2025

DEBATES AND DIDACTICS in Hematology and Oncology

EMORY WINSHIP CANCER INSTITUTE
National Cancer Institute-Designated Comprehensive Cancer Center

Where Science Becomes Hope

JULY 24 - 27, 2025 • SEA ISLAND, GEORGIA

This activity is jointly provided by Partners for Advancing Clinical Education and Bio Ascend

Disclosure Information

- Consultant: AbbVie, AstraZeneca, Autolus, Beigene, Ltd., Bristol Myers Squibb, Eli Lilly and Company, Janssen Oncology, Johnson and Johnson, Loxo Oncology, Inc. Merck, Pfizer, Pharmacyclics

- Research Support: Alliance, Caribou Biosciences, Inc., Nurix Therapeutics, Inc., Regeneron

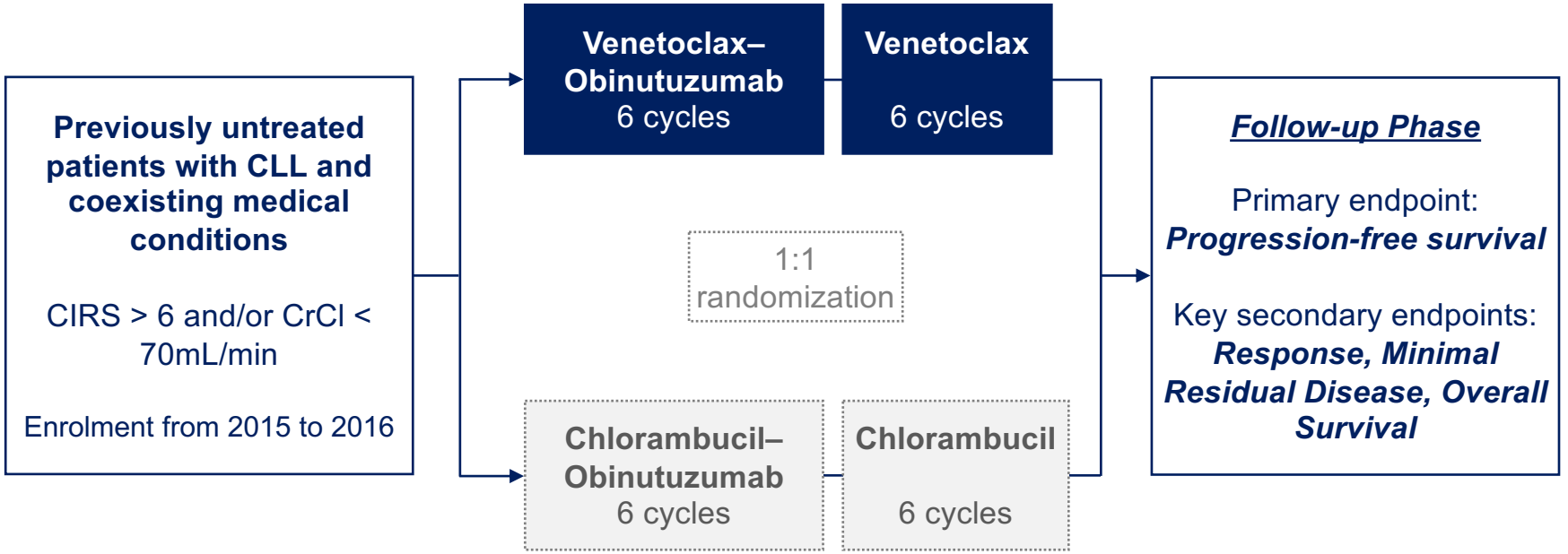
- Scientific Advisory Board: Somitomo

MRD is a Useful Tool in the Management of Patients with CLL Of Course!

- It is always better to have undetectable MRD than detectable MRD

- Effect size of uMRD depends on:
  - Disease characteristics (unmutated IGHV patients progress sooner than mutated)
  - Depth of uMRD (10X4 vs 10X5 vs 10x6)
  - Even in high-risk groups, it is still better to be uMRD than detectable MRD
  - It generally doesn’t matter how you get there

CLL14 TRIAL: VEN/OBIN VS CHLOR/OBIN

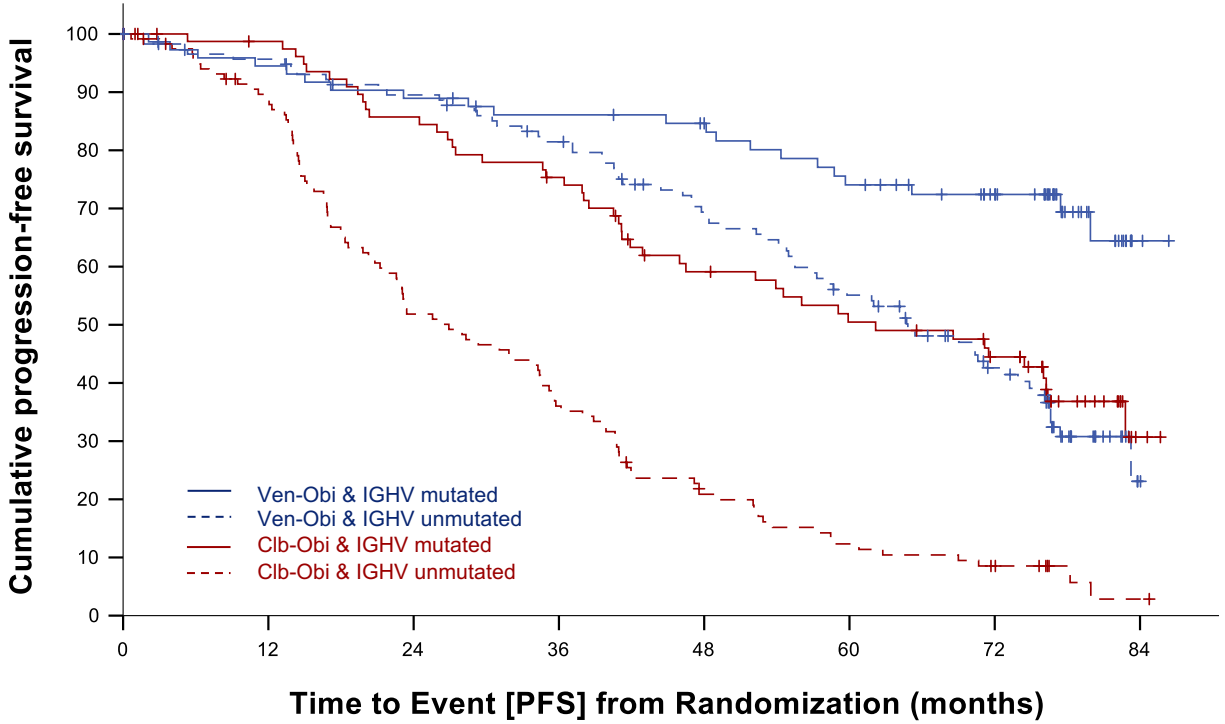


Current median observation time: 76.4 months

Al-Sawaf et al EHA 2023

PROGRESSION-FREE SURVIVAL – IGHV status

Median observation time 76.4 months



Ven-Obi & IGHV mutated	76	68	64	60	57	49	39	2
Ven-Obi & IGHV unmutated	121	110	101	90	73	57	37	1
Clb-Obi & IGHV mutated	83	76	66	57	42	35	28	2
Clb-Obi & IGHV unmutated	123	101	59	41	22	13	8	1

Median PFS

Ven-Obi & IGHVmut: NR

Ven-Obi & IGHVunmut: 64.8 m

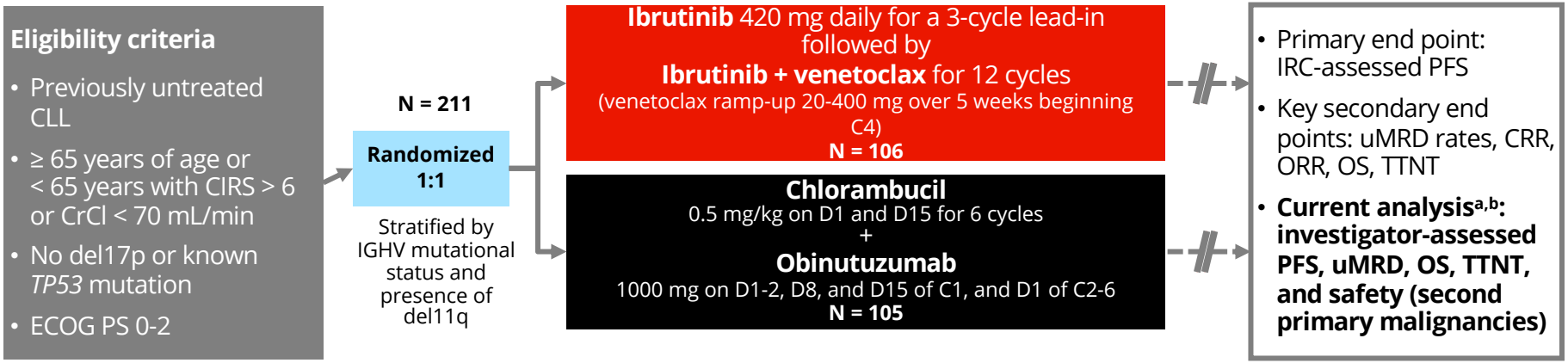
HR 0.38, 95%CI [0.23-0.61], p<0.001

Clb-Obi & IGHVmut: 62.2 m

Clb-Obi & IGHVunmut: 26.9 m

HR 0.33, 95% CI [0.23-0.47], p<0.001

GLOW: Phase 3 Study (NCT03462719) Evaluating Fixed-Duration Ibr+Ven in Previously Untreated CLL

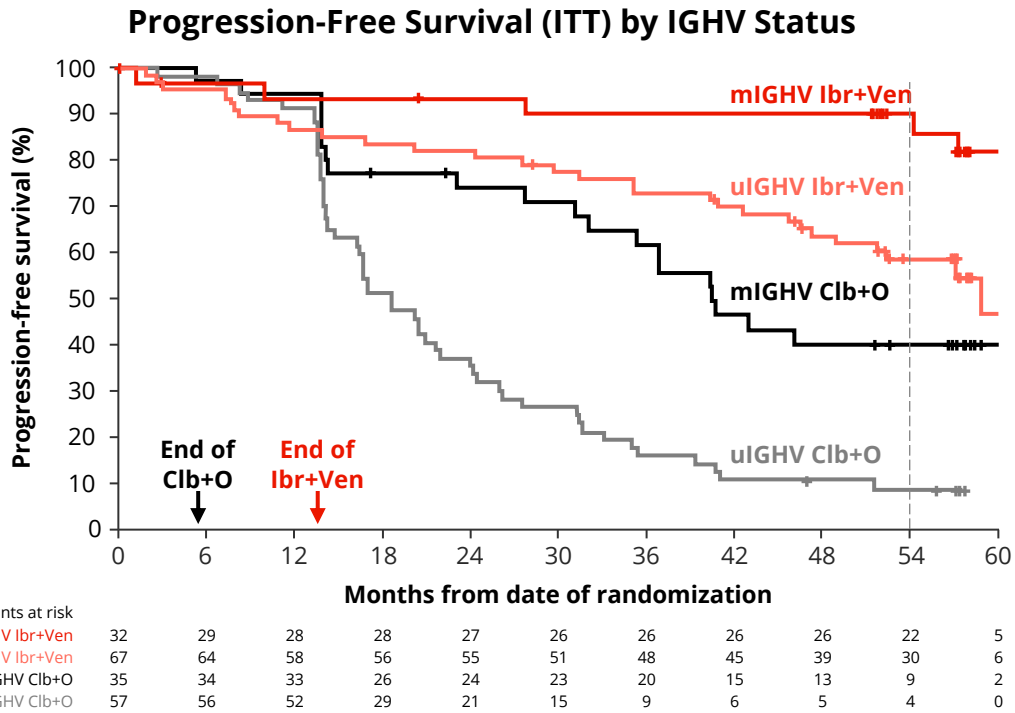


- **Here we present the updated clinical outcomes at a median follow-up of 57.3 months (range, 1.7-65.2)**
- Baseline characteristics (presented previously) were generally balanced between arms and reflective of an elderly and/or comorbid population[1]
- IGHV status at baseline:
  - Ibr+Ven arm: mIGHV 30.2%, uIGHV 63.2%
  - Clb+O arm: mIGHV 33.3%, uIGHV 54.3%

[a]All *p* values are nominal. [b]uMRD in PB by NGS via Clonoseq assay.
C, cycle (28 days); CIRS, Cumulative Illness Rating Scale score; CrCl, creatinine clearance; CRR, complete response rate; D, day; ECOG PS, Eastern Cooperative Oncology Group performance status; IRC, independent review committee; mIGHV, mutated IGHV; NGS, next-generation sequencing; ORR, overall response rate; PB, peripheral blood; uIGHV, unmutated IGHV.
1. Niemann CU, et al. *Lancet Oncol*. 2023;24:1423-1433.

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

GLOW: At 57 Months of Follow-up, Ibr+Ven Improved PFS Versus Clb+O Regardless of IGHV Status



- 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

Results based on updated IGHV reclassifications. Investigator-assessed progression-free survival was analyzed.

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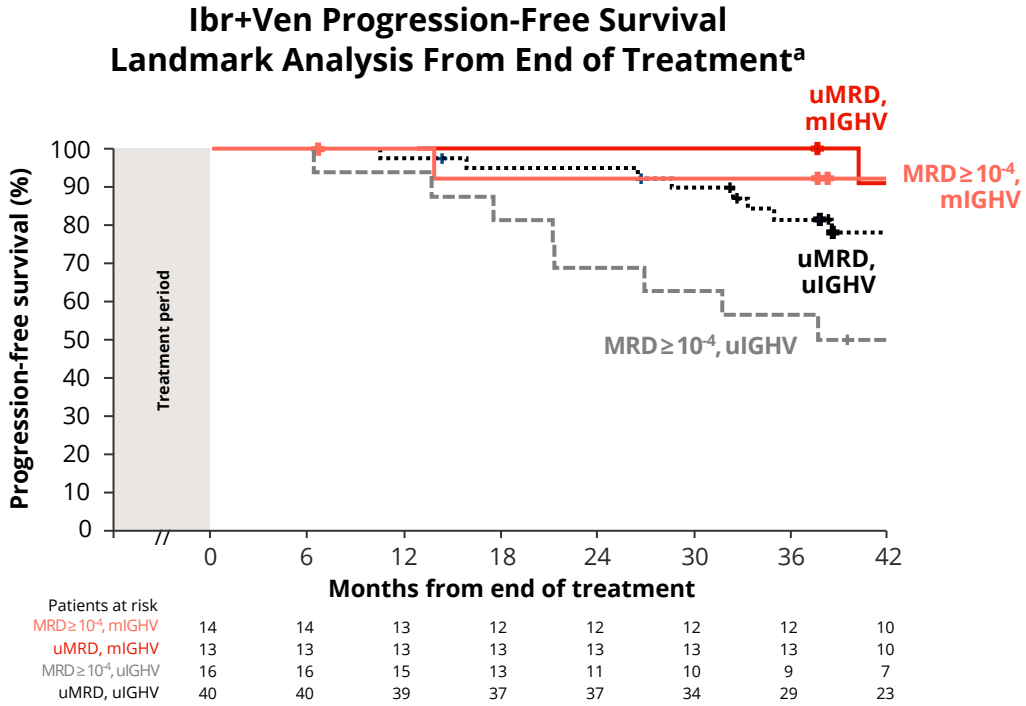
GLOW: PFS by MRD and IGHV Status for Ibr+Ven



- With Ibr+Ven, achieving uMRD at EOT+3 is more critical for long-term PFS benefit in uIGHV versus mIGHV
- Estimated PFS rates at 42 months post treatment:
  - **mIGHV** CLL:
    - 91% for patients with uMRD at EOT+3
    - 92% for patients with MRD ≥ 10^{-4} at EOT+3
  - **uIGHV** CLL:
    - 78% for patients with uMRD at EOT+3
    - 50% for patients with MRD ≥ 10^{-4} at EOT+3

[a]Curves generated from EOT (C15 for Ibr+Ven, C6 for Clb+O).
Investigator-assessed progression-free survival was analyzed. All patients who had MRD outcome at EOT+3 were included in this analysis; uMRD was defined as < 1 CLL cell per 10,000 leukocytes (< 10^{-4}). Results based on updated IGHV reclassifications.

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MRD is a Useful Tool in the Management of Patients with CLL: Of Course!

- It is always better to have undetectable MRD than detectable MRD

- Effect size of uMRD depends on:
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  - Depth of uMRD (10X4 vs 10X5 vs 10x6)
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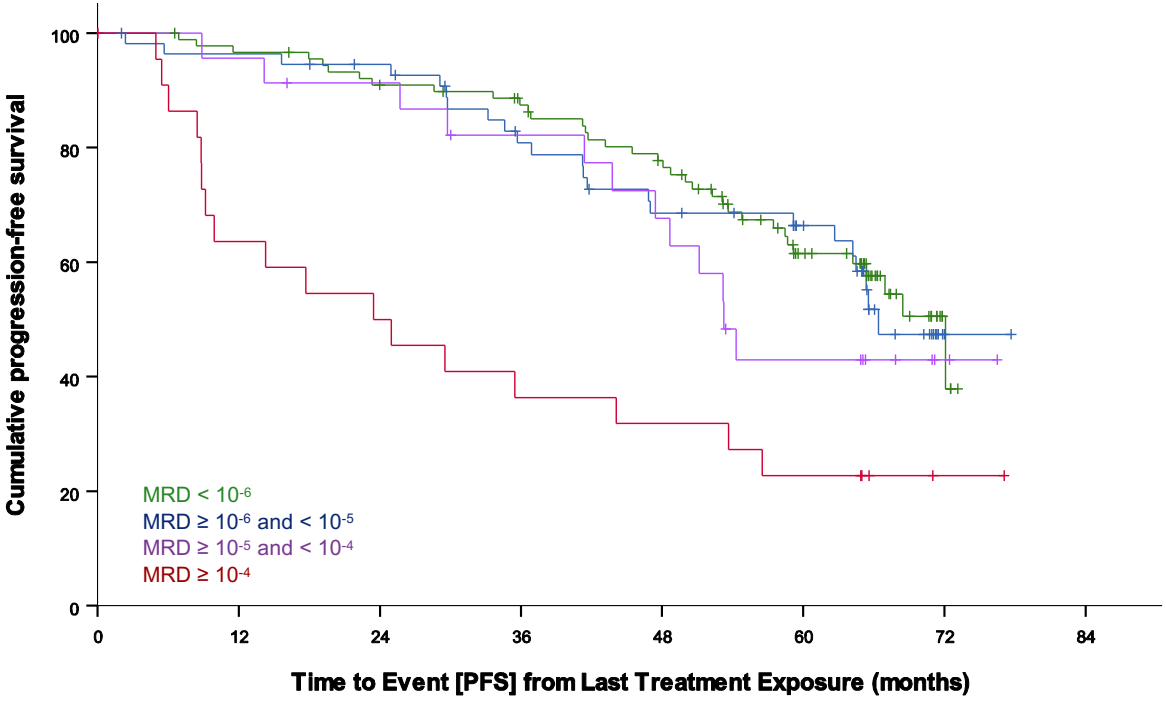
PFS AFTER VEN-OBI ACCORDING TO *MRD STATUS*

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

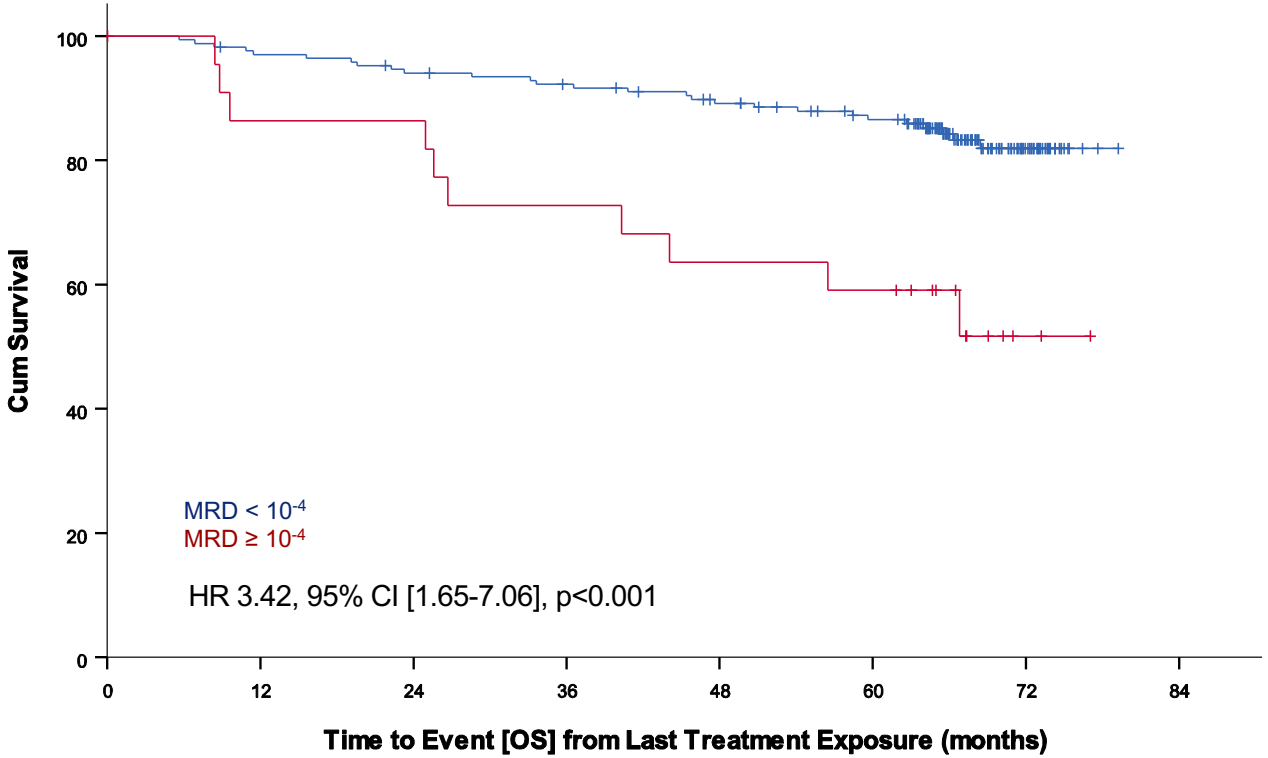


MRD < 10^{-6}	90	86	79	73	63	38	4	0
MRD ≥ 10^{-6} and < 10^{-5}	56	53	50	40	33	26	2	0
MRD ≥ 10^{-5} and < 10^{-4}	23	22	20	17	14	8	2	0
MRD ≥ 10^{-4}	23	14	11	8	7	5	1	0

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

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.

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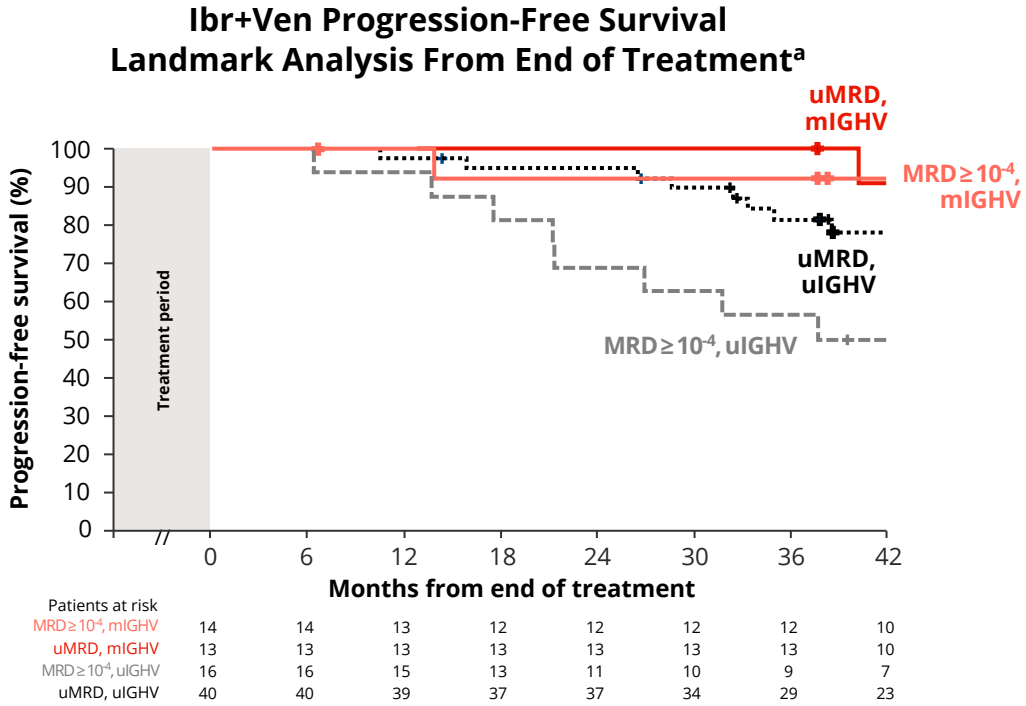

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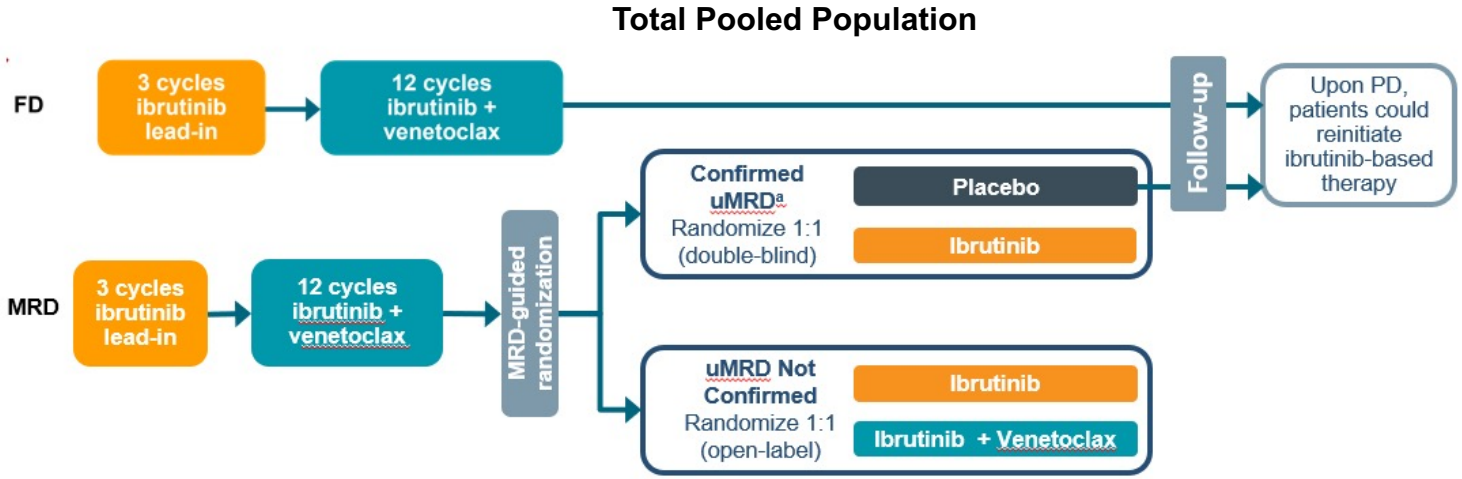
CAPTIVATE Study Design: FD Cohort and MRD Cohort Placebo Arm

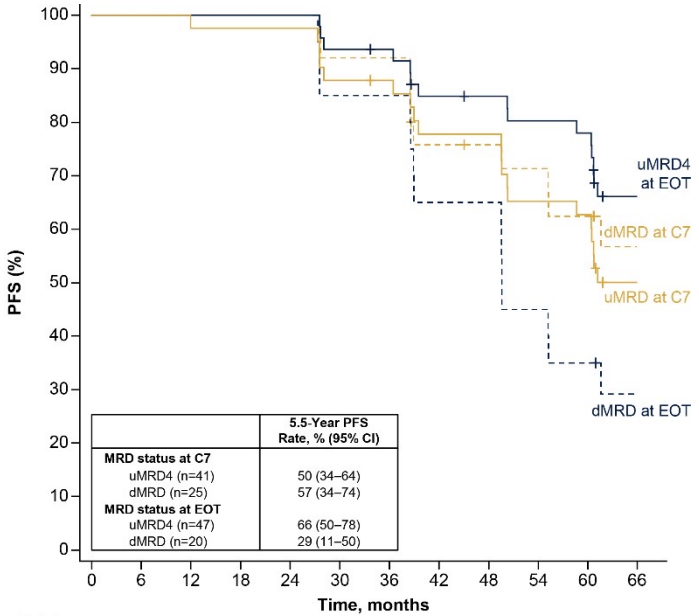


- Patients aged ≤70 years with previously untreated CLL/SLL received 3 cycles of ibrutinib, then 12 cycles of ibrutinib + venetoclax (ibrutinib, 420 mg/day orally; venetoclax, 5-week ramp up to 400 mg/day orally)
  - Patients in the FD cohort received no further treatment (n=159)
  - Patients in the MRD cohort placebo arm with confirmed uMRD4 (n=43) received 1 additional cycle of ibrutinib + venetoclax during the MRD-guided randomization, then placebo treatment
- In patients with confirmed PD, on-study retreatment included single-agent ibrutinib
  - FD cohort patients with PD occurring >2 years after EOT could be retreated with FD ibrutinib + venetoclax

[a]Patients with confirmed uMRD4 (defined as uMRD $<10^{-4}$ by 8-color flow cytometry serially over ≥3 cycles in both peripheral blood and bone marrow) after 12 cycles of ibrutinib + venetoclax were randomly assigned 1:1 to receive placebo or ibrutinib; the placebo arm was included in the current analysis.
EOT, end of treatment; PD, progressive disease; uMRD, undetectable minimal residual disease.

MRD Status at EOT Is Predictive of Long-Term PFS Regardless of IGHV Status (No del(17p/*TP53*))

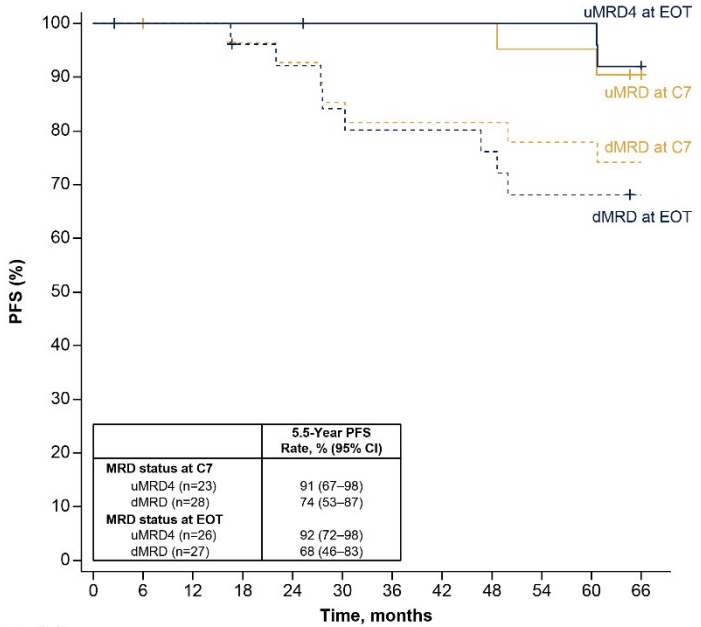
PFS by MRD Status in Patients With uIGHV (FD Cohort only)



Patients at risk

uMRD4 at C7	41	41	41	40	40	36	35	31	31	26	25	18
dMRD at C7	25	25	25	25	25	23	23	18	17	16	14	10
uMRD4 at EOT	47	47	47	47	47	44	43	38	37	35	34	25
dMRD at EOT	20	20	20	20	20	17	17	13	13	9	7	5

PFS by MRD Status in Patients With mIGHV (FD Cohort only)

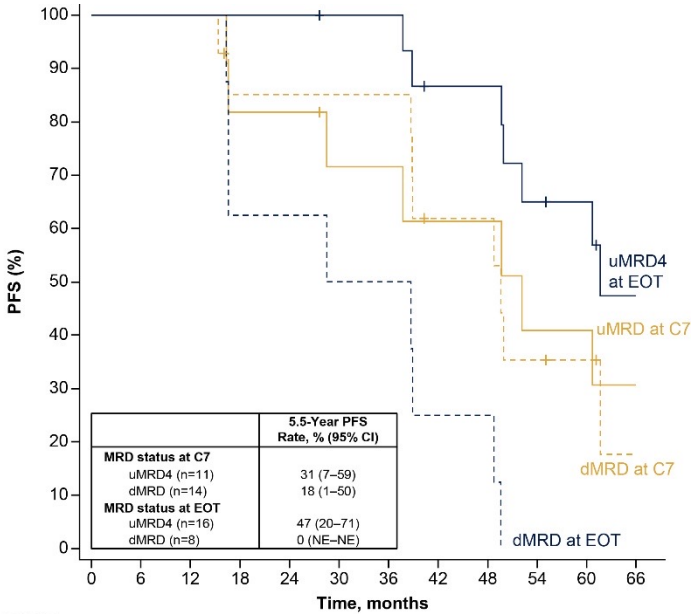


Patients at risk

uMRD4 at C7	23	23	22	22	22	21	21	21	21	20	20	18
dMRD at C7	28	28	28	26	25	23	22	22	22	21	21	20
uMRD4 at EOT	26	26	26	26	26	25	25	25	25	25	25	23
dMRD at EOT	27	26	26	24	23	21	20	20	19	17	17	16

MRD Status at EOT Is Predictive of Long-Term PFS Regardless of del(17p)/*TP53* Status (FD Cohort Patients)

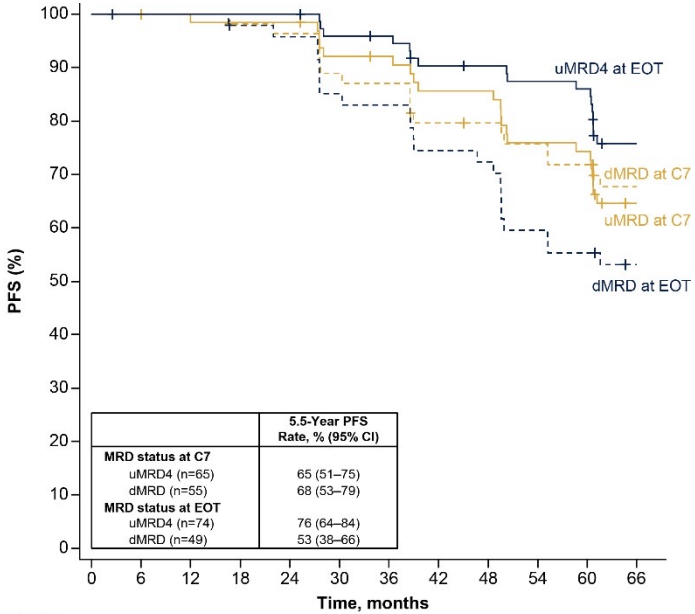
PFS by MRD Status in Patients With del(17p)/mutated *TP53* (FD Cohort only)



Patients at risk

uMRD4 at C7	11	11	11	9	9	7	7	6	6	4	4	3
dMRD at C7	14	14	14	11	11	11	11	7	7	4	3	1
uMRD4 at EOT	16	16	16	16	16	15	15	12	12	9	8	5
dMRD at EOT	8	8	8	5	5	4	4	2	2	0	0	0

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



Patients at risk

uMRD4 at C7	65	65	64	63	63	58	57	53	53	47	46	37
dMRD at C7	55	55	55	53	52	48	47	42	41	39	37	32
uMRD4 at EOT	74	74	74	74	74	70	69	64	63	61	60	49
dMRD at EOT	49	48	48	46	45	40	39	35	34	28	26	23

NE, not estimable.

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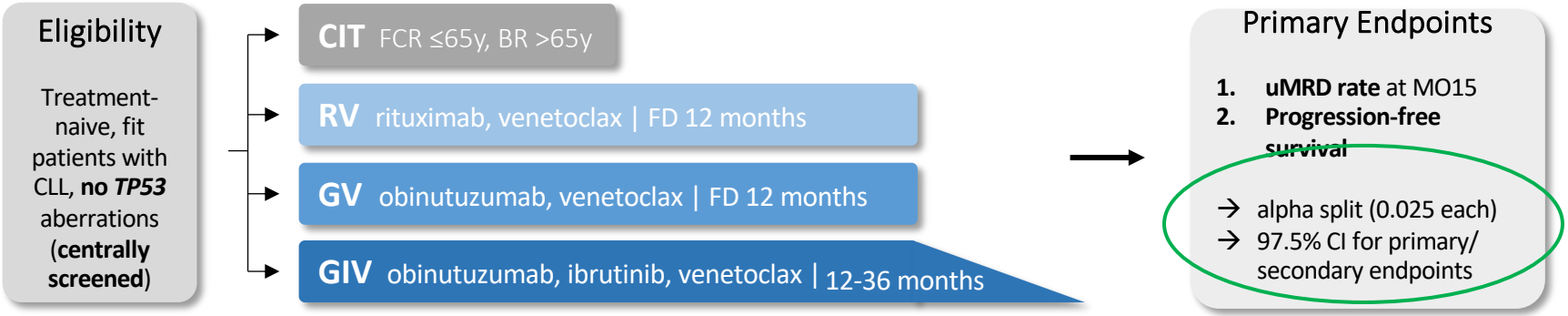
Study Design - GAIA/CLL13



Key patient characteristics

Randomized patients (=ITT population): **n= 926**

Median age:	**61 years** (range: 27-84)
Median CIRS score:	**2** (range: 0-7)
Unmutated IGHV:	**56%** of all patients
Complex karyotype:	**17%** of all patients

Follow-up analysis (data cut-off: 01/2023)

Median observation time
50.7 months (IQR: 44.6-57.9)

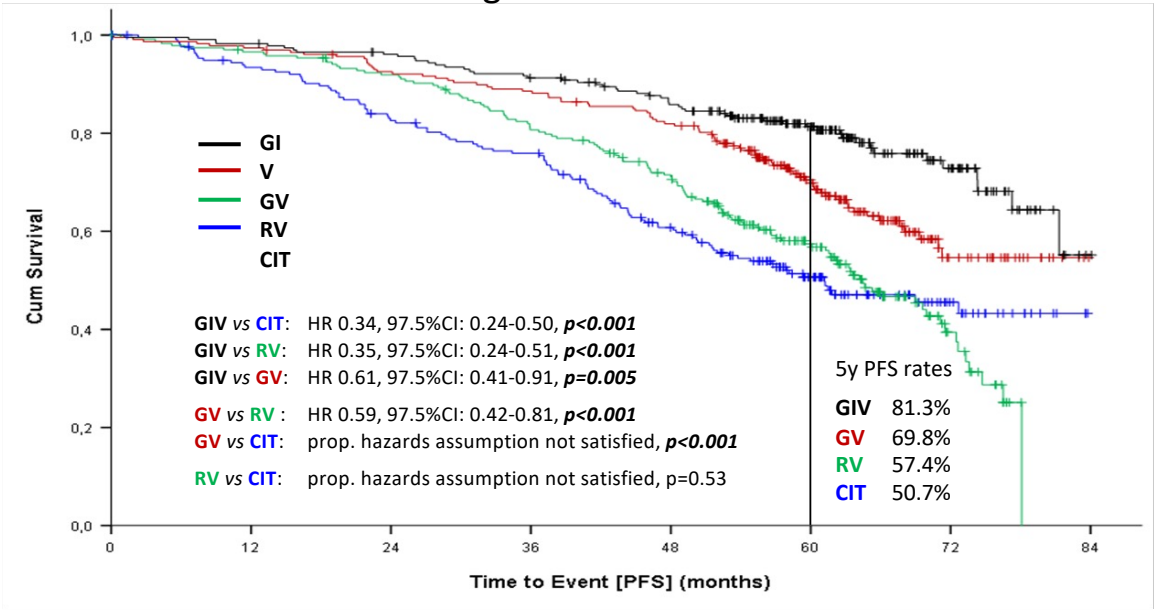
Median observation time after end of treatment
40.7 months (IQR: 34.5-47.9)

Furstenau et al ASH 2023

Efficacy – PFS

Median observation time: 63.8 months

Progression-free survival

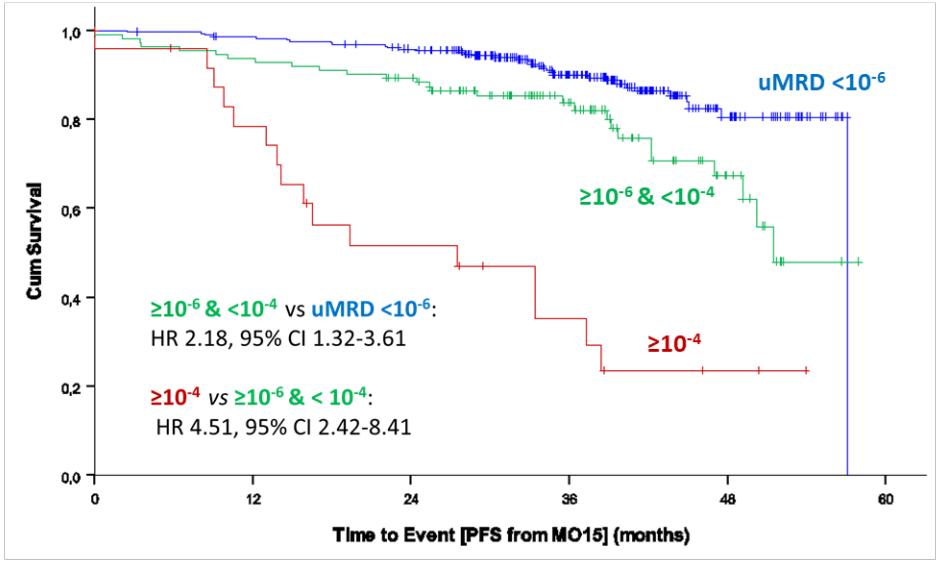


Patients at risk

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

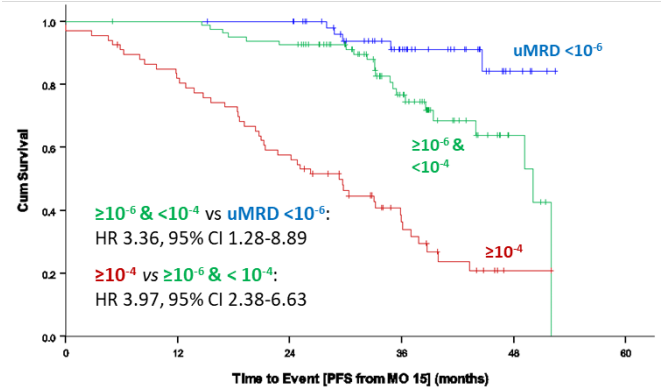
Correlation PB MRD/PFS

PFS by MRD level at MO15, GV/GIV

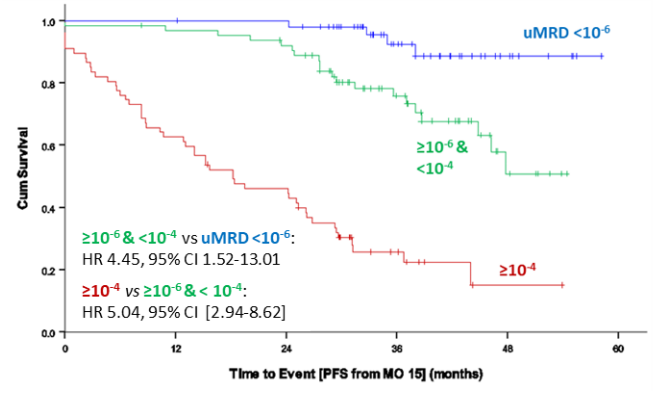


Pts at risk					
uMRD <10-6	291	283	269	162	39
≥10-6 & <10-4	112	105	95	53	15
≥10-4	25	18	11	6	2

PFS by MRD level at MO15, RV



PFS by MRD level at MO15, CIT



MRD is a Useful Tool in the Management of Patients with CLL: Of Course!

- MRD is always important with fixed duration therapy
- So what is the issue?
  - Not actionable at present in standard practice
  - There are trials comparing fixed duration therapy to MRD guided therapy but we don’t have data yet
  - So how does it help us to have the data now??
  - **Monitoring the patient (frequency of visits) and to give the patient some idea of what to expect**