ALMA MATER STUDIORUM
UNIVERSITÀ DI BOLOGNA
DIPARTIMENTO DI
SCIENZE MEDICHE E CHIRURGICHE

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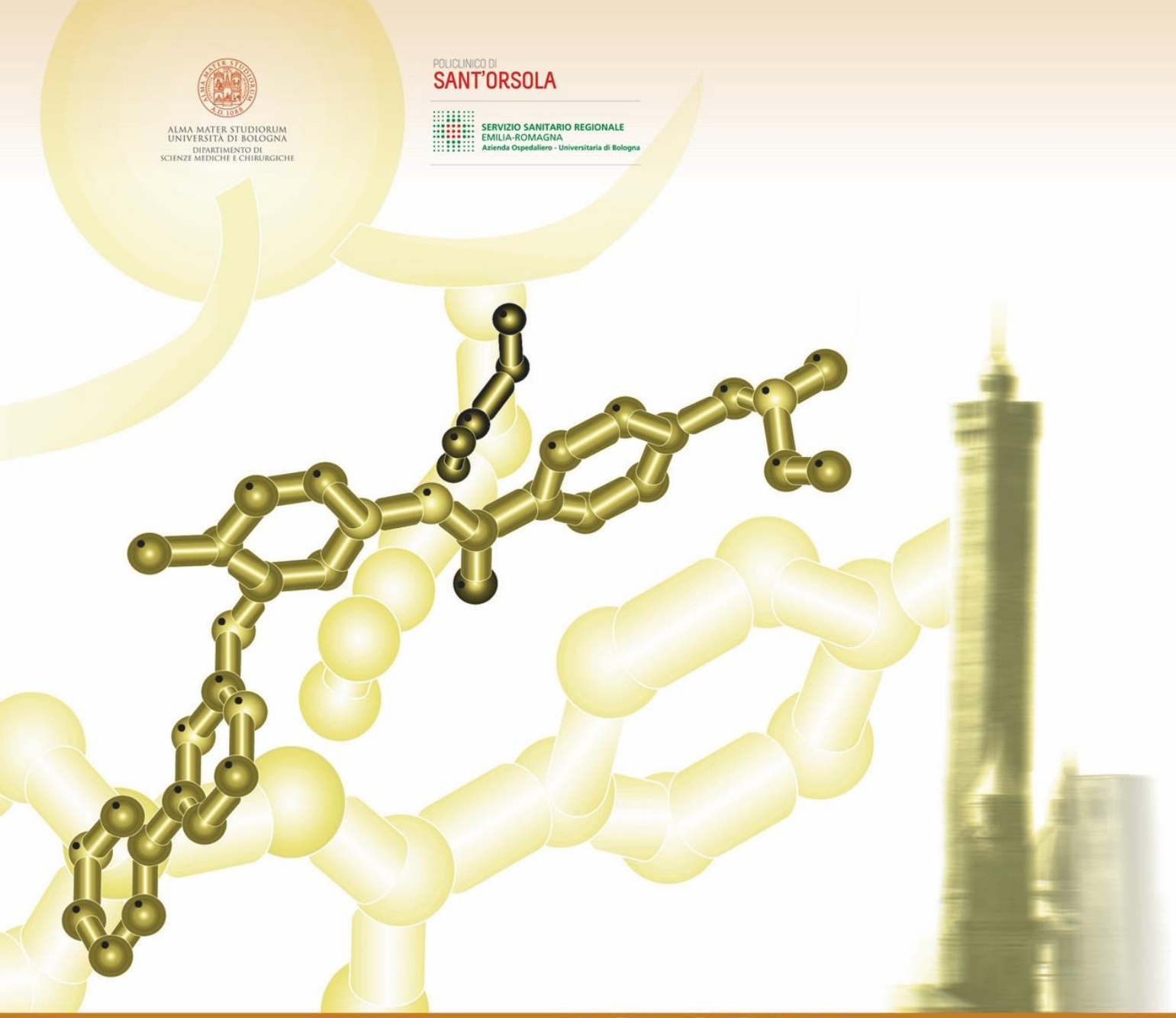

New Drugs in Hematology

President: Pier Luigi Zinzani
Co-President: Michele Cavo

Bologna,
Royal Hotel Carlton
January 15-17, 2024

BOLOGNA BOLOGNA, ROYAL HOTEL CARLTON

Disclosures of Wojciech Jurczak

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
Lilly	x					X	
Janssen	x					x	
Astra Zeneca	x					x	
BeiGene	x					x	

Pirtobrutinib in CLL/SLL

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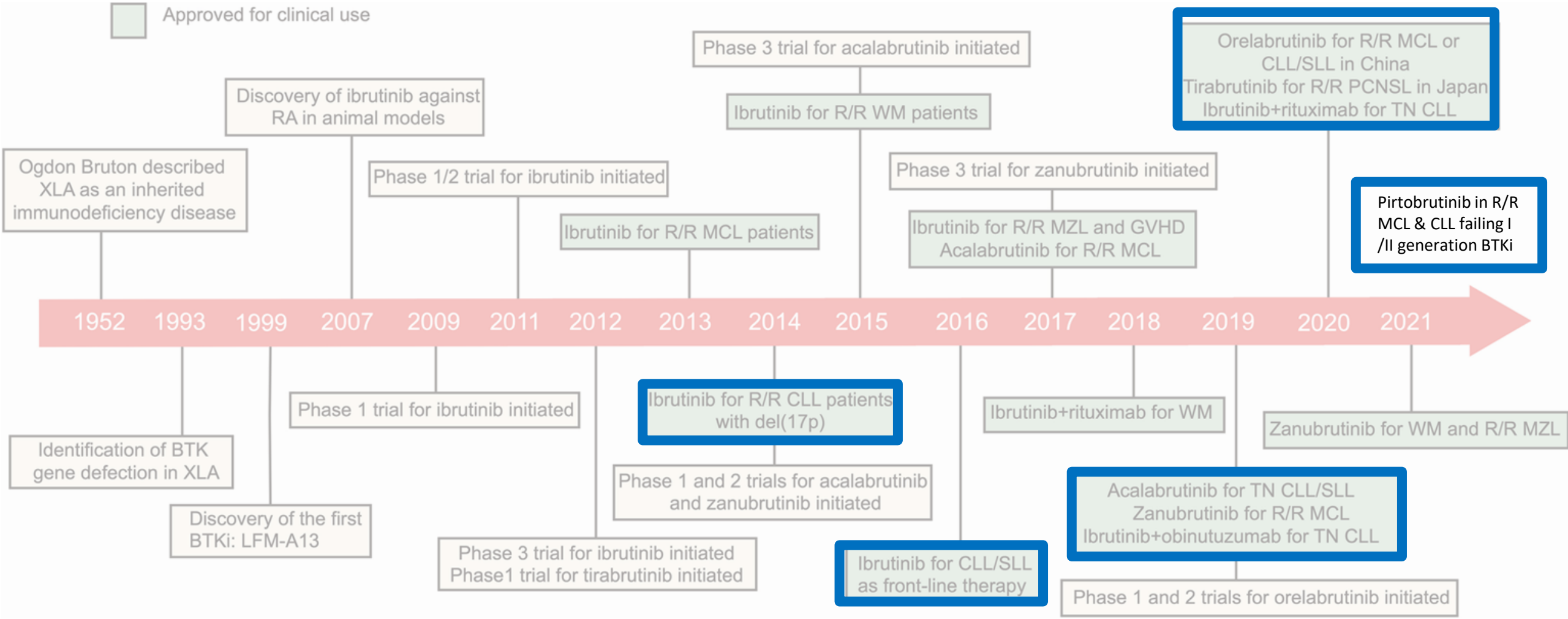
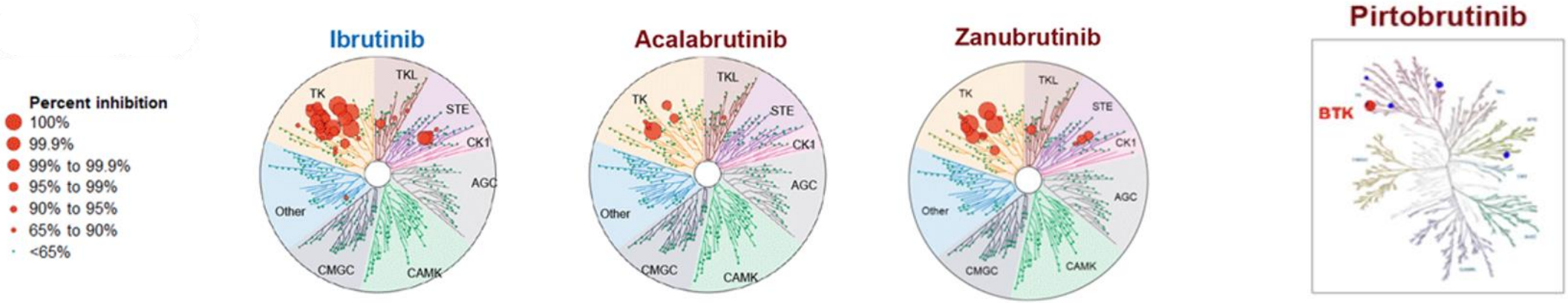

Approved for clinical use
1952
Ogdon Bruton described XLA as an inherited immunodeficiency disease
1993
Identification of BTK gene defection in XLA
1999
Discovery of the first BTKi: LFM-A13
2007
Discovery of ibrutinib against RA in animal models
2009
Phase 1 trial for ibrutinib initiated
2011
Phase 1/2 trial for ibrutinib initiated
2012
Phase 3 trial for ibrutinib initiated
Phase1 trial for tirabrutinib initiated
2013
Ibrutinib for R/R MCL patients
2014
Ibrutinib for R/R CLL patients with del(17p)
Phase 1 and 2 trials for acalabrutinib and zanubrutinib initiated
2015
Phase 3 trial for acalabrutinib initiated
Ibrutinib for R/R WM patients
2016
Ibrutinib for CLL/SLL as front-line therapy
2017
Phase 3 trial for zanubrutinib initiated
Ibrutinib for R/R MZL and GVHD
Acalabrutinib for R/R MCL
2018
Ibrutinib+rituximab for WM
2019
Acalabrutinib for TN CLL/SLL
Zanubrutinib for R/R MCL
Ibrutinib+obinutuzumab for TN CLL
Phase 1 and 2 trials for orelabrutinib initiated
2020
Orelabrutinib for R/R MCL or CLL/SLL in China
Tirabrutinib for R/R PCNSL in Japan
Ibrutinib+rituximab for TN CLL
2021
Pirtobrutinib in R/R MCL & CLL failing I /II generation BTKi
Zanubrutinib for WM and R/R MZL

BTKi - differences in potential off target effect

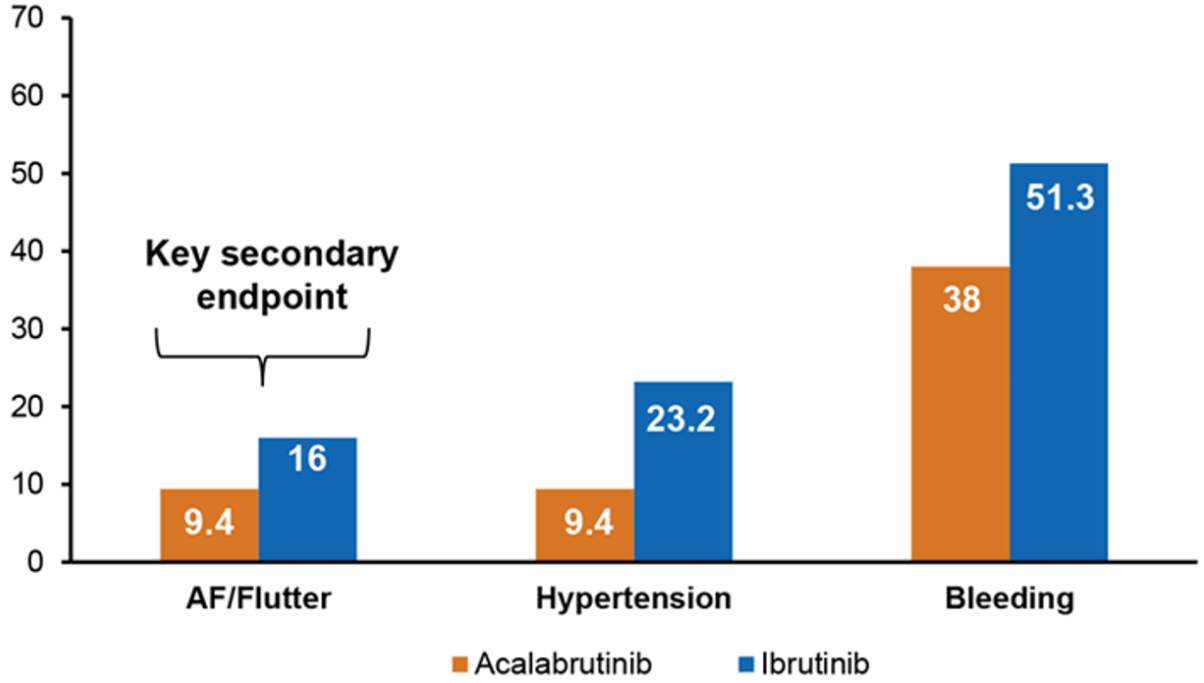


Less selective BTK inhibitors (eg, ibrutinib) have more off-target effects, which contribute to more toxicity compared with more selective agents[2]

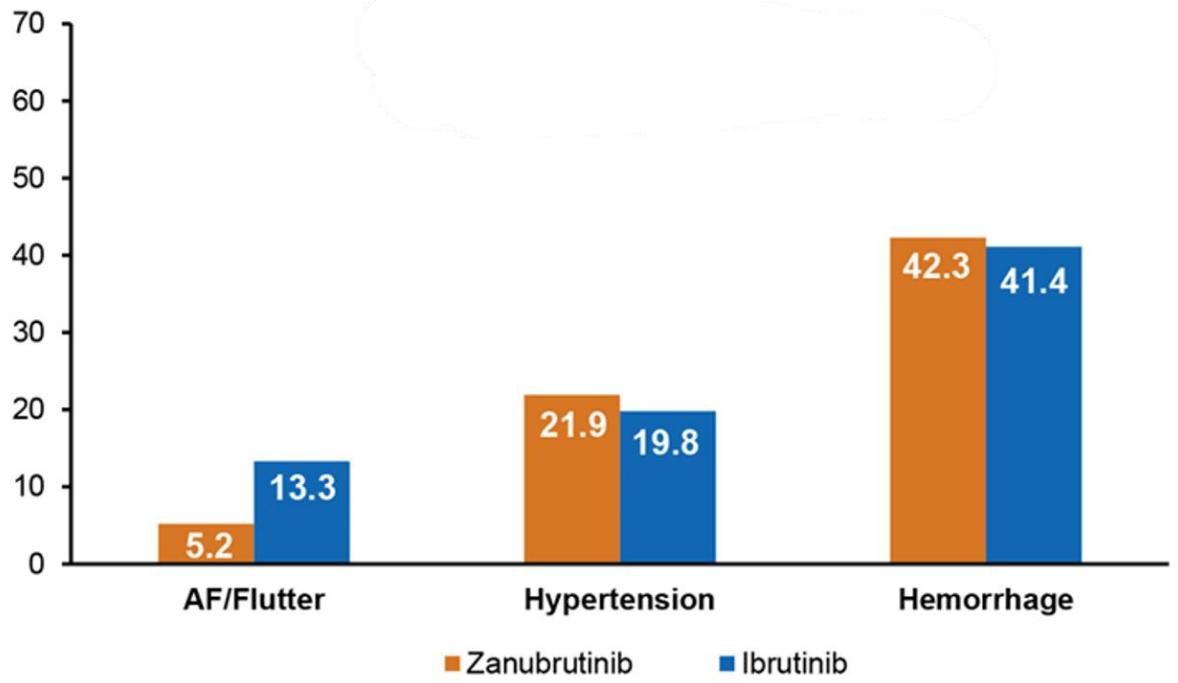
Potential off-target effects include:

BTK inhibitors - differences in „head to head“ comparisons

ELEVATE R/R



ALPINE

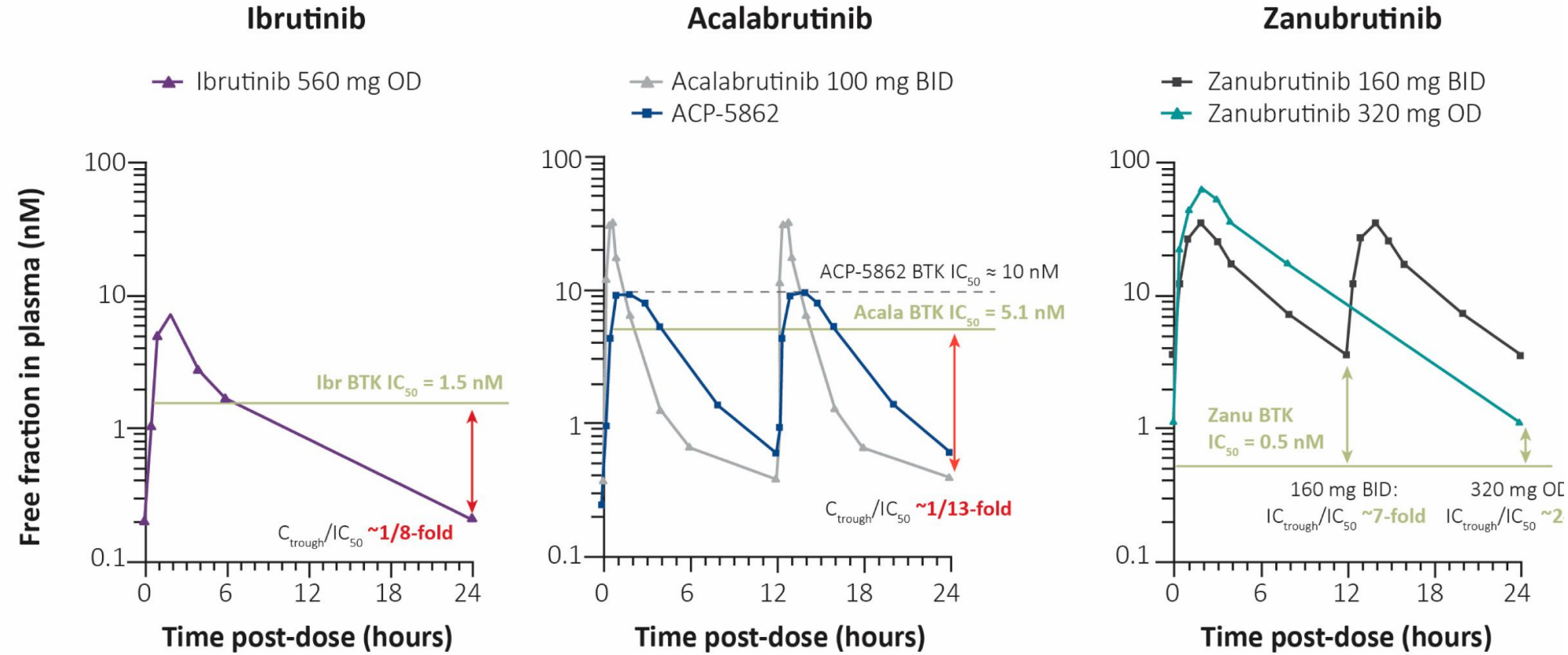


Byrd et al., JCO 2021, Brown et al., NEJM 2023

Pirtobrutinib Safety Profile

	All doses and patients (n=618)						
	Treatment-emergent AEs, (≥15%), %					Treatment-related AEs, %	
Adverse Event	Grade 1	Grade 2	Grade 3	Grade 4	Any Grade	Grades 3/4	Any Grade
Fatigue	13%	8%	1%	-	23%	1%	9%
Diarrhea	15%	4%	<1%	<1%	19%	<1%	8%
Neutropenia[a]	1%	2%	8%	6%	18%	8%	10%
Contusion	15%	2%	-	-	17%	-	12%
AEs of special interest[b]							
Bruising[c]	20%	2%	-	-	22%	-	15%
Rash[d]	9%	2%	<1%	-	11%	<1%	5%
Arthralgia	8%	3%	<1%	-	11%	-	3%
Hemorrhage[e]	5%	2%	1%[g]	-	8%	<1%	2%
Hypertension	1%	4%	2%	-	7%	<1%	2%
Atrial fibrillation/flutter[f]	-	1%	<1%	<1%	2%[h]	-	<1%

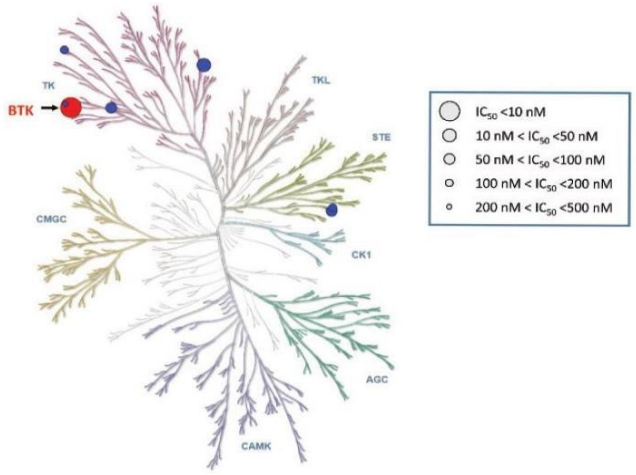
IC50 of the 1-st and 2-nd generation BTKi



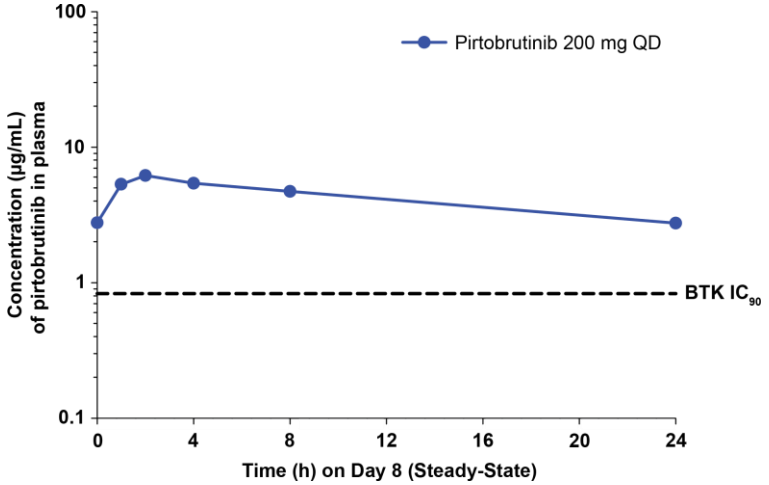
IC50 - Half maximal inhibitory concentration - indicates how much of a particular inhibitory substance (e.g. drug) is needed to inhibit, *in vitro*, a given biological process or biological component by 50%

Pirtobrutinib is a Highly Selective, Non-Covalent BTKi

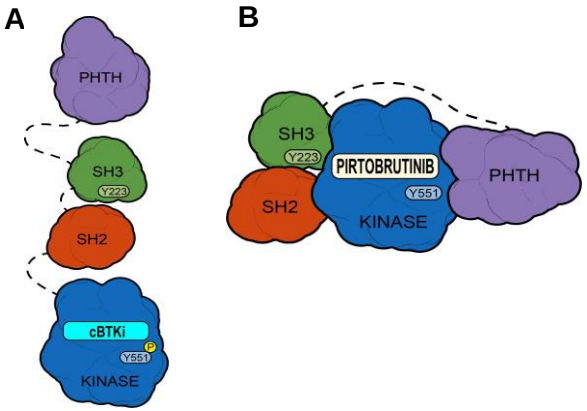
Highly selective for BTK[1-2]



Plasma exposures exceeded BTK IC_{90} throughout dosing interval



Pirtobrutinib may stabilize/maintain BTK in a closed inactive conformation



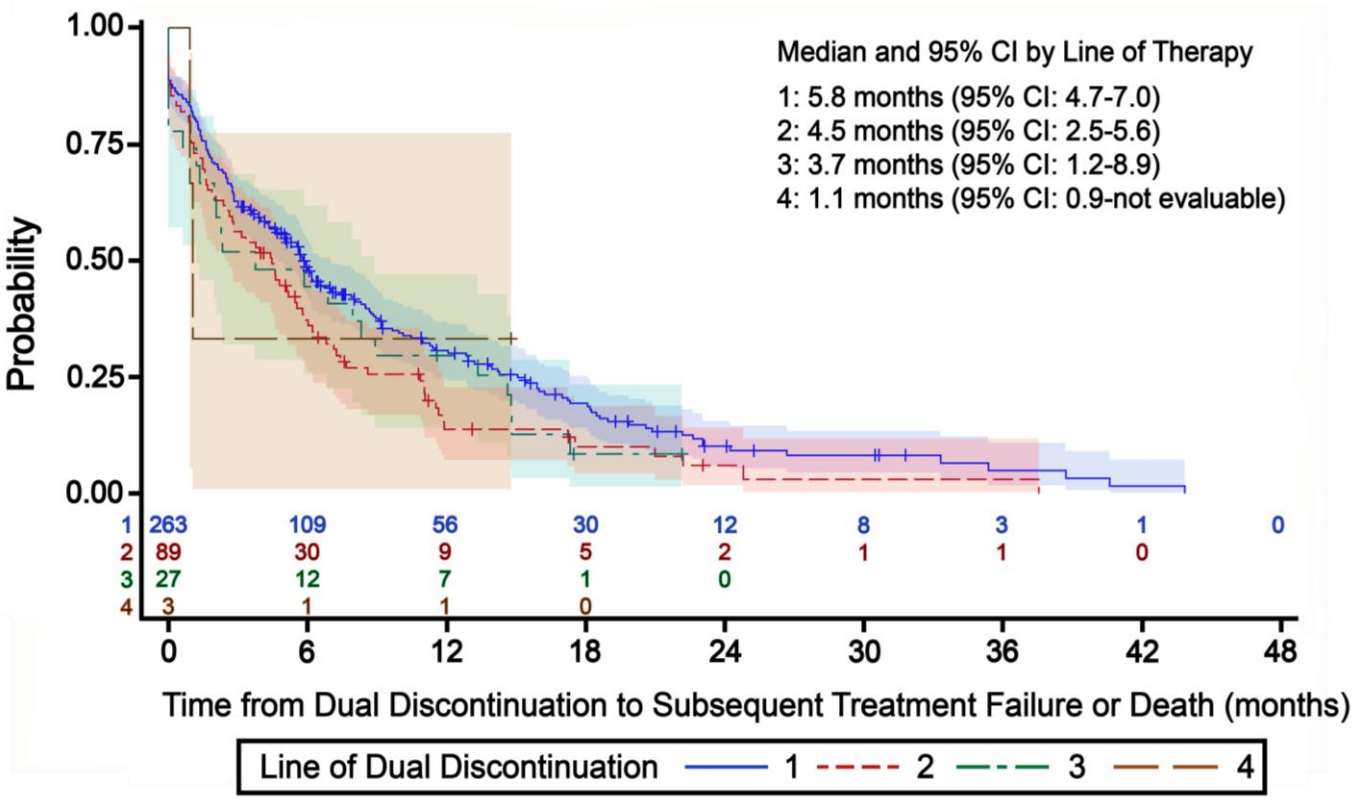
- EMA approved pirtobrutinib for the treatment of adult patients with relapsed or refractory mantle cell lymphoma (MCL) who have been previously treated with a Bruton's tyrosine kinase (BTK) inhibitor
- Inhibits **both Wild Type and C481-mutant BTK** with equal low nM potency[4]
- In contrast to cBTKi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

1. Mato AR et al, *Lancet* 2021;397:892-901, 2. Brandhuber BJ et al. *Clin Lymphoma Myeloma Leuk* 2018;18:S216, 3. Jaypirca [Prescribing Information]. Indianapolis, IN: Eli Lilly and Company, 2023, 4. Gomez EB et al. *Blood* 2023. (Ahead of print)

Limited Therapeutic Options after cBTKi in CLL/SLL

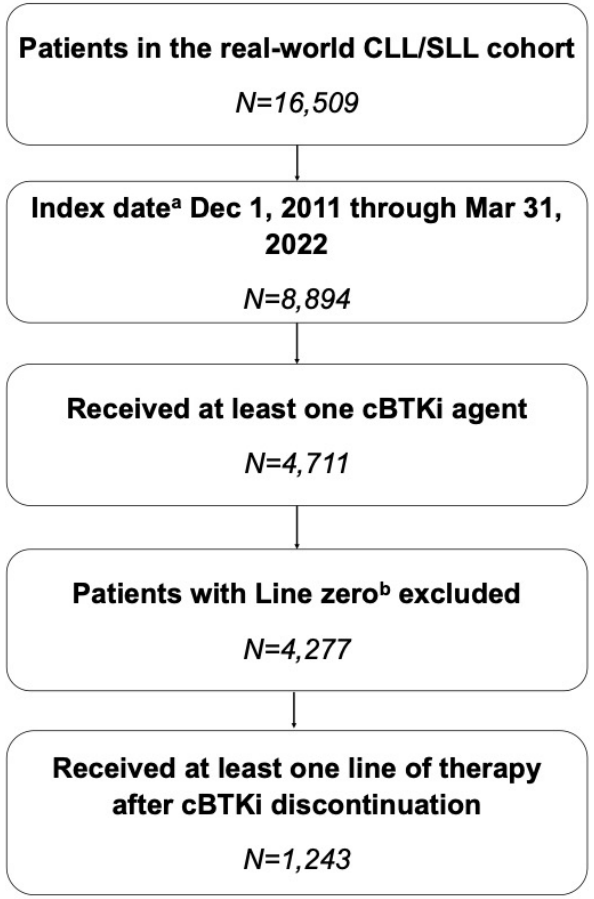
- **The vast majority of patients discontinue cBTKi for either progression or intolerance[1-3]**
- Limited prospective data and treatment options in the post-cBTKi setting currently exist
- **Venetoclax** (BCL2i) based regimens have often been a next treatment option after cBTKi for patients with CLL/SLL
- **An increasing number of patients who have discontinued cBTKi have also discontinued venetoclax**
  - Outcomes are poor and there is a need for additional treatment options[4]

Time from cBTKi/BCL2i Discontinuation to Subsequent Treatment Failure or Death[4]



[1]Woyach et al. *J Clin Oncol*. 2017; 35:1437–43. [2]Barr et al. *Blood Adv*. 2022; 6:3440-50. [3]Byrd et al. Ash 2022. [4]Mato et al. *Clinical Lymphoma Myeloma and Leukemia. 2022;* S2152-2650(22)01691-3.

Real-World Use and Outcomes of Therapies after cBTKi

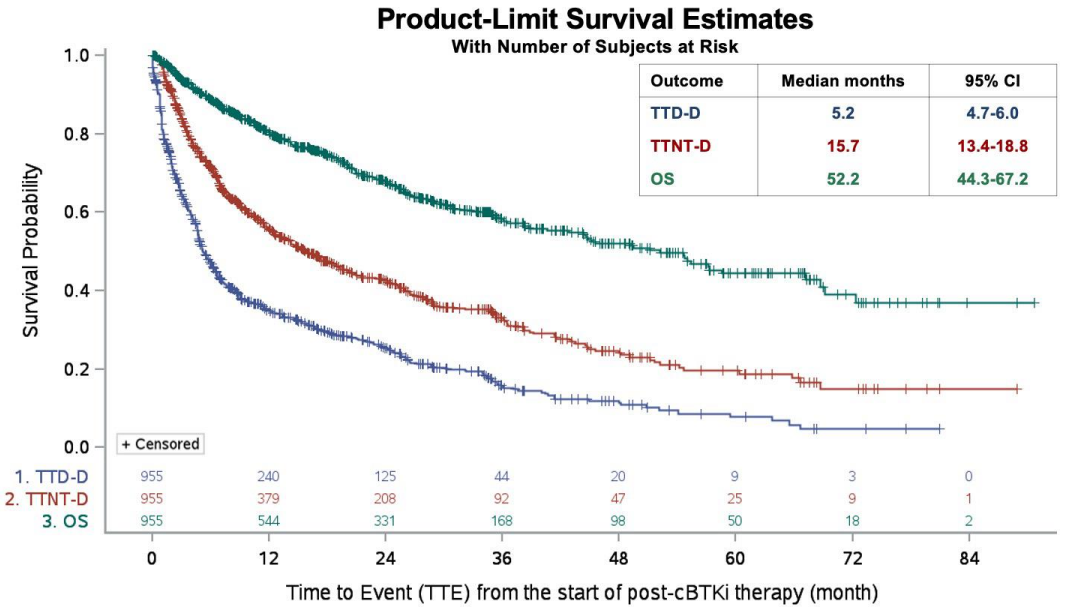


Characteristic[a]	Overall post-cBTKi *N=1243*	Non ven-containing post-cBTKi *N=955*	All ven-containing post-cBTKi *N=288*
Age, median (range)	72 (37, 86)	72 (37, 85)	71 (40, 86)
Male sex, n (%)	793 (64)	600 (63)	193 (67)
Race[c], n/N (%)			
Asian	18/1170 (2)	10/902 (1)	8/268 (3)
Black or African American	131/1170 (11)	104/902 (12)	27/268 (10)
White	924/1170 (79)	708/902 (78)	216/268 (81)
Other	97/1170 (8)	80/902 (9)	17/268 (6)
Received post-cBTKi treatment in community setting, n (%)	1026 (83)	782 (82)	244 (85)
ECOG PS 0-1[c] (%)	844/988 (85)	634/753 (84)	210/235 (89)
Disease subtype, n (%)			
CLL	986 (79)	757 (79)	229 (79)
CLL/SLL	170 (14)	136 (14)	34 (12)
SLL	87 (7)	62 (7)	25 (9)
Deletion 17p present[c], n/N (%)	234/1080 (22)	157/813 (19)	77/267 (29)
IgHV unmutated[c], n/N (%)	388/624 (62)	291/474 (61)	97/150 (65)
Rai stage at initial diagnosis[c], n/N (%)			
0	271/791 (34)	209/606 (34)	62/185 (34)
I	183/791 (23)	137/606 (23)	46/185 (25)
II	105/791 (13)	80/606 (13)	25/185 (14)
III	86/791 (11)	64/606 (11)	22/185 (12)
IV	146/791 (18)	116/606 (19)	30/185 (16)
Line of therapy in which the first post-cBTKi treatment was received, n (%)			
2	754 (61)	590 (62)	164 (57)
3	351 (28)	256 (27)	95 (33)
4	87 (7)	65 (7)	22 (8)
5 or greater	51 (4)	44 (5)	7 (2)
Follow-up time from start of immediate post-cBTKi treatment to last confirmed activity or death (months), median (range)	15.5 (0, 90.7)	15.0 (0, 90.7)	17.3 (0.1, 77.0)

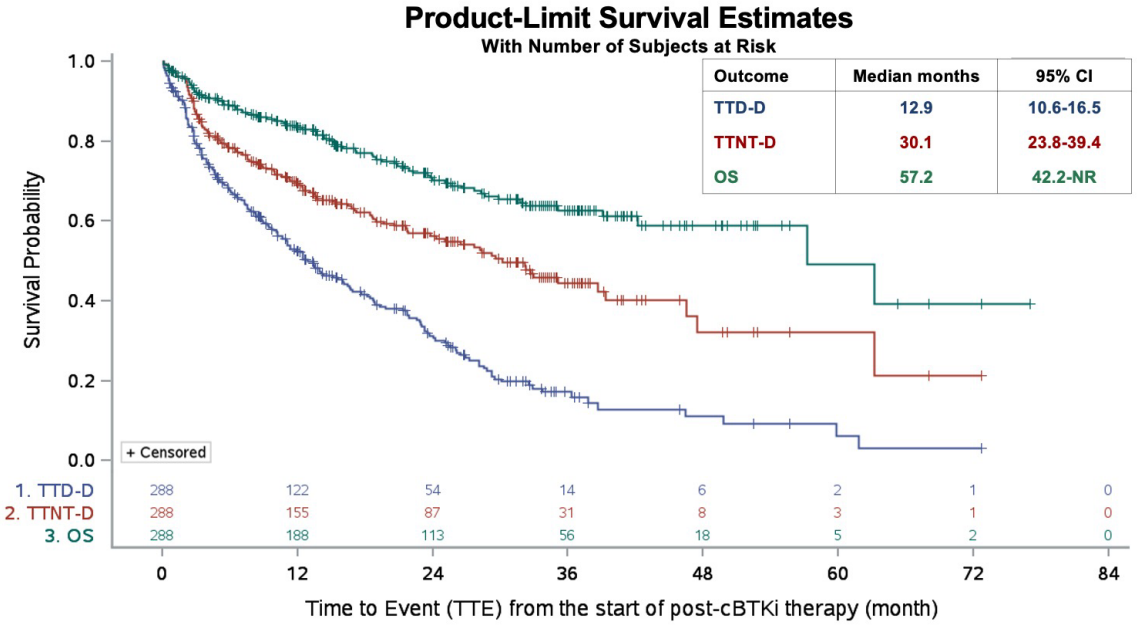
Real-World Use and Outcomes of Therapies after cBTKi

- **Time to treatment discontinuation or death (TTD-D):**
- **Time to next treatment or death (TTNT-D):**
- **Overall survival (OS):**

Clinical outcomes in non venetoclax-containing post-cBTKi group



Clinical outcomes in venetoclax-containing post-cBTKi group



Jain, et al.; ASH 2023

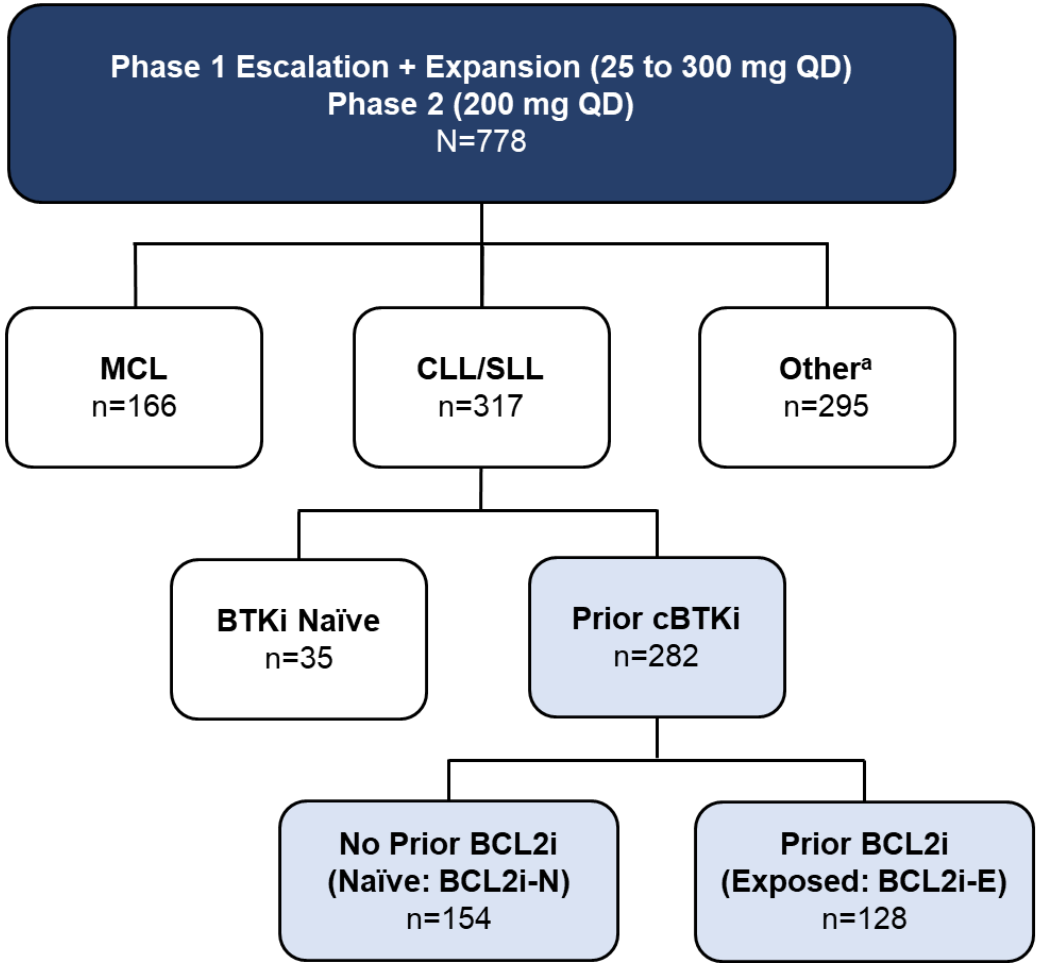
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Pirtobrutinib after a Covalent BTK Inhibitor in Chronic Lymphocytic Leukemia

A.R. Mato, J.A. Woyach, J.R. Brown, P. Ghia, K. Patel, T.A. Eyre, T. Munir, E. Lech-Maranda, N. Lamanna, C.S. Tam, N.N. Shah, C.C. Coombs, C.S. Ujjani, B. Fakhri, C.Y. Cheah, M.R. Patel, A.J. Alencar, J.B. Cohen, J.N. Gerson, I.W. Flinn, S. Ma, D. Jagadeesh, J.M. Rhodes, F. Hernandez-Ilizaliturri, P.L. Zinzani, J.F. Seymour, M. Balbas, B. Nair, P. Abada, C. Wang, A.S. Ruppert, D. Wang, D.E. Tsai, W.G. Wierda, and W. Jurczak

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



Phase 1 3+3 design

- 28-day cycles
- Intra-patient dose escalation allowed
- Cohort expansion permitted at doses deemed safe

Eligibility

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

Key endpoints

- Safety/tolerability
- Determine MTD and RP2D
- Pharmacokinetics
- Efficacy (ORR according to iwCLL 2018 criteria, DoR, PFS, and OS)

Data cutoff of 05 May 2023 (NCT03740529); [a]Other includes DLBCL, WM, FL, MZL, Richter transformation, B-PLL, Hairy Cell Leukemia, PCNSL, and other transformation.

Baseline characteristics CLL/SLL Pts who receive prior cBTKi

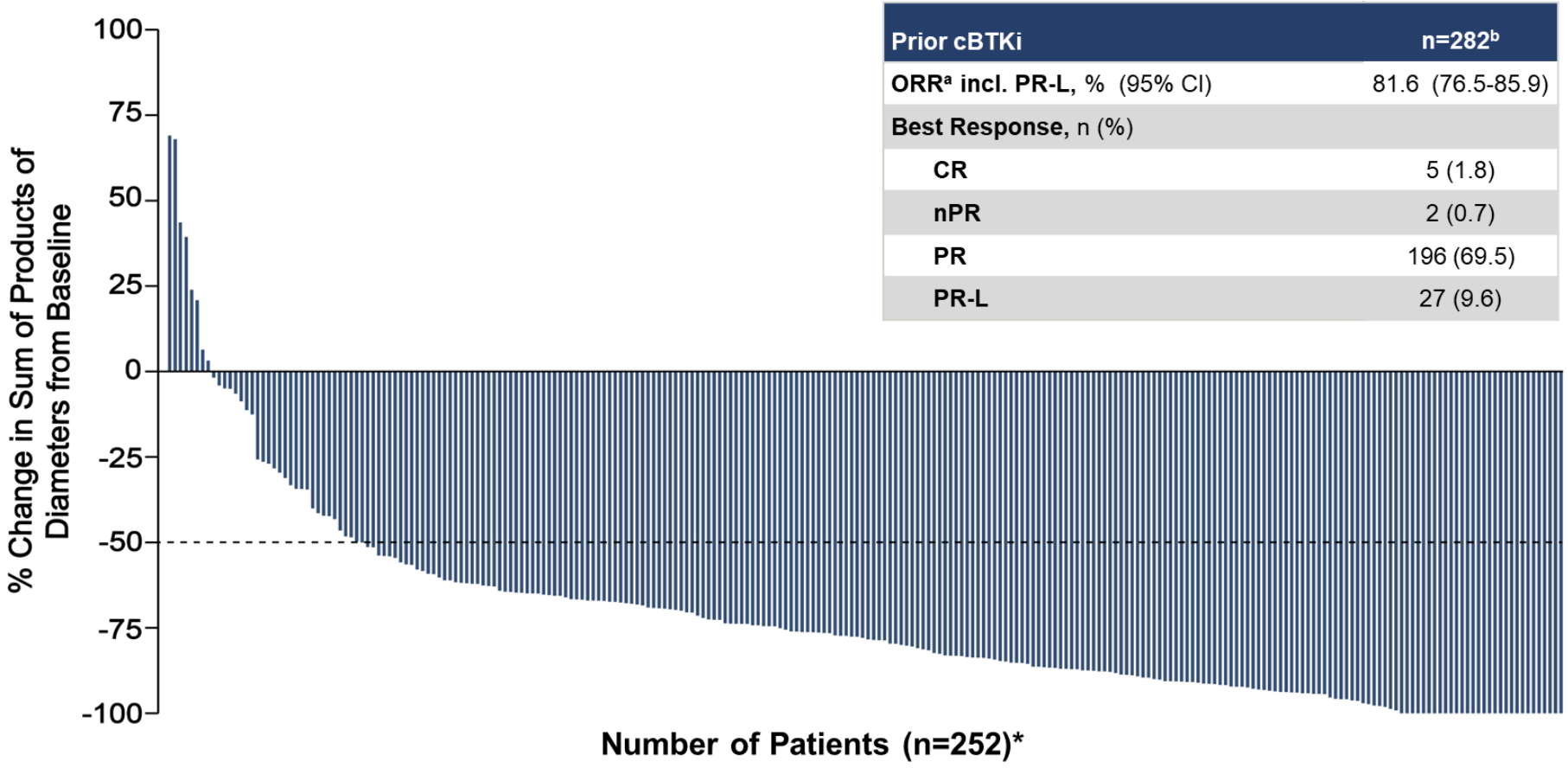
Characteristics	Prior cBTKi (n=282)	BCL2i-N (n=154)	BCL2i-E (n=128)
Median age, years (range)	69 (36-88)	69 (36-87)	68 (41-88)
Male, n (%)	192 (68)	106 (69)	86 (67)
Rai staging, n (%)			
0-II	147 (52)	94 (61)	53 (41)
III-IV	120 (43)	58 (38)	62 (48)
Missing	15 (5)	2 (1)	13 (10)
Bulky Lymphadenopathy ≥5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

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

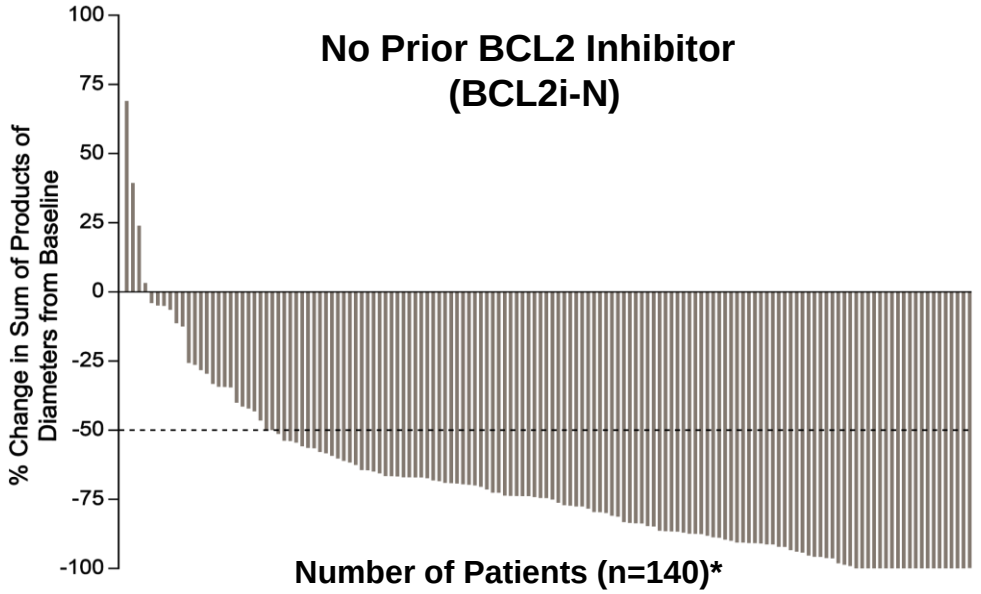
Baseline Molecular Characteristics[b]	Prior cBTKi (n=282)	BCL2i-N (n=154)	BCL2i-E (n=128)
Mutation status, n/n available (%)			
BCL2 mutated	19/246 (8)	0/133 (0)	19/113 (17)
BTK C481-mutant	96/245 (39)	57/138 (41)	39/107 (36)
PLCG2-mutant	18/245 (7)	10/138 (7)	8/107 (8)
High Risk Molecular Features,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

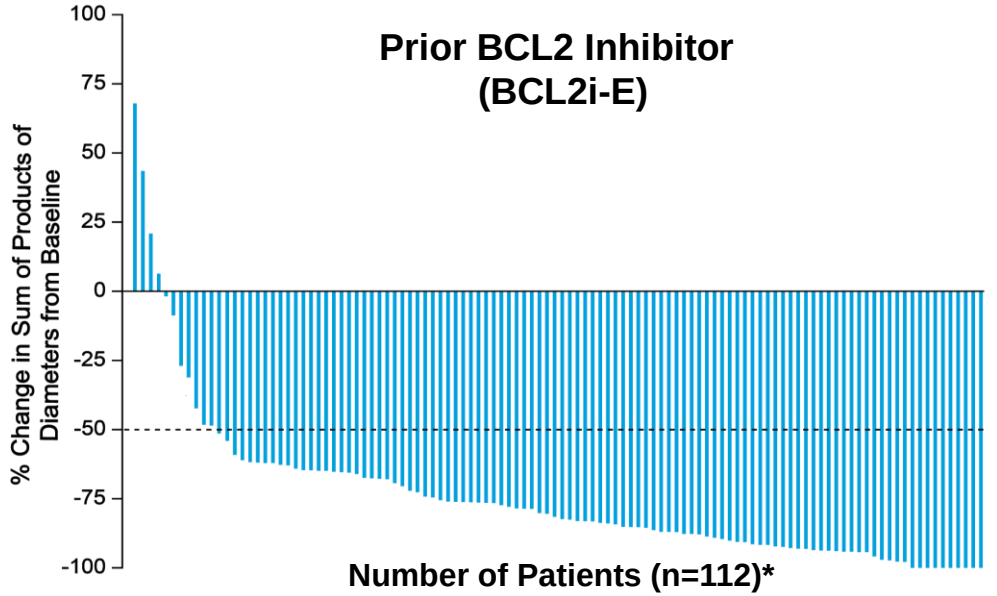
Pirtobrutinib Efficacy in CLL/SLL Pts who Received Prior cBTKi

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



Pirtobrutinib Efficacy in Pts with or wihout Prior BCL2i



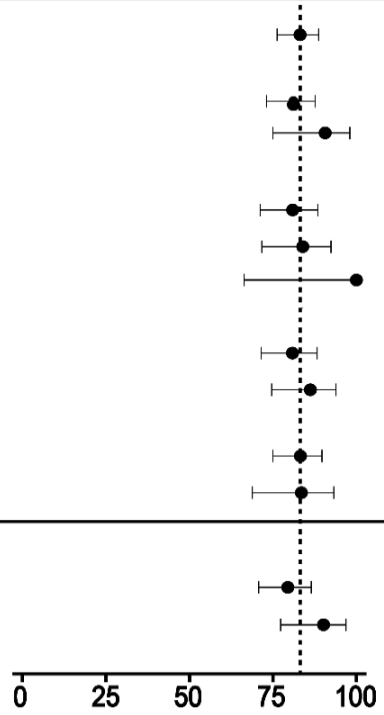


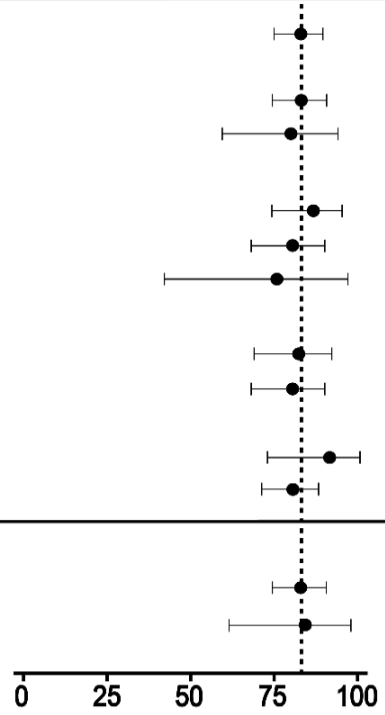
BCL2i-N	(n=154)[b]
ORR[a] incl. PR-L, % (95% CI)	83.1 (76.2-88.7)
Best Response, n (%)	
CR	5 (3.2)
nPR	2 (1.3)
PR	108 (70.1)
PR-L	13 (8.4)

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)

Pirtobrutinib ORR in Pts with or wihout Prior BCL2i

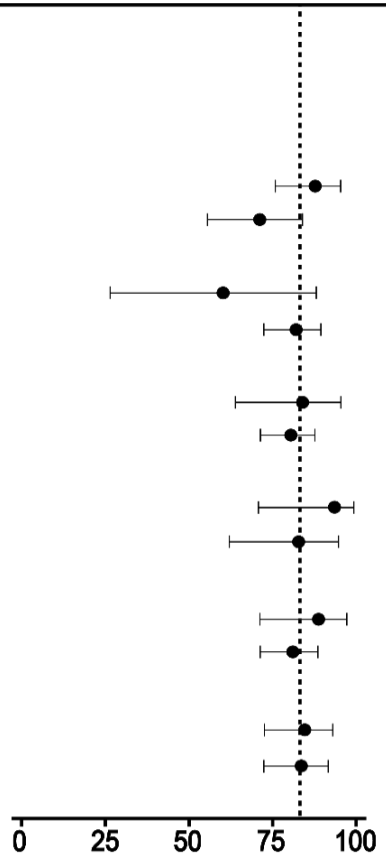
	BCL2i-N		BCL2i-E	
	Responders/Patients	ORR[a] % (95% CI)	Responders/Patients	ORR[a] % (95% CI)
All Patients with Prior cBTKi	128/154	83.1 (76.2 - 88.7)	102/128	79.7 (71.7 - 86.3)
Age (years)				
< 75	99/122	81.1 (73.1 - 87.7)	82/102	80.4 (71.4 - 87.6)
≥ 75	29/32	90.6 (75.0 - 98.0)	20/26	76.9 (56.4 - 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)
Reason for any Prior BTKi Discontinuation[b]				
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 - 94.6)

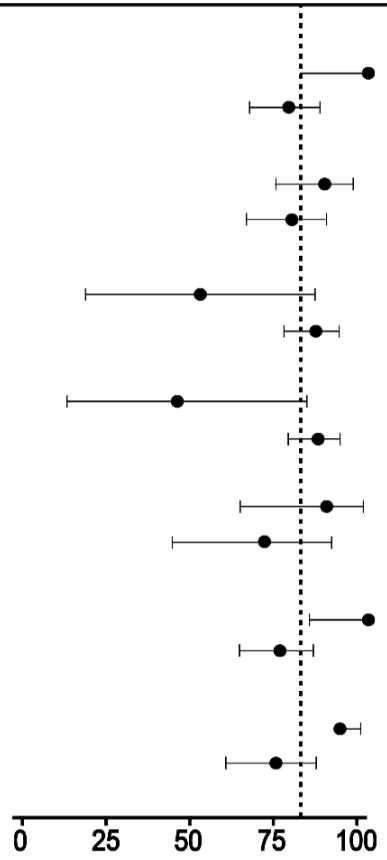




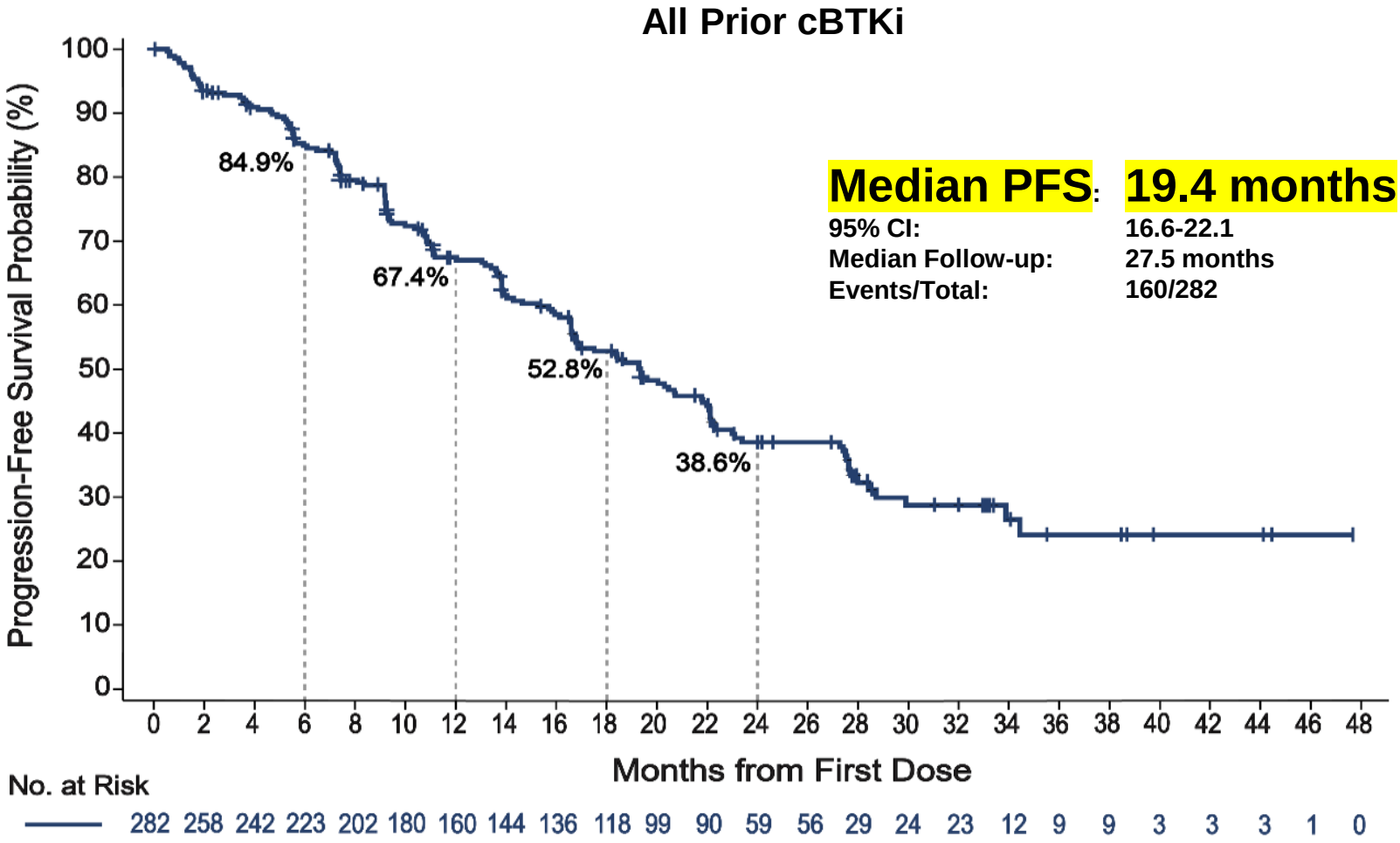
Pirtobrutinib ORR in Pts with or wihout Prior BCL2i

	BCL2i-N		BCL2i-E	
	Responders/Patients	ORR[a] % (95% CI)	Responders/Patients	ORR[a] % (95% CI)
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 - 97.6)
No	55/66	83.3 (72.1 - 91.4)	34/47	72.3 (57.4 - 84.4)



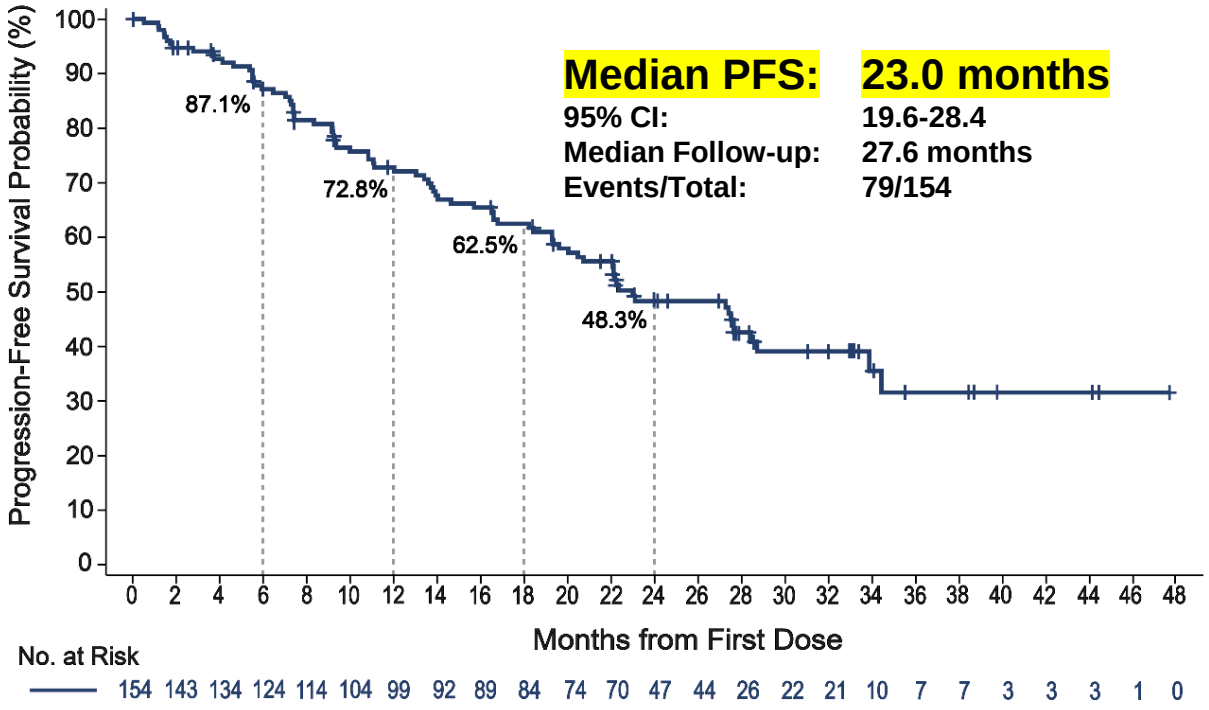


Pirtobrutinib Progression-Free Survival in Pts with Prior cBTKi



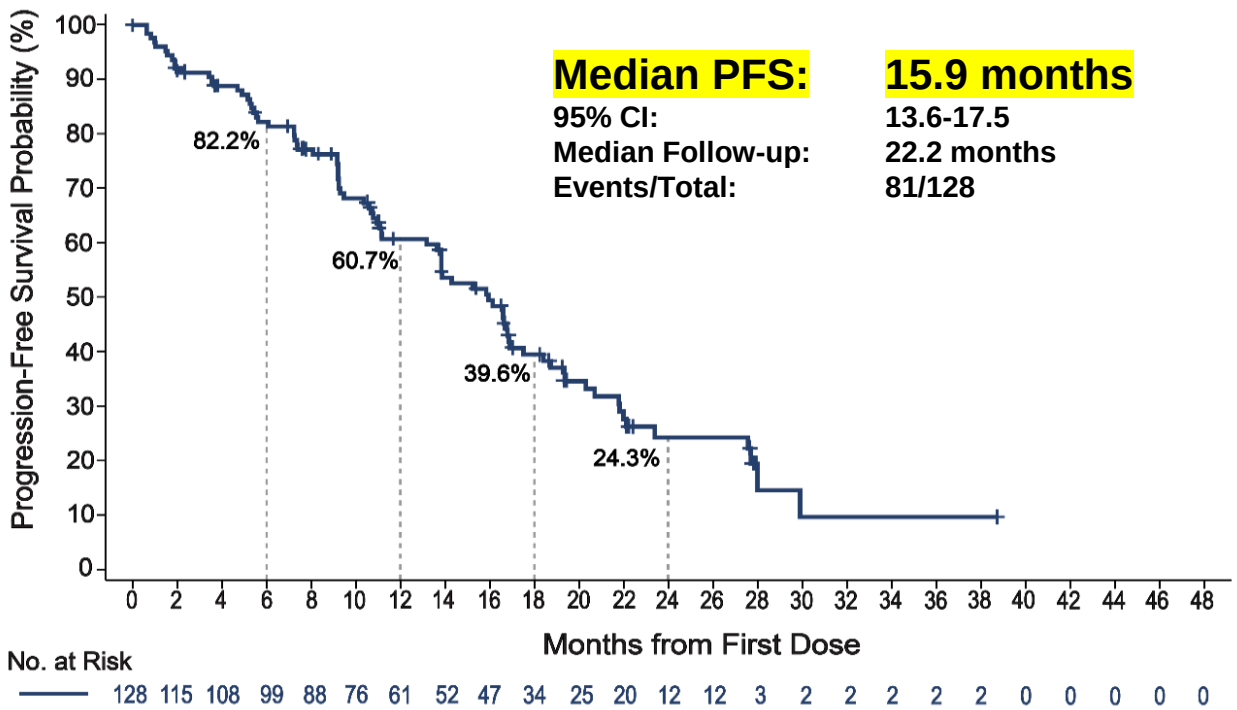
PFS in Pts with Prior cBTKi, with or without Prior BCL2i

BCL2i-N



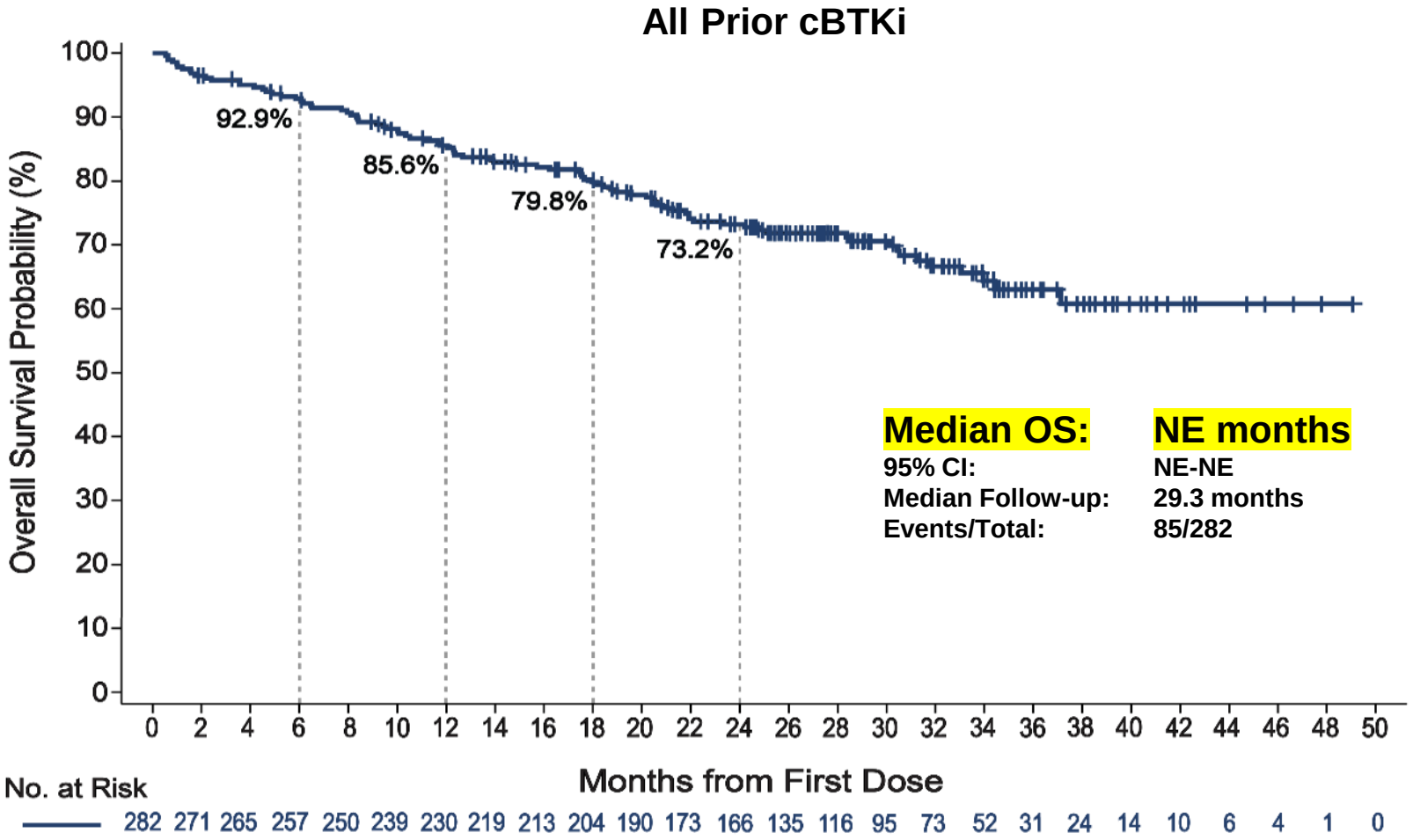
Median PFS: 23.0 months
95% CI: 19.6-28.4
Median Follow-up: 27.6 months
Events/Total: 79/154

BCL2i-E



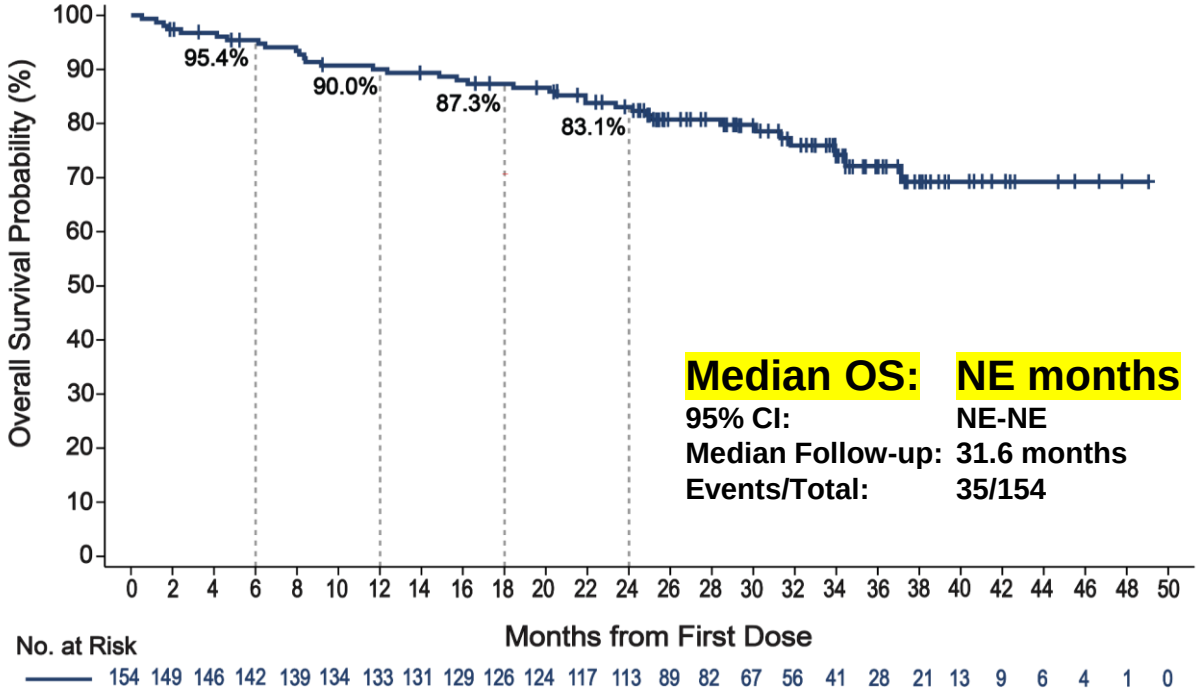
Median PFS: 15.9 months
95% CI: 13.6-17.5
Median Follow-up: 22.2 months
Events/Total: 81/128

Pirtobrutinib Overall Survival in Patients with Prior cBTKi



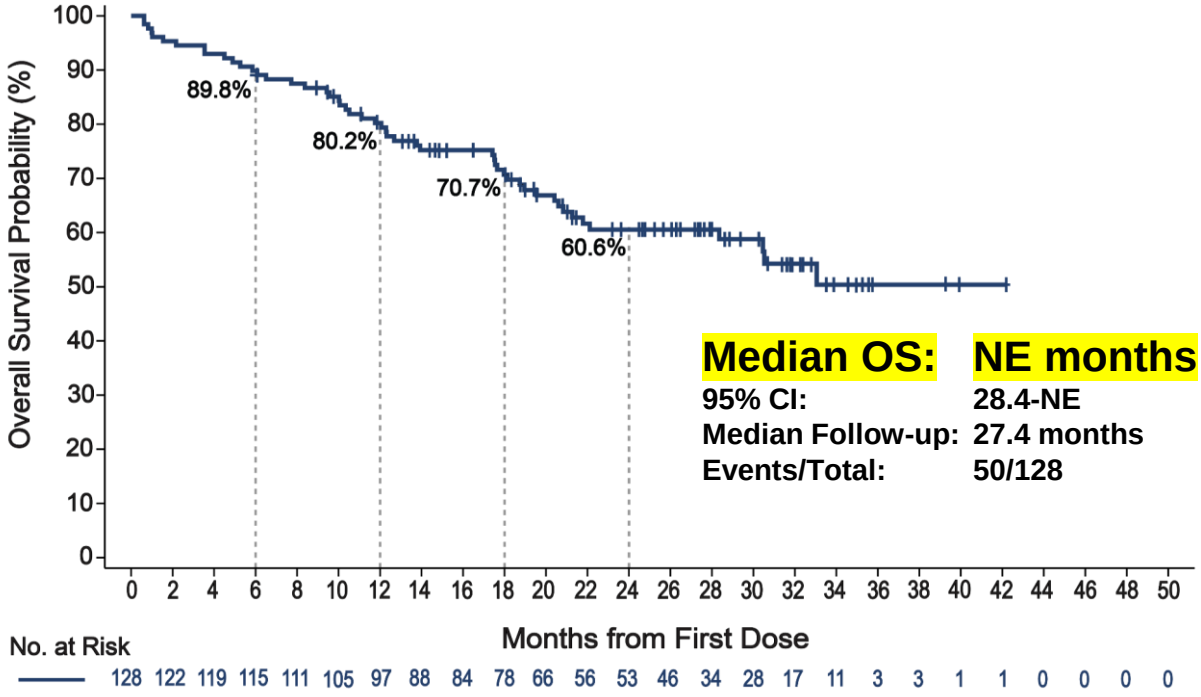
OS in Pts with Prior cBTKi, with or without Prior BCL2i

BCL2i-N



Median OS: NE months
95% CI: NE-NE
Median Follow-up: 31.6 months
Events/Total: 35/154

BCL2i-E



Median OS: NE months
95% CI: 28.4-NE
Median Follow-up: 27.4 months
Events/Total: 50/128

Pirtobrutinib Safety Profile in Prior cBTKi Patients

	Treatment-Emergent AEs in Patients with CLL/SLL (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 BTKi), 24.3 months (BCL2i-N) and 15.3 months (BCL2i-E)

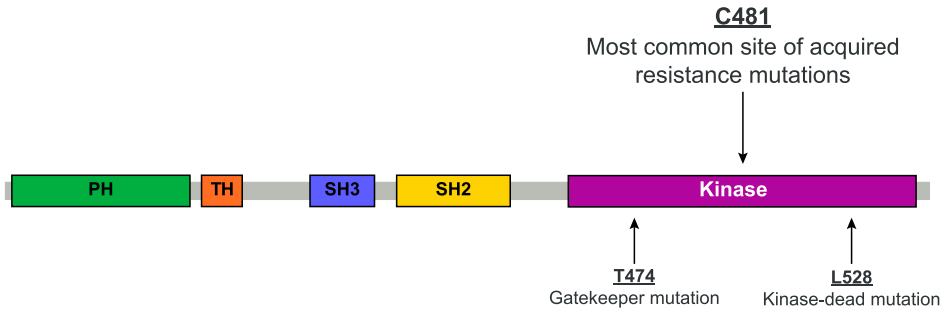
11 (3.9%; 9 BCL2i-N, 2 BCL2i-E) patients had TRAEs leading to pirtobrutinib dose reduction; 7 (2.5%; 4 BCL2i-N, 3 BCL2i-E) had TRAEs leading to pirtobrutinib discontinuation

Phase 1/2 BRUIN Study: Conclusions for CLL

- With median follow-up of 30 months, **pirtobrutinib demonstrates clinically meaningful and durable efficacy in heavily pretreated patients with CLL/SLL who received prior covalent BTK inhibitor**
  - ORR including PR-L was ~80% regardless of prior BCL2 inhibitor exposure
  - Median PFS was 19.4 months overall, with 23.0 months for BCL2i-N patients and 15.9 months for BCL2i-E patients
- Pirtobrutinib was **well-tolerated** with low-rates of discontinuation due to drug-related toxicity among both BCL2i-N and BCL2i-E patients
- On December 1, 2023, the **FDA granted accelerated approval** to pirtobrutinib for adults with CLL/SLL who have received at least two prior lines of therapy, including a BTK inhibitor and a BCL2 inhibitor

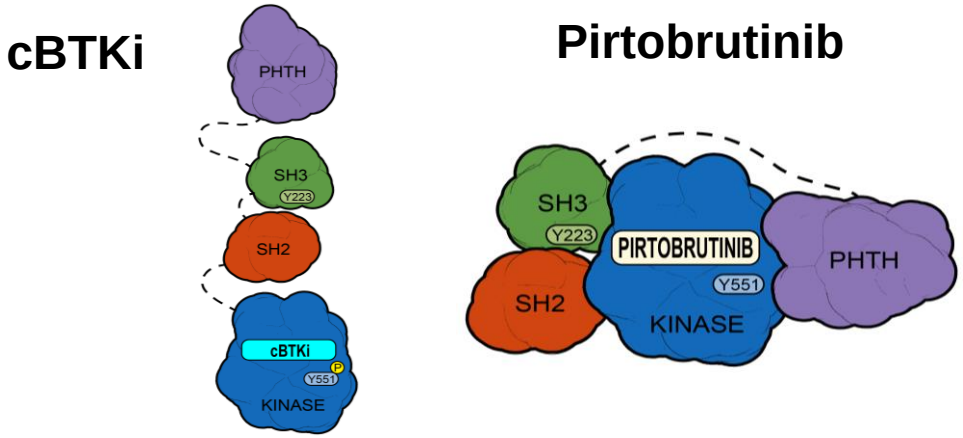
Pirtobrutinib Non-covalent Binding Inhibits both WT and C481-mutated *BTK*

BTK sites with known cBTKi resistance mutations



- The majority of patients discontinue covalent BTK inhibitors (cBTKi) due to intolerance or progression[1,2,3]
- BTK C481 substitutions are the most common resistance mechanism to cBTKi[4,5,6]
- Acquired mutations have been identified in a limited number of patients treated with pirtobrutinib[7,8]

Pirtobrutinib may stabilize BTK in a closed inactive conformation[9]

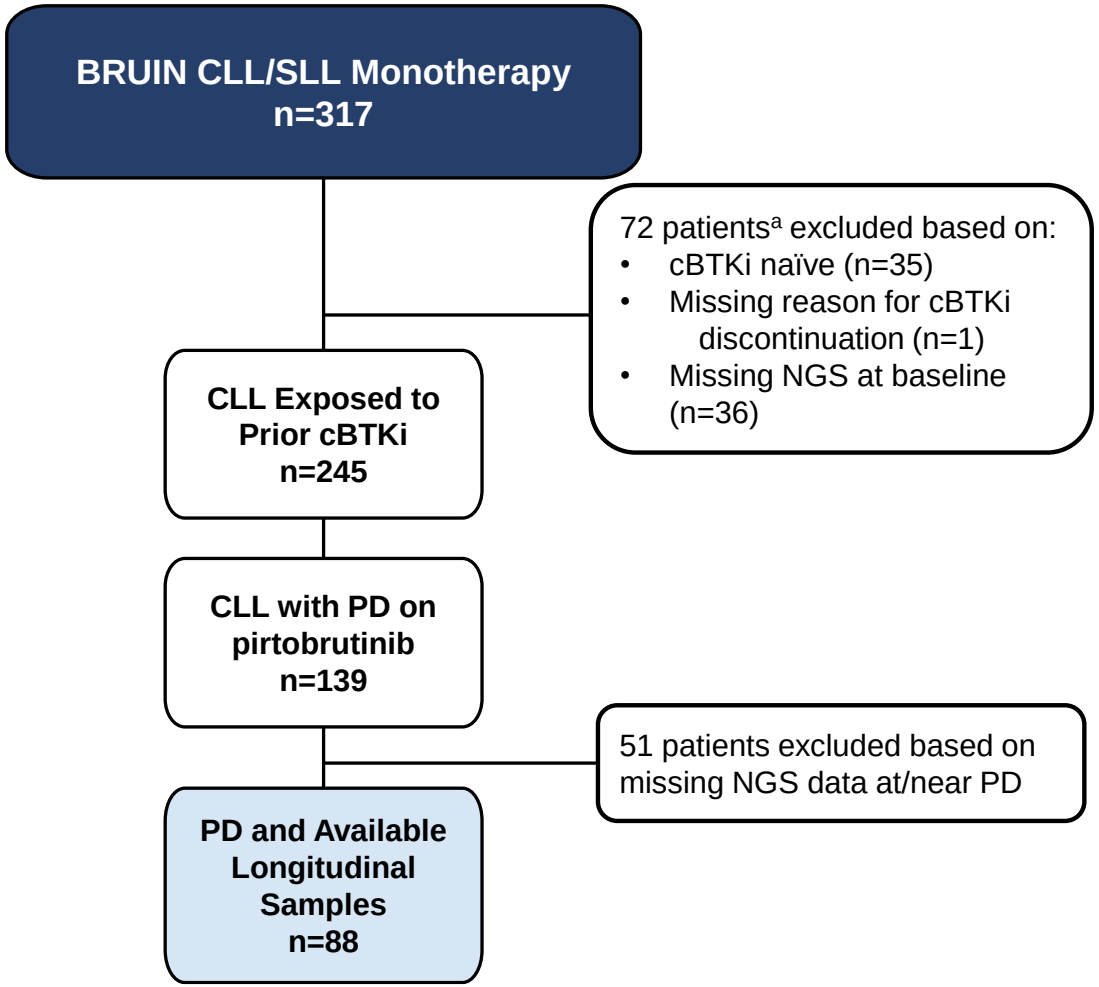


Inactive conformation of BTK by pirtobrutinib:

- blocks access to upstream kinases and phosphorylation of Y551
- inhibits both WT and C481-mutant BTK with equal low nM potency[7,9]
- may inhibit kinase-independent BTK signaling[9]

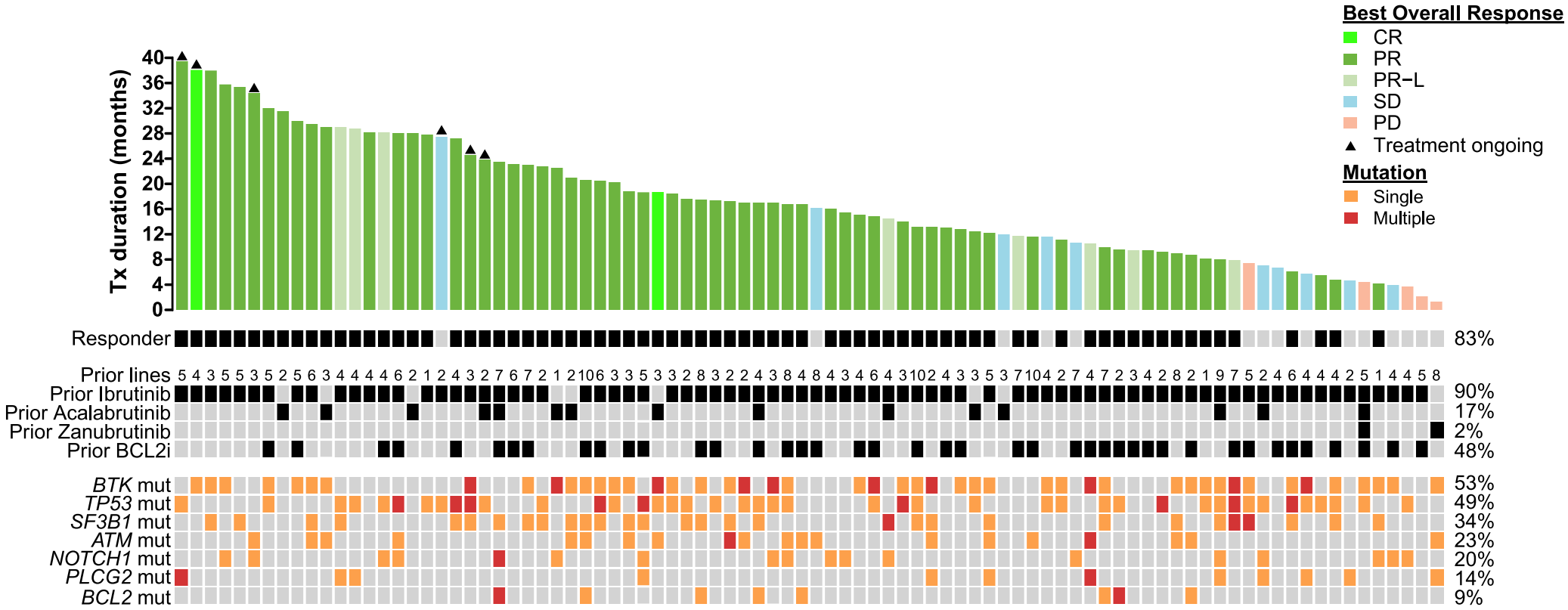
[1]Woyach et al. *JCO*. 2017. [2]Barr et al. *Blood Adv*. 2022. [3]Byrd et al. ASH. 2022. [4]Estupinan et al. Leukemia. 2021. [5]Handunnetti et al. ASH. 2019. [6]Blombery et al. Blood Advances. 2022. [7]Wang et al. NEJM. 2022 [8]Naeem et al. Blood Advances. 2023. [9]Gomez et al. Blood.2023.

Genomic Evolution and Resistance during Pirtobrutinib Therapy



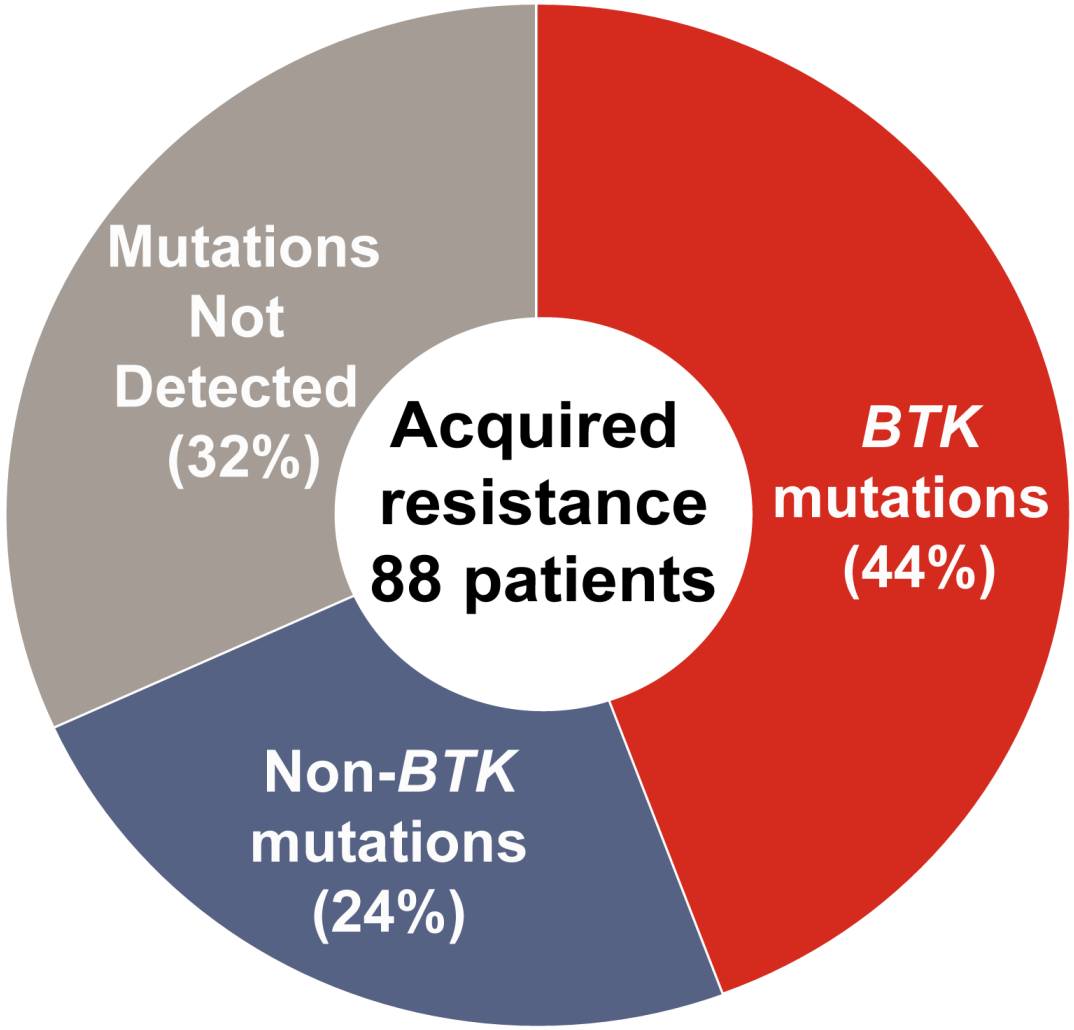
- Next-generation sequencing (NGS) of paired baseline and progression PBMC samples from 88 cBTKi pre-treated CLL patients who progressed on pirtobrutinib
- Targeted NGS (5% VAF limit of detection [LoD]) gene list (all exons, 74 genes):
  - ***BTK***, ***PLCG2***, ***TP53***, *ABL1, APC, ARID1A, ATM, 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

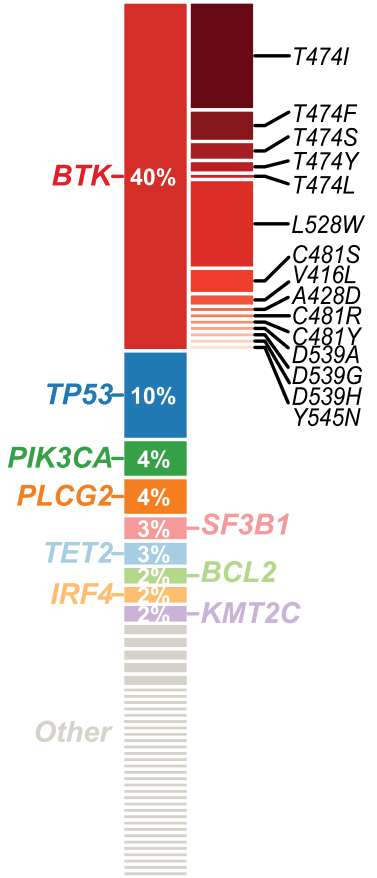
Baseline Genomics in Patients with PD on Pirtobrutinib (n=88)



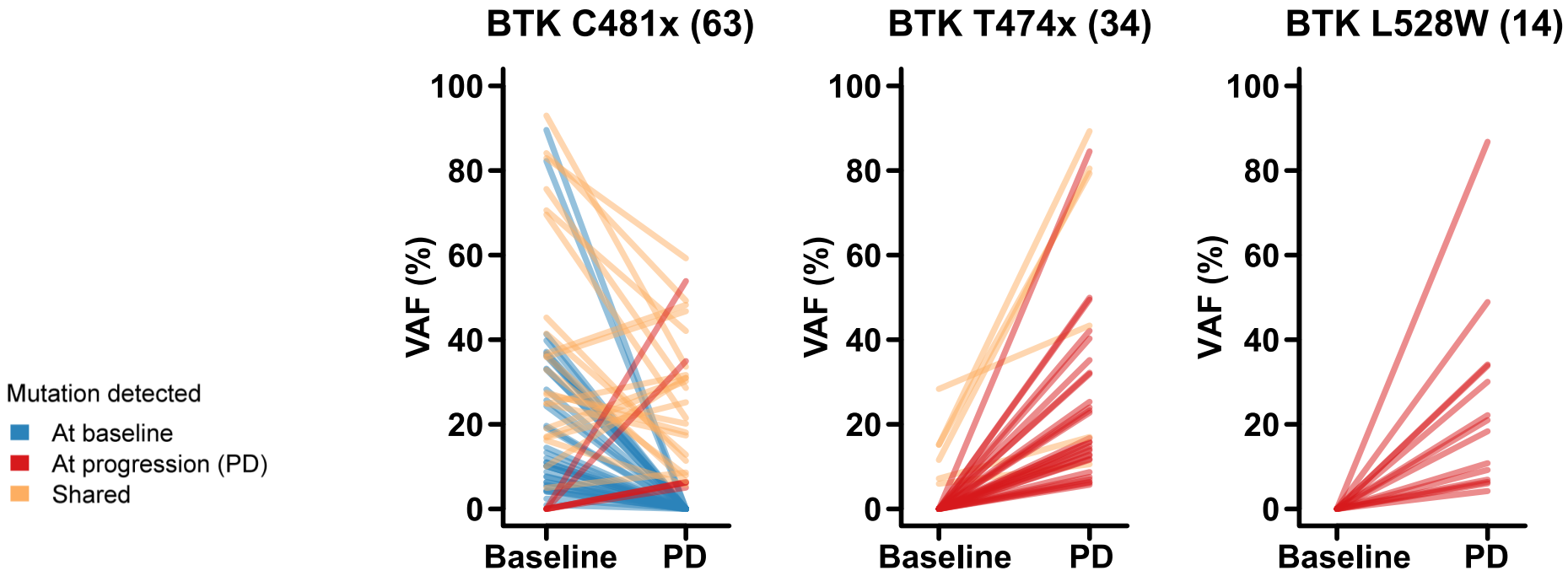
- The most common mutations detected at baseline were *BTK* (53%), *TP53* (49%), *SF3B1* (34%), *ATM* (23%), *NOTCH1* (20%), *PLCG2* (14%), *BCL2* (9%)
- Pirtobrutinib demonstrated efficacy, with an ORR of 83% (73/88)
  - Baseline genomic features did not predict response to pirtobrutinib treatment

Acquired Mutations were Detected at PD in 68% of Patients



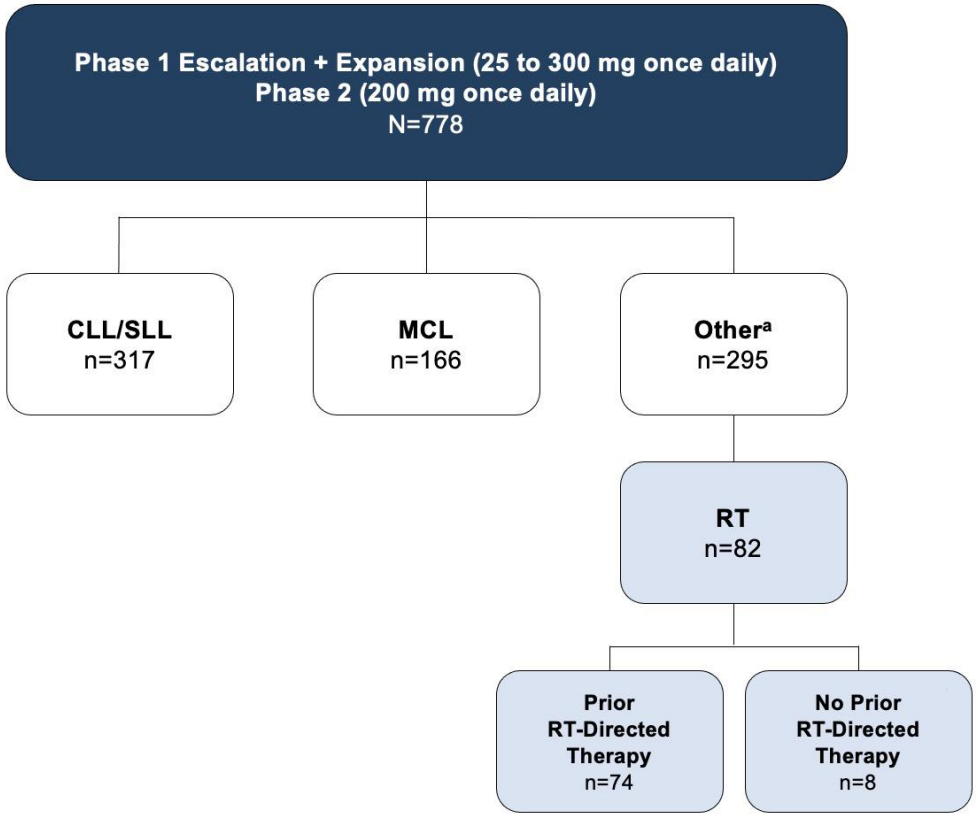


The Majority of *BTK* Acquired Mutations were T474x and L528W



- 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%)

Pirtobrutinib in Richter Transformation (phase 1/2 Bruin study)



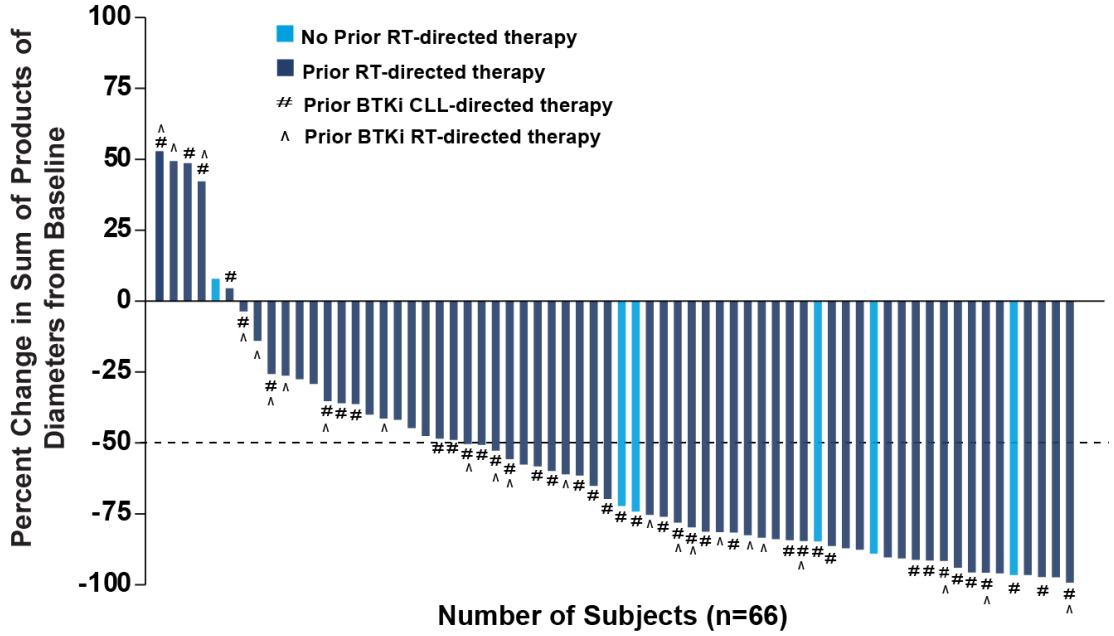
Eligibility

- Age ≥18
- ECOG PS 0-2
- Previously treated
- No limit on prior lines of therapy
- Prior cBTKi permitted
- Protocol later amended to allow patients with no prior RT-directed therapies[b]

Key Endpoints

- Safety/tolerability
- Determine MTD and RP2D
- Pharmacokinetics
- Efficacy (ORR according to Lugano criteria, DoR, PFS, and OS)

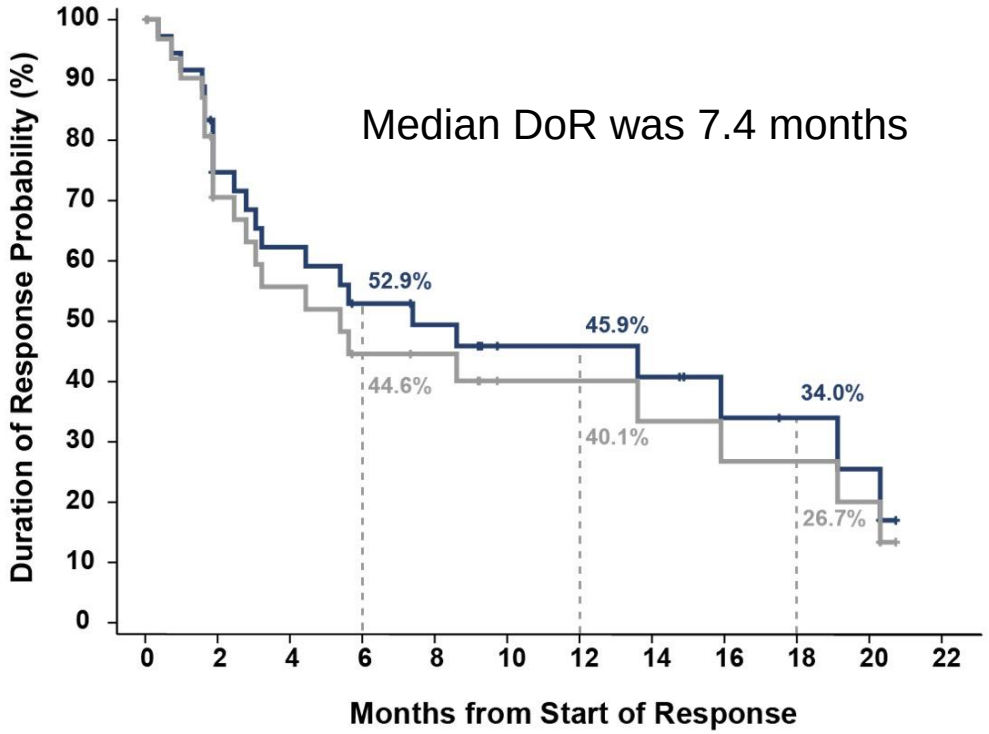
Pirtobrutinib in Richter Transformation



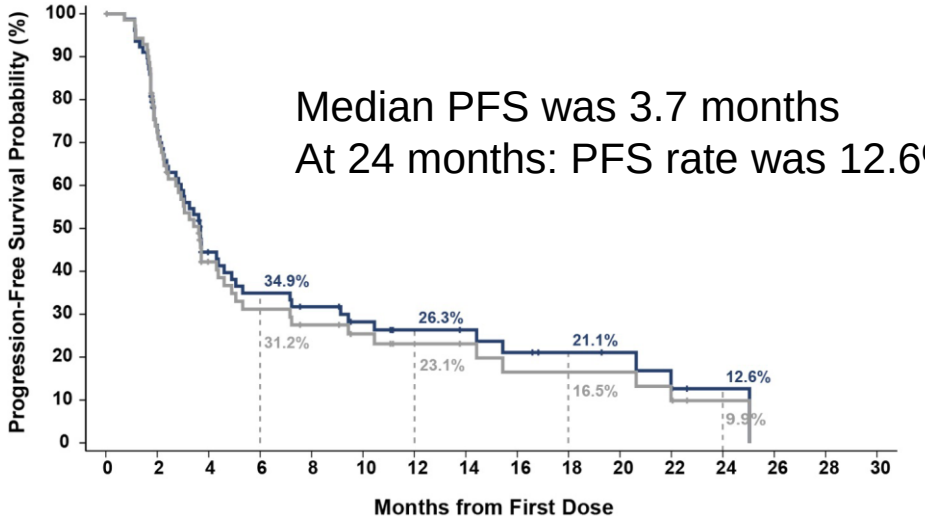
	All n=82	Prior RT Therapy n=74
Overall Response Rate[a], % (95% CI)	50.0 (38.7-61.3)	48.6 (36.9-60.6)
Best Response,n (%)		
CR	11 (13.4)	9 (12.2)
PR	30 (36.6)	27 (36.5)

- The median time-to-response was 1.9 months (range, 0.9-9.2)
- For patients with adequate post-baseline assessment, the ORR was similar between Lugano assessments done by PET vs. CT
- ORR for PET (n=49) was 57.1% (95%CI: 42.2-71.2), and for CT only (n=62), the ORR was 54.8% (95% CI: 41.7-67.5)

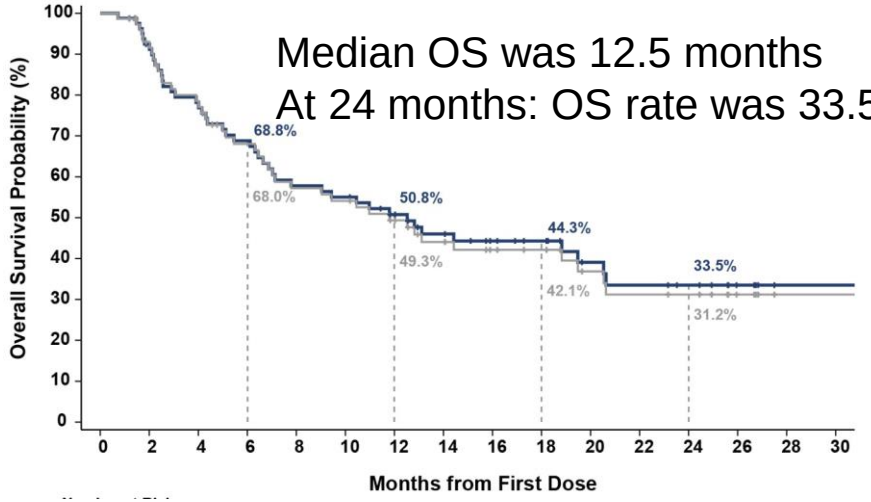
Pirtobrutinib in Richter Transformation



Median DoR was 7.4 months

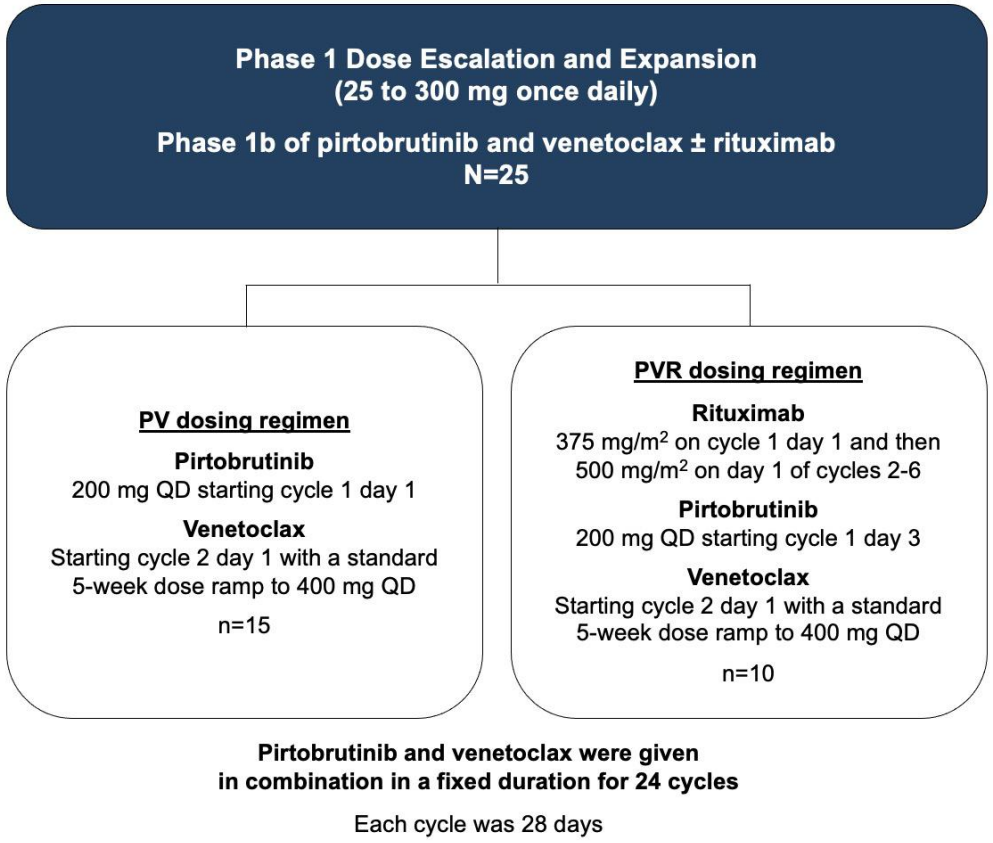


Median PFS was 3.7 months
At 24 months: PFS rate was 12.6%



Median OS was 12.5 months
At 24 months: OS rate was 33.5%

Fixed-Duration Pirtobrutinib with Venetoclax ± Rit in R/R CLL



Phase 1b Design

- A 3+3 safety assessment for each combination arm
- No plan for dose escalation of any study drug
- Enrollment could be expanded by up to 30 additional patients

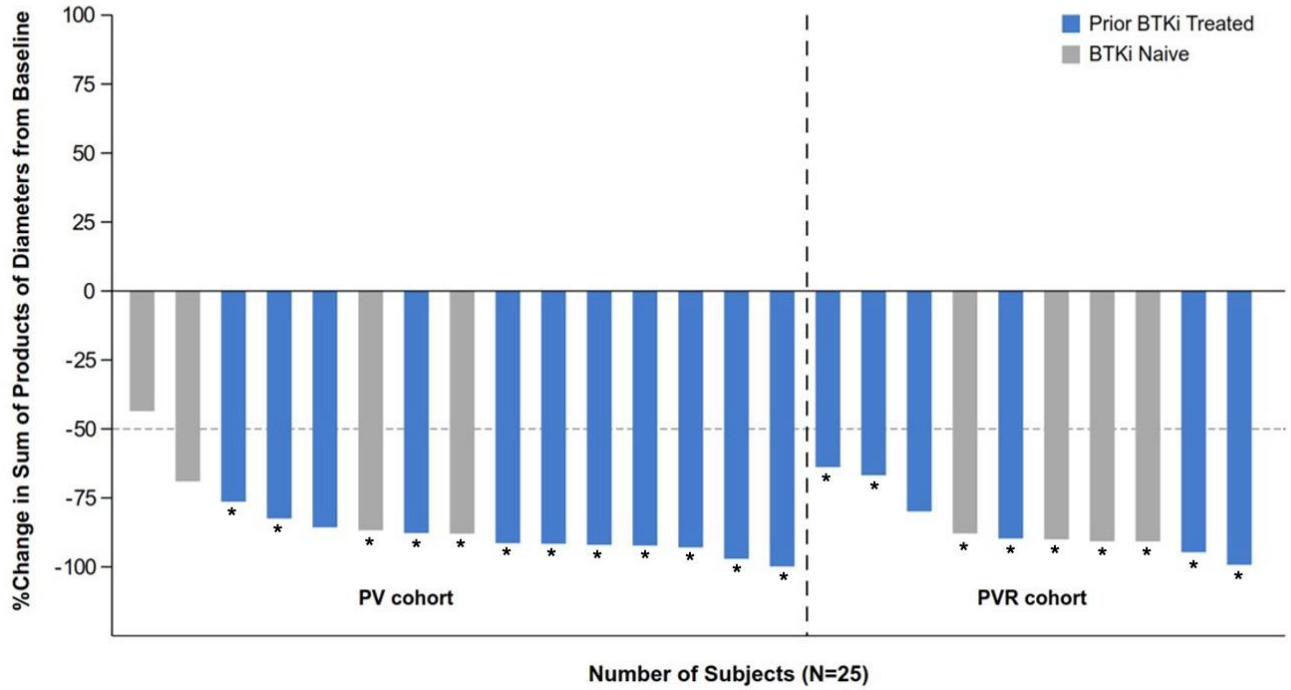
Eligibility

- Age ≥18
- ECOG PS 0-2
- Histologically confirmed r/r CLL/SLL
- Active disease and in need of treatment
- Prior covalent BTK inhibitors permitted
- Prior venetoclax or other BCL-2 inhibitors were not permitted

Key Endpoints[a]

- Safety assessed by TEAEs graded by CTCAE v5.0
- ORR and PFS based on investigator assessment
- Undetectable MRD defined as <1 CLL cell/10,000 nucleated cells in peripheral blood via clonoSEQ assay (Adaptive Biotechnologies, Seattle WA)
- Pharmacokinetics for pirtobrutinib and venetoclax

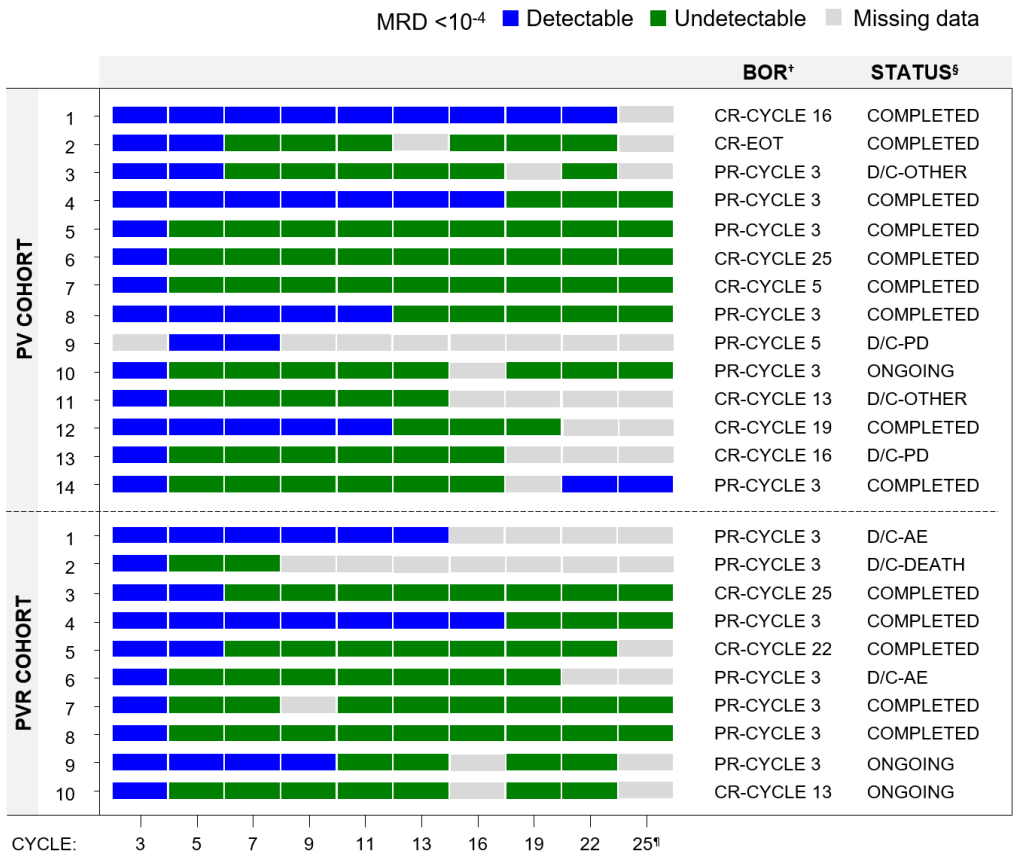
Fixed-Duration Pirtobrutinib with Venetoclax ± Rit in R/R CLL



	PV (n=15)	PVR (n=10)	Total (N=25)
ORR[a], % (95% CI)	93.3 (68.1-99.8)	100 (69.2-100)	96 (79.6-99.9)
Best response, n (%)			
CR	7 (46.7)	3 (30.0)	10 (40.0)
PR	7 (46.7)	7 (70.0)	14 (56.0)
SD	1 (6.7)	0	1 (4.0)

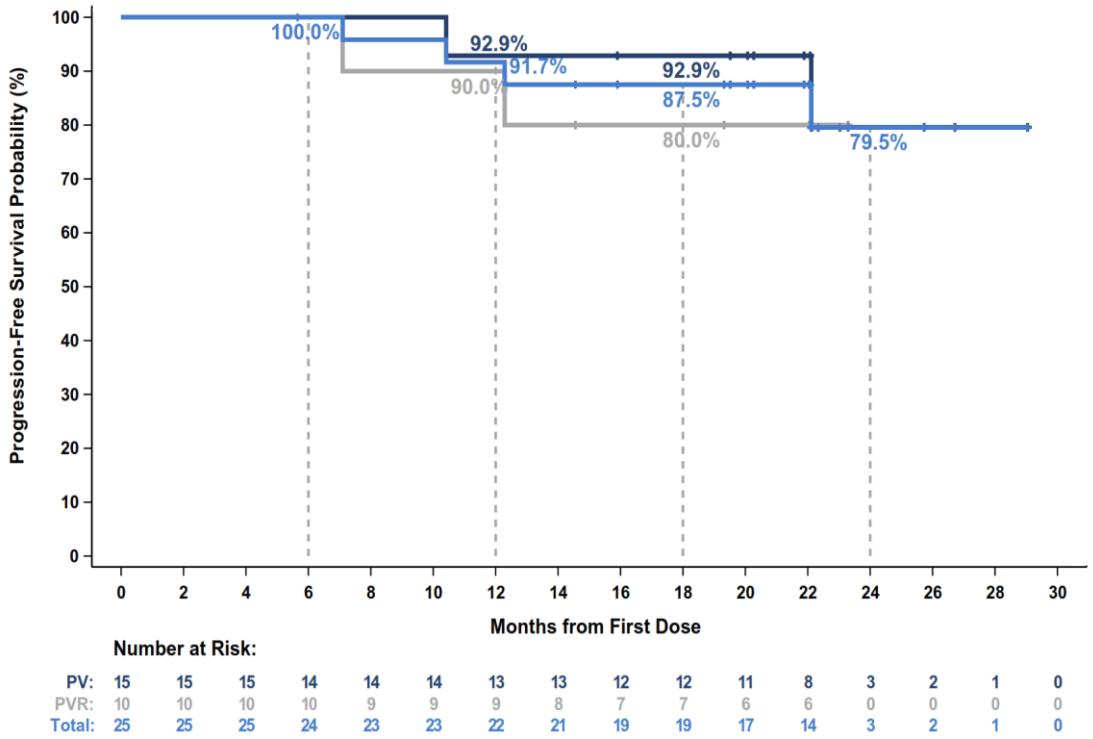
- Changes in SPD were similar among patients who were BTKi naïve and previously BTKi treated
- Median time to best response was 2.4 months (IQR, 1.87-14.32) for all patients
- Median time on treatment was 23.0 months (IQR, 21.98-23.29)
- Median time on study was 25.3 months (IQR, 23.34-28.44)
- Treatment has been discontinued for 22 patients and is ongoing for 3 (PV:1; PVR: 2)

Fixed-Duration Pirtobrutinib with Venetoclax ± Rit in R/R CLL



- 70.8% (PV=10; PVR=7) of patients achieved uMRD rate at cycle 13
- 87.5% of patients (PV=12; PVR=9) achieved uMRD at some time during the trial
- Median time-to-first uMRD was 4.3 months for patients receiving PV and 3.7 months for patients receiving PVR
- All but one patient sustained uMRD during subsequent MRD assessments

Fixed-Duration Pirtobrutinib with Venetoclax ± Rit in R/R CLL



- Median (IQR) duration of follow-up for PFS was 22.1 months (20.1-23.0) for all patients
- PFS rate at 18 months was 87.5% (95% CI: 66.1-95.8) for all patients
- The 24-month PFS rate was 79.5% (95% CI: 52.0-92.3) for all patients

Ongoing phase III studies with Pritobrutinib in CLL

Trial	Population	Experimental Arm	Control Arm
NCT05023980, phase 3	Untreated CLL/SLL	Pirtobrutinib	Bendamustine + Rituximab
NCT04965493, phase 3	Previously treated CLL/SLL	Pirtobrutinib + Venetoclax + Rituximab	Venetoclax + Rituximab
NCT04666038, phase 3	BTK inhibitor pre-treated CLL/SLL	Pirtobrutinib	Investigator's choice of Idelalisib + Rituximab or Bendamustine + Rituximab

I would like to thank Loxo/ Lilly, for making Kraków one of the important centres, where Pirtobrutinib was developped