Terapia di prima linea della leucemia linfatica cronica: fissa e continuativa

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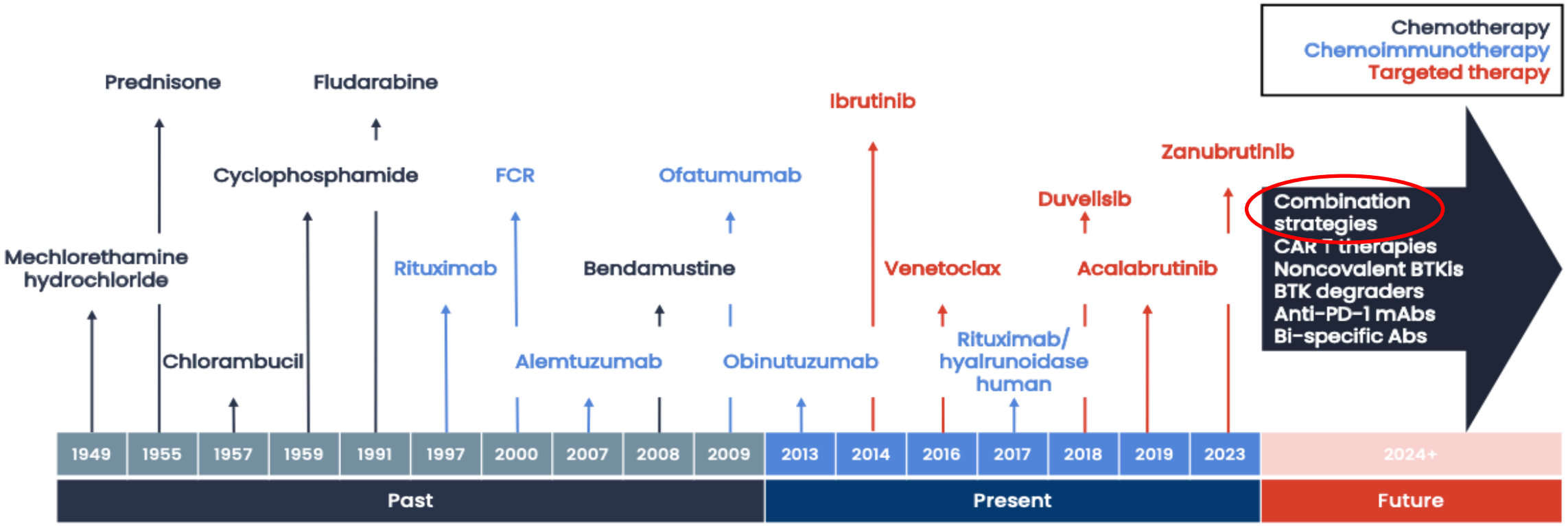
Disclosures of Claudia Giordano

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
None							

Evolution of treatment
A shift in treatment strategy:

time-limited vs continuous therapy



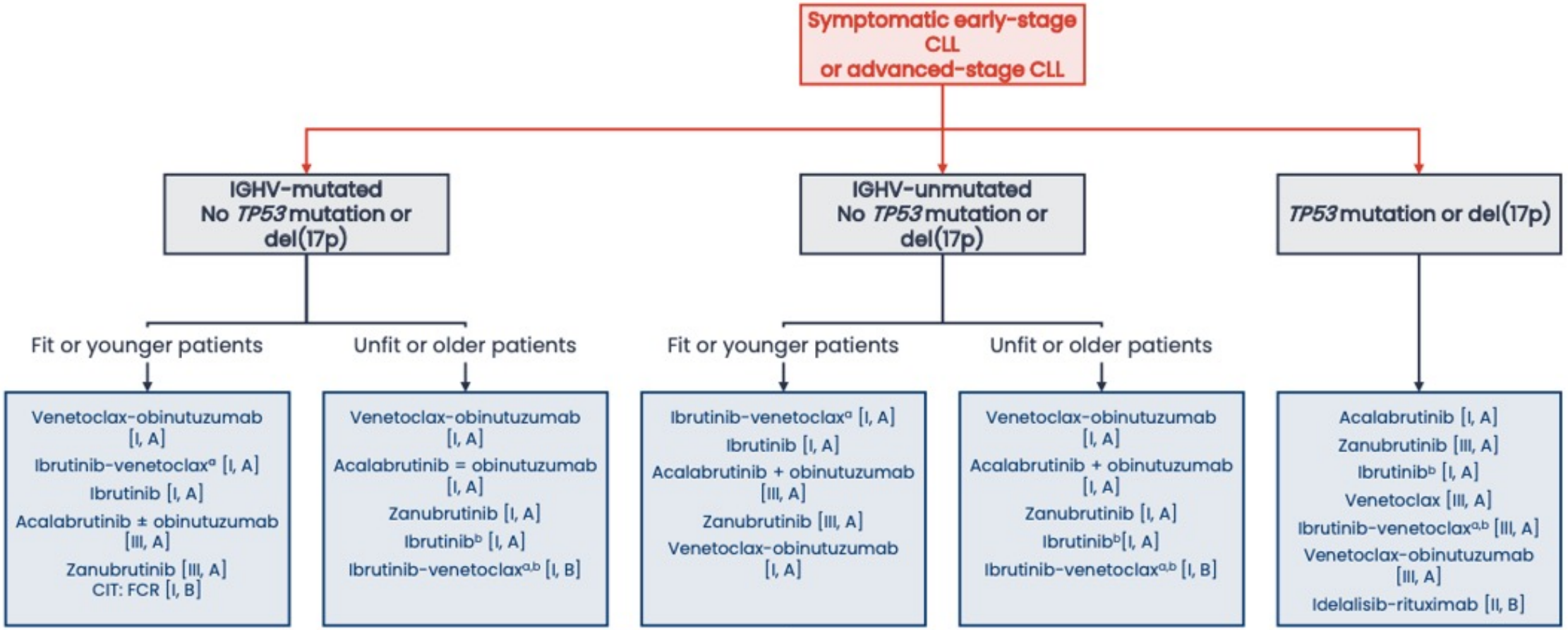
Targeted therapies are now treatment of choice for CLL

Chemotherapy and chemoimmunotherapy approaches are no longer recommended in the latest guidelines

Treatment approaches

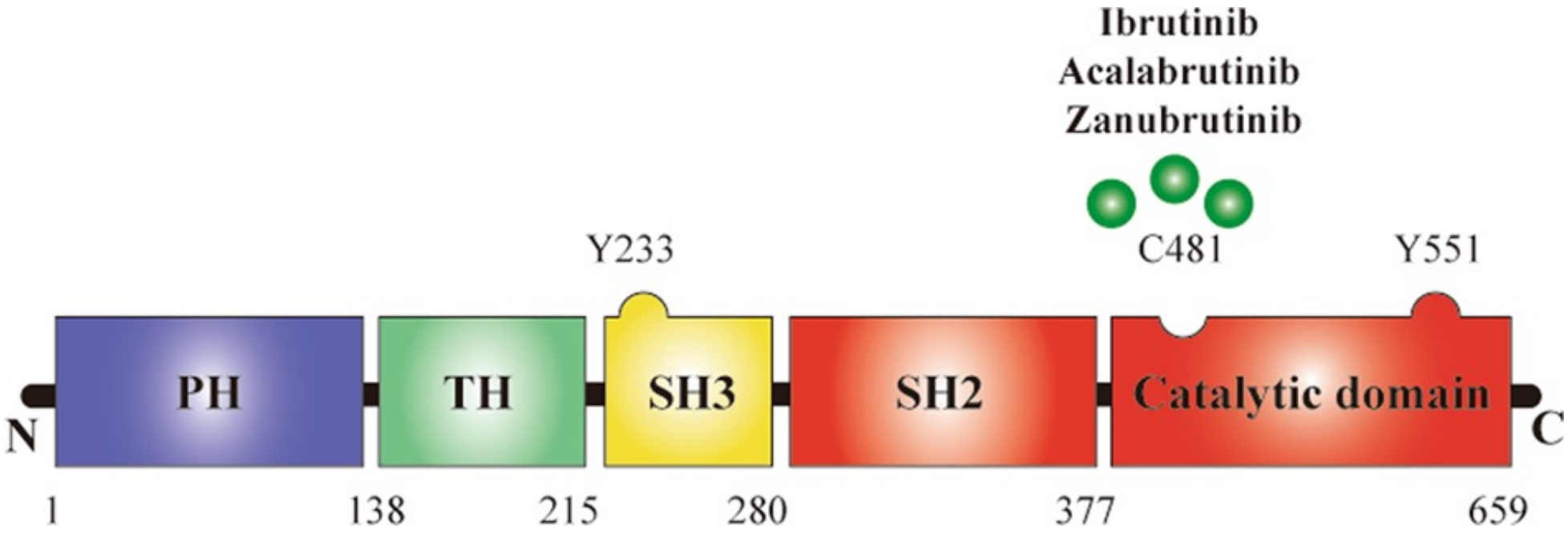
- Venetoclax-based therapy given as fixed-duration therapy in combination with either obinutuzumab or ibrutinib
- BTK inhibitor therapy as continuous treatment

2024 ESMO guidelines for first line CLL treatment



Indications of approved products may differ outside of the European Union. Zanubrutinib is authorized under different conditions (e.g., different government-approved professional information: indications, warnings, etc.) in Switzerland. For country-specific information, refer to the prescribing information for the country in which you practice medicine.
[a]Ibrutinib-venetoclax with a 15-month fixed duration or with an MRD-guided duration. [b]Ibrutinib or ibrutinib-venetoclax should be considered carefully in older patients with cardiac comorbidities.
CIT, chemoimmunotherapy; CLL, chronic lymphocytic leukemia; del, deletion; ESMO, European Society for Medical Oncology; FCR, fludarabine, cyclophosphamide, rituximab; IGHV, immunoglobulin heavy chain variable region; MRD, minimal residual disease; TN, treatment naive.
Adapted from Eichhorst B, et al. *Ann Oncol.* 2024;35(9):762-768.

Continuos treatment strategy: BTK-i



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RESONATE-2

Naïve ≥ 65 y
Ibrutinib vs chlorambucil

Ibrutinib provides **durable disease control (~9-year PFS)**

Benefit maintained across high-risk subgroups
Median OS not reached

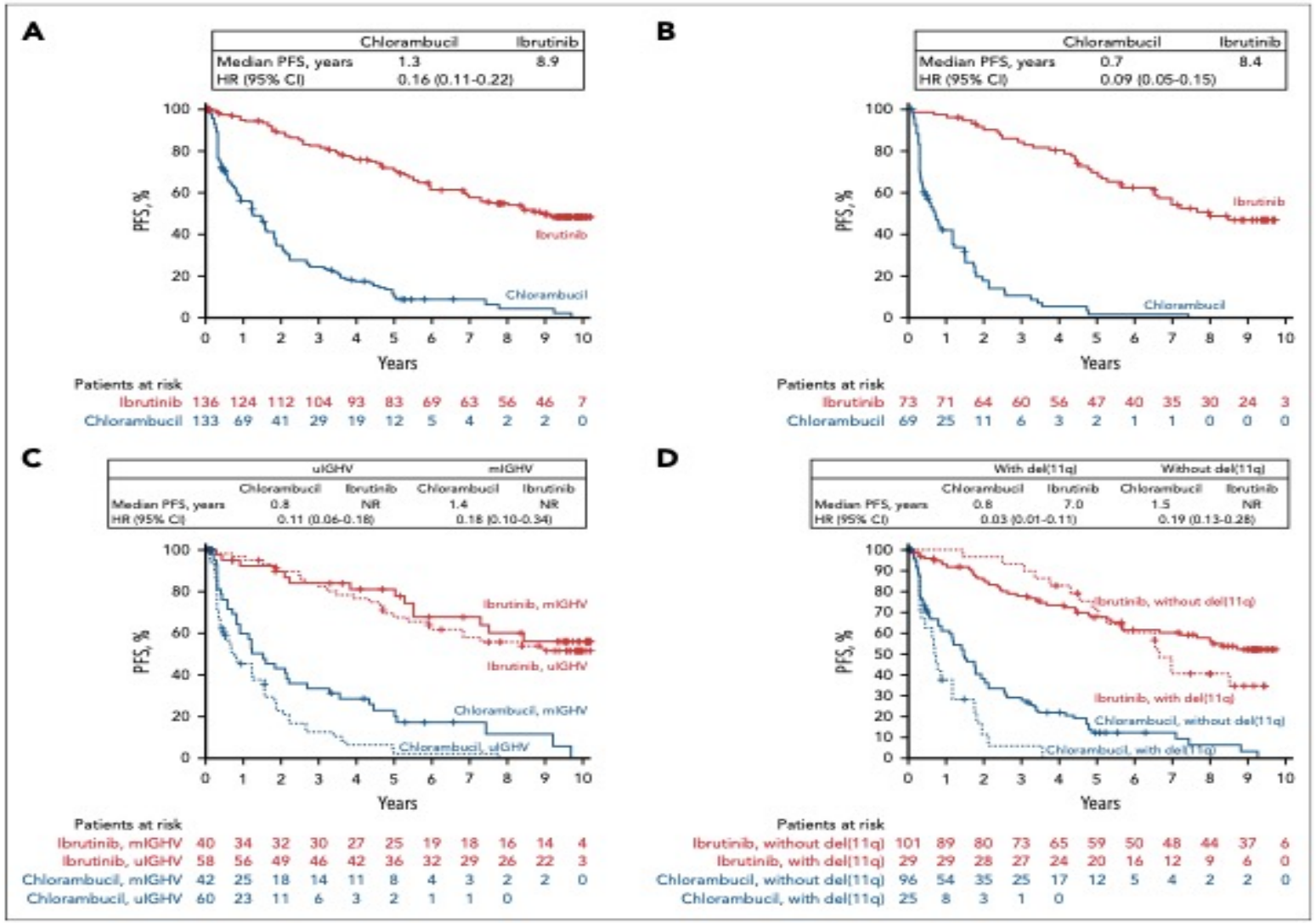
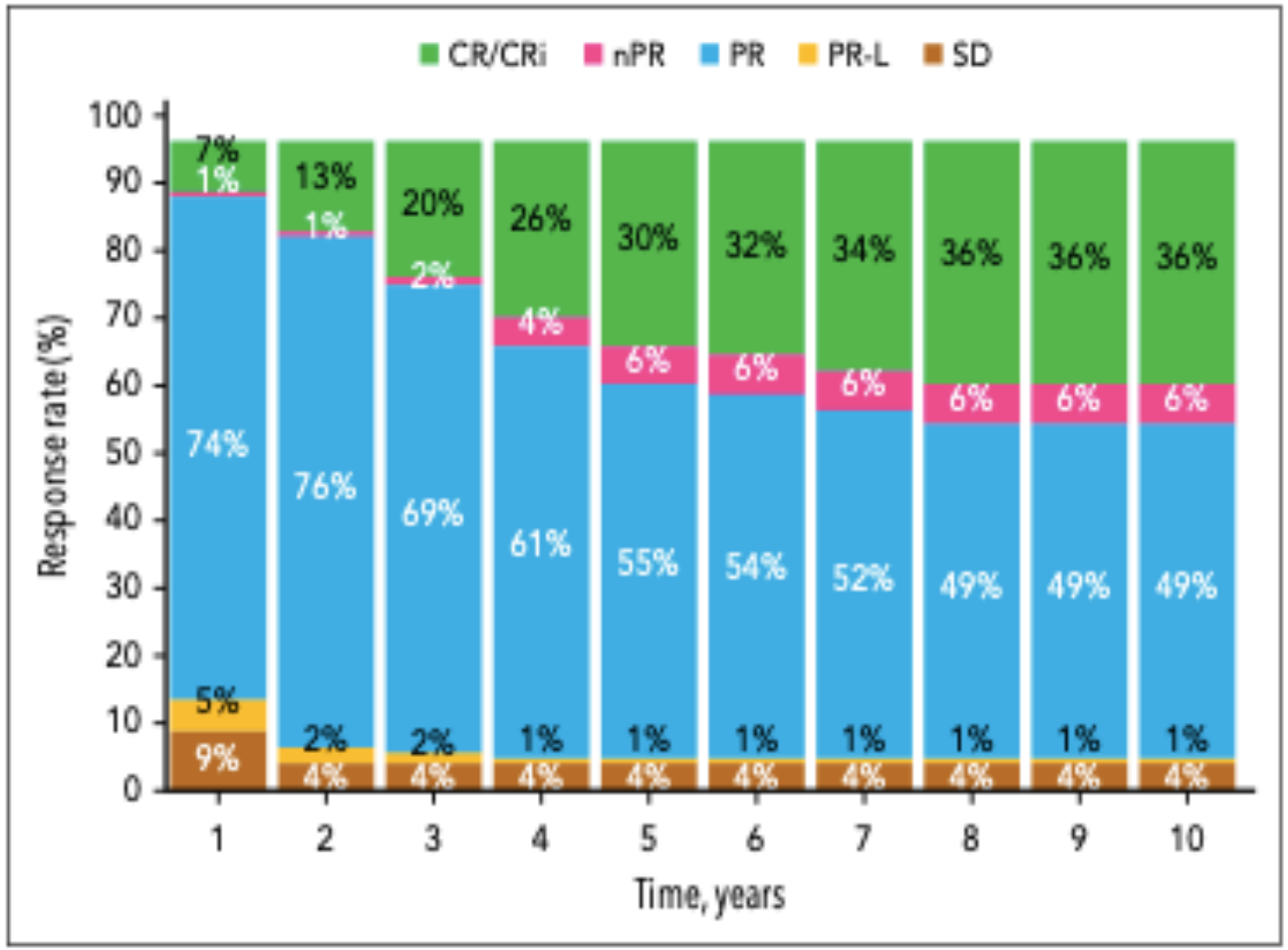


Figure 1. Investigator-assessed PFS. (A) All randomly assigned patients. (B) Patients with ≥1 high prognostic risk factor including mutated *TP53*, uIGHV, del(11q), and/or CK. (C) Patients with uIGHV or mIGHV. (D) Patients with or without del(11q). CK, complex karyotype; HR, hazard ratio; mIGHV, mutated immunoglobulin heavy chain variable; NR, not reached; PFS, progression-free survival; uIGHV, unmutated immunoglobulin heavy chain variable.

Figure 4. Change in investigator-assessed responses over time. CR, complete response; CRi, complete response with incomplete bone marrow recovery; nPR, nodular partial response; PR, partial response; PRL, partial response with lymphocytosis; SD, stable disease.



ELEVATE-TN

6-year PFS: **78% with acalabrutinib–obinutuzumab, 62% with acalabrutinib**

Median PFS not reached in both acalabrutinib arms

Benefit maintained in high-risk subgroups

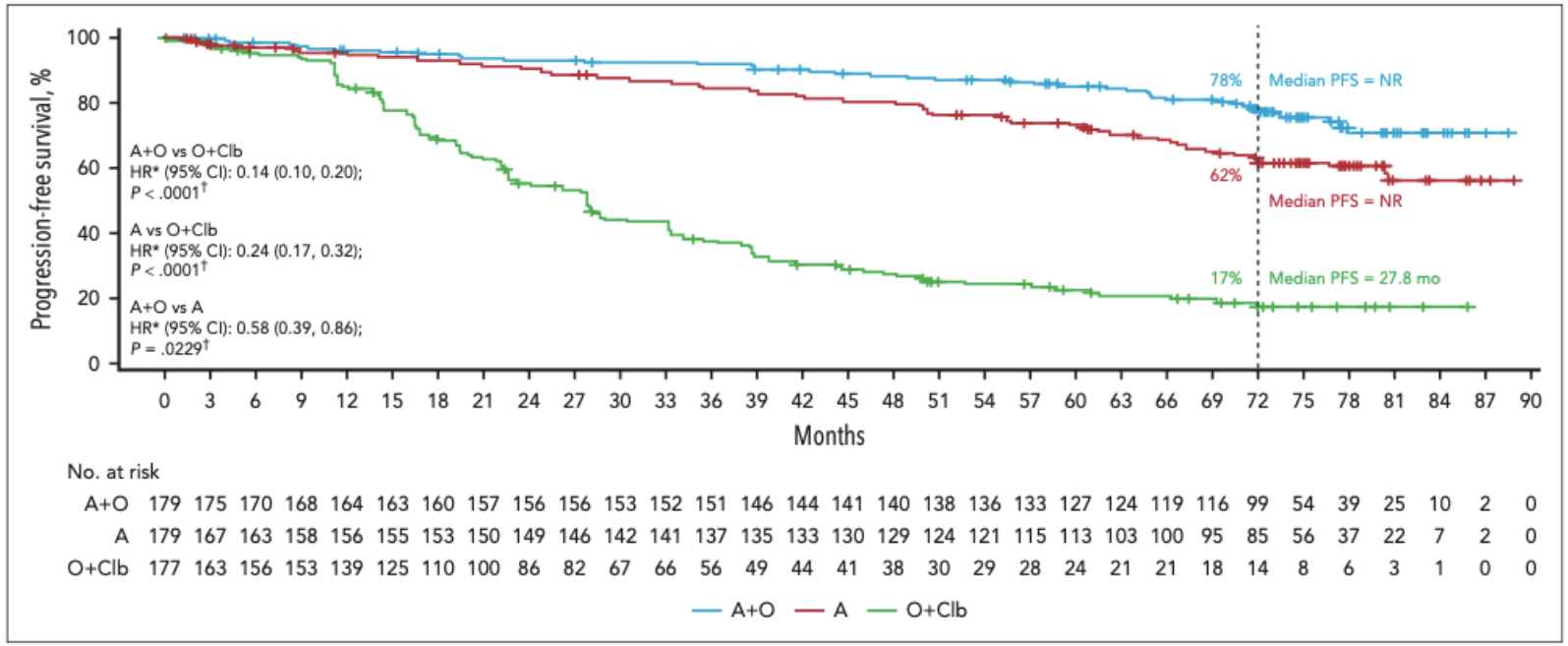


Figure 1. Investigator-assessed PFS overall. *HR based on stratified Cox proportional hazards model; †*P* value based on stratified log-rank test. ‡HR based on unstratified Cox proportional hazards model; §*P* value based on unstratified log-rank test. A, acalabrutinib; Clb, chlorambucil; O, obinutuzumab.

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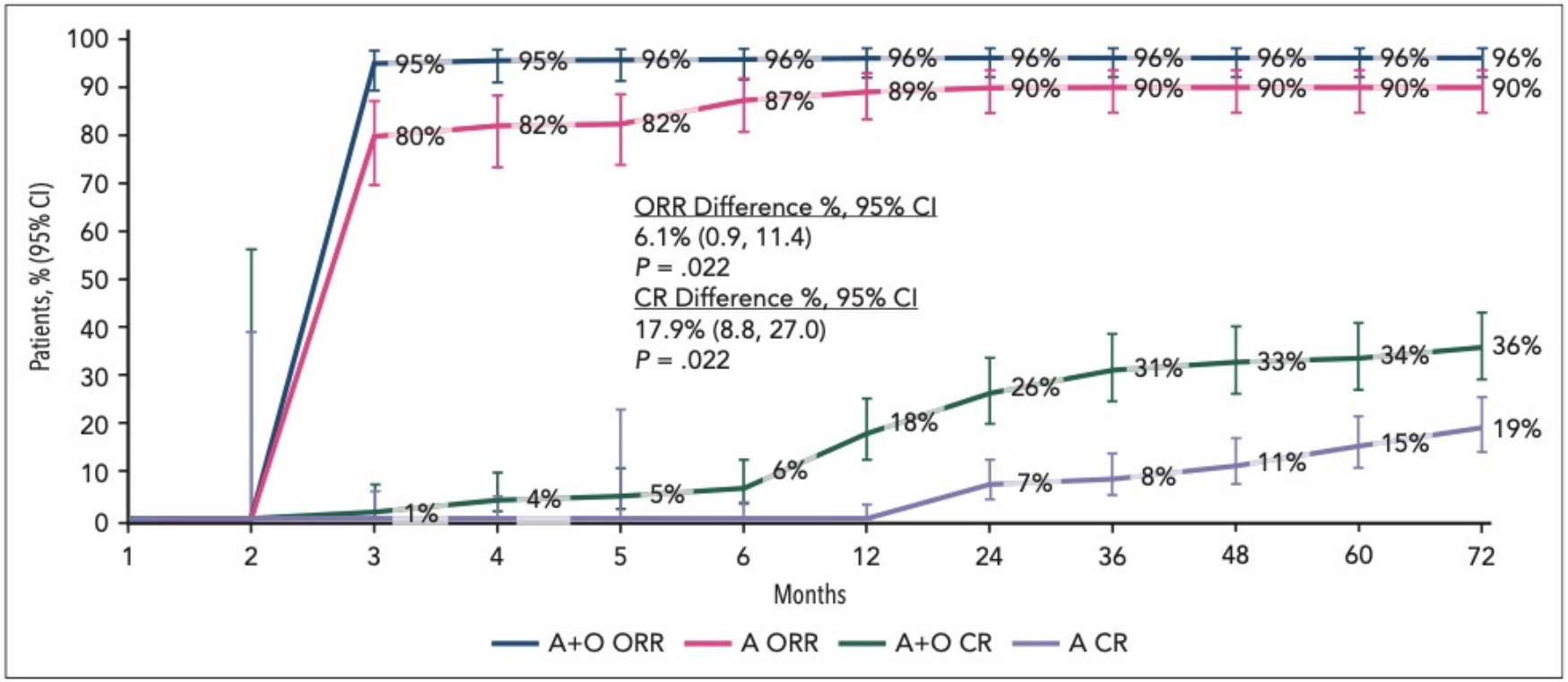
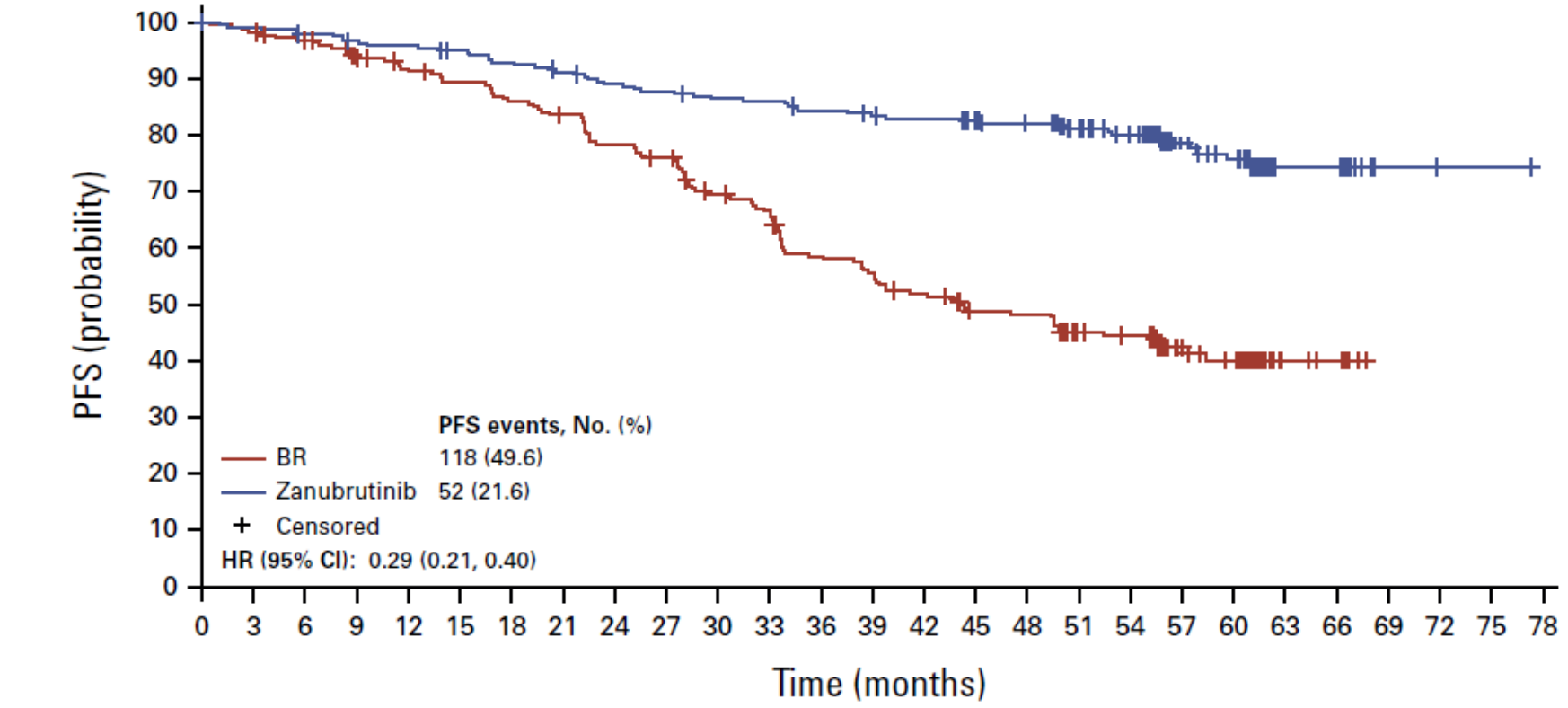


Figure 2. ORRs* and CR/CRi rates over follow-up period in patients treated with A-O or A monotherapy. *Best investigator-assessed response could be determined at any scheduled, per-protocol follow-up visit. ORR is defined as achieving CR, CRi, nPR, or PR per the investigator per International Workshop on CLL 2008 criteria[21] at or before initiation of subsequent anticancer therapy. ORR does not include partial response except for lymphocytes. A, acalabrutinib; nPR, nodular partial response; O, obinutuzumab; PR, partial response.

Median 5-Year Follow-Up of SEQUOIA study

A

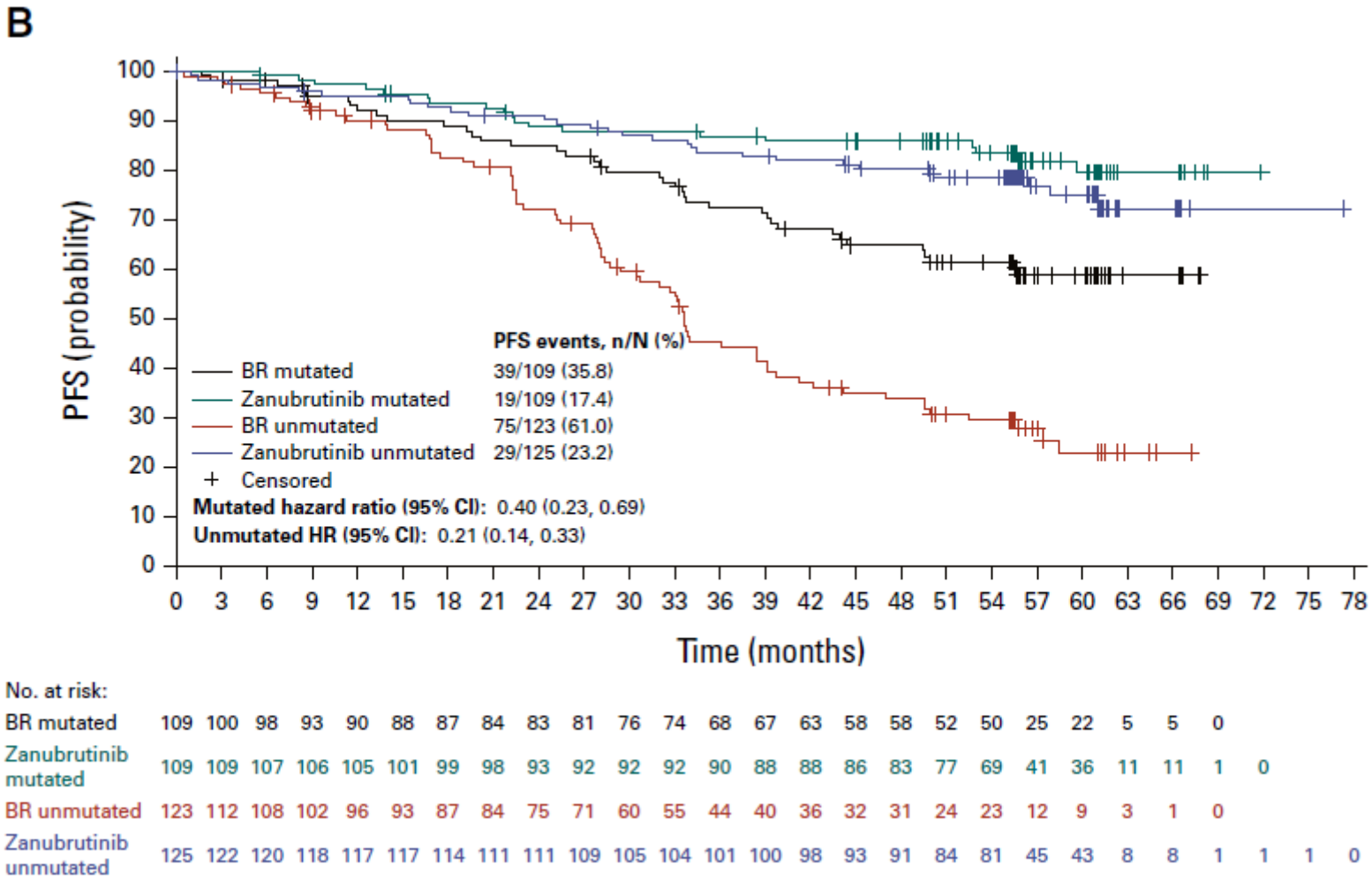
Estimated 60-month PFS rates were 75.8%



No. at risk:

BR	238	218	212	201	192	187	180	174	163	157	141	134	116	110	102	92	91	77	74	38	32	8	6	0			
Zanubrutinib	241	238	234	230	228	224	219	214	208	205	201	200	195	192	190	183	178	164	153	89	81	19	19	2	1	1	0

Median 5-Year Follow-Up of SEQUOIA study



The comparison of **any grade adverse** events

A

	Ibru	Acala	Zanu
Anemia	27	14	22
Neutropenia	23	10.6	53
Thrombocytopenia	16	7.3	32
Infection	83	79.4	75.8
Diarrhea	53	34.6	23.8
Fatigue	36	18.4	/
Upper respiratory infection	29	18.4	39
Arthralgia	22	15.6	17.4
Pneumonia	18	7.3	25
Hypertension	21	6.7	15.4
Headache	17	36.9	/
Atrial fibrillation	11	3.9	/
Rash	35	14	36
Bleeding/Bruising	55	39.1	28.4
Median treatment exposure	29mon	27.7mon	6mon
Numbers	330	179	118
Patients	CLL/SLL	CLL/SLL	MCL

≥40 ≥30 ≥20 ≥10

The comparison of grade **3-5 adverse events**

B

	Ibru	Acala	Zanu
Anemia	7	6.7	8
Neutropenia	18	9.5	15
Thrombocytopenia	6	2.8	5
Infection	31	14	10.8
Diarrhea	5	0.6	0.8
Fatigue	3	1.1	/
Upper respiratory infection	1	0	0
Arthralgia	2	0.6	3.4
Pneumonia	12	2.2	10
Hypertension	7	2.2	3.4
Headache	2	1.1	/
Atrial fibrillation	5	0	/
Rash	3	0.6	0
Bleeding/Bruising	6	1.7	3.4
Median treatment exposure	29mon	27.7mon	6mon
Numbers	330	179	118
Patients	CLL/SLL	CLL/SLL	MCL

≥10 ≥7.5 ≥5 ≥2.5

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Continuous BTKi therapy: strengths and limitations

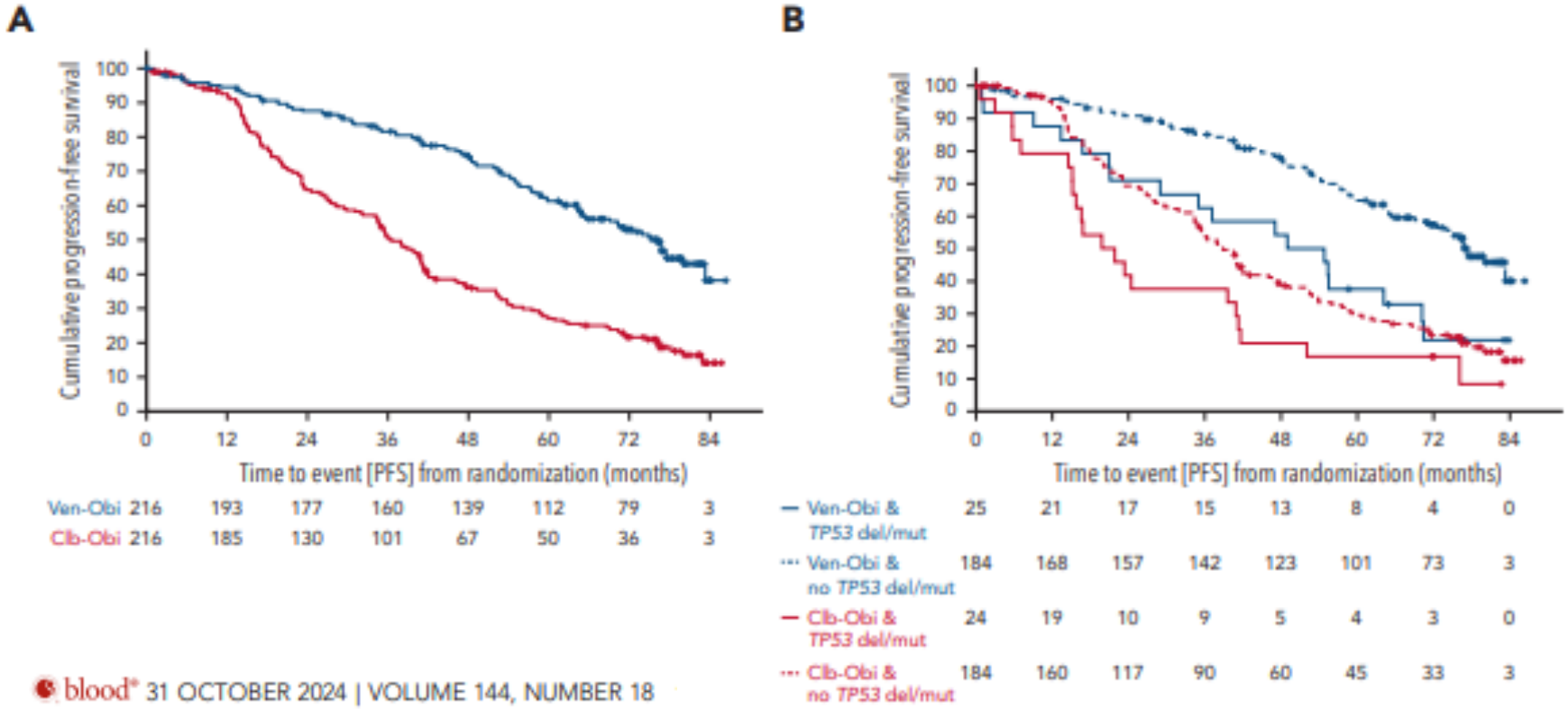
- **Durable disease control** (long-term PFS across trials)
- **Efficacy maintained in high-risk genomics**
- Oral, continuous treatment
- Costs

Unmet needs

- **Indefinite treatment exposure**
- Cumulative toxicity (CV events, adherence)
- Limited rates of **deep responses (uMRD)**
- Need for **treatment-free intervals**

Can we achieve deep, durable responses without continuous therapy?

Venetoclax-obinutuzumab for previously untreated chronic lymphocytic leukemia: 6-year results of the randomized phase 3 CLL14 study



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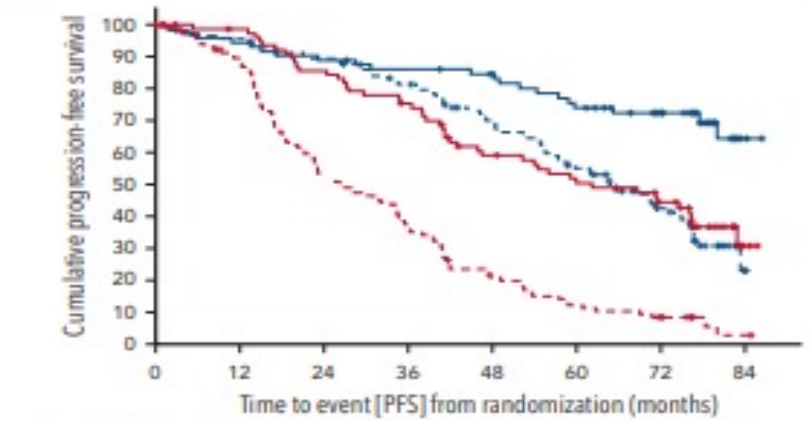
Progression-Free Survival (PFS)

- **PFS a 6 anni: ~53%**
- HR ~0.40 vs Clb-Obi

More than half of patients remain progression-free without therapy.

Venetoclax-obinutuzumab for previously untreated chronic lymphocytic leukemia: 6-year results of the randomized phase 3 CLL14 study

C

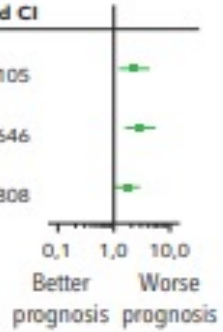


Ven-Obi & mIGHV	76	68	64	60	57	49	39	2
Ven-Obi & uIGHV	121	110	101	90	73	57	37	1
Clb-Obi & mIGHV	83	76	66	57	42	35	28	2
Clb-Obi & uIGHV	123	101	59	41	22	13	8	1

D

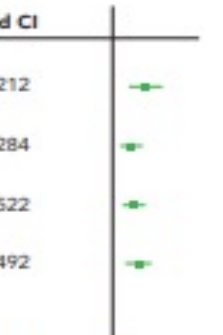
Ven-Obi

Cox regression PFS		Hazard ratio	95% Wald CI
IGHV mutational status			
unmutated	vs. mutated	2.310	1.300-4.105
Deletion 17p			
del(17p)	vs. no del(17p)	2.941	1.532-5.646
Lymph node size			
≥ 5 cm	vs. < 5 cm	1.768	1.114-2.808



Clb-Obi

Cox regression PFS		Hazard ratio	95% Wald CI
Deletion 17p			
del(17p)	vs. no del(17p)	3.766	1.967-7.212
Deletion 11q			
del(11q)	vs. no del(11q)	2.110	1.355-3.284
IGHV mutational status			
unmutated	vs. mutated	2.386	1.617-3.522
Complex karyotype			
complex karyotype/ highly complex karyotype	vs. noncomplex karyotype	2.789	1.732-4.492
Lymph node size			
≥ 5 cm	vs. < 5 cm	1.493	1.023-2.178
Absolute lymphocyte count			
≥ 50 × 10^9/L	vs. < 50 × 10^9/L	1.654	1.155-2.368



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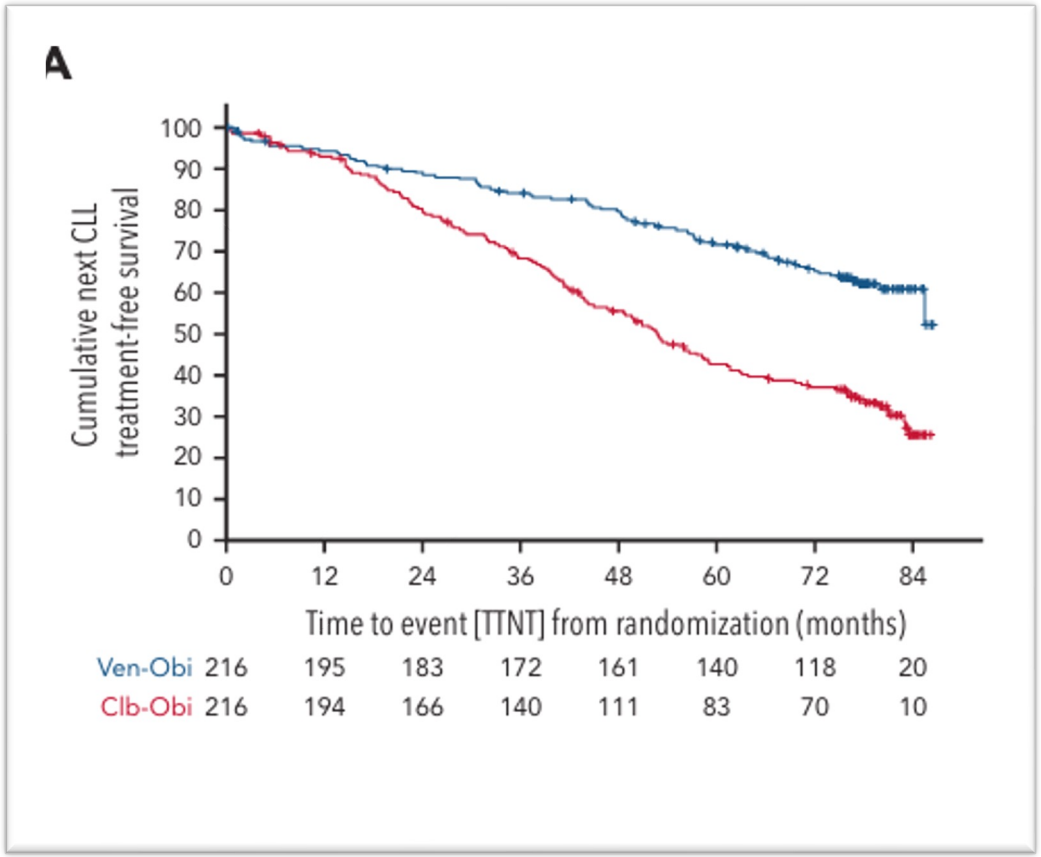
Venetoclax-obinutuzumab for previously untreated chronic lymphocytic leukemia: 6-year results of the randomized phase 3 CLL14 study

TTNT at 6 years: ~65%
The majority of patients do not require second-line therapy



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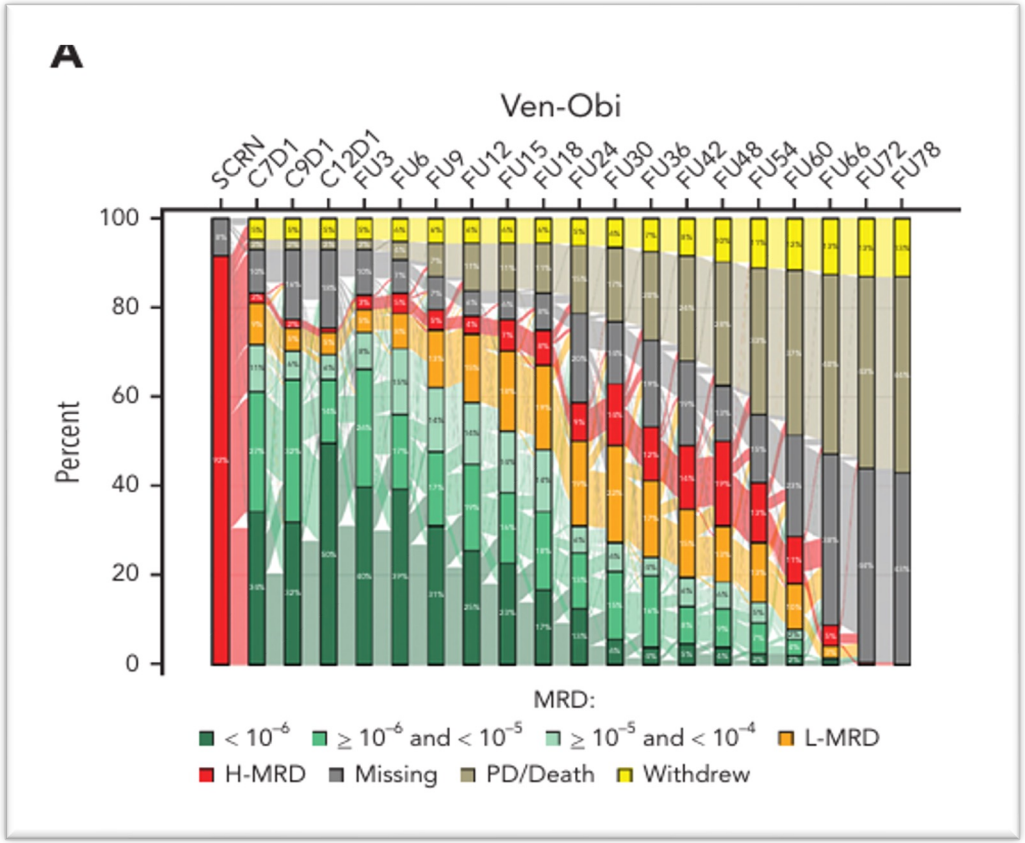


High uMRD rates with Ven-Obi
End of treatment (EOT): **uMRD <10⁻⁴ in ~76%**

Durability but not permanence
At 5 years post-treatment: **~8% uMRD (<10⁻⁴) in ITT population**

Biological complementarity: foundation for combination therapies

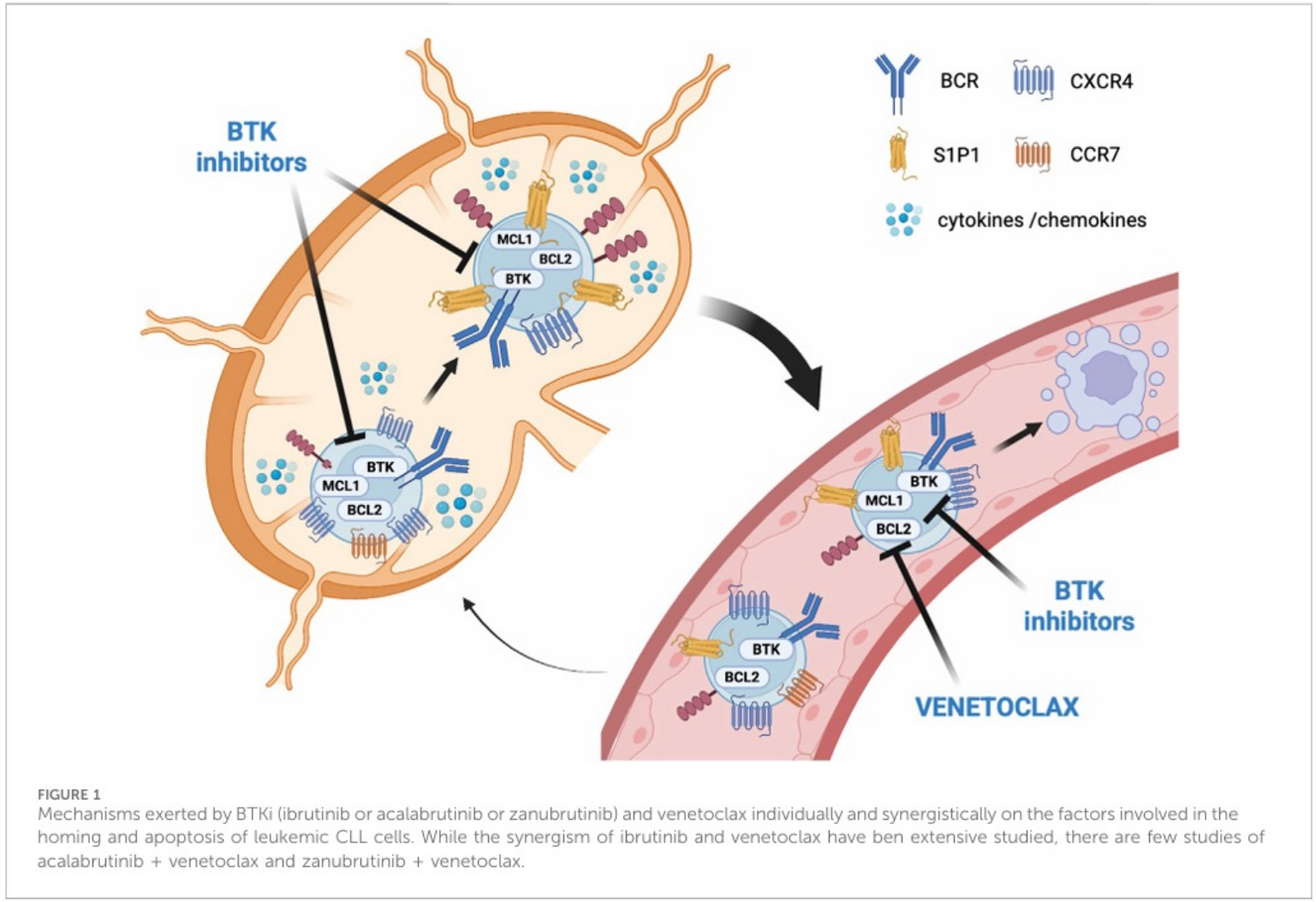
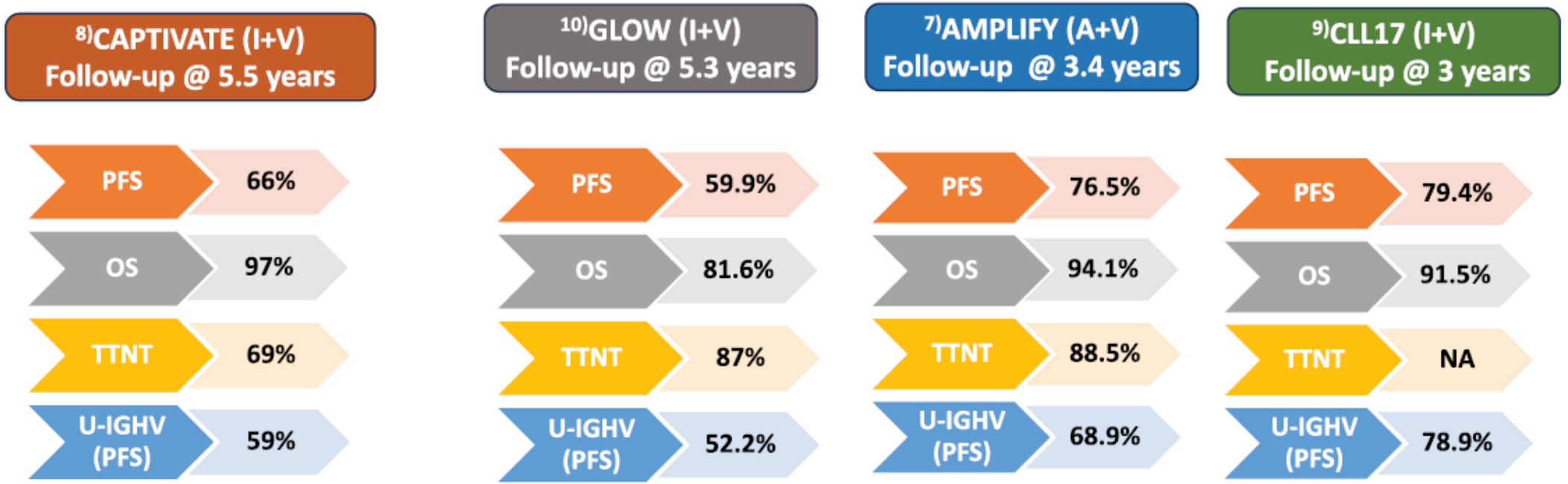


FIGURE 1
Mechanisms exerted by BTKi (ibrutinib or acalabrutinib or zanubrutinib) and venetoclax individually and synergistically on the factors involved in the homing and apoptosis of leukemic CLL cells. While the synergism of ibrutinib and venetoclax have ben extensive studied, there are few studies of acalabrutinib + venetoclax and zanubrutinib + venetoclax.

Visentin A, Mauro FR. Lights and shades of front-line treatment with covalent BTK inhibitors combined with venetoclax in patients with chronic lymphocytic leukemia. Oncol Rev. 2025 Dec 18;19:1703228. doi: 10.3389/or.2025.1703228. PMID: 41488721; PMCID: PMC12756417.

Fixed duration BTK-i + Venetoclax

S. MOLICA AND D. ALLSUP



I+V: Ibrutinib+Venetoclax; A+V: Ibrutinib+Venetoclax; PFS: Progression-free survival; OS: Overall survival;TTNT: Time to Next Treatment U-IGHV: Unmutated immunoglobulin heavy variable

Fixed-duration versus continuous targeted treatment for previously untreated chronic lymphocytic leukemia: Results from the randomized CLL17 trial

Othman Al-Sawaf, Janina Stumpf, Can Zhang, Florian Simon, Francesc Bosch, Emadoldin Feyzi, Paolo Ghia, Michael Gregor, Arnon Kater, Vesa Lindstrom, Mattias Mattsson, Carsten U Niemann, Philipp Staber, Tamar Tadmor, Patrick Thornton, Clemens Wendtner, Ann Janssens, Thomas Nösslinger, Jan-Paul Bohn, Casper da Cunha-Bang, Christian Poulsen, Juha Ranti, Thomas Illmer, Björn Schöttker, Sebastian Böttcher, Tobias Gaska, Elisabeth Vandenberghe, Ruth Clifford, Ohad Benjamini, Anna Maria Frustaci, Lydia Scarfo, Paolo Sportoletti, John Schreurs, Mark David Levin, H.M. van der Straaten, Marjolein van der Klift, Hoa Thi Tuyet, Javier de la Serna Torroba, Javier Loscertales, Oscar Lindblad, Anna Bergendahl Sandstedt, Jeroen Goede, Michael Baumann, Anna Fink, Kirsten Fischer, Matthias Ritgen, Karl-Anton Kreuzer, Christof Schneider, Eugen Tausch, Stephan Stilgenbauer, Sandra Robrecht, Barbara Eichhorst, Michael Hallek

Sunday, December 7th, 2025, ASH Annual Meeting, Orlando, USA

CLL17 STUDY DESIGN

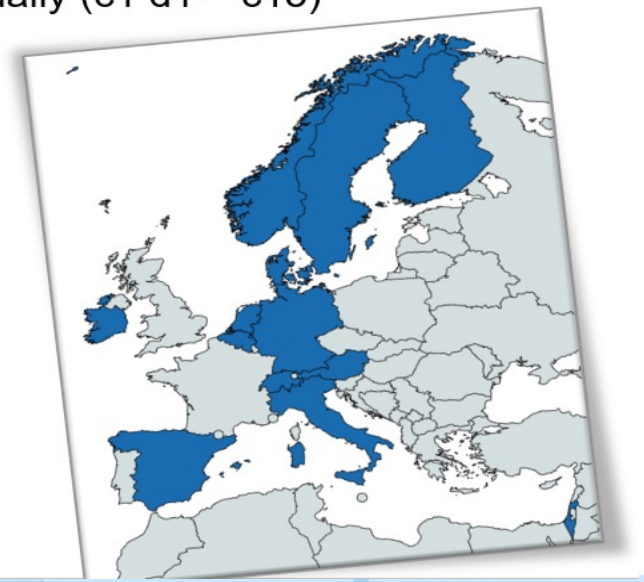
Patients with previously untreated CLL

1:1:1 randomization
Stratification according to fitness, del17p/*TP53*, IGHV

Ibrutinib 420 mg po daily until PD

Venetoclax 400 mg po daily (c1 d22 – c12)
Obinutuzumab 1000 mg iv (c1 d1(2)/8/15, c 2-6 d1)

Venetoclax 400 mg po daily (c4 d1 – c15)
Ibrutinib 420 mg po daily (c1 d1 – c15)



976 patients screened, in 174 sites, across 13 countries.

Patient enrollment from February 2021 to November 2022.

Median observation time: 34.2 months (IQR 30.3-39.3)

OBJECTIVES AND ENDPOINTS

Primary objective:

Testing PFS non-inferiority of **fixed-duration venetoclax-obinutuzumab (VO) versus continuous ibrutinib (I)** and **fixed-duration venetoclax-ibrutinib (VI) versus continuous I**.

VO *vs* I

Hypothesis:

A ≤ 8% reduction in 3-yr PFS rates was considered clinically not meaningful.

A non-inferiority margin of a HR = 1.608 was defined for each hypothesis test, based on available literature in 2020.

VI *vs* I

In clinical terms:

A short-term combination treatment (VO, VI) **is non-inferior (i.e. clinically equally effective)** to a long-term monotherapy (I).

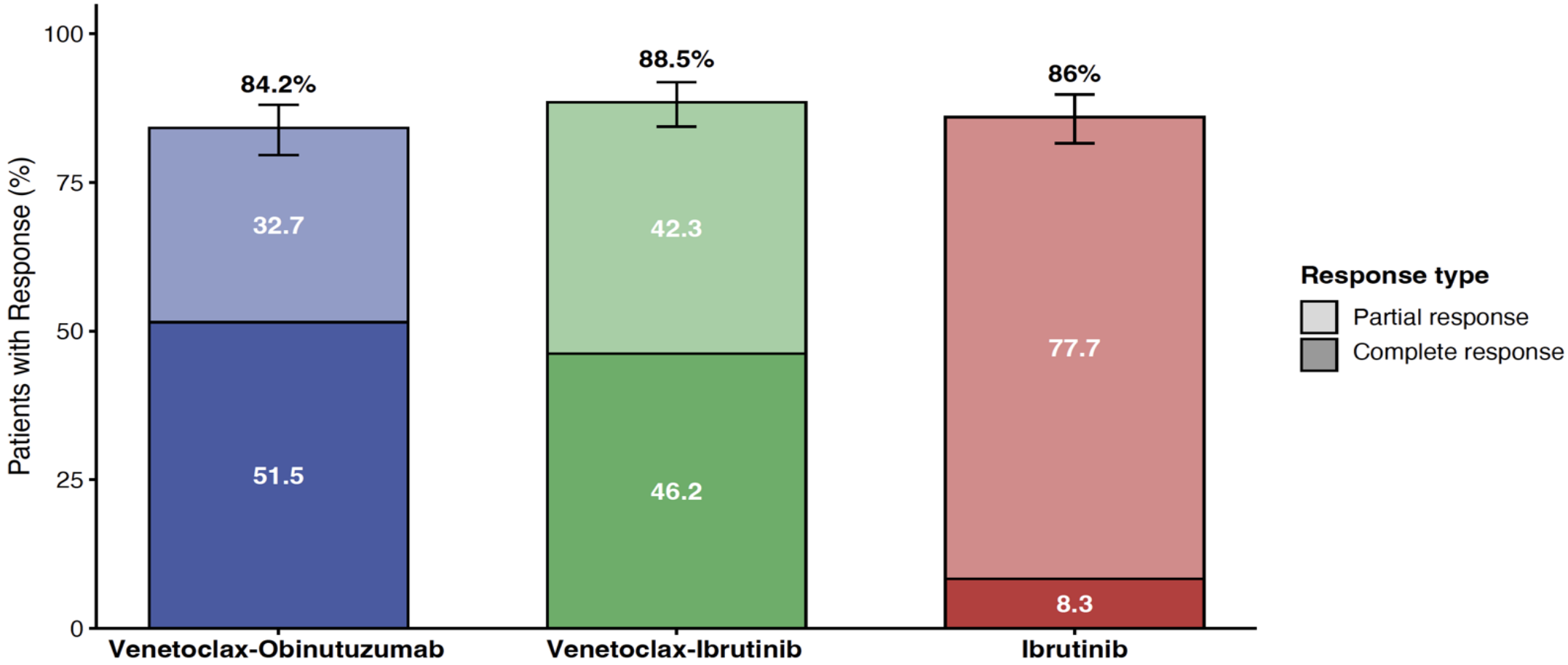
PATIENT CHARACTERISTICS

		VO	VI	I
	N	**303**	**305**	**301**
Demographics	Male (%)	216 (71.3)	204 (66.9)	196 (65.1)
	Median age (range)	66 (40-90)	66 (37-83)	65 (34-85)
	Age >65 (%)	155 (51.2)	158 (51.8)	146 (48.5)
	Median CIRS (range)	3 (0-17)	3 (0-18)	3 (1-15)
	GFR <70 (%)	101 (33.6)	109 (35.7)	95 (31.7)
	Unfit* (%)	134 (44.5)	136 (44.6)	130 (43.2)
Risk factors	High TLS risk (by ALC and LN)	76 (25.7)	70 (23.0)	67 (22.6)
	Unmutated IGHV status	171 (56.4)	172 (56.4)	171 (56.8)
	*TP53*mut/del17p	23 (7.6)	25 (8.2)	21 (7.0)
	High/Very High CLL-IPI	176 (61.5)	172 (59.3%)	172 (59.9%)
	Binet B/C	232 (76.6%)	213 (69.8%)	225 (75.0%)
	CKT ≥ 3	42 (15.8)	53 (20.0)	58 (21.9)

* Defined by cumulative illness rating scale >6 and/or GFR <70 ml/min

RESPONSE TO TREATMENT

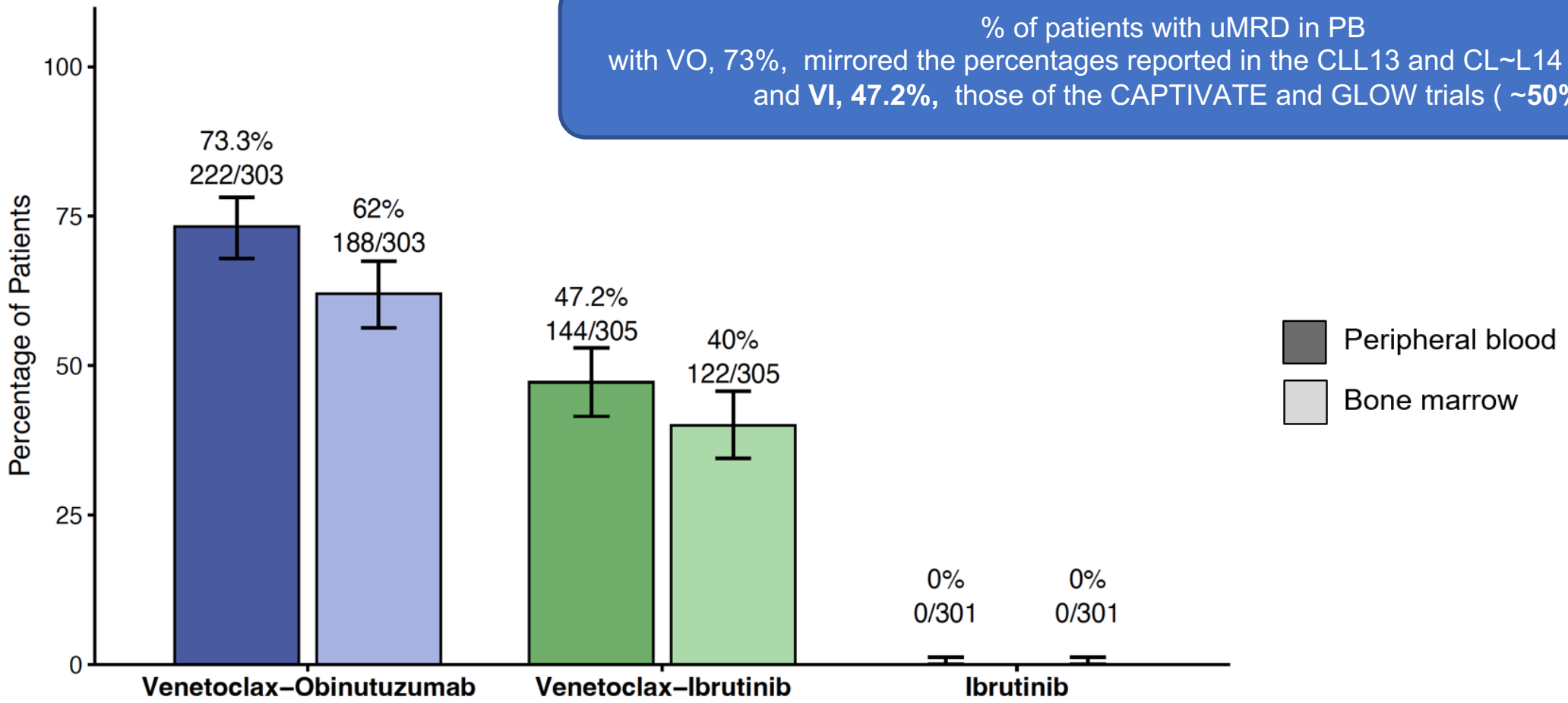
iwCLL response at final restaging (C18D1)



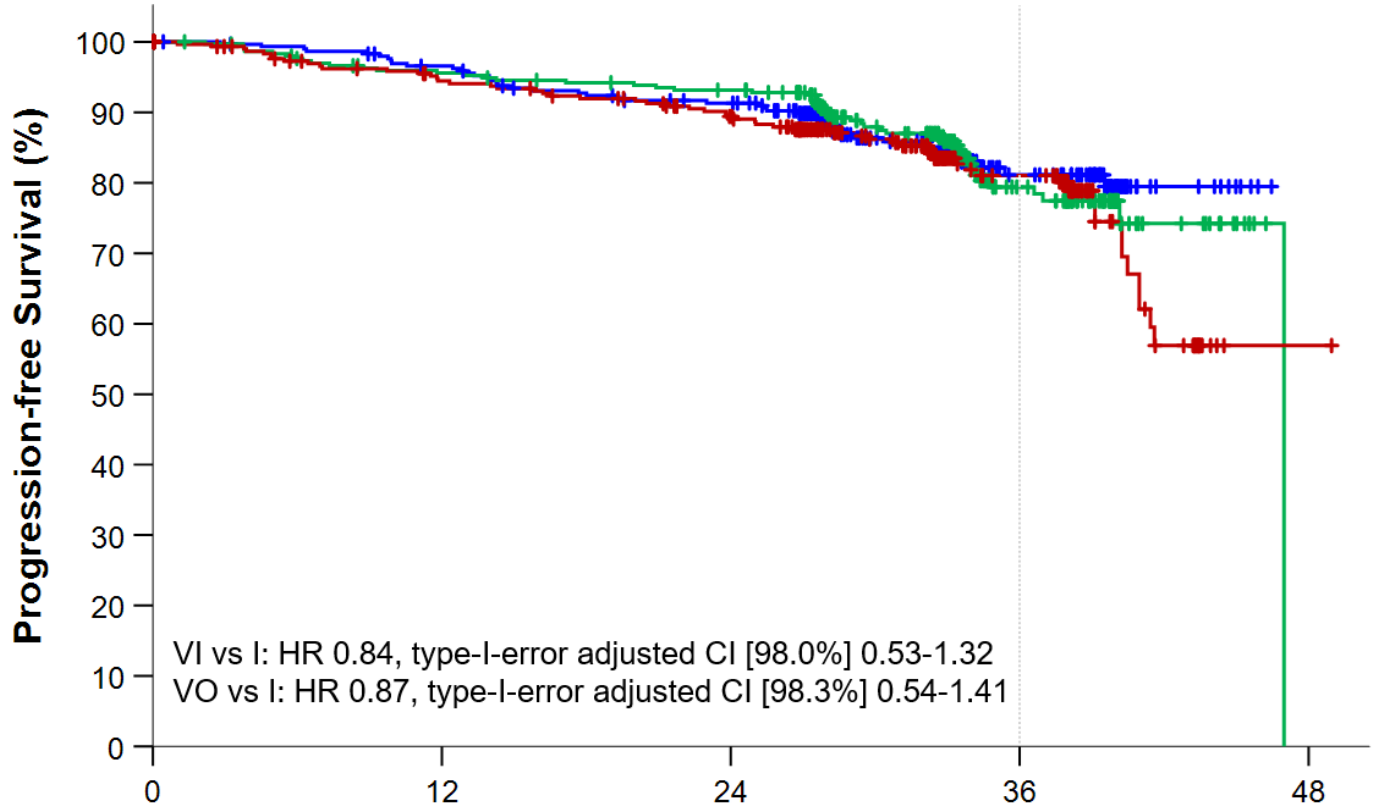
RESPONSE TO TREATMENT

uMRD <10^{-4} in **peripheral blood** and **bone marrow**, by flow cytometry, at final restaging

% of patients with uMRD in PB
with VO, 73%, mirrored the percentages reported in the CLL13 and CL~L14 trials (>70%),
and **VI, 47.2%,** those of the CAPTIVATE and GLOW trials (**~50%)**



PROGRESSION-FREE SURVIVAL



Patients at risk					
VO	303	278	256	77	0
VI	305	278	267	82	0
I	301	267	243	94	1

3-year-PFS

I 81.0%

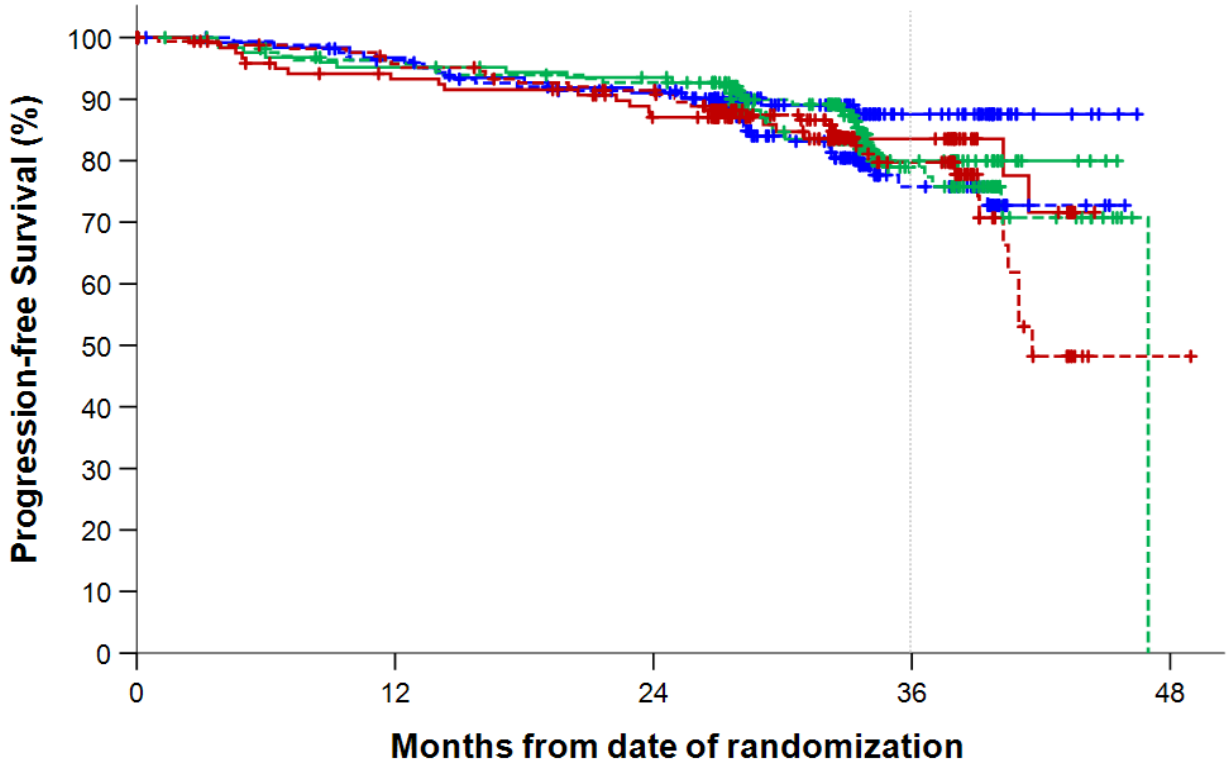
VI 79.4 %

VO 81.1%

	PD	Death
I	46	11
VI	37	13
VO	25	21

PROGRESSION-FREE SURVIVAL

According to IGHV status



Patients at risk					
VO, unmutated	171	156	142	40	0
VO, mutated	129	119	111	36	0
VI, unmutated	172	157	151	50	0
VI, mutated	129	117	112	32	0
I, unmutated	171	156	145	55	1
I, mutated	126	108	95	37	0

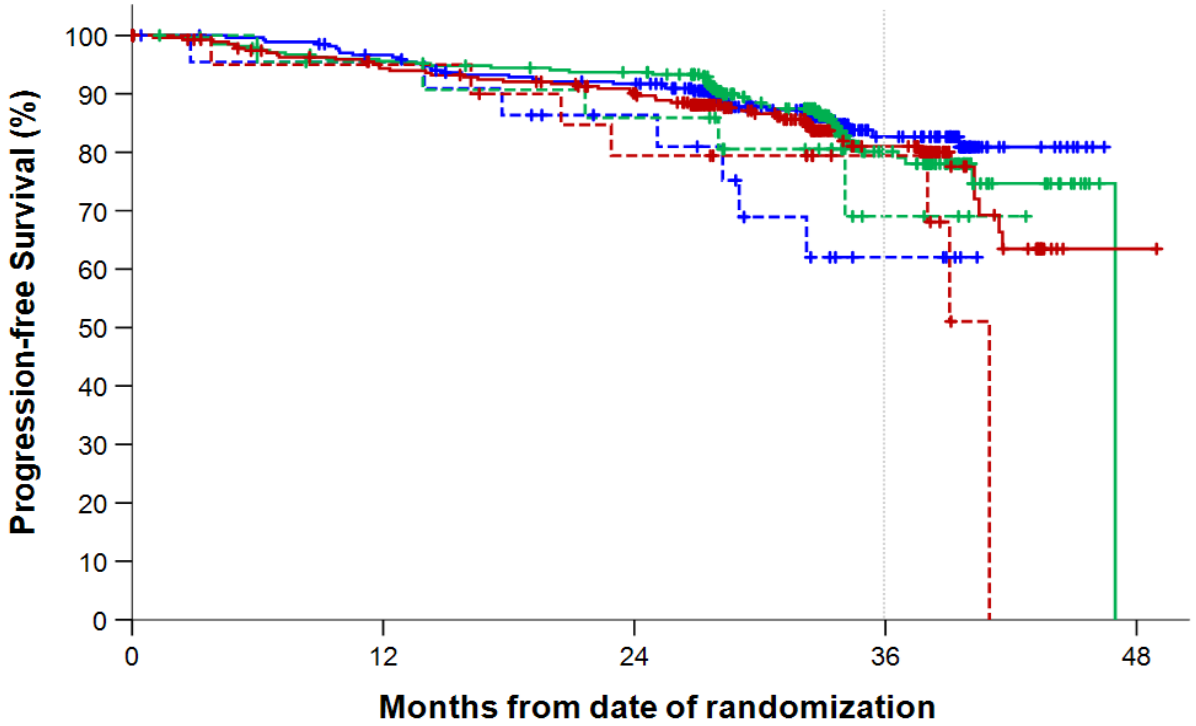
3-year-PFS

----	I, uIGHV	79.7%
—	I, mIGHV	83.5%
----	VI, uIGHV	78.9%
—	VI, mIGHV	80.0%
----	VO, uIGHV	75.8%
—	VO, mIGHV	87.6%

Unmutated IGHV:
VI vs I: HR 0.81, 95% CI 0.49-1.32
VO vs I: HR 0.98, 95% CI 0.61-1.59

PROGRESSION-FREE SURVIVAL

According to *TP53*/del17p status



Patients at risk					
VO, del/mut	23	21	16	5	0
VO, WT	280	257	240	72	0
VI, del/mut	25	20	18	4	0
VI, WT	279	257	248	78	0
I, del/mut	21	19	15	7	0
I, WT	279	247	227	87	1

3-year-PFS

---- I, *TP53*del/mut 79.4%
— I, *TP53*-WT 81.0%

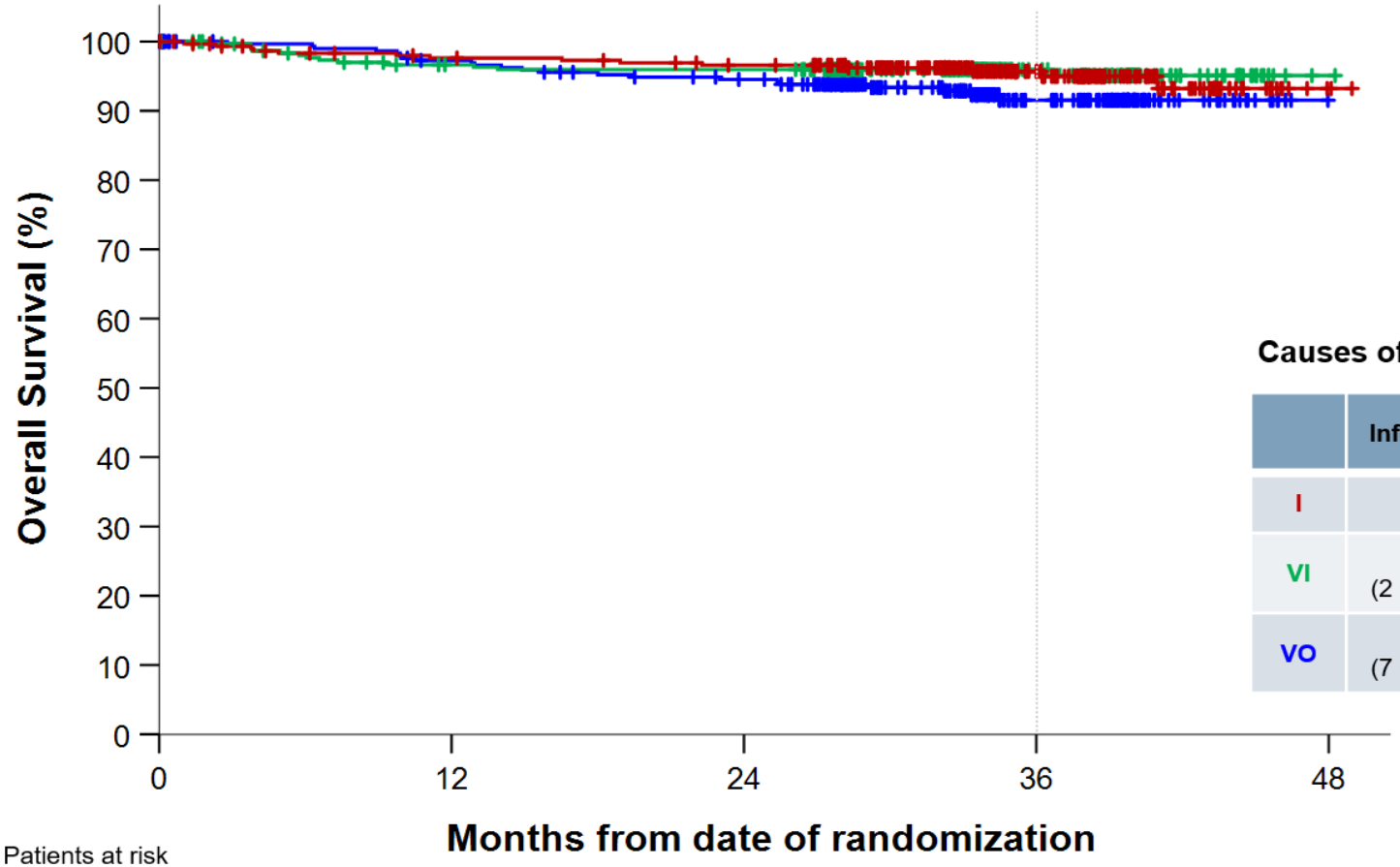
---- VI, *TP53*del/mut 69.0%
— VI, *TP53*-WT 80.1%

---- VO, *TP53*del/mut 62.0%
— VO, *TP53*-WT 82.7%

***TP53* del/mut:**
VI vs I: HR 0.70, 95% CI 0.22-2.16
VO vs I: HR 1.20, 95% CI 0.40-3.59

In patients with *TP53* aberration, HR favored arms containing I for PFS
3-year PFS rates were 62.0%, 69.0%, and 79.4% for VenO, VenI, and I, respectively

OVERALL SURVIVAL



Patients at risk					
VO	303	284	269	102	0
VI	305	281	279	114	1
I	301	284	276	141	2

3-year-OS

I 95.7%

VI 96.0%

VO 91.5%

Causes of death

	Infection	Cardio-vascular	PD/RT	SPM	Other	Total
I	3	5	0	2	4	14
VI	7 (2 Covid)	3	0	2	1	13
VO	12 (7 Covid)	5	1	4	0	22

VI vs I: HR 0.96, 95% CI 0.45-2.05

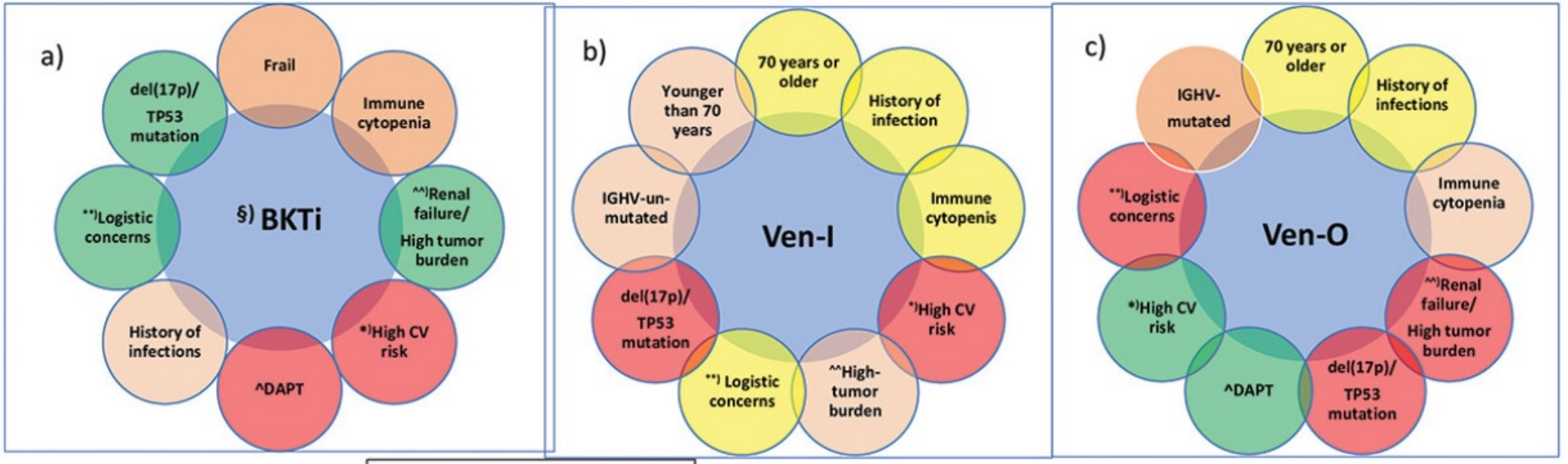
VO vs I: HR 1.67, 95% CI 0.86-3.28

ADVERSE EVENTS

Selected adverse events of interest, all CTC grades

	VO	VI	I
Safety population – No. (%)	**295**	**303**	**298**
Blood and lymphatic system disorders	174 (59.0)	130 (42.9)	85 (28.5)
Febrile neutropenia	14 (4.7)	7 (2.3)	0 (0)
Neutropenia	155 (52.5)	110 (36.3)	49 (16.4)
Cardiac disorders	41 (13.9)	72 (23.8)	103 (34.6)
Atrial fibrillation	11 (3.7)	38 (12.5)	50 (16.8)
Gastrointestinal disorders	176 (59.7)	225 (74.3)	189 (63.4)
Diarrhea	80 (27.1)	143 (47.2)	104 (34.9)
Infections and infestations	225 (76.3)	243 (80.2)	238 (79.9)
COVID-19	113 (38.3)	128 (42.2)	117 (39.3)
Pneumonia	41 (13.9)	28 (9.2)	40 (13.4)

Grade 3-5 Infections	**VO**	**VI**	**I**
	295	**303**	**298**
Infections and infestations	103 (34.9)	76 (25.1)	74 (24.8)
COVID-19	47 (15.9)	26 (8.6)	20 (6.7)
Pneumonia	29 (9.8)	22 (7.3)	22 (7.4)



§) second-generation BTKis preferred

Recommended highly suitable and supported by robust evidence or established guidelines

Preferable lacking definitive evidence but aligned with sound clinical principles

Acceptable not ideal but may be reasonable within established principles of care

Not recommended deemed unsuitable due to conflicting evidence or clinical best practices

*) - History of ventricular arrhythmia
- Family history of sudden cardiac death
- Congestive heart failure (LVEF <30%)
- Severe, uncontrolled hypertension

**) – No caregiver available
- Distance from the hospital
- Transportation barriers

^) DAPT= Dual Antiplatelet Therapy
^^) a high tumor burden (e.g., any LND ≥10 cm or ALC≥ 25.000/mmc and any LND ≥5 cm or massive splenomegaly or chronic renal failure, Cockcroft-Gault GFR)below 30 mL/min,

Molica, S. (2025). Navigating the gap between guidelines and practical challenges in selecting first-line therapy for chronic lymphocytic leukemia. *Expert Review of Hematology*, *18*(3), 195–200. https://doi.org/10.1080/17474086.2025.2469719

Conclusion

Historically: treatable, but not curable!

With targeted therapies: the concept of “cure” is being redefined

Younger patients:
- Time-limited therapy
- Lifelong disease control
- No relapse expected
- uMRD

Older patients:
- Normal life expectancy
- No CLL-related symptoms
- Functional cure

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EDITORIAL

Is CLL curable?

Nitin Jain[1] | Alessandra Ferrajoli[1] | Susan O'Brien[2] | William Wierda[1]

“Cure” is **not a uniform endpoint**
Treatment goals must be **patient-adapted**