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

- Nel paziente in prima linea

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università di ferrara
DA SEICENTO ANNI GUARDIAMO AVANTI.

REVOLUTIONARY ROAD IN CLL

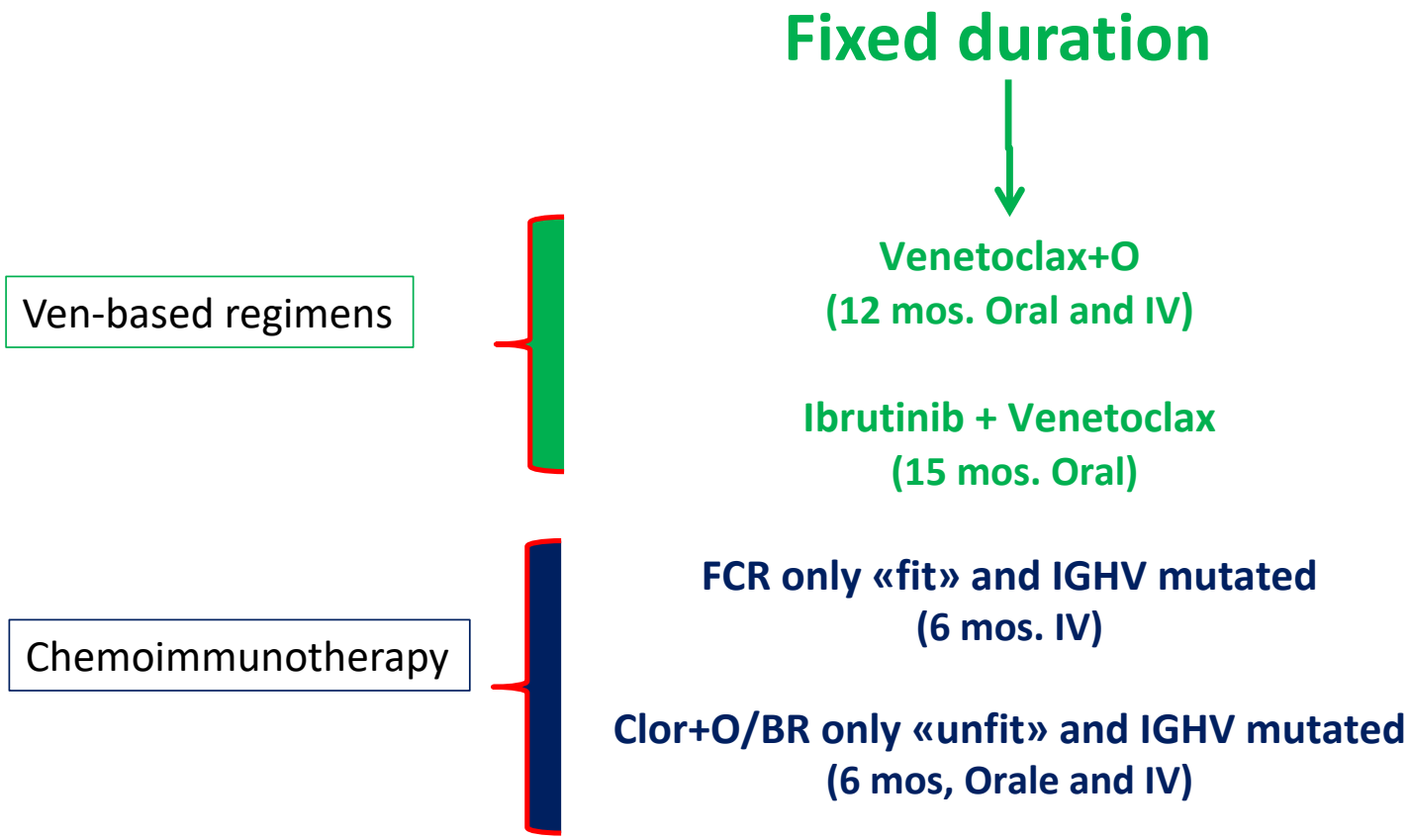
Innovazione rivoluzionaria nella terapia della leucemia linfatica cronica

Bologna, 20 maggio 2024
Royal Hotel Carlton

DISCLOSURE - Antonio Cuneo

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
Abbvie					X	X	
Astrazeneca					X	X	
Beigene					X	X	
Janssen					X	X	
Lilly					x	X	

Options for fixed duration therapy for first-line treatment of CLL



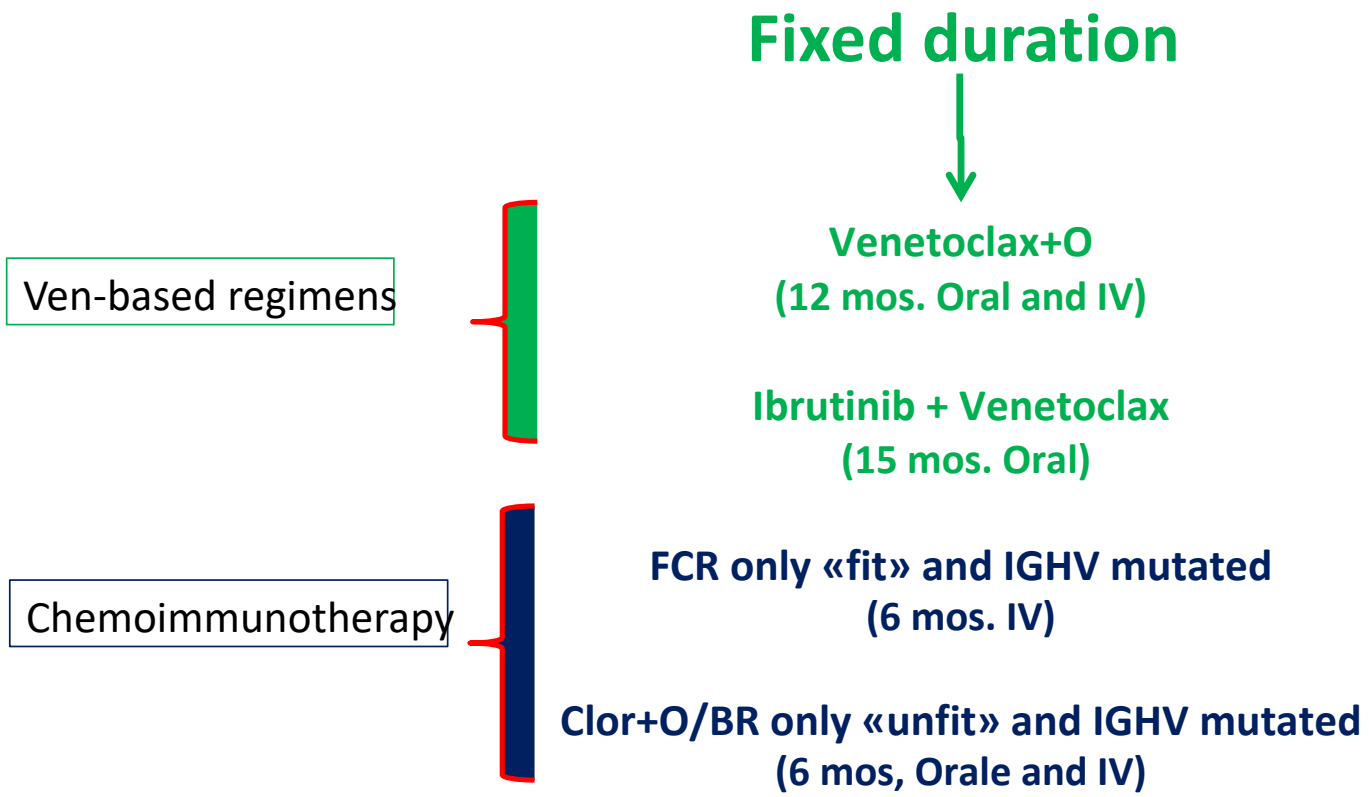
Assessing Adoption of Standard of Care and Comparing Clinical and Demographic Differences in First-Line Treatment of CLL

- Community oncologists since 2020
- Integra Connect PrecisionQ real-world de-identified database of over3 million cancer patients (pts) across 500 sites of care
- 1L tx of 6,328 CLL pts between 1/1/2020 and 6/30/2023

Drug Utilization in 1L: 2020 to June 2023					
		2020	2021	2022	Jan-Jun 2023
Drug Class	BTKI	1065 (55.8%)	1069 (56.6%)	984 (58.2%)	473 (56.3%)
	BCL2i	278 (14.6%)	305 (16.1%)	317 (18.7%)	166 (19.8%)
	aCD20	186 (9.8%)	107 (5.7%)	67 (4.0%)	44 (5.2%)
	Chemo	377 (19.8%)	409 (21.6%)	322 (19.0%)	156 (18.6%)
BTKi	acalabrutinib	330 (31.0%)	548 (51.3%)	613 (62.3%)	258 (54.5%)
	zanubrutinib	2 (0.2%)	13 (1.2%)	48 (4.9%)	124 (26.2%)
	ibrutinib	733 (68.8%)	508 (47.5%)	323 (32.8%)	91 (19.2%)

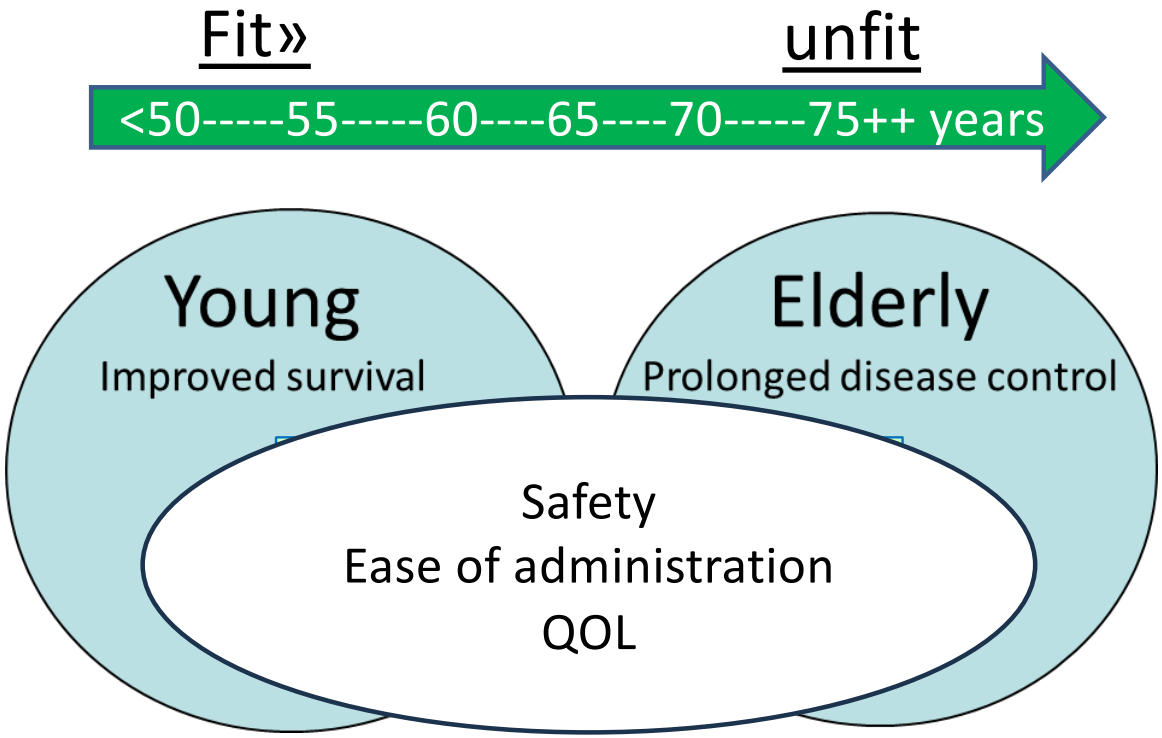
Jing-Zhou Hou - University of Pittsburgh Medical Center, Pittsburgh, PA

Options for fixed duration therapy for first-line treatment of CLL



- Any role for CIT?
- Ven based combinations
- MRD-guided treatment

Goals of treatment in CLL



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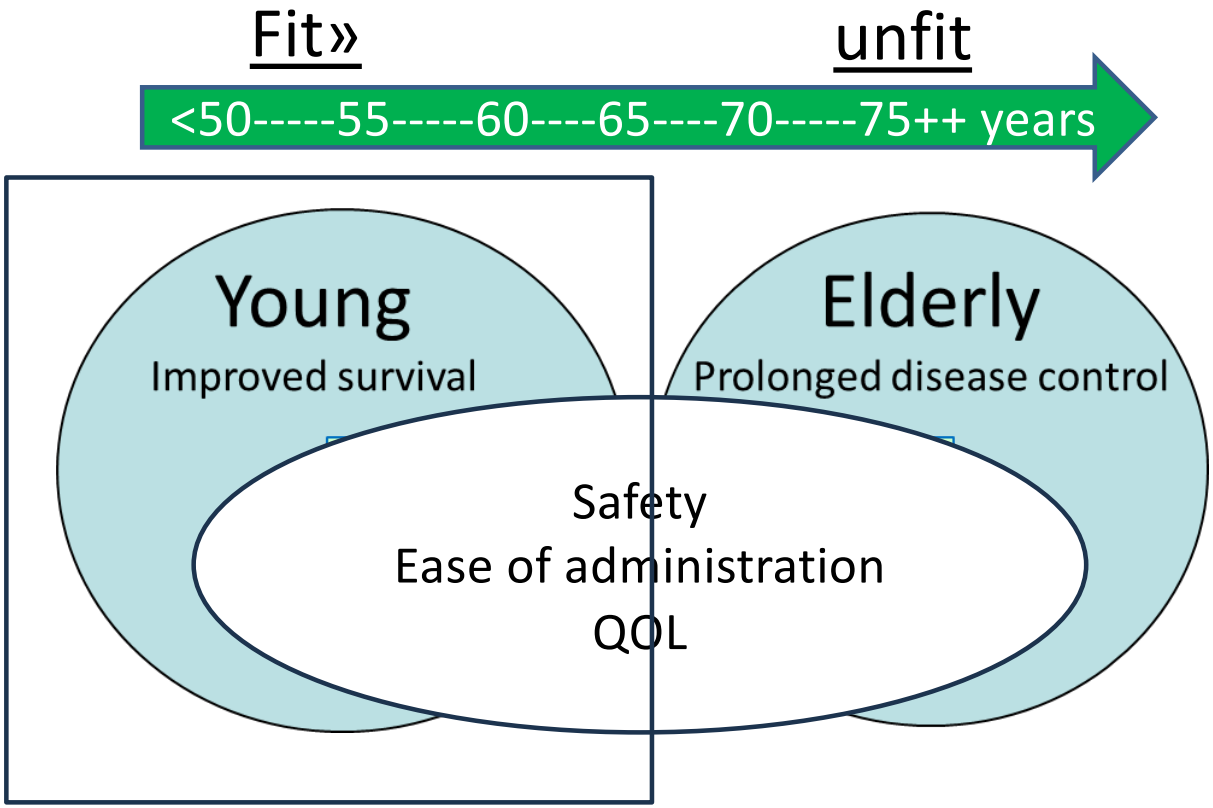
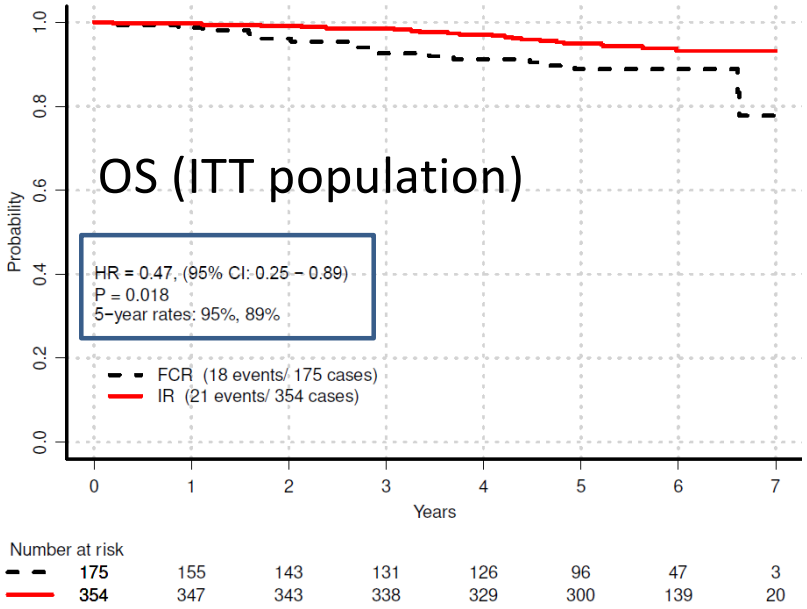


Improved **Overall survival** with Ibrutinib+Rituximab vs FCR: Updated Results of the E1912 Trial with a 5.8 years median follow-up

Ibrutinib 420 mg PO QD for cycles 1-7 +
Rituximab 50 mg/m² IV on Day 1, cycle 2, then 325 mg/mg² on Day 2, cycle 2, then 500 mg/m² on Day 1, cycles 3-7
(n = 354)

→ Ibrutinib

Fludarabine 25 mg/m² IV on Days 1-3 +
Cyclophosphamide 250 mg/m² IV on Days 1-3 for cycles 1-6 +
Rituximab 50 mg/m² IV on Day 1, cycle 1, then 325 mg/mg² on Day 2, cycle 1, then 500 mg/m² on Day 1, cycles 2-6
(n = 175)



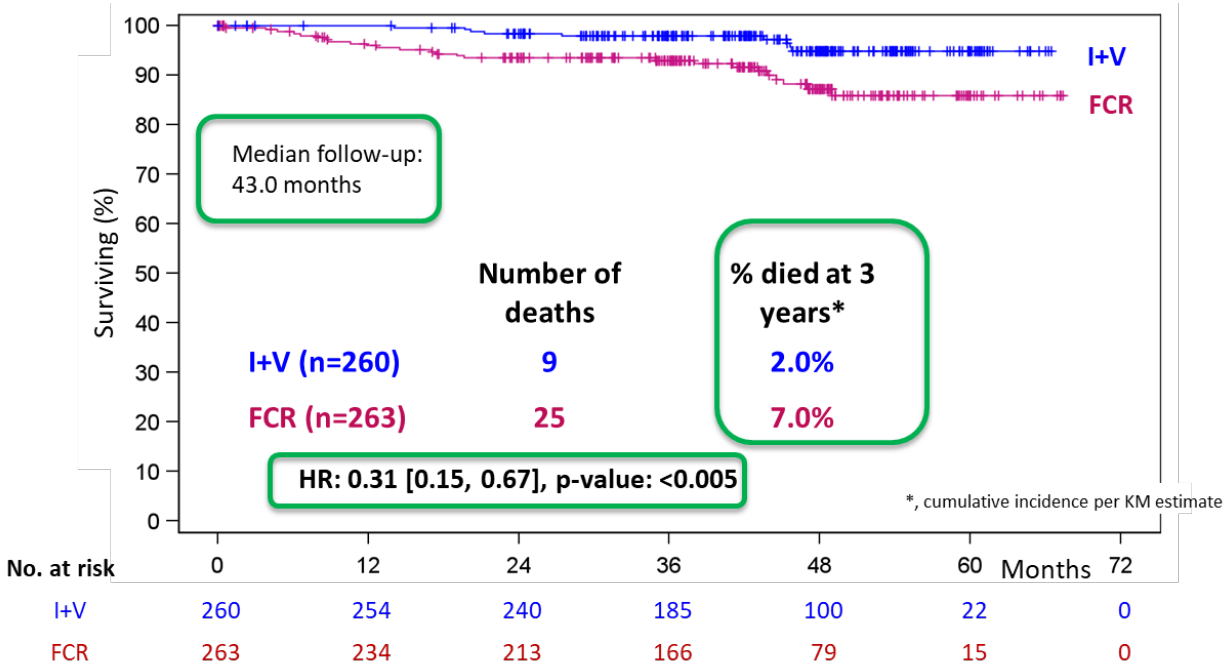
Supplemental Table 3a: Causes of Death

Cause of Death	IR (n=354)	FCR (n=175)
AML	0	3
Cardiac	1	1
CLL	5	6
COVID-19	3	0
Other cancer	5	3
Other cause	2	1
Other medical cause	3	2
Sepsis	1	1
Unknown	1	1
Total	21	18

1 cardiac death to date in E1912

Shanafelt. Blood 2022

Flair Safety and Toxicity: Deaths



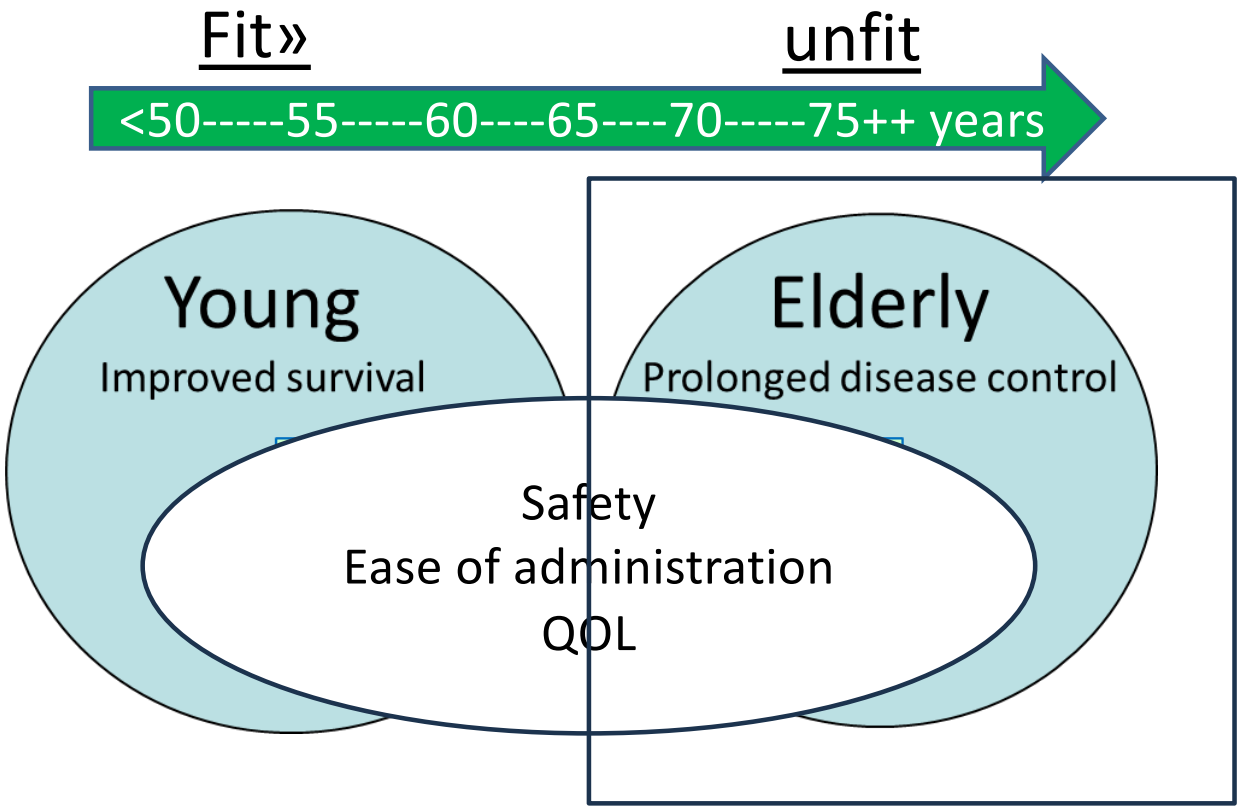
	FCR	I+V
Infection	7	1
Sudden/Cardiac	2	3
COVID-19	2	2
Richter's transformation	2	1
Non-haem malignancy	2	1
Allogeneic SCT – infection	1	0
Allogeneic SCT – GvHD	1	0
Disease progression	1	0
Hemorrhage	1	0
Lymphoma	1	0
Treatment related MDS/BMF	3	0
Total:	**23**	**8**

National Cancer Research Institute

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

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

Goals of treatment in CLL

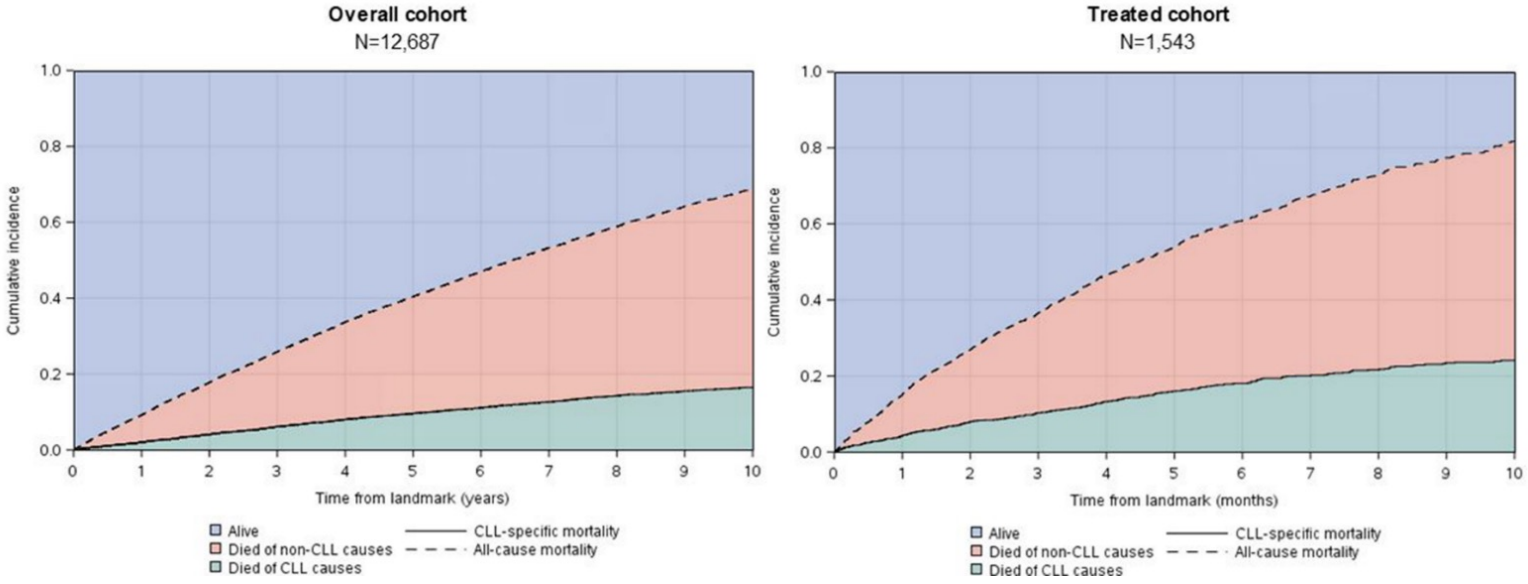


Prognosis of Older Adults with CLL By Comorbidity and Frailty: A SEER-Medicare Cohort Study:

Most older adults diagnosed with CLL die from non-CLL causes

- 12,687 patients (1,543 treated) patients.
- Mean age at diagnosis (SD) in the overall cohort was 77 (7.3) years

Figure. Landmark analysis of the cumulative incidence of mortality, broken down by cause of death. The blue section indicates the proportion of patients alive; the green section indicates the proportion of deaths attributed to CLL; the red section indicates the proportion of deaths attributable to other causes.



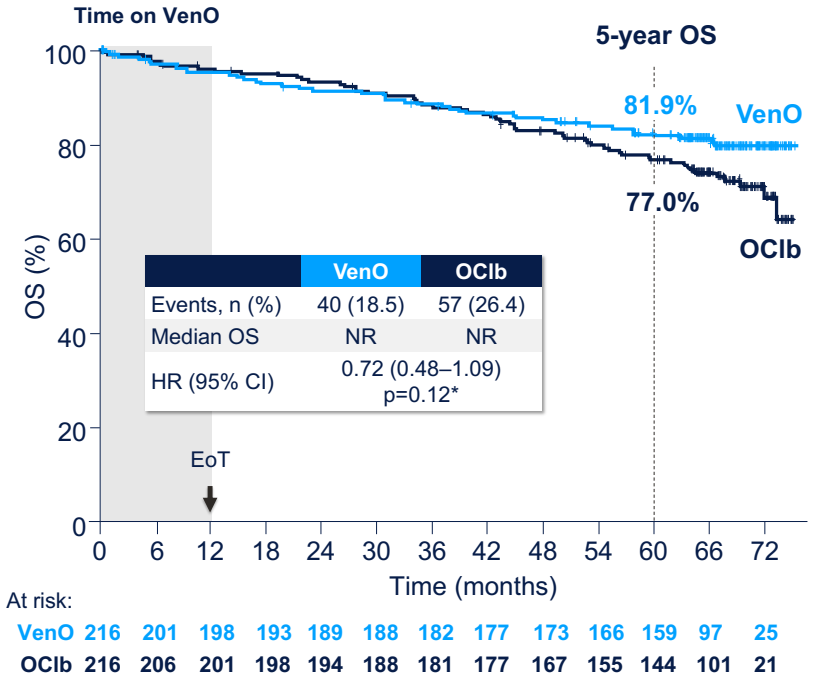
Emilie D Duchesneau, BA – Blood (2020) 136 (Supplement 1): 44–45.

5-y analysis
6-y analysis

Overall survival

8 November 2021[1]

Median follow-up: 65.4 months



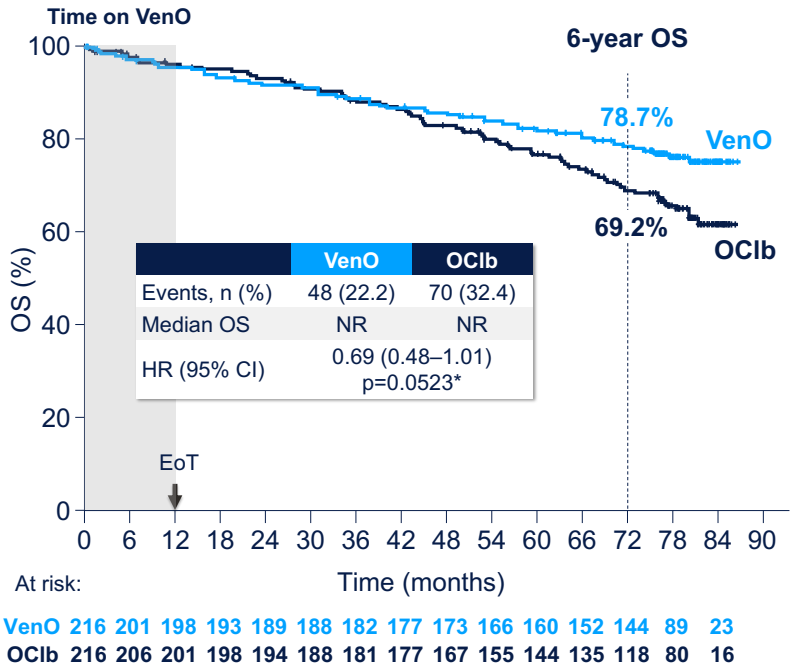
	VenO	OClb
Events, n (%)	40 (18.5)	57 (26.4)
Median OS	NR	NR
HR (95% CI)	0.72 (0.48–1.09) p=0.12*	

At risk:

VenO	216	201	198	193	189	188	182	177	173	166	159	97	25
OClb	216	206	201	198	194	188	181	177	167	155	144	101	21

14 November 2022[2]

Median follow-up: 76.4 months



	VenO	OClb
Events, n (%)	48 (22.2)	70 (32.4)
Median OS	NR	NR
HR (95% CI)	0.69 (0.48–1.01) p=0.0523*	

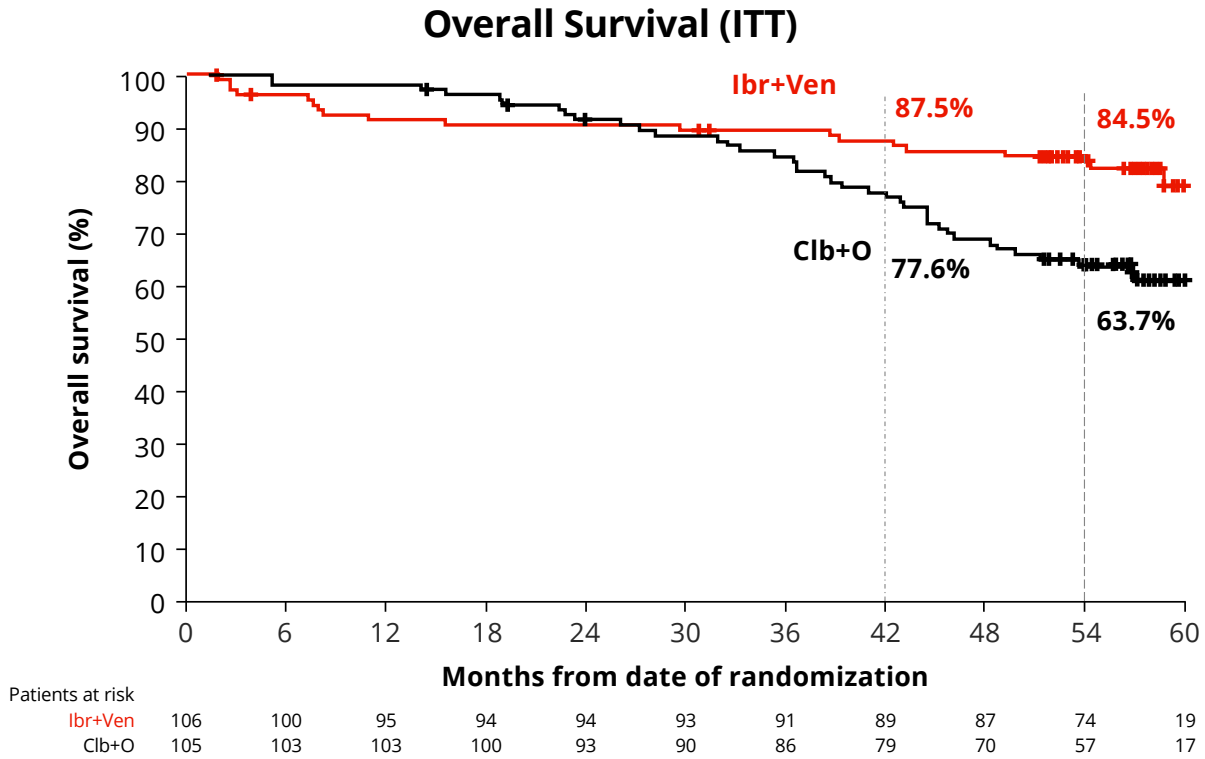
At risk:

VenO	216	201	198	193	189	188	182	177	173	166	160	152	144	89	23
OClb	216	206	201	198	194	188	181	177	167	155	144	135	118	80	16

Patients treated with VenO fixed treatment combination continued to show a consistent improvement in OS compared to patients treated with OClb.

*Descriptive.
CI, confidence interval; EoT, end of treatment; HR, hazard ratio; IGHV, immunoglobulin heavy chain; NR, not reached; OClb, obinutuzumab and chlorambucil; OS, overall survival; VenO, venetoclax and obinutuzumab.
1. Al-Sawaf O, et al. *Nat Commun* 2023; 14:2147; 2. Al-Sawaf O, et al. EHA 2023. Abstract S145 (Oral).

GLOW: Ibr+Ven Remained Associated With Improved Overall Survival at 57 Months of Study Follow-up



- **Ibr+Ven reduced the risk of death by 55%** versus Clb+O
  - HR 0.453 (95% CI, 0.261-0.785); *p* = 0.0038
- Estimated 54-month OS rates:
  - **84.5%** for patients treated with Ibr+Ven
  - **63.7%** for patients treated with Clb+O

p value is nominal.

Presented by G. Follows at the 65th ASH Annual Meeting and Exposition; December 9-12, 2023; San Diego, CA, USA

GLOW: Summary of Deaths

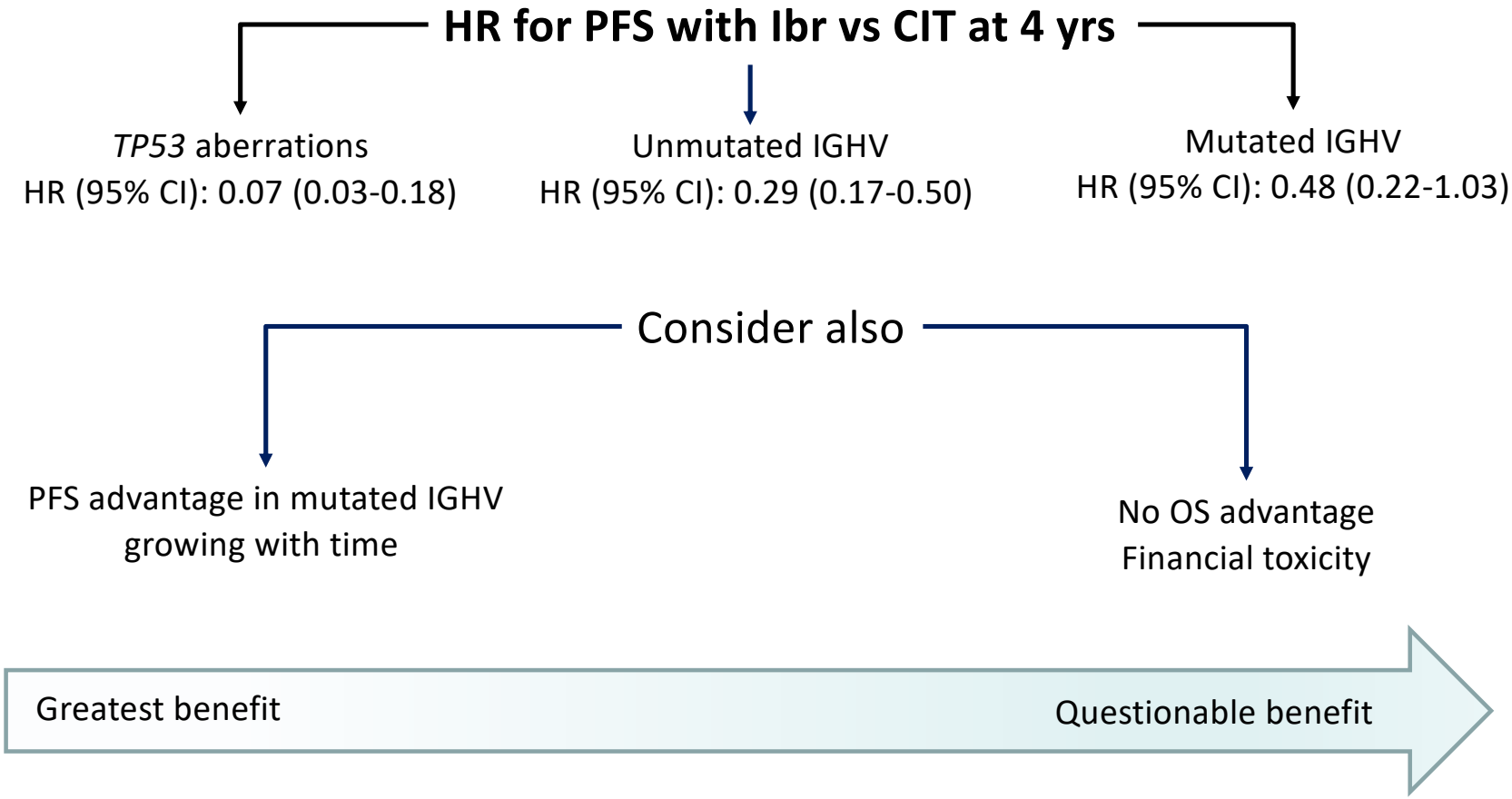
	Ibr+Ven (n = 106)		Clb+O (n = 105)	
Total number of deaths	**19**		**39**	
Reasons for deaths	**On treatment**	**Post randomized treatment[a]**	**On treatment**	**Post randomized treatment[a]**
Infection related[b]	1	3	1	13
Second primary malignancy	1	1	0	7
Cardiac	2[c]	0	0	4
Sudden/unknown	2	3	0	4
Progressive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

[a]Either before or after initiation of subsequent antileukemic therapy. [b]Including 2 and 7 deaths due to COVID-19 in the Ibr+Ven and Clb+O arm, respectively. [c]1 patient had 3 causes of death: tachy-brady syndrome, cardiac failure, and pneumonia.

Presented by G. Follows at the 65th ASH Annual Meeting and Exposition; December 9-12, 2023; San Diego, CA, USA

BTKI in CLL: benefit for all?



"With universalistic national health-systems at breaking point (10) we are facing times when one has to consider the magnitude of clinical benefit (figure 1) and to adapt this to the patient expectations in each and every economical context rather than to choose simply based on the medical reasoning and the efficacy and tolerability of the treatments".

Cuneo A, Ghia P. Blood 2024 – editorial comment on the paper by Woyach J et al publshed in Blood 2024

Cost-effectiveness analyses of BTKi in first line treatment of CLL

Source/ country	WTP/QALY	Treatment	Comparator	Target population	ICER	Comments	Cost effective
NICE/ UK	£20.000-30.000	V+O	Chlor+O	Unsuitable for FCR/BB	NR	Dominant effect V+O vs Chlor+O° (more effective and less costly)	YES^
NICE/ UK	£20.000-30.000	Acalabrutinib	Chlor+O	CLL unsuitable for FRC/BR, including 17p-	<£30,000 per QALY gained	/	YES ^

^Considering commercial arrangements

Data From: Urso A et al. Cancers (Basel). 2023 Jul 29;15(15):3859. doi: 10.3390/cancers15153859.

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NICE/UK	£20.000-30.000	Acalabrutinib	Chlor+O	CLL unsuitable for FRC/BR, including 17p-	<£30,000 per QALY gained	Considering confidential discounts	YES
NICE/UK	£20,000-30,000	Ibrutinib and Venetoclax	FRC/BR	CLL suitable for FRC/BR, including 17p-	<£30,000 per QALY gained	Considering confidential discounts	YES
			Chlor+O and V+O	unsuitable for FRC/ BR, including 17p-	<£30,000 per QALY gained	Dominant effect vs Chlo+O°	YES
			Acalabrutinib and Ibrutinib		NR	Cost saving and a small QALY loss compared with acalabrutinib and ibrutinib	YES

Data From: Urso A et al. Cancers (Basel). 2023 Jul 29;15(15):3859. doi: 10.3390/cancers15153859.

Fixed duration

↓

Venetoclax+O
(12 mos. Oral and IV)

Ibrutinib + Venetoclax
(15 mos. Oral)

FCR only «fit» and IGHV mutated
(6 mos. IV)

Clor+O/BR only «unfit» and e IGHV mutated
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- Any role for CIT? NO
  - ***OS advantage with targeted agents is a possible goal***
  - ***increased rate of death due to infections and SPM (FCR) with CIT***
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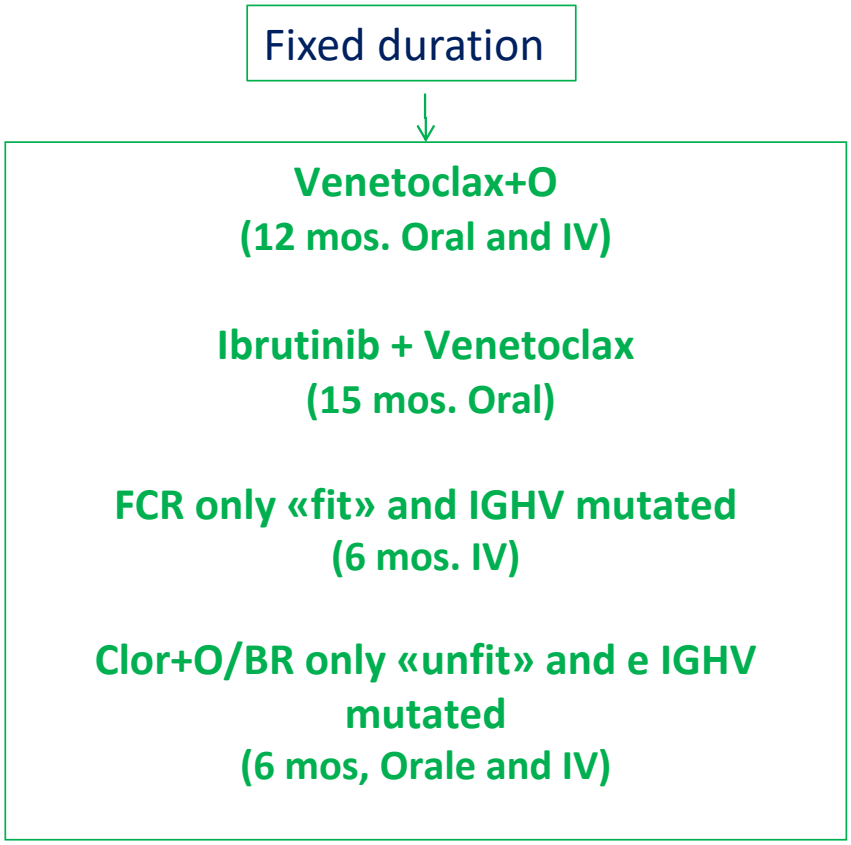
  - ***Pharmaco economic evaluation: dominant effect with ven based combo***
- Ven based combinations
- MRD-guided treatment



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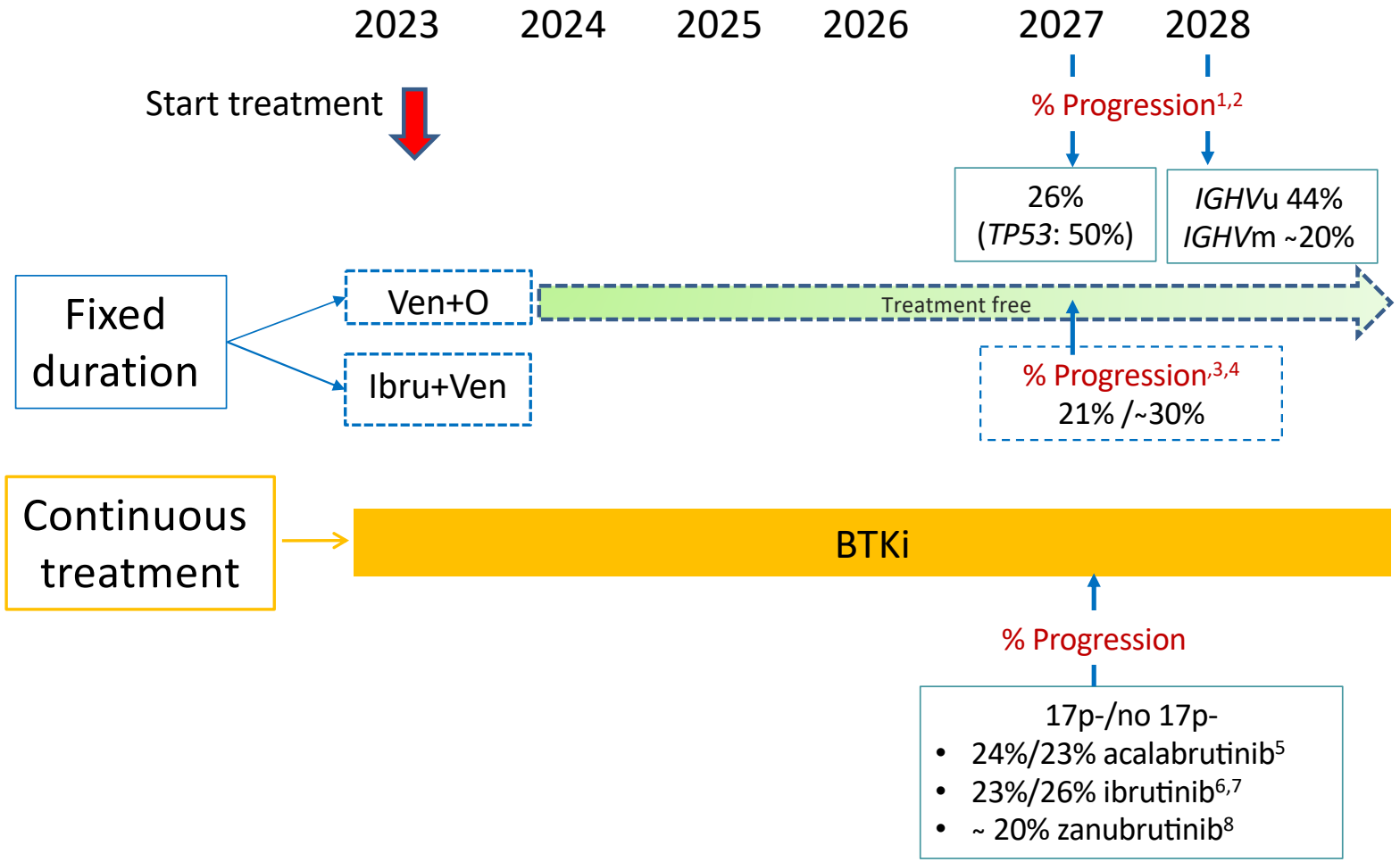
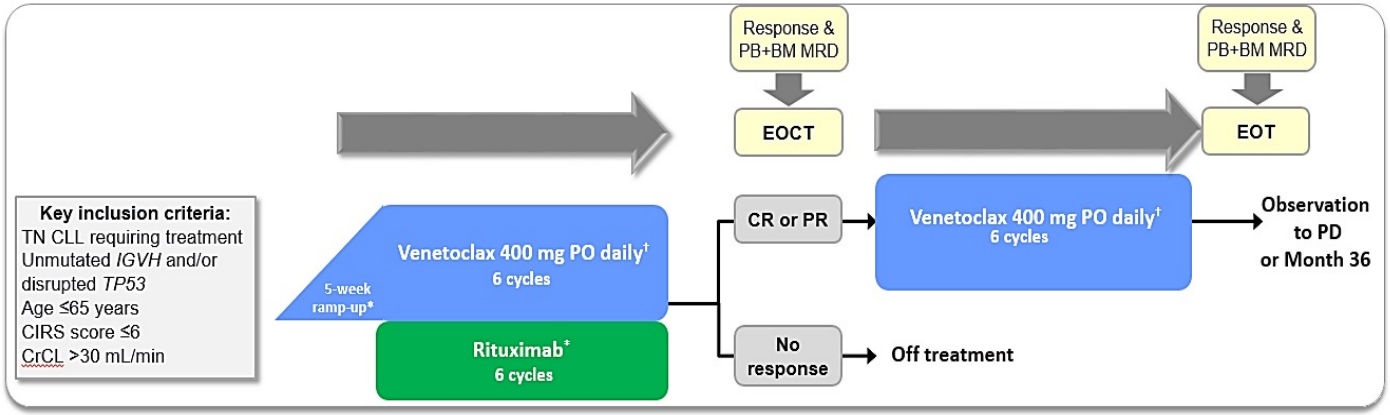
Prolonged disease control in CLL treated with 1st line target therapy



[1]**Al-Sawaf O**. JCO 2021; [2]**Al-Sawaf O**. Nat Comm 2023; [3]**Tedeschi EHA 2023;** [4]**Ghia P,** ASH 2023; [5]**Sharman JP**. Leukemia. 2022; [6]**Woyach J** ASH 2021; [7]**Moreno C**. Haematologica, 2022**;** [8]**Munir T** #639; EHA2023

Front-Line Venetoclax and Rituximab for the Treatment of Young Patients with CLL and Unfavorable Biologic Profile. The GIMEMA Study 'Veritas'



* Venetoclax, PO daily: 20 mg week 1, 50 mg week 2, 100 mg week 3, 200 mg week 4, 400 mg week 5 onwards;
† Venetoclax 400 mg PO daily, day 1–28 of each cycle;
‡ Rituximab IV: 375 mg/m2 on day 1 month 1, 500 mg/m2 on day 1 months 2–6.
EOCT, end of combination therapy; EOT, end of treatment ; ORR, overall response rate.

Primary endpoint:

CR rate at EOT

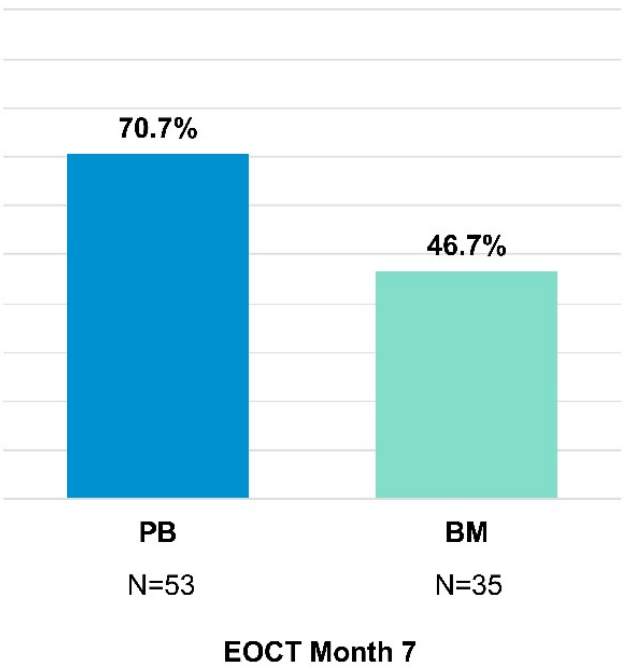
Key Secondary endpoints:

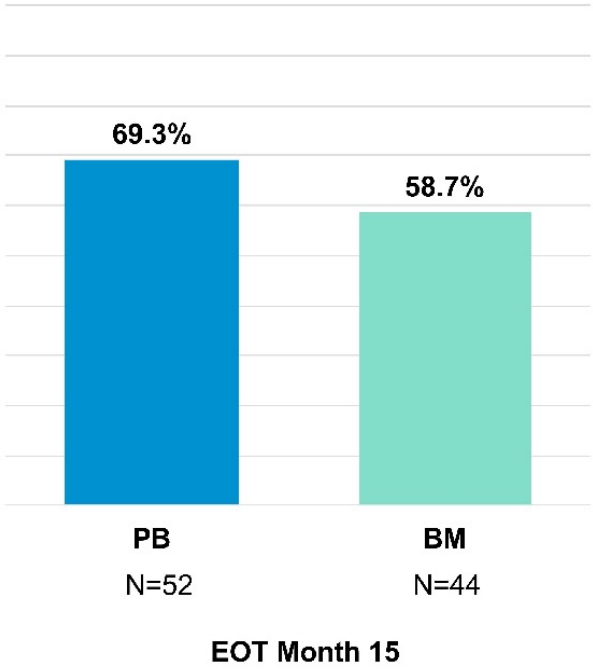
- ORR at EOT
- uMRD response rate at EOT
- PFS
- OS
- Safety

Baseline characteristics, n (%)	N=75*
Median age, years (range)	53.45 (38–65)
Lymphocyte count x 10^9/L (range)	96.2 (5.3–556.5)
Bulky nodes (lymph nodes size ≥5 cm) (%)	18 (25)
Binet stage B/C (%)	37 (49) - 26 (35)
TLS risk: high (%)	33 (44)
Beta-2 microglobulin ≥ 3.5 mg/L	27 (41)
Increased LDH	26 (35)
CD38 ≥30%	38 (51)
TP53 mutation	9 (12)
Unmutated *IGHV*	71 (96)

Mauro F. et al Haematologica 2023 Aug 1;108(8):2091-2100

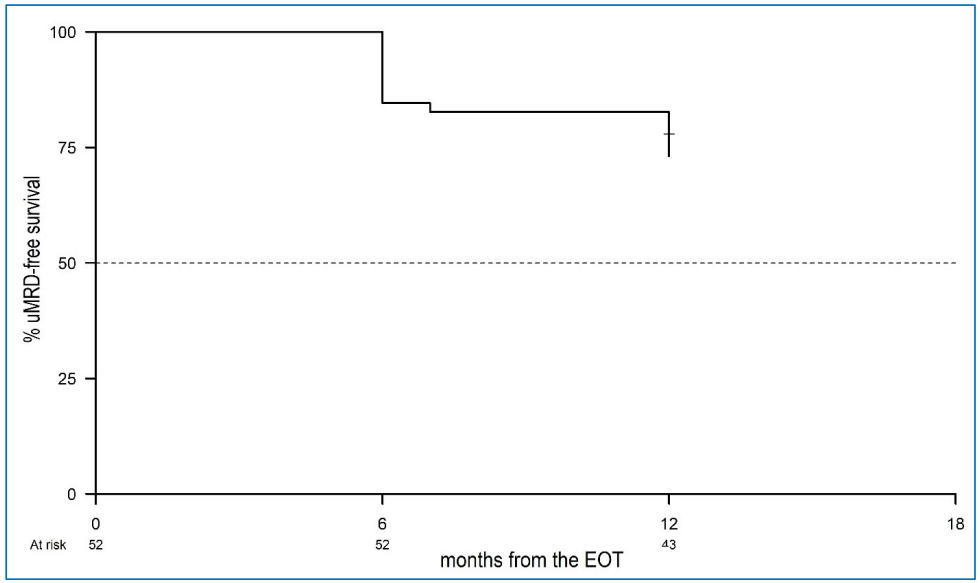
Rates of responses with undetectable MRD (10-4) in the PB and BM by allele-specific oligonucleotide PCR at the end of combination therapy and end of treatment





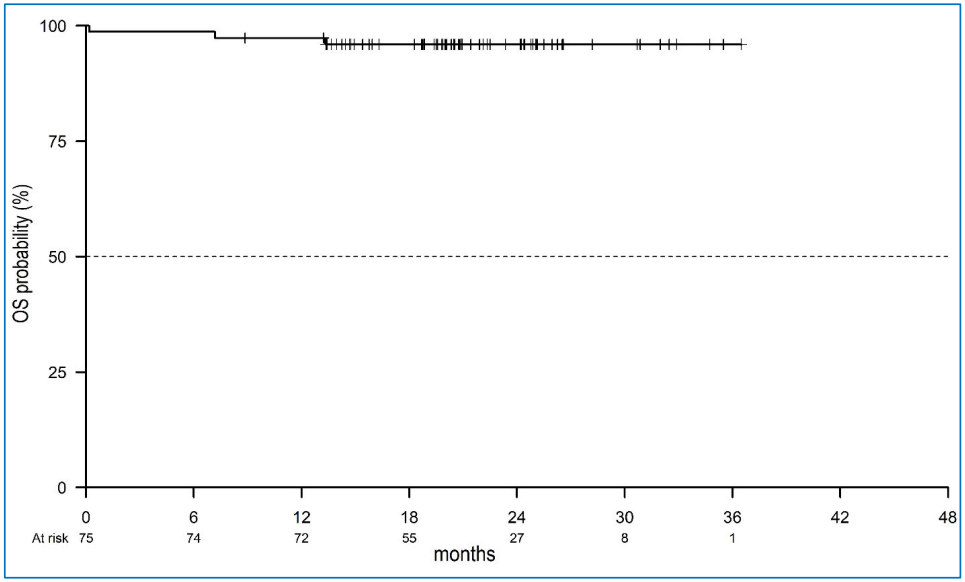
Mauro F. et al Haematologica 2023 Aug 1;108(8):2091-2100

Undetectable minimal residual disease-free survival.



Overall survival of the whole cohort of 75 patients enrolled in the study

median follow-up of 20.8 months



Mauro F. et al Haematologica 2023 Aug 1;108(8):2091-2100

Fixed duration

↓

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- Ven based combinations
  - *Prolonged disease control and long treatement-free interval*
  - *uMRD in a sizebale fraction of cases*

- MRD-guided treatment

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  - ***Prolonged disease control and long treatement-free interval***
  - ***uMRD in a sizebale fraction of cases***

- MRD-guided treatment

Examples of studies used MRD assessment to guide treatment decision

Relapsed refractory CLL

- *Clarity*[1]*:*
  - MRD- after 6-12 mos: ibru ven for the same time required to achieve uMRD
  - MRD+ after 6-12 mos: ibru ven for </= 2yrs and then Ibrutinib

- *HOVON141/VISION*[2]*:*
  - MRD- after 15 mos: randomize stop vs ibrutinib until progression
  - MRD+ after 15 mos: ibrutinib until progression

First line CLL

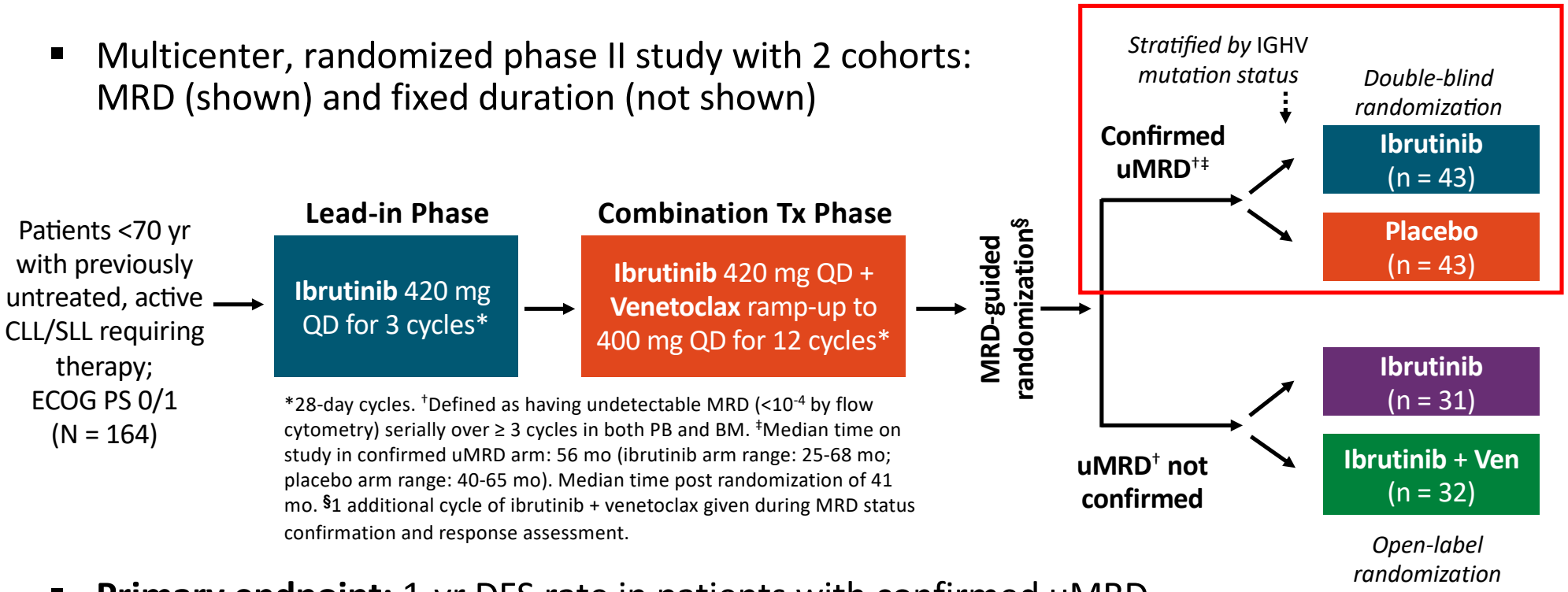
- Flair[3]:
  - Ibru ven for twice as long time to achieve u MRD

- CAPTIVATE[4]
  - MRD- after 15 mos: randomize stop vs ibrutinib until progression
  - MRD+ after 15 mos: ibrutinib vs Ibru + ven

[1]Hillmen P. J Clin Oncol. 2019 Oct 20;37(30):2722-2729. [2]Kater A. Lancet Oncol. 2022 Jun;23(6):818-828;
[3]Hillmen P. 2024 Jan 25;390(4):326-337; . [4]Allan. ASH 2022. Abstr 92.

CAPTIVATE MRD Cohort Update: Study Design

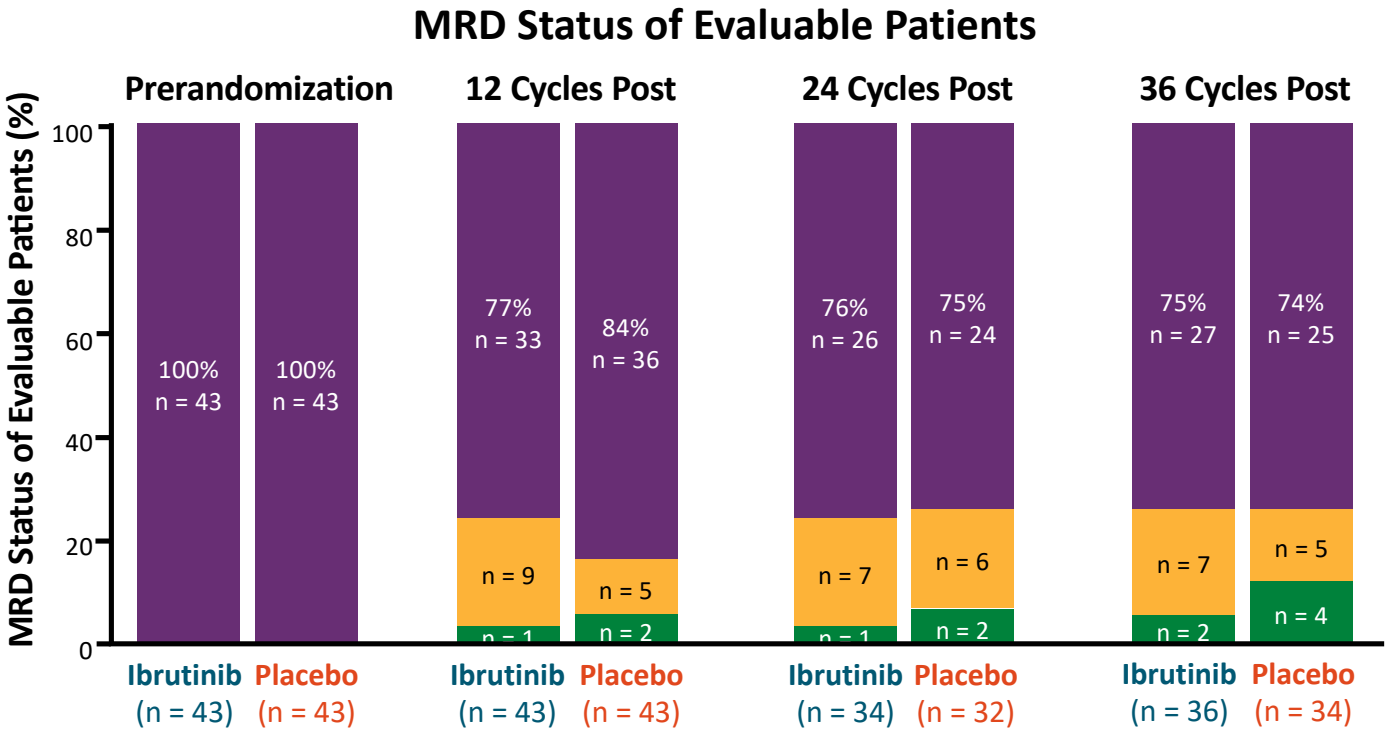
- Multicenter, randomized phase II study with 2 cohorts: MRD (shown) and fixed duration (not shown)



*28-day cycles. †Defined as having undetectable MRD ($<10^{-4}$ by flow cytometry) serially over ≥ 3 cycles in both PB and BM. ‡Median time on study in confirmed uMRD arm: 56 mo (ibrutinib arm range: 25-68 mo; placebo arm range: 40-65 mo). Median time post randomization of 41 mo. §1 additional cycle of ibrutinib + venetoclax given during MRD status confirmation and response assessment.

- **Primary endpoint:** 1-yr DFS rate in patients with confirmed uMRD
- **Secondary endpoints:** undetectable MRD, response rates, safety

CAPTIVATE MRD Cohort Update: CR and MRD Status (Secondary Endpoints)



MRD negative ($<10^{-4}$)*
MRD positive ($\geq 10^{-4}$)
Off MRD follow-up†

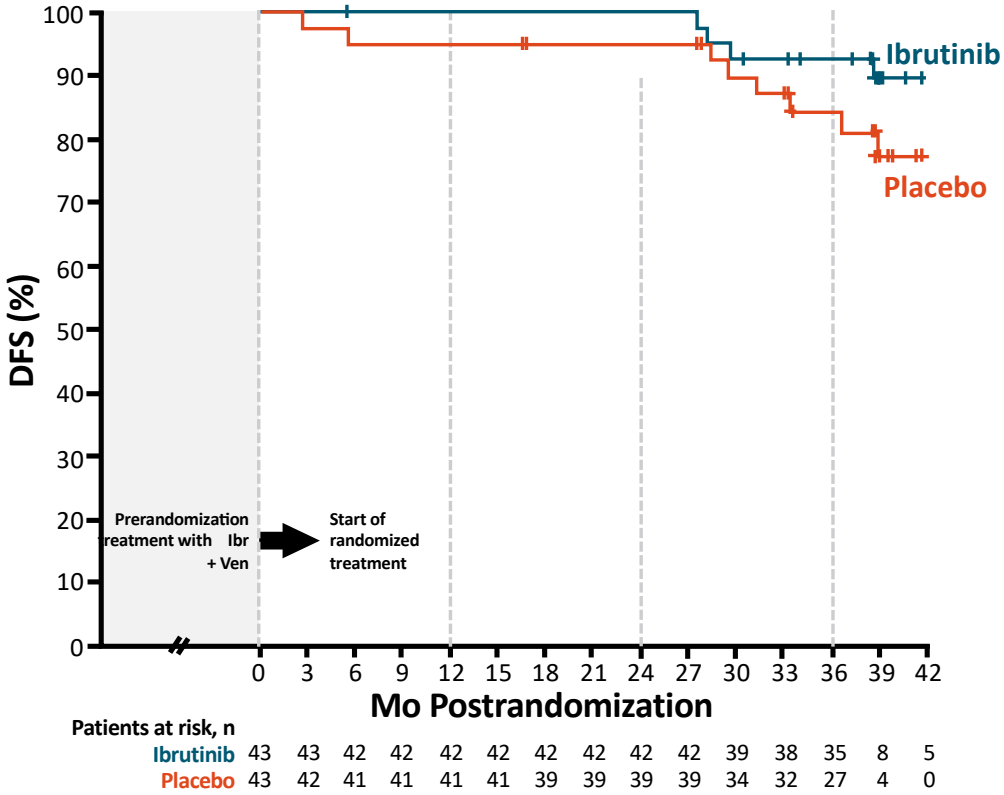
*By 8-color flow cytometry. †Includes patients who met any 1 of following criteria: PD, initiation of subsequent therapy, death, or withdrawal from study.

- Sustainability of uMRD similar in ITT population

Allan. ASH 2022. Abstr 92.

Slide credit: clinicaloptions.com

CAPTIVATE MRD Cohort Update: 3-Yr DFS (Primary Endpoint)



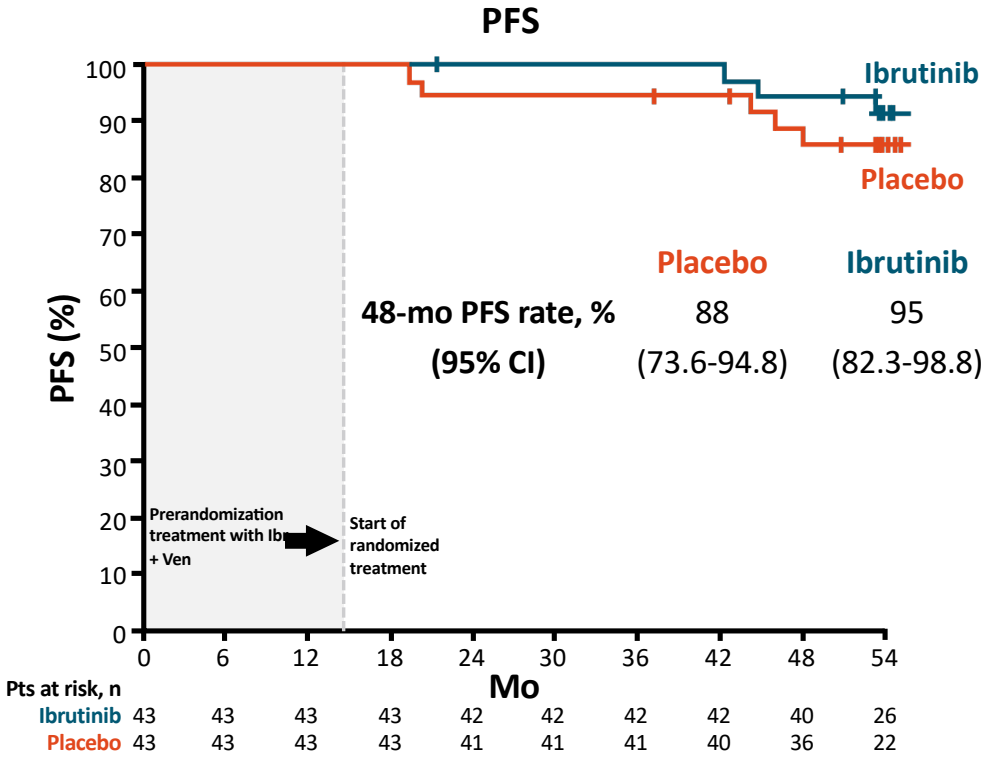
Outcome	Confirmed uMRD (n = 86)	
	Ibrutinib (n = 43)	Placebo (n = 43)
3-yr DFS,* %	93	85
Difference, % (95% CI)	8.3 (-5.5 to 22.1)	
Log-rank *P* value	.1621	
HR (95% CI)	0.435 (0.131-1.446)	

*DFS = time from randomization to MRD relapse, PD per investigator assessment, or death, whichever soonest.

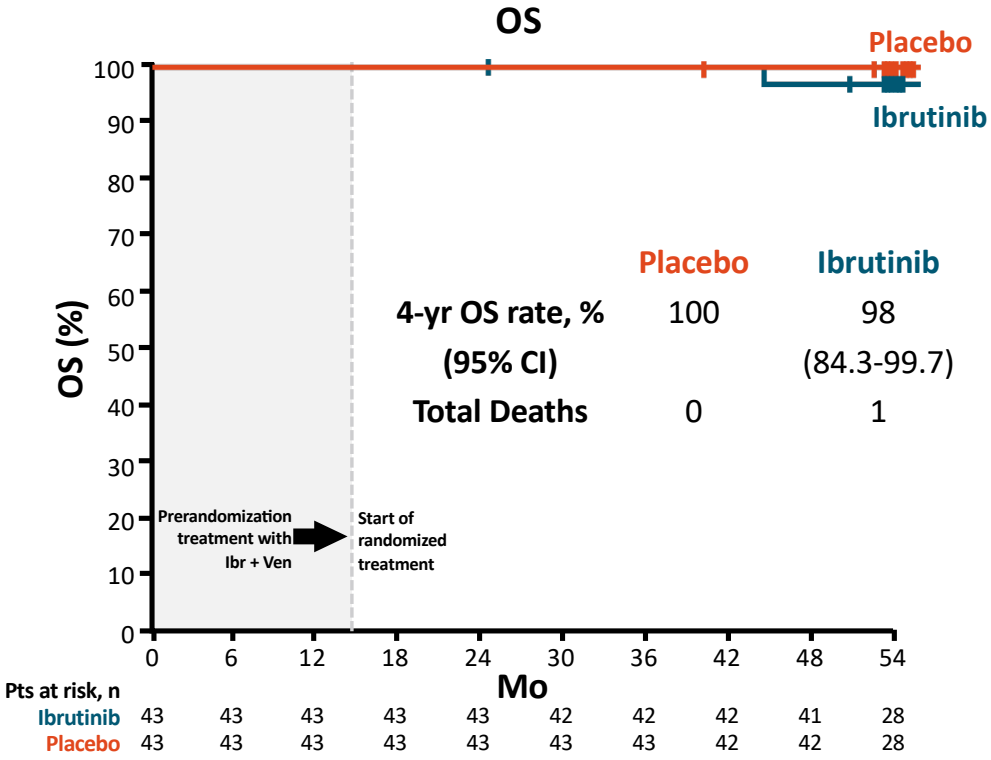
Allan. ASH 2022. Abstr 92.

Slide credit: clinicaloptions.com

CAPTIVATE MRD Cohort Update: PFS and OS (Secondary Endpoints)



	Placebo	Ibrutinib
48-mo PFS rate, %	88	95
(95% CI)	(73.6-94.8)	(82.3-98.8)



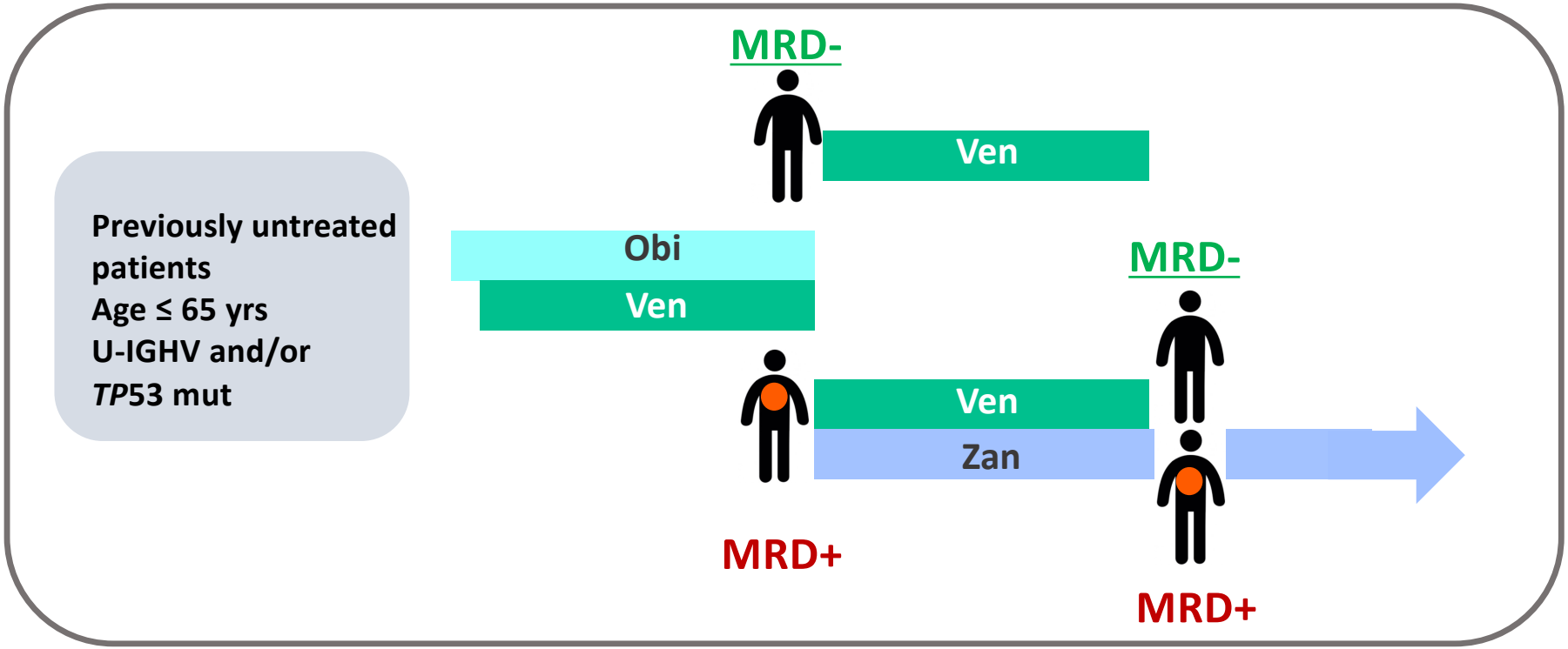
	Placebo	Ibrutinib
4-yr OS rate, %	100	98
(95% CI)		(84.3-99.7)
Total Deaths	0	1

- 48-mo PFS rates in patients with unmutated *IGHV* similar to overall population
- 3-yr DFS, 4-yr PFS, 4-yr OS rates in patients with del(17p), TP53, or complex karyotype similar to overall population

Allan. ASH 2022. Abstr 92.

Slide credit: clinicaloptions.com

THE GIMEMA VIS TRIAL: STUDY DESIGN



P.I.: F. Mauro

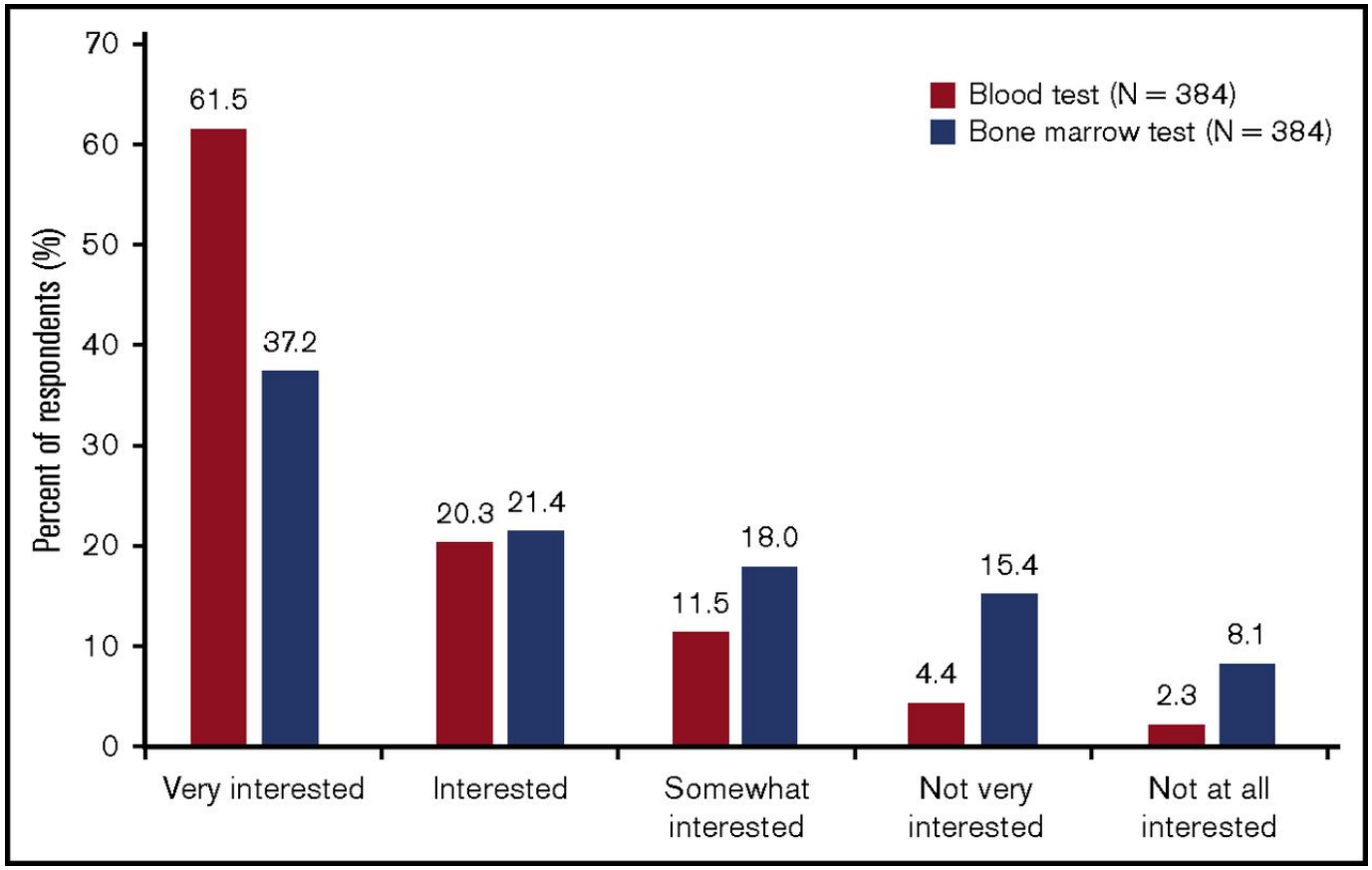
The patients' priorities

- 384 patients with a self-reported physician diagnosis of CLL
- Choice between pairs of hypothetical treatments for CLL
- Each treatment was defined by 5 attributes with several predefined levels

- progression-free survival (PFS; 10-60 months),
- diarrhea (none to severe),
- chance of severe infection (0-30%),
- chance of organ damage (0-8%),
- mode and schedule of administration (pill versus intravenous administration)

Mansfield C, et al. Blood Adv. 2017 Oct 31;1(24):2176-2185.

MRD testing: “Suppose that you have finished a 6-month course of medicine for CLL. The standard blood test does not find any cancer cells in your blood. Your doctor offers you one of the new, more sensitive blood tests. How interested would you be in getting this new?



Mansfield C, et al. Blood Adv. 2017 Oct 31;1(24):2176-2185.

Patient Preferences for Fixed Versus Treat-to-Progression Therapies in Chronic Lymphocytic Leukemia

Arliene Ravelo,[1]* Kelley Myers,[2] Claire Ervin,[2] Robyn Brumble,[3] Cooper Bussberg,[2] Brian Koffman,[3] Beenish S. Manzoor,[4] Juliana M.L. Biondo,[1] Carol Mansfield[2]

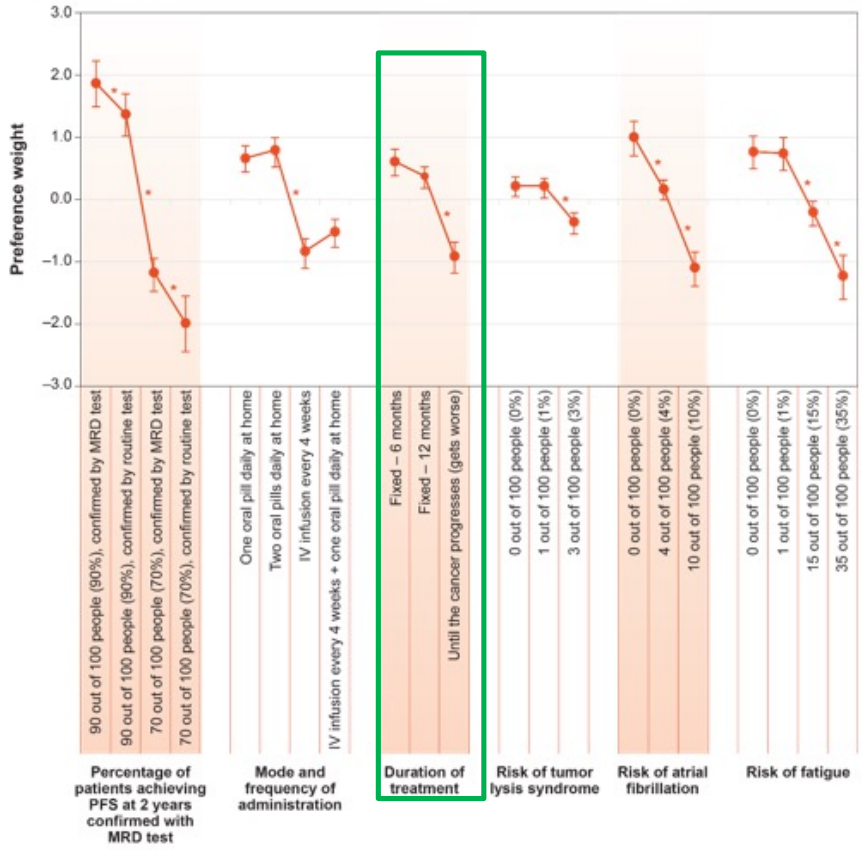
Table 1. Attributes and levels for the DCE.

Type of attribute	Technical attribute label	Attribute levels
Efficacy	Percentage of patients achieving PFS at 2 years confirmed with MRD test *	90 out of 100 people (90%), confirmed by MRD test
		90 out of 100 people (90%), confirmed by routine test
		70 out of 100 people (70%), confirmed by MRD test
		70 out of 100 people (70%), confirmed by routine test
Process	Mode and frequency of administration	One oral pill daily at home
		Two oral pills daily at home
		IV infusion every 4 weeks
		IV infusion every 4 weeks + one oral pill daily at home
Process	Duration of treatment	Fixed -- 6 months
		Fixed -- 12 months
		Until the cancer progresses (gets worse)
Safety	Risk of TLS	0 out of 100 people (0%)
		1 out 100 people (1%)
		3 out of 100 people (3%)
Safety	Risk of atrial fibrillation	0 out of 100 people (0%)
		4 out of 100 people (4%)
		10 out of 100 people (10%)
Safety	Risk of fatigue	0 out of 100 people (0%)
		1 out 100 people (1%)
		15 out of 100 people (15%)
		35 out of 100 people (35%)

*In the online survey, the attribute defined by chance of PFS and results confirmed with MRD testing were presented as two distinct attributes. There are four combinations between the two levels of chance of PFS (70% vs 90%) and the two testing confirmation levels (routine tests vs. MRD tests).
IV, intravenous; MRD, measurable residual disease; PFS, progression-free survival.

Ravelo A et al ASH 2023 p#3706

Figure 2. Relative preference weights for treatment attributes (N=229).



*Asterisks placed above line segments denote attribute level changes that are statistically different from 0 at the 95% CI.

Note: The preference weights measure the relative impact each attribute level has on the average respondent's treatment choice. Preference weights are relative to one another and do not have an absolute interpretation. The attribute levels with larger preference weights are preferred to attribute levels associated with smaller preference weights. The utility variation caused by a change in the levels of each attribute is represented by the vertical distance between the preference weights for any two levels of that attribute. Larger differences between preference weights indicate that respondents viewed the change as relatively more important. The vertical bars surrounding each mean preference weight denote the 95% CI (computed by the delta method).

Summary

Past research has shown efficacy as the most important factor, yet qualitative interview participants in this study also identified treatment duration as an important factor in their decision when choosing a chronic lymphocytic leukemia (CLL) therapy

This finding was confirmed by the quantitative preference study, which revealed a preference for fixed-duration therapies over treat-to-progression regardless of the timeframe (6 or 12 months)

The results from this study provide insight into which features adults with CLL consider important for their treatments and can help inform shared decision-making when selecting alternative therapies for CLL

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Fixed duration

↓

Venetoclax+O
(12 mos. Oral and IV)

Ibrutinib + Venetoclax
(15 mos. Oral)

FCR only «fit» and IGHV mutated
(6 mos. IV)

Clor+O/BR only «unfit» and e IGHV mutated
(6 mos, Orale and IV)

- Any role for CIT? NO
  - *OS advantage with targeted agents is a possible goal*
  - *increased rate of death due to infections and SPM (FCR) with CIT*
  - *PFS advantage with targeted agents*
  - *Pharmaco economic evaluation: dominant effect with ven based combo*

- Ven based combinations
  - *Prolonged disease control and long treatement-free interval*
  - *uMRD in a sizebale fraction of cases*

- MRD-guided treatment
  - *Prolonged disease control*
  - *Surrogate endpoint of PFS/OS in trials*
  - *Need to take into account patients' preferences*