Consensus or Controversy? Clinical Investigators Provide Perspectives on the Current and Future Care of Patients with Chronic Lymphocytic Leukemia

Sunday, June 1, 2025
7:00 AM – 8:00 AM CT (8:00 AM – 9:00 AM ET)

Faculty

Catherine C Coombs, MD
William G Wierda, MD, PhD

Moderator

Neil Love, MD

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Faculty

Catherine C Coombs, MD
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MODERATOR
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Miami, Florida

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Cell Transplantation
Director, Chronic Lymphocytic Leukemia Program
City of Hope
Duarte, California

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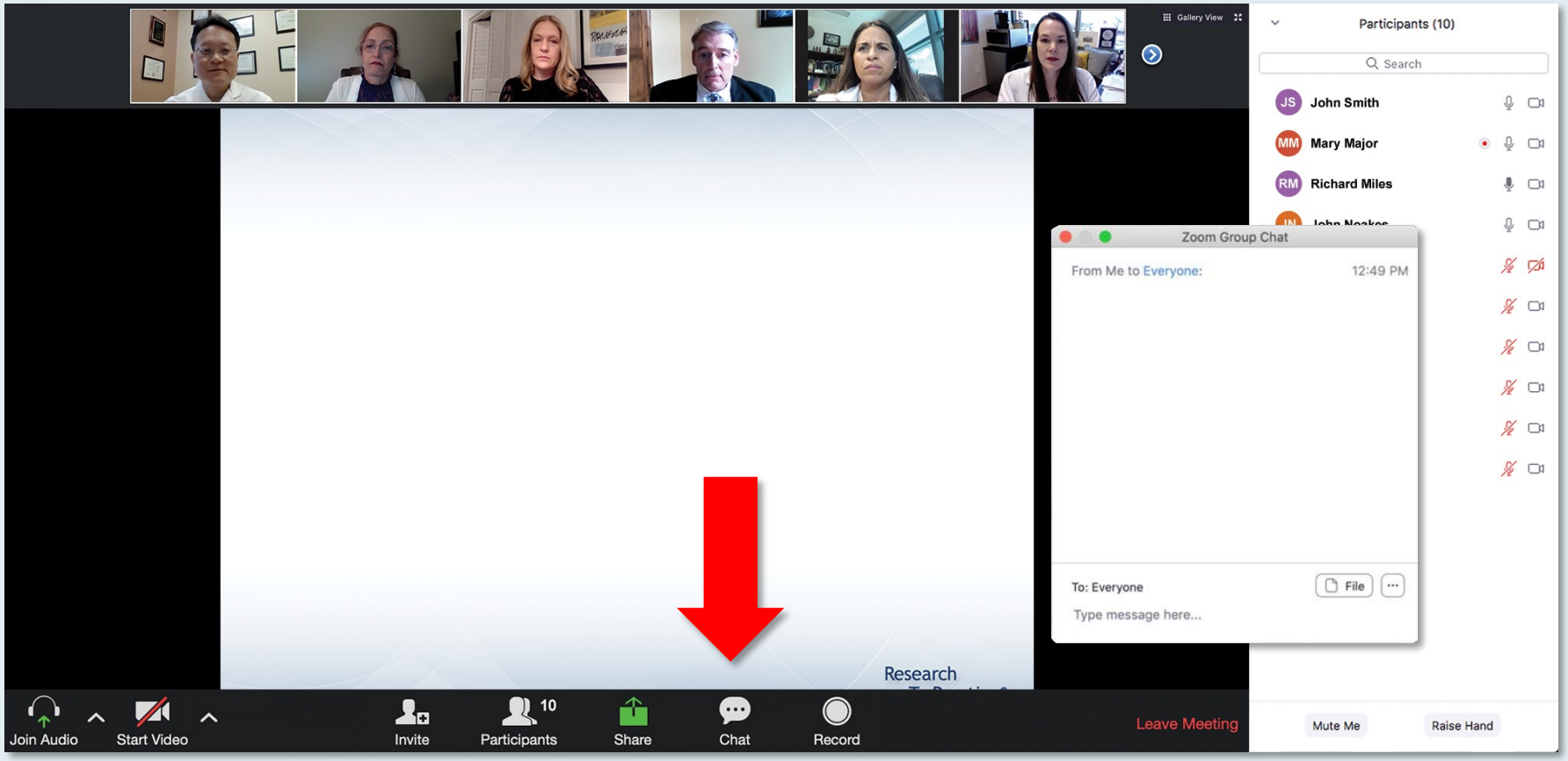
We Encourage Clinicians in Practice to Submit Questions



Feel free to submit questions now before the program begins and throughout the program.

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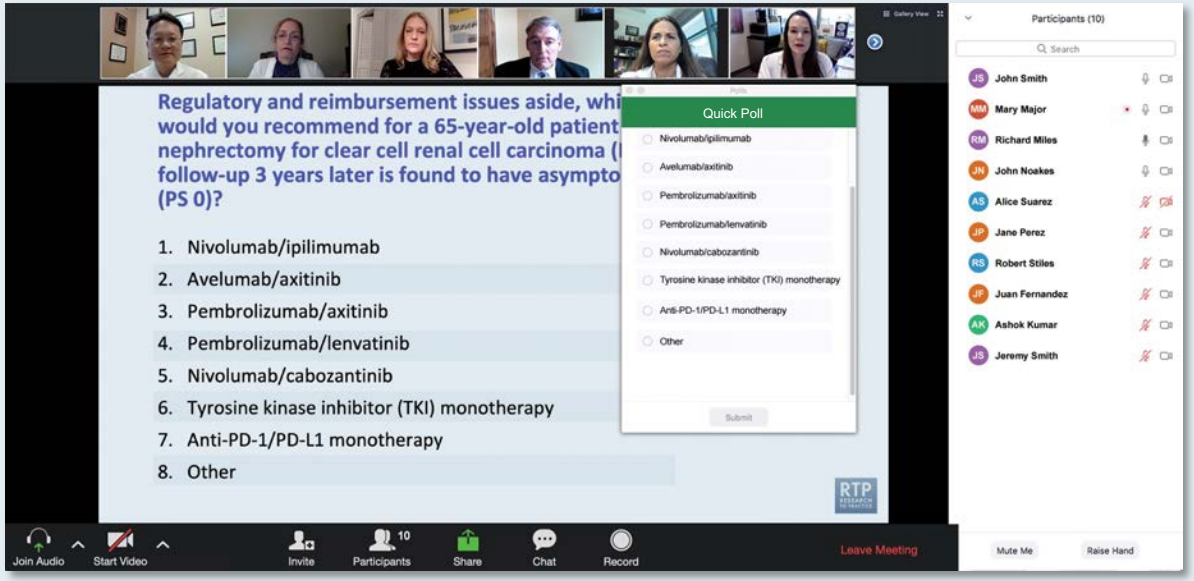
Clinicians in the Audience, Please Complete the Pre- and Postmeeting Surveys



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Friday May 30	**Immunotherapy and Antibody–Drug Conjugates in Lung Cancer** 11:15 AM – 12:45 PM CT (12:15 PM – 1:45 PM ET)
	Colorectal Cancer 6:30 PM – 8:30 PM CT (7:30 PM – 9:30 PM ET)
	EGFR Mutation–Positive Non–Small Cell Lung Cancer 6:30 PM – 8:30 PM CT (7:30 PM – 9:30 PM ET)
Saturday May 31	**Urothelial Bladder Cancer** 6:45 AM – 7:45 AM CT (7:45 AM – 8:45 AM ET)
	Non–Hodgkin Lymphoma 7:00 PM – 9:00 PM CT (8:00 PM – 10:00 PM ET)
	Prostate Cancer 7:00 PM – 9:00 PM CT (8:00 PM – 10:00 PM ET)
Sunday June 1	**Chronic Lymphocytic Leukemia (Webinar)** 7:00 AM – 8:00 AM CT (8:00 AM – 9:00 AM ET)
	HER2–Positive Gastrointestinal Cancers 7:00 PM – 8:30 PM CT (8:00 PM – 9:30 PM ET)
	Ovarian and Endometrial Cancer 7:00 PM – 9:00 PM CT (8:00 PM – 10:00 PM ET)
Monday June 2	**Renal Cell Carcinoma (Webinar)** 7:00 AM – 8:00 AM CT (8:00 AM – 9:00 AM ET)
	Multiple Myeloma (Webinar) 6:00 PM – 7:00 PM CT (7:00 PM – 8:00 PM ET)
	Metastatic Breast Cancer 7:00 PM – 9:00 PM CT (8:00 PM – 10:00 PM ET)
Tuesday June 3	**Soft Tissue Sarcoma and Other Connective Tissue Neoplasms (Webinar)** 7:00 AM – 8:00 AM CT (8:00 AM – 9:00 AM ET)

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Dr Coombs — Disclosures
Faculty

Advisory Committees	AbbVie Inc, Allogene Therapeutics, AstraZeneca Pharmaceuticals LP, BeiGene Ltd, Bristol Myers Squibb, Genentech, a member of the Roche Group, Janssen Biotech Inc, Lilly, MingSight Pharmaceuticals, Pharmacyclics LLC, an AbbVie Company
Consulting Agreements	AbbVie Inc, AstraZeneca Pharmaceuticals LP, BeiGene Ltd, Lilly, Octapharma
Contracted Research	AbbVie Inc, BeiGene Ltd, Carna Biosciences, Lilly
Speakers Bureaus	AbbVie Inc, AstraZeneca Pharmaceuticals LP, BeiGene Ltd, Genentech, a member of the Roche Group, Lilly
Stock Options/Stock — Public Companies	Geron Corporation, Pfizer Inc

Dr Wierda — Disclosures
Faculty

Consulting Agreements	BeiGene Ltd, Numab Therapeutics AG
Contracted Research	AbbVie Inc, Acerta Pharma — A member of the AstraZeneca Group, Bristol Myers Squibb, Cyclacel Pharmaceuticals Inc, Genentech, a member of the Roche Group, Gilead Sciences Inc, GSK, Janssen Biotech Inc, Juno Therapeutics, a Celgene Company, Kite, A Gilead Company, Loxo Oncology Inc, a wholly owned subsidiary of Eli Lilly & Company, Novartis, Nurix Therapeutics Inc, Oncternal Therapeutics, Pharmacyclics LLC, an AbbVie Company
Nonrelevant Financial Relationships	National Comprehensive Cancer Network (Chair, CLL), Support by the NIH/NCI under award number P30 CA016672 and use of MD Anderson Cancer Center Support Grant (CCSG) shared resources

Dr Allan — Disclosures
Survey Participant

Advisory Committees	NeoGenomics
Consulting Agreements	AbbVie Inc, Adaptive Biotechnologies Corporation, ADC Therapeutics, AstraZeneca Pharmaceuticals LP, BeiGene Ltd, Genentech, a member of the Roche Group,Janssen Biotech Inc, Lilly, Pharmacyclics LLC, an AbbVie Company
Contracted Research	BeiGene Ltd, Bristol Myers Squibb, Genentech, a member of the Roche Group
Data and Safety Monitoring Boards/Committees	Merck
Speakers Bureaus	AbbVie Inc, BeiGene Ltd

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Dr Davids — Disclosures
Survey Participant

Consulting Agreements	AbbVie Inc, Adaptive Biotechnologies Corporation, Ascentage Pharma, AstraZeneca Pharmaceuticals LP, BeiGene Ltd, 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, Secura Bio, Takeda Pharmaceuticals USA Inc, TG Therapeutics Inc
Contracted Research	Ascentage Pharma, MEI Pharma Inc, Novartis
Nonrelevant Financial Relationships	UpToDate

Dr Sharman — Disclosures
Survey Participant

Consulting Agreements and Contracted Research	AbbVie Inc, AstraZeneca Pharmaceuticals LP, BeiGene Ltd, Bristol Myers Squibb, Genentech, a member of the Roche Group, Lilly, Merck

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Dr Siddiqi — Disclosures
Survey Participant

Advisory Committees	AbbVie Inc, AstraZeneca Pharmaceuticals LP, BeiGene Ltd, Bristol Myers Squibb, Celgene Corporation, Gilead Sciences Inc
Contracted Research	Bristol Myers Squibb
Data and Safety Monitoring Boards/Committees	BeiGene Ltd
Speakers Bureaus	AstraZeneca Pharmaceuticals LP

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Dr Love — Disclosures

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This educational activity contains discussion of non-FDA-approved uses of agents and regimens. Please refer to official prescribing information for each product for approved indications.

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Agenda

Module 1: Selection and Sequencing of Therapy for Relapsed/Refractory (RR) Chronic Lymphocytic Leukemia (CLL) — Dr Wierda

Module 2: First-Line Therapy for CLL — Dr Coombs

Module 3: Novel Agents and Strategies for RR CLL — Dr Wierda

Module 4: ASCO and EHA 2025

Agenda

Module 1: Selection and Sequencing of Therapy for Relapsed/Refractory (RR) Chronic Lymphocytic Leukemia (CLL) — Dr Wierda

Module 2: First-Line Therapy for CLL — Dr Coombs

Module 3: Novel Agents and Strategies for RR CLL — Dr Wierda

Module 4: ASCO and EHA 2025

Beyond Covalent BTK Inhibitors and Venetoclax

Regulatory and reimbursement issues aside, what would be your preferred third-line systemic therapy for a 60-year-old patient with double-refractory CLL?

Regulatory and reimbursement issues aside, what would be your preferred third-line systemic therapy for an 80-year-old patient with double-refractory CLL?

Beyond Covalent BTK Inhibitors and Venetoclax

Regulatory and reimbursement issues aside, what second-line systemic therapy would you recommend for a 60-year-old patient who has experienced disease progression on a covalent BTK inhibitor and is not a candidate for venetoclax because of comorbidities?

Regulatory and reimbursement issues aside, what second-line systemic therapy would you recommend for an 80-year-old patient who has experienced disease progression on a covalent BTK inhibitor and is not a candidate for venetoclax because of comorbidities?

Beyond Covalent BTK Inhibitors and Venetoclax

Regulatory and reimbursement issues aside, what systemic therapy would you recommend next for a 60-year-old patient who has experienced disease progression on venetoclax/obinutuzumab and developed unacceptable tolerability issues (bleeding, arthralgias) on a covalent BTK inhibitor?

Regulatory and reimbursement issues aside, what systemic therapy would you recommend next for an 80-year-old patient who has experienced disease progression on venetoclax/obinutuzumab and developed unacceptable tolerability issues (bleeding, arthralgias) on a covalent BTK inhibitor?

In which line of therapy are you currently using pirtobrutinib for your patients with CLL?

 Dr Coombs	Third line
 Dr Wierda	Second line and beyond
 Dr Allan	Third line
 Dr Davids	Third line
 Dr Sharman	Third line
 Dr Siddiqi	Fourth line

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Based on current clinical trial data and your personal experience, how would you compare the global efficacy and tolerability/toxicity of pirtobrutinib to those 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 Wierda	There are not enough available data at this time	Pirtobrutinib has the least toxicity
 Dr Allan	About the same	Pirtobrutinib has the least toxicity
 Dr Davids	There are not enough available data at this time	Pirtobrutinib has the least toxicity
 Dr Sharman	There are not enough available data at this time	Pirtobrutinib has the least toxicity
 Dr Siddiqi	About the same	Pirtobrutinib has the least toxicity

Based on the published literature and/or your clinical experience, please estimate the percent chance that a patient with CLL who is receiving ibrutinib will experience toxicity during treatment that will require withholding or permanently discontinuing administration.
What is the primary toxicity patients experience that leads to withholding this drug/regimen?

	Chance of withholding	Chance of discontinuation	Primary toxicity
 Dr Coombs	50%	40%	Cardiac; myalgias/arthralgias
 Dr Wierda	40%	40%	Various
 Dr Allan	20%	20%	BTKi class effects
 Dr Davids	40%	20%	Atrial fibrillation
 Dr Sharman	50%	40%	Arthralgias
 Dr Siddiqi	20%	20%	Arthralgias

BTKi = BTK inhibitor

Based on the published literature and/or your clinical experience, please estimate the percent chance that a patient with CLL who is receiving acalabrutinib will experience toxicity during treatment that will require withholding or permanently discontinuing administration.
What is the primary toxicity patients experience that leads to withholding this drug/regimen?

	Chance of withholding	Chance of discontinuation	Primary toxicity
 Dr Coombs	15%	10%	Headache
 Dr Wierda	20%	10%	Various
 Dr Allan	15%	15%	BTKi class effects
 Dr Davids	20%	10%	Headache
 Dr Sharman	20%	10%	Various
 Dr Siddiqi	15%	10%	Fatigue

Based on the published literature and/or your clinical experience, please estimate the percent chance that a patient with CLL who is receiving zanubrutinib will experience toxicity during treatment that will require withholding or permanently discontinuing administration.
What is the primary toxicity patients experience that leads to withholding this drug/regimen?

	Chance of withholding	Chance of discontinuation	Primary toxicity
 Dr Coombs	15%	10%	I've not recognized a predominant toxicity yet
 Dr Wierda	20%	10%	Various
 Dr Allan	15%	15%	BTKi class effects
 Dr Davids	20%	10%	Hypertension
 Dr Sharman	25%	10%	Various
 Dr Siddiqi	10%	5%	Fatigue

Based on the published literature and/or your clinical experience, please estimate the percent chance that a patient with CLL who is receiving pirtobrutinib will experience toxicity during treatment that will require withholding or permanently discontinuing administration.
What is the primary toxicity patients experience that leads to withholding this drug/regimen?

	Chance of withholding	Chance of discontinuation	Primary toxicity
 Dr Coombs	5%	5%	Neutropenia; GI
 Dr Wierda	15%	5%	Various
 Dr Allan	10%	10%	BTKi class effects
 Dr Davids	15%	5%	Bleeding
 Dr Sharman	10%	10%	Infection
 Dr Siddiqi	5%	5%	Bleeding

Select Questions on Chimeric Antigen Receptor (CAR) T-Cell Therapy

Are there any differences in the way you think through eligibility in terms of patient age, comorbidities, et cetera for CAR T-cell therapy versus other available treatments?

For patients who are eligible to receive pirtobrutinib and CAR T-cell therapy, which one do you generally recommend first?

Select Questions on CAR T-Cell Therapy

In general, do you use bridging therapy for your patients who are being referred for CAR T-cell therapy? If so, what's your usual treatment approach?

Do you believe patients with RR CLL have been "cured" with CAR T-cell therapy?

Select Questions on CAR T-Cell Therapy

Based on the published literature and/or your clinical experience, what is the chance that a patient with CLL receiving CAR T-cell therapy will experience CRS? What about ICANS?

What is your approach to monitoring and managing these toxicities?

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

 Dr Coombs	Case by case basis; third line for young, fit patients
 Dr Wierda	Depends more on the patient's clinical situation
 Dr Allan	After third relapse
 Dr Davids	At second relapse
 Dr Sharman	When pirtobrutinib treatment is initiated
 Dr Siddiqi	At second relapse

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To approximately how many patients with CLL have you administered lisocabtagene maraleucel (liso-cel) within or outside of a protocol setting?

 Dr Coombs	0
 Dr Wierda	25
 Dr Allan	0
 Dr Davids	0
 Dr Sharman	4
 Dr Siddiqi	~30

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Selection and Sequencing of Therapy for Relapsed/Refractory CLL

June 1, 2025

WILLIAM G. WIERDA MD, PHD

PROFESSOR OF MEDICINE

SECTION HEAD, CLL

DEPARTMENT OF LEUKEMIA

U.T. M.D. ANDERSON CANCER CENTER

HOUSTON, TX USA

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

Selected First-line Phase III Trials in CLL

Trial	N	Treatment Arms		
		Control	Investigational	
EA9161	720	IBR + OBIN	IBR + OBIN + VEN	
A041702	454	IBR + OBIN	IBR + OBIN + VEN	
CLL17	909	IBR	VEN + OBIN	VEN + IBR
MAJIC	750	VEN + OBIN	ACA + VEN	
CLL16 (del(17p) / *TP53*-m / CK)	178	VEN + OBIN	ACA + VEN + OBIN	
CELESTIAL-TNCLL	640	VEN + OBIN	SONRO + ZANU	
BRUIN CLL-313	250	BR	PIRTO	
BRUIN CLL-314	650#	IBR	PIRTO	
CLL18	813	VEN + OBIN	VEN + PIRTO (Fixed)	VEN + PIRTO (uMRD)
BELLWAVE-011	1200	IBR or ACA	NEMTA	
BELLWAVE-008	300	FCR/BR	NEMTA	

enrolls both frontline and R/R BTK-naïve CLL

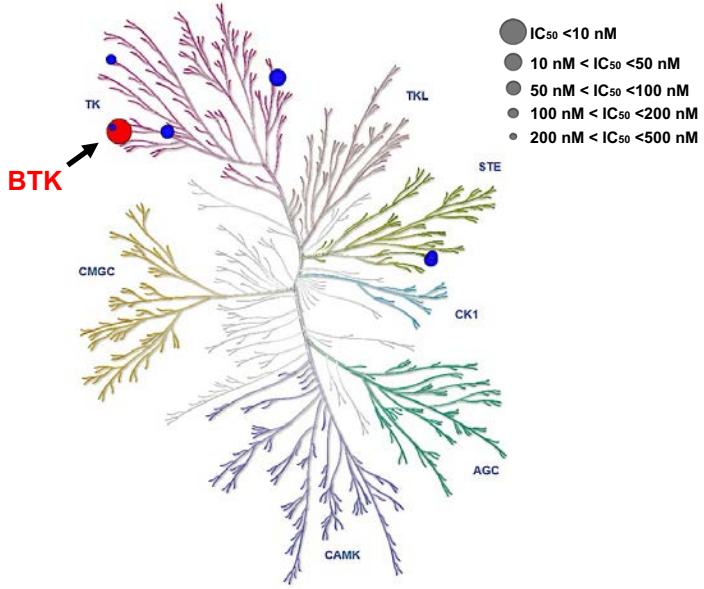
Differentiated Kinase Inhibition Profile

		TEC Family Kinases					Inhibition of Other Kinases
	IC_{50} (nM)	BTK	ITK	Tec#	TXK*	BMX*	Notable Target Kinases
Irreversible (covalent)	Ibrutinib[2]	0.5	10.7	78	2.0[3]	0.8	>10 more: EGFR family
	Acalabrutinib[3]	5.1	>1000	93	368	46	Selective
	Zanubrutinib[4]	0.22	30	1.9	n/a	n/a	N/A (not published)
Reversible (non-covalent)	Vecabrutinib[1]	3	14	14	474	224	Selective -4 non-Tec family kinases: SRC family, NEK11
	Nemtabrutinib[5]	4.23	>10000	5.8	36.4	5.23	>20 more: SRC & TRK families, RAF1, MEK1
	Pirtobrutinib[6]	3.15	>5000	1234	209	1155	Very Selective
	Luxeptinib[7]	8.4	4.3	>1000	n/a	14.5	18 w/ IC_{50} <10 nM: FLT3 (wt, ITD) c-MET, TRK family & Aurora kinases

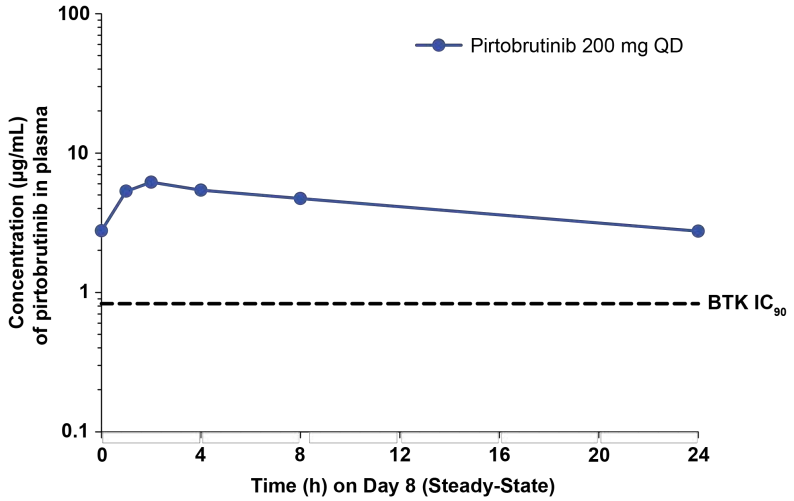
n/a=not available
* Determined with vecabrutinib free base (also relevant for SRC and EGFR)
# Activated (also relevant for LCK)
[1] Neuman et al., ASH 2016
[2] Honigberg et al., PNAS 2010
[3] Byrd et al., NEJM 2016
[4] Tam et al., ASH 2016
[5] Eathiraj et al., Pan Pacific Lymphoma Conference 2016
[6] Brandhuber et al., SOHO 2018
[7] Zhang et al, EHA 2018

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

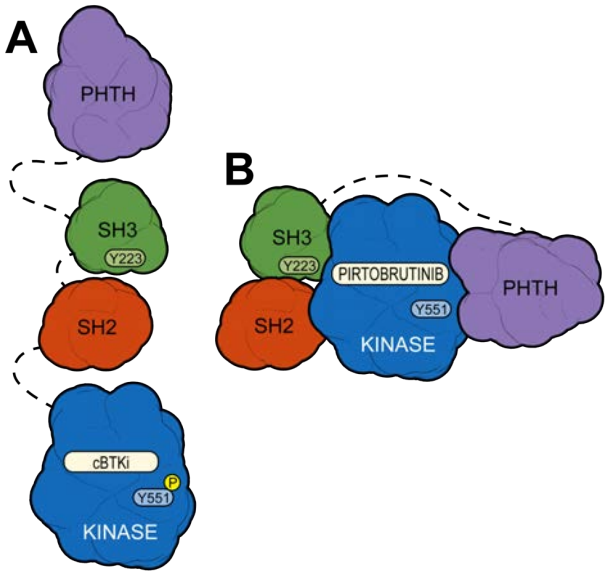
Highly selective for BTK[8-9]



Plasma exposures exceeded BTK IC_{90} throughout dosing interval



Pirtobrutinib may stabilize/maintain BTK in a closed inactive conformation[11]



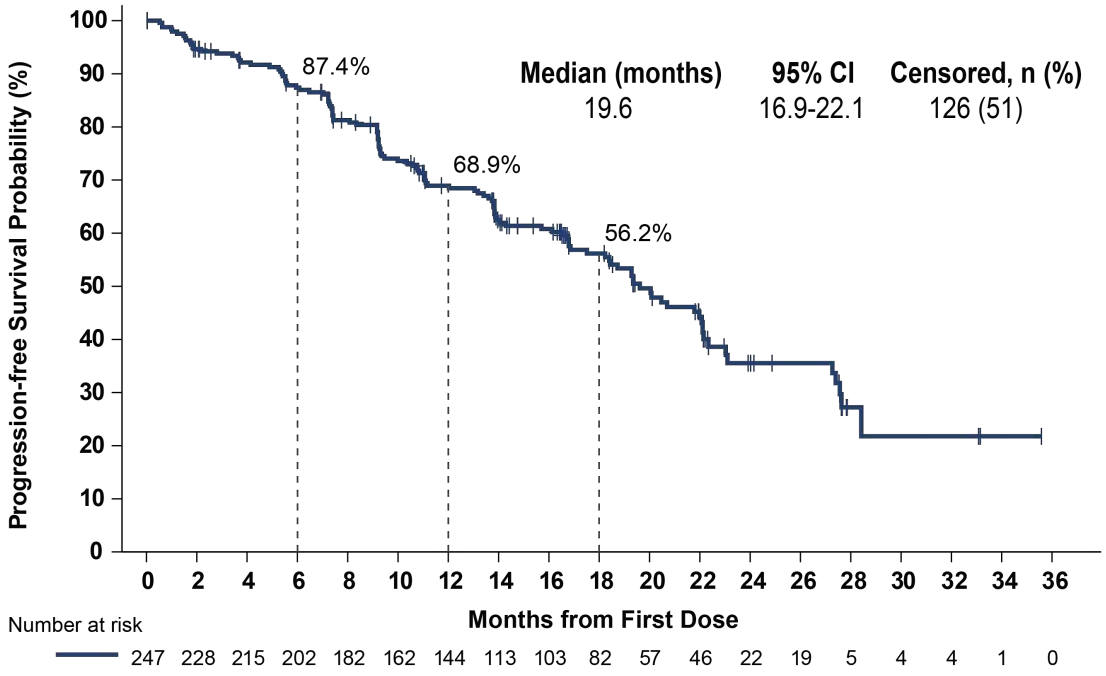
- **Pirtobrutinib is approved in the USA to treat relapsed or refractory MCL after at least two lines of systemic therapy, including prior BTK inhibitor[10]**
- **Inhibits both WT and C481-mutant BTK with equal low nM potency in *in vitro* models[11] and CLL cells[12]**
- **Steady state plasma exposure corresponding to 96% BTK target inhibition and a pirtobrutinib-BTK binding complex half-life of about 2 hrs**

- **In contrast to cBTKi (A), pirtobrutinib (B) appears to stabilize BTK in a closed, inactive conformation, blocking access to upstream kinases and phosphorylation of Y551, thus inhibiting scaffolding interactions that support kinase-independent BTK signaling[11]**

[8]Mato et al, *Lancet* 2021. [9]Brandhuber et al. *Clin Lymphoma Myeloma Leuk* 2018.[10] Pirtobrutinib [Prescribing Information]. Indianapolis, IN: Eli Lilly and Company, 2023. [11]Gomez et al. Blood.2023. [12] Aslan B et al. Blood Cancer J 2022.

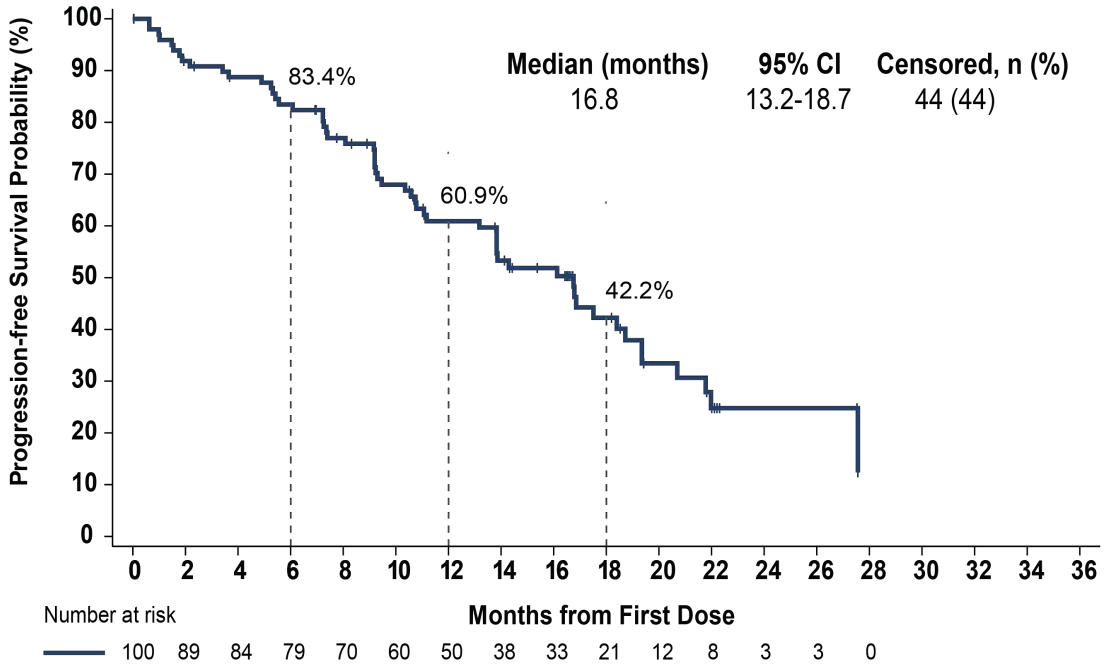
Pirtobrutinib:
Progression-Free Survival in CLL/SLL Patients who Received Prior BTKi Treatment

All prior BTKi patients
Median prior lines = 3



- Median follow-up of 19.4 months for patients who received prior BTKi

Prior BTKi and BCL2i patients
Median prior lines = 5



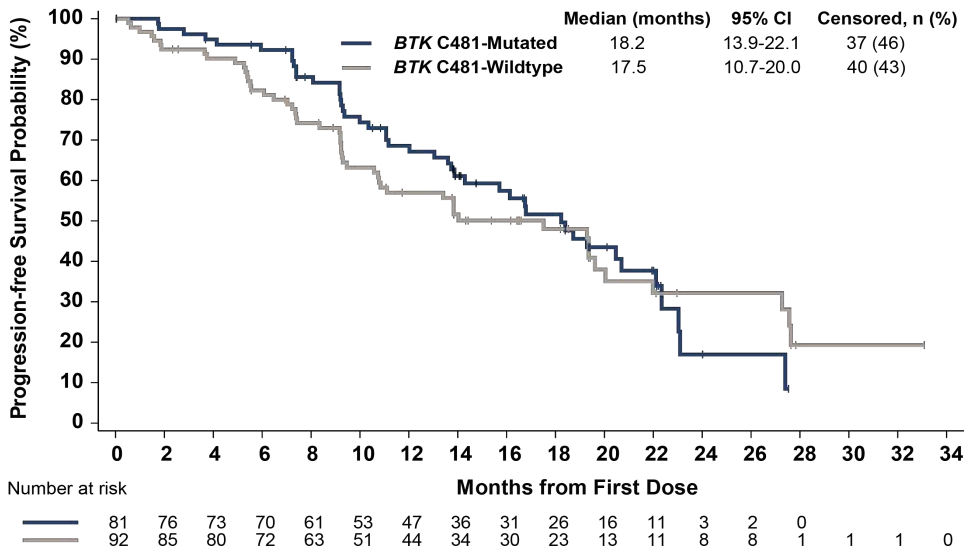
- Median follow-up of 18.2 months for patients who received prior BTKi and BCL2i

Data cutoff date of 29 July 2022. Response status per iwCLL 2018 according to independent review committee assessment.

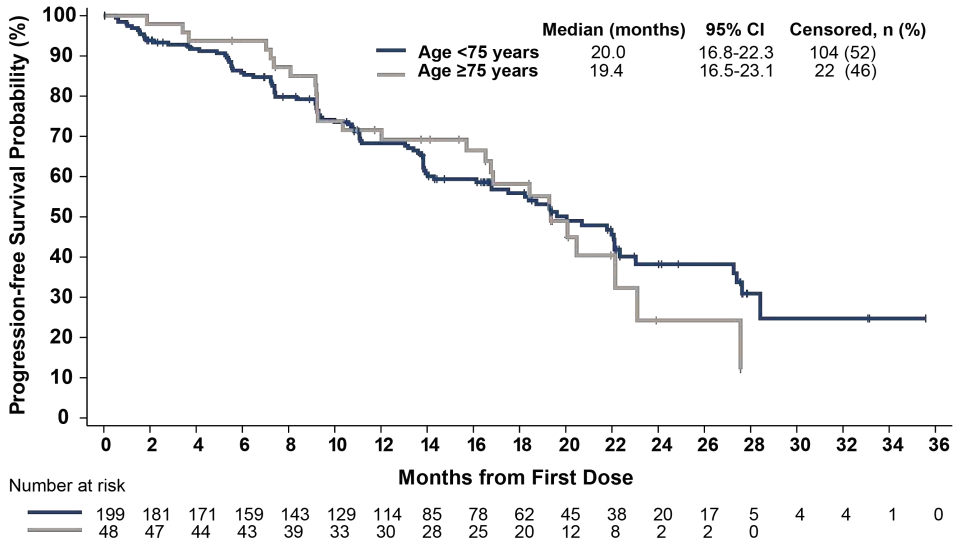
Mato et al. ASH 2022, Abstract #961

Pirtobrutinib:
Progression-Free Survival in CLL/SLL Subgroups

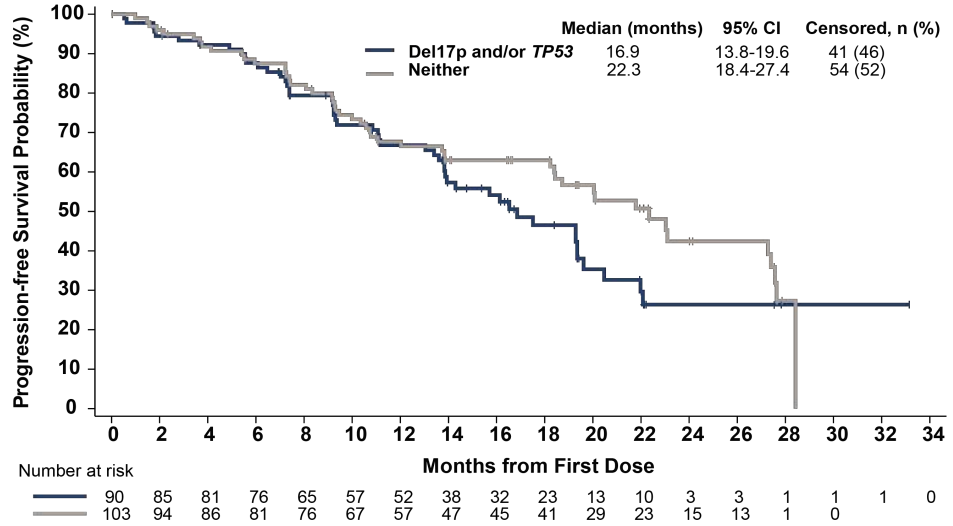
BTK C481 mutation status[a,b]



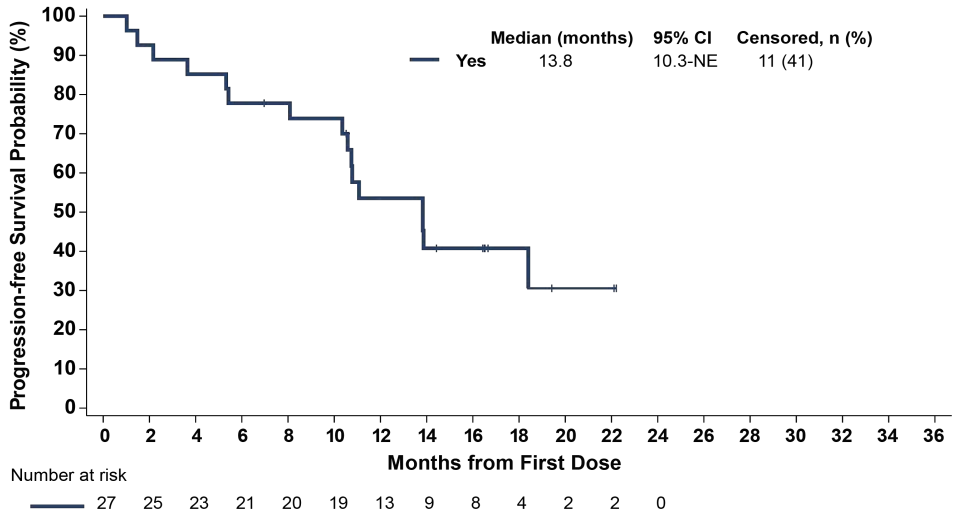
Age



del(17p) and/or *TP53* mutation[a]



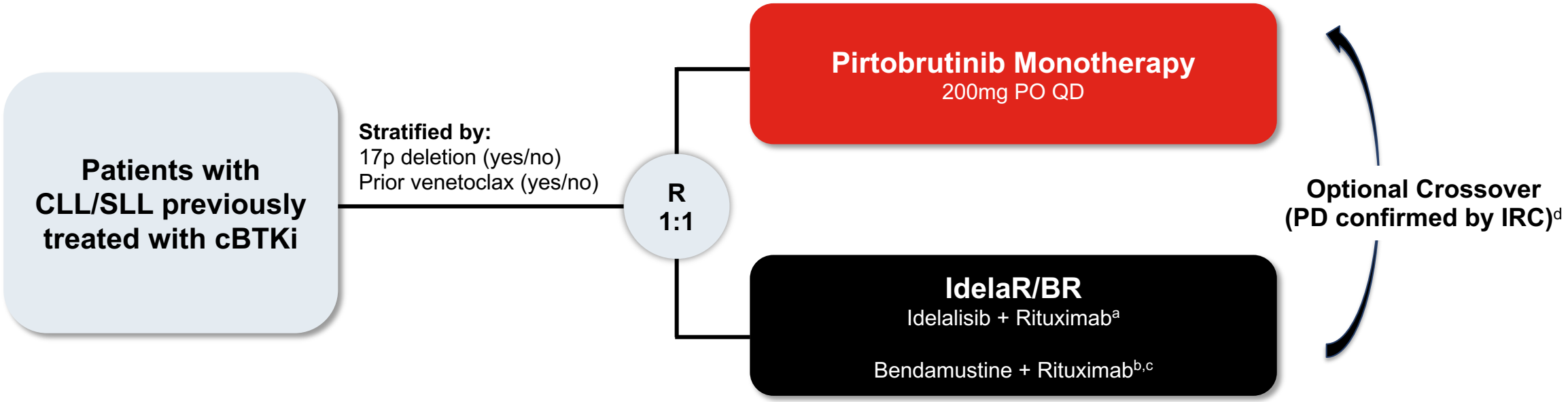
Prior BTKi, CIT, BCL2i, and PI3Ki therapy



Data cutoff date of 29 July 2022. Response status per iwCLL 2018 according to independent review committee assessment. [a]*BTK* C481 mutation status, del(17p), and *TP53* mutation status were centrally determined and based on pre-treatment samples. [b]Patients with available mutation data who progressed on any prior BTKi.

Mato et al. ASH 2022, Abstract #961

BRUIN CLL-321: Study Design



Key Eligibility

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

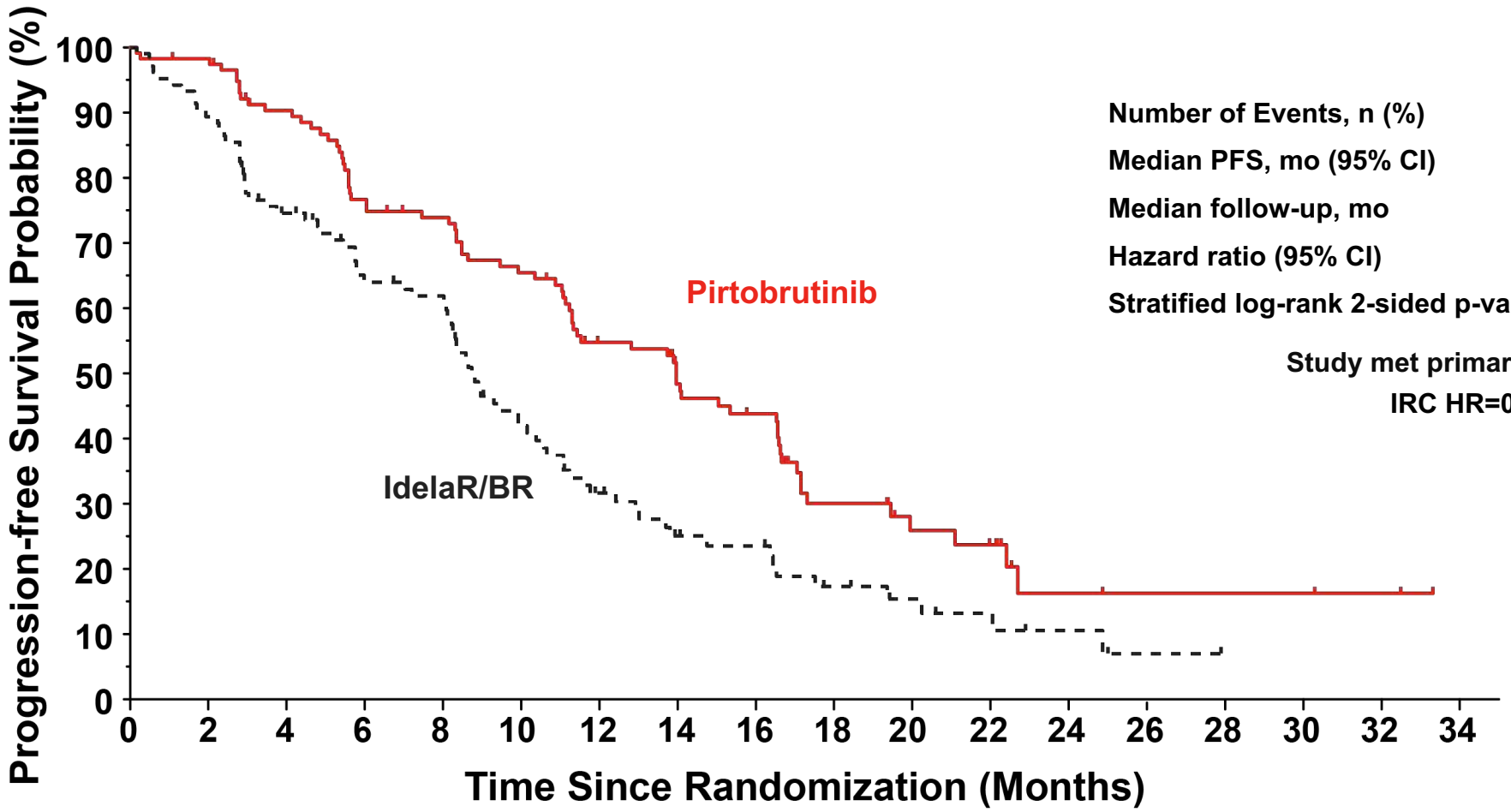
Key Endpoints

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

Treatment was given in 28-day cycles. PFS assessed based on iwCLL2018. [a]Idelalisib dosed at 150mg PO BID. Day 1 of cycle 1, first dose of rituximab at 375 mg/m^2, next 4 infusions at 500 mg/m^2 every 2 weeks, next 3 infusions at 500 mg/m^2 every 4 weeks. [b]Bendamustine (70 mg/m^2) administered IV D1, D2 of cycles 1-6. [c]Day 1 of cycle 1, first dose of rituximab at 375 mg/m^2, next 5 infusions day 1 of cycle 2 through cycle 6 at 500 mg/m^2. [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, et al., ASH 2024, Abstract #886

BRUIN CLL-321: IRC-Assessed Progression-free Survival



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

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

Number at Risk

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

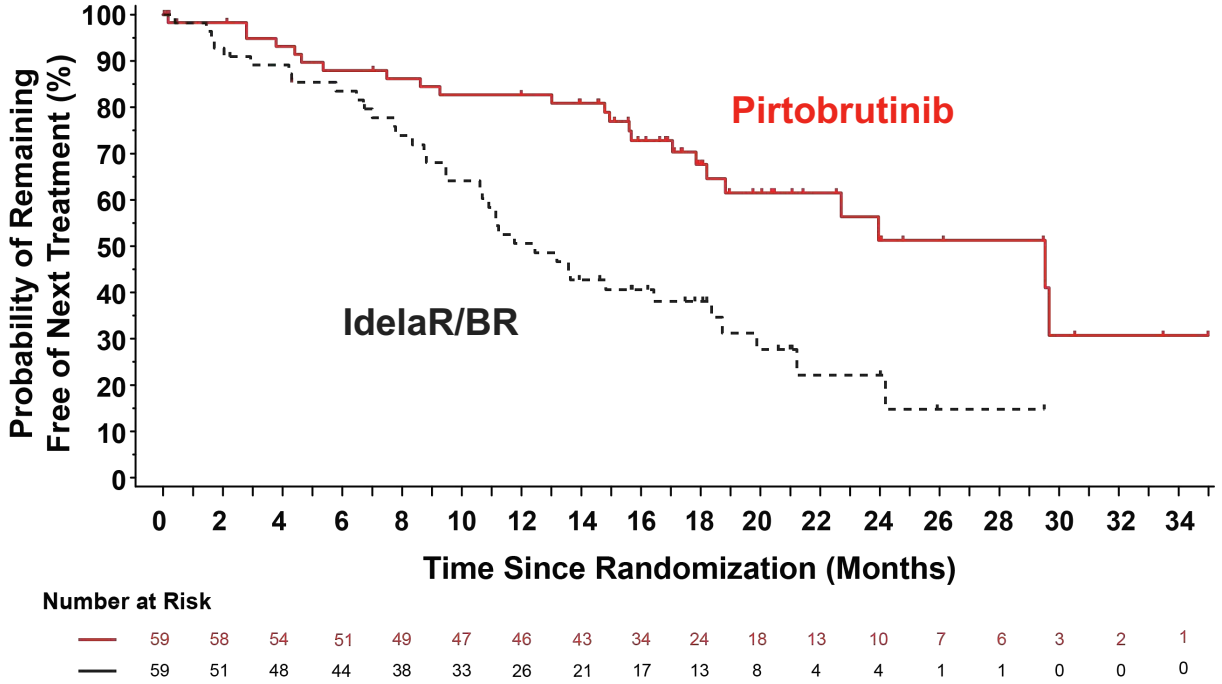
Pirtobrutinib reduced risk of progression or death by 46% according to IRC assessment

*nominal p-value. Abbreviations: BR, bendamustine + rituximab; CI, confidence interval; HR, hazard ratio (pirtobrutinib vs. IdelaR/BR); IdelaR, idelalisib + rituximab; IRC, Independent Review Committee; mo, months; PFS, progression-free survival.

Sharman, et al., ASH 2024, Abstract #886

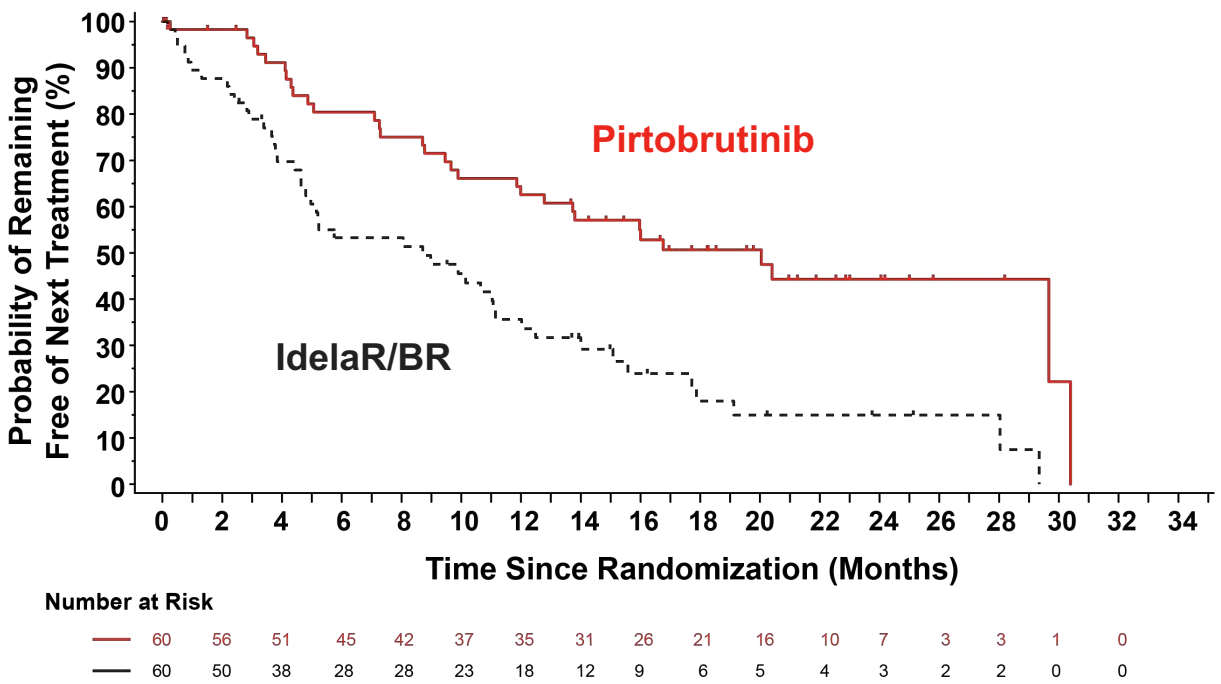
BRUIN CLL-321: Time to Next Treatment or Death in Venetoclax Naïve and Treated Patients

Venetoclax Naïve n=59/arm



	Pirtobrutinib n=119	IdelaR/BR n=119
Median TTNT, mo (95% CI)	29.5	12.5
Hazard ratio (95% CI)	0.36 (0.21- 0.61)	
Stratified log-rank 2-sided p-value	0.0001*	

Venetoclax Treated n=60/arm

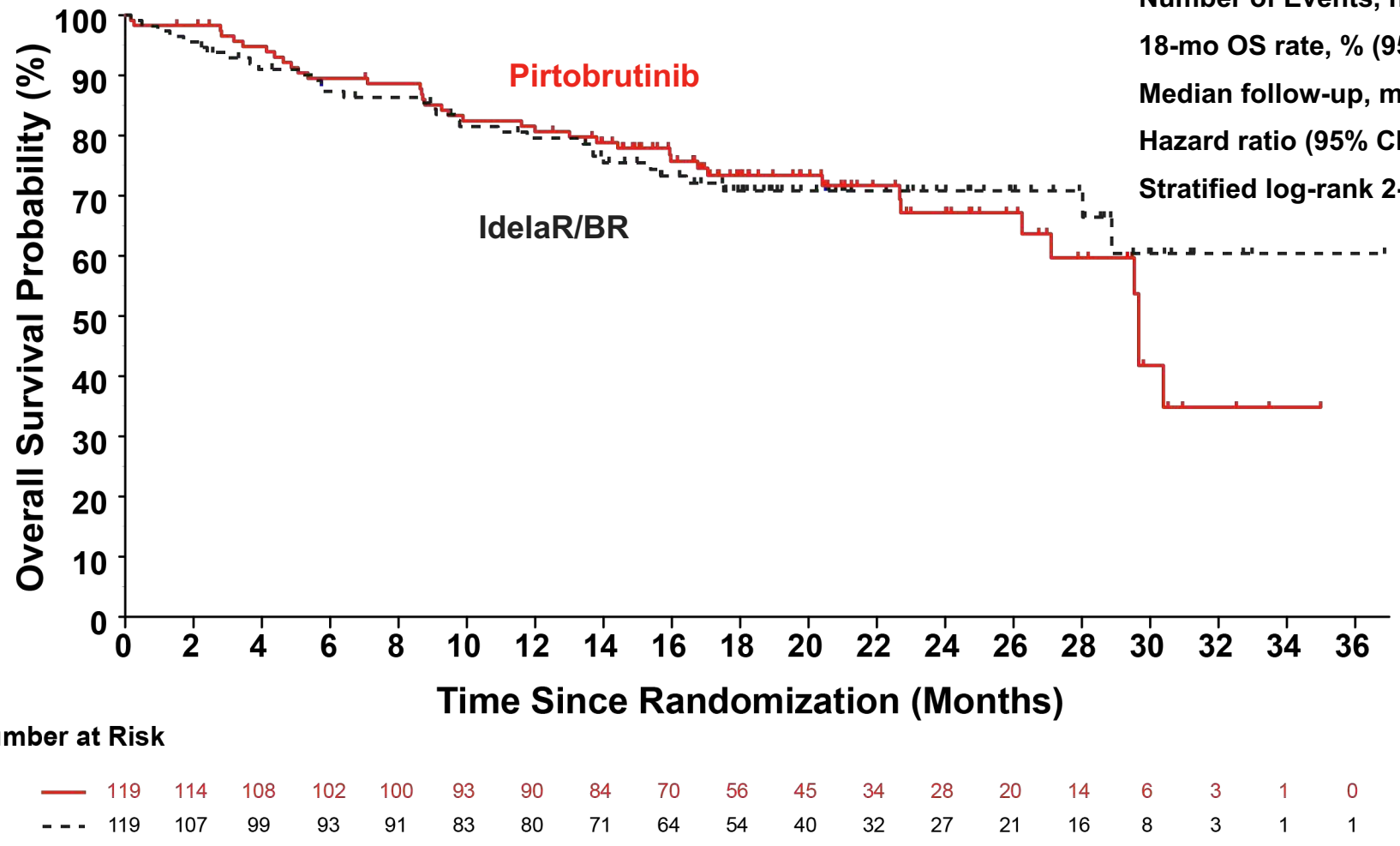


	Pirtobrutinib n=119	IdelaR/BR n=119
Median TTNT, mo (95% CI)	20.0	8.7
Hazard ratio (95% CI)	0.37 (0.23- 0.60)	
Stratified log-rank 2-sided p-value	<0.0001*	

*nominal p-value. Abbreviations: BR, bendamustine + rituximab; CI, confidence interval; HR, hazard ratio; IdelaR, idelalisib + rituximab; IRC, independent review committee; mo, months; TTNT, time to next treatment.

Sharman, et al., ASH 2024, Abstract #886

BRUIN CLL-321: Overall Survival



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

	Pirtobrutinib n=119	IdelaR/BR n=119
Number of Events, n (%)	38 (32)	32 (27)
18-mo OS rate, % (95% CI)	**73.4** (63.9-80.7)	**70.8** (60.9-78.7)
Median follow-up, mo	20.4	19.2
Hazard ratio (95% CI)	**1.09 (0.68-1.75)**	
Stratified log-rank 2-sided p-value	0.7202	

Crossover Rate*: 76% (50/66)

- IPCW crossover adjusted OS analysis: HR 0.89 (95%CI, 0.52-1.53)
- Two-stage AFT crossover adjusted OS analysis: HR 0.77 (95%CI, 0.45-1.26)

Overall survival follow-up limited and confounded by high rate of post-progression crossover

*Defined as patients with investigator-defined PD events other than death. Abbreviations: BR, bendamustine + rituximab; CI, confidence interval; IdelaR, idelalisib + rituximab; IPCW, inverse-probability-of-censoring weighting; AFT, adjusted for treatment; mo, months; NE, not estimable; NR, not reached; OS, overall survival.

Sharman, et al., ASH 2024, Abstract #886

BRUIN CLL-321: Adverse Events of Interest for Pirtobrutinib

Adverse Events of Interest	Pirtobrutinib (n=116)	
	Any grade n (%)	Grade 3+ n (%)
Bleeding	25 (21.6)	4 (3.4)
Bruising	9 (7.8)	1 (0.9)
Petechiae and purpura	6 (5.2)	1 (0.9)
Hemorrhage	18 (15.5)	3 (2.6)
Anemia	24 (20.7)	13 (11.2)
Neutropenia	31 (26.7)	24 (20.7)
Thrombocytopenia	11 (9.5)	9 (7.8)
Infection	74 (63.8)	34 (29.3)
Infection without Covid-19	67 (57.8)	30 (25.9)
Atrial fibrillation and atrial flutter	3 (2.6)[a]	2 (1.7)
Hypertension	8 (6.9)	3 (2.6)

[a]2 of 3 patients with atrial fibrillation had a past medical history of atrial fibrillation

Overall pirtobrutinib AESI rates were comparable to those seen in the Phase 1/2 BRUIN Study[5]

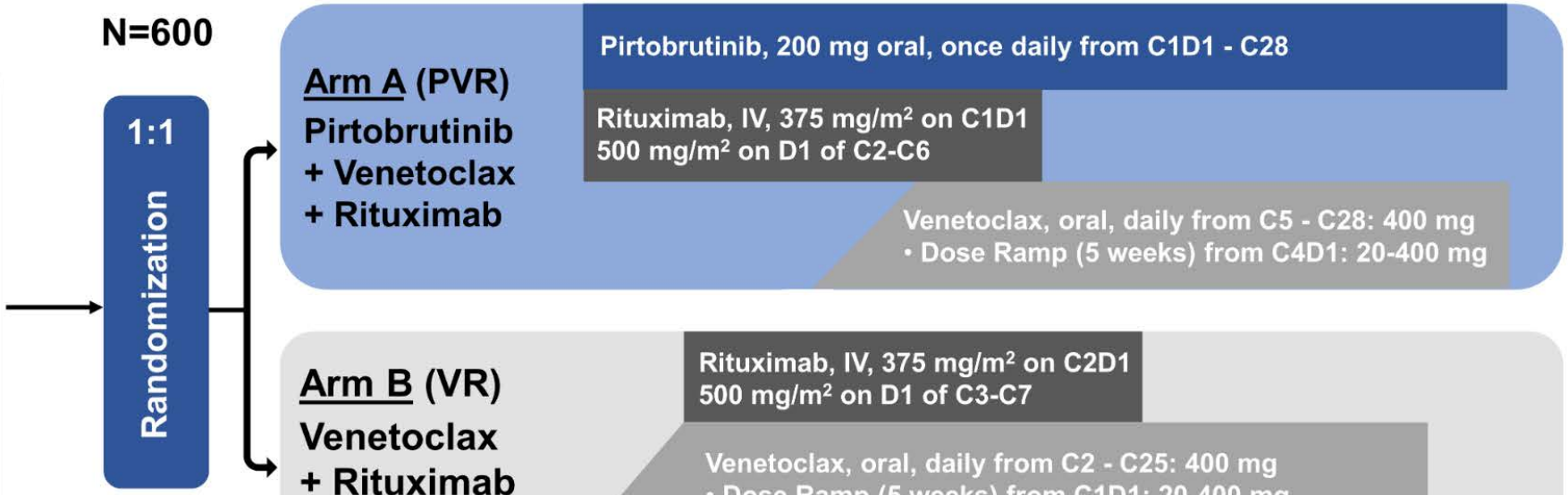
[5]Mato et al.NEJM 2023;389:33-44.

Sharman, et al., ASH 2024, Abstract #886

BRUIN CLL-322: A phase 3 open-label, randomized study of fixed duration pirtobrutinib plus venetoclax and rituximab versus venetoclax and rituximab in previously treated chronic lymphocytic leukemia/small lymphocytic lymphoma

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

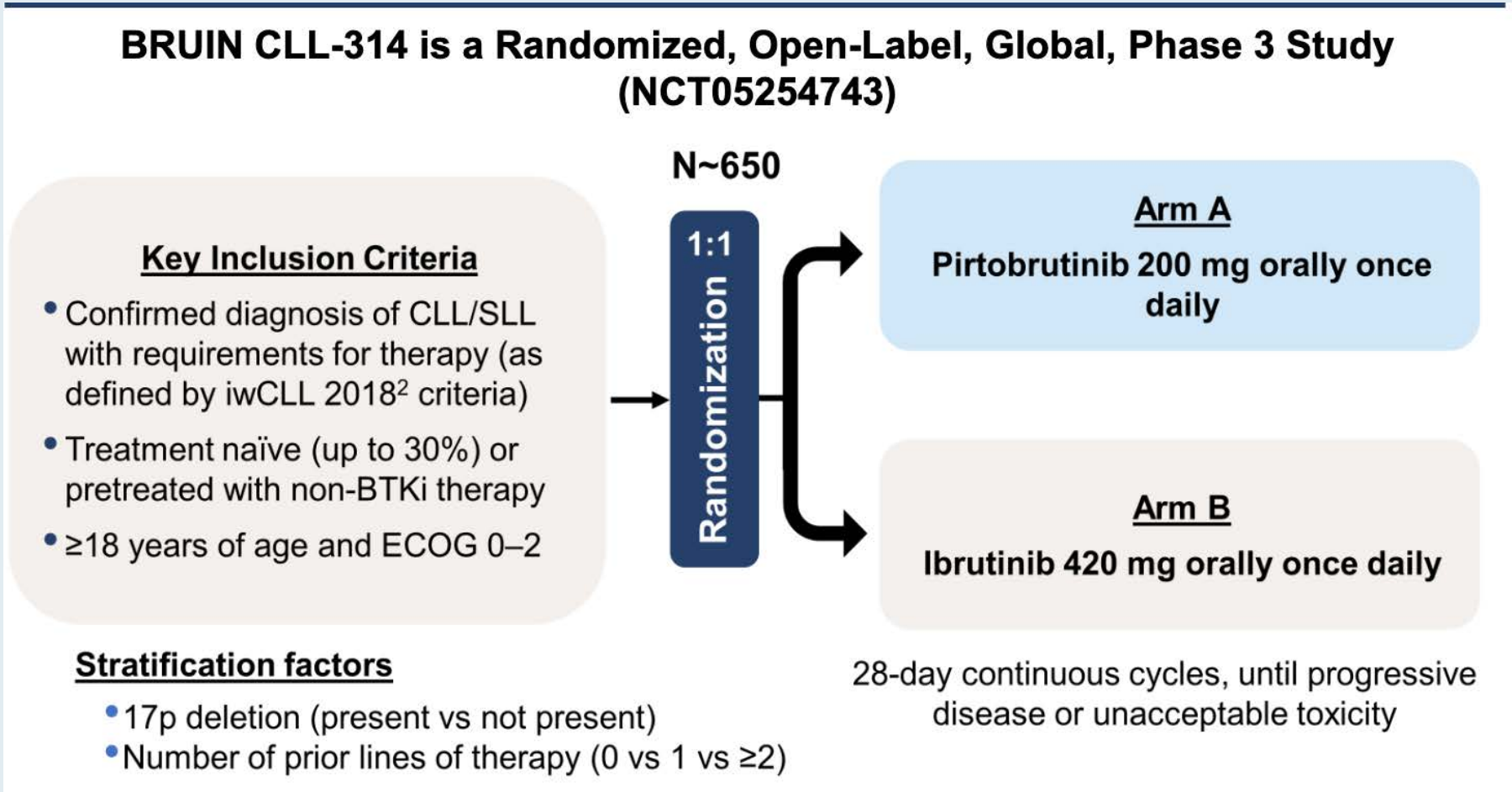
- 17p status (deleted/wildtype)
- Prior experience of BTKi (discontinuation due to PD or other vs no prior BTKi)

Each cycle is 28 days; C1 of Arm B is 35 days

Primary endpoint: PFS
Secondary endpoints: ORR, OS, TTNT, EFS, Safety, PROs

Eyre TA et al. ASCO 2023; Abstract TPS7583.
Mato AR et al. ASH 2021; Abstract 3742.

BRUIN CLL-314: A phase 3, open-label, randomized study of pirtobrutinib versus ibrutinib in patients with CLL/SLL



Primary Endpoints

– To establish non-inferiority of pirtobrutinib versus ibrutinib by comparing the overall response rate per iwCLL 20182 criteria as assessed by IRC

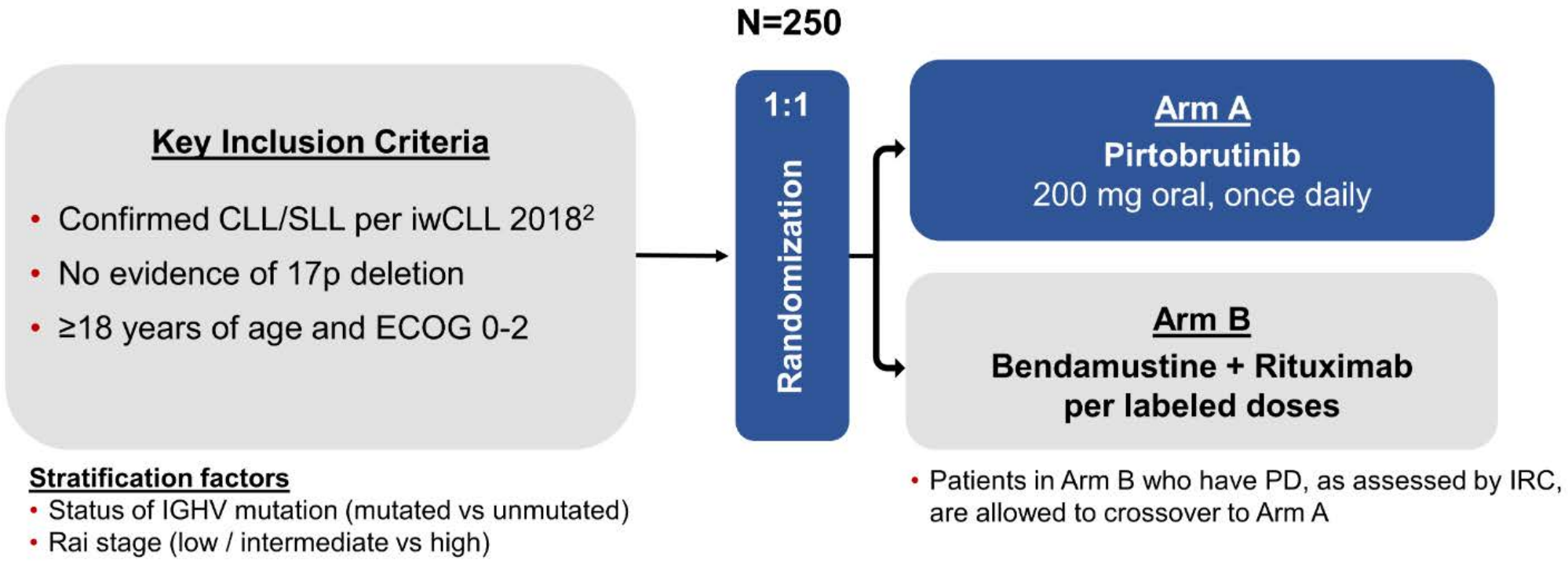
Key Secondary Endpoints

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

Escalón MP et al. iwCLL 2023; Abstract 1548596.

BRUIN CLL-313: A phase 3 open-label, randomized study of pirtobrutinib versus bendamustine plus rituximab in untreated patients with CLL/SLL

BRUIN CLL-313 is a randomized, open-label, global phase 3 study (NCT05023980)



Jurczak W et al. ASH 2021; Abstract 3732.

Cardiovascular Toxicity with BTKi

BTKi	Mechanism	Approved Indications (United States)	Key Trials	Cardiac Adverse Events		
First Generation						
Ibrutinib	Irreversible, covalent binding to Cysteine-481	CLL/SLL Waldenstrom's Macroglobulinemia Chronic Graft versus Host Disease (GVHD)	RESONATE RESONATE-2 ILLUMINATE	*Arrhythmia*	*AF:* *VA:*	13-16 % 1.9 %
				Hypertension:		9-23 %
				Major Bleeding:		3.9-10 %
Second Generation						
Acalabrutinib	Irreversible, covalent binding to Cysteine-481	CLL/SLL Mantle Cell Lymphoma*	ELEVATE T-N ELEVATE R-R	*Arrhythmia*	*AF:* *VA:*	9.4% 0.4 %
				Hypertension:		9.4 %
				Major Bleeding:		4.5 %
Zanubrutinib	Irreversible, covalent binding to Cysteine-481	CLL/SLL Mantle cell lymphoma* Relapsed/refractory Marginal zone lymphoma** Waldenstrom's Macroglobulinemia	SEQUOIA ASPEN ALPINE	*Arrhythmia*	*AF:* *VA:*	2-5 % 0.2-0.8 %
				Hypertension:		10-23.5 %
				Major Bleeding:		2.9-5.9 %
Third Generation						
Pirtobrutinib	Reversible, non-covalent binding to ATP pocket	Relapsed or Refractory CLL/SLL Mantle Cell Lymphoma***	BRUIN	*Arrhythmia*	*AF:* *VA:*	3.9 % NR
				Hypertension:		2.3 %
				Major Bleeding		2.4 %

NG J et al. American College of Cardiology, 16 Aug, 2023.

RTP RESEARCH TO PRACTICE

TRANSCEND CLL 004: Demographics & Baseline

	DL2 + ibrutinib set (n = 51)	Total liso-cel + ibrutinib combination set (n = 56)
Median (range) age, y	65 (44–77)	65 (44–77)
Median (range) prior lines of systemic therapy	**5 (1–13)**	**5 (1–13)**
≤ 3 prior therapies, n (%)	19 (37)	20 (36)
Prior BTKi, n (%)	51 (100)	56 (100)
Prior venetoclax, n (%)	39 (76)	42 (75)
Prior BTKi and venetoclax, n (%)	39 (76)	42 (75)
BTKi progression/venetoclax failure,[a] n (%)	**28 (55)**	**31 (55)**
High-risk cytogenetics, n (%)	50 (98)	55 (98)
Del(17p)	23 (45)	25 (45)
Mutated *TP53*	23 (45)	24 (43)
Unmutated IGHV	37 (73)	39 (70)
Complex karyotype[b]	25 (49)	29 (52)
Bulky disease (≥ 5 cm) per INV before LDC,[c] n (%)		
Yes	18 (35)	18 (32)
Unknown	4 (8)	5 (9)
Median (range) SPD per INV before LDC,[d] cm^2	29 (1–218)	27 (1–218)
LDH ≥ ULN before LDC, n (%)	22 (43)	24 (43)
Received bridging therapy (in addition to ibrutinib),[e] n (%)	13 (25)	16 (29)

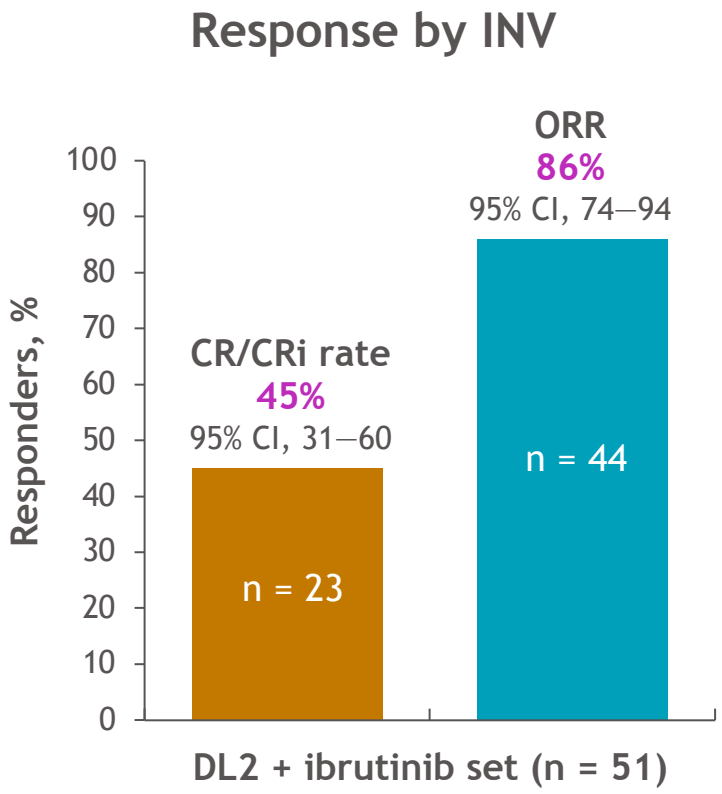
- Median (range) ibrutinib exposure was 34 days (15–188) before and 95 days (6–1517) after liso-cel in the total combination-treated set
- Liso-cel was manufactured for 63/65 (97%) patients in the leukapheresed set
  - Median (range) time from leukapheresis to liso-cel availability was 25 (17–79) days (n = 62)

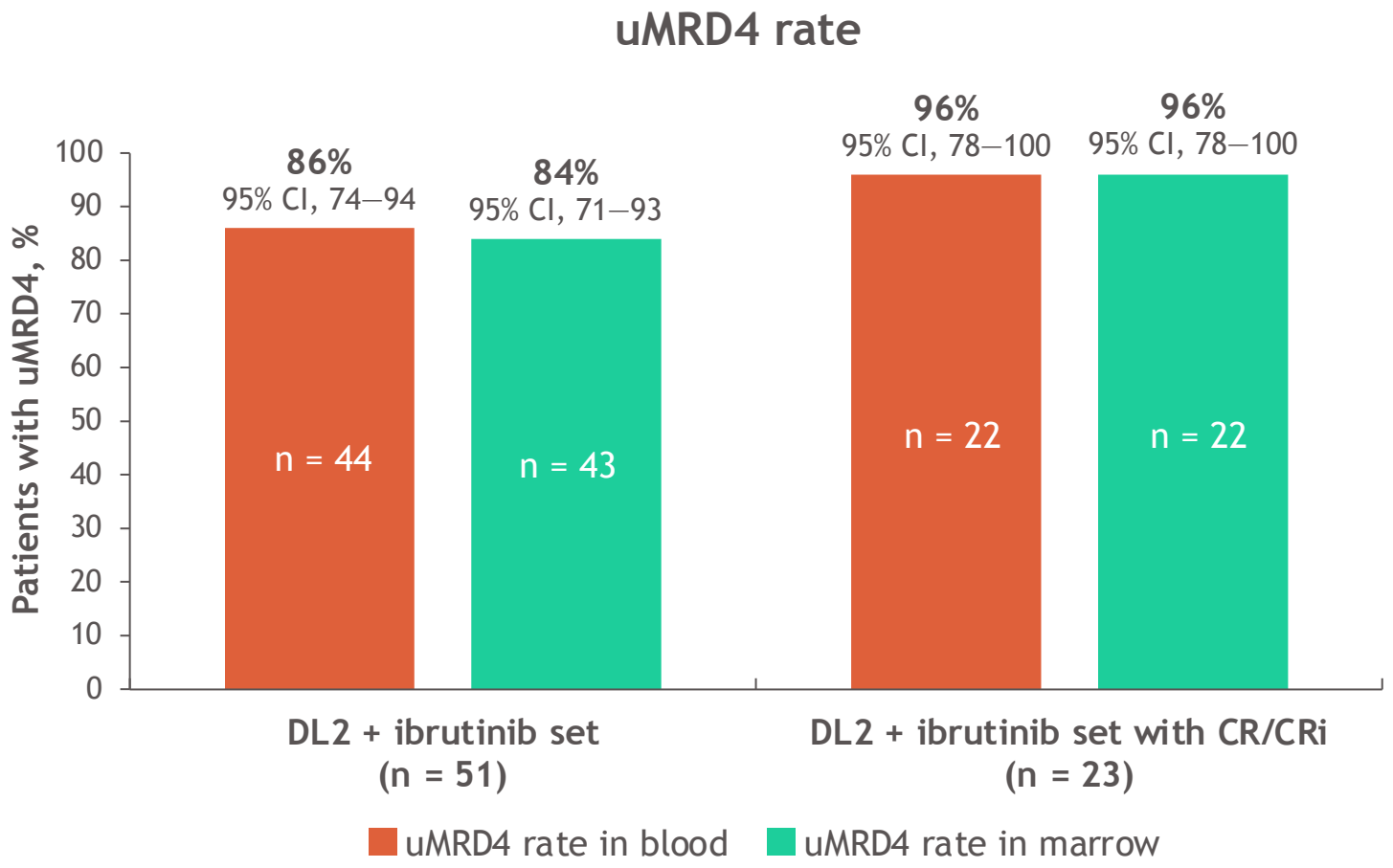
[a]Includes patients who progressed on a BTKi and met 1 of the following criteria: 1) discontinued venetoclax due to disease progression or intolerability and the patient's disease met indications for further treatment per iwCLL 2018 criteria or 2) failed to achieve an objective response within 3 months of initiating therapy; [b]At least 3 chromosomal aberrations; [c]At least 1 lesion with a longest diameter ≥ 5 cm; [d]Forty-seven patients at DL2 and 51 patients in the total combination-treated set had SPD measurements; [e]Included other anticancer therapies in addition to concurrent ibrutinib treatment given for disease control during liso-cel manufacturing. IGHV, immunoglobulin heavy-chain variable region; LDC, lymphodepleting chemotherapy; SPD, sum of the product of perpendicular diameters.

Wierda W, et al. ASH 2024 TRANSCEND CLL 004: Liso-cel + Ibrutinib Cohort [Abstract #887]

Efficacy outcomes: response by investigator and uMRD4

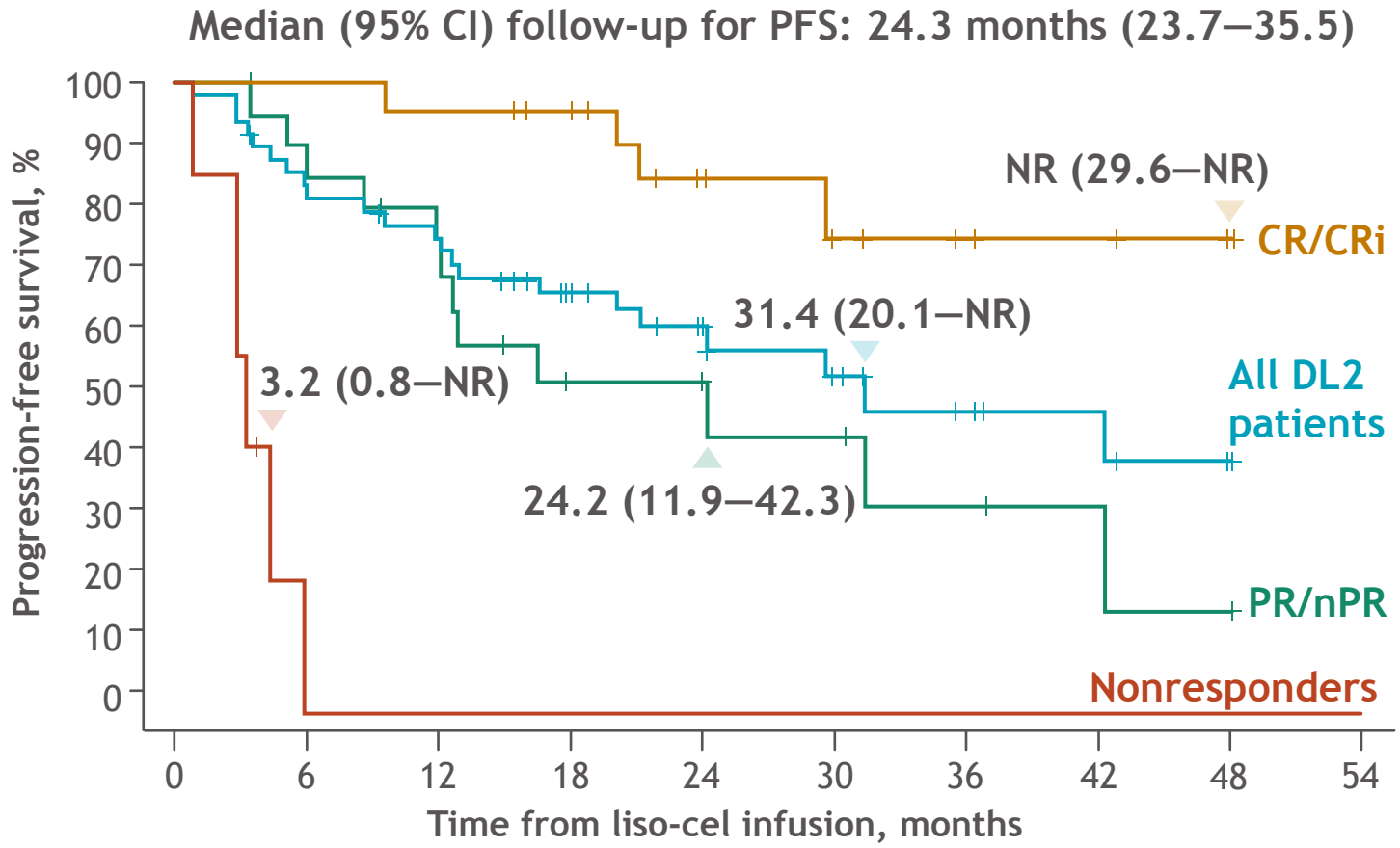
- Median (IQR) on-study follow-up (including LTFU): 24.8 months (14.2—34.6)
- Median (range) time to first response: 1 month (0.9—6.0)
- Median (range) time to first CR/CRi: 3 months (0.9—12.1)





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

Progression-free survival by best overall response at DL2



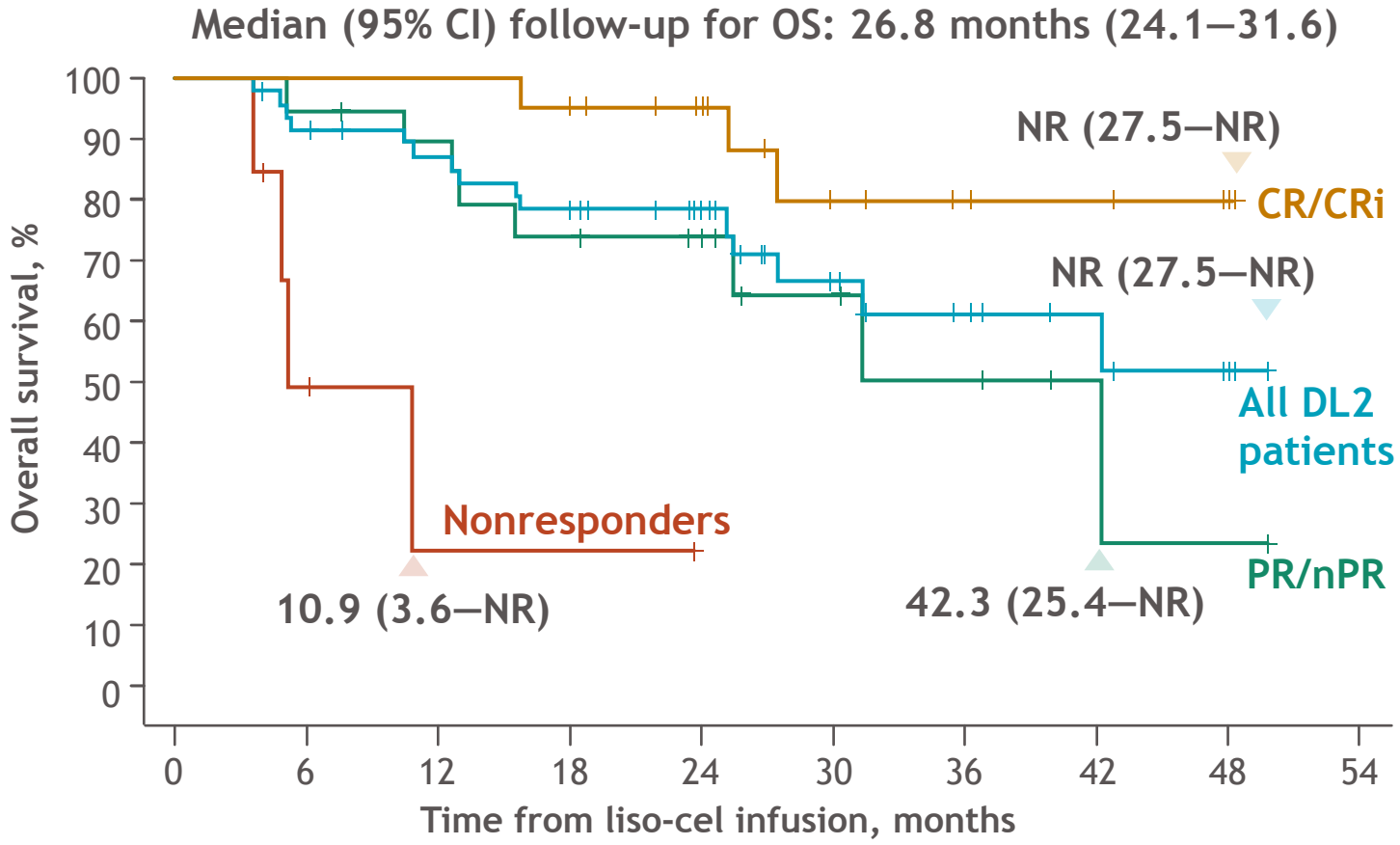
No. at risk										
CR/CRi	23	23	22	20	12	7	5	4	2	0
PR/nPR	21	17	14	7	6	5	3	2	1	0
Nonresponders	7	0	0	0	0	0	0	0	0	0
All DL2 patients	51	40	36	27	18	12	8	6	3	0

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

Data on KM curves are expressed as median (95% CI). No formal landmarking analyses were conducted.

Wierda W, et al. ASH 2024 TRANSCEND CLL 004: Liso-cel + Ibrutinib Cohort [Abstract #887]

Overall survival by best overall response at DL2



No. at risk										
CR/CRi	23	23	23	22	17	9	6	5	2	0
PR/nPR	21	20	18	15	12	6	4	2	1	0
Nonresponders	7	3	1	1	0	0	0	0	0	0
All DL2 patients	51	46	42	38	29	15	10	7	3	0

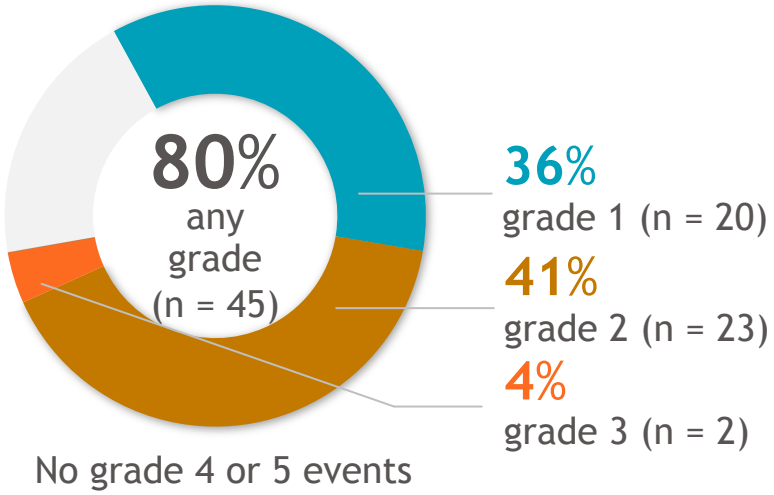
	% survival (95% CI)	
	12 months	24 months
All DL2 patients (n = 51)	88 (75—94)	80 (65—88)
Patients with CR/CRi (n = 23)	100 (NR—NR)	96 (73—99)

Data on KM curves are expressed as median (95% CI). No formal landmarking analyses were conducted.

Wierda W, et al. ASH 2024 TRANSCEND CLL 004: Liso-cel + Ibrutinib Cohort [Abstract #887]

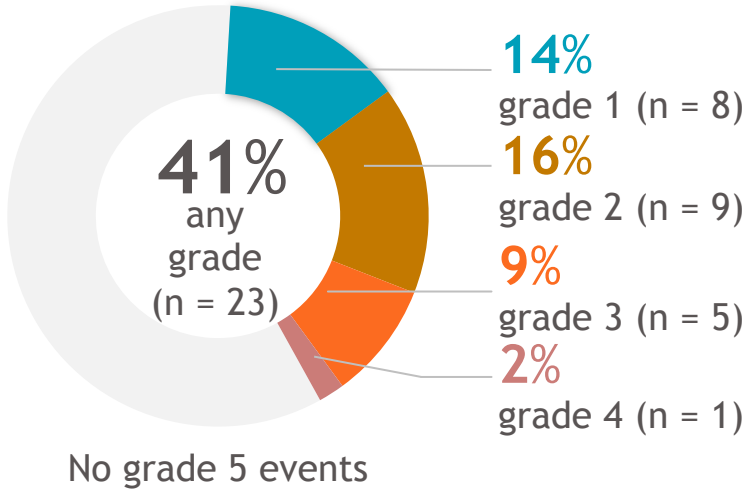
Safety: incidence of CRS and NEs

CRS[a,b]



No grade 4 or 5 events

NEs[a,c]



No grade 5 events

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

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

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

Wierda W, et al. ASH 2024 TRANSCEND CLL 004: Liso-cel + Ibrutinib Cohort [Abstract #887]

Agenda

Module 1: Selection and Sequencing of Therapy for Relapsed/Refractory (RR) Chronic Lymphocytic Leukemia (CLL) — Dr Wierda

Module 2: First-Line Therapy for CLL — Dr Coombs

Module 3: Novel Agents and Strategies for RR CLL — Dr Wierda

Module 4: ASCO and EHA 2025

Regulatory and reimbursement issues aside, outside of a clinical trial, have you or would you administer a BTKi inhibitor in combination with venetoclax +/- an anti-CD20 antibody as first-line treatment for CLL?
If you were going to administer a BTKi in combination with venetoclax +/- an anti-CD20 antibody as first-line treatment for CLL, which would be your preferred BTKi?

	BTK inhibitor + venetoclax +/- anti-CD20 antibody	Preferred BTK inhibitor
 Dr Coombs	I have	Acalabrutinib
 Dr Wierda	I have	Ibrutinib
 Dr Allan	I have	Zanubrutinib
 Dr Davids	I have	Acalabrutinib
 Dr Sharman	I haven't but would for the right patient	Acalabrutinib
 Dr Siddiqi	I haven't but would for the right patient	Zanubrutinib

Regulatory and reimbursement issues aside, in what specific clinical situations would you prefer to administer the time-limited regimen of a BTK inhibitor in combination with venetoclax with or without an anti-CD20 antibody as first-line therapy for CLL?

 Dr Coombs	AV: pt desiring time limited but prefers all oral AVO: pt desiring time limited with higher-risk markers
 Dr Wierda	This is my preferred first-line treatment approach
 Dr Allan	Bulky unmutated IGHV del(17p) or del(11q) CLL
 Dr Davids	AV: older pts/those with comorbidities and low-risk genetics AVO: younger or fit pts/those with higher-risk genetics desiring time-limited therapy
 Dr Sharman	Bulky nodes, higher risk for TLS, patient preference
 Dr Siddiqi	Younger patient, high-risk cytogenetics, desire for fixed-duration therapy but not keen on multiple infusions

AV = acalabrutinib and venetoclax; AVO = acalabrutinib, venetoclax and obinutuzumab; TLS = tumor lysis syndrome

Regulatory and reimbursement issues aside, and assuming equal access to acalabrutinib, zanubrutinib and pirtobrutinib, in general, which BTK inhibitor would you prefer to administer as first-line treatment for CLL?

 Dr Coombs	Zanubrutinib
 Dr Wierda	Acalabrutinib or zanubrutinib
 Dr Allan	Zanubrutinib
 Dr Davids	Acalabrutinib
 Dr Sharman	Zanubrutinib
 Dr Siddiqi	Zanubrutinib

RTP RESEARCH TO PRACTICE

Regulatory and reimbursement issues aside, what would be your preferred initial regimen for a patient with CLL and an IGHV mutation and no del(17p) or TP53 mutation requiring treatment?

	60-year-old patient	80-year-old patient
 Dr Coombs	Venetoclax + obinutuzumab	Venetoclax + obinutuzumab
 Dr Wierda	Venetoclax + obinutuzumab	Venetoclax + obinutuzumab
 Dr Allan	Venetoclax + obinutuzumab	Zanubrutinib
 Dr Davids	Venetoclax + obinutuzumab	Venetoclax + obinutuzumab
 Dr Sharman	Venetoclax + obinutuzumab	Venetoclax + obinutuzumab
 Dr Siddiqi	Venetoclax + obinutuzumab	Venetoclax + obinutuzumab

Regulatory and reimbursement issues aside, what would be your preferred initial regimen for a patient with CLL and no IGHV mutation or del(17p) or TP53 mutation requiring treatment?

	60-year-old patient	80-year-old patient
 Dr Coombs	Venetoclax + obinutuzumab	Zanubrutinib
 Dr Wierda	Ibrutinib + venetoclax	Acalabrutinib + venetoclax; acalabrutinib + venetoclax + obinutuzumab
 Dr Allan	Zanubrutinib + venetoclax + obinutuzumab	Zanubrutinib
 Dr Davids	Venetoclax + obinutuzumab	Venetoclax + obinutuzumab
 Dr Sharman	Acalabrutinib + obinutuzumab	Zanubrutinib
 Dr Siddiqi	Venetoclax + obinutuzumab	Zanubrutinib

Regulatory and reimbursement issues aside, what would be your preferred initial regimen for a patient with CLL and no IGHV mutation but with a del(17p) or TP53 mutation requiring treatment?

	60-year-old patient	80-year-old patient
 Dr Coombs	Zanubrutinib	Zanubrutinib
 Dr Wierda	Ibrutinib + venetoclax	Acalabrutinib or zanubrutinib
 Dr Allan	Zanubrutinib + venetoclax + obinutuzumab → zanubrutinib	Zanubrutinib
 Dr Davids	Zanubrutinib	Zanubrutinib
 Dr Sharman	Zanubrutinib + venetoclax	Zanubrutinib
 Dr Siddiqi	Zanubrutinib + venetoclax	Zanubrutinib

First-line therapy for chronic lymphocytic leukemia

Callie Coombs, MD

Associate Clinical Professor

University of California Irvine

What do the guidelines say?

SUGGESTED TREATMENT REGIMENS[a,b,c,d]
CLL/SLL Without del(17p)/*TP53* Mutation
(alphabetical by category)

FIRST-LINE THERAPY[e]		
Preferred Regimens	**Other Recommended Regimens**	**Useful in Certain Circumstances**
• BCL2i-containing regimens ▸ Venetoclax[f,h] + obinutuzumab (category 1) ▸ Venetoclax[f,h] + acalabrutinib ± obinutuzumab (category 1) • cBTKi-based regimens ▸ Acalabrutinib[f,g] ± obinutuzumab (category 1) ▸ Zanubrutinib[f,g] (category 1)	• BCL2i-containing regimen ▸ Venetoclax[f,h] + ibrutinib[f,g] • cBTKi-based regimen ▸ Ibrutinib[f,g,i] (category 1)	• Consider for IGHV-mutated CLL in patients aged <65 y without significant comorbidities ▸ FCR (fludarabine, cyclophosphamide, rituximab)[j,k] • cBTKi-based regimen ▸ Ibrutinib[f,g] + anti-CD20 mAb (category 2B)[l] • Consider when cBTKi and BCL2i are not available or contraindicated or rapid disease debulking needed ▸ Bendamustine[m] + anti-CD20 mAb[l,n] ▸ Obinutuzumab ± chlorambucil[o] ▸ High-dose methylprednisolone (HDMP) + anti-CD20 mAb[l] (category 2B; category 3 for patients <65 y without significant comorbidities)

- Guidelines for patients *with* 17p/TP53 mutation are similar but advise *against* CIT (and no category 1 regimens in first-line)

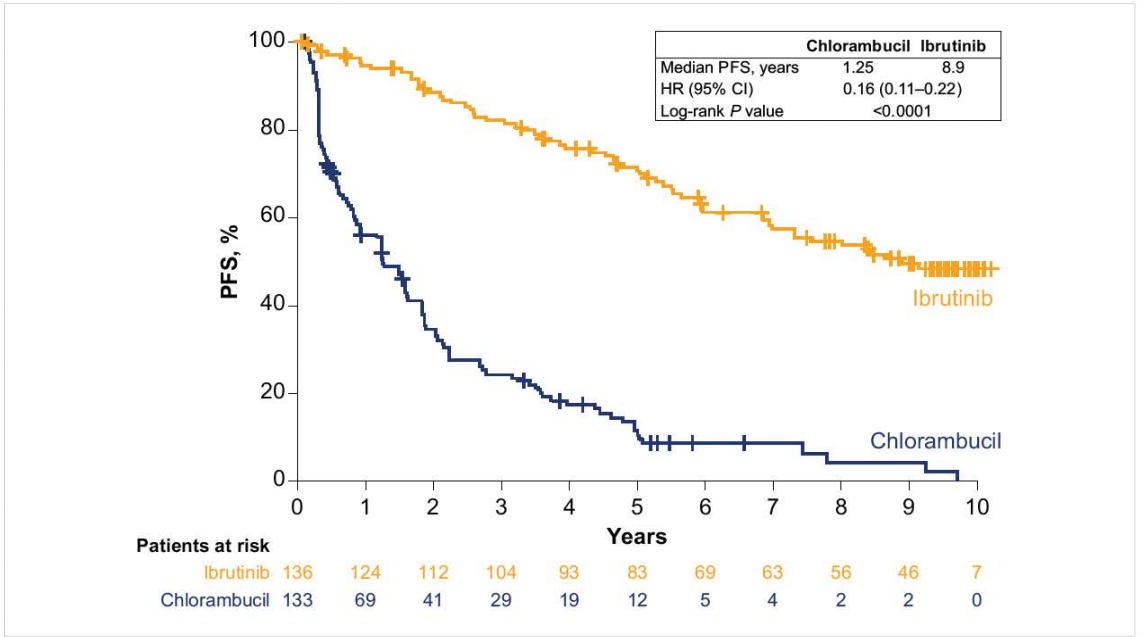
NCCN guidelines – Accessed 5/24/25

Ibrutinib provides **long-term** disease control

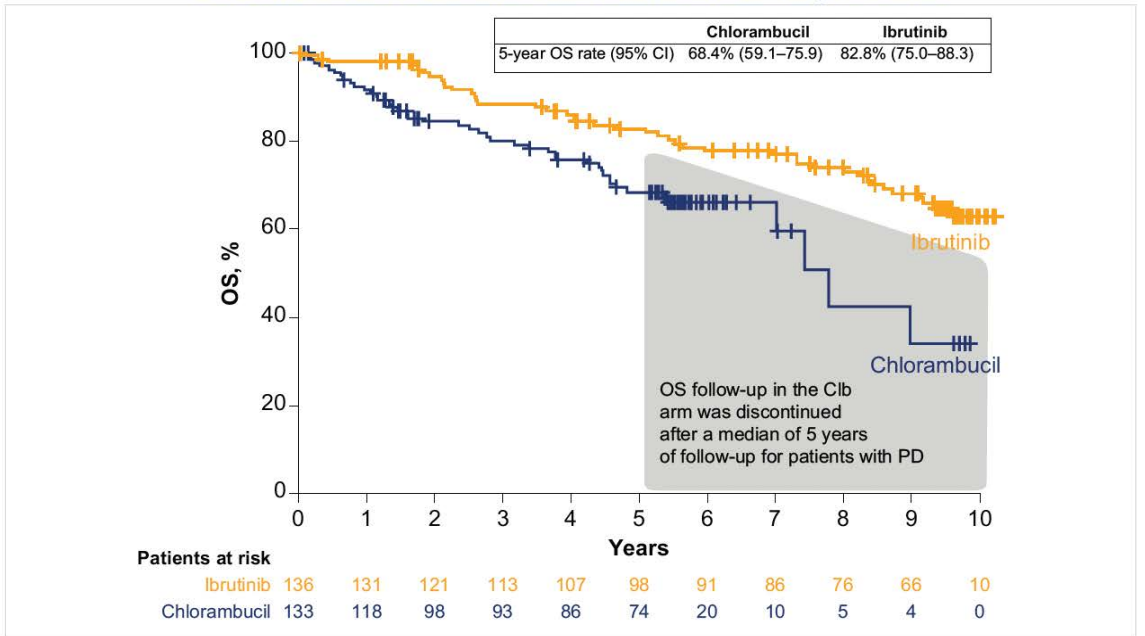
- With up to 10-years of follow up from RESONATE-2 trial demonstrates median PFS of 8.9 years for ibrutinib-treated patients compared to 1.3 years for chlorambucil-treated patients

Burger J et al. EHA 2024

At Final Analysis, Median PFS With Ibrutinib Was Reached at 8.9 Years

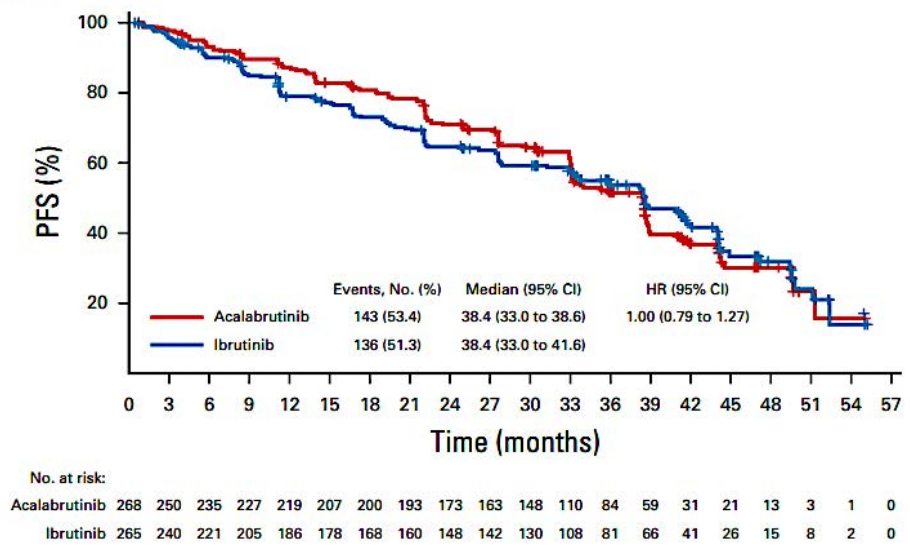


OS Benefit Was Sustained for Patients Receiving Ibrutinib

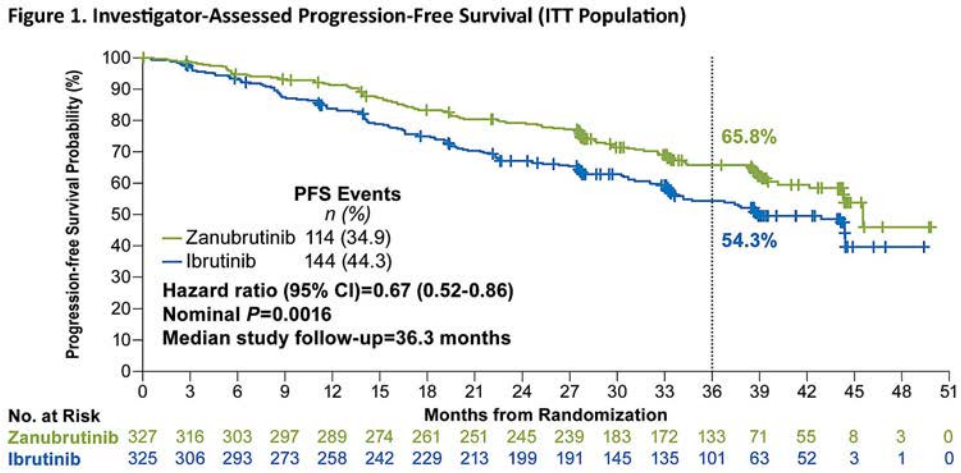


Clb, chlorambucil.

Ibrutinib is no longer a favored BTKi due to toxicity profile



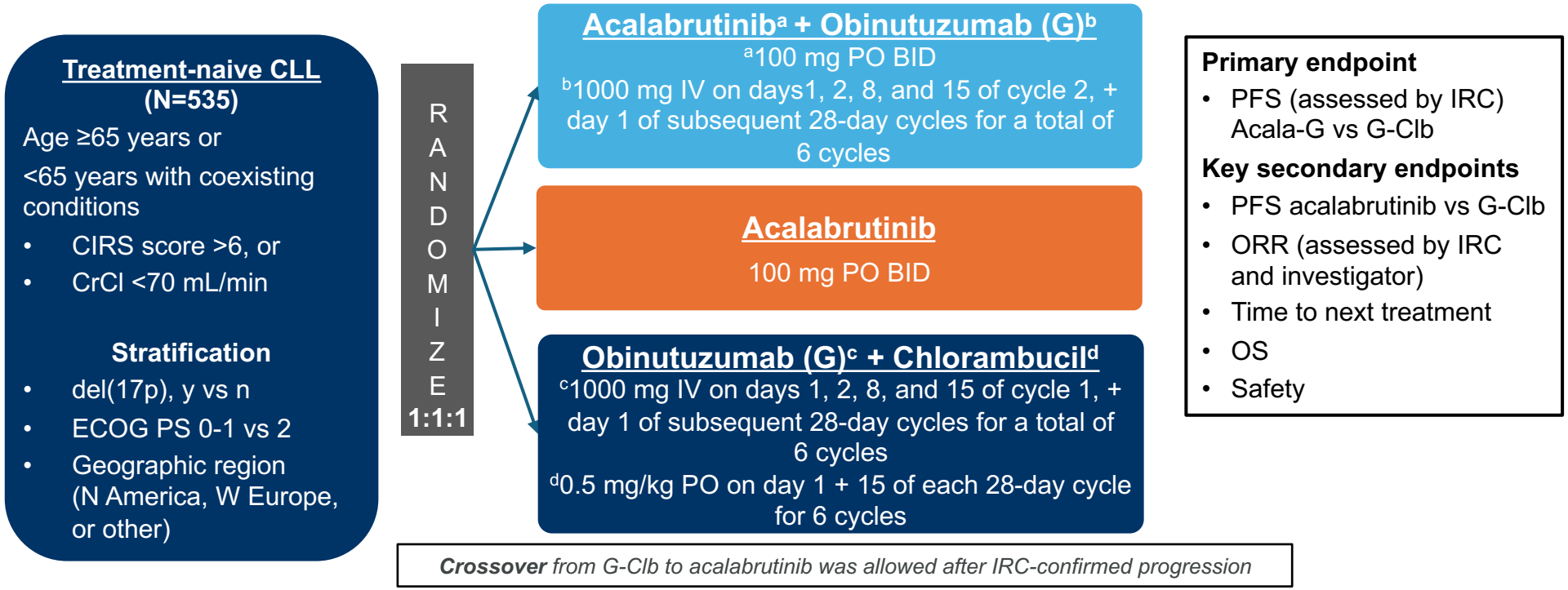
ELEVATE-RR: Acalabrutinib has non-inferior efficacy to ibrutinib in high-risk relapsed population, but superior safety ⬇️afib/flutter, ⬇️HTN



ALPINE: Zanubrutinib has superior efficacy vs. ibrutinib in all-comer relapsed population, also superior safety ⬇️afib/flutter, but similar HTN

Byrd et al. JCO 2021 and Brown et al. ASH 2023

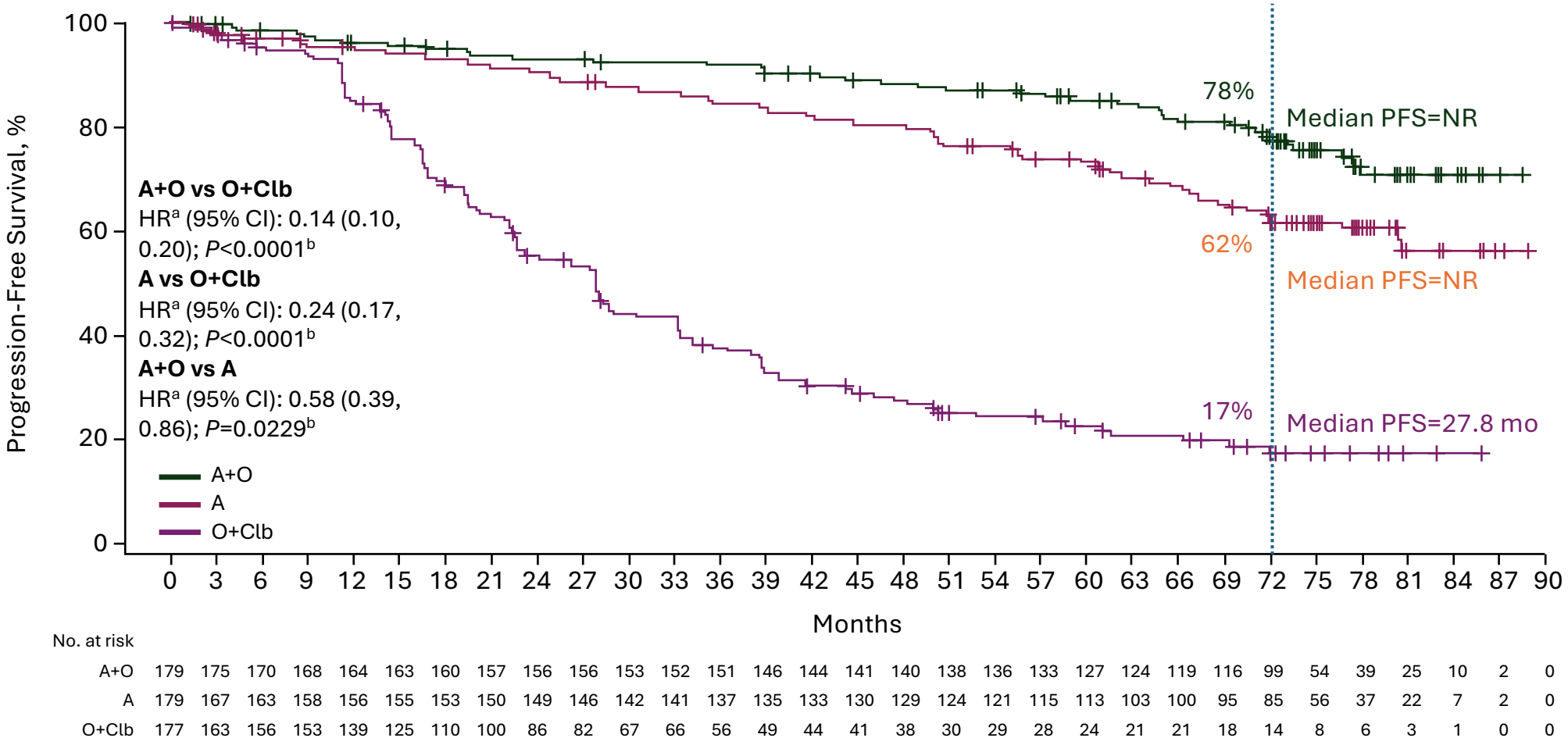
ELEVATE TN: Study Design



- Interim analysis was planned based on events (after occurrence of ~111 IRC-assessed PFS events in the combination therapy arms) or after 24 months if the required number of events was not met by this time

Sharman JP et al. *Lancet*. 2020;395(10232):1278-91.

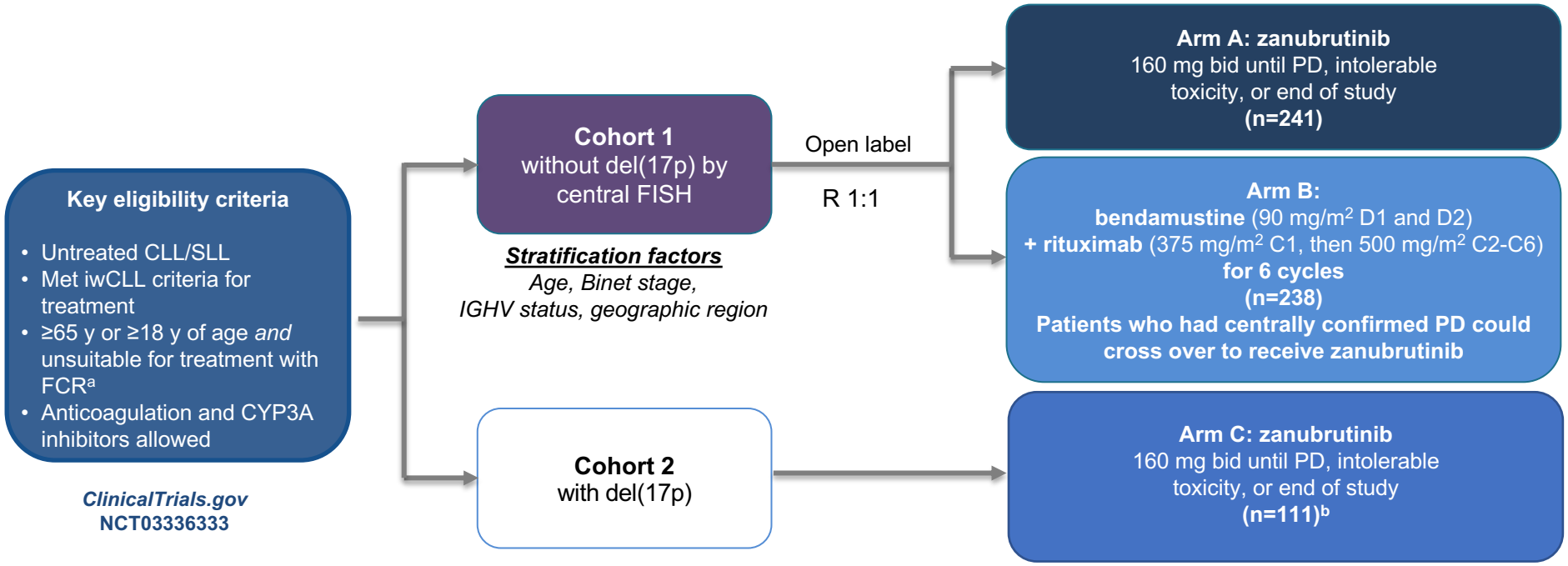
Median PFS was significantly higher for A-containing arms vs O+Clb



- Median PFS was significantly higher for A+O vs A

[a]Hazard ratio based on stratified Cox proportional-hazards model.
[b]*P*-value based on stratified log-rank test.
Sharman et al. ASH 2023

SEQUOIA study design

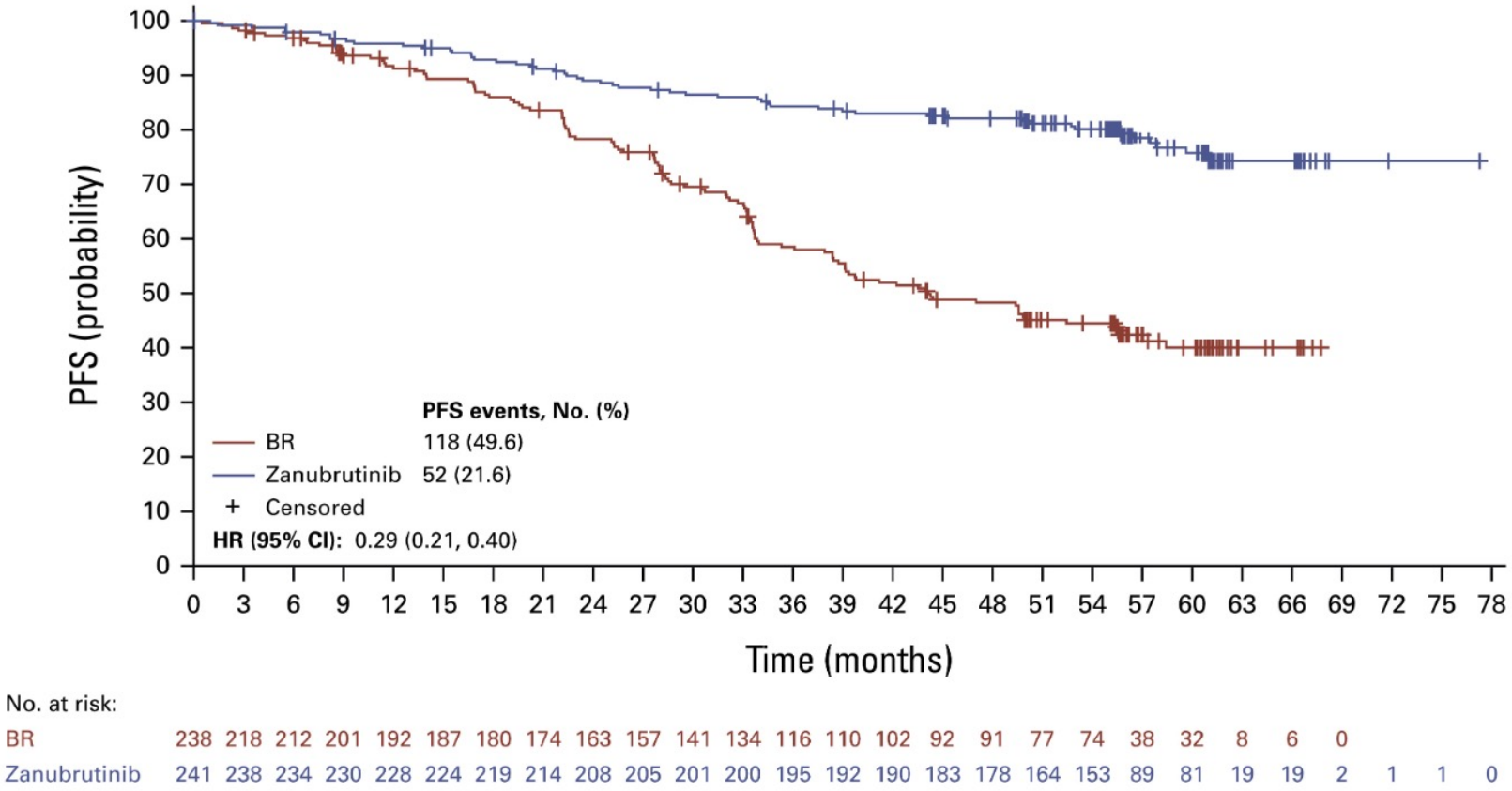


Assessments
- Response assessments were conducted every 12 weeks from start of C1 for 96 weeks and every 24 weeks until PD
- CR/CRi confirmed via bone marrow biopsy
- AEs documented until PD or start of next CLL therapy

Statistical analysis
- Efficacy endpoints analyzed using ITT analysis and the per-protocol analysis set
- Safety was assessed in all pts who received ≥1 dose of treatment

Outcomes
- PFS assessed by investigator
- OS in cohorts 1 and 2
- PFS 2[c]
- Clinical outcomes (correlated with baseline prognostic and predictive markers)
- Safety

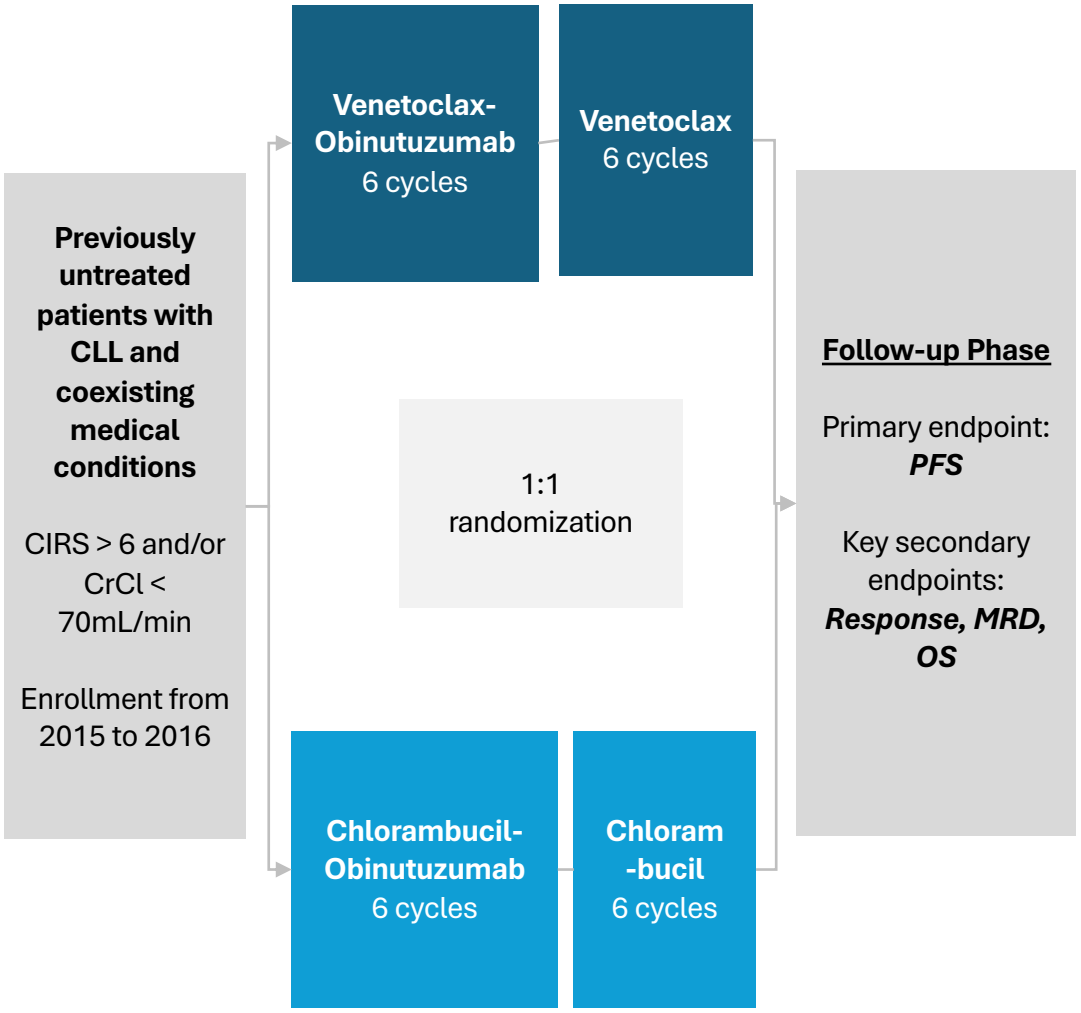
5-year SEQUOIA follow up



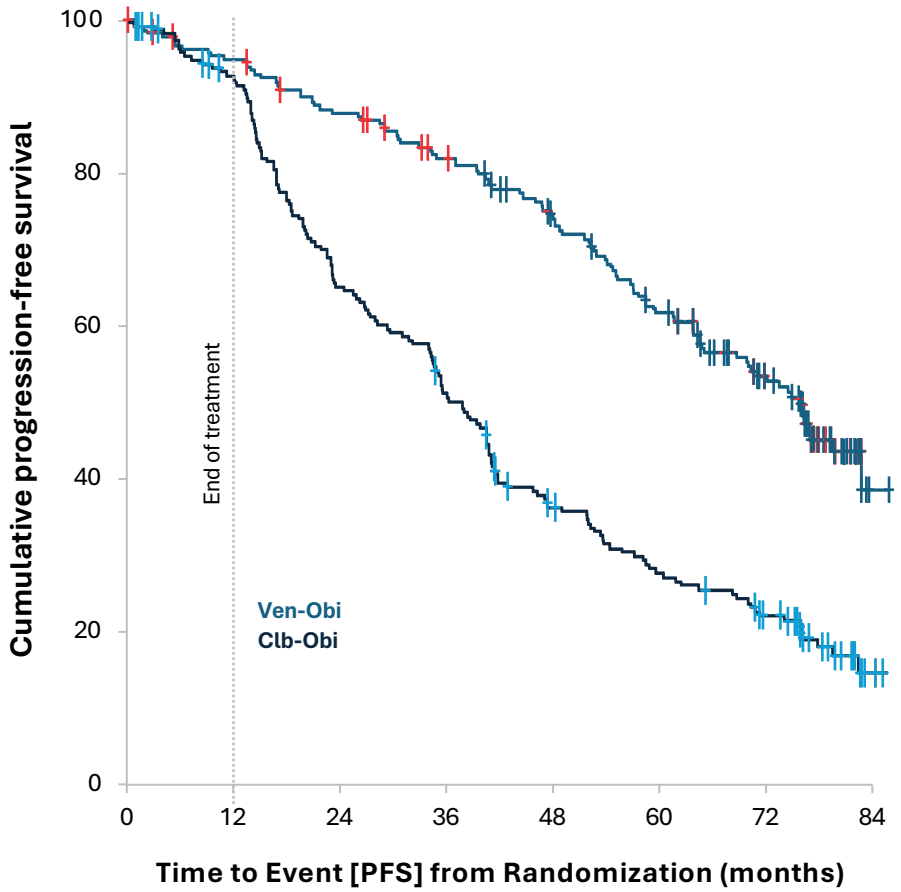
Shadman M et al. JCO 2024

Phase III CLL14 Study: 6-Year Update

Study Design



Investigator Assessed Progression-Free Survival



Median PFS
Ven-Obi: 76.2 months
Clb-Obi: 36.4 months

6-year PFS rate
Ven-Obi: 53.1%
Clb-Obi: 21.7%

HR 0.40, 95% CI [0.31-0.52]
P<0.0001

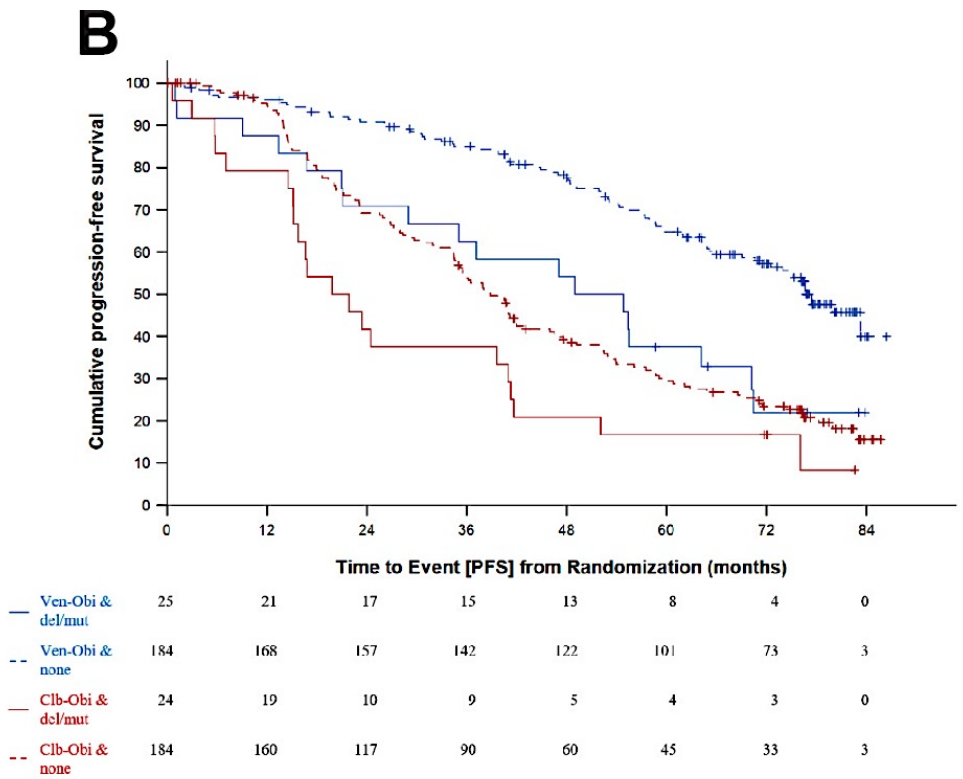
6-Year OS rate = 78%

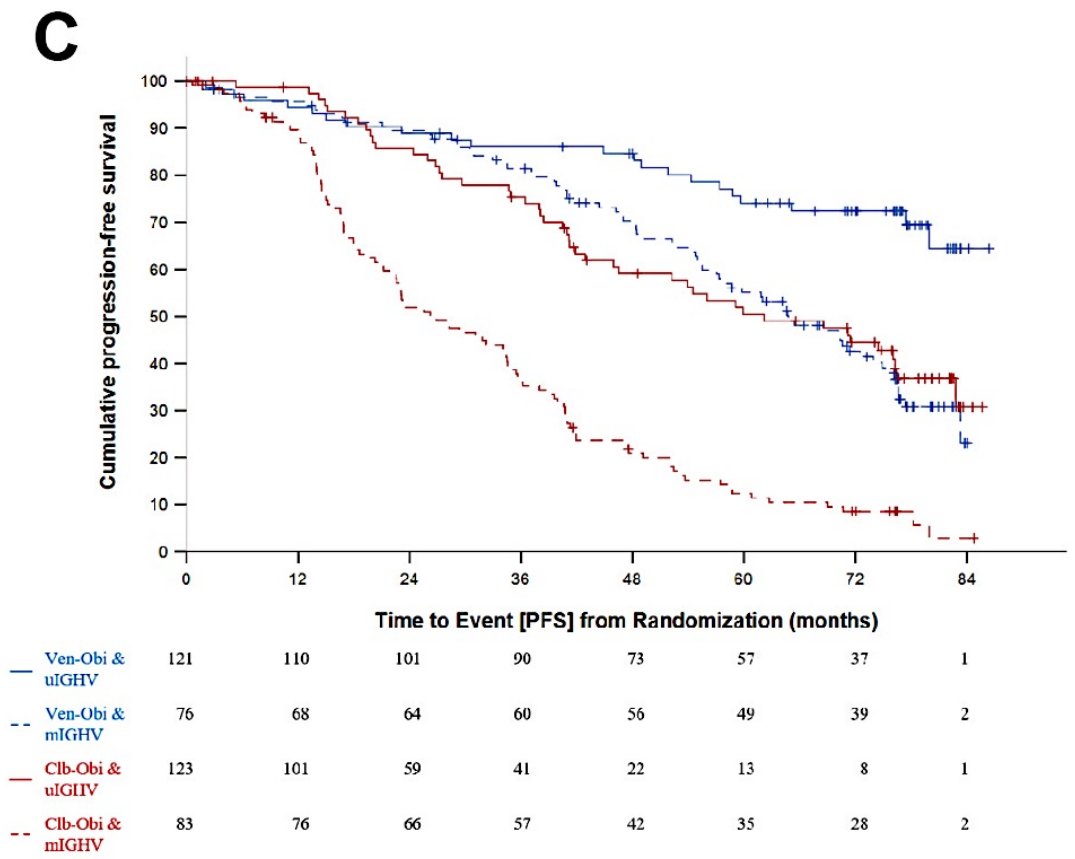
- Reformatted from Al-Sawaf et. al. EHA 2023. Presentation ID S145

Venetoclax in frontline setting: CLL14 trial

<u>Updates from 6 year follow up:</u>

- Median PFS reached: 76.2 months
- Median PFS for TP53 aberrant pts: 51.9 months
- Median PFS for unmut IGHV pts: 64.8 months

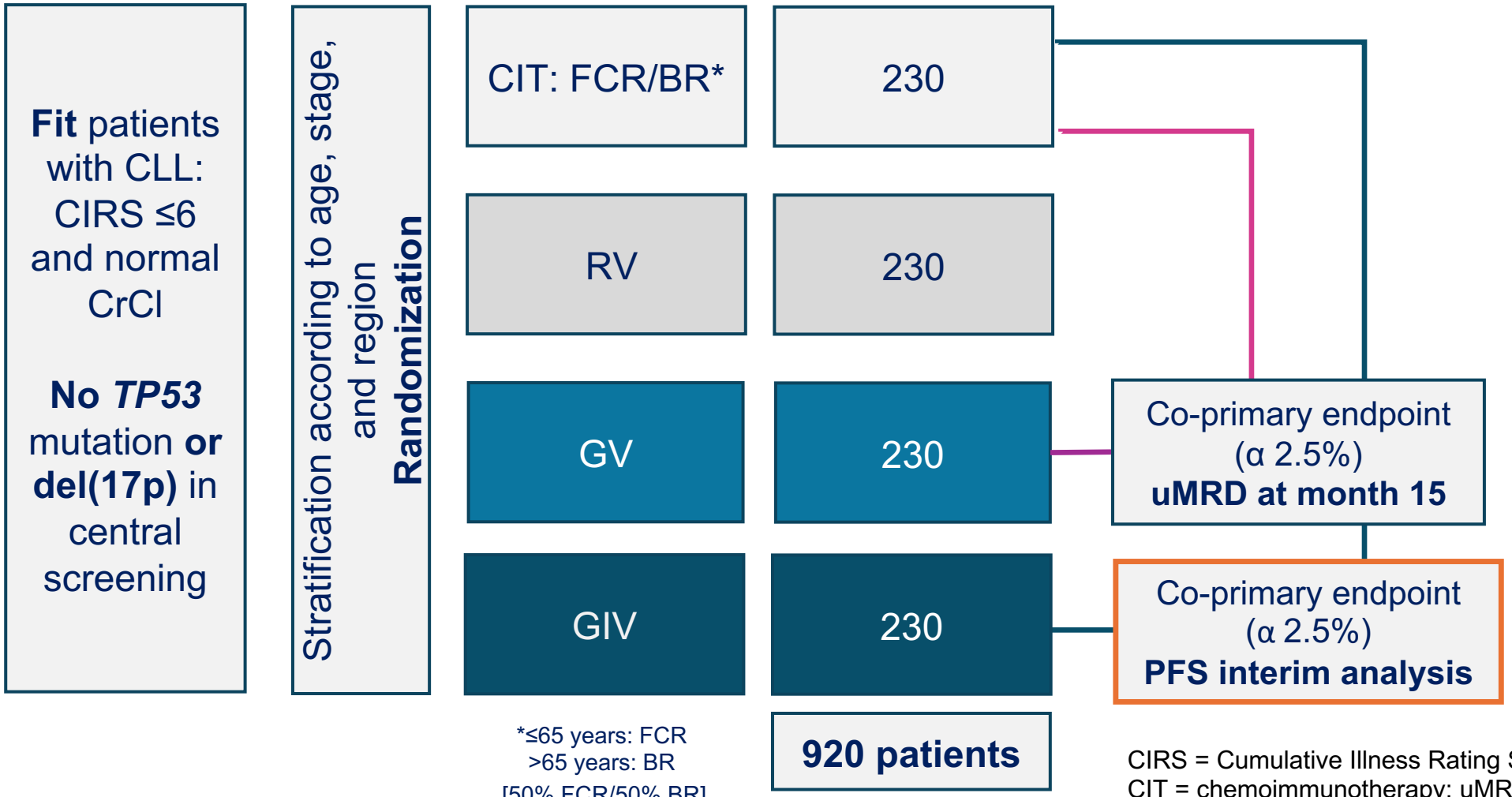




Al-Sawaf O et al. EHA 2023

GAIA/CLL13 Study Design for **Fit Patients** With CLL

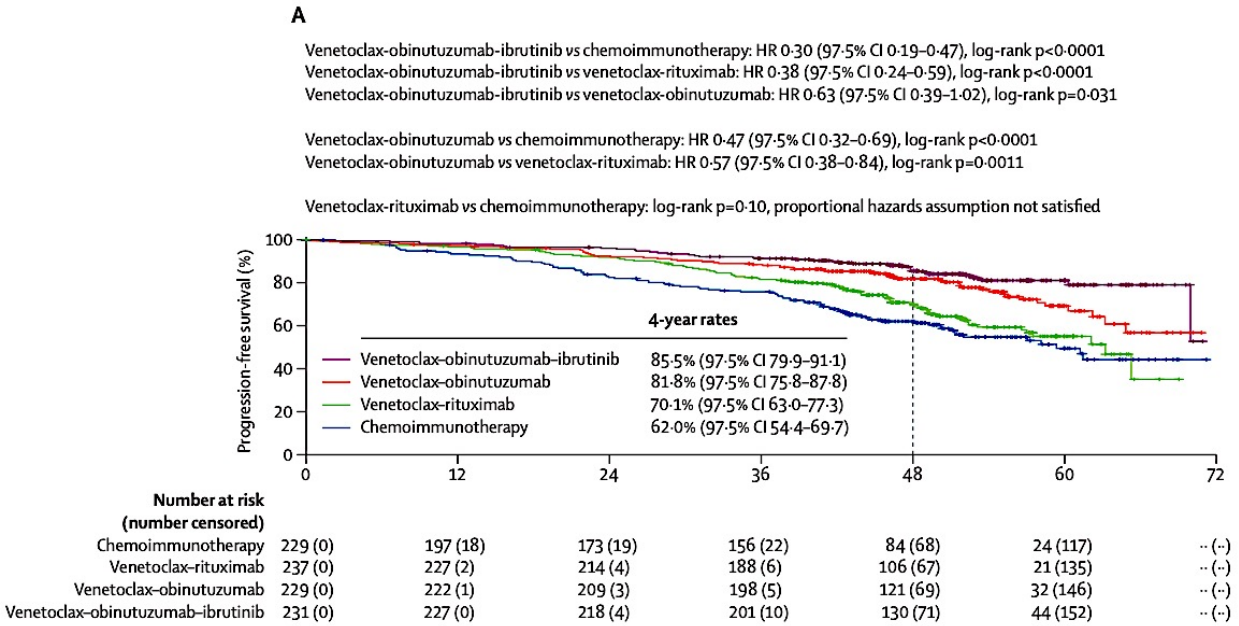
Chemoimmunotherapy (**FCR/BR**) vs **R**ituximab + **V**enetoclax vs Obinutuzumab (**G**) + **V** vs **G** + **I**brutinib + **V**
Recruitment in 10 countries (DE, AT, CH, NL, BE, DK, SE, FI, IE, IL)



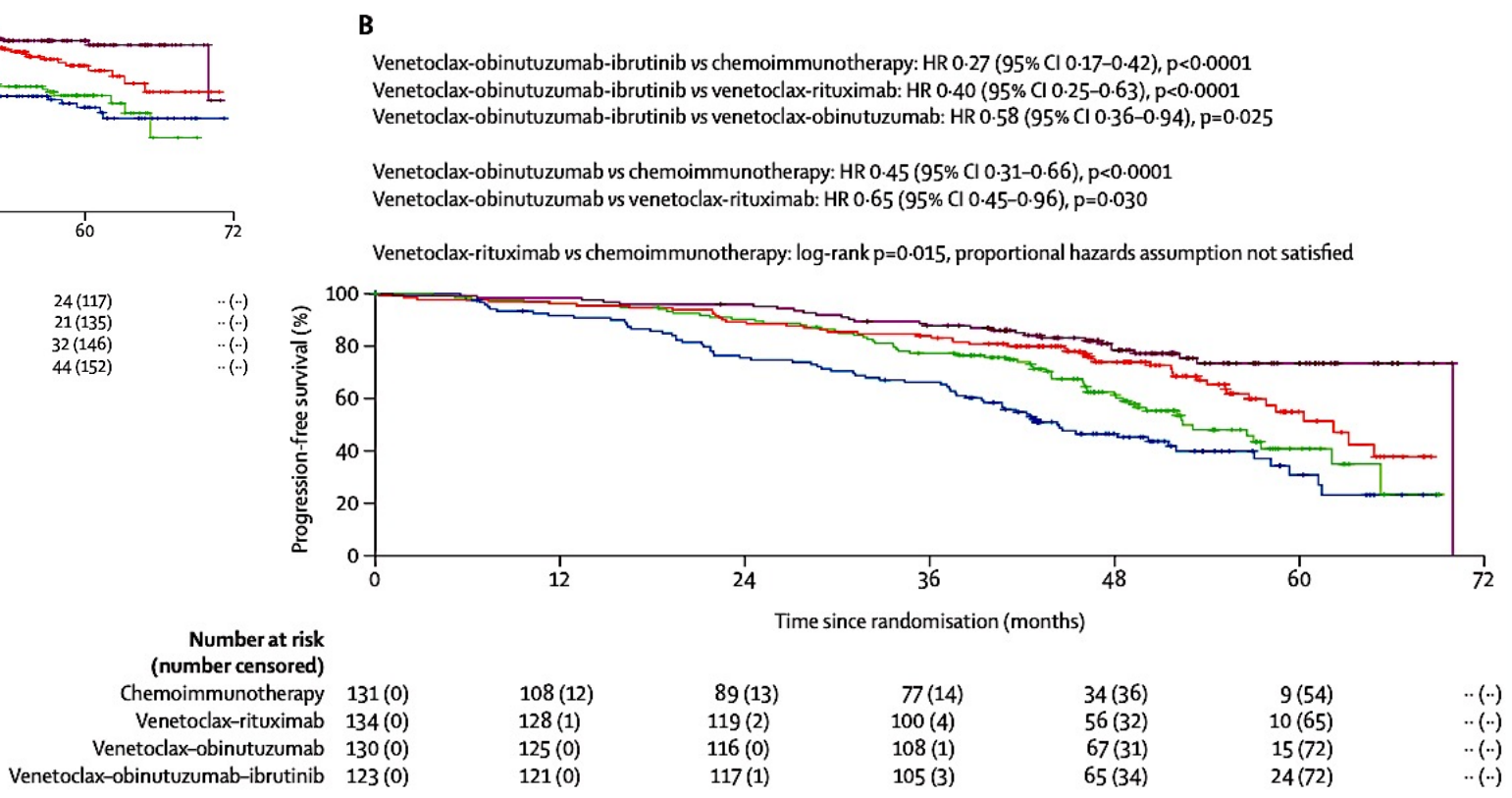
CIRS = Cumulative Illness Rating Scale;
CIT = chemoimmunotherapy; uMRD = undetectable minimal residual disease

Eichhorst B et al. 2022 EHA; Abstract LB2365.

4-year follow up of CLL13 trial support VO-containing regimen superiority

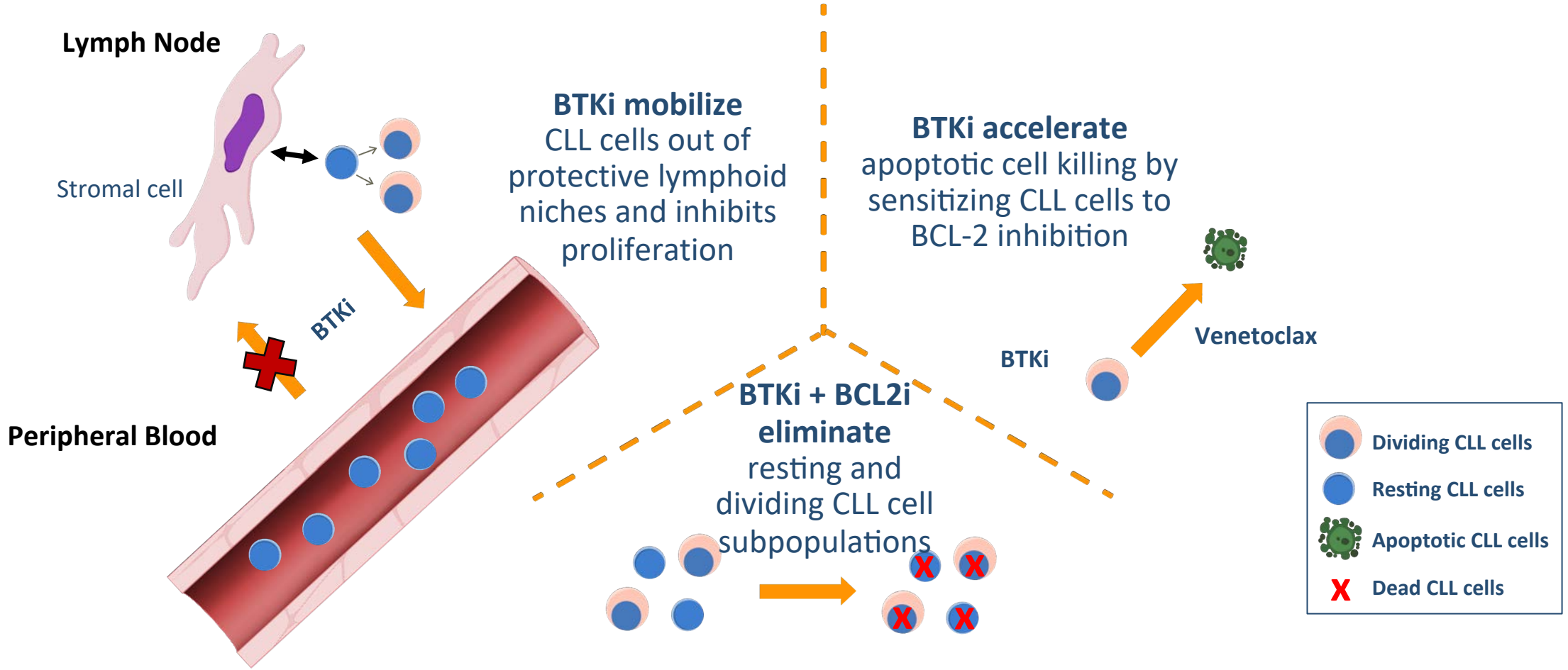


Unmutated IGHV only



Fürstenau M et al. Lancet Oncol. 2024

Rationale to combine BTKi with BCL2i



1. Lu P et al. *Blood Cancer J.* 2021; 11:39; 2. Deng J et al. *Leukemia.* 2017; 31:2075-2084; 3. Herman ES et al. *Clin Cancer Res.* 2015; 21:4642-4651; 4. Burger JA et al. *Leukemia.* 2020;34:787-798; 5. Shanafelt T et al. *N Engl J Med.* 2019;381:432-443; 6. Cervantes-Gomez, F. et al. *Clin. Cancer Res*. 2015; 21:3705–3715; 7. Slinger E, et al. *Blood*. 2017; 130: 3018-3018; 8. Haselager MV, et al. *Blood.* 2020 ;136:2918-2926; 9. Slinger E et al. Leukemia. 2017 Dec;31(12):2601-2607.

AMPLIFY: Combination cBTKi and BCL2i Therapy in 1L CLL

AMPLIFY

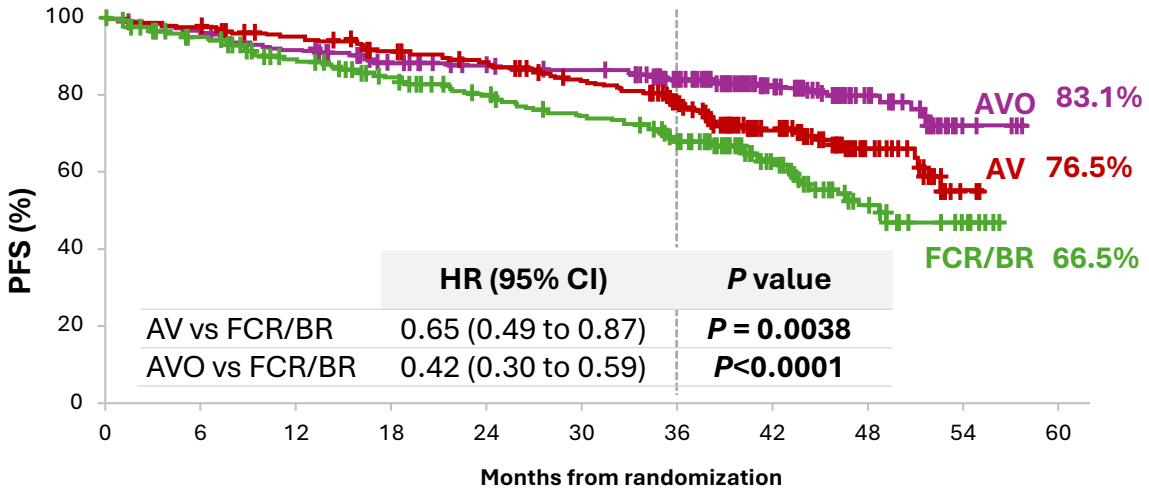
Treatment-naive CLL
- Age ≥ 18y/o
- ECOG: 0-2
- Active disease per IWCLL 2018 criteria

Exclusion
- del(17p), TP53

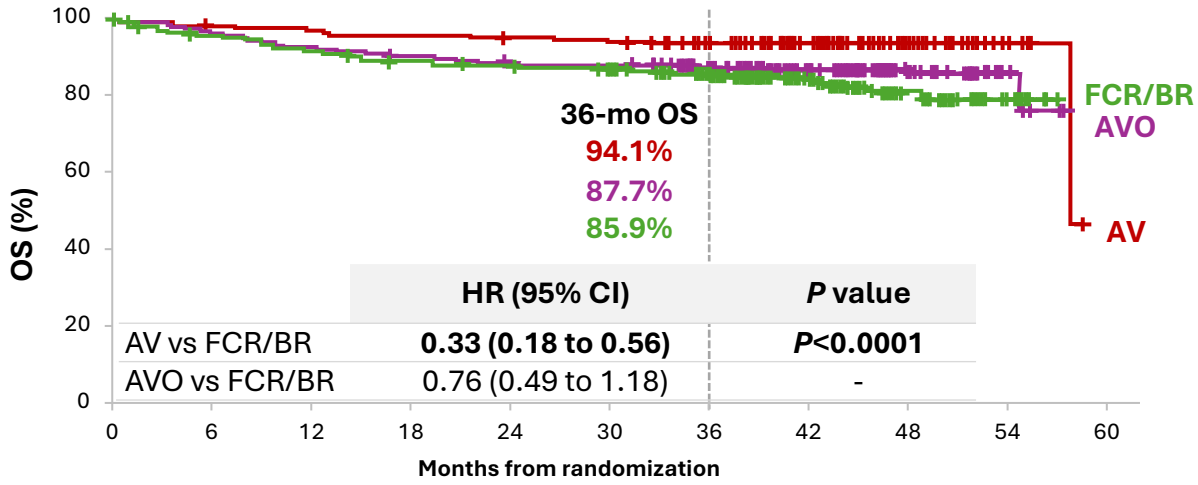
RANDOMIZE 1:1:1

- **Acalabrutinib + Venetoclax**
- **Acalabrutinib + Venetoclax + Obinutuzumab**
- **Chemo/IO (FCR or BR)**

Primary endpoint: PFS (assessed by IRC)



	HR (95% CI)	*P* value
AV vs FCR/BR	0.65 (0.49 to 0.87)	***P* = 0.0038**
AVO vs FCR/BR	0.42 (0.30 to 0.59)	***P*<0.0001**



	HR (95% CI)	*P* value
AV vs FCR/BR	**0.33 (0.18 to 0.56)**	***P*<0.0001**
AVO vs FCR/BR	0.76 (0.49 to 1.18)	-

Patients at Risk

AV	291	282	269	251	237	219	177	102	35	3	0
AVO	286	272	258	237	225	219	191	116	51	7	0
FCR/BR	290	236	208	189	170	154	127	66	28	6	0

Patients at Risk

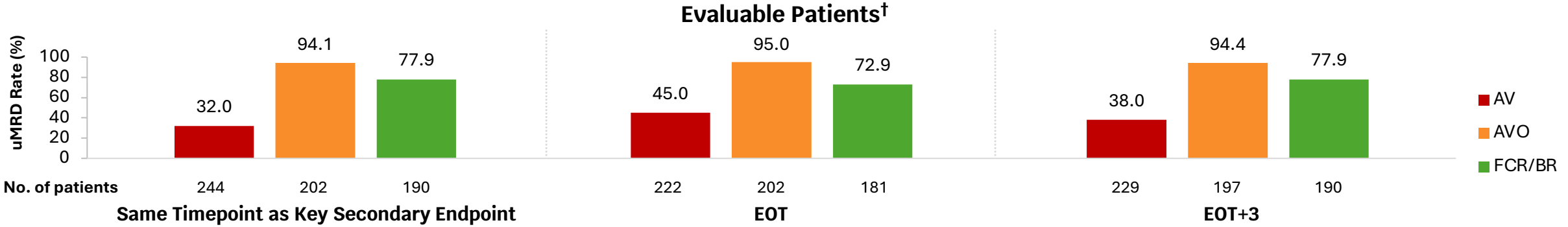
AV	291	286	281	277	275	270	233	142	58	10	0
AVO	286	276	265	257	252	250	223	143	64	10	0
FCR/BR	290	247	236	228	223	217	182	98	45	13	0

Median PFS was NR for AV and AVO, and was 47.6 mo for FCR/BR

- Brown, JR et. al. Blood. 2024; 144: abstract 1009.

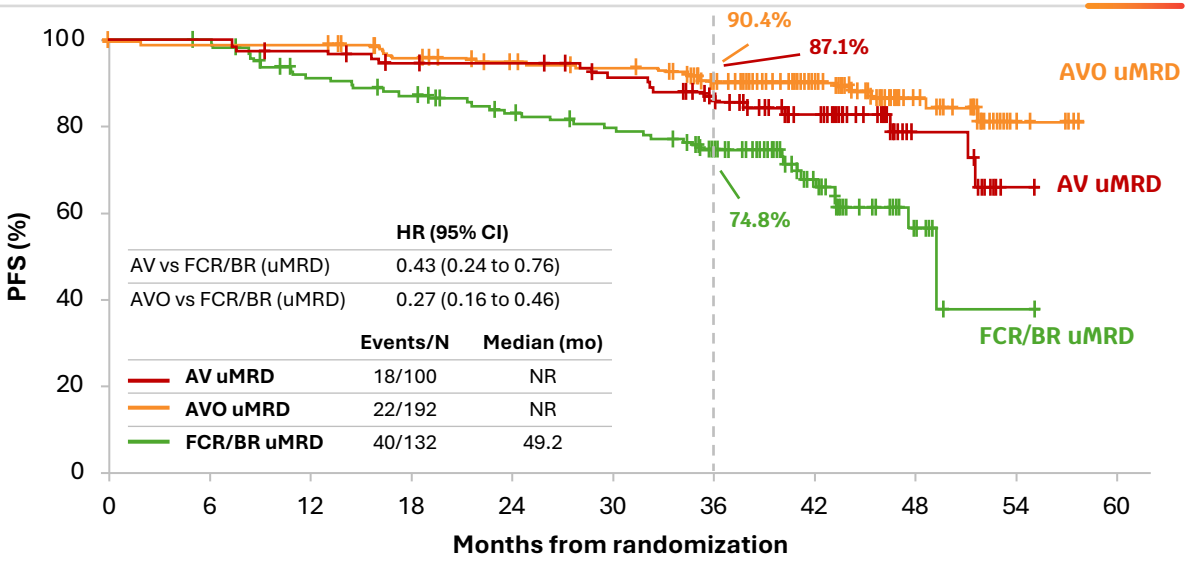
AMPLIFY: Secondary Endpoints

uMRD Rates (Flow Cytometry [<10^{-4}] in PB)

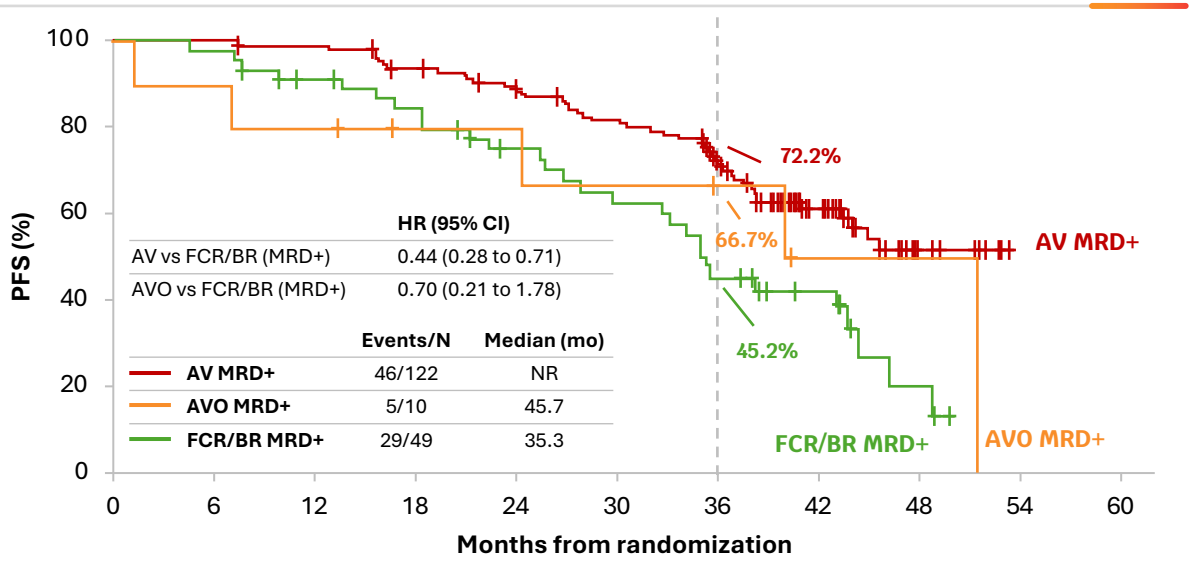


Key secondary endpoint timing: cycle 9, day 1 (AV arm), cycle 10, day 1 (AVO arm), and cycle 6, day 1 plus 12 weeks (FCR/BR)

PFS in the uMRD Subgroup at EOT (Flow Cytometry [<10^{-4}] in PB)



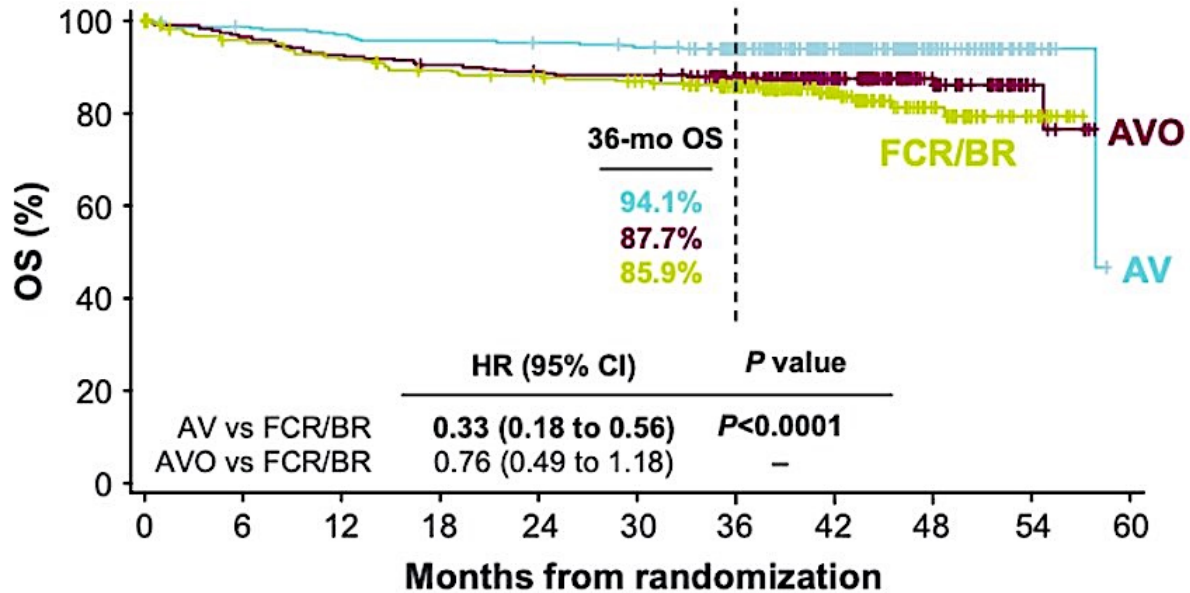
PFS in the MRD+ Subgroup at EOT (Flow Cytometry [<10^{-4}] in PB)



- Brown, JR et. al. Blood. 2024; 144: abstract 1009.

Overall Survival

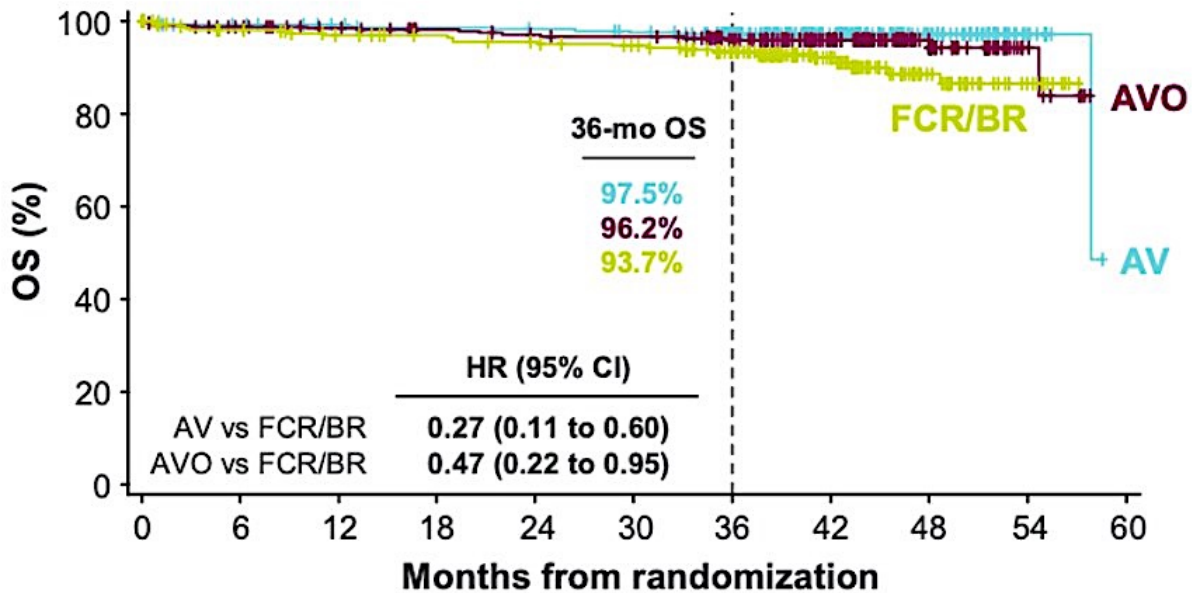
OS Prolonged With AV vs FCR/BR



Patients at risk

AV	291	286	281	277	275	270	233	142	58	10	0
AVO	286	276	265	257	252	250	223	143	64	10	0
FCR/BR	290	247	236	228	223	217	182	98	45	13	0

OS Prolonged With AV and AVO vs FCR/BR (COVID-19 Deaths Censored)



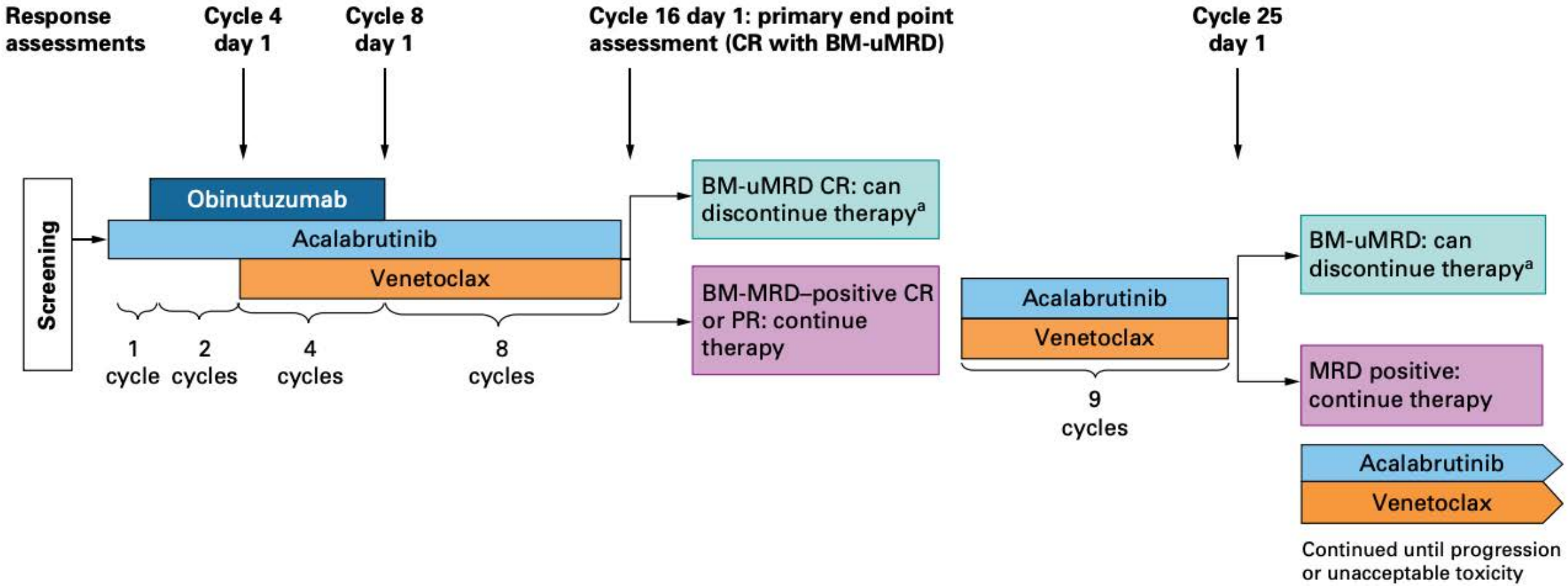
Patients at risk

AV	291	286	281	277	275	270	233	142	58	10	0
AVO	286	276	265	257	252	250	223	143	64	10	0
FCR/BR	290	247	236	228	223	217	182	98	45	13	0

COVID-19 deaths: 10 (AV), 25 (AVO), 21 (FCR/BR)

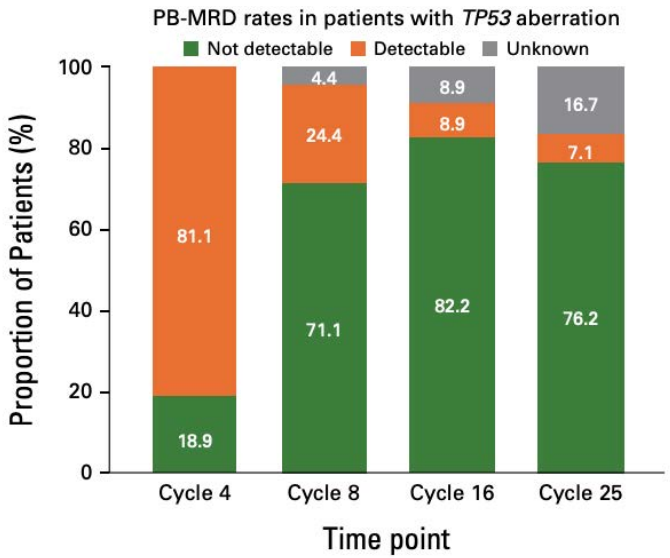
Brown, JR et. al. Blood. 2024; 144: abstract 1009.

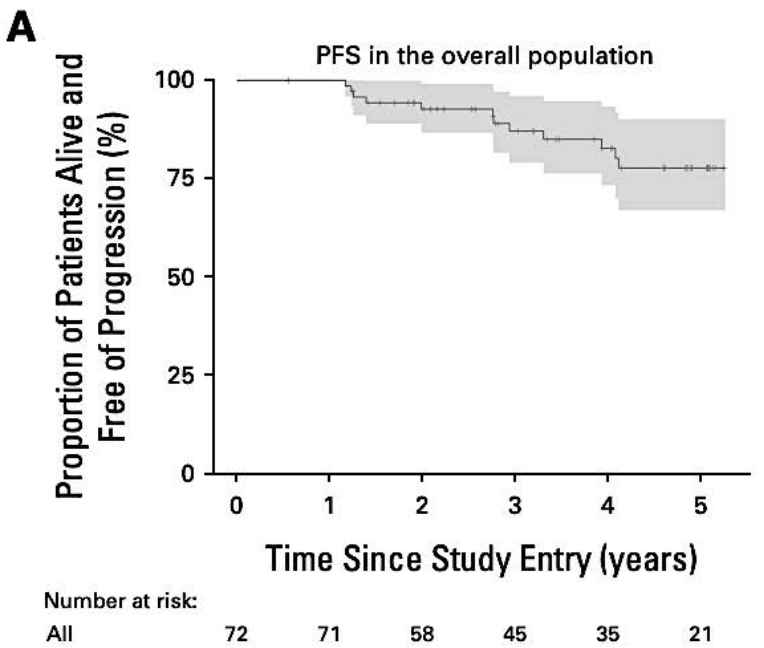
AVO in patients with TP53 aberrations?

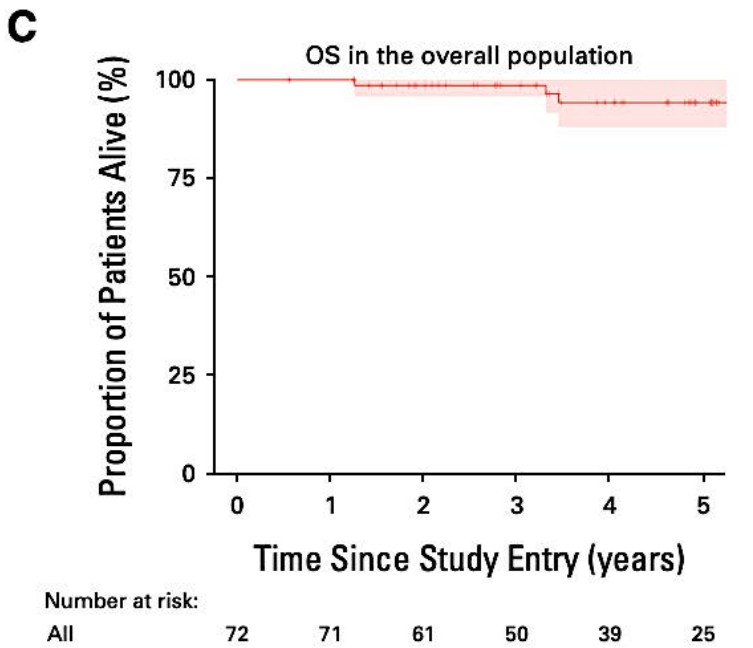


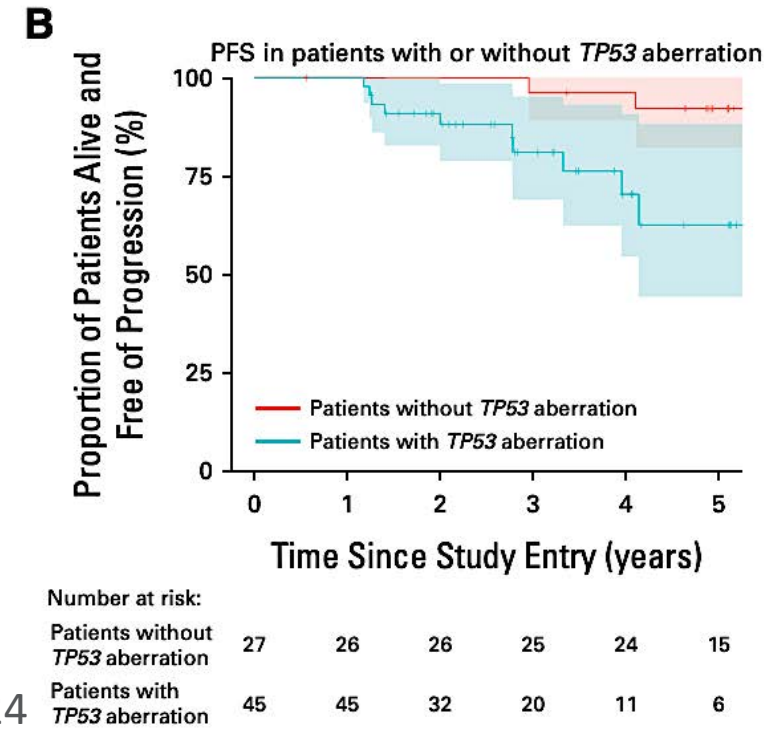
Davids MS et al, JCO 2024

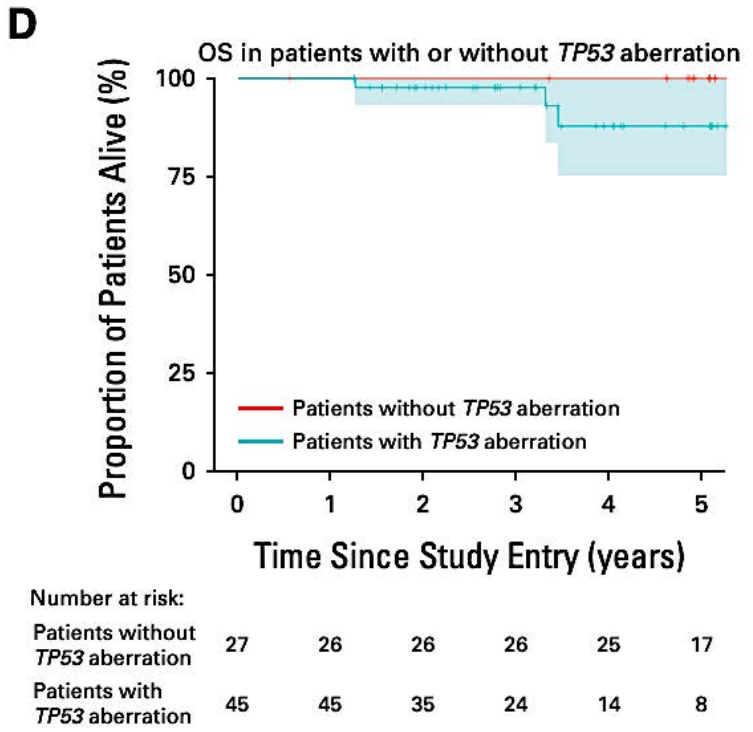
AVO remains highly effective in high-risk patients







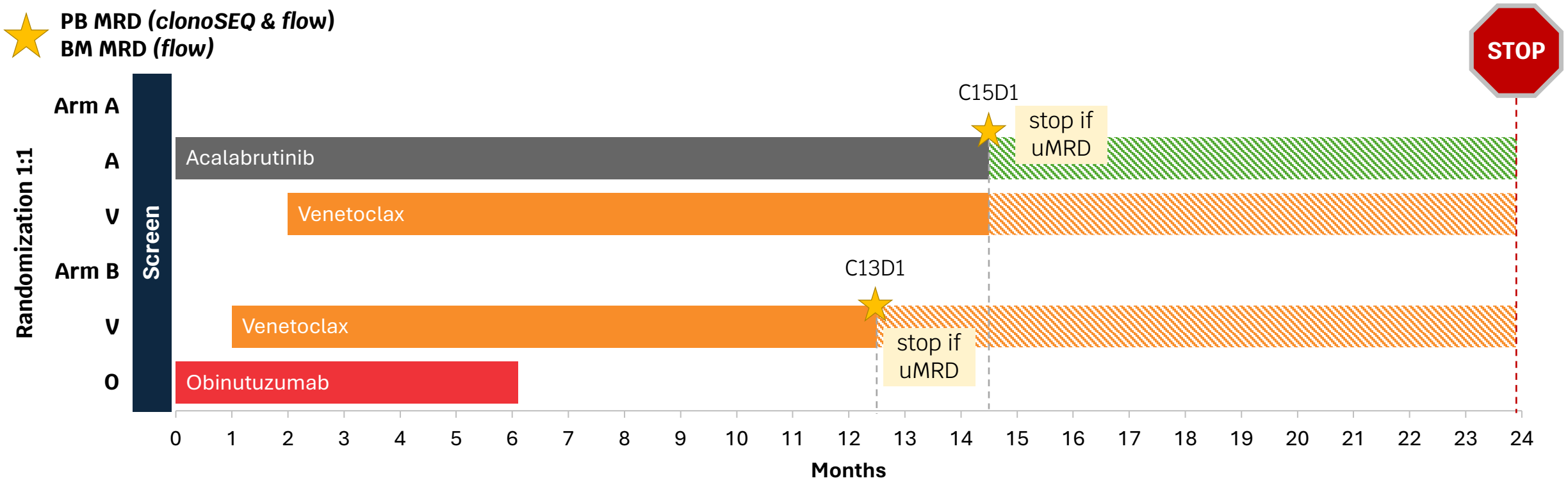




Davids MS et al, JCO 2024

MAJIC Study Design

Arm A	**Acalabrutinib (A)** 100 mg po BID, **Venetoclax (V)** 400 mg po daily (C3D1-C14), including 5 week ramp up STOP if uMRD and at least PR. If MRD+ continue AV to 24 months
Arm B	**Venetoclax (V)** 400 mg po daily (C1D22-C12), including 5 week ramp up **Obinutuzumab (O)** 1000 mg iv. (C1D1-2/8/15, C2-6 D1) STOP if uMRD and at least PR. If MRD+ continue V to 24 months



Ryan, C. E., Davids, M. S., Hermann, R., Shahkarami, M., Biondo, J., Abhyankar, S., ... Roeker, L. E. (2022). MAJIC: A Phase III Trial of Acalabrutinib + Venetoclax versus Venetoclax + Obinutuzumab in Previously Untreated Chronic Lymphocytic Leukemia or Small Lymphocytic Lymphoma. Future Oncology, 18(33), 3689–3699.

BGB-11417-101: Phase 1/2 Evaluating Sonrotoclax + Zanu

Study Design

Sonrotoclax + zanubrutinib dose -finding (weekly/daily ramp-up)

R/R CLL/SLL, MCL, **TN CLL/SLL**

- 640 mg
- 320 mg
- 160 mg
- 80 mg
- 40 mg

160 mg and 320 mg selected for expansion

Sonrotoclax + zanubrutinib expansion

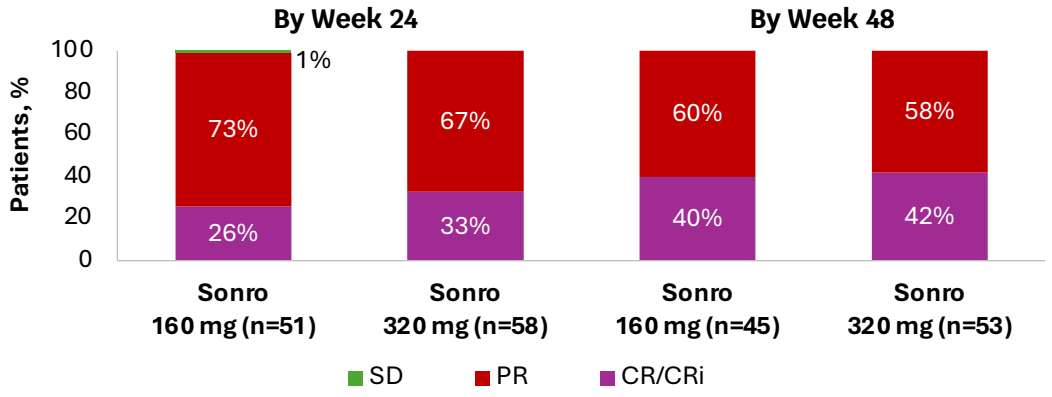
R/R CLL/SLL, MCL, **TN CLL/SLL**

- 320 mg
- 160 mg

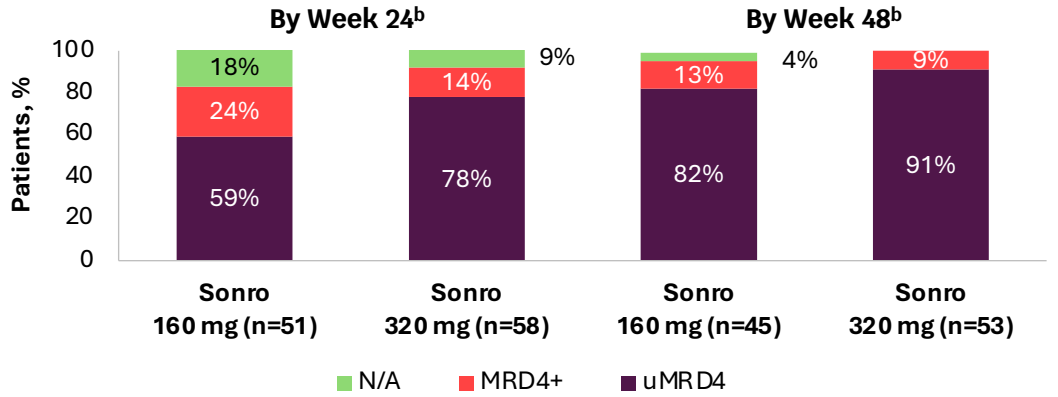
- 8 to 12 weeks of zanubrutinib monotherapy was given prior to sonrotoclax dosing (12 weeks if high tumor burden)
- Sonrotoclax was dosed orally, once daily, using a weekly or daily ramp-up schedule to reach the target dose

TN CLL/SLL Responses

Best Response[a]



Best Blood MRD[a]



Reformatted from Soumerai et. al. ASH 2024. Oral Presentation. Abstract 1012.

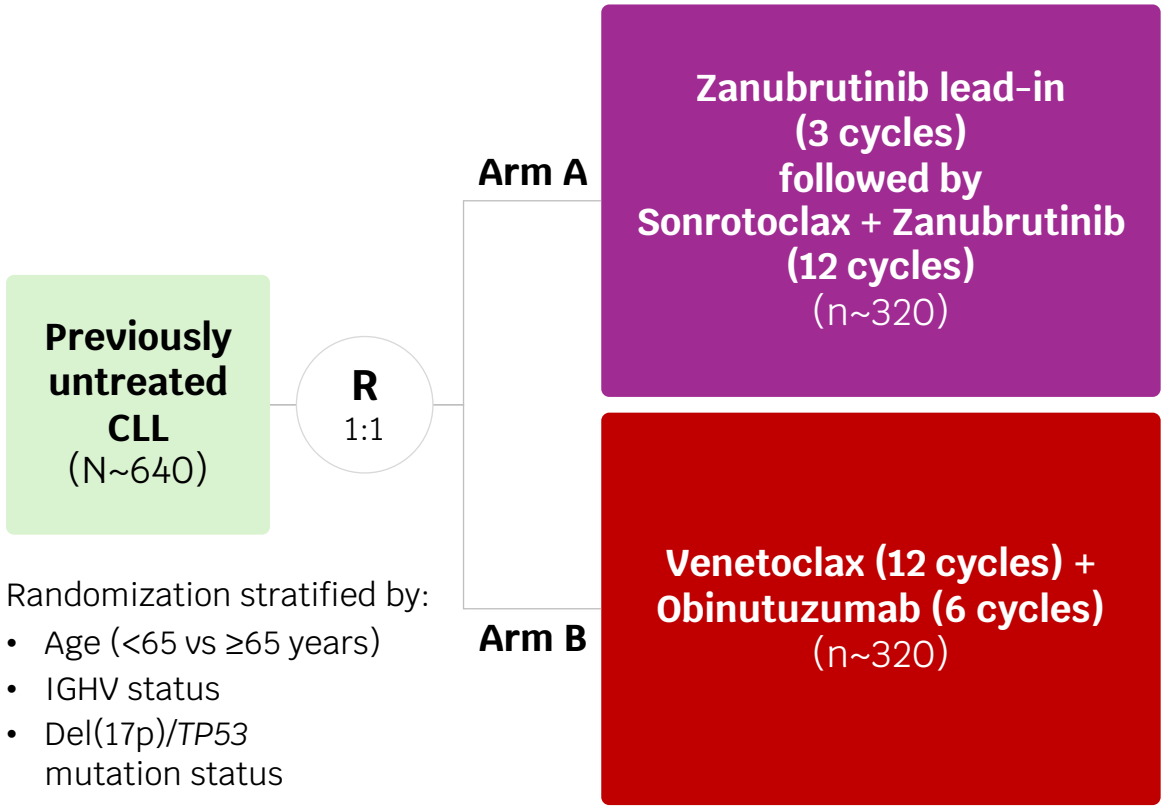
More to come on Zanu + Sonrotoclax in the 1L

CELESTIAL-TNCLL Study Design

Key Eligibility Criteria

- Age 18 years and above
- Confirmed CLL diagnosis, no previous treatment
- Measurable disease by CT/MRI
- ECOG PS of 0-2
- Adequate BM and organ function
- No history of, or currently suspected, Richter's transformation

Study Design



Randomization stratified by:

- Age (<65 vs ≥65 years)
- IGHV status
- Del(17p)/*TP53* mutation status

Endpoints

Primary

- PFS (IRC; iwCLL 2018[5])

Secondary

- CRR[a] (IRC and INV)
- Rates of uMRD4 (BM and PB)[b]
- OS
- PFS (INV)
- ORR (IRC and INV)
- DOR (IRC and INV)
- Patient-reported outcomes
- Safety and tolerability

[a] Defined as CR or CR with incomplete recovery. [b] At[<10^{4} sensitivity at the first post-treatment follow-up based on next-generation sequencing by clonoSEQ® and flow cytometry. BM, bone [marrow]; CRR, complete [response] rate; DOR, duration of response; INV, assessed by investigator; IRC, assessed by independent review committee; PB, [peripheral] blood, R, randomized; TN, treatment naive; uMRD4, undetectable measurable residual disease.

Shadman et.al. ASCO 2024. Poster 68a.

Approved Treatments in Frontline CLL: *Pros and Cons*

Ibrutinib	Acalabrutinib/Zanubrutinib	Venetoclax + Obinutuzumab (VO), Acala-Ven (AV), Acala-Ven-Obin (AVO)
• **Pro** – Longest follow-up – Median PFS 8.9 years from RESONATE-2 trial – Once daily oral drug • **Con** – Indefinite duration – Low CR/uMRD – Atrial fibrillation, bleeding	• **Pro** – Reduced off-target effects lead to improved safety vs. ibrutinib – Zanubrutinib with superior efficacy vs. ibrutinib (in relapsed setting) • **Con** – Shorter follow-up – Indefinite duration – Low CR/uMRD – Atrial fibrillation, bleeding	• **Pro** – Time-limited – High CR/uMRD (VO/AVO likely > AV) • **Con** – Shorter follow-up – TLS logistics – IV administration of obinutuzumab aside from AV – Neutropenia, infection risk – Shorter remissions in del(17p)/*TP53*-m with VO (not included in AMPLIFY trial)

• Barr PM, et al. Blood Adv. 2022;6:3440-3450. O'Brien SM, et al. Front Oncol. 2021; 11: 720704. Brown JR, et al. N Engl J Med. 2025;392:748-762.

Conclusions

- There are several effective first-line therapies in CLL
- Likely will not have a “one-size-fits-all” first-line regimen
- Shared decision making hugely important to select the best therapy for any given patient

Agenda

Module 1: Selection and Sequencing of Therapy for Relapsed/Refractory (RR) Chronic Lymphocytic Leukemia (CLL) — Dr Wierda

Module 2: First-Line Therapy for CLL — Dr Coombs

Module 3: Novel Agents and Strategies for RR CLL — Dr Wierda

Module 4: ASCO and EHA 2025

New Agents for Relapsed/Refractory CLL

- **Old targets:**
  - BTK only degrader (bexobrutideg [NX-5948]; BGB-16673; ABBV-101)
  - ncBTKi (nemtabrutinib; TT-01488; LP-168)
  - ngBCL2i (lisaftoclax; sonrotoclax; ABBV-453)
  - CD20xCD3 bispecifics (mosunetuzumab; epcoritamab; glofitamab; odronextamab)
- **New targets:**
  - BCL-xL/BCL-2 – (LP-118)
  - PKCβ inhibitor – (MS-553)
  - MALT1 (ABBV-525)
  - ROR1 (xCD3 bispecific; CAR-T cells)

Epcoritamab in CLL: Deep Responses Across Subgroups

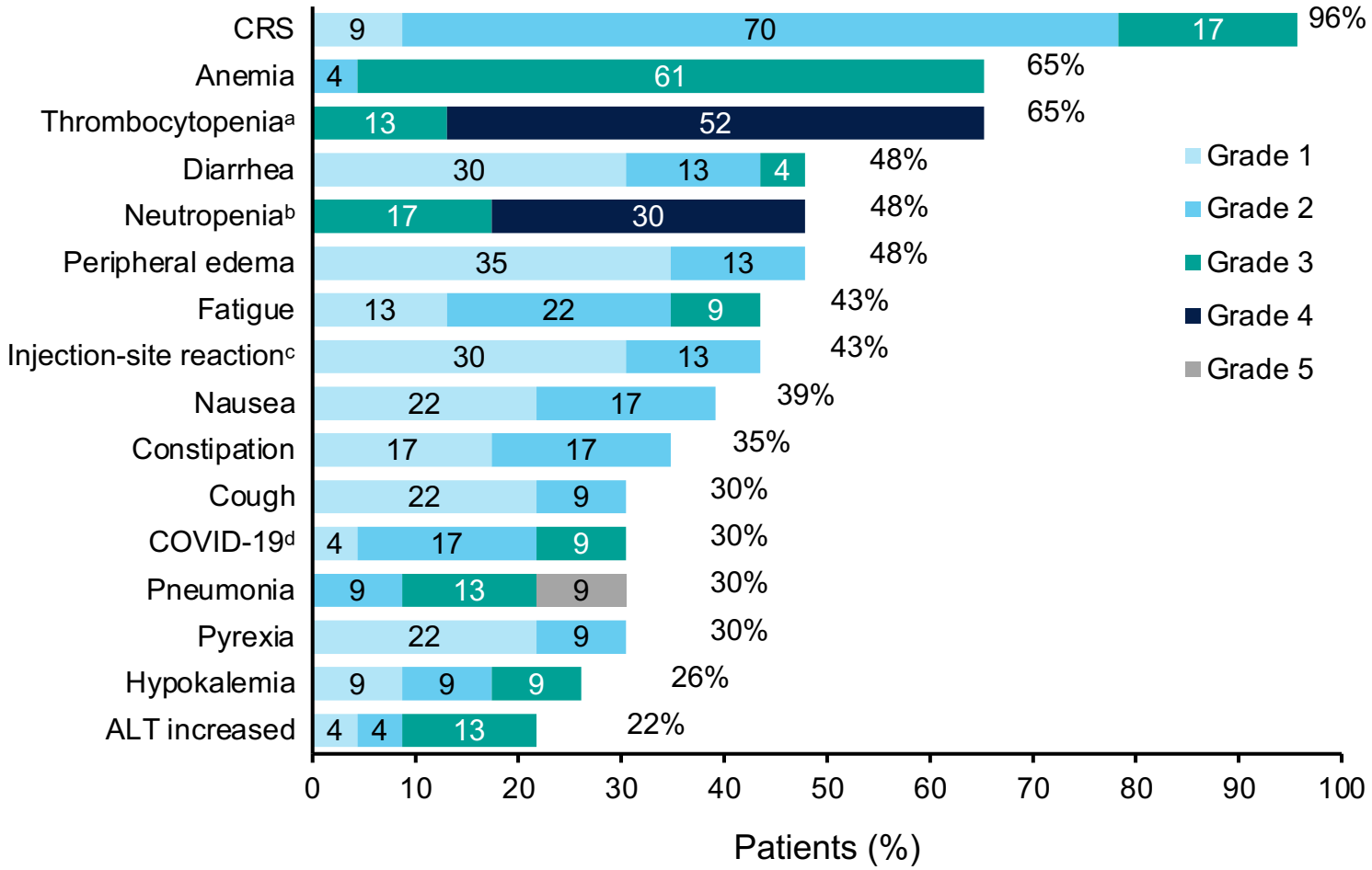
Response, n (%)	EXP mFU: 22.8 months					C1 OPT mFU: 2.9 months
	Full Analysis Set N=23	Response Evaluable n=21	*TP53* Aberration n=15	*IGHV* Unmutated n=16	Double Exposed[a] n=19	Response Evaluable n=10
Overall response[b]	**14 (61)**	**14 (67)**	**10 (67)**	**10 (63)**	**10 (53)**	**6 (60)**
Complete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

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

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

Four patients (*TP53* aberration, n=2; *IGHV* unmutated, n=3; double exposed, n=4) in EXP and 1 in C1 OPT shown above were not evaluable or had no assessment, including 3 in EXP (*TP53* aberration, n=2; *IGHV* unmutated, n=2; double exposed, n=3) and 1 in C1 OPT who died without 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.

Epcoritamab in CLL: Treatment-Emergent AEs (>20%) in EXP

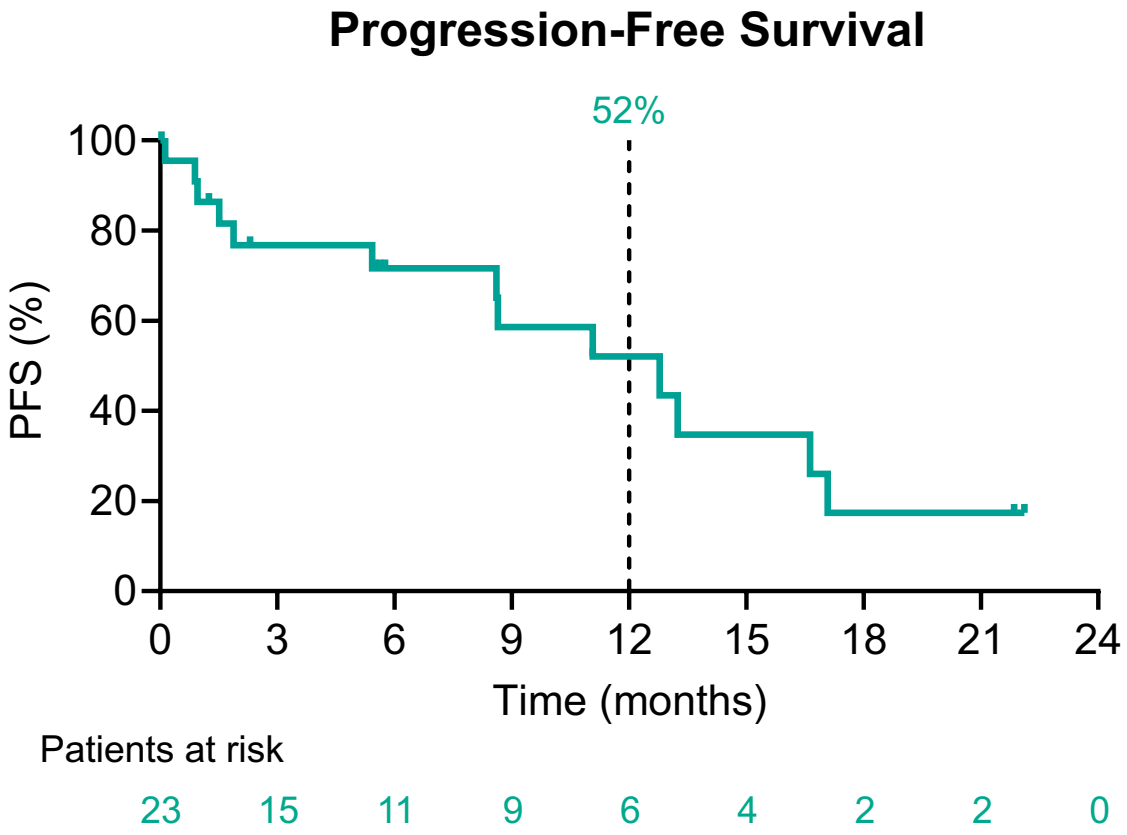


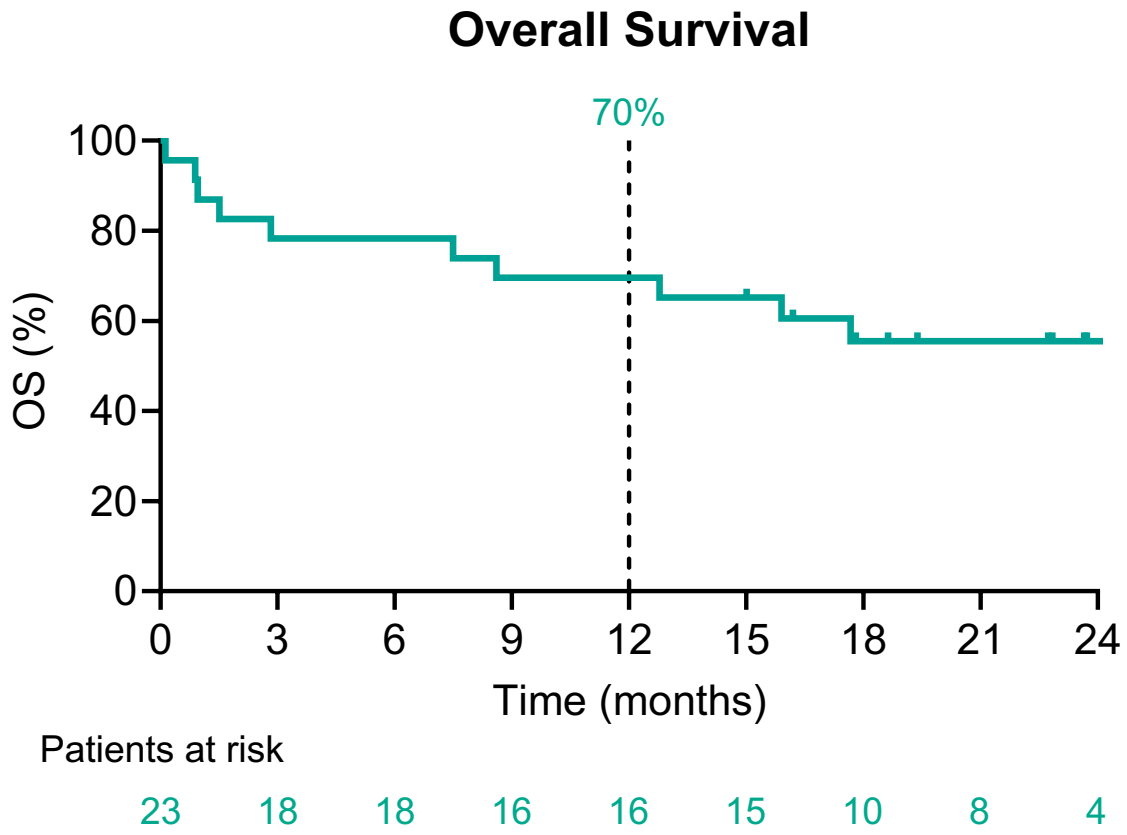
Patients With ≥1 Event, n (%)	EXP N=23
Anemia	15 (65)
At study entry	14 (61)
In first 8 weeks	15 (65)
Thrombocytopenia	15 (65)
At study entry	14 (61)
In first 8 weeks[a]	14 (61)
Neutropenia	11 (48)
At study entry	1 (4)
In first 8 weeks[b]	11 (48)

- 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.

Epcoritamab in CLL: Progression-Free and Overall Survival in EXP



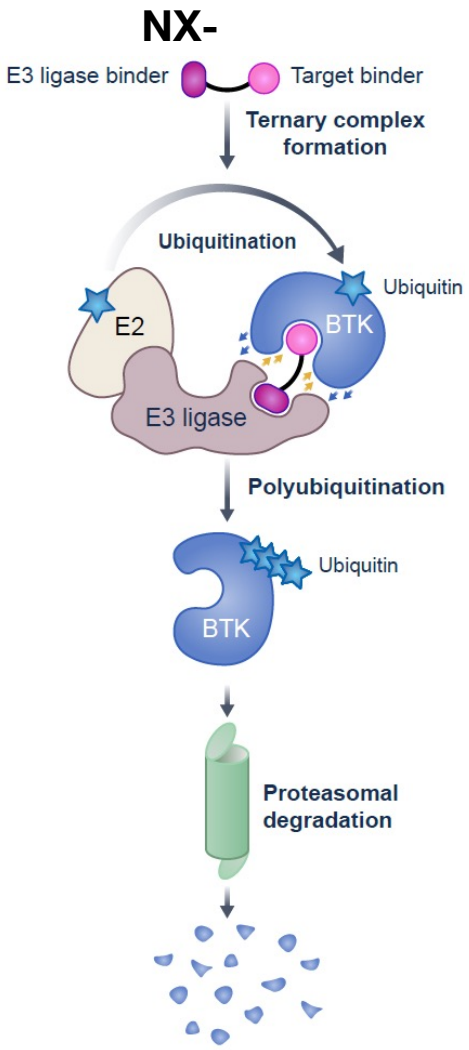


- Median PFS was 12.8 months (95% CI, 5.4–17.1); median OS was not reached (95% CI, 8.6 months–NR)

Kaplan–Meier estimates are shown.

Background

Novel BTK degrader NX-5948 addresses current unmet need in CLL treatment



- The current standard of care in CLL focuses on utilizing the inhibitors of two key signaling pathways – BTK and BCL2
- Unmet need still exists in the CLL treatment landscape:
  - Covalent and non-covalent BTKi resistance mutations[1] are found in more than half of patients who progress on BTKi therapies[2]
  - Some mutations in *BTK* can maintain intact B-cell receptor signaling through a scaffolding function of BTK[3]
  - The number of BCL2i refractory and double (BTKi/BCL2i) refractory patients is growing[4]
- Novel BTK degrader NX-5948 offers an additional treatment modality:
  - Can overcome treatment-emergent BTKi resistance mutations[5] and disrupt BTK scaffolding[3,5]

BCL2, B-cell lymphoma 2; **BCL2i**, BCL2 inhibitor; **BTK**, Bruton's tyrosine kinase; **BTKi**, BTK inhibitor; **CLL**, chronic lymphocytic leukemia

References
1. Noviski et al. 20th Biennial International Workshop on CLL Meeting, Boston, MA. October 6–9, 2023
2. Molica et al. 66th ASH Annual Meeting, December 7–10, 2024
3. Montoya et al. Science 2024;383
4. Hayama and Riches. Onco Targets 2024;17
5. Linton K, et al. Oral presentation at European Hematology Association Hybrid Congress; 16 June 2024

NX-5948-301 (Bexobrutideg): Safety Profile

TEAEs in ≥10% of overall population or Grade ≥3 TEAEs or SAEs in >1 patient

TEAEs, n (%)	**Patients with CLL/SLL (n=60)**			**Overall population (N=125)**		
	Any grade	**Grade ≥3**	**SAEs**	**Any grade**	**Grade ≥3**	**SAEs**
Purpura/contusion[a]	22 (36.7)	–	–	42 (33.6)	–	–
Fatigue[b]	16 (26.7)	–	–	29 (23.2)	2 (1.6)	–
Petechiae	16 (26.7)	–	–	28 (22.4)	–	–
Thrombocytopenia[c]	10 (16.7)	1 (1.7)	–	26 (20.8)	7 (5.6)	–
Rash[d]	14 (23.3)	1 (1.7)	1 (1.7)	24 (19.2)	2 (1.6)	1 (0.8)
Neutropenia[e]	14 (23.3)	11 (18.3)	–	23 (18.4)	18 (14.4)	–
Anemia	11 (18.3)	4 (6.7)	–	21 (16.8)	10 (8.0)	–
Headache	10 (16.7)	–	–	21 (16.8)	1 (0.8)	1 (0.8)
COVID-19[f]	10 (16.7)	–	–	19 (15.2)	2 (1.6)	2 (1.6)
Diarrhea	12 (20.0)	1 (1.7)	–	18 (14.4)	1 (0.8)	–
Cough	9 (15.0)	–	–	16 (12.8)	1 (0.8)	–
Pneumonia[g]	4 (6.7)	2 (3.3)	2 (3.3)	10 (8.0)	6 (4.8)	6 (4.8)
Lower respiratory tract infection	3 (5.0)	1 (1.7)	1 (1.7)	9 (7.2)	3 (2.4)	2 (1.6)
Fall	1 (1.7)	1 (1.7)	1 (1.7)	8 (6.4)	2 (1.6)	2 (1.6)
Hypertension	2 (3.3)	1 (1.7)	–	7 (5.6)	5 (4.0)	–
Hyponatremia	–	–	–	3 (2.4)	2 (1.6)	–
Pulmonary embolism	1 (1.7)	1 (1.7)	1 (1.7)	2 (1.6)	2 (1.6)	2 (1.6)
Subdural hematoma	1 (1.7)	–	1 (1.7)	2 (1.6)	1 (0.8)	2 (1.6)

- Tolerable safety profile consistent with prior disclosures
- 1 case of Grade 1 AFib in a CLL patient with pre-existing AFib
- 6 TEAEs resulted in drug discontinuation (1 CLL; 5 NHL)
- 2 Grade 5 AEs (1 pulmonary embolism; 1 case pending) deemed not related to NX-5948

[a]Purpura/contusion includes episodes of contusion or purpura; [b]Fatigue was transient; [c]Aggregate of 'thrombocytopenia' and 'platelet count decreased'; [d]Aggregate of 'rash' and 'rash maculopapular' and 'rash pustular'; [e]Aggregate of 'neutrophil count decreased' or 'neutropenia'; [f]Aggregate of 'COVID-19' and 'COVID-19 pneumonia'; [g]Aggregate of 'pneumonia' and 'pneumonia klebsiella'

AE, adverse event; **AFib**, atrial fibrillation; **CLL**, chronic lymphocytic leukemia; **NHL**, non-Hodgkin's lymphoma; **SAE**, serious adverse event; **SLL**, small lymphocytic lymphoma; **TEAE**, treatment emergent AE

Shah, et al., ASH 2024, Abstract #884

NX-5948-301 (Bexobrutideg): Overall Response Assessment

Response rate deepens with longer time on treatment

CLL response-evaluable patients	**Primary ORR analysis[b]** ≥1 response assessment(s) at 8 weeks (n=49)[c]	**Exploratory ORR analysis[b]** ≥2 response assessments at 16 weeks (n=38)[c]
Objective response rate (ORR),[a] % (95% CI)	75.5 (61.1–86.7)	84.2 (68.7–94.0)
Best response, n (%)		
CR	0 (0.0)	0 (0.0)
PR	36 (73.5)	32 (84.2)
PR-L	1 (2.0)	0 (0.0)
SD	10 (20.4)	4 (10.5)
PD	2 (4.1)	2 (5.3)

[a]Objective response rate includes CR + PR + PR-L

[b]Patients who progressed prior to their first response assessment and patients who discontinued for any reason after their first response assessment are included in the denominators

[c]Patients without identified target lesion(s) at baseline are evaluated as disease-evaluable per iwCLL criteria, while they may not be represented in waterfall plot

CLL, chronic lymphocytic leukemia; **CR**, complete response; **iwCLL**, International Workshop on CLL; **ORR**, objective response rate; **PD**, progressive disease; **PR**, partial response; **PR-L**, partial response with rebound lymphocytosis; **SD**, stable disease

Shah, et al., ASH 2024, Abstract #884

BGB-16673: Overall Response Rate
Significant Responses, Particularly at 200 mg Dose Level

CaDAnCe-101: R/R CLL/SLL

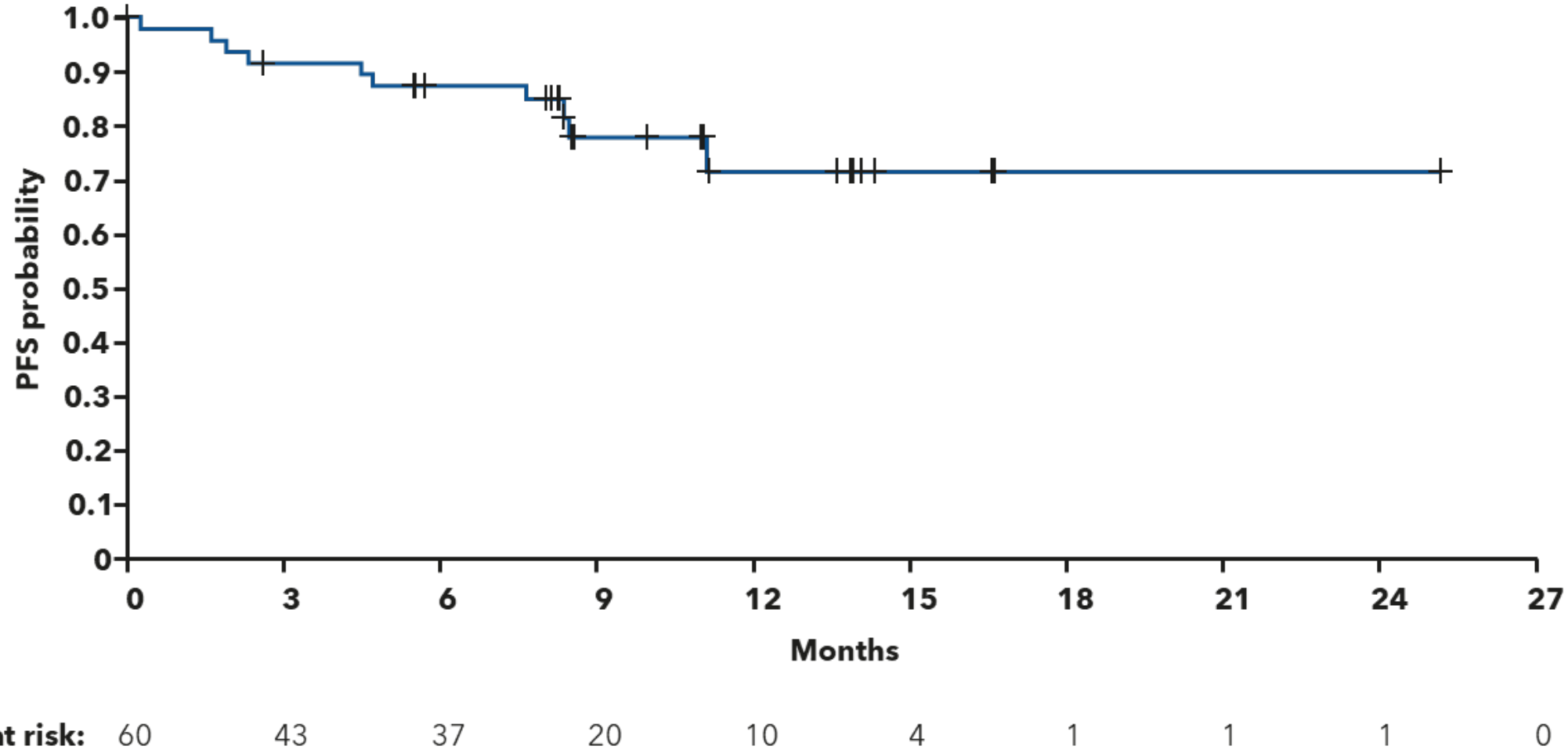
	50 mg (n=1)	100 mg (n=5)	200 mg (n=16)	350 mg (n=15)	500 mg (n=12)	Total[a] (N=49)
Best overall response, n (%)						
CR/CRi	0	1 (20.0)	1 (6.3)	0	0	**2 (4.1)**
PR[b]	1 (100)	3 (60.0)	12 (75.0)	10 (66.7)	7 (58.3)	33 (67.3)
PR-L	0	0	2 (12.5)	0	1 (8.3)	3 (6.1)
SD	0	1 (20.0)	0	1 (6.7)	4 (33.3)	6 (12.2)
PD	0	0	1 (6.3)	1 (6.7)	0	2 (4.1)
Discontinued prior to first assessment	0	0	0	3 (20.0)	0	3 (6.1)
ORR, n (%)[c]	1 (100)	4 (80.0)	**15 (93.8)**	10 (66.7)	8 (66.7)	**38 (77.6)**
Disease control rate, n (%)[d]	1 (100)	5 (100)	15 (93.8)	11 (73.3)	12 (100)	44 (89.8)
Time to first response, median (range), months[e]	2.9 (2.9-2.9)	4.2 (2.8-6.2)	2.9 (2.6-8.3)	2.8 (2.6-8.3)	2.8 (2.6-8.3)	2.8 (2.6-8.3)
Time to best response, median (range), months	2.9 (2.9-2.9)	5.6 (2.8-11.1)	3.4 (2.6-13.8)	5.6 (2.6-8.3)	4.2 (2.6-8.6)	3.6 (2.6-13.8)
Duration of exposure, median (range), months	26.4 (26.4-26.4)	13.8 (13.6-18.6)	10.6 (2.9-18.9)	10.3 (0.2-16.8)	9.3 (6.8-15.4)	10.4 (0.2-26.4)

[a]Efficacy-evaluable population. [b]Out of 33 patients with PR, 8 achieved all nodes normalized. [c]Includes best overall response of PR-L or better. [d]Includes best overall response of SD or better. [e]In patients with a best overall response of PR-L or better.
CR=complete response, CRi=complete response with incomplete marrow recovery, ORR=overall response rate, PD=progressive disease, PR=partial response, PR-L=partial response with lymphocytosis, SD=stable disease.

Thompson et al. BGB-16673-101 ASH 2024

BGB-16673: Progression-Free Survival

CaDAnCe-101: R/R CLL/SLL



Data cutoff: September 2, 2024.
PFS=progression-free survival.

Thompson et al. BGB-16673-101 ASH 2024

Conclusions

- Treatment for relapsed disease directed by prior treatment, duration of last remission, and clinical resistance to targeted agent(s)
- Refractory disease remains unmet need – promising agents in development
  - Alternative targeted therapies
  - CD19-CAR T-cells
  - Bispecific antibodies

Agenda

Module 1: Selection and Sequencing of Therapy for Relapsed/Refractory (RR) Chronic Lymphocytic Leukemia (CLL) — Dr Wierda

Module 2: First-Line Therapy for CLL — Dr Coombs

Module 3: Novel Agents and Strategies for RR CLL — Dr Wierda

Module 4: ASCO and EHA 2025

SEQUOIA 5-year follow-up in arm C: Frontline zanubrutinib monotherapy in patients with del(17p) and treatment-naive chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL).

Tam C et al.

ASCO 2025; Abstract 7011.

RAPID ORAL ABSTRACT SESSION | SATURDAY, MAY 31 | 8:12 AM CT

Combination of zanubrutinib (zanu) + venetoclax (ven) for treatment-naive (TN) CLL/SLL: Results in SEQUOIA arm D.

Shadman M et al.

ASCO 2025; Abstract 7009.

RAPID ORAL ABSTRACT SESSION | SATURDAY, MAY 31 | 8:00 AM CT

Impact of venetoclax-based therapies on autoimmune cytopenias in patients with chronic lymphocytic leukemia: Final analysis of a multicenter study conducted by ERIC.

Vitale C et al.

EHA 2025; Abstract S157

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.

Scarfò L et al.

EHA 2025; Abstract S158

Updated results from the phase 1 study of sonrotoclax (BGB-11417), a novel BCL2 inhibitor, in combination with zanubrutinib for relapsed/refractory CLL/SLL demonstrate deep and durable responses.

Cheah CY et al.

EHA 2025; Abstract S159

EHA 2025 | ORAL PRESENTATION SESSION | SUNDAY, JUNE 15

RTP RESEARCH TO PRACTICE

Data + Perspectives: Clinical Investigators Discuss the Current and Future Clinical Care of Patients with HER2-Positive Gastrointestinal Cancers

A CME Symposium Held in Conjunction with the 2025 ASCO® Annual Meeting

Sunday, June 1, 2025

7:00 PM – 8:30 PM CT (8:00 PM – 9:30 PM ET)

Faculty

Haley Ellis, MD

Sara Lonardi, MD

Kanwal Raghav, MD, MBBS

Moderator

Christopher Lieu, MD

RTP RESEARCH TO PRACTICE

Cases from the Community: Investigators Discuss Available Research Guiding the Care of Patients with Ovarian and Endometrial Cancer

A CME Symposium Held in Conjunction with the 2025 ASCO® Annual Meeting

Sunday, June 1, 2025

7:00 PM – 9:00 PM CT (8:00 PM – 10:00 PM ET)

Faculty

Joyce F Liu, MD, MPH
David M O'Malley, MD
Ritu Salani, MD, MBA
Alessandro D Santin, MD

Moderator

Shannon N Westin, MD, MPH, FASCO, FACOG

RTP RESEARCH TO PRACTICE

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Information on how to obtain CME credit is provided in the Zoom chat room. Attendees will also receive an email in 1 to 3 business days with these instructions.

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