SESSIONE 1

Il concetto della "durata fissa" dal farmacologo all'ematologo

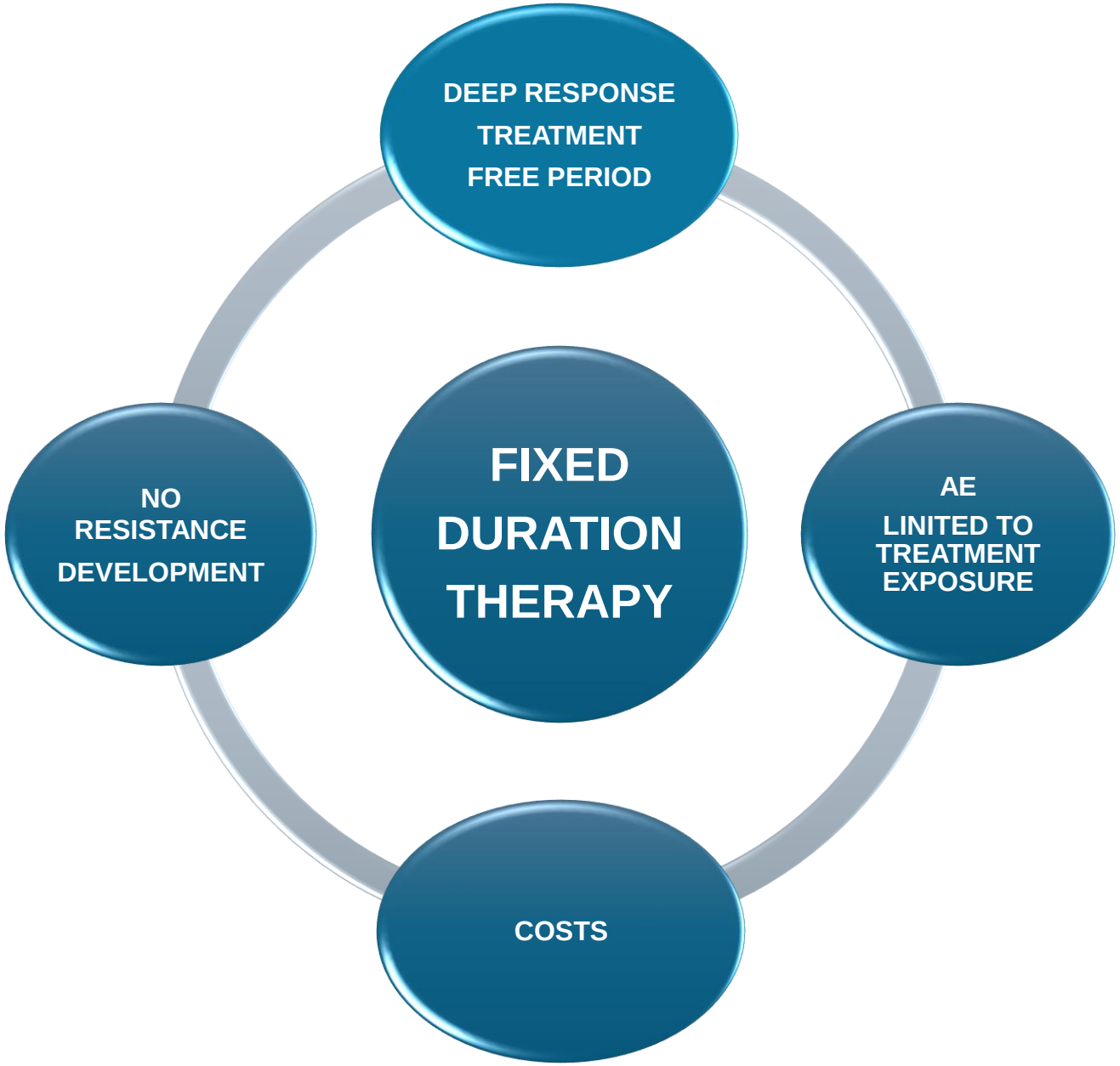
NEL PAZIENTE IN PRIMA LINEA

Alessandra Tedeschi
ASST GOM Niguarda
Milano

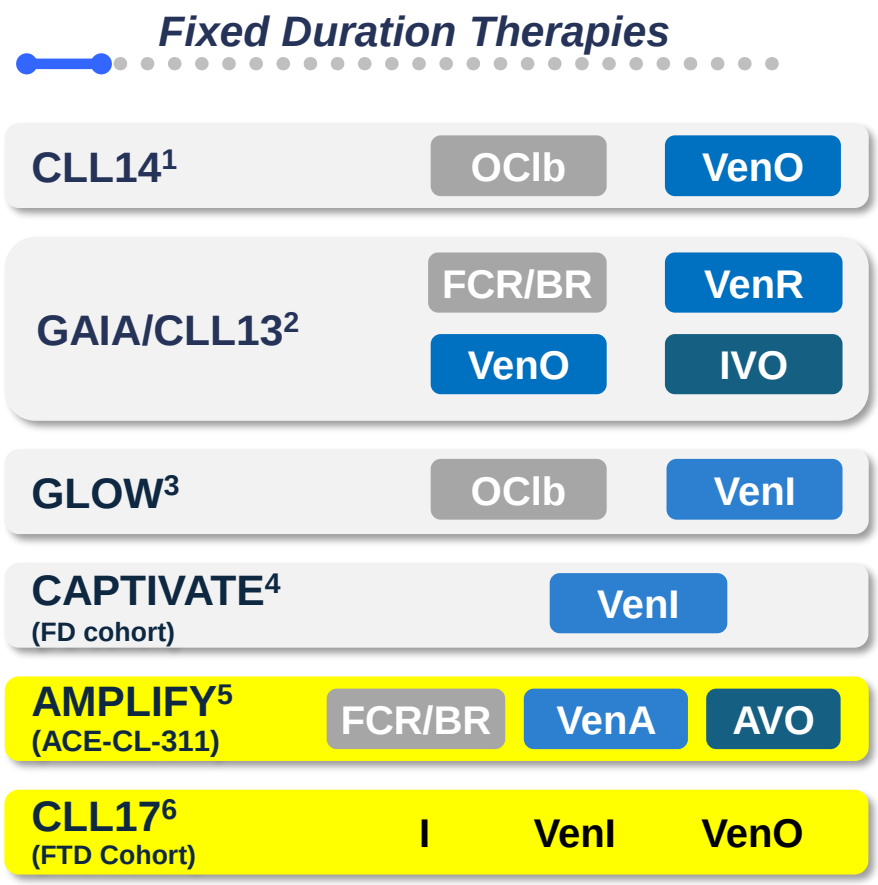
REVOLUTIONARY ROAD IN CLL

Innovazione rivoluzionaria nella terapia della leucemia linfatica cronica

Milano, 10 luglio 2024
Starhotels E.c.ho.


DEEP RESPONSE
TREATMENT
FREE PERIOD
NO
RESISTANCE
DEVELOPMENT
FIXED
DURATION
THERAPY
AE
LINITED TO
TREATMENT
EXPOSURE
COSTS

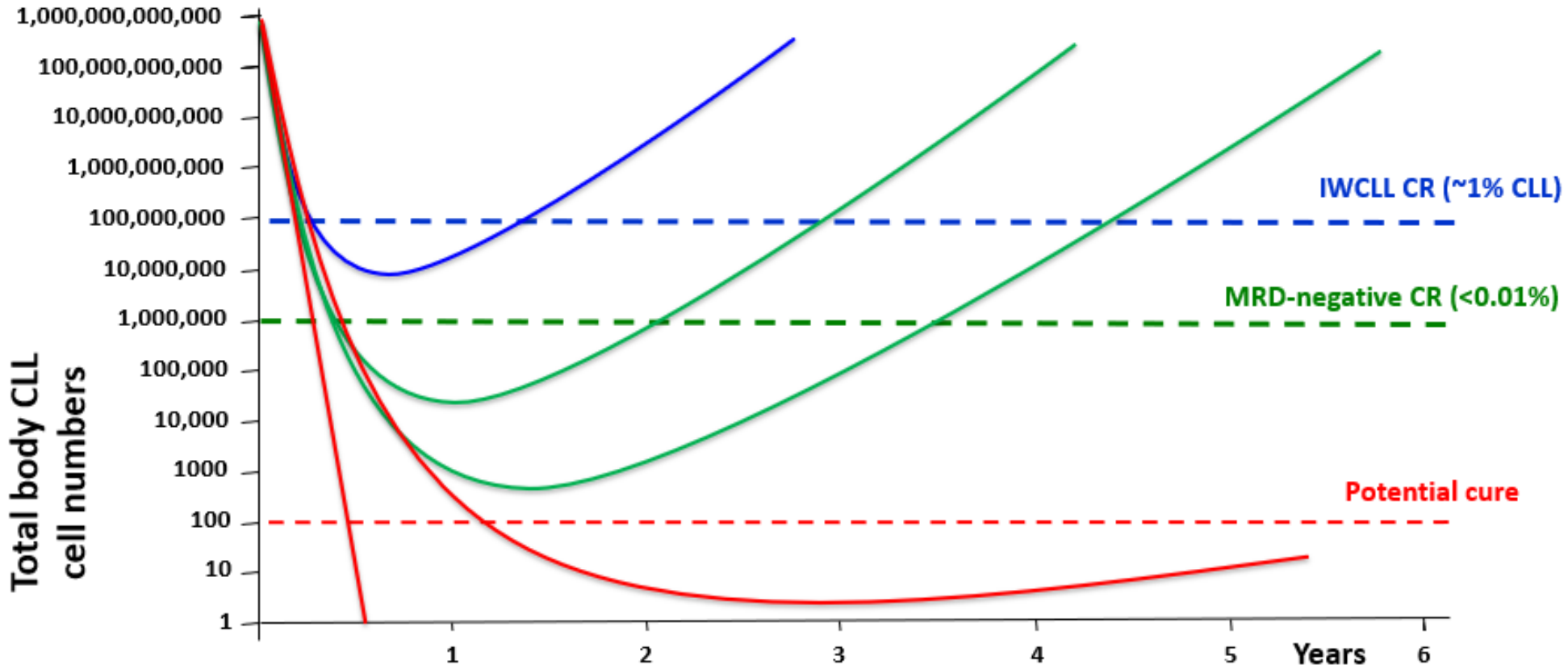
FIRST LINE CLL: FIXED DURATION THERAPY



1. Al Sawaf O, et al. *Nat Commun.* 2023;**14**:2147
2. Eichhorst B, et al. *N Engl J Med.* 2023;**388**(19):1739-54. 3. Kater AP, et al, *NEJM Evid.* 2022;**1**(7).
4. Tam CS, et al. Blood.2022;139(22):3278-3289.
5. Clinicaltrials.gov. NCT03836261. Accessed May 2024.
6. Clinicaltrials.gov. NCT04608318. Accessed May 2024.

DEEP RESPONSE TREATMENT FREE PERIOD

Hypothetical disease outcome based on depth of response[1-3]



Szczepański T, et al. *Lancet Oncol.* 2001; 2:409–417. 2. Böttcher S, et al. *J Clin Oncol.* 2012; 30:980–988. 3. Böttcher S, et al. *Hematol Oncol Clin North Am.* 2013; **27**:267–288

DEEP RESPONSE TREATMENT FREE PERIOD

FIRST LINE CLL

VENETOCLAX OBINUTUZUMAB

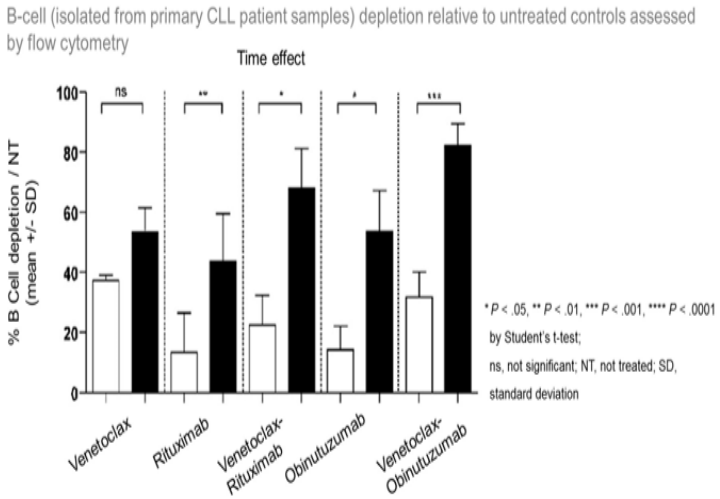
Anti CD20 MoAb

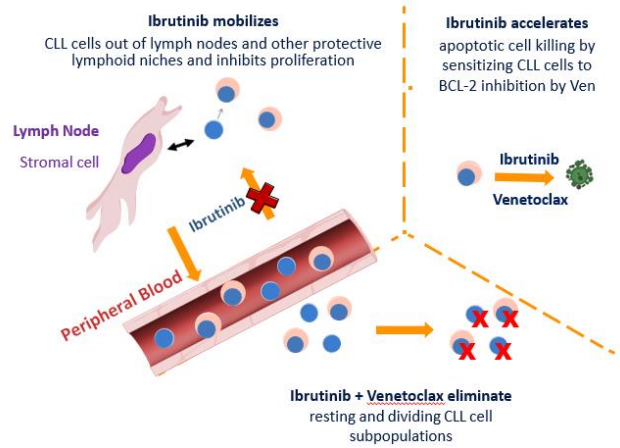
VENETOCLAX
-deep responses
- HIGH uMRD

VENETOCLAX IBRUTINIB

IBRUTINIB

- **Different sites of activity**
- **Ibrutinib enhances venetoclax activity**
- **Prevention of resistance mechanisms**





VENETOCLAX OBINUTUZUMAB: PFS

CLL14 OClb VenO

Older/with Comorbidities
Median Age 72y

Progression-Free Survival[1]

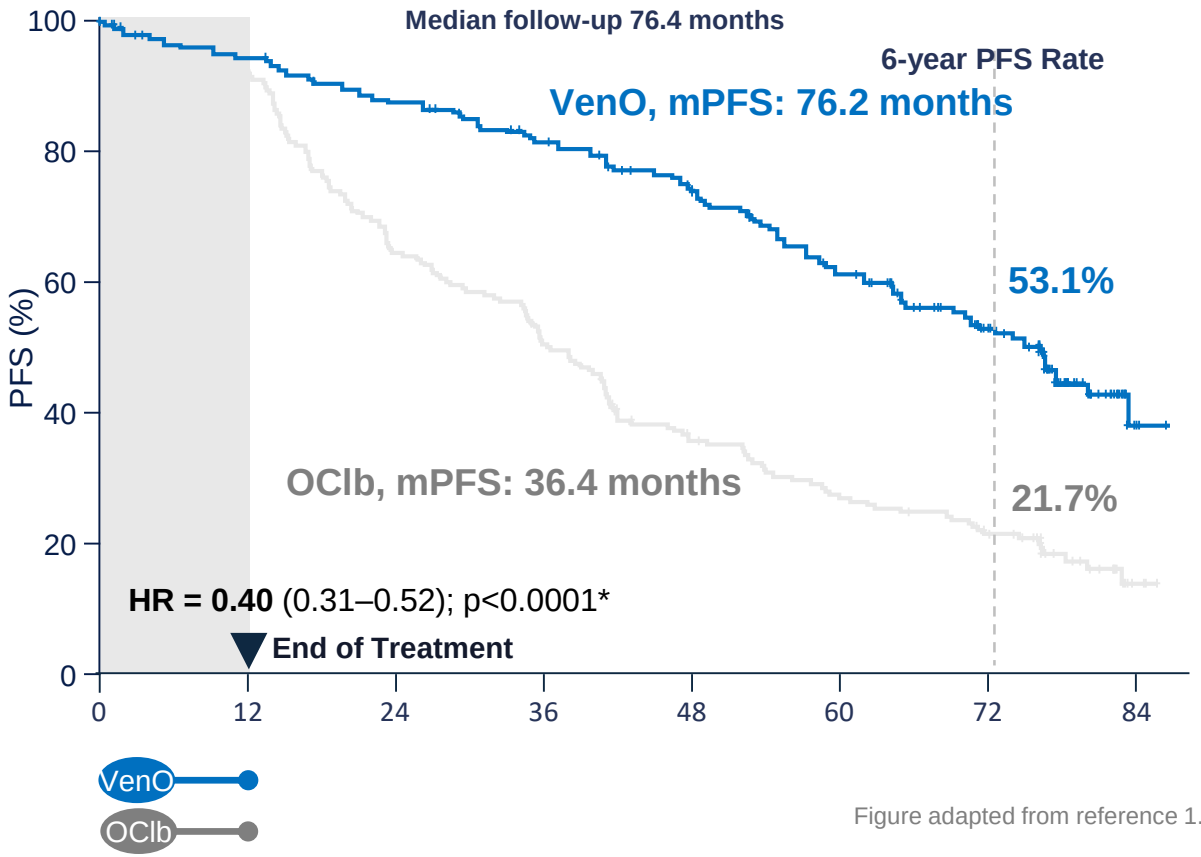


Figure adapted from reference 1.

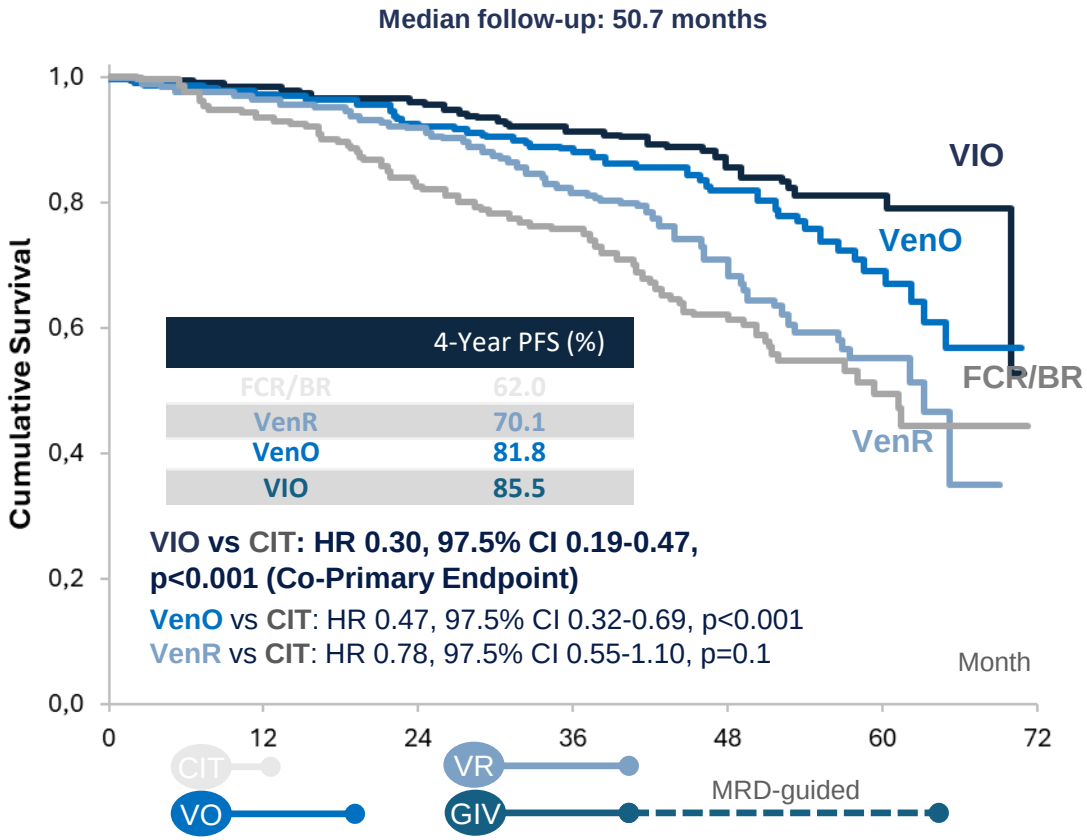
uMRD rates† in PB at Month 15[2]

OClb	VenO
35%	76%

GAIA/CLL13 FCR/BR VenO VenR GIVe

Fit No del(17p)/*TP53*^{mu}
Median Age 61y

Progression-Free Survival[1]



uMRD rates* in PB at Month 15[2]

FCR/BR	VenO	VenR	VIO
52.0%†	86.5%†	57.0%	92.2%

1. Al-Sawaf O, *et al.* EHA 2023. Abstract S145 (Oral).
2. Al-Sawaf O, et al. *J Clin Oncol* 2021; **39**(36):4049-4060 (incl. Appendix).

1. Fürstenau M, et al. ASH 2023. Abstract 635 (Oral).
2. Eichhorst B, et al. *N Engl J Med.* 2023; **388**(19):1739-54

DEEP RESPONSE TREATMENT FREE PERIOD

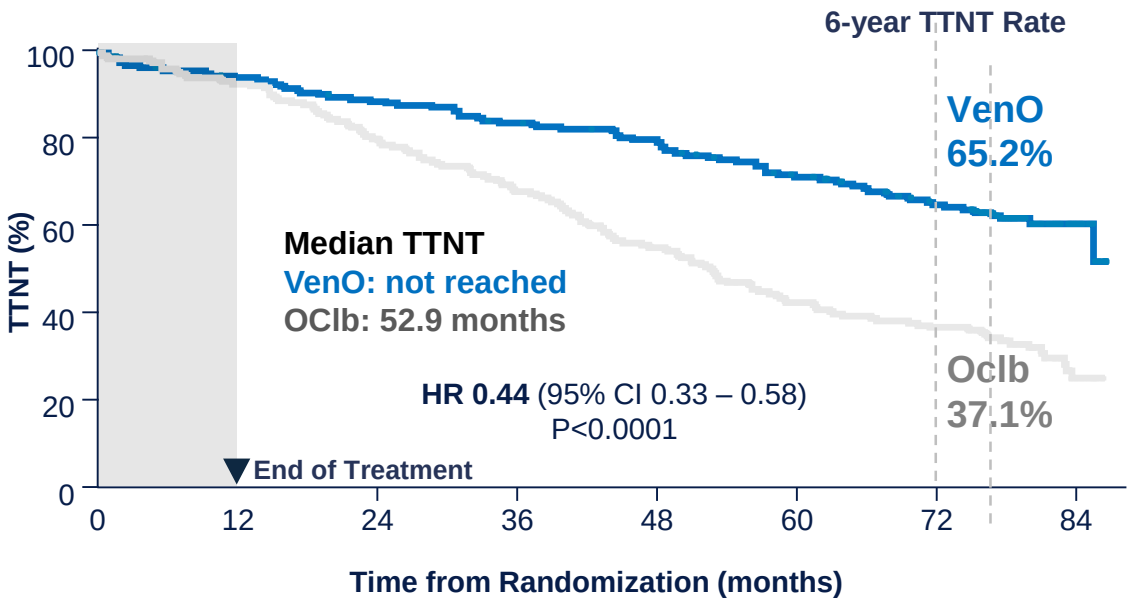
VENETOCLAX OBINUTUZUMAB: TTNT

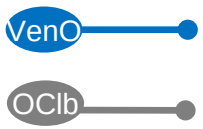
TTNT: *Durable efficacy of fixed duration VenO translates to prolonged treatment-free time for fit & unfit pts*

CLL14[1]

Older/with comorbidities

Median follow-up 76.4 months





GAIA/CLL13[2]

Fit. No *TP53* aberrations

Median follow-up: 50.7 months

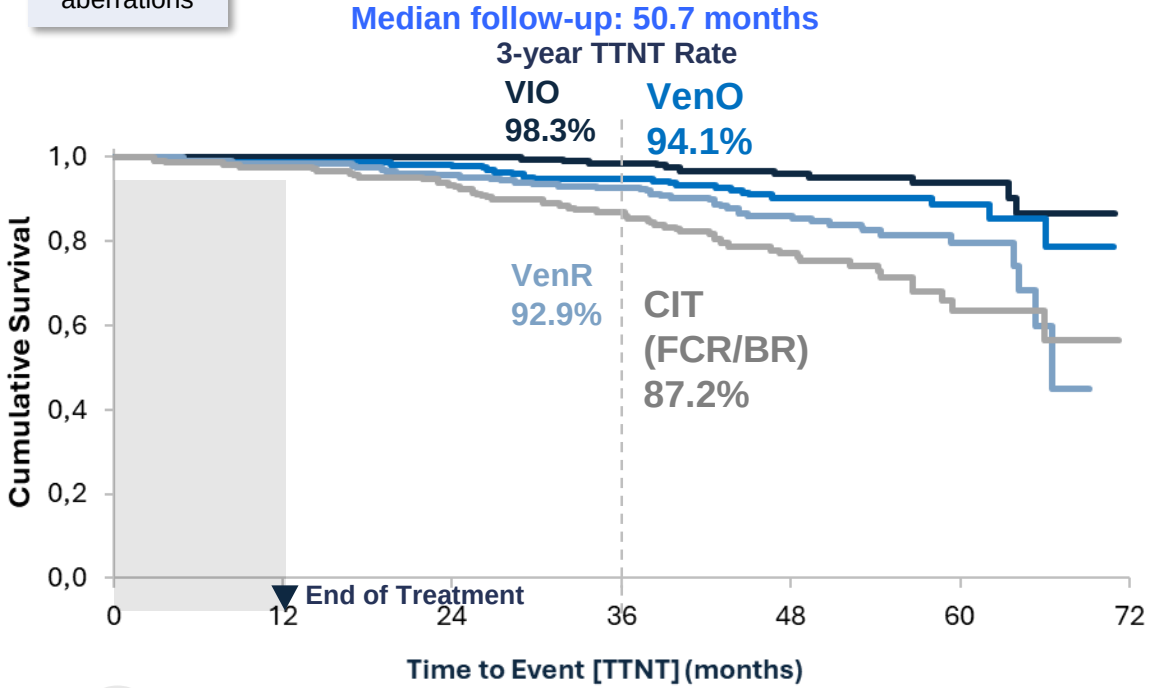


Figure adapted from reference 2 (incl. suppl.).

1. Al-Sawaf O, et al. EHA 2023. Abstract S145 (Oral).
2. Fürstenau M, et al. ASH 2023. Abstract 635 (Oral).

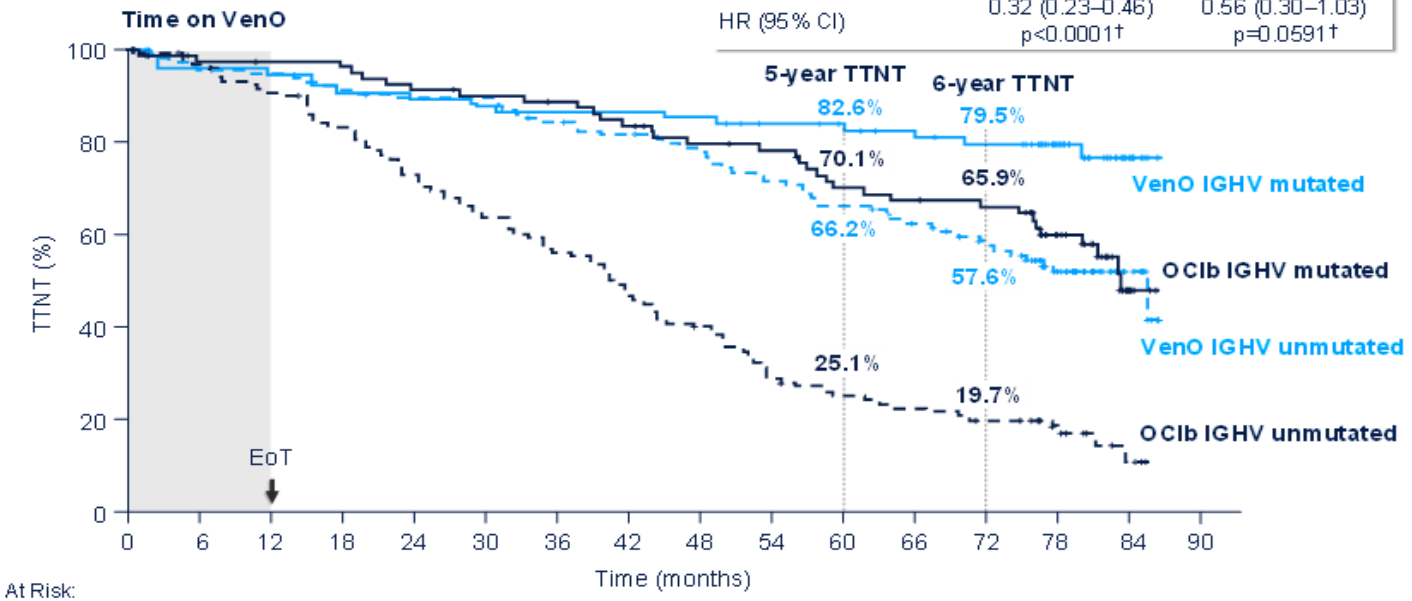
DEEP RESPONSE TREATMENT FREE PERIOD

VENETOCLAX OBINUTUZUMAB: TTNT

TTNT ACCORDING TO IGHV MUTATION

ollow-up: 76.4 months

	IGHV unmutated		IGHV mutated	
	VenO	OClb	VenO	OClb
Median TTNT,* months	85.4	40.6	NR	83.1
HR (95% CI)	0.32 (0.23–0.46) p<0.0001†		0.56 (0.30–1.03) p=0.0591†	



At Risk:															
OClb IGHV mutated	83	79	78	77	73	71	69	65	60	58	51	49	47	31	6
VenO IGHV mutated	76	72	71	68	67	66	65	65	64	60	57	54	52	38	10
OClb IGHV unmutated	123	116	108	98	85	75	66	55	46	32	28	25	21	13	3
VenO IGHV unmutated	121	110	109	105	102	102	95	91	86	79	73	66	57	34	9

Al Sawaf et al, EHA 2022

AE
LINITED TO TREATMENT EXPOSURE

VENETOCLAX OBINUTUZUMAB: AE

CLL 14

Venetoclax Obinutuzumab versus Chlorambucil Obinutuzumab

Median follow-up 76.4 months

Dose modifications and discontinuations due to adverse events

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

- **Time-limited exposure to treatment-toxicities**

Most frequent ≥ grade 3 adverse events

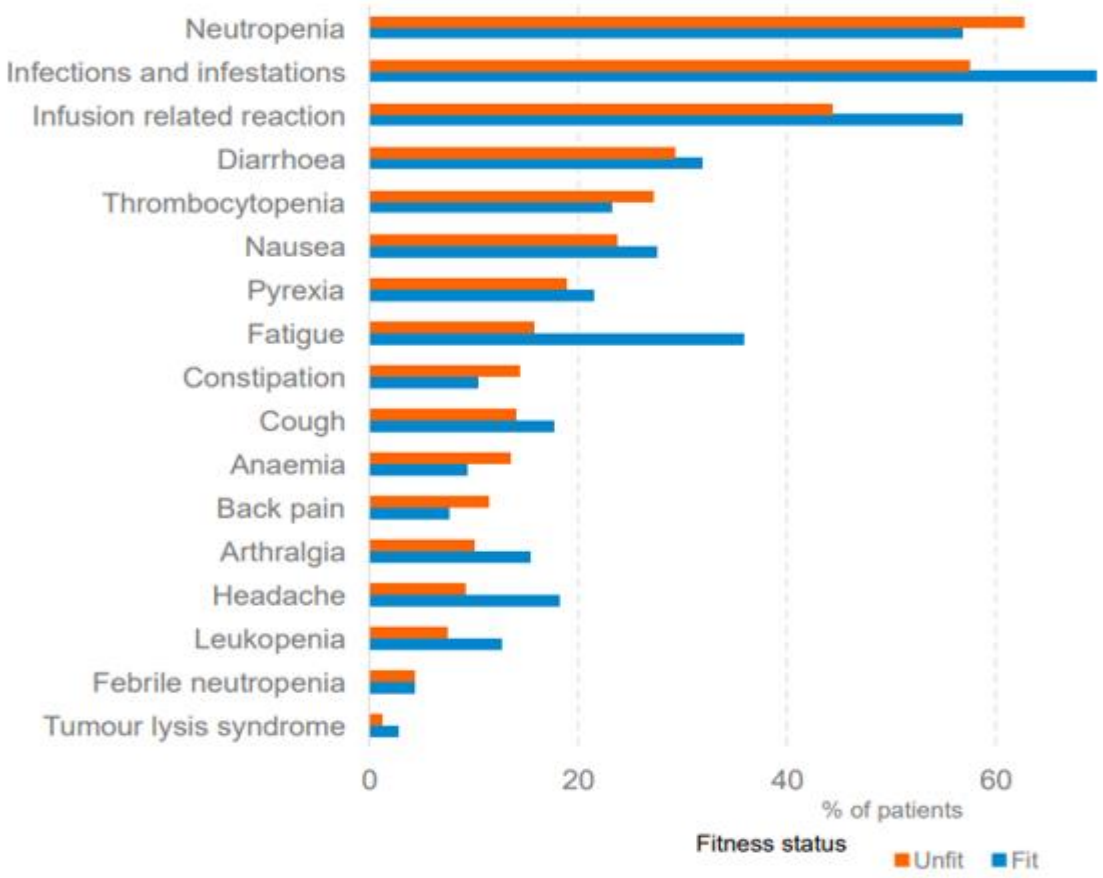
	Venetoclax-obinutuzumab (N=212)	
	During Treatment	After Treatment
Neutropenia	51.9%	3.8%
Thrombocytopenia	14.2%	0.5%
Anemia	7.5%	1.9%
Febrile neutropenia	4.2%	0.9%
Leukopenia	2.4%	0.0%
Pneunomia	3.8%	3.3%
Infusion-related reaction	9.0%	0.0%
Tumour lysis syndrome	1.4%	0.0%

Al Sawaf et al, EHA 2023

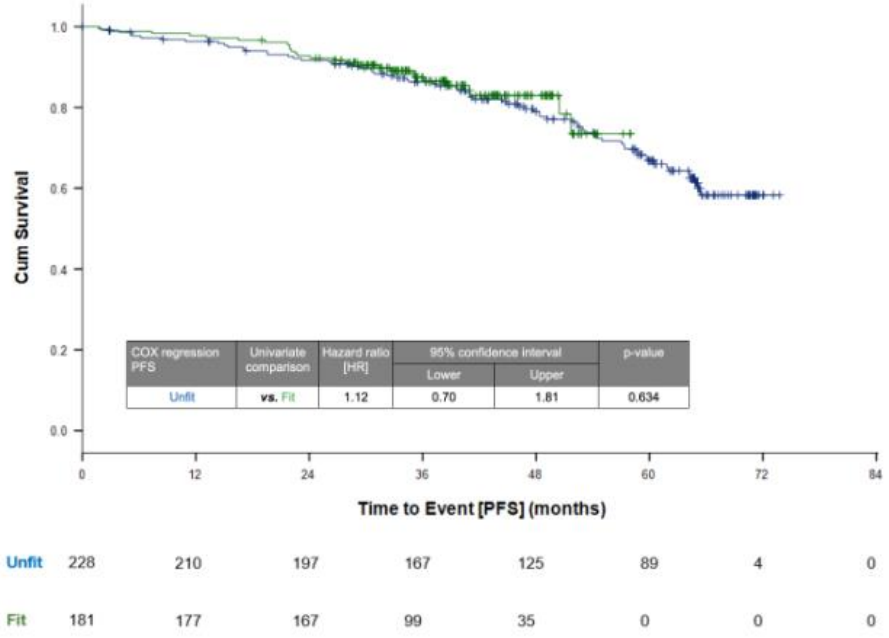
VENETOCLAX OBINUTUZUMAB: AE

CLINICAL TRIALS

CLL13 and CLL14 [1]



CLL13 and CLL14 [1]

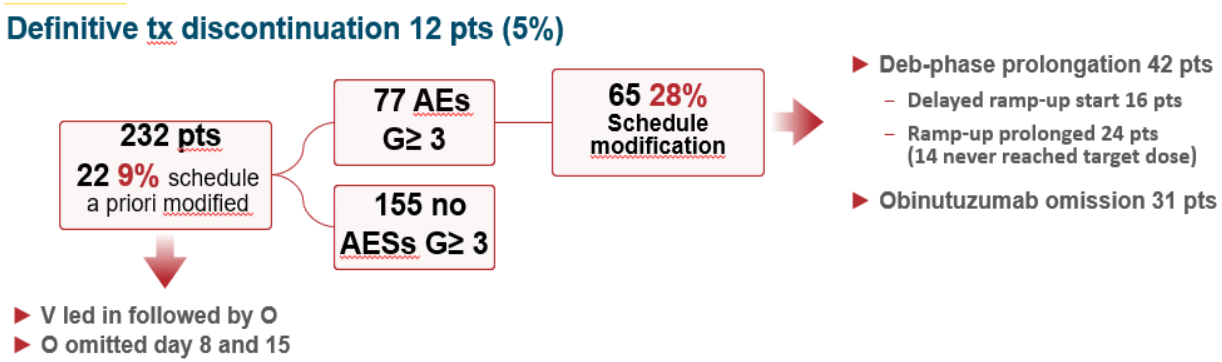


No substantial impact of fitness on toxicity and efficacy of Ven-Obi.

1 Al Sawaf O et al., IWCLL 2023

VENETOCLAX OBINUTUZUMAB

ITALIAN EXPERIENCE



Baseline factor	OR	95%CI	p
Tox-DTD			
Need of caregiver	4.2	1.2 - 13.6	0.02
Endocrine comorbidities	3.7	1.3 -10.1	0.01
Steroid>6days	4.9	1.9 - 13.3	0.001
Global feasibility			
Age	1.04	1.01 -1.08	0.01
IgG<700	1.78	1.0 - 3.19	0.058
Steroid>6days	2.54	1.27 - 5.1	0.008

Tedeschi et al., ASH 2023

VENETOCLAX IBRUTINIB: PFS

GLOW | OClb | IVen

Unfit No del(17p)/*TP53*^{mut}
Median Age 71y

CAPTIVATE (FD cohort) | IVen

FIT
Median Age 60 y

GLOW PFS by IRC (median follow-up 57 months)[1]

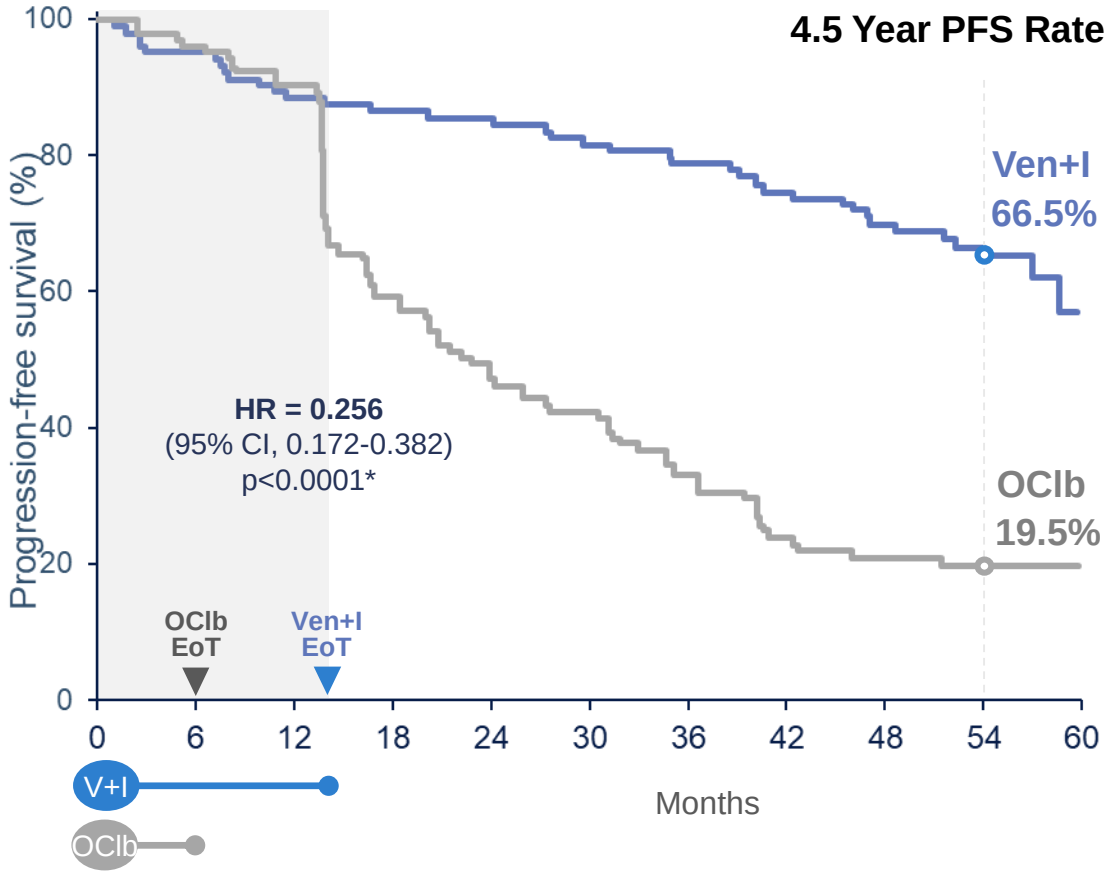


Figure adapted from reference 1.

CAPTIVATE PFS by INV (median follow-up 61.2 mo)[2]

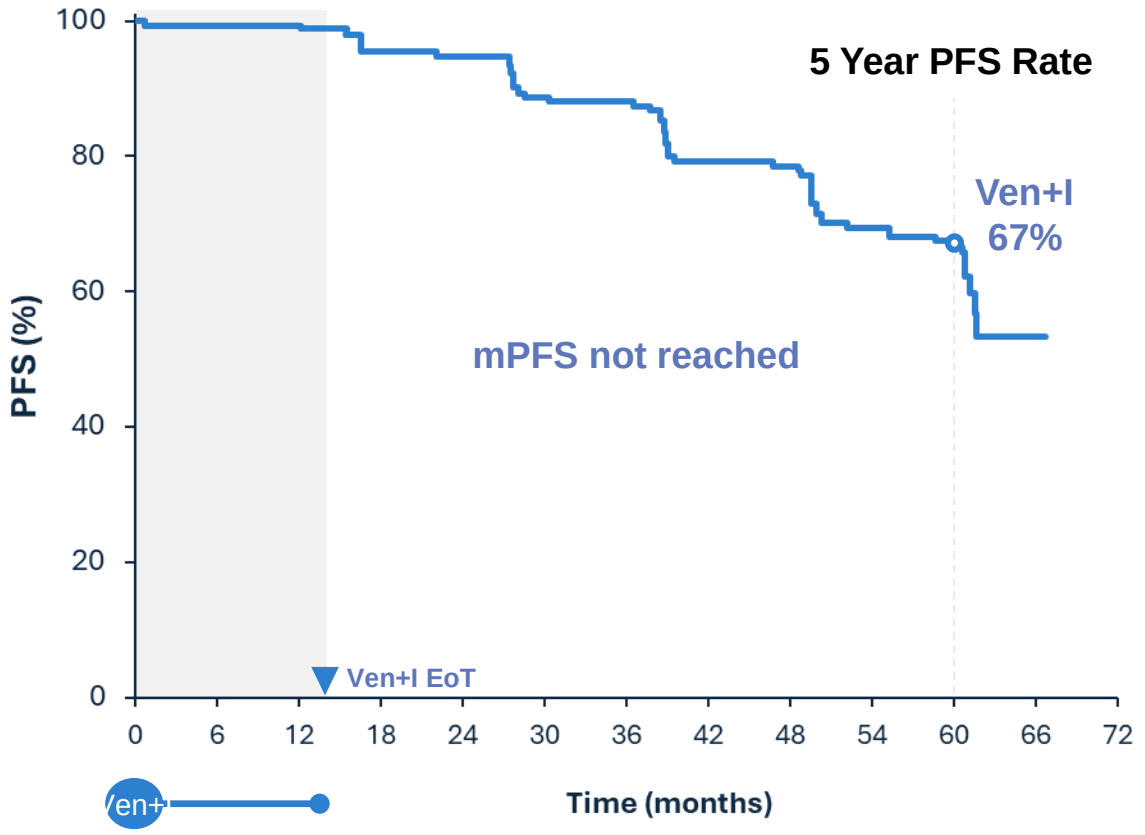


Figure adapted from reference 2.

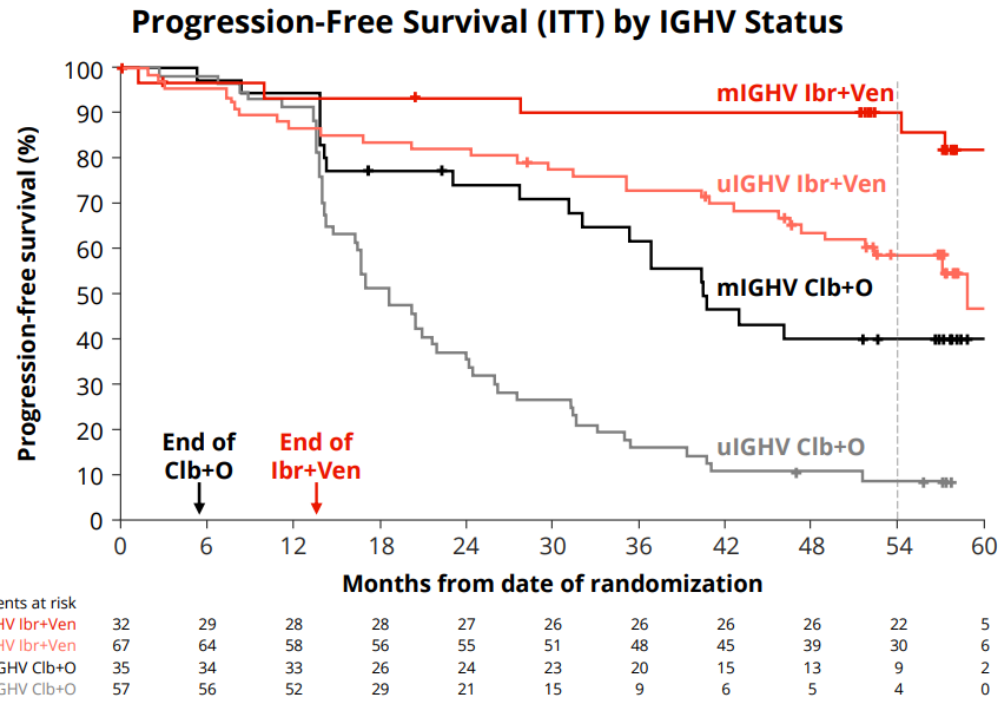
INV, Investigator; ITT, Intention to Treat; OClb, Obinutuzumab+Chlorambucil; Ven+I, Ibrutinib+Venetoclax.

1. Moreno C, et al. ASH 2023. Abstract 634 (Oral). 2. Wierda WG, et al. ASCO 2024. Abstract 7009 (Oral).

VENETOCLAX IBRUTINIB: GLOW study

Glow
Venetoclax Ibrutinib vs Chl obinutuxumab

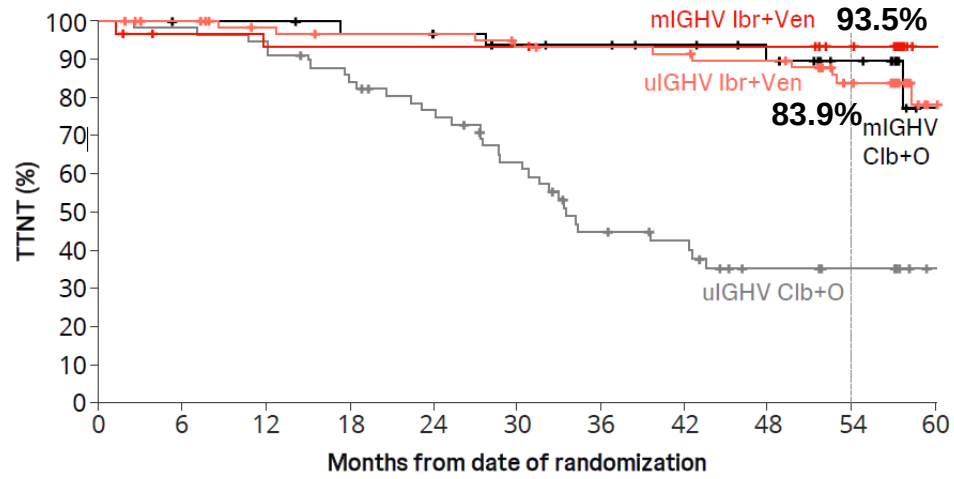
Median study follow-up: 57months



Patients at risk											
mIGHV Ibr+Ven	32	29	28	28	27	26	26	26	26	22	5
uIGHV Ibr+Ven	67	64	58	56	55	51	48	45	39	30	6
mIGHV Clb+O	35	34	33	26	24	23	20	15	13	9	2
uIGHV Clb+O	57	56	52	29	21	15	9	6	5	4	0

EHA2024 poster
6 y TTNT Extrapolation Curve for GLOW Study

TTNT by IGHV status at 54 mos FU



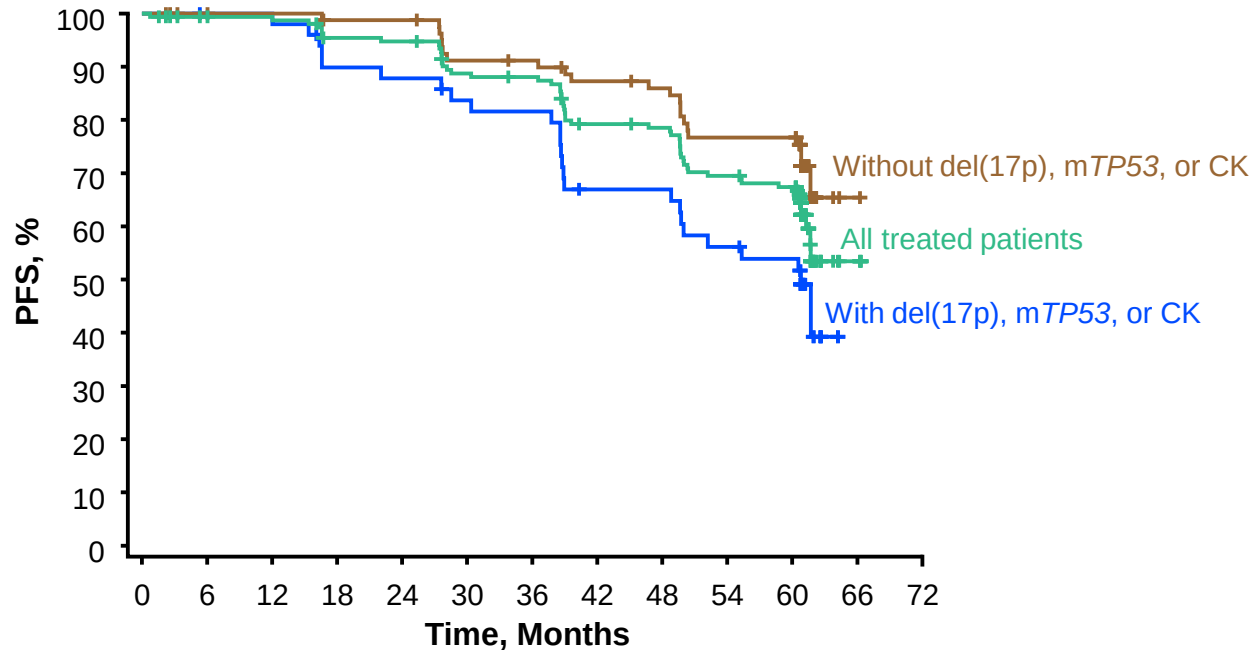
Patients at risk											
mIGHV Ibr+Ven	32	29	28	28	28	28	27	27	27	23	6
uIGHV Ibr+Ven	67	64	59	57	57	54	53	52	50	41	11
mIGHV Clb+O	35	34	34	32	31	29	28	25	22	16	4
uIGHV Clb+O	57	56	52	47	41	32	21	18	11	9	3

Munir P et et al, ,ASH 2023

VENETOCLAX IBRUTINIB: Captivate study

PFS in All Treated Patients and by del(17p), m*TP53*, or CK Status

Median time on study: 61.2 months (range, 0.8–66.3)



Patients at risk

All treated patients	159	153	152	144	143	132	130	115	113	100	96	3	0
With del(17p), m*TP53*, or CK	51	50	50	44	43	40	39	31	31	26	24	0	
Without del(17p), m*TP53*, or CK	86	82	81	79	79	72	71	67	65	58	58	1	0

PFS by IGHV Mutation Status (Excluding Patients With del(17p), m*TP53*, or CK)

	5-Year PFS Rate, % (95% CI)
uIGHV (n=40)	68 (50–80)
mIGHV (n=44)	85 (69–93)

NT: Up to 5.5 Years of Follow-Up

In total, 202 pts completed fixed-duration
(FD cohort, N=159; MRD cohort placebo arm, n=43)

↓

63 pts (31%) PD to date
PD occurred >2 y after EOT in most pts (43/63; 68%)

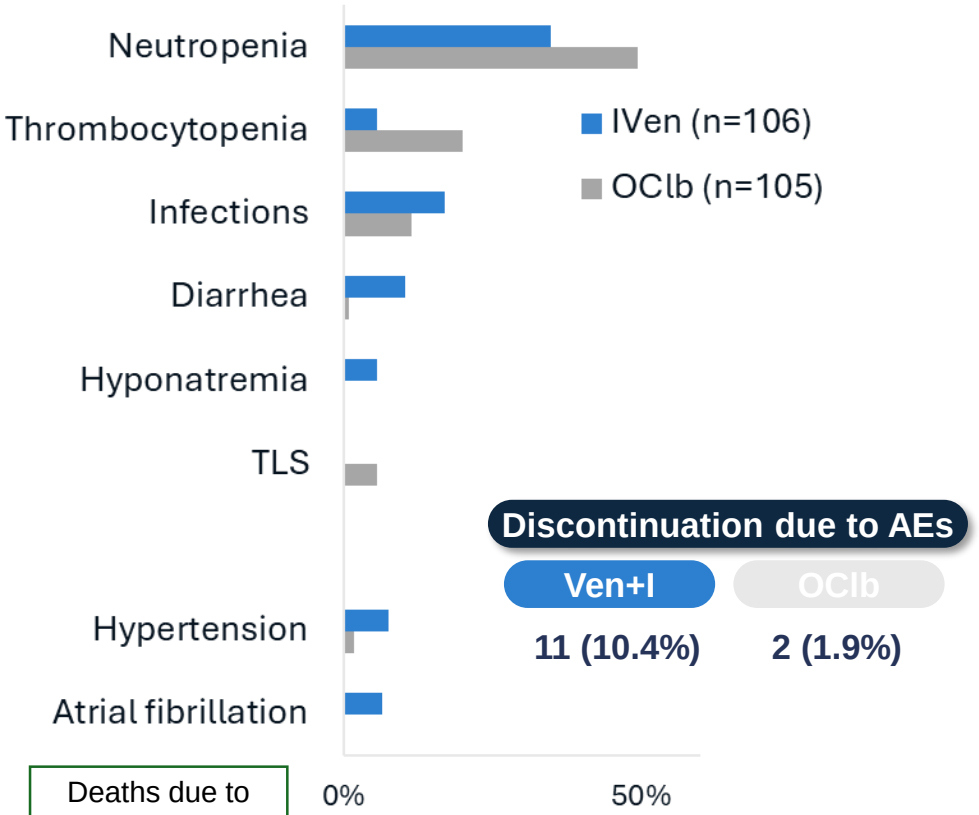
↓

32 pts (16%) initiated retreatment

Wierda et al ASCO 2024

VENETOCLAX IBRUTINIB

GLOW Grade ≥3 AEs[1]

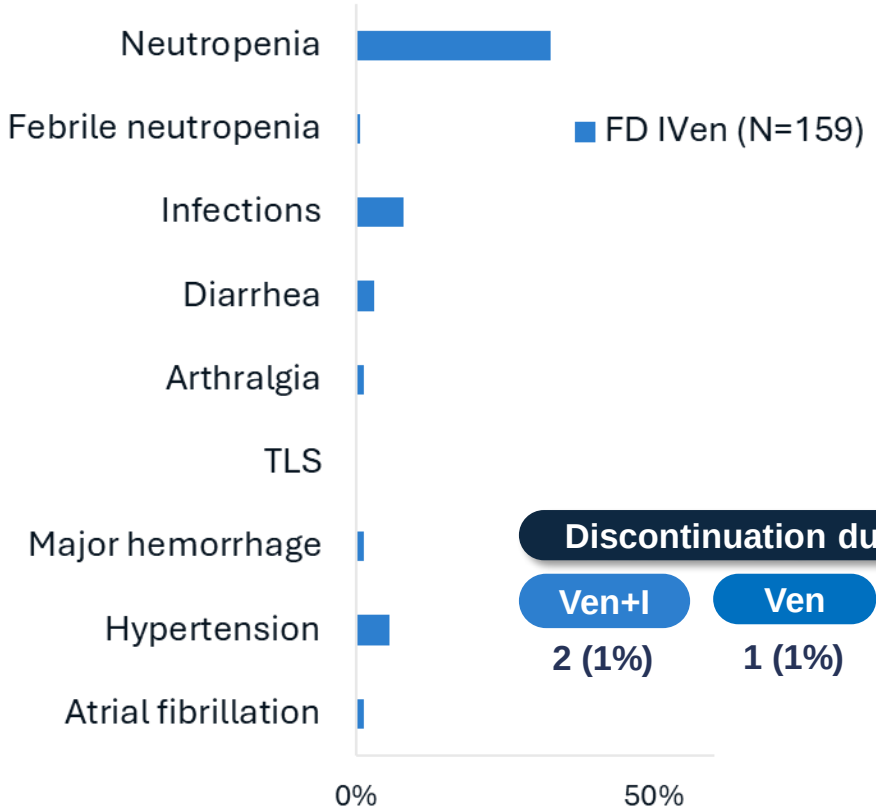


Discontinuation due to AEs

Ven+I	OClb
11 (10.4%)	2 (1.9%)

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

CAPTIVATE Grade ≥3 AEs[2]



Discontinuation due to AEs

Ven+I	Ven	Ibr
2 (1%)	1 (1%)	5 (3%)

Figure adapted from reference 1.

uMRD cutoff = 10^{-4}

1. Kater et al, *NEJM Evid* 2022; **1**(7). 2. Tam CS, et al. *Blood* 2022; **139**:3278–3289.

FIXED DURATION TREATMENT

TREATMENT FREE PERIOD

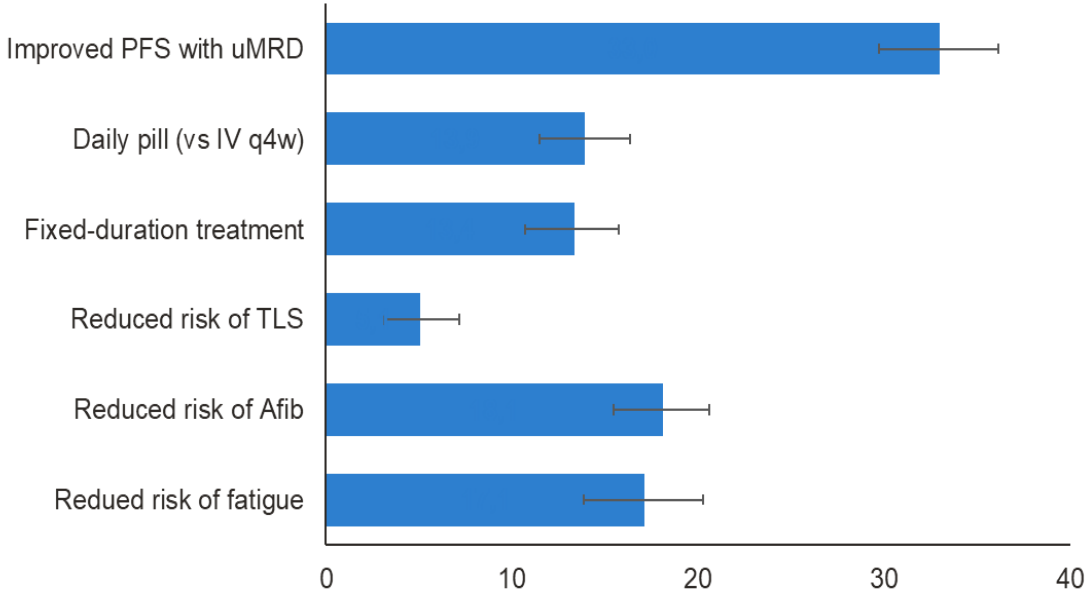
- allows immune recovery

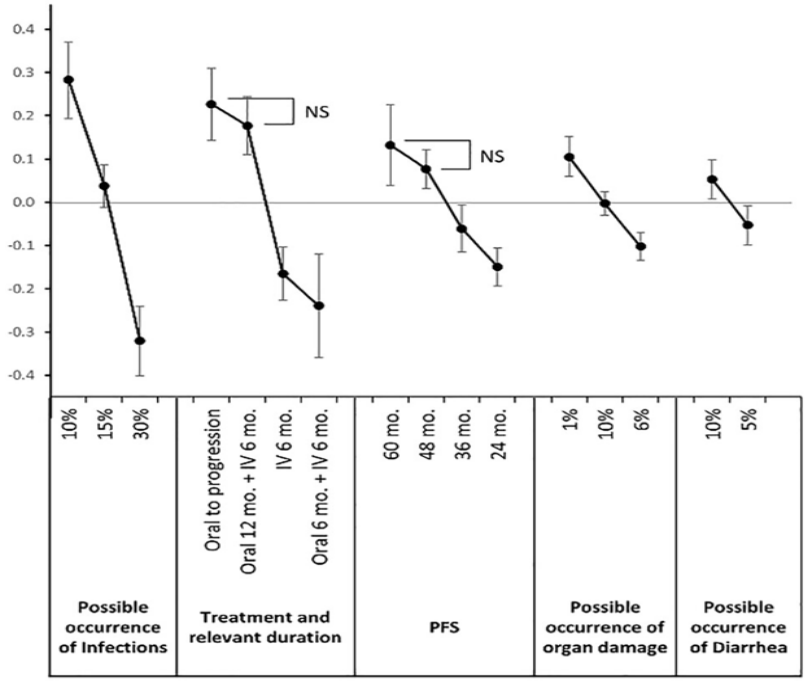
FIXED DURATION TREATMENT

- ***Patients perception***
- ***Quality of Life/ Improvement in the physical and emotional health in treatment-free patients***

Current treatment options cannot fully meet all patient preferences at once

Conditional relative attribute importance for pts (N=229)



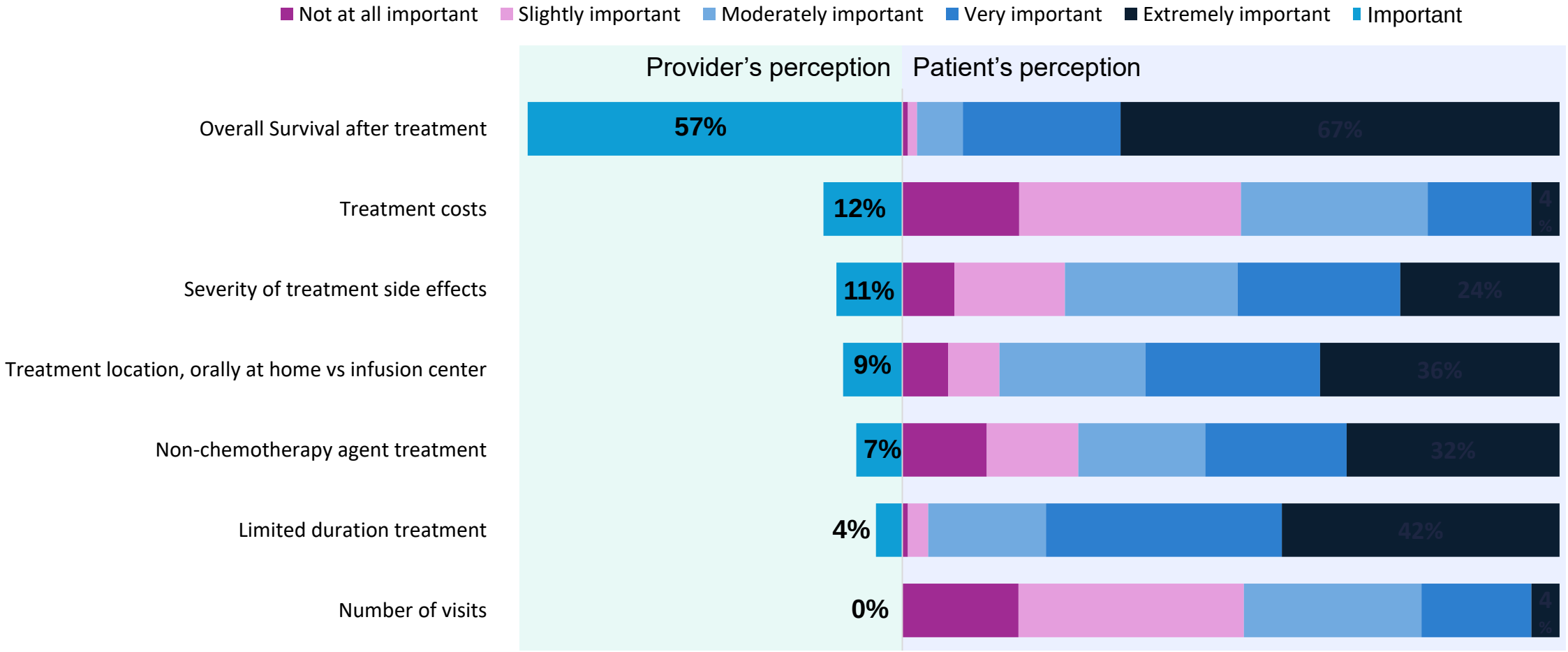


Ravelo A, et al. *Blood.* 2022;140(Supplement 1):10803–10805.

Sportoletti P et et al,, Hemato Oncol 2023

FIXED DURATION TREATMENT

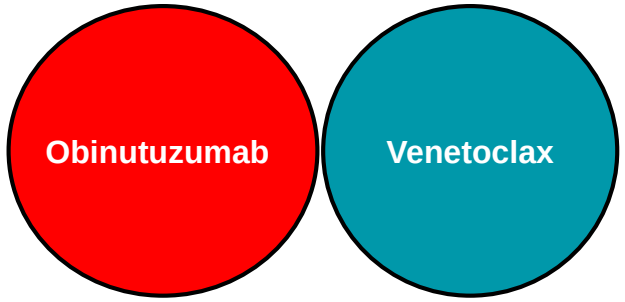
- ***Patients perception***
- ***Quality of Life/ Improvement in the physical and emotional health in treatment-free patients***

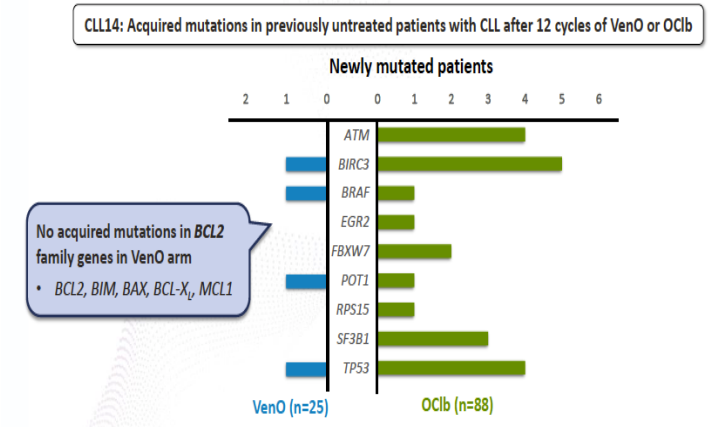


ACCC. Are we speaking the same language. Insights from a patient and provider survey on CLL. Dec. 2022. https://www.accc-cancer.org/projects/cll-care/overview.
CLL Society: https://cllsociety.org/2022/12/are-we-speaking-the-same-language-insights-from-a-patient-and-provider-survey-on-cll-chronic-lymphocytic-leukemia/

FIXED DURATION IN TN PATIENTS AND RETREATMENT

✓ **No Resistance Development At 1 y**





Tausch E, et al. EHA 2021; Abstract S144 (Oral)

ReVenG study: efficacy of fixed duration VenO retreatment in patients with CLL after prior Ven-based therapy

ACTIVELY RECRUITING PHASE 2

ReVenG:
VenO re-treatment in patients with relapsed CLL who received 1L Ven + anti-CD20 ± X* and achieved a clinical response (CR, CRi, PR, or nPR) without intervening treatment after 1L therapy (N=75)[1]

Cohort 1
Patients who progressed >24 mo after 1L Ven + anti-CD20 ± X* completion

N~60

- Venetoclax 12C†
- Obinutuzumab 6C†

Cohort 2
Patients who progressed ≥12–24 mo after 1L Ven + anti-CD20 ± X* completion

N≤15

- Venetoclax 24C†‡
- Obinutuzumab 6C†

Primary endpoint:

ORR at EoCT
(3 months after completing 6 cycles of VenO[1])

Key secondary endpoints (Cohort 1):

- CR/CRi at EoCT and EoT
- ORR at EoT
- uMRD at EoCT and EoT
- PFS
- OS
- TTNT
- Safety

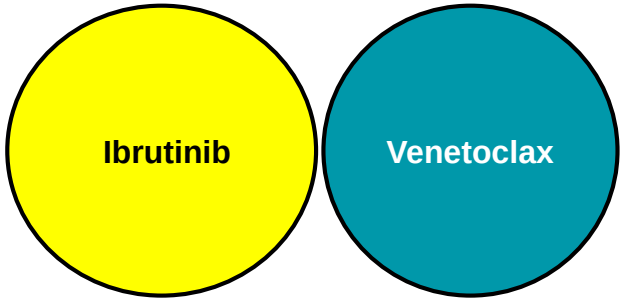
Exploratory endpoints (Cohort 2):

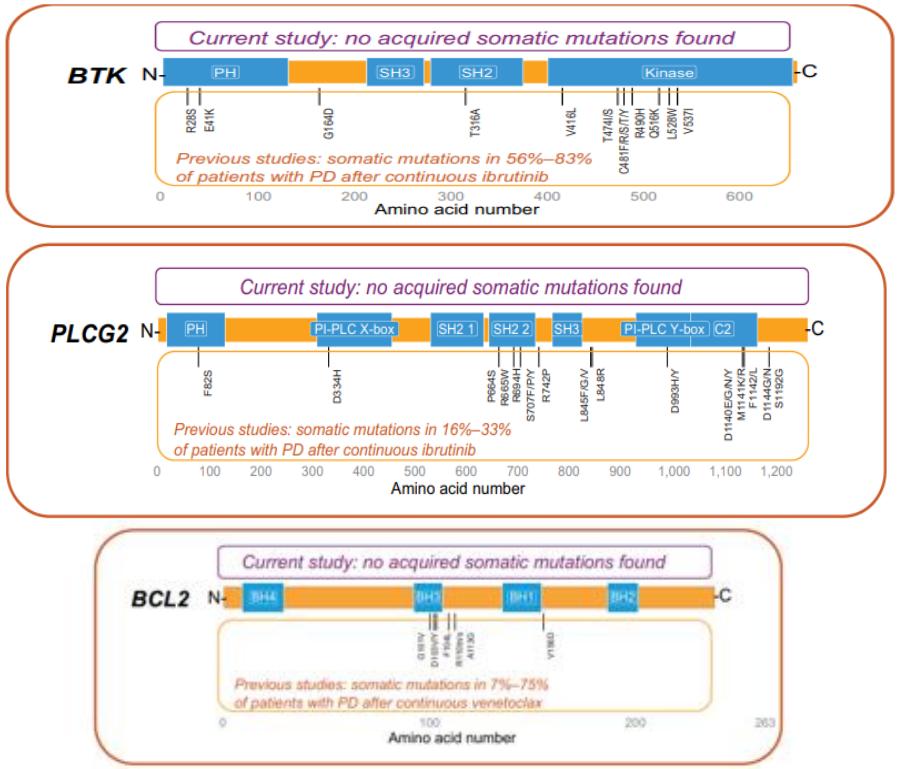
- PROs
- MRD kinetics ≤12 months post treatment
- Correlations of IGHV, *TP53* mutation, and del(17p) at baseline with treatment outcomes

1. ClinicalTrials.gov. NCT04895436 (accessed April 2024);
2. Davids M, et al. ASH 2021. Abstract 2634 (Poster).

FIXED DURATION IN TN PATIENTS AND RETREATMENT

✓ **No Resistance Development At 1 y**





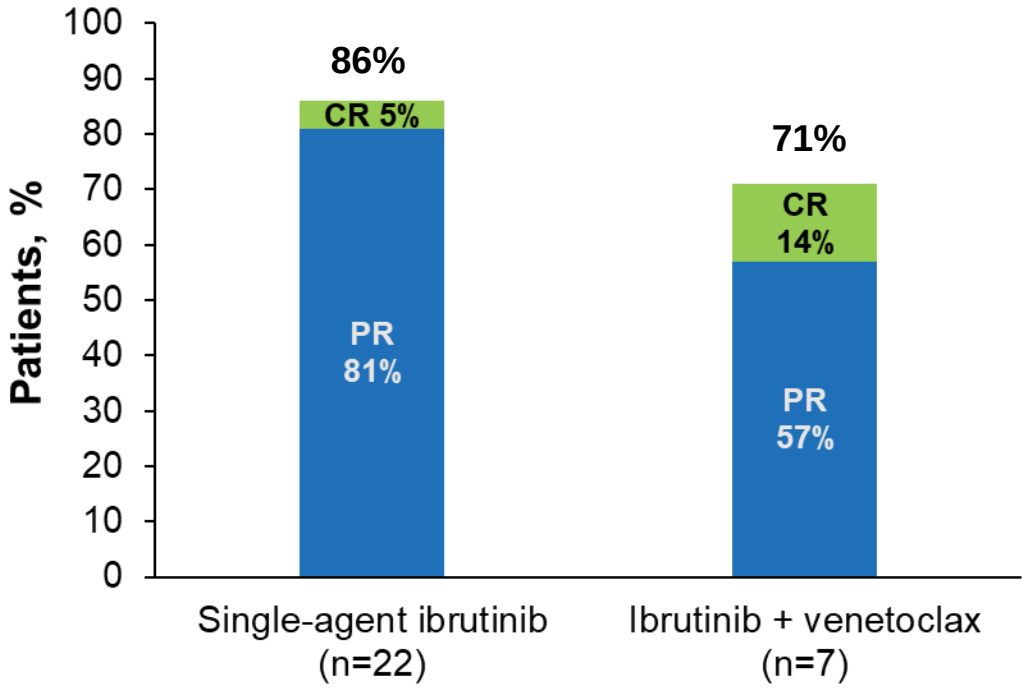
Responses Observed With Ibrutinib-Based Retreatment

- Of 61 patients with CLL PD after completion of fixed-duration ibrutinib + venetoclax, 32 (52%) initiated retreatment with single-agent ibrutinib (n=25) or ibrutinib + venetoclax (n=7)[a]
- Median time on retreatment on study:
  - 21.9 months (range, 0.0–50.4) for single-agent continuous ibrutinib
  - 13.8 months (range, 3.7–15.1) for 15-month fixed-duration ibrutinib + venetoclax[a,b]

Study Entry Baseline Characteristics: Retreated Patients

Characteristic	Single-agent ibrutinib (n=25)	Ibrutinib + venetoclax (n=7)	All Retreated Patients (n=32)
Median age (range), years	56 (39–71)	63 (49–69)	59 (39–71)
Male, n (%)	15 (60)	6 (86)	21 (66)
Rai stage III/IV, n (%)	4 (16)	2 (29)	6 (19)
High-risk genomic features, n (%)			
Unmutated IGHV	20 (80)	5 (71)	25 (78)
del(17p)/mutated *TP53*	5 (20)	5 (71)	10 (31)
del(11q)[d]	6 (24)	1 (14)	7 (22)
Complex karyotype[e]	9 (36)	2 (29)	11 (34)
Bulky LN disease ≥5 cm, n (%)	10 (40)	1 (14)	11 (34)

Best Response in Evaluable Patients to Date[c]



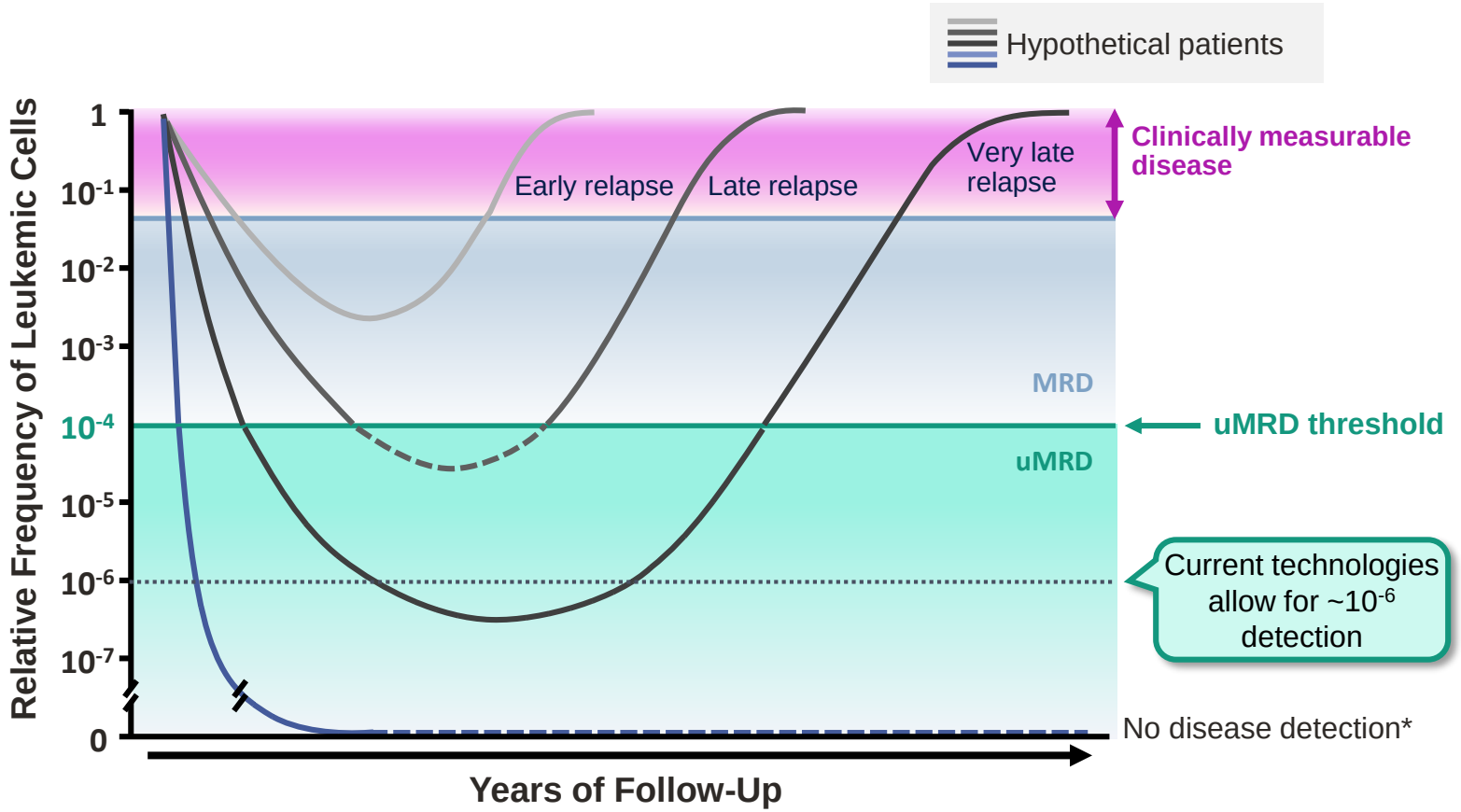
Wierda et al ASCO 2024

FIXED DURATION

…….HOW LONG?

Potential Solution: MRD-guided approach

Hypothetical disease outcome based on depth of response[1-3]



Pros

- Gives options for patients who have residual disease after a fixed treatment duration; more tailored treatment
- Still allows limited-duration therapy
- Can minimize unnecessary drug exposure
- Methods have been standardized

Cons

- Not available for all HCPs
- Gives variabilities for treatments, making it more complicated
- Adds extra testing and monitoring burden
- FTD may be sufficient in most cases

Trial Examples

- CAPTIVATE MRD arm (Ven+I)[4]
- FLAIR (Ven+I vs FCR)[5]
- AVO[6]
- MAJIC (Ven+Acala vs VenO)[7]
- MIRACLE (Ven+Pirto)[8]
- BruVenG (Ven+Zanu±O)[9]

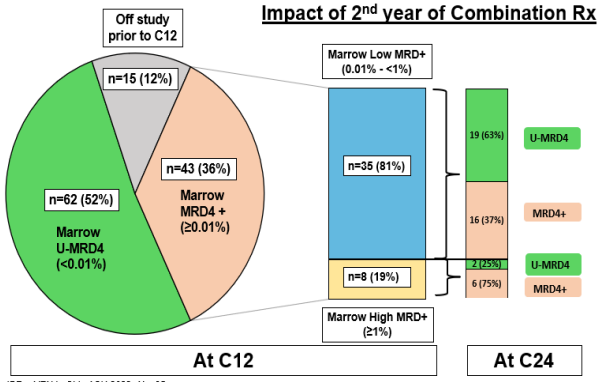
- *No limit of detection has been established to be indicative of a cure.

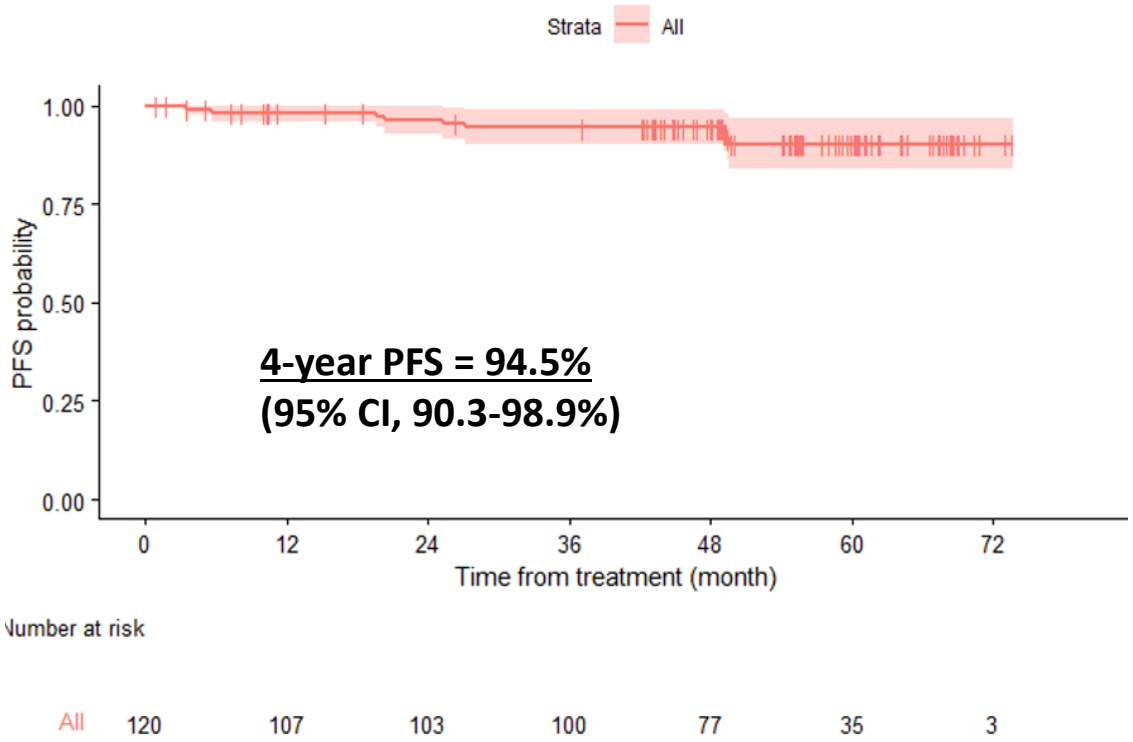
- 1. Szczepański T, et al. *Lancet Oncol.* 2001; 2:409–417. 2. Böttcher S, et al. *J Clin Oncol.* 2012; 30:980–988. 3. Böttcher S, et al. *Hematol Oncol Clin North Am.* 2013; **27**:267–288. 4. Wierda WG, et al. *J Clin Oncol*. 2021;**39**(34):3853. 5. Hillmen P, et al. EHA 2022. Abstract S145 (Oral). 6. Ryan CE, et al. *Blood.* 2022; **140**(Suppl 1):837–838 (Oral). 7. MAJIC: NCT05057494. 8. MIRACLE: NCT05677919. 9. BruVenG: NCT05650723

I plus V: Phase 2 MD Anderson Cancer Center Trial

<u>Duration of therapy</u>: 24 cycles of combined IBR and VEN

Marrow MRD (flow cytometry) at end of cycle 24 of combined Rx
- **Negative (<0.01%): Stop both IBR and VEN**
- **Positive (≥0.01%): Continue 12 additional cycles of IBR + VEN**





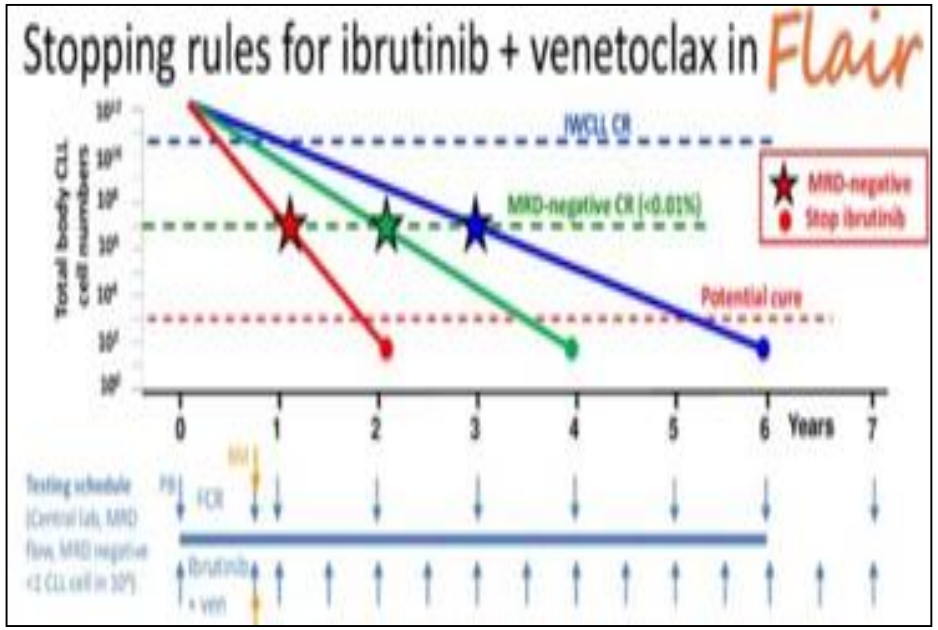
<u>4-year PFS = 94.5%</u>
(95% CI, 90.3-98.9%)

Group	4-year PFS	Lower CI	Upper CI
ighv2=Mutated	100%	100%	100%
ighv2=Unmutated	93.44%	88.49%	98.66%

Group	4-year PFS	Lower CI	Upper CI
tp53.aber=No	95.47%	91.22%	99.91%
tp53.aber=Yes	90.91%	79.66%	100%

Jain N et al 2022

FLAIR: stopping rules and MRD



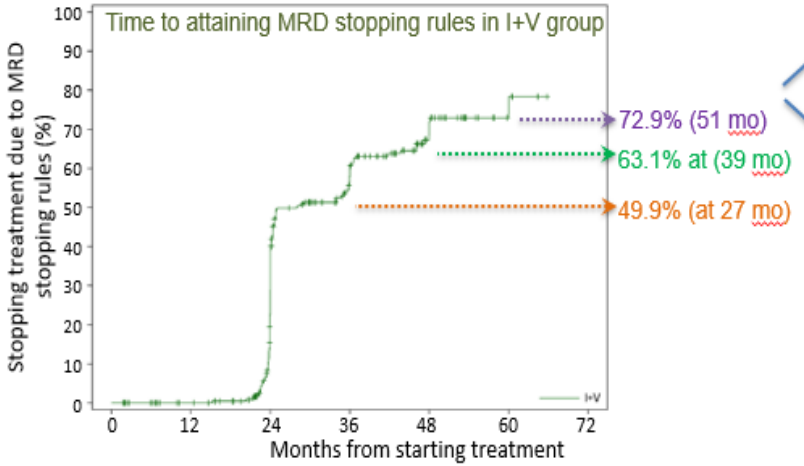
Flair iwCLL response and MRD stopping rules

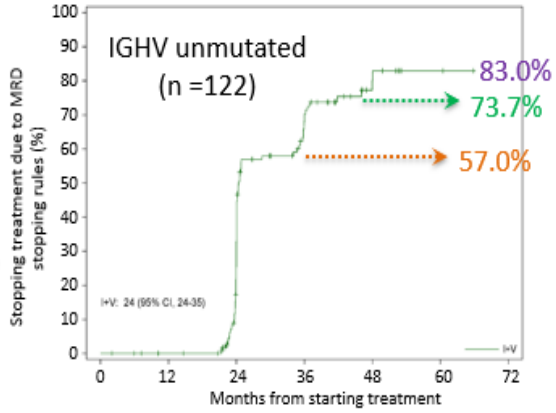
iwCLL Responses

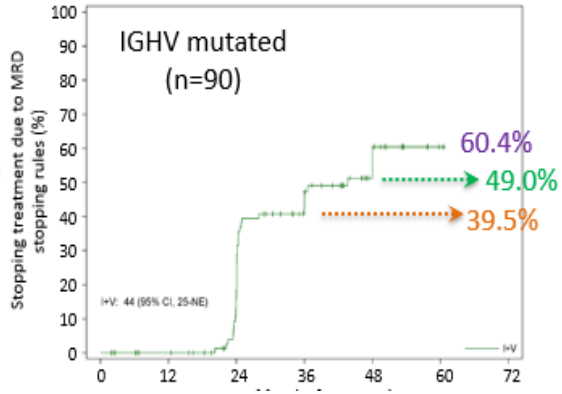
	Complete Response/CRi		Overall Response		BM uMRD
	9 months	Anytime	9 months	Anytime	Anytime
FCR	49%	71.5%	76.4%	83.7%	40.3%
I+V	59.2%	92.3%	86.5%	95.4%	61.9%

Odds ratio: 1.51 P<0.05

Odds ratio: 2.0 P<0.005

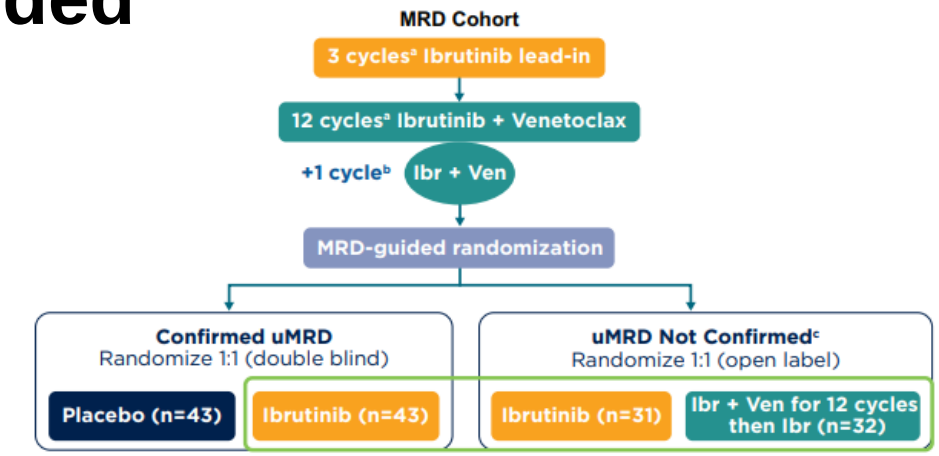




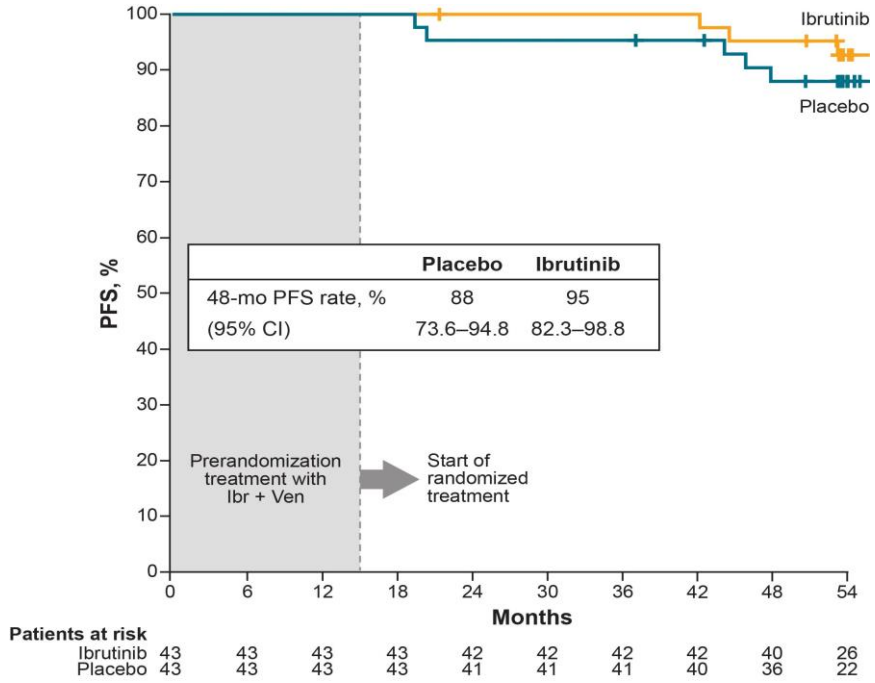


Hillmen et al ASH 2023

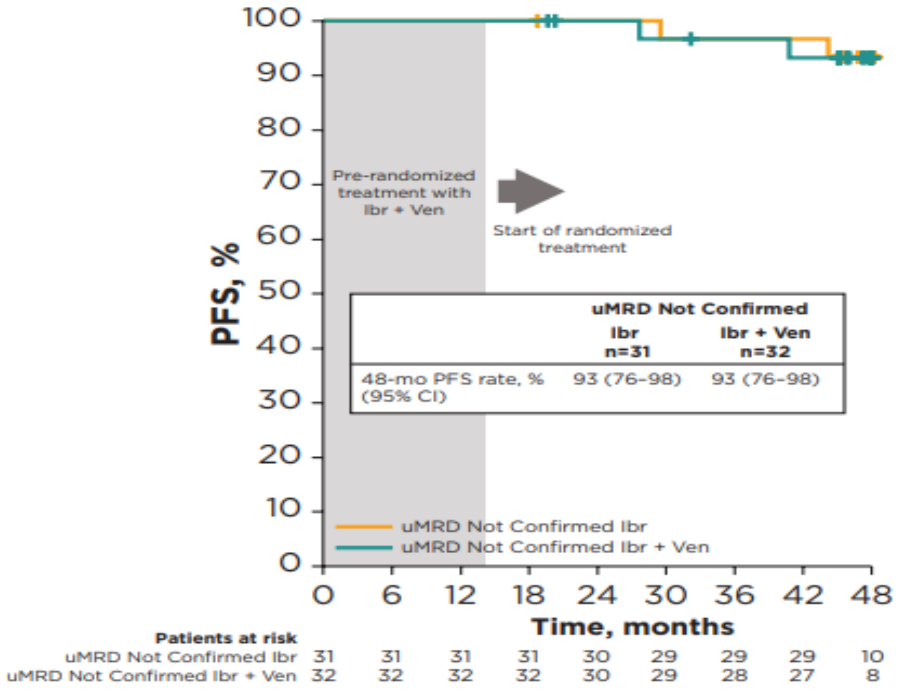
CAPTIVATE: MRD guided



CONFIRMED uMRD



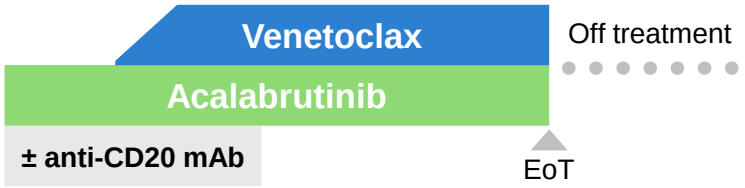
uMRD NOT CONFIRMED



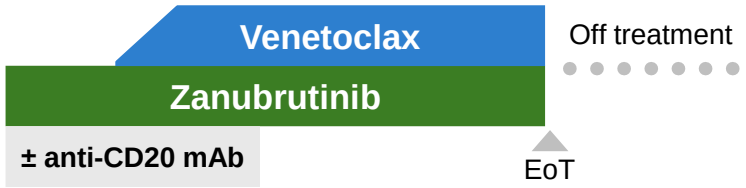
Aillan et al 2022

Siddiqi T et al 2023

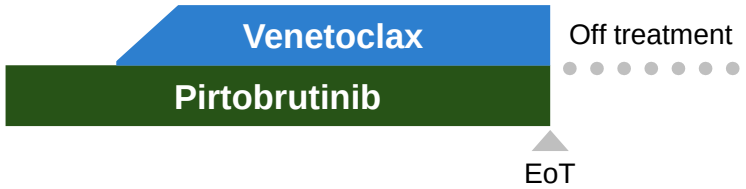
Select Ongoing Venetoclax + X Trials



Ven+Acala trials	Ph	n	Patient population	Comparator arm(s)	Latest results
AVO[6]	2	72	TN	--	No PD at 19-mo mF/U
AMPLIFY[7]	3	780	TN, *TP53* wildtype	FCR/BR	Q4 2026
MAJIC[8]	3	602	TN	VenO	Q3 2026



Ven+Zanu trials	Ph	n	Patient population	Arms	Latest results
BruVenG[9]	2	50	TN	Ven+Zanu, Ven+Zanu+Obin	Q4 2027 (est.)
SEQUOIA ArmD[10]	3	66	TN, with del(17p)	Ven+Zanu, Zanu, BR	Est. 36-mo PFS: 92%

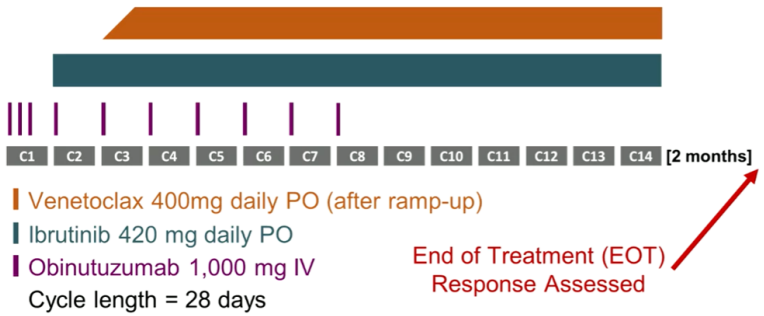


Ven+Pirto trial	Ph	n	Patient population	Arms	Latest results
CLL18[11]	3	813	TN	VenO, FD VenP, MRD-guided VenP	N/A

1. Kater AP, et al, *NEJM Evid.* 2022;**1**(7). 2. Moreno C, et al. ASH 2023. Abstract 634 (Oral). 3. Tam CS, et al. *Blood.* 2022;**139**(22):3278-3289. 4. Wierda WG, et al. ASCO 2024. Abstract 7009 (Oral). 5. CLL17: NCT04608318.
6. Ryan CE, et al. *Blood.* 2022; 140(Suppl 1):837–838 (Oral). 7. AMPFILY: NCT03836261. 8. MAJIC, NCT05057494. 9. BruVenG, NCT05650723. 10. Ghia P, et al. EHA 2024. Abstract S160 (oral). 11. Cramer P, GCSLC International Workshop 2024.

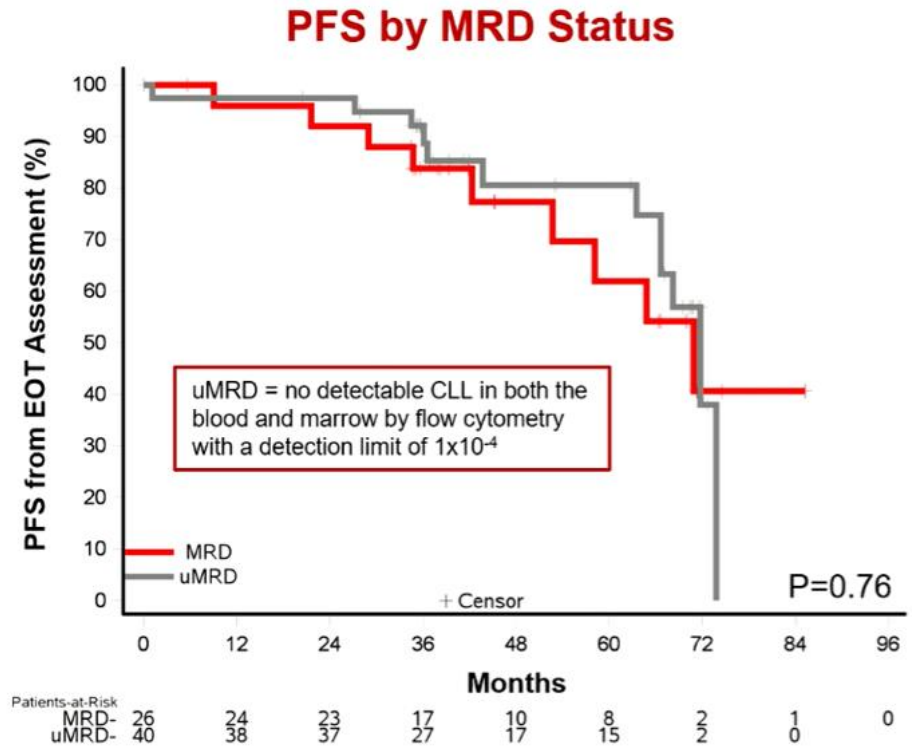
7-year Update on a Phase 2 Trial of Fixed-Duration Obinutuzumab, Ibrutinib, and Venetoclax for CLL

Study Treatment Diagram



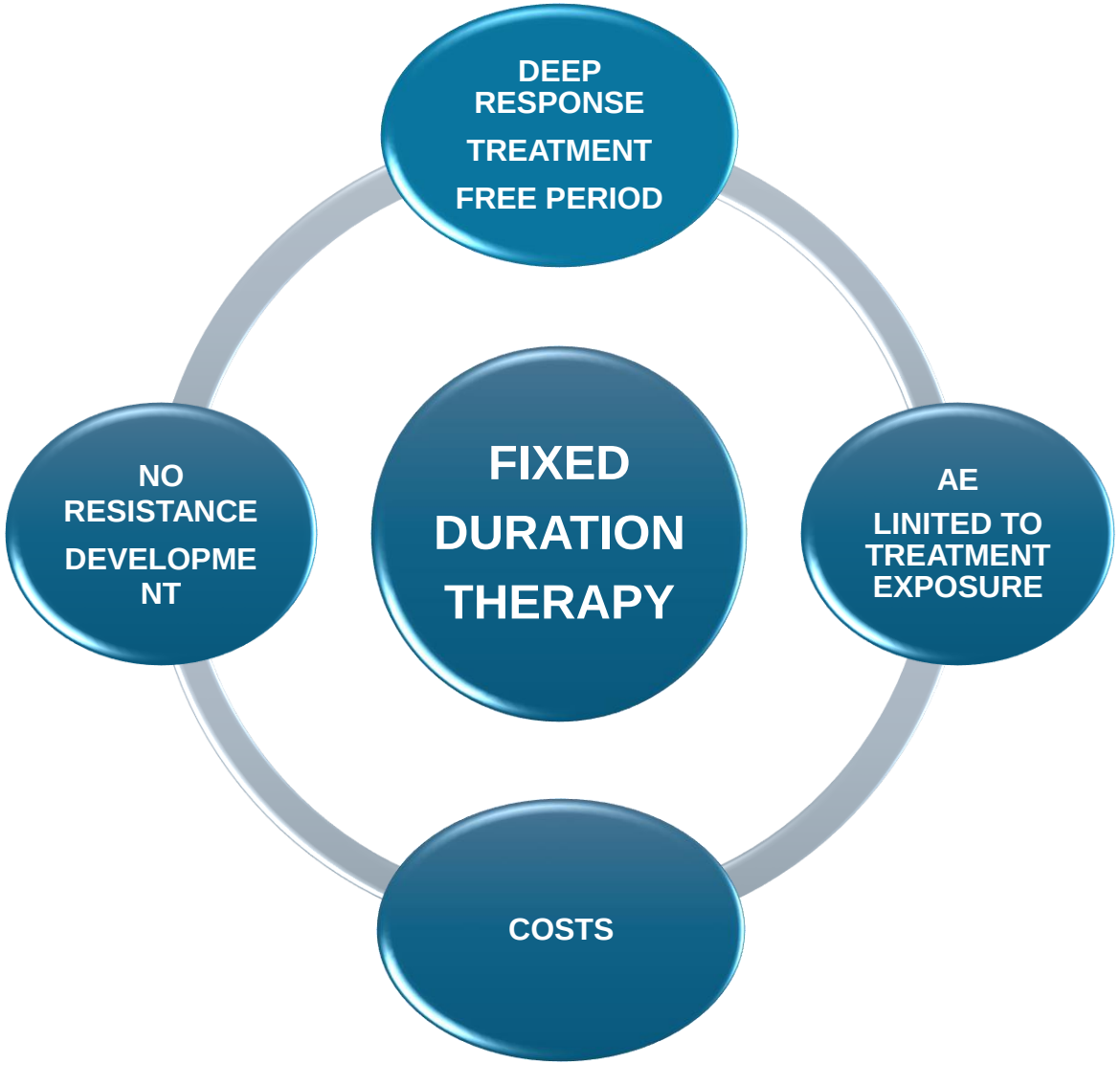
- Median PFS for **RR** was **81.8 months** (95% CI 57.3-NR)
- Median PFS for **TN1** was **88.5 months** (95% CI 80.6-NR)
- For **TN2** the median PFS was **not reached**, and the 48-month estimate was 91% (95% CI: 71.1-97.9)

Landmark Analysis of PFS by uMRD Status at EOT



- PFS was determined from EOT by MRD status
- 88% (66/75) of patients had MRD results and were included in the analysis
- There was no difference in PFS after treatment between patients with detectable vs uMRD

Rogers K A et al 2024



OPEN QUESTIONS

FIXED DURATION FOR ALL PTS?

FIXED DURATION:

- ✓ **MRD oriented?**
- ✓ **How Long is a FIIXED DURATION?**

RETREATMENT:

- ✓ **Early relpse/late relapse?**
- ✓ **Same target agent for every pt?**