CLL: State of the Art 2024

Elias Jabbour

Treatment Evolution in CLL

1960s

Alkylating agents
- Chlorambucil
- Cyclophosphamide

1970s

Purine nucleosides
- Fludarabine
- Pentostatin
- Cladribine

1980s

1990s

Purine nucleosides and alkylators

2000s

Chemoimmunotherapy (FCR, BR)
Alemtuzumab
Lenalidomide

2014-

BTK inhibitors (Ibrutinib, Acalabrutinib)
PI3K inhibitors (Idelalisib, Duvelisib)
BCL-2 inhibitor (Venetoclax)
Novel CD20 mAb (Obinutuzumab)

2023

BTK inhibitors (Zanubrutinib, Pirtobrutinib)

2024+

CAR T, CD20 bispecifics, novel BCL2i, BTK PROTACs, etc.

CLL Evolving Treatment Paradigm

Chemoimmunotherapy era

- FCR (young fit)
- BR / Chlorambucil-based (older adults)

Targeted Therapies era

- FCR (young fit *IGHV*-m)
- Targeted therapies – BTK inhibitors +venetoclax (all; or all others)

Targeted Therapies in Frontline CLL

Indefinite

- Ibrutinib
- Acalabrutinib +/- Obinutuzumab
- Zanubrutinib

Time-limited

- Venetoclax + Obinutuzumab
- Venetoclax + Ibrutinib (approved ex-US)

Cure of CLL – Couplets vs Triplets

- Ibrutinib-venetoclax finite Rx duration = cure
- Questions : duration (2 vs more years); couplets vs triplets

BTK inhibitors	BCL2 inhibitors	CD20 Ab
Ibrutinib	Venetoclax	Rituximab
Acalabrutinib; zanubrutinib	---	Obinutuzumab
Pirtobrutinib (Loxo305)	---	Bi-specific T-cell engagers(BiTEs)

VOLUME 23 · NUMBER 18 · JUNE 20 2005

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Early Results of a Chemoimmunotherapy Regimen of Fludarabine, Cyclophosphamide, and Rituximab As Initial Therapy for Chronic Lymphocytic Leukemia

Michael J. Keating, Susan O'Brien, Maher Albitar, Susan Lerner, William Plunkett, Francis Giles, Michael Andreeff, Jorge Cortes, Stefan Faderl, Deborah Thomas, Charles Koller, William Wierda, Michelle A. Detry, Alice Lynn, and Hagop Kantarjian

From the Departments of Leukemia, Hematopathology, Experimental Therapeutics, Blood and Marrow Transplantation, and the Biostatistics and Applied Mathematics, The University of Texas M.D. Anderson Cancer Center, Houston, TX.

Submitted December 9, 2003; accepted November 11, 2004.

ABSTRACT

Purpose

Fludarabine and cyclophosphamide (FC), which are active in treatment of chronic lymphocytic leukemia (CLL), are synergistic with the monoclonal antibody rituximab in vitro in lymphoma cell lines. A chemoimmunotherapy program consisting of fludarabine, cyclophosphamide, and rituximab (FCR) was developed with the goal of increasing the complete remission (CR) rate in previously untreated CLL patients to ≥ 50%.

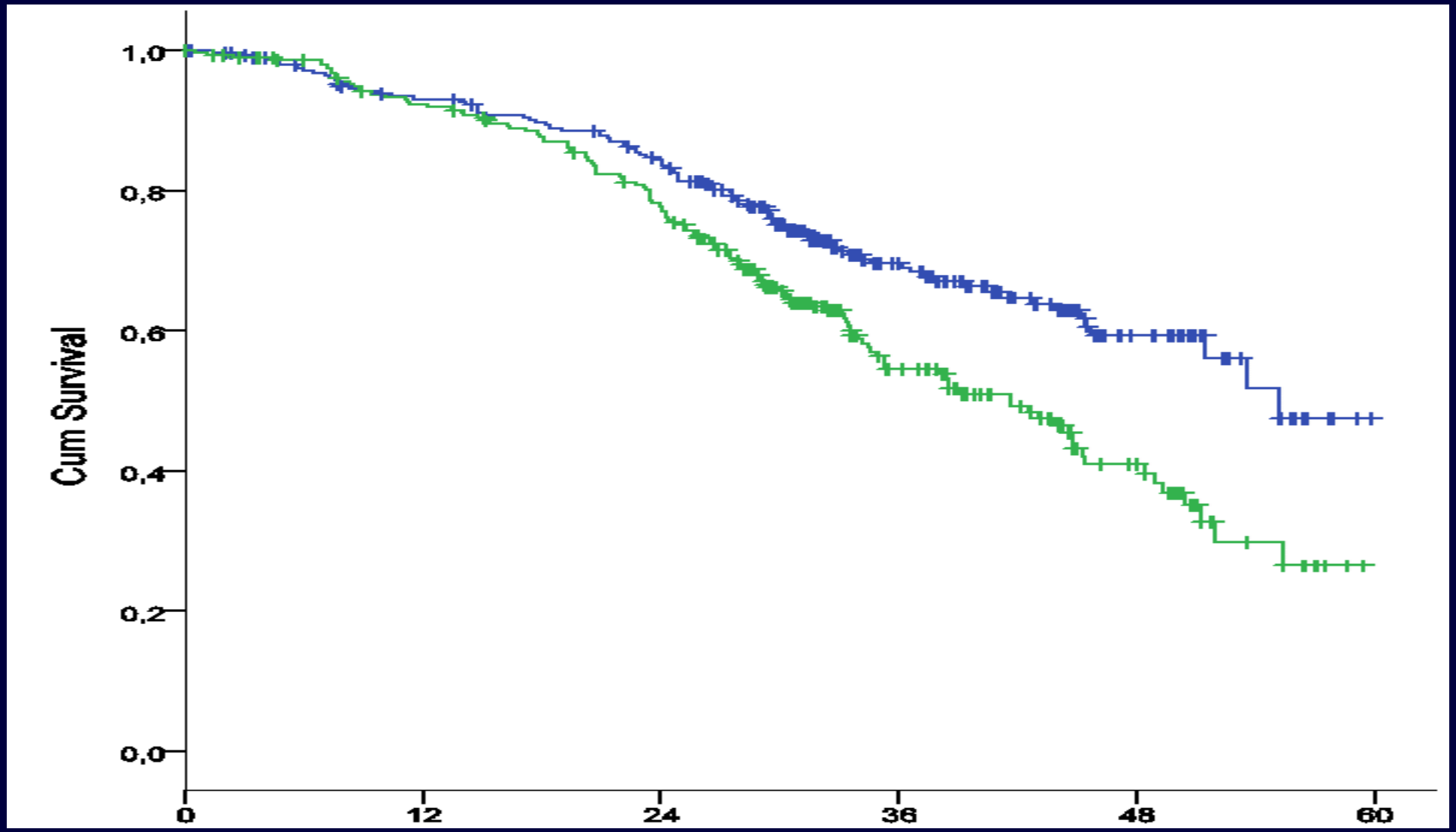
CLL Frontline Treatment with FCR

Response	# Pts	%	
CR	217	(72)	95%
Nodular PR	31	(10)	
PR	37	(12)	
No Response	13	(4)	
Early Death	2	(1)	

Keating . J Clin Oncol. 2005;23:4079.

CLL10 Study: FCR VS BR in Front-Line

ITT Progression-free Survival = Primary Endpoint



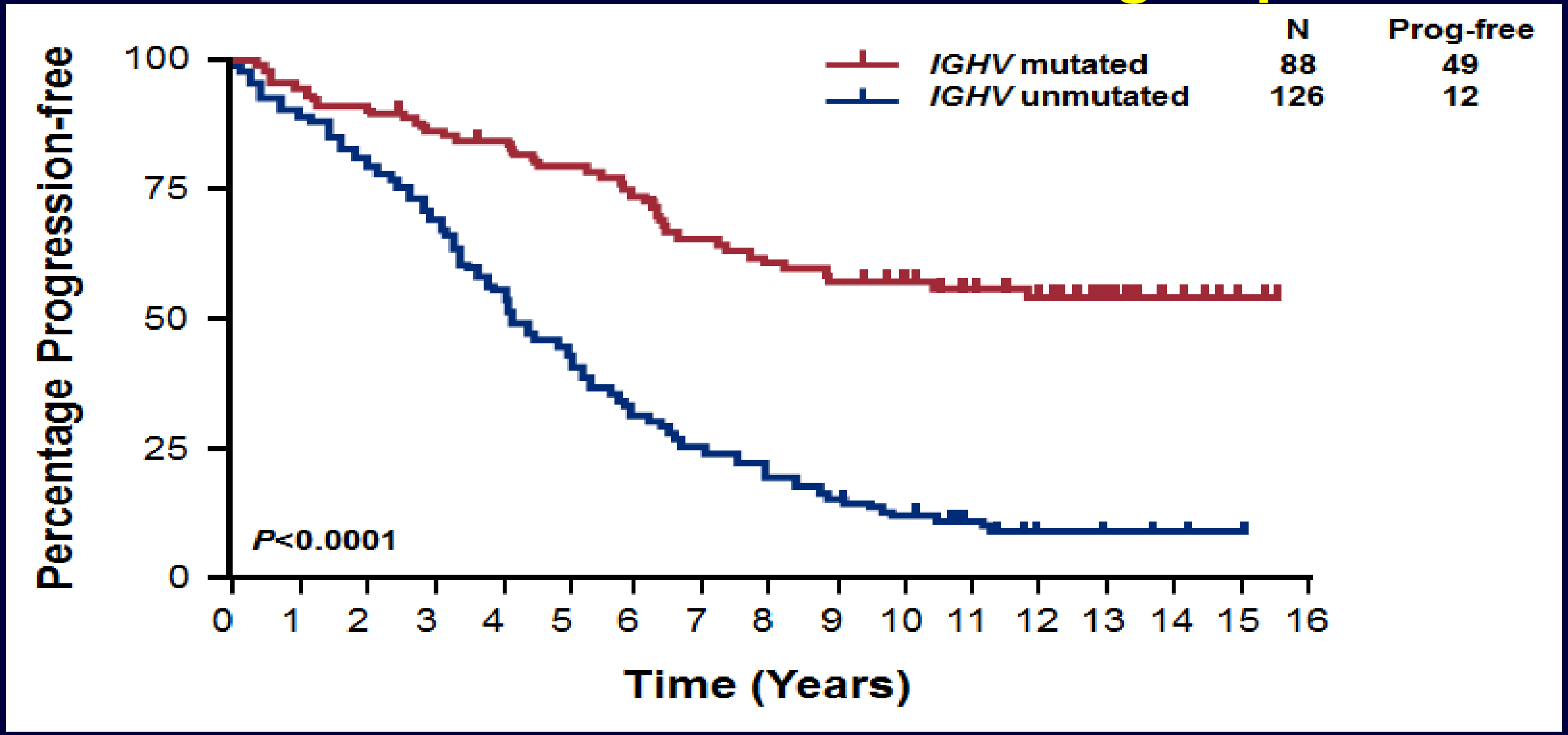
Median PFS

FCR 55.2 months

BR 41.7 months

***P* < 0.001**
HR = 1.626 = > 1.388

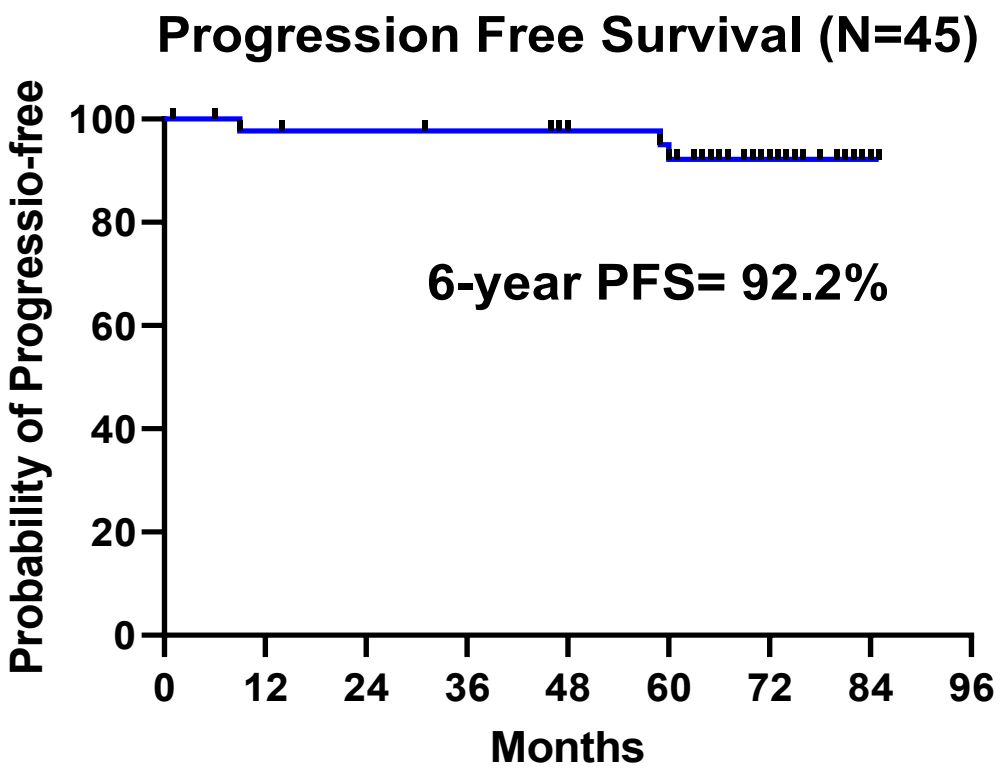
Favorable Long-term PFS with Firstline FCR in *IGHV*-M Subgroup

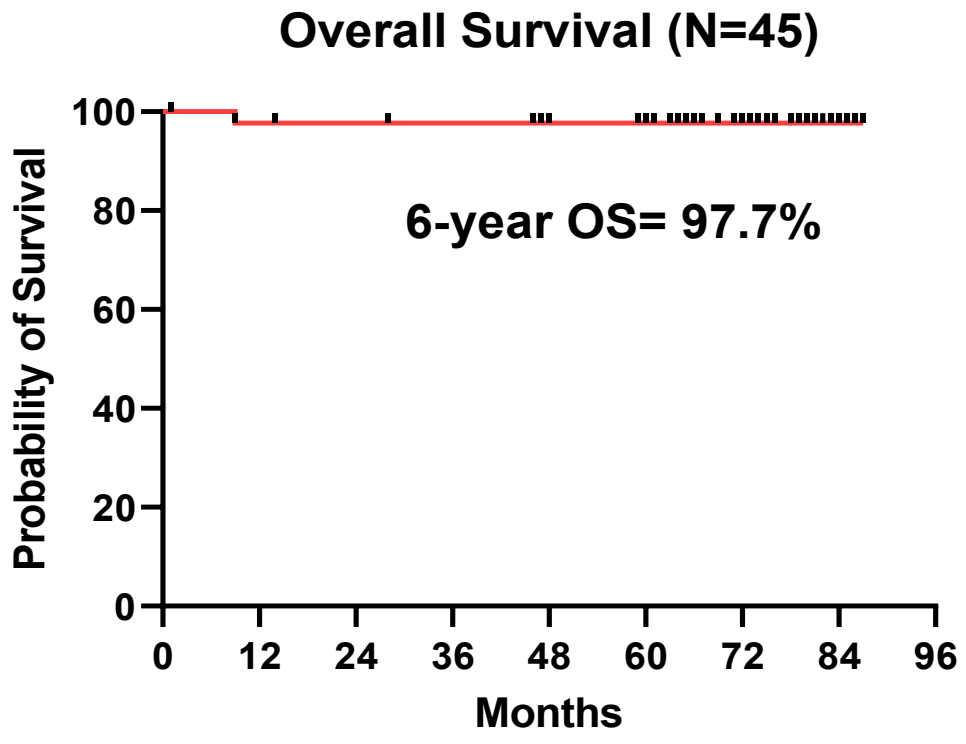


Thompson, Blood 2016.

iFCG in *IGHV*-M, non-del(17p)/*TP53*-mutated CLL

- 45 pts, median age 60 [25-71]; median FU 6 yrs
- iFCG x 3 cycles, followed by 9 cycles of ibrutinib (with 3 or 9 cycles of obin)
- Best bone marrow U-MRD4 = 44/45 (98%) (ITT analysis).
- 2 CLL progression; no Richter transformation. 1MDS





*sole event in both PFS and OS curve is patient's death from CHF

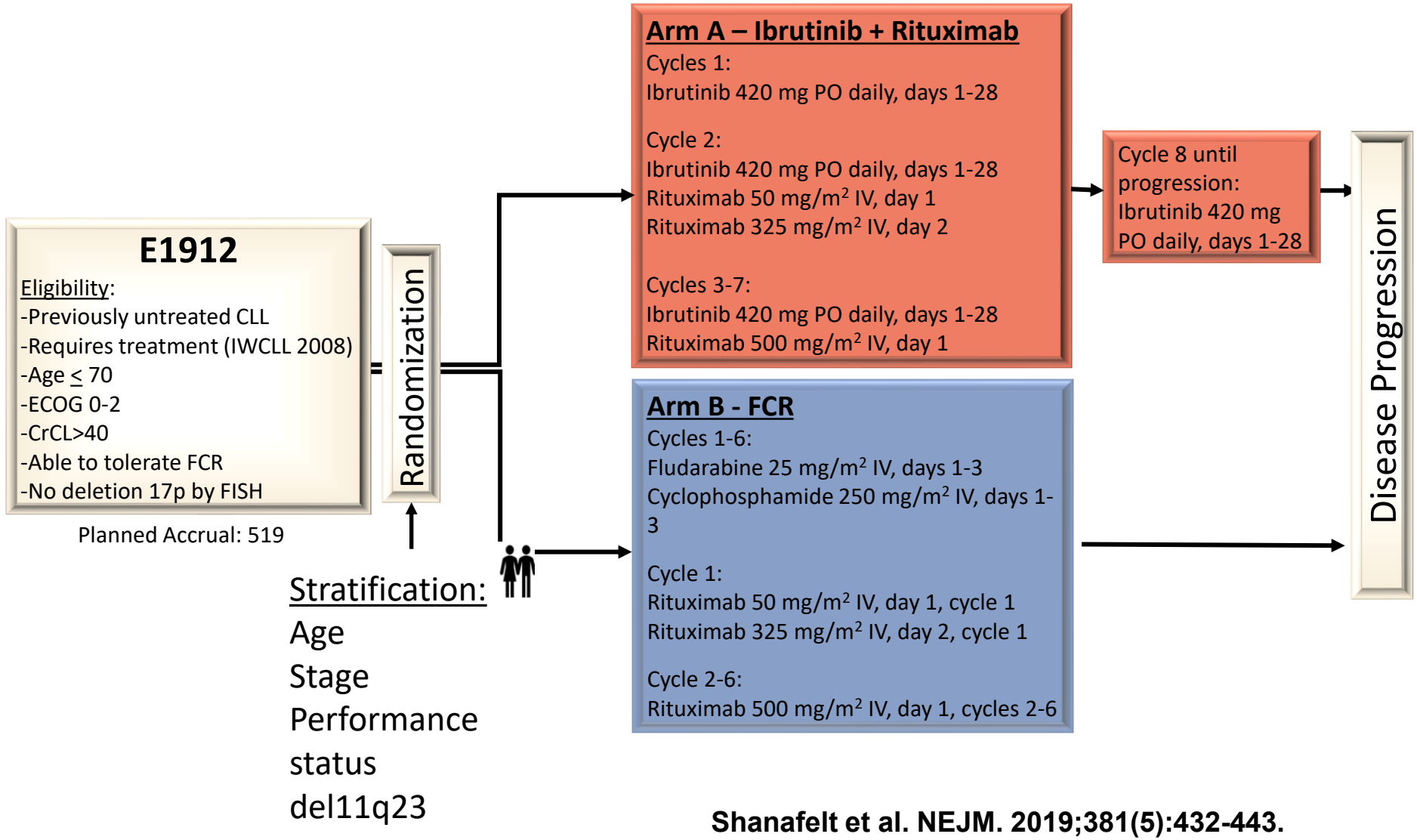
Jain. Leukemia. 2021 Dec;35: 3421-3429. Jain. Blood 142: abstr 3267;2023

YOUNG ‘FIT’ PATIENTS (FCR ELIGIBLE)

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

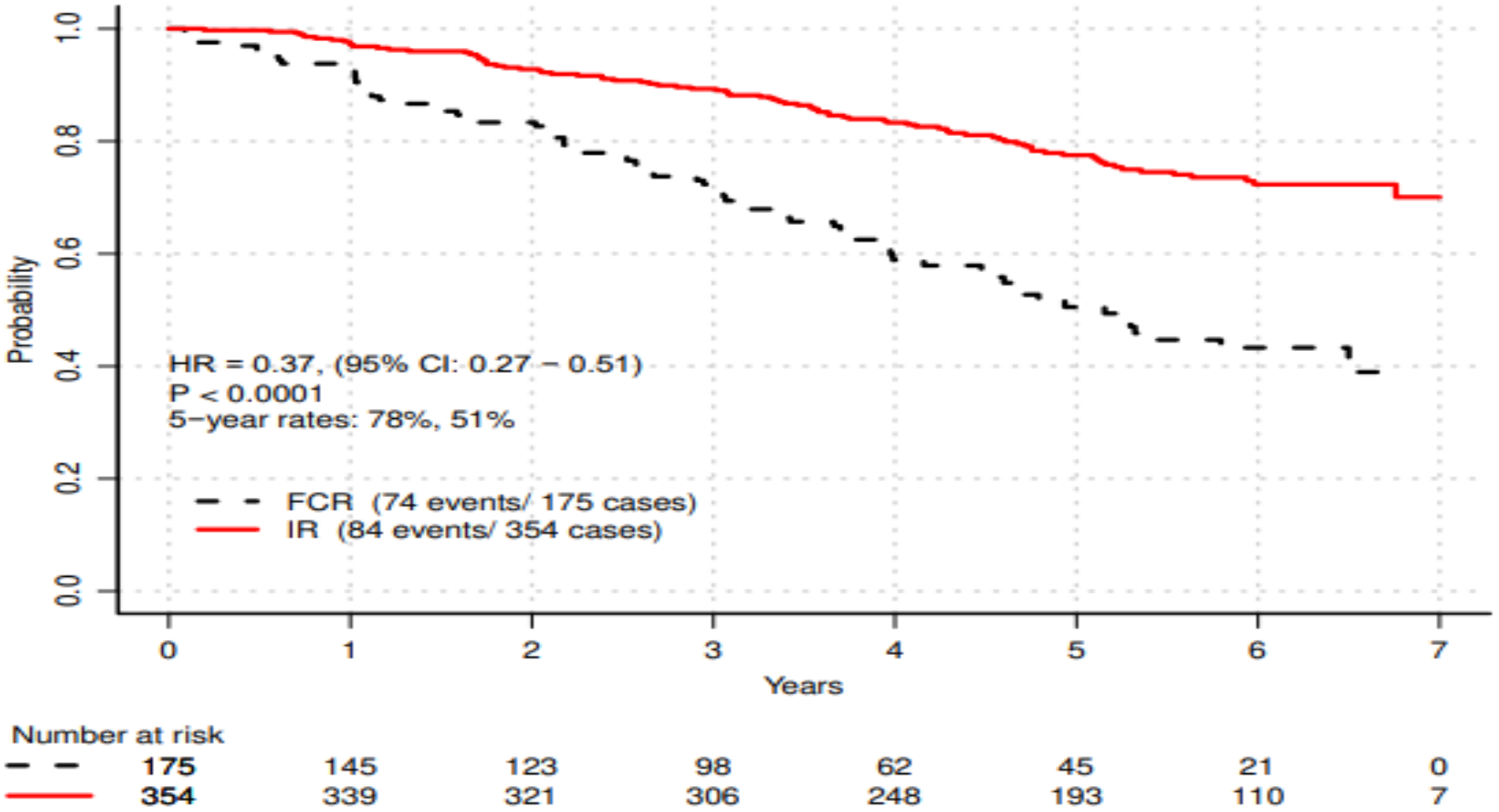
Tait Shanafelt, Xin Victoria Wang, Neil E. Kay, Susan O'Brien, Jacqueline Barrientos , Curt Hanson, Harry Erba, Rich Stone, Mark Litzow, Marty Tallman

E1912 Study design



Shanafelt et al. NEJM. 2019;381(5):432-443.
Updated in Shanafelt et al. Blood. 2022 Apr 15.

Progression-Free Survival

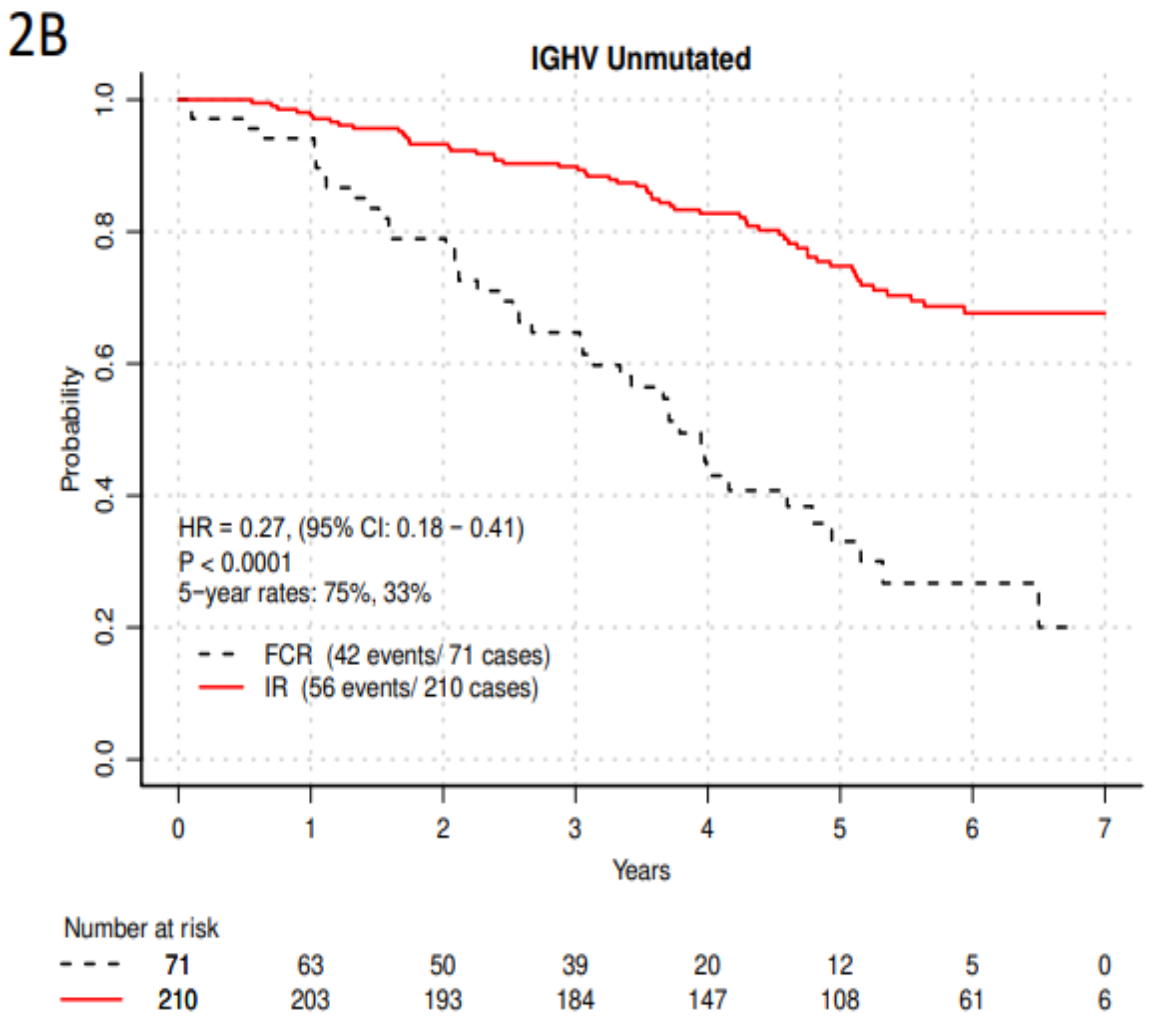


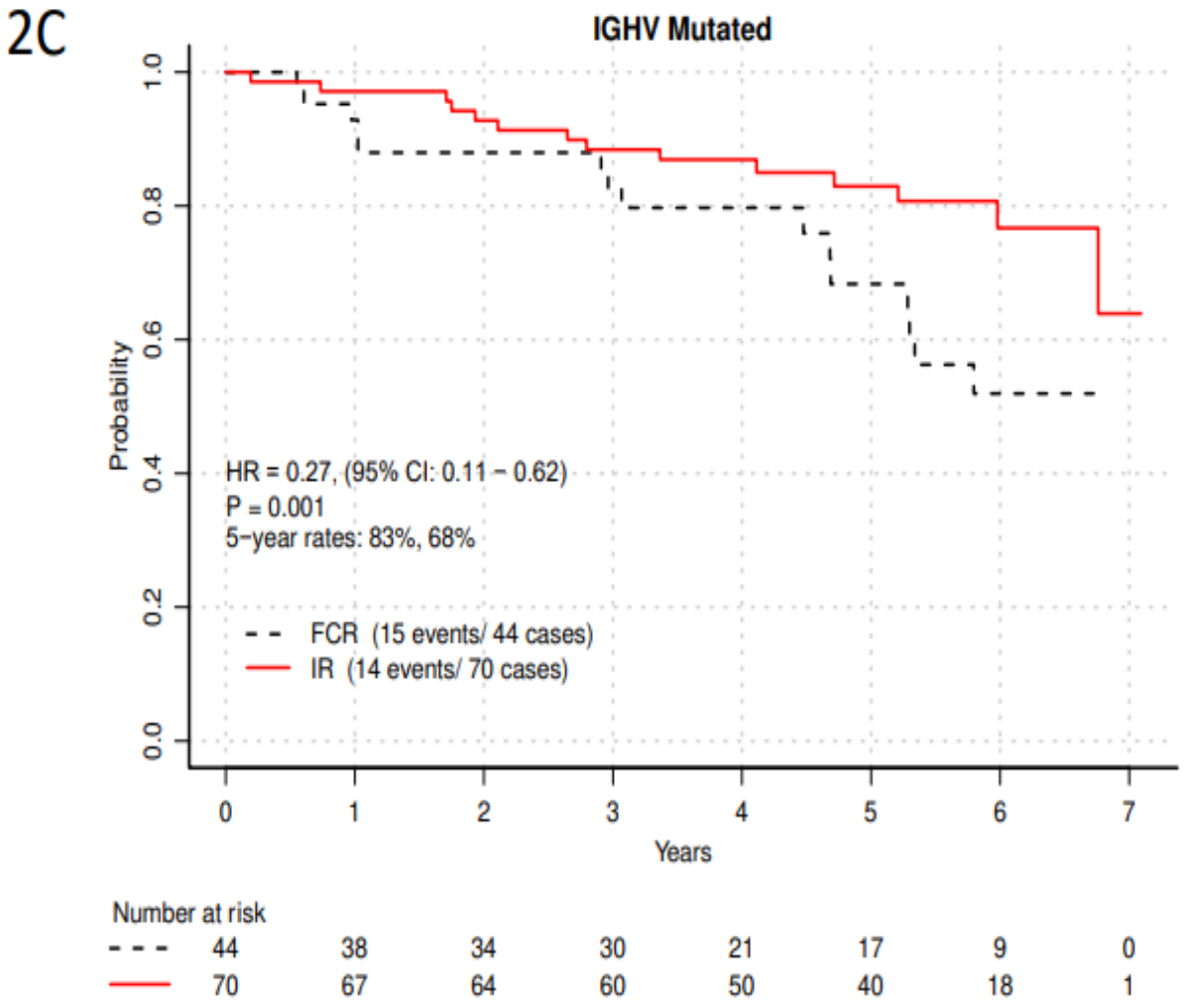
Median follow-up 5.8 yr

Shanafelt et al. NEJM. 2019;381(5):432-443.
Updated in Shanafelt et al. Blood. 2022 Apr 15.

ECOG-ACRIN cancer research group | Reshaping the future of patient care

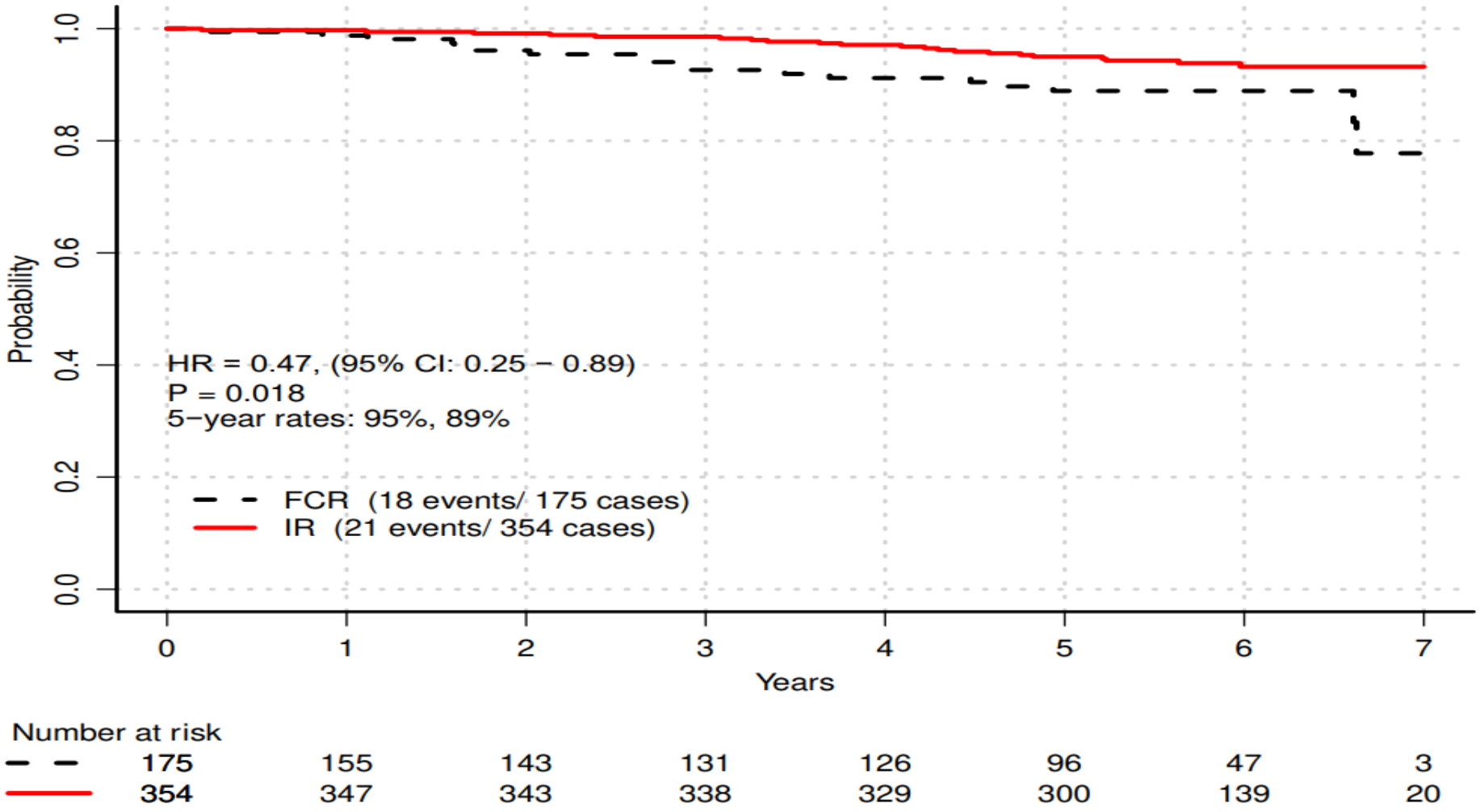
Progression-Free Survival by IGHV Status





Shanafelt et al. NEJM. 2019;381(5):432-443.
Updated in Shanafelt et al. Blood. 2022 Apr 15.

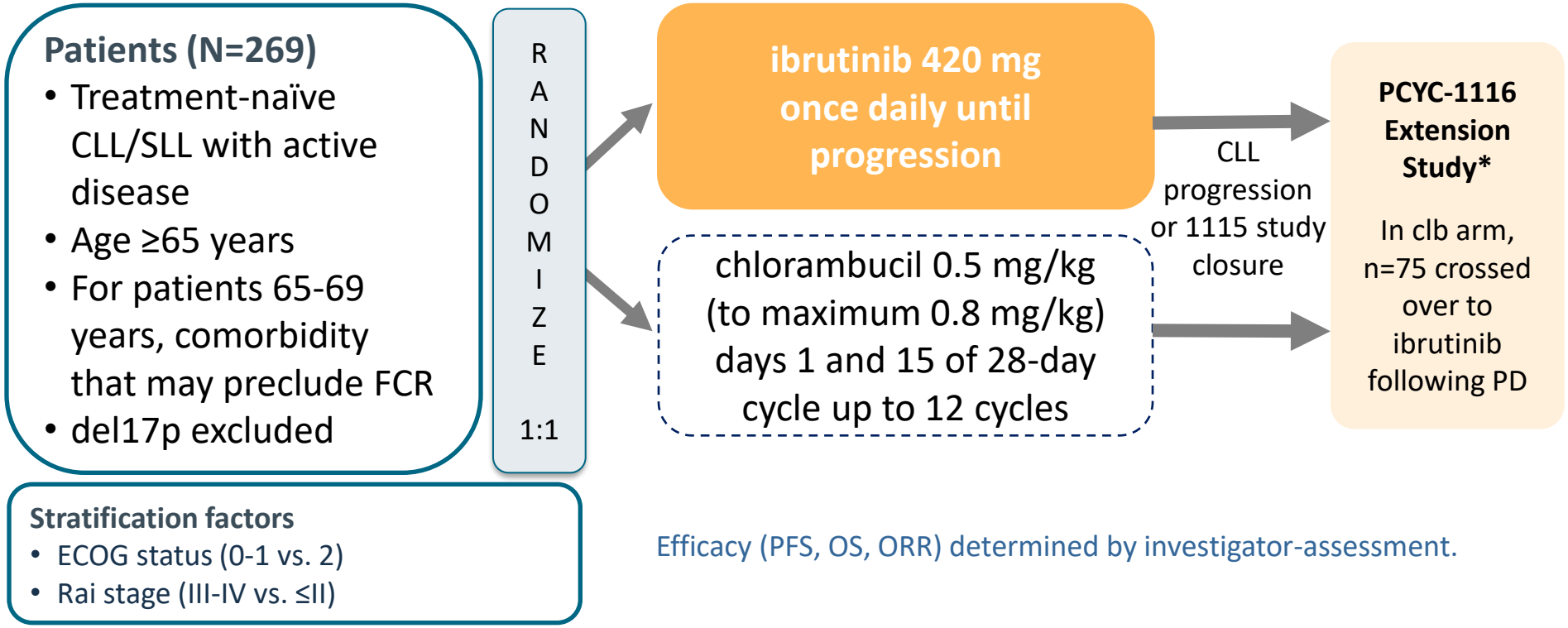
Overall Survival



Shanafelt . NEJM. 2019;381(5):432-443.
Updated in Shanafelt . Blood. 2022 Apr 15.

PATIENTS ≥65 YRS (FCR INELIGIBLE)

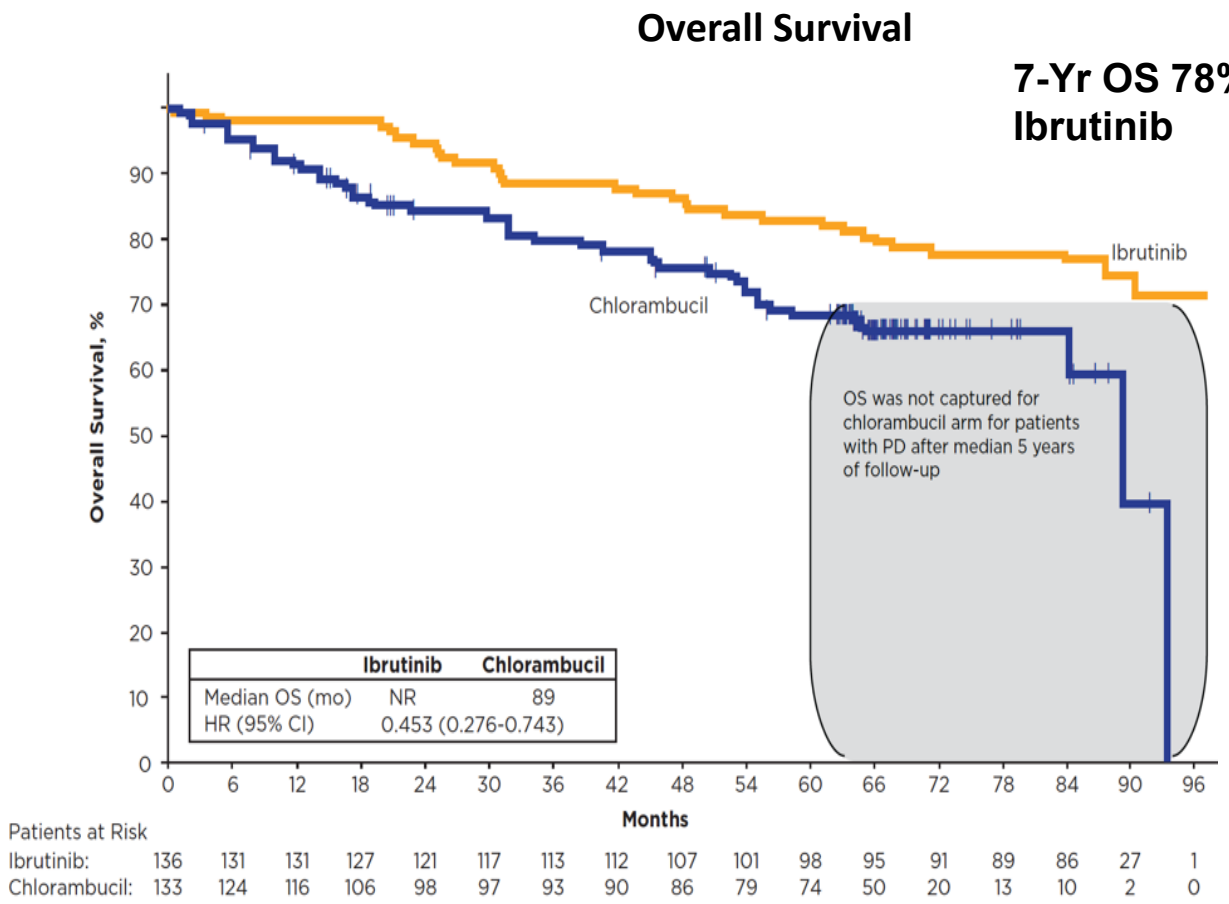
RESONATE-2 (PCYC-1115/1116) Study Design

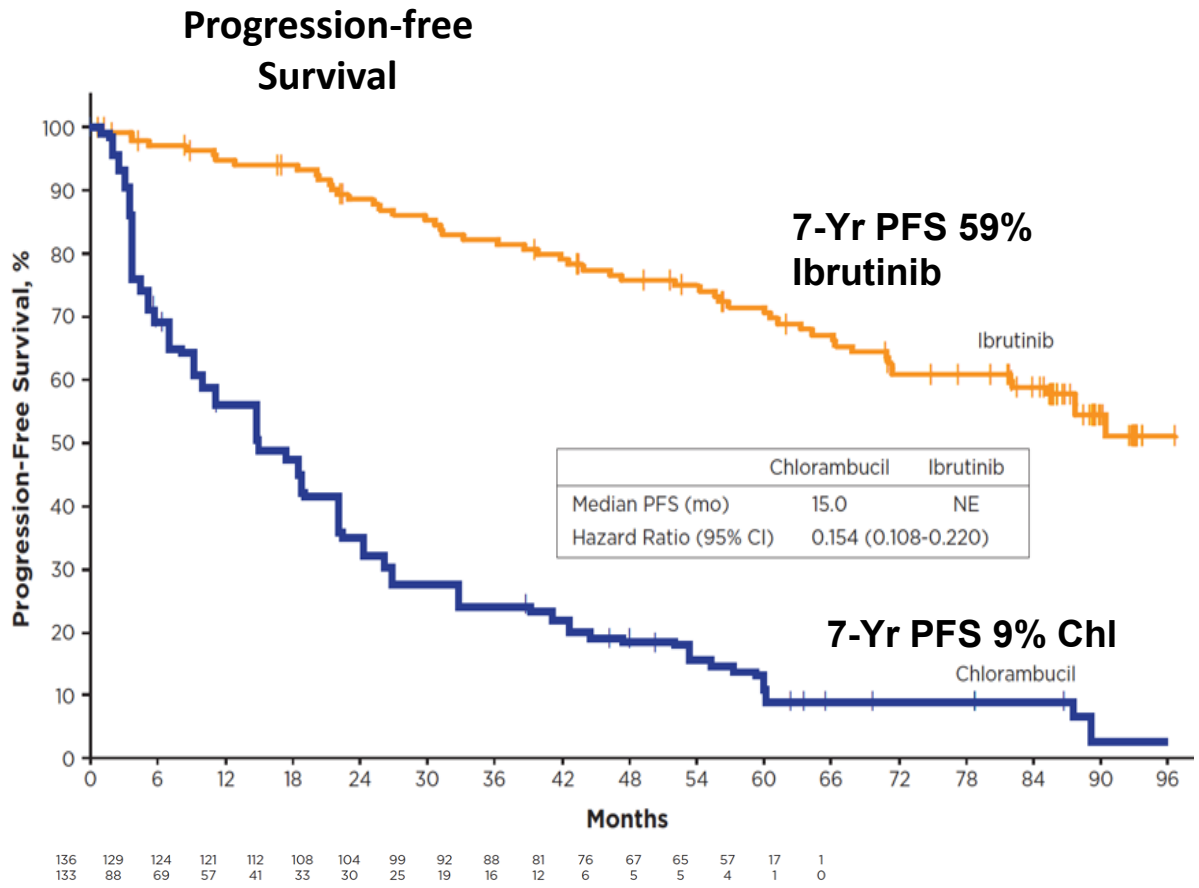


Efficacy (PFS, OS, ORR) determined by investigator-assessment.

Burger. Leukemia. 2020 Mar;34(3):787-798.

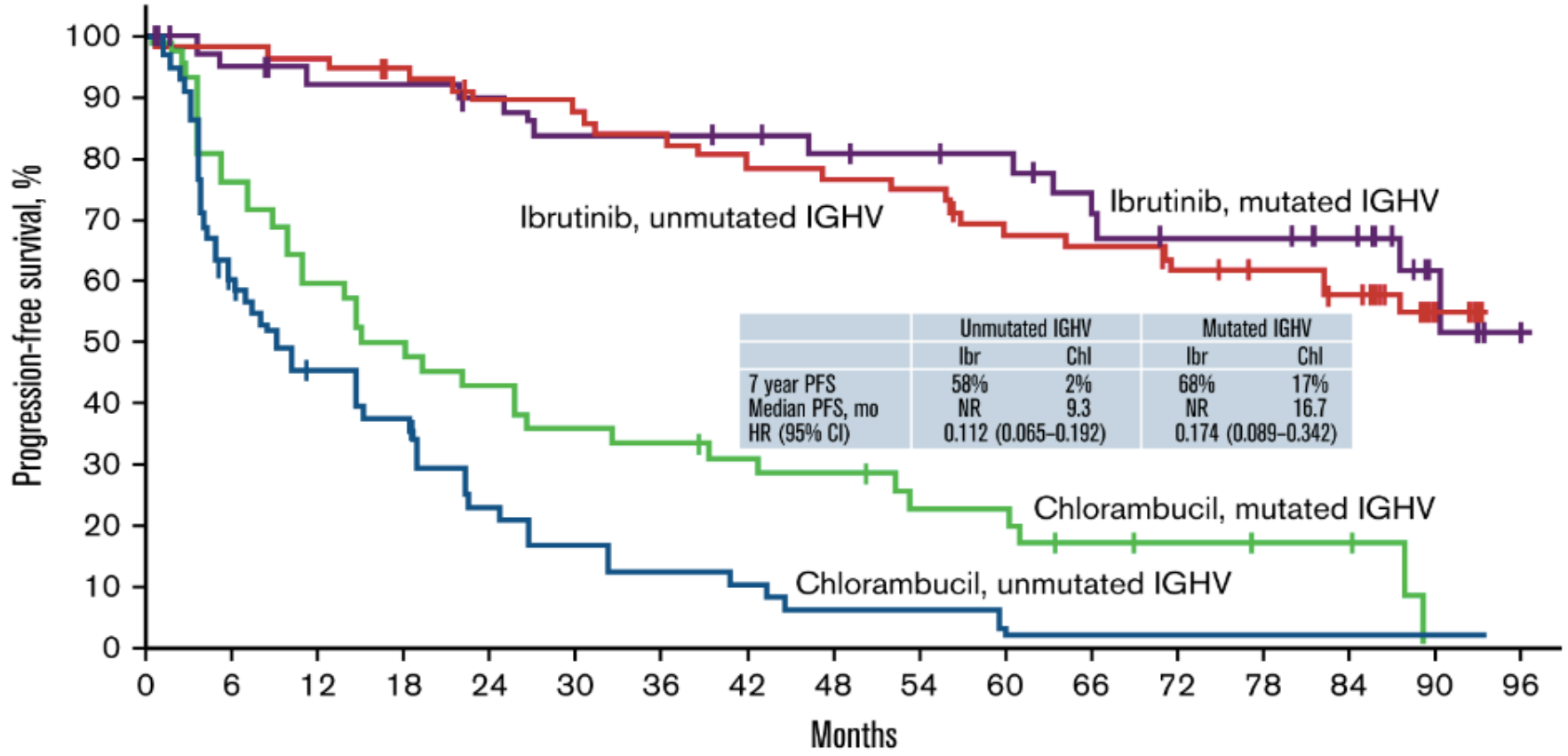
Up to 8 Years of Follow-up in RESONATE-2: OS and PFS





1. Barr *Blood Adv*. 2022 Apr 4:bloodadvances.2021006434.doi:10.1182/bloodadvances.2021006434

PFS by Mutation Status



	Unmutated IGHV		Mutated IGHV	
	Ibr	Chl	Ibr	Chl
7 year PFS	58%	2%	68%	17%
Median PFS, mo	NR	9.3	NR	16.7
HR (95% CI)	0.112 (0.065–0.192)		0.174 (0.089–0.342)	

Patients at risk																	
Ibrutinib, mutated IGHV:	40	37	34	34	32	30	30	29	27	26	25	22	19	19	16	6	1
Ibrutinib, unmutated IGHV:	58	57	56	53	49	48	46	43	42	41	36	35	32	30	27	10	0
Chlorambucil, mutated IGHV:	42	32	25	21	18	15	14	12	11	8	8	5	4	4	3	0	0
Chlorambucil, unmutated IGHV:	60	33	23	19	11	8	6	5	3	3	2	1	1	1	1	1	0

Barr Blood Adv 2022 April

Presentation #636

Acalabrutinib ± Obinutuzumab vs Obinutuzumab + Chlorambucil in Treatment-naive Chronic Lymphocytic Leukemia: 6-Year Follow-up of ELEVATE-TN

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[1]Willamette Valley Cancer Institute and Research Center/US Oncology Research, Eugene, OR, USA; [2]Somogy County Mór Kaposi General Hospital, Kaposvár, Hungary; [3]Maria Skłodowska-Curie National Research Institute of Oncology, Krakow, Poland; [4]Novant Health Cancer Institute, Charlotte, NC, USA; [5]Swedish Cancer Institute, Seattle, WA, USA; [6]Sarah Cannon Research Institute, Tennessee Oncology, Nashville, TN, USA; [7]University of Colorado Cancer Center, Aurora, CO, USA; [8]Haematology, Haematological Malignancy Diagnostic Service (HMDS), St. James's Institute of Oncology, Leeds, United Kingdom; [9]Cancer Care, University Hospitals Dorset, Bournemouth, United Kingdom; [10]Tauranga Hospital, Tauranga, New Zealand; [11]Hospital de Clinicas de Porto Alegre, Porto Alegre, Brazil; [12]Tel Aviv Sourasky Medical Center, Tel Aviv, Israel; [13]Departments of Internal Medicine, Biochemistry & Medical Genetics, Max Rady College of Medicine, Rady Faculty of Health Sciences, University of Manitoba and CancerCare Manitoba, Winnipeg, Canada; [14]Department of Haematology, Addenbrooke's Hospital NHS Trust, Cambridge, United Kingdom; [15]Peninsula Health and Peninsula Private Hospital, Frankston, Melbourne, Australia; [16]Skåne University Hospital, Lund, Sweden; [17]Università Vita-Salute San Raffaele and IRCCS Ospedale San Raffaele, Milano, Italy; [18]University Hospitals Leuven, Leuven, Belgium; [19]Bobigny: Hématologie, CHU Avicennes, Bobigny, France; [20]The Ohio State University Comprehensive Cancer Center, Columbus, OH, USA; [21]Hospices Civils de Lyon, Centre Hospitalier Lyon Sud, Service d'Hématologie Clinique, Pierre-Bénite, France; [22]University of Texas MD Anderson Cancer Center, Houston, TX, USA; [23]AstraZeneca, South San Francisco, CA, USA; [24]AstraZeneca, New York, NY, USA

Presented at the American Society of Hematology (ASH) Annual Meeting; December 9–12, 2023

ELEVATE-TN study design

TN CLL (N=535)

Key inclusion criteria

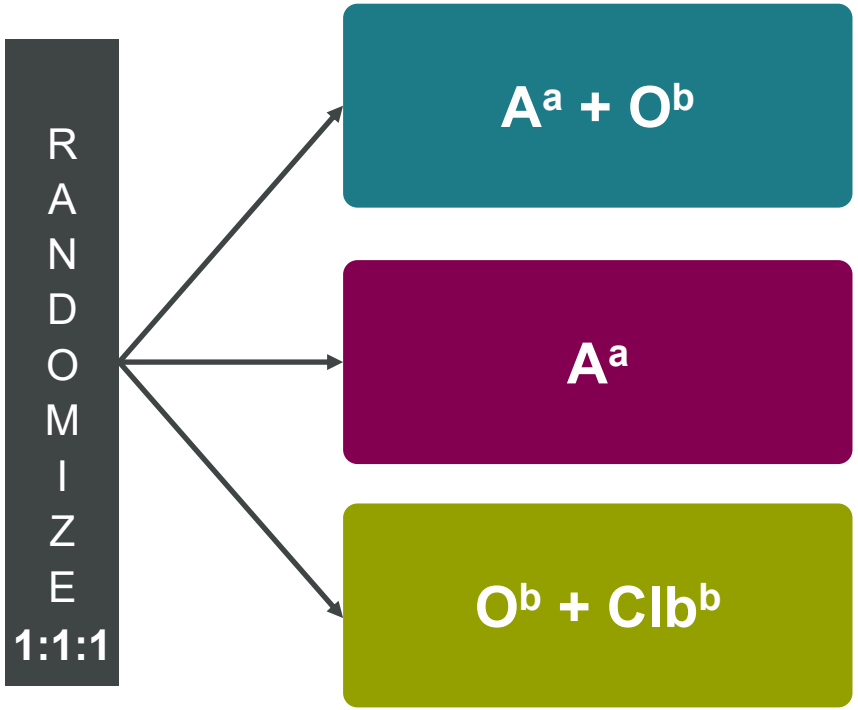
- Age ≥65 years, or >18 to <65 years with:
  - Creatinine clearance 30–69 mL/min (by Cockcroft-Gault equation)
  - CIRS-G score >6
- TN CLL requiring treatment per iwCLL 2008 criteria[6]
- ECOG PS ≤2

Key exclusion criteria

- Significant cardiovascular disease

Stratification

- del(17p), yes vs no
- ECOG PS 0–1 vs 2
- Geographic region



Primary endpoint

- PFS (IRC-assessed): A+O vs O+Clb

Secondary/other endpoints

- PFS (IRC-assessed): A vs O+Clb
- PFS (INV-assessed)
- ORR (IRC- and INV-assessed)
- TTNT
- OS
- uMRD
- Safety

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

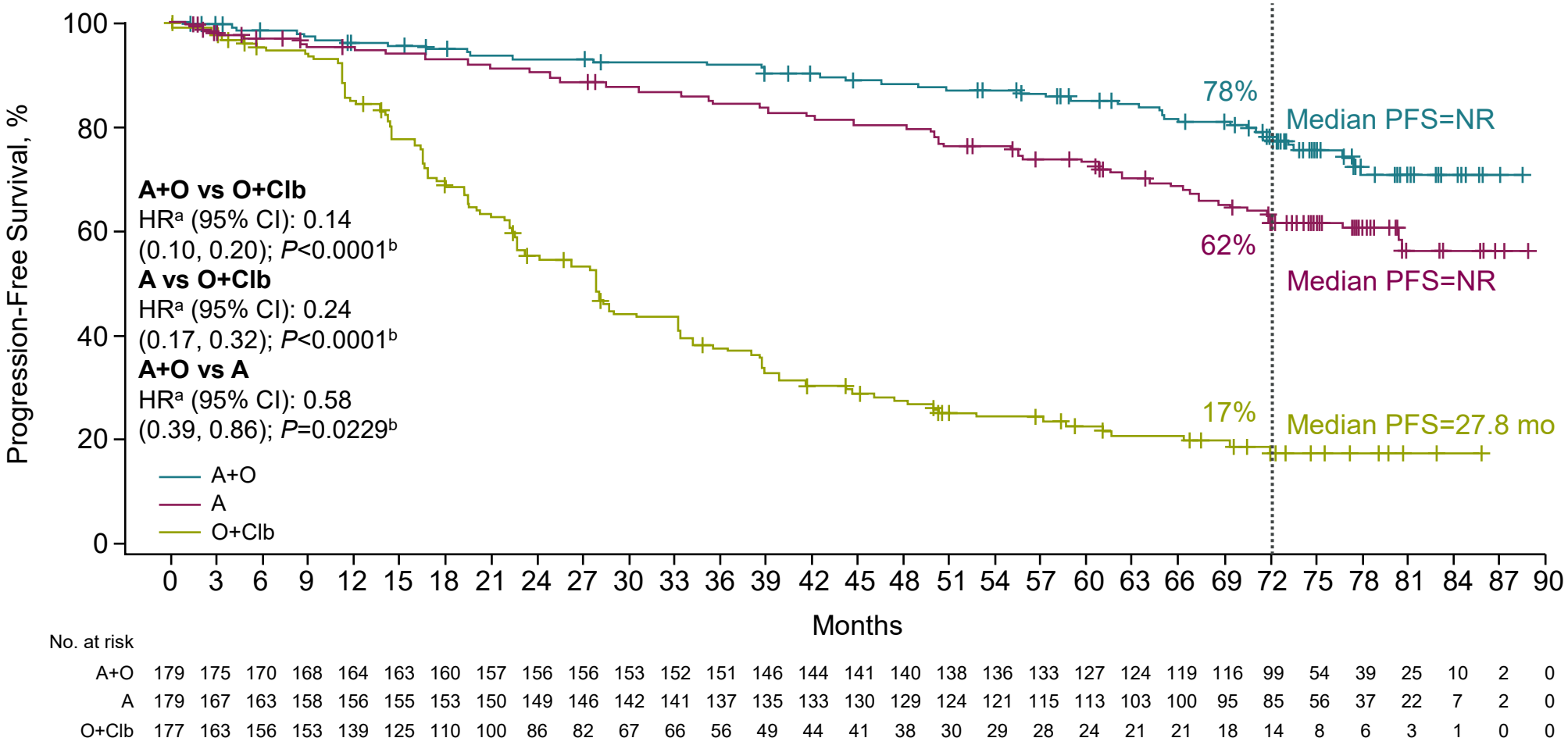
Note: After interim analysis, PFS assessments were by investigator only.[3] All analyses are ad-hoc and *P*-values are descriptive.

NCT02475681. Data cutoff: March 3, 2023. Patients were enrolled between September 2015 and February 2017.

[a]Continued until disease progression or unacceptable toxicity at 100 mg PO BID.

[b]Treatments were fixed duration and administered for 6 cycles.

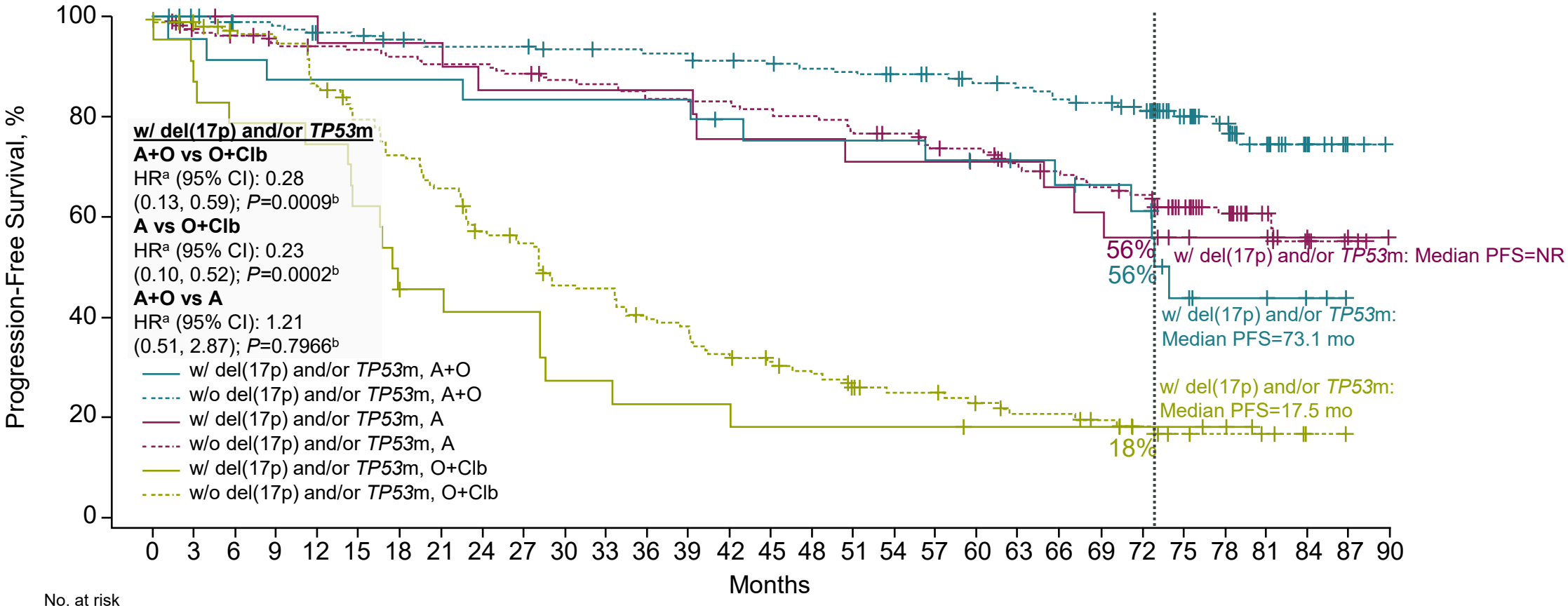
Median PFS was significantly higher for A-containing arms vs O+Clb



- Median PFS was significantly higher for A+O vs A

[a]Hazard ratio based on stratified Cox proportional-hazards model.
[b]*P*-value based on stratified log-rank test.

Median PFS was significantly higher for A-containing arms vs O+Clb in patients with del(17p) and/or *TP53*m

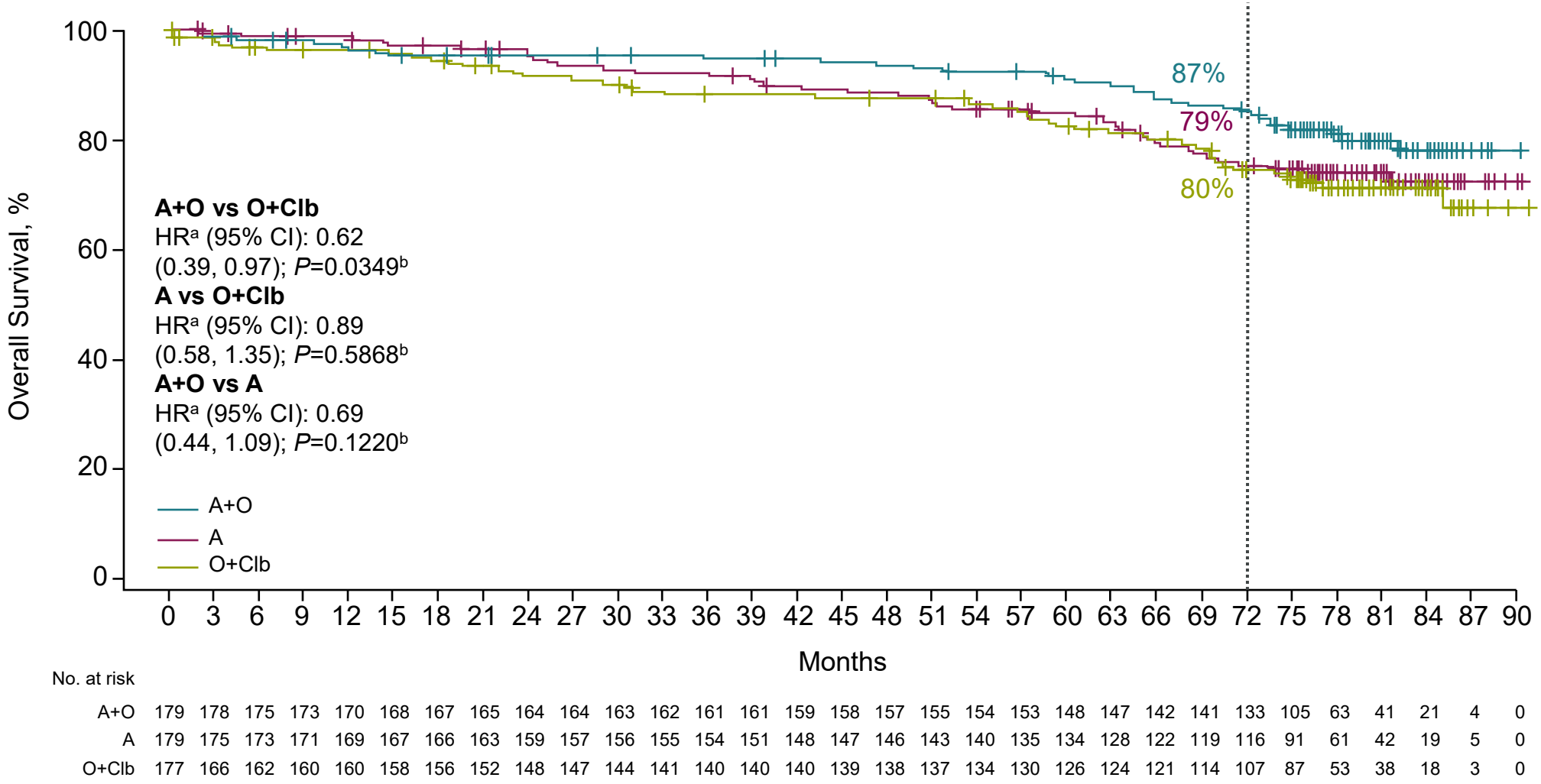


No. at risk																													
w/ del(17p) and/or *TP53m*, A+O	25	24	23	22	22	22	22	22	21	21	21	21	21	20	19	18	18	18	18	17	16	15	14	13	10	5	5	3	2	0
w/o del(17p) and/or *TP53m*, A+O	154	151	147	146	142	141	138	135	135	135	132	131	130	126	125	123	122	120	118	116	111	109	105	103	89	49	34	22	8	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.

[b]*P*-value based on unstratified log-rank test.

OS was not reached in any treatment arm and was longer with A+O vs O+Clb

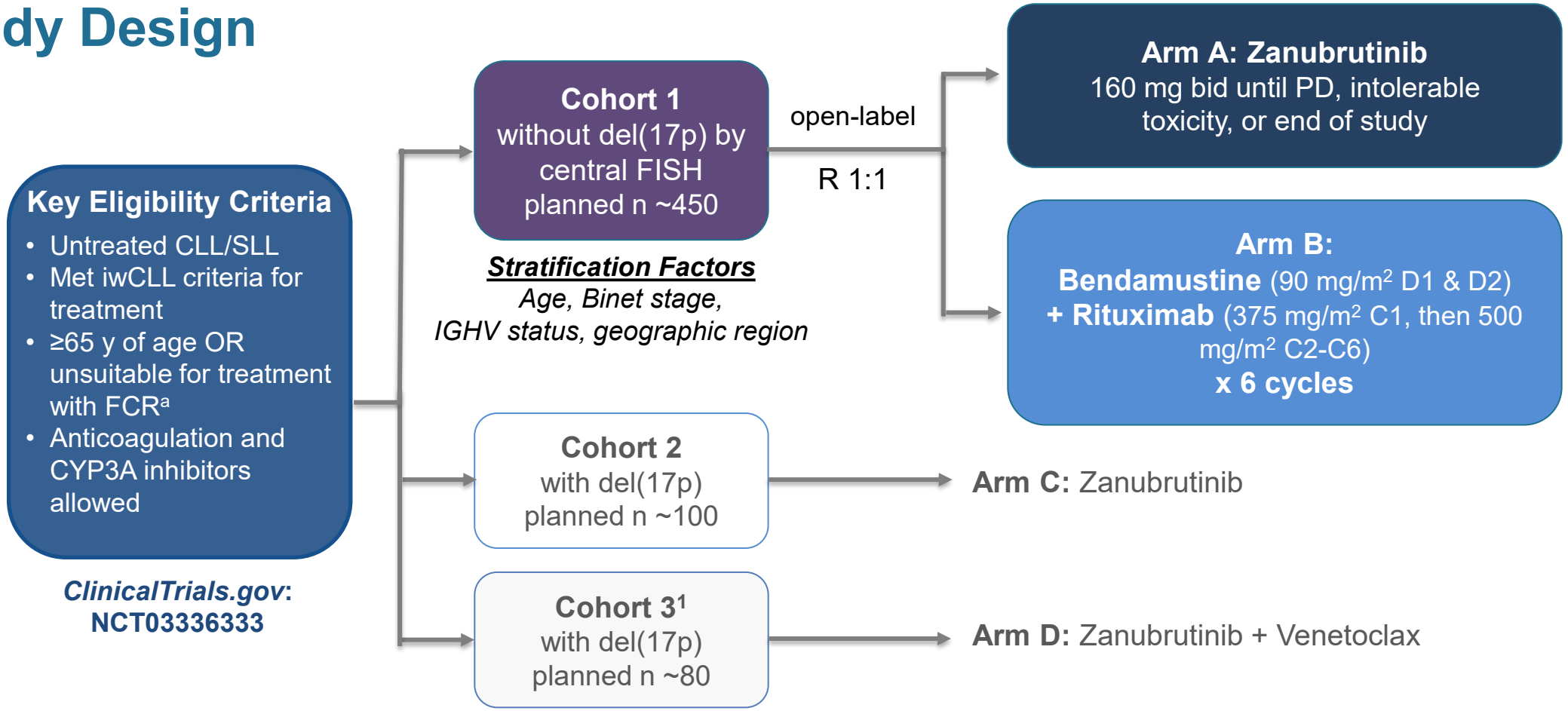


No. at risk

A+O	179	178	175	173	170	168	167	165	164	164	163	162	161	161	159	158	157	155	154	153	148	147	142	141	133	105	63	41	21	4	0
A	179	175	173	171	169	167	166	163	159	157	156	155	154	151	148	147	146	143	140	135	134	128	122	119	116	91	61	42	19	5	0
O+Clb	177	166	162	160	160	158	156	152	148	147	144	141	140	140	140	139	138	137	134	130	126	124	121	114	107	87	53	38	18	3	0

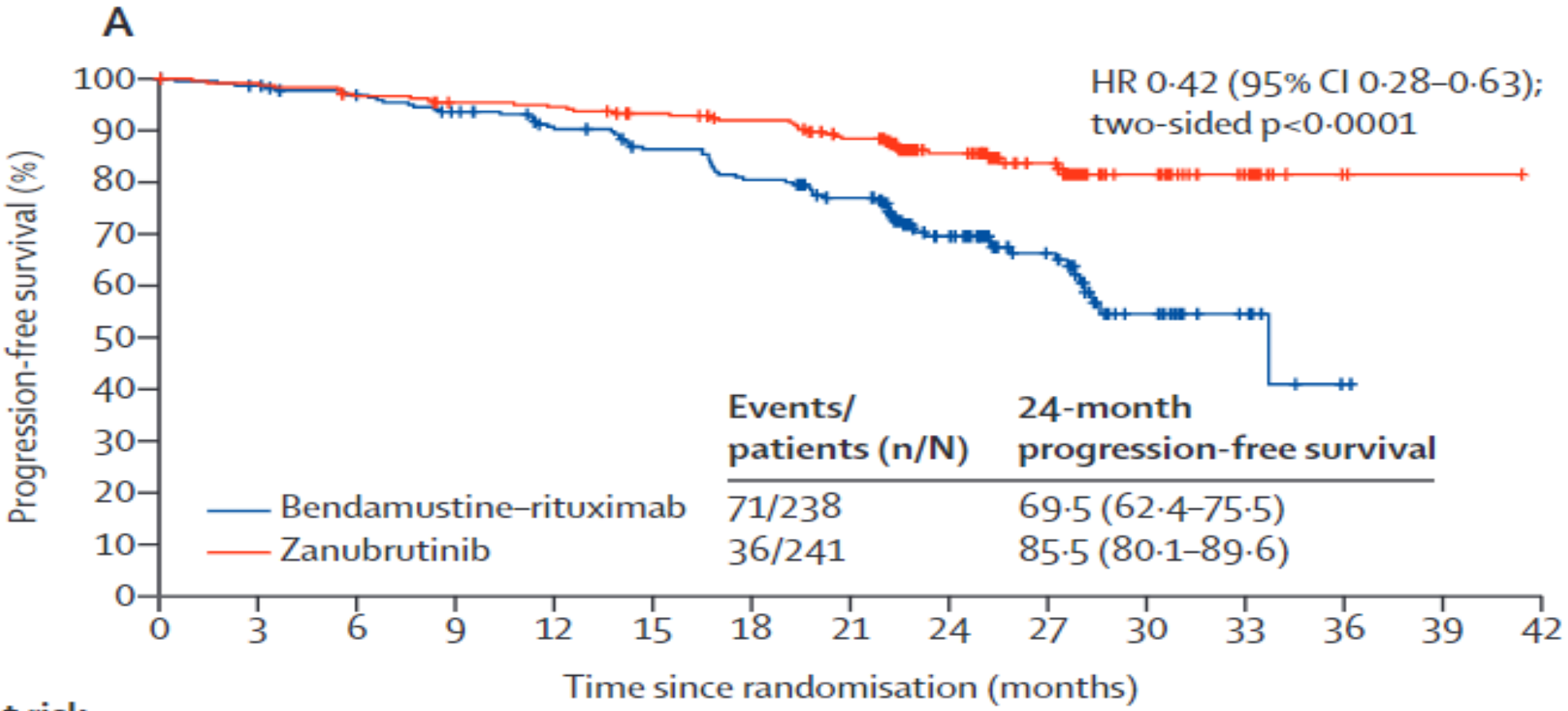
[a]Hazard ratio based on stratified Cox proportional-hazards model.
[b]*P*-value based on stratified log-rank test.

SEQUOIA (BGB-3111-304)
Study Design



1. Tedeschi A, et al. ASH 2021. Abstract 67.

SEQUOIA trial: PFS



Number at risk (number censored)

Bendamustine–rituximab	238 (0)	218 (17)	210 (21)	200 (24)	187 (30)	176 (33)	164 (33)	150 (40)	89 (89)	54 (121)	20 (148)	8 (160)	1 (166)	0 (167)	.. ..
Zanubrutinib	241 (0)	237 (2)	230 (3)	224 (6)	222 (6)	214 (11)	208 (14)	195 (19)	123 (86)	79 (128)	31 (174)	17 (188)	2 (203)	1 (205)	0 (205)

Tam . Lancet Oncol. 2022;23(8):1031-1043.

BTKi lead to impressive PFS in Firstline setting

Improved PFS vs. CIT

However

Indefinite Therapy, Low CR, U-MRD Rare

EHA EUROPEAN HEMATOLOGY ASSOCIATION
EHA2022 HYBRID VIRTUAL

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

DEUTSCHE STUDIENGRUPPE

Abstract S145

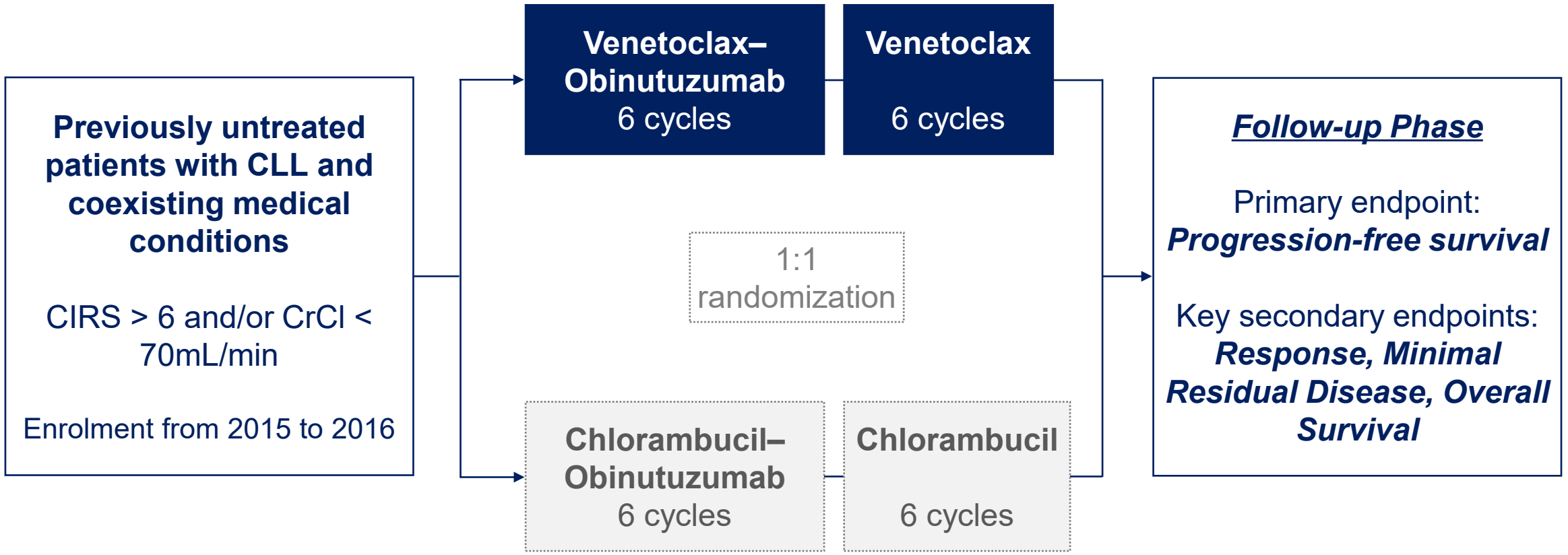
Venetoclax-Obinutuzumab for previously untreated chronic lymphocytic leukemia: 6-year results of the randomized CLL14 study

Othman Al-Sawaf, Sandra Robrecht, Can Zhang, Stefano Olivieri, Naomi Chang, Anna Maria Fink, Eugen Tausch, Christof Schneider, Matthias Ritgen, Karl-Anton Kreuzer, Liliya Sivcheva, Carsten Niemann, Anthony Schwarer, Javier Loscertales, Robert Weinkove, Dirk Strumberg, Allanah Kilfoyle, Eva D Runkel, Barbara Eichhorst, Stephan Stilgenbauer, Yanwen Jiang, Michael Hallek, Kirsten Fischer

June 9th, 2023
Clinical CLL Session

TRIAL DESIGN

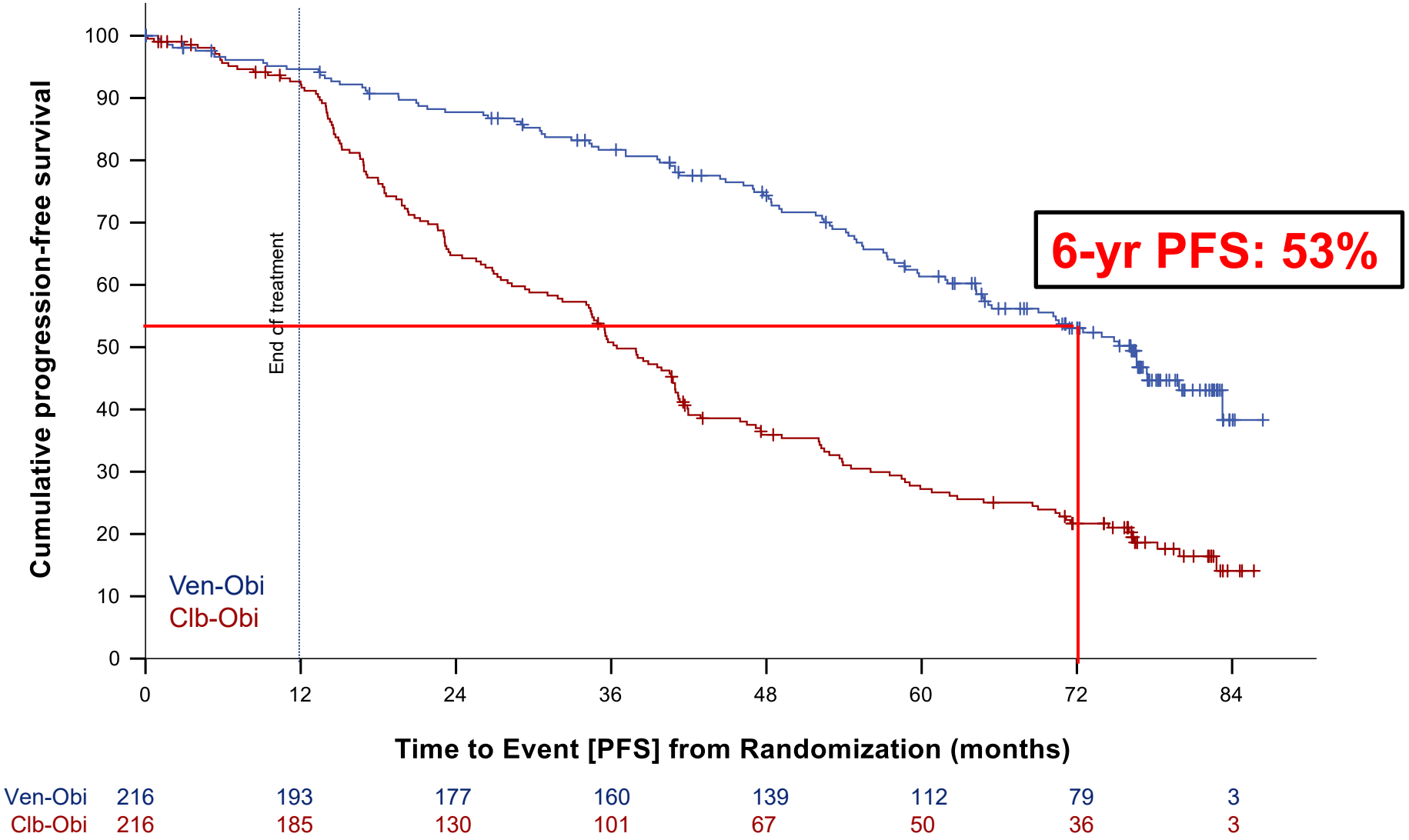
CLL-14



Current median observation time: 76.4 months

PROGRESSION-FREE SURVIVAL

Investigator-assessed PFS



Median PFS

Ven-Obi: 76.2 months

Clb-Obi: 36.4 months

6-year PFS rate

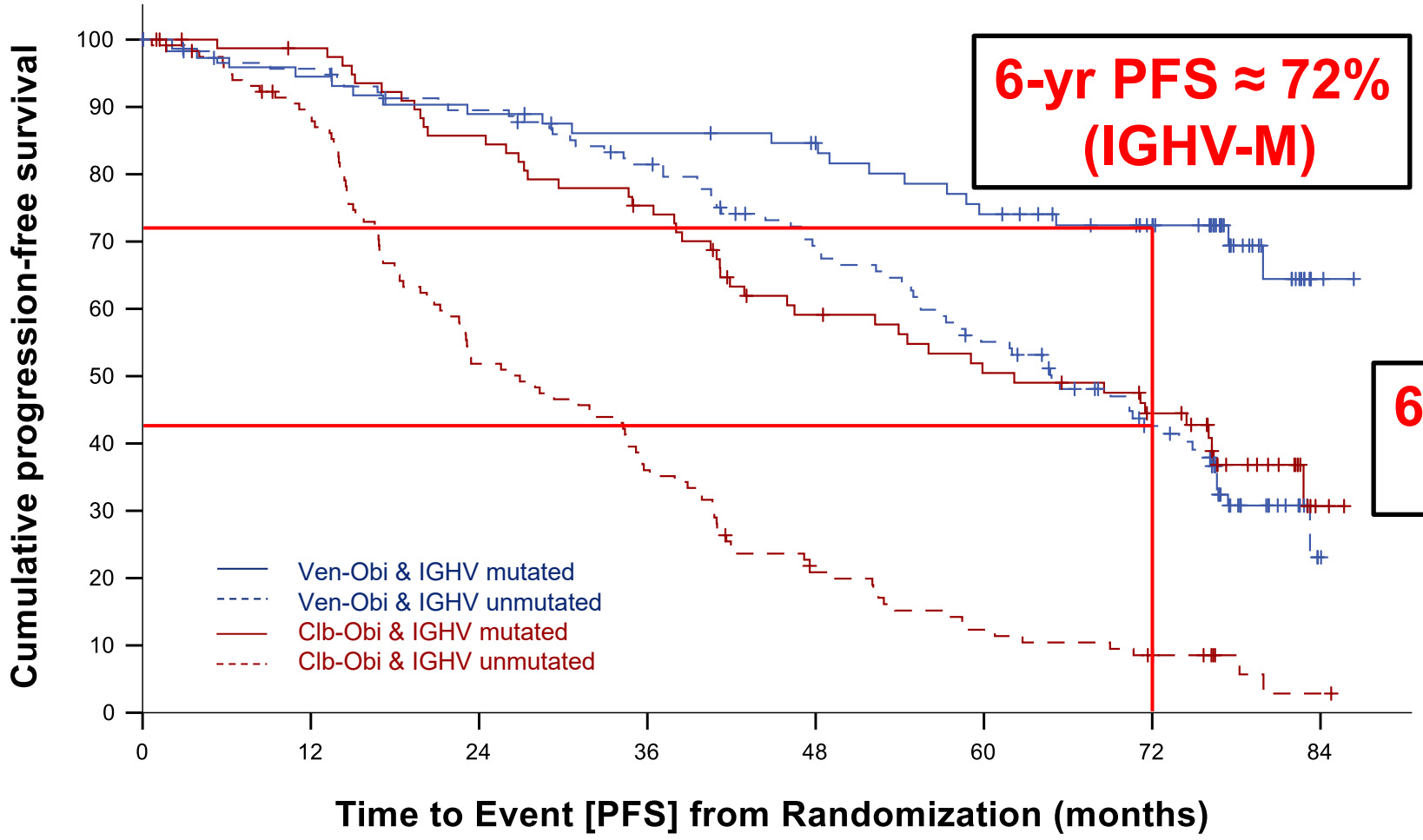
Ven-Obi: 53.1%

Clb-Obi: 21.7%

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

PROGRESSION-FREE SURVIVAL – IGHV status

Median observation time 76.4 months



6-yr PFS ≈ 72% (IGHV-M)

6-yr PFS ≈ 43% (IGHV-UM)

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

Median PFS

Ven-Obi & IGHVmut: NR

Ven-Obi & IGHVunmut: 64.8 m

HR 0.38, 95%CI [0.23-0.61], p<0.001

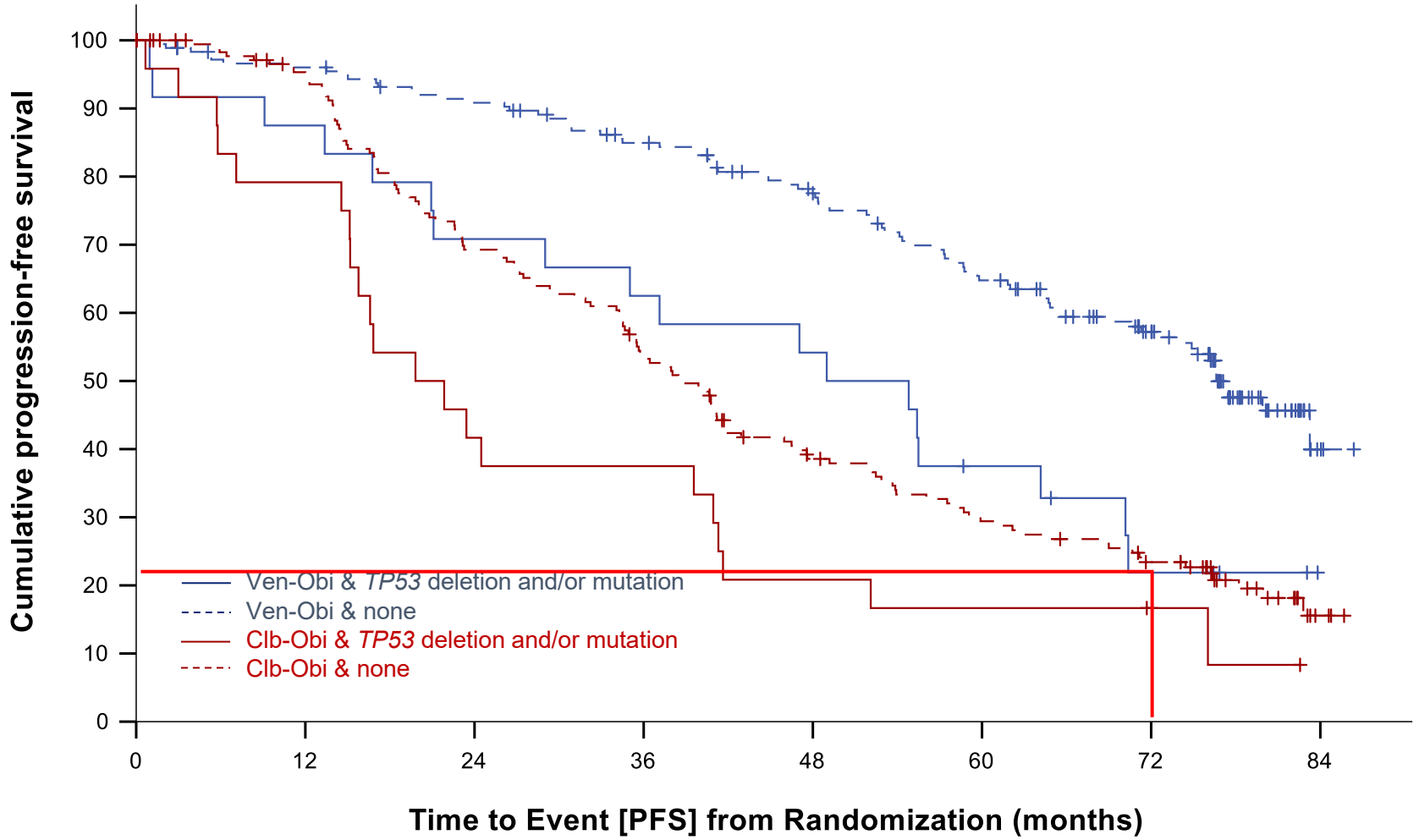
Clb-Obi & IGHVmut: 62.2 m

Clb-Obi & IGHVunmut: 26.9 m

HR 0.33, 95% CI [0.23-0.47], p<0.001

PROGRESSION-FREE SURVIVAL – *TP53* status

Median observation time 76.4 months



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

Median PFS

Ven-Obi & no *TP53*del/mut: 76.6 m

Ven-Obi & *TP53*del/mut: 51.9 m

HR 2.29, 95% CI [1.37-3.83], p=0.001

Clb-Obi & no *TP53*del/mut: 38.9 m

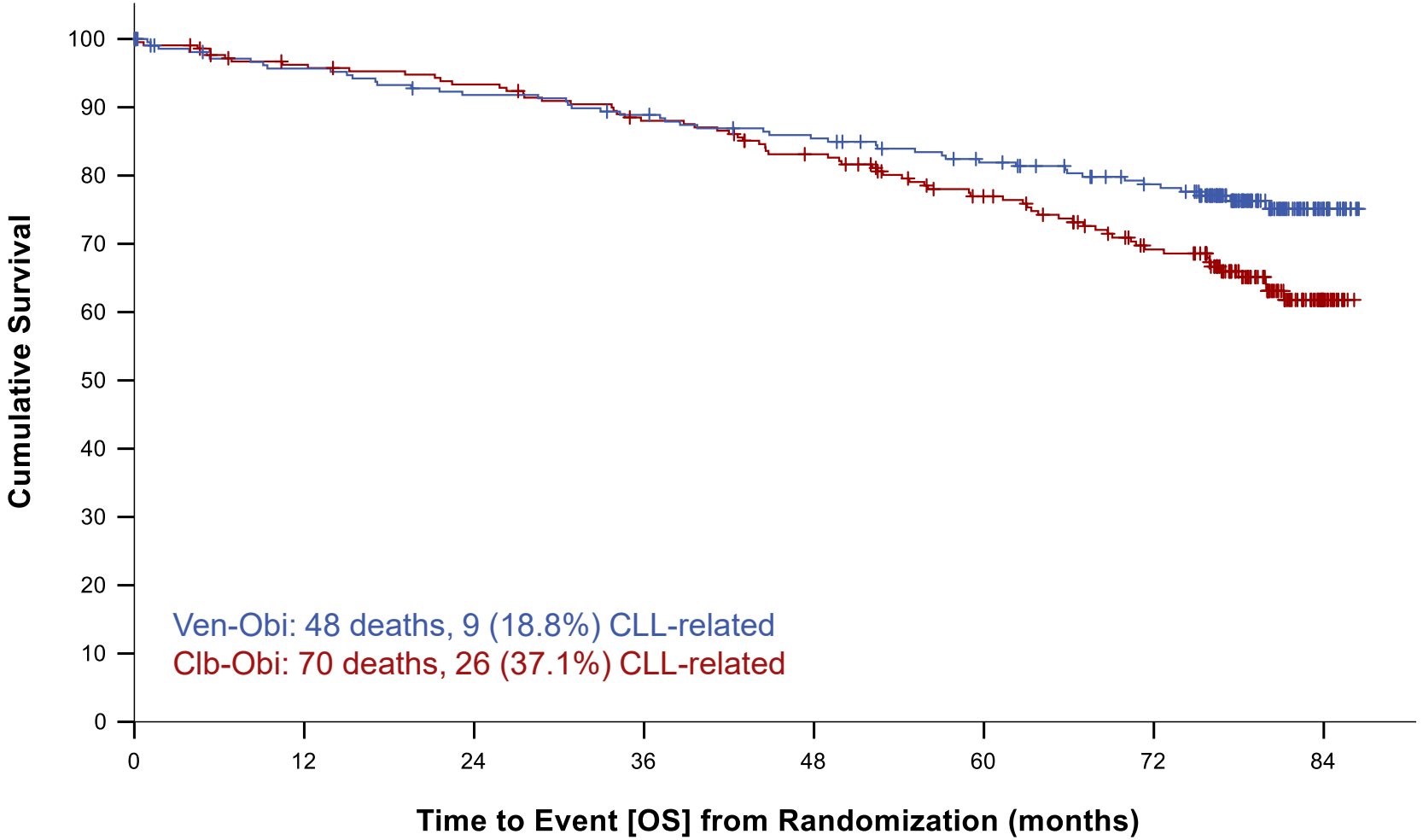
Clb-Obi & *TP53*del/mut: 20.8 m

HR 1.66, 95% CI [1.05-2.63], p=0.03

6-yr PFS ≈ 22%
[del(17p)/*TP53*-m]

OVERALL SURVIVAL

Median observation time 76.4 months



Ven-Obi	216	198	189	182	173	160	144	23
Clb-Obi	216	201	194	181	167	144	118	16

Median OS

Ven-Obi: not reached

Clb-Obi: not reached

6-year OS rate

Ven-Obi: 78.7%

Clb-Obi: 69.2%

HR 0.69, 95% CI [0.48-1.01], p=0.052

Monotherapy, Doublet, or Triplet?

Monotherapy

- BTKi (**ibrutinib**, **acalabrutinib**, ***zanubrutinib***)

Doublet

- BCL2i + CD20 mAb (**VEN + obinutuzumab**)
- BTKi + BCL2i (***ibrutinib*** + ***VEN***)

Triplet

- BTKi + BCL2i + CD20 mAb

Combined Ibrutinib and Venetoclax for First-Line Treatment of Patients with Chronic Lymphocytic Leukemia (CLL) 5-Year Follow-up Data

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

Department of Leukemia
The University of Texas MD Anderson Cancer Center
ASH 2023, Abstract 4635

Treatment Schema

	C1	C2	C3	C4 --> 27 (24 cycles of Combined Rx)
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 combined IBR and VEN

Marrow MRD (flow cytometry) at end of cycle 24 of combined Rx

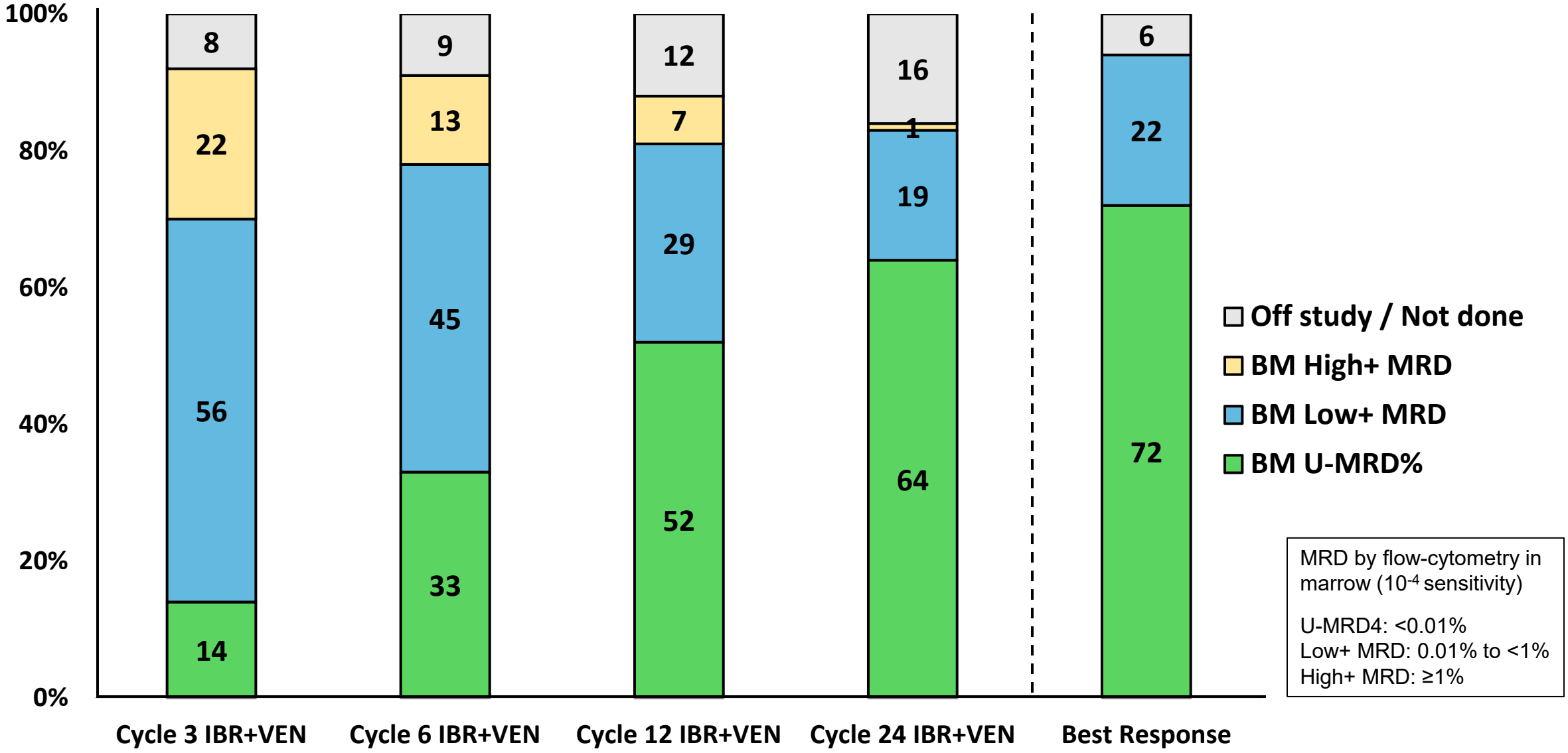
- Negative (<0.01%): Stop both IBR and VEN
- Positive (≥0.01%): Continue 12 additional cycles of IBR + VEN

Baseline Characteristics (N=120)

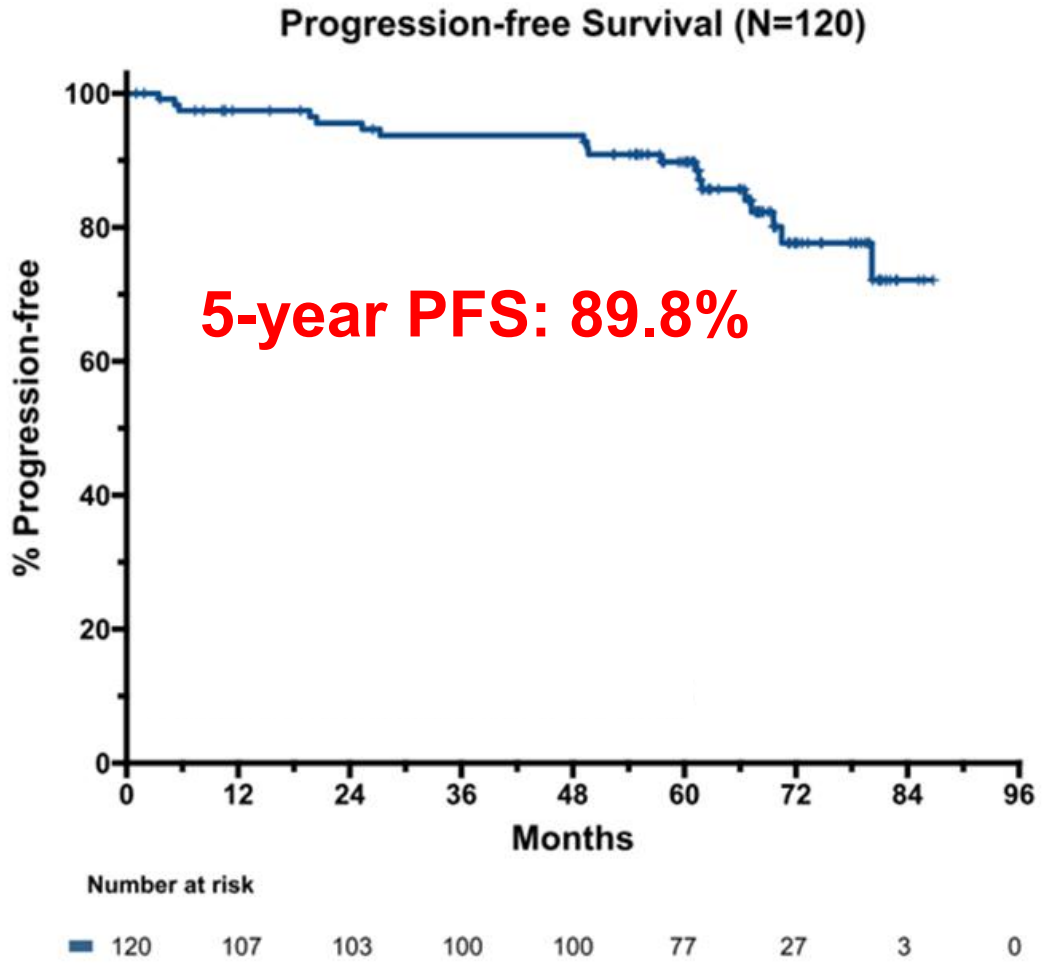
Between August 2016 and February 2019, 120 pts were enrolled

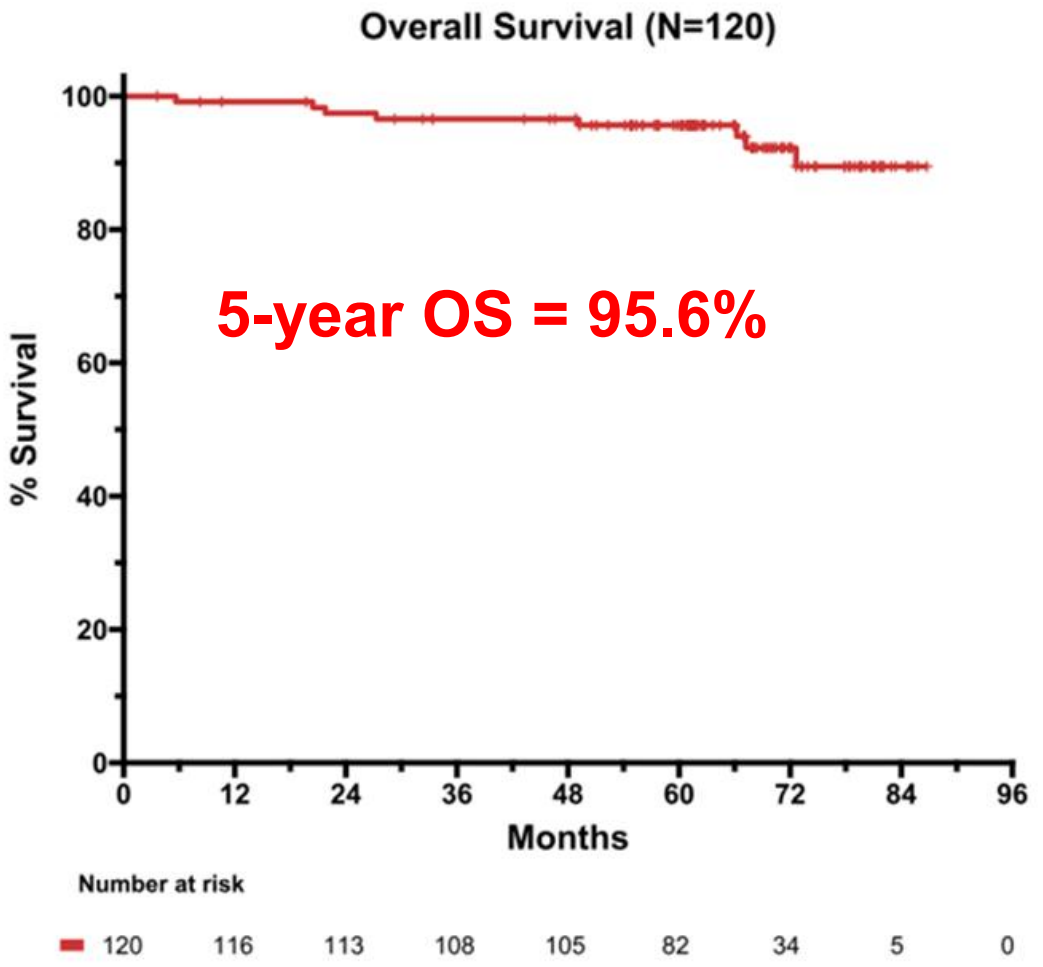
		n (%) or median [range]
Age, years		64.5 [26-88]
	≥65	60 (50)
	≥70	35 (29)
Gender, M		87 (73)
ALC, K/μL		76.3 [1.14-366]
PLT, K/μL		140 [28-334]
HGB, g/dL		12.0 [7.7-18.4]
B2M, mg/L		3.6 [1.7-13.7]
FISH	Del(17p)	20 (17)
	Del(11q)	31 (26)
	Trisomy 12	23 (19)
	Negative	19 (16)
	Del(13q)	27 (22)
IGHV status (n=116)	Unmutated	100 (86)
Cytogenetics (n=115)	Complex	15 (13)
Mutations (n=119)	*TP53*	19 (16)
	NOTCH1	35 (29)
	SF3B1	26 (22)
	BIRC3	10 (8)
Del(17p) / *TP53*-m		27 (23)

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

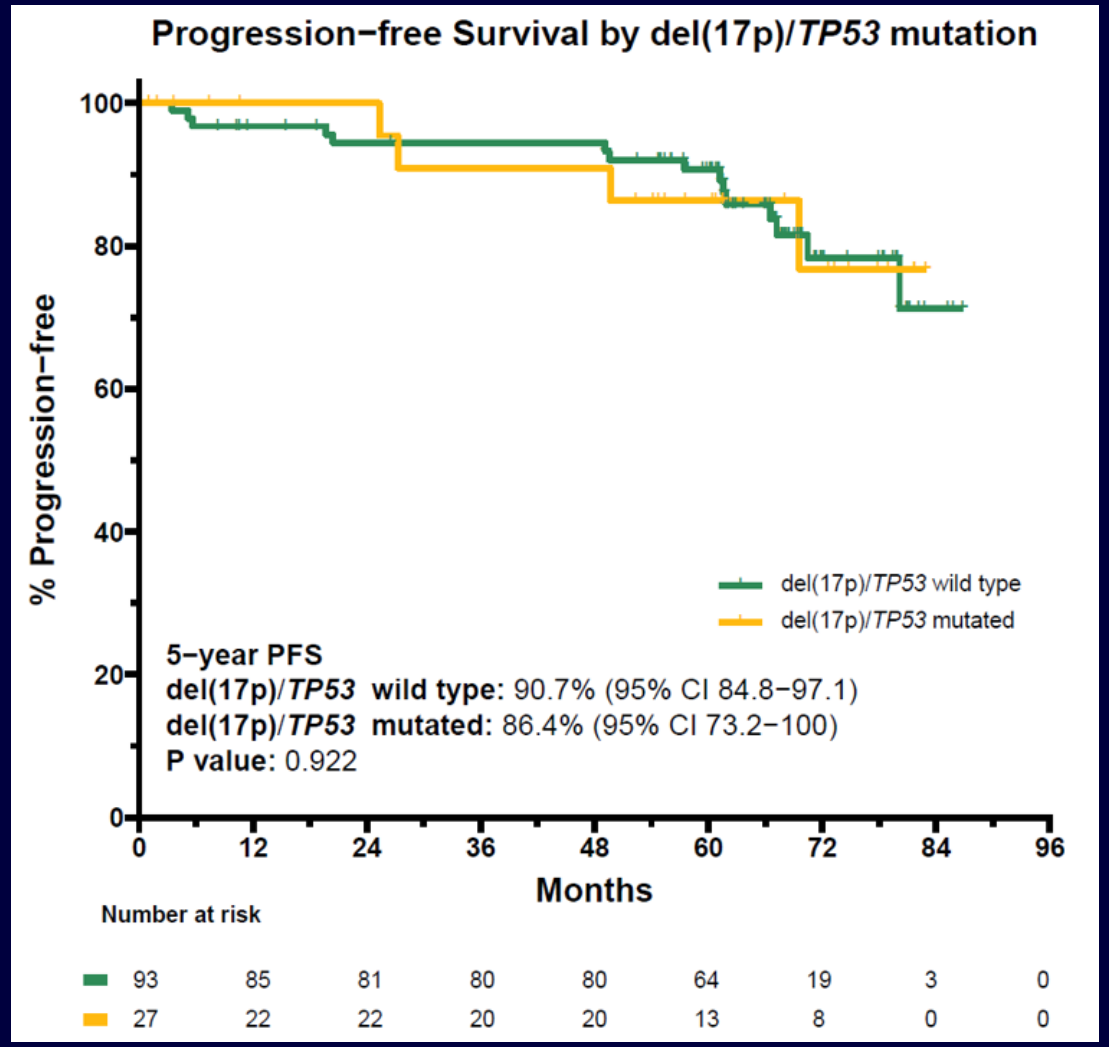


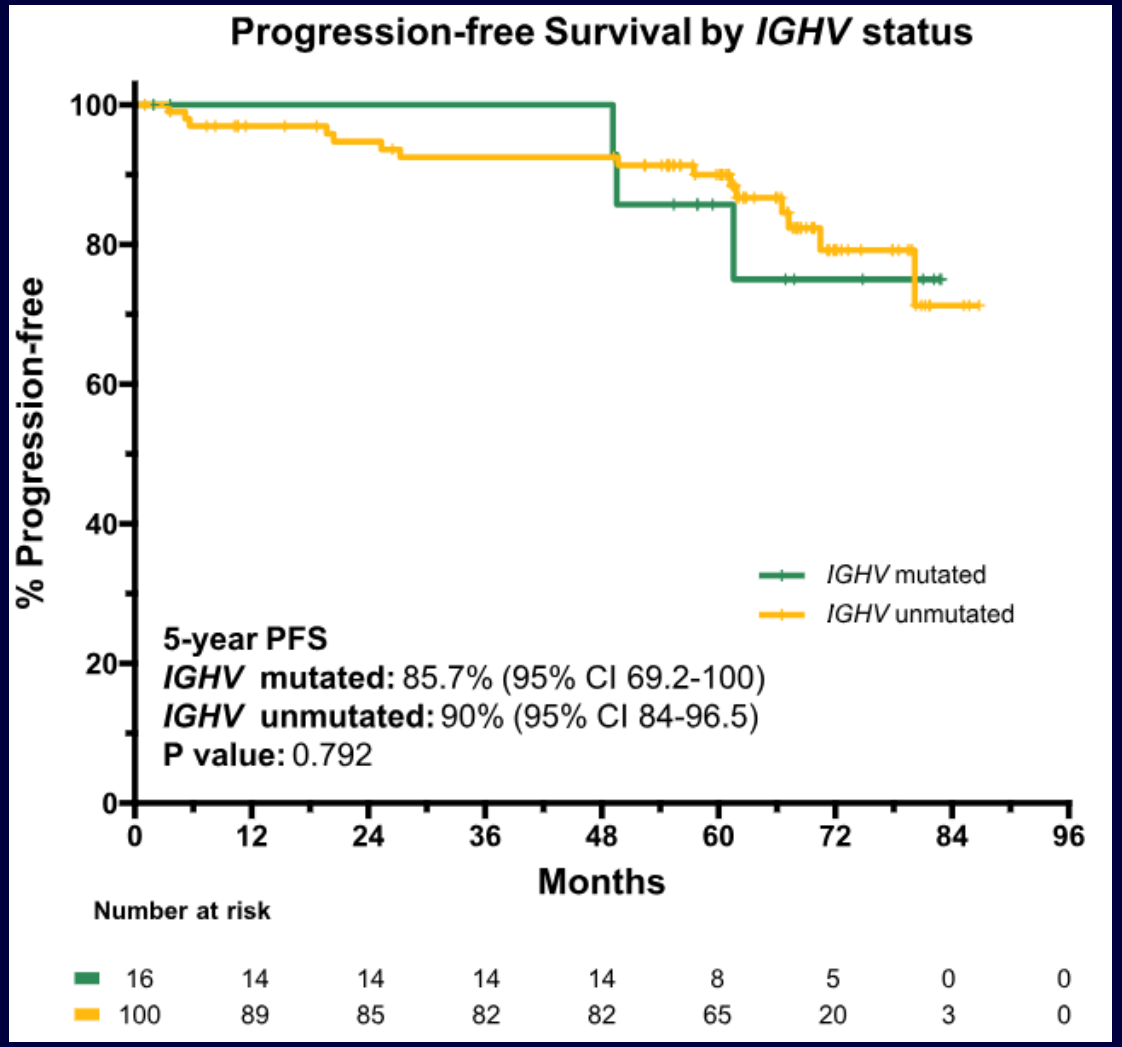
PFS and OS for all Patients (N=120)





PFS by Genomics



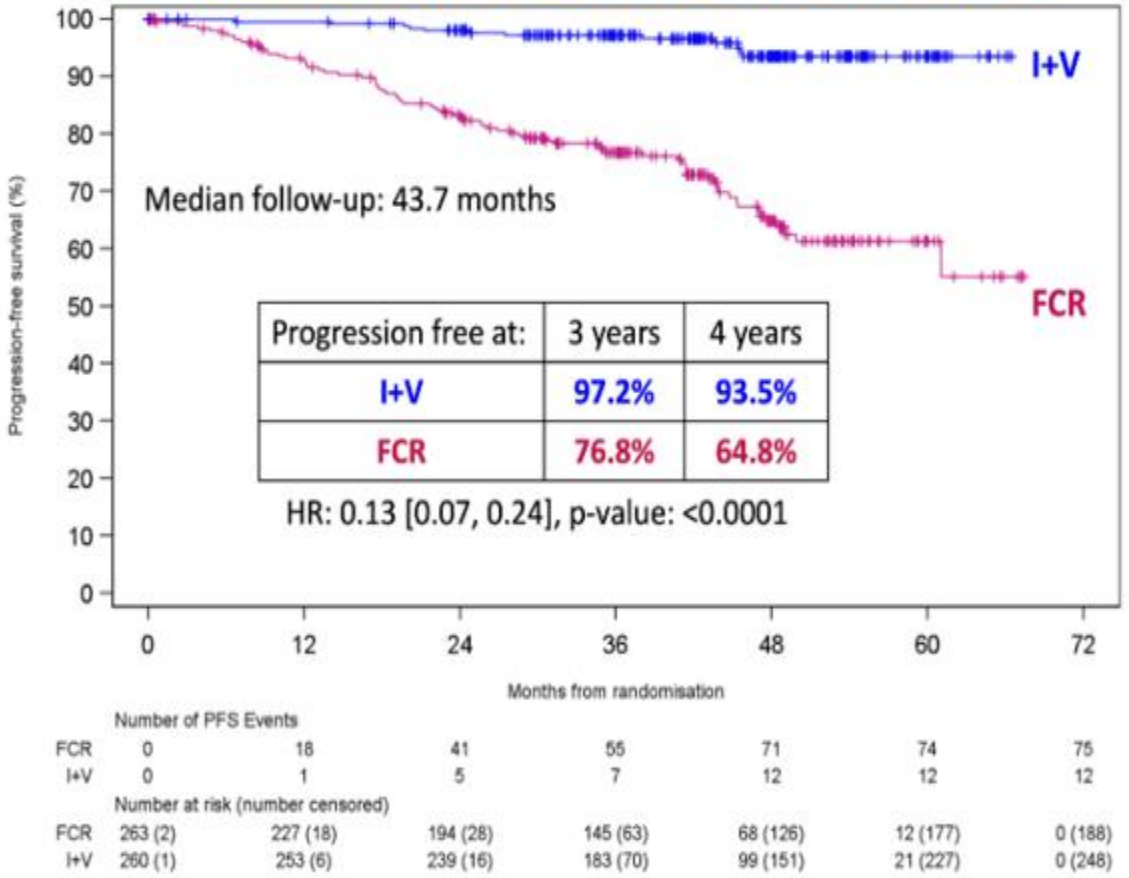


UK FLAIR Phase III Trial
FCR vs. Ibrutinib + Venetoclax in Firstline CLL

FCR (n=263); Ibrutinib + Ven (n=260)
FCR for 6 cycles; Ibrutinib + Ven duration based on MRD

Hillmen, ASH 2023, abst 631

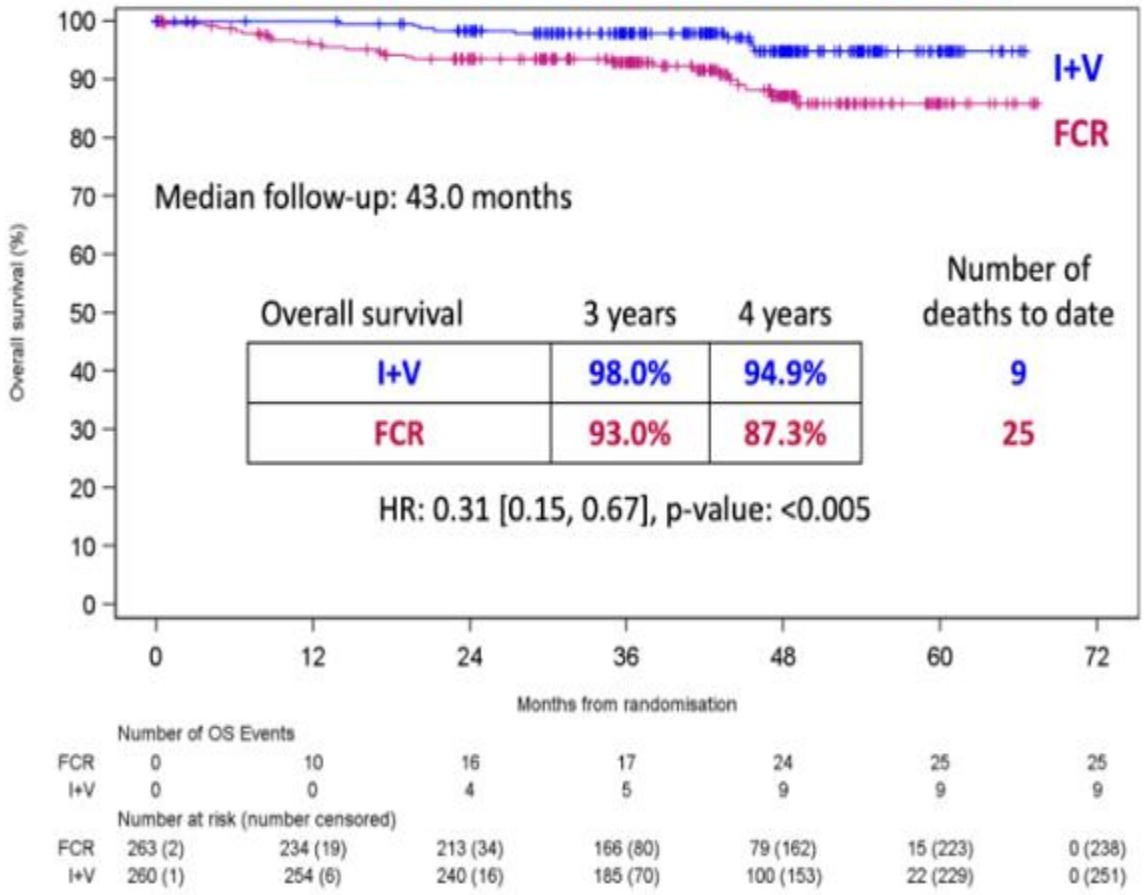
Primary analysis of PFS in FCR vs. I+V



Progression free at:	3 years	4 years
I+V	97.2%	93.5%
FCR	76.8%	64.8%

HR: 0.13 [0.07, 0.24], p-value: <0.0001

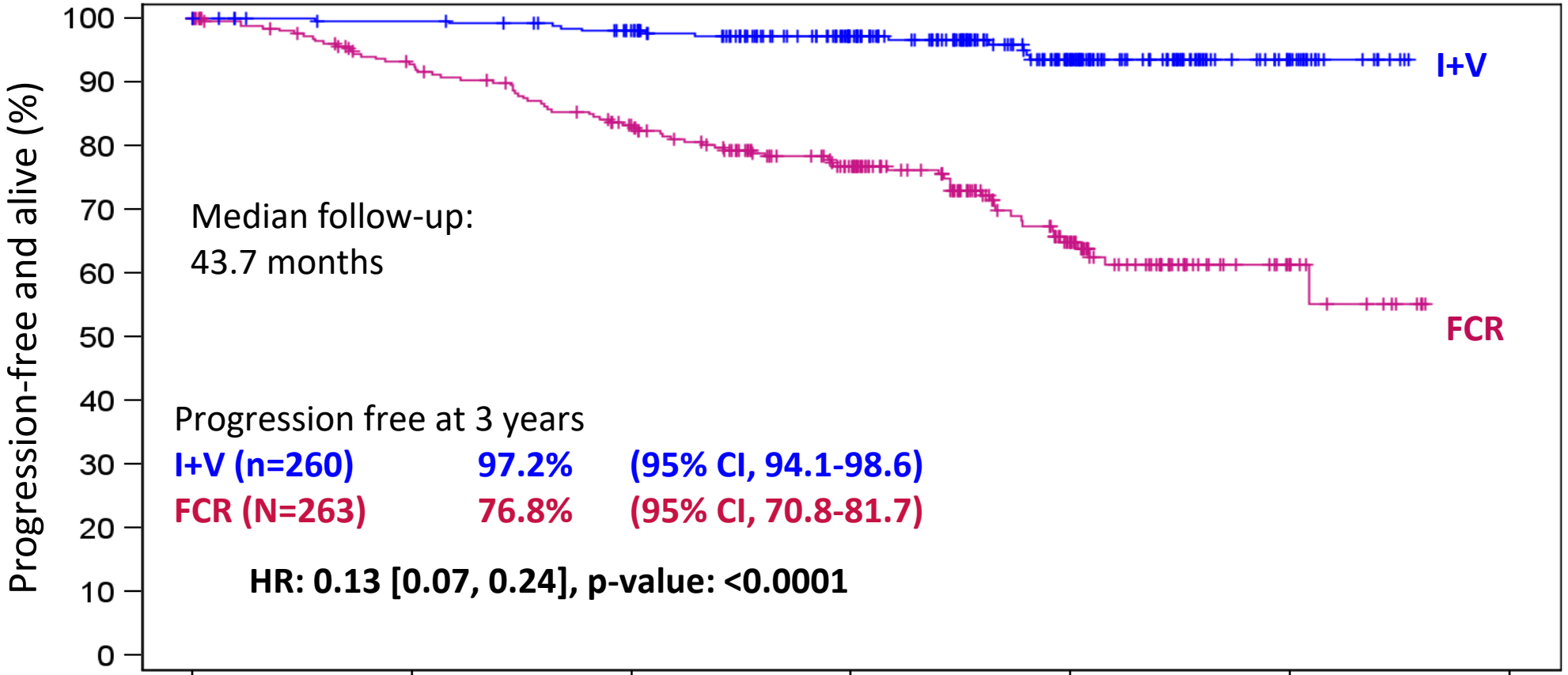
Overall Survival in FCR vs. I+V



Overall survival	3 years	4 years	Number of deaths to date
I+V	98.0%	94.9%	9
FCR	93.0%	87.3%	25

HR: 0.31 [0.15, 0.67], p-value: <0.005

Flair Primary end-point: PFS for FCR versus I+V



No. at risk						
I+V	260	253	239	183	99	21	0
FCR	263	227	194	145	68	12	0

National Cancer Research Institute

Hillmen *et al.*, Abstract 631, ASH 2023

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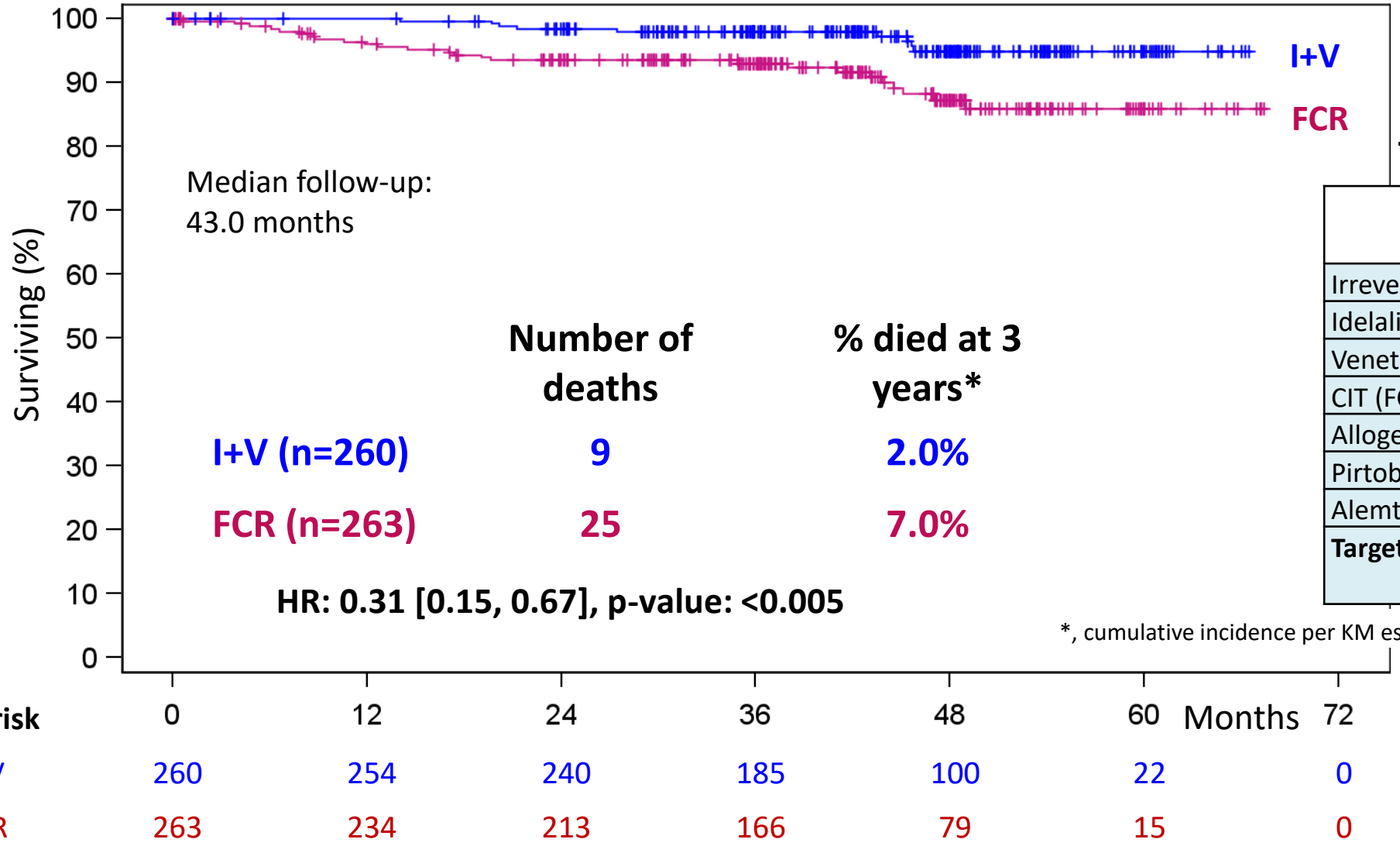
Overall Survival in FCR versus I+V



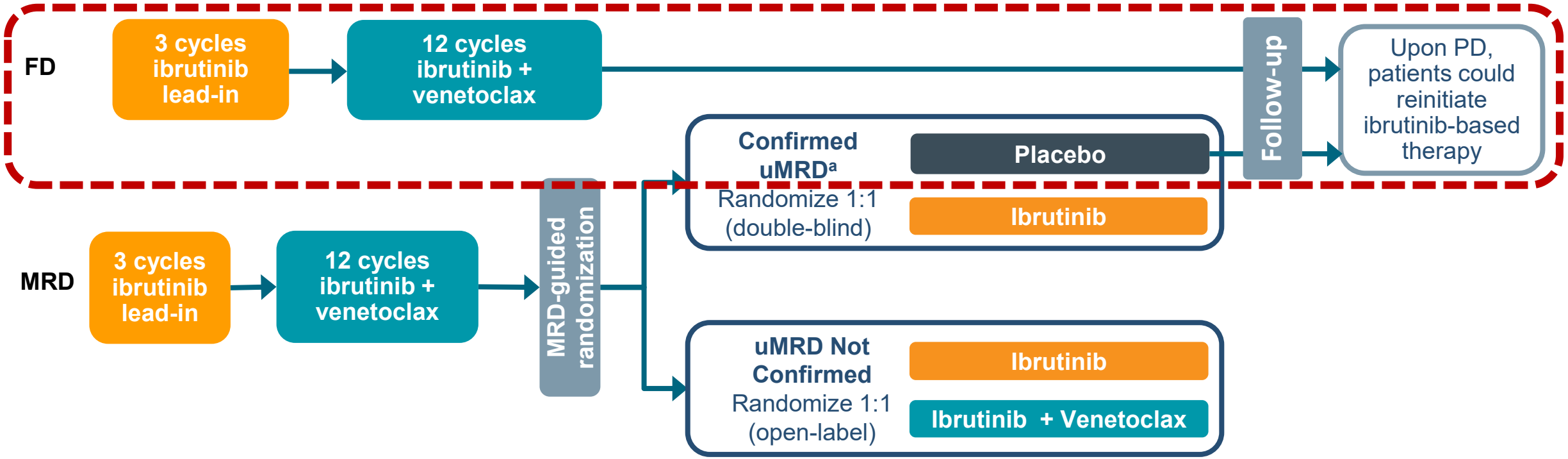
Treatment after progression

	FCR (n=42)	I+V (n=5)
Irreversible BTKi	23	2
Idelalisib + R	1	0
Venetoclax + R	11	0
CIT (FCR/BR/ChlR)	6	1
Allogeneic SCT	1	0
Pirtobrutinib	0	1
Alemtuzumab	0	1
Targeted therapy for CLL	**35/42 (83%)**	**3/5 (60%)**

Hillmen *et al.*, Abstract 631, ASH 2023

CAPTIVATE Study Design

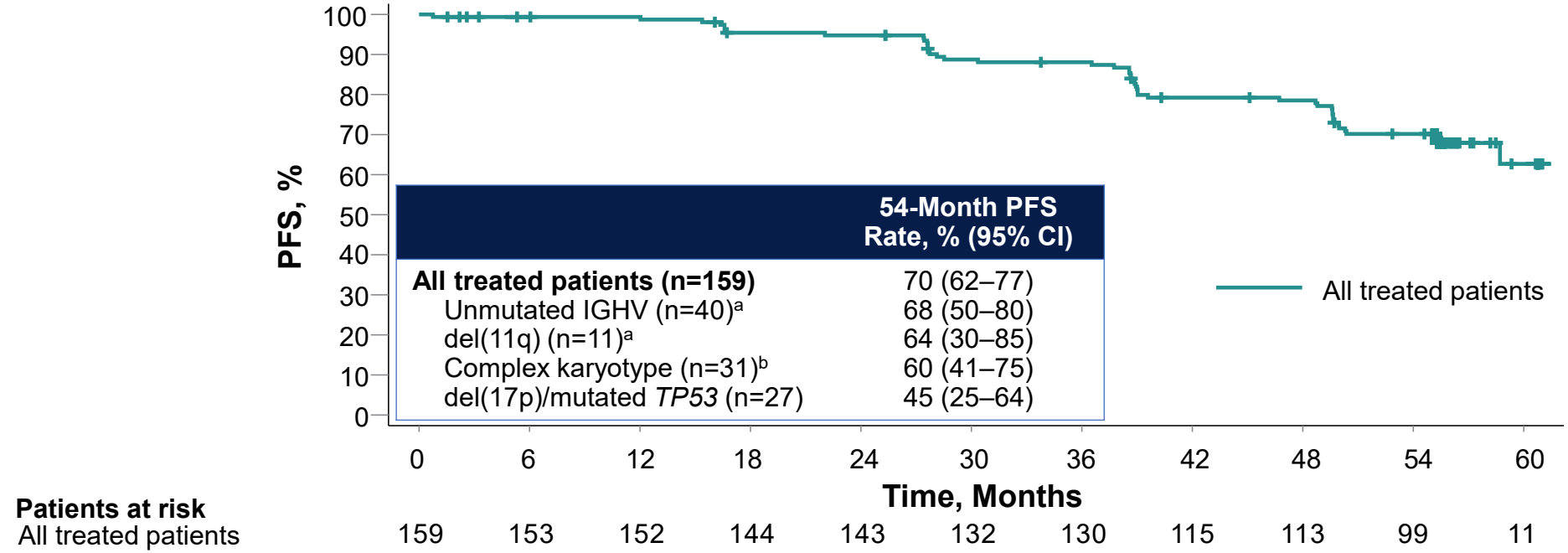
- CAPTIVATE (PCYC-1142; NCT02910583) is an international, multicenter phase 2 study evaluating first-line treatment with ibrutinib + venetoclax that comprises 2 cohorts: MRD[1] and FD[2]
  - Per protocol, patients with PD after completion of fixed-duration ibrutinib + venetoclax in the FD cohort or MRD cohort placebo arm could reinitiate treatment with single-agent ibrutinib
  - Patients with PD >2 years after treatment completion in the FD cohort could be retreated with the fixed-duration regimen (3 cycles of ibrutinib then 12 cycles of ibrutinib + venetoclax)



FD, fixed duration; MRD, minimal residual disease; PD, progressive disease.
[a]Confirmed uMRD was defined as uMRD ($<10^{-4}$ by 8-color flow cytometry) serially over at least 3 cycles in both peripheral blood and bone marrow.
[1]Wierda, WG. *J Clin Oncol.* 2021;39:3853-3865. [2]Tam CS et al. *Blood.* 2022;139:3278-3289.

FD Cohort: Overall Median PFS Was Not Reached With Up To 5 Years Of Follow-Up

- With median time on study of 56 months (range, 1–61), 54-month PFS and OS rates were 70% (95% CI, 62–77) and 97% (95% CI, 93–99), respectively
  - PFS promising across most high-risk features; numerically lower in those with del(17p)/mutated *TP53*

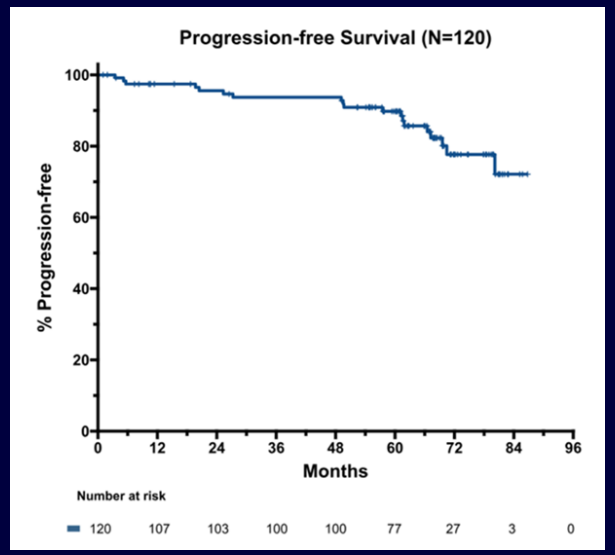


- Best response rates remain: CR/CRi, 58%; ORR, 96%[1]
  - In patients who achieved CR/CRi (n=92), median duration of CR/CRi was not reached

CRi, complete response with incomplete bone marrow recovery; ORR, overall response rate; PFS, progression-free survival.
[a]Excluding patients with del(17p)/mutated *TP53* or complex karyotype. [b]Defined as ≥3 abnormalities by conventional CpG-stimulated cytogenetics.
[1]Barr PM et al. *J Clin Oncol.* 2023;41(suppl 16). Abstract 7535.

I + V Regimen Comparisons

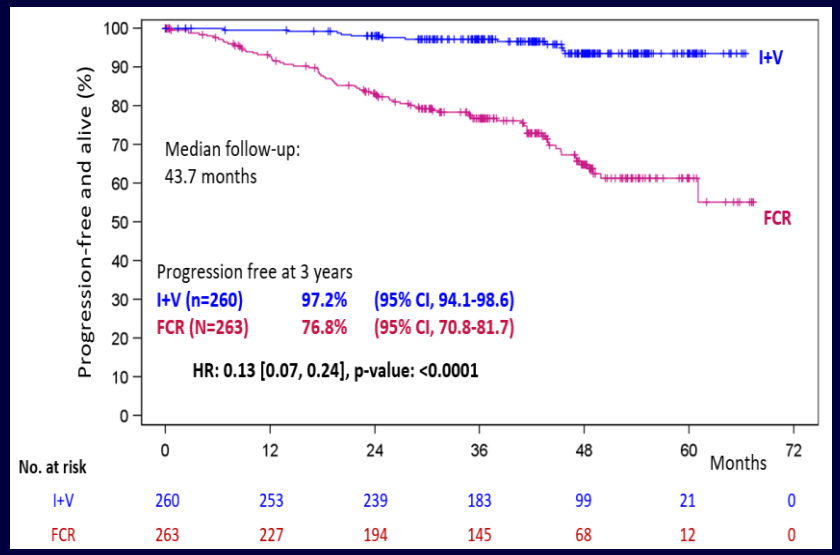
MDACC, I+V 24 cycles



N=120
Median age = 64.5 yrs
IGHV-UM = 86%
Del(17p) / *TP53*-m = 23%

5-yr PFS = 89.8%

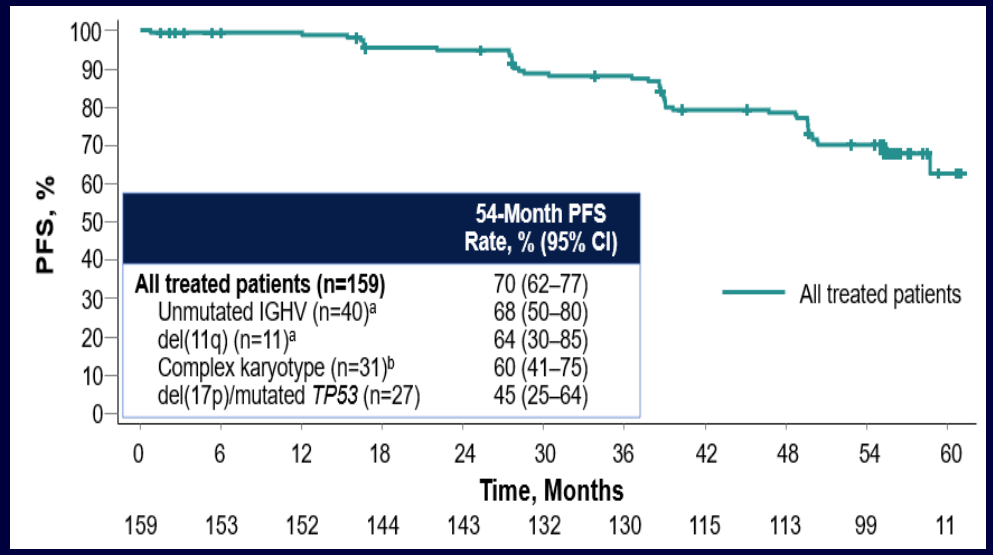
FLAIR, UK, I+V 2-6 years



N=260
Median age = 62 yrs
IGHV-UM = 48%
Del(17p) = excluded

3-yr PFS = 97.2%

CAPTIVATE, I+V 12 cycles



N=159
Median age = 60 yrs
IGHV-UM = 56%
Del(17p) / *TP53*-m = 17%

4.5 yr PFS = 70%

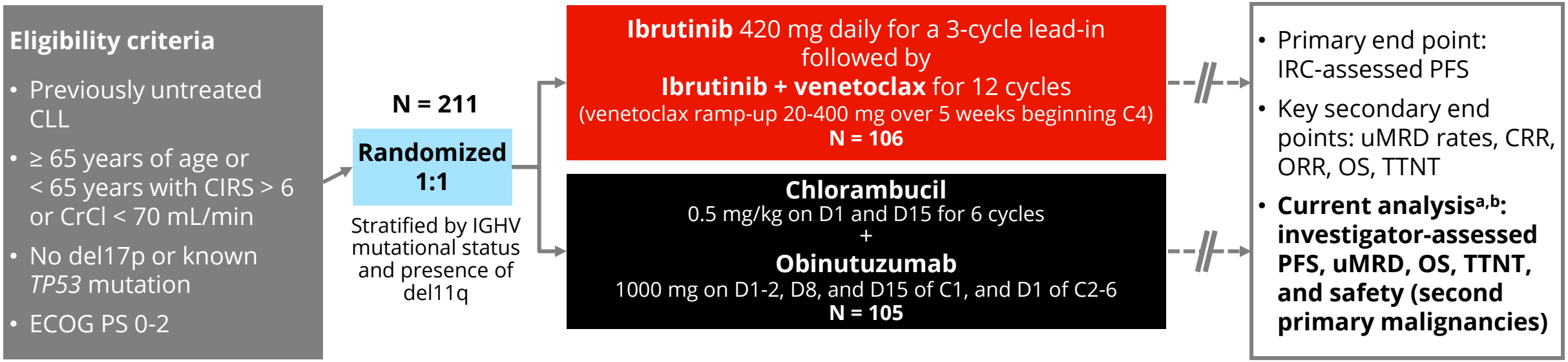
First-Line Fixed-Duration Ibrutinib Plus Venetoclax (Ibr+Ven) Versus Chlorambucil Plus Obinutuzumab (Clb+O): 57-Month Follow-up From the GLOW Study

Carol Moreno,[1] Talha Munir,[2] Carolyn Owen,[3] George Follows,[4] José-Ángel Hernández-Rivas,[5] Ohad Benjamini,[6] Ann Janssens,[7] Mark-David Levin,[8] Tadeusz Robak,[9] Martin Simkovic,[10] Sergey Voloshin,[11] Vladimir Vorobyev,[12] Munci Yagci,[13] Loic Ysebaert,[14] Qianya Qi,[15] Emma Smith,[15] Srimathi Srinivasan,[16] Natasha Schuier,[15] Kurt Baeten,[17] Donne Bennett Caces,[15] Carsten U. Niemann,[18] Arnon P. Kater[19]

[1]Hospital de la Santa Creu i Sant Pau, Autonomous University of Barcelona, Josep Carreras Leukaemia Research Institute, Barcelona, Spain; [2]St James's Hospital, Leeds, UK; [3]Tom Baker Cancer Centre, Calgary, AB, Canada; [4]Addenbrookes Hospital, Cambridge, UK; [5]Hospital Universitario Infanta Leonor, Universidad Complutense, Madrid, Spain; [6]Sheba Medical Center, Ramat Gan, Israel; [7]Universitaire Ziekenhuizen Leuven, Leuven, Belgium; [8]Albert Schweitzer Hospital, Dordrecht, Netherlands; [9]Medical University of Lodz, Copernicus Memorial Hospital, Lodz, Poland; [10]4th Department of Internal Medicine – Haematology, Faculty of Medicine in Hradec Králové, University Hospital and Charles University in Prague, Hradec Kralove, Czech Republic; [11]Russian Scientific and Research Institute of Hematology and Transfusiology, St. Petersburg, Russia; [12]S.P. Botkin Moscow City Clinical Hospital, Moscow, Russia; [13]Gazi Universitesi Tip Fakultesi, Ankara, Turkey; [14]Institut Universitaire du Cancer Toulouse Oncopole, Toulouse, France; [15]Janssen Research & Development, Raritan, NJ; [16]Oncology Translational Research, Janssen Research & Development, Lower Gwynedd Township, PA; [17]Janssen Research & Development, Beerse, Belgium; [18]Rigshospitalet Copenhagen University Hospital, Copenhagen, Denmark; [19]Amsterdam University Medical Centers, Cancer Center Amsterdam, University of Amsterdam, Amsterdam, Netherlands

Presented at the 65th ASH Annual Meeting and Exposition; December 9-12, 2023; San Diego, CA, USA

GLOW: Phase 3 Study (NCT03462719) Evaluating Fixed-Duration Ibr+Ven in Previously Untreated CLL



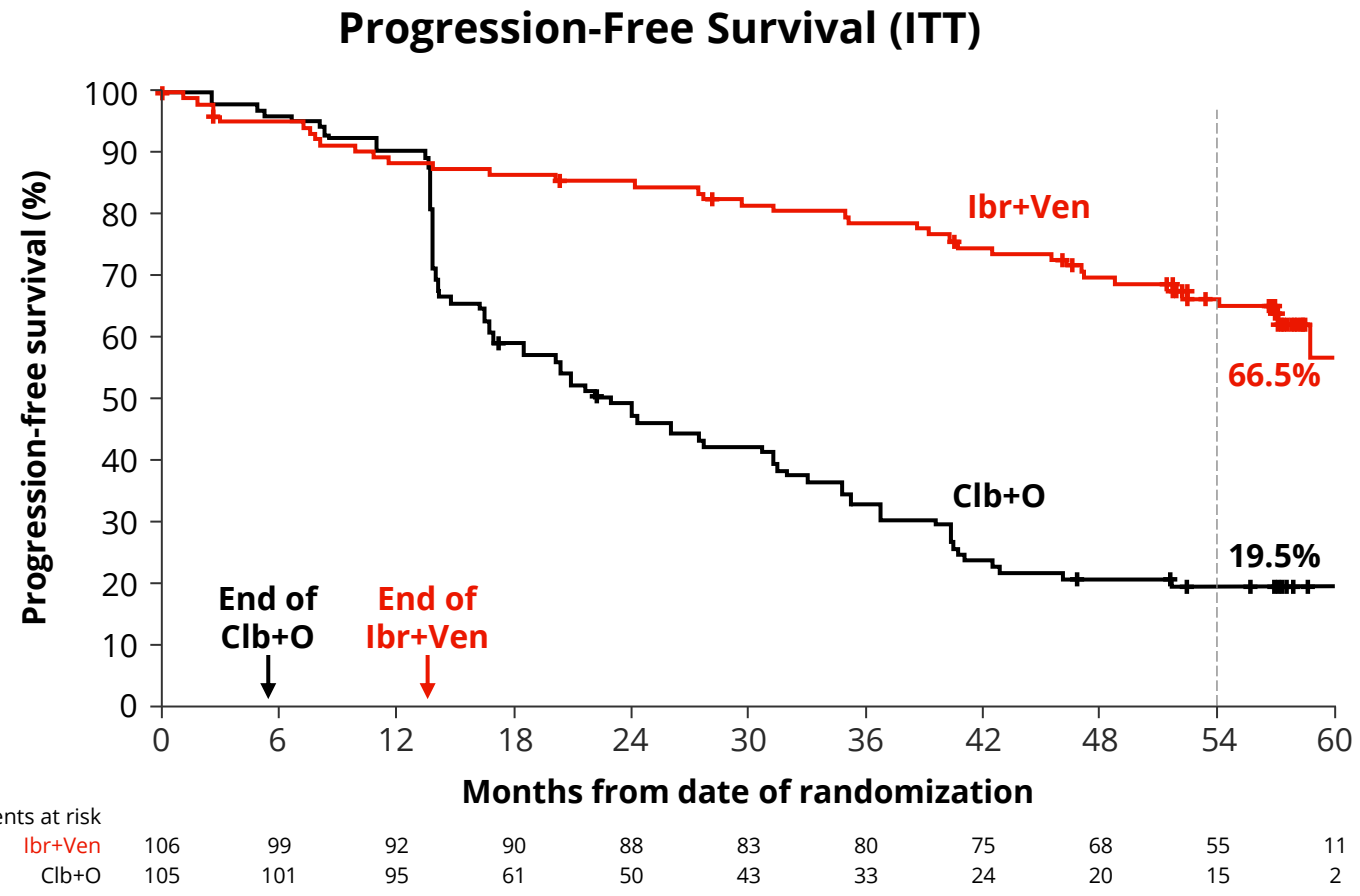
- **Here we present the updated clinical outcomes at a median follow-up of 57.3 months (range, 1.7-65.2)**
- Baseline characteristics (presented previously) were generally balanced between arms and reflective of an elderly and/or comorbid population[1]
- IGHV status at baseline:
  - Ibr+Ven arm: mIGHV 30.2%, uIGHV 63.2%
  - Clb+O arm: mIGHV 33.3%, uIGHV 54.3%

[a]All *p* values are nominal. [b]uMRD in PB by NGS via Clonoseq assay.
C, cycle (28 days); CIRS, Cumulative Illness Rating Scale score; CrCl, creatinine clearance; CRR, complete response rate; D, day; ECOG PS, Eastern Cooperative Oncology Group performance status; IRC, independent review committee; mIGHV, mutated IGHV; NGS, next-generation sequencing; ORR, overall response rate; PB, peripheral blood; uIGHV, unmutated IGHV.

1. Niemann CU, et al. *Lancet Oncol*. 2023;24:1423-1433.

Presented by G. Follows at the 65th ASH Annual Meeting and Exposition; December 9-12, 2023; San Diego, CA, USA

GLOW: PFS Remained Superior for Ibr+Ven Versus Clb+O at 57 Months of Study Follow-up

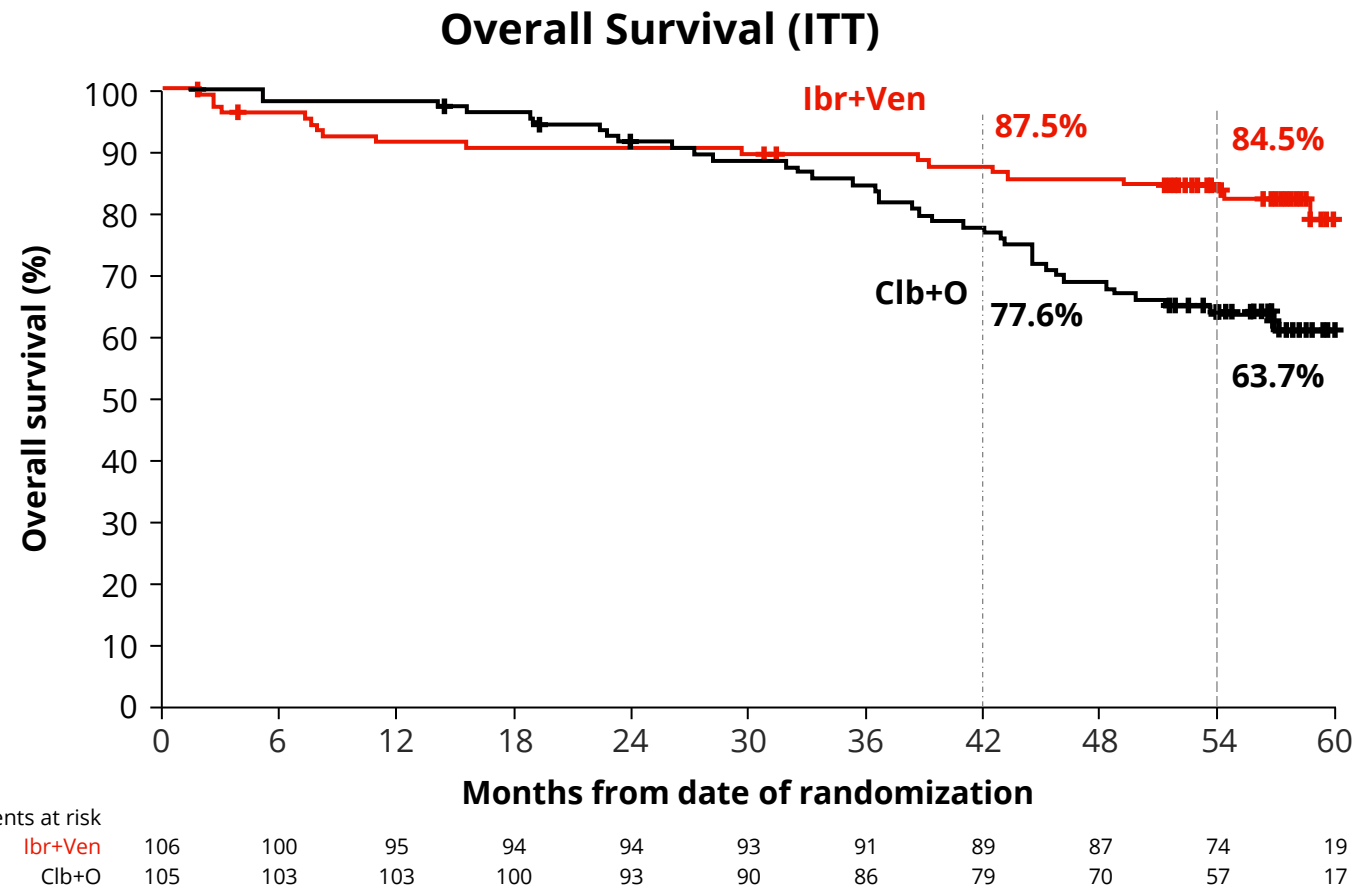


- **Ibr+Ven reduced the risk of progression or death by 74%** versus Clb+O
  - HR 0.256 (95% CI, 0.172-0.382); $p < 0.0001$
- Estimated 54-month PFS rates at 57 months of follow-up:
  - **66.5%** for Ibr+Ven
  - **19.5%** for Clb+O

p value is nominal. Investigator-assessed progression-free survival was analyzed.
ITT, intention to treat.

Presented by G. Follows at the 65th ASH Annual Meeting and Exposition; December 9-12, 2023; San Diego, CA, USA

GLOW: Ibr+Ven Remained Associated With Improved Overall Survival at 57 Months of Study Follow-up



- **Ibr+Ven reduced the risk of death by 55%** versus Clb+O
  - HR 0.453 (95% CI, 0.261-0.785); *p* = 0.0038
- Estimated 54-month OS rates:
  - **84.5%** for patients treated with Ibr+Ven
  - **63.7%** for patients treated with Clb+O

p value is nominal.

Presented by G. Follows at the 65th ASH Annual Meeting and Exposition; December 9-12, 2023; San Diego, CA, USA

GLOW: Summary of Deaths

	Ibr+Ven (n = 106)		Clb+O (n = 105)	
Total number of deaths	**19**		**39**	
Reasons for deaths	**On treatment**	**Post randomized treatment[a]**	**On treatment**	**Post randomized treatment[a]**
Infection related[b]	1	3	1	13
Second primary malignancy	1	1	0	7
Cardiac	2[c]	0	0	4
Sudden/unknown	2	3	0	4
Progressive disease	0	1	0	2
Vascular disorders	1	2	0	3
Other	0	2	1	4
Total	**7**	**12**	**2**	**37**

- **At 57 months of follow-up, there were 19 deaths in Ibr+Ven versus 39 in Clb+O arms**
  - 3 deaths in Ibr+Ven and 13 in Clb+O were due to post-treatment infections
  - 2 deaths in Ibr+Ven and 7 in Clb+O were due to second primary malignancies

[a]Either before or after initiation of subsequent antileukemic therapy. [b]Including 2 and 7 deaths due to COVID-19 in the Ibr+Ven and Clb+O arm, respectively. [c]1 patient had 3 causes of death: tachy-brady syndrome, cardiac failure, and pneumonia.

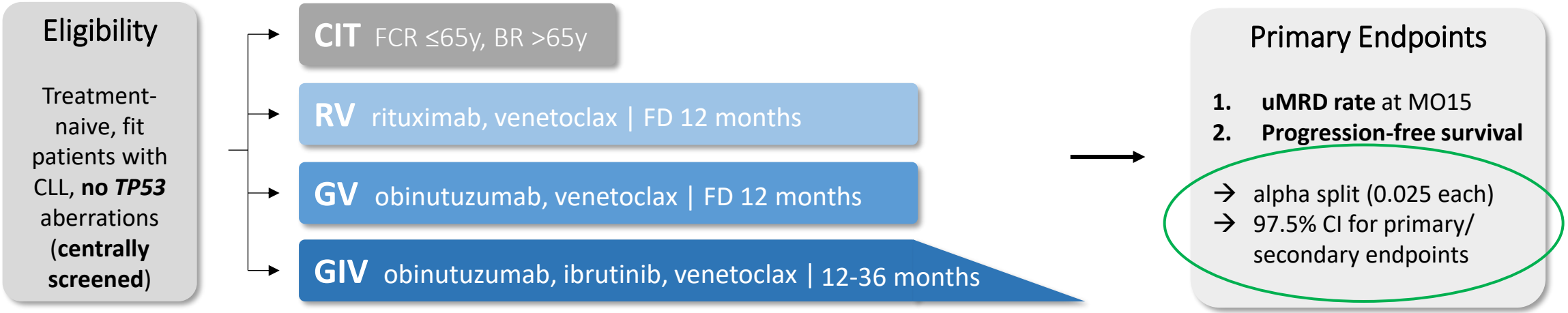
Presented by G. Follows at the 65th ASH Annual Meeting and Exposition; December 9-12, 2023; San Diego, CA, USA

First-line venetoclax combinations in CLL: 4-year follow-up from the phase 3 GAIA/CLL13 trial

Moritz Fürstenau, Matthias Ritgen, Sandra Robrecht, Julia von Tresckow, Can Zhang, Anke Schilhabel, Michael Gregor, Patrick Thornton, Philipp B. Staber, Tamar Tadmor, Vesa Lindström, Gunnar Juliusson, Ann Janssens, Mark-David Levin, Caspar da Cunha-Bang, Christof Schneider, Neta Goldschmidt, Elisabeth Vandenberghe, Davide Rossi, Rudolf Benz, Daniel Heintel, Christian B Poulsen, Ilse Christiansen, Henrik Frederiksen, Lisbeth Enggaard, Eduardus FM Posthuma, Djamila E Issa, Hein PJ Visser, Mar Bellido, Nadine Kutsch, Jan Dürig, Alexander Stehle, Matthias Vöhringer, Sebastian Böttcher, Clemens Schulte, Florian Simon, Anna-Maria Fink, Kirsten Fischer, Emily Holmes, Karl-Anton Kreuzer, Matthias Ritgen, Monika Brüggemann, Eugen Tausch, Stephan Stilgenbauer, Michael Hallek, Arnon P Kater, Carsten U Niemann, Barbara Eichhorst

65th ASH annual meeting | December 9-12, 2023 | San Diego, USA

Study Design - GAIA/CLL13



Key patient characteristics

Randomized patients (=ITT population): **n= 926**

Median age:	**61 years** (range: 27-84)
Median CIRS score:	**2** (range: 0-7)
Unmutated IGHV:	**56%** of all patients
Complex karyotype:	**17%** of all patients

Follow-up analysis (data cut-off: 01/2023)

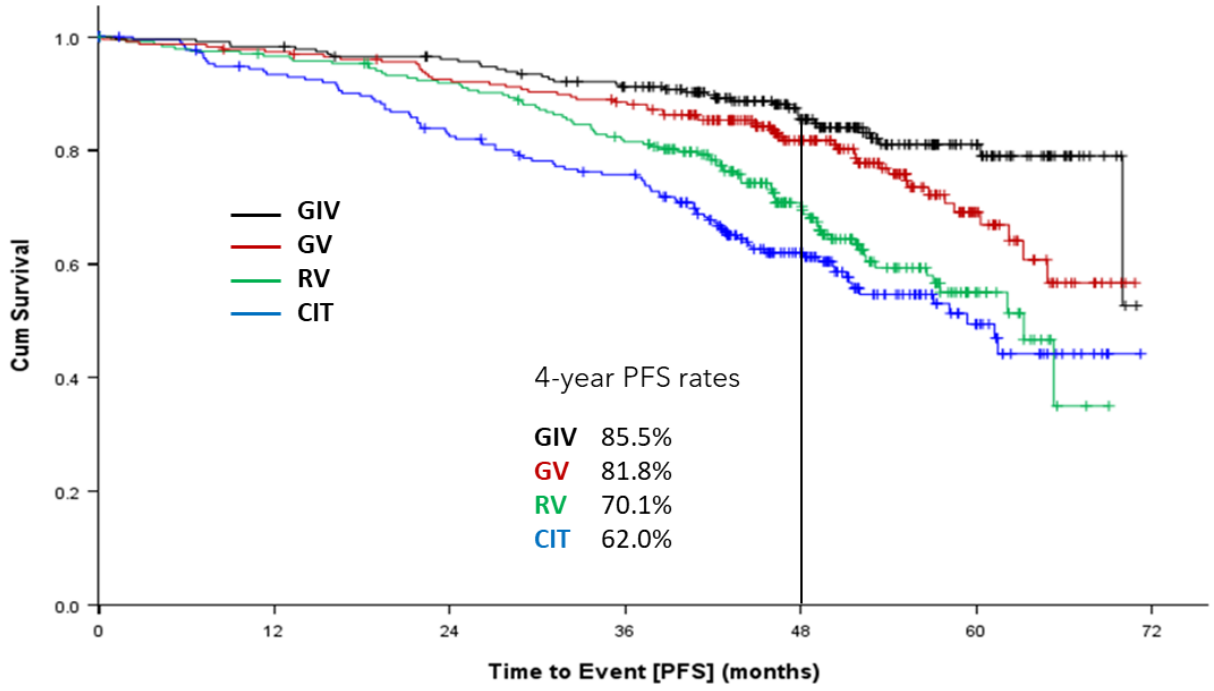
Median observation time
50.7 months (IQR: 44.6-57.9)

Median observation time after end of treatment
40.7 months (IQR: 34.5-47.9)

Efficacy – PFS

Median observation time: 50.7 months

Progression-free survival



Patients at risk

CIT	229	197	173	156	84	24
RV	237	227	214	188	106	21
GV	229	222	209	198	121	32
GIV	231	227	218	201	130	44

PFS comparisons

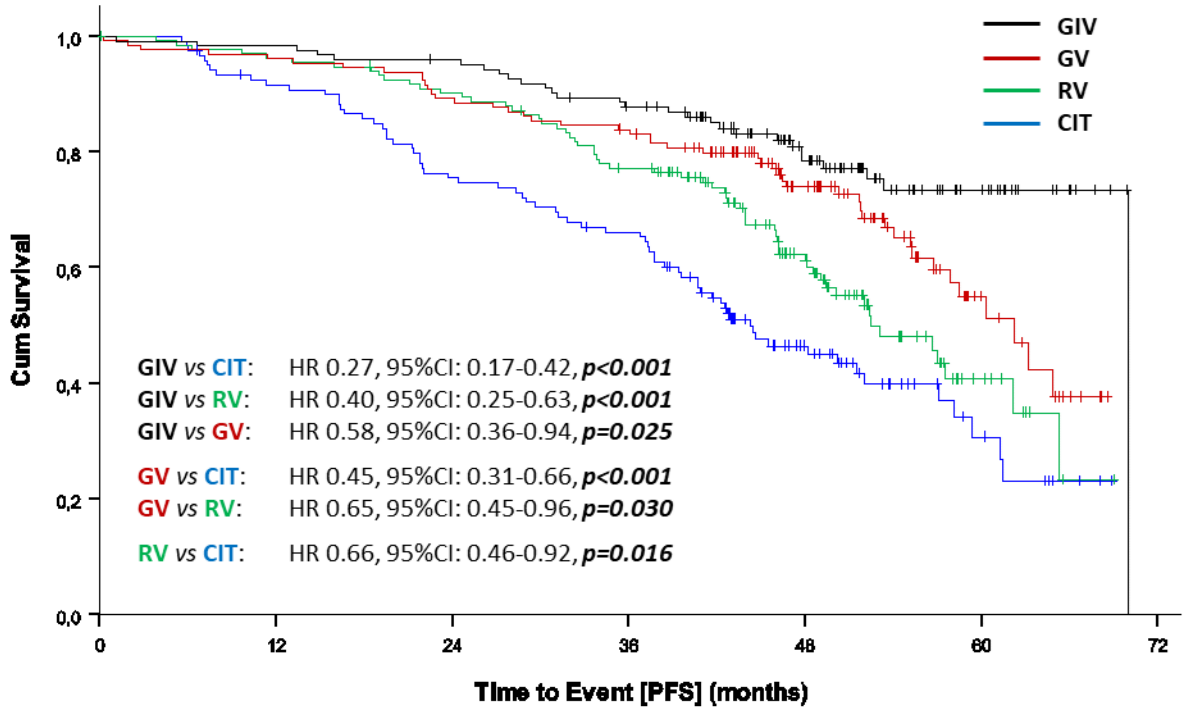
GIV *vs* **CIT**: HR 0.30, 97.5%CI: 0.19-0.47, ***p<0.001***
GIV *vs* **RV**: HR 0.38, 97.5%CI: 0.24-0.59, ***p<0.001***
GIV *vs* **GV**: HR 0.63, 97.5%CI: 0.39-1.02, p=0.03

GV *vs* **CIT**: HR 0.47, 97.5%CI: 0.32-0.69, ***p<0.001***
GV *vs* **RV**: HR 0.57, 97.5%CI: 0.38-0.84, ***p=0.001***

RV *vs* **CIT**: HR 0.78, 97.5%CI: 0.55-1.10, p=0.1

Efficacy – PFS

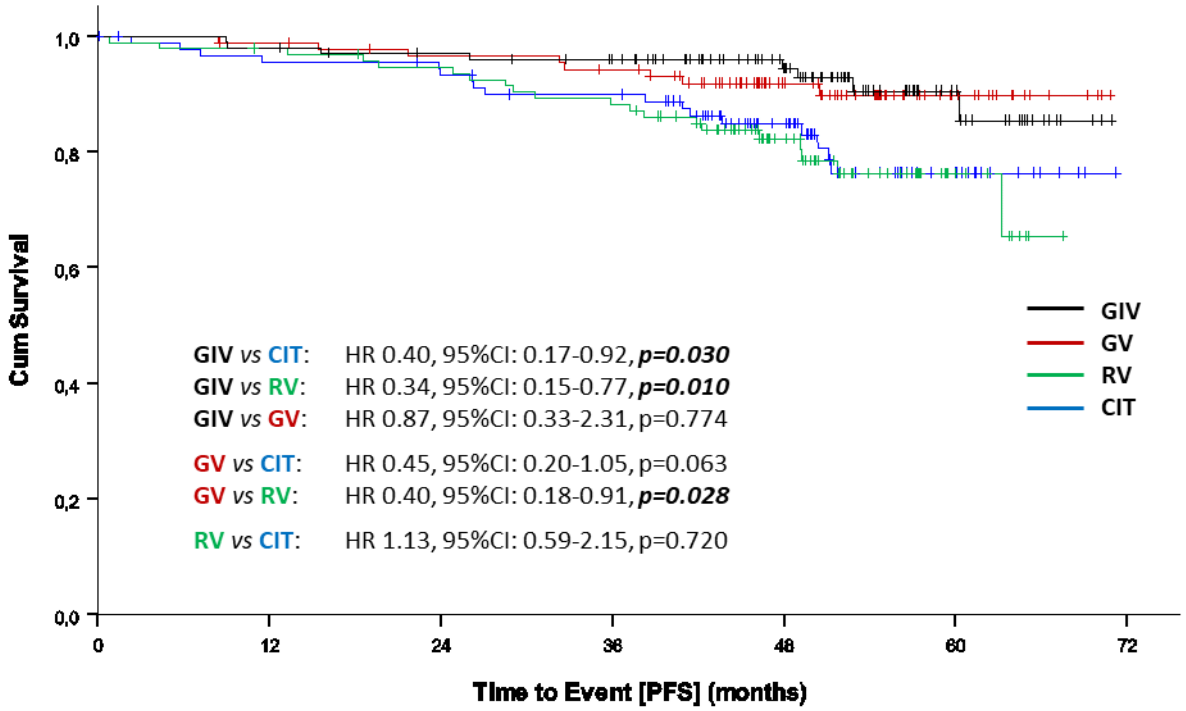
PFS, patients with unmutated IGHV



Pts at risk

CIT	131	108	89	77	34	9
RV	134	128	119	100	56	10
GV	130	125	116	108	67	15
GIV	123	121	117	105	65	24

PFS, patients with mutated IGHV

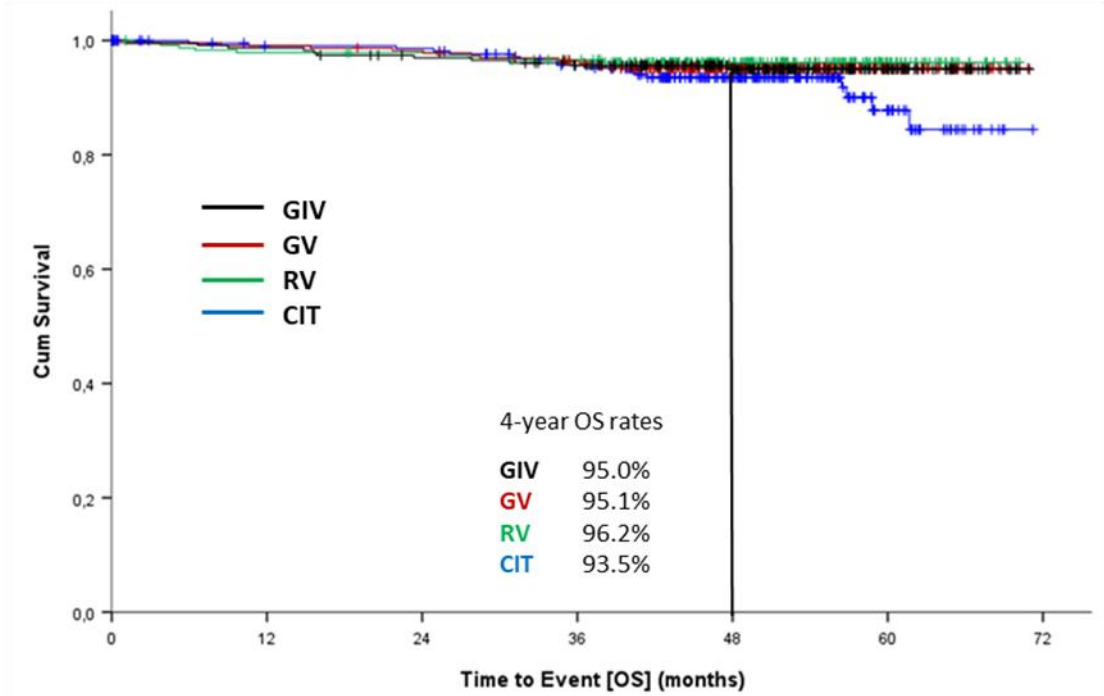


Pts at risk

CIT	95	86	83	78	50	15
RV	95	92	88	82	47	11
GV	89	87	83	80	48	15
GIV	101	99	95	90	60	20

Efficacy – OS

Overall survival



Patients at risk

CIT	229	209	208	192	120	34
RV	237	231	229	221	142	38
GV	229	227	224	215	136	39
GIV	231	228	220	211	142	48

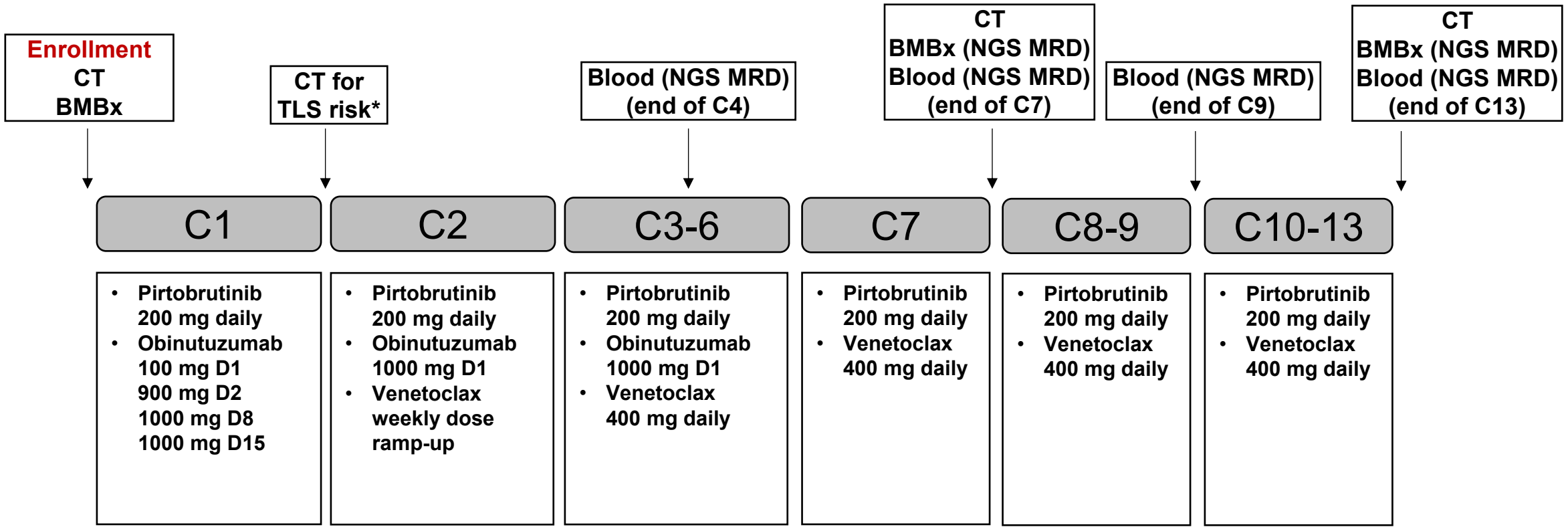
OS comparisons

GIV *vs* **CIT**: HR 0.58, 97.5%CI: 0.24-1.38, p=0.15
GIV *vs* **RV**: HR 1.25, 97.5%CI: 0.46-3.43, p=0.62
GIV *vs* **GV**: HR 1.00, 97.5%CI: 0.39-2.61, p=0.99

GV *vs* **CIT**: HR 0.58, 97.5%CI: 0.24-1.38, p=0.15
GV *vs* **RV**: HR 1.25, 97.5%CI: 0.46-3.43, p=0.62

RV *vs* **CIT**: HR 0.46, 97.5%CI: 0.18-1.17, p=0.056

Frontline Pirtobrutinib + VEN + Obin Trial (MDACC)



*only if baseline CT had nodes ≥5 cms

- All pts will be monitored by PB MRD by NGS q3 mos for first 12 mos off therapy, and then q6 mos

Jain/Wierda, Clinicaltrials.gov NCT05536349

CASE-1

72 male ECOG 0 with HTN Initially presented at age 68 with an 8cm abdominal mass and anemia – Dxn CLL

- Received Obi/Ven x 1 year and had complete remission for 3 years
- 1 year ago progressed with uptrending WBC and worsening anemia
- Started acalabrutinib with complete response and good tolerability except for rash that resolved
- Now having progressive lymphadenopathy and night sweats
- LN biopsy consistent with CLL
- BTK mutation profile showed C481S mutation

What would be the next recommeneded step in management?

CASE-2

54 year old woman with CLL/SLL (IGHV mutated, del13q, trisomy 12, non-TP53 mutated) diagnosed 2019 on active surveillance, poorly controlled insulin-dependent diabetes

- Recent progressive cytopenias requiring RBC transfusion, without evidence of bleeding or hemolysis

- Bone marrow biopsy shows near replacement by CLL
- CT with stable small diffuse adenopathy and mild splenomegaly

Best choice of initial therapy?

Lee

CASE-3

70 y/o M with PMH HTN referred by PCP for leukocytosis

- 2019 WBC 9.9 and ALC 1436
- June 2022 WBC 43.4 and ALC 32.1 Hb 13.5 Hct 42.2 Plt 147
- Flow consistent with CLL CD 38+ ZAP 70+
- IgVH umutated - FISH del 17p
- 2 cm palpable cervical LN, 3 cm L axillary LN, palpable splenomegaly
- December 2022; worsening fatigue, night sweats and 7 pound weight loss
- WBC 54.9 ALC 42 Bh 12.4 Hct 39 Plt 84
- Progressive lymphadenopathy and splenomegaly
- Discussed initial treatment options of single agent acalabrutinib continuously vs fixed duration venetoclax-obinituzumab

Seidman

CASE-4

71 y/o man with HTN (well controlled on 2 medications), stage IV CLL with 17p deletion.

- Unmutated IgH, p53 wild type, no other cytogenetuc abnormalities.
- Was on ibrutunib for 3 yrs, now progressed, mutation analysis showed no mutation.

What would you recommend?

Venetoclax or Pirtobrutinib?

Wu

CASE-5

81 y/o M originally presented with leukocytosis in 2008. His wbc count at the time was 32.5. Flow 11/16/09 confirmed diagnosis of B-CLL. FISH negative for Immunoglobulin heavy chain rearrangement, +deletion chromosome 13, negative for trisomy 12, del chrom 11, monosomy13,and del chrom 17 Hypoglobulinemia sec CLL: IgG=601, IgA=39, IgM=5. Observtion….

- 2/16/17 wbc=417, hct=33, plt=195
- 3/1/17 Started Ibrutinib 140mg tab, take three tabs (420mg total)
- 3/29/17 wbc=506.3 hb=9.4 plt=152 and 4/25/17 wbc=279.7
- Questions:

If asymptomatic, at what absolute number of lymph would u pull the trigger to treat, even if doubling time was prolonged?

Would you ever treat hypoglobulinemia in CLL if no severe infections? In what instances?

Given patient is elderly, to minimize cardiac toxicity, would you consider switching to new generation BTK inhibitor?

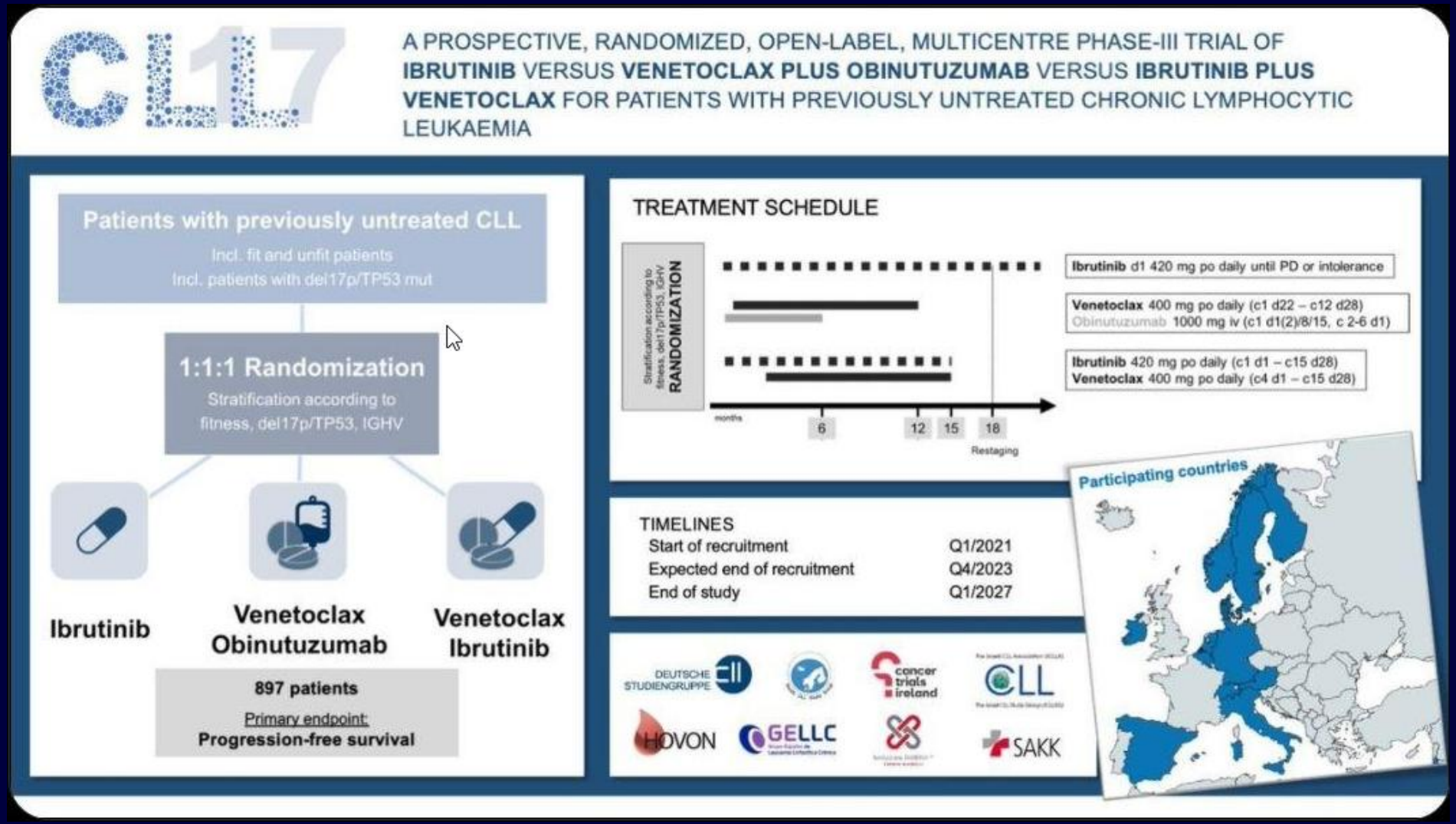
Blokh

Some Unanswered Questions in Firstline Rx?

- What is the ideal firstline Rx?
  - BTKi – approved
  - BCL2i + CD20 mAb – approved
  - BCL2i + BTKi – soon to be approved
  - BCL2i + BTKi + CD20 mAb – randomized studies to clarify role

- Ideal treatment duration?
  - 1 year, 2 year, MRD-based

CLL17 trial


CLL17
A PROSPECTIVE, RANDOMIZED, OPEN-LABEL, MULTICENTRE PHASE-III TRIAL OF IBRUTINIB VERSUS VENETOCLAX PLUS OBINUTUZUMAB VERSUS IBRUTINIB PLUS VENETOCLAX FOR PATIENTS WITH PREVIOUSLY UNTREATED CHRONIC LYMPHOCYTIC LEUKAEMIA
Patients with previously untreated CLL
Incl. fit and unfit patients
Incl. patients with del17p/TP53 mut
1:1:1 Randomization
Stratification according to fitness, del17p/TP53, IGHV
Ibrutinib
Venetoclax Obinutuzumab
Venetoclax Ibrutinib
897 patients
Primary endpoint:
Progression-free survival
TREATMENT SCHEDULE
Stratification according to fitness, del17p/TP53, IGHV
RANDOMIZATION
months
6
12
15
18
Restaging
Ibrutinib d1 420 mg po daily until PD or intolerance
Venetoclax 400 mg po daily (c1 d22 – c12 d28)
Obinutuzumab 1000 mg iv (c1 d1(2)/8/15, c 2-6 d1)
Ibrutinib 420 mg po daily (c1 d1 – c15 d28)
Venetoclax 400 mg po daily (c4 d1 – c15 d28)
TIMELINES
Start of recruitment Q1/2021
Expected end of recruitment Q4/2023
End of study Q1/2027
Participating countries
DEUTSCHE STUDIENGRUPPE
cancer trials ireland
CLL
HOVON
GELLC
SAKK

CLL frontline Tx in 10 years

SUGGESTED TREATMENT REGIMENS[a,b,c,d]
CLL/SLL Without del(17p)/*TP53* Mutation
(alphabetical by category)

FIRST-LINE THERAPY[e]		
Preferred Regimens	**Other Recommended Regimens**	**Useful in Certain Circumstances**
• Acalabrutinib[f,g,*] ± obinutuzumab (category 1) • Venetoclax[f,h] + obinutuzumab (category 1) • Zanubrutinib[f,g,*] (category 1)	• Ibrutinib [f,g,i,*] (category 1) • Ibrutinib[f,g,*] + obinutuzumab (category 2B) • Ibrutinib[f,g,*] + rituximab[j] (category 2B) • Ibrutinib[f,g,*] + venetoclax[f,h] (category 2B)	• Consider for IGHV-mutated CLL in patients aged <65 y without significant comorbidities ▸ FCR (fludarabine, cyclophosphamide, rituximab)[k,l,m] • Consider when BTKi and venetoclax are not available or contraindicated or rapid disease debulking needed ▸ Bendamustine[n] + anti-CD20 mAb[o,p] ▸ Obinutuzumab ± chlorambucil[q] ▸ High-dose methylprednisolone (HDMP) + anti-CD20 mAb[o] (category 2B; category 3 for patients <65 y without significant comorbidities)

* Covalent (irreversible) BTKi.

Footnotes on CSLL-D 4 of 6

Suggested Regimens for Second-Line and Third-Line Therapy for CLL/SLL without del(17p)/*TP53* Mutation (CSLL-D 2 of 6)

Therapy for Relapsed or Refractory Disease After Prior BTKi-and Venetoclax-Based Regimens for CLL/SLL Without del(17p)/*TP53* Mutation (CSLL-D 2 of 6)

Suggested Regimens for CLL/SLL With del(17p) (CSLL-D 3 of 6)

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

SUGGESTED TREATMENT REGIMENS[a,b,c,d]
CLL/SLL Without del(17p)/*TP53* Mutation

SECOND-LINE OR THIRD-LINE THERAPY[e]

Preferred Regimens	Other Recommended Regimens	Useful in Certain Circumstances
• Acalabrutinib[f,g,r,*] (category 1) • Venetoclax[f,h] + rituximab (category 1) • Zanubrutinib[f,g,r,*] (category 1)	• Ibrutinib[f,g,i,*] (category 1) • Venetoclax[f,h] • Ibrutinib[f,g,*] + venetoclax[f,h] (category 2B)	• For relapse after a period of remission (if previously used) ▸ Venetoclax[f,h] ± anti-CD20 mAb (venetoclax + obinutuzumab preferred) • Resistance or intolerance to prior covalent BTKi therapy ▸ Pirtobrutinib[f,**]

THERAPY FOR RELAPSED OR REFRACTORY DISEASE AFTER PRIOR BTKi- AND VENETOCLAX-BASED REGIMENS[e]

Other Recommended Regimens (alphabetical order by category)

- Small-molecule inhibitors[f]
  - Duvelisib
  - Idelalisib[s] ± rituximab
  - Pirtobrutinib[**] (if not previously given)
  - Ibrutinib[g,*] + venetoclax[h] (category 2B)
- FCR[j,l,m]
- Lenalidomide[t] ± rituximab
- Obinutuzumab
- Bendamustine[n] + rituximab[p] (category 2B for patients ≥65 y or patients <65 y with significant comorbidities)
- HDMP + anti-CD20 mAb[p] (category 2B)

[*] Covalent (irreversible) BTKi.
[**] Non-covalent (reversible) BTKi.

Footnotes on CSLL-D 4 of 6

Suggested Regimens for CLL/SLL with del(17p) (CSLL-D 3 of 6)

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

SUGGESTED TREATMENT REGIMENS[a,b,c,d]
CLL/SLL With del(17p)/*TP53* Mutation
(alphabetical by category)

CIT is not recommended since del(17p)/*TP53* mutation is associated with low response rates.

FIRST-LINE THERAPY[e]

Preferred Regimens	Other Recommended Regimens	Useful in Certain Circumstances
• Acalabrutinib[f,g,*] ± obinutuzumab • Venetoclax[f,h] + obinutuzumab • Zanubrutinib[f,g,*]	• Ibrutinib[f,g,i,*] • Ibrutinib[f,g,*] + venetoclax[f,h] (category 2B)	• Consider when BTKi and venetoclax are not available or contraindicated or rapid disease debulking needed ▸ HDMP + anti-CD20 mAb[o] ▸ Obinutuzumab

SECOND-LINE OR THIRD-LINE THERAPY[e]

Preferred Regimens	Other Recommended Regimens	Useful in Certain Circumstances
• Acalabrutinib[f,g,r,*] (category 1) • Venetoclax[f,h] + rituximab (category 1) • Venetoclax[f,h] • Zanubrutinib[f,g,r,*] (category 1)	• Ibrutinib[f,g,i,*] (category 1) • Ibrutinib[f,g,*] + venetoclax[f,h] (category 2B)	• For relapse after a period of remission (if previously used) ▸ Venetoclax[f,h] ± anti-CD20 mAb (venetoclax + obinutuzumab preferred) • Resistance or intolerance to prior covalent BTKi therapy ▸ Pirtobrutinib[f,**]

THERAPY FOR RELAPSED OR REFRACTORY DISEASE AFTER PRIOR BTKi- AND VENETOCLAX-BASED REGIMENS[e]

Other Recommended Regimens

- Small-molecule inhibitors[f] (in alphabetical order by category)
  - ▸ Duvelisib
  - ▸ Idelalisib[s] ± rituximab
  - ▸ Pirtobrutinib[**] (if not previously given)
  - ▸ Ibrutinib[g,*] + venetoclax[h] (category 2B)
- Alemtuzumab[u] ± rituximab
- HDMP + anti-CD20 mAb[o]
- Lenalidomide[t] ± rituximab

Footnotes on CSLL-D 4 of 6

Suggested Regimens for CLL/SLL without del(17p) (CSLL-D 1 of 6)

* Covalent (Irreversible) BTKi.
** Non-covalent (reversible) BTKi.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

Leukemia Questions?

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