

MEET THE **EXPERT** *in CLL*

MESTRE (VE), 19 OTTOBRE 2026

Aula Verde-Padiglione Giovanni Rama, Ospedale dell'Angelo



Terapia a durata fissa nel paziente di prima linea
e nel paziente ricaduto/refrattario

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Disclosures: Gianluca Gaidano

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
AbbVie					√	√	
AstraZeneca			√		√	√	
BeOne						√	
Gilead	√						
Incyte					√	√	
Johnson & Johnson					√	√	
Oncopeptides						√	



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Agenda

- **Evolution of CLL treatment**
- FTD therapy in 1L CLL treatment
- FTD therapy in R/R CLL treatment

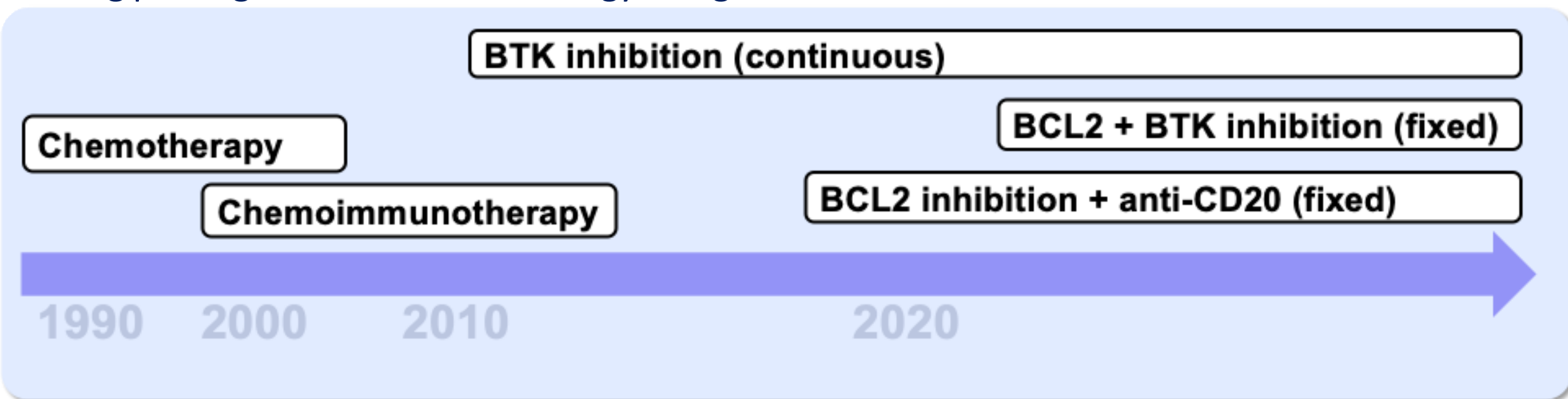


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Treatment evolution in 1L CLL:

shifting paradigms in treatment strategy and goals



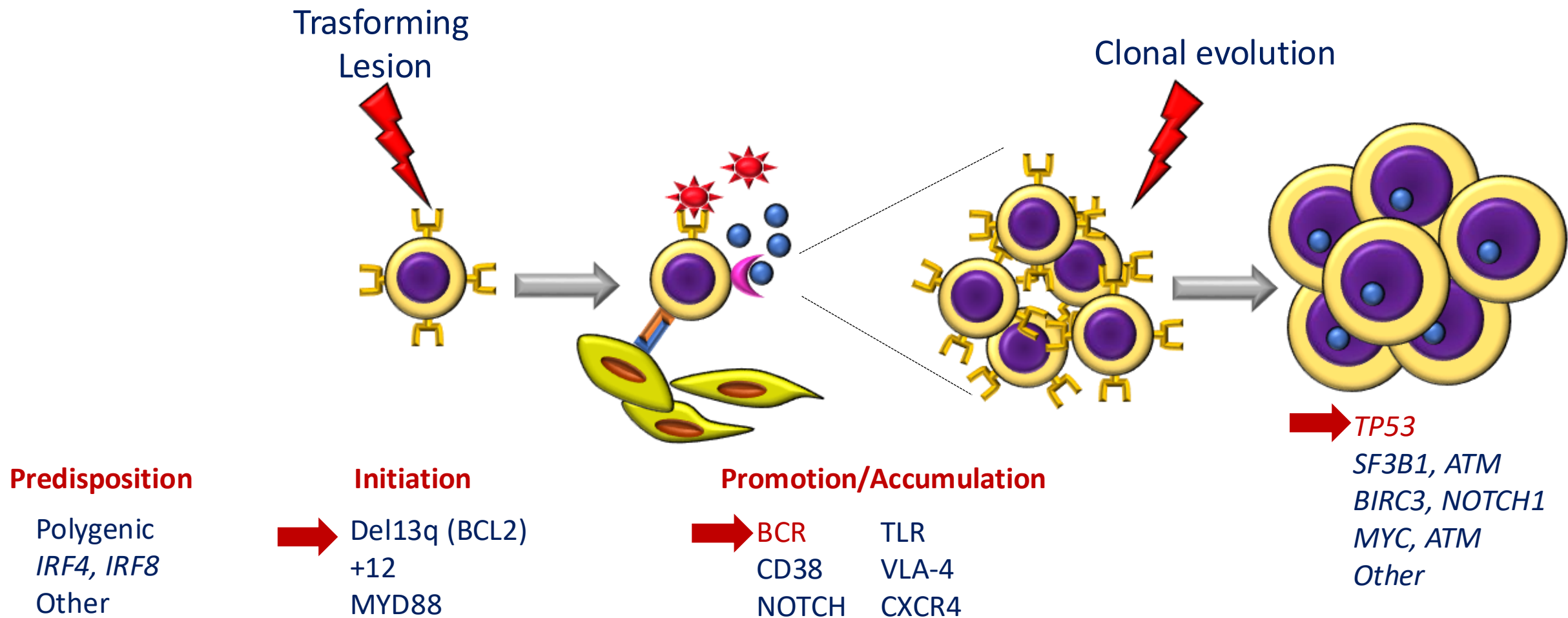
Author's personal opinion and elaboration



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Pathogenesis of CLL reveals therapeutic predictors and targets



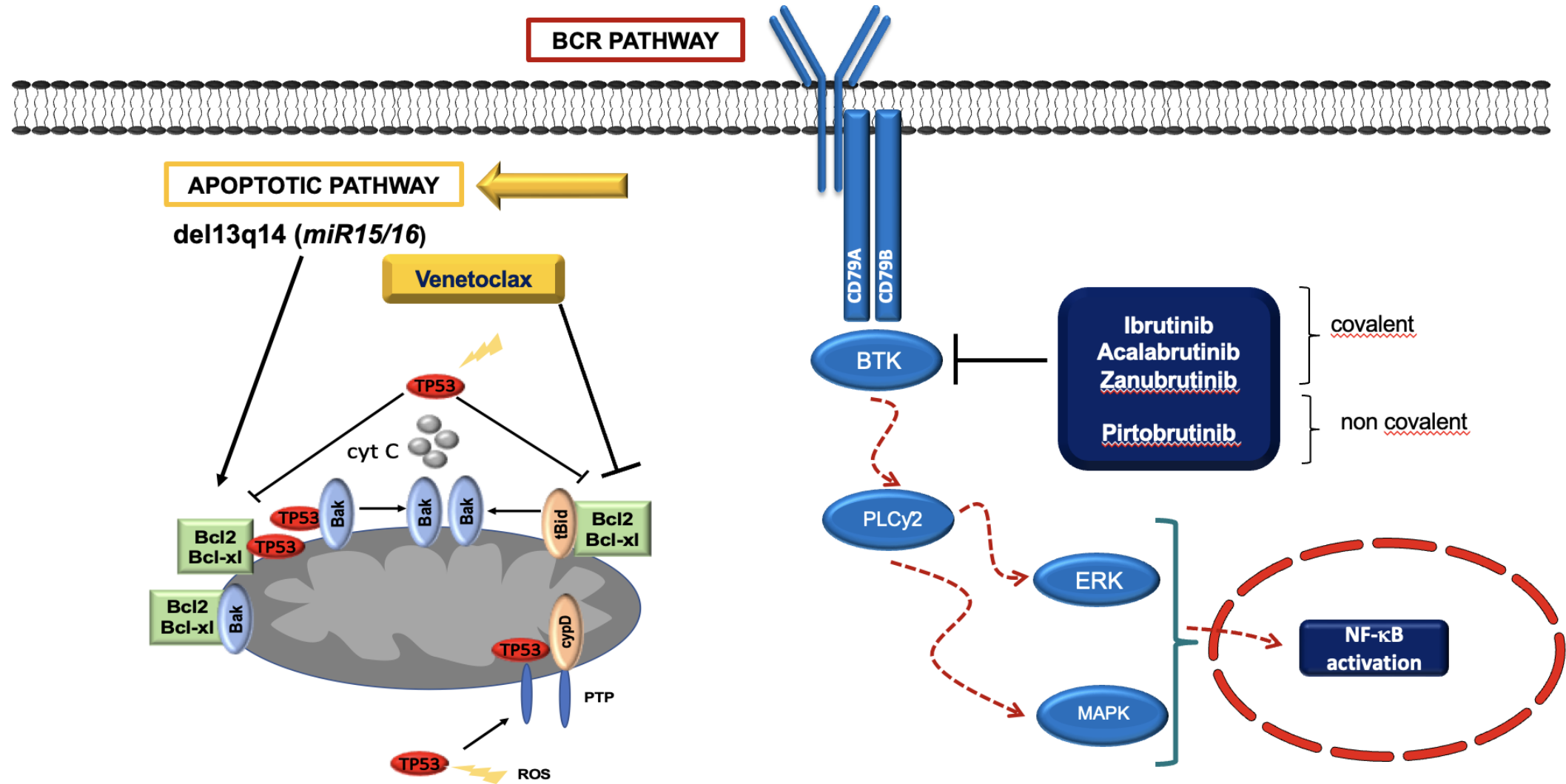
Gaidano et al, Hematology 2017; Moia and Gaidano, Semin Hematol 2024



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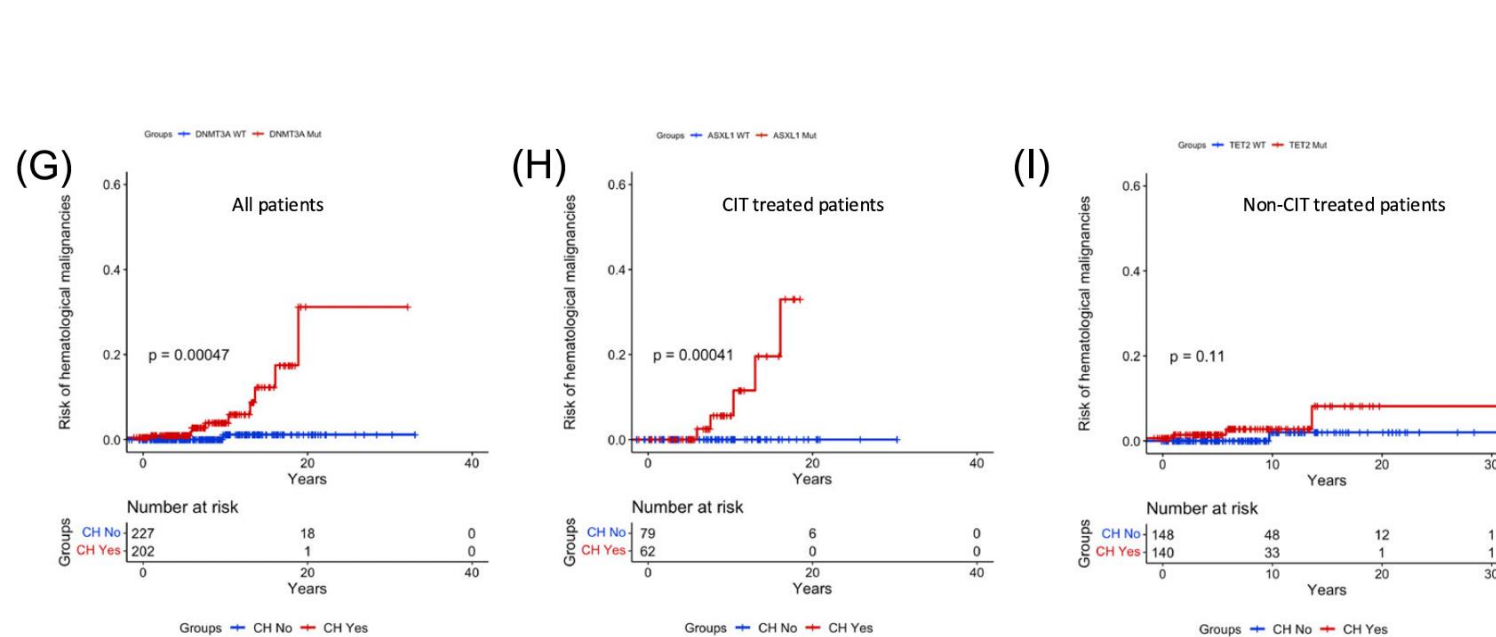
Molecular targets for CLL therapy



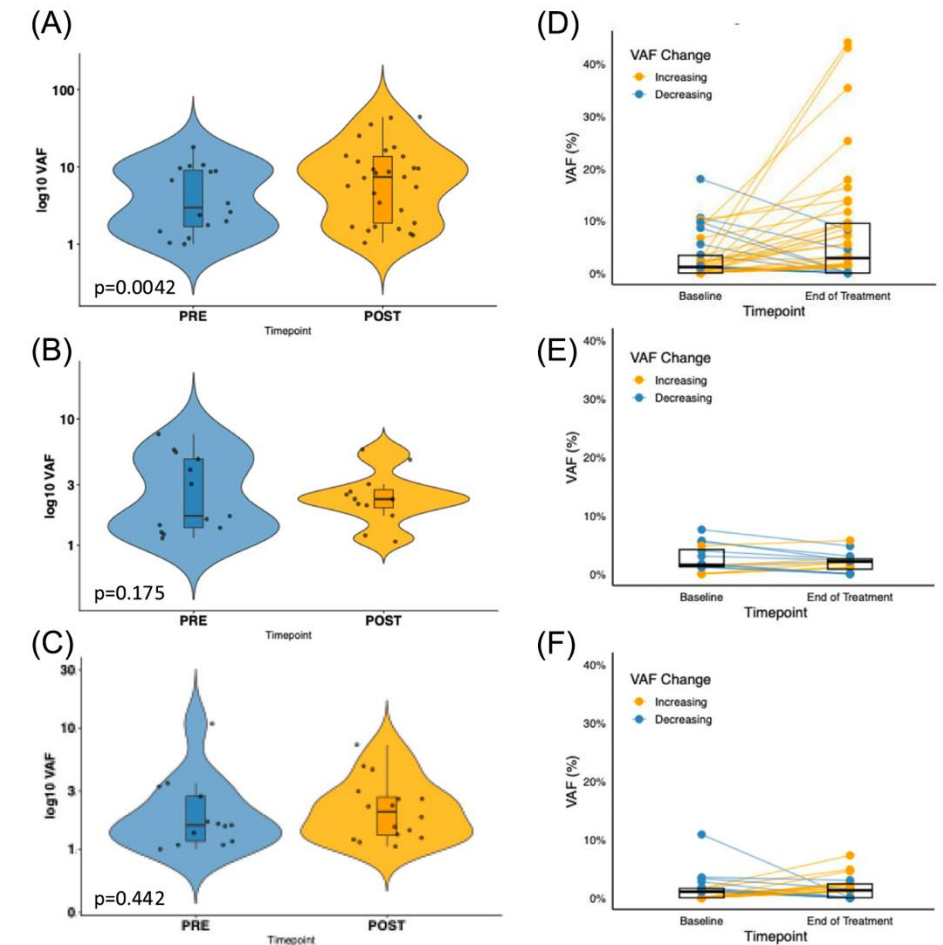
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Clonal hematopoiesis (CH) and risk of SPM in CLL according to treatment



- BCL2i and BTKi do not induce CH expansion, which was instead driven by chemotherapy
- CH is significantly associated with a higher risk of second hematological malignancies **only** in chemo-exposed patients



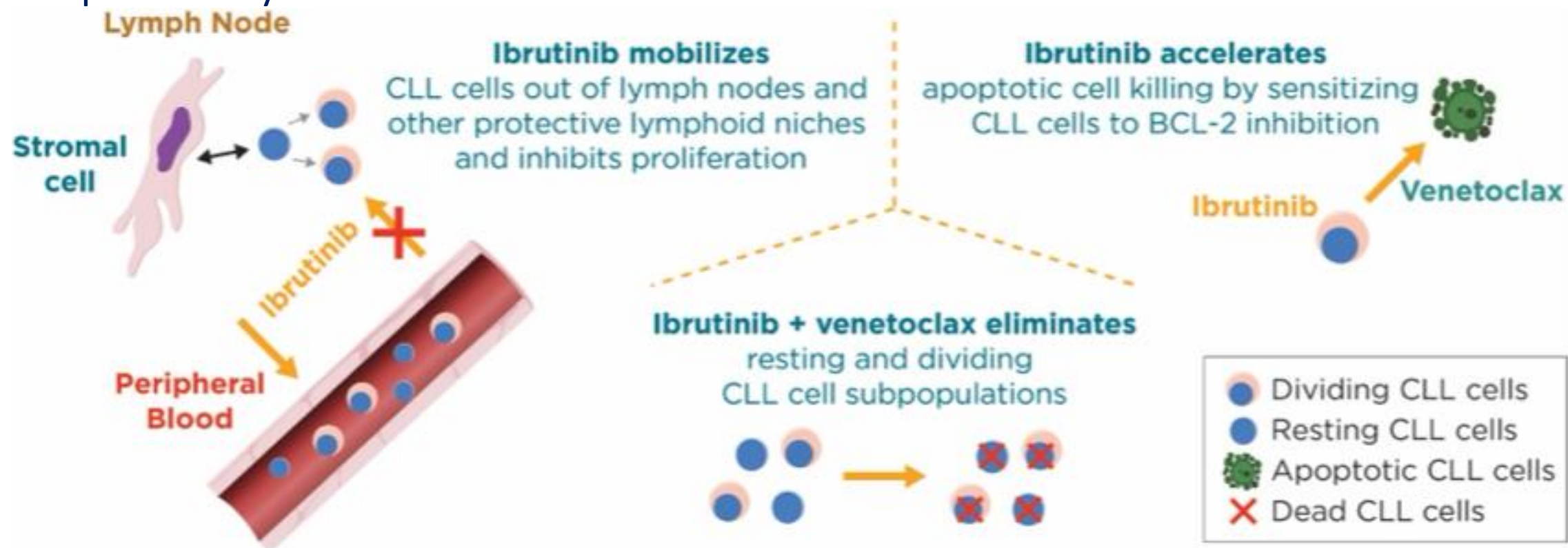
Cosentino et al., HemaSphere 2026



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Venetoclax and Ibrutinib work synergistically through distinct and complementary modes of action



BCL-2, B cell lymphoma 2; BTKi, Bruton tyrosine kinase inhibitor; CLL, chronic lymphocytic leukemia; EU, European Union; OS, overall survival; SLL, small lymphocytic lymphoma; uMRD, undetectable minimal residual disease. ¹Lu P et al. *Blood Cancer J.* 2021;11:39. ²Deng J et al. *Leukemia.* 2017;31:2075-2084. ³Herman ES et al. *Clin Cancer Res.* 2015;21:4642-4651. ⁴Burger JA et al. *Leukemia.* 2020;34:787-798. ⁵Shanafelt T et al. *N Engl J Med.* 2019;381:432-443. ⁶Venclexta [package insert]. South San Francisco, CA: Genentech USA Inc; 2021.

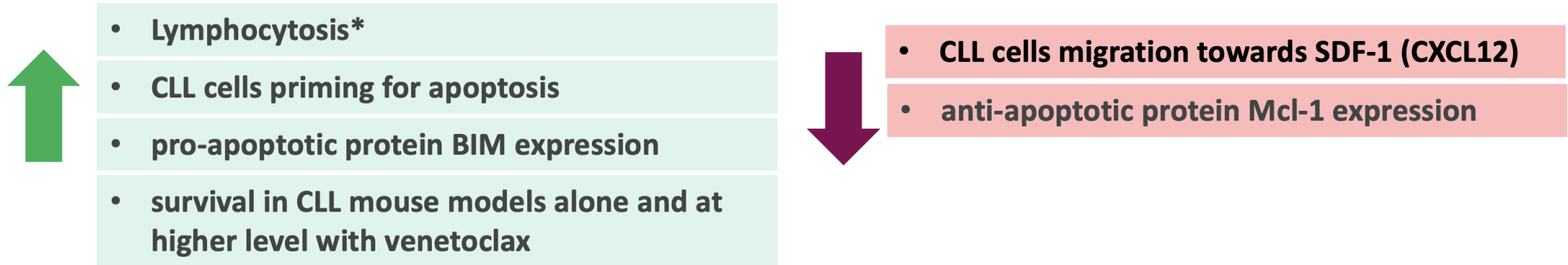


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Sinergy of BTKi-BCL2i as a class effect

Synergy of venetoclax with acalabrutinib¹



When acalabrutinib and ibrutinib were tested in the same *ex vivo* experiment at same conditions they similarly Increased^{1,2}:

- BCL-2 dependence in CLL cells
- CLL cell sensitivity to BCL-2 inhibition
- expression of the BH3-only protein BIM
- CLL cell death when combined with venetoclax

*LYMPHOCYTOSIS^{1,3,4,5} was consistently associated to acalabrutinib treatment, with early onset (peak at 3/7/14 days) and ALC increase of 40-67%, followed by a decline

In one study⁶ Acalabrutinib exhibited lower ALC from Month 6 to Month 12 compared to ibrutinib especially in IGHV mutated pts. Kinetics of BTKi-induced lymphocytosis vary according to +12 presence and CD49d expression^{6,7}.

1. Patel et al. Leukemia. 2018 April ; 32(4): 920–930. doi:10.1038/leu.2017.321; 2. Deng Leukemia. 2017 October ; 31(10): 2075–2084. doi:10.1038/leu.2017.32; 3. Byrd 2016 N Engl J Med 2016;374:323-32; 4. Furman Leukemia 2021 Nov, 35(11):3201-3211.; 5 Alsadhan Clin Cancer Res. 2023 September 15; 29(18): 3612–3621; 6. Innocenti 2024 HemaSphere. 2024;8:e144; 7. Laurenti Poster iwCLL 2025



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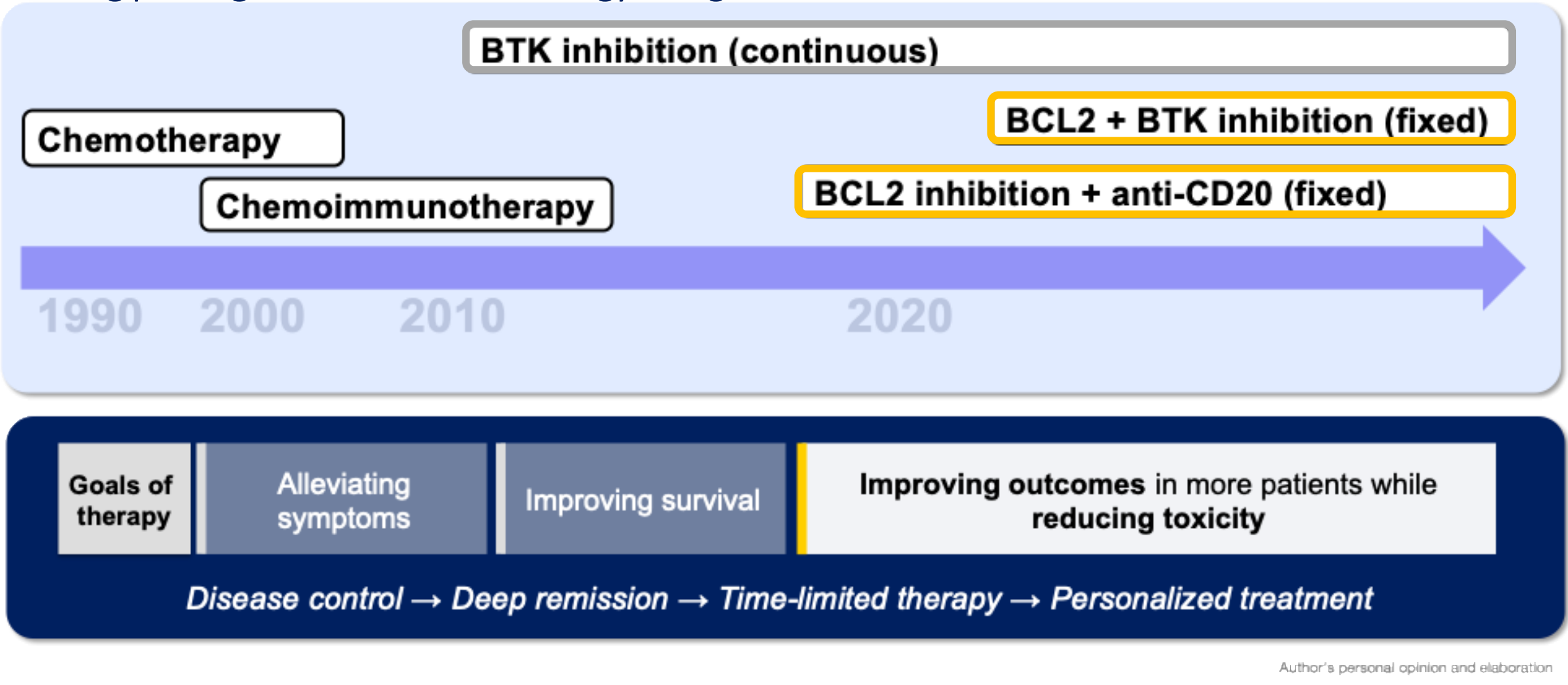
- Evolution of CLL treatment
- **FTD therapy in 1L CLL treatment**
- FTD therapy in R/R CLL treatment



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Treatment evolution in 1L CLL: shifting paradigms in treatment strategy and goals



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Considerations for treatment: Continuous vs FTD (1L and RR)

	Advantages	Disadvantages
Continuous	- Route of administration¹ - Efficacy (PFS1) sustained over long periods² - Minor effect of adverse prognostic factors on efficacy²⁻⁴ - Assurance of continuous therapy¹	- Cumulative toxicity² - CV side effects^{2,3,5} - Burden of therapy; lack of compliance^{2,6} - Cost^{1,2} - Potential for resistance⁷
FTD	- Patient preference¹ - Convenience and time off treatment¹ - Cost/anticipating expenses¹ - Reduced potential for resistance⁷	- Initial management (TLS monitoring, potential hospitalizations)^{2,3,8} - Patient's worry that CLL might worsen or spread during time off treatment¹



CLL, chronic lymphocytic leukemia; CV, cardiovascular; FTD, fixed treatment duration; PFS1, time from start of therapy to the occurrence of first relapse; TLS, tumor lysis syndrome.

1. Ravelo A, et al. ASH 2023. Abstract P3706 (Poster); 2. Seymour JF. *Blood Adv* 2022; **6**:1365–1370; 3. Brem EA & O'Brien S. *Blood Adv* 2022; **6**:1361–1364; 4. Barr PM, et al. *Blood Adv* 2022; **6**:3440–3450;

5. Bhat SA, et al. *Blood* 2022; **140**:2142–2214; 6. Alu A, et al. *J Hematol Oncol* 2022; **15**:138; 7. Al-Sawaf O & Davids MS. *Clin Cancer Res* 2024; **30**:471–473; 8. Coombs C, et al. Fixed-Duration vs Continuous Therapy–First-Line Choices in CLL. Onco Live 2025. Available at: <https://www.onclive.com/view/fixed-duration-vs-continuous-therapy-first-line-choices-in-cll> (accessed August 2025).



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What is new in the EHA guidelines?

For the first time, **published as EHA** and not ESMO

MCBS:H score inclusion

V+A and **ncBTKi** included into the algorithms

No more room for chemo (CIT)

No fitness stratification into the 1L algorithm

Patient advocacy inclusion into the committee

Eichhorst, B et al. HemaSphere 2026; 10:e70403



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Frontline recommendations: FTD is preferred

Recommendation	Time-limited targeted therapies should be preferred over continuous therapy in patients with CLL without <i>TP53</i> aberrations (Figure 1)
Relevant for:	All patients
Level of Evidence	I
Grade of Recommendation	A

Recommendation	Acalabrutinib and zanubrutinib should be preferred over ibrutinib for continuous treatment of all new patients on the basis of their favorable toxicity profiles
Relevant for:	All patients
Level of Evidence	I
Grade of Recommendation	A

Recommendation	CITs are no longer recommended, because they are either inferior (BR, chlorambucil + obinutuzumab) to targeted agents or associated with a higher risk for adverse events including secondary neoplasia such as myeloid malignancies (FCR)
Relevant for:	All patients
Level of Evidence	I
Grade of Recommendation	A

Recommendation	Acalabrutinib and zanubrutinib should be preferred over ibrutinib for continuous treatment of all new patients on the basis of their favorable toxicity profiles
Patients who are well controlled on ibrutinib without notable adverse events should not be switched to second-generation BTK inhibitors	

Eichhorst, B et al. HemaSphere 2026; 10:e70403



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Frontline recommendations for cases with *TP53* disruption

FTD should be discussed

Continuous treatment is suggested over time-limited treatment, unless time-limited treatment is preferred by shared decision-making	
Recommendation	
Relevant for:	All patients with <i>TP53</i> disruption
Level of Evidence	I
Grade of Recommendation	A

Triplet therapies may add additional benefit with respect to longer treatment-free intervals in vs doublet combinations	
Recommendation	
Relevant for:	Patients with <i>TP53</i> disruption who may tolerate the higher risk of infections associated with triplet therapy
Level of Evidence	III
Grade of Recommendation	B

Eichhorst, B et al. HemaSphere 2026; 10:e70403

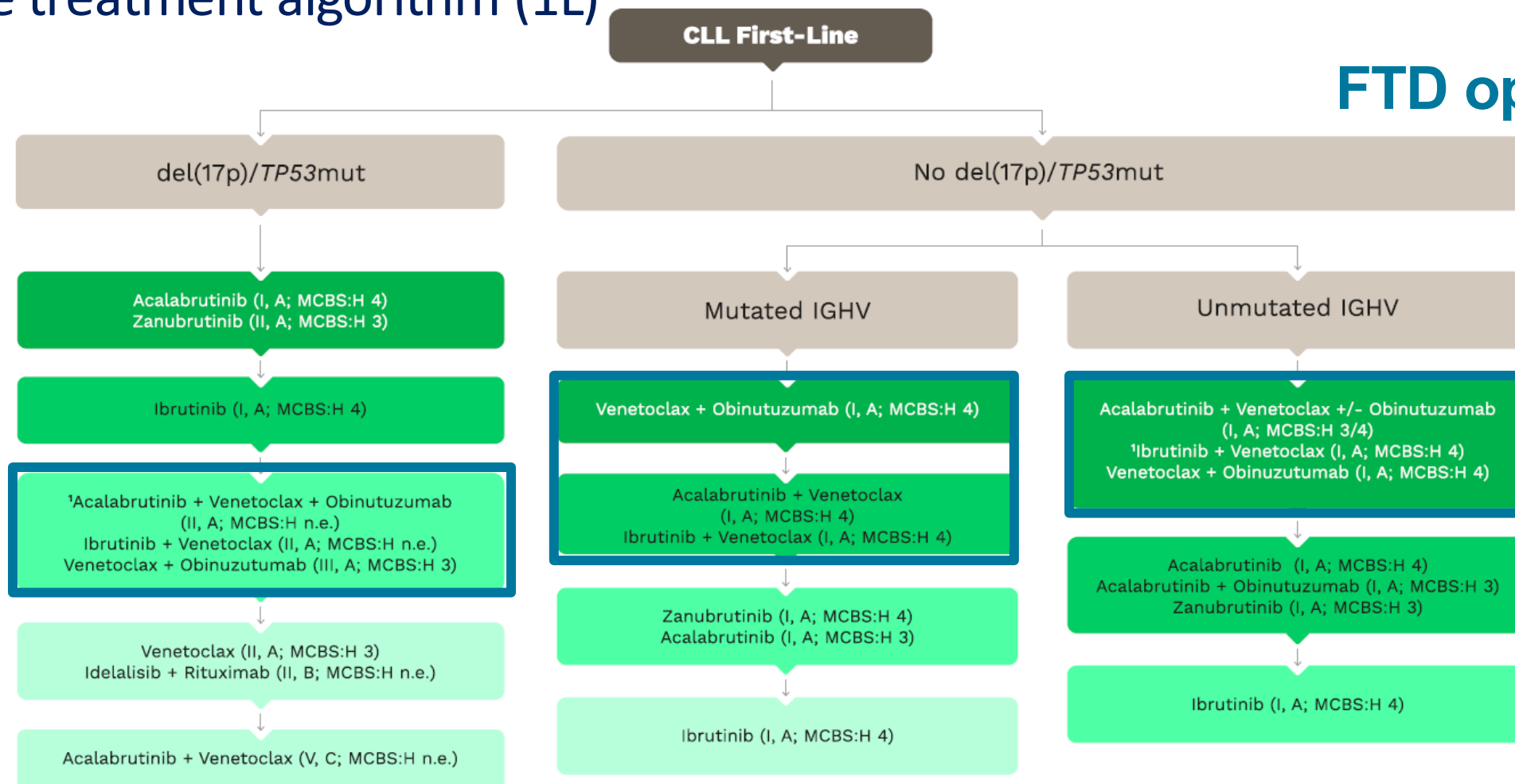


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Frontline treatment algorithm (1L)

FTD options



The order of each box listed reflects the ranking based on the recommendations, highlighted also by the different shades of green.

The order within each box is based on the MCBS:H score or otherwise preference, as the therapeutic choice should be guided not only by efficacy but also by comorbidities, drug interactions, logistics, and patient's preferences (see figure 2 "Heat map").

¹This combination has potentially more efficacy in an MRD-guided approach, but is not approved (see the text). N.e. = not evaluated.

Eichhorst, B et al. HemaSphere 2026; 10:e70403

Heatmap of individual features to guide treatment decision



Finite duration,
treatment-free interval and
accumulation of AEs
not mentioned in the figure

CLL First-Line Integrated vision of individual features to guide treatment decision

	Biological Profile			Infection risk	Ease of treatment	Concomitant comorbidities & comedication		
	M-IGHV	UM-IGHV	TP53mut/del(17p)			Cardio-vascular Disease	Impaired Renal Function	Anticoagulation/bleeding risk
Venetoclax - Obinutuzumab	A	A	B	C	C	A	B ²	A
Venetoclax + Ibrutinib ¹	A	A	B	B	B	C	B ²	B ³
Venetoclax + Acalabrutinib	A	A	B	B	B	B	B ²	B ³
Venetoclax + Acalabrutinib + obinutuzumab	A	A	B	C	C	C	B ²	B ³
Acalabrutinib	B	A	A	A	A	B	A ²	B ³
Zanubrutinib	B	A	A	A	A	B	A ²	B ³
Ibrutinib	B	A	A	A	A	C	A ²	B ³

Assess specific interactions

A= Strongly recommended; **B**= Recommended; **C**= consider alternatives.

¹: This combination appears particularly effective in UM-IGHV when used within an MRD-guided strategy, but is not currently approved.

²: caution with CrCl < 50 mL/min for venetoclax and < 30 mL/min for BTKi. For venetoclax recommended TLS preventions should be followed in patients with CrCl 50 -79 mL/min.

³: contraindicated with anti-Vitamin K.

Figure adapted from Ref. 85.

Eichhorst, B et al. HemaSphere 2026; 10:e70403



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Treatment Choice: the value of Treatment Duration and Cumulative Tox

 **Finite duration, treatment-free interval and accumulation of AEs not mentioned in the figure**

Continuous
BTK inhibition

Fixed
Ven-Based

	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	yellow	green	green	red	green	orange	orange	green	orange	green	green
acalabrutinib	green	green	green	red	green	yellow	yellow	green	yellow	green	green
zanubrutinib	green	green	green	red	green	yellow	yellow	green	yellow	green	green
obinutuzumab + venetoclax	green	green	green	green	orange	green	green	yellow	green	orange	yellow
ibrutinib + venetoclax	green	green	green	green	yellow	green	green	green	orange	yellow	green

Color code rating for treatment options:



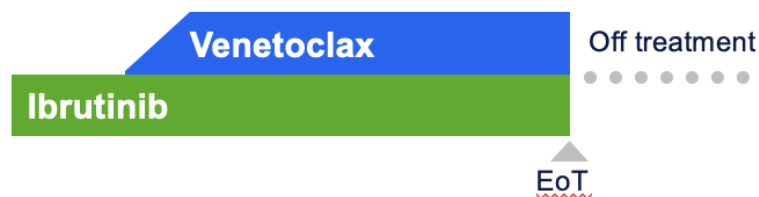
Tausch E et al., ASH Educational Program 2024; 2024, 457-466



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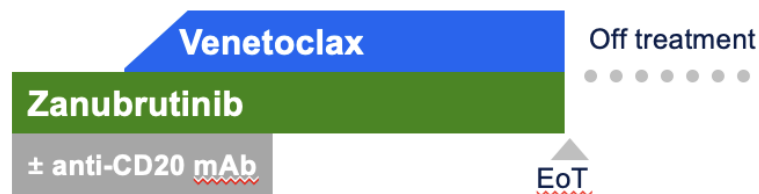
Venetoclax is the backbone therapy in CLL



Ven+Ibr trials
GLOW ¹
CAPTIVATE ²
FLAIR ³
CLL17 ⁴



Ven+Acala trials
AVO ^{5*}
CLL16 ^{6*}
AMPLIFY ⁷
MAJIC ^{8,9*}



Ven+Zanu trials*
BruVenG ¹⁰
SEQUOIA ArmD ¹¹



Ven+Pirto trial*
CLL18 ^{11,13}

*These regimens are under investigation and not yet approved by any health authorities

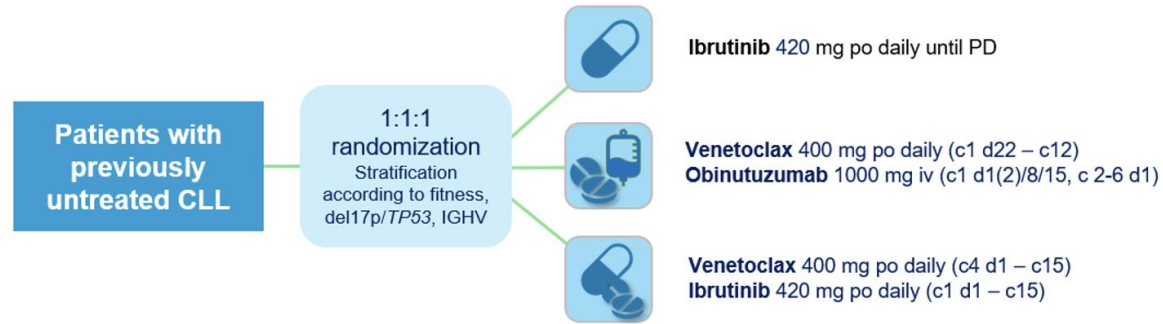
1. Niemann CU, et al. ASH 2024. Abstract 1871 (Poster). 2. Wierda WG, et al. ASCO 2024. Abstract 7009 (Oral). 3. Munir T, et al. EHA 2025. Abstract S155 (Oral). 4. CLL17: NCT04608318. 5. Davids MS, et al. J Clin Oncol. 2025;43(7):788-799. 6. CLL16: NCT05197192. 7. Brown JR, et al. N Engl J Med. 2025;392(8):748-762. 8. MAJIC, NCT05057494. 9. Ryan CE, et al. Future Med. 2022;18:3689-3699. 10. BruVenG, NCT05650723. 11. Ghia P, et al. EHA 2024. Abstract S160 (oral). 12. Cramer P, GCSLC International Workshop 2024. 13. CLL18, GCLLSG, <https://www.dcllsg.com/ctl18/>.



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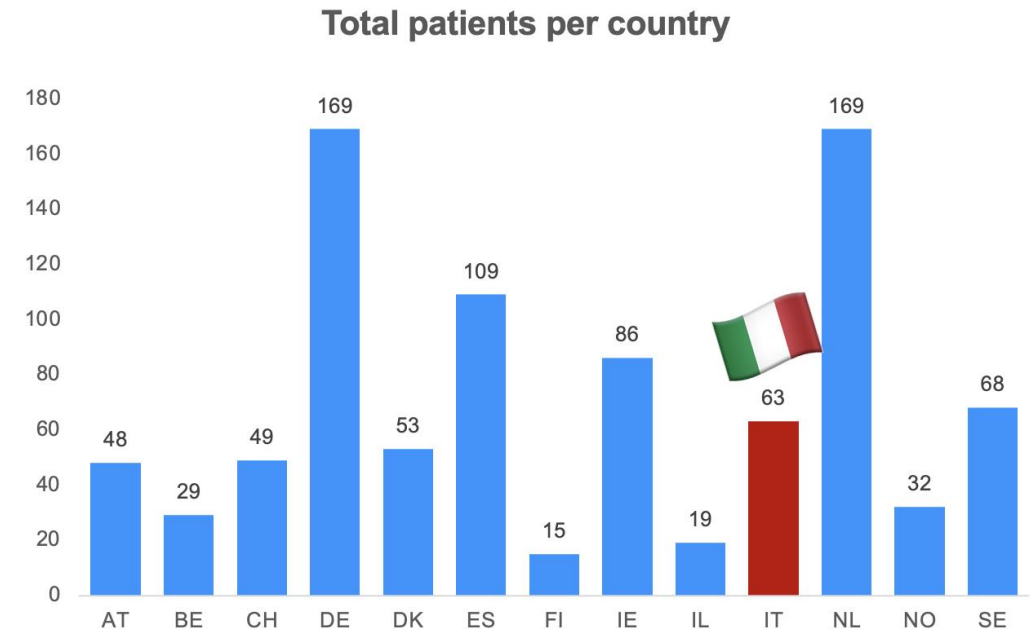
Continuous versus FTD: the CLL17 trial



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**.

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

From Feb 2021 to Nov 2022
976 patients screened, in 174 sites, 13 countries.



7.0% from Italy

Al-Sawaf O, et al. N Engl J Med. 2025

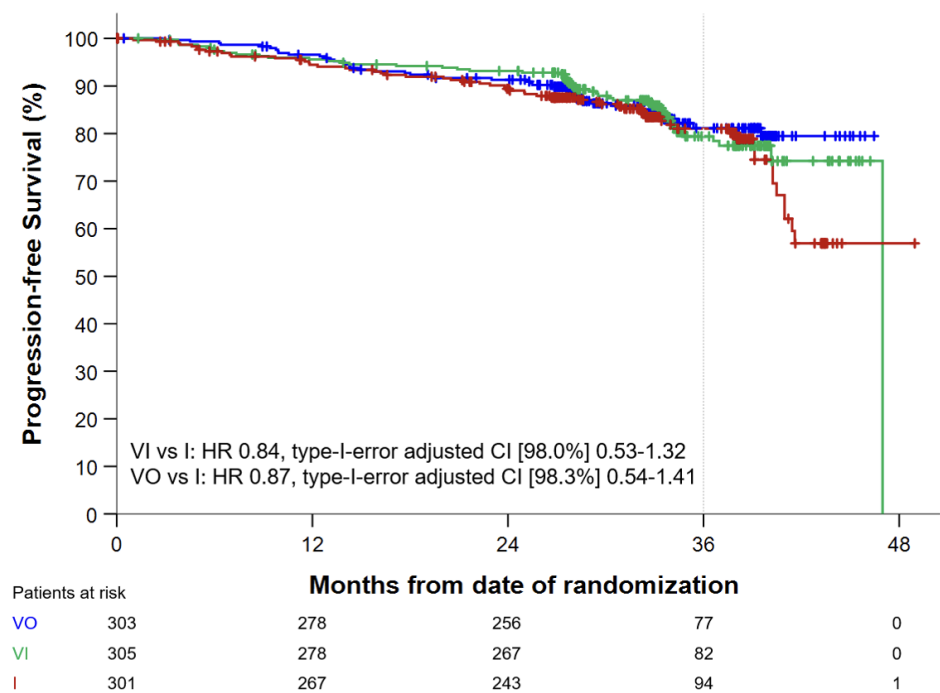


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CLL17: PFS rates and response to treatment

The study met the primary endpoint showing non inferiority PFS for FTD with venetoclax-based regimens (V+X) vs continuous therapy with I

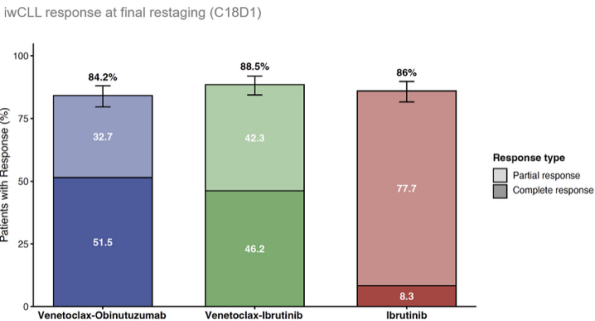


3-year-PFS

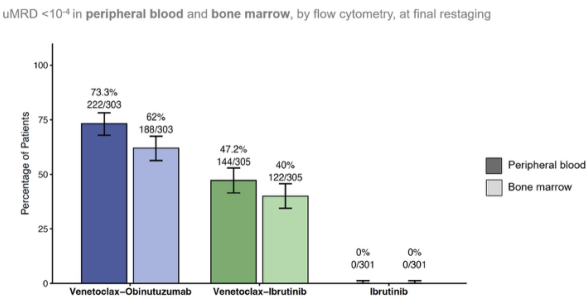
I 81.0%
VI 79.4 %
VO 81.1%

	PD	Death
I	46	11
VI	37	13
VO	25	21

ORR



MRD Rates

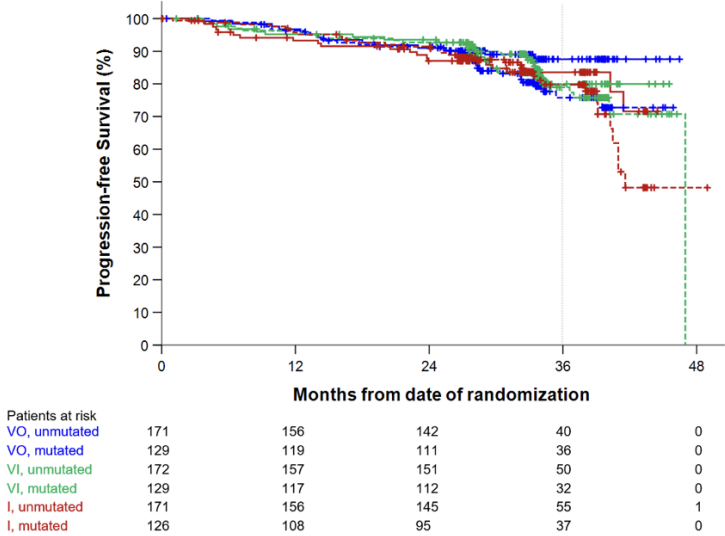


Al-Sawaf O, et al. N Engl J Med. 2025

CLL17: Fixed venetoclax-based therapies are also effective in intermediate-high risk patients

PROGRESSION-FREE SURVIVAL

According to IGHV status



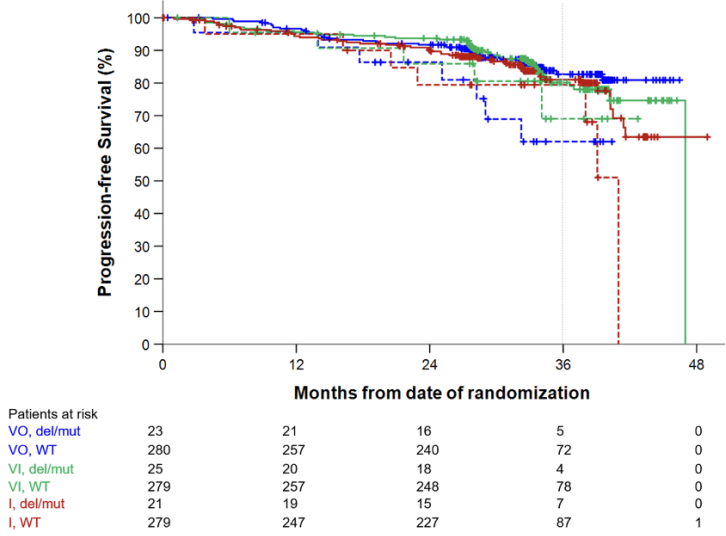
3-year-PFS

--- 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



3-year-PFS

--- I, TP53del/mut	79.4%
— I, TP53-WT	81.0%
--- VI, TP53del/mut	69.0%
— VI, TP53-WT	80.1%
--- VO, TP53del/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

Al-Sawaf O, et al. N Engl J Med. 2025



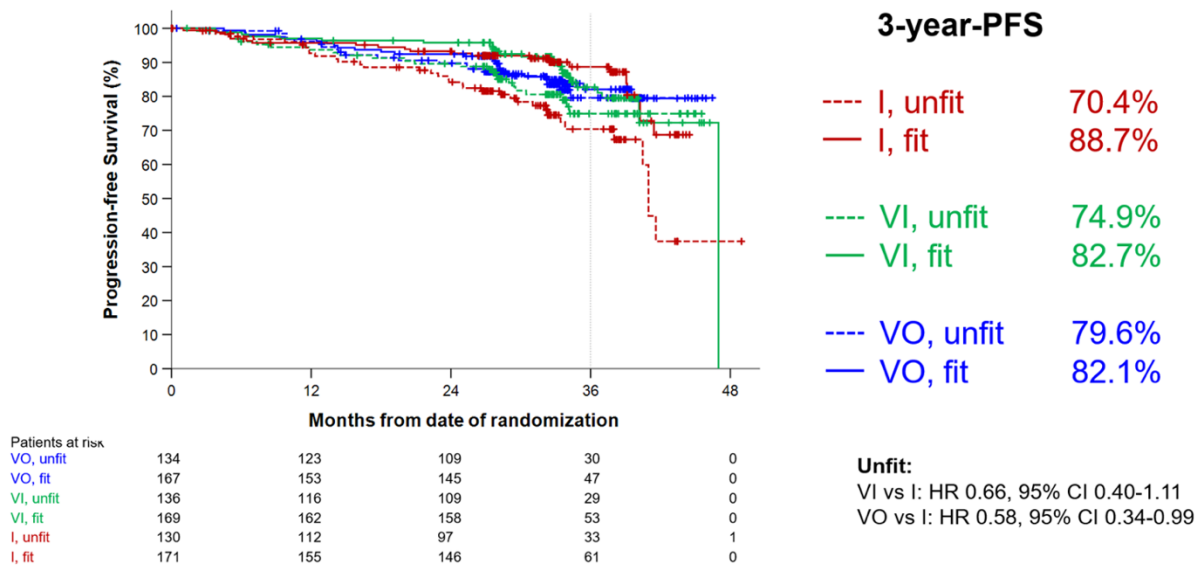
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CLL17: Safety profile consistent with known adverse events but time-limited therapies show a better outcome in elderly, unfit patients

PROGRESSION-FREE SURVIVAL

According to fitness (cumulative illness rating scale >6 and/or GFR <70 ml/min)



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)

Al-Sawaf O, et al. N Engl J Med. 2025



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CLL14: V+O - 9-year follow-up at EHA 2026

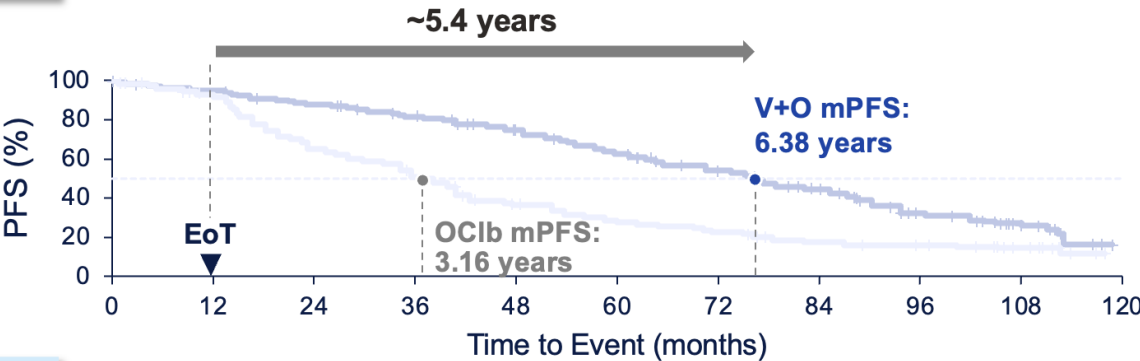
Ph3

CLL14 (Median follow-up: 9,2 years)

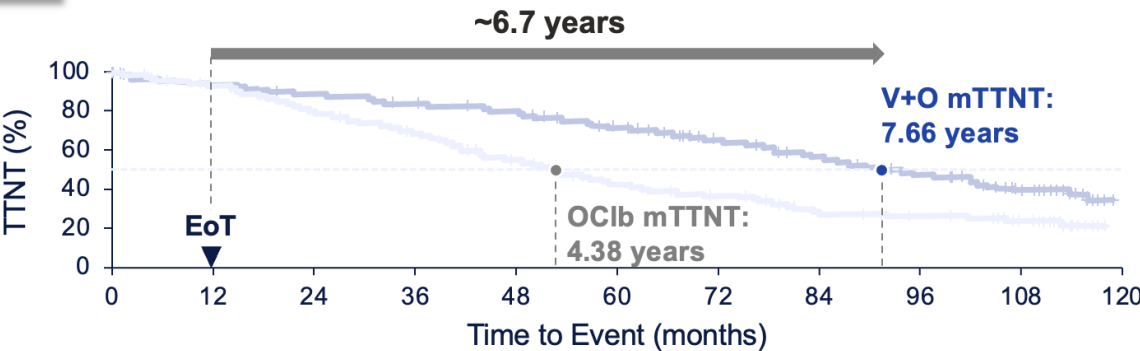
Median Age at the end of observation: 79

TREATMENT	VEN-Obi (N=216)
MEDIAN AGE	72 years
MEDIAN CIRS SCORE	9
MEDIAN CREATININE CLEARANCE	65.2 ml/min
IGHV UNMUTATED	61%
TP53 DELETED AND/OR MUTATED	12%

PFS



TTNT



Median PFS	V+O	OC1b
ITT	76.6 mo	37.9 mo
uIGHV	64.7 mo	
mIGHV	104.9 mo	
del(17p) and/or TP53 ^{mut}	49.0 mo	
TP53 wild type	79.2 mo	

Median TTNT	V+O	OC1b
ITT	91.9 mo	52.5 mo
uIGHV	78.6 mo	
mIGHV	NR	
del(17p) and/or TP53 ^{mut}	57.3 mo	
TP53 wild type	98.3 mo	

~3.8 years between EoT V+O and 2L treatment/death

Fischer K, et al. EHA 2026. Abstract S146 (Oral).



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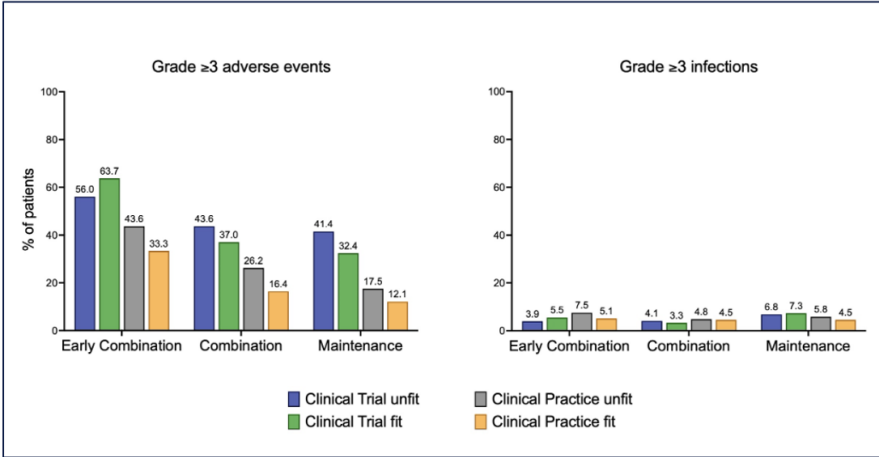
Feasibility and safety of Venetoclax–Obinutuzumab in fit and unfit CLL patients: Comparison of CLL13 and CLL14 pooled analysis with an Italian clinical practice cohort



CLL13/CLL14	Real life V+O
440 pts (257 unfit e 182 fit)	271 pts (133 unfit e 138 fit)

aderenza al trattamento	CLL13/CLL14	real life italiana
Completamento trattamento	86.6%	89.3%
Completamento trattamento – unfit	81.7%	88.0%
Completamento trattamento – fit	93.4%	90.6%
Discontinuazione per tossicità	8.0%	10.0%
Discontinuazione per tossicità – unfit	10.5%	11.3%
Discontinuazione per tossicità – fit	4.4%	8.7%
V dose intensity <70% – EaC	22.7%	7.0%
V dose intensity <70% – COMB	18.9%	10.4%

	CITr unfit %	CITr fit %	CP unfit %	CP fit %
PFS	88.7	92.8	87.7	96.3
OS	92.5	99.4	89.2	98.5
TTNT	95.9	97.8	97.7	97.8
TFS	89.7	97.2	87.7	96.3



Conclusions: In this large comparative analysis, VO appeared consistent with trials and feasible in clinical practice.

(EaC;cycles, C1–2), combination (COMB;C3–6) and maintenance phases (MAINT;C7 to end of treatment +28 days)

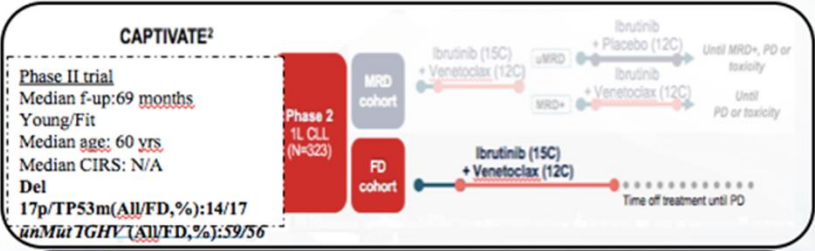
Zappaterra A. EHA 2026 Poster #PF607



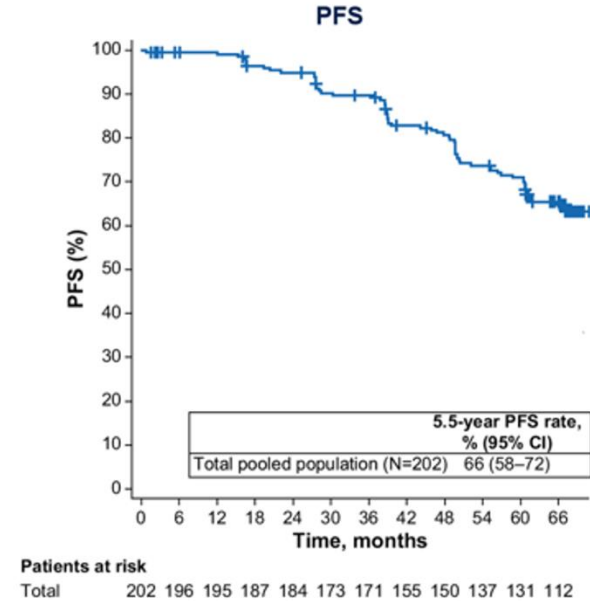
MEET THE
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MESTRE (VE), 19 OTTOBRE 2026
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CAPTIVATE Study: V+I at 5.5- year follow-up

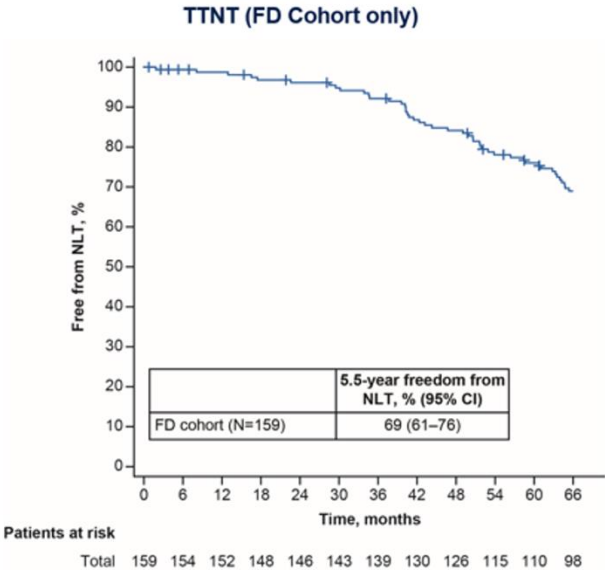


5.5- year PFS 66% (pooled population)



LONG-TERM FOLLOW-UP
(5.5 ANNI)

5.5- year TTNT 69% (FD coorte)



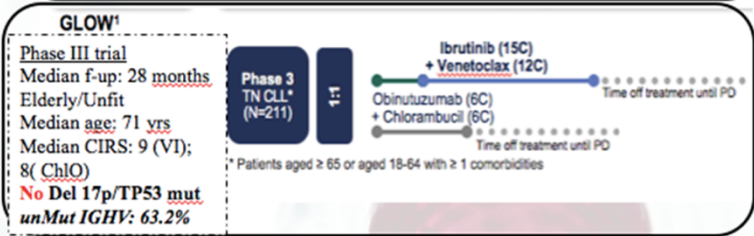
Wierda et al, EHA 2025



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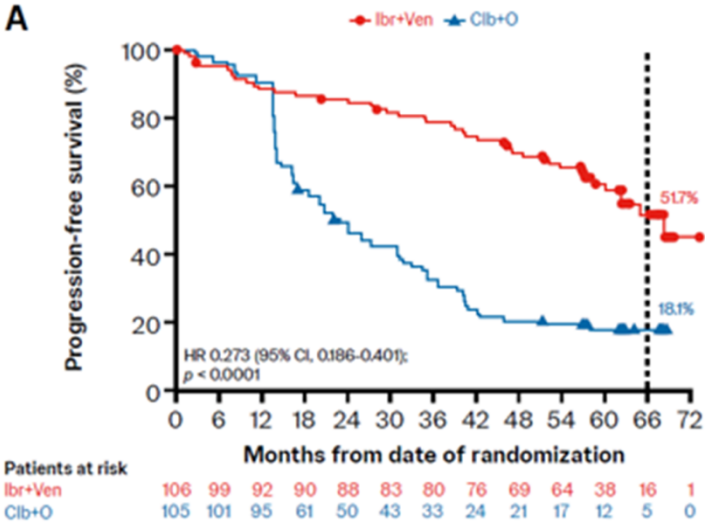
GLOW Study: V+I at 5.5- year follow-up



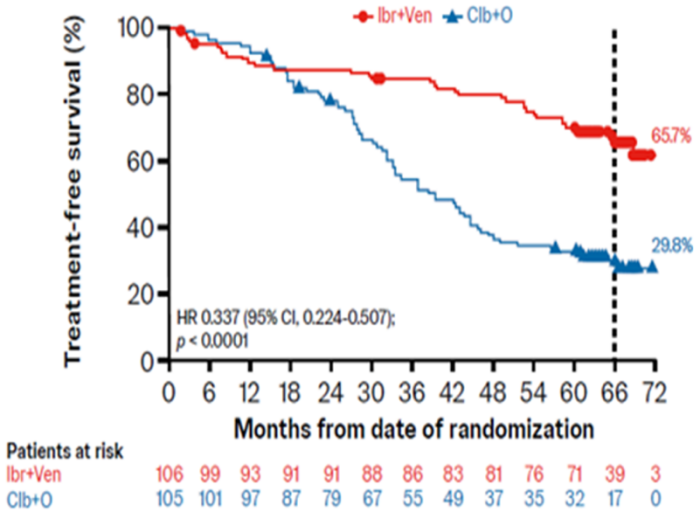
Manuscript Updated

67 months-PFS 51.7%

Treatment-free survival 65.7% a 67 mesi



LONG-TERM FOLLOW-UP
67 months



Niemann et al, 2026 Leukemia



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GLOW and CAPTIVATE-FD: Safety results

PhIII **GLOW (N=211)¹** Median age: 71
Unfit, No del(17p)/TP53^{mut} Median CIRS: 9 (VI); 8 (OCib)

Grade 3–5 adverse events occurring in ≥5% of patients in either arm (safety population)^a

	Ven+I (n=106)		O+Clb (n=105)	
	Grade 3/4	Grade 5	Grade 3/4	Grade 5
Neutropenia ^b	37 (34.9)	0	52 (49.5)	0
Thrombocytopenia	6 (5.7)	0	21 (20.0)	0
Infections and infestations ^c	16 (15.1)	2 (1.9) ^d	11 (10.5)	1 (1.0)
Diarrhoea ^e	11 (10.4)	0	1 (1.0)	0
Hyponatremia	6 (5.7)	0	0	0
TLS	0	0	6 (5.7)	0
Hypertension	8 (7.5)	0	2 (1.9)	0
Atrial fibrillation	7 (6.6)	0	0	0
AEs leading to discontinuation	11 (10.4%)		2 (1.9%)	

Deaths due to sudden/cardiac events (Ven+I arm): n=4

PhIII **CAPTIVATE-FD (N=159)²** Median age: 60
Fit, includes del(17p)/TP53^{mut} Median CIRS: N/A

Grade 3/4 adverse events occurring in ≥5% of patients

Adverse events	All treated patients (n=159), n (%)	Adverse events	All treated patients (n=159), n (%)
	Grade 3/4		Grade 3/4
Most common AEs ^f		Laboratory safety parameters	
Diarrhoea	5 (3)	Haematology	
Nausea	2 (1)	Neutrophils decreased	60 (38)
Neutropenia	52 (33)	Platelets decreased	20 (13)
Arthralgia	2 (1)	Haemoglobin decreased	0
Hypertension	9 (6)	Chemistry	
Neutrophil count decreased	8 (5)	Corrected calcium decreased	1 (1)
Other AEs of clinical interest		Potassium increased	4 (3)
Atrial fibrillation	2 (1)	Uric acid increased	34 (21)
Major haemorrhage ^g	2 (1)	Creatinine increased	0

Deaths due to sudden events: n=1

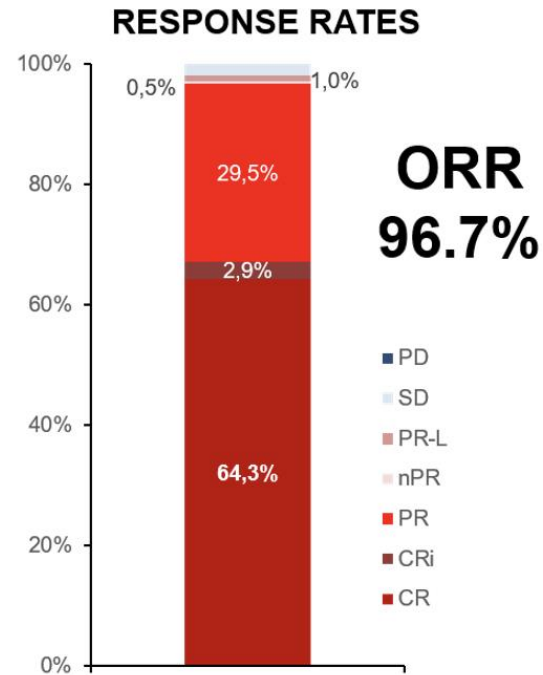
^a15 28-day cycles are equivalent to 13.8 months for Ven+I, and 6 28-day cycles are equivalent to 5.5 months for O+Clb. Patients may have treatment exposure times exceeding these limits due to cycle holds. ^bIncludes 'neutrophil count decreased'. Rates of febrile neutropenia (Grade ≥3): 1.9% for Ven+I versus 2.9% for O+Clb. ^cIncludes multiple preferred terms. Only pneumonia (Grade ≥3) occurred in ≥5% of patients in the Ven+I (7 patients [6.6%]) and O+Clb (6 patients [5.7%]) arms. ^dBoth Grade 5 AEs were pneumonia (one patient experienced three Grade 5 AEs: pneumonia, cardiac failure, and sinus node dysfunction). ^eIn the Ven+I arm, 3 diarrhoea events (Grade ≥3) resolved or improved after a median of 9.0 days. ^fAEs of any grade occurring in ≥30% of patients or Grade 3/4 occurring in ≥5% of patients; ^gMajor haemorrhage was identified using the Standardised MedDRA Query for Haemorrhage, excluding laboratory terms.
AE, adverse event; CIRS, Cumulative Illness Rating Scale; Clb, chlorambucil; del, deletion; FTD, fixed treatment duration; I/Ibr, ibrutinib; O, obinutuzumab; Ph, Phase; TLS, tumour lysis syndrome; TP53^{mut}, TP53 mutation; Ven, venetoclax.
1. Kater A, et al. NEJM Evid. 2022; 1(7):EVIDoa2200006; 2. Tam CS, et al. Blood. 2022;139:3278–89.



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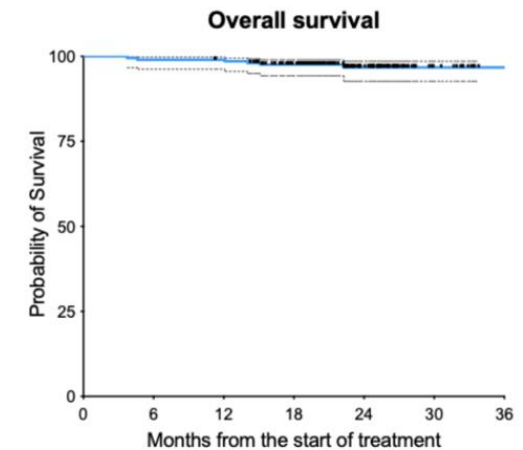
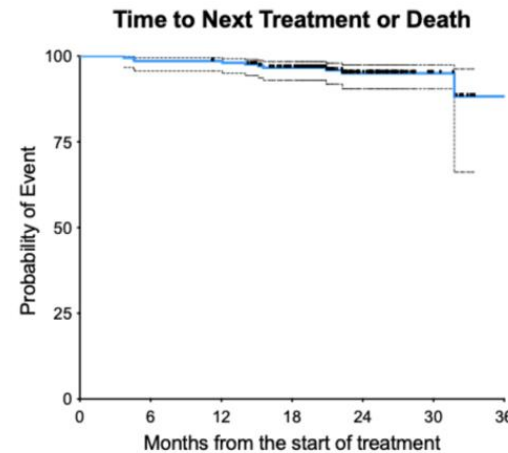
Real-life experience of Ibrutinib plus Venetoclax as front-line therapy in patients with CLL: an ERIC Study



median follow-up of 21.4 months

Efficacy of I+V

- The median TTNTD and OS were not reached. The 18 months and estimated 24 months TTNTD and OS were 96.6% and 97.7%, 95.0% and 96.7%, respectively.



Visentin A. Oral Presentation SIE 2026

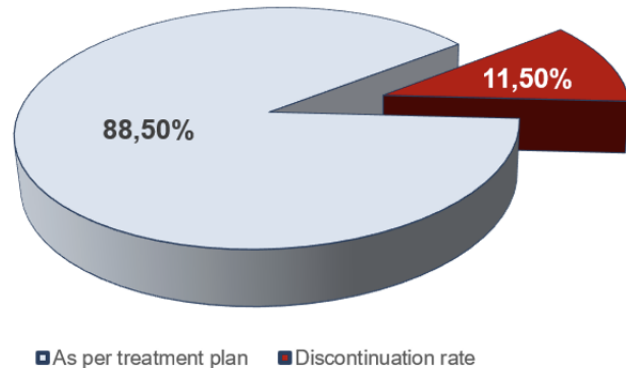


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Real-life experience of Ibrutinib plus Venetoclax as front-line therapy in patients with CLL: an ERIC Study

Discontinuation rates of I+V



The median time to discontinuation was 13.7 months (IQR 6.7-14.9).

median follow-up of 21.4 months

Safety of I+V (any AE occurring in $\geq 2\%$ or any event G ≥ 3)

Hematological adverse event	Any grade, n (%)	Grade 3, n (%)	Grade 4, n (%)
Neutropenia	81 (40.3)	25 (30.9)	29 (35.8)
Anemia	45 (22.7)	4 (8.7)	0 (0.0)
Thrombocytopenia	45 (22.3)	9 (19.6)	0 (0.0)
No-Hematological adverse event	Any grade, n (%)	Grade 3, n (%)	Grade 4, n (%)
Diarrhea	31 (14.8)	2 (1.0)	0 (0.0)
Upper respiratory tract infection	13 (6.2)	0 (0.0)	1 (0.5)
Arthralgia	11 (5.3)	2 (1.0)	0 (0.0)
Other infections	11 (5.3)	2 (1.0)	0 (0.0)
Atrial fibrillation/flutter	10 (4.8)	4 (1.9)	1 (0.5)
Pneumonia	9 (4.3)	4 (1.9)	0 (0.0)
Dizziness	8 (3.8)	0 (0.0)	0 (0.0)
Hypertension	7 (3.3)	3 (1.4)	0 (0.0)
Hemorrhage	6 (2.9)	0 (0.0)	0 (0.0)
Hyponatremia	1 (0.5)	1 (0.5)	0 (0.0)
Nausea	5 (2.4)	0 (0.0)	0 (0.0)
Rash	5 (2.4)	2 (1.0)	0 (0.0)
Urinary tract infection	5 (2.4)	2 (1.0)	0 (0.0)
Transaminitis	4 (1.9)	1 (0.5)	0 (0.0)
Febrile neutropenia	3 (1.4)	2 (1.0)	1 (0.5)
Back pain	3 (1.4)	1 (0.5)	0 (0.0)
Stomatitis	2 (1.0)	1 (0.5)	0 (0.0)
Ventricular arrhythmia	1 (0.5)	0 (0.0)	1 (0.5)

- Any adverse events were reported in 138 patients (66.7%).
- 42 (20.1%) infections were recorded. Most infective events were low grade but 7 grade 3 or higher event occurred.
- 23 cardiovascular adverse events occurred (11.0%) and atrial fibrillation/flutter was the most common.
- TLS events were reported in 6 patients (2.9%), with no cases of clinical TLS.

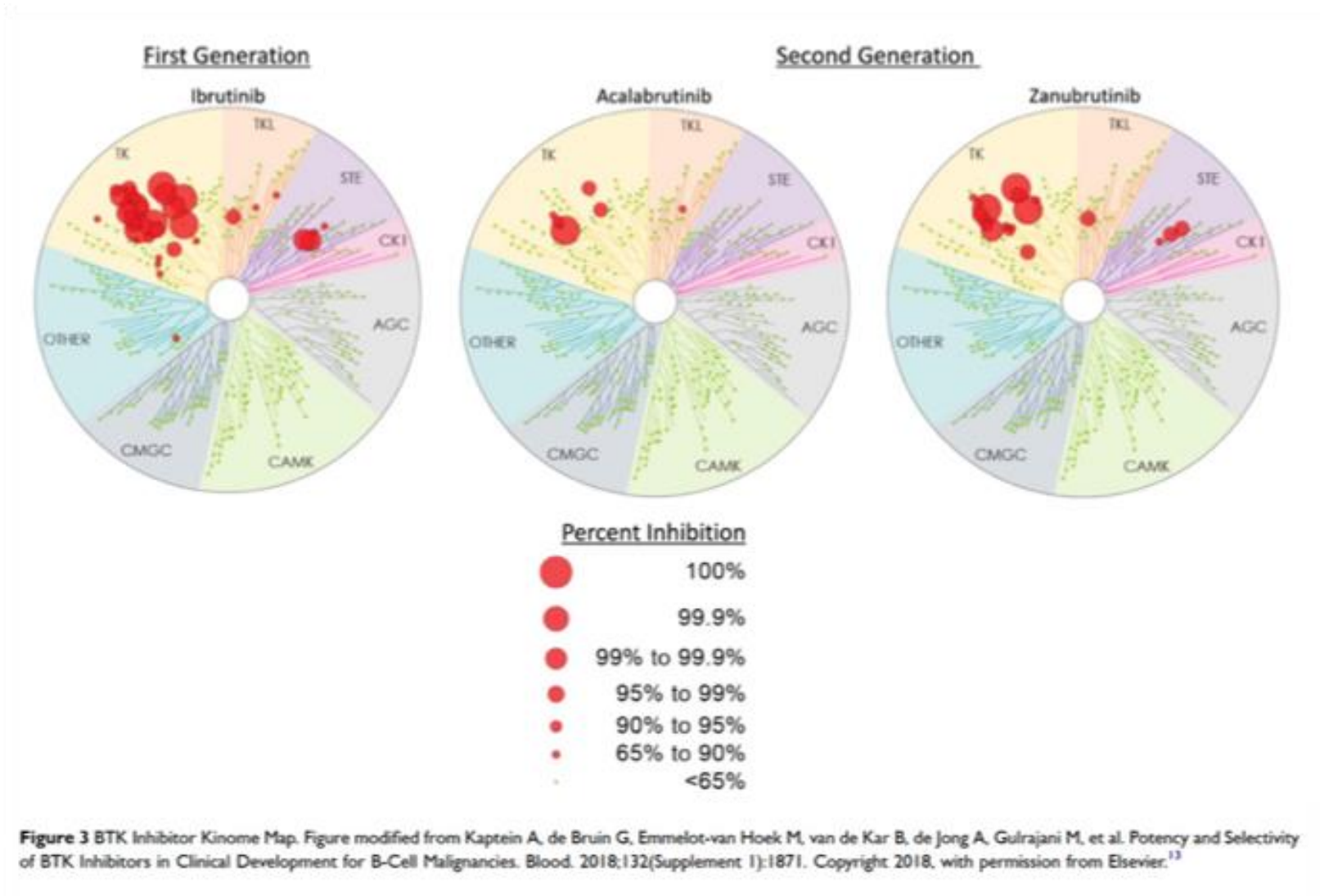
Visentin A. Oral Presentation SIE 2026



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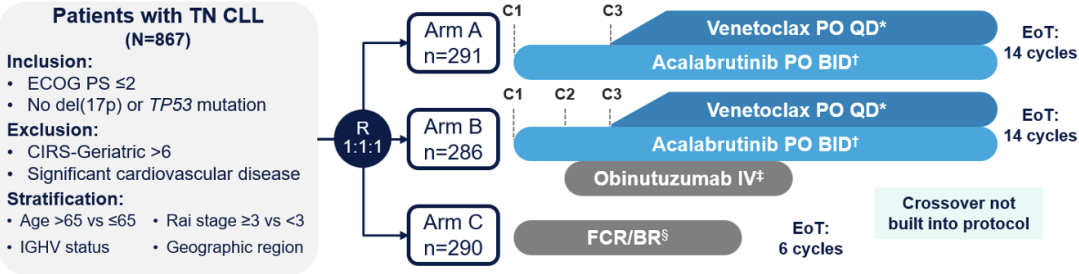
Kinome selectivity of cBTKi



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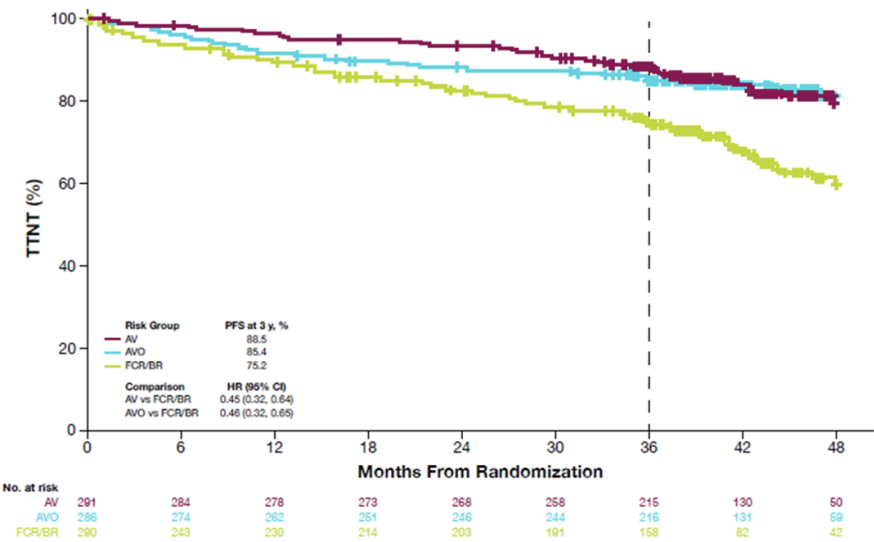
V+A: AMPLIFY study design, PFS and TTNT



Progression Free Survival

	VA (N=291)	FCR/BR (N=290)
36-mo PFS	76.5%	66.5%
Median PFS*	NR	47.6 mo
HR (95% CI)	0.65 (0.49-0.87) P=0.0038	

Time to Next Treatment



3-y TTNT rate V+A: 88.5%

Brown J.R. NEJM 2025
Ghia P. ASH 2025 P. 3998



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AMPLIFY: V+A offers manageable safety limiting long-term drug exposure

- The most common any-grade AEs with Ven+A were headache (35.1%), diarrhoea (32.6%) and neutropenia (30.9%)^{1a}
- Ven+A demonstrated a low incidence of Grade ≥ 3 cardiac AEs (1.7%) over the 14-month treatment period^{1a}
- The safety profile of fixed-duration V+A in this trial aligned with that in previous studies of acalabrutinib.

^aAll the treatments were administered in 28-day cycles. The patients in the Ven+A group received acalabrutinib at a dose of 100 mg twice daily during Cycles 1–14 and Ven once daily during Cycles 3–14 (including a 5-week ramp-up of Ven from 20 mg once daily to the target dose of 400 mg once daily).

^bData are n (%) unless otherwise noted. Median follow-up: 40.8 months. AEs with an onset date or that worsened on or after the date of first dose and up to and including 30 days following the date of last dose of treatment or up to the day prior to start of subsequent anti-CLL therapy, whichever came first.

A, acalabrutinib; AE, adverse event; BR, bendamustine + rituximab; FCR, fludarabine + cyclophosphamide + rituximab; FTD, fixed treatment duration; IC, immunochemotherapy; mo, month; Ven, venetoclax.

1. Brown JR, et al. *N Engl J Med.* 2025;392(8):748–62; 2. Calquence (acalabrutinib) EU Summary of Product Characteristics (AstraZeneca AB).

Safety summary (safety population)^b

	Ven+A (n=291)	FCR/BR (n=259)
Duration of exposure, median (range), mo	12.9 (1–18)	5.6 (1–11)
Summary of AEs		
Any AE	270 (92.8)	236 (91.1)
Any AE Grade ≥ 3	156 (53.6)	157 (60.6)
Any serious AE	72 (24.7)	71 (27.4)
Serious AEs leading to death	10 (3.4)	9 (3.5)
AE leading to treatment discontinuation	23 (7.9)	28 (10.8)



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AMPLIFY: Events of clinical interest

	AV (n=291)		AVO (n=284)		FCR/BR (n=259)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Any ECI	222 (76.3)	136 (46.7)	242 (85.2)	188 (66.2)	185 (71.4)	141 (54.4)
Cardiac events	27 (9.3)	5 (1.7)	34 (12.0)	7 (2.5)	9 (3.5)	3 (1.2)
Atrial fibrillation	2 (0.7)	1 (0.3)	6 (2.1)	2 (0.7)	2 (0.8)	2 (0.8)
Ventricular tachyarrhythmias^a	2 (0.7)	0	3 (1.1)	0	0	0
Hypertension	12 (4.1)	8 (2.7)	11 (3.9)	6 (2.1)	7 (2.7)	2 (0.8)
Hemorrhage	94 (32.3)	3 (1.0)	86 (30.3)	6 (2.1)	11 (4.2)	1 (0.4)
Major hemorrhage	3 (1.0)	3 (1.0)	8 (2.8)	6 (2.1)	2 (0.8)	1 (0.4)
Neutropenia (any)^b	108 (37.1)	94 (32.3)	143 (50.4)	131 (46.1)	132 (51.0)	112 (43.2)
Infections (any)	148 (50.9)	36 (12.4)	153 (53.9)	67 (23.6)	82 (31.7)	26 (10.0)
Second primary malignancies	15 (5.2)	5 (1.7)	12 (4.2)	5 (1.8)	2 (0.8)	0
Excl. non-melanoma skin	8 (2.7)	5 (1.7)	7 (2.5)	4 (1.4)	1 (0.4)	0
Tumor lysis syndrome	1 (0.3)	1 (0.3)	1 (0.4)	1 (0.4)	8 (3.1)	8 (3.1)

Data are n (%). ECIs listed by category and sub-category.

^aVentricular tachyarrhythmias consisted of ventricular extrasystoles (n=1 in AV arm; n=2 in AVO arm) and ventricular tachycardia (n=1 each in AV and AVO arms).

^bIncludes neutropenia, neutrophil count decreased, and febrile neutropenia.

AEs with an onset date or that worsen on or after the date of first dose and up to and including 30 days following the date of last dose of treatment or up to the day prior to start of subsequent anti-CLL therapy, whichever comes first.

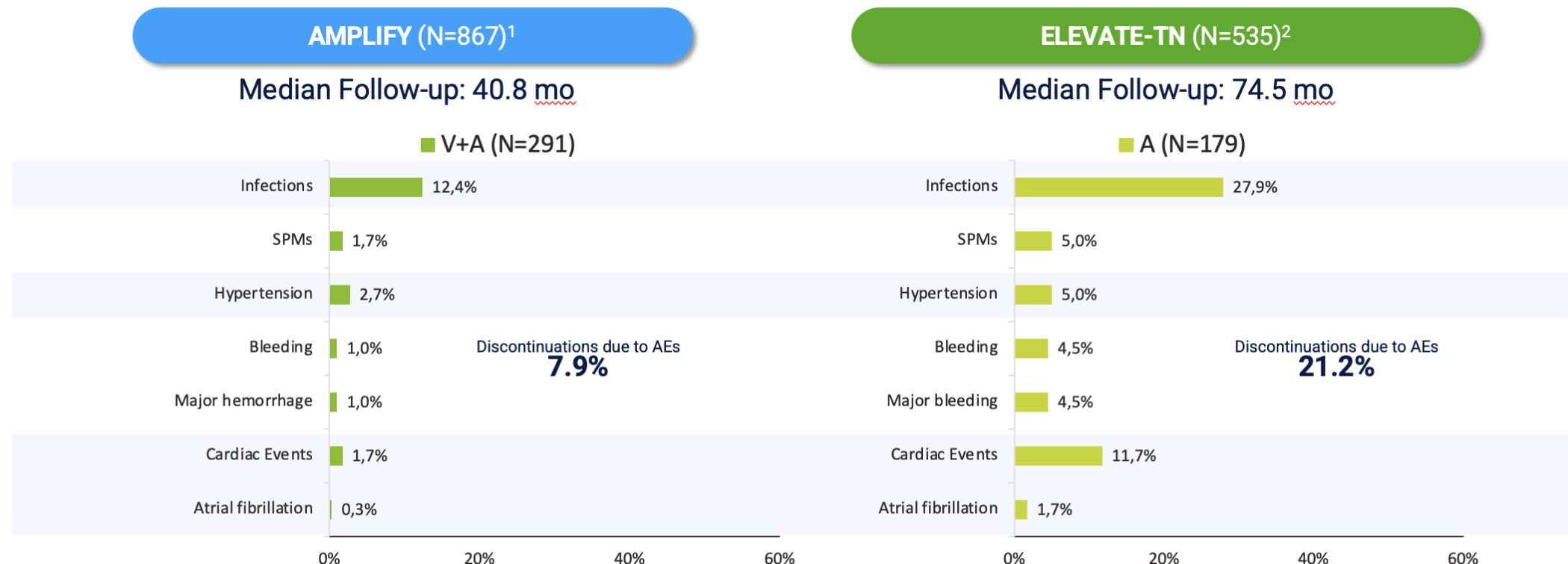
Brown JF et al, oral presentation ASH 2024; N Eng J Med 2025



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V+A vs A mono - Safety (Grade ≥ 3 TEAEs)



Venetoclax FTD reduces the accumulation of AE observed with treat-to-progression regimens, and thus offers a favorable safety profile

1. Brown JR, et al. *N Engl J Med*. 2025;**392**(8):748-762. 2. Sharman JP, et al. ASH 2023. Abstract 636 (Oral).



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V+A vs A mono - Safety (Grade ≥ 3 TEAEs)

Table 2. ECIs by Age, All Grades^a

N (%)	AV (n=291)	
	<65 y (n=194)	≥ 65 y (n=97)
Cardiac events	17 (8.8)	10 (10.3)
Atrial fibrillation	0	2 (2.1)
Ventricular arrhythmias (grouped term)	2 (1.0)	0
Anemia	13 (6.7)	7 (7.2)
Leukopenia	68 (35.1)	41 (42.3)
Neutropenia	68 (35.1)	40 (41.2)
Other leukopenia	4 (2.1)	7 (7.2)
Thrombocytopenia	12 (6.2)	5 (5.2)
Hemorrhage	58 (29.9)	36 (37.1)
Major hemorrhage	1 (0.5)	2 (2.1)
Hepatotoxicity	12 (6.2)	5 (5.2)
Hypertension	10 (5.2)	2 (2.1)
Infections	104 (53.6)	44 (45.4)
Interstitial lung disease/pneumonitis	0	0
Second primary malignancies	7 (3.6)	8 (8.2)
Second primary malignancies, excluding non-melanoma skin	5 (2.6)	3 (3.1)
Secondary primary malignancies, non-melanoma skin	4 (2.1)	5 (5.2)
Tumor lysis syndrome^b	0	1 (1.0)

^aEvents of clinical interest categories are by grouped terms.

^bTumor lysis syndrome events were limited to laboratory tumor lysis syndrome only; no clinical tumor lysis syndrome was observed.

Table 3. TEAEs Leading to Discontinuation of Treatment by Age, All Grades

	AV (n=291)	
	<65 y (n=194)	≥ 65 y (n=97)
Patients with discontinuation of any treatment due to TEAE,^a n (%)	11 (5.7)	12 (12.4)
COVID-19	2 (1.0)	0
COVID-19 pneumonia	2 (1.0)	4 (4.1)
Patients with discontinuation of acalabrutinib due to TEAE,^a n (%)	10 (5.2)	12 (12.4)
COVID-19	1 (0.5)	0
COVID-19 pneumonia	2 (1.0)	4 (4.1)
Patients with discontinuation of venetoclax due to TEAE,^a n (%)	10 (5.2)	8 (8.2)
COVID-19	1 (0.5)	0
COVID-19 pneumonia	1 (0.5)	3 (3.1)

^aTEAEs, by preferred term, reported in $>3\%$ of patients in any subgroup.

Conclusions

- Fixed-duration AV-containing regimens had generally similar within-treatment safety profiles across age groups (<65 and ≥ 65 years), with modest increases, particularly in AE-related discontinuations, in patients aged ≥ 65 years
 - COVID-19-related AEs were the leading cause of AE-related discontinuations
- No new safety signals were identified

Seymour J. et al, EHA 2026



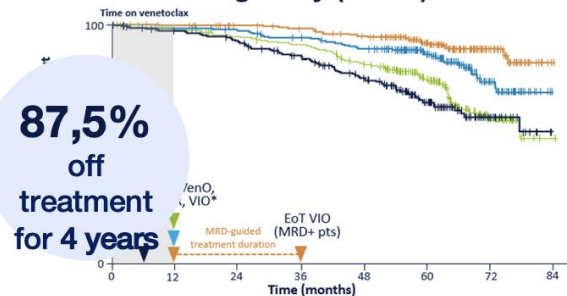
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The consistent value of TTNT across V+X regimens

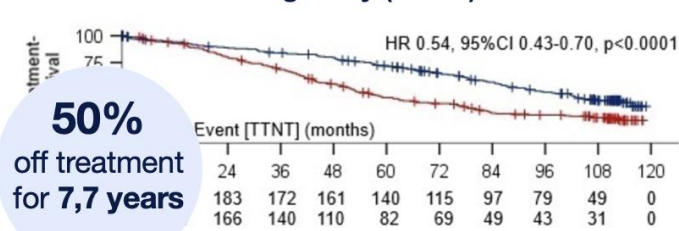
V+O - CLL13 (5y)

Age: 62y (31–83)



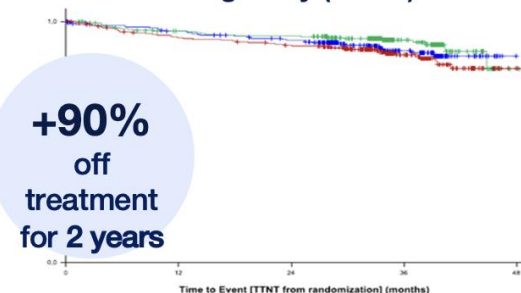
V+O - CLL14 (9y)

Age: 72y (43–89)



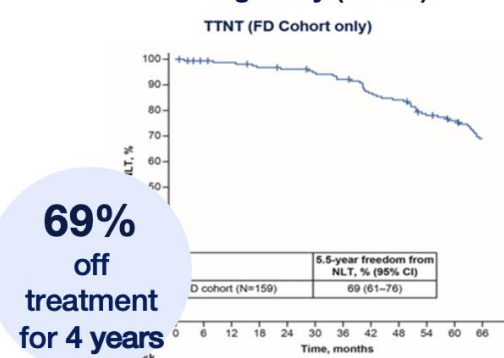
V+O - V+I - CLL17 (3y)

Age: 66y (58–73)



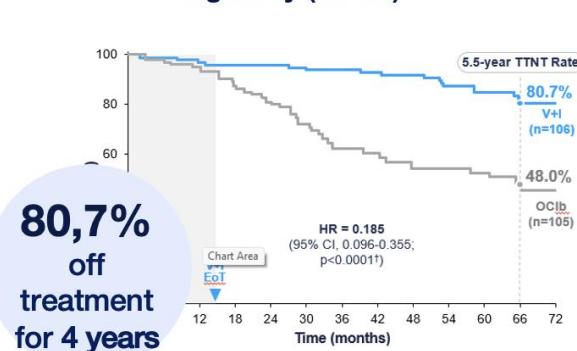
V+I - CAPTIVATE (5.5y)

Age: 60y (33–71)



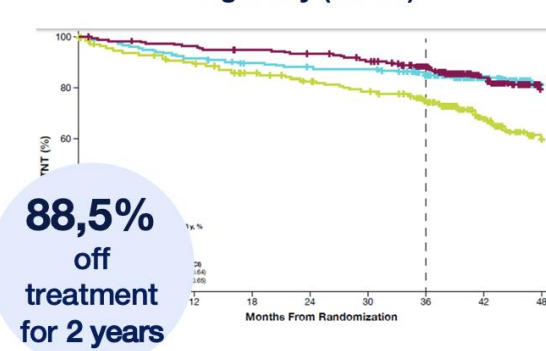
V+I - GLOW (5.5y)

Age: 71y (47–93)



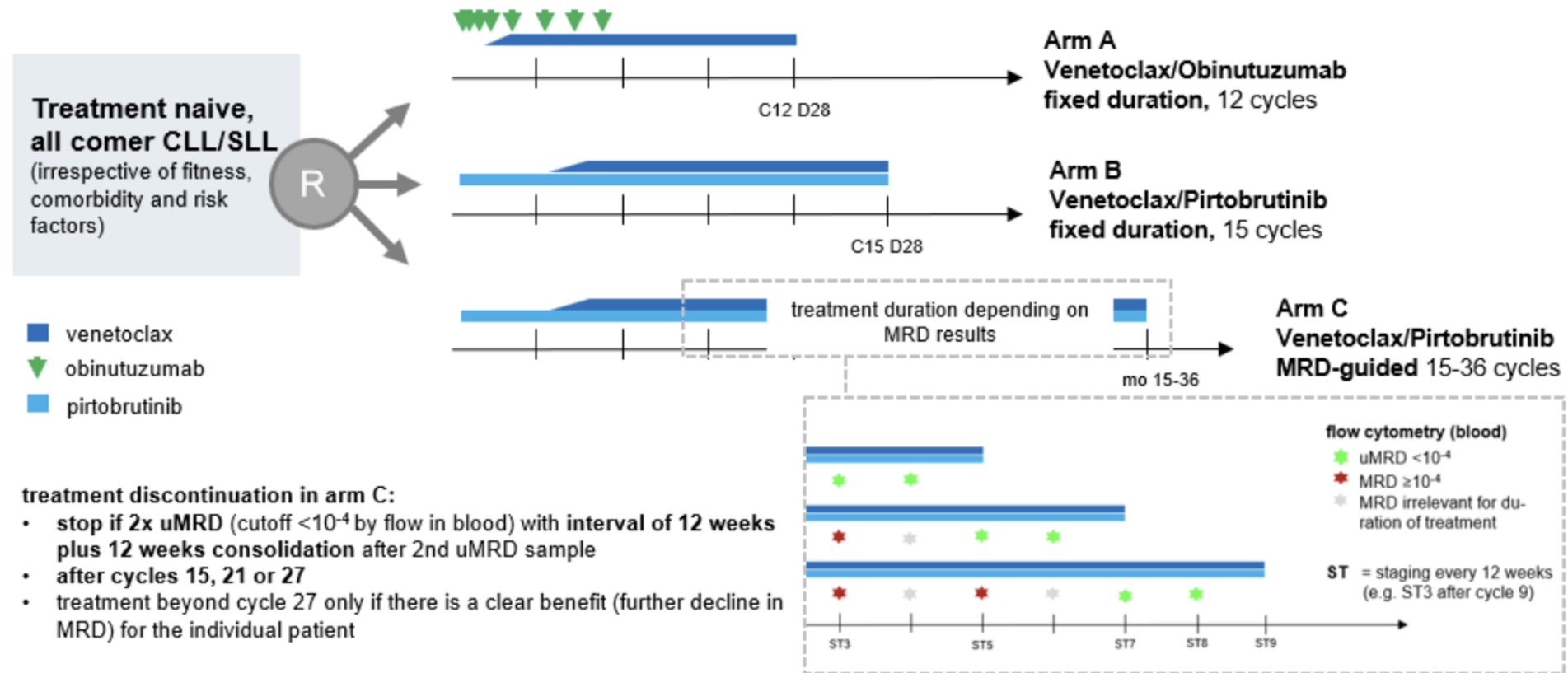
V+A - AMPLIFY (3y)

Age: 61y (31–84)



Fischer K, et al. EHA 2026; Fürstenau M, et al. 2025; Al-Sawaf O, et al. 2025; Ghia P. ASH 2025; Niemman, et al. ASH 2024; Wierda, et al. ASCO 2024

A look to the future: the CLL18 trial



Primary endpoint: investigator-assessed PFS

Key secondary endpoints: iwCLL response, MRD, OS and safety parameters

Cramer P. o et al, EHA2025



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Agenda

- Evolution of CLL treatment
- FTD therapy in 1L CLL treatment
- **FTD therapy in R/R CLL treatment**



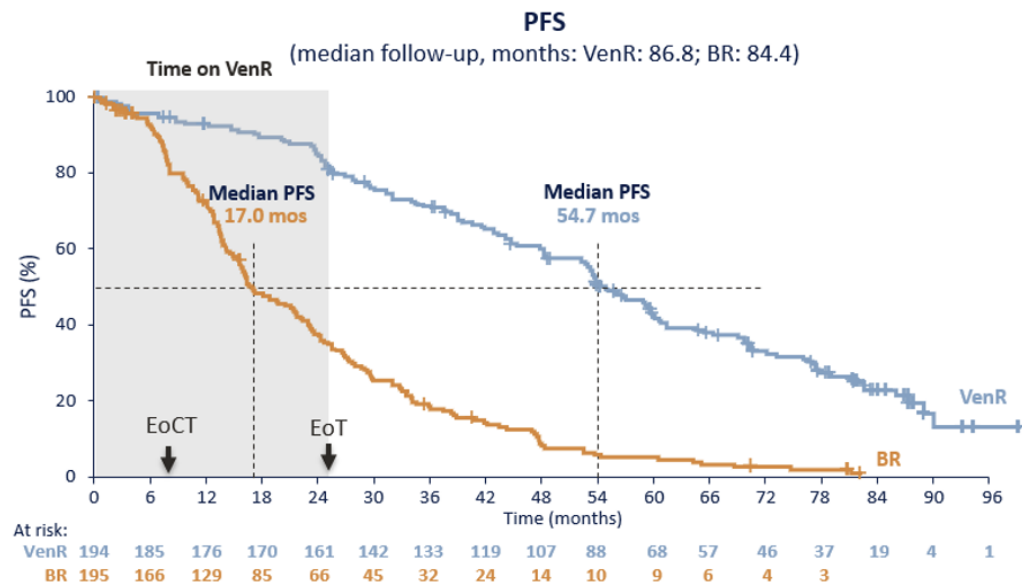
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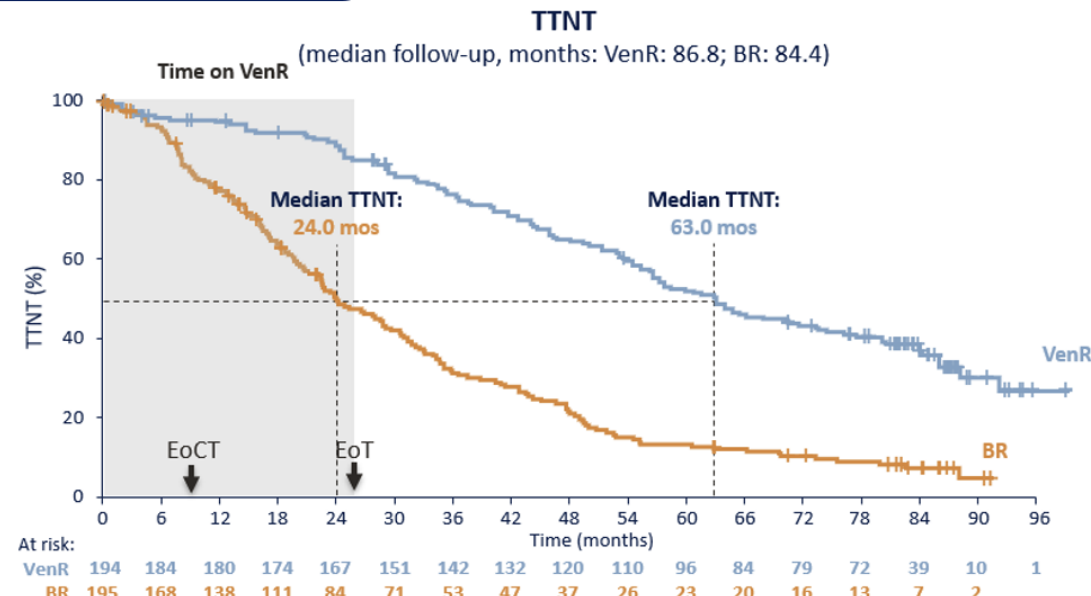
V+R, the only FTD in the R/R setting (post CIT)

MURANO - 7 y Final Analysis

V+R post CIT



At 7 years, **5 years after the end of treatment**, **23%** of patients (2 out of 10) are **still progression-free with V+R**, unlike the BR arm where no patients are still progression-free.



At 7 years, **5 years after the end of treatment**, the **median TTNT with V+R was 63m** (about 5 years) compared to 24m with BR. Specifically, 73 pts in the V+R arm did not receive any subsequent treatment, and 26 died without the need for further treatments.

Kater et al., Blood 2025



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V+R MURANO: Safety overview

V+R post CIT

Grade 3–4 AEs during treatment, with $\geq 2\%$ difference between arms, n (%)	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	6 (3.1)	0
Clinical TLS	1 (0.5)	0
Infusion-related reaction	4 (2.1)	0
Hyperglycemia	4 (2.1)	0
Hypogammaglobulinemia	3 (1.5)	1 (0.6)

Updated safety profile

- At the 5-year analysis, excluding non-melanoma skin cancer, 2 new secondary malignancies were reported since the previous update:³
 - VenR: n=2 (1 AML, 1 plasma cell myeloma)
 - BR: n=0
- Since the 5-year data cutoff, there has been 1 additional Richter's transformation in the VenR arm and 6 in the BR arm^{†,4}
- No new safety signals were observed** with 11 patients enrolled in the retreatment sub-study¹
- In the final analysis at 7 years,[‡] no new safety signals identified 5 years after EoT⁴**

* Grade 3–4 AEs were not actively monitored after EoT; only deaths, serious AEs, or other AEs of concern believed to be related to prior treatment with study drug were reported; † Throughout the study to 7-year analysis (data cutoff Aug 3, 2022), Richter transformation was reported in 8 (4.1%) patients in the VenR arm and 6 (3.2%) patients in the BR arm; ‡ Median follow-up 86.8 months for VenR. B, bendamustine; EoT, end of treatment; R, rituximab; TLS, tumor lysis syndrome; Ven, venetoclax.

Kater et al., Blood 2025

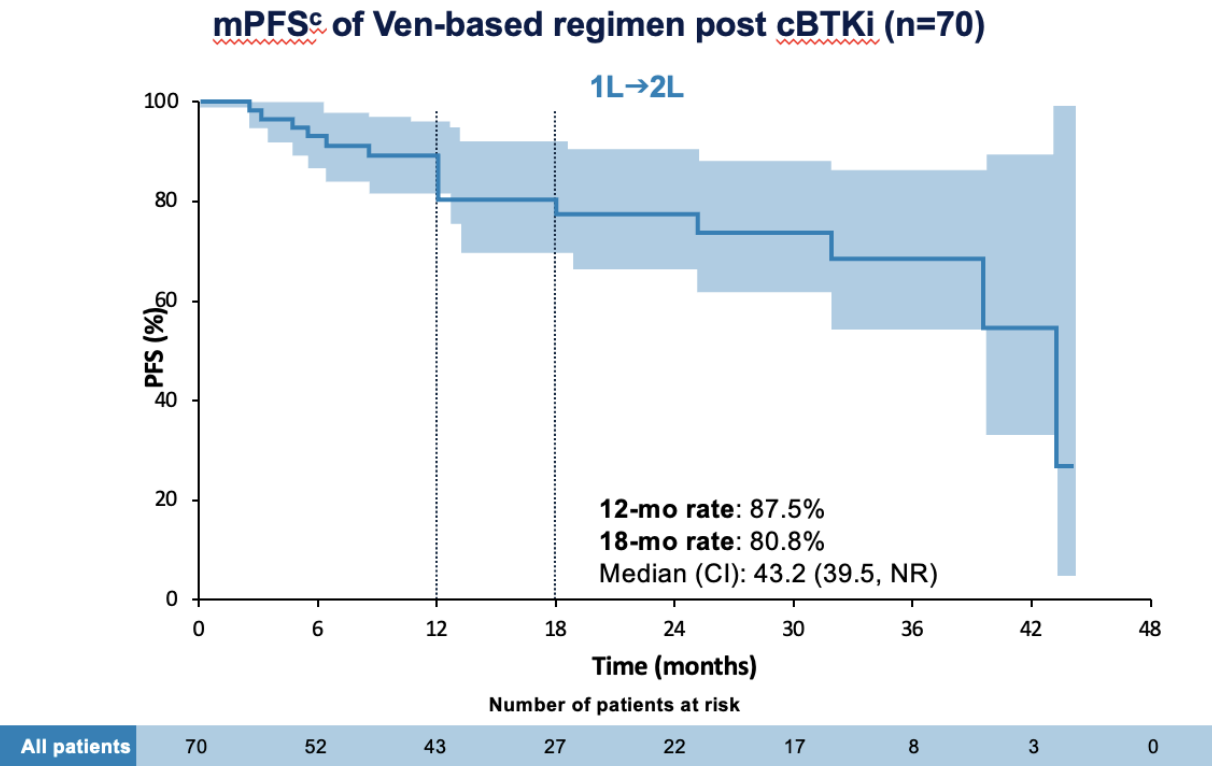


MEET THE
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MESTRE (VE), 19 OTTOBRE 2026
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CLL CORE RWE study: mPFS of a Ven-based regimen post-cBTKi in 2L setting

V+R 2L
(post BTKi)
43,2 m
mPFS



Overall population	
ORR, ^b %	79.4
mPFS, months	44.1 (95% CI: 36.3, NR)
18-month PFS rate, %	76.2
mTTNT-D, months	44.2 (95% CI: 31.9, NR)
18-month TTNT rate, %	73.7

Ven-based therapy after 1L cBTKi	
ORR, ^b %	85.1
mPFS, ^c months	43.2 (95% CI: 39.5, NR)
mTTNT-D, ^d months	NR (95% CI: 31.9, NR)
12-month TTNT rate, %	86.1
18-month TTNT rate, %	73.6

^aReal-world evidence is collected outside of controlled clinical trials and has inherent limitations, including a lesser ability to control for confounding factors. Results are descriptive and have not been tested for statistical significance; ^bORR was measured as the proportion of patients with CR or PR among those with available information on responses in their medical charts based on physician assessment. CR and PR were based on physician-reported information as recorded in the patient charts; ^cPFS was defined as the time from the start of Ven-based therapy to disease progression or death (i.e. event). Patients without events were censored at the last date of follow-up; ^dTTNT-D was defined as the time from the start of Ven-based therapy to alternative treatment or death (i.e. event). Patients without events were censored at the last date of follow-up. L, first-line; 2L, second-line; cBTKi, covalent Bruton's tyrosine kinase inhibitor; CI, confidence interval; mPFS, median progression-free survival; mTTNT, median time to next treatment; mTTNT-D, median time to next treatment or death; NR, not reported; ORR, overall response rate; PFS, progression-free survival; RW, real-world; TTNT, time to next treatment; Ven, venetoclax.

1. Ghosh N, et al. Am J Hematol. 2024;100(3):511–15 and supplementary information.



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RWE – 2L V + R in CLL after progression on BTKi

RWE

CORE - EHA 2025
Real-world retrospective observational study

V+R 2L
(post BTKi)
39,3 m

Retrospective observational study

Pts post cBTKi progression* (N=145)

Ven mono n=93
2L: n=22
3L: n=33

V+R n=52
2L: n=21
3L: n=22

Efficacy

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)

	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%

- This cohort of 145 patients focuses on patients who interrupted cBTKi because of PROGRESSION
- Also in this more unfavorable setting, Ven-based therapies show very good efficacy
- In patients treated with V+R in «pure» 2L after progression on a cBTKi, the median PFS mediana is 39,3 months and TTNT is NR.

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



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Novel evidence from the BRUIN 322 study

V+R post cBTKi

RWE

CORE - Ghosh et al. 2024 Real-world retrospective observational study

RR CLL Patients who discontinued previous treatment for **Disease Progression or Intolerance**

V+R 2L
(post BTKi)
43.2 mo
mPFS

RWE

CORE – EHA 2025 Real-world retrospective observational study

RR CLL Patients who discontinued previous treatment for **Disease Progression ONLY**

V+R 2L
(post BTKi)
39.3 mo
mPFS

Ph3

BRUIN 322 – EHA 2026 Phase 3 Randomized Clinical Trial – PVR vs VR

RR CLL Patients who may have received a cBTKi (median 2 prior LoT)

V+R 2L+
(post BTKi)
39.7 mo
mPFS

Pirto
(BRUIN 321)
14m
mPFS

Sharman et al. 2025; Flery et al EHA 2025; Ghosh et al. AJH 2025; Davids et al. EHA 2026



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Fixed-duration pirtobrutinib plus venetoclax–rituximab versus venetoclax–rituximab for patients with previously treated CLL/SLL: A phase 3, randomized trial (BRUIN CLL-322)

Matthew S. Davids¹, Toby A. Eyre², Jennifer A. Woyach³, Lindsey E. Roeker⁴, Alessandra Ferrajoli⁵, Yucai Wang⁶, Constantine S. Tam⁶, Wojciech Jurczak⁷, Pier Luigi Zinzani⁸, Martin Simkovic⁹, Jian-Yong Li¹⁰, Francesc Bosch¹¹, Damien Roos-Weil¹², Paula Cramer¹³, Anders Osterborg¹⁴, Priyot Islam¹⁵, Ryan Jacobs¹⁶, Alan Skarbnik¹⁷, Seema A. Bhat¹⁸, Suhyun Kang¹⁹, Bastien Nguyen¹⁹, Samuel C. McNeely¹⁹, Karen Lee Chung¹⁹, Joana M. Oliveira¹⁹, Rodrigo Ito¹⁹, Paolo Ghia^{19,20}, William G. Wierda⁵

BRUIN CLL-322 Trial Design

Phase 3, Randomized, Open-Label, Global, Multicenter Trial | 22 Countries | NCT04965493

Stratified by:

- Del(17p) status (negative vs. positive)
- Prior cBTKi experience
 - Discontinuation due to PD vs.
 - Discontinuation due to other reasons vs.
 - No prior cBTKi exposure^a

Patients with R/R CLL/SLL

**R
1:1**

Pirtobrutinib + Venetoclax + Rituximab (PVR)

Fixed-Duration, 28 Cycles

- Pirtobrutinib 200 mg QD (C1–C28)
- Venetoclax 400 mg QD (C5–C28, with C4/C5 weekly ramp-up from 20 mg to 400 mg)
- Rituximab 375 mg/m² IV (C1D1), 500 mg/m² IV (C2–C6, D1)

Venetoclax + Rituximab (VR)

Fixed-Duration, 25 Cycles

- Venetoclax 400 mg QD (C2–C25, with C1 weekly ramp-up from 20 mg to 400 mg)
- Rituximab 375 mg/m² IV (C2D1), 500 mg/m² IV (C2–C7, D1)

Key Eligibility Criteria

- Confirmed CLL/SLL requiring treatment (iwCLL 2018¹)
- Age ≥18 years
- R/R disease, ≥1 prior line (may include cBTKi)
- Known del(17p) status (FISH)
- ECOG PS ≤2
- **No prior noncovalent BTKi or venetoclax/BCL2i**

Primary Endpoint

- IRC-assessed PFS (iwCLL 2018¹)

Exploratory Endpoint

- MRD (peripheral blood, clonoSEQ®)

Secondary Endpoints

- OS
- INV-assessed PFS
- TTNT
- ORR (IRC)
- Safety



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Patient Demographics & Baseline Characteristics

ITT Population

Characteristics	PVR n=321	VR n=318
Median age, years (range)	68.0 (32, 85)	67.0 (37, 87)
Male, n (%)	216 (67.3)	223 (70.1)
Region, n (%)		
Europe	149 (46.4)	141 (44.3)
North America	104 (32.4)	110 (34.6)
Asia	55 (17.1)	50 (15.7)
Australia/New Zealand	8 (2.5)	9 (2.8)
Middle East	5 (1.6)	8 (2.5)
ECOG PS, n (%)		
0-1	300 (93.5)	301 (94.7)
2	20 (6.2)	16 (5.0)
Rai stage^a, n (%)		
0-II	188 (64.2)	180 (61.4)
III-IV	105 (35.8)	113 (38.6)
Median duration of disease, years (range)	8.6 (0.4, 33.7)	8.4 (0.2, 27.9)
Bulky disease^b, n (%)	116 (36.1)	107 (33.6)
High-risk features^c, n (%)		
IGHV unmutated	203 (63.2)	225 (70.8)
Complex karyotype (≥3 abnormalities)	84 (26.2)	117 (36.8)
Del(17p)	66 (20.6)	71 (22.3)
TP53 mutation	106 (33.0)	112 (35.2)
TP53 mutation and/or Del(17p), n (%)	126 (39.3)	132 (41.5)

Characteristics	PVR n=321	VR n=318
Median lines of prior systemic therapy, n (range)	2 (1, 7)	2 (1, 9)
Prior lines of systemic therapy, n (%)		
1	135 (42.1)	143 (45.0)
2	90 (28.0)	88 (27.7)
≥3	96 (29.9)	87 (27.4)
Prior therapy, n (%)		
cBTKi	256 (79.8)	254 (79.9)
Ibrutinib	168 (65.6)	175 (68.9)
Acalabrutinib	64 (25.0)	57 (22.4)
Zanubrutinib	38 (14.8)	39 (15.4)
Other ^d	23 (9.0)	20 (7.9)
Anti-CD20 antibody	219 (68.2)	210 (66.0)
Chemotherapy	213 (66.4)	208 (65.4)
Other^e	75 (23.4)	76 (23.9)
Prior cBTKi experience^f, n (%)		
Discontinued due to PD	181 (56.4)	181 (56.9)
Discontinued due to intolerance	44 (13.7)	35 (11.0)
Discontinued due to other reasons	31 (9.7)	38 (11.9)
No prior cBTKi	65 (20.2)	64 (20.1)

Baseline characteristics were balanced and representative of a contemporary R/R CLL population.
~80% of patients had received a prior cBTKi.

^a Summarized for subjects with CLL (n=293, in both arms), and percentages use the number of subjects with CLL as the denominator. ^b ≥5 cm - measurable target lesion (lymph node). Patients with no measurable target lesions (lymph node) at baseline: PVR, n=30 (9.3%); VR, n=19 (6.0%) and data were missing for 1 patient in PVR. ^c Central lab test. Missing data are due to the reasons samples not collected, received out of stability, inadequate, failed testing, etc. Patients with missing data for each category in PVR and VR, respectively: IGHV unmutated, 68 vs 57; complex karyotype, 116 vs 98; Del(17p), 20 vs 30; TP53 mutation, 65 vs 55; TP53 mutation and/or Del(17p), 65 vs 52. ^d Other cBTKi included investigational drugs and orelabrutinib. ^e Other prior therapies included: other systemic therapy (PVR, n=67; VR, n=72; PI3K agent, steroids, IMiD/immunomodulator, other immunotherapies excluding anti-CD20, other molecular pathways/small molecule inhibitors, clinical trial), stem cell transplant therapy (PVR, n=7; VR, n=3); other transplant (PVR, n=1; VR, n=0); CAR-T (PVR, n=0; VR, n=1). ^f Prior cBTKi experience as reported in the EDC.

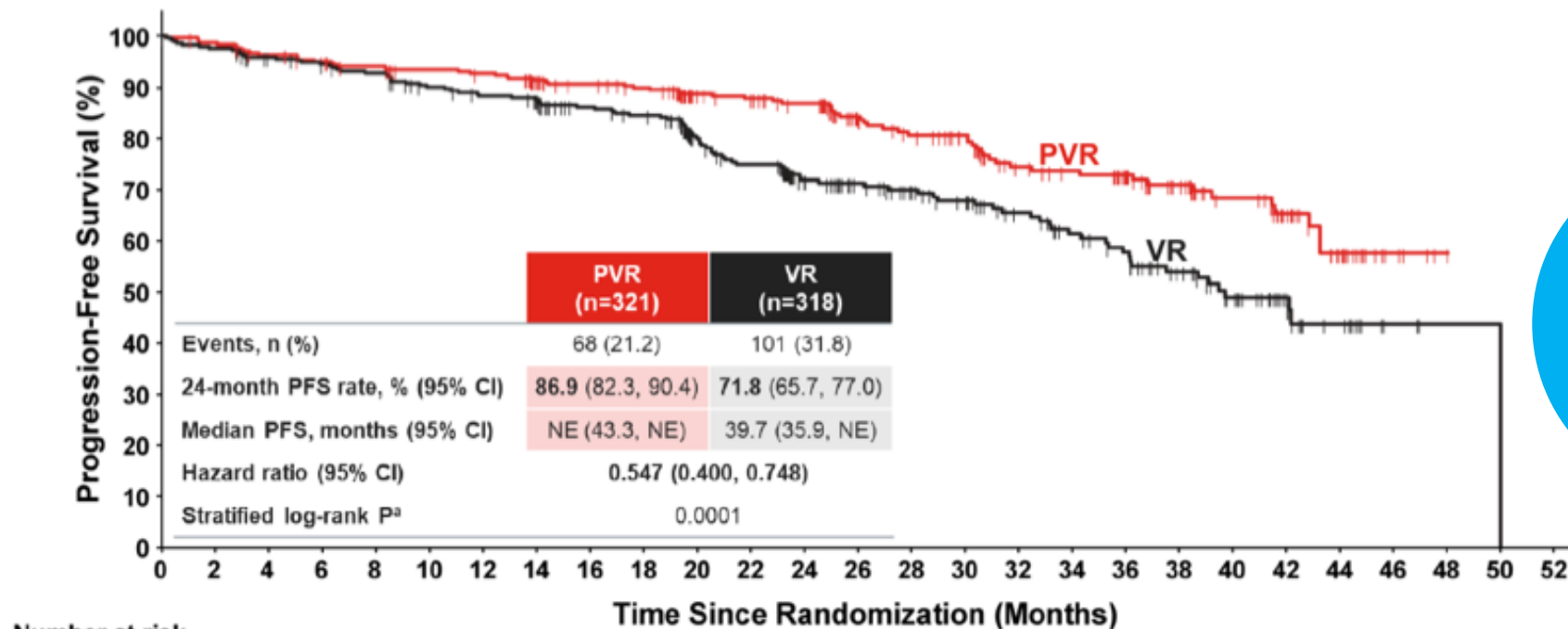
Abbreviations: cBTKi, covalent Bruton tyrosine kinase inhibitor; CAR-T, chimeric antigen receptor T-cell therapy; ECOG PS, Eastern Cooperative Oncology Group Performance Status; EDC, electronic data capture; IGHV, Immunoglobulin Heavy-Chain Variable; ITT, intent-to-treat; PVR, pirtobrutinib + venetoclax + rituximab; VR, venetoclax + rituximab.



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Progression-Free Survival by IRC (ITT population)



V+R 2L+
(post BTKi)

**39.7 mo
mPFS**

With a median follow-up of 27.3 months, PVR demonstrated superiority in IRC-assessed PFS compared with VR, reducing the risk of progression or death by 45%

^aTwo-sided p-value based on the stratified log-rank test, stratified by prior cBTKi experience and Del(17p).
Abbreviations: CI, confidence interval; HR, hazard ratio; IRC, independent review committee; ITT, intent-to-treat; NE, not estimable; PFS, progression-free survival; PVR, pirtobrutinib + venetoclax + rituximab; VR, venetoclax + rituximab.



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Adverse Events of Interest

Safety population

Adverse Event, n (%)	PVR n=316		VR n=311	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Infections ^a	249 (78.8)	107 (33.9)	224 (72.0)	72 (23.2)
COVID-19	98 (31.0)	17 (5.4)	80 (25.7)	12 (3.9)
Upper respiratory tract infection	69 (21.8)	5 (1.6)	64 (20.6)	6 (1.9)
Pneumonia	56 (17.7)	35 (11.1)	46 (14.8)	23 (7.4)
Neutropenia ^b	194 (61.4)	159 (50.3)	168 (54.0)	136 (43.7)
Febrile neutropenia	8 (2.5)	7 (2.2)	11 (3.5)	11 (3.5)
Thrombocytopenia ^c	84 (26.6)	31 (9.8)	84 (27.0)	34 (10.9)
Bleeding	82 (25.9)	9 (2.8)	44 (14.1)	8 (2.6)
Hemorrhage ^d	45 (14.2)	9 (2.8)	33 (10.6)	8 (2.6)
Bruising ^e	40 (12.7)	0	16 (5.1)	0
Petechiae and purpura	12 (3.8)	0	1 (0.3)	0
Atrial fibrillation/flutter	11 (3.5)	6 (1.9)	8 (2.6)	3 (1.0)
Hypertension ^f	38 (12.0)	16 (5.1)	23 (7.4)	9 (2.9)
Tumor lysis syndrome	4 (1.3)	3 (0.9)	13 (4.2)	12 (3.9)



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Venetoclax monotherapy post-cBTKi

Ven mono

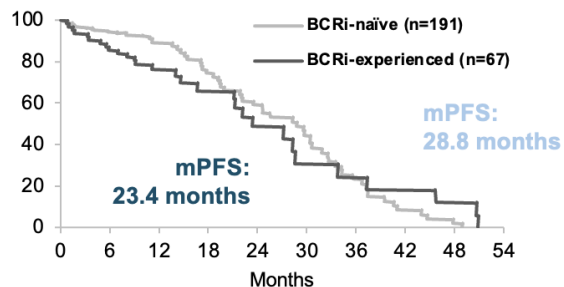
VENICE-1

Median follow-up: 49.5 months

Median prior LOT: 3 (2-4) Reasons for BCRi discontinuation: both progression or intolerance
Median age years: 69 $TP53^{mut}$ 21 % - del(17p) 22% IGHV _{unmut} 37% High GC 21%
mPFS: 23.4 months mOS: not estimable

ORR 64%

PFS Stratified by Prior BCRi



VeRve

Median follow-up: 24 months

Median prior LOT: 3 (1-10), including ibr Reasons for Ibrutinib discontinuation: both progression or intolerance
Median Age (years): 63.5 $TP53^{mut}$ 36% del(17p) 34% IGHV _{unmut} 34%
24 months PFS: 62.5% 24 months OS: 73.2%

ORR 76%

Estimated 24-mo PFS and OS

24-mo **PFS** 62.5%
24-mo **OS** 73.2%

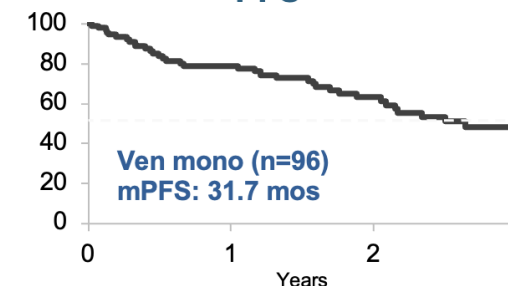
CORE

Median follow-up: 20,7 months

Median prior LOT: 2L (26%); 3L (34%); 4L+ (40%) Reasons for cBTKi discontinuation: progression only
Median Age (years): 71.8 $TP53^{mut}$ /del(17p) 32.4% IGHV _{unmut} 79.5%
mPFS: 31.7 months mOS: NR

ORR 82%

PFS



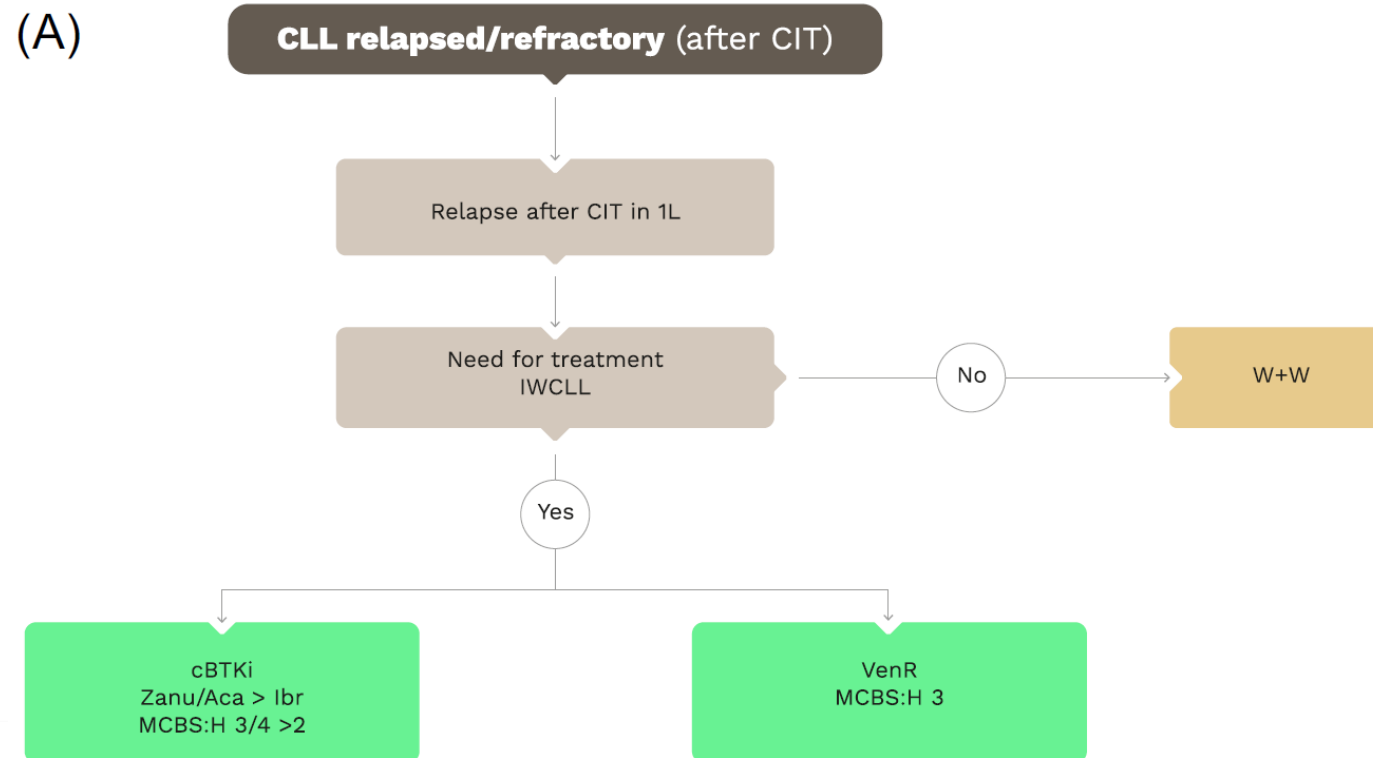
Kater AP, et al. Lancet Oncol. 2024; Schwaner I, et al. EHA 2025; Fleury I, et al. EHA 2025



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R/R treatment algorithms: relapse after CIT



Relapse after CIT

Patients relapsing after CIT should not be re-treated with chemotherapy if targeted therapies are available and accessible. Randomized trials and real-world data have shown superior efficacy of targeted agents over repeated CIT. Venetoclax + rituximab¹⁰⁷ or a second-generation covalent BTK inhibitor (cBTKi) such as acalabrutinib⁹⁵ or zanubrutinib⁹⁶ is preferred (Figure 3A).

V+R, supported by the long-term evidence from the MURANO trial, remains the only treatment option in the 2L+ setting that provides an FTD approach with a defined time off treatment

Eichhorst, B et al. HemaSphere 2026; 10:e70403

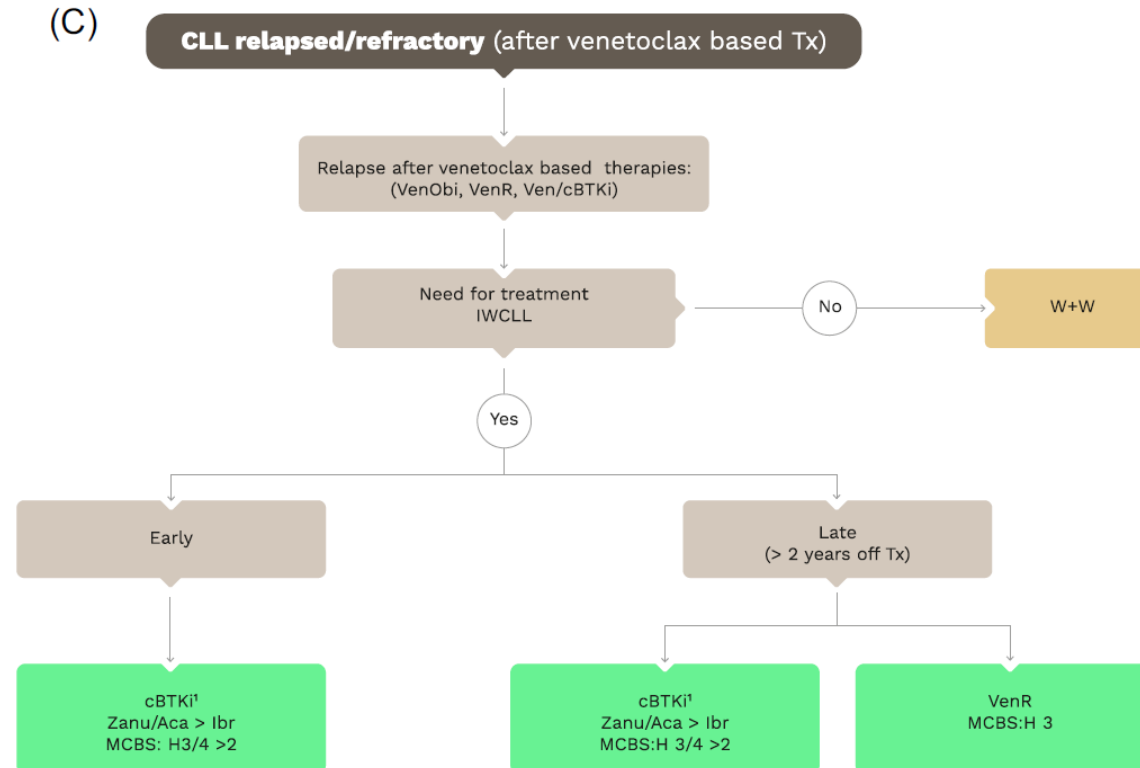


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R/R treatment algorithms: relapse after 1L Ven

(C)



¹ In case of previous failure of a combination of Ven + cBTKi

Relapse after time-limited treatment venetoclax

Re-treatment with a venetoclax-based regimen, especially venetoclax + rituximab, is feasible in selected patients who have had a durable prior response.^{90,107,113,114} Re-treatment is more effective when the prior treatment-free interval exceeds 2 years, whereas early relapse warrants switching drug class (Figure 3C).^{107,116} In both clinical trials and in

V+R remains the only treatment option in the 2L+ setting that provides an FTD approach with a defined time off treatment

Eichhorst, B et al. HemaSphere 2026; 10:e70403

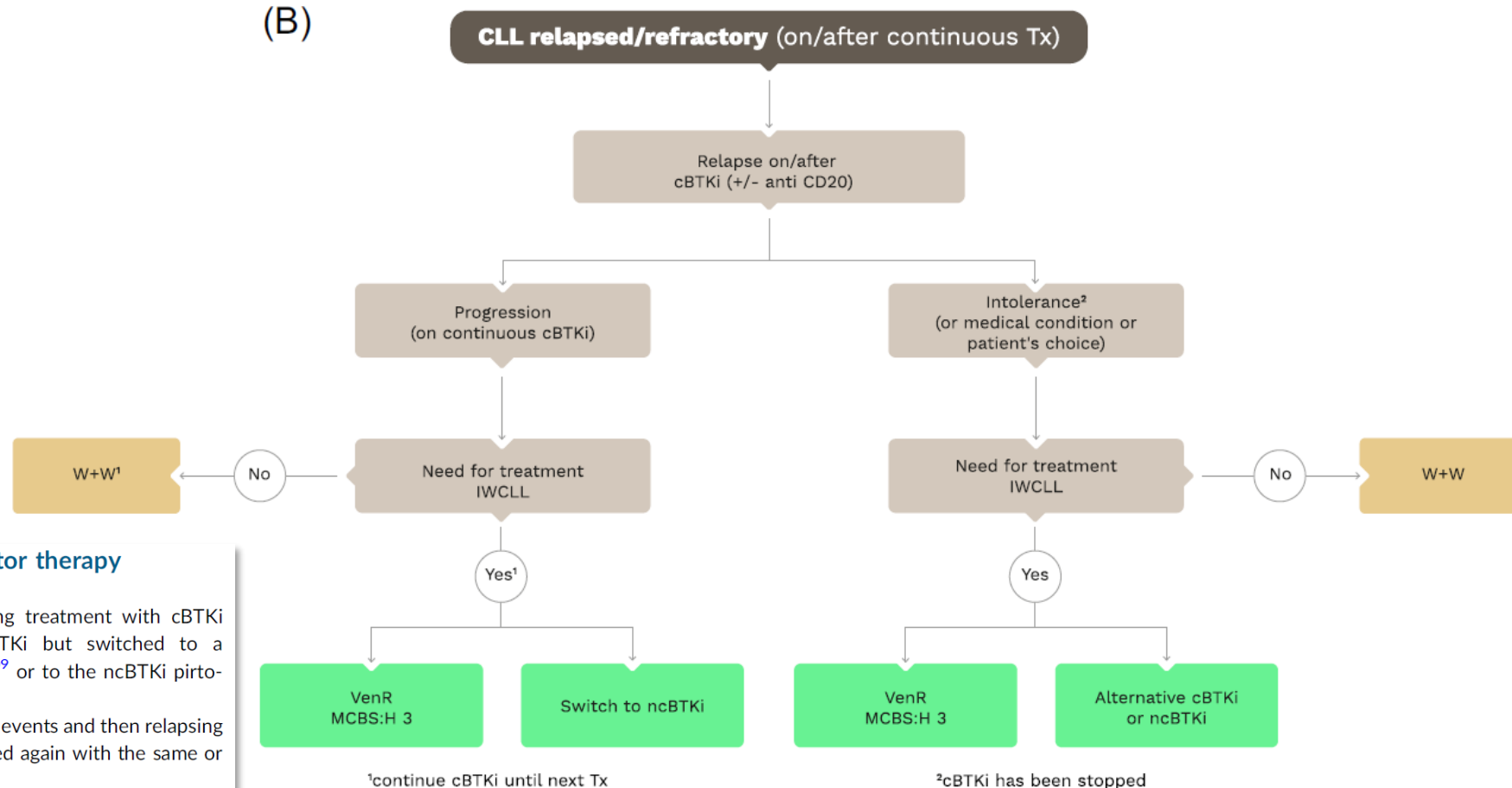


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R/R treatment algorithms: relapse after cBTKi

(B)



Relapse after covalent BTK inhibitor therapy

Patients with disease progression following treatment with cBTKi should not be exposed to another cBTKi but switched to a venetoclax-based regimen (Figure 3B)^{108,109} or to the ncBTKi pirtobrutinib (approved in this setting).

Patients stopping cBTKi due to adverse events and then relapsing after a period of observation may be treated again with the same or another cBTKi or ncBTKi¹¹⁰⁻¹¹²

Studies have reported overall response rates (ORRs) of 70%–80% for venetoclax after cBTKi failure, with improved outcomes versus idelalisib or CIT.¹¹³ Venetoclax+rituximab offers the advantage of time-limited treatment, and is often preferred for patients with comorbidities or intolerance to cBTKi¹¹⁴ Pirtobrutinib has shown a 69%

V+R remains the only treatment option in the 2L+ setting that provides an FTD approach with a defined time off treatment

Eichhorst, B et al. HemaSphere 2026; 10:e70403

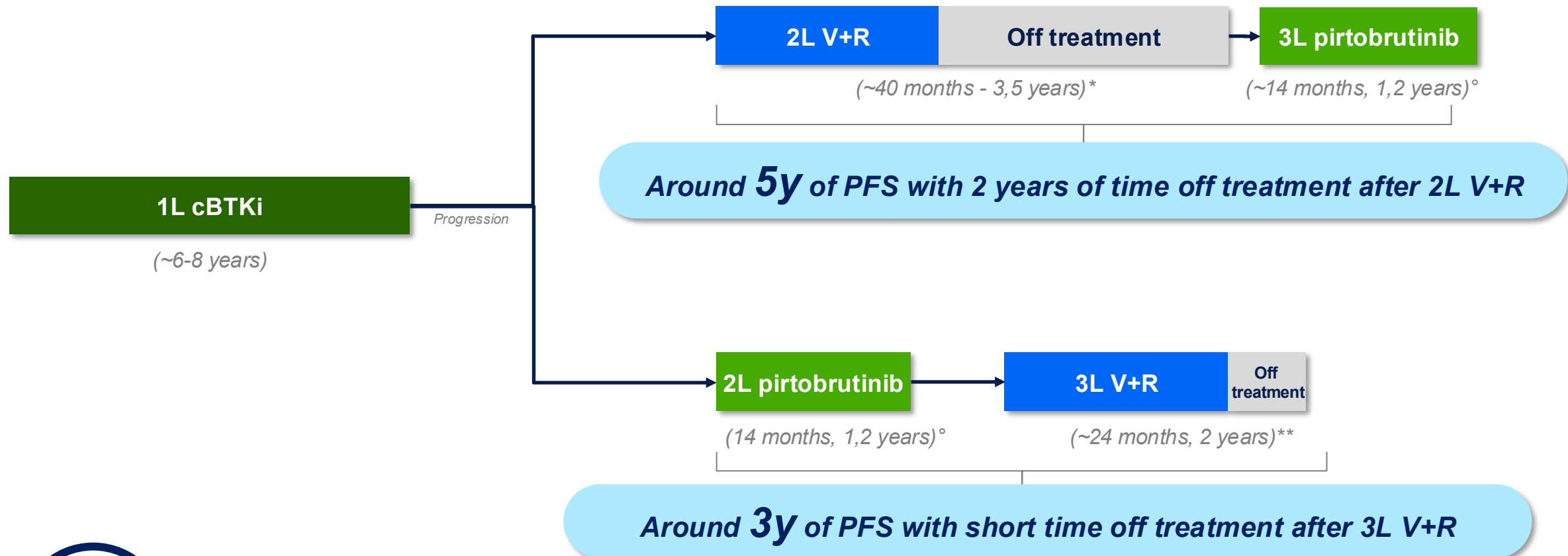


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Sequencing strategies in the R/R setting



V+R remains the only treatment option in the 2L+ setting that provides an FTD approach with a defined time off treatment

*BRUIN 322 – Davids et al. 2026; ** Thompson et al. 2024; °BRUIN-321 – Sharman et al. 2024



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Key takeaways

Venetoclax si conferma la backbone therapy nella CLL con i regimi V+X, sia nel setting di prima linea (1L) sia in quello recidivato/refrattario (R/R)

Lo studio CLL17 segna un cambio di paradigma nella CLL, consolidando la FTD con V+X come standard di cura in 1L, con efficacia non inferiore rispetto alla terapia continuativa con BTKi

I risultati dello studio AMPLIFY su V+A ampliano il paradigma della FTD in 1L, offrendo un'opzione a durata definita anche a pazienti precedentemente non candidabili per motivi di sicurezza

L'analisi finale dello studio MURANO conferma benefici duraturi di PFS e TTNT con V+R, consolidandone il profilo di efficacia e sicurezza nel setting R/R

Studi clinici e RWE confermano l'efficacia e la sicurezza di venetoclax, in combinazione o in monoterapia, anche in pazienti pluritrattati e dopo esposizione a cBTKi

Author's opinion



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Author's own c