First-line therapy for adult and elderly patients

Luca Laurenti Fondazione Policlinico A Gemelli IRCCS

COACHES
Current Opinions, Advances, Controversies in HEmatology in Salerno

Updates in **Chronic Lymphocytic Leukemia** and **Lymphomas**

Salerno | **14 aprile 2025** | Grand Hotel Salerno

Disclosures of Luca Laurenti

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
Abbvie	X				X	X	
AstraZeneca	X				X	X	
Beigene					X	X	
Johnson & Johnson					X	X	
Lilly						X	

ESMO GUIDELINE 2024

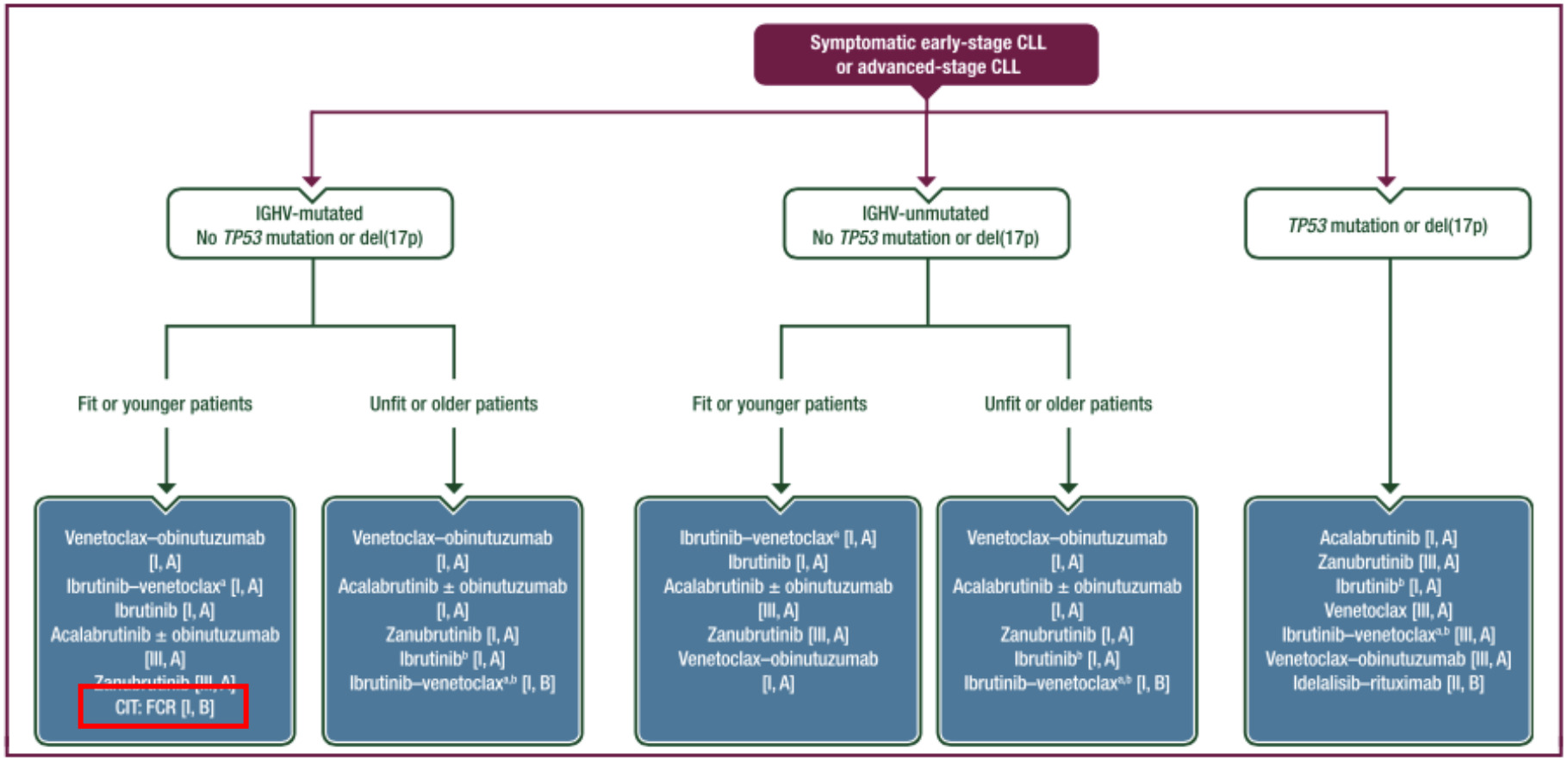


Figure 1. First-line therapy.

The order of the recommended treatments for each subgroup is based on the authors' expert opinion, which considers time-limited therapy as more valuable, if there is equal evidence for different treatment options.

Purple: algorithm title; blue: systemic anticancer therapy or their combination; white: other aspects of management and non-treatment aspects.

CIT, chemoimmunotherapy; CLL, chronic lymphocytic leukaemia; del, deletion; FCR, fludarabine–cyclophosphamide–rituximab; IGHV, immunoglobulin heavy chain variable; MRD, minimal residual disease.

[a]Ibrutinib–venetoclax with a 15-month fixed duration or with an MRD-guided duration.

[b]Ibrutinib or ibrutinib–venetoclax should be considered carefully in older patients with cardiac comorbidities.

Eichhorst B, Ghia P et al. Ann Oncol 2024

ESMO GUIDELINE 2024

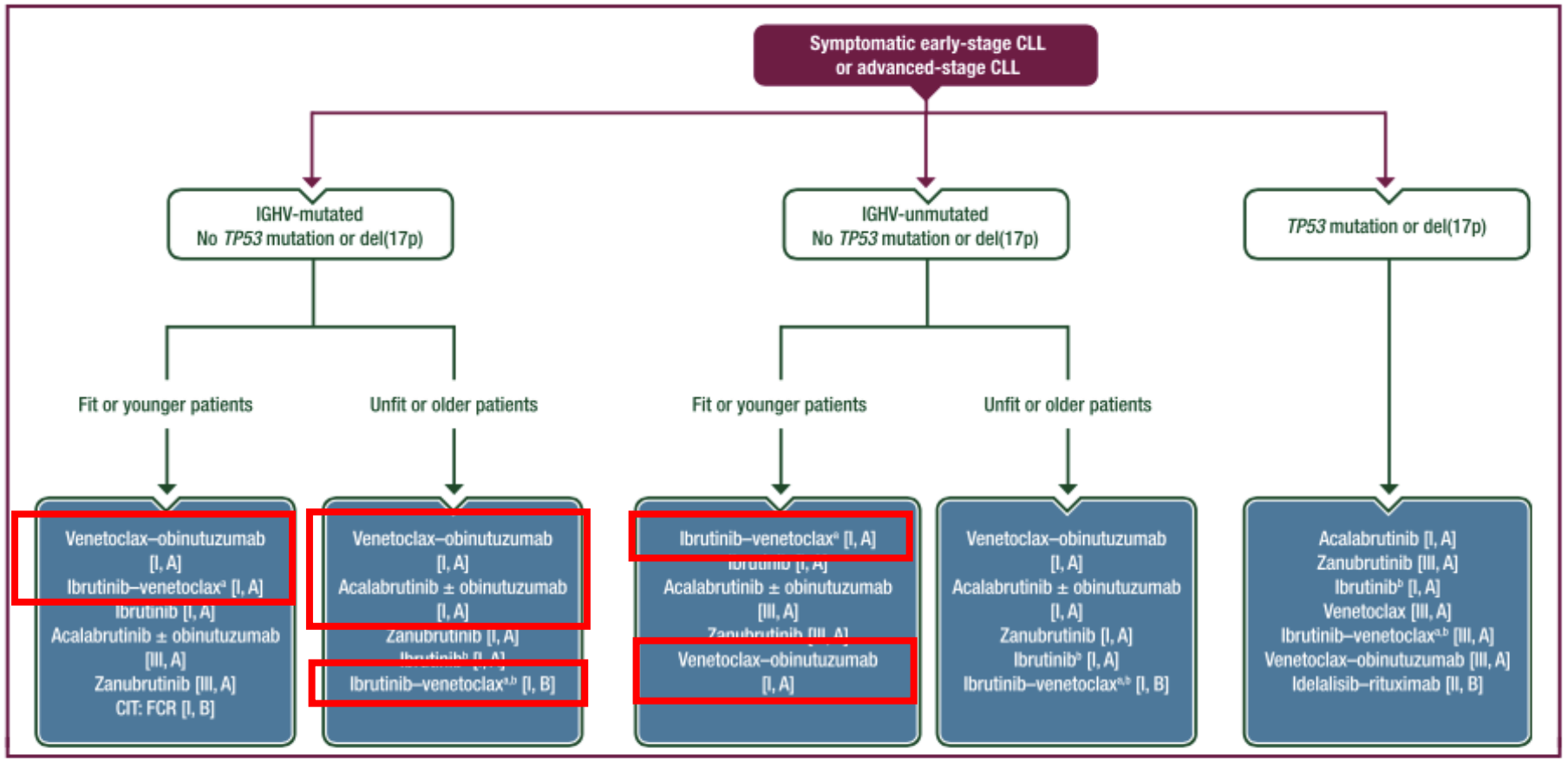
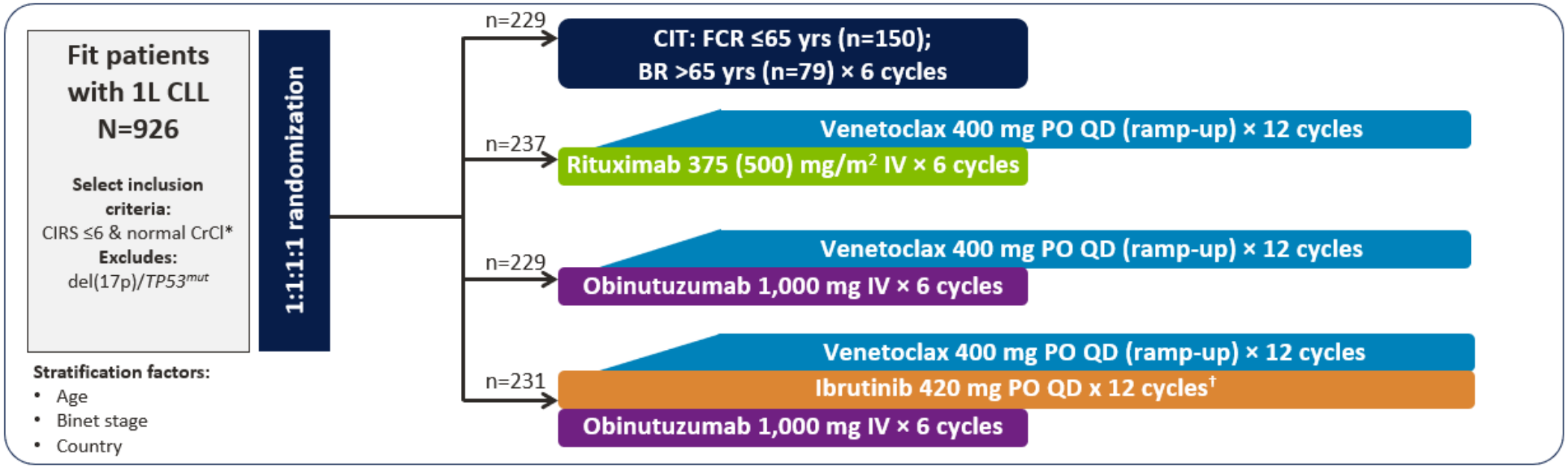


Figure 1. First-line therapy.
The order of the recommended treatments for each subgroup is based on the authors' expert opinion, which considers time-limited therapy as more valuable, if there is equal evidence for different treatment options.
Purple: algorithm title; blue: systemic anticancer therapy or their combination; white: other aspects of management and non-treatment aspects.
CIT, chemoimmunotherapy; CLL, chronic lymphocytic leukaemia; del, deletion; FCR, fludarabine–cyclophosphamide–rituximab; IGHV, immunoglobulin heavy chain variable; MRD, minimal residual disease.
[a]Ibrutinib–venetoclax with a 15-month fixed duration or with an MRD-guided duration.
[b]Ibrutinib or ibrutinib–venetoclax should be considered carefully in older patients with cardiac comorbidities.

Eichhorst B, Ghia P et al. Ann Oncol 2024

Study Design - GAIA Phase 3 Study



Co-Primary Endpoints:

- uMRD ($<10^{-4}$) in PB at month 15 (VenO vs CIT)
- PFS (IVO vs CIT)

Key Secondary Endpoints:

- MRD in PB at month 15 (all other comparisons)
- MRD in BM at final restaging
- PFS (all other comparisons)
- ORR
- CR/CRi rate
- Overall survival

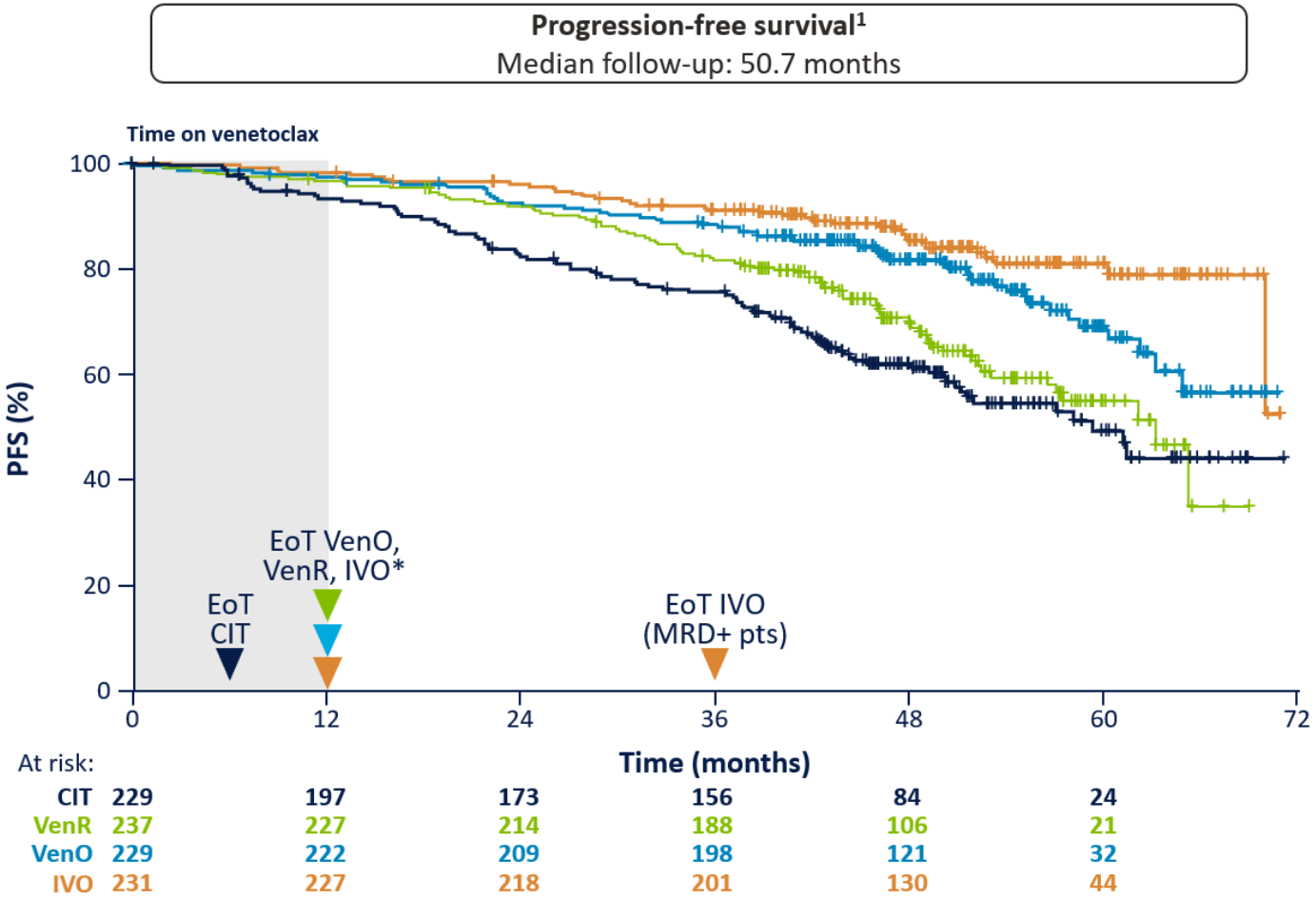
1. Eichhorst B, et al. Oral #71. 63rd ASH Annual Meeting and Exposition. December 11-14, 2021. Atlanta, GA.
2. ClinicalTrials.gov. NCT02950051. https://clinicaltrials.gov/ct2/show/NCT02950051

Baseline charateristics confirm fit population

Baseline characteristics (ITT)	CIT (n=229)*	VenR (n=237)	VenO (n=229)	IVO (n=231)	Total (N=926)
Median age, years (range)	61 (29–84) FCR: 55; BR: 71	62 (27–84)	62 (31–83)	60 (30–84)	61 (27–84)
Age >65 years, n (%)	79 (34.5)	85 (35.9)	82 (35.8)	83 (35.9)	329 (35.5)
Median CrCl[†,‡], mL/min (range)	86.3 (39.5–223.6)	84.5 (42.6–268.3)	86.3 (41.5–180.2)	86.2 (43.5–178.5)	85.7 (39.5–268.3)
Median CIRS score (range)	2 (0–6)	2 (0–7)	2 (0–6)	2 (0–7)	2 (0–7)
Male sex, n (%)	163 (71.2)	175 (73.8)	171 (74.7)	158 (68.4)	667 (72.0)
ECOG PS=0, n (%)	164 (71.6)	172 (72.6)	165 (72.1)	163 (70.6)	664 (71.7)
Cytogenetic subgroup, n (%)					
Deletion 11q	41 (17.9)	45 (19.0)	44 (19.2)	32 (13.9)	162 (17.5)
Trisomy 12	34 (14.8)	34 (14.3)	47 (20.5)	35 (15.2)	150 (16.2)
No abnormalities	53 (23.1)	45 (19.0)	44 (19.2)	59 (25.5)	201 (21.7)
Deletion 13q	101 (44.1)	113 (47.7)	94 (41.0)	105 (45.5)	413 (44.6)
IGHV mutational status, n (%)[†]					
Mutated	95 (41.5)	95 (40.1)	89 (39.0)	101 (43.7)	380 (41.1)
Unmutated	131 (57.2)	134 (56.5)	130 (57.0)	123 (53.2)	518 (56.0)
Not evaluable	3 (1.3)	8 (3.4)	9 (3.9)	7 (3.0)	27 (2.9)
Complex karyotype, n/total n (%)					
<3 aberrations	177/223 (79.4)	187/231 (81.0)	182/218 (83.5)	195/223 (87.9)	741/895 (82.8)
≥3 and <5 aberrations	30/223 (13.5)	34/231 (14.7)	25/218 (11.5)	21/223 (9.4)	110/895 (12.7)
≥5 aberrations	16/223 (7.2)	10/231 (4.3)	11/218 (5.0)	6/223 (2.7)	43/895 (4.8)

Eichhorst B, *et al. N Engl J Med* 2023; **388:**1739–1754 (incl. suppl)

Sustained PFS of Ven-based treatments vs CIT

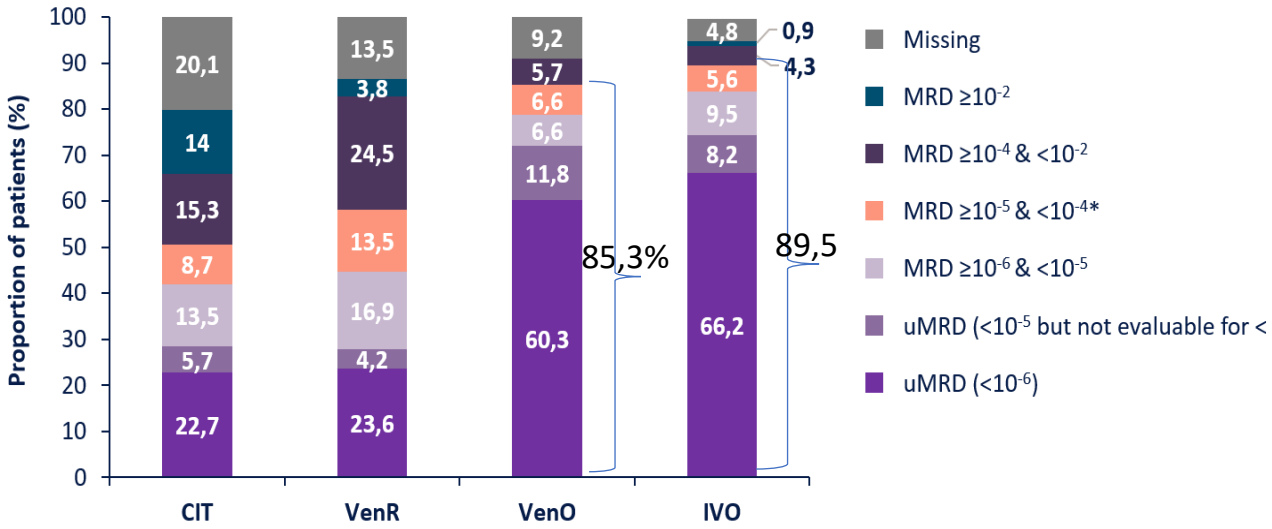


	CIT	VenR	VenO	IVO
HR vs CIT (97.5% CI) p-value[1]	–	0.78 (0.55–1.10) p=0.1	0.47 (0.32–0.69) p<0.001	0.30† (0.19–0.47) p<0.001
4-year PFS, %[1]	62.0	70.1	81.8	85.5
Median PFS, months[2]	52.0	52.3	NR	NR

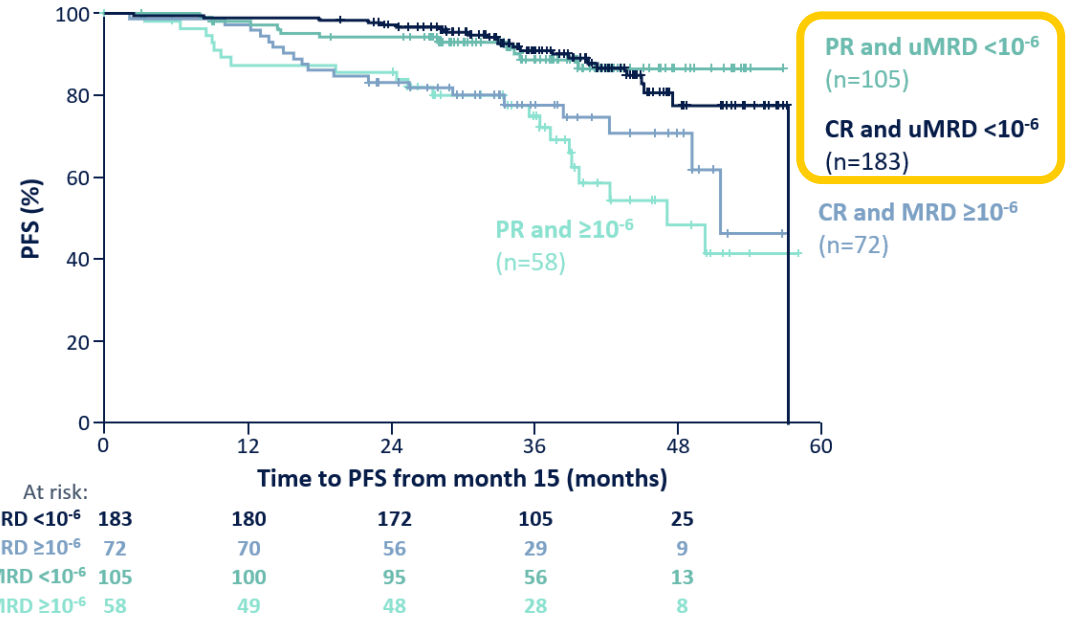
1. Fürstenau M, *et al.* ASH 2023. Abstract 635 (Oral); 2. Eichhorst B, *et al.* EHA 2022. Abstract LB2365 (Oral).

uMRD rates in PB by NGS at month 15

MRD rates by NGS in PB at month 15



PFS by MRD status* and response at month 15 in pooled IVO and VenO arms



* MRD assessed by NGS.

Fürstenau M, *et al.* ASH 2023. Abstract 635 (Oral).

Most common **Grade ≥3 TEAEs** and **AEs**

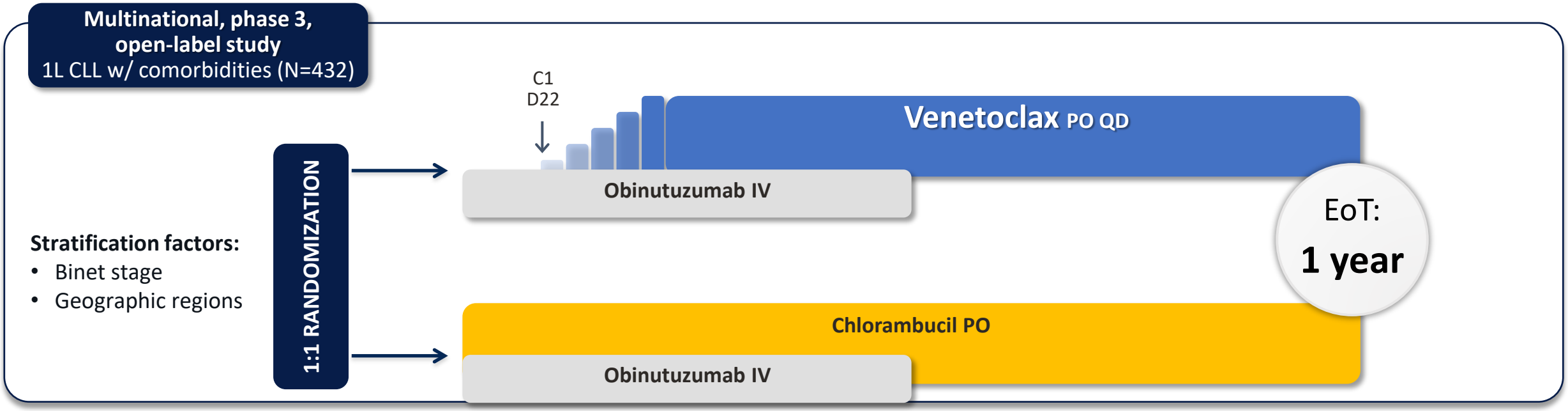
CTC Grade ≥3 AEs (≥5%) and AEs of interest	CIT (n=216)	VenR (n=237)	VenO (n=228)	IVO (n=231)	Total (N=912)
Anemia*	16 (7.4)	9 (3.8)	11 (4.8)	9 (3.9)	45 (4.9)
Neutropenia*	98 (45.4)	94 (39.7)	103 (45.2)	95 (41.1)	390 (42.8)
Thrombocytopenia*	18 (8.3)	8 (3.4)	34 (14.9)	26 (11.3)	86 (9.4)
Febrile neutropenia*	24 (11.1)	10 (4.2)	7 (3.1)	18 (7.8)	59 (6.5)
Infections†	40 (18.5)	25 (10.5)	30 (13.2)	49 (21.2)	144 (15.8)
TLS*,‡	9 (4.2)	24 (10.1)	19 (8.3)	15 (6.5)	67 (7.3)
Atrial fibrillation*	1 (0.5)	1 (0.4)	0 (0.0)	6 (2.6)	8 (0.9)
Infusion-related reaction*	12 (5.6)	19 (8.0)	26 (11.4)	10 (4.3)	67 (7.3)
Hypertension*	3 (1.4)	5 (2.1)	4 (1.8)	13 (5.6)	25 (2.7)
Pneumonia*	12 (5.6)	4 (1.7)	12 (5.3)	15 (6.5)	43 (4.7)

The **most common Grade ≥3 TEAEs** reported overall were **neutropenia** (42.8%), **infections** (15.8%), **thrombocytopenia** (9.4%), **TLS** (7.3%), **infusion-related reactions** (7.3%), and **febrile neutropenia** (6.5%)

No major differences observed in hematologic AEs among all four arms.
Grade ≥3 infections were more common with IVO and CIT vs VenO or VenR

Eichhorst B, *et al. N Engl J Med* 2023; **388:**1739–1754.

CLL-14



Primary endpoint (ITT population):

- PFS – investigator assessed

Key secondary endpoints (ITT population):

- PFS – IRC assessed
- ORR and CR 3 months after EoT
- uMRD rate (PB and BM) 3 months after EoT
- OS

Key inclusion criteria

- Previously untreated CLL according to iwCLL criteria
- CIRS >6 and/or CrCl <70 mL/min

MRD was a secondary efficacy endpoint, not a determinant of treatment duration

Fischer K, *et al. N Engl J Med* 2019; **380:**2225–2236 (incl. appendix).

Characteristic	VenO (n=216)	OClb (n=216)
Median age, years	72	71
Binet stage, %		
A	21	20
B	35	37
C	44	43
Median total CIRS score	9 (0–23)	8 (1–28)
Median estimated CrCl, mL/min	65.2	67.4
TLS risk category, %		
Low	13	12
Intermediate	64	68
High	22	20
IGHV mutational status, %		
Unmutated	61	59
Mutated	38	40
Not evaluable	1	1
TP53^{mut} and/or del(17p), %	12	12
Cytogenetic subgroups, %		
Deletion in 17p	8	7
Deletion in 11q	17	18
Trisomy in 12	17	19
No abnormalities	24	20
Deletion in 13q alone	34	36

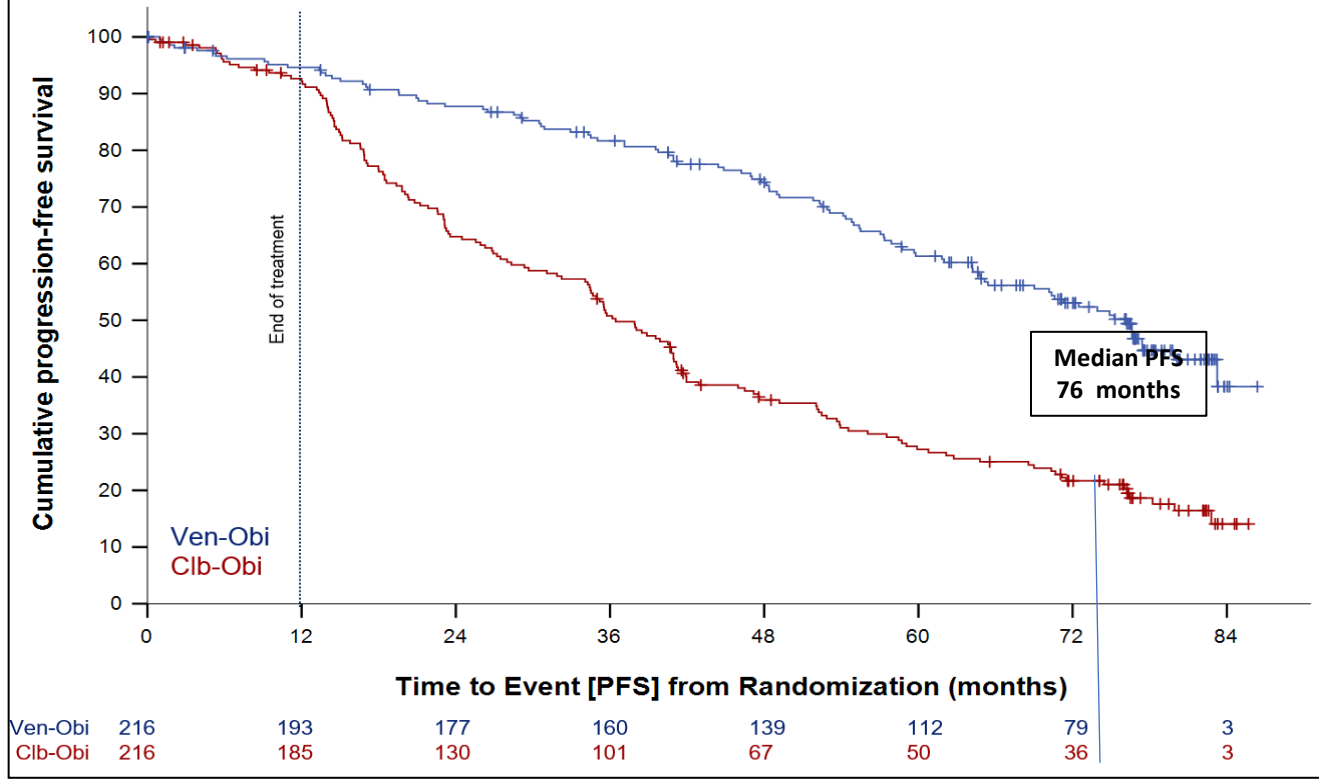
CIRS, cumulative illness rating scale; CrCl, creatinine clearance; OClb, obinutuzumab + chlorambucil; TLS, tumor lysis syndrome.

Al-Sawaf O, *et al. Lancet Oncol* 2020; **21**:1188–1200 (incl. suppl);
Al-Sawaf O, *et al.* EHA 2023. Abstract S145 (Oral).

Fixed duration Ven-Obi in TN – CLL14 @ 6-year follow-up

PROGRESSION-FREE SURVIVAL

Investigator-assessed PFS



Median PFS

Ven-Obi: 76.2 months

Clb-Obi: 36.4 months

6-year PFS rate

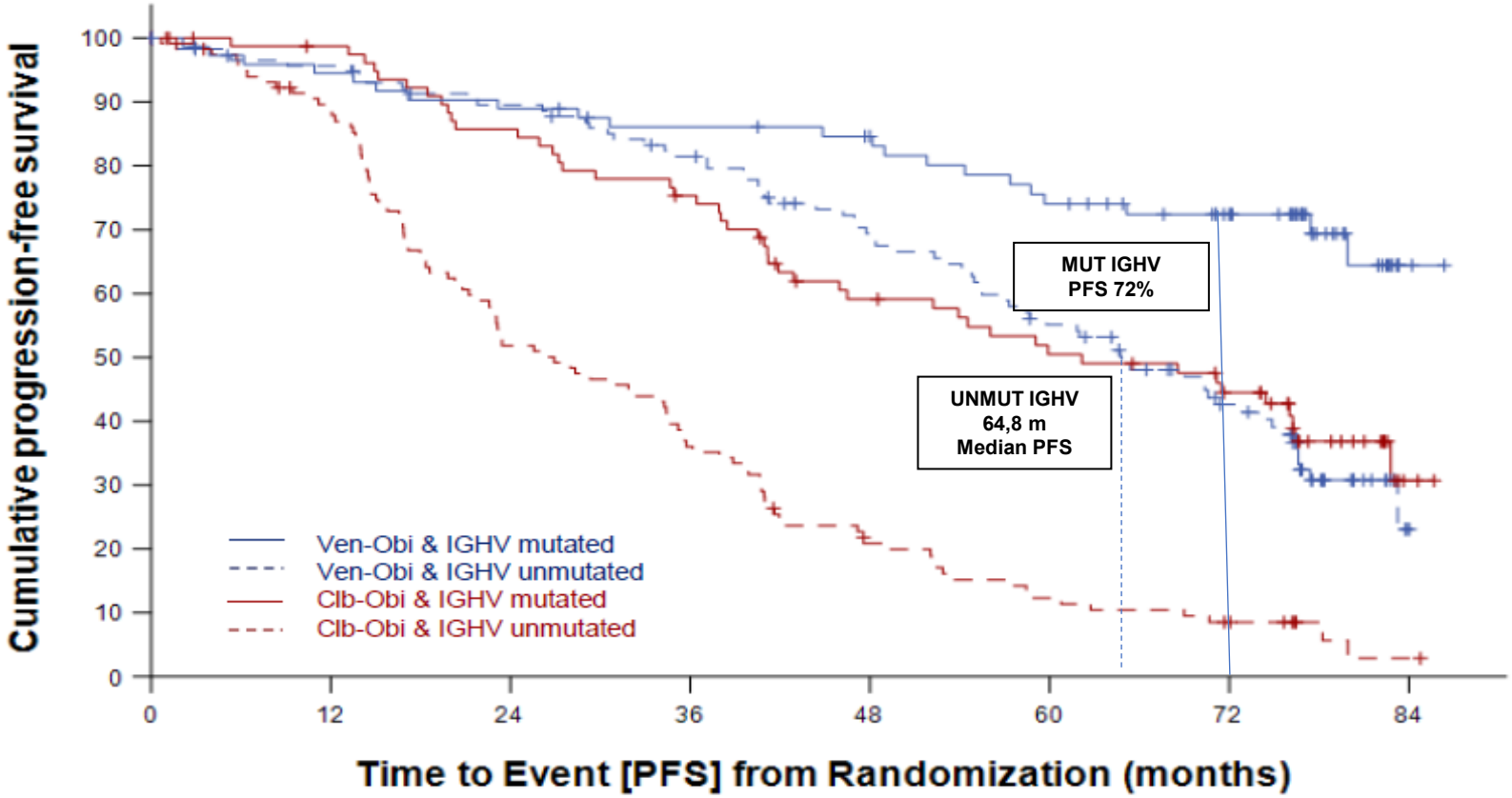
Ven-Obi: 53.1%

Clb-Obi: 21.7%

HR 0.40, 95% CI [0.31-0.52]
P<0.0001

Progression-Free Survival by IGHV status

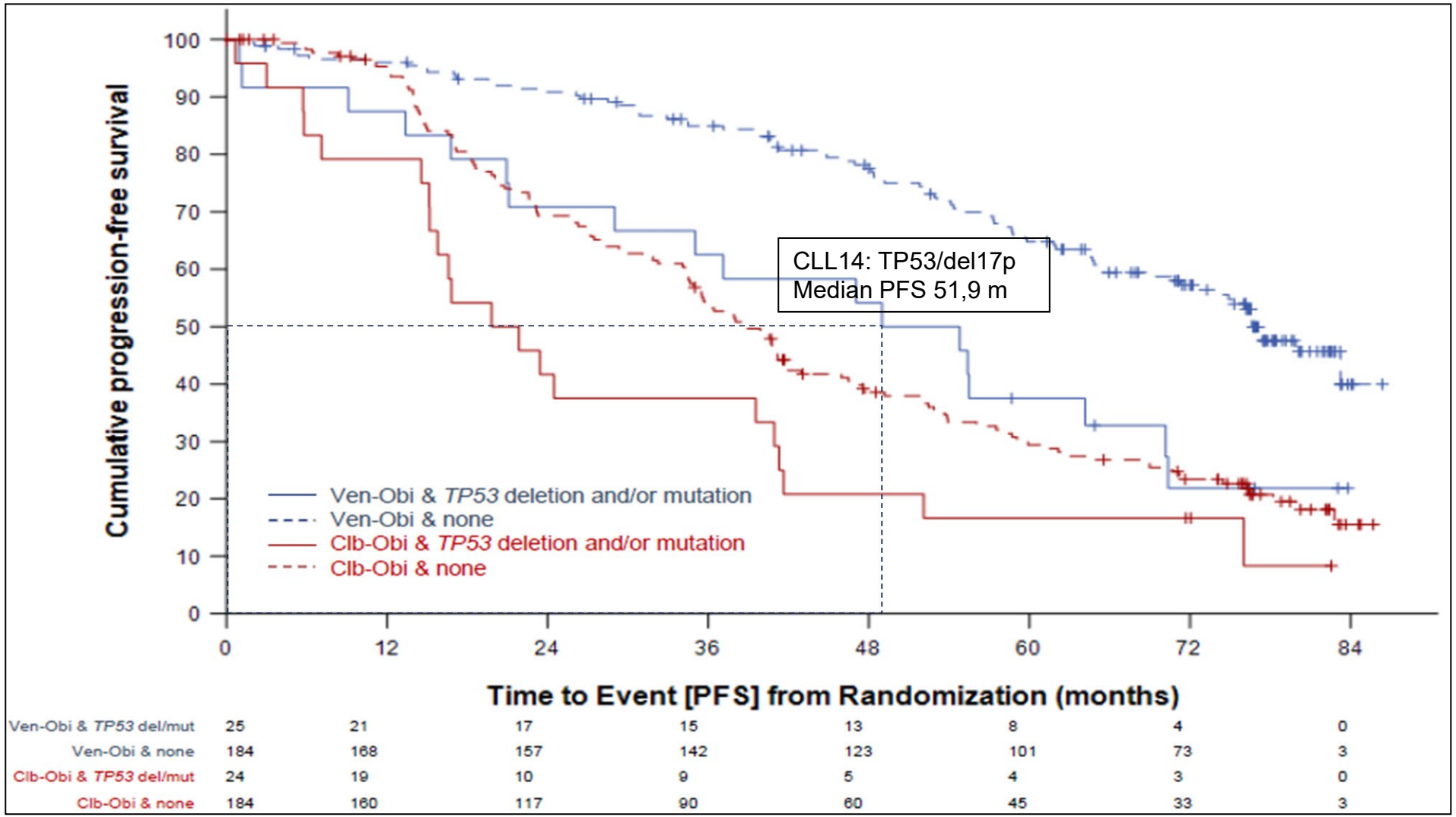
Fixed duration Ven-Obi in TN – CLL14 @ 6-year follow-up



Ven-Obi & IGHV mutated	76	68	64	60	57	49	39	2
Ven-Obi & IGHV unmutated	121	110	101	90	73	57	37	1
Clb-Obi & IGHV mutated	83	76	66	57	42	35	28	2
Clb-Obi & IGHV unmutated	123	101	59	41	22	13	8	1

Al-Sawaf O et al. EHA 2023

Progression-Free Survival by del17p/TP53



Ven-Obi & *TP53* del/mut	25	21	17	15	13	8	4	0
Ven-Obi & none	184	168	157	142	123	101	73	3
Clb-Obi & *TP53* del/mut	24	19	10	9	5	4	3	0
Clb-Obi & none	184	160	117	90	60	45	33	3

Most common Grade ≥3 adverse events during and after treatment

Rates of select Grade ≥3 AEs over time,* %[1]	VenO (N=212)		OClb (N=214)	
	During treatment†	After treatment*	During treatment	After treatment*
Neutropenia	**51.9**	**3.8**	**47.2**	**1.9**
Thrombocytopenia	14.2	0.5	15.0	0.0
Anemia	7.5	1.9	6.1	0.5
Febrile neutropenia	4.2	0.9	3.3	0.5
Leukopenia	2.4	0.0	4.7	0.0
Pneumonia	3.8	3.3	3.7	1.4
Infusion-related reaction	9.0	0.0	9.8	0.5
TLS	1.4	0.0	3.3	0.0

The safety profile of VenO was consistent with the known safety profile of venetoclax; similar rates of Grade ≥3 AEs were reported between treatment arms

1. Al-Sawaf O, *et al.* EHA 2023. Abstract S145 (Oral).
2. Al-Sawaf O, *et al. Lancet Oncol* 2020; **21:**1188–1200 (incl. appendix).

- * Grade 3/4 AEs were reported for up to 6 months after EoT; Grade ≥3 infections were reported for 2 years after EoT or until disease progression or NLT; after disease progression, only treatment-related SAEs and SPMs were reported [2]; † Nine patients received obinutuzumab only.[2]

EoT, end of treatment; NLT, next line of therapy; NMSC, non-melanoma skin cancer; SPM, second primary malignancy; TLS, tumor lysis syndrome.

Outcomes in High-risk Subgroups After Fixed-Duration Ibrutinib + Venetoclax for Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma: Up To 5.5 years of Follow-up in the Phase 2 CAPTIVATE Study

William G. Wierda, MD, PhD,[1] Ryan Jacobs, MD,[2] Paul M. Barr, MD,[3] John N. Allan, MD,[4] Tanya Siddiqi, MD,[5] Alessandra Tedeschi, MD,[6] Thomas J. Kipps, MD, PhD,[7] Susan M. O'Brien, MD,[8] Xavier C. Badoux, MBBS, FRACP, FRCPA,[9] Andrea Visentin, MD, PhD[10] Masa Lasica, MBBS, FRACP, FRCPA,[11] Dennis Carney, MBBS, FRACP, FRCPA,[12] Anna Elinder Camburn, MBChB, FRACP, FRCPA,[13] Javier De la Serna, MD,[14] Edith Szafer-Glusman, PhD,[15] Cathy Zhou, MS,[15] Anita Szoke, MD,[15] James P. Dean, MD, PhD,[15] Paolo Ghia, MD, PhD,[16,17] Constantine S. Tam, MBBS, MD[18]

[1]The University of Texas MD Anderson Cancer Center, Houston, TX, USA; [2]Levine Cancer Institute, Charlotte, NC, USA; [3]Wilmot Cancer Institute, University of Rochester Medical Center, Rochester, NY, USA; [4]Weill Cornell Medicine, New York, NY, USA; [5]City of Hope National Medical Center, Duarte, CA, USA; [6]ASST Grande Ospedale Metropolitano Niguarda, Milan, Italy; [7]University of California San Diego Moores Cancer Center, La Jolla, CA, USA; [8]UC Irvine, Chao Comprehensive Cancer Center, Orange, CA, USA; [9]Ministry of Health, Kogarah, NSW, Australia; [10]University of Padova, Padova, Italy; [11]St Vincent's Hospital Melbourne, Melbourne, VIC, Australia; [12]Peter MacCallum Cancer Centre, Melbourne, Australia; [13]North Shore Hospital, Auckland, New Zealand; [14]Hospital Universitario 12 de Octubre, Madrid, Spain; [15]AbbVie, North Chicago, IL, USA; [16]Università Vita-Salute San Raffaele, [17]IRCCS Ospedale San Raffaele, Milan, Italy; [18]Alfred Hospital and Monash University, Melbourne, VIC, Australia

2024 ASCO Annual Meeting; May 31–June 4, 2024; Chicago, IL, USA

FD Cohort: Baseline Characteristics (N=159)

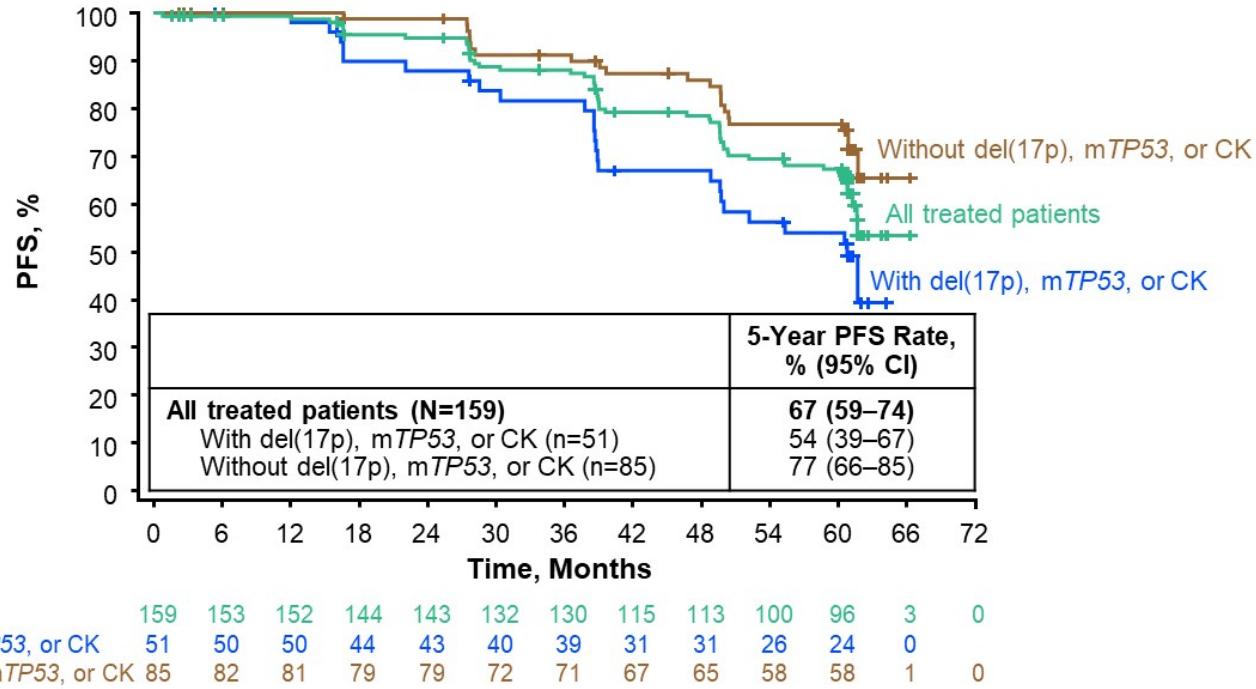
Characteristic	FD Cohort All Treated Patients N=159
Median age (range), years	60 (33–71)
Male, n (%)	106 (67)
Rai stage III/IV, n (%)	44 (28)
High-risk genomic features, n (%)	
Unmutated IGHV	89 (56)
del(17p)/mutated *TP53*[a]	27 (17)
del(17p)	20 (13)
del(11q)[b]	28 (18)
Complex karyotype[c]	31 (23)
Any cytopenia, n (%)	54 (34)
ANC ≤1.5 × 10^9/L	13 (8)
Hemoglobin ≤11 g/dL	37 (23)
Platelet count ≤100 × 10^9/L	21 (13)
Bulky LN disease ≥5 cm, n (%)	48 (30)
Median ALC × 10^9/L (range)	70 (1–503)
ALC ≥25 × 10^9/L, n (%)	120 (75)

ALC, absolute lymphocyte count; ANC, absolute neutrophil count; LN, lymph node.
[a]del(17p)/*TP53* status was missing for 3 patients. [b]Without del(17p) per Döhner hierarchy. [c]Defined as ≥3 abnormalities by conventional CpG-stimulated cytogenetics; complex karyotype status was missing for 26 patients.

FD Cohort: Overall Median PFS Was Not Reached With Up to 5.5 Years of Follow-Up

- Median time on study: 61.2 months (range, 0.8–66.3)

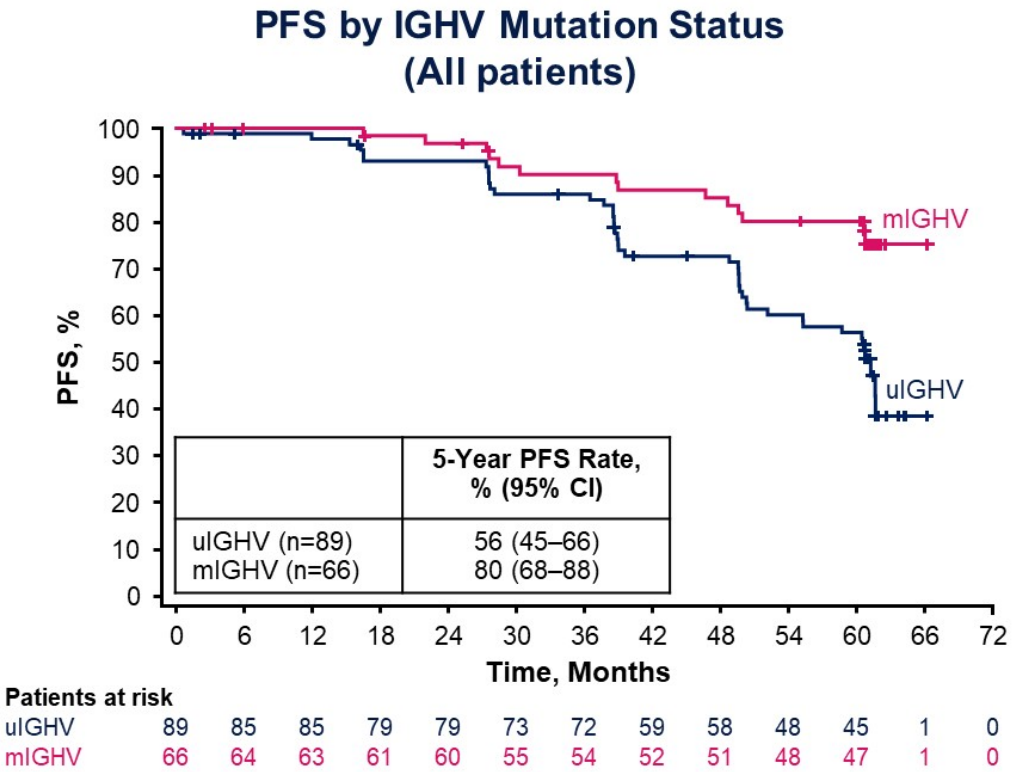
PFS in All Treated Patients and by del(17p), m*TP53*, or CK Status

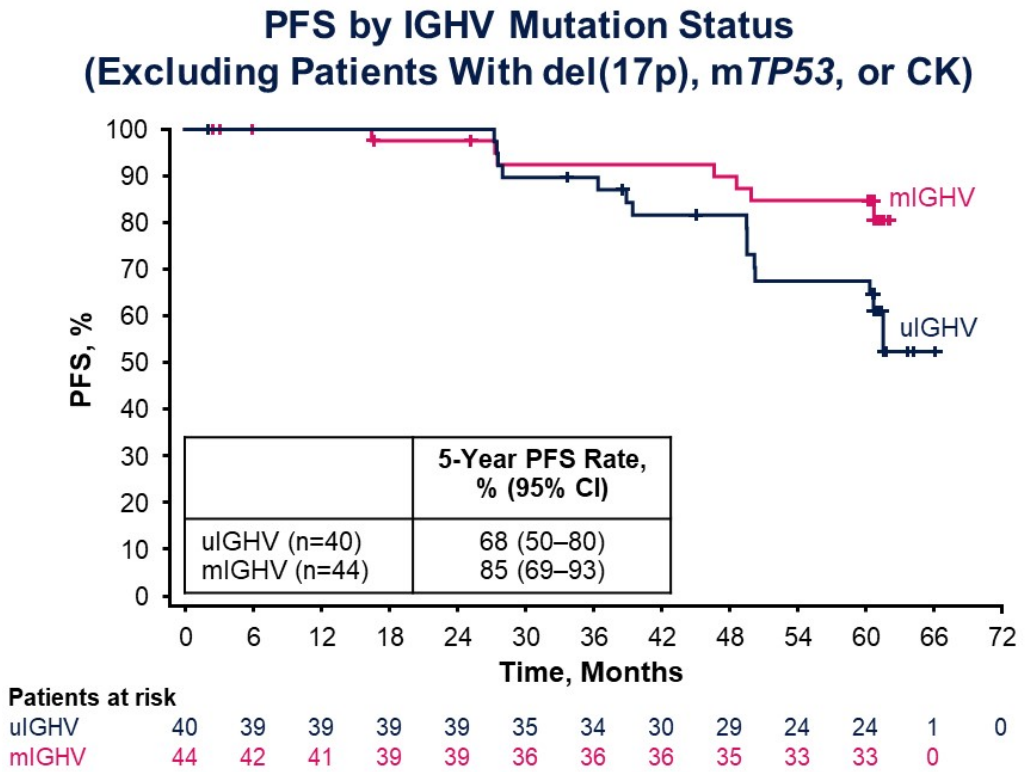


	With feature		Without feature	
High-risk feature	**n**	**5-Year PFS rate, % (95% CI)**	**n**	**5-Year PFS rate, % (95% CI)**
del(17p)/m*TP53*	27	41 (21–59)	129	73 (64–80)
CK[a]	31	57 (37–72)	102	72 (61–80)
del(11q)[b]	11	64 (30–85)	74	79 (67–87)

CK, complex karyotype; m*TP53*, mutated *TP53*; PFS, progression-free survival. [a]Defined as ≥3 chromosomal abnormalities by conventional CpG-stimulated cytogenetics; [b]Excluding patients with del(17p)/mutated *TP53* or CK.

FD Cohort: 5-Year PFS Rates by IGHV Mutation Status (N=159)



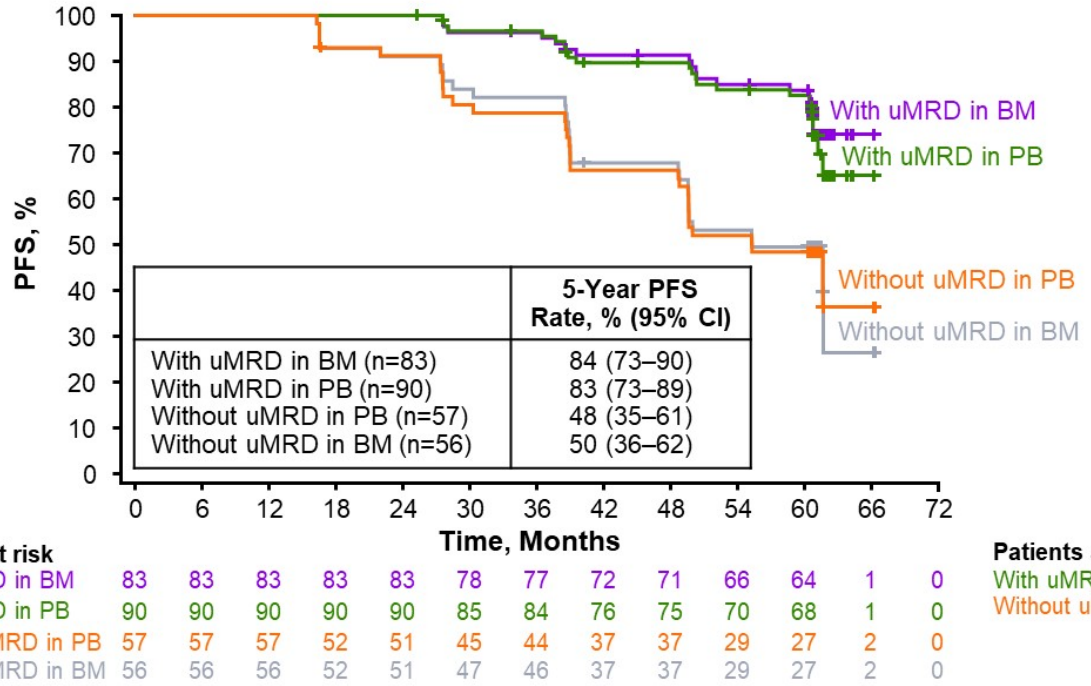


- Presence of del(17p), m*TP53*, and/or CK had a substantial impact on PFS in patients with uIGHV and mIGHV

mIGHV, mutated IGHV; uIGHV, unmutated IGHV.

FD Cohort: Improved 5-Year PFS Rates With uMRD in BM and PB (N=159)

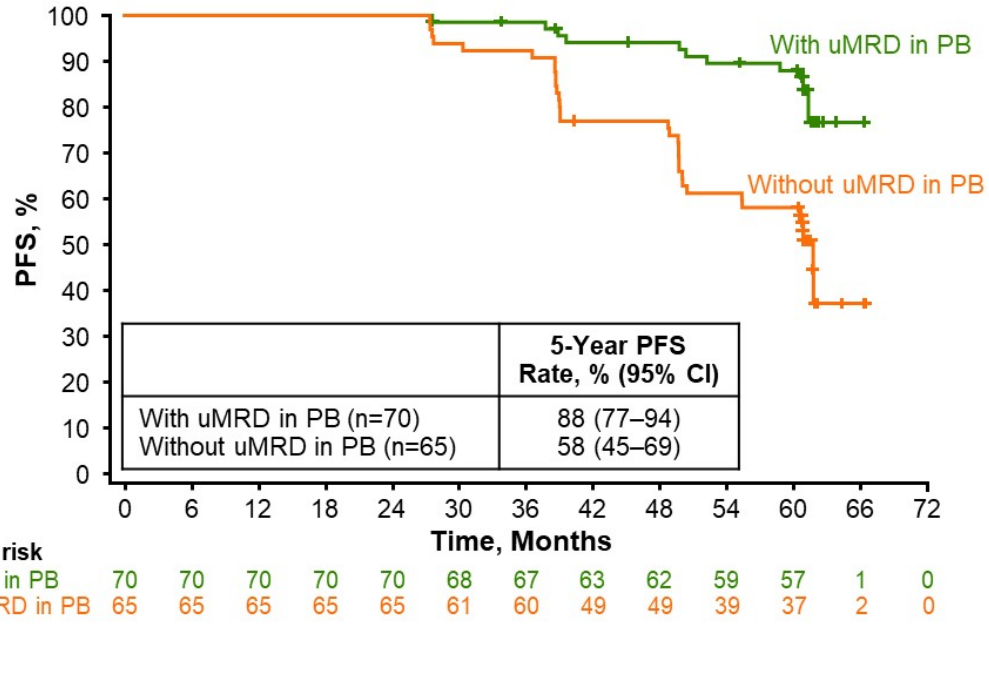
PFS by MRD Status at 3 Months After EOT[a]



	5-Year PFS Rate, % (95% CI)
With uMRD in BM (n=83)	84 (73–90)
With uMRD in PB (n=90)	83 (73–89)
Without uMRD in PB (n=57)	48 (35–61)
Without uMRD in BM (n=56)	50 (36–62)

Patients at risk													
With uMRD in BM	83	83	83	83	83	78	77	72	71	66	64	1	0
With uMRD in PB	90	90	90	90	90	85	84	76	75	70	68	1	0
Without uMRD in PB	57	57	57	52	51	45	44	37	37	29	27	2	0
Without uMRD in BM	56	56	56	52	51	47	46	37	37	29	27	2	0

PFS by MRD Status at 12 Months After EOT[a]



	5-Year PFS Rate, % (95% CI)
With uMRD in PB (n=70)	88 (77–94)
Without uMRD in PB (n=65)	58 (45–69)

Patients at risk													
With uMRD in PB	70	70	70	70	70	68	67	63	62	59	57	1	0
Without uMRD in PB	65	65	65	65	65	61	60	49	49	39	37	2	0

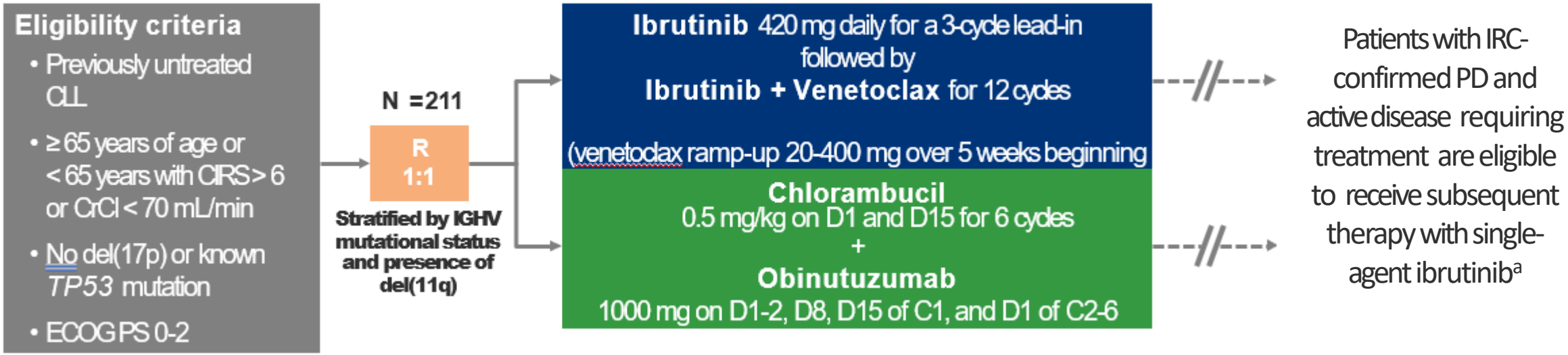
- In high-risk genomic subgroups with del(17p)/m*TP53*, CK, or uIGHV, 5-year PFS rates were also consistently higher in patients with uMRD4 in PB or BM at 3 months after EOT than in those without uMRD4[b]

BM, bone marrow; EOT, end of treatment; NE, not estimable; PB, peripheral blood.
[a]Analyzed in patients who completed FD treatment with ibrutinib + venetoclax and had valid MRD results at the specified time point. [b]uMRD $<10^{-4}$ by 8-color flow cytometry.

Most common AEs

AEs, n (%)	All treated patients (N=159)	
	Any grade	Grade 3/4
Most common AEs		
Diarrhoea	99 (62)	5 (3)
Nausea	68 (43)	2 (1)
Neutropenia	66 (42)	52 (33)
Arthralgia	53 (33)	2 (1)
Hypertension	25 (16)	9 (6)
Neutrophil count decreased	16 (10)	8 (5)
Other AEs of clinical interest		
Atrial fibrillation	7 (4)	2 (1)
Major haemorrhage*	3 (2)	2 (1)
Laboratory safety parameters		
Haematology		
Neutrophils decreased	115 (72)	60 (38)
Platelets decreased	94 (59)	20 (13)
Haemoglobin decreased	31 (19)	0
Chemistry		
Corrected calcium decreased	61 (38)	1 (1)
Potassium increased	39 (25)	4 (3)
Uric acid increased	34 (21)	34 (21)
Creatinine increased	27 (17)	0

6-year Time To Next Treatment (TTNT) extrapolation curve for GLOW study: first-line I+V offers long treatment-free period for elderly/unfit CLL patients



Primary end point: IRC-assessed PFS

Niemann, 2023

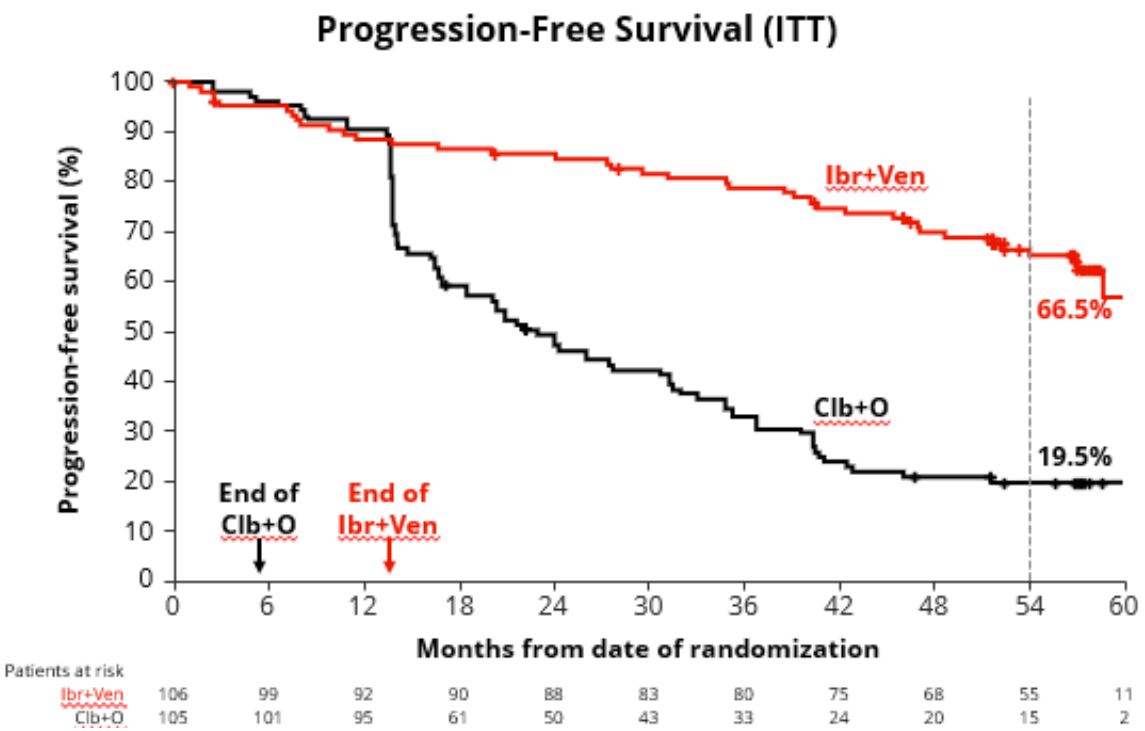
GLOW study: patients' characteristics:

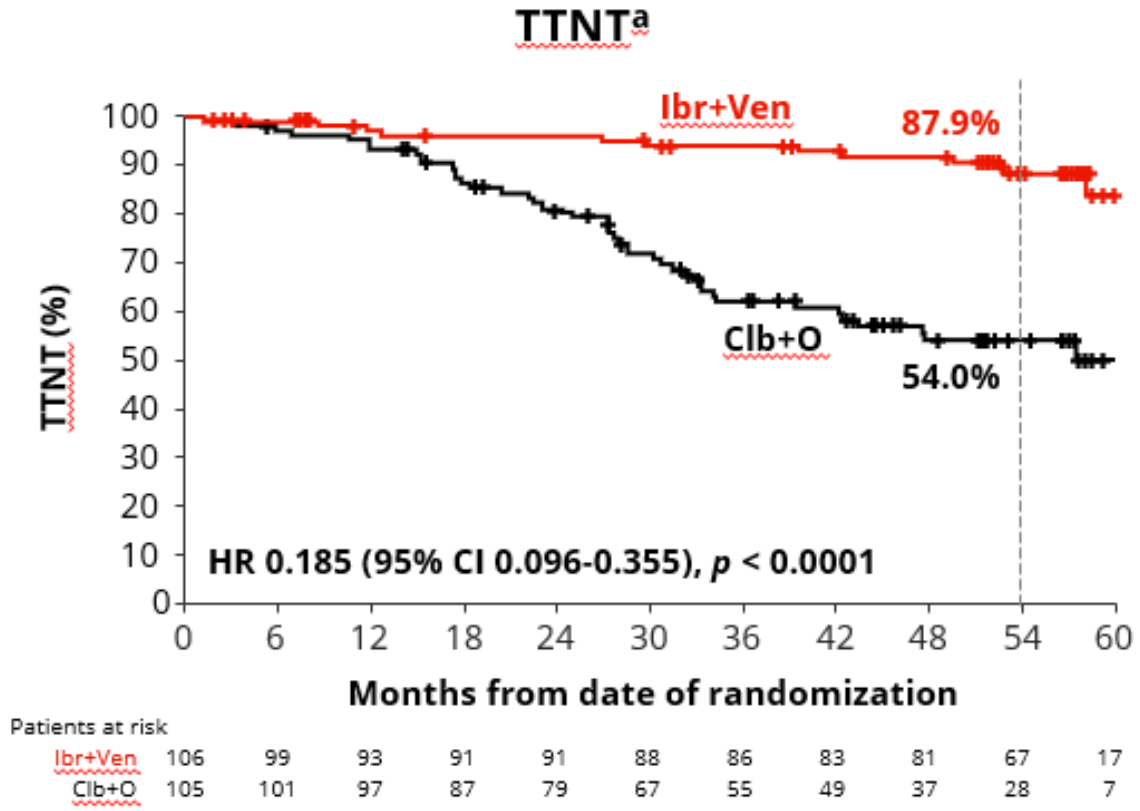
Table 1. Baseline Patient Demographics and Disease Characteristics (Intent-to-Treat Population).*

Characteristic	Ibrutinib-Venetoclax (n=106)	Chlorambucil-Obinutuzumab (n=105)
Age, yr	71.0 (47–93)	71.0 (57–88)
≥75	35 (33.0)	37 (35.2)
Men	59 (55.7)	63 (60.0)
ECOG PS 1 to 2	71 (67.0)	66 (62.9)
CIRS score	9 (1–20)	8 (0–22)
>6†	74 (69.8)	61 (58.1)
CrCl, ml/min‡	66.5 (34.0–168.1)	63.2 (32.3–180.9)
Rai stage III to IV§	55 (57.3)	53 (52.5)
Binet stage (CLL only)	96	101
A	7 (7.3)	8 (7.9)
B	46 (47.9)	53 (52.5)
C	43 (44.8)	40 (39.6)
Ann Arbor stage (SLL only)	10	4
IV	10 (100)	4 (100)
Bulky disease ≥5 cm	41 (39.0)	38 (36.2)
Elevated LDH¶	35 (33.0)	51 (48.6)
IGHV status		
Mutated	27 (25.5)	27 (25.7)
Unmutated	55 (51.9)	54 (51.4)
Unknown	24 (22.6)	24 (22.9)
Del(11q)	20 (18.9)	18 (17.1)
TP53 mutation	7 (6.6)	2 (1.9)

Kater, NEJM 2022

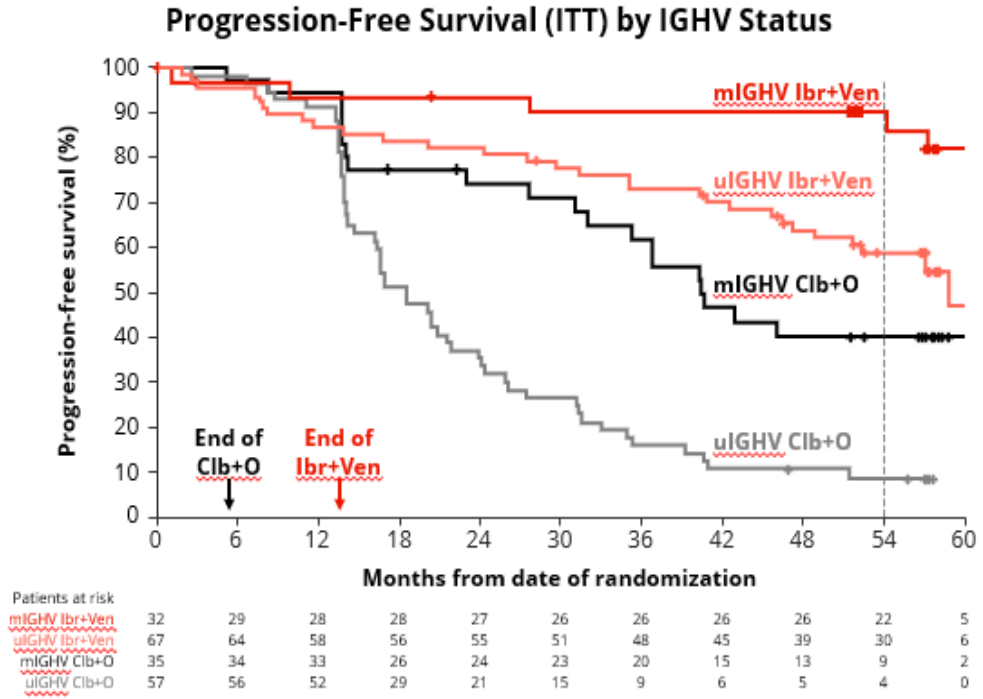
Progression-Free Survival and TTNT: 55-months FU





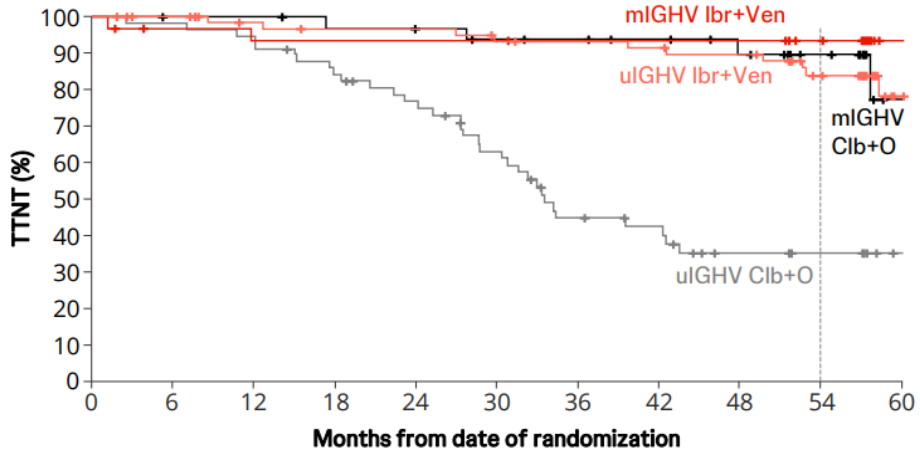
Moreno, ASH 2023

Ibr+Ven PFS and TTNT Versus Clb+O Regardless of IGHV Status



- Estimated 54-month PFS rates:
  - **Ibr+Ven:**
    - 90% for patients with mIGHV
    - 59% for patients with uIGHV
  - **Clb+O:**
    - 40% for patients with mIGHV
    - 8% for patients with uIGHV

Figure 1: TTNT by IGHV status



Patients at risk

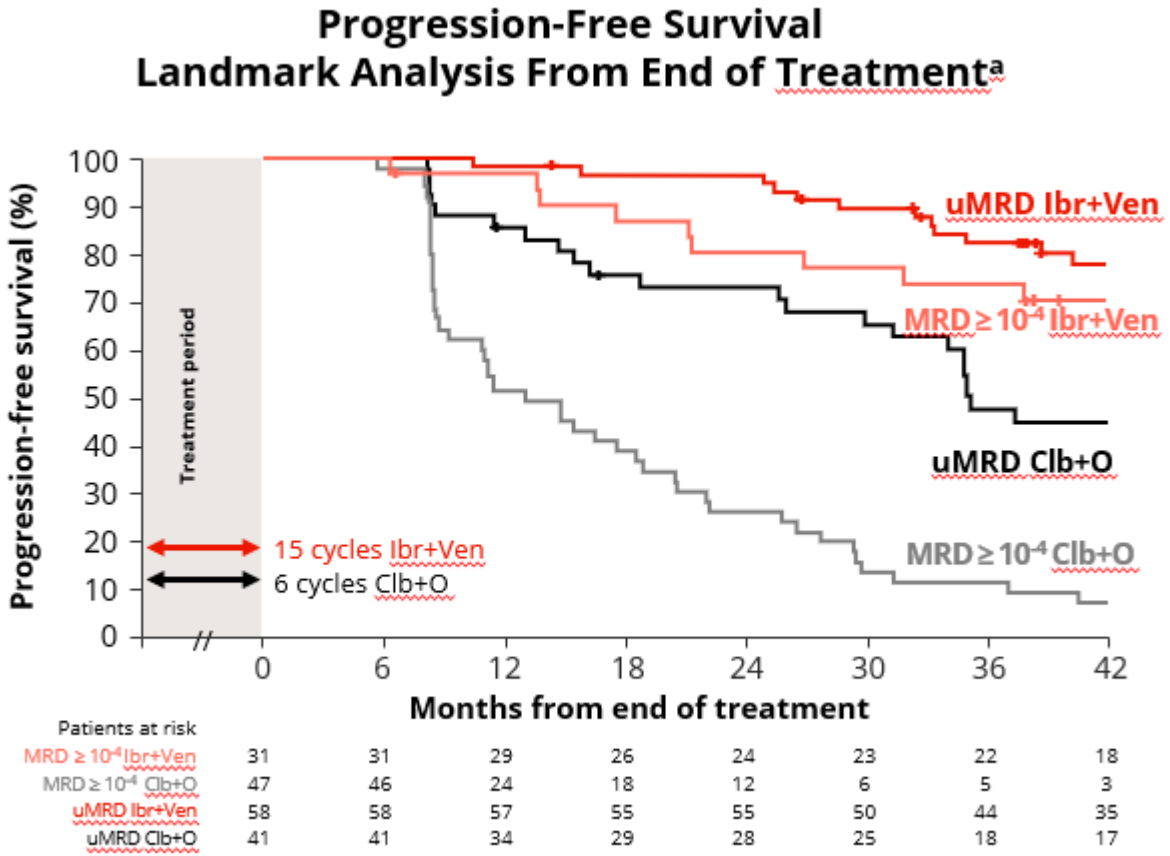
mIGHV Ibr+Ven	32	29	28	28	28	28	27	27	27	23	6
uIGHV Ibr+Ven	67	64	59	57	57	54	53	52	50	41	11
mIGHV Clb+O	35	34	34	32	31	29	28	25	22	16	4
uIGHV Clb+O	57	56	52	47	41	32	21	18	11	9	3

At latest data cut, 57-month follow-up, the majority of patients treated with I+V did not initiate a second line of treatment regardless of IGHV mutational status. Estimated percentage of patients not requiring second-line treatment at 54 months by IGHV status (Figure 1). This data was not available at the moment of this extrapolation.

– Ibr+Ven:	– Clb+O:
▪93.5% for mIGHV	▪89.8% for mIGHV
▪83.9% for uIGHV	▪35.1% for uIGHV

Moreno, ASH 2023

At 57 Months of Follow-up, Ibr+Ven Improved PFS Versus Clb+O Regardless of MRD Status at EOT+3



Estimated PFS rates at 42 months post treatment:

Ibr+Ven:

- 78% for patients with uMRD at EOT+3
- 70% for patients with MRD ≥ 10-4 at EOT+3

Clb+O:

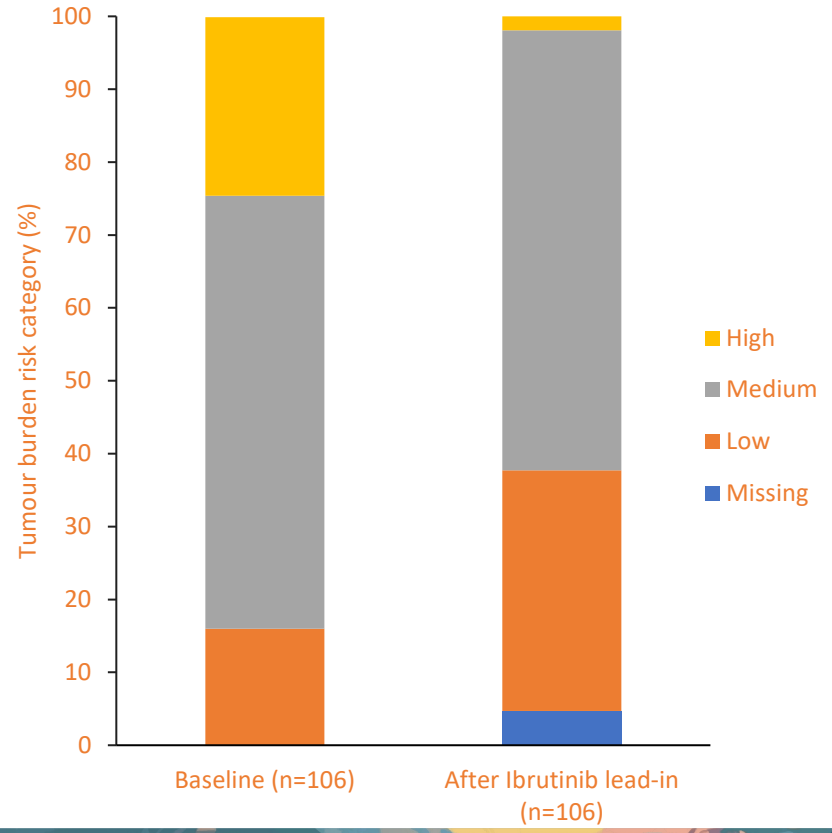
- 44% for patients with uMRD at EOT+3
- 6% for patients with MRD ≥ 10-4 at EOT+3

Moreno, ASH 2023

Ibrutinib and venetoclax demonstrate largely non-overlapping toxicities, and adverse events are generally manageable

	All pts N=106 %
Grade 3/4 AEs (≥5%)	75.5
Neutropenia	34.9
Infections	17
Hypertension	7.5
AEs of clinical interest (any grade)	
Atrial fibrillation	6.6
AEs leading to discontinuation	10.4
Death from any cause during tx	7.4

GLOW: Tumour burden risk category for TLS in patients with untreated CLL treated with I+V[1]



ESMO GUIDELINE 2024

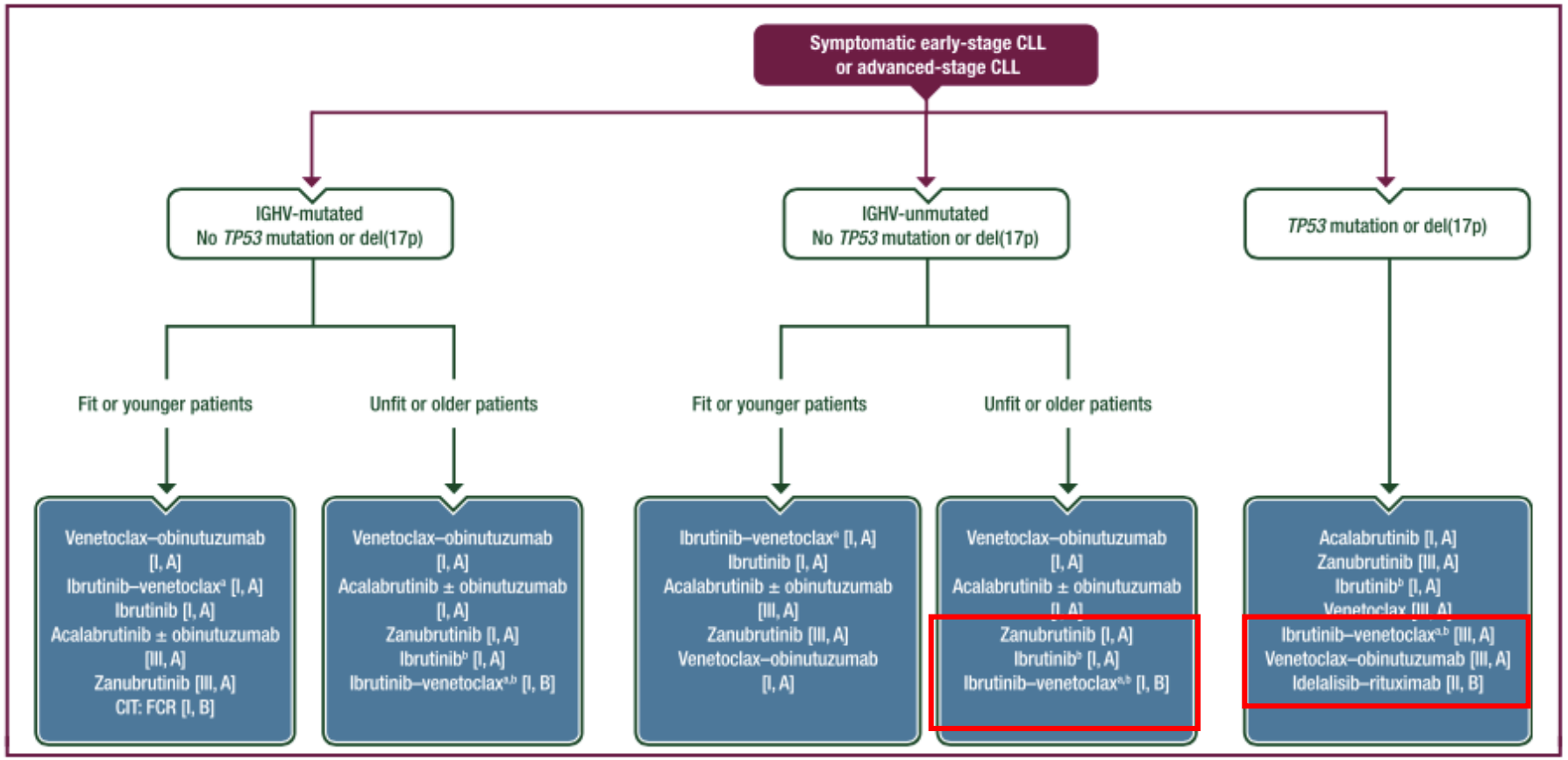
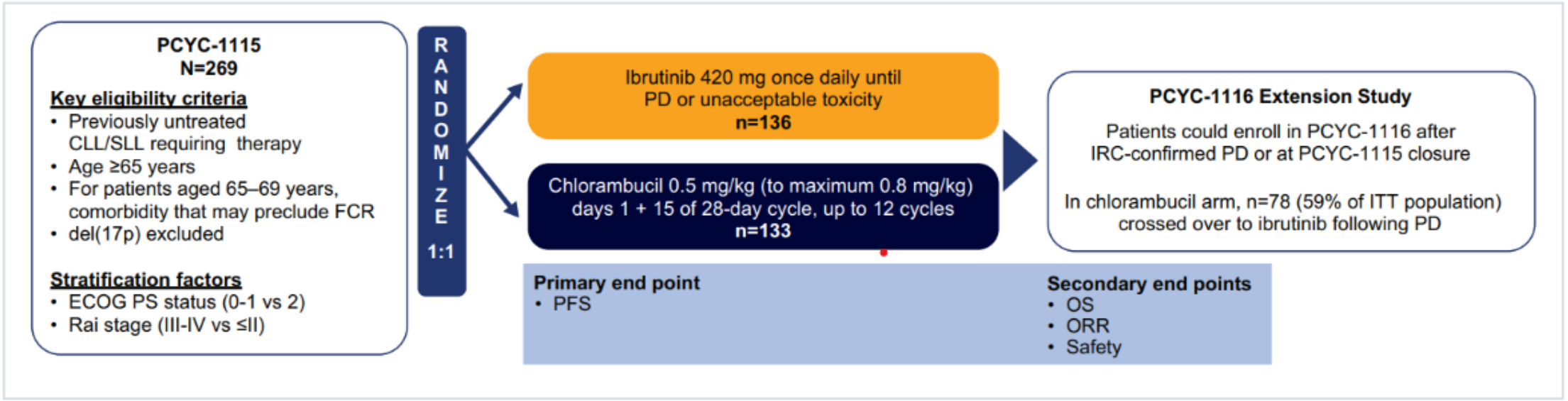


Figure 1. First-line therapy.
The order of the recommended treatments for each subgroup is based on the authors' expert opinion, which considers time-limited therapy as more valuable, if there is equal evidence for different treatment options.
Purple: algorithm title; blue: systemic anticancer therapy or their combination; white: other aspects of management and non-treatment aspects.
CIT, chemoimmunotherapy; CLL, chronic lymphocytic leukaemia; del, deletion; FCR, fludarabine–cyclophosphamide–rituximab; IGHV, immunoglobulin heavy chain variable; MRD, minimal residual disease.
[a]Ibrutinib—venetoclax with a 15-month fixed duration or with an MRD-guided duration.
[b]Ibrutinib or ibrutinib—venetoclax should be considered carefully in older patients with cardiac comorbidities.

Eichhorst B, Ghia P et al. Ann Oncol 2024

Final Analysis of the RESONATE-2 Study: Up to 10 Years of Follow-Up of First-Line Ibrutinib Treatment in Patients With CLL

Study Design of RESONATE-2



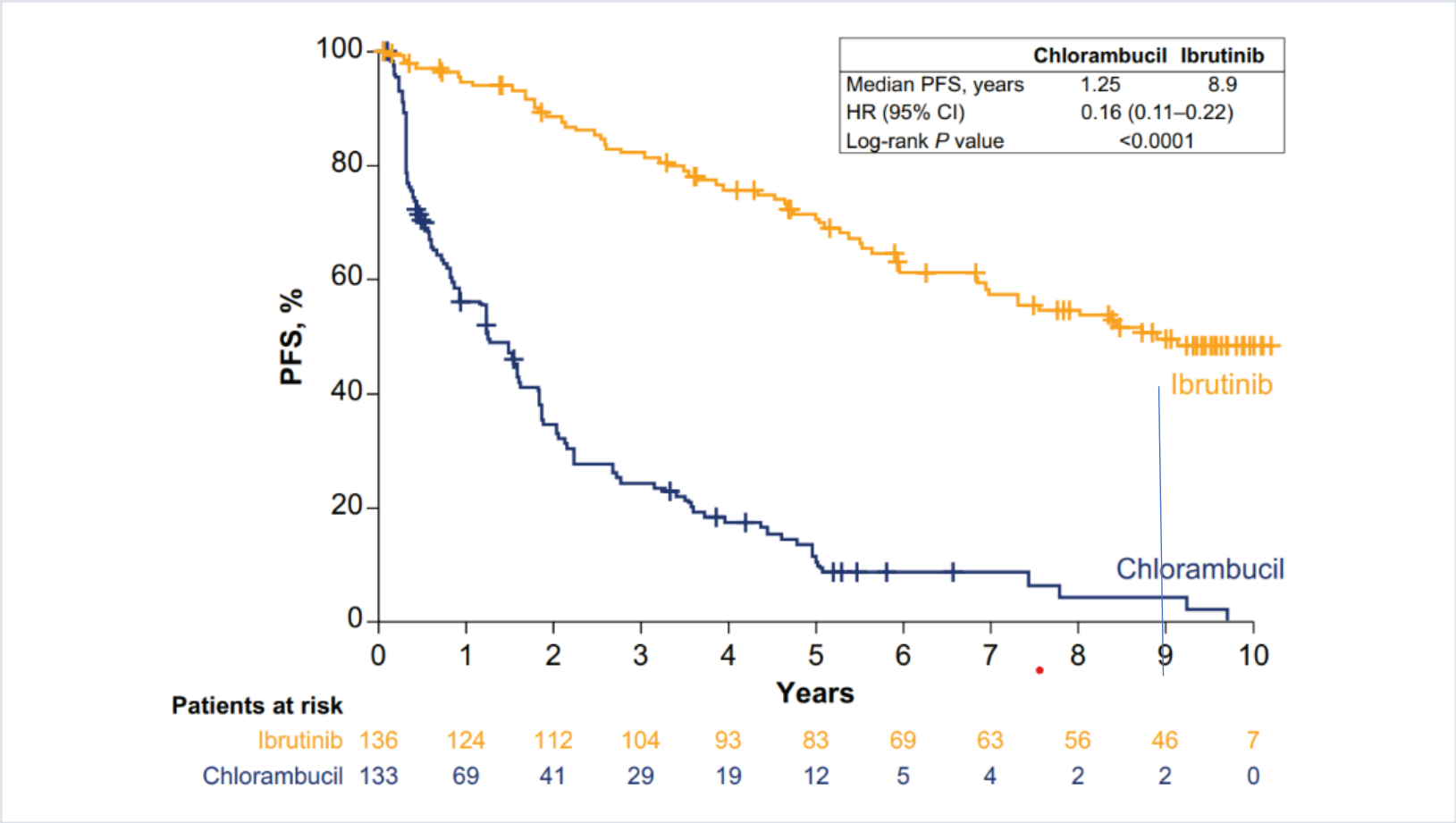
ECOG PS, Eastern Cooperative Oncology Group Performance Status; FCR, fludarabine, cyclophosphamide, and rituximab; IRC, independent review committee; ITT, intent to treat; PD, progressive disease.

Among patients in the ibrutinib and chlorambucil arms, respectively, 29 of 130 patients with testing results (22%) and 25 of 121 patients (21%) had **del(11q) mutation**, 58 of 101 patients (57%) and 60 of 103 patients (58%) had **unmutated IGHV**, 12 of 124 patients (10%) and 3 of 94 patients (3%) had **TP53 mutation**, and 6 of 93 patients (7%) and 8 of 90 patients (9%) had **complex karyotype.**

Burger, EHA 2024

Final Analysis of the RESONATE-2 Study: Up to 10 Years of Follow-Up of First-Line Ibrutinib Treatment in Patients With CLL

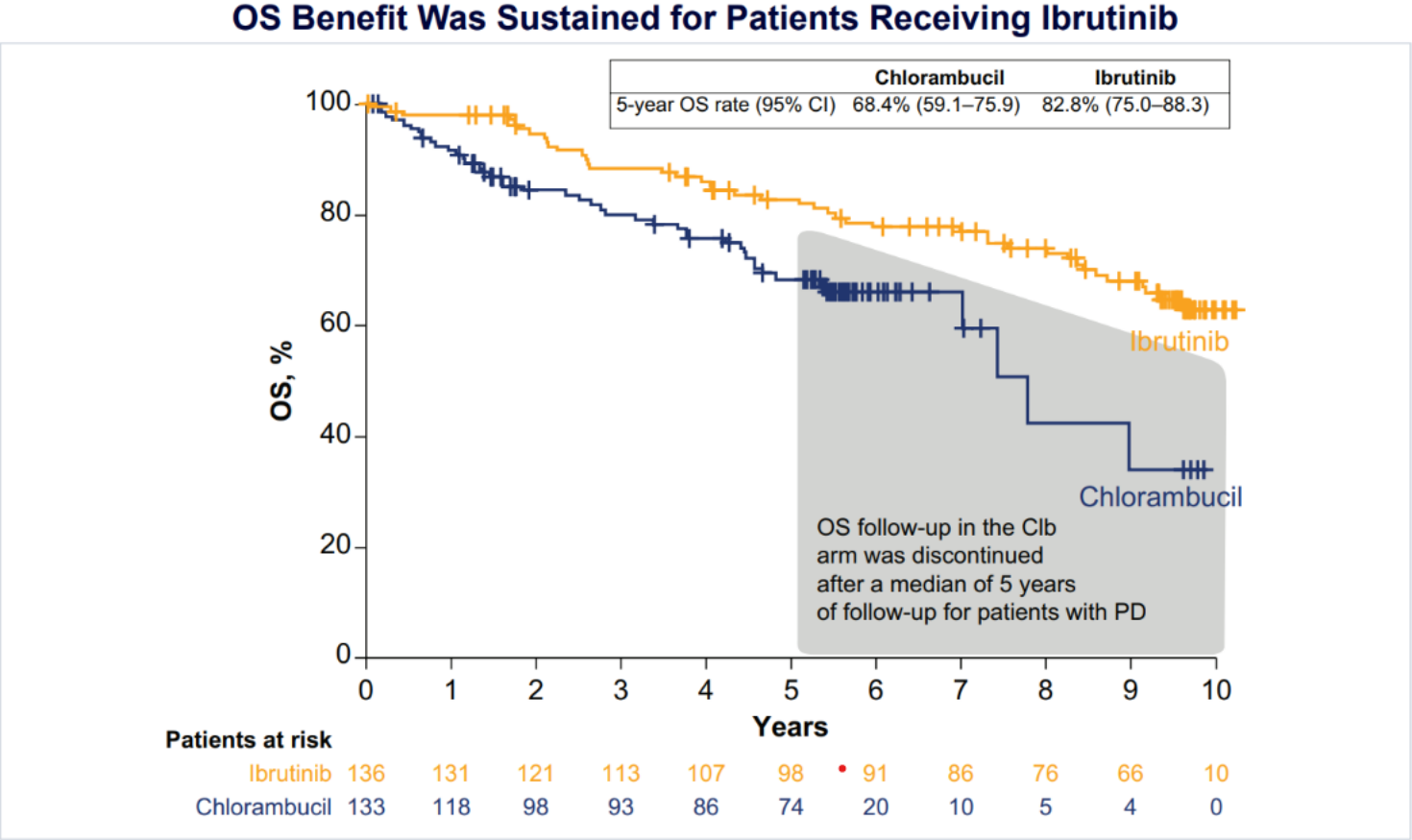
At Final Analysis, Median PFS With Ibrutinib Was Reached at 8.9 Years



At 9 years, the PFS rates were 49.7% (95% CI, 40.2–58.4) in the ibrutinib arm and 4.4% (95% CI, 1.1–11.5) in the chlorambucil arm

Burger, EHA 2024

Final Analysis of the RESONATE-2 Study: Up to 10 Years of Follow-Up of First-Line Ibrutinib Treatment in Patients With CLL



At 9 years, the OS rate was 68.0% (95% CI, 58.6–75.7) in the ibrutinib arm.

In patients with ≥1 high prognostic risk factors including mutated TP53/unmutated IGHV/del(11q), OS was significantly longer for patients treated with ibrutinib versus chlorambucil.

Burger, EHA 2024

Final Analysis of the RESONATE-2 Study: Up to 10 Years of Follow-Up of First-Line Ibrutinib Treatment in Patients With CLL

After up to 10 Years of Follow-Up, 27% of Patients Initially Randomly Assigned to Ibrutinib Remained on Ibrutinib Treatment

	Ibrutinib N=135
Median (range) duration of ibrutinib treatment, years	6.2 (0.06–10.2)
Continuing ibrutinib at study closure, n (%)	37 (27)
Discontinued ibrutinib, n (%)	
Due to AE	44 (33)
Due to PD	18 (13)

AE, adverse event.

After discontinuation of 1L ibrutinib, 24 patients (18%) received subsequent antineoplastic therapies.

Burger, EHA 2024

Final Analysis of the RESONATE-2 Study: Up to 10 Years of Follow-Up of First-Line Ibrutinib Treatment in Patients With CLL

Baseline Clinical and Genomic Characteristics of Patients Remaining on Ibrutinib at Study Closure and of Patients Who Discontinued Were Largely Similar

	On Ibrutinib N=37	Discontinued Ibrutinib N=98
Age, median (range), years	71 (65–82)	73 (65–89)
Men, n (%)	16 (43)	72 (74)
ECOG PS, n (%)		
0	19 (51)	41 (42)
1–2	18 (49)	57 (58)
Rai stage III or IV, n (%)	18 (49)	42 (43)
CIRS score >6, n (%)	10 (27)	32 (33)
Creatinine clearance <60 mL/min, n (%)	15 (41)	45 (46)
Bulky disease ≥5 cm, n (%)	11 (30)	43 (44)
β2-macroglobulin >3.5 mg/L, n (%)	23 (62)	62 (63)
Hemoglobin ≤11 g/dL, n (%)	14 (38)	37 (38)
Platelet count ≤100 x 10^9 /L, n (%)	12 (32)	23 (24)
High prognostic risk features,[a] n (%)	19 (51)	54 (55)
del(11q), n/N (%)	5/35 (14)	24/94 (26)
Unmutated IGHV, n/N (%)	17/32 (53)	41/89 (46)
TP53 mutation, n/N (%)	2/36 (6)	9/94 (10)
Complex karyotype, n/N (%)	1/24 (4)	5/68 (7)
NOTCH1 mutation, n/N (%)	8/36 (22)	23/88 (26)

[a]del(11q), unmutated IGHV, and/or *TP53* mutation.
CIRS, Cumulative Illness Rating Scale; *NOTCH1*, neurogenic locus notch homolog protein 1.

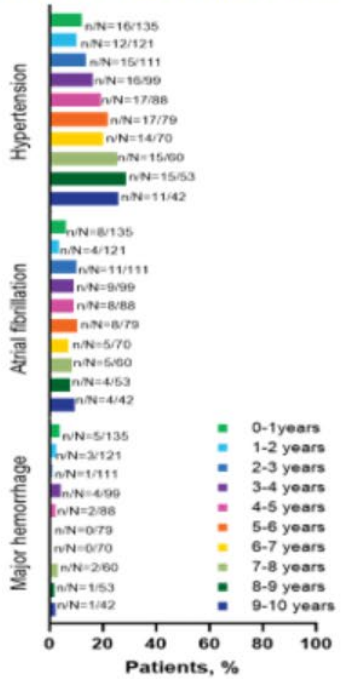
Burger, EHA 2024

Final Analysis of the RESONATE-2 Study: Up to 10 Years of Follow-Up of First-Line Ibrutinib Treatment in Patients With CLL

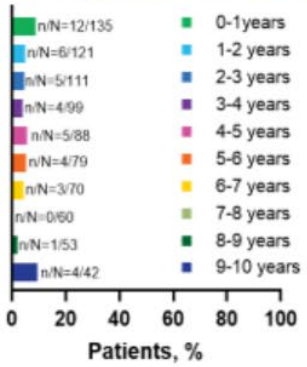
Safety and tolerability were consistent with previous follow-up; frequency of AEs of most interest decreased over time

Burger J, et al;
Abstract P670
Friday, June 14;
18:00-19:00 CEST; Hall

Frequency of AEs of Most Interest

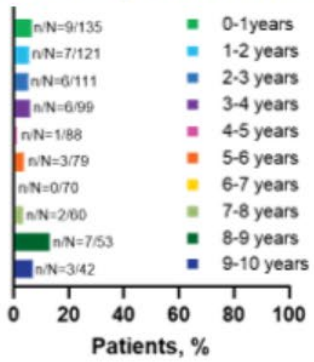


AEs Leading to Dose Reductions



- Of 34 patients who had AEs of any grade leading to dose reduction, 28 patients (82%) had all AEs resolved

AEs Leading to Discontinuations



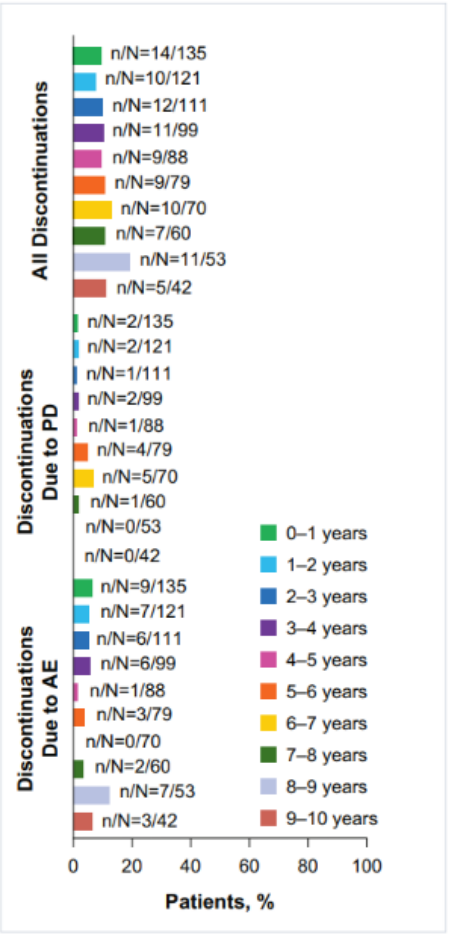
- AEs (any grade) leading to discontinuation: 33% (44/136)

At study completion, 27% of patients remained on ibrutinib treatment; median duration of 1L ibrutinib treatment: 6.2 years (range 0.06-10.2)

J&J Innovative Medicine

21

No Increasing Trend in Discontinuations Was Observed Over Time

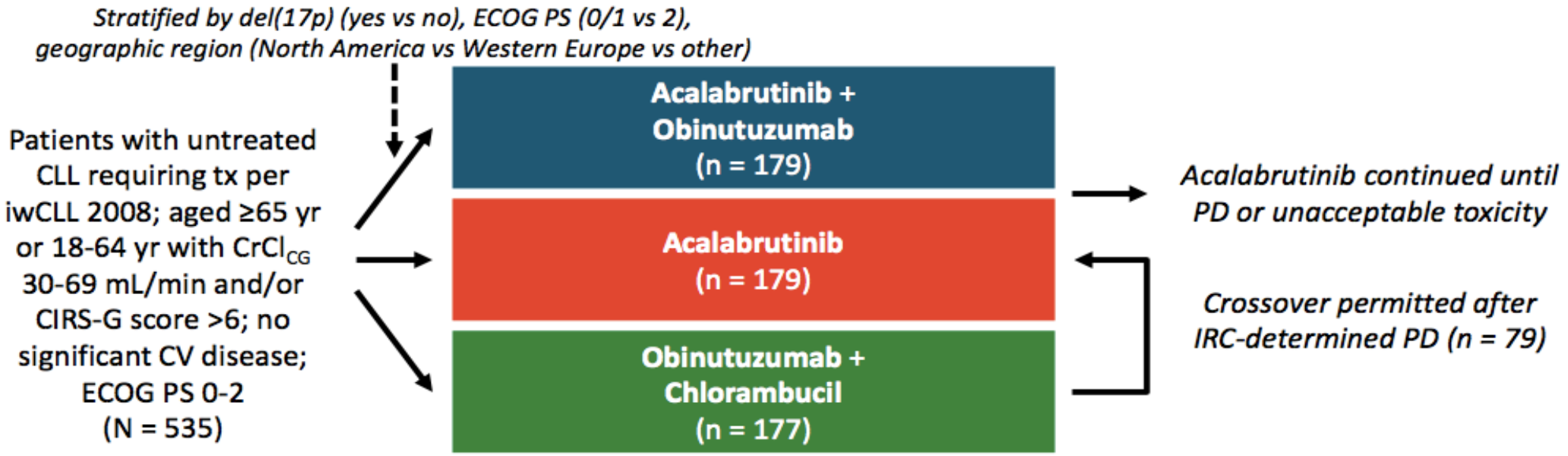


- **Safety and tolerability were consistent with previous follow-up**
- COVID-19 disease occurred in 24 patients (18%), grade 3–5 COVID-19 in 8 patients
- **Dose reductions due to AEs generally decreased over time**
- Of 34 patients who had AEs of any grade leading to **dose reduction**, 28 **patients (82%) had all AEs resolved**

Burger, EHA 2024

ELEVATE-TN 6-Yr Update: Study Design

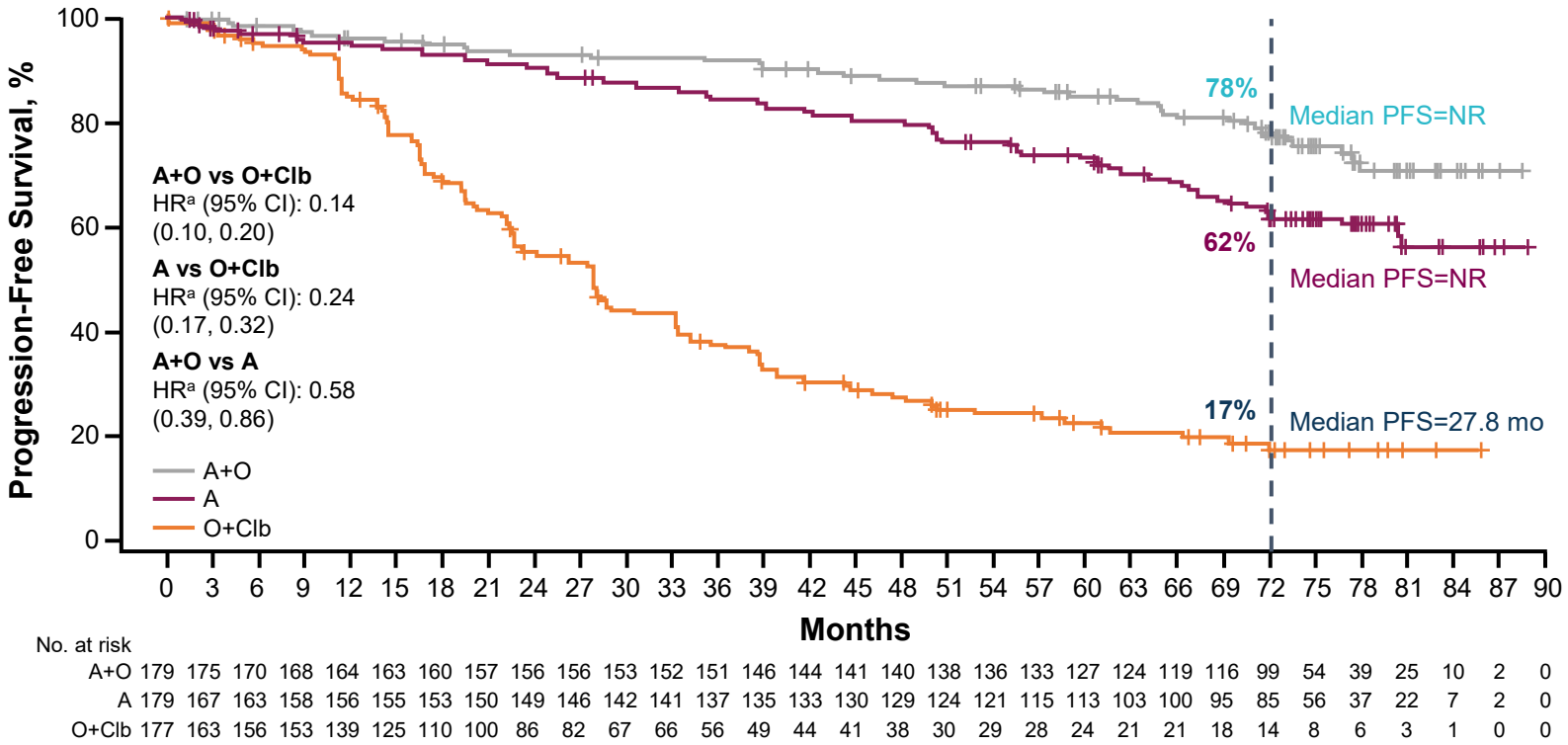
- International, randomized, open-label phase III trial (data cutoff: March 3, 2023)



- **Primary endpoint:** IRC-assessed PFS for A + O vs O + Clb; after interim analysis, PFS assessed by investigator
- **Secondary/other endpoints:** IRC-assessed PFS for A vs O + Clb; investigator-assessed PFS, ORR (IRC-assessed and investigator-assessed), TTNT, OS, uMRD, and safety

Investigator-Assessed PFS

- Median PFS was NR for A+O and A vs. 27.8 months for O+Clb.
- Estimated 72 months PFS rates were 78% for A+O, 62% for A monotherapy, and 17% for O+Clb.



No. at risk

A+O	179	175	170	168	164	163	160	157	156	156	153	152	151	146	144	141	140	138	136	133	127	124	119	116	99	54	39	25	10	2	0
A	179	167	163	158	156	155	153	150	149	146	142	141	137	135	133	130	129	124	121	115	113	103	100	95	85	56	37	22	7	2	0
O+Clb	177	163	156	153	139	125	110	100	86	82	67	66	56	49	44	41	38	30	29	28	24	21	21	18	14	8	6	3	1	0	0

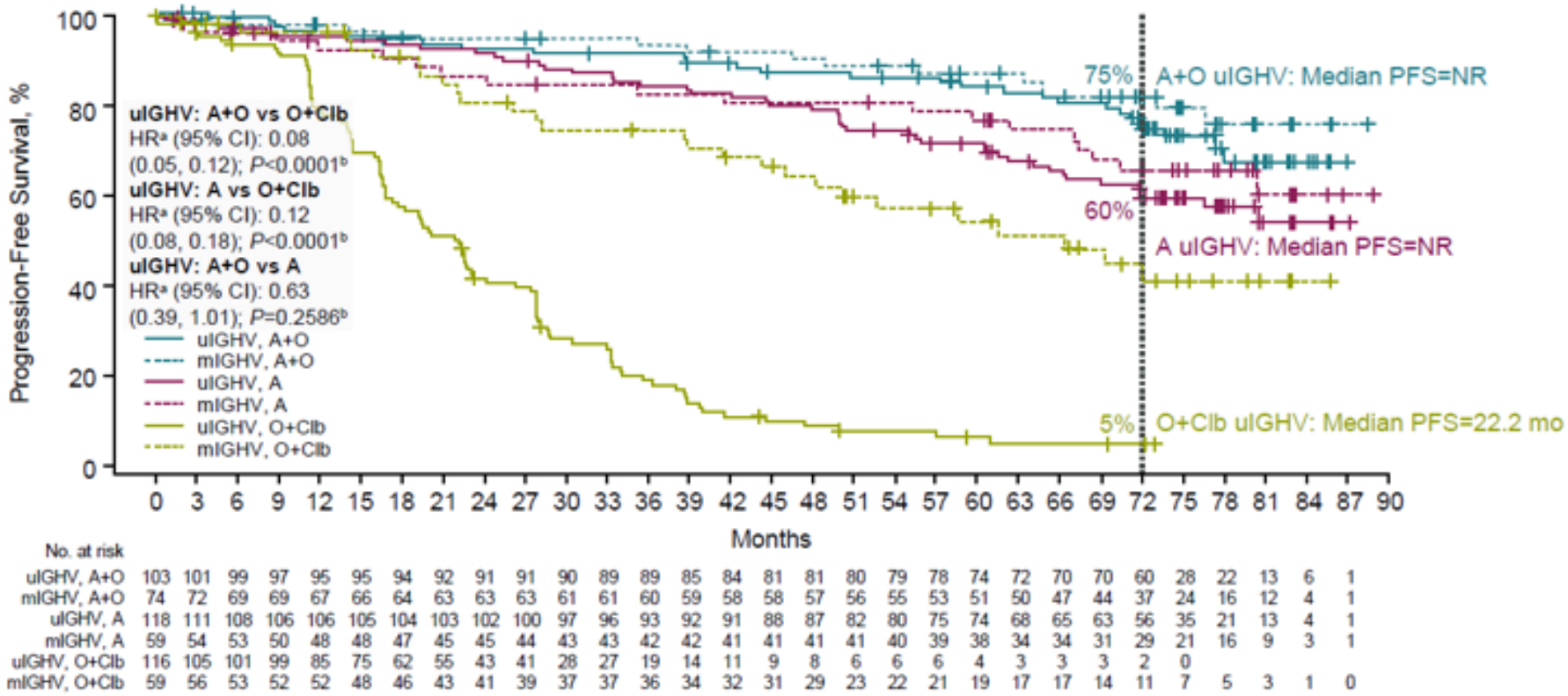
[a]Hazard ratio based on stratified Cox proportional-hazard model.

A = acalabrutinib; CI = confidence interval; Clb = chlorambucil; HR = hazard ratio; NR = not reached; O = Obinutuzumab; PFS = progression free survival; PFS 2 = time to second disease progression or death; vs = versus.

Sharman JP et al. Oral Presentation Presented at: ASH; December 9-12, 2023; San Diego.

Investigator-Assessed PFS in Patients with uIGHV

- PFS result in A-treated patients with uIGHV was consistent with overall result
- Median PFS was NR in patients with uIGHV treated with A+O and A vs. 22.2 months in O+Clb arm

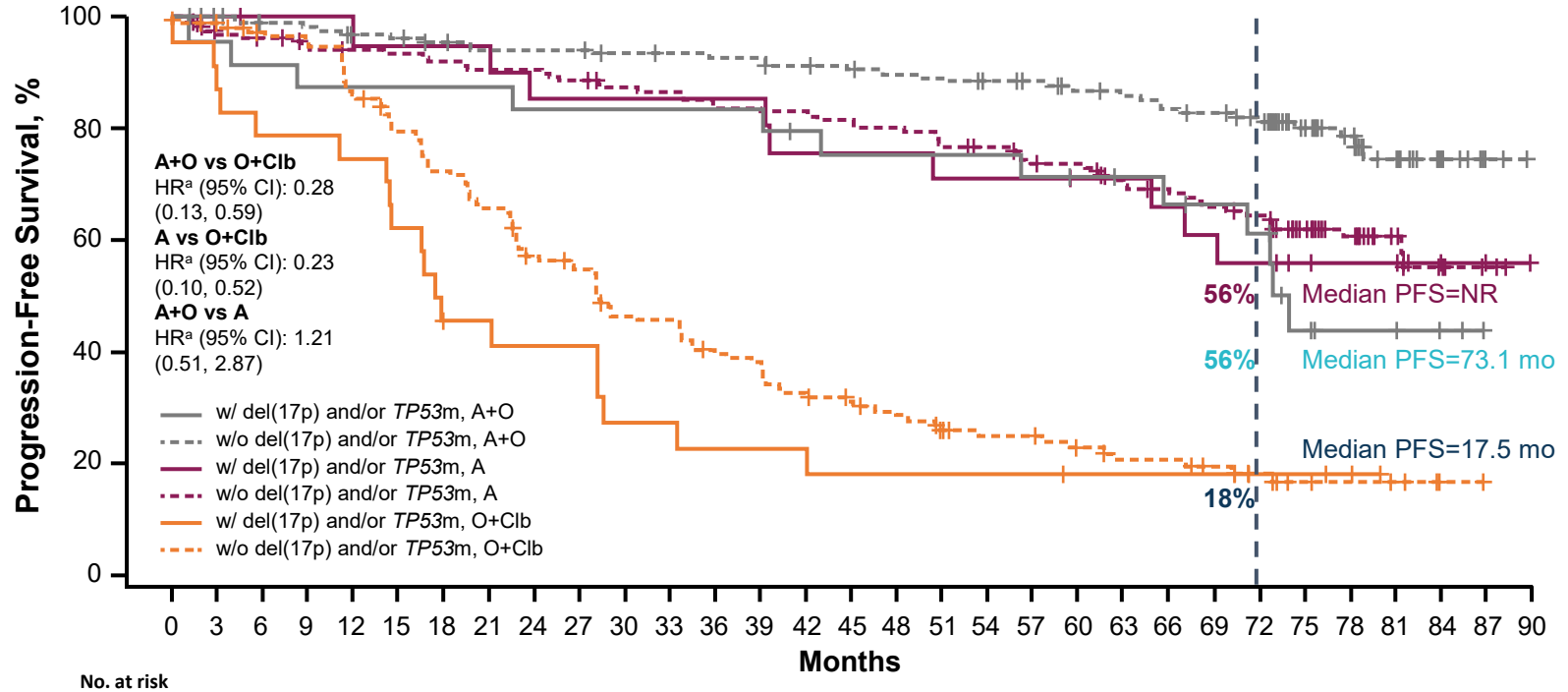


[a]Hazard ratio was based on unstratified Cox-Proportional-Hazards model.

A = acalabrutinib; CI = confidence interval; Clb = chlorambucil; HR = hazard ratio; IGHV = immunoglobulin heavy chain variable; mIGHV = mutated IGHV; NR = not reached; O = Obinutuzumab; PFS = progression free survival; uIGHV = unmutated IGHV; vs = versus.

Sharman JP et al. Oral Presentation Presented at: ASH; December 9-12, 2023; San Diego.

Investigator-Assessed PFS in Patients With Del(17p) and/or Mutated *TP53*



No. at risk

w/ del(17p) and/or *TP53m*, A+O	25	24	23	22	22	22	22	22	21	21	21	21	21	20	19	18	18	18	18	17	16	15	14	13	10	5	5	3	2	0
w/o del(17p) and/or *TP53m*, A+O	154	151	147	146	142	141	138	135	135	135	132	131	130	126	125	123	122	120	118	116	111	109	105	103	89	49	34	22	8	2
w/ del(17p) and/or *TP53m*, A	23	22	21	21	20	20	20	19	18	18	18	18	18	17	16	16	16	15	15	15	14	14	13	11	11	7	7	4	2	1
w/o del(17p) and/or *TP53m*, A	156	145	142	137	136	135	133	131	131	128	124	123	119	118	117	114	113	109	106	100	99	89	87	84	74	49	30	18	5	1
w/ del(17p) and/or *TP53m*, O+Clb	25	21	19	19	18	15	10	9	9	9	6	6	5	5	4	4	4	4	4	4	3	3	3	3	3	3	1	0		
w/o del(17p) and/or *TP53m*, O+Clb	152	142	137	134	121	110	100	91	77	73	61	60	51	44	40	37	34	26	25	24	21	18	18	15	11	5	5	3	1	0

[a]Hazard ratio based on unstratified Cox proportional-hazards model.

A = acalabrutinib; CI = confidence interval; Clb = chlorambucil; HR = hazard ratio; NR = not reached; O = Obinutuzumab; PFS = progression free survival; *TP53* = tumour protein p53; vs = versus.

Sharman JP et al. Oral Presentation Presented at: ASH; December 9-12, 2023; San Diego.

Safety: Events of Clinical Interest

- The median duration of treatment was 74.4 months for A in A+O, and 72 months for A monotherapy, and 5.5 and 5.6 months for O in the A+O and O+Clb arms respectively, and 5.5 months for Clb in O+Clb arm.
- The events of clinical interest are summarized in the table below.

	A+O (n=178)		A (n=179)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Cardiac events	49 (27.5)	22 (12.4)	42 (23.5)	21 (11.7)
Atrial fibrillation	13 (7.3)	3 (1.7)	16 (8.9)	3 (1.7)
Bleeding	95 (53.4)	12 (6.7)	81 (45.3)	8 (4.5)
Major bleeding	16 (9.0)	12 (6.7)	10 (5.6)	8 (4.5)
Hypertension[a]	20 (11.2)	8 (4.5)	20 (11.2)	9 (5.0)
Infections	147 (82.6)	63 (35.4)	144 (80.4)	50 (27.9)
SPMs	36 (20.2)	18 (10.1)	35 (19.6)	9 (5.0)
SPMs excluding non-melanoma skin	24 (13.5)	13 (7.3)	22 (12.3)	7 (3.9)

Data are n (%) unless otherwise specified.

[a]Hypertension events were based on Standardized MedDRA query (SMQ) Hypertension (narrow).

A = acalabrutinib; Clb = chlorambucil; O = obinutuzumab; SPM = secondary primary malignancies.

Sharman JP et al. Oral Presentation Presented at: ASH; December 9-12, 2023; San Diego.

SEQUOIA – Extended Follow-Up

Cohort 1 43,7 m
Cohort 2 47,9 m

Study Design[1-3]

PHASE 3

Study Identifier: BGB-3111-304, NCT03336333

Primary Endpoint: PFS by IRC in Cohort 1

Key Secondary Endpoints: Cohort 1: ORR, DOR, safety; Cohort 2: ORR, PFS, DOR; Cohort 3: ORR, PFS, DOR, rate of undetectable MRD at $<10^{-4}$ sensitivity, safety

KEY ELIGIBILITY CRITERIA

- Treatment-naïve CLL/SLL
- Met iwCLL criteria for treatment
- ≥65 years of age or <65 years of age and unsuitable for FCR treatment[a]
- Measurable disease by CT/MRI
- No current or past history of Richter's transformation

STRATIFICATION FACTORS

- Age (<65 vs. ≥65 years)
- Binet stage (C vs. A or B)
- *IGHV* mutational status (mutated vs. unmutated)
- Geographic region (NA vs. EU vs. APAC)

TREATMENT

del(17p) FISH test

Cohort 1 without del(17p) → R 1:1

- **Arm A: Zanubrutinib 160 mg PO BID until PD (n=241)**
- **Arm B: Bendamustine + rituximab × 6 (n=238)**

Cohort 2 with del(17p)

- **Arm C: Zanubrutinib 160 mg PO BID until PD (n=111)[b]**

Cohort 3 with del(17p)

- **Arm D: Zanubrutinib 160 mg PO BID + venetoclax (n= ~80)**

FOLLOW-UP

Safety and survival

Assessments

- Response assessments were conducted every 12 weeks from start of cycle 1 for 96 weeks and then every 24 weeks until PD
- CR/CRi confirmed via bone marrow biopsy
- AEs documented until PD or start of next CLL therapy

Statistical Analysis

- Efficacy endpoints analyzed using ITT analysis and the per-protocol analysis set
- Safety was assessed in all pts who received ≥1 dose of treatment

[a]Defined as Cumulative Illness Rating Scale >6, creatinine clearance <70 mL/min, or a history of previous severe infection or multiple infections within the last 2 years; [b]One patient without del(17p) was misassigned to the nonrandomly assigned cohort of patients with del(17p). The patient is excluded from the efficacy analysis in this cohort

1L=first line, AE=adverse event, APAC=Asia/Pacific, BID=twice daily, CLL=chronic lymphocytic leukemia, CR=complete response, CRi=complete response with incomplete hematologic recovery, CT=computed tomography, DOR=duration of response, EU=Europe, FCR=fludarabine, cyclophosphamide, and rituximab (chemotherapy regimen), FISH=fluorescence in situ hybridization, IGHV=immunoglobulin heavy-chain variable region gene, IRC=independent review committee, ITT=intention-to-treat, iwCLL=International Workshop on Chronic Lymphocytic Leukemia, MRD=minimal residual disease, MRI=magnetic resonance imaging, NA=North America, ORR=overall response rate, OS=overall survival, PD=progressive disease, PFS=progression-free survival, PO=per oral, R=randomized, SLL=small lymphocytic lymphomae.

1. ClinicalTrials.gov. https://clinicaltrials.gov/ct2/show/NCT03336333. Accessed January 2021. 2. Tam et al. Lancet Oncology. 2022. 22;S1460-2045. 3.Munir T et al. Poster presented at EHA 2023; Abstract number: P639

Patient Characteristics and Baseline Demographics

	Patients without del(17p)		Patients with del(17p)
	Arm A: zanubrutinib (n=241)	Arm B: BR (n=238)	Arm C: zanubrutinib (n=111)[a]
Age, median (range), years	70 (40-86)	70 (35-87)	71 (42-87)
Age ≥65 years, n (%)[b]	198 (82)	195 (82)	95 (86)
Male, n (%)	154 (64)	144 (61)	79 (71)
ECOG PS 2, n (%)	15 (6)	20 (8)	14 (13)
Geographic region, n (%)			
North America	34 (14)	28 (12)	12 (11)
Europe	174 (72)	172 (72)	52 (47)
Asia-Pacific	33 (14)	38 (16)	47 (42)
Binet stage C, n (%)[c]	70 (29)	70 (29)	39 (35)
Bulky disease ≥5 cm, n (%)	69 (29)	73 (31)	44 (40)
Cytopenia at baseline, n (%)[d]	102 (42)	110 (46)	61 (55)
Unmutated IGHV, n/N (%)[e]	125/234 (53)	121/231 (52)	67/103 (65)
del(11q), n (%)	43 (18)	46 (19)	37 (33)
TP53 mutation, n/N (%)	15/232 (6)	13/223 (6)	47/109 (43)
Complex karyotype with ≥3 abnormalities, n/N (%)[f]	23/164 (14)	22/161 (14)	33/88 (38)

Data cutoff: 31 October 2022

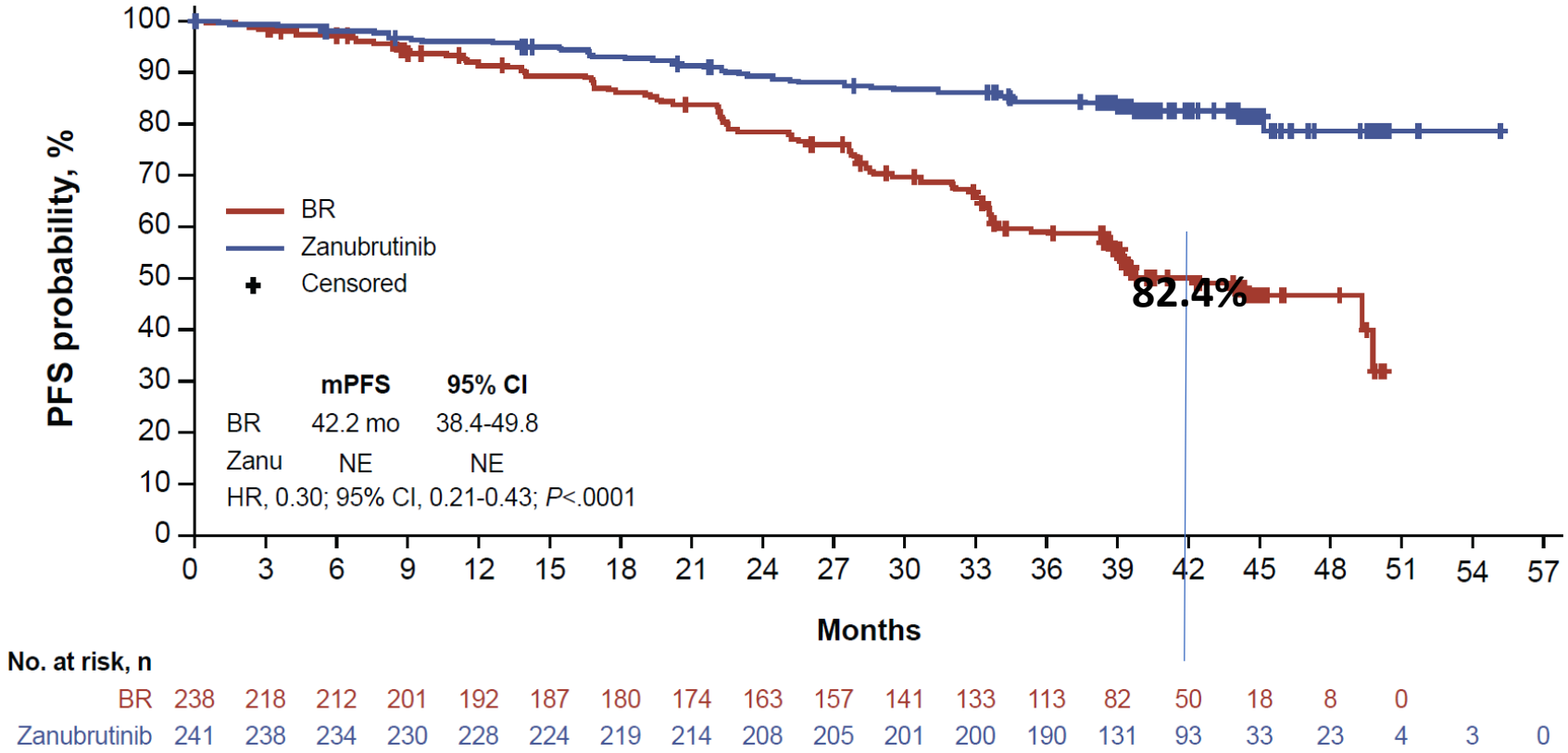
[a]One patient without del(17p) was misassigned to the nonrandomly assigned cohort of patients with del(17p). The patient is excluded from the efficacy analysis in this cohort; [b]Patients aged ≥75 years included 63 patients in group A (26%), 53 patients in group B (22%), and 27 patients in group C (24%); [c]Patients with SLL had Binet stage calculated as if they had CLL; [d] Defined as having anemia (hemoglobin ≤110 g/L), thrombocytopenia (platelets ≤100×10^9/L), or neutropenia (absolute neutrophil count ≤1.5×10^9/L); [e]Twenty-two patients had insufficient RNA quantity/quality for polymerase chain reaction amplification of immunoglobulin heavy chain variable region for sequencing or had missing data; [f]Patients with missing/insufficient metaphase activity were omitted from the complex karyotype analysis.

BR=bendamustine plus rituximab, CLL=chronic lymphocytic leukemia, ECOG=Eastern Cooperative Oncology Group, IGHV=immunoglobulin heavy chain variable, PS=performance status, SLL=small lymphocytic lymphoma,

Munir T et al. Poster presented at EHA 2023; Abstract number: P639

Progression-Free Survival

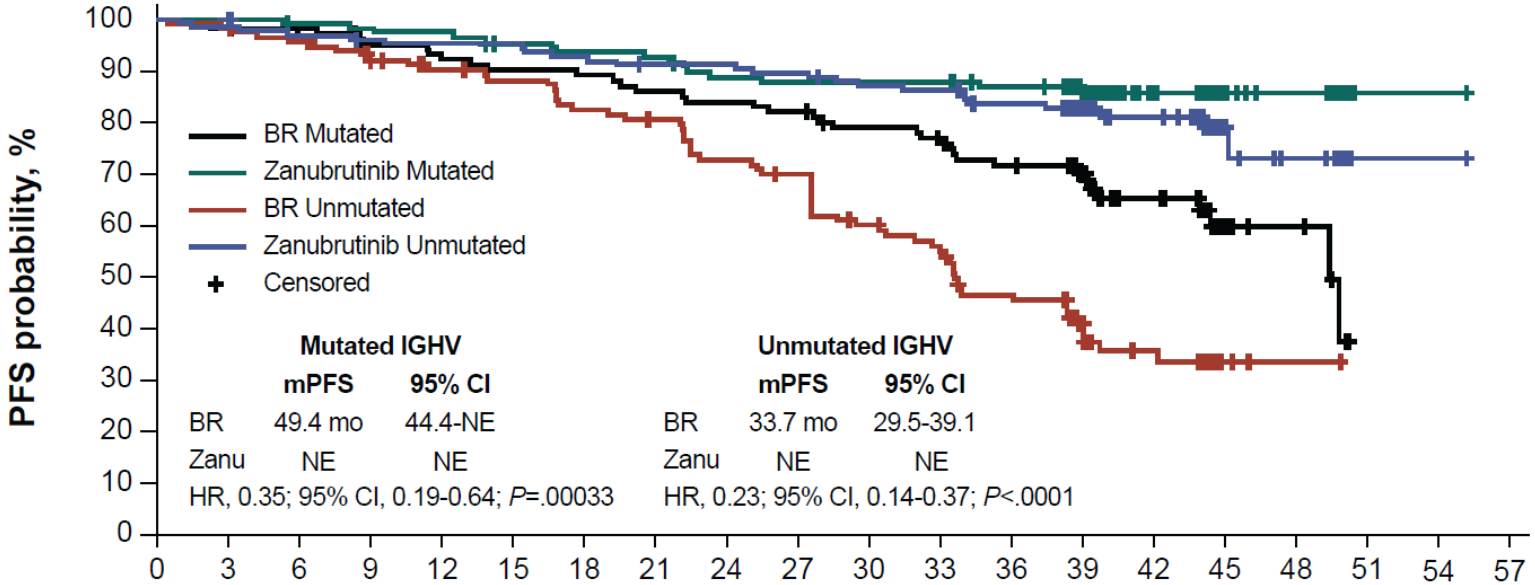
Cohort 1 – Overall Population



- In cohort 1, median PFS was not reached in patients who received zanubrutinib; in patients who received BR, median PFS was 42.2 months
- Estimated 42-month PFS rates with zanubrutinib and BR were **82.4%** and 50.0%, respectively

Data cutoff: 31 October 2022. All *P* values are two-sided. BR=bendamustine plus rituximab; CI=confidence interval; HR=hazard ratio; NE=not estimable. Munir T et al. Poster presented at EHA 2023; Abstract P1439

Progression-Free Survival by IGHV Mutation Status Cohort 1 – Overall Population

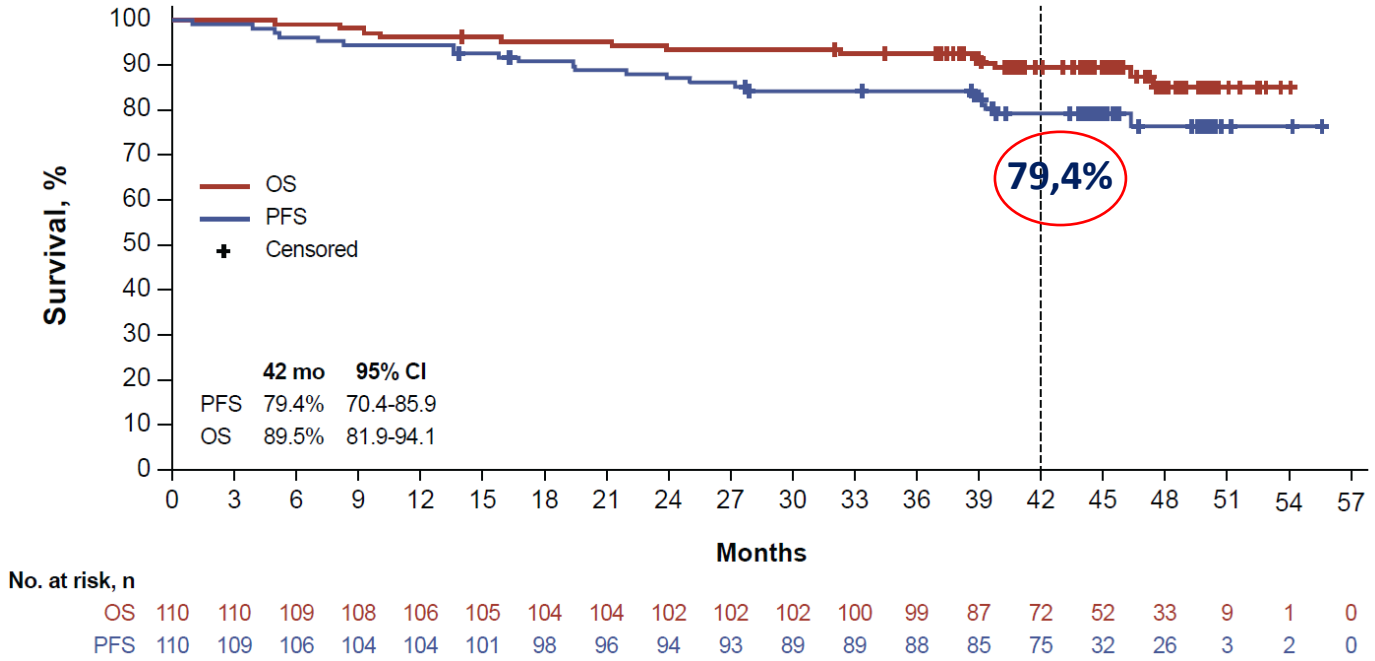


No. at risk, n																				
BR Mutated	110	101	99	94	91	89	88	85	83	81	76	73	67	53	31	14	7	0		
Zanubrutinib Mutated	109	109	107	106	105	101	99	98	93	92	92	92	89	63	43	18	13	1	1	0
BR Unmutated	121	110	107	101	95	92	86	83	75	71	60	55	43	26	17	4	1	0		
Zanubrutinib Unmutated	125	122	120	118	117	117	114	111	111	109	105	104	97	65	47	14	9	2	2	0

- PFS was significantly improved with zanubrutinib vs BR in patients with mutated IGHV (2-sided P=.00033) and unmutated IGHV (2-sided P<.0001)

Progression-Free Survival by del17p/TP53

SEQUOIA – Extended Follow-Up



	Cohort 2 – Del(17p) Zanubrutinib (n=111)
CR / CRi Rate	14.5%

- Median PFS was not reached
  - Estimated 42-month PFS rate was 79.4%

- Median OS was not reached
  - Estimated 42-month OS rate was 89.5%

Treatment-Emergent and Post-treatment AEIs[a]

Cohorts 1 and 2 (Any Grade and Grade ≥3)[b]

AEIs, n (%)	Patients without del(17p)				Patients with del(17p)	
	Arm A: zanubrutinib (n=240)[a]		Arm B: BR (n=227)[b]		Arm C: zanubrutinib (n=111)	
	Any grade	Grade ≥3	Any grade	Grade ≥3	Any grade	Grade ≥3
Infections	175 (72.9)	57 (23.8)	142 (62.6)	50 (22.0)	89 (80.2)	30 (27.0)
Bleeding	117 (48.8)	14 (5.8)	28 (12.3)	4 (1.8)	64 (57.7)	6 (5.4)
Other malignancies	45 (18.8)	22 (9.2)	28 (12.3)	11 (4.8)	27 (24.3)	8 (7.2)
Hypertension	42 (17.5)	22 (9.2)	31 (13.7)	15 (6.6)	15 (13.5)	7 (6.3)
Diarrhea	41 (17.1)	4 (1.7)	32 (14.1)	5 (2.2)	22 (19.8)	1 (0.9)
Neutropenia	40 (16.7)	30 (12.5)	129 (56.8)	116 (51.1)	21 (18.9)	18 (16.2)
Arthralgia	37 (15.4)	2 (0.8)	23 (10.1)	1 (0.4)	26 (23.4)	1 (0.9)
Anemia	17 (7.1)	1 (0.4)	47 (20.7)	5 (2.2)	7 (6.3)	0 (0)
Thrombocytopenia	15 (6.3)	5 (2.1)	41 (18.1)	18 (7.9)	9 (8.1)	2 (1.8)
Atrial fibrillation/flutter	12 (5.0)	3 (1.3)	6 (2.6)	3 (1.3)	7 (6.3)	5 (4.5)
Myalgia	9 (3.8)	0 (0)	4 (1.8)	0 (0)	8 (7.2)	1 (0.9)
Opportunistic infection	6 (2.5)	1 (0.4)	4 (1.8)	3 (1.3)	1 (0.9)	1 (0.9)

Data cutoff: 31 October 2022.

[a]Patients who did not receive zanubrutinib are not included in the safety analysis; [b]Patients who did not receive BR are not included in the safety analysis.

AEI=adverse event of interest, BR=bendamustine plus rituximab,

Munir T et al. Poster presented at EHA 2023; Abstract number: P639

UNIVERSITÀ CATTOLICA del Sacro Cuore

Grazie per l'attenzione