Updates & Impacts: Treating Heme Malignancies in 2022: CLL ASH Updates

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Disclosures

- **Research Funding: Acerta/AstraZeneca, Beigene, Janssen, TG Therapeutics**
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- **DSMB: Incyte**

ASH 2021: Data for Review

1. CAPTIVATE
2. GLOW
3. GAIA / CLL13

First-Line Treatment With Ibrutinib Plus Venetoclax for CLL: 2-Year Post-randomization Disease-Free Survival Results From the Minimal Residual Disease Cohort of the Phase 2 CAPTIVATE Study

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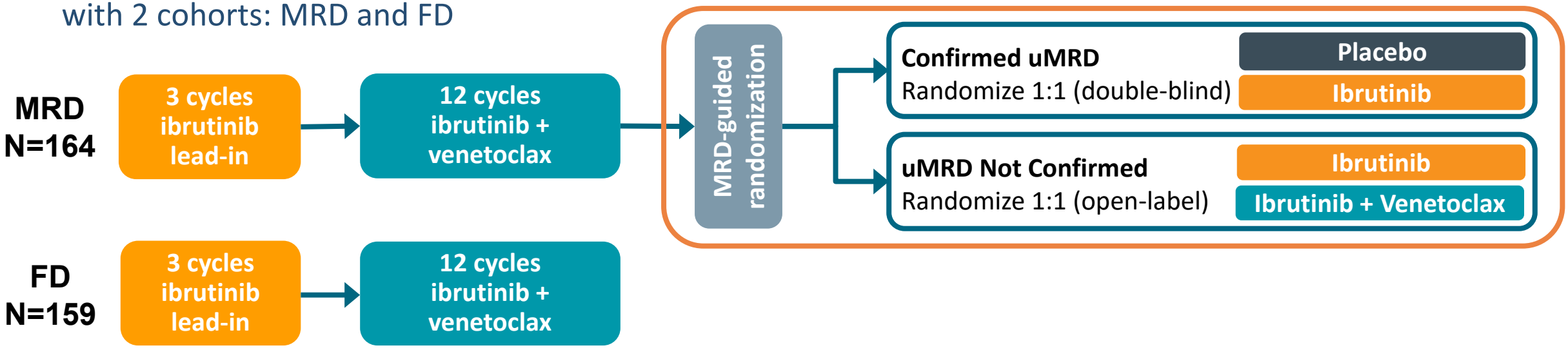
Ghia P. abstract 68, ASH 2021.

Phase 2 CAPTIVATE Study

- CAPTIVATE (PCYC-1142) is an international, multicenter phase 2 study evaluating first-line treatment with 3 cycles of ibrutinib followed by 12 cycles of combined ibrutinib + venetoclax with 2 cohorts: MRD and FD



- Primary analyses of both cohorts have been previously reported[1,2]
- Presented are updated results from the MRD cohort, with median time on study: 38.2 months (range, 15.0–47.9)
  - Median postrandomization follow-up: 24.0 months (range, 5.8–33.1)

1. Wierda WG et al. ASH 2020. Abstract #123. 2. Ghia P et al. ASCO 2021. Abstract #7501.

MRD Cohort: Patient Disposition and Randomization

Best MRD response after 12 cycles ibrutinib + venetoclax prerandomization

- **74% uMRD in PB**
- **68% uMRD in BM**

Enrolled to CAPTIVATE MRD Cohort N=164

Not eligible for randomization (n=15)

- 5 patients discontinued during ibrutinib lead-in
- 10 patients discontinued during ibrutinib + venetoclax combination

Eligible for randomization n=149[a]

Confirmed uMRD defined as uMRD (<10^{-4} by 8-color flow cytometry) over ≥2 assessments ≥3 months apart and in both PB and BM

Confirmed uMRD: 86/149 (58%)

uMRD Not Confirmed[b]: 63/149 (42%)

Randomize 1:1
Stratified by IGHV status

Placebo (n=43)
Median follow-up: 38.0 months

Ibrutinib (n=43)
Median follow-up: 39.6 months

Randomize 1:1
Stratified by IGHV status

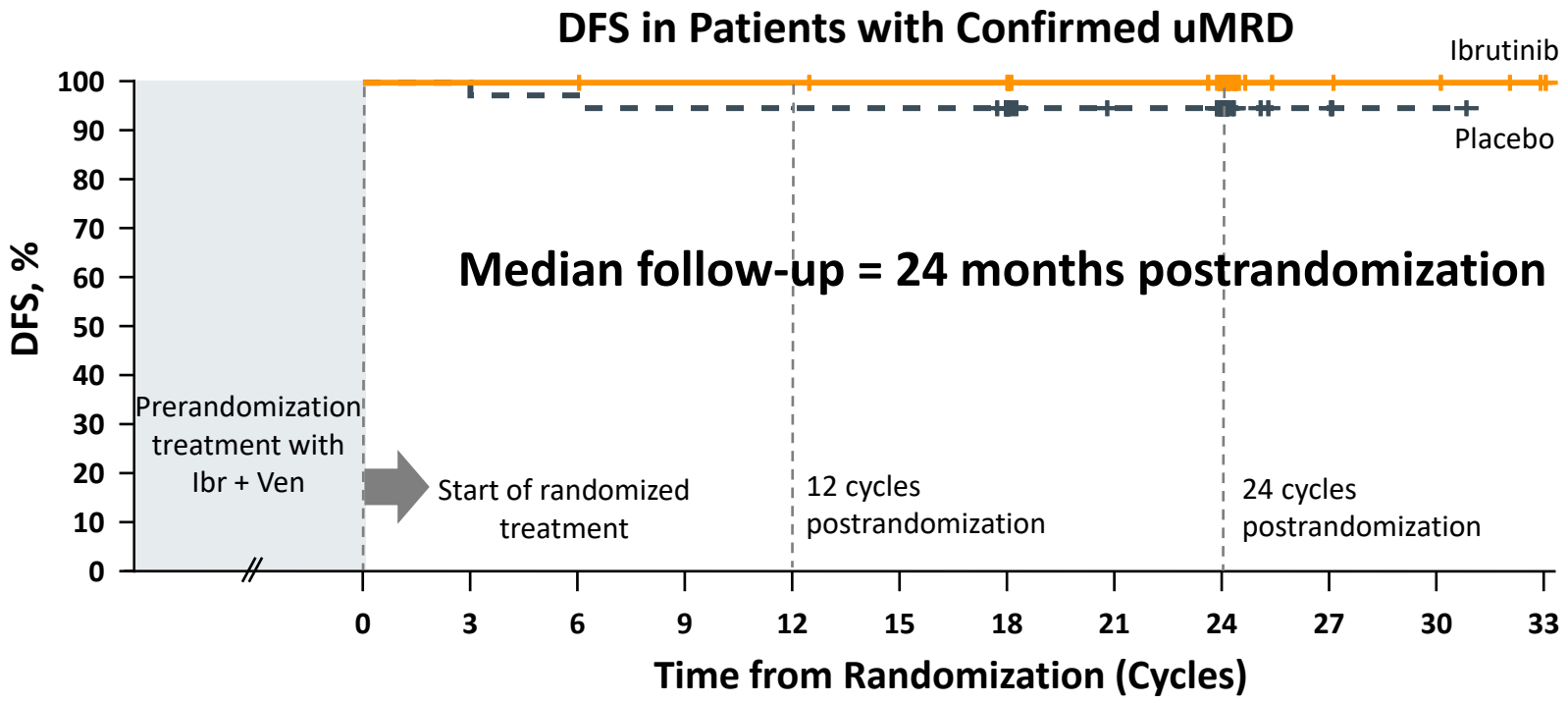
Ibrutinib (n=31)
Median follow-up: 39.2 months

Ibrutinib + Venetoclax (n=32)
Median follow-up: 37.9 months

[a]Includes 1 patient who discontinued venetoclax but completed planned treatment with ibrutinib. [b]Did not meet criteria for uMRD because of detectable MRD in PB and/or BM *or* undetectable MRD in PB that was not confirmed at consecutive assessments.

ASH 2021, CAPTIVATE-MRD; Ghia et al.

No New DFS Events Occurred Since Primary Analysis

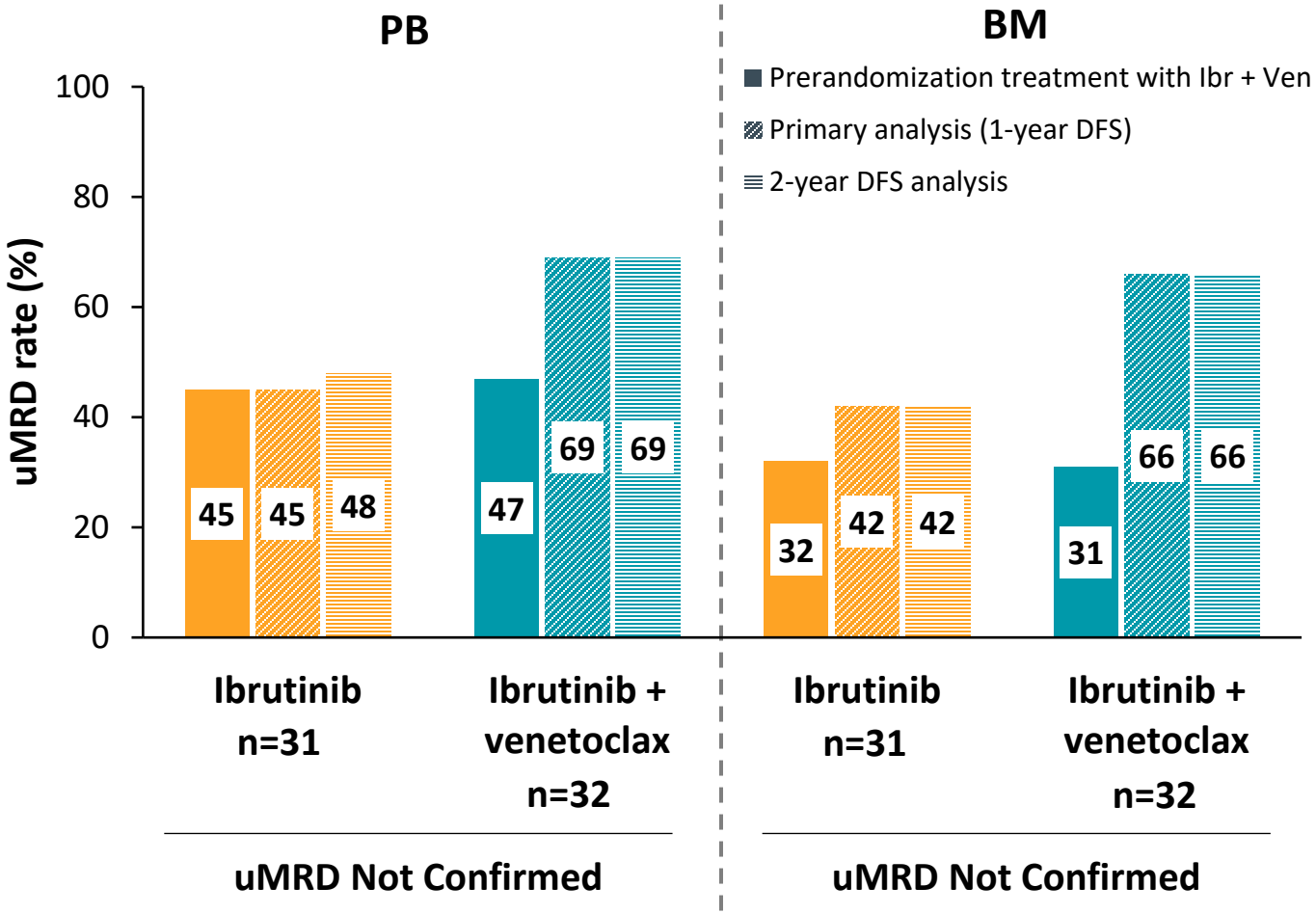


	Placebo	Ibrutinib
2-year DFS rate	95.3	100.0
Arm difference, % (95% CI)	4.7 (-1.6 to 10.9)	
Log-rank *P*-value	0.1573	

- DFS was defined as freedom from MRD relapse ($\geq 10^{-2}$ confirmed on 2 separate occasions) and without PD or death starting from randomization after 15 cycles of treatment
- In the additional year of follow-up since the 1-year DFS primary analysis, no new MRD relapses, PD, or deaths occurred in patients with confirmed uMRD randomized to ibrutinib or placebo

ASH 2021, CAPTIVATE-MRD; Ghia et al.

Best uMRD Rates Improved With Further Treatment in uMRD Not Confirmed Population



- Greatest uMRD rate improvements occurred during the first year of randomized treatment
  - Greater improvements with ibrutinib + venetoclax than with ibrutinib
  - Suggests possible need for further therapy duration to maximize benefit
- Improvements in uMRD rates were similar between patients achieving CR or PR

ASH 2021, CAPTIVATE-MRD; Ghia et al.

Retreatment Data From the MRD Placebo Arm and FD Cohorts

- 12 patients progressed after FD treatment[a] with ibrutinib + venetoclax retreated with single-agent ibrutinib
  - Median follow-up on retreatment: 4.9 months (range, 0.0–27.6)
  - Of 9 patients with available response, all have PR; 3 patients have pending responses
  - 8 of 9 had high-risk features

Patient	Cohort	Baseline high-risk features				Response to fixed-duration Ibr + Ven	
		del(17p)	*TP53* mutated	Unmutated IGHV	Complex karyotype	PFS (months)	Best response
1	FD	No	No	Yes	No	36.5	CR
2	FD	No	No	Yes	Yes	27.6	CR
3	FD	Yes	No	No	No	28.5	CRi
4	FD	No	No	No	Yes	30.4	PR
5	FD	No	No	No	No	27.4	PR
6	FD	No	No	No	Yes	22.0	PR
7	MRD-placebo	No	No	Yes	No	20.3	PR
8	MRD-placebo	No	No	Yes	No	19.4	PR
9	FD	Yes	No	Yes	Yes	16.6	PR

[a]MRD cohort placebo arm and FD cohort.

ASH 2021, CAPTIVATE-MRD; Ghia et al.

Summary

- With an additional year of follow-up since the primary analysis, there were no new MRD relapses, PD, or deaths in patients with confirmed uMRD treated with placebo or ibrutinib
  - The 2-year DFS rate with fixed-duration treatment (randomized to placebo) was maintained at 95%
- Early data suggest that patients who progress after fixed-duration treatment with ibrutinib + venetoclax can be successfully retreated with single-agent ibrutinib; but much more data is required!
- With median study follow-up of 38 months, AEs remained consistent with known profiles for single-agent ibrutinib and venetoclax; no new safety signals emerged

ASH 2021, CAPTIVATE-MRD; Ghia et al.

First Prospective Data on Minimal Residual Disease (MRD) Outcomes After Fixed-Duration Ibrutinib Plus Venetoclax (Ibr+Ven) Versus Chlorambucil Plus Obinutuzumab (Clb+O) for First-Line Treatment of CLL in Elderly or Unfit Patients: The GLOW Study

Talha Munir,[1] Carol Moreno,[2] Carolyn Owen,[3] George Follows,[4] Ohad Benjamini,[5] Ann Janssens,[6] Mark-David Levin,[7] Anders Osterborg,[8] Tadeusz Robak,[9] Martin Simkovic,[10] Don Stevens,[11] Sergey Voloshin,[12] Vladimir Vorobyev,[13] Munci Yagci,[14] Loic Ysebaert,[15] Qianya Qi,[16] Andrew J. Steele,[17] Natasha Schuier,[18] Kurt Baeten,[19] Donne Bennett Caces,[16] Carsten U. Niemann,[20] Arnon P. Kater[21]

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GLOW: Ibrutinib + Venetoclax vs Obinutuzumab + Chlorambucil

Eligibility criteria:

- Untreated CLL
- Aged ≥65 yr or <65 yr with CIRS >6 or CrCl <70 mL/min
- No del(17p) or *TP53* mutation
- ECOG PS 0-2

Ibrutinib 420 mg PO QD x 3 cycles, Ibrutinib + Venetoclax 12 cycles (n = 106)

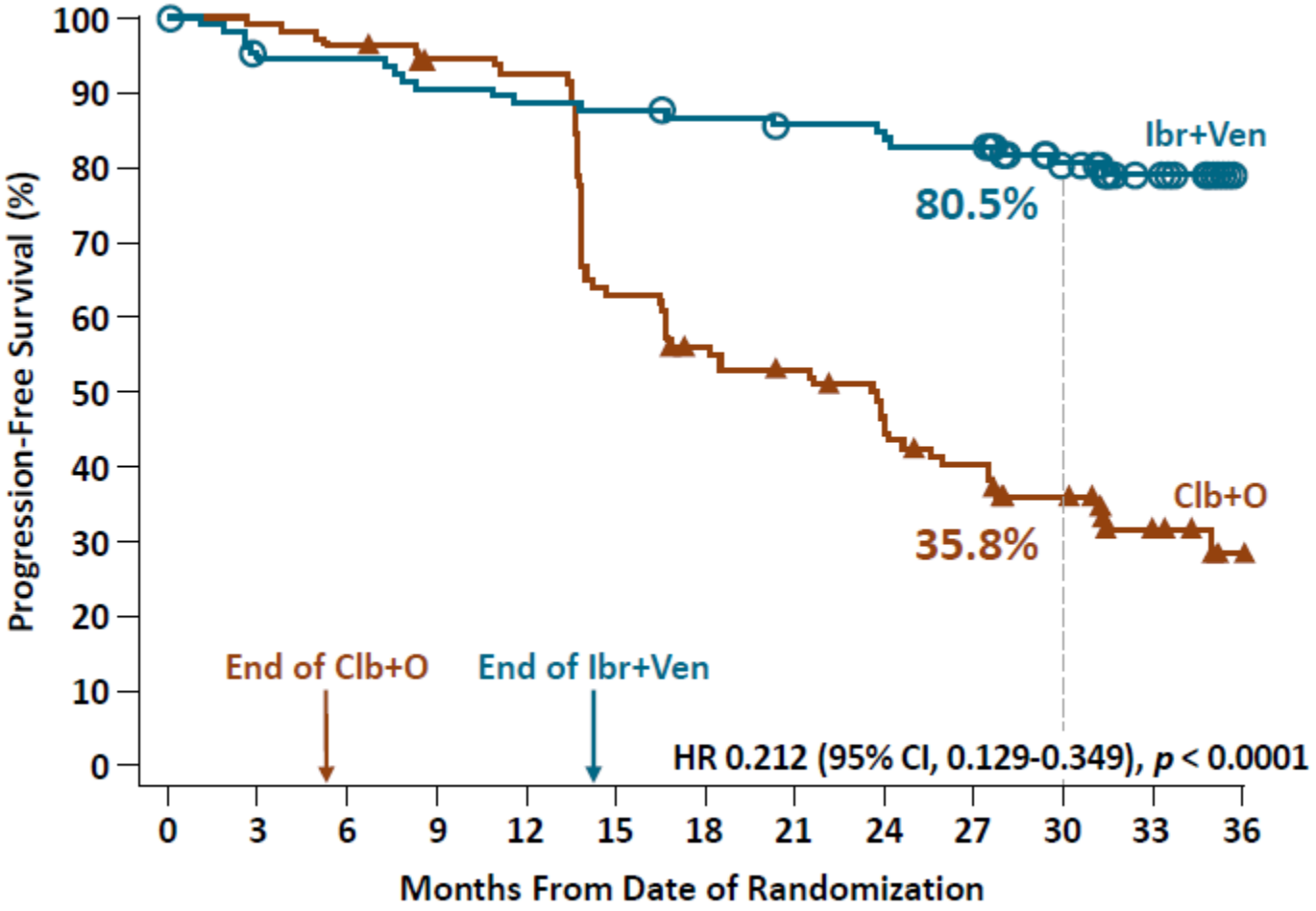
Chlorambucil 0.5 mg/kg on D1, 15 + Obinutuzumab 1000 mg x 6 cycles (n = 105)

If IRC-confirmed PD and active disease requiring tx, eligible for single-agent ibrutinib

- Primary endpoint: PFS per IRC
  - 71 PFS events to detect effect size with HR of 0.5 (80% power, 2-sided α = 0.05)
- Key secondary endpoints: uMRD in BM, CR rate per IRC, ORR per IRC, OS, safety

Munir T. abstract 70, ASH 2021.

GLOW: Progression-Free Survival



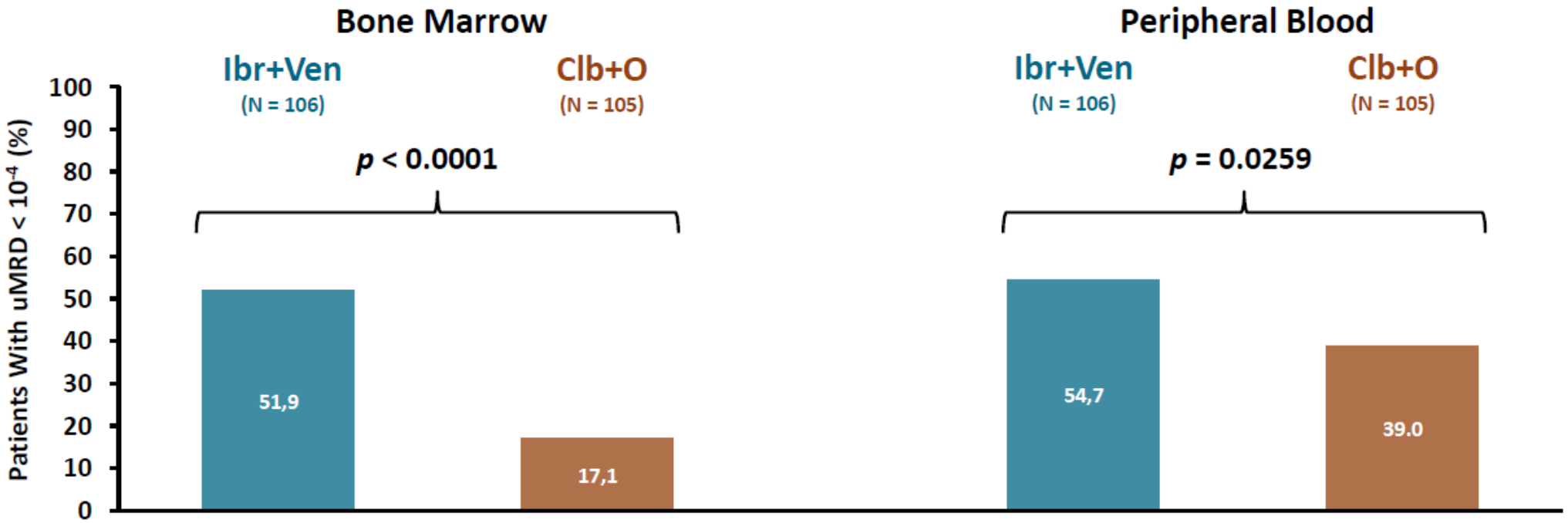
Primary PFS at 27.7 months
PFS HR = 0.216

Updated PFS at 34.1 months
PFS hazard ratio = 0.212; p<0.0001
30-months PFS:
- **Ibr+Ven: 80.5%**
- **Clb+O: 35.8%**

OS: hazard ratio = 0.76 (0.35-1.64)

Munir T. abstract 70, ASH 2021.

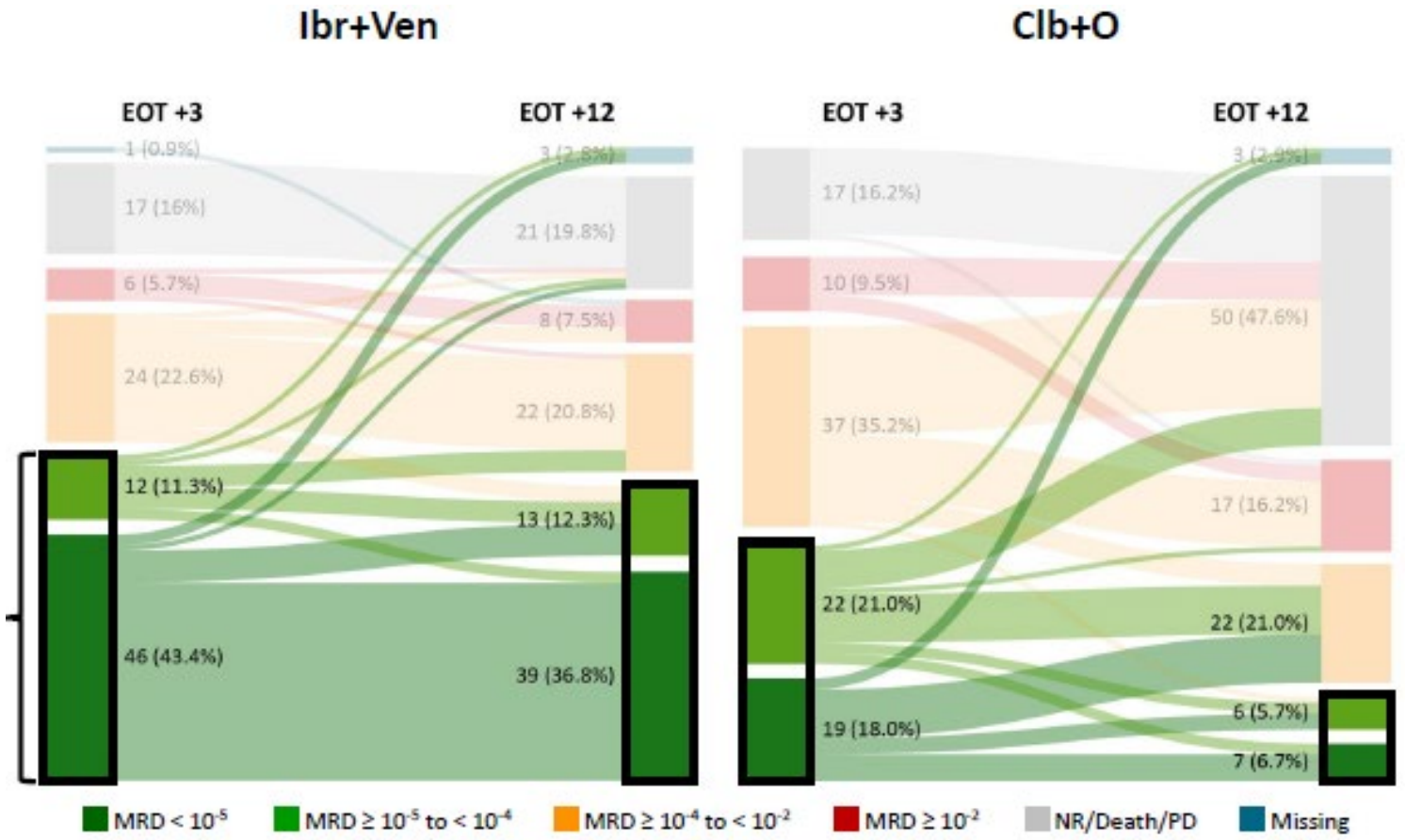
GLOW: uMRD at EOT+3



- Rate of uMRD was significantly higher with Ibr+Ven vs Clb+O in BM and PB
- uMRD concordance in PB/BM: **92.9%** for Ibr+Ven vs **43.6%** for Clb+O

Munir T. abstract 70, ASH 2021.

uMRD PB Rates: EOT+3 to EOT+12



Sustained uMRD seen in:

Ibr+Ven: 80.4%

Clb+O: 29.3%

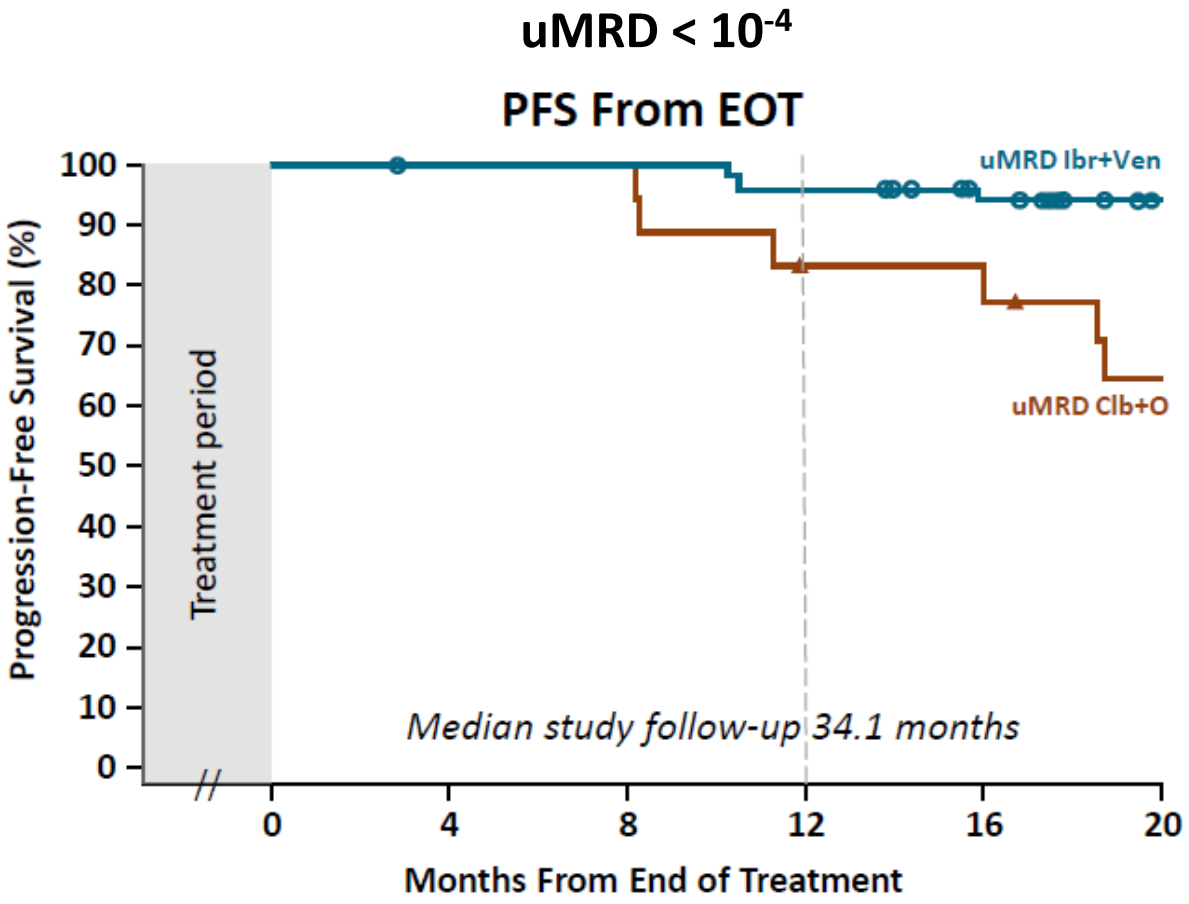
uMRD rate EOT+3 to EOT+12

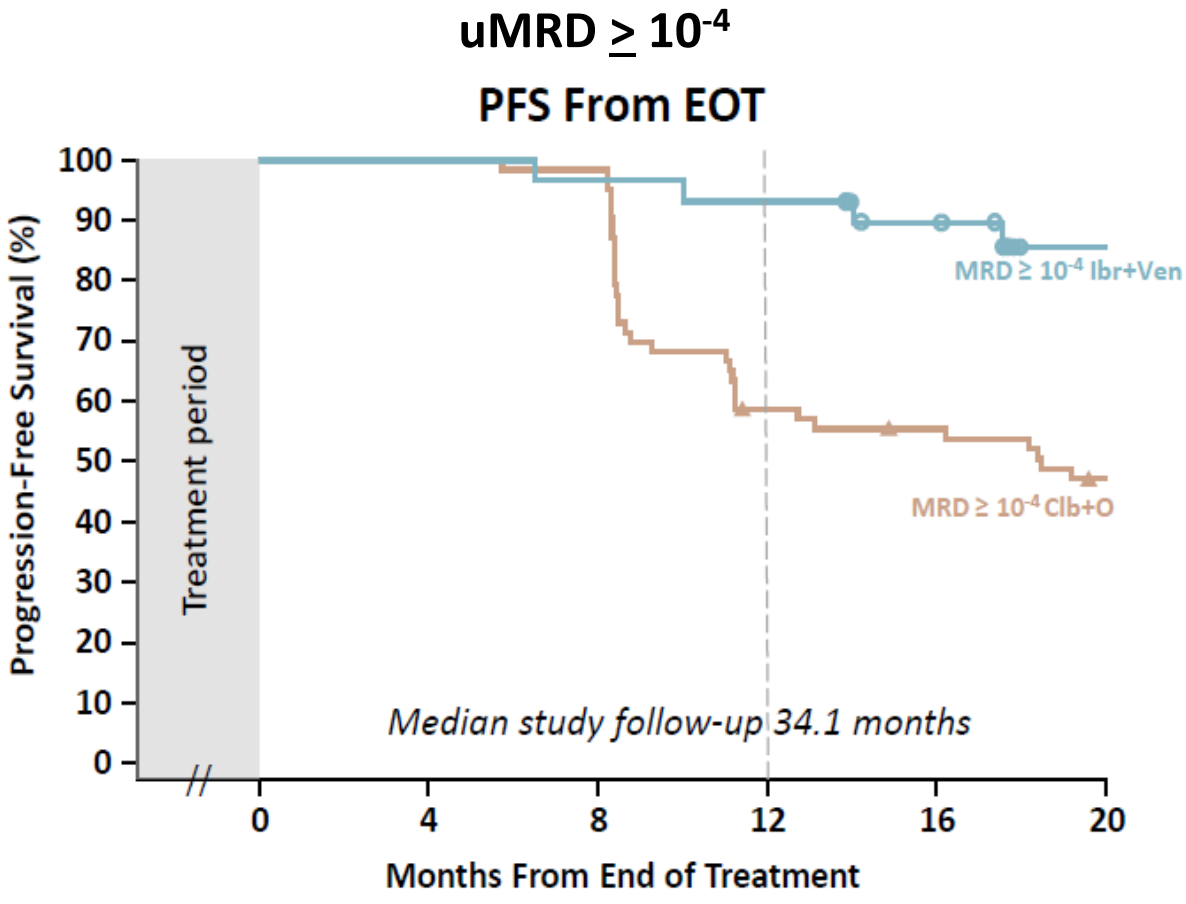
Ibr+Ven: decrease 6%

Clb+O: decrease 27%

Munir T. abstract 70, ASH 2021.

PFS Based on BM uMRD Status at EOT+3





- PFS rate during first year post-EOT sustained at >90% in Ibr+Ven, independent of BM MRD status
- Rapid relapse in non-uMRD patients treated with Clb+O

Munir T. abstract 70, ASH 2021.

Summary

- Ibr+Ven achieved deeper and better sustained uMRD compared with Clb+O
- Molecular and clinical relapses less frequent with Ibr+Ven
- Patients not attaining uMRD on Ibr+Ven still had PFS > 90% at 1 year
- Correlation between MRD status and PFS important predictor in era of novel agents
  - Lymphocytosis
  - Persistent LAD/organomegaly

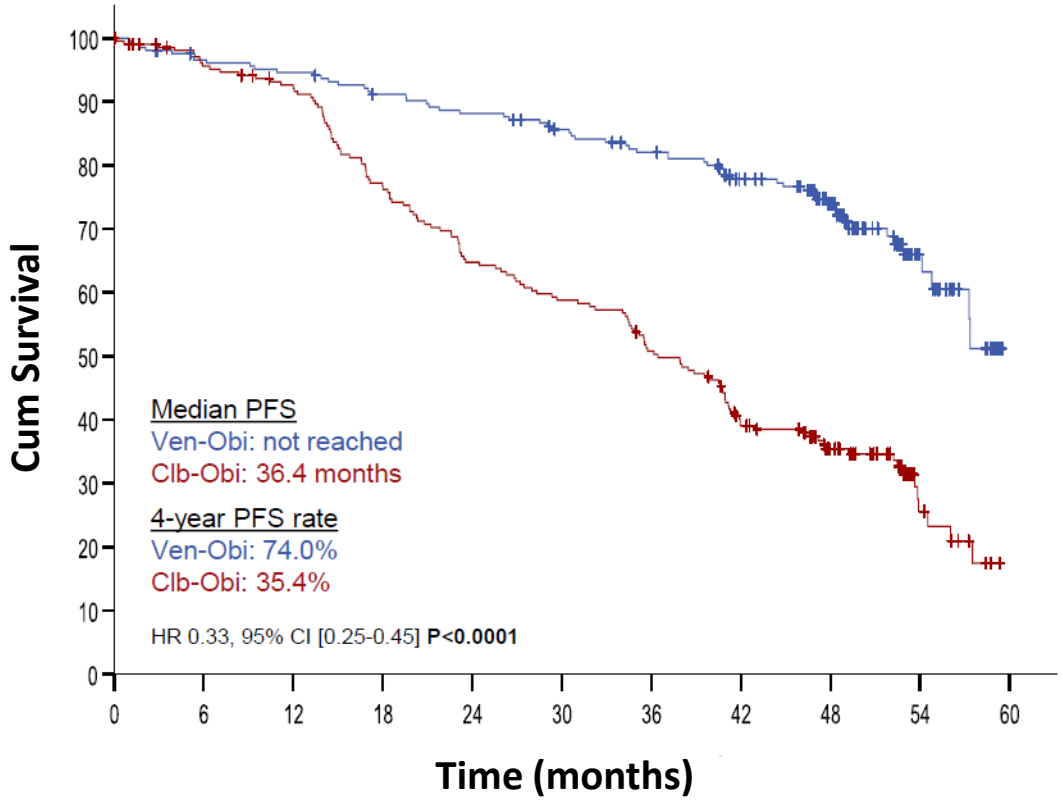
A RANDOMIZED PHASE III STUDY OF VENETOCLAX-BASED TIME-LIMITED COMBINATION TREATMENTS (RVE, GVE, GIVE) VS STANDARD CHEMOIMMUNOTHERAPY (CIT: FCR/BR) IN FRONTLINE CHRONIC LYMPHOCYTIC LEUKEMIA OF FIT PATIENTS: FIRST CO-PRIMARY ENDPOINT ANALYSIS OF THE INTERNATIONAL INTERGROUP GAIA (CLL13) TRIAL

Barbara Eichhorst, Carsten U Niemann, Arnon P Kater, Moritz Fürstenau, Julia von Tresckow, Can Zhang, Sandra Robrecht, Michael Gregor, Gunnar Juliusson, Patrick Thornton, Philipp B. Staber, Tamar Tadmor, Vesa Lindström, Caspar da Cunha-Bang, Christoph Schneider, Christian Poulsen, Thomas Illmer, Björn Schöttker, Ann Janssens, Use Christiansen, Thomas Nösslinger, Michael Baumann, Marjolein van der Klift, Ulrich Jäger, Henrik Frederiksen, Maria BL Leys, Mels Hoogendoorn, Kourosh Lotfi, Holger Hebart, Tobias Gaska, Harry Koene, Florian Simon, Nisha De Silva, Anna Fink, Kirsten Fischer, Clemens Wendtner, Karl A Kreuzer, Matthias Ritgen, Monika Brüggemann, Eugen Tausch, Mark-David Levin, Marinus van Oers, Christian Geisler, Stephan Stilgenbauer, Michael Hallek

Eichhorst B. ASH 2021 abstract 71.

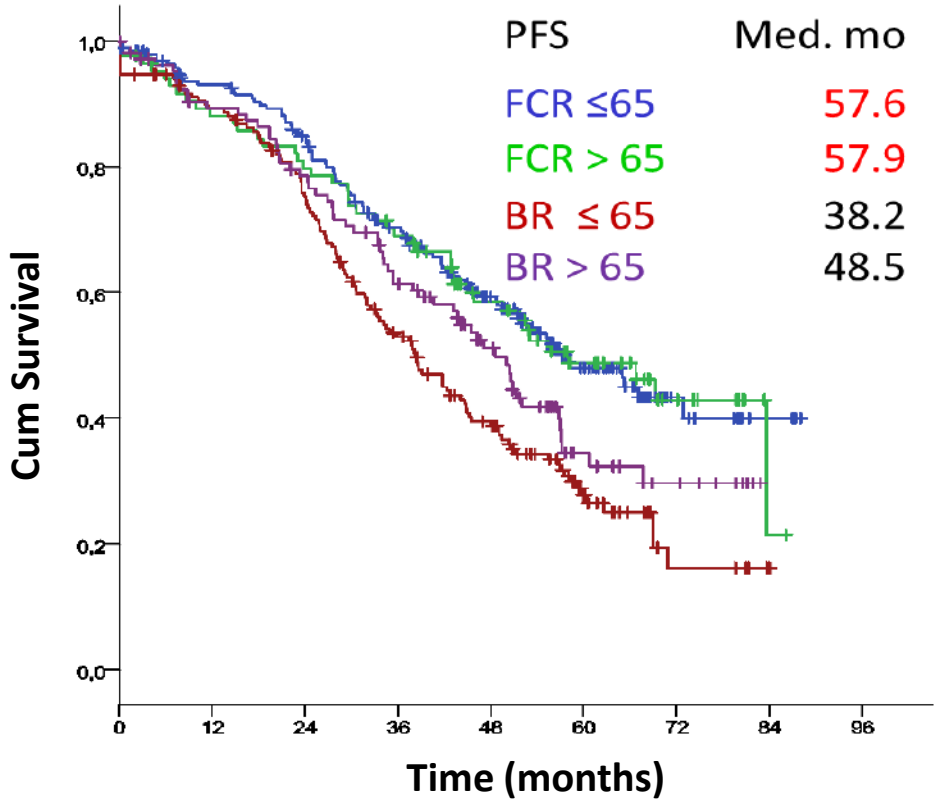
Comparison of time limited therapies in frontline of CLL: Are venetoclax-based, time limited therapies superior to BR/FCR ?

CLL14 Study of the GCLLSG in **less fit** patients



Al Sawaf O et al. J Clin Oncol Oct 2021: doi. org/10.1200/JCO.21. 01181

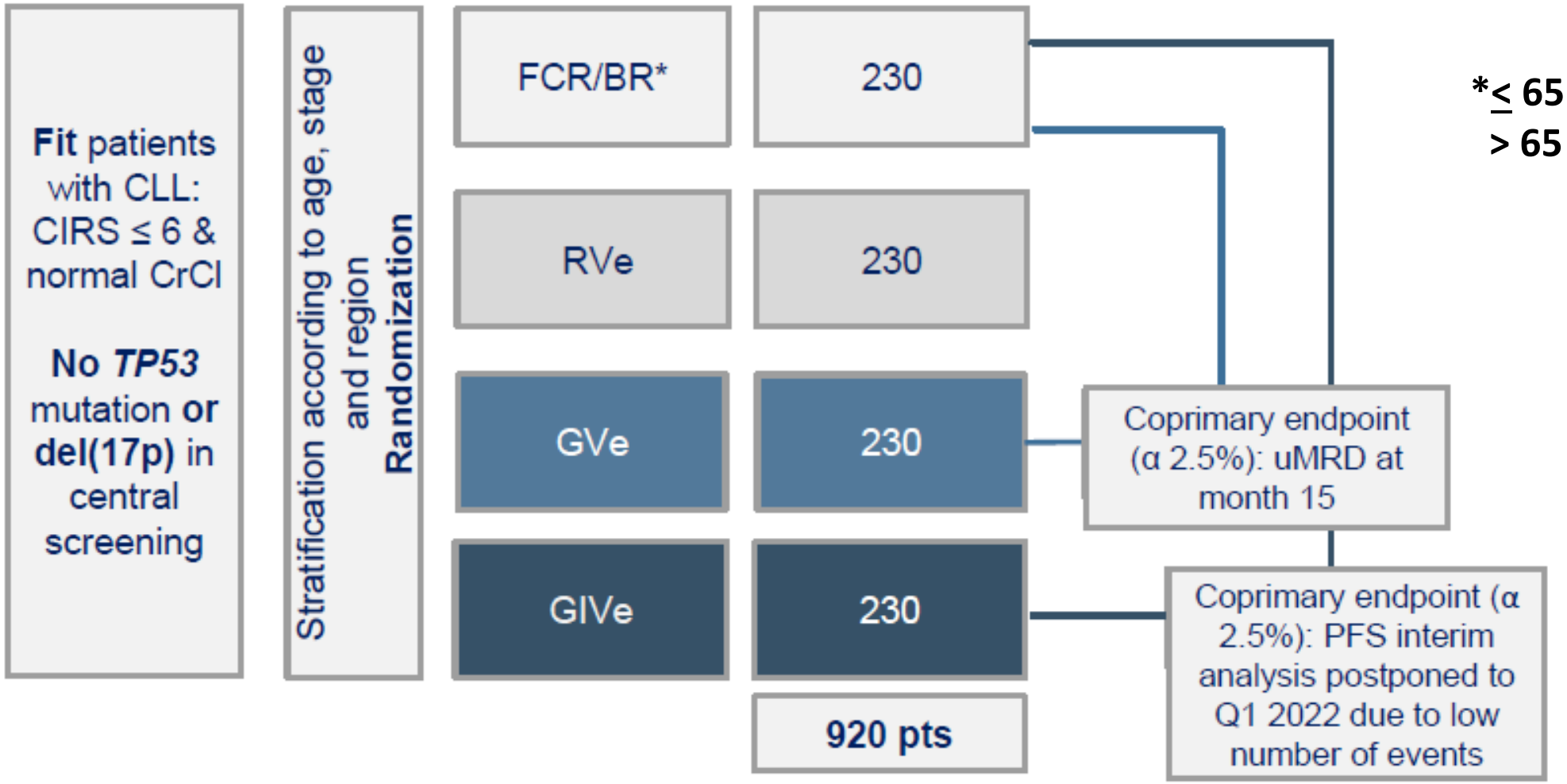
CLL10 Study of the GCLLSG in **fit** patients



Kutsch N. et al., HemaSphere Jan 2020: 4(1):e336

GAIA/CLL13 Study : Design

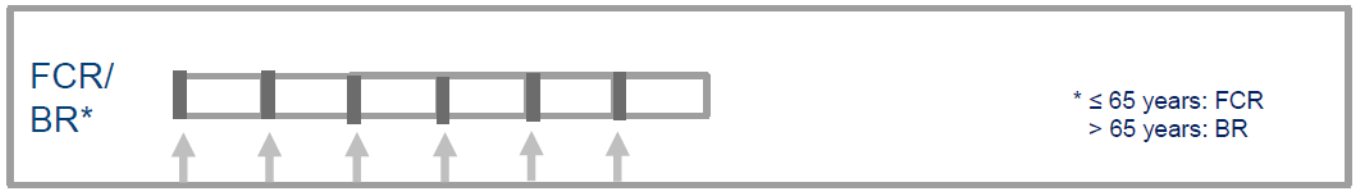
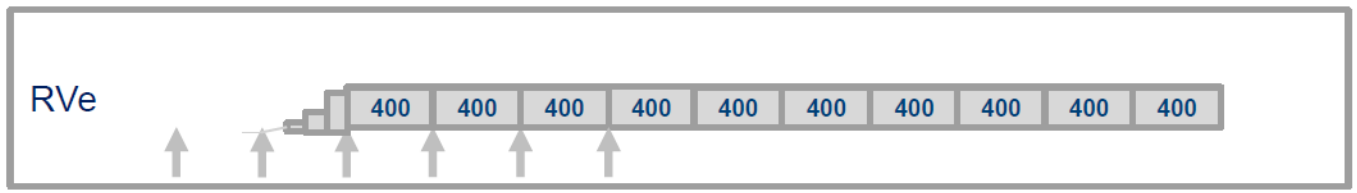
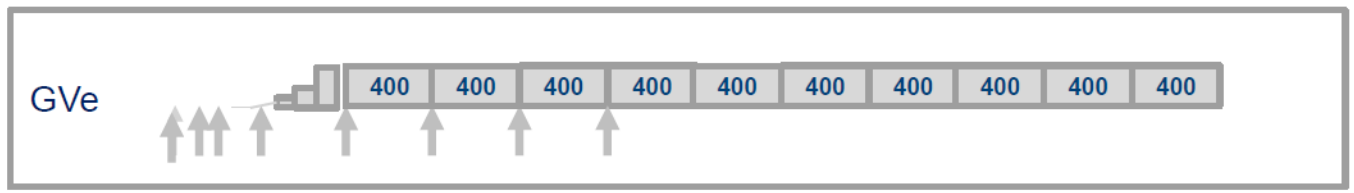
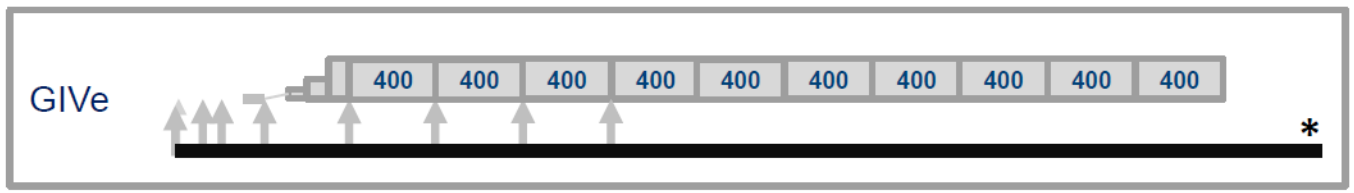
Chemoimmunotherapy (**FCR/BR**) versus **R**ituximab + **Ve**netoclax versus Obinutuzumab (**G**) + **Ve** versus **G** + Ibrutinib + **Ve**



***≤ 65 years: FCR**
> 65 years: BR

GAIA/CLL13 Study : Treatment regimen

Treatment regimen in 28 days (D) interval cycles (C)

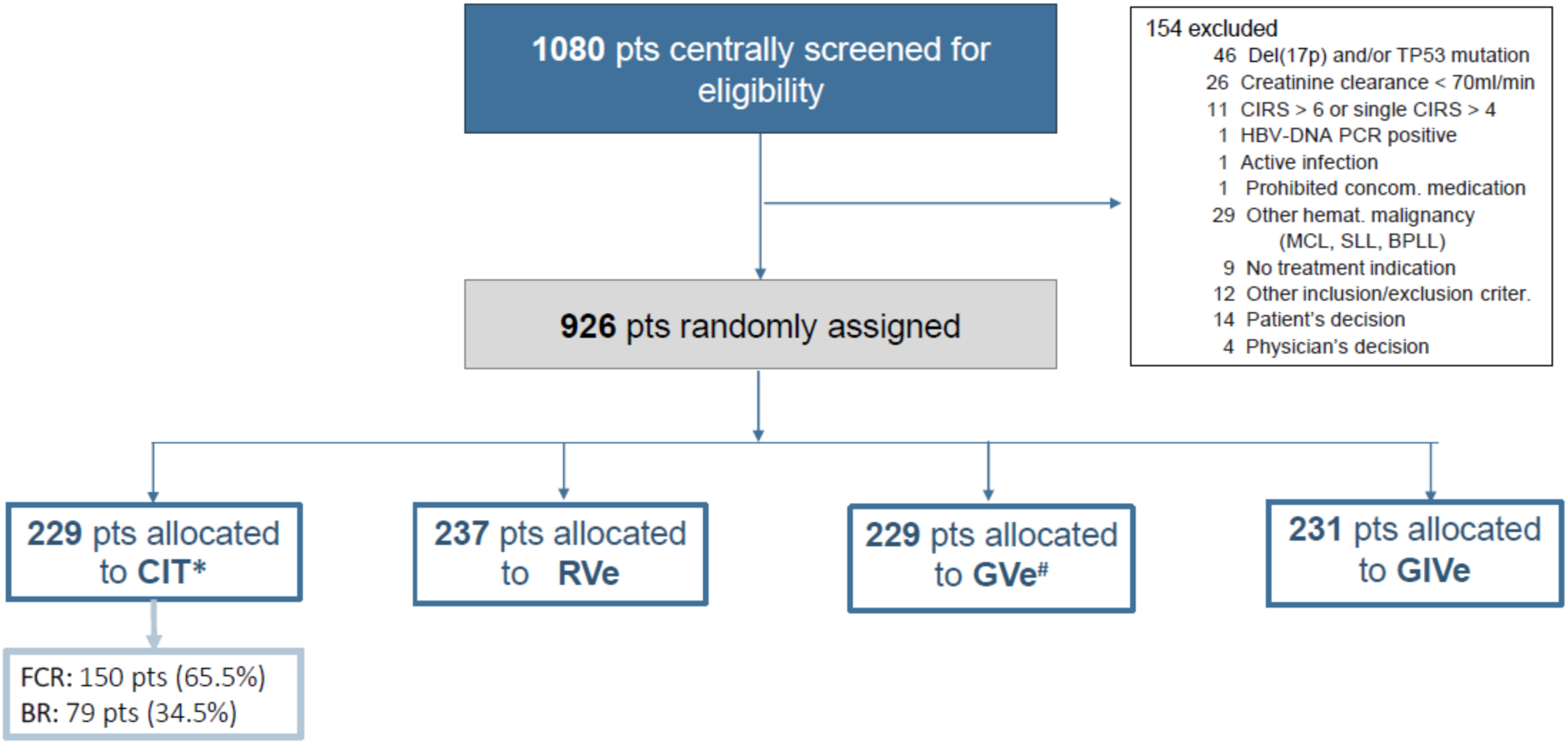
FCR/BR*		Fludarabine 25mg/m² d1-3 iv Cyclophosphamide 250mg/m² d1-3 iv Rituximab 375/500mg/m² d1 iv Bendamustine 90mg/m² d1+2 iv Rituximab 375/500mg/m² d1iv
RVe		Venetoclax ramp up 20 – 400mg po Venetoclax 400mg po C3-C12 Rituximab 375/500mg/m² d1 iv
GVe		Venetoclax ramp up 20 – 400mg po Venetoclax 400mg po C3-C12 Obinutuzumab 1000mg/m² iv d1+8+15 during C1, d1 C2-C6
GIVe		Ibrutinib 420mg po from d1 C1 Venetoclax ramp up 20 – 400mg po Venetoclax 400mg po C3-C12 Obinutuzumab 1000mg/m² iv d1+8+15 during C1, d1 C2-C6

* Continuation of ibrutinib up to cycle 36 allowed, if MRD still detectable

Chemotherapy | CD20-antibody | 400 Venetoclax (V) | Ramp-Up | Ibrutinib (I)

GAIA/CLL13 Study : Flow diagram

Eudract 2015-004936-36; NCT 02950051



* 13 pts did not receive treatment

1 pt died before receiving treatment

Treatment exposure

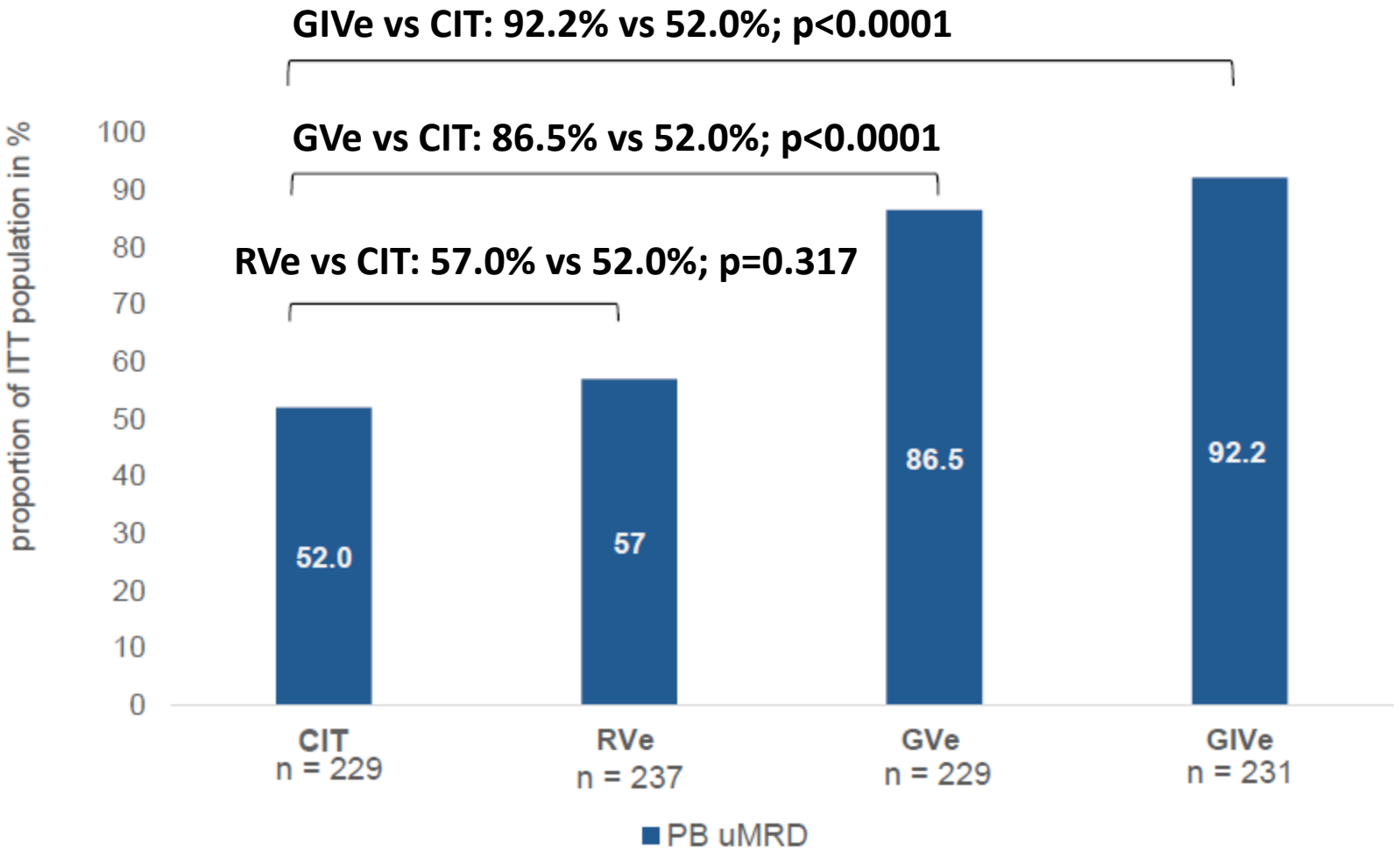
Median FU 27.9 months (range: 0.0 – 49.0)

	CIT	RVe	GVe	GIVe
Planned number of cycles	**6**	**12**	**12**	**12-36**
All patients of safety population	**216**	**237**	**228**	**231**
Pts completed treatment (%)	**176 (81.5%)**	**219 (92.4 %)**	**214 (93.9%)**	**197 (85.3%)***
Reason for discontinuation[+]				
AEs or intercurrent illness	33	14	13	28
Progressive disease	2	4	3	0
Other	9	6	3	6
Reduced dose intensity (%)	**32 (14.8%)**	**44 (19.3%)**	**47 (21.5%)**	**81 (36.5%)**

*In GIVe arm: Pts with at least 12 cycles were considered as completed treatment: (ibrutinib alone beyond cycle 12)
Therapy received: 12 cycles **(35, 19%)**, 13-15 cycles **(135, 72%)**, 16-36 cycles **(18, 10%)**

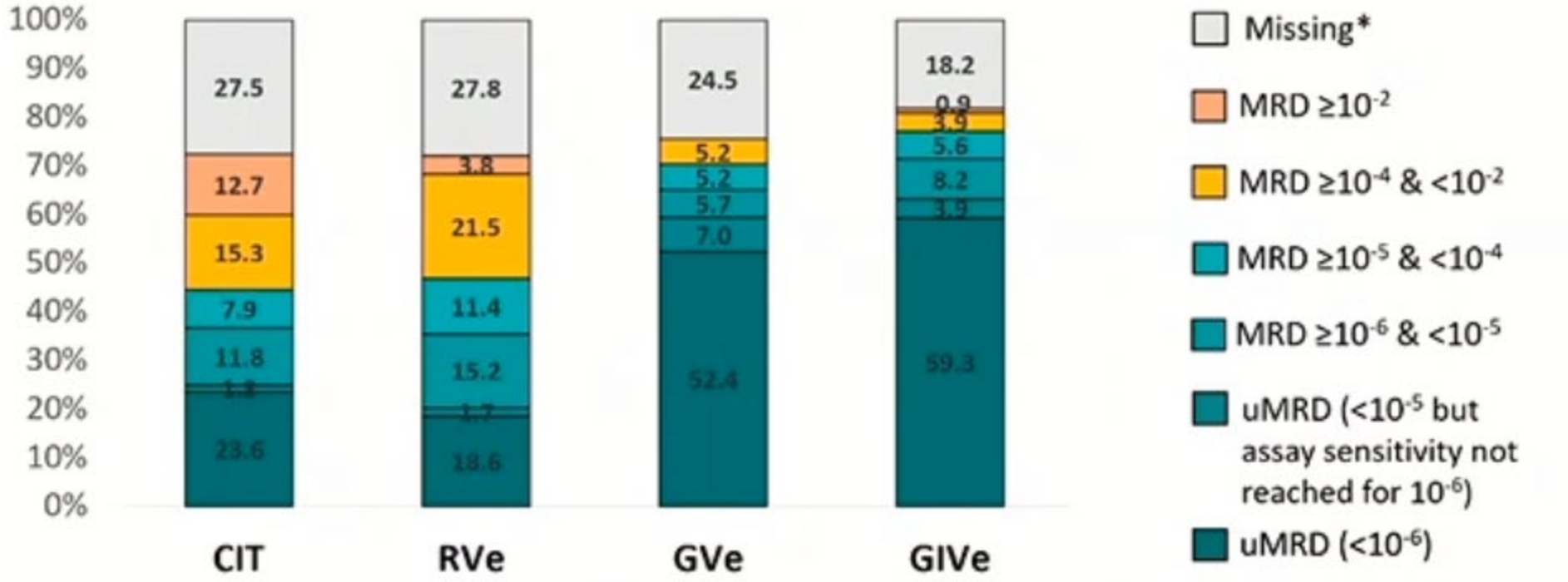
[+]Early treatment discontinuations might be caused by more than one reason

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



	uMRD%	97.5% CI
GIVe	92.2	87.3 – 95.7
GVe	86.5	80.6 – 91.1
RVe	57.0	49.5 – 64.2
SCIT	52.0	44.4 – 59.5

PB MRD rates by NGS at Mo15



Furstenau M. ASH 2021 abstract 72.

Adverse Events ≥ Grade 3

Severe AEs occurring in ≥5% of patients and AEs of interest

	CIT	Rve	Gve	GIVe
All patients	216	237	228	231
Anemia	16 (7.4)	9 (3.8)	11 (4.8)	9 (3.9)
Neutropenia	113 (52.3)	109 (46.0)	127 (55.7)	112 (48.5)
Thrombocytopenia	22 (10.2)	10 (4.2)	7 (3.1)	18 (7.8)
Febrile Neutropenia	24 (11.1)	10 (4.2)	7 (3.1)	18 (7.8)
Infections	43 (19.9)	27 (11.4)	32 (14.0)	51 (22.1)
TLS	9 (4.2)	24 (10.1)	20 (8.8)	15 (6.5)
Bleeding	1 (0.5)	1 (0.4)	1 (0.4)	4 (1.7)
Atrial Fibrillation	1 (0.5)	1 (0.4)	0 (0.0)	6 (2.6)

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Summary

- GVe-based regimens superior to CIT in achieving uMRD in fit patients
  - GVe vs CIT: 86.5% vs 52.0%
  - GIVe vs CIT: 92.2% vs 52.0%
- RVe not superior to CIT in achieving uMRD: 57.0% vs 52.0%
- PFS
- GVe exceeded CLL14
  - GAIA excluded deletion 17p
  - Better treatment adherence with fit patients (CLL14: 70%; GAIA: 93.9%)
- GVe comparable to GIVe
  - uMRD rates not statistically compared; will be for PFS
  - uMRD measured at month 15; GVe 12 months vs GIVe longer if not uMRD