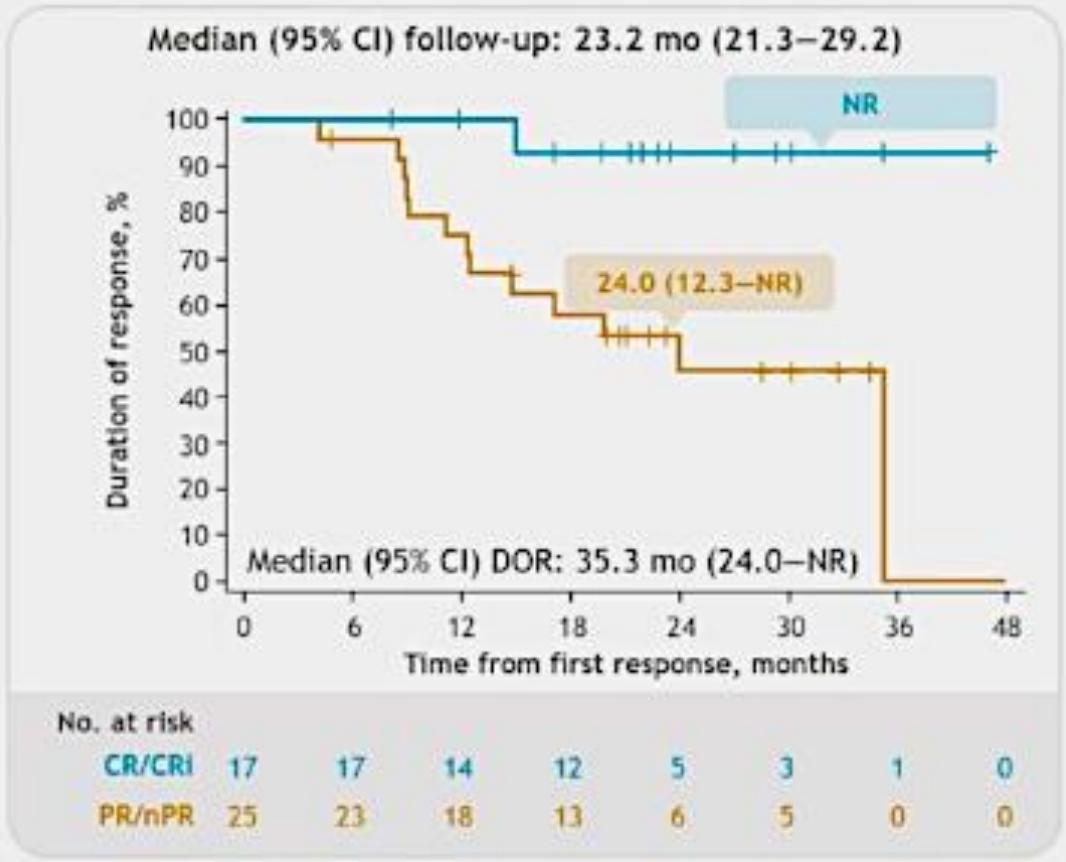
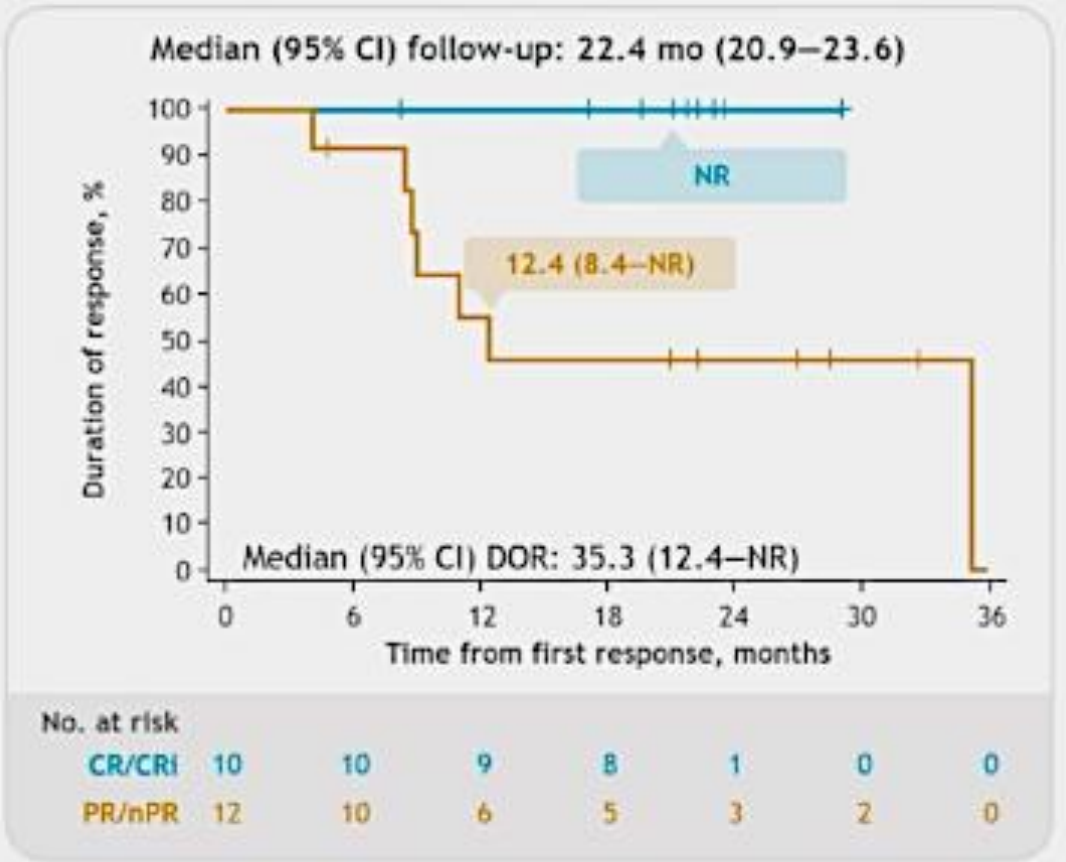
ASH 2023, Presentation 330

TRANSCEND CLL 004: Duration of Response by Best Overall Response

Full Study Population at DL2 (n = 88)



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



Data on KM curves are expressed as median (95% CI, if available). DOR, duration of response; NR, not reached.

Siddiqi T et al. ASH 2023;Abstract 330.

RTP RESEARCH TO PRACTICE

FDA Grants Accelerated Approval to Lisocabtagene Maraleucel for Relapsed/Refractory (R/R) CLL or SLL

Press Release: March 14, 2024

"… the US Food and Drug Administration (FDA) has granted accelerated approval of lisocabtagene maraleucel (liso-cel), a CD19-directed chimeric antigen receptor (CAR) T cell therapy, for the treatment of adult patients with relapsed or refractory chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL) who have received at least two prior lines of therapy, including a Bruton tyrosine kinase (BTK) inhibitor and a B-cell lymphoma 2 (BCL-2) inhibitor. This indication is approved under accelerated approval based on response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trial(s). In R/R CLL or SLL, liso-cel is delivered through a treatment process which culminates in a one-time infusion with a single dose containing 90 to 110 x 10^6 CAR-positive viable T cells."

Accelerated approval was based on results from the Phase I/II open-label, single-arm TRANSCEND CLL 004 study for patients with R/R CLL or SLL.

https://news.bms.com/news/details/2024/U.S.-FDA-Approves-Bristol-Myers-Squibbs-Breyanzi--as-the-First-and-Only-CAR-T-Cell-Therapy-for-Adults-with-Relapsed-or-Refractory-Chronic-Lymphocytic-Leukemia-CLL-or-Small-Lymphocytic-Lymphoma-SLL/default.aspx

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

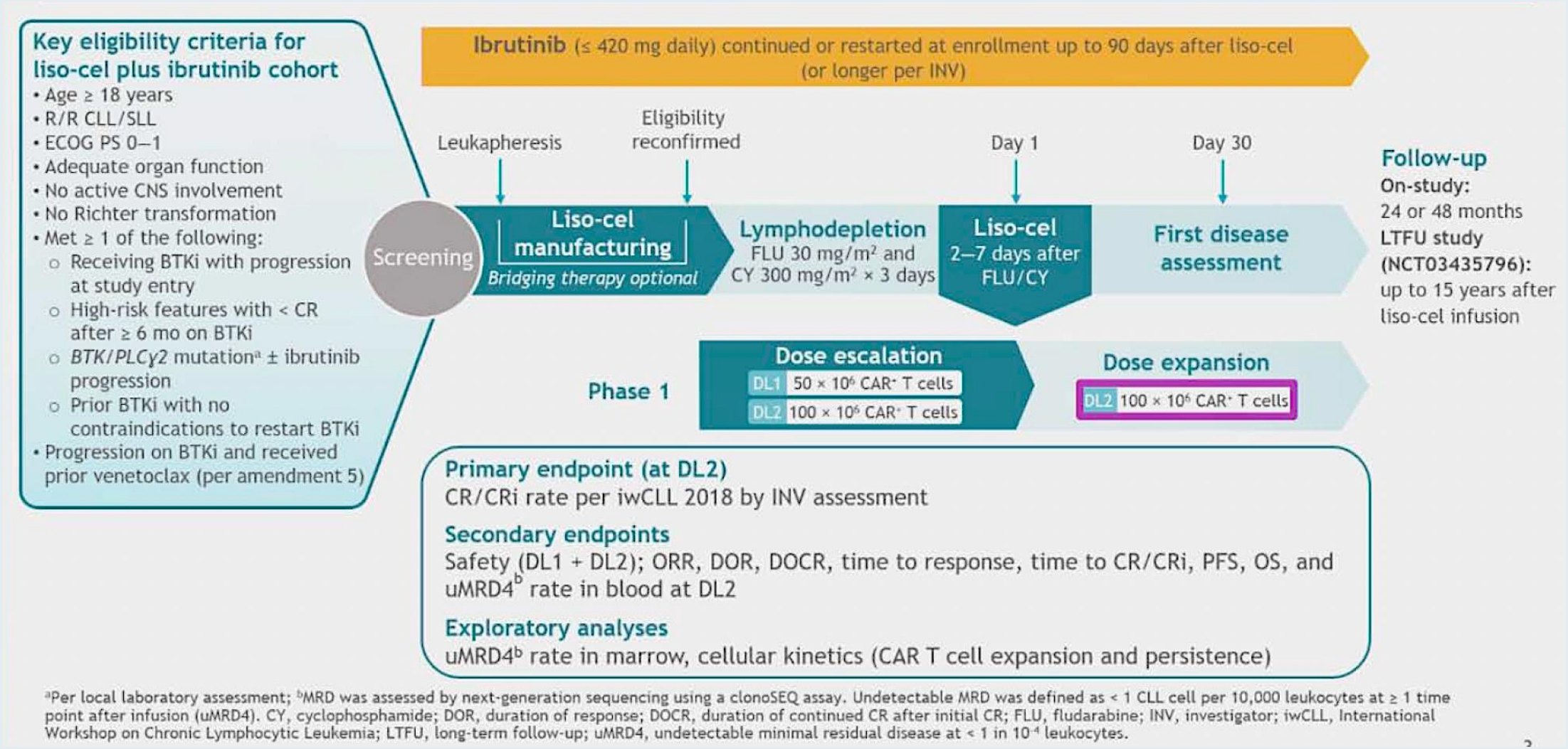
William G. Wierda, MD, PhD,[1] Kathleen Dorritie, MD,[2] Jordan Gauthier, MD, MSc,[3] Rajneesh Nath, MD,[4] Thomas Kipps, MD, PhD,[5] Peter A. Riedell, MD,[6] Herbert A. Eradat, MD,[7] Saad S. Kenderian, MB, ChB,[8] Mohamed A. Kharfan-Dabaja, MD, MBA,[9] Nirav N. Shah, MD,[10] Scott R. Solomon, MD,[11] 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]

[1]The University of Texas MD Anderson Cancer Center, Houston, TX, USA; [2]UPMC Hillman Cancer Center, University of Pittsburgh, Pittsburgh, PA, USA; [3]Fred Hutchinson Cancer Center, Seattle, WA, USA; [4]Banner MD Anderson Cancer Center, Gilbert, AZ, USA; [5]Moores UCSD Cancer Center, San Diego, CA, USA; [6]David and Etta Jonas Center for Cellular Therapy, University of Chicago, Chicago, IL, USA; [7]University of California, Los Angeles, Santa Monica Cancer Center, Santa Monica, CA, USA; [8]Mayo Clinic, Rochester, MN, USA; [9]Mayo Clinic Comprehensive Cancer Center, Jacksonville, FL, USA; [10]Medical College of Wisconsin, Milwaukee, WI, USA; [11]Northside Hospital Cancer Institute, Atlanta, GA, USA; [12]Huntsman Cancer Institute, University of Utah, Salt Lake City, UT, USA; [13]Beth Israel Deaconess Medical Center, Boston, MA, USA; [14]Barbara Ann Karmanos Cancer Institute, Wayne State University, Detroit, MI, USA; [15]John Theurer Cancer Center at Hackensack Meridian Health, HMH School of Medicine, Hackensack, NJ, USA; [16]University of California, San Francisco, San Francisco, CA, USA; [17]University of Michigan Health System, Ann Arbor, MI, USA; [18]Robert H. Lurie Comprehensive Cancer Center of Northwestern University, Chicago, IL, USA; [19]Lymphoma Program, Abramson Cancer Center, University of Pennsylvania, Philadelphia, PA, USA; [20]Thomas Jefferson University, Philadelphia, PA, USA; [21]University of Nebraska Medical Center, Omaha, NE, USA; [22]Center for Lymphoma, Massachusetts General Hospital Cancer Center, Boston, MA, USA; [23]Weill Cornell Medical College, New York, NY, USA; [24]Bristol Myers Squibb, Seattle, WA, USA; [25]Bristol Myers Squibb, Princeton, NJ, USA; [26]City of Hope National Medical Center, Duarte, CA, USA

*Affiliation at the time the research was conducted

ASH 2024, Presentation 887

TRANSCEND CLL 004: Lisocabtagene Maraleucel (Liso-cel) and Ibrutinib Combination Cohort

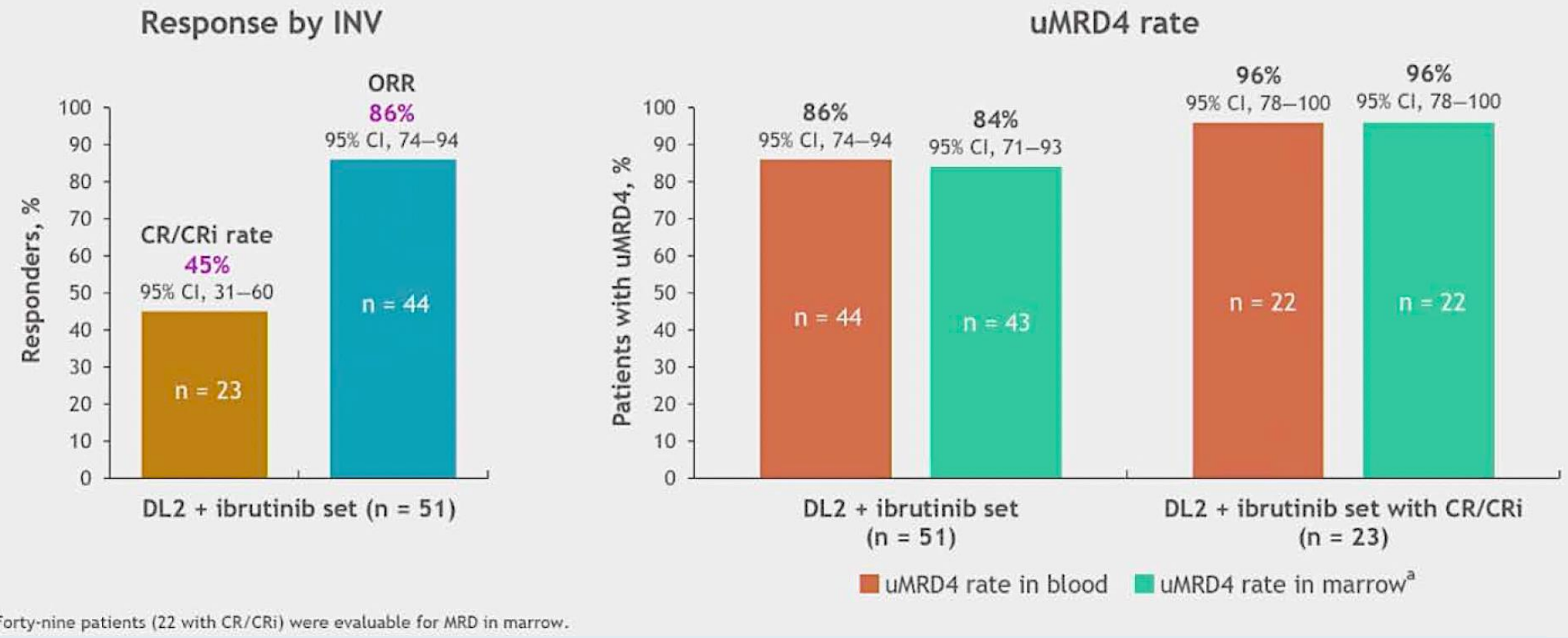


[a]Per local laboratory assessment; [b]MRD was assessed by next-generation sequencing using a clonoSEQ assay. Undetectable MRD was defined as < 1 CLL cell per 10,000 leukocytes at ≥ 1 time point after infusion (uMRD4). CY, cyclophosphamide; DOR, duration of response; DOCR, duration of continued CR after initial CR; FLU, fludarabine; INV, investigator; iwCLL, International Workshop on Chronic Lymphocytic Leukemia; LTFU, long-term follow-up; uMRD4, undetectable minimal residual disease at < 1 in 10^{-4} leukocytes.

Wierda WG et al. ASH 2024;Abstract 887.

TRANSCEND CLL 004: Efficacy Outcomes with Liso-cel and Ibrutinib

- 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)

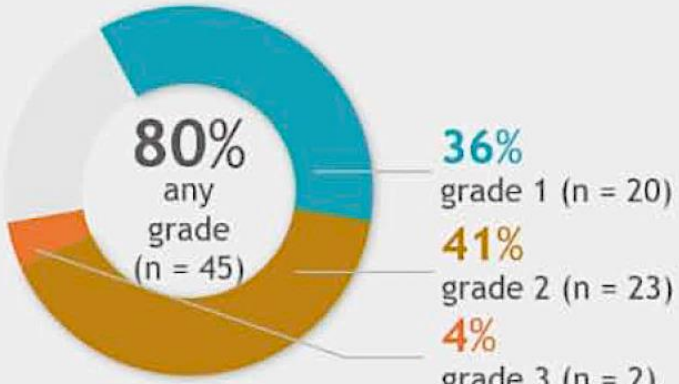


CR = complete response; CRi = CR with incomplete marrow recovery; ORR = overall response rate

Wierda WG et al. ASH 2024;Abstract 887.

TRANSCEND CLL 004: Incidence of Cytokine Release Syndrome (CRS) and Neurological Adverse Events (NEs) with Liso-cel and Ibrutinib

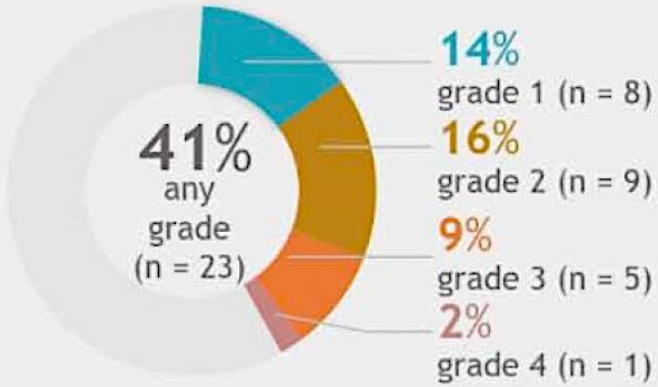
CRS[a,b]



No grade 4 or 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)

NEs[a,c]



No grade 5 events

	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. ASH 2024;Abstract 887.

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Module 5: Clinician Survey Results

Module 6: Bispecific Antibodies and Promising Investigational Strategies

At what point in the treatment course are you referring patients with multiregimen-relapsed CLL for consultation regarding chimeric antigen receptor (CAR) T-cell therapy?

 Dr Coombs	After third relapse
 Dr Davids	After third relapse
 Dr Fakhri	At third relapse
 Dr Lamanna	After third relapse
 Dr Sharman	At second relapse
 Dr Wierda	At second relapse
 Dr Woyach	At second relapse

RTP RESEARCH TO PRACTICE

Approximately how many patients with CLL in your practice have received CAR T-cell therapy on or off protocol?

 Dr Coombs	0 patients
 Dr Davids	10 patients
 Dr Fakhri	20 patients
 Dr Lamanna	5 patients
 Dr Sharman	4 patients
 Dr Wierda	30 patients
 Dr Woyach	10 patients

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RTP RESEARCH TO PRACTICE

Key Datasets

- Cassanello G et al**. Trial watch: Bispecific antibodies** for the treatment of relapsed or refractory large B-cell lymphoma. *Oncoimmunology* 2024 March 3;13(1):2321648.
- Danilov A et al. **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**. ASH 2024;Abstract 883.
- Ahn I et al. **Updated efficacy and safety results** of the Bruton tyrosine kinase **(BTK) degrader BGB-16673** in patients with relapsed/refractory chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) from the ongoing **phase 1 CaDAnCe-101 study**. ASH 2025;Abstract 85.
- Shah NN et al. **Efficacy and safety** of the Bruton's tyrosine kinase **(BTK) degrader NX-5948** in patients with relapsed/refractory (R/R) chronic lymphocytic leukemia (CLL): Updated results from an **ongoing phase 1a/b study**. ASH 2024;Abstract 884.
- Woyach JA et al. **First-in-human study** of the **reversible BTK inhibitor nemtabrutinib** in patients with relapsed/refractory chronic lymphocytic leukemia and B-cell non-Hodgkin lymphoma. *Cancer Discov* 2024;14(1):66-75.

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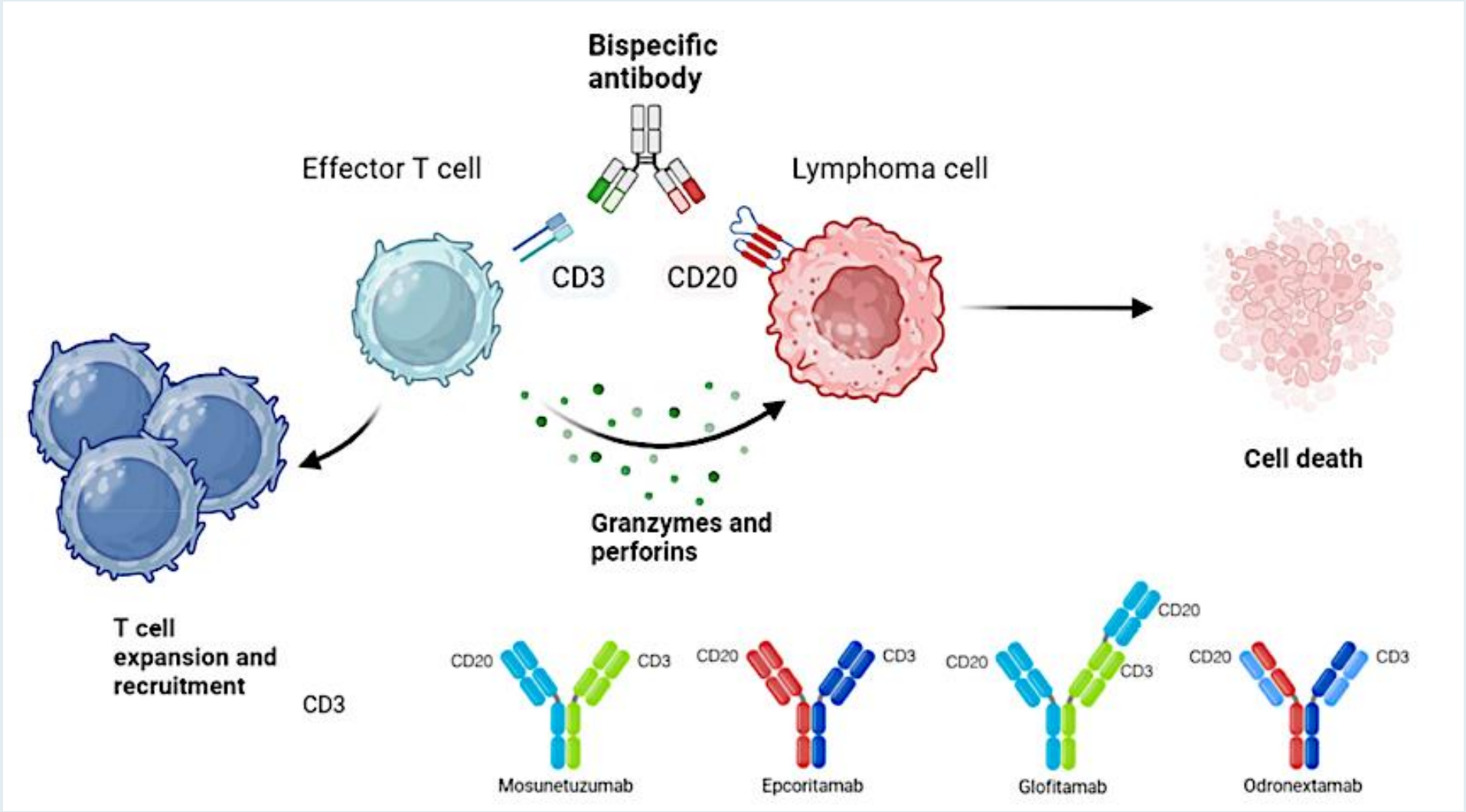
Mechanism of Action of CD20 x CD3 Bispecific Antibodies



Cassanello G et al. *Oncoimmunology* 2024;13(1):2321648.

883

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]

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Presented at the American Society of Hematology Annual Meeting; December 7–10, 2024; San Diego, CA

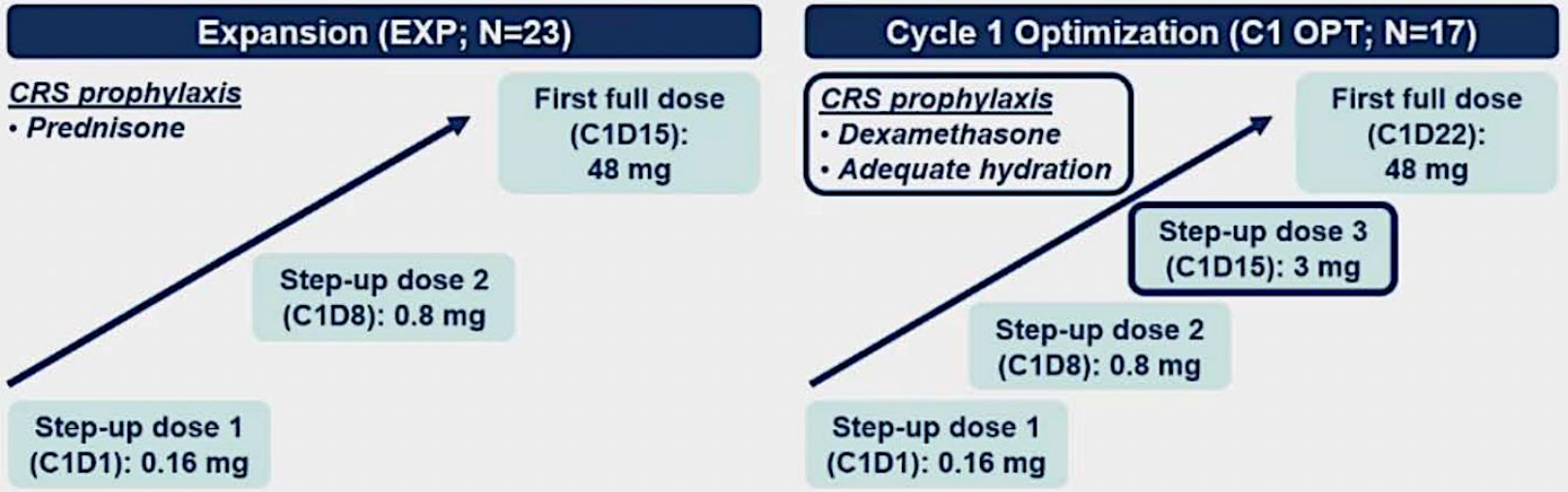
ASH 2024;Abstract 883

RTP RESEARCH TO PRACTICE

EPCORE CLL-1 Trial Expansion and Cycle 1 Optimization

Key inclusion criteria

- CD20+ R/R CLL
- ≥2 prior lines of systemic therapy
- ECOG PS 0–2
- Measurable disease with ≥5×10⁹/L B lymphocytes (expansion only)
- No prior allogeneic HSCT



Data cutoff: May 28, 2024
Median follow-up: 22.8 months

Data cutoff: May 28, 2024
Median follow-up: 2.9 months

- **Primary endpoint (EXP):** Overall response rate
- **Primary endpoint (C1 OPT):** Incidence and severity of CRS, ICANS, and clinical TLS
- **Key secondary endpoints (EXP):** CR rate, time to response, MRD (PBMCs using the clonoSEQ® assay), and safety/tolerability

- To ensure patient safety and better characterize CRS, inpatient monitoring was required for at least 24 hours after each epcoritamab dose in C1

ClinicalTrials.gov: NCT04623541; EudraCT: 2023-504828-25.

ICANS = immune effector cell-associated neurotoxicity syndrome; TLS = tumor lysis syndrome; PMBC = peripheral blood mononuclear cell

Danilov A et al. ASH 2024;Abstract 883.

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EPCORE CLL-1: Response 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)

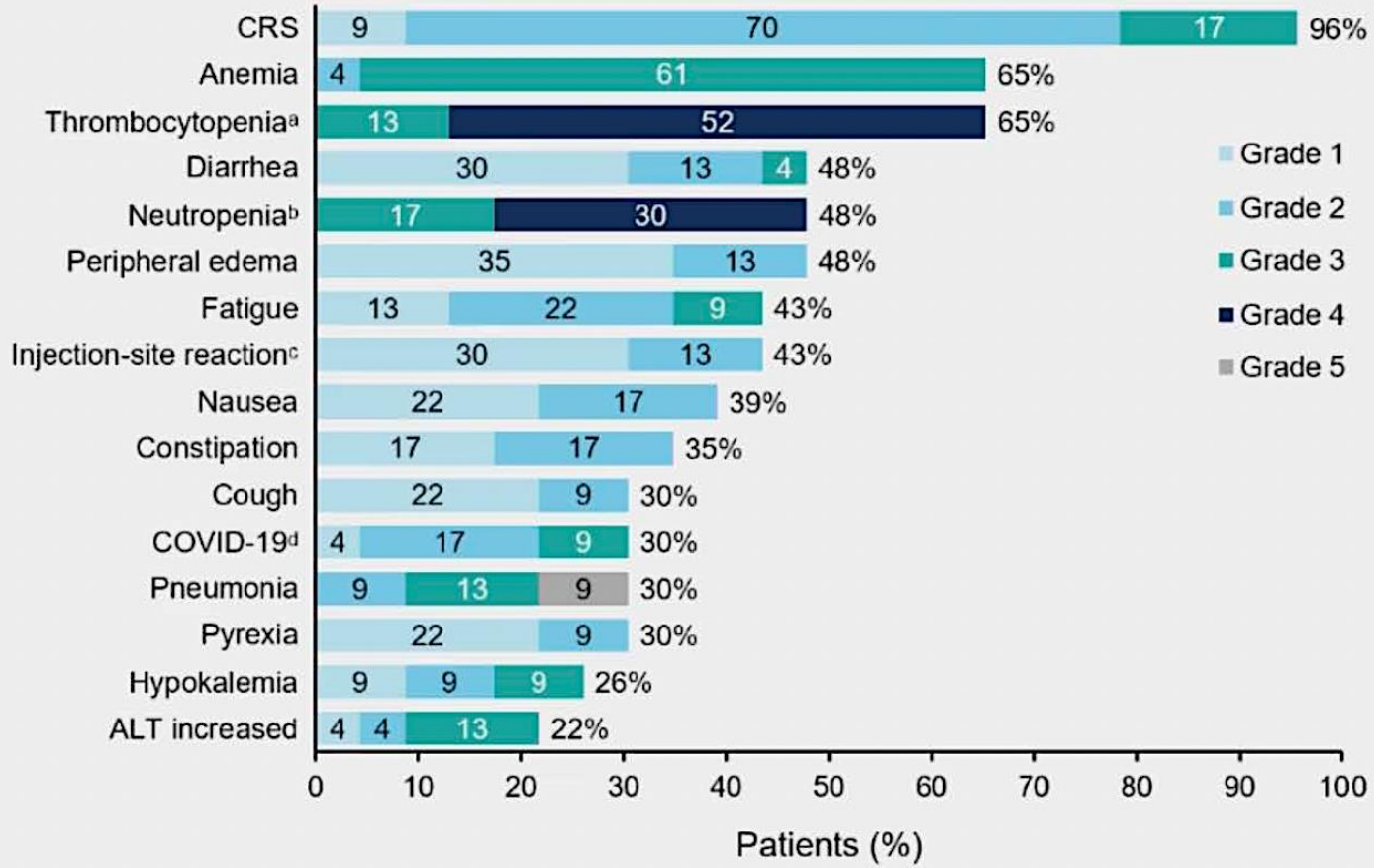
- With limited follow-up, the C1 OPT regimen does not appear to affect epcoritamab efficacy
- uMRD4 in PBMCs was observed in most responders, including all patients with CR who were tested for MRD

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 postbaseline 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.

Danilov A et al. ASH 2024;Abstract 883.

EPCORE CLL-1: Treatment-Emergent Adverse Events (TEAES)



Patients With ≥1 Event, n (%)	EXP N=23
Anemia	15 (65)
At study entry	14 (61)
In first 8 weeks	15 (65)
Thrombocytopenia	15 (65)
At study entry	14 (61)
In first 8 weeks[a]	14 (61)
Neutropenia	11 (48)
At study entry	1 (4)
In first 8 weeks[b]	11 (48)

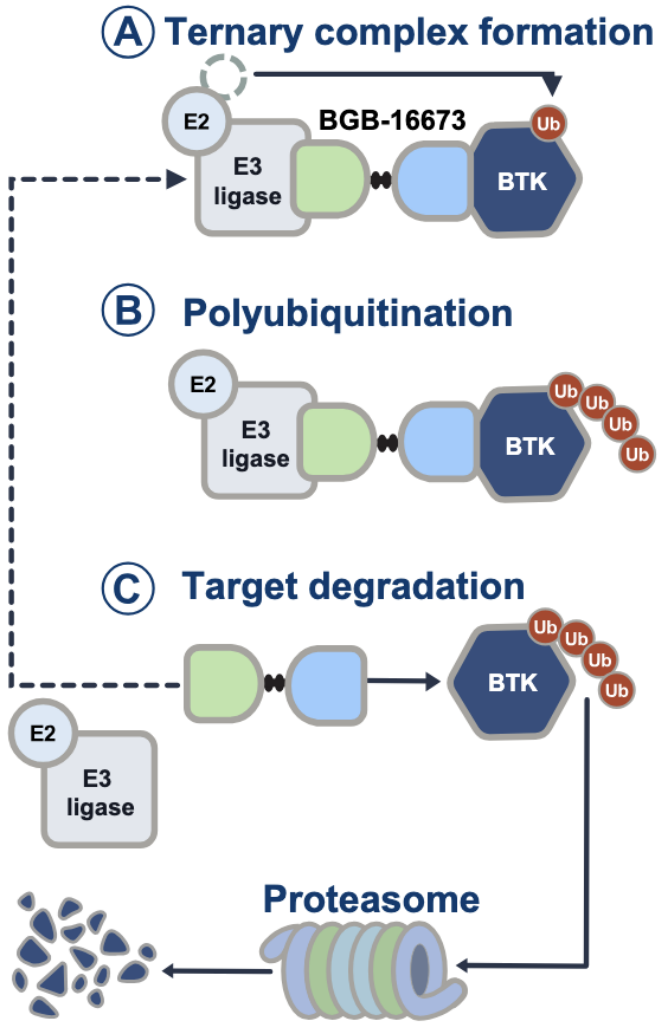
- TEAEs were primarily low grade (G1–2)
- TEAEs led to treatment discontinuation in 5 patients from EXP and 1 patient from C1 OPT
- 4 fatal TEAEs[e] occurred in EXP; none occurred in C1 OPT

[a]Combined term includes thrombocytopenia and decreased platelet count. [b]Combined term includes neutropenia, decreased neutrophil count, and febrile neutropenia. Three patients had febrile neutropenia (EXP, n=2 [grades 1 and 3]; C1 OPT, n=1 [grade 3]). [c]Combined term includes injection-site reaction, bruising, erythema, rash, and swelling. [d]Combined term includes COVID-19 and COVID-19 pneumonia. [e]Fatal TEAEs were pneumonia (n=2), sepsis (n=1), and squamous cell carcinoma of the skin (n=1); 1 case of pneumonia was considered related to epcoritamab.

Danilov A et al. ASH 2024;Abstract 883.

BGB-16673: A Chimeric Degradation Activating Compound

BGB-16673 is an orally available protein degrader that blocks BTK signaling by tagging BTK for degradation through the cell's proteasome pathway, leading to tumor regression

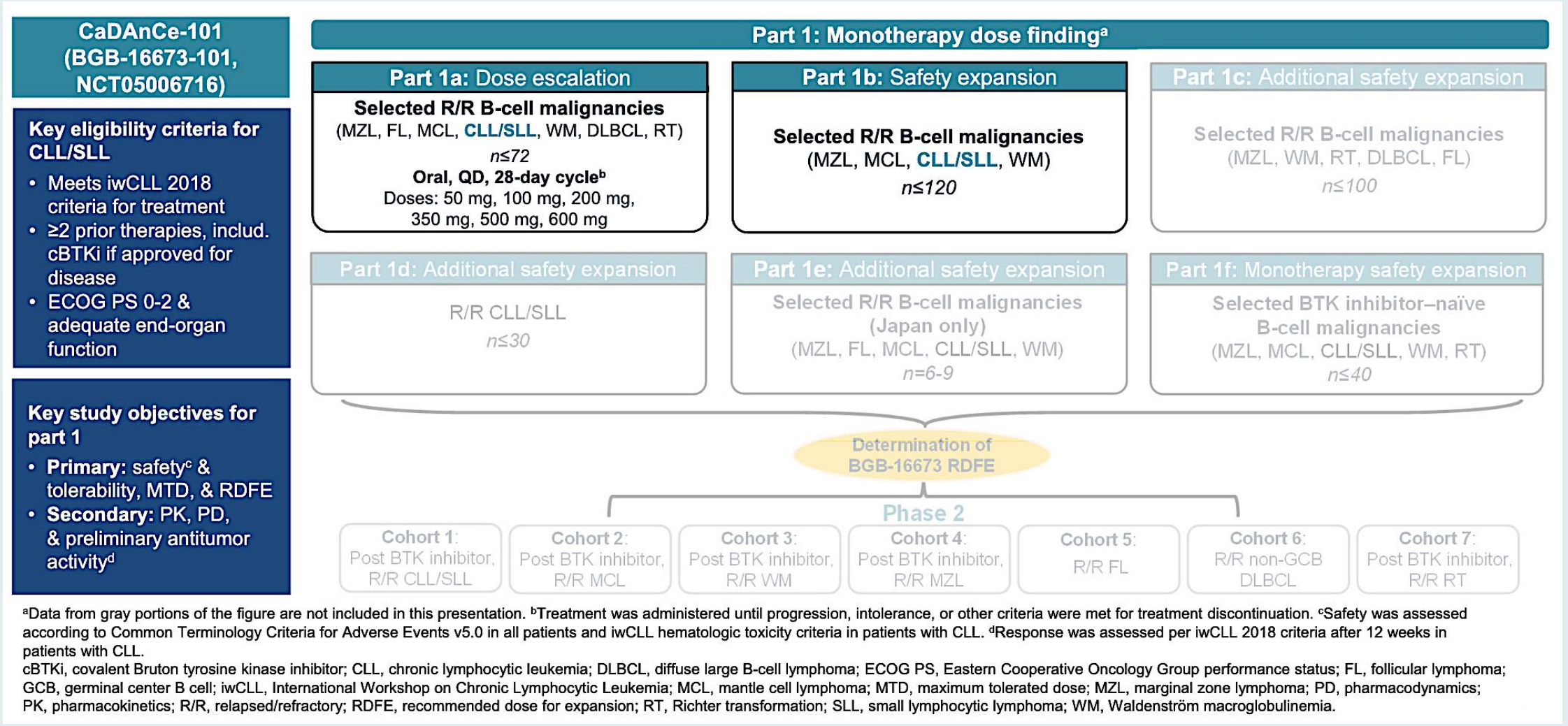


BTK, Bruton tyrosine kinase; cBTK, covalent Bruton tyrosine kinase; CLL/SLL, chronic lymphocytic leukemia/small lymphocytic lymphoma; CNS, central nervous system; ncBTK, noncovalent Bruton tyrosine kinase; R/R, relapsed/refractory; ub, ubiquitin.

1. Moreno C. *Hematol Am Soc Hematol Educ Program*. 2020;2020:33-40; 2. Woyach JA, et al. *N Engl J Med*. 2014;370:2286-2294; 3. Wang E, et al. *N Engl J Med*. 2022;386:735-743; 4. Feng X, et al. EHA 2023. Abstract P1239; 5. Wang H, et al. EHA 2023. Abstract P1219; 6. Seymour JF, et al. ASH 2023; Abstract 4401.

Scarfò L et al. EHA 2025;Abstract S158.

CaDAnCe-101: A Phase I/II Dose-Escalation/Expansion Study of BGB-16673 for R/R B-Cell Cancers



[a]Data from gray portions of the figure are not included in this presentation. [b]Treatment was administered until progression, intolerance, or other criteria were met for treatment discontinuation. [c]Safety was assessed according to Common Terminology Criteria for Adverse Events v5.0 in all patients and iwCLL hematologic toxicity criteria in patients with CLL. [d]Response was assessed per iwCLL 2018 criteria after 12 weeks in patients with CLL.

cBTKi, covalent Bruton tyrosine kinase inhibitor; CLL, chronic lymphocytic leukemia; DLBCL, diffuse large B-cell lymphoma; ECOG PS, Eastern Cooperative Oncology Group performance status; FL, follicular lymphoma; GCB, germinal center B cell; iwCLL, International Workshop on Chronic Lymphocytic Leukemia; MCL, mantle cell lymphoma; MTD, maximum tolerated dose; MZL, marginal zone lymphoma; PD, pharmacodynamics; PK, pharmacokinetics; R/R, relapsed/refractory; RDFE, recommended dose for expansion; RT, Richter transformation; SLL, small lymphocytic lymphoma; WM, Waldenström macroglobulinemia.

Scarfò L et al. EHA 2025;Abstract S158.

CaDAnCe-101: Response Data

	50 mg (n=1)	100 mg (n=22)	200 mg (n=18)	350 mg (n=15)	500 mg (n=12)	Total (N=68)
Best overall response, n (%)						
CR/CRi	0	1 (4.5)	1 (5.6)	0	0	**2 (2.9)**
PR[a]	1 (100)	14 (63.6)	12 (66.7)	11 (73.3)	11 (91.7)	49 (72.1)
PR-L	0	2 (9.1)	4 (22.2)	0	1 (8.3)	7 (10.3)
SD	0	5 (22.7)	0	0	0	5 (7.4)
PD	0	0	1 (5.6)	1 (6.7)	0	2 (2.9)
Discontinued prior to first assessment	0	0	0	3 (20.0)	0	3 (4.4)
ORR, n (%)[b]	1 (100)	17 (77.3)	**17 (94.4)**	11 (73.3)	12 (100)	**58 (85.3)**
Time to first response, median (range), months[c]	2.9 (2.9-2.9)	2.8 (2.0-6.2)	2.9 (2.6-8.3)	2.9 (2.6-19.4)	2.8 (2.7-13.8)	2.8 (2.0-19.4)
Time to best response, median (range), months	2.9 (2.9-2.9)	2.9 (2.0-11.1)	3.0 (2.6-13.8)	5.6 (2.6-19.4)	8.4 (2.7-13.8)	4.2 (2.0-19.4)
Duration of exposure, median (range), months	29.6 (29.6-29.6)	12.3 (3.4-25.4)	14.4 (2.9-30.3)	19.8 (0.2-28.5)	20.4 (6.8-27.1)	13.6 (0.2-30.3)

Ahn I et al. ASH 2025;Abstract 85.

CaDAnCe-101: Overall Response Rate in High-Risk Subgroups

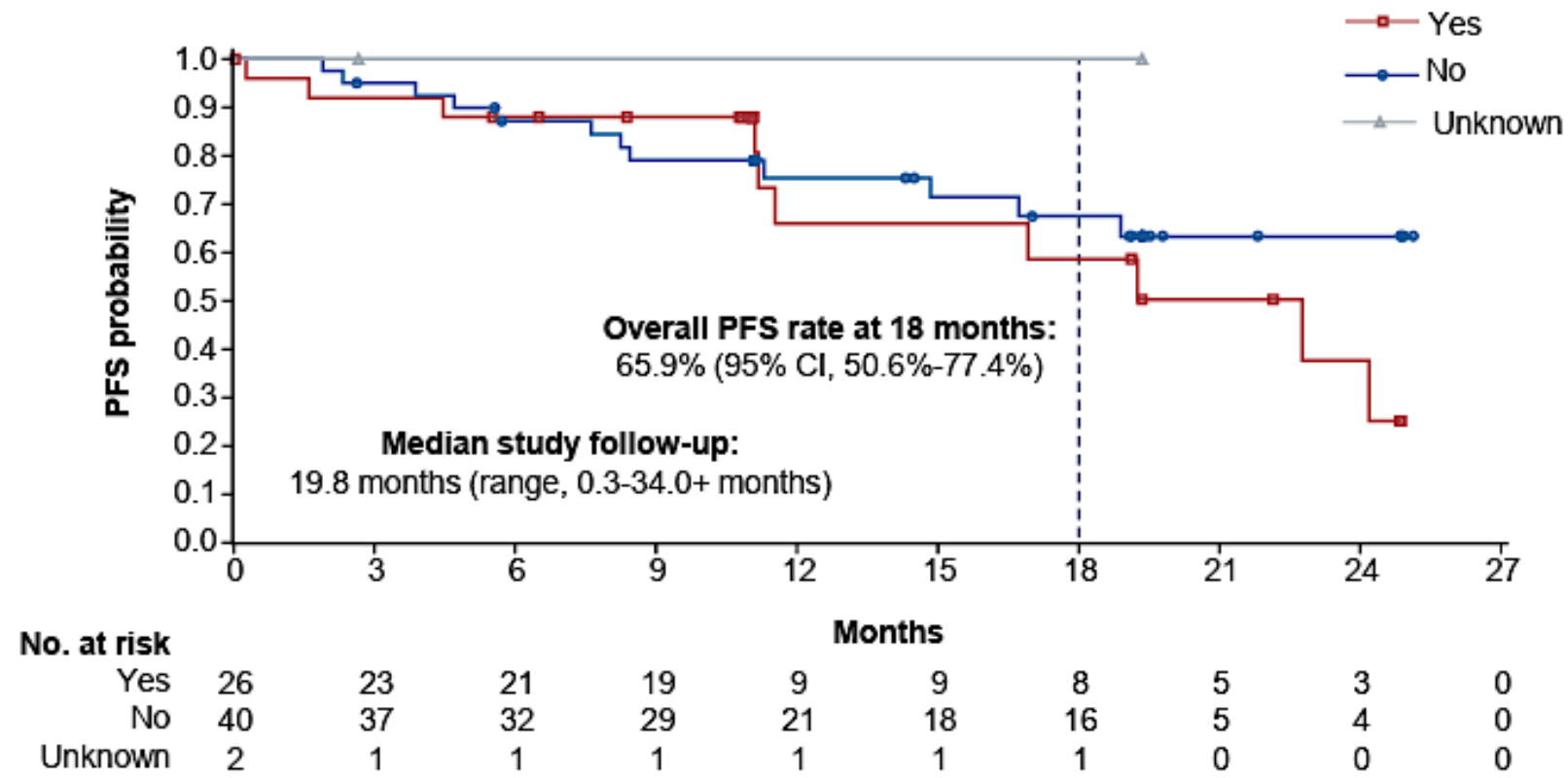
Characteristic, n/N with known status (%)	ORR
Prior cBTKi + BCL2i	41/44 (93.2)
Prior cBTKi + BCL2i + ncBTKi	9/12 (75.0)
6 or more prior lines of therapy	13/16 (81.3)
del(17p) and/or *TP53* mutation	37/46 (80.4)
Complex karyotype (≥3 abnormalities)	16/22 (72.7)
BTK mutations	20/26 (76.9)
PLCG2 mutations	9/10 (90.0)

cBTKi = covalent BTK inhibitor; BCL2i = Bcl-2 inhibitor; ncBTKi = noncovalent BTK inhibitor

Ahn I et al. ASH 2025;Abstract 85.

CaDAnCe-101: PFS Outcomes

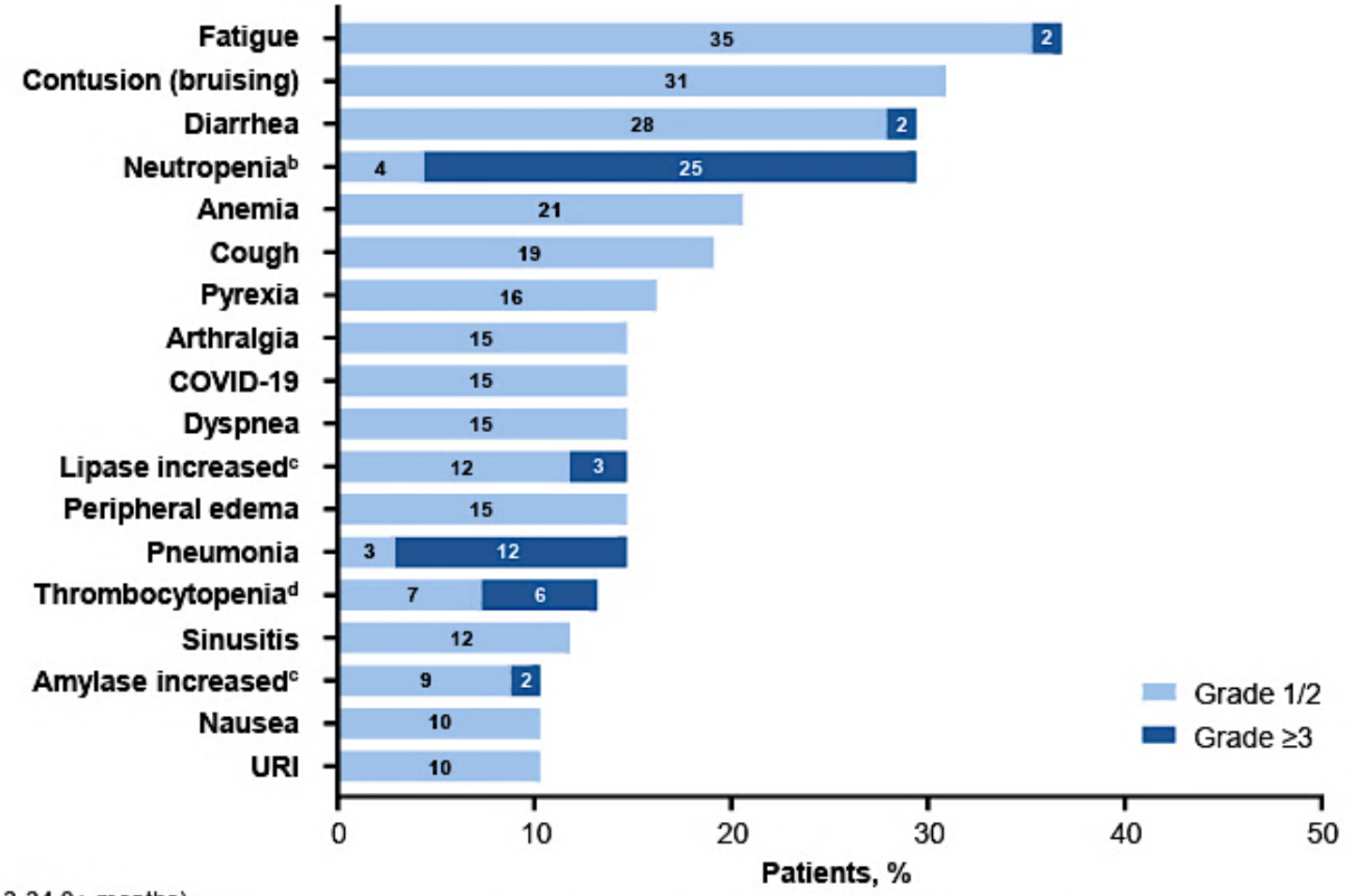
BTK mutation status	18-month PFS rate, % (95% CI)
Yes	58.7 (30.6-78.7)
No	67.5 (48.2-80.9)
Unknown	100 (100-100)



Ahn I et al. ASH 2025;Abstract 85.

CaDAnCe-101: Safety Profile

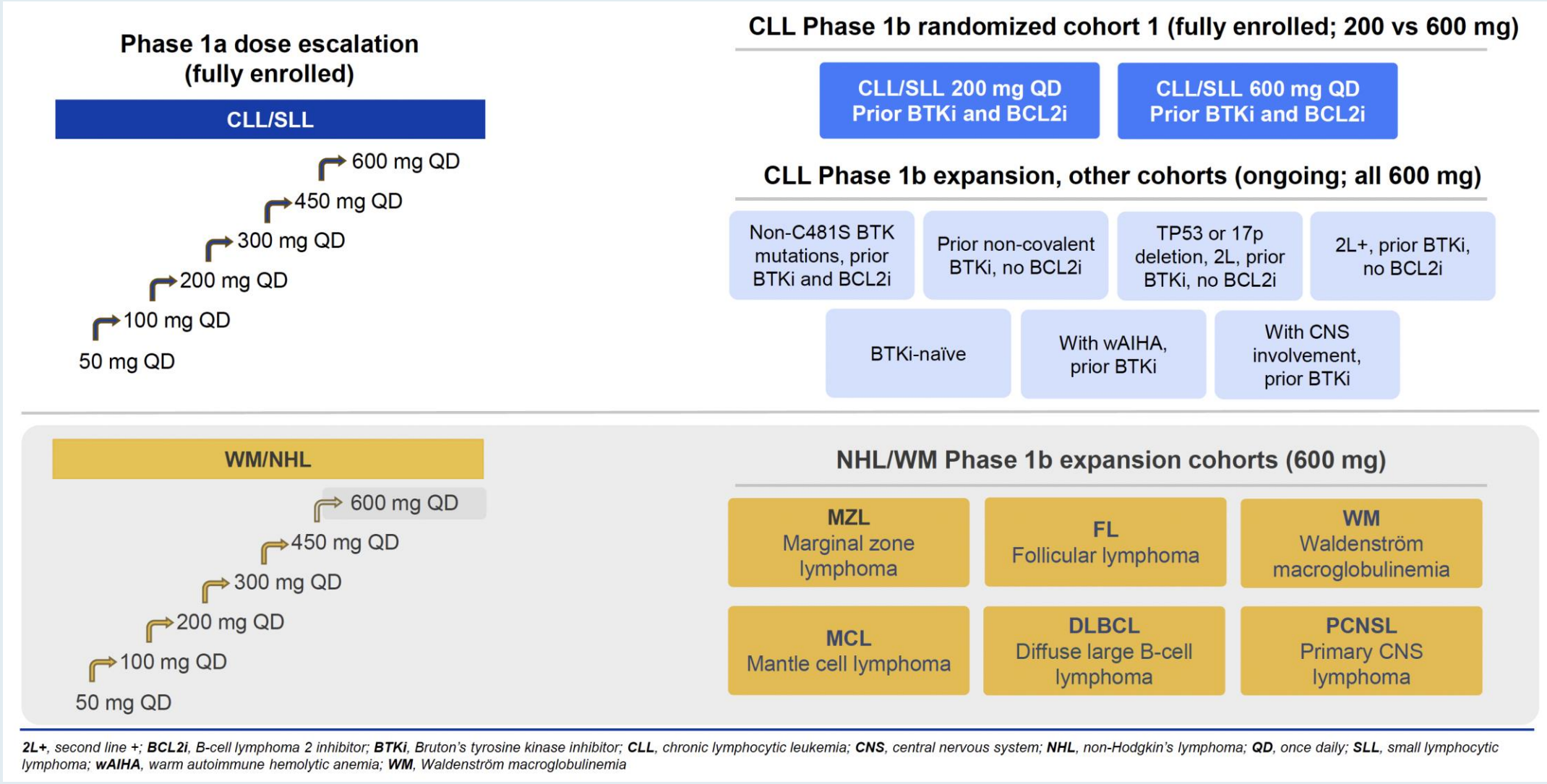
- The most common TEAEs were fatigue (36.8%) and contusion (bruising; 30.9%)
- Grade ≥3 neutropenia: n=17 (25.0%); 16 patients (23.5%) had grade ≥2 neutropenia at baseline
  - Neutropenic fever: n=1
- Atrial fibrillation: n=3 (grade 1, n=1; grade 2, n=2; all transient (2 of them lasting 1 day) in the context of infection and PD, assessed as unrelated to treatment)
- Treatment-related major hemorrhage[a]: n=2 (one grade 3 subdural hemorrhage and one grade 3 post-procedural hematuria)



Median follow-up in safety-evaluable patients: 19.8 months (range, 0.3-34.0+ months).
[a]Grade ≥3, serious, or any central nervous system bleeding. [b]Neutropenia combines preferred terms *neutrophil count decreased* and *neutropenia*. [c]All events were laboratory findings and were transient, mostly occurring during the first 1-3 cycles of treatment, with no clinical pancreatitis. [d]Thrombocytopenia combines preferred terms *platelet count decreased* and *thrombocytopenia*.
PD, progressive disease; TEAE, treatment-emergent adverse event; URI, upper respiratory tract infection.

Ahn I et al. ASH 2025;Abstract 85.

Bexobrutideg (NX-5948): A Novel BTK Degrader
Phase Ia/b Trial Design



***2L+**, second line +; **BCL2i**, B-cell lymphoma 2 inhibitor; **BTKi**, Bruton's tyrosine kinase inhibitor; **CLL**, chronic lymphocytic leukemia; **CNS**, central nervous system; **NHL**, non-Hodgkin's lymphoma; **QD**, once daily; **SLL**, small lymphocytic lymphoma; **wAIHA**, warm autoimmune hemolytic anemia; **WM**, Waldenström macroglobulinemia*

Omer Z et al. ASH 2025;Abstract 86.

Bexobrutideg (NX-5948): Overall Safety Summary

Tolerable safety profile, consistent between the RP2D 600 mg and overall study population

	Phase 1a/b – all patients (n=126)	Phase 1a/b 600 mg (n=70)
Any TEAE, n (%)	114 (90.5)	60 (85.7)
Treatment related	95 (75.4)	51 (72.9)
Grade ≥3	62 (49.2)	31 (44.3)
Treatment-related	31 (24.6)	18 (25.7)
SAE	27 (21.4)	10 (14.3)
Treatment-related	7 (5.6)	3 (4.3)
Grade 5[a]	3 (2.4)	1 (1.4)
Treatment-related	0	0
Leading to treatment discontinuation	8 (6.3)	4 (5.7)
Treatment-related	5 (4.0)	2 (2.9)
DLT	0	0
Median duration of treatment, months (range)	7.1 (0.0–32.3)	3.6 (0.0–18.0)

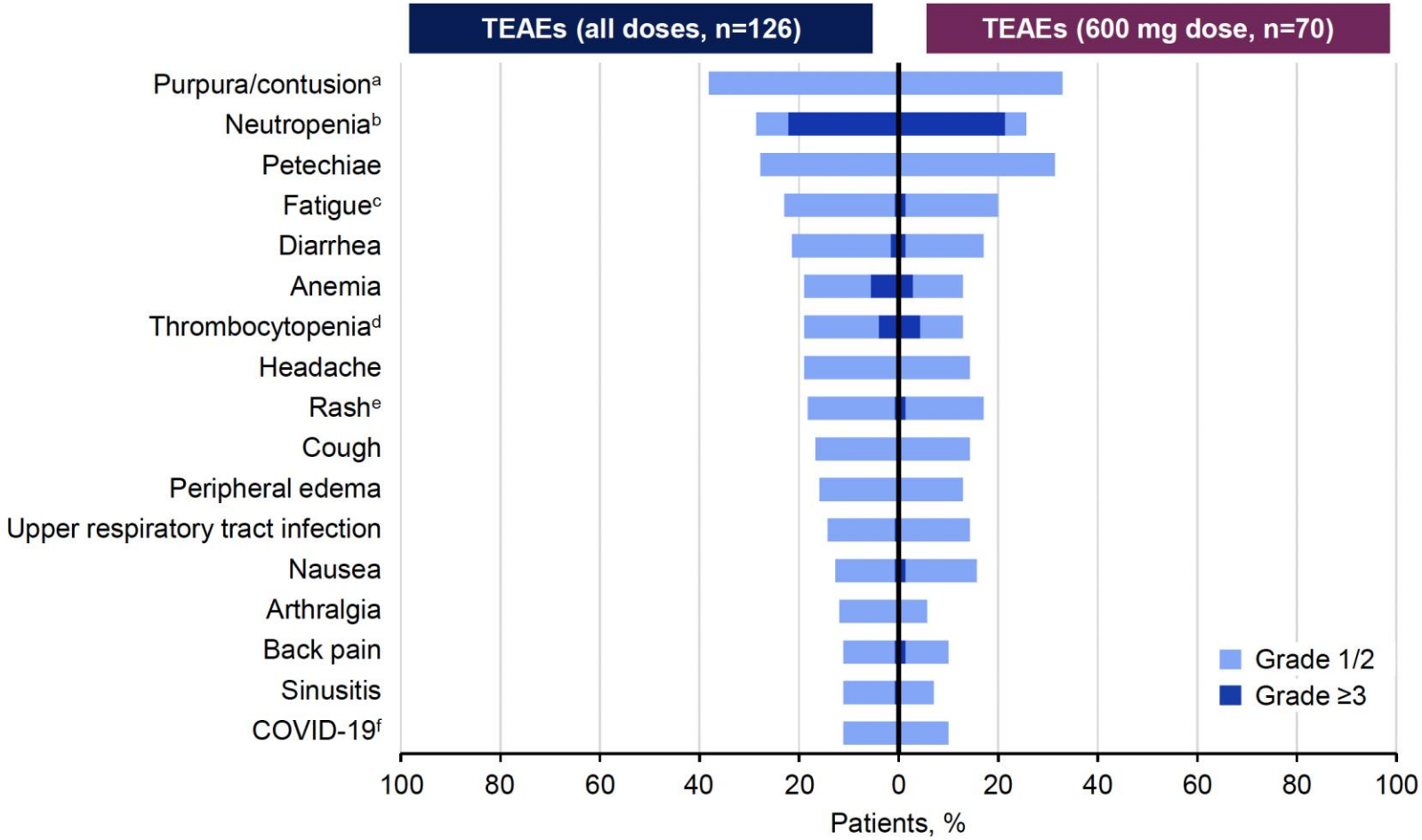
[a]Grade 5 AEs: pulmonary embolism; death not otherwise specified; pneumonia
***AE**, adverse event; **DLT**, dose-limiting toxicity; **RP2D**, recommended Phase 2 dose; **SAE**, serious AE; **TEAE**, treatment-emergent AE*

Data cutoff: 19 Sep 2025

Omer Z et al. ASH 2025;Abstract 86.

Bexobrutideg (NX-5948): Treatment-Emergent Adverse Events

Comparable AE profile for patients at the RP2D 600mg dose and overall population



- Tolerable safety profile consistent with prior disclosures
- No dose-limiting toxicities
- No systemic fungal infections or Grade 4 infections of any kind reported
- Single event of new onset atrial fibrillation consistent with the rate in the age-matched general population
- 3 Grade 5 AEs (death not otherwise specified; pulmonary embolism; pneumonia; all deemed not related to bexobrutideg)

[a]Purpura/contusion includes episodes of contusion or purpura; [b]Aggregate of 'neutrophil count decreased' or 'neutropenia'; [c]Fatigue was transient; [d]Aggregate of 'thrombocytopenia' and 'platelet count decreased'; [e]Aggregate of 'rash' and 'rash maculopapular' and 'rash pustular'; [f]Aggregate of 'COVID-19' and 'COVID-19 pneumonia'
***AE**, adverse event; **NOS**, not otherwise specified; **RP2D**, recommended Phase 2 dose; **TEAE**, treatment-emergent adverse event*

Data cutoff: 19 Sep 2025

Omer Z et al. ASH 2025;Abstract 86.

Bexobrutideg (NX-5948): Objective Response Rate and Median Duration of Response

Encouraging ORR and long median duration of response

Response-evaluable patients	Phase 1a (n=47)
Objective response rate (ORR),[a] % (95% CI)	**83.0 (69.2–92.4)**
Disease control rate (DCR),[b] % (95% CI)	95.7 (85.5–99.5)
Best response,[c] n (%)	
Complete response (CR)	2 (4.3)
Nodal partial response (nPR)	1 (2.1)
Partial response (PR/PR-L)	36 (76.6)
Stable disease (SD)	6 (12.8)
Progressive disease (PD)	2 (4.3)
Median follow-up,[d] months (range)	19.0 (13.5–32.3)
Median duration of response, months (95% CI)	20.1 (12.2–NE) (n=39)

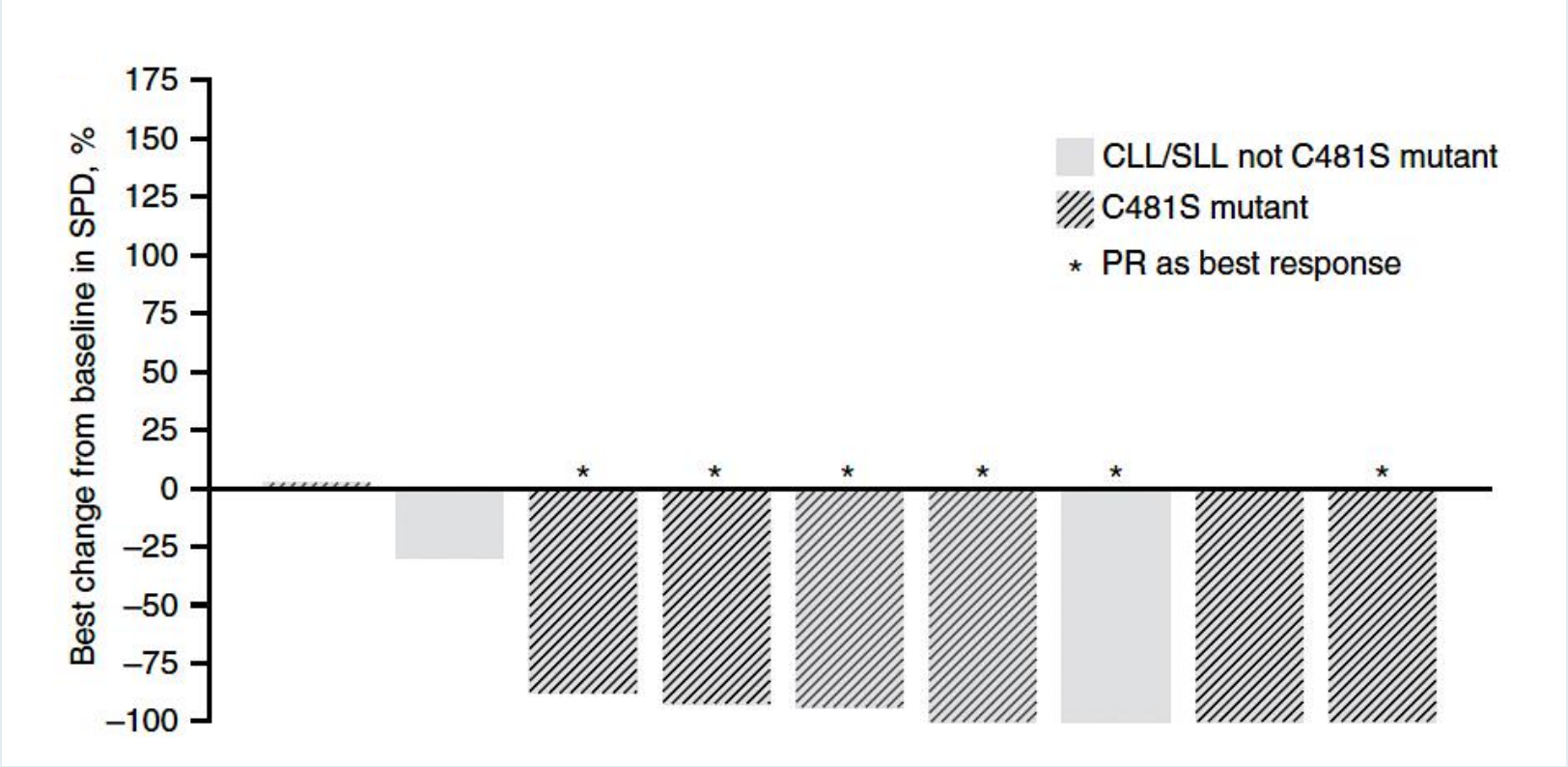
[a]Objective response rate includes CR + nPR + PR + PR-L; [b]Disease control rate includes CR + nPR + PR/PR-L + SD; [c]Percentages are based on the number of patients dosed who had at least one post-baseline disease assessment or documented clinical PD; [d]Time from treatment start to data cutoff

Data cutoff: 19 Sep 2025

***CI**, confidence interval; **CR**, complete response; **DCR**, disease control rate; **NE**, not evaluable; **nPR**, nodal partial response; **ORR**, objective response rate; **PD**, progressive disease; **PR**, partial response; **PR-L**, partial response with lymphocytosis; **SD**, stable disease*

Omer Z et al. ASH 2025;Abstract 86.

Nemtabrutinib: A Novel Reversible BTK Inhibitor



In a Phase I study, among the 22 patients with CLL, 8 (36.4%) achieved at least a partial remission with lymphocytosis as best response.

Among the 47 patients with CLL or NHL in the safety analysis, atrial fibrillation was reported in 1 patient (Grade 3), and no ventricular arrhythmias or unexplained deaths were reported. Hypertension was reported in 32% of patients (Grade 2 in 17%, Grade 3 in 15%).

Woyach JA et al. *Cancer Discov* 2024;14(1):66-75.