Il concetto della «durata fissa» dal farmacologo all'ematologo

Nel paziente in prima linea

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REVOLUTIONARY ROAD IN CLL

Innovazione rivoluzionaria nella terapia della leucemia linfatica cronica

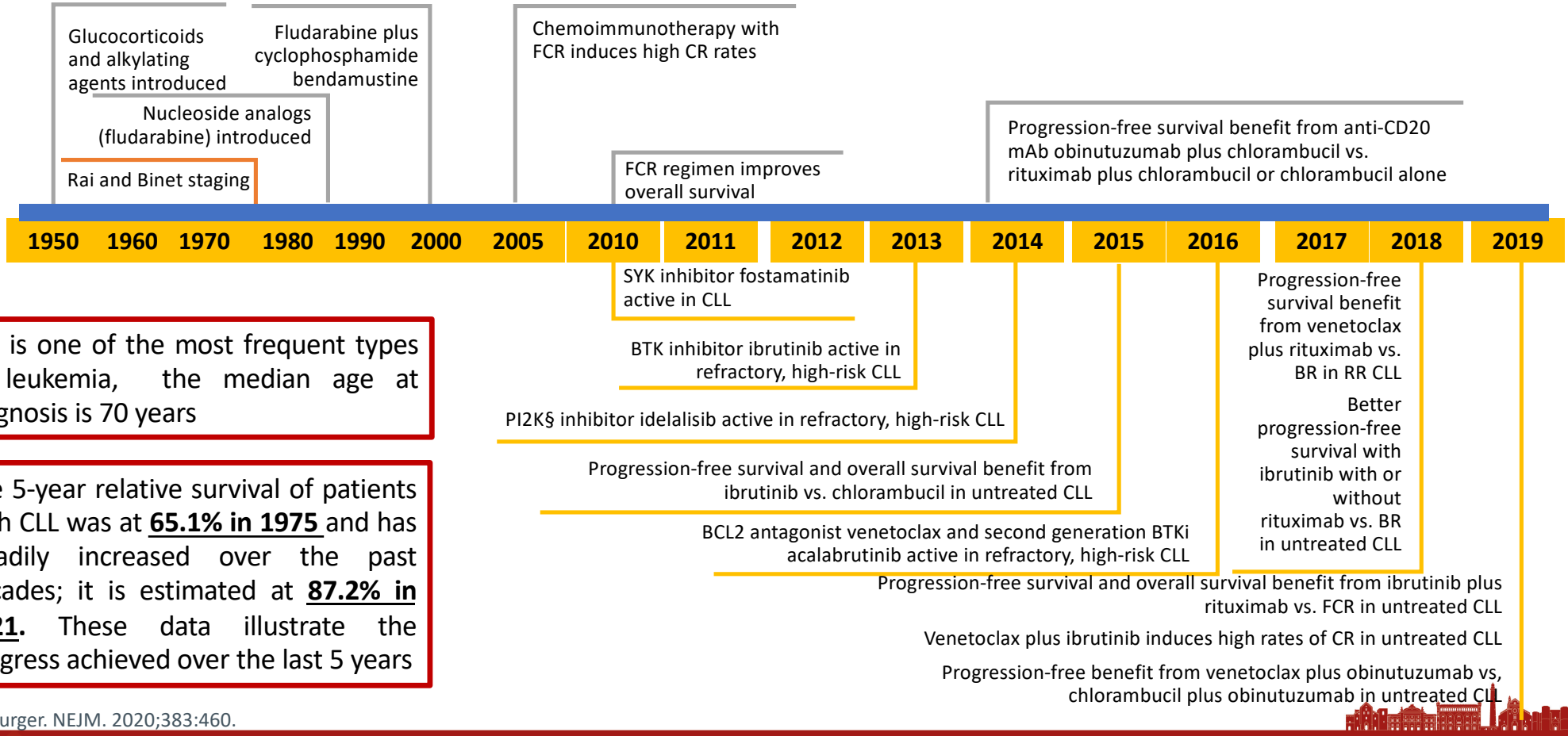
Bari, 29 maggio 2024

Mercure Villa Romanazzi Carducci

Disclosure

- I have no actual or potential conflict of interest in relation to this program/presentation.

Milestones in Clinical CLL Research



CLL is one of the most frequent types of leukemia, the median age at diagnosis is 70 years

The 5-year relative survival of patients with CLL was at **65.1% in 1975** and has steadily increased over the past decades; it is estimated at **87.2% in 2021**. These data illustrate the progress achieved over the last 5 years

Burger. NEJM. 2020;383:460.

BTKi: SURVIVAL DATA AND ADVERS EVENTS

Summary table with data from the RESONATE-2, E1912, ELEVATE-TN, and SEQUOIA trials with survival data and pertinent adverse events.

	RESONATE – 2 [15]		E1912 [23]		ELEVATE-TN [24]			SEQUOIA [26]	
Median follow up	18.4 months		33.6 months		28.3 months			26.2 months	
	Ibrutinib	Chlorambucil	I + R	FCR	Acalabrutinib	A + O	C + O	Zanubrutinib	B + R
N	136	133	354	175	179	179	177	241	238
OS	98%	85%	99%	92%	95%	95%	92%	94%	95%
PFS	90%	52%	89%	73%	87%	93%	47%	86%	70%
ORR	86%	35%	96%	81%	86%	94%	79%	95%	85%
Atrial fibrillation [a]	6%	0.76%	7.4%	3.2%	3.9%	3.4%	0.6%	3.3%	2.6%
Infection [b]	-	-	9.4%	9.5%	14.0%	20.8%	8.3%	16.3%	18.9%
Major Hemorrhage	4%[c]	2%[c]	1.1%[b]	0%[b]	1.7%[c]	2.8%[c]	1.2%[c]	5.0%[c]	1.8%[c]

[a]Any Grade, [b] Grade ≥3, [c] Grade ≥3 or central nervous system hemorrhage of any grade.

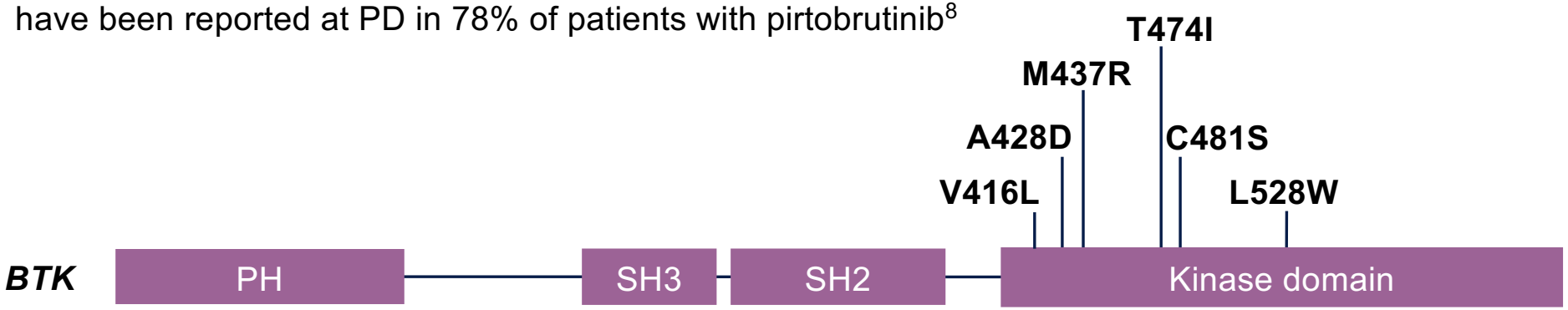
Abbreviations- Overall Survival (OS), Progression Free Survival (PFS), Overall Response Rate (ORR), Ibrutinib + Rituximab (I + R), Fludarabine/Cyclophosphamide/ Rituximab (FCR), Acalabrutinib + Obinutuzumab (A + O), Chlorambucil + Obinutuzumab (C + O), Bendamustine + Rituximab (B + R)

As the efficacy is similar between these irreversible BTK inhibitors,
their adverse event profile needs to be considered when selecting treatment for individual patients

1. Barr PM Blood Adv 2022
3. Sharman JB JCO 2021
4. Tam C The Lancet Oncol 2022

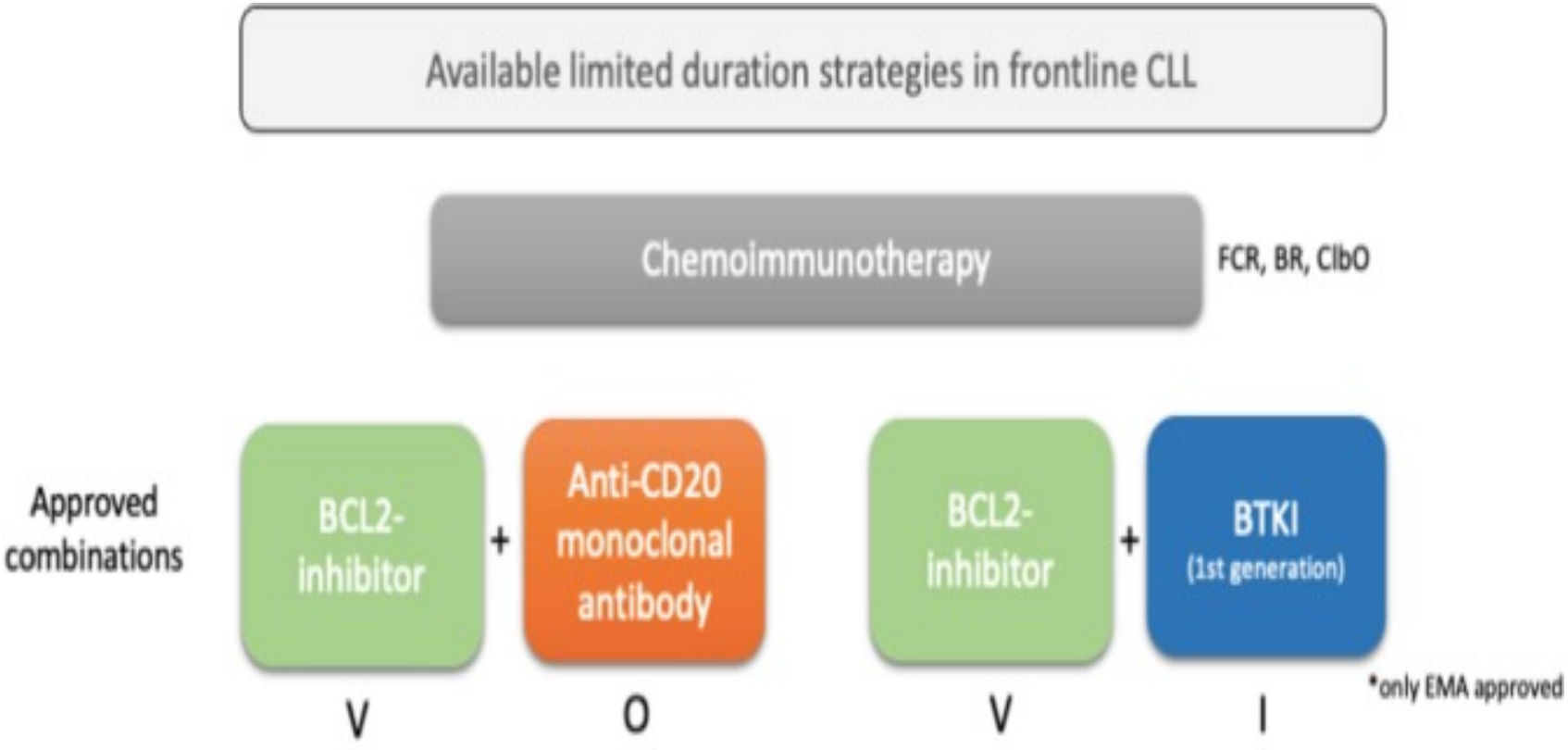
Differences in Profiles of Acquired Mutations of Resistance to BTK Inhibitors Might Have Implications for Treatment Sequencing

- Clinical resistance to Bruton tyrosine kinase (BTK) inhibitors is associated with mutations in *BTK*
- Emerging data indicate different *BTK* mutation profiles across BTK inhibitors[1-8]
  - C481S is the most frequent mutation at PD with both ibrutinib and acalabrutinib[1-6]
  - T474I has been reported at PD in ~20% of patients with acalabrutinib and <1% with ibrutinib[4,6]
  - L528W has been reported at PD in 54% of patients with zanubrutinib[7] and <1% with ibrutinib[4]
  - Non-C481 mutations within the kinase domain (including V416L, A428D, M437R, T474I, and L528W) have been reported at PD in 78% of patients with pirtobrutinib[8]



PH, pleckstrin homology domain; PD, progressive disease; SH, SRC homology domain.

[1]Woyach JA et al. *N Engl J Med.* 2014;370:2286-2294; [2]Woyach JA et al. *J Clin Oncol*. 2017;35:1437-1443; [3]Ahn IE et al. *Blood*. 2017;129:1469-1479; [4]Ahn IE et al. Presented at: International Workshop on CLL; October 6-9, 2023; Boston, MA. Abstract 1549556; [5]Sun C et al. Presented at: 65th ASH Annual Meeting and Exposition; December 9-12, 2023; San Diego, CA. Abstract 1891; [6]Woyach JA et al. Presented at: International Conference on Malignant Lymphoma; June 13-17, 2023; Lugano, Switzerland. Poster 163; [7]Blombery P et al. *Blood Adv.* 2022;6:5589-5592; [8]Wang E et al. *N Engl J Med*. 2022;386:735-743.



Currently, two time-limited, targeted treatment regimens are approved, both of which use the BCL2 inhibitor venetoclax as a backbone

CLL 14: VenO was studied as a 1-year FTD regimen in 1L CLL

Multinational, phase 3, open-label study
1L CLL w/ comorbidities (N=432)

Stratification factors:
- Binet stage
- Geographic regions

1:1 RANDOMIZATION

C1 D22

Venetoclax PO QD
Obinutuzumab IV

Chlorambucil PO
Obinutuzumab IV

EoT: **1 year**

Primary endpoint (ITT population):
- PFS – investigator assessed

Key secondary endpoints (ITT population):
- PFS – IRC assessed
- ORR and CR 3 months after EoT
- uMRD rate (PB and BM) 3 months after EoT
- OS

Key inclusion criteria
- Previously untreated CLL according to iwCLL criteria
- CIRS >6 and/or CrCl <70 mL/min

MRD was a secondary efficacy endpoint, not a determinant of treatment duration

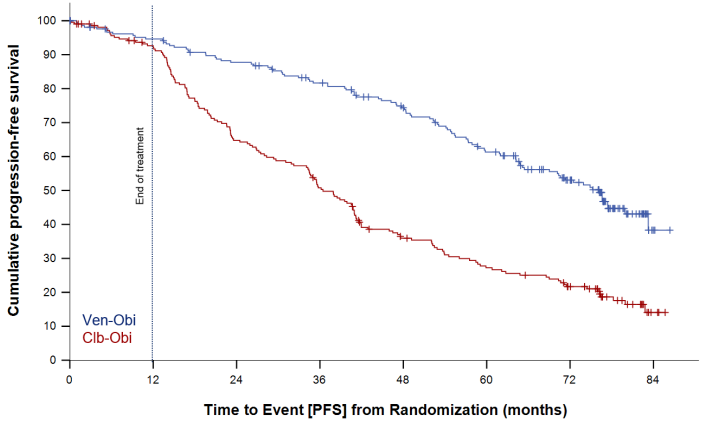
BM, bone marrow; C, cycle; CIRS, cumulative illness rating scale; CrCl, creatinine clearance; D, day; EoT, end of treatment; FTD, fixed treatment duration; IRC, independent review committee; ITT, intent to treat; iwCLL, International Workshop on CLL; PB, peripheral blood; VenO, venetoclax + obinutuzumab.

Fischer K, *et al. N Engl J Med* 2019

CLL 14: Phase 3 Study of Venetoclax-Obinutuzumab vs Chlorambucil-Obinutuzumab in Unfit Patients

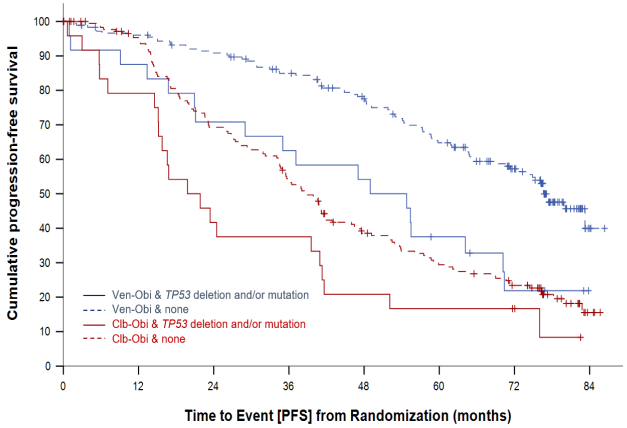
PROGRESSION-FREE SURVIVAL

Investigator-assessed PFS



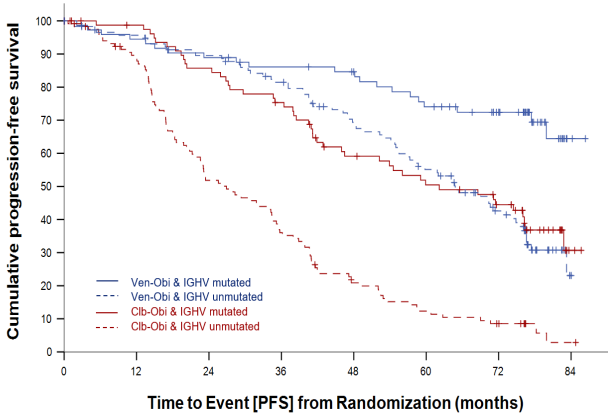
PROGRESSION-FREE SURVIVAL – *TP53* status

Median observation time 76.4 months



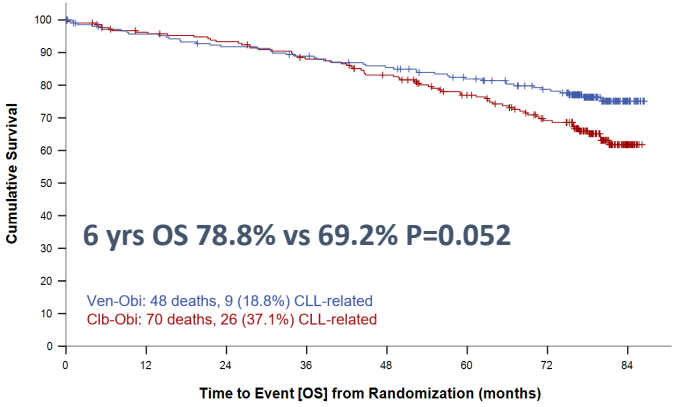
PROGRESSION-FREE SURVIVAL – IGHV status

Median observation time 76.4 months



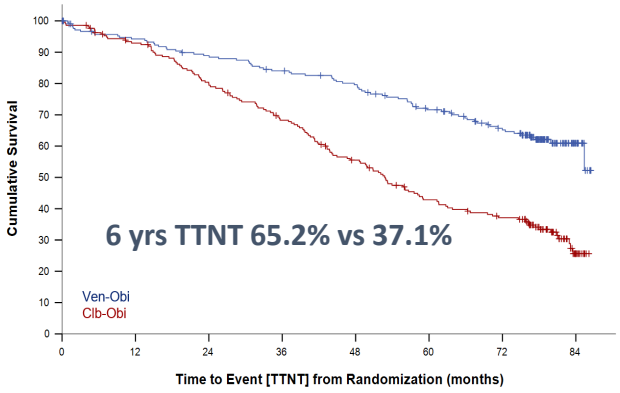
OVERALL SURVIVAL

Median observation time 76.4 months



TIME TO NEXT TREATMENT

Defined as time to death or next-antileukemic treatment

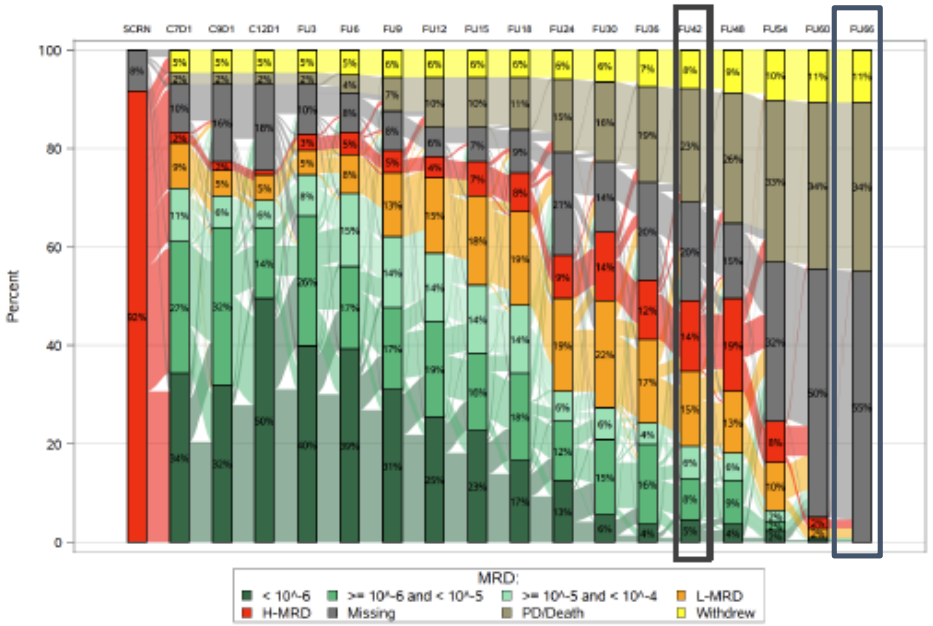


PFS by subgroup		VEN-OBI (n=216)	Clb-OBI (n=216)
All pts	Median, m	76.2	36.4
	6-yrs, rate %	53.1	21.7
	HR (95, CI); p-value	0.40 (0,31-0,52) < 0,0001	
Median PFS, m			
TP 53 mut/del	no	73.6	38.9
	yes	51.9	20.8
IGHV status	Mutated	NR	62.2
	Unmutated	64.8	26.9

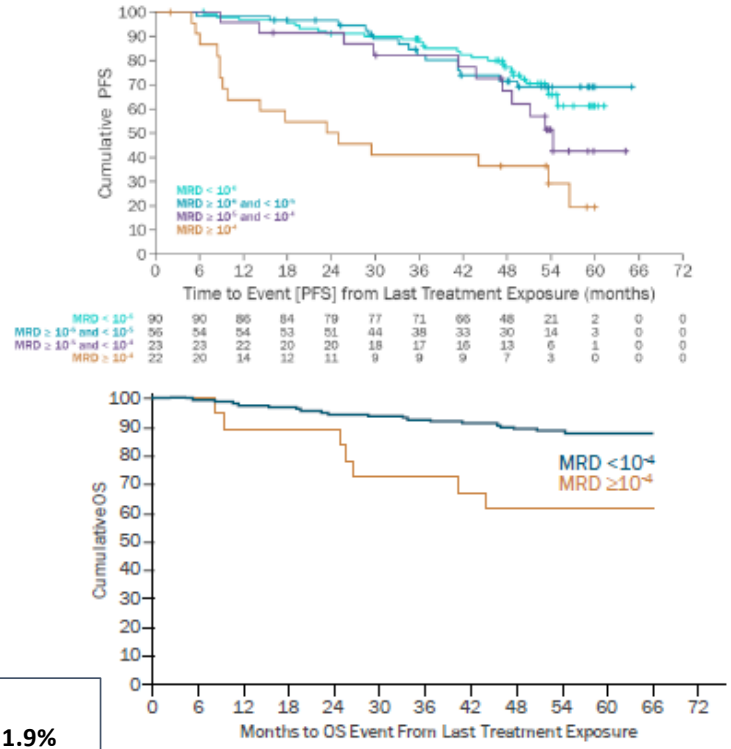
CLL14: Phase 3 Study of Venetoclax-Obinutuzumab vs Chlorambucil-Obinutuzumab in Unfit Patients

MRD Assessments

Longitudinal MRD Assessment by NGS in PB: Ven-Obi



PFS and OS After Ven-Obi According to MRD Status



Depth of remission correlates with long-term PFS indicating the **prognostic role of EOT MRD status**

Pts with MRD $\geq 10^{-4}$ after VO have a shorter OS than pts with MRD $< 10^{-4}$, **higlighting the need for dedicated MRD-guided approaches.**

uMRD (< 10^{-4} by NGS In PB) VO vs CO

EOT: 74% vs 32.8% **5 yrs after the EOT: 7.9% vs 1.9%**

End of treatment MRD status in peripheral blood by next-generation sequencing.

Al-Sawaf O, et al. EHA 2022. Abstract S148.

Consistent safety profile for VenO, with no new safety signals identified with longer follow-up

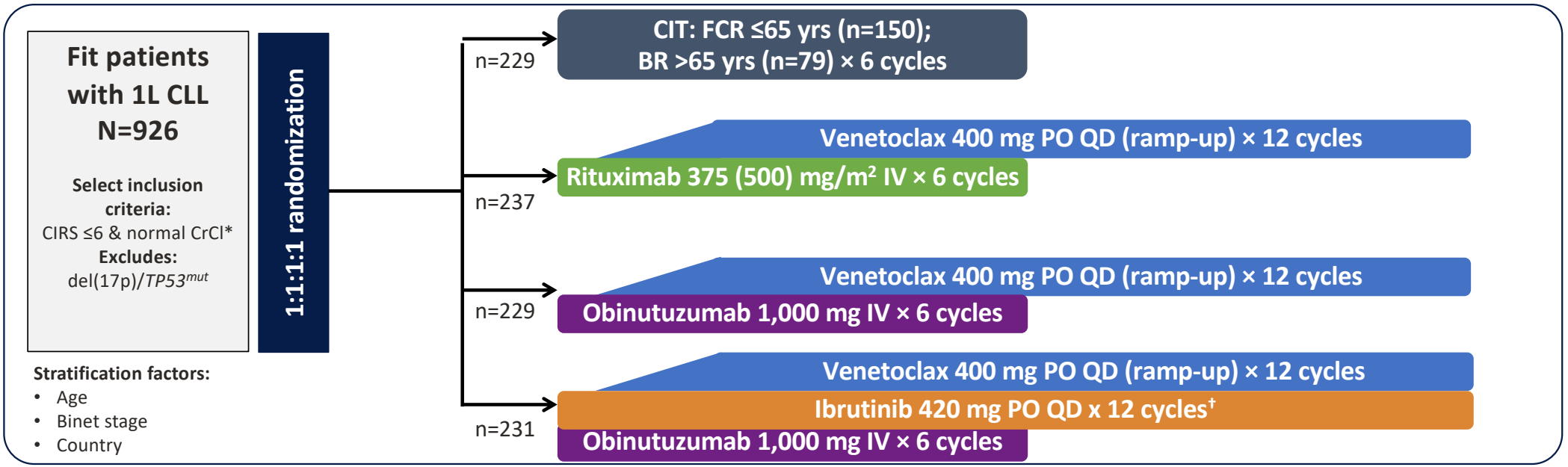
Rates of select Grade ≥3 AEs over time,* %[1]	VenO (N=212)	
	During treatment (months 1–12)†	After treatment*
Neutropenia	**51.9**	**3.8**
Thrombocytopenia	14.2	0.5
Anemia	7.5	1.9
Febrile neutropenia	4.2	0.9
Leukopenia	2.4	0.0
Pneumonia	3.8	3.3
Infusion-related reaction	9.0	0.0
TLS	1.4	0.0

- No new safety signals identified with **longer follow-up (76.4 months)**[1]
- SPMs reported in 30 (14.2%) and 18 (8.4%) patients in VenO and OClb arms, respectively[1]
- No statistical difference in cumulative incidence of SPMs between VenO and OClb arms[1]
- SPM incidence rate was 2.3% with VenO vs 1.4% with OClb[2]

* Grade 3/4 AEs were reported for up to 6 months after EoT; Grade ≥3 infections were reported for 2 years after EoT or until disease progression or NLT; after disease progression, only treatment-related SAEs and SPMs were reported[3]; † Nine patients received obinutuzumab only.[3]
EoT, end of treatment; NLT, next line of therapy; NMSC, non-melanoma skin cancer; SPM, second primary malignancy; TLS, tumor lysis syndrome.

1. Al-Sawaf O, *et al.* EHA 2023. Abstract S145 (Oral).
2. Al-Sawaf O, *et al.* ICML 2023. Abstract 025 (Oral);
3. Al-Sawaf O, *et al. Lancet Oncol* 2020; **21**:1188–1200 (incl. appendix).

CLL 13 STUDY DESIGN



Co-Primary Endpoints:

- uMRD ($<10^{-4}$) in PB at month 15 (VenO vs CIT)
- PFS (IVO vs CIT)

Key Secondary Endpoints:

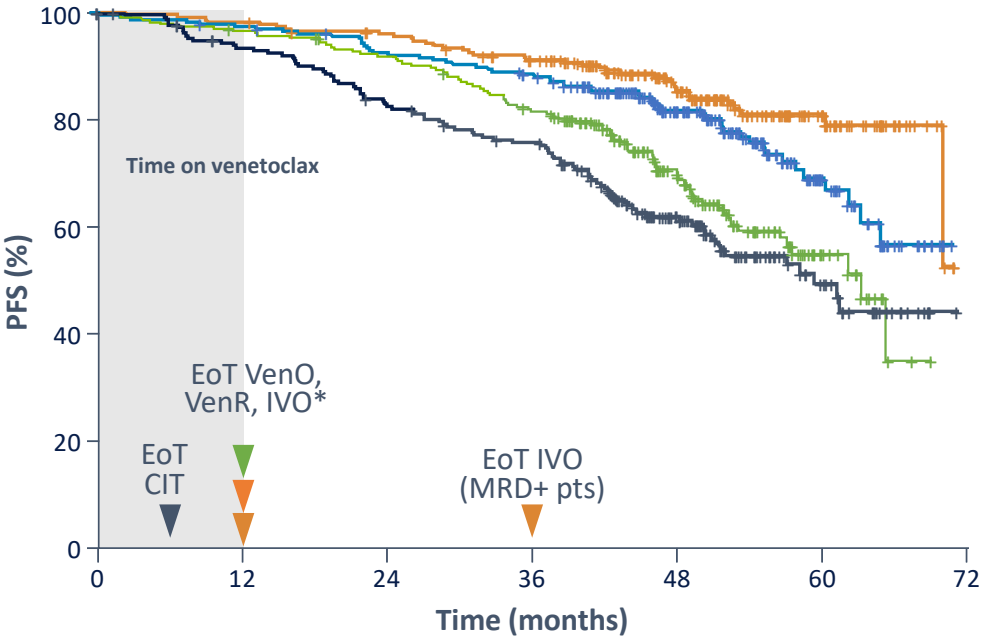
- MRD in PB at month 15 (all other comparisons)
- MRD in BM at final restaging
- PFS (all other comparisons)
- ORR
- CR/CRi rate
- Overall survival

Analyses: at the fixed time point of month 61 for interim analysis of PFS, an independent data monitoring committee recommended full analysis

28-day cycles; * Normal CrCl defined as ≥70 mL/min; † Continuation of ibrutinib up to cycle 36 allowed if MRD still detectable (80% received 12–15 cycles);
Data cut for first co-primary endpoint analysis (uMRD): February 28, 2021; data cut for second co-primary endpoint analysis (PFS): January 20, 2022.
BM, bone marrow; BR, bendamustine + rituximab; CIRS, cumulative illness rating scale; CIT, chemoimmunotherapy; CrCl, creatinine clearance; EFS, event-free survival;
FCR, fludarabine + cyclophosphamide + rituximab; IVO, ibrutinib + venetoclax + obinutuzumab; O, obinutuzumab; PB, peripheral blood; Ven, venetoclax.

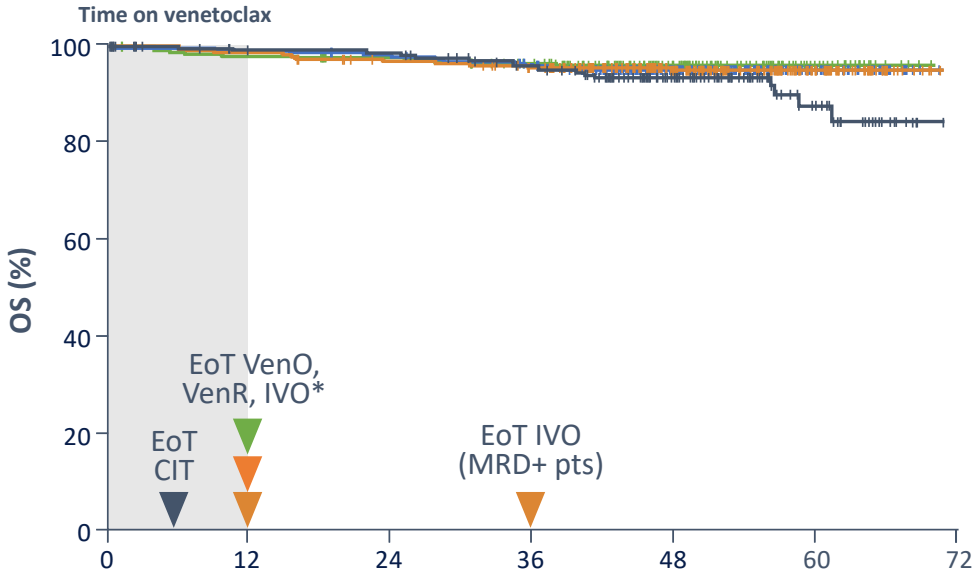
Eichhorst B, *et al.* ASH 2021. Abstract 71 (Oral);
Eichhorst B, *et al.* EHA 2022. Abstract LB2365 (Oral).

PFS across all treatment arms[1]
Median follow-up: 50.7 months



	CIT	VenR	VenO	IVO
HR vs CIT (97.5% CI) p-value[1]	–	0.78 (0.55–1.10) p=0.1	0.47 (0.32–0.69) p<0.001	0.30† (0.19–0.47) p<0.001
4-year PFS, %[1]	62.0	70.1	81.8	85.5
Median PFS, months[2]	52.0	52.3	NR	NR

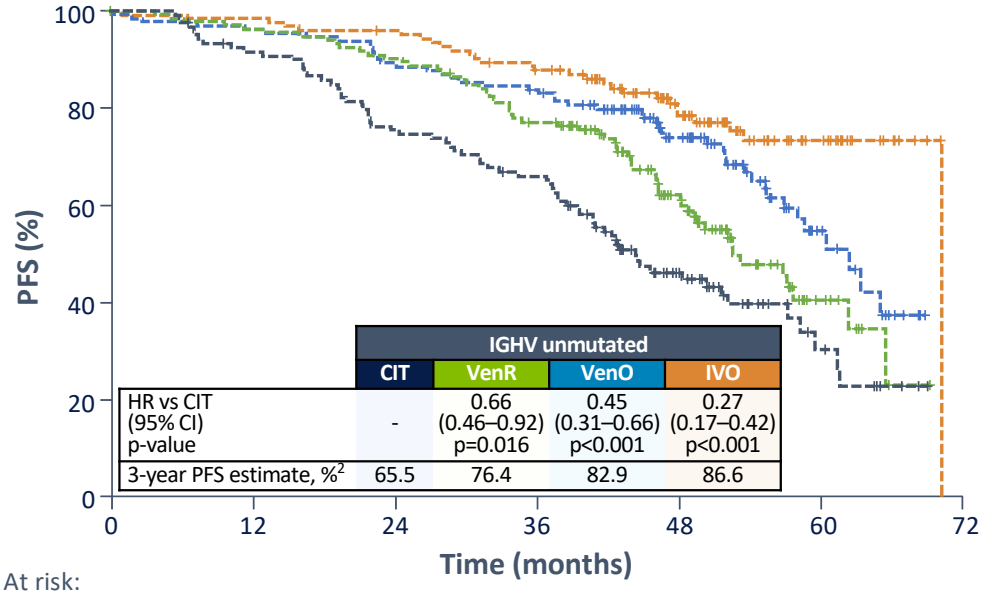
Overall survival
Median follow-up: 50.7 months



	CIT	VenR	VenO	IVO
HR vs CIT (97.5% CI) p-value	–	0.46 (0.18–1.17) p=0.056	0.58 (0.24–1.38) p=0.15	0.58 (0.24–1.38) p=0.15
4-year OS, %	93.5	96.2	95.1	95.0

1. Fürstenau M, *et al.* ASH 2023. Abstract 635 (Oral);

PFS: IGHV unmutated[1]
Median follow-up: 50.7 months

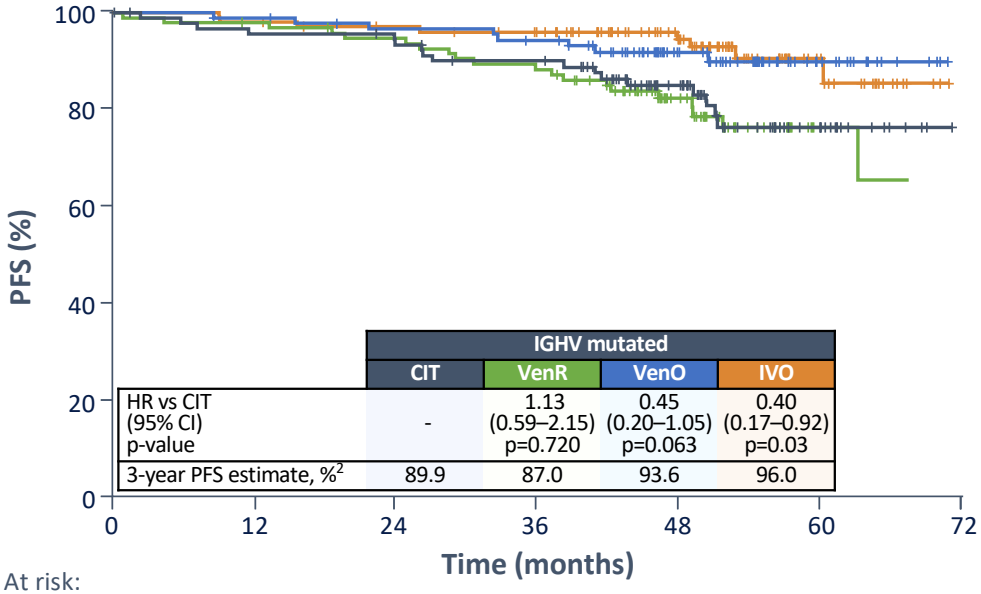


IGHV unmutated	CIT	VenR	VenO	IVO
HR vs CIT (95% CI) p-value	-	0.66 (0.46–0.92) p=0.016	0.45 (0.31–0.66) p<0.001	0.27 (0.17–0.42) p<0.001
3-year PFS estimate, %[2]	65.5	76.4	82.9	86.6

At risk:

CIT	131	108	89	77	34	9
VenR	134	128	119	100	56	10
VenO	130	125	116	108	67	15
IVO	123	121	117	105	65	24

PFS: IGHV mutated[1]
Median follow-up: 50.7 months



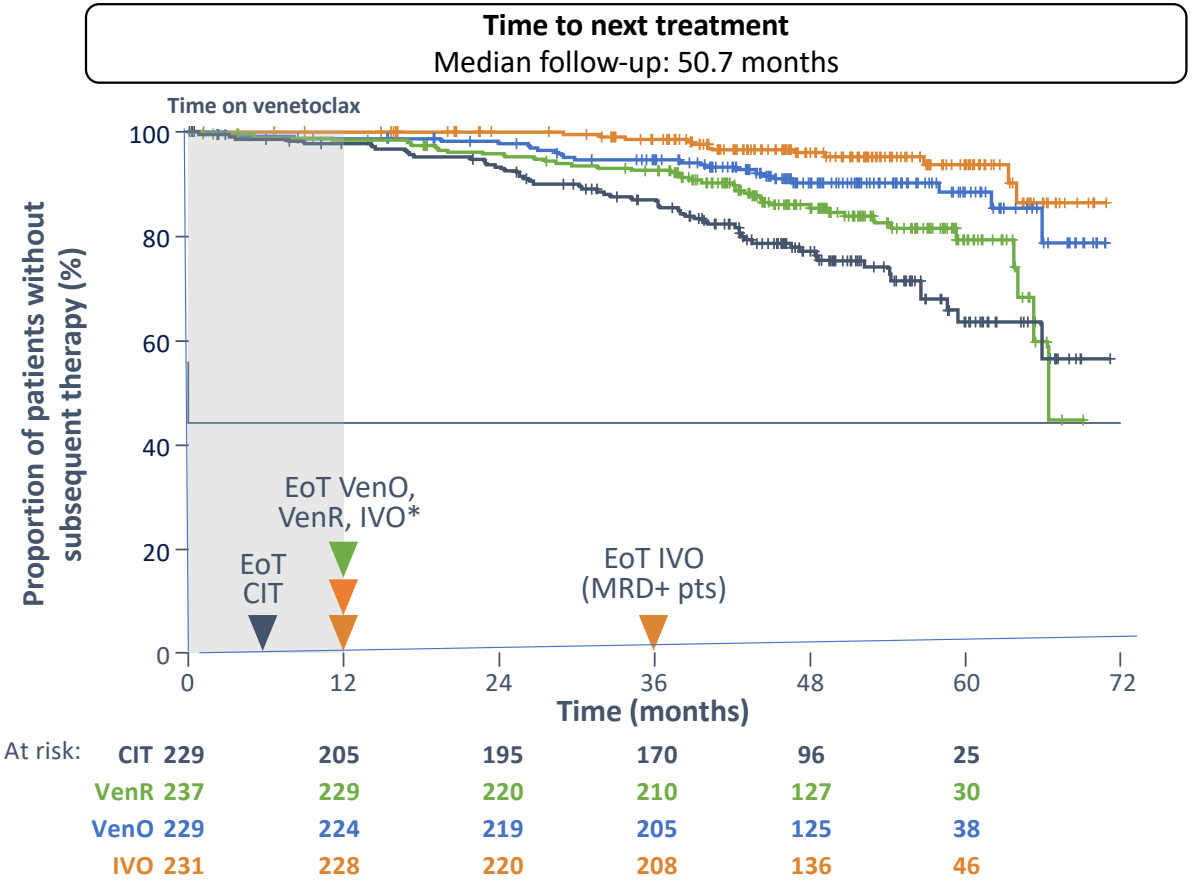
IGHV mutated	CIT	VenR	VenO	IVO
HR vs CIT (95% CI) p-value	-	1.13 (0.59–2.15) p=0.720	0.45 (0.20–1.05) p=0.063	0.40 (0.17–0.92) p=0.03
3-year PFS estimate, %[2]	89.9	87.0	93.6	96.0

At risk:

CIT	95	86	83	78	50	15
VenR	95	92	88	82	47	11
VenO	89	87	83	80	48	15
IVO	101	99	95	90	60	20

1. Fürstenau M, *et al.* ASH 2023. Abstract 635 (Oral);

TTNT at the 4-year analysis

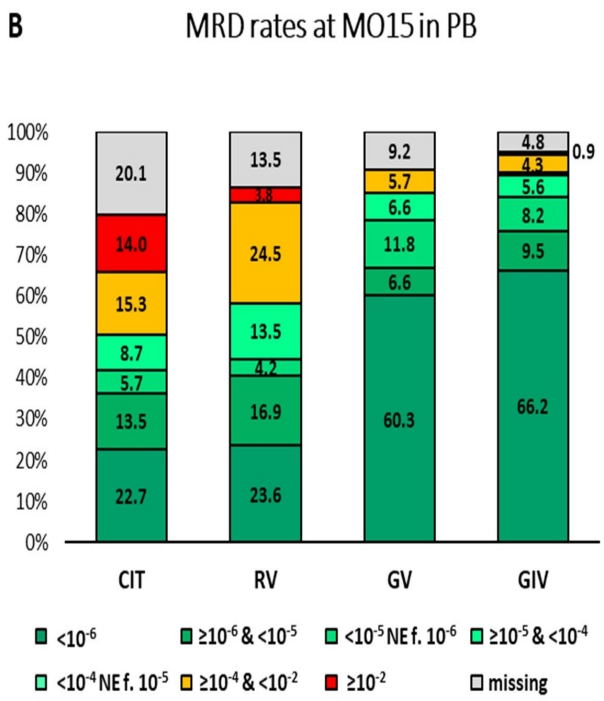


	CIT	VenR	VenO	IVO
HR vs CIT (97.5% CI) p-value	–	0.62 (0.39–1.00) p=0.023	0.34 (0.20–0.60) p<0.001	0.17 (0.09–0.36) p<0.001
4-year TTNT, %	77.2	86.2	90.4	96.0

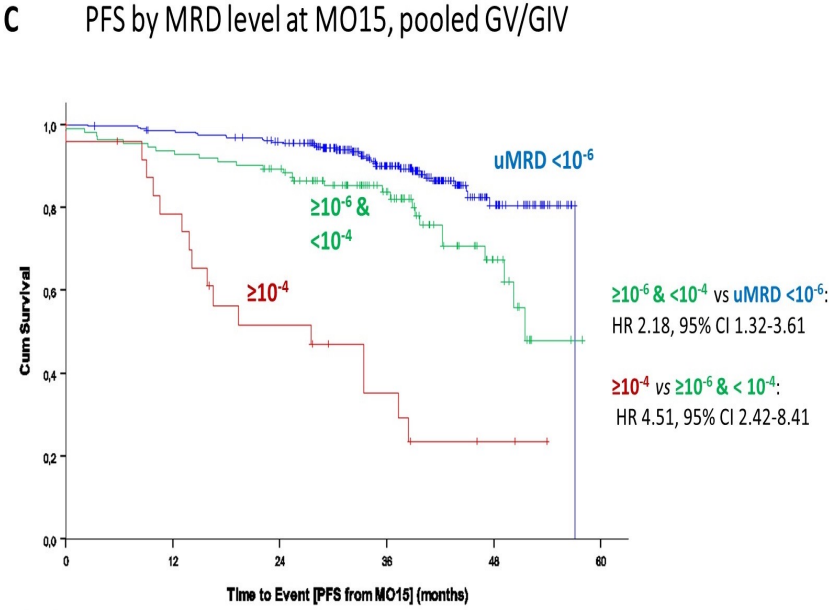
1. Fürstenau M, *et al.* ASH 2023. Abstract 635 (Oral);
2. Eichhorst B, *et al.* EHA 2022. Abstract LB2365 (Oral).

GAIA/CLL13: uMRD in PB at 15 Mo

Pts who achieved uMRD below the conventional cut-off of 10^{-4} by FCM but still had low levels of detectable MRD ($\geq 10^{-6}$ & $<10^{-4}$) by NGS had shorter PFS than pts achieving uMRD6 in the pooled GV/GIV arms (HR 2.18 [95% CI 1.32-3.61],



NGS-based MRD data in PB
uMRD < 10^{-6}



Patients at risk

uMRD <10^{-6}	291	283	269	162	39
≥10^{-6} & <10^{-4}	112	105	95	53	15
≥10^{-4}	25	18	11	6	2

Exposure-adjusted incidence rates of AEs

Overall AEs and AEs of interest

Events/1,000 patient-months	CIT (n=216)	VenR (n=237)	VenO (n=228)	IVO (n=231)
AE (any grade)	1,230	713	801	894
CTC grade ≥3	296	140	178	170
Infections	132	89	108	122
CTC grade ≥3	33	10	14	20
Cardiac AEs	12	7	7	15
Hypertension	6	5	8	9

- Events per 1,000 patient-months **based on treatment period**
- Treatment period = **start of treatment until end of treatment + 84 days** or until start of first subsequent treatment, whichever occurs first.

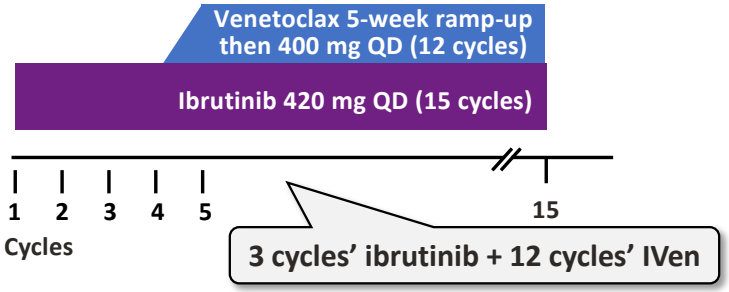
Median follow-up: 50.7 months.
AE, adverse event; CIT, chemoimmunotherapy; IVO, ibrutinib + venetoclax + obinutuzumab; O, obinutuzumab; R, rituximab; Ven, venetoclax.

Fürstenau M, *et al.* ASH 2023. Abstract 635 (Oral).

CAPTIVATE FD Cohort: Venetoclax + Ibrutinib in Previously Untreated Patients with CLL

CAPTIVATE: Phase 2 Trial in Previously Untreated CLL (Aged ≤70 Years)[1,2]

FD Cohort



Primary endpoint:
CR rate
for patients without del(17p)

Key secondary endpoints:
- uMRD rates, PFS, OS
- Duration of response, ORR
- Safety, including TLS risk reduction after 3 cycles of ibrutinib

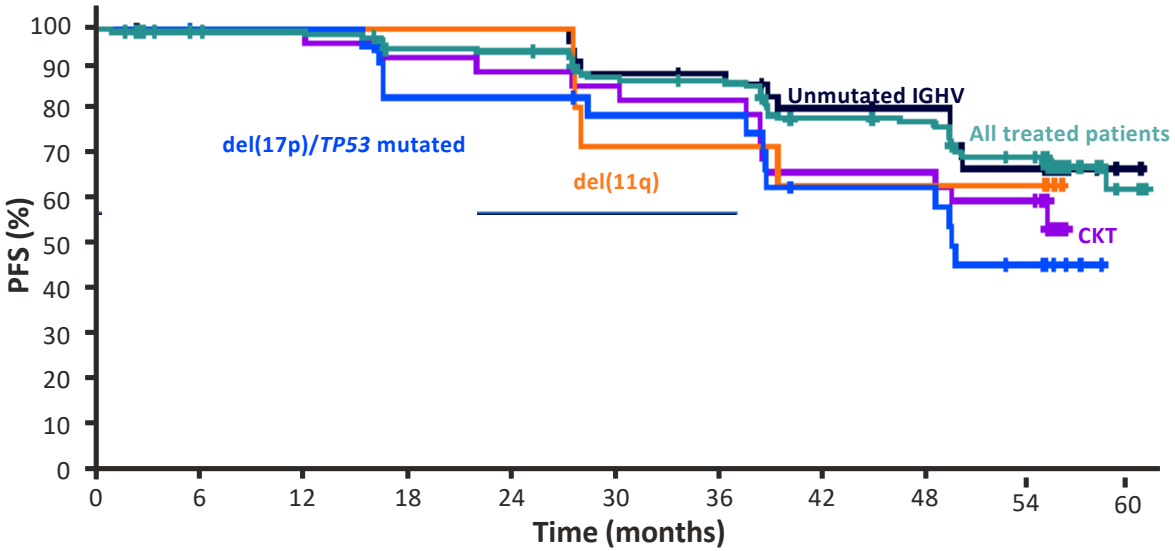
After completion of the FD regimen, patients who subsequently had confirmed PD by iwCLL criteria could be retreated with single-agent ibrutinib until PD or unacceptable toxicity. For patients who had PD 2 years after completion of the FD regimen, retreatment with the FD ibrutinib plus venetoclax regimen could be considered. * Without del(17p) per Dohner hierarchy; † Defined as ≥3 abnormalities by conventional CpG-stimulated cytogenetics. ALC, absolute lymphocyte count; ANC, absolute neutrophil count; CpG, 5'—C—phosphate—G—3';
FD, fixed duration; IVen, ibrutinib + venetoclax; TLS, tumor lysis syndrome.

Baseline Characteristics – FD Cohort	IVen (N=159)
Median age, years (range)	60 (33–71)
Male sex, n (%)	106 (67)
Rai Stage III/IV disease, n (%)	44 (28)
Any cytopenia at baseline, n (%)	54 (34)
ANC ≤1.5×10^9/L	13 (8)
Hemoglobin ≤11 g/dL	37 (23)
Platelets ≤100×10^9/L	21 (13)
Lymph node diameter ≥5 cm, n (%)	48 (30)
Median ALC, ×10^9/L (range)	70 (1–503)
ALC ≥25×10^9/L, n (%)	120 (75)
High-risk features, n (%)	
Unmutated IGHV	89 (56)
del(17p)/*TP53* mutation	27 (17)
del(17p)	20 (13)
del(11q)*	28 (18)
Complex karyotype†	31 (19)

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

CAPTIVATE FD Cohort: PFS and OS (ASH 2023)

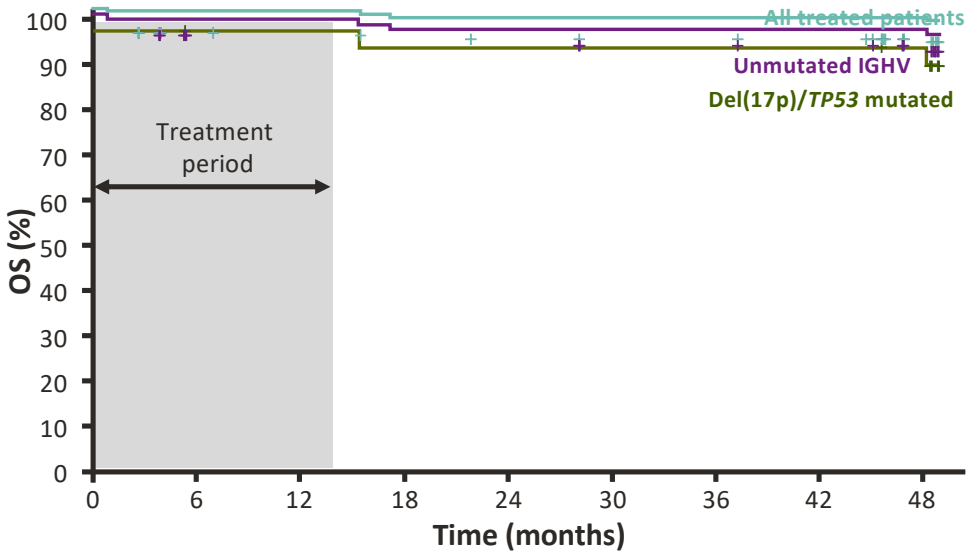
Investigator-assessed PFS[1]
(Median time on study: 56 months)



	FD cohort				
	del(11q)* (n=11)	CKT† (n=31)	del(17p)/*TP53* (n=27)	Unmutated IGHV* (n=40)	All (N=159)
54-month PFS rate, % (95% CI)	64 (30–85)	60 (41–75)	45 (25–64)	68 (50–80)	70 (62–77)

* Excluding patients with del(17p)/mutated *TP53* or complex karyotype; † Defined as 3 abnormalities by conventional CpG-stimulated cytogenetics. CKT, complex karyotype; FD, fixed duration.

OS[2,3]
(Median time on study: 49.8 months)

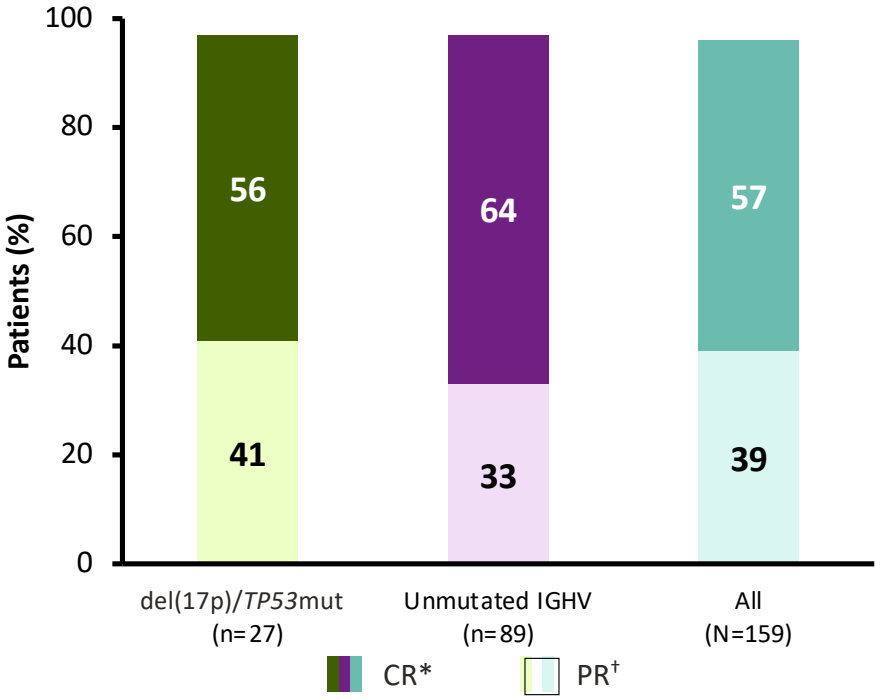


	FD cohort		
	del(17p)/*TP53* (n=27)	Unmutated IGHV* (n=89)	All (N=159)
48-month OS rate, % (95% CI)	96 (76–99)	97 (90–99)	98 (94–99)

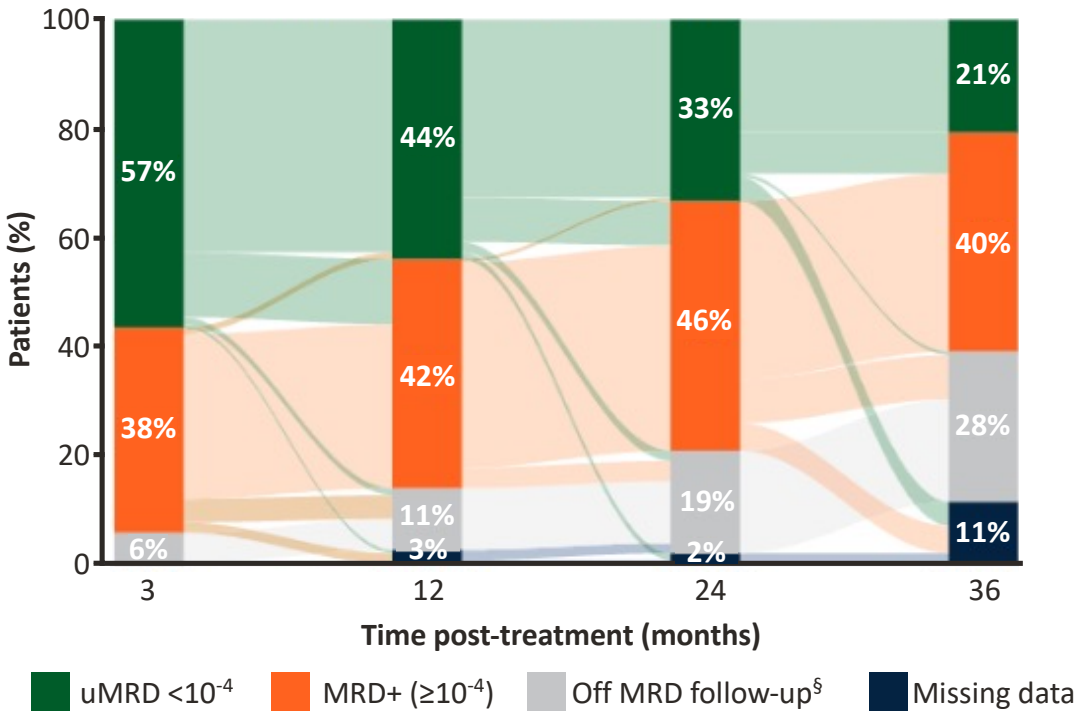
1. Ghia P, *et al.* ASH 2023. Abstract 633 (Oral); 2. Barr PM, *et al.* ASCO 2023. Abstract 7535 (Poster); 3. Tedeschi A, *et al.* EHA 2023. Abstract P817 (Poster).

CAPTIVATE FD Cohort: Response rates

Best Overall Response[1]
(Median time on study: 38.7 months)



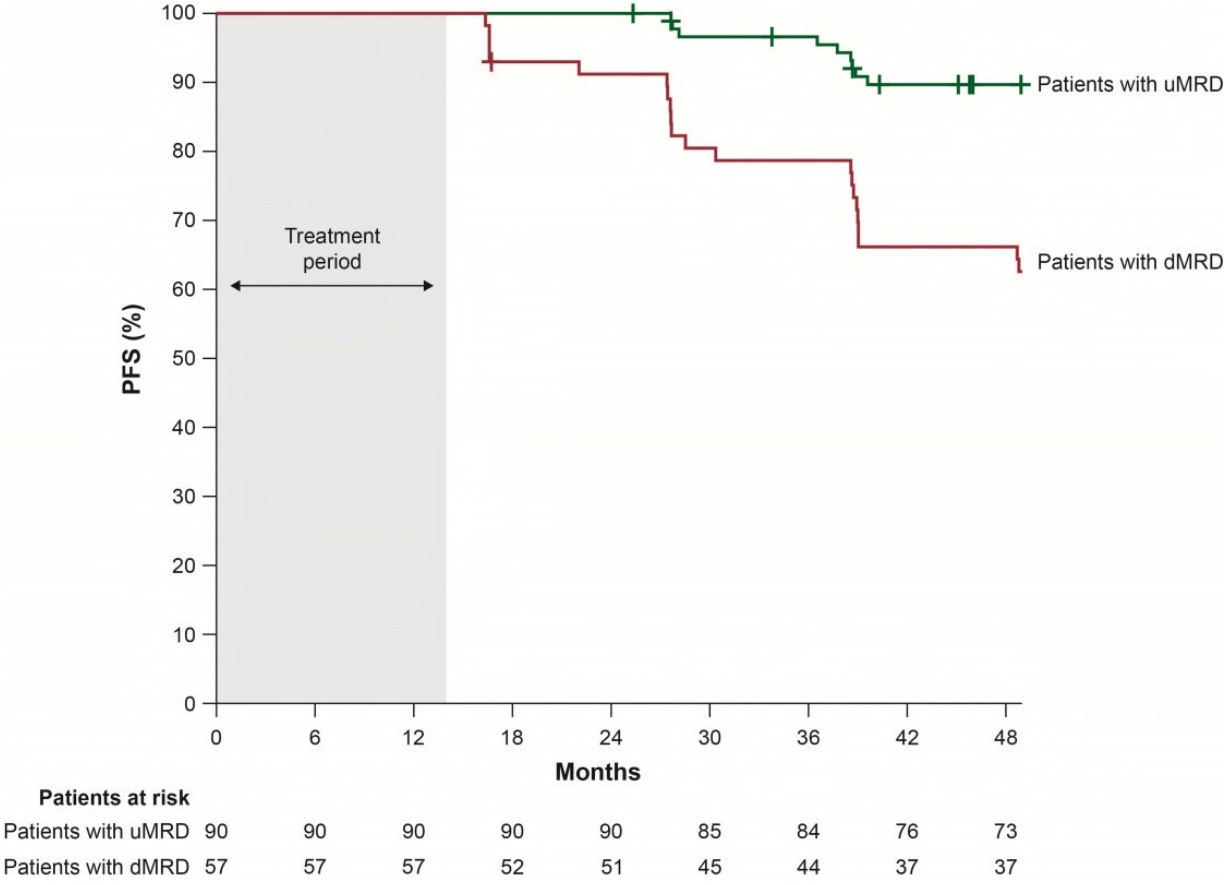
Rates of uMRD in PB by Flow Cytometry[2,‡]
(Median time on study: 49.8 Months)



* Included patients achieving CRi; † Included patients achieving nPR; ‡ uMRD <10^{-4}; § Off MRD follow-up included patients who met any one of the criteria: PD, initiation of subsequent therapy, death, or withdrawal from study. FD, fixed duration; PB, peripheral blood.

1.Moreno C, *et al.* EHA 2022. Abstract P669 (Poster);
2. Tedeschi A, *et al.* EHA 2023. Abstract P617 (Poster).

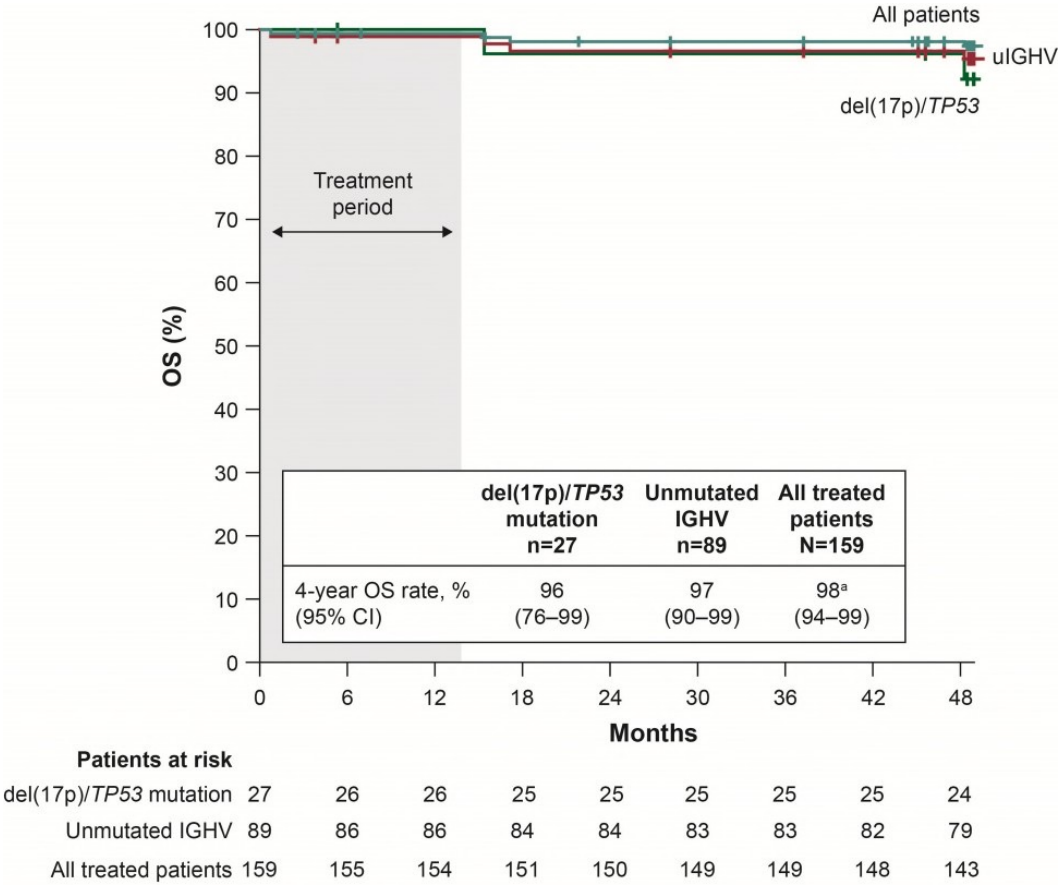
4-Year PFS Rates by MRD Status 3 Months After Stopping Treatment Were Significantly Higher in Patients With Undetectable Versus Detectable MRD in PB



Landmark PFS rates at 48 months in patients who had uMRD in PB 3 months posttreatment were higher (90%) than those with detectable MRD in PB 3 months posttreatment (66%)

dMRD, detectable minimal residual disease; PB, peripheral blood; PFS, progression-free survival; uMRD, undetectable minimal residual disease.

Fixed-Duration Ibr + Ven Continues to Provide Durable, High PFS Rates



	del(17p)/*TP53* mutation n=27	Unmutated IGHV n=89	All treated patients N=159
4-year OS rate, % (95% CI)	96 (76–99)	97 (90–99)	98[a] (94–99)

Patients at risk									
del(17p)/*TP53* mutation	27	26	26	25	25	25	25	25	24
Unmutated IGHV	89	86	86	84	84	83	83	82	79
All treated patients	159	155	154	151	150	149	149	148	143

Time to Next Treatment

- Median TTNT was not reached (n=28; range 1–53 months)
- Landmark estimate of the proportion of patients who had not started a next treatment at 4 years was 84% (95% CI 77–89)

[a]One patient died due to COVID-19 since the primary analysis.
IGHV, immunoglobulin heavy chain variable region gene; OS, overall survival; TTNT, time to next treatment.

CAPTIVATE FD Cohort: Safety (ASH 2023)

AE summary, n (%)[1]	All patients (N=159)
Most common AEs (any grade, ≥30%)	
Diarrhea	99 (62)
Nausea	68 (43)
Neutropenia	66 (42)
Arthralgia	53 (33)
Most common Grade 3/4 AEs (≥5%)	
Neutropenia	52 (33)
Hypertension	9 (6)
Neutrophil count decreased	8 (5)
AEs of clinical interest (any grade)	
Atrial fibrillation	7 (4)
Major hemorrhage*	3 (2)
Any serious AE	36 (23)
Fatal AEs	1 (1)†

AE summary, n (%)[1]	All patients (N=159)
AEs leading to discontinuation	**10 (6)**
Ibrutinib only	5 (3)
Venetoclax only	1 (1)‡
AEs leading to dose reduction	**39 (25)**
Ibrutinib only	9 (6)
Venetoclax only	18 (11)

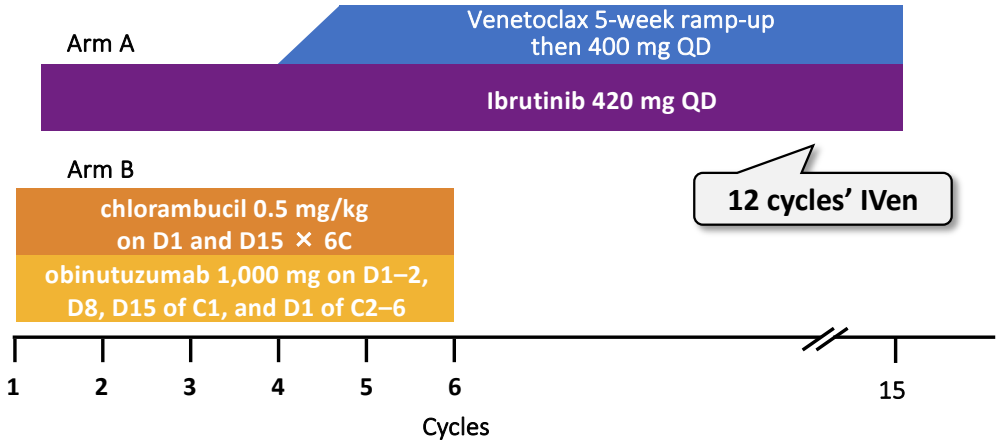
- No TLS events were observed during venetoclax onboarding in combination with ibrutinib[1]
- In the 5-year follow-up, the safety profile remained consistent[2]
  - No new serious AEs related to treatment were reported
  - In total, second malignancies have occurred in 8% of patients
  - Data on serious AEs and SPMs continue to be collected

* Major hemorrhage was identified using the Standardized MedDRA Query for Hemorrhage, excluding laboratory terms;
† Sudden death in 1 patient during ibrutinib lead-in; ‡ Patient discontinued venetoclax because of AE after discontinuing ibrutinib as a result of investigator decision. FD, fixed duration; SPM, secondary primary malignancy.

1. Tam CS, *et al. Blood* 2022; **139**:3278–3289;
2. Ghia P, *et al.* ASH 2023. Abstract 633 (Oral).

GLOW: Venetoclax + Ibrutinib vs Chlorambucil + Obinutuzumab in Previously Untreated CLL

GLOW: Phase 3 Trial in Previously Untreated CLL (Aged ≥65 Years *OR* <65 Years with CIRS >6 or CrCl <70 mL/min)[1,2]



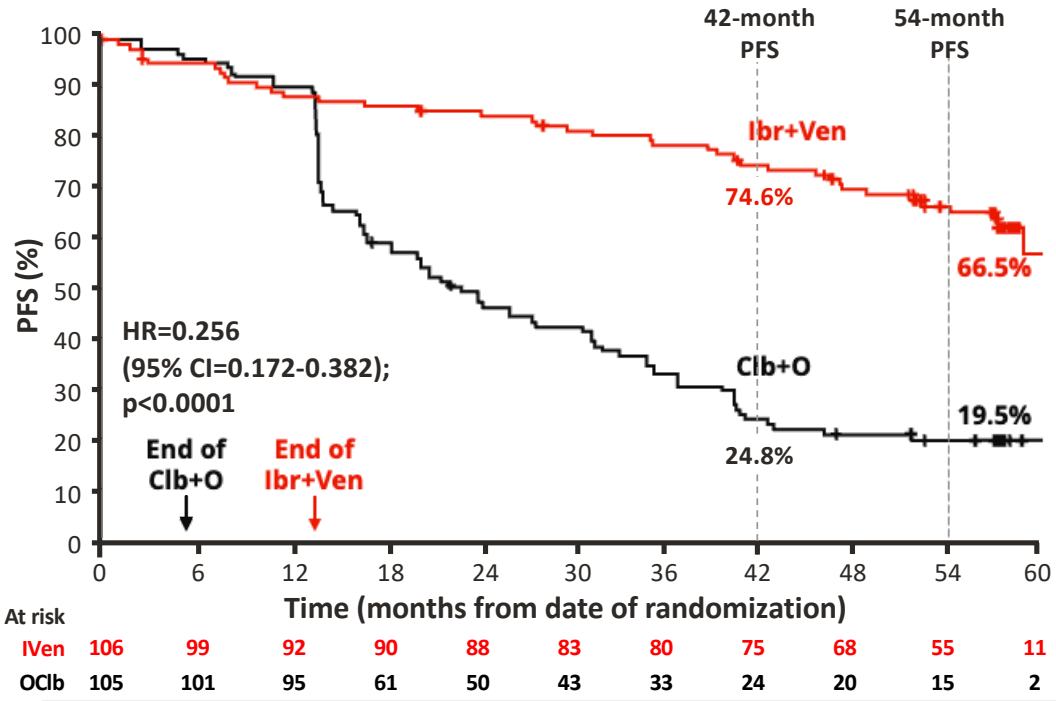
Patient Characteristic[1,2,]	IVen (n=106)	OClb (n=105)
Median age, years (range) ≥75 years, n (%)	**71.0 (47–93)** 35 (33.0)	71.0 (57–88) 37 (35.2)
Male, n (%)	59 (55.7)	63 (60.0)
ECOG PS 1–2, n (%)	71 (67.0)	66 (62.9)
Median CIRS score (range) >6, n (%)*	9 (1–20) 74 (69.8)*	8 (0–22) 61 (58.1)*
Median CrCl, mL/min† (range)	66.5 (34.0–168.1)	63.2 (32.3–180.9)
Bulky disease ≥5cm, n (%)	41 (39.0)	38 (36.2)
Elevated LDH, n (%)	35 (33.0)*	51 (48.6)*
IGHV status,‡ n (%) Mutated Unmutated Unknown	 32 (30.2) 67 (63.2) 7(6.6)	 35 (33.3) 57 (54.3) 13 (12.4)
del(11q), n (%)	20 (18.9)	18 (17.1)
TP53 mutation, n (%)	7 (6.6)	2 (1.9)

* >10% numeric difference between arms; † Using the Cockcroft–Gault equation; ‡ IGHV status of baseline samples were updated since primary analysis based on *post hoc* reclassification using clonoSEQ (Adaptive biotechnologies, Seattle, WA).
CIRS, Cumulative Illness Rating Scale; CrCl, creatinine clearance; LDH, lactate dehydrogenase;
OClb, obinutuzumab + chlorambucil; IVen, ibrutinib + venetoclax.

1. Kater AP, *et al. N Engl J Med Evid* 2022; doi: 10.1056/EVIDoa2200006 (incl. suppl.);
2. Niemann CU, *et al.* ASH 2022. Abstract 93 (Oral).

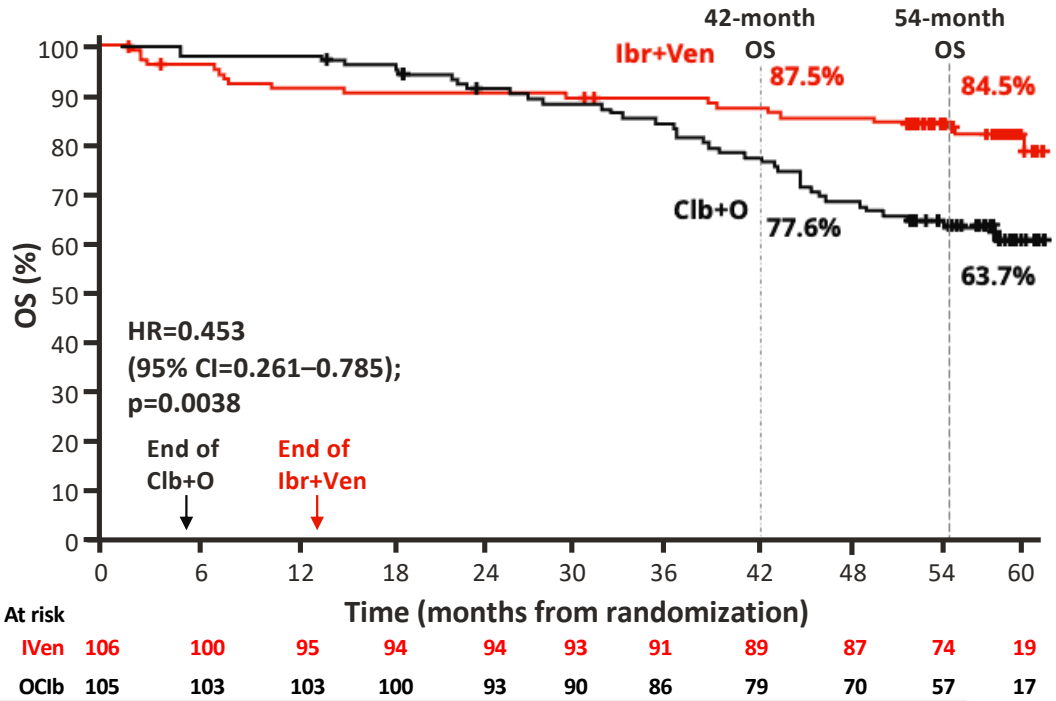
GLOW: PFS and OS at 57 months (ASH 2023)

Primary Endpoint: PFS by IRC[1,2]
(Median follow-up: 57.3 months)



At risk											
IVen	106	99	92	90	88	83	80	75	68	55	11
OClb	105	101	95	61	50	43	33	24	20	15	2

OS[1]
(Median follow-up: 57.3 months)



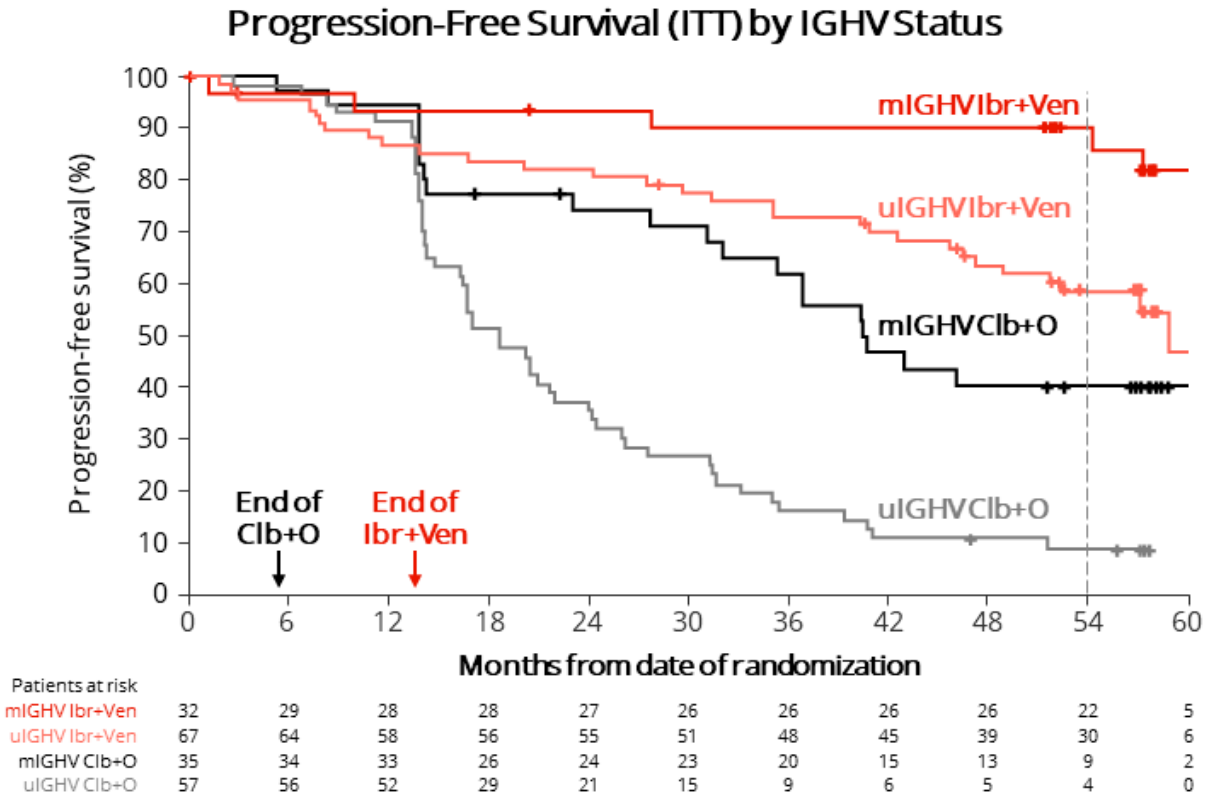
At risk											
IVen	106	100	95	94	94	93	91	89	87	74	19
OClb	105	103	103	100	93	90	86	79	70	57	17

With a median follow-up of 57.3 months, OS and IRC-assessed PFS for IVen was superior to OClb

IRC, independent review committee; ITT, intention to treat; IVen, ibrutinib + venetoclax; OClb, obinutuzumab + chlorambucil.

1. Moreno C, *et al*. ASH 2023. Abstract 634 (Oral);
2. Niemann CU, *et al*. ASH 2022. Abstract 93 (Oral).

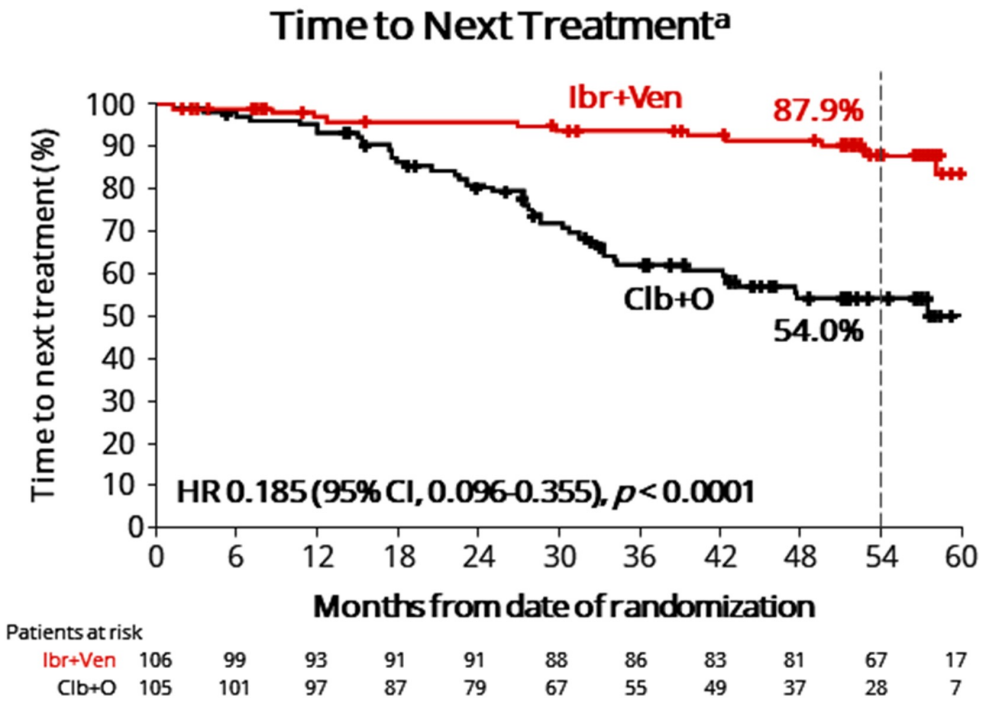
GLOW: Efficacy by IGHV status at 57 months (ASH 2023)

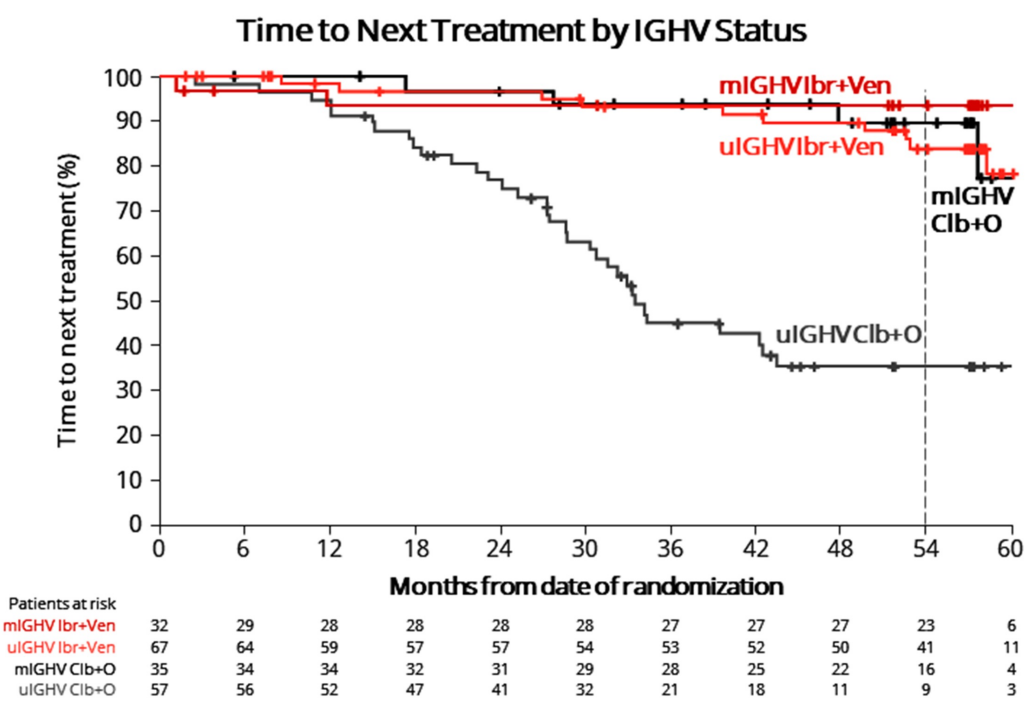


- Estimated 54-month PFS rates:
  - **Ibr+Ven:**
    - 90% for patients with mIGHV
    - 59% for patients with uIGHV
  - **Clb+O:**
    - 40% for patients with mIGHV
    - 8% for patients with uIGHV

1. Moreno C, *et al*. ASH 2023. Abstract 634 (Oral);
2. Niemann CU, *et al*. ASH 2022. Abstract 93 (Oral).

GLOW: EFFICACY – TTNT (ASH 2023)

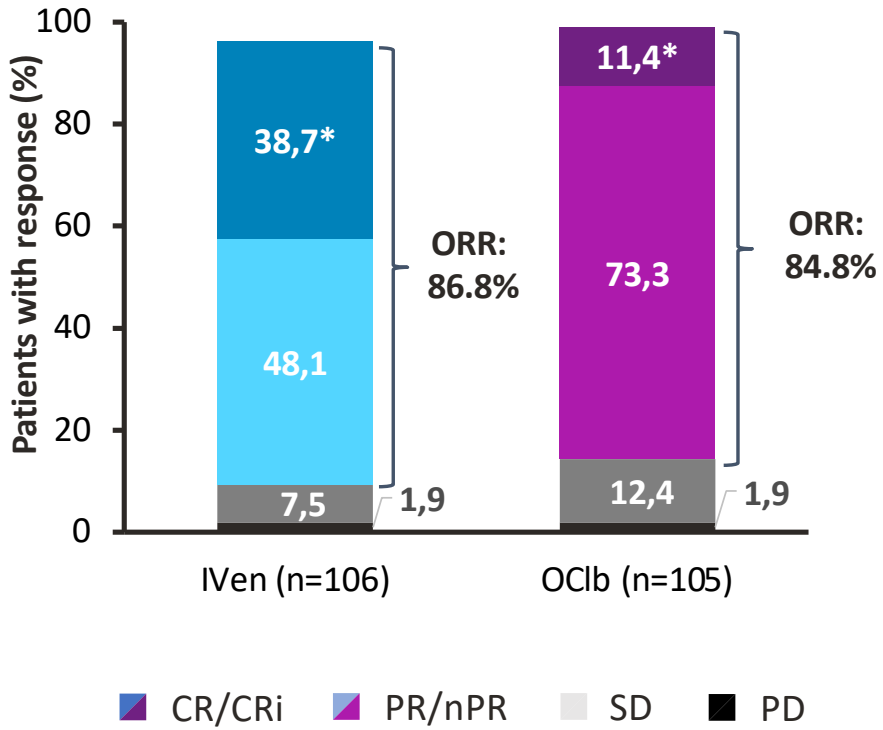




1. Moreno C, et al. ASH 2023. Abstract 634 (Oral);

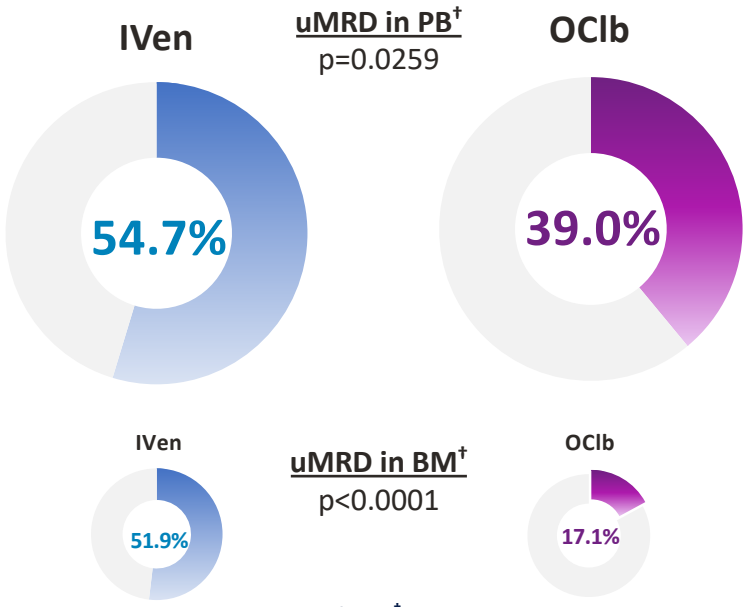
GLOW: Response rates

IRC-Assessed Response Rates[1]



*p<0.0001; † uMRD <10^{-4}; ‡ PB/BM uMRD concordance calculated for patients with uMRD in PB and a paired BM sample at EoT+3.
BM, bone marrow; EoT, end of treatment; IRC, independent review committee; ITT, intention to treat; IVen, ibrutinib + venetoclax; OClb, obinutuzumab + chlorambucil; PB, peripheral blood.

uMRD at EoT+3 by NGS (ITT Population)[1,2]

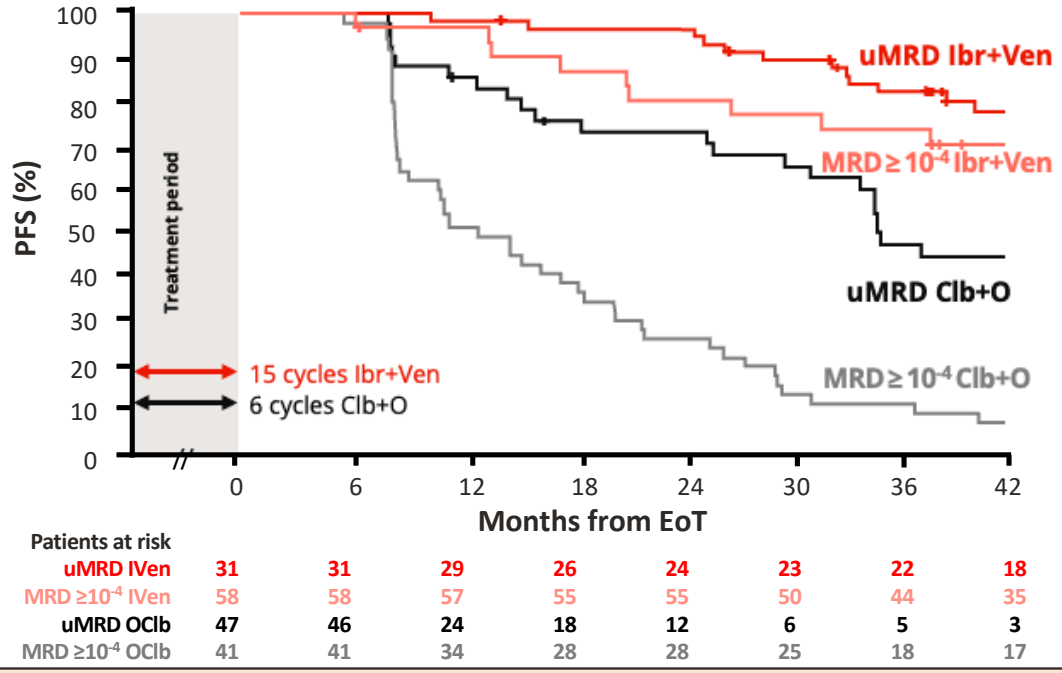


Concordance‡ PB vs BM:
92.9% for IVen vs 43.6% for OClb

1. Moreno C, *et al*. ASH 2023. Abstract 634 (Oral);
2. Niemann CU, *et al*. ASH 2022. Abstract 93 (Oral).

GLOW: Progression-Free Survival by MRD Status (ASH 2023)

PFS* by MRD Status† at EoT+3
(Median follow-up: 57.3 Months)



Patients at risk								
uMRD IVen	31	31	29	26	24	23	22	18
MRD ≥10^{-4} IVen	58	58	57	55	55	50	44	35
uMRD OClb	47	46	24	18	12	6	5	3
MRD ≥10^{-4} OClb	41	41	34	28	28	25	18	17

	IVen		OClb	
	uMRD (n=31)	MRD ≥10^{-4} (n=58)	uMRD (n=47)	MRD ≥10^{-4} (n=41)
42-month PFS rate, %	78	70	44	6

IVen improved PFS vs OClb irrespective of MRD status at EoT+3

* Curves generated from EoT (cycle 15 for IVen, cycle 6 for OClb); all patients who had MRD outcome at EoT+3 were included; † uMRD in PB by NGS via ClonoSEQ® assay.
EoT, end of treatment; IVen, ibrutinib + venetoclax; MRD, minimal residual disease; OClb, obinutuzumab + chlorambucil; PB, peripheral blood; uMRD, undetectable MRD.

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

GLOW: Safety (ASH 2023)

Grade 3/4 AEs in ≥5% of patients[1]	IVen (n=106)	OClb (n=105)
Median treatment exposure, months (range)	13.8 (0.7–19.5)	5.1 (1.8–7.9)
Patients with ≥1 AE, n (%)	73 (68.9)	71 (67.6)
Neutropenia*	37 (34.9)	52 (49.5)
Infections and infestations†	16 (15.1)	11 (10.5)
Diarrhea	11 (10.4)	1 (1.0)
Hypertension	8 (7.5)	2 (1.9)
Atrial fibrillation	7 (6.6)	0
Thrombocytopenia	6 (5.7)	21 (20.0)
Hyponatremia	6 (5.7)	0
TLS	0	6 (5.7)

- No TLS events were observed during venetoclax onboarding in combination with ibrutinib[1]
- With patients off treatment in the primary analysis (median follow-up: 27.7 months), there were no major changes in the safety profile with a median follow-up of 34.1 months, except for one patient in the OClb arm with a new serious TEAE of MDS/MPN[2]
- With a median follow-up of 57.3 months, there were 14 (13.2%) secondary primary malignancies in the IVen arm and 18 (17.1%) in the OClb arm[3]
- There were four cardiac or sudden deaths reported in the IVen arm and none in the OClb arm[‡,1,3]

Higher rates of neutropenia, thrombocytopenia, and TLS observed with OClb;
whereas rates of infections, diarrhea, hypertension, atrial fibrillation, and hyponatremia were higher with IVen[1]

1. Kater AP, *et al. NEJM Evid* 2022; doi: 10.1056/EVIDoa2200006;
2. Munir T, *et al. J Clin Oncol* 2023; **41**:3689–3699;
3. Moreno C, *et al*. ASH 2023. Abstract 634 (Oral).

* Includes neutrophil count decreased; Grade ≥3 febrile neutropenia: 1.9% for IVen vs 2.9% for OClb; † Includes multiple preferred terms;
‡ Two deaths due to cardiac disorders occurred during ibrutinib lead-in and two sudden deaths occurred during IVen combination.
IVen, ibrutinib + venetoclax; MPN, myeloproliferative neoplasm; OClb, obinutuzumab + chlorambucil; TEAE, treatment-emergent adverse event; TLS, tumor lysis syndrome.

GLOW: Summary of Deaths (ASH 2023)

	Ibr+Ven (n = 106)		Clb+O (n = 105)	
Total number of deaths	19		39	
Reasons for deaths	On treatment	Post randomized treatment[a]	On treatment	Post randomized treatment[a]
Infection related[b]	1	3	1	13
Second primary malignancy	1	1	0	7
Cardiac	2[c]	0	0	4
Sudden/unknown	2	3	0	4
Progressive disease	0	1	0	2
Vascular disorders	1	2	0	3
Other	0	2	1	4
Total	**7**	**12**	**2**	**37**

- **At 57 months of follow-up, there were 19 deaths in Ibr+Ven versus 39 in Clb+O arms**
  - 3 deaths in Ibr+Ven and 13 in Clb+O were due to post-treatment infections
  - 2 deaths in Ibr+Ven and 7 in Clb+O were due to second primary malignancies

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

Long-term survival outcomes of FD trials in 1L CLL

Unfit

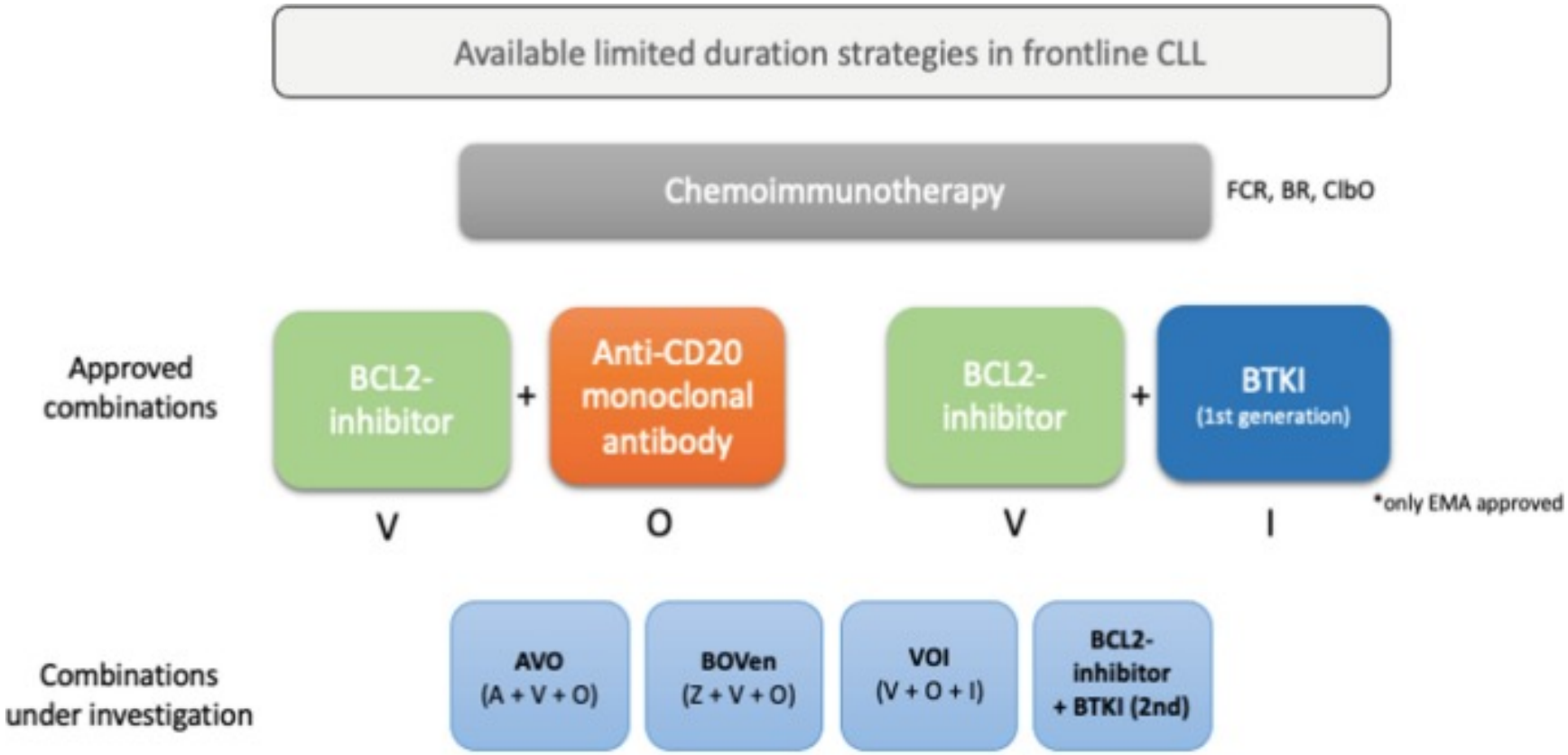
CLL 14 6 yrs FU	
Median Age	72 yrs
uIGHV	61%
Del/TP53	12%
PFS	53.1%
OS	78.7%
TTNT	65.2%
EOT uMRD PB (ASO-PCR)	76%

GLOW 57 months FU	
Median Age	71 yrs
uIGHV	63.2%
Del/TP53	-
PFS	66.5%
OS	84.4%
TTNT	87.9%
EOT uMRD PB (NGS)	55%

Fit

CLL 13 (VO arm) 4 yrs FU	
Median Age	62 yrs
uIGHV	57%
Del/TP53	-
PFS	81.8%
OS	95.1%
TTNT	90.4%
EOT uMRD PB (FLC)	87%

CAPTIVATE FD 4 yrs FU	
Median Age	60 yrs
uIGHV	56%
Del/TP53	17%
PFS	79%
OS	98%
TTNT	84%
EOT uMRD PB (FLC)	79%



A = Acalabrutinib; BR = Bendamustin, rituximab; BTKI = Bruton tyrosin kinase inhibitor; ClbO = Chlorambucil, obinutuzumab; FCR = Fludarabine, cyclophophamide, rituximab; I = Ibrutinib; O = Obinutuzumab; V = Venetoclax; Z = Zanubrutinib

Venetoclax with covalent BTKi and antiCD20Abs (triplets) in 1FL CLL: Phase III clinical trials

Treatment	*N*	Age	*TP53 ab*	ORR/CR	PFS	OS	uMRD (10^{-4})	uMRD (10^{-5})	Median FU
IBRU + VEN + OBINU (vs. FCR/BR) [GAIA/CLL13]	231	61	Excluded	94.4%/ 61.9%	3-yr 90.5%	3-yr 95.3%	92.2%/77.9% (PB/BM) at 15 months	NR	38.8 months
IBRU + VEN + OBINU	25	59	12%	84%/ 32%	4-yr 96%	4-yr 85%	67% (PB + BM) at EOT	NR	57 months
IBRU + VEN + OBINU [CLL2-GIVe]	41	62	100%	100%/ 58.5%	3-yr 79.7%	3-yr 92.6%	78%/65.9% (PB/BM) at cycle 15	NR	36 months
ACALA + VEN + OBINU (AVO)	68	63	45.6%	98%/ 48%	3-yr 93%	NR	86% (PB and BM) at 16 months (+1 mo EoT)	59% (PB)	35 months
ZANU + VEN [SEQUOIA D]	35	NR	100%	96.8%/ 12.9%	NR	NR	NR	NR	9.7 months
ZANU + VEN + OBINU (ZVO)	39	62	13%	100%/ 57%	NR	NR	92%/84% (PB/BM) at best	40% (PB)	25.8 months

uIGHV, unmutated IGHV; ORR, overall response rate; CR, complete response; PFS, progression-free survival; OS, overall survival; FU, follow-up; mo, months; uMRD, undetectable measurable residual disease; PB, peripheral blood; BM, bone marrow; c/ncMRD, confirmed MRD; FCR, fludarabine plus cyclophosphamide plus rituximab; BR, bendamustine plus rituximab; IBRU, ibrutinib; VEN, venetoclax; OBINU, obinutuzumab; ACALA, acalabrutinib; ZANU, zanubrutinib; NR, not reported; TP53 ab, TP53 aberrations.

Ongoind Clinical Trial in 1FL CLL:

Study	Trial population	Study treatment	Primary endpoint
CLL17 (NCT04608318)	$N=897$ ≥ 18 y Fit/unfit No aberrations excl	I: until progression VO: 12 months VI: 15 months; venetoclax 12 months	PFS
FLAIR (ISRCTN01844152)	$N=1516$ ≤ 75 y Fit/ eGFR > 30 mL/min del (17p) < 20%	IR → I*: until progression VI: flexible duration according to MRD CIT: FCR 6 cycles *IR replaced by I mono in 2018	PFS
AMPLIFY (NCT03836261)	$N=780$ ≥ 18 y Fit/ *TP53* aberrations excl	AV: 15 months, venetoclax 12 months AVO: 15 months, venetoclax 12 months CIT: FCR/BR 6 cycles	PFS
MAJIC (NCT05057494)	$N=600$ ≥ 18 y Fit/ unfit No aberrations excl	AV: 15 months; Ven 12 months VO: 12 months (dMRD after 12 months venetoclax = additional 12 months treatment)	PFS MRD-guided AV/VO
CRISTALLO (NCT04285567)	$N=165$ ≥ 18 y Fit/ *TP53* aberrations excl	VO: 12 months CIT: FCR/BR 6 cycles	MRD BM at month 15
ECOG-ACRIN EA9161 (NCT03701282)	$N=720$ 18– 69 y del (17p) excl	IO: until progression VOI: 19 months; venetoclax 12 months	PFS
FILO ERADIC (NCT04010668)	$N=120$ ≥ 18 y Fit/ *TP53* aberrations excl	VI: 15 or 27 months according to MRD CIT: FCR 6 cycles	MRD BM at month 27
CLL 16 (NCT05197192)	$N=178$ ≥ 18 y del(17p) and/or *TP53* mutation and/or complex karyotype	AVO:15 months, venetoclax 12 months VO: 12 months (dMRD after 14 cycles AVO = additional 12 cycles treatment with acalabrutinib)	PFS

OS overall survival; *PFS* progression-free survival; *MRD* minimal residual disease; *dMRD* detectable minimal residual disease; *BM* bone marrow; *A* acalabrutinib; *BR* bendamustine, rituximab; *CIT* chemoimmunotherapy; *FCR* fludarabine, cyclophosphamide, rituximab; *I* ibrutinib; *O* obinutuzumab; *V* venetoclax

CLL

1L	2L	NOTE
IBRUTINIB	IBRUTINIB ✖ ACALABRUTINIB ▲ ZANUBRUTINIB ▲ VENETOCLAX ± RITUXIMAB ✔	BTKi: 2L con Acalabrutinib o Zanubrutinib consentito **SOLO in caso di tossicità inaccettabile** di IBRUTINIB in 1L (non per progressione)
ACALABRUTINIB	IBRUTINIB ✖ ACALABRUTINIB ✖ ZANUBRUTINIB ✖ VENETOCLAX ± RITUXIMAB ✔	IBR dopo Acalabrutinib non consentito
ZANUBRUTINIB	IBRUTINIB ✖ ACALABRUTINIB ✖ ZANUBRUTINIB ✖	IBR dopo Zanubrutinib non consentito
VENETOCLAX+ OBINOTUZUMAB	VENETOCLAX ± RITUXIMAB ✔ IBRUTINIB ✔ ACALABRUTINIB ✖ ZANUBRUTINIB ✔ VENETOCLAX ± RITUXIMAB ✖	Per Venetoclax non è possibile il ritrattamento con la stessa classe. Dopo VG, è consentito il trattamento con tutti i BTKi in 2L, eccetto Acalabrutinib.
IBRUTINIB VENETOCLAX	IBRUTINIB ✔ ACALABRUTINIB ✖ ZANUBRUTINIB ✖ ? VENETOCLAX ± RITUXIMAB ✔	Dopo I+V è permesso il **RITRATTAMENTO** con IBRUTINIB o Venetoclax (monoterapia o combinazione con Rituximab)

✔ *Nessun blocco in scheda monitoraggio* ✖ *Blocco in scheda monitoraggio* ▲ *Switch per tossicità inaccettabile*

https://www.aifa.gov.it/documents/20142/2193567/Registri_PT_attivi_15.04.2024.csv

FD Therapy in FL CLL: conclusion

- Fixed-duration (FD) therapy is an appealing approach to initial treatment of CLL from a patient's and a clinician's perspective.
- Patients are interested in being able to stop treatment once the disease is in remission and tend to have better adherence to treatment and laboratory monitoring when therapy is FD
- Although patients will need to continue to be monitored after treatment completion for long-term toxicities, infections, recurrent disease, and the development of resistance, monitoring is generally less intense after FD therapy.
- Mild toxicities can be less burdensome if the treatment duration is finite.
- The financial burden associated with therapy becomes less of a concern with FD.

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