Fixed duration vs until the progression in young and elderly patients in frontline

Othman Al-Sawaf

University Hospital of Cologne
German CLL Study Group

REVOLUTIONARY ROAD IN CLL

Innovazione rivoluzionaria nella terapia della leucemia linfatica cronica

Roma, 11 aprile 2024
UNAHOTELS Decò

Disclosures

Honoraria: Roche, Janssen, Gilead, AbbVie, Lilly, AstraZeneca, Adaptive, BeiGene

Advisory boards: AstraZeneca, Roche, Janssen, Gilead, AbbVie

Personal fees: Roche, Janssen, Gilead, AbbVie, AstraZeneca

Research grants: Beigene, Roche, Janssen, AbbVie

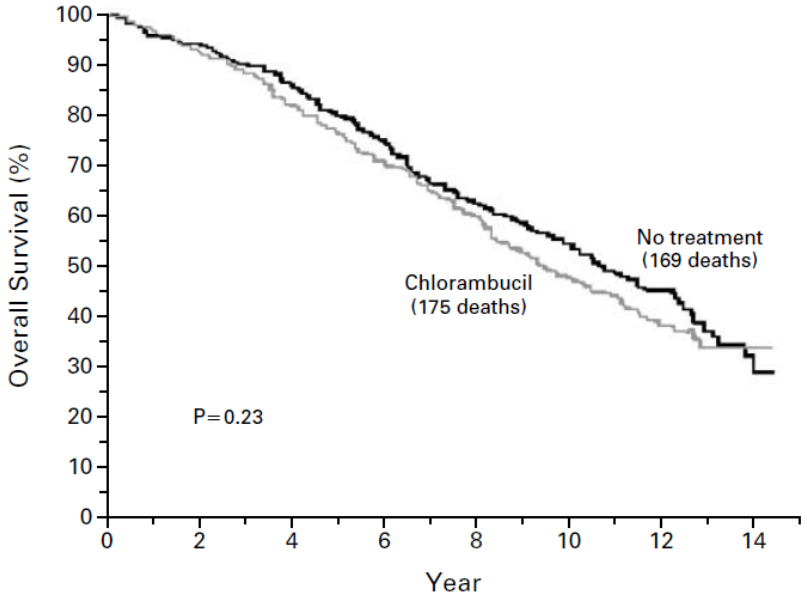

GLOW
ILLUMINATE
ELEVATE-TN
ECOG1912
ALLIANCE 202
CLL14
CLL13

Asymptomatic CLL – any news?

CHLORAMBUCIL IN INDOLENT CHRONIC LYMPHOCYTIC LEUKEMIA

GUILLAUME DIGHIERO, M.D., PH.D., KARIM MALOUM, M.D., PH.D., BERNARD DESABLENS, M.D., BRUNO CAZIN, M.D., MAURICE NAVARRO, M.D., ROBERT LEBLAY, M.D. MICHEL LEPORRIER, M.D., JROME JAUBERT, M.D., GERARD LEPEU, M.D. BRIGITTE DREYFUS, M.D., JACQUES-LOUIS BINET, M.D., AND PHILIPPE TRAVADE, M.D.
(FOR THE FRENCH COOPERATIVE GROUP ON CHRONIC LYMPHOCYTIC LEUKEMIA)

Dighiero G et al., N Engl J Med. 1998 May 21;338(21):1506-14.

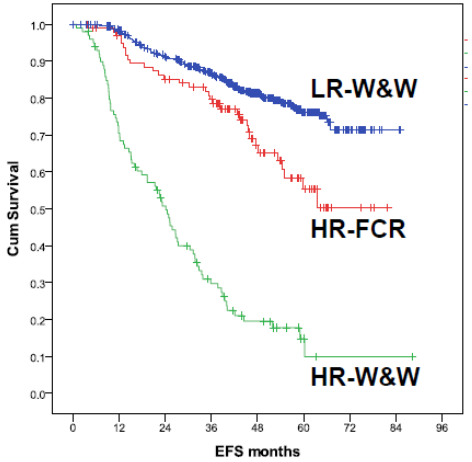


Asymptomatic CLL – any news?

CLL7 TRIAL
EARLY TREATMENT WITH FCR IMPROVES EFS

DEUTSCHE STUDIENGRUPPE CLL

n=800 (ITT)

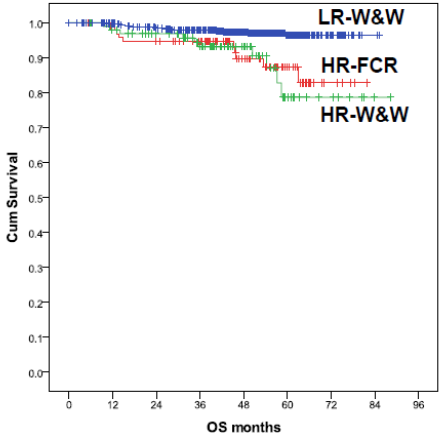


Log rank *P* < 0.001

	N events	Median EFS	5 year EFS
HR-FCR	33	n. r.	55.3%
HR-W&W	78	n. r.	14.8%
LR-W&W	111	24.2 months	80.1%
Cox regression: Variable	**P Value**	**Hazard Ratio**	**95% CI**
Cohort assignment	3.815E-43		
HR-FCR vs. LR-W&W	0.001	1.9	1.3 – 2.8
HR-W&W vs. LR-W&W	3.881E-44	8.2	6.1 – 11.0
HR-FCR vs. HR-W&W	5.846E-12	0.2	0.1 – 0.4

Herling C et al., Leukemia, 2020 Aug;34(8):2038-2050

.....BUT NOT OS: CLL7 TRIAL

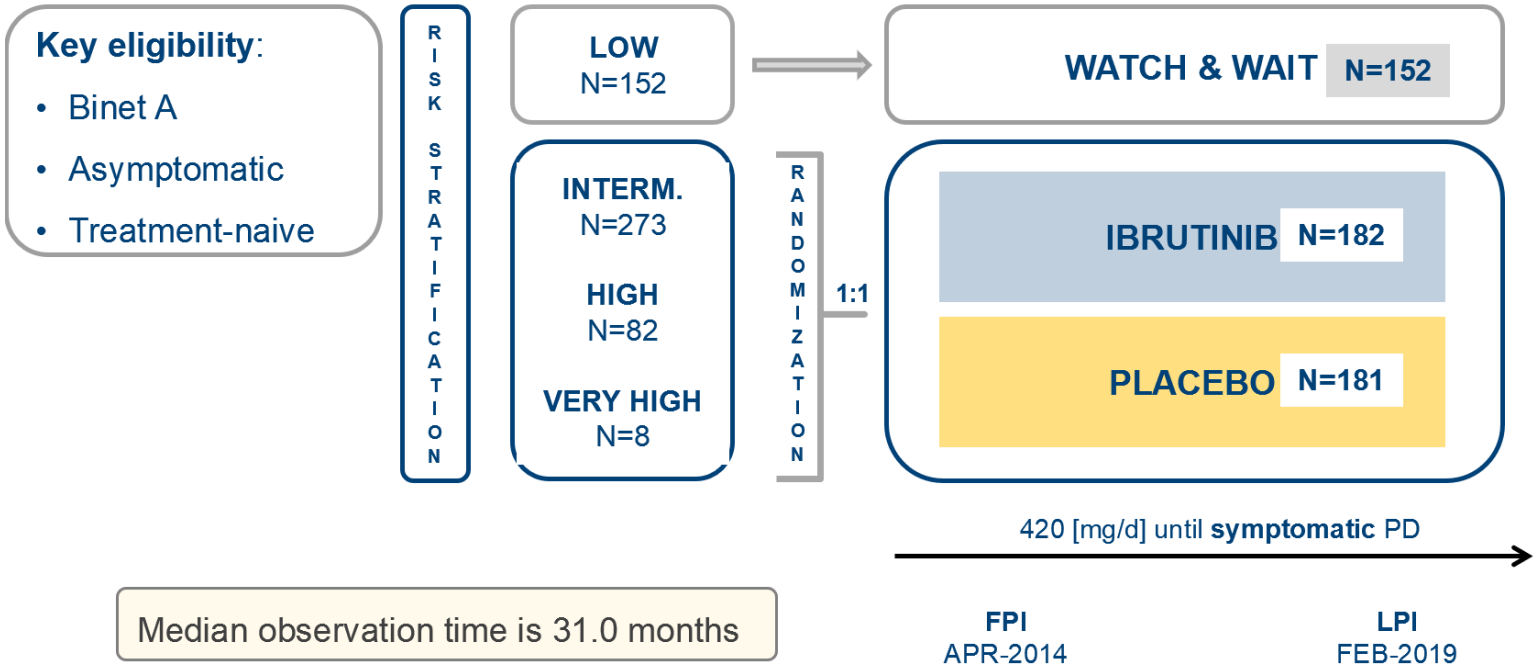


Log rank *P* < 0.001

	N events	Median OS	5 year OS
HR-FCR	10	n. r.	87.4%
HR-W&W	10	n. r.	78.7%
LR-W&W	16	n. r.	96.4%
Cox regression: Variable	**P Value**	**Hazard Ratio**	**95% CI**
Cohort assignment	1.961E-04		
HR-FCR vs. LR-W&W	0.001	3.8	1.7 – 8.4
HR-W&W vs. LR-W&W	3.717E-04	4.2	1.9 – 9.3
HR-FCR vs. HR-W&W	0.742	0.9	0.4 – 2.1

Asymptomatic CLL – any news?

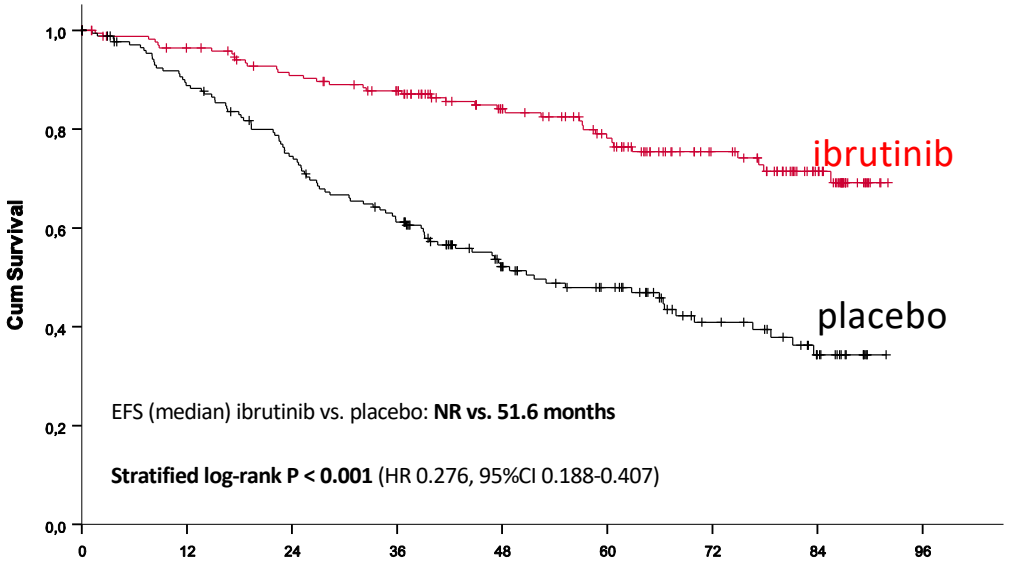
CLL12 STUDY DESIGN

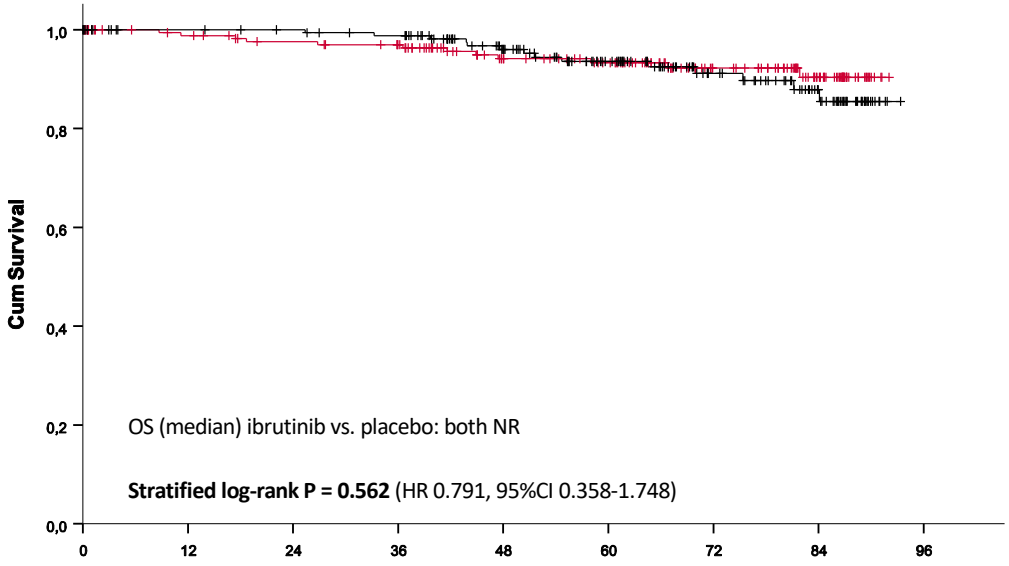


Langerbeins P et al. Blood 2022; 139(2) 177-187

Asymptomatic CLL – any news?

CLL12



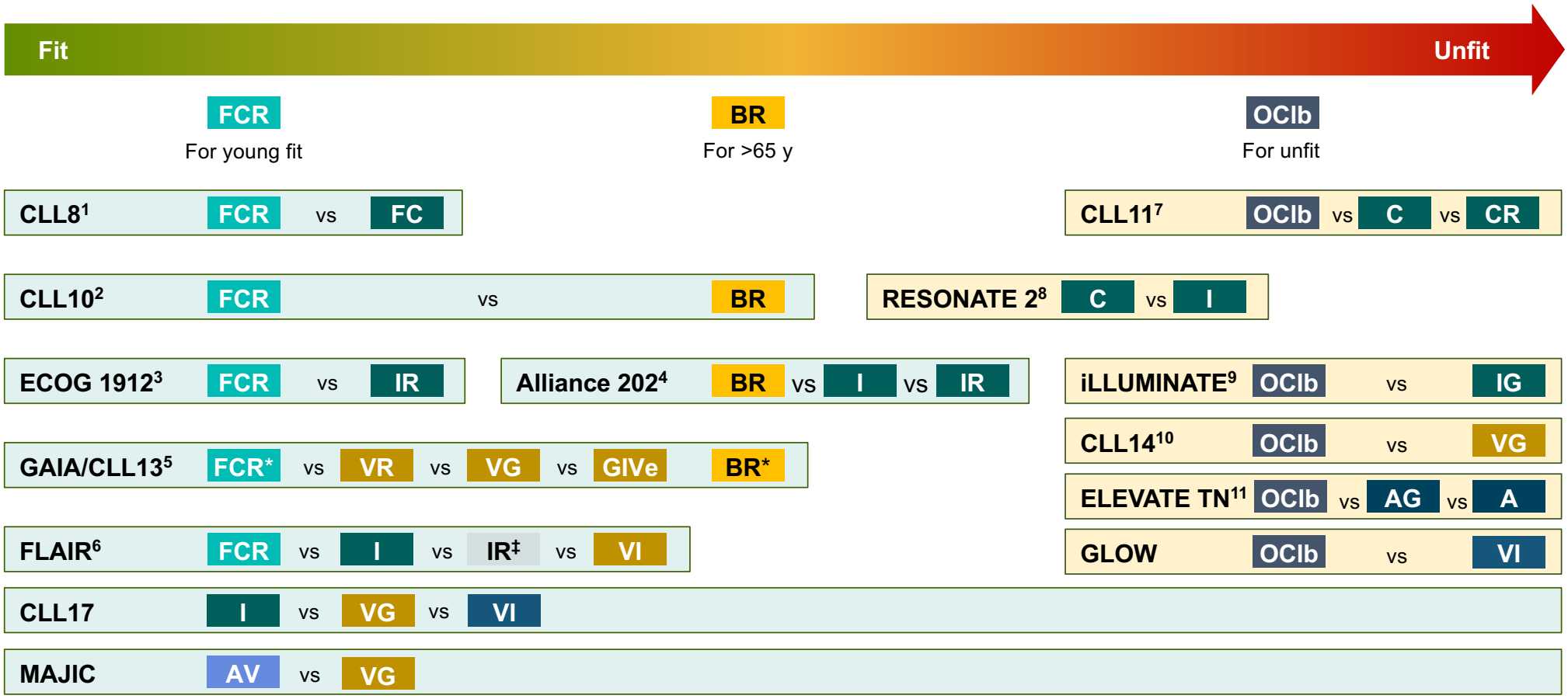


Langerbeins et al, EHA 2023

No OS difference

👉 in the past and present, **asymptomatic CLL should be managed with ‘watch & wait’**

CLL Firstline Studies



Clinicaltirals.gov: 1. NCT00281918; 2. NCT00769522; 3. NCT02048813; 4. NCT01886872 5. NCT02950051; 6. EudraCT number 2013-001944-76. 7. NCT01010061; 8. NCT01722487; 9.; NCT02264574 10. NCT02242942; 11. NCT02475681.

What kind of *fixed-duration* 1L approaches are available?

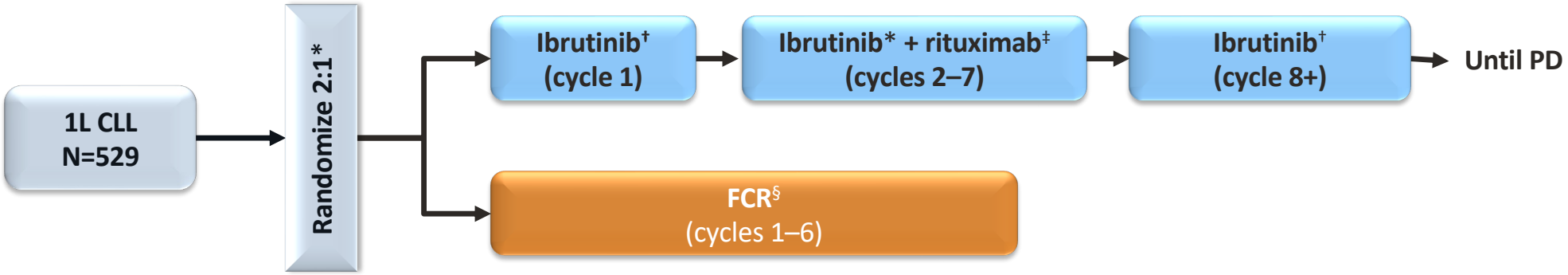
1. Chemoimmunotherapy: FCR, BR, Clb-Obi
2. Ven-Obi
3. Ven + BTKi

What kind of *continuous* 1L approaches are available?

1. Ibrutinib / Acalabrutinib / Zanubrutinib

ECOG 1912: Study design

Open-label, multicenter, randomized, phase 3 study assessing the efficacy and safety of IR vs FCR in younger patients



Key inclusion criteria

- Age ≤70 years
- ECOG PS 0–2
- Life expectancy ≥12 months
- Ability to tolerate FCR-based therapy
- No del(17p)
- Glomerular filtration rate >40 mL/min¶

Primary endpoints

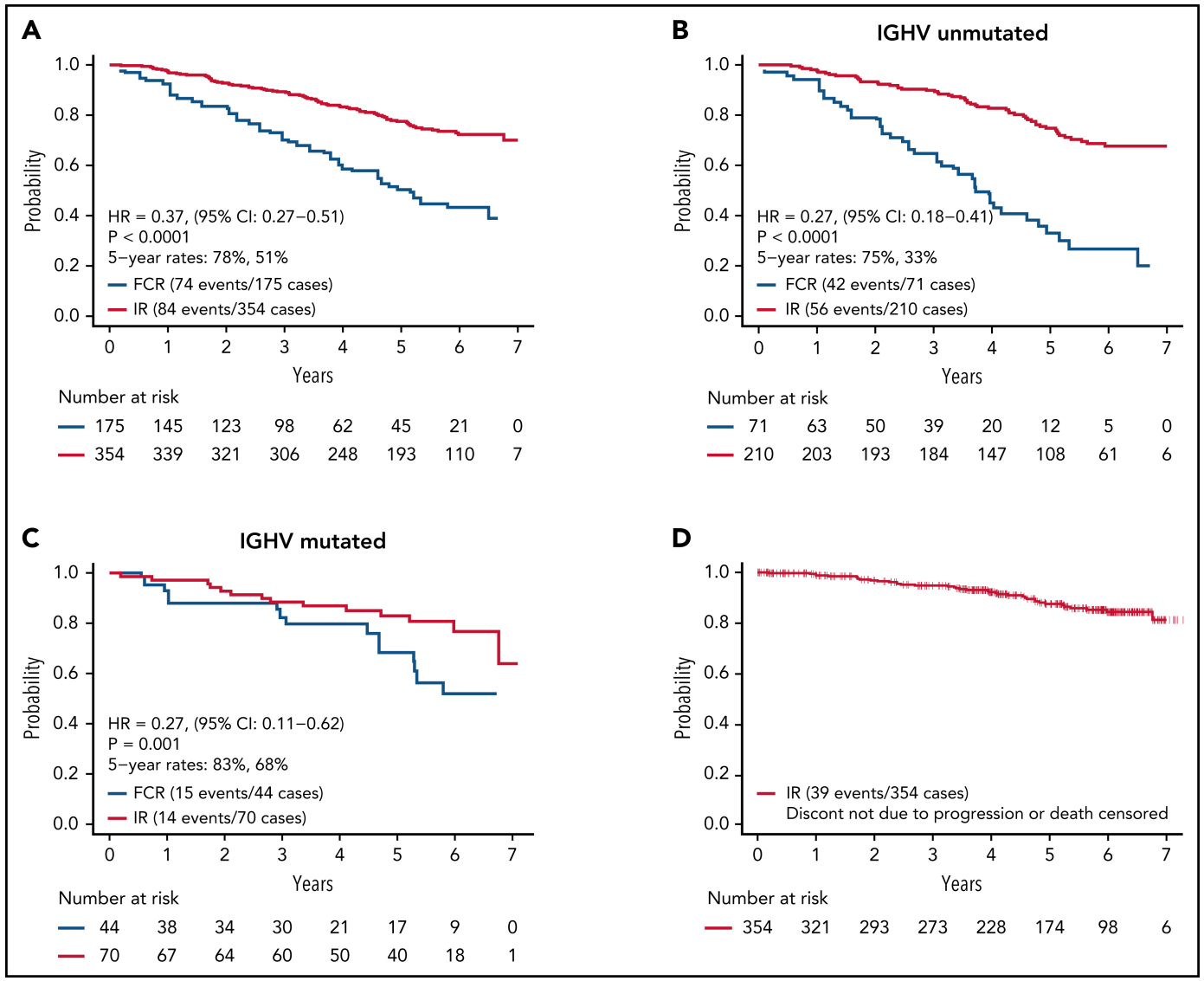
- PFS
- QoL (FACT-Leu TOI)

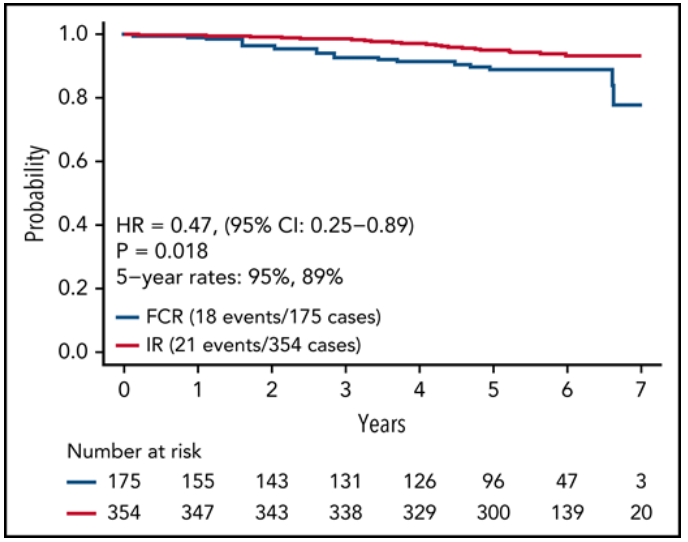
Secondary endpoints

- Overall survival
- Safety
- Change in QoL
- Adherence (ibrutinib arm only)

* Stratification according to age, ECOG PS, Rai stage, and del(11q);
† Ibrutinib PO 420 mg daily, D1–28; ‡ rituximab IV 50 mg/m^2 C2D1, 325 mg/m^2 C2D2, then 500 mg/m^2 day 1 of C3–7;
§ Fludarabine 25 mg/m^2 days 1–3, cyclophosphamide 250 mg/m^2 days 1–3, rituximab as per ibrutinib arm but starting on cycle 1; q28 cycles 1–6.
¶ By Cockcroft-Gault formula.

1. ClinicalTrials.gov. NCT02048813 (accessed February 2020); 2. Shanafelt TD, *et al. N Engl J Med* 2019; **381**:432–443 (incl. suppl.).

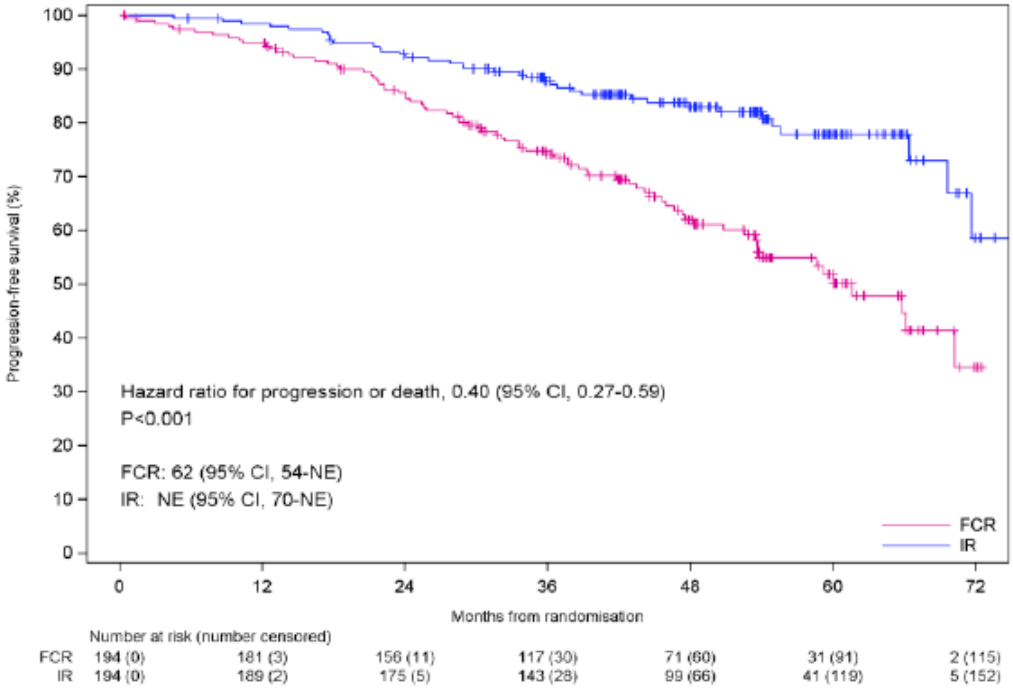




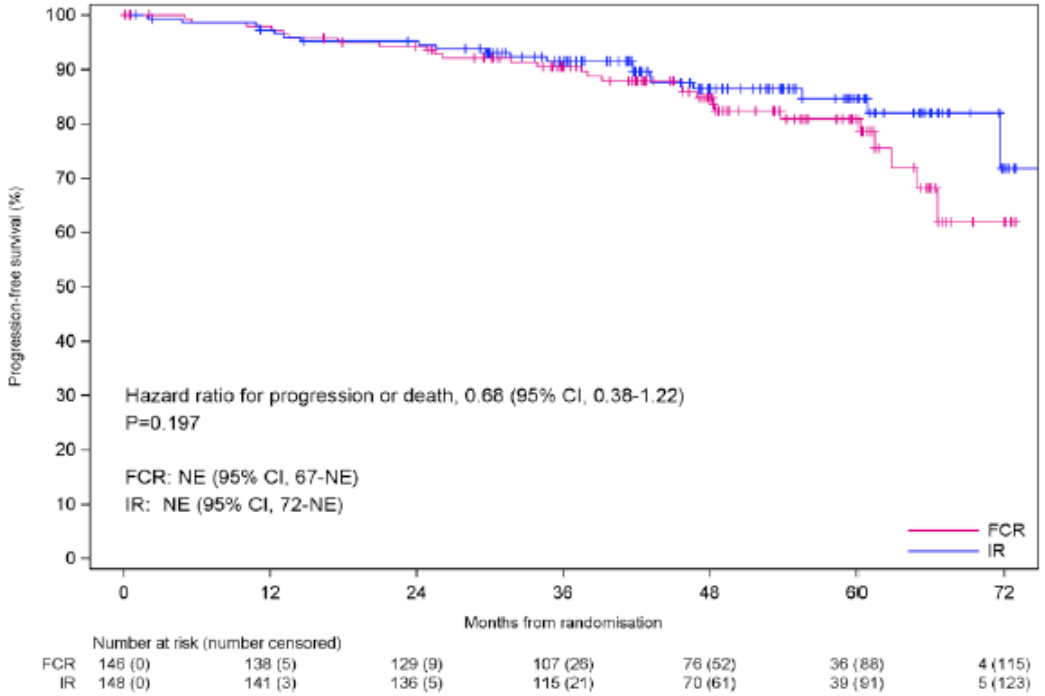
Shanafelt et al, Blood 2022

Flair PFS by IGHV mutation status

IGHV unmutated excl. Subset 2 CLL (n=388)



IGHV mutated CLL excl. Subset 2 (n=294)

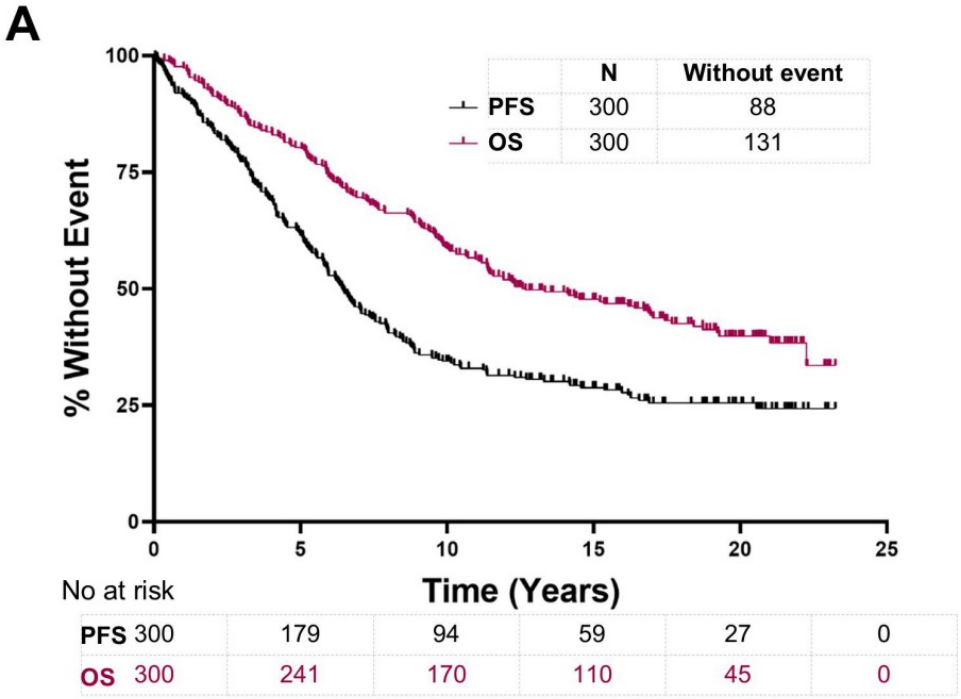


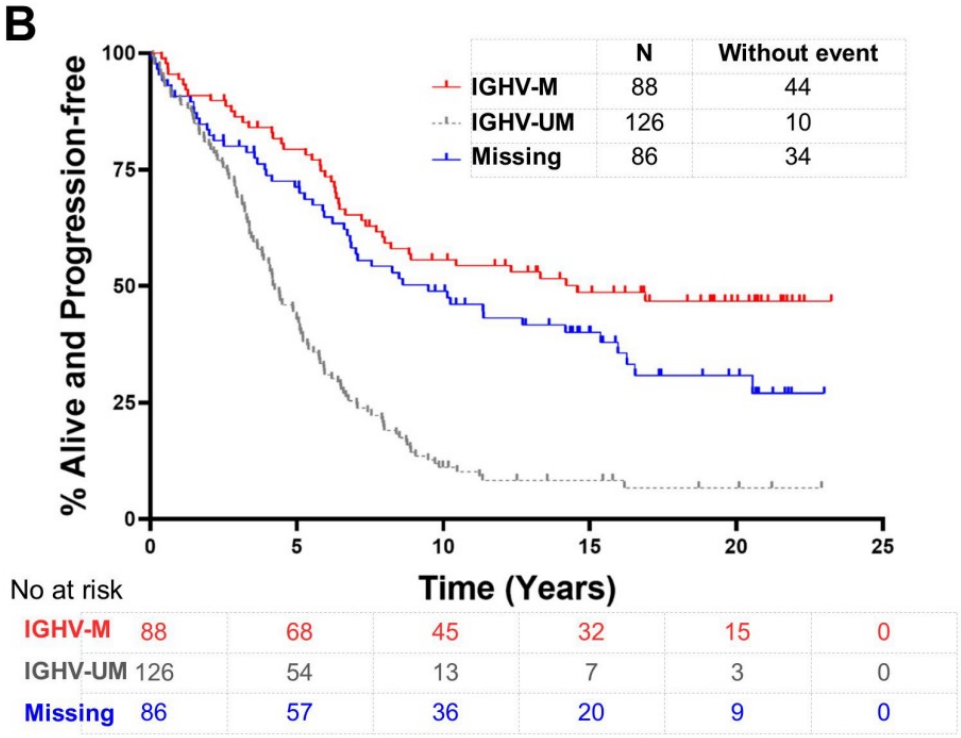
Stereotype Subset 2: n=46 (FCR 20; IR 26) → HR for PD or death 0.32 (95% CI, 0.06-1.76), p=0.191

Data-lock: 24th May 2021

Hillmen *et al.*, Abstract 642, ASH 2021

Longterm remission after FCR in IGHVmut





Thompson et al, Blood, 2023

Downsides of fixed-duration CIT

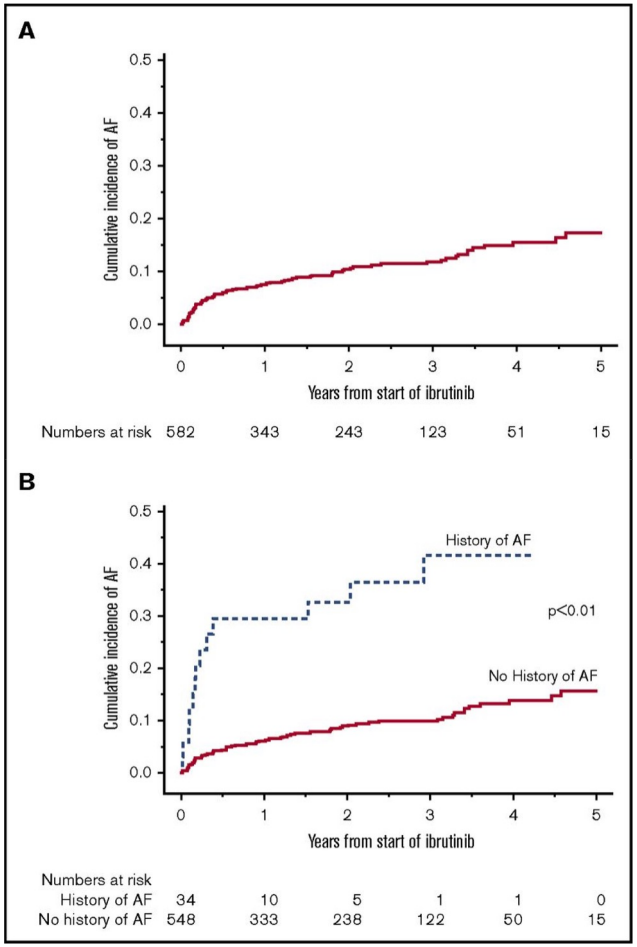
	Total	
Long-term safety	**Cases N (%)**	**Patients N (%)**
Total patients (safety population), N		800
Total cases [N (%)] and patients [N (%)] with ≥1 SPM	136 (100)	122 (15)
Secondary malignancies		
Richter's transformation	38 (28)	38 (5)
Solid tumors	55 (40)	52 (7)
Lung	18/55 (33)	18 (2)
Prostate	8/55 (15)	8 (1)
Renal/bladder	7/55 (13)	6 (1)
Colorectal	2/55 (4)	2 (<1)
Melanoma	8/55 (15)	8 (1)
Breast	3/55 (6)	3 (<1)
Pancreatic	2/55 (4)	2 (<1)
Ovarian/uterine/cervical	1/55 (2)	1 (<1)
Liver/gall bladder	1/55 (2)	1 (<1)
Thyroid	2/55 (4)	2 (<1)
Pharyngeal/laryngeal	1/55 (2)	1 (<1)
Other	2/55 (4)	2 (<1)
Hematologic neoplasia	24 (18)	23 (3)
AML/MDS	14/24 (58)	13 (2)
Indolent B-non-Hodgkin lymphoma	3/24 (13)	3 (<1)
Aggressive B-non-Hodgkin lymphoma	2/24 (8)	2 (<1)
ALL	1/24 (4)	1 (<1)
CML	1/24 (4)	1 (<1)
Other	3/24 (13)	3 (<1)
Basalioma, squamous cell	19 (14)	17 (2)
Prolonged neutropenia		
2 months after end of treatment		101 (13)
12 months after end of treatment		30 (4)

Fischer et al, Blood 2016

Increased risk of secondary malignancies after FC/FCR

Issues with 1st generation BTKi

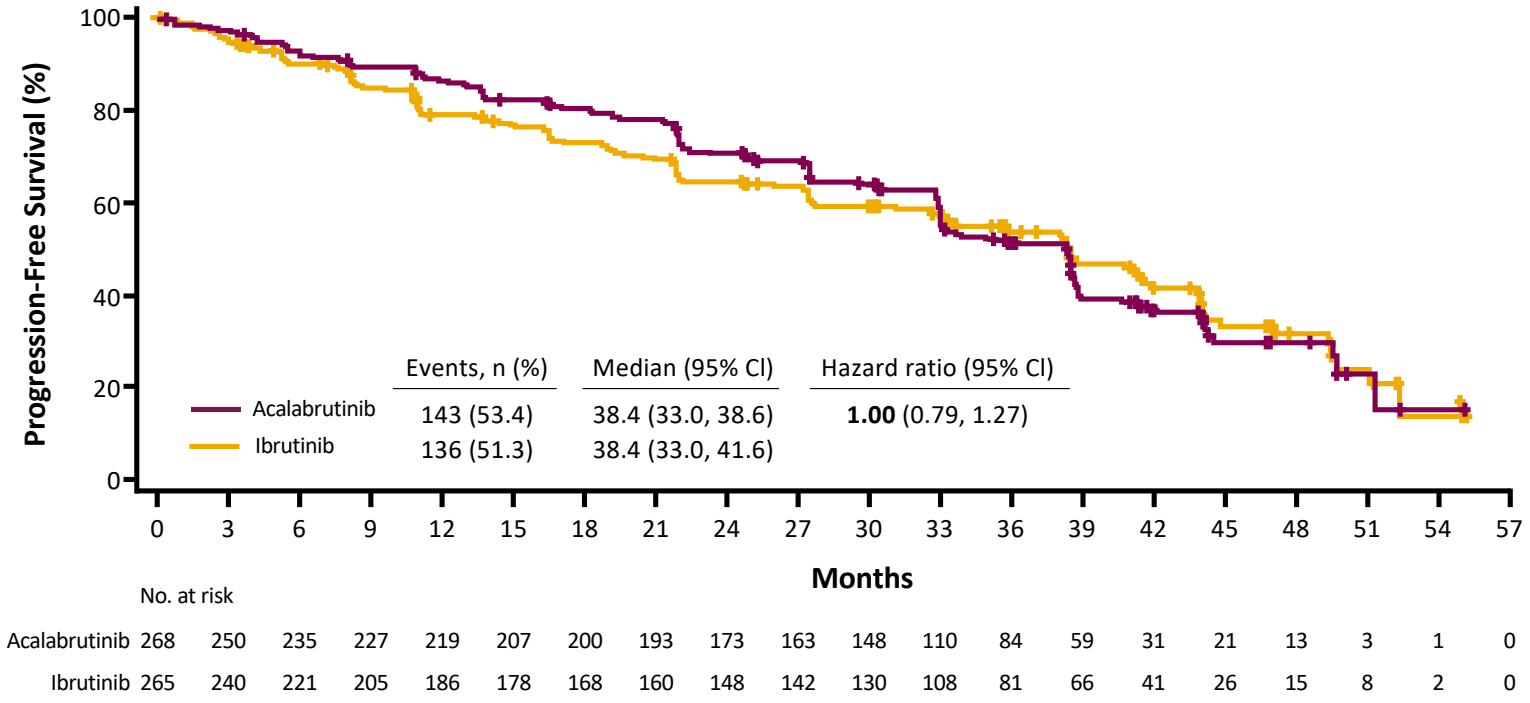
- Distinct toxicity profile
  - Cardiovascular toxicity
    - Atrial fibrillation
    - Ventricular fibrillation/arrythmia
    - Cardiac arrests / sudden death
    - Congestive heart failure
  - Bleeding disorder
  - Hypertension
- High discontinuation rates (up to 40% in the first 24 months)



Wiczer et al, Blood Advances 2021

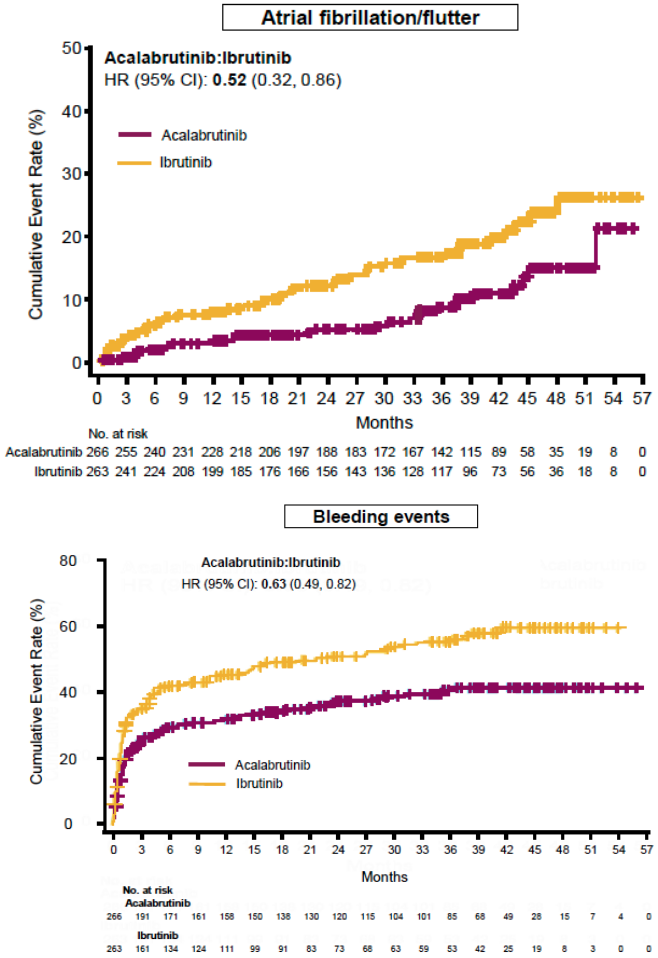
Can continuous next-generation BTKi overcome this?

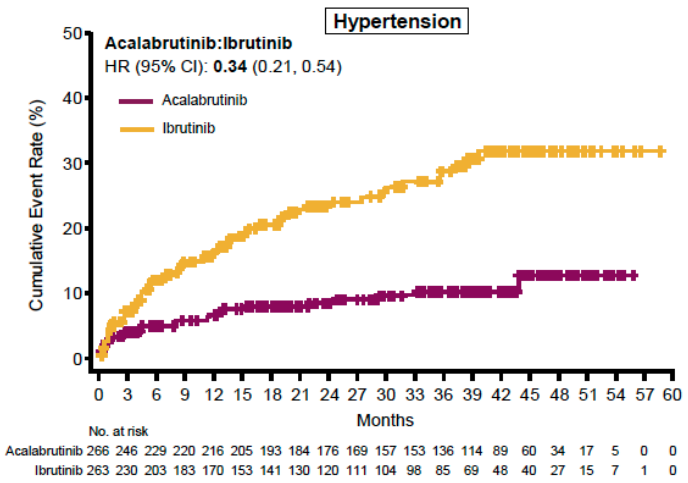
PFS Acalabrutinib = Ibrutinib



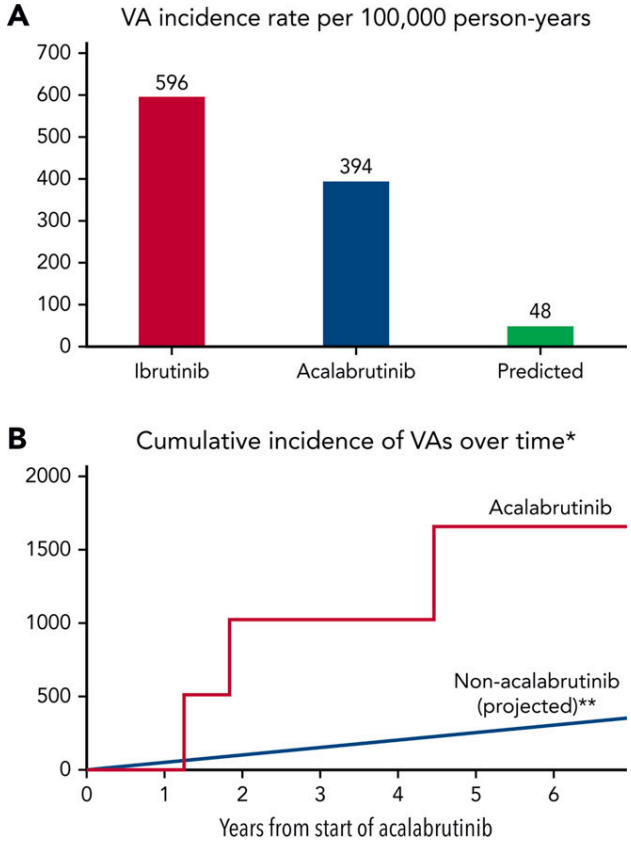
Byrd et al, JCO, 2021

Downsides of continuous BTKi





AF, hypertension, bleeding less common with acalabrutinib than with ibrutinib, but <u>only relative risk reduction</u>



Byrd et al, JCO, 2021

Bhat et al, 2022

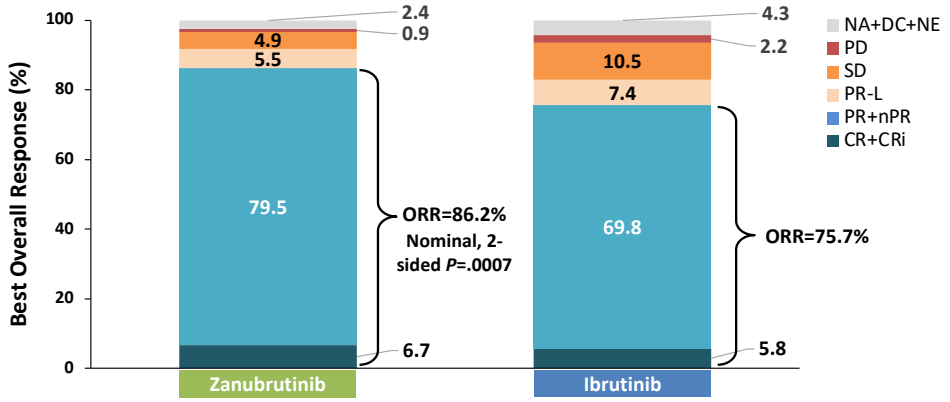
What about Zanubrutinib?

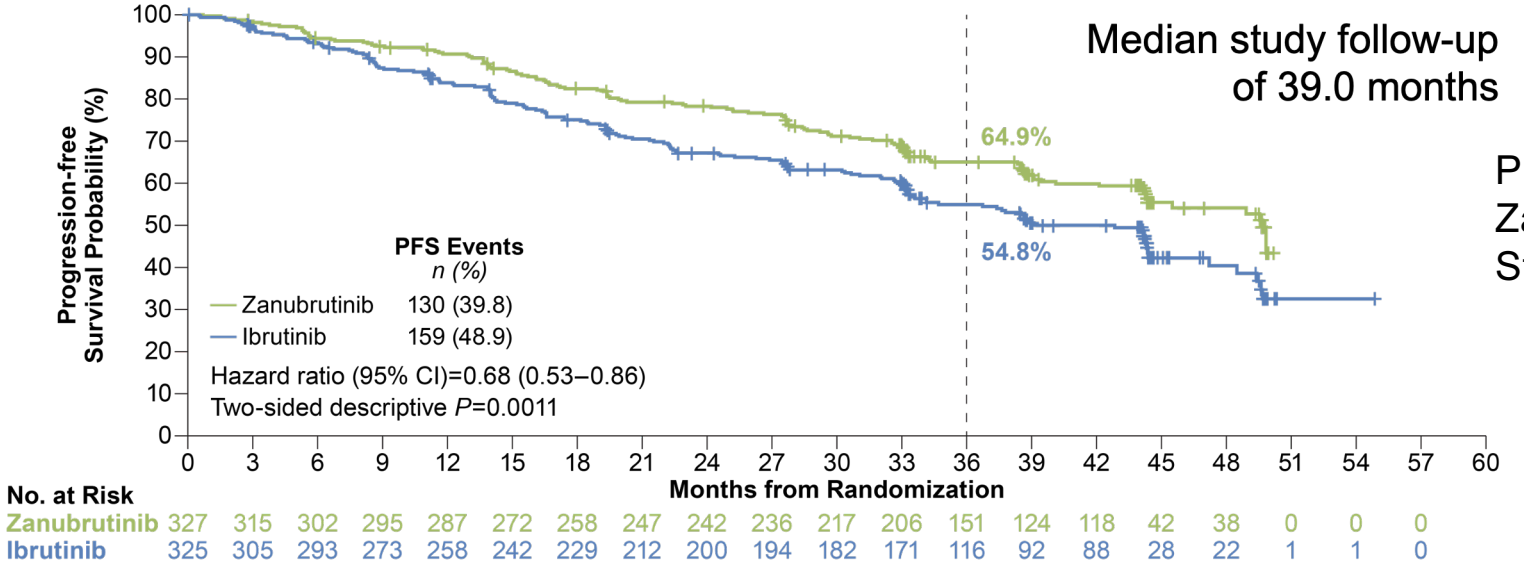
AESI, n (%)	Any Grade		Grade ≥3	
	Zanubrutinib (n=324)	**Ibrutinib (n=324)**	**Zanubrutinib (n=324)**	**Ibrutinib (n=324)**
≥1 AESI	**294 (90.7)**	**300 (92.6)**	**186 (57.4)**	**184 (56.8)**
Anemia	50 (15.4)	53 (16.4)	7 (2.2)	8 (2.5)
Atrial fibrillation and flutter	17 (5.2)	43 (13.3)	8 (2.5)	13 (4.0)
Hemorrhage	137 (42.3)	134 (41.4)	11 (3.4)	12 (3.7)
Major hemorrhage	12 (3.7)	14 (4.3)	11 (3.4)	12 (3.7)
Hypertension	76 (23.5)	74 (22.8)	49 (15.1)	44 (13.6)
Infections	231 (71.3)	237 (73.1)	86 (26.5)	91 (28.1)
Opportunistic infection	7 (2.2)	10 (3.1)	5 (1.5)	5 (1.5)
Neutropenia†	95 (29.3)	79 (24.4)	68 (21.0)	59 (18.2)
Secondary primary malignancies	40 (12.3)	43 (13.3)	22 (6.8)	17 (5.2)
Skin cancers	21 (6.5)	28 (8.6)	7 (2.2)	4 (1.2)
Thrombocytopenia	42 (13.0)	50 (15.4)	11 (3.4)	17 (5.2)
Tumor lysis syndrome	1 (0.3)	0	1 (0.3)	0

Atrial fibrillation less common with zanubrutinib compared with ibrutinib, but other toxicities equally common.

Brown et al, ASH 202

What about Zanubrutinib?





Median study follow-up of 39.0 months

PFS **möglicherweise** mit Zanubrutinib. Caveats bezgl Studiendesign.

Brown et al, ASH 202

Fixed-duration targeted treatment

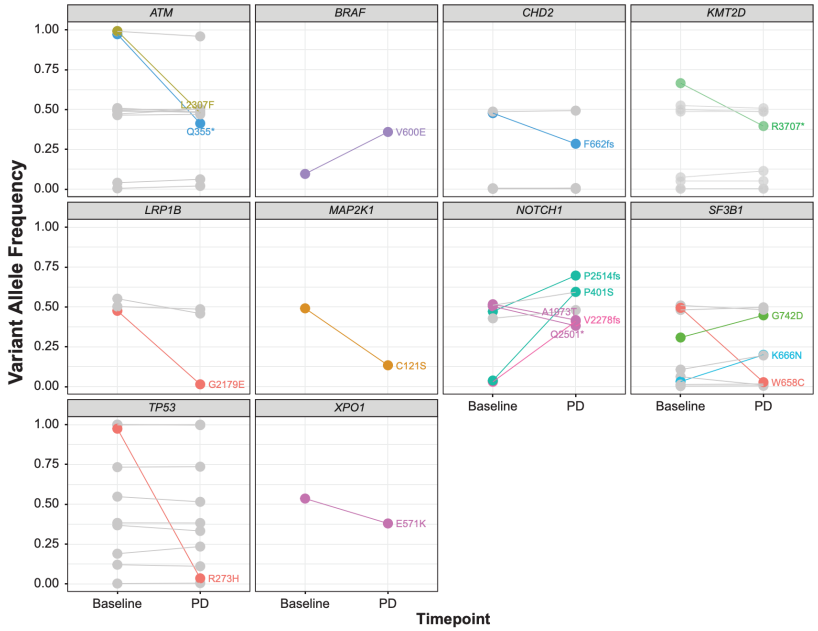
Established:
- Venetoclax – Obinutuzumab
- Venetoclax – Ibrutinib

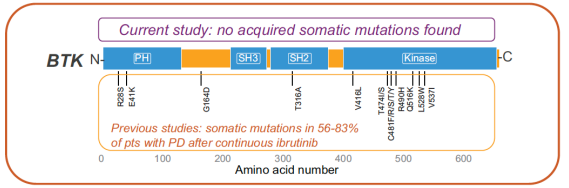
Phase 2 / in development:
- Venetoclax – Obinutuzumab - Ibrutinib
- Venetoclax – Obinutuzumab - Acalabrutinib
- Venetoclax – Acalabrutinib
- Sonrotoclax – Zanubrutinib
- …

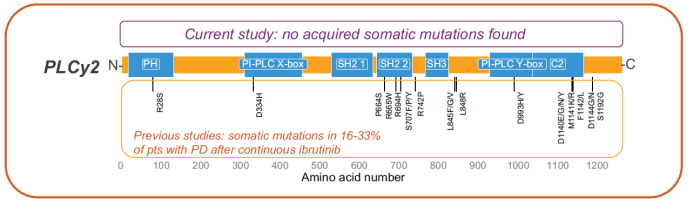
Rationale for limited- or fixed-duration therapy

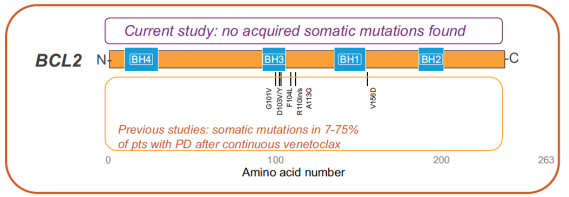
Three key advantages

- Less toxicity
- less drug-exposure
- less resistance development => re-treatment possibility







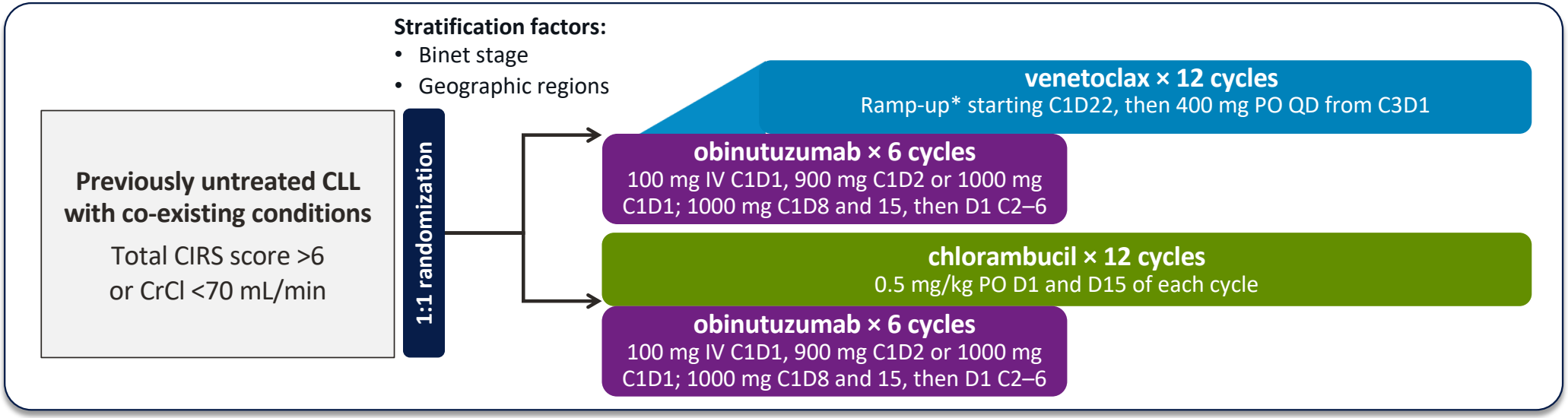


Croner et al, EHA 2022

CLL14 Study

A fixed-duration 1L approach for unfit patients with CLL

CLL14 Study Design



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

Key Secondary Endpoints (ITT population):
- PFS – IRC-assessed
- ORR and CR 3 months after EoT
- MRD response rate (PB and BM) 3 months after EoT:
  - All patients
  - Patients with CR
- Overall survival

Analyses:
- Interim analysis: 110 PFS events
- Final PFS analysis: 170 PFS events
- Final OS analysis: End of study, 5 years after last patient enrolled

28-day cycles.
* Venetoclax 5-week dose ramp-up starting C1D22: 1 week each of 20, 50, 100, and 200 mg, then 400 mg for 1 week, thereafter continuing at 400 mg until completion of cycle 12. BM, bone marrow; CIRS, cumulative illness rating scale; CR, complete remission; CrCl, creatinine clearance; EoT, end of treatment; IRC, Independent Review Committee; ITT, intention-to-treat; IV, intravenous; ORR, overall response rate; PB, peripheral blood; PO, orally; QD, daily.

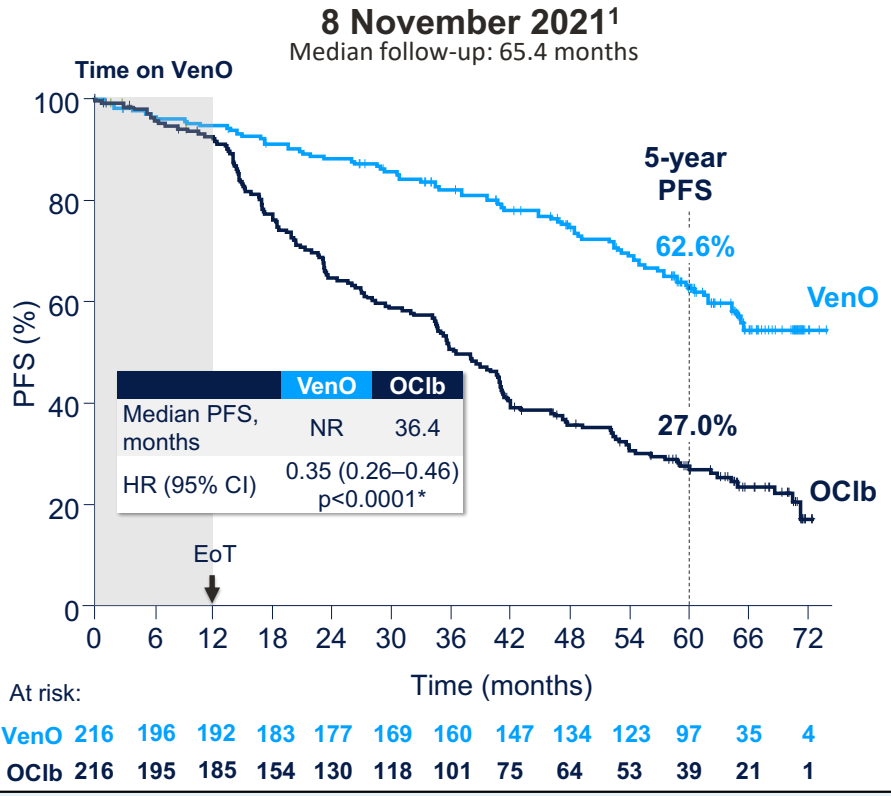
Fischer K, *et al. N Engl J Med* 2019; **380:**2225–2236.

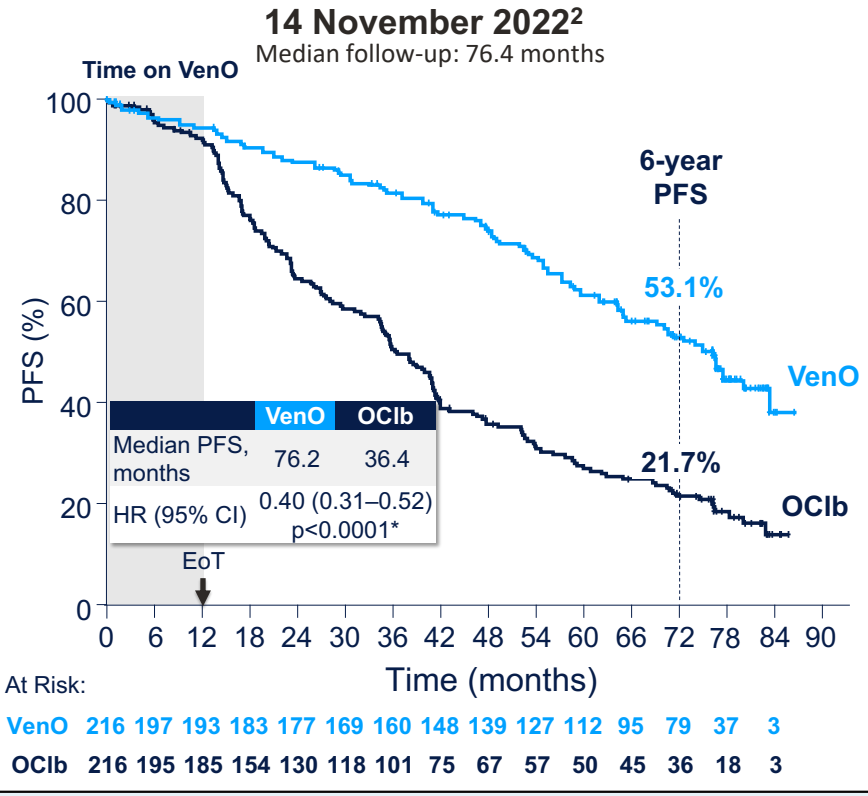
Baseline characteristics

Characteristic		VenG (N=216)	GClb (N=216)
Age	Median, years (range)	72 (43–89)	71 (41–89)
	≥75 years, n (%)	72 (33.3)	78 (36.1)
Male, n (%)		146 (67.6)	143 (66.2)
Binet stage, n (%)	A	46 (21.3)	44 (20.4)
	B	77 (35.6)	80 (37.0)
	C	93 (43.1)	92 (42.6)
TLS risk category, n (%)	Low	29 (13.4)	26 (12.0)
	Intermediate	139 (64.4)	147 (68.1)
	High	48 (22.2)	43 (19.9)
Total CIRS score	Median (range)	9 (0–23)	8 (1–28)
	>6, n (%)	186 (86.1)	177 (81.9)
Estimated CrCl*	Median, mL/min (range)	65.2 (0.1–3670.0)	67.5 (31.0–2217.6)
	<70 mL/min, n/N (%)	128/215 (59.5)	118/213 (55.4)
del(17p), n/N (%)		17/200 (8.5)	14/193 (7.3)
Other cytogenetic subgroups as per hierarchy, n/N (%)	del(11q)	36/200 (18.0)	38/193 (19.7)
	Trisomy in 12	36/200 (18.0)	40/193 (20.7)
	No abnormality	50/200 (25.0)	42/193 (21.8)
	del(13q) alone	61/200 (30.5)	59/193 (30.6)
***TP53* mutation status, n/N (%)**	Mutated	19/171 (11.1)	13/157 (8.3)
	Unmutated	152/171 (88.9)	144/157 (91.7)
***TP53* deleted and/or mutated, n/N (%)**		24/172 (14.0)	22/161 (13.7)
***IGHV* mutation status, n/N (%)**	Mutated	76/200 (38.0)	83/208 (39.9)
	Unmutated	121/200 (60.5)	123/208 (59.1)
	Not evaluable	3/200 (1.5)	2/208 (1.0)

Fischer K, Al-Sawaf O *et al. N Engl J Med* 2019; **380:**2225–2236.

Progression-free survival





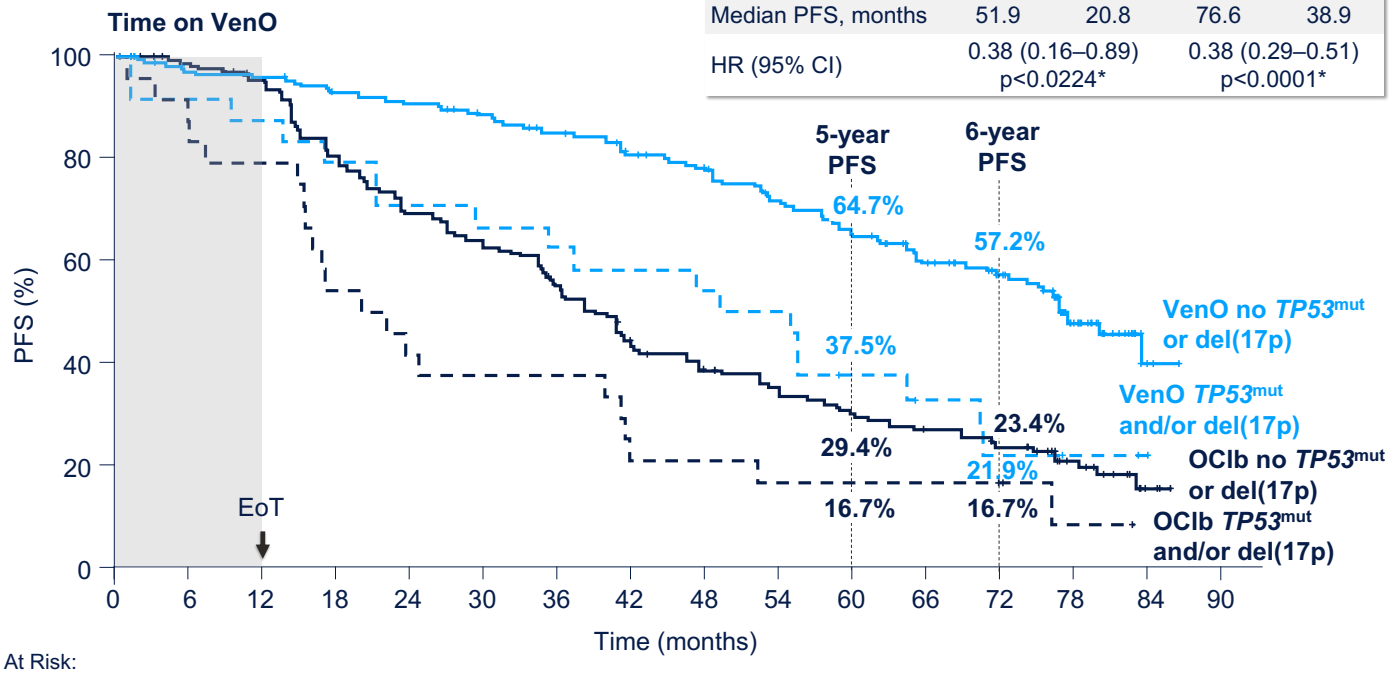
PFS benefit was sustained 5 years after completing VenO, with a 60% reduction in risk of PD or death

1. Al-Sawaf O, et al. *Nat Commun* 2023; 14:2147; 2. Al-Sawaf O, et al. EHA 2023. Abstract S145.

PFS according to *TP53* status

Median follow-up: 76.4 months

	TP53^{mut} and/or del(17p)		No *TP53*^{mut} or del(17p)	
	VenO	OClb	VenO	OClb
Median PFS, months	51.9	20.8	76.6	38.9
HR (95% CI)	0.38 (0.16–0.89) p<0.0224*		0.38 (0.29–0.51) p<0.0001*	



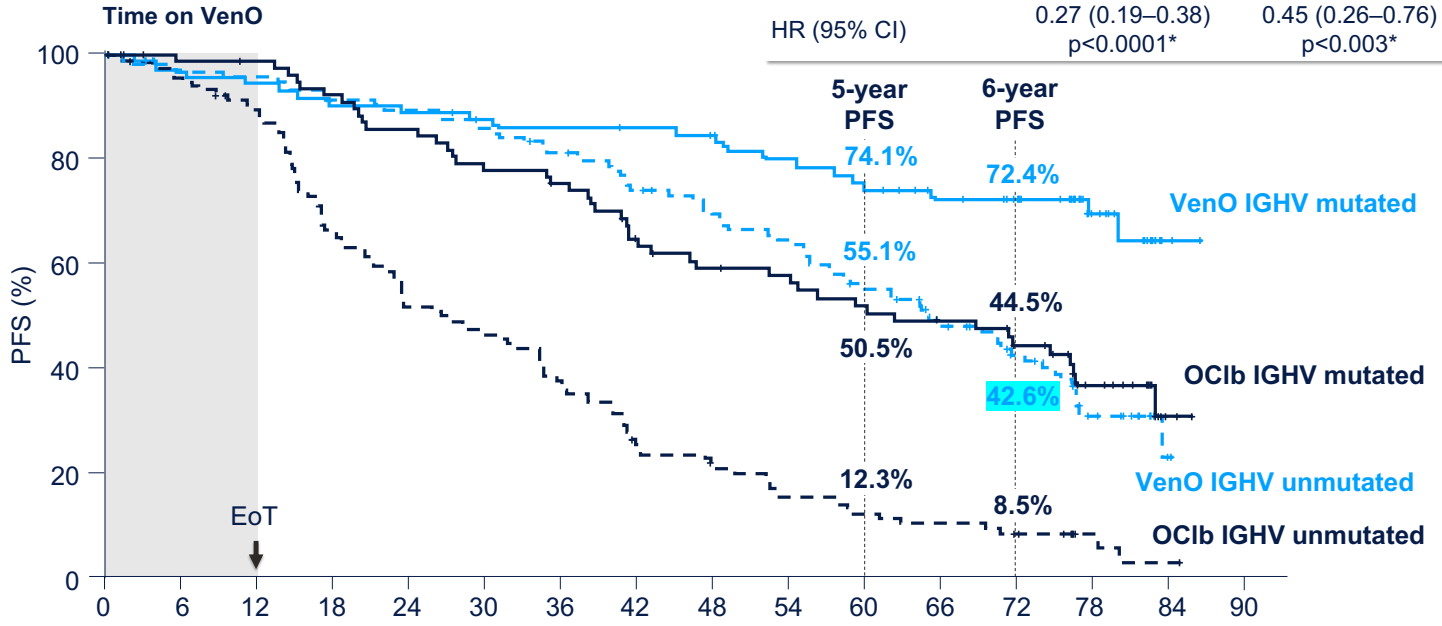
At Risk:

OClb *TP53*^{mut} and/or del(17p)	24	20	19	13	10	9	9	5	5	4	4	4	3	1	
VenO *TP53*^{mut} and/or del(17p)	25	22	21	19	17	16	15	14	13	12	8	6	4	2	
OClb no *TP53*^{mut} or del(17p)	184	169	160	135	117	106	90	68	60	51	45	40	33	17	3
VenO no *TP53*^{mut} or del(17p)	184	170	168	161	157	150	142	131	123	112	101	87	73	34	3

PFS according to *IGHV* status

Median follow-up: 76.4 months

	IGHV unmutated		IGHV mutated	
	VenO	OCIb	VenO	OCIb
Median PFS, months	64.8	26.9	NE	62.2
HR (95% CI)	0.27 (0.19–0.38) p<0.0001*		0.45 (0.26–0.76) p<0.003*	

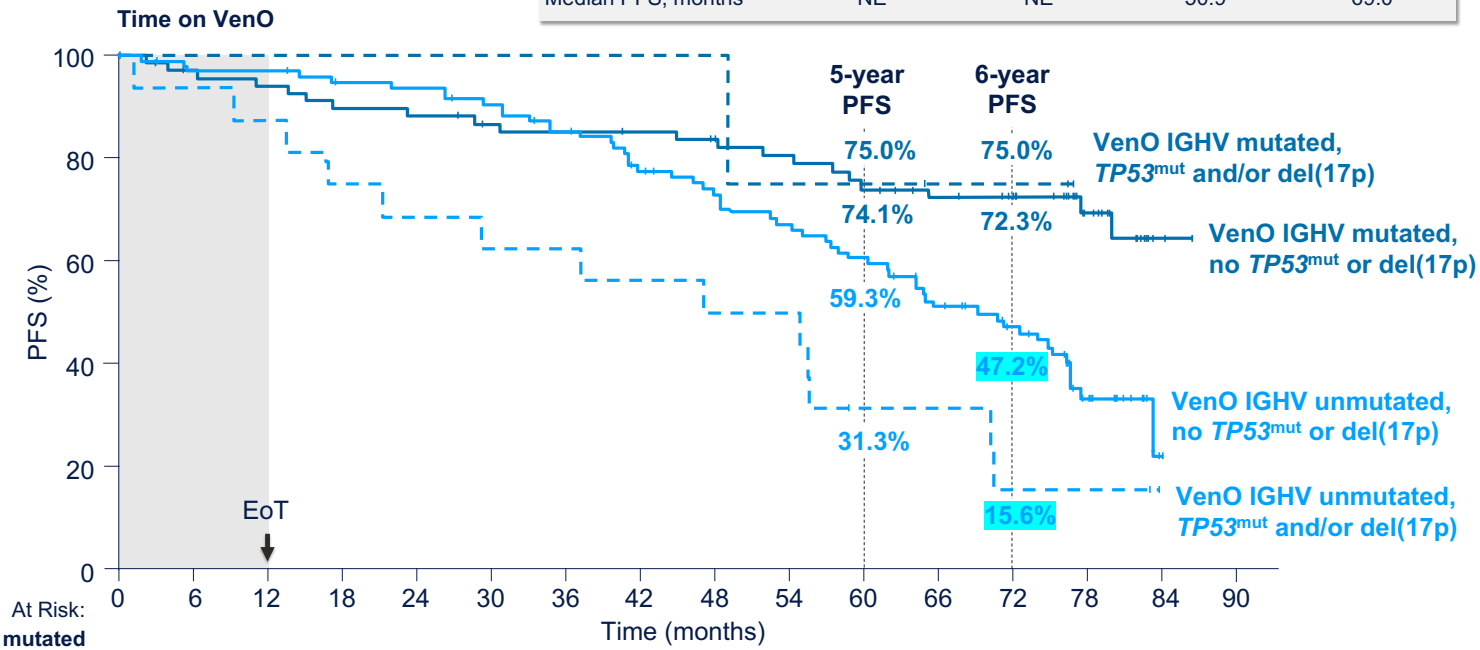


At Risk:															
OCIb IGHV mutated	83	77	76	71	66	60	57	46	42	39	35	33	28	15	2
VenO IGHV mutated	76	70	68	65	64	61	60	59	57	53	49	44	39	19	2
OCIb IGHV unmutated	123	110	101	75	59	53	41	26	22	16	13	11	8	3	1
VenO IGHV unmutated	121	111	110	103	101	96	90	80	73	68	57	47	37	17	1

PFS by IGHV & *TP53* Status

Median follow-up: 76.4 months

	VenO			
	IGHV mutated		IGHV unmutated	
	With *TP53*^{mut} and/or del(17p)	No *TP53*^{mut} or del(17p)	With *TP53*^{mut} and/or del(17p)	No *TP53*^{mut} or del(17p)
Median PFS, months	NE	NE	50.9	69.0



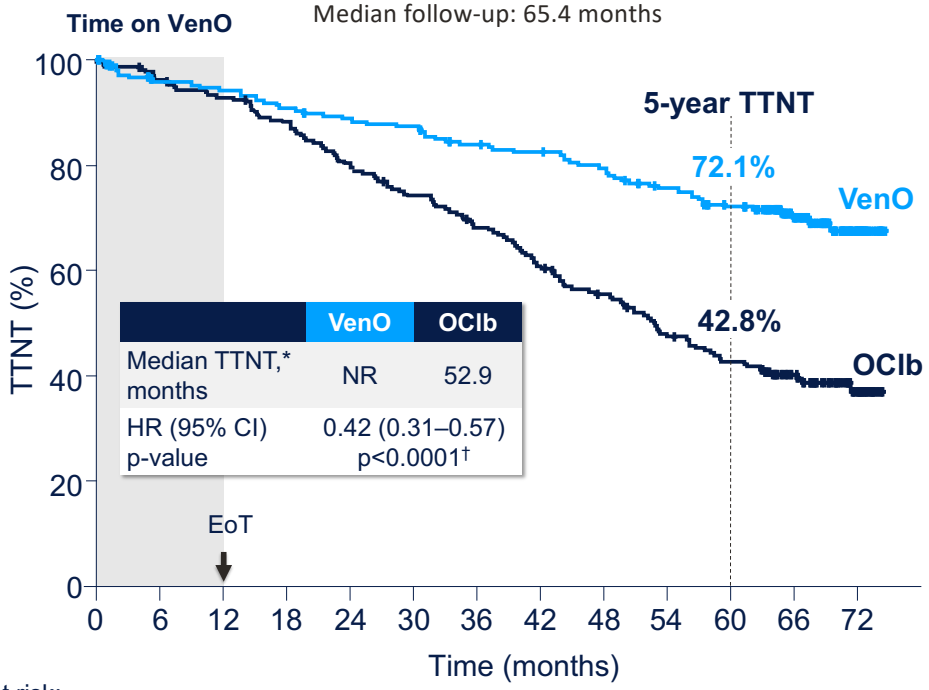
At Risk:															
VenO IGHV mutated															
***TP53*^{mut} and/or del(17p)**	5	4	4	4	4	4	4	4	4	3	3	2	2		
No *TP53*^{mut} or del(17p)	71	66	64	61	60	57	56	55	53	50	46	42	37	19	2
VenO IGHV unmutated															
***TP53*^{mut} and/or del(17p)**	16	15	14	12	11	10	10	9	8	8	4	4	2	2	
No *TP53*^{mut} or del(17p)	103	94	94	90	89	85	79	70	64	59	52	43	35	15	1

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

Time-to-next-treatment

8 November 2021[1]

Median follow-up: 65.4 months

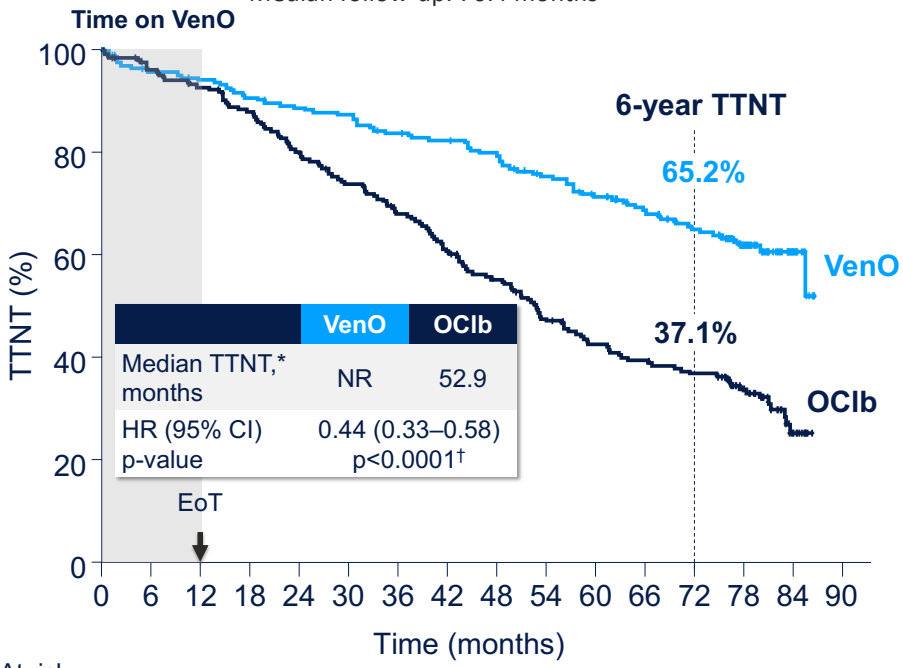


At risk:

VenO	216	198	195	188	183	180	172	168	161	150	140	85	22
OCIb	216	203	194	183	166	153	140	125	111	94	83	59	17

14 November 2022[2]

Median follow-up: 76.4 months

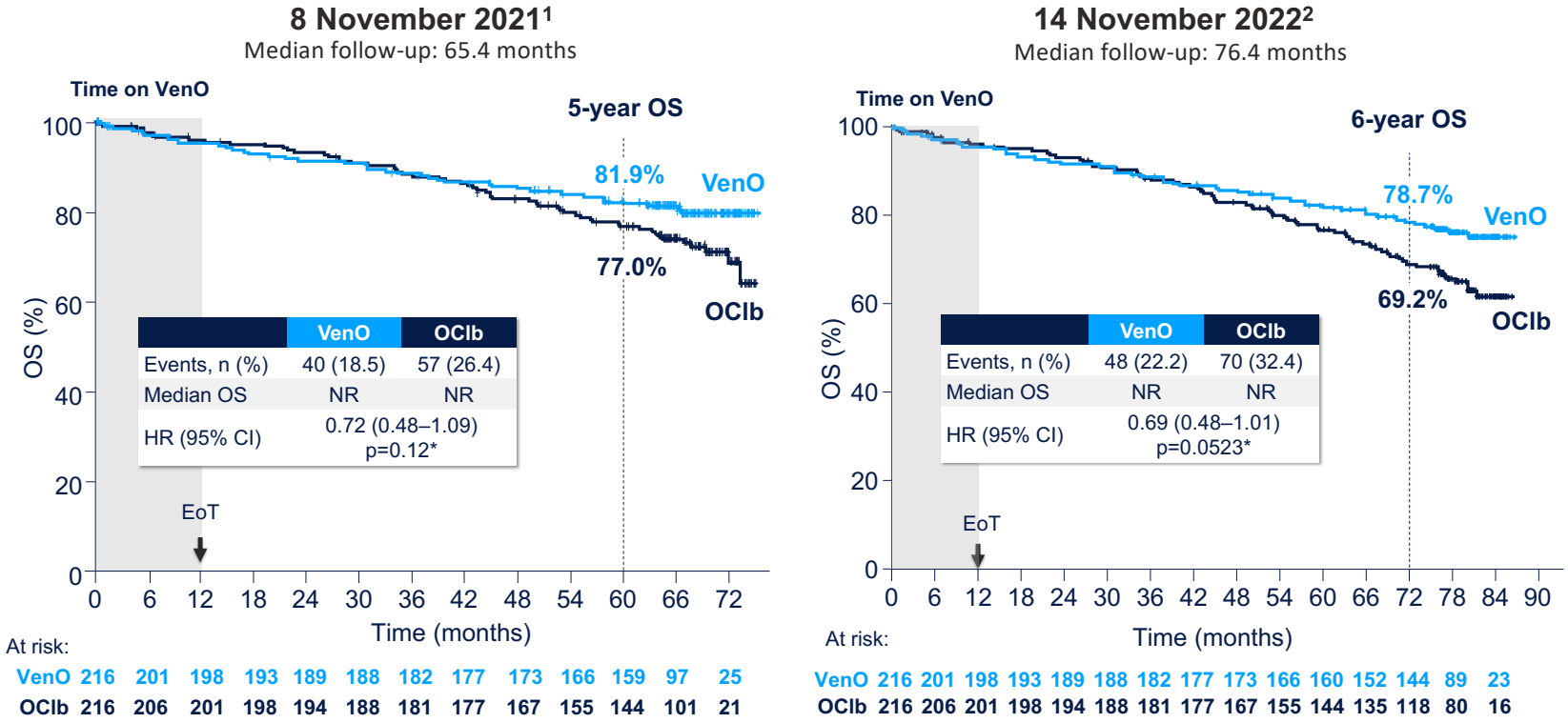


At risk:

VenO	216	198	195	188	183	180	172	168	161	150	140	130	118	73	20
OCIb	216	203	194	183	166	153	140	125	111	94	83	77	70	46	10

1. Al-Sawaf O, et al. *Nat Commun* 2023; 14:2147; 2. Al-Sawaf O, et al. EHA 2023. Abstract S145.

Overall survival

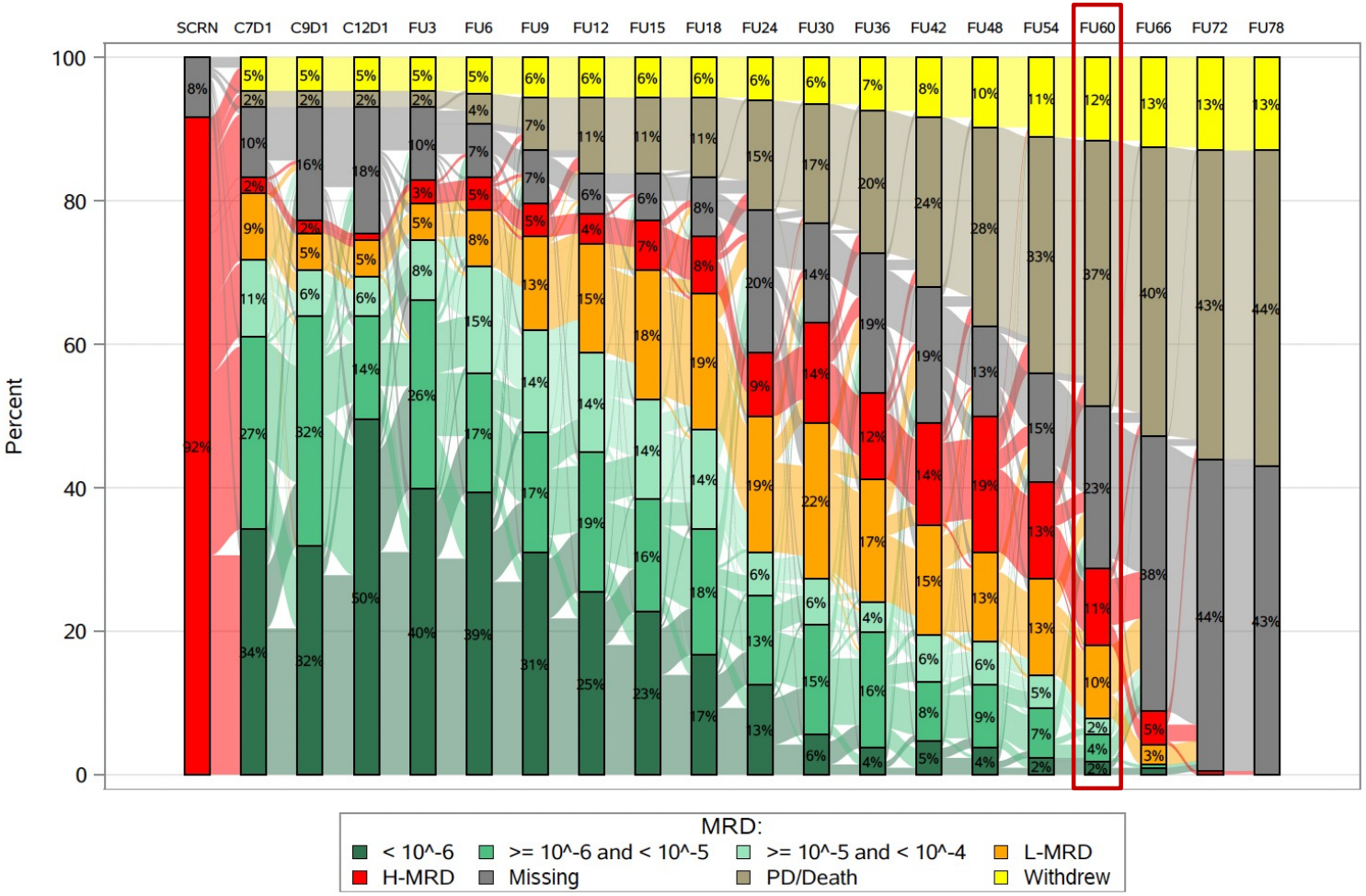


Patients treated with VenO fixed treatment combination continued to show a consistent improvement in OS compared to patients treated with OClb.

1. Al-Sawaf O, et al. *Nat Commun* 2023; 14:2147; 2. Al-Sawaf O, et al. EHA 2023. Abstract S145.

LONGITUDINAL MRD ASSESSMENTS

By NGS in peripheral blood: **Ven-Obi**

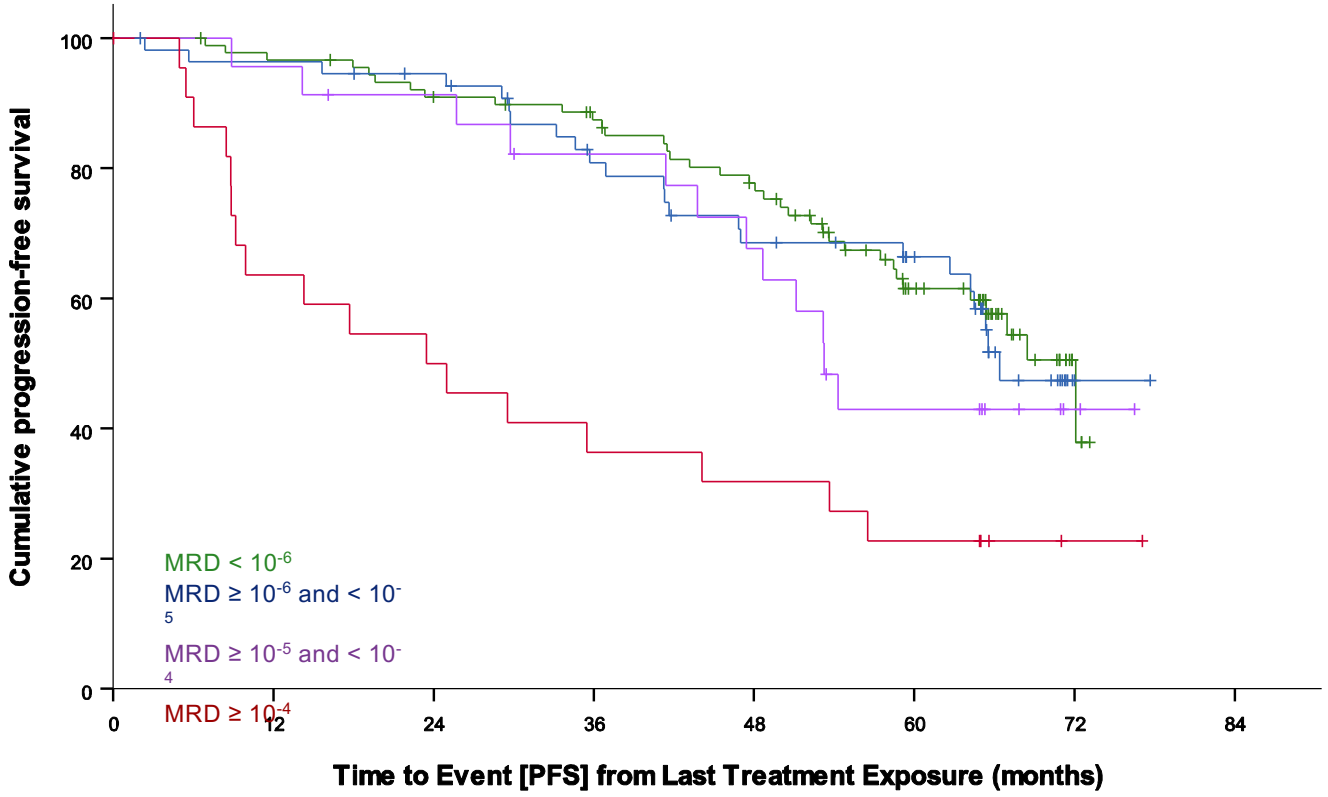


5 years after Ven-Obi, **7.9%** of patients had sustained MRD $<10^{-4}$.

Al-Sawaf et al, EHA 2023

PFS AFTER VEN-OBI ACCORDING TO *MRD STATUS*

End-of-treatment MRD status in peripheral blood, by NGS



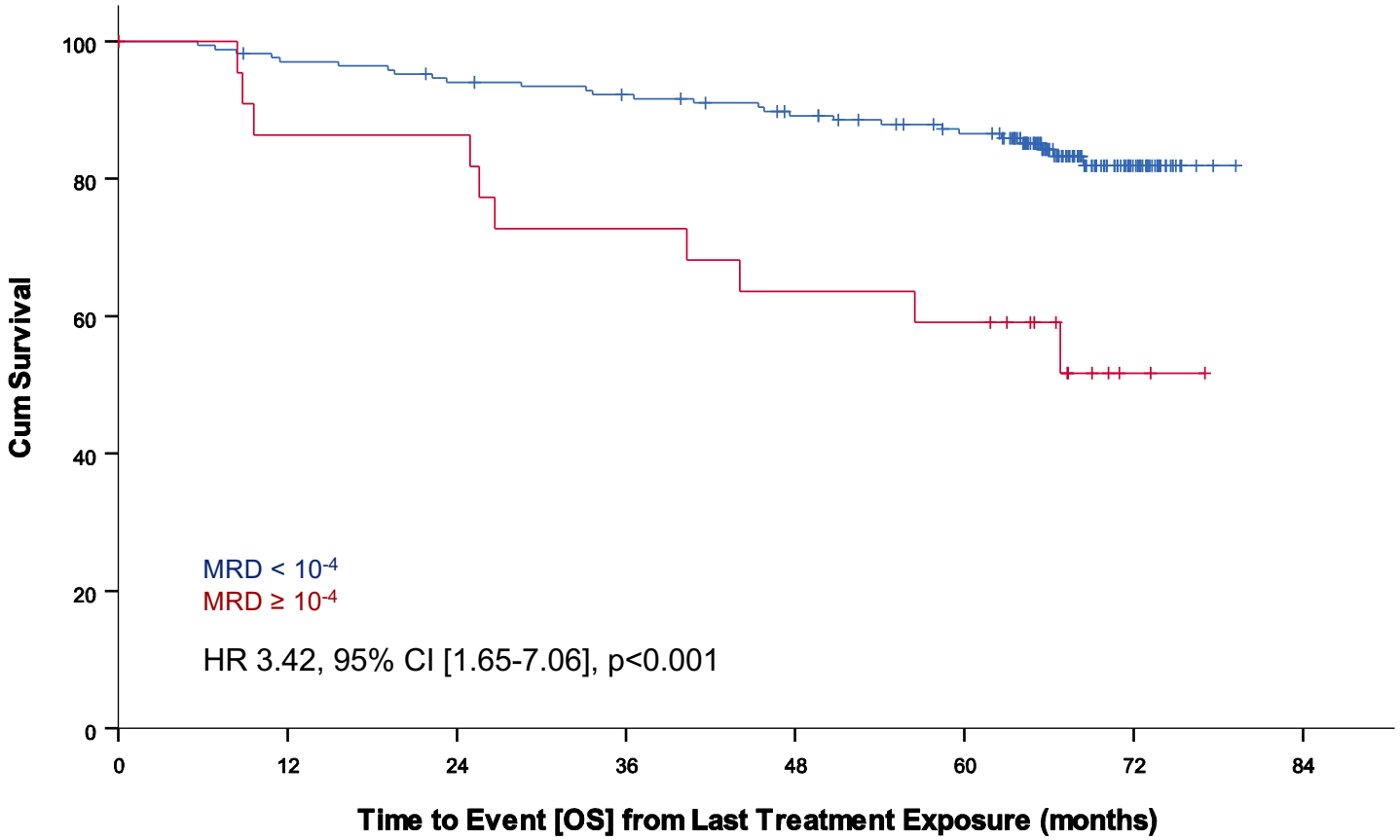
MRD < 10^{-6}	90	86	79	73	63	38	4	0
MRD ≥ 10^{-6} and < 10^{-5}	56	53	50	40	33	26	2	0
MRD ≥ 10^{-5} and < 10^{-4}	23	22	20	17	14	8	2	0
MRD ≥ 10^{-4}	23	14	11	8	7	5	1	0

Depth of remission correlates with **long-term PFS**, indicating the prognostic value of the end-of-treatment MRD status.

Al-Sawaf O, et al. *Lancet Oncol*. 2020;21(9):1188-1200
Al-Sawaf et al, EHA 2023

OS AFTER VEN-OBI ACCORDING TO MRD STATUS

End of treatment MRD status in peripheral blood, by NGS



MRD < 10^{-4}	169	163	157	152	143	131	32	0
MRD ≥ 10^{-4}	23	19	19	16	14	13	2	0

Patients with MRD ≥10^{-4} after Ven-Obi have **a shorter OS** than patients with MRD <10^{-4}, highlighting the need for dedicated MRD-guided approaches.

Al-Sawaf et al, EHA 2023

Safety

	Venetoclax-obinutuzumab (N=212)		Chlorambucil-obinutuzumab (N=214)	
	During Treatment	**After Treatment**	**During Treatment**	**After Treatment**
Neutropenia	51.9%	3.8%	47.2%	1.9%
Thrombocytopenia	14.2%	0.5%	15.0%	0.0%
Anemia	7.5%	1.9%	6.1%	0.5%
Febrile neutropenia	4.2%	0.9%	3.3%	0.5%
Leukopenia	2.4%	0.0%	4.7%	0.0%
Pneunomia	3.8%	3.3%	3.7%	1.4%
Infusion-related reaction	9.0%	0.0%	9.8%	0.5%
Tumour lysis syndrome	1.4%	0.0%	3.3%	0.0%

No new safety signals identified with longer follow-up (76.4 months)

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

CLL13 Study

A fixed-duration 1L approach for fit patients with CLL

CLL13 Study design

Fit patients with CLL N=926

Select inclusion criteria:
CIRS ≤6 & normal CrCl*
Excludes:
del(17p)/*TP53*^{mut}

Stratification factors:
- Age
- Binet stage
- Country

1:1:1:1 randomization

n=229 — CIT: FCR ≤65 yrs (n=150); BR >65 yrs (n=79) × 6 cycles

n=237 — Venetoclax 400 mg PO QD (ramp-up) × 12 cycles
Rituximab 375 (500) mg/m^2 IV × 6 cycles

n=229 — Venetoclax 400 mg PO QD (ramp-up) × 12 cycles
Obinutuzumab 1,000 mg IV × 6 cycles

n=231 — Venetoclax 400 mg PO QD (ramp-up) × 12 cycles
Ibrutinib 420 mg PO QD x 12 cycles up to cycle 36 if no uMRD
Obinutuzumab 1,000 mg IV × 6 cycles

Co-Primary Endpoints

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

Key Secondary Endpoints

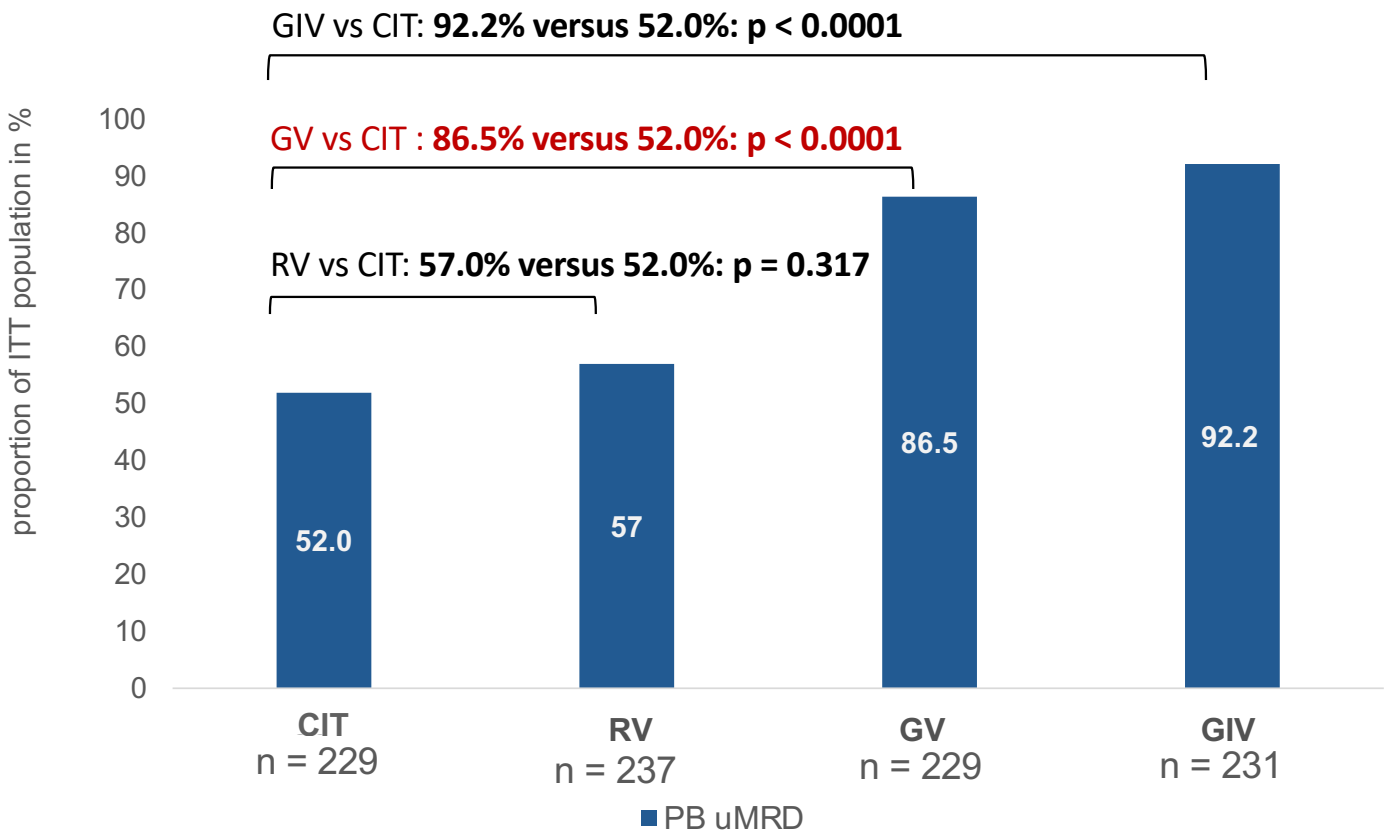
- MRD in PB at month 15 (all other comparisons)
- MRD in BM at final restaging
- PFS (all other comparisons)
- ORR
- CR/CRi rate
- OS

* Normal CrCl defined as ≥70 mL/min; 28-day cycles; Data cut for first co-primary endpoint analysis: February 28, 2021.
BM, bone marrow; BR, bendamustine + rituximab; CIRS, cumulative illness rating scale; CIT, chemoimmunotherapy; CrCl, creatinine clearance; FCR, fludarabine + cyclophosphamide + rituximab; IVO, ibrutinib + venetoclax + obinutuzumab; PB, peripheral blood.

ClinicalTrials.gov: http://clinicaltrials.gov/ct2/show/NCT02950051 (accessed December 2021);
Eichhorst B, *et al.* ASH 2021. Abstract 71 (Oral).

Results of coprimary endpoint rate of undetectable minimal residual disease (uMRD)

Coprimary endpoint: uMRD (< 10^{-4}) at Mo15 in PB by 4-colour-flow

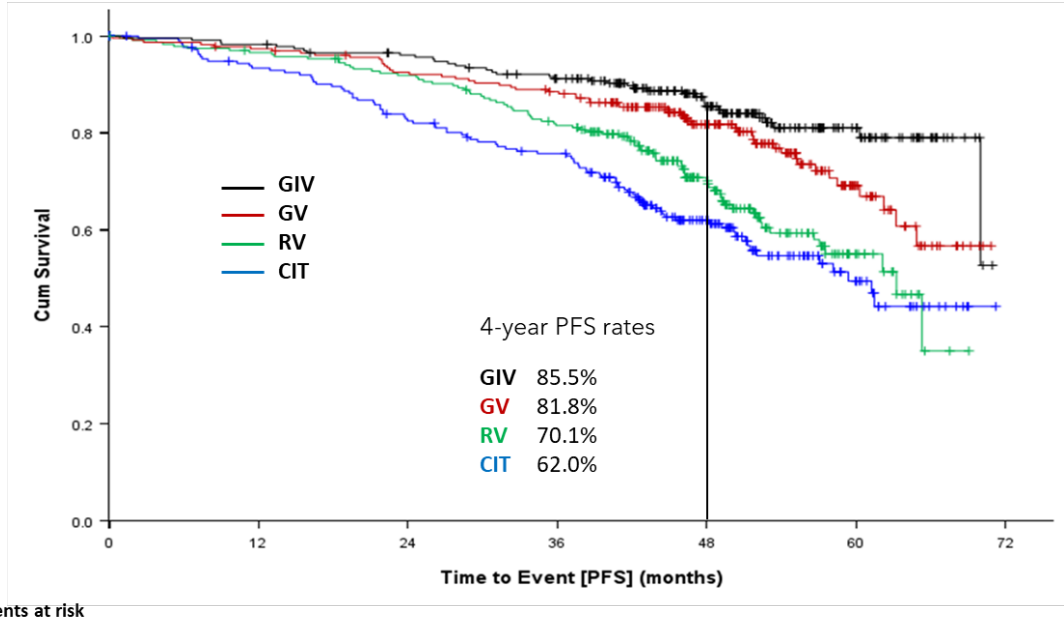


	uMRD%	97.5% CI
GIV	92.2	87.3 – 95.7
GV	86.5	80.6 – 91.1
RV	57.0	49.5 – 64.2
CIT	52.0	44.4 – 59.5

Eichhorst B. et al., ASH 2021: abstract 72

PFS according to treatment arm

Progression-free survival



Patients at risk

CIT	229	197	173	156	84	24
RV	237	227	214	188	106	21
GV	229	222	209	198	121	32
GIV	231	227	218	201	130	44

PFS comparisons

GIV *vs* **CIT**: HR 0.30, 97.5%CI: 0.19-0.47, ***p<0.001***
GIV *vs* **RV**: HR 0.38, 97.5%CI: 0.24-0.59, ***p<0.001***
GIV *vs* **GV**: HR 0.63, 97.5%CI: 0.39-1.02, p=0.03

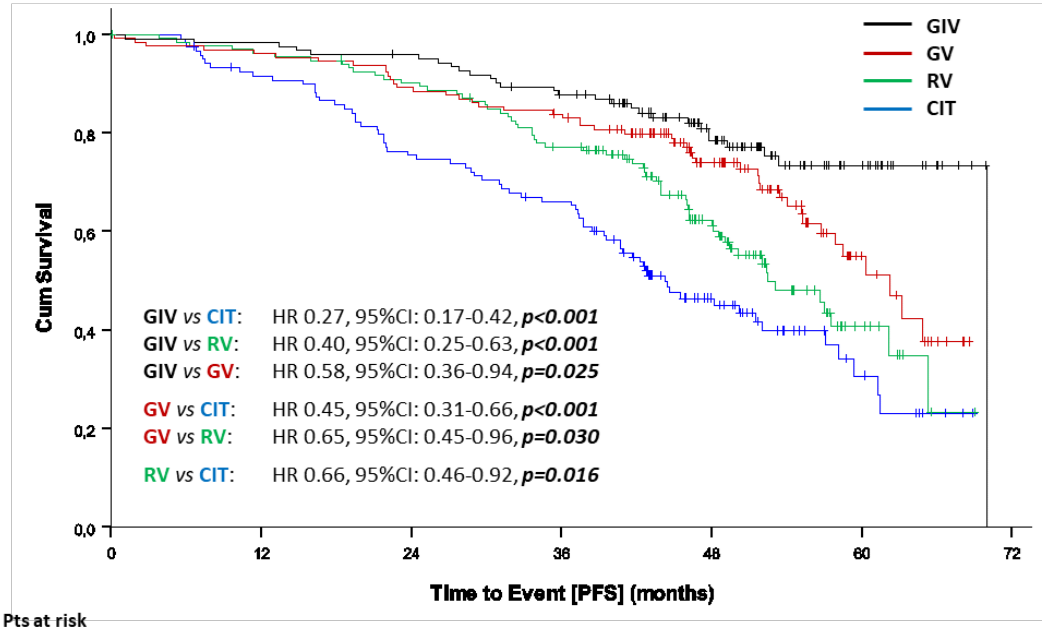
GV *vs* **CIT**: HR 0.47, 97.5%CI: 0.32-0.69, ***p<0.001***
GV *vs* **RV**: HR 0.57, 97.5%CI: 0.38-0.84, ***p=0.001***

RV *vs* **CIT**: HR 0.78, 97.5%CI: 0.55-1.10, p=0.1

Fürstenau et al, ASH 2023

PFS according to IGHV status and treatment arm

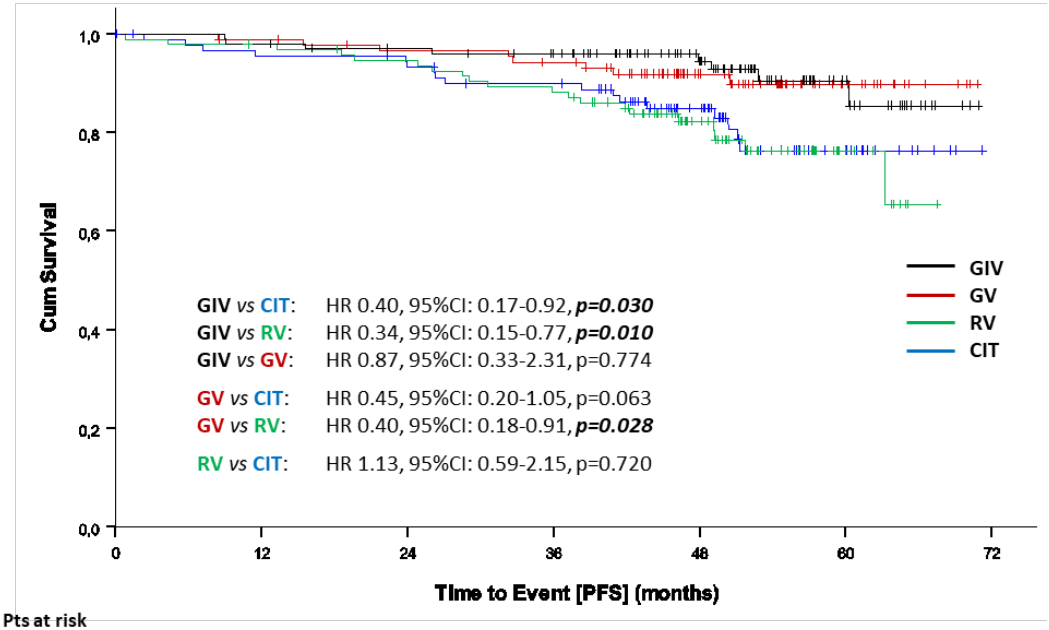
PFS, patients with unmutated IGHV



Pts at risk

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

PFS, patients with mutated IGHV



Pts at risk

CIT	95	86	83	78	50	15
RV	95	92	88	82	47	11
GV	89	87	83	80	48	15
GIV	101	99	95	90	60	20

Fürstenau et al, ASH 2023

Adverse Events ≥ CTC Grade 3 Overview

Severe AEs occurring in ≥5% of pts in at least one arm and of interest

	CIT	RV	GV	GIV
All patients of safety population	**216**	**237**	**228**	**231**
All ≥ CTC grade 3 events (%)	**176 (81.5)**	**173 (73.0)**	**192 (84.2)**	**193 (83.5)**
Blood and lymphatic system (%)	122 (56.5)	103 (43.5)	128 (56.1)	117 (50.6)
Infections and infestations (%)	44 (20.4)	27 (11.4)	34 (14.9)	51 (22.1)
Febrile neutropenia (%)	24 (11.1)	10 (4.2)	7 (3.1)	18 (7.8)
Infusion related reaction (%)	12 (5.6)	19 (8)	26 (11.4)	10 (4.3)
Tumor lysis syndrome (%) *	9 (4.2)	24 (10.1)	19 (8.3)	15 (6.5)
Hypertension (%)	3 (1.4)	5 (2.1)	4 (1.8)	13 (5.6)

* Defined by Cairo-Bishop criteria

Second primary malignancy & RT

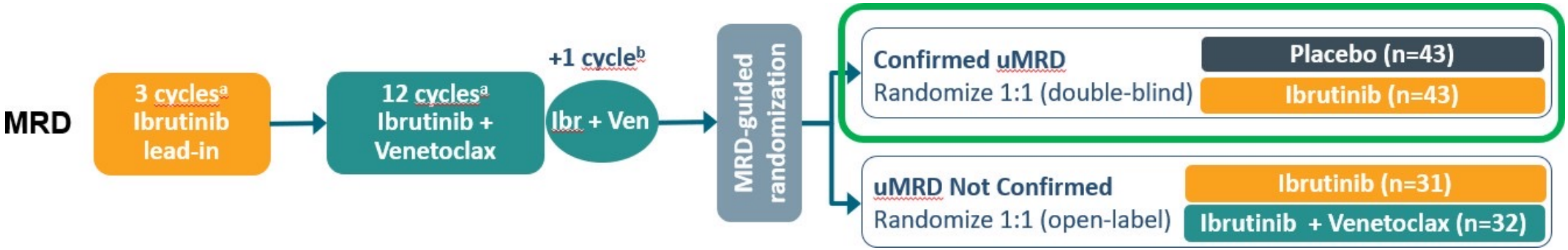
Cases of second cancers	**CIT**	**RV**	**GV**	**GIV**	**Total**
Hematological malignancies	4	2	0	8	14
Solid tumors	19	13	15	18	65
Non-melanoma skin cancer	33	15	16	11	75
Richter's transformations	6	5	7	3	21
Incidence rates (per 1000 pt-months)					
All SPM (excl. NMSC and Richter's)	2.21	1.21	1.16	2.36	1.71

GLOW und CAPTIVATE Studie

Venetoclax plus Ibrutinib in 1L CLL

CAPTIVATE MRD Cohort Study Design

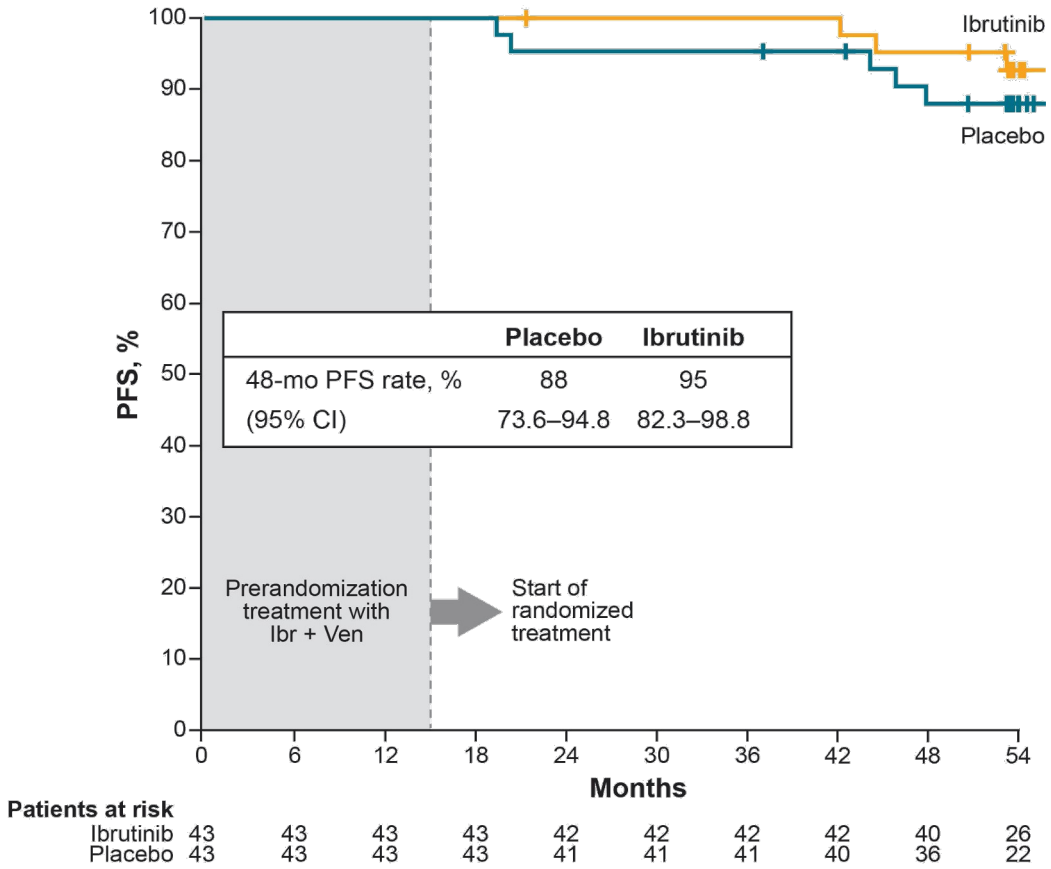
- CAPTIVATE (NCT02910583) is an international, multicenter phase 2 study evaluating first-line treatment with the Ibr + Ven combination
- The CAPTIVATE study comprises 2 cohorts: FD[1] and MRD[2]
- In this MRD cohort, after completion of Ibr + Ven, patients with Confirmed uMRD* were randomly assigned to double- blind treatment with placebo (ie, a fixed-duration regimen), or continued ibrutinib



1. *Tam CSet al. Blood. 2022;139:3278-3289.* 2. Wierda, WG. *J Clin Oncol*, 2021;39:3853-3865.

ASH 2022; Allan JN et al.

3-year Progression-free survival



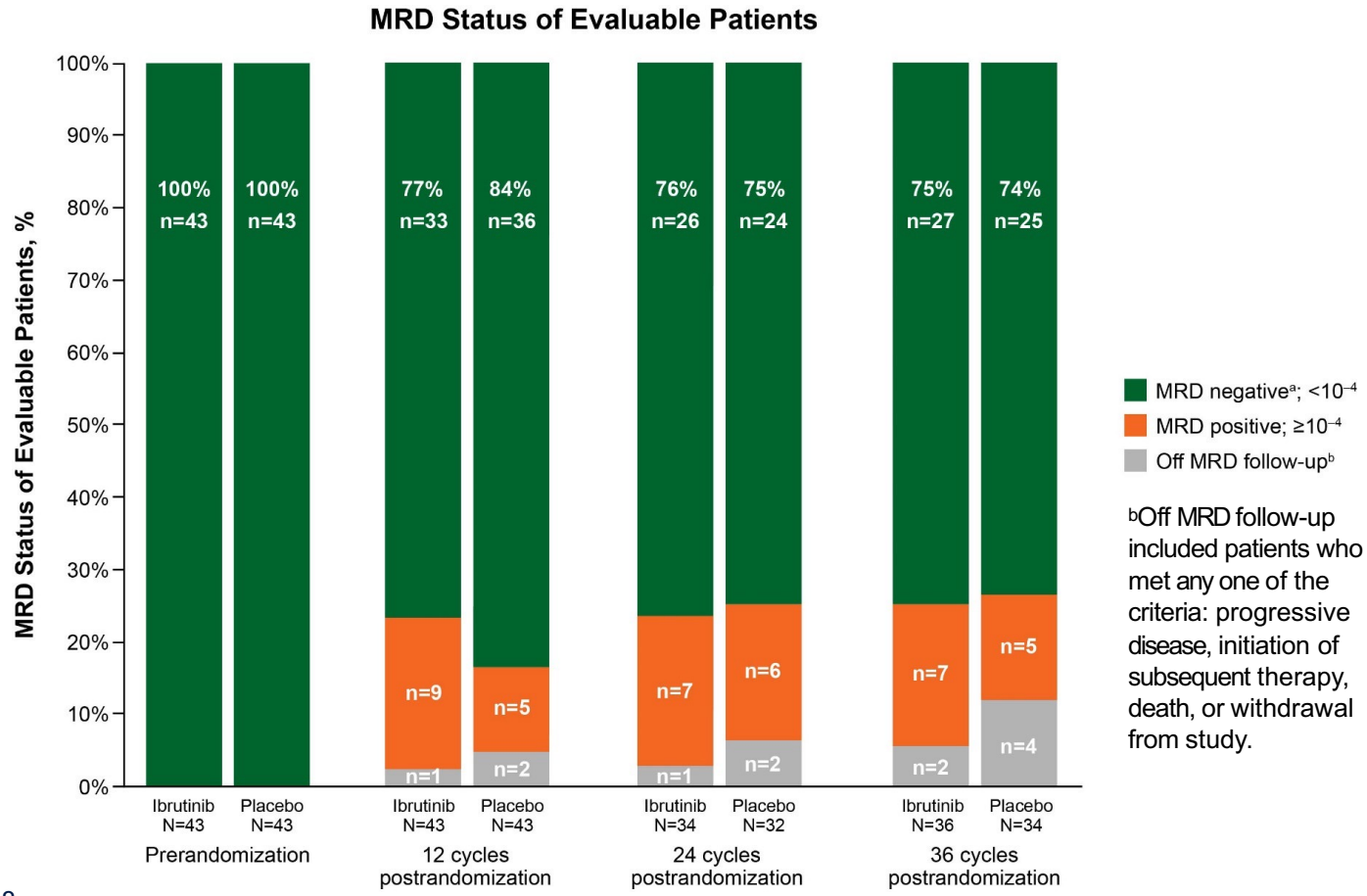
- At 48 months, PFS was 88% (95% CI, 74–95) with placebo and 95% (95% CI, 82–99) with continued ibrutinib

PD and Retreatment Outcomes

- 3 of 7 patients with PD in the placebo arm have initiated retreatment with ibrutinib; all 3 patients had PR
- 2 patients in the ibrutinib arm had PD; none have initiated retreatment

ASH 2022; Allan JN et al.

MRD Negativity Rates Were Sustained 3-years Post-randomization



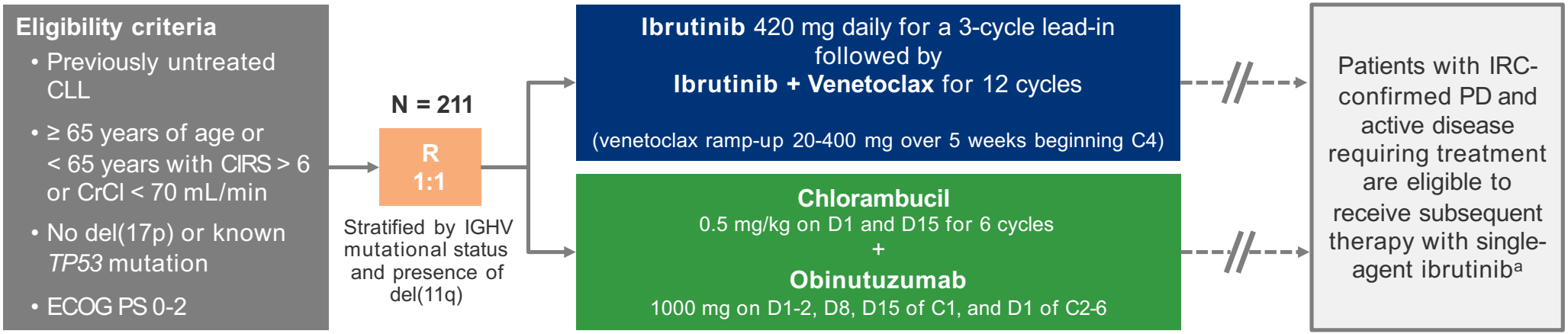
[b]Off MRD follow-up included patients who met any one of the criteria: progressive disease, initiation of subsequent therapy, death, or withdrawal from study.

- **The sustainability of MRD negativity in the ITT population was comparable to that observed in the evaluable population**
  - Ibrutinib arm (ITT): 77% (33/43), 60% (26/43) and 63% (27/43) at 12, 24, and 36 cycles postrandomization, respectively
  - Placebo arm (ITT): 84% (36/43), 56% (24/43), and 58% (25/43) at 12, 24, and 36 cycles postrandomization, respectively

[a]MRD negative status <10–4 by 8-color flow cytometry.

ASH 2022; Allan JN et al.

Phase 3 GLOW Study



- **Primary end point: IRC-assessed PFS**
- Key secondary end points: uMRD rates, response rates, overall survival, time to next treatment, and safety
- Current analysis
  - Median study follow-up of 46 months (range, 1.7-51.7)
  - MRD assessed in peripheral blood in responders by NGS

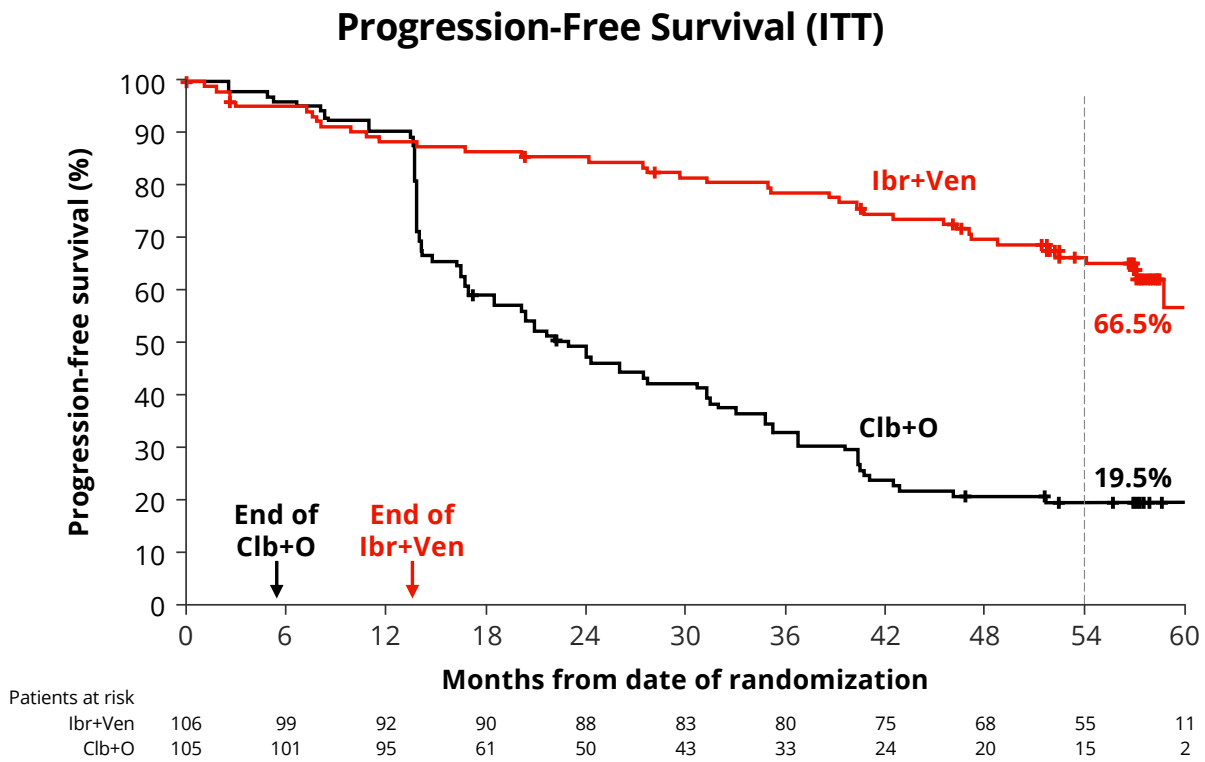
[a]Ibrutinib provided by the Sponsor to patients from both arms who were eligible to participate in the Subsequent Therapy Phase of the study.
C, cycle (28 days); CIRS, Cumulative Illness Rating Scale score; CrCl, creatinine clearance; D, day; ECOG PS, Eastern Cooperative Oncology Group performance status; IRC, independent review committee; PD, progressive disease; R, randomization; uMRD, undetectable minimal residual disease; NGS, next-generation sequencing.

GLOW Baseline Demographics and Characteristics

Characteristics	Ibr+Ven (N = 106)	Clb+O (N = 105)
Age, median (range), years	71.0 (47-93)	71.0 (57-88)
≥ 75 years, n (%)	35 (33.0)	37 (35.2)
Male, n (%)	59 (55.7)	63 (60.0)
ECOG PS 1-2, n (%)	71 (67.0)	66 (62.9)
CIRS score, median (range)	9 (1-20)	8 (0-22)
> 6,[a] n (%)	**74 (69.8)**	**61 (58.1)**
CrCl,[b] mL/min, median (range)	66.5 (34.0-168.1)	63.2 (32.3-180.9)
Bulky disease ≥ 5 cm, n (%)	41 (39.0)	38 (36.2)
Elevated LDH,[a] n (%)	**35 (33.0)**	**51 (48.6)**
IGHV status,[c] n (%)		
Mutated	32 (30.2)	35 (33.3)
Unmutated	67 (63.2)	57 (54.3)
Unknown	7 (6.6)	13 (12.4)
Del11q, n (%)	20 (18.9)	18 (17.1)
TP53 mutation, n (%)	7 (6.6)	2 (1.9)

[a]Denotes > 10% numerical difference between arms. [b]Using the Cockcroft-Gault equation. [c]IGHV status of baseline samples were updated since primary analysis based on post hoc reclassification using clonoSEQ (Adaptive Biotechnologies, Seattle, WA).
ECOG PS, Eastern Cooperative Oncology Group performance status; CIRS, Cumulative Illness Rating Scale score; CrCl, creatinine clearance; LDH, lactate dehydrogenase.

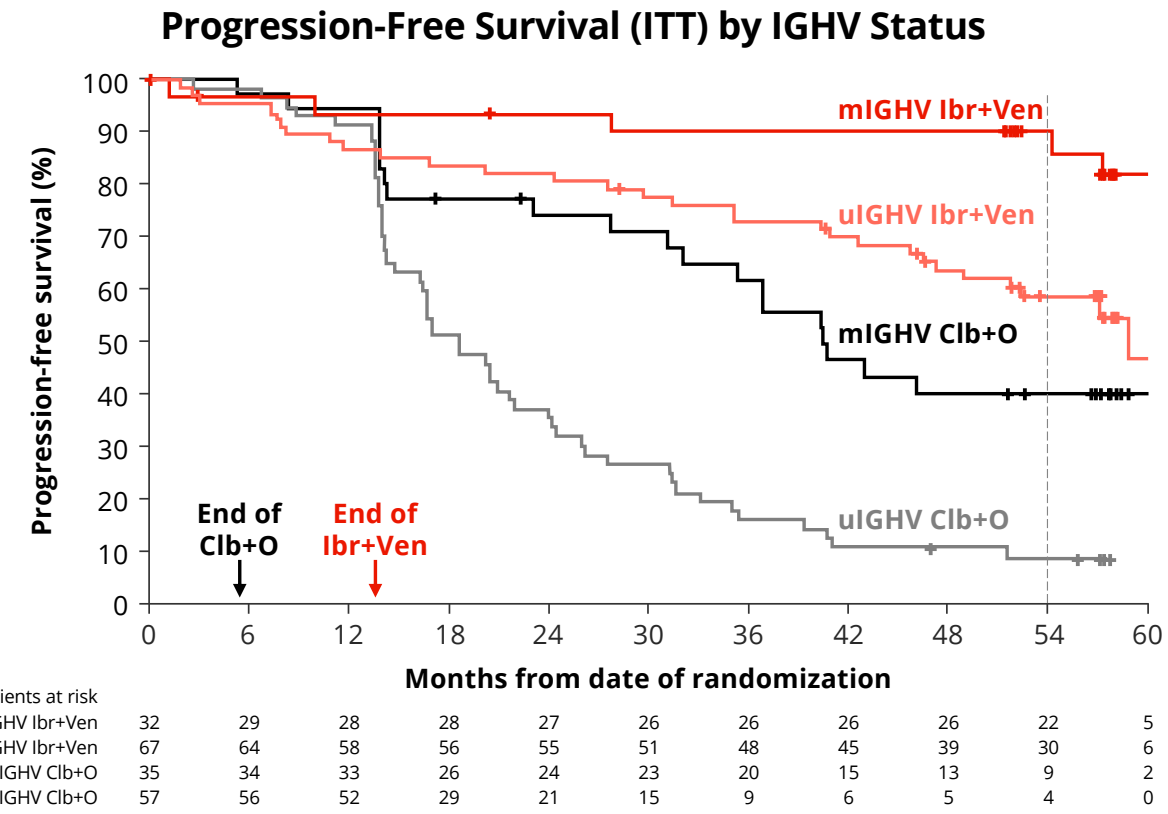
GLOW: Progression-Free Survival



- **Ibr+Ven reduced the risk of progression or death by 74%** versus Clb+O
  - HR 0.256 (95% CI, 0.172-0.382); $p < 0.0001$
- Estimated 54-month PFS rates at 57 months of follow-up:
  - **66.5%** for Ibr+Ven
  - **19.5%** for Clb+O

Follows et al, ASH 2023

GLOW: PFS by IGHV

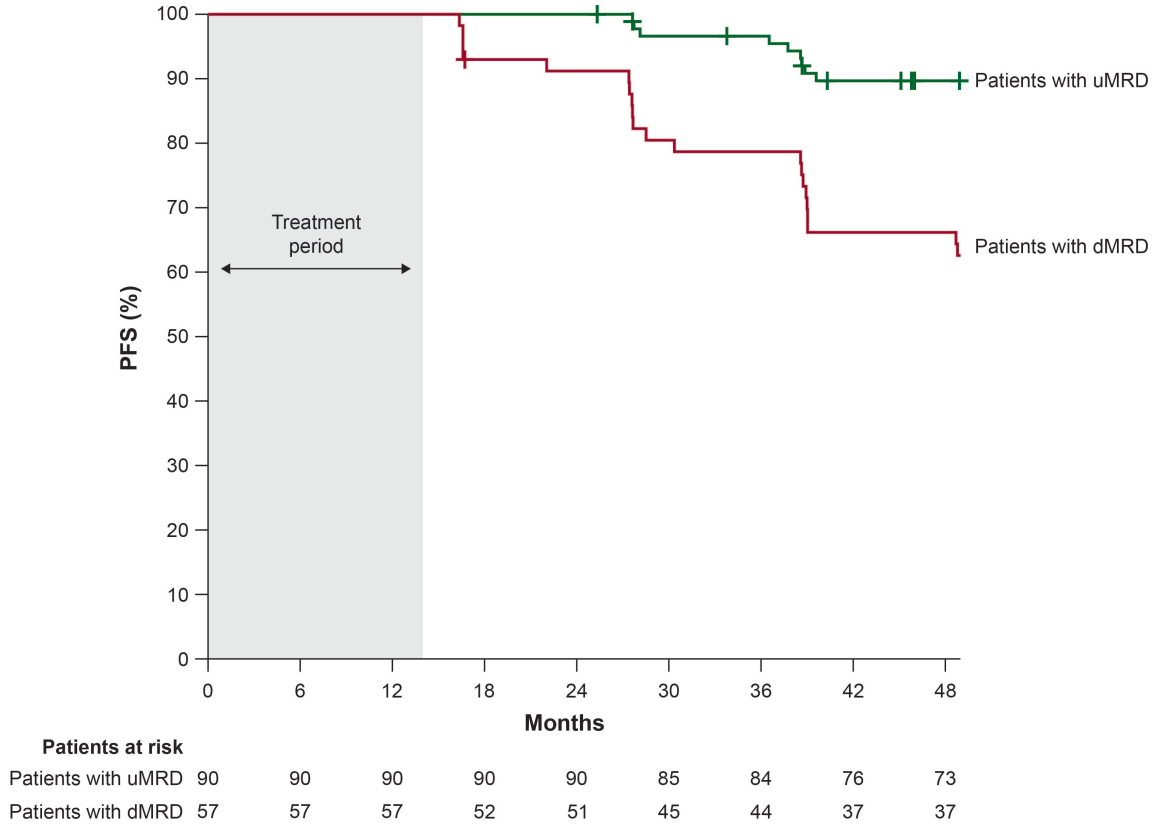


Patients at risk											
mIGHV Ibr+Ven	32	29	28	28	27	26	26	26	26	22	5
uIGHV Ibr+Ven	67	64	58	56	55	51	48	45	39	30	6
mIGHV Clb+O	35	34	33	26	24	23	20	15	13	9	2
uIGHV Clb+O	57	56	52	29	21	15	9	6	5	4	0

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

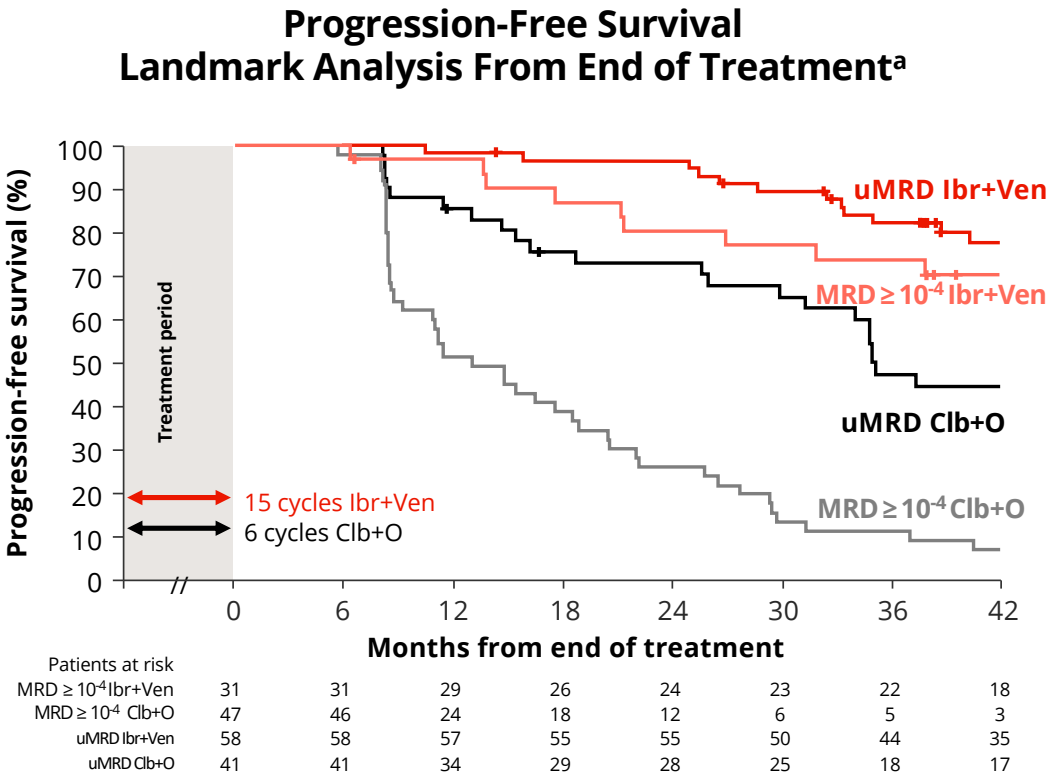
Follows et al, ASH 2023

Captivate: PFS by EoT-MRD



Ghia et al, ICML 2023

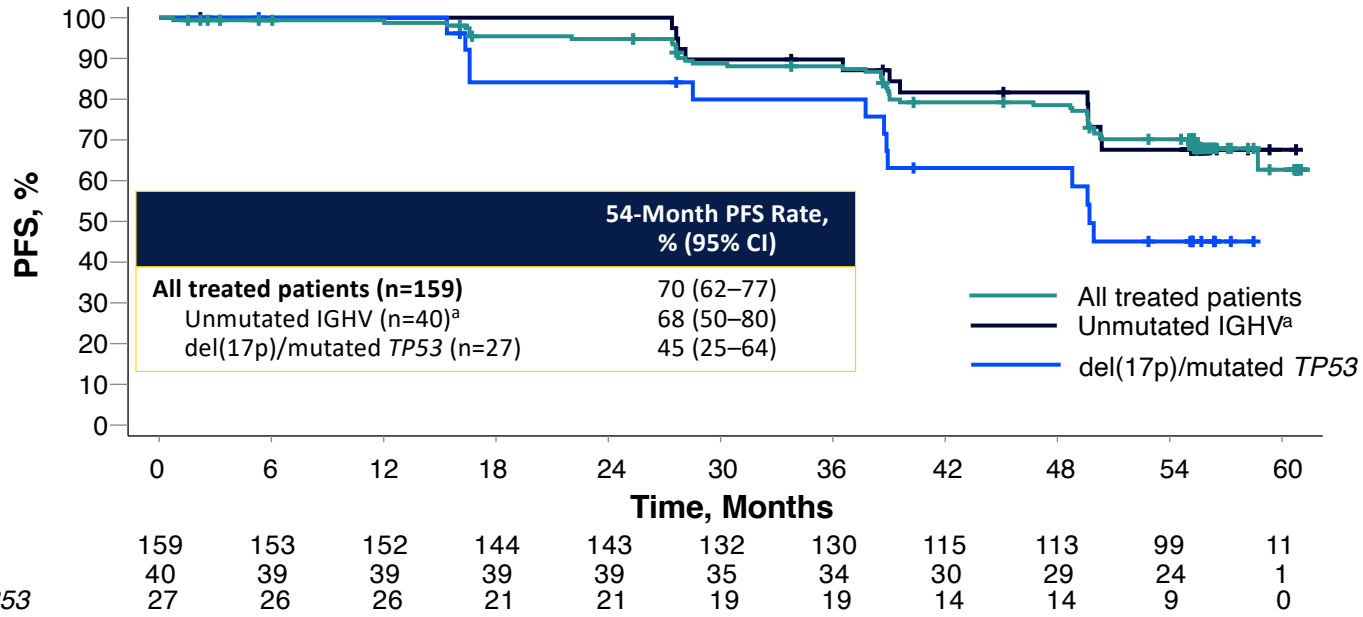
GLOW: PFS by EoT-MRD



- Estimated PFS rates at 42 months post treatment:
  - **Ibr+Ven:**
    - 78% for patients with uMRD at EOT+3
    - 70% for patients with MRD ≥ 10^{-4} at EOT+3
  - **Clb+O:**
    - 44% for patients with uMRD at EOT+3
    - 6% for patients with MRD ≥ 10^{-4} at EOT+3

Follows et al, ASH 2023

Captivate: PFS according to IGHV and TP53

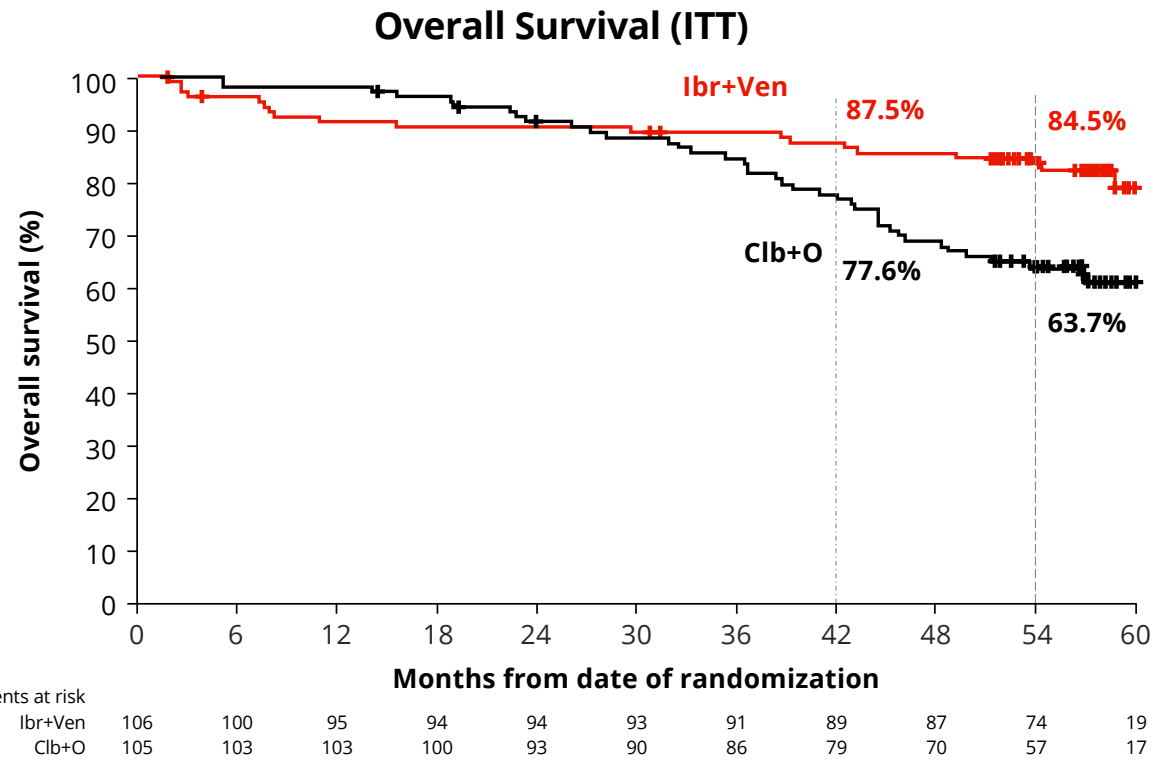


Patients at risk

All treated patients	159	153	152	144	143	132	130	115	113	99	11
Unmutated IGHV[a]	40	39	39	39	39	35	34	30	29	24	1
del(17p)/mutated *TP53*	27	26	26	21	21	19	19	14	14	9	0

Ghia et al, ASH 2023

GLOW: Overall survival



- **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

Follows et al, ASH 2023

CLL17

A PROSPECTIVE, RANDOMIZED, OPEN-LABEL, MULTICENTRE PHASE-III TRIAL OF **IBRUTINIB** VERSUS **VENETOCLAX PLUS OBINUTUZUMAB** VERSUS **IBRUTINIB PLUS VENETOCLAX** FOR PATIENTS WITH PREVIOUSLY UNTREATED CHRONIC LYMPHOCYTIC LEUKAEMIA

Patients with previously untreated CLL

Incl. fit and unfit patients
Incl. patients with del17p/TP53 mut

1:1:1 Randomization

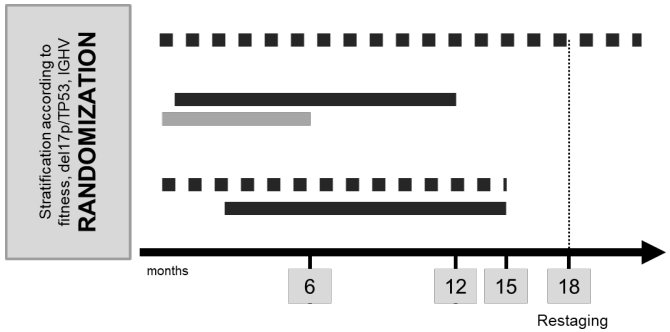
Stratification according to fitness, del17p/TP53, IGHV

Ibrutinib	Venetoclax Obinutuzumab	Venetoclax Ibrutinib

909 patients

Primary endpoint:
Progression-free survival

TREATMENT SCHEDULE



Ibrutinib d1 420 mg po daily until PD or intolerance

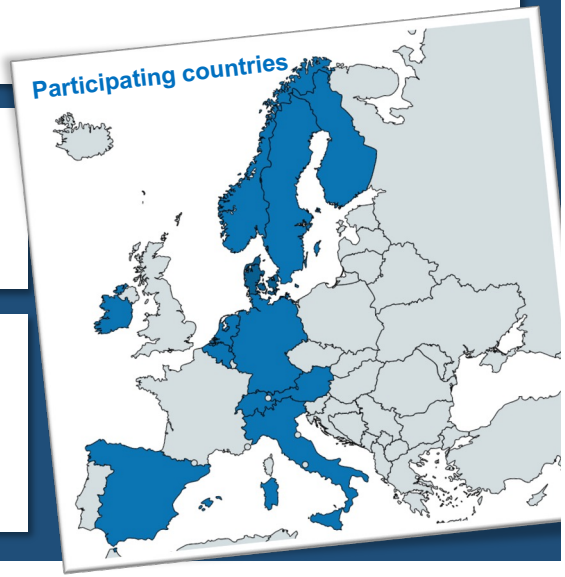
Venetoclax 400 mg po daily (c1 d22 – c12 d28)
Obinutuzumab 1000 mg iv (c1 d1(2)/8/15, c 2-6 d1)

Ibrutinib 420 mg po daily (c1 d1 – c15 d28)
Venetoclax 400 mg po daily (c4 d1 – c15 d28)

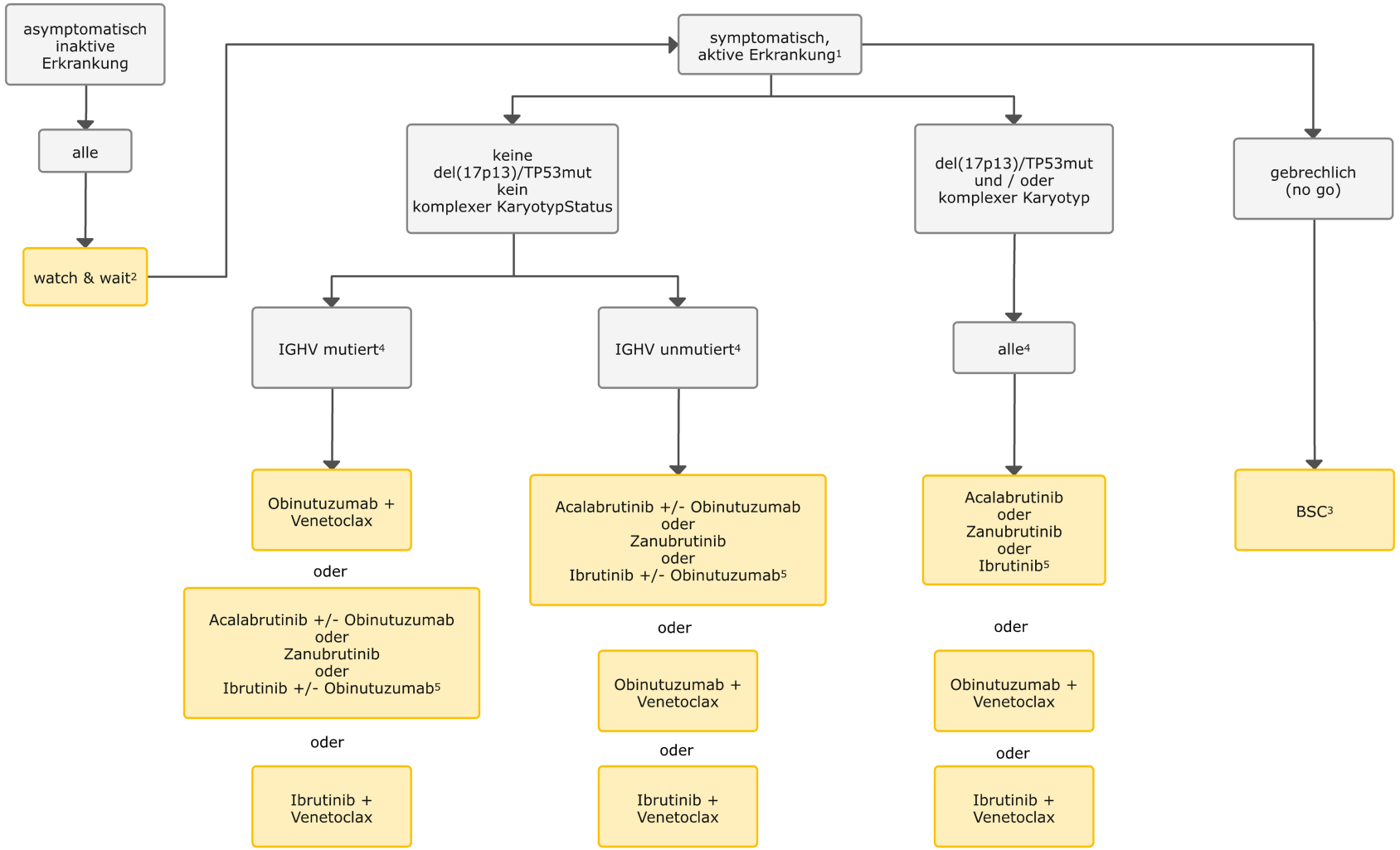
TIMELINES

Start of recruitment	Q1/2021
End of recruitment	Q4/2022
End of study	Q1/2027

DEUTSCHE CLL STUDIENGRUPPE · Nordic CLL Study Group · cancer trials ireland · The Israeli CLL Association (ICLLA) · The Israeli CLL Study Group (ICLLSG) · HOVON · GELLC Grupo Español de Leucemia Linfocítica Crónica · fondazione GIMEMA Franco Mandelli · SAKK

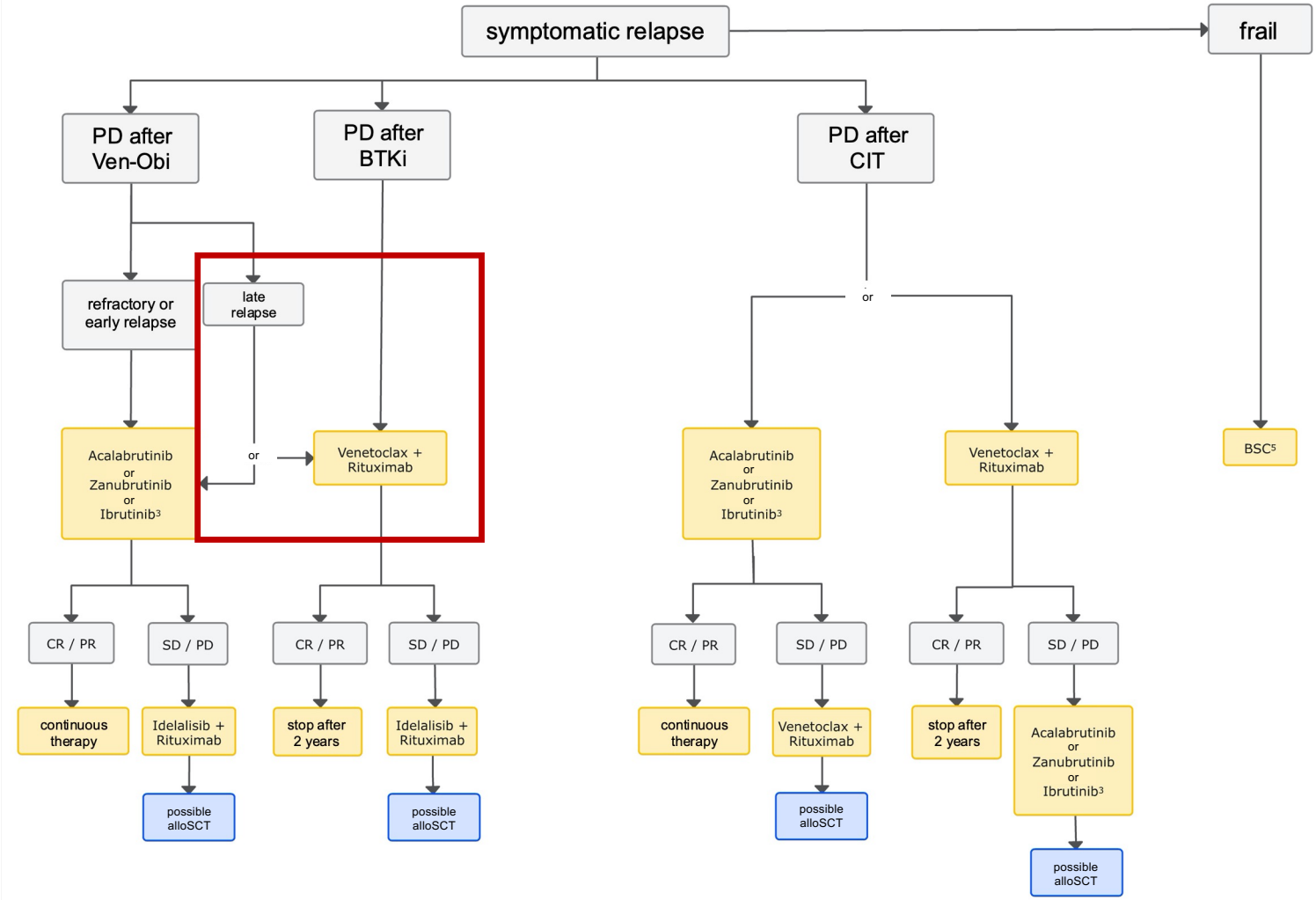


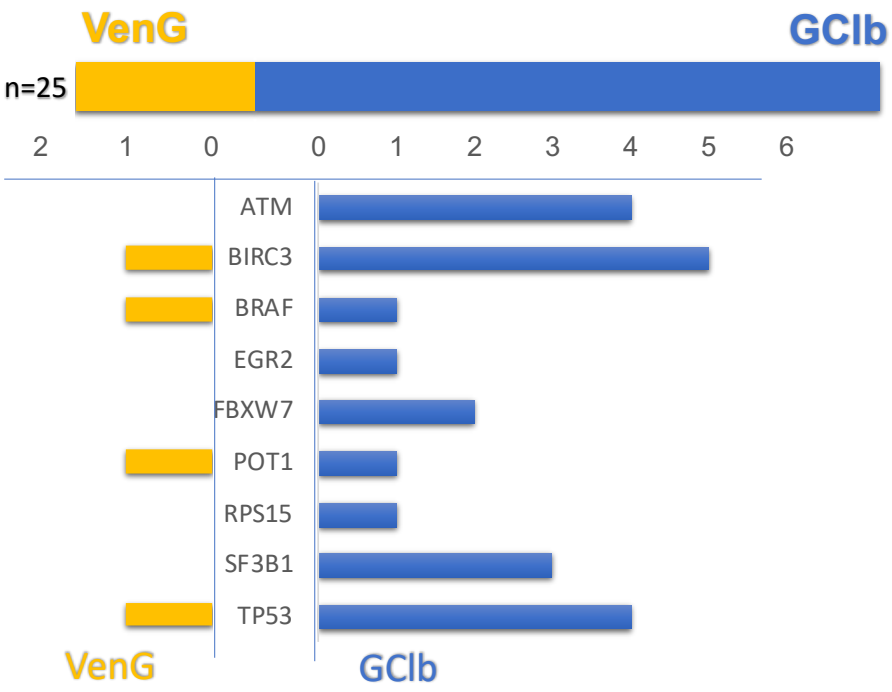
The German Onkopedia Guideline 2023



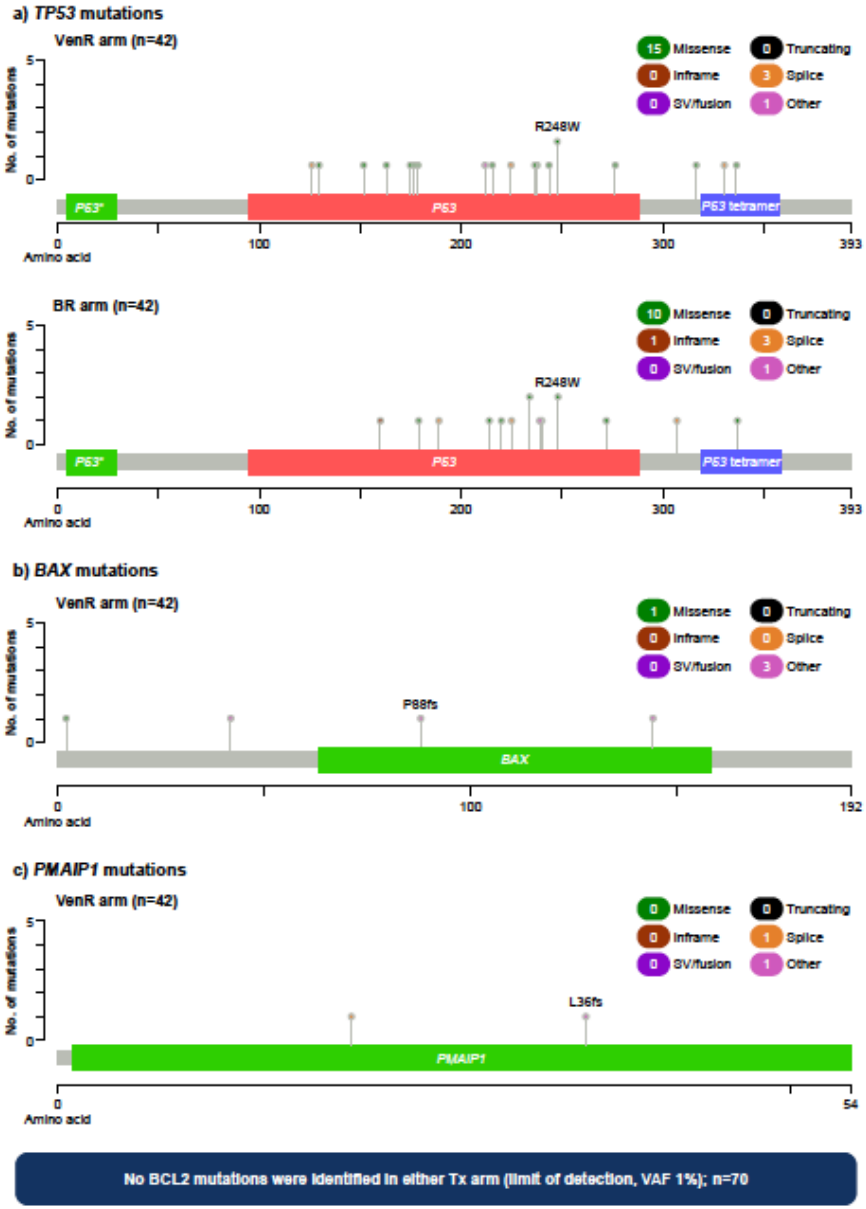
Onkopedia.de

Onkopedia 2023 – relapsed CLL





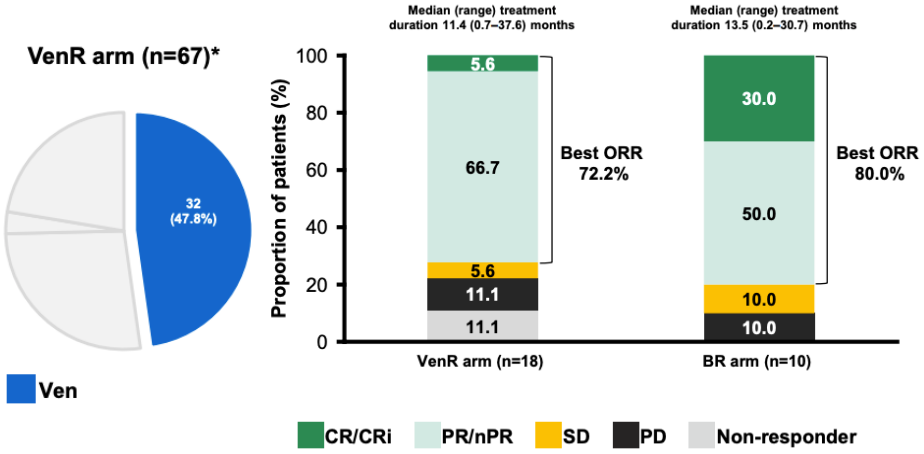
No BCL2 mutations after Ven-Obi or Ven-R.



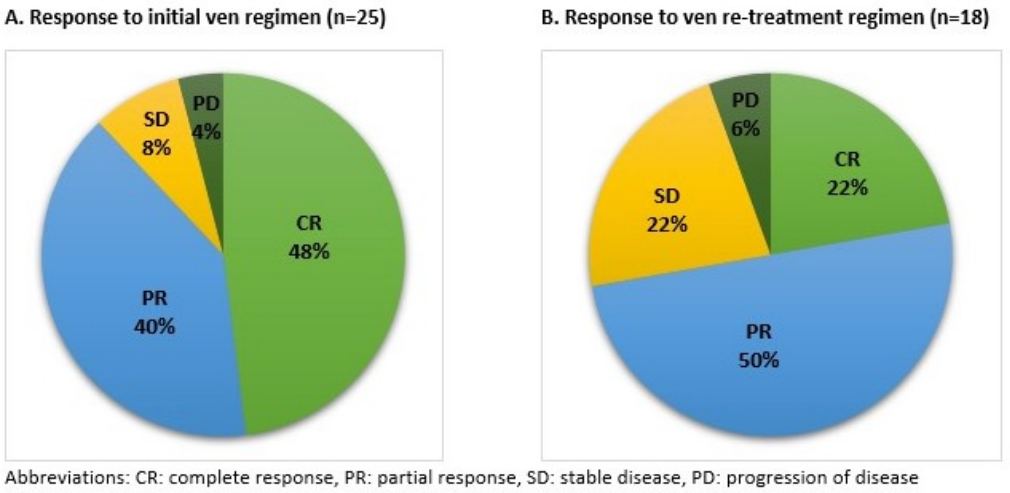
Tausch et al, EHA 2021
Al-Sawaf et al, JCO, 2021
Seymour et al, ASH 2021

Rezidiv nach zeitlich begrenzter Therapie – was nun?

Venetoclax → Venetoclax				
M13-365 *Harrup et al ASH 2020*	Venetoclax	Venetoclax	3	**100%**
MURANO *Harrup et al, ASH2020*	VenR	Venetoclax	32	**72%**
CORE registry *Thompson et al, ASH 2020*	Ven/VenR/VenO	Ven/VenR/VenO/VenI	25 (18)	**72%**



Harrup et al, ASH 2020



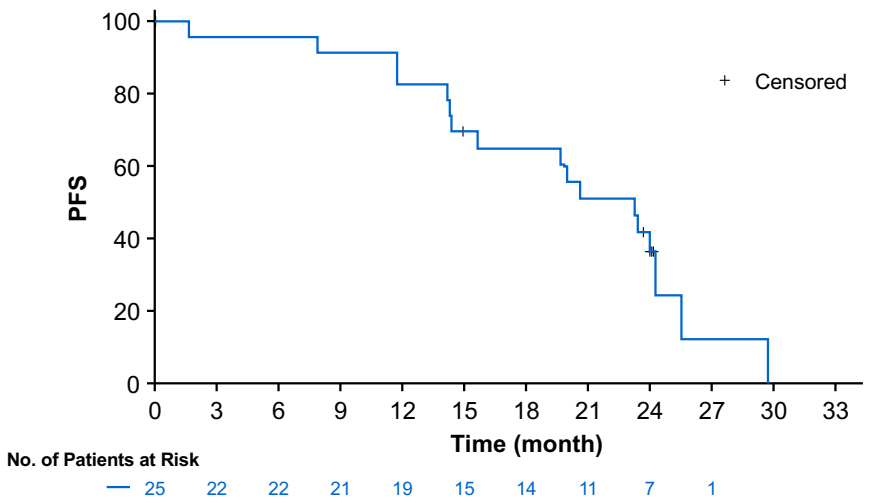
Thompson et al, ASH 2020

MURANO: VenR retreatment

- Amongst VenR-retreated patients, median follow up (range) was 33.4 months (2.7–44.0)
  - Best ORR was high at 72.0%; CR rate was 24%
  - 8 patients (32%) achieved uMRD at the retreatment EOCT; all were MRD+ at EOT
  - Median PFS (95% CI) was 23.3 months (15.6–24.3)
  - Median OS was not reached

VenR retreatment is a viable option for patients with R/R CLL

PFS for VenR-retreated patients in the substudy

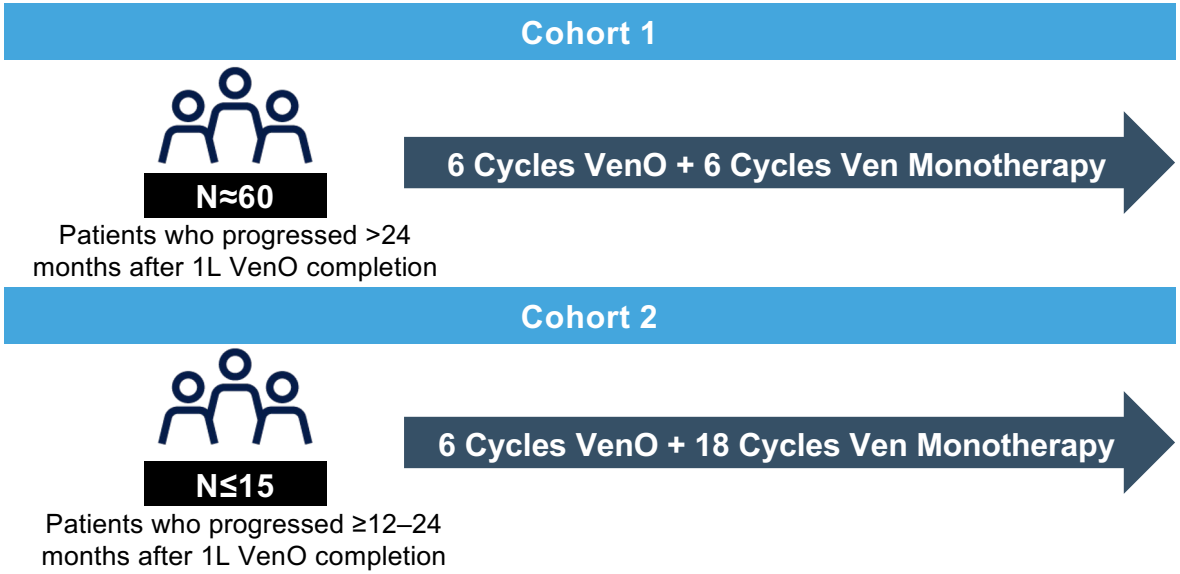


- CR, complete response.

Seymour et al, ICML 2023

BCL2 INHIBITOR RE-TREATMENT

Prospective re-treatment: ReVenG – Study design



Endpoints

Primary Endpoint

- ORR at EoCT (3 months after completing VenO)

Secondary Endpoints

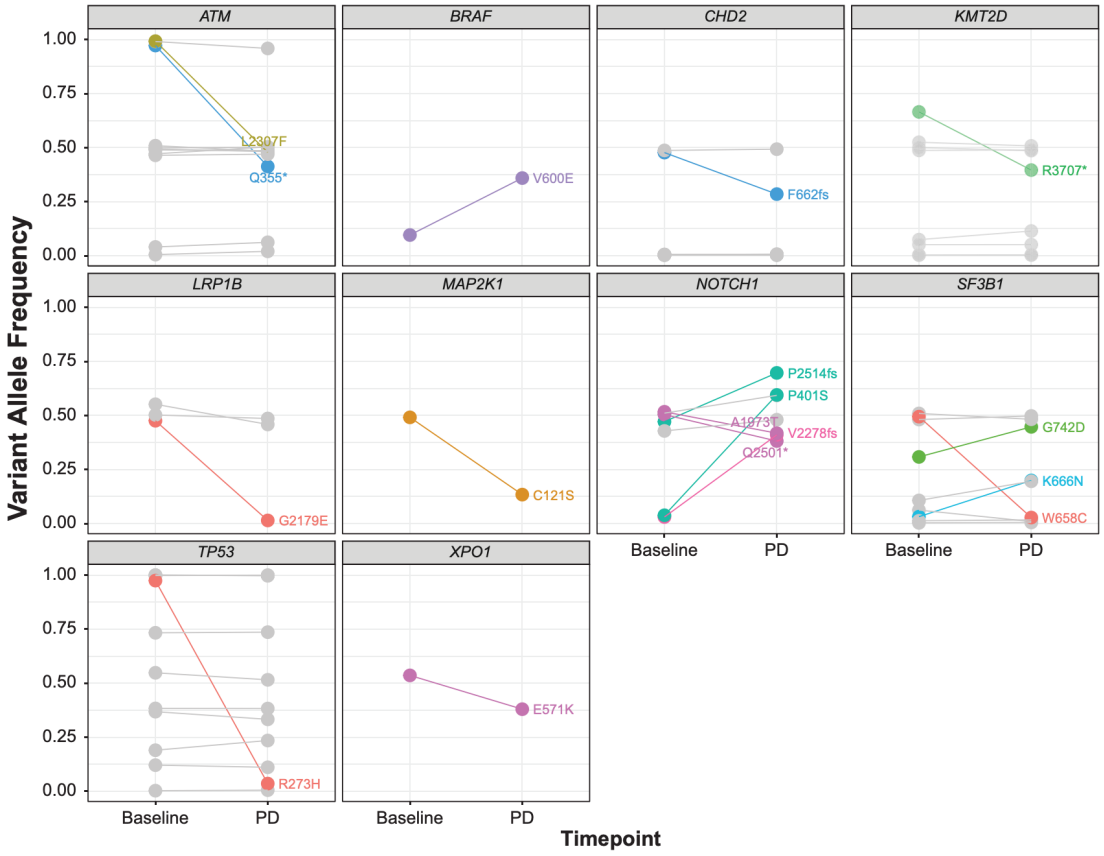
- CR/CRi at EoCT and EoT (3 months after completing Ven monotherapy)
- ORR at EoT
- TTR
- DOR
- uMRD (10^{-4}) measured in PB at EoCT and EoT
- PFS
- OS
- TTNT
- Safety

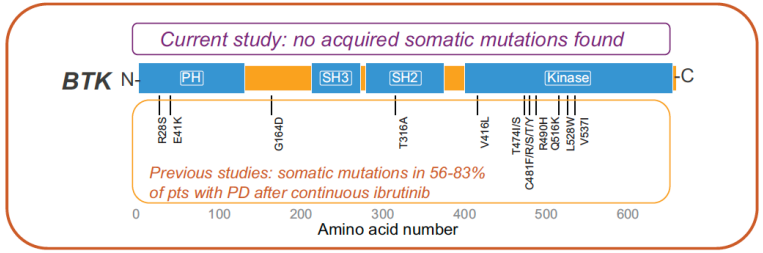
Exploratory Endpoints

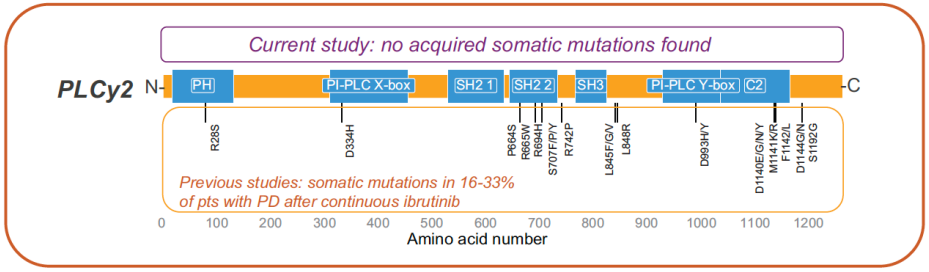
- PROs
- MRD kinetics up to 12 months post-treatment
- Correlations of IgHV, *TP53* mutation, and del(17p) at baseline with treatment outcomes

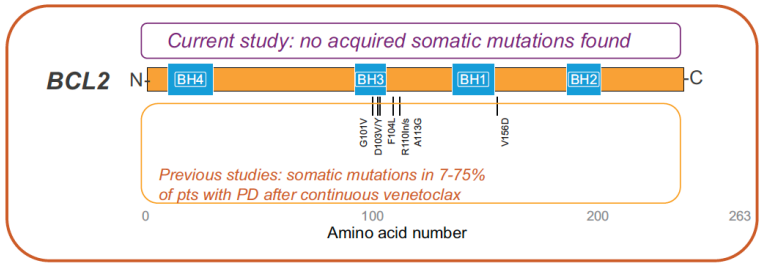
Interested? Please reach out under cll-studie@uk-koeln.de or othman.al-sawaf@uk-koeln.de

BTKi retreatment?









No BTK or BCL2 mutations detected after I+V fixed-duration treatment.

CAPTIVATE: Ibrutinib re-treatment

To date, 19 patients who have progressed after completing fixed-duration ibrutinib + venetoclax (in either the FD or MRD cohort placebo arm) have initiated retreatment with ibrutinib; the median (range) retreatment duration is 11.1 (0–38.6) months

Patient	Baseline high risk features[a]				Response to FD ibrutinib + venetoclax[a]		Response to retreatment with ibrutinib
	del(17p)	TP53 mutated	uIGHV	Complex karyotype	PFS (months)	Best response	Best Response
1	No	No	Yes	Unknown	38.6	CR	CR
2	No	No	Yes	No	20.3	PR	PR
3	No	No	Yes	No	19.4	PR	PR
4	No	No	Yes	No	44.2	CR	PR
5	No	No	Yes	Yes	38.6	CR	PR
6	No	No	Yes	No	27.4	PR	PR
7	No	No	Yes	Yes	38.6	PR	PR
8	No	No	Yes	Yes	27.6	CR	PR
9	Yes	No	No	No	28.5	CRi	PR
10	Yes	No	Yes	Yes	16.6	PR	PR
11	No	No	Yes	No	36.5	CR	PR
12	No	No	No	No	27.4	PR	PR
13	No	No	No	Yes	22.0	PR	PR
14	No	No	No	Yes	30.4	PR	PR
15	No	No	Yes	Yes	38.6	CR	PRL
16	No	No	Yes	No	39.6	PR	SD
17	Yes	Yes	Yes	Yes	48.8	PR	PD[b]

Response data are available for 17 of these patients:

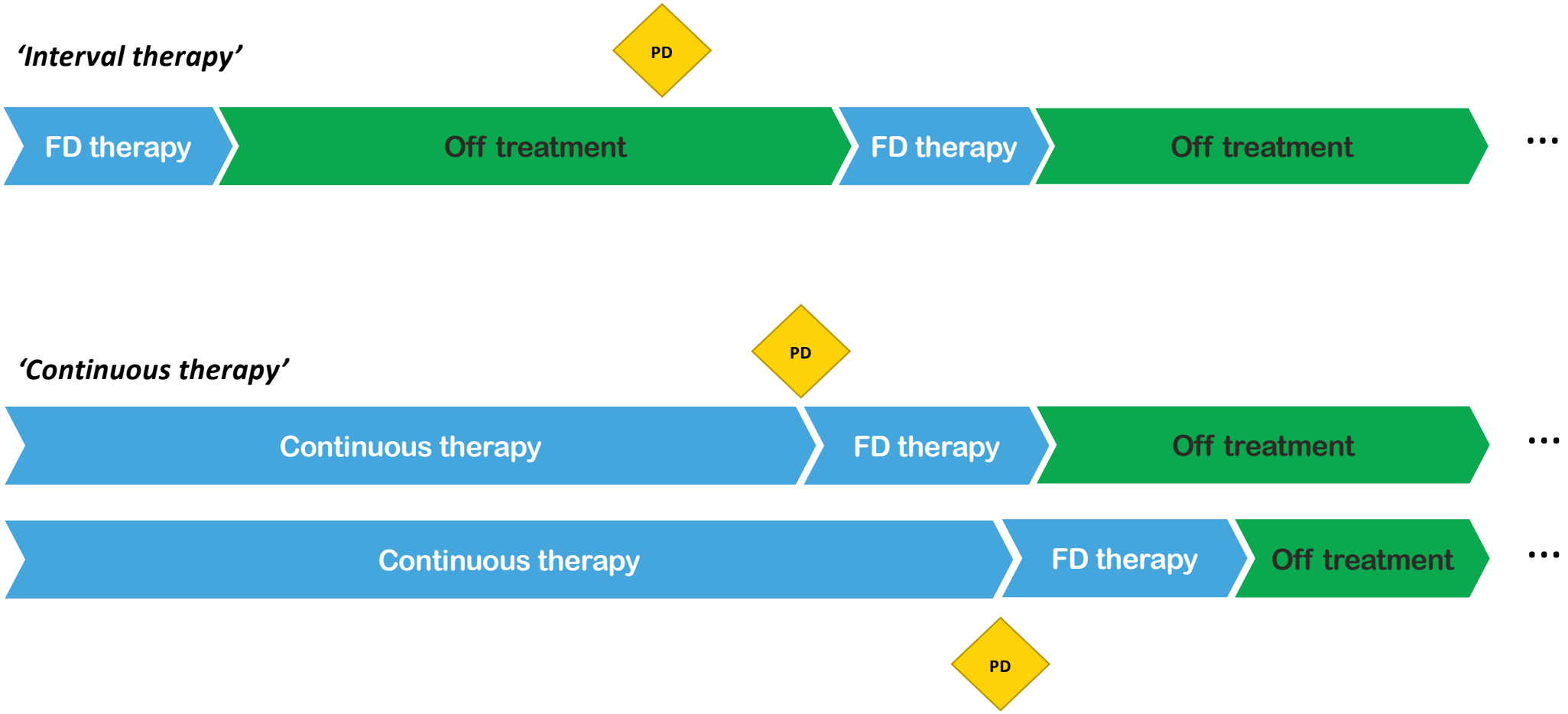
- CR, n=1
- PR, n=13
- PR with lymphocytosis, n=1
- Stable disease, n=1
- PD, n=1[b]

[a]Per August 5, 2022 data cut. [b]Patient had Richter's Transformation to DLBCL diagnosed 1 month after starting retreatment.

IGHV, immunoglobulin heavy chain variable region gene; PFS, progression-free survival.

Ghia et al, EHA/ICML 2023

Fixed-duration versus continuous strategies



Conclusions

- **Targeted therapies** have demonstrated high(er) efficacy compared with chemoimmunotherapy in all CLL settings

- The majority of patients with CLL can be **offered long-term disease control** using cBTKi, BCL2i and CD20ab in different lines

- Decision **between continuous or fixed-duration** treatment should be primarly based on patient preference, side effect profile and disease genetics