EVOLVING THERAPEUTIC STRATEGIES IN R/R CLL

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COACHES
Current Opinions, Advances, Controversies in HEmatology in Salerno

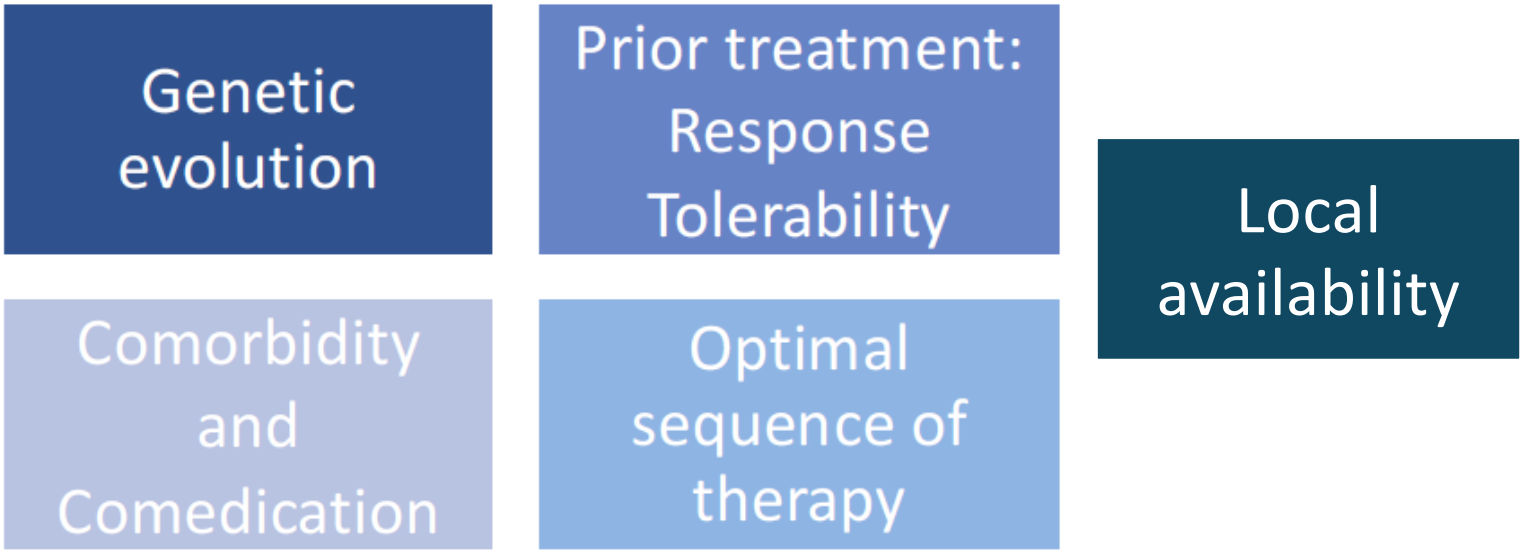
Updates in **Chronic Lymphocytic Leukemia** and **Lymphomas**

Salerno | **14 aprile 2025** | Grand Hotel Salerno

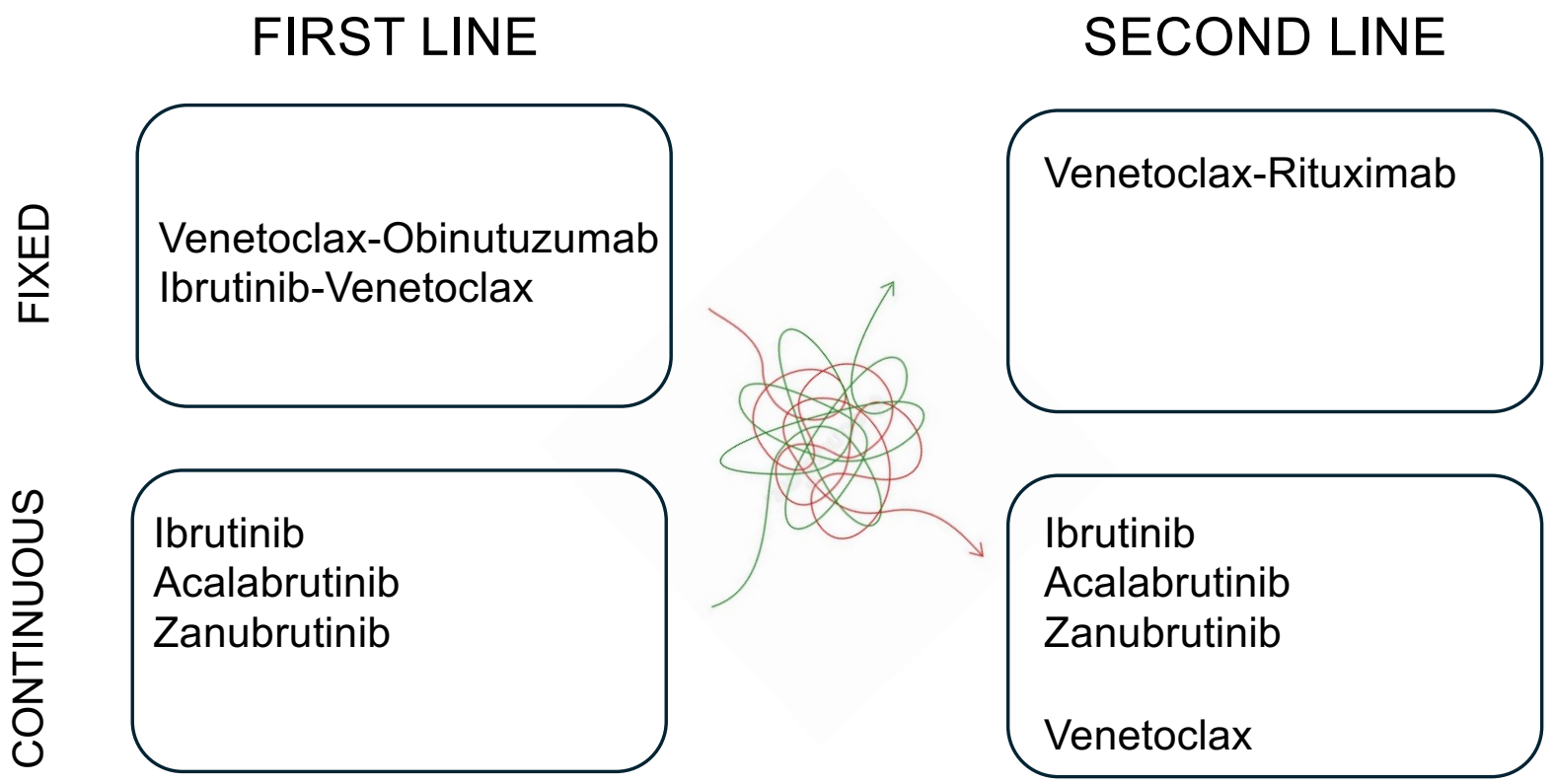
DISCLOSURES: Marta Coscia

Company	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
Abbvie	**X**					**X**	
AstraZeneca					**X**	**X**	
Beigene						**X**	
GSK	**X**					**X**	
J&J	**X**					**X**	

Relevant factors to choose **relapse therapy**



Fixed vs Continuous: a wide range of possible sequencing combinations



Both cBTKi and BCL2i +/- anti-CD20 mAb are highly effective therapies for R/R CLL

These therapies may be used sequentially in either order (independent mechanisms of action and resistance)

SECOND-LINE THERAPY IN CLL

Frontline therapy →

CIT

Second-line therapy →

Fixed duration (VenR)

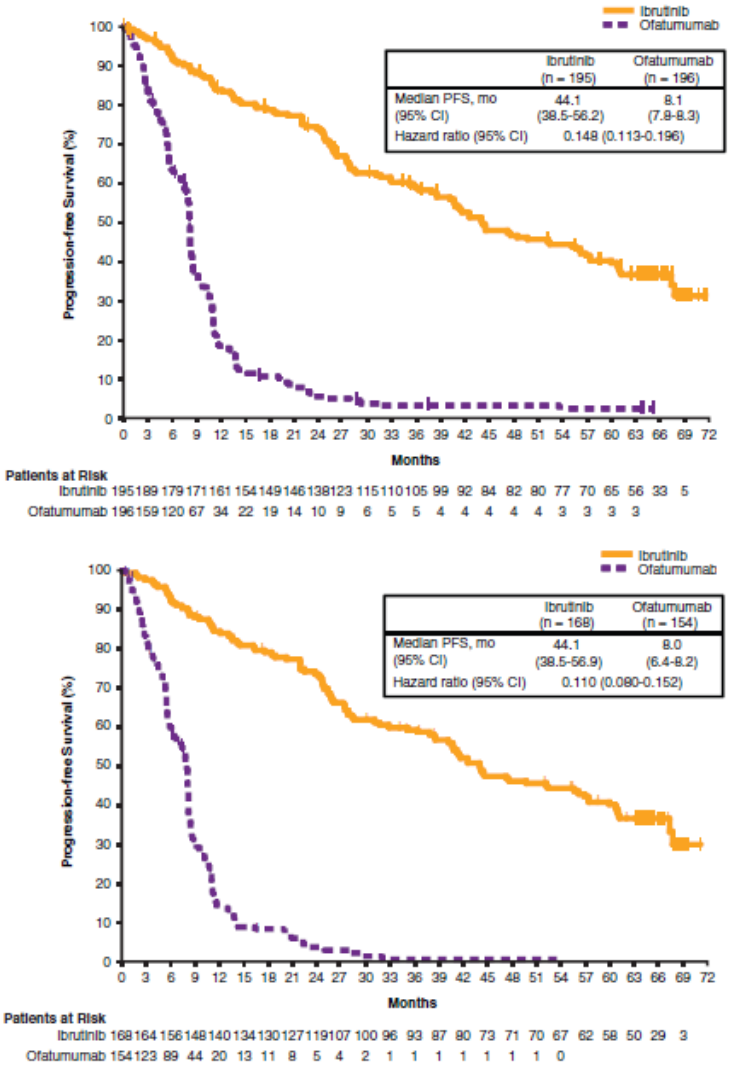
Continuous (cBTKi)

- **Acalabrutnib**
- **Ibrutinib**
- **Zanubrutinib**

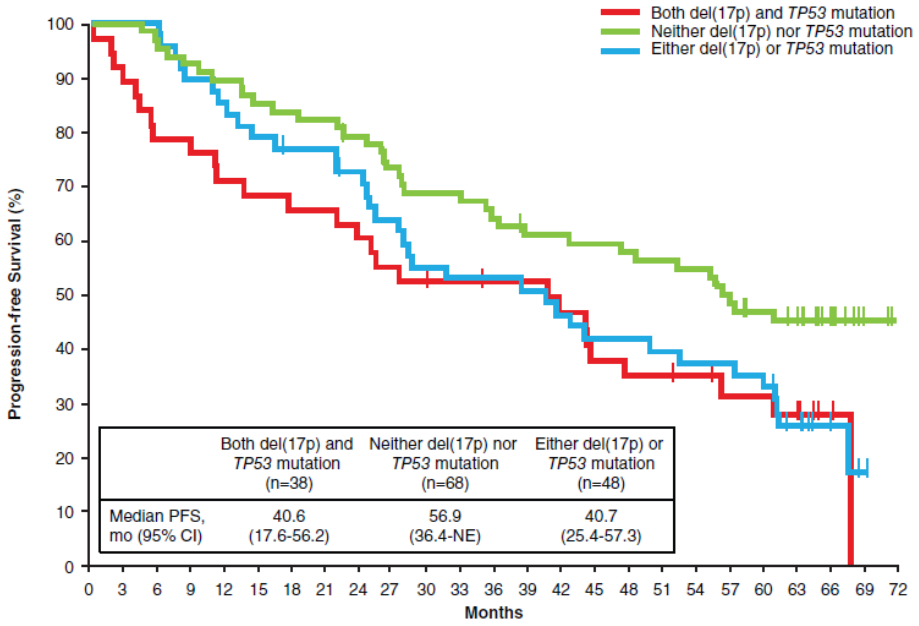
Decision Criteria

DISEASE RELATED	PATIENT RELATED
<u>Genetic risk</u>	<u>Age & Fitness status</u>
• Del17p	• Comorbidities
• TP53 gene mutations	• Concomitant medications
• IGHV mutational status	• Renal function

Ibrutinib in R/R CLL patients – final analysis of RESONATE



Median follow up 65 months

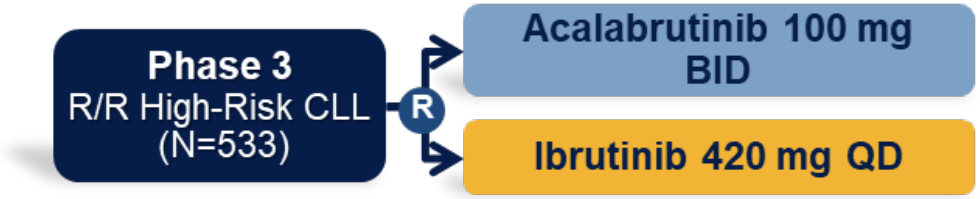


CIT → Progression → cBTKi

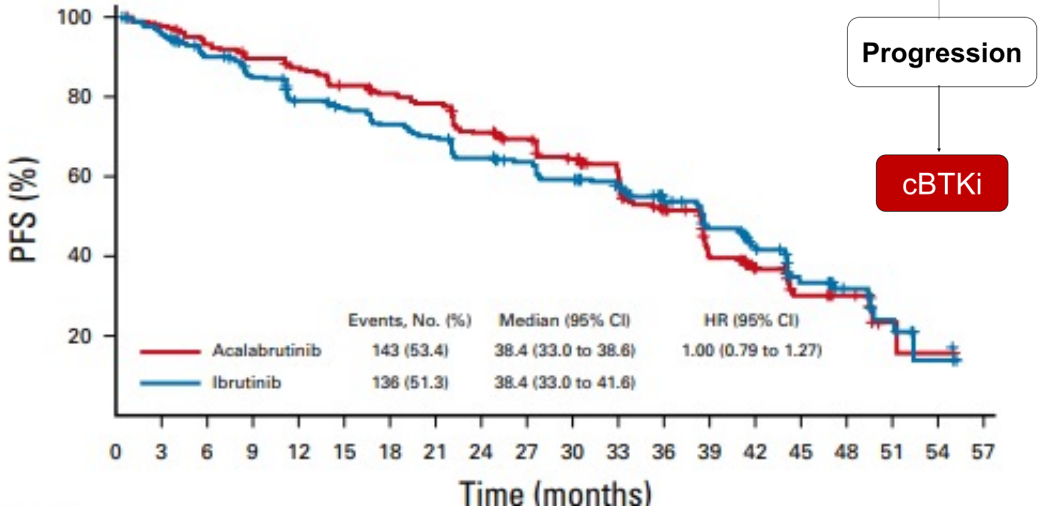
Munir T et al. Am J Hematol 2019

Acalabrutinib in R/R CLL patients – ELEVATE-RR

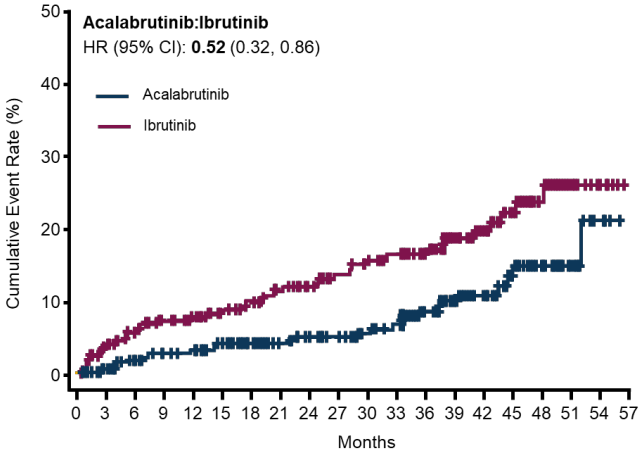
ELEVATE-RR (ACE-CL-006)



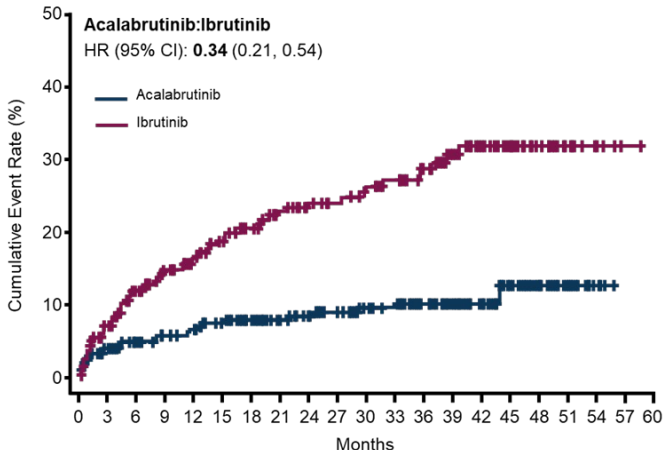
- Randomized, open-Label, non-inferiority, phase 3 study in previously treated CLL with del(17p) or del(11q)
- 45.2% del(17p) and 64.2% del(11q)



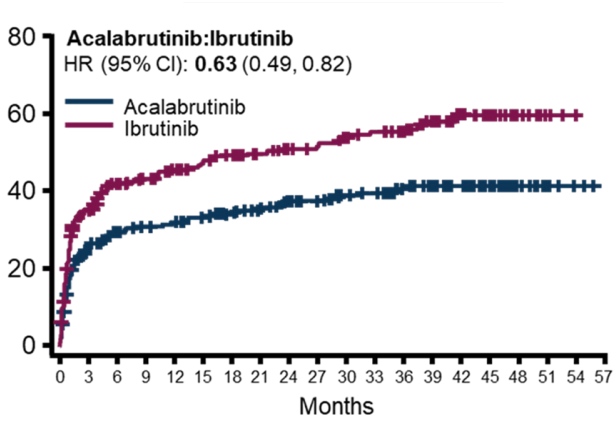
Atrial fibrillation/flutter



Hypertension

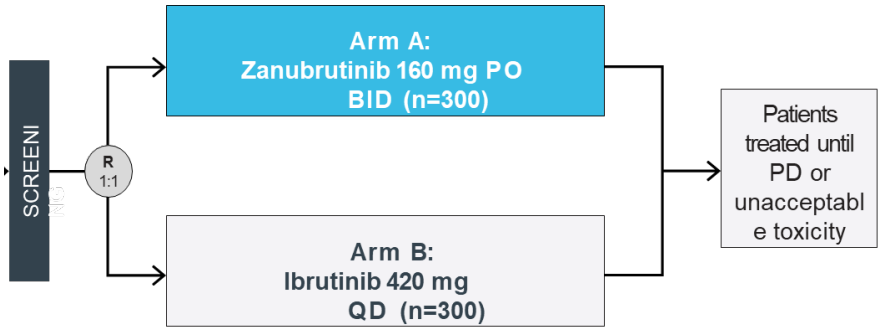


Bleeding events

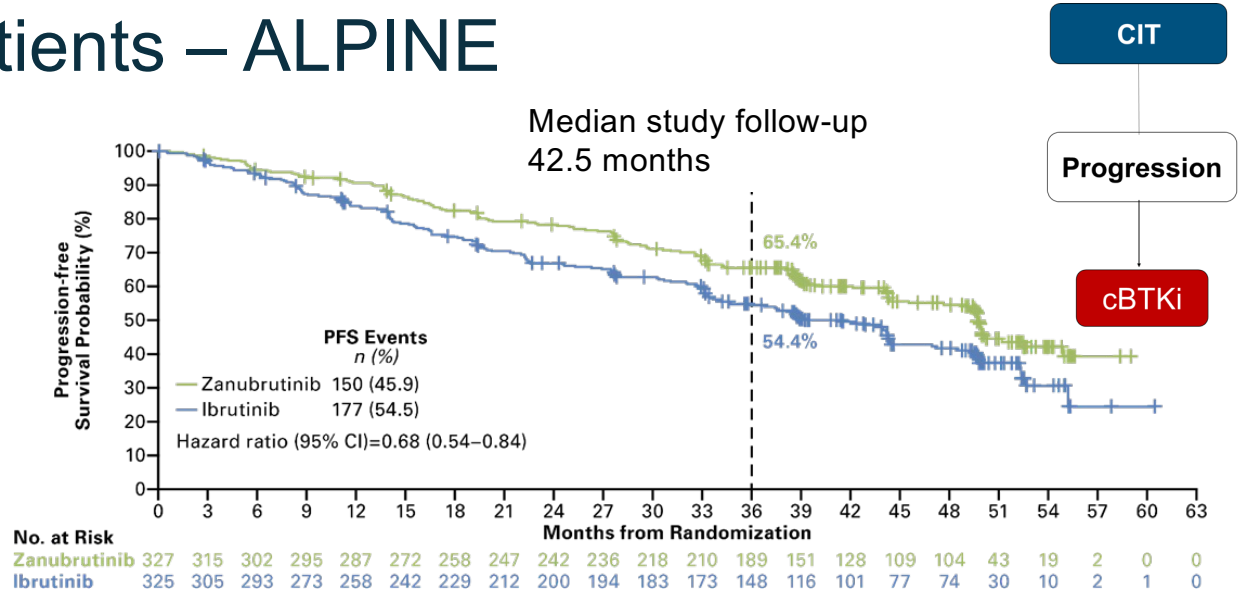


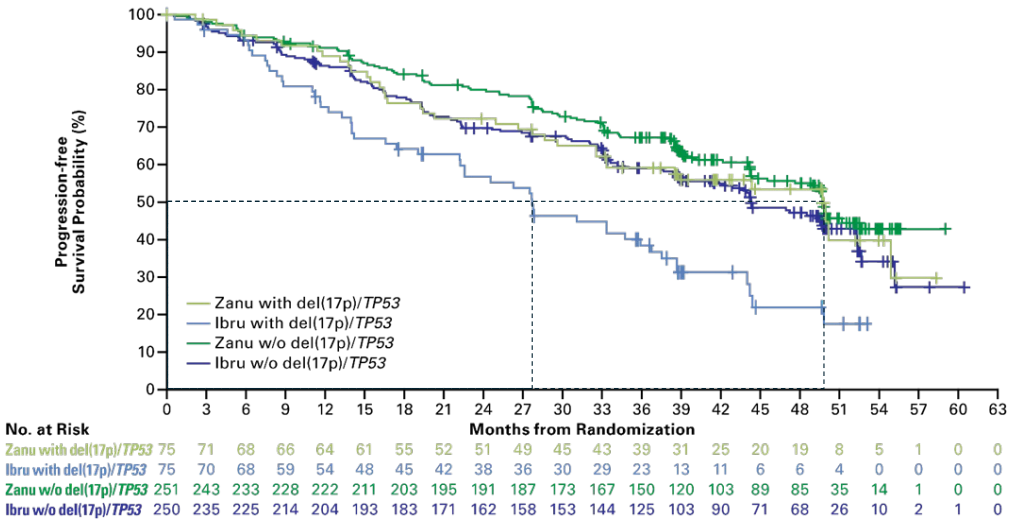
1. Hillmen P, et al. Oral S145. EHA2021 Congress. June 9-17, 2021; 2. Byrd JC, et al. J Clin Oncol . 2021

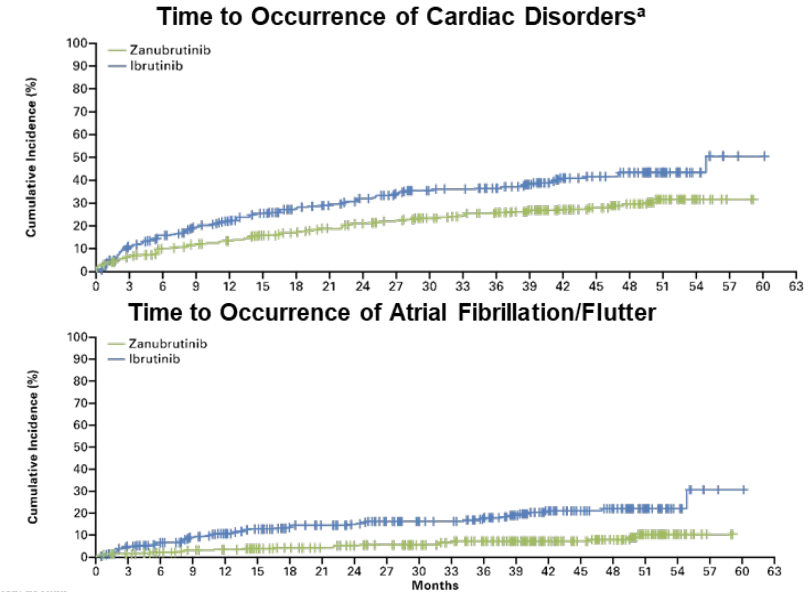
Zanubrutinib in R/R CLL patients – ALPINE



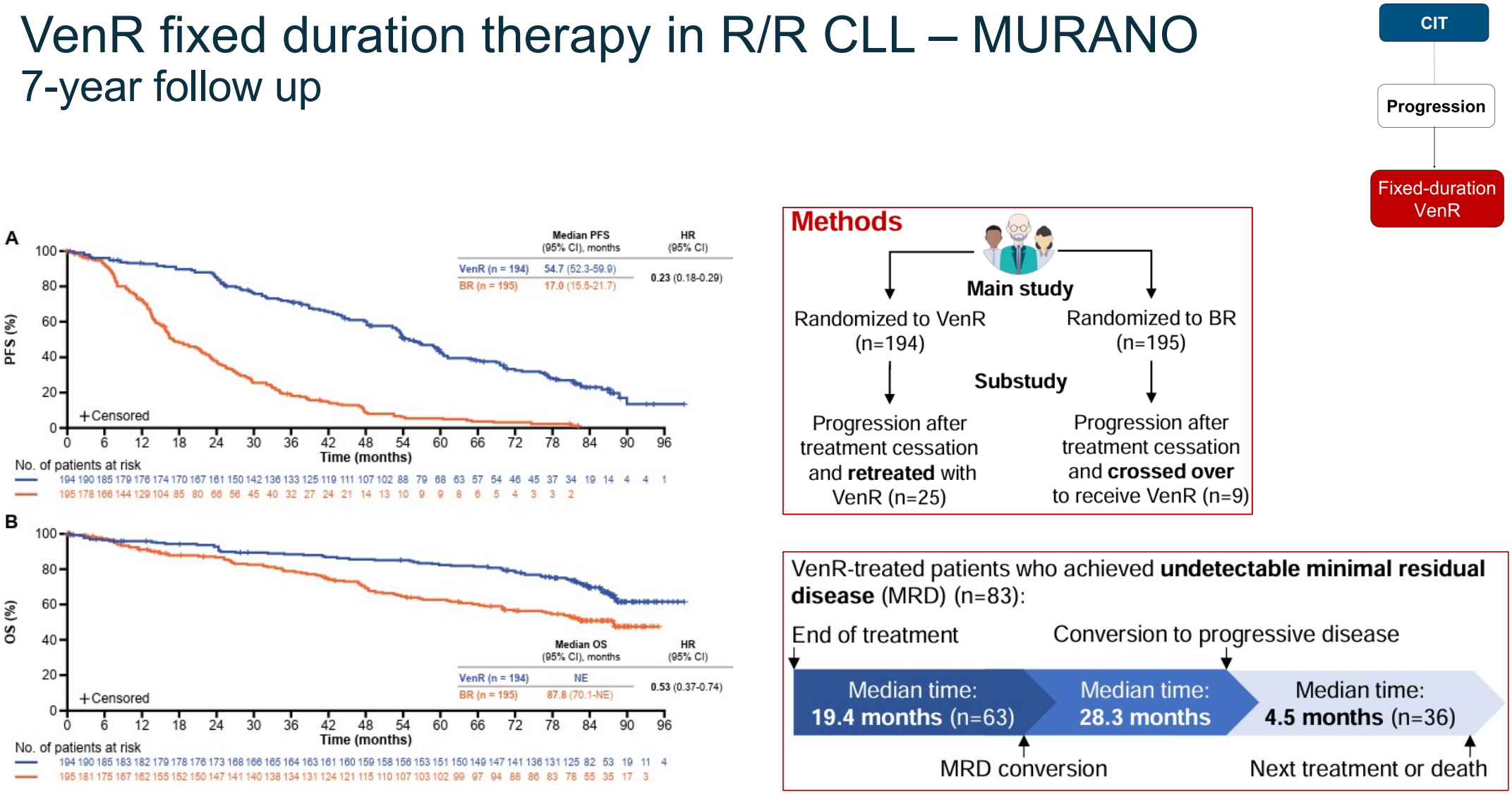
Randomized, open-Label, phase 3 study in previously treated CLL





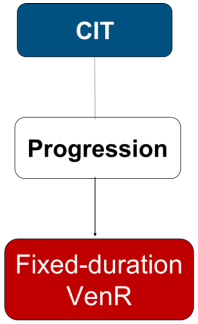


VenR fixed duration therapy in R/R CLL – MURANO
7-year follow up



Kater AP et al. Blood 2025

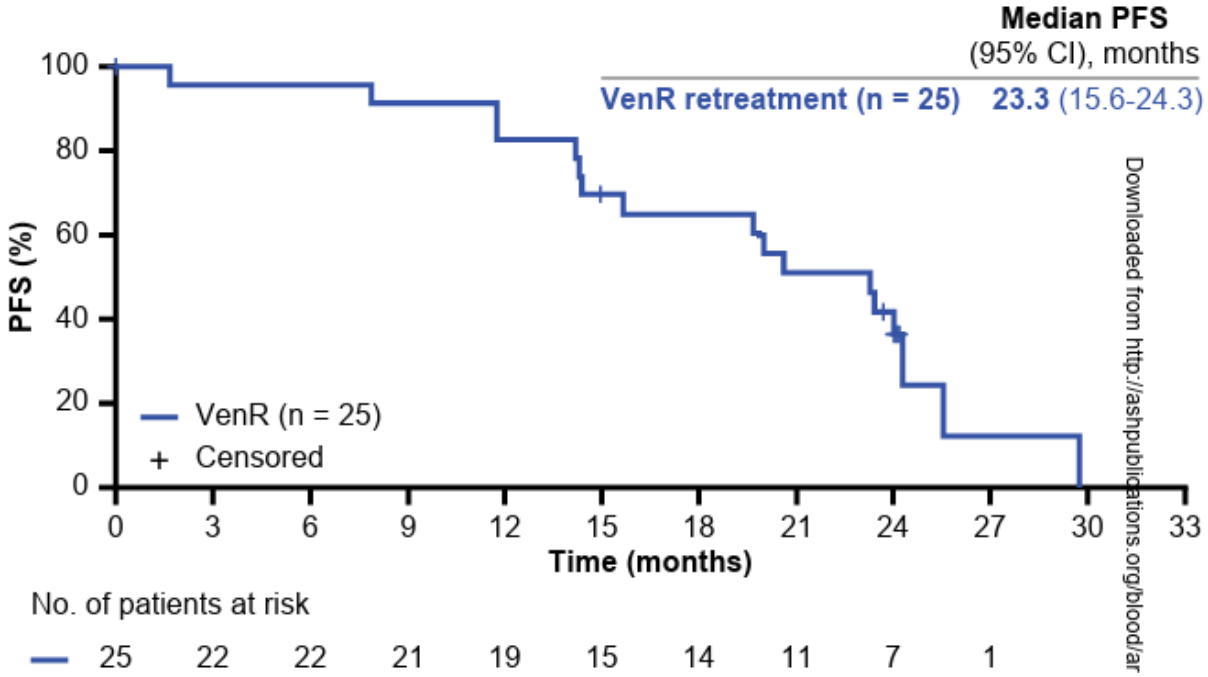
VenR fixed duration therapy in R/R CLL – MURANO
7-year follow up



Substudy Results

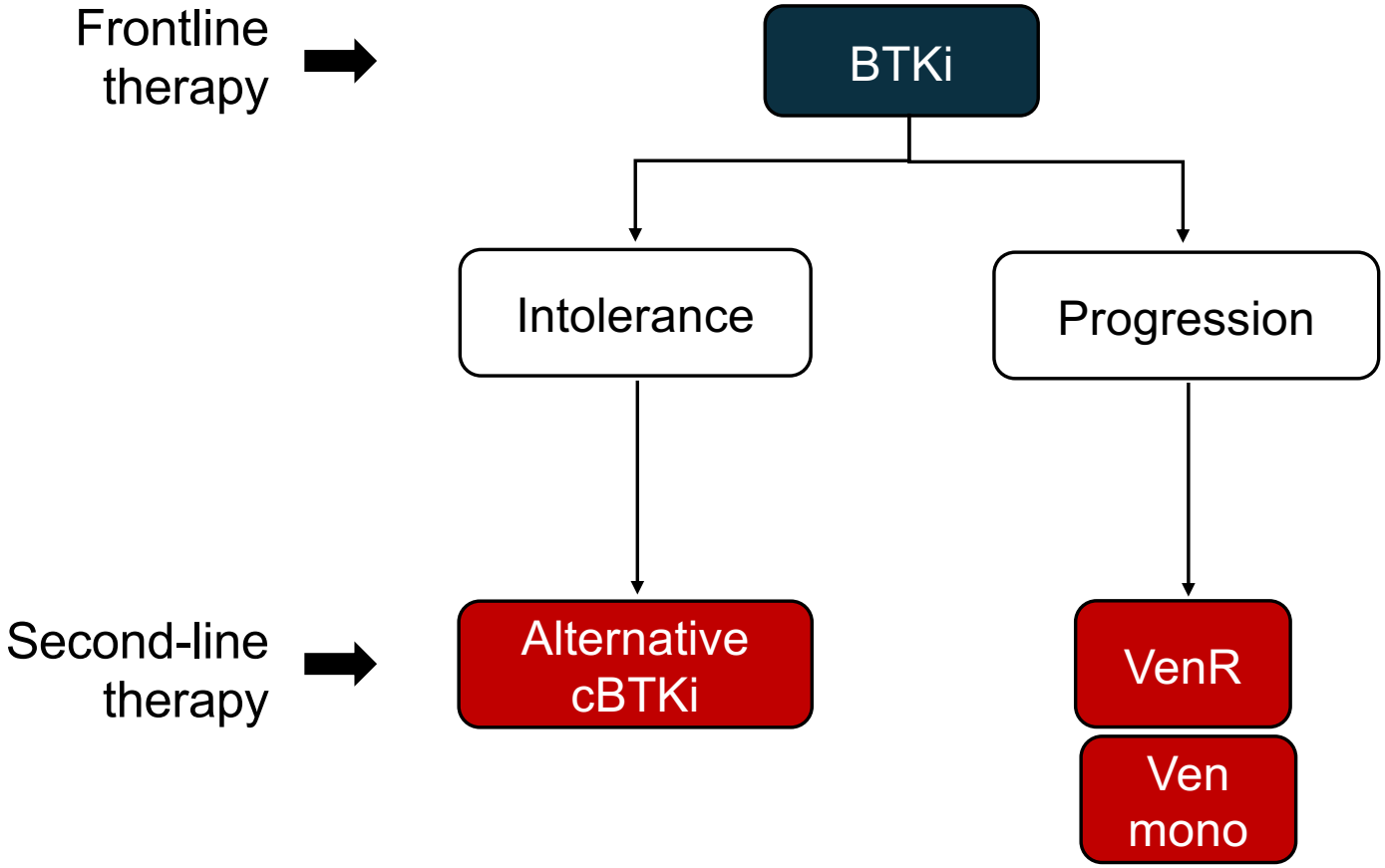
VenR retreatment (n=25)
Median PFS: 23.3 months
Best overall response rate: 72.0%

VenR crossover (n=9)
Median PFS: 26.7 months
Best overall response rate: 88.9%

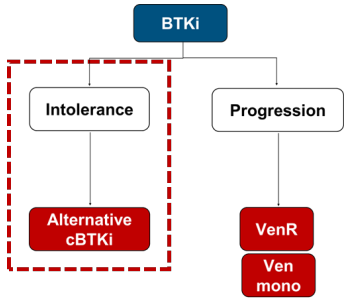


Kater AP et al. Blood 2025

SECOND-LINE THERAPY IN CLL

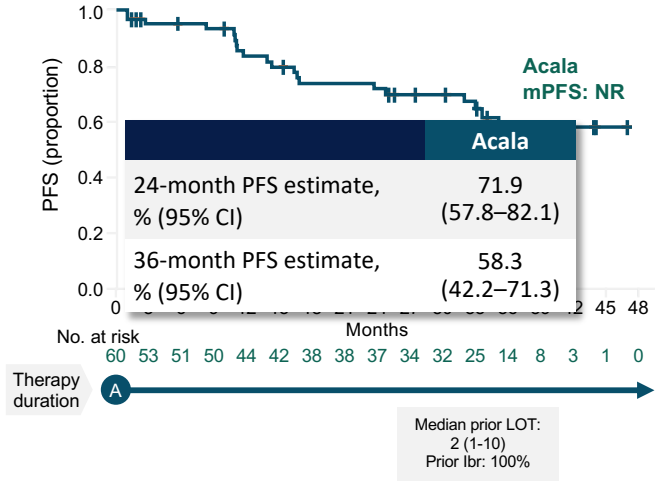


cBTKi shifting in patients intolerant to a previous cBTKi

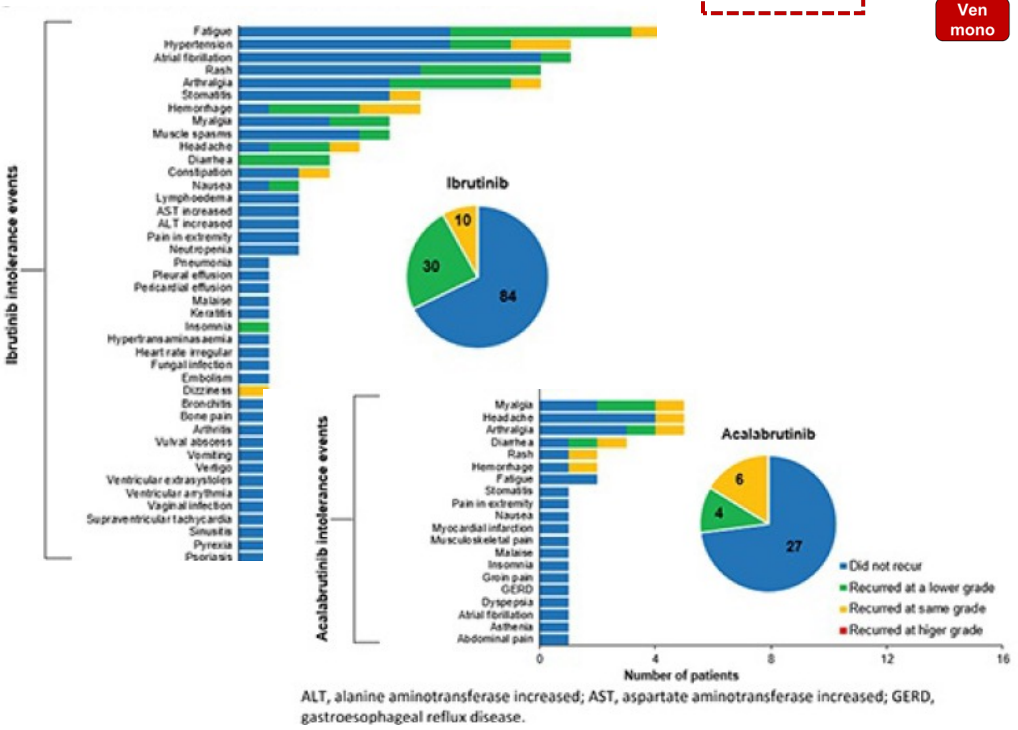


Ibru → Acala (ACE-CL-208)

Events Resulting in Ibrutinib Intolerance*	No. of Patients	Acalabrutinib Experience for Same Patient, n			
		Overall	Lower Grade	Same Grade	Higher Grade
Atrial fibrillation	16†	2	2	0	0
Diarrhea	7	5	3	2	0
Rash	7	3	3	0	0
Bleeding‡¶	6	5	3	2	0
Arthralgia	7§	2	1	1	0



Ibru/Acala → Zanu (BGB-3111-215)



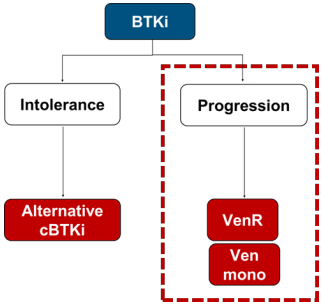
ALT, alanine aminotransferase increased; AST, aspartate aminotransferase increased; GERD, gastroesophageal reflux disease.

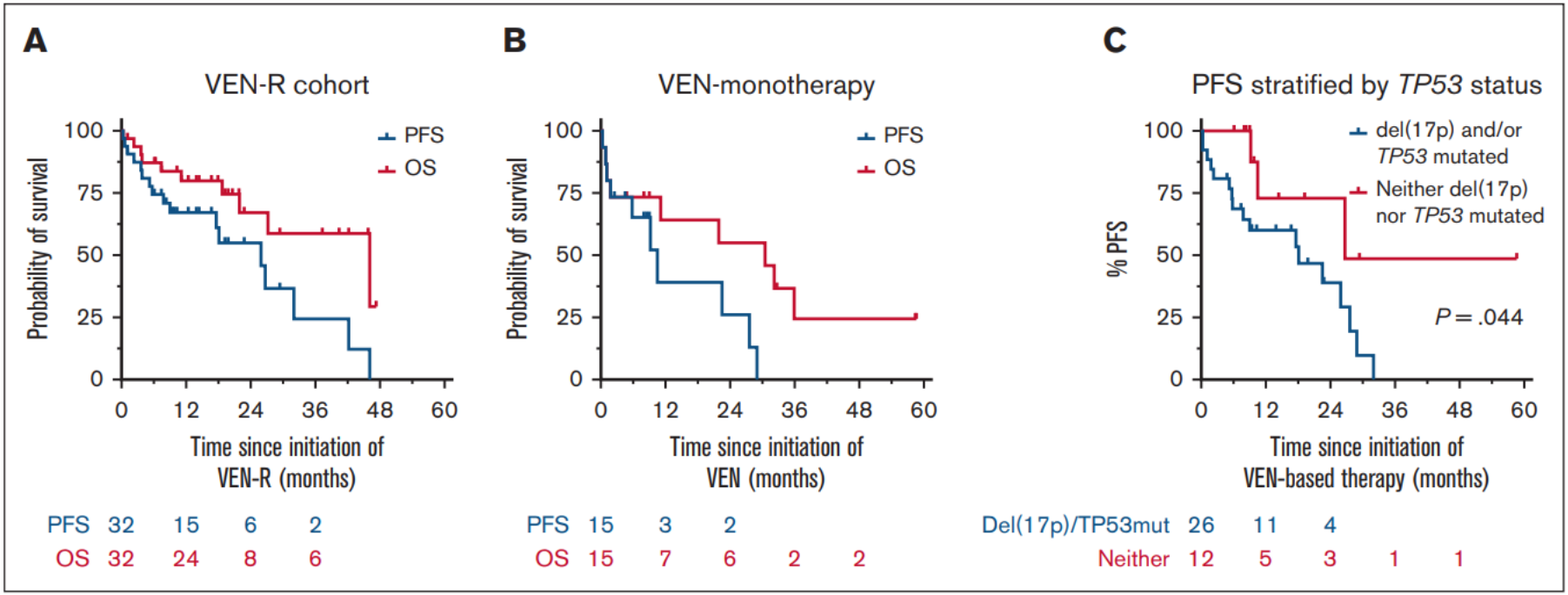
In efficacy evaluable pts, disease was controlled (SD/PR/CR) in 96% pts previously intolerant of only ibrutinib and 95% pts previously intolerant of acalabrutinib

Rogers KA, et al. *Haematologica* 2021
Shadman M, et al. *Lancet Haematol*. 2023
Shadman M, et al. *EHA*. 2023

BTKi cycling is effective

Ven-R in BTKi-exposed CLL

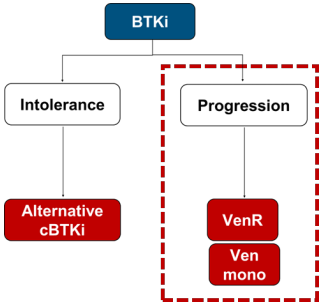




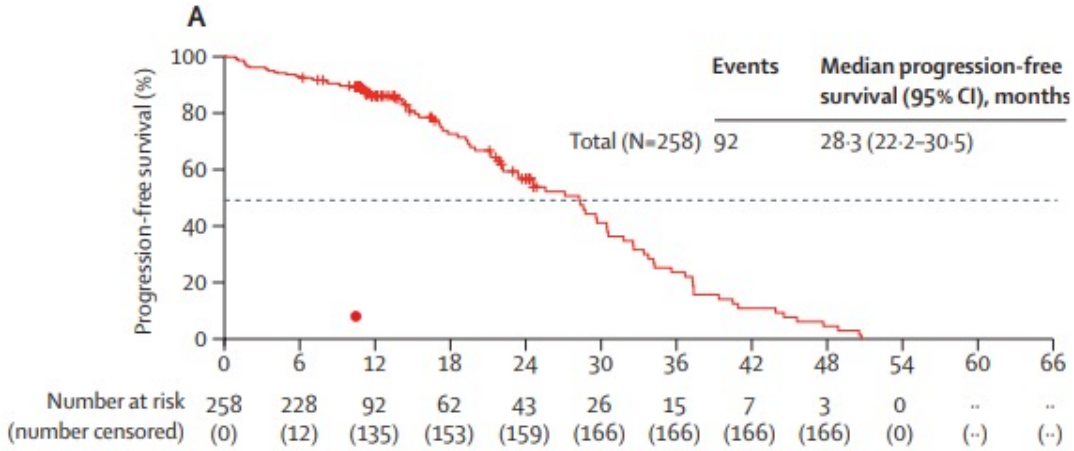
- The median PFS after VEN-R initiation was 25.9 months and the median OS was 46.1 months
- The median PFS for patients receiving continuous VEN monotherapy was 10.5 months and the median OS was 30.5 months

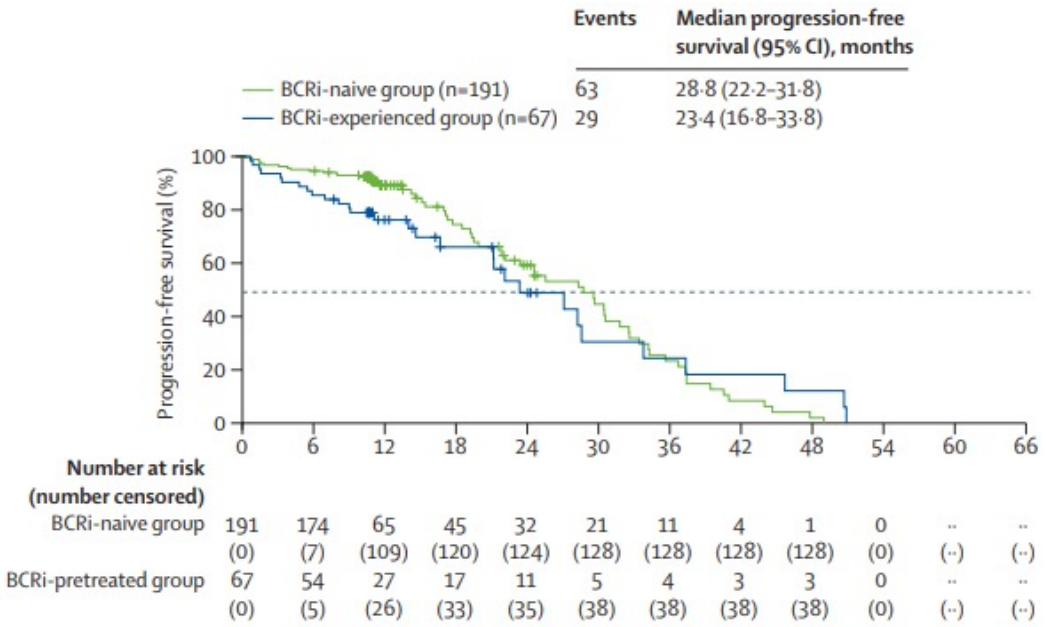
Lew et al, Blood Adv 2024

Ven monotherapy (continuous) in BTKi-exposed CLL



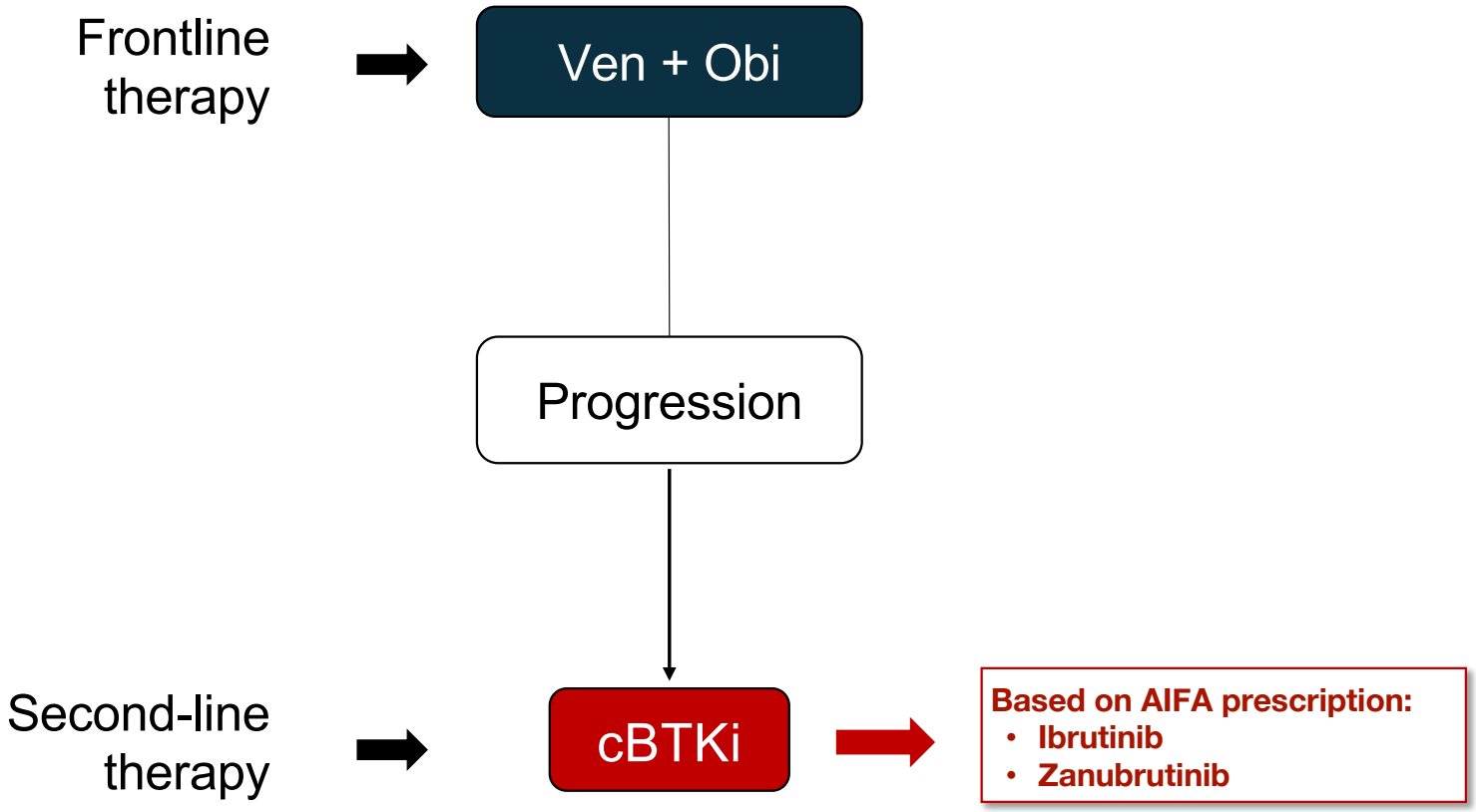
Single-arm, phase 3b trial (VENICE-1) in R/R CLL stratified by previous exposure to a BCRi



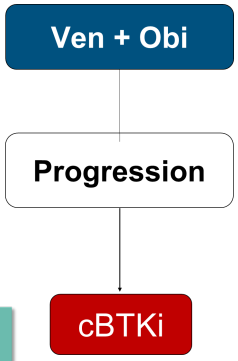


Kater et al Lancet Oncology 2024

SECOND-LINE THERAPY IN CLL



BTKi post venetoclax therapy is an effective sequence in the CLL14 trial

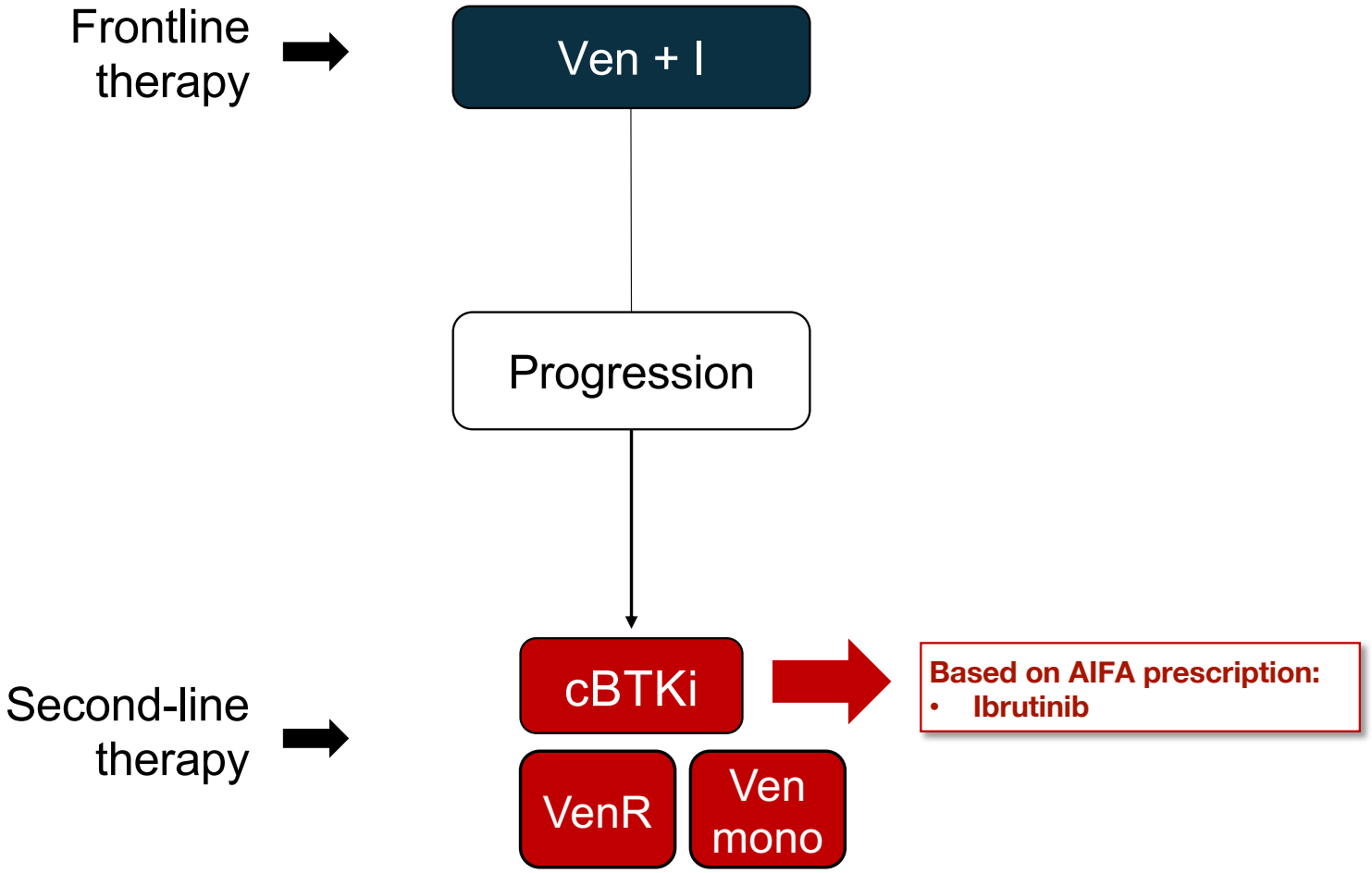


2nd-line therapy, n	VenO					OClb				
	All	OR	SD	PD	Unknown	All	OR	SD	PD	Unknown
Total	**14**	7		1	6	**63**	27	12	2	22
BTKi	**8**	3		1	4	**35**	15	4	2	14
Venetoclax	**2**	1			1	**8**	4			4
CIT	**3**	3				**15**	5	7		3
PI3Ki						**1**		1		
Rituximab monotherapy						**1**				1
Others	**1**				1	**3**	3			

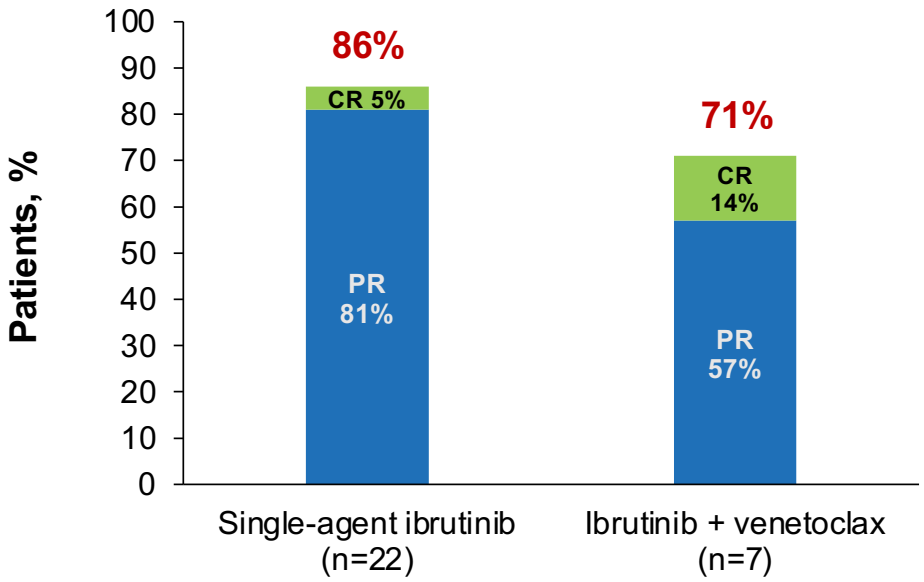
- **Median observation time: 52 months**
- **All patients off treatment for ≥3 years**

Al-Sawaf O, *et al.* EHA 2021. Abstract S146; Al-Sawaf O, et al. J Clin Oncol 2021

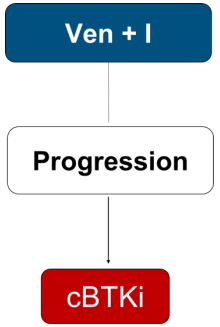
SECOND-LINE THERAPY IN CLL



Ibrutinib post I+V is an effective and safe sequence in the CAPTIVATE trial



AEs, n (%)	Single-agent ibrutinib (n=25)	Ibrutinib + venetoclax (n=7)
Any AE	18 (72)	7 (100)
Most frequent AEs[b]		
COVID-19[c]	5 (20)	2 (29)
Diarrhea	5 (20)	3 (43)
Hypertension	4 (16)	4 (57)
Pyrexia	3 (12)	0
Upper respiratory tract infection	3 (12)	0
Nausea	1 (4)	2 (29)
Grade 3/4 AEs	6 (24)	2 (29)
Serious AEs	5 (20)	0
AEs leading to discontinuation	1 (4)	0
AEs leading to dose reduction	0	0

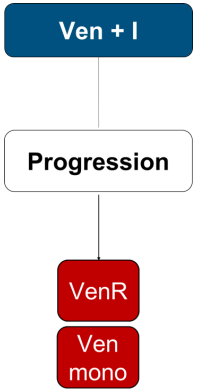


Median time on retreatment:
21.9 months (range, 0.0–50.4) for ibrutinib
13.8 months (range, 3.7–15.1) for ibrutinib + venetoclax

AEs during retreatment were consistent with known safety profiles for single-agent ibrutinib and ibrutinib + venetoclax

Wierda WG et al ASCO 2024

Continuous Ven or fixed duration Ven-R post I+V are feasible options



AGENZIA ITALIANA DEL FARMACO

DETERMINA 26 febbraio 2024

Modifica delle condizioni e modalita' di monitoraggio nell'ambito dei registri AIFA del medicinale per uso umano «Venclyxto». (Determina n. 2/2024). (24A01189)

(GU n.55 del 6-3-2024)

Il paziente ha manifestato tossicità inaccettabile oppure è risultato refrattario al trattamento (recidiva o progressione di malattia nell'arco dei 6 mesi successivi al termine della terapia)?

E	*Campo obbligatorio ai fini dell'eleggibilità*	VENCLYXTO (venetoclax) Leucemia Linfatica Cronica (LLC)
O	*Campo obbligatorio*	

1. VENCLYXTO in monoterapia è indicato per il trattamento della Leucemia Linfatica Cronica (LLC) in presenza della delezione 17p o della mutazione TP53 in pazienti adulti non idonei o che hanno fallito la terapia con un inibitore della via del recettore delle cellule B.

2. VENCLYXTO in monoterapia è indicato per il trattamento di pazienti adulti con LLC in assenza della delezione 17p o mutazione TP53 che hanno fallito la chemioimmunoterapia e la terapia con un inibitore della via del recettore delle cellule B.

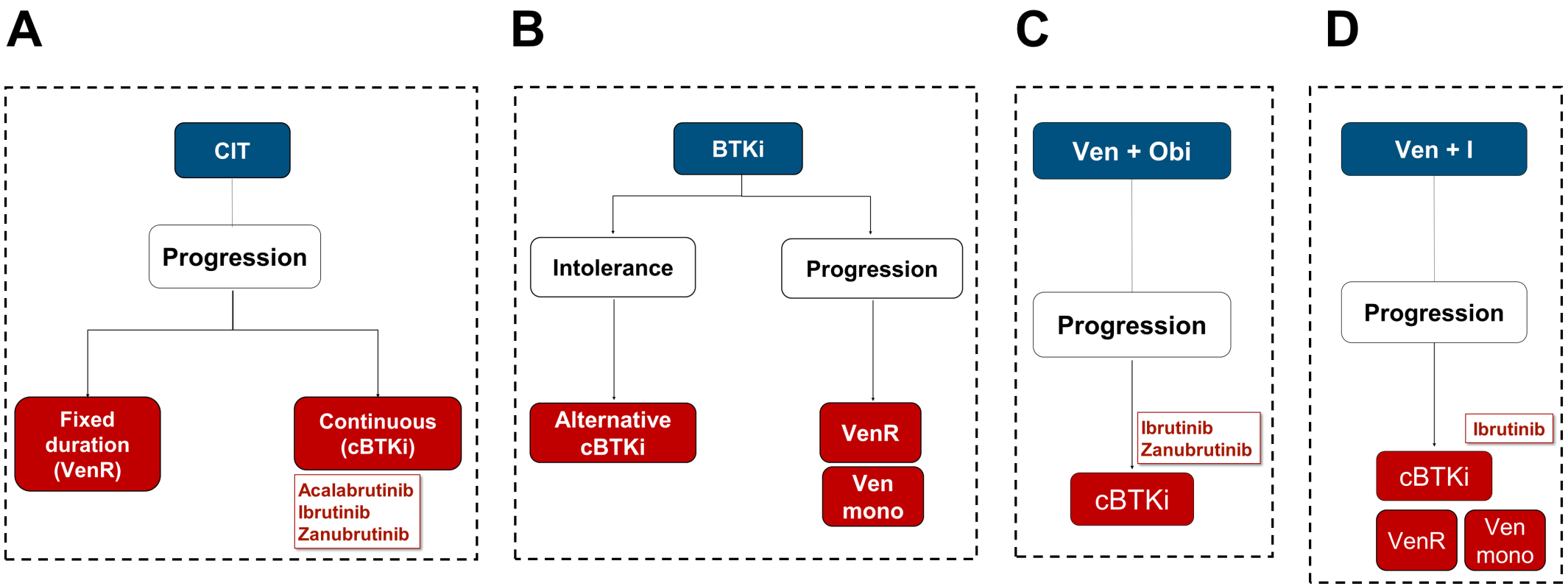
3. Venclyxto in combinazione con rituximab è indicato per il trattamento di pazienti adulti con leucemia linfatica cronica (LLC) che hanno ricevuto almeno una terapia precedente.

4. Venclyxto in combinazione con obinutuzumab è indicato per il trattamento di pazienti adulti con leucemia linfatica cronica (LLC) non trattati in precedenza.

Indicazione ammessa alla rimborsabilità:

Venclyxto in combinazione con obinutuzumab è indicato per il trattamento di pazienti adulti con leucemia linfatica cronica (LLC) non trattati in precedenza e non candidabili ad immunochemioterapia di prima linea tipo FCR

Second line treatment choice



DOUBLE REFRACTORY PATIENTS ARE AN UNMET CLINICAL NEED

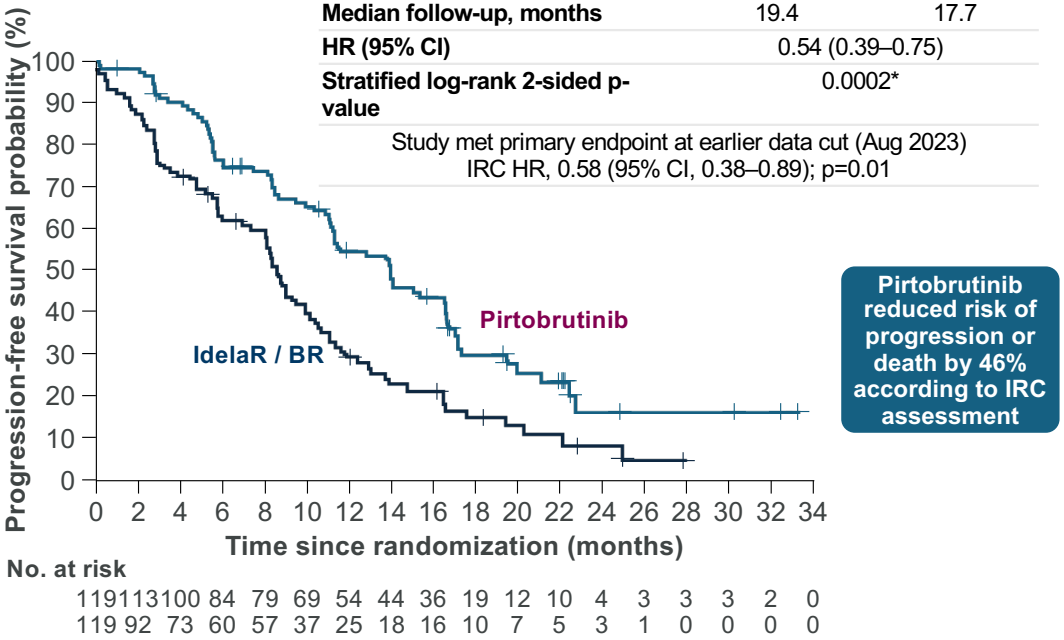
Pirtobrutinib in BTKi pretreated CLL/SLL

Phase 3 BRUIN CLL-321 | **Study drug:** Pirtobrutinib | **Population:** R/R CLL / SLL | **Clinical trial #:** NCT04666038

PFS by IRC

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

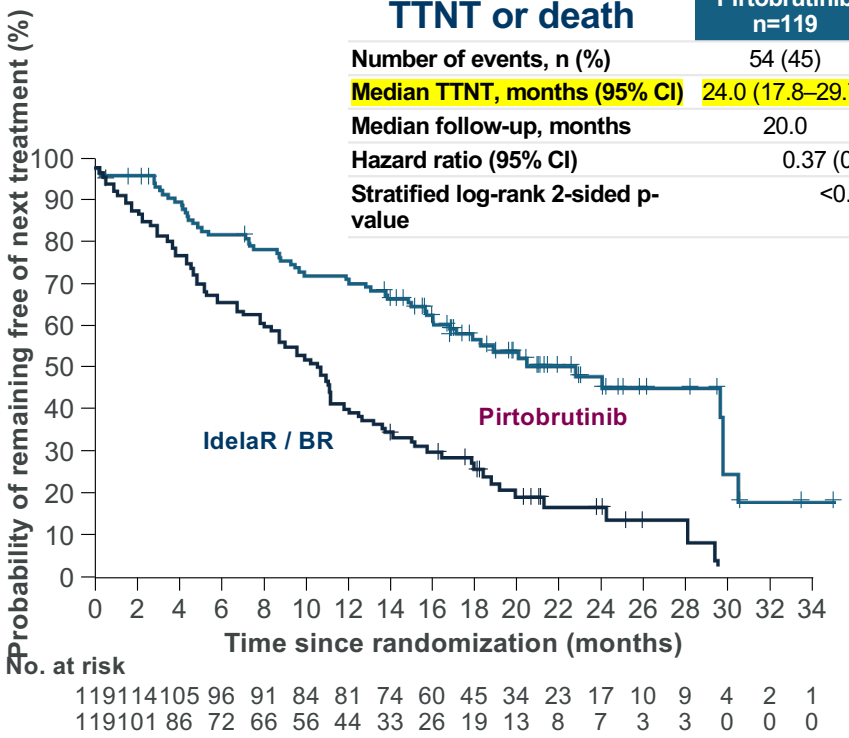
Study met primary endpoint at earlier data cut (Aug 2023)
IRC HR, 0.58 (95% CI, 0.38–0.89); p=0.01



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

TTNT or death

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



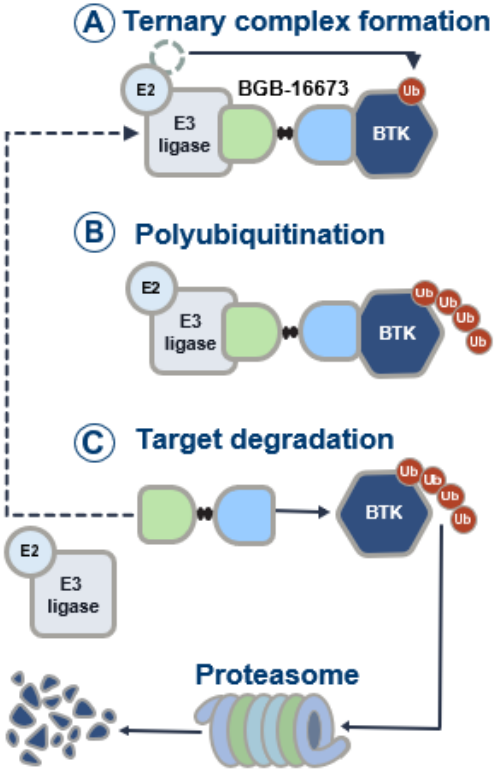
Pirtobrutinib reduced risk of starting next treatment or death by 63% with a median TTNT of ~24 months

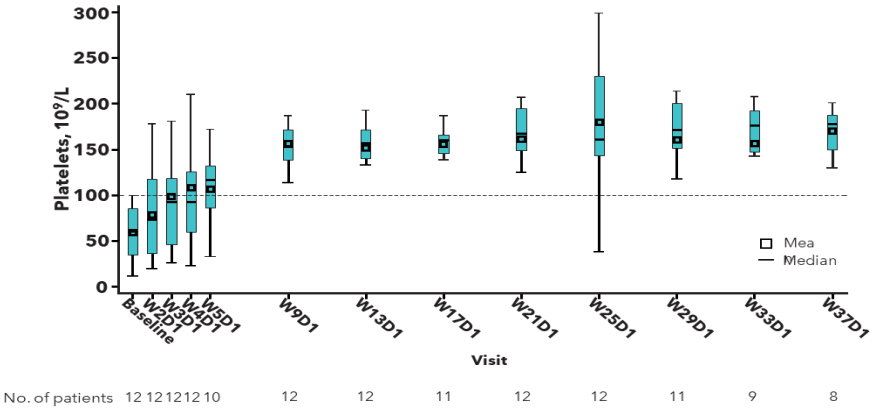
- **PFS benefit also in patients with high-risk features** compared with IdelaR / BR
- Good tolerability with **very low rate of treatment discontinuation** (5.2% in pirtobrutinib arm vs 21.1% in IdelaR / BR arm)

Sharman JP, et al. ASH 2024. Abstract 886

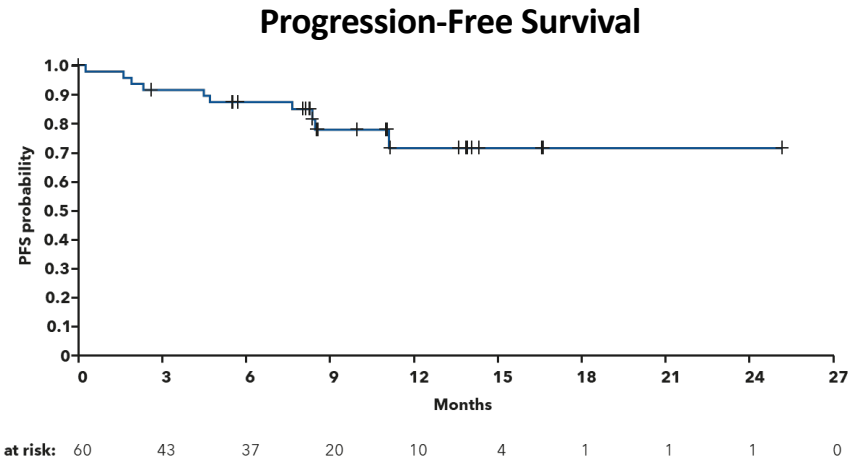
The BTK Degrader BGB-16673 in patients with R/R CLL

BGB-16673: Phase 1 CaDAnCe-101 Study





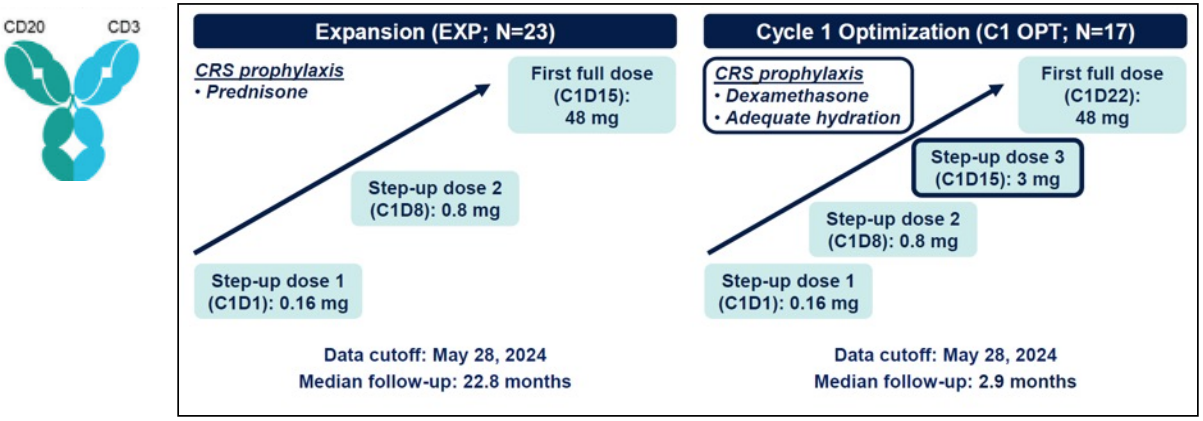
Rapid and significant cytopenia improvement in patients with treatment response



Thompson MC et al ASH 2024

Epcoritamab monotherapy in pts with R/R CLL

EPCORE CLL-1



Expansion Cohort: 23 pts

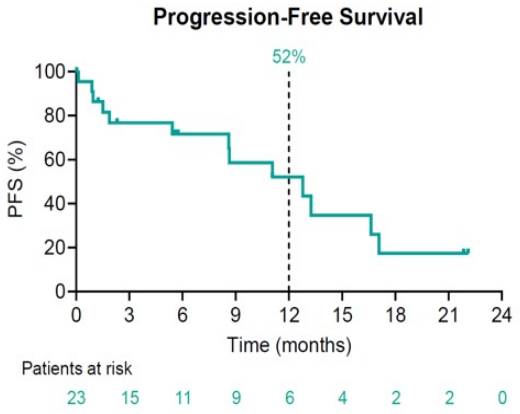
Median Age: 67 y

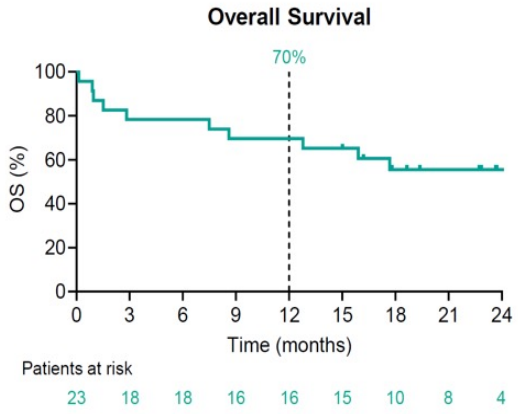
TP53^{m} and or del17p: 65%

Median prior lines tx: 4 (≥ 4: 61%) - CIT 71%,

- cBTKi plus anti BCL2:81.7%

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



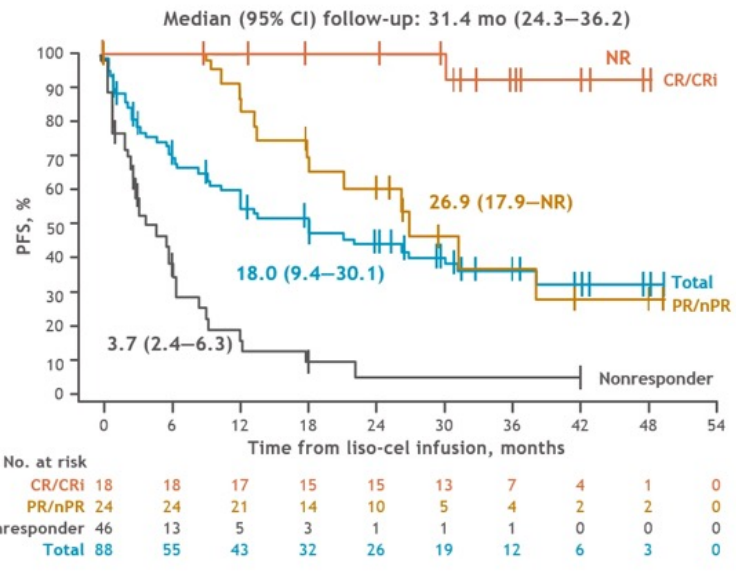


Danilov et al ASH 2024

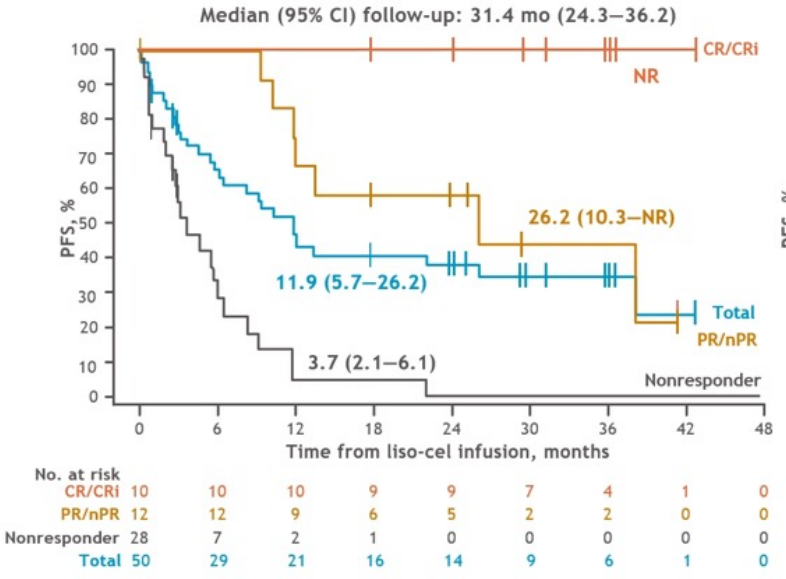
Lisocel in R/R CLL/SLL – TRANSCEND CLL004

	Full study population at DL2 (n = 88)	BTKi progression/venetoclax failure subset at DL2 (n = 50)	Prior BTKi exposure and venetoclax-naïve subset at DL2 (n = 18)
Primary endpoint: IRC-assessed CR/CRi rate per iwCLL 2018, n (%) [95% CI]	18 (20) [13–30]	10 (20) [10–34]	4 (22) [6–48]
Key secondary endpoints			
IRC-assessed ORR, n (%) [95% CI]	42 (48) [37–59]	22 (44) [30–59]	11 (61) [36–83]
uMRD4 rate in blood, n (%) [95% CI]	58 (66) [55–76]	32 (64) [49–77]	12 (67) [41–87]
Exploratory endpoint: uMRD4 rate in marrow, n (%) [95% CI]	53 (60) [49–70.5]	30 (60) [45–74]	12 (67) [41–87]

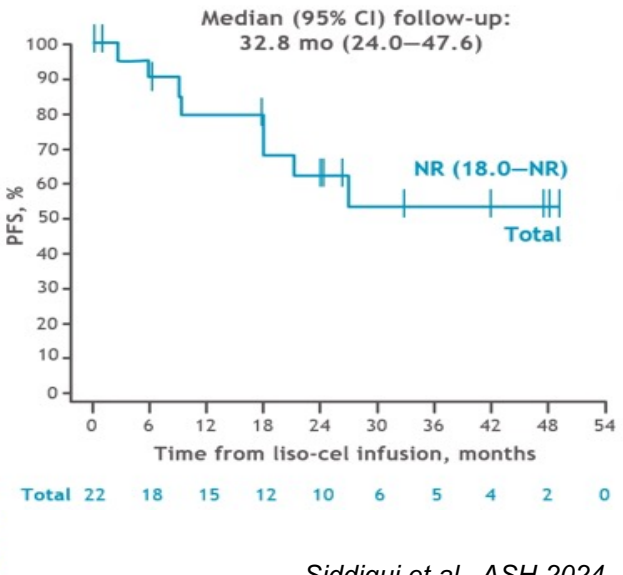
PFS full population at DL2



PFS BTK progression Ven failure DL2



PFS BTK progression Ven naive



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Grazie per la vostra attenzione!

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