Front-Line Treatment of Chronic Lymphocytic Leukemia

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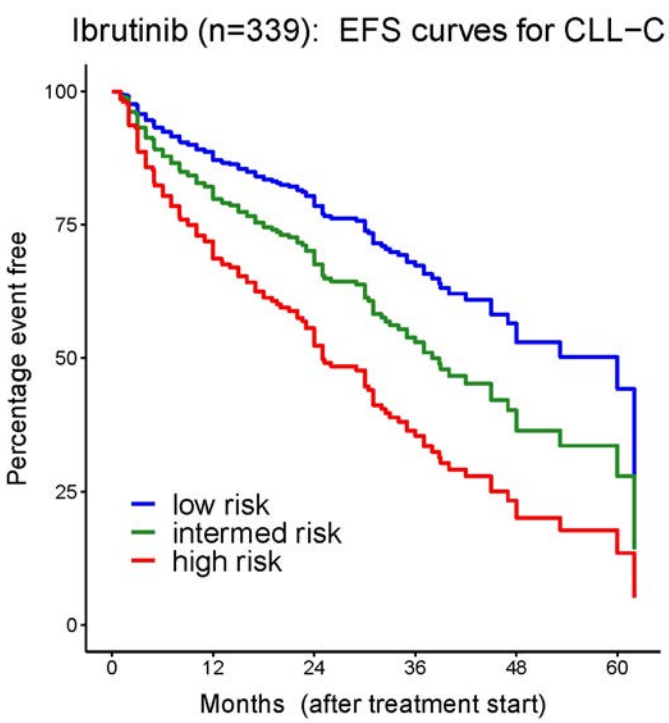
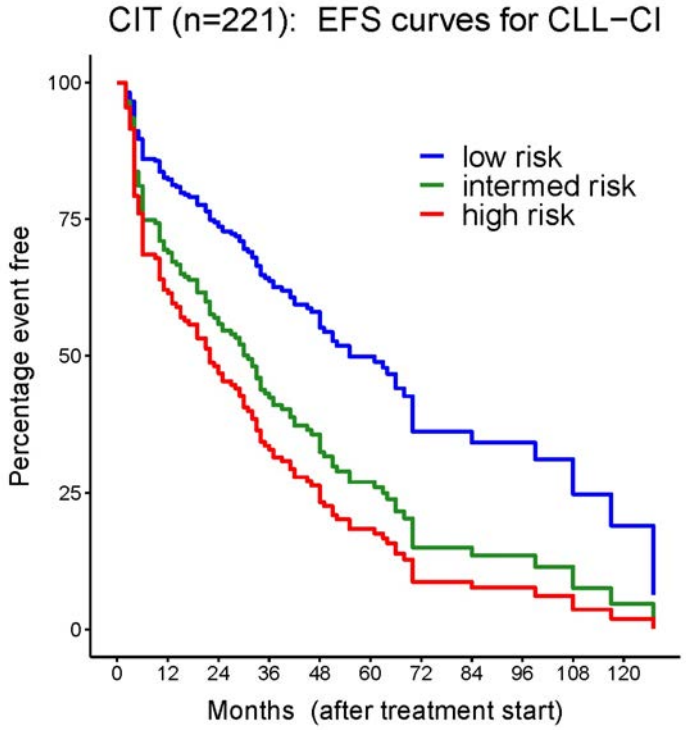
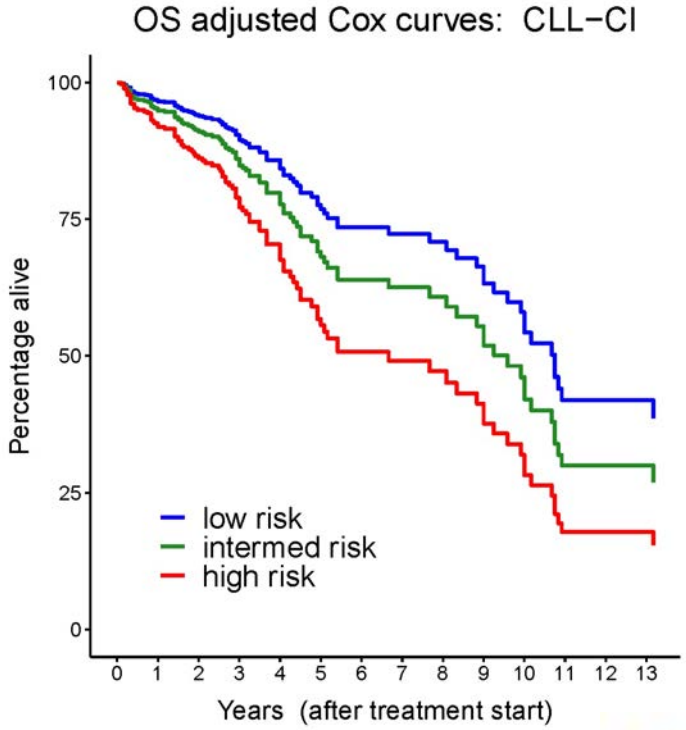
Factors to Consider when Selecting Treatment for CLL

- ***IGHV*** mutation status: <u>once</u>
- **del(17p)** by FISH and ***TP53*** mutation status: <u>frontline and before each line of therapy</u>
- Patient's age and comorbidities (cardiac, vascular)







Gordon et al, 2021

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Frontline Phase III Randomized Trials in CLL

BTKi	BCL2i	Novel-novel
RESONATE-2 (>65 or comorbidities) Ibrutinib *vs.* **Chlorambucil**	**CLL14** (CIRS >6; CrCl <70 mL/min) Venetoclax + O *vs.* **Chlorambucil + O**	**GLOW** (>65 or comorbidities) Ibrutinib + Venetoclax *vs.* **Chlorambucil + O**
iLLUMINATE (PCYC-1130) (>65 or comorbidities) Ibrutinib + O *vs.* **Chlorambucil + O**		**CLL13** (>65yo or ≤65yo with comorbidities) I+V+O *vs.* Ven+O *vs.* Ven+R *vs.* **FCR/BR**
ECOG E1912 [<70; non-del(17p)] Ibrutinib + R *vs.* **FCR**		
Alliance A041202 (>65) Ibrutinib *vs.* Ibrutinib + R *vs.* **BR**		
ELEVATE-TN (>65 or comorbidities) Acala *vs.* Acala + O *vs.* **Chlorambucil + O**		
SEQUOIA [≥65 OR comorbidities; non-del(17p)] Zanubrutinib *vs.* **BR**		
FLAIR [≤75; non-del(17p)] Ibrutinib + R *vs.* **FCR**		

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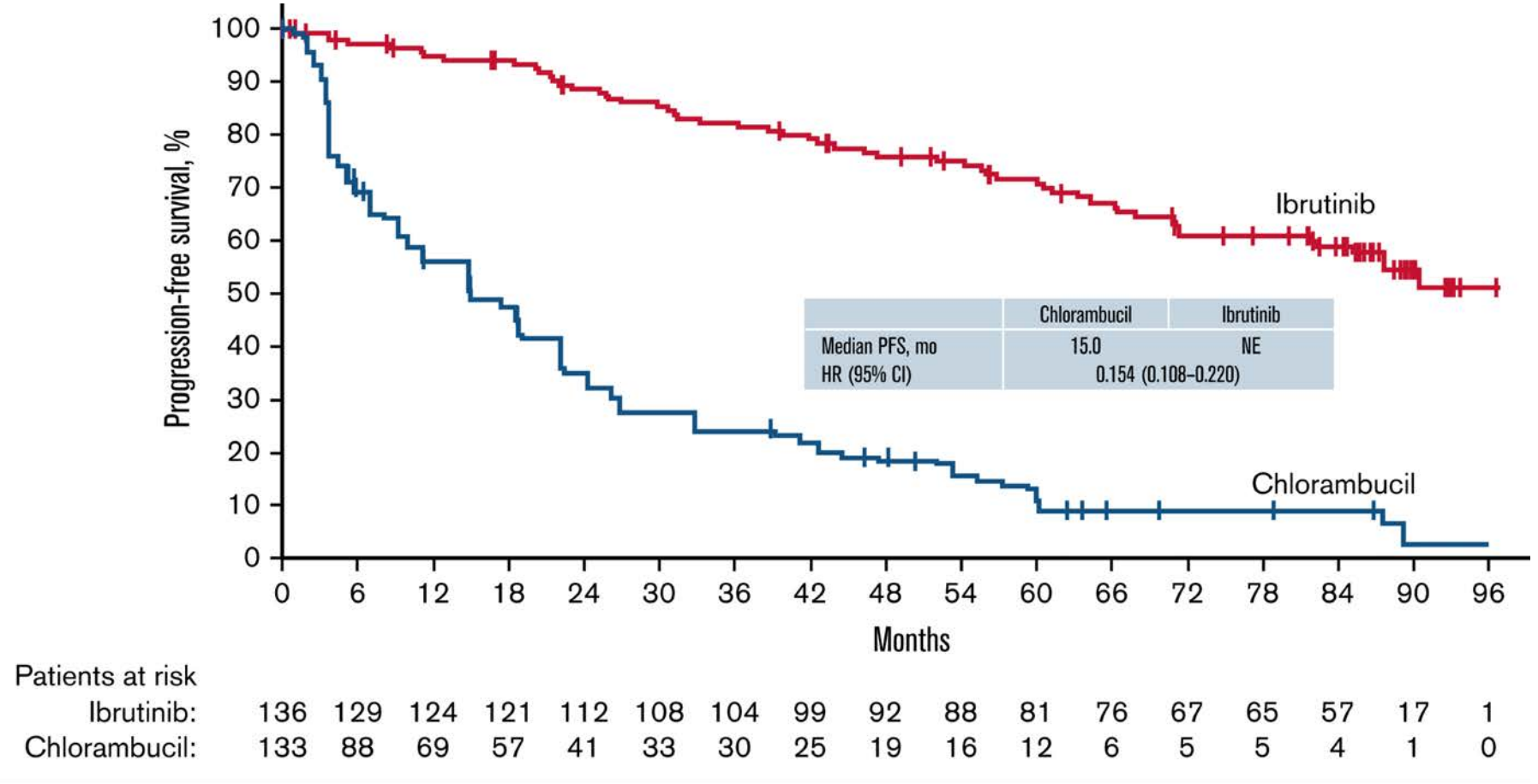
RESONATE-2: PFS after 8-year follow-up



Barr et al 2022

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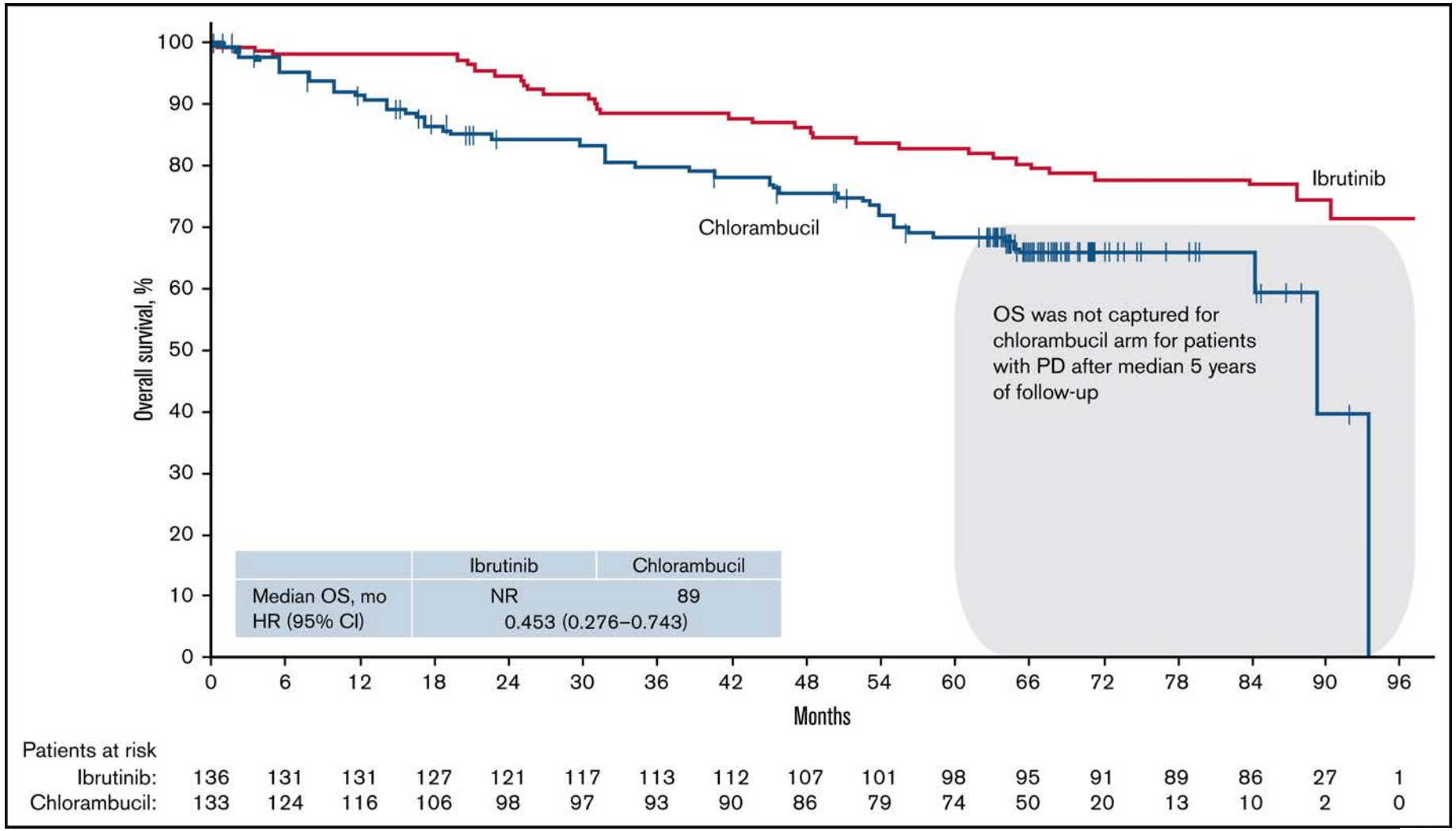
RESONATE-2: OS after 8-year follow-up



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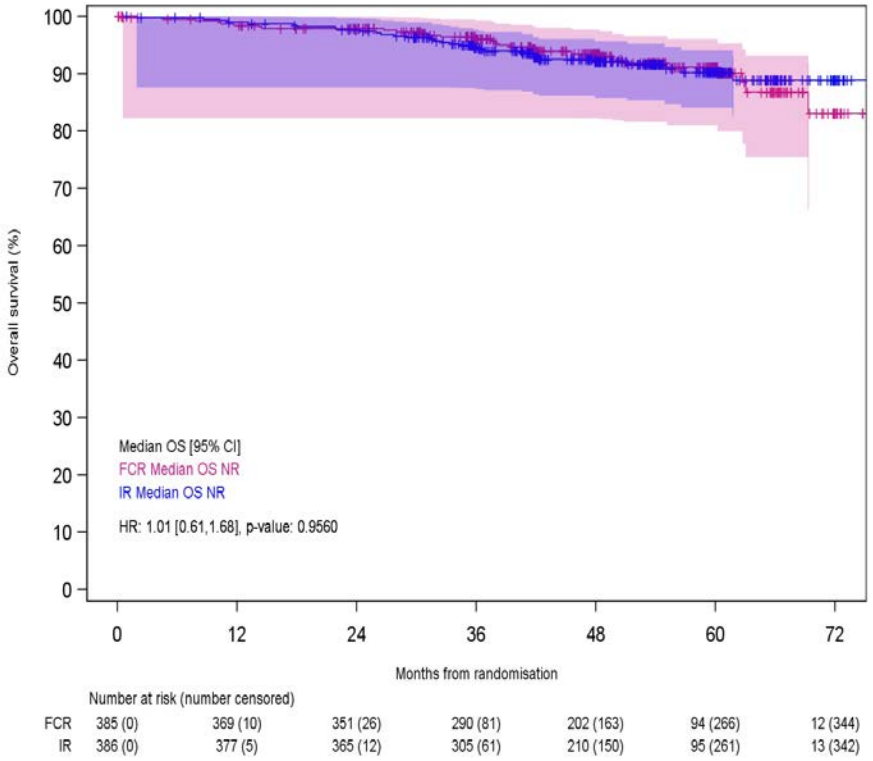
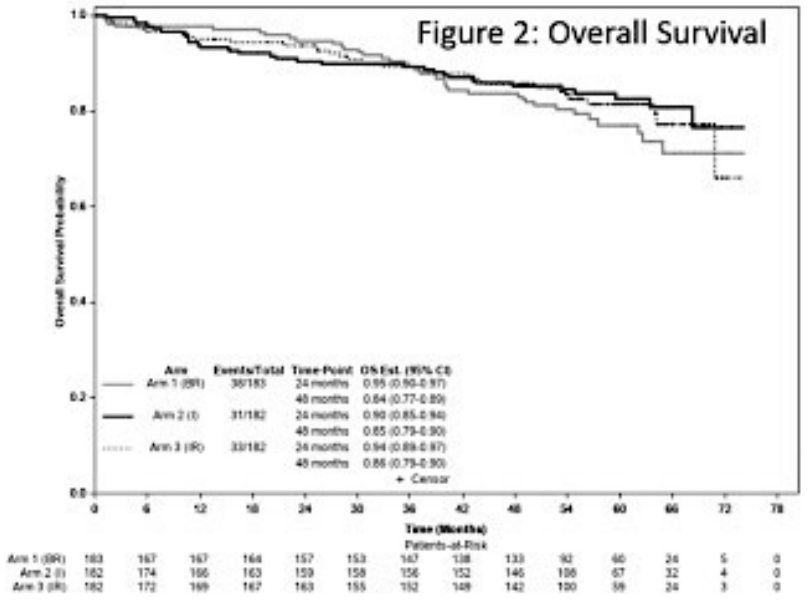
OS across frontline Phase III ibrutinib *vs* chemo studies

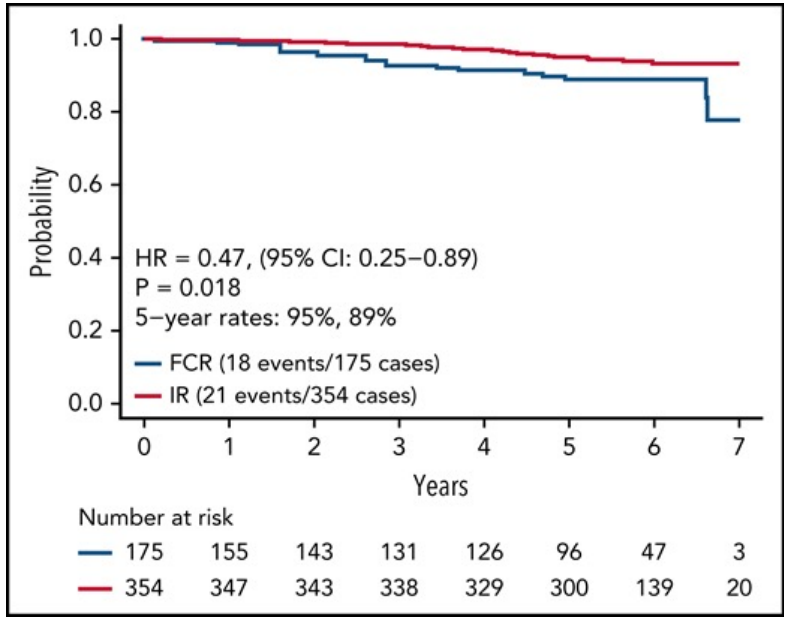
FLAIR (Hillmen, 2021)



Alliance (Woyach, 2021)



ECOG1912 (Shanafelt, 2022)



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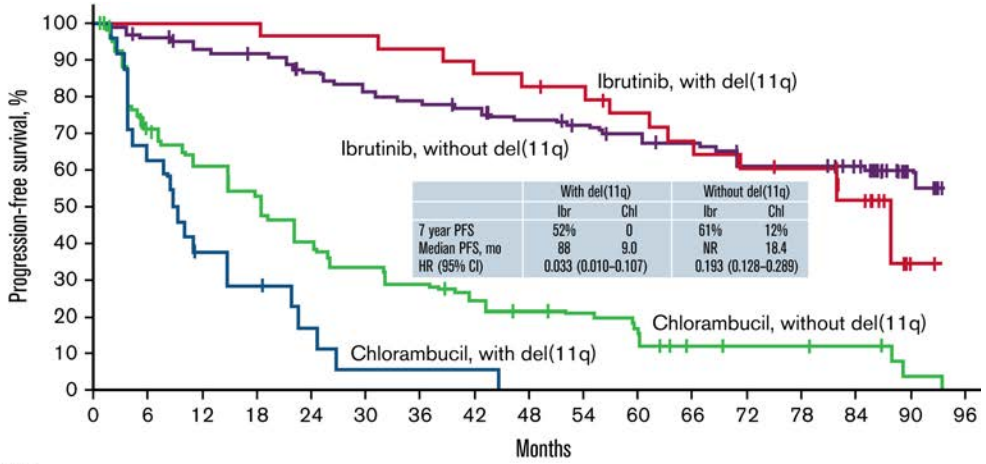
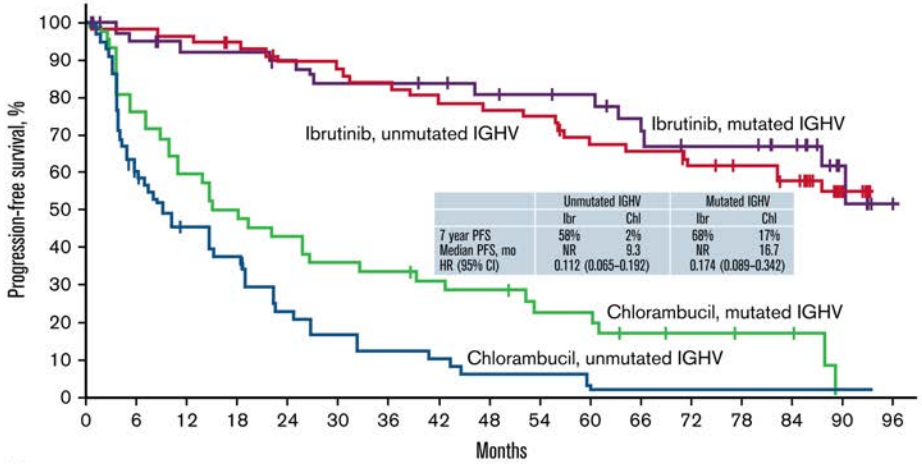
Ibrutinib Overcomes del(11q) and U-*IGHV* in RESONATE-2



Patients at risk																	
Ibrutinib, without del(11q):	101	94	89	87	80	76	73	70	64	61	57	55	48	47	43	13	0
Ibrutinib, with del(11q):	29	29	29	29	28	28	27	25	24	23	20	18	16	16	12	2	0
Chlorambucil, without del(11q):	96	64	54	45	35	29	25	21	17	15	12	6	5	5	4	1	0
Chlorambucil, with del(11q):	25	15	8	6	3	1	1	1	0								



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 et al 2022

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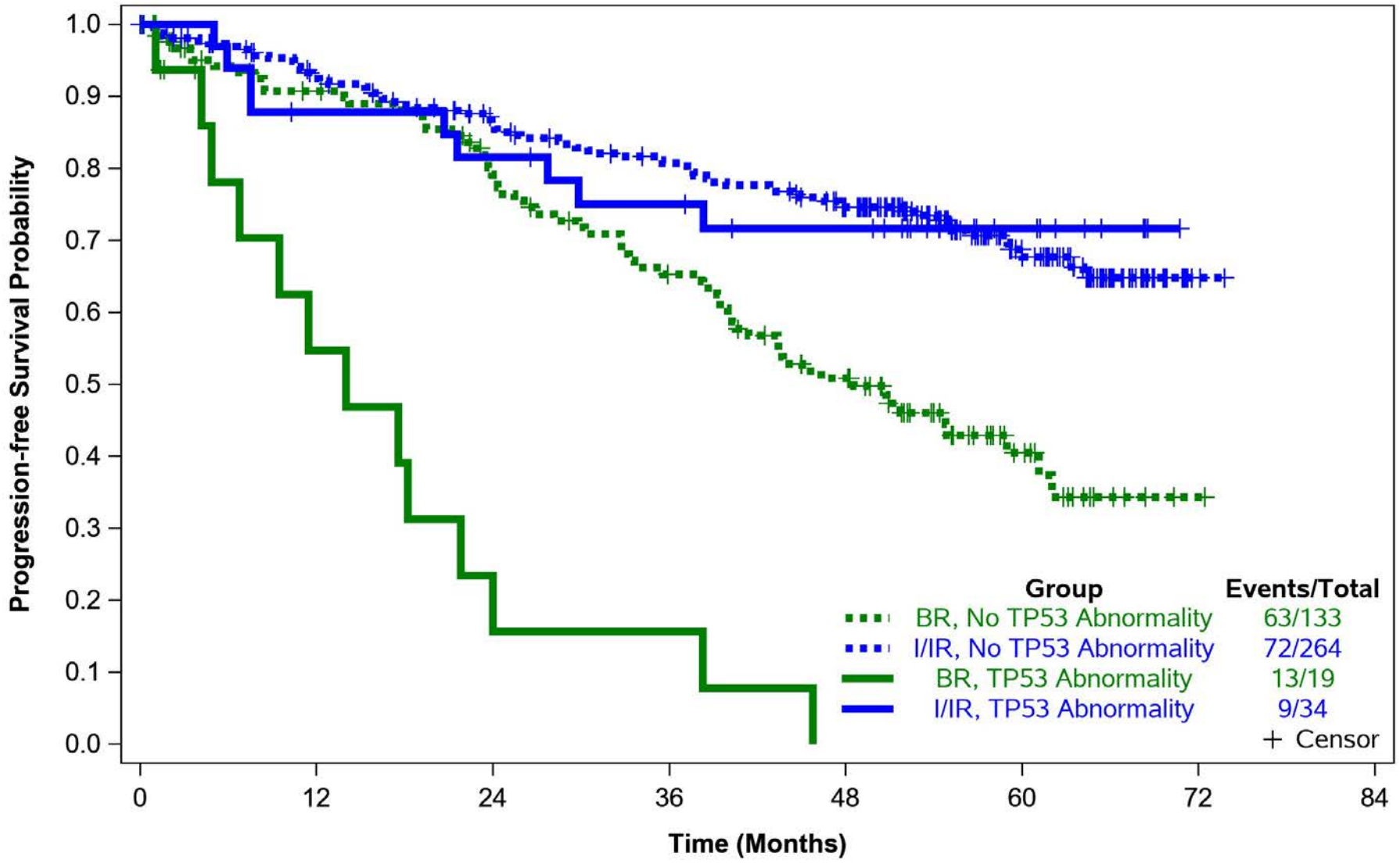
Ibrutinib and TP53 abnormalities: Alliance study



Treatment Effect
I/IR vs BR

No TP53 Abn
Hazard Ratio 0.39
95% CI: 0.27-0.55

TP53 Abn
Hazard Ratio 0.07
95% CI: 0.03-0.18

Interaction P = 0.0006

Woyach, et al. 2021

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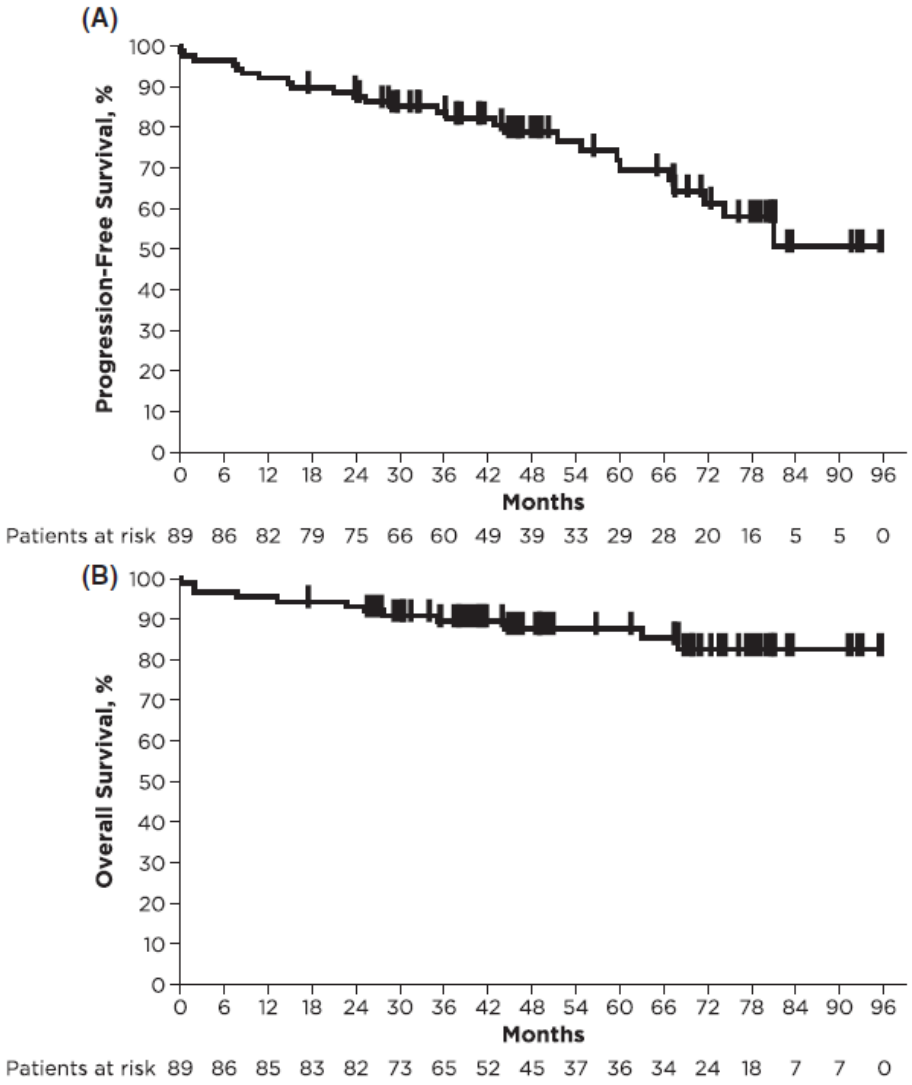
Pooled analysis of ibrutinib in TN *TP53*^{mut} CLL



4-year PFS – 80%

4-year OS – 88%

Allan et al., 2022

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Cardiac toxicity with ibrutinib

	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.

Hillmen P, et al. *Blood.* 2021;138(Suppl 1):642.

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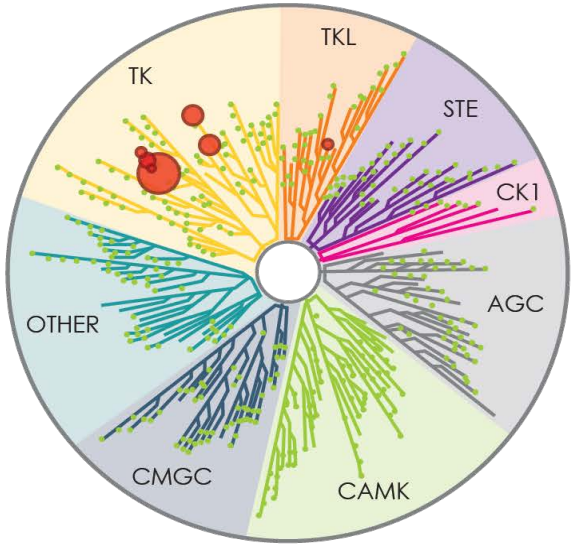
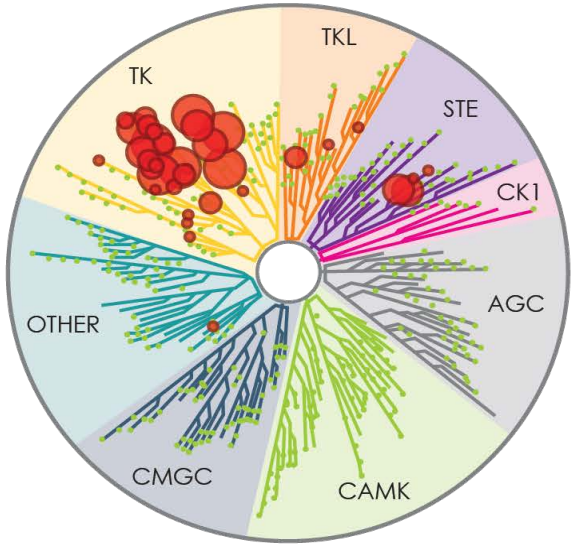
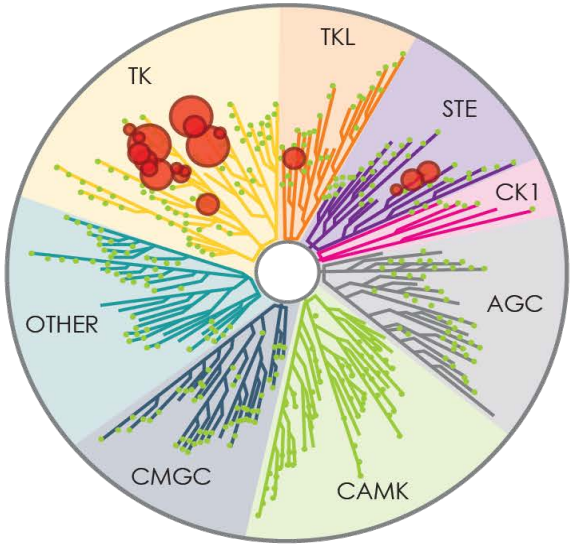
BTKI's: Kinase Selectivity



Acalabrutinib



Ibrutinib



Zanubrutinib

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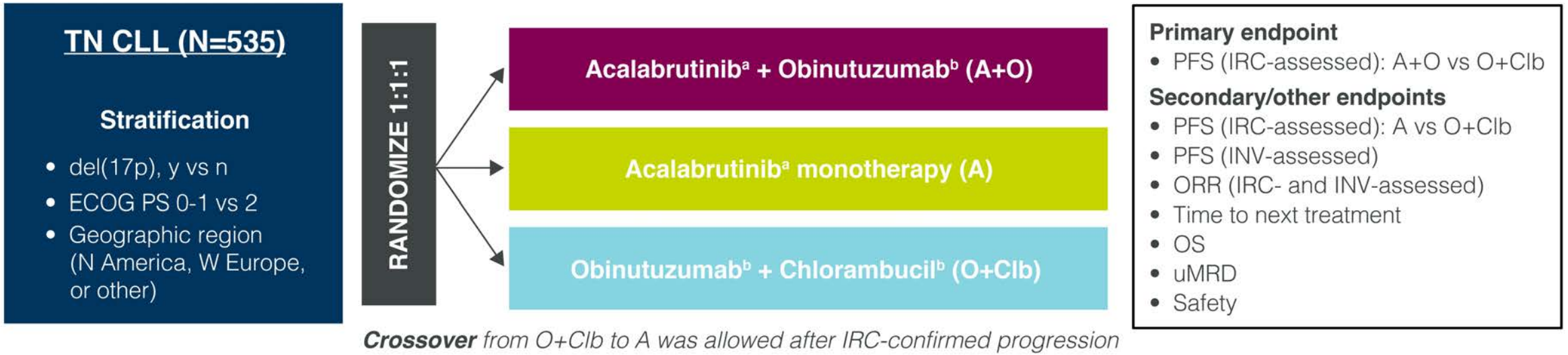
Acalabrutinib in frontline CLL: ELEVATE-TN



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

Note: After interim analysis,[7] PFS assessments were by investigator only

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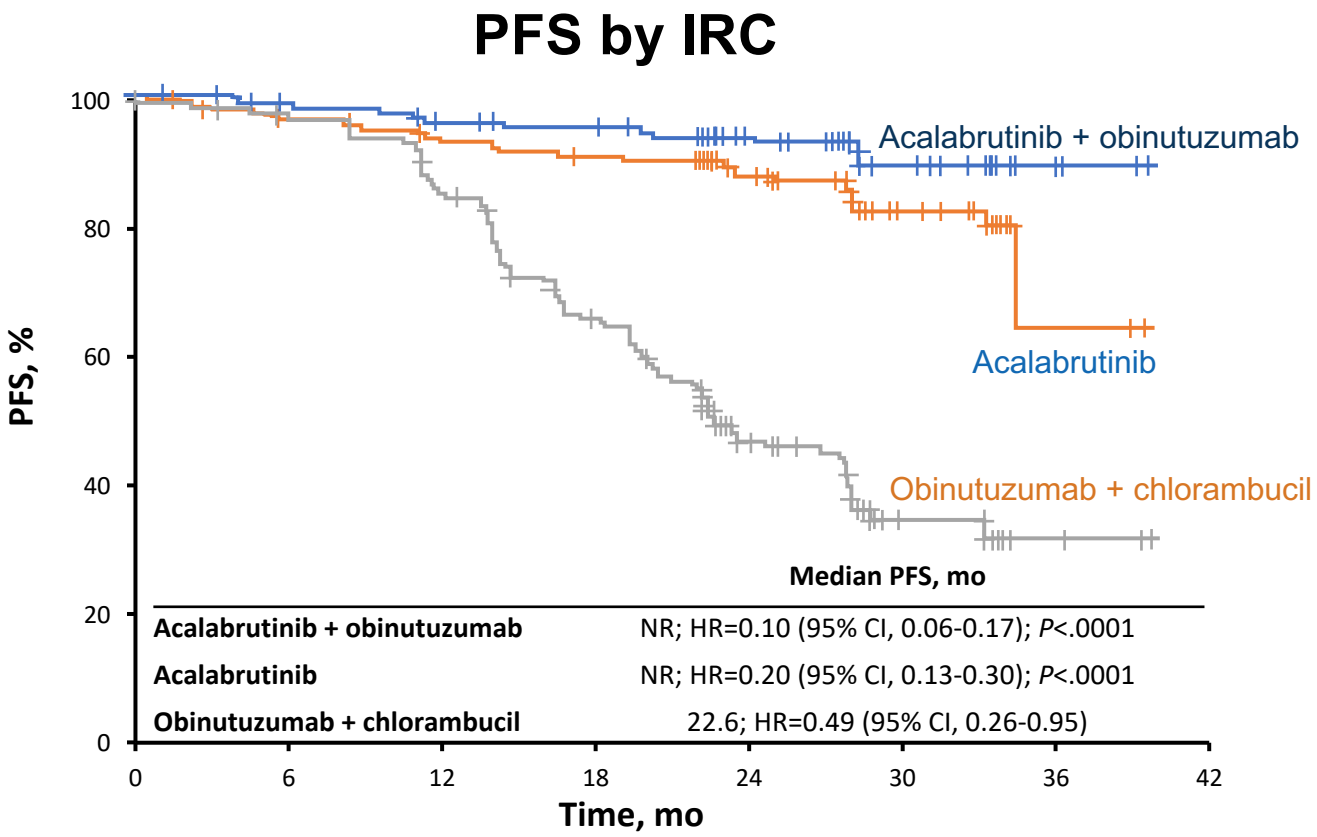
ELEVATE-TN: PFS (Primary Endpoint)



Estimated PFS at 24 months

- 93% with acalabrutinib + obinutuzumab (95% CI, 87%-96%)
- 87% with acalabrutinib monotherapy (95% CI, 81%-92%)
- 47% with obinutuzumab + chlorambucil (95% CI, 39%-55%)

Post-hoc analysis: HR for PFS between acalabrutinib-obinutuzumab and acalabrutinib monotherapy was 0.49 (95% CI, 0.26-0.95)

Sharman JP, et al. *Lancet*. 2020;395(10232):1278-1291.

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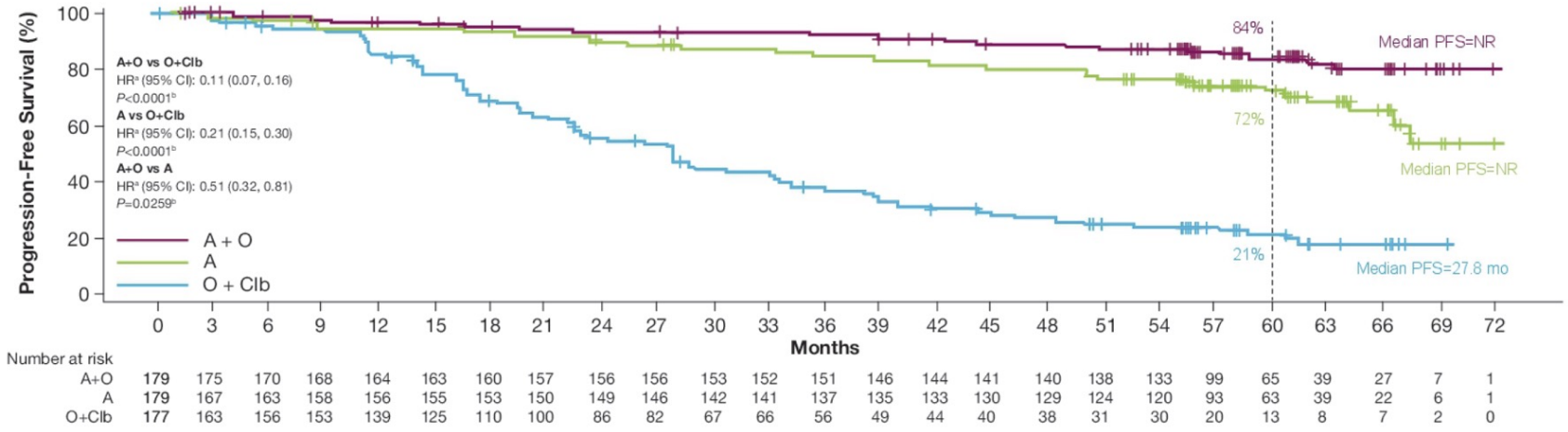
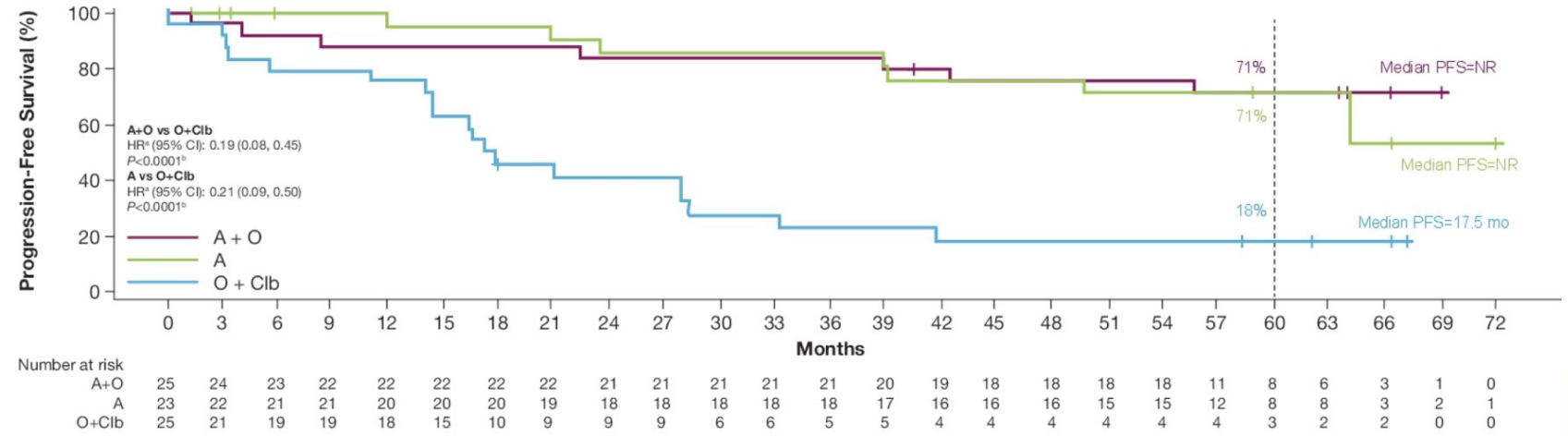
5-Year Follow-Up of the ELEVATE-TN Phase 3 Study: PFS

INV-Assessed PFS



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



Median follow-up:
58.2 months
(range, 0.0-72.0)

Sharman JP, et al. EHA 2022. Abstract P666.

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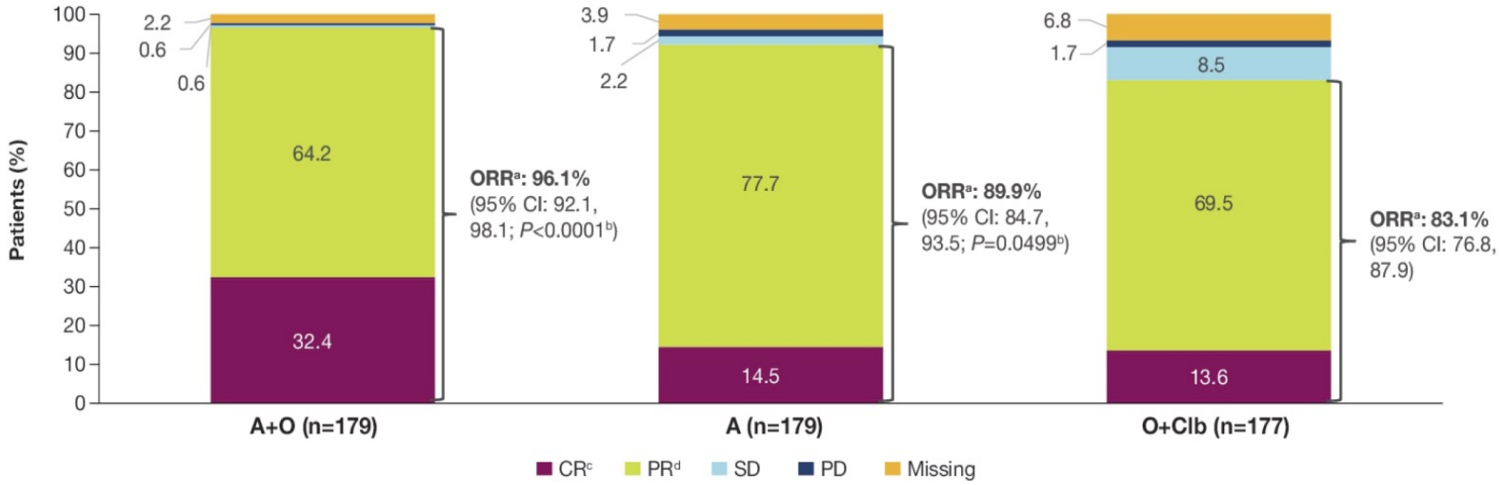
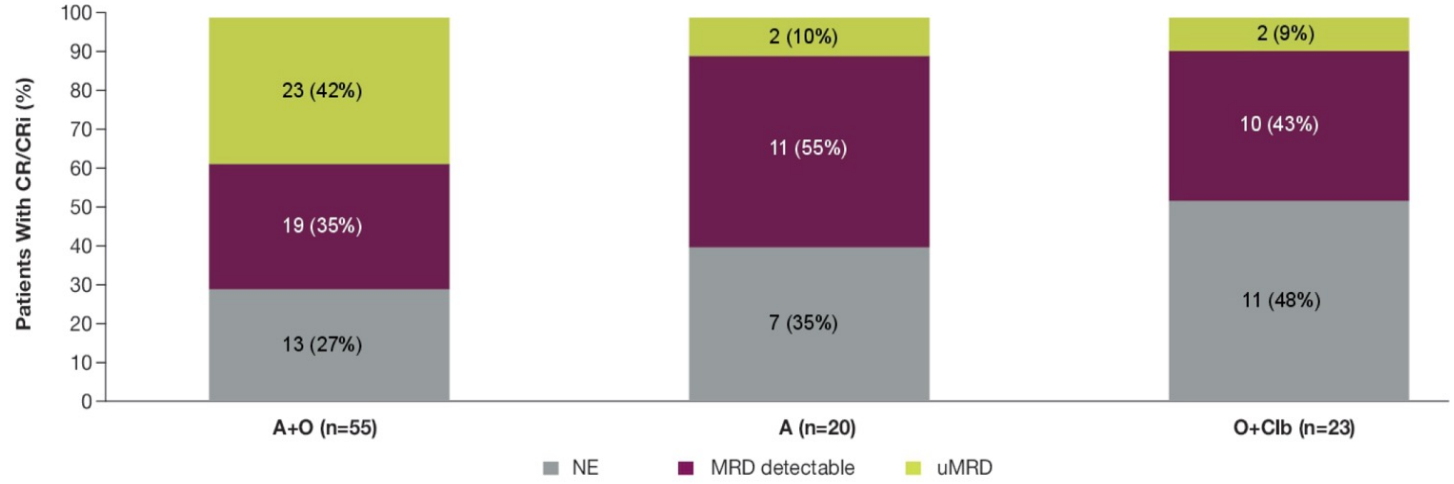
5-Year Follow-Up of the ELEVATE-TN Phase 3 Study: ORR and uMRD

INV-Assessed ORR



MRD Status in Patients With CR/CRi



Sharman JP, et al. ASCO 2022. Abstract 7539. Sharman JP, et al. EHA 2022. Abstract P666.

5-Year Follow-Up of the ELEVATE-TN Phase 3 Study: AEs of Clinical Interest

AEs of Clinical Interest, n (%)	A+O (n=178)		A (n=179)		O+Clb (n=169)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Cardiac events	43 (24.2)	17 (9.6)	39 (21.8)	18 (10.1)	13 (7.7)	3 (1.8)
AFib	11 (6.2)	2 (1.1)	13 (7.3)	2 (1.1)	1 (0.6)	0
Bleeding	88 (49.4)	8 (4.5)	78 (43.6)	6 (3.4)	20 (11.8)	0
Major bleeding	12 (6.7)	8 (4.5)	8 (4.5)	6 (3.4)	2 (1.2)	0
Hypertension	17 (9.6)	8 (4.5)	16 (8.9)	7 (3.9)	6 (3.6)	5 (3.0)
Infections	140 (78.7)	50 (28.1)	135 (75.4)	35 (19.6)	75 (44.4)	14 (8.3)
SPMs	31 (17.4)	14 (7.9)	27 (15.1)	7 (3.9)	7 (4.1)	3 (1.8)
Excluding non-melanoma skin	17 (9.6)	12 (6.7)	13 (7.3)	5 (2.8)	3 (1.8)	2 (1.2)

Patient Disposition

- Treatment still ongoing: A+O 64.8% and A 59.8%
- Discontinuation rates: A+O 35.2%, A 40.2%, O+Clb 22.6%
  - Due to AEs: 17.3%, 15.6%, 14.1%
  - Due to PD: 5.6%, 10.1%, 1.7%

Safety

- Most common AEs were similar to prior analyses
- AEs that occurred more frequently in A+O and A vs O+Clb included headache, diarrhea, and arthralgia
- AEs that occurred more frequently with O+Clb included neutropenia, nausea, and IRR

Sharman JP, et al. EHA 2022. Abstract P666.

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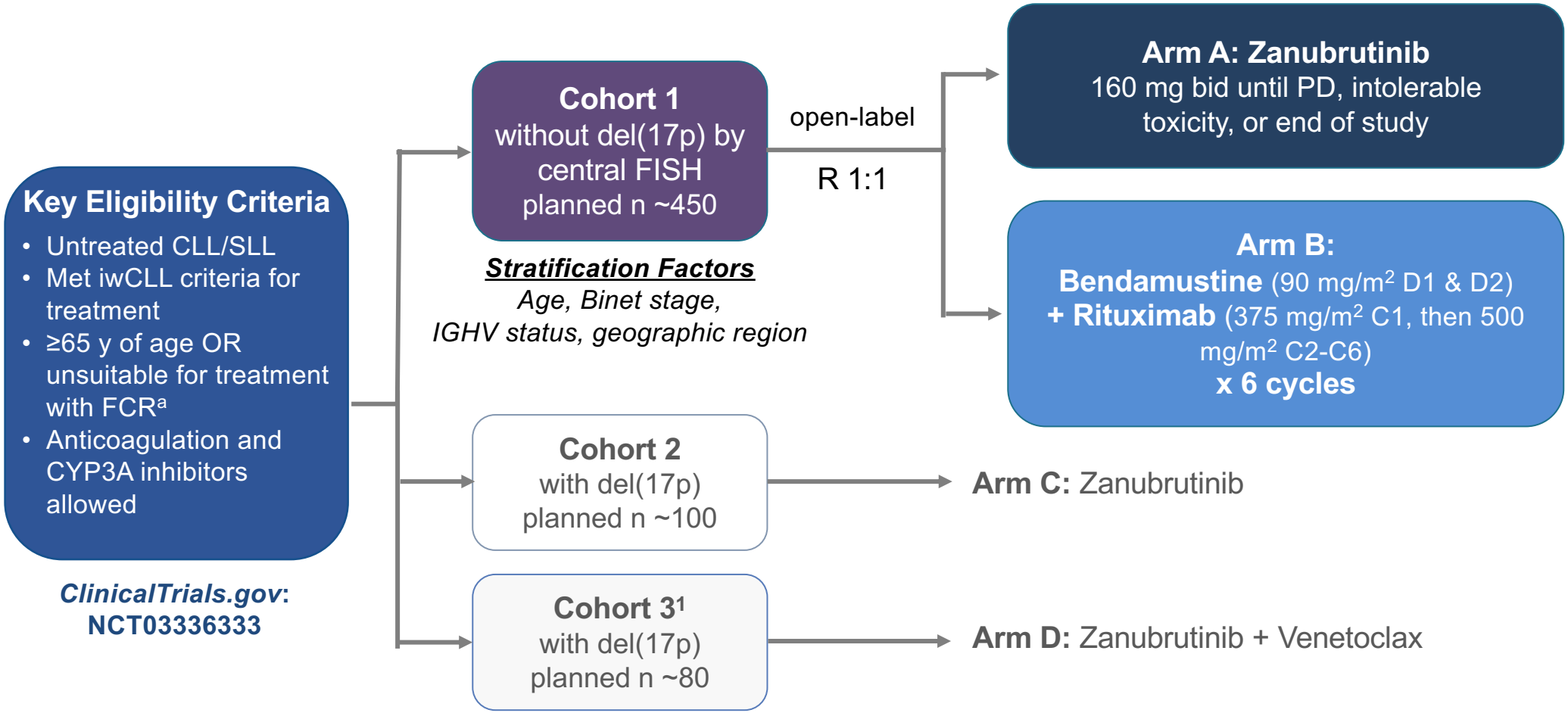
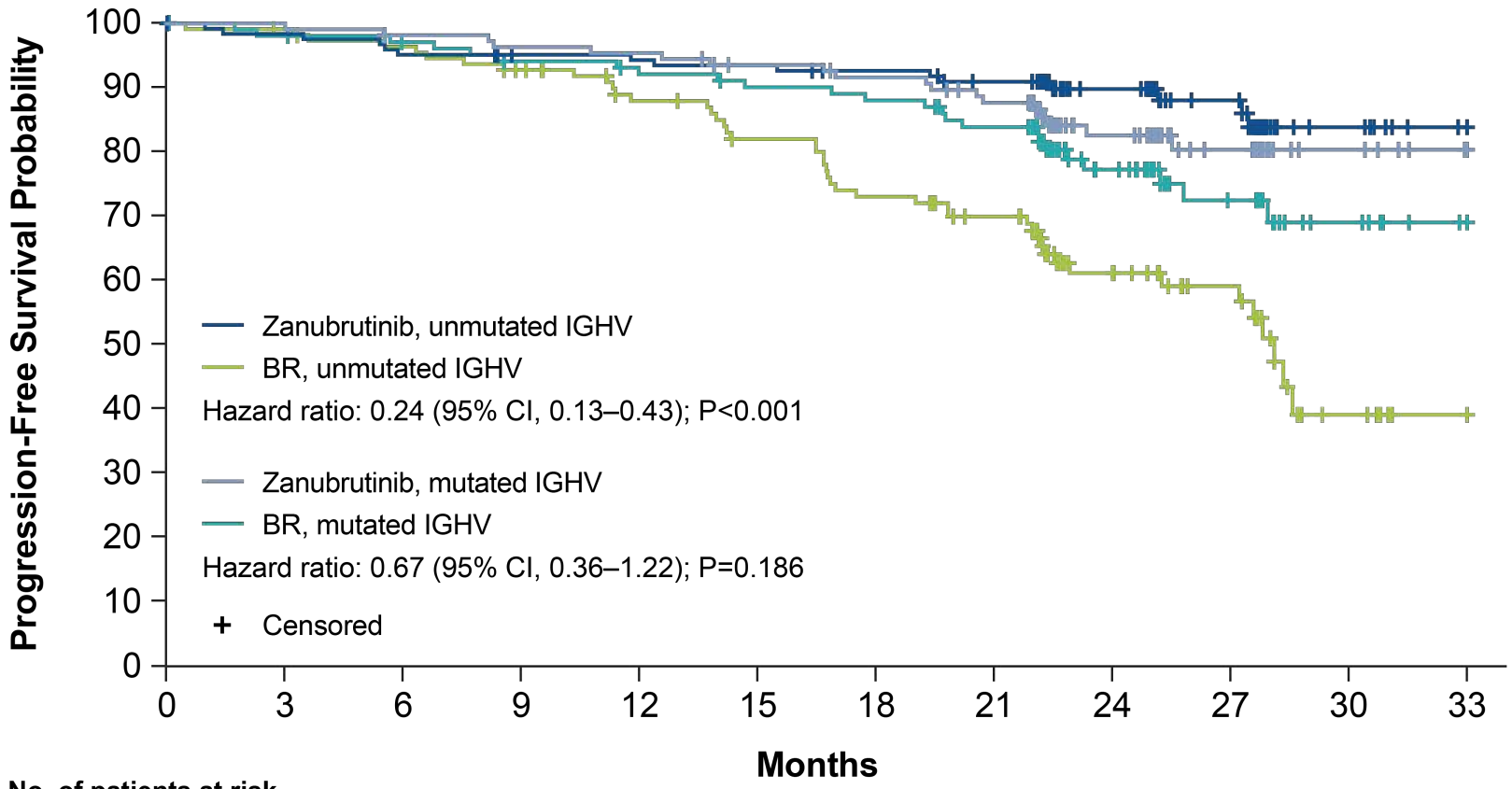
SEQUOIA (BGB-3111-304)
Study Design



[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.

Tam, et al. ASH 2021, Abstract #396

Progression-Free Survival Per IRC Assessment by IGHV Status



No. of patients at risk												
Zanubrutinib - Unmutated	125	121	117	114	113	112	109	104	68	44	14	6
BR - Unmutated	121	110	106	100	90	82	73	65	39	25	6	1
Zanubrutinib - Mutated	109	109	106	104	103	97	94	88	53	33	15	10
BR - Mutated	110	101	98	94	91	88	86	80	47	27	14	7

BR, bendamustine + rituximab; IGHV, gene encoding the immunoglobulin heavy chain variable region; IRC, independent review committee.

Tam, et al. ASH 2021, Abstract #396

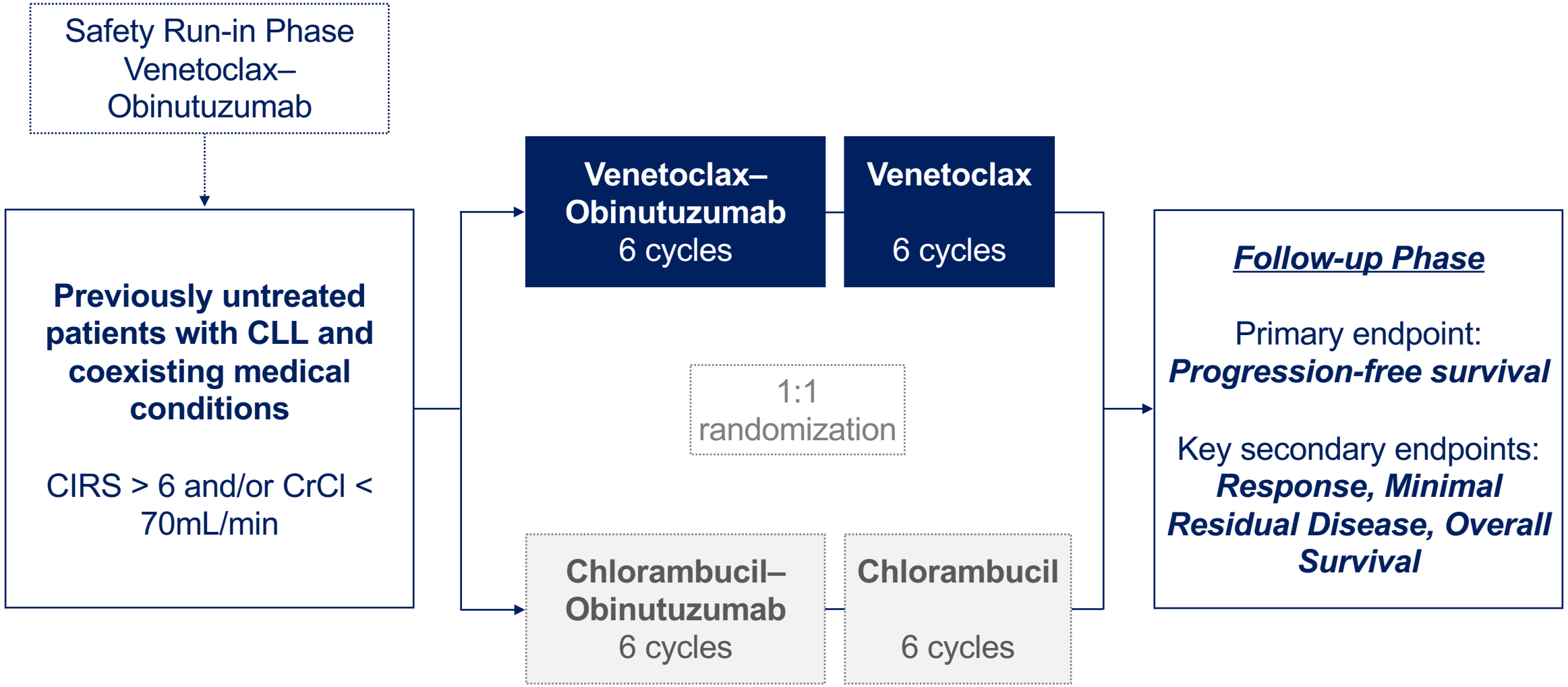
Adverse Events of Interest

AE, n (%)	Arm A Zanubrutinib (n=240[a]) Any Grade	Arm A Zanubrutinib (n=240[a]) Grade ≥3	Arm B Bendamustine + Rituximab (n=227[a]) Any Grade	Arm B Bendamustine + Rituximab (n=227[a]) Grade ≥3
Anemia	11 (4.6)	1 (0.4)	44 (19.4)	4 (1.8)
Neutropenia[b]	38 (15.8)	28 (11.7)	129 (56.8)	116 (51.1)
Thrombocytopenia[c]	11 (4.6)	5 (2.1)	40 (17.6)	18 (7.9)
Arthralgia	32 (13.3)	2 (0.8)	20 (8.8)	1 (0.4)
Atrial fibrillation	8 (3.3)	1 (0.4)	6 (2.6)	3 (1.3)
Bleeding[d]	108 (45.0)	9 (3.8)	25 (11.0)	4 (1.8)
Major bleeding[e]	12 (5.0)	9 (3.8)	4 (1.8)	4 (1.8)
Diarrhea	33 (13.8)	2 (0.8)	31 (13.7)	5 (2.2)
Hypertension[f]	34 (14.2)	15 (6.3)	24 (10.6)	11 (4.8)
Infections[g]	149 (62.1)	39 (16.3)	127 (55.9)	43 (18.9)
Myalgia	9 (3.8)	0 (0.0)	3 (1.3)	0 (0.0)
Other cancers	31 (12.9)	17 (7.1)	20 (8.8)	7 (3.1)
Dermatologic other cancers	16 (6.7)	2 (0.8)	10 (4.4)	2 (0.9)

[a]Safety was assessed in patients who received ≥1 dose of treatment; 1 patient in Arm A and 11 patients in Arm B did not receive treatment. [b]Neutropenia, neutrophil count decreased, or febrile neutropenia. [c]Thrombocytopenia or platelet count decreased. [d]Pooled term of all-cause bleeding including bruising, petechiae, purpura, and contusion. [e]Major bleeding included all grade ≥3, serious, and any-grade central nervous system hemorrhage. [f]Hypertension, blood pressure increased, or hypertensive crisis. [g]All infection terms pooled.
AE, adverse event.

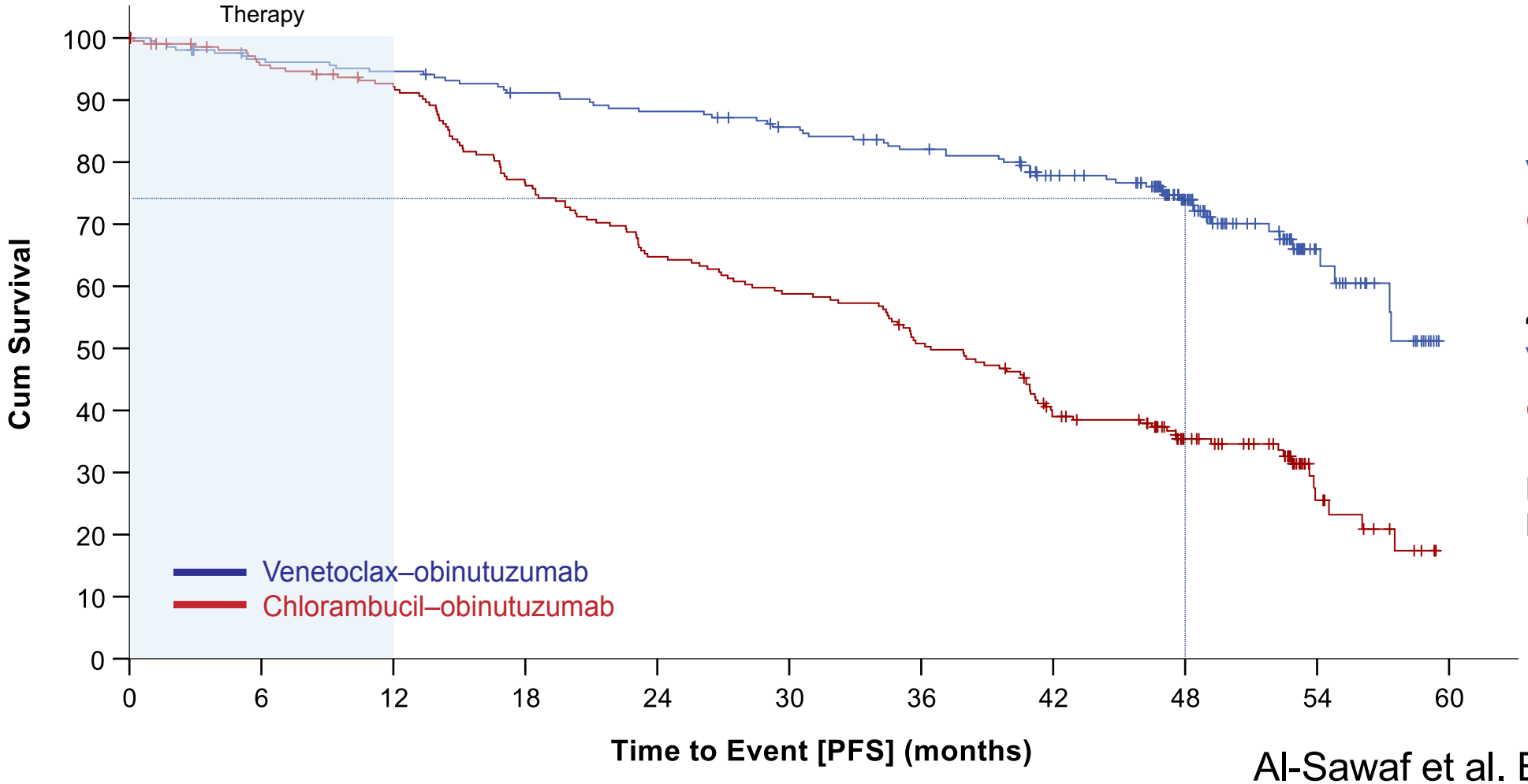
Tam, et al. ASH 2021, Abstract #396

CLL14: Trial Design



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%

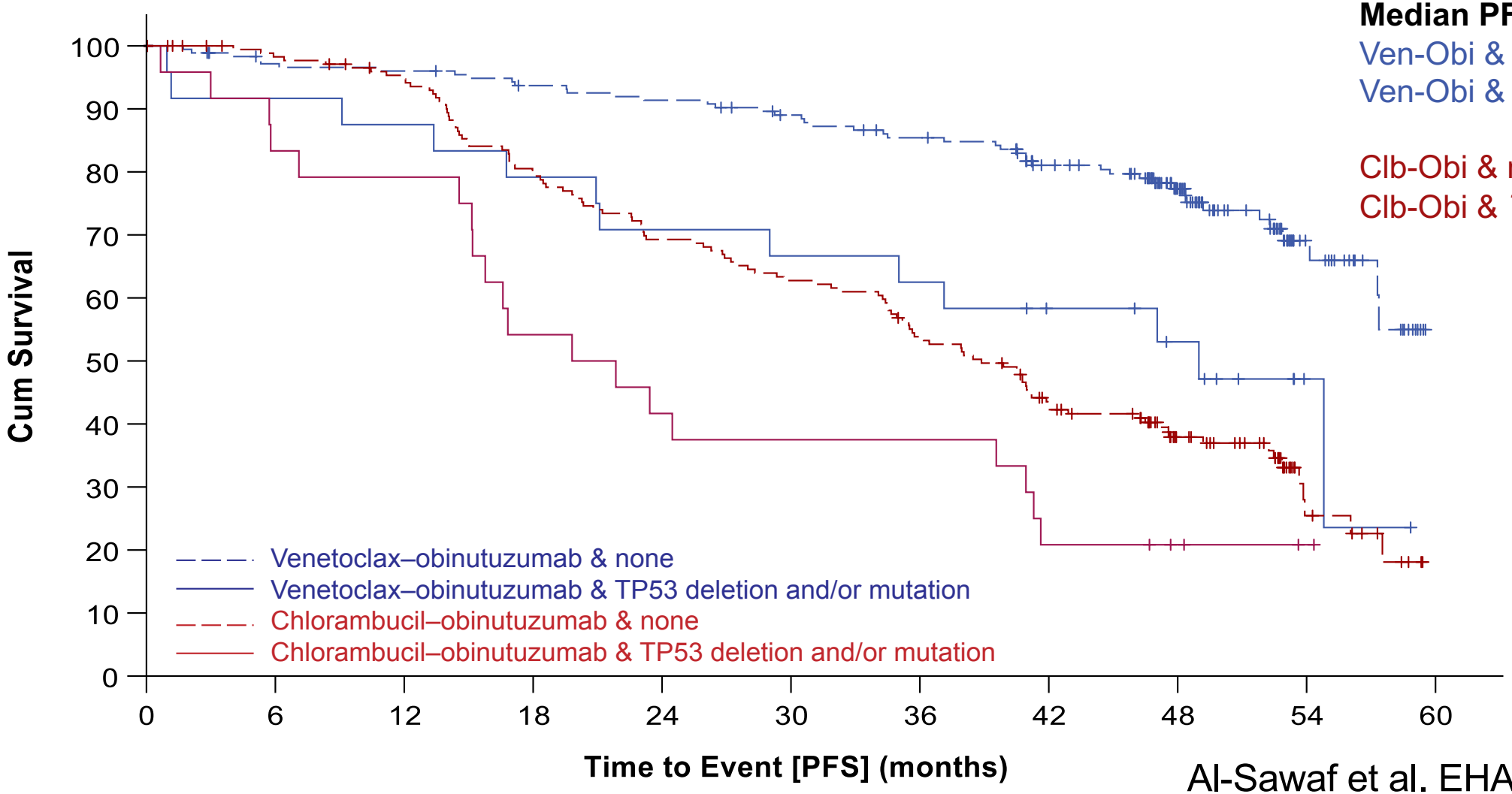
Clb-Obi: 35.4%

HR 0.33, 95% CI [0.25-0.45]
P<0.0001

Al-Sawaf et al. EHA 2021, Abstract S146

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

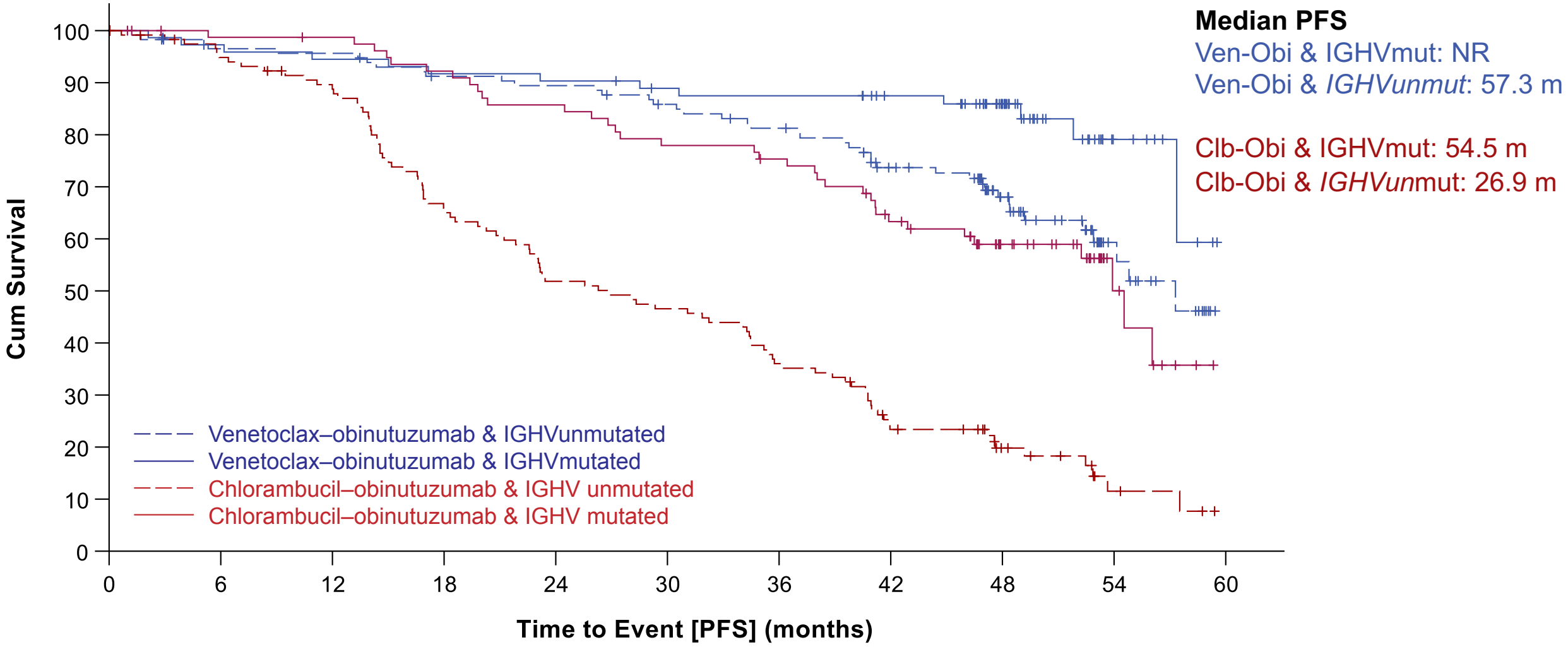
Clb-Obi & no *TP53*del/mut: 38.9 m

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

Al-Sawaf et al. EHA 2021, Abstract S146

Progression-free Survival – IGHV Status

Median observation time 52.4 months

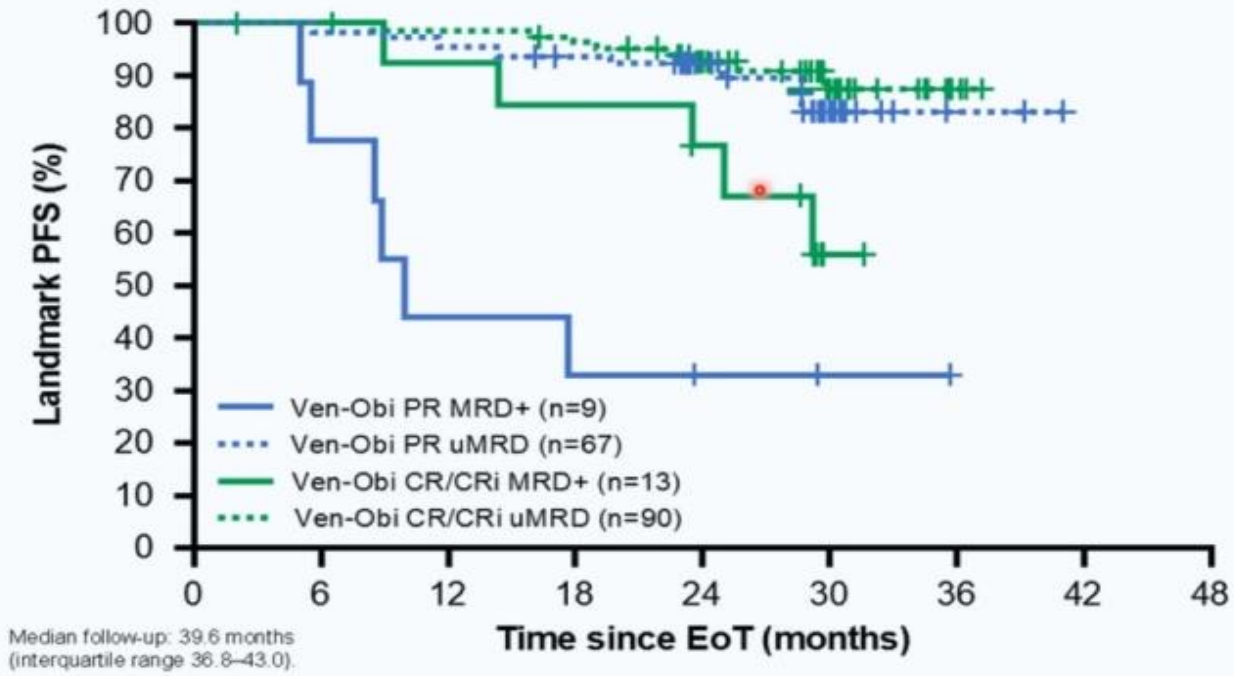


Al-Sawaf et al. EHA 2021, Abstract S146

uMRD associated with improved responses

CLL

LANDMARK PFS BY MRD/CLINICAL RESPONSE



Median follow-up: 39.6 months (interquartile range 36.8–43.0).

Patients from the Ven-Obi arm with uMRD levels and PR had a similar PFS to patients with uMRD and CR. Moreover, patients with uMRD and PR had a longer PFS than patients with detectable MRD and CR.

Al-Sawaf O, et al. *J Clin Oncol*. 2021;39(36):4049-4060.

Venetoclax vs Ibrutinib: Grade 3-4 events

	Venetoclax-Obinutuzumab (CLL14)	Ibrutinib (Alliance)
Number of patients, N	212	180
Follow up	28 months	38 months
Neutropenia	53 %	8 %
Thrombocytopenia	14 %	5 %
Anemia	8 %	7 %
Febrile neutropenia	5 %	2 %
Infections	18 %	16 %
Pneumonia	4 %	6%

Al-Sawaf O, et al. *J Clin Oncol*. 2021;39(36):4049-4060. Woyach JA, et al. *Blood*. 2021;138(Suppl 1):639.

BTKi- *vs.* BCL-2i-based Treatment

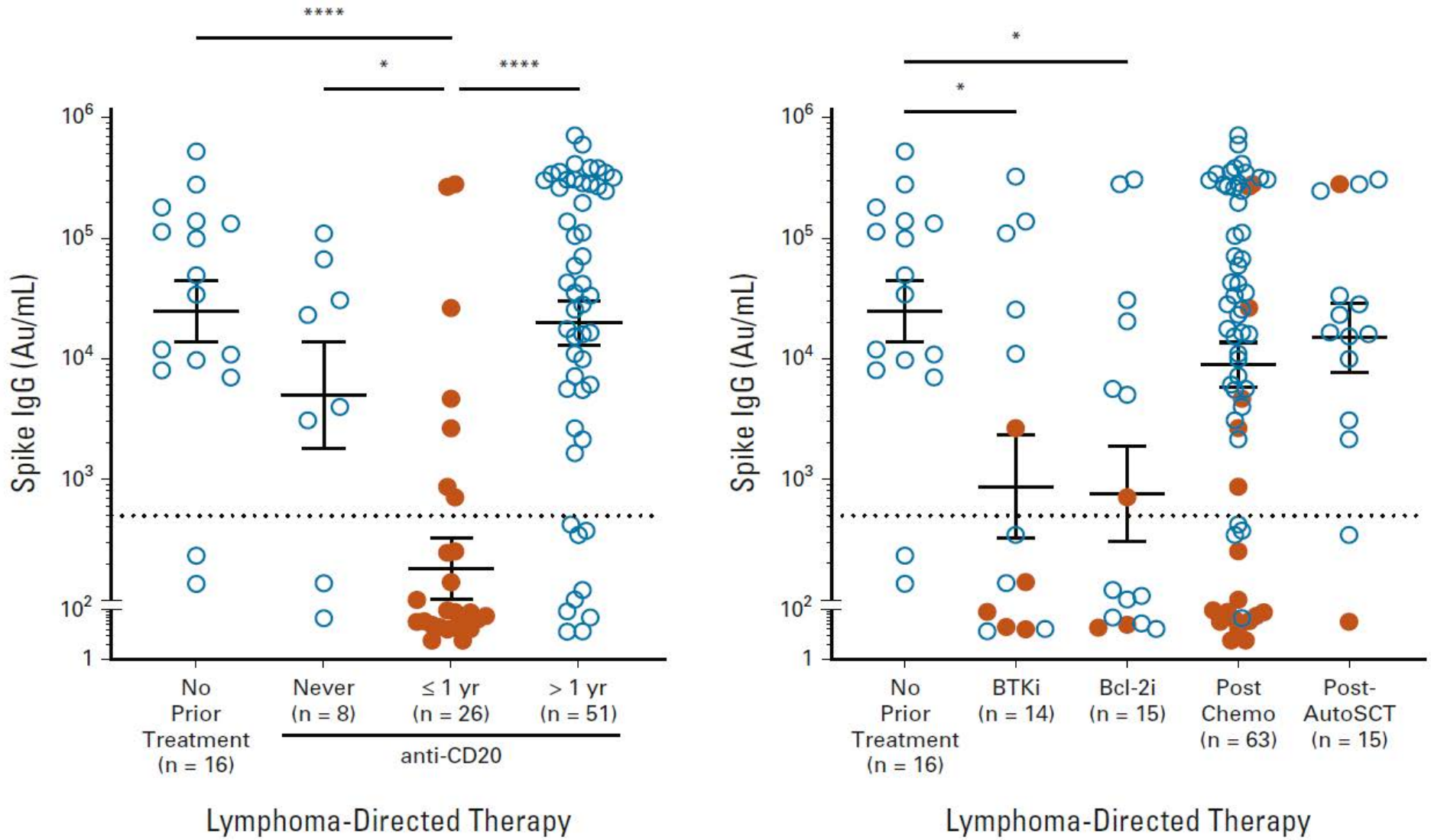
BTK Inhibitor

- Easy initiation
- Continuous and indefinite therapy
- Very low TLS risk
- More cardiac risk

BCL-2 Inhibitor

- Risk for TLS requires monitoring for initiation
- Includes CD20 mAb – immunosuppression
- Fixed duration
- GFR sensitivity
- Concern for del(17p)/mutated-*TP53*

COVID Vaccination Efficacy



Chang A, et al. *J Clin Oncol*. 2022;40(26):3020-3031.

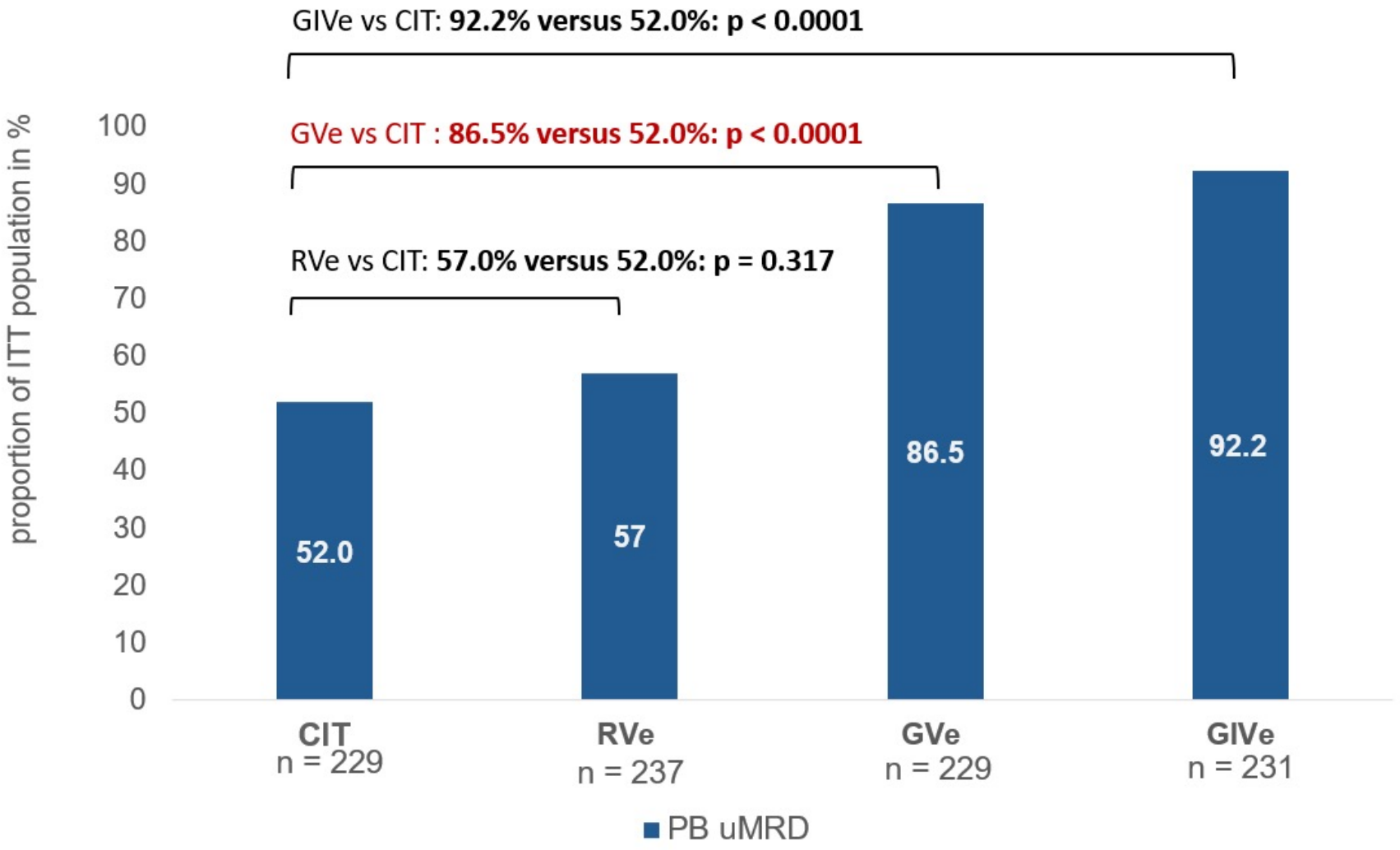
Appendix

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 (CLL) of Fit Patients: First Co-Primary Endpoint Analysis of the International Intergroup GAIA (CLL13) Trial

Eichhorst B et al.

ASH 2021;Abstract 71.

GAIA/CLL13 Coprimary Endpoint: Undetectable MRD (uMRD, <10^{-4}) at Month 15 in Peripheral Blood by 4-Color Flow



CIT
- BR >65
- ≤FCR 65

RVe
Rituximab/venetoclax

GVe
Obinutuzumab/venetoclax

GIVe
Obinutuzumab/ibrutinib/venetoclax

Eichhorst B et al. ASH 2021;Abstract 71.

EHA EUROPEAN HEMATOLOGY ASSOCIATION

EHA2022 HYBRID JUNE 9-17 VIENNA

EHA EUROPEAN HEMATOLOGY ASSOCIATION

Abstract S148

EHA2022 HYBRID VIRTUAL

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

DEUTSCHE STUDIENGRUPPE CLL

Othman Al-Sawaf

Abstract S148

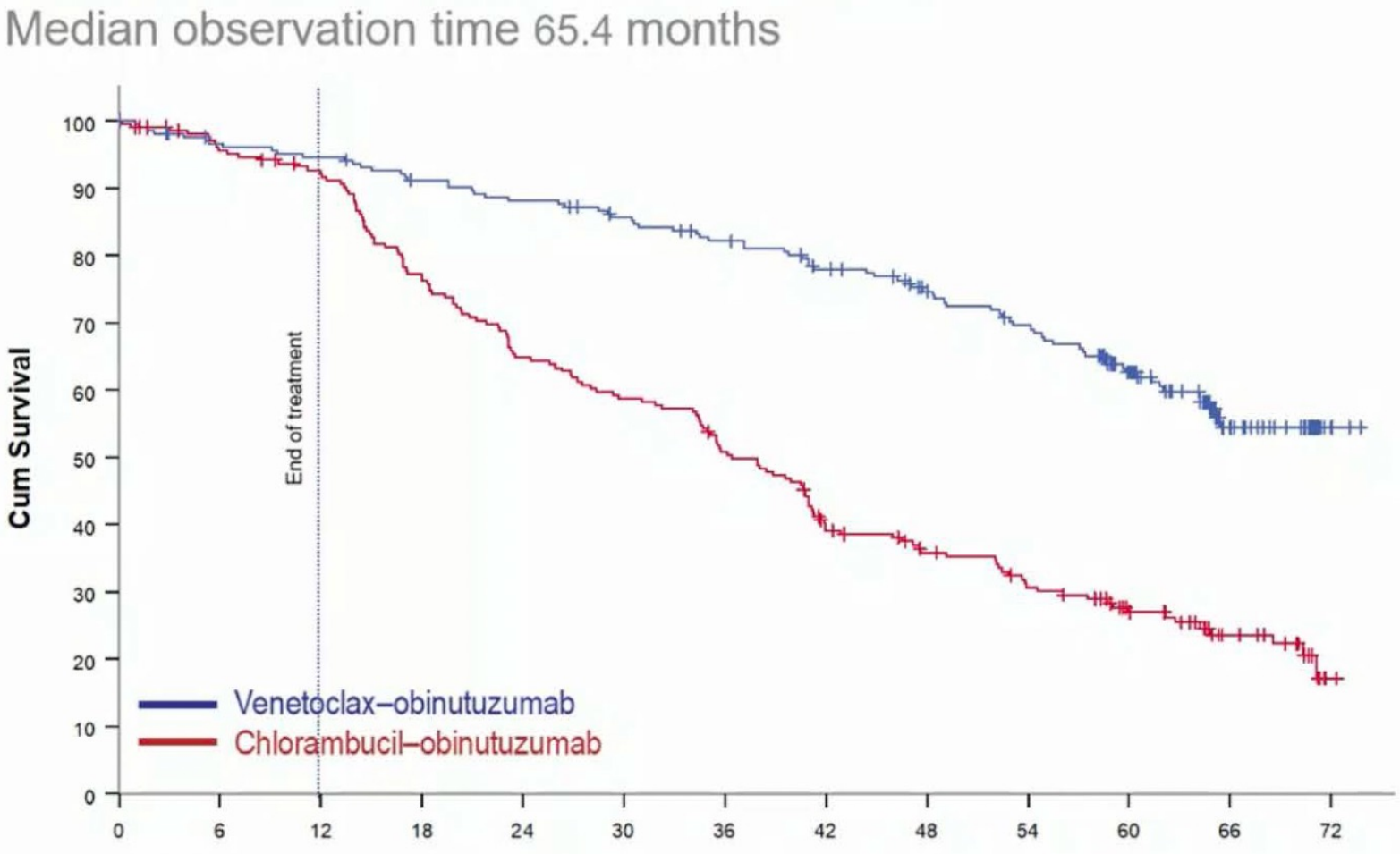
Venetoclax-Obinutuzumab for previously untreated chronic lymphocytic leukemia: 5-year results of the randomized CLL14 study

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

June 12th, 2022
Clinical CLL Session

RTP RESEARCH TO PRACTICE

CLL14: Progression-Free Survival



Median PFS

Ven-Obi: not reached

Clb-Obi: 36.4 months

5-year PFS rate

Ven-Obi: 62.6%

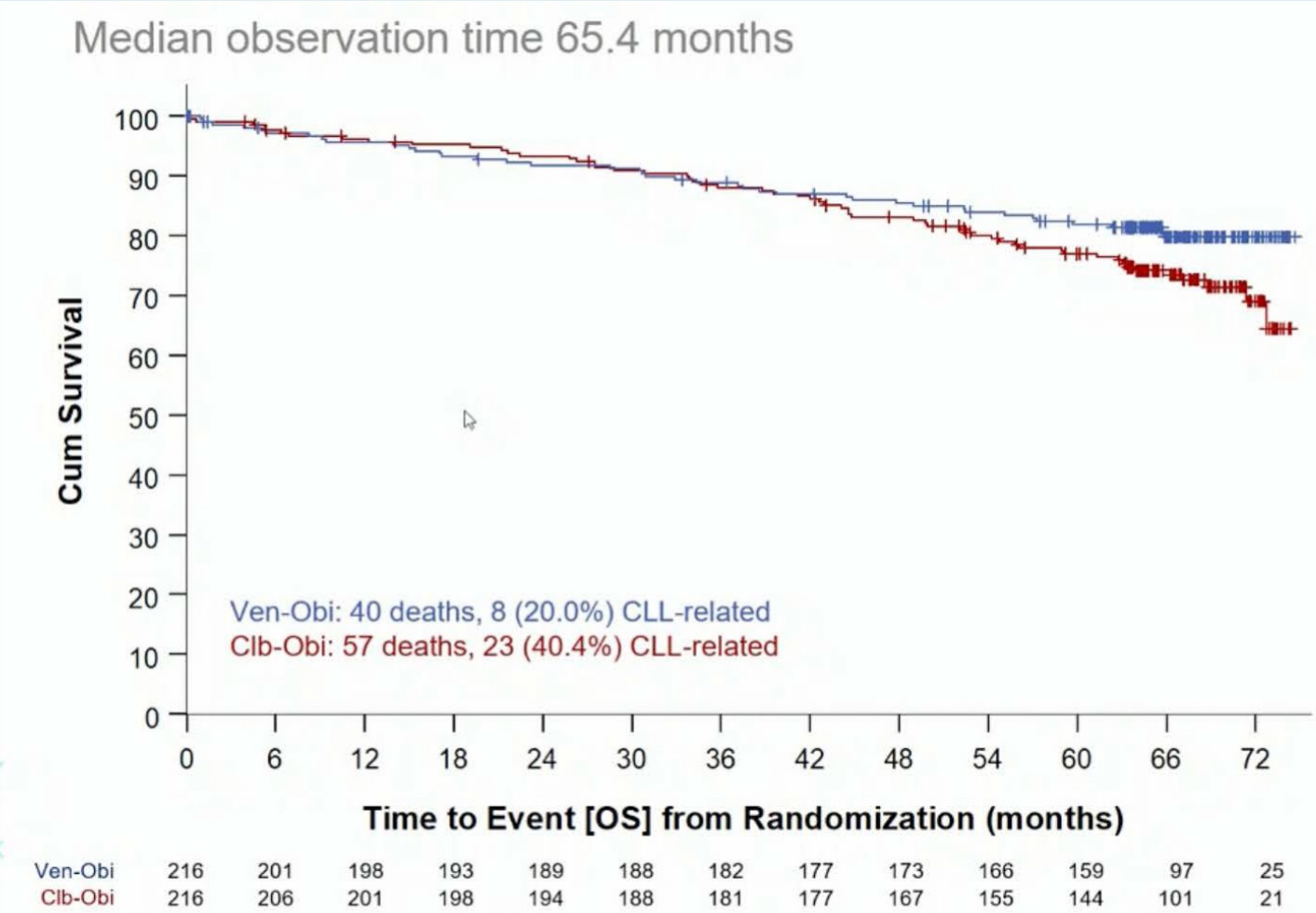
Clb-Obi: 27.0%

HR 0.35, 95% CI [0.26-0.46]
P<0.0001

Al-Sawaf O et al. EHA 2022;Abstract S148.

RTP RESEARCH TO PRACTICE

CLL14: Overall Survival



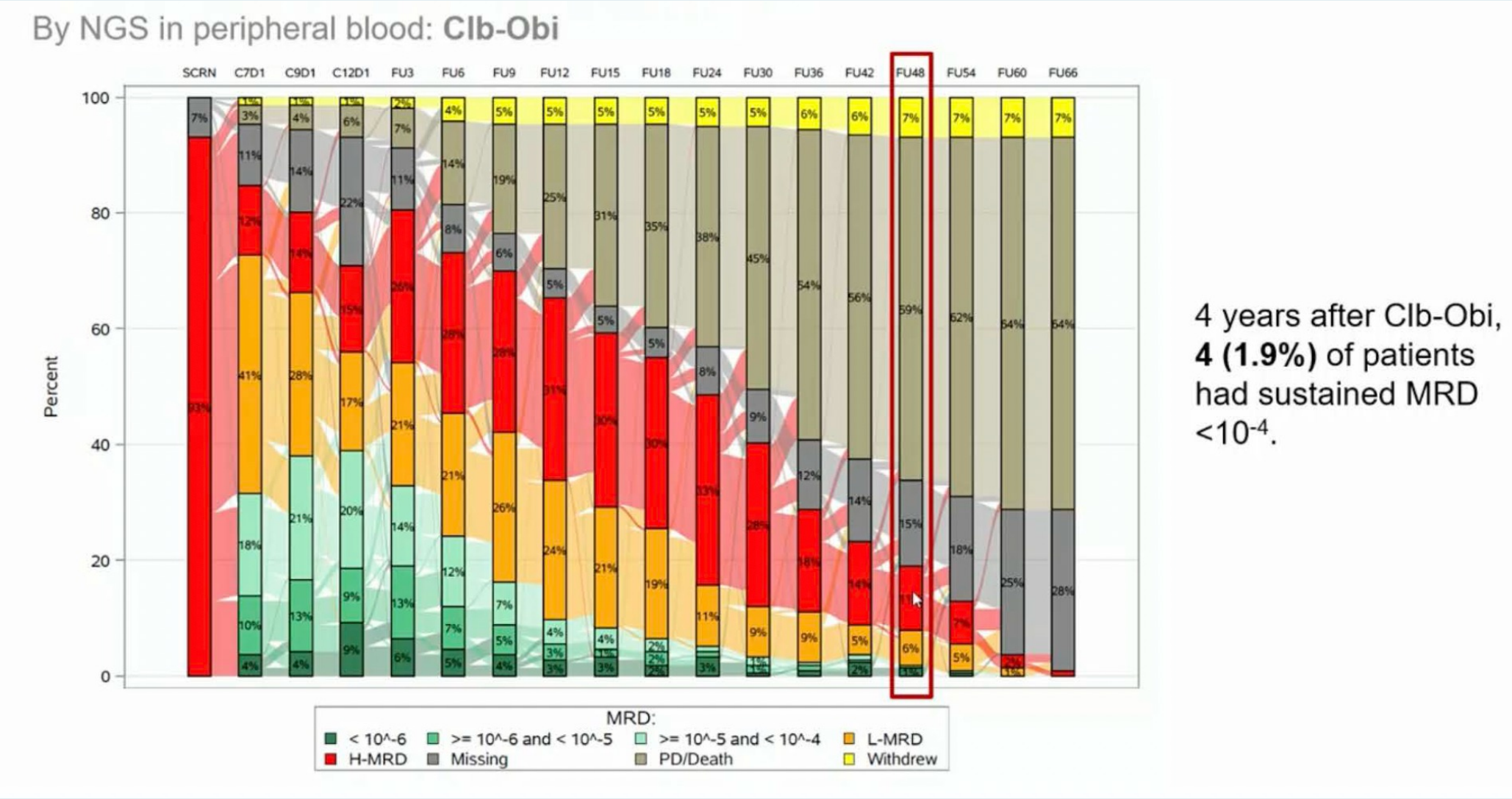
Median OS
Ven-Obi: not reached
Clb-Obi: not reached

5-year OS rate
Ven-Obi: 81.9%
Clb-Obi: 77.0%

HR 0.72, 95% CI [0.48-1.09]
P=0.12

Al-Sawaf O et al. EHA 2022;Abstract S148.

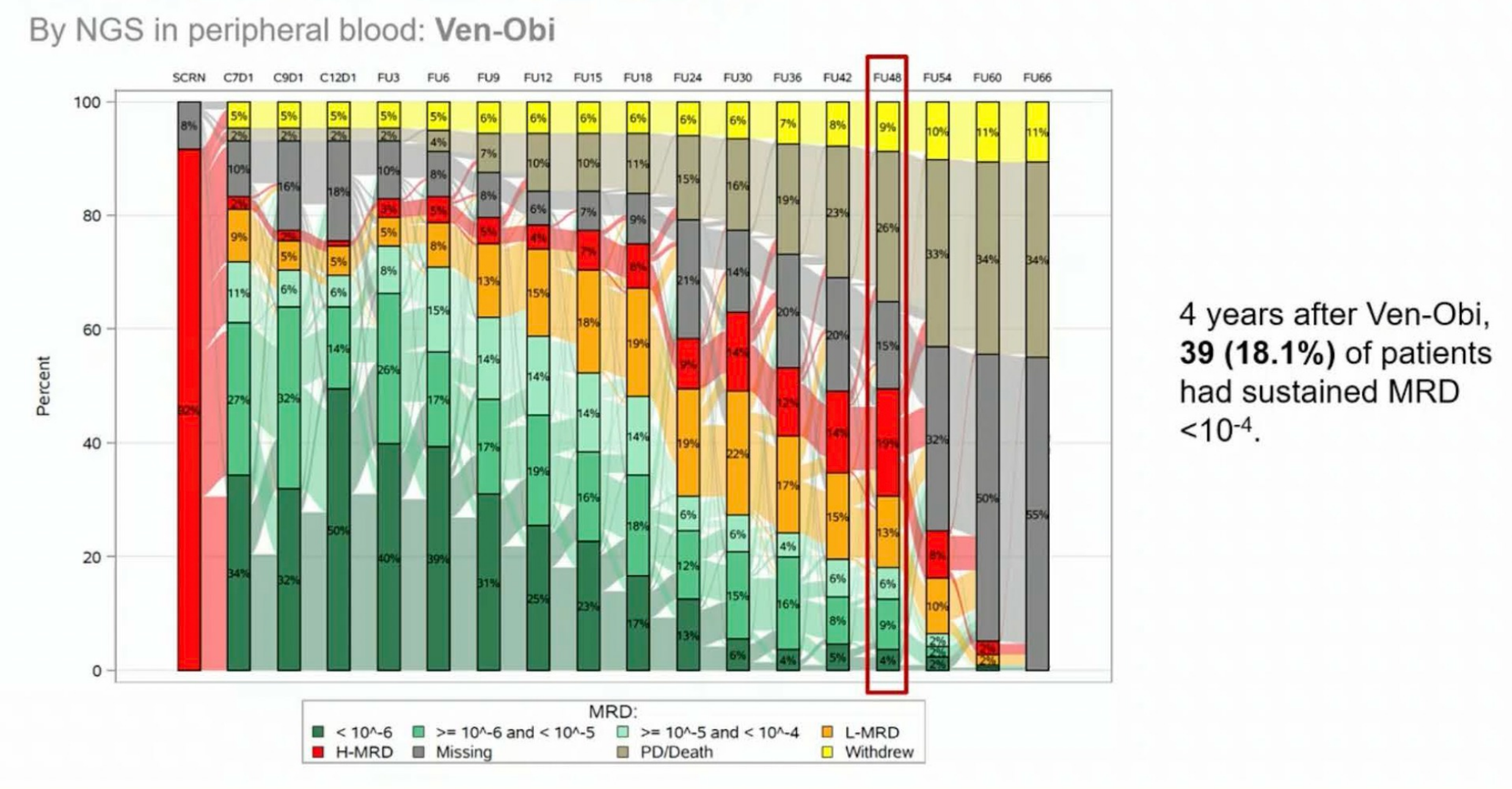
CLL14: Longitudinal MRD Assessments



4 years after Clb-Obi, **4 (1.9%)** of patients had sustained MRD $<10^{-4}$.

Al-Sawaf O et al. EHA 2022;Abstract S148.

CLL14: Longitudinal MRD Assessments



4 years after Ven-Obi, **39 (18.1%)** of patients had sustained MRD $<10^{-4}$.

Al-Sawaf O et al. EHA 2022;Abstract S148.

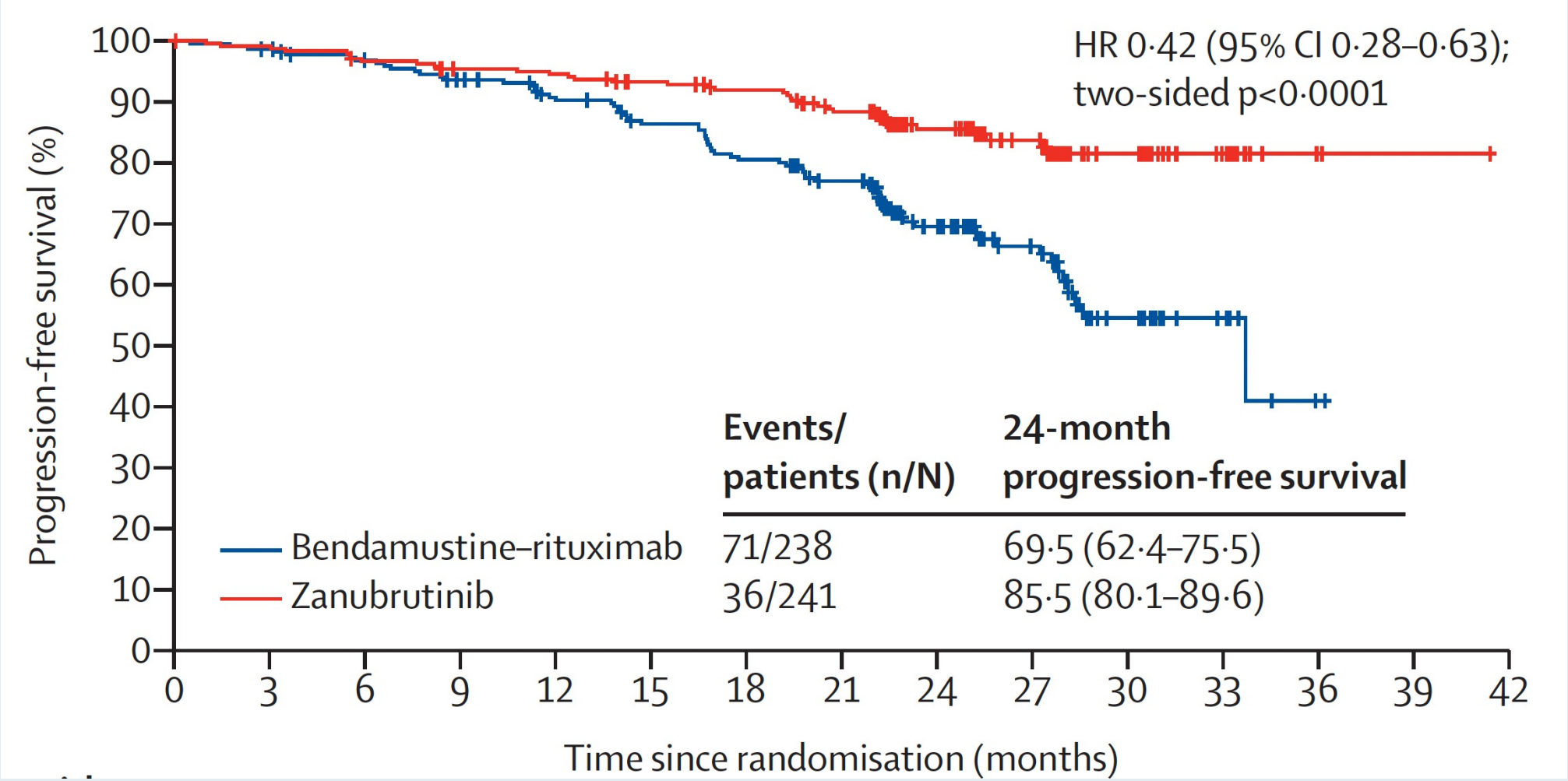
RTP RESEARCH TO PRACTICE

Lancet Oncol 2022 August;23(8):1031-43.

Zanubrutinib versus bendamustine and rituximab in untreated chronic lymphocytic leukaemia and small lymphocytic lymphoma (SEQUOIA): a randomised, controlled, phase 3 trial

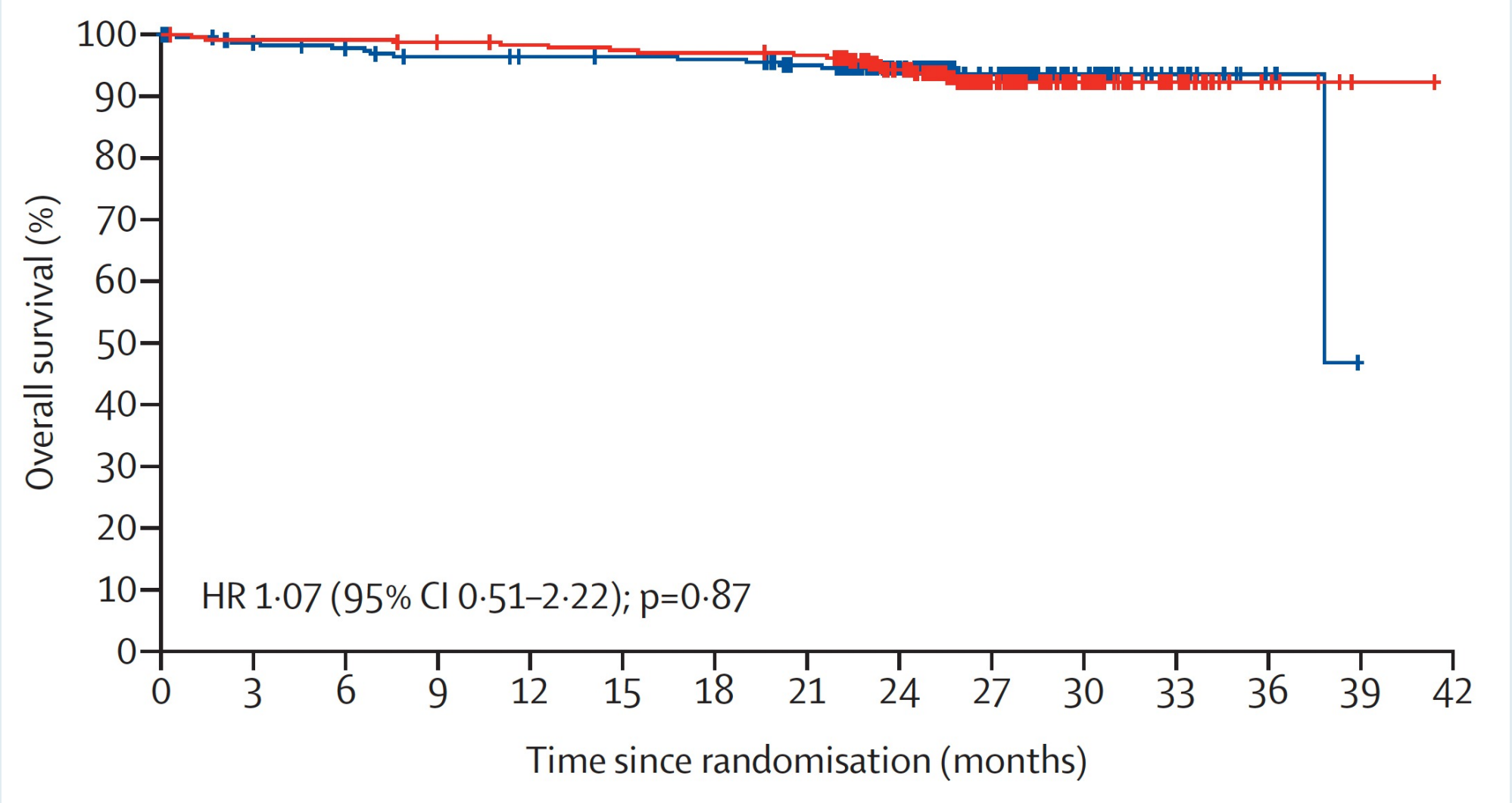
Constantine S Tam, Jennifer R Brown, Brad S Kahl, Paolo Ghia, Krzysztof Giannopoulos, Wojciech Jurczak, Martin Šimkovič, Mazyar Shadman, Anders Österborg, Luca Laurenti, Patricia Walker, Stephen Opat, Henry Chan, Hanna Ciepluch, Richard Greil, Monica Tani, Marek Trněný, Danielle M Brander, Ian W Flinn, Sebastian Grosicki, Emma Verner, Alessandra Tedeschi, Jianyong Li, Tian Tian, Lei Zhou, Carol Marimpietri, Jason C Paik, Aileen Cohen, Jane Huang, Tadeusz Robak, Peter Hillmen**

SEQUOIA: Progression-Free Survival by IRC (ITT)



Tam CS et al. *Lancet Oncol* 2022;23(8):1031-43.

SEQUOIA: Overall Survival



Tam CS et al. *Lancet Oncol* 2022;23(8):1031-43.

RTP RESEARCH TO PRACTICE

Abstract S145

EHA EUROPEAN HEMATOLOGY ASSOCIATION

EHA2022 HYBRID JUNE 9-17 VIENNA

The combination of ibrutinib plus venetoclax results in a high rate of MRD negativity in previously untreated CLL: The results of the planned interim analysis of the Phase III NCRI Flair Trial

Peter Hillmen, Alexandra Pitchford, Adrian Bloor, Andrew Pettitt, Piers Patten, Francesco Forconi, Anna Schuh, Christopher Fox, Simona Gatto, Ben Kennedy, John Gribben, Nicholas Pemberton, Oonagh Sheehy, Gavin Preston, Dena Howard, Anna Hockaday, David Cairns, Sharon Jackson, Natasha Greatorex, Nichola McWhirter, Surita Dalal, Jane Shingles, Kate Cwynarski, Shankara Paneesha, David Allsup, Andrew Rawstron, Talha Munir
on behalf of the NCRI CLL sub-group.

Peter Hillmen

Abstract No: S145, Oral Presentation, EHA Annual Meeting
Sunday, June 12th 2022

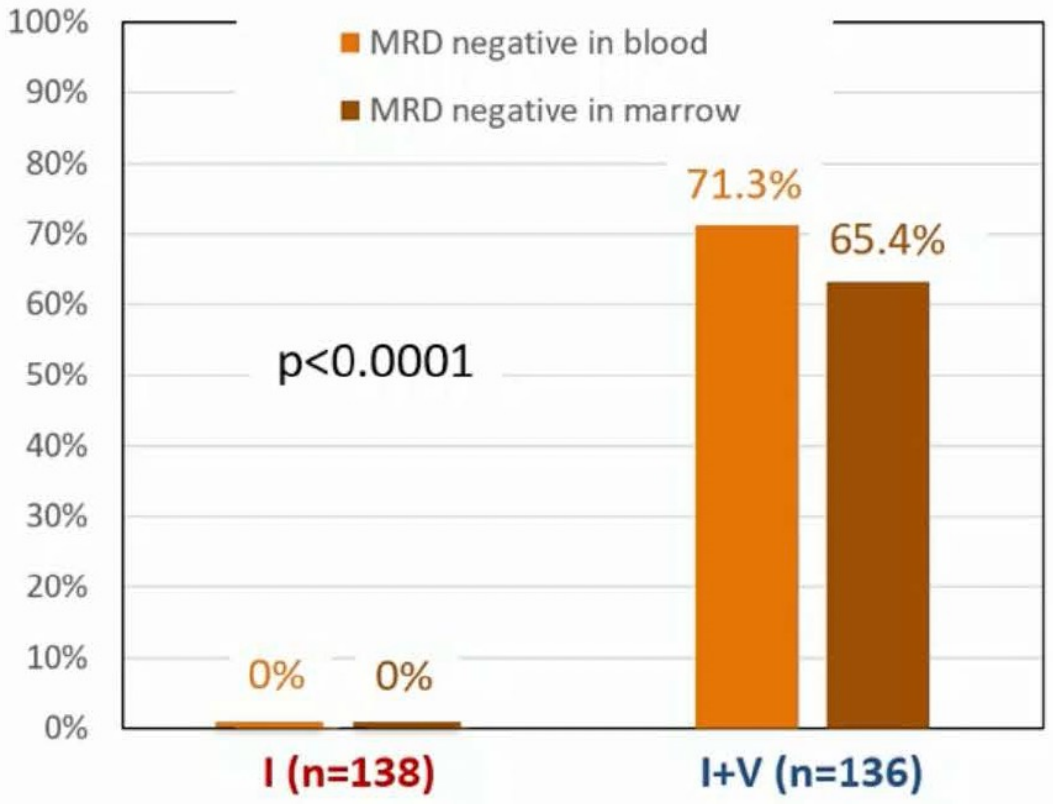
NCRI National Cancer Research Institute

CANCER RESEARCH UK | ctru University of Leeds | LEEDS CLINICAL TRIALS UNIT

Scan the QR code to access the session interactivity features

RTP RESEARCH TO PRACTICE

FLAIR Primary Endpoint: MRD Negativity at 2 Years



N (%), Exact 95% CI	I (n=138)	I+V (n=136)
MRD Negative in the marrow	**0** [0%, 2.64%]	**89 (65.4%)** [56.81%, 73.38%]
MRD Negative in the blood	**0** [0%, 2.64%]	**97 (71.3%)** [62.95%, 78.75%]

- MRD assessed by 8-colour flow cytometry
- MRD negative defined by IWCLL criteria of <1 CLL cell in 10,000 leucocytes

Hillmen P et al. EHA 2022;Abstract S145.

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