4th edition

Unmet challenges in high risk hematological malignancies: from benchside to clinical practice

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Starhotels Majestic

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How I treat BTKi failures

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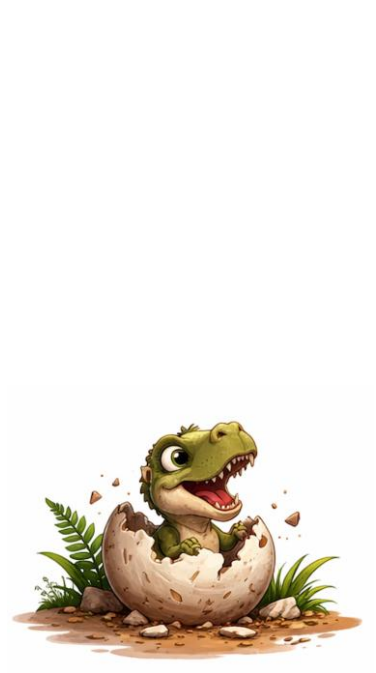
Disclosures of Name Surname

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
Abbvie	x					x	
Astra Zeneca	x					x	
BeOne	x					x	
Janssen	x					x	
Lilly	x					x	
Nurix	x					x	

BTK Failure - What do we exactly mean ?



Discontinued due to AE

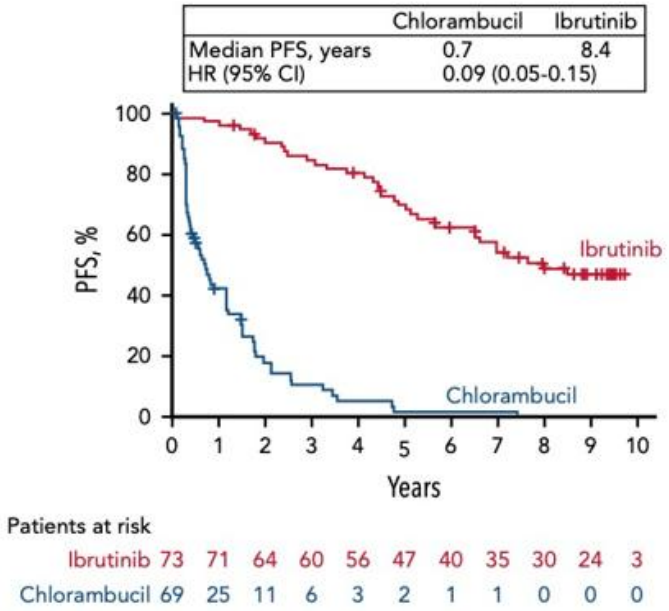
Refractory to BTKi

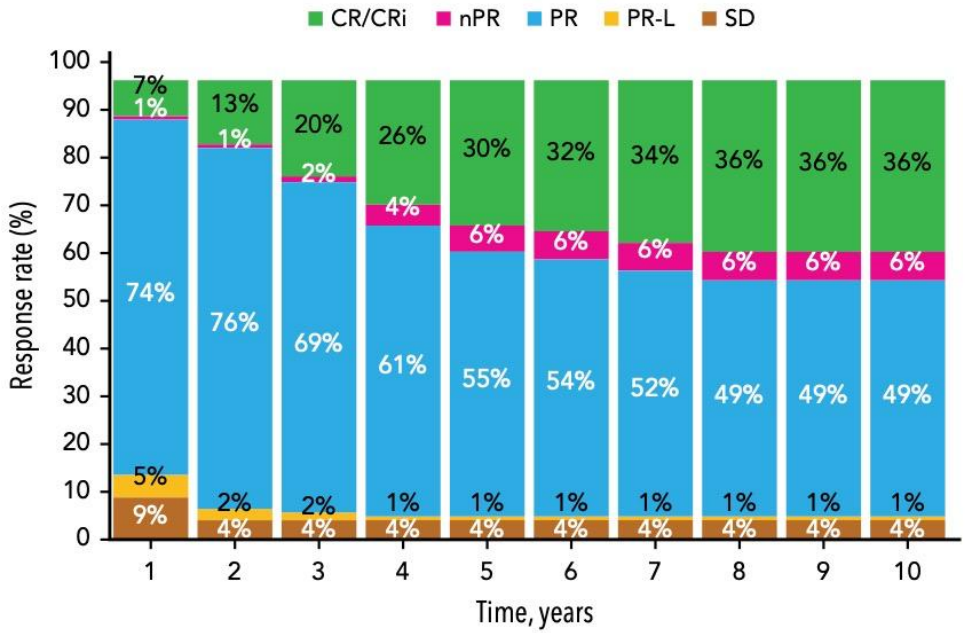
Double exposed to both BTKi and BCL-2i

Double refractory

RESONATE-2 study: 10 year follow-up

Discontinued due to AE





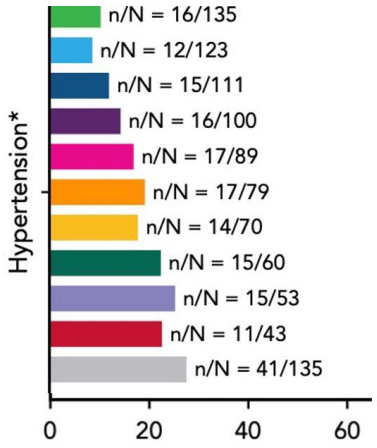
Burger et al., Blood 2025
Burger et al., NEJM – 2015

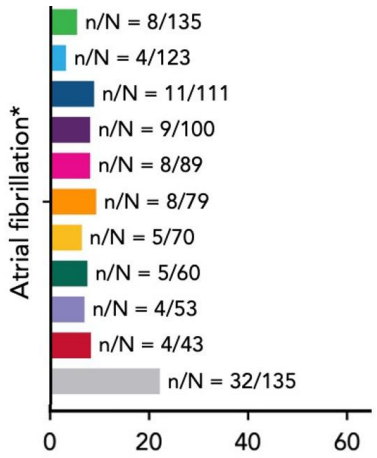
RESONATE-2 study: Ibrutinib AE

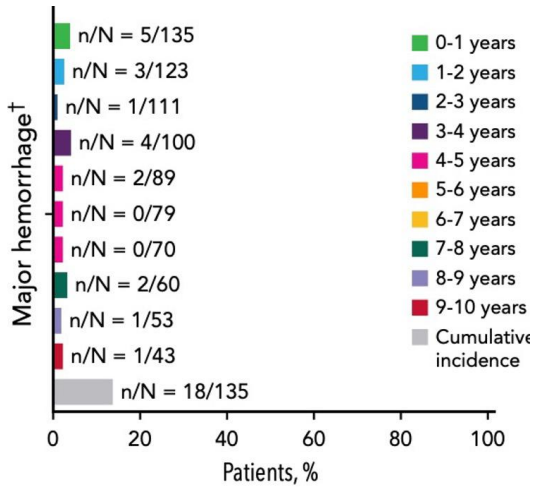
Discontinued due to AE

Secondary malignancies

- nonmelanoma skin cancers (n = 32 [24%])
- melanoma skin cancer (n = 2 [1%]),
- nonskin cancers (n = 23 [17%]);







	Ibrutinib, n = 135*
Duration of ibrutinib treatment, median (range), y	6.2 (0.06-10.2)
Continuing ibrutinib at study closure, n (%)	37 (27)
Reason for ibrutinib discontinuation, n (%)	
AE	44 (33)
PD	18 (13)
Death	12 (9)
Withdrawal of consent for treatment by patient	13 (10)
Investigator decision	11 (8)

33- 51%

Burger et al., Blood 2025
Burger et al., NEJM – 2015

BTKi after Ibrutinib intolerance

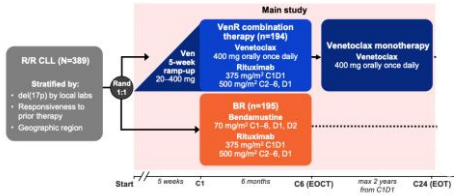
Discontinued due to AE

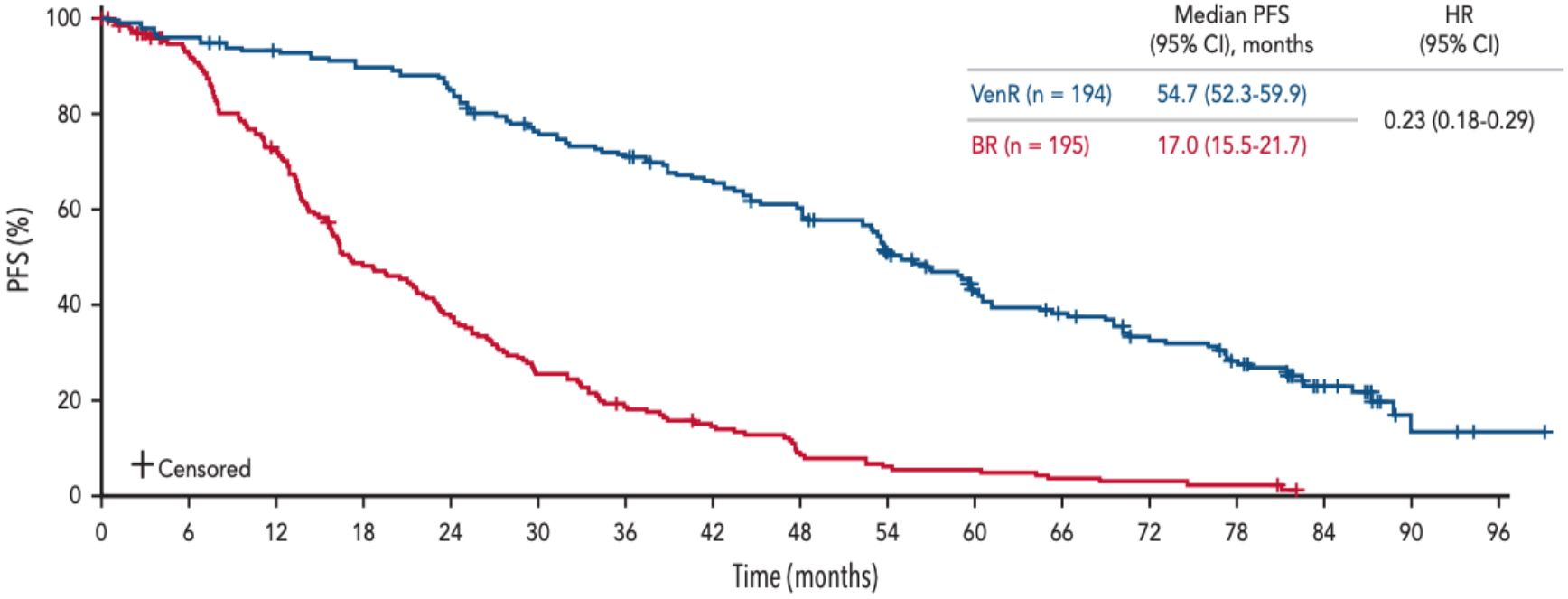
Study	N	ORR	Efficacy	Discontinued due to AE
Acalabrutinib, phase I/II study (NCT02029443) [1]	33	76%	1-year PFS 83.4%.	9 %
Acalabrutinib, ACE-CL-208 – Phase II study in R/R CLL[2]	60	73%	2 year PFS - 72%	17%
Zanubrutinib, BGB-3111-215 – CLL/SLL Phase II Study[3]	57	64%	Not reported in this cohort	11%
Pirtobrutinib, Bruin I/II study [4]	57	52%	Not reported in this cohort	3%

1) Awan et al., Blood Advances 2019; 2) Rogers et al., Haematologica 2021;
3) Shadman et al., Blood Advances 2025; 4) Mato et al., NEJM 2023

Refractory to BTKi

Murano study: 10 year follow-up





	Median PFS (95% CI), months	HR (95% CI)
VenR (n = 194)	54.7 (52.3-59.9)	0.23 (0.18-0.29)
BR (n = 195)	17.0 (15.5-21.7)	

Kater et al., Blood 2025

Refractory to BTKi

VR in R/R CLL after BTKi

Study	n	Prior Lines ot therapy	Reason for cBTKi Discontinuation	ORR	PFS
CORE study[1]	64	NR	PD: 43 AE: 37	71.4 %	39.5 mo (median)
Australian RWD[2]	32	2 (1–5)	PD: 25 (78) AE: 7 (22)	81 %	25.9 mo (median)
Austrian–German–Swiss RWD[3]	28	3 (1–10)	PD: 10 (35.7) AE: 14 (50)	100 %	72.9% @ 24 mo

1) Ghosh et al.: Am. J. Hematol. 2024; 2) Lew et al.: Blood Adv. 2024; 3) Schwaner et al., Blood. 2024

BTK Refractory CLL patients NOT exposed to BCL2i

Refractory to BTKi

Venetoclax - Obinutuzumab is not approved in R/R CLL (neither FDA nor EMA). Popularity of this protocol - 2A category in NCCN guidelisnes - is based on:

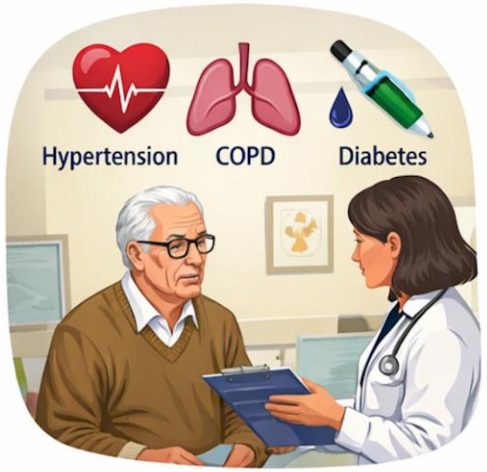
- assumption, that Obinutuzumab is a better MoAb,
- **phase 1 data** (Flinnet al., Blood 2019: ORR of 95%, CR/CRi 37% and uMRD rate of 64% in PB)
- **RWE** (Lei et al., Leukemia & Lymphoma 2024 : 40 R/R CLL/SLL patients 55% with prior BTKi exposure, ORR 90%, CR/CRi 27.5% and 2-year PFS was 81.2%)

Regimens combining BTKi & BCL2i, are not approved in R/R CLL (neither FDA nor EMA). However, both NCCN (category 2B) and ESMO (category IIIB) guidelines list **Ibrutinib – Vennetoclax** as a possible regiment, based on

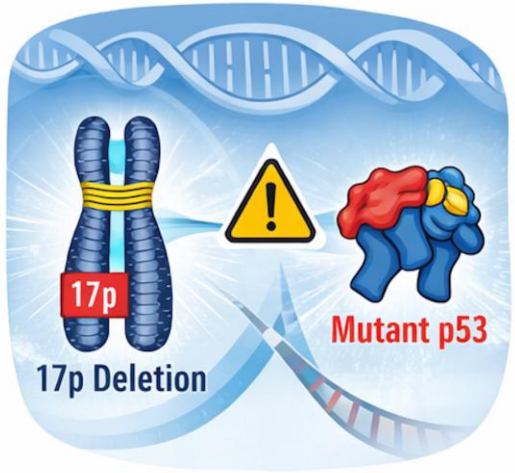
- **CLARITY 2 phase** protocol (Hillmen et al., JCO 2019, 53 R/R CLL pts, ORR: 89%, CR/CRi: 51%, uMRD rate of 53% in PB and 36% in BM)

Refractory to BTKi

Reasons for choosing BTKi monotherapy in a particular patient, usually don't change



Elderly / Comorbid Patients



Del 17p / Mut p53 Risk

Logistical Reasons

Effctive BTK inhibition after cBTKi failure is possible (Pirtobrutinib, BTK degradors)

New regimens are necessary to increase the chance of survival in high and very high risk cases

VS

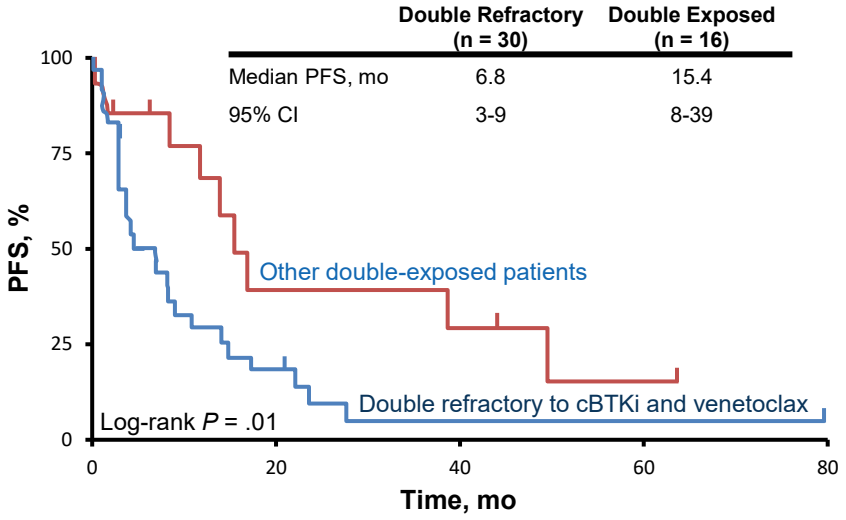
Double exposed to both BTKi and BCL-2i

Double refractory

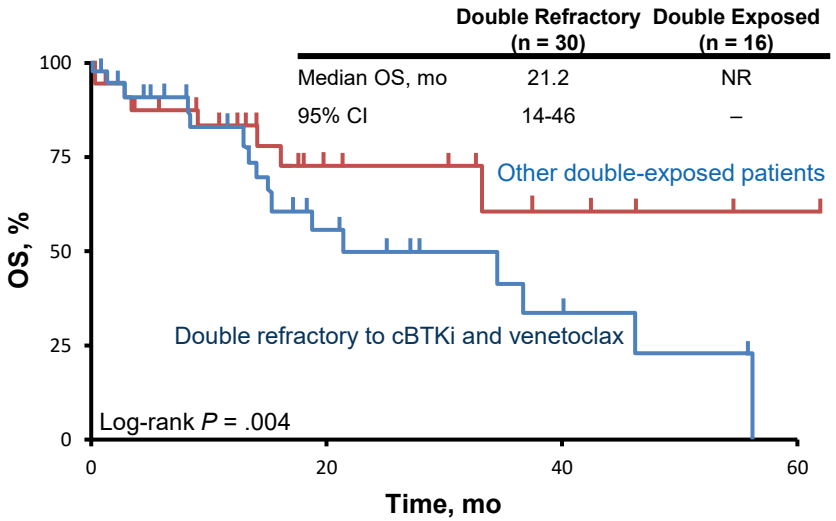
Double-Refractory vs Double Exposed Patients

- Patients with double-refractory CLL had a significantly shorter PFS and OS compared with those who were double exposed

PFS in Double-Refractory Patients vs Double-Exposed Patients



OS in Double-Refractory Patients vs Double-Exposed Patients

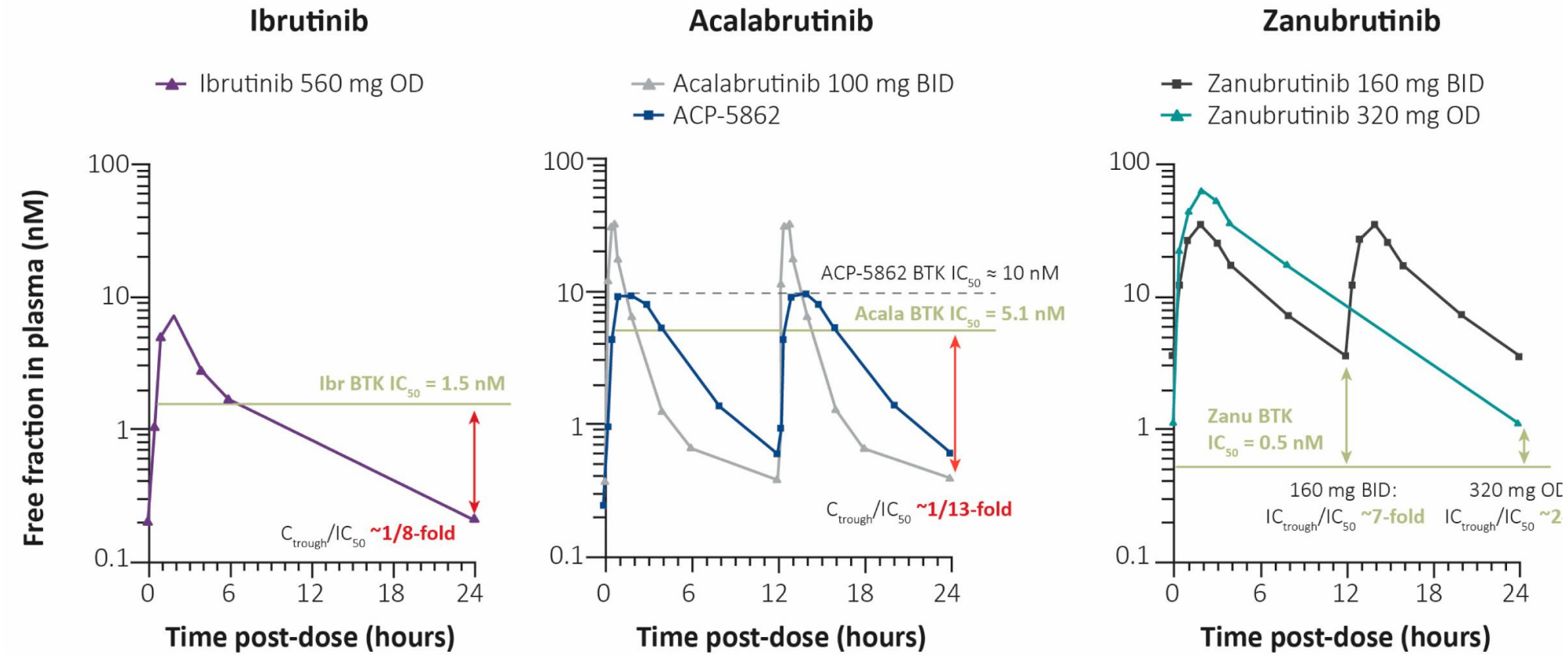


Overall, more effective options are needed for many patients previously treated with a cBTKi and venetoclax

Samples LS et al. ASH 2023. Abstract 4650.

BTKi – generations

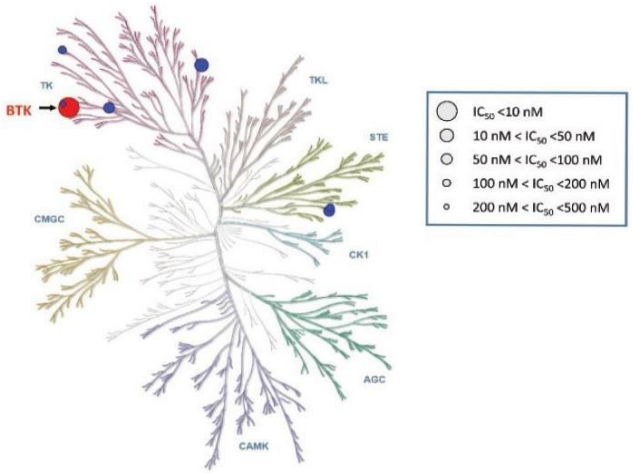
IC_{50} of I & II genetionBTKi



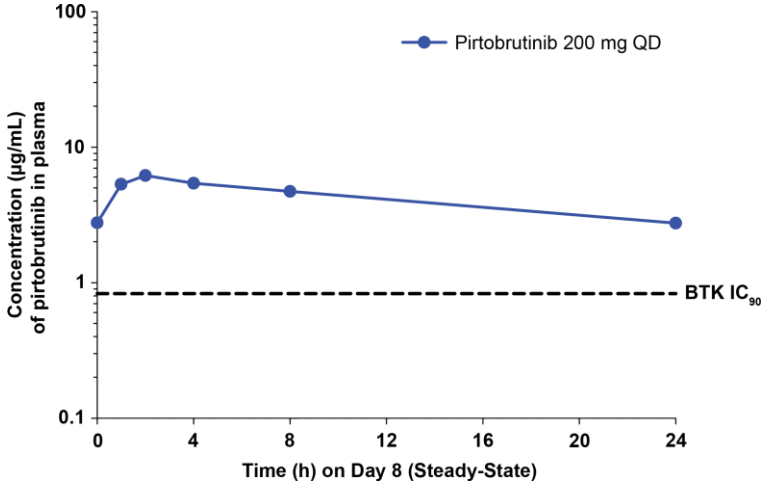
IC50 - Half maximal inhibitory concentration - indicates how much of a particular inhibitory substance (e.g. drug) is needed to inhibit, *in vitro*, a given biological process or biological component by 50%

Pirtobrutinib: a selective, non covalent BTKi

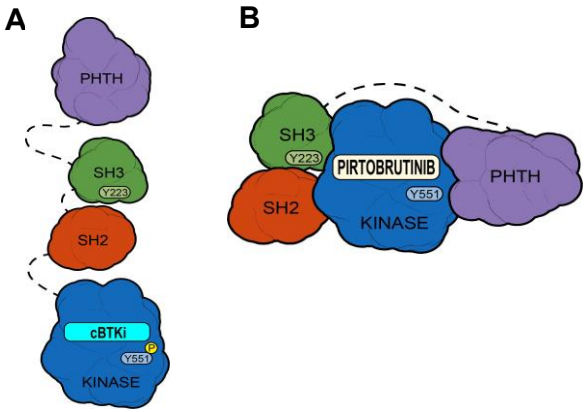
Highly selective for BTK[1-2]



Plasma exposures exceeded BTK IC_{90} throughout dosing interval



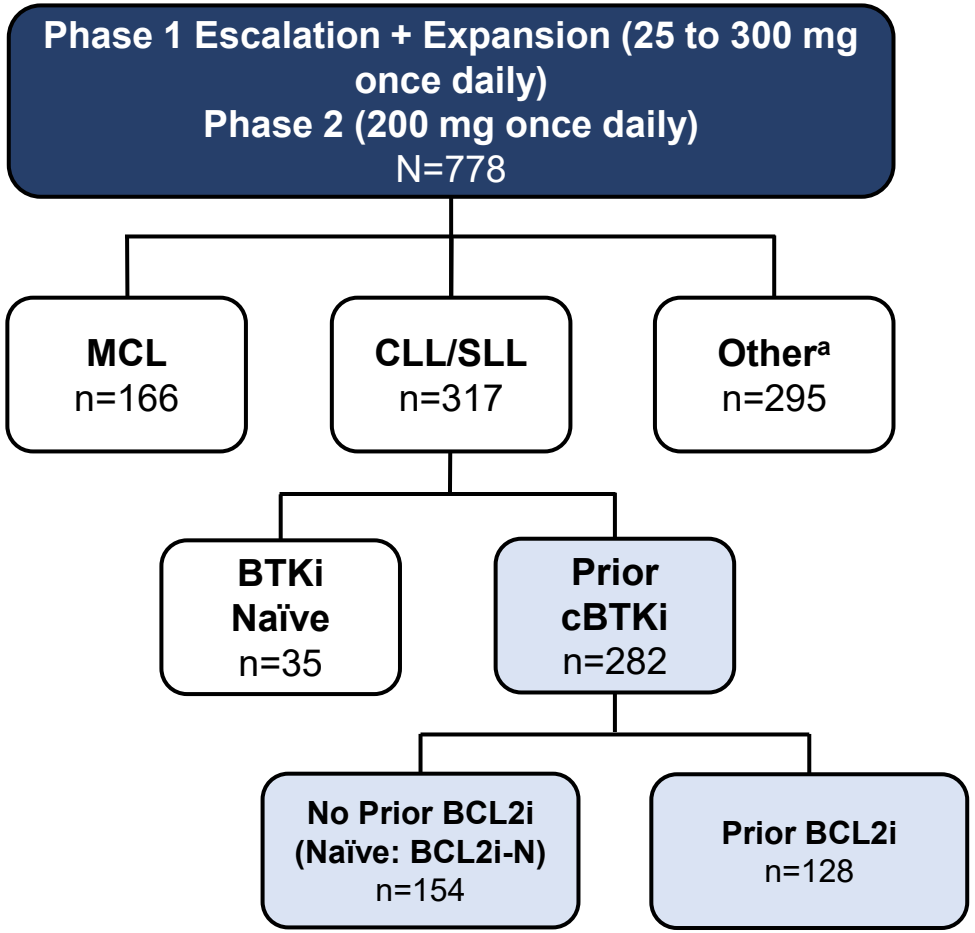
Pirtobrutinib may stabilize/maintain BTK in a closed inactive conformation



- EMA approved pirtobrutinib for the treatment of adult patients with relapsed or refractory mantle cell lymphoma (MCL) who have been previously treated with a Bruton's tyrosine kinase (BTK) inhibitor
- Inhibits **both Wild Type and C481-mutant BTK** with equal low nM potency[4]
- 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[4]

Mato AR et al, *Lancet* 2021;397:892-901, 2. Brandhuber BJ et al. *Clin Lymphoma Myeloma Leuk* 2018;18:S216, 3. Jaypirca [, Eli Lilly and Company, 2023, 4. Gomez EB et al. *Blood* 2023.

Phase 1/2 BRUIN Study: Design, Eligibility and Enrollment



Eligibility

- Age ≥18
- ECOG PS 0-2
- Active disease and in need of treatment
- Previously treated

Mato et al., NEJM 2023, Wierda et al., ASH 2025

Baseline Characteristics of Patients

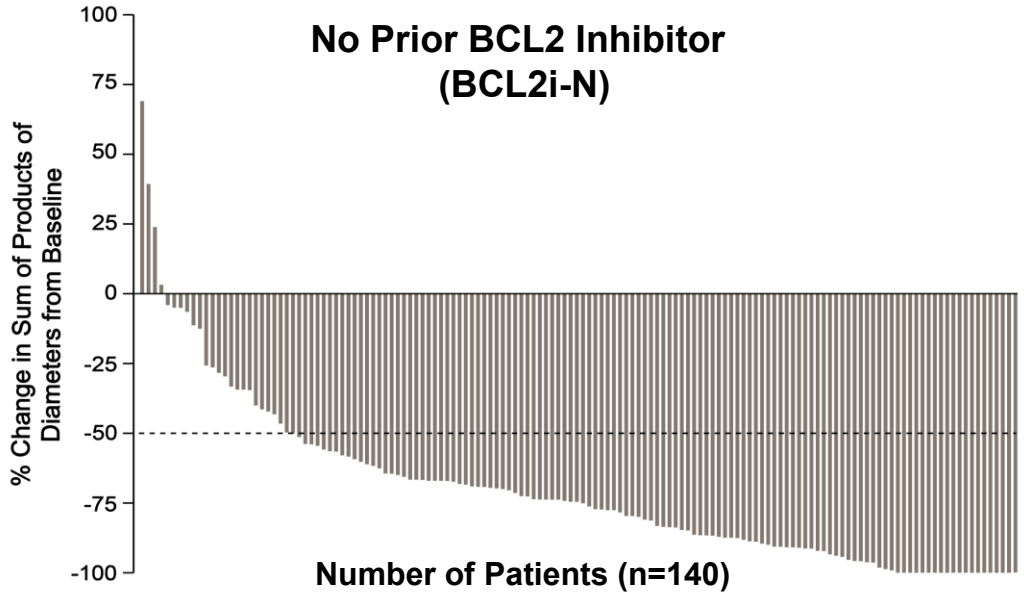
Characteristics	Prior cBTKi (n=282)	BCL2i-N (n=154)	BCL2i-E (n=128)
Median age, years (range)	69 (36-88)	69 (36-87)	68 (41-88)
Male, n (%)	192 (68)	106 (69)	86 (67)
Rai staging			
0-II	147 (52)	94 (61)	53 (41)
III-IV	120 (43)	58 (38)	62 (48)
Missing	15 (5)	2 (1)	13 (10)
Bulky Lymphadenopathy ≥5 cm, n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

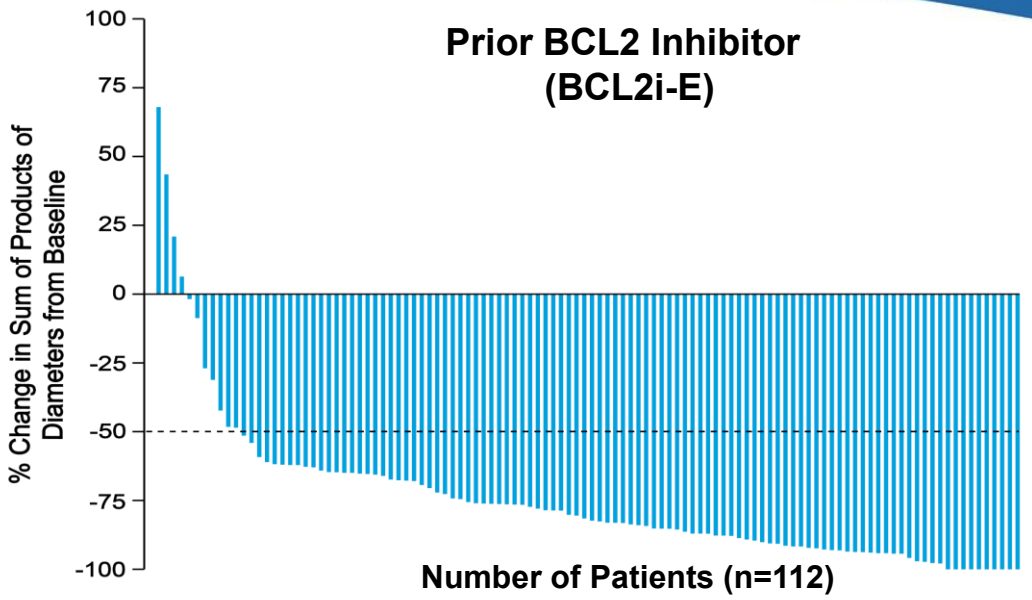
Characteristics	Prior cBTKi (n=282)	BCL2i-N (n=154)	BCL2i-E (n=128)
Median time from diagnosis to first dose, years (IQR)	11 (8-15)	11 (7-15)	12 (8-15)
Reason for any prior BTKi discontinuation[a], n (%)			
Progressive disease	217 (77)	110 (71)	107 (84)
Toxicity/Other	64 (23)	43 (28)	21 (16)

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

Mato et al., NEJM 2023, Wierda et al., ASH 2025

Pirtobrutinib Efficacy





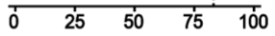
BCL2i-N	(n=154)[b]
ORR[a] incl. PR-L, % (95% CI)	83.1 (76.2-88.7)
Best Response, n (%)	
CR	5 (3.2)
nPR	2 (1.3)
PR	108 (70.1)
PR-L	13 (8.4)

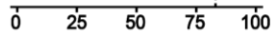
BCL2i-E	(n=128)[c]
ORR[a] incl. PR-L, % (95% CI)	79.7 (71.7-86.3)
Best Response, n (%)	
CR	0 (0)
nPR	0 (0)
PR	88 (68.8)
PR-L	14 (10.9)

Mato et al., NEJM 2023, Wierda et al., ASH 2025

Pirtobrutinib ORR (subgroup analysis)

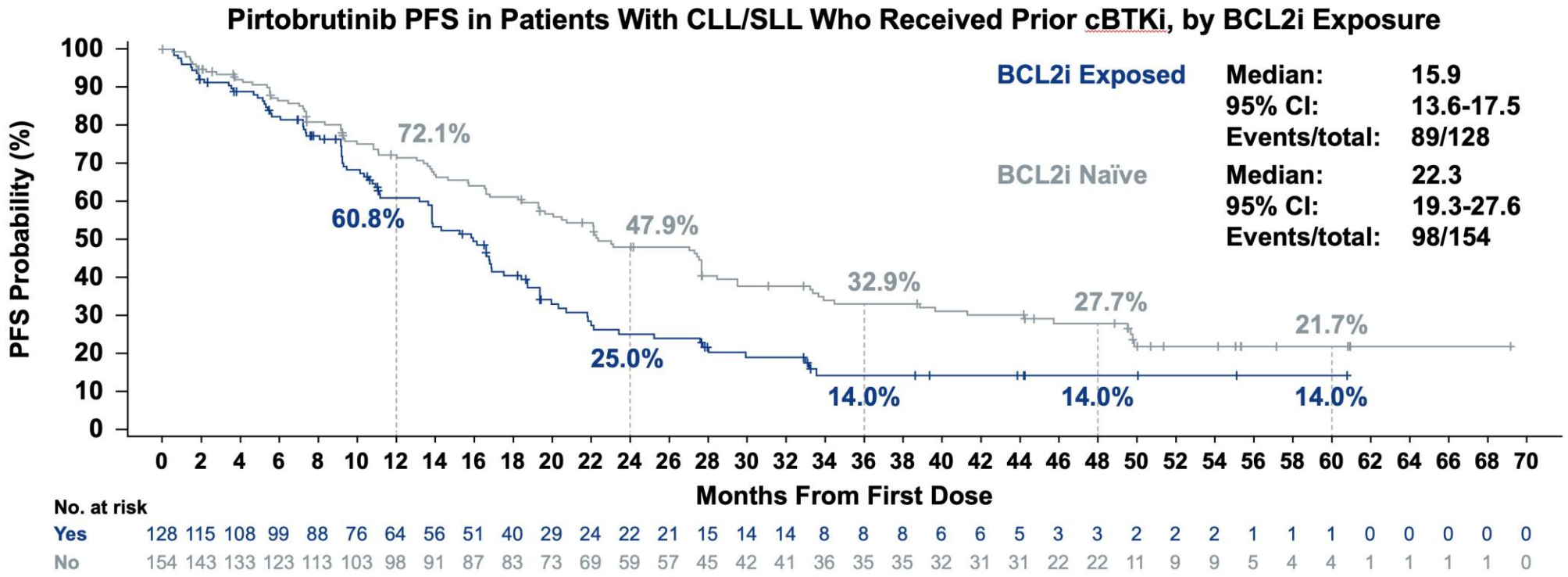
	BCL2i-N		BCL2i-E	
	Responders/Patients	ORR[a] % (95% CI)	Responders/Patients	ORR[a] % (95% CI)
All Patients with Prior cBTKi	128/154	83.1 (76.2 - 88.7)	102/128	79.7 (71.7 - 86.3)
Age (years)				
< 75	99/122	81.1 (73.1 - 87.7)	82/102	80.4 (71.4 - 87.6)
≥ 75	29/32	90.6 (75.0 - 98.0)	20/26	76.9 (56.4 - 91.0)
ECOG PS at Baseline				
0	72/89	80.9 (71.2 - 88.5)	46/55	83.6 (71.2 - 92.2)
1	47/56	83.9 (71.7 - 92.4)	48/62	77.4 (65.0 - 87.1)
2	9/9	100.0 (66.4 - 100.0)	8/11	72.7 (39.0 - 94.0)
Rai Staging at Baseline				
Stage 0 - II	76/94	80.9 (71.4 - 88.2)	42/53	79.2 (65.9 - 89.2)
Stage III - IV	50/58	86.2 (74.6 - 93.9)	48/62	77.4 (65.0 - 87.1)
Prior Lines of Systemic Therapies				
≤ 3	93/112	83.0 (74.8 - 89.5)	23/26	88.5 (69.8 - 97.6)
> 3	35/42	83.3 (68.6 - 93.0)	79/102	77.5 (68.1 - 85.1)
BCL2 Mutation Status[b]				
Mutated	--------	----------	16/16	100 (79.4 - 100.0)
Unmutated	--------	----------	54/71	76.1 (64.5 - 85.4)
BTK C481 Mutation Status[c]				
Mutated	47/54	87.0 (75.1 - 94.6)	34/39	87.2 (72.6 - 95.7)
Unmutated	31/44	70.5 (54.8 - 83.2)	41/53	77.4 (63.8 - 87.7)
PLCg2 Mutation Status[c]				
Mutated	6/10	60.0 (26.2 - 87.8)	4/8	50.0 (15.7 - 84.3)
Unmutated	72/88	81.8 (72.2 - 89.2)	71/84	84.5 (75.0 - 91.5)
IGHV Mutation Status				
Mutated	21/25	84.0 (63.9 - 95.5)	3/7	42.9 (9.9 - 81.6)
Unmutated	81/100	81.0 (71.9 - 88.2)	79/93	84.9 (76.0 - 91.5)
Complex Karyotype				
Yes	16/17	94.1 (71.3 - 99.9)	14/16	87.5 (61.7 - 98.4)
No	20/24	83.3 (62.6 - 95.3)	11/16	68.8 (41.3 - 89.0)
del(11q)				
Yes	25/28	89.3 (71.8 - 97.7)	19/19	100.0 (82.4 - 100.0)
No	71/87	81.6 (71.9 - 89.1)	50/68	73.5 (61.4 - 83.5)
del(17p) and/or *TP53* Mutation				
Yes	48/57	84.2 (72.1 - 92.5)	43/47	91.5 (79.6 - 97.5)
No	55/66	83.3 (72.1 - 91.4)	34/47	72.3 (57.4 - 84.4)
Reason for any Prior BTKi Discontinuation[d]				
Disease Progression	88/110	80.0 (71.3 - 87.0)	85/107	79.4 (70.5 - 86.6)
Toxicity/Other	39/43	90.7 (77.9 - 97.4)	17/21	81.0 (58.1 - 94.5)





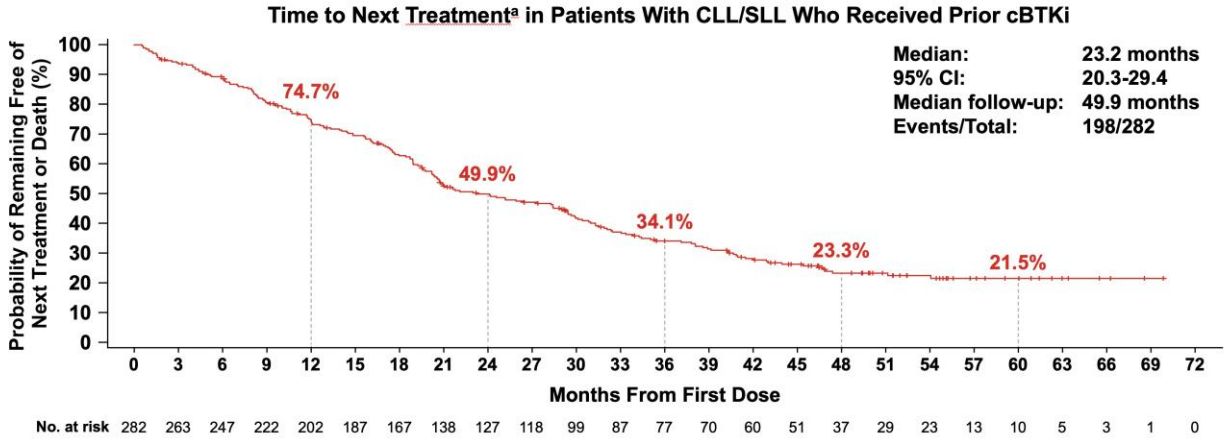
Mato et al., NEJM 2023, Wierda et al., ASH 2025

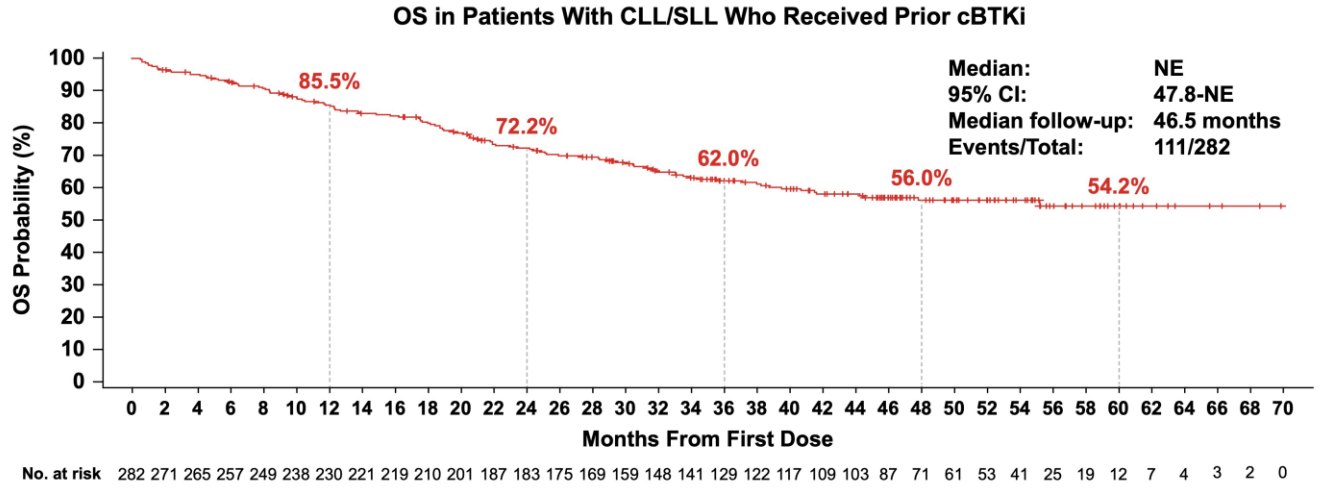
Phase 1/2 BRUIN Study: 5 year followup



Wierda et al., ASH 2025

Phase 1/2 BRUIN Study: 5 year follow-up





Wierda et al., ASH 2025

Pirtobrutinib Safety Profile of Patients who Received Prior cBTKi

	Treatment-Emergent AEs in Patients with CLL (n=282)			
	All Cause AEs, (≥20%), %		Treatment-Related AEs, %	
Adverse Event	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Fatigue	36.9	1.8	3.5	0.0
Neutropenia[b,c]	34.4	28.4	19.5	15.2
Diarrhea	28.4	0.4	7.8	0.0
Cough	27.3	0.0	1.8	0.0
Contusion	26.2	0.0	17.4	0.0
Covid-19	25.9	4.6	0.7	0.0
Dyspnea	22.3	2.1	0.7	0.4
Nausea	22.0	0.0	3.5	0.0
Abdominal pain	21.3	1.8	2.1	0.4
AEs of Interest[a]	**Any Grade**	**Grade ≥3**	**Any Grade**	**Grade ≥3**
Infections[d]	74.1	30.9	12.8	4.3
Bruising[e]	30.1	0.0	19.1	0.0
Rash[f]	24.5	1.1	5.7	0.4
Arthralgia	22.7	1.4	4.3	0.0
Hemorrhage[g]	13.5	2.1	4.6	1.1
Hypertension	14.2	4.3	3.5	0.4
Atrial Fibrillation/Flutter[h,i]	4.6	1.8	1.4	0.7

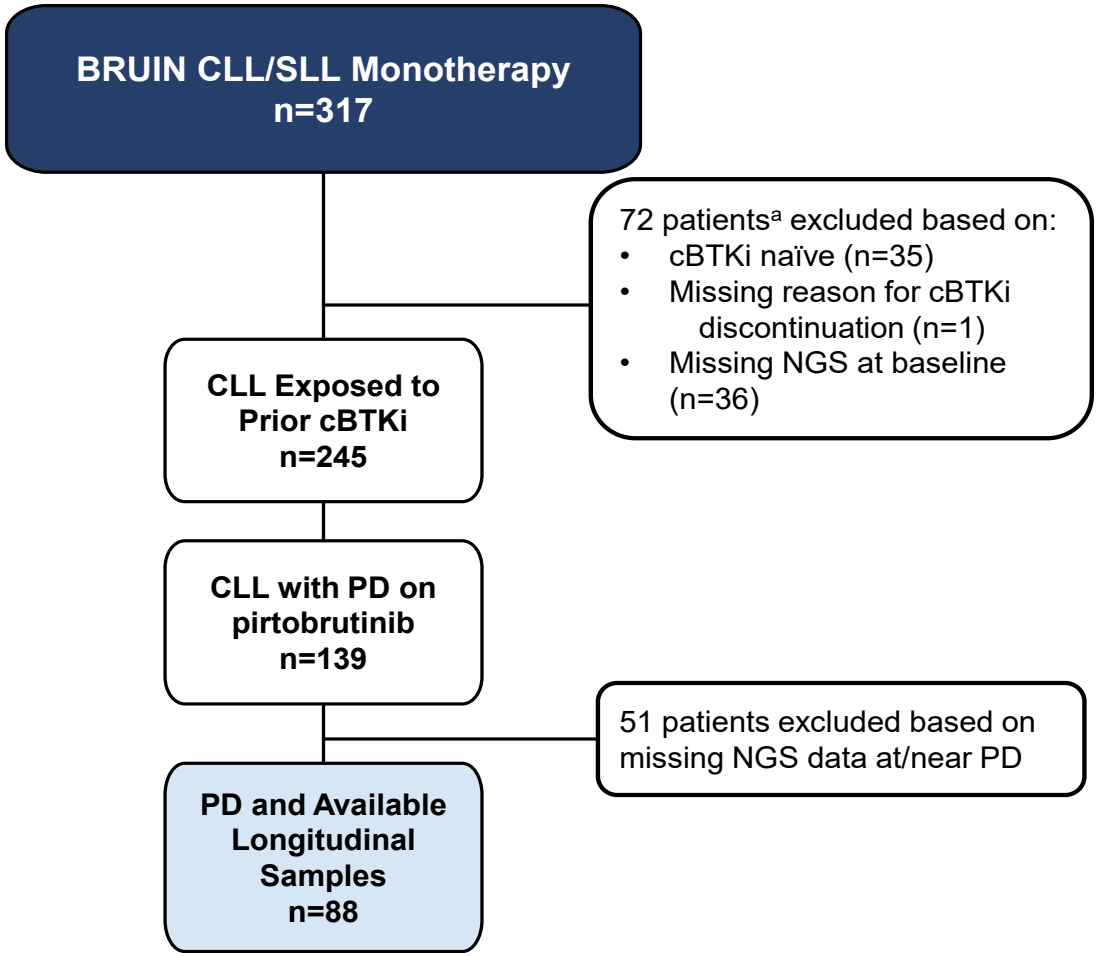
Median time on treatment was 18.7 months (prior cBTKi), 24.3 months (BCL2i-N) and 15.3 months (BCL2i-E)

11 (3.9%; 9 BCL2i-N, 2 BCL2i-E) pts had TRAE leading to pirtobrutinib dose reduction

7 (2.5%; 4 BCL2i-N, 3 BCL2i-E) pts had TRAE leading to pirtobrutinib discontinuation

Mato et al., NEJM 2023, Wierda et al., ASH 2025

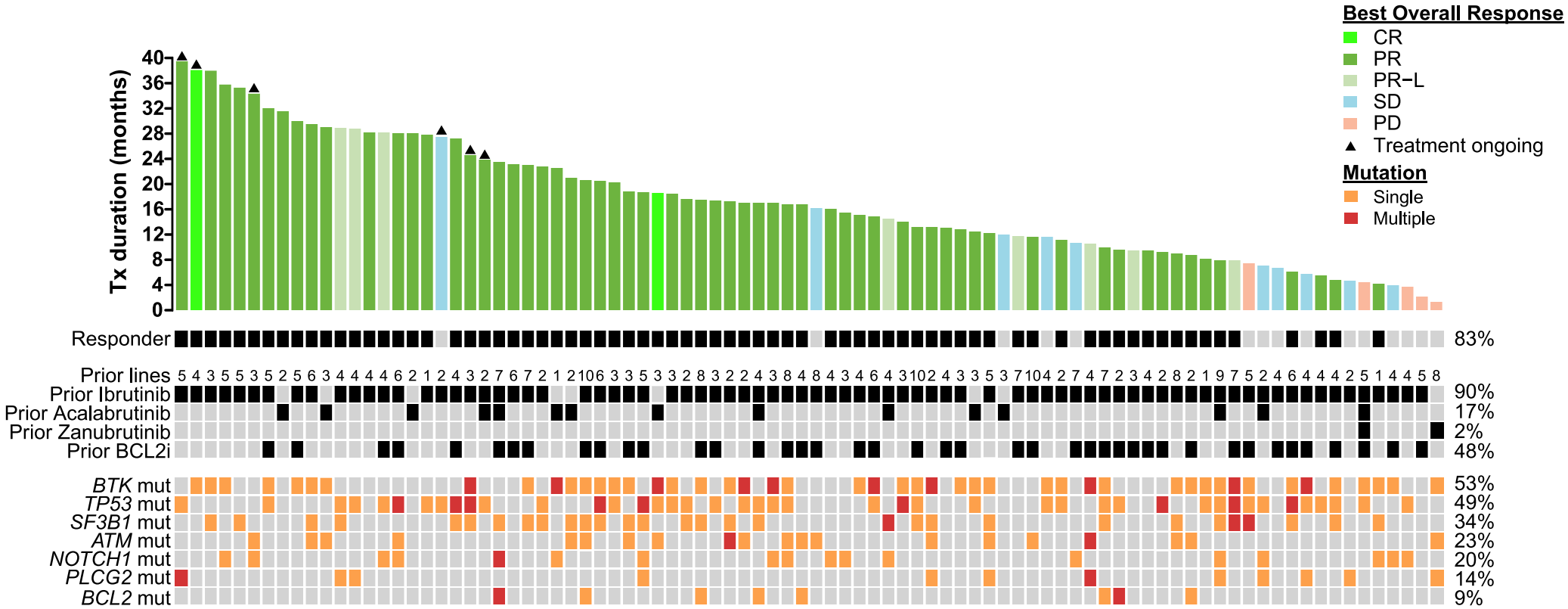
Genomic Evolution and Resistance during Pirtobrutinib Therapy



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

Brown et al., Blood 2026

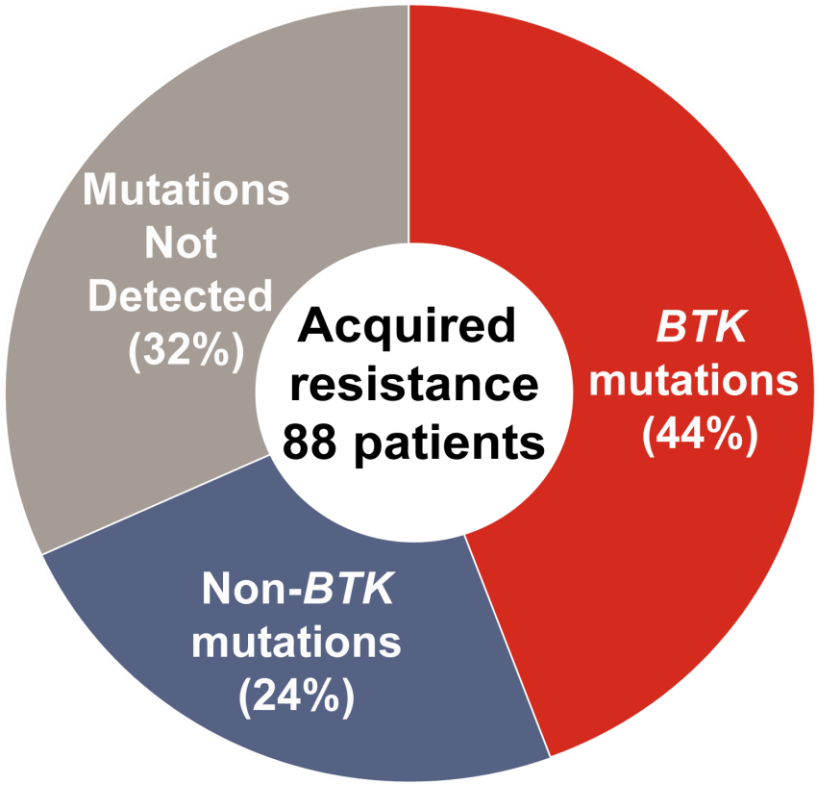
Baseline Genomics in Patients with PD on Pirtobrutinib (n=88)

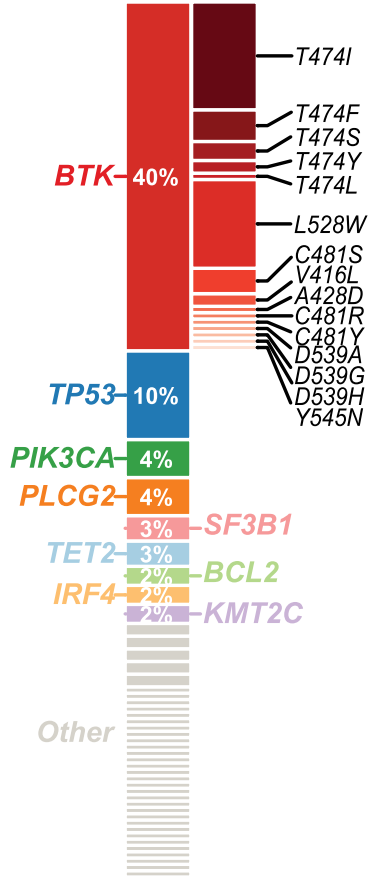


- The most common mutations detected at baseline were *BTK* (53%), *TP53* (49%), *SF3B1* (34%), *ATM* (23%), *NOTCH1* (20%), *PLCG2* (14%), *BCL2* (9%)
- Pirtobrutinib demonstrated efficacy, with an ORR of 83% (73/88)
  - Baseline genomic features did not predict response to pirtobrutinib treatment

Brown et al., Blood 2026

Acquired Mutations were Detected at PD in 68% of Patients

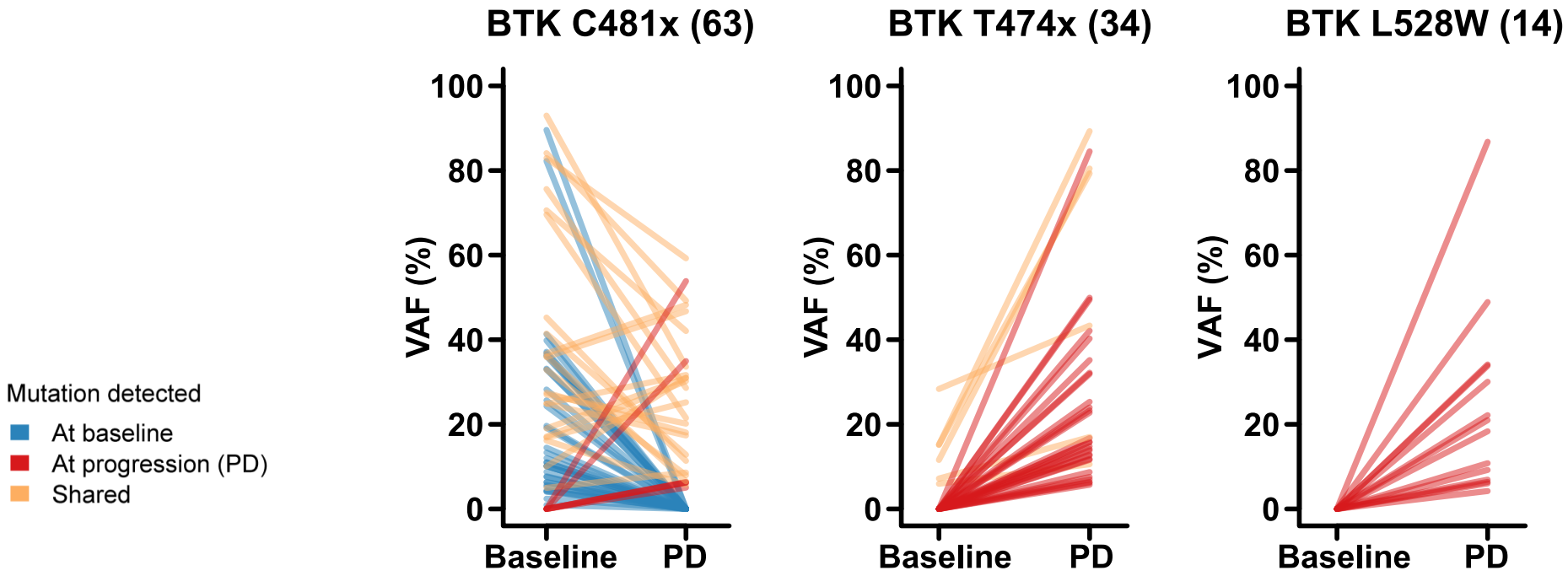




- 68% (60/88) patients had 138 acquired mutations:
  - 28% had a single acquired mutation and 40% had multiple acquired mutations (up to 8)
  - 30% had a single acquired BTK mutation and 14% had multiple acquired BTK mutations
  - 14% had TP53, 7% had PLCG2, 7% had PIK3CA, 3% BCL2 (all had prior venetoclax)
- 51% (24/47) had clearance of BTK mutations

Brown et al., Blood 2026

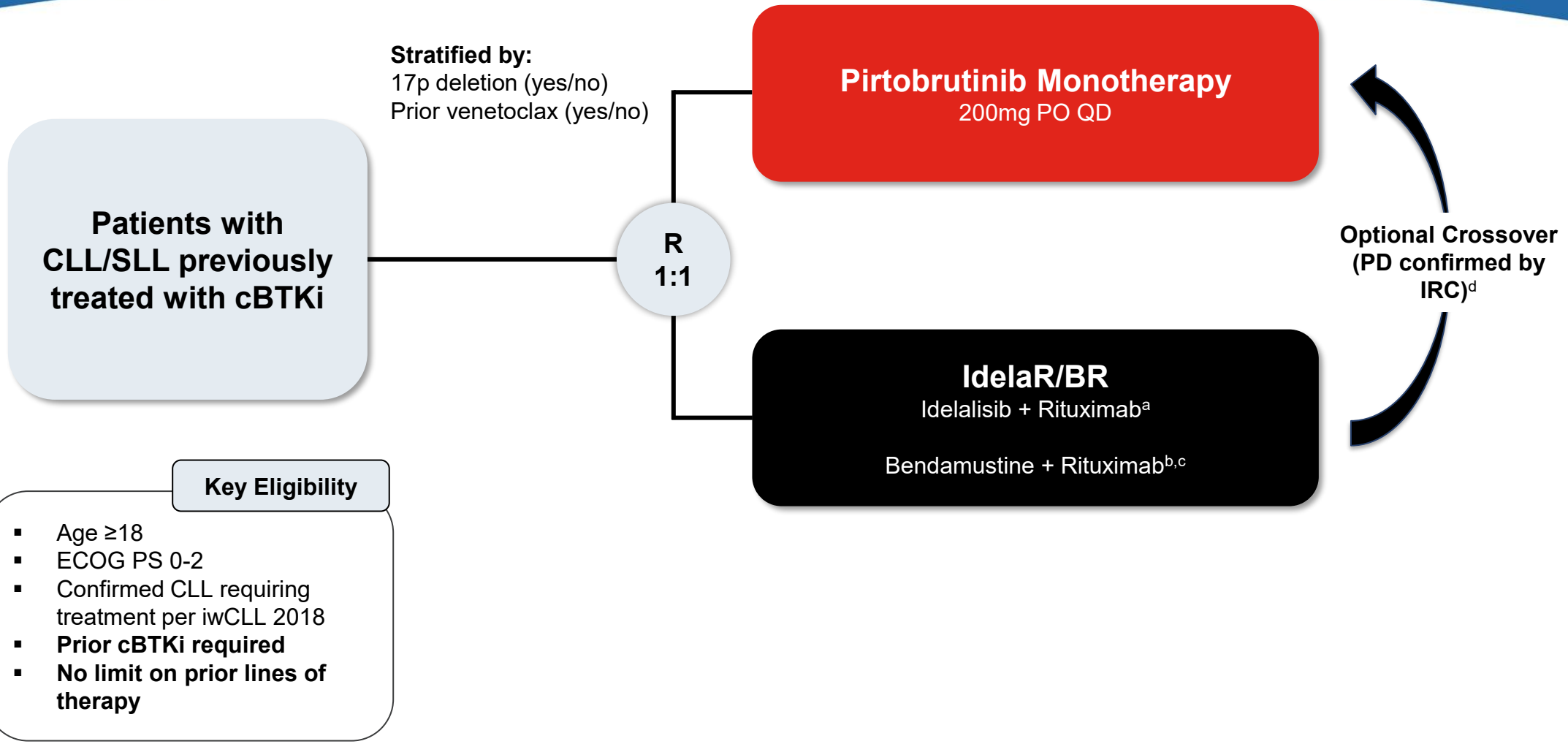
The Majority of *BTK* Acquired Mutations were T474x and L528W



- Decrease/clearance of C481x[a] clones observed at progression in 84% (36/43) patients (clearance = 23/43, 53%)
- *BTK* C481S/Y/R, T474x[a], L528W, other kinase mutations arose at/near progression (55 mutations in 39 patients, VAF range 3-86%)
- ORR was similar across groups regardless of the acquired *BTK* mutation (T474x, 22/23, 96%; L528W; 11/14, 79%)

Brown et al., Blood 2026

BRUIN CLL-321 Study Design



Key Eligibility

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

Sharman et al., JCO 2025

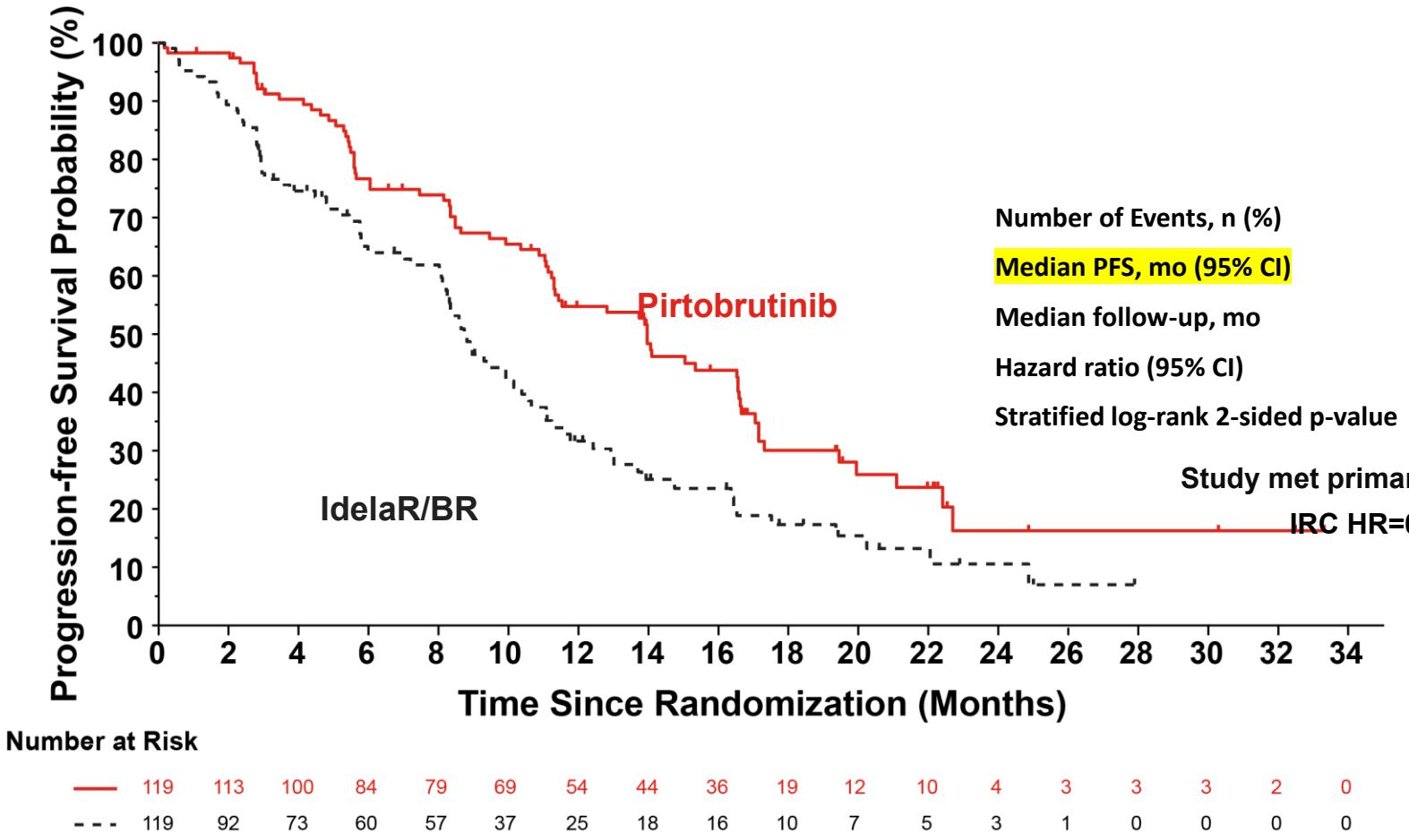
Patient Characteristics at Baseline

Characteristics	Pirtobrutinib n=119	IdelaR/BR n=119
Median Age, years (range)	66 (42-90)	68(42-85)
Male, n (%)	83 (70)	83 (70)
Region, n (%)		
North America	24 (20)	39 (33)
Europe	76 (64)	63 (53)
Asia	14 (12)	15 (13)
Australia	5 (4)	2 (2)
Histology, n (%)		
CLL	109 (92)	108 (91)
SLL	10 (8)	11 (9)
ECOG PS, n (%)		
0	51 (43)	50 (42)
1	56 (47)	64 (54)
2	12 (10)	5 (4)
Rai stage[a], n (%)		
0-II	58 (49)	60 (52)
III-IV	56 (47)	54 (45)
High-Risk Molecular Features (Central Lab), n/n available (%)		
TP53 mutation	36/97 (37)	30/94 (32)
17p deletion	39/111 (35)	43/112 (38)
17p deletion and/or *TP53* mutation	51/94 (54)	53/98 (54)
IGHV unmutated	90/97 (93)	74/93 (80)
Complex karyotype[b]	53/74 (72)	44/75 (59)

Characteristics	Pirtobrutinib n=119	IdelaR/BR n=119
Median lines of prior systemic therapy, n (range)	3 (1-13)	3 (1-11)
Prior therapy, n (%)		
cBTKi[c]	119 (100)	119 (100)
Ibrutinib	100 (84)	106 (89)
Acalabrutinib	17 (14)	20 (17)
Zanubrutinib	10 (8)	7 (6)
Other[d]	5 (4)	3 (3)
BCL2 inhibitor[e]	60 (50)	62 (52)
Chemotherapy	81 (68)	83 (70)
Anti-CD20 Antibody	86 (72)	83 (70)
PI3K inhibitor	11 (9)	11 (9)
Immunomodulator	2 (2)	3 (3)
Autologous Stem Cell Transplant	1 (1)	0 (0)
Allogeneic Stem Cell Transplant	2 (2)	1 (1)
Reason for any prior cBTKi discontinuation[f], n (%)		
Disease progression	85 (71)	87 (73)
Toxicity	20 (17)	22 (19)
Other	15 (13)	9 (8)

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

IRC-Assessed PFS



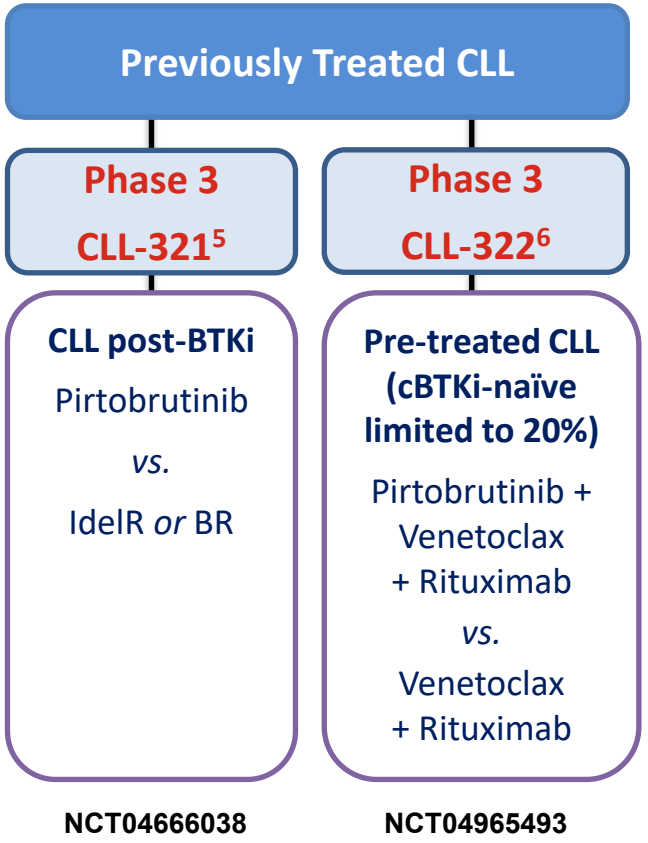
	Pirtobrutinib n=119	IdelaR/BR n=119
Number of Events, n (%)	74 (62)	79 (66)
Median PFS, mo (95% CI)	**14.0** (11.2-16.6)	**8.7** (8.1-10.4)
Median follow-up, mo	19.4	17.7
Hazard ratio (95% CI)	**0.54 (0.39- 0.75)**	
Stratified log-rank 2-sided p-value	0.0002*	

Study met primary endpoint at earlier data cut (Aug 2023)

IRC HR=0.58 (95% CI 0.38- 0.89); p = 0.01

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

Sharman et al., JCO 2025



BRUIN CLL 322 (NCT04965493)

The primary endpoint is PFS per iwCLL assessed by an independent review committee (IRC).

Secondary endpoints include:

- ORR
- OS
- time to next treatment (TTNT),
- EFS,
- safety and tolerability,
- patient-reported outcomes.

BELLWAVE-003 Patients & Methods

Total Enrolled CLL/SLL Population
N = 225

Aged ≥ 18 years treated with nemtabrutinib 65 mg or 80 mg PO QD	
Part 1	R/R after ≥2 prior lines
Part 2 Cohort A	R/R to covalent BTKi and a BCL2i; pts with CLL must be poor or ineligible candidates for PI3Ki
Part 2 Cohort B	R/R after ≥1 prior line and BTKi-naïve
Part 2 Cohort C	Del17p and/or TP53 mutation R/R after ≥1 prior line

Biomarker Evaluable
N = 100

Targeted NGS for over 400 genes on blood or bone marrow aspirate matched from baseline and end of treatment (or EOT proxy, last sample Cycle 7 or later).

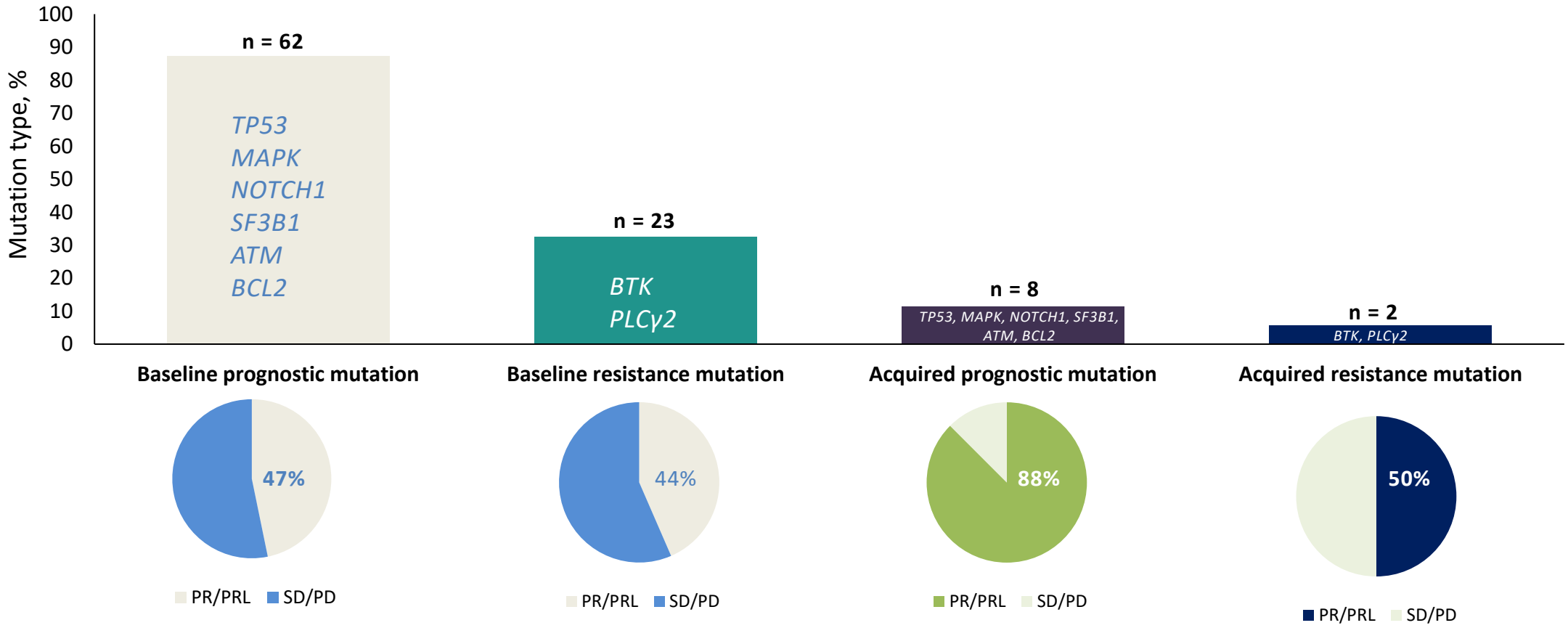
Biomarker + Clinically Evaluable
N = 71

Efficacy assessed by BICR (best response of PR/PRL, SD, or PD per iwCLL 2018 criteria) with both biomarker and BICR results available

Qualifying Adverse Mutations	
Poor-Prognosis Mutations	*TP53, MAPK, NOTCH, MYD88, SF3B1, ATM, BCL2*
Resistance Mutations	*BTK, PLCγ2*

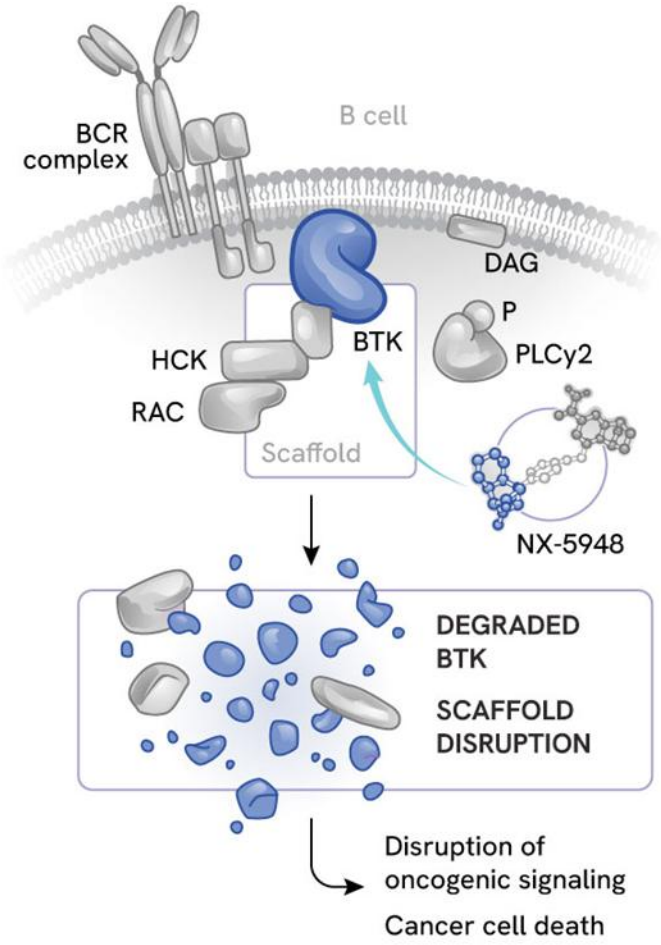
Kipps et al., ASH 2025

BELLWAVE-003
Efficacy Profile Among Participants With Adverse Mutations



Kipps et al., ASH 2025

Bexobrutideg (NX-5948) Degrader Properties
A novel BTK degrader distinct from BTK inhibitors

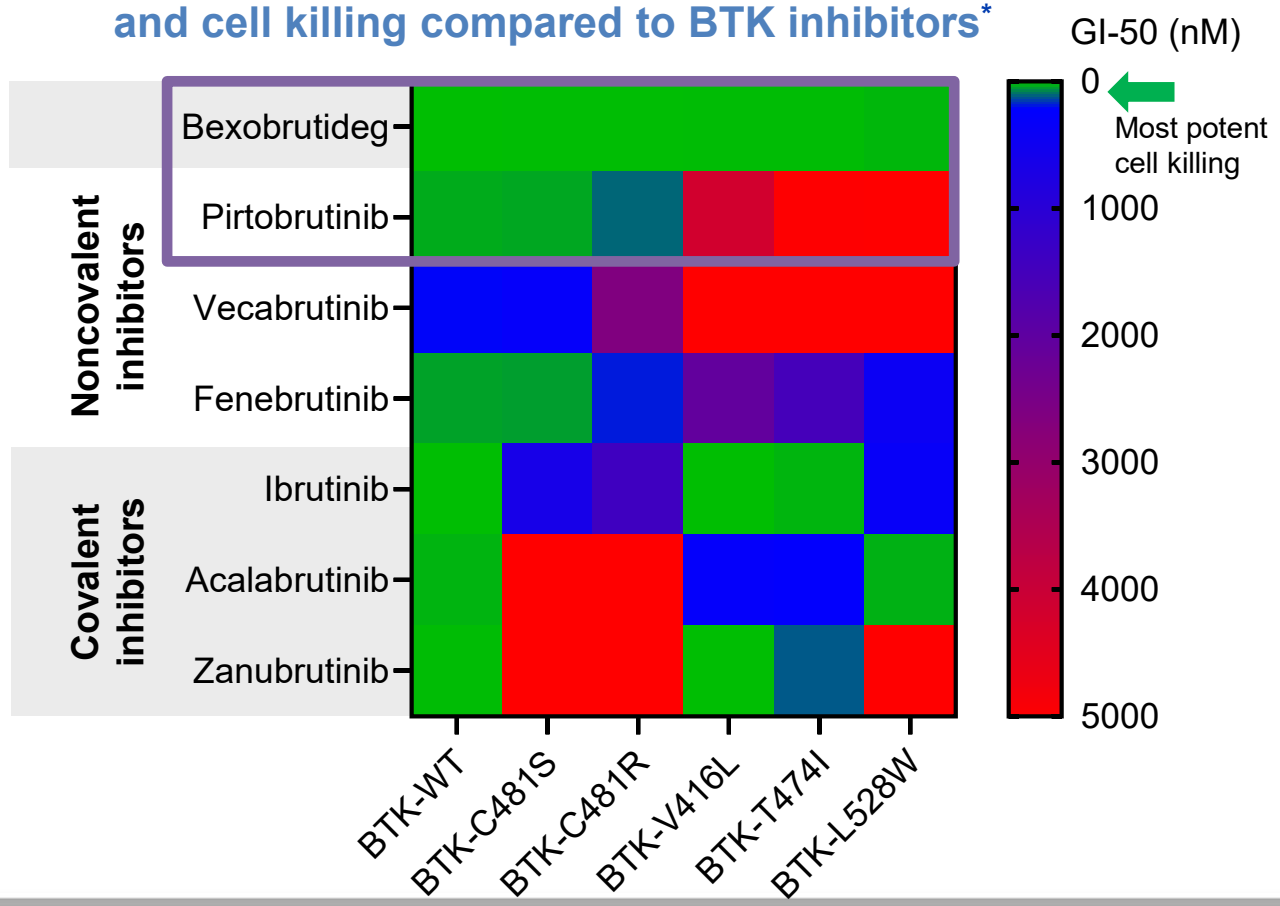


- ✓ Active against wildtype BTK and demonstrated ability to overcome treatment-emergent resistance mutations[1,2]
- ✓ Addresses BTK scaffolding function unlike current BTK inhibitors[3]
- ✓ Acts catalytically driving degradation at low free-plasma concentrations
- ✓ Crosses the blood brain barrier and demonstrated clinical activity in the CNS[4]
- ✓ Demonstrated robust clinical activity in difficult to treat B-cell malignancies[5–7]

Omer et al., ASH 2025

Bexobrutideg (NX-5948) Degrader Properties
A novel BTK degrader distinct from BTK inhibitors

Bexobrutideg shows superior mutational coverage and cell killing compared to BTK inhibitors*



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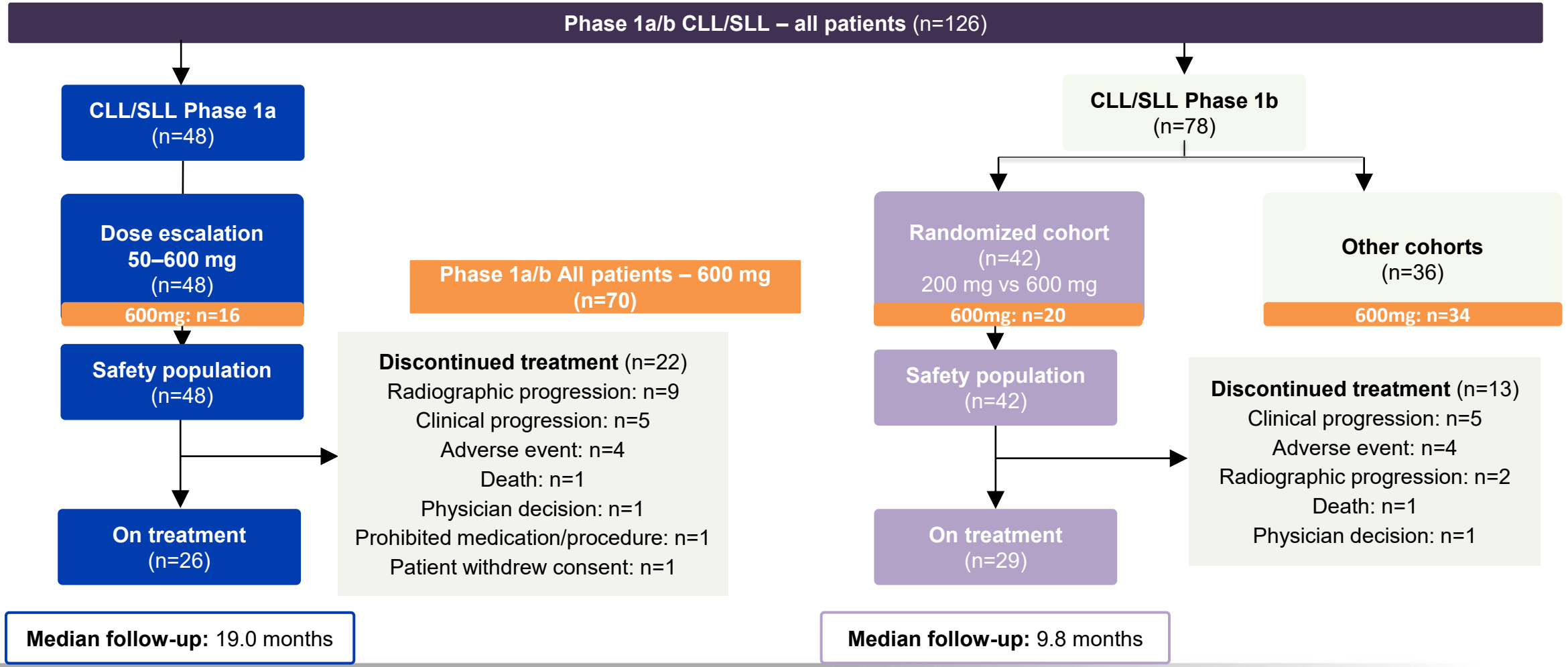
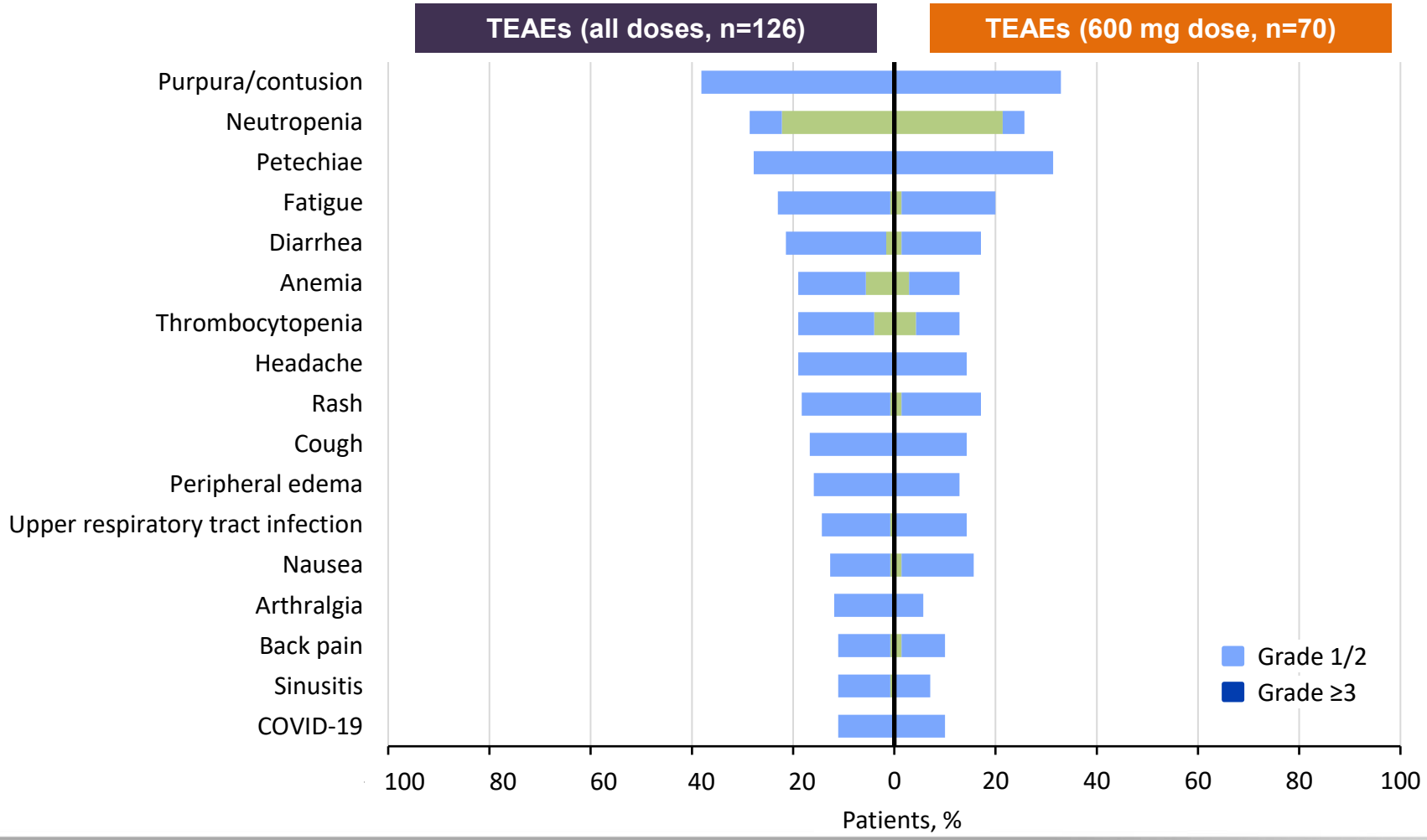
Omer et al., ASH 2025

NX-5948-301: CLL/SLL Patient Disposition



Omer et al., ASH 2025

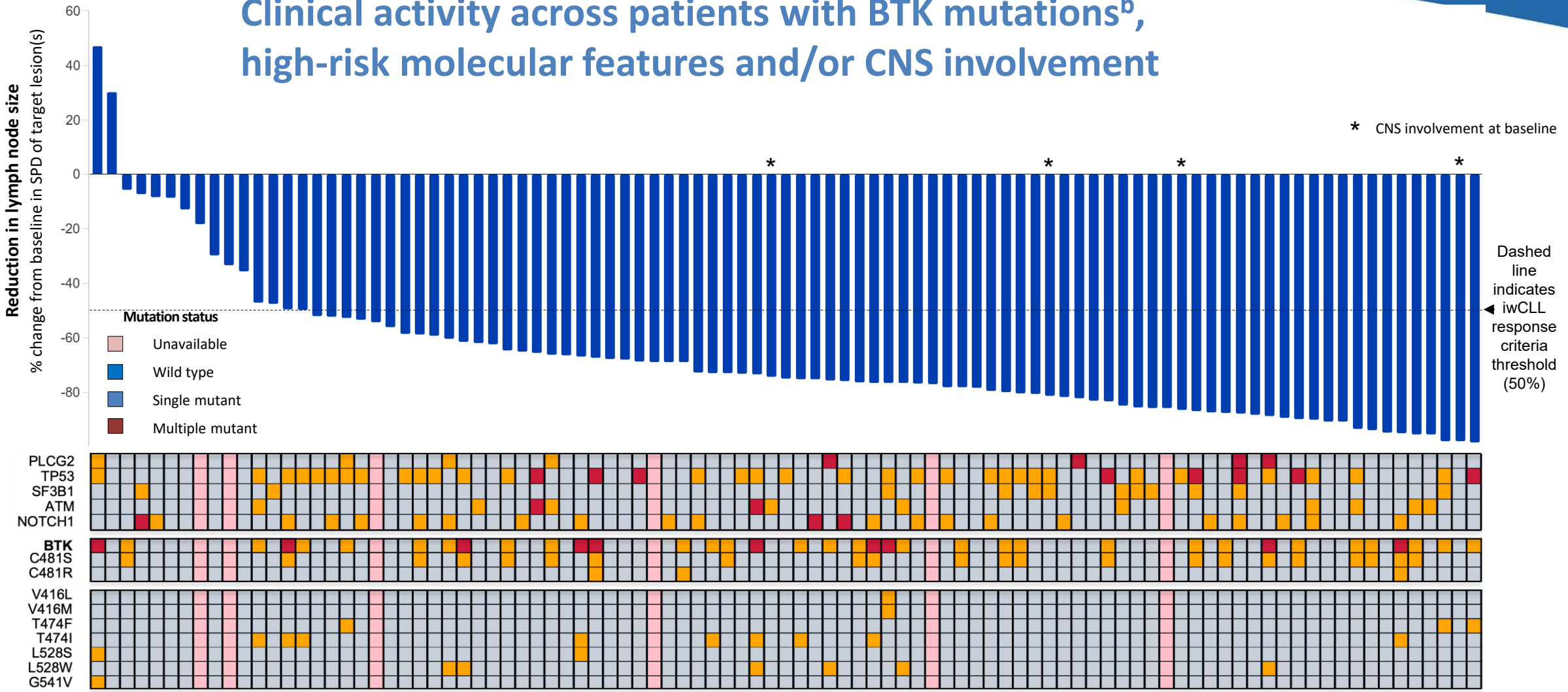
TEAEs in ≥10% in Phase 1a/b 600 mg Group vs All Patients



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

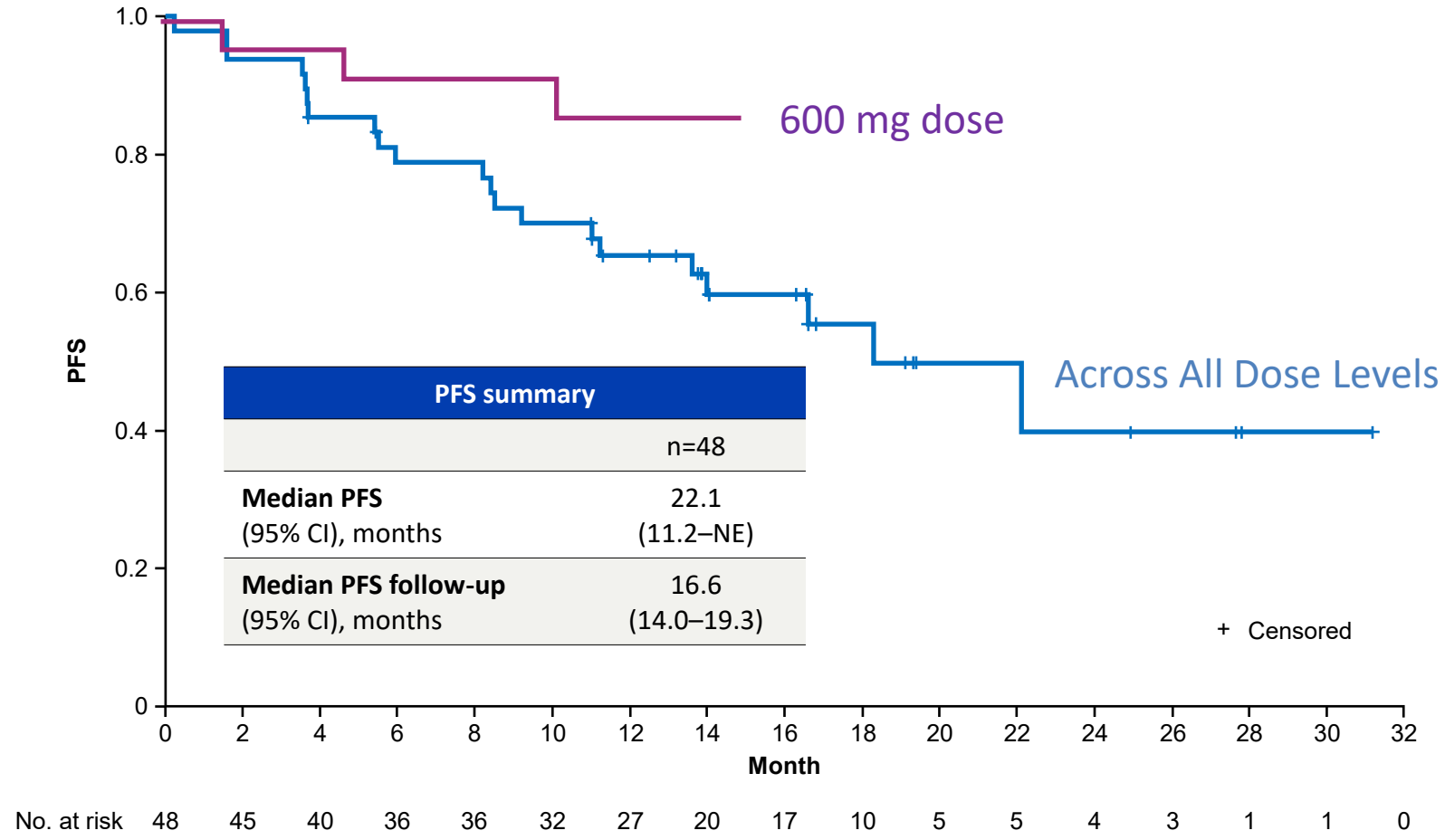
Omer et al., ASH 2025

Clinical activity across patients with BTK mutations[b], high-risk molecular features and/or CNS involvement



Omer et al., ASH 2025

PFS in Phase 1a (n=48)

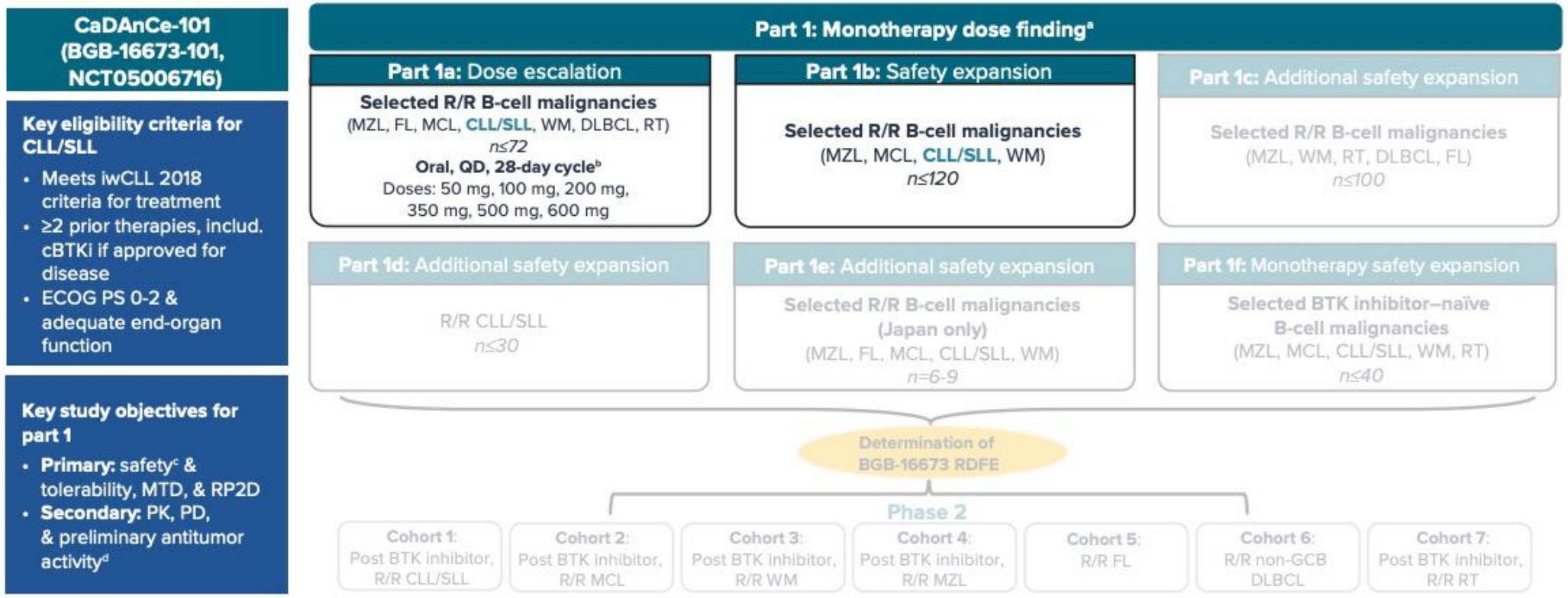


PFS summary	n=48
Median PFS (95% CI), months	22.1 (11.2–NE)
Median PFS follow-up (95% CI), months	16.6 (14.0–19.3)

Best response,[c]	n (%)
CR	2 (4.3)
nPR	1 (2.1)
PR/PR-L	36 (76.6)
SD	6 (12.8)
PD	2 (4.3)

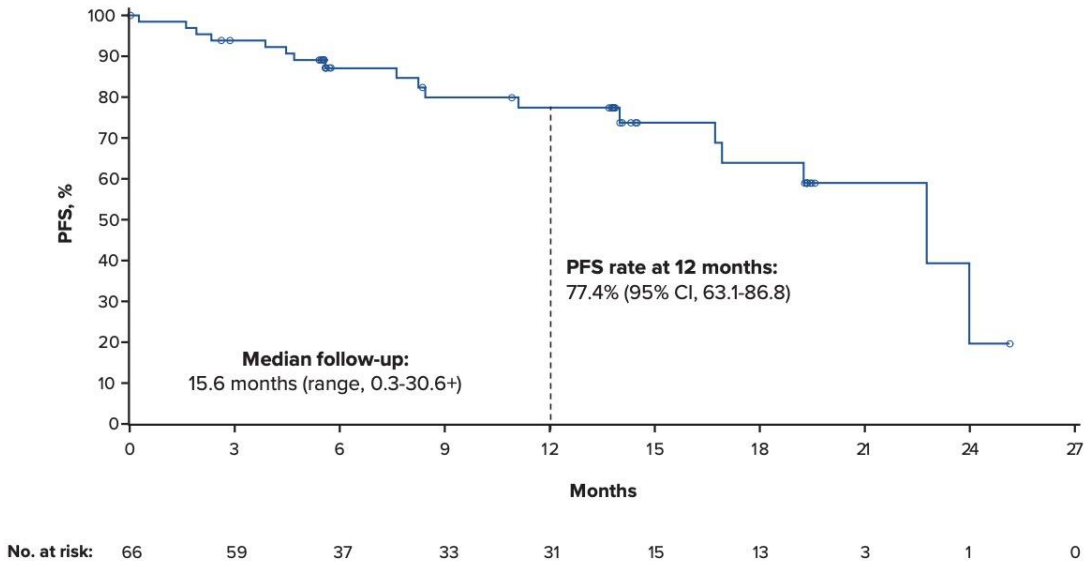
Omer et al., ASH 2025

BGB-16673 in Patients With R/R CLL – CaDAnCe-101 study



Stilgenbauer et.al., IwCLL 2025

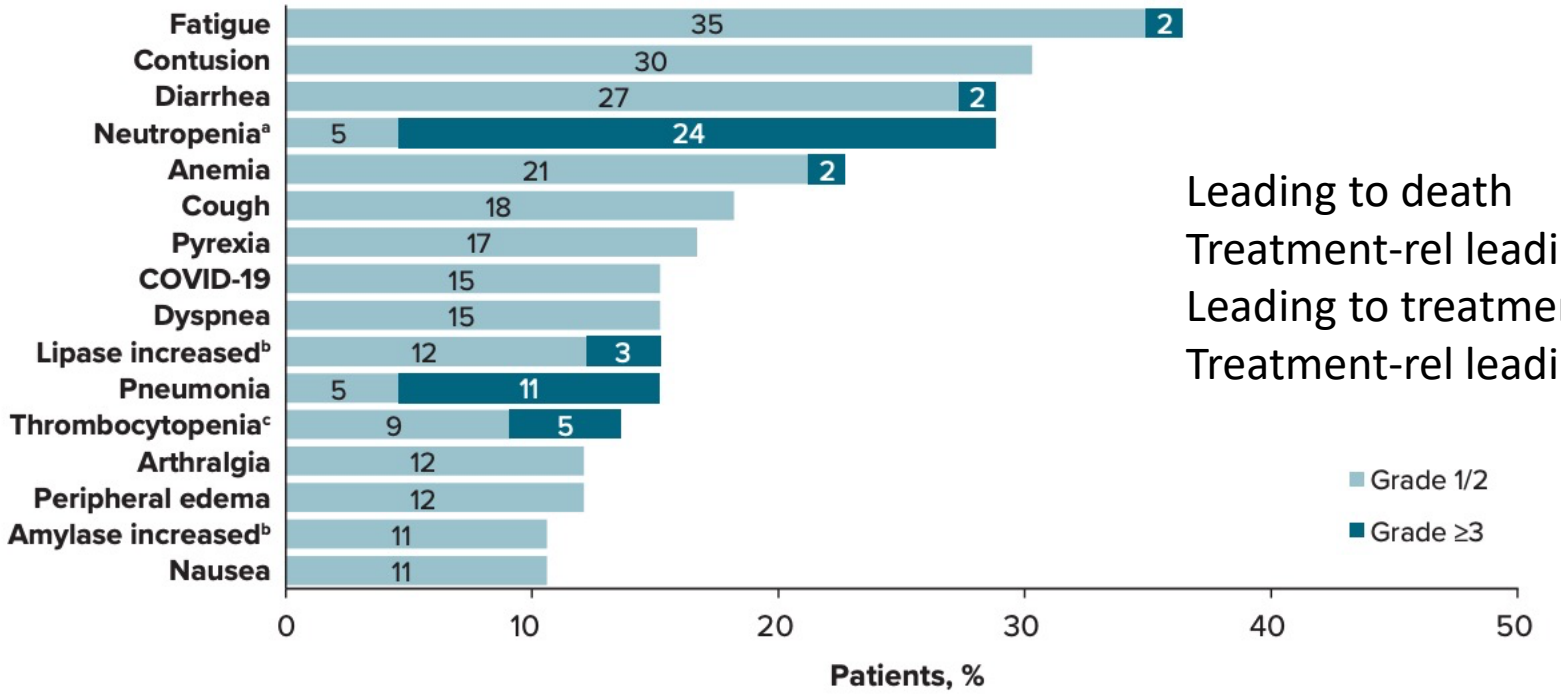
BGB-16673 in Patients With R/R CLL – Efficacy



	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)
ORR, 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 (2.8-11.1)	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 (29.6-29.6)	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)

Stilgenbauer et.al., IwCLL 2025

BGB-16673 in Patients With R/R CLL – TEAE



Leading to death	4 (6.1%)
Treatment-rel leading to death	0
Leading to treatment discontinuation	9 (13.6 %)
Treatment-rel leading to treatment discontin.	2 (3%)

Stilgenbauer et.al., IwCLL 2025

Phase III studies comparing BTK degradors with Pirtobrutinib in Double Exposed/ Double refractory CLL are planned / ongoing

Comparison of biological effects of BCL-2 inhibitors

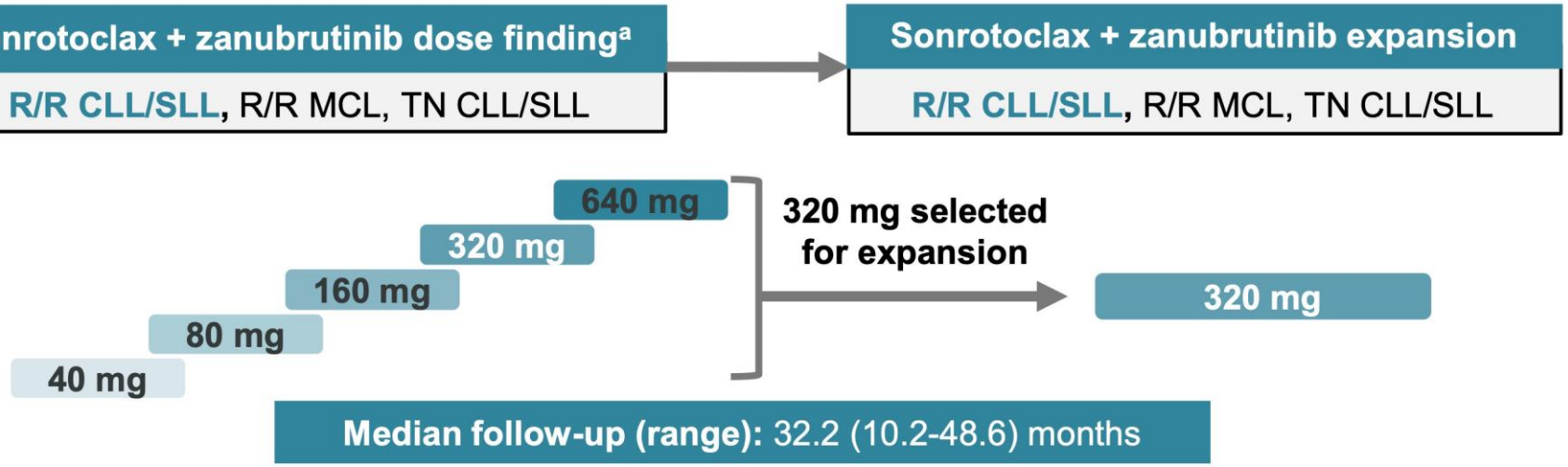
Biological Function	Primary Protein	Veneto-clax abbvie	Navito-clax abbvie	Lisafto-clax Ascentage	Sonroto-clax BeOne	Clinical Meaning / Practical Implications
Apoptosis inhibition	BCL-2	+++	++	+++	+++	**Therapeutic effect**. Rapid tumor cell death → **tumor lysis syndrome (TLS)** risk.
Platelets	BCL-xL	+	**+++** ⚠️	+	--	**Navitoclax: dose-limiting thrombocytopenia.** Venetoclax/Lisaftoclax mild; **sonrotoclax spares platelets.**
B lymphocytes	BCL-2	++	+	++	++	↑ infection risk (usually manageable). Vaccination response may be reduced.
Neutrophils	MCL-1	—	—	—	—	No direct inhibition
Mitochondrial bioenergetics	BCL-xL, BCL-2	++	**+++** ⚠️	++	+	Disruption causes **fatigue, asthenia**, exercise tolerance. **Labs:** ↑lactate (rare), mild ↑AST/ALT possible. **Navitoclax:** most pronounced due to BCL-xL inhibition → limits dosing.
ER–mitochondria Ca^{2+} signaling	BCL-2, BCL-xL	++	**+++**	++	+	Altered Ca^{2+} handling → **muscle cramps, weakness**, sometimes GI symptoms.
Stress adaptation	BCL-2, BCL-xL	++	**++**	++	+	Reduced tolerance to stress → **fatigue**

Sonrotoclax is a „better“ BCL-2i (preclinical)

Measure	Sonrotoclax	Venetoclax	Notes
IC_{50} for wild-type BCL-2	~0.014 nM	~0.20 nM	~14-fold higher biochemical potency for sonrotoclax in BCL-2 binding assays
Selectivity vs Bcl-xL, BCL-W & MCL-1	~2000 × Negligible	~325 × Detectable	~6-fold higher selectivity for BCL-2 vs BCL-xL may reduce off-target *toxicity* (e.g., platelet effects)
Half-life ($T_{1/2}$)	~4.5–5 h	~26 h	Shorter half-life for sonrotoclax no accumulation with daily dosing, may simplify TLS monitoring
Bcl-2 G101V mutant binding	0,28 nM	Not reported	Sonrotoclax retains inhibitory activity with common venetoclax-resistance mutations
Bcl-2 WT binding	0,035	Not reported	

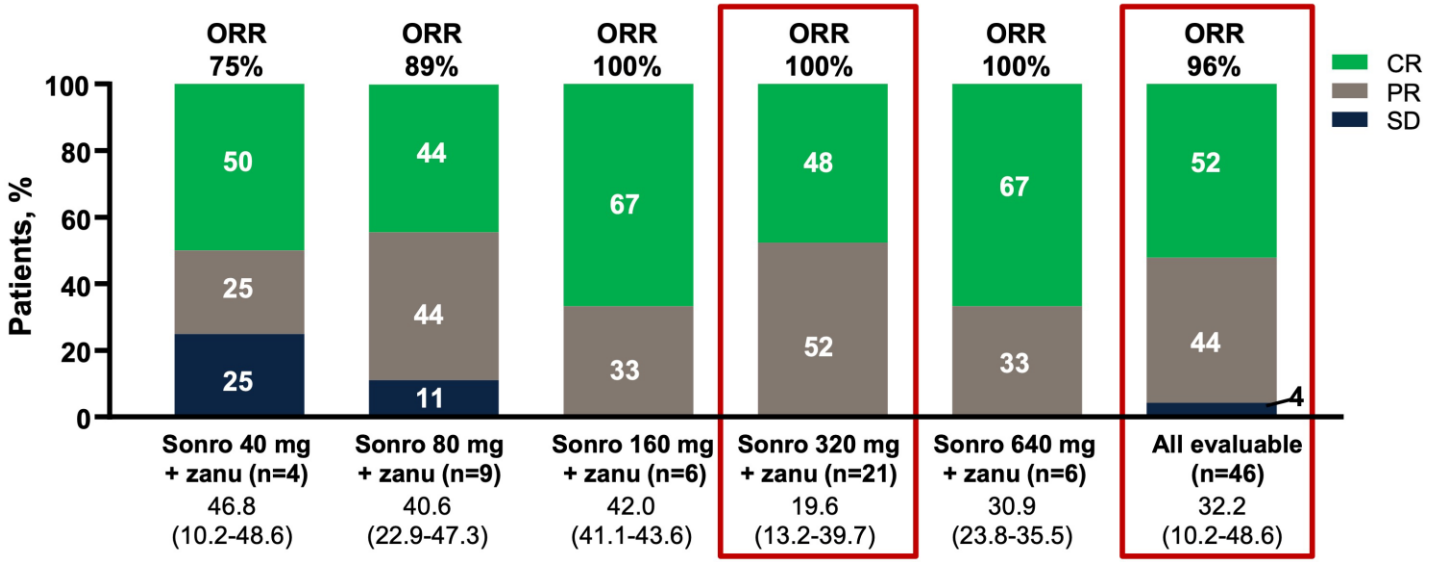
BGB-11417-101 (NCT04277637) Study Design

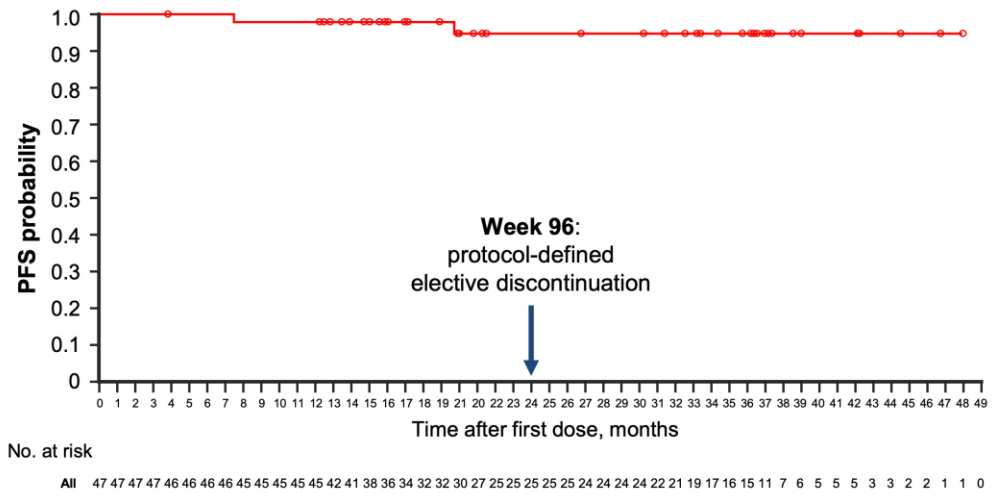
- Sonrotoclax (BGB-11417), a next-generation BCL2 inhibitor
- Zanubrutinib is a highly potent and selective next-generation BTK inhibitor
- Fixed-duration therapies are emerging as a new treatment option4; however, there are no approved BCL2 inhibitor + BTK inhibitor regimens for patients with R/R CLL/SLL



Opat et.al., IwCLL 2025

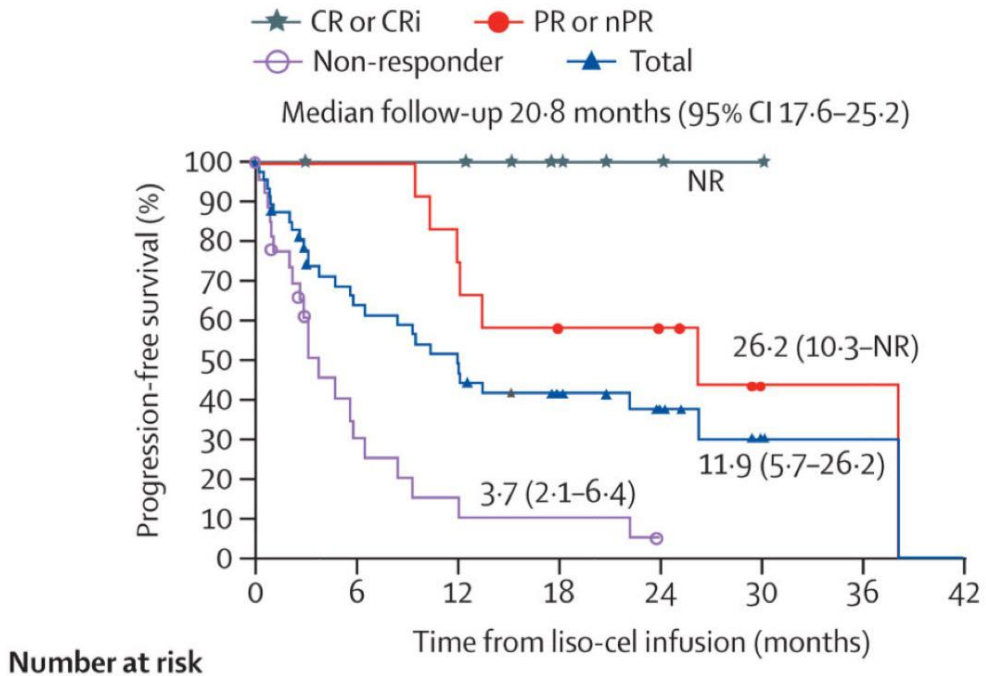
BGB-11417-101 (NCT04277637) Efficacy





Opat et.al., IwCLL 2025

Lisocabtagene maraleucel in CLL/SLL (TRANSCEND CLL 004):



Best overall response,	n (%)
CR	9 (18%)
PR	11 (24%)
SD	21 (43%)
PD	4 (8%)
Not evaluable	3 (6%0

DOR at 12mo – 74,7%

PFS at 12mo – 46,7%

OS at 12mo – 65,1%

Siddiqi ET AL., LANCET 2023

Clinical Practice Recommendations on the Role Of Allo SCT and CAR T-Cell Therapy in CLL

Empty Cell	**Treatment Setting***	**Clinical Scenario**	**Proposed Treatment**	**Recommendation**	**Percentage Voting in Support of Recommendation**
Responsive disease	Front-line consolidation	Objective response (CR/PR) to a covalent BTK inhibitor or a BCL2 inhibitor alone or in combination	Allo-HCT	Do not recommend	100%
			CAR T-cell therapy	Do not recommend	100%
	After 2nd line therapy	CLL relapse after covalent BTK inhibitor, but objective response (CR/PR) to a BCL2 inhibitor	Allo-HCT	Do not recommend	94%
			CAR T-cell therapy	Do not recommend	83%
	After 2nd line therapy	CLL relapse after a BCL2 inhibitor, but objective response (CR/PR) to a covalent BTK inhibitor	Allo-HCT	Do not recommend	94%
			CAR T-cell therapy	Do not recommend	94%
	After 3rd line therapy	CLL relapse after both a covalent BTK inhibitor and a BCL2 inhibitor and achieves at least a PR or better to a noncovalent BTK inhibitor†	Allo-HCT	Uncertain	56% in favor 44% against
		CLL relapse after both a covalent BTK inhibitor and a BCL2 inhibitor and responds to a noncovalent BTK inhibitor	CAR T-cell therapy	**Recommend**	78%
Nonresponsive disease	After 2nd line therapy	CLL relapse after a covalent BTK inhibitor and no response to a BCL2 inhibitor	Allo-HCT	Do not recommend	100%
			CAR T-cell therapy	**Recommend**	89%
	After 3rd line therapy	CLL relapse after a covalent BTK inhibitors but no response to a BCL2 inhibitor and a noncovalent BTK inhibitor‡	Allo-HCT	Do not recommend	100%
			CAR T-cell therapy	**Recommend**	89%
	CAR T-cell failure	CLL patients with R/R disease after CAR T-cell therapy§	Allo-HCT	**Recommend**‖	94%
	Allo-HCT failure	R/R CLL after allo-HCT	CAR T-cell therapy	**Recommend**	89%

Mohamed A. Kharfan-Dabaja, Ambuj Kumar, Javier Pinilla-Ibarz, Jennifer R. Brown, Mazyar Shadman, Farrukh T. Awan, Saad S. Kenderian, Tanya Siddiqi, Jeremy S. Abramson, Taha Al-Juhaishi, Danielle M. Brander, Catherine C. Coombs, Richard R. Furman, Nitin Jain, Nadia Khan, Nakhle S. Saba, Jennifer M. Collins, Amer Beitinjaneh, Deborah M. Stephens, Jennifer Woyach, Mehdi Hamadani – TRANSPLANTATION AND CELLULAR THERAPY 2025

Discontinued due to AE

Refractory to BTKi

Double exposed to both BTKi and BCL-2i

Double refractory

ACALABRUTINIB/ ZANUBRUTINIB

PIRTOBRUTINIB / BTK DEGRADORS

VENETOCLAX

SONROTOCLAX

CAR-T cells / Allo SCT

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Thank you