

MEET THE **EXPERT** *in CLL*

CREMA, 16 SETTEMBRE 2026

Sala Rotary, Ospedale Maggiore di Crema



Alessandra Tedeschi
ASST GOM Niguarda Milano

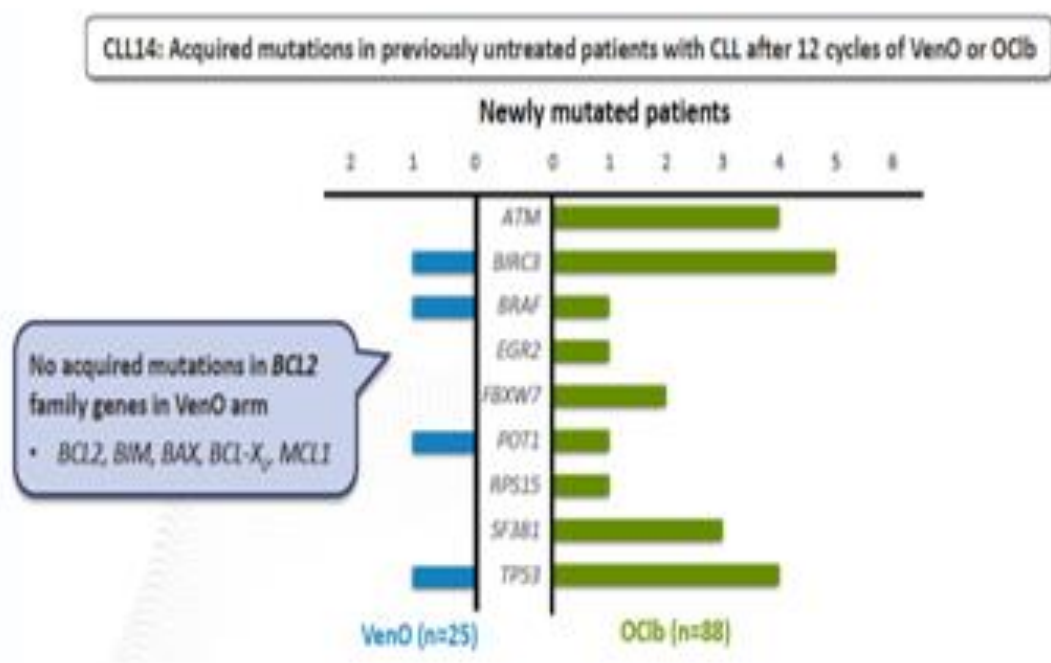
Disclosures Alessandra Tedeschi

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
AbbVie					X	x	
J & J					X	x	
Beone	x				X	x	
Lilly					X	x	
AstraZeneca						x	

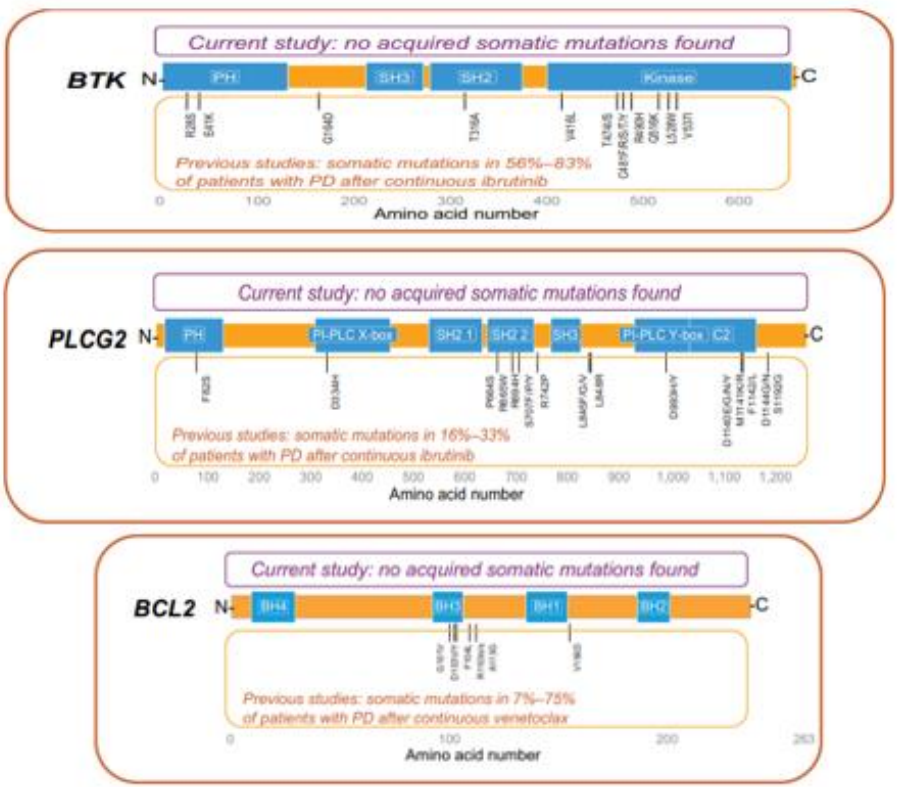
WHY FIXED DURATION therapy in TN CLL

- prolonged treatment free period
- drug exposure = less toxicity
- no resistance development allows retreatment with the same drugs

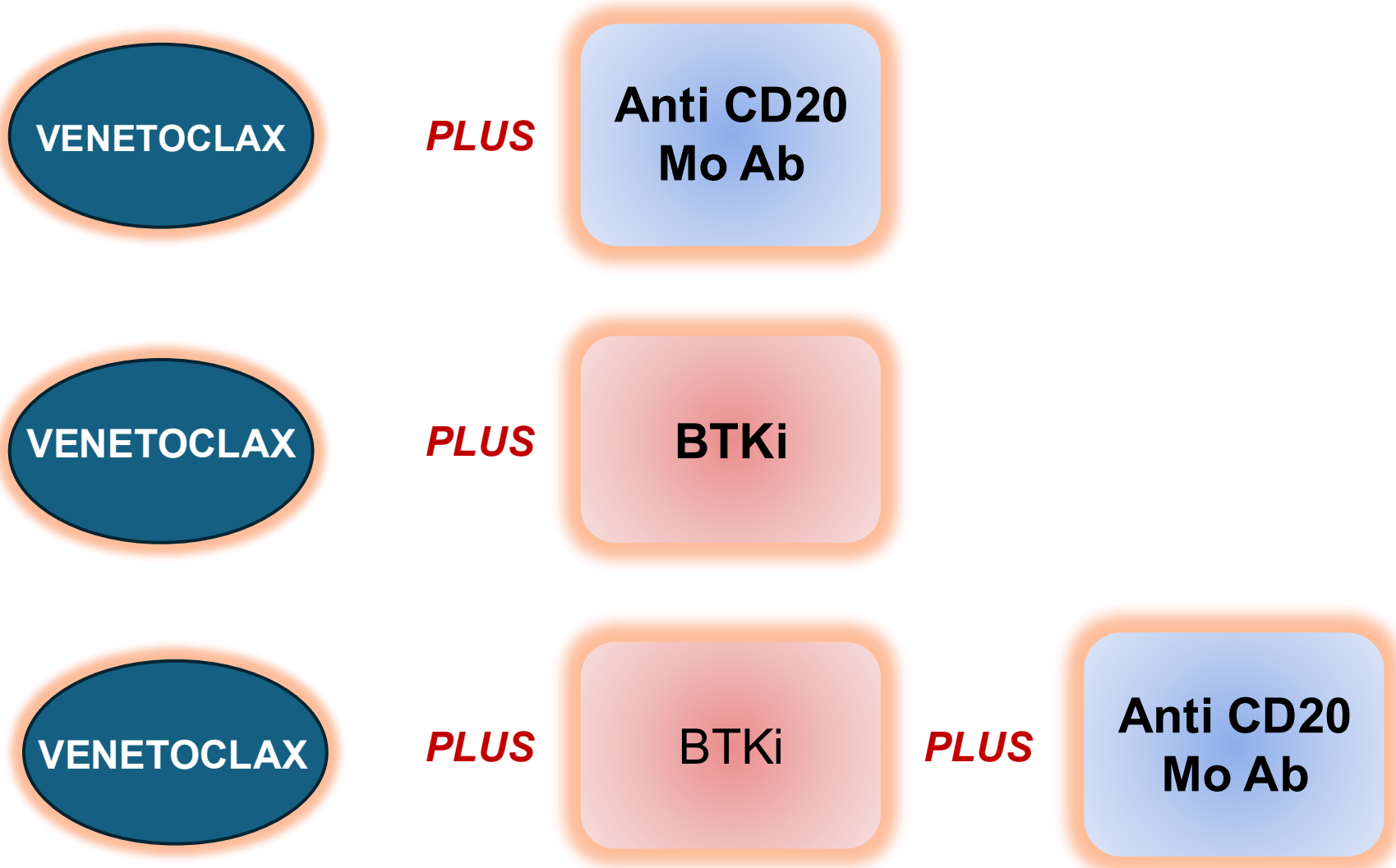
Venetoclax Obinutuzumab¹
No Resistance Development At 1 y



Venetoclax Ibrutinib²
No resistance developmentt At 1 y



FIXED DURATION therapy in TN CLL



Populations included in fixed-duration combination studies

	Median age <65	Median age >65	del(17p)/TP53-mt
I+V	CAPTIVATE ¹	GLOW ²	CAPTIVATE ¹
V+O	CLL13 ³	CLL14 ⁴	CLL14 ⁴
A+V	AMPLIFY ⁵		
A+V+O	AMPLIFY ⁵		Phase II ISS* ⁶

+
all comers
CLL17
*Al Sawaf ASH 2025
oral presentation*

There are no head-to-head trials for these treatments. This slide is intended to provide an overview of patient characteristics only. Cross-trial comparison should not be inferred.

*Study investigated A+V+O only.

A, acalabrutinib; I, ibrutinib; ISS, investigator-sponsored study; O, obinutuzumab; V, venetoclax.

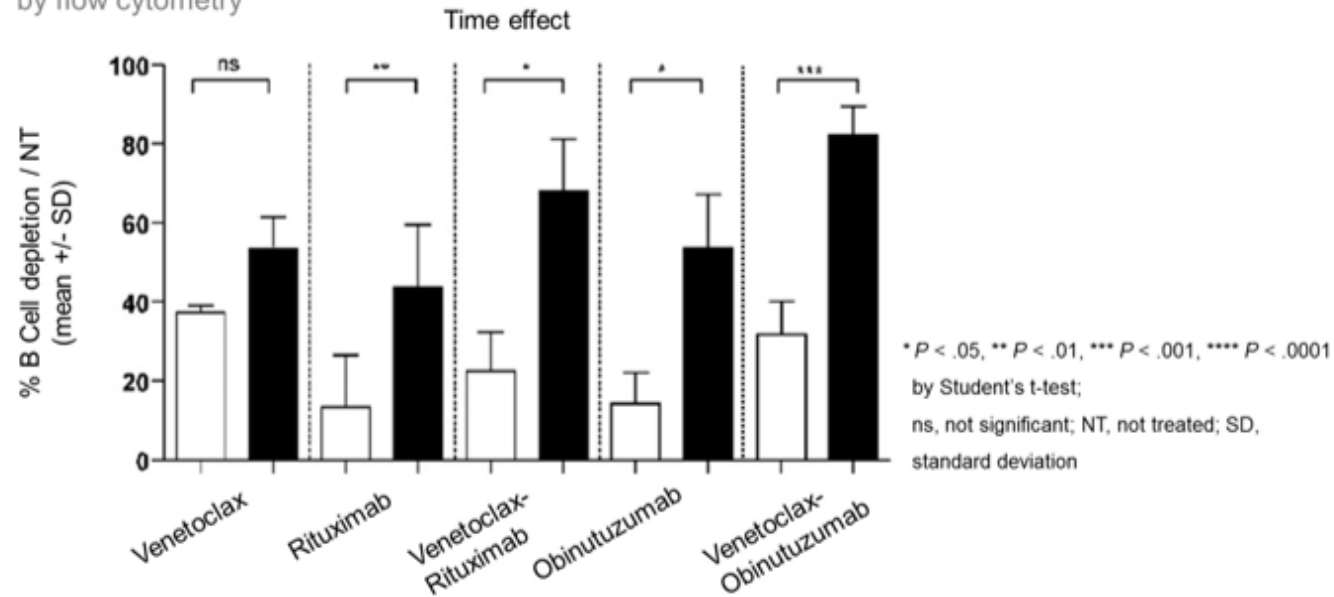
1. Tam CS, et al. Blood 2022;139:3278–3289; 2. Kater AP, et al. NEJM Evid 2022;1:EVIDoa2200006; 3. Eichhorst B, et al. N Engl J Med 2023;388:1729–1754; 4. Fischer K, et al. N Engl J Med 2019;380:2225–2236; 5. Brown JR, et al. N Engl J Med 2025;392:748–762; 6. Davids MS, et al. J Clin Oncol 2024;43:788–799.

Venetoclax + Obinutuzumab TN CLL

Rational



B-cell (isolated from primary CLL patient samples) depletion relative to untreated controls assessed by flow cytometry



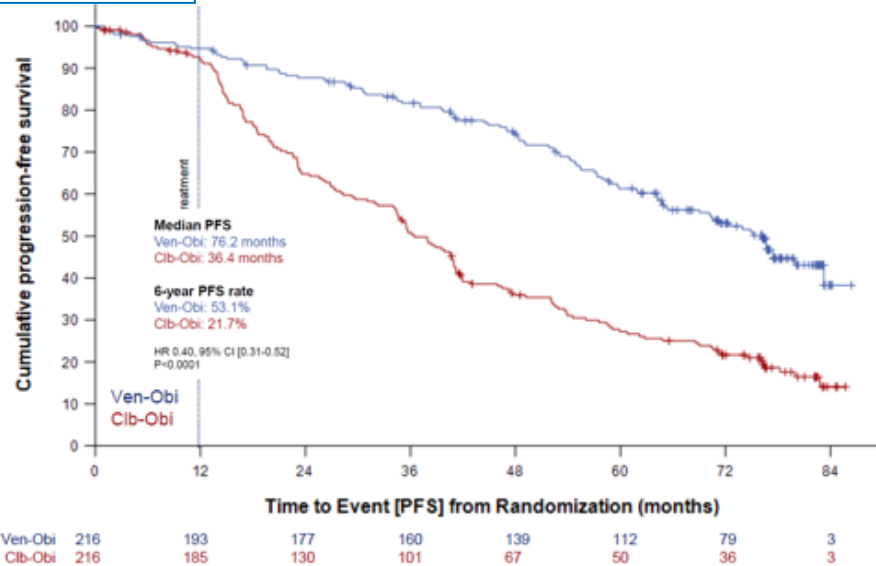
Venetoclax-obinutuzumab: prolonged PFS, high uMRD, with ~1y of tx

Elderly/Unfit

Young/Fit

CLL14 (vs O-Chl)¹ 9y FU

VO 216 pts, Median 72y
Median CIRS 9
8% del17p/TP53^m

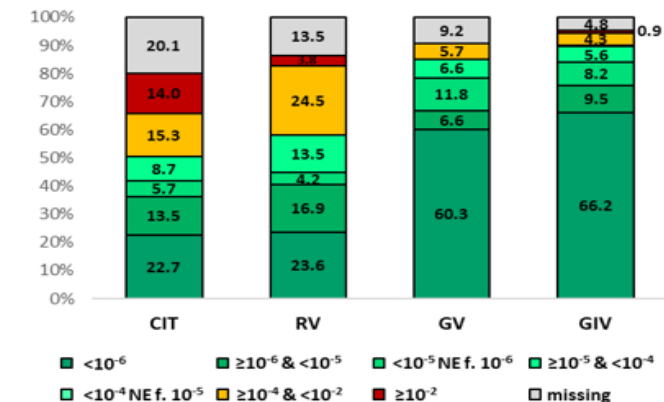
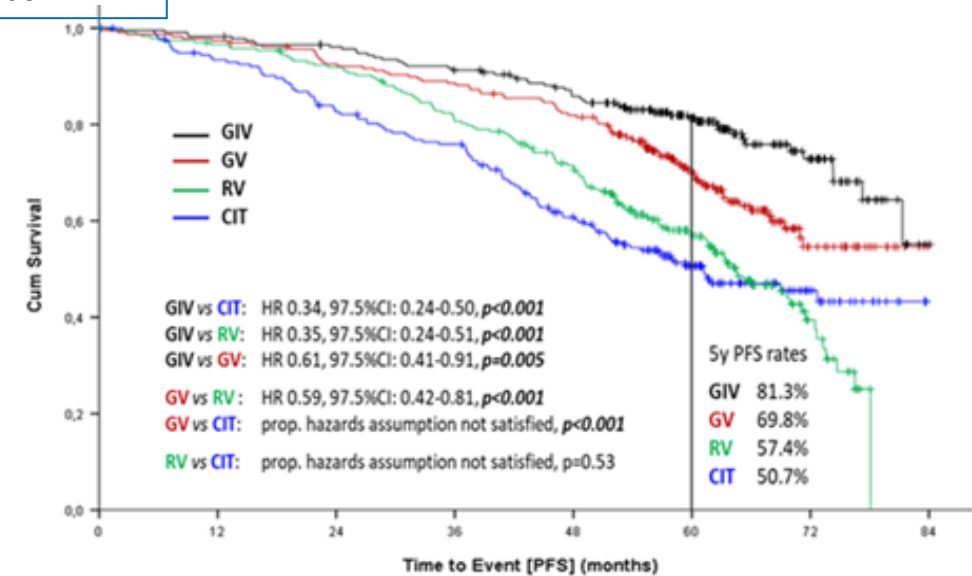


uMRD 2 m after tx completion (FU: m3)

PB MRD 10⁻⁴ by NGS: 74.5%

CLL13 (vs IVO, VR, CIT)² 5y FU

VO 229 pts, Median 62y
Median CIRS 2
No del17p/TP53^m



¹Fisher et al, EHA 2026 ²Furstenau et al, Blood 2026

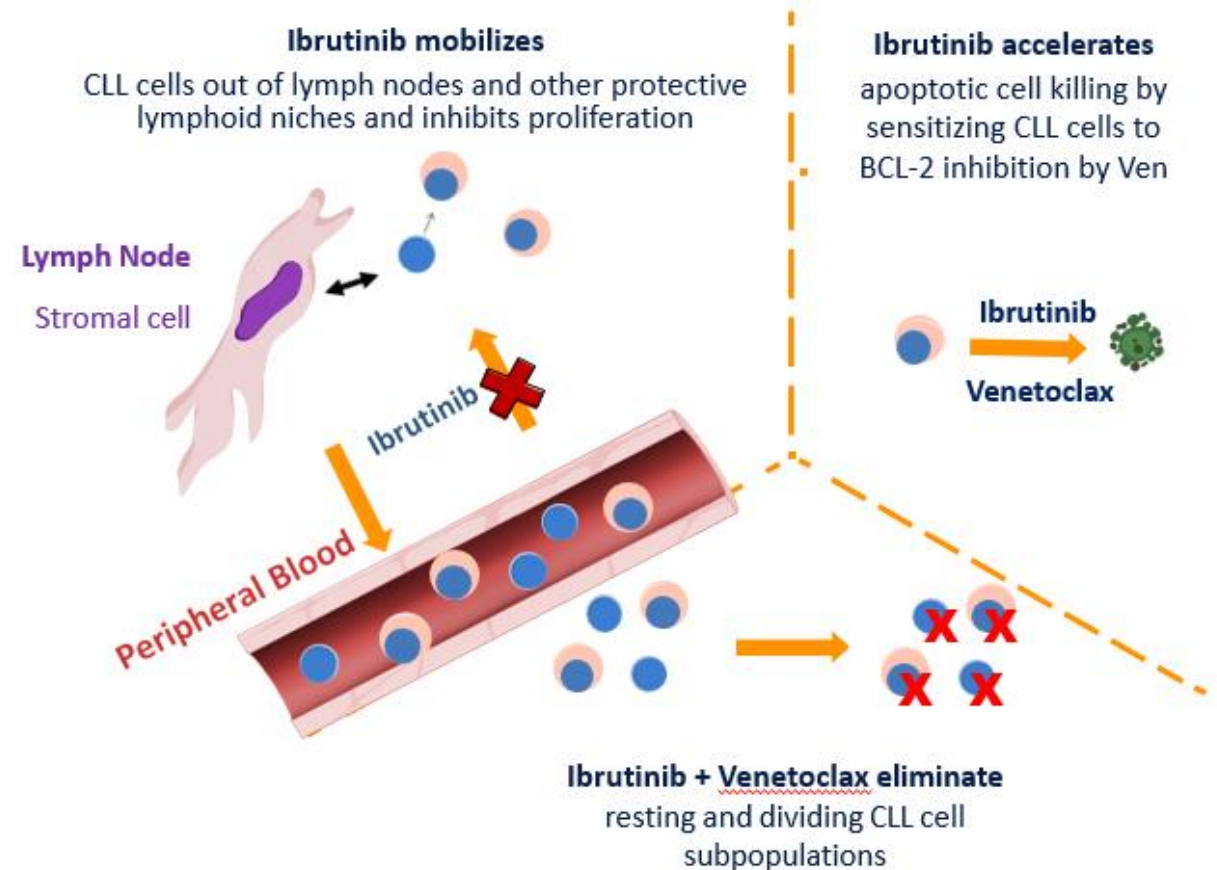
FIXED DURATION Therapy in TN CLL: Venetoclax plus cBTKi

Synergistic effect^{1,2}

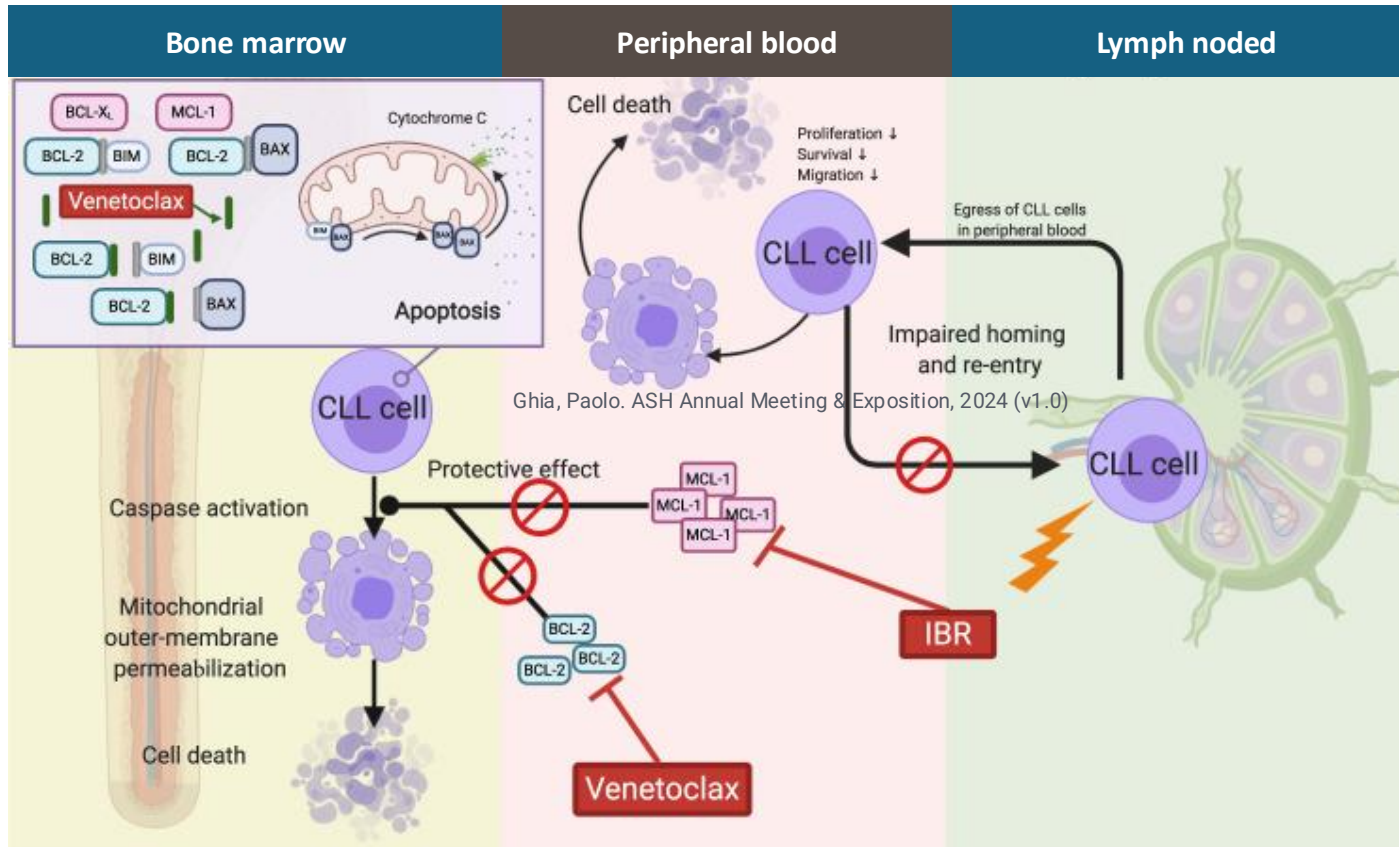


- Different sites of activity
- Ibrutinib enhances venetoclax activity
- Potentially reduces emergence of resistance mechanisms

Synergistic mechanism of action of ibrutinib and venetoclax in CLL/SLL³



Ibrutinib + venetoclax acting synergically

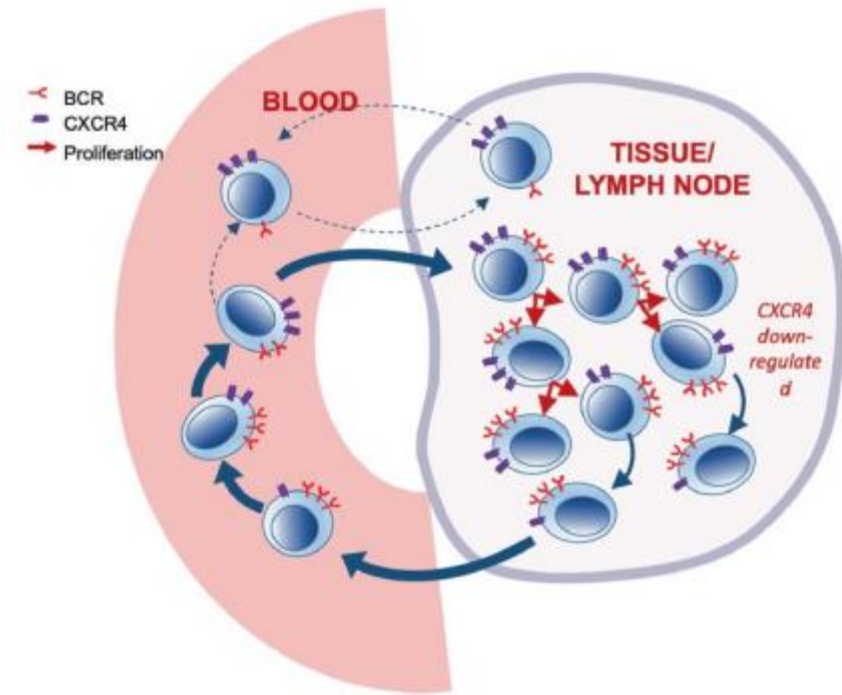


The **ibrutinib (IBR)** results in mobilization of CLL cells from niches in lymph nodes, while venetoclax targets CLL cells in the blood and bone marrow.

The **venetoclax** targets BCL-2 to induce apoptosis, but MCL-1 can protect malignant cells from mitochondrial-mediated cell death.

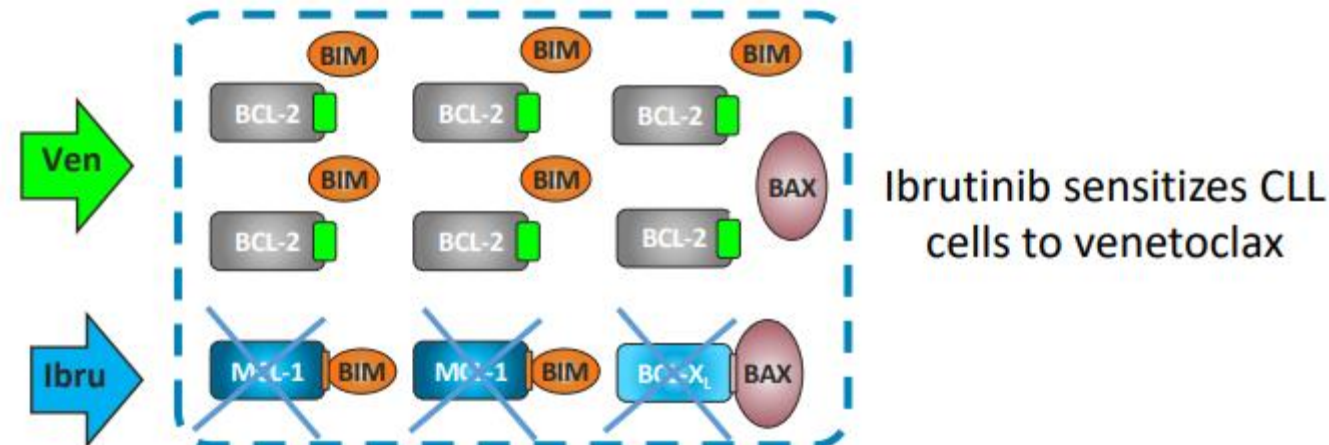
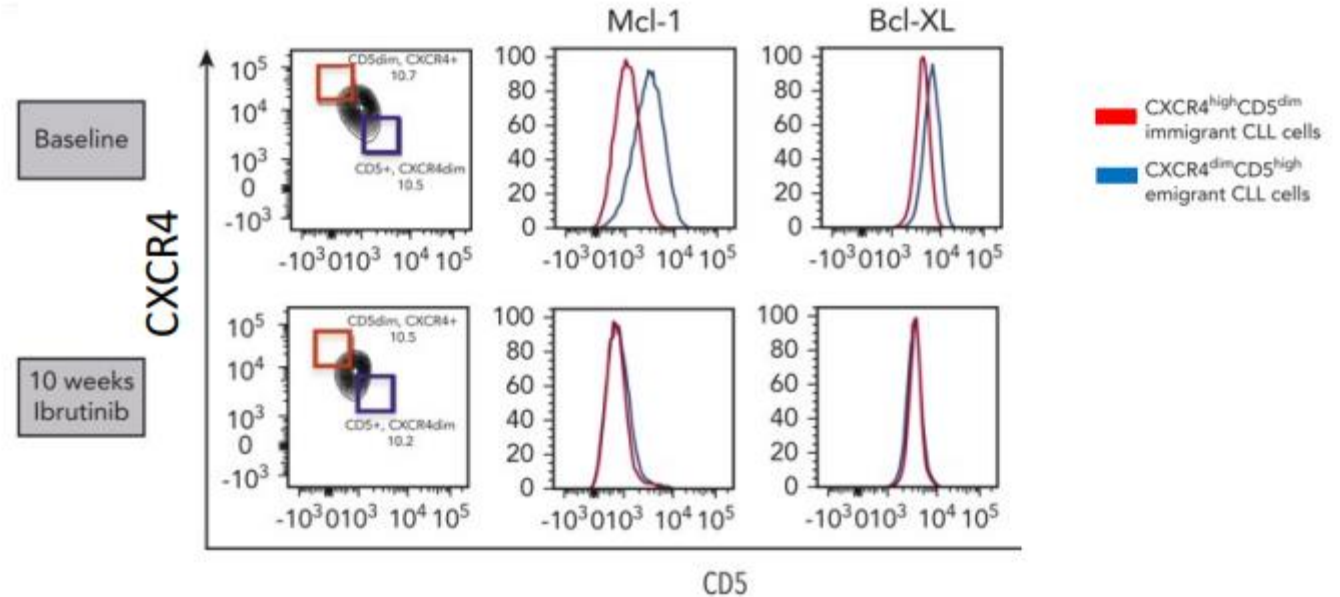
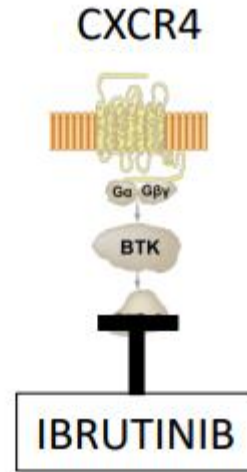
Treatment with IBR leads to a reduction in MCL-1 protein levels and results in synergy when combined with venetoclax.

Levels of the pro-survival BCL2 family members Bcl-XL and Mcl-1 collapse in LN emigrants (CXCR4dim) upon ibrutinib treatment



Emigrants (CXCR4^{dim}/CD5^{high}) recently divided and robust cells

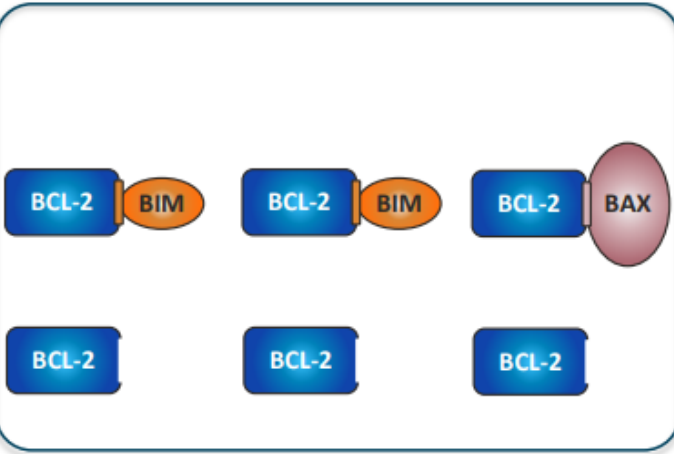
Immigrant (CXCR4^{high}/CD5^{dim}) older and less vital cells that need to immigrate back to lymphoid tissue to survive



BTK inhibition enhances mitochondrial BCL-2 dependence (“Death Priming”) accompanied by an increase in the pro-apoptotic protein BIM

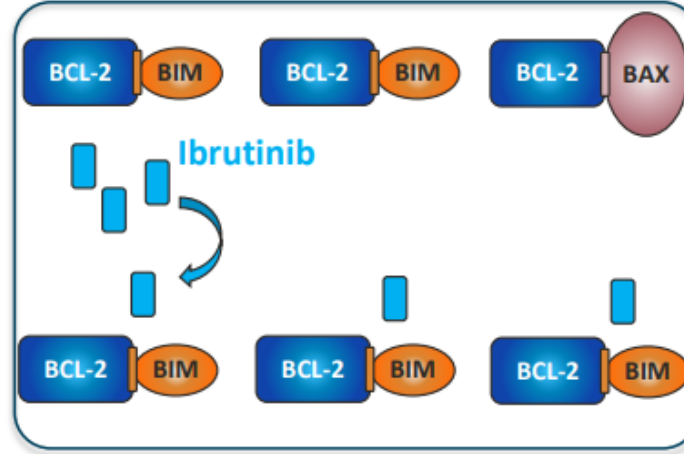
BIM

Pro-survival proteins (e.g. BCL-2) sequester pro-death proteins by binding to their **BH3 motifs**^{1,2}



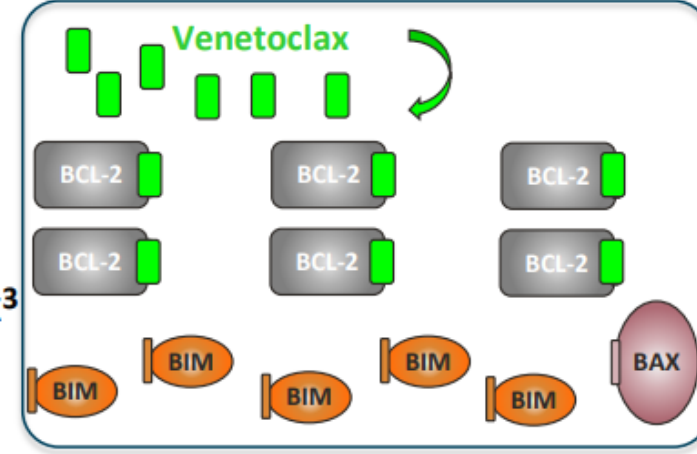
Ibrutinib

Ibrutinib increases BIM levels³ and its occupancy of BCL-2 (Primed cell with lower apoptotic threshold)

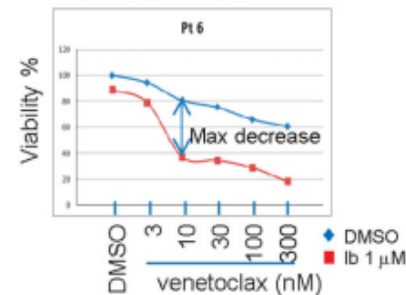


Venetoclax³

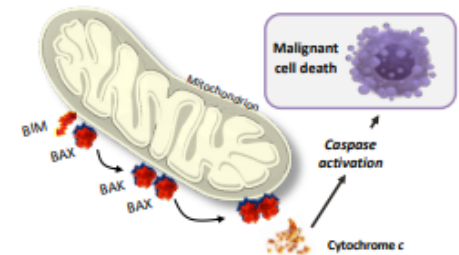
Venetoclax competes for binding to pro-survival proteins, freeing pro-death proteins⁴⁻⁶



Pretreated with ibrutinib



Apoptosis



- Plati J, et al. *Integr Biol (Camb)* 2011; **3**:279–296;
- Czabotar PE, et al. *Nat Rev Mol Cell Biol* 2014; **15**:49–63;
- Deng J *Leukemia* 2017
- Souers AJ, et al. *Nat Med* 2013; **19**:202–208 (incl. suppl.);
- Oltersdorf T, et al. *Nature* 2005; **435**:677–681;
- Tse C, et al. *Cancer Res* 2008; **68**:3421–3428.

Venetoclax + Ibrutinib: Prolonged PFS, high uMRD, with 15 m of therapy



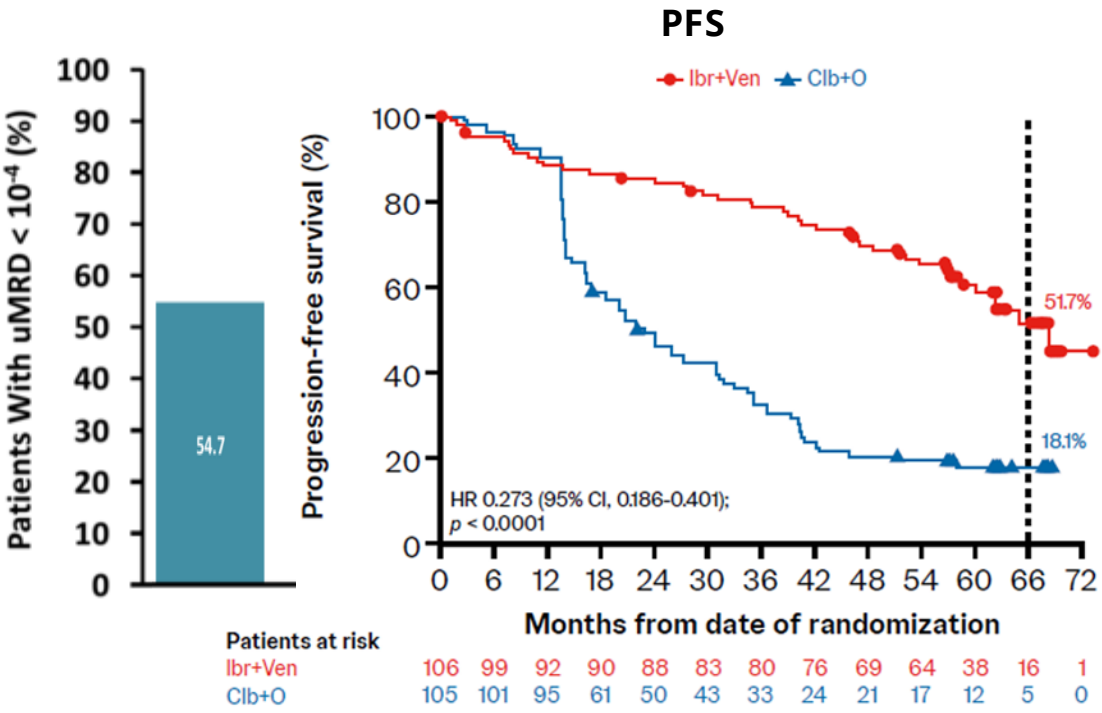
Young FIT

Elderly Unfit

GLOW phase 3 trial: Ibrutinib Venetoclax vs ClbO

106 pts, Median 71 y
Age ≥75 years: 33%
No del17p/TP53

Median age: 71y
67 m follow-up



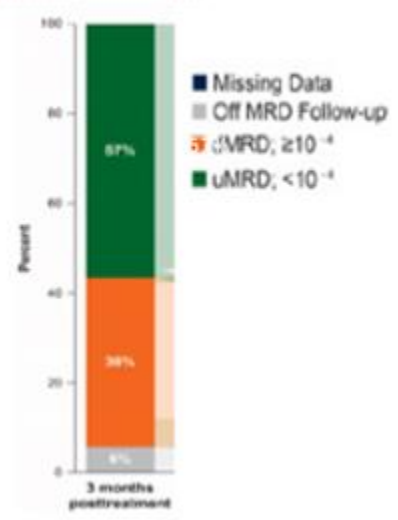
Niemman, et al. ASH 2024
Ghia et al., EHA 2025

CAPTIVATE (PCYC-1142) phase 2 trial

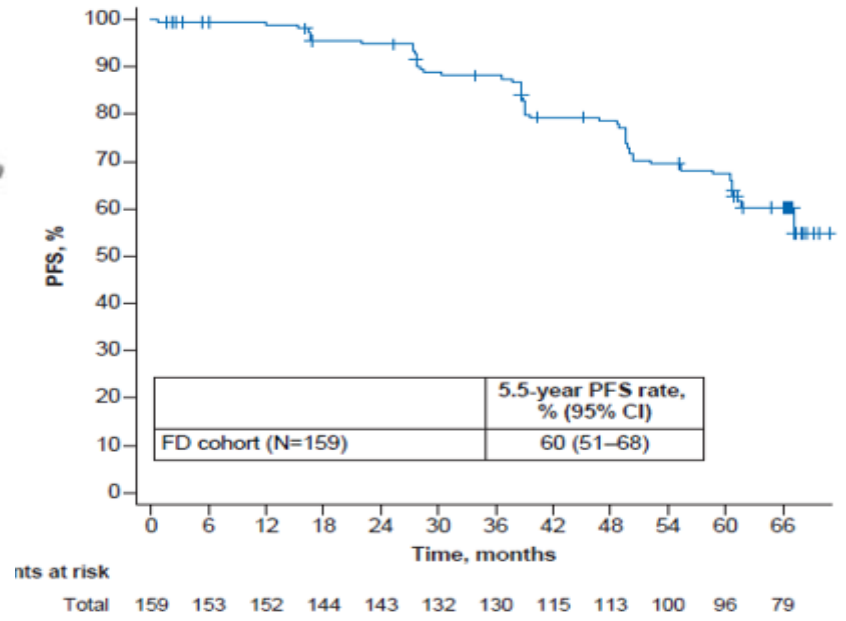
69 m median FU

159 pts, Median 60y
del17p/TP53^m 17%

uMRD Rates at PB EOT +3



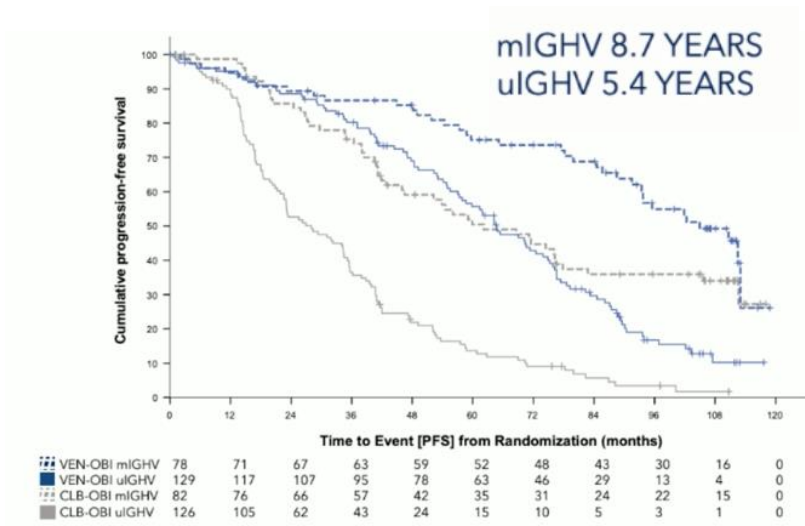
PFS (FD Cohort only)



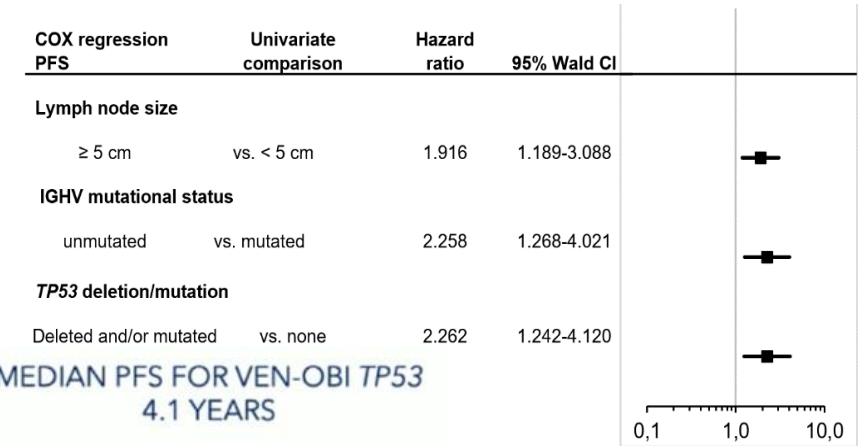
FD Venetoclax Obinutuzumab or cBTKi plus Venetoclax

□ Better PFS in mIGHV

CLL14 Ven O PFS according to IGHV

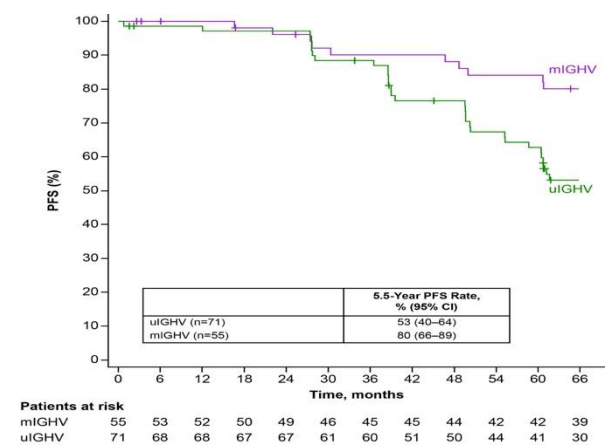


Negative prognostic factors for PFS

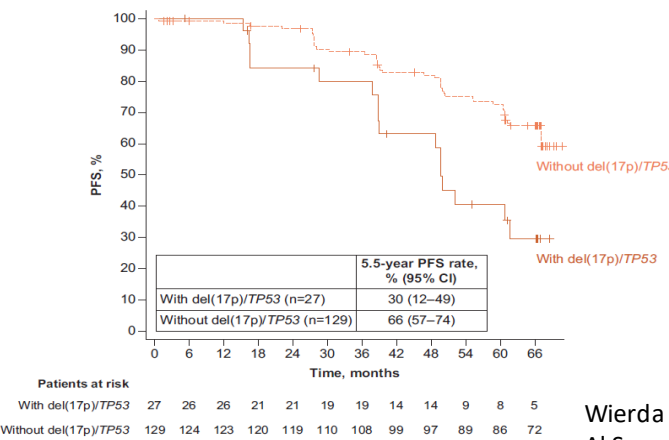


Captivate PFS according to IGHV

PFS by IGHV Status in Patients Without del(17p)/mutated TP53 (FD Cohort only)



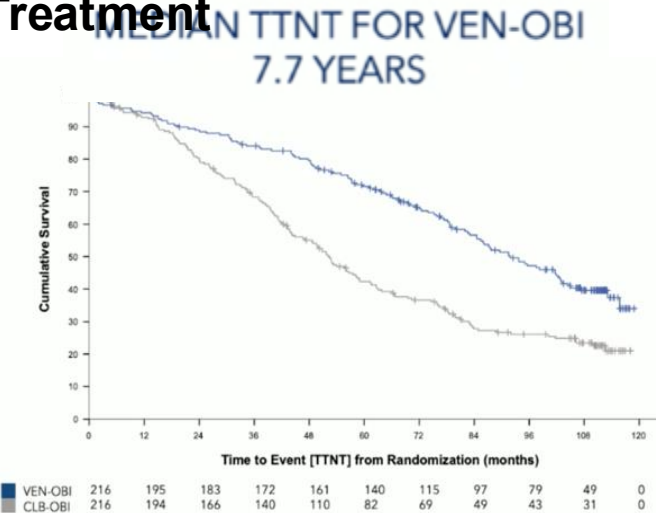
PFS by del(17p)/mutated TP53 (FD Cohort only)



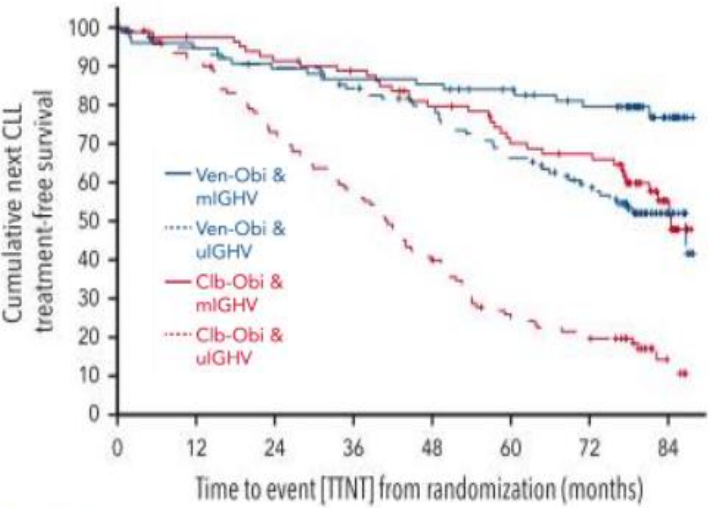
Time to next treatment

Venetoclax Obinotuzumab

- Prolonged Time To Next Treatment

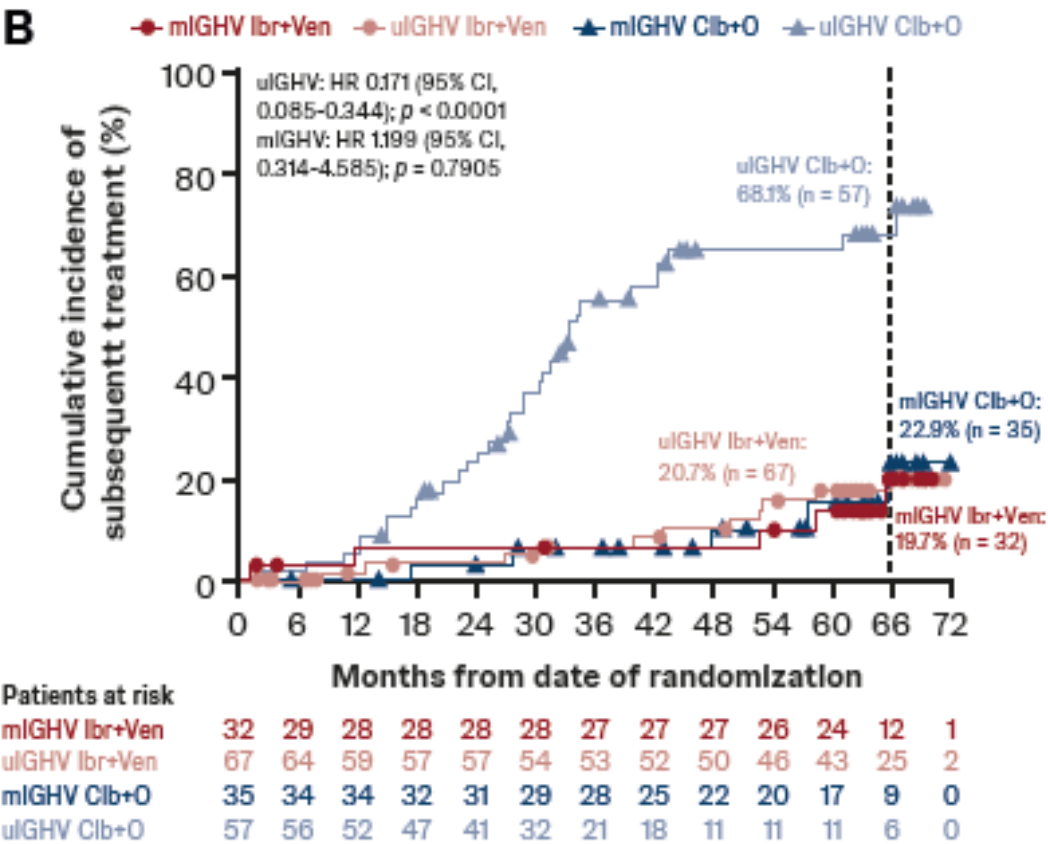


- Better Time To Next Treatment in mIGHV



Venetoclax Ibrutinib

- Prolonged Time To Next Treatment
- Same rterreatment rate mIGHV and uIGHV



Doublets with next generation BTKi?

Fixed-Duration Acalabrutinib plus Venetoclax With or Without Obinutuzumab versus Chemoimmunotherapy for First-Line Treatment of Chronic Lymphocytic Leukemia: Interim Analysis of the Multicenter, Open-Label, Randomized, Phase 3 AMPLIFY Trial

TN CLL (N=867)

Key inclusion criteria

- Age ≥18 years
- TN CLL requiring treatment per iwCLL 2018 criteria¹
- Without del(17p) or TP53^a
- ECOG PS ≤2

Key exclusion criteria

- CIRS-Geriatric >6
- Significant cardiovascular disease

Stratification

- Age (>65 vs ≤65 years)
- IGHV mutational status
- Rai stage (≥3 vs <3)
- Geographic region

AMPLIFY: randomized, multicenter, open-label, Ph 3 trial

RANDOMIZE 1:1:1

AV (14 cycles)

AVO (14 cycles)

FCR/BR (6 cycles)

Primary endpoint: IRC-assessed PFS (AV vs FCR/BR)

If primary endpoint met, secondary endpoints tested in fixed sequential hierarchy:

- 1) IRC-PFS (AVO vs FCR/BR)
- 2) uMRD (AV vs FCR/BR)
- 3) uMRD (AVO vs FCR/BR)
- 4) OS (AV vs FCR/BR)
- 5) OS (AVO vs FCR/BR)

Median Age 61 y
uIGHV: 57.4%

Median Age 61 y
uIGHV: 59.1%

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Crossover not built into protocol

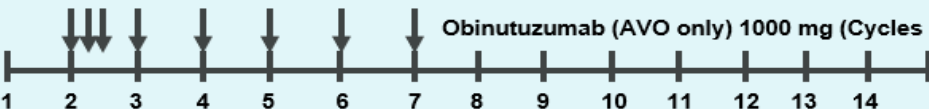
AV and AVO dosing schedule

Acalabrutinib 100 mg PO BID (Cycles 1–14)

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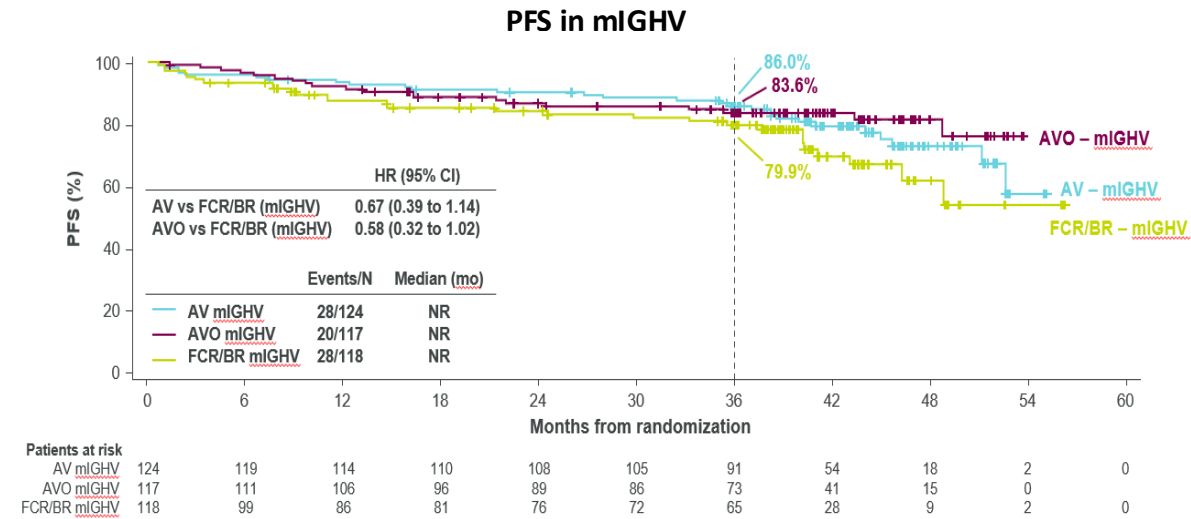
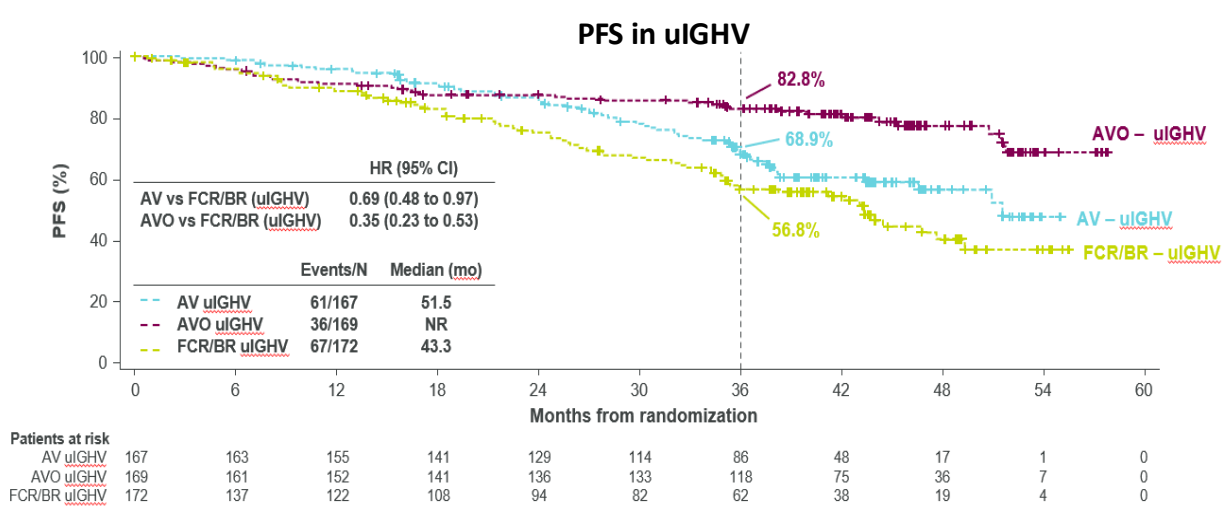
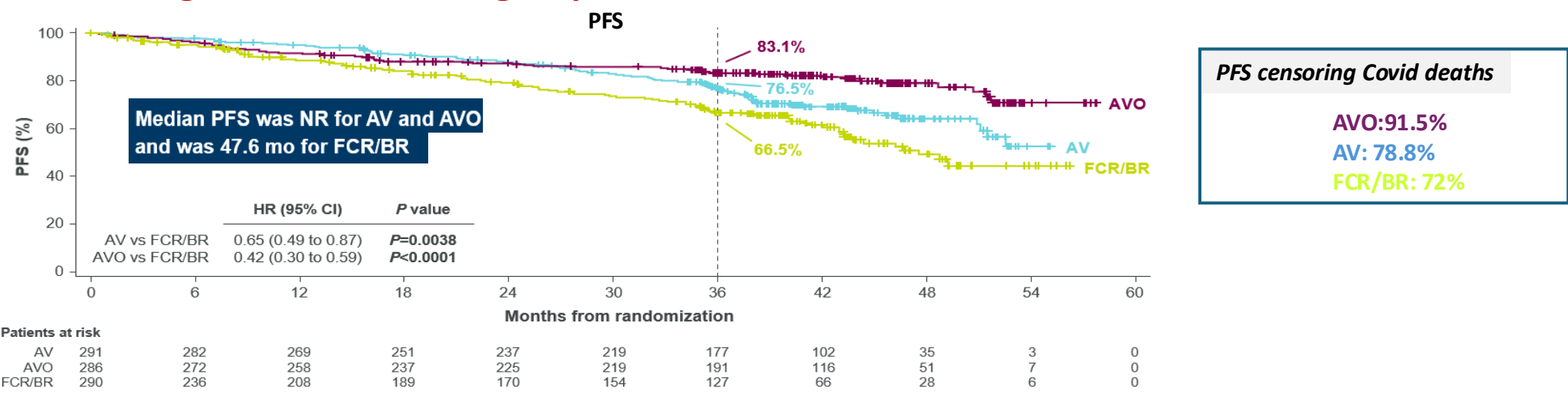
Cycles (28 days each)



NCT03836261. Data cutoff: April 30, 2024.
^aAssayed by central lab.

AV vs AVO vs FCR/BR: PFS

- Significantly improved PFS with fixed-duration AV and AVO vs FCR/BR
- Including in the uIGHV subgroup



AV vs AVO vs FCR/BR uMRD Rates (Flow Cytometry [$<10^{-4}$] in PB)

- Highest uMRD rates in the AVO arm (ITT and evaluable populations)
- Longer PFS in those with uMRD at EOT (all 3 treatment arms)

Secondary endpoint
AV vs FCR 26.8% vs 51%
Favours FCR



Key secondary endpoint timing: cycle 9, day 1 (AV arm), cycle 10, day 1 (AVO arm), and cycle 6, day 1 plus 12 weeks (FCR/BR)

Is *efficacy* the main driver of 1st line treatment choice?

	Population	Study drug(s)	Progression-free at ~4 y
RESONATE 2¹	Elderly/unfit	ibrutinib	70%
ALLIANCE²	Elderly/fit	Ibrutinib	76%
ECOG1912³	Young/fit	IR	78% (5 y)
FLAIR⁴	Young/fit	IR	86%
ELEVATE TN⁵	Elderly/unfit	acalabrutinib	78%
SEQUOIA (arm A)⁶	Elderly/fit	zanubrutinib	82%
SEQUOIA (arm C, 17p)⁷	Any	zanubrutinib	79%
CLL14⁸	Elderly/unfit	VO	74%
CLL13⁹	Young/fit	VO	82%
GLOW¹⁰	Elderly/unfit	I+V	75%
CAPTIVATE (FD cohort)¹¹	Young/fit	I+V	79%

PFS

~75% in elderly

~80% in young

With *both* cBTKi or FD

¹Burger et al, Blood 2025 ²Moreno et al, Haematologica 2022 ³Woyach et al. Blood 2024 ⁴Shanafelt et al, Blood 2022 ⁵Sharman et al, Blood 2025 ^{6,7}Tam et al, ASH 2025

⁸Fisher et al, EHA 2026 ⁹Furstenau et al, Blood 2026; ¹⁰Niemman, et al. ASH 2024

¹¹Ghia et al., EHA 2025

Is efficacy the main driver of 1st line treatment choice?

CLL17 TRIAL

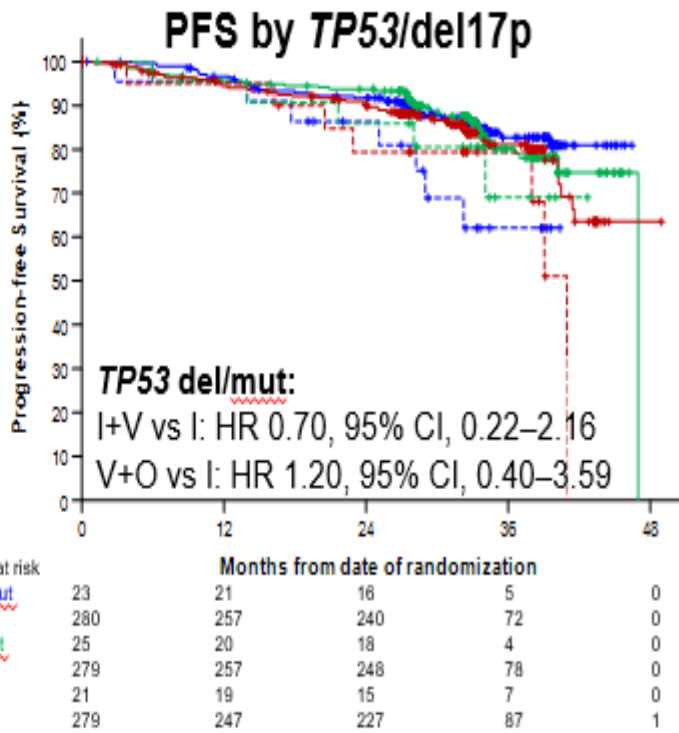
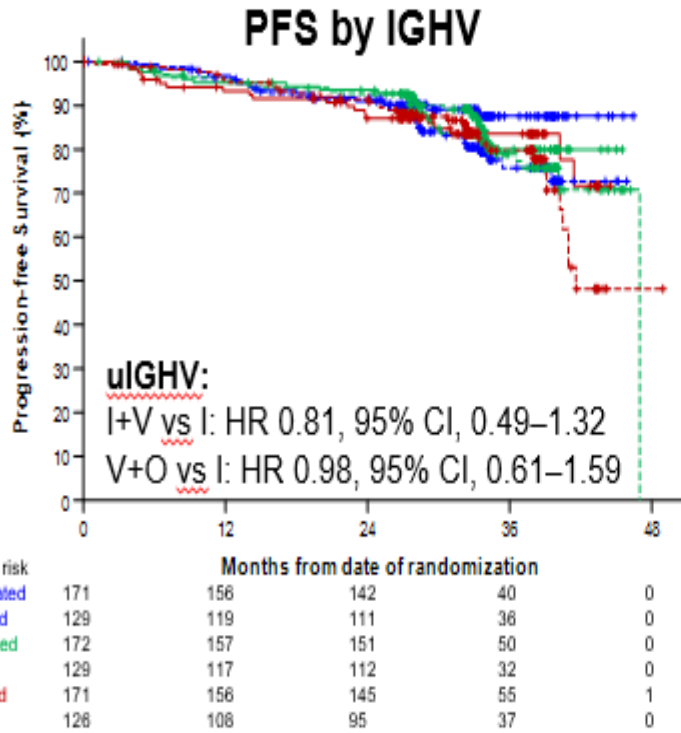
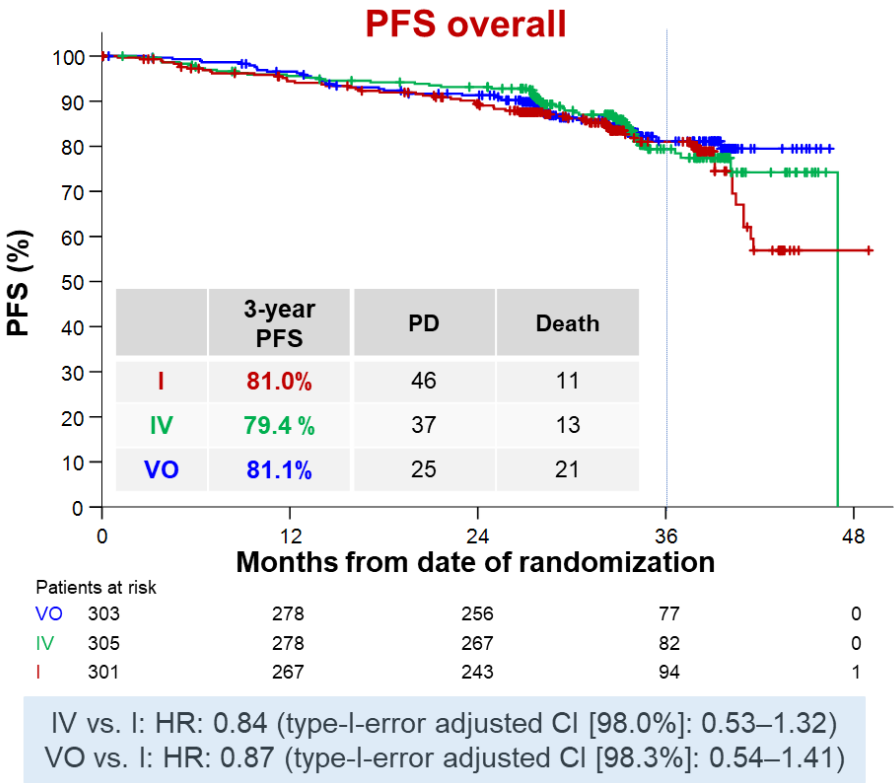
Patients with previously untreated CLL

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 split dose [D1 & D2], then D8, D15; C2–6 D1)

Ibrutinib 420 mg PO daily (C1 D1 – C15)
Venetoclax 400 mg PO daily (C4 D1 – C15)



Al Sawaf et al, NEJM 2023

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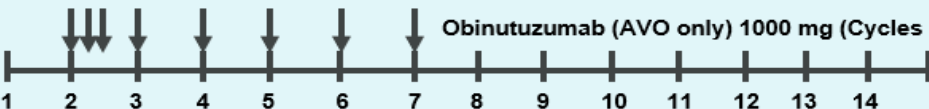
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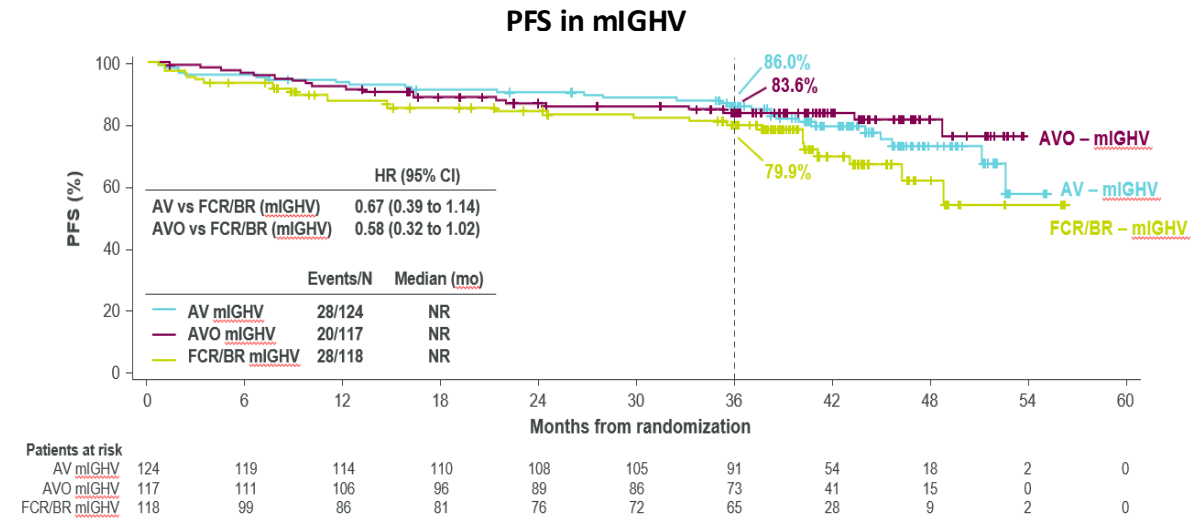
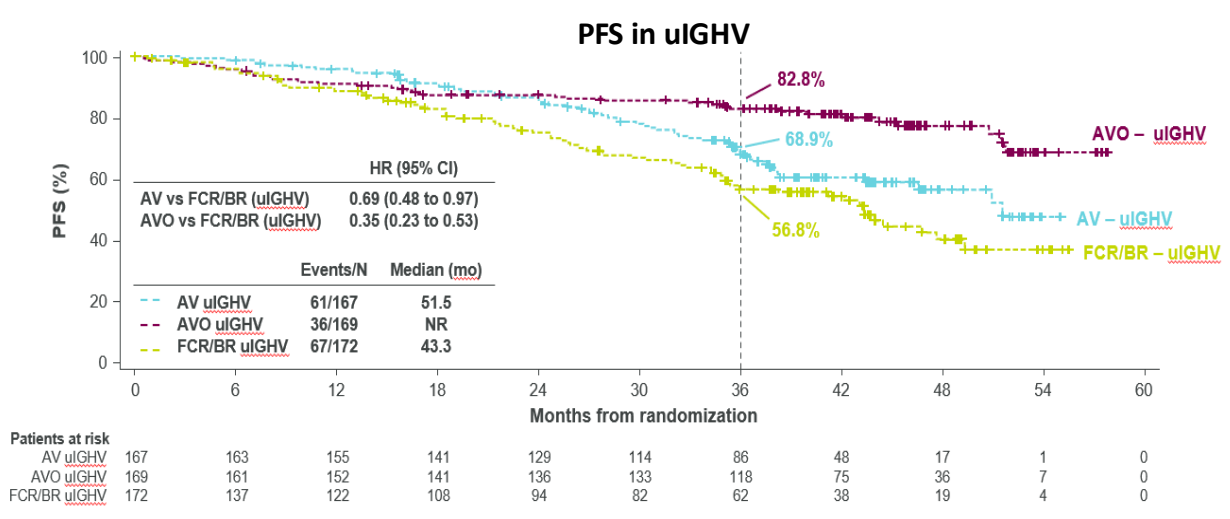
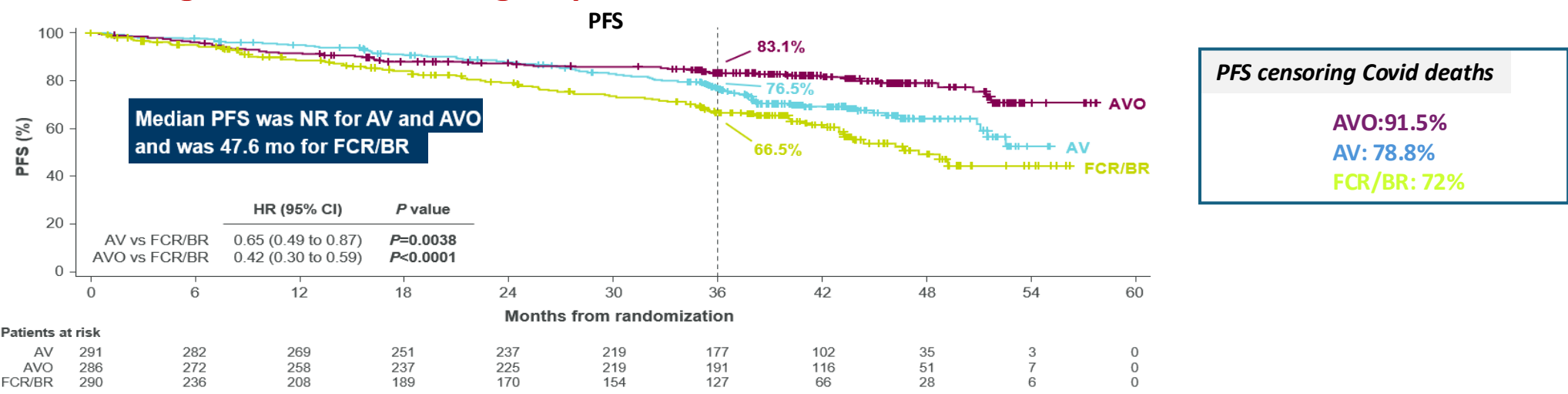
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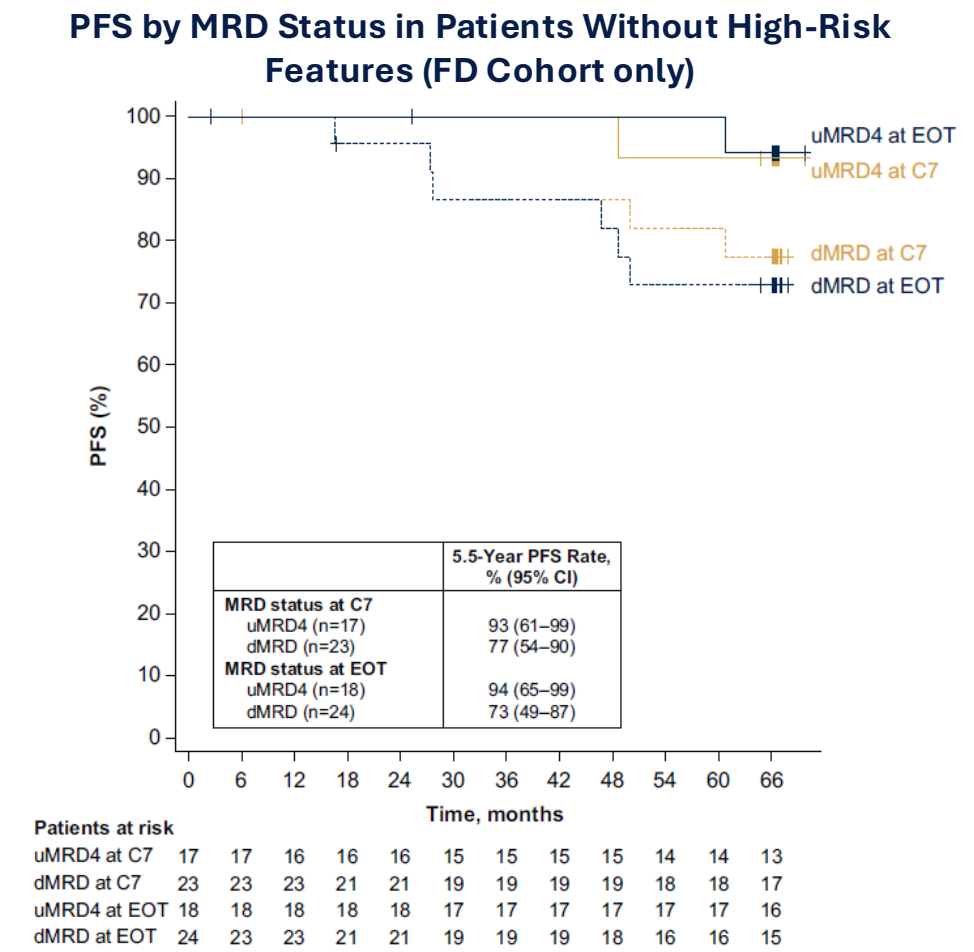
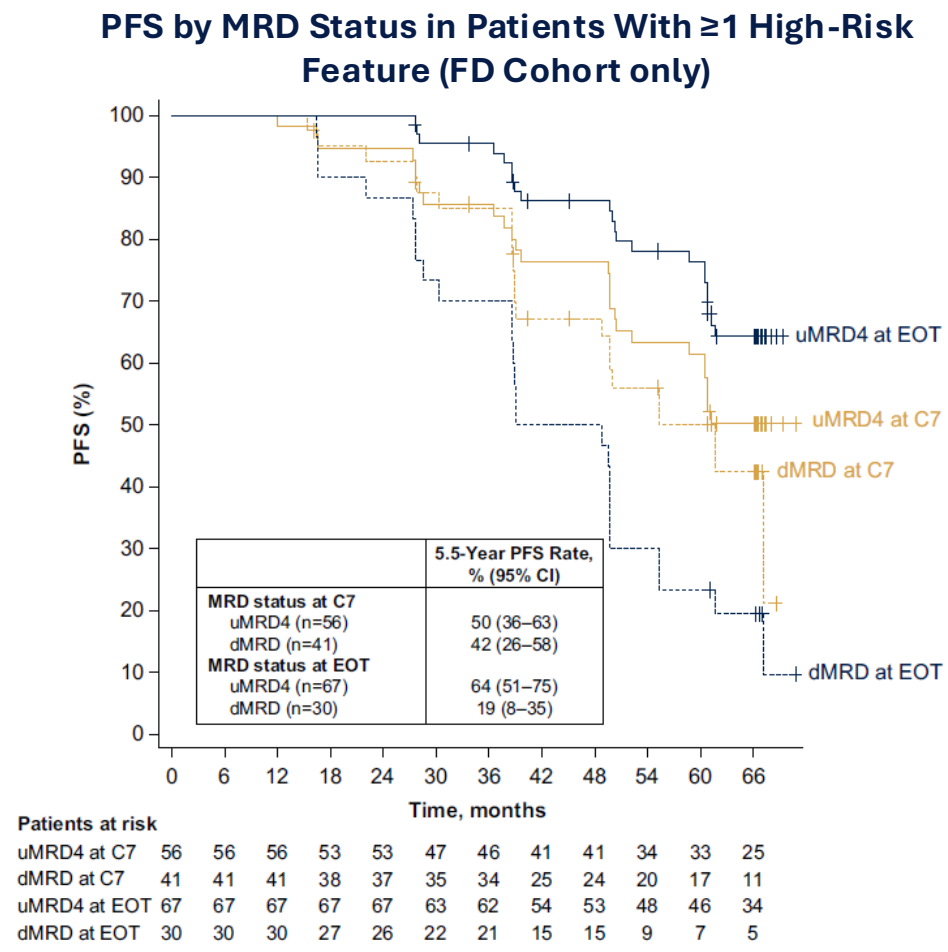


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WHY IS IMPORTANT uMRD with FD THERAPY

CAPTIVATE phase 2 study

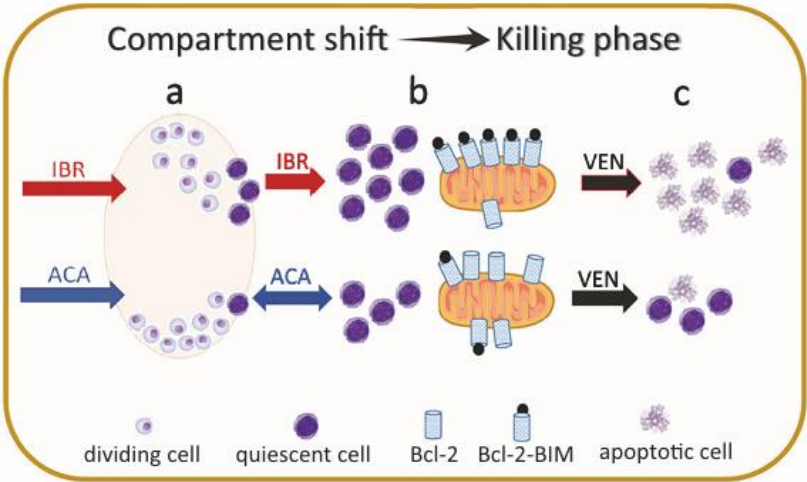
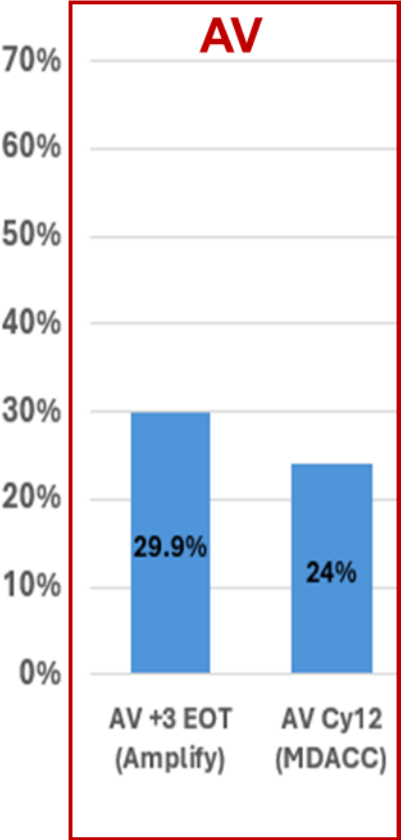
PFS according uMRD in Patients With and Without High-Risk Genomic Features



Are all the cBTKi plus Venetoclax doublets the same? ➡

No trial planned to compare BTKi plus venetoclax combinations

PB uMRD rates <10⁻⁴

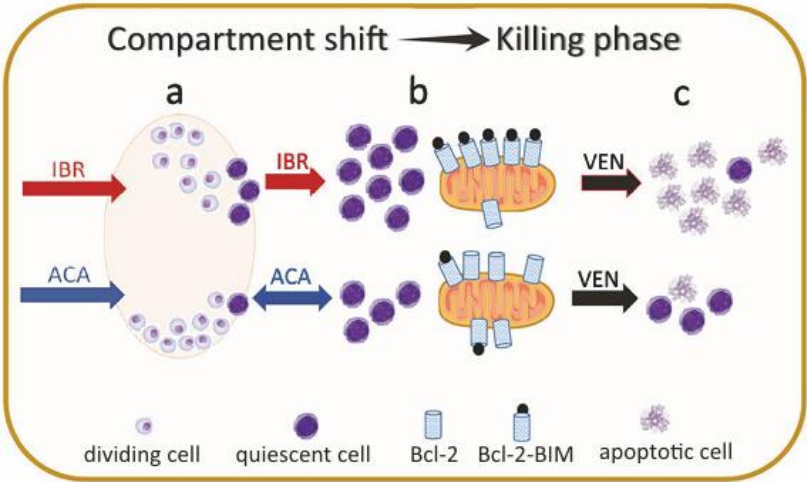
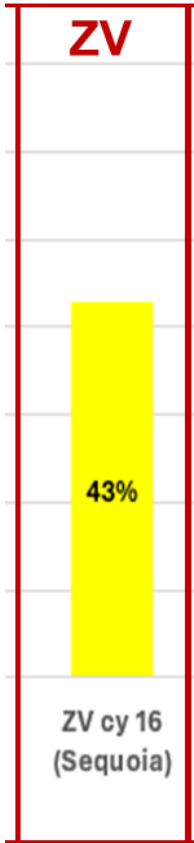


Tedeschi, Frustaci. Leukemia 2025

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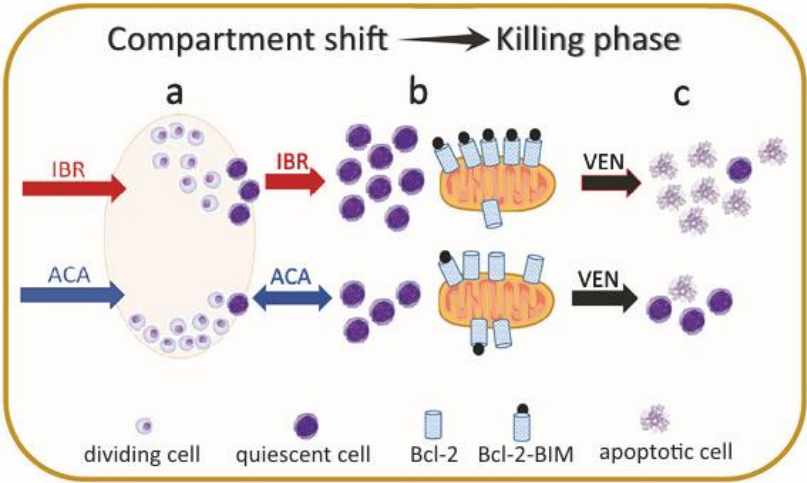
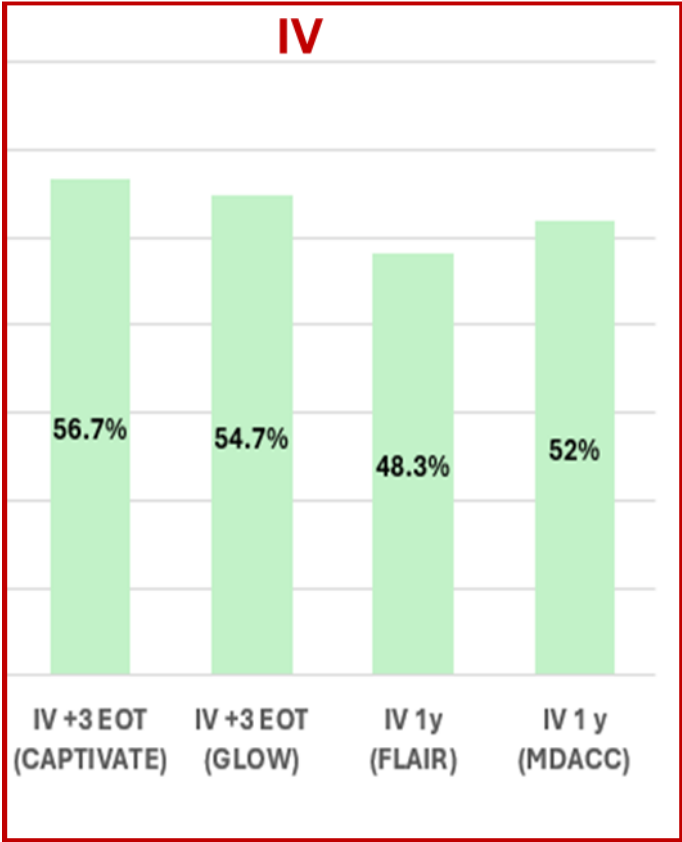


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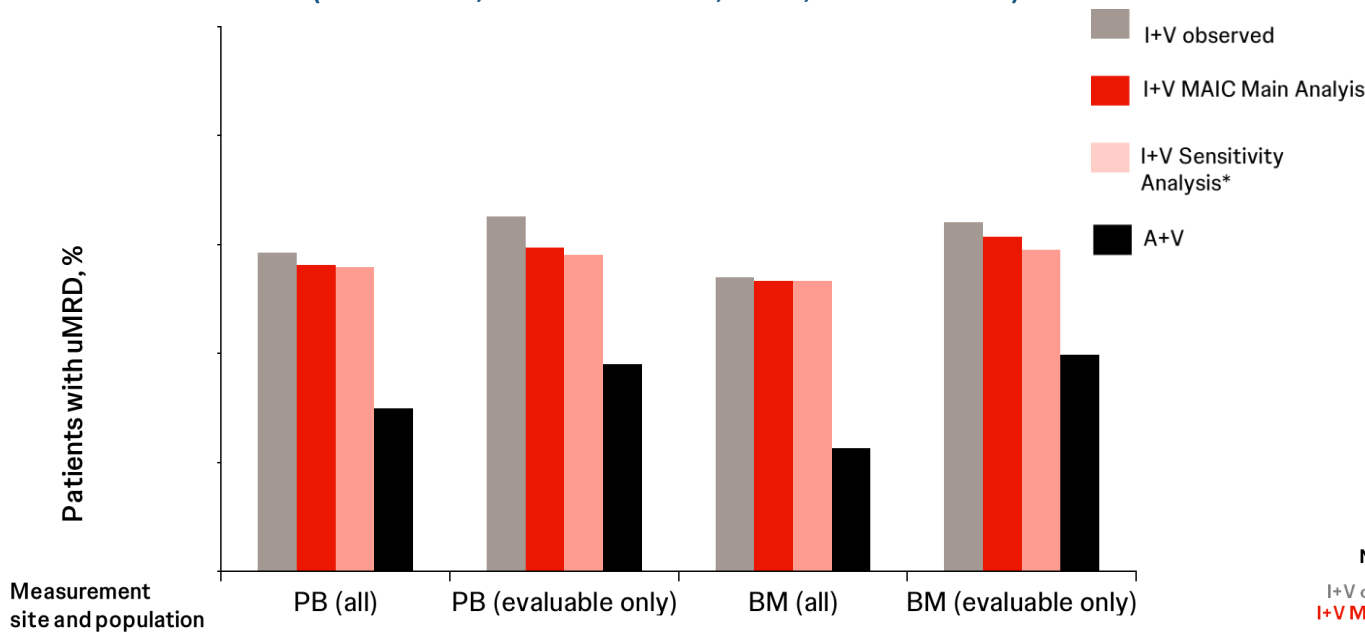
Tedeschi, Frustaci. Leukemia 2025

Cross-trial MAIC of I+V and A+V¹

Patient-level data from GLOW and CAPTIVATE were reweighted to match AMPLIFY baseline characteristics

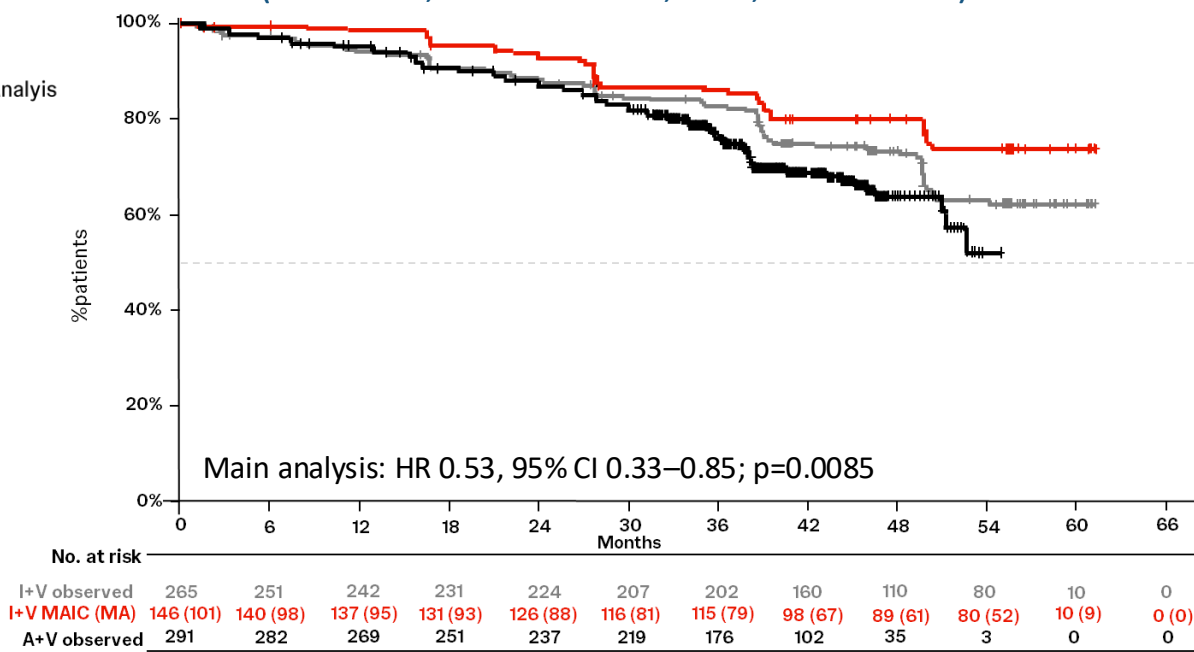
uMRD at EOT+3 months

(mFU: I+V, 55.7 months; A+V, 41 months)



PFS

(mFU: I+V, 55.7 months; A+V, 41 months)



Comparative analyses demonstrated a significantly longer PFS and higher probability of achieving uMRD at EOT+3 with I+V vs A+V

Methods of data selection, matching and comparison are described in the full poster. Numerous limitations associated with cross-trial comparisons should be considered. The data shown here are from the main analysis, which incorporates the observed and sensitivity analysis.

*Sensitivity analysis including Eastern Cooperative for Oncology Group performance status in matching.
A, acalabrutinib; BM, bone marrow; CI, confidence interval; EOT, end of trial; HR, hazard ratio; I, ibrutinib; MAIC, matching-adjusted indirect comparison; mFU, median follow-up; PB, peripheral blood; PFS, progression-free survival; uMRD, undetectable minimal residual disease; V, venetodax.

1. Munir T, et al. EHA 2025 (Abstract No, PF587 – poster).

VENETOCLAX plus OBINUTUZUMAB

✓ PROLONGED PFS

IMPACT ON PFS of

- **BULKY DISEASE**
- **del 17p**
- **CK (at 3y CLL17 trial)**

✓ PROLONGED TTNT

SIGNIFICANTLY DIFFERENT at 72m
mutated vs unmutated IGHV
curves starting to divide at 48m

VENETOCLAX plus IBRUTINIB

✓ PROLONGED PFS

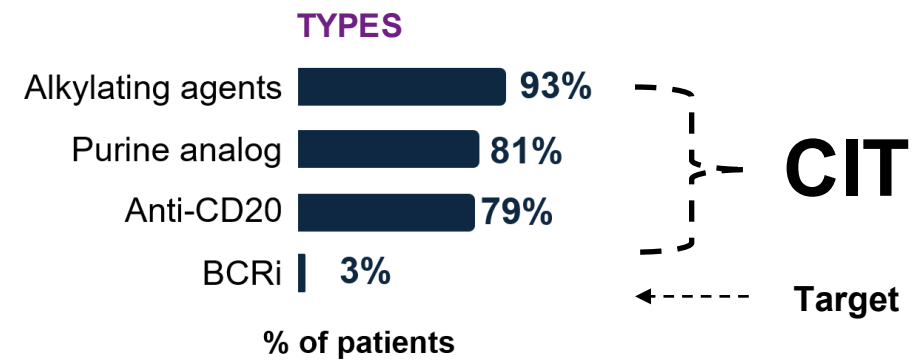
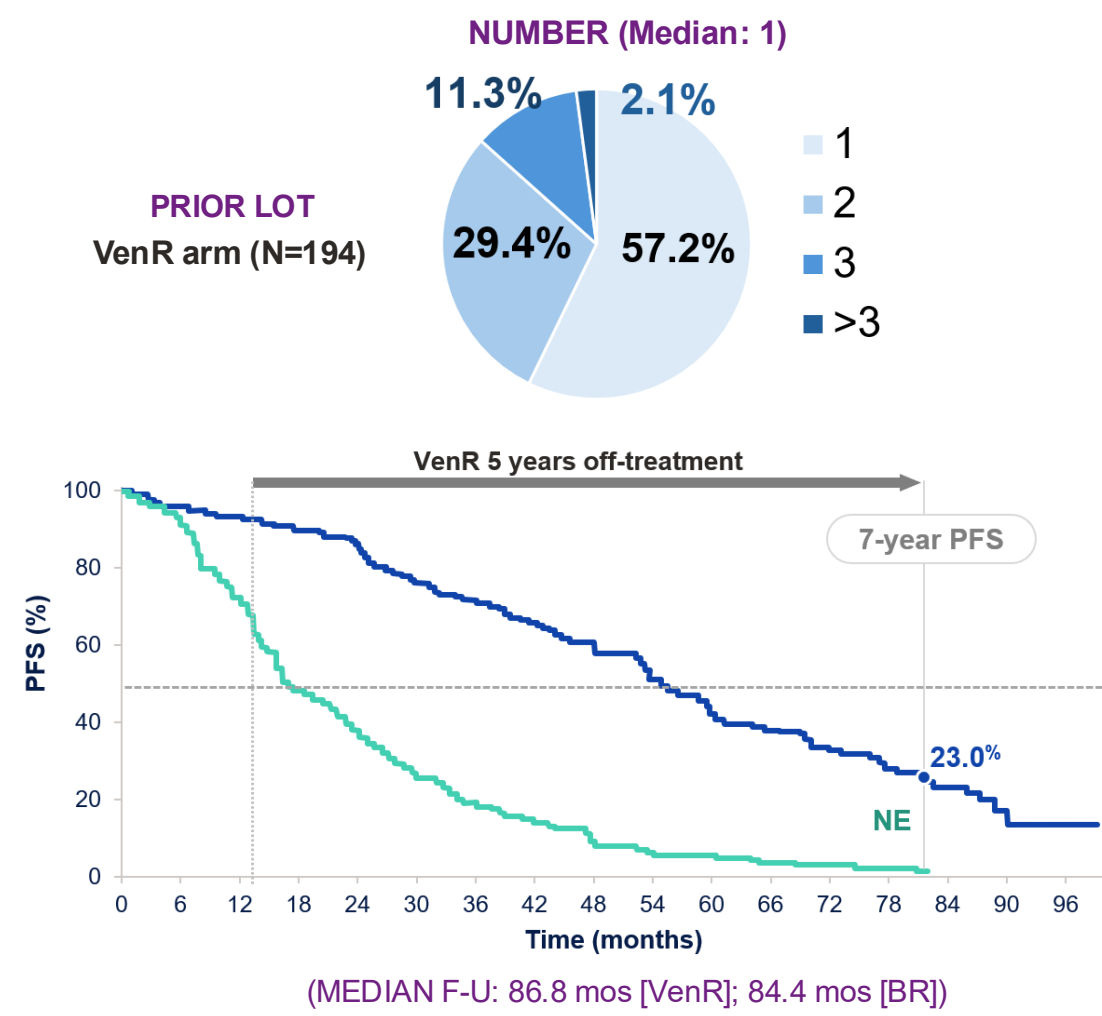
IMPACT ON PFS of

- **del 17p**

✓ PROLONGED TTNT

NO difference at 66 m
mutated vs unmutated IGHV

PFS benefits with V+R over BR were sustained at 7 years



V+R vs BR:

Median PFS 54.7 vs 17 mo

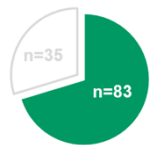
77% reduction in the risk of PD or death

Seymour JF, et al. N Engl J Med. 2018;378:1107-1120 (incl.appendix).
Kater AP, et al. EHA 2023. Oral S201.

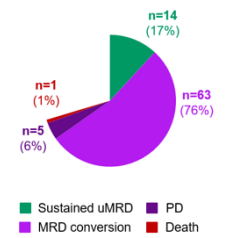
Venetoclax Rituximab RR: Murano trial

50% of V+R pts did not receive a new treatment >3 years after EoT

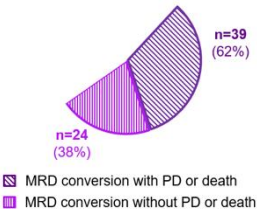
Ven-R
MRD EoT
24 months



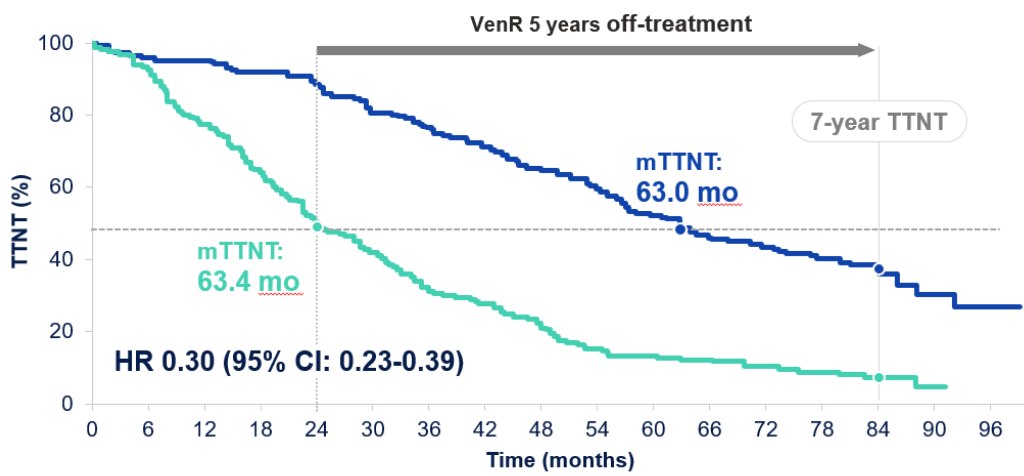
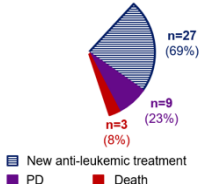
MRD
conversion
19.4 months



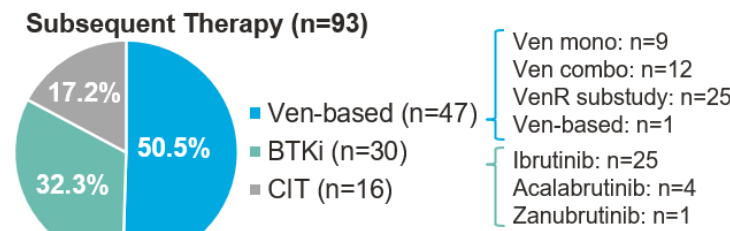
PD
28.3 months



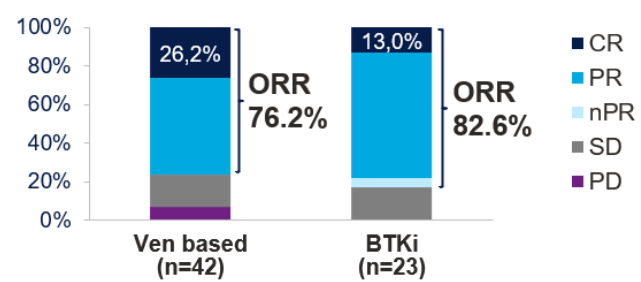
New T
4.5 months



Subsequent Anti-CLL Therapies (VenR Arm)



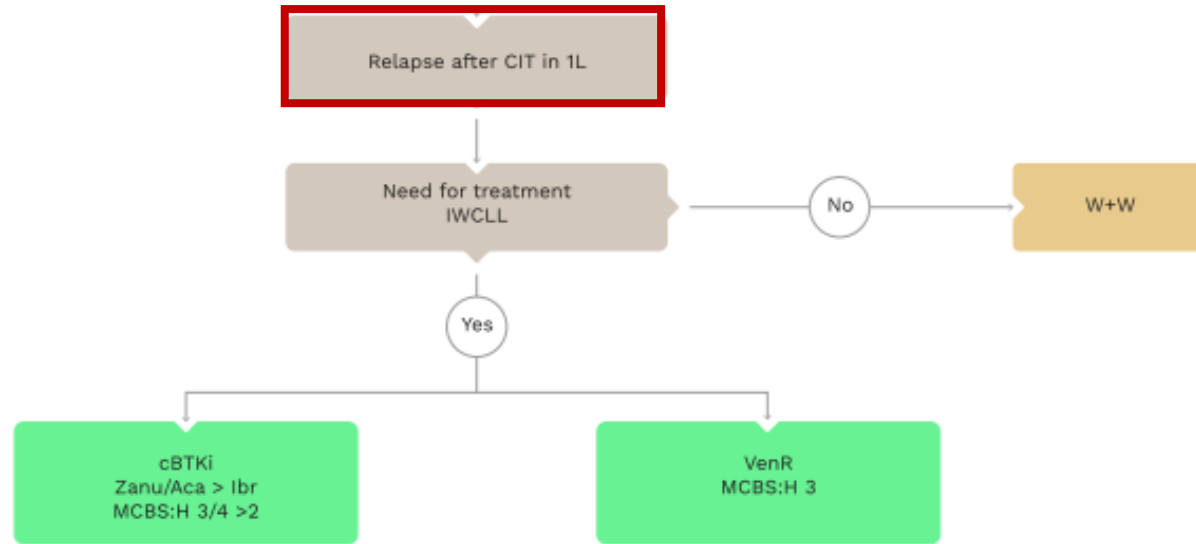
Response to Subsequent Therapies After VenR



In Italia, il ritrattamento con V+R o Ven mono è consentito solo dopo un trattamento di prima linea con V+I.

Kater A, et al. EHA 2023. Abstract S201
Seymour JF, et al. Blood 2022; 140:839–850
Harrup RA, et al. ASH 2023. Poster 1898

Relapsed Refractory



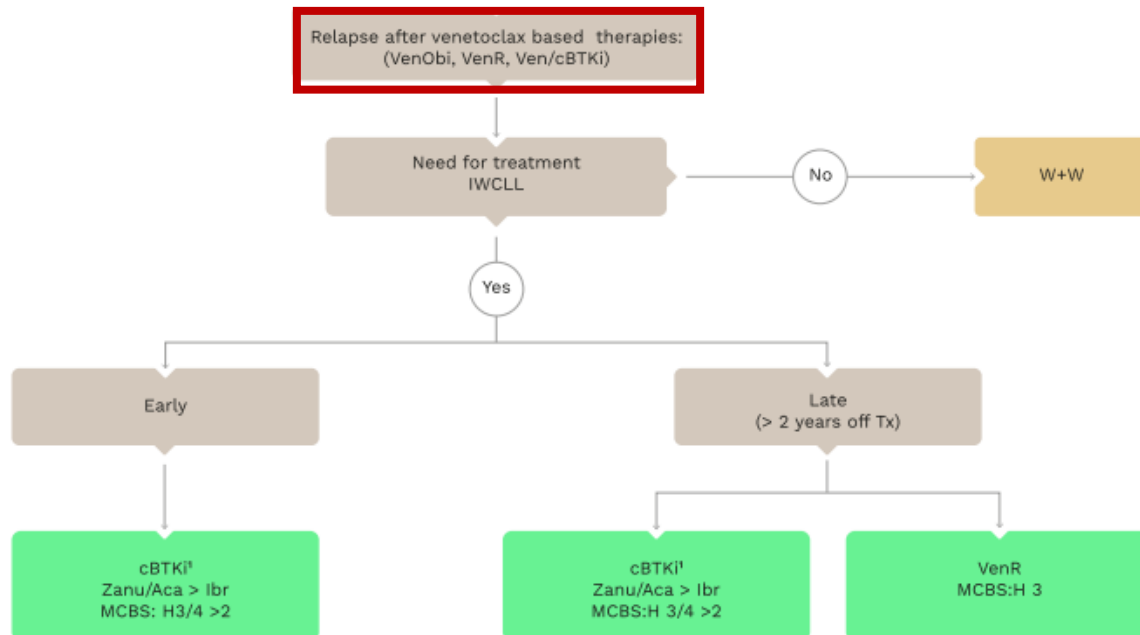
Randomized studies post immuno-CHT

Alpine: better PFS of zanubtutinib vs Ibrutinib
better tolerability of Zanubrutinib

Elevate RR: acalabrutinib non inferior to ibrutinib
better tolerability of Zanubrutinib

Murano: better PFS of FD Venetoclax R vs Benda R

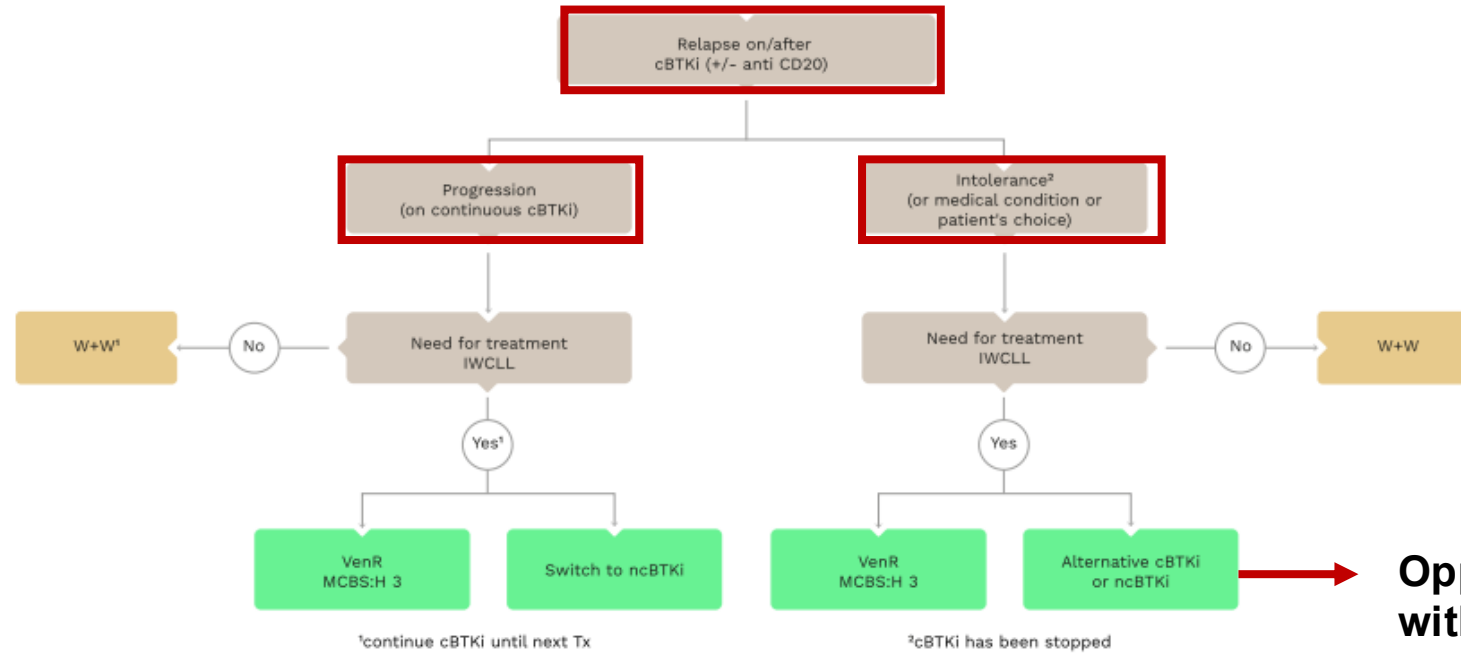
Brown. NEJM. 2023;388:319. Brown. Blood. 2024;144:2706 Kater et al 2025



According to AIFA:
cBTKi the only possible treatment
(retrospective data)

Retreatment with venetoclax not reimbursed

Relapsed Refractory



Ven R

Effective, data from retrospective series

Bruin CLL-321

Pirtobruinib vs idelaR or BendaR

in pts previously treated with cBTKi

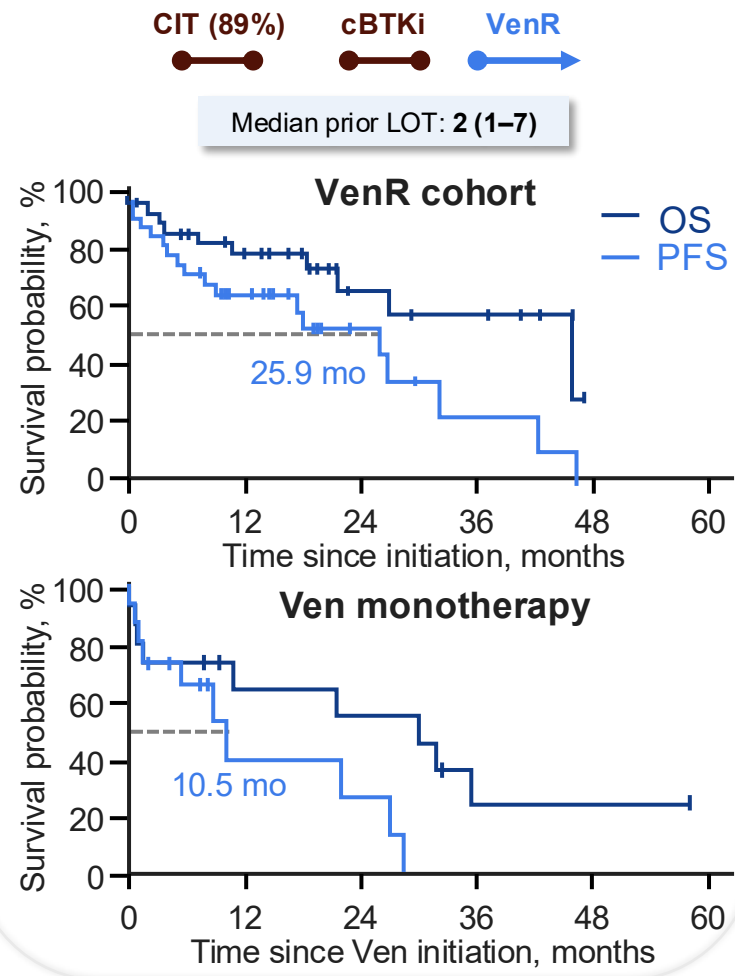
(the only controlled study in this population)

Opportunity to continue with BTKi supported by Phase 2 studies with Acalabrutinib, Zanubrutinib, Pirtobrutinib

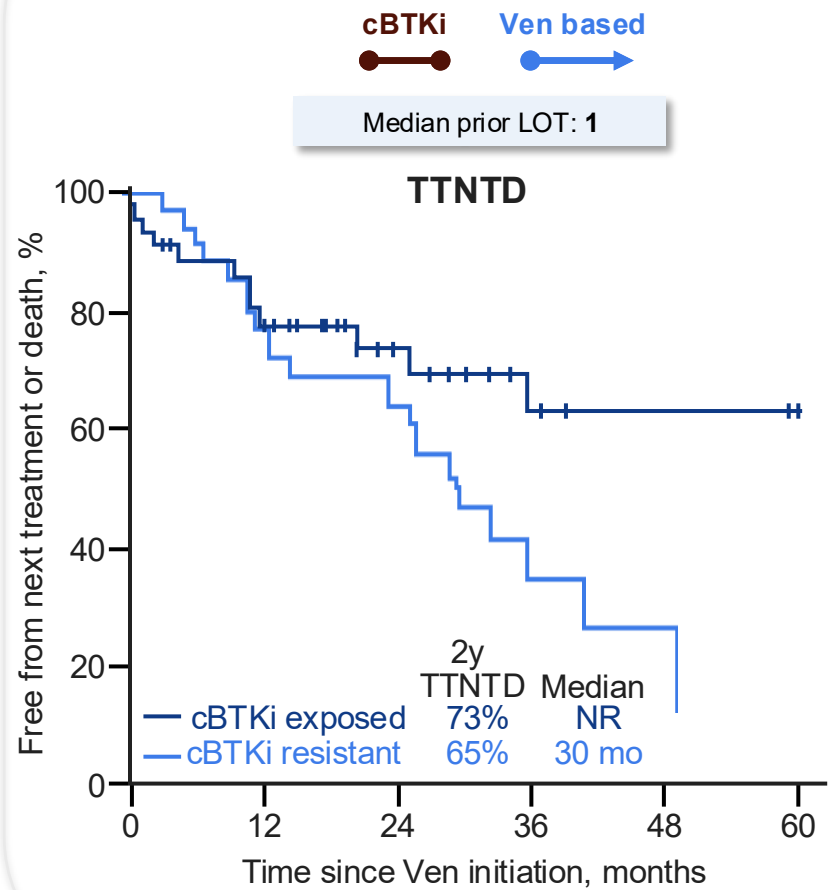
Shadman. Lancet Haematol 2023;10:e35.
Awan. Blood Adv. 2019;3:1553

Ventotoclax R after BTKi

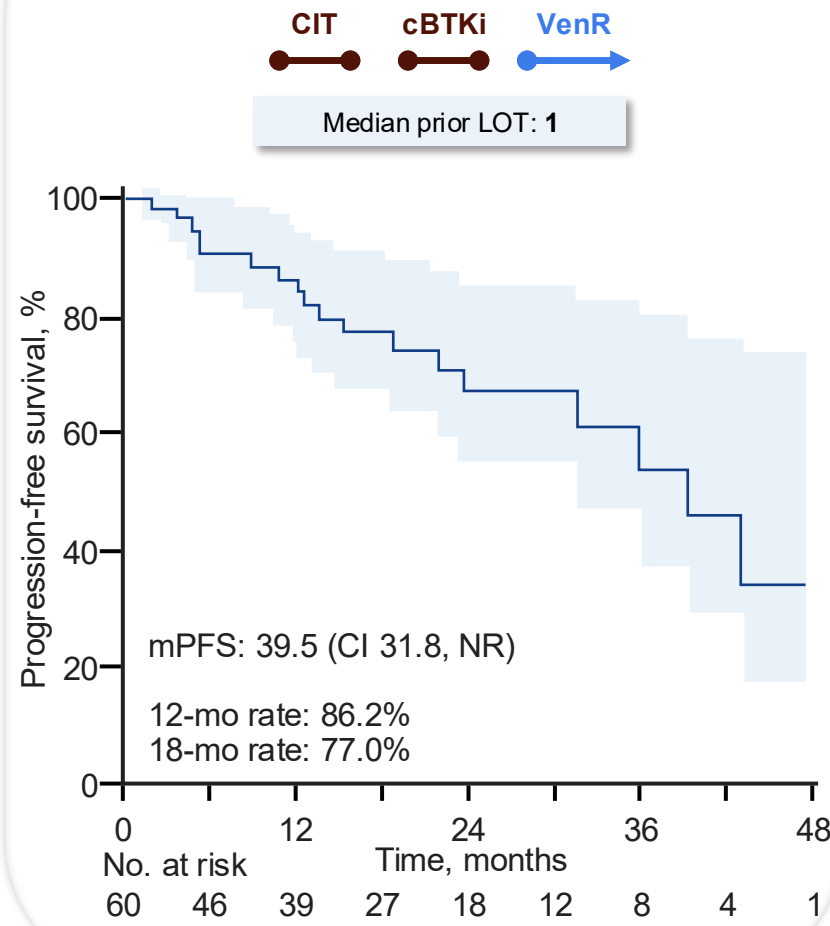
Australian Real World Cohort 32 pts¹



International Retrospective (Mayo Clinic, France) 85 pts²



Core Study USA Canada Europe 60 pts³



cBTKi, covalent Bruton's tyrosine kinase inhibitor; CIT, chemoimmunotherapy; LOT, line of treatment; m, months; OS, overall survival; PFS, progression-free survival; pts, patients; TTNTD, time to next treatment or death; Ven(R), venetoclax (+ rituximab); y, year.

1. Lew TE, et al. Blood Adv. 2024;8(6)1439-1443. 2. Hampel PJ, et al. Blood. 2024;144(suppl):1856-1857. 3. Ghosh N, et al. Am J Hematol. 2025;100(3):511-515.

Ventotoclax after BTKi

ERIC COHORT

624 pts received Venetoclax:
Ven monotherapy (n=278, 45%),
VenR (n=230, 37%)
VenO (n=78, 13%)

Median prior lines of therapy was 2

BTKi was 1L CLL tx for 153 (25%)

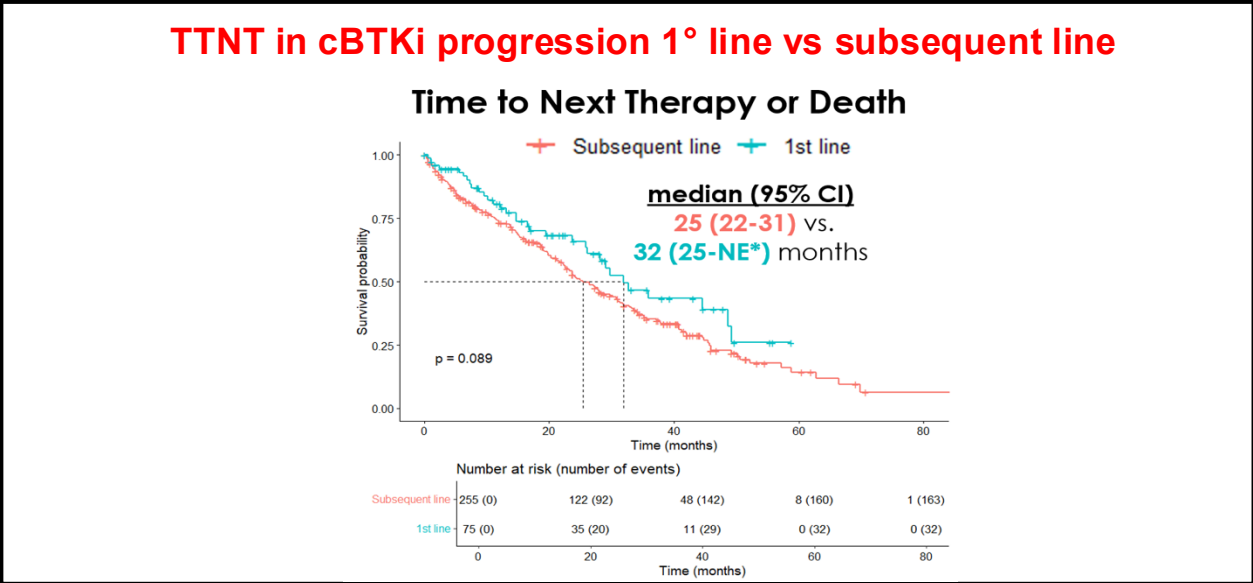
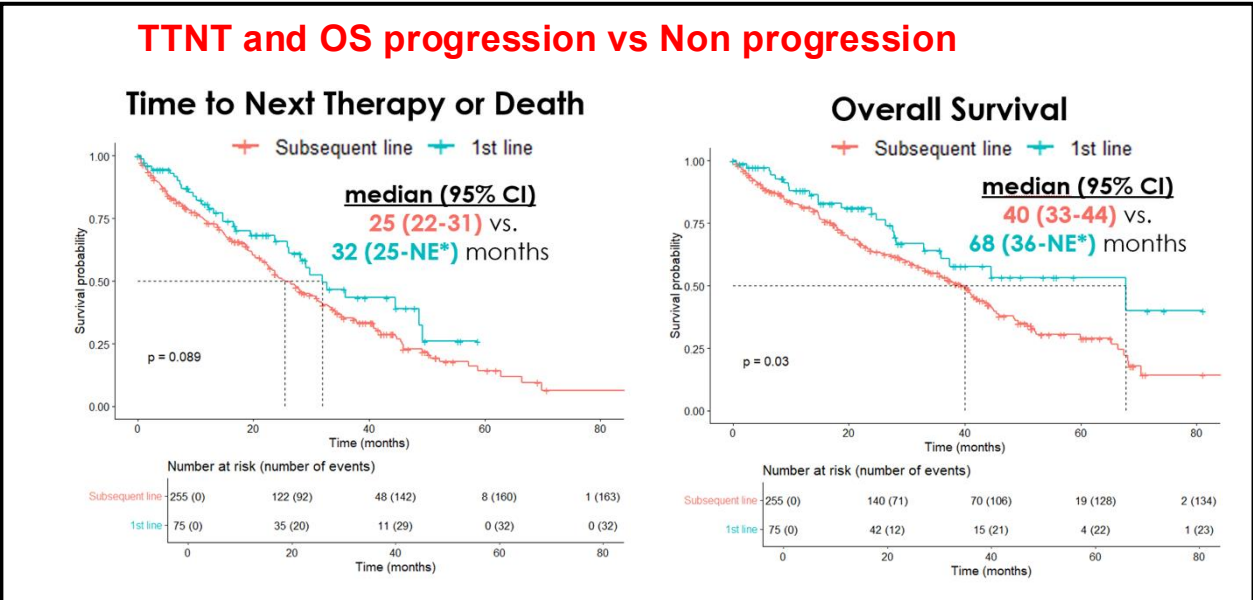
Progression on cBTKi: 330 (53%) pts

Other than progression: 294 (47%) pts

ENTIRE COHORT

median TTNTD: 33 mo (95% CI: 30-36)

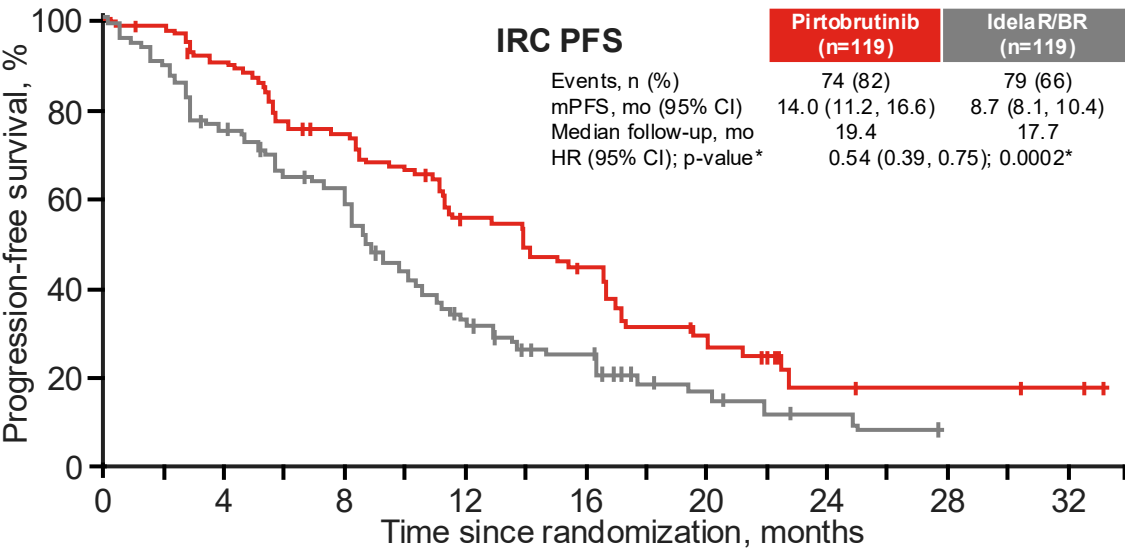
median OS: 46 mo (95% CI 42-54)



Pirtobrutinib in RR CLL

BRUIN CLL-321 phase 3 study: Pirtobrutinib vs IdelaR/BR in BTKi pretreated CLL/SLL¹

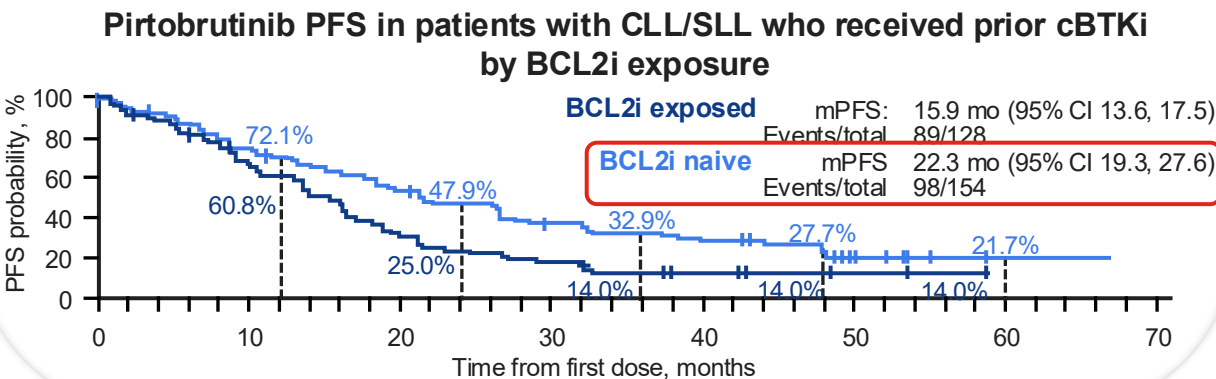
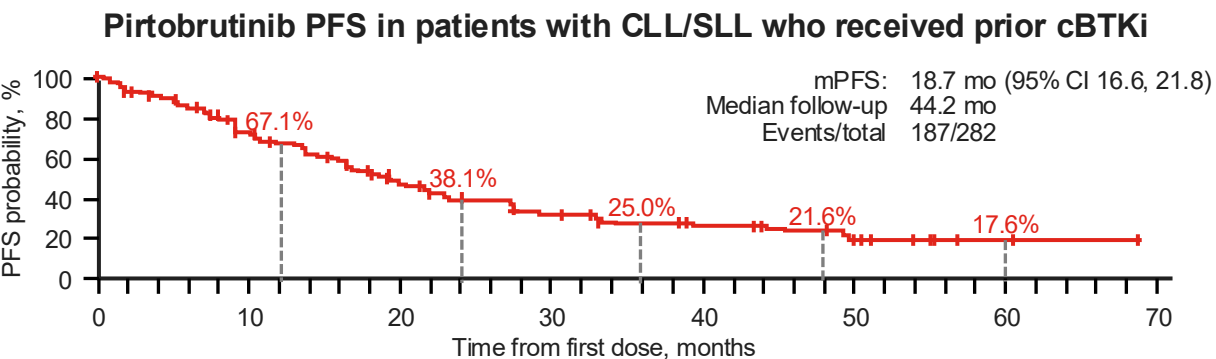
Pirto n=119 | median age 66 y | median prior tx: 3 | del(17p)/TP53m: 54%



TTNTD	Ven naive		Ven treated	
	Pirtobrutinib (n=59)	IdelaR/BR (n=59)	Pirtobrutinib (n=60)	IdelaR/BR (n=60)
Median TTNTD, mo	29.5	12.5	20.0	8.7
HR (95% CI); p-value*	0.36 (0.21, 0.61); 0.0001		0.37 (0.23, 0.60); <0.0001	

BRUIN phase 1/2 study: Subgroup analysis of pts with/without prior BCL2i²

Pirto n=282 | median age 66 y | prior BTKi: 100% | BCL2i exposed: 45%



*Stratified log-rank 2-sided p-value.

BCL2i, B-cell lymphoma 2 inhibitor; BR, bendamustine + rituximab; CI, confidence interval; BTKi, Bruton's tyrosine kinase inhibitor; CLL, chronic lymphocytic leukemia; del(17p), 17p deletion; HR, hazard ratio; IdelaR, idelalisib + rituximab; IRC, independent review committee; mo, months; (m)PFS, (median) progression-free survival; Pirto, pirtobrutinib; pts, patients; R/R, relapsed/refractory; SLL, small lymphocytic leukemia; TP53m, tumor protein p53 mutated; TTNTD, time to next treatment or death; tx, treatment; Ven, venetoclax; y, years.

1. Sharman JP, et al. J Clin Oncol. 2025;43:2538-2549. 2. Wierda WG, et al. Blood. 2025;146(suppl):Abstract 2115.

Pirtobrutinib in Second-Line CLL After First-Line cBTKi Therapy: Pooled Analysis of the BRUIN LOXO-BTK-18001 and BRUIN CLL-321 Studies

BRUIN LOXO-BTK-18001:

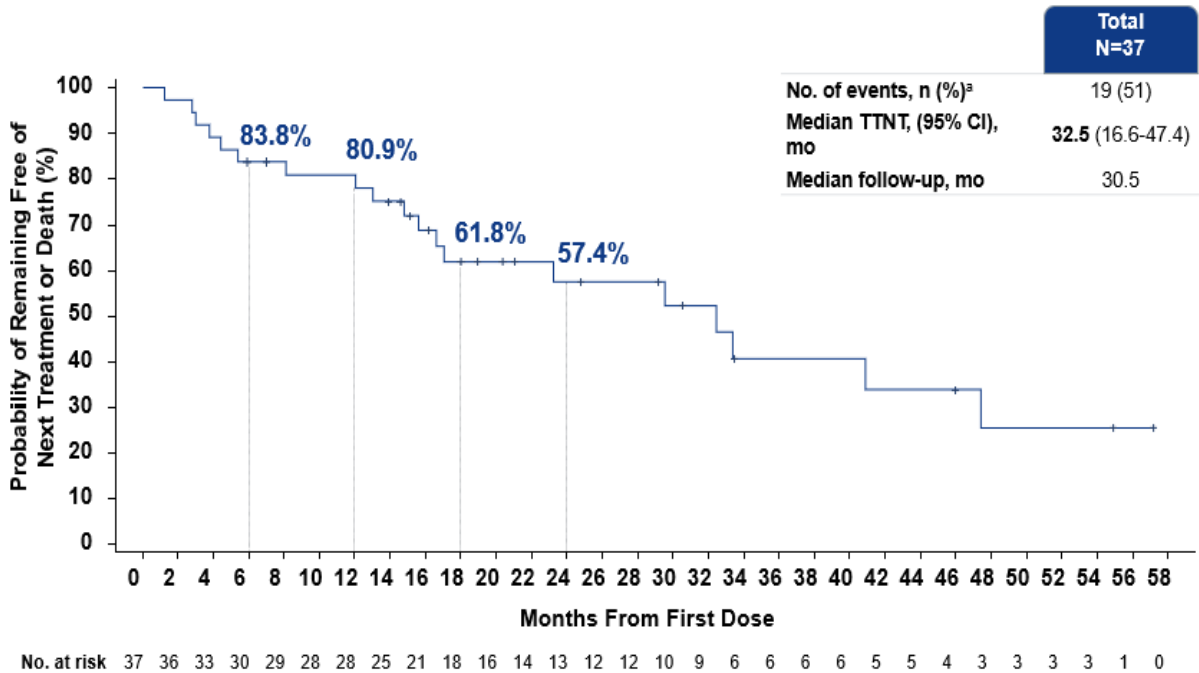
- Open-label, multi-center Phase 1/2 study of pirtobrutinib in patients with R/R B-cell malignancies⁵

BRUIN CLL-321:

- Randomized, open-label, multi-center Phase 3 study of pirtobrutinib in patients with CLL/SLL⁶

37 pts
Mutated *TP53* 13/30 (43%)
del17p 15/31 (48%)

Time to Next Treatment



Overall Survival

