Chronic Lymphocytic Leukemia
ASH 2019

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Disclosures

Institutional research funding

Abbvie, Acerta, Gilead, Janssen, Pharmacyclics, Takeda

Data Safety Monitoring Committee

Beigene

Clinical Trial Steering Committee

Acerta

Consultancy

Abbvie, Adaptive, Astellas, Astra Zeneca, Genentech, Gilead, Janssen, Pharmacyclics

Honoraria

Janssen, Pharmacyclics

(CME accredited) Imedex, Medscape

Travel Expenses

Abbvie, Beigene, Genentech, Janssen, Pharmacyclics

Expert Witness

Genentech

Questions we will address

- What upfront regimens should we consider?
  - Chemoimmunotherapy?
  - Ibrutinib?
  - Acalabrutinib
  - Venetoclax/obinutuzumab
- What are our best options for a previously treated patient?
  - Ibrutinib
  - Acalabrutinib
  - Venetoclax/rituximab
- What combination regimens appear promising?

Previously Untreated

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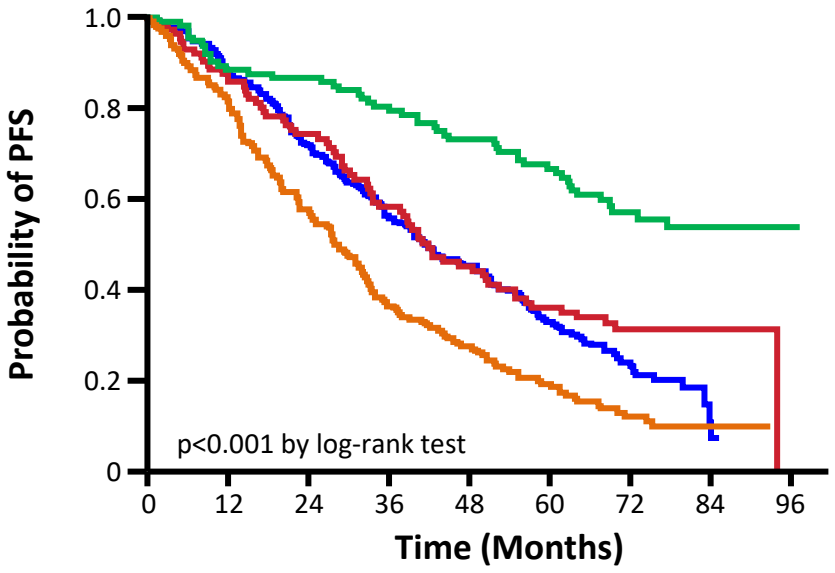
CHEMOIMMUNOTHERAPY

Long term remissions with FCR

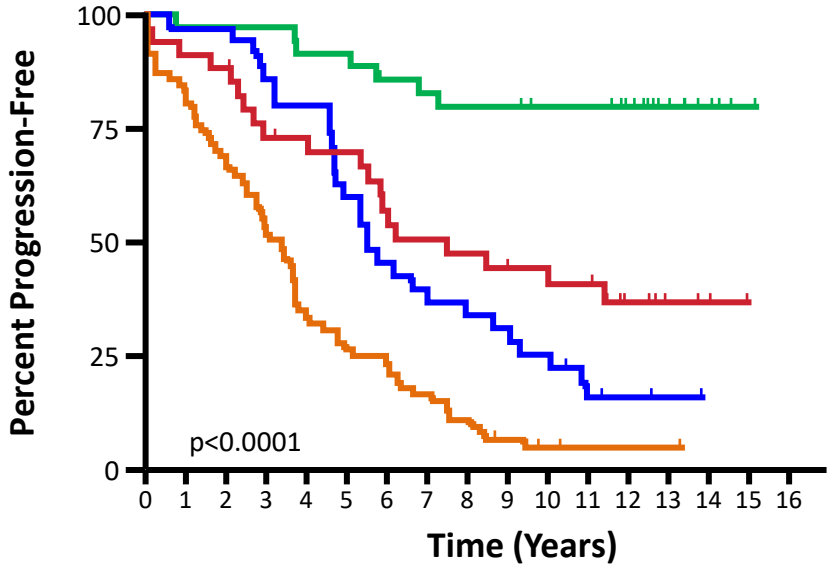
CLL8[1]

	N
FCR IGHV-M patients	113
FC IGHV-M patients	117
FCR IGHV-UM patients	197
FC IGHV-UM patients	195



MDACC[2]

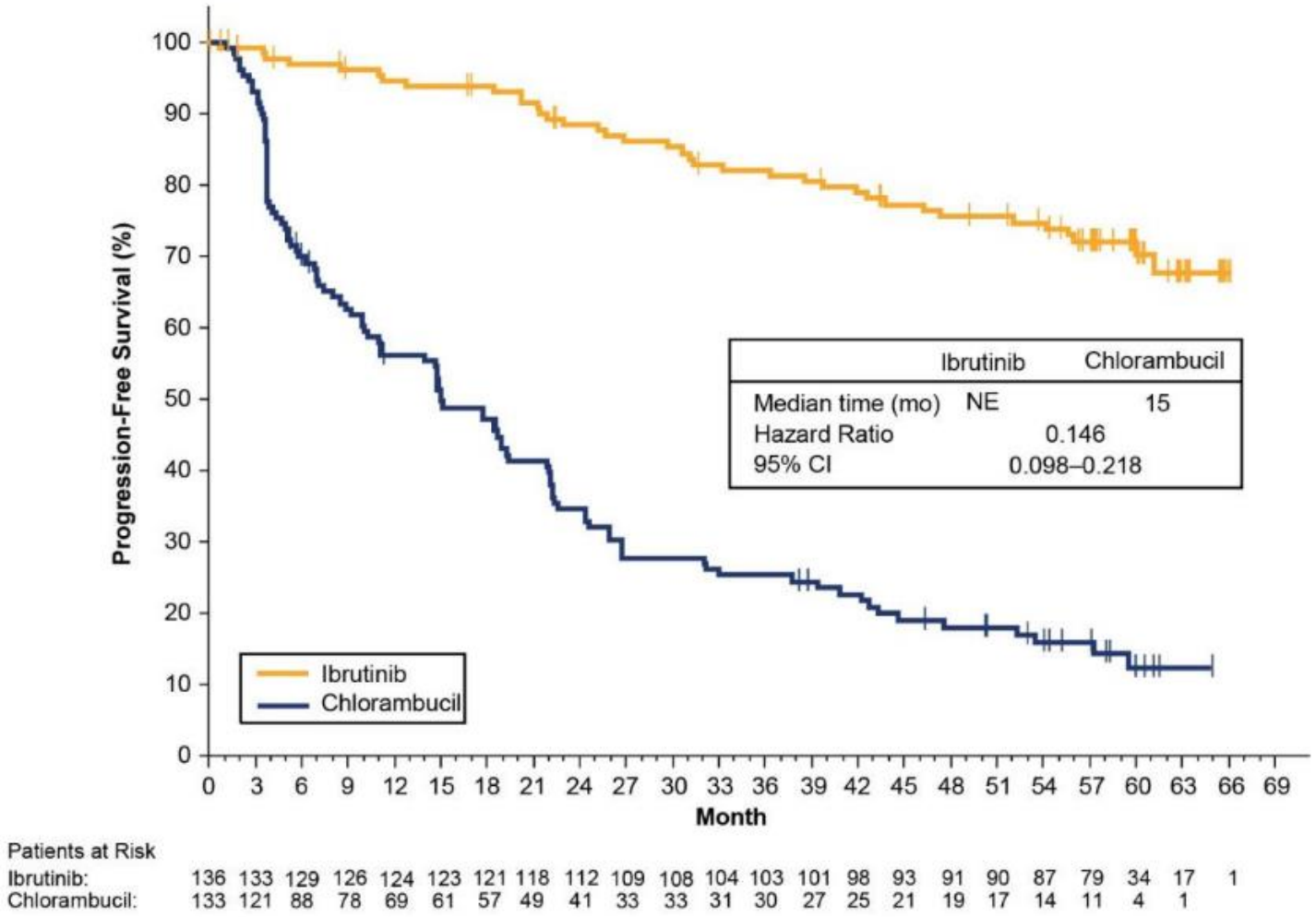
	N
IGHV-M, MRD neg	35
IGHV-M, MRD pos	34
IGHV-UM, MRD neg	35
IGHV-UM, MRD pos	66



1. Fischer K, et al. Blood 2016; 127:208–215.
2. Thompson PA, et al. Blood 2016; 127:303–309.

IBRUTINIB

Five-year follow-up of patients receiving ibrutinib for first-line treatment of CLL (RESONATE-2): PFS



- At 5 years, 70% of ibrutinib-treated patients and 12% (HR [95% CI]: 0.146 [0.098–0.218]) of chlorambucil-treated patients were estimated to be progression-free and alive
- Ibrutinib also resulted in improved OS vs chlorambucil: 83% vs 68% at 60 months; HR (95% CI): 0.450 (0.266–0.761)

Tedeschi et al., EHA 2019; S107

RESONATE-2: Over half of the patients remain on long-term ibrutinib with up to 5.5 years follow-up

	Ibrutinib n=136
Median duration of ibrutinib treatment, months (range)[a]	57.1 (0.7–66.0)
Treatment duration, n (%)	
>3 years	99 (73)
>4 years	88 (65)
>5 years	37 (27)
Continuing ibrutinib on study, n (%)	79 (58)
Discontinued ibrutinib, n (%)	
AE	29 (21)
PD[b]	8 (6)
Death	8 (6)
Withdrawal by patient	7 (5)
Investigator decision	4 (3)

[a]One patient received no doses of ibrutinib;
[b]Two patients discontinued due to Richter's transformation.

Tedeschi et al., EHA 2019; S107

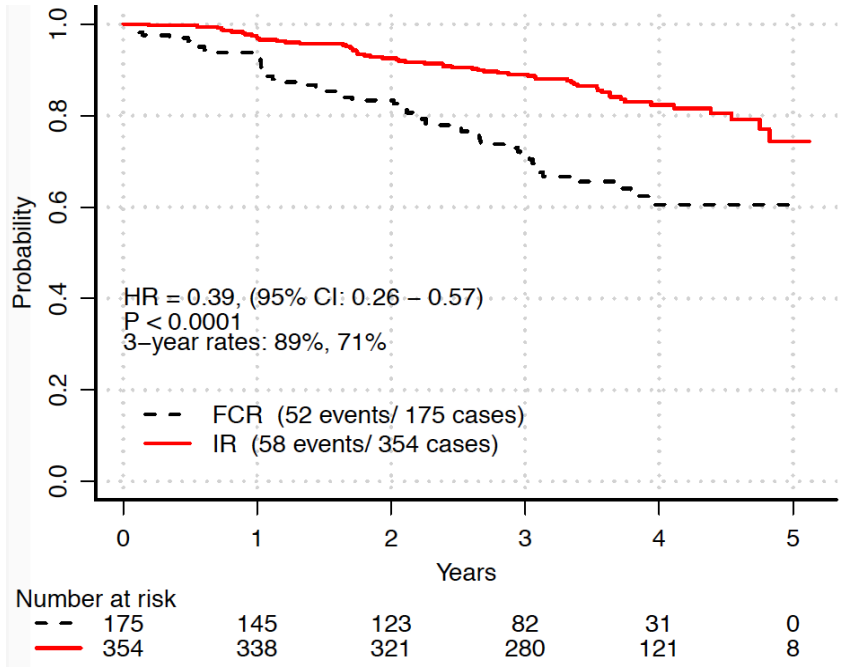
Update From the E1912 Trial Comparing Ibrutinib & Rituximab to FCR in Younger Patients with Previously Untreated Chronic Lymphocytic Leukemia (CLL)

Tait Shanafelt, Xin Victoria Wang, Neil E. Kay, Susan O'Brien, Jacqueline Barrientos , Curt Hanson, Harry Erba, Rich Stone, Mark Litzow, Marty Tallman

Shanafelt et al. ASH 2019. Abstract 33. NCT02048813.

Updated Results E1912
ASH 2019 with median f/u time 45 mos

Progression Free Survival

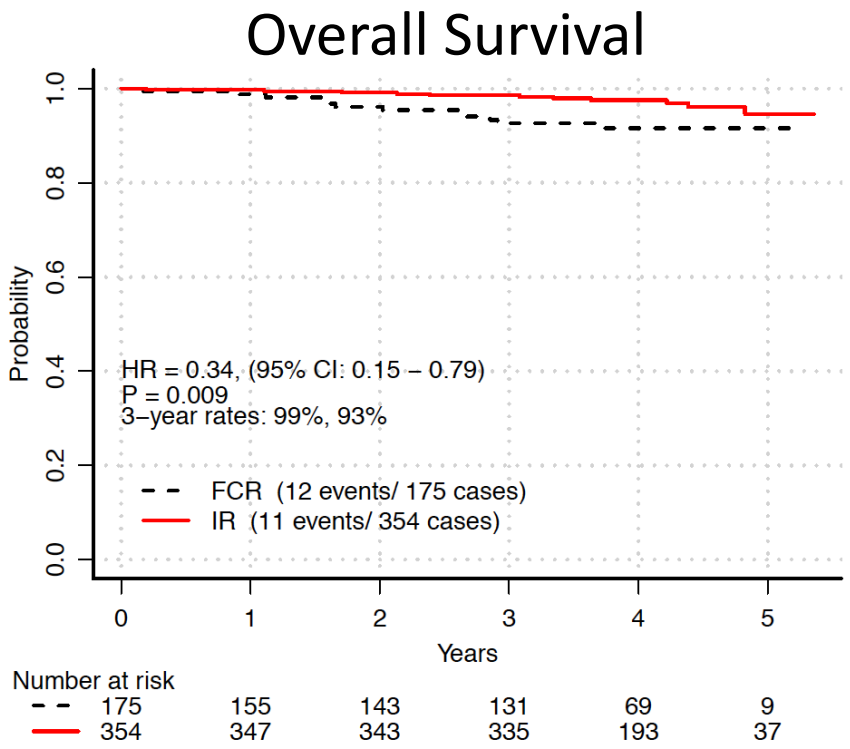


- 110 PFS events were observed
  - includes 15 deaths without documented progression
- Overall there have been 23 deaths
- Hazard ratio (HR) for PFS is stable and continues to favour IR over FCR
  - (HR=0.39; 95% CI 0.26-0.57; p < 0.0001)

IR was superior to FCR in unmutated CLL [HR 0.28 (0.17-0.48)] but not in mutated CLL [0.42 (0.16-1.16)]

Shanafelt et al. ASH 2019. Abstract 33. NCT02048813.

Updated Results E1912: ASH 2019



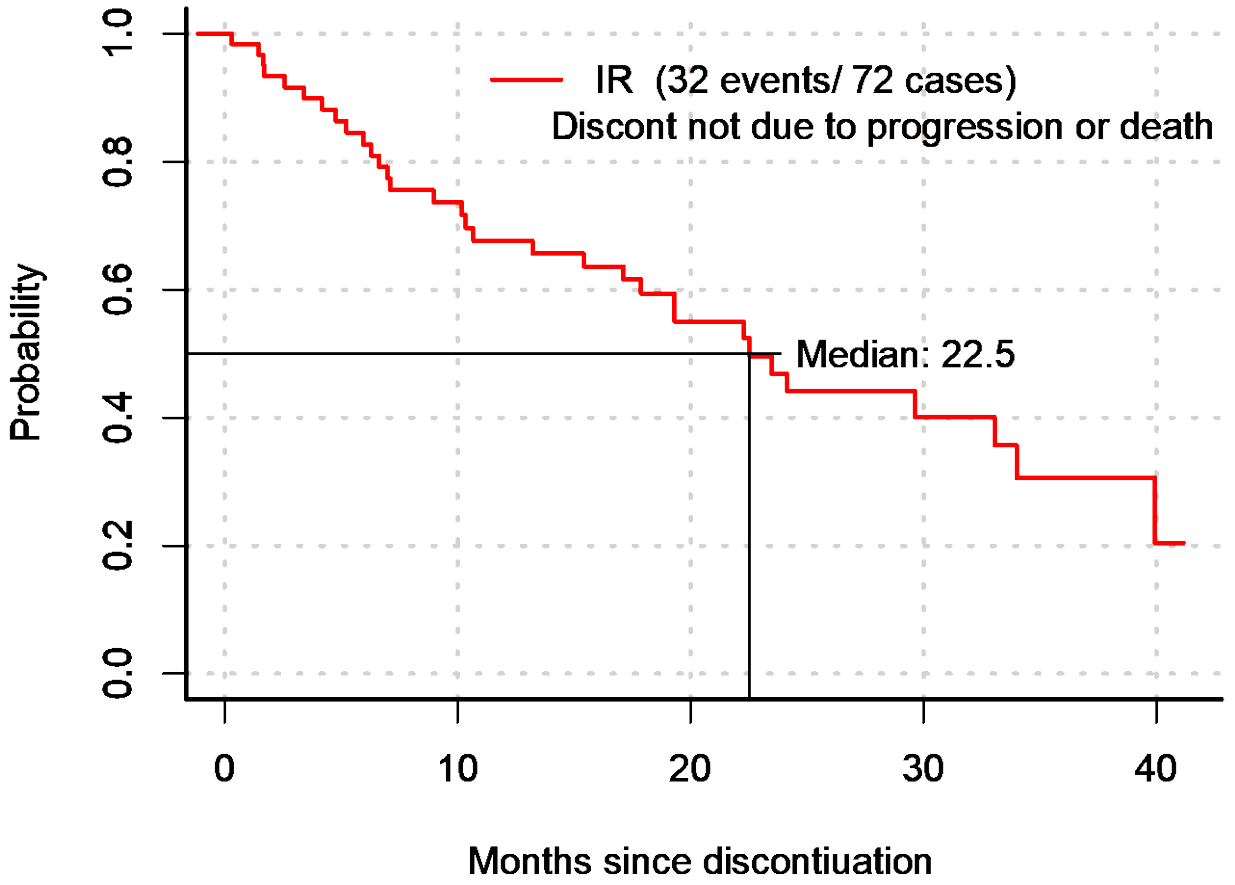
Shanafelt et al. ASH 2019. Abstract 33. NCT02048813.

Reasons for Ibrutinib Discontinuation

Reason for Discontinuation	All Patients Who Started IR N=352	Patients Discontinuing Treatment N= 95
Progression or death	23 (7%)	23 (24%)
Adverse event	48 (14%)	48 (51%)
Other reason*	24 (7%)	24 (25%)

*Other health conditions, patient preference, lost to follow-up

Progression Free Survival Post Discontinuation of Ibrutinib



N=72

Median time of therapy 15.1 months

Shanafelt et al. ASH 2019. Abstract 33. NCT02048813.

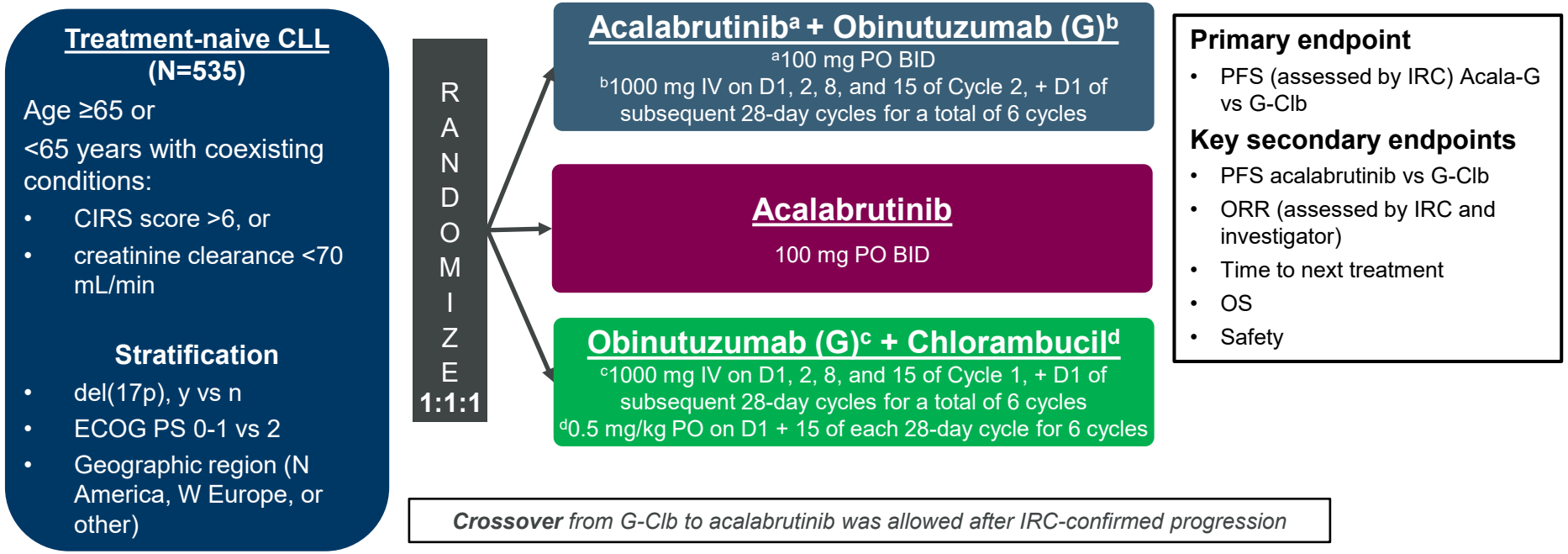
Grade 3-5 Treatment Related Adverse Events Throughout Observation

Adverse Event	IR (n=352, %)	FCR (n=158, %)	P-value
Anemia	4.3	**15.8**	<0.001
Arthralgia	**5.1**	0.6	0.011
Diarrhea	**2.6**	0.6	0.185
Hemolysis	0	**2.5**	0.009
Hypertension	**8.5**	1.9	0.003
Neutrophil count decreased	27	**43**	<0.001
Platelet count decreased	3.1	**15.8**	<0.001
Febrile neutropenia	2.3	**15.8**	<0.001
Infection	7.1	8.9	0.477
Sepsis	0.6	**3.2**	0.032
Other infections	7.1	6.3	0.851
Cardiac	**5.4**	0	0.001
Atrial fibrillation	**2.8**	0	0.036
Other cardiac	**3.4**	0	0.022
Any Grade 3 or higher AE	**69.6**	**80.4**	**0.013**

Shanafelt et al. ASH 2019. Abstract 33. NCT02048813.

ACALABRUTINIB

ELEVATE TN Study Design (ACE-CL-007)



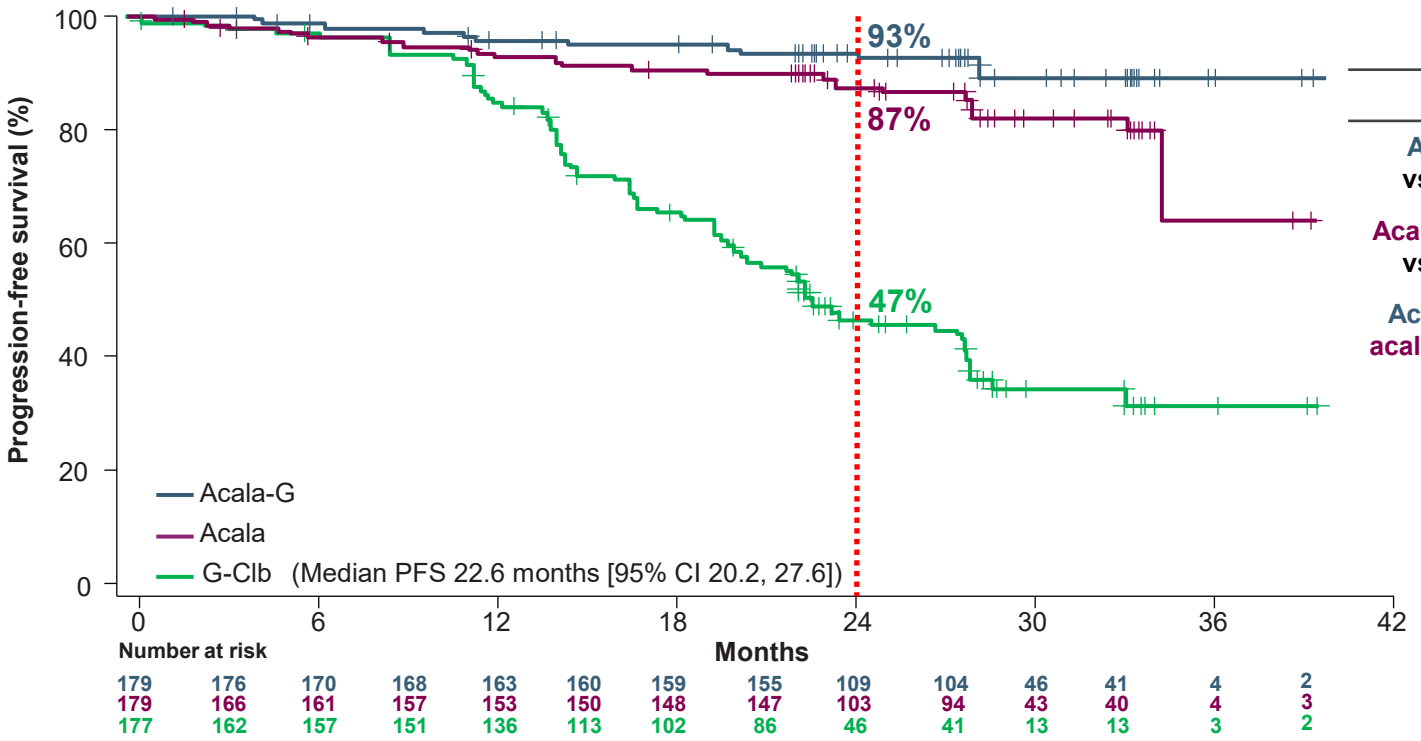
- Interim analysis was planned based on events (after occurrence of ~111 IRC-assessed PFS events in the combination therapy arms) or after 24 months if the required number of events was not met by this time

Acala, acalabrutinib; CIRS, Cumulative Illness Rating Scale; ECOG PS, Eastern Cooperative Oncology Group performance status; IRC, independent review committee; IV, intravenously; OS, overall survival; PO, orally

Sharman et al. ASH 2019. Abstract 31. NCT02475681.

IRC-Assessed Progression-Free Survival

Median follow-up 28.3 months



Hazard ratio (95% CI)	
Acala-G vs G-Clb	**0.10** (0.06, 0.17) p<0.0001
Acalabrutinib vs G-Clb	**0.20** (0.13, 0.30) p<0.0001
Acala-G vs acalabrutinib[a]	**0.49** (0.26, 0.95)

No difference in OS observed

Sharman et al. ASH 2019. Abstract 31. NCT02475681.

Most Common AEs (≥15% Patients) in Any Treatment Arm

	Acala-G N=178		Acalabrutinb N=179		G-Clb N=169	
AEs, n (%)	Any	Grade ≥3	Any	Grade ≥3	Any	Grade ≥3
Headache	71 (39.9)	2 (1.1)	66 (36.9)	2 (1.1)	20 (11.8)	0
Diarrhea	69 (38.8)	8 (4.5)	62 (34.6)	1 (0.6)	36 (21.3)	3 (1.8)
Neutropenia	56 (31.5)	53 (29.8)	19 (10.6)	17 (9.5)	76 (45.0)	70 (41.4)
Fatigue	50 (28.1)	3 (1.7)	33 (18.4)	2 (1.1)	29 (17.2)	1 (0.6)
Contusion	42 (23.6)	0	27 (15.1)	0	7 (4.1)	7 (4.1)
Arthralgia	39 (21.9)	2 (1.1)	28 (15.6)	1 (0.6)	8 (4.7)	2 (1.2)
Cough	39 (21.9)	0	33 (18.4)	1 (0.6)	15 (8.9)	0
URTI	38 (21.3)	4 (2.2)	33 (18.4)	0	14 (8.3)	1 (0.6)
Nausea	36 (20.2)	0	40 (22.3)	0	53 (31.4)	0
Dizziness	32 (18.0)	0	21 (11.7)	0	10 (5.9)	0
IRR	24 (13.5)	4 (2.2)	0	0	67 (39.6)	9 (5.3)
Pyrexia	23 (12.9)	0	12 (6.7)	1 (0.6)	35 (20.7)	1 (0.6)

AEs reported are from the treatment-emergent period (first dose through to 30 days after the last dose of study drug or the first date starting a new CLL therapy, whichever is earliest)
IRR, infusion-related reaction; URTI, upper respiratory tract infection

Sharman et al. ASH 2019. Abstract 31. NCT02475681.

Events of Clinical Interest for Acalabrutinib

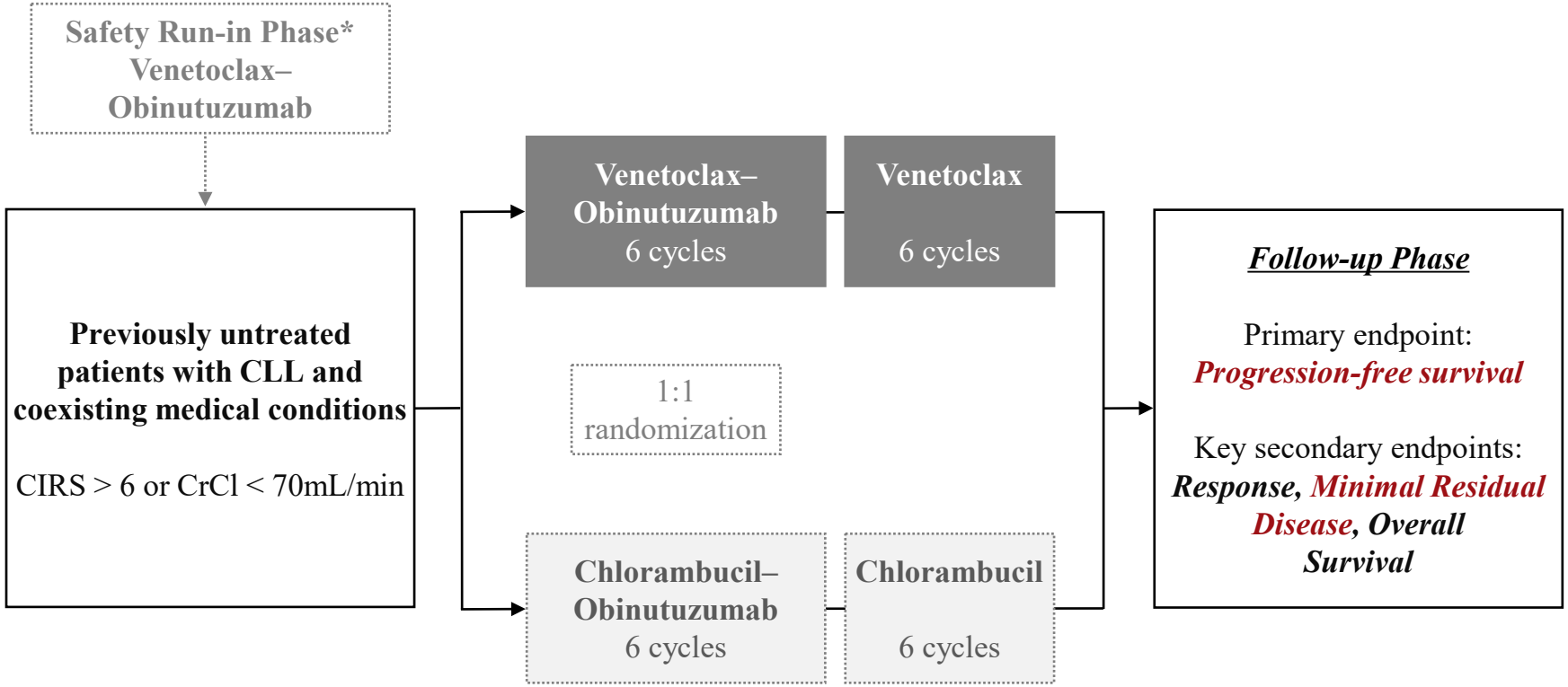
AEs, n (%)	Acala-G N=178		Acalabrutinib N=179		G-Clb N=169	
	Any	Grade ≥3	Any	Grade ≥3	Any	Grade ≥3
Atrial fibrillation	6 (3.4)	1 (0.6)	7 (3.9)	0	1 (0.6)	0
Hypertension	13 (7.3)	5 (2.8)	8 (4.5)	4 (2.2)	6 (3.6)	5 (3.0)
Bleeding	76 (42.7)	3 (1.7)	70 (39.1)	3 (1.7)	20 (11.8)	0
Major bleeding[a]	5 (2.8)[b]	3 (1.7)	3 (1.7)[c]	3 (1.7)	2 (1.2)[d]	0
Infections	123 (69.1)	37 (20.8)	117 (65.4)	25 (14.0)	74 (43.8)	14 (8.3)
Second primary malignancies, excluding NMSC	10 (5.6)[e]	6 (3.4)	5 (2.8)[f]	2 (1.1)	3 (1.8)[g]	2 (1.2)

There were no reported events of ventricular tachyarrhythmias
[a]Defined as any serious or grade ≥3 hemorrhagic event, or any grade hemorrhagic event in the central nervous system. [b]Includes gastric ulcer hemorrhage, gastrointestinal hemorrhage, hematemesis, postprocedural hemorrhage, and subdural hemorrhage. [c]Includes hemarthrosis, postprocedural hematoma, and retinal hemorrhage. [d]Includes subdural hemorrhage and hemoptysis. [e]Includes non-small cell lung cancer (n=2), squamous cell carcinoma (n=2), basosquamous carcinoma, bladder transitional cell carcinoma, breast cancer, gastric cancer stage IV, metastases to bone, prostate cancer, and renal cell carcinoma (all n=1). [f]Includes prostate cancer (n=2), glioblastoma, malignant melanoma in situ, transitional cell carcinoma (all n=1). [g]Includes prostate cancer, acute myelomonocytic leukemia, and lung adenocarcinoma (all n=1)
NMSC, nonmelanoma skin cancer

Sharman et al. ASH 2019. Abstract 31. NCT02475681.

VENETOCLAX/OBINUTUZUMAB

CLL14 Trial Design

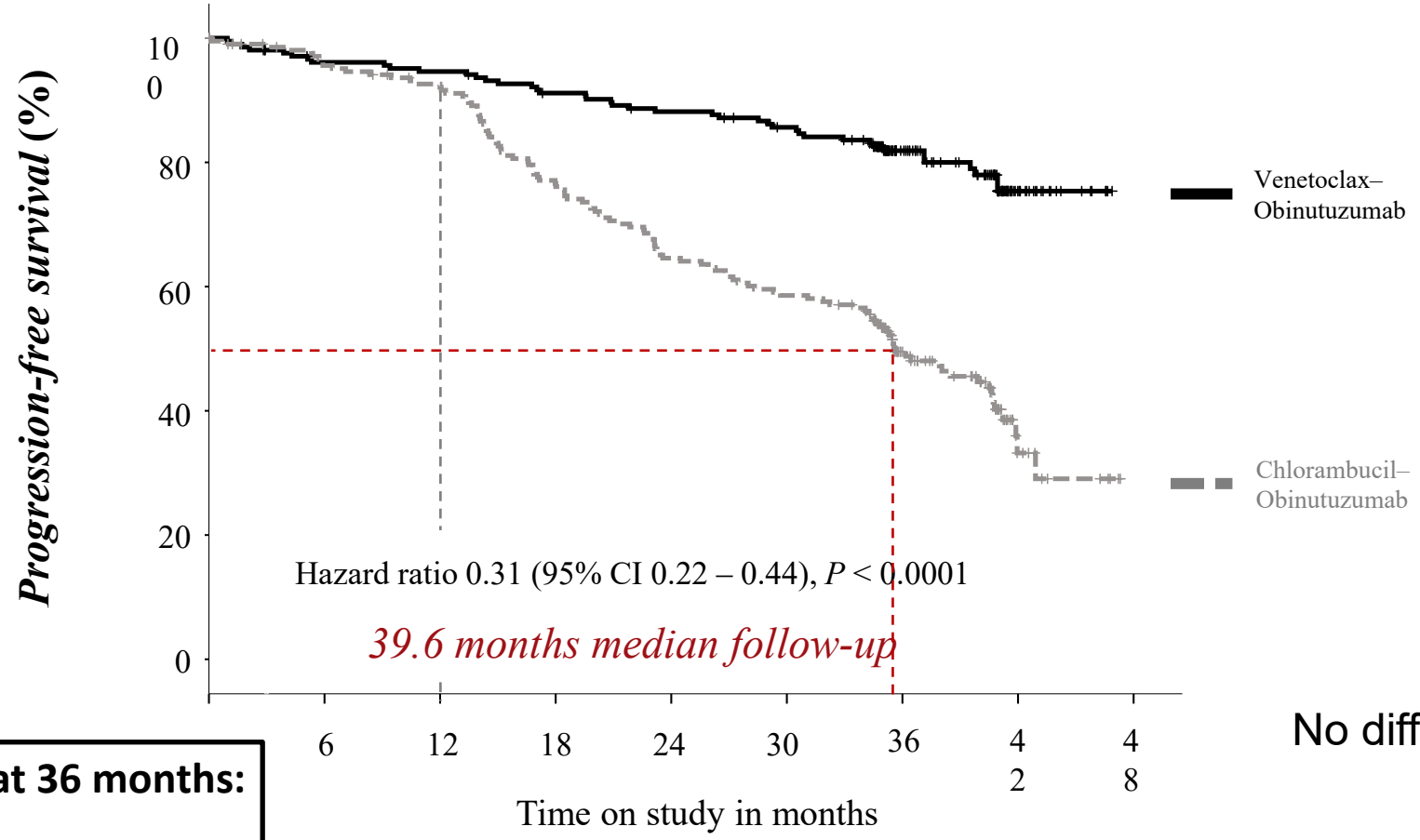


* Fischer K et al. Venetoclax and Obinutuzumab in chronic lymphocytic leukemia, Blood 11 May 2017

Fischer et al. N Engl J Med. 2019 Jun 6;380(23):2225-2236

Fischer et al. ASH 2019. Abstract 36. NCT02242942.

VO improves PFS compared to chlorambucil based treatment



PFS at 36 months:

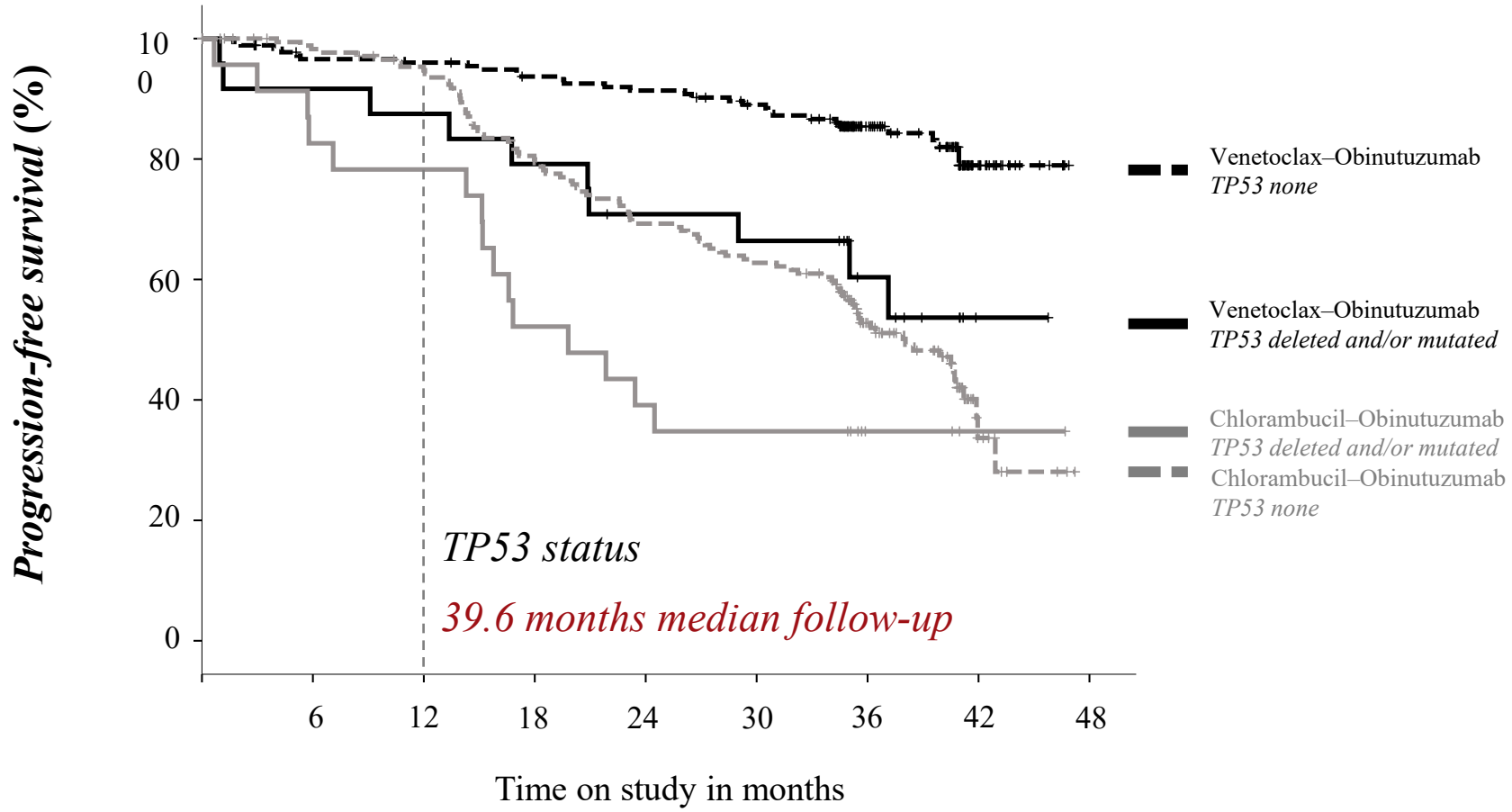
VO: 82%

Chlorambucil: 50%

No difference in OS

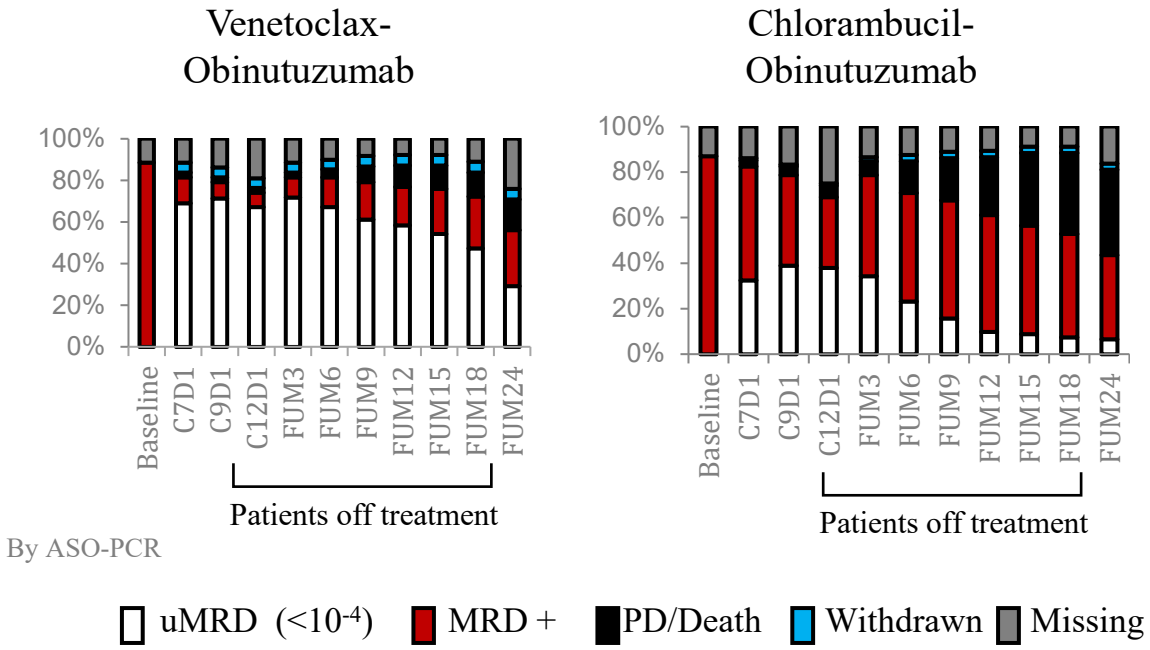
Fischer et al. ASH 2019. Abstract 36. NCT02242942.

Patients with TP53 mutations/deletions have inferior PFS

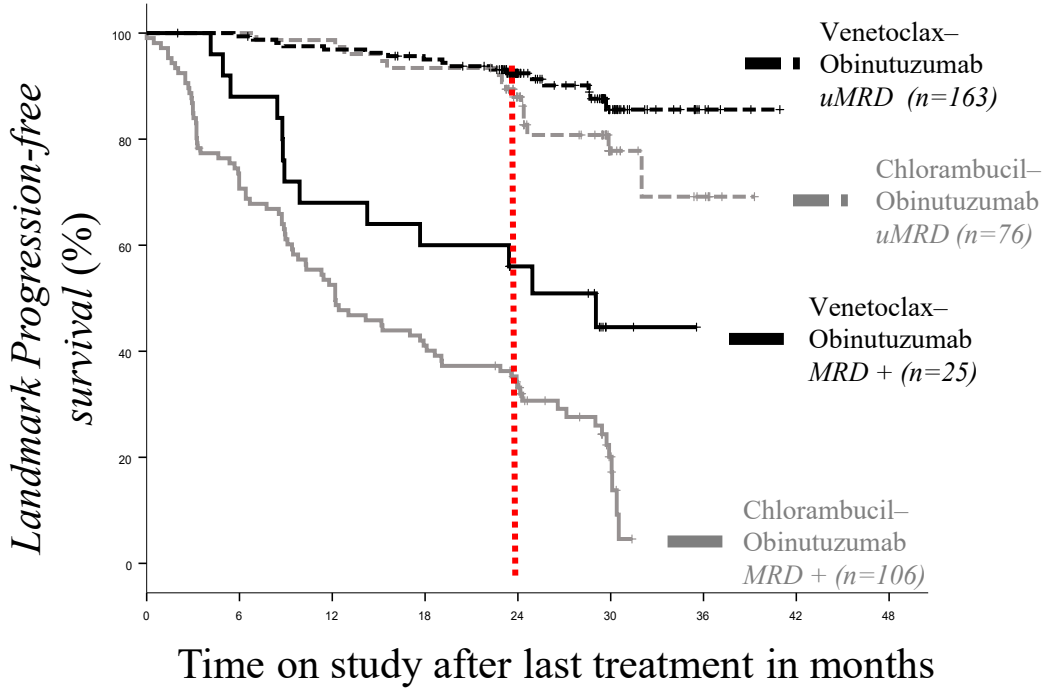


Fischer et al. ASH 2019. Abstract 36. NCT02242942.

MRD Rates and Effect on PFS



uMRD 76% (PB), 57% (BM) 3 mo after treatment (Concordance 86.8%)



Fischer et al. ASH 2019. Abstract 36. NCT02242942.

FIXED-DURATION *venetoclax and obinutuzumab …*

…continues to provide a superior outcome compared with chlorambucil and obinutuzumab

- regarding **PFS** across all relevant subgroups (including the IGHV mutated subgroup)
- but no difference in OS yet observed

…achieves high rates of undetectable MRD at EOT

- translating into sustained PFS benefits
- with more than 90% of these patients showing durable responses 24 months after EOT that appear to be sustained beyond this
- confirming the prognostic value of MRD in targeted combination therapy

Fischer et al. ASH 2019. Abstract 36. NCT02242942.

Previously Treated

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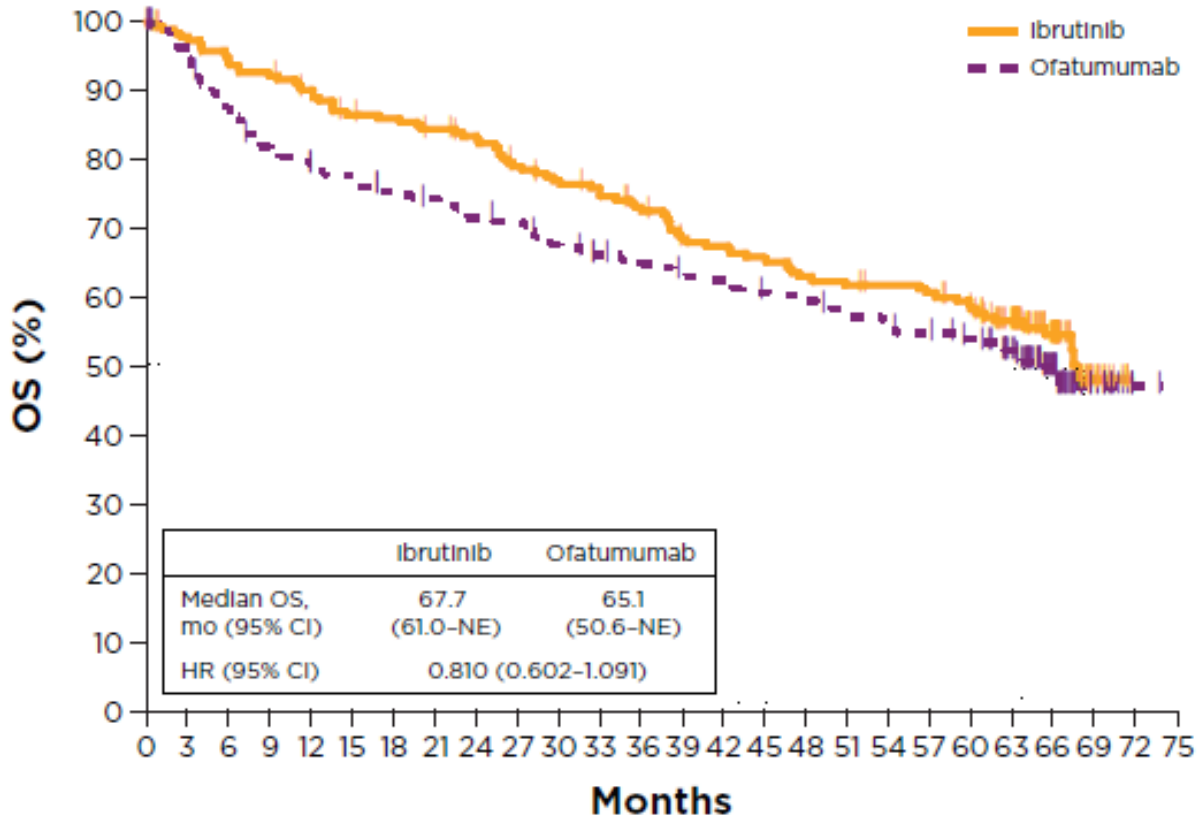
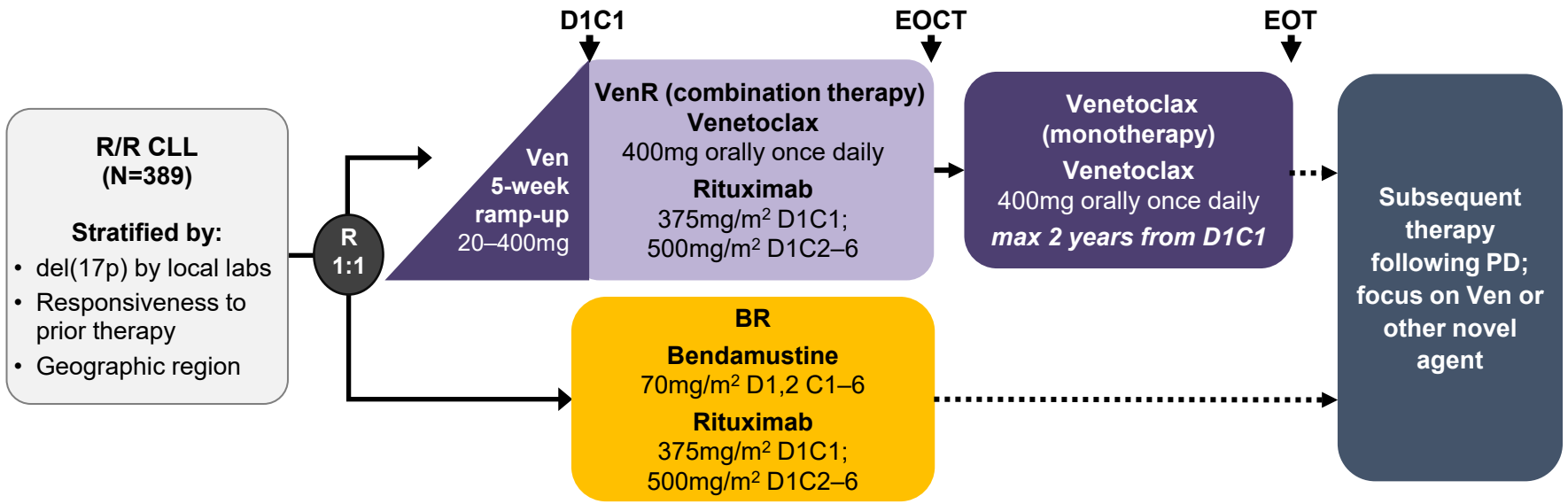
Final analysis from RESONATE: Six-year follow-up in previously treated CLL/SLL on ibrutinib: OS



- Median OS was 67.7 months in the ibrutinib arm and 65.1 months in the ofatumumab arm, without censoring or adjustment for crossover from ofatumumab to ibrutinib
- (HR: 0.810; 95% CI: 0.602–1.091)

RESONATE PCYC-1112; Munir et al, Am J Hematol 2019

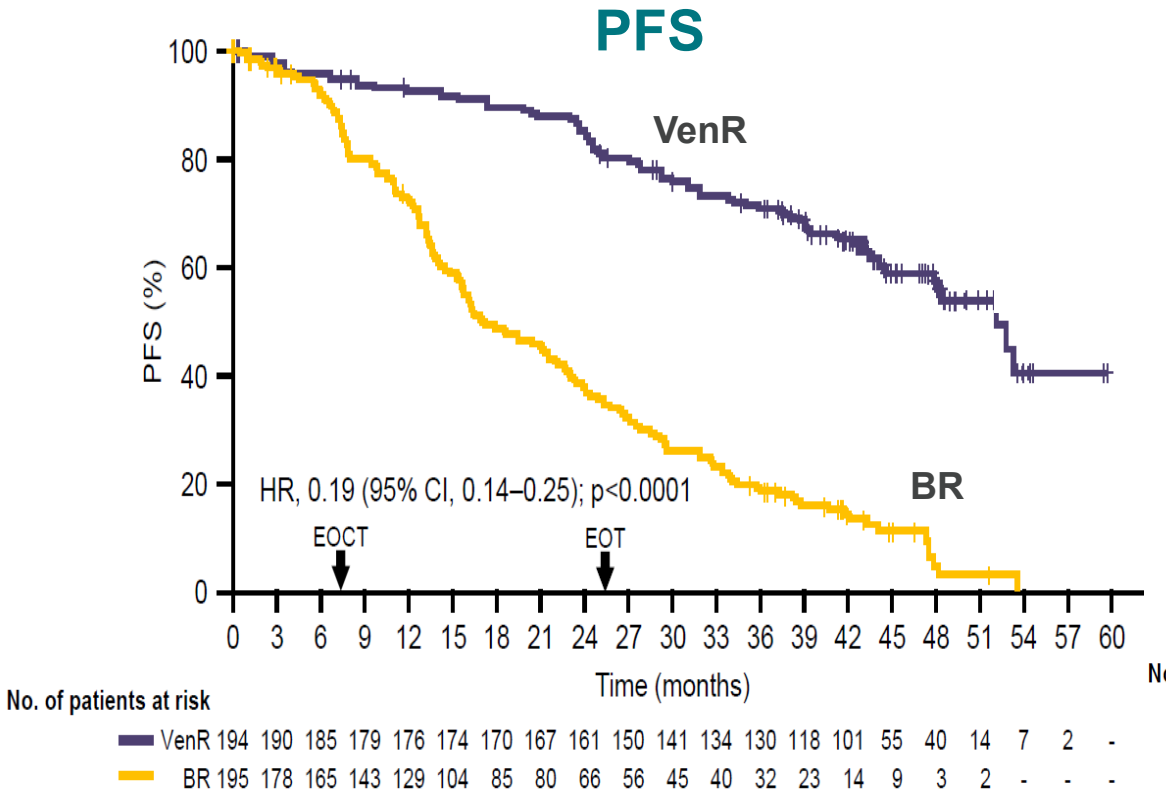
MURANO study design

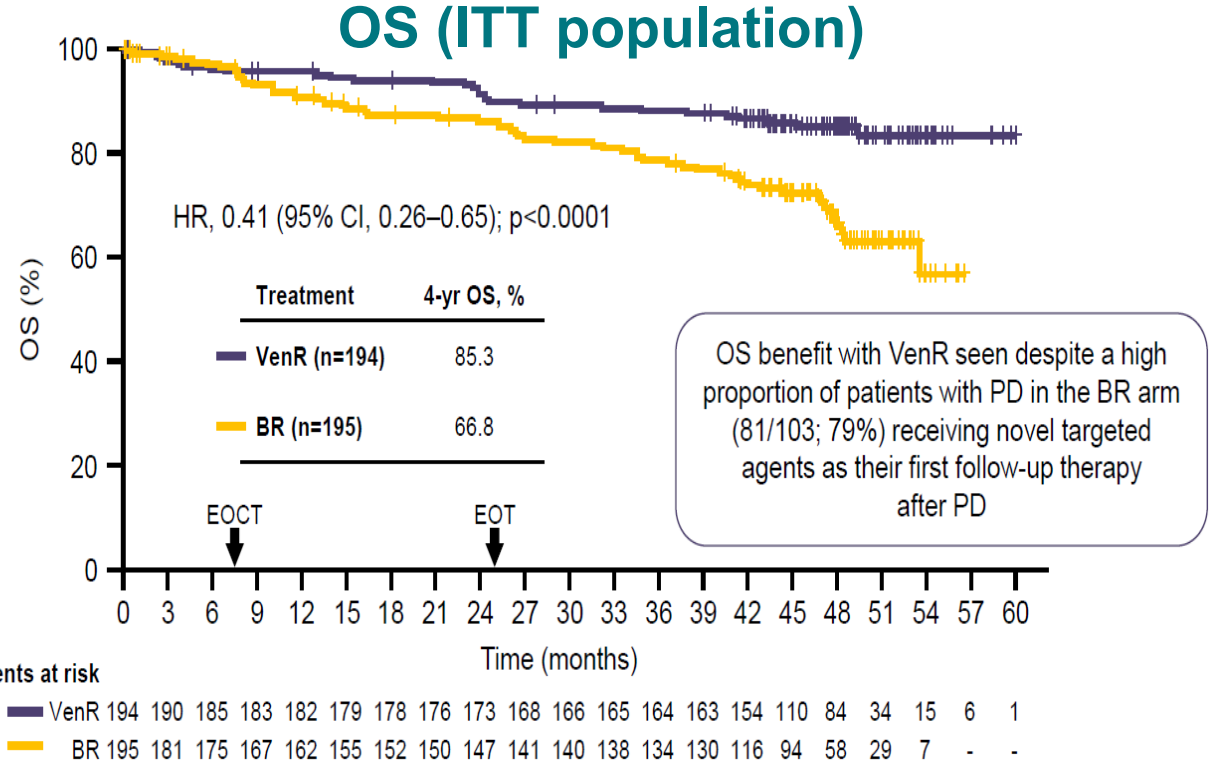


- **Primary endpoint:** investigator-assessed PFS
- **Secondary endpoint:** rates of clearance of MRD
- Clinical response and MRD* in PB during Ven monotherapy and follow-up visits were assessed every 3 months for 3 years, then every 6 months thereafter, or until PD

Seymour, et al ASH 2019 Abstract 355.

Four-year analysis of venetoclax-rituximab (VenR) vs bendamustine-rituximab (BR) in R/R CLL (MURANO)



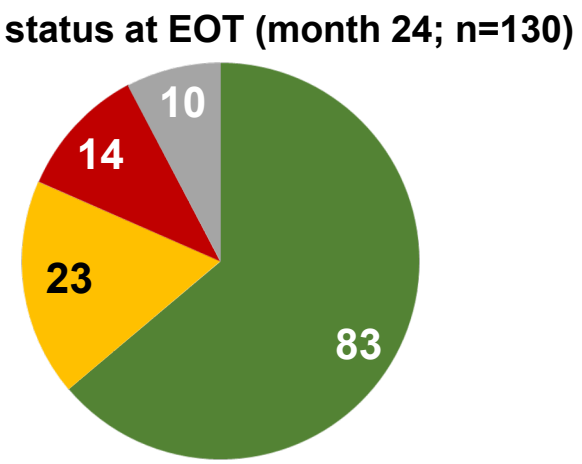


Treatment	4-year PFS, % (95% CI)
VenR (n=194)	57.3 (49.4-65.3)
BR (n=195)	4.6 (0.1-9.2)

Seymour et al., ASH 2019; abstract 355

Most patients had uMRD in PB upon completion of Ven monotherapy (EOT)

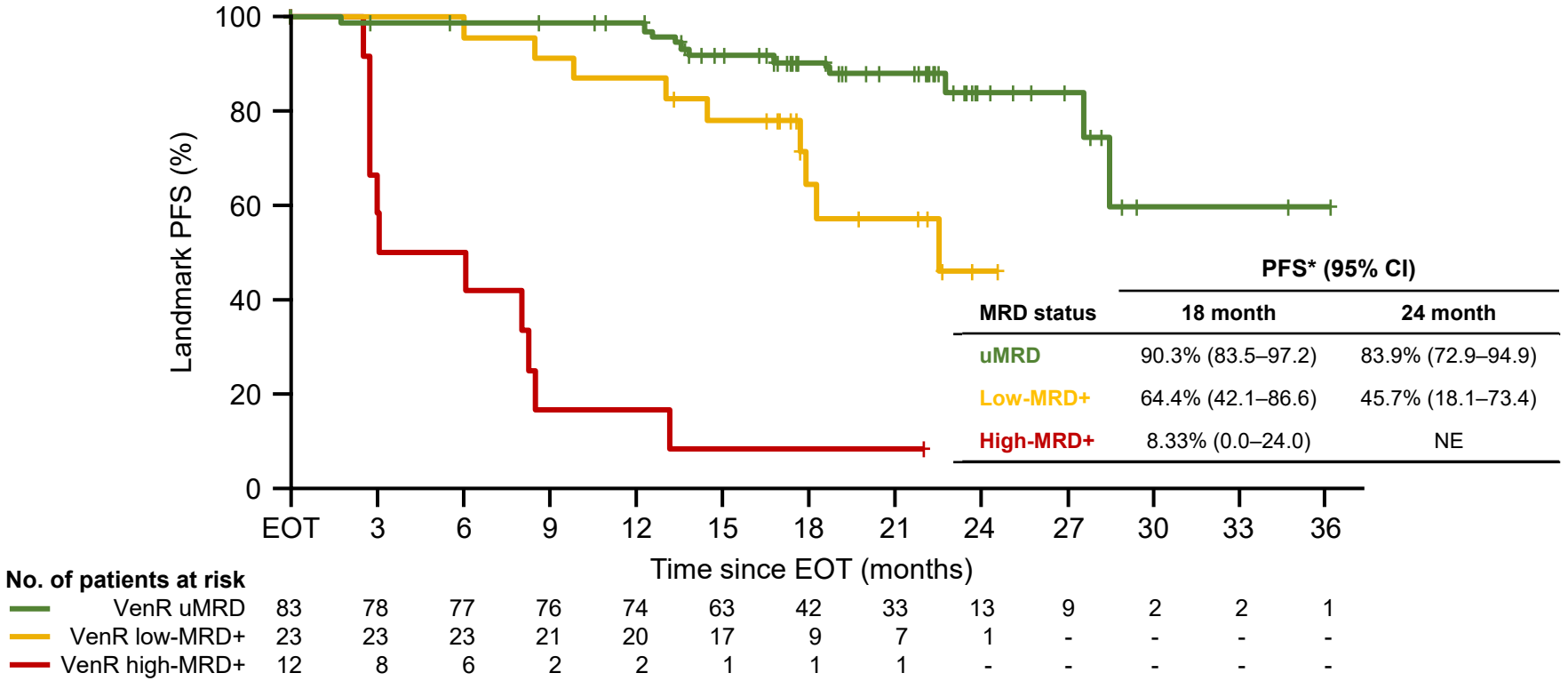
- In total, 130/194 patients completed 2 years of Ven therapy
- With a median 22 months off therapy (range 1–25 months), **35 progression events had occurred in 130 patients who completed 2 years of Ven**



Status off-therapy, n (%)	uMRD ($<10^{-4}$) n=83	Low-MRD+ (10^{-4}–10^{-2}) n=23	High-MRD+ ($>10^{-2}$) n=14	Unknown n=10
Progression-free	72 (86.7)	14 (60.9)	1 (7.1)	8 (80.0)
PD	11 (13.3)	9 (39.1)	13 (92.9)	2 (20.0)

Seymour, et al ASH 2019 Abstract 355.

PFS was longest in patients in the VenR arm with uMRD at EOT

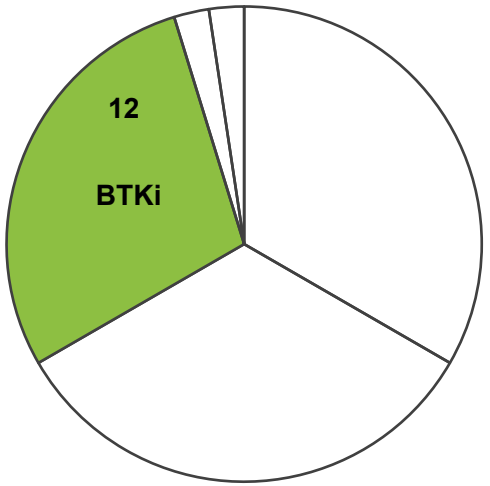


	PFS* (95% CI)	
MRD status	18 month	24 month
uMRD	90.3% (83.5–97.2)	83.9% (72.9–94.9)
Low-MRD+	64.4% (42.1–86.6)	45.7% (18.1–73.4)
High-MRD+	8.33% (0.0–24.0)	NE

Seymour, et al ASH 2019 Abstract 355.

Ibrutinib post venetoclax

- 12 patients treated with ibrutinib after venetoclax:
  - 9/12 patients completed MURANO therapy regimen
  - 2/12 discontinued treatment early due to AE, but had meaningful treatment-free intervals of 857 and 874 days
  - 1/12 progressed on active venetoclax therapy



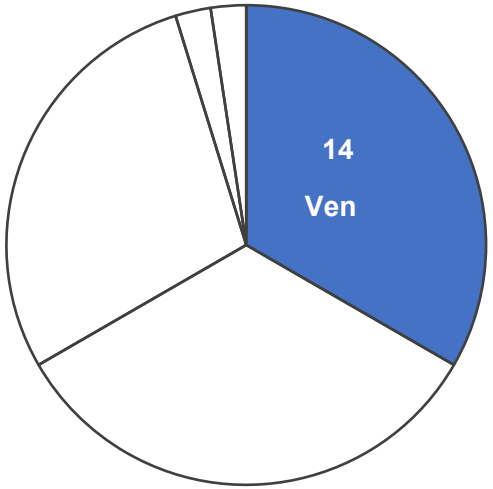
Time on Ibr	Best response to Ibr	Reason for discontinuation
190*	PR	
215	PR	New treatment (idelalisib + R)
250	Not available	Death (PD)
359*	PR	
364*	PR	
374*	PR	
431*	PR	
458	PR	Death (PD)
470*	PR	
665*	CR	
683*	Not available	
1304	PR	PD

Response rate Ibr post-Ven:
10/10 (100%)
(in evaluable patients)

Seymour, et al ASH 2019 Abstract 355.

Venetoclax re-treatment after trial

- 14 patients treated with venetoclax post trial
  - 13/14 patients completed MURANO therapy regimen
  - 1/14 discontinued treatment early
  - 4/14 achieved CR as best response on MURANO



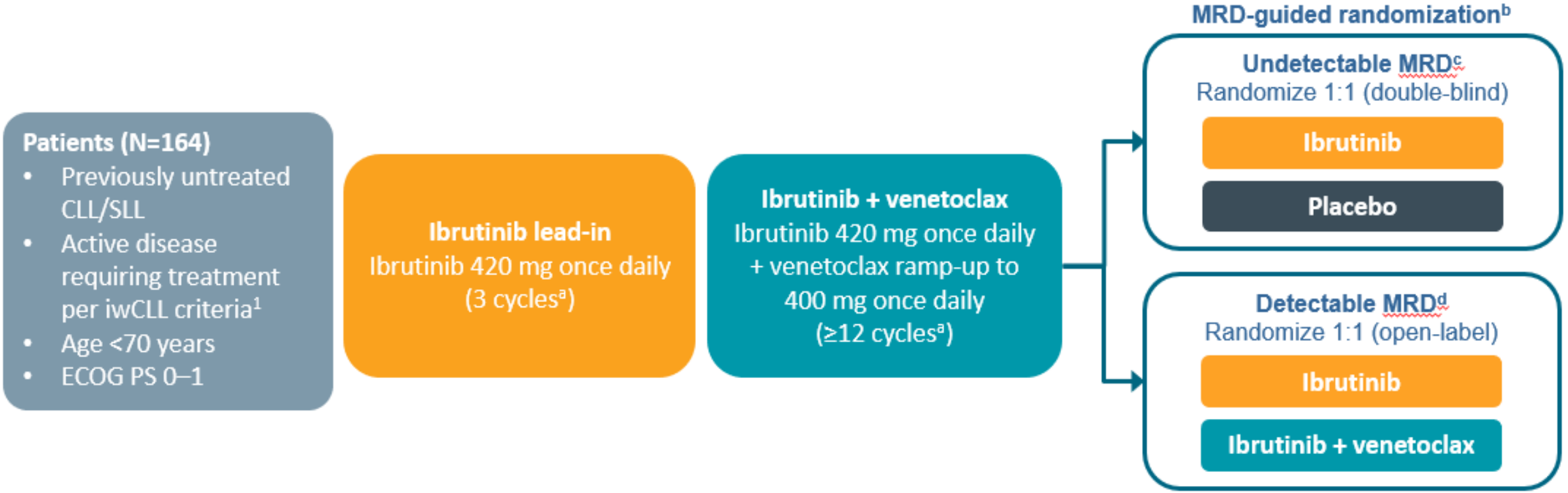
	Time on Ven-based regimen	Best response to Ven-based regimen	Reason for discontinuation
Ven	20	NR	Grade 3 diarrhea
	281*	Not available	
	504	PR	PD
VenR	221*	PR	
	59	PR	New treatment (Ibr)
Ven + Ibr	867*	PR	
VenR (MURANO regimen)	49	PD	Death (PD)
	160*	Not available	
	175*	Not available	
	243	PD	PD
	252*	PR	
	259*	PR	
	261*	SD	
	270*	SD	

Response rate Ven post-Ven: 6/11 (55%) (in evaluable patients)

Seymour, et al ASH 2019 Abstract 355.

Combination Regimens

Ibrutinib plus venetoclax: Phase 2 CAPTIVATE

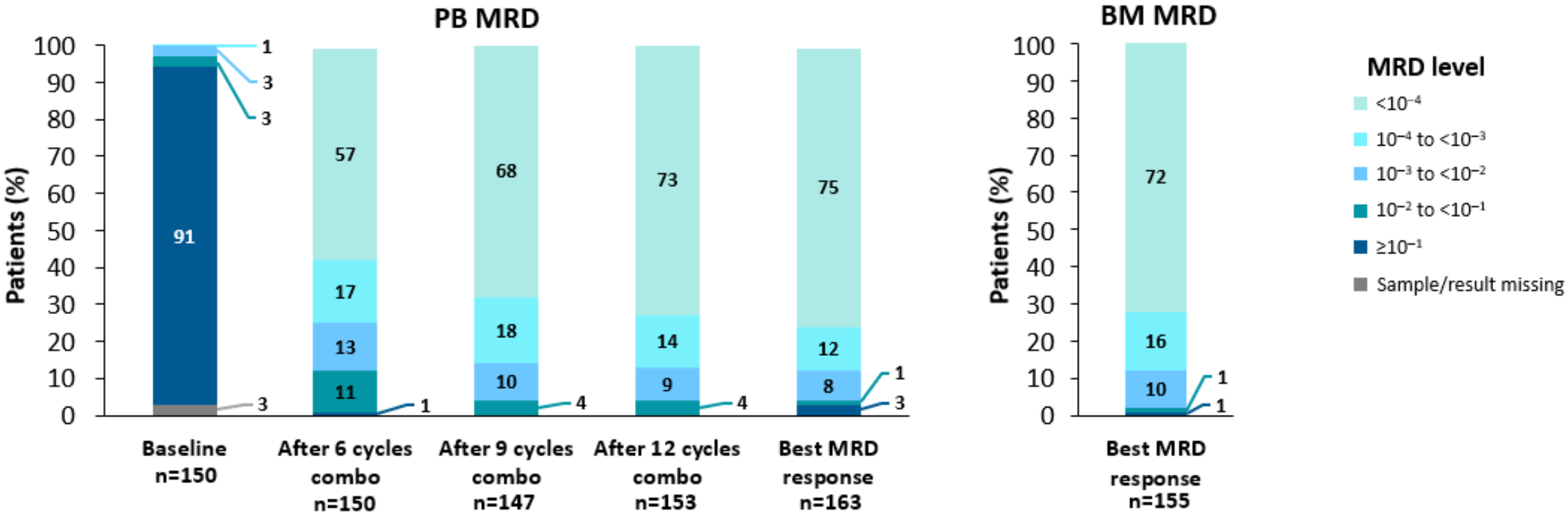


- **Results presented for pre-randomization phase of the CAPTIVATE MRD cohort (N=164) with 12 cycles of ibrutinib + venetoclax prior to MRD-guided randomization**
- **Time-limited therapy with 12 cycles of ibrutinib + venetoclax to be evaluated in a separate fixed-duration cohort (N=159)**

Tam et al., ASH 2019; abstract 35

Ibrutinib plus venetoclax: MRD cohort of CAPTIVATE

High Rates of Undetectable MRD[a] Sustained Over Time in MRD Evaluable Patients



- **Proportion of patients with undetectable MRD in PB increased over the course of combination therapy**

With the notable high rates (72%) of undetectable MRD in the bone marrow, ibrutinib + venetoclax may offer potent synergistic antitumor activity via mobilization and clearance of CLL cells from protective niches and disease compartments beyond peripheral blood

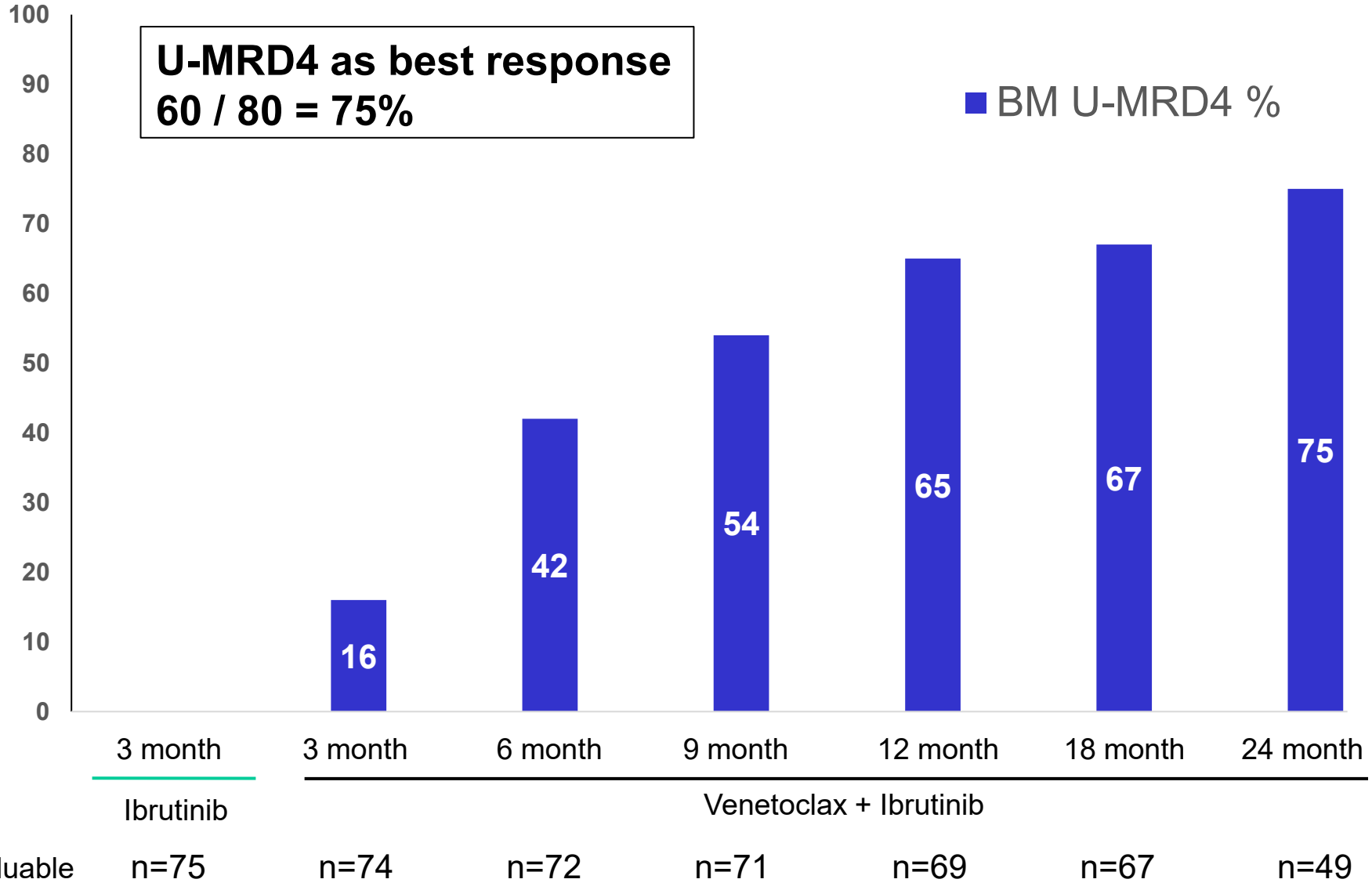
Tam et al., ASH 2019; abstract 35

Combined Ibrutinib and Venetoclax for First-Line Treatment for Patients with Chronic Lymphocytic Leukemia (CLL)

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

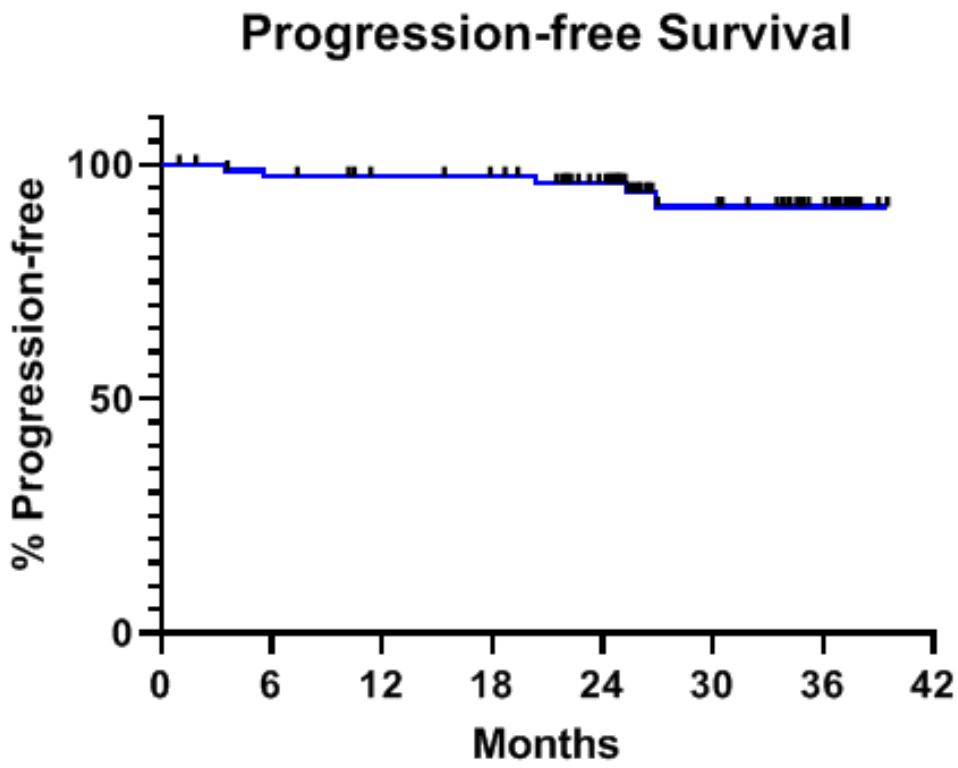
Jain et al., ASH 2019; abstract 34

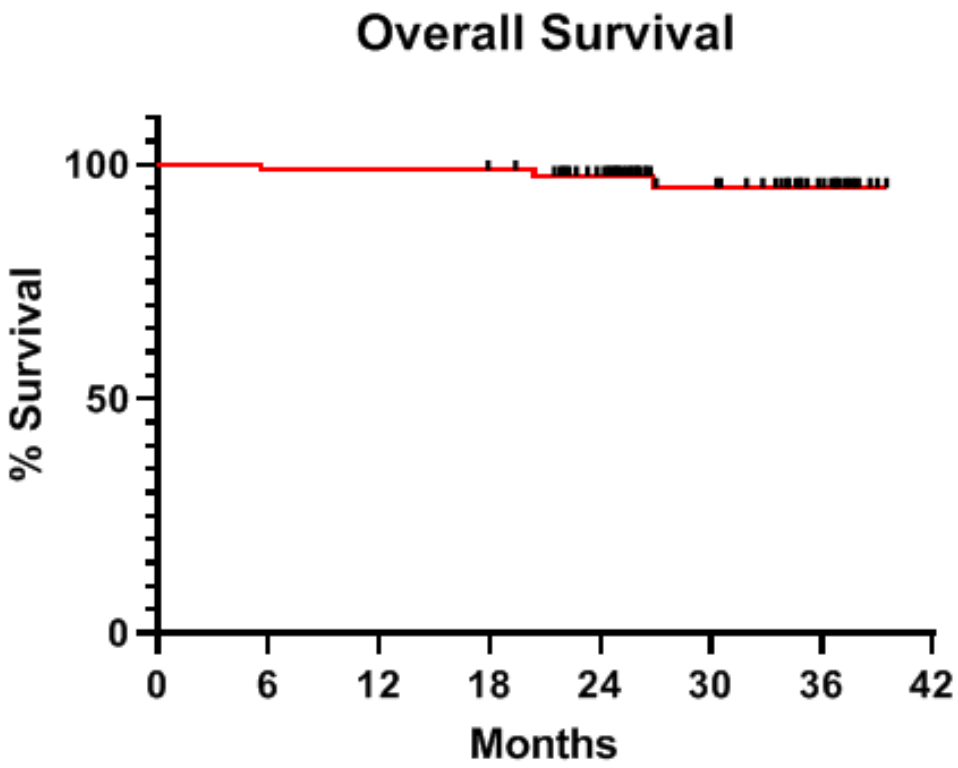
BM MRD4 Responses at Serial Time-Points



Jain et al., ASH 2019; abstract 34

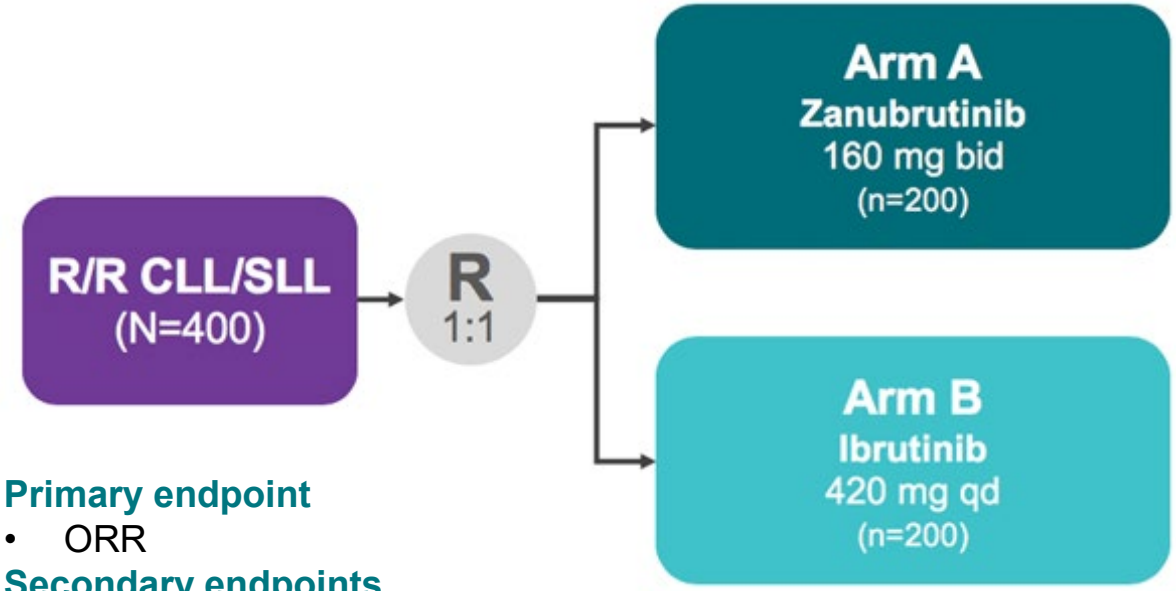
Ibrutiniub + Venetoclax: PFS and OS





Jain et al., ASH 2019; abstract 34

Alpine: Phase 3 trial of zanubrutinib (BGB-3111) vs ibrutinib in patients with R/R CLL/SLL



Primary endpoint
- ORR

Secondary endpoints
- Progression-free survival (PFS)
- Duration of response
- Time to treatment failure
- Rate of partial response with lymphocytosis or higher by IRC
- Overall survival
- Quality of Life
- Safety

Exploratory endpoints
- Correlation between clinical outcomes and prognostic and predictive biomarkers
- Pharmacokinetic parameters

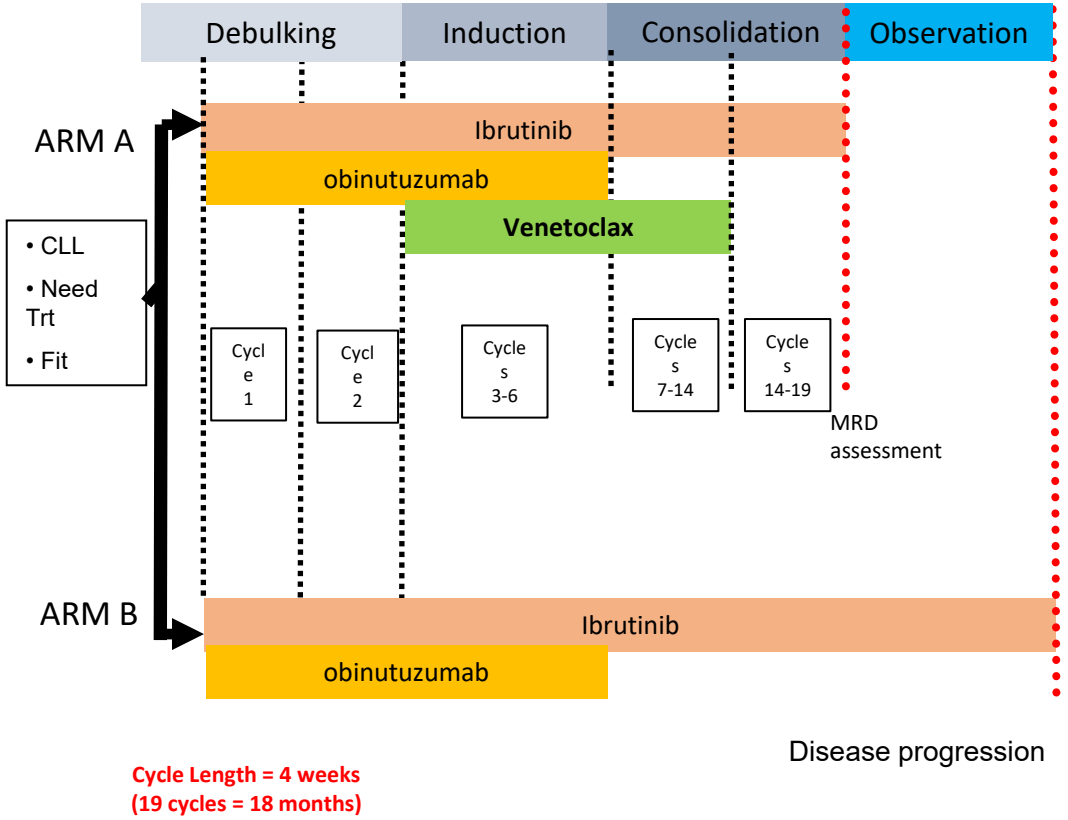
Key Inclusion Criteria	Key Exclusion Criteria
• CLL or SLL by iwCLL criteria requiring treatment • R/R to ≥1 prior systemic therapy for CLL/SLL[a] • Measurable lymphadenopathy by CT or MRI • Age ≥18 years • ECOG PS 0-2 • Adequate BM function[b] • Adequate organ function	• Known prolymphocytic leukemia • Current or past Richter transformation • History of severe bleeding • Prior treatment with a BTK inhibitor • Known infection with HIV • Active HBV or HCV • Clinically significant cardiovascular disease

BM, bone marrow; BTK, Bruton tyrosine kinase; CLL, chronic lymphocytic leukemia; CT, computed tomography; ECOG PS, Eastern Cooperative Oncology Group performance status; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; iwCLL, International Workshop on CLL; MRI, magnetic resonance imaging; R/R, relapsed/refractory; SLL, small lymphocytic lymphoma.
[a]A line of therapy is defined as completing ≥2 cycles of treatment of standard regimen according to current guidelines or of an investigational regimen on a clinical trial.
[b]Absolute neutrophil count ≥1000/μL and platelets ≥75,000/μL (≥750/μL and ≥50,000/μL, respectively, in patients with BM involvement).

The study opened to accrual in November 2018 and is recruiting patients from sites in 15 countries

Hillmen et al., ASH 2019; abstract 4307

EA9161 Trial



Primary endpoint:

- PFS

Secondary endpoint:

- MRD neg rates
- Time off therapy
- Clonal evolution
- Ibrutinib resist
- Richter's transformation
- Cost
- QOL

Current Accrual: 307

NCT03701282

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