MEET THE
EXPERT in CLL

MESSINA, 28 APRILE 2025

Azienda Ospedaliera Universitaria "Gaetano Martino"

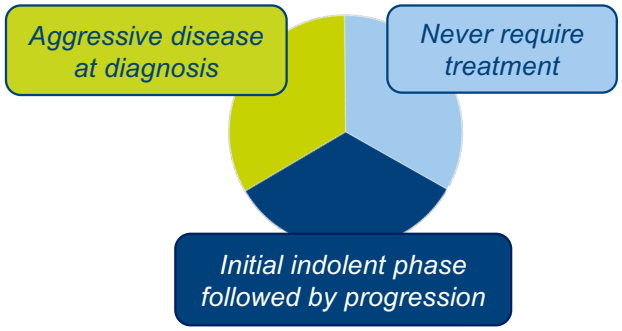
Terapia a durata fissa nel paziente di prima linea e nel paziente ricaduto/refrattaria, fitness e stato mutazionale

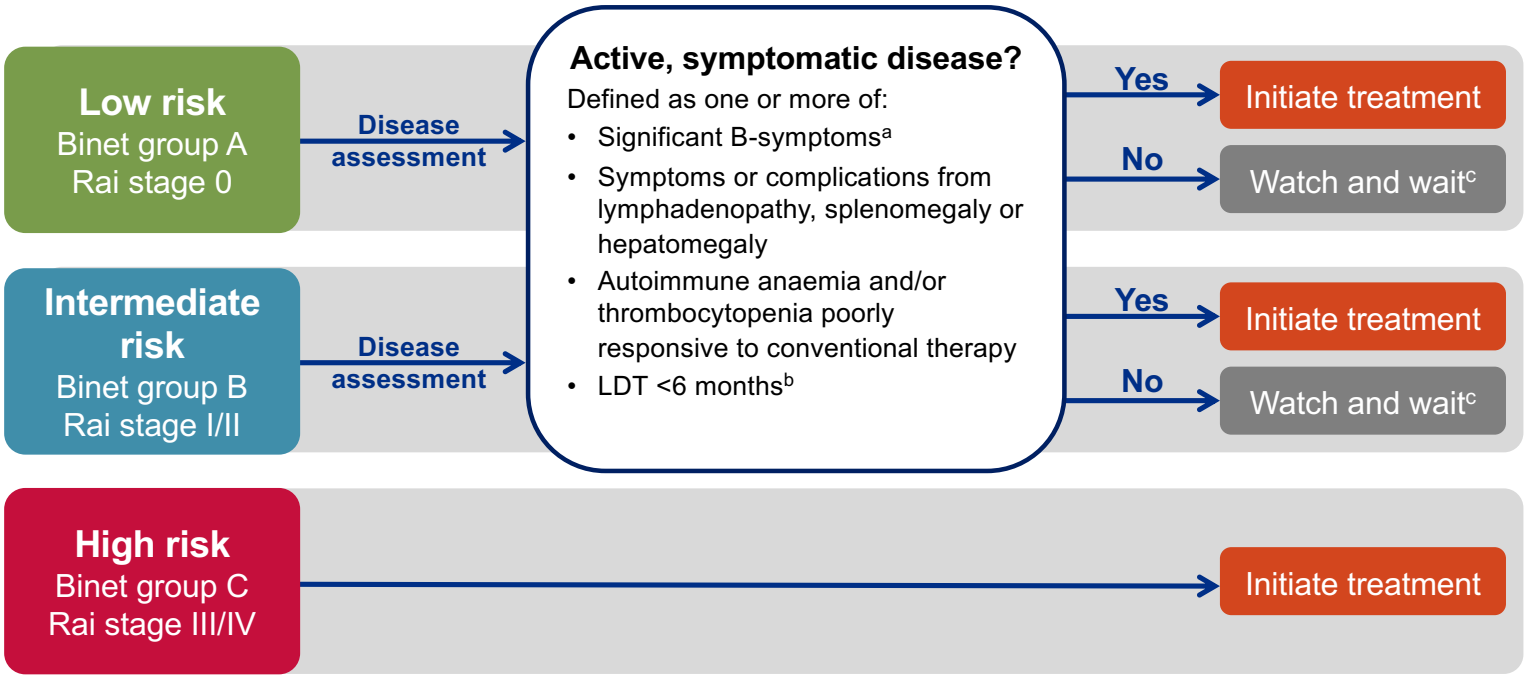
PAOLO SPORTOLETTI
Università degli Studi di Perugia

Disclosures PAOLO SPORTLETTI

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
Abbvie	x				x	x	
J&J					x	x	
Astrazeneca					x	x	
Beigene					x	x	
Novartis	x						

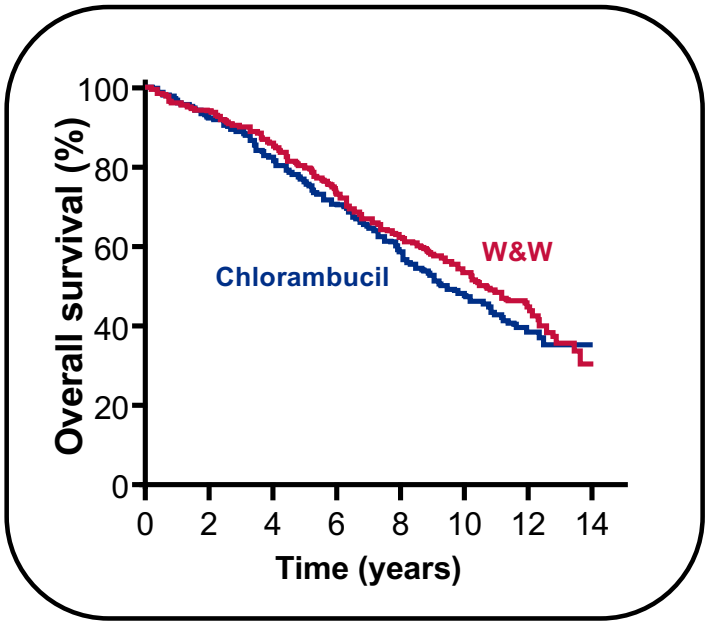
Treatment is not always required for CLL

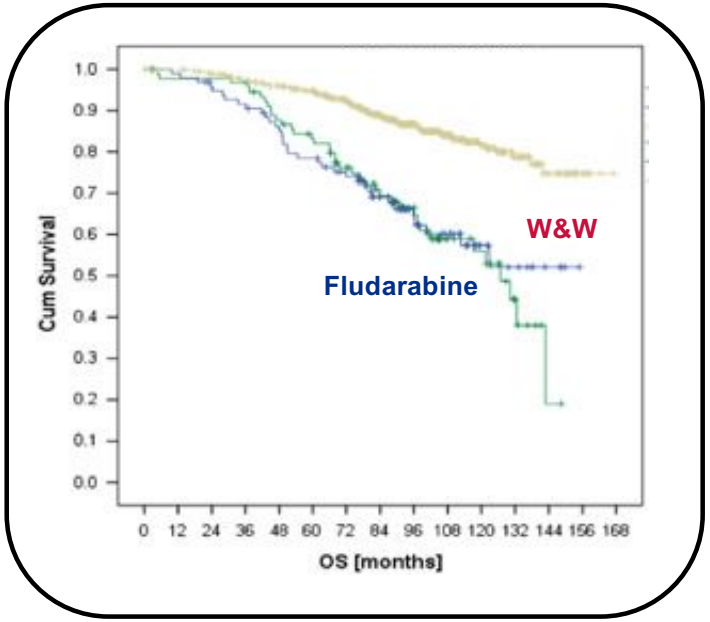


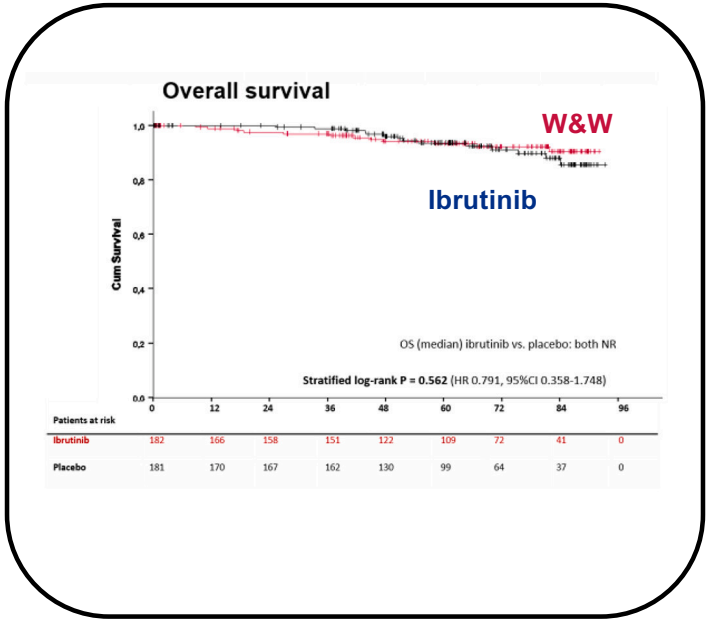


1. Eichhorst B, *et al. Ann Oncol* 2015; 26(Suppl 5):v78–v84.
2. Hallek M, *et al. Blood* 2018; 111:5446–5456.

Treating early-stage CLL does NOT result in survival benefit

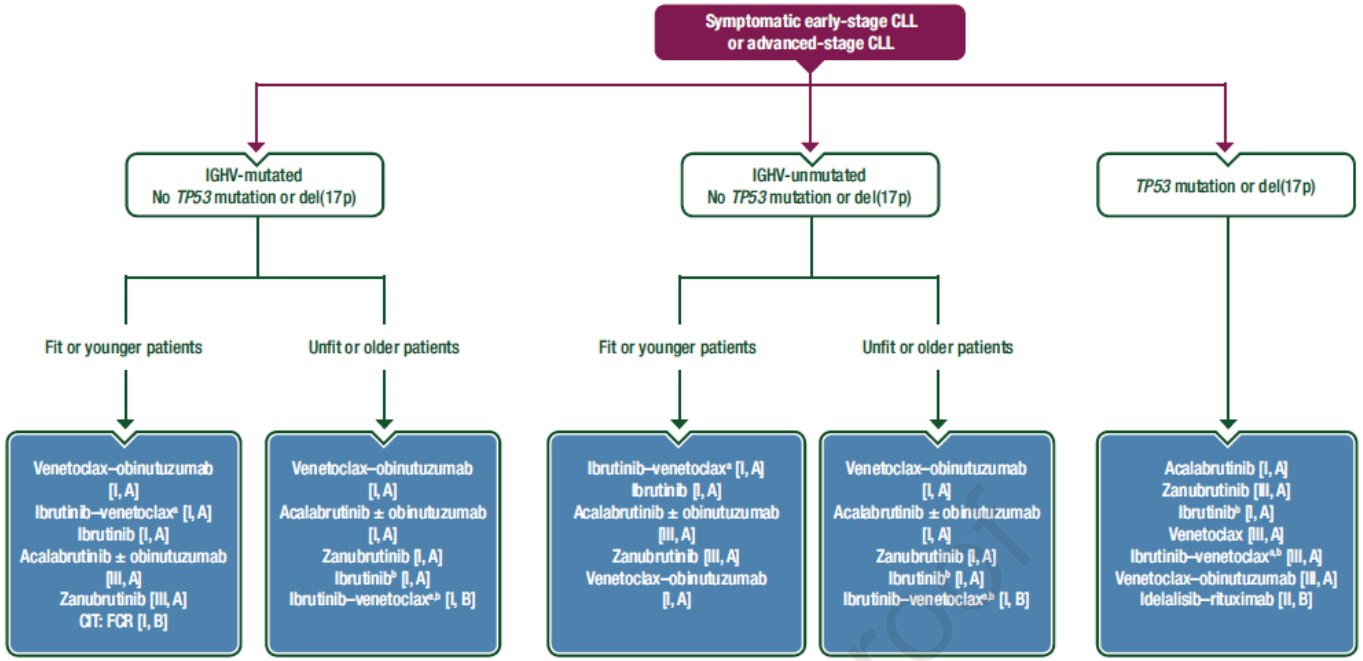






Dighiero G, *et al. N Engl J Med* 1998.;
Hoechstetter MA et al. Leukemia 2017
Langerbeins P et al. Hematol Oncol. 2023

ESMO 2024 1L CLL



Levels of evidence

I	Evidence from at least one large randomised, controlled trial of good methodological quality (low potential for bias) or meta-analyses of well-conducted randomised trials without heterogeneity
II	Small randomised trials or large randomised trials with a suspicion of bias (lower methodological quality) or meta-analyses of such trials or of trials demonstrated heterogeneity
III	Prospective cohort studies
IV	Retrospective cohort studies or case-control studies
V	Studies without control group, case reports, expert opinions

Grades of recommendation

A	Strong evidence for efficacy with a substantial clinical benefit, strongly recommended
B	Strong or moderate evidence for efficacy but with a limited clinical benefit, generally recommended
C	Insufficient evidence for efficacy or benefit does not outweigh the risk or the disadvantages (adverse events, costs, etc.), optional
D	Moderate evidence against efficacy or for adverse outcome, generally not recommended
E	Strong evidence against efficacy or for adverse outcome, never recommended

Eichhorst B et al, ESMO Clinical Practice Guideline interim update on new targeted therapies in the first-line and at relapse of chronic lymphocytic leukaemia† Annals of Oncology, 2024; doi: https://doi.org/10.1016/j.annonc.2024.06.016.

- In patients with CLL regardless of IGHV status but without a *TP53* mutation or del(17p), preference should be given to time-limited therapies and to therapies and/or combinations with longer follow-up data, if efficacy is similar.

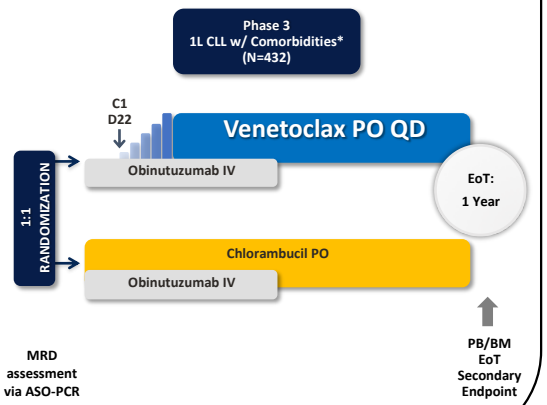
- When selecting a first-line treatment, the following could be taken into consideration [V, B]:

✓ Side-effect profile (e.g. renal impairment and risk of tumour lysis syndrome versus atrial fibrillation, hypertension and risk of bleeding versus accumulation of side-effects with continuous therapy)
✓ Drug administration (e.g. intravenous application for therapies including anti-CD20 antibody infusion versus oral medication only)
✓ Access and intensity of controls (e.g. 5-week ramp-up period with the use of a BCL2i)
✓ Shorter follow-up

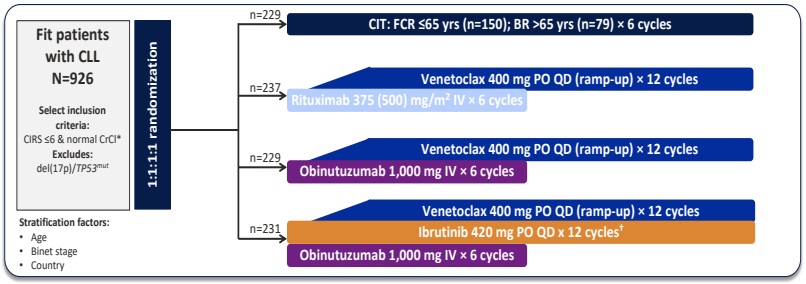
- Prefer proper fitness assessment rather than using age as the determing factor
- Genetic instability is a driver of BTKi resistance due continuous treatment; IV is ranked higher for del17p-deleted/TP53-mutated than VG; I+V does not trigger BTKi resistance and allows one more LOT in lifetime for the patient
- I+V after appropriate cardiovascular work-up → Highlight US PI (VA in 1%), cardiac surveilance mandatory
- VG in unfit unmutated patients: Del17p, uIGHV and bulk is an independent negative prognostic marker for VG

Fixed-duration trials in TN and R/R patients with CLL

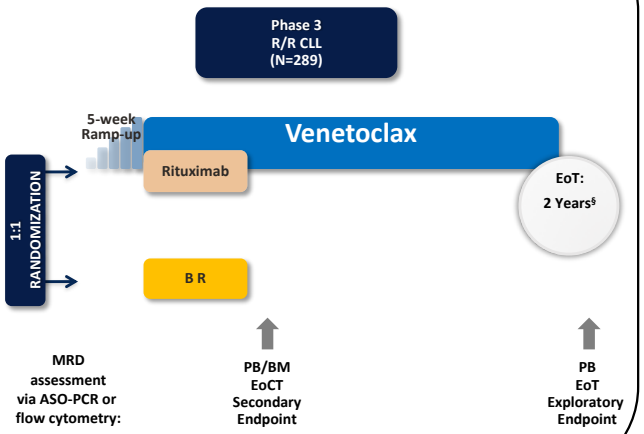
CLL14



CLL13

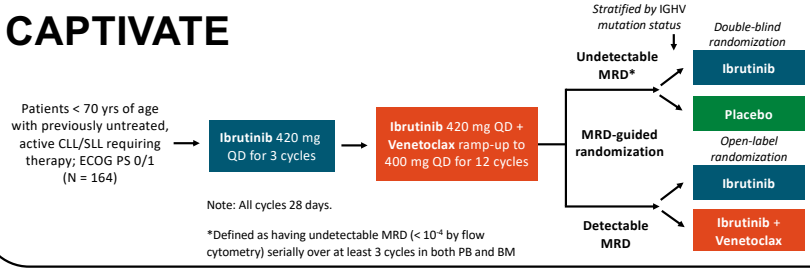


MURANO



GLOW

CAPTIVATE



Fischer K, et al. N Engl J Med. Seymour JF, et al. N Engl J Med. 2018
B Eichhorst et al. N Engl J Med 2023;388:1739-1754.
Kater et al., EHA 2021; LB1902 (oral presentation) Wierda et al. JCO 2021.

Why Fixed Duration Therapy in CLL?

- ✓ Efficacy
- ✓ Deep responses (MRD)
- ✓ Clonal evolution and resistance
- ✓ Safety and Tolerability
- ✓ QoL
- ✓ Cost-effectiveness
- ✓ Patient’s desire

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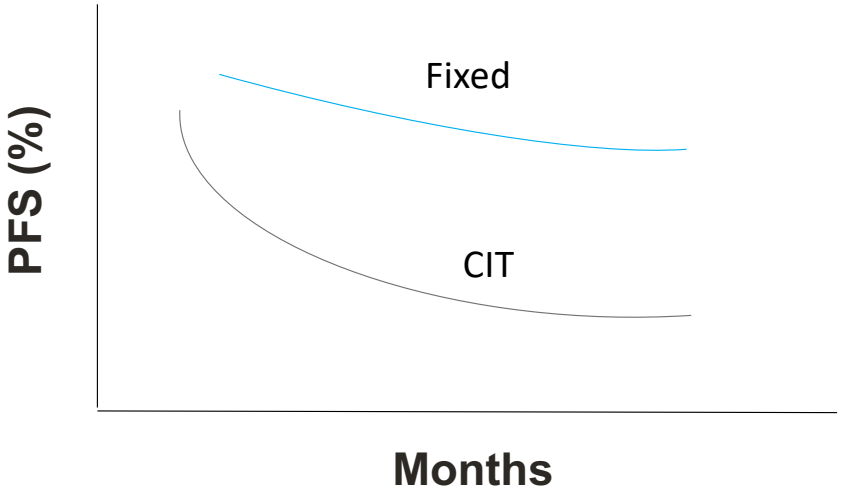
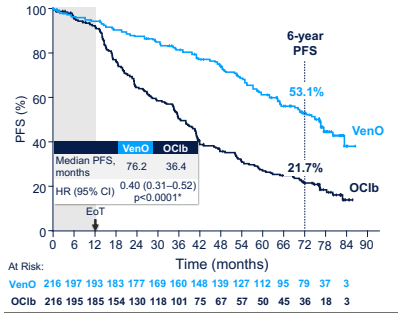
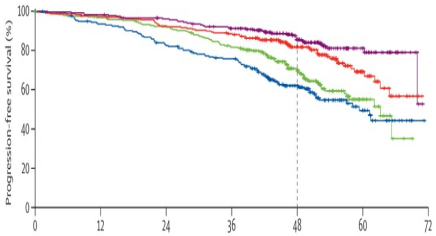
Efficacy of fixed-duration target therapy vs chemoimmunotherapy



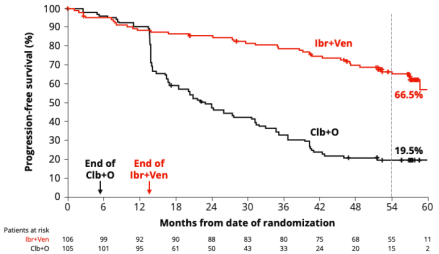
Ven-G (CLL14)



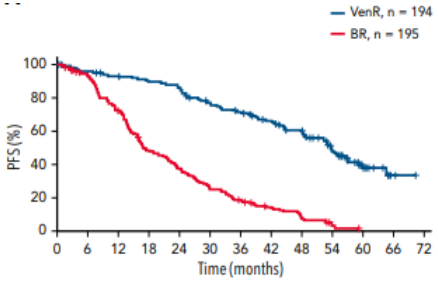
Ven-G o IVO (CLL13)



Ibrutininib-Venetoclax (Glow)



Ven-R (Murano)

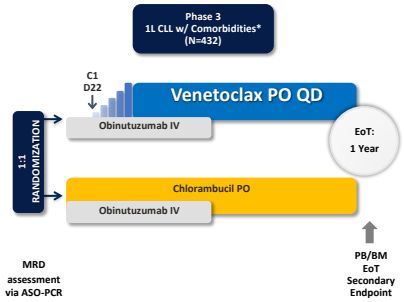


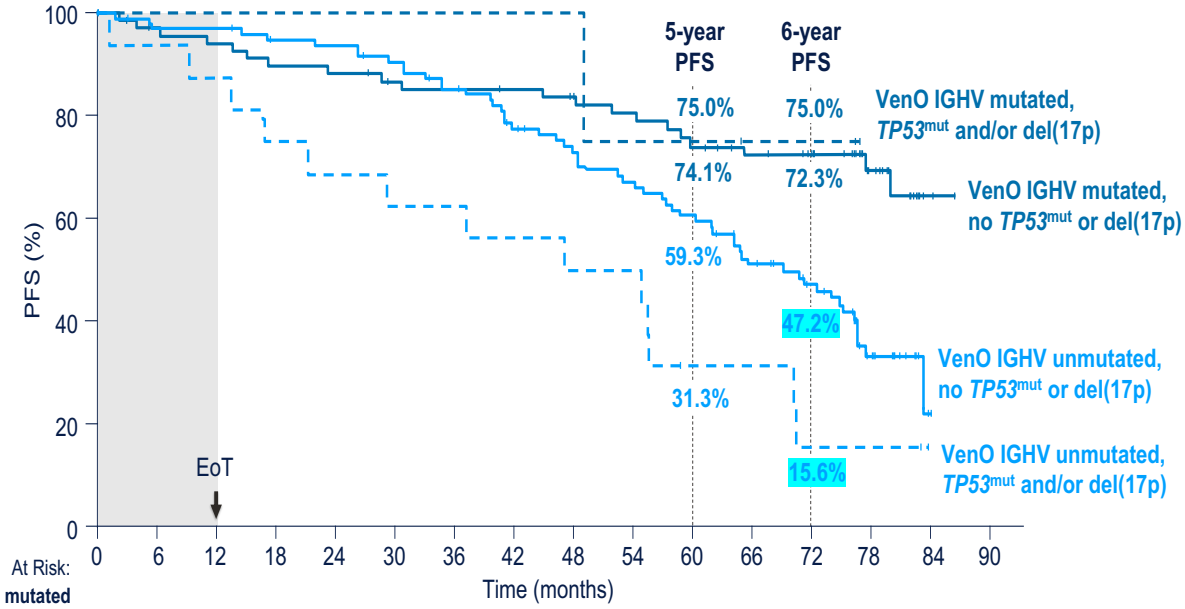
1. Al-Sawaf O, et al. EHA, 2023; Seymour et al., Blood 2022.

Challenging molecular subtypes

Does the TP53 and IGHV status still matter in the «targeted therapy era»?

VEN-O treatment in the CLL14 trial: PFS IGHV ± del(17p)/TP53 status





MUTATED IGHV

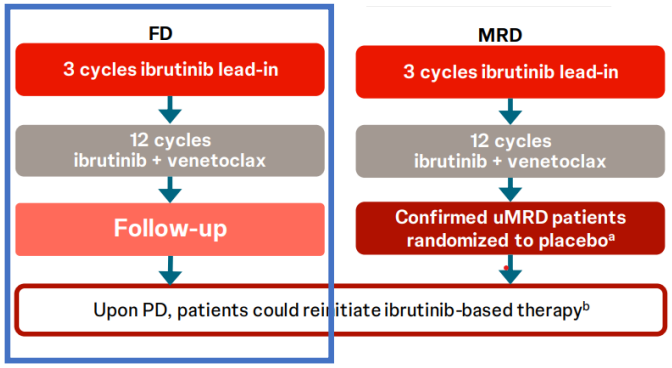
VS

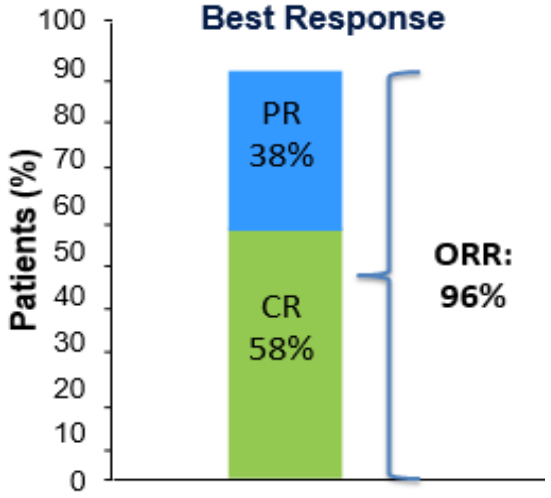
UNMUTATED IGHV

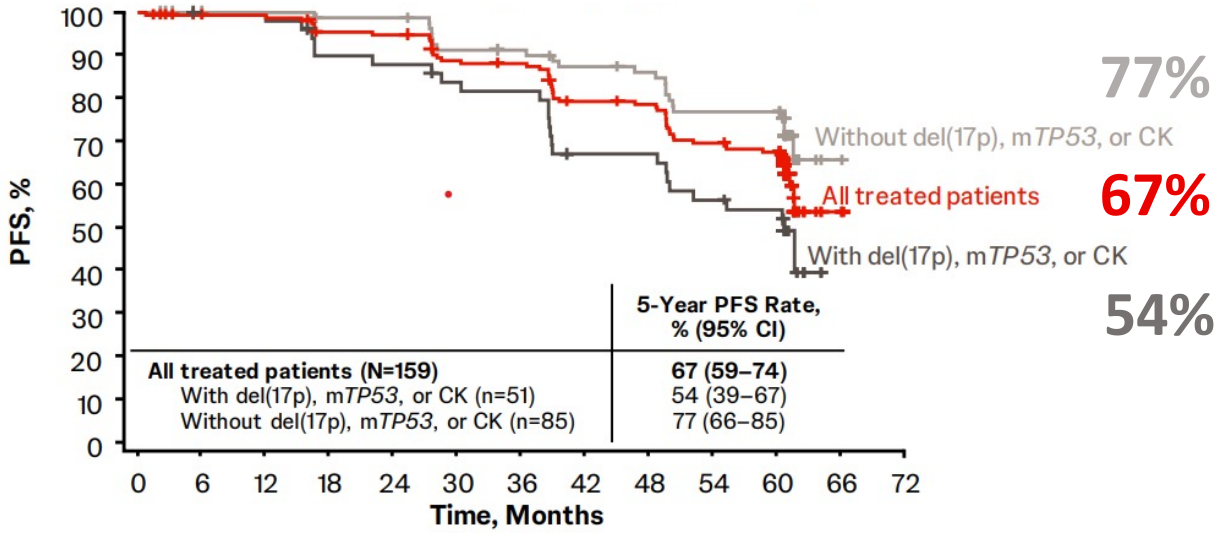
! 5-yy PFS in TP53
70% Ibrutinib
71% Acalabrutinib

Al-Sawaf O, et al. EHA 2023. Abstract S145 (Oral).

5-year ORR and PFS rates in the CAPTIVATE study





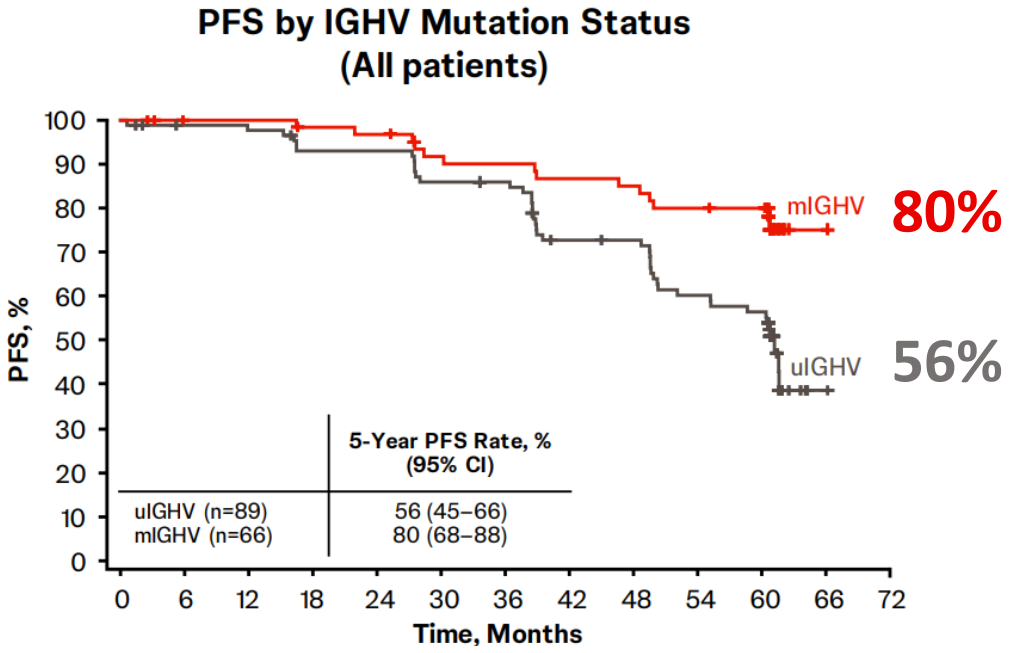


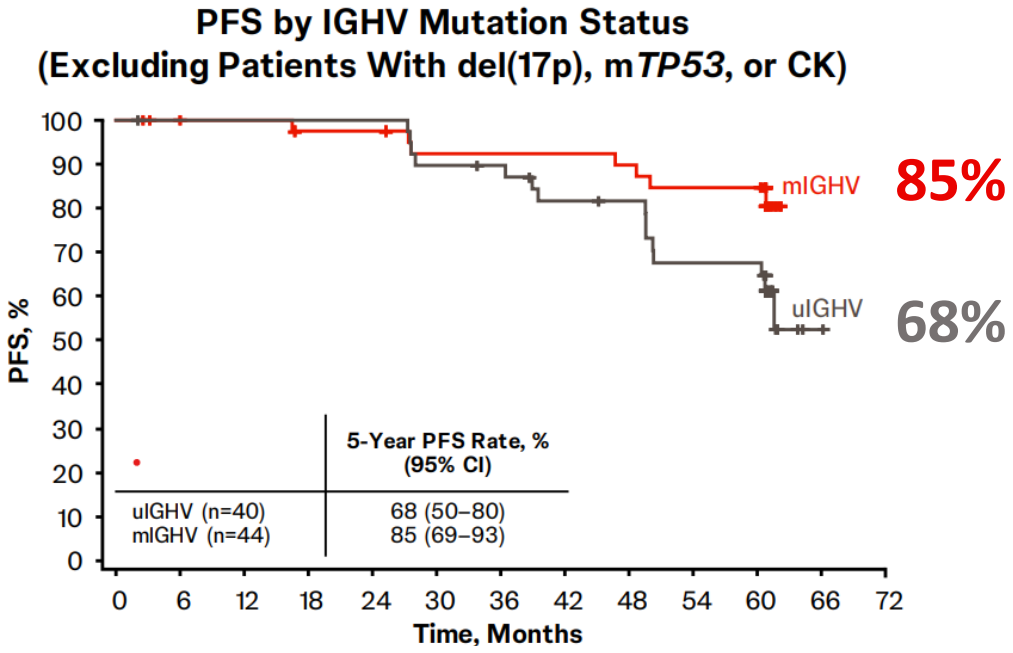
Median time on study: 61 months (range 0.8-66.3)

	With feature	
High-risk feature	n	5-Year PFS rate, % (95% CI)
del(17p)/m*TP53*	27	41 (21–59)
CK[a]	31	57 (37–72)
del(11q)[b]	11	64 (30–85)

Ghia, ASH 2023
Wierda, ASCO 2024

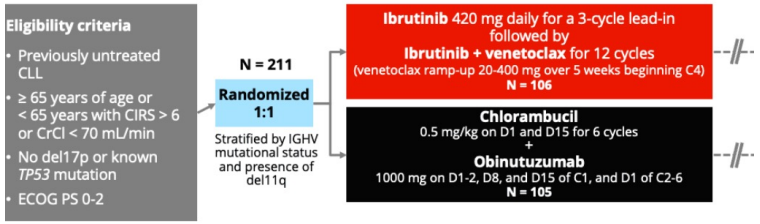
CAPTIVATE trial: co-existing del(17p), mTP53, or CK had a substantial impact on PFS in patients with uIGHV and mIGHV

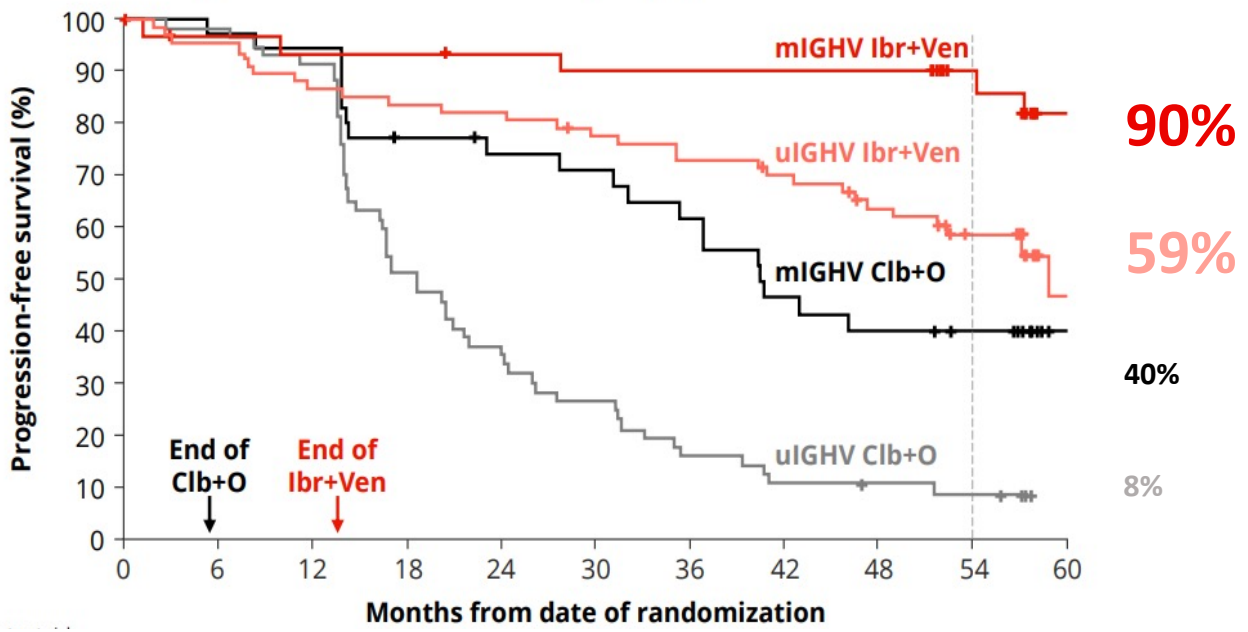




Wierda, ASCO 2024

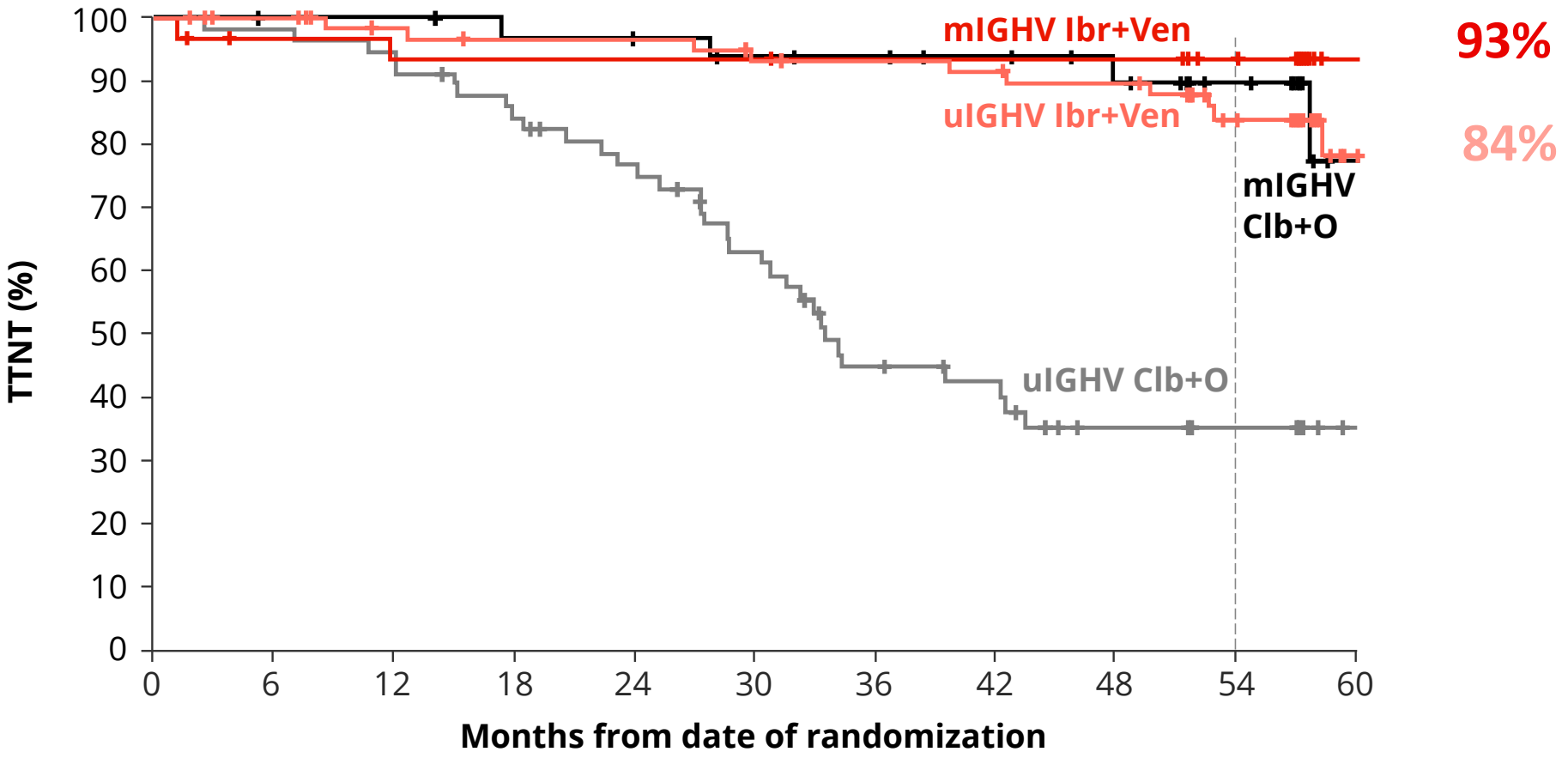
GLOW: At 57 months of follow-up, Ibr+Ven improved PFS versus Clb+O
The IGHV status still matters!





Results based on updated IGHV reclassifications. Investigator-assessed progression-free survival was analysed.
Clb, chlorambucil; Ibr, ibrutinib; (u/m)IGHV, (unmutated/mutated) immunoglobulin heavy-chain variable region; ITT, intention-to-treat; O, obinutuzumab; PFS, progression-free survival; Ven, venetoclax.
1. Moreno C, et al. ASH 2023 (Abstract No. 634 – presentation).

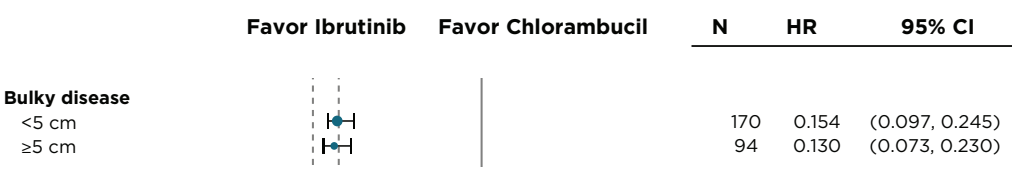
GLOW: Time To Next Treatment according to IGHV status



Osorio Prendes, EHA 2024

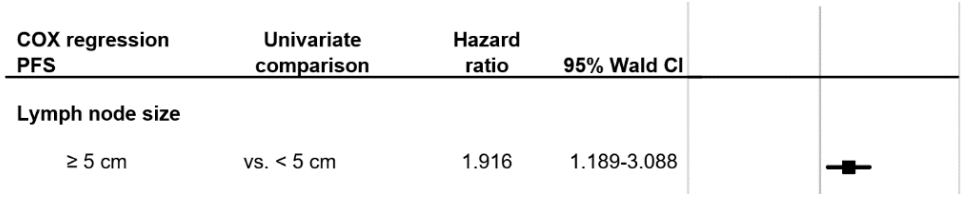
Efficacy on bulky nodes

IBRUTINIB – RESONATE2



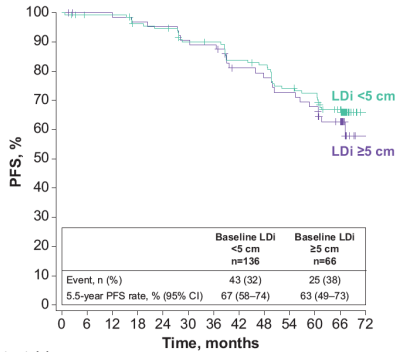
no influence

VENETOCLAX-O – CLL14



negative prognostic factor

Venetoclax-Ibrutinib - CAPTIVATE



Bulky Lymphoadenopathy at Baseline Does Not Impact Long-Term PFS

no influence

Wierda et al., ASH 2024

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

TN CLL (N=867)

Key inclusion criteria
- Age ≥18 years
- Without del(17p) or *TP53*
- ECOG PS ≤2

Key exclusion criteria
- CIRS-Geriatric >6
- Significant cardiovascular disease

RANDOMIZE 1:1:1

- **ACALABRUTNIB VENETOCLAX** (14 cycles)
- **ACALABRUTINIB VENETOCLAX OBINUTUZUMAB** (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 or AVO vs FCR/BR)
3) OS (AV or AVO vs FCR/BR)

Baseline Characteristics

YOUNG

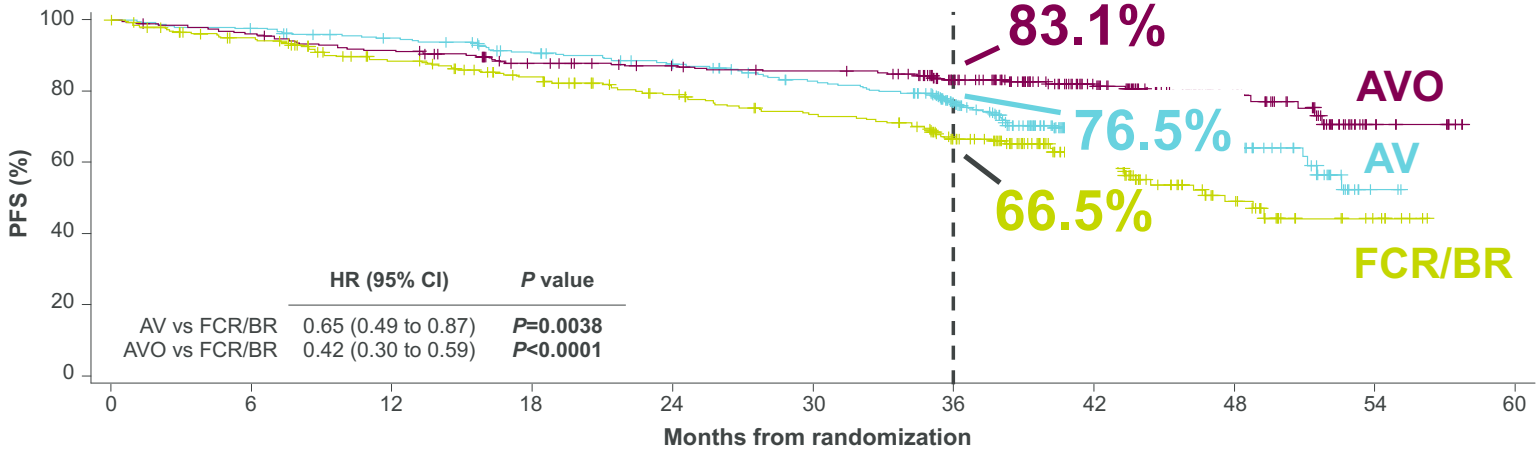
FIT

Characteristic	AV (n=291)	AVO (n=286)	FCR/BR (n=290)
Age, median (range), yr	61 (31–84)	61 (29–81)	61 (26–86)
≤65 yr	212 (72.9)	210 (73.4)	213 (73.4)
>65 yr	79 (27.1)	76 (26.6)	77 (26.6)
Male sex	178 (61.2)	198 (69.2)	183 (63.1)
ECOG PS score			
0–1	262 (90.0)	272 (95.1)	262 (90.3)
2	28 (9.6)	14 (4.9)	26 (9.0)

Brown JR ASH 2024

Significantly improved PFS with fixed-duration AV and AVO vs FCR/BR

Median PFS was NR for AV and AVO, and was 47.6 mo for FCR/BR



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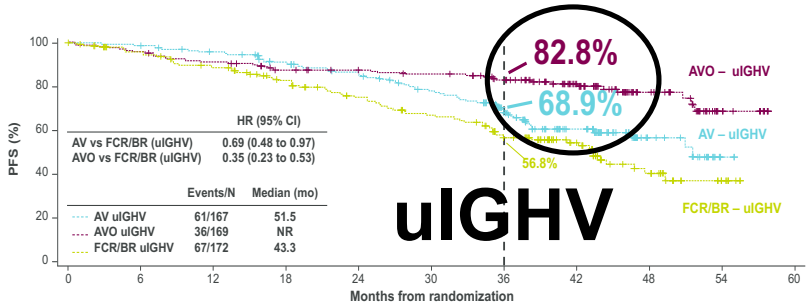
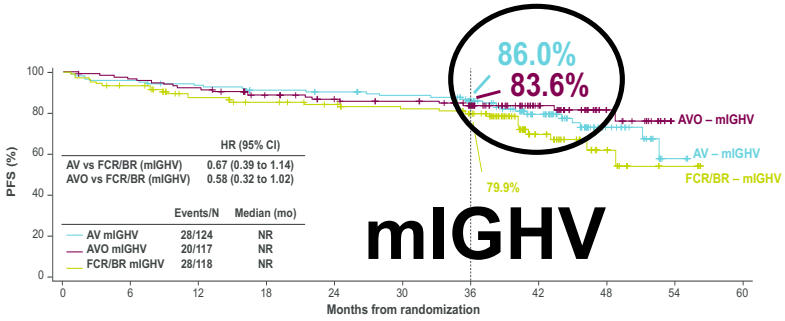
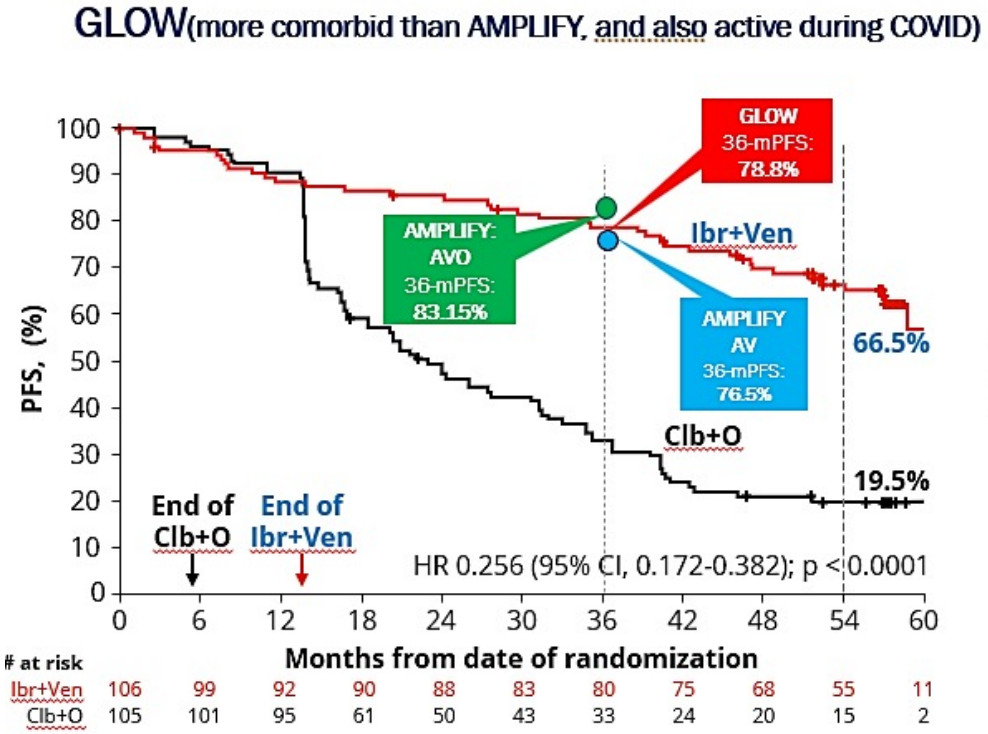
PFS evaluated by IGHV mutational status in a prespecified analysis

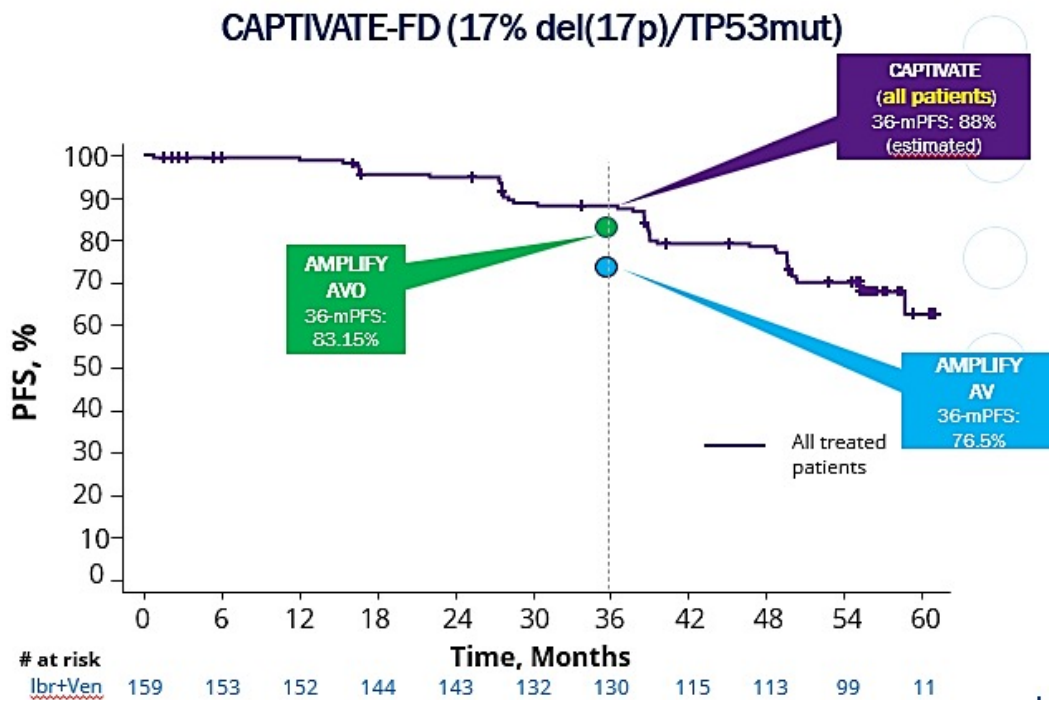




Brown JR ASH

I acknowledge the limitations in comparing I+V and A+V studies, but I take the liberty of doing so





Brown J, et al. oral presentation at ASH 2024. #1009

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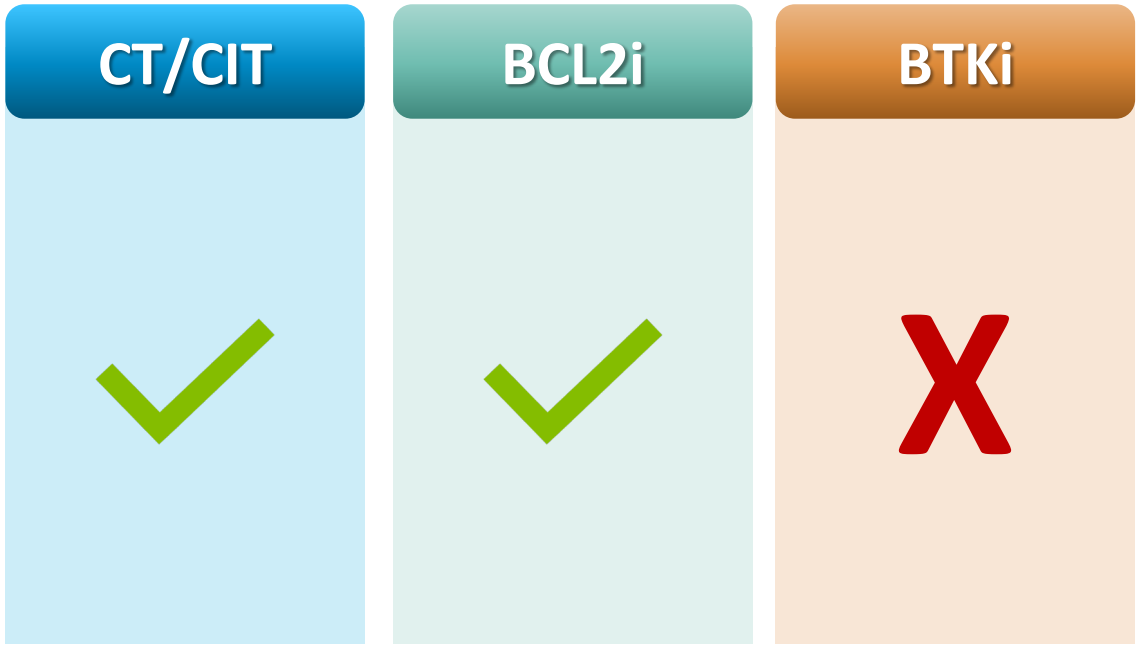
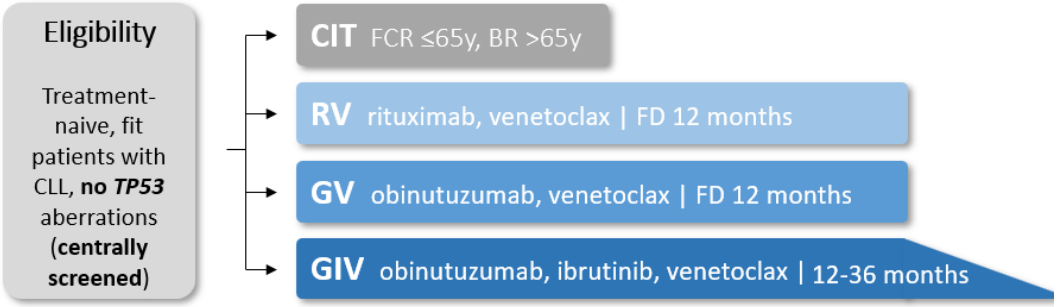
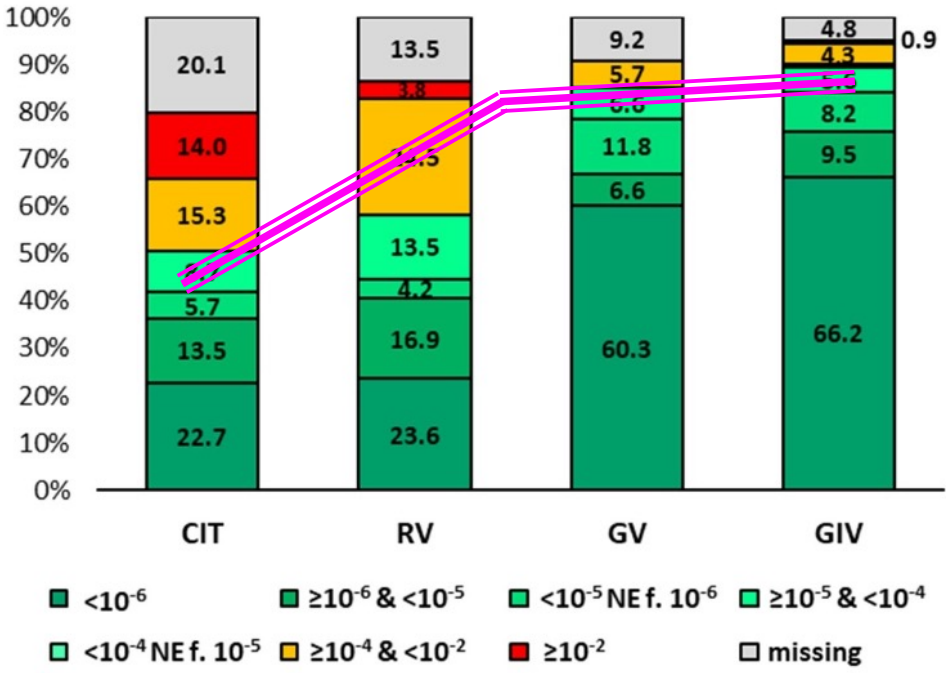

CT/CIT
BCL2i
BTKi

GAIA/CLL13 trial: MRD rates in PB at MO15 at 4 years follow-up

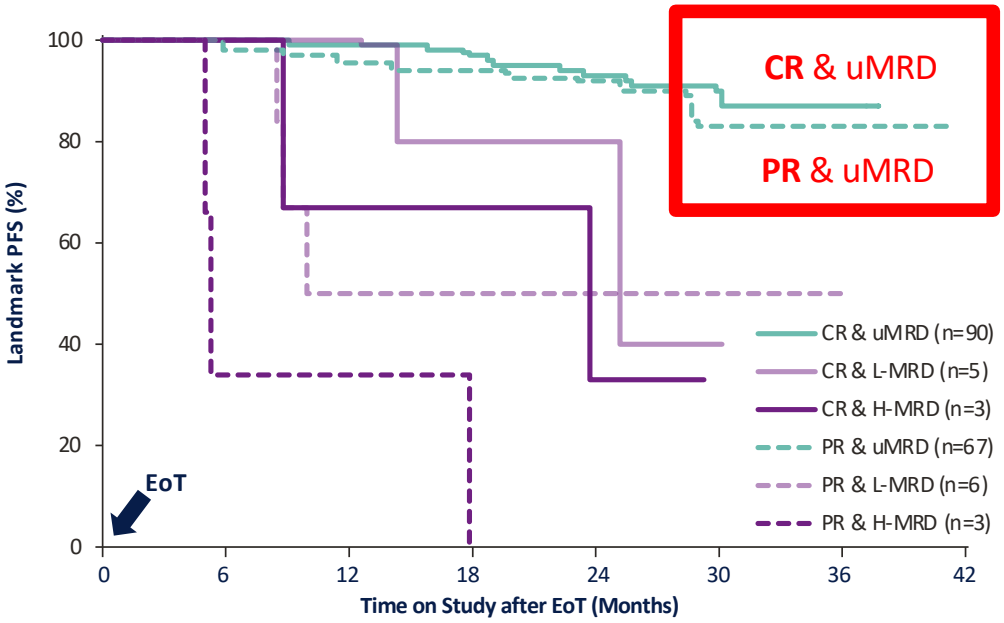




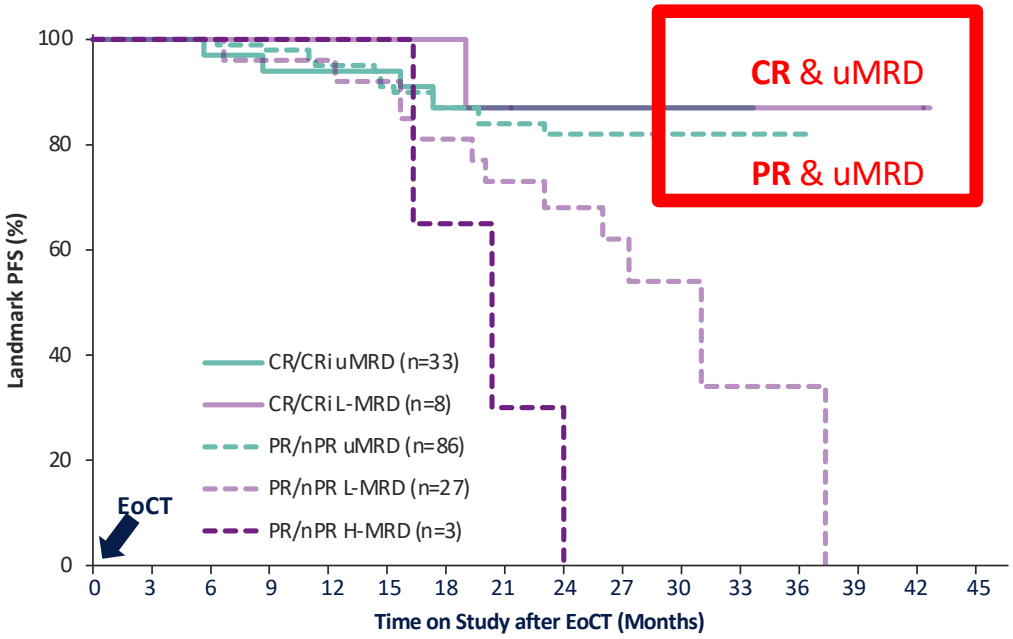
Fürstenau M, et al. ASH 2023 (Abstract No. 635 – presentation).

Ven-O and Ven-R: patients in PR have a similar outcome as patients with CR when uMRD levels are achieved

CLL14: VenO

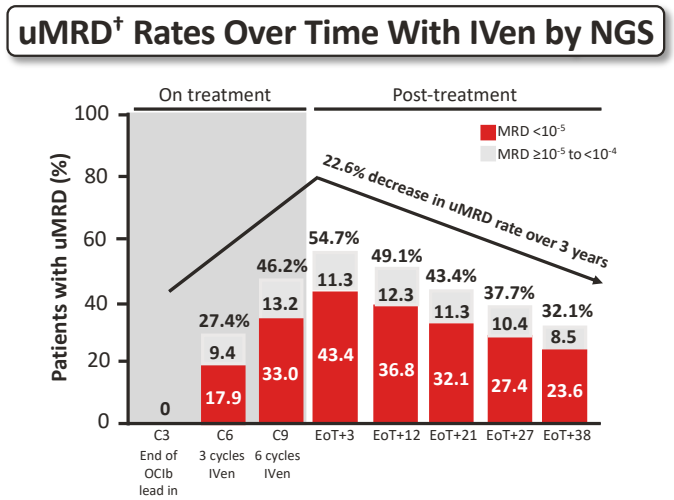


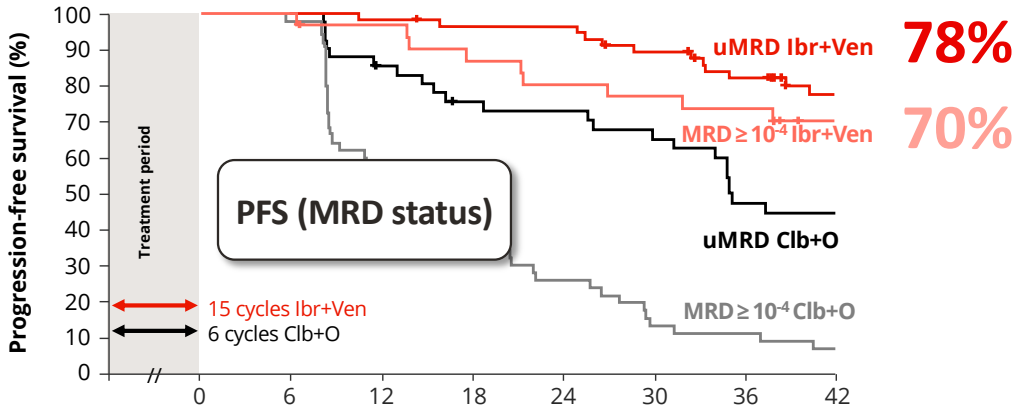
MURANO: VenR



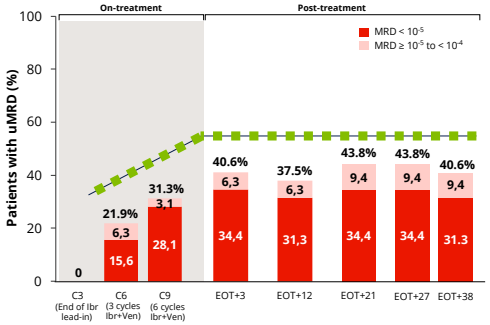
. 1. Al-Sawaf O, et al. Lancet Oncol 2020; 21:1188–1200). 2. Kater AP, et al. Oral #695. 60th ASH Annual Meeting. Dec 1-4, 2018. San Diego, CA.

GLOW: MRD rates and outcomes in I+V



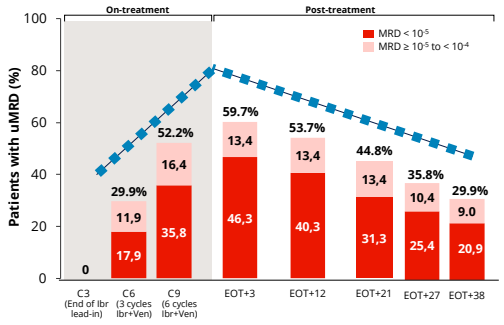


mIGHV (n = 32; ITT)

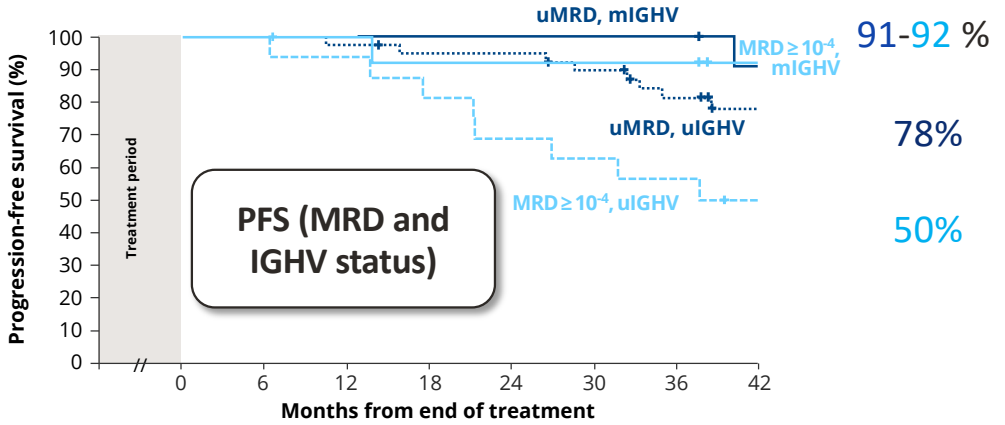


stable 3 years after treatment completion

uIGHV (n = 67; ITT)



From ~ 60% to ~ 30% at EOT+38



Moreno C, *et al*. ASH 2023. Abstract 634 (Oral)

median follow-up: 57.3 months

The MRD cohort of the CAPTIVATE trial

Patients < 70 yrs of age with previously untreated, active CLL/SLL requiring therapy; ECOG PS 0/1 (N = 164)

Ibrutinib 3 cycles

Ibrutinib Venetoclax 12 cycles

MRD-guided randomization

Undetectable MRD*

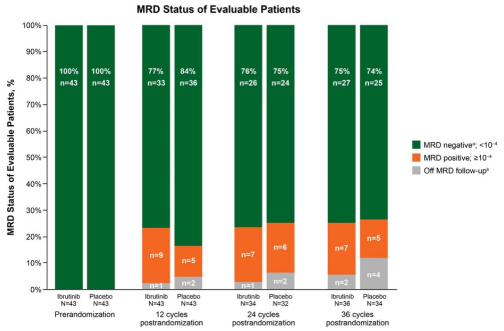
- **Ibrutinib**
- **Placebo**

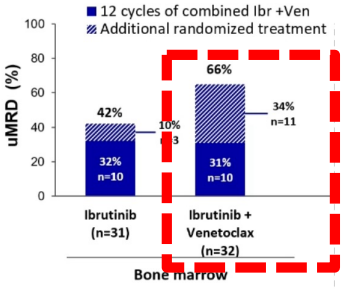
Detectable MRD

- **Ibrutinib**
- **Ibrutinib + Venetoclax**

*Defined as having undetectable MRD (< 10^{-4} by flow cytometry) serially over at least 3 cycles in both PB and BM

MRD Negativity Rates Were Sustained 3-years Post-randomization and Similar in Patients Randomized to Placebo vs Continued Ibrutinib



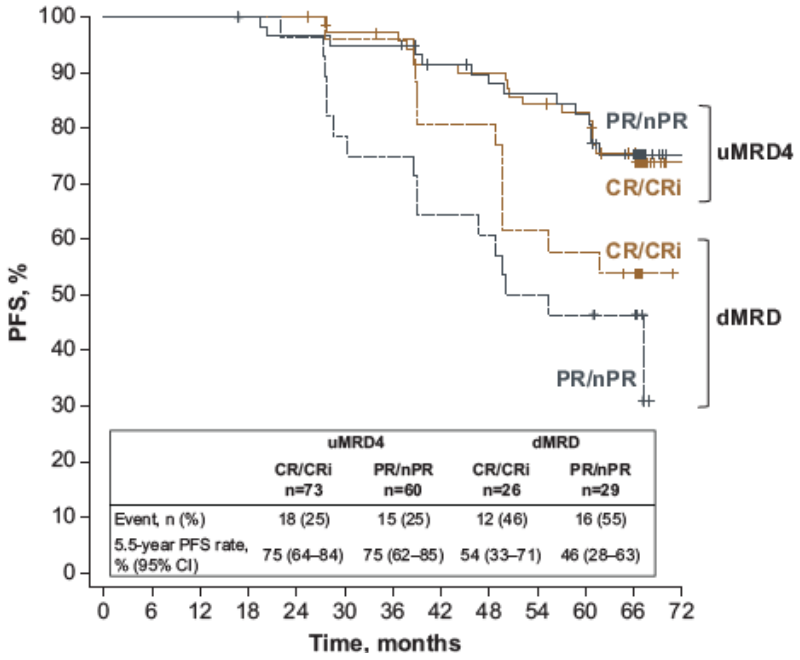


In patients WITHOUT confirmed uMRD after 12 cycles combination (I+V) increases in uMRD were greater with continued Ibrutinib + venetoclax versus Ibrutinib alone

ASH 2022; Allan JN et al.

Wierda et al. JCO 2021.

MRD Influences PFS

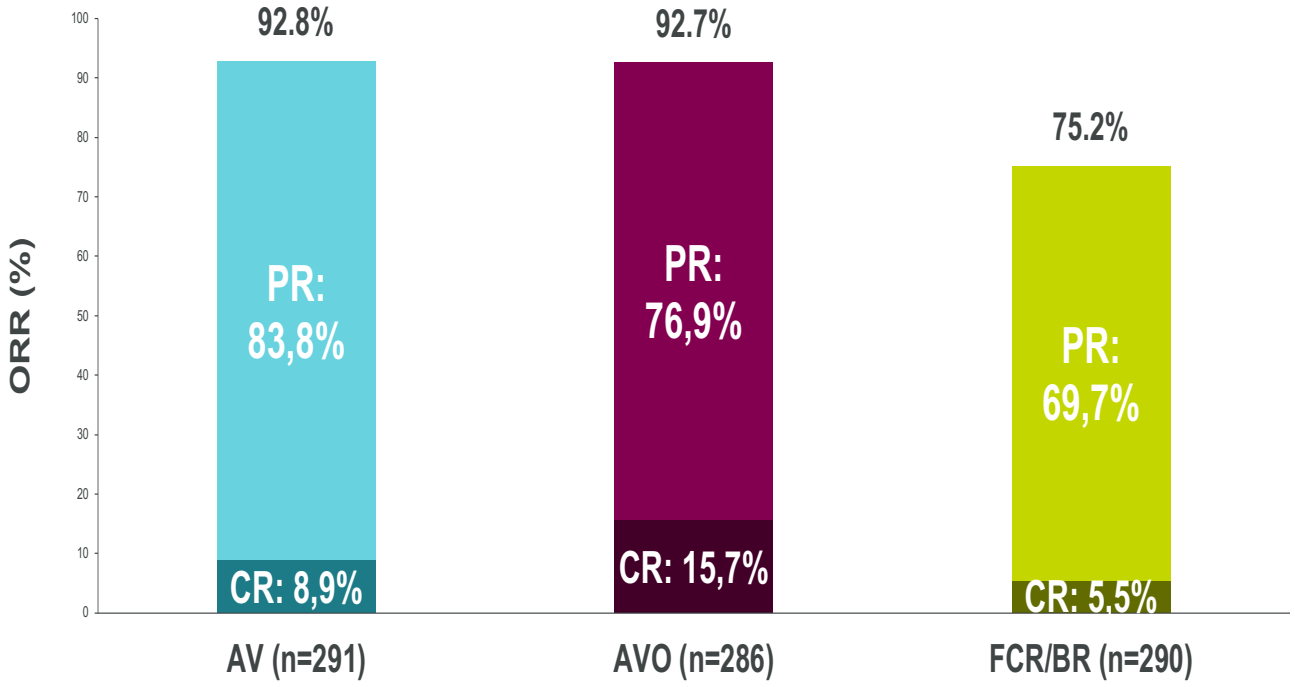


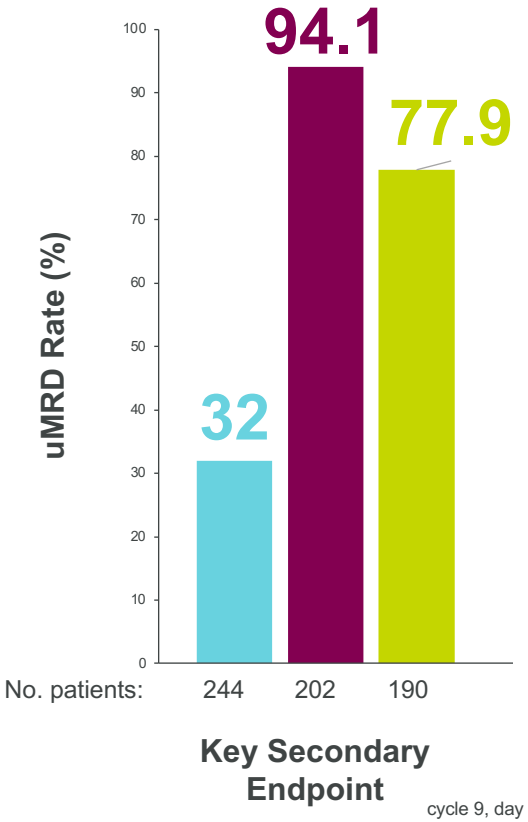
	uMRD4		dMRD	
	CR/CRi n=73	PR/nPR n=60	CR/CRi n=26	PR/nPR n=29
Event, n (%)	18 (25)	15 (25)	12 (46)	16 (55)
5.5-year PFS rate, % (95% CI)	75 (64–84)	75 (62–85)	54 (33–71)	46 (28–63)

EOT Peripheral Blood MRD Status Is More Predictive Thank iwCLL Response for Long-Term PFS

Wierda et al., ASH 2024

AMPLIFY: Overall Response with highest uMRD rates in the AVO arm





(Flow Cytometry [$<10^{-4}$] in PB)

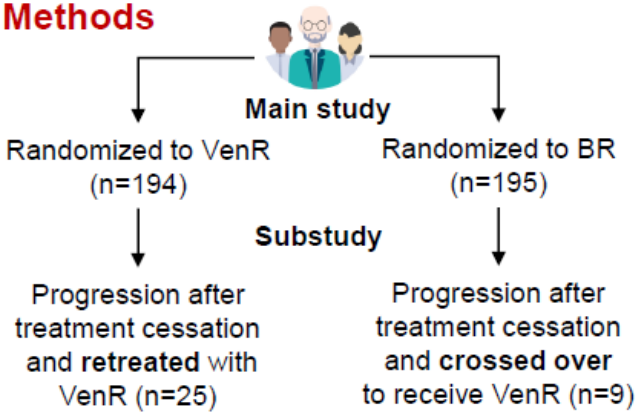
Brown JR ASH 2024

Final Analysis of the MURANO Trial: Venetoclax-Rituximab (VenR) vs Bendamustine-Rituximab (BR) in Patients With Relapsed/Refractory (R/R) Chronic Lymphocytic Leukemia (CLL)

Context of Research

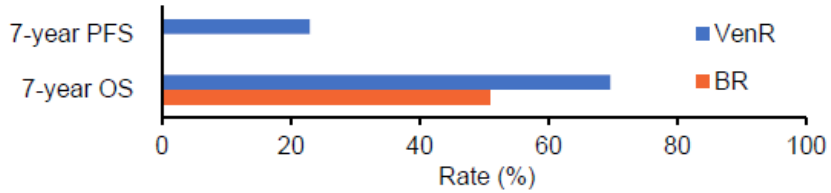
- In the **phase 3 MURANO trial** (**NCT02005471**), fixed-duration VenR resulted in superior progression-free survival (PFS) and overall survival (OS) vs BR
- We report the **final analyses** of MURANO (median follow-up: 7 years), including results of a **retreatment/crossover substudy**

Methods

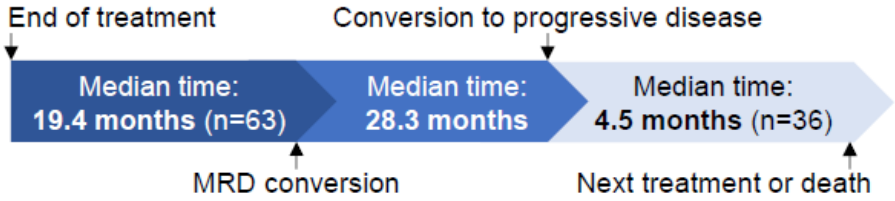


Main Findings

Survival benefits with VenR vs BR were **sustained**



VenR-treated patients who achieved **undetectable minimal residual disease** (MRD) (n=83):



Substudy Results

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

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

Conclusions: This final long-term analysis of the MURANO trial continues to demonstrate clinically meaningful benefits for fixed-duration VenR over BR in patients with R/R CLL. Retreatment with VenR is a viable option in pretreated patients.

Kater et al. Blood 2025

Progressione dopo BTKi

EHA2024
JUNE 13 - 16 | MADRID

American Journal of Hematology
WILEY

CORRESPONDENCE OPEN ACCESS

Treatment Effectiveness of Venetoclax-Based Therapy After Bruton Tyrosine Kinase Inhibitors in Chronic Lymphocytic Leukemia: An International Real-World Study

Real-Life from CORE (Ghosh *et al.* 2024)

Retrospective observational study

PATIENT POPULATION

Real-world patients who received Ven-based therapy after discontinuation of a cBTKi* (N=205)

cBTKi*
Median DOT 20.2 mo

Ven-based
Median DOT 14.4 mo

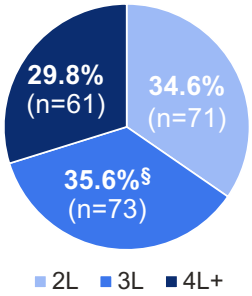
Median 0.6 mo between cBTKi end and Ven start

Reason for cBTKi discontinuation:
Intolerance 42.9%; Progression Disease 37.1%

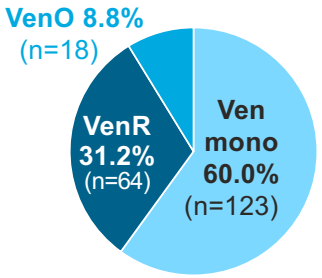
*Ibr 85.4%, Acala 6.8%, IR 2.9%.

TREATMENT CHARACTERISTICS

Ven LOT (N=205)

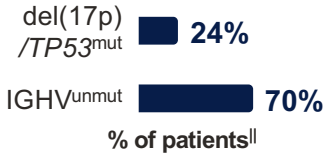


Ven Regimens (N=205)



§86% of 3L Ven had CT/CIT exposure prior to cBTKi

HIGH RISK FEATURES



Ghosh N, et al. American Journal of Hematology, 2024; 0:1–5

Progressione dopo BTKi

EFFECTIVENESS RESULTS

		Response			N	PFS		TTNT-D	
		N	ORR. %	CR, %		Median, mo (95% CI)	18-mo rate, %	Median, mo (95% CI)	18-mo rate, %
Overall	Overall	141	79.4	44.0	205	44.1 (36.3, NR)	76.2	44.2 (31.9, NR)	73.7
	1L→2L	47	85.1	53.2	71	43.2 (39.5, NR)	80.8	NR (31.9, NR)	73.6
	2L→3L	51	80.4	43.1	73	44.3 (36.3, NR)	82.1	44.2 (37.0, NR)	78.4
cBTKi - **Stop per intolleranza**	Overall	60	85.0	51.7	88	NR	84.1	NR	79.3
	1L→2L	22	86.4	59.1	36	39.5 (39.5, NR)	84.1	39.5 (39.5, NR)	77.5
	2L→3L	26	88.5	53.8	33	NR	89.0	NR	87.2
cBTKi - **Stop per progressione**	Overall	51	76.5	37.3	76	30.1 (22.1, NR)	71.0	30.4 (26.3, NR)	75.3
	1L→2L	10	90.0	50.0	15	31.9 (13.2, NR)	62.2	[illegible] (12.5, NR)	53.3
	2L→3L	19	68.4	26.3	30	31.8 (22.1, NR)	73.1	[illegible] (26.3, NR)	75.2
Patients treated with VenR	**Overall**	**42**	**71.4**	**40.5**	**64**	**39.5 (31.8, NR)**	**77.0**	**37.4 (31.6, NR)**	**75.7**
	1L→2L	**19**	**78.9**	**52.6**	**31**	**43.2 (39.5, NR)**	**88.4**	**NR (39.5, NR)**	**85.0**
	2L→3L	**15**	**73.3**	**33.3**	**23**	**36.3 (23.7, NR)**	**85.9**	**37.4 (31.6, NR)**	**79.8**

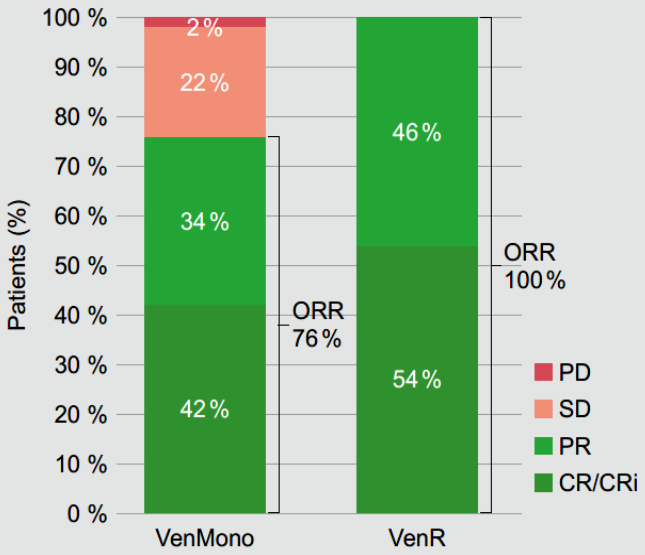
Questo studio RWE dimostra l'**efficacia dei trattamenti a base di Ven (Vmono e V+R) in 2L e 3L, dopo cBTKi**, indipendentemente dal motivo dell'interruzione dello stesso.
Risultati simili di efficacia sono stati osservati tra i pazienti che hanno interrotto cBTKi in 1L > 2L e 2L > 3L

Ghosh N, et al. American Journal of Hematology, 2024; 0:1–5

Progressione dopo BTKi

EFFECTIVENESS RESULTS

Figure 3: Best overall response after 24 months



The reported best overall response at 24 months after V initiation is 76 % (CR+CRi 42 %; PR: 34 %) for the VM arm and 100% (CR+CRi 54 %; PR: 46 %) for the VR arm (figure 3).

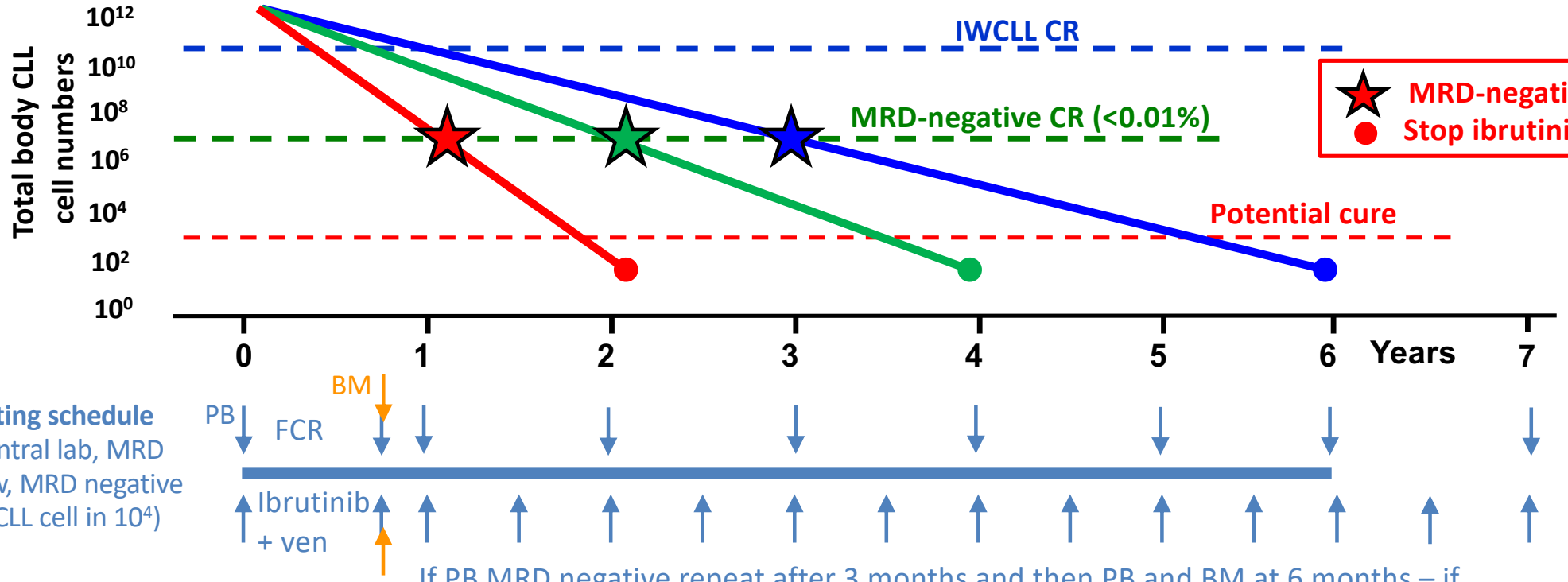
After a median follow-up of 23 months:

- estimated 24-months **OS rate** were **73.2% for VM** and **76.6% in VR**
- estimated 24-months **PFS rate** was **62.4% for VM** and **72.9% for VR**, respectively.

Anche questo studio RWE dimostra l'**efficacia dei trattamenti a base di Ven (VM e VR) dopo trattamento con cBTKi**.
Nonostante i fattori di rischio fossero simili tra i gruppi VR e VM, il gruppo **VR ha mostrato migliori tassi di OS, PFS e ORR.**
Il trattamento è stato ben tollerato in entrambi i gruppi, affermando V come una valida opzione per pazienti con **pretrattamenti intensivi e con esposizione a Ibru.**

Schwaner et al. ASH 2024, Blood 144 (2024) 6788-6789

Stopping rules for ibrutinib + venetoclax in Flair



Defining treatment duration
2 to 6 years Ibrutinib
or both ibr+venetoclax
Double time after MRD negative

Restart ibrutinib + venetoclax if becomes MRD positive prior to Year 6

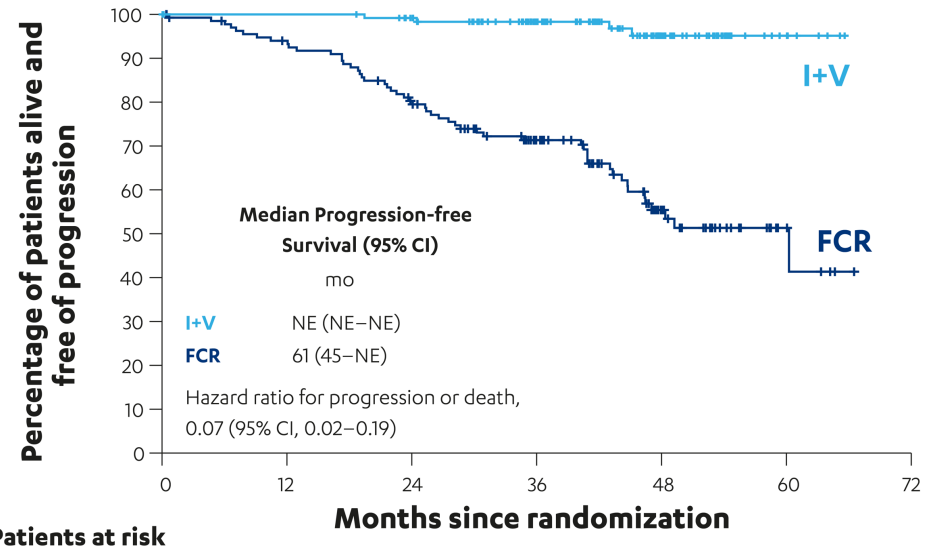
Hillmen *et al.*, Abstract 631, ASH 2023

National Cancer Research Institute

CANCER RESEARCH UK | ctru University of Leeds | LEEDS CLINICAL TRIALS UNIT

PFS is independent on *IGHV* status with I+V

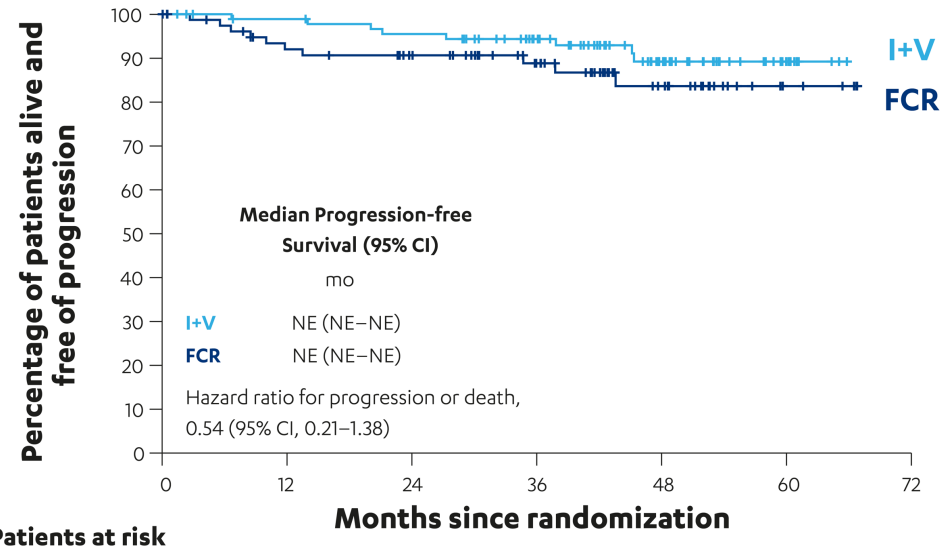
Patients with unmutated *IGHV*



Patients at risk (no. with data censored)

I+V	123 (1)	122 (1)	117 (5)	89 (32)	47 (72)	8 (111)	0 (119)
FCR	138 (1)	122 (8)	103 (10)	76 (25)	35 (54)	6 (80)	0 (85)

Patients with mutated *IGHV*



Patients at risk (no. with data censored)

I+V	93 (0)	88 (4)	84 (5)	70 (18)	42 (45)	11 (74)	0 (85)
FCR	80 (1)	67 (7)	61 (12)	49 (23)	25 (45)	5 (65)	0 (70)

BM, bone marrow; FCR, fludarabine, cyclophosphamide and rituximab; HR, hazard ratio; I, ibrutinib; I+V, ibrutinib plus venetoclax; MRD; minimal residual disease; OS, overall survival; PB, peripheral blood; PFS, progression-free survival; pts, patients; V, venetoclax.

Munir T et al. N Engl J Med. 2023; doi: 10.1056/NEJMoa2310063

Only 13 patients (8.2%) had MRD relapse necessitating retreatment

	Stopped I +V at 2 years	Stopped I + V at 3 years	Stopped I + V at 4 years	Total
Total	115 (100%)	25 (100%)	19 (100%)	159 (100%)
Restart I + V?				
Yes	8 (7.0%)	4 (16.0%)	1 (5.3%)	13 (8.2%)
No	107 (93.0%)	21 (84.0%)	18 (94.7%)	146 (91.8%)

Mutation Status	Stopped I + V at 2 years	Stopped I + V at 3 years	Stopped I + V at 4 years	Total
Mutated	1 (12.5%)	0 (0.0%)	0 (0.0%)	1 (7.7%)
Unmutated	7 (87.5%)	4 (100.0%)	1 (100.0%)	12 (92.3%)
Total	8 (100%)	4 (100%)	1 (100%)	13 (100%)

Median time to MRD relapse 20 months

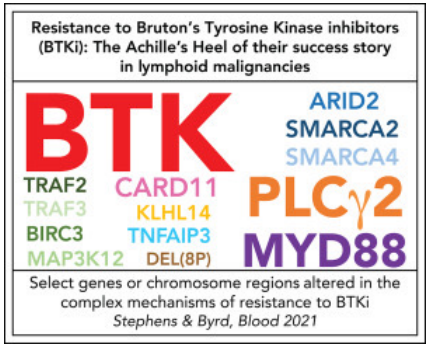
Munir T et al ASH 2024

Why Fixed Duration Therapy in CLL?

- ✓ Efficacy
- ✓ Deep responses (MRD)
- ✓ **Clonal evolution and resistance**
- ✓ Safety and Tolerability
- ✓ QoL
- ✓ Cost-effectiveness
- ✓ Patient’s desire

Acquired mutations in patients treated with targeted agents

BTKi/BCL2i continuous

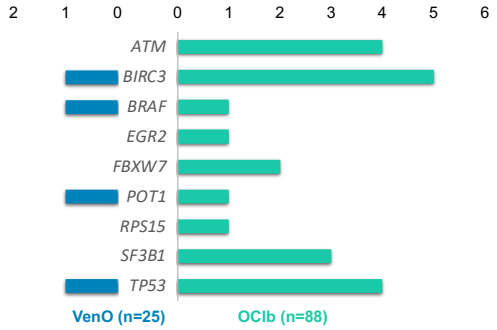


MANY

* RESONATE-2, iLLUMINATE, NCT01500733, RESONATE, and RESONATE-17.

BTK, Bruton's tyrosine kinase; mut, mutated; NE, not estimable.

Venetoclax-Obinutuzumab



NONE

1. Wiestner A, *et al.* ASH 2020. Abstract 2225 (Poster);
2. Tausch E, *et al.* EHA 2021. Abstract S144 (Oral).

Ibrutinib-Venetoclax

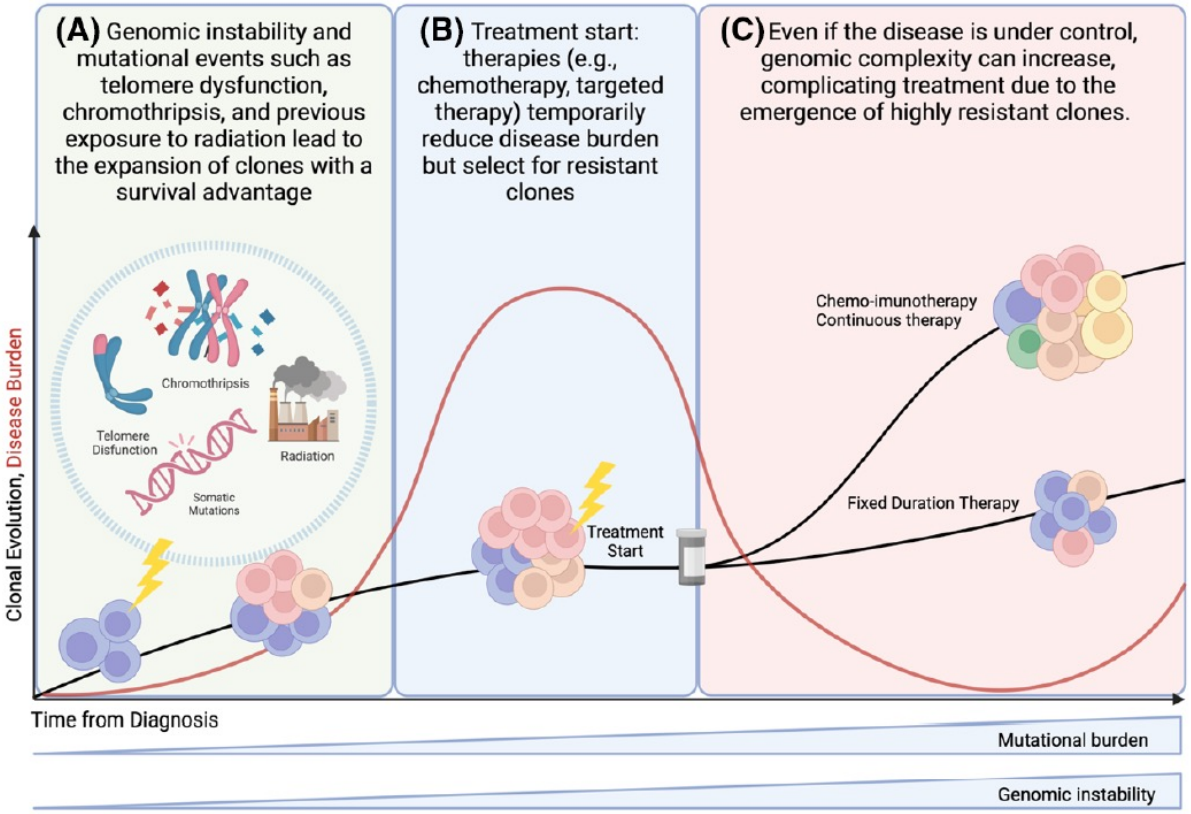
1 of 40 patients with acquired subclonal mutation in *BCL-2* (A113G, VAF 8.3%) was identified in the CAPTIVATE trial

**BCL-2* A113G identified in patients with PD on venetoclax (usually in combination with *BCL-2* G101V) has unclear clinical significance

ONE

[1]Popovic R et al, *Am J Hematol.* 2022;97(2):e47-e51. [2]Kotmayer L et al, *Int J Mol Sci.* 2023;24:5802. [3]Lucas F et al, *Blood.* 2020;135:2192-2195

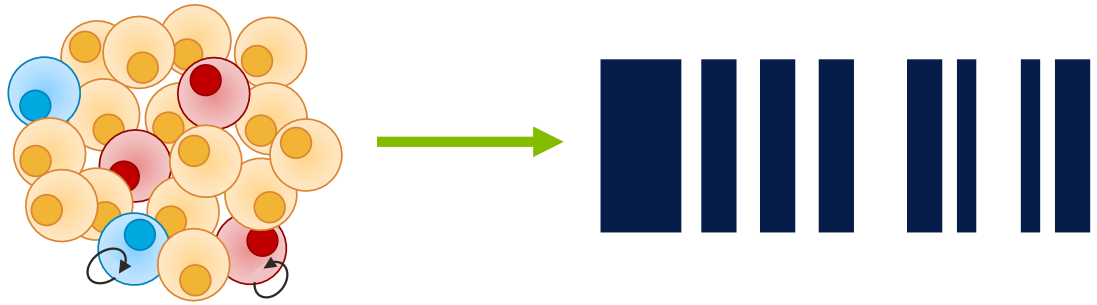
Clonal pressure and therapeutic resistance



I trattamenti continuativi aumentano l'**insorgenza di mutazioni e resistenze al trattamento** esercitando una **maggiore pressione clonale** rispetto ai trattamenti a durata fissa

Serafin et al. Br J Haematol 2025; 00:1-10

Adaptive therapy Concept



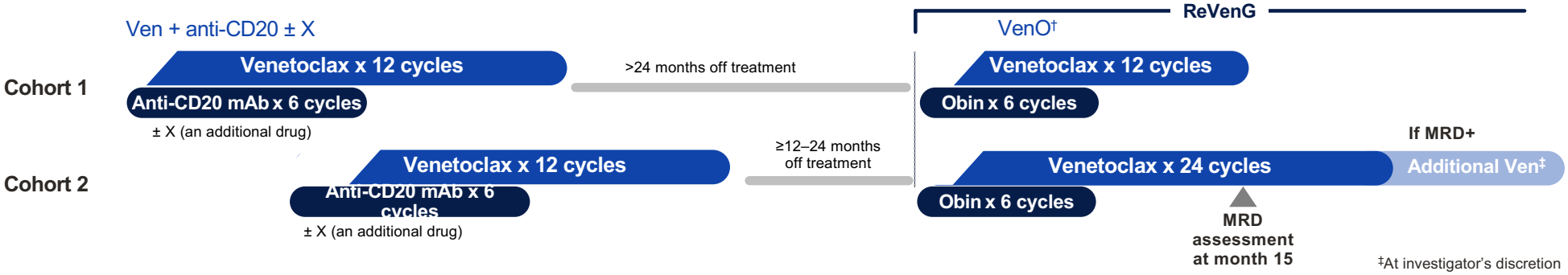
Cellular ecosystem ruled by evolutionary laws

Varying doses and schedules of therapy

ReVenG study: efficacy of VenO retreatment in CLL after prior Ven-based therapy

VENETOCLAX-OBI → VENETOCLAX

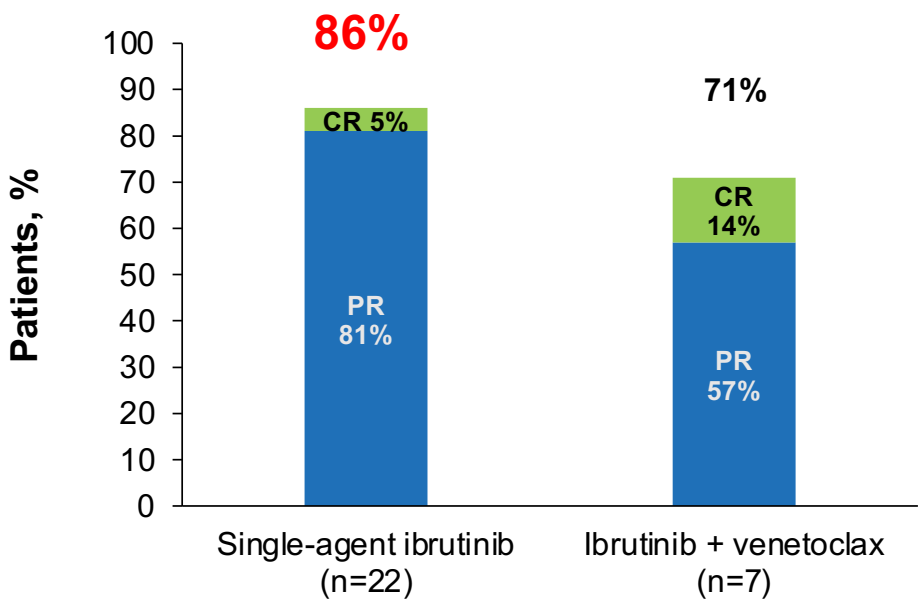
- Data for treatment sequencing after 1L VenO are limited; treatment options include retreatment with venetoclax-based therapy or subsequent cBTKi
- A prospective Phase 2 study (**ReVenG**) is ongoing to evaluate the efficacy and safety of FTD VenO retreatment in patients who previously achieved a clinical response and completed treatment with 1L fixed duration VenO



In Italy, this study is active in Turin and Terni

Davids M, et al. ASH 2021. Oral 2634. 2. Clinicaltrials.gov. NCT04895436. Accessed April 2024.

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



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

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

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

Wierda WG et al ASCO 2024

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

IBRUTINIB
VENETOCLAX

→

VENETOCLAX

VENETOCLAX
RITUXIMAB

AGENZIA ITALIANA DEL FARMACO

DETERMINA 26 febbraio 2024

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

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

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

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

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

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

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

Indicazione ammessa alla rimborsabilità:

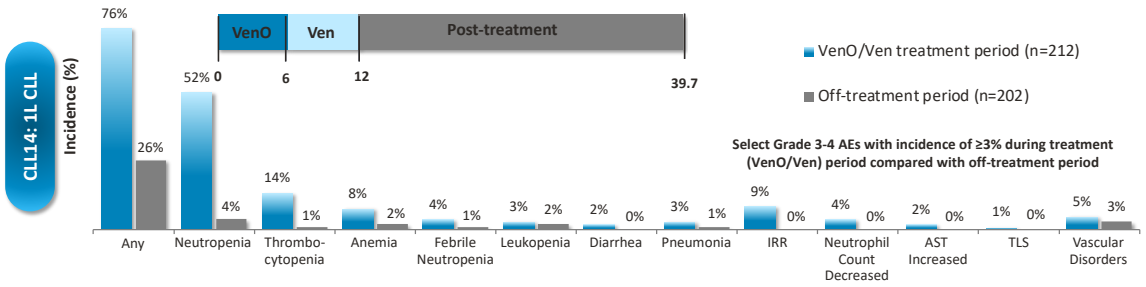
Venclyxto in combinazione con obinutuzumab è indicato per il trattamento di pazienti adulti con leucemia linfatica cronica (LLC) non trattati in precedenza e non candidabili ad immunochemioterapia di prima linea tipo FCR

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

Why Fixed Duration Therapy in CLL?

- ✓ Efficacy
- ✓ Deep responses (MRD)
- ✓ Clonal evolution and resistance
- ✓ **Safety and Tolerability**
- ✓ QoL
- ✓ Cost-effectiveness
- ✓ Patient’s desire

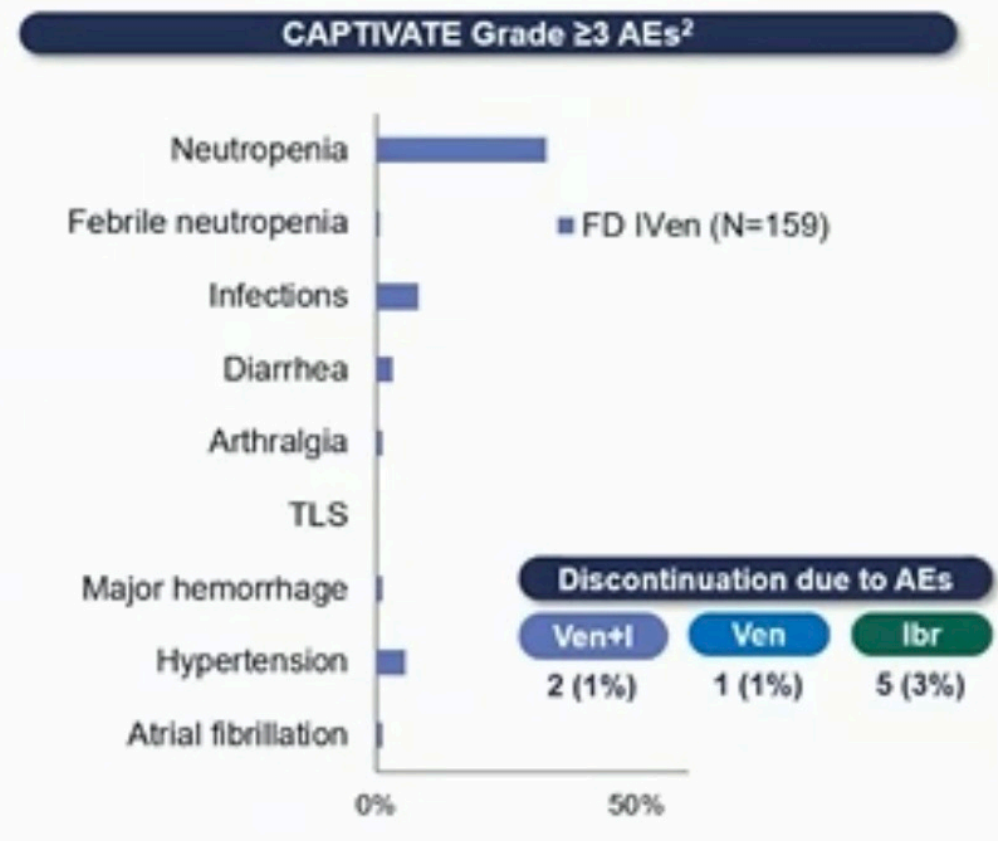
Venetoclax-Obinutuzumab safety profile

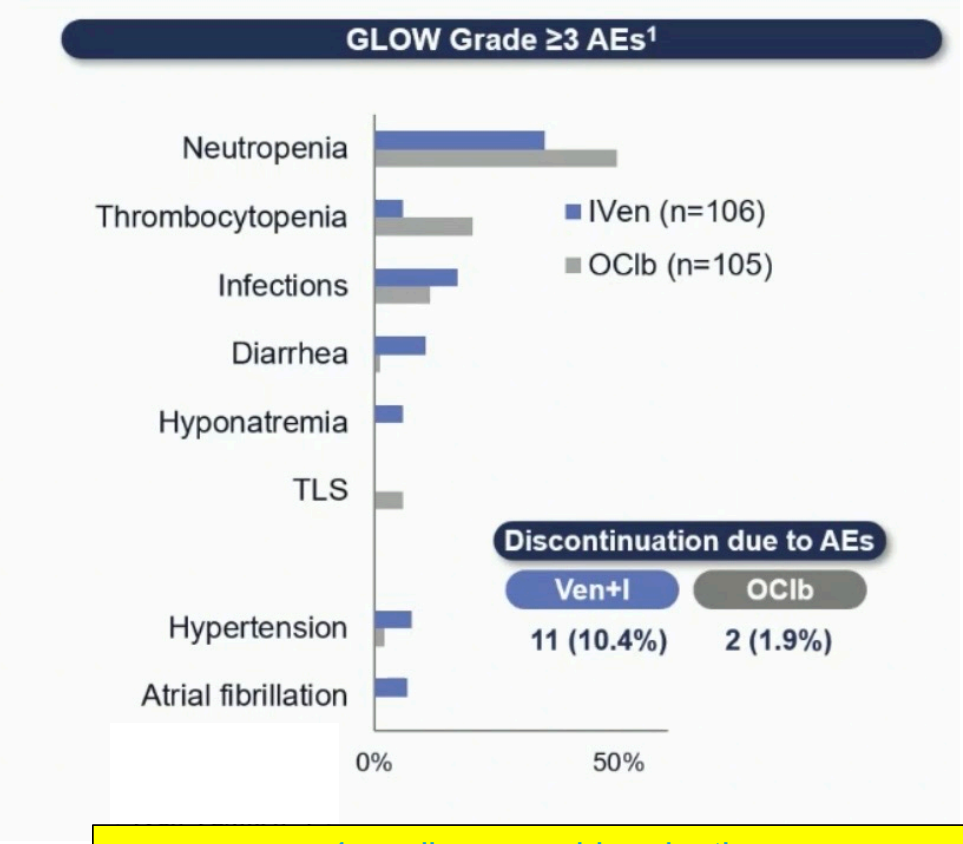


Patients	VenO arm (venetoclax) n=212	OClb arm (chlorambucil) n=214
Dose reduction due to AE, n (%)[1]	**43 (20)**	**17 (8)**
Due to neutropenia [most common cause]	28 (13)	13 (6)
Treatment-emergent (VenO or OClb) AE leading to treatment discontinuation, n (%)[1]	33 (16)	35 (16)
Treatment discontinuation due to any AE, n (%)[1]	**27 (13)**	**31 (15)**
Due to neutropenia [most common cause]	5 (2)	5 (2)
Median dose intensity, % (range)*,[2]	**95.1 (21–100)**	**95.4 (4–111)**

Barriers	Solutions
TLS	Ramp-up
IRRs	Management
Neutropenia	G-CSF

Ibrutinib + Venetoclax has a generally manageable safety profile





4 cardiac or sudden deaths,
all in patients with CIRS score of at least 10 and/or ECOG PS 2, and a history of hypertension, cardiovascular disease, and/or diabetes

- 1. Kater AP, *et al. NEJM Evid* 2022; doi: 10.1056/EVIDoa2200006;
  2. Munir T, *et al. J Clin Oncol* 2023; doi: 10.1200/JCO.22.02283.

1. Tam CS, *et al. Blood* 2022; **139:**3278–3289;
2. Moreno C, *et al.* EHA 2022. Abstract P669 (Poster);
3. Tedeschi A, *et al.* EHA 2023. Abstract P617 (Poster).

Summary of deaths during GLOW study

Treatment arm	On-treatment	Post-randomised treatment and prior to start of subsequent antileukemic therapy	After initiation of subsequent antileukemic therapy	Total
Ibrutinib-venetoclax	* 1 infection-related: • 1 pneumonia 2 cardiac* 2 sudden/unknown 1 secondary primary malignancy (metastatic squamous cell carcinoma) 1 ischemic stroke	* 3 infection-related: • 2 COVID/COVID-related infections • 1 septic shock 2 sudden/unknown 1 stroke	* 0 infection-related 1 progressive disease 1 euthanasia	**15**
Chlorambucil-obinutuzumab	* 1 infection-related: • 1 pneumonia 1 cholestasis	* 5 infection-related: • 4 COVID/COVID-related infections • 1 infection (non-COVID) 4 cardiac 3 sudden/unknown 3 secondary primary malignancies† 1 respiratory failure due to aspiration 1 progressive neurological deterioration 1 cerebral vascular occlusion 1 deterioration of general condition 1 progressive disease	* 5 infection-related: • 3 pneumonia • 2 COVID/COVID-related infections 1 acute brain bleed 1 ischemic stroke 1 suspected progressive disease	**30**
Total	**9**	**26**	**10**	**45**

*One patient listed as cardiac disorder had three causes of death: Tachy-brady syndrome, cardiac failure, and pneumonia.

Ibru lead-in

Cardiac-related deaths occurred in patients who were highly comorbid with significant cardiac history

Baseline CV risk assessment ensures the identification of patients who stand to benefit from I+V treatment

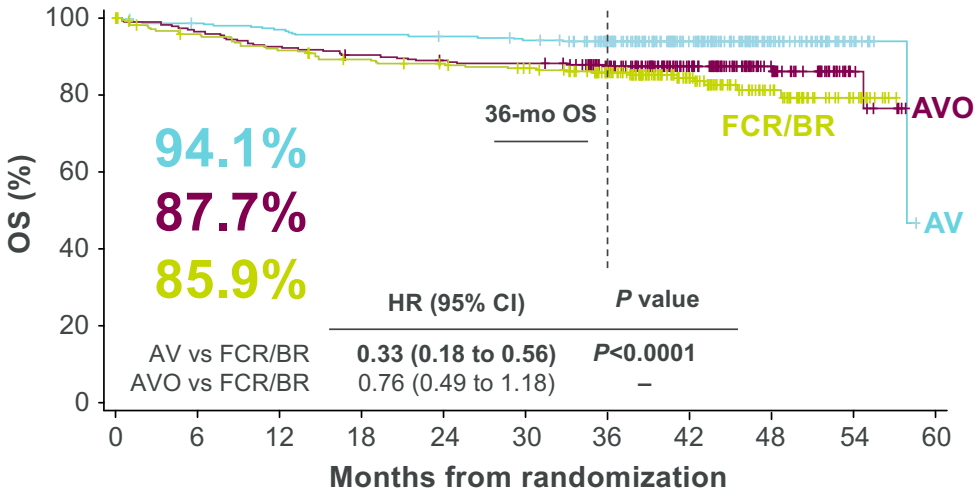
Niemann CU, Lancet Oncol 2023, supplementary appendix

Events of Clinical Interest in the AMPLIFY Study

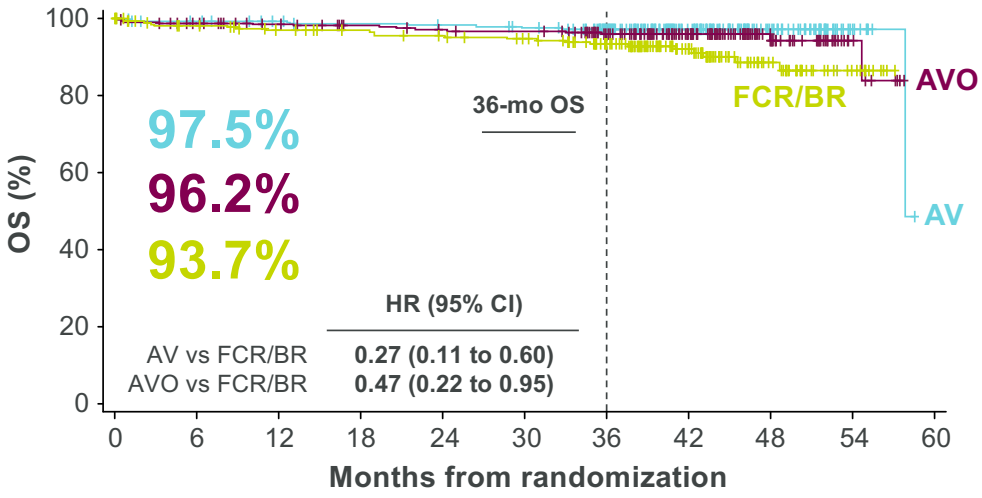
	AV (n=291)		AVO (n=284)		FCR/BR (n=259)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Any ECI	222 (76.3)	136 (46.7)	242 (85.2)	188 (66.2)	185 (71.4)	141 (54.4)
Cardiac events	27 (9.3)	5 (1.7)	34 (12.0)	7 (2.5)	9 (3.5)	3 (1.2)
Atrial fibrillation	2 (0.7)	1 (0.3)	6 (2.1)	2 (0.7)	2 (0.8)	2 (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
Any serious AE	72 (24.7)		109 (38.4)		71 (27.4)	
Serious AEs leading to death	10 (3.4)		17 (6.0)		9 (3.5)	
AE leading to treatment discontinuation	23 (7.9)		57 (20.1)		28 (10.8)	

Overall Survival: the impact of COVID-19 death

OS Prolonged With AV vs FCR/BR



OS Prolonged With AV and AVO vs FCR/BR (COVID-19 Deaths Censored)



COVID-19 deaths: 10 (AV), 25 (AVO), 21 (FCR/BR)

Brown JR ASH

A pilot study of lower doses of ibrutinib in patients with chronic lymphocytic leukemia

Ibrutinib occupancy data

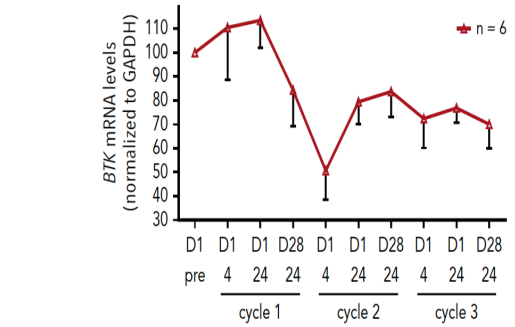
Even though at least 97% BTK occupancy was achieved at the 2.5 mg/kg/d dose level, which roughly corresponds to 175 mg/d, in the phase 1 trial, a 420 mg/d dose was selected for CLL

IBRUTINIB DOSE AND PHARMACODYNAMICS IN CLL

	Cycle 1	Cycle 2	Cycle 3
Dose/day	420 mg	280 mg	140 mg
BTK occupancy	99%	99%	99%
CCL3 decrease	56%	53%	57%
BTK(Tyr223) decrease	35%	37%	35%

Advani RH et al. J Clin Oncol. 2013;31(1):88-94.

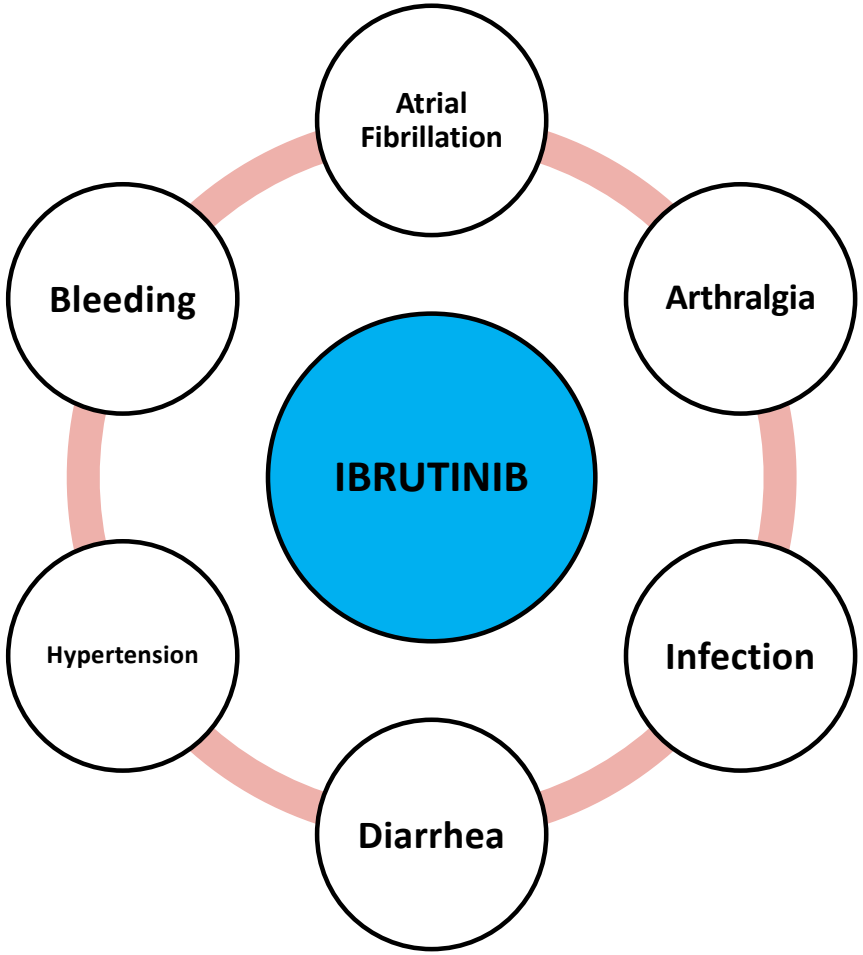
Effect of ibrutinib on BTK mRNA during dose reductions over the course of 3 cycles



Chen LS et al. Blood. 2018;132(21):2249-2259

Chen LS et al. Blood 2018

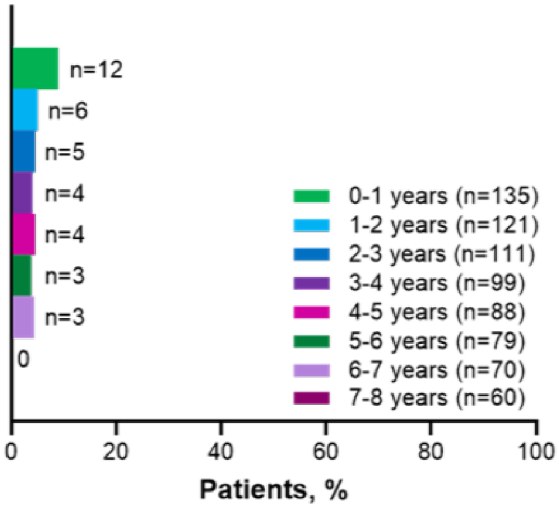
Ibrutinib Monotherapy: from early safety confidence to emerging concerns



RESONATE-2	Ibrutinib N=135
Median (range) duration of ibrutinib treatment, years	6.2 (0.06–10.2)
Continuing ibrutinib at study closure, n (%)	27%
Discontinued ibrutinib, n (%)	
AE	33%
PD	18 (13)

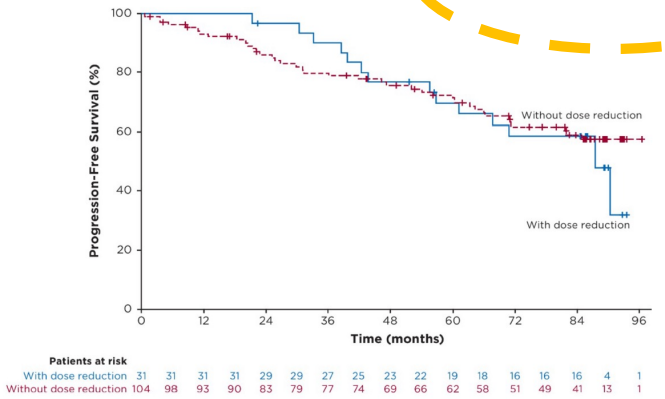
Burger J, et al. poster presented at EHA 2024. #P670

Ibrutinib dose modifications resolved AEs for most patients while did not impact efficacy in the RESONATE-2 trial

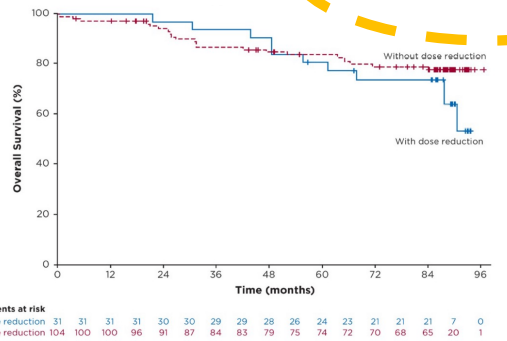


- Rate of dose reductions due to AEs was highest in Years 0-1 (9%) and lower in subsequent years
- 28/31 (90%) had improvement/resolution of the AE following dose reduction
- 19/31 (61%) had no recurrence or recurred at lower level

Estimated 7-year **PFS**: 59% vs 59%



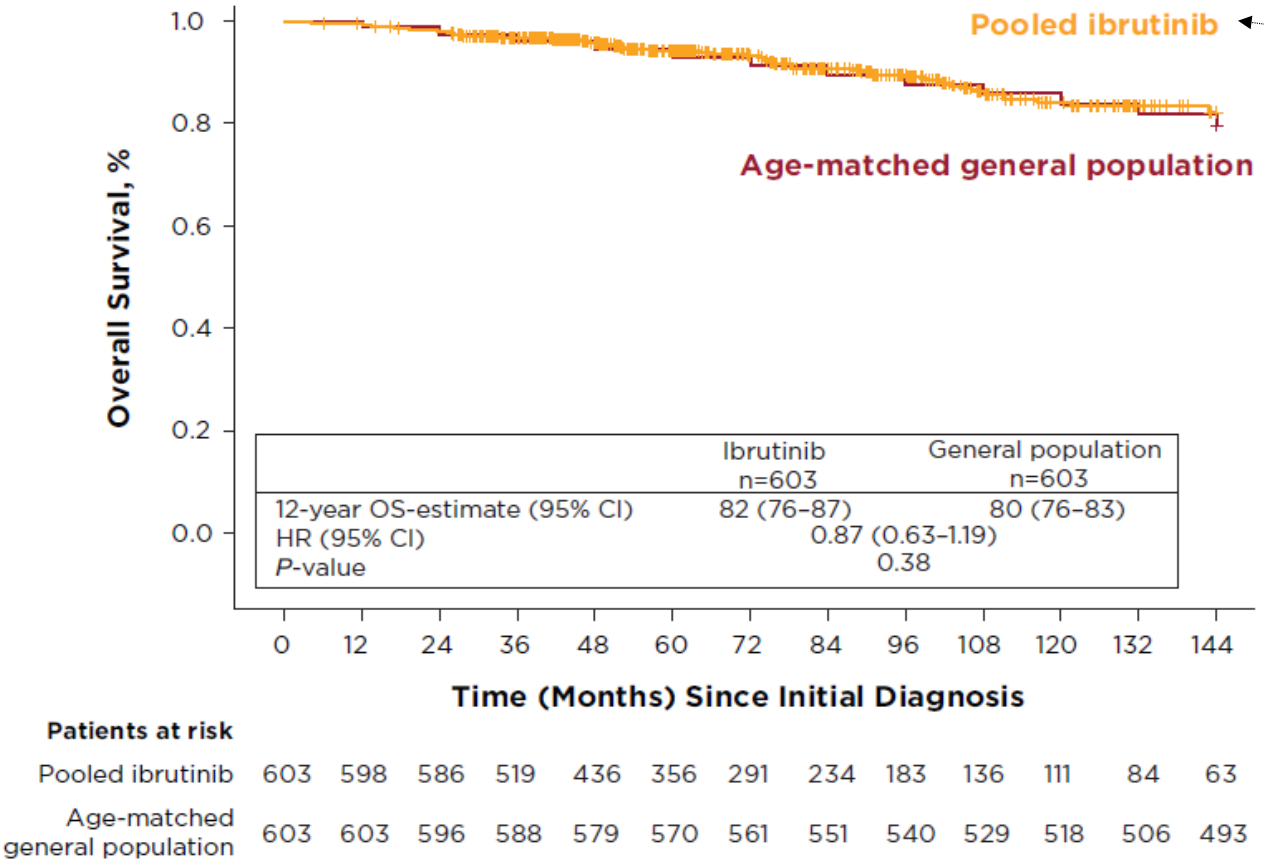
Estimated 7-year **OS**: 79% vs 74%



Barr PM, et al. *Blood Adv*. 2022 Apr 4 [Epub ahead of print].

Woyach, J.A et al. Cancers 2023, 15, 507

Ibrutinib provides patients a life as long as those without CLL



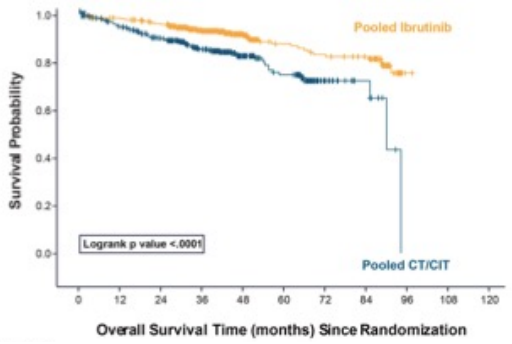
	Ibrutinib n=603	General population n=603
12-year OS-estimate (95% CI)	82 (76–87)	80 (76–83)
HR (95% CI)	0.87 (0.63–1.19)	
P-value	0.38	

Patients at risk

Pooled ibrutinib	603	598	586	519	436	356	291	234	183	136	111	84	63
Age-matched general population	603	603	596	588	579	570	561	551	540	529	518	506	493

Data for previously untreated CLL/SLL patients were pooled across 3 studies: ECOG-ACRIN E1912, RESONATE-2, and iLLUMINATE.

Survival estimates for the general population age-matched to the Ibrutinib and CT/CIT cohorts were obtained from the survival probability from life tables published by the CDC for total US population in 2019 (https://www.cdc.gov/nchs/products/life_tables.htm).



Ghia et al. Hemasphere 2024

TAILOR: Study of ibrutinib ± venetoclax to customize ibrutinib treatment regimens for participants with previously untreated CLL/SLL

Phase 2, randomized, multi-cohort study design

- Previously untreated CLL/SLL
- Measurable nodal disease by CT, defined as ≥1 lymph node ≥1.5 cm in longest diameter
- ECOG PS 0–2 for ibrutinib monotherapy; ECOG PS 0–1 for ibrutinib + venetoclax
- N=320

Ibrutinib (R)
- **420 mg** QD ibrutinib until PD or toxicity
- 1 cycle* **420 mg** QD ibrutinib lead-in → **280 mg** QD ibrutinib until PD or toxicity

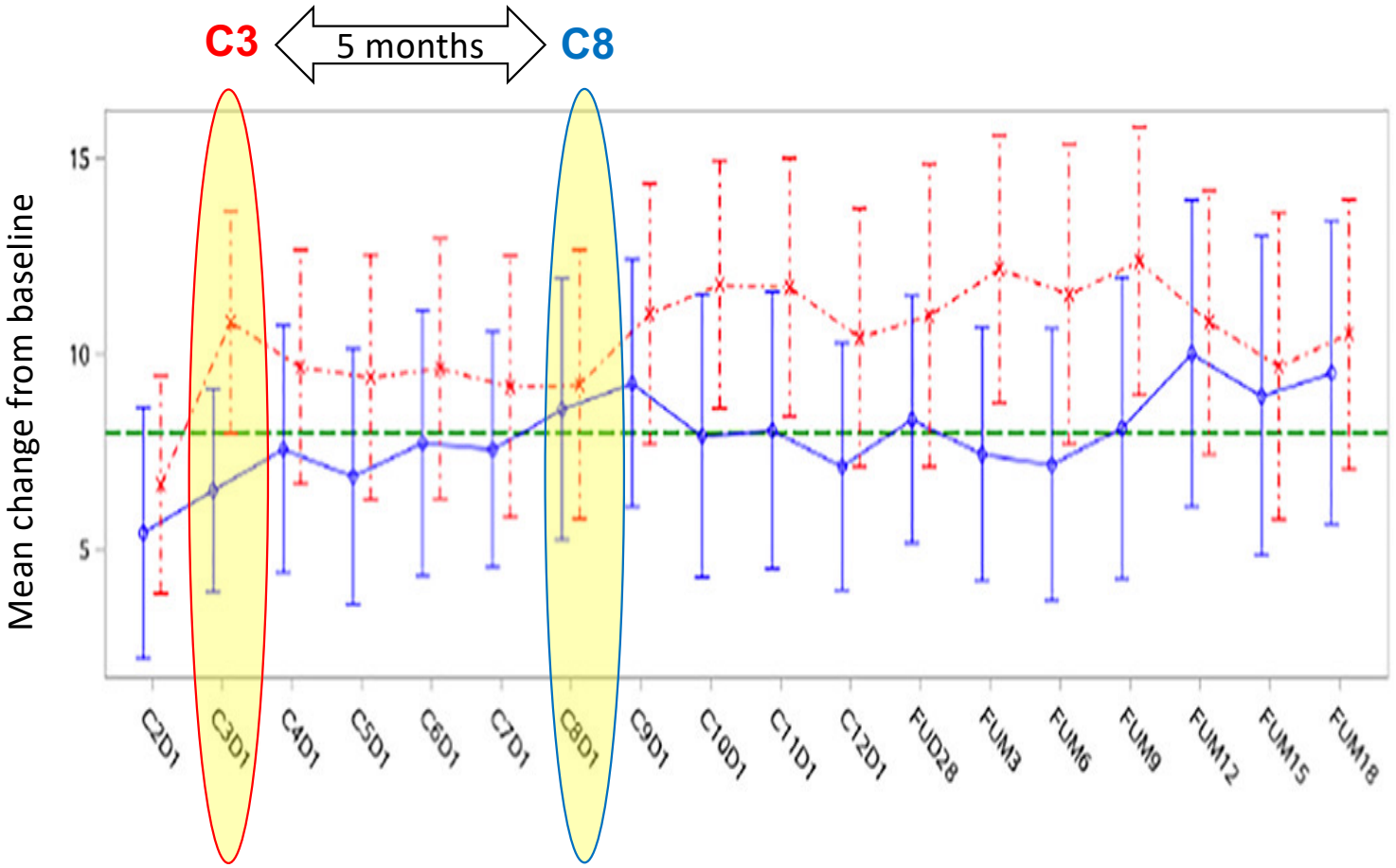
Ibrutinib + Venetoclax (R)
- 3 cycles* **420 mg** QD ibrutinib lead-in → 12 cycles* **420 mg** QD ibrutinib + 400 mg QD venetoclax
- 3 cycles* **420 mg** QD ibrutinib lead-in → 12 cycles* **280 mg** QD ibrutinib + 400 mg venetoclax QD

- **Primary endpoint:** Best ORR (proportion of participants who achieve CR, CRi, nPR, PRL, or PR) over the course of the study
- **Secondary endpoints:** CR rate, DoR, PFS, OS, MRD negativity rate (Cohorts 1a and 1b only), AEs, discontinuation due to AEs, adherence rates, PRO scores

Why Fixed Duration Therapy in CLL?

- ✓ Efficacy
- ✓ Deep responses (MRD)
- ✓ Clonal evolution and resistance
- ✓ Safety and Tolerability
- ✓ **QoL**
- ✓ Cost-effectiveness
- ✓ Patient’s desire

Earlier improvement on the GHS/QoL scale in patients treated with Ven-G compared with OClb



Global health status/quality of life according to EORTC-QLQ-C30

Ven-G

OClb

American J Hematol, Volume: 96, Issue: 9, Pages: 1112-1119, DOI:
(10.1002/ajh.26260)

Frailty is also a target for targeted drugs in CLL

HOVON139/GiVe trial: examine Geriatric assessments and frailty in the context of targeted CLL therapy

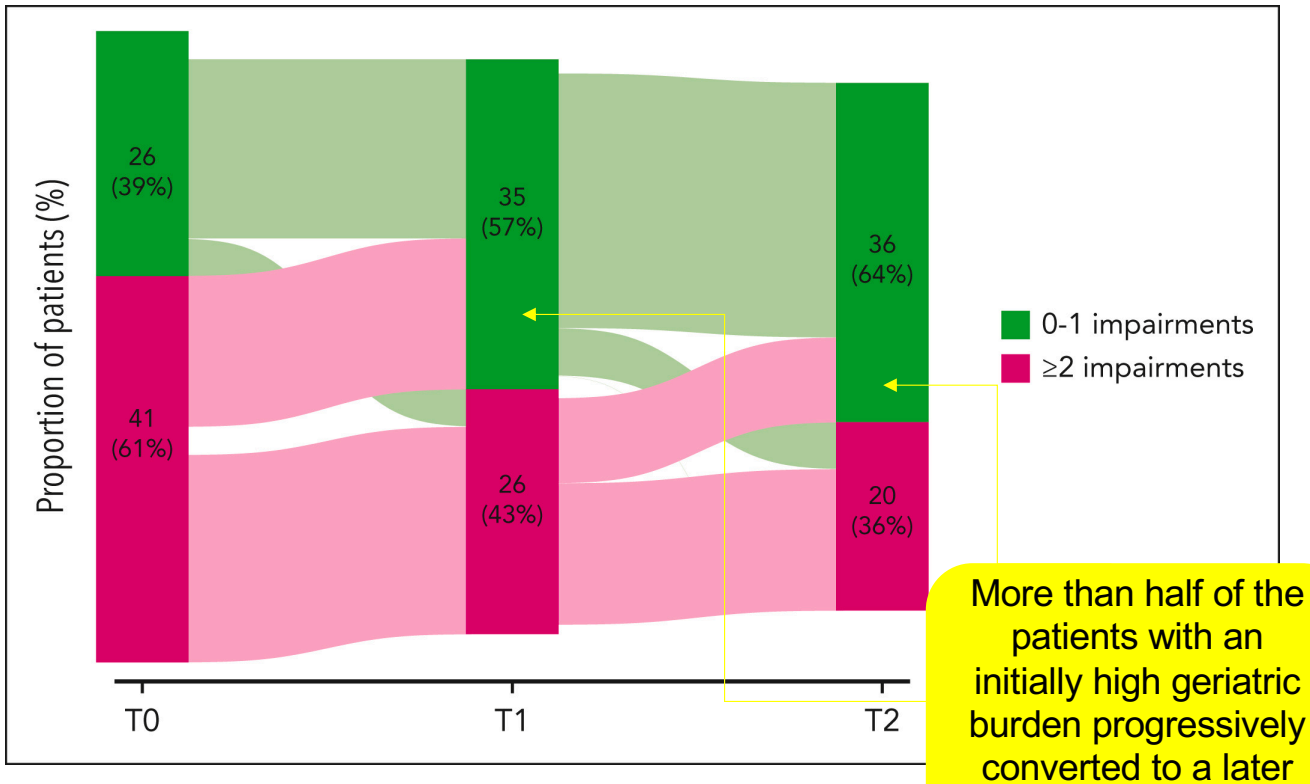
67 mostly older patients

median age 71 years

unfit for FCR

received 12 cycles of Ven-O

Ven-O is reduced the number of geriatric conditions as a surrogate of frailty



More than half of the patients with an initially high geriatric burden progressively converted to a later low one

Valentin Goede, Blood, 2023

Access to the outpatient clinic for i.v. drugs or venetoclax ramp-up might be an issue for some patients…

is easier to take pills at home

Why Fixed Duration Therapy in CLL?

- ✓ Efficacy
- ✓ Deep responses (MRD)
- ✓ Clonal evolution and resistance *
- ✓ Safety and Tolerability *
- ✓ QoL
- ✓ **Cost-effectiveness**
- ✓ Patient’s desire

Continuous

Anno I	Anno II	Anno III	Anno IV
x	x	x	x
	x	x	x
		x	x
			x

Fixed 1L

Anno I	Anno II	Anno III	Anno IV
X (X)			
	X (X)		
		X (X)	
			X (X)

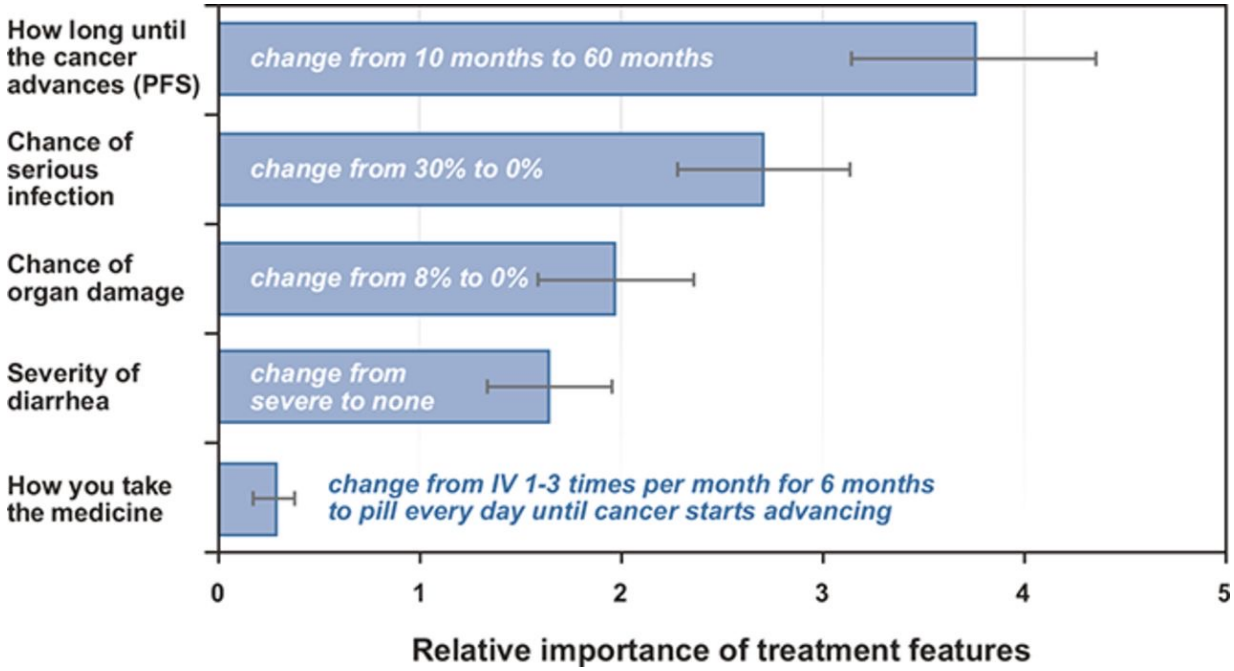
Fixed 2L

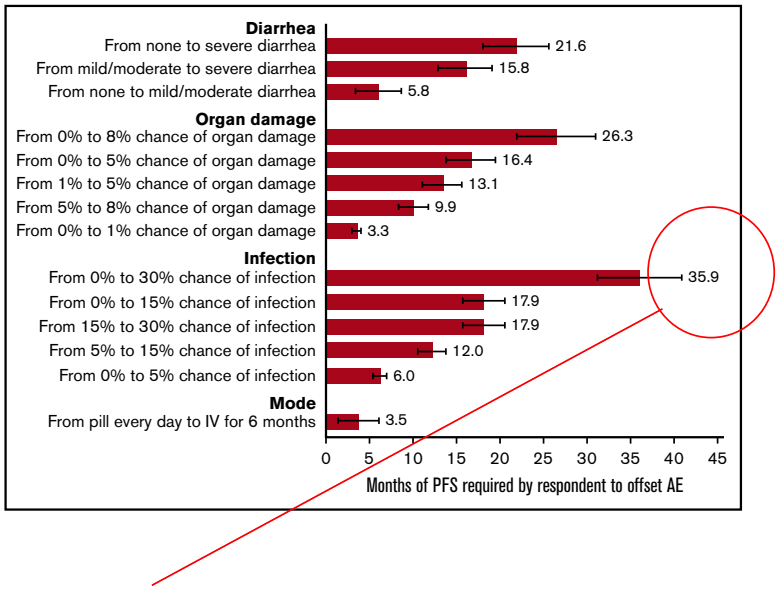
Anno I	Anno II	Anno III	Anno IV
x	x		
	x	x	
		x	x
			x

Why Fixed Duration Therapy in CLL?

- ✓ Efficacy
- ✓ Deep responses (MRD)
- ✓ Clonal evolution and resistance
- ✓ Safety and Tolerability
- ✓ QoL
- ✓ Cost-effectiveness
- ✓ **Patient's desire**

Patients' priorities in selecting treatments: CLL patients value higher PFS

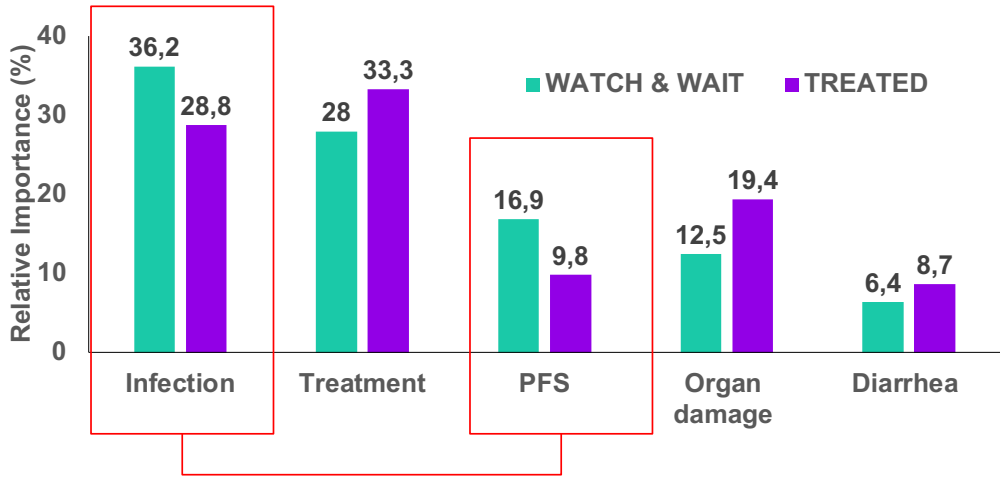




On average, 36 additional months of PFS would compensate respondents for an increase in the risk of serious infection from 0% to 30%.

Carol Mansfield et al., Blood Adv, 2017

In the CHOICE study patients had more concerns about possible infections



In contrast to previously published DCEs where PFS was the most important attribute

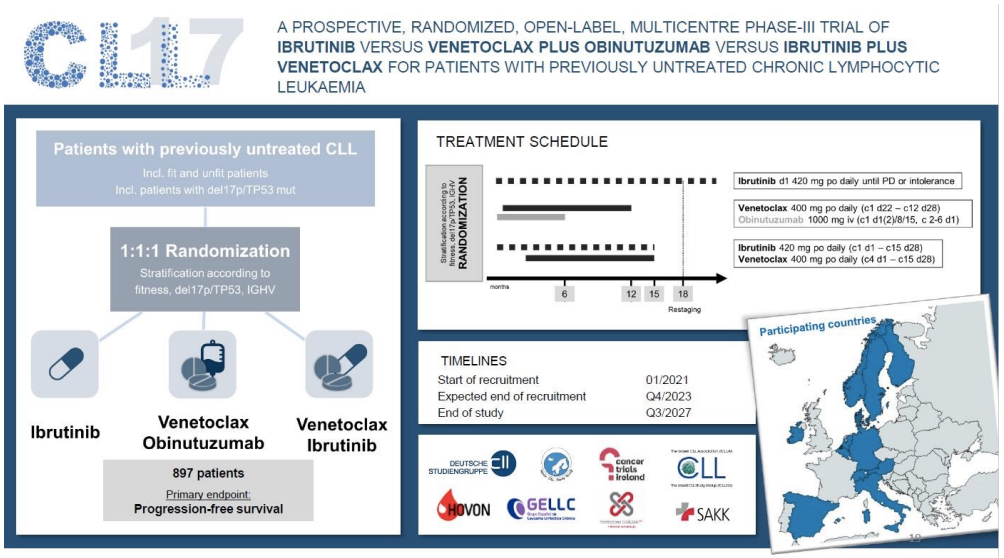
The limitation in hospital access during the 1st wave and the overall need of personal protection (masks usage) and social distancing might have influenced patients' responses

Sportoletti et al. Hematol Oncol 2024

Ven-Obi

I-V

BTKi



paolo.sportoletti@unipg.it