CLL: hot topics

- **MRD**
- Definiton of high risk disease: L. Laurenti
- CV safety: G. Boriani - M. Coscia

DISCLOSURE Antonio Cuneo

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

MRD in CLL

- **Methods**
- MRD and prognosis
- MRD as a tool to guide treatment

Undetectable MRD definition in CLL and its measurement

MRD negativity <1 CLL cell in 10000 leukocytes (MRD level < 10^{-4}) (Hallek M et al, Blood 2018)

1. Flow cytometry	2. PCR	3. NGS
Detection of surface markers	Detection of VDJ	Detection of V(D)J
Fast, reliable, inexpensive	Highly accurate, easy to standardise	Highly accurate, easy to standardise
Standardization and logistics are challenging	Expensive, time-consuming, and not widely available	Expensive, time-consuming, and not widely available
Sensitivity 10^{-4}	Sensitivity 10^{-5}	Sensitivity 10^{-6}

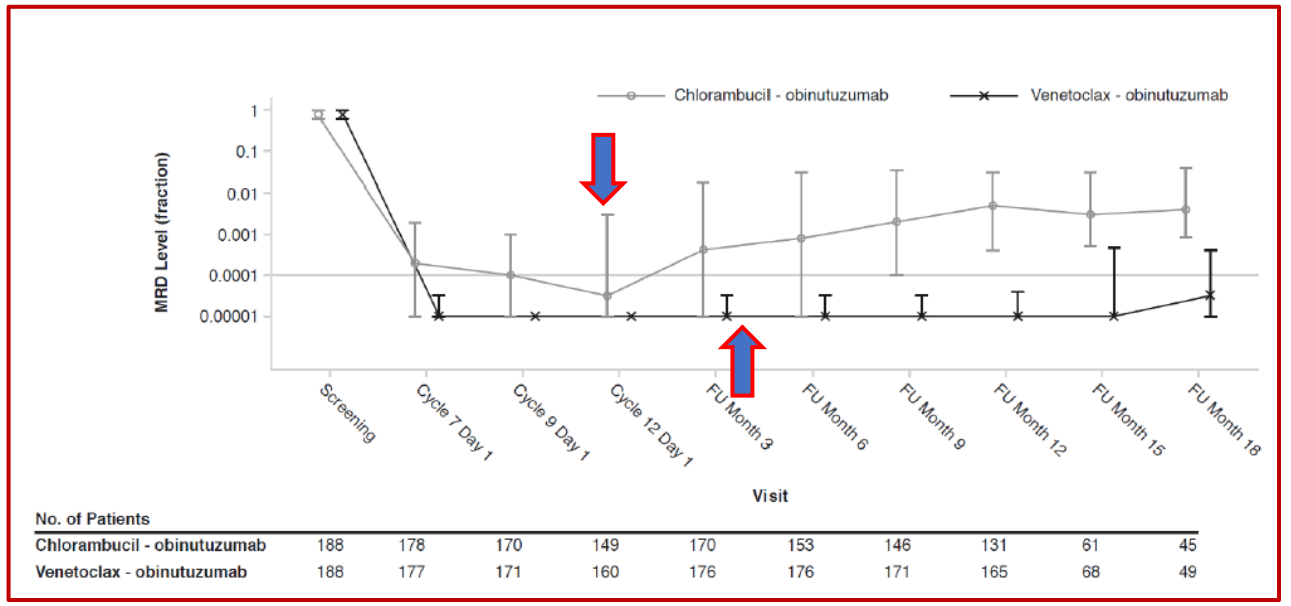
Harmonization of the methods is important to achieve a uniform level of MRD reporting (e.g. ERIC, The EuroFlow Consortium, The EuroClonality Consortium)

Courtesy of Davide Rossi Institute of Oncology Research; Oncology Institute of Southern Switzerland

Universita' della Svizzera Italiana Bellinzona, Switzerland

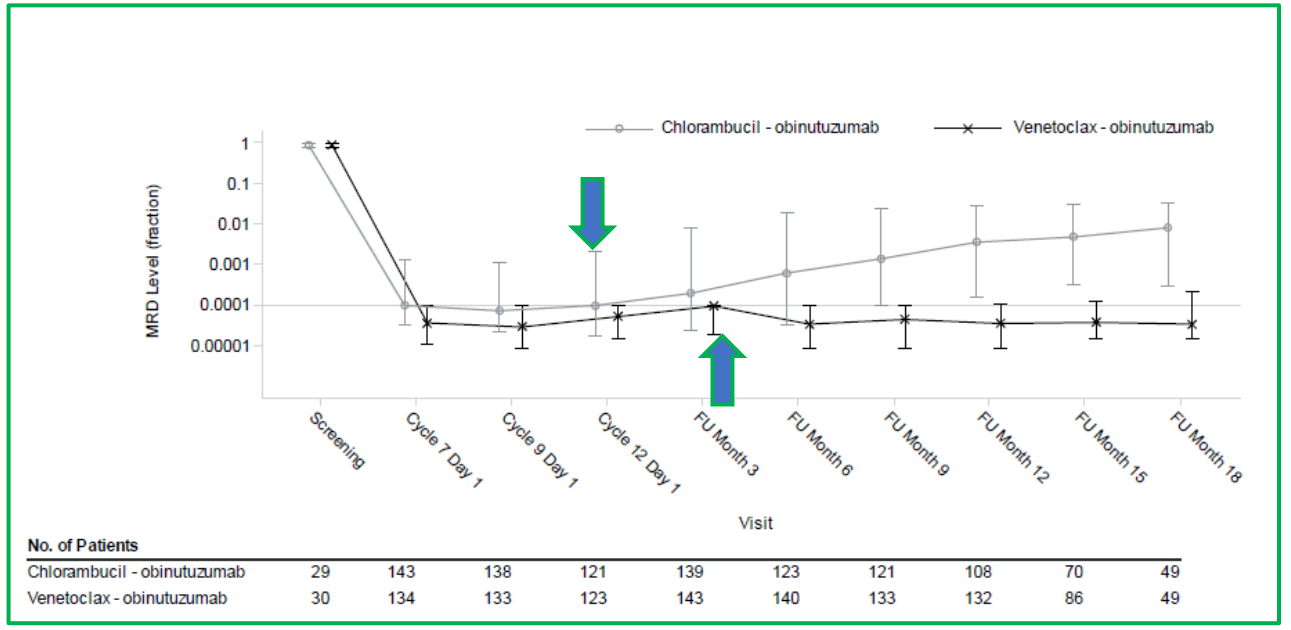
CLL 14: Minimal residual disease clearance by ASO-PCR and flow cytometry in peripheral blood

MRD clearance by ASO-PCR in PB blood during study



No. of Patients										
Chlorambucil - obinutuzumab	188	178	170	149	170	153	146	131	61	45
Venetoclax - obinutuzumab	188	177	171	160	176	176	171	165	68	49

MRD clearance by FLOW in PB blood during study



No. of Patients										
Chlorambucil - obinutuzumab	29	143	138	121	139	123	121	108	70	49
Venetoclax - obinutuzumab	30	134	133	123	143	140	133	132	86	49

Fischer K. NEJM 2019

MRD in CLL

- Methods

- **MRD and prognosis** (target agents: doublets and triplets)
  10^{-4}
  10^{-5} and 10^{-6}
  Quality of uMRD

- MRD as a tool to guide treatment

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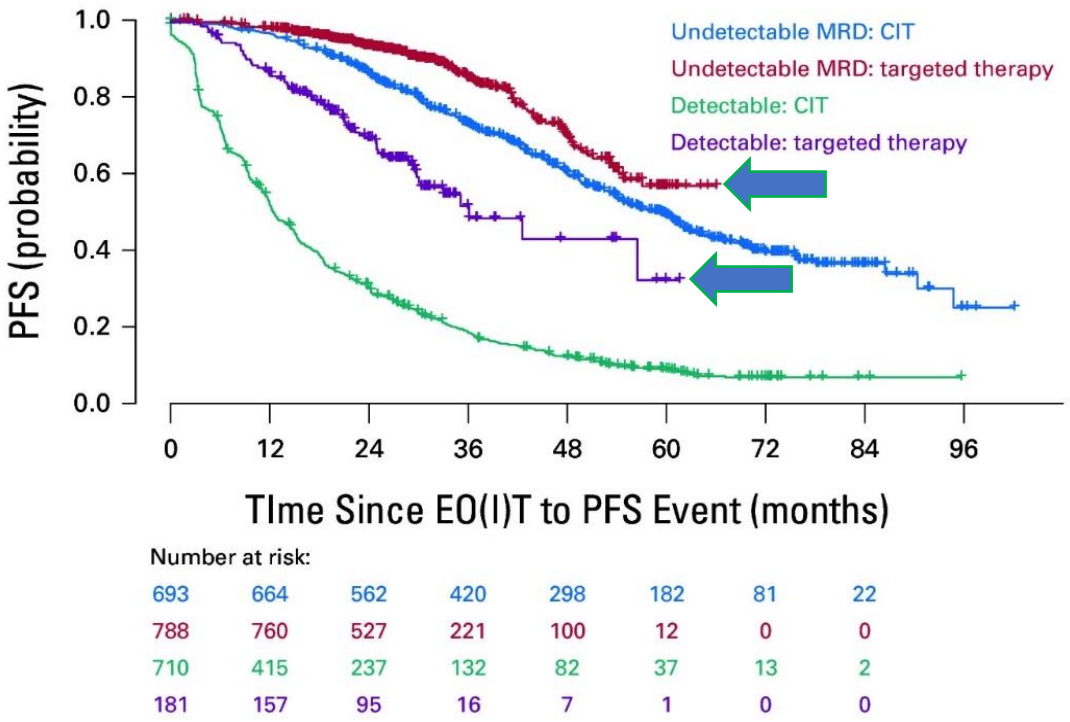
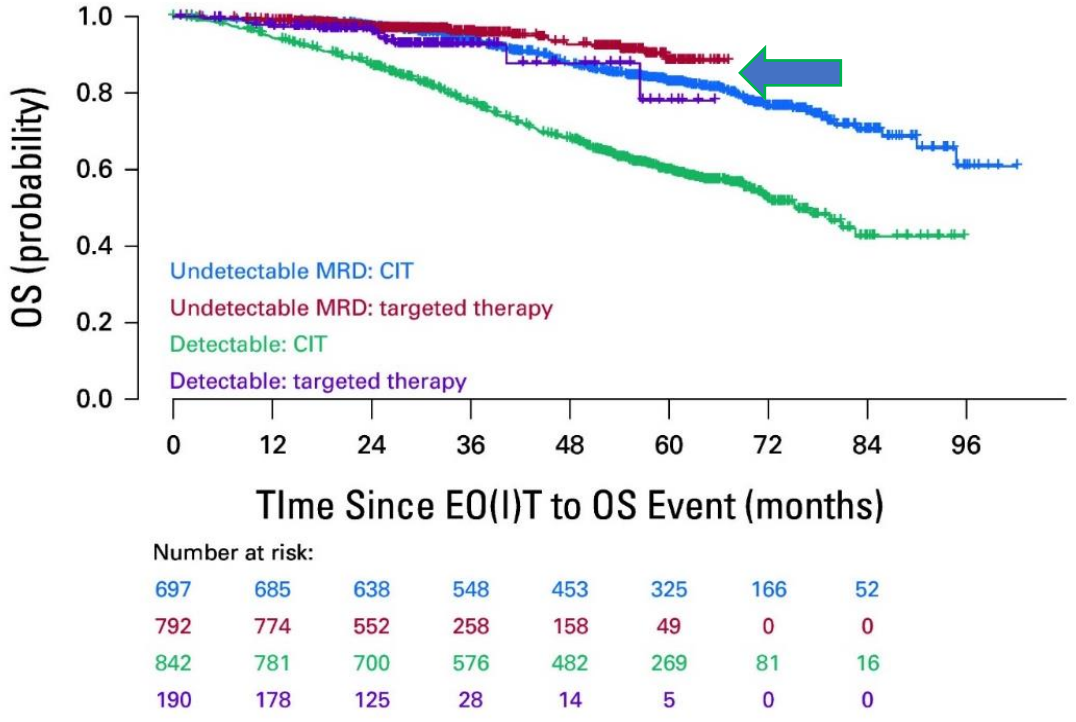
Clinical validity of MRD (10^{-4} PB) as a surrogate end point for PFS in the context of targeted TIME-LIMITED therapy

4,237 patients from 12 trials of the GCLLSG from 1999 to 2022





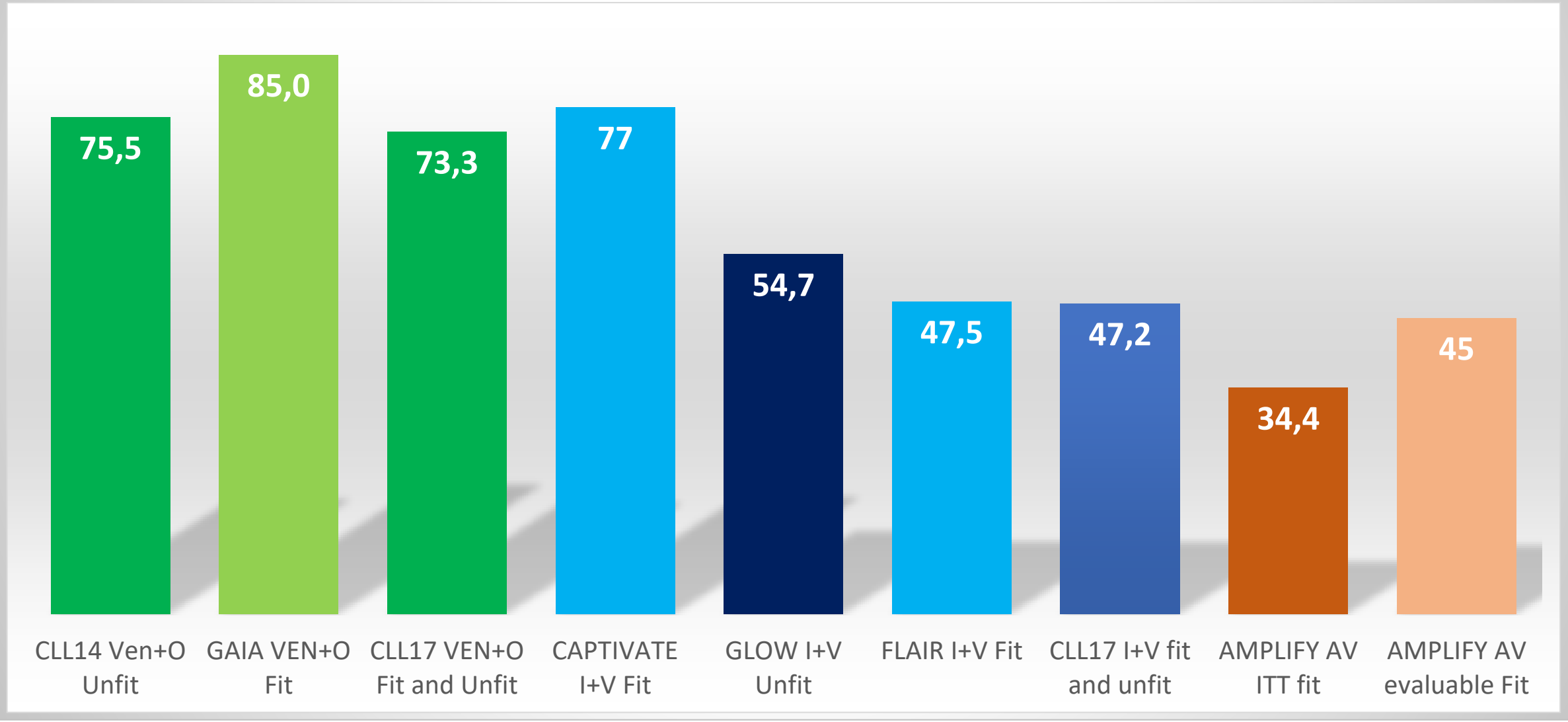
MRD response status showed a high treatment-effect correlation with PFS but not OS

Efforts are required to evaluate MRD-guided strategies to further optimize the treatment of CLL.
Long-term follow-up of CLL trials is, however, still vital to validate a possible surrogacy of MRD for PFS and OS.

Simon F, J Clin Oncol. 2025

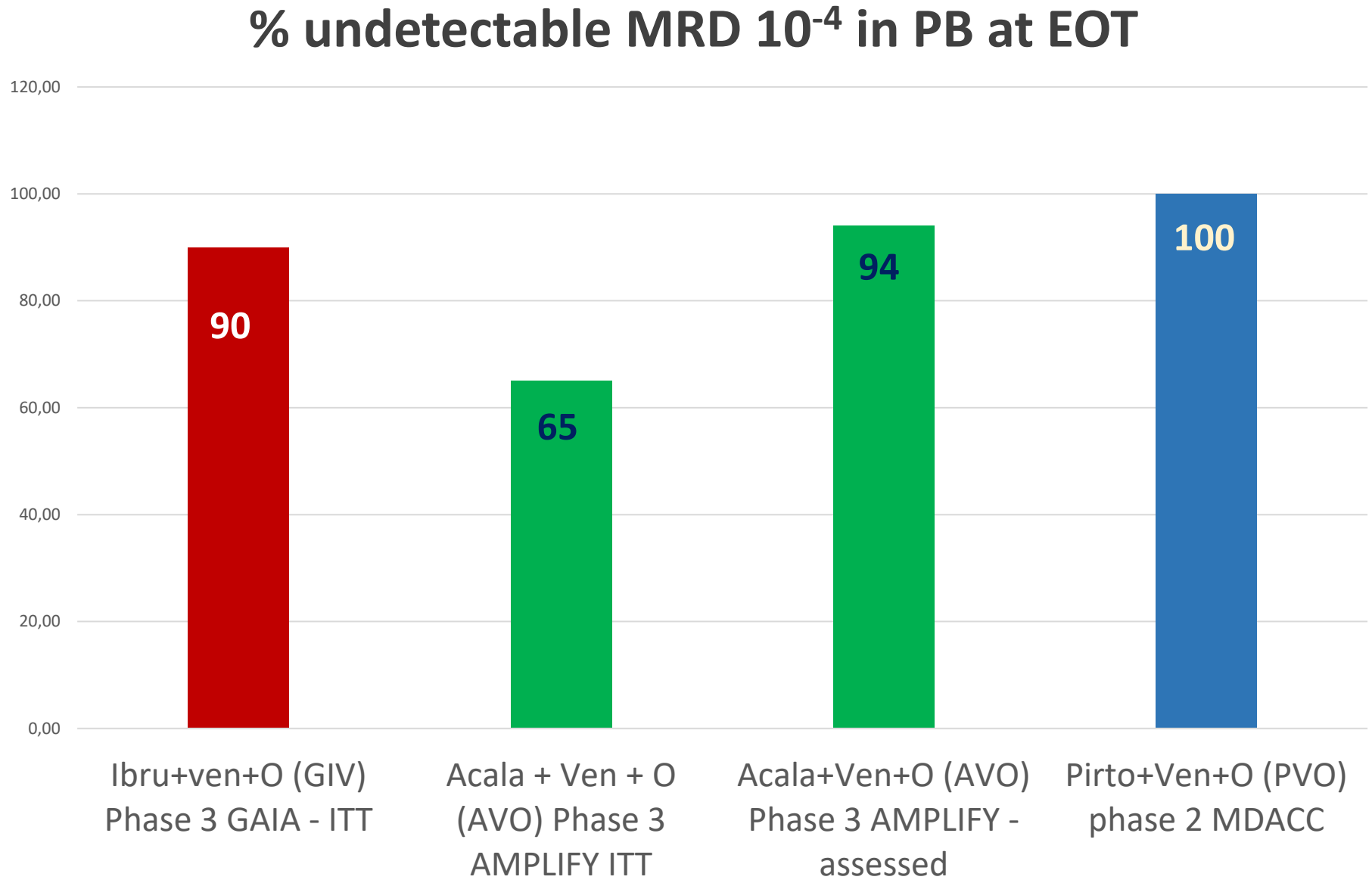
% uMRD 10-4 in PB at end of treatment with venetoclax based regimens

Ven + Obi | Ibru + Ven | Acala + Ven



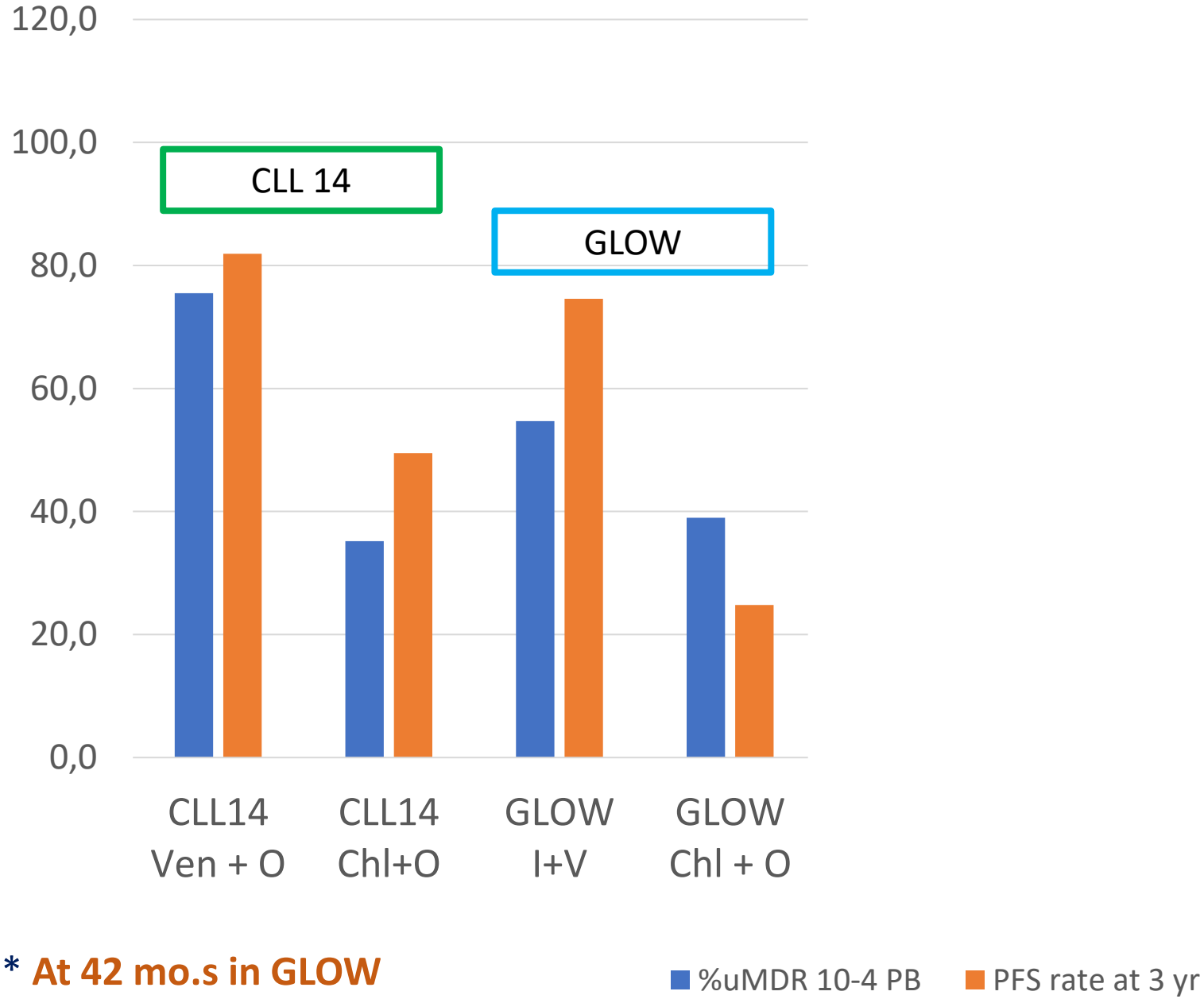
Al Sawaf O Lancet Oncol 2020; Al Sawaf O, ASH 2025; Fürstenau M, et al. Hematol Oncol: Volume 43, Issue S3, e70_70093; Kate NEJM evi 2022; Hillmen NEJM 2024; Tam,C Blood 2024; Brown J NEJM 2025

% uMRD 10-4 with triplets



Fürstenau M, et al. Hematol Oncol: Volume 43, Issue S3, e70_70093; Brown NEJM 2025; Jain EHA 2025

% uMRD 10-4 and PFS rate at 3 yrs* in phase 3 trials



* At 42 mo.s in GLOW

MRD in CLL

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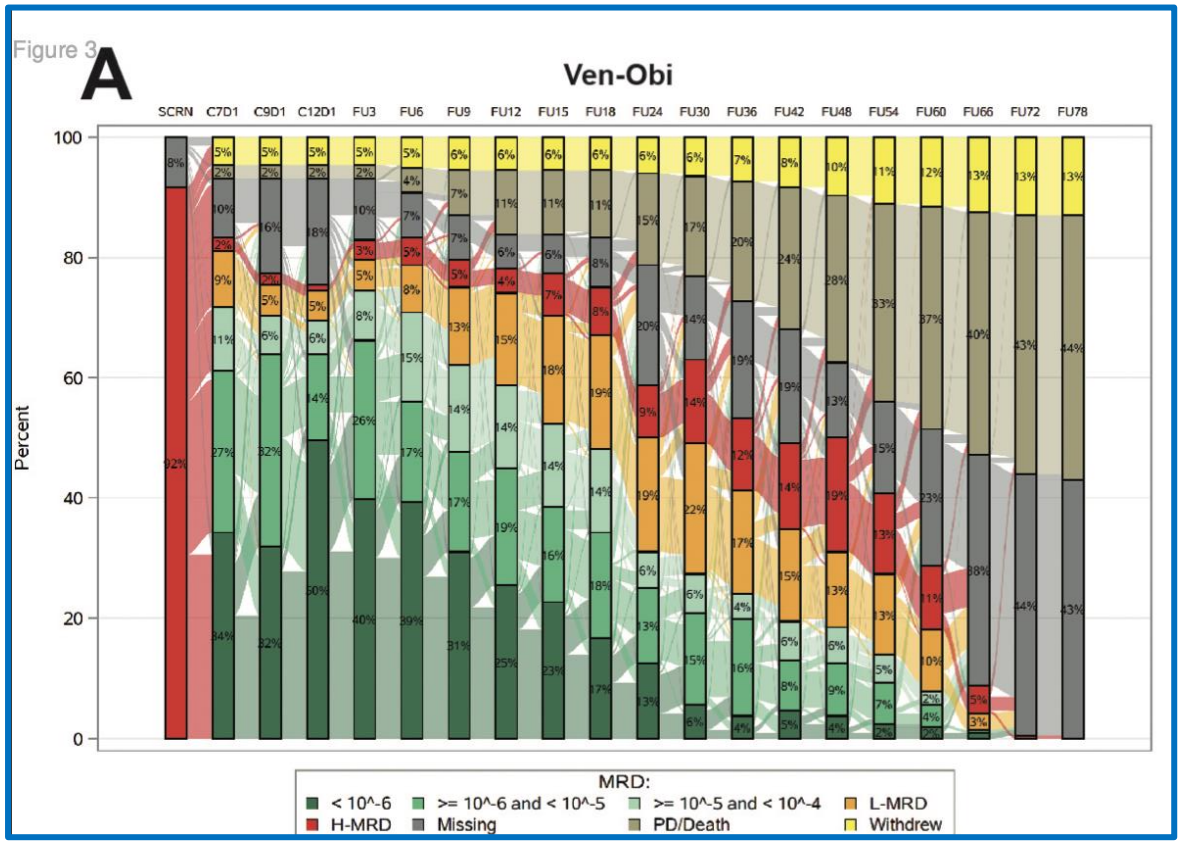
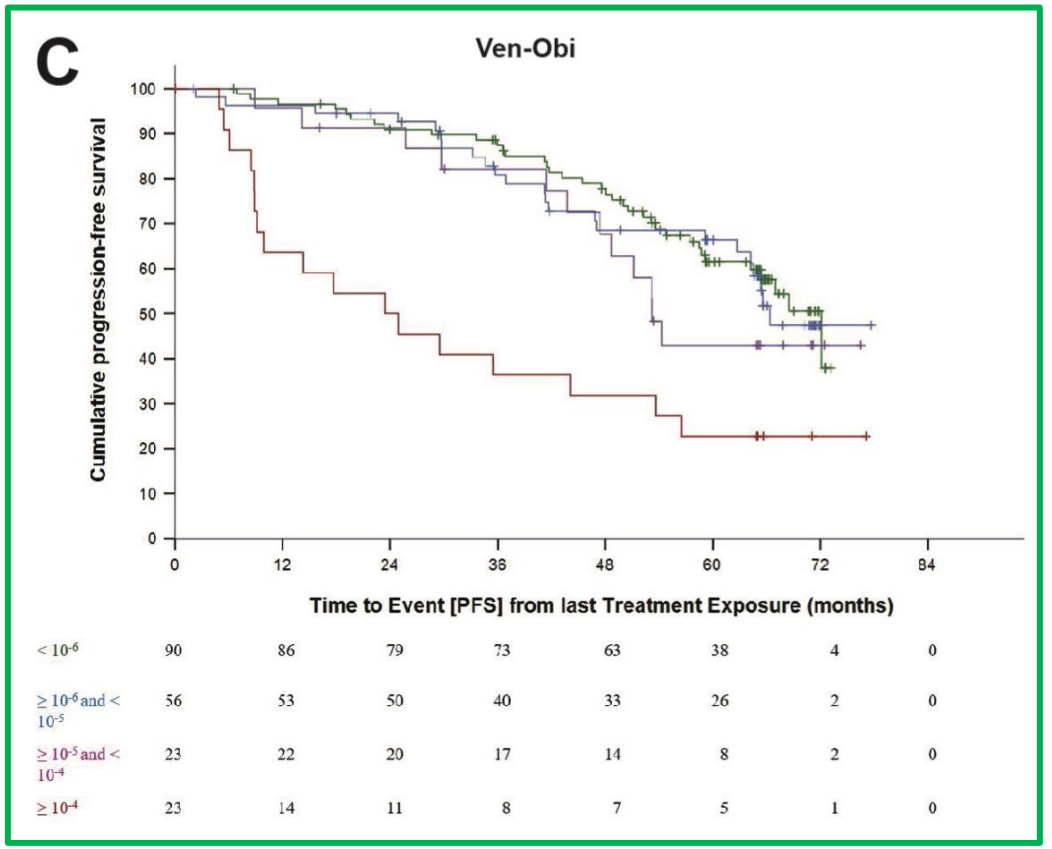
CLL14 Phase 3 trial: venetoclax + Obinutuzumab (6yr Follow-up)

PFS advantage for uMRD 10^{-4} --- No PFS difference in uMRD 10^{-4} vs 10^{-5} vs 10^{-6}





All patients with MRD <10^{-6} had MRD <10-4 in the bone marrow, as assessed by ASO-PCR

Othman Al-Sawaf. Blood. 2024 Jul 10:blood.2024024631.

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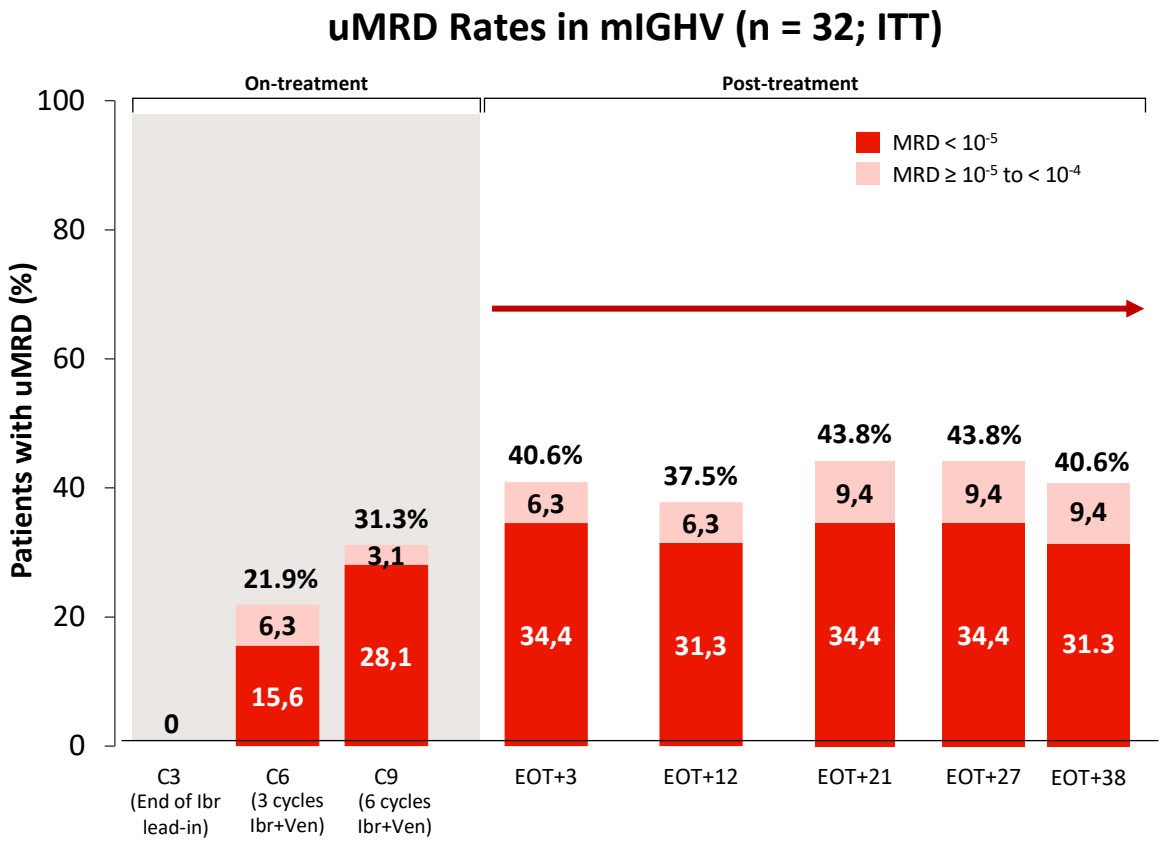
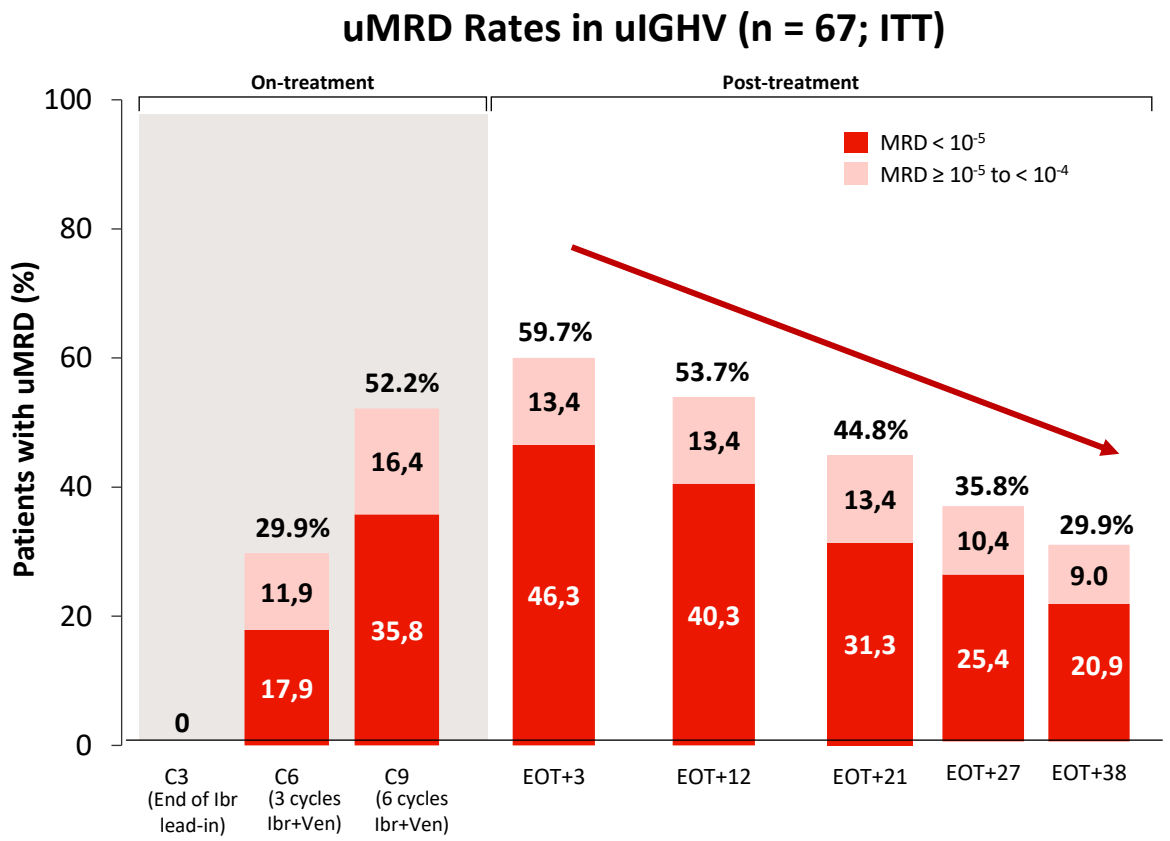
GLOW: Ibr+Ven uMRD Dynamics According to IGHV Status





- uMRD rate remained stable 3 years after treatment completion in patients with mIGHV CLL
- uMRD rate was ~ 60% after treatment completion in patients with uIGHV and decreased to ~ 30% at EOT+38

Numbers may not add up to exact total due to rounding. uMRD was defined as < 1 CLL cell per 10,000 leukocytes (< 10^{-4}).

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

MRD in CLL

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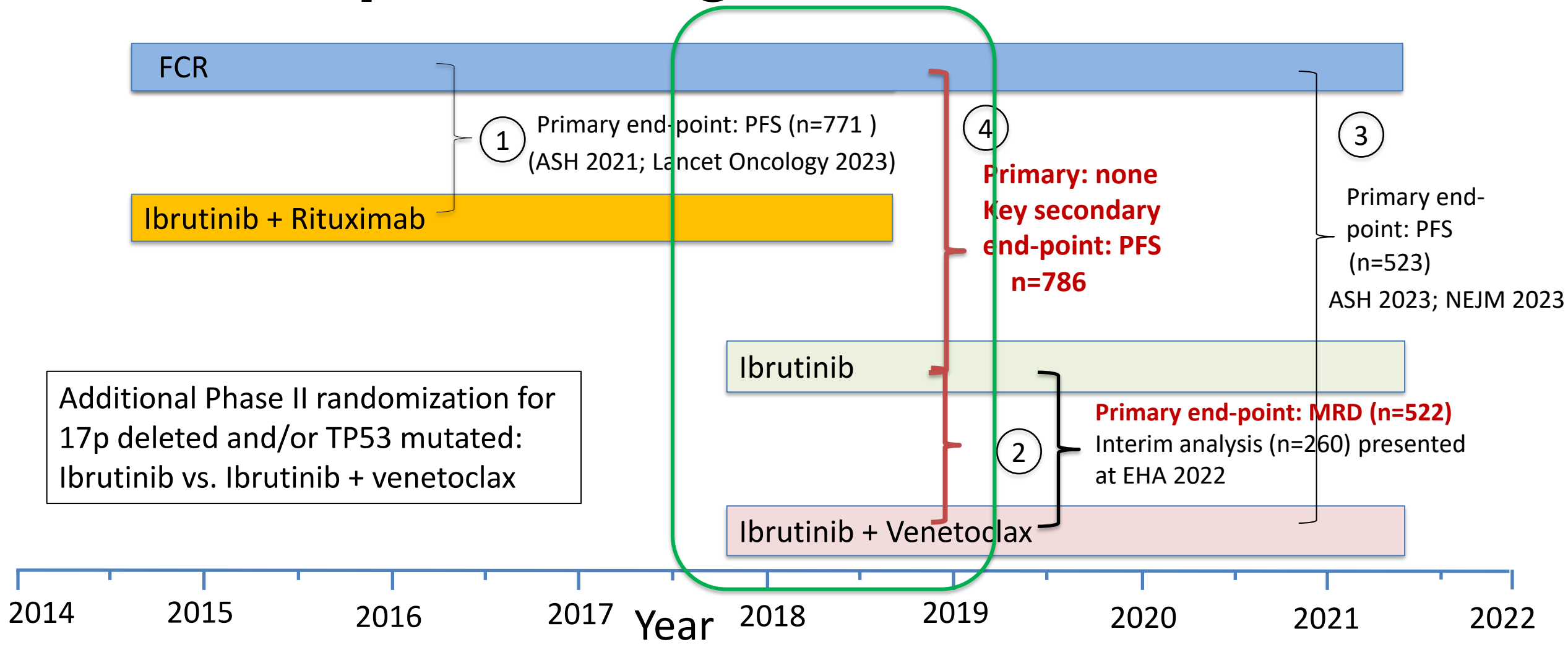
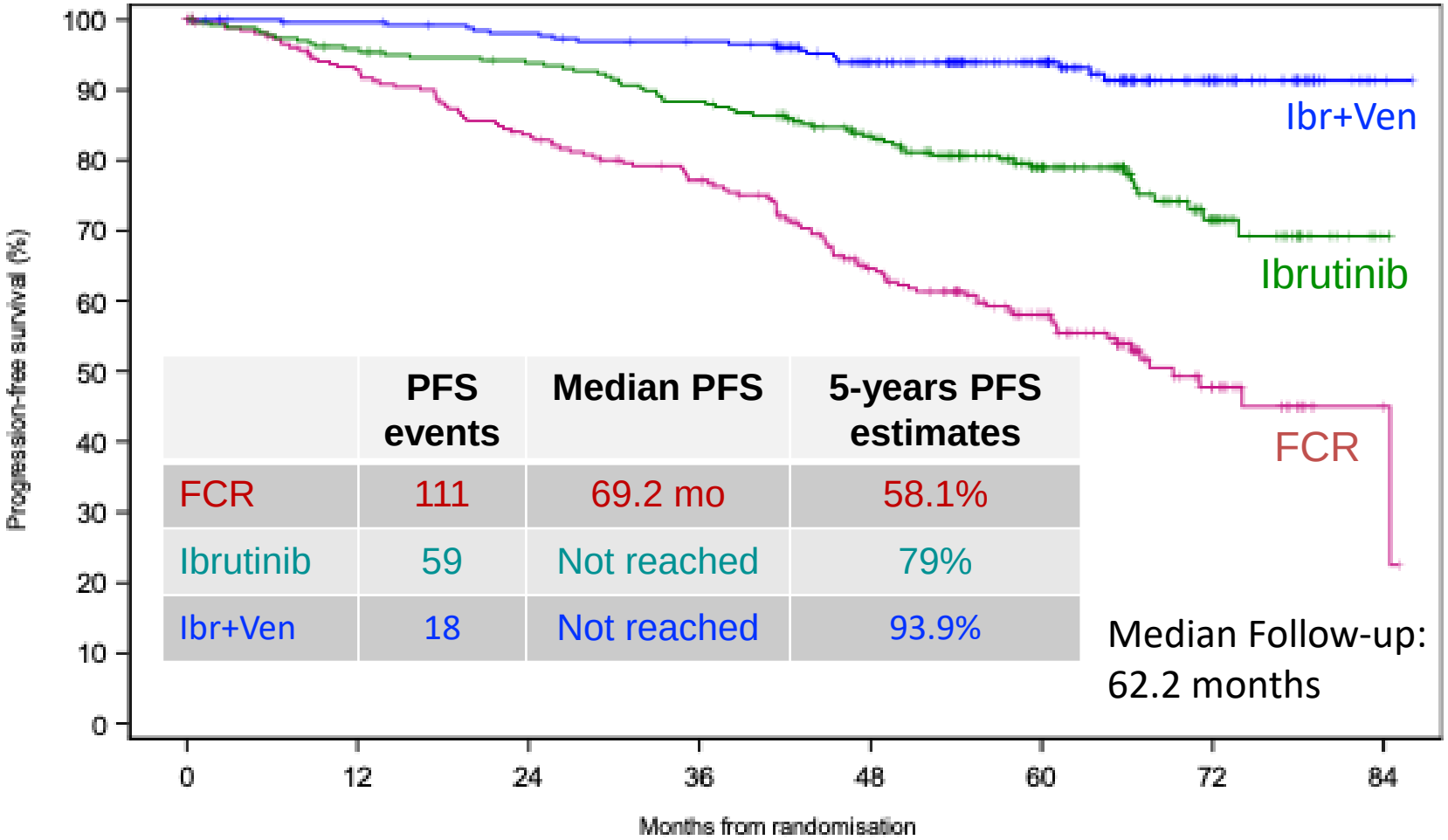
Adaptive design of Flair



Additional Phase II randomization for 17p deleted and/or TP53 mutated: Ibrutinib vs. Ibrutinib + venetoclax

Flair Progression-Free Survival: Superiority of MRD defined I+V to ibrutinib and FCR



	PFS events	Median PFS	5-years PFS estimates
FCR	111	69.2 mo	58.1%
Ibrutinib	59	Not reached	79%
Ibr+Ven	18	Not reached	93.9%

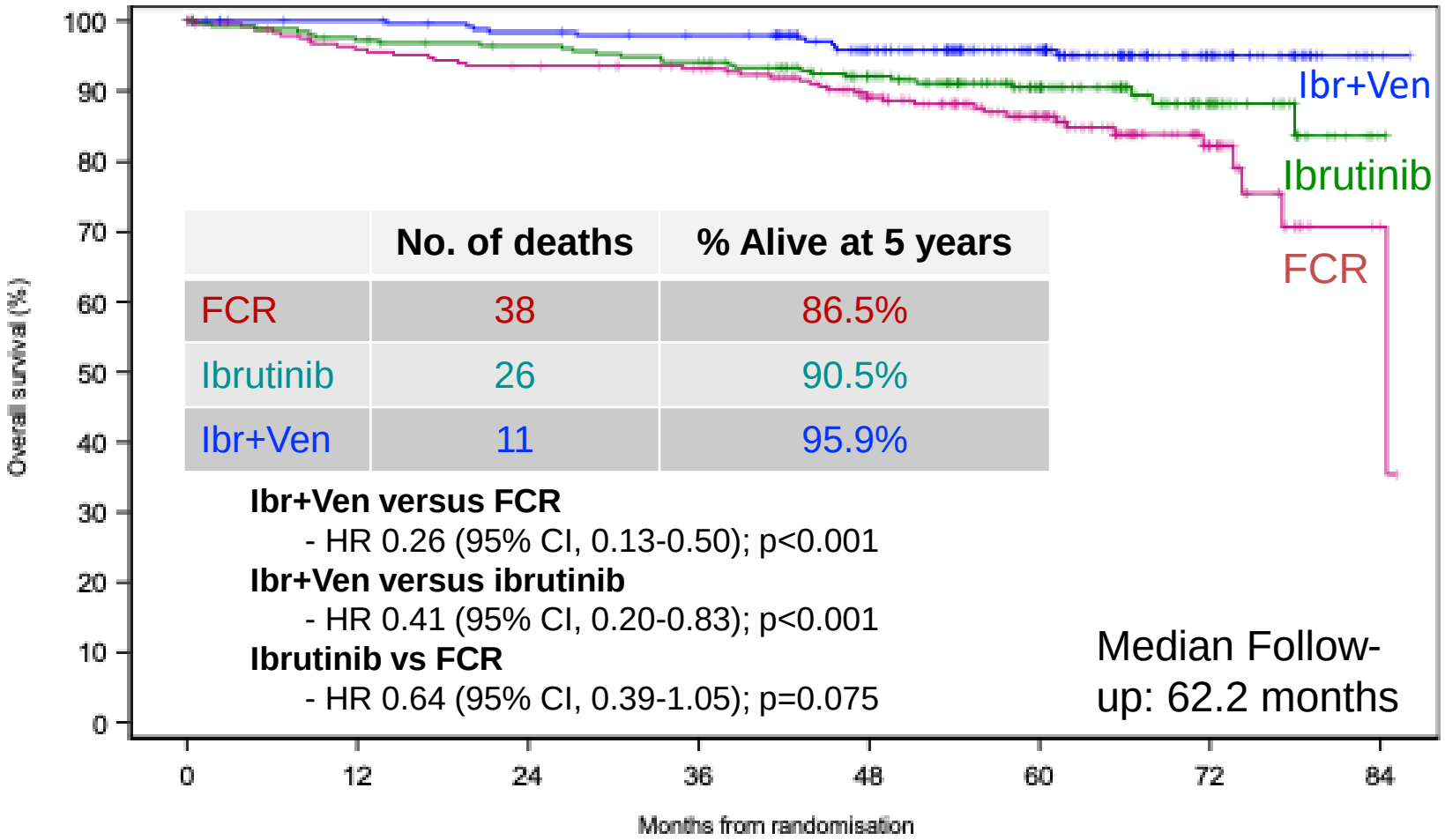
Median Follow-up: 62.2 months

Ibr+Ven reduced the risk of progression or death by <u>87%</u> compared to FCR
- HR 0.13 (95% CI, 0.08-0.21); p<0.001

Ibr+Ven reduced the risk of progression or death by <u>71%</u> compared to ibrutinib
- HR 0.29 (95% CI, 0.17-0.49); p<0.001

Ibrutinib reduced risk of progression or death by <u>56%</u> compared to FCR
- HR 0.44 (95% CI, 0.32-0.60); p<0.001

Overall Survival: Superiority of MRD defined I+V to ibrutinib and FCR



	No. of deaths	% Alive at 5 years
FCR	38	86.5%
Ibrutinib	26	90.5%
Ibr+Ven	11	95.9%

Ibr+Ven versus FCR
- HR 0.26 (95% CI, 0.13-0.50); p<0.001

Ibr+Ven versus ibrutinib
- HR 0.41 (95% CI, 0.20-0.83); p<0.001

Ibrutinib vs FCR
- HR 0.64 (95% CI, 0.39-1.05); p=0.075

Median Follow-up: 62.2 months

Data-lock: 4th Nov 2024

Munir *et al.*, Abstract S155, EHA 2025

Conclusions

- **Methods for MRD testing**[1]
  i) standardization (documented standards)
  ii) harmonization (ensure reproducibility)
  iii) validation (accuracy, predictivity)
  iv) verification (quality assurance)

- **uMRD** is a dynamic prognostic factor predicting for the duration of response and longer PFS with a given treatment while it does not always correlate with PFS or OS[2]

- **uMRD** may become critical to **optimizing finite-duration targeted therapy**[3]

[1]Wierda GW Leukemia 2021 https://doi.org/10.1038/s41375-021-01241-1; [2]Yang S Leukemia 2022; https://doi.org/10.1038/s41375-022-01699-7; [3]Munir T, NEJM DOI: 10.1056/NEJMoa2504341