Terapia di seconda linea nella LLC

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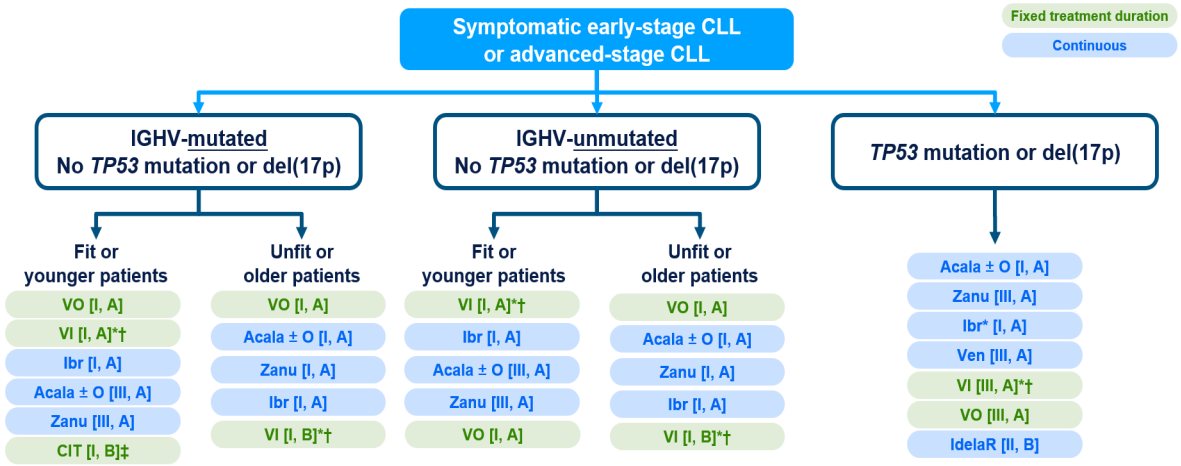
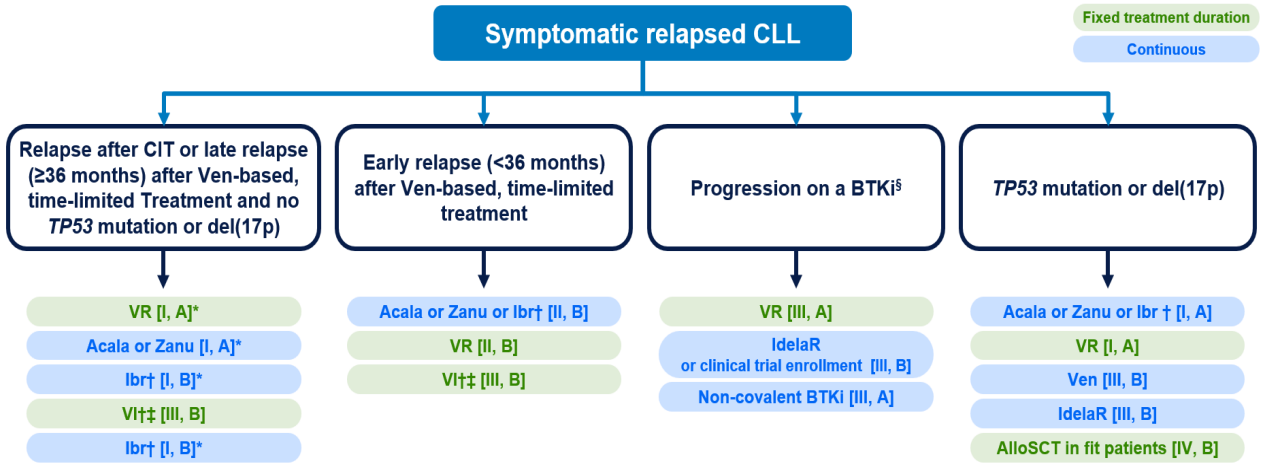
Disclosures of Idanna Innocenti

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
ABBVIE			X		X	X	
Astrazeneca					X	X	
Beigene/BeOne					X	X	
Johnson & Johnson					X	X	
Takeda			X		X		
Lilly					X	X	

2024 Guidelines for 1L and RR CLL Treatments



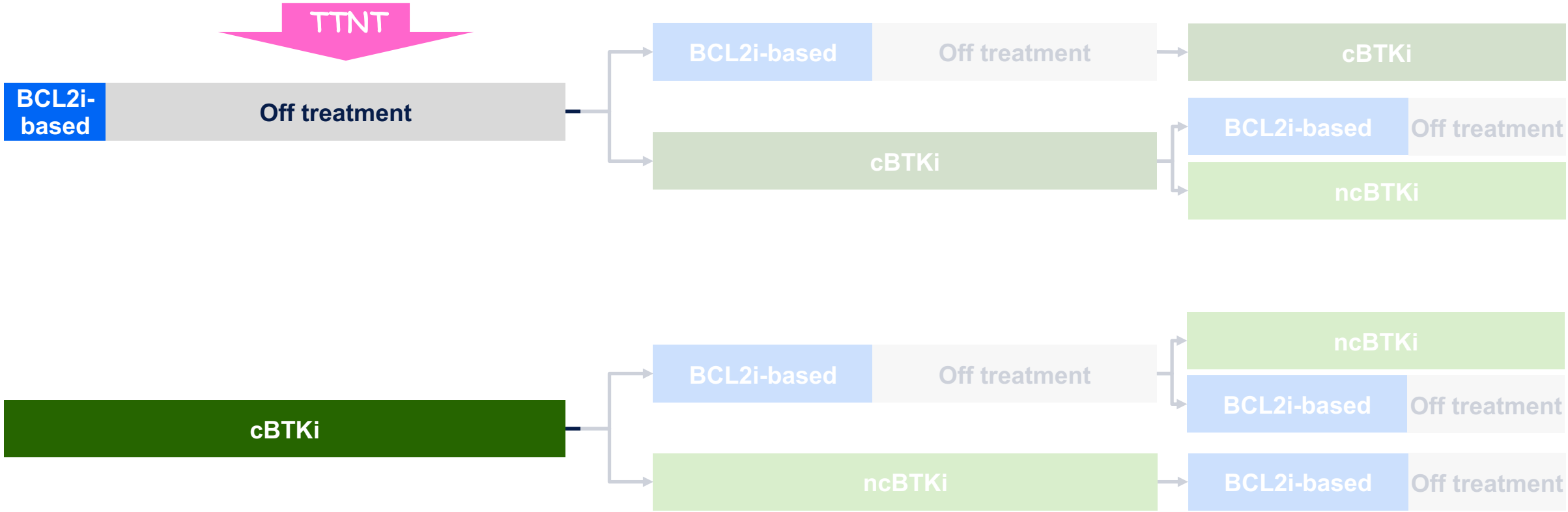


Recommendation

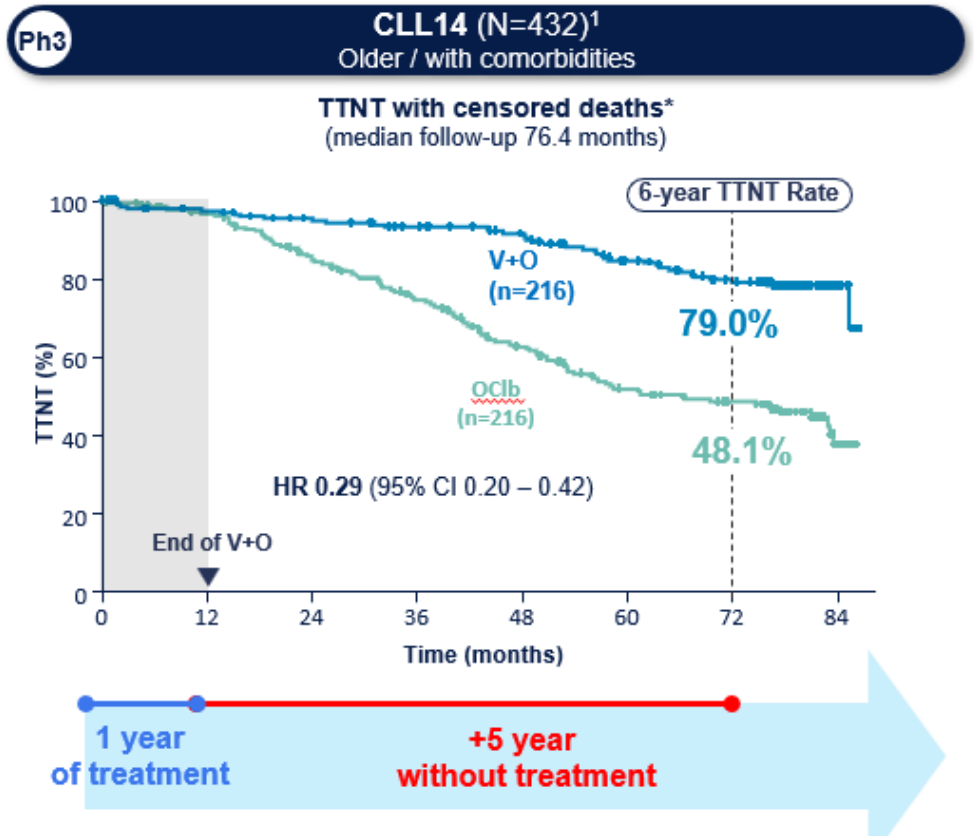
In patients with CLL ***regardless of IGHV status***, preference ***should be given to time-limited therapies***

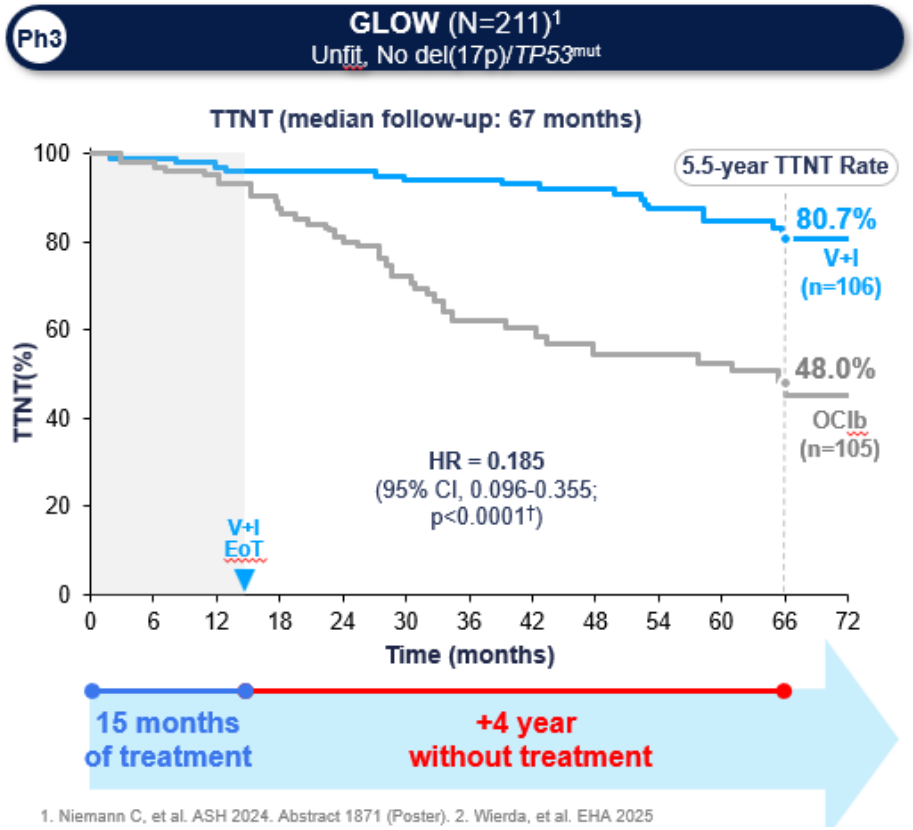
Eichhorst B, et al. Ann Oncol. 2024;35(9):762-768.

How Long a Time off Treatment Can a Patient Have?



TTNT with Fixed duration venetoclax- based regiments





1. Niemann C, et al. ASH 2024. Abstract 1871 (Poster). 2. Wierda, et al. EHA 2025

V+O 6-y TTNT 79%

V+I 5.5-y TTNT 80.7%

* TTNT with deaths prior to the next-line of treatment censored.

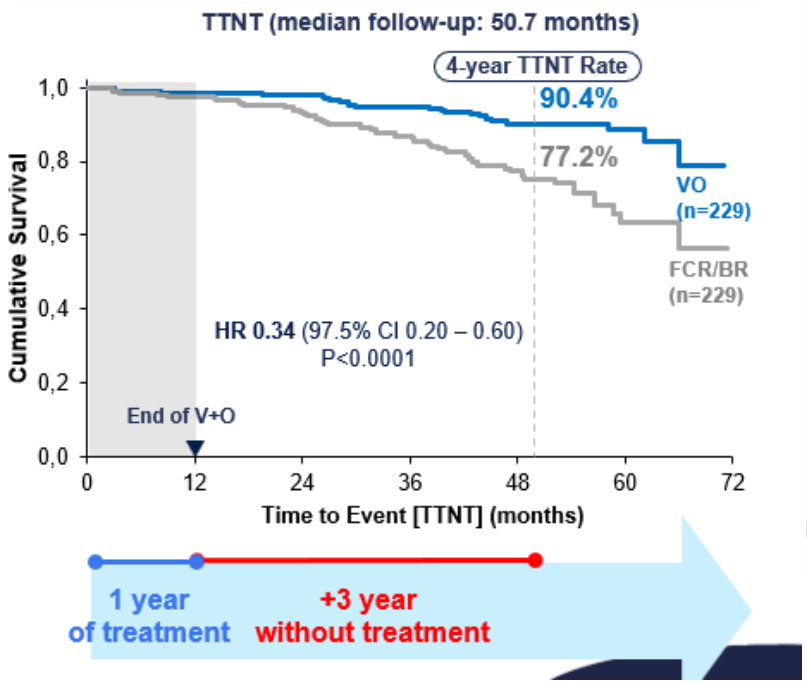
Al-Sawaf O, et al. Blood. 2024;144(18):1924-1935.

. Niemann C, et al. ASH 2024. Abstract 1871 (Poster). 2. Wierda, et al. EHA 2025

TTNT with Fixed duration venetoclax- based regiments

CLL13 (N=926)
Fit, No del(17p)/*TP53*^{mut}

Median f-up:50.7 months



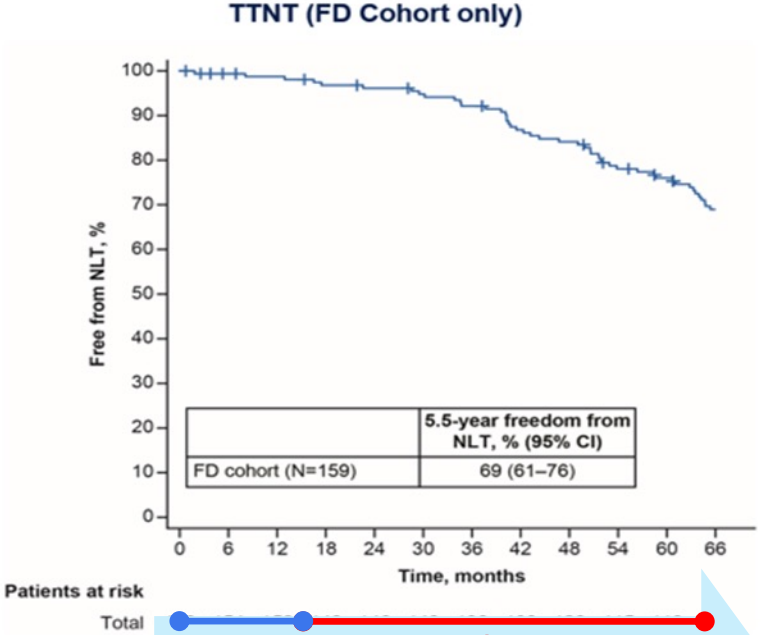
1 year of treatment → +3 year without treatment

V+O 4-y TTNT 90.4%

Fürstenau M, et al. Lancet Oncol 2024; 25:744–759 (incl. suppl.).

CAPTIVATE-FD (N=159)
Fit, includes del(17p)/*TP53*^{mut}

Median f-up:69 months



15 months of treatment → +4 year without treatment

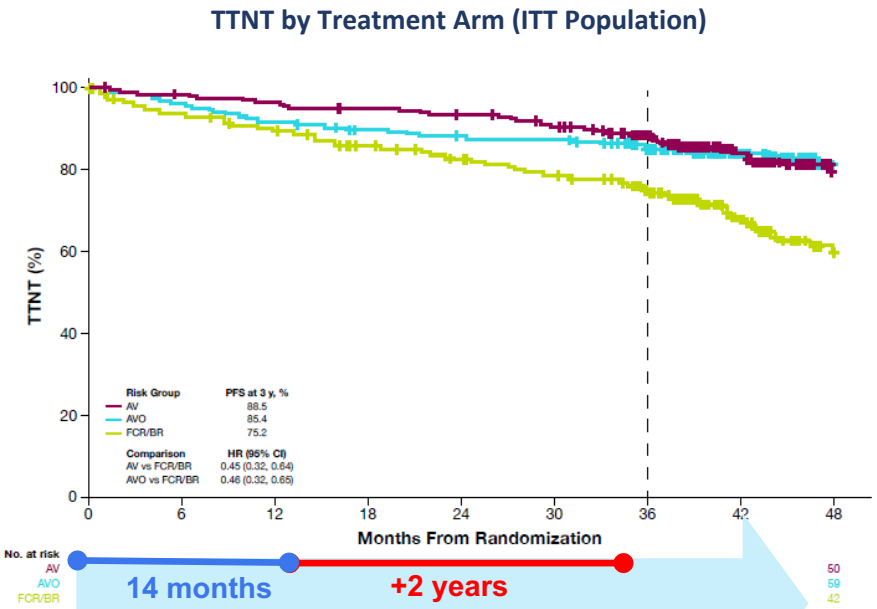
V+I Median 5.5-y TTNT NR

V+I Estimated 5.5-y TTNT 69 %

Wierda, et al. EHA 2025

Amplify (AV n=291; AVO n= 286; CIT n=290)
Fit, No del(17p)/*TP53*^{mut}

Median F-up:40.8 months



14 months of treatment → +2 years without treatment

A+V 3-y TTNT 88.5%

A+V+O 3-y TTNT 85.4%

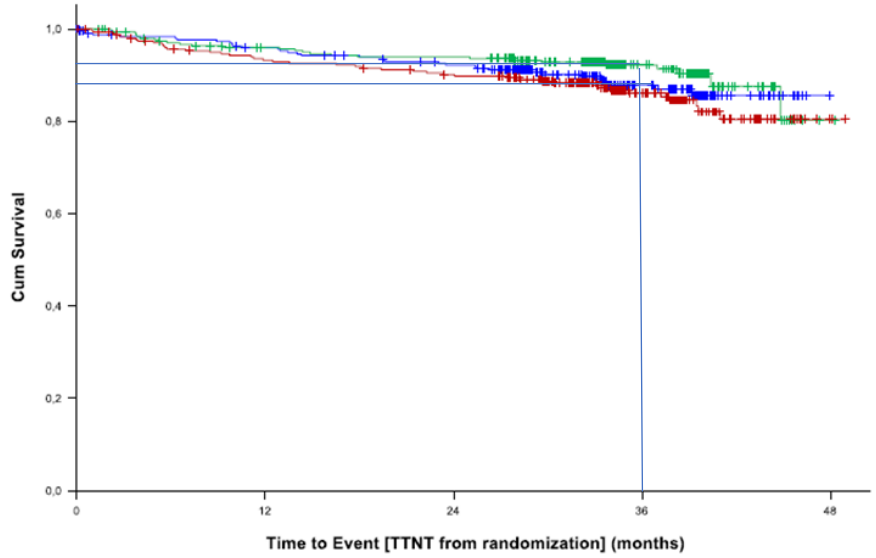
Ghia P. et al. ASH 2025. Poster n.3898.

TTNT fixed vs continous therapy from CLL 17 trial

CLL17

Figure S5. Time to next treatment

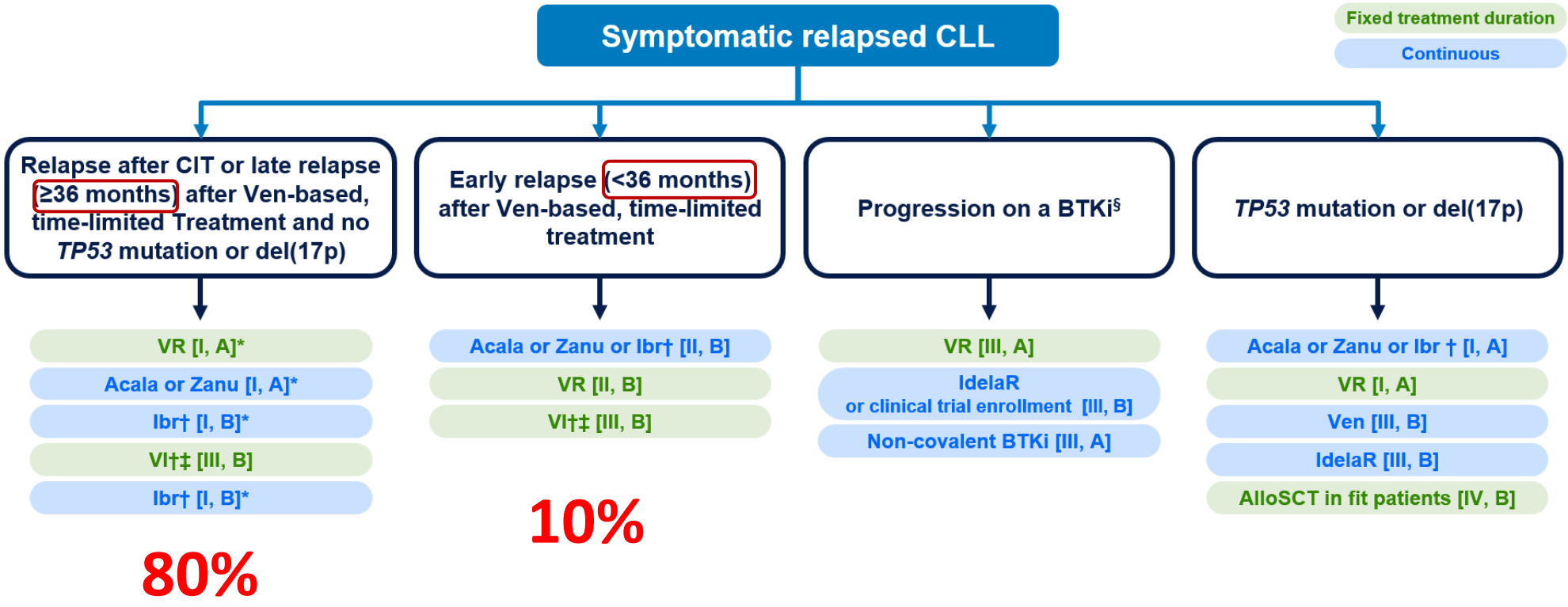
A. Time-to-next treatment according to treatment group



No. at Risk					
VO	303	280	263	95	0
VI	305	279	273	111	1
I	301	272	260	130	2

Al Sawaf O. et al., ASH 2025, NEJM 2025

ESMO 2024 Guidelines for RR CLL Treatments



RECOMMENDATION

For the choice between these treatment modalities, the same aspects as for first line should be considered and discussed with the patient (treatment duration, way of administration, compliance, number and complexity of clinical controls and side effect profile considering existing comorbidities).

Eichhorst B, et al. Ann Oncol. 2024;35(9):762-768.

Evoluzione dello scenario terapeutico di 1L *over time*

The Sequence in R/R CLL Depends on 1L Therapy

1L CLL therapy trends in Europe through the decades show increasing use of targeted therapy

CLL 1L Treatment, %	1990-1999	2000-2010	2011-2020	2021	2024
Chemotherapy	85-95	40-55	10-15	<5	<1
CIT	<5	40-50	50-60	20-25	5-10
BTKi-based therapy	0	0	15-25	45-50	45-50
Venetoclax-based therapy	0	0	<5	25-30	40-45

Nel 2026, verosimilmente, ipotizzando mediamente un efficacia di 1L di circa 5 anni, ***stiamo vedendo ricadere questi pazienti***

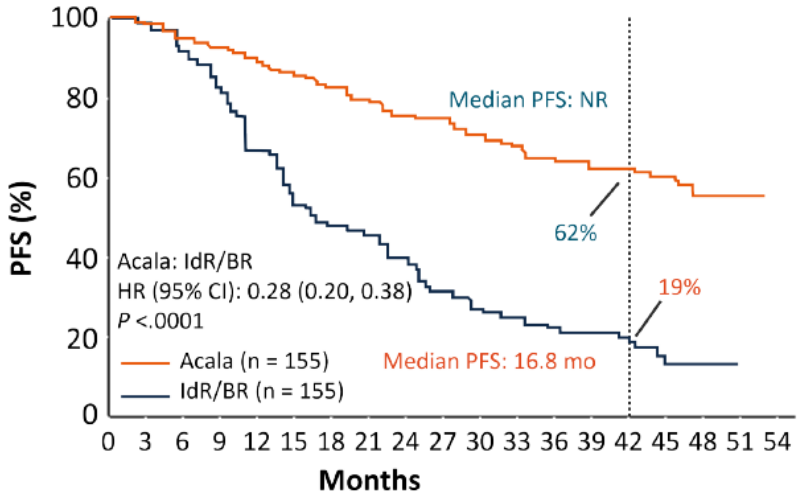
Nel 2029, verosimilmente, vedremo questi pazienti

Adapted by Jurczak et al. EHA2025.
Personal opinion.

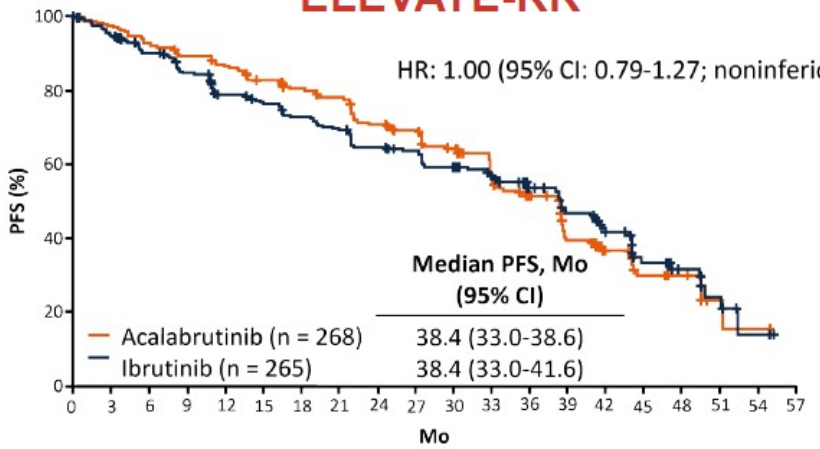
BTK Inhibitors Produce Extended PFS

XXI IWCLL International Workshop on CLL

ASCEND

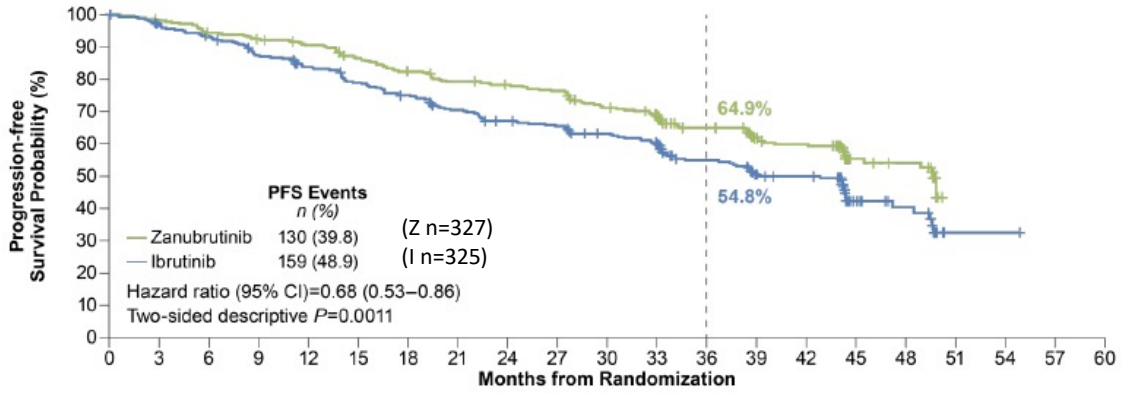


ELEVATE-RR



Median follow-up of 40.9 months (range, 0.0-59.1)

ALPINE



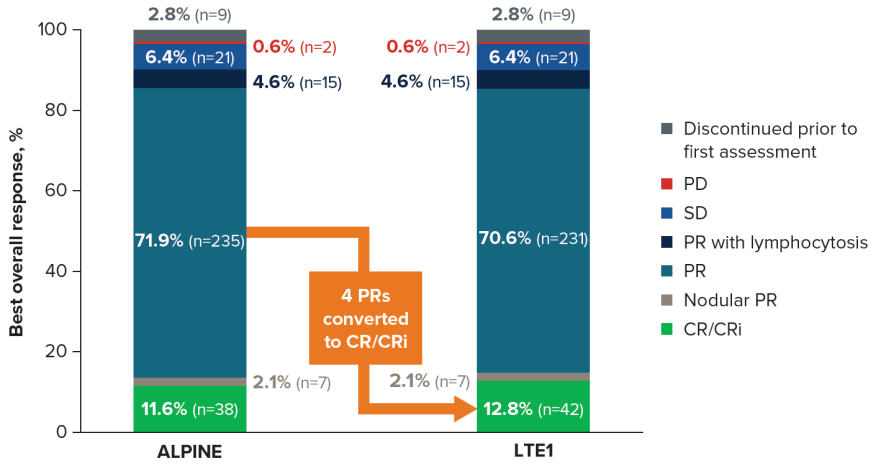
Adapted by Ghia et al, Hemasphere 2022; Byrd et al JCO. 2021; Brown et al, NEJM 2023

Phase 3 Study: ALPINE LTE1 (long-term extension)

between November 9, 2023, and February 28, 2024

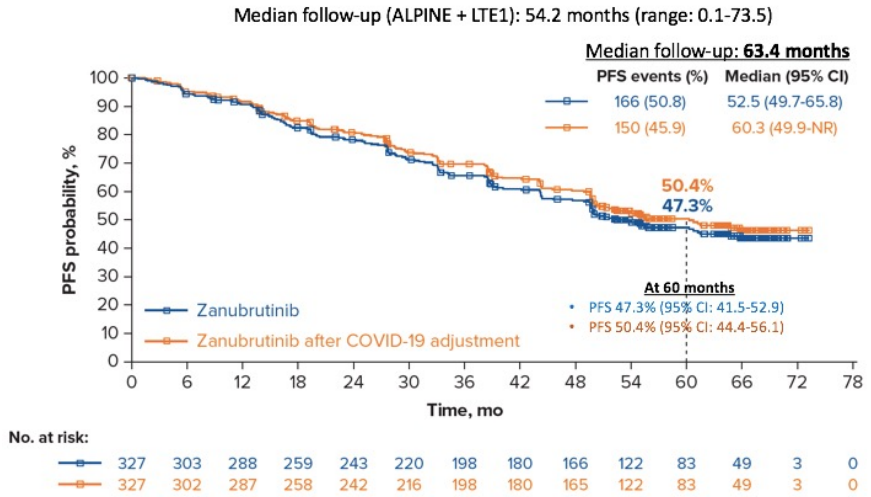
- R/R CLL/SLL (n=189/324)
- Median age, 67 years (35-90)
- 17p deletion [del(17p)] was present in 13.8% of pts
- number of prior lines of systemic therapy, median (range) 1 (1-6)

Best Overall Response per Investigator Assessment

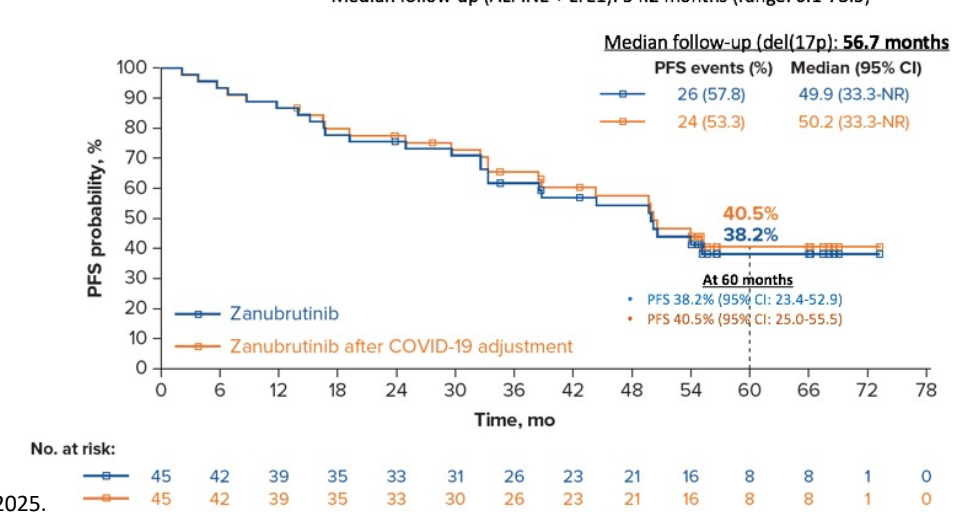


Zanubrutinib demonstrated statistically and clinically significant ***superiority over*** ibrutinib in ***PFS and ORR,*** with a ***favorable safety profile***[1]

PFS in the Overall Population



PFS Among Patients with Del(17p)



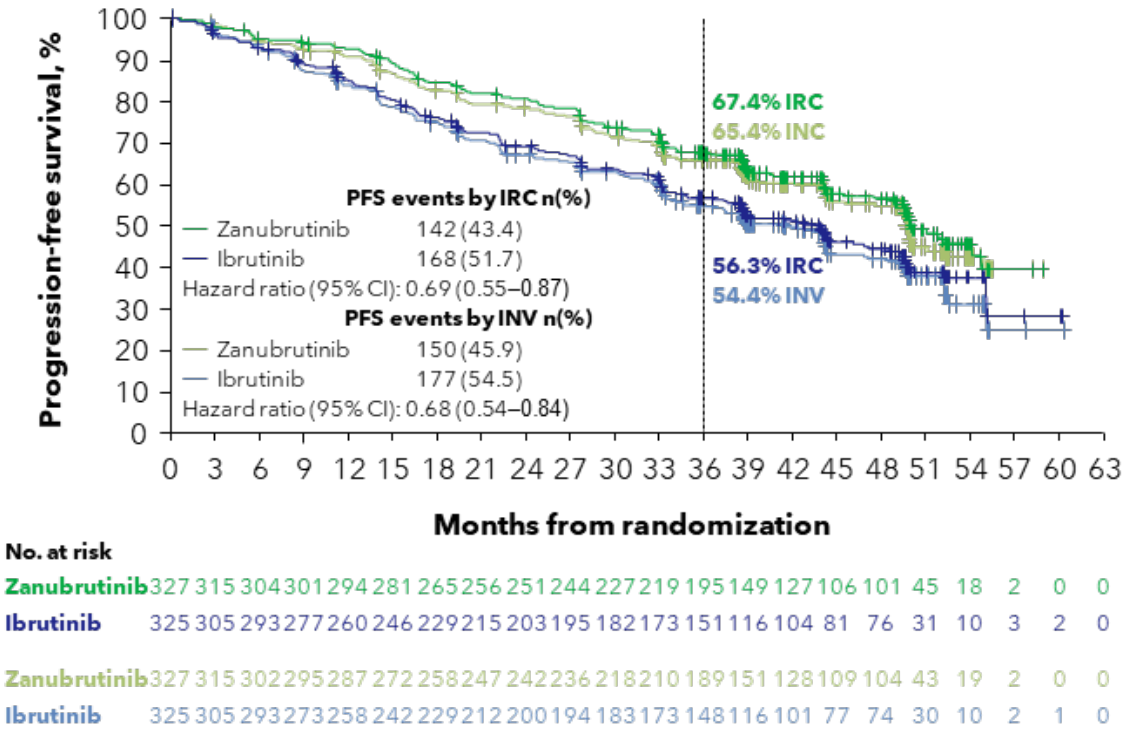
Data cut-off: April 1, 2025.

Tam CS, et al. Poster Presentation at ASH 2025;Poster 2123.

ALPINE PFS With 3.5 Years of Follow-Up

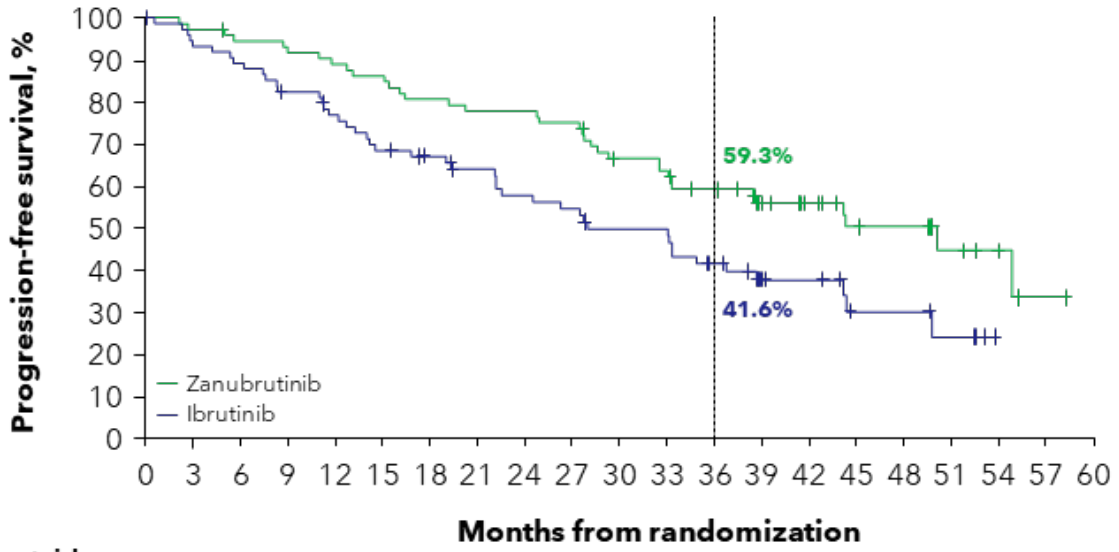
ALPINE: Symptom-Based PFS

PFS by INV and IRC (ITT)



	No. at risk																						
IRC	Zanubrutinib	327	315	304	301	294	281	265	256	251	244	227	219	195	149	127	106	101	45	18	2	0	0
	Ibrutinib	325	305	293	277	260	246	229	215	203	195	182	173	151	116	104	81	76	31	10	3	2	0
INV	Zanubrutinib	327	315	302	295	287	272	258	247	242	236	218	210	189	151	128	109	104	43	19	2	0	0
	Ibrutinib	325	305	293	273	258	242	229	212	200	194	183	173	148	116	101	77	74	30	10	2	1	0

PFS by IRC (del(17p)/*TP53* mut)



No. at risk																							
Zanubrutinib	75	71	68	67	64	62	58	56	56	54	46	44	39	29	23	18	17	8	4	1	0
Ibrutinib	75	70	66	60	55	49	45	41	37	35	30	30	23	14	12	7	7	4	0	0	0

Improved PFS in patients with R/R CLL treated with zanubrutinib versus ibrutinib[1,2]

1. Brown JR, et al. Blood. 2024;144(26):2706-2717; 2. Brown JR, et al. Poster presented at: 18th International Conference on Malignant Lymphoma; June, 2025; Lugano, Switzerland. Brown JR, et al. Oral Presentation at ASH 2025;8440.

Ph 3 GAIA/CLL13 (NCT02950051)

Efficacy of 2nd-line treatment in CLL after venetoclax-based 1st-line treatment: Results from the GAIA/CLL13 trial

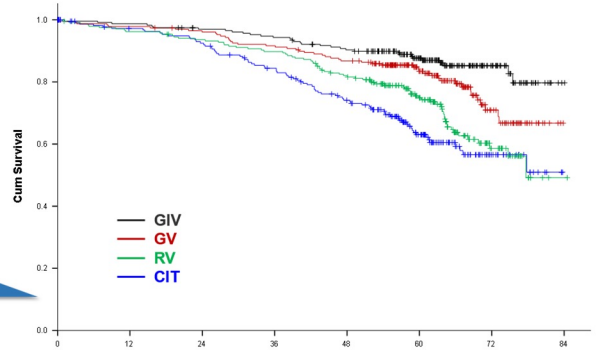
Treatment free survival from 1st-line treatment (TFS1)

Eligibility

Treatment-naive, fit patients with CLL, no *TP53* aberrations (centrally screened)

- **CIT** FCR ≤65y, BR >65y
- **RV** rituximab, venetoclax | FD 12 months
- **GV** obinutuzumab, venetoclax | FD 12 months
- **GIV** obinutuzumab, ibrutinib, venetoclax | 12-36 months

Median observation time 63.8 months



Patients at Risk	0	12	24	36	48	60	72	84
CIT	229	206	196	175	148	88	23	0
RV	237	227	219	210	188	119	33	1
GV	229	224	218	208	196	124	36	0
GIV	231	228	220	214	202	141	48	1

Median time from progression:

GIV	14.5 months
GV	11.3 months
RV	12.3 months
CIT	10.1 months

Population

- R/R CLL; with 2L treatment post-PD: 67% (CIT), 57% (RV), 54% (GV), 45% (GIV)
- CIT vs. RV vs. GV vs. GIV: uIGHV (82% vs. 83% vs. 84% vs. 82%); complex karyotype ≥3 (29% vs. 24% vs. 28% vs. 25%)

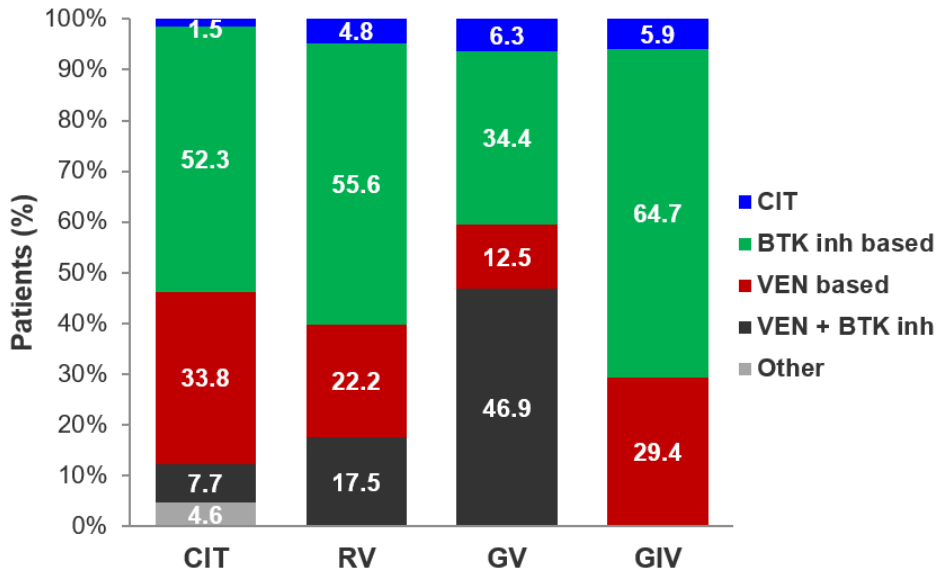
Baseline characteristics, patients receiving next line treatment

1st line Tx:	CIT (n 65)	RV (n 63)	GV (n 32)	GIV (n 17)
Age >65	30 (46%)	19 (30%)	8 (25%)	5 (29%)
CIRS >1	42 (65%)	29 (46%)	18 (56%)	14 (82%)
ECOG PS >0	18 (28%)	22 (35%)	10 (31%)	4 (24%)
IGHV unmut	53 (82%)	52 (83%)	27 (84%)	14 (82%)
Complex Karyo ≥3	18 (29%)	15 (24%)	8 (28%)	4 (25%)
Bulky disease ≥5cm	24 (37%)	19 (30%)	15 (47%)	5 (29%)
Serum β_2-microglobulin >3.5 mg/L	54 (83%)	46 (73%)	22 (69%)	9 (60%)

Reporting on the 177 patients receiving next line CLL treatment with prior progression, patients with Richter's transformation (n 13), along with 6 patients receiving next line treatment without prior progression are omitted from this chart (and from the analysis throughout)

Niemann. ASH 2025. #7495 (Oral Presentation)

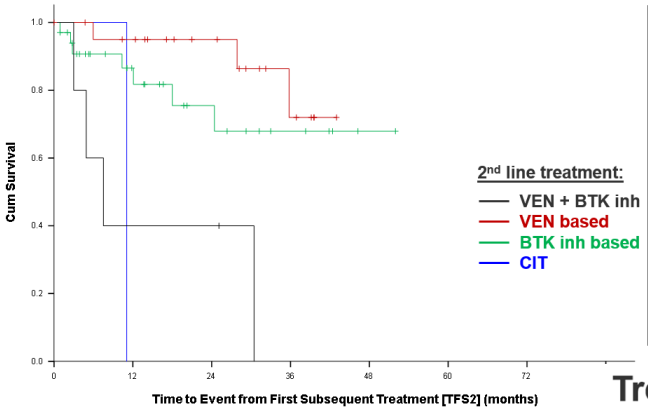
Next line treatment based on 1st line treatment



1st line Tx:	CIT (n 65)	RV (n 63)	GV (n 32)	GIV (n 17)
2nd line Tx:				
CIT	1 (2%)	3 (5%)	2 (6%)	1 (6%)
BTK inh based	34 (52%)	35 (56%)	11 (34%)	11 (65%)
VEN based	22 (34%)	14 (22%)	4 (13%)	5 (29%)
VEN + BTK inh	5 (8%)	11 (17%)	15 (47%)	0
Other	3 (5%)	0	0	0

Niemann. ASH 2025. #7495 (Oral Presentation)

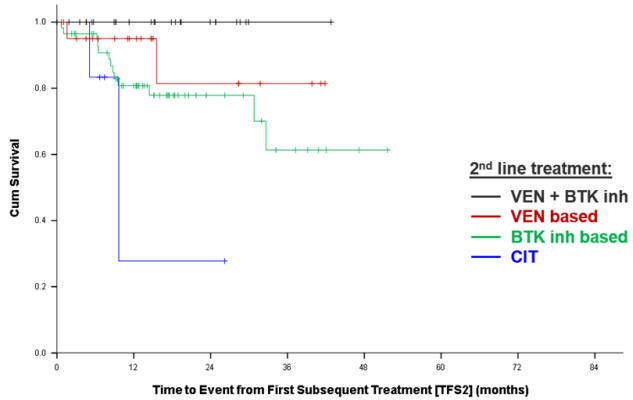
Treatment free survival from 2nd line treatment (TFS2); after 1st line CIT



Patients at Risk	0	12	24	36	48	60
CIT	1	0	0	0	0	0
BTK inh based	34	18	10	5	1	0
VEN based	22	18	12	5	0	0
VEN + BKT inh	5	2	2	0	0	0

TFS from 2nd line treatment (%)		
2nd line treatment	1-year rate	2-year rate
VEN + BTK inh	40.0	40.0
VEN based	95.0	95.0
BTK based	86.6	75.7
CIT	0.0	0.0

Treatment free survival from 2nd line treatment (TFS2); after 1st line RV/GV/GIV



Patients at Risk	0	12	24	36	48	60
CIT	6	1	1	0	0	0
BTK inh based	57	36	12	6	1	0
VEN based	23	12	6	3	0	0
VEN + BKT inh	26	15	7	1	0	0

TFS from 2nd line treatment (%)		
2nd line treatment	1-year rate	2-year rate
VEN + BTK inh	100.0	100.0
VEN based	95.0	81.4
BTK based	80.7	77.9
CIT	27.8	27.8

CI Comments

- Data provides evidence that even after progression post-Ven, retreatment (or alternative Ven combinations) can lead to good outcomes, offering more flexibility rather than forcing a switch away from BCL2i therapy
- Data can be leveraged to improve HCP confidence in prescribing 2L Ven-based regimens for patients whose disease already progressed on Ven

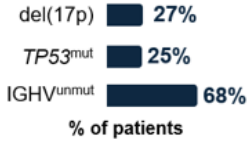
Niemann. ASH 2025. #7495 (Oral Presentation)

V+R MURANO (7y final analysis)

Trial

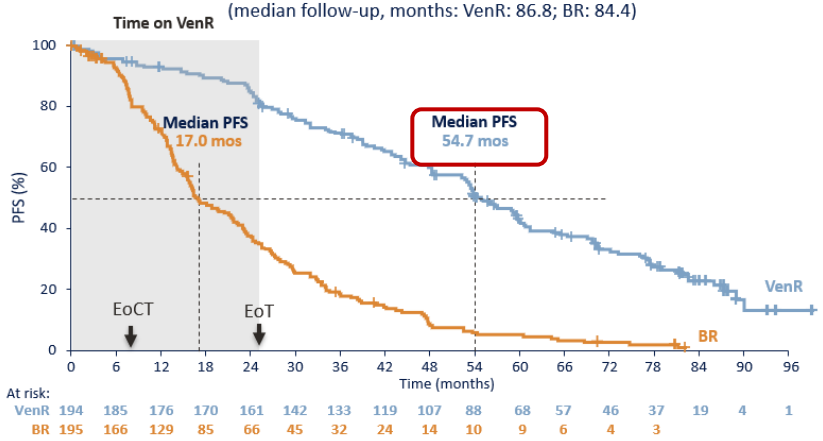
MURANO - RR pts

HIGH RISK FEATURES
VenR Arm



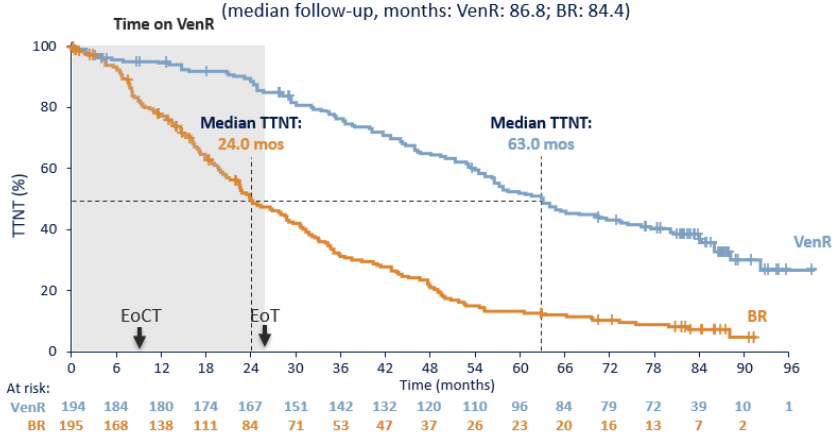
Characteristics		VenR (n=194)
Age[1]	Median, years (range)	64.5 (28–83)
Lymphocyte count, n (%)[1]	≥25×10⁹/L	129 (66.5)
del(17p)–(FISH),* n/N (%)[1]	Deleted	46/173 (26.6)
TP53 mutational status, n/N (%)[1]	Mutated *TP53*	48/192 (25.0)
IGHV mutational status, n/N (%)[1]	Unmutated IGHV Mutated IGHV Unknown	123/180 (68.3) 53/180 (29.4) 4/180 (2.2)
Number of prior therapies, n (%)[2]	1 2 ≥3	111 (57.2) 58 (29.9) 25 (12.9)
Prior therapies, n (%)[2]	Alkylating agent Purine analog† Anti-CD20 antibody BCRi Bendamustine	185 (95.4) 158 (81.4) 148 (76.3) 3 (1.5) 4 (2.1)
Fludarabine refractory, n/N (%)[1]	Yes	27/191 (14.1)

PFS
(median follow-up, months: VenR: 86.8; BR: 84.4)



A 7 anni, 5 anni EoT, il 23% dei pazienti è ancora libero da progressione con VR.

TTNT
(median follow-up, months: VenR: 86.8; BR: 84.4)

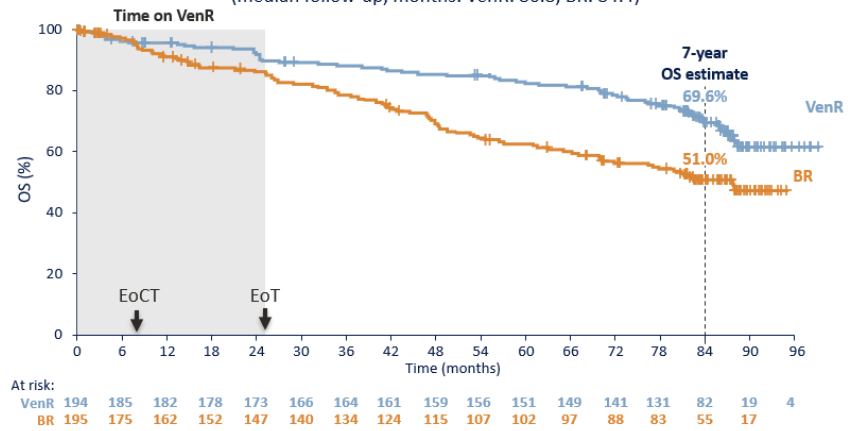


A 7 anni, 5 anni EoT:
- 73 pazienti nel braccio VR non hanno ricevuto alcun trattamento successivo;
- 26 sono deceduti senza necessità di ulteriori trattamenti.

Grade ≥3 AEs

Grade 3–4 AEs during treatment, with ≥2% difference between arms, n (%)*,[1]	VenR combination treatment period (months 1–6) N=194	Venetoclax single-agent treatment period (months 7–24) N=171
Neutropenia	**106 (54.6)**	**20 (11.7)**
Anemia	16 (8.2)	5 (2.9)
Thrombocytopenia	9 (4.6)	3 (1.8)
Febrile neutropenia	7 (3.6)	0
Pneumonia	8 (4.1)	2 (1.2)
TLS Clinical TLS	6 (3.1) 1 (0.5)	0 0
Infusion-related reaction	4 (2.1)	0
Hyperglycemia	4 (2.1)	0
Hypogammaglobulinemia	3 (1.5)	1 (0.6)

OS
(median follow-up, months: VenR: 86.8; BR: 84.4)



Kater AP, et al. *Blood.* 2025:blood.2024025525 (Online ahead of print).

RWE - 2L+ Ven dopo regimi BTKi

- Data were collected as part of the CLL Collaborative Study of RWE
- "CORE" (6/01/18–12/27/23):2293 pts
- *Ibr 85.4%, Acala 6.8%, IR 2.9%.

CORE - Ghosh et al. 2024

Patient characteristics	N=205
Age, median (range), years	68.7 (62.2–76.4)
Median prior lines of therapy, n	2 (1-3)
Ven monotherapy, %	60
Ven-based therapies, %	40
Reasons for BTKi discontinuation, %	
PD	37.1
Intolerance	42.9
Other	6.8
uIGHV, %	69.6
Del(17)p and/or TP53mut	24.2

		N	PFS Median, mo (95% CI)	TTNT-D Median, mo (95% CI)
Overall (ven based)	**Overall**	**205**	**44.1**	**44.2**
	1L→2L	71	43.2	NR – 73,6% (18m)
	2L→3L	73	44.3	44.2
cBTKi - **Stop per intolleranza**	Overall	88	NR – 84,1% (18m)	NR – 79,3% (18m)
	1L→2L	36	39.5	39.5
	2L→3L	33	NR – 89,0% (18m)	NR – 87,2% (18m)
cBTKi - **Stop per progressione**	Overall	76	30.1	30.4
	1L→2L	15	31.9	31.9
	2L→3L	30	31.8	37.4
Pazienti trattati con V+R	**Overall**	**64**	**39.5**	**37.4**
	1L→2L	31	43.2	NR– 85,0% (18m)
	2L→3L	23	36.3	37.4

- 71 (34.6%) patients initiated ven-based therapy in the 2L
- 73 (35.6%) pts were 3L
- 61 (29.7%) pts initiated venetoclax in 4L or later

V+R 2L
(post BTKi)

43,2 m

Ghosh, N. et al. Am J Hematol,2025; 100: 511-515.

- Data were collected as part of the CLL Collaborative Study of RWE
- "CORE" (6/01/18–12/27/23):2293 pts
- *Ibr 85.4%, Acala 6.8%, IR 2.9%.

RWE - 2L+ Ven dopo regimi BTKi

CORE - EHA 2025

Retrospective observational study

Pts post cBTKi progression*
(N=145)

Ven mono -> n=93 pts	V+R->n=52 pts
2L: n=22	**2L: n=21**
3L: n=33	3L: n=22

	PFS		TTNT		OS	
	Median, mo	18-mo rate	Median, mo	18-mo rate	Median, mo	18-mo rate
2L Ven mono (N=22)	25.0	71.2%	23.6	65.8%	NR	78.1%
2L V+R (N=21)	39.3	87.8%	NR	87.8%	NR	87.8%

Efficacia

- Median follow-up:
  - ➢ **20.3 mo** for Ven mono;
  - ➢ **20.0 mo** for VR (n=52)
- Median Ven duration:
  - ➢ **19.1 mo** for Ven mono (n=93)
  - ➢ **19.8 mo** for VR (n=52)

V+R 2L
(post BTKi)

39,3 m

Fleury I, et al. EHA 2025. PS1573 (Poster).

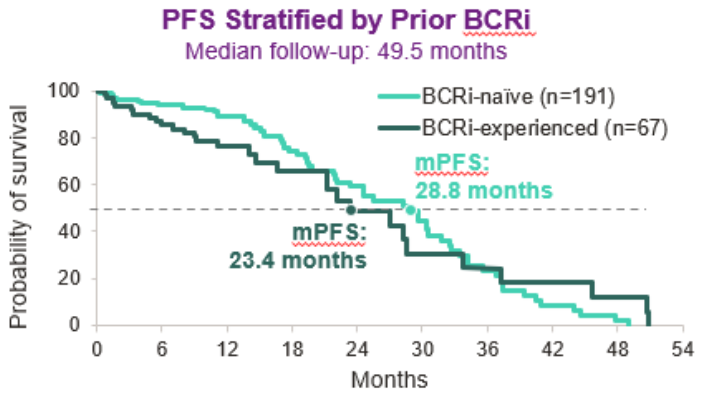
VEN post BTKi in RWE

Studio	n pts	Mediana linee di terapia (range)	% uIGHV	% Del17/tp53	ORR	PFS (mediana)	TTNTD (mediana)
Ghosh et al. 2025	64 **19 (2L)**	- (2L 34.6% 3L 35.6%)	69.6% (overall 205 pts)	25% (overall 205 pts)	71.4% (**2L:78.9%**)	39.5 (**2L:43.2**)	39.5
Fleury et al. 2025	56 **29 (2L)**	- (54% CIT exposed)	69.4% (79 pts VO/VR)	20.4% (79 pts VO/VR)	77.6% **(2L:87.5%)**	39.3 **(2L: 39.3)**	NR **(2L: NR)**
Lew et al. 2024	32	2 (1-5) (72% Ibr/ 89%CIT)	87%	71%	81%	25.9	N.A.
Schwanner et al. 2025 (VerVe)	28	3 (1-10)	43%	46%/36%	100%	24 mo-PFS: 68.6%	N.A.
Farina et al. 2026	23	>2 L (63%) 65% prior cBTKi	89% (overall-40 pts)	25% (overall-40 pts)	N.A	34 (tp53 mut) 45.7 (tp53 wild-type)	N.A.
Scarfò et al. 2021	24 (V+R post ibr)	2 (2-6)	81% (all 86 VR pts)	30% (all 86 VR pts)	85% (overall)	≈ 30	N.A

V+R in 2L post cBTKi ha una mPFS di ≈ 41 mesi (>3,5 anni)!

Efficacia sostenuta anche per Venetoclax monoterapia post cBTKi

VENICE-1



ORR: 64%

2L+
(post BTKi)
23,4 m

Kater AP, et al. *Lancet Oncol.* 2024

VERVE (post ibr)

Estimated 24-mo PFS and OS Rates
Median follow-up: 24 months

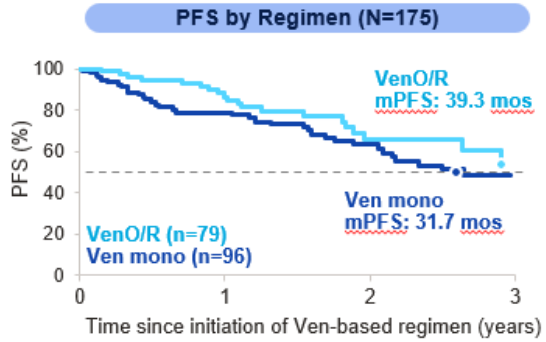
	Ven	VenR
24-mo PFS	62.5%	68.6%
24-mo OS	73.2%	76.9%

ORR: 76%

2L+
(post BTKi)
62,5%
(24m)

Schwaner I, et al. EHA 2025.

CORE
(FU 20,3m)



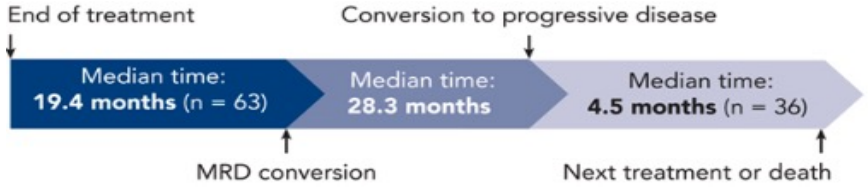
ORR: 82%

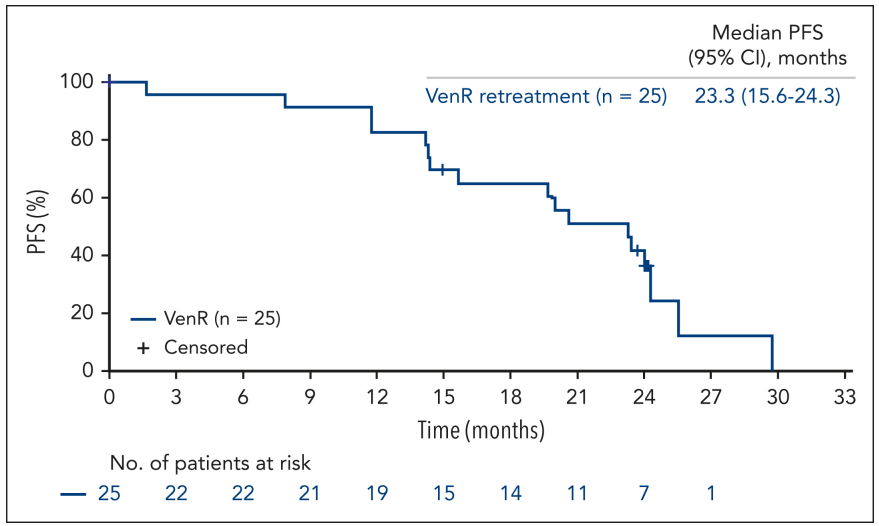
2L+
(post BTKi)
31,7 m

Fleury I, et al. EHA 2025. Poster PS1573.

Retreatment is effective after time-limited therapy

Retreatment with VR in MURANO (N=25)





- ✓ mPFS of Murano full cohort: 54.7 mo
- ✓ mTime from EoT to subsequent PD **~4.5 years** (52.3-59.9)
- ✓ Most patients were classified as high risk:
- 32% had del(17p) and/or *TP53* mutation, 88% IGHV unmutated, 32% GC‡ ≥ 5
- ✓ **Best ORR 72%**
- ✓ mTime off treatment from last dose of Ven to VR retreatment was **2.3 years** (1.2-3.1)
- ✓ mPFS: **23.3 months** (15.6-24.3)

Kater AP, et al. *Blood.* 2025:blood.2024025525 (Online ahead of print).

Retreatment:

- **Late relapse** after planned treatment cessation
- **Treatment cessation for reasons other than PD**

Prospective studies testing retreatment strategies:

- ✓ -BCL2i/anti-CD20 (ReVenG)
- ✓ -BTKi/BCL2i (Aca+Ven, MAVRiC)
- ✓ -Triplet regimen (BOVen)

Adapted from Inhye E. Ahn iwCLL 2025

Retreatment: V+O After 1L Ven-based

Phase 2 study of VO retreatment after 1L Ven + anti-CD20 ± X*

STUDY DESIGN[1]

Phase 2
R/R CLL who progressed after 1L Ven + anti-CD20 ± X*
(N~75)

Cohort 1: Patients who progressed >24 mo after 1L Ven + anti-CD20 ± X* completion (n~60)

Cohort 2: Patients who progressed ≥12–24 mo after 1L Ven + anti-CD20 ± X* completion (n≤15)

PRIMARY ENDPOINT:

ORR at EoCT

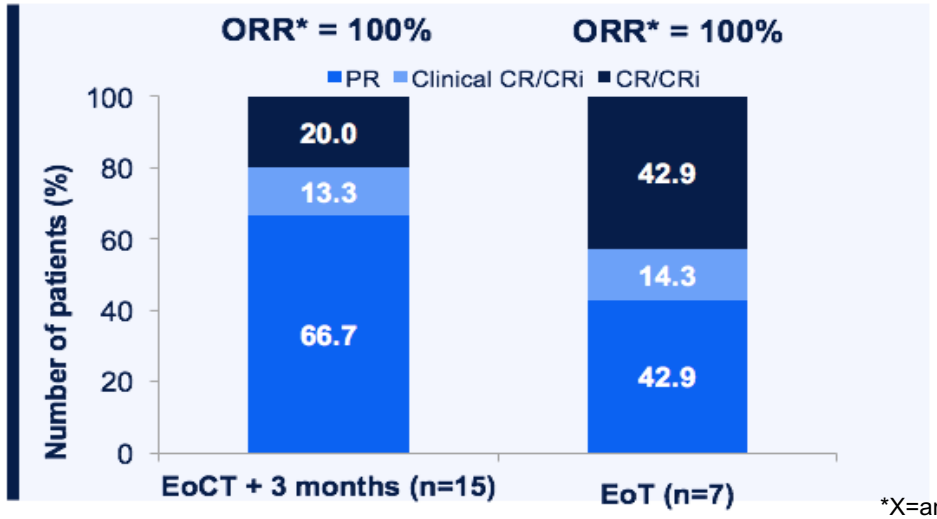
(3 months after completing 6 cycles of VO)

KEY SECONDARY ENDPOINTS:

- CR/CRi at EoCT and EoT
- ORR at EoT
- uMRD at EoCT and EoT
- PFS
- OS
- TTNT
- Safety

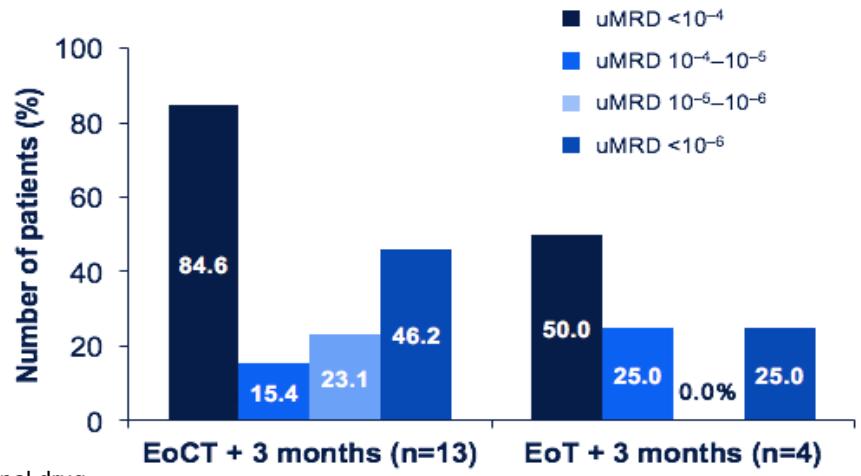
ORR by iwCLL criteria

mFU: 10.3 months



uMRD in PB by NGS

mFU: 10.3 months



*X=an additional drug.

1. Davids M, et al. EHA 2025. Abstract PF575 (Poster).

Reatretment after V+I: data from CAPTIVATE Study

Characteristic	Total Pooled Population (N=202)	FD Cohort Only (N=159)
Median age (range), years	60.0 (33–71)	60.0 (33–71)
Male, n (%)	131 (65)	106 (67)
Rai stage III/IV, n (%)	59 (29)	44 (28)
High-risk genomic features, n (%)		
uIGHV	119 (59)	89 (56)
del(17p)/TP53	29 (14)	27 (17)
del(11q)[a]	36 (18)	28 (18)
CK (≥3 abnormalities)[b]	35 (17)	31 (20)
CK (≥5 abnormalities)[b]	19 (9)	16 (10)
Bulky LN disease, n (%)		
≥5 cm	66 (33)	48 (30)
≥10 cm	6 (3)	5 (3)

Patients Who Initiated Ibrutinib-Based Retreatment: Study Baseline Characteristics

Characteristic	Single-agent ibrutinib n=25	FD ibrutinib + venetoclax n=11	All retreated patients n=36
Median age (range), years	56.0 (39–71)	63.0 (49–69)	58.5 (39–71)
Male, n (%)	16 (64)	8 (73)	24 (67)
Rai stage III/IV, n (%)	4 (16)	2 (18)	6 (17)
High-risk genomic features, n (%)			
uIGHV	20 (80)	8 (73)	28 (78)
del(17p)/TP53	4 (16)	6 (55)	10 (28)
del(11q)[b]	7 (28)	1 (9)	8 (22)
CK (≥3 abnormalities)[c]	8 (32)	3 (27)	11 (31)
CK (≥5 abnormalities)[c]	5 (20)	2 (18)	7 (19)
Bulky LN disease, n (%)			
≥5 cm	9 (36)	2 (18)	11 (31)
≥10 cm	1 (4)	1 (9)	2 (6)

[a]See Supplementary Information for additional details. [b]Without del(17p) per Döhner hierarchy. [c]By conventional CpG-stimulated cytogenetics.

- **73% remain free from next-line treatment at 5.5 years**
- **Only 36 patients initiated a retreatment**

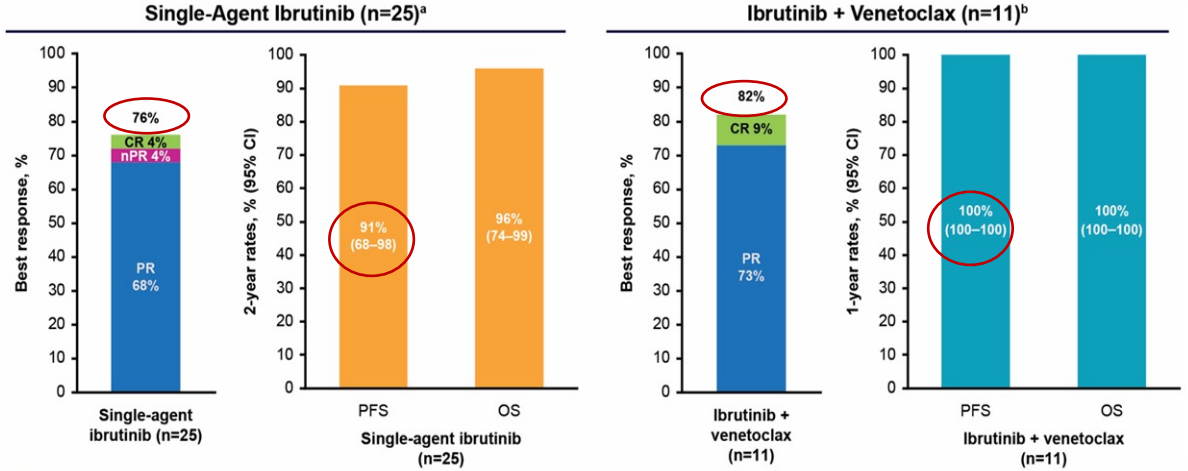
No Resistance-Associated Mutations Were Identified at PD

- In the total pooled population (FD and MRD-placebo cohorts) with a median follow-up of more than 5.5 years, 64/202 patients (32%) had PD after FD ibrutinib + venetoclax treatment
- No patients had resistance-associated mutations in *BTK* or *PLCG2* at PD among 53 patients with available samples
- Two patients were found with a subclonal *BCL2 A113G* mutation of unclear significance at PD: variant allele frequencies were only 8% and 9.3%, respectively
  - Patient 1: Achieved partial response with FD ibrutinib + venetoclax retreatment (complete response was not confirmed due to missing bone marrow assessment).
    - *BCL2 A113G* mutation was not detectable at the time of eventual relapse after retreatment[a]
  - Patient 2: Did not receive retreatment in the study

[a]Patient 1 *BCL2 A113G* variant allele frequency also was noted to decline spontaneously down to 6.7% before retreatment started.

Wierda, et al. EHA 2025
EHA 2025, William G. Final Analysis of FD IV for CLL/SLL in the Phase II CAPTIVATE Study.

Retreatment provides durable responses in patients needing subsequent therapy after completition of FD V+I



	Single-agent ibrutinib	FD ibrutinib + venetoclax
Median duration of follow-up, months (range)	28.4 (3.7–59.1)	15.2 (7.4–29.3)
Median duration of retreatment, months (range)	27.0 (1.1–59.1)	13.8 (6.7–18.3)

[a]Of the 6 non-responders, 4 patients achieved SD with reintroduced treatment duration ranging from 6.2–19.4 months; 1 patient was discontinued after reassessment of the putative progressive lesion as not PD, and 1 patient was diagnosed with Richter's Transformation after 1.1 month on retreatment.
[b]Of the 2 non-responders, both achieved SD with reintroduced treatment duration of 9.9 and 25.9 months, respectively.
CR, complete response; nPR, nodular partial response; PR, partial response.

Wierda, et al. EHA 2025

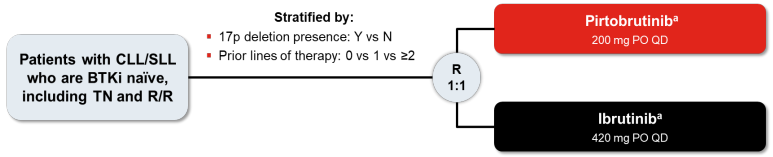
Safety of ibrutinib-based retreatment shows no new safety signals

TEAEs[c], n (%)	Single-agent ibrutinib n=25	FD ibrutinib + venetoclax n=11
Any AE	22 (88)	11 (100)
Most frequent AEs[d]		
COVID-19	6 (24)	2 (18)
Diarrhea	5 (20)	4 (36)
Hypertension	5 (20)	5 (45)
Grade 3 or 4 AEs	9 (36)	4 (36)
AEs leading to discontinuation	1 (4)	0
AEs leading to dose reduction	0	0

[a] Without del(17p) per Döhner hierarchy. [b] By conventional CpG-stimulated cytogenetics. [c] TEAEs were collected until 30 days after the last dose of study treatment or the start of subsequent therapy, whichever occurred first. [d] Occurring in ≥20% of patients who received single-agent ibrutinib or ibrutinib + venetoclax.

Ghia P, et al. oral presentation at ASCO 2025. #7036

BRUIN CLL-314 Study Design



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

Pirtobrutinib demonstrated consistently higher ORR than ibrutinib across all patients, including TN and R/R populations

Included 225 TN and 437 R/R patients

Planned: 30% TN, 70% R/R; Actual: 34% TN, 66% R/R.

ITT Population Characteristics[a]	Pirtobrutinib n=331	Ibrutinib n=331
Median age, years (range)	67 (39-90)	67 (34-86)
Male, n (%)	213 (64.4)	215 (65.0)
Region, n (%)		
North America	26 (7.9)	21 (6.3)
Europe	174 (52.6)	171 (51.7)
South America	61 (18.4)	64 (19.3)
Asia	42 (12.7)	51 (15.4)
Other[b]	28 (8.5)	24 (7.3)
Histology, n (%)		
CLL	306 (92.4)	294 (88.8)
SLL	25 (7.6)	37 (11.2)
ECOG PS, n (%)		
0-1	319 (96.4)	321 (97.0)
2	12 (3.6)	10 (3.0)
Rai stage[c], n (%)		
0-II	168 (54.9)	171 (58.2)
III-IV	135 (44.1)	119 (40.5)
Median duration of disease, years (Q1, Q3)	5.62 (2.20, 8.91)	5.26 (1.88, 9.73)
Bulky disease[d], n (%)	107 (32.3)	116 (35.0)
High-risk molecular features, n/n available (%)		
IGHV unmutated[e]	199/293 (67.9)	183/277 (66.1)
17p deletion presence[f]	50/331 (15.1)	52/331 (15.7)
TP53 mutation[e]	92/284 (32.4)	78/273 (28.6)
Complex karyotype[e,g]	104/259 (40.2)	78/227 (34.4)

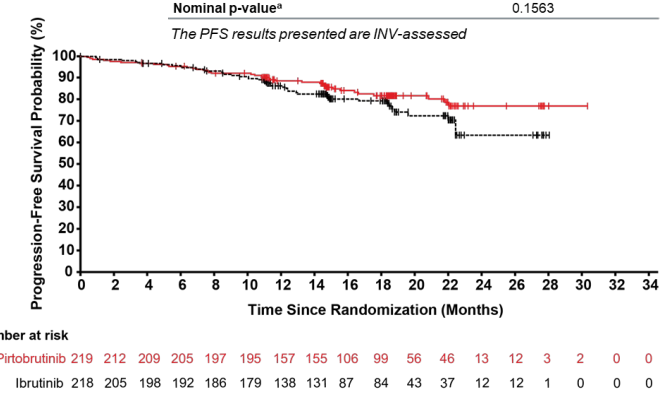
R/R Population	Pirtobrutinib n=219	Ibrutinib n=218
Median lines of prior systemic therapy, n (range)	1.0 (1-9)	1.0 (1-8)
Prior therapy, n (%)		
BCL2 inhibitor	22 (10.0)	17 (7.8)
Chemotherapy	201 (91.8)	208 (95.4)
Anti-CD20 Antibody	158 (72.1)	166 (76.1)
PI3K inhibitor	6 (2.7)	6 (2.8)
Immunomodulator	1 (0.5)	1 (0.5)
Autologous/Allogeneic Stem Cell Transplant	2 (0.9)	2 (0.9)
Reason for discontinuation of most recent prior therapy[h], n (%)		
Disease progression	31 (14.2)	35 (16.1)
Toxicity	23 (10.5)	25 (11.5)
Finished course of therapy	148 (67.6)	141 (64.7)
Other	16 (7.3)	16 (7.3)

	ITT Population		TN Population		R/R Population	
	Pirtobrutinib n=331	Ibrutinib n=331	Pirtobrutinib n=112	Ibrutinib n=113	Pirtobrutinib n=219	Ibrutinib n=218
ORR[a] (PR or better)						
%	**87.0**	**78.5**	92.9	85.8	**84.0**	**74.8**
95% CI[b]	82.90, 90.44	73.73, 82.85	86.41, 96.87	78.03, 91.68	78.48, 88.61	68.46, 80.39
Nominal p-value[c]	0.0035		0.0886		0.0175	
ORR[a] ratio						
ORR ratio (95% CI)	1.1080 (1.034, 1.187)		1.0797 (0.989, 1.179)		1.1233 (1.020, 1.237)	
p-value for NI[d]	<0.0001		-		<0.0001	
Best Overall Response[e], %						
CR or CRi	4.8	2.4	7.1	3.5	3.7	1.8
PR or nPR	82.2	76.1	85.7	82.3	80.4	72.9
PR-L	2.4	3.9	0.9	2.7	3.2	4.6
SD	5.4	10.9	2.7	4.4	6.8	14.2
PD	1.5	1.2	0	0	2.3	1.8
ORR including PR-L						
%	89.4	82.5	93.8	88.5	87.2	79.4
95% CI[b]	85.60, 92.52	77.95, 86.42	87.55, 97.45	81.13, 93.73	82.05, 91.33	73.37, 84.53
Nominal p-value[c]	0.0093		0.1692		0.0286	

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

Woyach,, et al.; ASH 2025

Treatment-Emergent Adverse Events

Preferred Term ≥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 TEAE	320 (97.0)	181 (54.8)	318 (97.8)	174 (53.5)
Neutropenia	75 (22.7)	57 (17.3)	58 (17.8)	43 (13.2)
Upper respiratory tract infection	59 (17.9)	2 (0.6)	63 (19.4)	0 (0)
Anemia	50 (15.2)	19 (5.8)	46 (14.2)	12 (3.7)
Pneumonia	45 (13.6)	21 (6.4)	49 (15.1)	28 (8.6)
Diarrhea	44 (13.3)	1 (0.3)	62 (19.1)	4 (1.2)
COVID-19	40 (12.1)	4 (1.2)	33 (10.2)	5 (1.5)
Hypertension	35 (10.6)	11 (3.3)	49 (15.1)	16 (4.9)
Contusion	33 (10.0)	0 (0)	30 (9.2)	0 (0)
Arthralgia	26 (7.9)	0 (0)	41 (12.6)	0 (0)
Thrombocytopenia	26 (7.9)	9 (2.7)	37 (11.4)	10 (3.1)
Urinary tract infection	26 (7.9)	3 (0.9)	40 (12.3)	3 (0.9)
Atrial fibrillation	8 (2.4)	3 (0.9)	41 (12.6)	12 (3.7)
Dose modifications due to TEAEs				
Reductions	26 (7.9)		59 (18.2)	
Discontinuations	31 (9.4)		35 (10.8)	

Median time on treatment was 20.5 months with pirtobrutinib and 19.3 months with ibrutinib;
1 patient developed Richter Transformation (RT) on pirtobrutinib; 4 patients developed RT on ibrutinib

Pirtobrutinib was well-tolerated with fewer dose reductions and discontinuations due to TEAEs than ibrutinib

Woyach,, et al.; ASH 2025

BRUIN CLL-321: ncBTKi pirtobrutinib for RR patients with CLL previously exposed to BTKi and/or venetoclax

Randomized, open-label Phase 3
R/R CLL after cBTKi N=250

Stratified by:
- Del(17p) status
- Prior venetoclax

R 1:1

n=119 **Pirtobrutinib 200 mg PO QD**

Investigator's Choice
n=82 **Idelalisib + rituximab***
or
n=37 **BR†‡**

Crossover allowed if PD confirmed by IRC§

Reported Characteristics (Pirto arm)

MEDIAN PRIOR LOT
3 (range, 1-13)

MEDIAN AGE
66 (range, 42-90)

Prior cBTKi
100% (**I** 84%; **A** 14%; **Z** 8%; Other 4%)

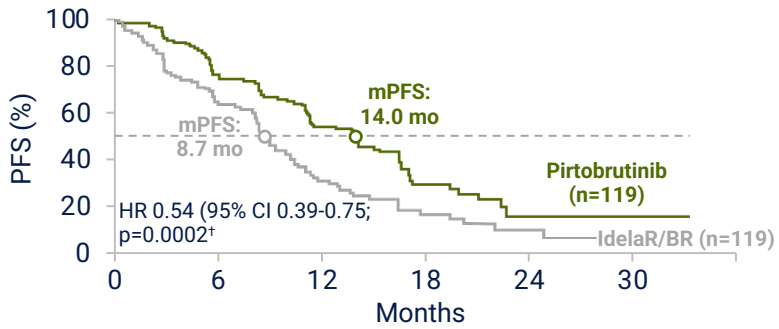
Prior BCL2i
50% (Ven)

UNMUTATED IGHV
93%

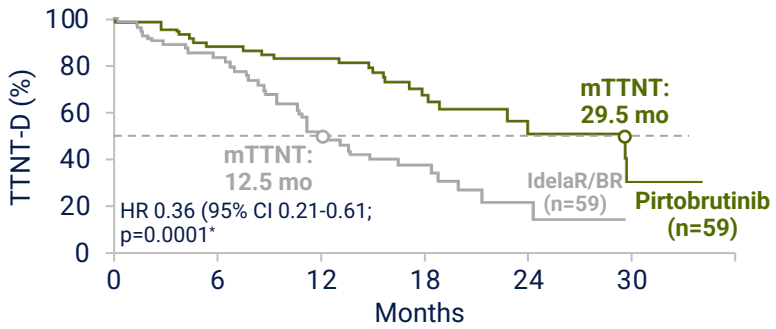
Del(17p) and/or *TP53*^{mut}
54%

CK (3 abn)
72%

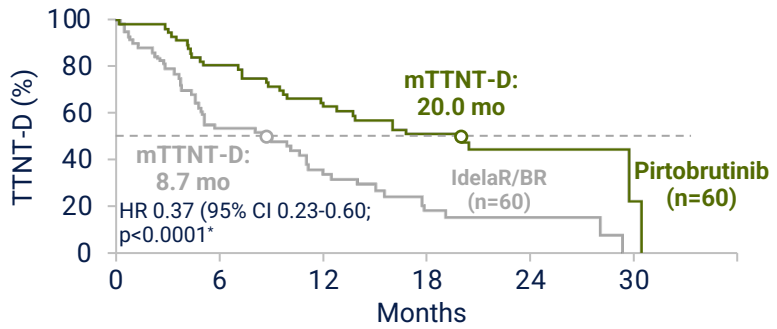
IRC-Assessed PFS
Median follow-up: 19.4 mo (Pirto arm)



TTNT-D in Ven-naïve patients (n=59/arm)



TTNT-D in Ven-treated patients (n=60/arm)



Primary endpoint:
- PFS (IRC)

Key secondary endpoints:
- Inv PFS, EFS, TTNT, OS, Safety

Highly pre-treated pts (58% 3L+).

Improved but underwhelming **mPFS** (Pirto 14.0 m vs. IdelaR/BR 8,7 m, HR = 0.54, 95% CI, 0.39-0.75)

Safety, particularly lower bleeding risk are viewed favorably vs other BTKis.

Sharman JP et al., JCO 2025

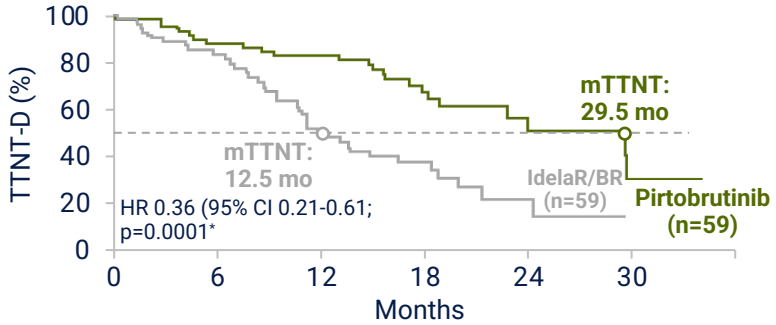
BRUIN CLL-321: ncBTKi pirtobrutinib for RR patients with CLL previously exposed to BTKi and/or venetoclax

	Pirtobrutinib (n = 119)		IdelaR/BR (n = 119)	
	Events/ Patients	Median TTNT (95% CI)	Events/ Patients	Median TTNT (95% CI)
Reason for discontinuation from most recent prior cBTKi				
PD	47/84	17.8 (13.7 to 24.0)	64/86	9.9 (5.2 to 11.8)
Toxicity	3/20	22.7 (22.7 to NE)	12/21	12.0 (8.3 to 29.3)
Other	4/15	NR (16.0 to NE)	4/9	18.7 (4.6 to NE)

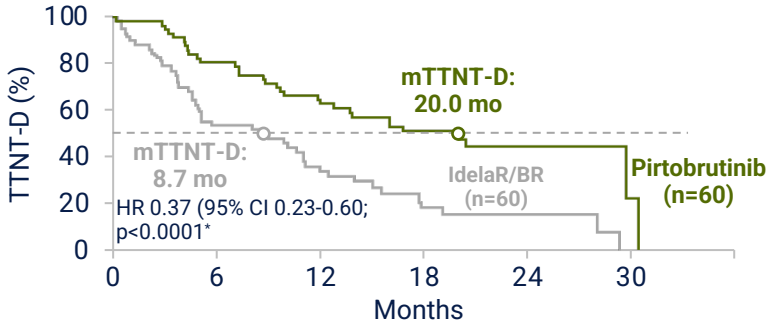
REASON FOR DISCONTINUATION OF BTKi
- **PD 71%**
- **Toxicity 17%**

IRC-Assessed PFS
Median follow-up: 19.4 mo (Pirto arm)

TTNT-D in Ven-naïve patients (n=59/arm)



TTNT-D in Ven-treated patients (n=60/arm)



Primary endpoint:
- PFS (IRC)

Key secondary endpoints:
- Inv PFS, EFS, TTNT, OS, Safety

Highly pre-treated pts (58% 3L+).

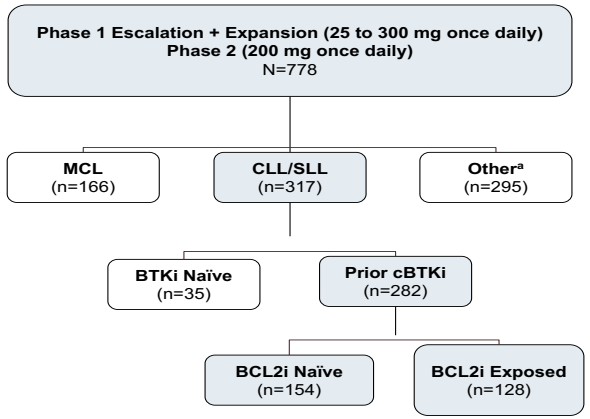
Improved but underwhelming **mPFS** (Pirto 14.0 m vs. IdelaR/BR 8,7 m, HR = 0.54, 95% CI, 0.39-0.75)

Safety, particularly lower bleeding risk are viewed favorably vs other BTKis.

Pirtobrutinib è approvato da EMA ma non ancora rimborsato da AIFA.

Sharman JP et al. JCO 2025

Phase 1/2 BRUIN Study: Baseline Characteristics of Patients With CLL/SLL Who Received Prior cBTKi, and by BCL2i Exposure



Characteristic	Prior cBTKi (n=282)	BCL2i-N (n=154)	BCL2i-E (n=128)
Median age (range), years	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 (%)			
BTKi	282 (100)	154 (100)	128 (100)
Anti-CD20 antibody	251 (89)	127 (83)	124 (97)
Chemotherapy	228 (81)	114 (74)	114 (89)
BCL2i	128 (45)	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)

Characteristic	Prior cBTKi (n=282)	BCL2i-N (n=154)	BCL2i-E (n=128)
Median time from diagnosis to first dose (IQR), years	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 Characteristic[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 mutated	96/245 (39)	57/138 (41)	39/107 (36)
PLCg2 mutated	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)

Wierda, et al; ASH 2025

Phase 1/2 BRUIN Study: PFS in CLL/SLL pts who Received Prior cBTKi, and by BCL2i Exposure

CLL/SLL pts who Received Prior cBTKi

La parte di immagine con ID relazione rId5 non è stata trovata nel file.

PFS

PFS

PFS in CLL pts who Received Prior cBTKi, by BCL2i Exposure

La parte di immagine con ID relazione rId2 non è stata trovata nel file.

TTNT

OS

Wierda, et al; ASH 2025

Pirtobrutinib in 2L post BTKi – ASH 2025

Publication Number: 5670

Pirtobrutinib Outcomes in Second-Line (2L) Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma (CLL/SLL) After First-Line (1L) cBTKi Therapy: A Pooled Analysis of the BRUIN LOXO-BTK-18001 and BRUIN CLL-321 Studies

OBJECTIVE

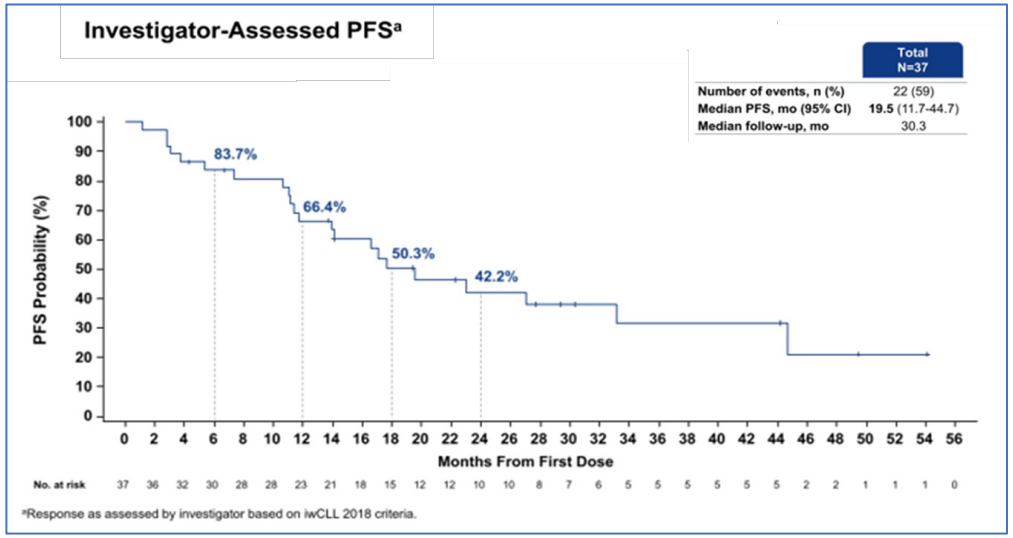
To evaluate the safety and efficacy of second-line (2L) pirtobrutinib specifically in patients with chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL) who previously received a first-line (1L) covalent Bruton tyrosine kinase inhibitor (cBTKi) and had no prior B-cell lymphoma 2 inhibitor (BCL2i) exposure, using pooled data from the BRUIN LOXO-BTK-18001 and BRUIN CLL-321 global studies

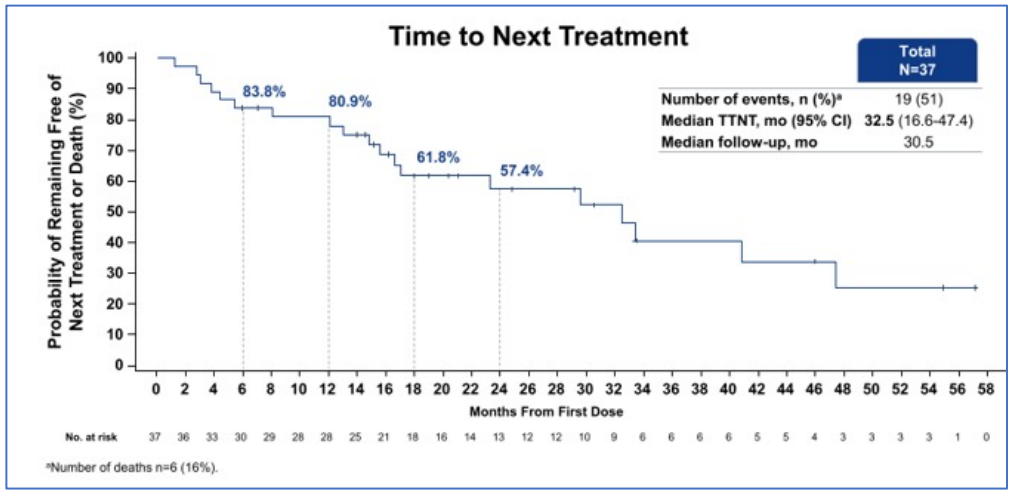
Pooled analysis 37 pazienti

Demographic and Clinical Characteristics

Characteristics	Total (N=37)
Age, median, (range), years	69 (42-87)
Male, n (%)	27 (73)
Region, n (%)	
US / Outside US	13 (35) / 24 (65)
Histology, n (%)	
CLL / SLL	35 (95) / 2 (5)
ECOG PS, n (%)	
0-1 / 2	31 (84) / 6 (16)
Rai stage, n (%)	
0-II / III-IV	23 (62) / 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)
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)

[a]Disease progression was selected if PD for any prior BTK; otherwise, toxicity was selected if toxicity from any prior BTK; otherwise, other was selected.





2L PFS 19,5 m

Eyre et al. ASH 2025

RWE: Informing outcomes of patients who progress on ncBTKi

cBTKi → ncBTKi → BCL2i

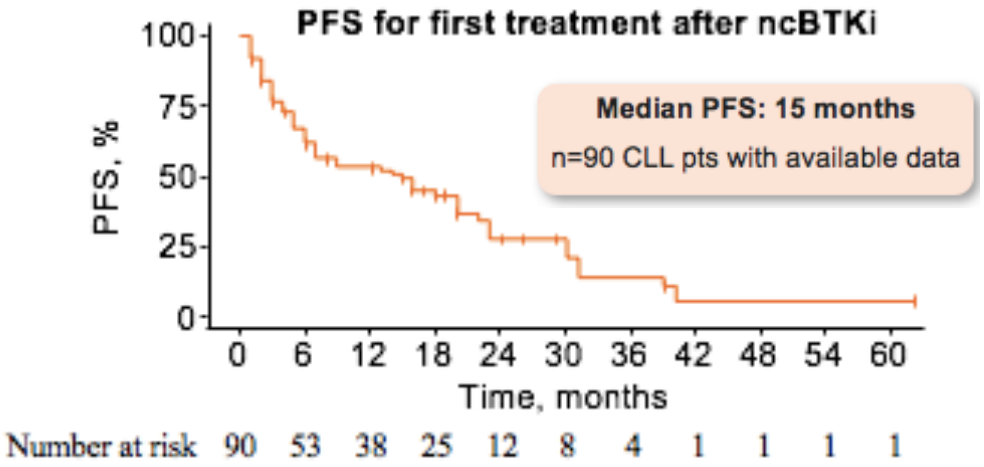
- 156 pts with CLL and RT
- 4 median prior lines of therapy prior to ncBTKi

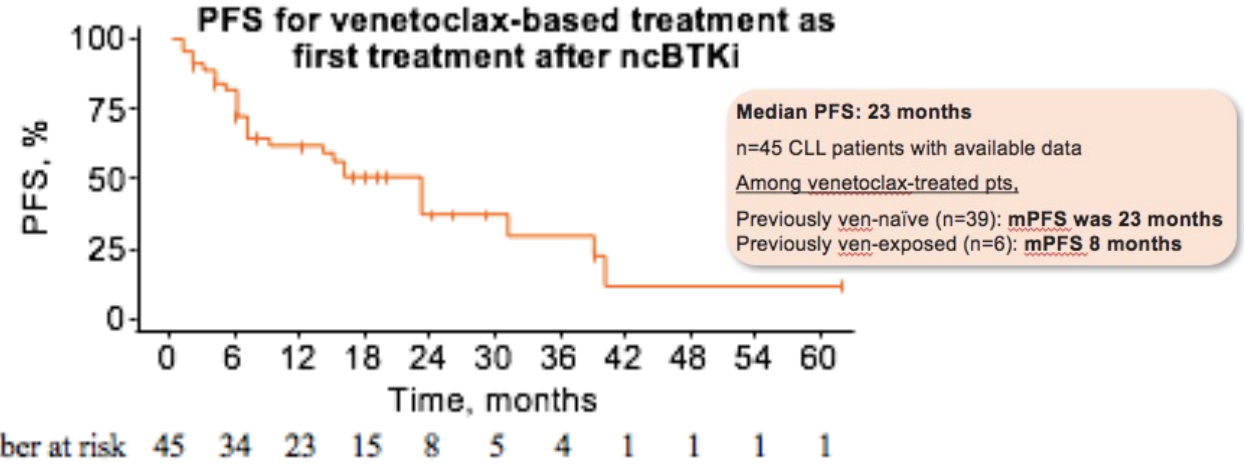
92 CLL patients received a LOT after ncBTKi;
43 patients received at least 2 treatments

Prior treatment	CLL patients (n=124)	RT patients (n=32)
CIT	86.3%	84.4%
cBTKi	95.2% *84.8% dc cBTKi for PD	87.5%
Venetoclax	40.3% *82.6% dc ven for PD	53.1%

THERAPIES AFTER ncBTKi DISCONTINUATION

THERAPY	# PTS	OVERALL RESPONSE RATE[a]
Venetoclax-based therapy[b]	53	75% (CR 11, PR 25, SD 5, PD 9, uk[c] 3) *88.6% of 53 patients previously ven-naive
CAR T-cell therapy	10	62.5% (CR 3, PR 2, SD 1, PD 2, uk 2)
Alternative ncBTKi	8	75% (PR 6, SD 2) *dc reason for prior ncBTKi: toxicity 4, PD3, other 1
PI3Ki	7	20% (PR 1, PD 4, uk 2)
Chemo+/-immunotherapy (CIT)	7	28.6% (PR 2, SD 2, PD 3)
cBTKi+/-antiCD20 mAb	6	80% (PR 4, PD 1, uk1)
antiCD20 mAb	6	0% (SD 2, PD 1, uk3)
Stem cell transplant	5	80% (CR 4, SD 1)
Other treatment	32	

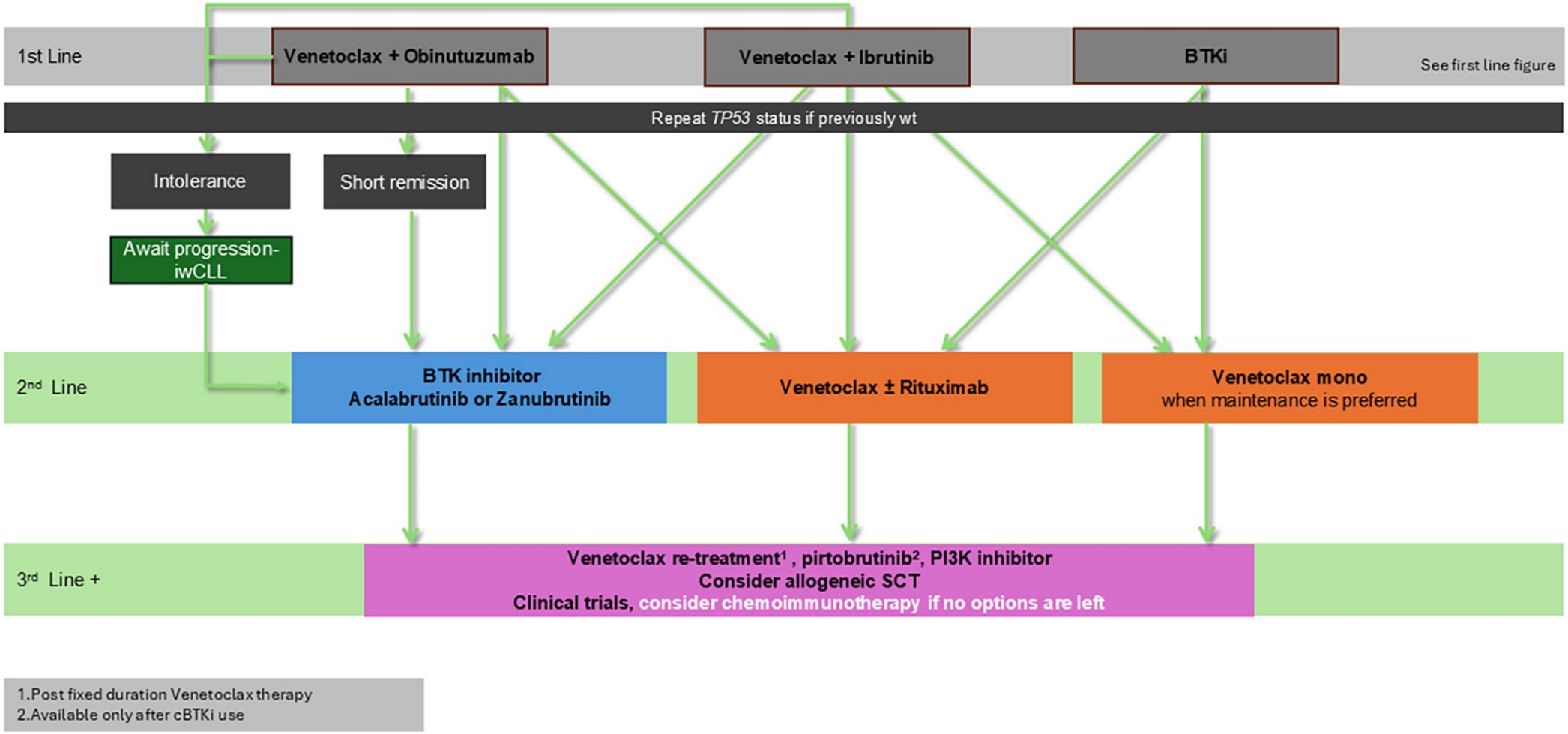




*Data available on reason for venetoclax discontinuation in 46 of 50 patients.

Thompson MC, et al. Blood. 2024;144(Supp 1):1870.

CLL Guidelines 2025 – British Society for Haematology

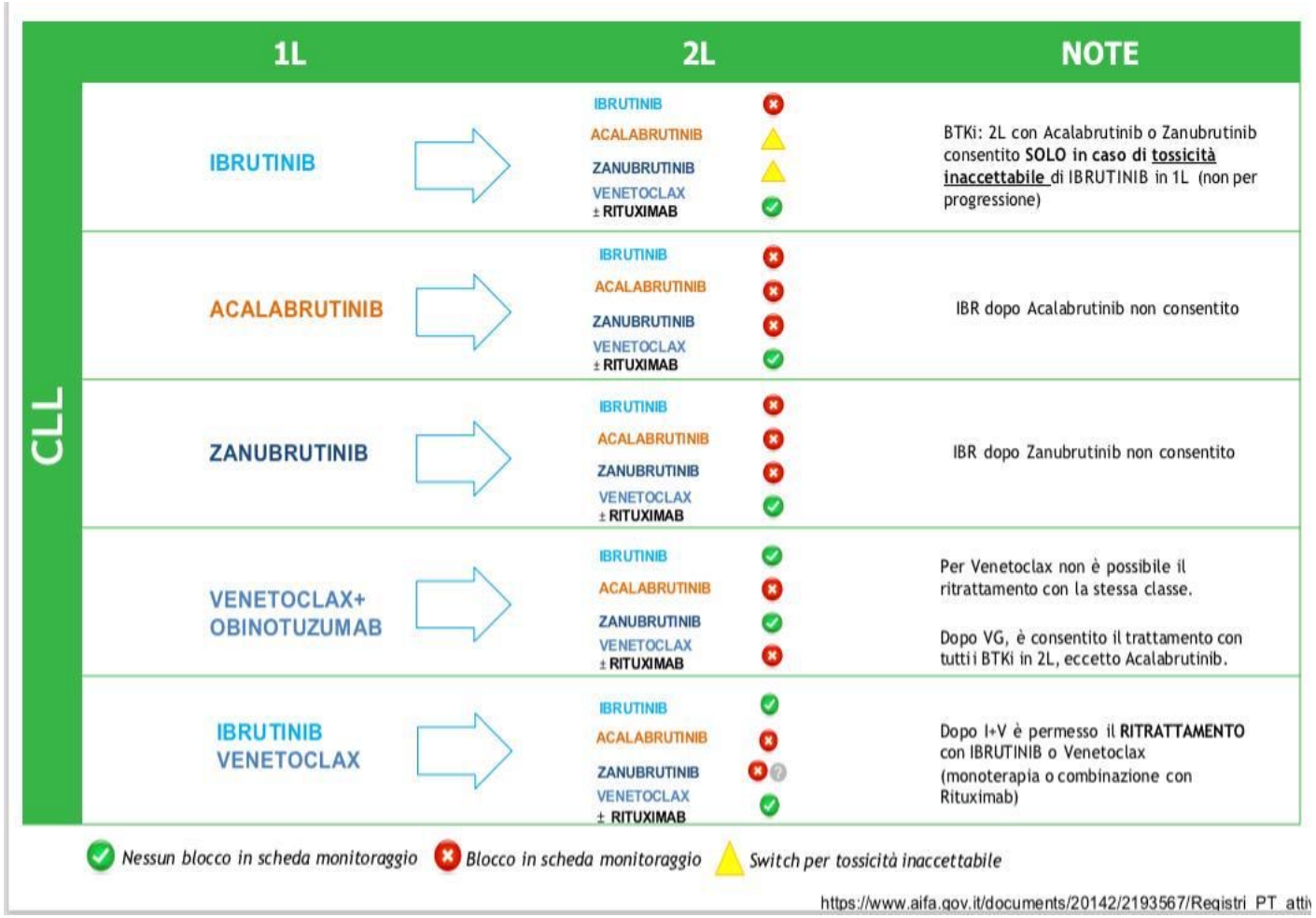


Walewska et al. BJHaem 2025

	treatment preference for genetic subgroups based on efficacy and tolerability			treatment-related logistics		adverse events, comorbidities and comedication					
	mIGHV	uIGHV	17p- / *TP53* mut	finite duration and treatment-free interval	convenient initiation of therapy	accumulation of adverse events	bleeding risk	TLS risk	cardiovascular events	reduced renal function	infection risk during treatment
ibrutinib											
acalabrutinib											
zanubrutinib											
obinutuzumab + acalabrutinib											
obinutuzumab + venetoclax											
ibrutinib + venetoclax											

Color code rating for treatment options: pro con

Tausch E et al., ASH Educational Program 2024



CLL 1L Treatment, %	2021
Chemotherapy	<5
CIT	20-25
BTKi-based therapy	45-50
Venetoclax-based therapy	25-30

Sequencing post VO vs IV vs BTKi

Drivers di scelta

- Biologia
- Pz anziano: età ?
- Presenza di masse bulk
- Comorbidità:
  - Insufficienza renale
  - Problemi CV
  - Bleeding
  - Rischio infettivo
- Polifarmacologia
- Preferenza paziente
- Logistica:
  - Caregiver
  - distanza centro
  - frequenza accessi
  - Vita sociale
- Costi
- Trials clinici

Goals della terapia

- Efficacia ⇆ Profilo di Sicurezza
- Rapido controllo malattia
- TTNT; uMRD; OS
- Drugs interaction
- QoL

CIT, Ven-based (V/VR), BTKi, ncBTKi
CIT, BTK, ncBTKi, Ven-based (V/VR)
CIT, ncBTKi, cBTKi,Ven-based (V/VR)-> NA
CIT, ncBTKi, Ven-based (V/VR), cBTKi-> NA

VO, cBTKi (I o Z), ncBTKi
VO, Ven, ncBTKi -> NA
VO, ncBTKi, Ven -> NA

IV, Ven-based (V/VR), ncBTKi
IV, cBTKi, ncBTKi, Ven-based (V/VR)
IV, switch cBTKi, Ven-based (V/VR), ncBTKi
IV, ncBTKi, Ven-based (V/VR)

BTKi, Ven-based (V/VR), ncBTKi
BTKi, switch cBTKi, Ven-based (V/VR), ncBTKi
BTKi, ncBTKi, Ven-based (V/VR)

Personal opinion

Adapted by Jurczak et al. EHA2025

Grazie
per l'attenzione

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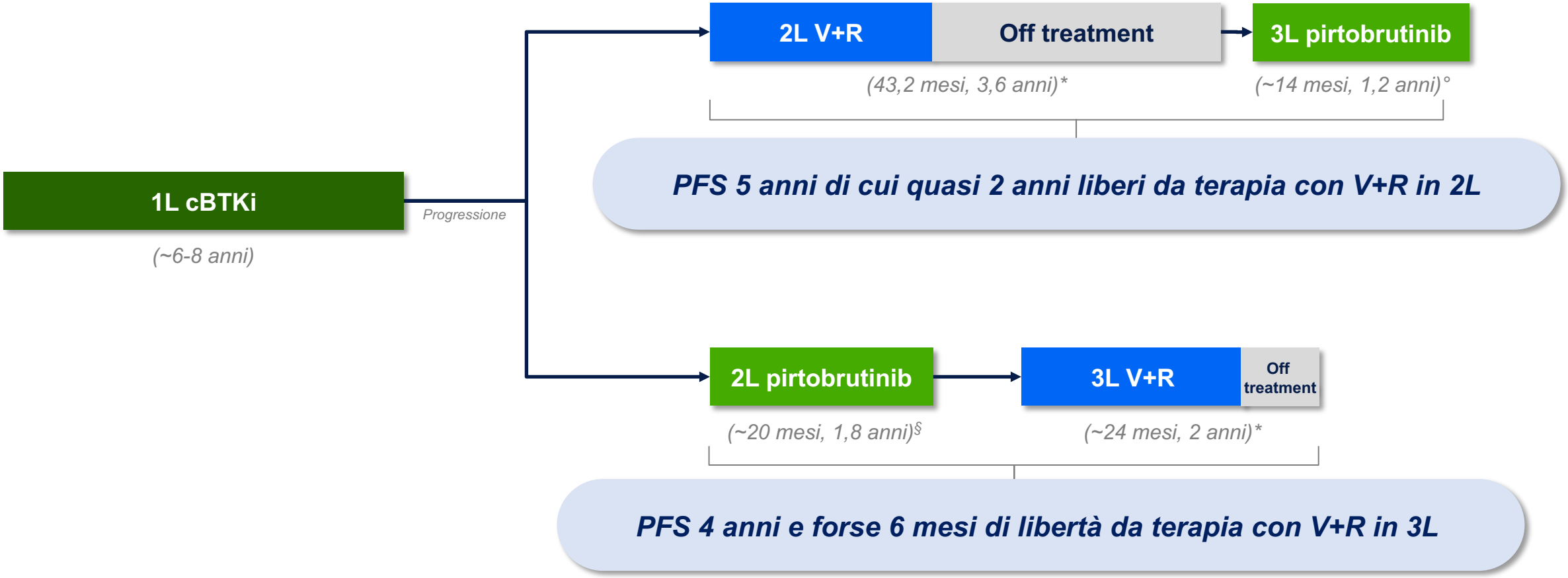
Possibili Sequencing in RR post BTKi



*RWE venetoclax; °BRUIN-321; §Pooled ASH2025

Pirtobrutinib Vs venetoclax in 2L pura (post cBTKi)

Pirto – BRUIN-321[1]

	Pirtobrutinib (n = 119)		IdelaR/BR (n = 119)	
	Events/ Patients	Median PFS (95% CI)	Events/ Patients	Median PFS (95% CI)
Lines of prior systemic therapy				
1	10/21	17.1 (8.6 to NE)	13/28	14.8 (8.6 to NE)
2	18/30	16.6 (8.3 to 22.7)	16/24	8.9 (7.0 to 13.7)
3	16/29	13.7 (8.5 to NE)	15/18	8.1 (1.7 to 11.6)
≥4	30/39	11.3 (5.6 to 15.1)	35/49	5.8 (3.5 to 9.0)

Prior 1L (cBTKi) **17,1 m**

Ven post BTKi – RWE[2]

		Response		PFS[a]			
						Rate, %	
		N	ORR[c]	*N*	Median (CI), months	12 months	18 months
Overall (*N* = 205)	Overall	141	79.4%	201	44.1 (36.3, NR)	84.0%	76.2%
	1 L → 2 L	47	85.1%	70	43.2 (39.5, NR)	87.5%	80.8%
	2 L → 3 L	51	80.4%	70	44.3 (36.3, NR)	86.5%	82.1%

Prior 1L (cBTKi) **43,2 m**

Ven – MURANO (5y)[3]

	Venetoclax+ Rituximab (N=194)			Bendamustine+ Rituximab (N=195)	
Baseline Characteristics	n	Median (Months)	Total n	n	Median (Months)
Number of Prior Regimens					
1	111	54.0	228	117	16.4
2	58	53.5	101	43	21.2
>=3	25	48.5	60	35	12.9

Prior 1L (CIT) **54 m**

1. Sharman JP et al., JCO 2025; 2.Ghosh N, et al. American Journal of Hematology, 2024; 0:1–5; 3.Seymour et al., Blood 2022

Targeted agents R/R CLL

Study	Treatment	N	Median Follow Up	PFS	OS	TP53	IGHV	Complex Cytogenetics
RESONATE[107]	I vs Ofa	391	65.3 months	Median PFS 44.1 vs 8.1months HR: 0.148; 95% CI: 0.113-0.196; $P < .0001$	Median OS 67.7 vs 65.1 months HR: 0.810; 95% CI: 0.602-1.091)	Median PFS 40.6 months in del(17p) and/or TP53 mutation ($n = 104$)	M-CLL ($n = 36$) and U-CLL ($n = 98$) similar PFS, median 48.4 vs. 49.7 months; HR: 1.208; 95% CI: 0.741-1.971	median PFS of 40.8 months in patients with CK ($n = 39$) and 44.6 months in patients without CK ($n = 114$) (HR: 1.279; 95% CI: 0.801-2.044)
ASCEND[108]	A vs. IdelaR or BR	310	46.5 months	Median PFS Acala vs. IdelaR/BR -NR vs. 16.8 months; HR, 0.28; 95% CI, 0.20–0.38; $P < .001$. 42-month PFS estimates 62% vs. 23% for IdelaR and 5% for BR	Median OS NR either arm (HR, 0.69; 95% CI, 0.46–1.04; $P = .078$); 42-month OS estimates 78% A vs. 65% idelaR/BR arm	del(17p) and/or TP53 28%. Median PFS 45.5 months for A vs. 11.1 months for IdelaR/BR (HR, 0.22; 95% CI, 0.12–0.39; $P < .001$)	74% U-CLL. Median PFS was NR A vs. 16.2 months for IdelaR/BR (HR, 0.29; 95% CI, 0.20-0.41; $P < .001$)	2%. PFS HR 0.18 (95% CI 0.02–1.84)
MURANO[109]	VR vs. BR	389	59.2 months	Median PFS 53.6 vs 17.0 months. HR, 0.19; 95% CI, 0.15- 0.26; $P < .0001$)	Median OS NR both arms. HR, 0.40; 95% CI, 0.26–0.62; $P < .0001$. 5-year OS estimates of 82.1% vs 62.2%	del(17p) 26.6 %. del(17p) and/or TP53-mut vs TP53-wild-type 37.4 vs 56.6 months (HR [95% CI], 2.04 [1.32, 3.15], $P = .010$) in VR	68.3% U-CLL. U-CLL vs M-CLL, 52.2 months vs NR, (HR, 2.96, 95% CI,1.64-5.34], $P = .0002$) in VR arm	GC vs no GC, 41.7 vs 59.8 months (HR, 2.50, 95% CI, 4.00–1.56; $P < .0001$)
ELEVATE-RR[74]	I vs. A	533	40.9 months	Median PFS 38.4 months in both arms. HR 1.00; 95% CI, 0.79-1.27	Median OS NR in either arm, with 23.5% deaths in A and 27.5% in I arm (HR, 0.82; 95% CI, 0.59-1.15	del(17p) 45.2%. HR, 1.00; 95% CI, 0.73-1.38 TP53 mutation 39.8%. HR, 0.95; 95% CI, 0.68-1.63.	85.7% U-CLL. No difference between arms HR, 1.09; 95% CI, 0.85-1.40	46.7%. No difference between arms HR, 1.04; 95% CI, 0.74-1.44
ALPINE[106]	Z vs. I	652	36.3 months	36-month PFS estimates 65.8% vs. 54.3%. HR: 0.67 [95% CI, 0.52–0.86, $P = .002$ favouring Z.	36-month OS estimates 82.6% vs. 79.7% HR: 0.76 [95% CI, 0.54–1.08]	23% TP53 mutation/ deletion. 36-month PFS estimates 60.1% and 43.6%. HR: 0.52 [95% CI, 0.32–0.83], $P = .005$	73% U-CLL. 29.6-months follow-up favours Z in U-CLL HR 0.64 (95% CI 0.47–0.87) and M-CLL HR 0.63 (95% CI 0.32–1.26)	17% in Z and 21% in I group. 29.6 months follow up; HR 0.91 (95% CI-0.50–1.66) with and HR 0.58 (95% CI-0.37–0.90) without.

Adapted from Varghese AM, Munir T. Clin Lymphoma Myeloma Leuk. 2025 Jun;25(6):381-394.