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Relapsed CLL in 2026: Sequencing BTK Inhibitors, Venetoclax, and Non-Covalent BTK Inhibitors (Pirtobrutinib)

Thursday May 14

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- Response to and tolerance of prior therapy
- Biologic features of CLL
 - FISH, karyotype
 - TP53 mutations – other mutations (i.e. BTK, PLCG2)?
 - IGHV
- Age and comorbidities
- Patient preferences
- Availability of clinical trial

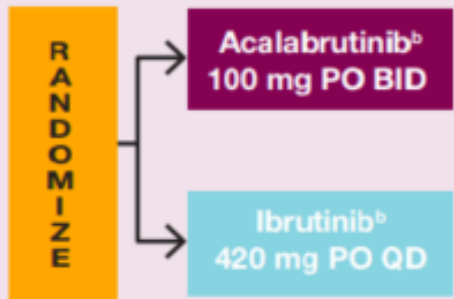
- Both cBTKi and ven-based are options
- Consider pt age, comorbidities, preference on treat-to-progression vs time-limited therapy

Patients (N=533)
Key Inclusion Criteria

- Adults with previously treated CLL requiring therapy (iwCLL 2008 criteria³)
- Presence of del(17p) or del(11q)^a
- ECOG PS ≤2

Key Exclusion Criteria

- Significant CV disease
- Concomitant treatment with warfarin or equivalent vitamin K antagonist
- Prior treatment with ibrutinib, a BCR inhibitor (eg, BTK, PI3K, or Syk inhibitors), or a BCL-2 inhibitor (eg, venetoclax)



Primary endpoint

- Non-inferiority on IRC-assessed PFS

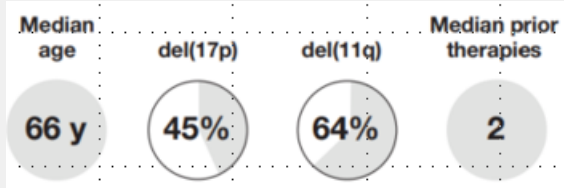
Secondary endpoints (hierarchical order):

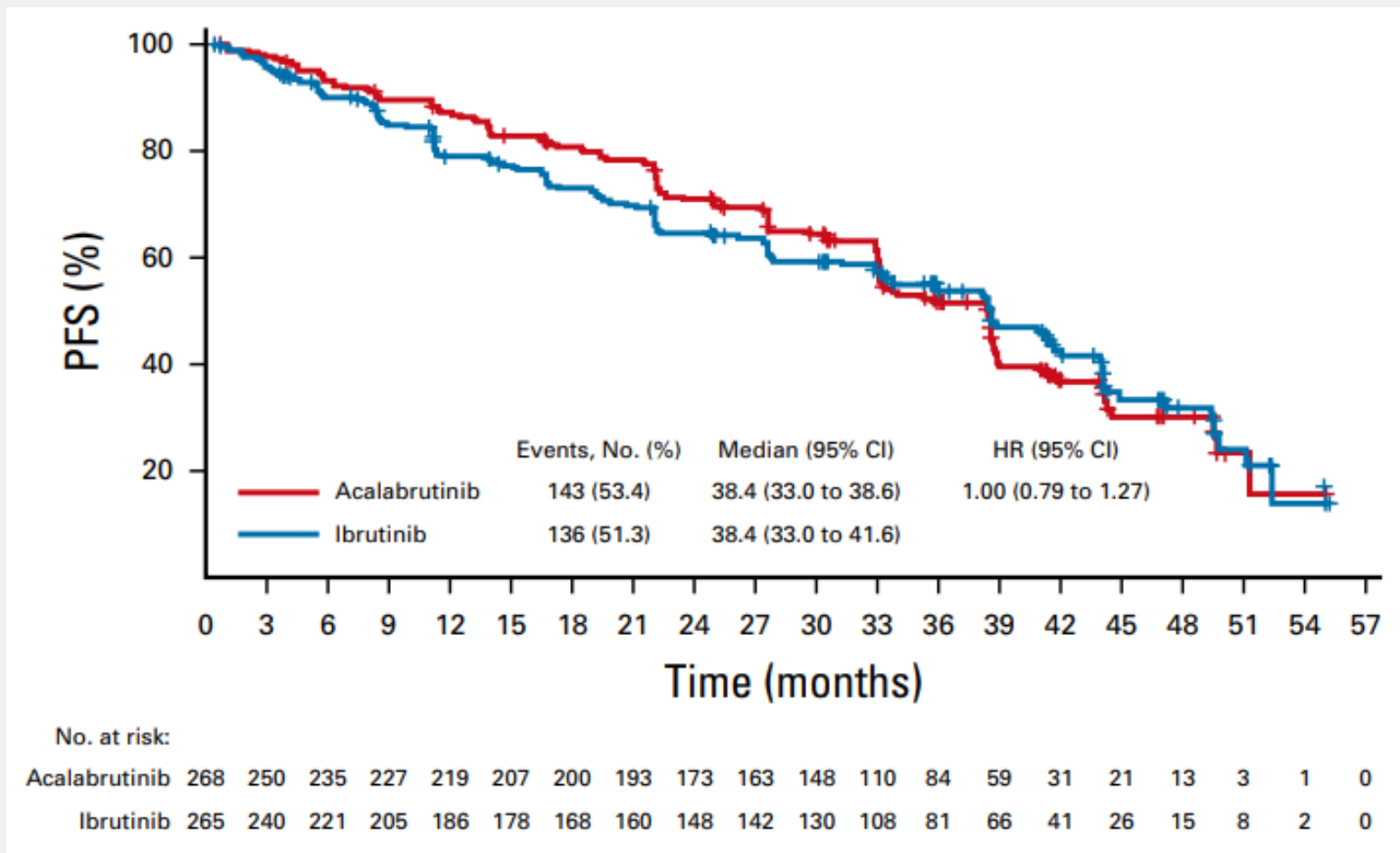
- Incidence of any-grade afib/flutter
- Incidence of grade ≥3 infection
- Incidence of Richter transformation
- Overall survival

Post hoc analysis^c: AE burden score

- Assessed for 1) AEs overall, 2) most common BTK inhibitor-associated AEs, and 3) ECIs afib/flutter, hypertension, hemorrhage, and infections
- The AE burden score was also analyzed by key baseline characteristics, time interval (yearly),^d and polypharmacy status (surrogate for comorbidities)

^aBy central laboratory testing. ^bContinued until disease progression or unacceptable toxicity. ^cData cutoff date for the post hoc analysis was the same as that used in the primary publication (September 15, 2020).² ^dFor the analysis of AE burden score by time interval, for each yearly interval, the end of the AE was defined as the earliest of the end of the AE, end of follow-up year, or end of treatment-emergent period; patients had to be exposed to treatment within the specific year of follow-up to be included in the analysis for that year.





- ELEVATE RR safety
 - Acala had less afib/flutter and less HTN than ibrutinib

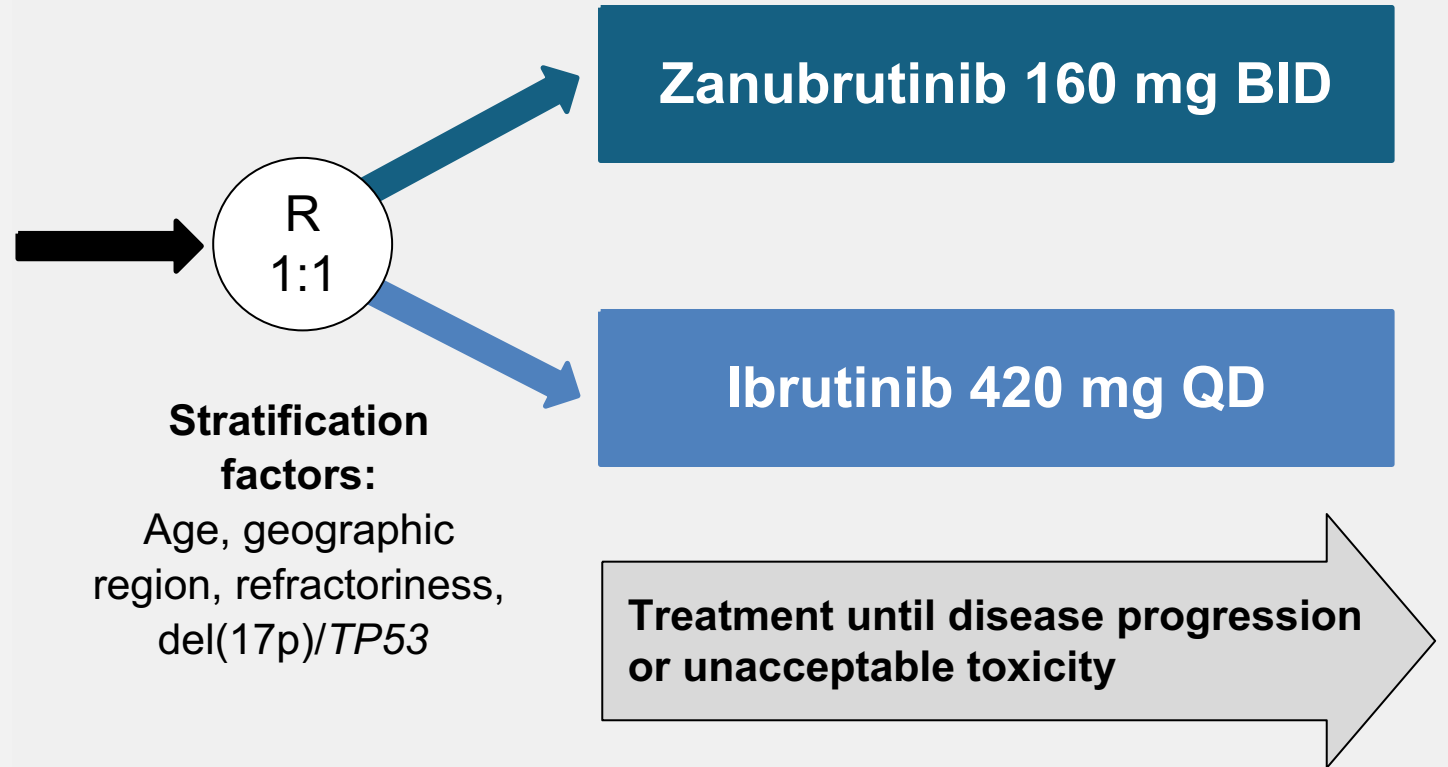
R/R CLL/SLL with ≥ 1 prior treatment (N=652)

Key Inclusion Criteria

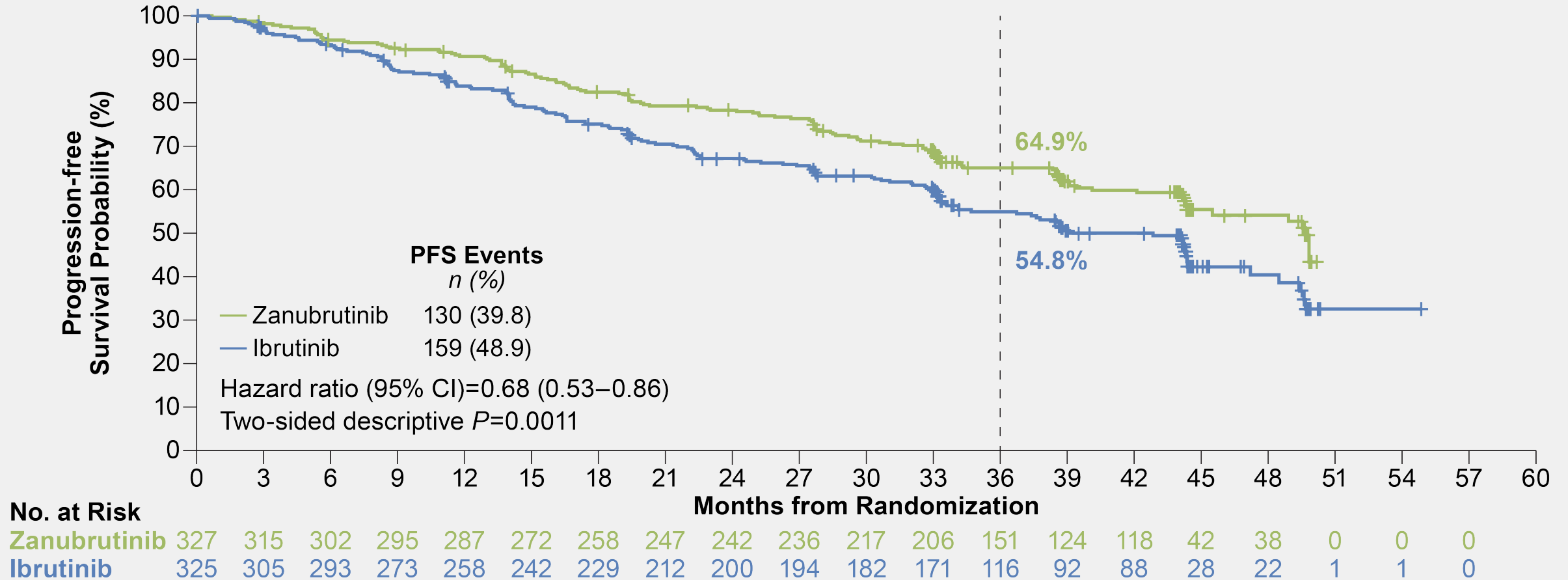
- R/R to ≥ 1 prior systemic therapy for CLL/SLL
- Measurable lymphadenopathy by CT or MRI
- Requires treatment per iwCLL

Key Exclusion Criteria

- Prior BTK inhibitor therapy
- Treatment with warfarin or other vitamin K antagonists



Zanubrutinib is superior to ibrutinib

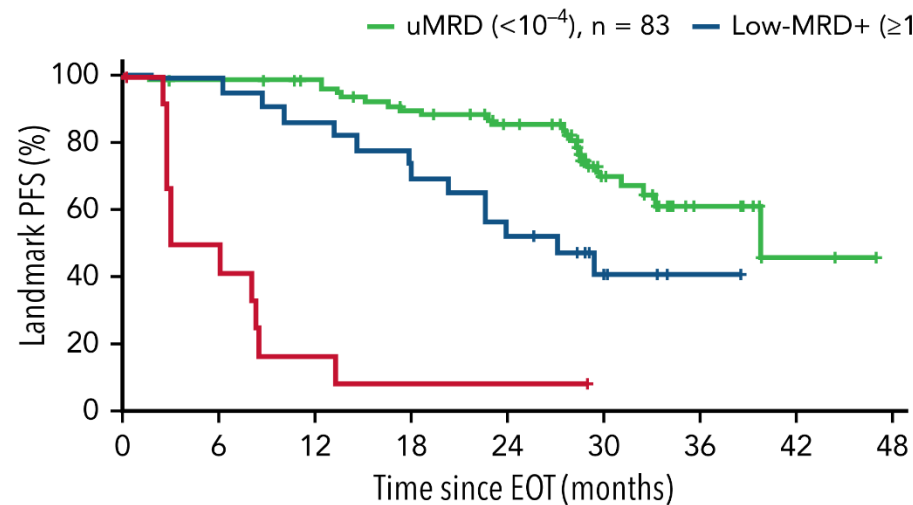


Summary of two H2H covalent BTKi trials

	ALPINE ^{1,2}		ELEVATE-RR ³	
	Zanubrutinib Arm <i>n</i> =327	Ibrutinib Arm <i>n</i> =325	Acalabrutinib Arm <i>n</i> =268	Ibrutinib Arm <i>n</i> =265
Patient Population	ITT in Relapsed CLL		Previously Treated CLL/SLL w/ del(17) or del(11)	
Treatment Duration	To progression or unacceptable toxicity			
Median Follow-up	42.5 months		40.9 months	
IRC-assessed Median PFS	NR	34.2 months	38.4 months	38.4 months
Hazard Ratio	ITT – 0.68 (95% CI; 0.54-0.84) del(17p)/TP53 – 0.51 (95%, CI; 0.33-0.78)		del(17p)/TP53 – 1.00 (95% CI; 0.79-1.27)	

Venetoclax + anti-CD20 antibody

A

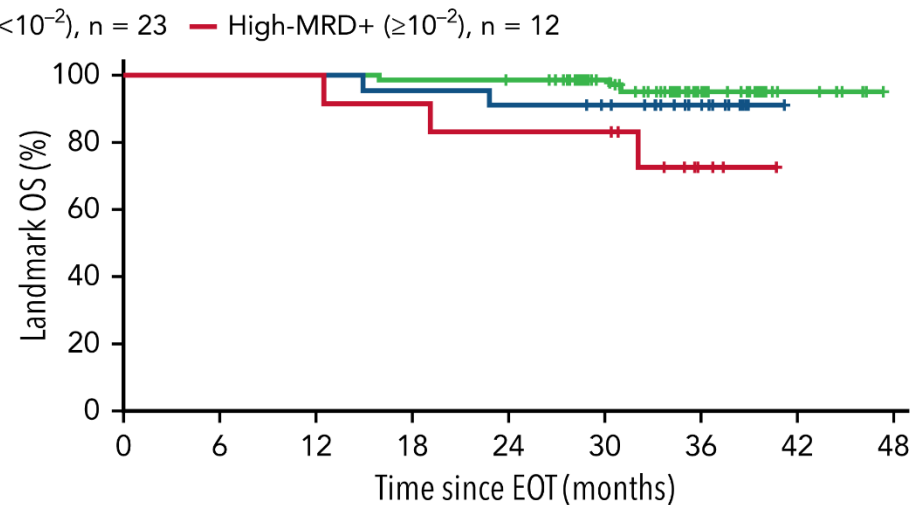


No. of patients at risk

—	83	79	76	67	57	26	9	2
—	23	23	20	16	12	4	1	
—	12	6	2	1	1			

Category	PFS (95% CI) since EOT	
	24-month	36-month
uMRD ($<10^{-4}$)	85.4 (77.4, 93.4)	61.3 (47.3, 75.2)
Low-MRD+ ($\ge 10^{-4}$ - $<10^{-2}$)	52.2 (31.8, 72.6)	40.7 (19.2, 62.2)
High-MRD+ ($\ge 10^{-2}$)	8.3 (0.0, 24.0)	NE
	HR (95% CI)	P value*
uMRD vs. low-MRD+	0.40 (0.18, 0.91)	.0246
uMRD vs. high-MRD+	0.02 (<0.01 , 0.18)	$<.0001$
Low-MRD+ vs. high-MRD+	0.32 (0.10, 0.99)	.0410

B



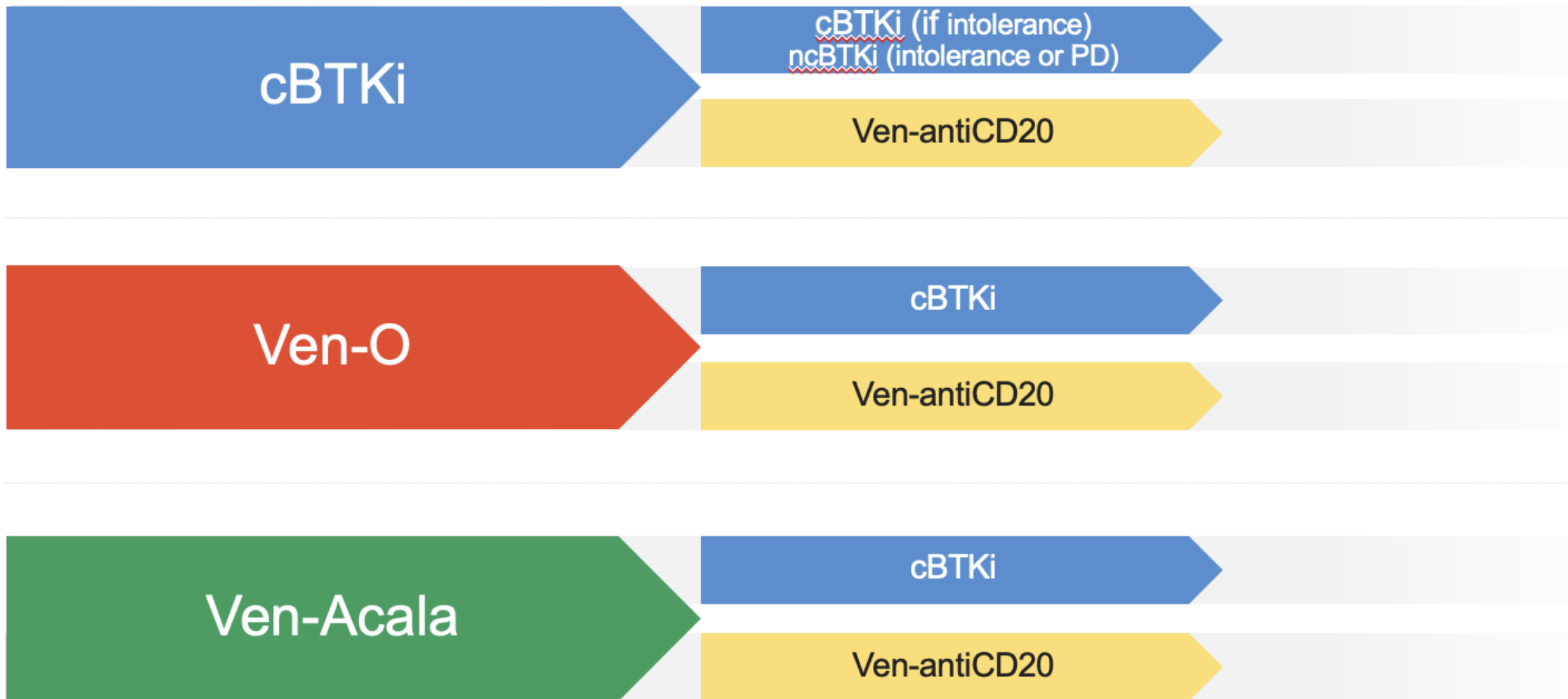
No. of patients at risk

—	83	81	81	80	78	59	26	6
—	23	23	23	22	21	18	9	
—	12	12	12	11	10	10	3	

Category	OS (95% CI) since EOT	
	24-month	36-month
uMRD ($<10^{-4}$)	98.8 (96.4, 100.0)	95.3 (90.0, 100.0)
Low-MRD+ ($\ge 10^{-4}$ - $<10^{-2}$)	91.3 (79.8, 100.0)	91.3 (79.8, 100.0)
High-MRD+ ($\ge 10^{-2}$)	83.3 (62.3, 100.0)	72.9 (46.4, 99.5)
	HR (95% CI)	P value*
uMRD vs. low-MRD+	0.72 (0.11, 4.84)	.7334
uMRD vs. high-MRD+	0.12 (0.01, 1.24)	.0385
Low-MRD+ vs. high-MRD+	0.34 (0.02, 5.33)	.4414

- After covalent BTKi
 - Reason for discontinuation important
 - If intolerance
 - Can switch to alternate covalent BTKi (or pirtobrutinib)
 - If progression
 - Need to switch
 - NCCN and FDA support venetoclax-based approach and pirtobrutinib
- After venetoclax-based
 - How well was ven1 tolerated
 - How long was duration of time off therapy

Many paths to successful CLL disease control in modern era

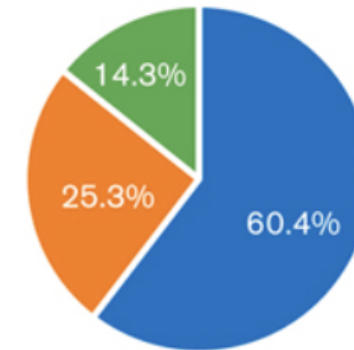


Changing to 2nd generation cBTKi is effective if prior cBTK intolerance

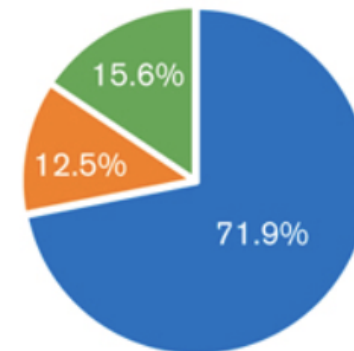
- Acala in setting of ibrutinib intolerance: Rogers et al *Haematologica* 2021
- Zanubrutinib in both ibrutinib and acala intolerance: Shadman et al. *Lancet Haematol* 2023, *Blood Advances* 2025
- Both studies show majority of pts (~70%) experience “improved tolerability” (prior AE resolves or recurs at lower grade) when switching cBTKi
- Another option is treatment holiday which can be considered in pts in good clinical remission when AE occurs

In patients with CLL/SLL, adverse events (AEs) did not recur or recurred at a lower/same grade

Ibrutinib-intolerance events



Acalabrutinib-intolerance events



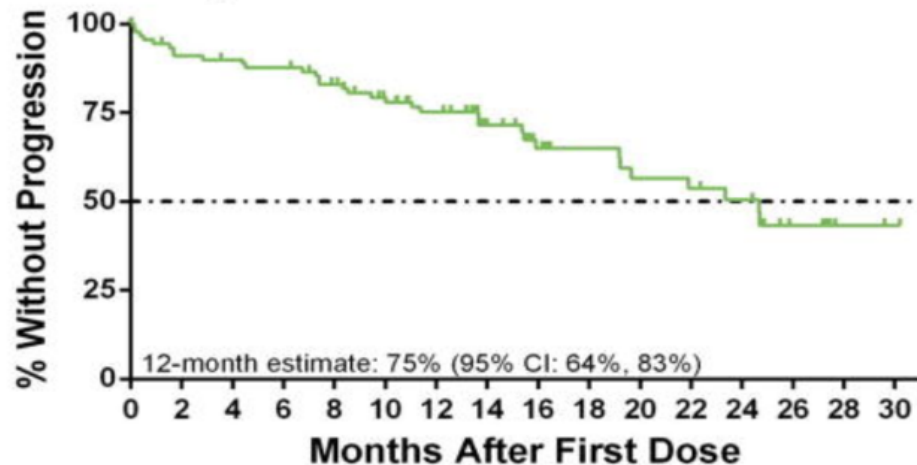
Phase 2¹ N=91

4 prior LOT, 47% del 17p, 33% TP53 mut

ORR 65% with 9% CR/CRi

Median PFS 24.7 mo

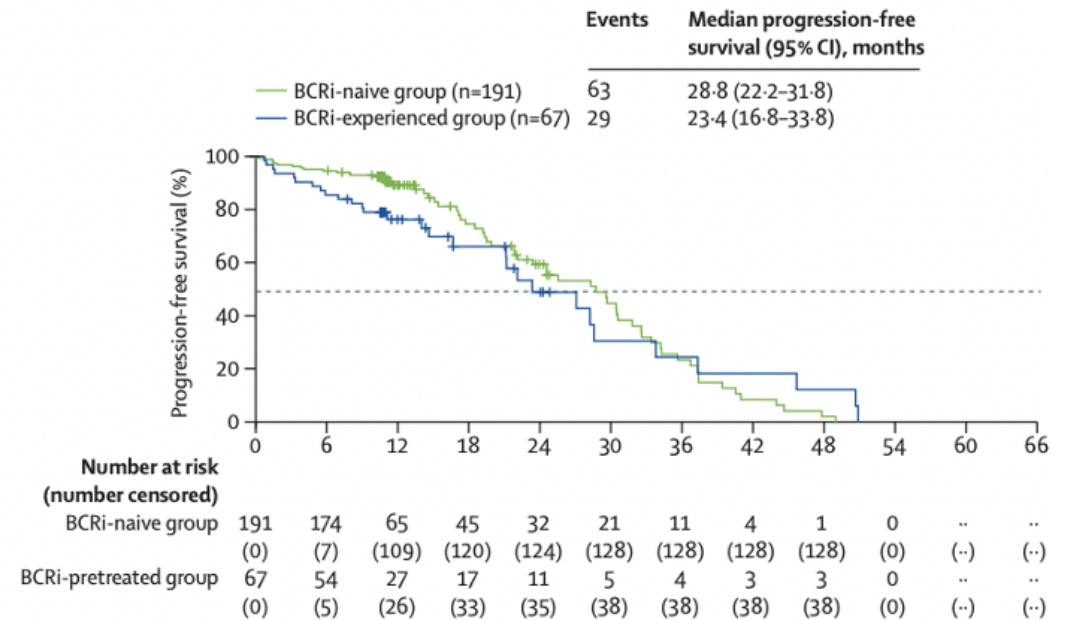
Progression-Free Survival



Number at risk	91	81	79	77	70	61	53	36	28	23	20	18	16	7	4	3
Number censored	0	2	3	3	6	12	17	32	37	42	42	42	44	51	55	56

VENICE-1 trial² (Ph 3b)

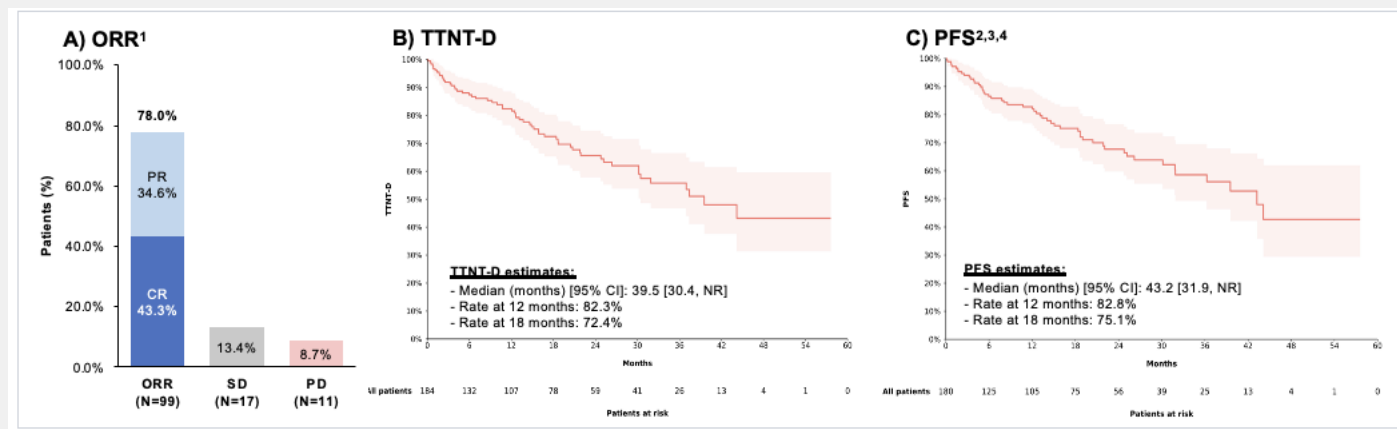
Assessed venetoclax monotherapy in R/R CLL, stratified by previous exposure to a BCRi



1. Jones JA, et al. Lancet Oncol. 2018;19(1):65-75. 2. Kater A, et al. 2024 Apr;25(4):463-473.

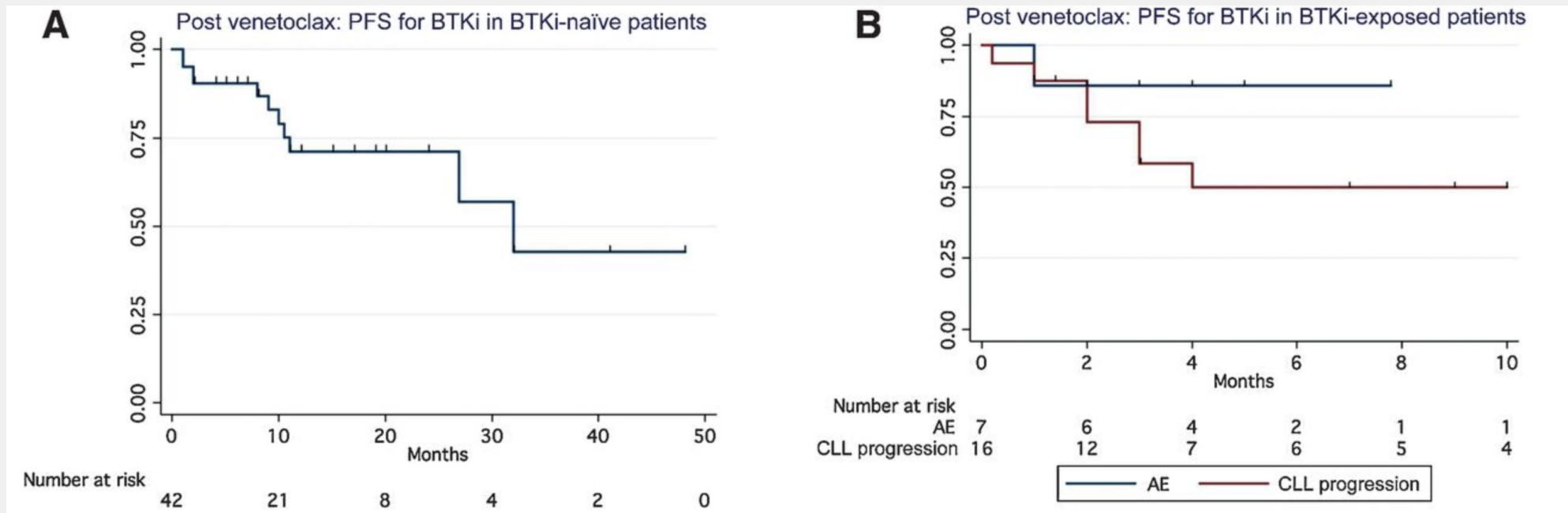
Real world data for venetoclax post-BTKi

- Data were collected as part of CORE study, a retrospective observational study of 23 centers; pts were eligible if they received a venetoclax-based therapy (i.e., monotherapy or combination therapy with rituximab or obinutuzumab) after discontinuation of a cBTKi-based regimen
- Of the 127/184 patients with a documented response, the ORR was 78.0%
- The median TTNT-D across all patients was 39.5 months (95% CI: 30.4, not reached [NR]), with 12- and 18-month rates of 82.3% and 72.4%, respectively
- The median PFS was 43.2 months (95% CI: 31.9, NR), with 18- month rates of 75.1%



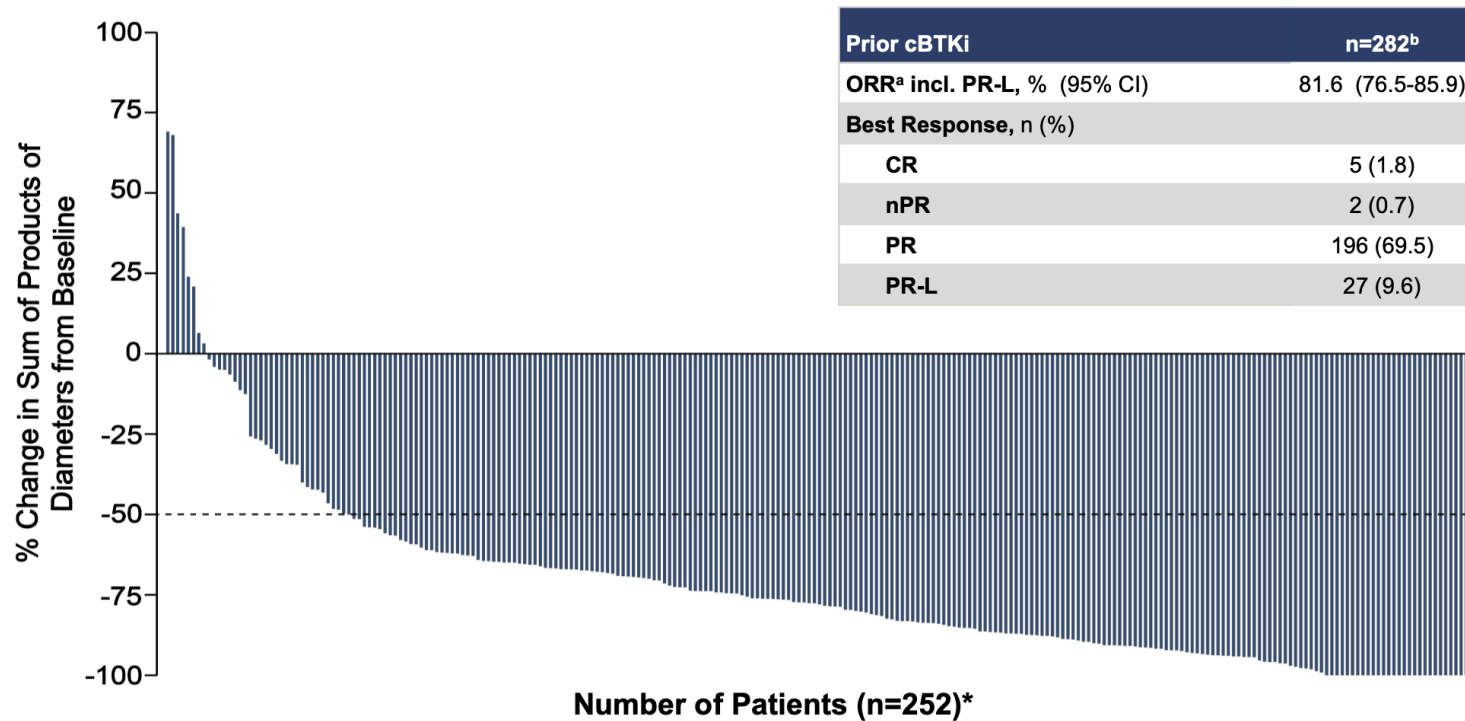
What if ven is used before BTKi?

- International cohort study of 326 patients who discontinued venetoclax and have been subsequently treated
 - 4% frontline ven, 96% ven in relapsed setting
- Patients received a median of three therapies prior to venetoclax; 40% were BTKi naïve ($n = 130$), and 81% were idelalisib naïve ($n = 263$).
- ORR to BTKi was 84% ($n = 44$) in BTKi-naïve patients versus 54% ($n = 30$) in BTKi-exposed patients.



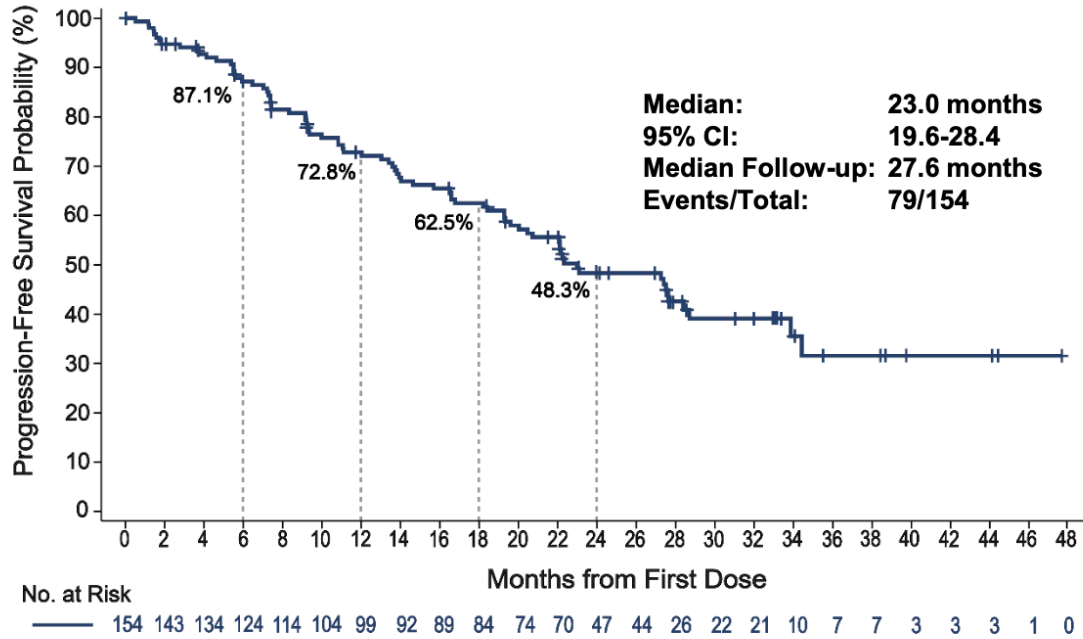
- Non-covalent BTKi that is active regardless of presence/absence of BTK C481S mutation
- Approved in Dec 2023 for pts failed by both cBTKi and venetoclax (accelerated approval) then full approval Dec 2025 based on BRUIN 321 trial

Pirtobrutinib Efficacy in All Patients with CLL/SLL who Received Prior cBTKi

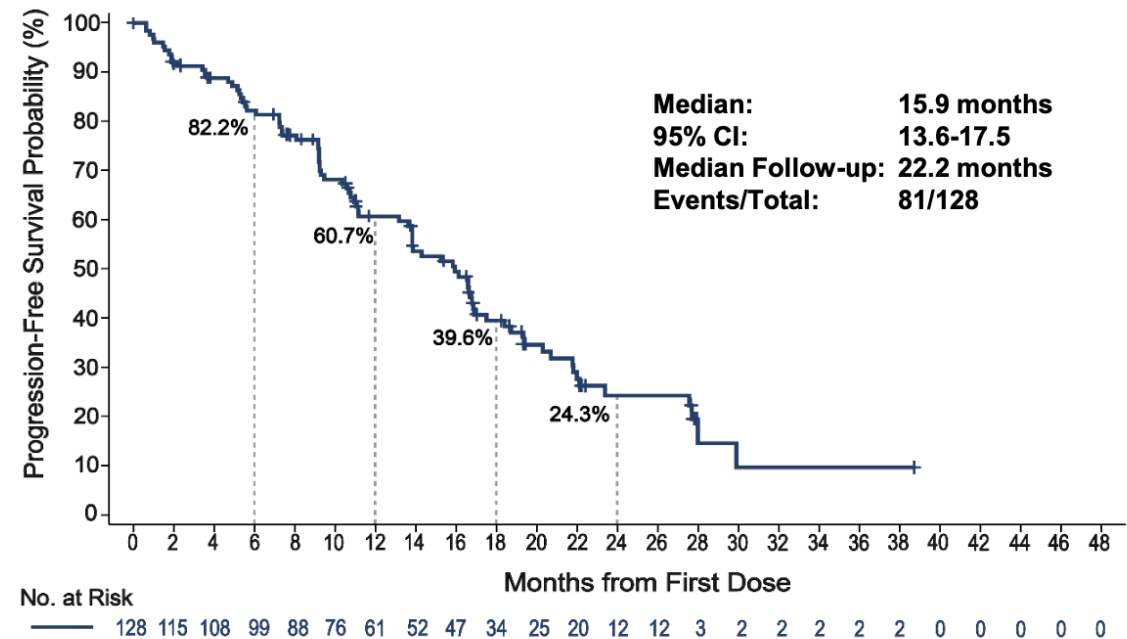


Pirtobrutinib PFS in ven naïve vs ven exposed

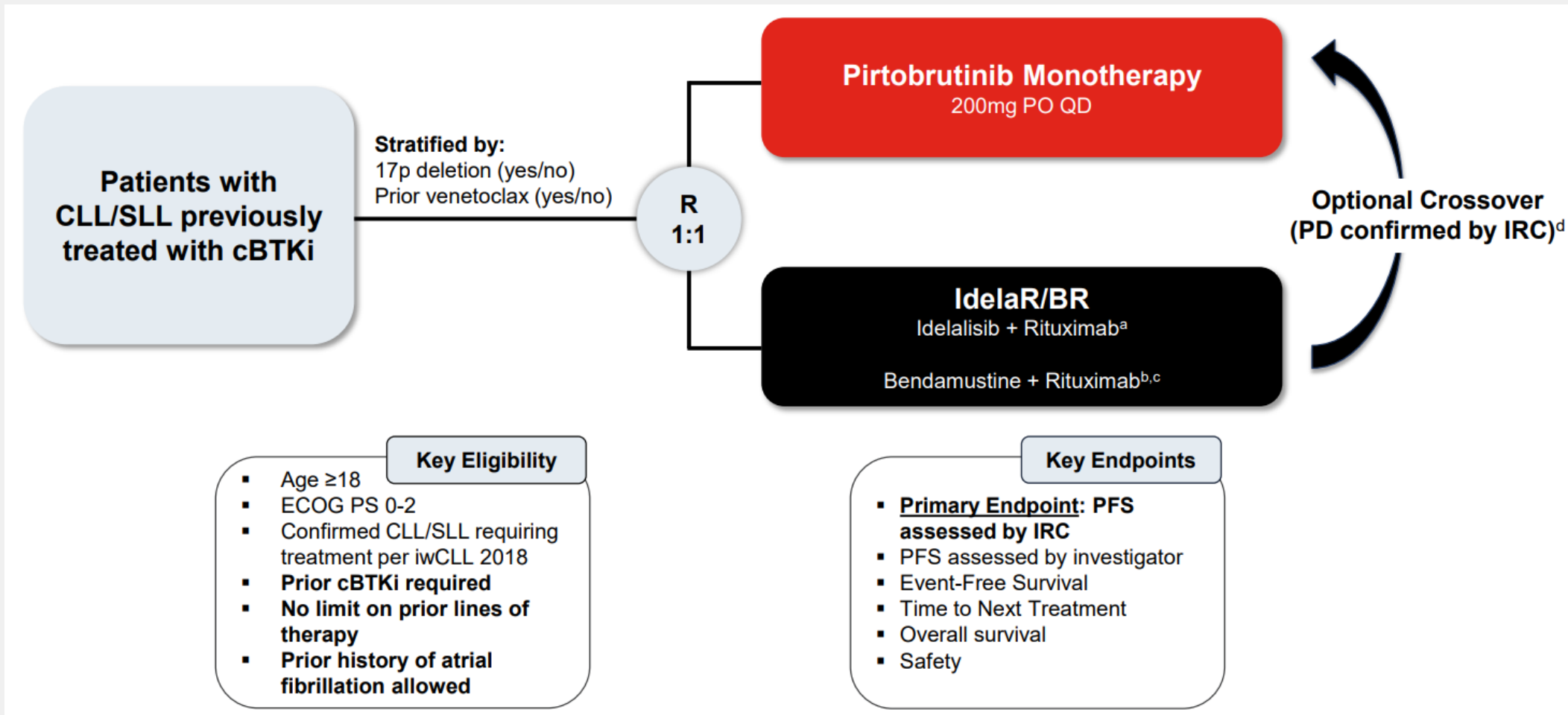
BCL2i-N



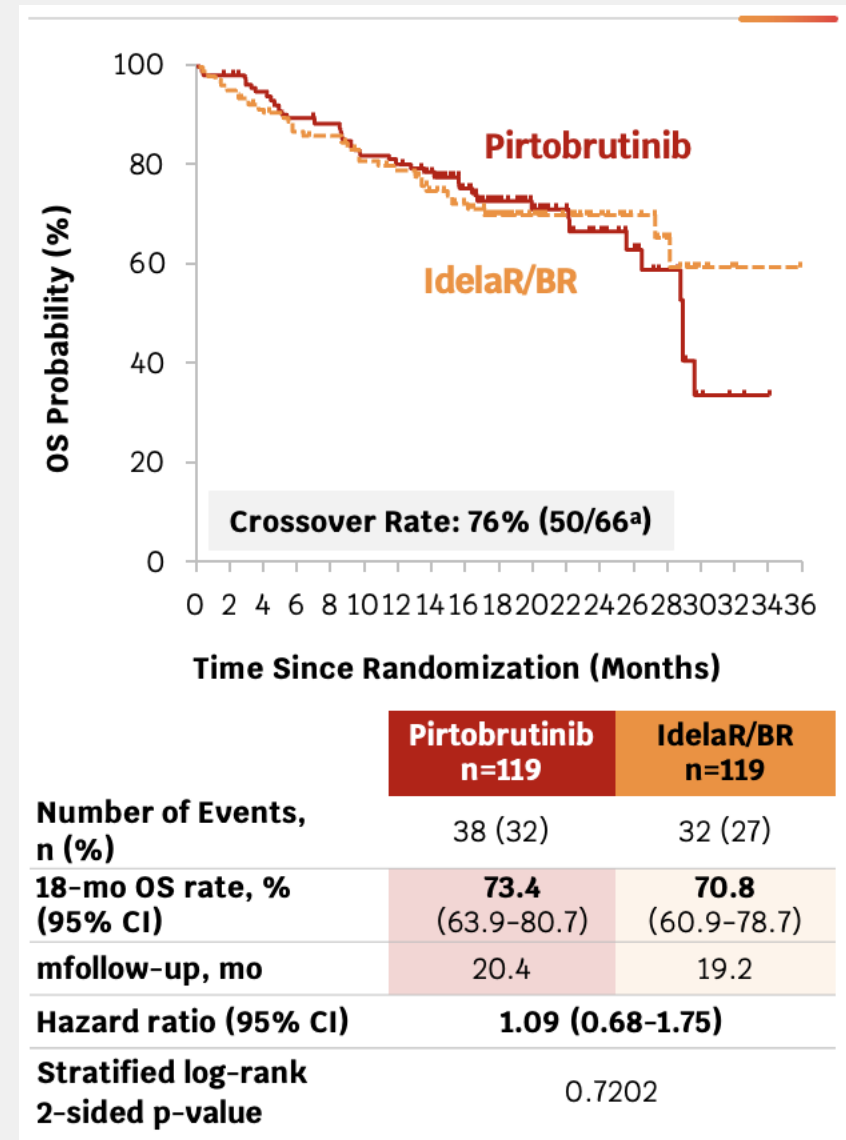
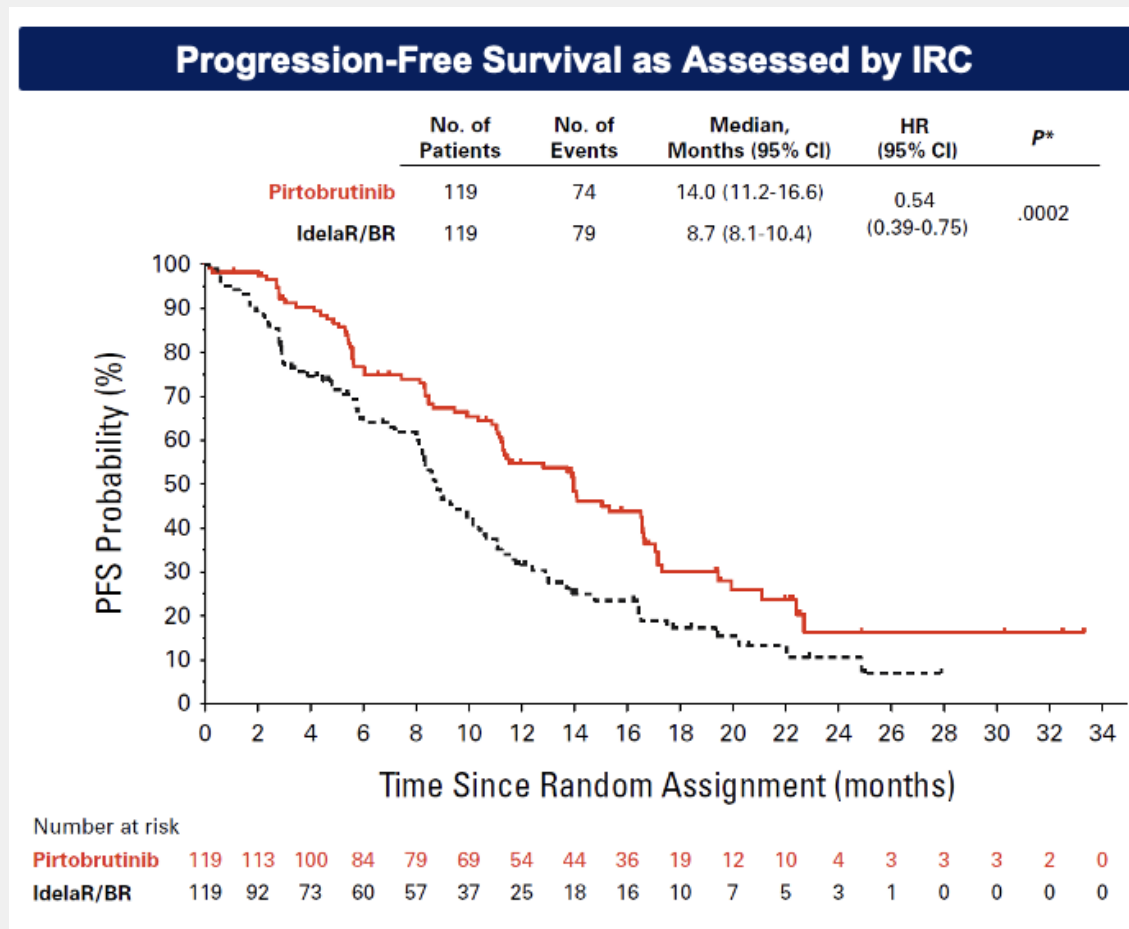
BCL2i-E



Pirtobrutinib after covalent BTKi: BRUIN CLL-321

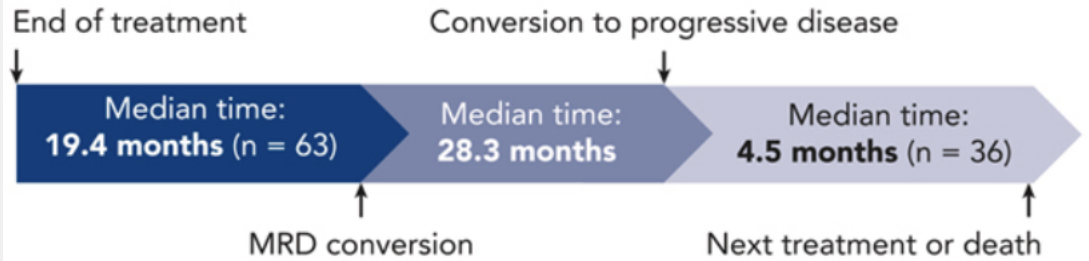


BRUIN CLL-321 key findings



AE	Pirtobrutinib (n = 116)		IdelaR/BR (n = 109)	
	Any Grade, No. (%)	Grade 3/4, No. (%)	Any Grade, No. (%)	Grade 3/4, No. (%)
Anemia	23 (19.8)	13 (11.2)	19 (17.4)	8 (7.3)
Pneumonia	26 (22.4)	18 (15.5)	13 (11.9)	9 (8.3)
Neutropenia	21 (18.1)	17 (14.7)	17 (15.6)	13 (11.9)
Diarrhea	19 (16.4)	0 (0)	34 (31.2)	6 (5.5)
Cough	19 (16.4)	0 (0)	19 (17.4)	0 (0)
COVID-19	15 (12.9)	0 (0)	20 (18.3)	4 (3.7)
Pyrexia	15 (12.9)	1 (0.9)	29 (26.6)	1 (0.9)
Fatigue	13 (11.2)	2 (1.7)	22 (20.2)	1 (0.9)
Nausea	13 (11.2)	1 (0.9)	22 (20.2)	0 (0)
Vomiting	8 (6.9)	1 (0.9)	19 (17.4)	0 (0)
ALT increased	4 (3.4)	1 (0.9)	19 (17.4)	10 (9.2)
Infusion-related reaction	0 (0)	0 (0)	19 (17.4)	3 (2.8)
Weight decreased	4 (3.4)	0 (0)	18 (16.5)	0 (0)

AE of Special Interest	Pirtobrutinib (n = 116)	IdelaR/BR (n = 109)
Anemia ^a	24 (20.7)	19 (17.4)
Atrial fibrillation and atrial flutter	3 (2.6)	1 (0.9)
Bleeding	25 (21.6)	11 (10.1)
Bruising ^b	9 (7.8)	3 (2.8)
Petechiae and purpura	6 (5.2)	1 (0.9)
Hemorrhage ^c	18 (15.5)	8 (7.3)
Hypertension	8 (6.9)	4 (3.7)
Infections ^d	74 (63.8)	54 (49.5)
Infection without COVID-19	67 (57.8)	47 (43.1)
Neutropenia ^e	31 (26.7)	37 (33.9)
Thrombocytopenia ^f	11 (9.5)	17 (15.6)



Kater et al. Blood 2025

Substudy Results

VenR retreatment (n = 25)

Median PFS: 23.3 months

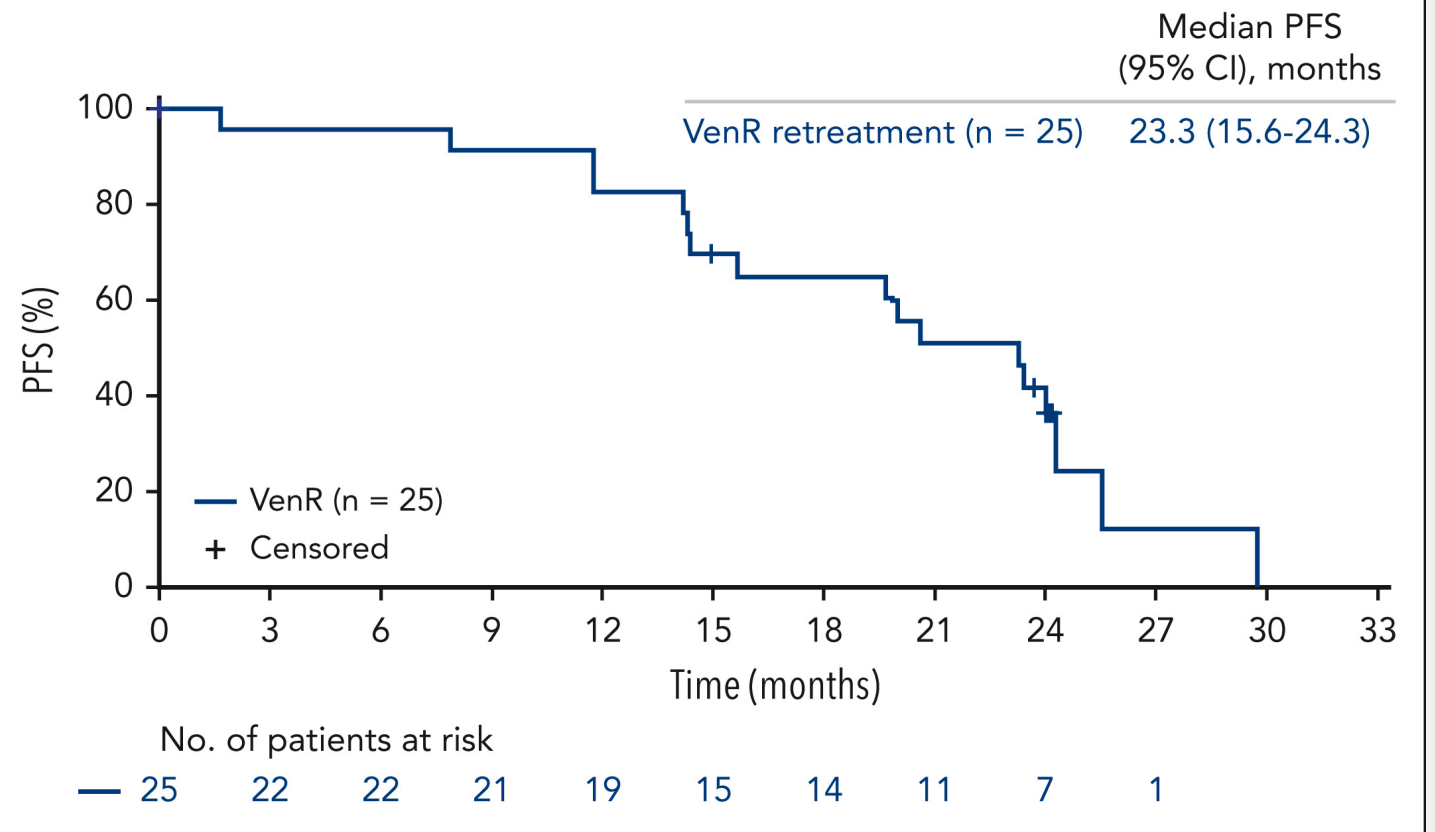
Best overall response rate: 72.0%

VenR crossover (n = 9)

Median PFS: 26.7 months

Best overall response rate: 88.9%

- The best ORR to VenR retreatment was 72.0%; 6 achieved CR, and 12 achieved PR.
- The median DOR was 15.5 months (95% CI, 11.5 to NR).



Study Design

Cohort 1

N≈60
Patients who progressed >24 months after 1L VenO completion

6 Cycles VenO + 6 Cycles Ven Monotherapy

Cohort 2

N≤15
Patients who progressed ≥12-24 months after 1L VenO completion

6 Cycles VenO + 18 Cycles Ven Monotherapy^b

Treatment

28-Day Cycles:

O: 100 mg (IV) D1, 900 mg D2, 1000 mg D8 and D15 of C1; continuing at 1000 mg IV D1 C2-6

Ven: Once-daily (oral) beginning on D22 of C1 with a 5-week dose ramp-up from 20 mg to a target dose of 400 mg; continuing at 400 mg oral daily C3-12 (Cohort 1) or C3-C24 (Cohort 2)

Endpoints^a

Primary Endpoint

- ORR at EoCT (3 months after completing VenO)

Secondary Endpoints

- CR/CRi at EoCT and EoT (3 months after completing Ven monotherapy)
- ORR at EoT
- TTR
- DOR
- uMRD (10^{-4}) measured in PB at EoCT and EoT
- PFS
- OS
- TTNT
- Safety

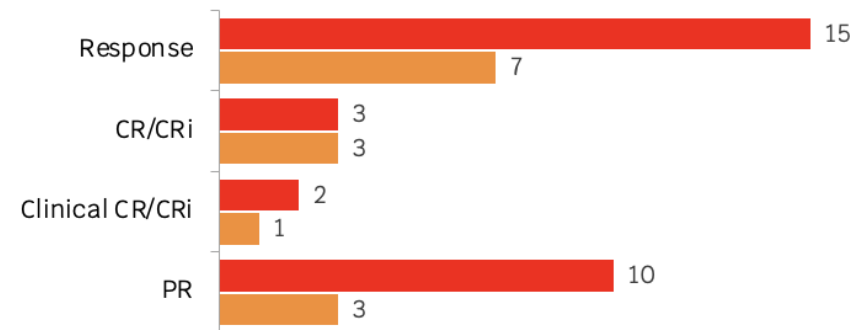
Exploratory Endpoints

- PROs
- MRD kinetics up to 12 months post-treatment
- Correlations of *IgHV*, *TP53* mutation, and *del(17p)* at baseline with treatment outcomes

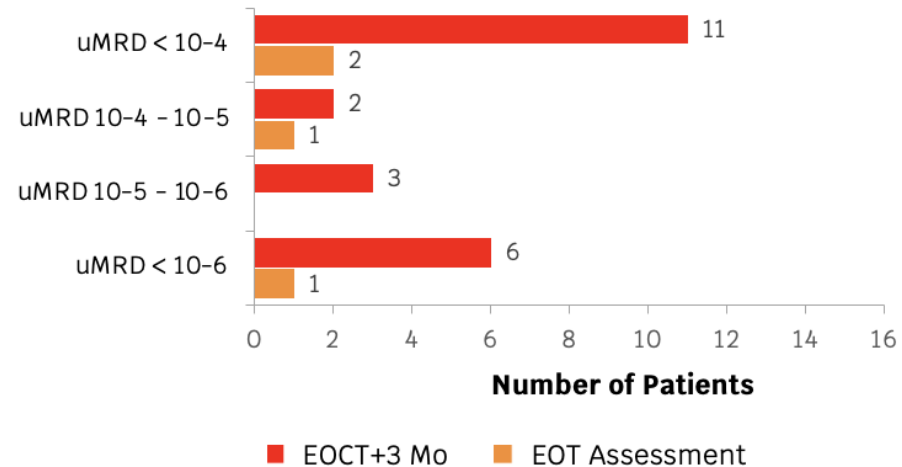
All 15 pts in Cohort 1 who have reached EoCT + 3 mo. to date have achieved response

With a median follow-up time on study of 10.3 mo. (range 2.4-25.1 mo.) one patient has progressed, and all 25 patients are alive

Response assessment (EOCT+3 Mo: N=15; EOT: N=7)



MRD assessment (EOCT+3 Mo: N=13; EOT + 3 Mo: N=4)



- **REtreatment With VEnetoclax and Acalabrutinib After Venetoclax Limited Duration**
- Patients receive 2 cycles of acalabrutinib, followed by 24 cycles VA.
- **44 patients accrued, results from 15 patients presented**
- After cycle 26, 3 (21%) patients had BM uMRD4 (primary endpoint), 6 (43%) low-MRD and 3 (21%) high-MRD.
- **ORR was 100% (36% CR)**
- There were no events of TLS, bleeding, cardiac arrhythmia, or death
- Conclusion: AV induced clinically relevant remission in all patients and decline of MRD rate in PB and BM, but only a minority attained uMRD4

Many potential journeys lead to effective disease control in CLL

- Journey 1: favorable risk pt (mutated IGHV, no TP53 aberration)



- In a higher risk pt



- Journey 2: favorable risk pt. More costly and potential for chronic toxicities.



- And the higher risk



Thank you!

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