Updates in CLL: DDHO

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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
Astellas	Consultant
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Regeneron	Research Support
TG Therapeutics	Consultant/Research Support
Vaniam Group LLC	Consultant
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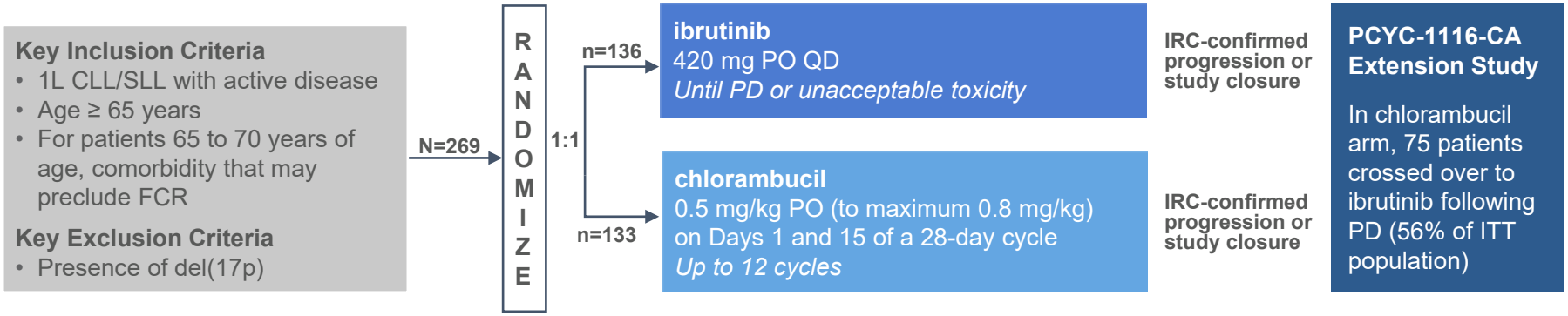
Updated January 2022

RESONATE-2: Phase 3 Trial in 1L CLL/SLL

Phase 3 randomized, multicenter, open-label trial of ibrutinib vs chlorambucil in patients ≥65 years of age with 1L CLL/SLL (NCT01722487)



Primary Endpoint[1]
- PFS by IRC according to 2008 iwCLL criteria

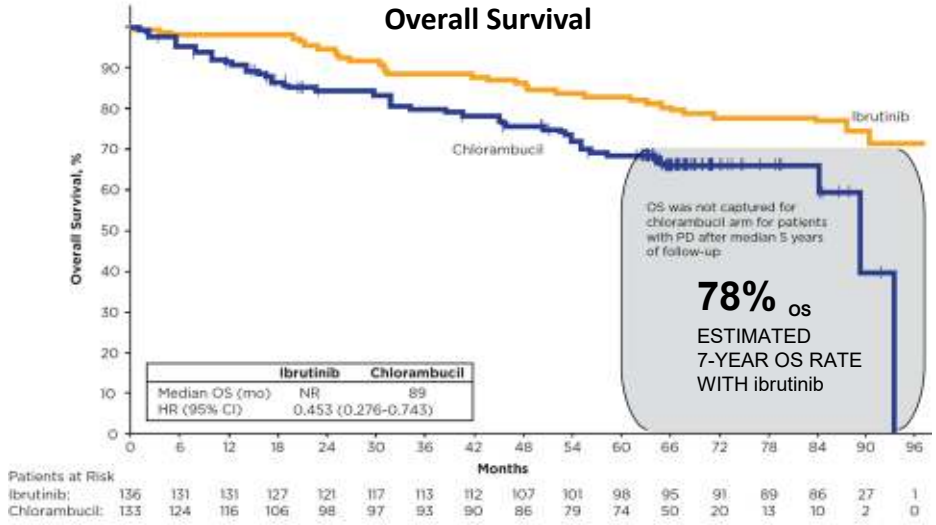
Secondary Endpoints[1]
- OS
- ORR
- Safety
- Proportion of sustained:
  - Hgb improvement (with and without baseline anemia)
  - Platelet improvement (with and without baseline thrombocytopenia)

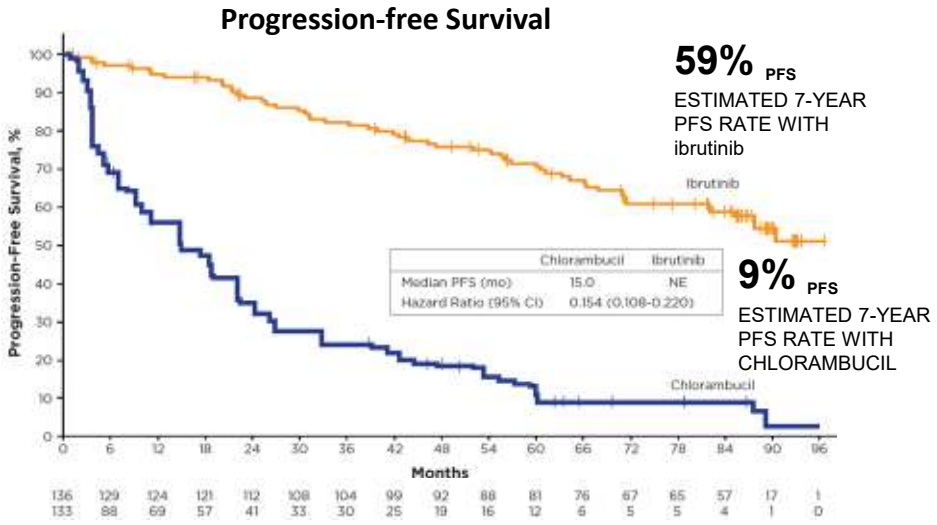
References:

1. Burger JA, Barr PM, Robak T, et al. Long-term efficacy and safety of first-line ibrutinib treatment for patients with CLL/SLL: 5 years of follow-up from the phase 3 RESONATE-2 study. *Leukemia*. 2020;34(3):787-798.

2. Clinicaltrials.gov. Open-label phase 3 btk inhibitor ibrutinib vs chlorambucil patients 65 years or older with treatment-naive cll or sll. https://clinicaltrials.gov/ct2/show/NCT01722487. Accessed May 2, 2022

Up to 8 Years of Follow-up in RESONATE-2: OS and PFS





- **78%** taking ibrutinib were estimated to be alive at 7 years
- **59%** taking ibrutinib were estimated to be progression-free and alive at 7 years vs 9% of patients taking chlorambucil

Reference:
1. Barr PM, Owen C, Robak T, et al. Up to 8 years follow-up from RESONATE-2: first-line ibrutinib treatment for patients with chronic lymphocytic leukemia. *Blood Adv*. 2022 Apr 4:bloodadvances.2021006434.doi:10.1182/bloodadvances.2021006434

Acalabrutinib ± Obinutuzumab vs Obinutuzumab + Chlorambucil in Treatment-Naïve Chronic Lymphocytic Leukemia: ELEVATE-TN 5-Year Follow-up

ASCO Congress 2022

Study Design[1]

A Phase III, Study of Acalabrutinib Combined with Obinutuzumab (O) or Alone vs O Plus Chlorambucil (Clb) in Patients (Pts) With Treatment-Naïve (TN) Chronic Lymphocytic Leukemia (CLL)

Previously untreated CLL

- Age ≥65 years OR
- Age >18 and <65 years AND
  - ≥1 of the following:
    - CrCl 30-69 mL/min
    - CIRS-G >6

Stratification

- ECOG status (≤1 vs 2), del(17p) status, and geographic region

R

1:1:1

- **Arm A**: Acalabrutinib to PD + obinutuzumab x 6 cycles
- **Arm B**: Acalabrutinib monotherapy to PD
- **Arm C**: Obinutuzumab x 6 cycles + chlorambucil x 6 cycles

Primary End Point

- PFS by IRC (Acalabrutinib-O vs. O-Clb)

Additional End Points

- PFS by IRC (A vs O-Clb)
- PFS (INV – assessed)
- ORR (IRC and INV assessed)
- TTNT
- OS
- uMRD[2]
- Safety

Crossover from O-Clb to A was allowed after IRC confirmed disease progression

Note: After interim analysis, PFS assessments were by investigator only[2]

Dosing was as follows:

- **Arm A**: Acalabrutinib dosed at 100 mg BID until disease progression or unacceptable toxicity. **Obinutuzumab was administered IV starting on Cycle 2 Day 1** for a maximum of six 28-day treatment cycles. Obinutuzumab 1000 mg was administered on Days 1 and 2 (100 mg on Day 1 and 900 mg on Day 2), 8, and 15 of Cycle 2 followed by 1000 mg on Day 1 of Cycles 3 up to 7
- **Arm B**: Acalabrutinib dosed at 100 mg BID until disease progression or unacceptable toxicity
- **Arm C**: Obinutuzumab and chlorambucil were administered for a maximum of six 28-day treatment cycles. Obinutuzumab 1000 mg IV was administered on Days 1 and 2 (100 mg on Day 1 and 900 mg on Day 2), 8, and 15 of Cycle 1 followed by 1000 mg on Day 1 of Cycles 2 up to 6. Chlorambucil 0.5 mg/kg was administered on Days 1 and 15 of Cycles 1 up to 6

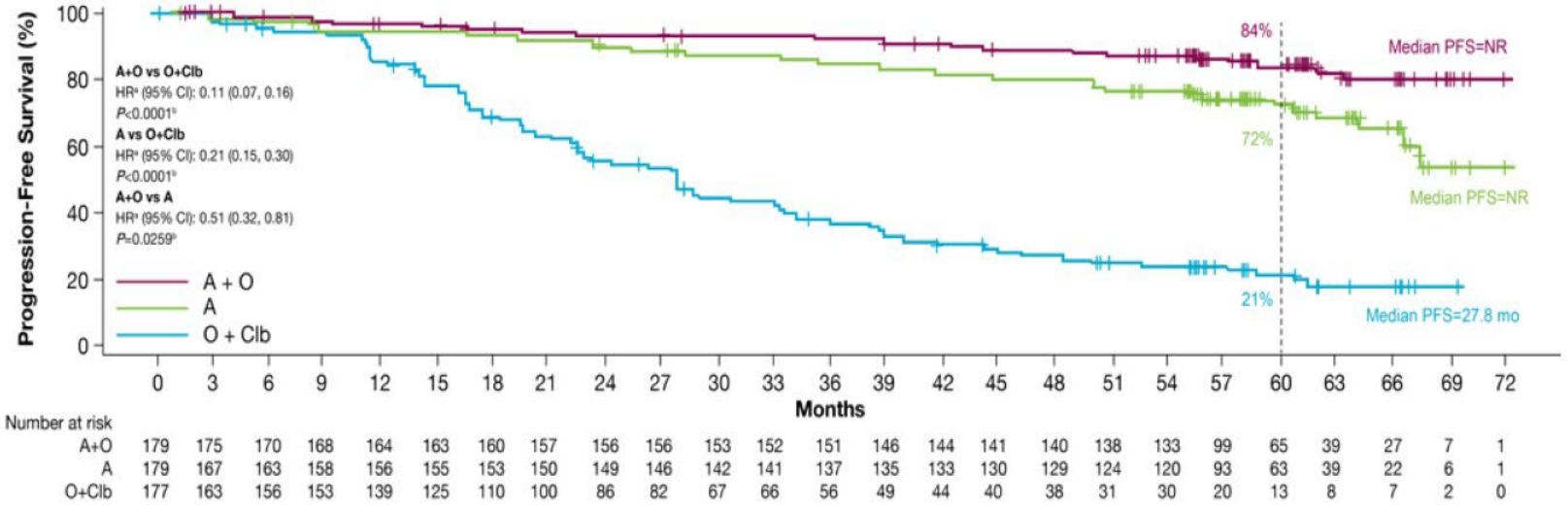
BID = twice daily; CIRS-G = Cumulative Illness Rating Scale-Geriatric; CLL = chronic lymphocytic leukemia; CrCl = creatinine clearance; IRC = independent review committee; IV = intravenous; O = obinutuzumab, ORR = overall response rate, OS = overall survival, PD = progressive disease; PFS = progression-free survival; R = randomize; TN = treatment-naive, TTNT= time to next treatment

1. Sharman JP et al. *Lancet*. 2020; 395: 1278–91. 2. Sharman JP et al. Poster Presented at: ASCO Virtual Annual Meeting; June 4-8, 2021.

Investigator-assessed PFS

- Median PFS was significantly longer for acalabrutinib containing arms than obinutuzumab and chlorambucil
- At 60 months, estimated PFS rates were in favor of A+O (84%) and A (72%)

A. Investigator-assessed PFS



[a]Hazard ratio based on Cox proportional-hazard model stratified by 17p deletion status (yes vs no based on interactive voice/web response system). [b]P-value based on log-rank test stratified by 17p deletion status (yes vs no based on interactive voice/web response system).

A = acalabrutinib; CI = confidence interval; Clb = chlorambucil; NR = not reached; O = Obinutuzumab; PFS = progression free survival; vs = versus.

Sharman JP et al. Poster Presented at: ASCO; June 3-7, 2022; Chicago, Illinois.

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UNIKLINIK KÖLN | Department I of Internal Medicine University Hospital of Cologne
DEUTSCHE STUDIENGRUPPE

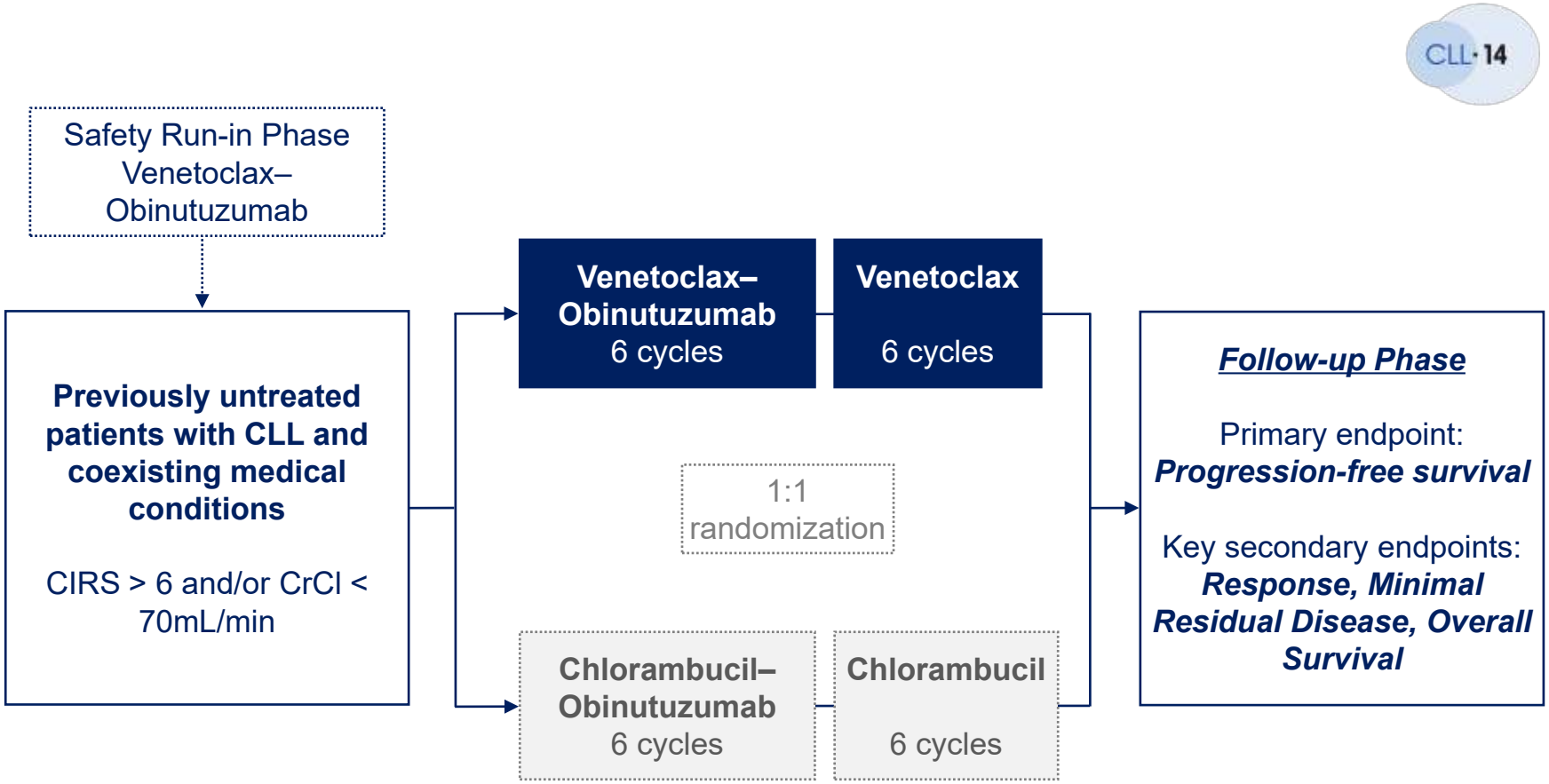
Abstract S148

Venetoclax-Obinutuzumab for previously untreated chronic lymphocytic leukemia: 5-year results of the randomized CLL14 study

Othman Al-Sawaf, Can Zhang, Sandra Robrecht, Alex Kotak, Naomi Chang, Anna Maria Fink, Eugen Tausch, Christof Schneider, Matthias Ritgen, Karl-Anton Kreuzer, Brenda Chyla, Barbara Eichhorst, Yanwen Jiang, Stephan Stilgenbauer, Michael Hallek, Kirsten Fischer

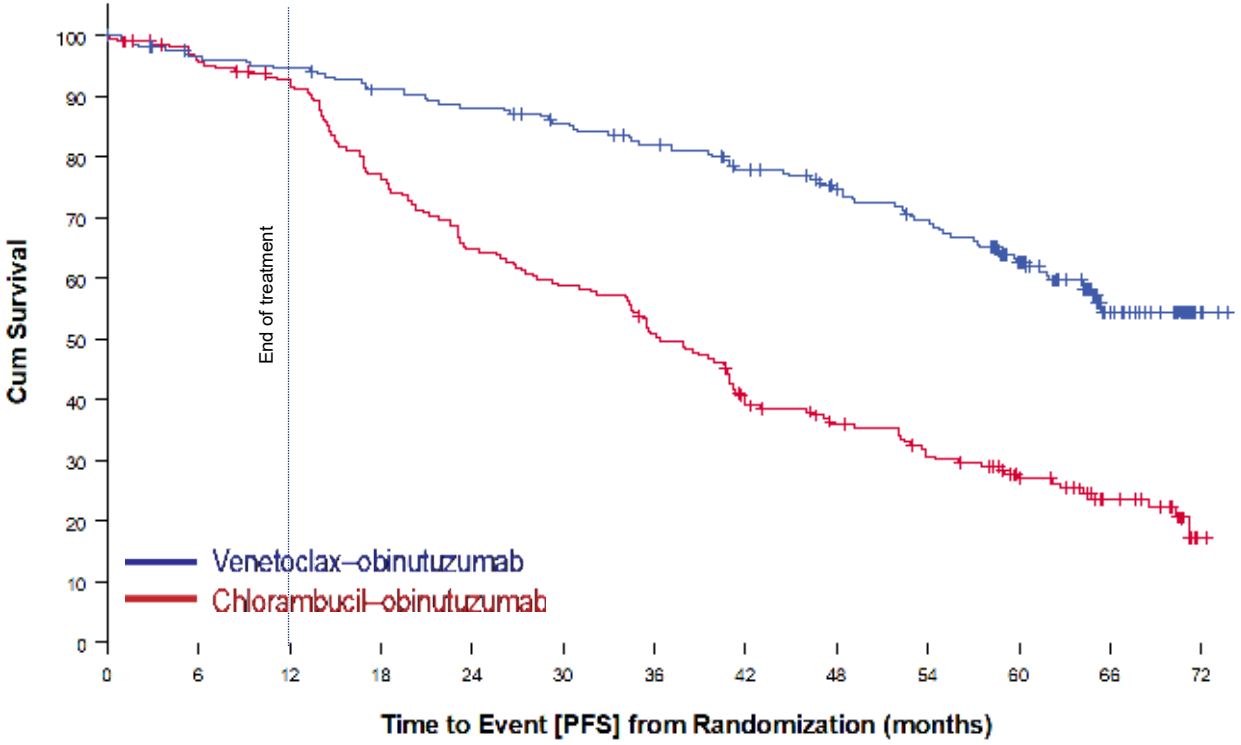
June 12th, 2022
Clinical CLL Session

TRIAL DESIGN



PROGRESSION-FREE SURVIVAL

Median observation time 65.4 months



Ven-Obi	216	196	192	183	177	169	160	147	134	123	97	35	4
Clb-Obi	216	195	185	154	130	118	101	75	64	53	39	21	1

Median PFS

Ven-Obi: not reached

Clb-Obi: 36.4 months

5-year PFS rate

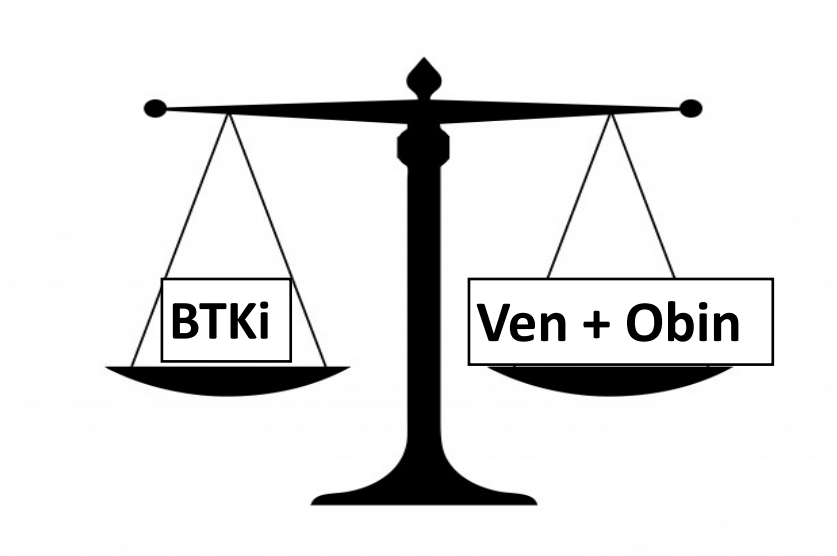
Ven-Obi: 62.6%

Clb-Obi: 27.0%

HR 0.35, 95% CI [0.26-0.46]

P<0.0001

Frontline BTKi vs. Ven + Obinutuzumab: Factors to Consider



- Convenience (no infusions, TLS monitoring)
- Long term efficacy data
- Phase 3 data compared to FCR and BR
- More data for efficacy of ven at time of ibrutinib progression

- Potential for 1-year time-limited therapy
- No known cardiac or bleeding risks
- Less concern for long term adherence
- Potential for cost-saving if 1-year of therapy is durable

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

IBR + VEN in TN CLL, ASH 2019, Abs 34

Treatment Schema

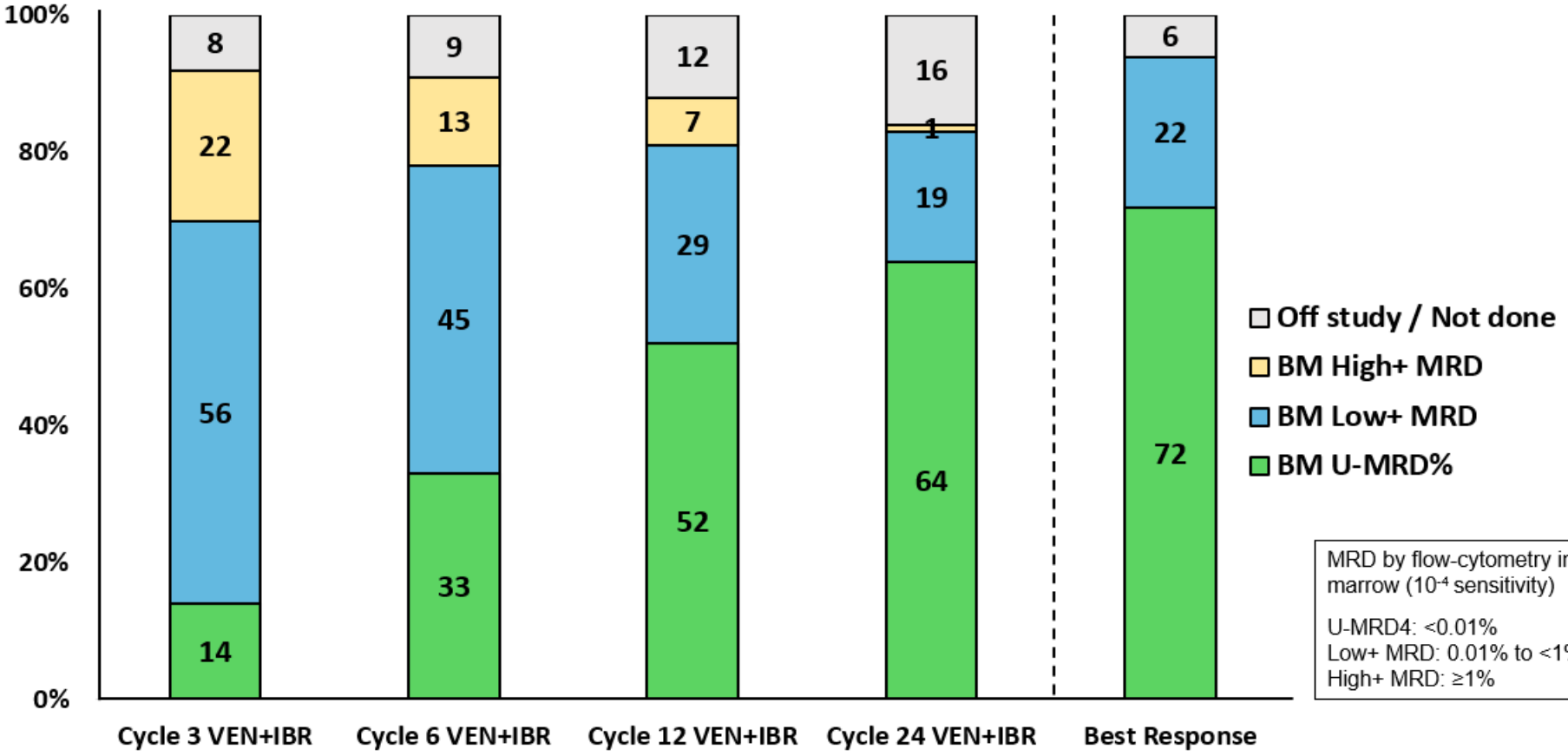
	C1	C2	C3	C4-->27
Ibrutinib	420mg daily	420mg daily	420mg daily	420mg daily
Venetoclax	-	-	-	20mg daily 1 week; 50mg daily 1 week; 100mg daily 1 week; 200mg daily 1 week; 400mg daily continuous

Duration of therapy: 24 cycles of combination treatment

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

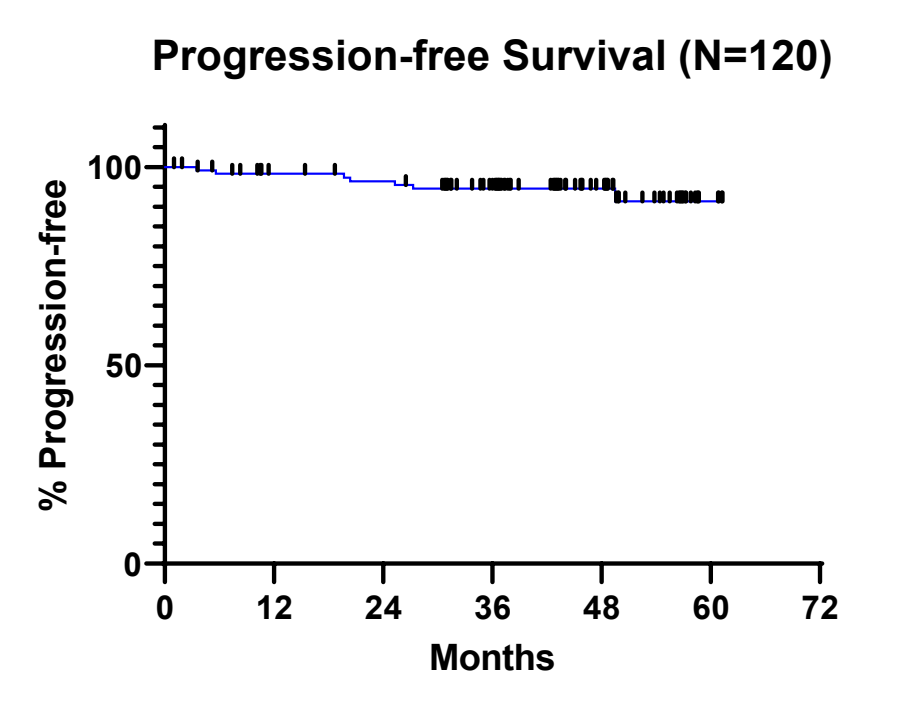
Protocol Amendment: up to 36 combination cycles allowed; as before, if still MRD + continue ibrutinib

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



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

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)

Near future:

- CLL17: I vs. IV vs. VO (n=882)

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

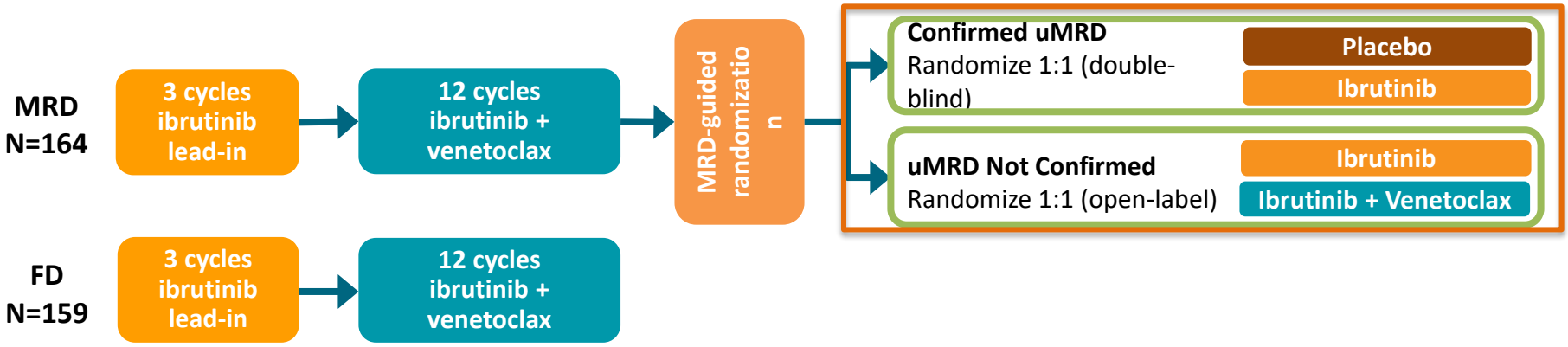
Paolo Ghia, MD, PhD[1]; John N. Allan, MD, PhD[2]; Tanya Siddiqi, MD[3]; Thomas J. Kipps, MD, PhD[4]; Bryone J. Kuss, MBBS, PhD, FRACP, FRCPA[5]; Stephen Opat, FRACP, FRCPA, MBBS[6]; Ian W. Flinn, MD, PhD[7]; Xavier C. Badoux, MBBS, FRACP, FRCPA[8]; Alessandra Tedeschi, MD[9]; Eva Gonzalez Barca, MD, 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 Catalá 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

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



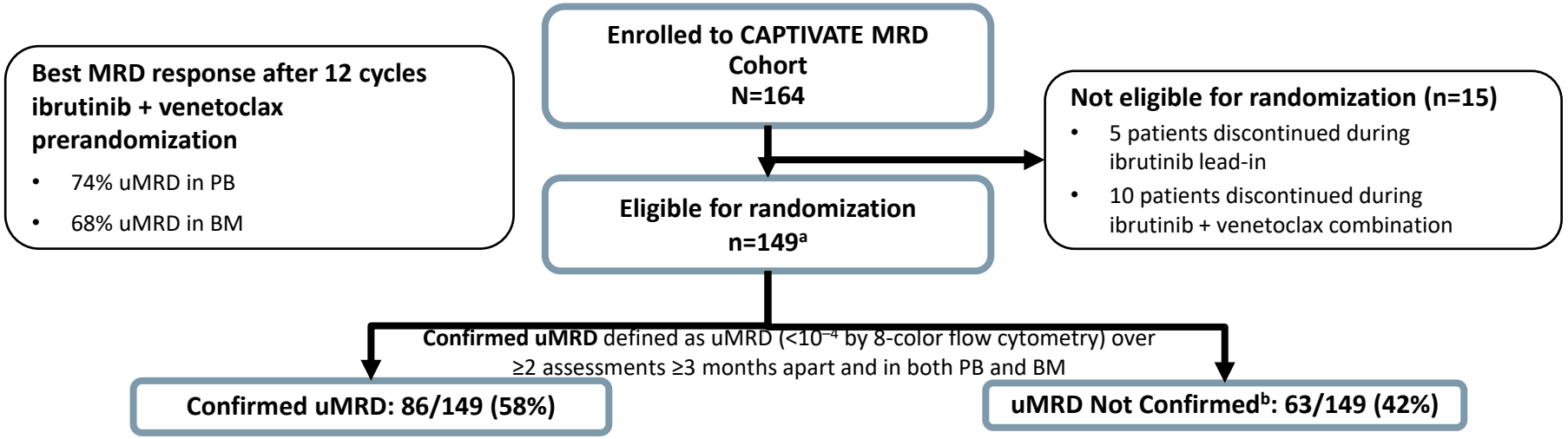
- Primary analyses of both cohorts have been previously reported[1,2]
- Presented are updated results from the MRD cohort, with median time on study: 38.2 months (range, 15.0–47.9)
  - Median postrandomization follow-up: 24.0 months (range, 5.8–33.1)

ASH 2021, CAPTIVATE-MRD; Ghia et al.

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.

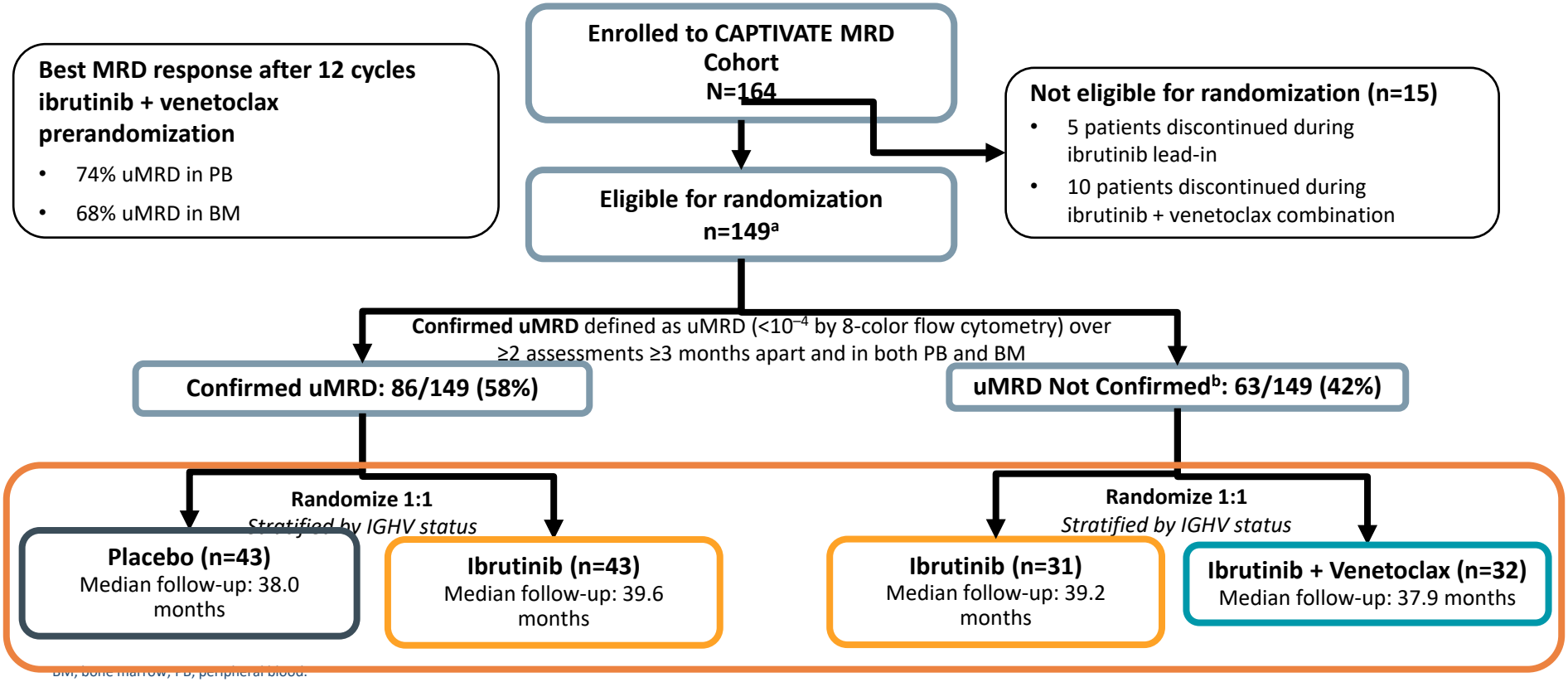
MRD Cohort: Patient Disposition and Randomization



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.

ASH 2021, CAPTIVATE-MRD; Ghia et al.

MRD Cohort: Patient Disposition and Randomization (cont.)



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.

ASH 2021, CAPTIVATE-MRD; Ghia et al.

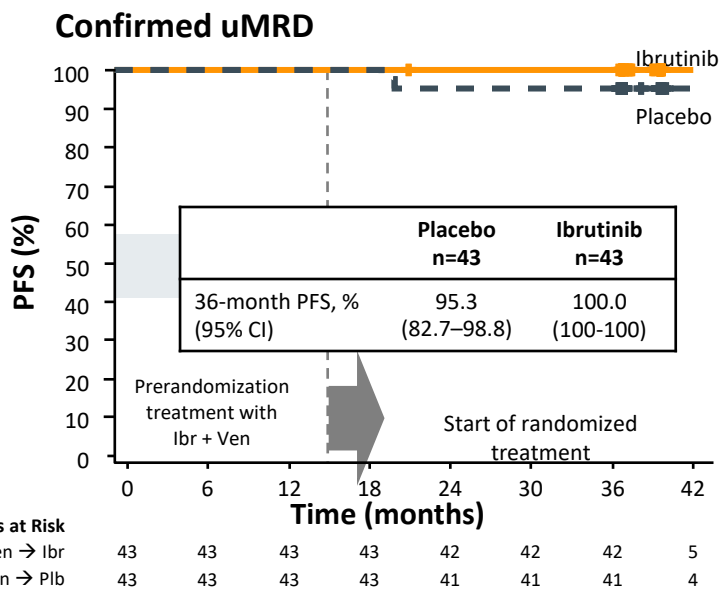
Most Patients Had High-Risk Disease Features

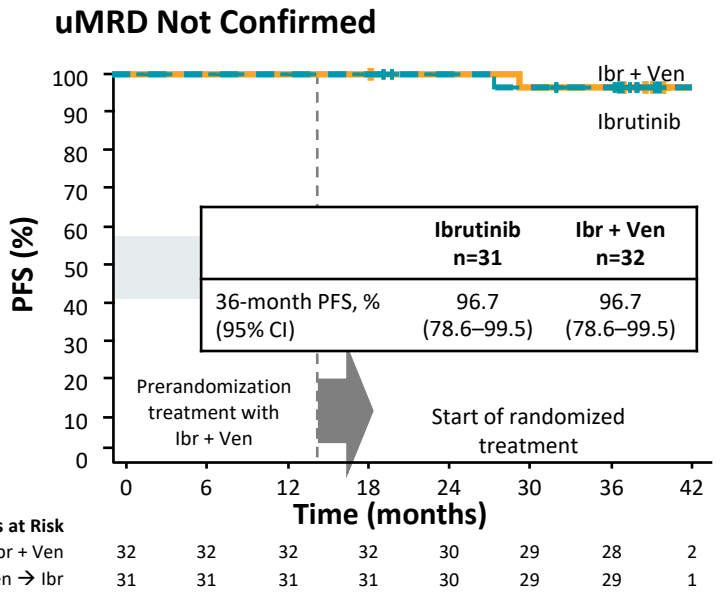
Characteristic	All Treated Population N=164	Confirmed uMRD (n=86)		uMRD Not Confirmed (n=63)	
		Placebo n=43	Ibrutinib n=43	Ibrutinib n=31	Ibrutinib + Venetoclax n=32
Median age (range), year	58 (28–69)	61 (43–69)	56 (34–69)	58 (28–69)	56 (37–69)
Rai stage III/IV disease, n (%)	53 (32)	15 (35)	8 (19)	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





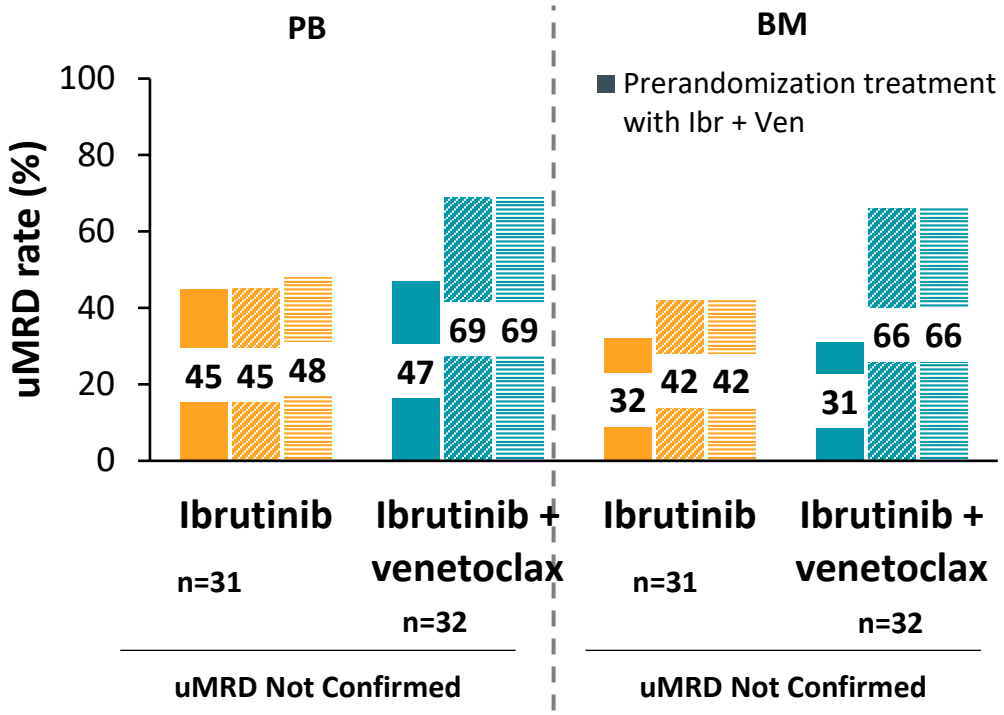
Median follow-up = 38 months

- 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.

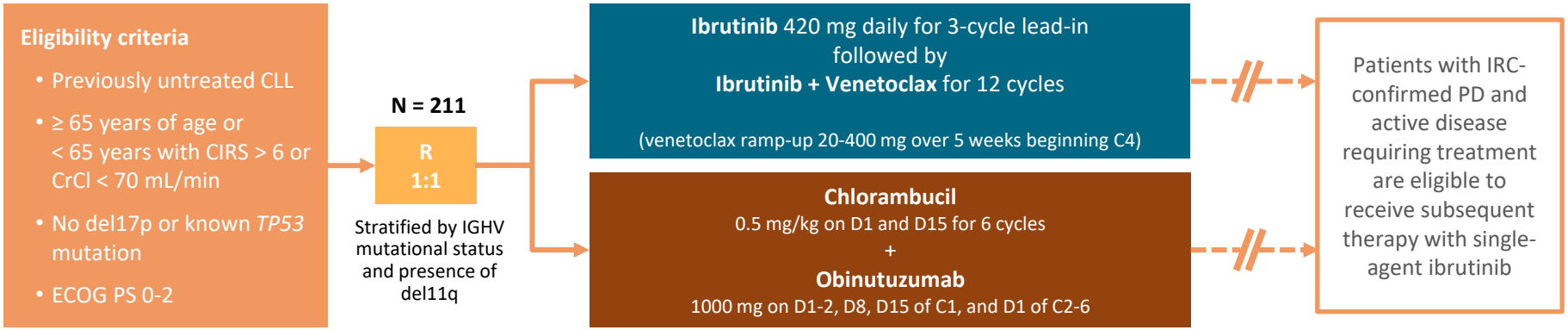
First Prospective Data on Minimal Residual Disease (MRD) Outcomes After Fixed-Duration Ibrutinib Plus Venetoclax (Ibr+Ven) Versus Chlorambucil Plus Obinutuzumab (Clb+O) for First-Line Treatment of CLL in Elderly or Unfit Patients: The GLOW Study

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

EHA 2021

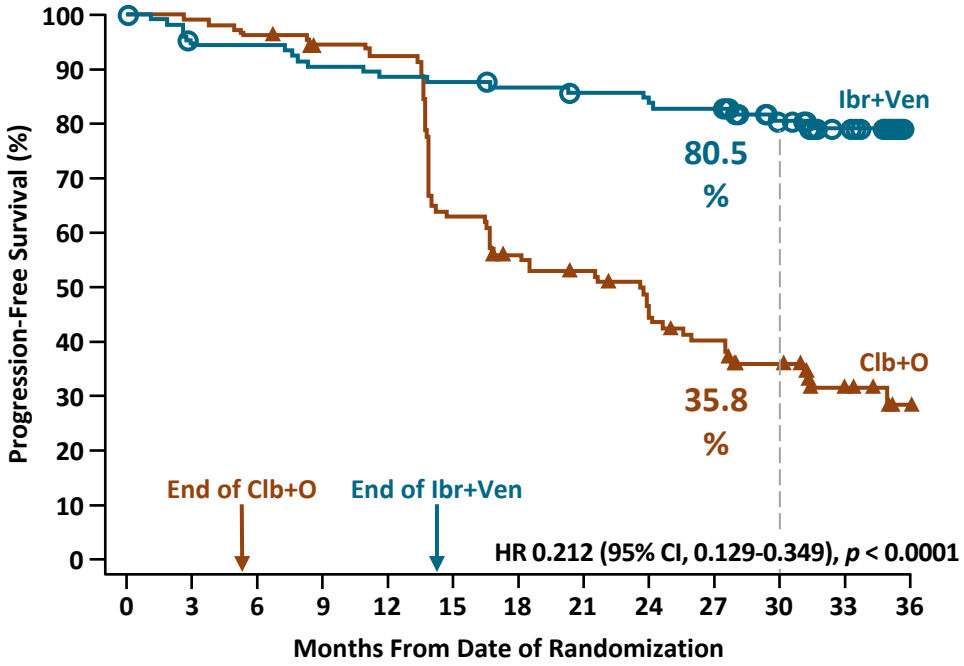
Phase 3 GLOW Study Design (NCT03462719)



- **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



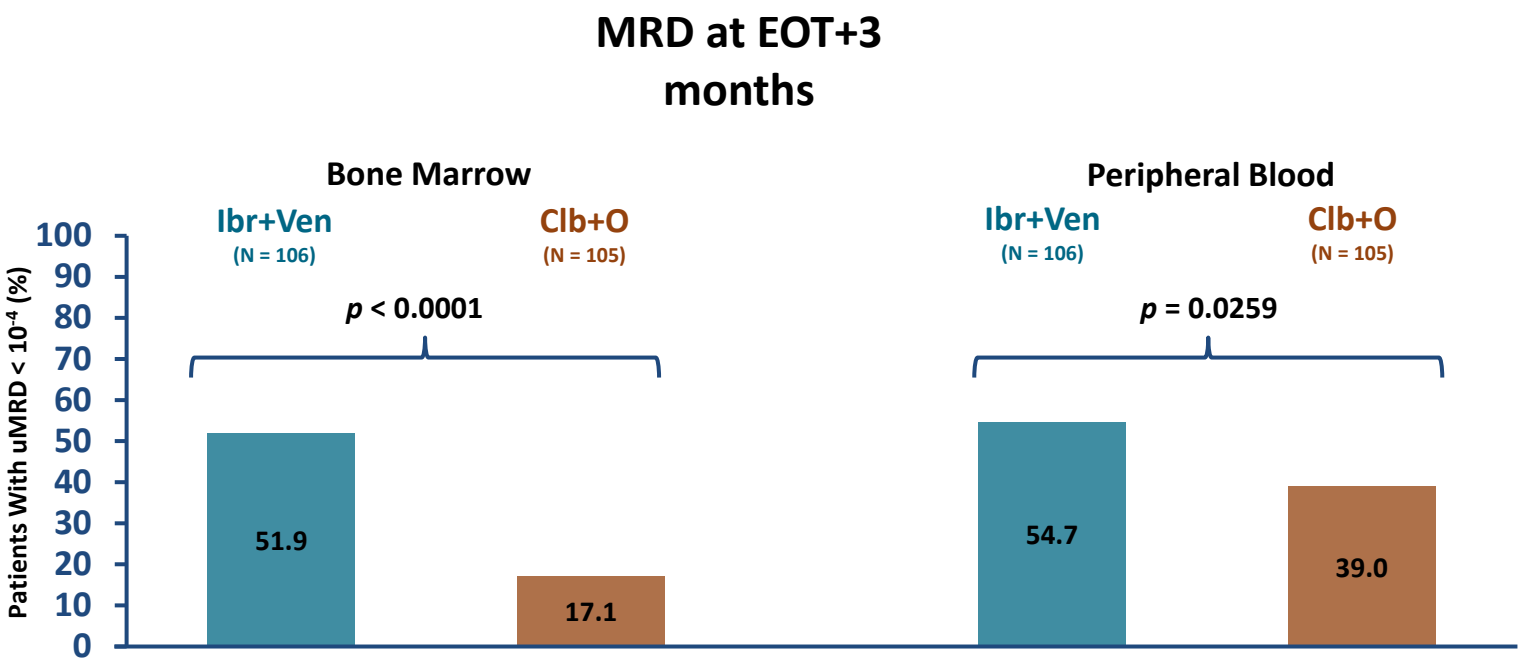
Patients at risk

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

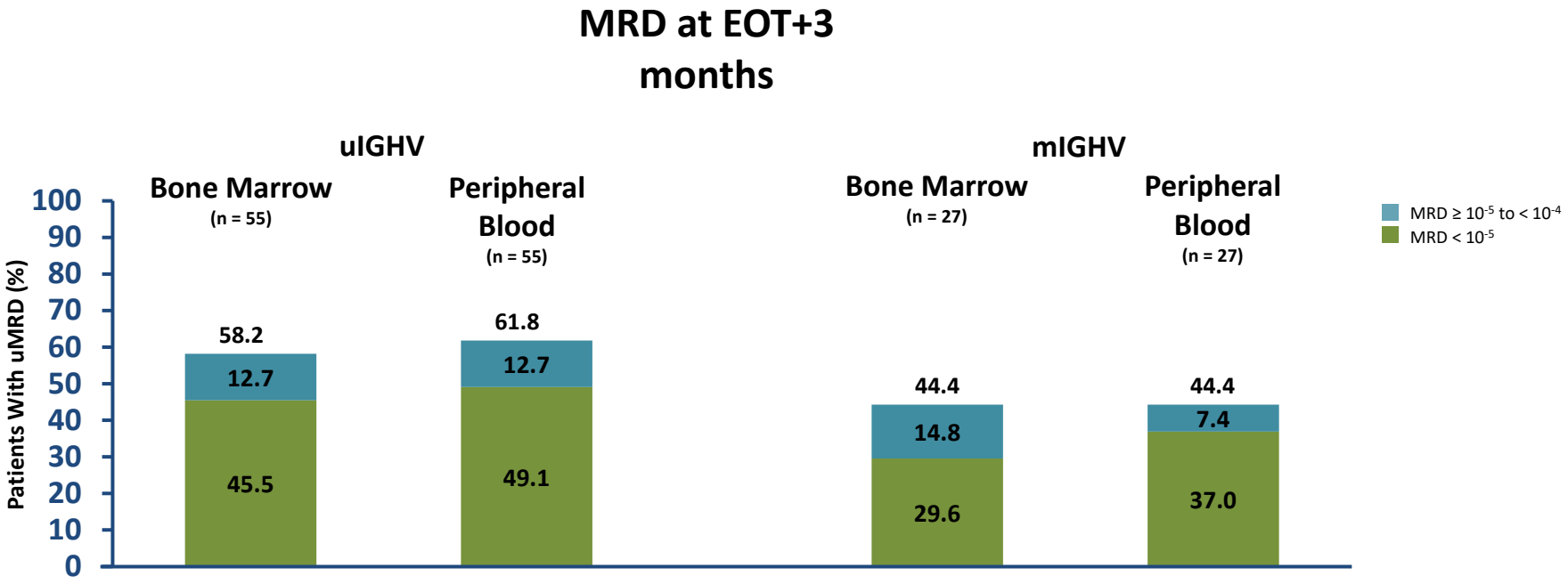
uMRD Rate < 10^{-4} Was Significantly Higher in Both Compartments With Ibr+Ven



- 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.

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.

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

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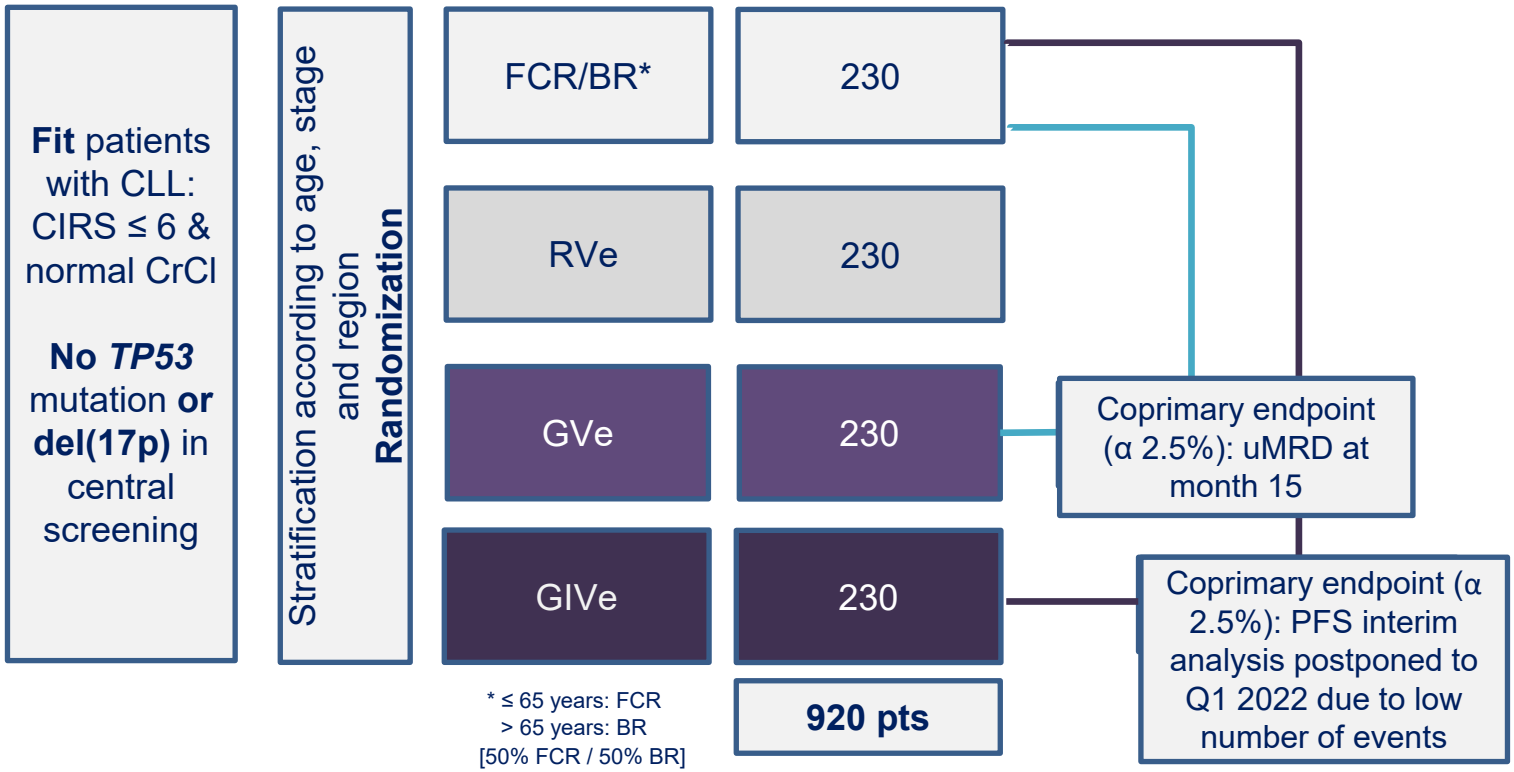
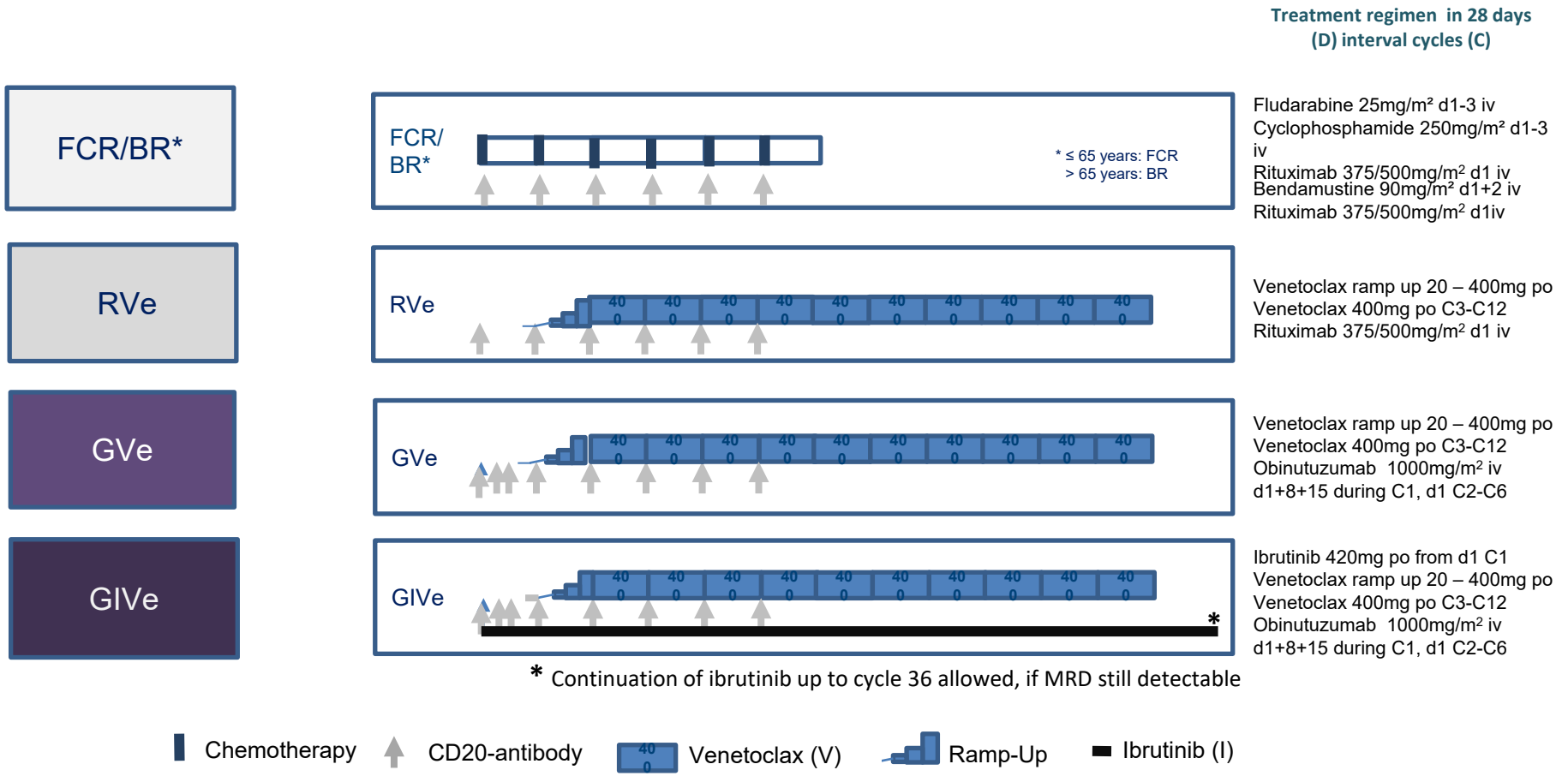
GAIA/CLL13 Study : Design

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)

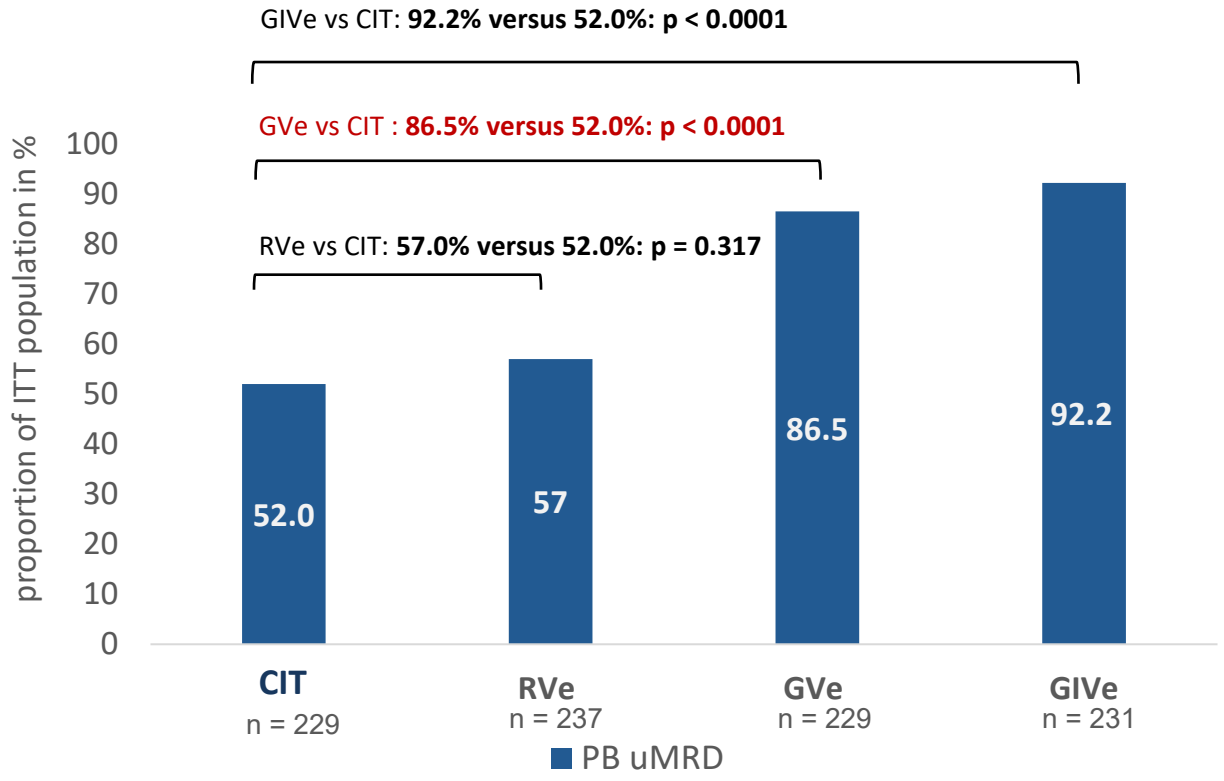


GAIA/CLL13 Study : Treatment Regimen



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

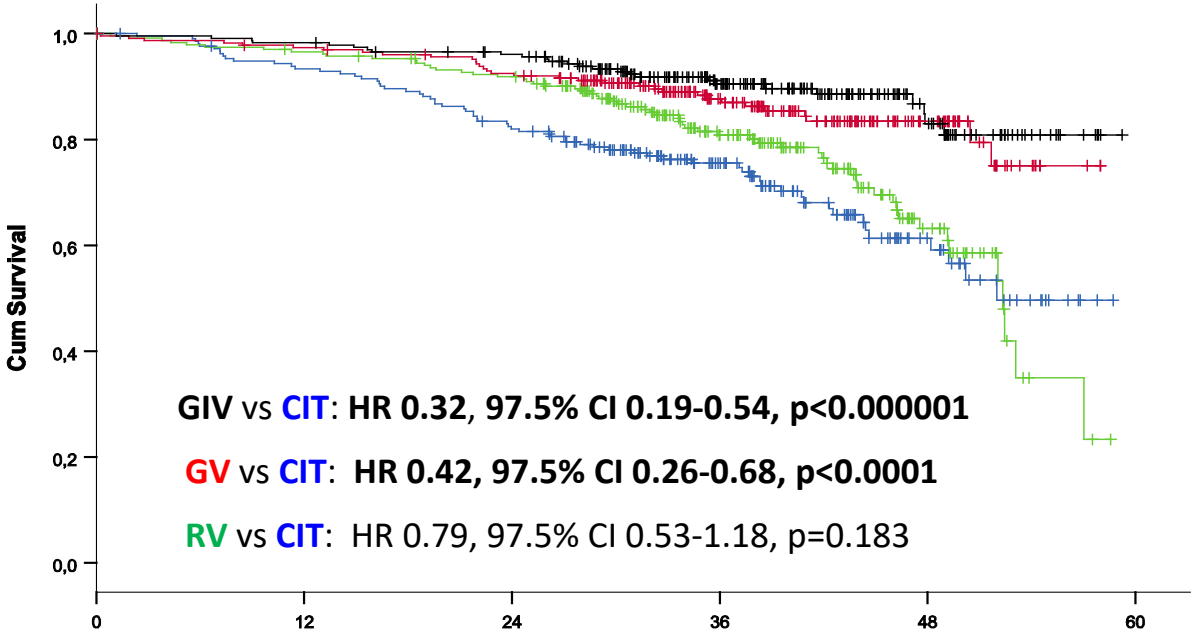
ITT analysis: 63 pts (34 CIT, 15 RVe, 10 GVe, 4 GIVe) with missing samples (6.8%) were counted as MRD positive



	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

Results of the coprimary endpoint progression-free survival (PFS)

Median FU 38.8 months (range: 0.0 – 59.2)



CIT	229	197	172	98	28
RV	237	226	212	119	32
GV	229	221	208	125	42
GIV	231	227	217	132	44

PFS	Median months	3y PFS (%)
CIT	52.0	75.5
RV	52.3	80.8
GV	Not reached	87.7
GIV	Not reached	90.5

Conclusions

- BTKi produce long remissions with continuous therapy
- Ven/Obin is finite 1 year therapy with high rates of uMRD
- Small molecule combinations result in high rates of uMRD
  - do we need antibody with small molecules?
  - Will GIVe be better than Gve?
  - Results of retreatment after finite regimens?