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

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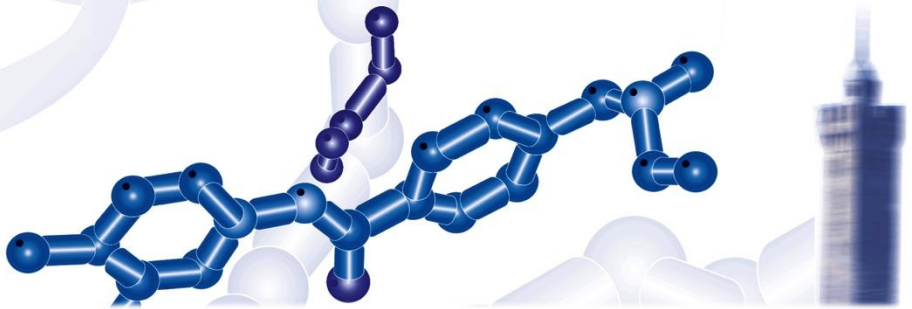
A Cancer Center Designated by the National Cancer Institute



New Drugs in Hematology

President: Pier Luigi Zinzani

Bologna,
Royal Hotel Carlton
May 18-19-20, 2026

Pirtobrutinib in CLL

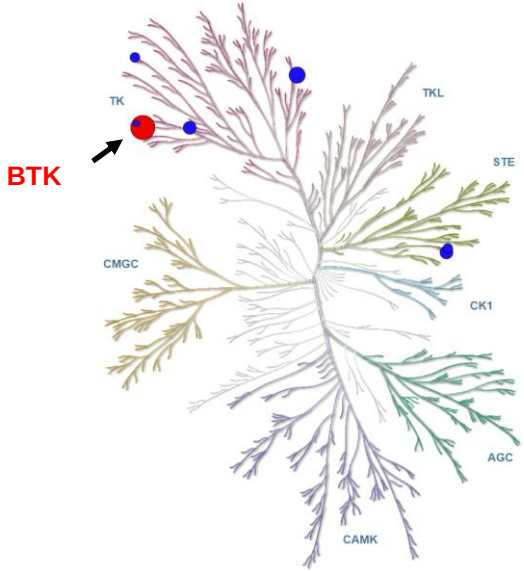
Paul Barr, MD
Wilmot Cancer Institute
University of Rochester

Disclosures

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
Abbvie			x				
Adaptive	x		x				
AstraZeneca	x		x				
Beigene			x				
Janssen			x				
Lilly			x				
Merck			x				
TG therapeutics			x			x	
Genentech	x		x				

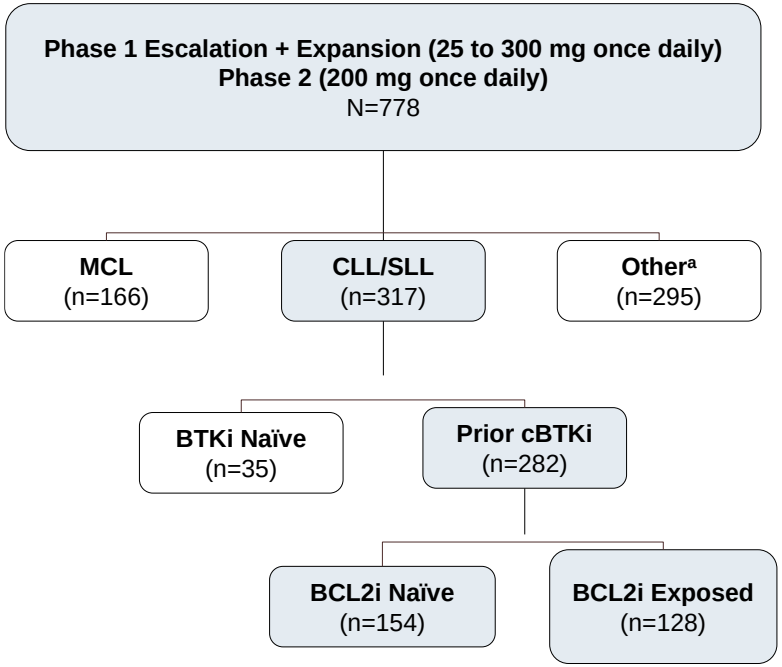
Preclinical

- >100-fold selectivity to BTK over other tested kinases
- Low-nanomolar potency against both BTK and BTK C481 substitution mutants
- More complete target inhibition
  - prevented Y551 phosphorylation in the activation loop in addition to Y223, stabilizing BTK in a closed inactive conformation.
- >90% inhibition of BTK at trough, regardless of the intrinsic BTK turnover rate.



Gomez EB, et al. *Blood*. 2023;142:62-72.

Phase 1/2 BRUIN Study



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

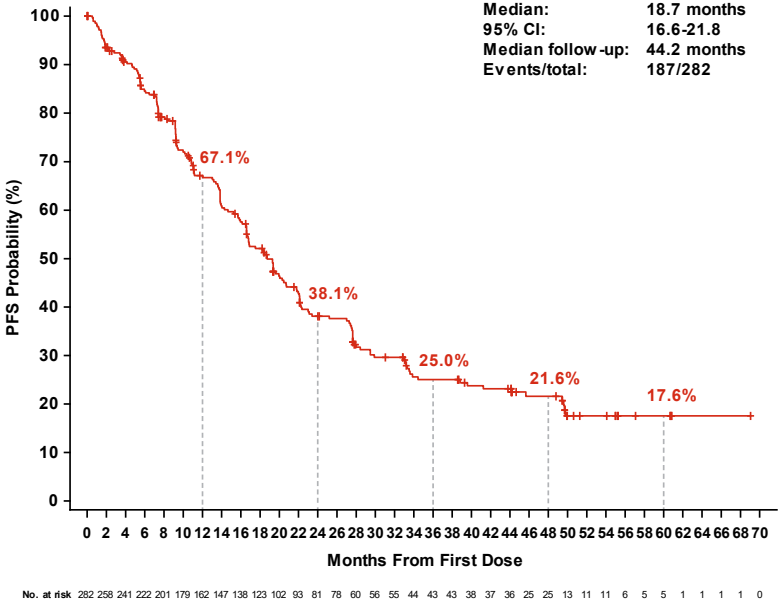
Key Endpoints

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

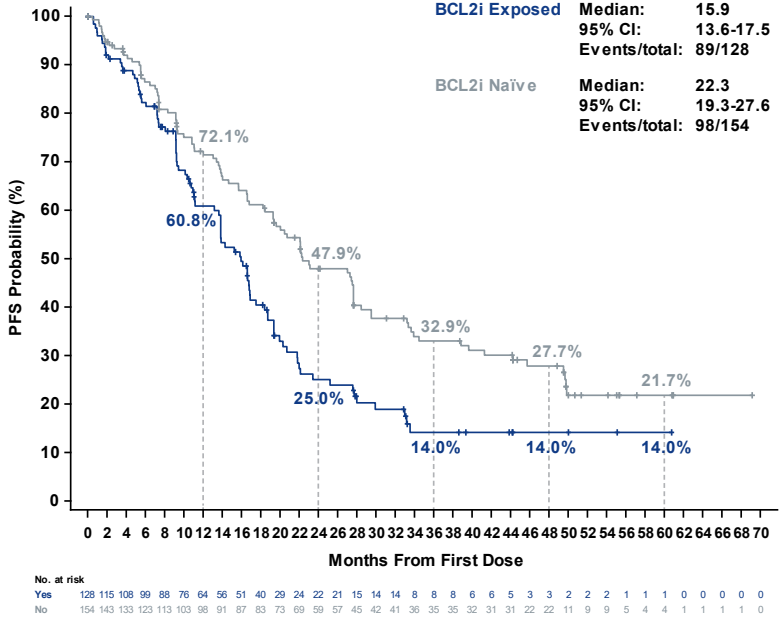
Wierda, et al; ASH 2025

Phase 1/2 BRUIN Study: CLL PFS

Pirtobrutinib PFS in Patients With CLL/SLL Who Received Prior cBTKi



Pirtobrutinib PFS in Patients With CLL/SLL Who Received Prior cBTKi, by BCL2i Exposure



Wierda, et al; ASH 2025

Safety Profile

AE, ≥20%	TEAEs in Patients With CLL/SLL (n=282)			
	All-Cause AEs		Treatment-Related AEs, %	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Fatigue	38.7	1.8	3.9	0.0
Neutropenia[a,b]	35.8	29.8	20.6	16.3
Diarrhea	30.5	0.4	8.9	0.0
Cough	29.8	0.0	2.1	0.0
Contusion	27.7	0.0	18.8	0.0
COVID-19	28.4	6.0	0.7	0.0
Dyspnea	23.4	2.5	0.7	0.4
Nausea	23.4	0.0	3.9	0.0
Abdominal pain	21.6	2.1	2.1	0.4
AEs of Interest[c]	**Any Grade**	**Grade ≥3**	**Any Grade**	**Grade ≥3**
Infections[d]	76.2	36.5	14.9	5.7
Bruising[e]	31.2	0.0	20.2	0.0
Rash[f]	25.2	1.1	5.7	0.4
Arthralgia	23.0	1.4	4.6	0.0
Hemorrhage[g]	25.2	3.2	8.2	1.4
Hypertension	16.0	5.3	3.9	0.7
Atrial fibrillation/flutter[h,i]	5.0	2.1	1.4	0.7

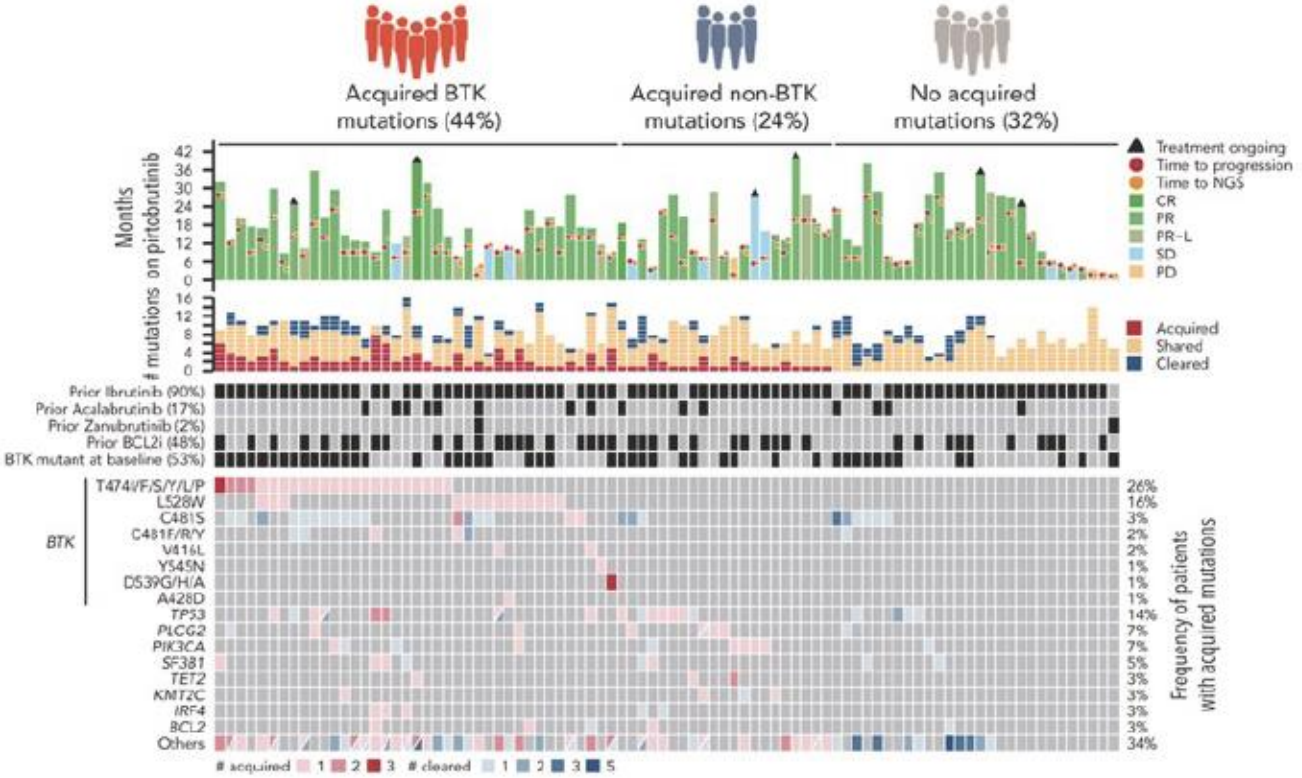
Median (IQR) time on treatment was 20.0 (9.6-37.7) months

11 (3.9%) patients had treatment-related AE leading to pirtobrutinib dose reduction

9 (3.2%) patients had treatment-related AE leading to pirtobrutinib discontinuation

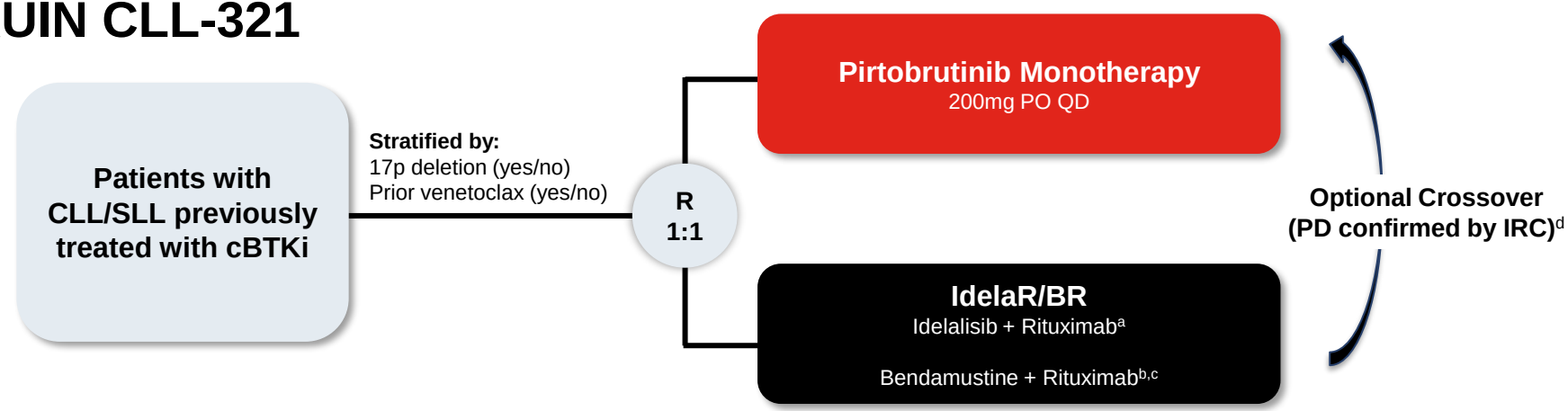
Wierda, et al; ASH 2025

Pirtobrutinib Resistance



Brown et al. Blood 2026; 147:24-34

BRUIN CLL-321



Key Eligibility

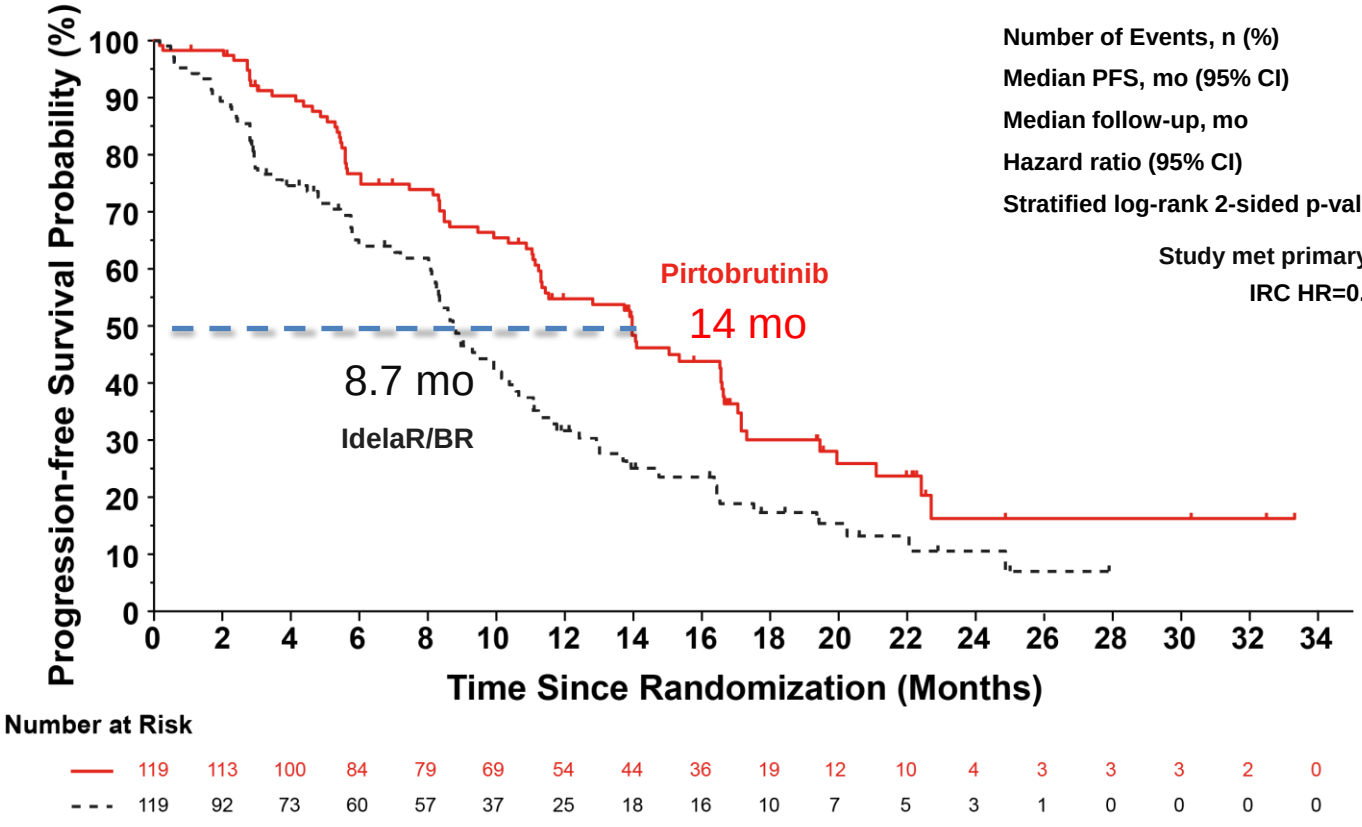
- Age ≥18
- ECOG PS 0-2
- Confirmed CLL/SLL requiring treatment per iwCLL 2018
- **Prior cBTKi required**
- **No limit on prior lines of therapy**
- **Prior history of atrial fibrillation allowed**

Key Endpoints

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

Sharman, et al; ASH 2024

IRC-Assessed Progression-free Survival



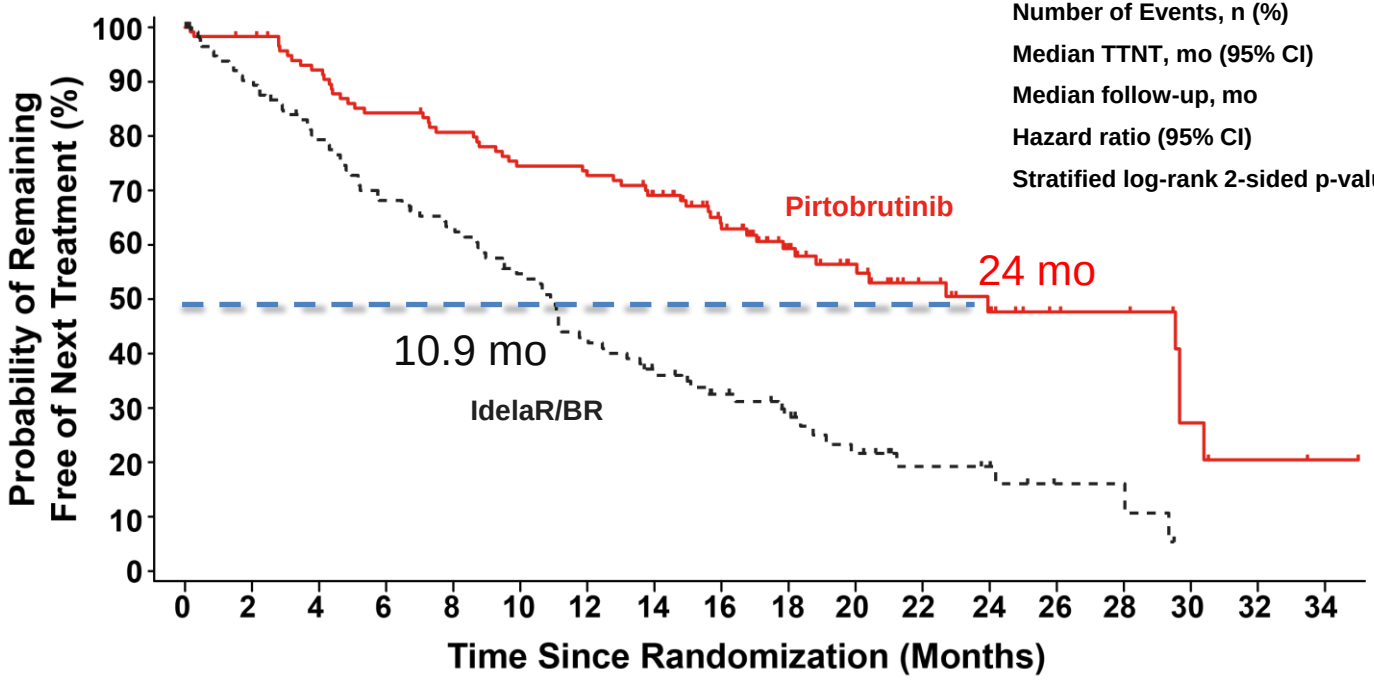
	Pirtobrutinib n=119	IdelaR/BR n=119
Number of Events, n (%)	74 (62)	79 (66)
Median PFS, mo (95% CI)	**14.0** (11.2-16.6)	**8.7** (8.1-10.4)
Median follow-up, mo	19.4	17.7
Hazard ratio (95% CI)	**0.54 (0.39- 0.75)**	
Stratified log-rank 2-sided p-value	0.0002*	

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

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

Sharman, et al; ASH 2024

Time to Next Treatment or Death



Number at Risk

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

	Pirtobrutinib n=119	IdelaR/BR n=119
Number of Events, n (%)	54 (45)	82 (69)
Median TTNT, mo (95% CI)	**24.0** (17.8-29.7)	**10.9** (8.7-12.5)
Median follow-up, mo	20.0	20.2
Hazard ratio (95% CI)	**0.37 (0.25-0.52)**	
Stratified log-rank 2-sided p-value	<0.0001*	

Pirtobrutinib reduced the risk of starting next treatment or death by 63% with a median TTNT of ~24 months

Pirobrutinib in 2nd line setting after cBTKi

BRUIN LOXO-BTK-18001:
- Open-label, multi-center Phase 1/2 study of pirtobrutinib in patients with R/R B-cell malignancies[5]

BRUIN CLL-321:
- Randomized, open-label, multi-center Phase 3 study of pirtobrutinib in patients with CLL/SLL[6]

Pooled population, eligibility criteria:
- All patients received pirtobrutinib 200 mg once daily
- BCL2i-naïve patients
- Prior 1L cBTKi therapy, with or without anti-CD20 antibody

Outcomes assessed:
- ORR, based on investigator assessment using iwCLL 2018 criteria
- Progression-free survival, based on investigator assessment using iwCLL 2018 criteria
- Time to next treatment
- Overall survival
- Safety

Eyre, et al; ASH 2025

Demographic and Clinical Characteristics

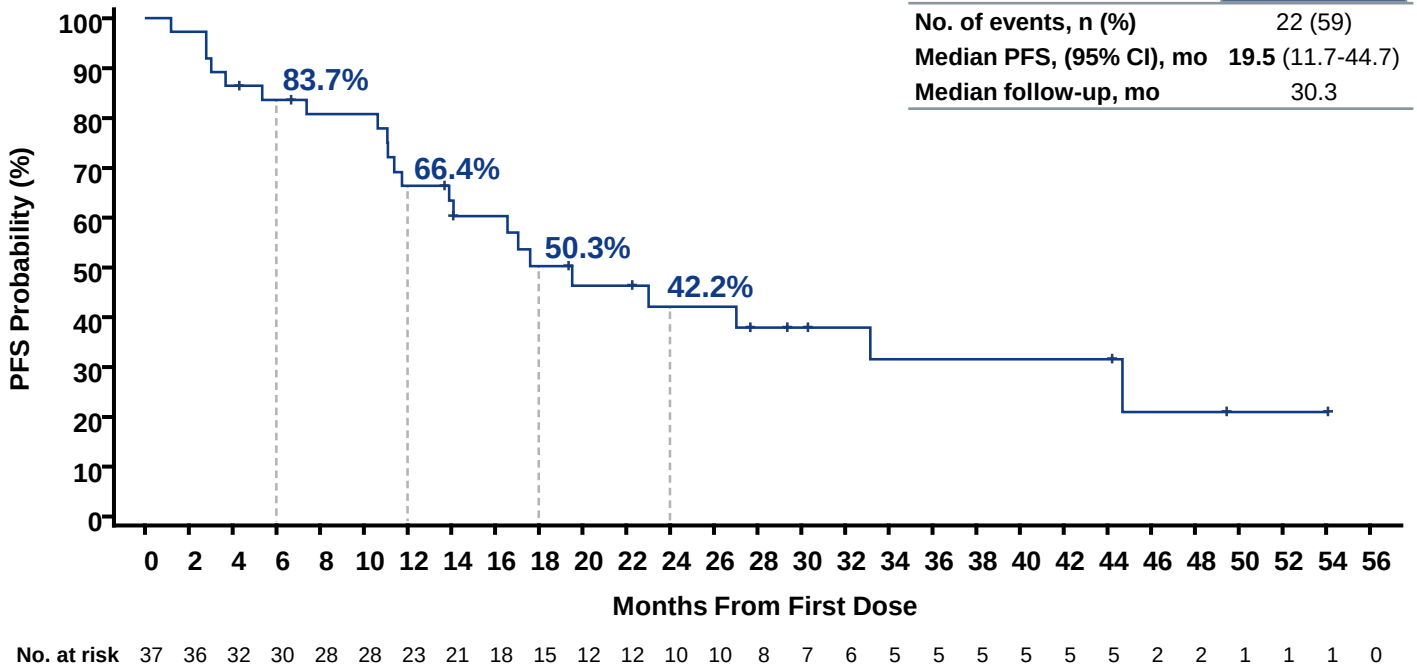
Characteristics	Total (N=37)
Age, median, (range), years	69 (42-87)
Male, n (%)	27 (73)
Region, n (%)	
US	13 (35)
Outside US	24 (65)
Histology, n (%)	
CLL	35 (95)
SLL	2 (5)
ECOG PS, n (%)	
0-1	31 (84)
2	6 (16)
Rai stage, n (%)	
0-II	23 (62)
III-IV	13 (35)
High-risk molecular features, n/N available (%)	
Unmutated *IGHV*	22/26 (85)
Complex karyotype (≥3 abnormalities)	11/17 (65)
Mutated *TP53*	13/30 (43)
del(17p)	15/31 (48)

Characteristics	Total (N=37)
Molecular characteristics, n/N available (%)	
BTK C481S mutated	10/30 (33)
PLCγ2 mutated	6/30 (20)
Prior therapy, n (%)	
cBTKi	37 (100)
Ibrutinib	28 (76)
Acalabrutinib	5 (14)
Zanubrutinib	3 (8)
Other	1 (3)
Anti-CD20 antibody	4 (11)
Reason for prior BTKi discontinuation, n (%)[a]	
Disease progression	21 (57)
Toxicity	13 (35)
Other	3 (8)

Eyre, et al; ASH 2025

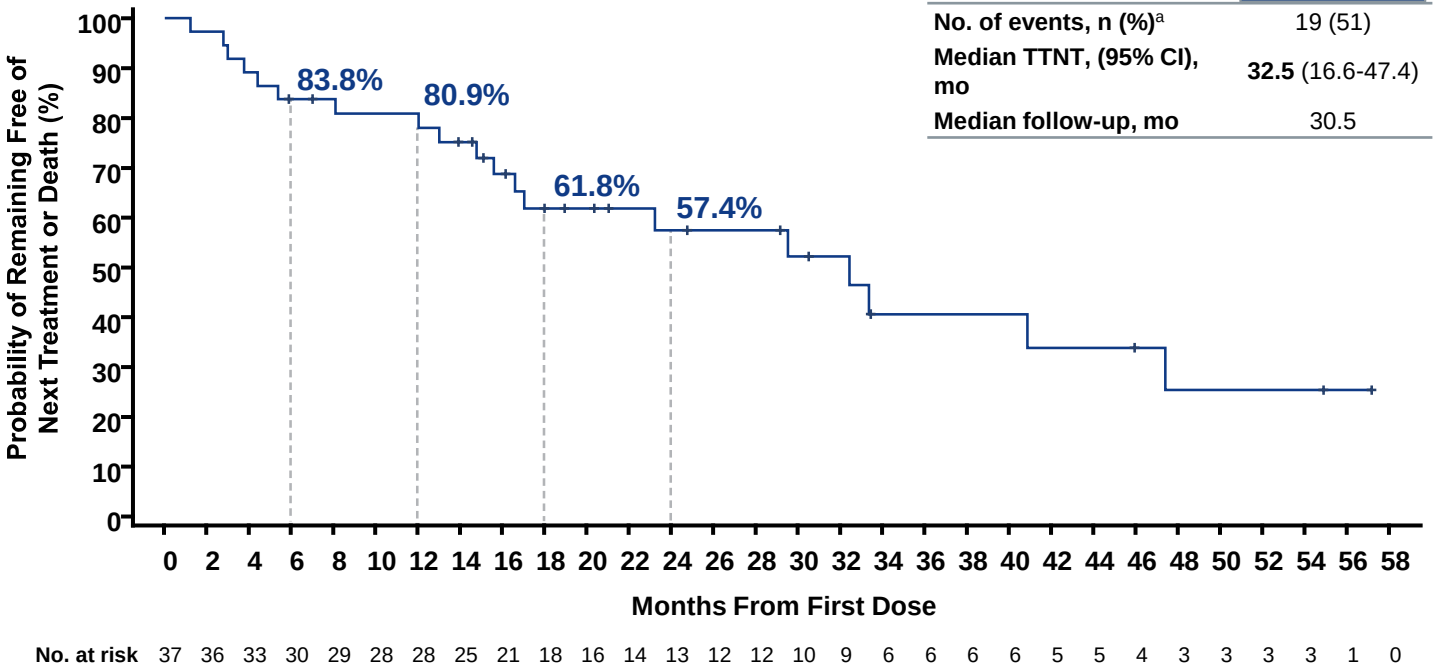
Investigator-Assessed PFS

	Total N=37
No. of events, n (%)	22 (59)
Median PFS, (95% CI), mo	**19.5** (11.7-44.7)
Median follow-up, mo	30.3



Eyre, et al; ASH 2025

Time to Next Treatment

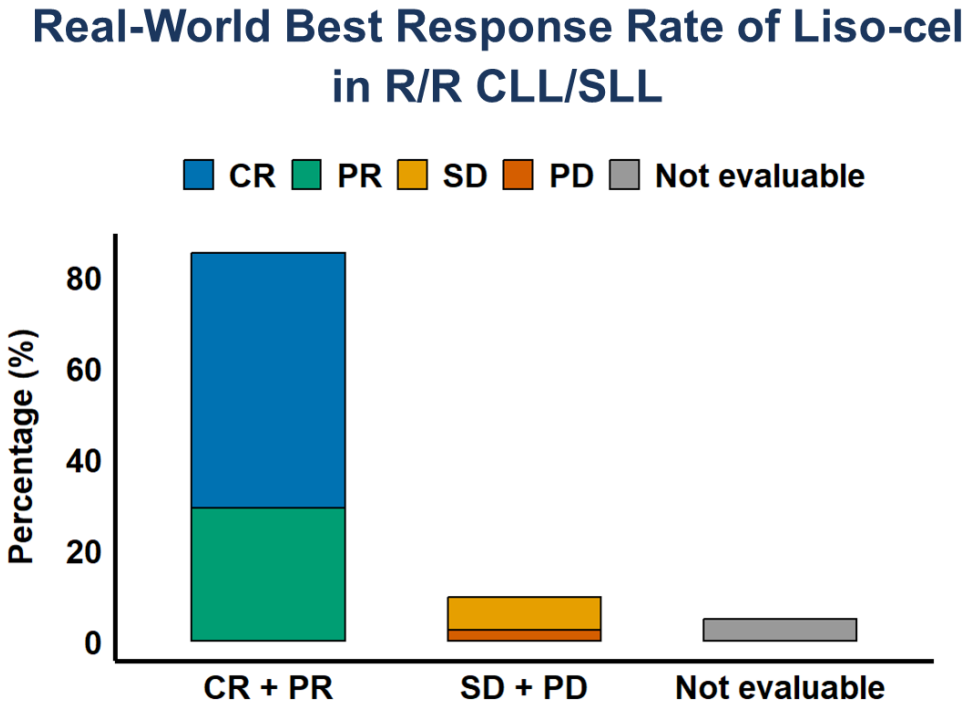


	Total N=37
No. of events, n (%)[a]	19 (51)
Median TTNT, (95% CI), mo	**32.5** (16.6-47.4)
Median follow-up, mo	30.5

Eyre, et al; ASH 2025

Liso-cel in the Real World

- Total number of patients: 41
- Median time to best response: 30 days
- Overall response rate: 85% (n = 35)
- CR: 56% (n = 23)
  - CR: 44% (n = 18)
  - uCR: 5% (n = 2)
  - CRi: 7% (n = 3)



Huang et al. ASH 2025, #642

Pirtobrutinib as Last Line of Therapy

Characteristic	Pirtobrutinib N = 24[1]	Other N = 17[1]	p-value[2]
Complete Response			0.3
Complete Response	15 (65%)	8 (35%)	
Not CR	8 (50%)	8 (50%)	
Not evaluable	1	1	
Overall Response Rate			0.6
CR/PR	20 (57%)	15 (43%)	
Not CR/PR	3 (75%)	1 (25%)	
Not evaluable	1	1	

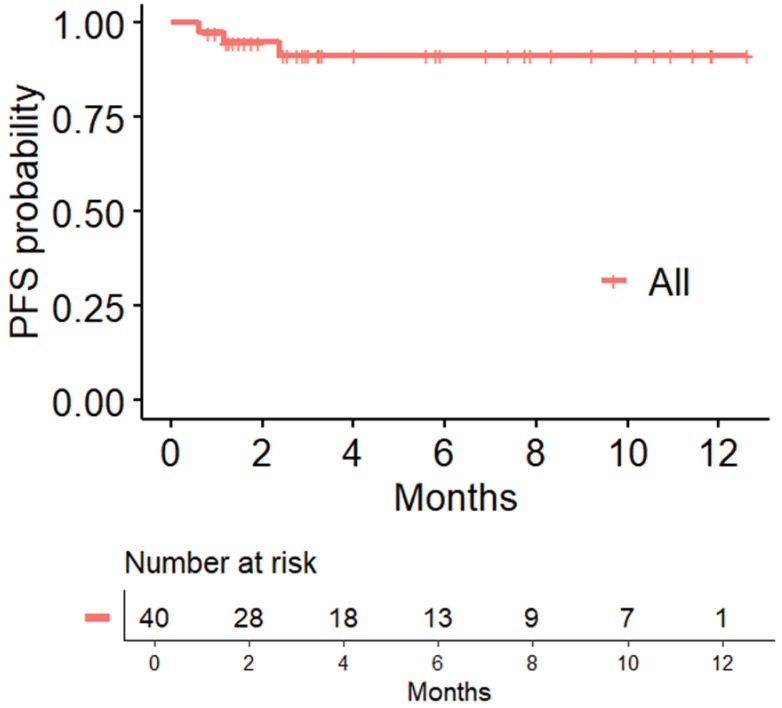
[1]n (%)

[2]Pearson's Chi-squared test; Fisher's exact test

Huang et al. ASH 2025, #642

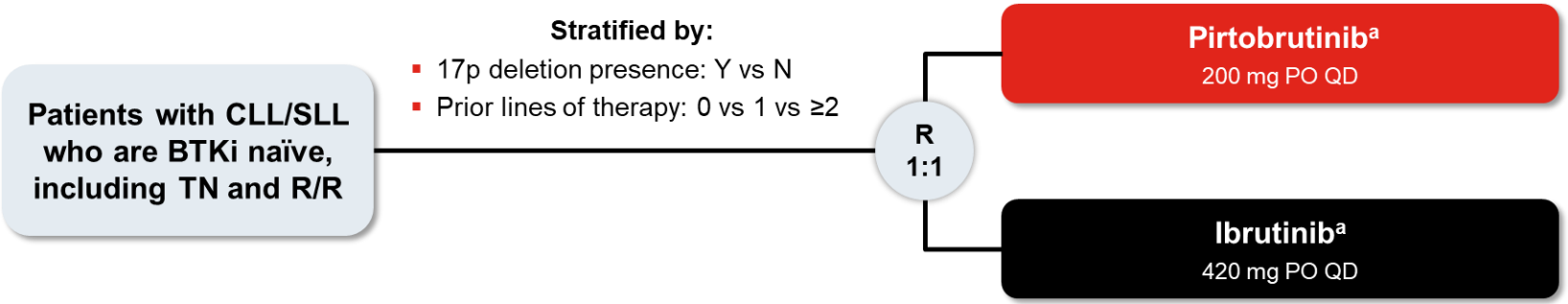
Progression-Free Survival

- Median follow-up: 3.3 months
- 6-month PFS: 92% (83% - 100%)
- 1 patient experienced disease relapse
- 6-month OS:
  - CR: 88% (74% - 100%)
  - Not CR: 100% (100% - 100%)
- 3 of 41 patients died
  - 1 prior to Day 25 secondary to IEC-HS
  - 1 due to CNS disease relapse after achieving CR
  - 1 without disease relapse



Huang et al. ASH 2025, #642

BRUIN CLL-314



Key Eligibility

- Confirmed diagnosis of CLL/SLL, with requirement for therapy (per iwCLL 2018 criteria)
- BTKi naïve[b]
- 17p deletion status (by FISH)
- ECOG PS 0 to 2

Primary Objectives

Non-inferiority of ORR[c,d,e] (per iwCLL 2018 criteria):

- In ITT population, or
- In R/R population

Key Secondary Objectives

Superiority of PFS[d,e] (per iwCLL 2018 criteria):

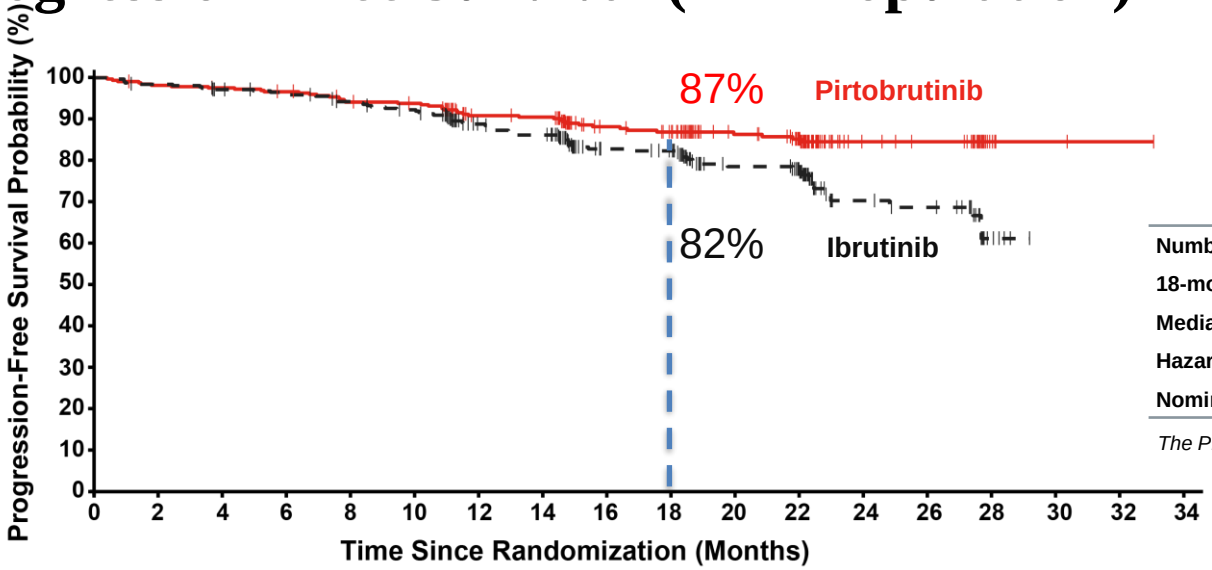
- In ITT population, or
- In R/R population

Exploratory

Analyses of endpoints in the TN population

Woyach,, et al.; ASH 2025

Progression-Free Survival (ITT Population)



Number at risk

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

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

The PFS results presented are INV-assessed

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

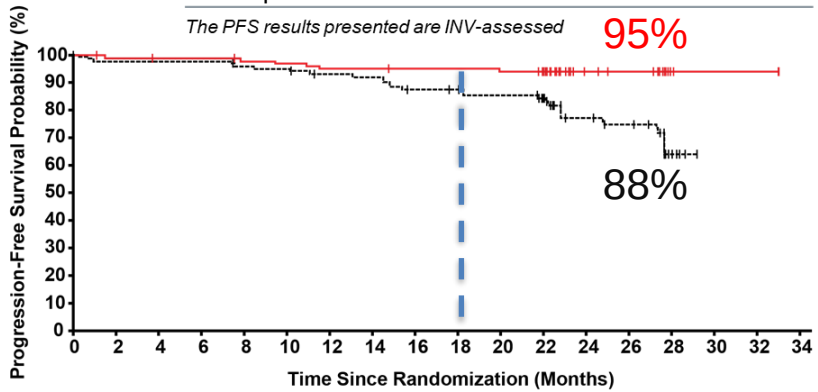
Woyach,, et al.; ASH 2025

Progression-Free Survival by Prior Treatment Status

TN population

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

The PFS results presented are INV-assessed



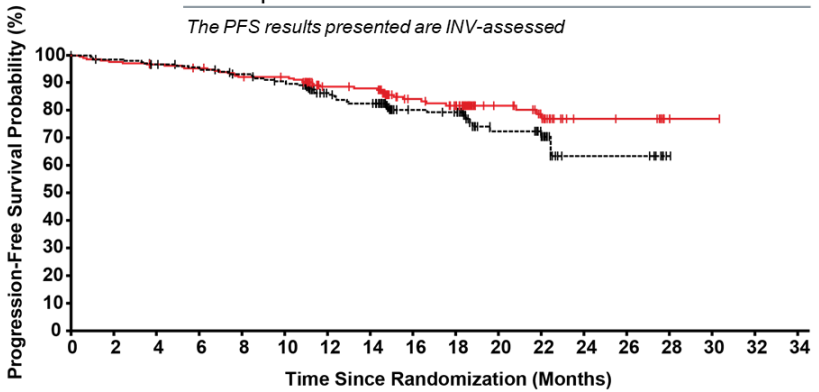
Number at risk

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

R/R population

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

The PFS results presented are INV-assessed



Number at risk

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

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

Woyach,, et al.; ASH 2025

Adverse Events of Special Interest

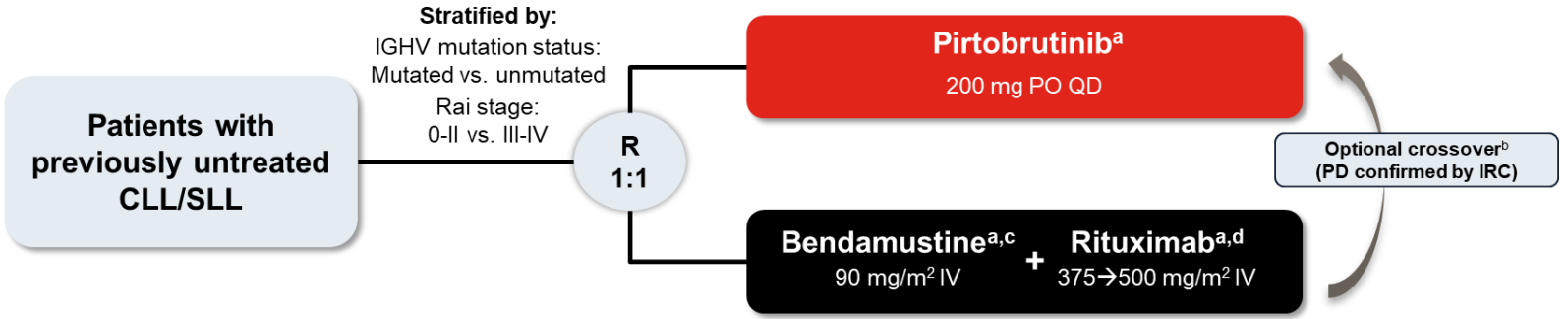
≥10% of Participants in Either Arm	Pirtobrutinib n=330		Ibrutinib n=325	
	Any Grade n (%)	Grade ≥3 n (%)	Any Grade n (%)	Grade ≥3 n (%)
Subjects with ≥1 AESI	288 (87.3)	127 (38.5)	288 (88.6)	117 (36.0)
Infections[a]	226 (68.5)	56 (17.0)	241 (74.2)	54 (16.6)
Infection without COVID-19	214 (64.8)	53 (16.1)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

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

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

Woyach,, et al.; ASH 2025

BRUIN CLL-313



Key Eligibility Criteria

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

Endpoints

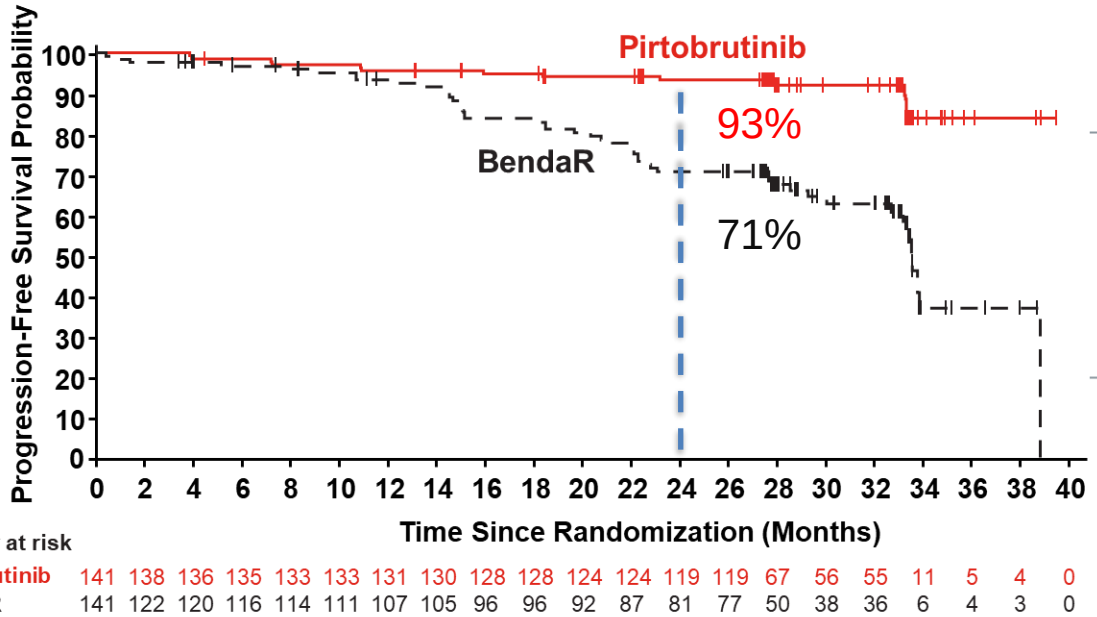
Primary
- PFS[e,f] (per iwCLL 2018 criteria)

Key secondary
- OS[f]

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

Jurczak,, et al.; ASH 2025

Progression-Free Survival



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

The PFS results presented are IRC assessed

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

Jurczak,, et al.; ASH 2025

Adverse Events of Special Interest

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

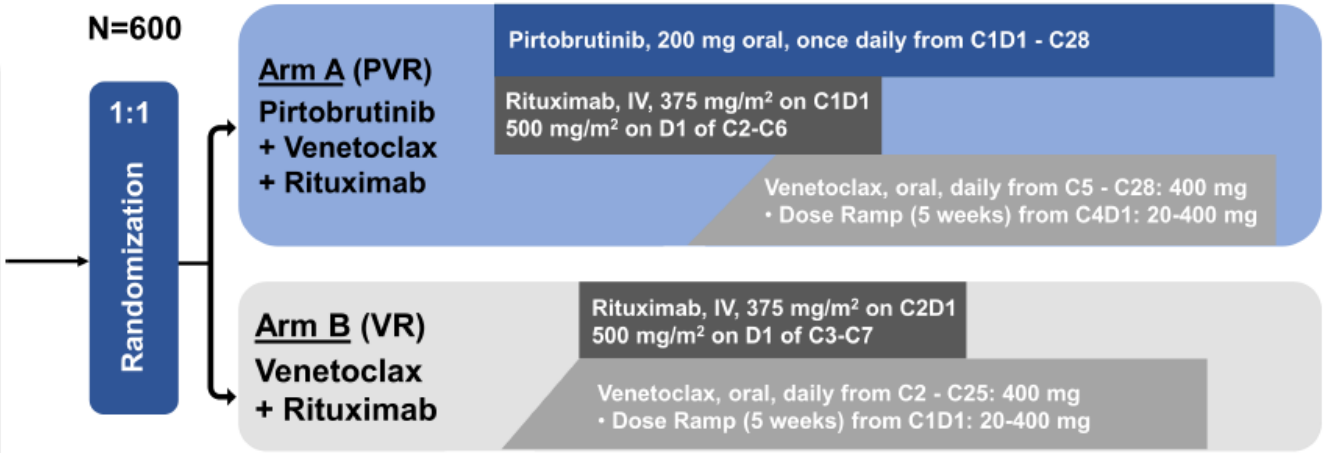
Incidence of atrial fibrillation/flutter remains low in older patients aged ≥75 years (5.0% with pirtobrutinib and 4.3% with BendaR)

Jurczak,, et al.; ASH 2025

BRUIN CLL-322: Venetoclax Rituximab +/- Pirtobrutinib

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



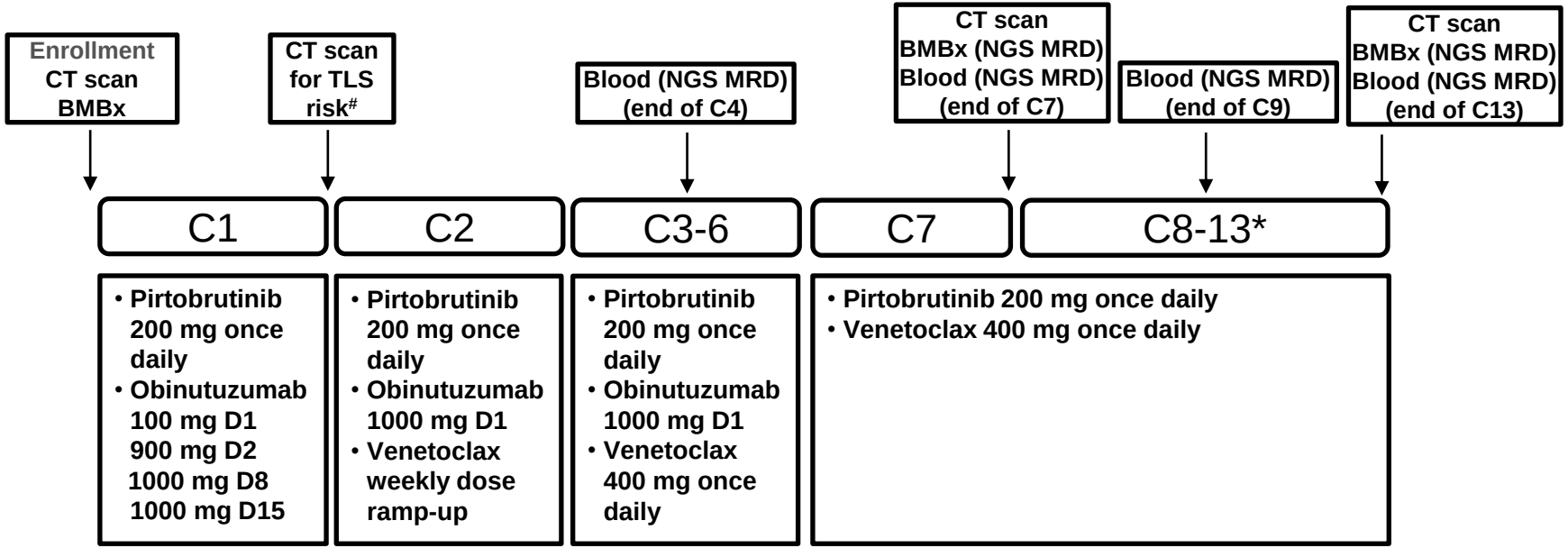
Stratification factors

- 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

Mato et al, ASCO 2021, #3742

PVO Trial: Treatment Schema

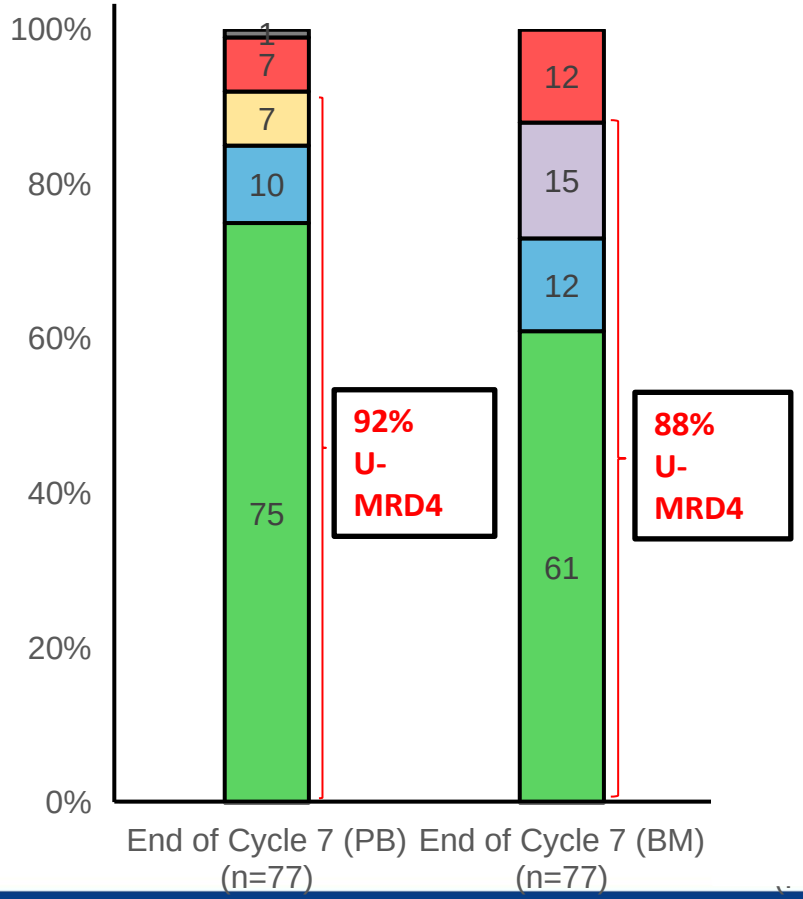


#CT imaging is repeated for TLS risk assessment only if baseline CT had nodes ≥5 cms

- Each cycle is 28 days
- NGS MRD assessed by clonoSEQ assay (Adaptive Biotechnologies)
- *For pts who are MRD+ at ≥10^{-5} in either PB or BM at end of C13 can continue pirtobrutinib + venetoclax for an additional 12 cycles
- All pts monitored by PB NGS MRD q3 mos for first 12 mos off therapy, and then q6 mos

Jain, ASH 2025, Abs 680

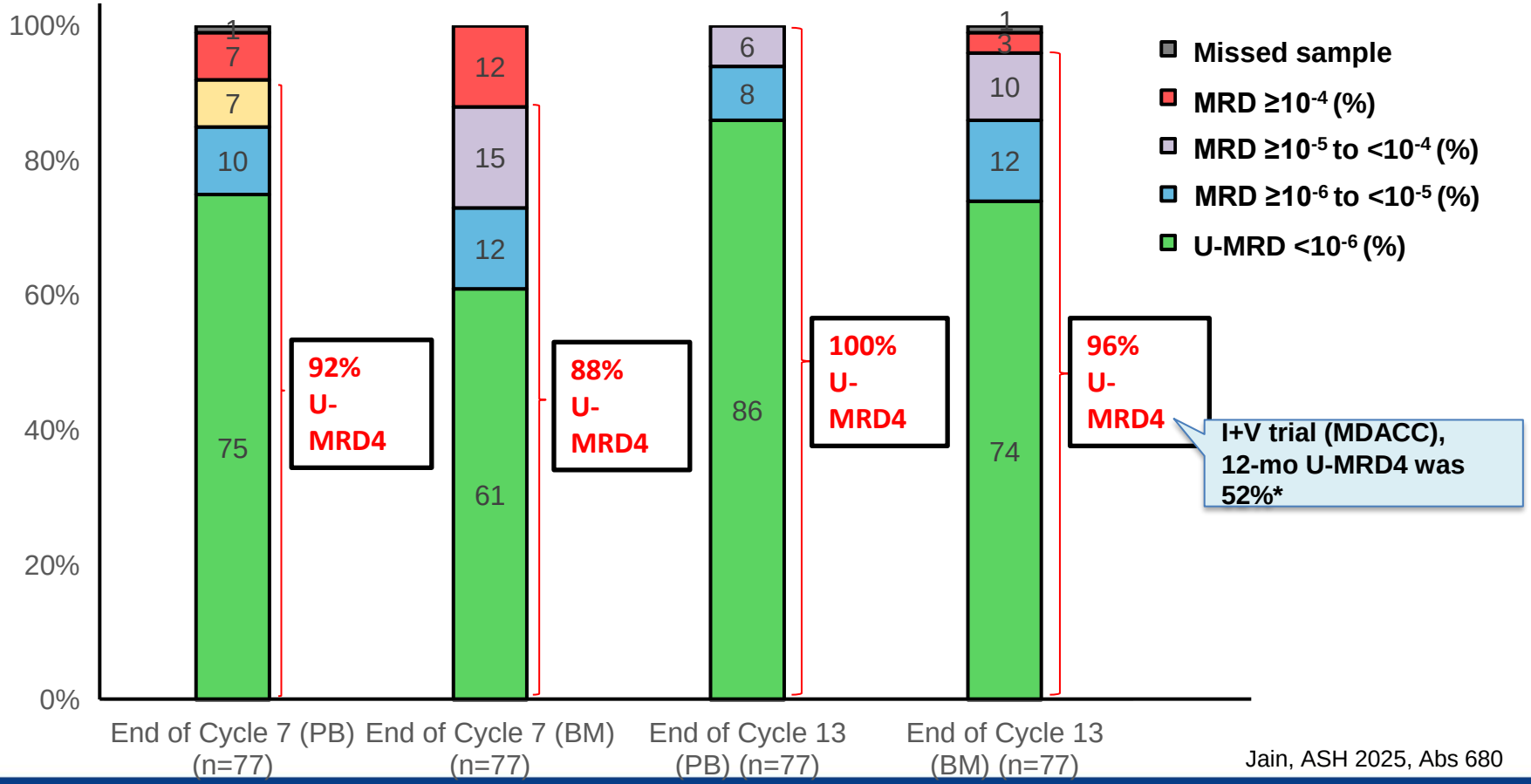
PVO Trial: NGS MRD in Blood and Marrow



- Missed sample
- MRD ≥10^{-4} (%)
- MRD ≥10^{-5} to <10^{-4} (%)
- MRD ≥10^{-6} to <10^{-5} (%)
- U-MRD <10^{-6} (%)

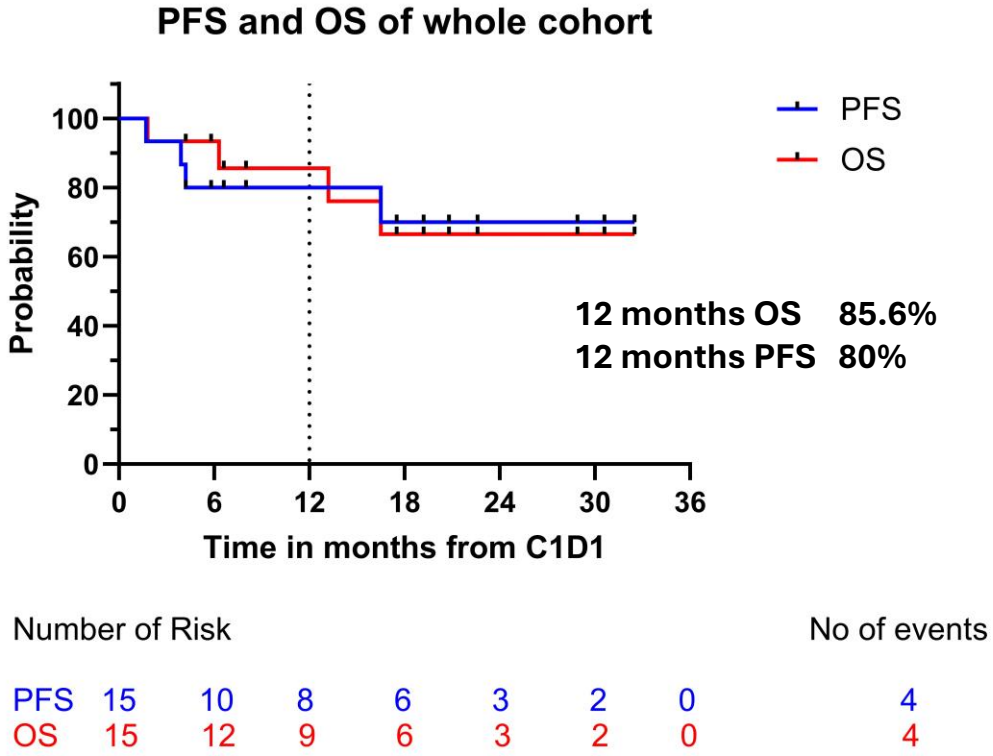
Jain, ASH 2025, Abs 680

PVO Trial: NGS MRD in Blood and Marrow



Jain, ASH 2025, Abs 680

PVO in RT: PFS and OS (N=15)



Jain, PVO in RT, ASH 2025, Abs 89

CLL18 MOIRAI

Treatment naive, all comer CLL/SLL
(irrespective of fitness, comorbidity and risk factors)

R

venetoclax
obinutuzumab
pirtobrutinib

Arm A
Venetoclax/Obinutuzumab
fixed duration, 12 cycles

C12 D28

Arm B
Venetoclax/Pirtobrutinib
fixed duration, 15 cycles

C15 D28

Arm C
Venetoclax/Pirtobrutinib
MRD-guided 15-36 cycles

treatment duration depending on MRD results

cycle 15-36

Rules for treatment duration in arm C:

- **stop if 2x uMRD** (cutoff $<10^{-4}$ by flow in blood) with **interval of 3 cycles + 12 weeks consolidation** after 2nd uMRD sample
- only **after cycles 15, 21 or 27**
- treatment **beyond cycle 27 only with a clear benefit** for the individual pt (further decline in MRD by at least one log)

flow cytometry (blood)
- uMRD $<10^{-4}$
- MRD $\geq 10^{-4}$
- MRD irrelevant for duration of treatment

ST = staging every 12 weeks (e.g. ST3 after cycle 9)

Conclusions

- Pirtobrutinib is effective in patient's previously treated with cBTKi
  - Established role in this setting
- Modest durability in heavily pre-treated & cBTKi refractory patients
  - Bridge to CAR-T therapy
- Well-tolerated with low rates of discontinuation and low rates of atrial fibrillation
  - Potential for single agent first line use in older patients
- Promising early data in combination with venetoclax and anti-CD20
  - Potential use in fixed duration regimens for higher risk patients