Navigating Frontline Therapies in CLL

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Financial Disclosures

Research Funding

Pharmacyclics, AbbVie, Genentech, AstraZeneca, BMS, Pfizer, Servier, ADC Therapeutics, Cellectis, Adaptive Biotechnologies, Incyte, Precision Biosciences, Aprea Therapeutics, Fate Therapeutics, Kite/Gilead, Mingsight, Takeda, Medisix, Loxo Oncology, Novalgen, Dialectic Therapeutics, Newave, TransThera Sciences

Advisory Board / Honoraria

Pharmacyclics, Janssen, AbbVie, Genentech, AstraZeneca, BMS, Adaptive Biotechnologies, Kite/Gilead, Precision Biosciences, Beigene, Cellectis, TG Therapeutics, MEI Pharma, Ipsen, CareDX

Treatment Evolution for 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)

2022+

BTK inhibitors (Zanubrutinib, Pirtobrutinib)
PI3K inhibitor ~~(Umbralisib)~~
CAR-T

Evolving Treatment Paradigm

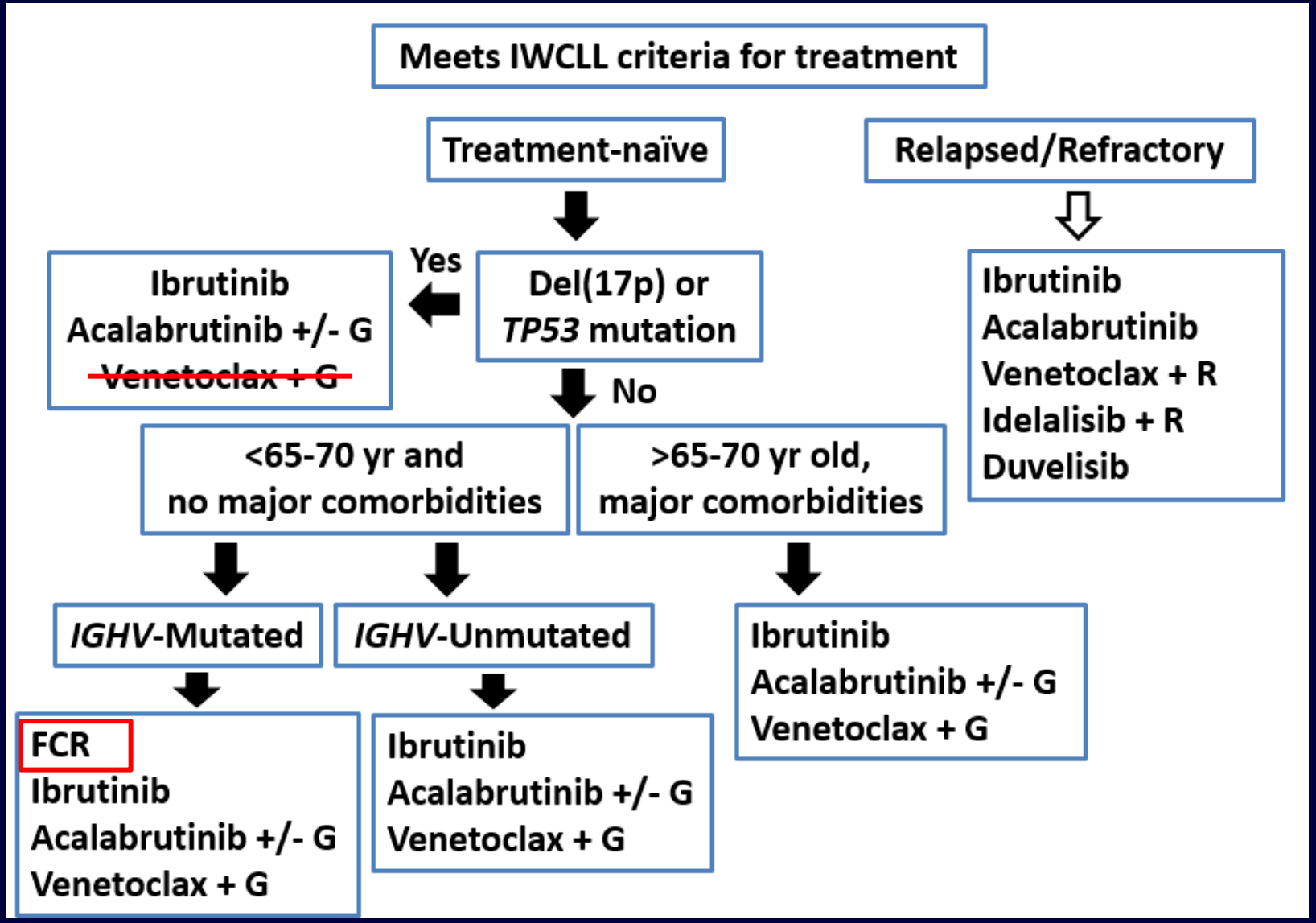
Chemoimmunotherapy era

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

Targeted Therapies era

- **FCR (consider in young fit *IGHV*-M, no del(17p)/ *TP53-m*)**
- **Targeted therapies (all others)**

Current Standard Rx of CLL



Adapted from Jain N, O'Brien S. Cancer J. 2019;25(6):374-377.

YOUNG ‘FIT’ PTS (FCR ELIGIBLE)

CLL10 Study: FCR vs. BR Frontline

Patients with untreated CLL without del(17p)
and good physical fitness
(CIRS ≤ 6, creatinine clearance ≥ 70 ml/min)

Randomization

FCR (n=282)

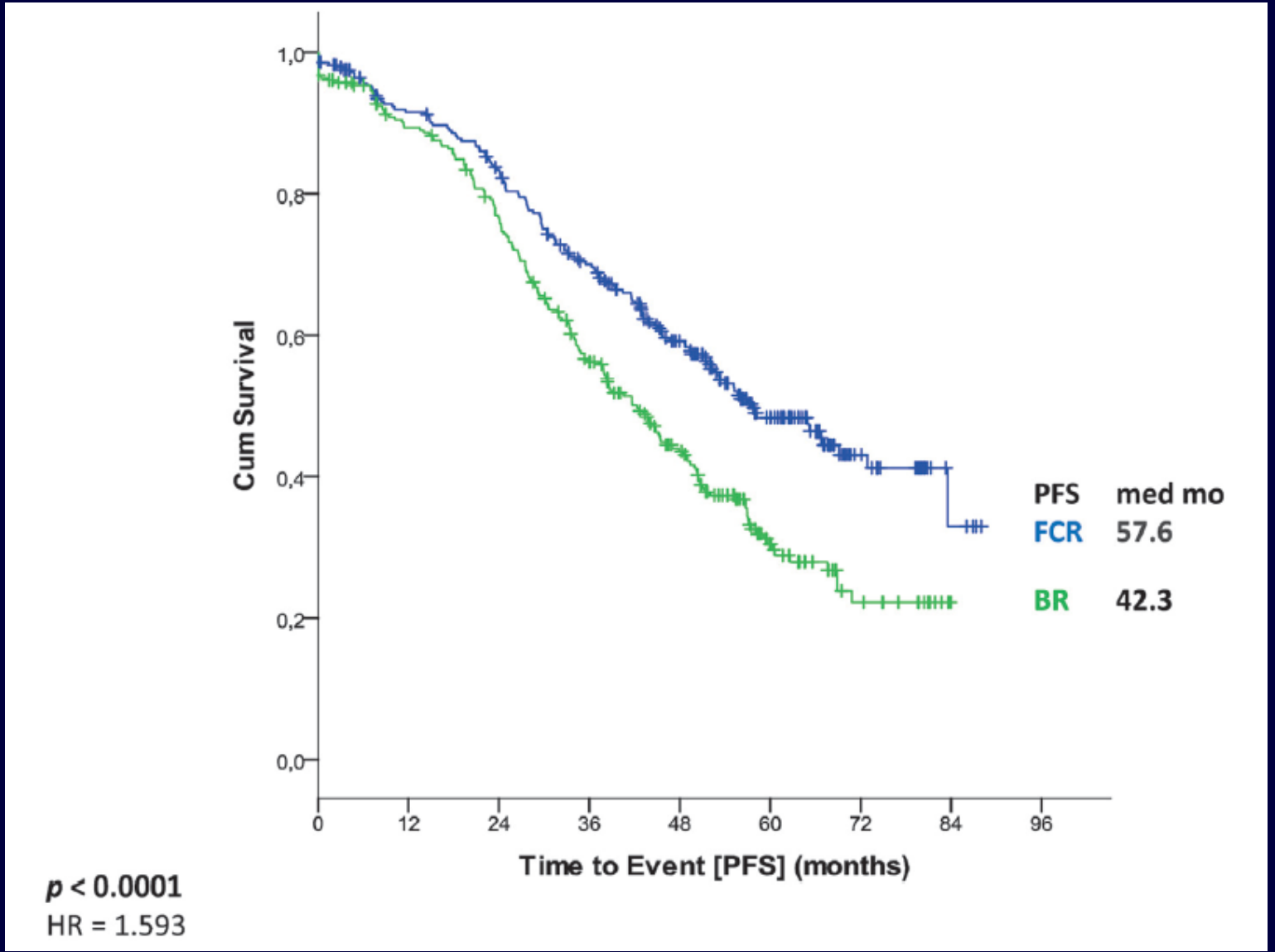
Fludarabine 25 mg/m² i.v., days 1-3
Cyclophosphamide 250 mg/m², days 1-3,
Rituximab 375 mg/ m² i.v. day 0, cycle 1
Rituximab 500 mg/m² i.v. day 1, cycle 2-6

BR (n=279)

Bendamustine 90mg/m² day 1-2
Rituximab 375 mg/m² day 0, cycle 1
Rituximab 500 mg/m² day 1, cycle 2-6

Eichhorst et al. Lancet Oncol. 2016;17(7):928-942.

Updated CLL10, PFS, all patients



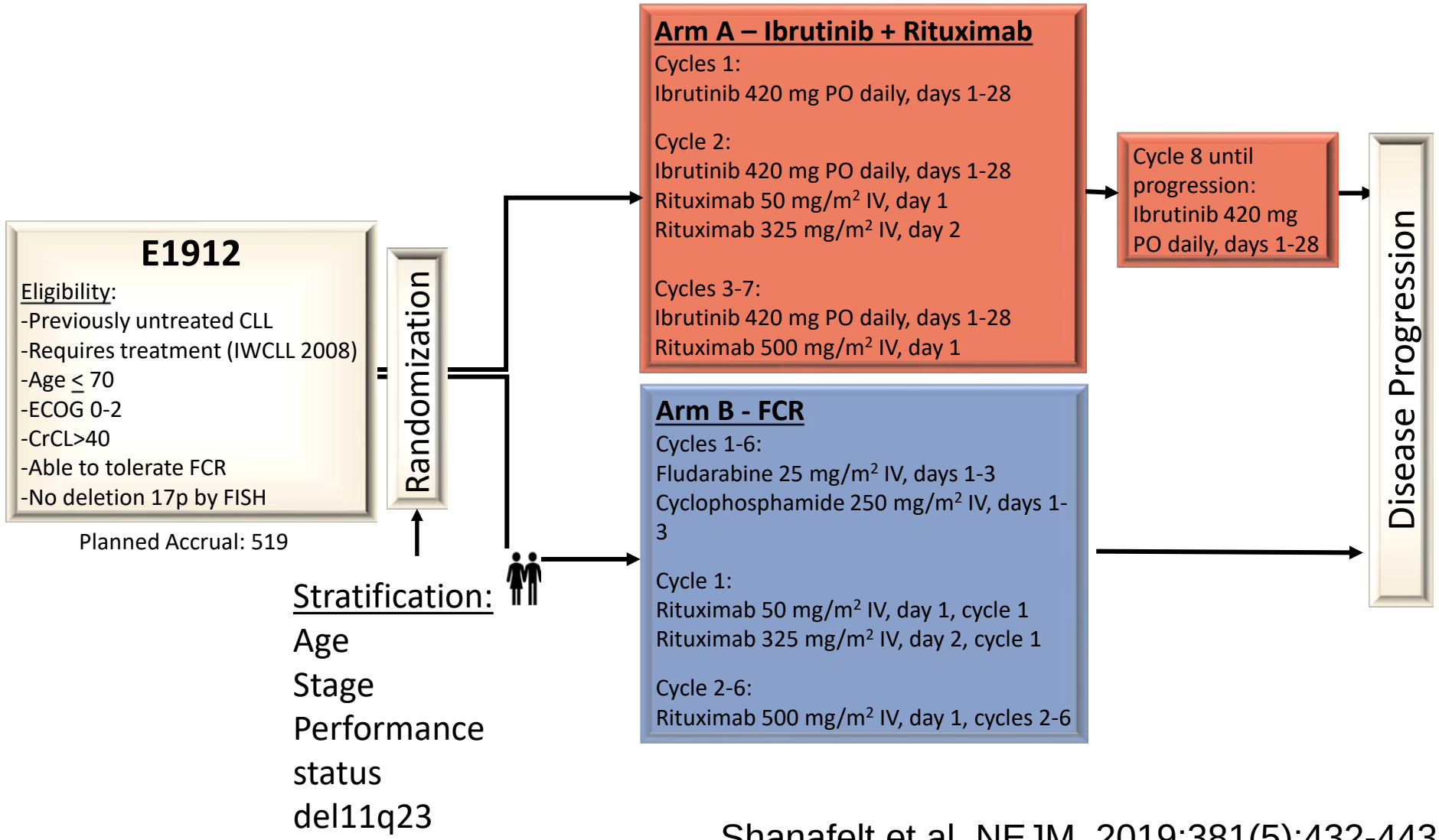
Median follow-up 58.2 mos

Kutsch et al. Hemasphere. 2020 Jan 27;4(1):e336.

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

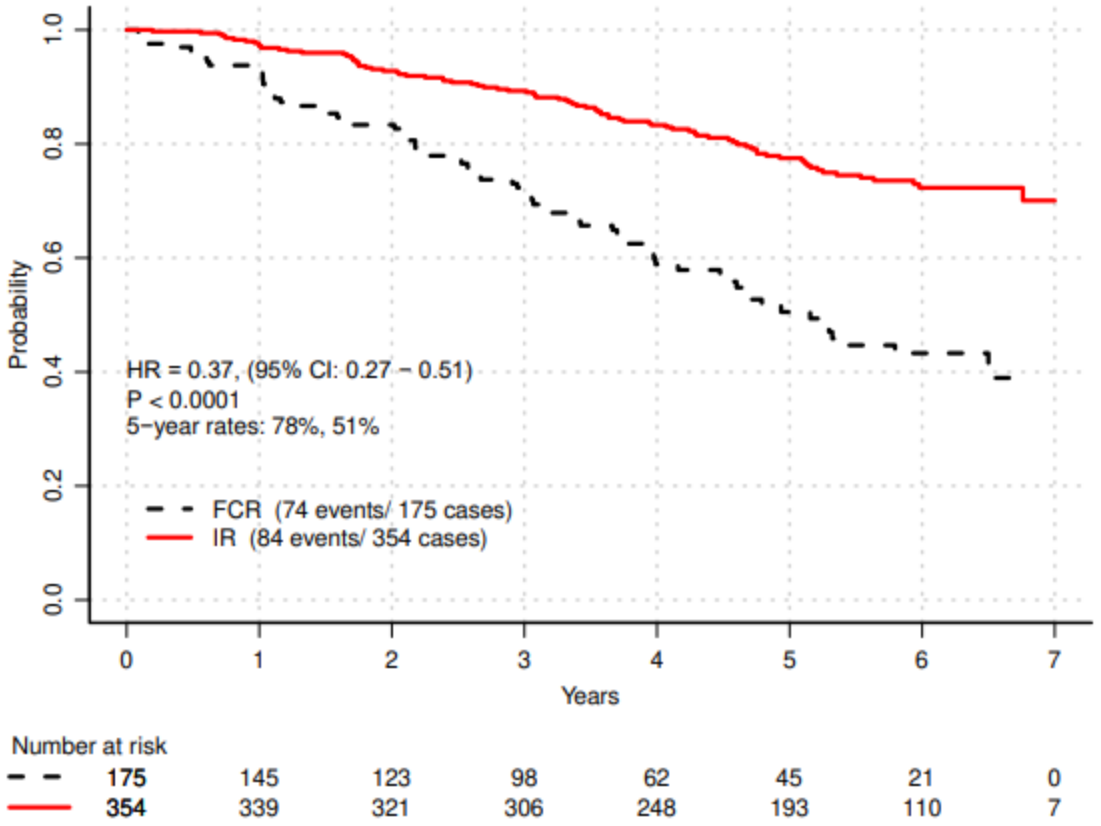
Tait Shanafelt, Xin Victoria Wang, Neil E. Kay, Susan O'Brien, Jacqueline Barrientos , Curt Hanson, Harry Erba, Rich Stone, Mark Litzow, Marty Tallman

E1912 Study design



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

Progression-Free Survival

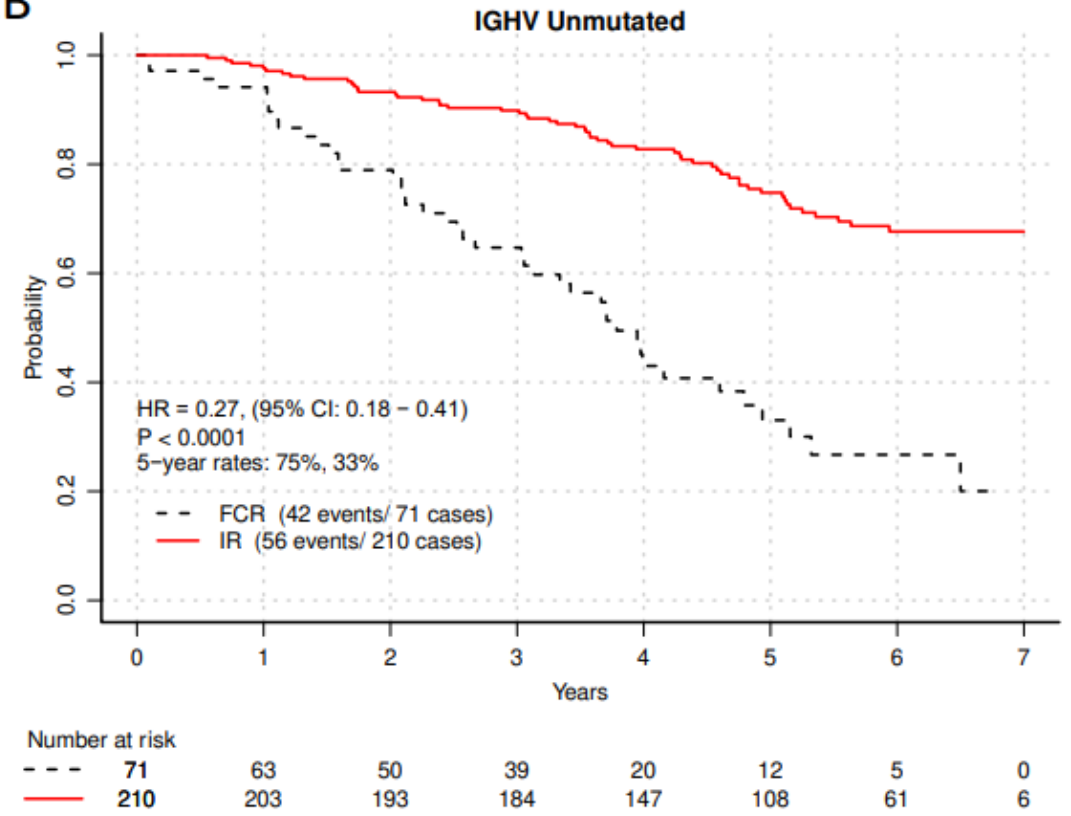


Median follow-up 5.8 yr

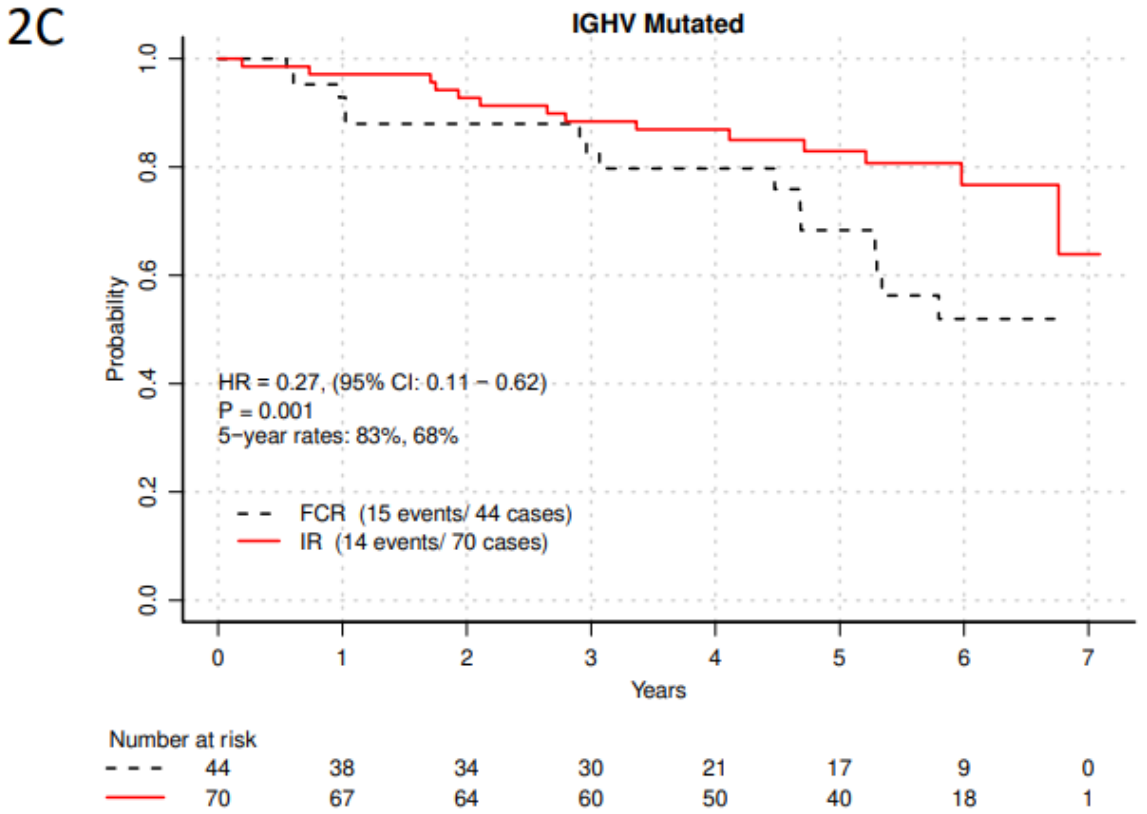
Shanafelt et al. NEJM. 2019;381(5):432-443.
Updated in Shanafelt et al. Blood. 2022 Apr 15.

Progression-Free Survival by IGHV Status

2B

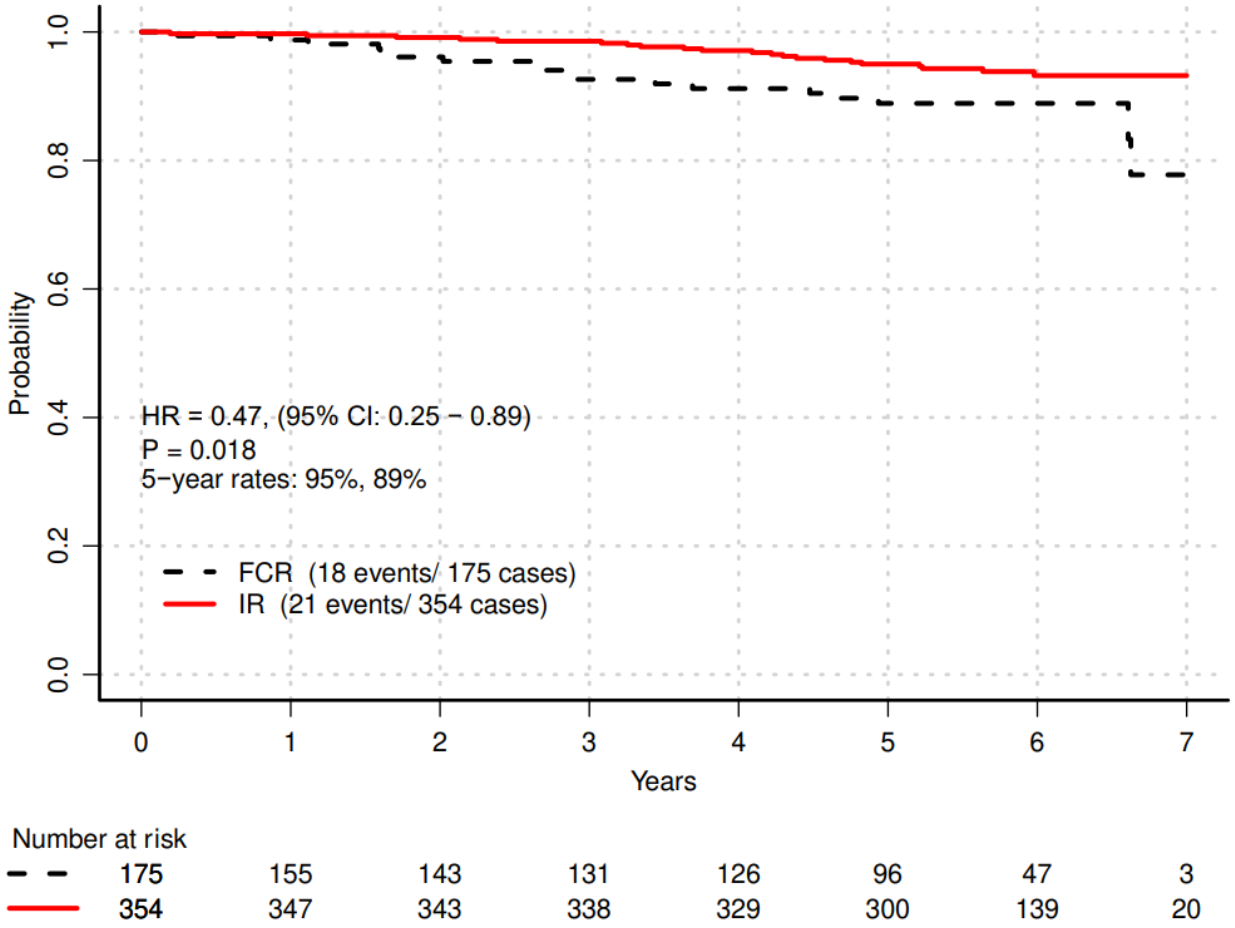


2C



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

Overall Survival



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

Ibrutinib Plus Rituximab Is Superior to FCR in Previously Untreated CLL: Results of the Phase III NCRI Flair Trial

Peter Hillmen, Alexandra Pitchford, Adrian Bloor, Angus Broom, Moya Young, Ben Kennedy, Renata Walewska, Michelle Furtado, Gavin Preston, Jeffrey R. Neilson, Nicholas Pemberton, Gamal Sidra, Nicholas Morley, Kate Cwynarski, Anna Schuh, Francesco Forconi, Nagah Elmusharaf, Shankara Paneesha, Christopher P. Fox, Dena Howard, Anna Hockaday, David Cairns, Sharon Jackson, Natasha Greatorex, Piers EM Patten, David Allsup and Talha Munir

Abstract No: 642, Oral Presentation, ASH Annual Meeting
Monday, December 13th 2021

National Cancer Research Institute

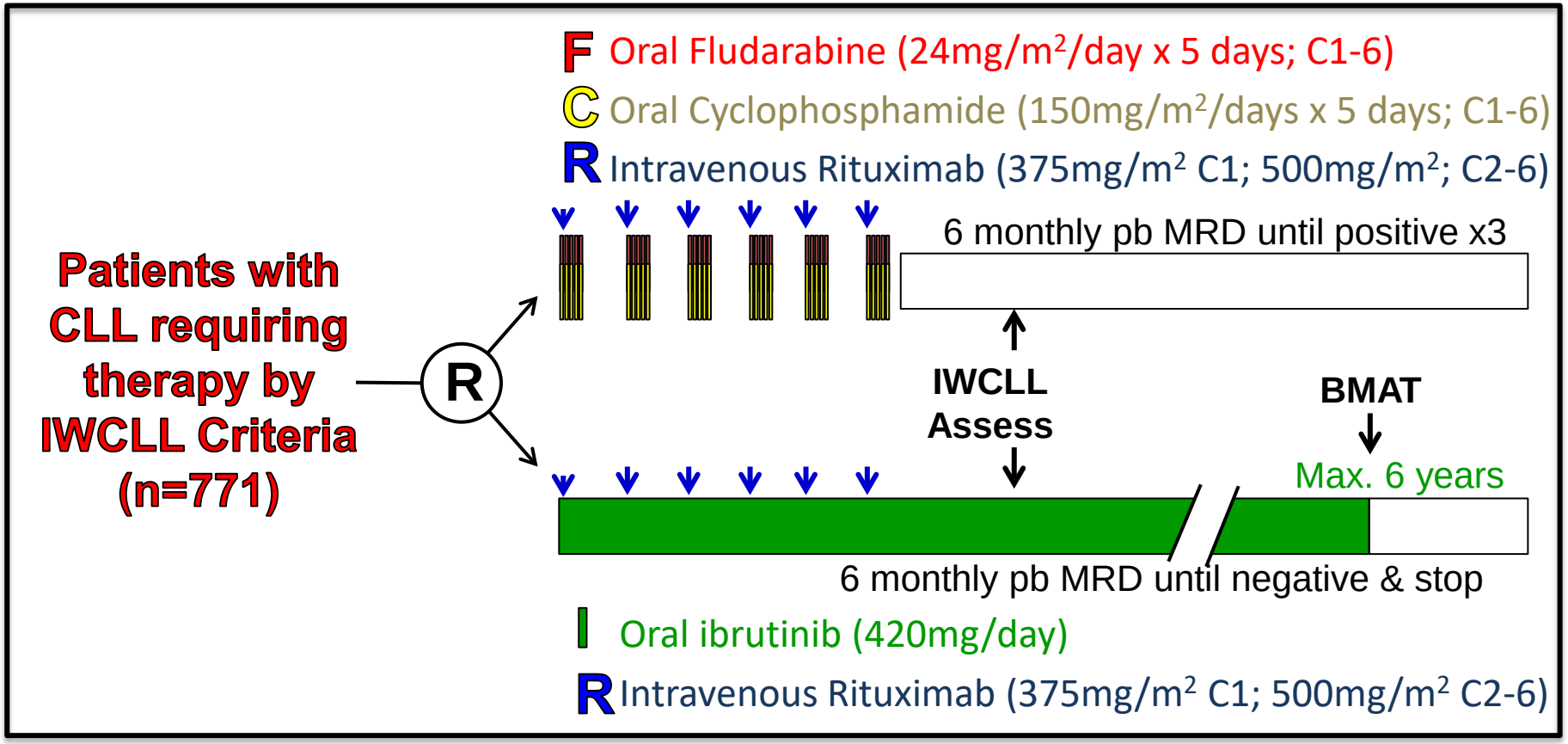
CANCER RESEARCH UK

ctru University of Leeds

LEEDS CLINICAL TRIALS UNIT

Front-line trial for patients fit for FCR: NCRI Flair Trial

Front Line therapy in CLL: Assessment of Ibrutinib plus Rituximab



Primary end-point:
To assess whether IR is superior to FCR in terms of PFS

Key secondary end-points:
Overall survival
Response including MRD
Safety and toxicity

Key Inclusion Criteria:

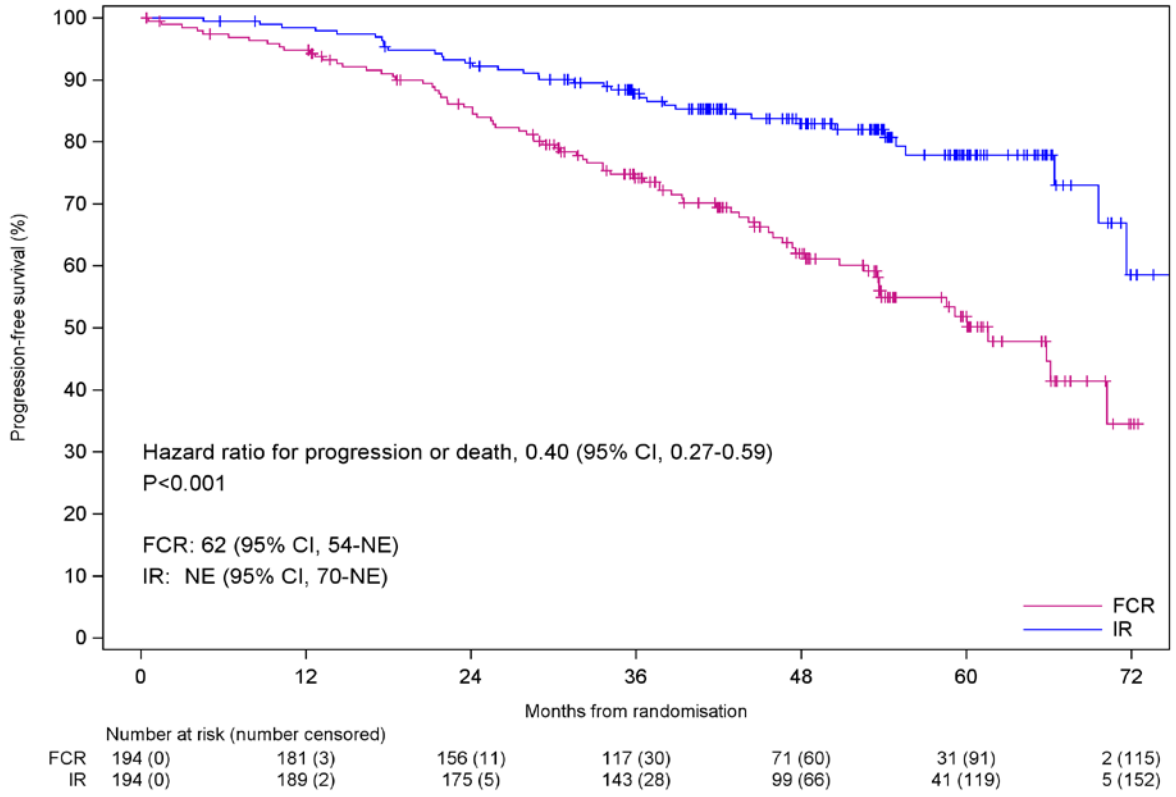
- Previously untreated CLL requiring therapy by IWCLL criteria
- Considered fit for FCR
- ≤75 years old

Key Exclusion Criteria:
Prior therapy for CLL; History of Richter's transformation; >20% TP53 deletion by FISH; Concomitant warfarin (or equivalent) Symptomatic cardiac failure or angina

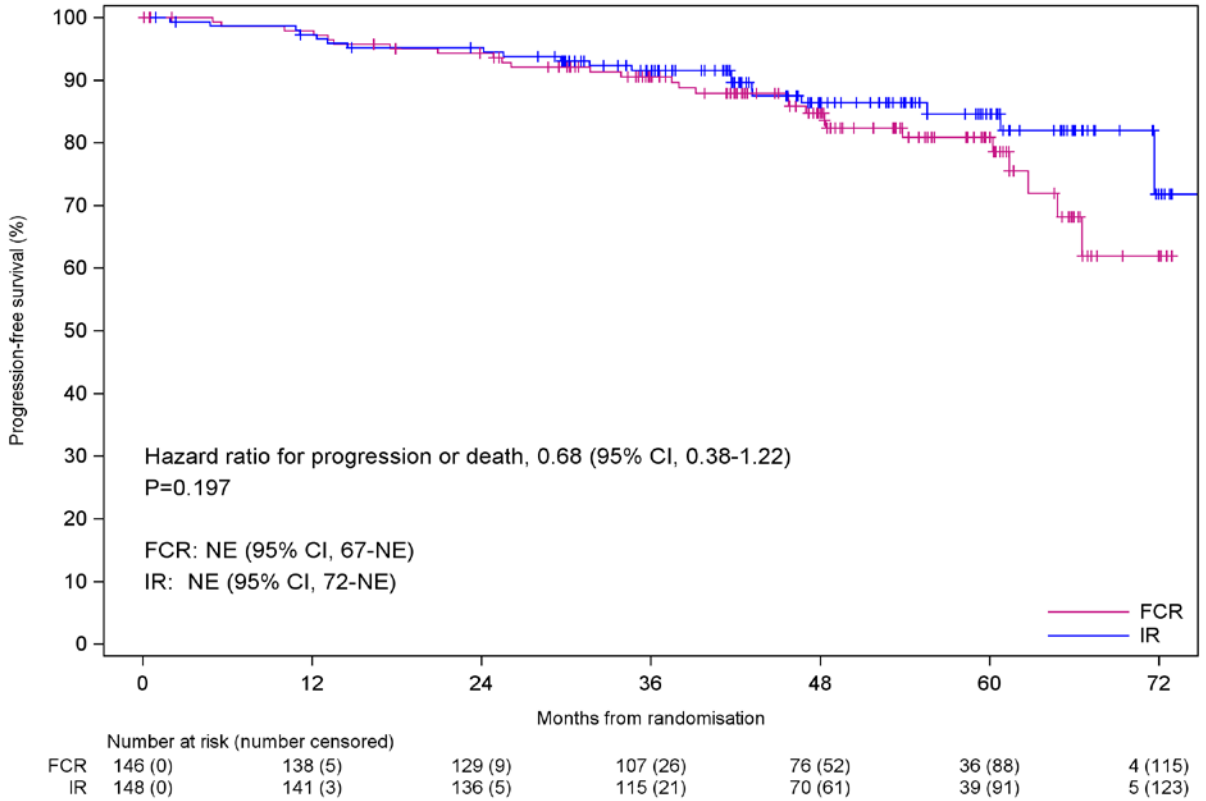
Hillmen *et al.*, Abstract 642, ASH 2021

Flair PFS by IGHV mutation status

IGHV unmutated excl. Subset 2 CLL (n=388)

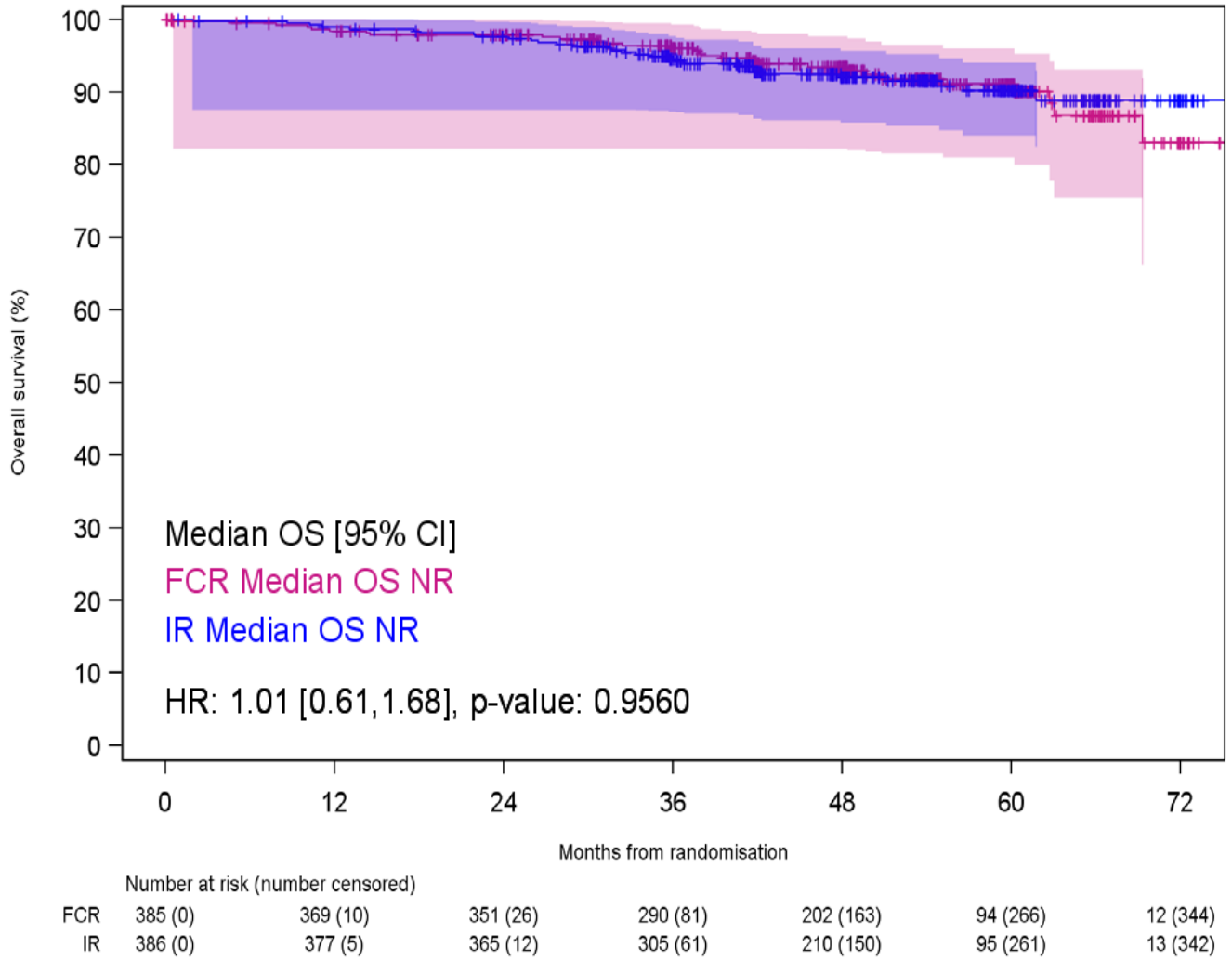


IGHV mutated CLL excl. Subset 2 (n=294)



Stereotype Subset 2: n=46 (FCR 20; IR 26) → HR for PD or death 0.32 (95% CI, 0.06-1.76), p=0.191

Flair Overall survival



Median FU 50.2 months

Data-lock: 24th May 2021

Hillmen *et al.,* Abstract 642, ASH 2021

Causes of death in Flair

Cause of death *	FCR (n=29)	IR (n=30)
CLL	4	3
Non-haematological malignancy	4	7
AML/MDS	3	0
ALL	1	0
Richters transformation	3	1
Infections (non-COVID)	6	4
COVID-19	3	3
Haemorrhage	1	2
Cardiac	2	9
Other	2	1
Total	**29**	**30**

Deaths in FCR arm were predominantly secondary haematological malignancies, Richter's transformation and infections.

Deaths in IR arm were predominantly CV-related and non-haematological malignancies.

*, Deaths at any time in follow-up

Relative risk of sudden unexplained death or cardiac death, accounting for pre-existing HTN/cardiac disorder at trial entry*, by Flair arm

*Defined as being on medication for HTN or CV conditions at study entry

	FCR				IR			
	Sudden unexplained death or cardiac death				Sudden unexplained death or cardiac death			
Hypertension or prior history of cardiac disorder (on treatment at trial entry)		No	Yes	Total		No	Yes	Total
	No	288	2	290	No	276	1	277
	Yes	88	0	88	Yes	100	7	107
	Total	376	2	378	Total	376	8	384
	Relative Risk IE* Fisher's Exact P IE*				Relative Risk 18.1, 95%CI (2.3-146) Fisher's Exact P <0.001			

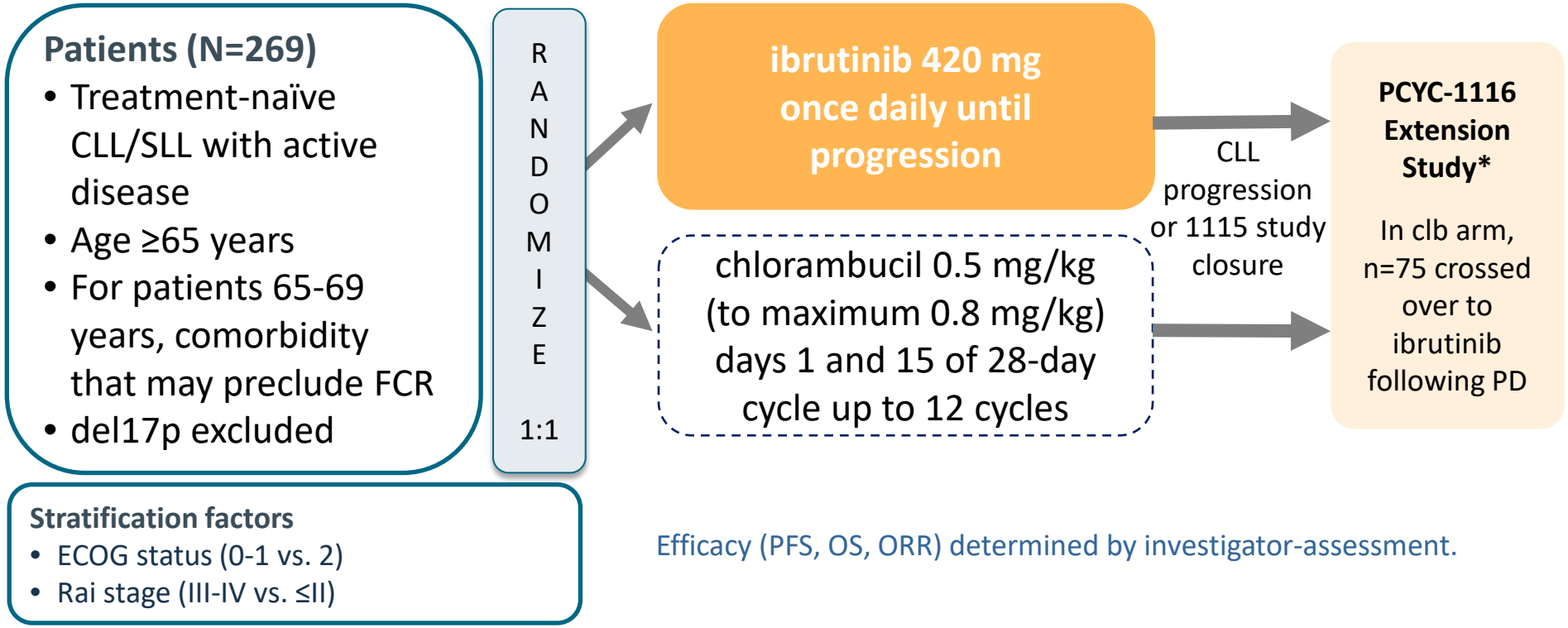
Meta-analysis

FLAIR is not an outlier for sudden unexplained or cardiac deaths in ibrutinib-containing arms and is consistent with other phase III CLL ibrutinib-containing trials including ALLIANCE, iLLUMINATE, RESONATE, GENUINE and HELIOS.

See poster abstract (#2636) for more details: *'Sudden or Cardiac Deaths on Ibrutinib-Based Therapy Were Associated with a Prior History of Hypertension or Cardiac Disease and the Use of ACE-Inhibitors at Study Entry: Analysis from the Phase III NCRI FLAIR Trial'',* Munir, T.

PATIENTS ≥65 YRS (FCR INELIGIBLE)

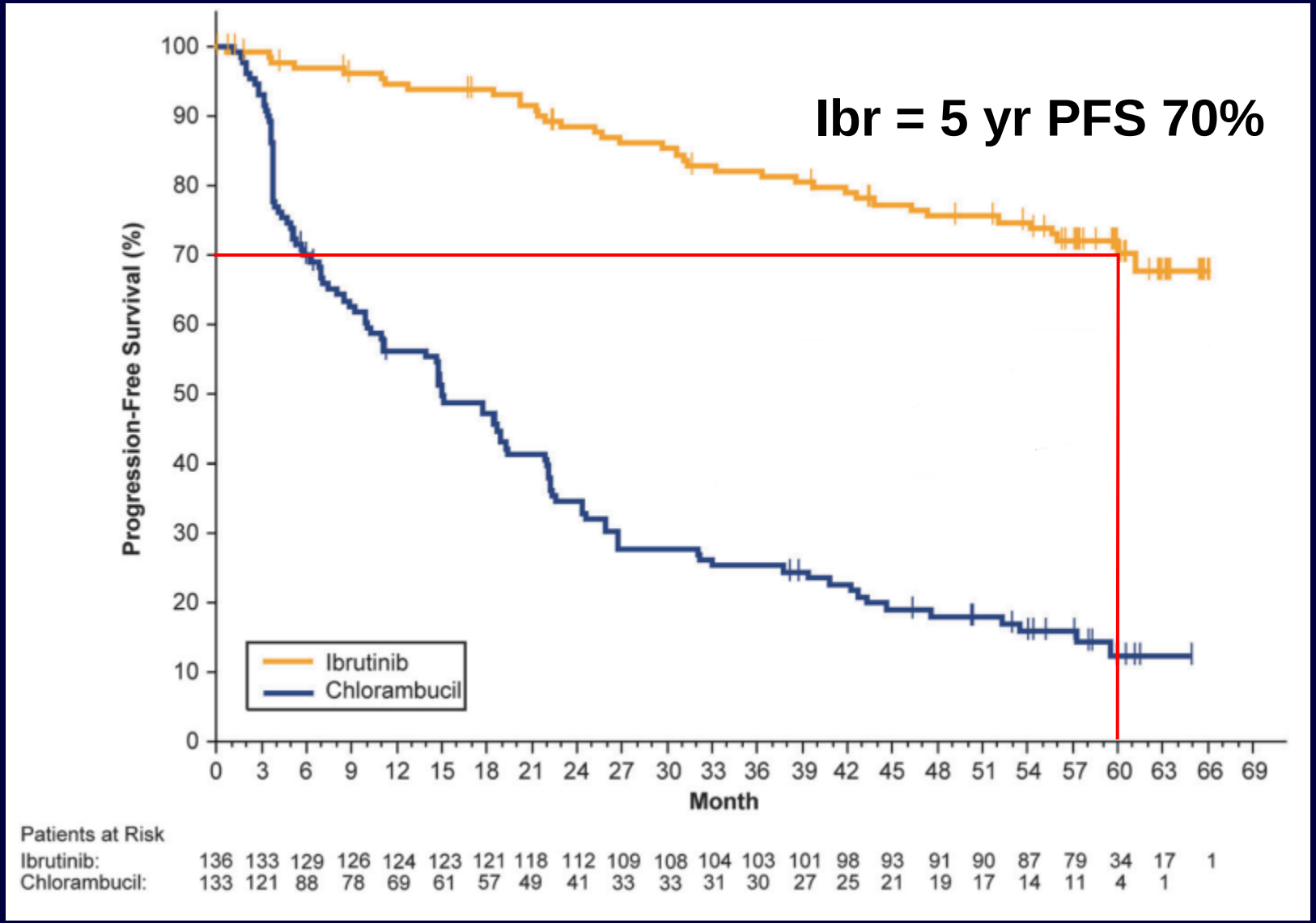
RESONATE-2 (PCYC-1115/1116) Study Design



*Patients could enroll in separate extension study PCYC-1116 after independent review committee-confirmed PD or at study PCYC-1115 closure for continuing treatment and follow-up.

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

RESONATE 2, 5-yr Follow-up

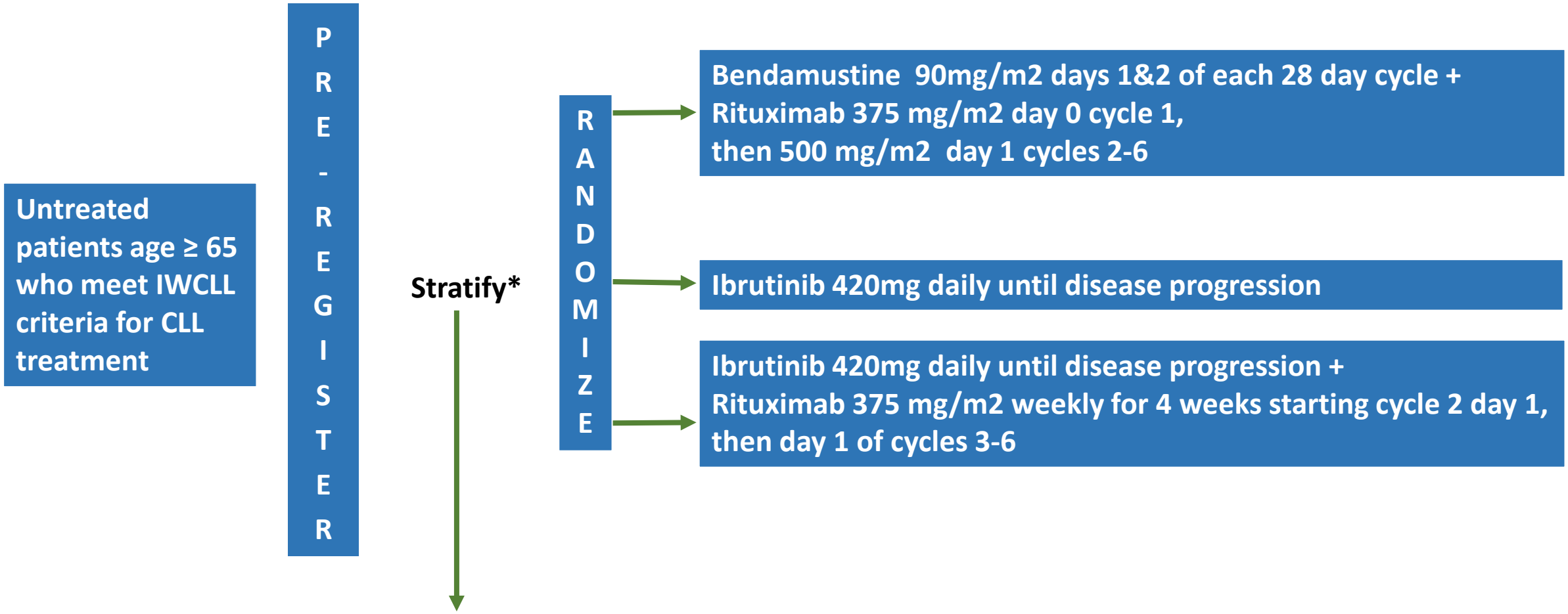


Burger et al. Leukemia. 2020 Mar;34(3):787-798.

Long term results of A041202 show continued advantage of ibrutinib-based regimens compared with bendamustine plus rituximab chemoimmunotherapy

Jennifer A. Woyach, Amy S. Ruppert, Nyla Heerema, Weiqiang Zhao, Allison M Booth, Wei Ding, Nancy L. Bartlett, Danielle M Brander, Paul M Barr, Kerry A Rogers, Sameer Parikh, Steven Coutre, Arti Hurria, Gerard Lozanski, Sreenivasa Nattam, Richard A. Larson, Harry Erba, Mark Litzow, Carolyn Owen, James Atkins, Jeremy Abramson, Rich Little, Scott E. Smith, Richard M. Stone, Sumithra Mandrekar, John C. Byrd

Schema

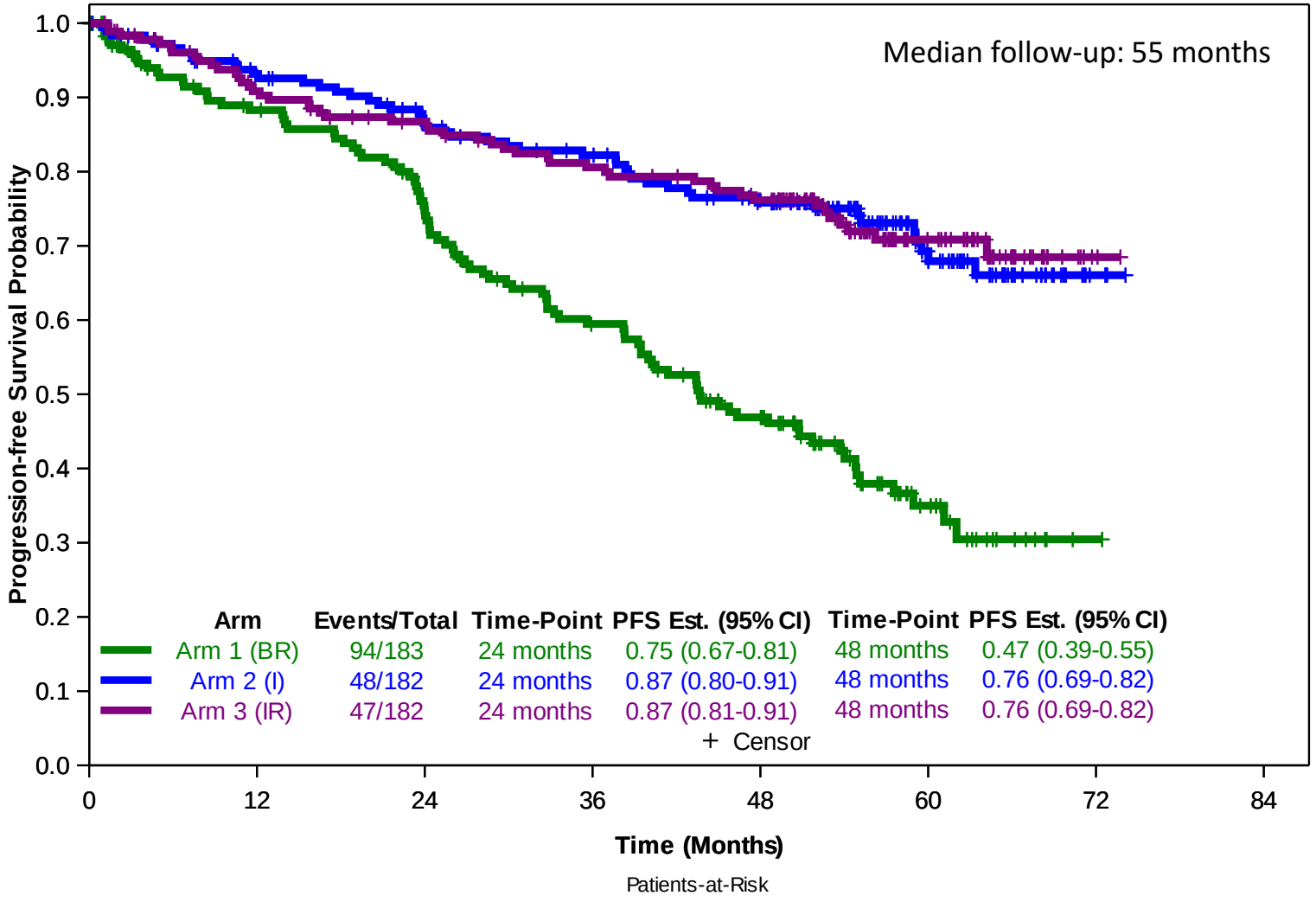


Stratification

- **High risk vs intermediate risk Rai Stage**
- **Presence vs absence of del(11q22.3) or del(17p13.1) on FISH performed locally**
- **< 20% vs ≥ 20% Zap-70 methylation of CpG 3 performed centrally**

ALLIANCE FOR CLINICAL TRIALS IN ONCOLOGY

Progression-free Survival



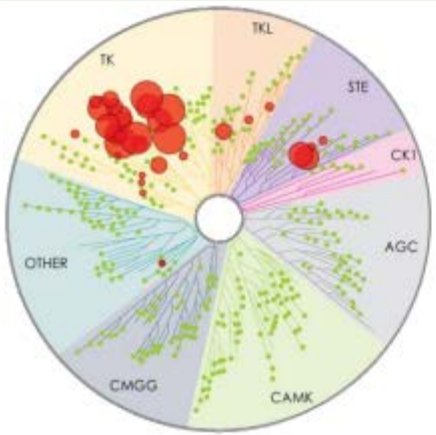
Pairwise Comparisons

I vs BR:
Hazard Ratio 0.36
95% CI: 0.26-0.52
P <0.0001

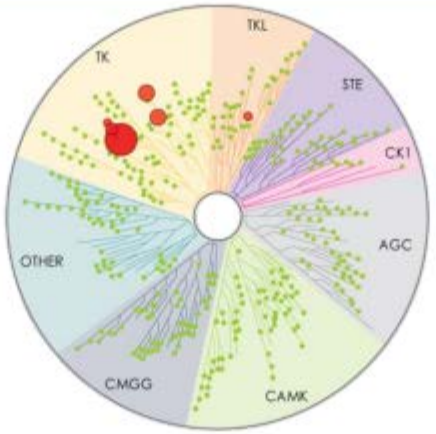
IR vs BR:
Hazard Ratio 0.36
95% CI: 0.25-0.51
P <0.0001

IR vs I:
Hazard Ratio 0.99
95% CI: 0.66-1.48
P = 0.96

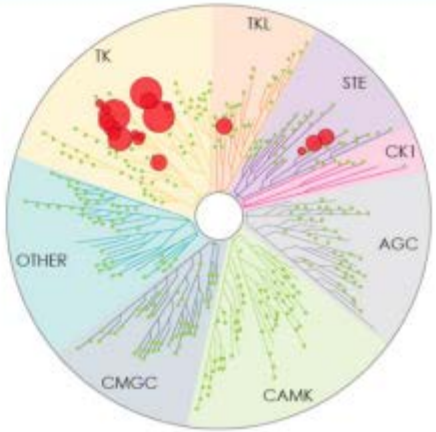
Ibrutinib



Acalabrutinib



Zanubrutinib

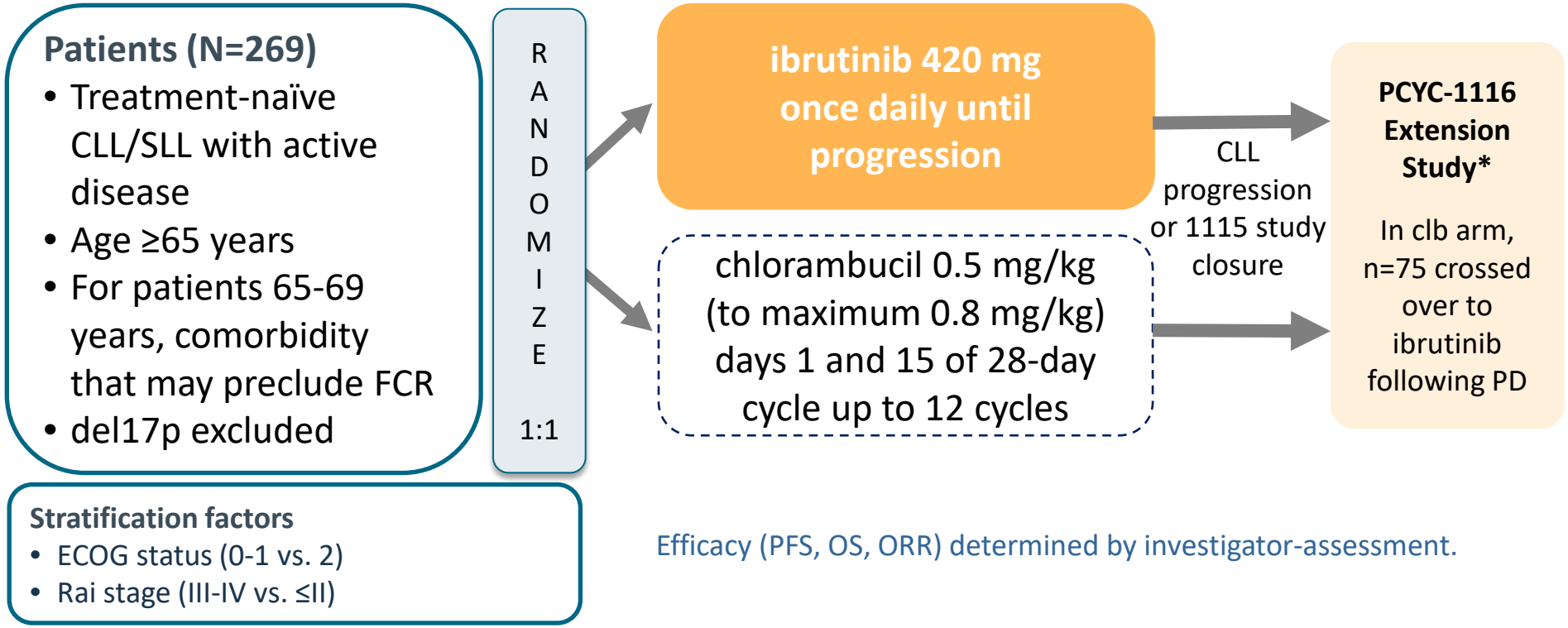


IC_{50}/EC_{50} (nM)

Kinase	Ibrutinib	Acalabrutinib	Zanubrutinib
BTK	1.5	5.1	0.5
TEC	10	126	44
ITK	4.9	> 1000	50
BMX	0.8	46	1.4
EGFR	5.3	> 1000	21
ERBB4	3.4	16	6.9
JAK3	32	> 1000	1377
BLK	0.1	> 1000	2.5

Slide adapted from Kaptein A et al. ASH 2018. Abs 1871.

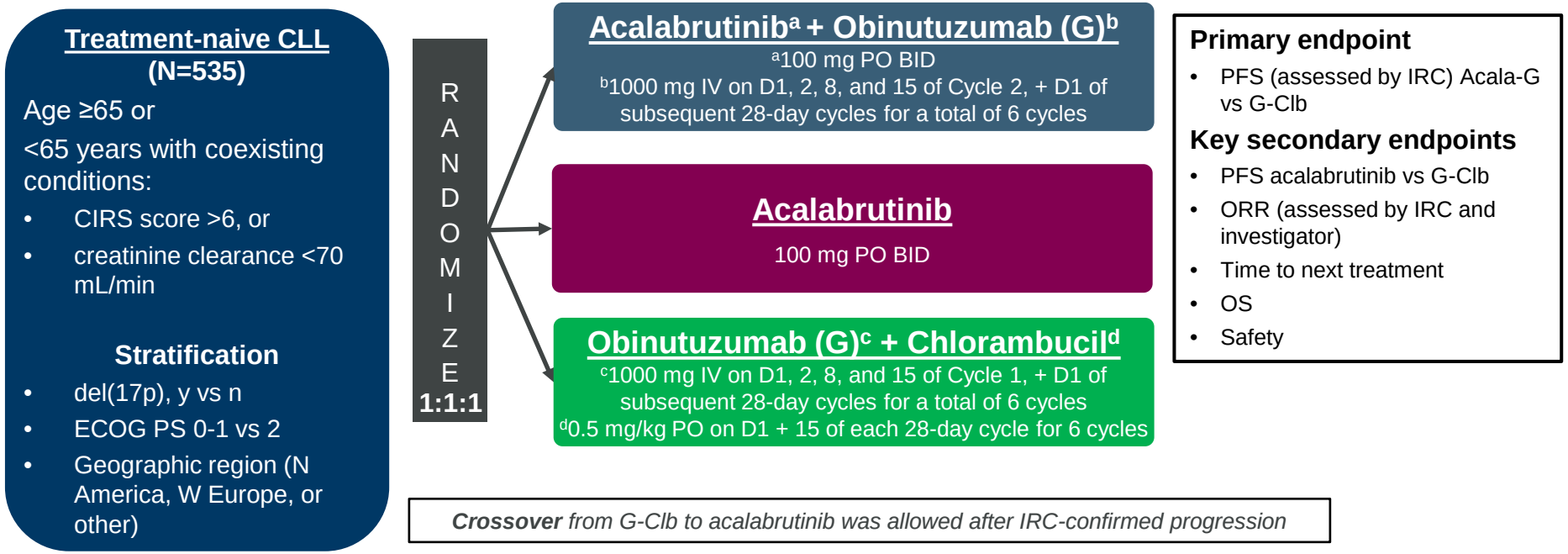
RESONATE-2 (PCYC-1115/1116) Study Design



*Patients could enroll in separate extension study PCYC-1116 after independent review committee-confirmed PD or at study PCYC-1115 closure for continuing treatment and follow-up.

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

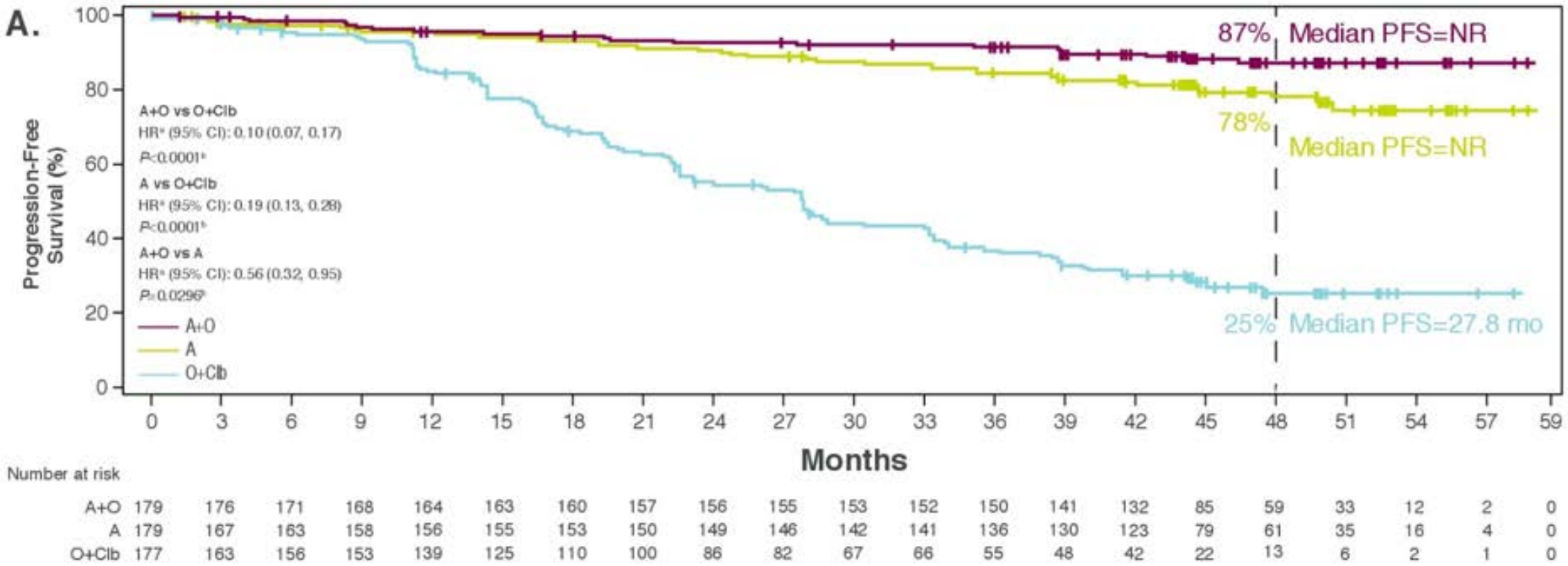
ELEVATE TN Study Design (ACE-CL-007)



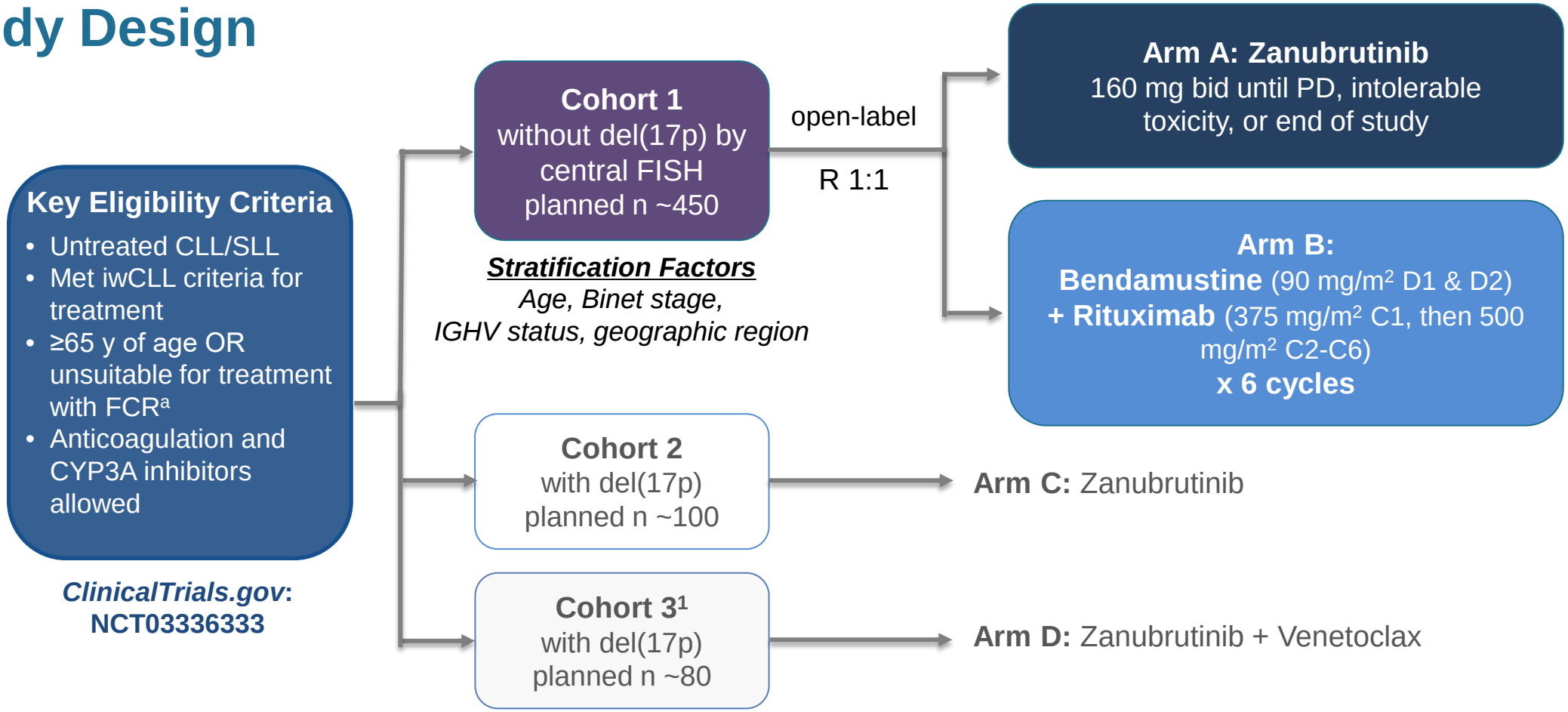
- Interim analysis was planned based on events (after occurrence of ~111 IRC-assessed PFS events in the combination therapy arms) or after 24 months if the required number of events was not met by this time

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

ELEVATE-TN, Updated data ASCO 2021

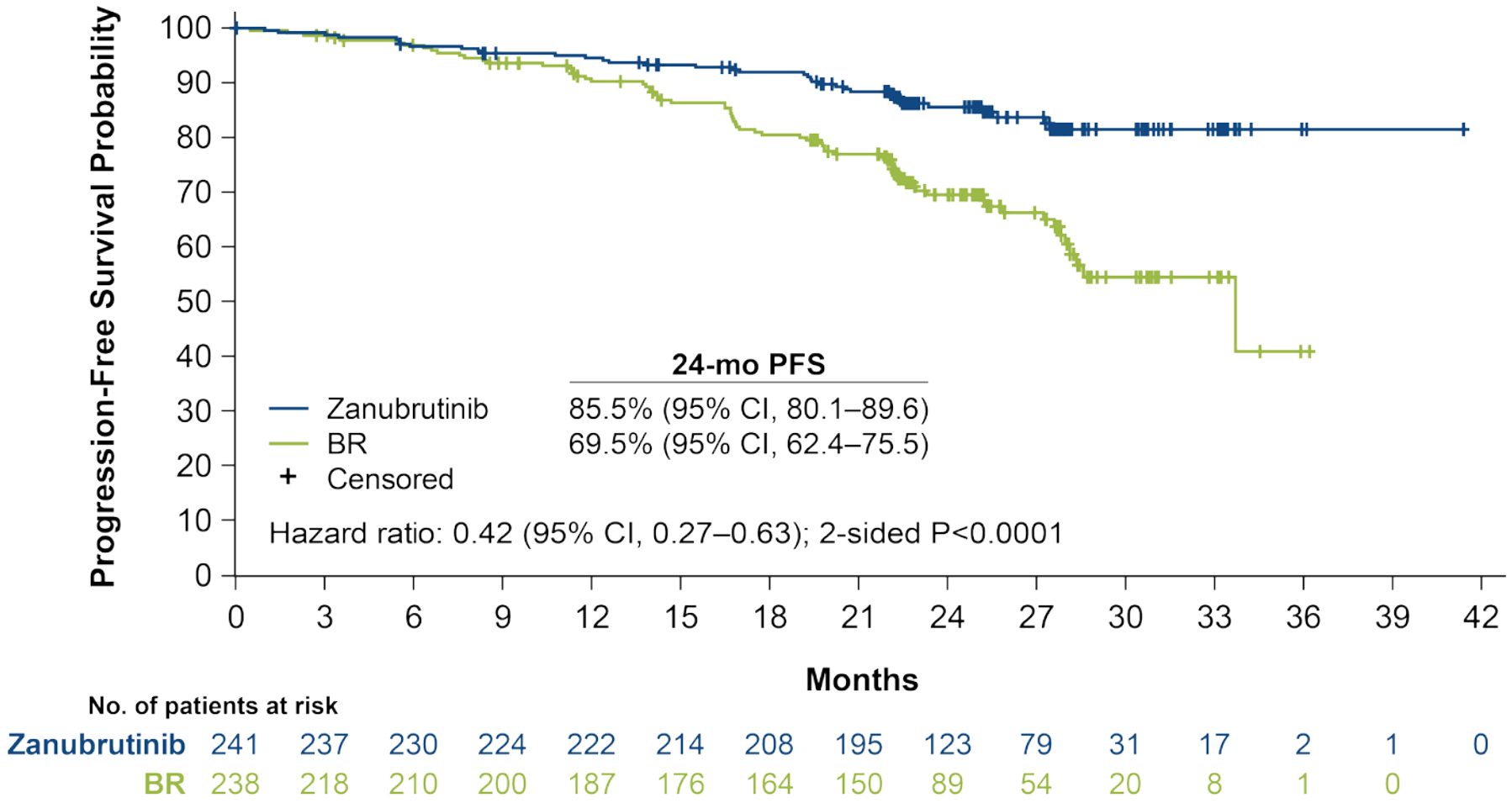


SEQUOIA (BGB-3111-304)
Study Design



[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.
C, cycle; CLL/SLL, chronic lymphocytic leukemia/small lymphocytic lymphoma; CYP3A, cytochrome P450, family 3, subfamily A; D, day; del(17p), chromosome 17p deletion; FCR, fludarabine, cyclophosphamide, and rituximab; FISH, fluorescence in-situ hybridization; IRC, independent review committee; IGHV, gene encoding the immunoglobulin heavy chain variable region; iwCLL, International Workshop on CLL; ORR, overall response rate; PD, progressive disease; R, randomized.
1. Tedeschi A, et al. ASH 2021. Abstract 67.

Progression-Free Survival Per IRC Assessment



BR, bendamustine + rituximab; IRC, independent review committee; PFS, progression-free survival.

BTKi lead to impressive PFS in Firstline setting

Indefinite Therapy

Low CR

U-MRD Rare

What else is exciting in firstline therapy for CLL?

Time Limited Therapies (1-2 yr)

High CR rate / High U-MRD

UNIKLINIK KÖLN
Department I of Internal Medicine
University Hospital of Cologne

DEUTSCHE STUDIENGRUPPE

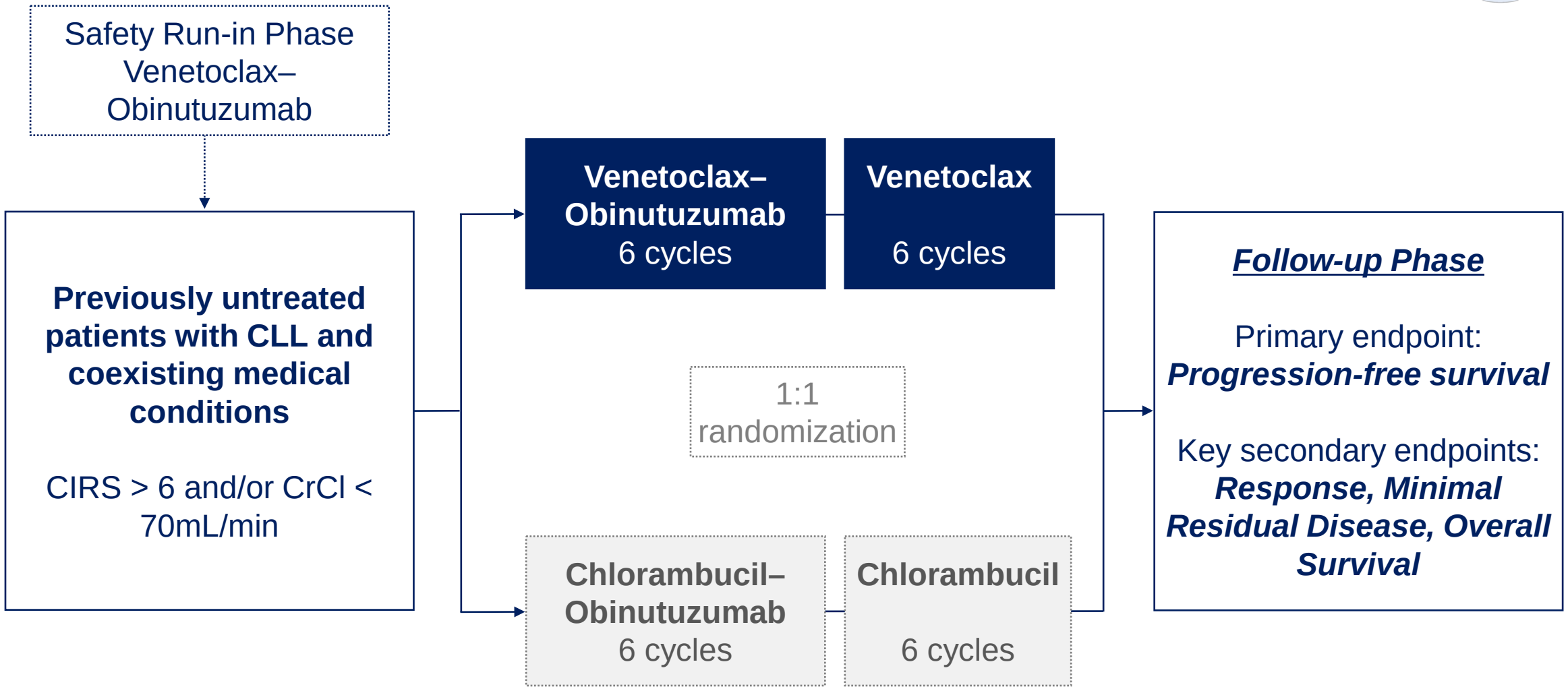
Abstract S146

VENETOCLAX-OBINUTUZUMAB FOR PREVIOUSLY UNTREATED CHRONIC LYMPHOCYTIC LEUKEMIA: 4-YEAR FOLLOW-UP ANALYSIS OF THE RANDOMIZED CLL14 STUDY

Othman Al-Sawaf, Can Zhang, Sandra Robrecht, Maneesh Tandon, Anesh Panchal, Anna-Maria Fink, Eugen Tausch, Matthias Ritgen, Karl-Anton Kreuzer, Su Young Kim, Clemens-Martin Wendtner, Barbara Eichhorst, Stephan Stilgenbauer, Yanwen Jiang, Michael Hallek, Kirsten Fischer

June 11th, 2021
Clinical trials with targeted therapies in CLL

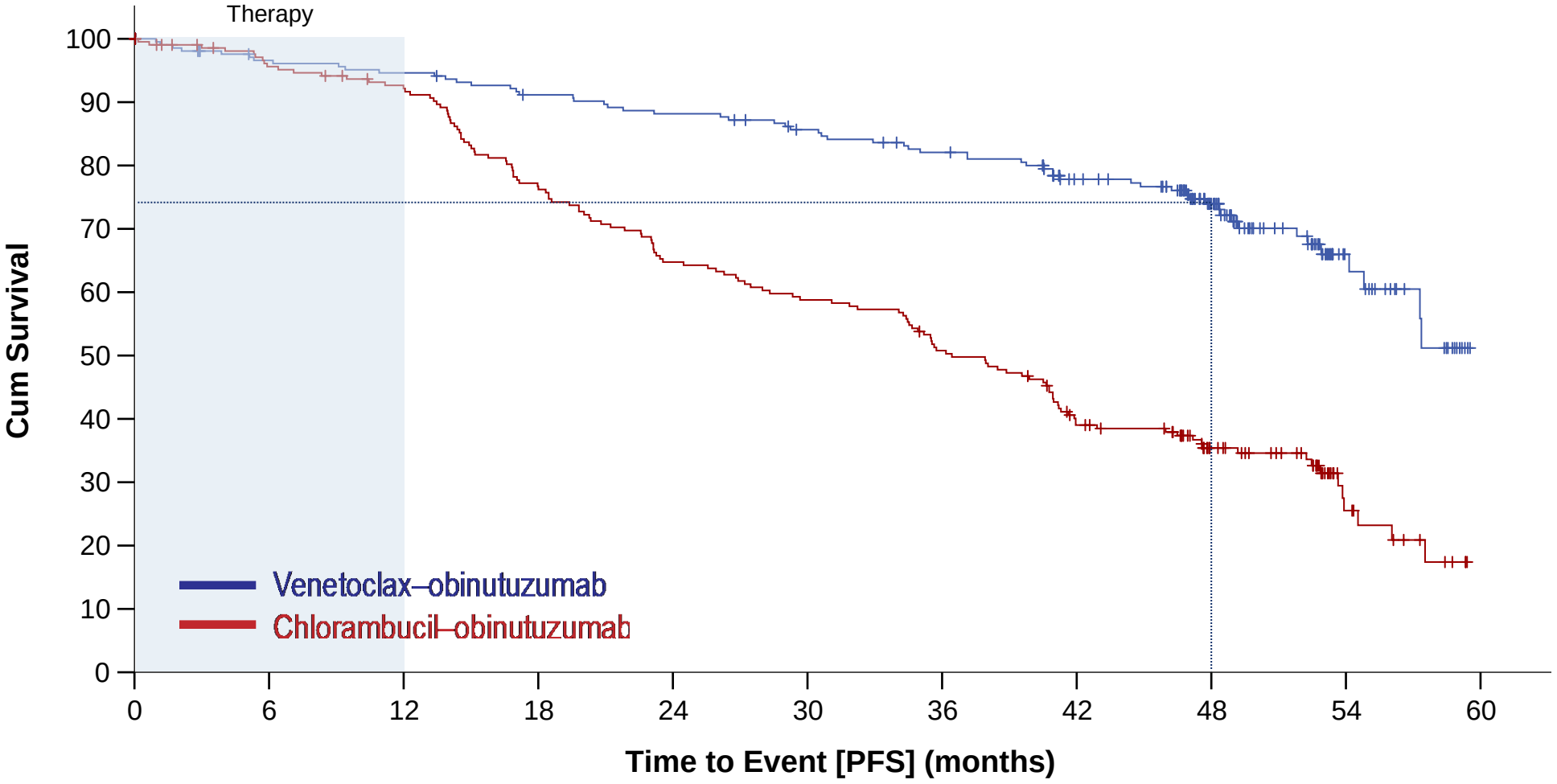
TRIAL DESIGN



Fischer et al., New Engl J Med 2019

CLL14: PROGRESSION-FREE SURVIVAL

Median observation time 52.4 months



Median PFS

Ven-Obi: not reached

Clb-Obi: 36.4 months

4-year PFS rate

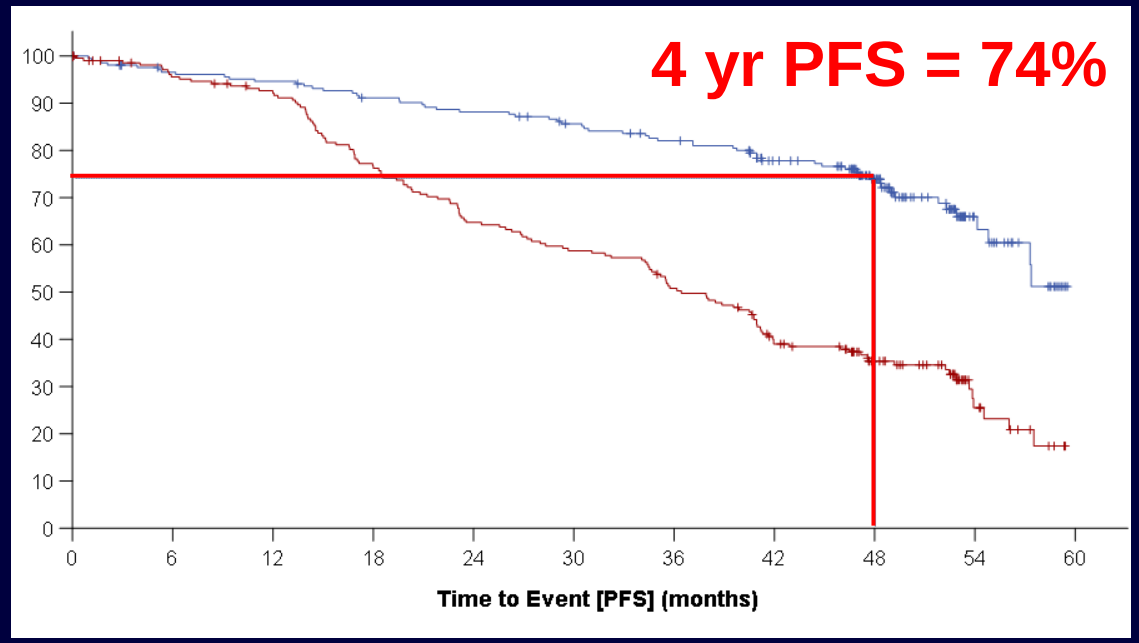
Ven-Obi: 74.0%

Clb-Obi: 35.4%

HR 0.33, 95% CI [0.25-0.45]

P<0.0001

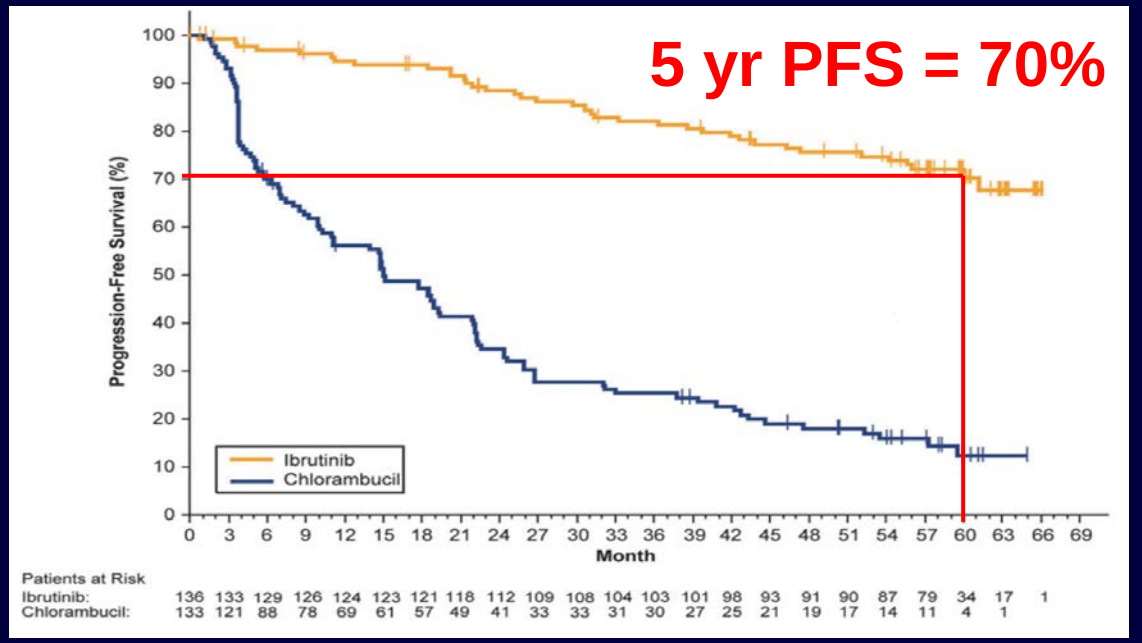
CLL14
VEN + Obin



Median age: 72
IGHV-UM: 61%
del(17p) / *TP53*-m: 12%
CIRS >6: 86%

Al-Sawaf, EHA 2021

RESONATE-2
Ibrutinib

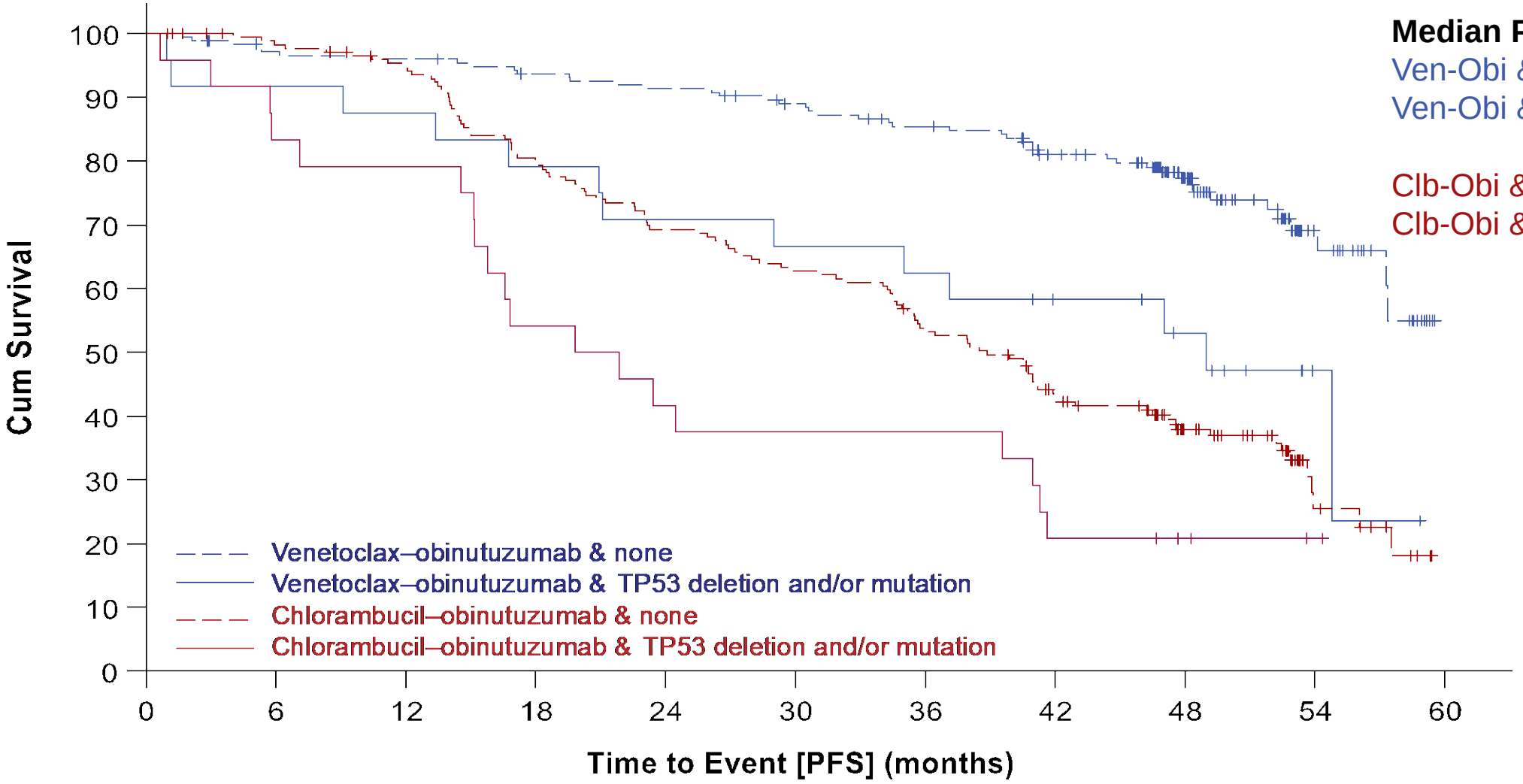


Median age: 73
IGHV-UM: 48%
del(17p) / *TP53*-m: 10%
CIRS >6: 31%

Burger, Leukemia 2020

PROGRESSION-FREE SURVIVAL – *TP53* status

Median observation time 52.4 months



Median PFS

Ven-Obi & no *TP53*del/mut: NR

Ven-Obi & *TP53*del/mut: 49.0 m

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

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

Approved Treatments in Firstline CLL
Pros and Cons

Ibrutinib	Acalabrutinib	Venetoclax + Obinutuzumab
• **Pro** – Longest follow-up – 5 yr PFS = 70% (RESONATE-2) – Once daily oral drug • **Con** – Indefinite duration – Low CR / U-MRD – Atrial fibrillation, bleeding	• **Pro** – Reduced off-target effects • **Con** – Shorter follow-up – Indefinite duration – Low CR / U-MRD – Atrial fibrillation, bleeding	• **Pro** – Time-limited – High CR / U-MRD • **Con** – Shorter follow-up – TLS logistics – IV administration of obinutuzumab – Neutropenia – Lack of durable remission in del(17p) / *TP53*-m

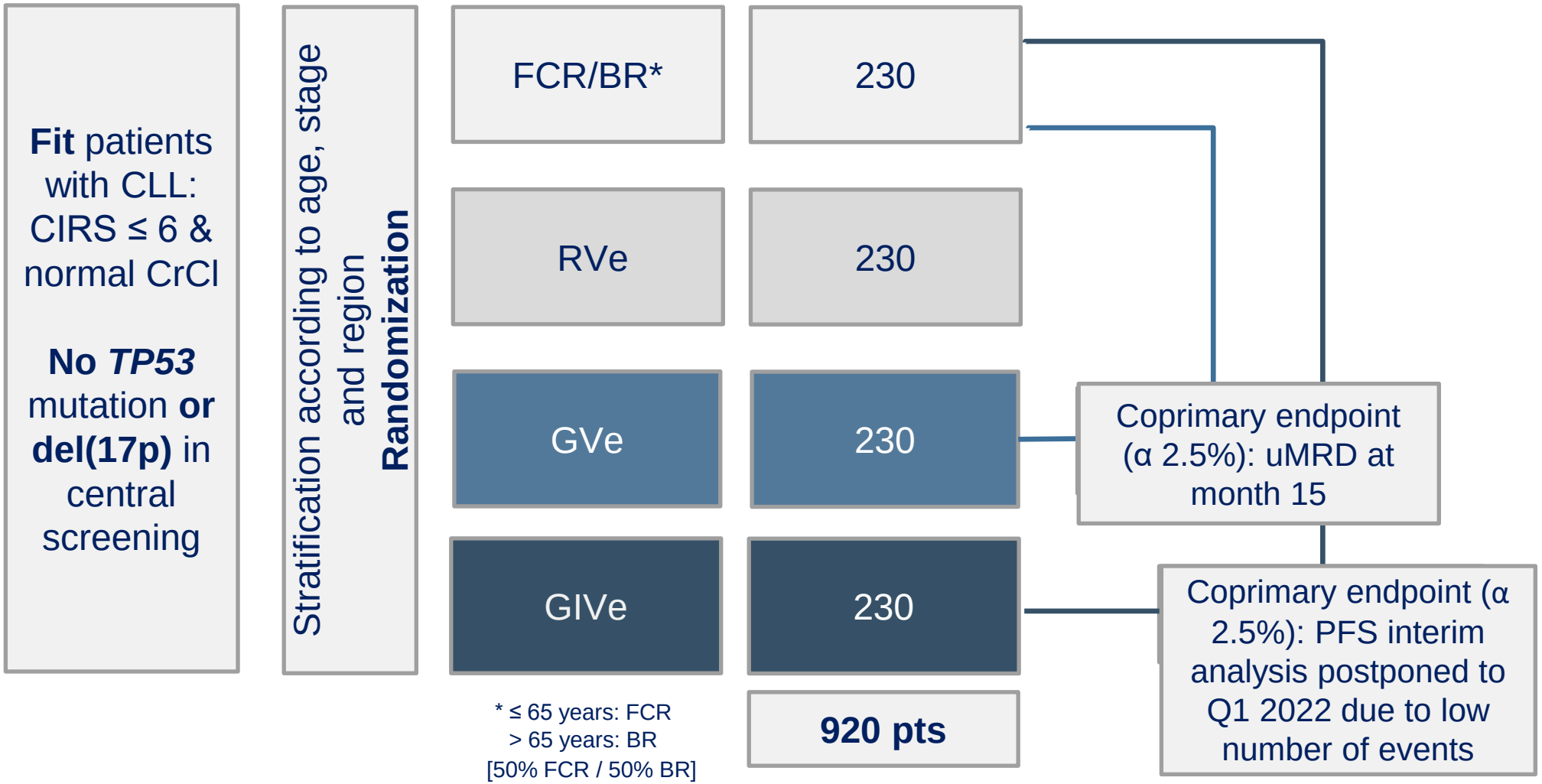
Cherng HJ, Jain N. Hematol Oncol Clin North Am. 2021;35(4):725-738.

A RANDOMIZED PHASE III STUDY OF VENETOCLAX-BASED TIME-LIMITED COMBINATION TREATMENTS (RVE, GVE, GIVE) VS STANDARD CHEMOIMMUNOTHERAPY (CIT: FCR/BR) IN FRONTLINE CHRONIC LYMPHOCYTIC LEUKEMIA OF FIT PATIENTS: FIRST CO-PRIMARY ENDPOINT ANALYSIS OF THE INTERNATIONAL INTERGROUP GAIA (CLL13) TRIAL

Barbara Eichhorst, Carsten U Niemann, Arnon P Kater, Moritz Fürstenau, Julia von Tresckow, Can Zhang, Sandra Robrecht, Michael Gregor, Gunnar Juliusson, Patrick Thornton, Philipp B. Staber, Tamar Tadmor, Vesa Lindström, Caspar da Cunha-Bang, Christoph Schneider, Christian Poulsen, Thomas Illmer, Björn Schöttker, Ann Janssens, Ilse Christiansen, Thomas Nösslinger, Michael Baumann, Marjolein van der Klift, Ulrich Jäger, Henrik Frederiksen, Maria BL Leys, Mels Hoogendoorn, Kourosh Lotfi, Holger Hebart, Tobias Gaska, Harry Koene, Florian Simon, Nisha De Silva, Anna Fink, Kirsten Fischer, Clemens Wendtner, Karl A Kreuzer, Matthias Ritgen, Monika Brüggemann, Eugen Tausch, Mark-David Levin, Marinus van Oers, Christian Geisler, Stephan Stilgenbauer, Michael Hallek

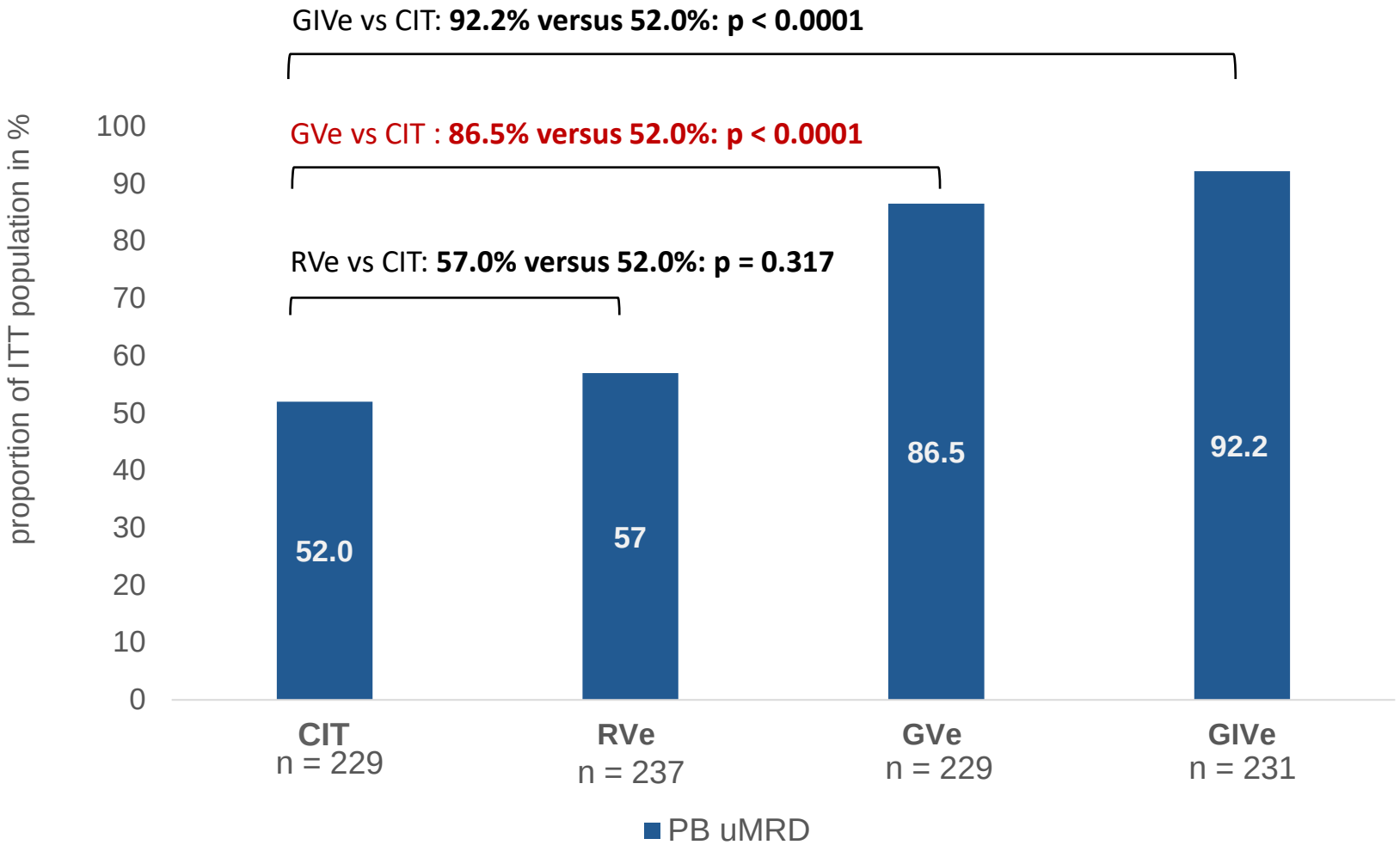
GAIA/CLL13 Study : Design

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



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

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



	uMRD%	97.5% CI
GIVe	92.2	87.3 – 95.7
GVe	86.5	80.6 – 91.1
RVe	57.0	49.5 – 64.2
SCIT	52.0	44.4 – 59.5

Monotherapy, Doublet, or Triplet?

Monotherapy

- BTKi

Doublet

- BCL2i + CD20 mAb
- BTKi + BCL2i

Triplet

- BTKi + BCL2i + CD20 mAb

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

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

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

Ibrutinib and Venetoclax Trial

- Investigator-initiated Phase II trial (NCT02756897)
- IBR for 3 cycles followed by combination with VEN
- Patients with treatment-naïve CLL/SLL with at least one of the following feature:
  - Del(17p) or mutated *TP53*
  - Del(11q)
  - Unmutated *IGHV*
  - Age ≥65 yrs

Treatment Schema

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

Duration of therapy: 24 cycles of combination treatment

- **Marrow U-MRD at 24 cycle: Both ibrutinib and venetoclax d/c**
- **Marrow MRD+ at 24 cycle: Both continue for another 1 year**

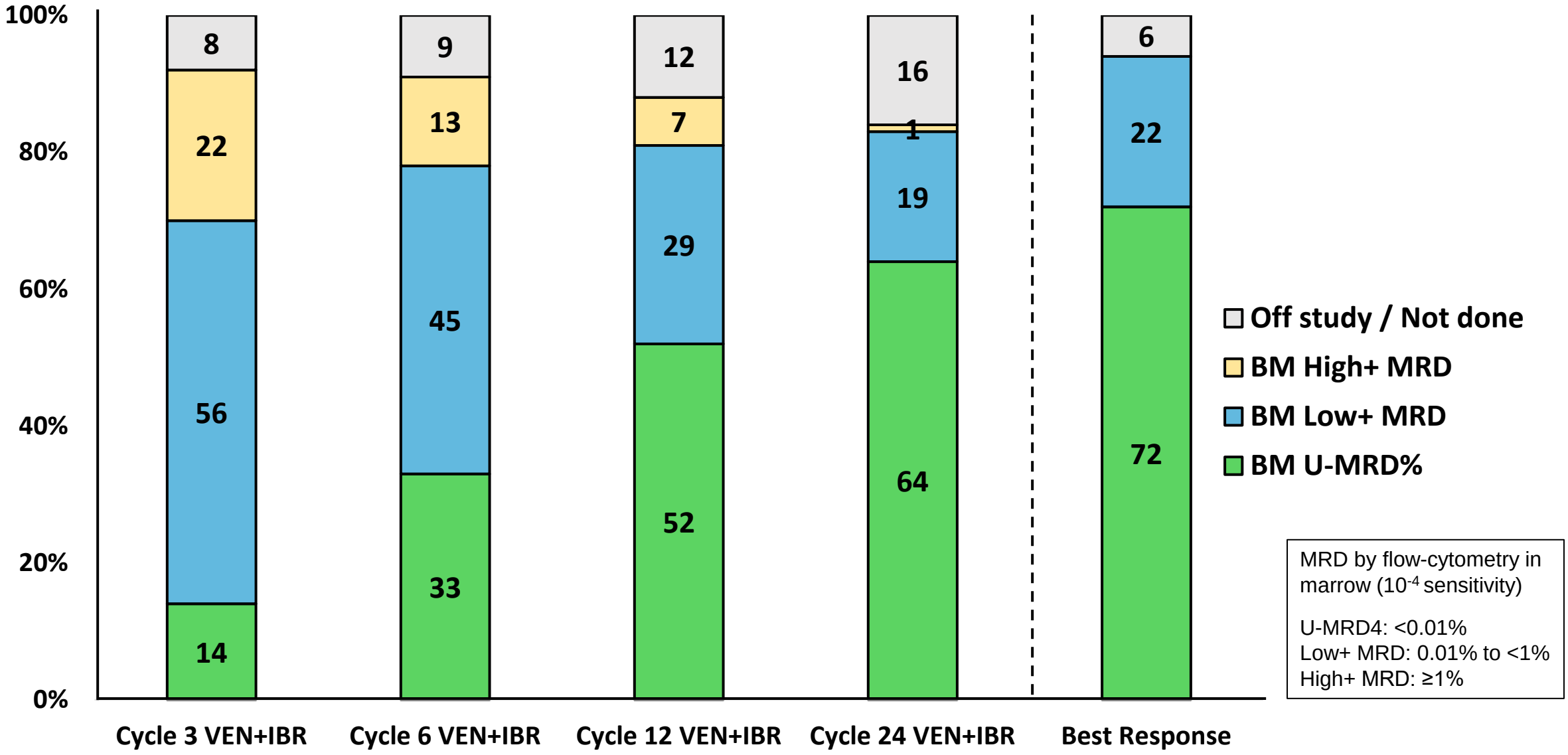
Jain N et al. N Engl J Med. 2019 May 30;380(22):2095-2103.
Jain N et al. JAMA Oncol. 2021 Aug 1;7(8):1213-1219.

Baseline Characteristics (N=120)

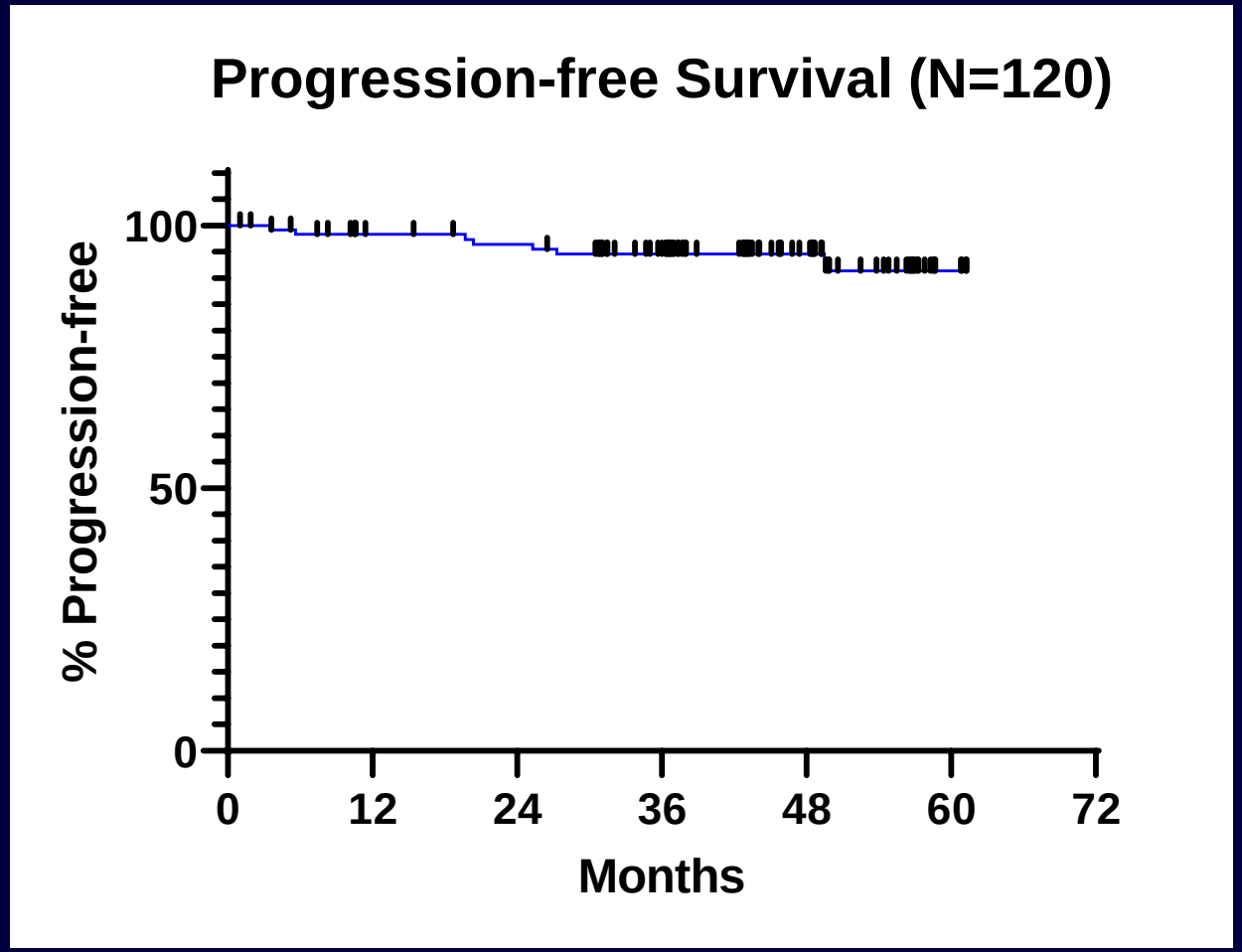
Between August 2016 and February 2019, a total of 120 pts were enrolled

		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	9 (8)
Del(17p) / *TP53*-m		27 (23)

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



PFS for all Patients (N=120)



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

Placeholder for Video

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

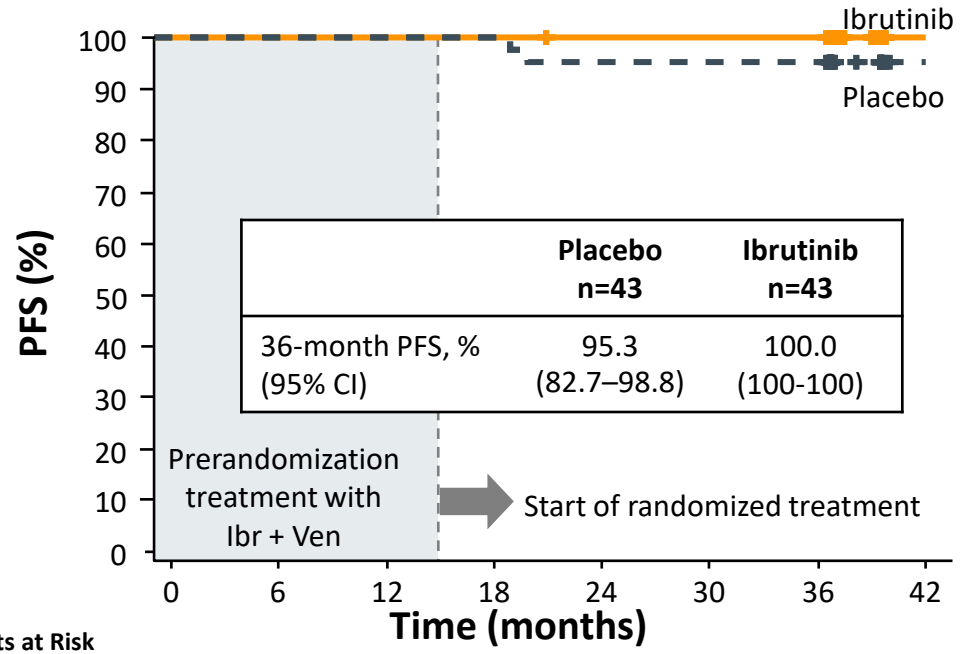
Paolo Ghia, MD, PhD[1]; John N. Allan, MD, PhD[2]; Tanya Siddiqi, MD[3]; Thomas J. Kipps, MD, PhD[4]; Bryone J. Kuss, MBBS, PhD, FRACP, FRCPA[5]; Stephen Opat, FRACP, FRCPA, MBBS[6]; Ian W. Flinn, MD, PhD[7]; Xavier C. Badoux, MBBS, FRACP, FRCPA[8]; Alessandra Tedeschi, MD[9]; Eva Gonzalez Barca, MD,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

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

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

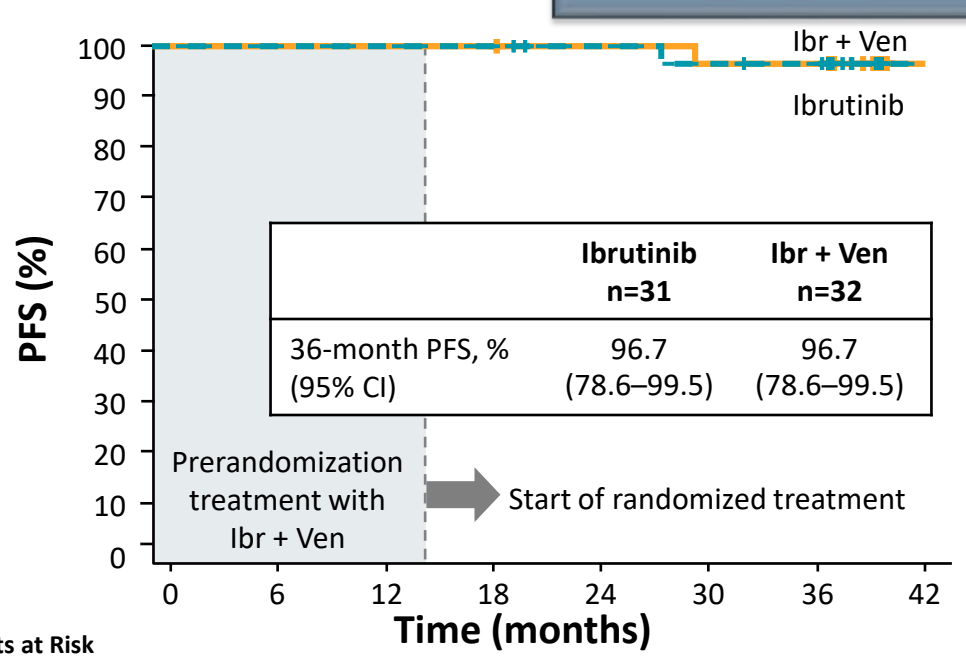
Placeholder for Video

Confirmed uMRD



Patients at Risk								
Ibr + Ven → Ibr	43	43	43	43	42	42	42	5
Ibr + Ven → Plb	43	43	43	43	41	41	41	4

uMRD Not Confirmed



Patients at Risk								
Ibr + Ven → Ibr + Ven	32	32	32	32	30	29	28	2
Ibr + Ven → Ibr	31	31	31	31	30	29	29	1

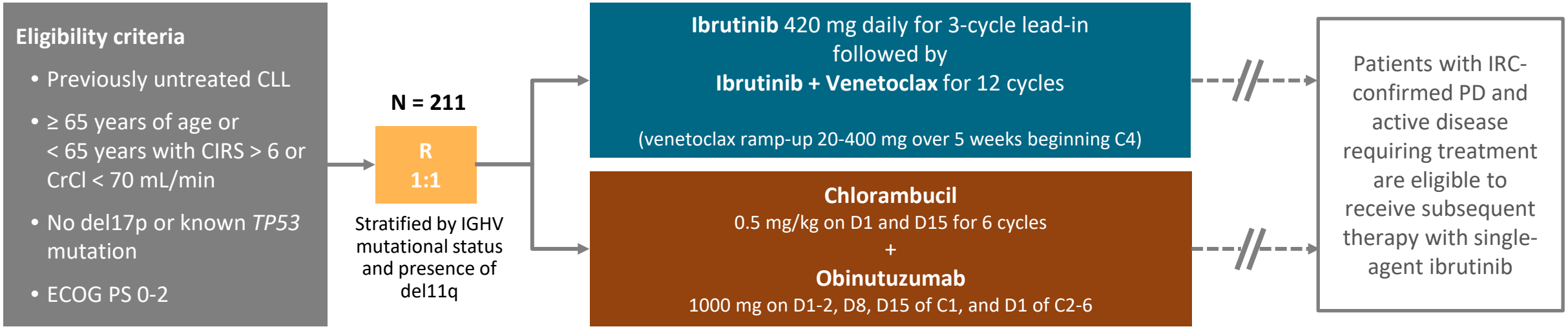
Median follow-up = 38 months

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

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

ASH 2021, CAPTIVATE-MRD; Ghia et al.

Phase 3 GLOW Study Design (NCT03462719)

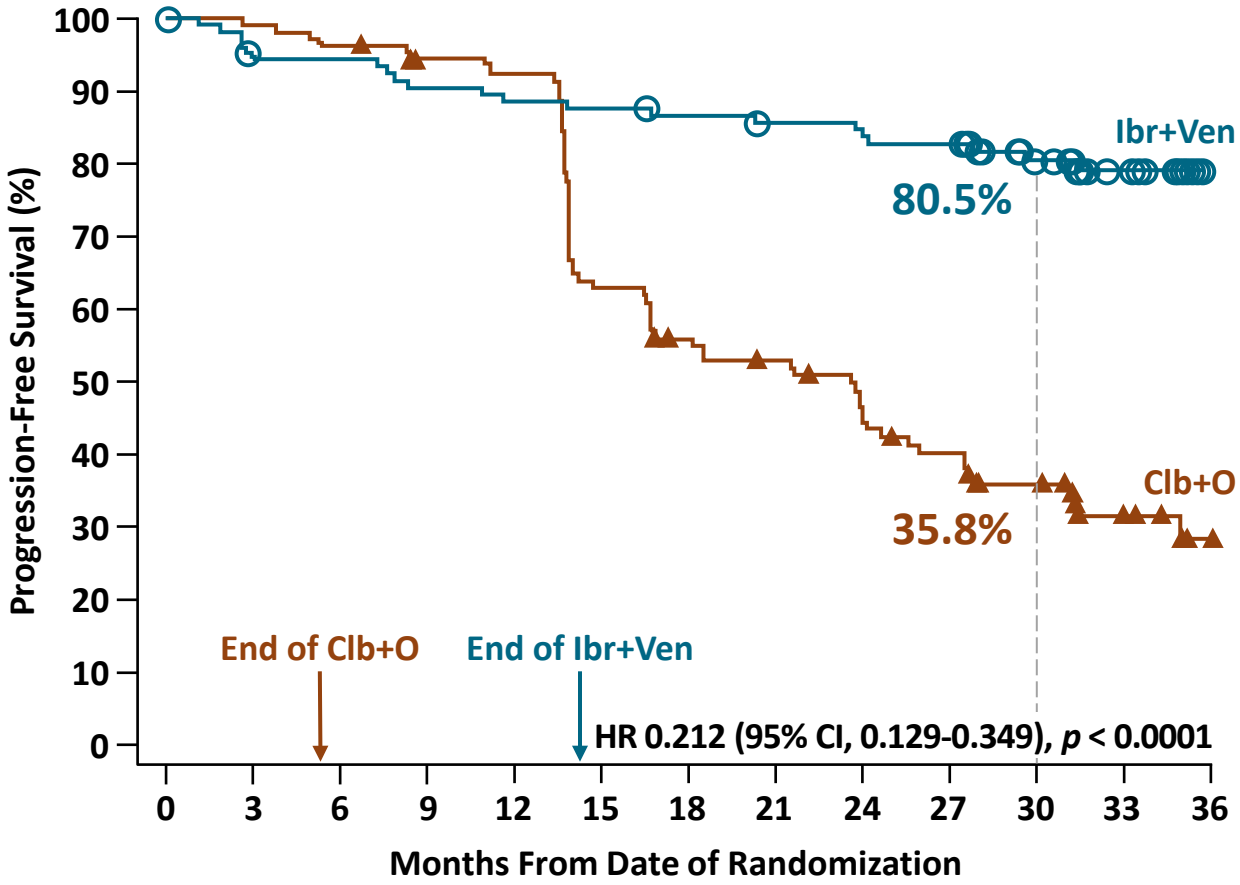


- **Study primary endpoint:** PFS as assessed by IRC
- **Current MRD analysis:**
  - MRD evaluated via NGS and reported with cutoffs of $<10^{-4}$ and $<10^{-5}$ (not all samples had sufficient cell yield to be analyzed at $< 10^{-6}$). NGS analysis not yet available beyond EOT+12 time point
  - PB/BM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

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

ASH 2021, Munir T, et al.

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



Patients at risk

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

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

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

Firstline Triplets
BTKi + VEN + Obin

- **Ibrutinib + Ven + G**
  - Rogers et al. J Clin Oncol. 2020;38(31):3626-3637
- **Ibrutinib + Ven + G in del(17p) / TP53m (CLL2-GIVE)**
  - Huber et al. Blood. 2022;139(9):1318-1329.
- **Acalabrutinib + Ven + G**
  - Davids et al. Lancet Oncol. 2021;22(10):1391-1402
- **Zanubrutinib + Ven + G**
  - Soumerai et al. Lancet Haematol. 2021;8(12):e879-e890

MRD Rates Across Selected Firstline Combination Trials in CLL

Regimen	Reference	N	U-MRD4 Rate	
			Peripheral Blood	Bone Marrow
VEN + G (CLL14)	Fischer, NEJM 2019	216	76% (C12)	57% (C12)
Ibrutinib + VEN (MDACC)	Jain, ASH 2021	120	-	52% (C12); 64% (C24), 72% (best)
Ibrutinib + VEN (CAPTIVATE)	Wierda, JCO 2021 (MRD cohort) Tam, Blood 2022 (FD Cohort)	164 159	70% (C12), 75% (best) 57% (C12), 77% (best)	68% (C12), 68% (best) 52% (C12), 60% (best)
Ibrutinib + VEN + G (OSU)	Rogers, JCO 2020	25	72% (C16)	60% (C16)
Ibrutinib + VEN + G (CLL2-GIVe) *TP53* aberrant only	Huber, Blood 2022	41	78% (C15)	66% (C15)
Acalabrutinib + VEN + G (DFCI)	Davids, Lancet Oncology 2021	37	86% (C16)	86% (C16)
Zanubrutinib + Ven + G (BOVen)	Soumerai, Lancet Hematology 2021	39	95% (best)	89% (best)

All data reported ITT

Firstline Phase III Trials in CLL

Trial	N	Randomization arms		
		Control	Investigational Arms	
ACE-CL-311 (AMPLIFY)	**780**	**FCR / BR**	**Acala + Ven**	**Acala + Ven + G**
EA9161	**720**	**Ibr + G**	**Ibr + G + Ven**	
A041702	**454**	**Ibr + G**	**Ibr + G + Ven**	
CLL17	**882**	**Ibr**	**Ven + G**	**Ven + Ibr**
MAJIC	**750**	**Ven + G**	**Acala + Ven**	
BRUIN CLL-313	**250**	**BR**	**LOXO-305**	

Some Unanswered Questions in Firstline Rx?

- **What's the ideal firstline treatment?**
  - 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

Main Highlights from ASH 2021 in Frontline CLL

- New likely frontline approvals in CLL
  - Zanubrutinib (SEQUOIA)
  - Ibrutinib + Venetoclax (CLL GLOW)
- VEN + G > VEN + R for MRD (CLL13)
- Del(17p) / *TP53* mutated CLL
  - BTKi monotherapy promising
  - BTKi + VEN – possibly better?
- Pirtobrutinib (LOXO-305): excellent safety and efficacy in R/R CLL
- Near Future (ASH 2022?): CAR-T

Frontline Trials at MDACC

Active

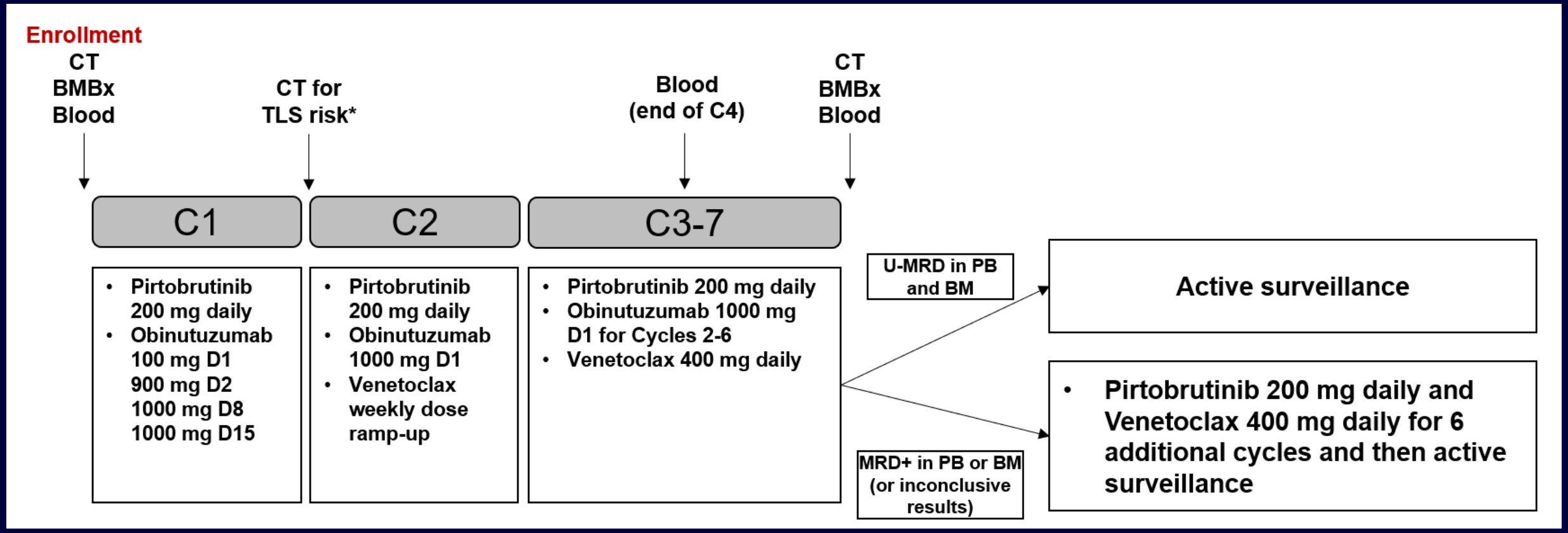
- **Acalabrutinib + Venetoclax +/- Obinutuzumab**
- **Venetoclax + Obinutuzumab + Atezolizumab (PD-L1 mAb)**
- **Acalabrutinib + Obinutuzumab**
- **Zanubrutinib + Rituximab**

Planned (June 2022)

- **Pirtobrutinib + Venetoclax + Obinutuzumab**

All are investigator-initiated trials

Pirtobrutinib + Venetoclax + Obinutuzumab Trial Schema



Thank you!

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