Optimizing Treatment for Patients with Relapsed/Refractory Chronic Lymphocytic Leukemia

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Division of Hematology
Department of Internal Medicine
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Columbus, Ohio

Disclosures

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Professor
Division of Hematology
Department of Internal Medicine
The Ohio State University Comprehensive Cancer Center
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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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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.
- Scarfò L et al. **Updated efficacy and safety** of the Bruton tyrosine kinase (BTK) degrader **BGB-16673** in patients (pts) with relapsed or refractory (R/R) CLL/SLL: Results from the ongoing **phase (ph) 1 CADANCE-101 study**. EHA 2025;Abstract S158.
- 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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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

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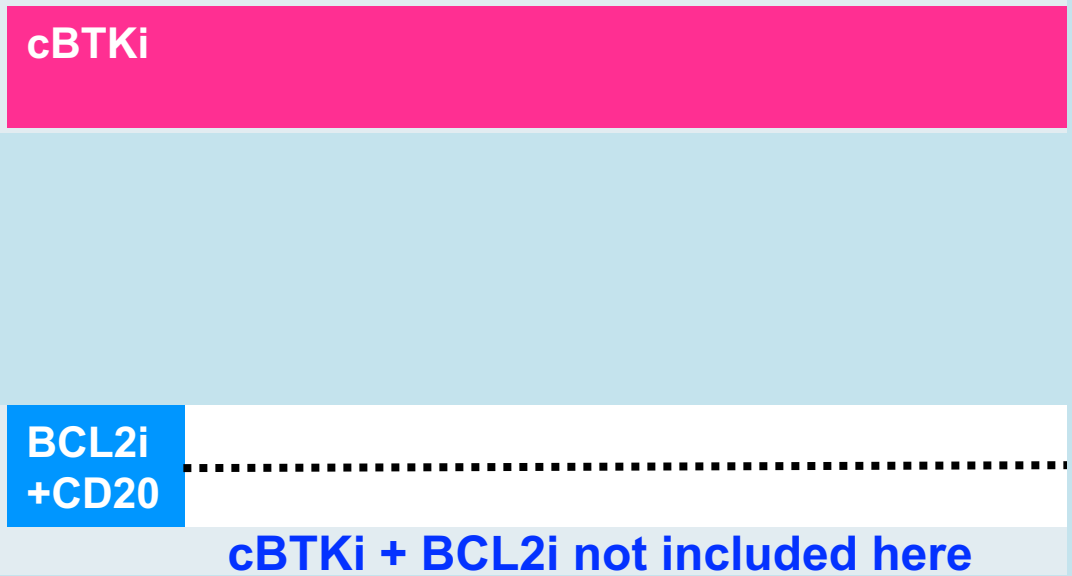
Module 6: Bispecific Antibodies and Promising Investigational Strategies

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

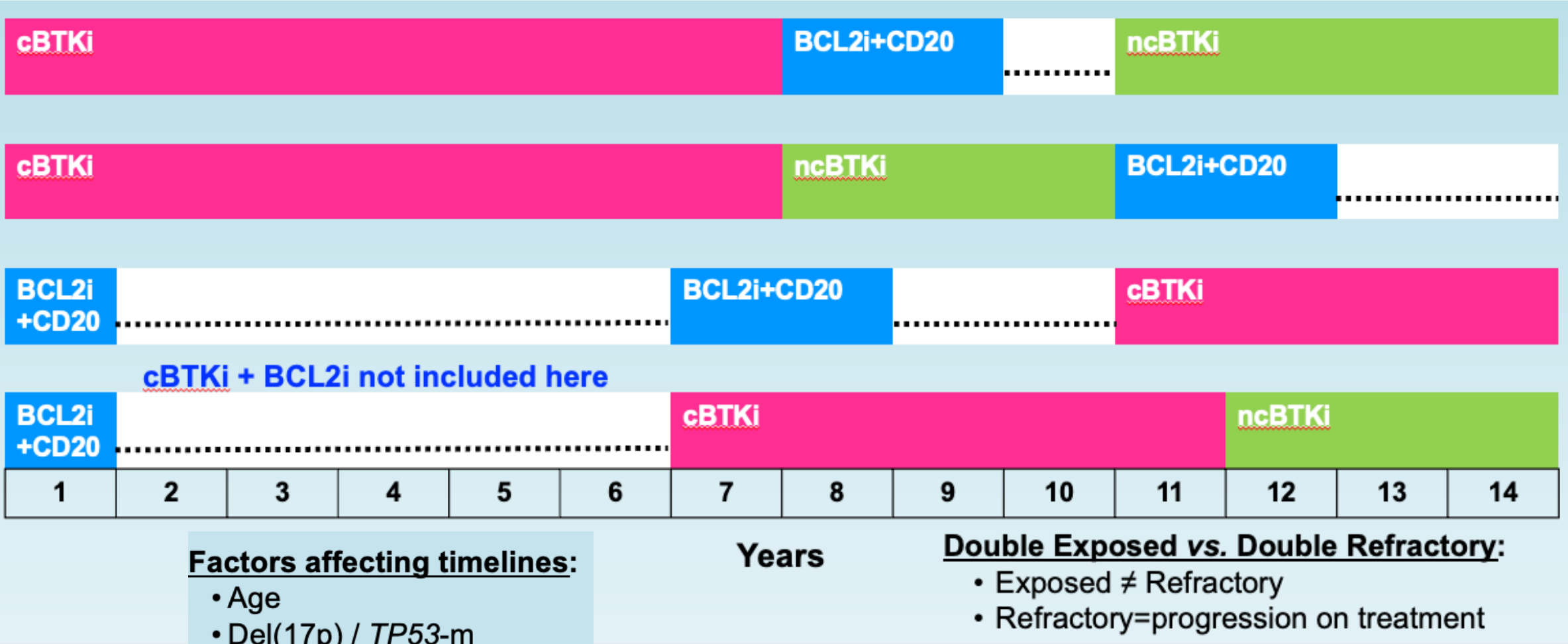
Years

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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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?

a. At least 6 months

b. At least 12 months

c. At least 24 months

d. At least 36 months

e. I'm not sure

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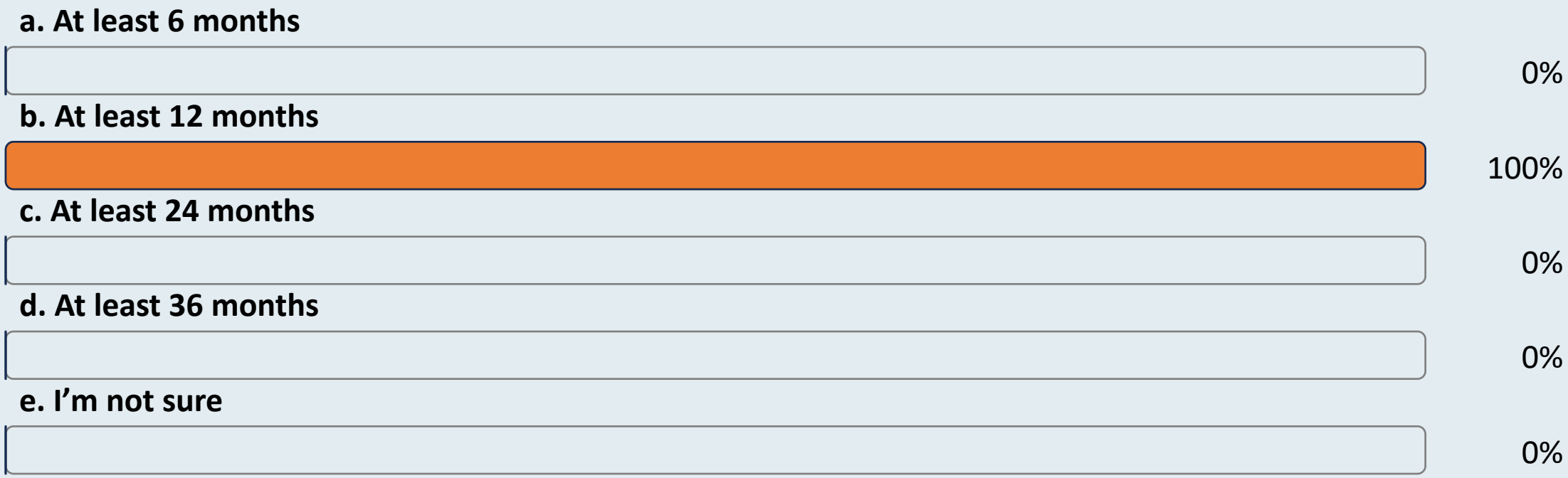
Showing Results

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?



RESULTS SLIDE

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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 Woyach	36 months

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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. What would be your preferred next treatment?

a. Alternative covalent BTK inhibitor

b. Venetoclax/anti-CD20 antibody

c. Pirtobrutinib

d. CAR T-cell therapy

e. Bispecific antibody

f. I'm not sure

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

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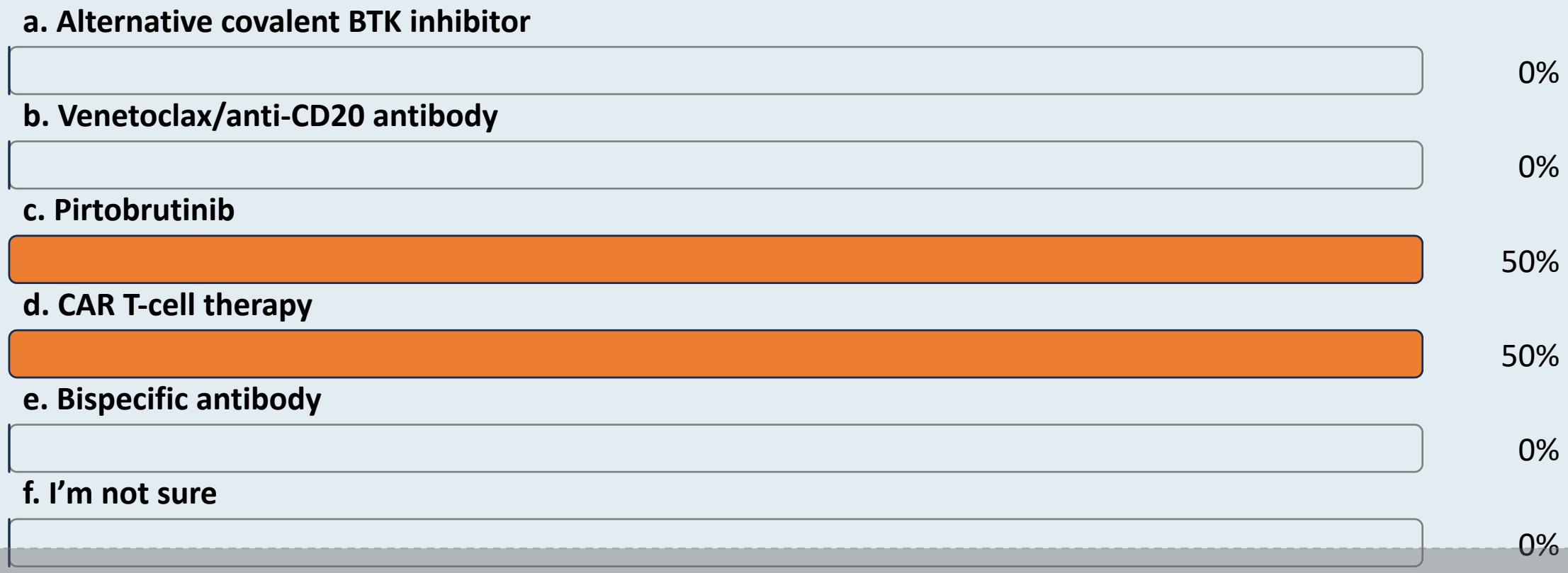
Showing Results

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. What would be your preferred next treatment?



RESULTS SLIDE

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

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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 Woyach	Pirtobrutinib

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

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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 Woyach	Pirtobrutinib

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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. What would be your preferred next treatment?

a. Alternative covalent BTK inhibitor

b. Venetoclax/anti-CD20 antibody

c. Pirtobrutinib

d. CAR T-cell therapy

e. Bispecific antibody

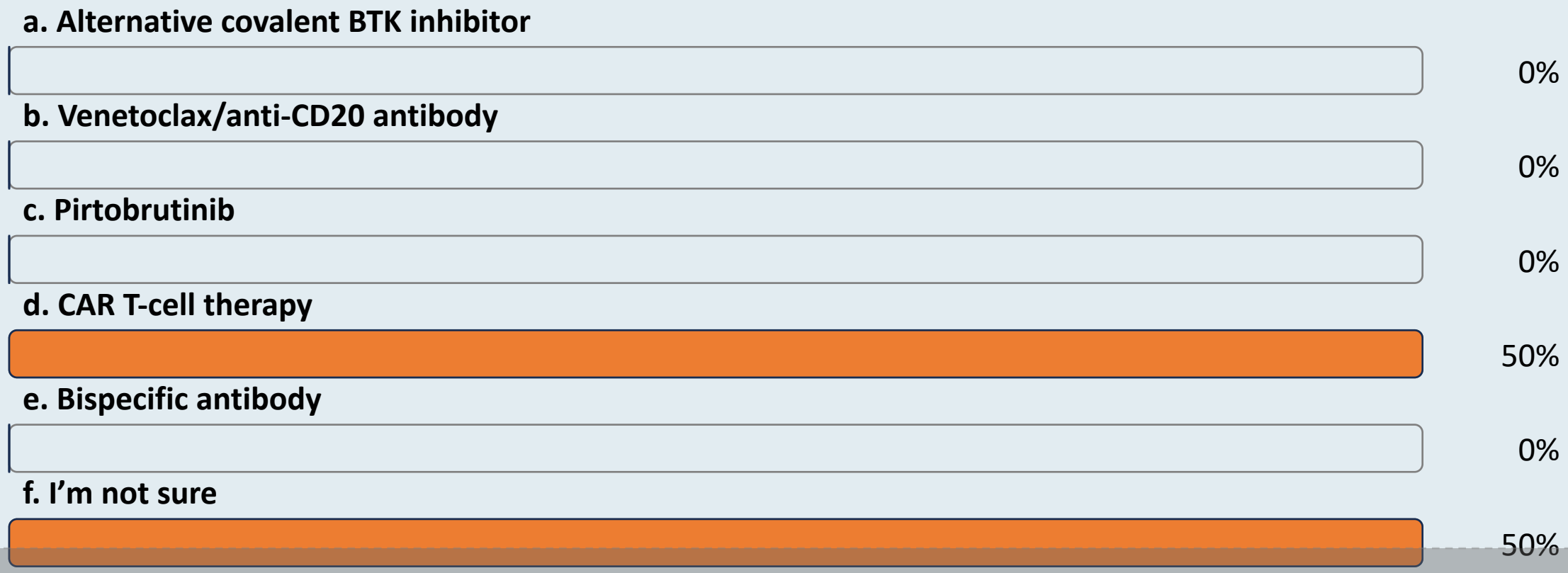
f. I'm not sure

Scan for live polling

RTP RESEARCH TO PRACTICE

Showing Results

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. What would be your preferred next treatment?



RESULTS SLIDE

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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 venetoclax/anti-CD20 antibody
 Dr Lamanna	Pirtobrutinib
 Dr Sharman	Pirtobrutinib
 Dr Woyach	Pirtobrutinib

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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 venetoclax/anti-CD20 antibody
 Dr Lamanna	Venetoclax/anti-CD20 antibody
 Dr Sharman	Pirtobrutinib
 Dr Woyach	Pirtobrutinib

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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 Woyach	Pirtobrutinib or CAR-T

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

 Dr Coombs	Alternative covalent BTKi
 Dr Davids	Alternative covalent BTKi
 Dr Fakhri	Alternative covalent BTKi
 Dr Lamanna	Alternative covalent BTKi or pirtobrutinib
 Dr Sharman	Alternative covalent BTKi
 Dr Woyach	Alternative covalent BTKi

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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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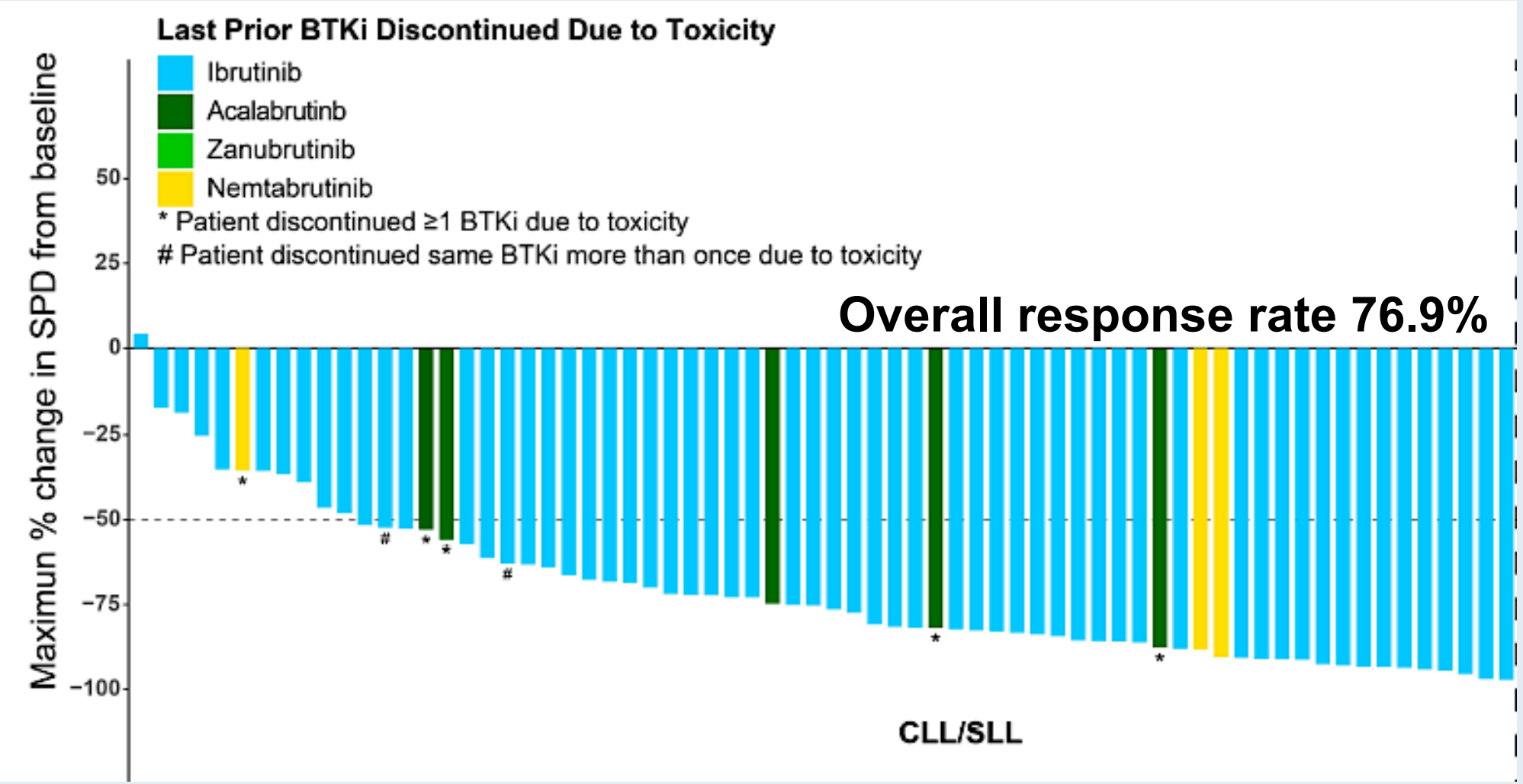
haematologica
Journal of the Ferrata Storti Foundation

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.

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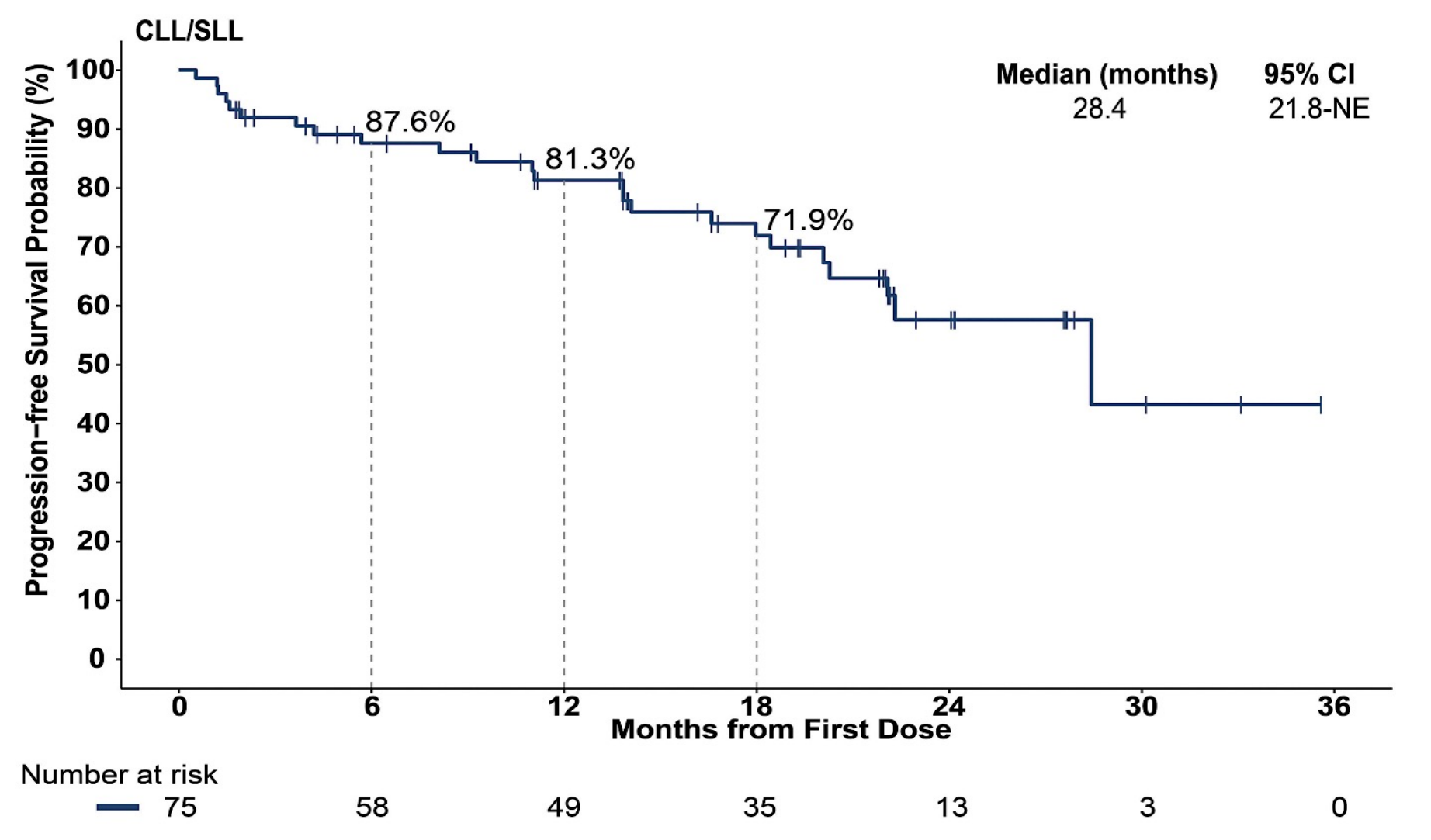
BRUIN: Median Progression-Free Survival for Patients with CLL/SLL



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

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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 Accelerated Approval to Pirtobrutinib for CLL or SLL

Press Release: December 1, 2023

"... the Food and Drug Administration granted accelerated approval to pirtobrutinib for adults with chronic lymphocytic leukemia or small lymphocytic lymphoma (CLL/SLL) who have received at least two prior lines of therapy, including a BTK inhibitor and a BCL-2 inhibitor.

Efficacy was evaluated in BRUIN (NCT03740529], an open-label, international, single-arm, multicohort trial that included 108 patients with CLL or SLL previously treated with at least two prior lines of therapy, including a BTK inhibitor and a BCL-2 inhibitor.

Pirtobrutinib was administered orally at 200 mg once daily and was continued until disease progression or unacceptable toxicity.

The main efficacy outcome measures were overall response rate (ORR) and duration of response (DOR), as assessed by an independent review committee using 2018 iwCLL criteria."

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

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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.

Which of the following best describes the major progression-free survival (PFS) findings from the Phase III BRUIN CLL-321 study of pirtobrutinib monotherapy versus idelalisib/rituximab or bendamustine/rituximab for relapsed/refractory CLL?

a. Inferior PFS outcomes with pirtobrutinib monotherapy

b. A numerical but nonsignificant improvement in PFS with pirtobrutinib monotherapy

c. A statistically significant improvement in PFS with pirtobrutinib monotherapy

d. I'm not sure

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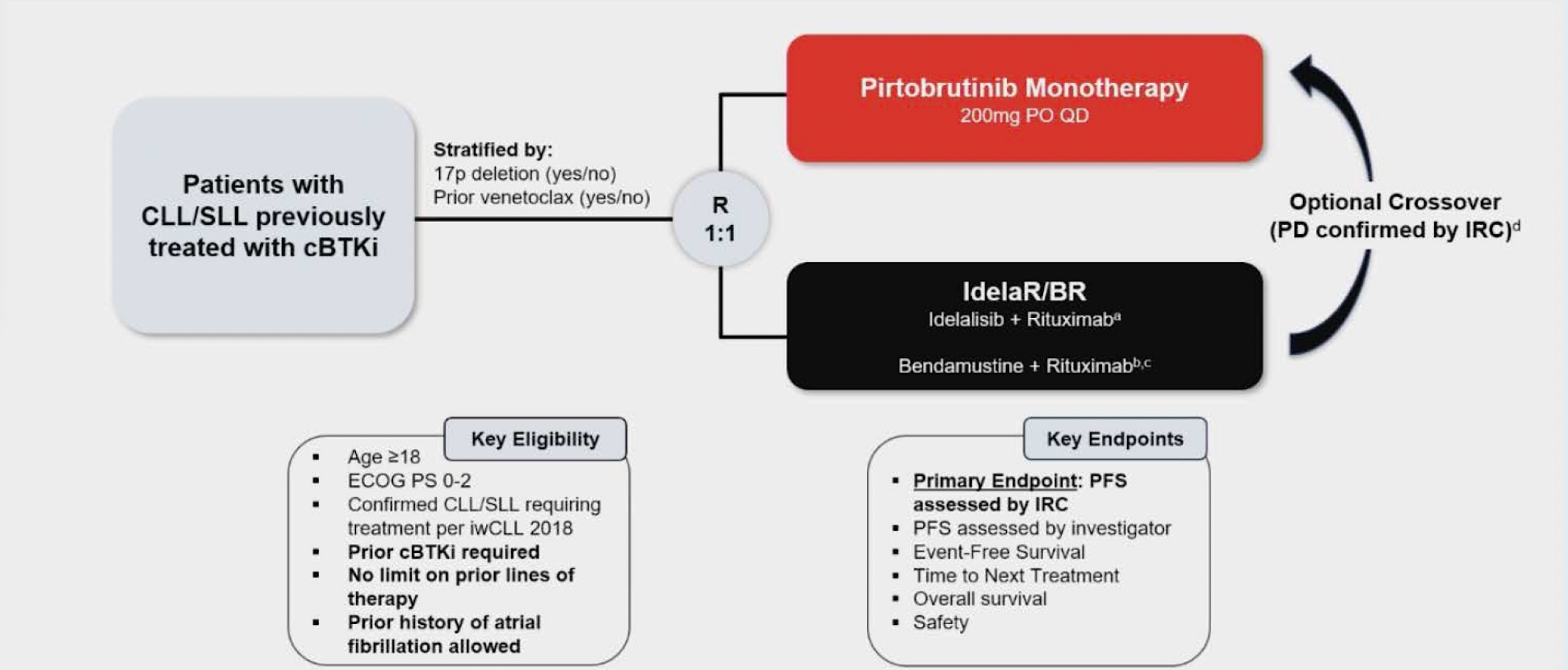
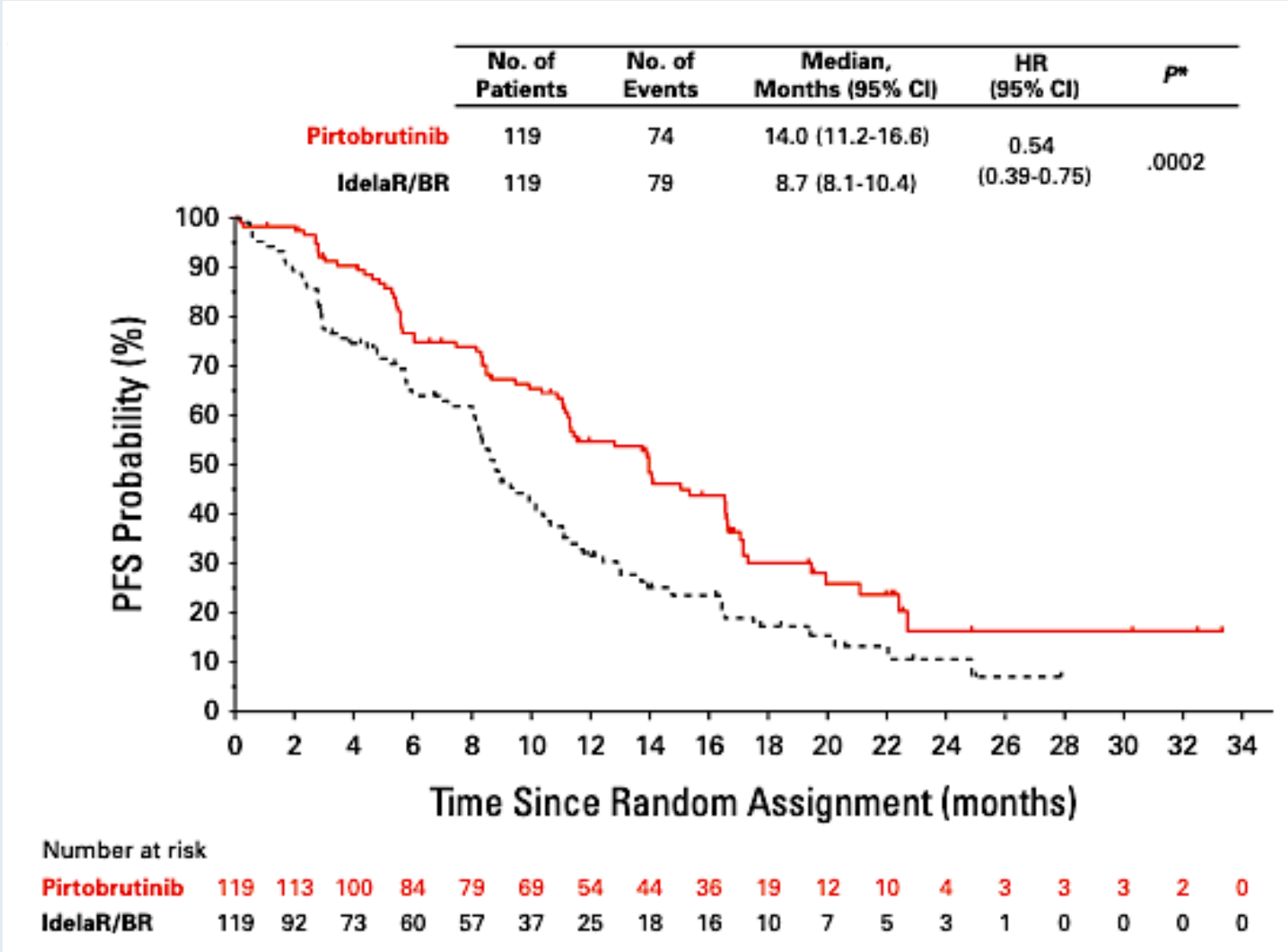
BRUIN CLL-321: A Phase III Trial of Pirtobrutinib Monotherapy for Relapsed/Refractory CLL



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)

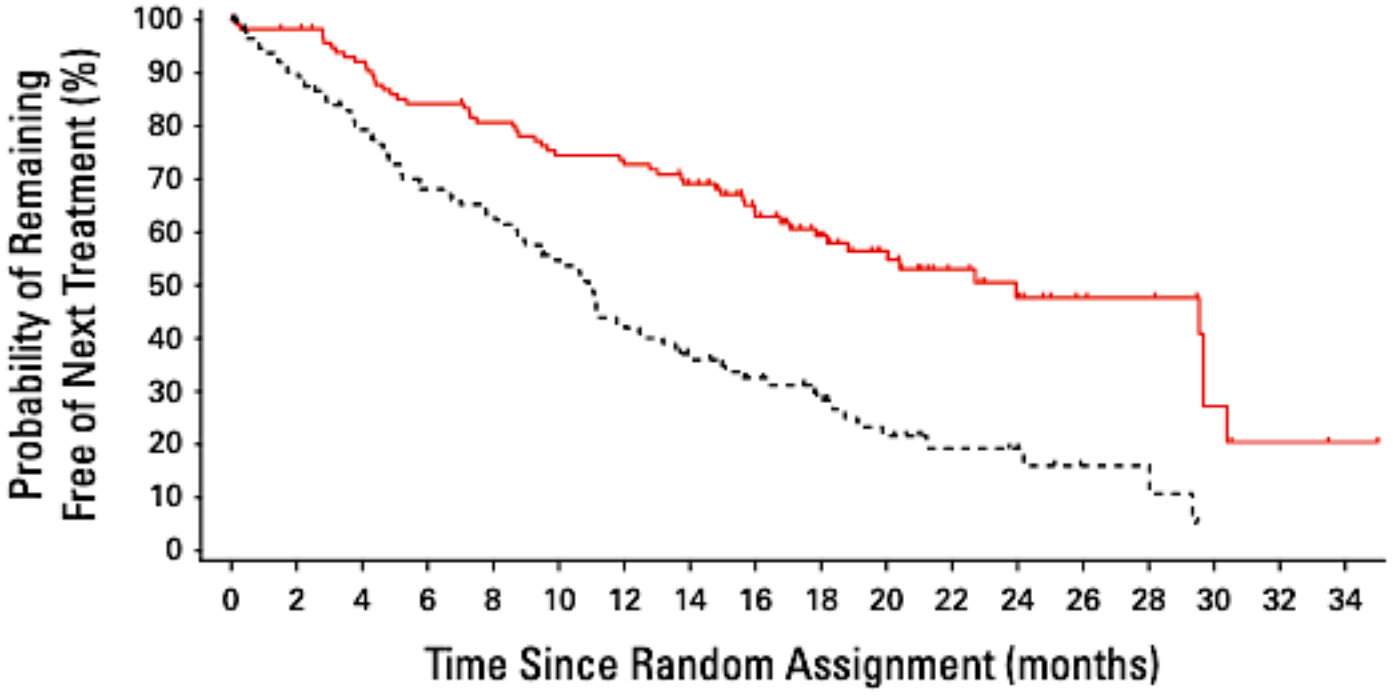


IRC = independent review committee

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)		



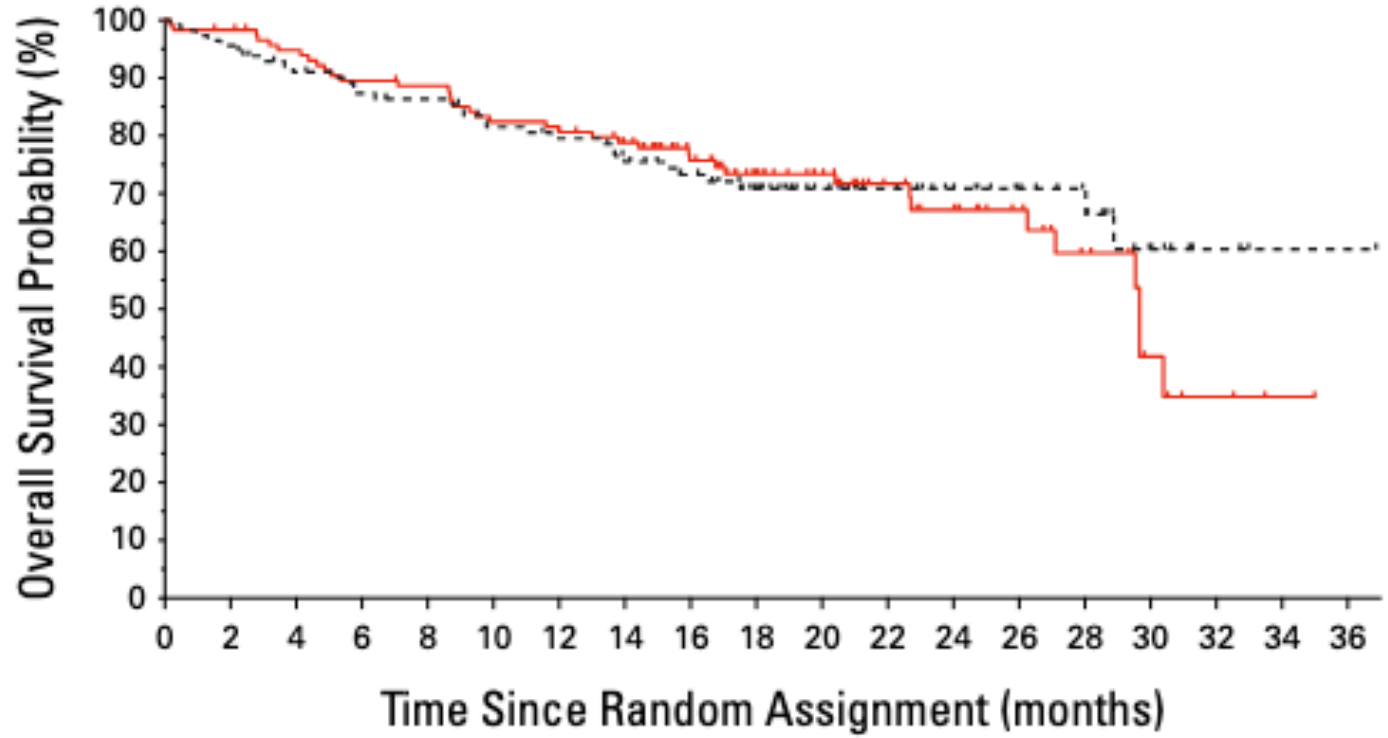
Number at risk:

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.

Which of the following ≥Grade 3 adverse events was most commonly reported in patients receiving pirtobrutinib for previously treated CLL in the Phase III BRUIN CLL-321 trial?

a. Atrial fibrillation

b. Infections

c. Keratitis

d. Hemorrhage

e. I’m not sure

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RTP RESEARCH TO PRACTICE

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

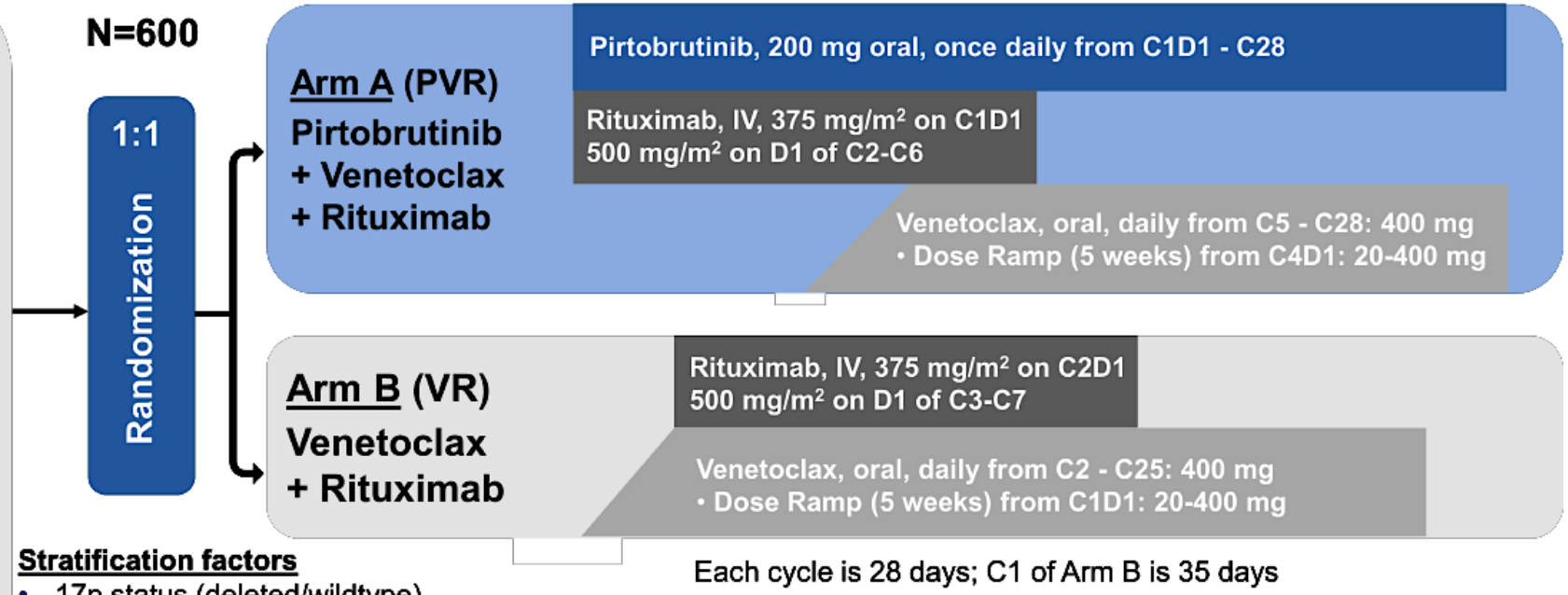
Adverse event	BTK inhibitor	Incidence Any grade, Grade ≥3 %	Management
Neutropenia	Ibrutinib	25-39, 13-31	Growth factor support
	Acalabrutinib	21-23, 13-19	
	Zanubrutinib	37-34, 15-19	
	Pirtobrutinib	25, 20.3	
Diarrhea	Ibrutinib	22-59, <1-4	Symptomatic treatments and dose adjustments Dietary modifications, 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.

Which of the following descriptions best characterizes the study design of the BRUIN CLL-314 trial?

a. A Phase II study evaluating time-limited pirtobrutinib for patients with CLL that was pretreated with prior BTK inhibitor and Bcl-2 inhibitor therapy

b. A Phase III superiority study evaluating pirtobrutinib versus ibrutinib for relapsed/refractory CLL

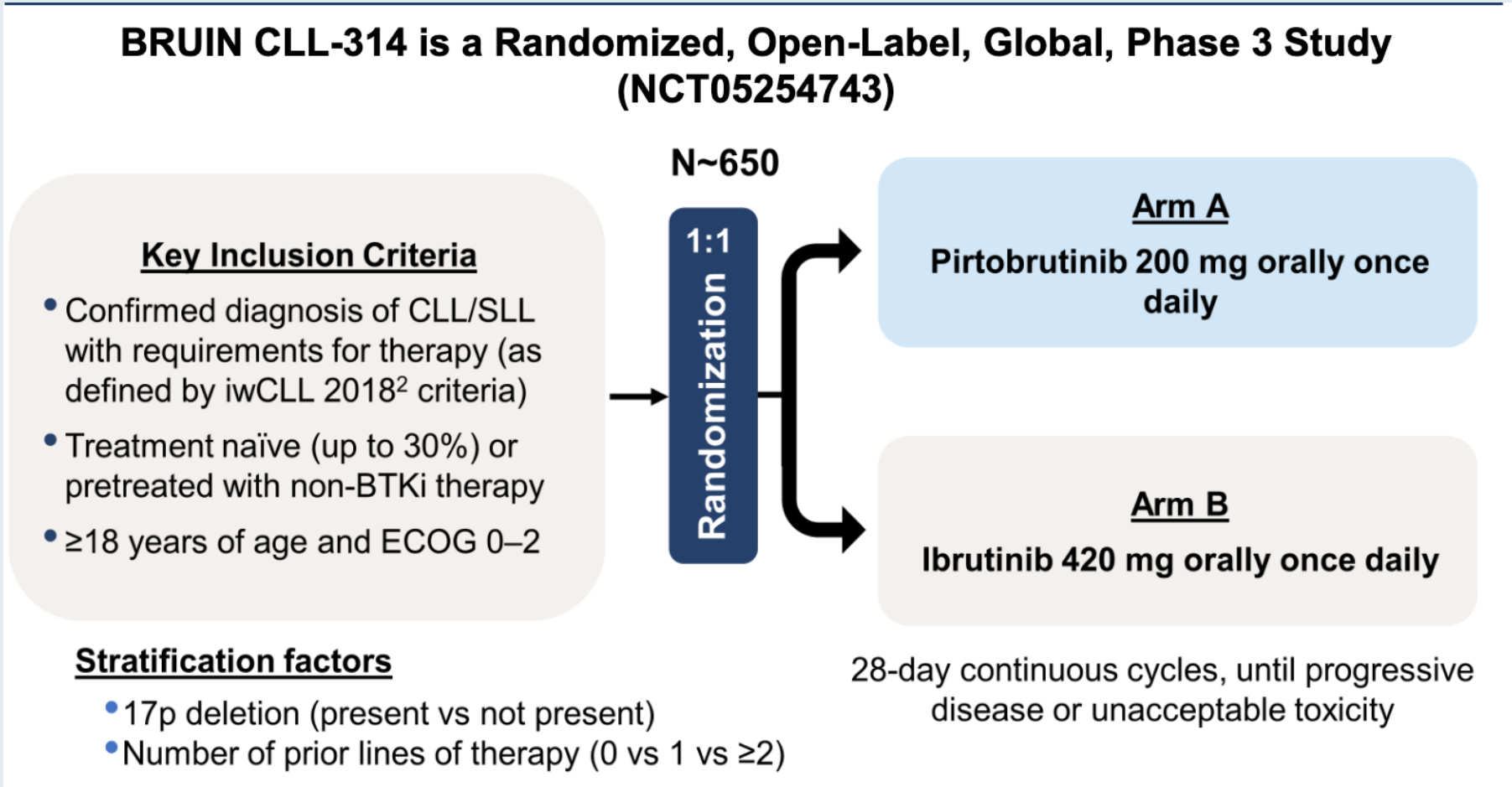
c. A Phase III noninferiority study evaluating pirtobrutinib versus ibrutinib for patients with CLL that was treatment-naïve or pretreated with non-BTK inhibitor therapy

d. I'm not sure

Scan for live polling

RTP RESEARCH TO PRACTICE

BRUIN CLL-314: A Phase III Trial of Pirtobrutinib versus Ibrutinib for Patients with CLL/SLL



Primary Endpoint

To establish noninferiority of pirtobrutinib to ibrutinib by comparing the overall response rate per iwCLL criteria as assessed by IRC

Key Secondary Endpoints

To determine the superiority of pirtobrutinib to ibrutinib with respect to IRC-assessed event-free survival and progression-free survival

Escalón MP et al. iwCLL 2023;Abstract 1548596.

Phase III BRUIN CLL-314 Trial of Pirtobrutinib versus Ibrutinib for CLL/SLL Meets Primary Endpoint

Press Release: July 29, 2025

Positive topline results were announced from the Phase III BRUIN CLL-314 trial comparing pirtobrutinib, a noncovalent (reversible) BTK inhibitor, to ibrutinib, a covalent BTK inhibitor, for patients with treatment-naïve CLL/SLL.

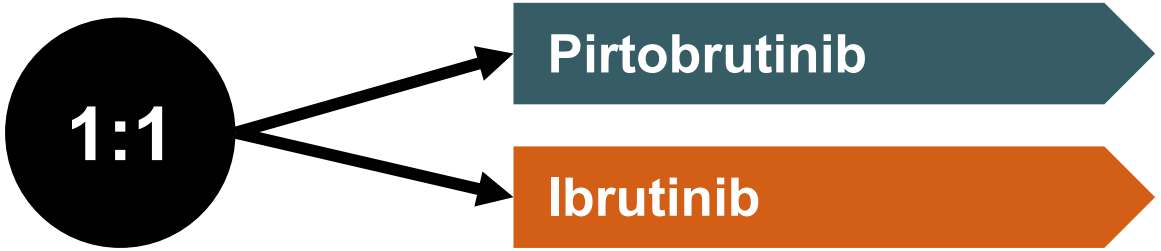
“This study enrolled patients with treatment-naïve CLL/SLL and those who had been previously treated but were BTK inhibitor-naïve. The study met its primary endpoint of non-inferiority on overall response rate (ORR) as assessed by an independent review committee (IRC) in both the pre-treated and intent-to-treat populations. ORR favored pirtobrutinib with a nominal P-value for superiority (p <0.05). Progression free survival (PFS), a key secondary endpoint, was not yet mature at this analysis, but was trending in favor of pirtobrutinib. A formal PFS analysis testing for superiority is planned at a future analysis. No detriment was observed for overall survival (OS).

The overall safety profile of pirtobrutinib in BRUIN CLL-314 was similar to previously reported trials. Detailed results will be presented at a medical congress later in 2025.”

https://investor.lilly.com/news-releases/news-release-details/lillys-jaypirca-pirtobrutinib-first-and-only-approved-non

BRUIN CLL-314: Pirtobrutinib vs Ibrutinib

- 662 patients were randomized: 225 TN and 437 R/R
- Primary endpoint was ORR and powered for non-inferiority
- Pirtobrutinib was non-inferior for ORR in ITT and R/R cohorts



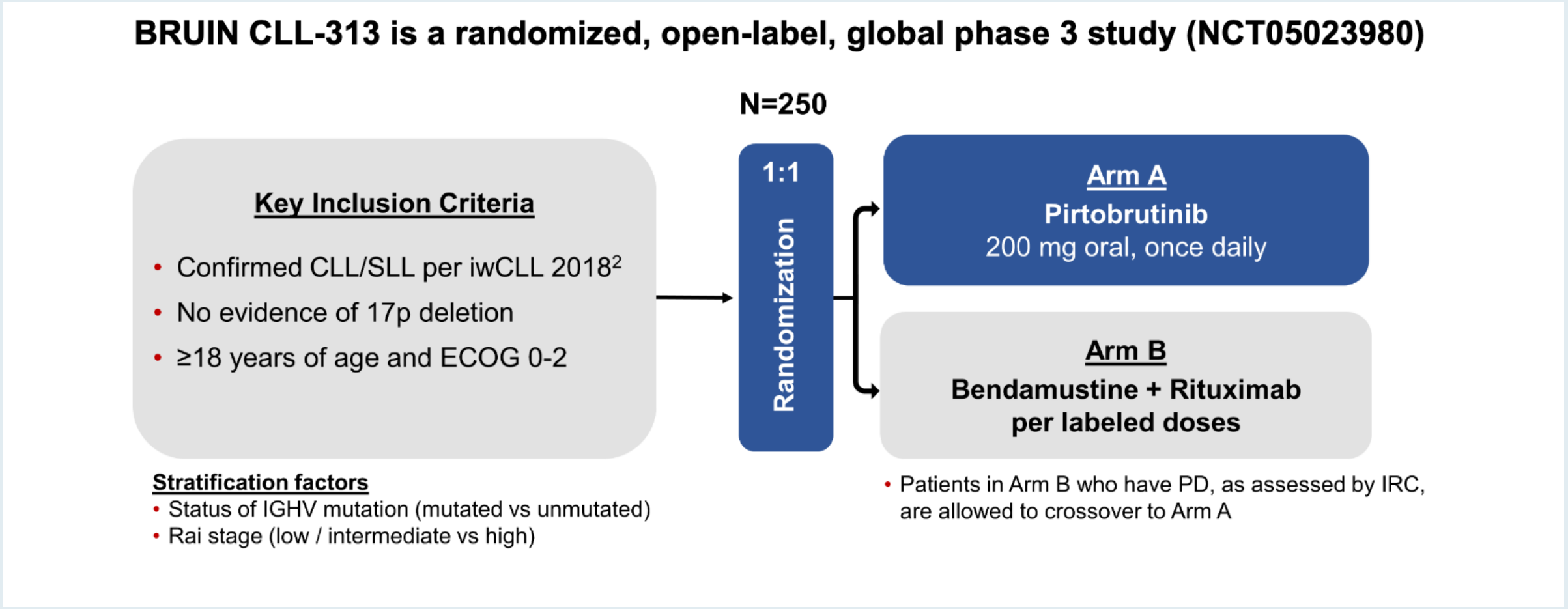
	ORR ITT	18-month PFS ITT	Atrial Fibrillation Hypertension
Pirtobrutinib	87.0%	86.9%	2.4% 10.6%
Ibrutinib	78.6%	82.3%	13.5% 15.1%

p<0.0001

Woyach et al., ASH 2025 (abstract)

Courtesy of Kerry A Rogers, MD

BRUIN CLL-313: A Phase III Trial Comparing Pirtobrutinib to Bendamustine/Rituximab for Untreated CLL/SLL



PD = disease progression

Jurczak W et al. ASH 2021;Abstract 3732.

Phase III BRUIN CLL-313 Trial of First-Line Pirtobrutinib versus Bendamustine/Rituximab in CLL Meets Primary Endpoint

Press Release: September 8, 2025

Positive topline results were announced from the Phase III BRUIN CLL-313 trial of pirtobrutinib, a noncovalent (reversible) BTK inhibitor, versus chemoimmunotherapy (bendamustine and rituximab) for patients with treatment-naïve CLL/SLL without 17p deletions.

“The study met its primary endpoint, demonstrating a highly statistically significant and clinically meaningful improvement in progression-free survival (PFS) compared to chemoimmunotherapy, as assessed by an independent review committee (IRC), indicating one of the most compelling effect sizes ever observed for a single agent BTK inhibitor in a front-line CLL study.

Overall survival (OS), a key secondary endpoint, was not yet mature at this analysis, but was trending strongly in favor of pirtobrutinib and will be tested for statistical significance at the time of the primary OS analysis, which is anticipated to occur in 2026. The overall safety profile of pirtobrutinib in BRUIN CLL-313 was generally consistent with previously reported trials across treatment settings.

Detailed results will be presented at a medical congress and submitted to a peer-reviewed journal.”

https://www.prnewswire.com/news-releases/lillys-jaypirca-pirtobrutinib-the-first-and-only-approved-non-covalent-reversible-btk-inhibitor-significantly-improved-progression-free-survival-in-patients-with-treatment-naive-cllsll-302548399.html

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

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

a. About the same

b. Ibrutinib has the least toxicity

c. Acalabrutinib has the least toxicity

d. Zanubrutinib has the least toxicity

e. Pirtobrutinib has the least toxicity

f. I'm not sure

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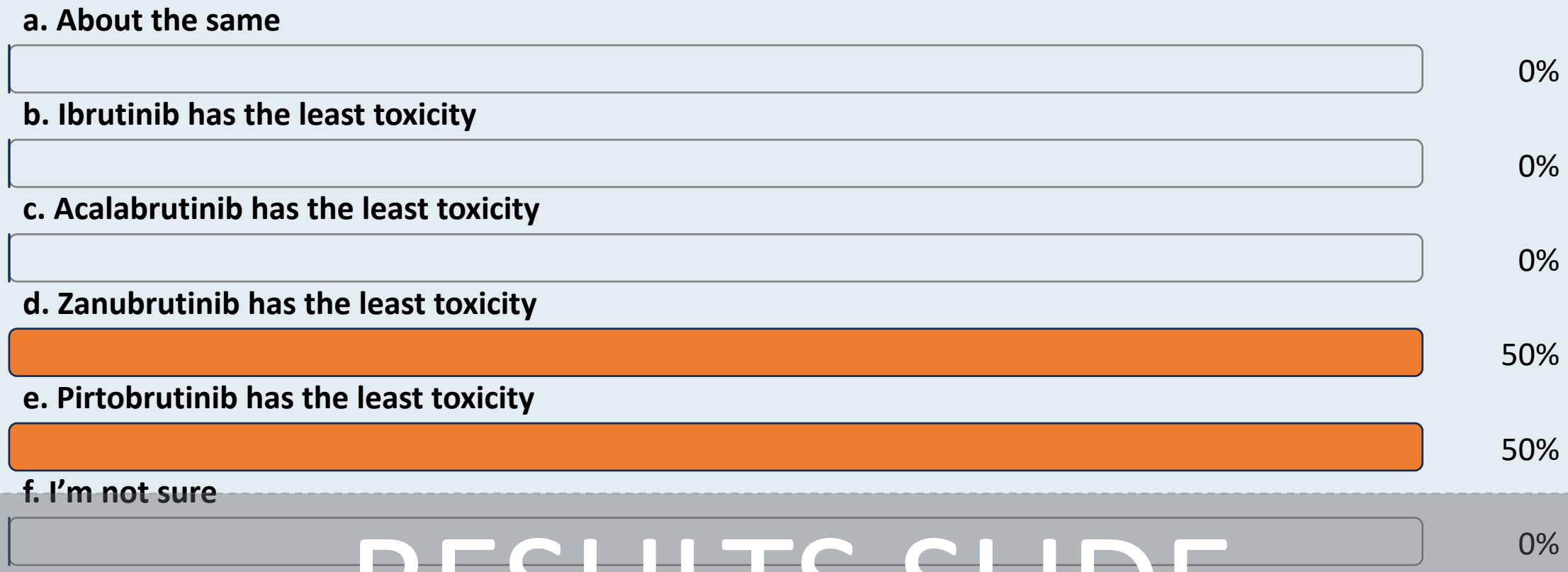
RTP RESEARCH TO PRACTICE

Showing Results

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



RESULTS SLIDE

RTP RESEARCH TO PRACTICE

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 Woyach	Acalabrutinib and zanubrutinib are the most efficacious	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 following the recommendation of first-line treatment with pirtobrutinib. How would you respond?

a. I agree with this recommendation

b. I do not agree with the recommendation, but it is a valid option

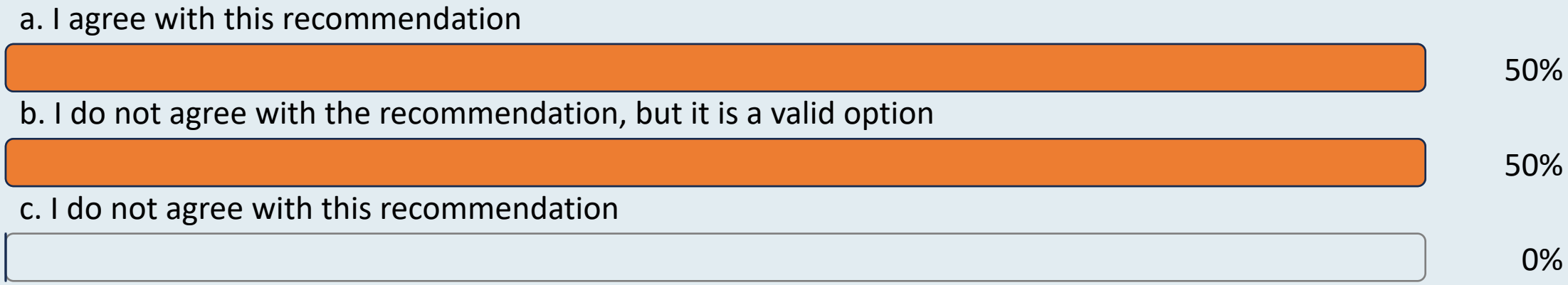
c. I do not agree with this recommendation

Scan for live polling

RTP RESEARCH TO PRACTICE

Showing Results

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



RESULTS SLIDE

RTP RESEARCH TO PRACTICE

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 Woyach	I agree with this recommendation

RTP
RESEARCH
TO PRACTICE

Management of Double-Refractory CLL

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Module 3: Clinician Survey Results

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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

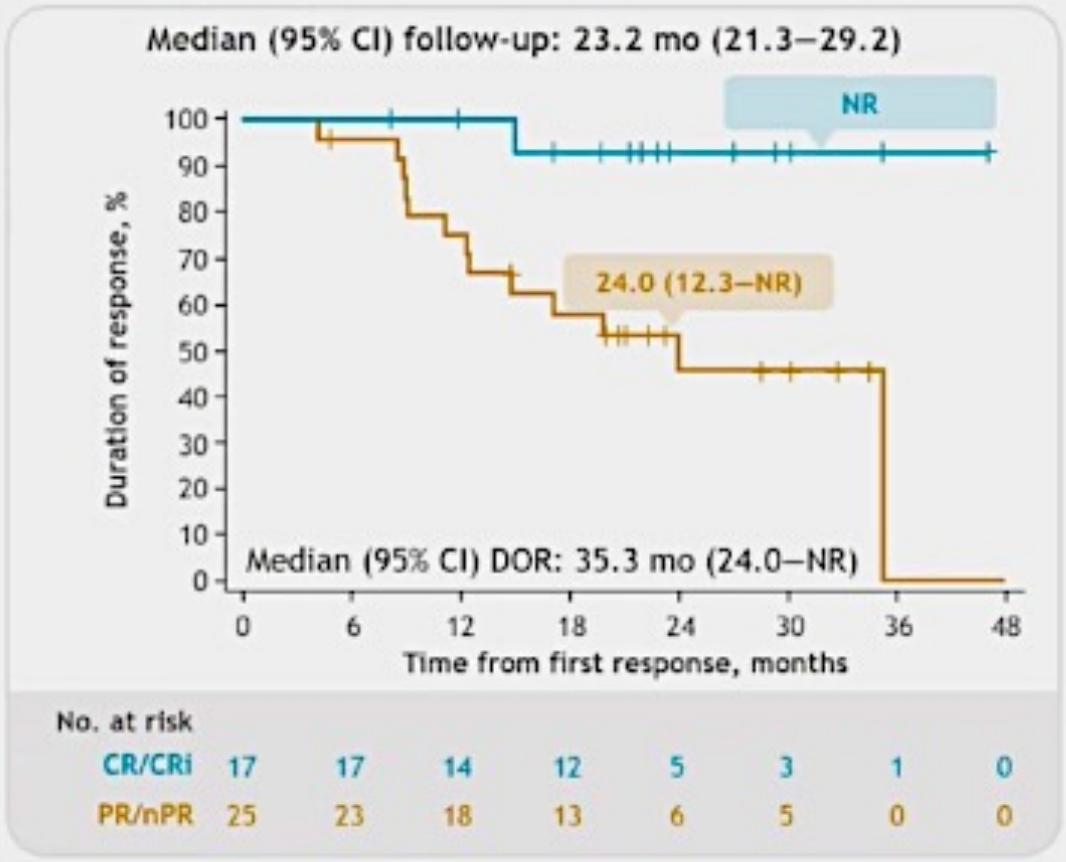
Tanya Siddiqi,[1] David G. Maloney,[2] Saad S. Kenderian,[3] Danielle M. Brander,[4] Kathleen Dorritie,[5] Jacob Soumerai,[6] Peter A. Riedell,[7] Nirav N. Shah,[8] Rajneesh Nath,[9] Bita Fakhri,[10] Deborah M. Stephens,[11] Shuo Ma,[12] Tatyana Feldman,[13] Scott R. Solomon,[14] Stephen J. Schuster,[15]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

[1]City of Hope National Medical Center, Duarte, CA, USA; [2]Fred Hutchinson Cancer Research Center, Seattle, WA, USA; [3]Mayo Clinic, Rochester, MN, USA; [4]Duke University Health System, Durham, NC, USA; [5]UPMC Hillman Cancer Center, University of Pittsburgh, Pittsburgh, PA, USA; [6]Center for Lymphoma, Massachusetts General Hospital Cancer Center, Boston, MA, USA; [7]David and Etta Jonas Center for Cellular Therapy, University of Chicago, Chicago, IL, USA; [8]Medical College of Wisconsin, Milwaukee, WI, USA; [9]Banner MD Anderson Cancer Center, Gilbert, AZ, USA; [10]University of California San Francisco, San Francisco, CA, USA; [11]Huntsman Cancer Institute, University of Utah, Salt Lake City, UT, USA; [12]Robert H. Lurie Comprehensive Cancer Center of Northwestern University, Chicago, IL, USA; [13]John Theurer Cancer Center at Hackensack Meridian Health, HMH School of Medicine, Hackensack, NJ, USA; [14]Northside Hospital Cancer Institute, Atlanta, GA, USA; [15]Abramson Cancer Center, University of Pennsylvania, Philadelphia, PA, USA; [16]Bristol Myers Squibb, Princeton, NJ, USA; [17]Bristol Myers Squibb, Seattle, WA, USA; [18]The University of Texas MD Anderson Cancer Center, Houston, TX, USA

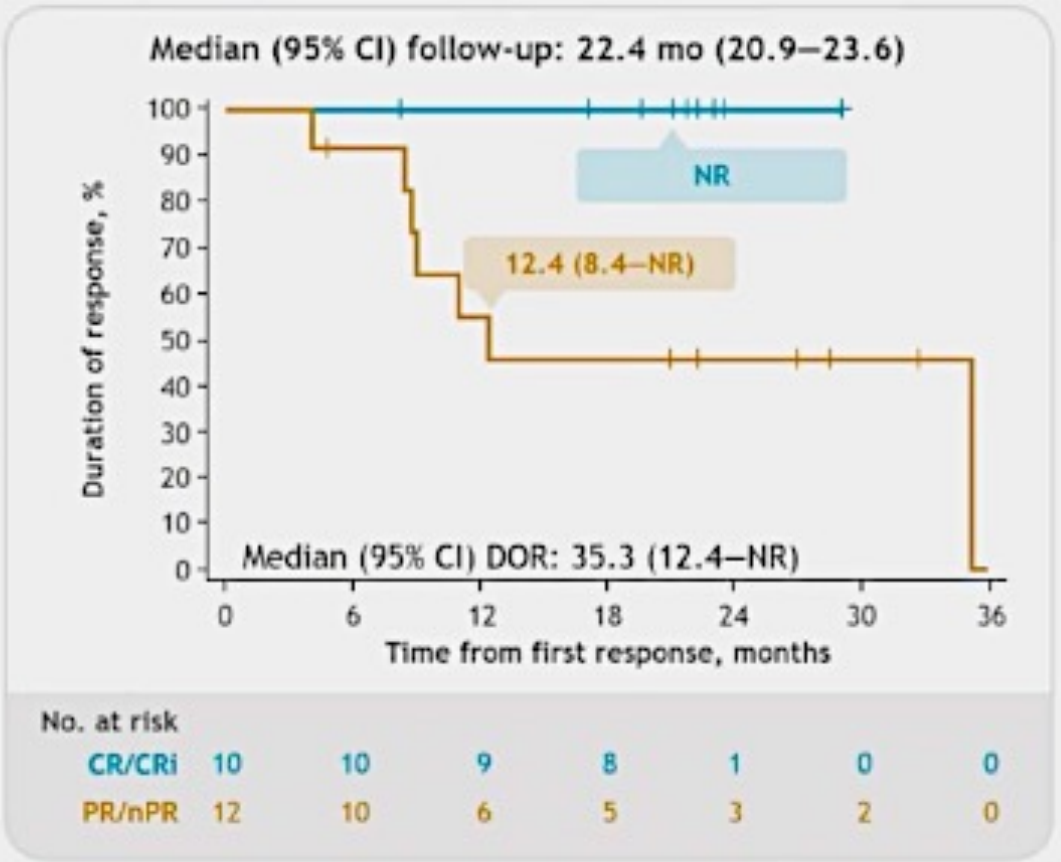
ASH 2023, Presentation 330

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

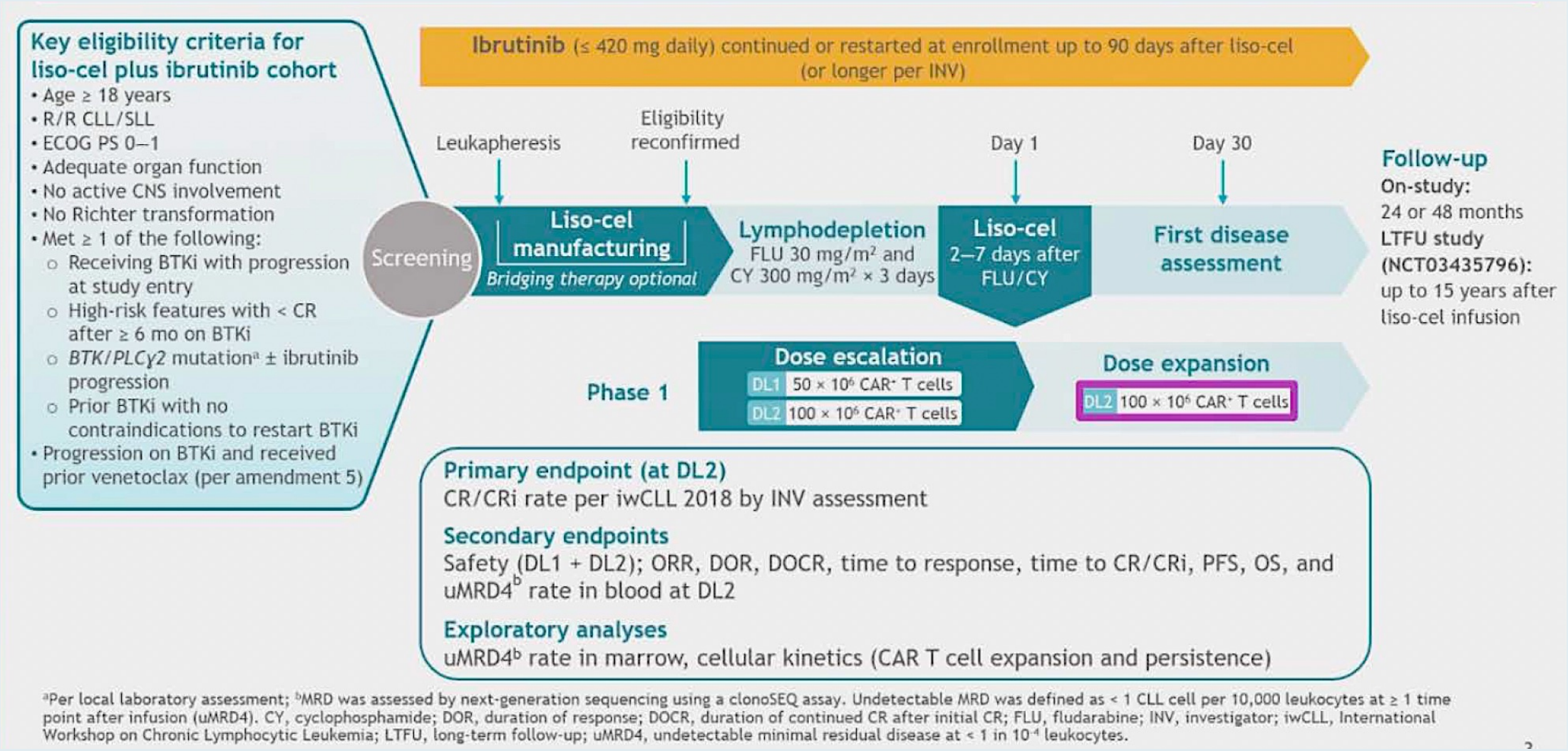
William G. Wierda, MD, PhD,[1] Kathleen Dorritie, MD,[2] Jordan Gauthier, MD, MSc,[3] Rajneesh Nath, MD,[4] Thomas Kipps, MD, PhD,[5] Peter A. Riedell, MD,[6] Herbert A. Eradat, MD,[7] Saad S. Kenderian, MB, ChB,[8] Mohamed A. Kharfan-Dabaja, MD, MBA,[9] Nirav N. Shah, MD,[10] Scott R. Solomon, MD,[11]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

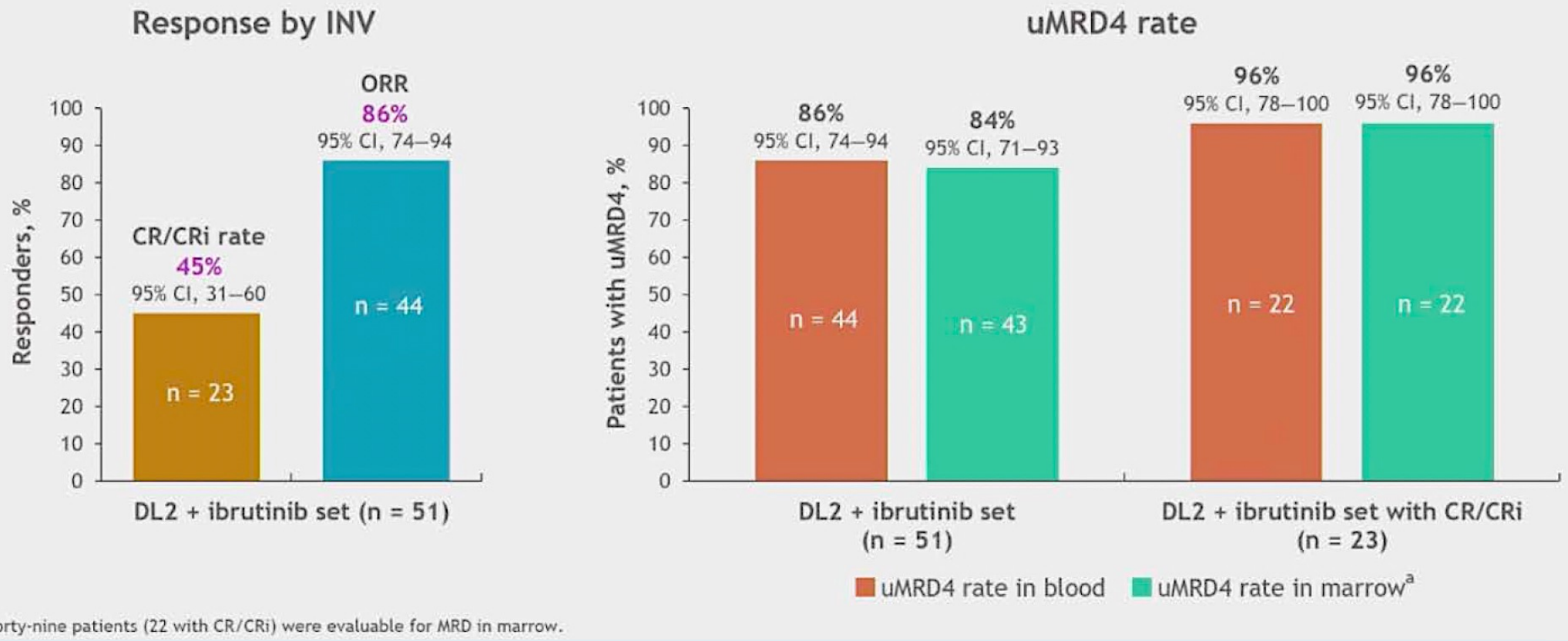


[a]Per local laboratory assessment; [b]MRD was assessed by next-generation sequencing using a clonoSEQ assay. Undetectable MRD was defined as < 1 CLL cell per 10,000 leukocytes at ≥ 1 time point after infusion (uMRD4). CY, cyclophosphamide; DOR, duration of response; DOCR, duration of continued CR after 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)



[a]Forty-nine patients (22 with CR/CRi) were evaluable for MRD in marrow.

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

Wierda WG et al. ASH 2024;Abstract 887.

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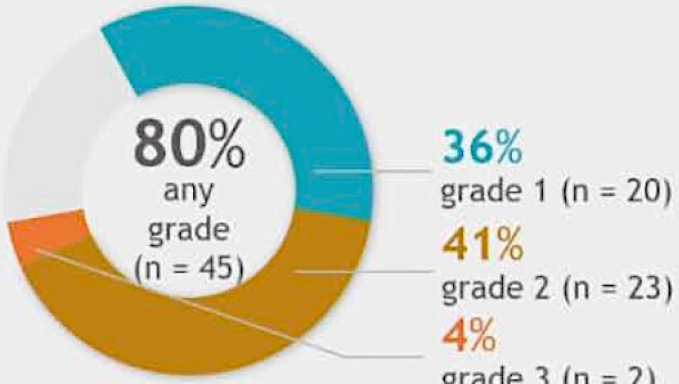
TRANSCEND CLL 004: Incidence of Cytokine Release Syndrome (CRS) and Neurological Adverse Events (NEs) with Liso-cel and Ibrutinib

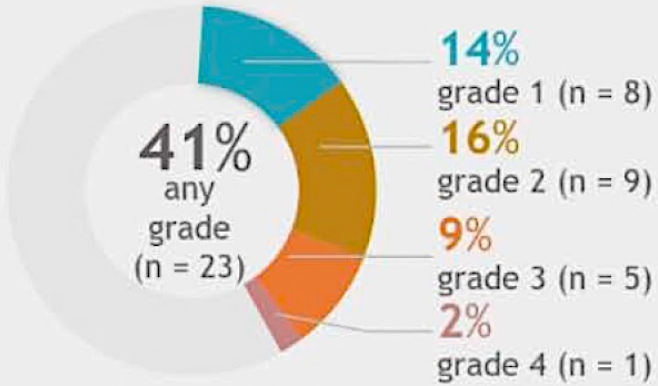
CRS[a,b]



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.

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

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?

a. At first relapse

b. At second relapse

c. At third relapse

d. After third relapse

e. I am not referring patients with CLL for CAR T-cell therapy

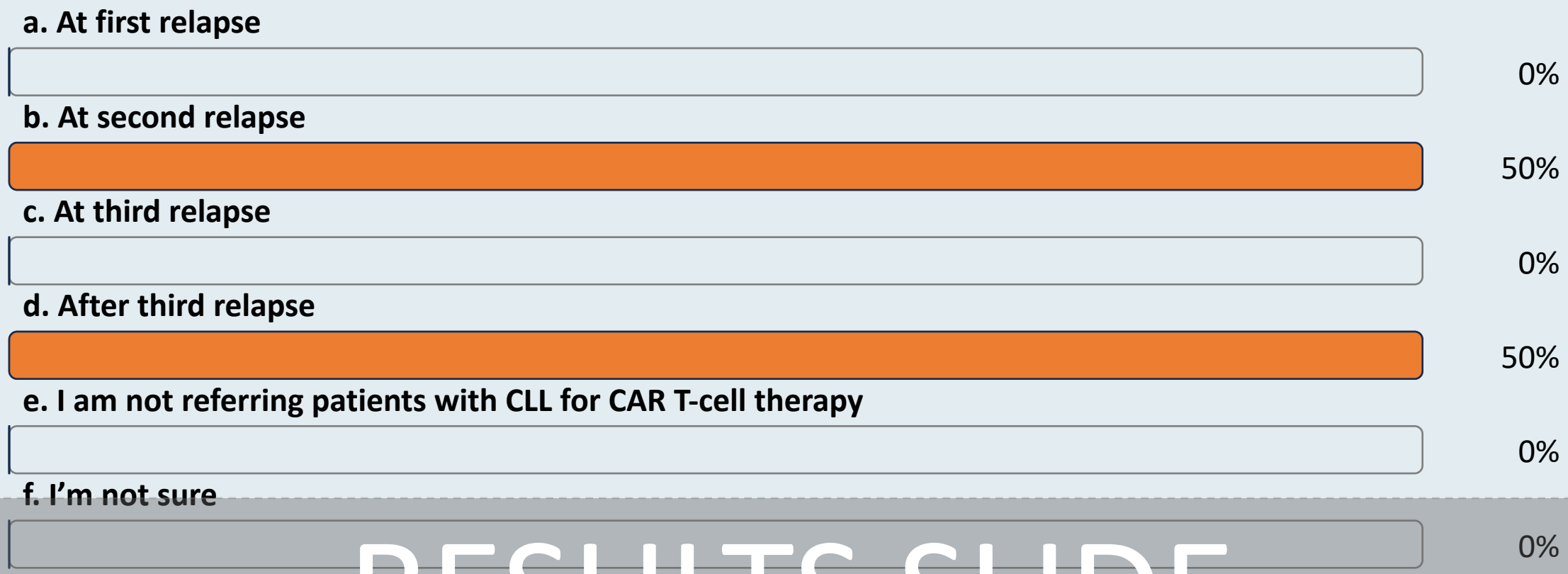
f. I’m not sure

Scan for live polling

RTP RESEARCH TO PRACTICE

Showing Results

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?



RESULTS SLIDE

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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	After third relapse
 Dr Lamanna	After third relapse
 Dr Sharman	At second relapse
 Dr Woyach	At second relapse

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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 Woyach	5 patients

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

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.
- Scarfò L et al. **Updated efficacy and safety** of the Bruton tyrosine kinase (BTK) degrader **BGB-16673** in patients (pts) with relapsed or refractory (R/R) CLL/SLL: Results from the ongoing **phase (ph) 1 CADANCE-101 study**. EHA 2025;Abstract S158.
- 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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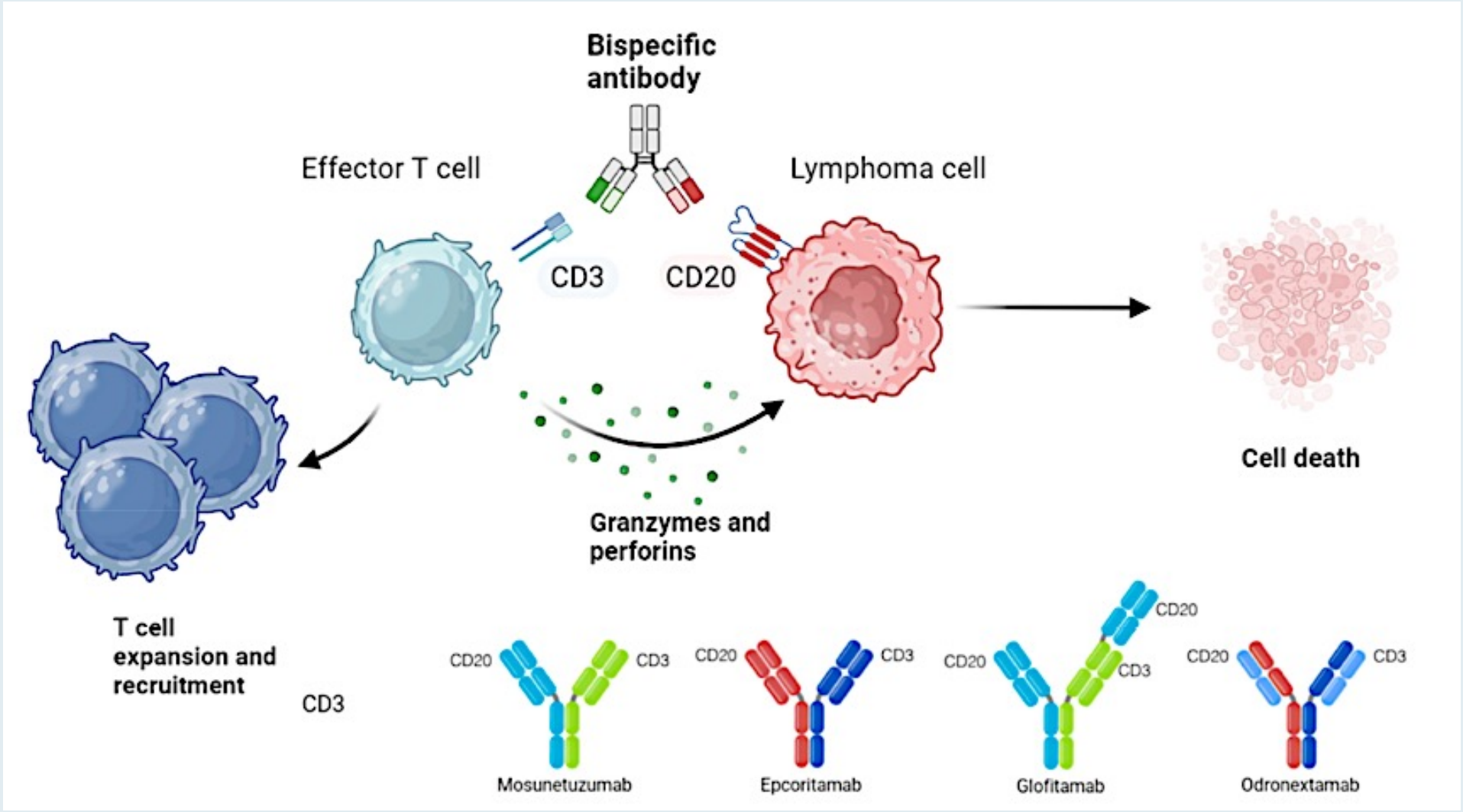
Mechanism of Action of CD20 x CD3 Bispecific Antibodies



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

RTP RESEARCH TO PRACTICE

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

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

ASH 2024;Abstract 883

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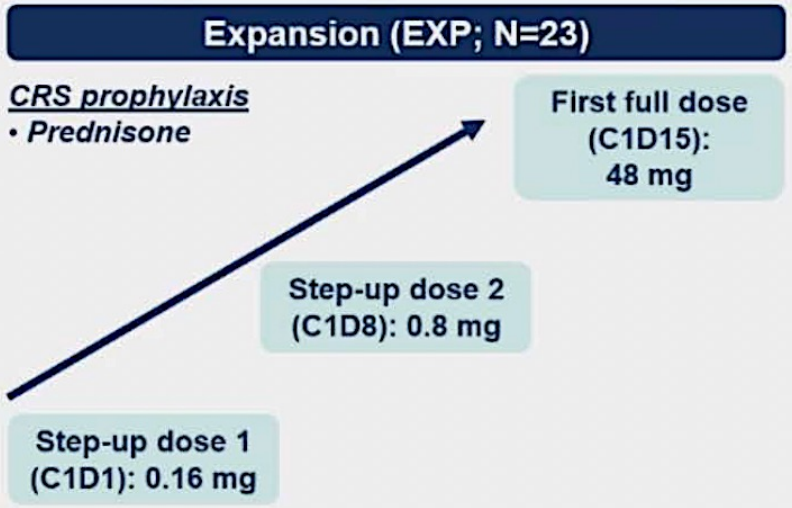
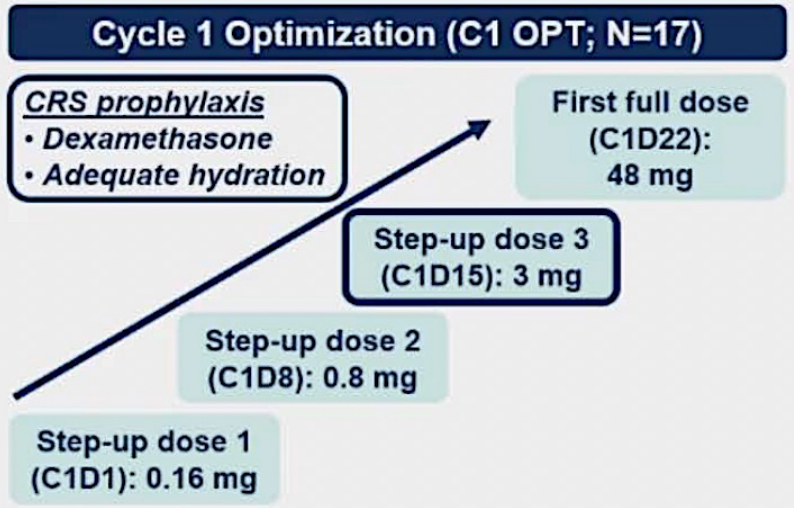
EPCORE CLL-1 Trial Expansion and Cycle 1 Optimization

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)

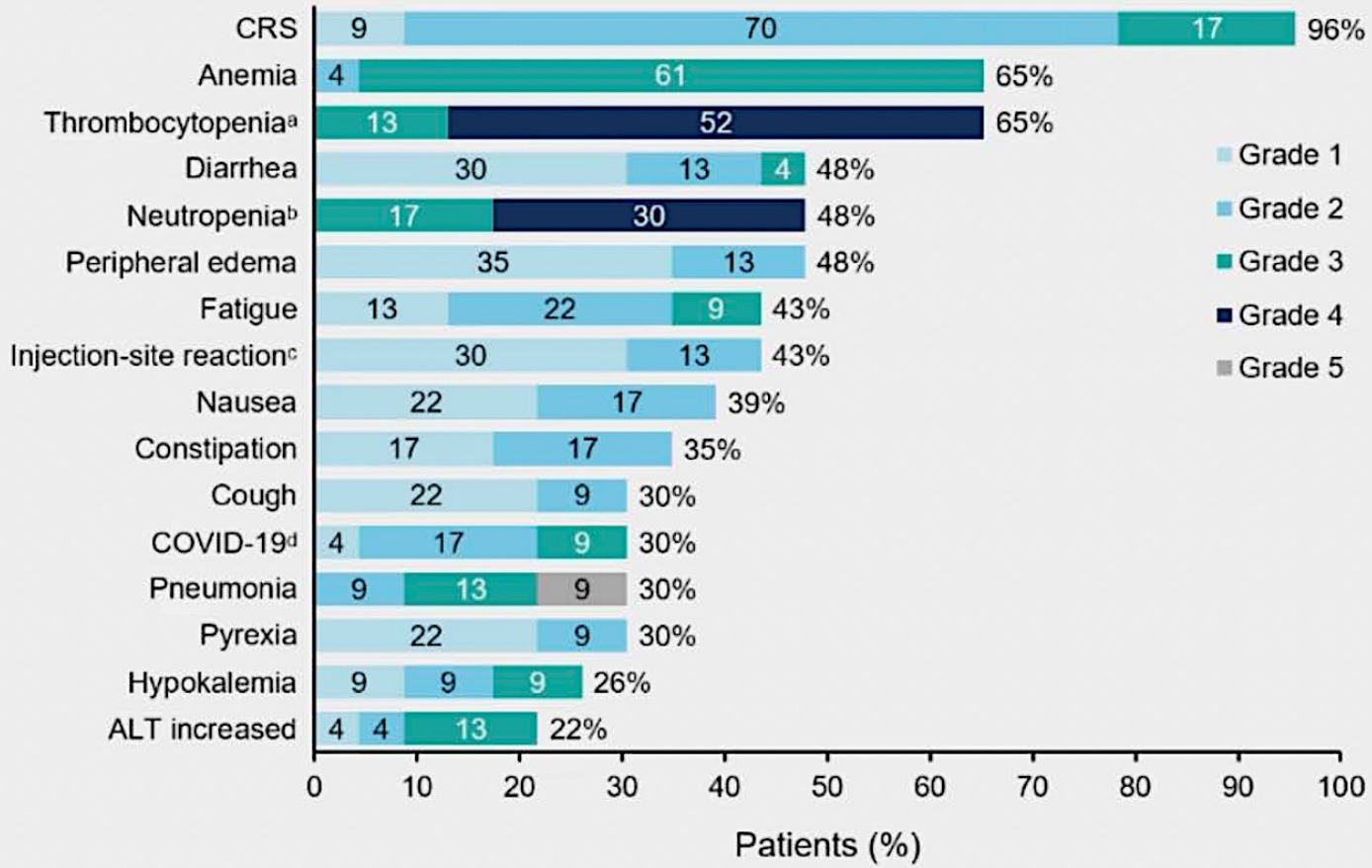
- With limited follow-up, the C1 OPT regimen does not appear to affect epcoritamab efficacy
- uMRD4 in PBMCs was observed in most responders, including all patients with CR who were tested for MRD

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)

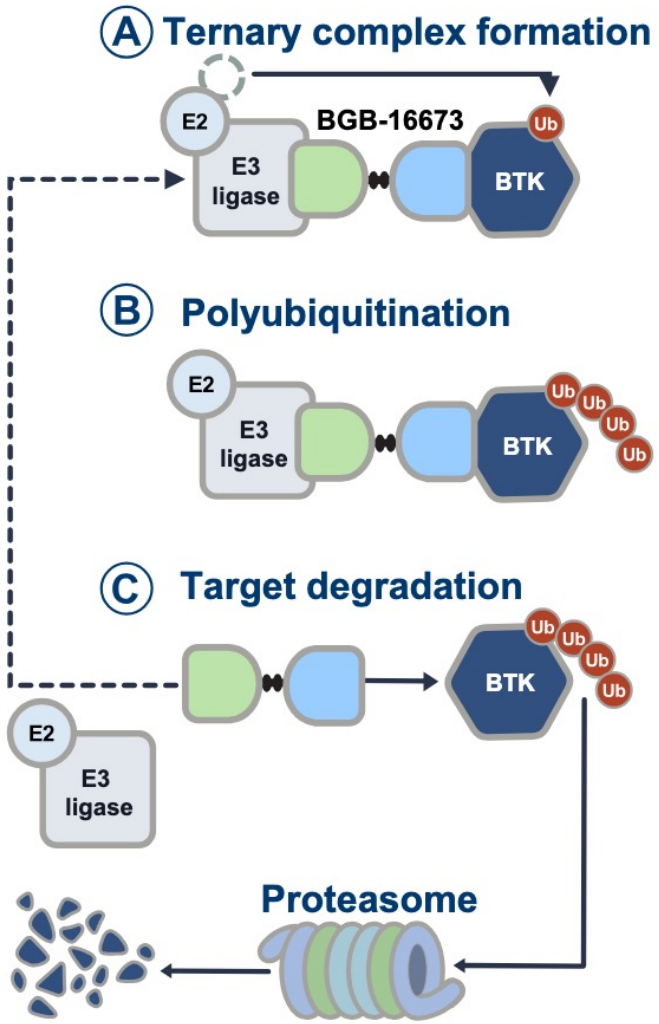
- TEAEs were primarily low grade (G1–2)
- TEAEs led to treatment discontinuation in 5 patients from EXP and 1 patient from C1 OPT
- 4 fatal TEAEs[e] occurred in EXP; none occurred in C1 OPT

[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

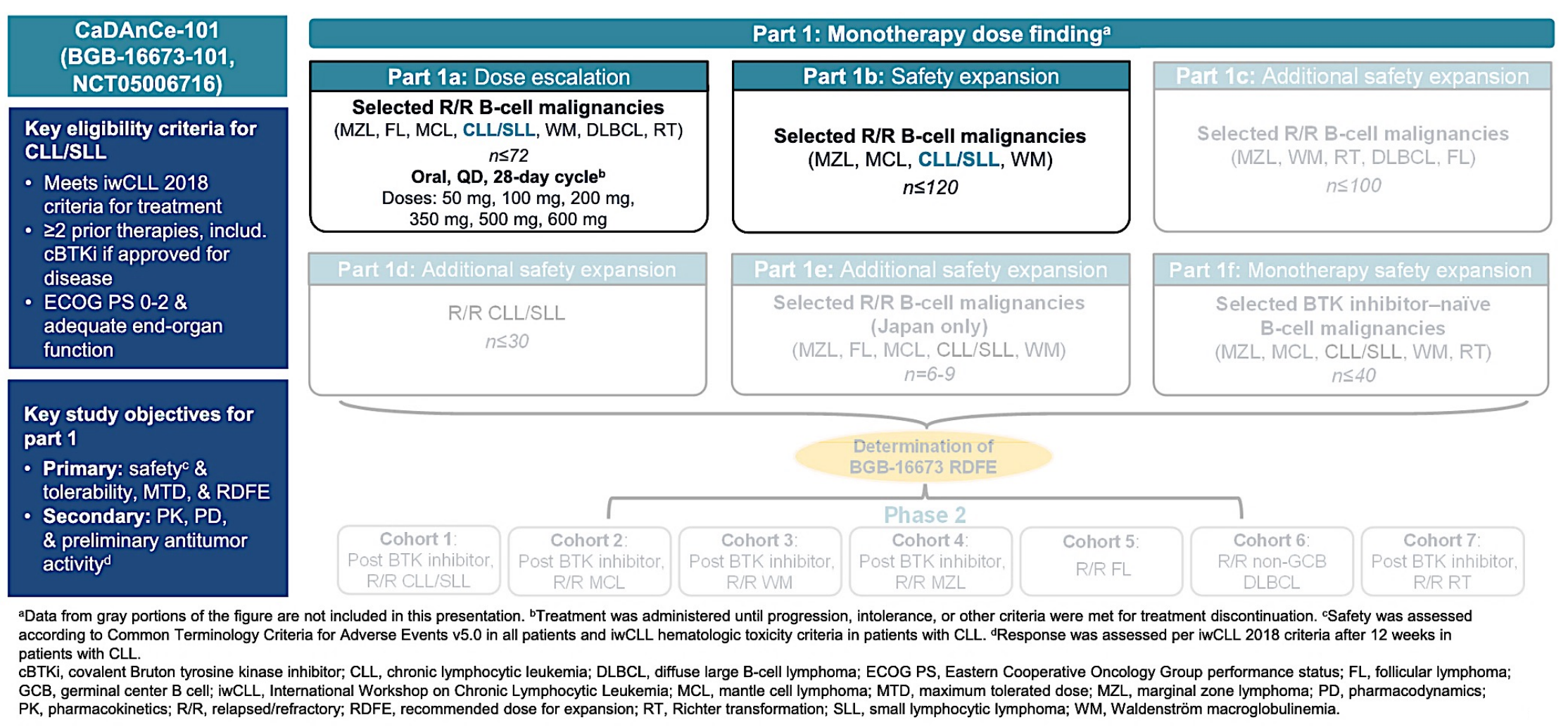


BTK, Bruton tyrosine kinase; cBTK, covalent Bruton tyrosine kinase; CLL/SLL, chronic lymphocytic leukemia/small lymphocytic lymphoma; CNS, central nervous system; ncBTK, noncovalent Bruton tyrosine kinase; R/R, relapsed/refractory; ub, ubiquitin.

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: Overall Response Rate

	50 mg (n=1)	100 mg (n=22)	200 mg (n=16)	350 mg (n=15)	500 mg (n=12)	Total (N=66)
Best overall response, n (%)						
CR/CRi	0	1 (4.5)	1 (6.3)	0	1 (8.3)	**3 (4.5)**
PR[a]	1 (100)	11 (50.0)	12 (75.0)	11 (73.3)	9 (75.0)	44 (66.7)
PR-L	0	6 (27.3)	2 (12.5)	0	1 (8.3)	9 (13.6)
SD	0	4 (18.2)	0	0	1 (8.3)	5 (7.6)
PD	0	0	1 (6.3)	1 (6.7)	0	2 (3.0)
Discontinued prior to first assessment	0	0	0	3 (20.0)	0	3 (4.5)
Overall response rate, n (%)[b]	1 (100)	18 (81.8)	**15 (93.8)**	11 (73.3)	11 (91.7)	**56 (84.8)**
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)	2.8 (2.6-19.4)	2.8 (2.6-13.8)	2.8 (2.0-19.4)
Time to best response, median (range), months	2.9 (2.9-2.9)	2.8 (2.0-11.1)	3.4 (2.6-13.8)	5.6 (2.6-19.4)	8.3 (2.7-13.8)	3.4 (2.0-19.4)
Duration of exposure, median (range), months	29.6 (29.6-9.6)	7.1 (3.7-23.7)	16.2 (2.9-24.6)	15.6 (0.2-22.8)	15.3 (6.8-21.4)	12.9 (0.2-29.6)

[a]Of 44 patients with PR, 12 achieved all nodes normalized. [b]Includes best overall response of PR-L or better. [c]In patients with a best overall response of PR-L or better.
CR, complete response; CRi, complete response with incomplete marrow recovery; PD, progressive disease; PR, partial response; PR-L, partial response with lymphocytosis; SD, stable disease.

Scarfò L et al. EHA 2025;Abstract S158.

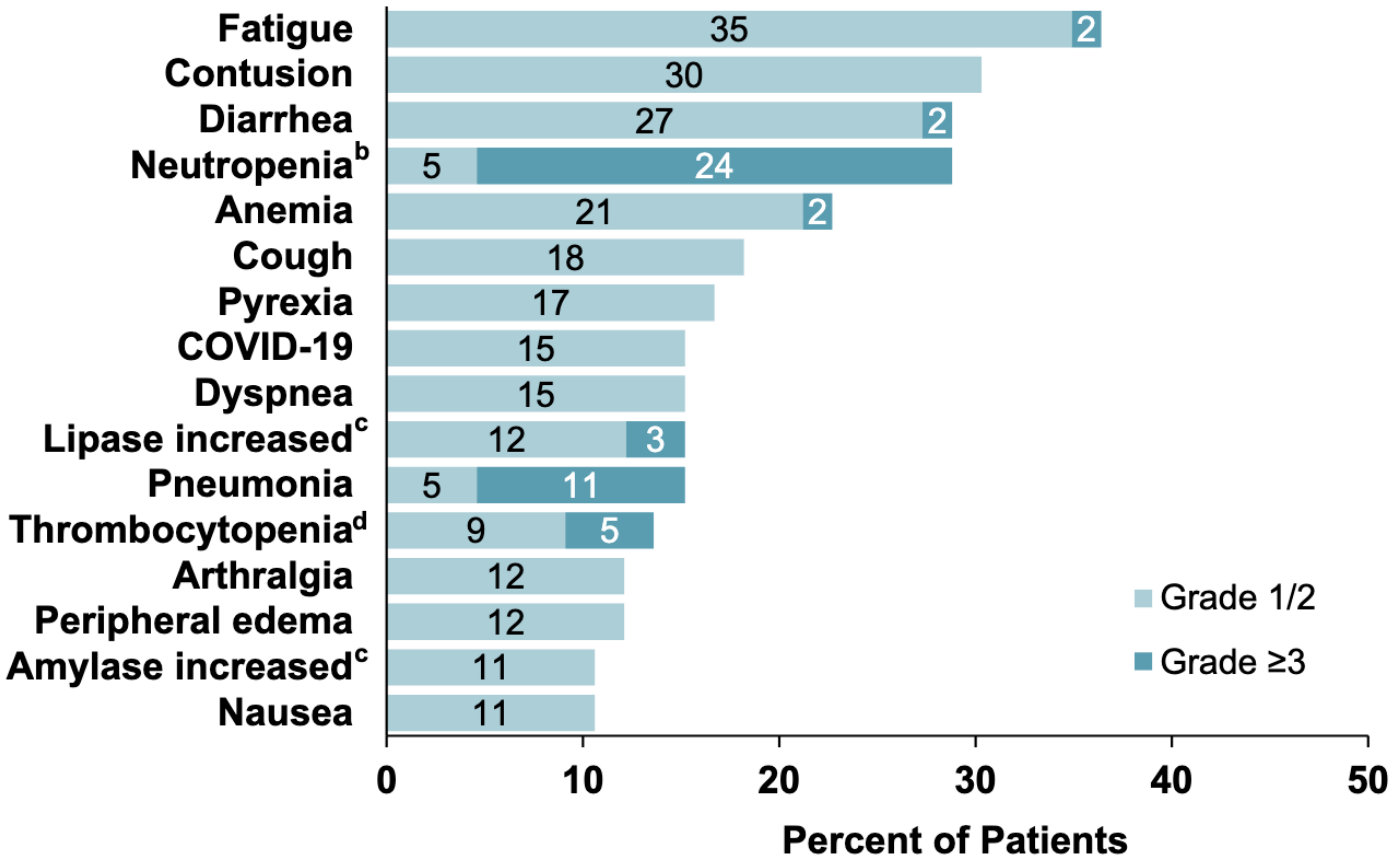
CaDAnCe-101: Overall Response Rate in High-Risk Subgroups

Subgroup	ORR, n/N with known status (%)
Double exposure (previously received cBTKi + BCL2i)	38/42 (90.5)
Triple exposure (previously received cBTKi + ncBTKi + BCL2i)	9/12 (75.0)
del(17p) and/or *TP53* mutation	35/43 (81.4)
Complex karyotype (≥3 abnormalities)	16/22 (72.7)
***BTK* mutations**	18/24 (75.0)
***PLCG2* mutations**	9/10 (90.0)

Scarfò L et al. EHA 2025;Abstract S158.

CaDAnCe-101: Summary of All-Grade TEAEs in ≥10% of All Patients

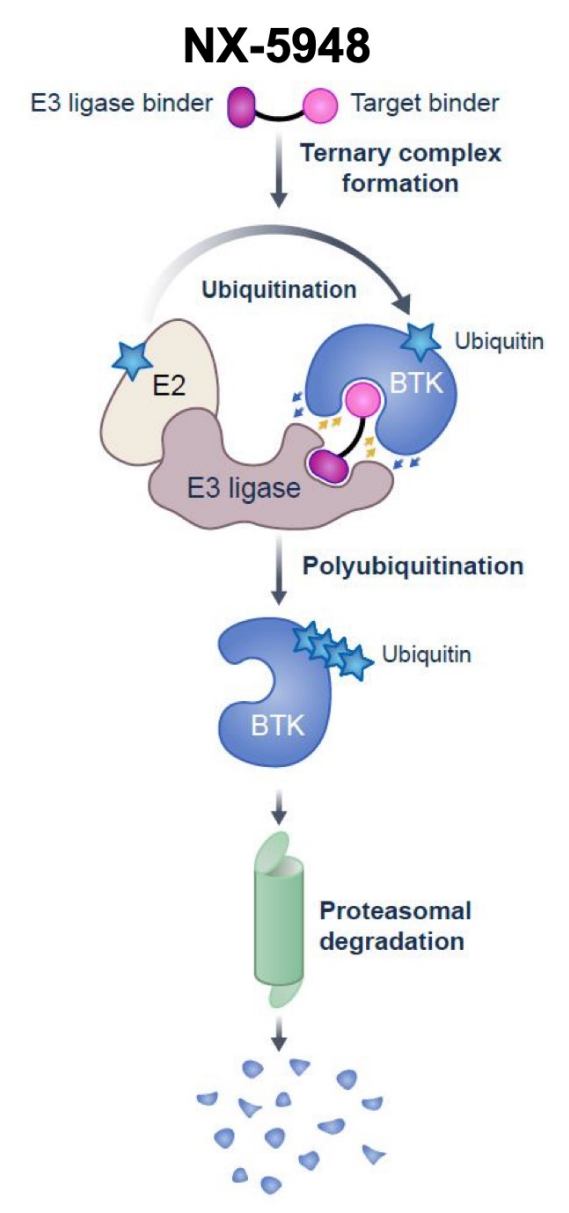
- Most common TEAEs were fatigue in 37% and contusion (bruising) in 30% of patients
- Atrial fibrillation: n=2 (one grade 1 and one grade 2 in the context of infection and PD, respectively)
- Major hemorrhage[a]: n=2 (one grade 1 subarachnoid hemorrhage and one grade 3 subdural hemorrhage)
  - No new events occurred since the last update
- No pancreatitis



Median follow-up in safety-evaluable patients: 15.6 months (range, 0.3-30.6+ 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; SAE, serious adverse event; TEAE, treatment-emergent adverse event.

Scarfò L et al. EHA 2025;Abstract S158.

NX-5948: A Novel BTK Degrader



CLL response-evaluable patients	Primary ORR analysis ≥1 response assessment(s) at 8 weeks (n=49)
Objective response rate (ORR), % (95% CI)	75.5 (61.1–86.7)
Best response, n (%)	
CR	0 (0.0)
PR	36 (73.5)
PR-L	1 (2.0)
SD	10 (20.4)
PD	2 (4.1)

Shah NN et al. ASH 2024;Abstract 884.

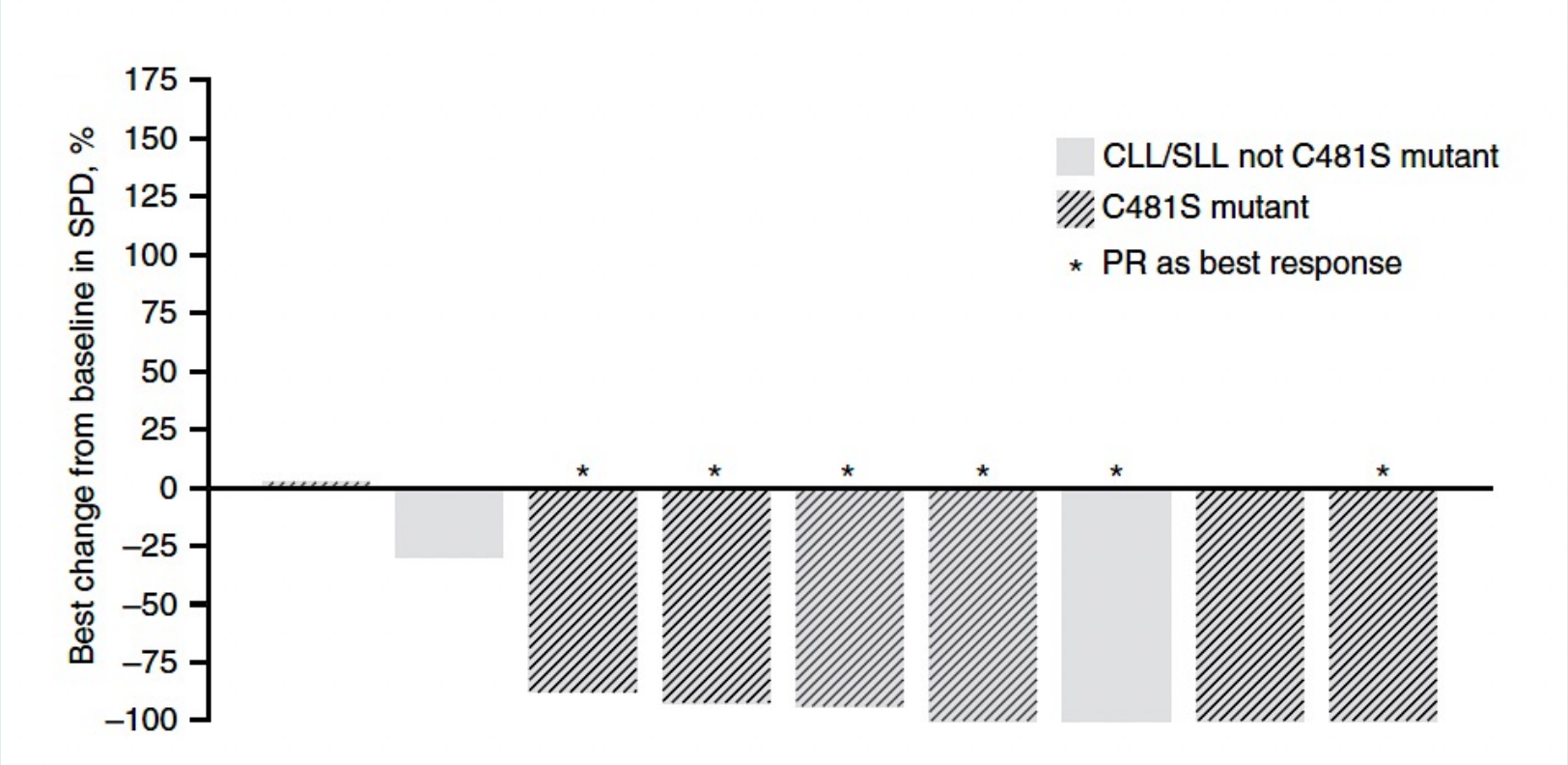
NX-5948: A Novel BTK Degrader – Safety Profile

TEAEs, n (%)	Patients with CLL/SLL (n=60)		
	Any grade	Grade ≥3	SAEs
Purpura/contusion[a]	22 (36.7)	–	–
Fatigue[b]	16 (26.7)	–	–
Petechiae	16 (26.7)	–	–
Thrombocytopenia[c]	10 (16.7)	1 (1.7)	–
Rash[d]	14 (23.3)	1 (1.7)	1 (1.7)
Neutropenia[e]	14 (23.3)	11 (18.3)	–
Anemia	11 (18.3)	4 (6.7)	–
Headache	10 (16.7)	–	–
COVID-19[f]	10 (16.7)	–	–
Diarrhea	12 (20.0)	1 (1.7)	–
Cough	9 (15.0)	–	–
Pneumonia[g]	4 (6.7)	2 (3.3)	2 (3.3)
Lower respiratory tract infection	3 (5.0)	1 (1.7)	1 (1.7)
Fall	1 (1.7)	1 (1.7)	1 (1.7)
Hypertension	2 (3.3)	1 (1.7)	–
Hyponatremia	–	–	–
Pulmonary embolism	1 (1.7)	1 (1.7)	1 (1.7)
Subdural hematoma	1 (1.7)	–	1 (1.7)

TEAE = treatment-emergent adverse event; SAE = serious adverse event

Shah NN et al. ASH 2024;Abstract 884.

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.

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