New Therapeutic Options in Frontline CLL: Updates from ASH

Dr. Susan O'Brien, MD
Professor of Medicine
University of California Irvine

Disclosure Information

Susan O'Brien, MD

I have the following financial relationships to disclose:

Sponsor/Company	Affiliation(s)
AbbVie	Consultant
Acerta	Research Support
Alexion	Consultant
Alliance	Research Support
Amgen	Consultant
Aptose Biosciences Inc.	Consultant
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Caribou Biosciences, Inc.	Research Support
Celgene	Consultant
DynaMed	Consultant
Eli Lilly and Company	Consultant
Gilead	Consultant/Research Support
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Janssen Oncology	Consultant
Johnson and Johnson	Consultant
Juno Therapeutics	Consultant
Kite	Research Support
Loxo Oncology, Inc.	Research Support
MEI Pharma, Inc.	Consultant
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Nurix Therapeutics, Inc.	Research Support
Pfizer	Consultant/Research Support
Pharmacyclics	Consultant/Research Support
Regeneron	Research Support
TG Therapeutics	Consultant/Research Support
Vaniam Group LLC	Consultant
Verastem	Consultant
Vida Ventures	Consultant

Updated January 2022

Where are we heading in 1L CLL?

Ongoing phase 3 trials:

- CLL13/GAIA: FCR/BR vs. VR, vs. VO, vs. IVO (n=920)
- UK NCRI FLAIR: FCR vs. I vs. IV (vs. IR) (n=1,522)
- Alliance A041702: IO vs. IVO (older pts, n=454)
- ECOG EA9161: IO vs. IVO (younger pts, n=720)
- ACE-CL-311: FCR/BR vs AV vs AVO (n=780)
- CLL GLOW: IV vs. Chl/O (n=200)
- CLL17: I vs. IV vs. VO (n=882)

Combined Ibrutinib and Venetoclax For First-line treatment of Patients with Chronic Lymphocytic Leukemia (CLL): Focus on Long-term MRD Results

Nitin Jain, Michael Keating, Philip Thompson, Alessandra Ferrajoli, Jan Burger, Gautam Borthakur, Koichi Takahashi, Zeev Estrov, Koji Sasaki, Tapan Kadia, Marina Konopleva, Yesid Alvarado, Musa Yilmaz, Courtney DiNardo, Prithviraj Bose, Maro Ohanian, Naveen Pemmaraju, Elias Jabbour, Rashmi Kanagal-Shamanna, Keyur Patel, Wei Wang, Jeffrey Jorgensen, Sa Wang, Naveen Garg, Xuemei Wang, Chongjuan Wei, Nichole Cruz, Ana Ayala, William Plunkett, Hagop Kantarjian, Varsha Gandhi, William Wierda

Department of Leukemia
The University of Texas MD Anderson Cancer Center
ASH 2021, Abstract 3720

Treatment Schema

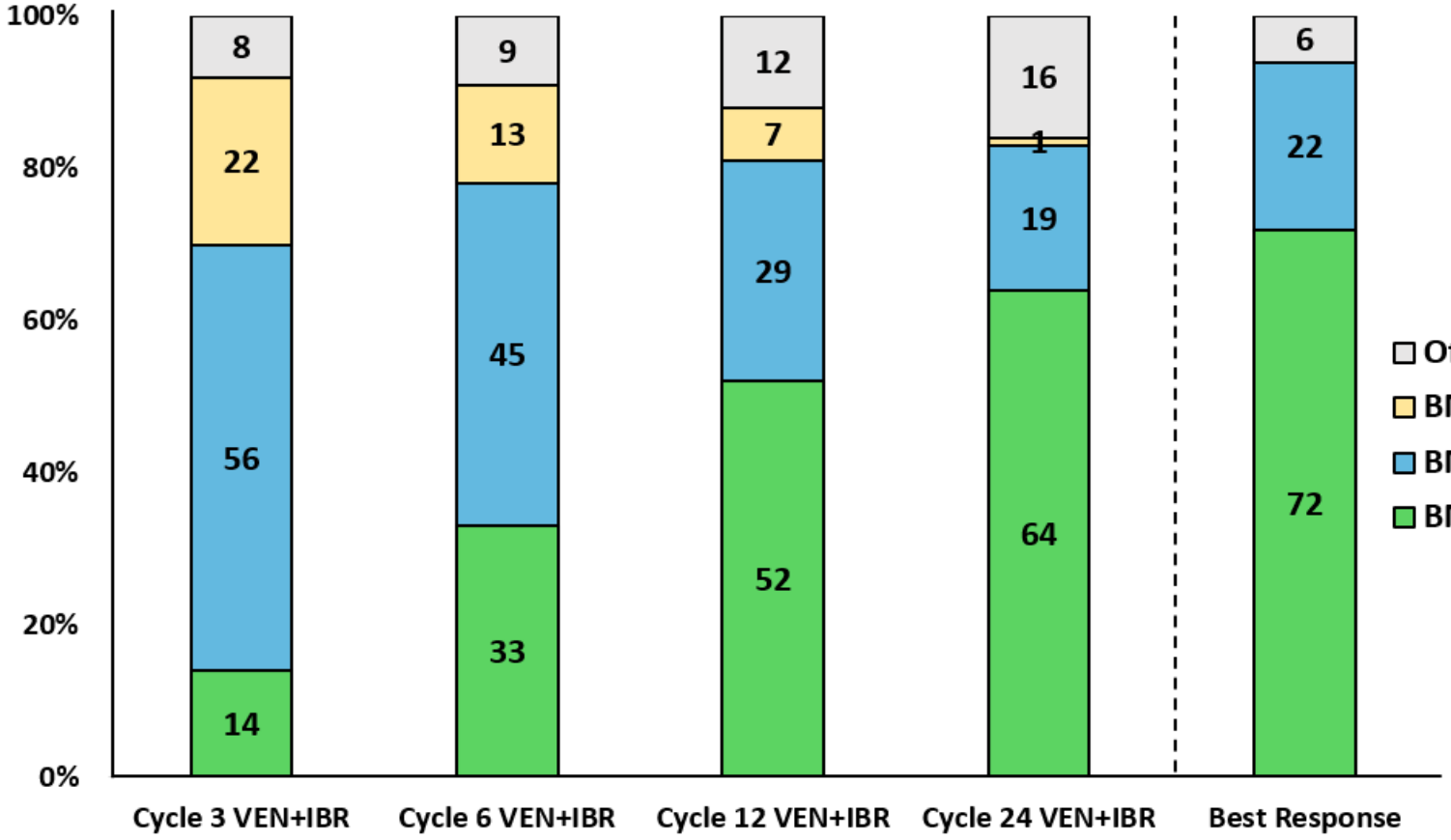
	C1	C2	C3	C4-->27
Ibrutinib	420mg daily	420mg daily	420mg daily	420mg daily
Venetoclax	-	-	-	20mg daily 1 week; 50mg daily 1 week; 100mg daily 1 week; 200mg daily 1 week; 400mg daily continuous

Duration of therapy: 24 cycles of combination treatment

- **If BM MRD+ at 24 cycles, ibrutinib alone until PD**

Protocol Amendment: up to 36 combination cycles allowed; as before, if still MRD + continue ibrutinib

Marrow MRD Response at Serial Time-Points
Intent-to-Treat (N=120)

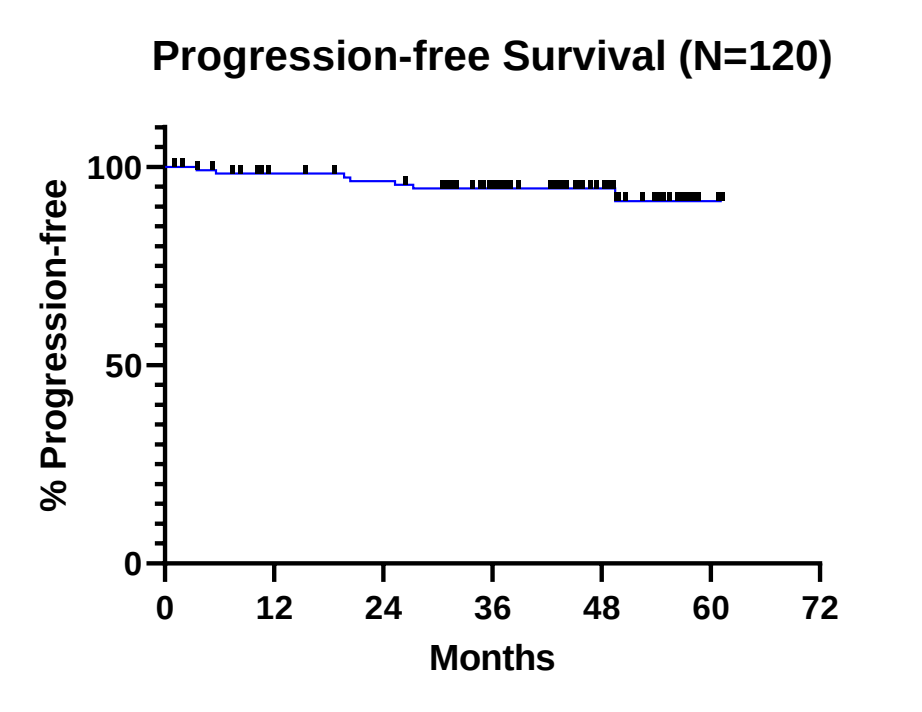


MRD by flow-cytometry in marrow (10^{-4} sensitivity)

U-MRD4: <0.01%
Low+ MRD: 0.01% to <1%
High+ MRD: ≥1%

Jain et al ASH 2021

PFS for all Patients (N=120)



7 events on PFS curve include 2 Richter transformation (RT), 2 CLL PD and 3 deaths.

Jain et al ASH 2021

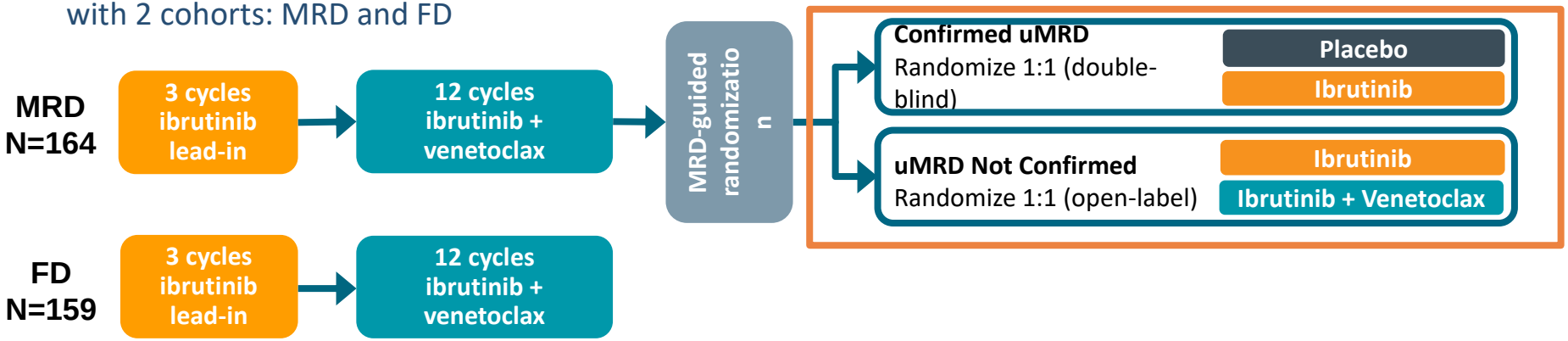
First-Line Treatment With Ibrutinib Plus Venetoclax for Chronic Lymphocytic Leukemia: 2-Year Post-randomization Disease-Free Survival Results From the Minimal Residual Disease Cohort of the Phase 2 CAPTIVATE Study

Paolo Ghia, MD, PhD[1]; John N. Allan, MD, PhD[2]; Tanya Siddiqi, MD[3]; Thomas J. Kipps, MD, PhD[4]; Bryone J. Kuss, MBBS, PhD, FRACP, FRCPA[5]; Stephen Opat, FRACP, FRCPA, MBBS[6]; Ian W. Flinn, MD, PhD[7]; Xavier C. Badoux, MBBS, FRACP, FRCPA[8]; Alessandra Tedeschi, MD[9]; Eva Gonzalez Barca, MD, PhD[10]; John M. Pagel, MD, PhD[11]; Ryan Jacobs, MD[12]; Jacqueline C. Barrientos, MD, MS[13]; Edith Szafer-Glusman, PhD[14]; Cathy Zhou, MS[14]; Joi Ninomoto, PharmD[14]; James P. Dean, MD, PhD[14]; Constantine S. Tam, MBBS, MD[15]; William G. Wierda, MD, PhD[16]

[1]Division of Experimental Oncology, Università Vita-Salute San Raffaele and IRCCS Ospedale San Raffaele, Milan, Italy; [2]Weill Cornell Medicine, New York, NY, USA; [3]City of Hope National Medical Center, Duarte, CA, USA; [4]UCSD Moores Cancer Center, San Diego, CA, USA; [5]Flinders University and Medical Center, Bedford Park, SA, Australia; [6]Monash University, Clayton, VIC, Australia; [7]Sarah Cannon Research Institute/Tennessee Oncology, Nashville, TN, USA; [8]Ministry of Health, Kogarah, NSW, Australia; [9]ASST Grande Ospedale Metropolitano Niguarda, Milan, Italy; [10]Institut Català d'Oncologia Hospitalet, Universitat de Barcelona, Barcelona, Spain; [11]Swedish Cancer Institute Hematologic Malignancies Program, Seattle, WA, USA; [12]Levine Cancer Institute, Charlotte, NC, USA; [13]Division of Medical Oncology and Hematology, Northwell Health Cancer Institute, Donald & Barbara Zucker School of Medicine at Hofstra/Northwell, Lake Success, NY, USA; [14]Pharmacyclics LLC, an AbbVie Company, South San Francisco, CA, USA; [15]Peter MacCallum Cancer Center & St. Vincent's Hospital and the University of Melbourne, Melbourne, VIC, Australia; [16]Department of Leukemia, University of Texas MD Anderson Cancer Center, Houston, TX, USA

Phase 2 CAPTIVATE Study

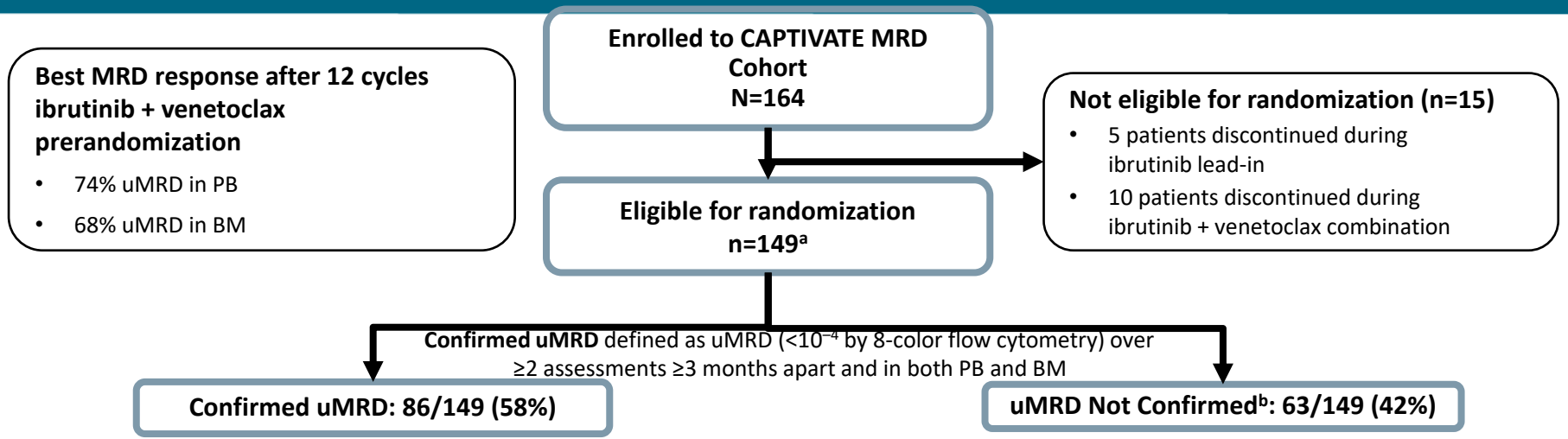
- CAPTIVATE (PCYC-1142) is an international, multicenter phase 2 study evaluating first-line treatment with 3 cycles of ibrutinib followed by 12 cycles of combined ibrutinib + venetoclax with 2 cohorts: MRD and FD



- 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)

MRD, minimal residual disease; FD, fixed-duration.
1. Wierda WG et al. ASH 2020. Abstract #123. 2. Ghia P et al. ASCO 2021. Abstract #7501.

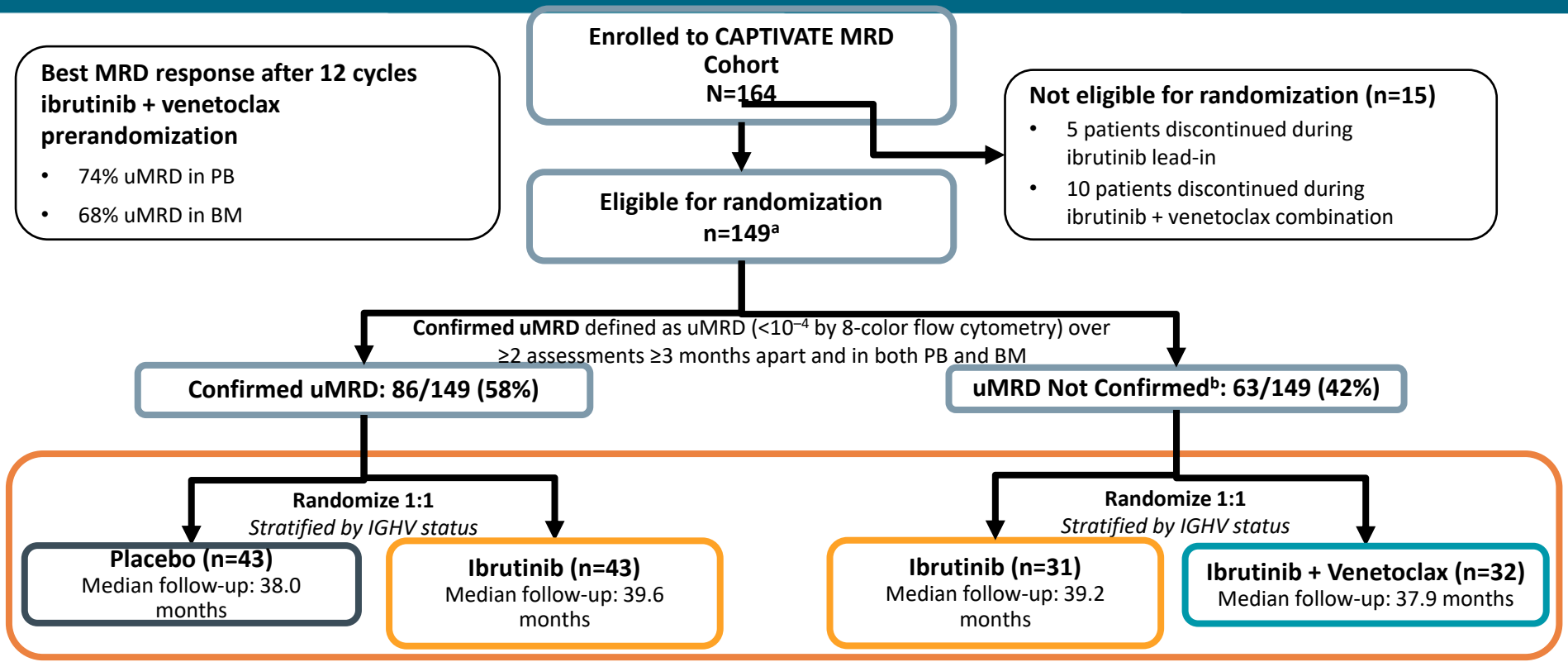
MRD Cohort: Patient Disposition and Randomization



BM, bone marrow; PB, peripheral blood.

[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.

MRD Cohort: Patient Disposition and Randomization (cont.)



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ASH 2021, CAPTIVATE-MRD; Ghia et al.

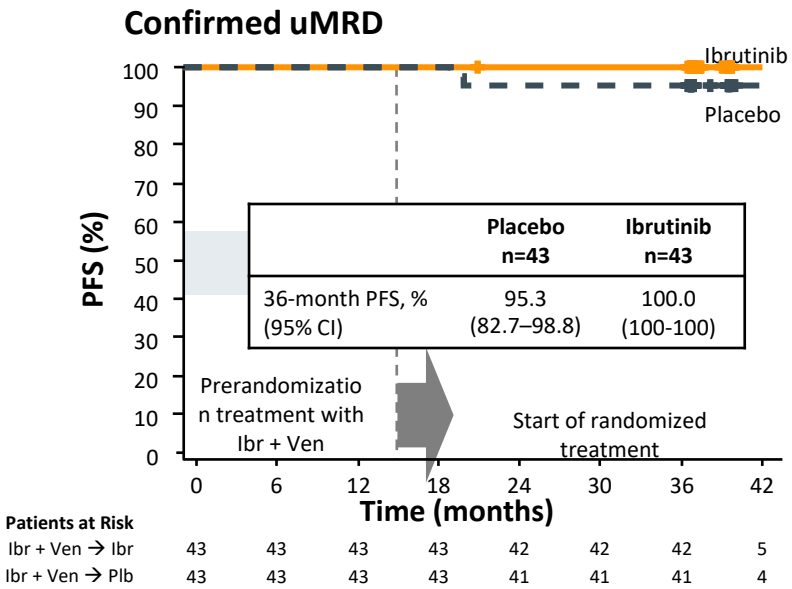
Most Patients Had High-Risk Disease Features

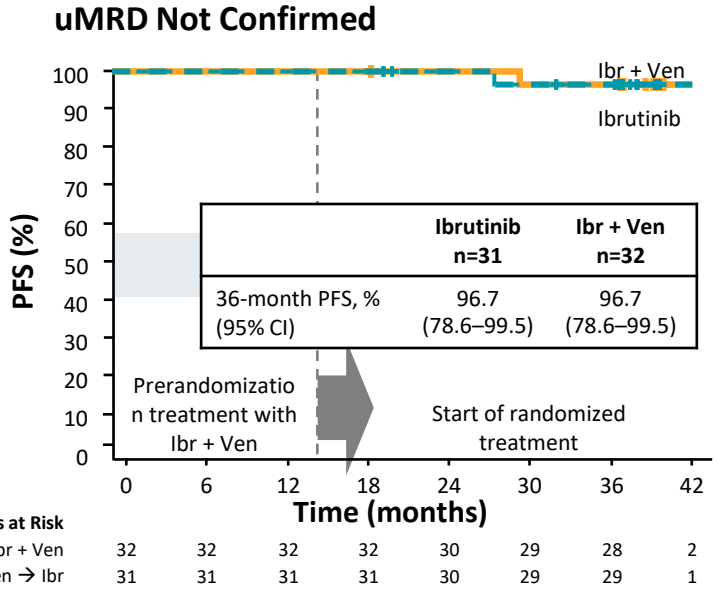
Characteristic	All Treated Population N=164	Confirmed uMRD (n=86)		uMRD Not Confirmed (n=63)	
		Placebo n=43	Ibrutinib n=43	Ibrutinib n=31	Ibrutinib + Venetoclax n=32
Median age (range), year	58 (28–69)	61 (43–69)	56 (34–69)	58 (28–69)	56 (37–69)
Rai stage III/IV disease, n (%)	53 (32)	15 (35)	8 (19)	14 (45)	11 (34)
High-risk features, n (%)					
del(17p)/*TP53* mutation	32 (20)	2 (5)	13 (30)	5 (16)	8 (25)
del(11q)[a]	28 (17)	8 (19)	10 (23)	3 (10)	2 (6)
Complex karyotype[b]	31 (19)	4 (9)	13 (30)	5 (16)	4 (13)
Unmutated IGHV	99 (60)	30 (70)	30 (70)	14 (45)	15 (47)
Any cytopenia, n (%)	59 (36)	19 (44)	6 (14)	13 (42)	14 (44)
ANC ≤1.5 × 10^9/L	14 (9)	5 (12)	0	2 (6)	4 (13)
Hemoglobin ≤11 g/dL	35 (21)	14 (33)	2 (5)	9 (29)	7 (22)
Platelets ≤100 × 10^9/L	30 (18)	4 (9)	4 (9)	9 (29)	9 (28)
Lymph node diameter, n (%)					
≥5 cm	53 (32)	18 (42)	10 (23)	7 (23)	11 (34)
Median ALC × 10^9/L (range)	56 (1–419)	53 (1–235)	56 (2–256)	85 (1–342)	87 (3–419)
ALC ≥25 × 10^9/L, n (%)	125 (76)	32 (74)	34 (79)	25 (81)	24 (75)

ALC, absolute lymphocyte count; ANC, absolute neutrophil count.
[a]Without del(17p) per Dohner hierarchy. [b]Defined as ≥3 abnormalities by CpG-stimulated cytogenetics.

ASH 2021, CAPTIVATE-MRD; Ghia et al.

3-Year PFS Rates Were ≥95% Across All Randomized Arms





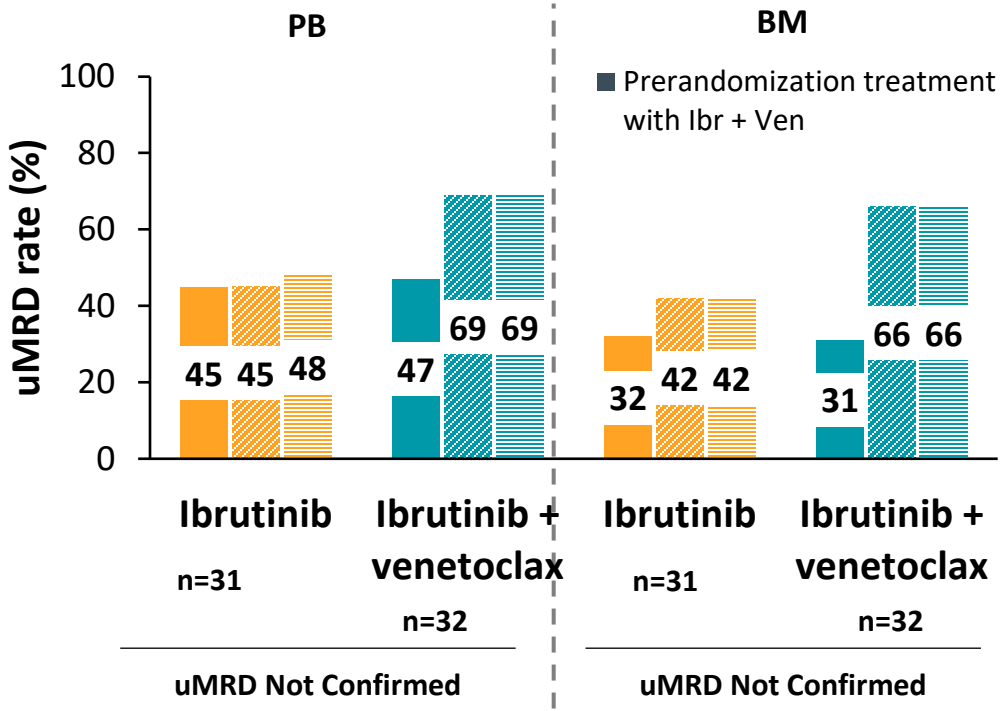
Median follow-up = 38 months

- With an additional year of follow-up since the primary analysis, only 1 new PFS event occurred on study; a patient in the uMRD Not Confirmed ibrutinib arm who had PD after 42 months
- 36-month OS was 99% overall (97%–100% across randomized treatment arms)

PFS, progression-free survival; Plb, placebo. Tick marks indicate patients with censored data.

ASH 2021, CAPTIVATE-MRD; Ghia et al.

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



- As with CR rates, greatest uMRD rate improvements occurred during the first year of randomized treatment
  - Greater improvements with ibrutinib + venetoclax than with ibrutinib
- Improvements in uMRD rates were similar between patients achieving CR or PR

PR, partial response.

[a]Confirmed uMRD defined as having uMRD ($<10^{-4}$ by 8-color flow cytometry) serially over ≥2 assessments ≥3 months apart and in both PB and BM; the best uMRD rates in the Confirmed uMRD population were 100% in both PB and BM.

ASH 2021, CAPTIVATE-MRD; Ghia et al.

Retreatment Data From the MRD Placebo Arm and FD Cohorts

- As of August 4, 2021, 12 patients who progressed after fixed-duration treatment[a] with ibrutinib + venetoclax had been 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

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.

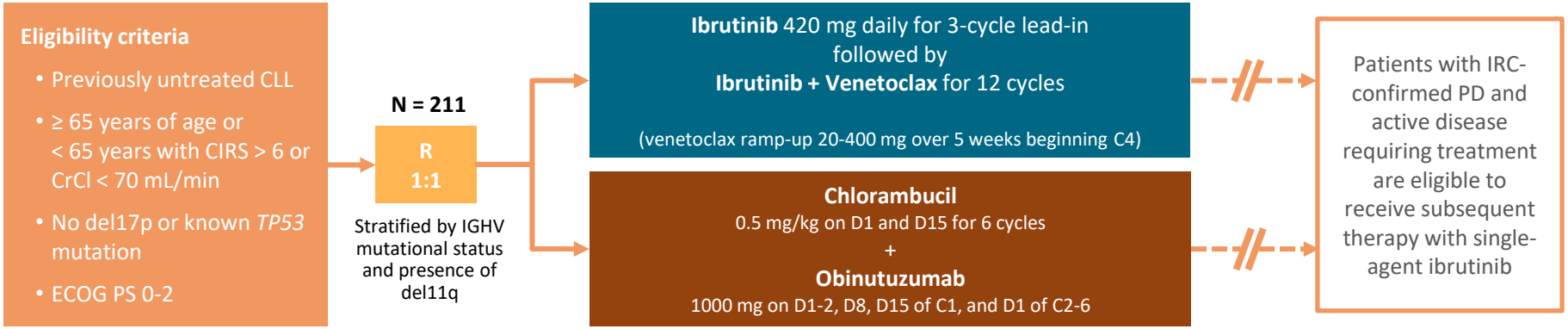
ASH 2021, CAPTIVATE-MRD; Ghia et al.

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]

[1]St James's Hospital, Leeds, UK; [2]Hospital de la Santa Creu i Sant Pau, Autonomous University of Barcelona, Spain; [3]Tom Baker Cancer Centre, Calgary, Canada; [4]Addenbrookes Hospital, Cambridge, UK; [5]Sheba Medical Center, Ramat Gan, Israel; [6]UZ Leuven Gasthuisberg, Leuven, Belgium; [7]Albert Schweitzer Hospital, Dordrecht, Netherlands; [8]Karolinska University Hospital, Stockholm, Sweden; [9]Medical University of Lodz, Copernicus Memorial Hospital, Lodz, Poland; [10]University Hospital Hradec Kralove, Hradec Kralove, Czech Republic; [11]Norton Cancer Institute, Louisville, KY, USA; [12]Russian Scientific and Research Institute of Hematology and Transfusiology, St. Petersburg, Russia; [13]S.P. Botkin Moscow City Clinical Hospital, Moscow, Russia; [14]Gazi Universitesi Tip Fakultesi, Ankara, Turkey; [15]Institut Universitaire du Cancer Toulouse Oncopole, Toulouse, France; [16]Janssen Research & Development, Raritan, NJ, USA; [17]Janssen Research & Development, Spring House, PA, USA; [18]Janssen Research & Development, Düsseldorf, Germany; [19]Janssen Research & Development, Beerse, Belgium; [20]Rigshospitalet Copenhagen University Hospital, Copenhagen, Denmark; [21]Amsterdam University Medical Centers, Cancer Center Amsterdam, University of Amsterdam, Netherlands

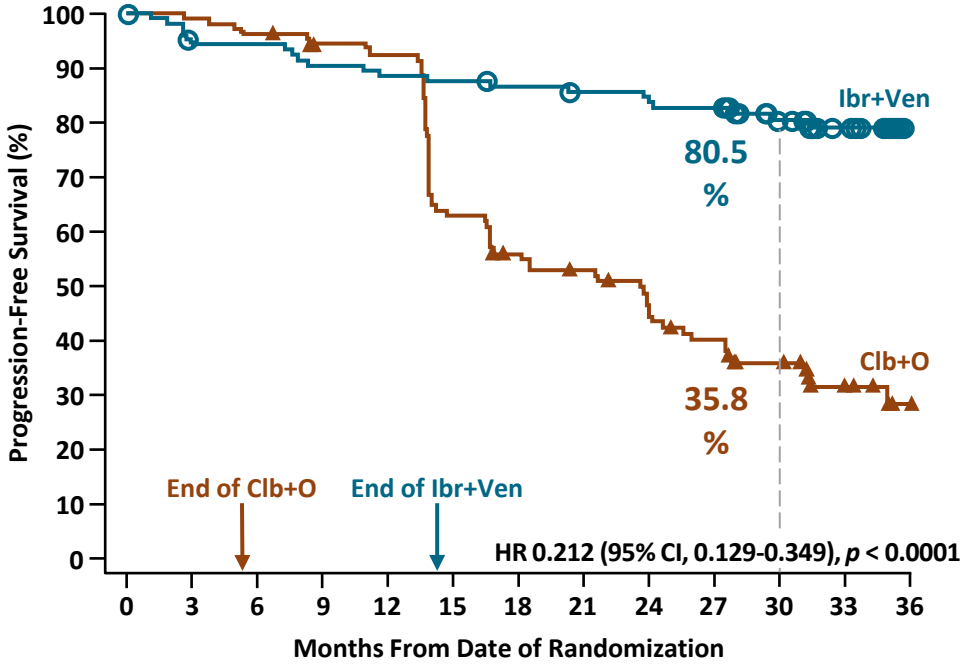
Phase 3 GLOW Study Design (NCT03462719)



- **Study primary endpoint:** PFS as assessed by IRC
- **Current MRD analysis:**
  - MRD evaluated via NGS and reported with cutoffs of < 10^{-4} and < 10^{-5} (not all samples had sufficient cell yield to be analyzed at < 10^{-6}). NGS analysis not yet available beyond EOT+12 time point
  - PB/BM concordance calculated for patients with uMRD in PB at EOT+3 who had a paired BM sample
  - PFS results updated with 34.1 months of follow-up

BM, bone marrow; C, cycle (28 days); CIRS, Cumulative Illness Rating Scale score; CrCl, creatinine clearance; D, day; ECOG PS, Eastern Cooperative Oncology Group performance status; EOT, end of treatment; EOT+3, 3 months after EOT; EOT+12, 12 months after EOT; IRC, independent review committee; NGS, next-generation sequencing; PB, peripheral blood; PD, progressive disease; R, randomization; uMRD, undetectable minimal residual disease.

Superior Progression-Free Survival With Ibr+Ven vs Clb+O Was Maintained With Median 34.1 Months of Follow-up



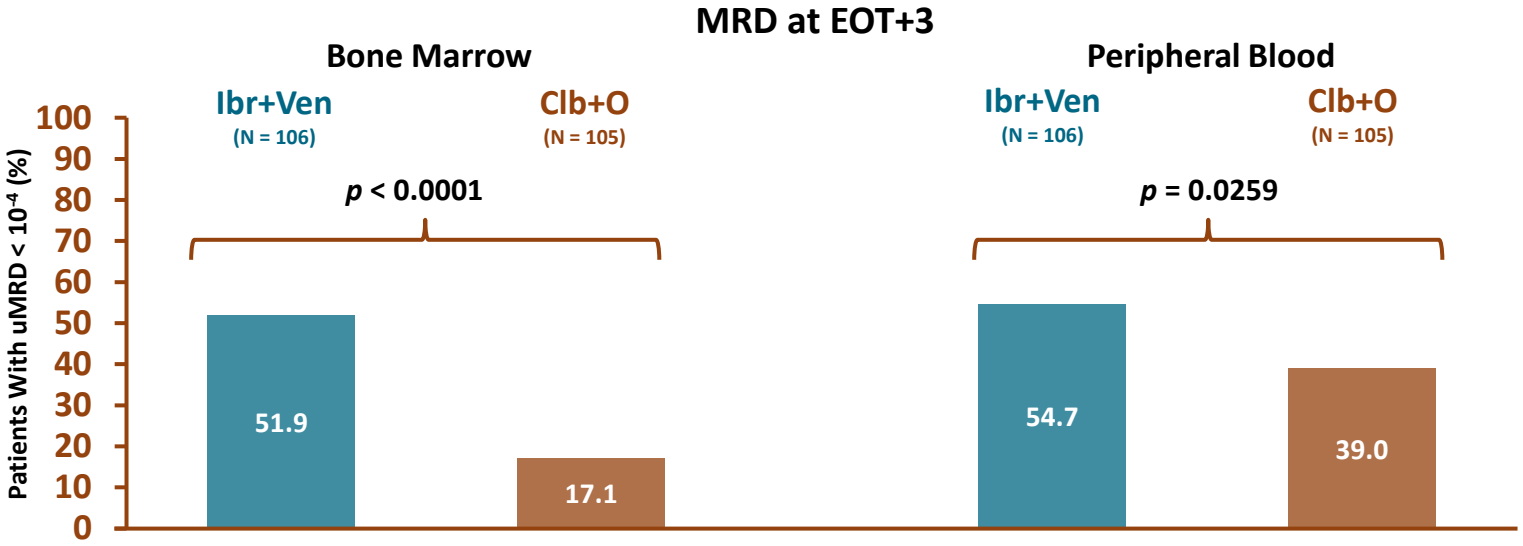
Patients at risk

Ibr+Ven	106	98	98	94	92	91	89	87	86	84	71	42	1
Clb+O	105	104	101	96	94	64	55	51	43	37	30	13	3

CI, confidence interval; HR, hazard ratio; OS, overall survival.

- IRC-assessed PFS for Ibr+Ven was superior to Clb+O at primary analysis (median 27.7 months of follow-up)
  - HR 0.216 (95% CI, 0.131-0.357; $p < 0.0001$)
- **With median follow-up of 34.1 months:**
  - IRC-assessed PFS remained superior for Ibr+Ven (HR 0.212, 95% CI, 0.129-0.349; $p < 0.0001$)
  - 30-month PFS: 80.5% for Ibr+Ven vs 35.8% for Clb+O
  - Overall survival HR 0.76 (95% CI, 0.35-1.64), with 11 deaths for Ibr+Ven vs 16 for Clb+O

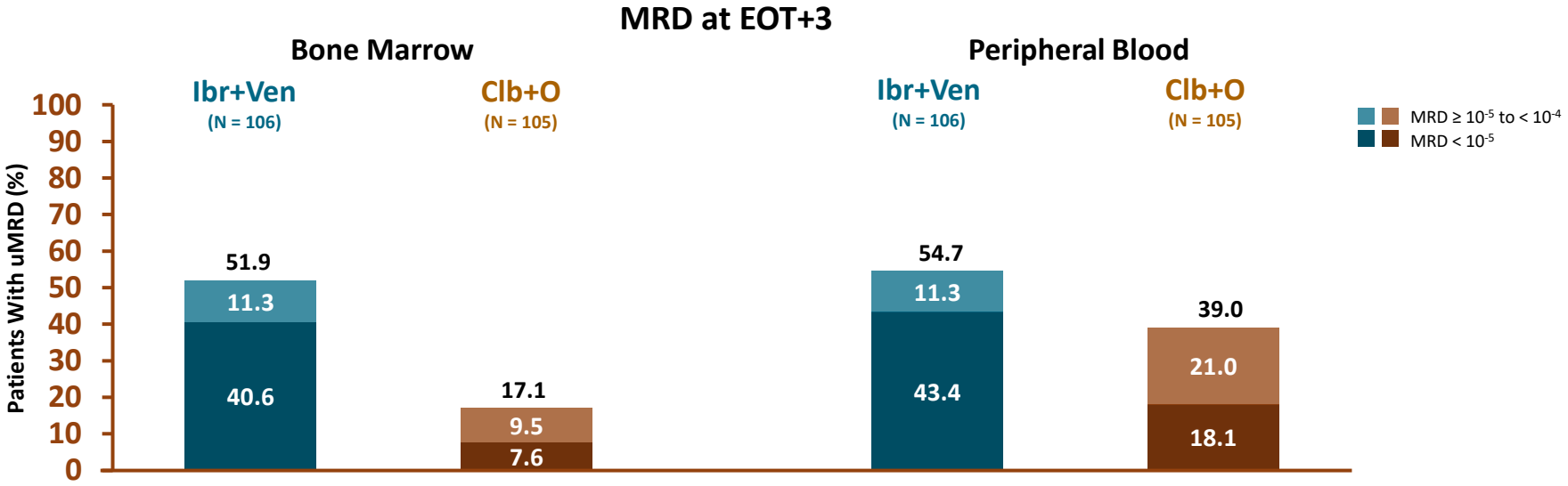
uMRD Rate < 10^{-4} Was Significantly Higher in Both Compartments With Ibr+Ven



- 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

MRD results by next-generation sequencing at EOT+3.
BM, bone marrow; EOT, end of treatment; PB, peripheral blood.

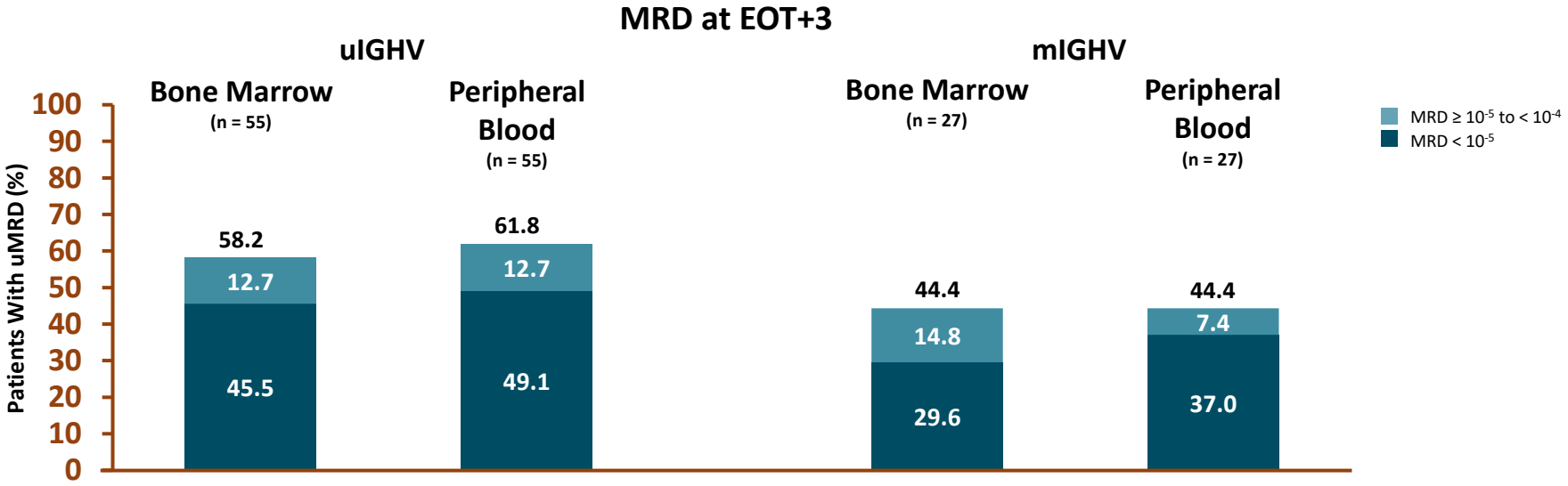
uMRD Rate < 10^{-5} Was Higher With Ibr+Ven vs Clb+O in Both Compartments



- In the Ibr+Ven arm, but not the Clb+O arm, most patients with uMRD < 10^{-4} had deep responses of uMRD < 10^{-5}
- uMRD concordance at < 10^{-5} in PB/BM: **90.9%** for Ibr+Ven vs **36.8%** for Clb+O

MRD results by next-generation sequencing at EOT+3. Note: Numbers may not add up due to rounding.
BM, bone marrow; EOT, end of treatment; PB, peripheral blood.

Ibr+Ven: uMRD Rates Were High in BM and PB for Patients With uIGHV CLL



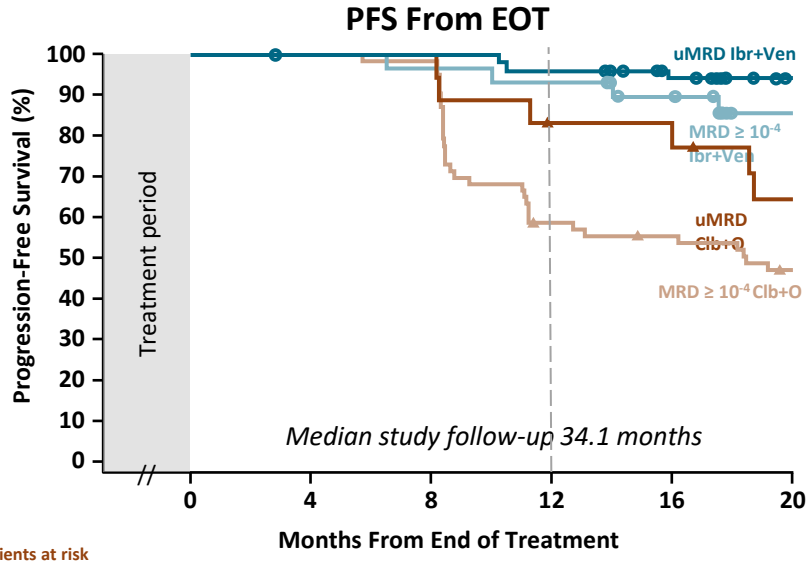
- With Ibr+Ven, depth of MRD response was similar in BM and PB for patients with uIGHV CLL
- Among patients with mutated *TP53*, 5 of 7 achieved uMRD < 10^{-5} in both BM and PB with Ibr+Ven

Patients with IGHV status not available (n = 24): 45.8% (BM) and 50.0% (PB) had uMRD < 10^{-4}.

MRD results by next-generation sequencing at EOT+3.

BM, bone marrow; EOT, end of treatment; mIGHV, mutated IGHV; PB, peripheral blood; uIGHV, unmutated IGHV.

With Ibr+Ven, PFS Rate Was Sustained in the First Year Post-treatment Irrespective of MRD Status in BM at EOT+3



Patients at risk						
uMRD Ibr+Ven	55	54	54	52	46	25
uMRD Clb+O	18	18	18	14	13	10
MRD ≥ 10^{-4} Ibr+Ven	30	30	29	28	24	14
MRD ≥ 10^{-4} Clb+O	63	63	62	36	33	27

- PFS rate during the first year post-treatment was sustained > 90% with Ibr+Ven, independent of BM MRD status

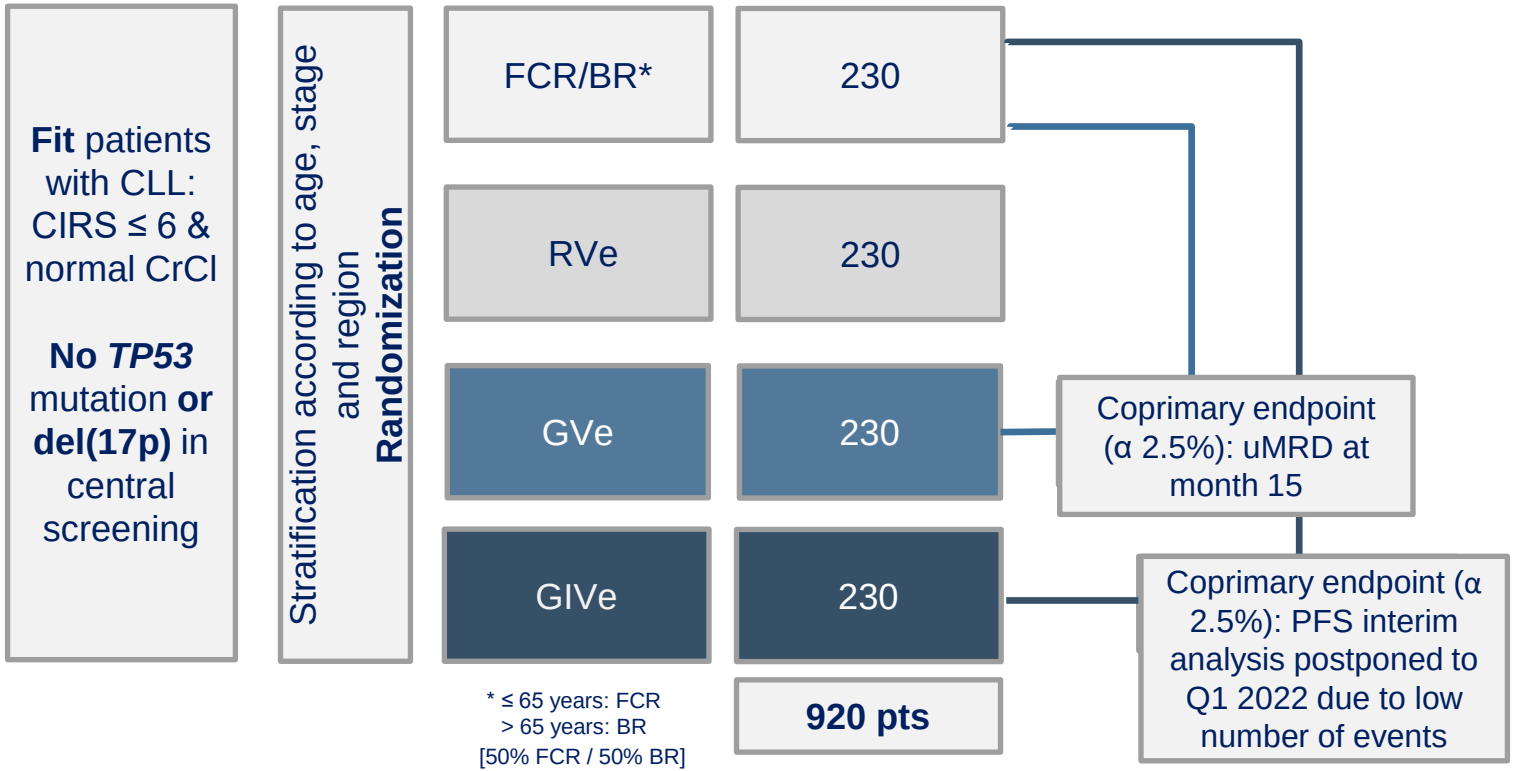
MRD assessed by next-generation sequencing.
BM, bone marrow; EOT, end of treatment.

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

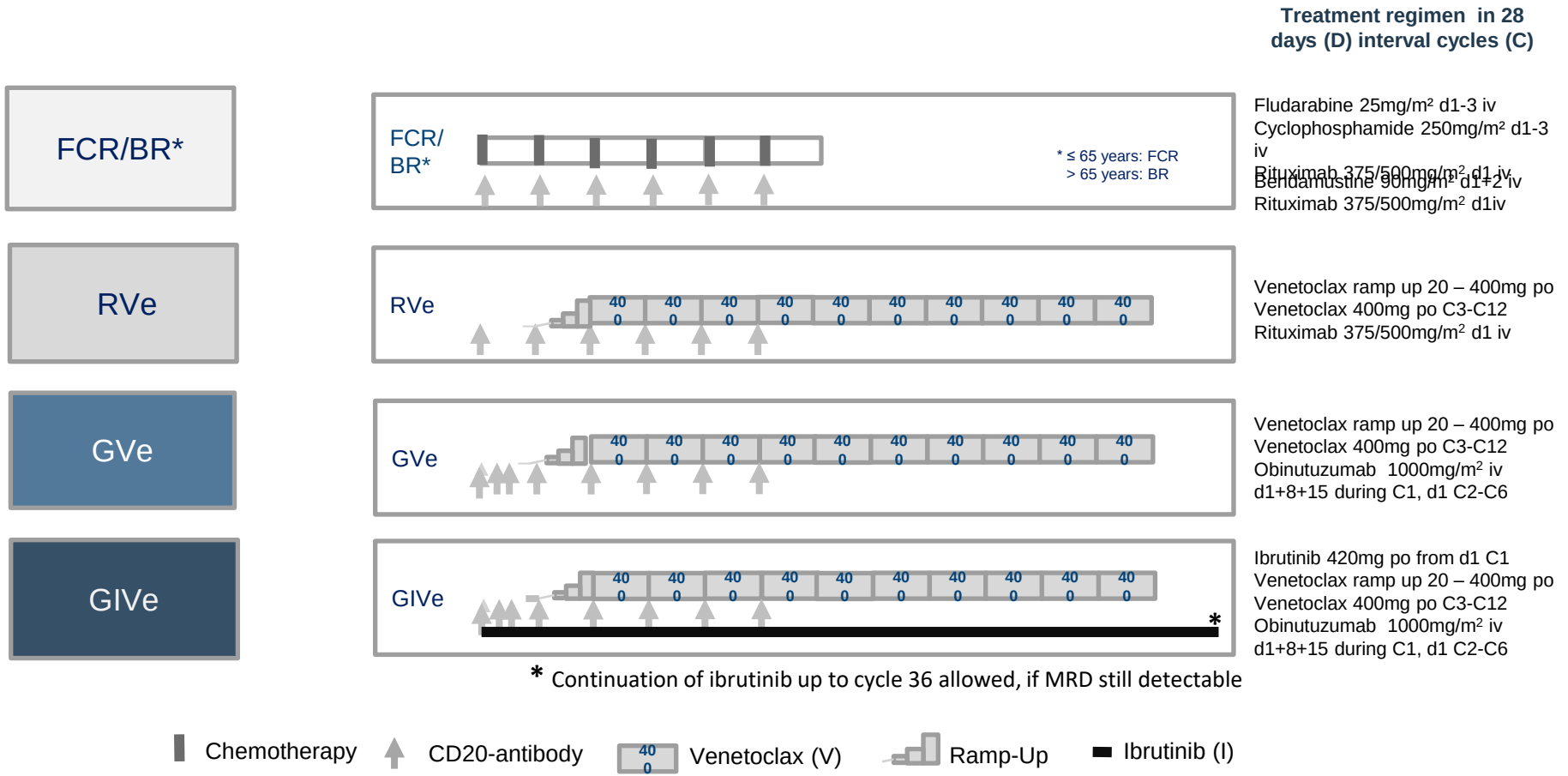
Barbara Eichhorst, Carsten U Niemann, Arnon P Kater, Moritz Fürstenau, Julia von Tresckow, Can Zhang, Sandra Robrecht, Michael Gregor, Gunnar Juliusson, Patrick Thornton, Philipp B. Staber, Tamar Tadmor, Vesa Lindström, Caspar da Cunha-Bang, Christoph Schneider, Christian Poulsen, Thomas Illmer, Björn Schöttker, Ann Janssens, Ilse 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

GAIA/CLL13 Study : Design

Chemoimmunotherapy (**FCR/BR**) versus **R**ituximab + **Ve**netoclax versus Obinutuzumab (**G**) + **Ve** versus **G** + **I**brutinib + **Ve**
Recruitment in 10 countries (DE, AU, CH, NL, BE, DK, SE, FL, IR, IL)

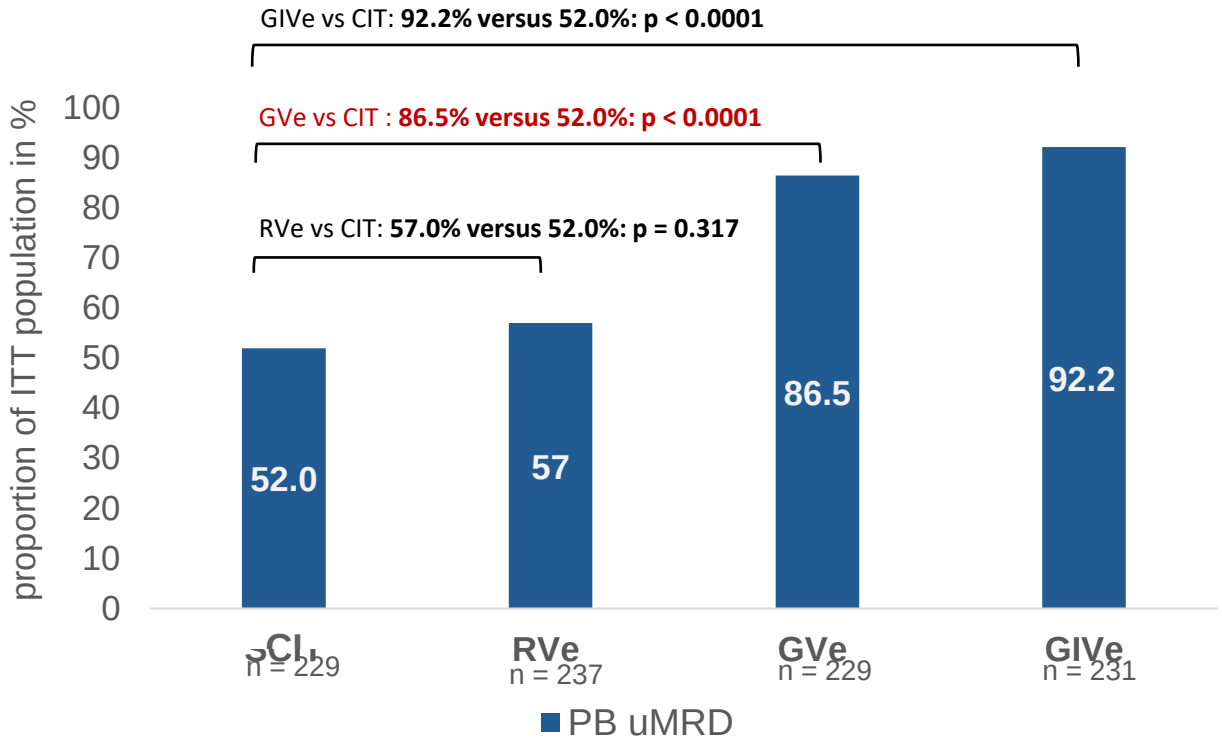


GAIA/CLL13 Study : Treatment regimen



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

ITT analysis: 63 pts (34 CIT, 15 RVe, 10 GVe, 4 GIVe) with missing samples (6.8%) were counted as MRD positive



	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

Adverse Events ≥ CTC Grade 3 Overview

Severe AEs occurring in ≥5% of pts and AEs of interest independent from incidence

	CIT	RVe	GVe	GIVe
All patients [SP]	**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)	42 (18.4)	37 (16.0)
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)**
Tumor lysis syndrome*	**9 (4.2)**	**24 (10.1)**	**20 (8.8)**	**15 (6.5)**
Bleeding events	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)

* Including clinical and laboratory TLS according to Cairo-Bishop

Conclusions

Small molecule combinations produce high MRD undetectability rates and durable remissions

- Will antibody add anything further?
- Will results be better than sequencing the single agents?
- Clearly the wave of the future