MEET THE

EXPERT *in CLL*

CASTELFRANCO VENETO (TV), 27 GIUGNO 2025

Ospedale San Giacomo Apostolo, Sala Scarpa

13.45-14.05 Terapia a durata fissa nel paziente di prima linea e nel paziente ricaduto/refrattario

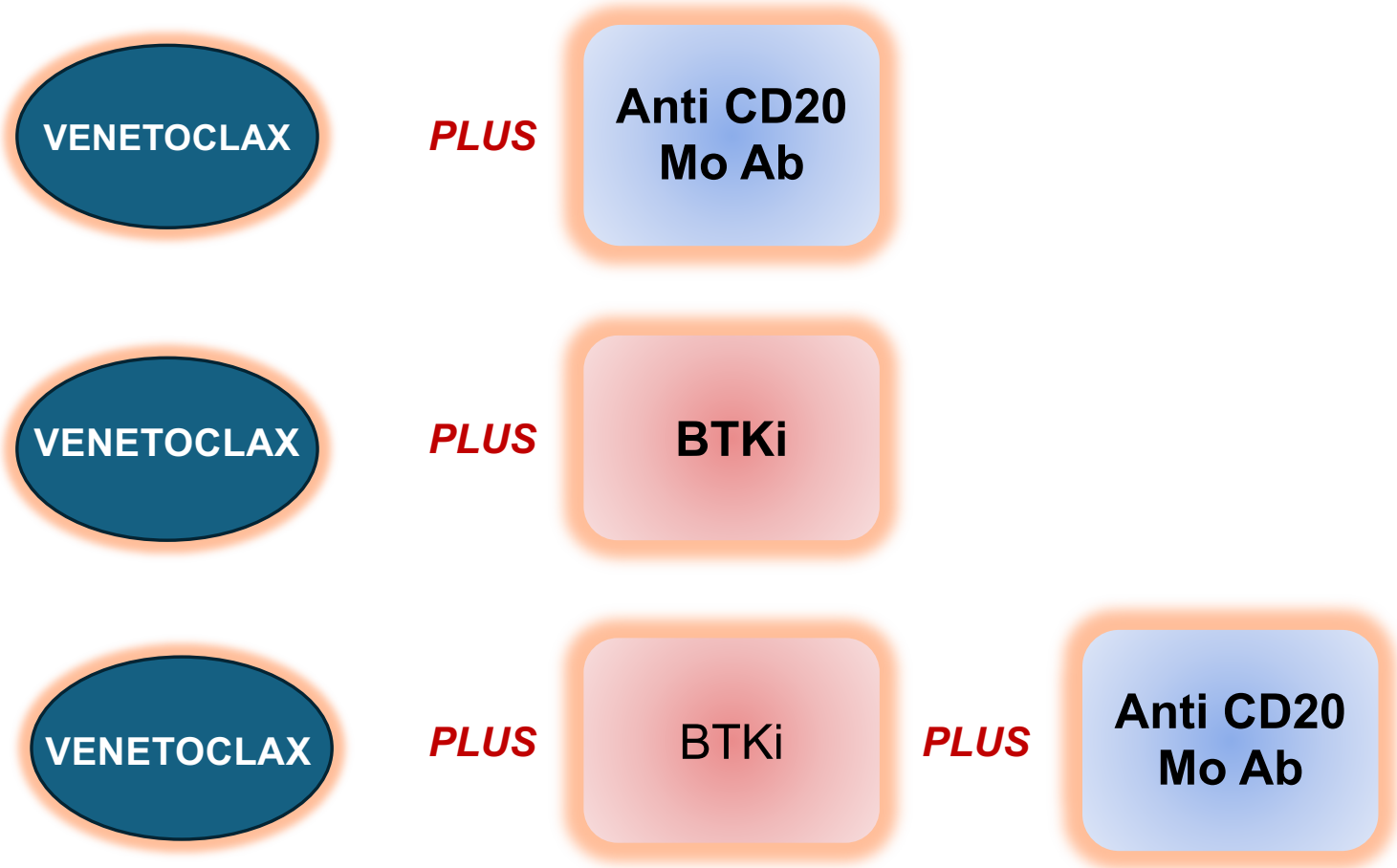
Moderatori: M. Gottardi (Castelfranco Veneto-TV), **P.L. Zinzani** (Bologna)

Esperto: A. Tedeschi (Milano)

Disclosures Alessandra Tedeschi

Company name	Consultant	Speakers bureau	Advisory board
J&J	X	X	X
Beone	X	X	X
Lilly		X	X
AbbVie		X	X

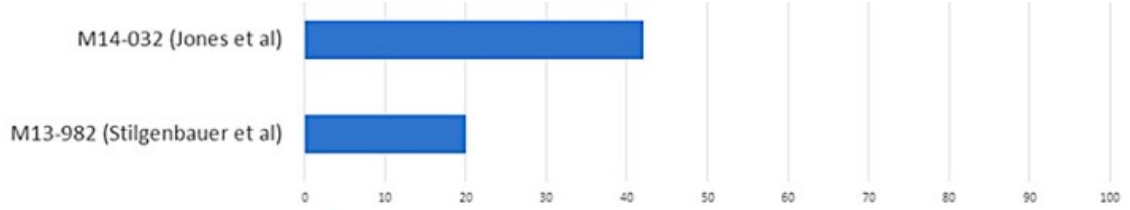
Venetoclax: the backbone of fixed duration therapy



Why Venetoclax

VENETOCLAX DEEP RESPONSES

Venetoclax showed from the very beginning the potential to reach good quality of responsesn and uMRD

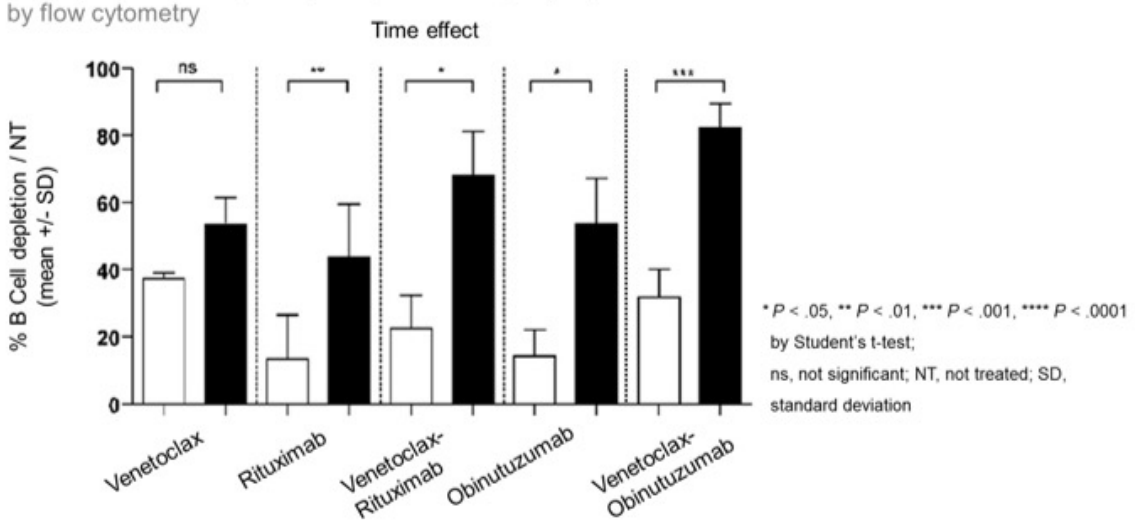


uMRD after venetoxlax in havely pretreated and high risk pts

Venetoclax + Obinutuzumab TN CLL
Rational

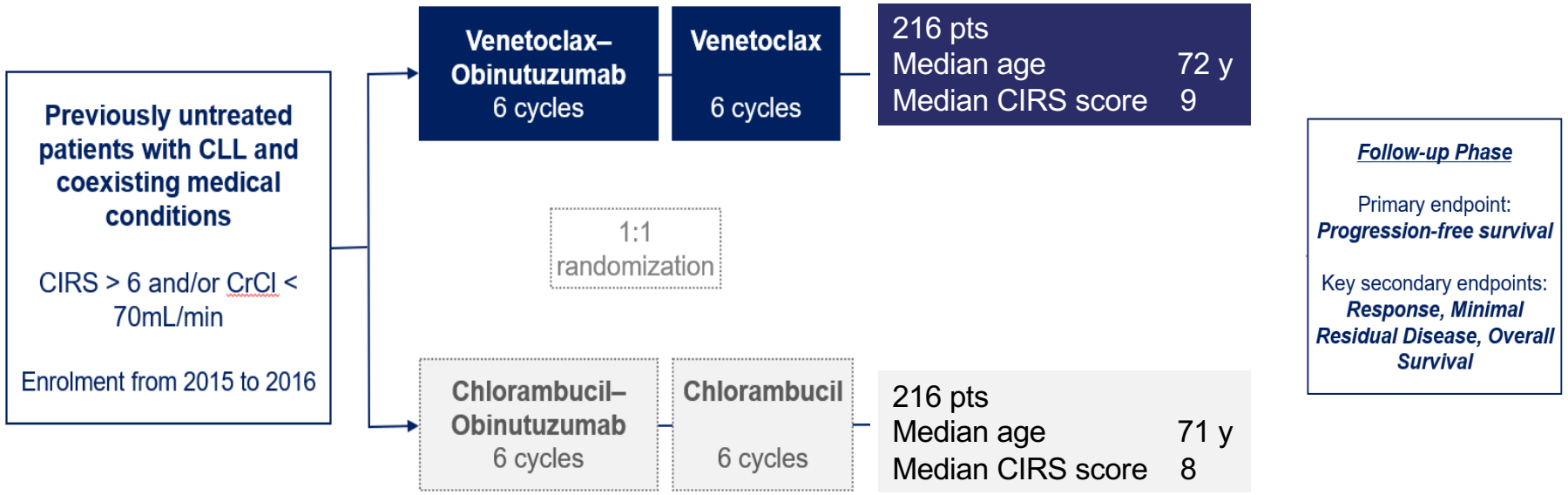
VENETOCLAX ***PLUS*** **OBINUTUZUMAB**

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



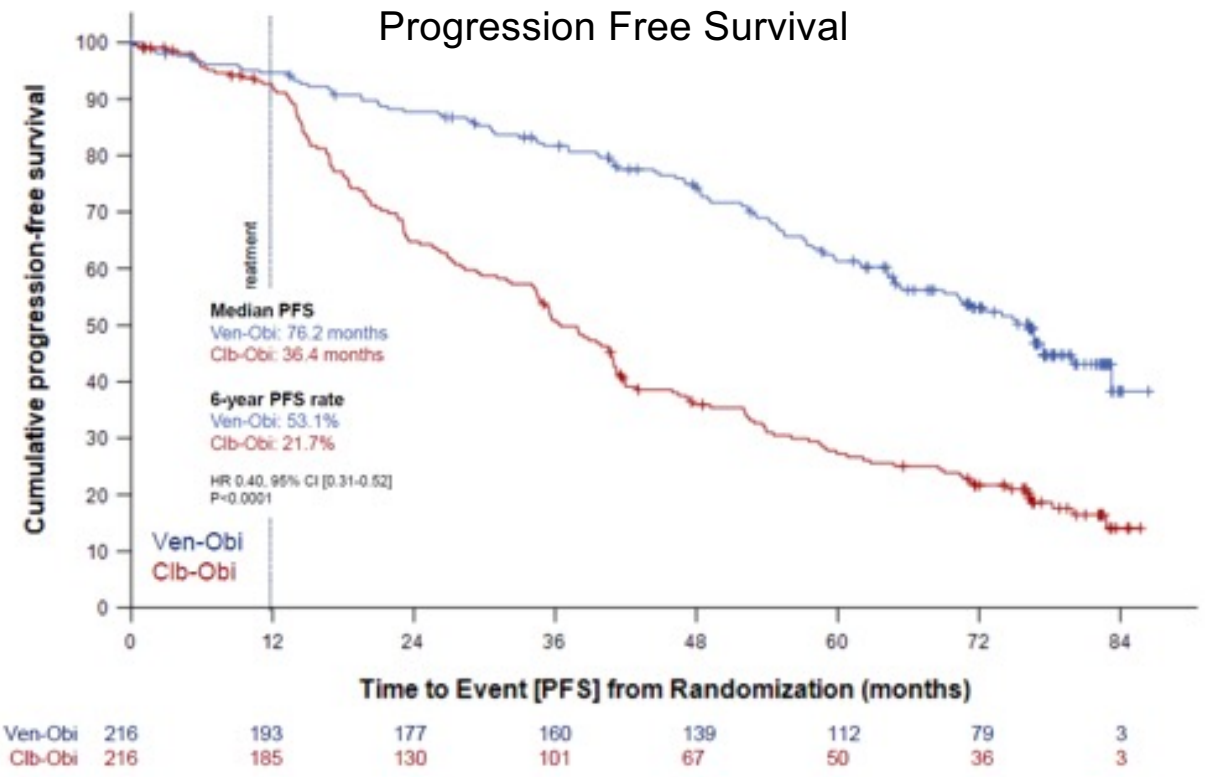
Fisher et al N Eng J Med 2019 2023

Venetoclax + Obinutuzumab TN CLL
CLL14 phase 3 randomized trial



Al Sawaf et al EHA 2023
Al Sawaf et al Nature Com 2023

Venetoclax + Obinutuzumab TN CLL
CLL14 phase 3 randomized trial: PFS



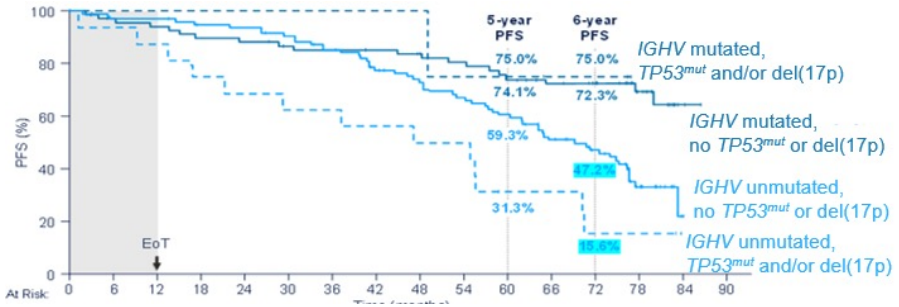
Al Sawaf O et al., Blood 2024

Venetoclax + Obinutuzumab TN CLL

CLL14 phase 3 randomized trial: PFS according to disease biology

Venetoclax Obinutuzumab

Ven + Obi: PFS according to *IGHV* and del(17p)/*TP53*[2]

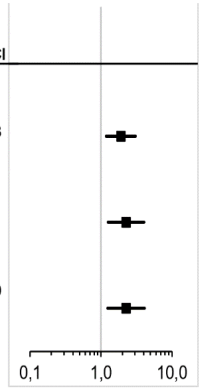


uIGHV-mPFS: 65 m

del17p/TP53m mPFS: 52 m

Negative prognostic factors for PFS

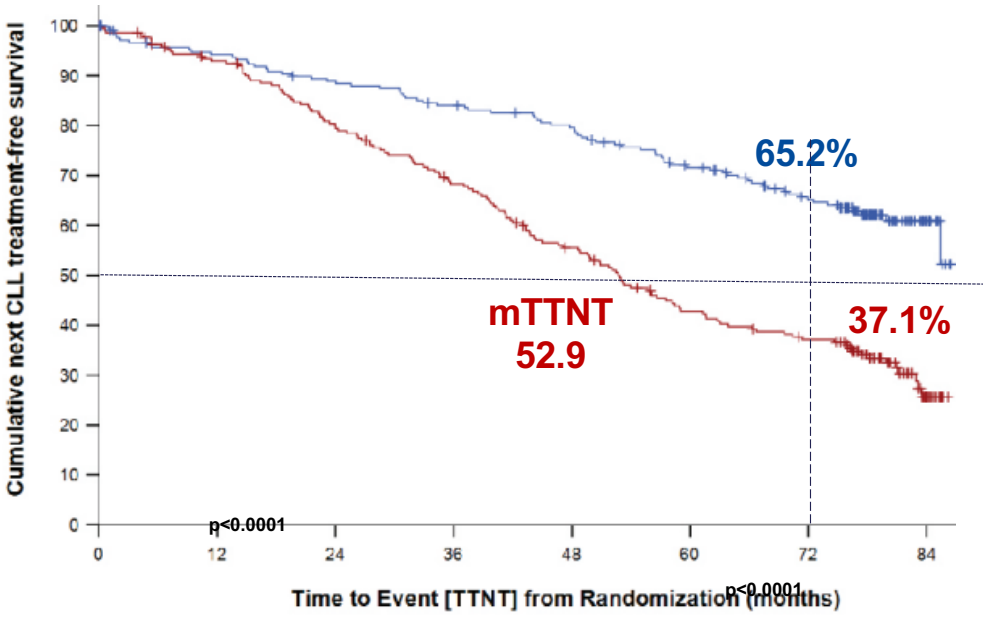
COX regression PFS	Univariate comparison	Hazard ratio	95% Wald CI
Lymph node size			
≥ 5 cm	vs. < 5 cm	1.916	1.189-3.088
IGHV mutational status			
unmutated	vs. mutated	2.258	1.268-4.021
***TP53* deletion/mutation**			
Deleted and/or mutated	vs. none	2.262	1.242-4.120



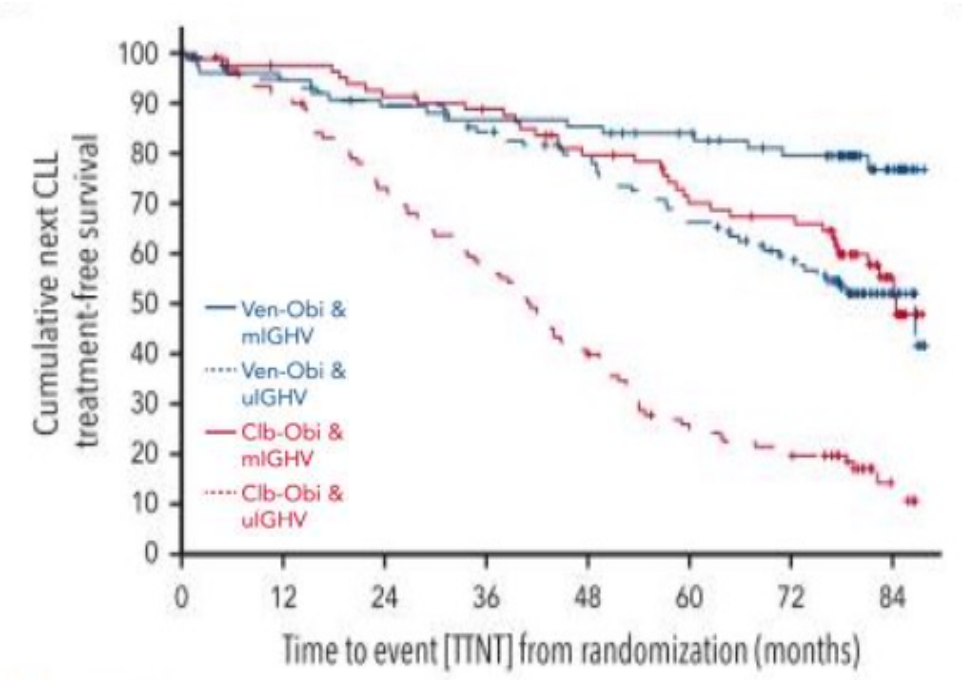
Al Sawaf O et al., Nature Com 2023

Venetoclax + Obinutuzumab TN CLL
CLL14 phase 3 randomized trial: TTNT

Time To Next Treatment



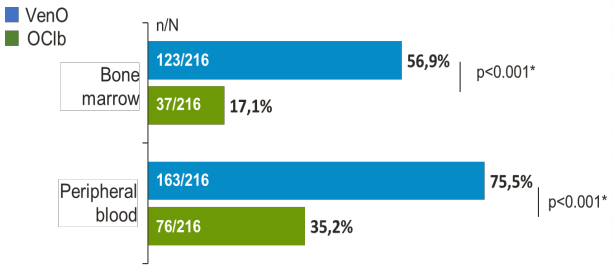
Time To Next Treatment according to IGHV



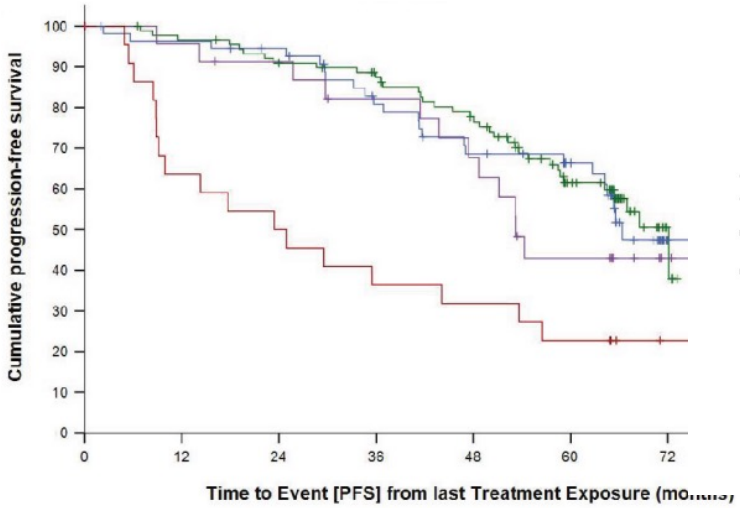
Al Sawaf O et al., Blood 2024

Venetoclax + Obinutuzumab TN CLL
CLL14 phase 3 randomized trial: uMRD

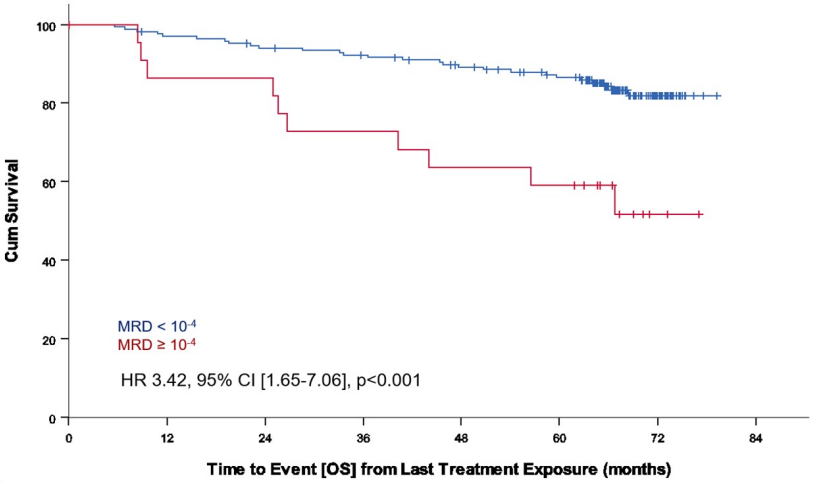
Proportion of uMRD



PFS according to MRD

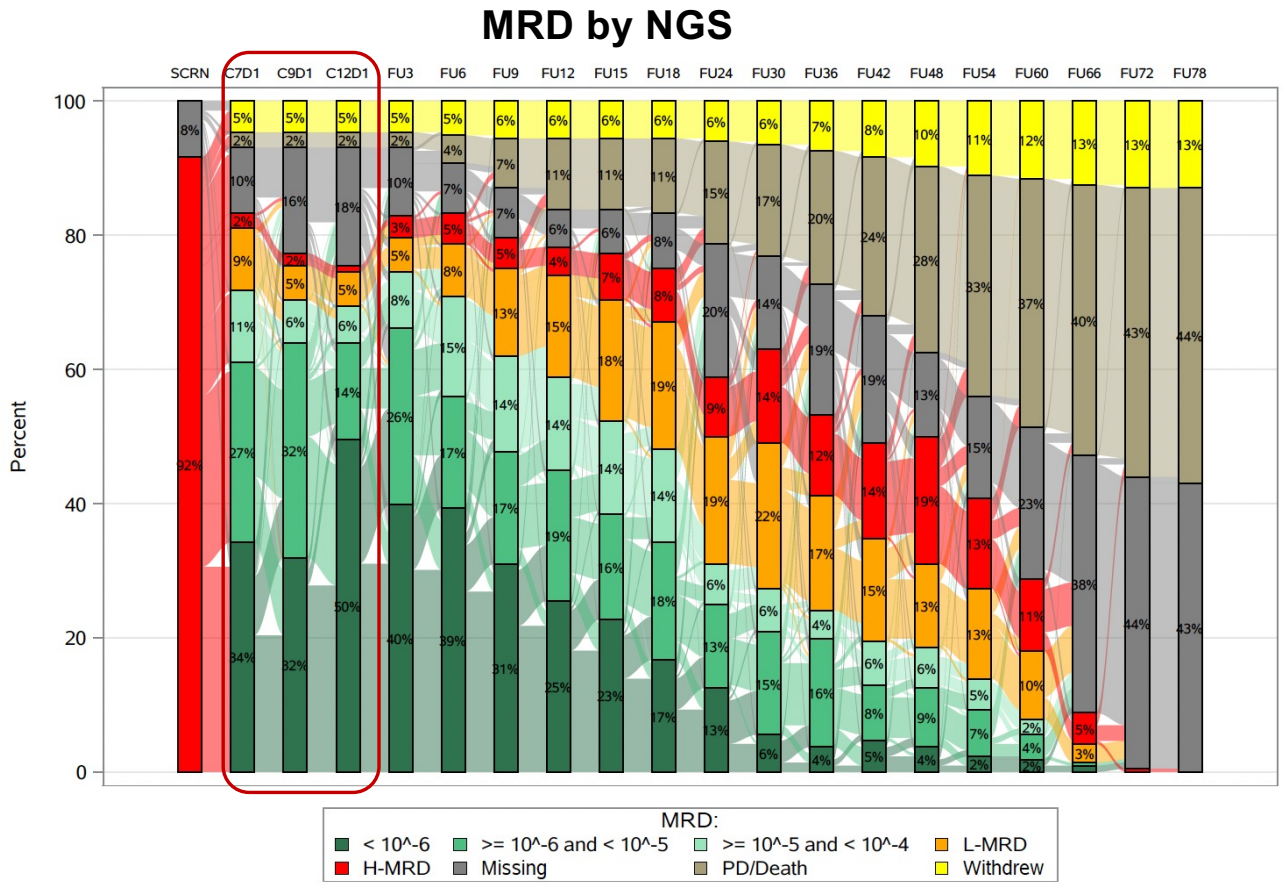


OS according to MRD



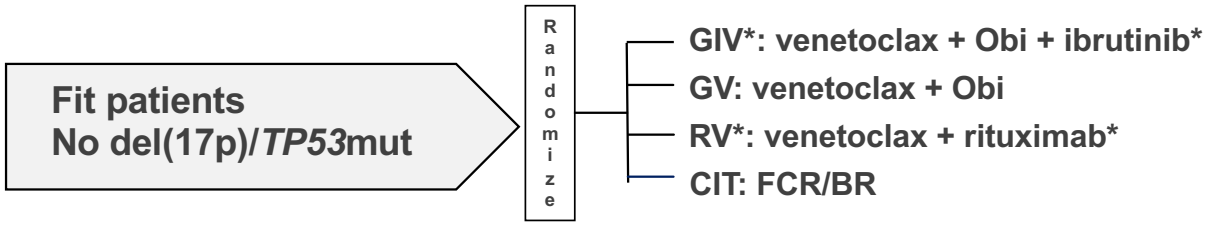
Al Sawaf et al, Blood 2024

Venetoclax + Obinutuzumab TN CLL
CLL14 phase 3 randomized trial: uMRD

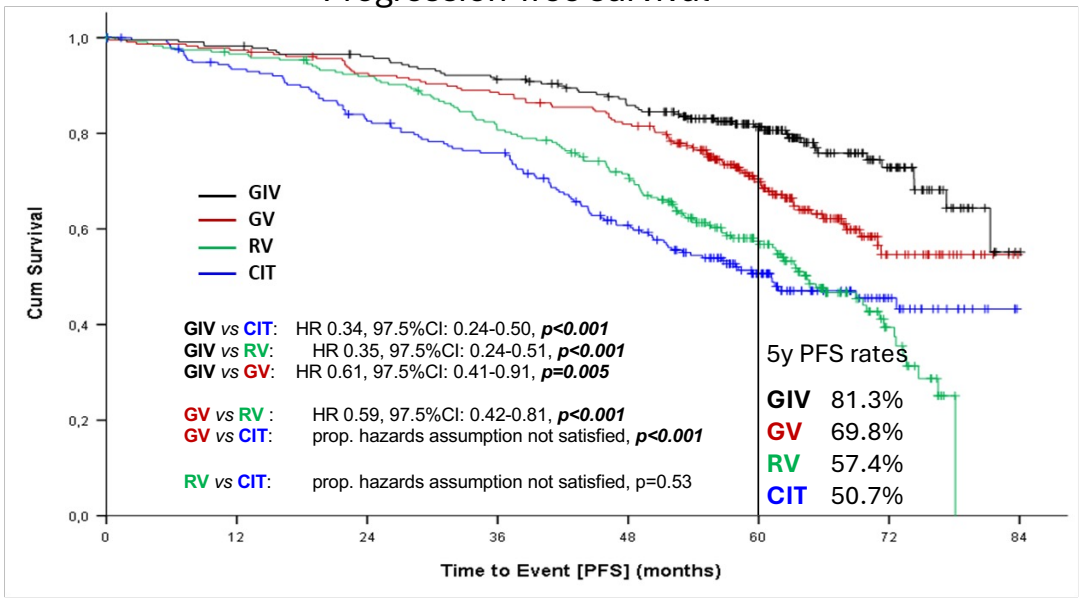


Al Sawaf et al, Blood 2024

Venetoclax + Obinutuzumab TN CLL
GAIA phase 3 randomized trial: PFS, MRD



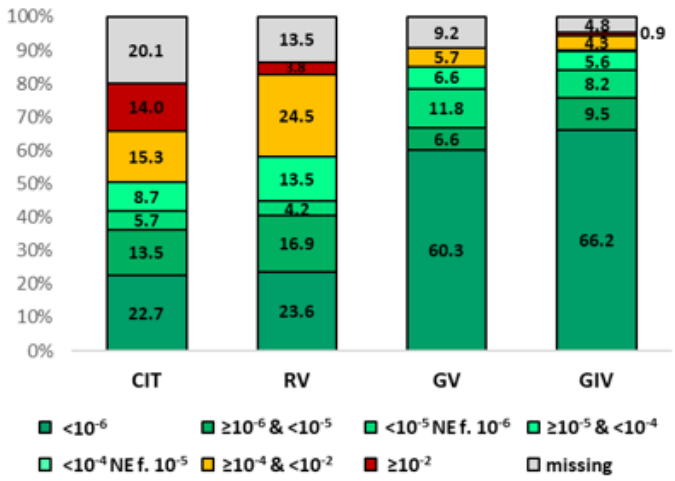
Progression-free survival



Patients at risk

CIT	229	198	174	159	119	67	21
RV	237	227	214	187	160	89	20
GV	229	223	210	201	185	109	25
GIV	231	227	219	207	189	126	44

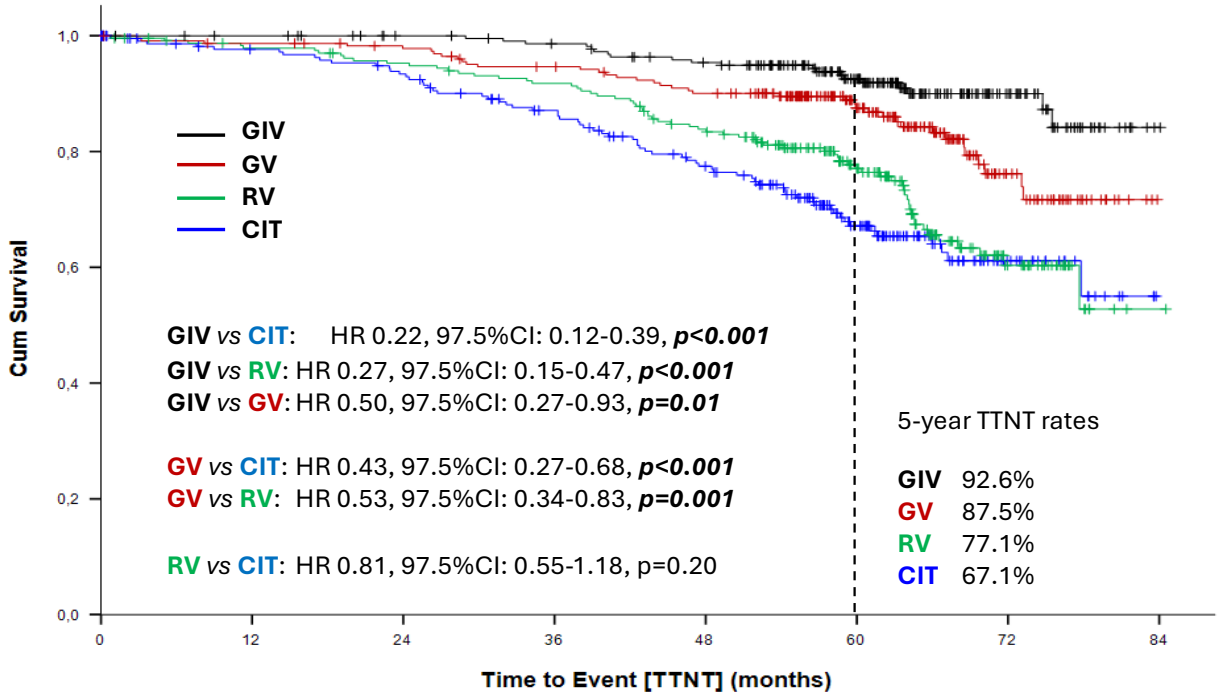
NGS MRD level in PB at MO15



Fürstenau M et al., EHA 2024

Venetoclax + Obinutuzumab TN CLL
GAIA phase 3 randomized trial: TTNT

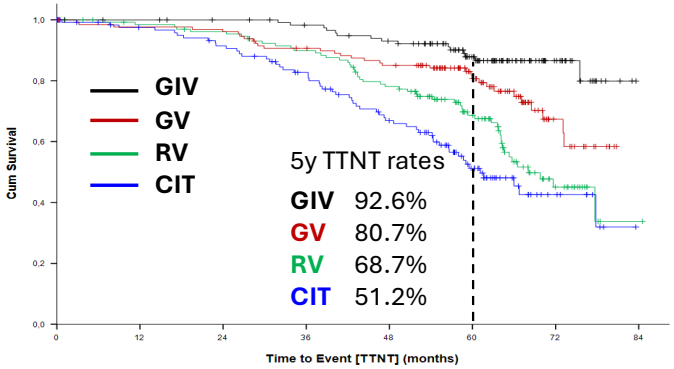
Time to next treatment



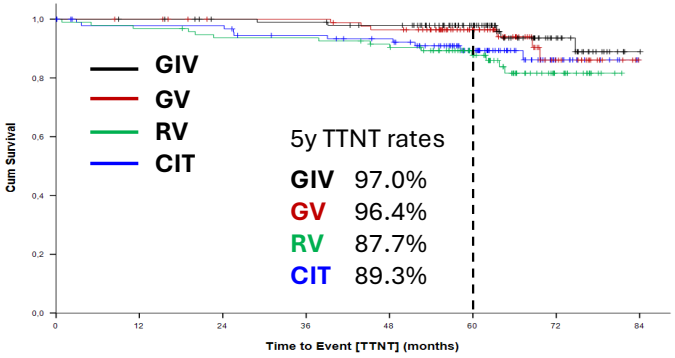
Patients at risk

CIT	229	206	196	175	148	88	23
RV	237	227	219	210	188	119	33
GV	229	224	218	208	196	124	36
GIV	231	228	220	214	202	141	48

TTNT, unmutated IGHV



TTNT, mutated IGHV

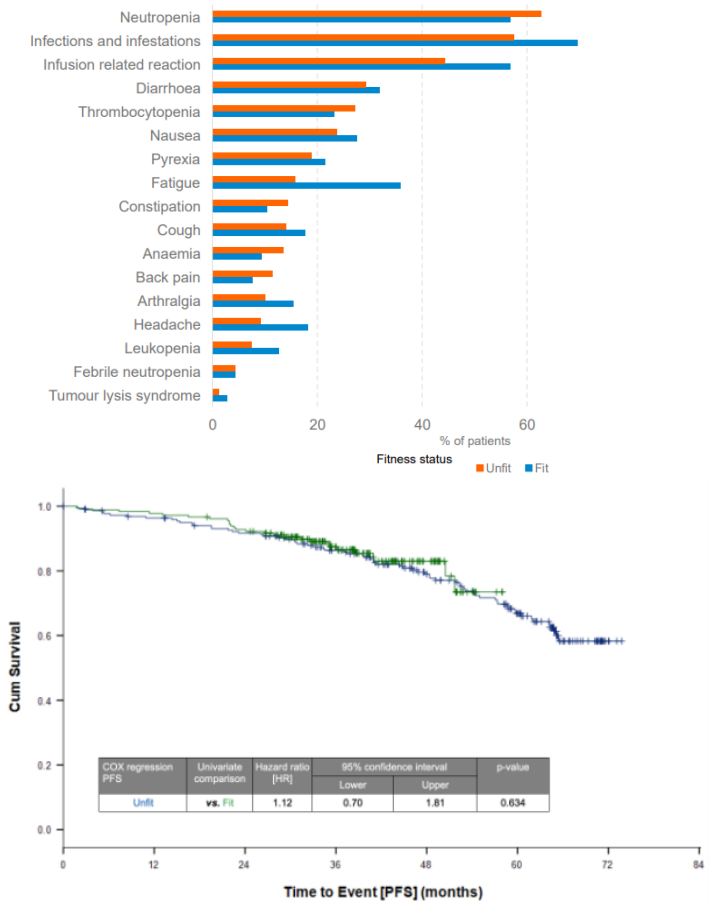


Fürstenau M et al., EHA 2024

Venetoclax + Obinutuzumab TN CLL

CLL13 and CLL14 phase 3 randomized trials: Safety

No substantial impact of fitness on toxicity



CLL14: Most frequent ≥ grade 3 adverse events

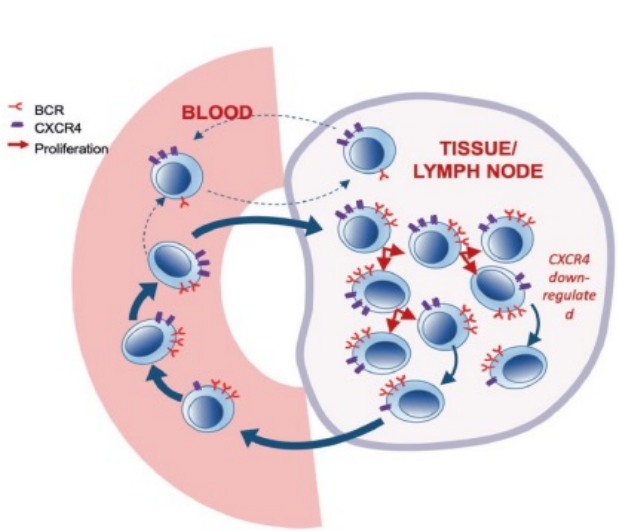
	Venetoclax-obinutuzumab (N=212)	
	During Treatment	After Treatment
Neutropenia	51.9%	3.8%
Thrombocytopenia	14.2%	0.5%
Anemia	7.5%	1.9%
Febrile neutropenia	4.2%	0.9%
Leukopenia	2.4%	0.0%
Pneunomia	3.8%	3.3%
Infusion-related reaction	9.0%	0.0%
Tumour lysis syndrome	1.4%	0.0%

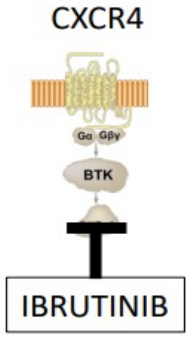
Al Sawaf et al Nature Com 2023
Al Sawaf et al EHA 2023

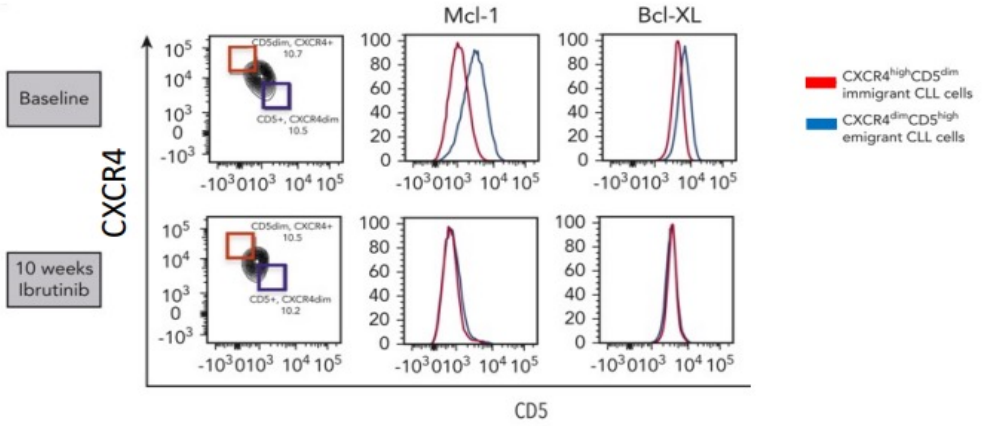
Venetoclax: the backbone of combination therapy

Venetoclax + Ibrutinib
Strong synergism

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

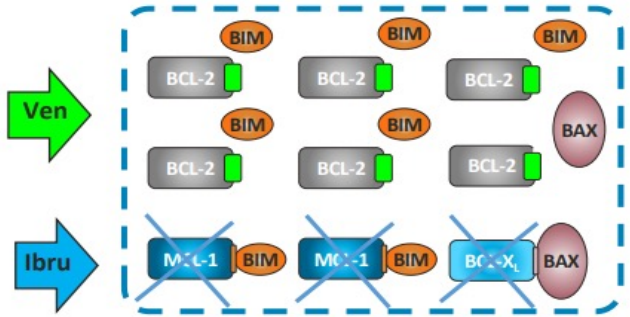






Emigrants (CXCR4^{dim}/CD5^{high}) recently divided and robust cells

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



Ibrutinib sensitizes CLL cells to venetoclax

Leukemia (2022) 36:2233 – 2241

Haselager et al. Blood 2020

Venetoclax + Ibrutinib TN CLL

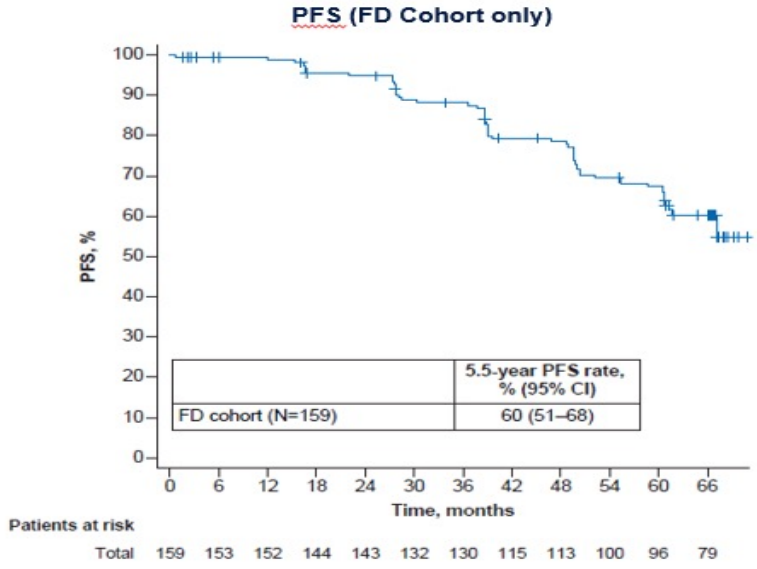
Captivate phase 2 and Glow phase randomized 3 trials: PFS

Young FIT → **Elderly Unfit**

CAPTIVATE (PCYC-1142) phase 2 trial

Median age: 60y

69 m median FU

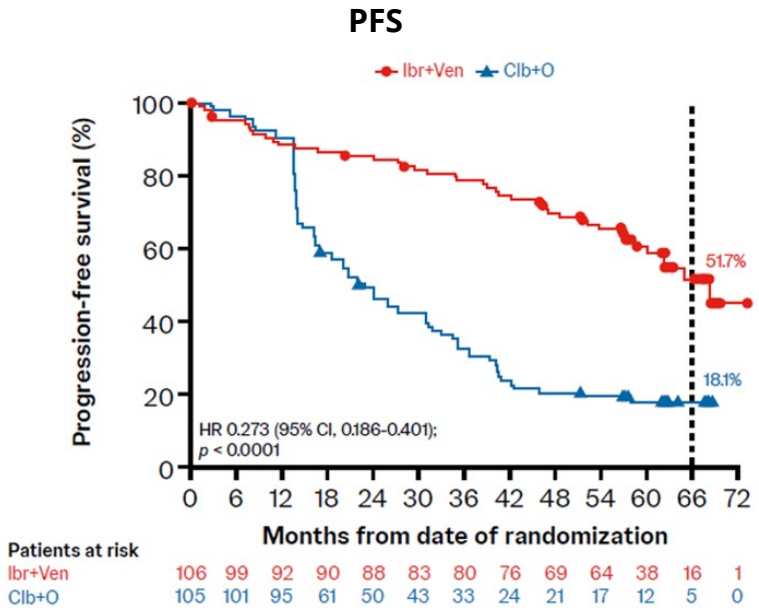


Ghia et al., EHA 2025

GLOW phase 3 trial: Ibrutinib Venetoclax vs ClbO

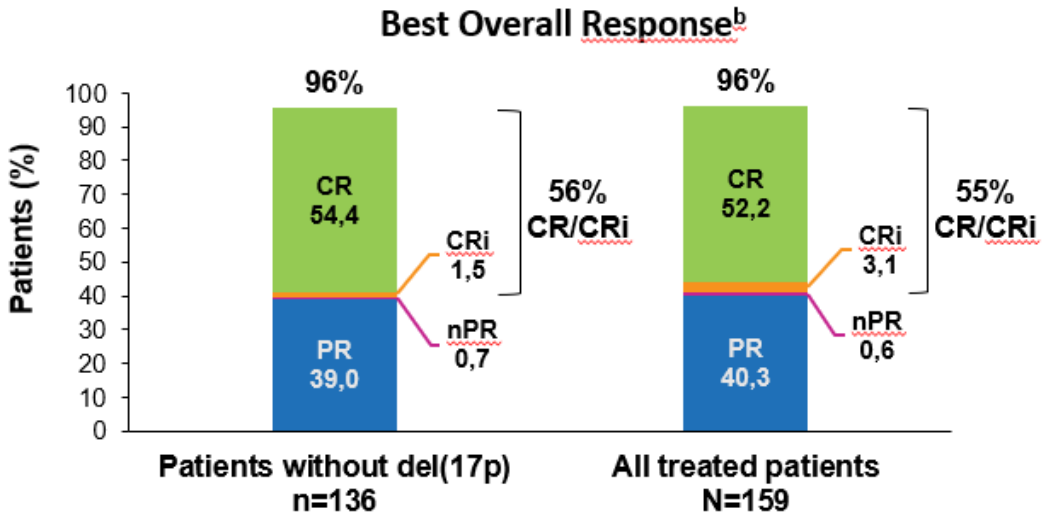
Median age: 71y

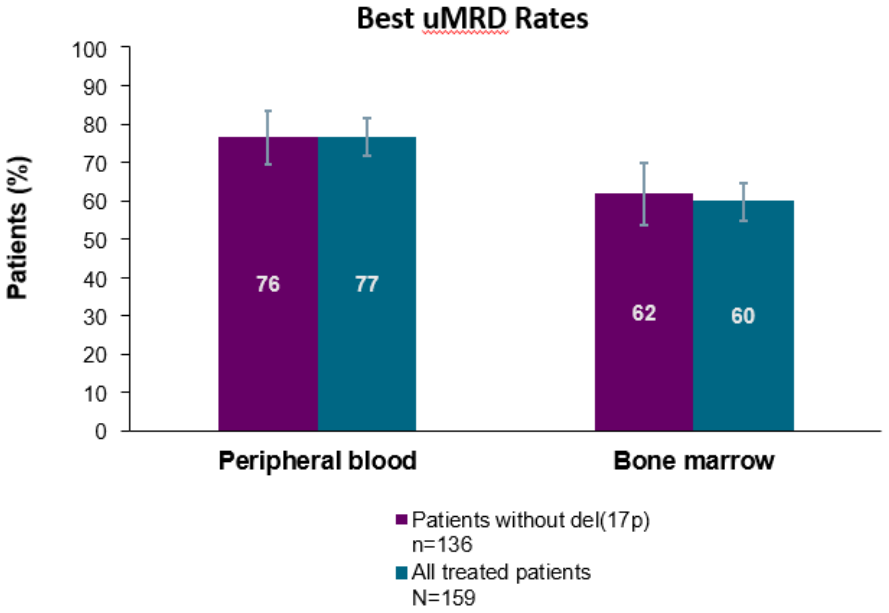
67 m follow-up



Niemman , et al. ASH 2024

Venetoclax + Ibrutinib TN CLL
Captivate phase 2: Responses and uMRD





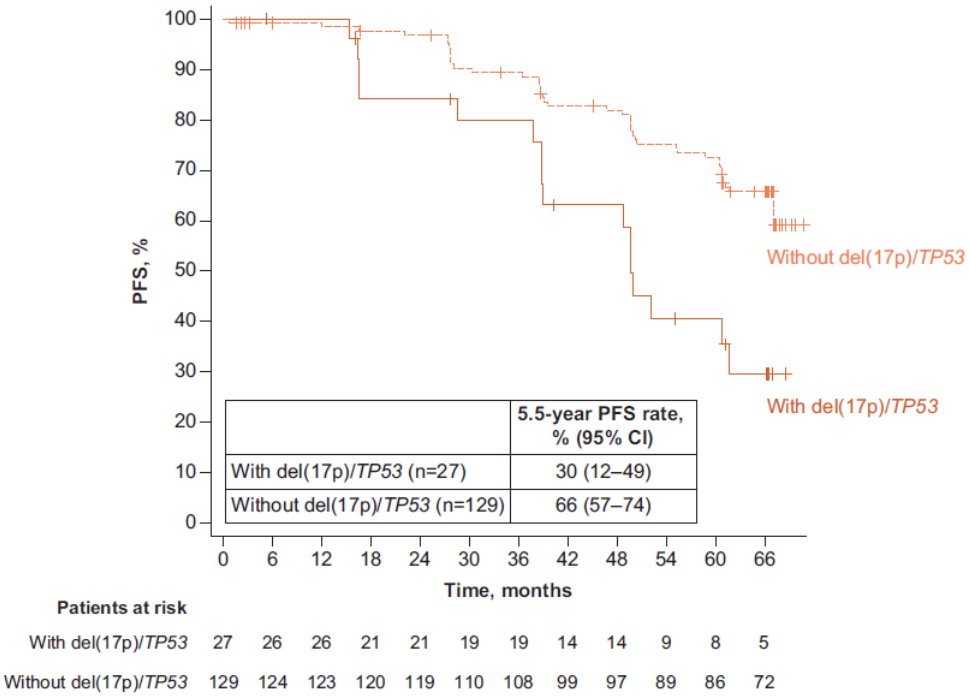
Allan et al., EHA 2021

Venetoclax + Ibrutinib TN CLL

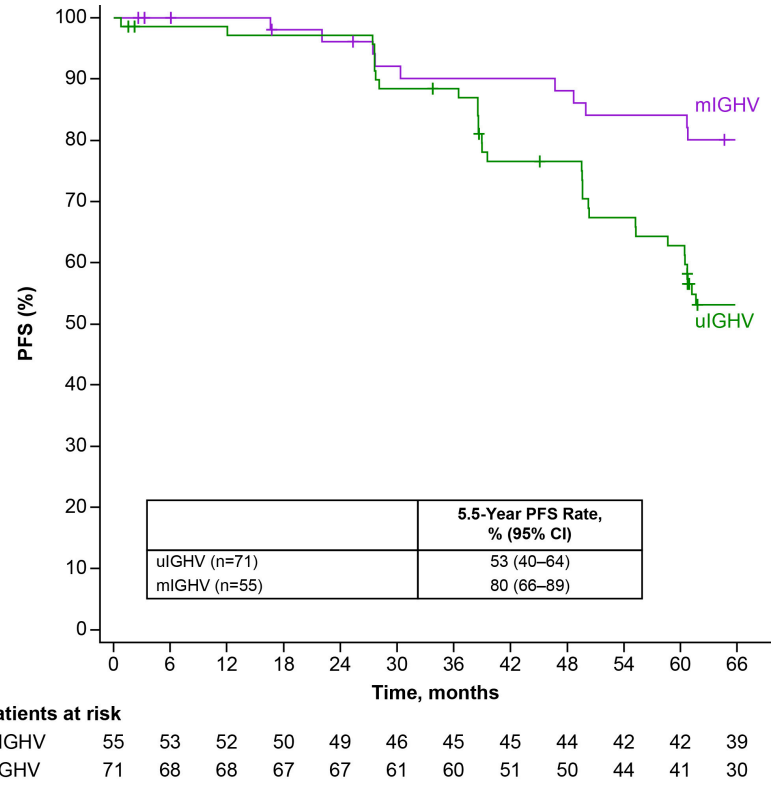
Captivate phase 2 study: PFS according to disease biology

Presence of del(17p), m*TP53*, and/or CK had a substantial impact on PFS in patients with uIGHV and mIGHV

PFS by del(17p)/*TP53* Mutation Status (FD Cohort only)



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

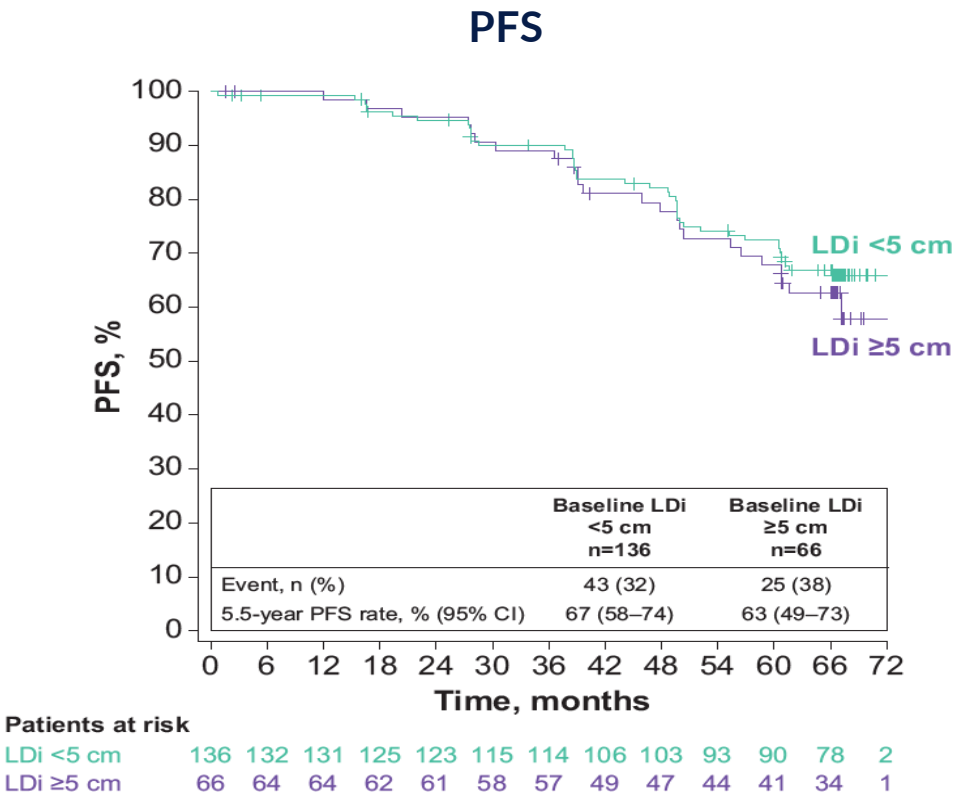


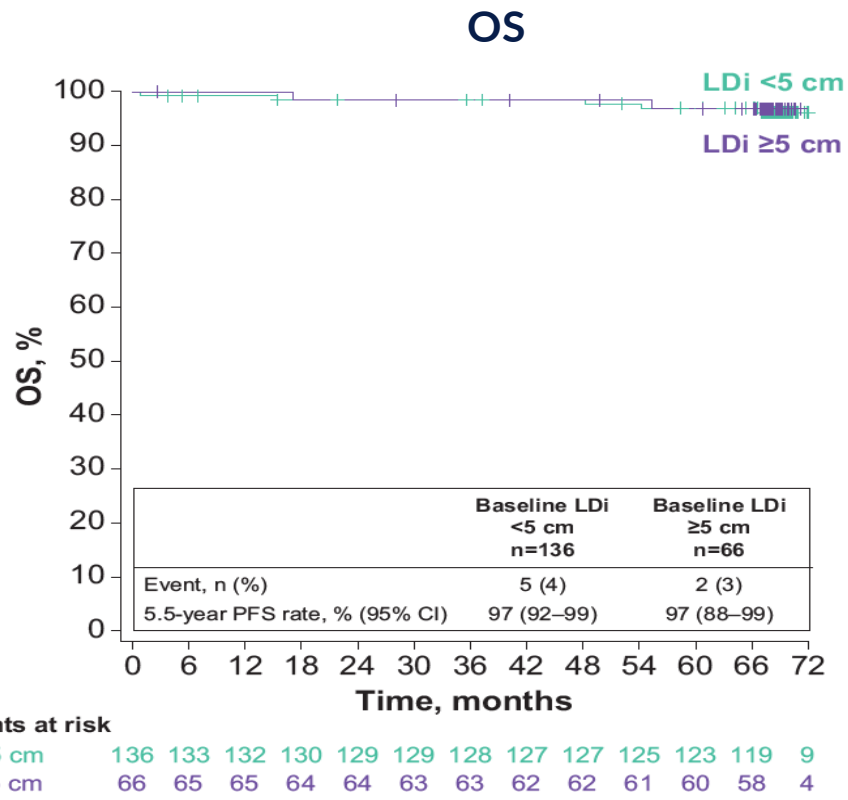
Ghia et al., EHA 2025

Venetoclax + Ibrutinib TN CLL

Captivate phase 2 study: role of bulky disease at baseline

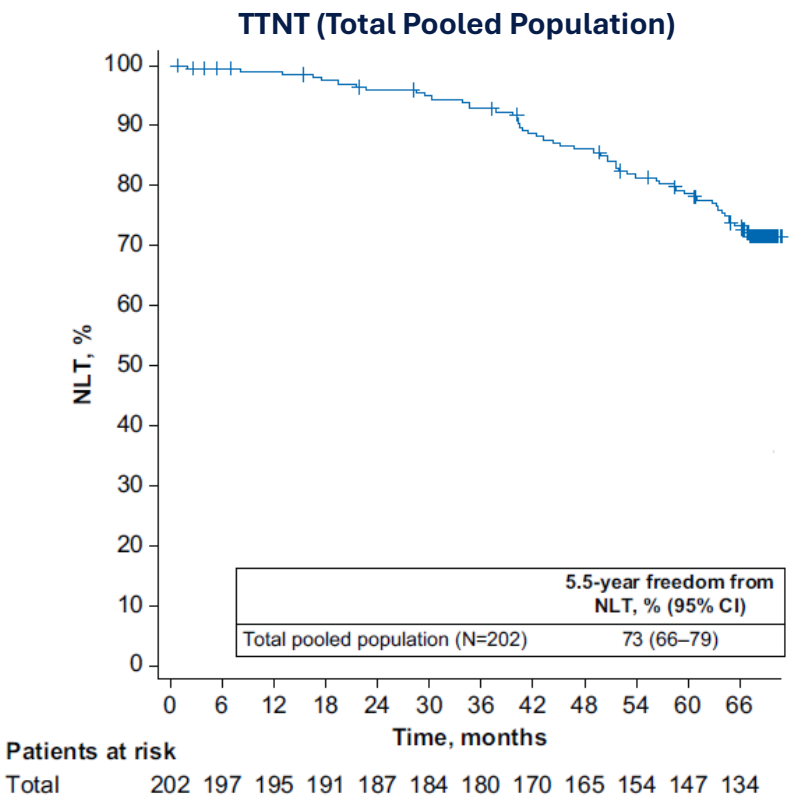
Bulky Lymphadenopathy at Baseline (Longest Diameter <5 cm vs ≥5 cm) does not Impact Long-Term PFS and OS

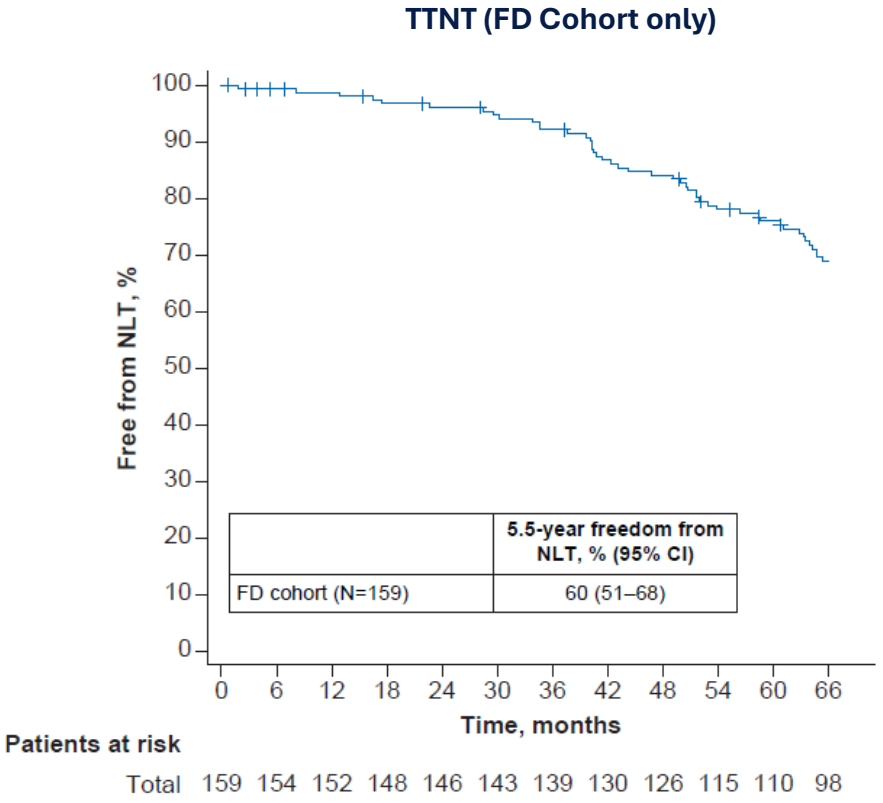




Wierda et al I ASH 2024

Time to Next Treatment in the Total Pooled Population and FD Cohort Only

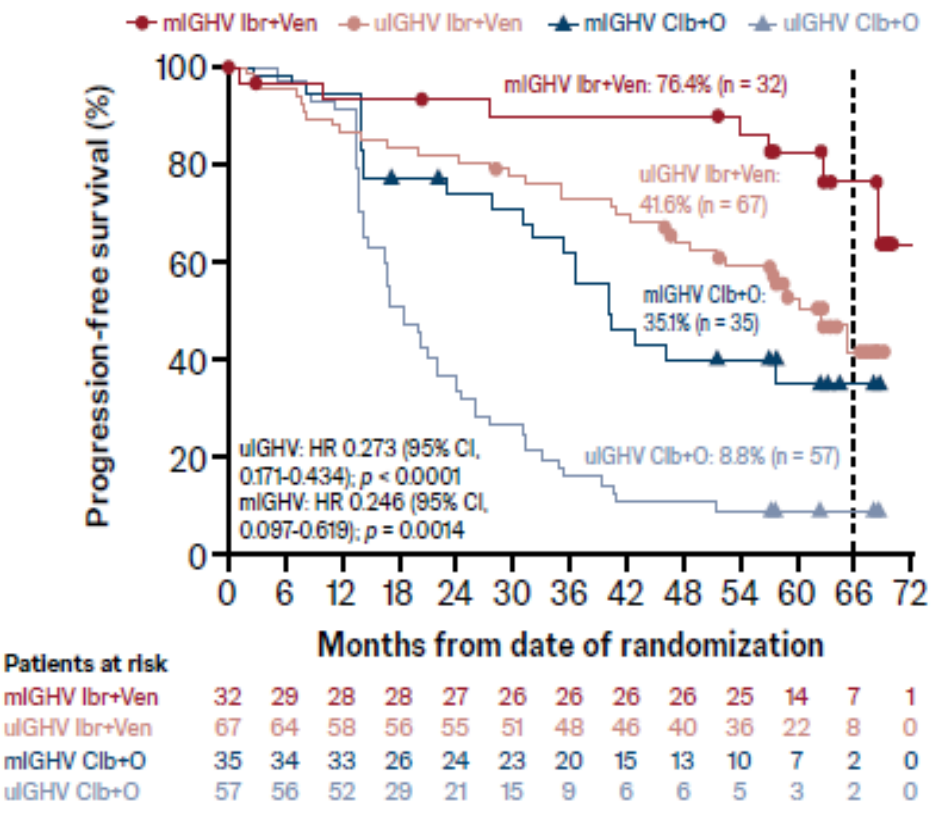


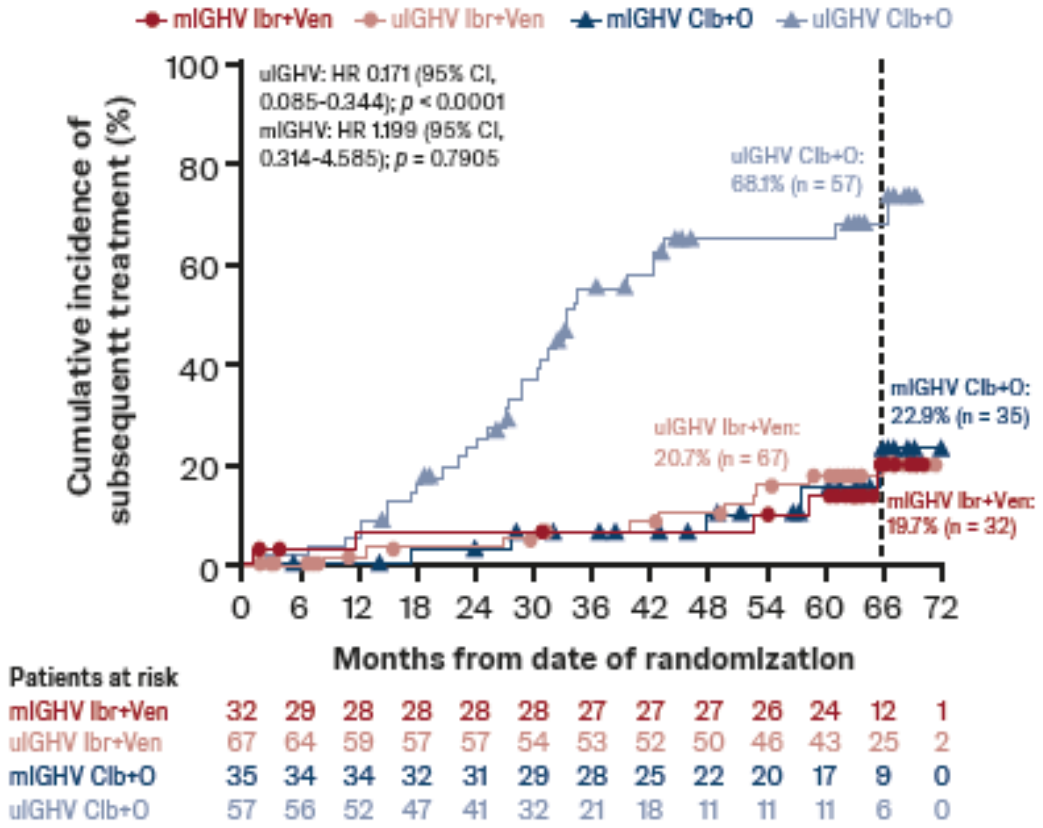


NLT, next-line treatment; TTNT, time to next treatment.

Venetoclax + Ibrutinib TN CLL

GLOW phase 3 randomized study: PFS and TTNT by IGHV





Niemman , et al. ASH 2024

No Resistance-Associated Mutations Were Identified at PD

- In the total pooled population (FD and MRD-placebo cohorts) with a median follow-up of more than 5.5 years, 64/202 patients (32%) had PD after FD ibrutinib + venetoclax treatment
- No patients had resistance-associated mutations in *BTK* or *PLCG2* at PD among 53 patients with available samples
- Two patients were found with a subclonal *BCL2 A113G* mutation of unclear significance at PD: variant allele frequencies were only 8% and 9.3%, respectively
  - Patient 1: Achieved partial response with FD ibrutinib + venetoclax retreatment (complete response was not confirmed due to missing bone marrow assessment).
    - *BCL2 A113G* mutation was not detectable at the time of eventual relapse after retreatment[a]
  - Patient 2: Did not receive retreatment in the study

[a]Patient 1 *BCL2 A113G* variant allele frequency also was noted to decline spontaneously down to 6.7% before retreatment started.

CAPTIVATE: No Resistance-Associated Mutations Were Identified at PD

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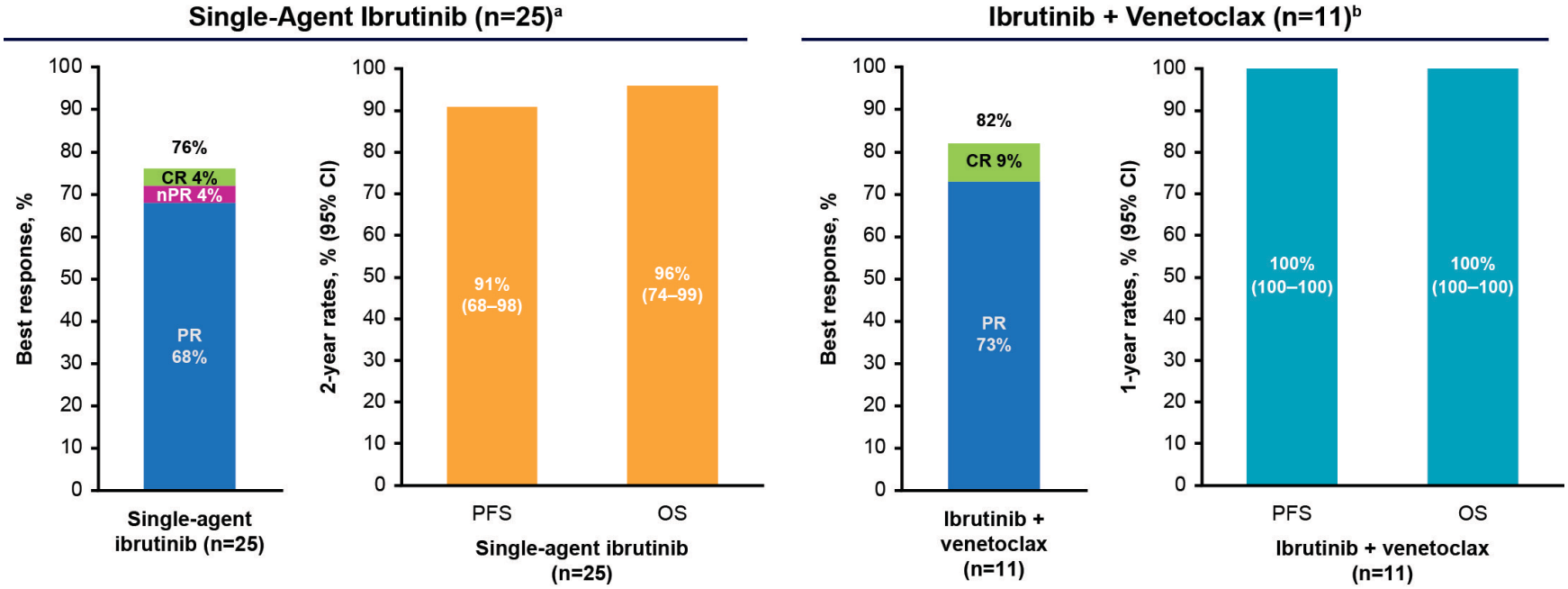
Ibrutinib-Based Retreatment Confers Promising Overall Response Rates, PFS, and OS in Patients Needing Subsequent Treatment



	Single-agent ibrutinib	FD ibrutinib + venetoclax
Median duration of follow-up, months (range)	28.4 (3.7–59.1)	15.2 (7.4–29.3)
Median duration of retreatment, months (range)	27.0 (1.1–59.1)	13.8 (6.7–18.3)

[a]Of the 6 non-responders, 4 patients achieved SD with reintroduced treatment duration ranging from 6.2–19.4 months; 1 patient was discontinued after reassessment of the putative progressive lesion as not PD, and 1 patient was diagnosed with Richter's Transformation after 1.1 month on retreatment.
[b]Of the 2 non-responders, both achieved SD with reintroduced treatment duration of 9.9 and 25.9 months, respectively.
CR, complete response; nPR, nodular partial response; PR, partial response.

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 criteria[1]
- 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

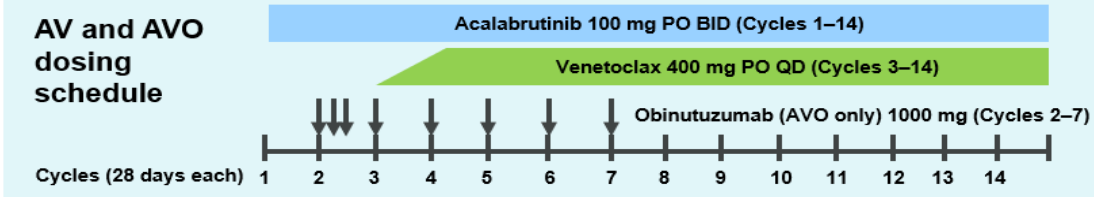
- AV (14 cycles) — Median Age 61 y; uIGHV: 57.4%
- AVO (14 cycles) — Median Age 61 y; uIGHV: 59.1%
- FCR/BR (6 cycles) — Median Age 61 y; uIGHV: 59.1%

Crossover not built into protocol

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)

AV and AVO dosing schedule



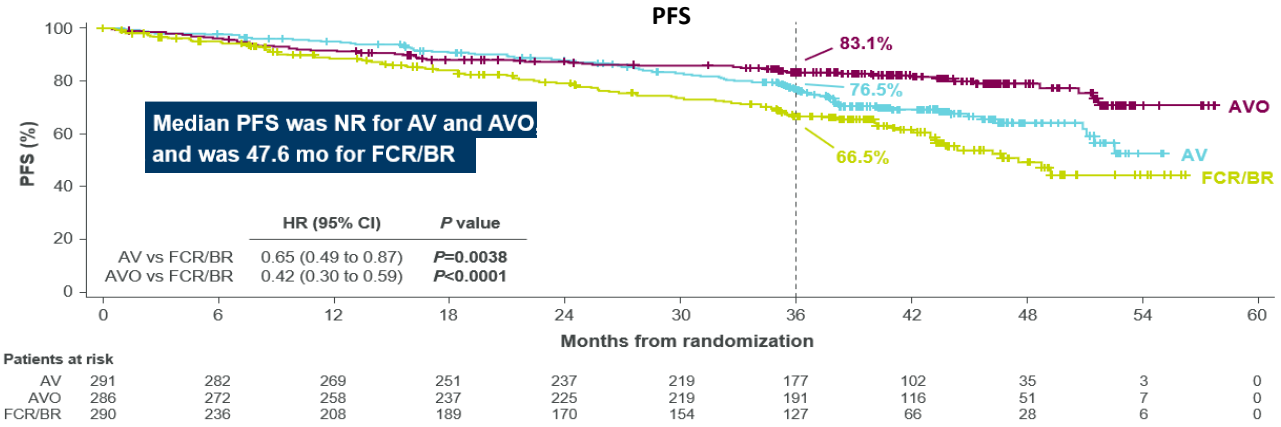
NCT03836261. Data cutoff: April 30, 2024.
[a]Assayed by central lab.

Brown J et N Eng J Med 2025

Doublets with next generation BTKi?

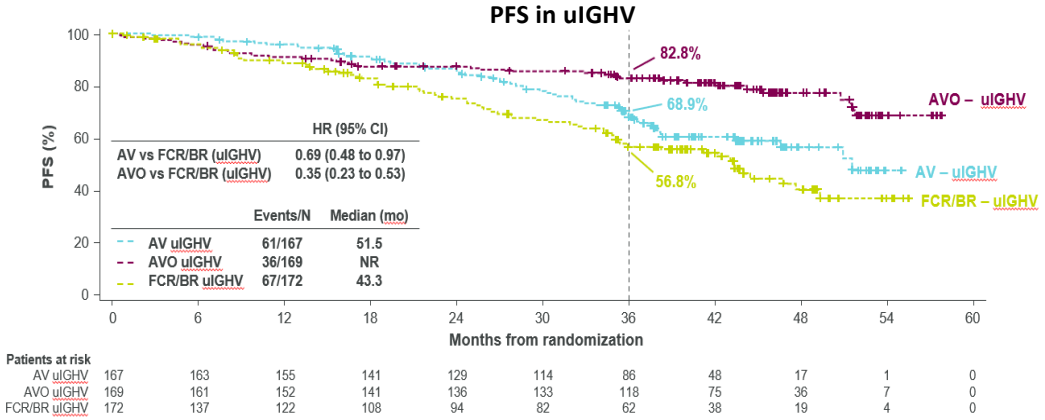
AV vs AVO vs FCR/BR: PFS

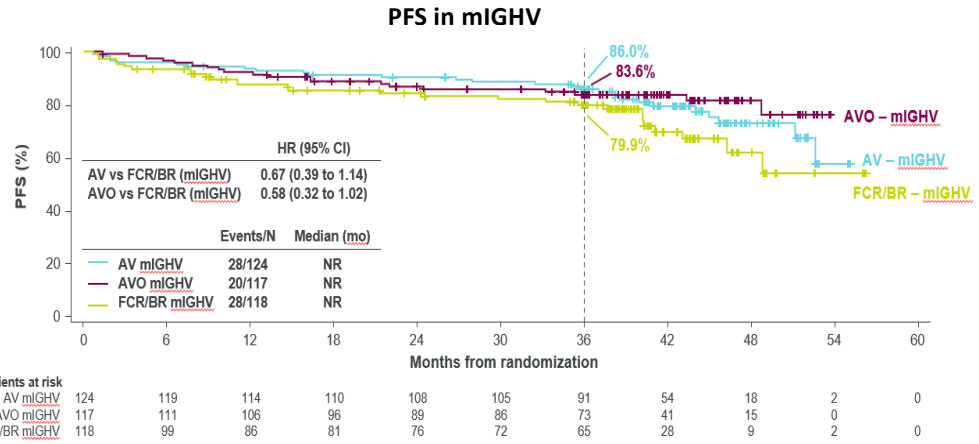
- **Significantly improved PFS with fixed-duration AV and AVO vs FCR/BR**
- **Including in the uIGHV subgroup**



PFS censoring Covid deaths

AVO:91.5%
AV: 78.8%
FCR/BR: 72%



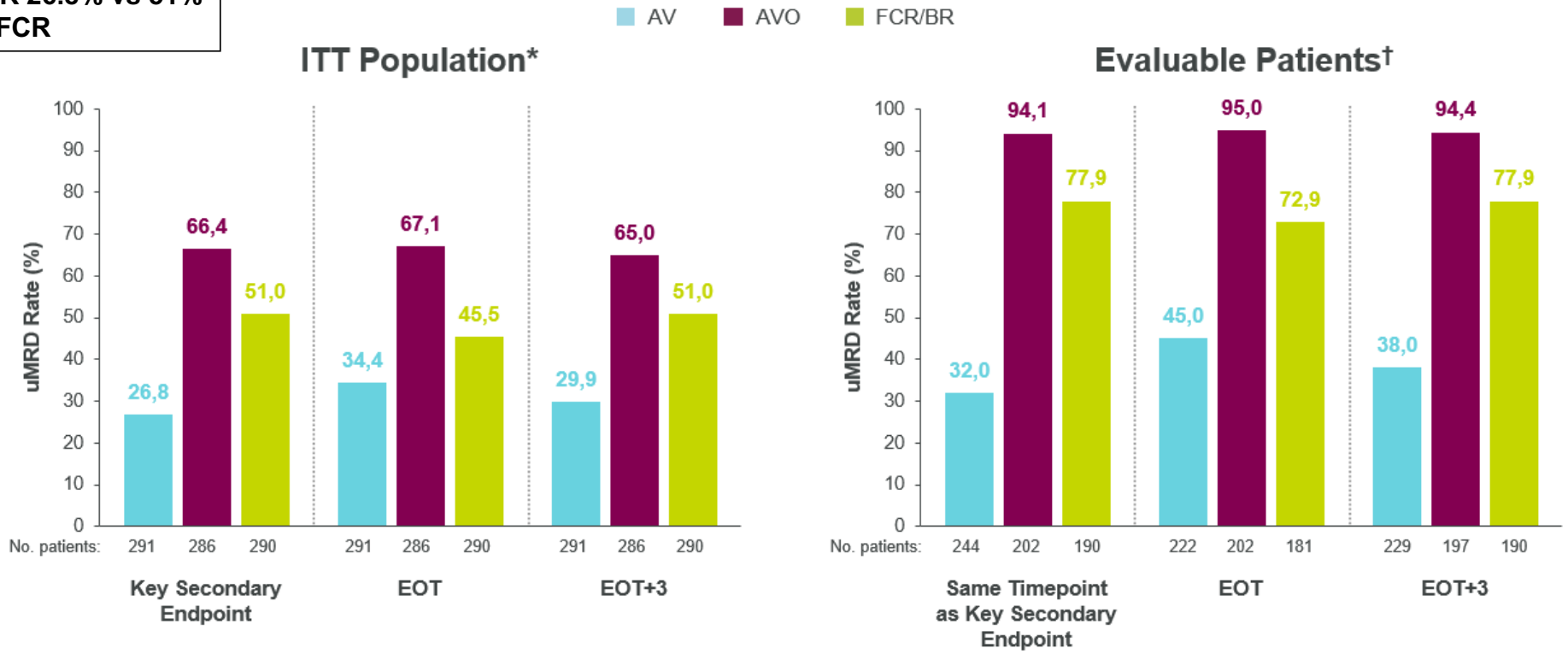


Brown J et N Eng J Med 2025

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)

Brown J et al ASH 2024

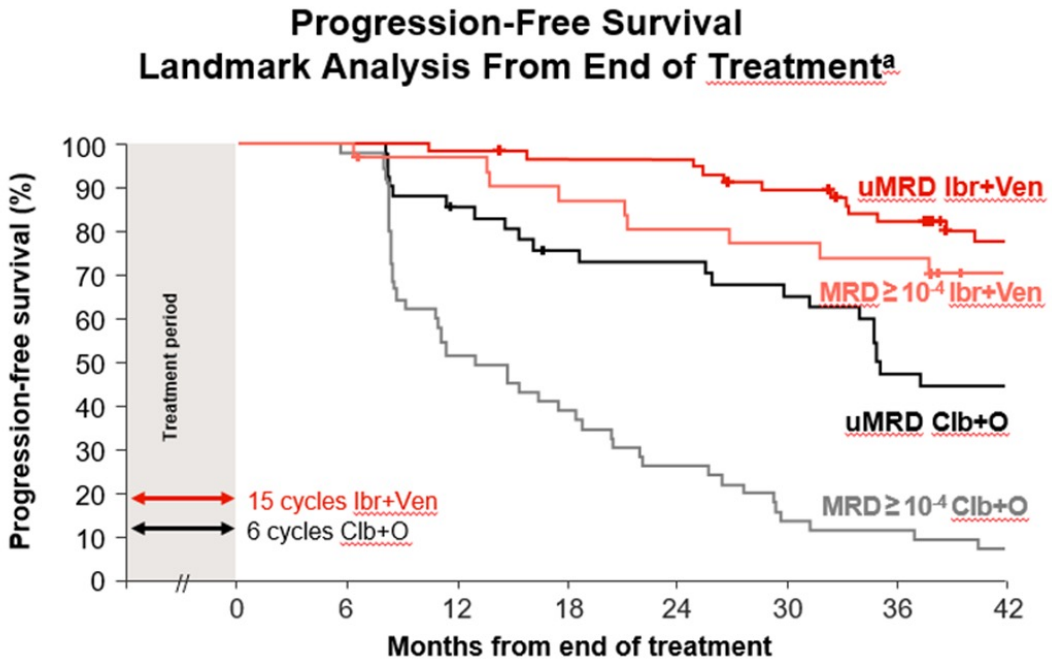
Study	Tx	N°pts	Median Age	Del17p /*TP53m*	PFS	ORR CR	uMRD <10–4 ITT
Captivate[1]	I V Fixed D	159	60 y	17%	3 y PFS 88% all 86% uIGHV 80% del17p	96% 57%	57% (PB)
Amplify[3]	A V Fixed D	291	61y	no	3 y PFS 76.5% all 68.9 %uIGHV	92.8% 8.3%	34.4% (PB)

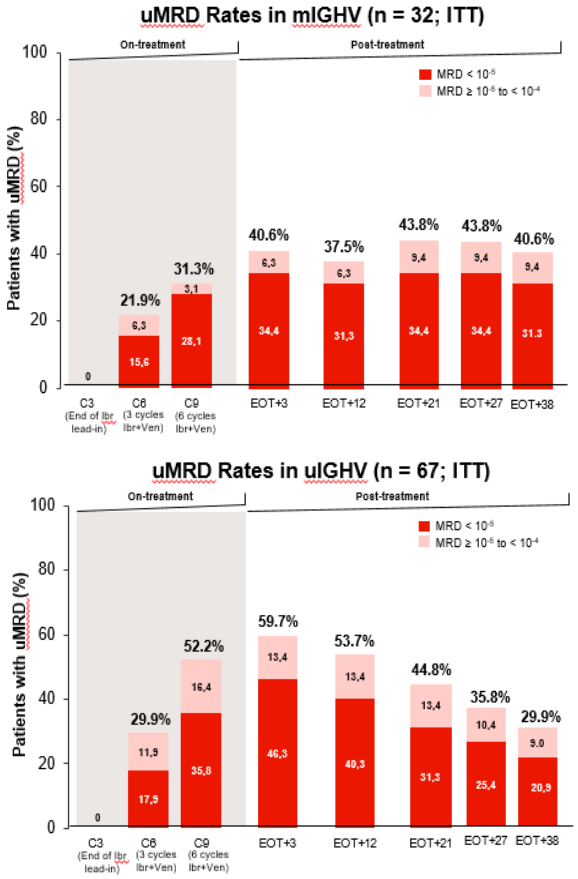
Study	Tx	N°pts	Median Age	SAE	SAE leading to death	AE leading to disc.	Infections	Hypertension	AF/Flutter	Ventricular events
Captivate[1]	I V Fixed D	159	60 y	23%	1 pt	5%	G>2: 6%	G>2: 8%	Any G: 4%	1 (Death) cardiac arrest
Amplify[2]	A V Fixed D	291	61y	25%	3.4%	7.4%	Any G:50.9% G> 2: 12.4%	Any G: 4.1% G> 2: 2.7%	Any G: 1%	1 ventricular tachycardia

1 Wierda et al ASCO 2024
2 Brown J et N Eng J Med 2025

Venetoclax + Ibrutinib TN CLL

GLOW phase 3 randomized study: MRD

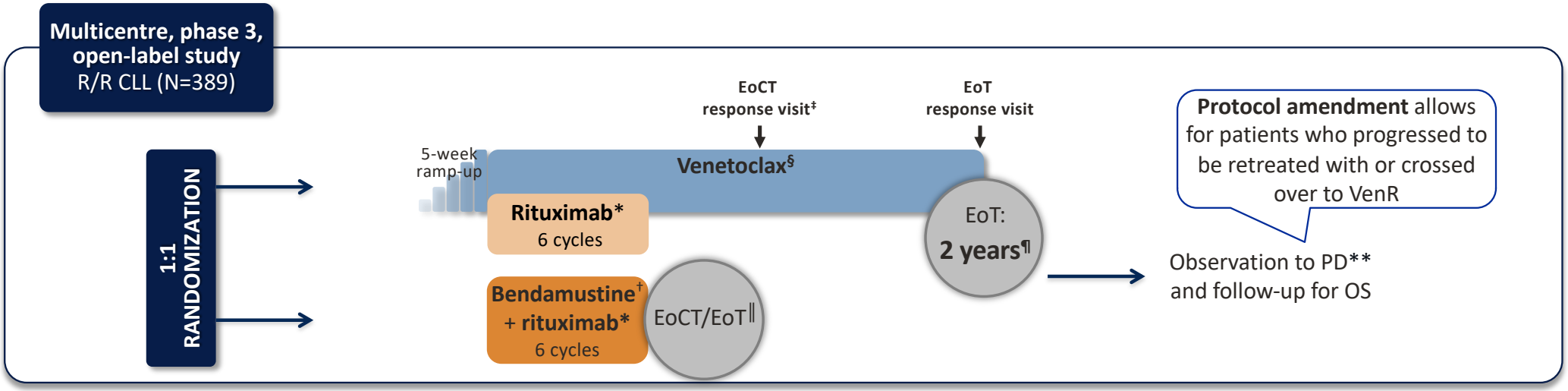




Niemann et al, Lancet Oncol 2023

Paziente ricaduto refrattario

MURANO (NCT02005471) study design[1,2]



Primary endpoint:
- INV-assessed PFS

Key secondary endpoints:
- IRC-assessed PFS
- PFS in patients with del(17p)
- ORR (IRC- and INV-assessed) at EoCT
- OS, uMRD at EoCT, DoR, EFS, TTNT

Key inclusion criteria
- 1–3 lines of prior therapy††
- Prior bendamustine if DoR was ≥2 years
  ECOG PS ≤1

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

*Rituximab: 375 mg/m2 C1D1 and 500 mg/m2 D1C2–6; † Bendamustine: 70 mg/m2 days 1 and 2 of each cycle; ‡ 8 to 12 weeks after C6D1; § Venetoclax 400 mg PO daily; ‖EoCT corresponds to EoT in BR arm; patients received a total treatment of 6 cycles; ¶ From C1D1; ** Or unacceptable toxicity; †† Including ≥1 chemotherapy-containing regimen.

CLL, chronic lymphocytic leukaemia; DoR, duration of response; ECOG PS, Eastern Cooperative Oncology Group Performance Status; EFS, event free survival; EoCT, end of combination therapy; EoT, end of treatment; INV, investigator; IRC, independent review committee; OS, overall survival; PD, progressive disease; PFS, progression-free survival; ORR, objective response rate; OS, overall survival; R/R, relapsed/ refractory; TTNT, time to next treatment; uMRD, undetectable minimal residual disease; VenR, venetoclax and rituximab.

1. Kater AP, et al. *J Clin Oncol* 2020; 38:4042–4054; 2. ClinicalTrials.gov. NCT02005471 (accessed January 2022).

Venetoclax Rituximab after CIT initial therapy
Murano trial

Immuno CHT → Venetoclax Rituxmab

R/R CLL after 1 line of Tx → R 1:1

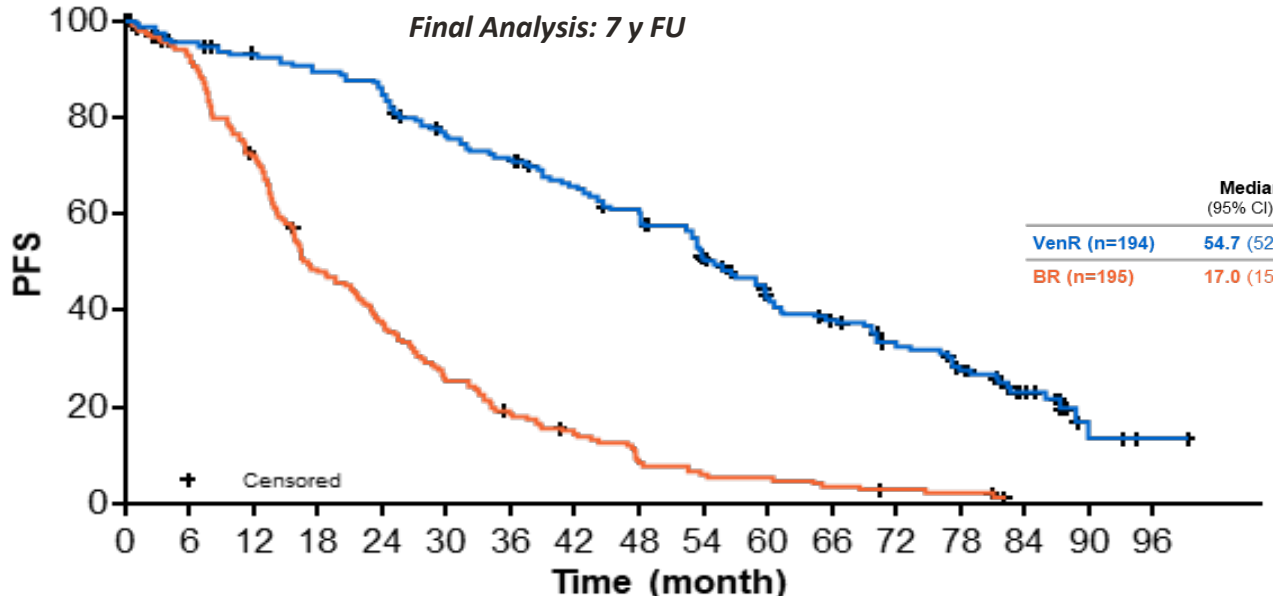
- Venetoclax 2 y Rituximab 6 infusions — 194 pts

Median prior Tx	1
IGHV^{unmut}	68.3%
del(17p) / *TP53*^{mut}	26% / 25%

- Bendamustine Rituximab 6 cycles — 195 pts

Median prior Tx	1
IGHV^{unmut}	68.3%
del(17p) / *TP53*^{mut}	26% / 25%

Final Analysis: 7 y FU



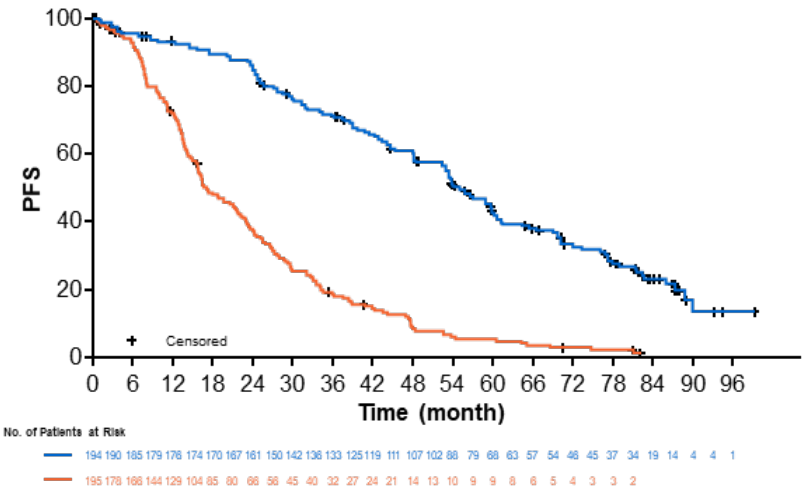
	Median PFS (95% CI), months	HR* (95% CI)	7-year PFS (%)
VenR (n=194)	54.7 (52.3–59.9)	0.23 (0.18–0.29) Stratified P-value <0.0001†	23.0
BR (n=195)	17.0 (15.5–21.7)		NE

Kater et al., EHA 2023

7-year PFS and OS benefits were sustained with VenR compared to BR

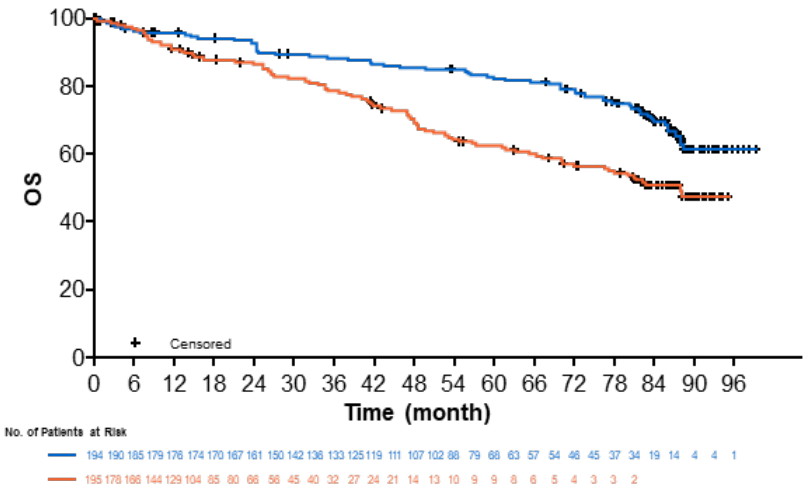
Progression-free survival[1,2]

	Median PFS (95% CI), months	HR* (95% CI)	7-year PFS (%)
VenR (n=194)	54.7 (52.3–59.9)	0.23 (0.18–0.29) Stratified P-value <0.0001†	23.0
BR (n=195)	17.0 (15.5–21.7)		NE



Overall survival[1,2]

	Median OS (95% CI), months	HR‡ (95% CI)	7-year OS (%)
VenR (n=194)	NE	0.53 (0.37–0.74) Stratified P-value <0.0002†	69.6
BR (n=195)	87.8 (70.1–NE)		51.0



- No new safety signals were identified since the 5-year data cut[3] and patients are outside of the AE reporting window§

Median follow up for efficacy (range) was 86.8 months (0.3–99.2) for VenR and 84.4 months (0.0–95.0) for BR

*Stratified HR is presented, unstratified HR=0.25. †P-values are descriptive only. ‡Stratified HR is presented, unstratified HR=0.54. §All AEs were reported until 28 days after the last dose of venetoclax or 90 days after last dose of rituximab, whichever was longer. After this, only deaths, serious AEs or AEs of concern that were believed to be venetoclax-related were reported.

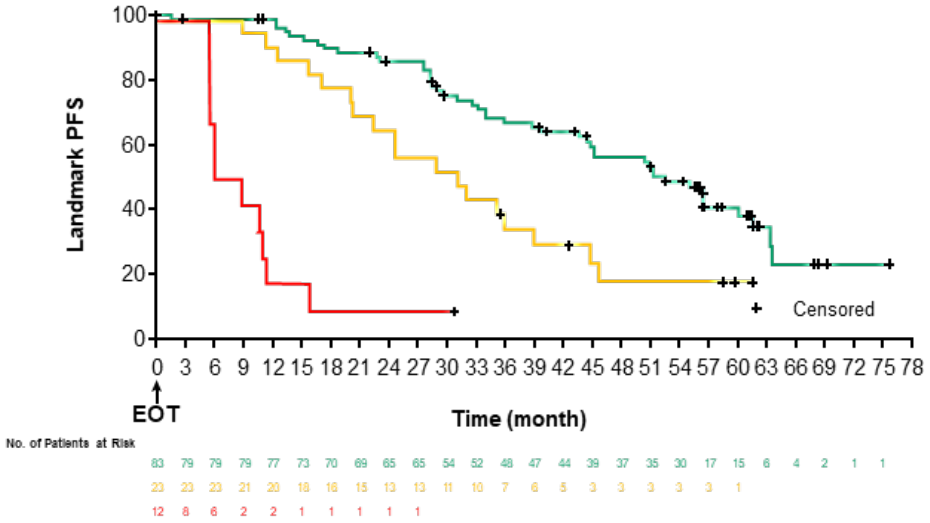
AE, Adverse event; BR, bendamustine and rituximab; CI, confidence interval; HR, hazard ratio; ITT, intention-to-treat; NE, not estimable; OS, overall survival; PFS, progression-free survival; VenR, venetoclax and rituximab.

1. Kater AP, et al. EHA 2023: Abstract S201; 2. Kater AP, et al. EHA 2023: Abstract S201; oral presentation; 3. Seymour JF, et al. *Blood* 2022;140:839–850.

Achievement of uMRD was associated with prolong PFS in VenR-treated patients

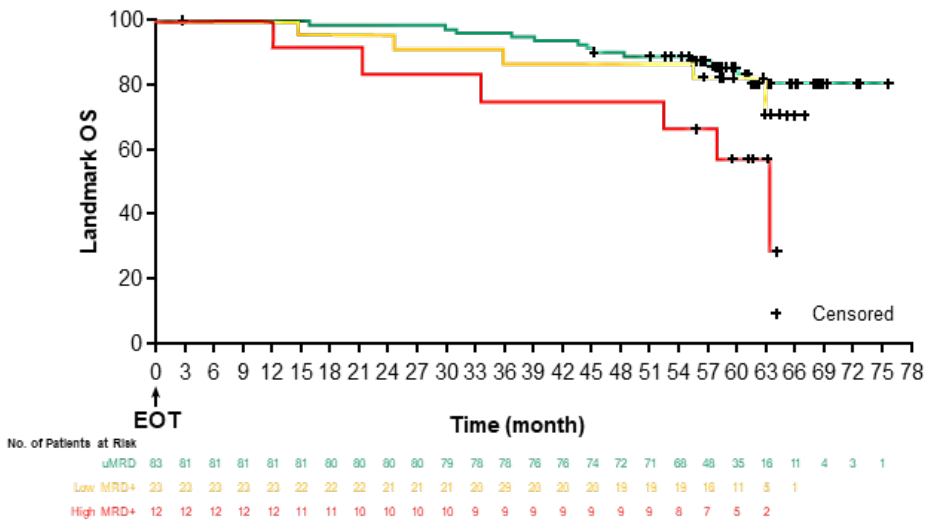
Progression-free survival[1]

VenR-treated patients who completed 2 years of Ven without PD	Median PFS since EOT (95% CI), months	HR* (95% CI)
uMRD (n=83)	**52.5** (44.5–61.5)	**4.47** (2.39–8.36) Stratified P-value <0.0001†
MRD+ (n=35)	**18.0** (8.5–29.3)	



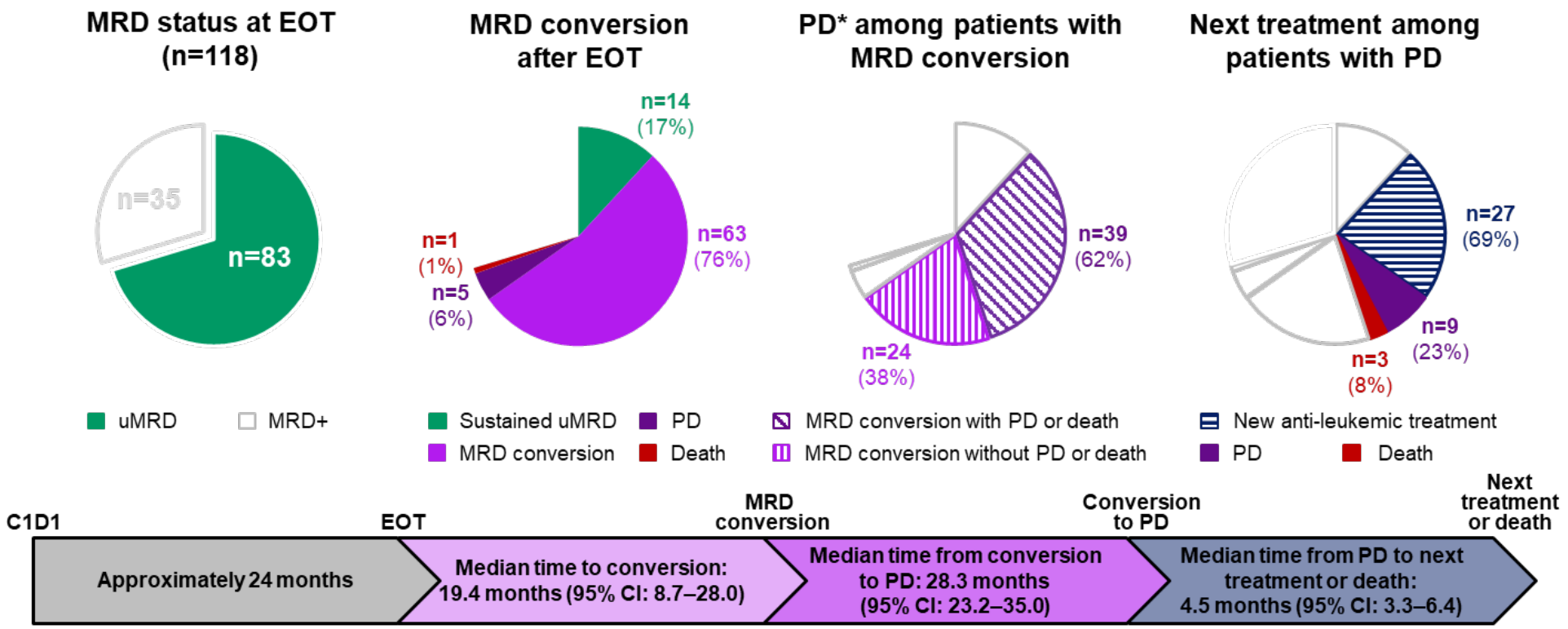
Overall survival

VenR-treated patients who completed 2 years of Ven without PD	Median OS since EOT (95% CI), months	HR‡ (95% CI)
uMRD (n=83)	**NE** (NE–NE)	**1.50** (0.60–3.77) Stratified P-value <0.3805†
MRD+ (n=35)	**NE** (62.7–NE)	



Low MRD+ is defined as ≥1 CLL cell/10,000 leukocytes to <1 CLL cell/100 leukocytes, high MRD+ is defined as ≥1 CLL cell/100 leukocytes.
*Stratified HR is presented, unstratified HR=3.45. †P-values are descriptive only. ‡Stratified HR is presented, unstratified HR=0.0796. .
EOT, end of treatment; HR, hazard ratio; OS, overall survival; PD; progressive disease; (u)MRD, undetectable minimal residual disease.
1. Kater AP, et al. EHA 2023: Abstract S201; 2. Kater AP, et al. EHA 2023: Abstract S201; oral presentation.

Most patients who received the full 2 years of VenR treatment had uMRD at EOT; generally MRD conversion with subsequent PD did not occur until ~4 years post EOT



*Investigator-assessed PD according to iwCLL criteria.

*CI, confidence interval; EOT, end of treatment; (u)MRD, undetectable minimal residual disease; PD, progressive disease; uMRD, undetectable minimal residual disease.

1. Kater AP, et al. EHA 2023: Abstract S201; 2. Kater AP, et al. EHA 2023: Abstract S201; oral presentation.

Favorable baseline characteristics were over-represented among patients with enduring uMRD

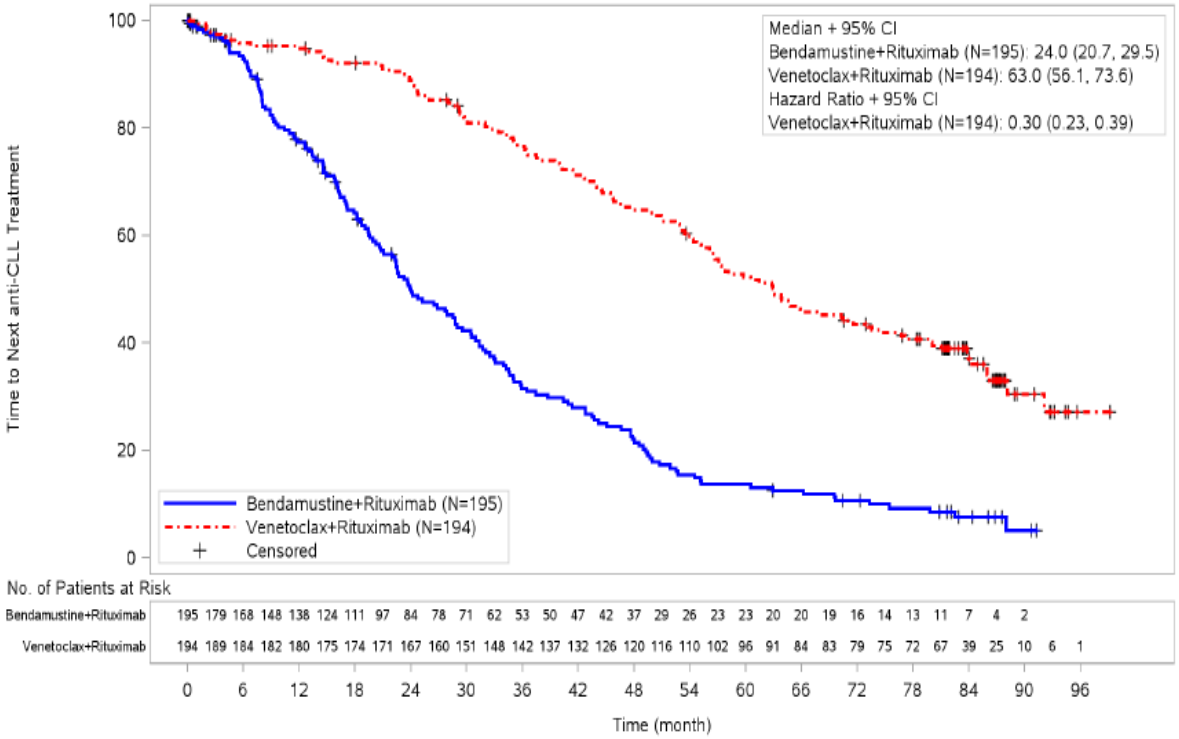
- Among the 14 patients with sustained uMRD after EOT, median number of prior therapies was 1 (range 1–3)
- *TP53* status among VenR-treated patients:
  - 13/144 (9.0%) patients without *TP53* mutation (wild-type) had sustained uMRD vs 1/48 (2.1%) patients with *TP53* mutation
- IGHV status among VenR-treated patients:
  - 7/53 (13.5%) patients who had mutated IGHV had sustained uMRD vs 6/123 (4.9%) patients with unmutated IGHV

VenR-treated patients, n (%)	*TP53** (n=192)†		IGHV‡ (n=176)†	
	unmutated (n=144)	mutated (n=48)	mutated (n=53)	unmutated (n=123)
Patients with sustained uMRD (n=14)	13/144 (9.0)	1/48 (2.1)	7/53 (13.2)	6/123 (4.9)
Patients without sustained uMRD (n=180)	131/144 (91.0)	47/48 (97.9)	46/53 (86.8)	117/123 (95.1)

Among the small group of patients with favorable disease biology there is a moderate portion (7/43 [16.3%]) who have very long term enduring uMRD following 2 years of VenR

*Investigator-assessed PD according to International Workshop on Chronic Lymphocytic Leukaemia (iwCLL) criteria.
CI, confidence interval; EOT, end of treatment; (u)MRD, undetectable minimal residual disease; PD, progressive disease; uMRD, undetectable minimal residual disease.
1. Kater AP, et al. EHA 2023: Abstract S201; 2. Kater AP, et al. EHA 2023: Abstract S201; oral presentation.

Time To Next anti-leukaemic Treatment (TTNT)



	Median TTNT (95% CI), months	**HR*** (95% CI)
VenR	**63.0** (56.1–73.6)[1]	**0.30** (0.23–0.39) Stratified P-value <0.0001[1†]
BR	**24.0** (20.7–29.5)[1]	

Overall, 95 (49.0%) VenR-treated patients and 131 (67.2%) BR-treated patients received subsequent anti-leukemic treatment

*Stratified HR is presented, unstratified HR=0.32. †P-values are descriptive only.
BR, bendamustine and rituximab; CI, confidence interval; EOT, end of treatment; HR, hazard ratio; TTNT, time to next treatment; (u)MRD, (undetectable) minimal residual disease; VenR, venetoclax and rituximab.
1. Kater AP, et al. EHA 2023: Abstract S201; 2. Kater AP, et al. EHA 2023: Abstract S201; oral presentation.

MURANO safety is consistent with previous analyses[1–3]

Grade 3–4 AEs during treatment, with ≥2% difference between arms, n (%)	VenR combination treatment period (months 1–6) N=194	Venetoclax single-agent treatment period (months 7–24) N=171
Neutropenia	**106 (54.6)**	**20 (11.7)**
Anaemia	16 (8.2)	5 (2.9)
Thrombocytopaenia	9 (4.6)	3 (1.8)
Febrile neutropaenia	7 (3.6)	0
Pneumonia	8 (4.1)	2 (1.2)
TLS Clinical TLS	6 (3.1) 1 (0.5)	0 0
Infusion-related reaction	4 (2.1)	0
Hyperglycaemia	4 (2.1)	0
Hypogammaglobulinaemia	3 (1.5)	1 (0.6)

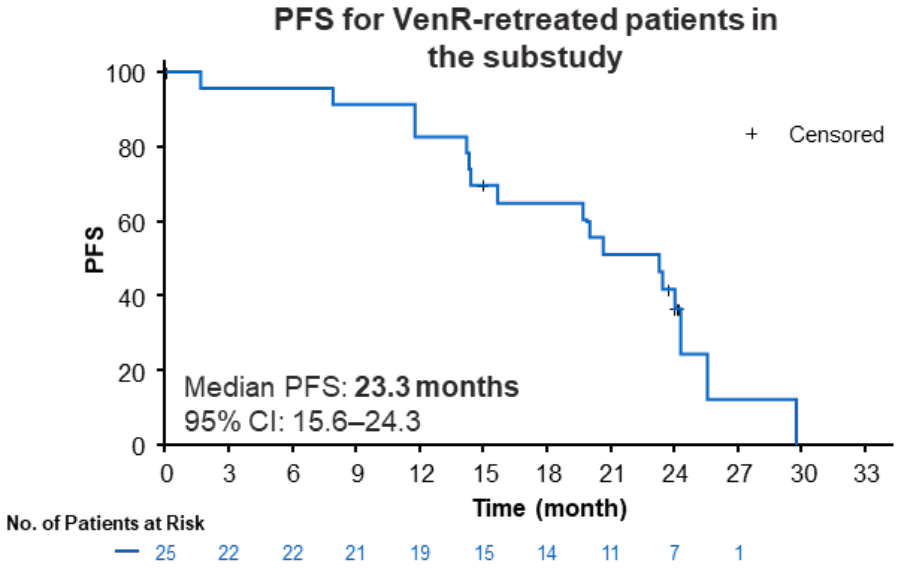
No new safety signals were identified since the 5-year data cut[2] and patients are outside of the AE reporting window*

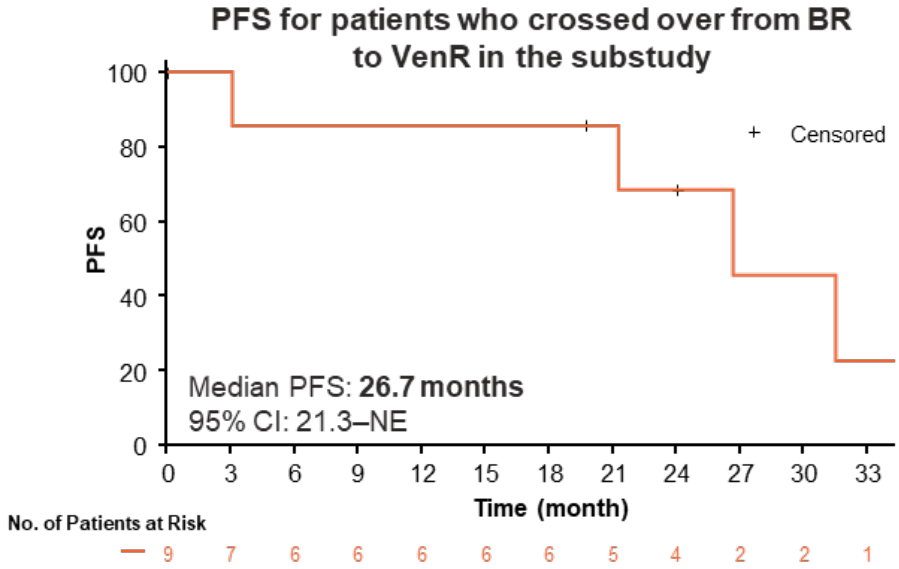
*All AEs were reported until 28 days after the last dose of venetoclax or 90 days after last dose of rituximab, whichever was longer. After this, only deaths, serious AEs or AEs of concern that were believed to be venetoclax-related were reported.

AE, adverse events; TLS, tumour lysis syndrome; VenR, venetoclax and rituximab.

1. Kater AP, et al. EHA 2023: Abstract S201; oral presentation; 2. Seymour JF, et al. *Blood* 2022;140:839–850; 3. Seymour JF, et al. *New Engl J Med* 2018;378:1107–1120.

Clinical outcomes indicate that VenR is a feasible option for pre-treated patients





- Median follow up (range) was 33.4 months (2.7–44.0)
- Best ORR was high for both retreated patients (72.0%) and patients who crossed over (88.9%)
- Median duration of response (95% CI) was 15.5 months (11.5–NE) for retreated patients and 22.5 months (12.7–NE) for patients who crossed over
- Median OS was not reached for either the retreated patients or patients who crossed over

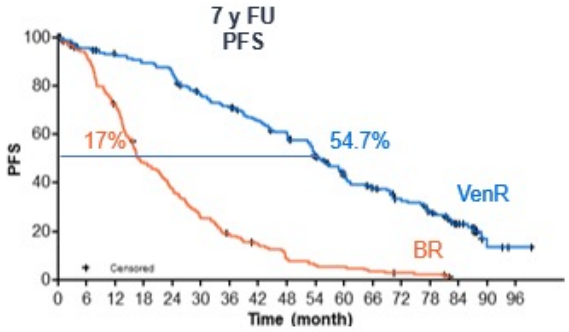
CI, confidence interval; DOR, duration of response; NE, not estimable; ORR, objective response rate; OS, overall survival; PFS, progression free survival; VenR, venetoclax and rituximab.

1. Kater AP, et al. EHA 2023: Abstract S201; 2. Kater AP, et al. EHA 2023: Abstract S201; oral presentation.

SEQUENCING

R/R after Immuno-CHT

Murano: Venetoclax Rituximab vs BR



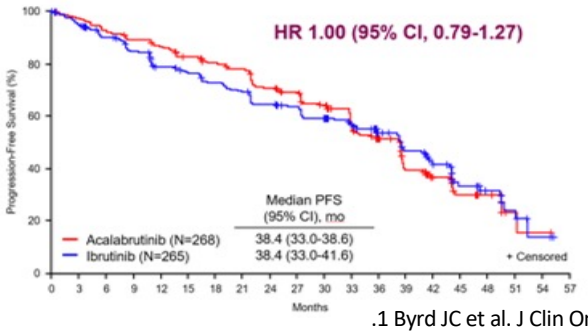
	Median PFS (95% CI), months	HR* (95% CI)	7-year PFS (%)
VenR (n=194)	**54.7** (52.3–59.9)	**0.23** (0.18–0.29) Stratified P-value <0.0001†	**23.0**
BR (n=195)	**17.0** (15.5–21.7)		**NE**

- **U-IGHV: median PFS 52.2 mo.**
- **TP53 and or del17p: median 45.3 mo.**

Seymour et al 2022

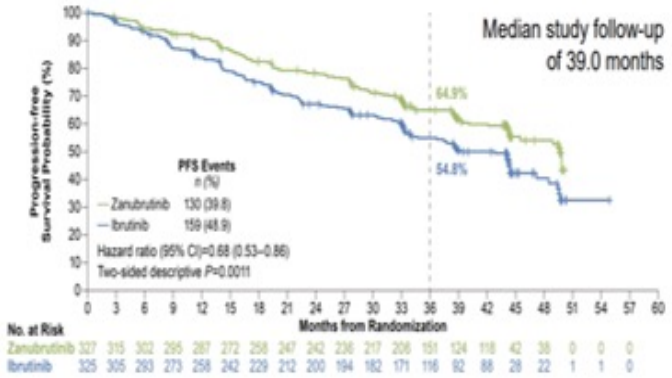
ELEVATE-RR study only del(17p) or del(11q)
40.9 months median follow-up
Acalabrutinib vs ibrutinib

- **No different PFS**



.1 Byrd JC et al. J Clin Oncol. 2021

Alpine study
39 months median follow-up
Zanubrutinib vs ibrutinib



2 Brown et al, A SH 2023

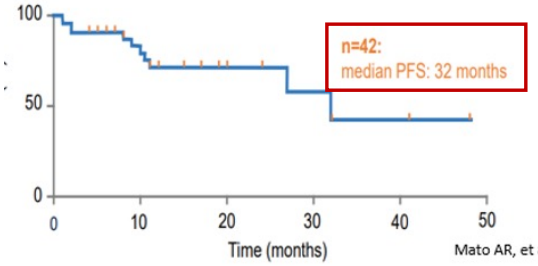
SEQUENCING

Murano Trial

PFS according to susequent therapy in R/R pts after Ven R

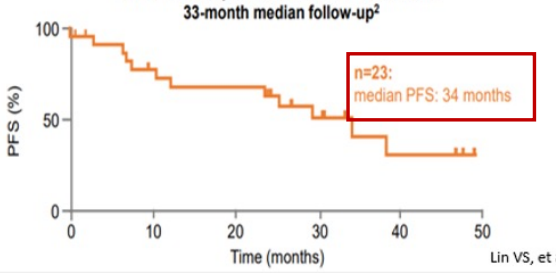
	Median PFS (95% CI), months
VenR-BTKi (n=30)	42.9 (27.2–NE)

Retrospective cohort study: PFS with BTKi* in BTKi-naive patients after discontinuing venetoclax
10.5-month median follow-up[1]



Mato AR, et al. Clin Cancer Res 2020

Retrospective pooled analysis: PFS with BTKi† in BCRi-naive patients after PD on venetoclax
33-month median follow-up[2]

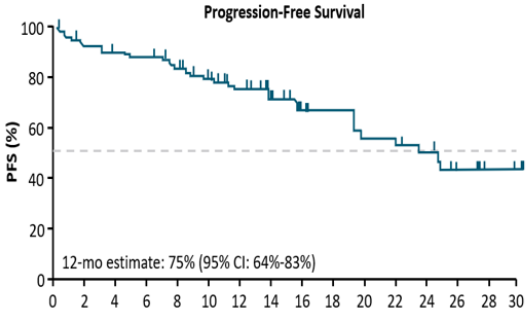


Lin VS, et al. Blood 2020

Phase 2 trial: Venetoclax monotherapy after BCRi

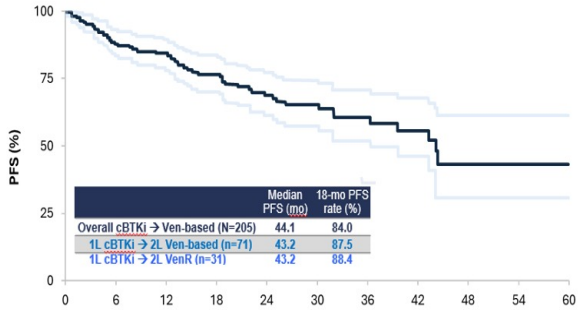
- **Median of 4 prior therapies**
- **47% del(17p)**

ORR: 70%



Retrospective Trial

Jones et al, Lancet Hematol 2018



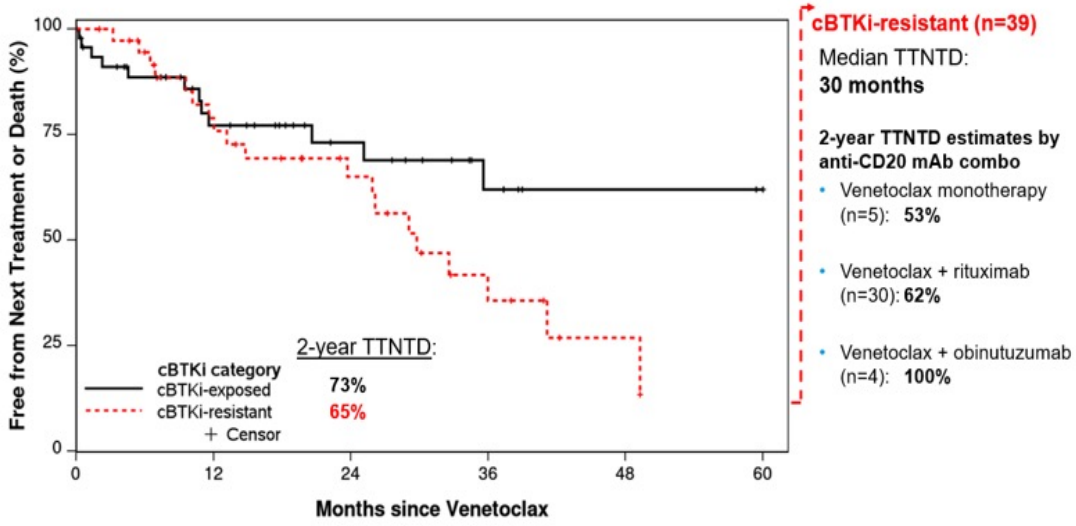
Ghosh N, et al, EHA 2024.

SEQUENCING *The only study (clinical practice) in patients not pretreat with immuno-CHT*

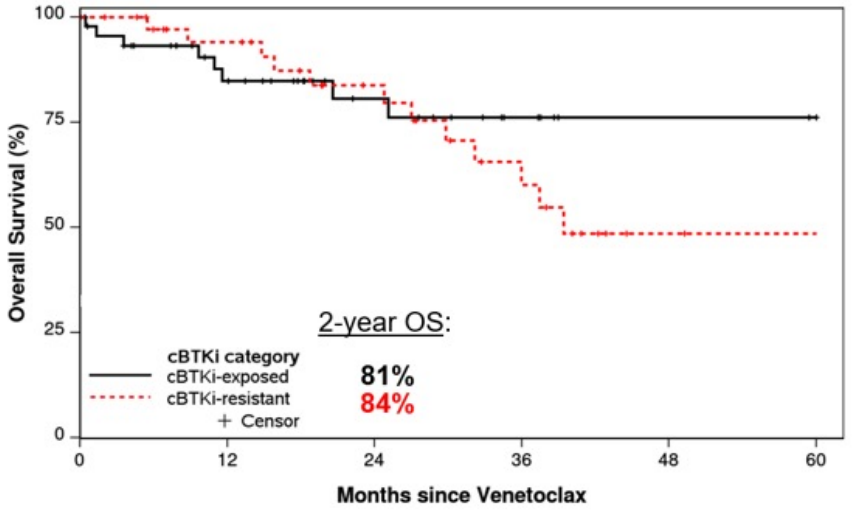
Outcomes with Venetoclax-Based Treatment in Patients with Covalent Bruton Tyrosine Kinase Inhibitor (cBTKi)-Treated, Chemotherapy-Naïve Chronic Lymphocytic Leukemia (CLL): An International Retrospective Study

Complex karyotype*, n=37	Complex (≥3 abnormalities)	15 (41)
***TP53* disruption*, n=73**	Present (Abnormal)	33 (45)

Free from Next Treatment or Death



Overall Survival



Hampelet al,ASH 2024

Summary

Investigator-assessed PFS consistent with previous years

- Similar results to previous years PFS and OS are improved with VenR compared to BR

Achievement of uMRD was associated with a prolong PFS

Retreatment with VenR is a feasible option for pretreated patients based on ORR and uMRD findings

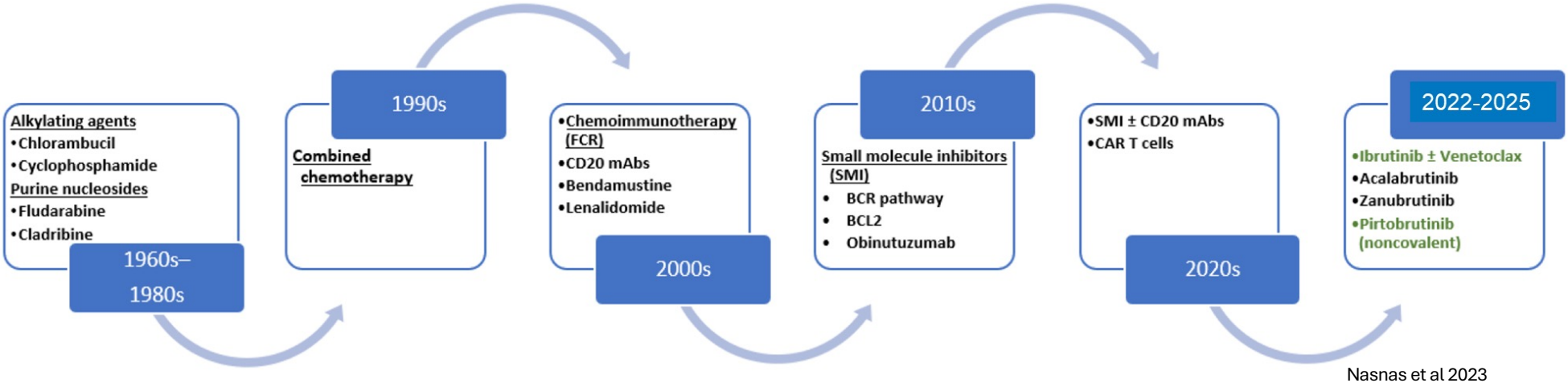
The safety profile remains unchanged, and overall, the benefit–risk assessment remains favorable from the 5 year analysis

MEET THE
EXPERT *in CLL*

CASTELFRANCO VENETO (TV), 27 GIUGNO 2025
Ospedale San Giacomo Apostolo, Sala Scarpa

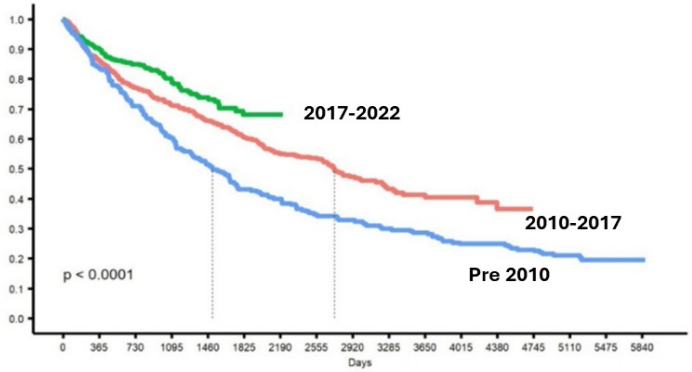
14.05-14.25	Terapia a durata fissa: fitness e stato mutazionale **Moderatori: M. Gottardi** (Castelfranco Veneto-TV), **P.L. Zinzani** (Bologna) **Esperto: A. Tedeschi** (Milano)

The successful history of CLL



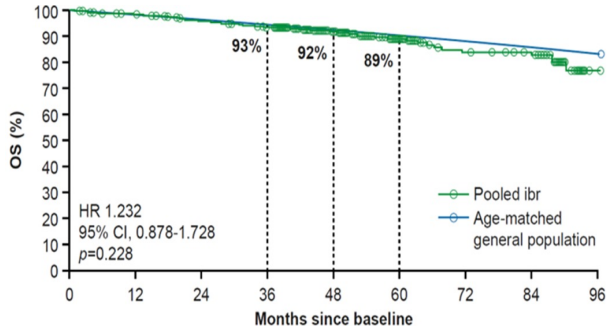
Nasnas et al 2023

Survival according to treatment period

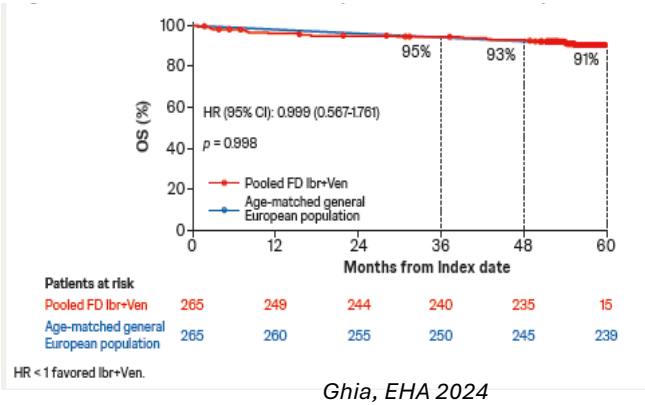


Tadmor, Hemasphere 2023

Similar OS estimate for overall pooled Ibr and Ibr+Ven–treated pts



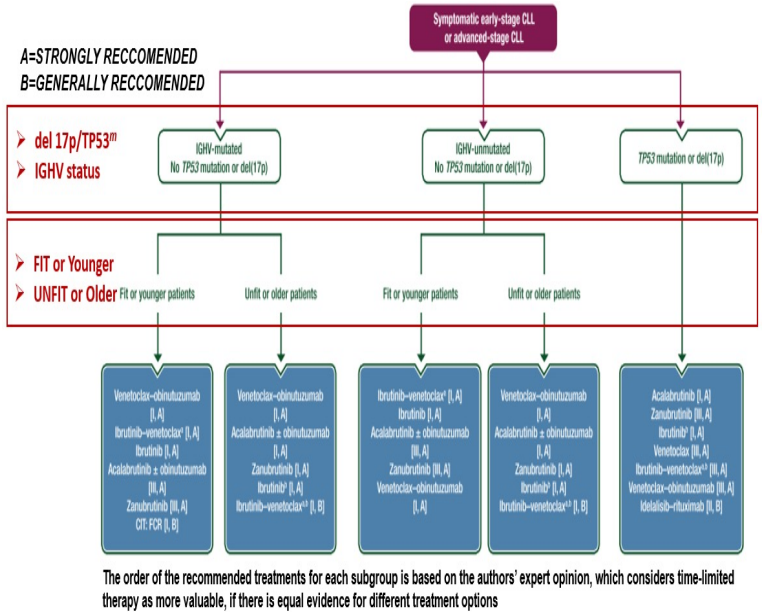
Ghia, EHA 2024



Ghia, EHA 2024

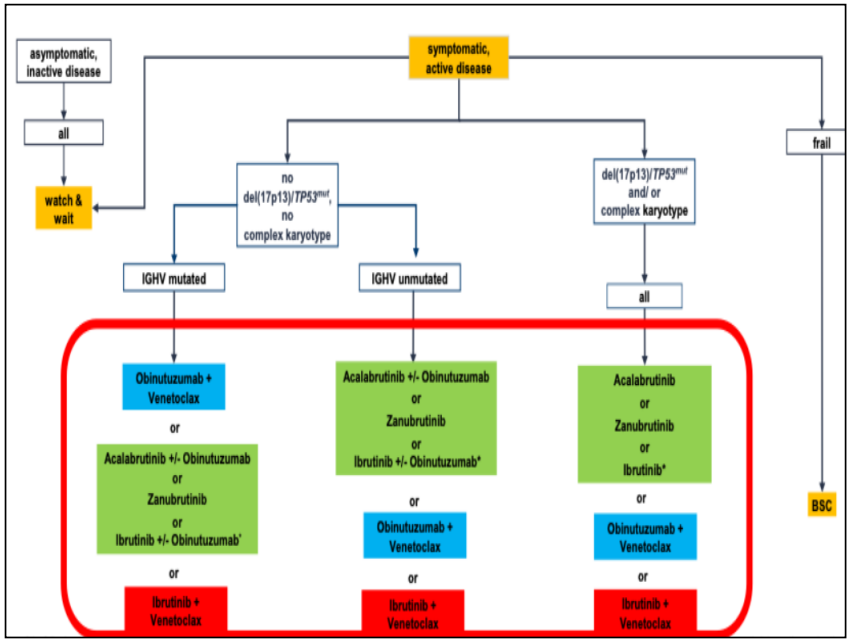
CLL guidelines

ESMO Clinical Practice Guideline interim update on new targeted therapies in the first line and at relapse of chronic lymphocytic leukaemia☆



The order of the recommended treatments for each subgroup is based on the authors' expert opinion, which considers time-limited therapy as more valuable, if there is equal evidence for different treatment options

Onkopedia CLL 2023 – 1L



- del 17p/TP53^{m}
- IGHV
- Complex K

Wendtner st et al, 2024

National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2025
Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma

- del 17p/TP53^{m}

ESMO Clinical Practice Guideline interim update on new targeted therapies in the first line and at relapse of chronic lymphocytic leukaemia☆

CIT such as FCR should only be considered for pts with a good genetic risk profile [defined as: mutated IGHV status and no TP53 aberrations and, in addition, a non CK (defined by <5 aberrations)

if targeted therapies are not reimbursed

FIT UNFIT
YOUNGER OLDER

No Fitness tools in CLL Age?

Choice should be based on:

- **-comorbidities (cardiac assessment when planning to use a BTKi)**
- **-preference**
- **-drug availability**
- **-expected treatment adherence**

Side-effect profile

- **Drug administration (iv versus oral)**
- **Access/intensity of controls**
- **Shorter follow-up**

THE ORDER OF THE RECOMMENDED TREATMENTS FOR EACH SUBGROUP IS BASED ON THE AUTHORS' EXPERT OPINION, WHICH CONSIDERS TIME-LIMITED THERAPY AS MORE VALUABLE, IF THERE IS EQUAL EVIDENCE FOR DIFFERENT TREATMENT OPTIONS

Eichhorst et al, Annals Oncol 2024

Tools to assess fitness in clinical trials are practical but limited[1]

Tool	Pros	Cons
Age[1,2]	• Defined the cut-off for CIT • Immediately available	• Limited evidence to suggest interaction with targeted agents • No impact with continuous BTKis
ECOG PS[3,4]	• Easy to apply • Reflect patients' ability to participate in daily activities	• Limited information/subjective • Has only shown impact retrospectively
CrCl[1,5]	• Easy to apply • Validated with CIT in CLL	• No clear impact on outcomes with targeted agents
CIRS[4,6,7]	• Validated with CIT in CLL • Easy to apply • Widely used	• Has low impact if comorbidities are irrelevant • Different organ systems have the same value • Has only shown impact in a proportion of retrospective series using BTKis
CCI[1,8,9]	• Specific scores for different comorbidities • Easy to apply, binary measure	• Mostly applicable for hospitalised patients • Validated in population series not analysing type of therapy
CLL-CI[1,7]	• Based on comorbidities (vascular, endocrine, and upper gastrointestinal) • Simpler scoring system than CIRS	• Validated in a retrospective series of patients treated with CIT-based therapy and BTKi

BTKi, Bruton's tyrosine kinase inhibitor; CCI, Charlson Comorbidity Index; CIT, chemoimmunotherapy; CLL-CI, chronic lymphocytic leukaemia comorbidity index; CIRS, cumulative illness rating scale; CrCl, creatinine clearance; ECOG PS, Eastern Cooperative Oncology Group Performance Status.

1. Tedeschi A, et al. Blood Adv 2021;5:5490–5500; 2. Mauro FR, et al. Expert Rev Haematol 2016;9:1165–1175; 3. Scott JM, et al. J Clin Oncol 2021;38:2424–2829; 4. Frustaci MA, et al. Clin Lymphoma Myeloma Leuk 2022;22:356–361; 5. Martell RE, et al. Cancer Chemother Pharmacol 2002;50:37–45; 6. Miller MD, et al. Psychiatry Res 1992;41:237–248; 7. Gordon MJ, et al. Clin Cancer Res 2021;27:4814–4824; 8. Charlson M, et al. J Clin Epidemiol 1994;47:1245–1251; 9, Strati P, et al. Br J Haematol 2017;178:394–402.

Comorbidities ➡

BTKis **NOT** recommended for patients with:

- History of ventricular arrhythmia
- Family history of sudden cardiac death
- Severe, uncontrolled HTN
- Severe or uncontrolled congestive heart failure (LVEF <30%)

Anti BCL2 NOT recommended
Renal Impairment

Age ➡ **Elderly?**

Age *per se* should not preclude treatment with target agents

- different treatmnet goals

-QOL

Fitness ➡ **Fitness in the era of target agents (?)**

There is no standardised definition of patient fitness across key clinical trials of targeted agents in 1L[1–9]

Key inclusion criteria	FD I+V		FD V+O		FD A+V±O*	Cont. A±O	Cont. I	Cont. Z
	GLOW[1]	CAPTIVATE[2]	CLL13[3]	CLL14[4]	AMPLIFY[5,6]	ELEVATE-TN[7]	RESONATE-2[8]	SEQUOIA[9]
Age (years)	≥65, *or <65 with comorbidities*	18–70	≥18	≥18	≥18	≥65 *or <65 with comorbidities*	≥65	≥18
CIRS	*>6* *if <65 years**	-	≤6	>6	≤6†	*>6* *if <65 years**	-	-
CrCl (mL/min)	*<70* *if <65 years**	-	≥70	-	-	*30–69* *if <65 years**	<70 *if 65–70 years*	-
ECOG PS	0–2	-	0–2	-	0–2	0–2	0–2 *(1–2 if 65–70 years)*	0–2

Inclusion criteria indicate a patient who is ≥65-years-old, with CIRS ≥6 and/or CrCl <70 mL/min, may be considered 'unfit'[1–9]

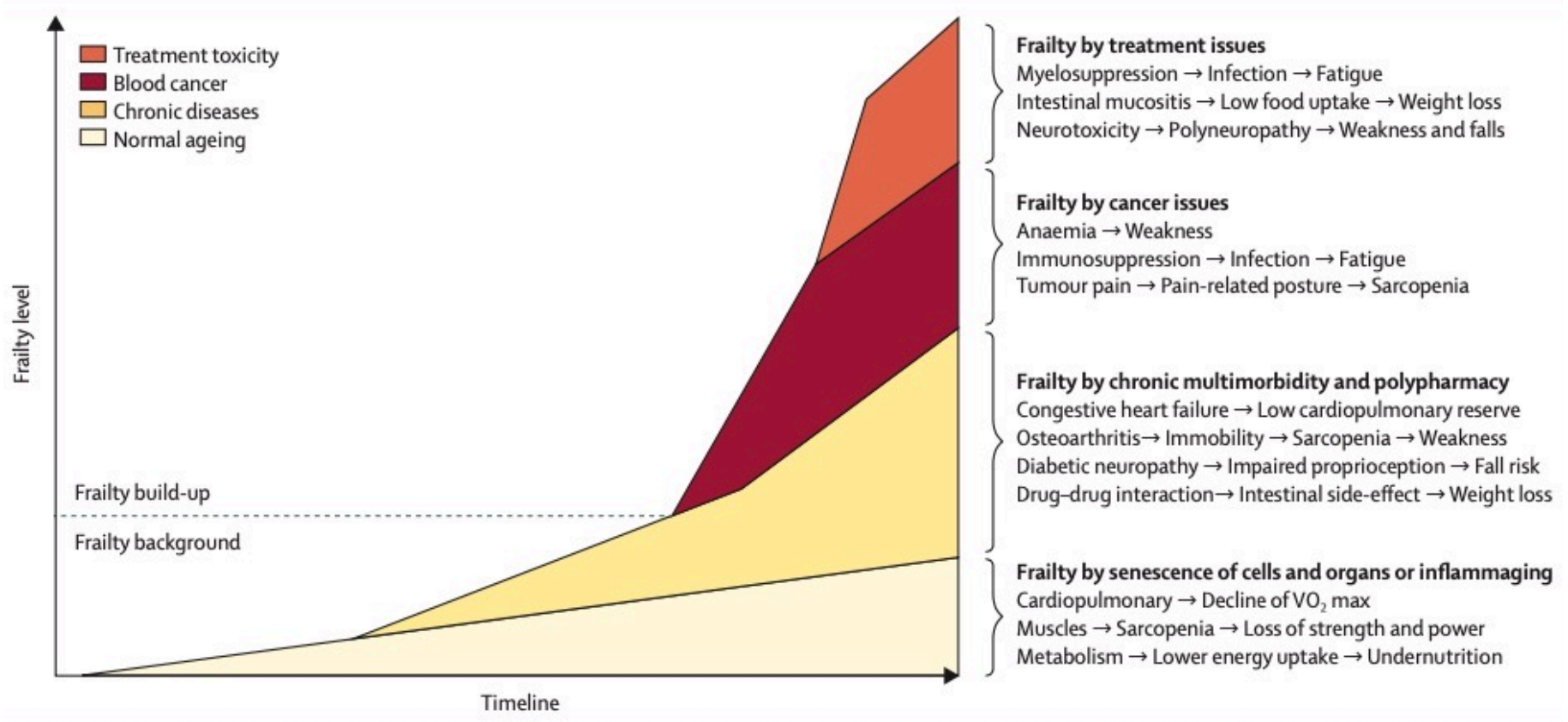
These data are not from head-to-head trials. They are intended to provide an overview of patient characteristics only. Cross-trial comparison should not be inferred.

*Patients aged <65 years had to have at least one of CIRS>6 or CrCl<70 mL/min, but not both;[1,7] †CIRS for geriatrics was used in the AMPLIFY trial.[6]

1L, first-line; A, acalabrutinib; CIRS, cumulative illness rating scale; CrCl, creatinine clearance; ECOG PS, Eastern Cooperative Oncology Group performance status; FD, fixed duration; I, ibrutinib; O, obinutuzumab; V, venetoclax; Z, zanubrutinib.

1. NCT03462719; 2. NCT02910583; 3. NCT02950051; 4. NCT02242942; 5. NCT03836261; 6. Brown JR, et al. N Engl J Med 2025;392:748–762; 7. NCT02475681; 8. NCT01722487; 9. NCT03336333. All NCT pages available from https://clinicaltrials.gov/study/. Last accessed May 2025.

‘Frailty’ is a multifactorial concept in patients with CLL[1–3]



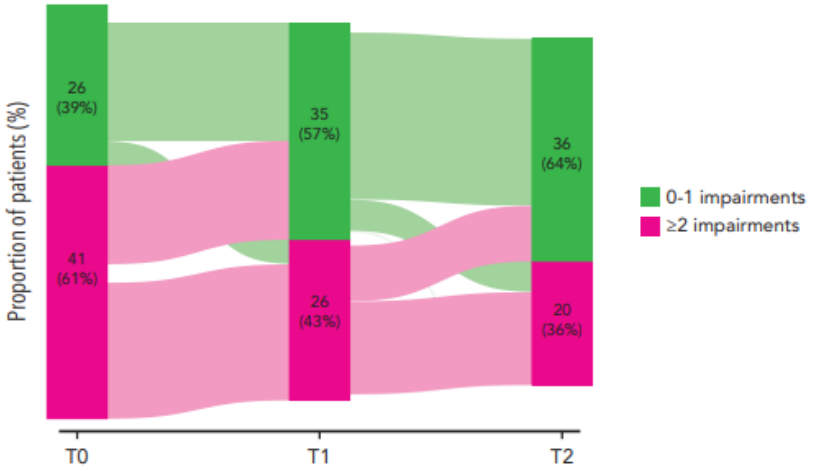
Growing evidence has shown the influence of **age on prognosis is less pronounced** with targeted agents vs CIT[2,3]

Figure from Goede V, et al. Lancet Healthy Longev 2021.[1]
CIT, chemoimmunotherapy.
1. Goede V, et al. Lancet Healthy Longev. 2021;2:e736-e745; 2. González-Gascón-y-Marín I, et al. Cancers 2023;15:4391; 3. Tedeschi A, et al. Blood Adv 2021;5:5490–5500.

Frailty is also a target for targeted drugs in CLL

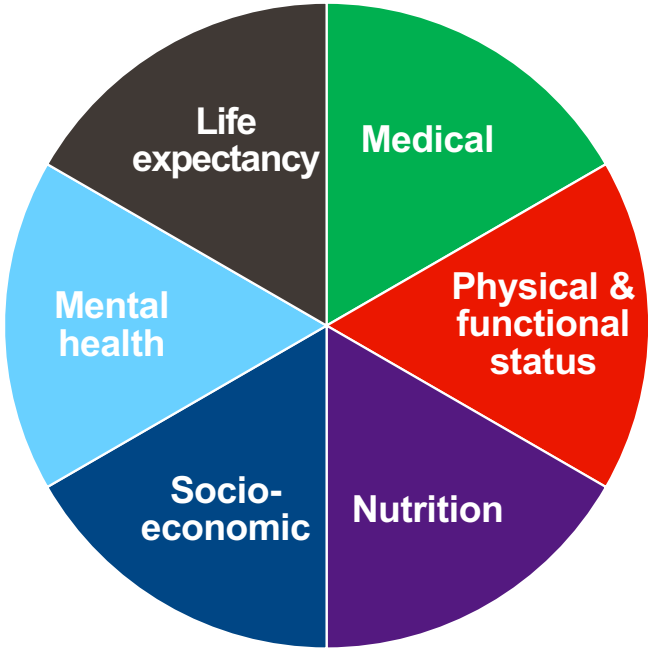
Valentin Goede | St. Marien-Hospital

In this issue of *Blood*, van der Straten et al[1] report that frailty, as measured by geriatric assessment (GA) in older patients with chronic lymphocytic leukemia (CLL), is likely to improve with targeted drug therapy. This observation was based on the HOVON139/GiVe trial, in which 67 mostly older patients (median age, 71 years) who were unfit for chemoimmunotherapy with fludarabine/cyclophosphamide/rituximab received 12 cycles of chemotherapy-free treatment with venetoclax/obinutuzumab (Ven-O) followed by prolonged venetoclax consolidation.[2]



Goede V. Blood 2023

Comprehensive geriatric assessment is recommended before treatment selection in patients aged >65 years, and when clinically relevant[1]



In a comprehensive geriatric assessment:[1,2]

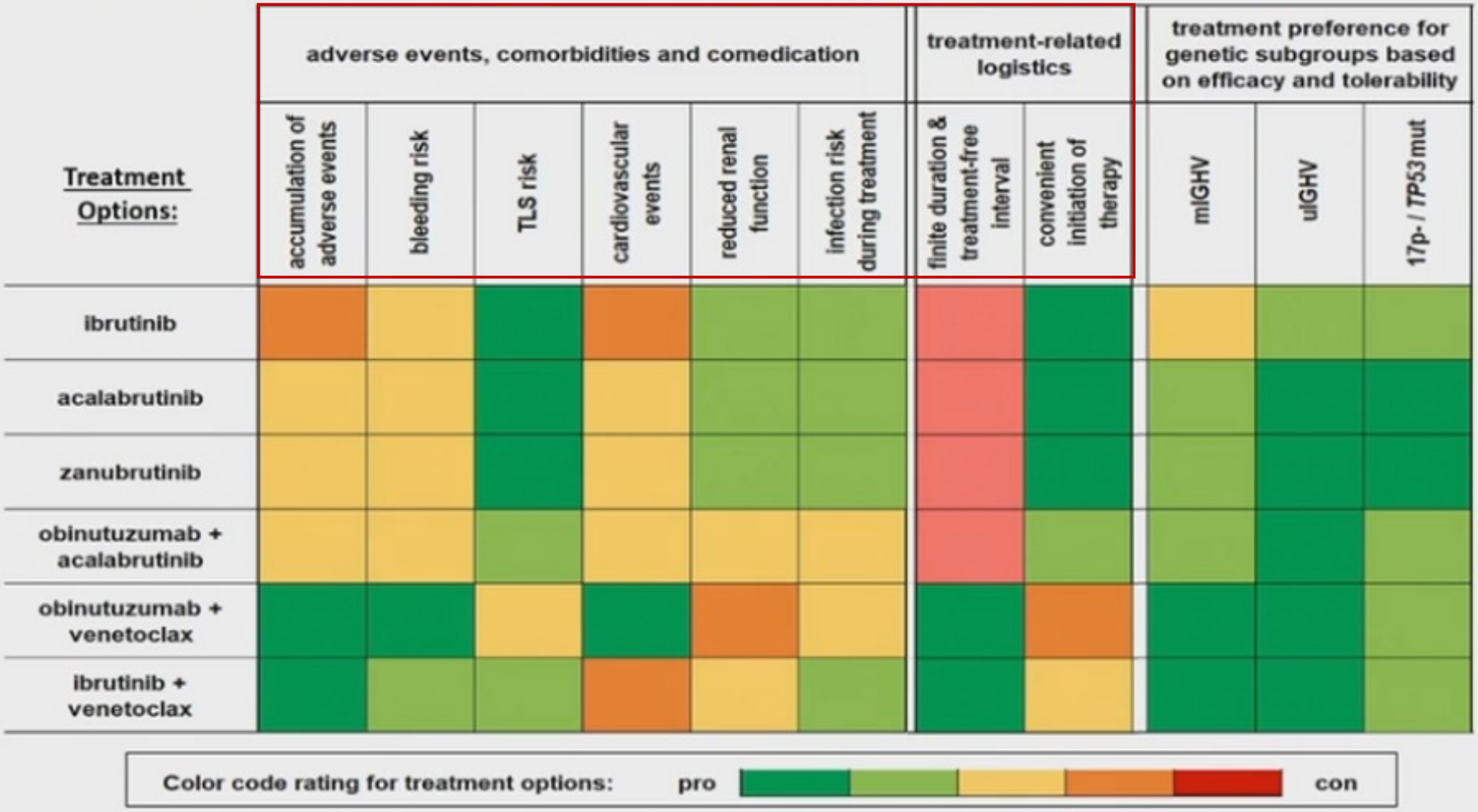
- Multiple domains of a patient's health and well-being are assessed
- Any validated tool can be used to assess each domain
- The tools used should be adapted based on resource availability (e.g. by using PRO measures)

GA results can inform treatment decision-making and the implementation of targeted interventions (e.g referrals to nutritional services, physical therapy, and other care teams)[1]

ASCO, American Society of Clinical Oncology; PRO, patient-reported outcome.

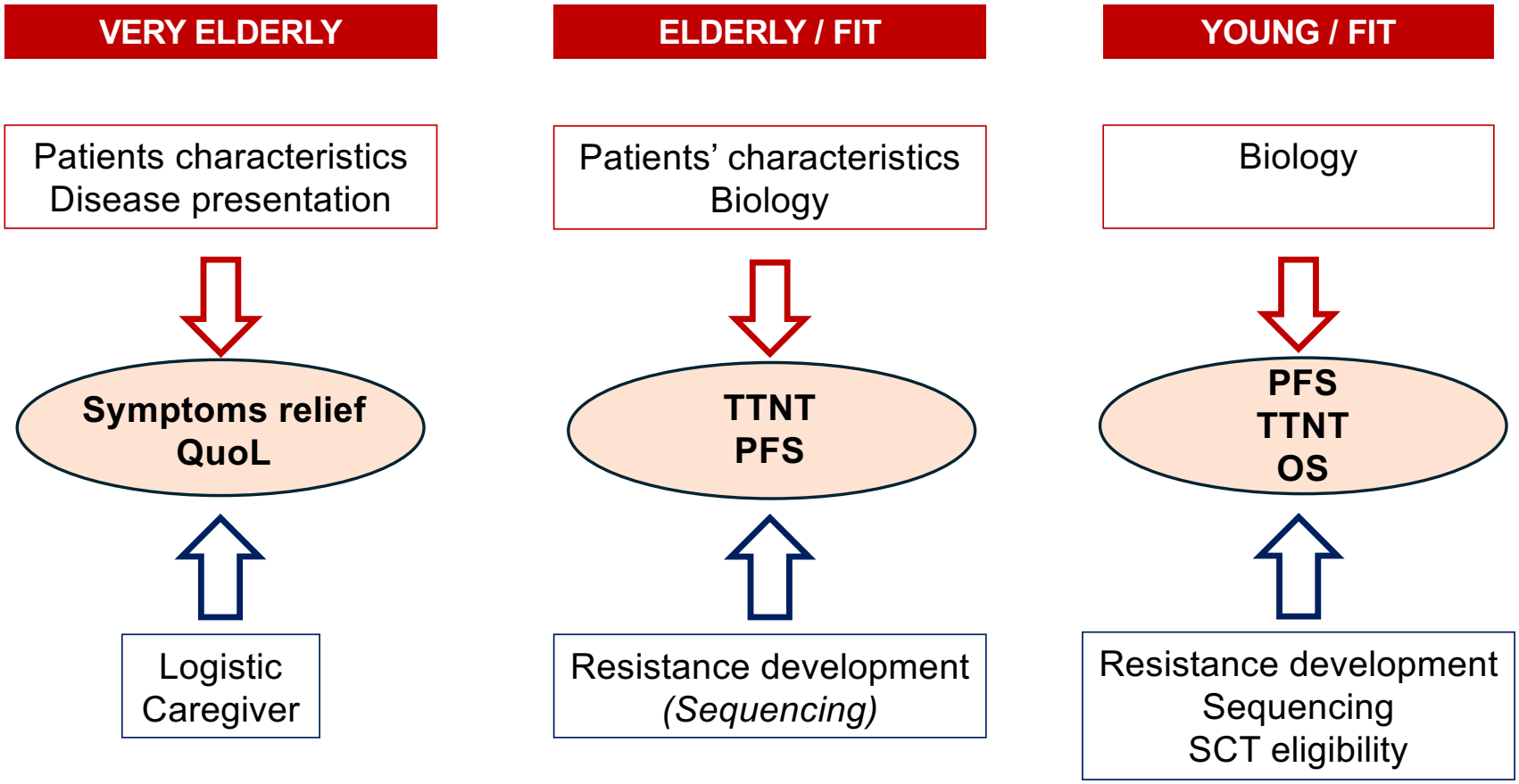
1. González-Gascón-y-Marín I, et al. Cancers 2023;15:4391; 2. Dale W, et al. J Clin Oncol 2023;41:4293-4312.

Optimal Frontline CLL Treatment – Balance of Tolerability and Efficacy



Tausch E. Schneider C. Stilgenbauer S. Risk-stratification in frontline CLL: standard of care; ASH Education Program 2024

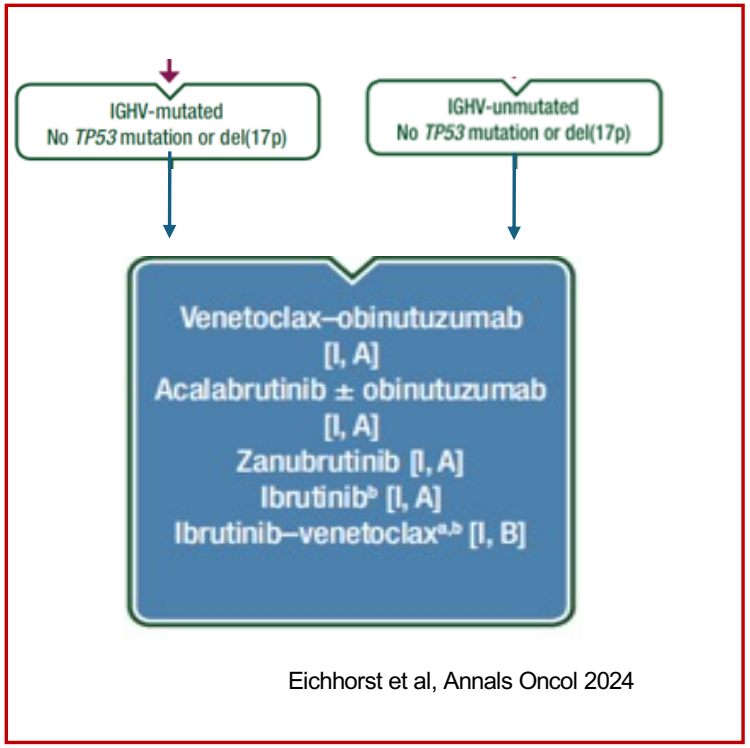
What is the objective?



Personal opinion

UNFIT ELDERLY

ESMO Clinical Practice Guideline interim update on new targeted therapies in the first line and at relapse of chronic lymphocytic leukaemia☆



Eichhorst et al, Annals Oncol 2024

Personal treatment alghoritm choice

DIFFERENT TREATMENT GOAL IN THE ELDERLY: QoL

1

Pt Characteristics

AGE (very elderly)
FITNESS
COMORBIDITIES (renal/cardiac)
COGNITIVE STATUS
LOGISTICS: care giver
distance from hospital

2

Disease Characteristics

IGHV
Bulky DISEASE

VERY ELDERLY

NO MAJOR CARDIOLOGICAL Comorb
NO CARE GIVER
DISTANCE FROM HOSPITAL

→ ***Still role of Continuous Therapy***

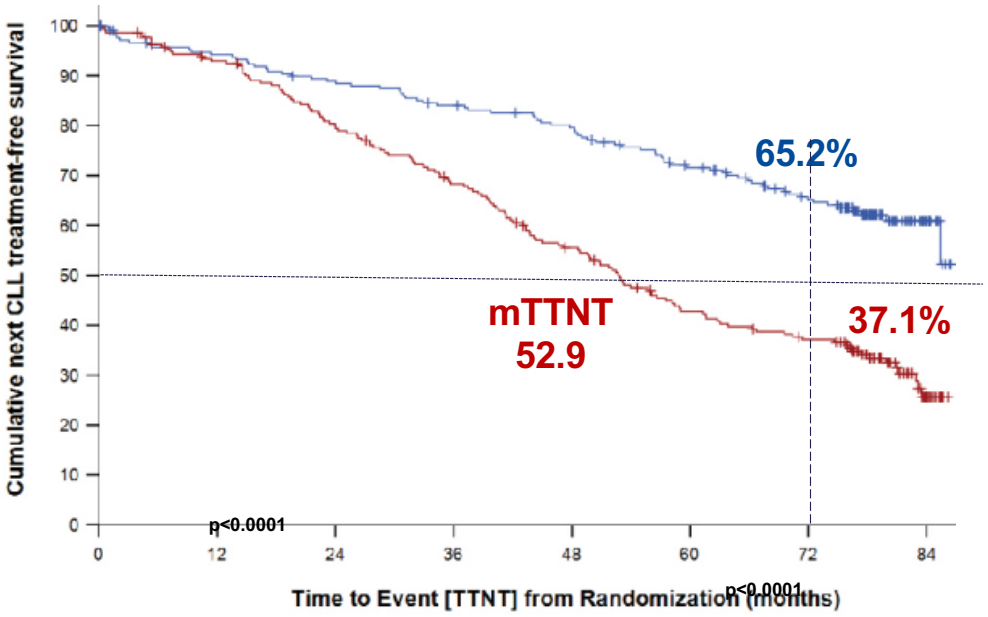
ELDERLY MORE FIT

IGHV status
Bulky Disease

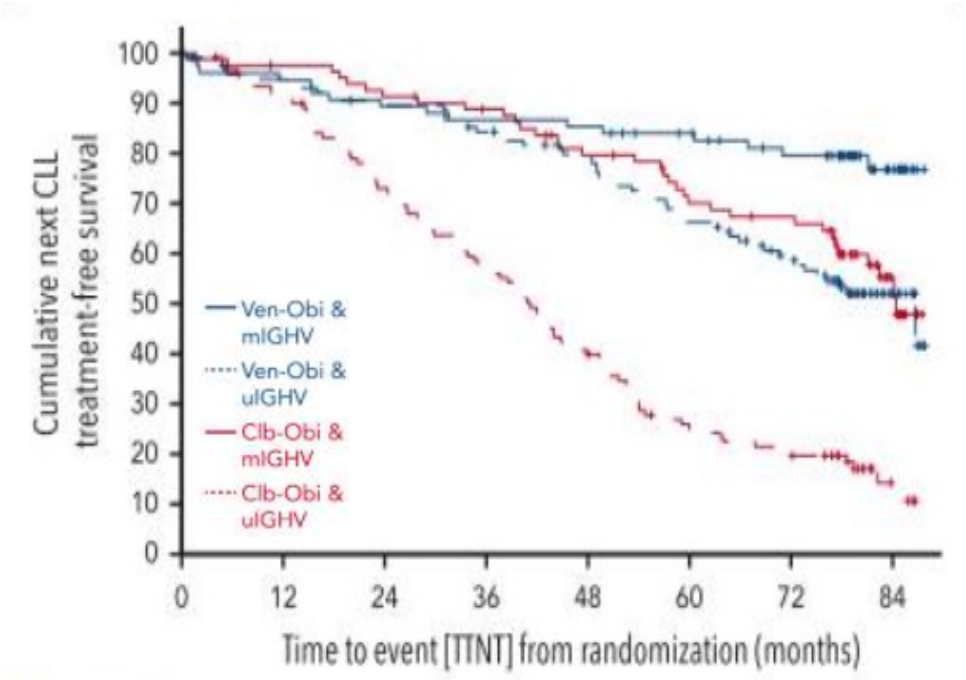
→ ***FD therapy***
IGHV mutated:Ven O
IGHVunmutated:V I
Bulky Disease: VI

Venetoclax + Obinutuzumab TN CLL
CLL14 phase 3 randomized trial: TTNT

Time To Next Treatment



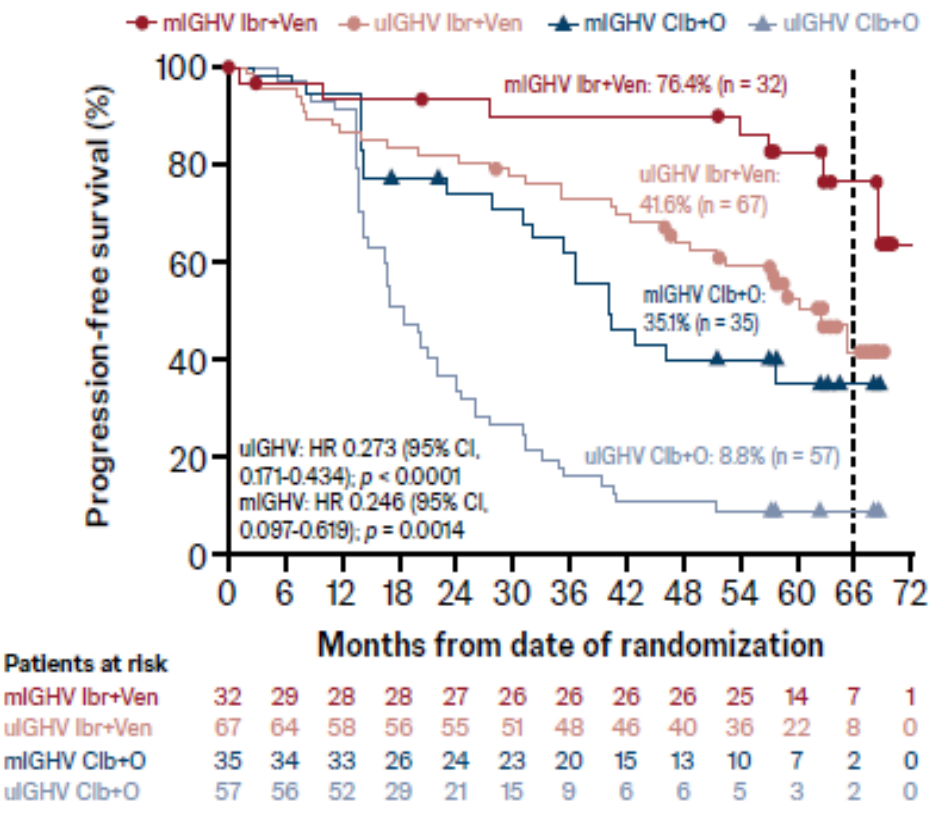
Time To Next Treatment according to IGHV

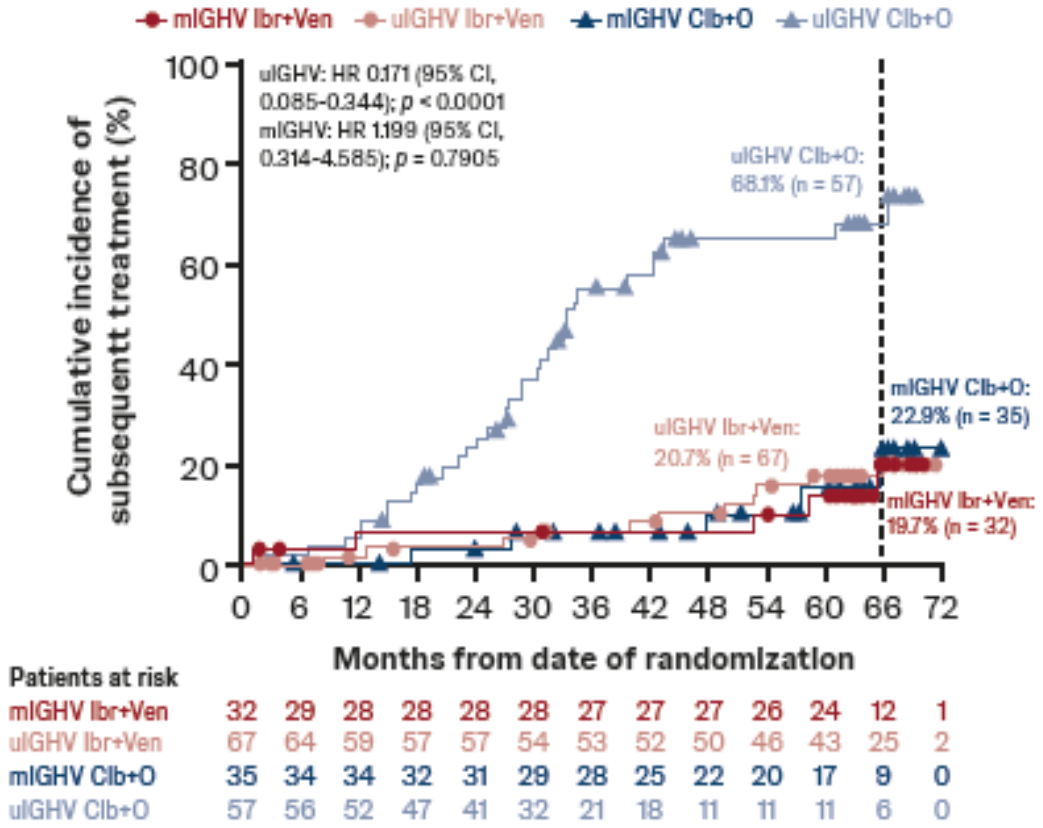


Al Sawaf O et al., Blood 2024

Venetoclax + Ibrutinib TN CLL

GLOW phase 3 randomized study: PFS and TTNT by IGHV





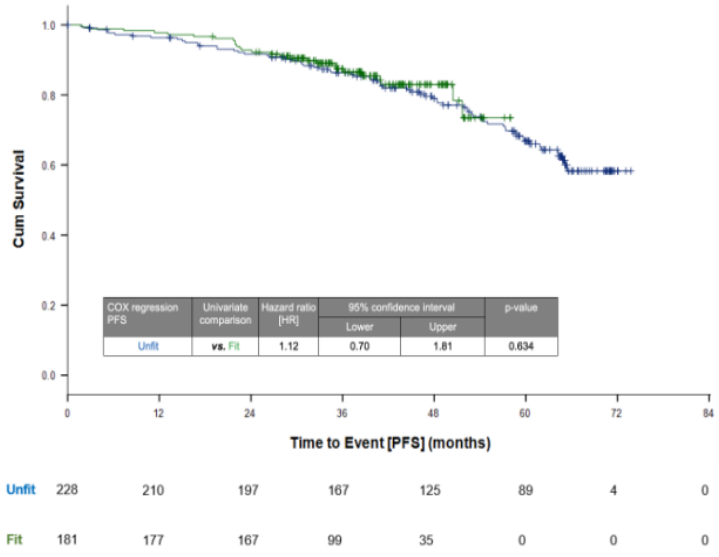
Niemman , et al. ASH 2024

Treatment Decision in CLL

Age and FD venetoclax based

Venetoclax Obinutuzumab

CLL13 and CLL14 [1]



Venetoclax Ibrutinib

Captivate[3]**: median age 60 y**

	N=159 %
Grade 3/4 AEs (≥5%)	62
Neutropenia	33
Infections	8
Hypertension	6
Neutrophil count decreased	5
AEs of clinical interest (any G)	
Atrial fibrillation	4
Major hemorrhage	2
AEs leading to discontinuation	5
AEs leading to dose reductions	21
Death from any cause during tx	1.5

Glow[4]**: median age 71 y**

	N=106 %
Grade 3/4 AEs (≥5%)	75.5
Neutropenia	34.9
Infections	17
Hypertension	7.5
AEs of clinical interest (any G)	
Atrial fibrillation	6.6
AEs leading to discontinuation	10.4
Death from any cause during tx	7.4

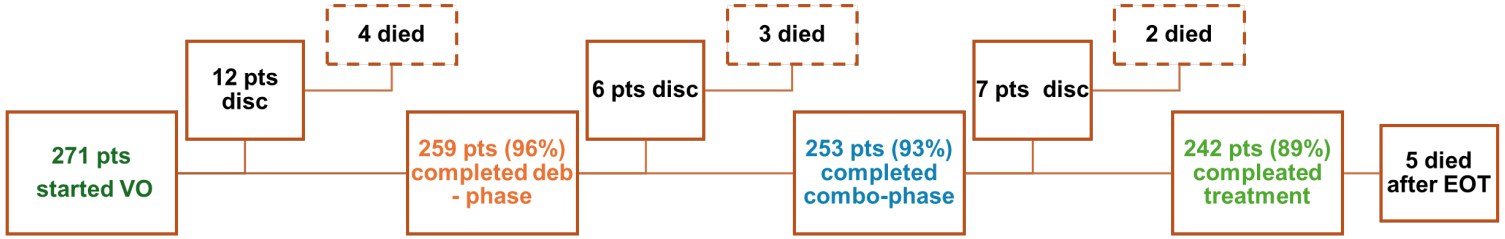
ESMO GOOD SCIENCE BETTER MEDICIN BEST PRACTICE

ELDERLY: Careful evaluation before ibrutinib venetoclax

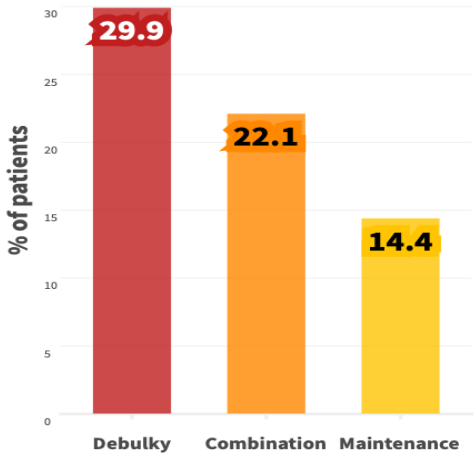
1 Al Sawaf O et al., IWCLL 2023
2 Galitzia et al., SIR 2024
3 Allan et al, ASH 2021
4 Kater et al, EHA 2021

VEN O
Italian Real Life

Patients disposition across the various phases

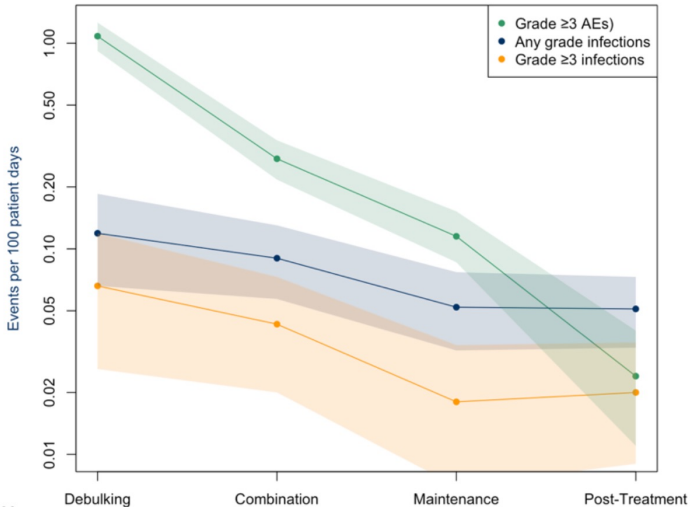


Schedule modifications



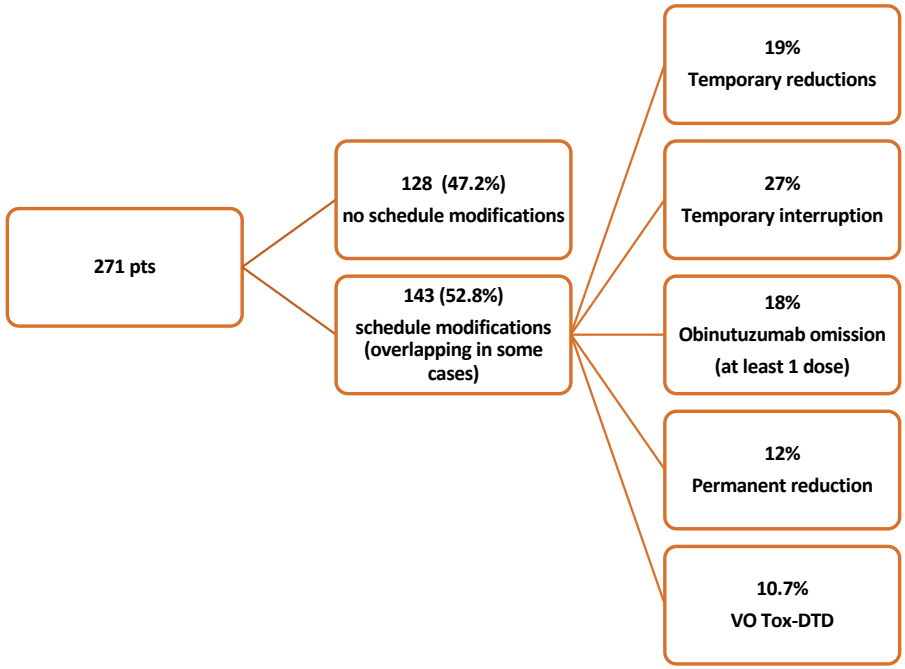
Incidence of AEs and infections

145 pts (53.5%) AE G>3



VEN O
Italian Real Life

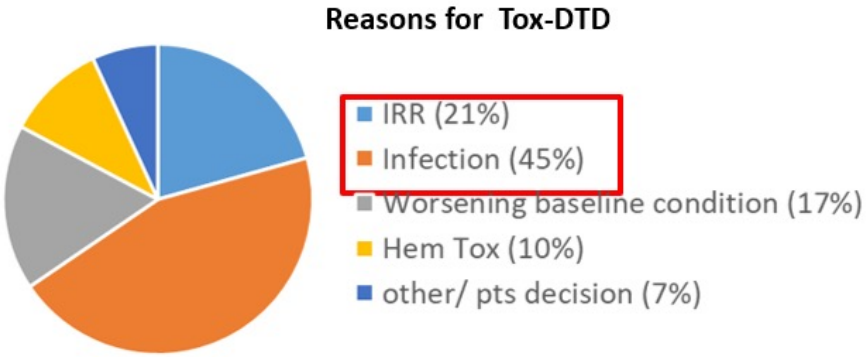
Global feasibility



Multivariate analysis

Baseline factor	OR(95%CI)	p
Global feasibility		
Age	1.05 (1.02 -1.08)	<0.001
Steroid>6days	3.02 (1.65 - 5.6)	<0.001

Definitive discontinuation due to toxicity

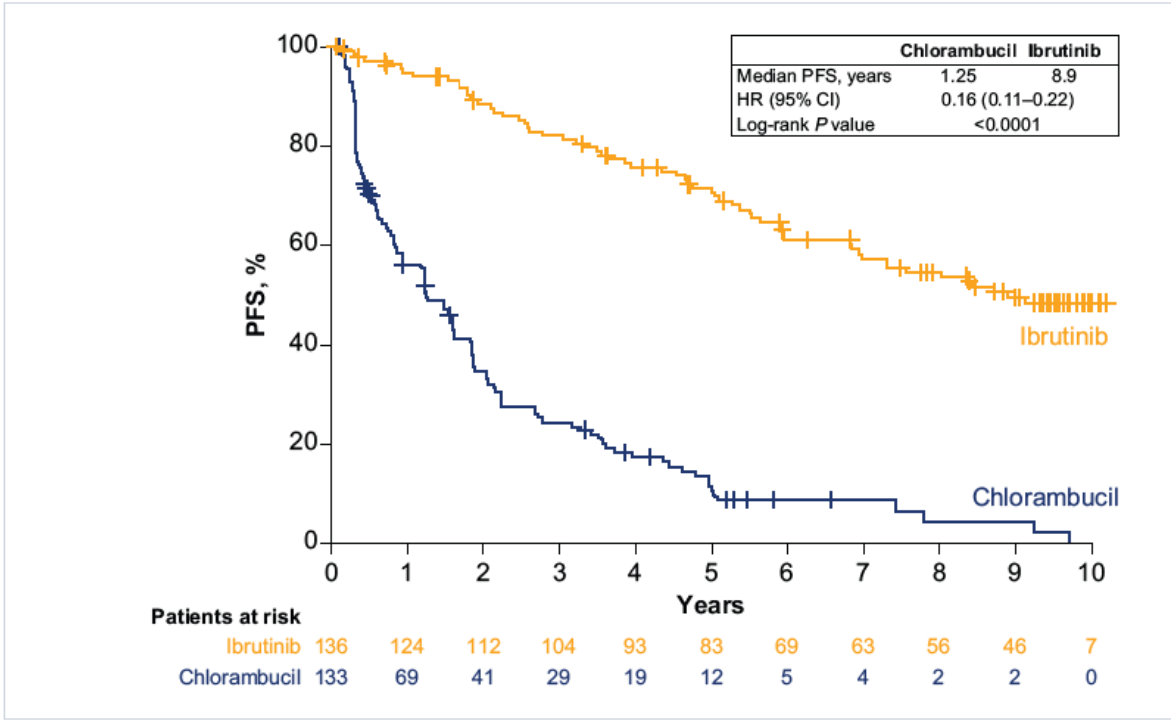


Multivariate analysis

Baseline factor	OR(95%CI)	p
Tox-DTD		
Need of caregiver	3.1 (1.2 - 8.5)	0.03
Endocrine Comorb	3.3 (1.3 -7.9)	0.007
Steroid>6days	3.4 (1.5 - 7.5)	0.005

Final Analysis of the RESONATE-2 Study: Up to 10 Years of Follow-Up of First-Line Ibrutinib Treatment in Patients With CLL/SLL

At Final Analysis, Median PFS With Ibrutinib Was Reached at 8.9 Years



- At 9 years, the PFS rates were 49.7% (95% CI, 40.2–58.4) in the ibrutinib arm and 4.4% (95% CI, 1.1–11.5) in the chlorambucil arm

10 y FU discontinuations due to AE: 33%

24/136 (18%) received subsequent therapy

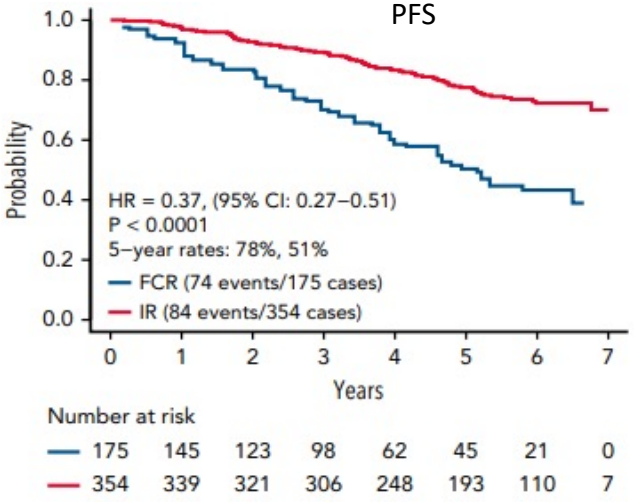
Burger et al EHA 2024

CONTINUOUS THERAPY
cBTKi monotherapy

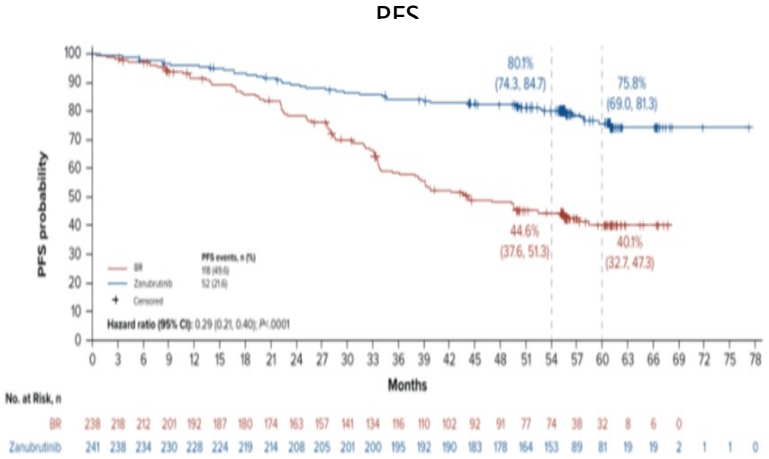
Young FIT → Elderly Unfit

✓ **PFS Benefit With cBTKi compared to immuno-CHT**

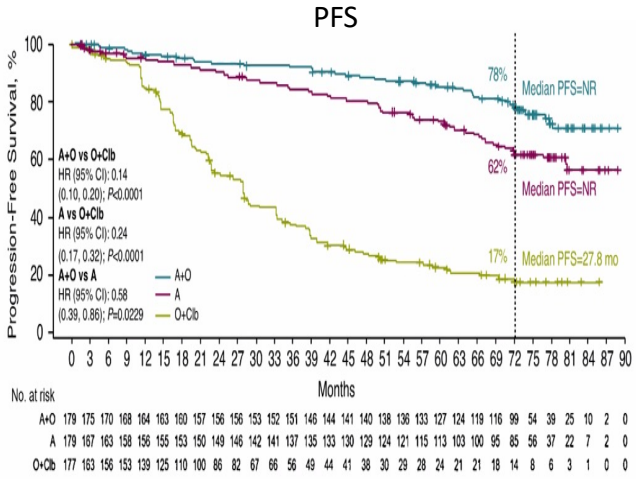
ECOG
Ibrutinib R vs FCR
Median FU 70 m



Sequoia
Zanubrutinib vs BR
Median FU 61.2 m



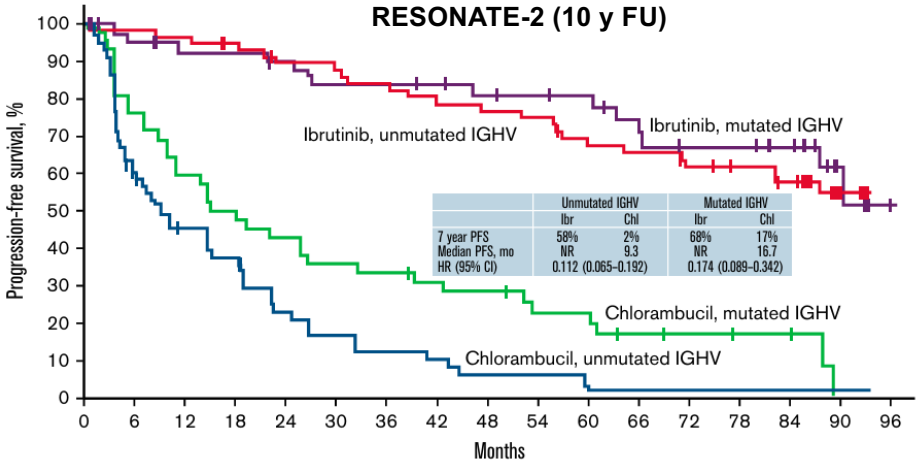
Elevate TN
Acala vs Acala O vs Chl Ob
Median FU 6 y



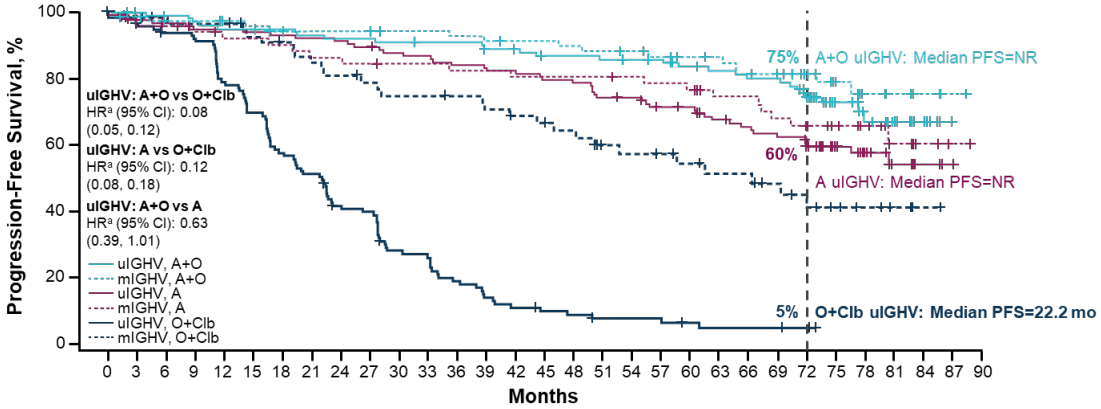
Shanafelt TD, et al. Blood 2022
Munhir T, et al. EHA 2023
Shadman JP, et al. ASH 2024

Continous BTKi in TN CLL: IgHV mutational status

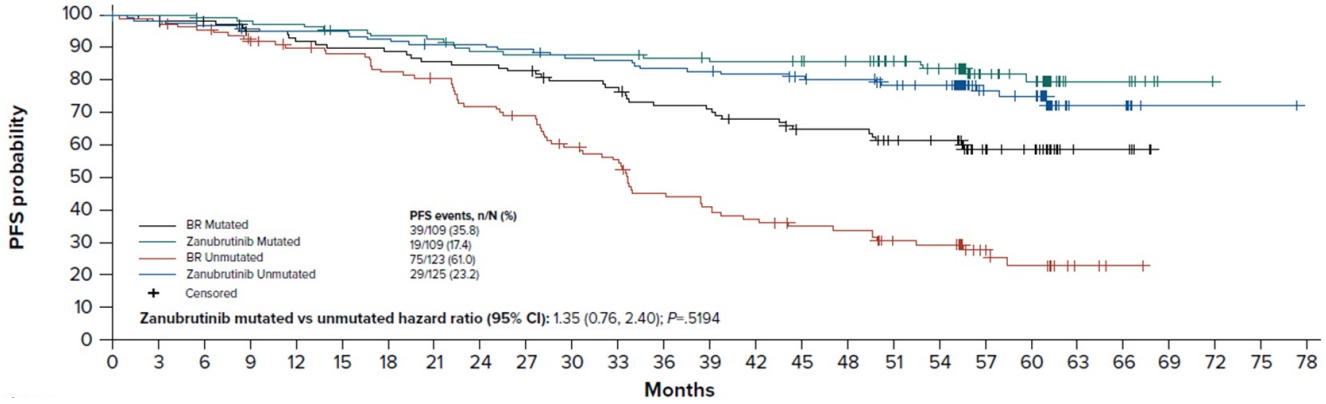
RESONATE-2 (10 y FU)



ELEVATE TN (6y FU)



SEQUOIA (5y FU)



Barr Blood Adv 2022; Burger EHA, 2024; Sharman ASH 2023; Shadman ASH 2024

Maria 78 aa

ANAMNESI

Ipertensione

Diabete Mellito

LLC necessità terapia:

IGHV non mutato, anemia, LN 6 cm

MOTIVO DEL RICOVERO

Infezione Vie Urinaria

DECORSO CLINICO

-Impostazione di terapia antibiotica empirica

- Complicato da Delirium
- Remissione del delirium

- DIMISSIONE IN BUONE CONDIZIONI GENERALI

&

Maria 78 aa

ANAMNESI

Ipertensione

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MOTIVO DEL RICOVERO

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- Remissione del delirium

DIMISSIONE IN SCADUTE CONDIZIONI GENERALI

PRESIDI PER DEAMBULAZIONE

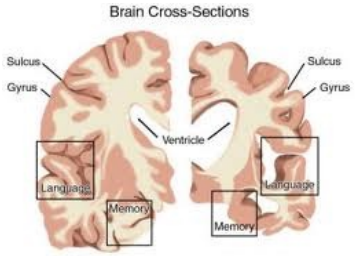
INCONTINENZA

SAECOPENIA

Maria 78 aa & Maria 78 aa

AUTONOMIA

COGNITIVITA’



TONO DELL’UMORE’

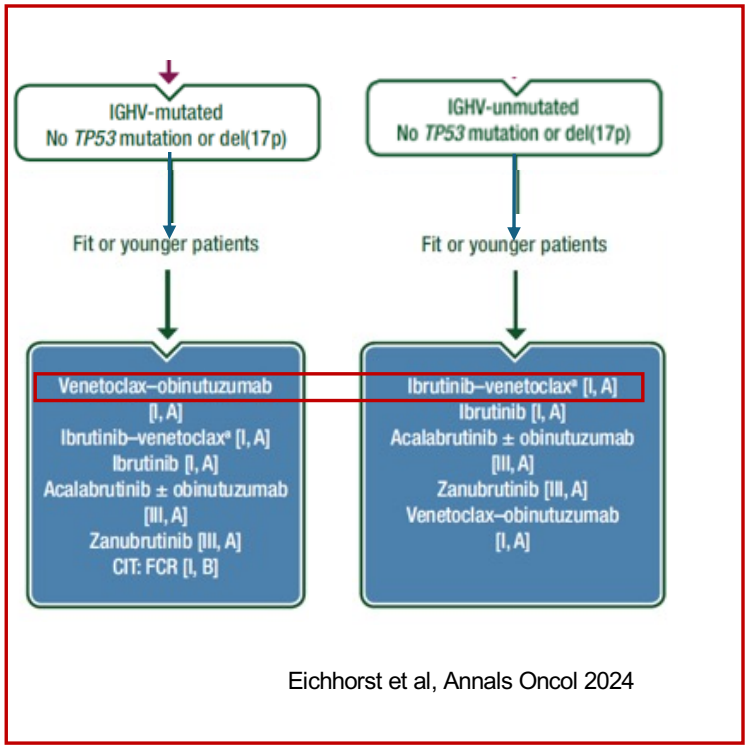
SUPPORTO SOCIALI

TREATMENT factors

BTKi Ibruitnib Acalabruitinib Zanubruitnib	Obinutuzumab + Venetoclax	Ibrutinib + Venetoclax
 ✓ Easy to initiate ✓ Oral administration ✓ Rare TLS	✓ Resistace ✓ AE limited to adm, period ✓ Cost	✓ Easy to initiate ✓ Oral Therapy ✓ Low TLS risk ✓ AE limited to adm, period ✓ Resistace ✓ Retreatment ✓ Cost
 ✓ Continuous exposure AE ✓ Resistace development ✓ Retreatment	✓ Retreatment	✓less Intensive monitoring
 ✓ Cost	✓ Intensive monitoring ✓ IV Therapy ✓ TLS risk ✓ IRR	

FIT YOUNGER

ESMO Clinical Practice Guideline interim update on new targeted therapies in the first line and at relapse of chronic lymphocytic leukaemia☆



Eichhorst et al, Annals Oncol 2024

Personal treatment choice

FD therapy

IGHV mutated:Ven O

IGHV unmutated:V I

Bulky Disease: V I