Beyond the Guidelines: Clinical Investigator Perspectives on the Management of Chronic Lymphocytic Leukemia (Part 3 of a 4-Part Series)

A CME Friday Satellite Symposium and Virtual Event Preceding the 65th ASH Annual Meeting

Friday, December 8, 2023

3:15 PM – 5:15 PM PT (6:15 PM – 8:15 PM ET)

Faculty

Farrukh T Awan, MD
Matthew S Davids, MD, MMSc
Stephen J Schuster, MD
William G Wierda, MD, PhD
Jennifer Woyach, MD

Moderator

Neil Love, MD

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Moderator

Neil Love, MD
Research To Practice
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Dr Awan — Disclosures

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Contracted Research	Pharmacyclics LLC, an AbbVie Company

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Dr Davids — Disclosures

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Contracted Research (Investigator on the Grant)	Novartis and Ascentage Pharma (grants manager to Dr Davids: Roberto Avalos, DFCI)
Nonrelevant Financial Relationship	German CLL Study Group (CLL17 safety monitoring board chair), UpToDate (authorship royalties)

Dr Schuster — Disclosures

Advisory Committee	Caribou Biosciences Inc, Genentech, a member of the Roche Group, Nordic Nanovector, Novartis, viTToria Biotherapeutics Inc
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Data and Safety Monitoring Board/Committee	Fate Therapeutics
Inventor on Patent	“Combination therapies of chimeric antigen receptors and PD-1 inhibitors,” Owned by Penn and licensed by Novartis

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Dr Wierda — Disclosures

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Nonrelevant Financial Relationship	National Comprehensive Cancer Network (Chair, CLL)

Dr Woyach — Disclosures

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Beyond the Guidelines: Clinical Investigator Perspectives on the Management of Multiple Myeloma (Part 4 of a 4-Part Series)

A CME Friday Satellite Symposium and Virtual Event Preceding the 65th ASH Annual Meeting

Friday, December 8, 2023

7:00 PM – 9:00 PM PT (10:00 PM – 12:00 AM ET)

Faculty

Amrita Krishnan, MD
Sagar Lonial, MD
Robert Z Orlowski, MD, PhD
Noopur Raje, MD
Paul G Richardson, MD

Moderator

Neil Love, MD

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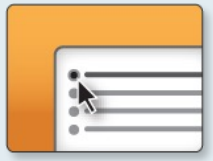

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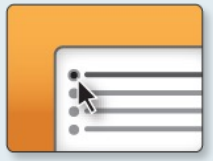

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About the Enduring Program

- The live meeting is being video and audio recorded.
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Moderator

Neil Love, MD

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Agenda

Module 1: Front-Line Treatment for Chronic Lymphocytic Leukemia (CLL) — Dr Wierda

Module 2: Novel Strategies Combining Bruton Tyrosine Kinase (BTK) and Bcl-2 Inhibitors in the Treatment of CLL — Dr Davids

Module 3: Optimal Management of Adverse Events with BTK and Bcl-2 Inhibitors; Considerations for Special Patient Populations — Dr Awan

Module 4: Selection and Sequencing of Therapies for Relapsed/Refractory CLL — Dr Woyach

Module 5: Promising Investigational Agents and Strategies — Dr Schuster

CLL Survey Respondents

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John Byrd, MD

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Nitin Jain, MD

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FDA Investigating 'Serious Risk' of Secondary Cancer After CAR-T Therapy

Press Release: November 29, 2023

“The FDA has launched an investigation into what it called a ‘serious risk’ of T-cell malignancies in patients treated with autologous chimeric antigen receptor (CAR) T-cell therapies targeting B-cell maturation antigen (BCMA) or CD19.

The agency has received multiple reports of T-cell malignancies, including CAR-positive lymphomas, from clinical trials and postmarketing adverse event data sources, according to a statement posted on the FDA website. Serious outcomes of these secondary malignancies have included hospitalization and death. The notice and investigation pertain to all currently approved BCMA- and CD19-targeted CAR T-cell products.

‘Although the overall benefits of these products continue to outweigh their potential risks for their approved uses, FDA is investigating the identified risk of T-cell malignancy with serious outcomes, including hospitalizations and death, and is evaluating the need for regulatory action,’ agency officials said in the statement. ‘As with all gene therapy products with integrating vectors (lentiviral or retroviral vectors), the potential risk of developing secondary malignancies is labeled as a class warning in the US prescribing information for approved BCMA-directed and CD19-directed genetically modified autologous T-cell immunotherapies.’”

https://www.medpagetoday.com/hematologyoncology/hematology/107569

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Agenda

Module 1: Front-Line Treatment for Chronic Lymphocytic Leukemia (CLL) — Dr Wierda

Module 2: Novel Strategies Combining Bruton Tyrosine Kinase (BTK) and Bcl-2 Inhibitors in the Treatment of CLL — Dr Davids

Module 3: Optimal Management of Adverse Events with BTK and Bcl-2 Inhibitors; Considerations for Special Patient Populations — Dr Awan

Module 4: Selection and Sequencing of Therapies for Relapsed/Refractory CLL — Dr Woyach

Module 5: Promising Investigational Agents and Strategies — Dr Schuster

Regulatory and reimbursement issues aside, what would be your preferred initial regimen for a 60-year-old patient with IGHV-mutated CLL without del(17p) or TP53 mutation who requires treatment?

Survey of 21 US-based clinical investigators November 2023

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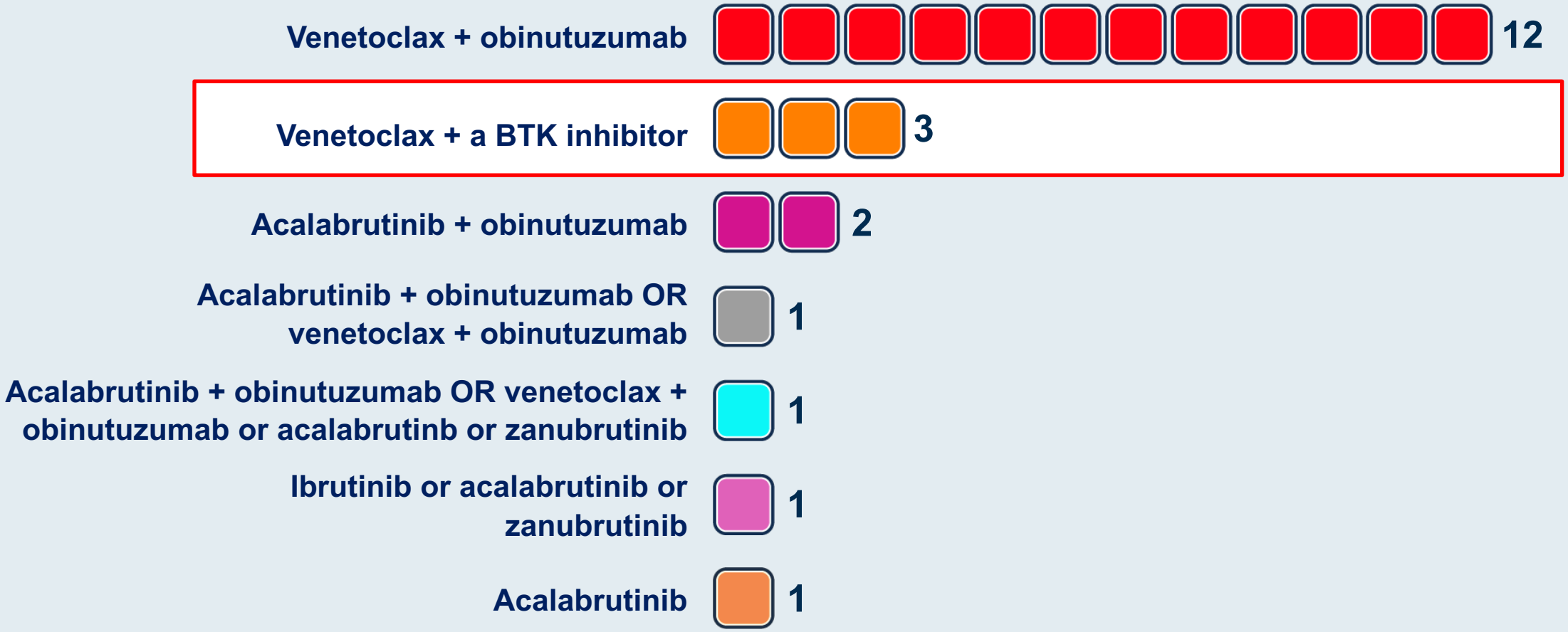
Regulatory and reimbursement issues aside, what would be your preferred initial regimen for a 60-year-old patient with IGHV-unmutated CLL without del(17p) or TP53 mutation who requires treatment?



Survey of 21 US-based clinical investigators November 2023

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Regulatory and reimbursement issues aside, what would be your preferred initial regimen for a 60-year-old patient with IGHV-mutated CLL with del(17p) who requires treatment?

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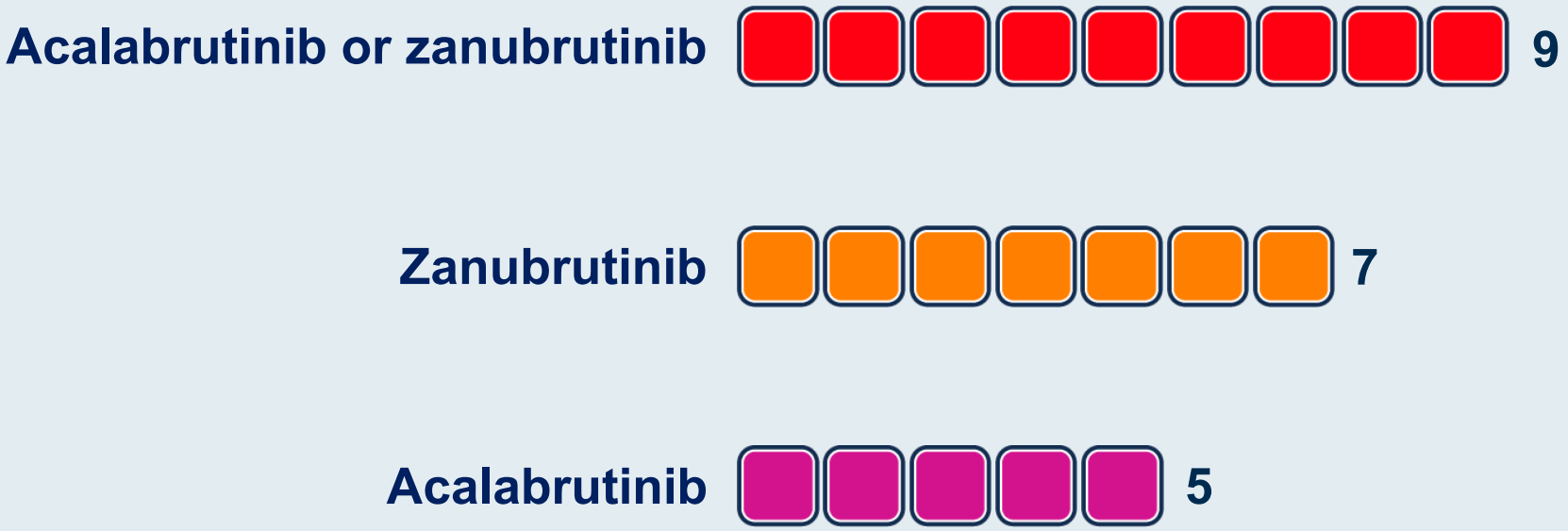
Regulatory and reimbursement issues aside, when you are going to administer a BTK inhibitor as initial treatment for CLL, which do you generally prefer?



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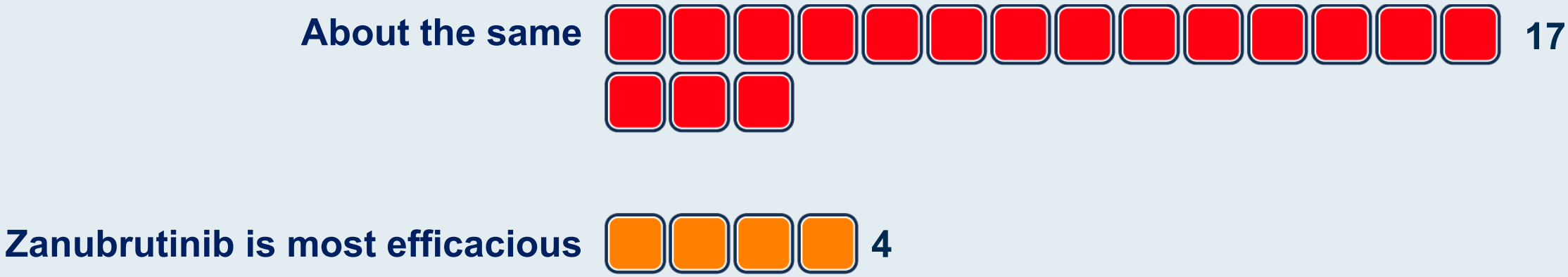
Based on current clinical trial data and your personal experience, how would you compare the global efficacy of ibrutinib, acalabrutinib and zanubrutinib for patients with CLL?



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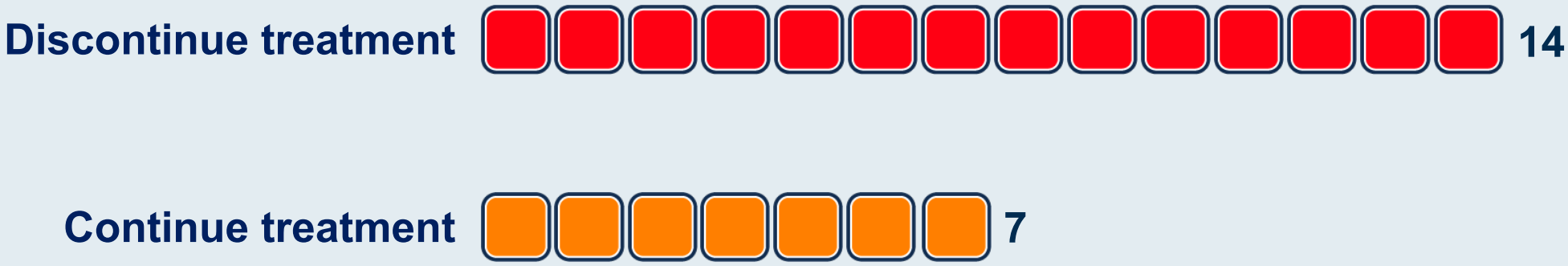
What would be your most likely approach for a patient with newly diagnosed CLL to whom you decided to administer up-front venetoclax/obinutuzumab and who had detectable MRD (minimal residual disease) after completing 1 year of treatment?



Survey of 21 US-based clinical investigators November 2023

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Selection of first-line treatment for patients with CLL requiring active therapy; sequencing of BTK inhibitors and venetoclax/obinutuzumab

Professor Constantine Tam, MBBS, MD

Jan A Burger, MD, PhD

Choice of first-line BTK inhibitor

Shuo Ma, MD, PhD

Professor Constantine Tam, MBBS, MD

Update on Treatments for Patients with CLL

08 DEC 2023

William G. Wierda MD,PhD

Professor of Medicine

Section Head, CLL

Department of Leukemia

U.T. M.D. Anderson Cancer Center

Houston, TX USA

First-line Treatment for CLL

- First treatment is best opportunity to achieve therapeutic objectives – deepest and most durable response
- Strategy to use best treatment option first
- Deeper remission correlated with longer remission duration – uMRD important endpoint for finite-duration therapy
- Progression after finite-duration treatment ≠ resistance; targeted therapy retreatment is option

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

BTK Inhibitor[1-4]

- Easy initiation
- Continuous and indefinite therapy
- Very low TLS risk
- More cardiac risk
- Some favor in del(17p)/ mutated-*TP53*
- Activity in nodal disease

BCL-2 Inhibitor[4,5]

- Risk for TLS requires monitoring for initiation
- Includes CD20 mAb – immunosuppression
- Fixed duration
- Intact renal function important
- Concern for del(17p)/mutated-*TP53*
- Activity in BM and blood

1. Acalabrutinib PI. 2. Ibrutinib PI. 3. Zanubrutinib PI. 4. Awan. Am Soc Clin Oncol Educ Book. 2020;40:1. 5. Venetoclax PI.

Important for Selecting Treatment in CLL

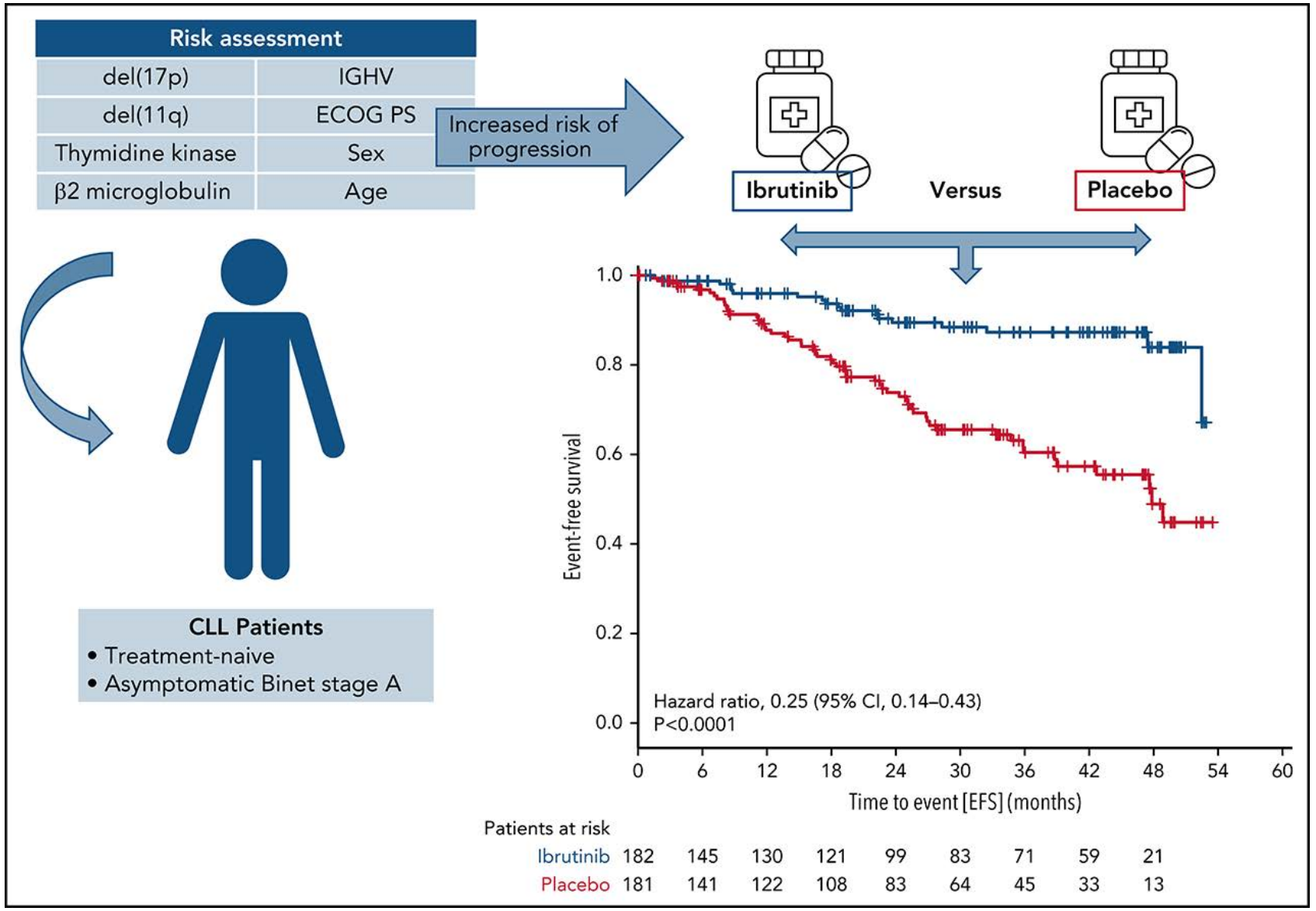
- IGHV mutation status (for first line): **does not change**[1]
- del(17p) status by FISH: **can change**[2]
  - Know % of cells with deletion
- *TP53* mutation status: **can change**[2]

- Age and comorbidities (cardiac and renal)

- *BTK* and *PLCG2* mutation status (in BTKi treated): **can change**[3]

1. Crombie. Am J Hematol. 2017;92:1393. 2. Chauffaille. Hematol Transfus Cell Ther. 2020;42:261. 3. Hallek. Am J Hematol. 2019;94:1266.

CLL12 Trial: IBR vs PBO in TN, Early-stage CLL



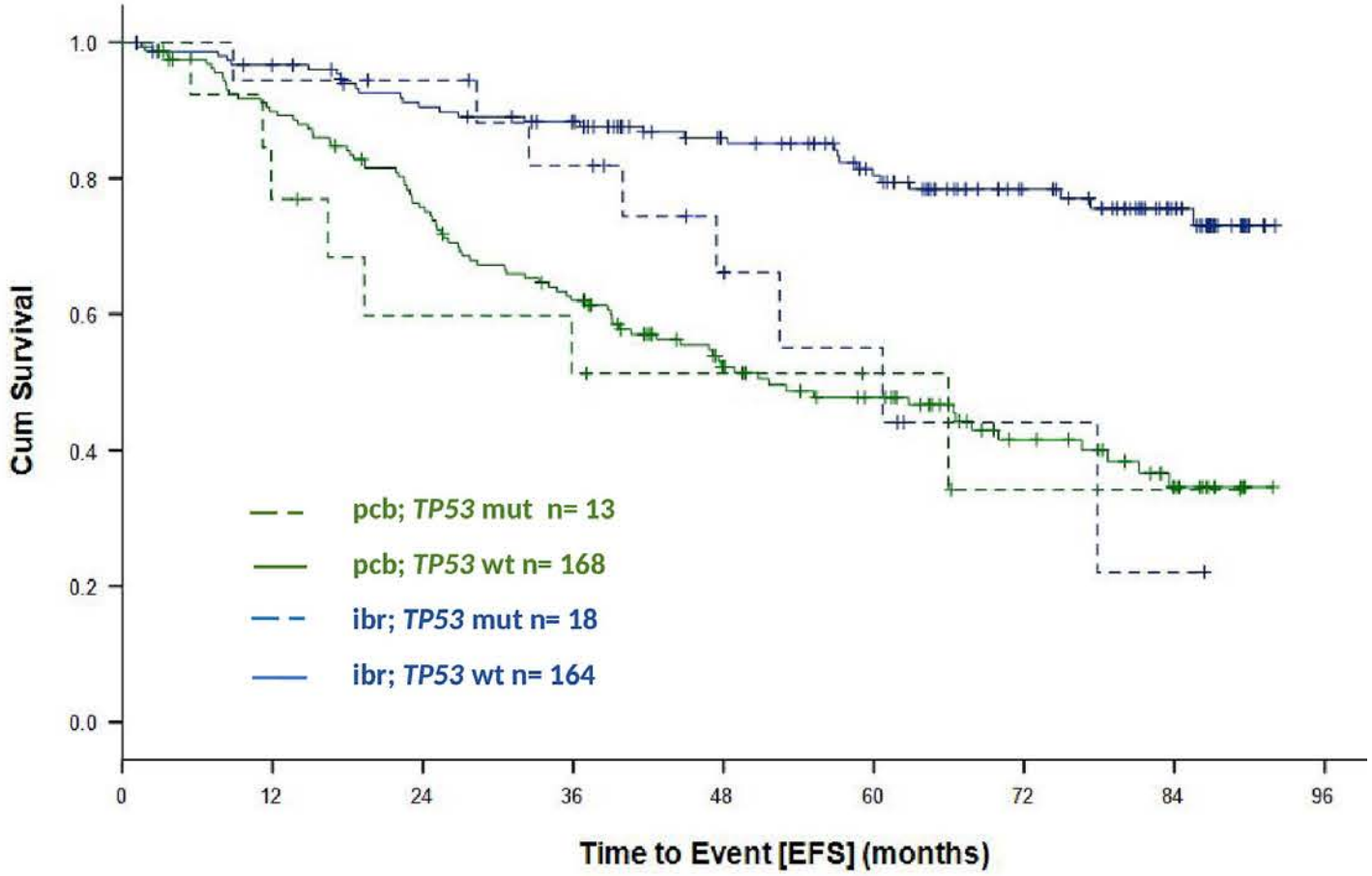
Langerbeins, P., et al. Blood 139(2):177, 2022

GCLLSG CLL12 – Genetic Markers

Table 1: Prevalence of genomic aberrations and gene mutations

Aberrations and mutations [%]	all n=515	ibr n=182	pcb n=181	w+w n=152
U-IGHV	28.8	38.7	38.7	5.3
del (17p)	2.5	3.3	3.9	0.0
del (11q)	7.8	11.5	10.5	0.0
+ (12)	10.9	13.2	15.5	2.6
no abnormalities	18.1	19.8	16.6	17.8
del (13q)	60.8	52.2	53.6	79.6
NOTCH1	7.6	8.2	12.7	0.7
SF3B1	7.4	7.7	11.0	2.6
TP53	6.8	9.9	7.2	2.6
BIRC3	5.2	4.4	7.7	3.3
NFKBIE	4.9	7.7	4.4	2.0
MYD88	3.3	3.3	3.3	3.3
FBXW7	2.9	3.8	3.9	0.7
XPO1	1.9	1.1	4.4	0.0
NRAS/KRAS/BRAF	1.4	1.1	2.8	0.0
EGR2	0.6	1.6	0.0	0.0

Figure 1: Event free survival *TP53*



Riecke, A, et al. ASH 2023, Abstract 199

Ibrutinib - 10-Yr Follow-up Phase 2 Study

Table 1. Ibrutinib Efficacy Outcomes by Subgroup

Median follow-up time (mo)*		113			117		
	N	mPFS (mo)	PFS at mFU	p	mOS (mo)	OS at mFU	p
All evaluable patients	84	85.9	39.5%		NR	58.5%	
No *TP53* alteration	31	NR	56.9%		NR	75.3%	
TP53 alteration	53	67.3	30.3%	0.004	118	54.1%	0.036
IGHV mutated	28	117.2	57.1%		NR	77.0%	
IGHV unmutated	56	80.6	29.7%	0.057	118	52.7%	0.036
Treatment naïve	52	108	48.7%		NR	73.8%	
Prior treatment	32	49	22.4%	0.016	104	41.6%	0.004
TP53 alteration, treatment-naïve	34	81	38.6%		NR	69.7%	
TP53 alteration, prior treatment	19	44.4	19.7%	0.044	63	25.3%	0.002

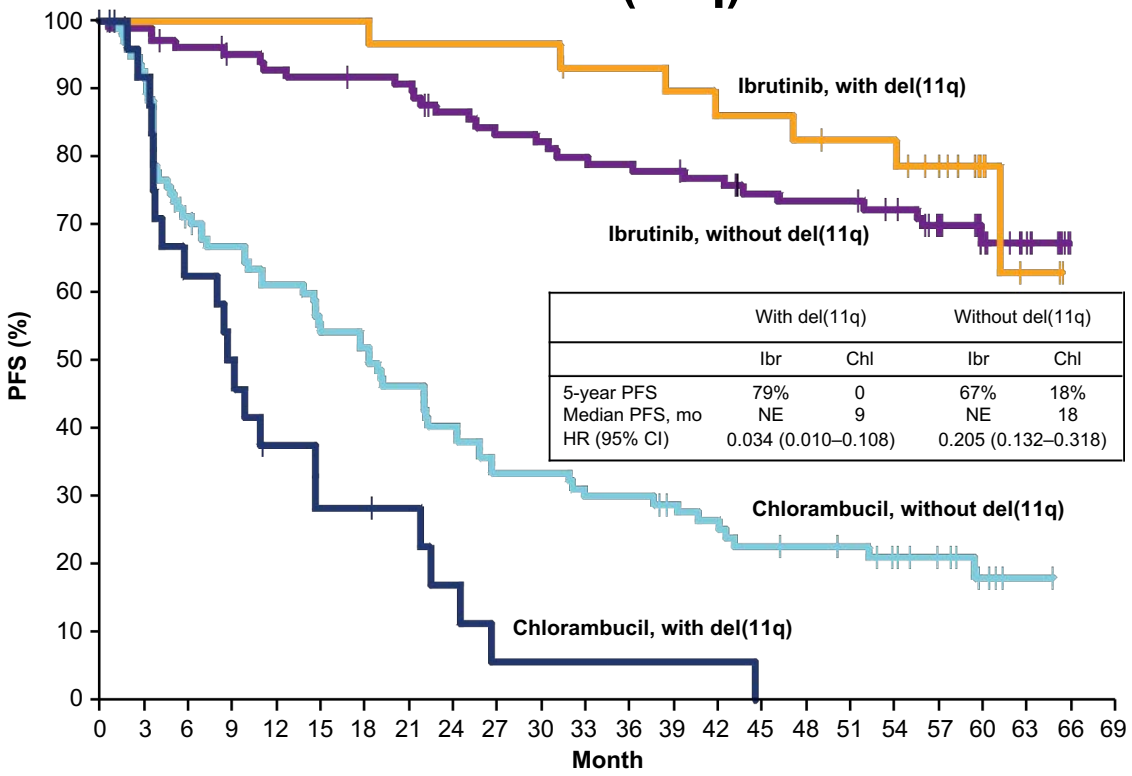
*Reverse Kaplan-Meier estimate

FU - follow-up; m - median; mo – months; NR – not reached; OS - overall survival; PFS - progression-free survival

Itsara, A, et al. ASH 2023, Abstract 201

Ibrutinib Overcomes Poor Prognosis of Del(11q) and Unmutated IGHV in RESONATE-2

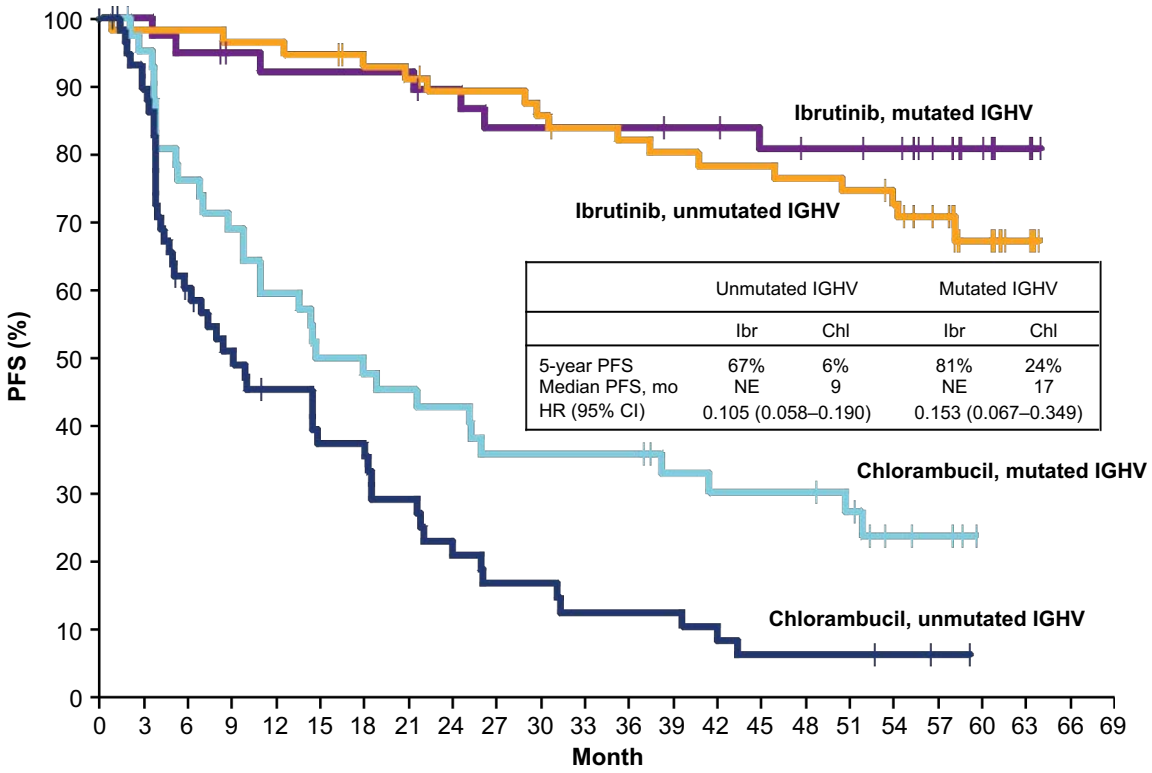
Del(11q)



	With del(11q)		Without del(11q)	
	Ibr	Chl	Ibr	Chl
5-year PFS	79%	0	67%	18%
Median PFS, mo	NE	9	NE	18
HR (95% CI)	0.034 (0.010–0.108)		0.205 (0.132–0.318)	

	Ibrutinib	
	With del(11q)	Without del(11q)
5-year PFS	79%	67%
Median PFS, mo	NE	NE
HR (95% CI)	0.719 (0.315–1.642)	

IGHV



	Unmutated IGHV		Mutated IGHV	
	Ibr	Chl	Ibr	Chl
5-year PFS	67%	6%	81%	24%
Median PFS, mo	NE	9	NE	17
HR (95% CI)	0.105 (0.058–0.190)		0.153 (0.067–0.349)	

	Ibrutinib	
	Unmutated IGHV	Mutated IGHV
5-year PFS	67%	81%
Median PFS, mo	NE	NE
HR (95% CI)	0.632 (0.262–1.525)	

Tedeschi A, et al. Presented at: European Hematology Association (EHA) Congress; June 14, 2019; Amsterdam, NL. Abstract S107.

ELEVATE-TN 6-Yr Follow-up – ACA±OBIN vs. Chl+OBIN

Figure 1. Investigator-assessed progression-free survival. [a]HR based on stratified Cox proportional-hazards model; [b]*P*-value based on stratified log-rank test. A, acalabrutinib; Clb, chlorambucil; O, obinutuzumab.

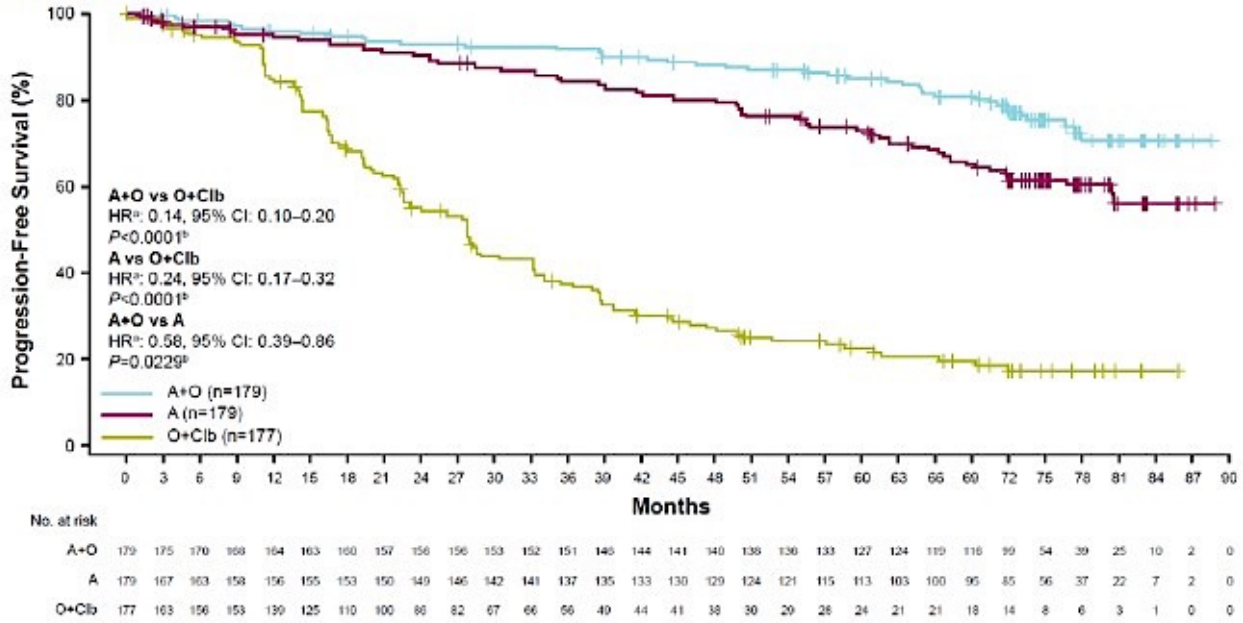
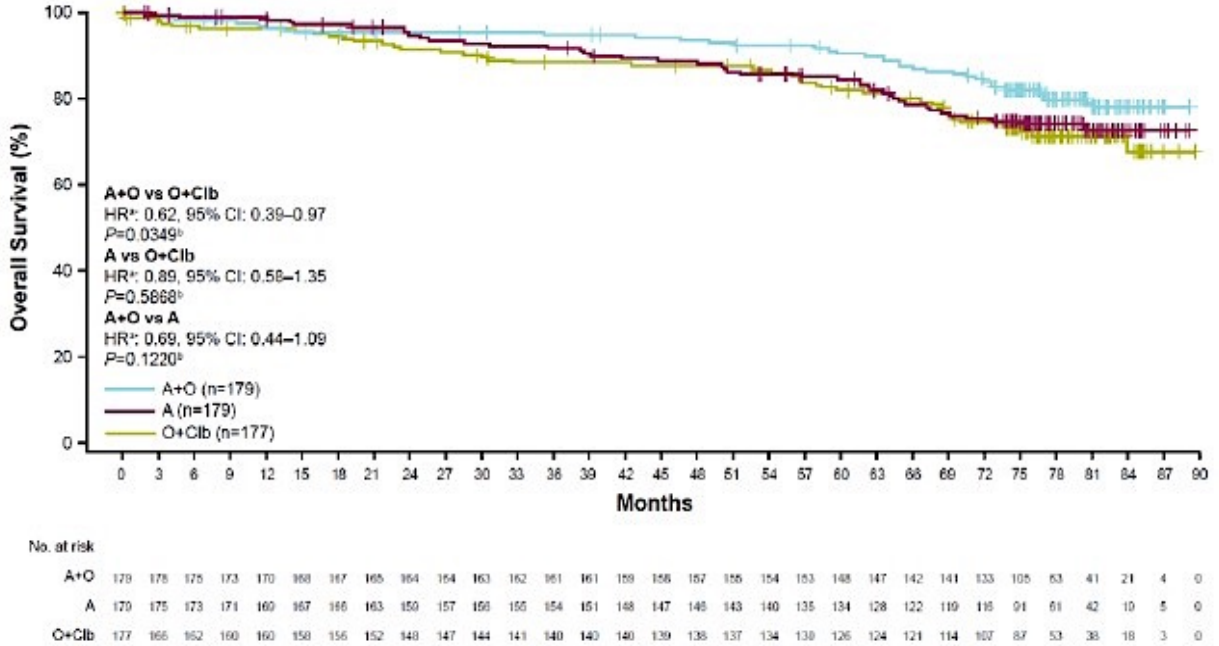


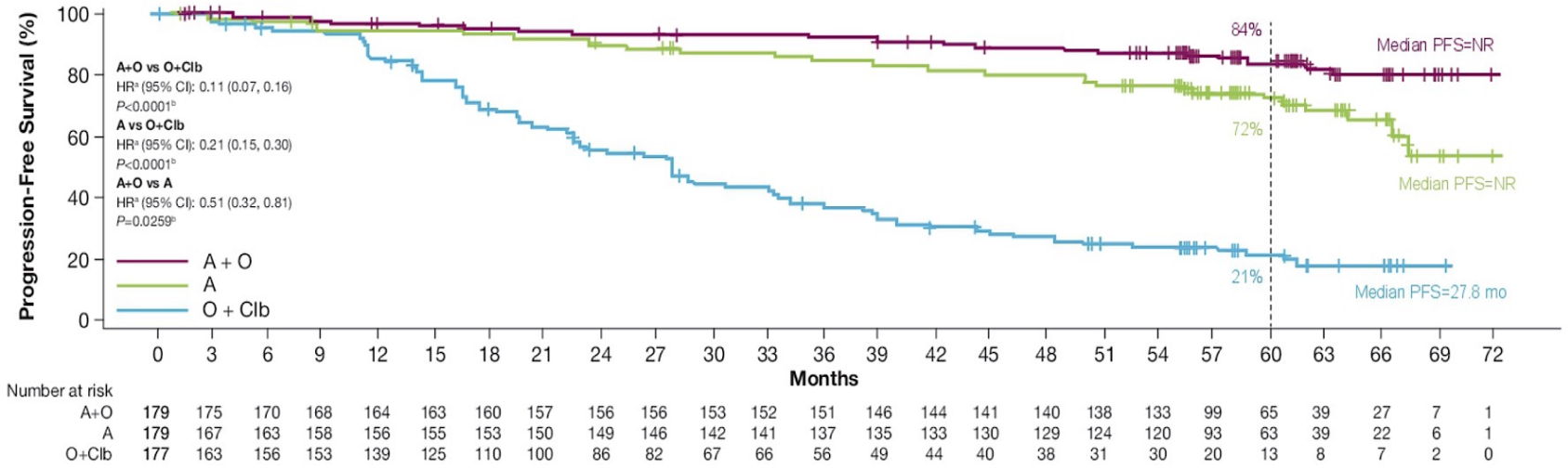
Figure 2. Overall survival. [a]HR based on stratified Cox proportional-hazards model; [b]*P*-value based on stratified log-rank test. A, acalabrutinib; Clb, chlorambucil; O, obinutuzumab.



Sharman, J, et al. ASH 2023, Abstract 636

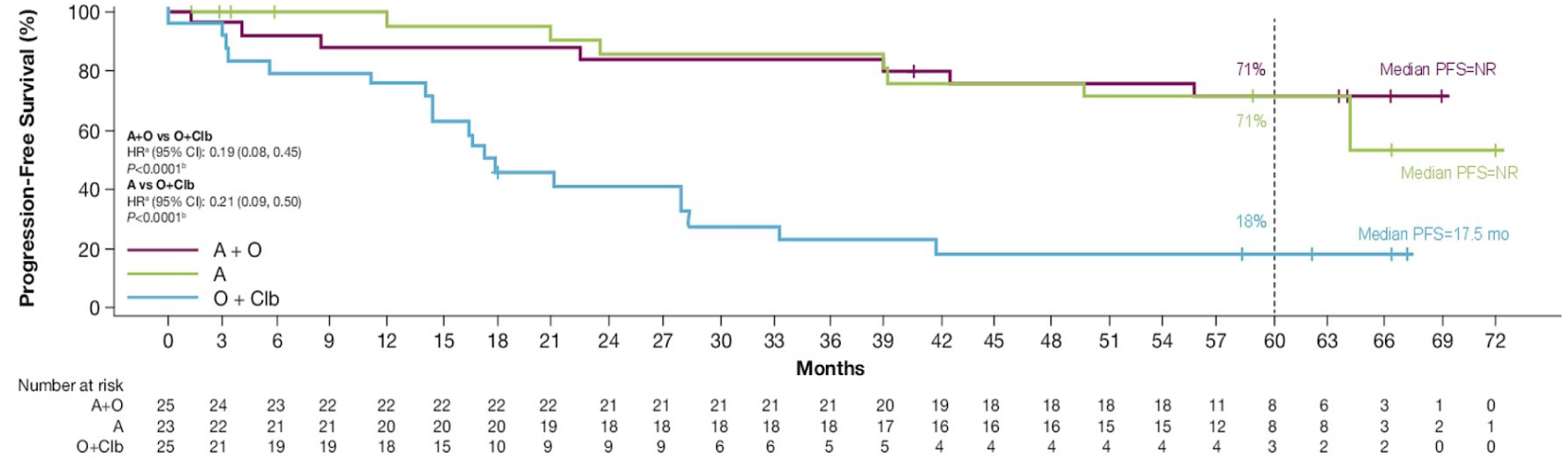
ELEVATE-TN Phase 3 Study: 5-Year Follow-Up PFS

INV-Assessed PFS



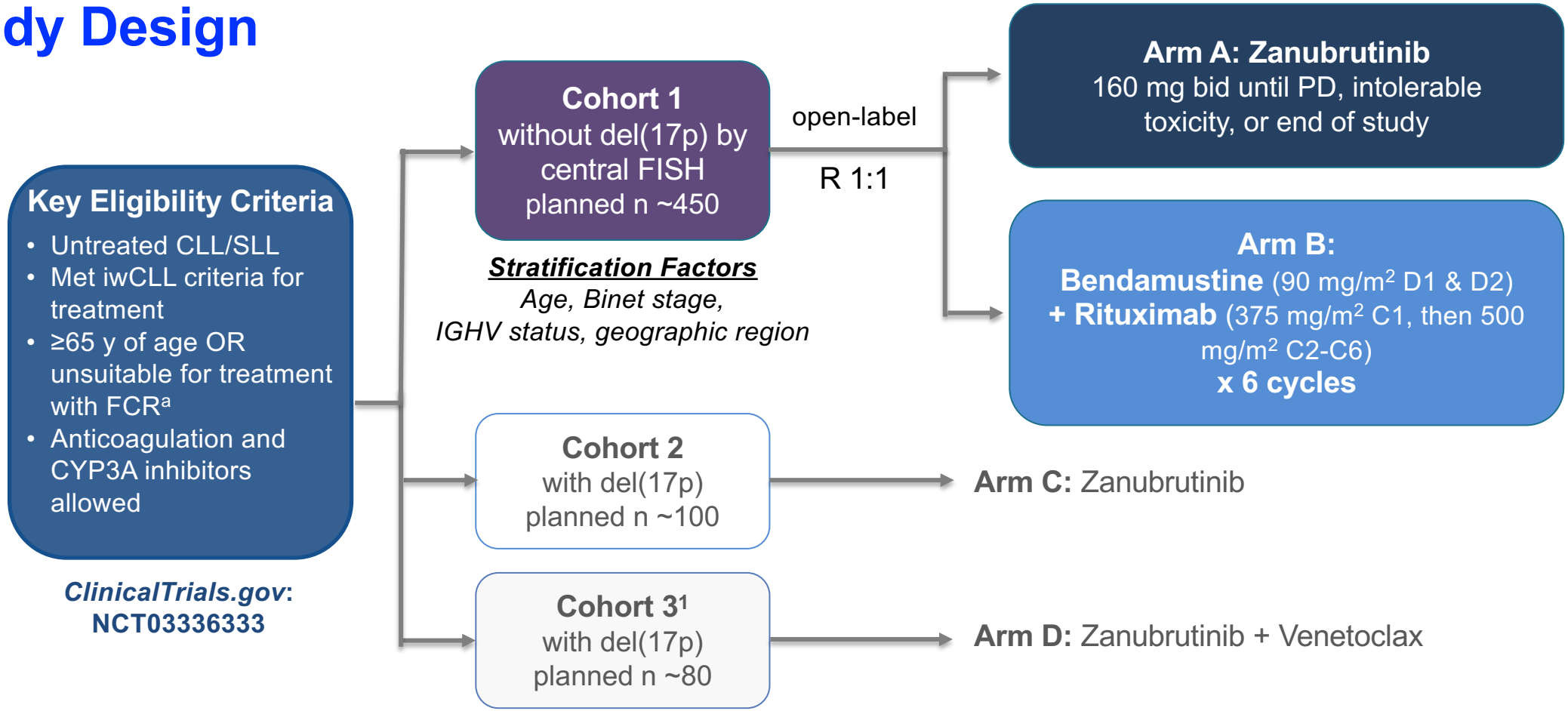
Median follow-up:
58.2 months
(range, 0.0-72.0)

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



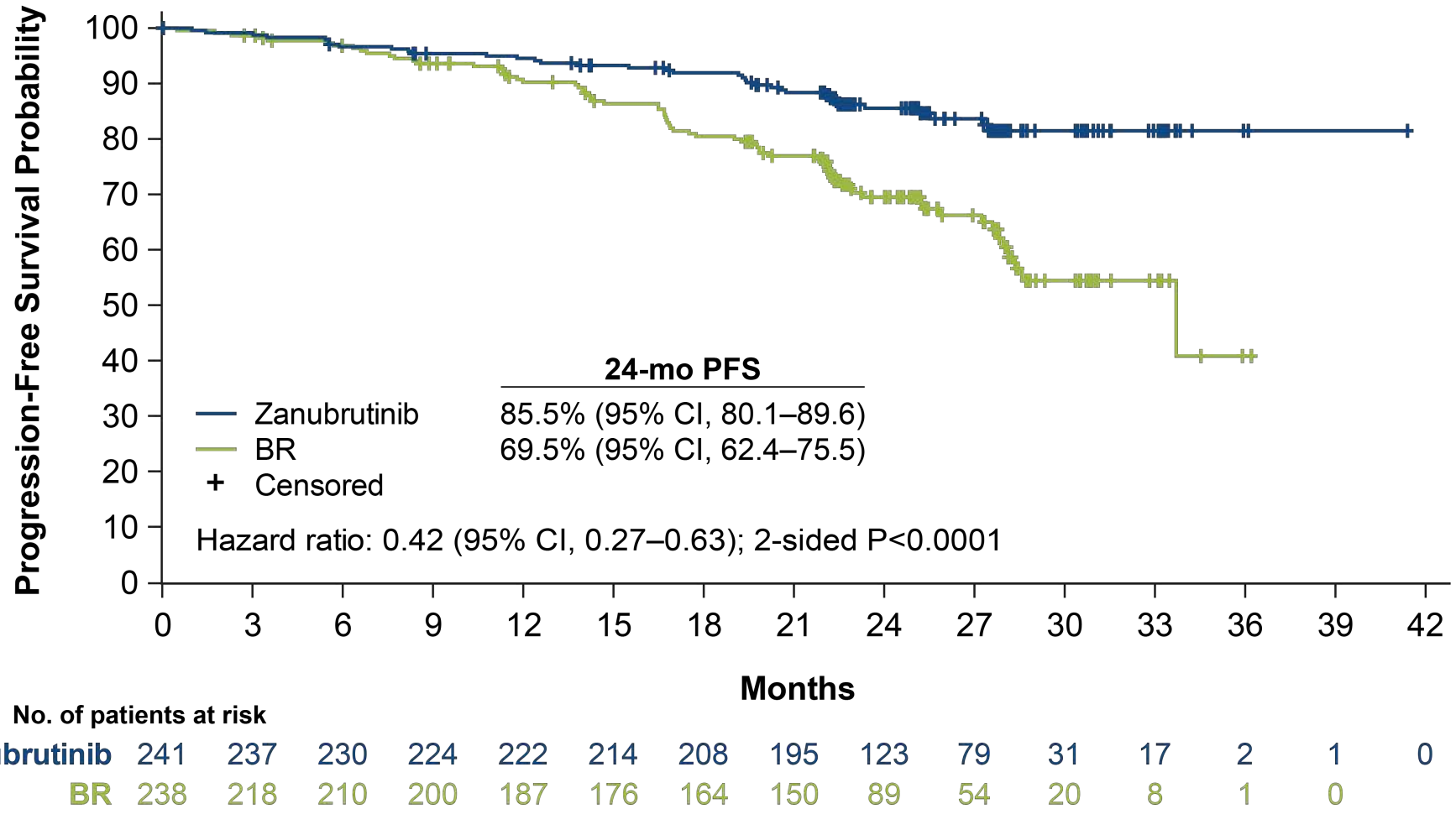
Sharman JP, et al. ASCO 2022. Abstract 7539. Sharman JP, et al. EHA 2022. Abstract P666

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.

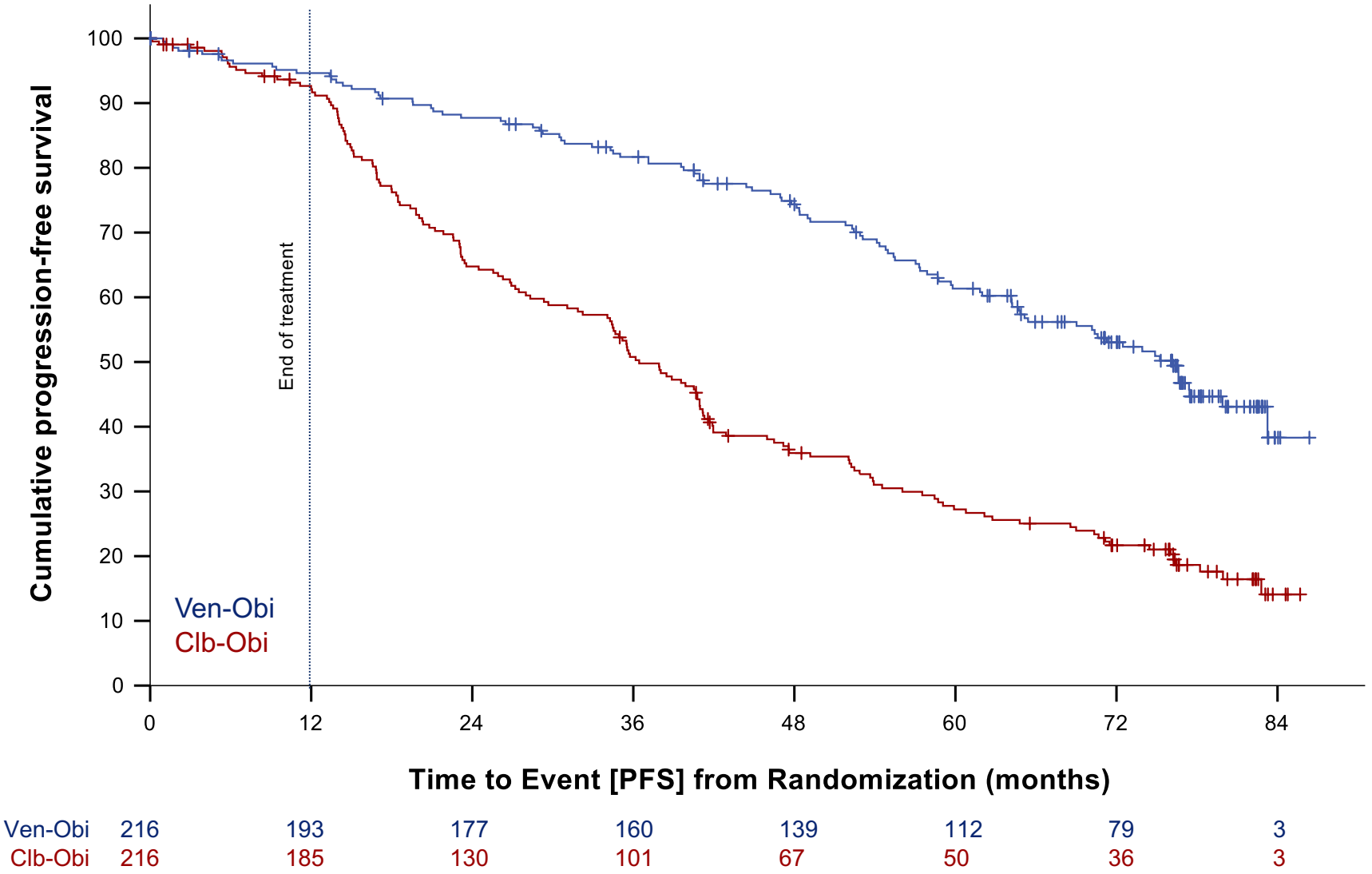
SEQUOIA: Progression-Free Survival Per IRC Assessment



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

CLL14: 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%

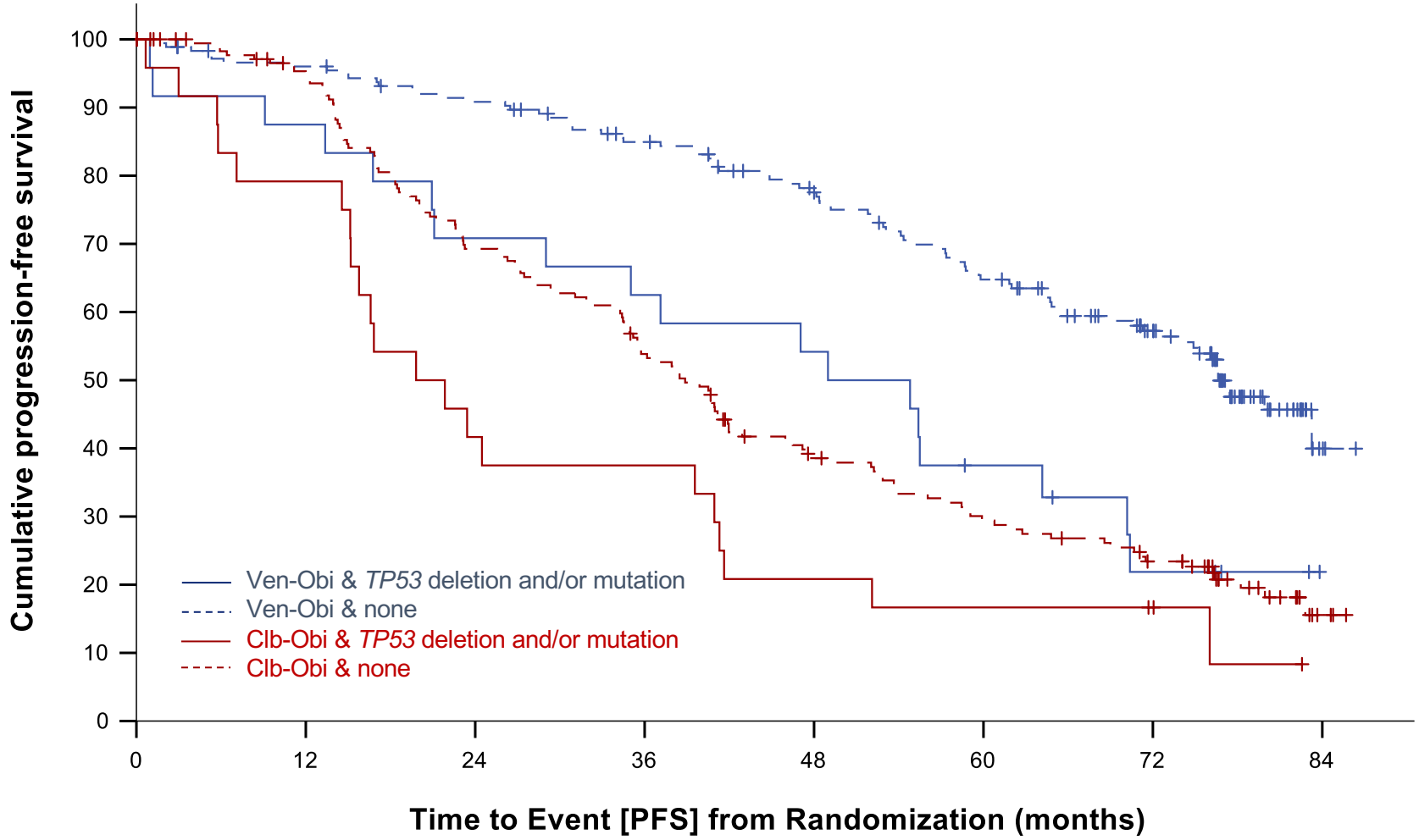
Clb-Obi: 21.7%

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

Al-Sawaf, O., et al., EHA 2023, Abstract S145

CLL14: 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

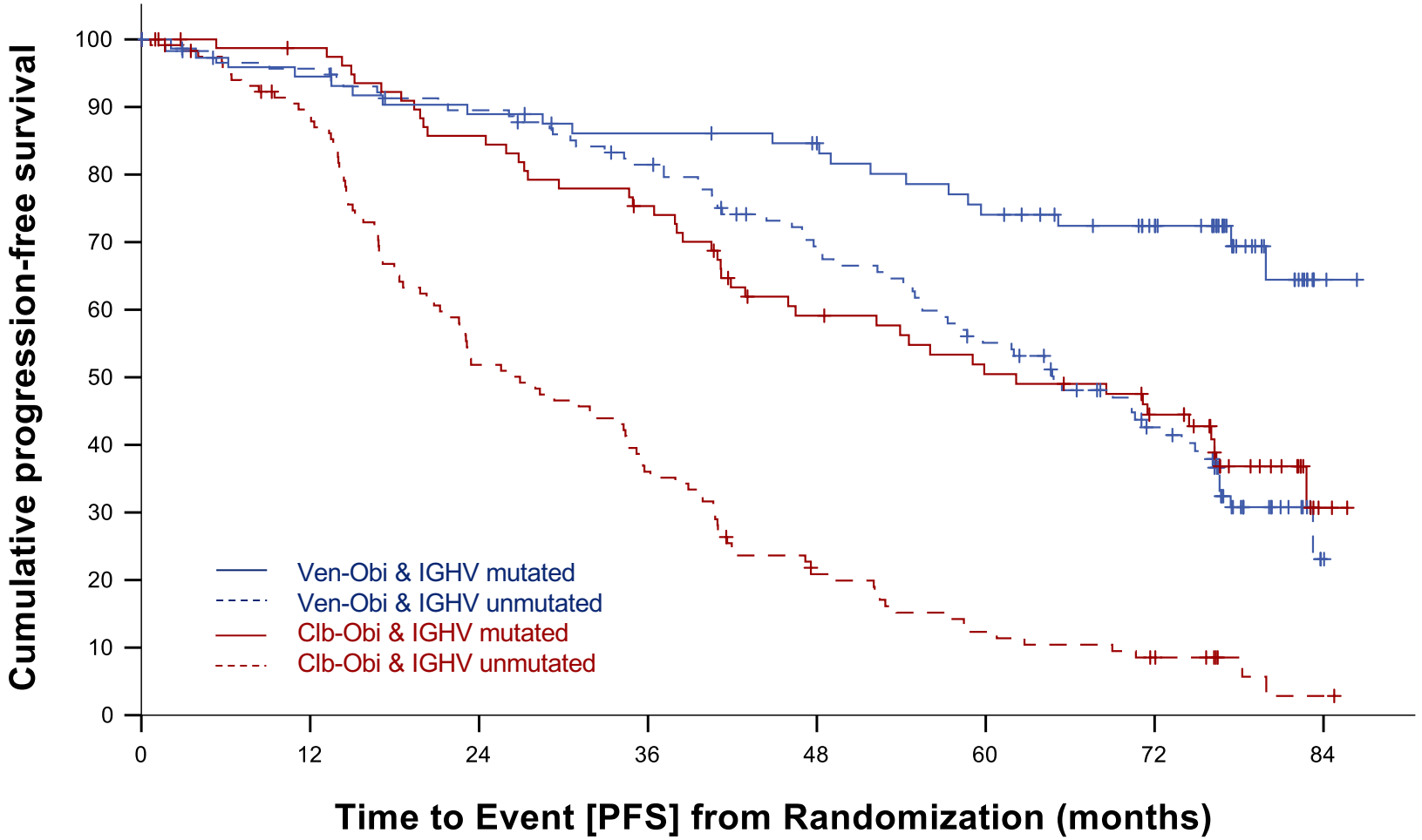
Clb-Obi & *TP53*del/mut: 20.8 m

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

Al-Sawaf, O., et al., EHA 2023, Abstract S145

CLL14: PROGRESSION-FREE SURVIVAL – IGHV STATUS

Median observation time 76.4 months



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

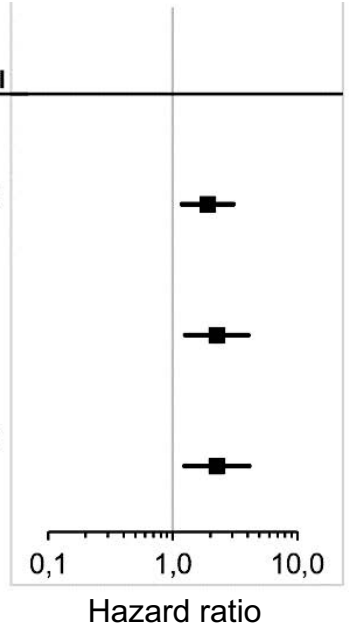
Al-Sawaf, O., et al., EHA 2023, Abstract S145

CLL14: PROGRESSION-FREE SURVIVAL

Multivariable models

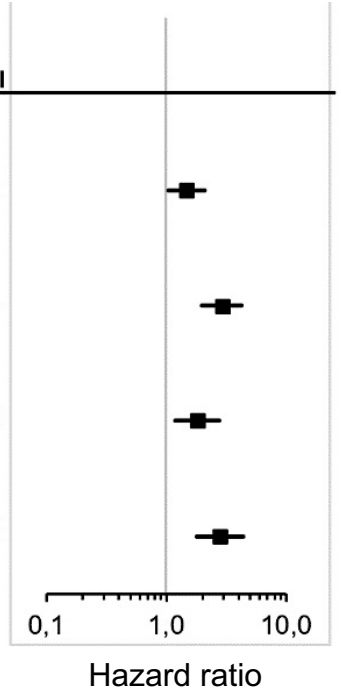
Ven-Obi

COX regression PFS	Univariate comparison	Hazard ratio	95% Wald CI
Lymph node size			
≥ 5 cm	vs. < 5 cm	1.916	1.189-3.088
IGHV mutational status			
unmutated	vs. mutated	2.258	1.268-4.021
***TP53* deletion/mutation**			
Deleted and/or mutated	vs. none	2.262	1.242-4.120



Clb-Obi

COX regression PFS	Univariate comparison	Hazard ratio	95% Wald CI
Absolute lymphocyte count			
≥ 50 x 10^9/L	vs. < 50 x 10^9/L	1.467	1.038-2.073
IGHV mutational status			
unmutated	vs. mutated	2.908	2.002-4.224
Deletion 11q			
del(11q)	vs. no del(11q)	1.823	1.194-2.785
Complex Karyotype			
CKT/HCKT	vs. NCKT	2.811	1.788-4.420

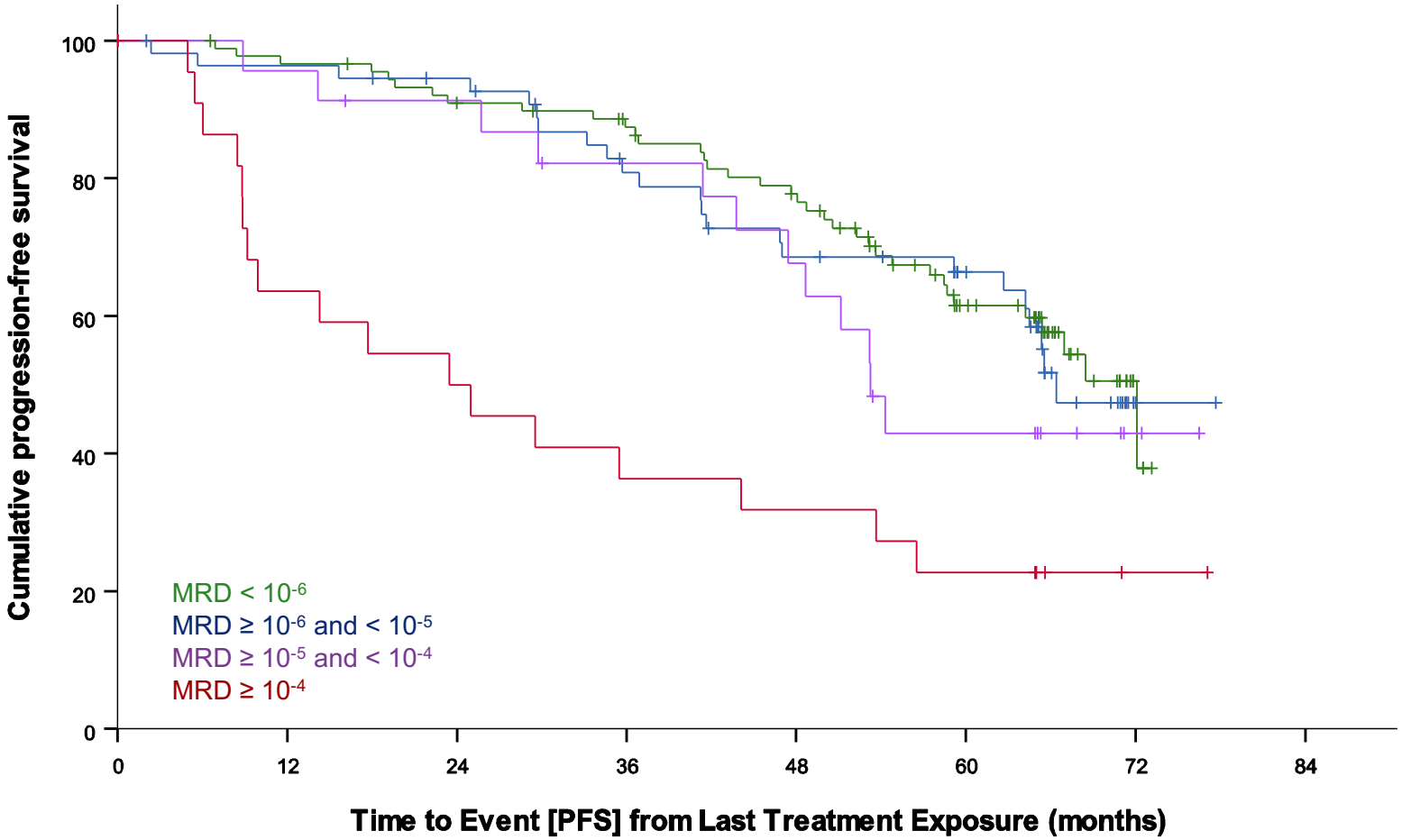


In the context of Ven-Obi, **max. lymph node size ≥ 5 cm, unmutated IGHV and *TP53* deletion/mutation** are independent negative prognostic factors for PFS.

Al-Sawaf, O., et al., EHA 2023, Abstract S145

CLL14: PFS AFTER VEN-OBI ACCORDING TO *MRD STATUS*

End-of-treatment MRD status in peripheral blood, by NGS

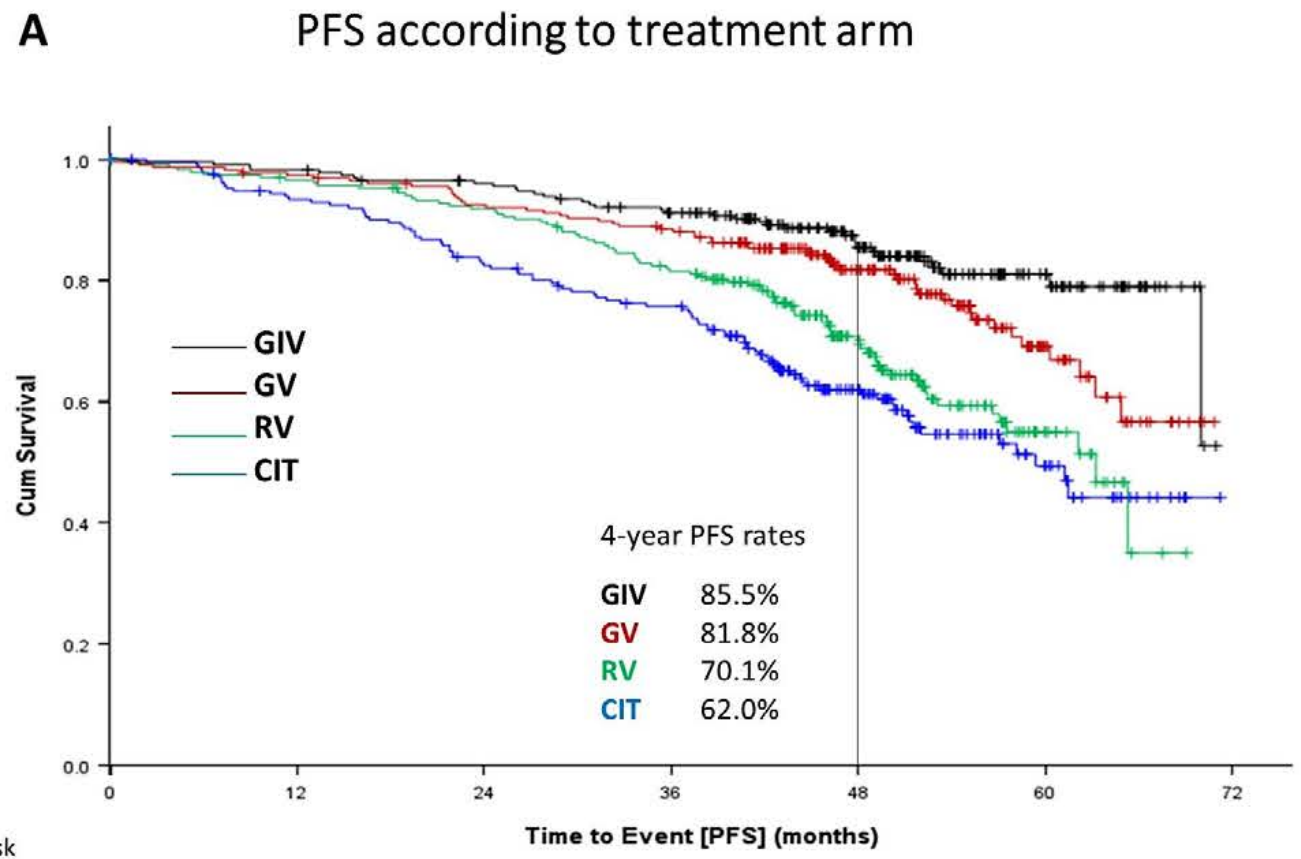


MRD < 10^{-6}	90	86	79	73	63	38	4	0
MRD ≥ 10^{-6} and < 10^{-5}	56	53	50	40	33	26	2	0
MRD ≥ 10^{-5} and < 10^{-4}	23	22	20	17	14	8	2	0
MRD ≥ 10^{-4}	23	14	11	8	7	5	1	0

Depth of remission correlates with **long-term PFS**, indicating the prognostic value of the end-of-treatment MRD status.

Al-Sawaf, O., et al., EHA 2023, Abstract S145

First-line Venetoclax-based Combinations - PFS GAIA/CLL13 4-Yr Follow-up



Patients at risk

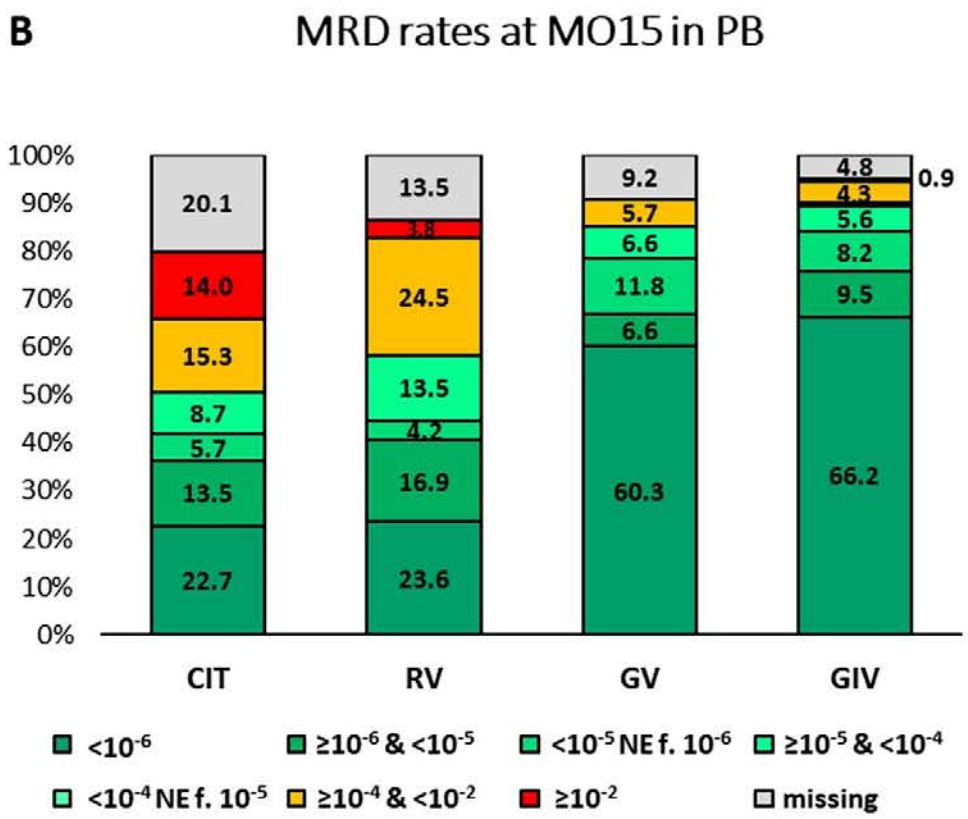
GIV	231	227	218	201	130	44
GV	229	222	209	198	121	32
RV	237	227	214	188	106	21
CIT	229	197	173	156	84	24

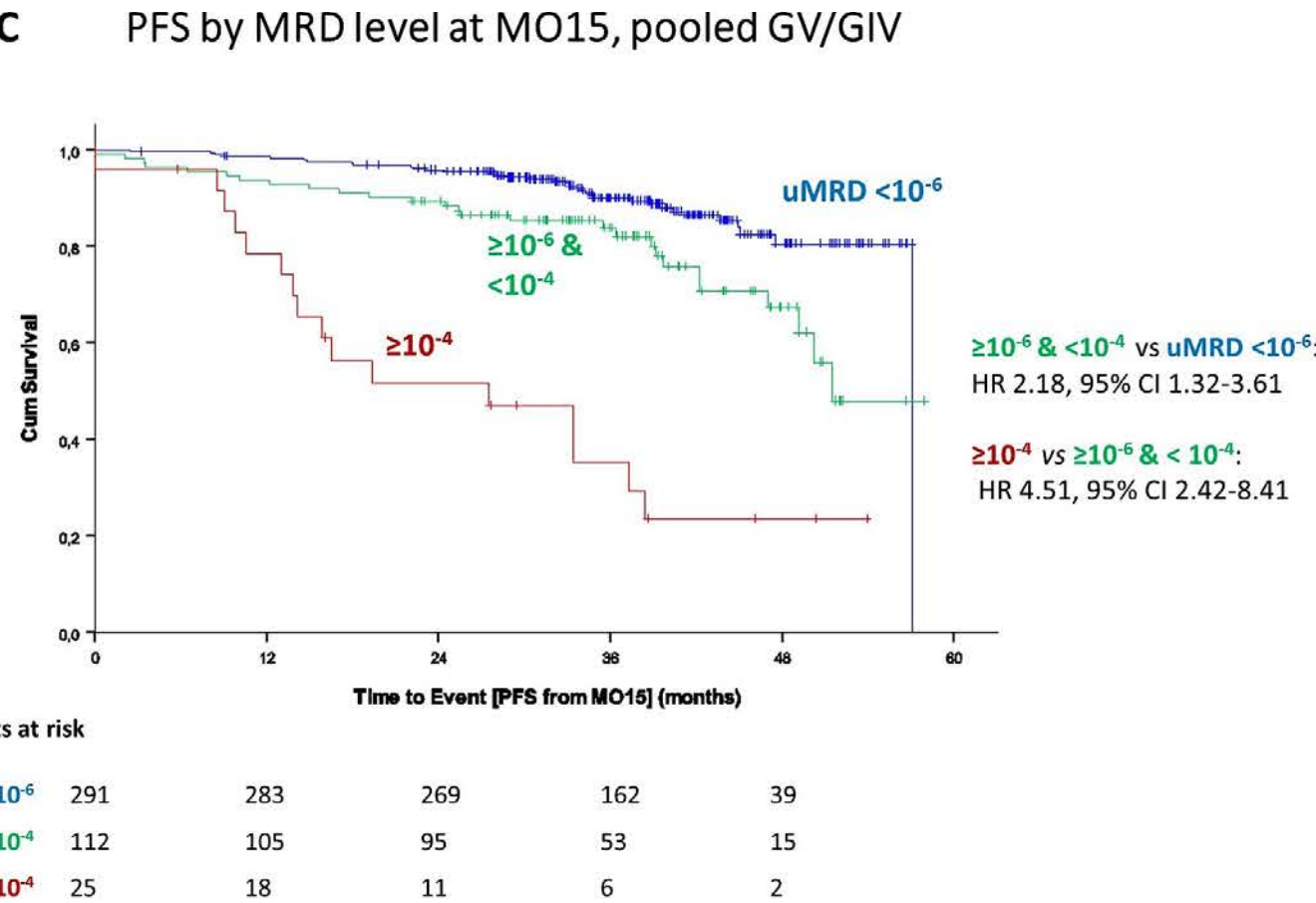
PFS comparisons

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

Furstenau, M, et al. ASH 2023, Abstract 635

First-line Venetoclax-based Combinations - MRD GAIA/CLL13 4-Yr Follow-up





Patients at risk

uMRD <10-6	291	283	269	162	39
≥10-6 & <10-4	112	105	95	53	15
≥10-4	25	18	11	6	2

Furstenau, M, et al. ASH 2023, Abstract 635

GAIA/CLL13: Multivariate Analysis for PFS with RVe/GVe/GIVe

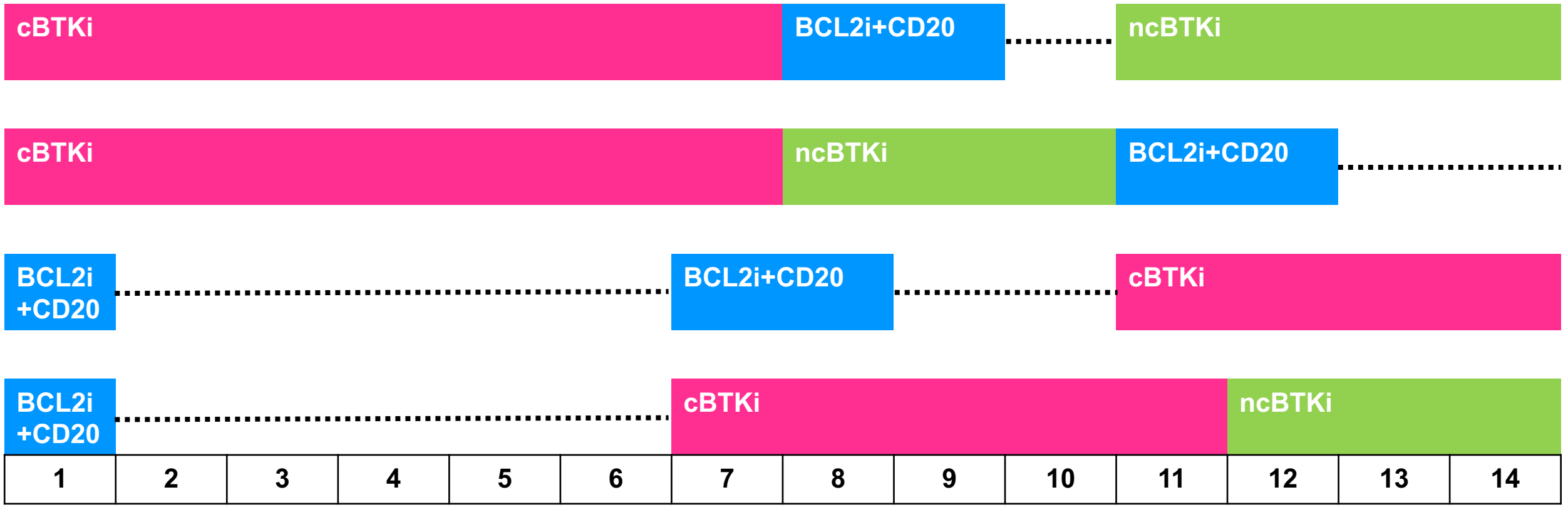
	HR	95%CI	p
U-IGHV	1.85	1.20-2.84	0.005
RAS/RAFmut	1.87	1.14-3.06	0.01
CKT	1.66	1.07-2.56	0.02
β2MG>3.5mg/L	1.56	1.03-2.36	0.04
NOTCH1mut	1.54	1.02-2.33	0.04

U-IGHV, CKT and *NOTCH1* mutations were independent prognostic factors for CIT and RVe/GVe/GIVe.

RAS/RAF mutations were only prognostic with venetoclax therapy.

Tausch et al. ASH 2022, Abstract 345

Conceptual Targeted Agent Sequencing for CLL



Years

Factors affecting timelines:

- Age
- Del(17p)/TP53-m
- IGHV-unmutated
- Del(11q)
- Complex karyotype

Double Exposed *vs.* Double Refractory:

- Exposed ≠ Refractory
- Refractory=progression on treatment

Select Ongoing First-line Phase III Clinical Trials

Trial	Subgroup	N	Status*	MRD	Treatment Arms			
GAIA/CLL13 (NCT02950051)	Fit pts	926	Enrolled	Co-Primary	IbrVenOb	VenOb	VenR	FCR/BR
EA9161 (NCT03701282)	Fit, 18-69 yo	720	Enrolled	Secondary	IbrVenOb	IbrOb		
A041702 (NCT03737981)	≥70 yo	454	Enrolled	Secondary	IbrVenOb	IbrOb		
CRISTALLO (NCT04285567)	Fit pts [no del(17p)]	165	Enrolled	Primary	VenOb			FCR/BR
CLL17 (NCT04608318)	All pts	897	Enrolled	Secondary	IbrVen	VenOb	Ibr	
ACE-CL-311 (NCT03836261)	All pts	780	Enrolling	Secondary	AcaVenOb	AcaVen		FCR/BR
GCLLSG (NCT05197192)	High-risk	650	Enrolling	Secondary	AcaVenOb	VenOb		
MAJIC (NCT05057494)	All	600	Enrolling	Secondary	AcaVen	VenOb		

*Status as of April 2023

Conclusions

- First-line treatment best opportunity to achieve goals of treatment
- No benefit to treating with first-line chemoimmunotherapy for most patients
- Individualize for selection of first-line treatment:
  - Age and comorbidities (cardiac, renal)
  - Del(17p)/*TP53*-m
  - IGHV-unmutated/del(11q)
  - Complex karyotype
- First-line cBTKi-based for del(17p)/*TP53*-m
- Emerging data will provide insights on optimizing finite-duration first-line treatments

Agenda

Module 1: Front-Line Treatment for Chronic Lymphocytic Leukemia (CLL) — Dr Wierda

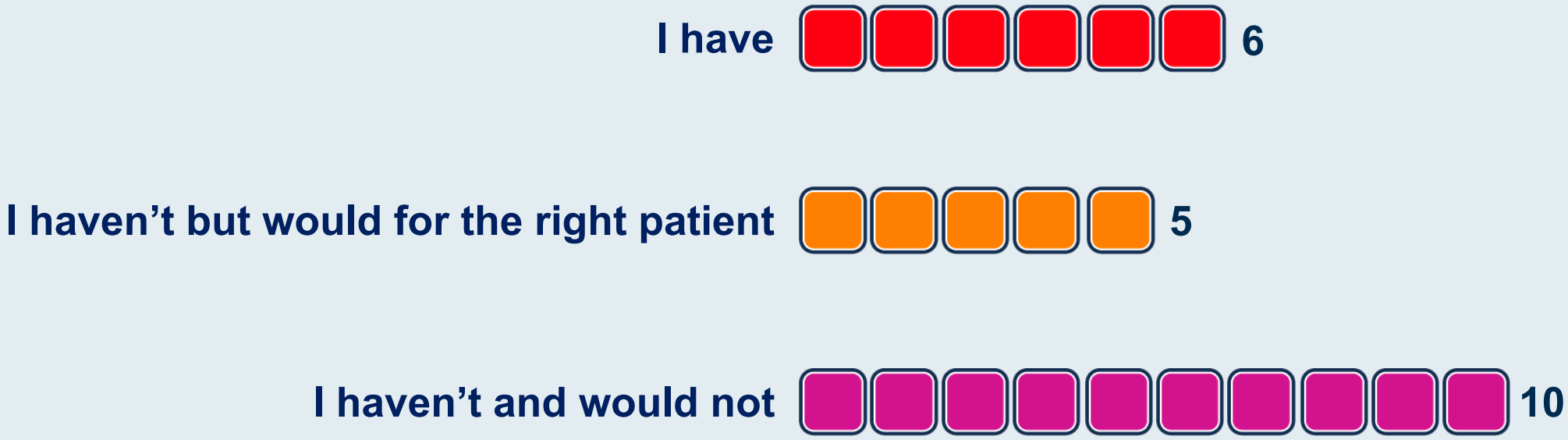
Module 2: Novel Strategies Combining Bruton Tyrosine Kinase (BTK) and Bcl-2 Inhibitors in the Treatment of CLL — Dr Davids

Module 3: Optimal Management of Adverse Events with BTK and Bcl-2 Inhibitors; Considerations for Special Patient Populations — Dr Awan

Module 4: Selection and Sequencing of Therapies for Relapsed/Refractory CLL — Dr Woyach

Module 5: Promising Investigational Agents and Strategies — Dr Schuster

Have you administered or would you administer a BTK inhibitor in combination with venetoclax as first-line treatment for CLL outside of a clinical trial?



Survey of 21 US-based clinical investigators November 2023

RTP RESEARCH TO PRACTICE

Please describe a clinical scenario in which you have administered a BTK inhibitor in combination with venetoclax as first-line treatment for CLL outside of a clinical trial:

Patient age	Treatment	Response	Tolerability
60 years	Ibrutinib + venetoclax	uMRD	Palpitations, switched to acalabrutinib
65 years	Ibrutinib + venetoclax	CR, uMRD	Well tolerated
77 years	Ibrutinib + venetoclax	CR	Some side effects but continued both drugs
65 years	Ibrutinib + venetoclax	CR, uMRD	Besides cytopenia issues, well tolerated
50 years	Ibrutinib + venetoclax	CR, uMRD	Well tolerated
50 years	Ibrutinib + venetoclax	uMRD	Well tolerated, completed w/o dose reduction/interruption

CR = complete response; uMRD = undetectable minimal residual disease

Survey of 21 US-based clinical investigators November 2023

RTP RESEARCH TO PRACTICE

Please describe a clinical scenario in which you would administer a BTK inhibitor in combination with venetoclax as first-line treatment for CLL outside of a clinical trial:

- TP53-mutated CLL in a patient with low tumor burden who wants a time-limited therapy
- Patient unable to take obinutuzumab but a candidate for combination therapy and interested in time-limited treatment
- Patient who insisted on an all-oral, time-limited therapy or had a severe allergic reaction to obinutuzumab and could not receive additional antibody
- Younger (<65) with IGHV-UM, NO del(17p)/TP53-M
- I would consider this for someone who had contraindications to obinutuzumab or needed to avoid infusions and preferred a fixed-duration treatment
- Younger and low-risk CLL
- I would consider for young pts with unmutated IGHV
- Need more data, but would consider for younger patient with high-risk CLL
- High-risk, bulky disease, younger than 70
- I would consider this only for patients who wants a time-limited approach and do not want to receive intravenous therapy.

Survey of 21 US-based clinical investigators November 2023

RTP RESEARCH TO PRACTICE

Effectiveness and advantages of BTK/Bcl-2 combinations over obinutuzumab-containing regimens

Shuo Ma, MD, PhD

Professor Constantine Tam, MBBS, MD

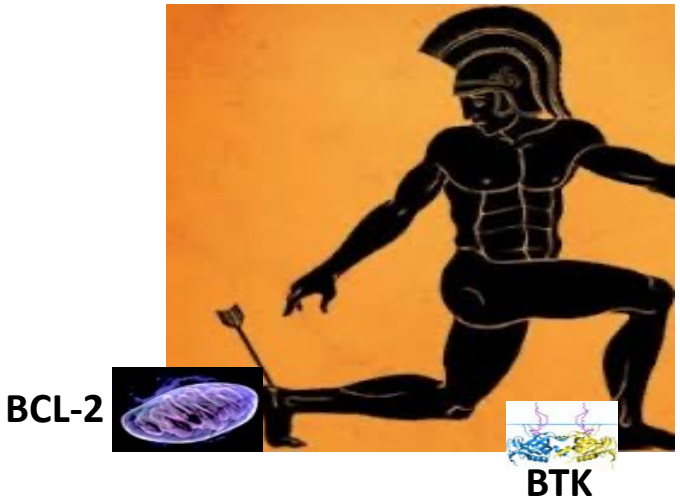
RTP RESEARCH TO PRACTICE

Activity, safety and durability of responses with BTK inhibitors in combination with venetoclax

Jan A Burger, MD, PhD

RTP
RESEARCH
TO PRACTICE

Novel Strategies Combining BTK and Bcl-2 Inhibitors in CLL



Matthew S. Davids, MD, MMSc
Clinical Research Director | Division of Lymphoma Dana-Farber Cancer Institute
Associate Professor of Medicine
Harvard Medical School

December 8, 2023

San Diego, California, USA

Dana-Farber Cancer Institute

Harvard Medical School

Rationale for Combination BTKi/BCL-2i Therapy

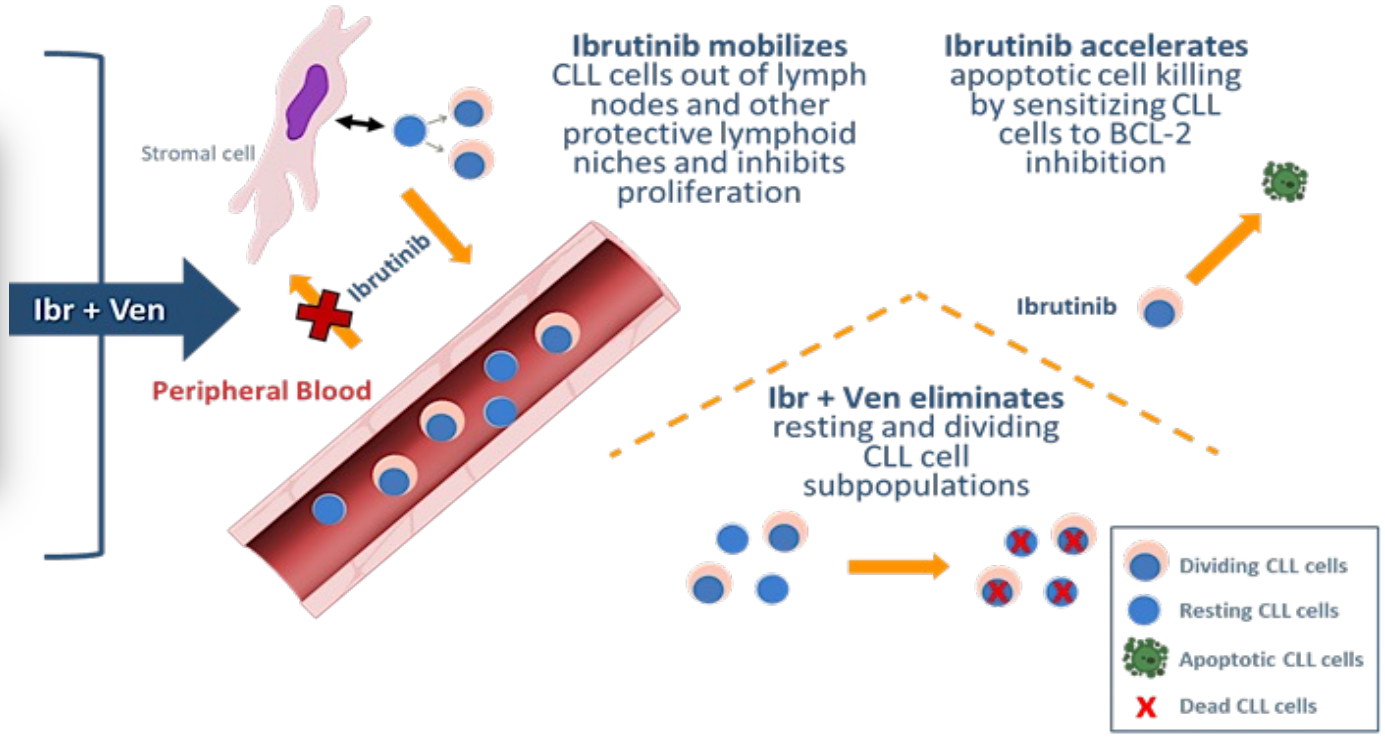
Leukemia (2017), 1–10

www.nature.com/leu

ORIGINAL ARTICLE

Bruton's tyrosine kinase inhibition increases BCL-2 dependence and enhances sensitivity to venetoclax in chronic lymphocytic leukemia

J Deng, E Isik, SM Fernandes, JR Brown, A Letai[1] and MS Davids[1]

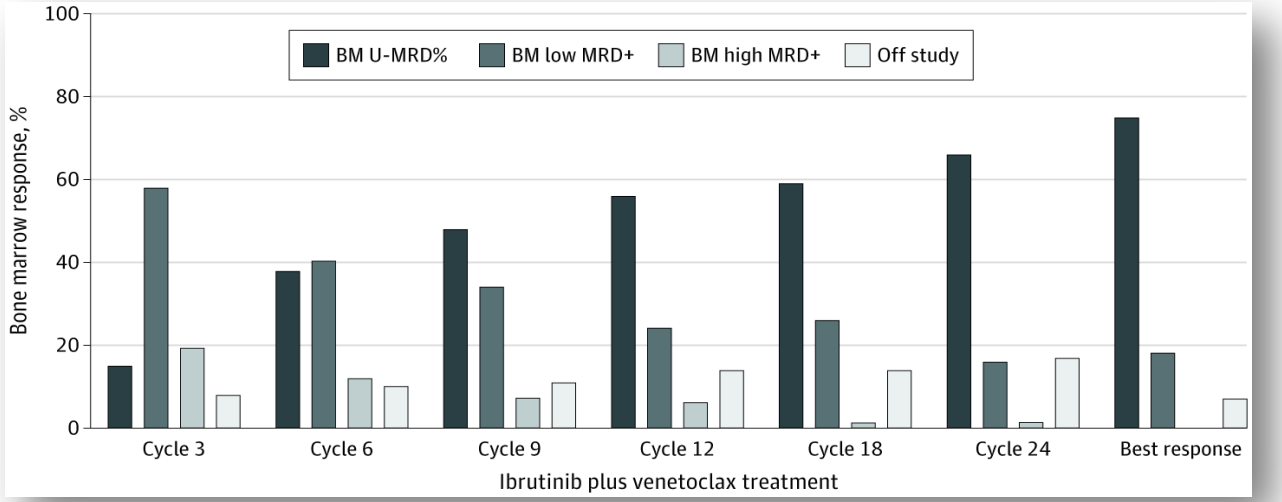


Deng et al., *Leukemia*, 2017

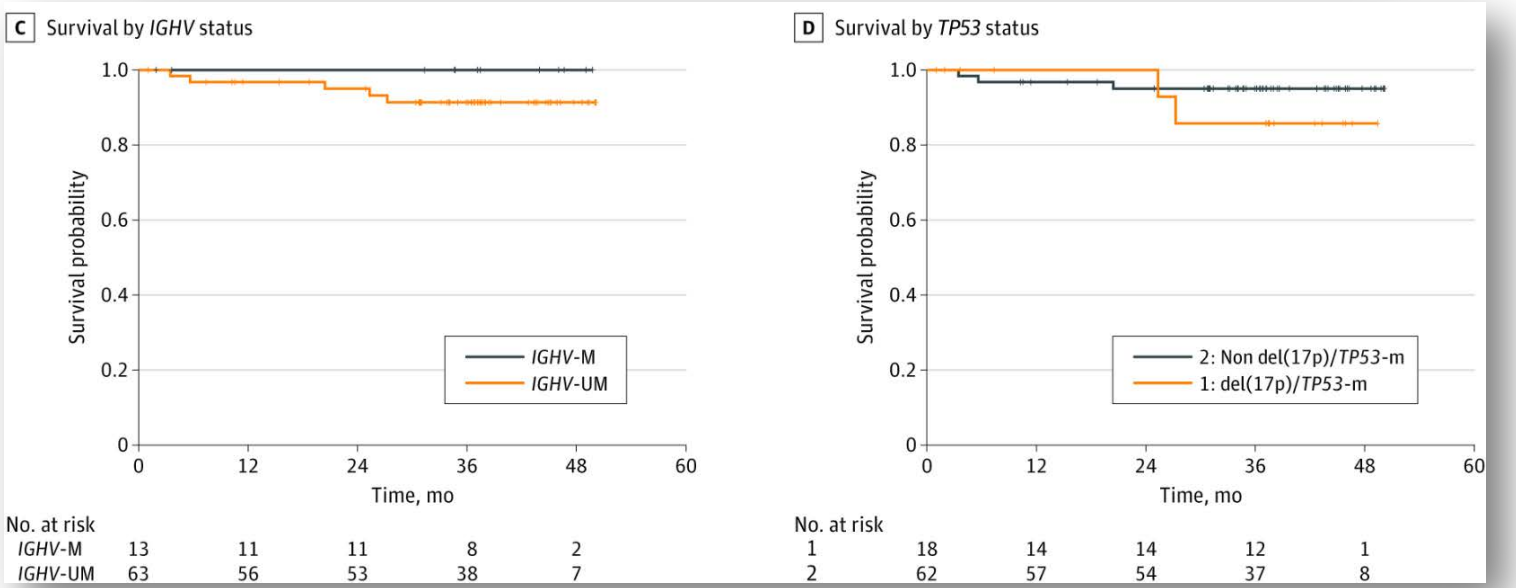
Adapted from: Allan et al EHA, 2021

MD Anderson Ibr/Ven Phase 2 IST for Frontline CLL

Median follow-up (n=80): 38.5 months



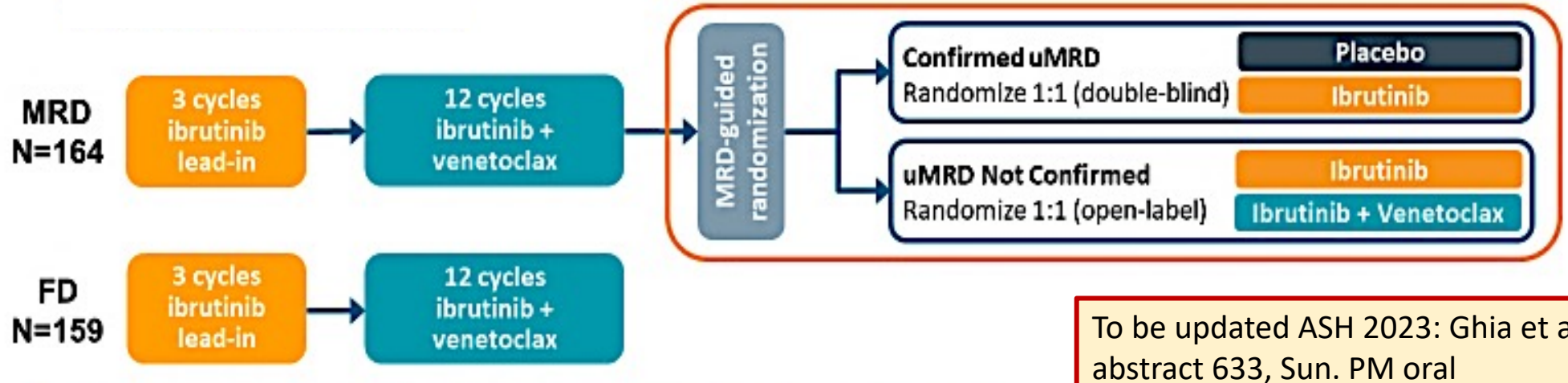
To be updated ASH 2023: Jain et al., abstract 4635, Mon. PM poster



Jain N et al., JAMA Oncol. 2021;7(8):1213-1219

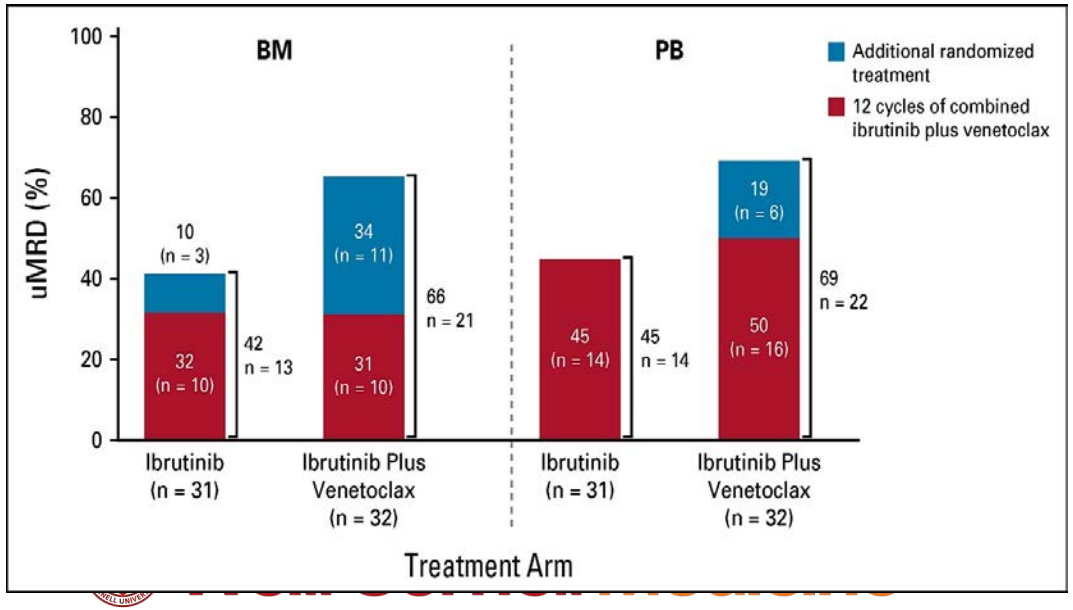
CAPTIVATE: Ibr/Ven in a young, fit population

Median age: 58



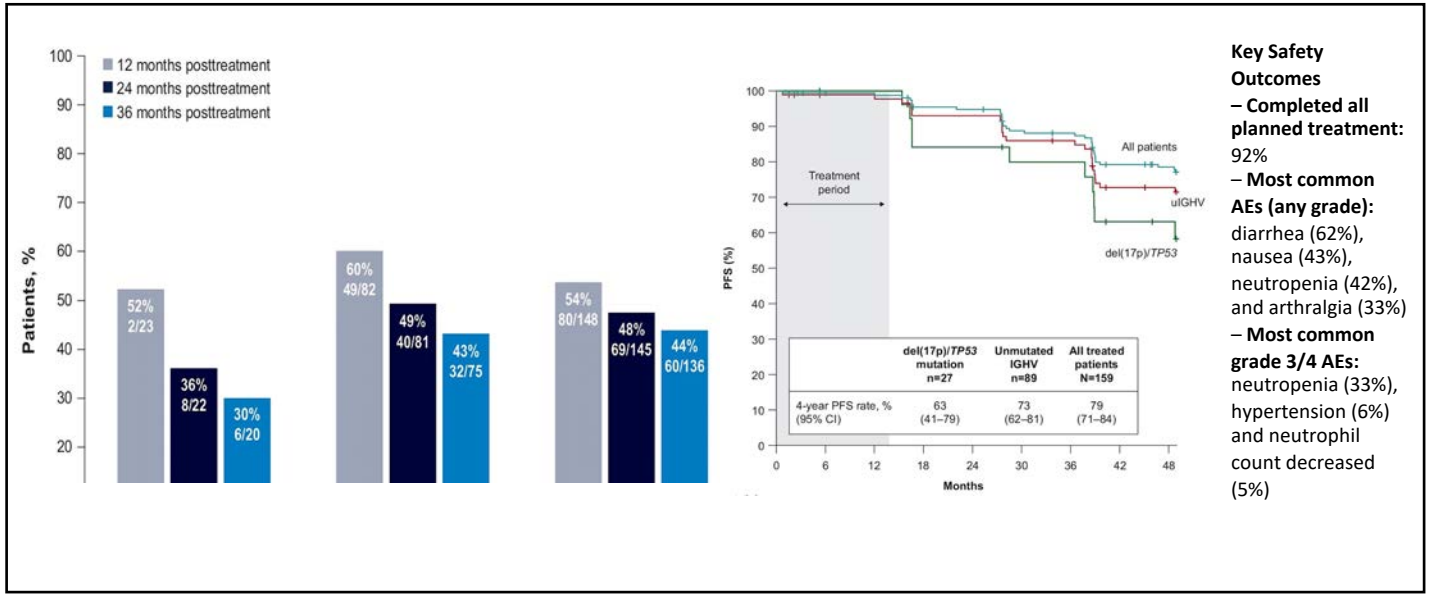
To be updated ASH 2023: Ghia et al., abstract 633, Sun. PM oral

MRD Cohort



Wierda et al. J Clin Oncol, 2021

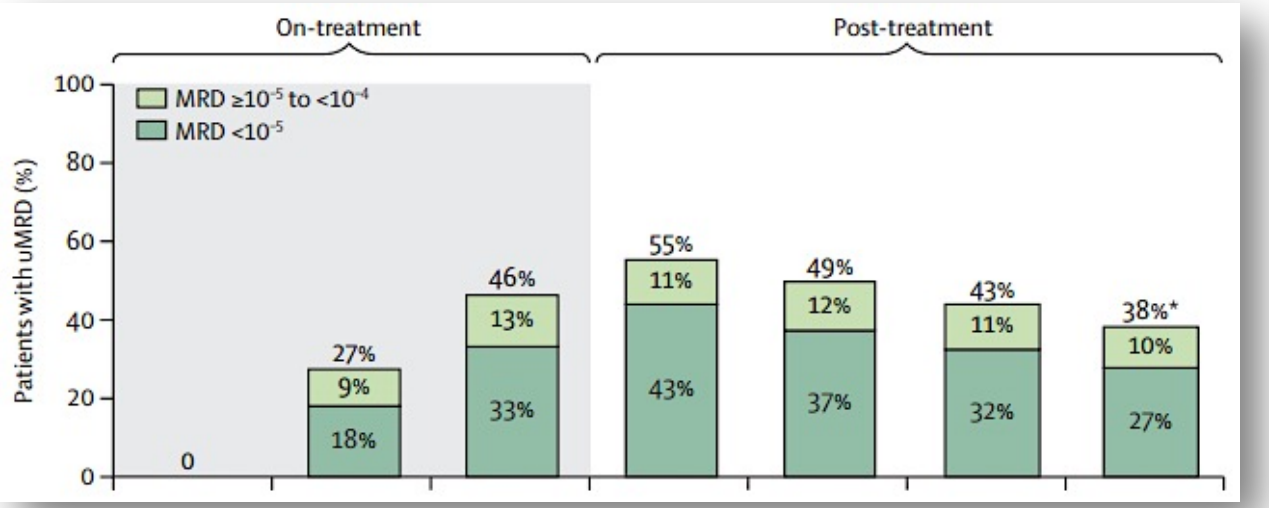
FD Cohort



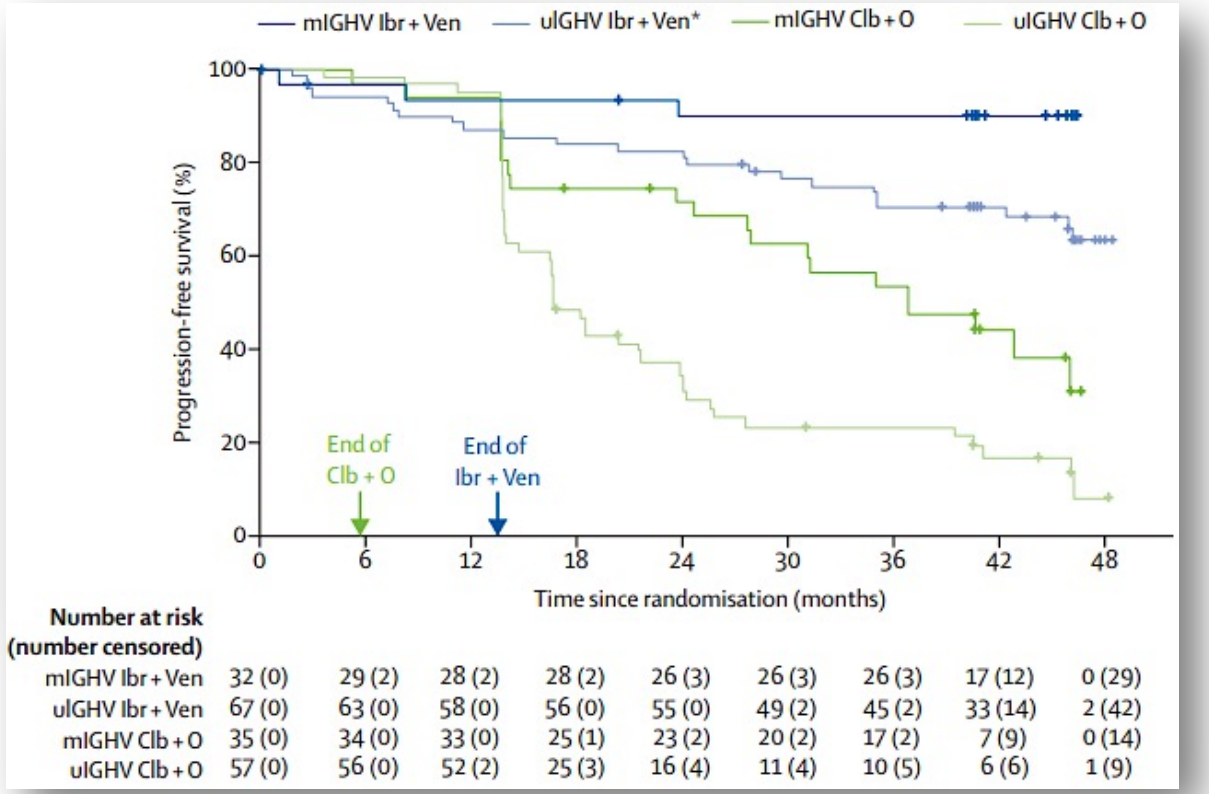
Key Safety Outcomes
– **Completed all planned treatment:** 92%
– **Most common AEs (any grade):** diarrhea (62%), nausea (43%), neutropenia (42%), and arthralgia (33%)
– **Most common grade 3/4 AEs:** neutropenia (33%), hypertension (6%) and neutrophil count decreased (5%)

Barr PM et al. ASCO 2023; Abstract 7535.

GLOW: Ibr/Ven in an older, co-morbid population



Median age: 71



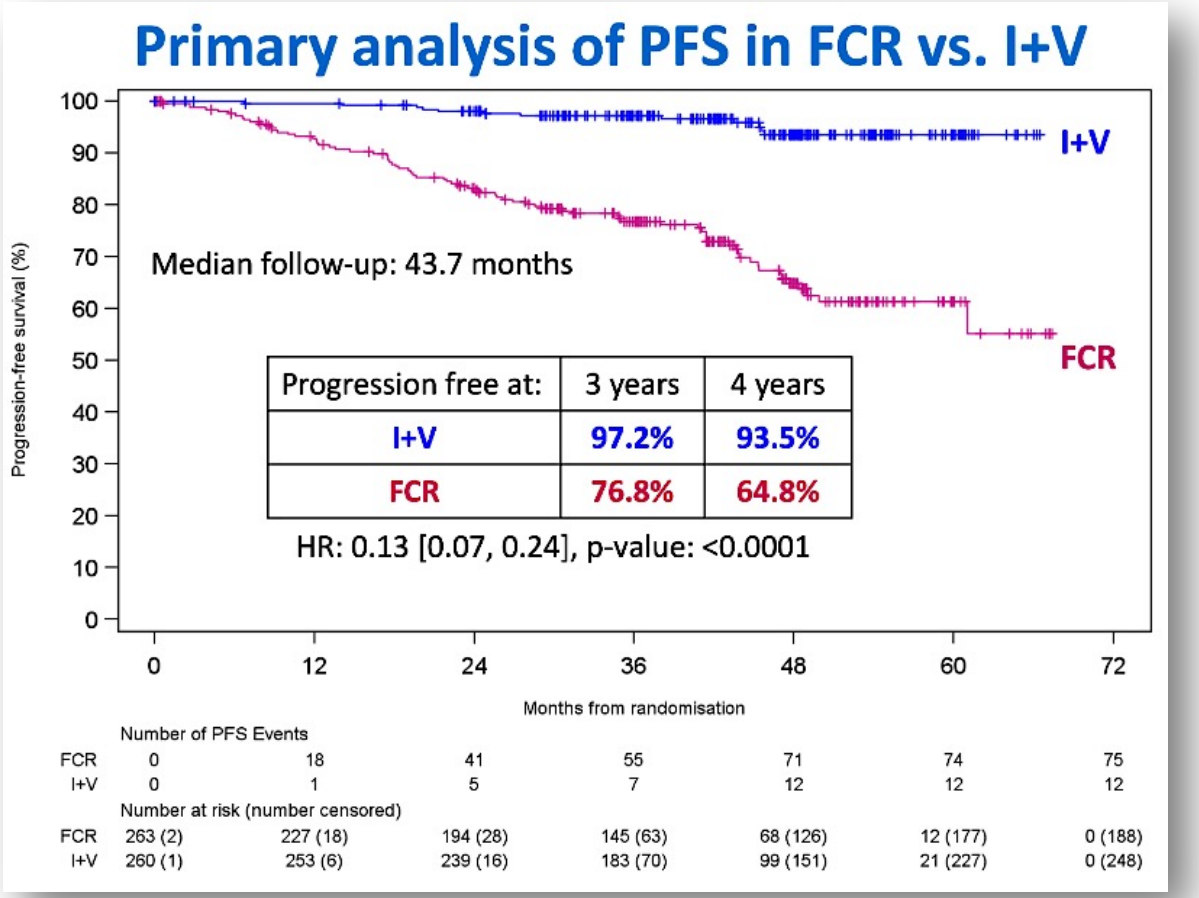
With median follow-up of 46 mo.:

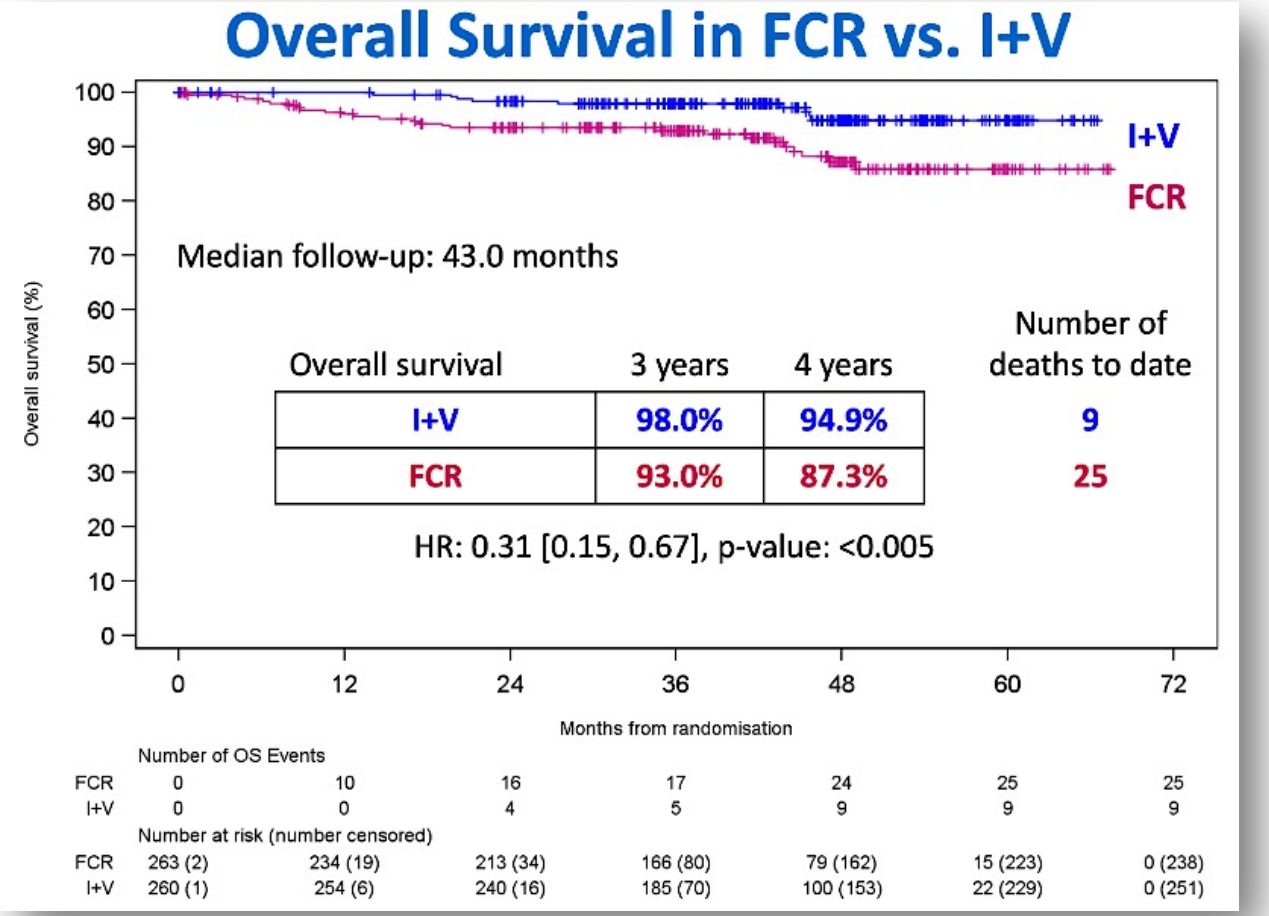
- 7/106 (6.6%) deaths due to TEAE
- 4 on treatment deaths due to CV complications in IV arm

To be updated ASH 2023: Follows et al., abstract 634, Sun. PM oral

Niemann et al., *Lancet Oncol*, [Epub ahead of print], 2023

Phase 3 FLAIR: Ibr/Ven improves survival over FCR

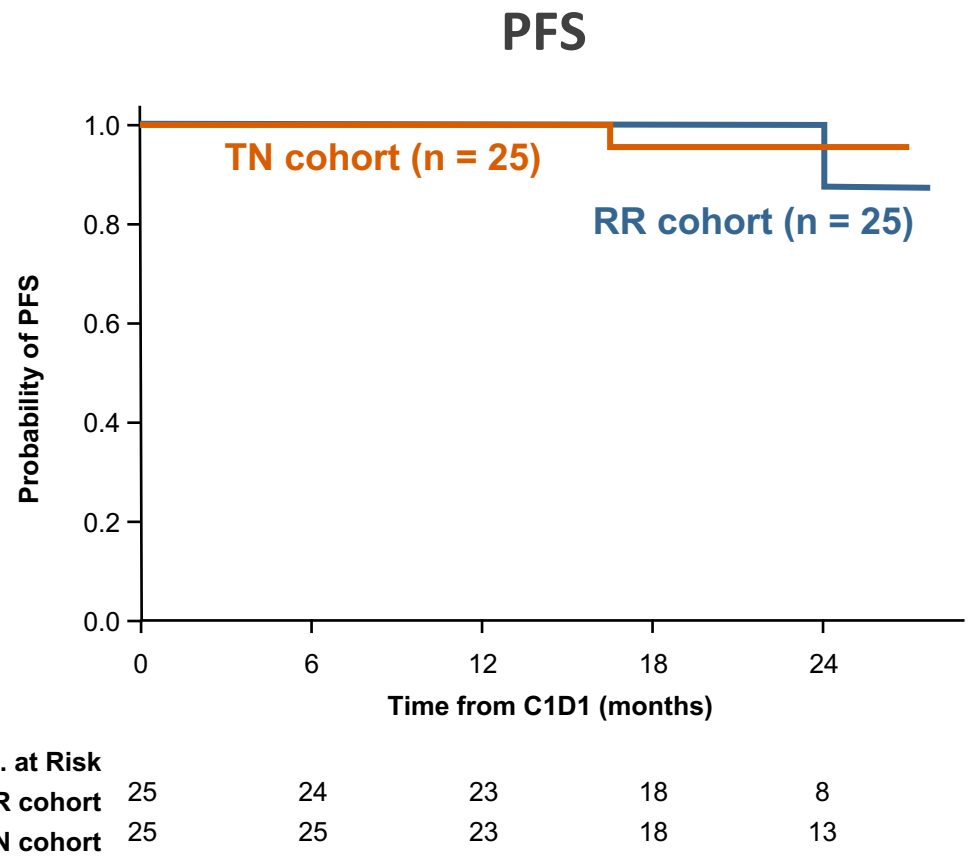


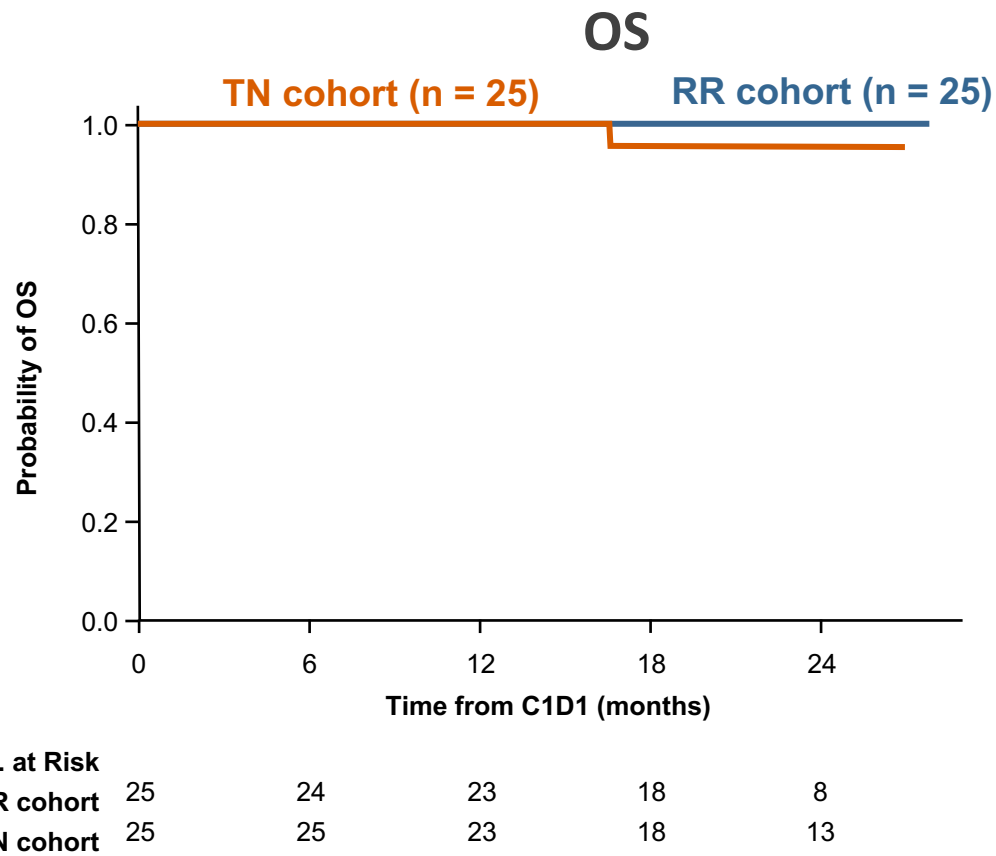


Median age: 62

To be presented ASH 2023: Hillmen et al., abstract 631, Sun. PM oral

Triplet Therapy With IVO is Active, but Additional Toxicity is Observed





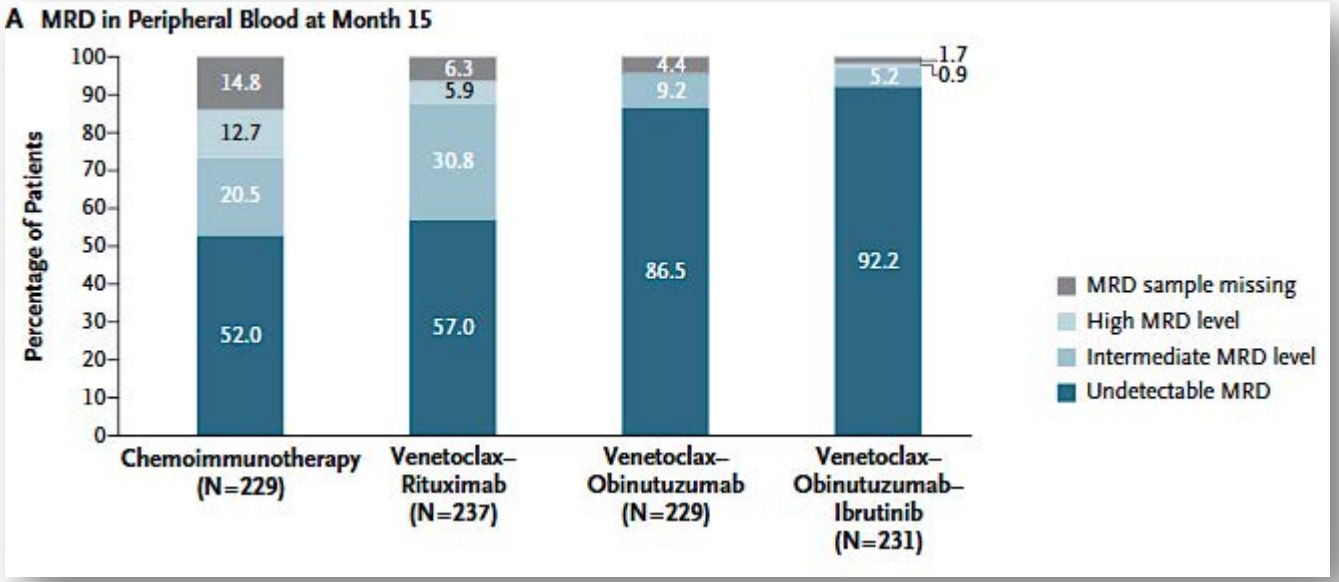
- **Cardiovascular toxicities were common:** HTN: 82%; AFib: 10%
- **Grade 3/4 neutropenia: 66%**

Rogers KA, et al. *J Clin Oncol.* 2020;38(31):3626-3637

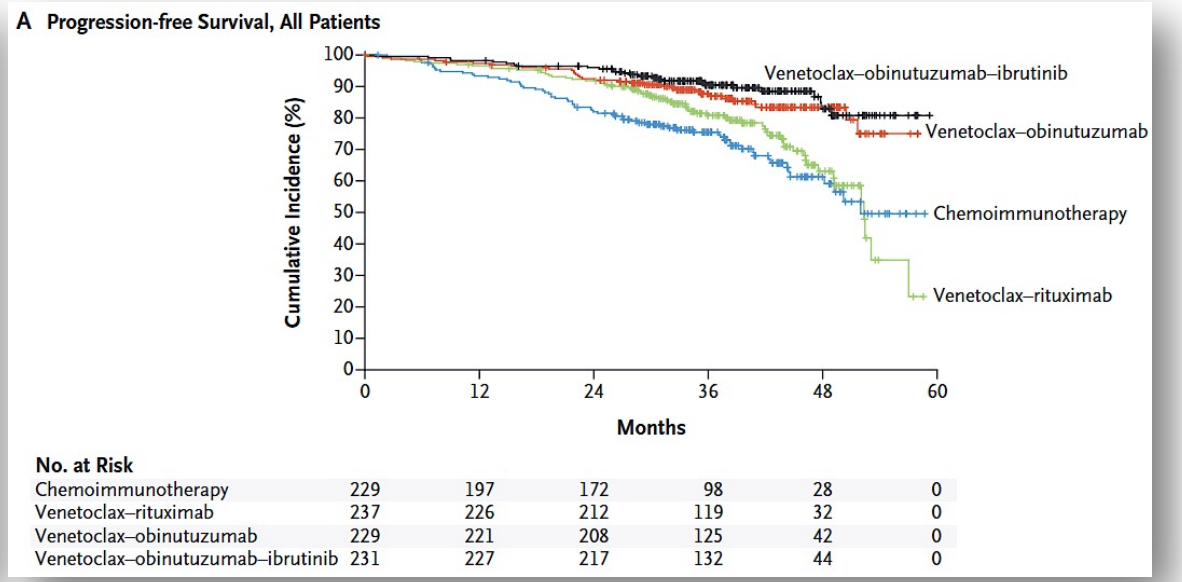
How do triplet combos compare to doublets?

CLL13

MRD



PFS



Median follow-up: 38.8 mo.

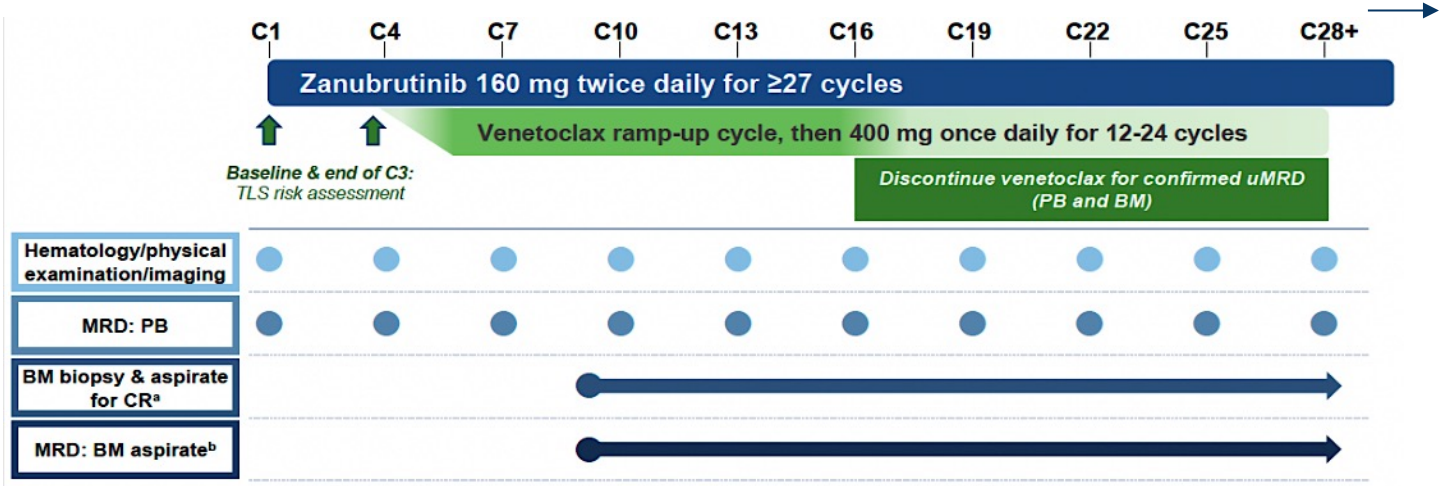
PFS	Median months	3y PFS (%)
CIT	52.0	75.5
RV	52.3	80.8
GV	Not reached	87.7
GIV	Not reached	90.5

To be updated ASH 2023: Fürstenau et al., abstract 635, Sun. PM oral

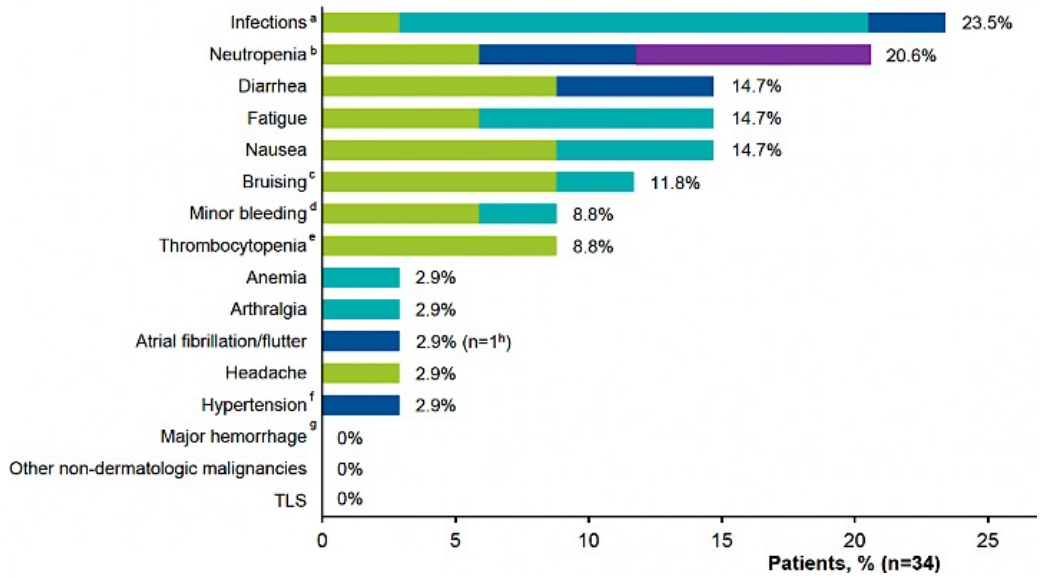
Eichhorst B, et al. *N Engl J Med*, 2023

SEQUOIA Phase 3 Trial: Zanubrutinib + Venetoclax for Patients With TN Del(17p) CLL/SLL (Cohort 3)

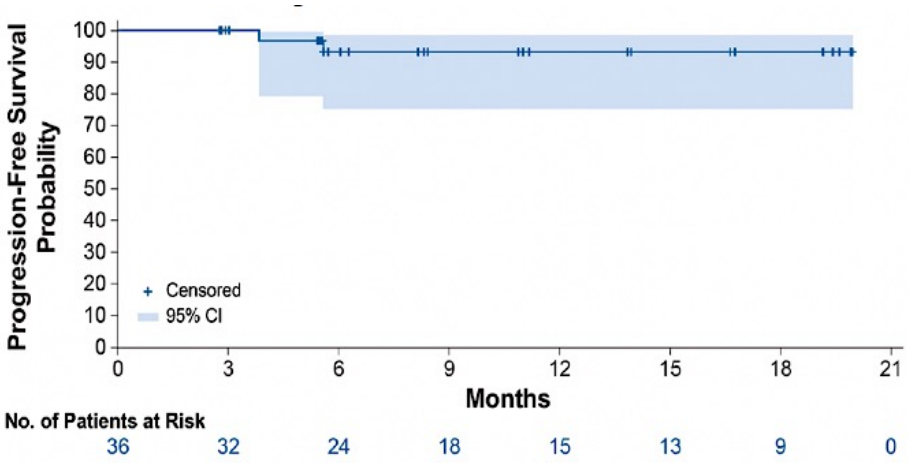
Treatment Regimen



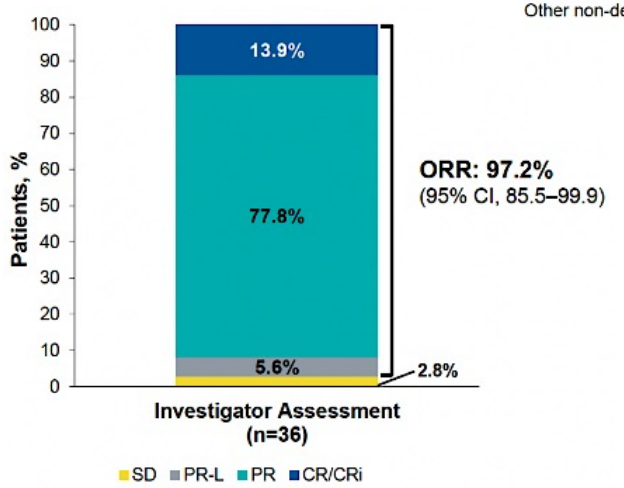
Starting at C28, discontinue zanubrutinib upon confirmed uMRD



PFS



ORR

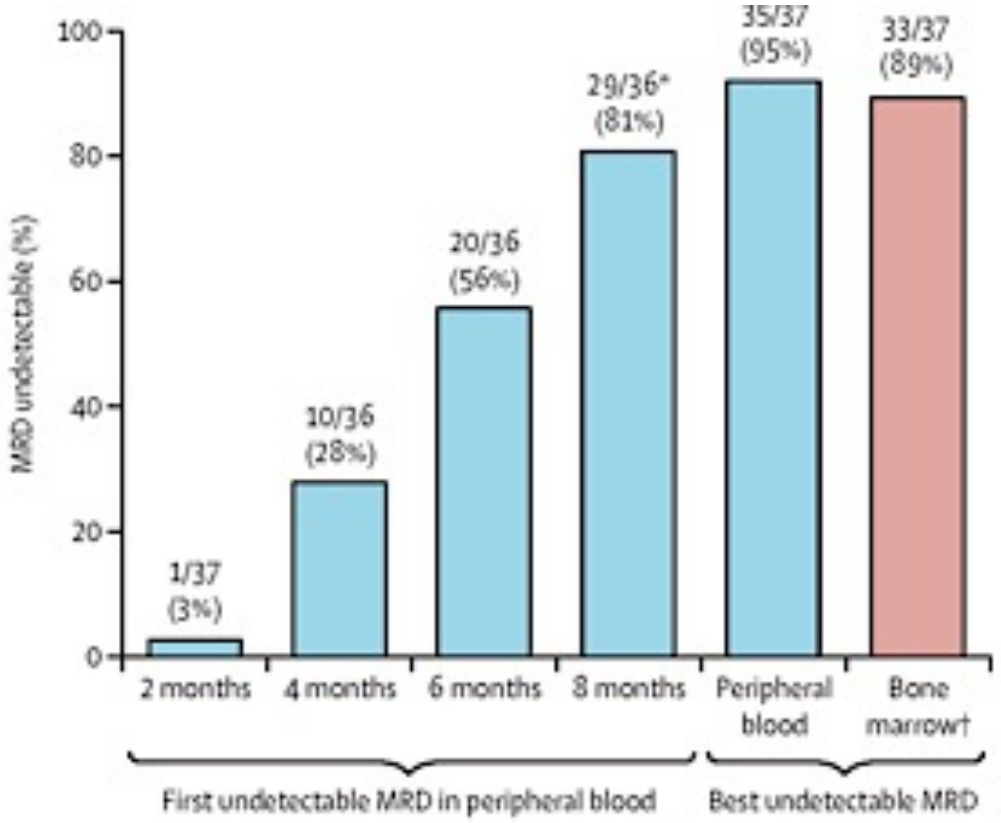


- No clinical TLS reported

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

Triplet therapy with Zanubrutinib + Venetoclax + Obinutuzumab is active and well-tolerated (Phase 2 BOVen trial)

MRD Response



Safety profile

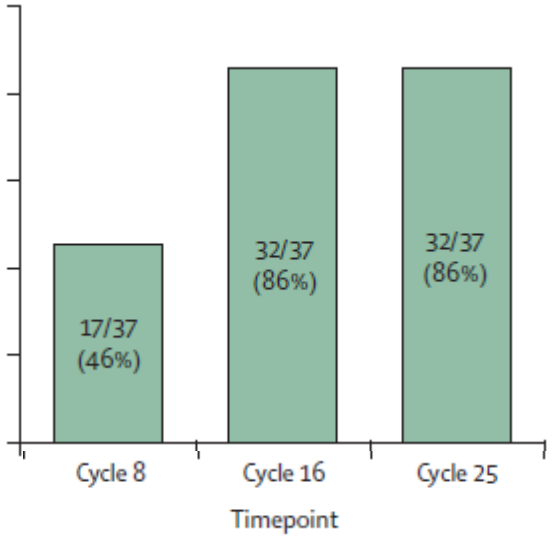
	Grade 1–2	Grade 3	Grade 4
Thrombocytopenia	20 (51%)	3 (8%)	0
Fatigue	20 (51%)	1 (3%)	0
Neutropenia	13 (33%)	2 (5%)	5 (13%)
Bruising	20 (51%)	0	0
Diarrhoea	18 (46%)	0	0
Infusion-related reaction	15 (39%)	1 (3%)	1 (3%)
Anaemia	16 (41%)	0	0
Cough	14 (36%)	0	0
Rash	10 (26%)	3 (8%)	0
Nausea	12 (31%)	0	0
Constipation	11 (28%)	0	0
Nasal congestion	10 (26%)	0	0
Gastroesophageal reflux disease	10 (26%)	0	0
Insomnia	9 (23%)	0	0
Myalgia	9 (23%)	0	0
Arthralgia	8 (21%)	0	0

Soumerai, JD, et al. *Lancet Haem*, 2021

The Acalabrutinib + Venetoclax + Obinutuzumab (AVO) triplet is also active and well-tolerated

Initial Cohort (n=37)

BM MRD Response



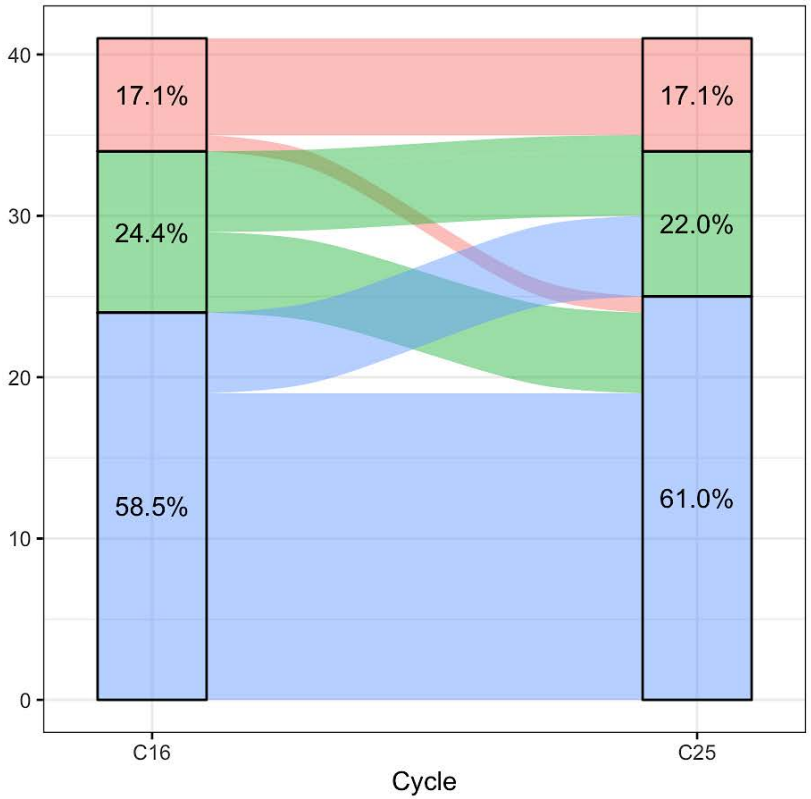
Safety profile

AEs (N=37), %		All Grades	Grade ≥3
Most frequent hematologic	Neutropenia	84	43
	Thrombocytopenia	81	27
	Anemia	59	5
Non-hematologic (≥50%)	Fatigue	89	3
	Headache	76	3
	Bruising	59	0
AEs of special interest	IRR	25	3
	Hypertension	11	0
	Atrial fibrillation	3	3
	Laboratory TLS	5	5

Davids MS, et al. *Lancet Oncol*. 2021.

Updated analysis (n=68)

Blood MRD (ClonoSEQ) n=68



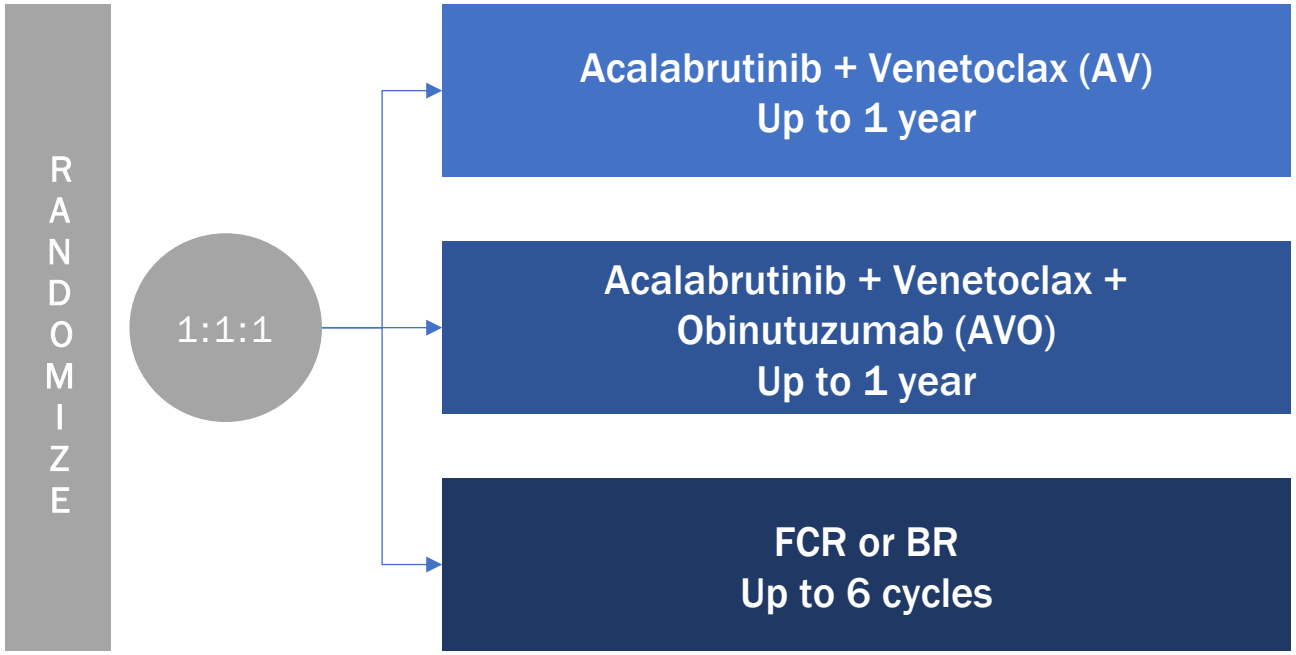
- **93% PFS with median follow-up ~3 yrs**

Ryan et al., ASH, 2022

AMPLIFY (ACE-CL-311): Phase 3 Study of Acalabrutinib + Venetoclax ± Obinutuzumab vs FCR/BR in TN CLL Without Del(17p) or *TP53* Mutations

Key Eligibility Criteria

- Previously untreated CLL
- Without del(17p) or *TP53* mutations
- ECOG PS ≤2



Primary endpoint

- PFS (IRC assessed) of AV vs FCR/BR

Key secondary endpoints

- PFS (IRC assessed) of AVO vs FCR/BR
- PFS (INV assessed) of AV vs FCR/BR

ClinicalTrials.gov identifier: NCT03836261. Accessed October 4, 2022. https://clinicaltrials.gov/ct2/show/NCT03836261

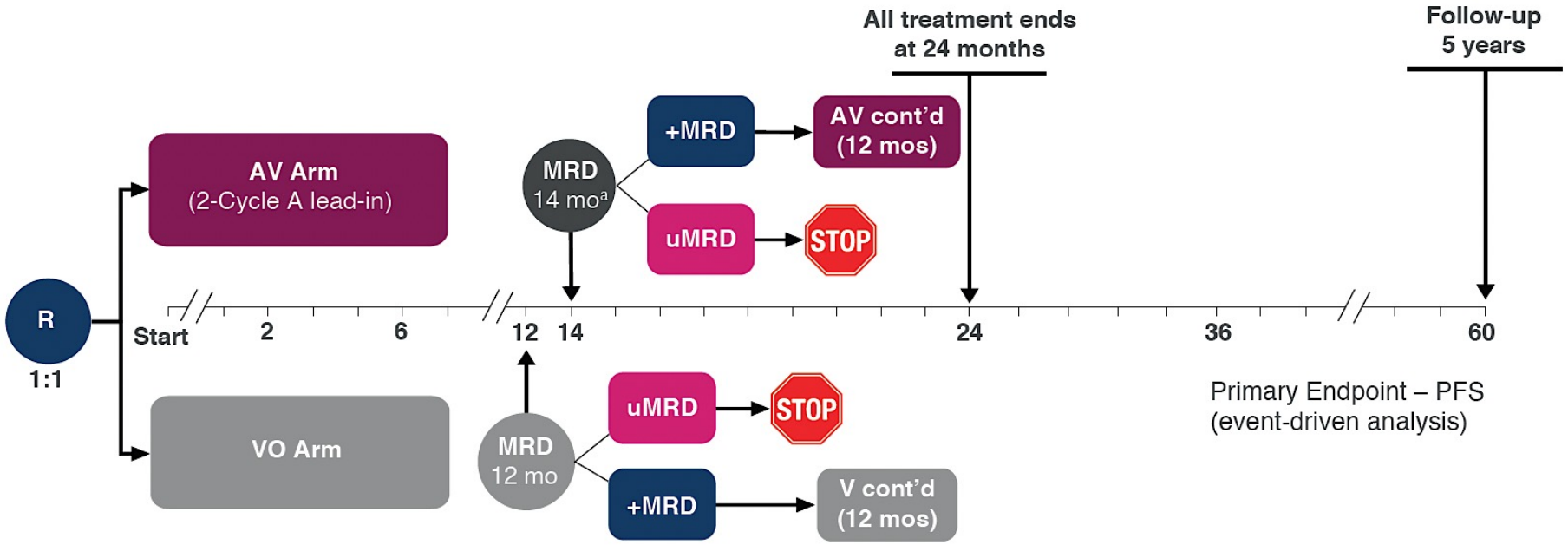
The global MAJIC phase 3 study seeks to define the optimal MRD-guided venetoclax doublet for frontline CLL treatment

- N=~750 patients to be recruited
- Global study with ~40 sites
- FPI: Sept 2022

Key Eligibility Criteria

- TN CLL/SLL requiring treatment per 2018 iwCLL guidelines
- ECOG PS 0-2
- Anti-thrombotic agents permitted except for warfarin or equivalent vitamin K antagonists

Primary endpoint: INV-assessed PFS



Davids et al., ASH, 2021. Abstract 1553; Ryan CE, et al. [published correction appears in Future Oncol. 2023 Jan;19(3):271]. *Future Oncol*. 2022;18(33):3689-3699.

The CLL17 trial is comparing continuous BTKi to time-limited venetoclax-based doublets

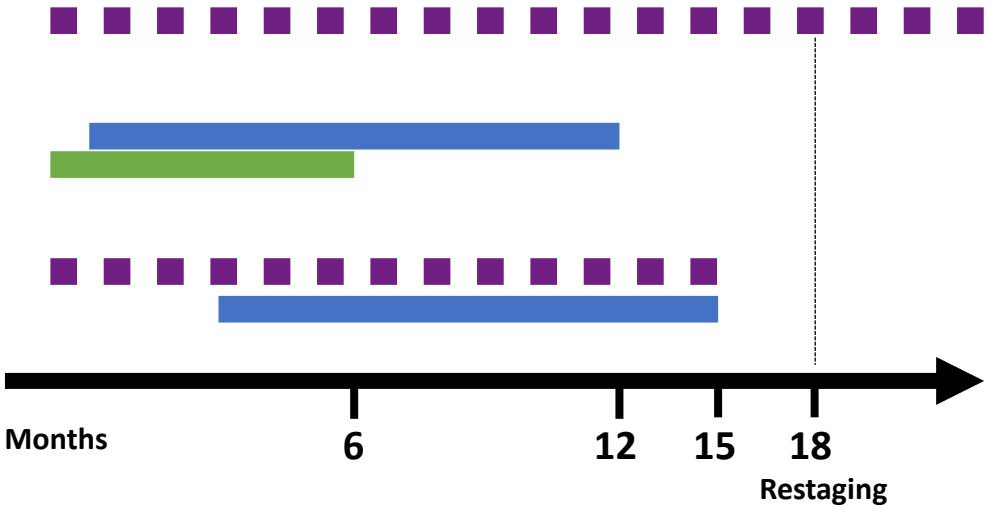
CLL17[1,2]

Phase 3 trial in 1L CLL, including those with adverse prognostic factors

- Ibr mono
- Ven + Obin
- Ven + I

Stratification by fitness, del(17p)/*TP53*^{mut}, IGHV

RANDOMIZATION[2]



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, C2–6 D1)

Ibrutinib 420 mg PO daily (C1 D1 – C15 D28)
Venetoclax 400 mg PO daily (C4 D1 – C15 D28)

1. ClinicalTrials.gov. NCT04608318. Available at: https://www.clinicaltrials.gov/ct2/show/NCT04608318 (accessed August 2021);
2. DCLLSG. CLL17 Trial. Available at: https://www.dcllsg.de/en/trial/cll17/CLL17_Synopsis_v1.2_20200923.pdf (accessed August 2021)

Dana-Farber Cancer Institute

Harvard Medical School

Conclusions

- Ibrutinib + venetoclax is a highly active doublet, but tolerability can vary depending on the patient population
- This regimen has gained regulatory approval outside the US. It is not FDA-approved, but is listed as an option in NCCN guidelines
- Early data for more selective BTKi zanubrutinib and acalabrutinib with venetoclax look promising, with excellent activity and tolerability across a broad population of patients
- Whether triplets with obinutuzumab are better than doublets remains to be determined
- We await several ongoing randomized, phase 3 trials that will help to define the role for such regimens in clinical practice

Agenda

Module 1: Front-Line Treatment for Chronic Lymphocytic Leukemia (CLL) — Dr Wierda

Module 2: Novel Strategies Combining Bruton Tyrosine Kinase (BTK) and Bcl-2 Inhibitors in the Treatment of CLL — Dr Davids

Module 3: Optimal Management of Adverse Events with BTK and Bcl-2 Inhibitors; Considerations for Special Patient Populations — Dr Awan

Module 4: Selection and Sequencing of Therapies for Relapsed/Refractory CLL — Dr Woyach

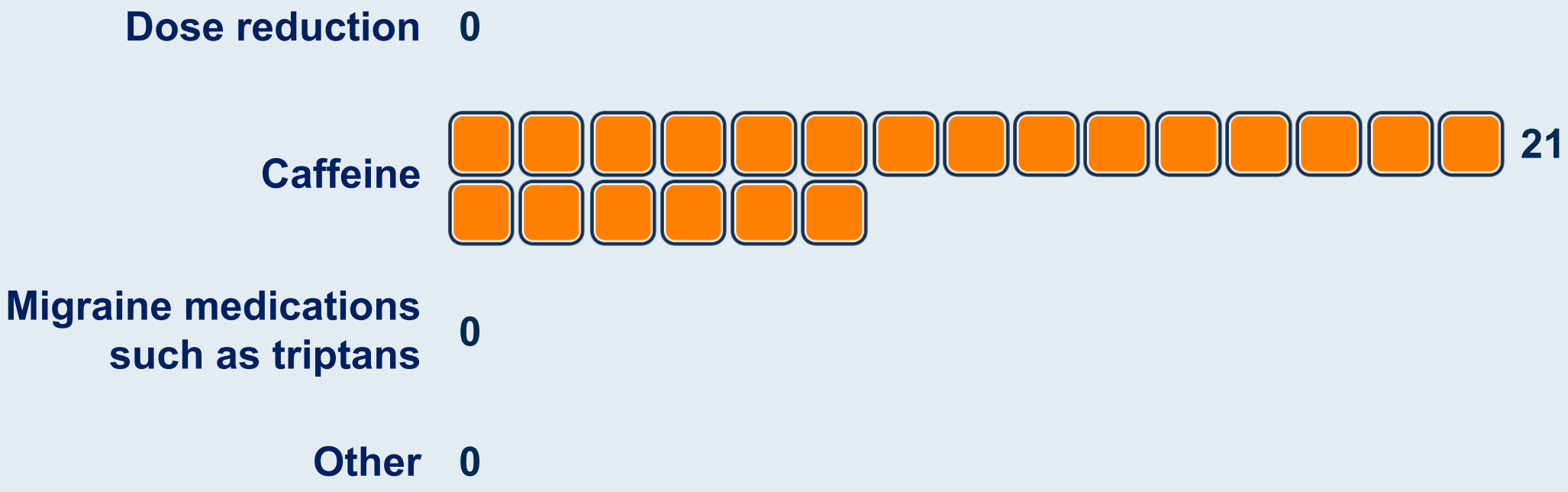
Module 5: Promising Investigational Agents and Strategies — Dr Schuster

Regulatory and reimbursement issues aside, do you have a preferred BTK inhibitor for a patient with a history of migraine headache?

Survey of 21 US-based clinical investigators November 2023

RTP RESEARCH TO PRACTICE

Which management strategy would you generally recommend for a patient who was experiencing acalabrutinib-associated headache?



Survey of 21 US-based clinical investigators November 2023

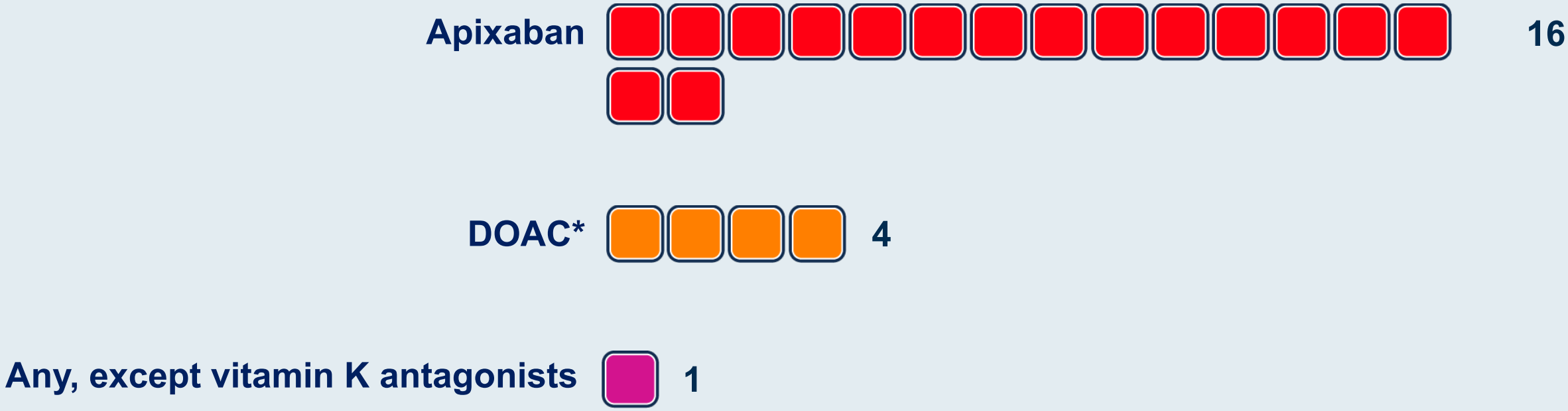
RTP RESEARCH TO PRACTICE

Regulatory and reimbursement issues aside, do you have a preferred BTK inhibitor for a patient with a history of difficult-to-control hypertension?

Survey of 21 US-based clinical investigators November 2023

RTP RESEARCH TO PRACTICE

Which anticoagulant do you prefer for patients who are also receiving BTK inhibitors?



* Direct oral anticoagulant

Survey of 21 US-based clinical investigators November 2023

RTP RESEARCH TO PRACTICE

Use of BTK inhibitors for patients with CLL and a history of atrial fibrillation (A-fib); monitoring and treatment for patients who develop A-fib while on a BTK inhibitor

Professor Constantine Tam, MBBS, MD

Frequency of tumor lysis syndrome with venetoclax/obinutuxumab for CLL; monitoring, prophylaxis and management

Jan A Burger, MD, PhD

Shuo Ma, MD, PhD

RTP
RESEARCH
TO PRACTICE

Farrukh T. Awan, M.D.
Professor of Internal Medicine
Director of Lymphoid Malignancies Program
Dallas, TX, USA

Optimal Management of Adverse Events (AEs) with BTK and Bcl-2 Inhibitors; Considerations for Special Patient Populations

UT Southwestern
Harold C. Simmons
Comprehensive Cancer Center

Safety Issues

BTK Inhibitors

Ibrutinib/BTKi related toxicities of interest

- Bleeding
- Cardiovascular toxicities
  - Atrial fibrillation
  - Ventricular arrhythmias
  - Hypertension
- Infectious complications

Shanafelt. Blood. 2022;140:112

Comparison of E1912 and Alliance A041202 Trials: Median Age and Grade ≥3 TRAEs on IR Arm

Adverse Event	E1912[1] (N = 352)	Alliance A041202[2] (N = 181)
Median age, yr (range)	58 (28-70)	71 (65-86)
Infection, %	11.4	18
Atrial fibrillation, %	4.5	5
Bleeding, %	1.1	1
Hypertension, %	11.4	34
Deaths during active treatment +30 days, %	1	7

TRAEs = Treatment related Adverse events

1. Shanafelt. Blood. 2022;140:112. 2. Woyach. NEJM. 2018;379:2517.

This slide contains indirect trial comparisons. In the absence of head-to-head studies cross-trial comparisons cannot be made. Trials differ in design, study population, size, time period of recruitment, location of study sites.

ELEVATE-TN – Safety Analysis

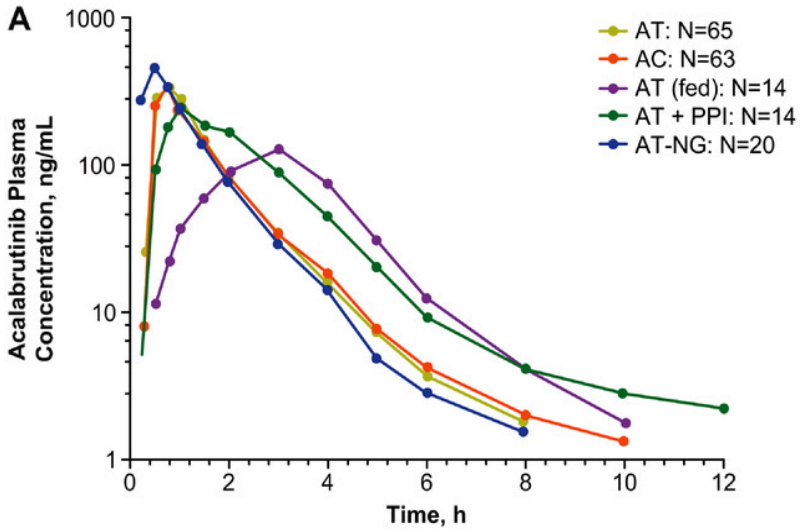
5- Year Follow-Up

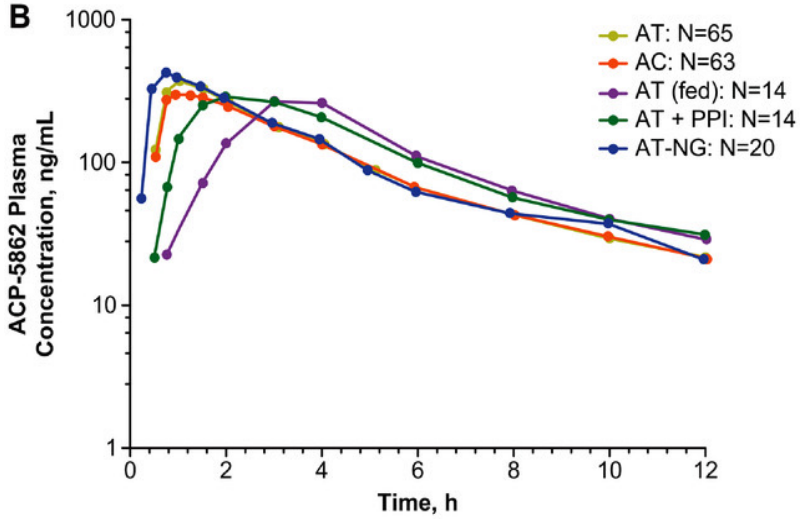
AEs of Clinical Interest, n (%)	A+O (n=178)		A (n=179)		O+Clb (n=169)	
	Any grade	Grade ≥3	Any grade	Grade ≥3	Any grade	Grade ≥3
Cardiac events	43 (24.2)	17 (9.6)	39 (21.8)	18 (10.1)	13 (7.7)	3 (1.8)
Atrial fibrillation	11 (6.2)	2 (1.1)	13 (7.3)	2 (1.1)	1 (0.6)	0
Bleeding	88 (49.4)	8 (4.5)	78 (43.6)	6 (3.4)	20 (11.8)	0
Major bleeding[a]	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)
Secondary primary malignancies	31 (17.4)	14 (7.9)	27 (15.1)	7 (3.9)	7 (4.1)	3 (1.8)
Excluding nonmelanoma skin	17 (9.6)	12 (6.7)	13 (7.3)	5 (2.8)	3 (1.8)	2 (1.2)

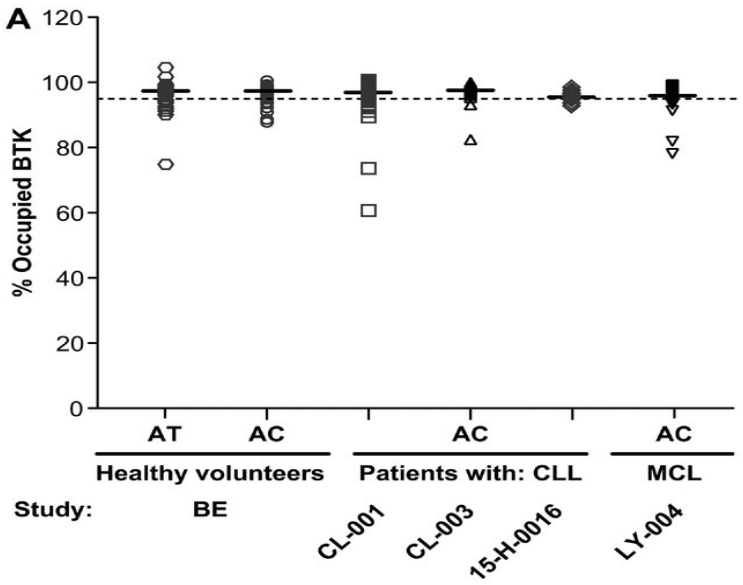
[a] Defined as any serious or grade ≥3 hemorrhagic event, or any grade hemorrhagic event in the central nervous system.

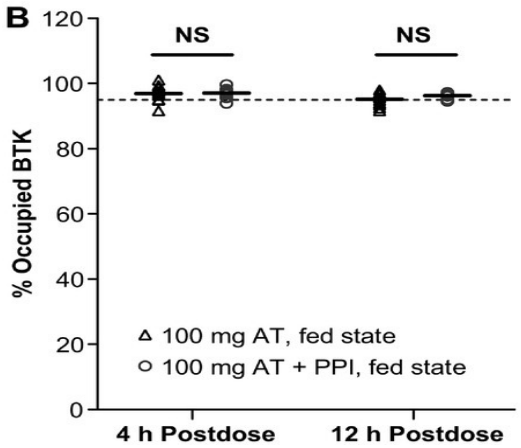
1. Sharman JP, et al. ASCO 2022. Abstract 7539. **2.** Sharman JP, et al. EHA 2022. Abstract P666.

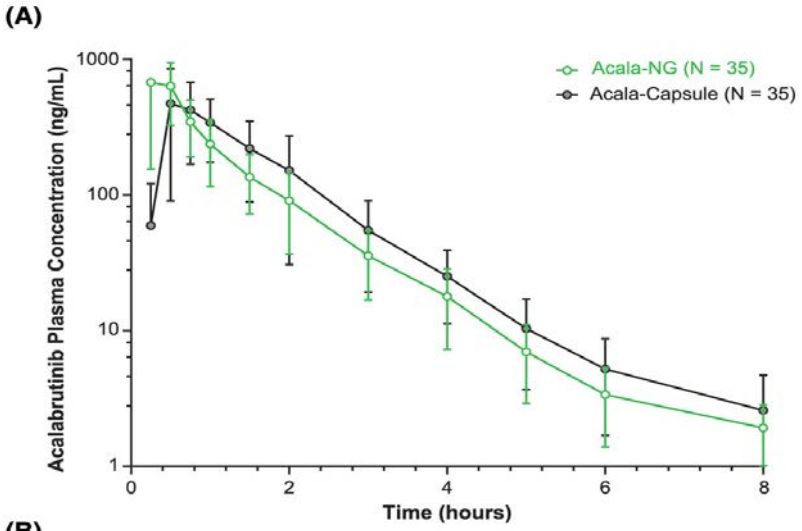
ELEVATE-PLUS
(New Acalabrutinib tablet formulation)

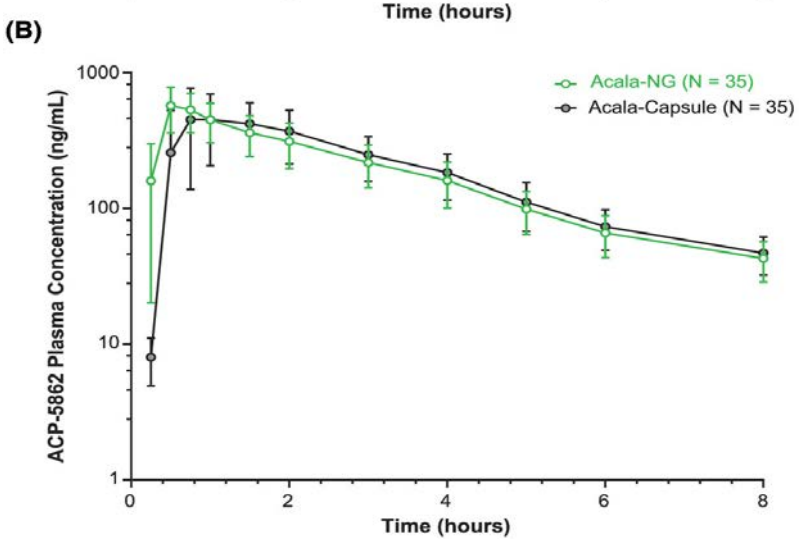












Clinical Pharm in Drug Dev, Volume: 11, Issue: 11, Pages: 1294-1307, First published: 27 August 2022, DOI: (10.1002/cpdd.1153); Brit J Clinical Pharma, Volume: 88, Issue: 10, Pages: 4573-4584, First published: 25 April 2022, DOI: (10.1111/bcp.15362)

SEQUOIA – Safety Analysis

Select AEs, %	Cohort 1 – Without del(17p)						Cohort 2 – With del(17p)		
	Group A Zanubrutinib (n=240[a])			Group B BR (n=227[b])			Group C Zanubrutinib (n=111)		
	All grade, %	Grade 3/4, %	Grade 5, %	All grade, %	Grade 3/4, %	Grade 5, %	All grade, %	Grade 3/4, %	Grade 5, %
Any	93	48	5	96	74	5[c]	98	52	3
Serious	37	25	5	50	39	5	41	32	3
Common AEs									
Contusion	19	0	0	4	0	0	20	0	0
Upper respiratory tract infection	17	1	0	12	1	0	21	0	0
Diarrhea	14	1	0	13	1	1	17	1	0
Arthralgia	14	1	0	9	<1	0	20	1	0
Neutropenia	15	11	0	57	51	0	18	15	0
Hypertension	12	6	0	9	5	0	9	5	0
Headache	11	0	0	7	0	0	11	2	0
Rash	11	0	0	19	3	0	14	0	0
Nausea	10	0	0	33	1	0	15	0	0
Anemia	5	<1	0	19	2	0	5	0	0
Thrombocytopenia	4	2	0	13	7	0	4	1	0
Infusion-related reaction	<1[d]	0	0	19	3	0	0	0	0
All bleeding AEs[e]	45	3	<1	11	2	0	51	5	0
All cardiac AEs[e]	14	4	1	11	4	<1	15	4	1

[a] One patient in group A did not receive zanubrutinib and is not included in the safety analysis. [b] 11 patients in group B did not receive bendamustine-rituximab and are not included in the safety analysis. [c] Includes 1 patient who had a grade 5 event (confusion) that began prior to but ended after the data cutoff. [d] Due to amphotericin B infusion. [e] Grouped analyses.

Tam CS, et al. *Lancet Oncol.* 2022;23(8):1031-1043.

ELEVATE-RR: Acalabrutinib vs Ibrutinib

Comparison of Adverse Events

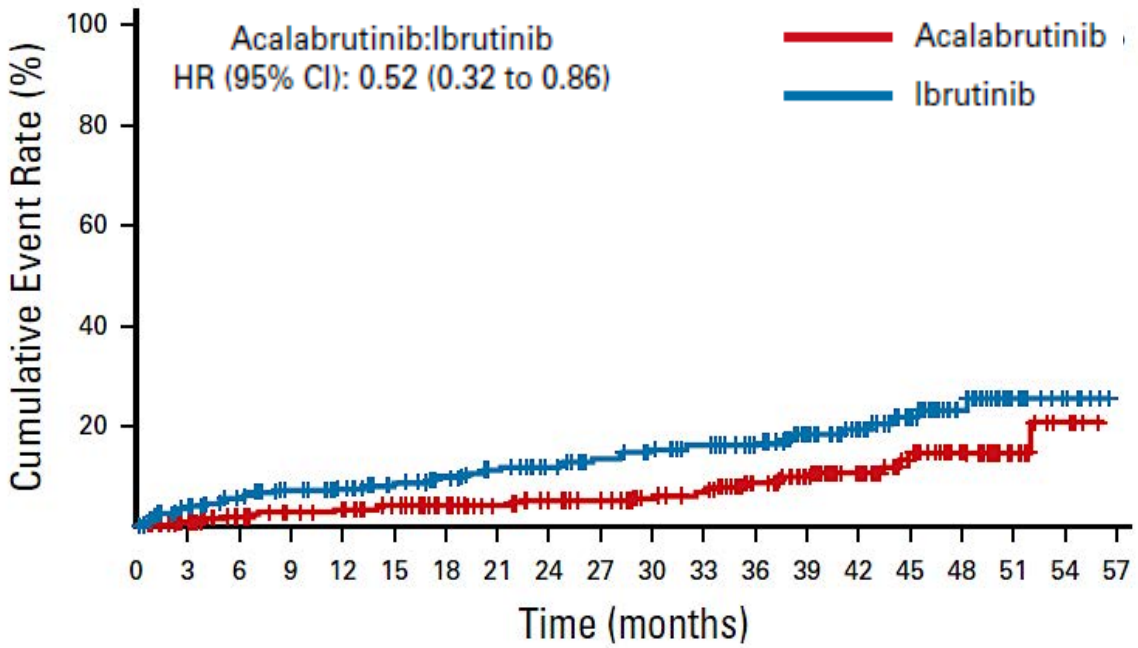
	Acalabrutinib (n = 266)		Ibrutinib (n = 263)	
Event	**Any Grade**	**Grade ≥ 3**	**Any Grade**	**Grade ≥ 3**
Diarrhea[a,b]	92 (34.6)	3 (1.1)	**121 (46.0)**	**13 (4.9)**
Headache[a,b]	**92 (34.6)**	**4 (1.5)**	53 (20.2)	0
Cough[a]	**77 (28.9)**	2 (0.8)	56 (21.3)	1 (0.4)
Fatigue[b]	54 (20.3)	**9 (3.4)**	44 (16.7)	0
Arthralgia[a]	42 (15.8)	0	**60 (22.8)**	2 (0.8)
Hypertension[a,b]	23 (8.6)	11 (4.1)	**60 (22.8)**	**23 (8.7)**
Contusion[a]	31 (11.7)	0	**48 (18.3)**	1 (0.4)
Atrial fibrillation[a]	24 (9.0)	*12 (4.5)	**41 (15.6)**	*9 (3.4)
Urinary tract infection[a]	22 (8.3)	3 (1.1)	**36 (13.7)**	6 (2.3)
Back pain[a]	20 (7.5)	0	**34 (12.9)**	2 (0.8)
Dyspepsia[a]	10 (3.8)	0	**32 (12.2)**	0

* *Symptomatic, requiring urgent attention, and incompletely controlled medically, or controlled with device (e.g., pacemaker)*

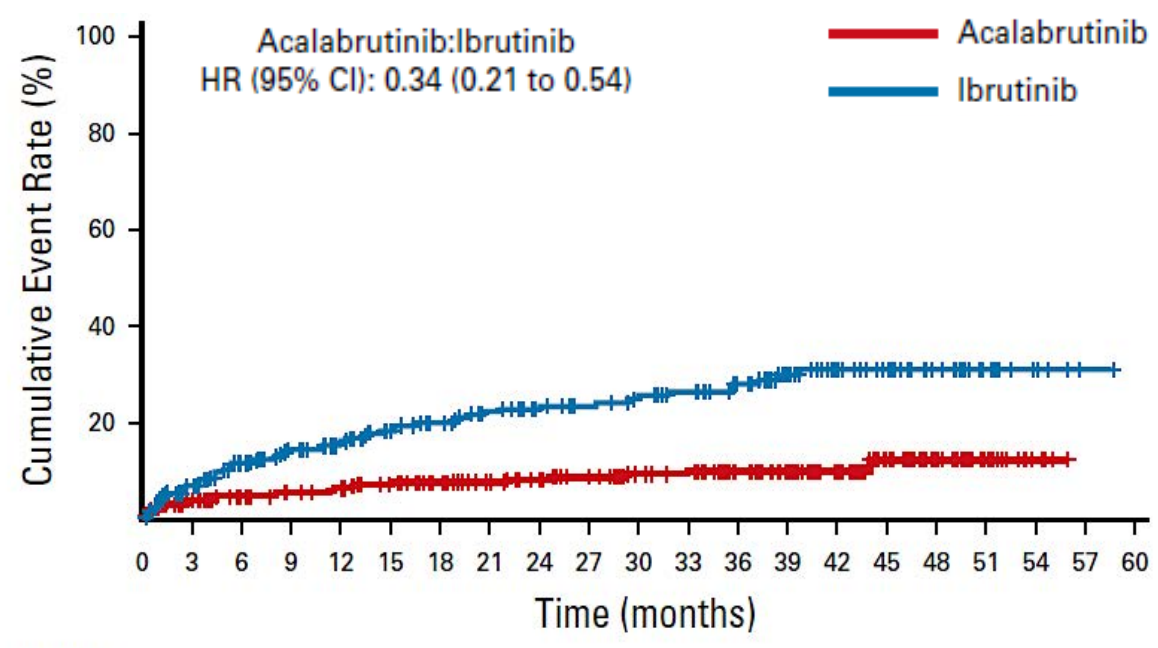
Byrd JC, et al. *J Clin Oncol.* 2021;39:3441-3452; Seymour JF et al. Blood 2023;142(8):687-99.

ELEVATE-RR: Safety Analysis

Cumulative Incidence of Atrial Fibrillation/Flutter

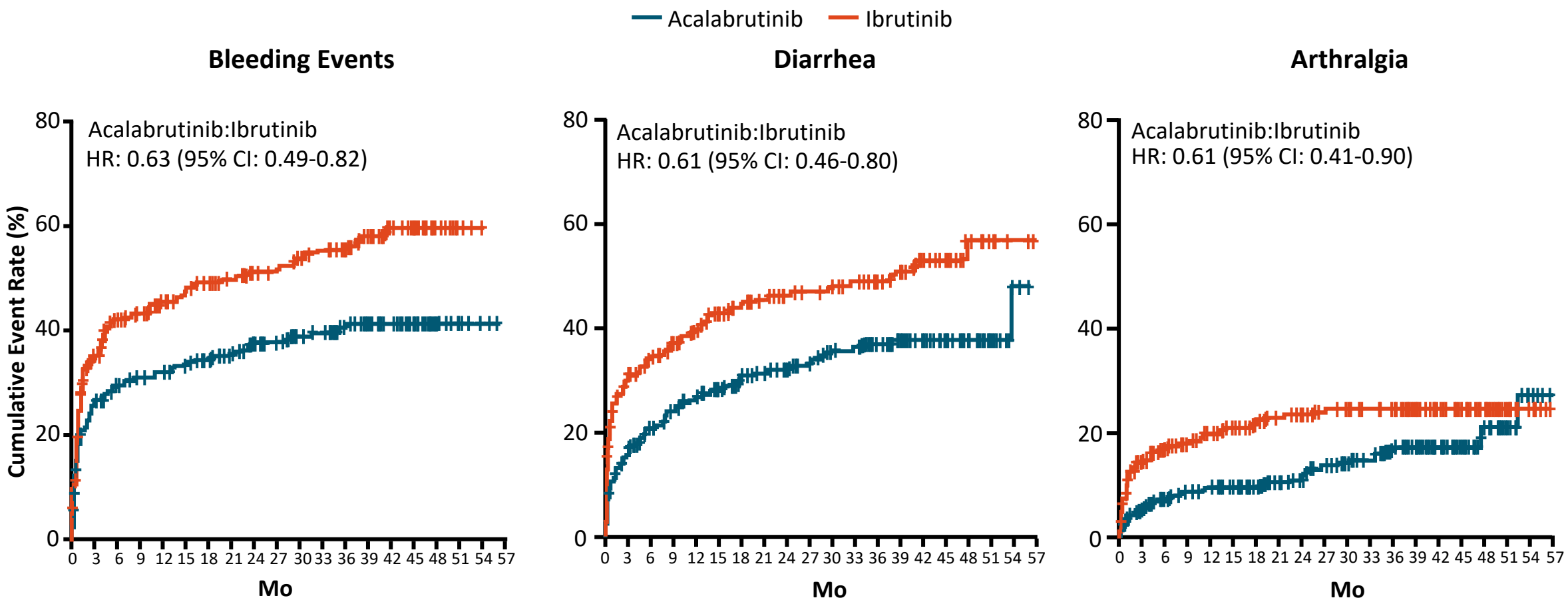


Cumulative Incidence of Hypertension



Byrd JC, et al. *J Clin Oncol.* 2021;39:3441-3452.

ELEVATE-RR: Additional Safety



Hillmen. EHA 2021. Abstr S145.

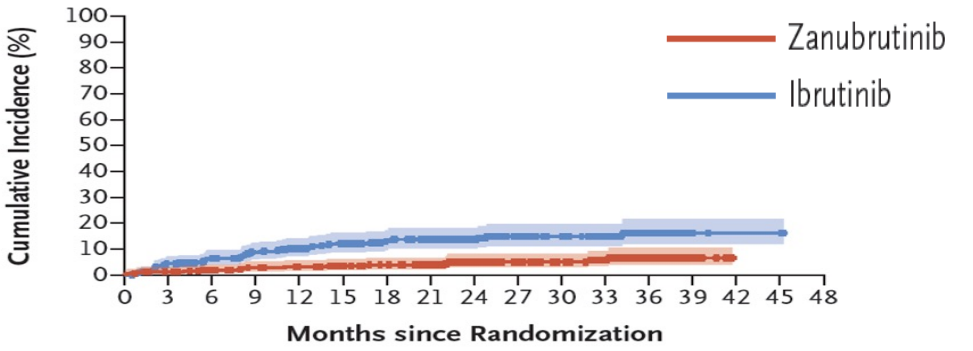
ALPINE: Events of Clinical Toxicity Interest

Safety analysis population	Zanubrutinib (n=324), n (%)		Ibrutinib (n=324), n (%)	
	Any grade	Grade ≥ 3	Any grade	Grade ≥ 3
Cardiac disorders[a]	1 (0.3)		14 (4.3)	
Atrial fibrillation and flutter (key 2º endpoint)	**17 (5.2)**	**8 (2.5)**	**43 (13.3)**	**13 (4.0)**
Hemorrhage Major hemorrhage[b]	137 (42.3) 12 (3.7)	11 (3.4) 11 (3.4)	134 (41.4) 14 (4.3)	12 (3.7) 12 (3.7)
Hypertension	76 (23.5)	49 (15.1)	74 (22.8)	44 (13.6)
Infections	231 (71.3)	86 (26.5)	237 (73.1)	91 (28.1)
Neutropenia[c]	95 (2.3)	68 (21.0)	79 (24.4)	59 (18.2)
Thrombocytopenia[c]	42 (13)	11 (3.4)	50 (15.4)	17 (5.2)
Secondary primary malignancies Skin cancers	40 (12.3) 21 (6.5)	22 (6.8) 7 (2.2)	43 (13.3) 28 (8.6)	17 (5.2) 4 (1.2)

[a]Cardiac disorders leading to treatment discontinuation: zanubrutinib 0 patients and ibrutinib 7 (3.4%) patients. [b]Includes serious or grade ≥3 hemorrhage and CNS bleeding of all grades. [c]Pooled terms including neutropenia, neutrophil count decreased, and febrile neutropenia; thrombocytopenia and platelet count decreased.
AE = adverse event. All events are of any grade unless otherwise specified.
Brown JR, et al. *N Engl J Med*. 2023;388(4):319-332 & Supplementary appendix

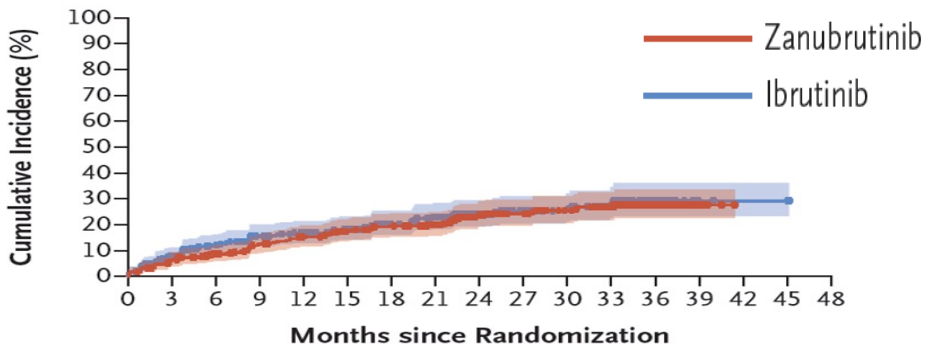
ALPINE: Safety Analysis

Cumulative Incidence of Atrial Fibrillation/Flutter



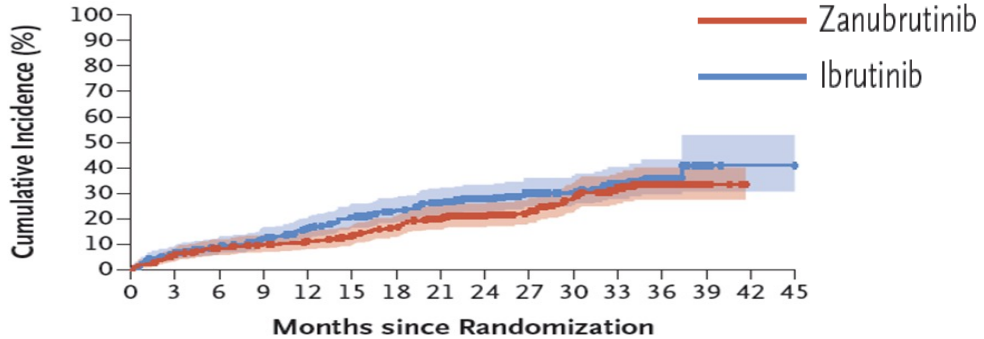
No. at Risk									
Zanubrutinib	324	302	288	268	199	148	51	10	0
Ibrutinib	324	278	247	211	153	108	40	3	2	1	0

Cumulative Incidence of Hypertension



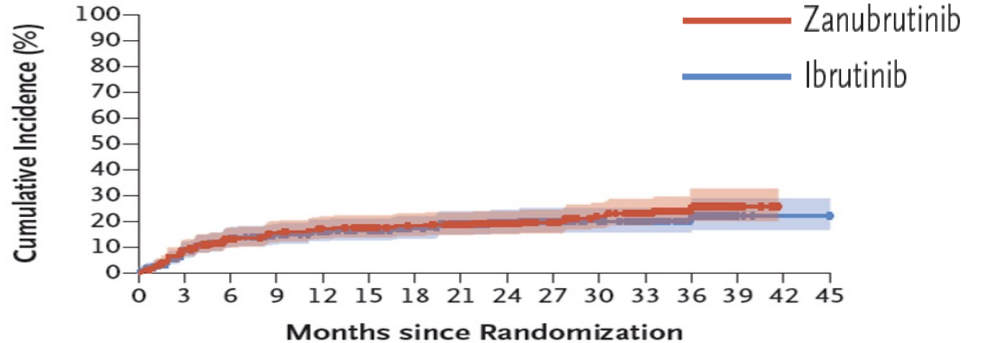
No. at Risk									
Zanubrutinib	324	280	248	221	157	115	35	6	0
Ibrutinib	324	254	222	186	129	84	28	3	2	1	0

Cumulative Incidence of Grade ≥3 Infection



No. at Risk									
Zanubrutinib	324	289	272	247	180	125	40	7	0
Ibrutinib	324	272	234	198	136	95	33	3	1	0

Cumulative Incidence of Grade ≥3 Neutropenia



No. at Risk									
Zanubrutinib	324	264	245	229	175	128	40	8	0
Ibrutinib	324	253	225	199	143	101	37	3	1	0

Brown JR, et al. *N Engl J Med*. 2023;388(4):319-332.

Adverse Events of Clinical Interest in H2H studies

In my opinion worth considering with each patient…

All grades	Ibrutinib Elevate RR % (n=263)	Acalabrutinib Elevate RR % (n=266)	Ibrutinib Alpine % (n=324)	Zanubrutinib Alpine % (n=324)
Atrial Fib/Flutter	15.6	9.0	13.3	5.2
Hypertension	22.8	8.6	22.8	23.5
Bleeding events	51.3	38.0	41.1	42.3
Neutropenia	24.7	21.1	24.4	29.3

This slide contains indirect trial comparisons. In the absence of head-to-head studies cross-trial comparisons cannot be made. Trials differ in design, study population, size, time period of recruitment, location of study sites. Ref: Byrd JC, et al. *J Clin Oncol.* 2021;39:3441-3452, Brown JR, et al. *N Engl J Med*. 2023;388(4):319-332 & Supplementary Appendix

Ibrutinib in combination with venetoclax

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

Tam, et al. Blood. 2022

NCCN Guidelines del(17p)/*TP53* Wildtype

	1L Therapy	2L & Subsequent Therapy
Preferred	• Acalabrutinib ± obinutuzumab (category 1) • Venetoclax + obinutuzumab (category 1) • Zanubrutinib (category 1)	• Acalabrutinib (category 1) • Venetoclax + rituximab (category 1) • Zanubrutinib (category 1)
Other recommended (BTKi-based only)	• Ibrutinib (category 1) • Ibrutinib + obinutuzumab (category 2B) • Ibrutinib + rituximab (category 2B) • Ibrutinib + venetoclax (category 2B)	• Ibrutinib (category 1) • Venetoclax • Ibrutinib + venetoclax (category 2B)

1. NCCN Clinical Practice Guidelines in Oncology. Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma. Version 1.2024. https://www.nccn.org/professionals/physician_gls/pdf/cll.pdf.

NCCN Guidelines del(17p)/*TP53* Mutation-Positive

	1L Therapy	2L & Subsequent Therapy
Preferred	• Acalabrutinib ± obinutuzumab • Venetoclax + obinutuzumab • Zanubrutinib	• Acalabrutinib (category 1) • Venetoclax + rituximab (category 1) • Venetoclax • Zanubrutinib (category 1)
Other recommended (BTKi-based only)	• Ibrutinib (category 1) • Ibrutinib + venetoclax (category 2B)	• Ibrutinib (category 1) • Ibrutinib + venetoclax (category 2B)

1. NCCN Clinical Practice Guidelines in Oncology. Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma. Version 1.2024. https://www.nccn.org/professionals/physician_gls/pdf/cll.pdf.

Recommendations for the management of Bleeding and Cardiovascular Issues – BTKi

- Consider discontinuation of anti-platelet and anti-coagulants prior to starting
- Watch for bleeding closely – especially early in the disease course
- Hold BTKi for 3-7 days prior to minor and major procedures
- Watch for signs and symptoms of cardiac arrhythmias
- Work closely with Cardio-Oncology colleagues
- Control hypertension aggressively
- Avoid the use of medications that impact drug concentrations

BTK Inhibitors: Cardiovascular Adverse Event Management

- **Atrial fibrillation/flutter**
  - Regularly monitor for cardiac arrythmias; ECG if symptoms develop (eg, palpitations, lightheadedness, syncope, chest pain) or new-onset dyspnea
  - Cardiology comanagement recommended
  - **Not an absolute indication to discontinue BTK inhibitors**
  - Use anticoagulation with caution
  - Manage cardiac arrythmias as appropriate
  - For persistent atrial fibrillation, consider dose modification

- **Hypertension**
  - Document baseline blood pressure
  - Monitor for new/ uncontrolled hypertension
  - Initiate hypertensives as needed
  - New or worsening hypertension increases risk of major cardiovascular events

Ibrutinib PI. Acalabrutinib PI. Zanubrutinib PI. Rogers. J Adv Pract Oncol. 2017;8:97. Dickerson. Blood. 2019;134:1919.
NCCN Guidelines®. Version 2.2022.

Bcl-2 Antagonists

CLL14: Most Frequent Grade ≥3 Adverse Events With Obinutuzumab + Venetoclax or Chlorambucil

	Venetoclax-obinutuzumab (N=212)		Chlorambucil-obinutuzumab (N=214)	
	During Treatment	After Treatment	During Treatment	After Treatment
Neutropenia	51.9%	3.8%	47.2%	1.9%
Thrombocytopenia	14.2%	0.5%	15.0%	0.0%
Anemia	7.5%	1.9%	6.1%	0.5%
Febrile neutropenia	4.2%	0.9%	3.3%	0.5%
Leukopenia	2.4%	0.0%	4.7%	0.0%
Pneunomia	3.8%	3.3%	3.7%	1.4%
Infusion-related reaction	9.0%	0.0%	9.8%	0.5%
Tumour lysis syndrome	1.4%	0.0%	3.3%	0.0%

Al-Sawaf. EHA 2023. Abstr S145.

CLL11: Overview of Adverse Events

Event, n (%)	Obin-Clb vs Clb		Obin-Clb vs R-Clb	
	Obin-Clb (n = 241)	Clb (n = 116)	Obin-Clb (n = 336)	R-Clb (n = 321)
≥1 AEs (any grade)	228 (95)	96 (83)	316 (94)	290 (90)
Grade 3-5 AEs	179 (74)	59 (51)	241 (72)	191 (60)
Serious AEs	113 (47)	45 (39)	150 (45)	124 (39)
Grade 5 AEs	19 (8)	13 (11)	23 (7)	31 (10)
▫ Second malignancies	11 (5)	1 (<1)	12 (4)	13 (4)
▫ Infections	1 (<1)	7 (6)	2 (<1)	2 (<1)

Goede. EHA 2018. Abstr S151.

Management of Venetoclax-Associated Toxicities

Toxicity Management

Tumor Lysis Syndrome

Laboratory TLS

- Potassium ↑
- Uric acid ↑
- Phosphate ↑
- Calcium ↓

Clinical TLS

- Creatinine ↑, cardiac arrythmia, seizure

Debulking Strategies

Prior to venetoclax ramp-up

- Chemotherapy (eg, 2x bendamustine)

  OR

- Anti-CD20 Ab (eg, 3x obinutuzumab)

  OR

- BTK inhibitor (eg, ibrutinib for 3 mo)

Neutropenia

In cases of grade 3/4 neutropenia or febrile neutropenia

- Pause venetoclax and resume when resolved to grade ≤1
- Use G-CSF when clinically indicated

Risk Assessment

- **Low**
  - All LN <5 cm ***AND*** ALC <25 x 10^9/L
- **Intermediate**
  - Any LN 5-10 cm ***OR*** ALC ≥25 x 10^9/L
- **High**
  - Any LN ≥10 cm ***OR***
  - Any LN ≥5 cm ***AND*** ALC ≥25 x 10^9/L

Risk Mitigation

- Allopurinol (or rasburicase); oral hydration
- Allopurinol (or rasburicase); oral/IV hydration
- Allopurinol (or rasburicase); IV hydration
- Consider hospitalization

Fischer. Hemtology Am Soc Hematol Educ Program. 2020;2020:357.

Conclusions

- Majority of patients do well with most novel therapies currently used for the treatment of patients with CLL
- Obinutuzumab more effective in CLL than rituximab but associated with greater infusion toxicity and TLS risk
- Consider patient and disease characteristics to determine if suitable for specific class of treatment
- TLS risk category can be reduced with obinutuzumab pretreatment
- Infusion reactions with obinutuzumab can be reduced by BTKi pretreatment
- Careful lab monitoring for TLS with hospitalization for selected patients has been shown to be safe

1. Kater. NEJM Evid. 2022;1(7). 2. Eichhorst. EHA 2022. Abstr LB2365. 3. Goede. EHA 2018. Abstr S151. 4. Bourrier. BMC Cancer. 2022;22:article 148. 5. Obinutuzumab PI. 6. Gribben. Br J Haematol. 2020;188:844.

Agenda

Module 1: Front-Line Treatment for Chronic Lymphocytic Leukemia (CLL) — Dr Wierda

Module 2: Novel Strategies Combining Bruton Tyrosine Kinase (BTK) and Bcl-2 Inhibitors in the Treatment of CLL — Dr Davids

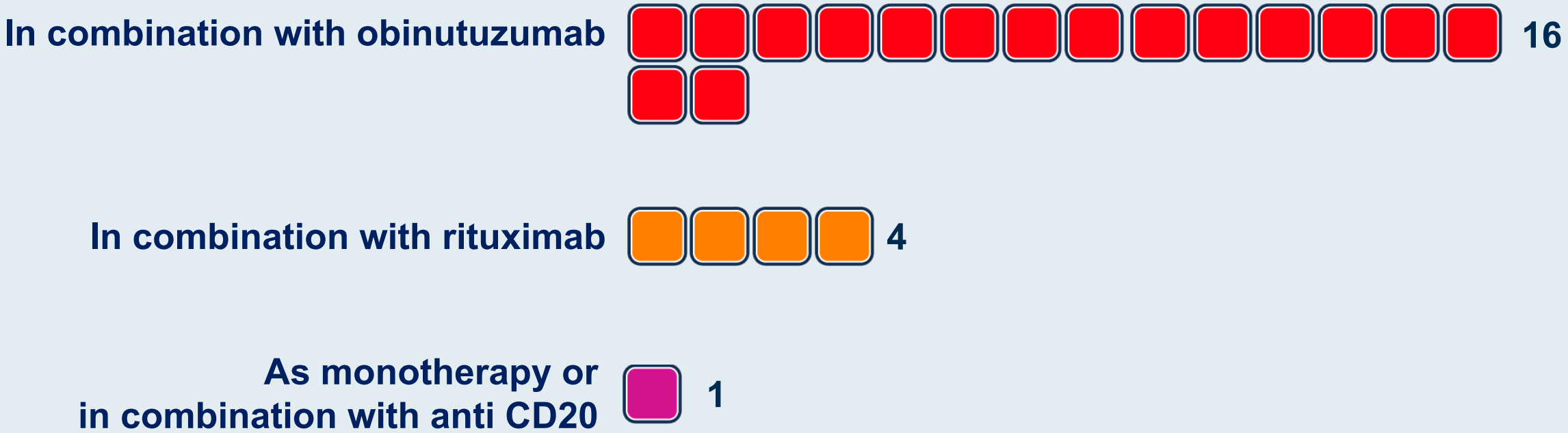
Module 3: Optimal Management of Adverse Events with BTK and Bcl-2 Inhibitors; Considerations for Special Patient Populations — Dr Awan

Module 4: Selection and Sequencing of Therapies for Relapsed/Refractory CLL — Dr Woyach

Module 5: Promising Investigational Agents and Strategies — Dr Schuster

RTP RESEARCH TO PRACTICE

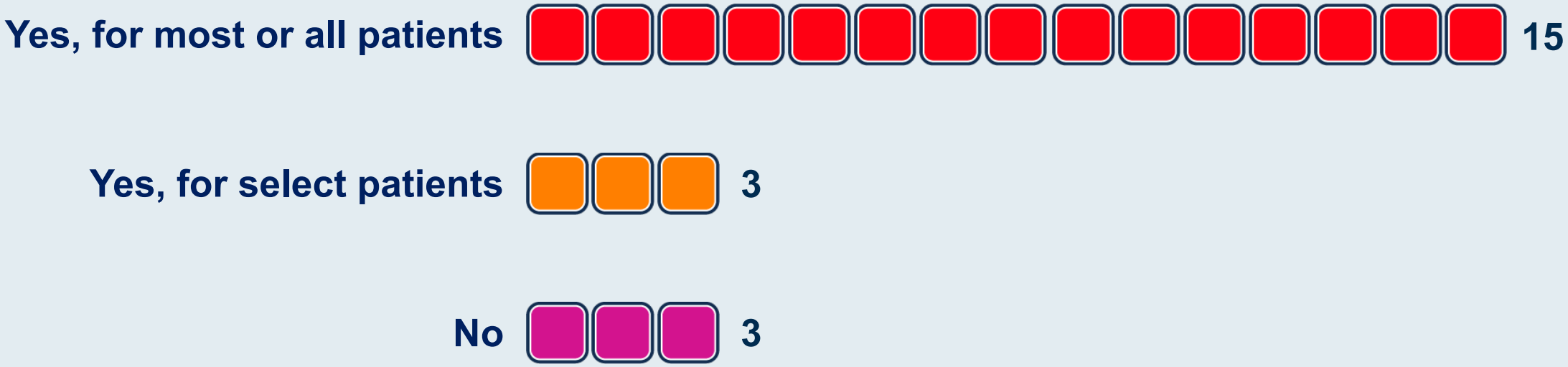
How do you generally administer venetoclax to patients with CLL who have experienced disease progression on a BTK inhibitor in the first-line setting?



Survey of 21 US-based clinical investigators November 2023

RTP RESEARCH TO PRACTICE

For a patient with CLL whose disease is progressing on a BTK inhibitor and for whom you are about to initiate venetoclax, do you generally continue the BTK inhibitor?



Survey of 21 US-based clinical investigators November 2023

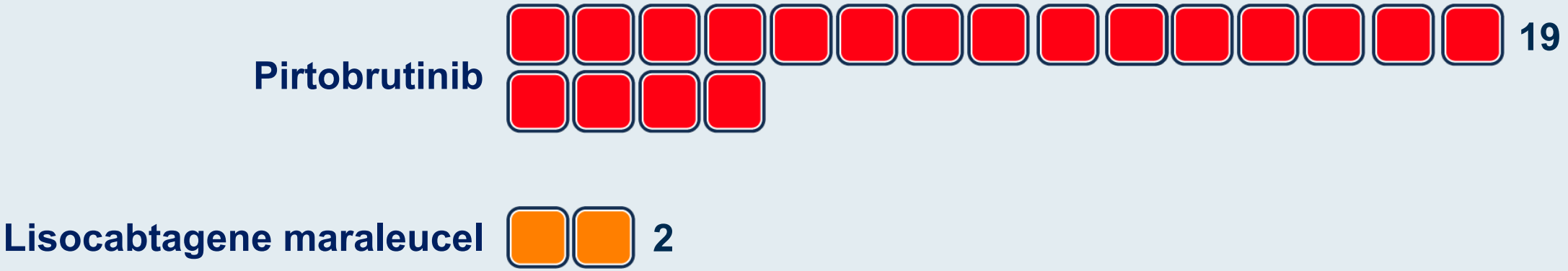
RTP RESEARCH TO PRACTICE

Which second-line systemic therapy would you recommend for a 60-year-old patient with IGHV-unmutated CLL without del(17p) or TP53 mutation who responds to venetoclax/obinutuzumab and then experiences disease progression 3 years after completing treatment?

Survey of 21 US-based clinical investigators November 2023

RTP RESEARCH TO PRACTICE

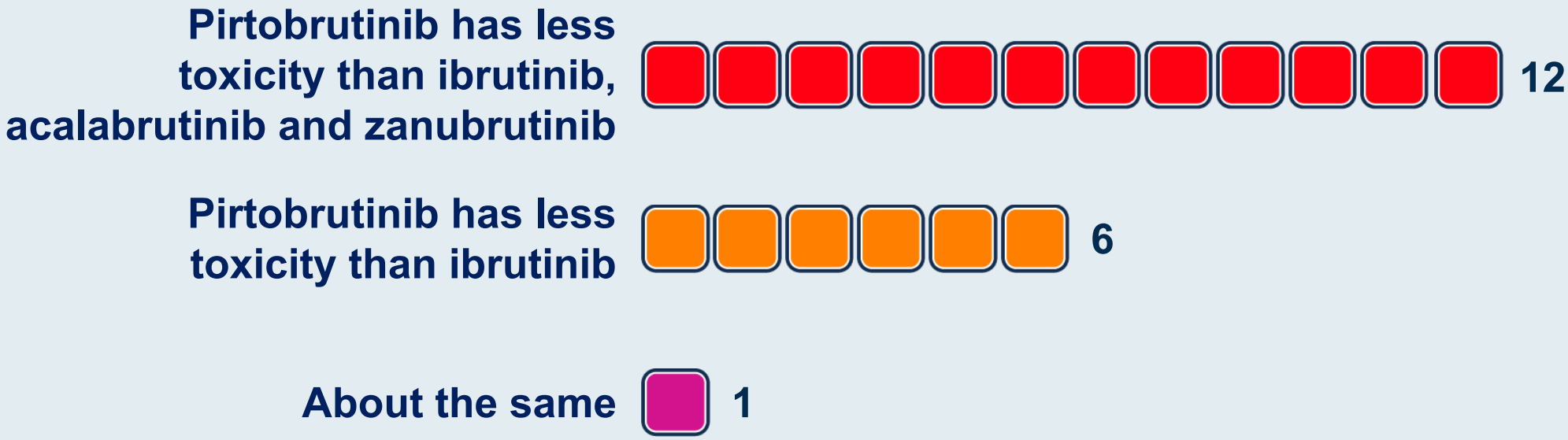
Regulatory and reimbursement issues aside, which third-line therapy would you generally prefer for a patient with double-refractory CLL?



Survey of 21 US-based clinical investigators November 2023

RTP RESEARCH TO PRACTICE

Based on current clinical trial data and your personal experience, how would you compare the global tolerability/toxicity of pirtobrutinib to that of available covalent BTK inhibitors for patients with relapsed/refractory CLL?



Survey of 21 US-based clinical investigators November 2023

RTP RESEARCH TO PRACTICE

Based on current clinical trial data and your personal experience, is pirtobrutinib efficacious for patients with CLL who experience disease progression on a covalent BTK inhibitor?

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RTP RESEARCH TO PRACTICE

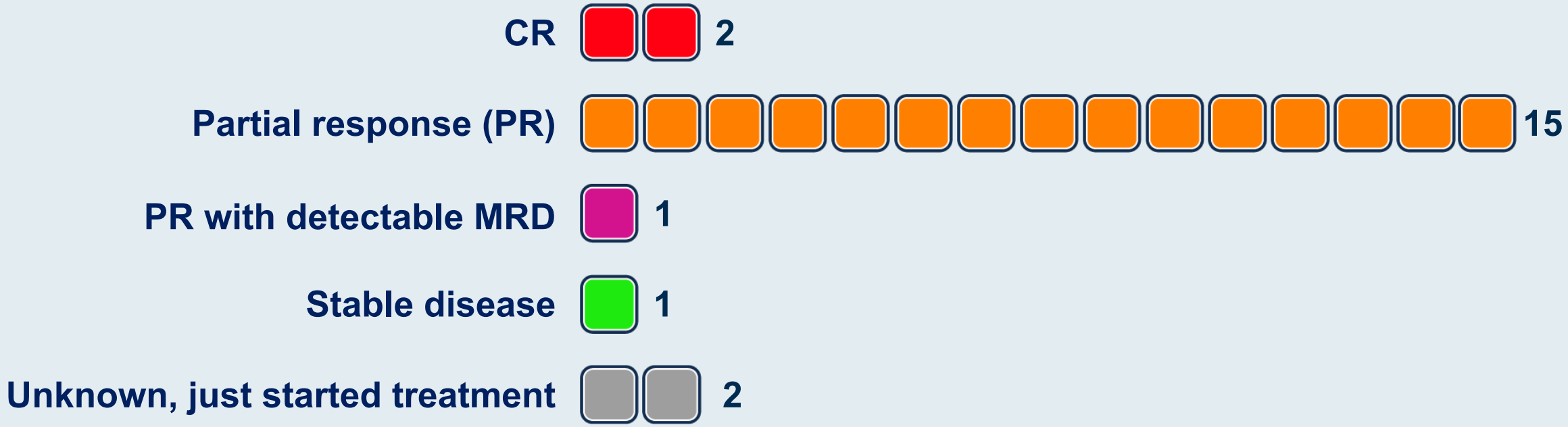
To approximately how many patients with CLL have you adminstered pirtobrutinib on or off protocol?

Median number of patients: 10 (range 1-40)

Describe the last patient with CLL to whom you administered pirtobrutinib:

Patient age: 69 (median; range 47-77)

Patient's response to therapy:

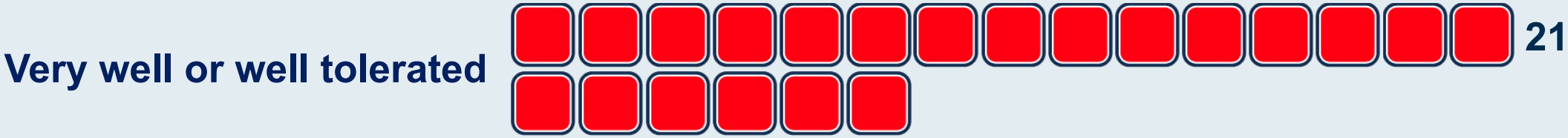


Survey of 21 US-based clinical investigators November 2023

RTP RESEARCH TO PRACTICE

Describe the last patient with CLL to whom you administered pirtobrutinib:

Patient's tolerance of therapy:



Had the patient received a prior BTK inhibitor?

Survey of 21 US-based clinical investigators November 2023

RTP RESEARCH TO PRACTICE

Approach for patients with R/R CLL who have received at least 2 prior lines of therapy, including a BTK inhibitor and a Bcl-2 inhibitor; activity and tolerability of pirtobrutinib

Professor Constantine Tam, MBBS, MD

RTP
RESEARCH
TO PRACTICE

Strategies for overcoming resistance to BTK inhibitors in CLL

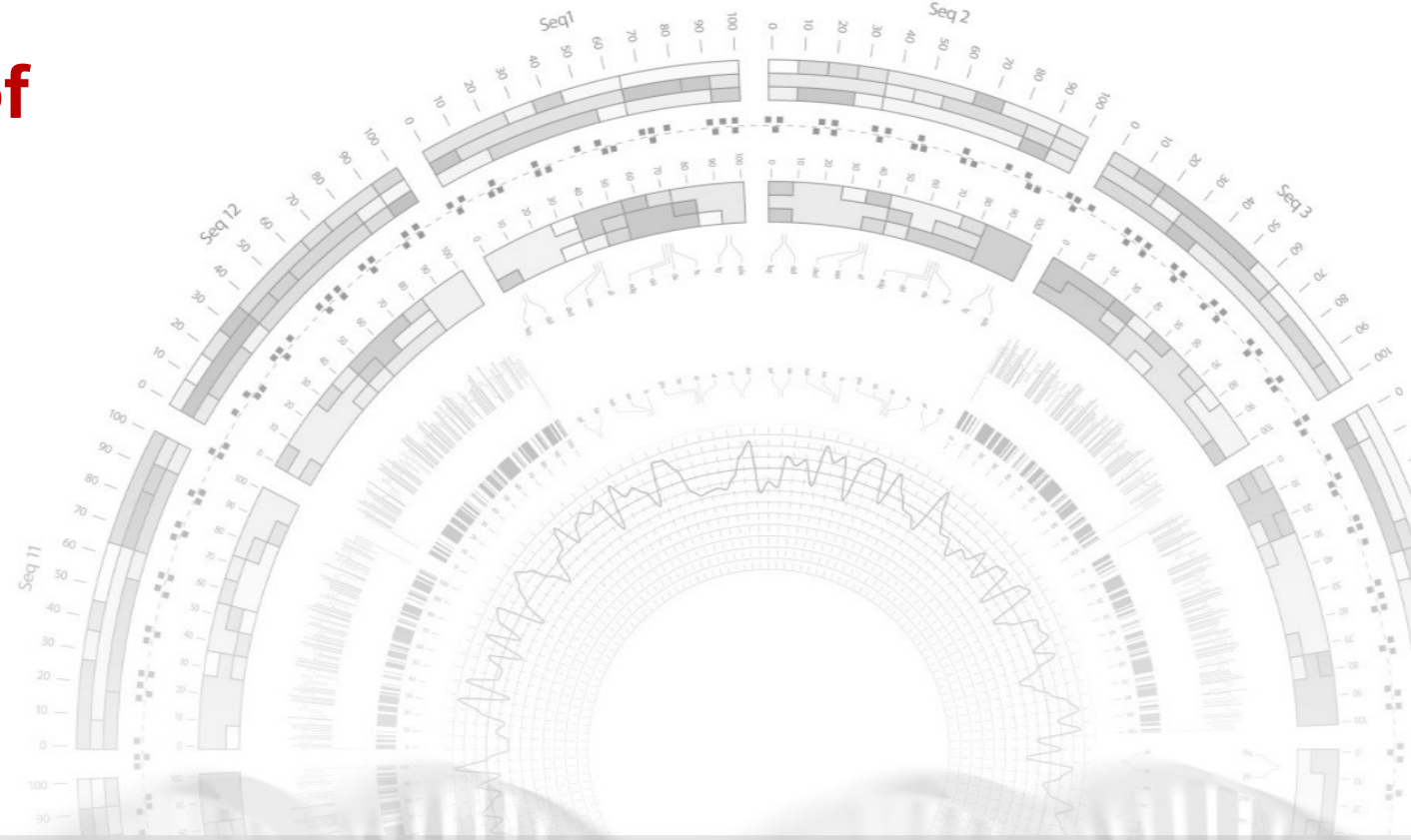
Shuo Ma, MD, PhD

Selection and Sequencing of Therapies for R/R CLL

Jennifer Woyach MD

The James

THE OHIO STATE UNIVERSITY
COMPREHENSIVE CANCER CENTER



NCCN Guidelines for Relapsed/Refractory CLL

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

SECOND-LINE THERAPY OR THIRD-LINE THERAPY		
Preferred regimens • BTKi ▸ Acalabrutinib[f,p,*] (category 1) ▸ Zanubrutinib[f,p,*] (category 1) • BCL-2 inhibitor ▸ Venetoclax[f,g] + rituximab[e] (category 1)	**Other recommended regimens** • Ibrutinib (category 1)[f, h,*] • Venetoclax[f, g]	**Useful in certain circumstances** • Retreatment with venetoclax[f,g] + obinutuzumab (for relapse after a period of remission if previously used as first line therapy) • Non-covalent (reversible) BTK inhibitor ▸ Pirtobrutinib (resistance or intolerance to prior covalent BTKi therapy)[q]

* Covalent (irreversible) BTK inhibitors.

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

SECOND-LINE OR THIRD-LINE THERAPY[e]		
Preferred regimens	**Other recommended regimens**	**Useful in certain circumstances**
• Acalabrutinib[f,p,*] (category 1) • Venetoclax[f,g] + rituximab (category 1) • Venetoclax[f,g] • Zanubrutinib[f,p,*] (category 1)	• Ibrutinib[f,h,*] (category 1) • Alemtuzumab[t] ± rituximab • Duvelisib[f] • HDMP + rituximab • Idelalisib[f,u] ± rituximab • Lenalidomide[s] ± rituximab	• Non-covalent (reversible) BTK inhibitor ▸ Pirtobrutinib (resistance or intolerance to prior covalent BTKi therapy)[q]

NCCN Guidelines for Relapsed/Refractory CLL

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

SECOND-LINE THERAPY OR THIRD-LINE THERAPY		
Preferred regimens	**Other recommended regimens**	**Useful in certain circumstances**
• BTKi ▸ Acalabrutin ▸ Zanubrutini • BCL-2 inhibi ▸ Venetoclax		binutuzumab sion if py) bitor erance to prior

* Covalent (i

Objective: To understand the data behind these guidelines

Preferred regimens	**Other recommended regimens**	**Useful in certain circumstances**
• Acalabrutinib[f,p,*] (category 1) • Venetoclax[f,g] + rituximab (category 1) • Venetoclax[f,g] • Zanubrutinib[f,p,*] (category 1)	• Ibrutinib[f,h,*] (category 1) • Alemtuzumab[t] ± rituximab • Duvelisib[f] • HDMP + rituximab • Idelalisib[f,u] ± rituximab • Lenalidomide[s] ± rituximab	• Non-covalent (reversible) BTK inhibitor ▸ Pirtobrutinib (resistance or intolerance to prior covalent BTKi therapy)[q]

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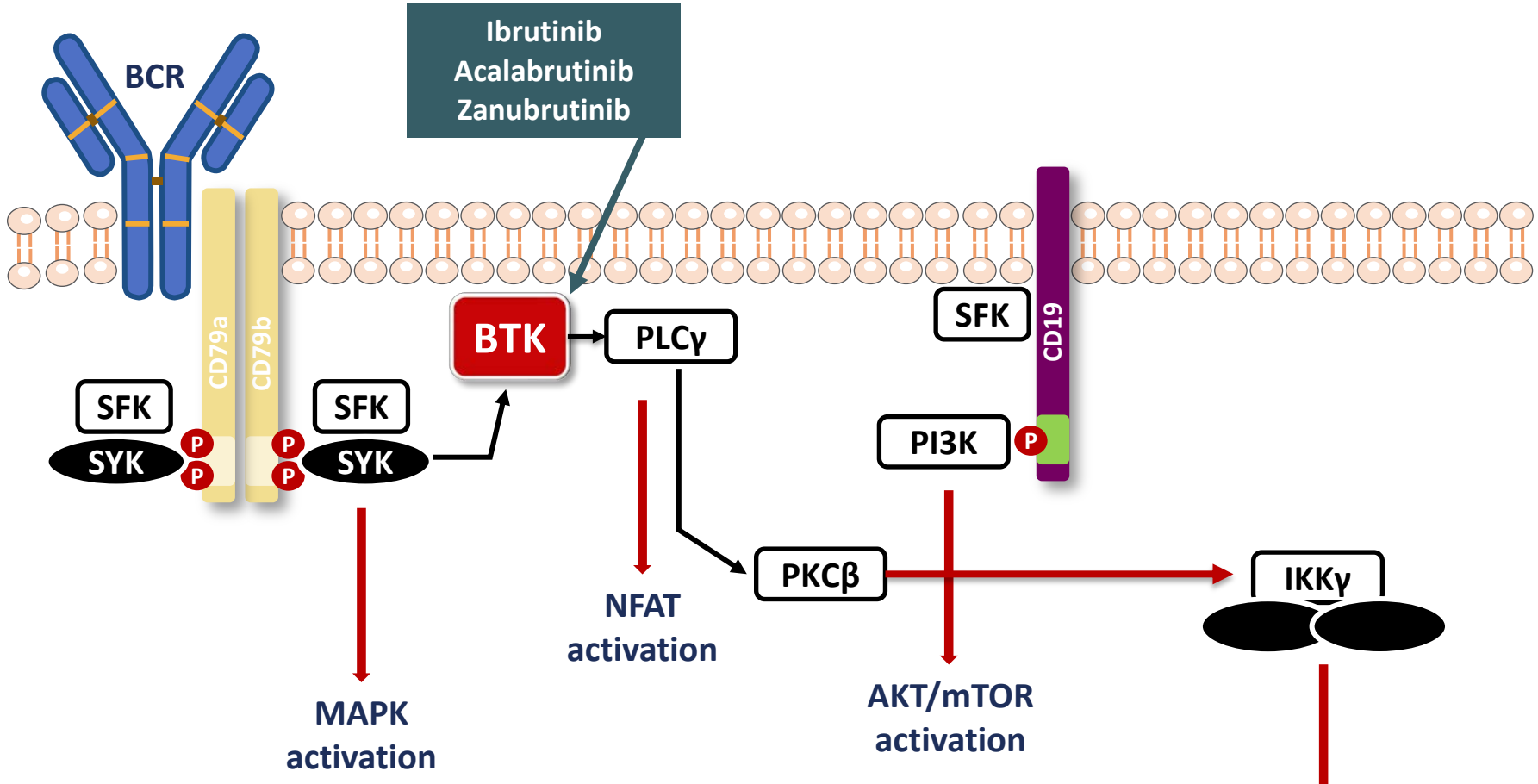
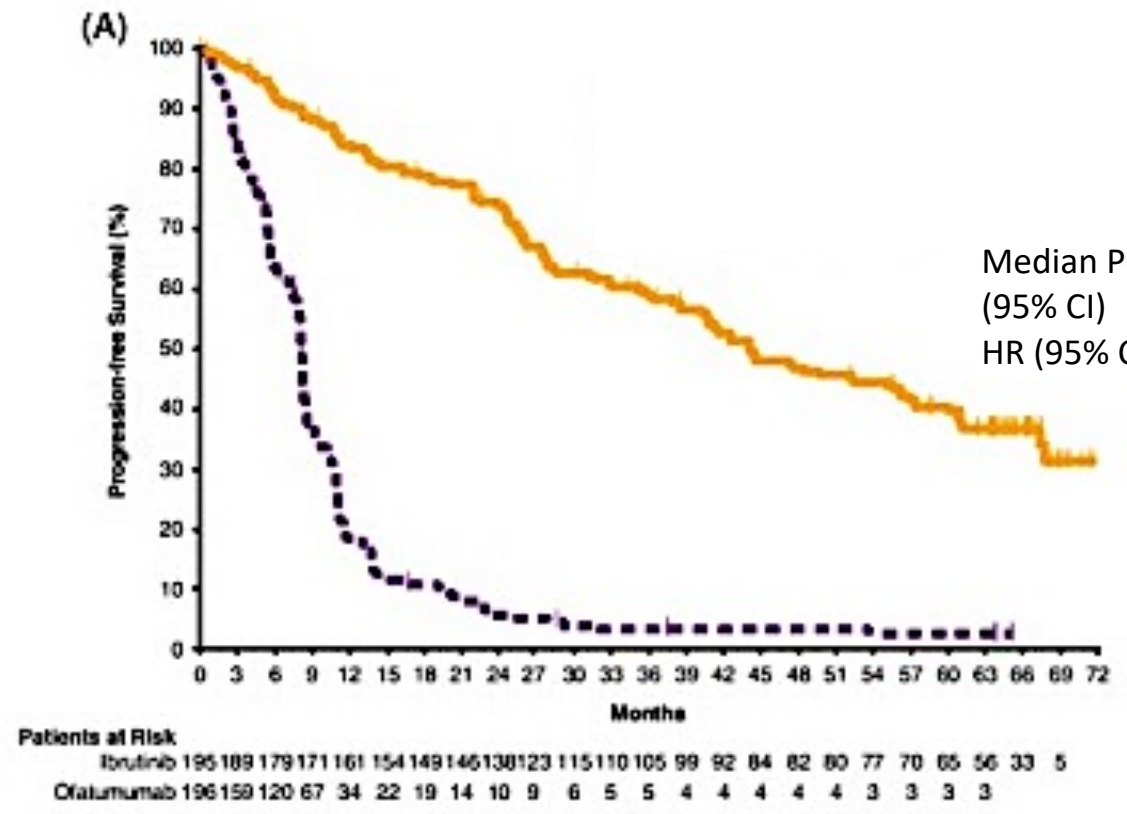
Targeting BCR Signaling in CLL



Young. Nat Rev Drug Discov. 2013;12:229. Burger. Nat Rev Cancer. 2018;18:148.

BTK Inhibitors Demonstrate Long Remission Durations: RESONATE

Phase III trial of **ibrutinib** vs **ofatumumab** for patients with CLL/SLL, ≥1 prior therapy

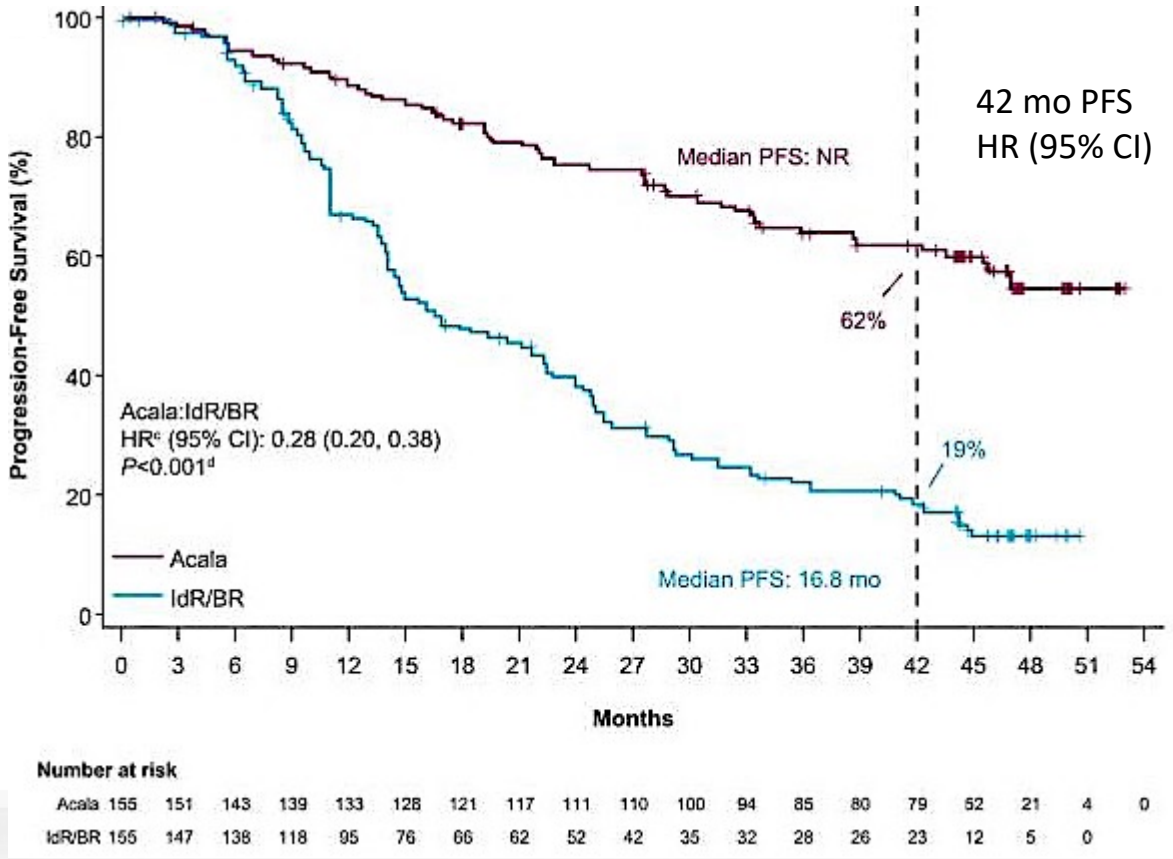


	Ibrutinib (n = 195)	Ofatumumab (n = 196)
Median PFS, mo	44.1	8.1
(95% CI)	(38.5-56.2)	(7.8-8.3)
HR (95% CI)	0.148 (0.113-0.196)	

Munir. Am J Hematol. 2019

BTK Inhibitors Demonstrate Long Remission Durations: ASCEND

Phase III trial of **acalabrutinib** vs **idelalisib + rituximab** or **bendamustine + rituximab** for patients with R/R CLL

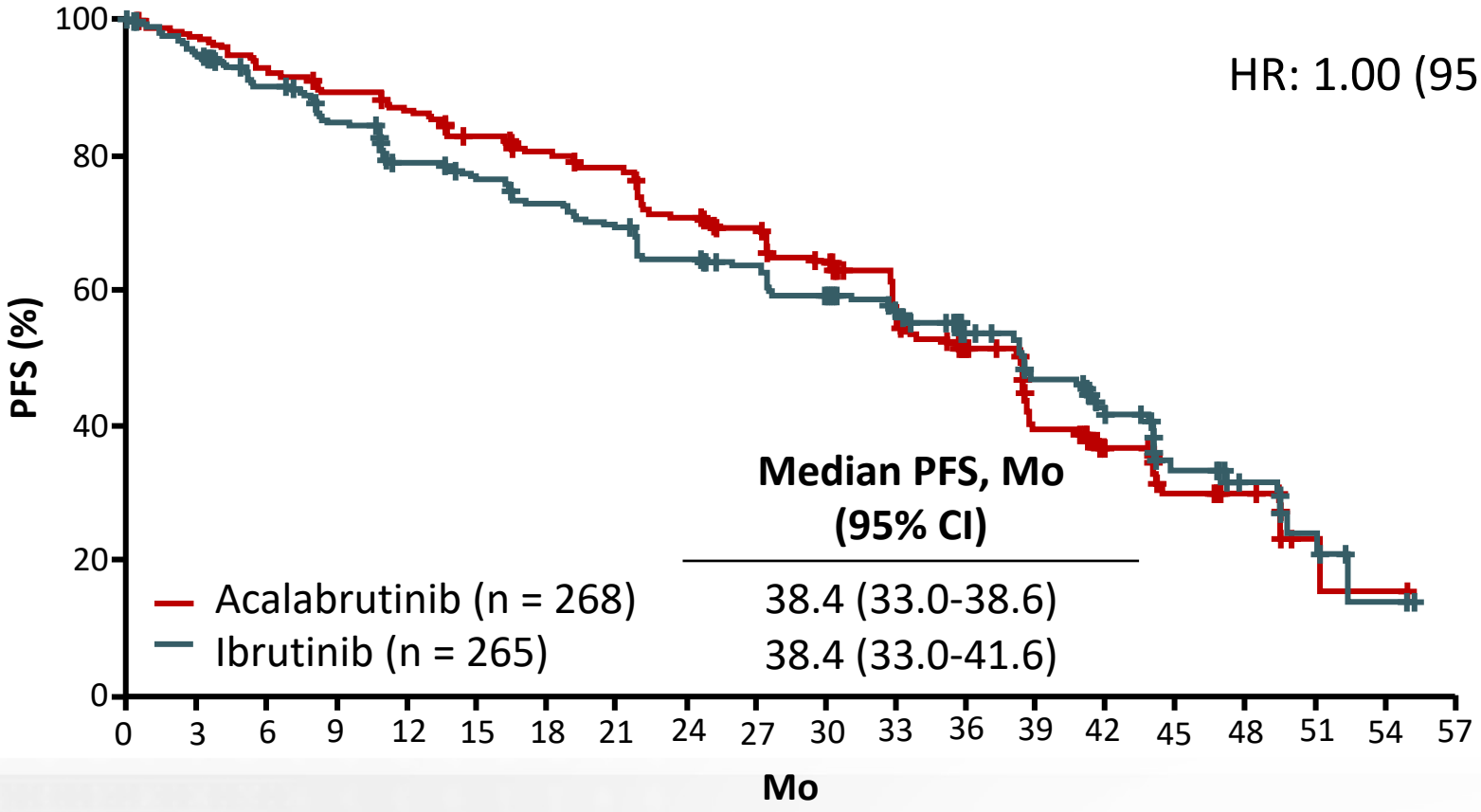


	Acalabrutinib (n = 155)	IdR/BR (n = 147)
42 mo PFS	62%	19%
HR (95% CI)	0.28 (0.2-0.38)	

Ghia et al, Hemasphere 2022

Acalabrutinib vs Ibrutinib: ELEVATE-RR

Phase III noninferiority trial of **acalabrutinib** vs **ibrutinib** for patients with previously treated CLL; presence of del(17p) or del(11q)



HR: 1.00 (95% CI: 0.79-1.27)

Byrd. JCO. 2021.

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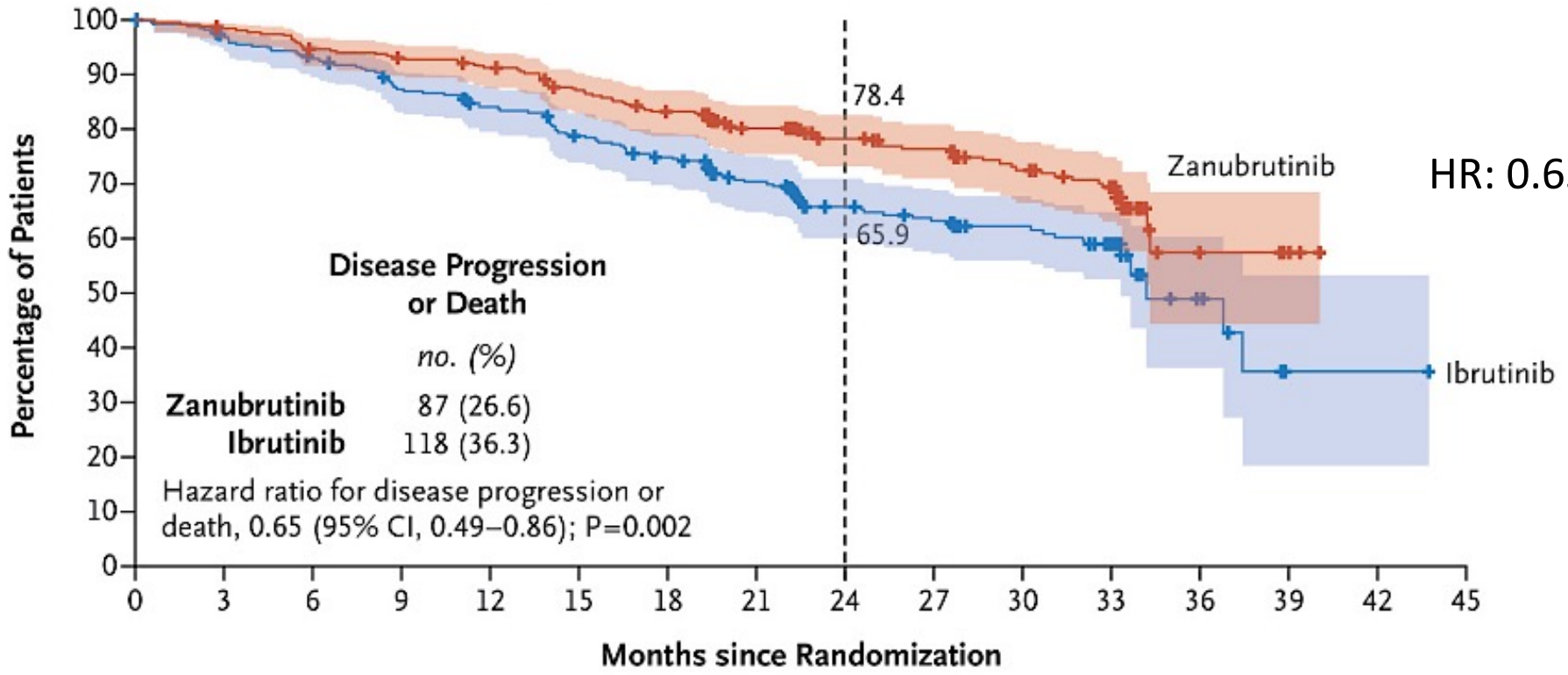
Zanubrutinib vs Ibrutinib: ALPINE

Phase III trial of zanubrutinib vs ibrutinib for patients with relapsed/refractory CLL



HR: 0.65 (95% CI: 0.49-0.86)

No. at Risk															
Zanubrutinib	327	316	303	297	290	274	260	221	165	158	122	111	12	2	0
Ibrutinib	325	306	293	273	259	241	227	186	128	121	97	87	9	1	1	0

Brown. NEJM 2023

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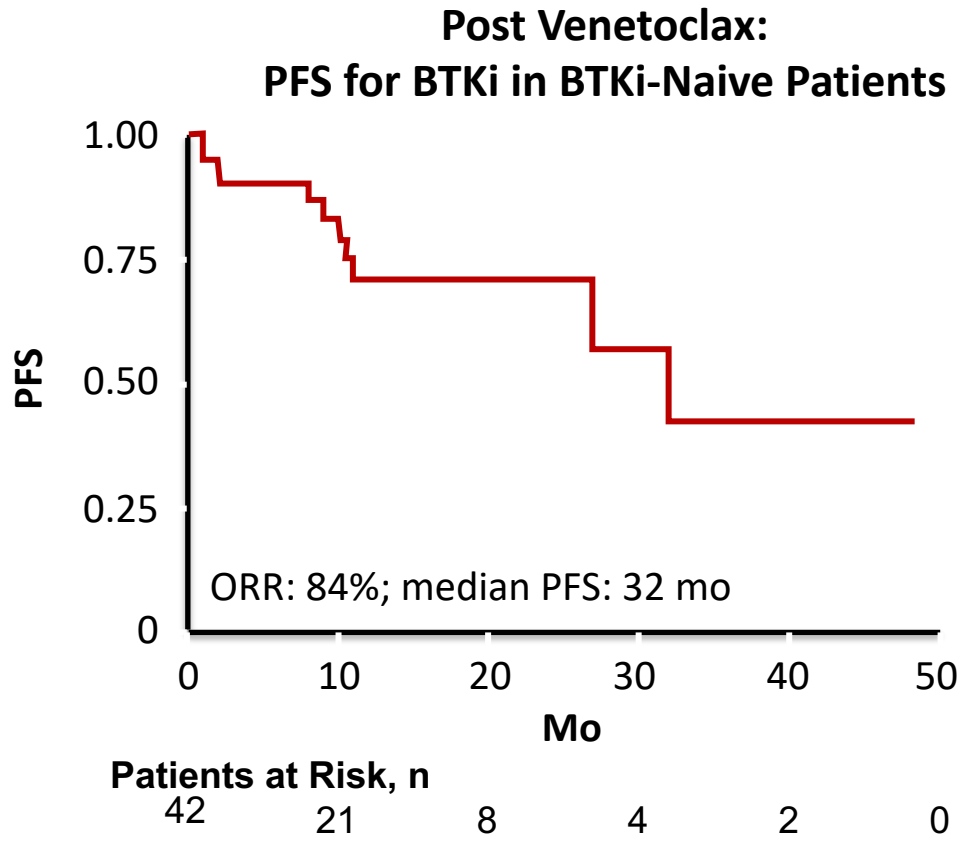
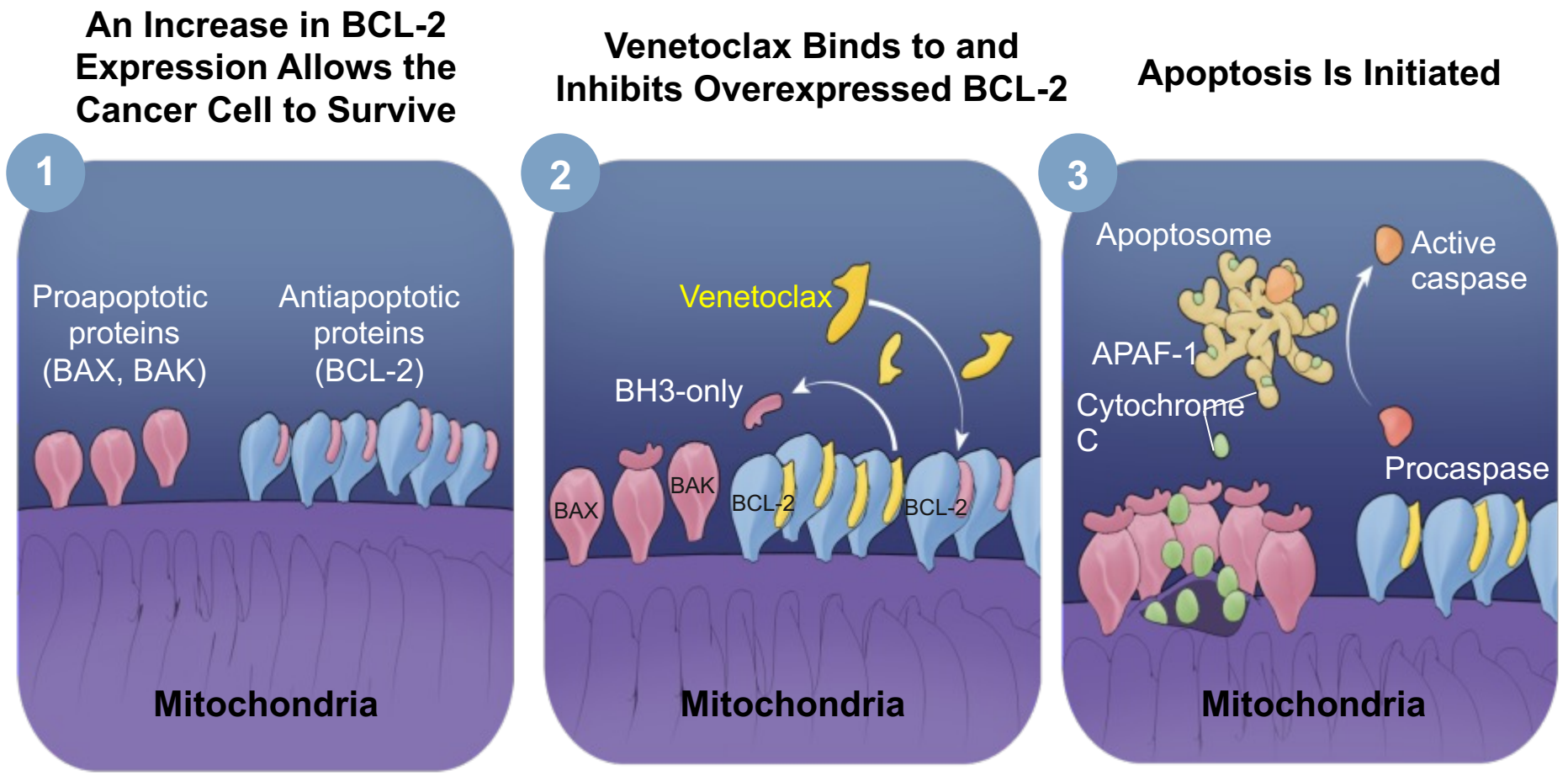
BTKi Demonstrate Efficacy Post-Venetoclax

Multicenter retrospective study of outcomes in patients with CLL who discontinued venetoclax-based therapy (N = 326)



Mato. Clin Cancer Res. 2020

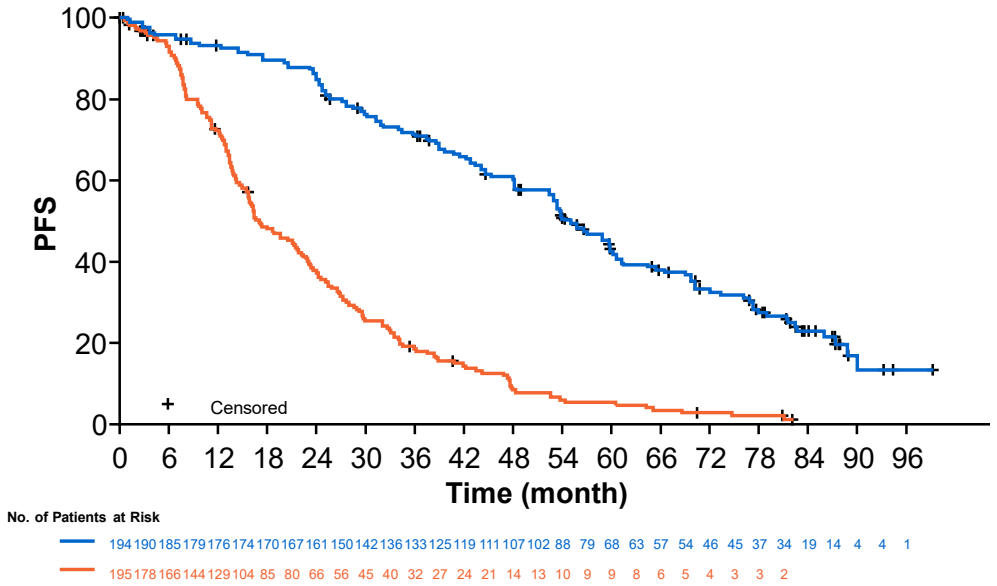
BCL-2 Inhibition With Venetoclax



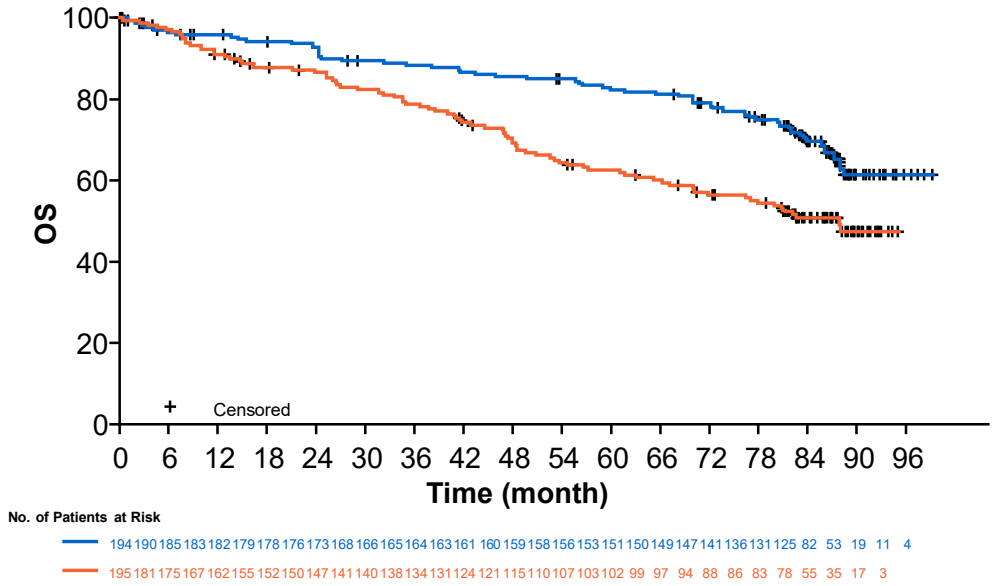
Kumar. ASCO 2015. Abstr 8576.

MURANO: 7-Year Progression-Free Survival and Overall Survival with Venetoclax in Combination with Rituximab

	Median PFS (95% CI), months	HR* (95% CI)	7-year PFS (%)
VenR (n=194)	**54.7** (52.3–59.9)	**0.23** (0.18–0.29) Stratified P-value <0.0001†	**23.0**
BR (n=195)	**17.0** (15.5–21.7)		**NE**



	Median OS (95% CI), months	HR‡ (95% CI)	7-year OS (%)
VenR (n=194)	**NE**	**0.53** (0.37–0.74) Stratified P-value <0.0002†	**69.6**
BR (n=195)	**87.8** (70.1–NE)		**51.0**

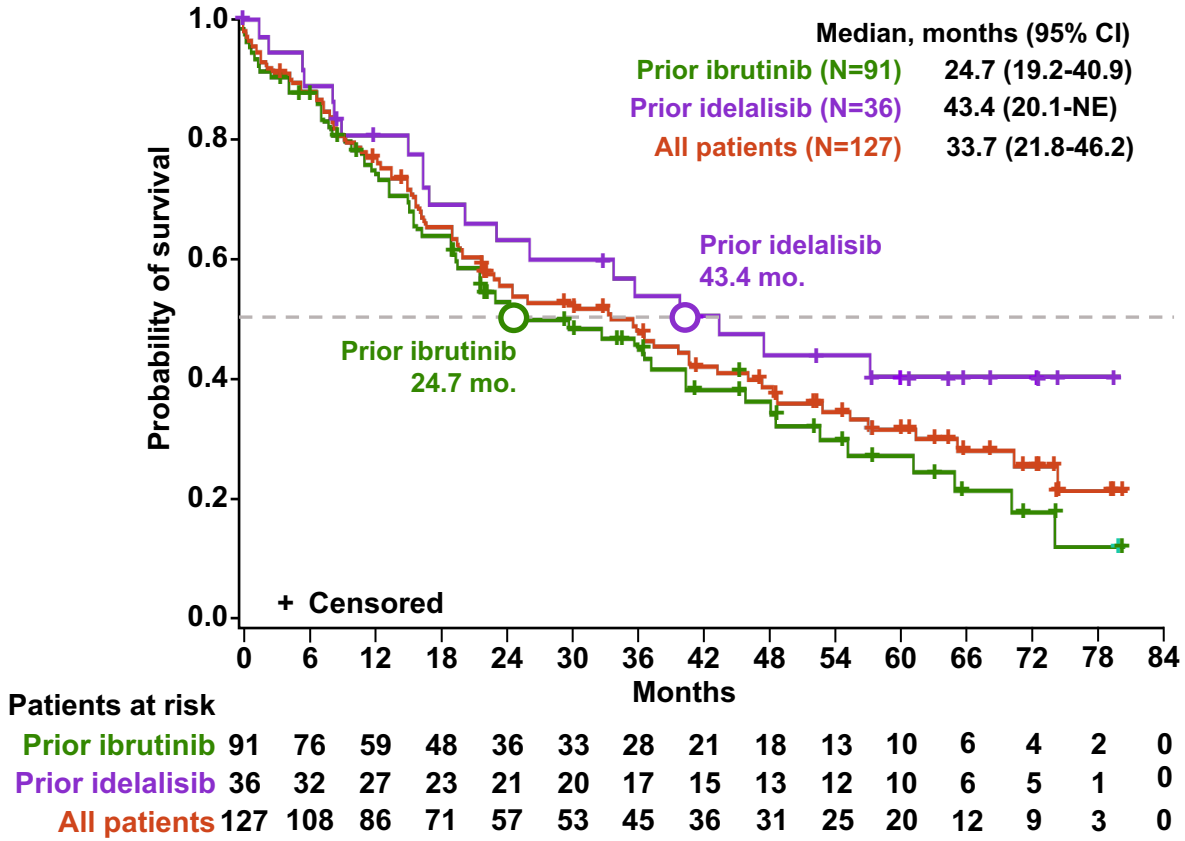


- Median follow-up for efficacy (range) was 86.8 months (0.3-99.2) for VenR and 84.4 months (0.0-95.0) for BR
- No new safety signals were identified since the 5-year data cut,[1] with all patients outside of the AE reporting window§

Kater AP et al. EHA 2023;Abstract S201.

Venetoclax is Effective in the Post-BTKi Setting

Multicenter study of venetoclax monotherapy in patients previously treated with ibrutinib or idelalisib



Woyach et al. iwCLL 2023

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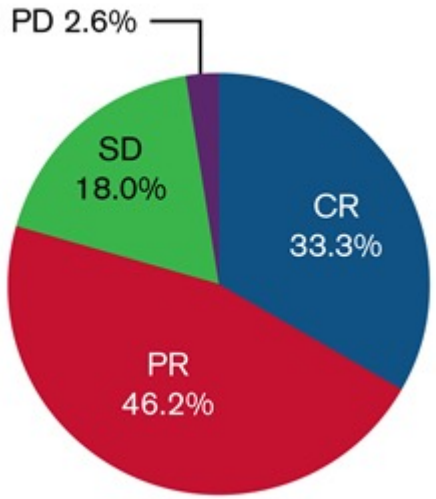
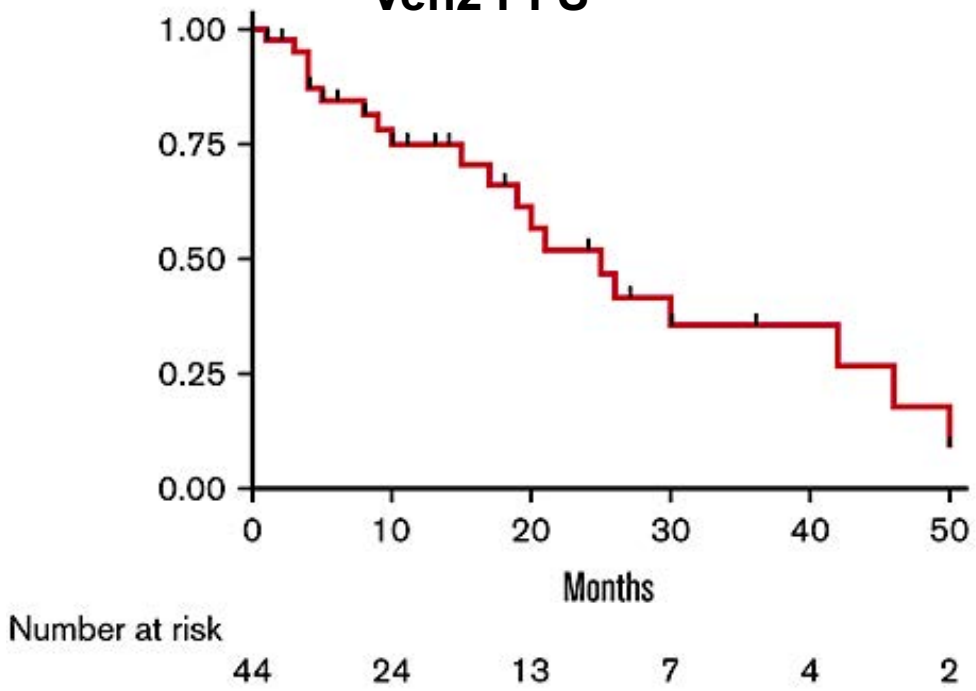
Venetoclax Retreatment Appears Promising

- MURANO retreatment data
  - 18 evaluable patients received subsequent venetoclax post-relapse
    - ORR 72.2%, 5.6% CR/Cri
- Retrospective multicenter data
  - 46 patients, 91% R/R
    - ORR 79.5%, med PFS 25 mo

Ven2 ORR



Ven2 PFS



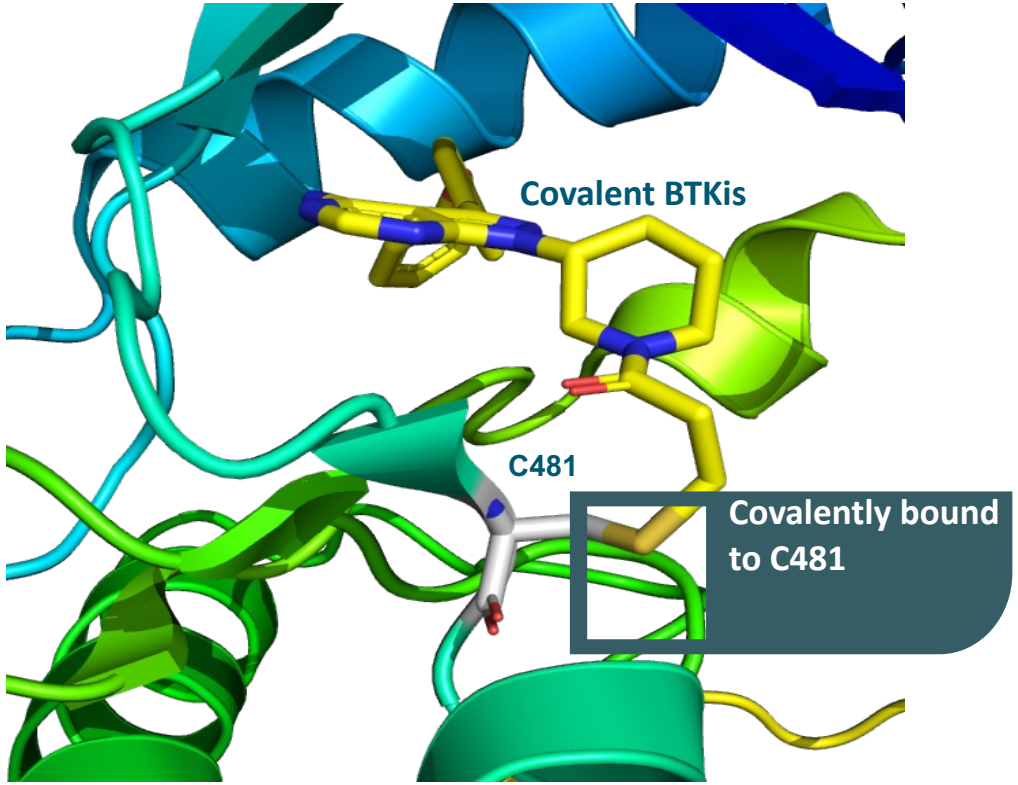
Seymour. Blood. 2022; Thompson. Blood. 2022

What Do These Data Tell Us?

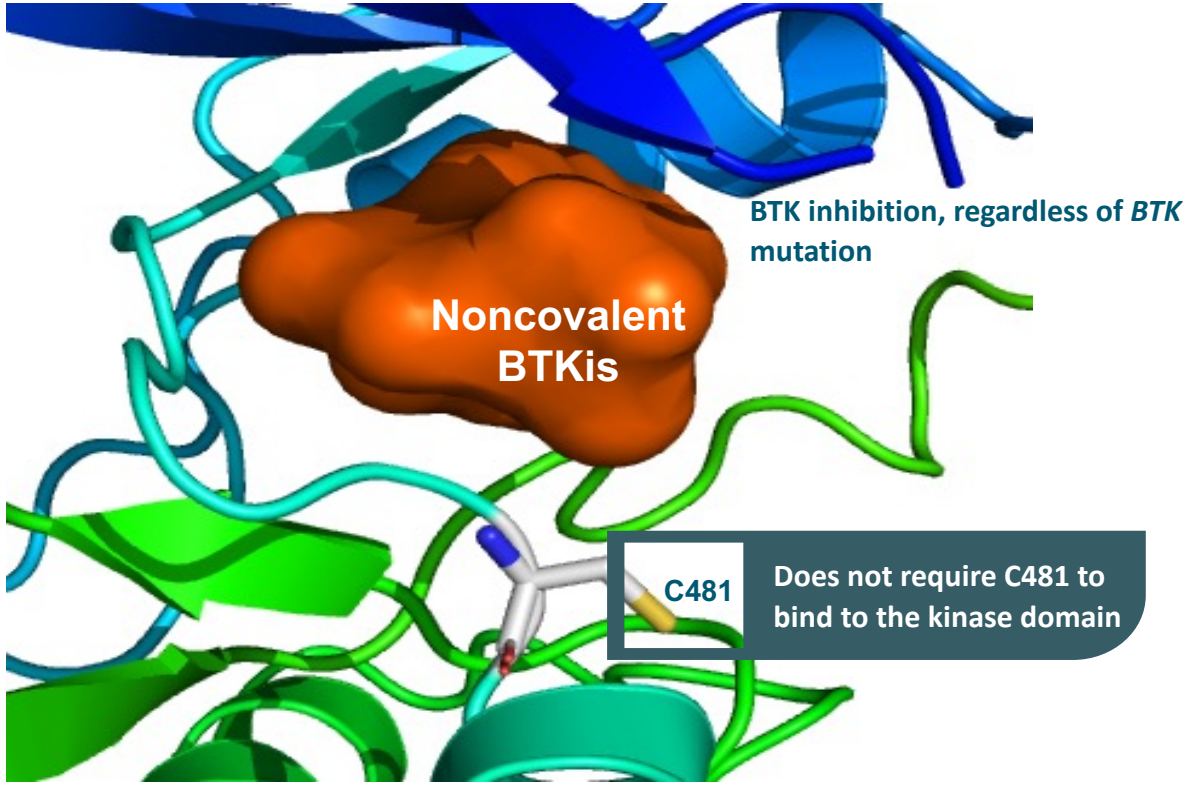
- In the R/R setting (post-chemotherapy), both BTK and BCL-2 inhibitors are very effective
- With available data, it appears that BTKi and BCL-2i can be sequenced in either order
- Venetoclax has prospective evidence of efficacy post-BTKi
- Limited data on venetoclax re-treatment are promising

Noncovalent BTK Inhibition

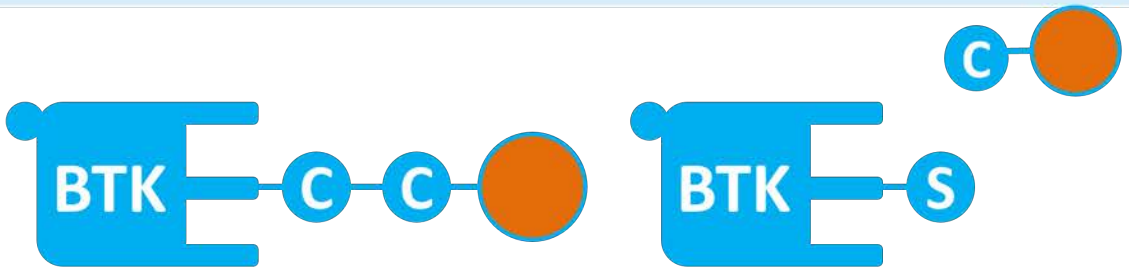
Covalent BTK Inhibitors (Ibrutinib, Acalabrutinib, Zanubrutinib) Require C481 WT *BTK* for Activity



Noncovalent BTK Inhibitors (Pirtobrutinib, Nemtabrutinib) Are Active Against Both WT and C481-Mutated *BTK*

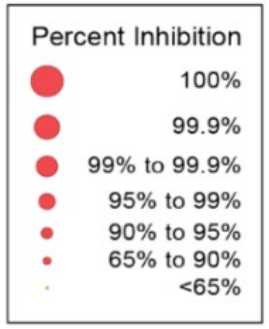


Noncovalent BTK Inhibition

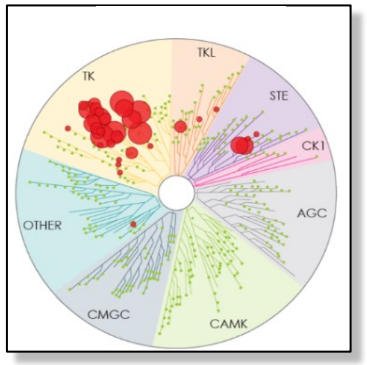
Irreversible BTKi	Reversible BTKi
Ibrutinib Acalabrutinib Zanubrutinib	Pirtobrutinib
	
Inhibited No inhibition	Both wild type and mutant BTK inhibited

Tambaro. J Exp Pharmacol 2021

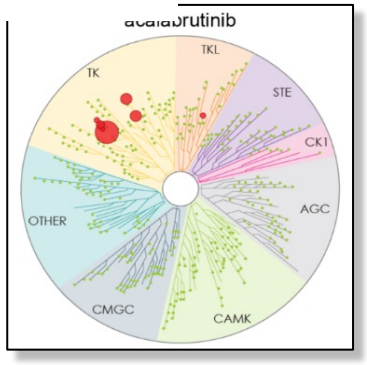
Selectivity Profile of Available BTKi



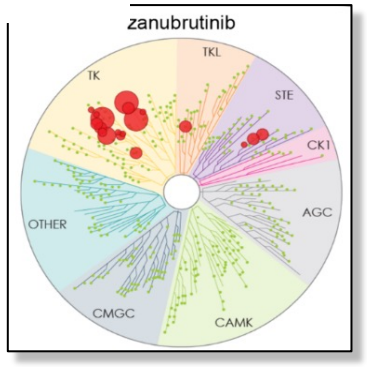
Ibrutinib



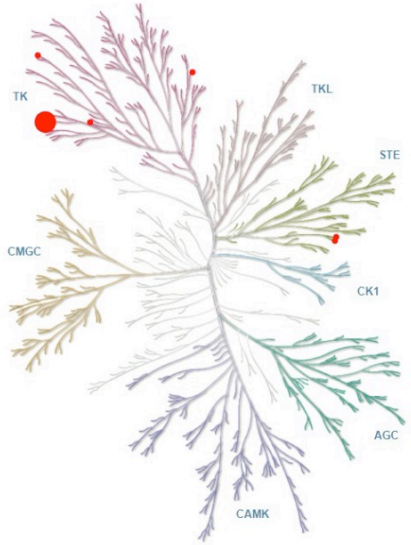
Acalabrutinib



Zanubrutinib



Pirtobrutinib

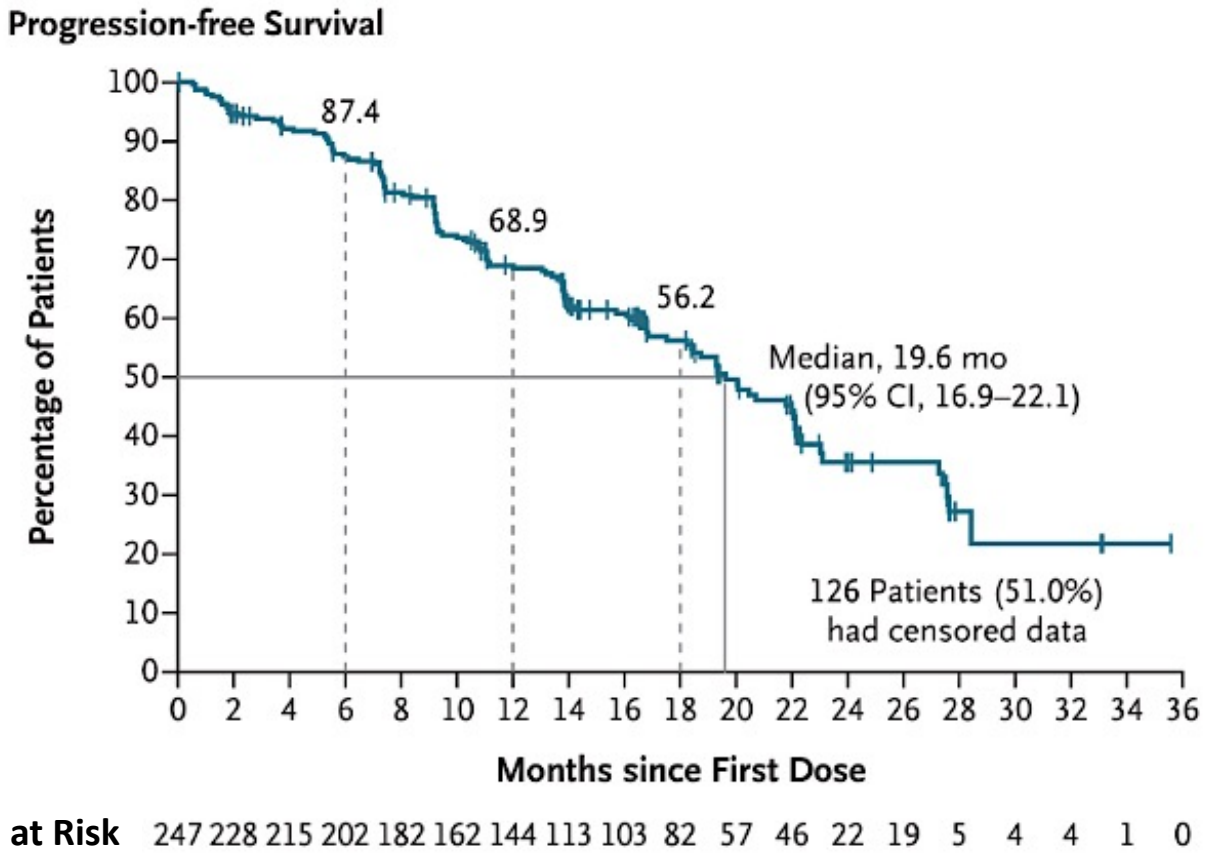


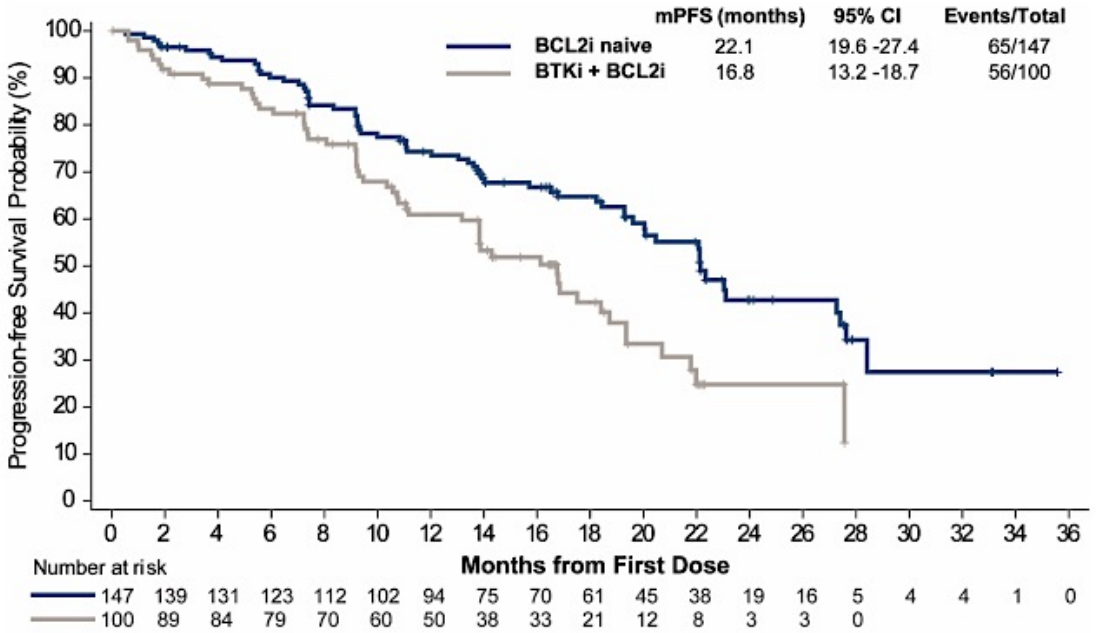
Increased selectivity is expected to lead to improved tolerability

Kaptein A. *Blood*. 2018

Pirtobrutinib in Relapsed/Refractory CLL: BRUIN

Phase 1/2 study of 296 patients with CLL/SLL





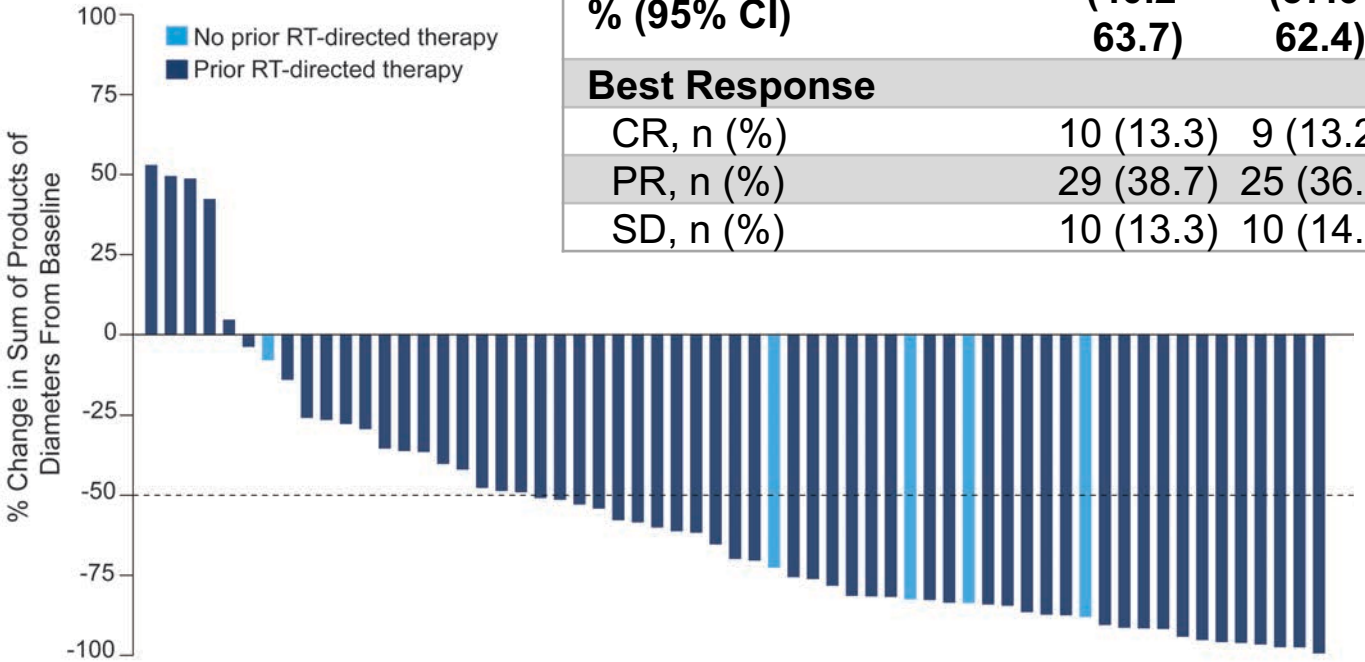
Progression-free survival of patients previously treated with BTKi, and with or without a prior BCL2i treatment.

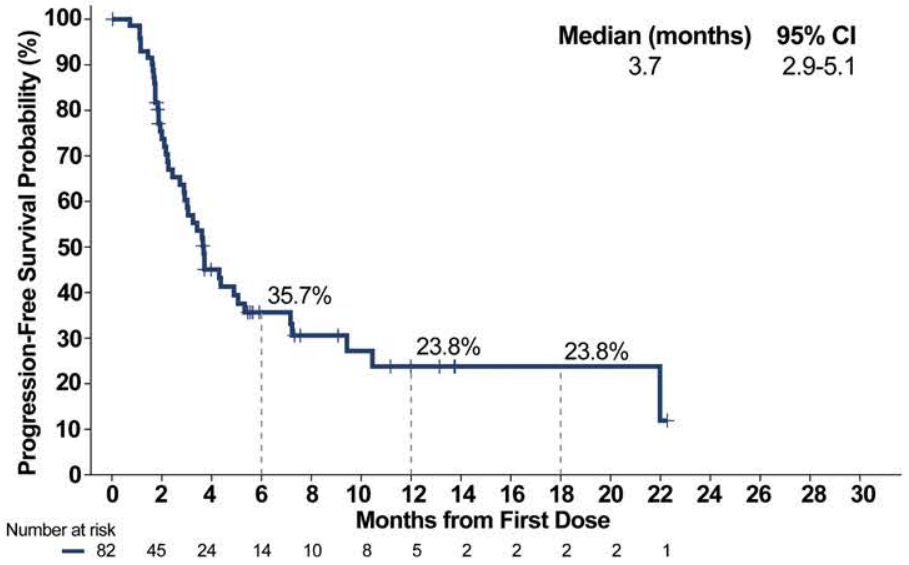
Mato, Woyach. NEJM 2023

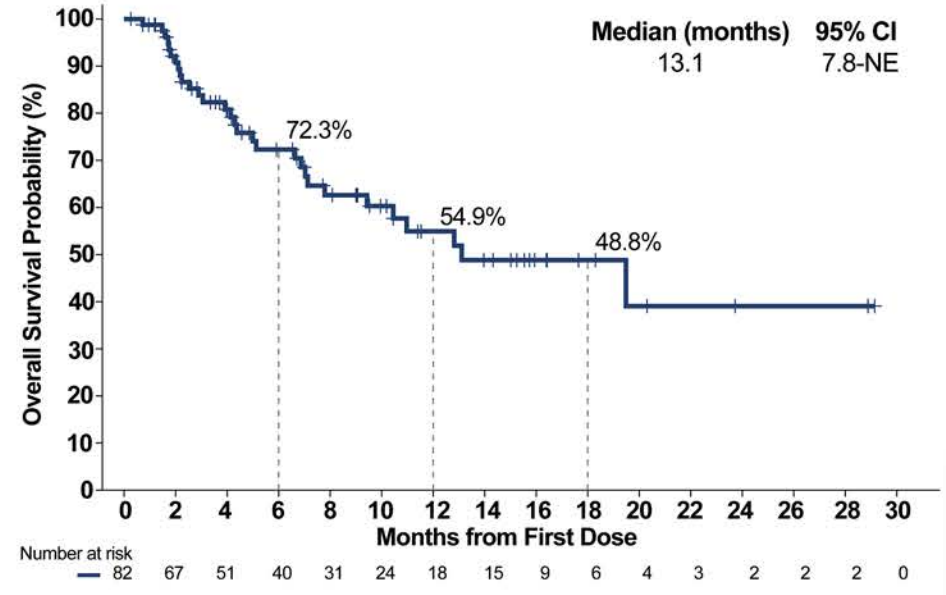
The James
The Ohio State University
Comprehensive Cancer Center

Pirtobrutinib in Richter Transformation: BRUIN

Response Evaluable RT Patients[a]	All n=75	Prior RT Therapy n=68
Overall Response Rate, % (95% CI)	**52.0 (40.2-63.7)**	**50.0 (37.6-62.4)**
Best Response		
CR, n (%)	10 (13.3)	9 (13.2)
PR, n (%)	29 (38.7)	25 (36.8)
SD, n (%)	10 (13.3)	10 (14.7)







Weirda. ASH 2022

Ongoing Phase 3 studies of pirtobrutinib in CLL

Phase 3 Studies of Pirtobrutinib in CLL
NCT05254743: A study of pirtobrutinib versus ibrutinib in participants with CLL/SLL
NCT05023980: A study of pirtobrutinib versus bendamustine plus rituximab (BR) in untreated patients with CLL/SLL
NCT04965493: A trial of pirtobrutinib plus venetoclax and rituximab (PVR) versus venetoclax and rituximab (VR) in previously treated CLL/SLL
NCT04666038: Study of pirtobrutinib versus investigator's choice (IdelaR or BR) in patients with previously treated CLL/SLL

What do these data tell us?

- Noncovalent BTKi like pirtobrutinib, have efficacy in patients previously treated with cBTKi and those with dual-refractory CLL
- Pirtobrutinib also has preliminary efficacy in Richter's transformation
- Phase 3 studies are ongoing to compare pirtobrutinib versus standard of care agents in a variety of settings

Take home points

- Long-term follow-up confirms efficacy of BTKi and BCL2i in patients with R/R CLL
- While the definitive trials have not included patients previously treated with targeted agents, retrospective data suggest that BTKi → BCL2i or BCL2i → BTKi is appropriate
- Noncovalent BTKi like pirtobrutinib have demonstrated efficacy in patients previously treated with cBTKi
- Ongoing studies will confirm the place of pirtobrutinib in the current armamentarium of CLL therapies

FDA Grants Accelerated Approval to Pirtobrutinib for CLL and Small Lymphocytic Lymphoma

Press Release: December 1, 2023

"On December 1, 2023, the Food and Drug Administration granted accelerated approval to pirtobrutinib for adults with chronic lymphocytic leukemia or small lymphocytic lymphoma (CLL/SLL) who have received at least two prior lines of therapy, including a BTK inhibitor and a BCL-2 inhibitor.

Efficacy was evaluated in BRUIN (NCT03740529], an open-label, international, single-arm, multicohort trial that included 108 patients with CLL or SLL previously treated with at least two prior lines of therapy, including a BTK inhibitor and a BCL-2 inhibitor. Patients received a median of 5 prior lines of therapy. Seventy-seven percent of patients discontinued the last BTK inhibitor for refractory or progressive disease. Pirtobrutinib was administered orally at 200 mg once daily and was continued until disease progression or unacceptable toxicity.

The main efficacy outcome measures were overall response rate (ORR) and duration of response (DOR), as assessed by an independent review committee using 2018 iwCLL criteria. The ORR was 72% and median DOR was 12.2 months. All responses were partial responses.

The recommended pirtobrutinib dose is 200 mg orally once daily until disease progression or unacceptable toxicity."

https://www.fda.gov/drugs/resources-information-approved-drugs/fda-grants-accelerated-approval-pirtobrutinib-chronic-lymphocytic-leukemia-and-small-lymphocytic

RTP RESEARCH TO PRACTICE

Agenda

Module 1: Front-Line Treatment for Chronic Lymphocytic Leukemia (CLL) — Dr Wierda

Module 2: Novel Strategies Combining Bruton Tyrosine Kinase (BTK) and Bcl-2 Inhibitors in the Treatment of CLL — Dr Davids

Module 3: Optimal Management of Adverse Events with BTK and Bcl-2 Inhibitors; Considerations for Special Patient Populations — Dr Awan

Module 4: Selection and Sequencing of Therapies for Relapsed/Refractory CLL — Dr Woyach

Module 5: Promising Investigational Agents and Strategies — Dr Schuster

RTP RESEARCH TO PRACTICE

To approximately how many patients with CLL have you adminstered CAR (chimeric antigen receptor) T-cell therapy on or off protocol?

Median number of patients: 5 (range 0-20)

Which specific clinical situations do you consider ideal for the use of CAR T-cell therapy for CLL?

- Failed BTK inhibitor, Bcl-2 inhibitor, anti-CD20
- Dual refractory disease, Richter’s transformation
- Double refractory
- Richter’s transformation
- Would like to see it explored in earlier lines of therapy, such as at time of progression on 1L covalent BTKi in high risk patients, or as a consolidation strategy in patients with suboptimal response to time-limited 1L ven combinations
- Richter's transformation to DLBCL or double-refractory CLL
- Consolidation of BTK response and for patients with Richter's transformation
- Richter’s transformation
- Double refractory if pirtobrutinib not available
- High-risk CLL in MRD+ remission on 2nd- or 3rd-line therapy
- Double-refractory CLL
- Double refractory to ven and covalent BTKi and also refractory to pirtobrutinib, Still with adequate PS/comorbidities to permit CAR-T administration
- Triple refractory
- Richter’s transformation, triple-refractory CLL
- Double refractory and/or when behaving like Richter's transformation
- Best outcomes for patients with stable or responsive disease to bridging therapies, i.e., pirtobrutinib or venetoclax + REPOCH followed by CAR-T or ven + BTKi

Survey of 21 US-based clinical investigators November 2023

RTP RESEARCH TO PRACTICE

Regulatory and reimbursement issues aside, what would be your preferred approach to Richter's transformation in a patient with CLL?

- Combined targeted BTK inhibitor and venetoclax + anti-CD20
- Clinical trial; CAR-T if trial not possible
- Chemoimmunotherapy then allo-SCT
- R-CHOP
- Cytoreduction without chemotherapy if possible and then CAR-T as soon as approved
- Venetoclax + R-CHOP
- Depends on prior treatment and TP53 status.
- Clinical trial or R-CHOP or R-EPOCH +/- BTK
- R-CHOP plus ven
- Pola-R-CHP
- Bispecific or chemo followed by CAR-T
- Ven/R-CHOP followed by alloSCT if in remission
- Epcoritamab
- R-CHOP + venetoclax or BTKi + venetoclax in patients who are not resistant to these agents
- Chemo + ven and then alloSCT
- R-EPOCH/ibrutinib

Survey of 21 US-based clinical investigators November 2023

RTP RESEARCH TO PRACTICE

Investigation of CD19-directed chimeric antigen receptor (CAR) T-cell therapy for patients with CLL

Jan A Burger, MD, PhD

RTP
RESEARCH
TO PRACTICE

Antitumor activity observed with pirtobrutinib and the bispecific antibody epcoritamab among patients with Richter's transformation

Professor Constantine Tam, MBBS, MD

RTP
RESEARCH
TO PRACTICE

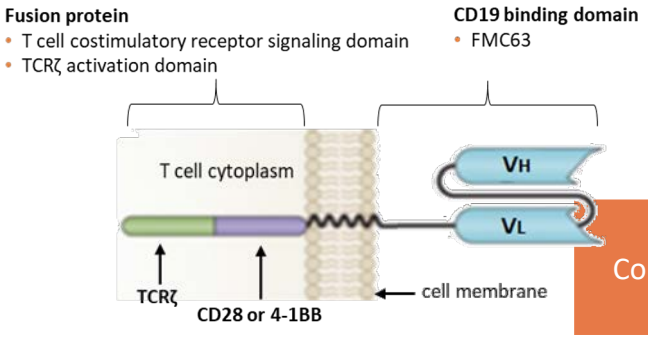
Beyond the Guidelines:
Promising Investigational Agents and Strategies for CLL

Stephen J. Schuster, M.D.

Professor of Medicine
Perelman School of Medicine, University of Pennsylvania

Director, Lymphoma Program & Lymphoma Translational Research
Abramson Cancer Center, University of Pennsylvania

FDA-approved CD19-directed CAR-T products for mature B-cell cancers



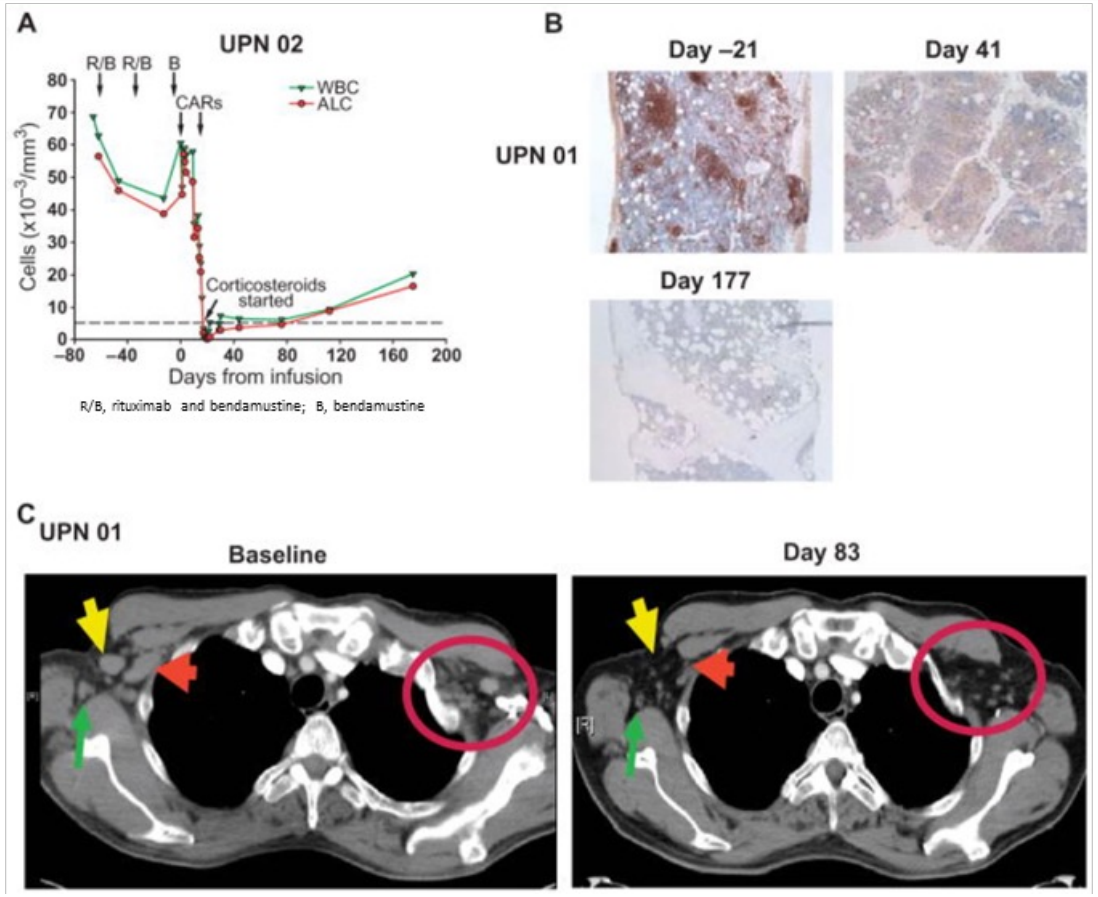
	Construct	Indication(s)	Approval date	Apheresis product for manufacturing	CAR+ cell dose	Bridging therapy	Lymphodepletion
Axicabtagene ciloleucel [1,2,3]	CD3ζ - CD28 - scFv FMC63	≥ 3rd line of therapy for **LBCL**	October 2017	Fresh, bulk PBMC	0.6 - 6.0 ×10^8	Not studied in pivotal trial	Cy/Flu 500/30 × 3d
		≥ 3rd line of therapy for **FL**	March 2021				
		1° refractory or relapsed < 12 months of 1st line therapy for **LBCL**	April 2022				
Tisagenlecleucel [4,5]	CD3ζ - 4-1BB - scFv FMC63	≥ 3rd line of therapy for **LBCL**	May 2018	Cryopreserved, bulk PBMC	2 × 10^6 / kg (max. 2 × 10^8)	92% received in pivotal trial	Cy/Flu 250/25 × 3d or benda. 90 x 2d
		≥ 3rd line of therapy for **FL**	May 2022				
Lisocabtagene maraleucel [6,7]	tEGFR - CD3ζ - 4-1BB - scFv FMC63	≥ 3rd line of therapy for **LBCL**	February 2021	Fresh, isolated CD8+ & CD4+ cells	100 × 10^6 as 1:1 CD8+:CD4+	59% received in pivotal trial	Cy/Flu 300/30 × 3d
	CD3ζ - CD28 - scFv FMC63	1° refractory or relapsed < 12 months of 1st line therapy for **LBCL**	June 2022				
Brexucabtagene autoleucel [8]		relapsed / refractory **MCL**	July 2020	Fresh, B cell depleted	1 - 2 × 10^8	91% received in pivotal trial	Cy/Flu 500/30 × 3d

LBCL, large B-cell lymphomas
FL, follicular lymphoma
MCL, mantle cell lymphoma
PBMC, peripheral blood mononuclear cells
Cy/Flu, cyclophosphamide/fludarabine
Benda, bendamustine

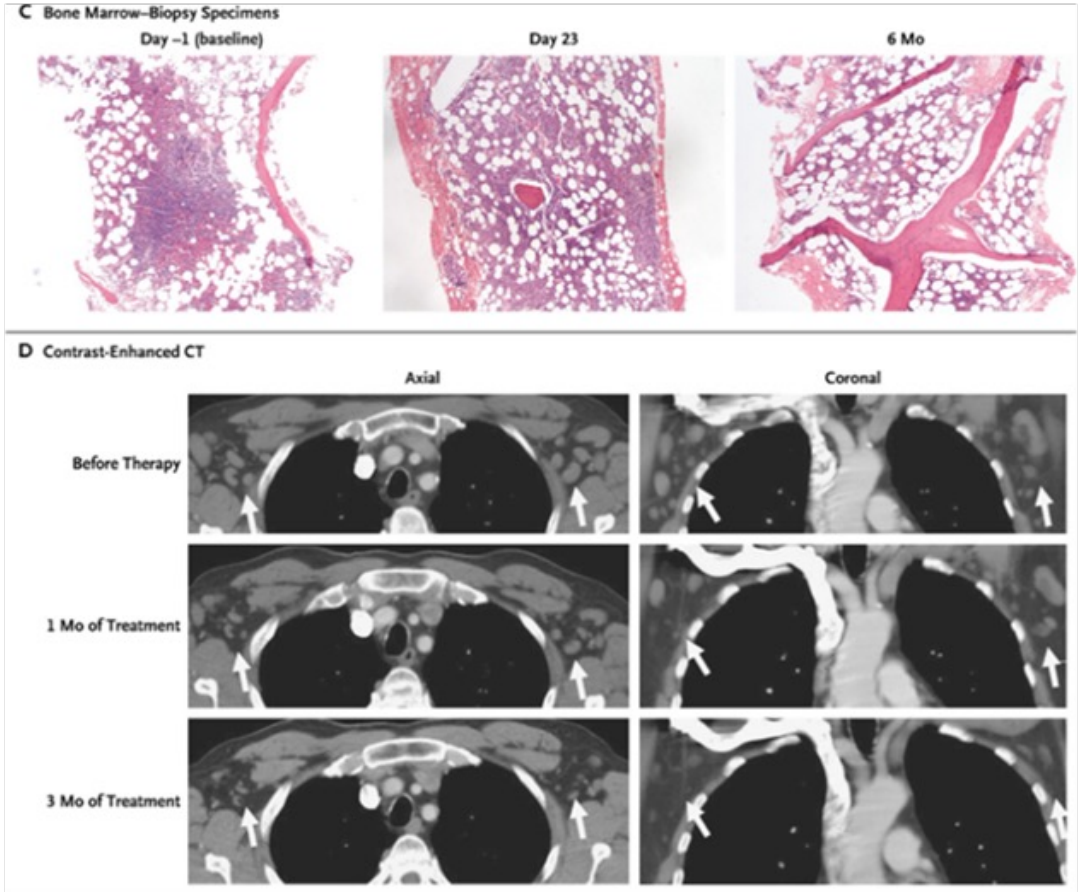
[1] Locke, et al. Lancet Oncol. 2019;20:31-42.
[2] Jacobson et al. Lancet Oncol. 2022;23(1):91-103.
[3] Locke et al. N Engl J Med. 2022;386(7):640-654.
[4] Schuster, et al. N Engl J Med. 2019;380:45-56.
[5] Fowler et al. Nat Med. 2022;28(2):325-332.
[6] Abramson et al. Lancet 2020;396: 839–52.
[7] Abramson et al. Blood. 2023;141(14):1675-1684.
[8] Wang, et al. N Engl J Med. 2020;382(14):1331-1342.

CTL019: 2nd-generation CD19-directed 4-1BB-TCRζ CAR-T cells

T Cells with Chimeric Antigen Receptors Have Potent Antitumor Effects and Can Establish Memory in Patients with Advanced Leukemia[1]

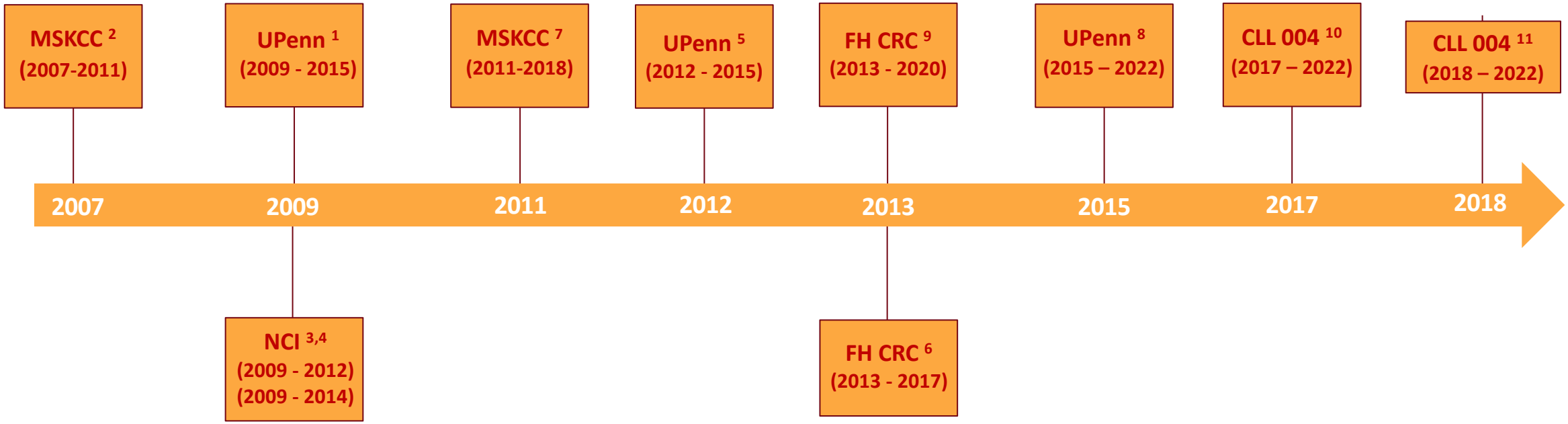


Chimeric Antigen Receptor-modified T Cells in Chronic Lymphoid Leukemia[2]



[1.] Kalos M, et al. Sci Transl Med. 2011;10:95ra73; [2.] Porter DL, et al. N Engl J Med. 2011;365:725-33.

CAR-T cell therapy of CLL: a decade of progress



[1] Porter, et al. Sci Transl Med. 2015;7:303ra139.
[2] Brentjens, et al. Blood. 2011;118(18):4817-4828.
[3] Kochenderfer, et al. Blood. 2012;119(12):2709-2720.
[4] Kochenderfer, et al. J Clin Oncol. 2014;33:540-549.
[5] Frey, et al. J Clin Oncol. 2020;38:2862-2871.
[6] Turtle, et al. J Clin Oncol. 2017;35:3010-3020.
[7] Geyer, et al. Molecular Therapy 2018;26(8):1896-1905.
[8] Gill, et al. Blood Adv. 2022;6(21):5774-5785.
[9] Gauthier et al. Blood. 2020;135(19):1650-1660.
[10] Siddiqi, et al. Blood. 2022;139(12):1794-1806.
[11] Siddiqi, et al. The Lancet. 2023;402(10402):641-654.

Clinical trials of autologous CD19-directed CAR-T cell therapy for CLL

Trial (year posted – published)	N	CAR	CAR T combination	Prior BTKi / BCL-2i	Risk Factors	Lympho-depletion	ORR / CRR	Progression-free survival	CRS* ≥Gr.3	Neurotoxicity ≥Gr.3
UPenn [1] (2009 - 2015)	14	āCD19 + 4-1BB-CD3ζ	no	0 / 0	median prior Rx: 5 del17p: 6 (43%)	Benda, n = 6 Flu/Cy, n = 3 Pent/Cy, n = 5	57% / 29%	18 month PFS = 29%	43%	7%
MSKCC [2] (2007-2011)	8	āCD19 + CD28-CD3ζ	no	0 / 0	median prior Rx: 3 del17p: 2 (25%)	none, n = 4 Cy, n = 4	0% / 0 %	n/a	not reported	not reported
NCI [3] (2009 - 2012)	4	āCD19 + CD28-CD3ζ	no	0 / 0	median prior Rx: 4	Flu/Cy + IL-2, n = 4	75% / 25%	not reported 1 CR at 15 mo. 2 PR at 7 mo. 1 SD at 6 mo.	100%	25%
NCI [4] (2009 - 2014)	4	āCD19 + CD28-CD3ζ	no	0 / 0	median prior Rx: 3	Flu/Cy, n = 4	100% / 75%	not reported 3 CR at 14, 15, 23 mo. 1 PR at 4 mo.	50%	25%
UPenn [5] (2012 - 2015)	32	āCD19 + 4-1BB-CD3ζ	no	9 (28%) / 1 (3%)	median prior Rx: 3.5 del17p/TP53m: 9 (28%)	Flu/Cy, n = 20 Benda, n = 8 Pent/Cy, n = 2 OFAO, n = 1 GEMOX, n = 1	44% / 28%	median PFS, all patients = 1 mo. 36-month PFS, CR patients = 67%	24%	8%
Fred Hutchinson CRC [6] (2013 - 2017)	24	āCD19 + 4-1BB-CD3ζ-EGFRt with 1:1 CD4:CD8 CAR-T cell ratio	no	24 (100%) / 6 (25%)	median prior Rx: 5 del17p: 14 (58%)	Flu/Cy, n = 21 Cy, n = 1 Flu, n = 2	71% / 17%	median PFS, all patients = 8.5 mo.	8%	25%
MSKCC [7] (2011-2018)	8	āCD19 + CD28-CD3ζ	PCR → CAR T	0 / 0	<CR after 1st Rx (PCR x 6)	Cy, n = 8	38% / 25% (*post* CAR T)	median PFS = 13.6 mo. (2 CRs with PD at 29 and 53 mo.)	0	0
UPenn [8] (2015 - 2022)	19	āCD19 + 4-1BB-CD3ζ	Ibr → CAR T + Ibr	19 (100%) / NR	median prior Rx: 2 del17p: 13 (68%)	Benda, n = 6 Flu/Cy, n = 13	68% / 53%* (*best CRR; 72% MRD-)	48-month PFS = 70%	11%	5%
Fred Hutchinson CRC [9] (2013 - 2020)	19	āCD19 + 4-1BB-CD3ζ-EGFRt with 1:1 CD4:CD8 CAR-T cell ratio	Ibr → CAR T + Ibr	19 (100%) / 11 (58%)	median prior Rx: 5 (all failed prior Ibr) del17p: 14 (74%)	Flu/Cy, n = 19	83% / 22%* (*at 1-mo.; 61% MRD-)	1-year PFS = 38% with Ibr vs. 1-year PFS = 50% without Ibr	0	26%
BMS sponsored [10] (2017 – 2022)	23	āCD19 + 4-1BB-CD3ζ-EGFRt with 1:1 CD4:CD8 CAR-T cell ratio	no	23 (100%) / 15 (65%)	median prior Rx: 4 del17p/TP53m: 22 (96%)	Flu/Cy, n = 23	82% / 45% (65% MRD-)	median PFS = 18 mo.	9%	22%
BMS sponsored [11] (2018 – 2022)	117	āCD19 + 4-1BB-CD3ζ-EGFRt with 1:1 CD4:CD8 CAR-T cell ratio	no	117 (100%) / 89 (76%)	all (100%) BTKi failures 70 (60%) BCL-2i failures median prior Rx: 5 del17p/TP53m: 103 (88%)	Flu/Cy, n=117	48% / 18% (n=96, efficacy-evaluable)	median PFS = 18 mo.	9%	19%

N, number infused; CAR, chimeric antigen receptor; BTKi, Bruton tyrosine kinase inhibitor; BCL-2i, venetoclax; NR, not, reported; OOR, overall response rate, CRR, complete response rate; SD, stable, disease; mo., month; PFS, progression-free survival; CRS, cytokine release syndrome (*scales differ between studies); Benda, bendamustine; Flu/Cy, fludarabine/cyclophosphamide; Pent/Cy, pentostatin/cyclophosphamide; OFAO, oxaliplatin, fludarabine, cytarabine, ofatumumab; GEMOX, gemcitabine, oxaliplatin; PCR, pentostatin, cyclophosphamide, rituximab; Ibr, ibrutinib

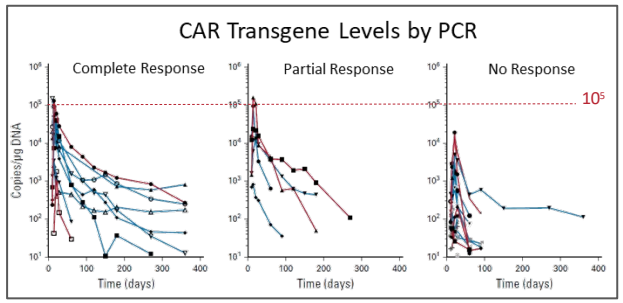
[1] Porter, et al. Sci Transl Med. 2015;7:303ra139.; [2] Brentjens, et al. Blood. 2011;118(18):4817-4828.; [3] Kochenderfer, et al. Blood. 2012;119(12):2709-2720.; [4] Kochenderfer, et al. J Clin Oncol. 2014;33:540-549.; [5] Frey, et al. J Clin Oncol. 2020;38:2862-2871.; [6] Turtle, et al. J Clin Oncol. 2017;35:3010-3020.;
[7] Geyer, et al. Molecular Therapy 2018;26(8):1896-1905.; [8] Gill, et al. Blood Adv. 2022;6(21):5774-5785.; [9] Gauthier et al. Blood. 2020;135(19):1650-1660.; [10] Siddiqi, et al. Blood. 2022;139(12):1794-1806.; [11] Siddiqi, et al. The Lancet. 2023;402(10402):641-654.

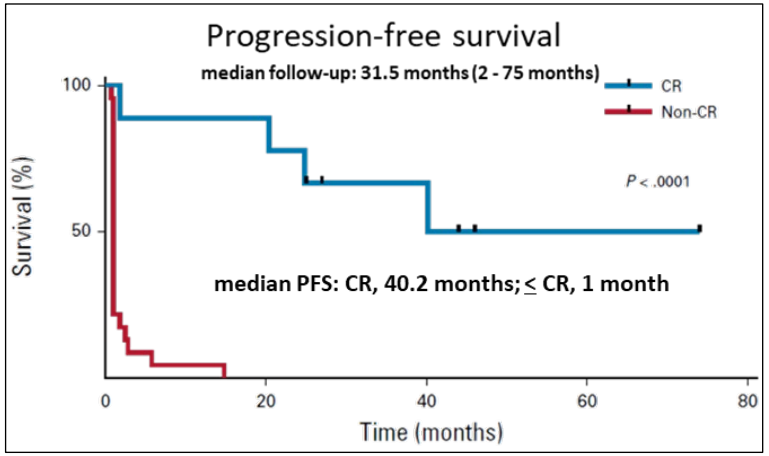
Outcomes of CAR-T cells in relapsed CLL

UPenn (2012 - 2015)

UPenn CTL019 Dose Optimization Study

N = 32
4-week CR rate: **28%**
4-week OR rate: **44%**
Median PFS: **1 months** (for CR: 40.2 months)



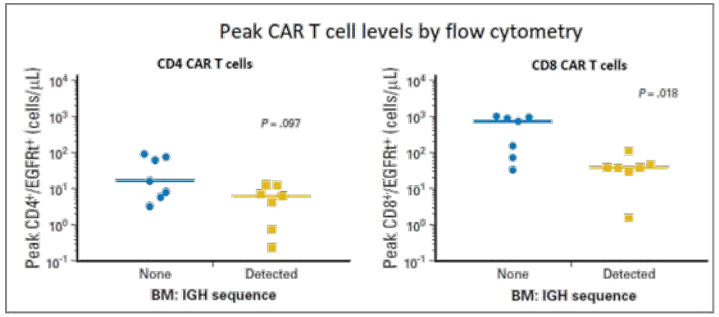


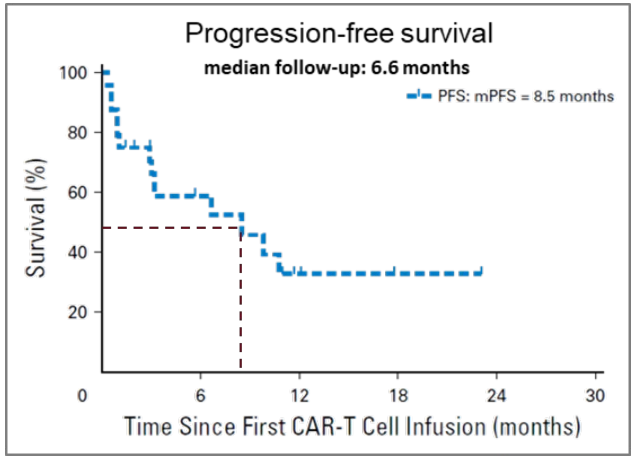
Frey, et al. J Clin Oncol. 2020;38:2862-2871.

Fred Hutchinson CRC (2013 - 2017)

Prior Ibrutinib Study

N = 24 [19/24 (79%) with PD on Ibrutinib]
4-week CR rate: **21%**
4-week OR rate: **74%**
Median PFS: **8.5 months**





Turtle, et al. J Clin Oncol. 2017;35:3010-3020.

Outcomes of CAR-T cells in relapsed CLL

Multicenter Study
(2018 – 2022)

Multicenter Study: 21/23 (91%) with **PD on Ibrutinib**

and 10/23 (43%) **venetoclax exposed**

N = 23

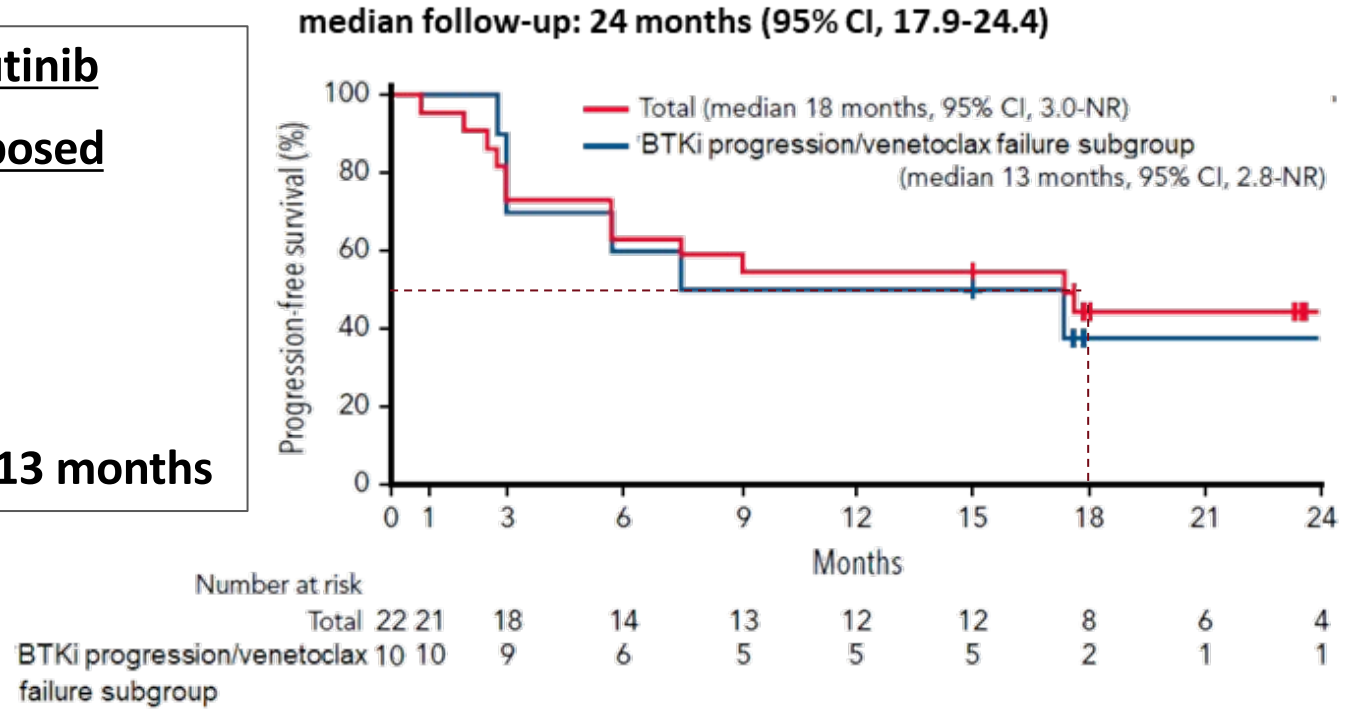
Best CR rate: **45%**

Best OR rate: **82%**

Median PFS: **18 months**

Median PFS, BTKi failure/venetoclax exposed: 13 months

Progression-free survival



Siddiqi, et al. Blood. 2022;139(12):1794-1806.

Outcomes of CAR-T cells in relapsed CLL

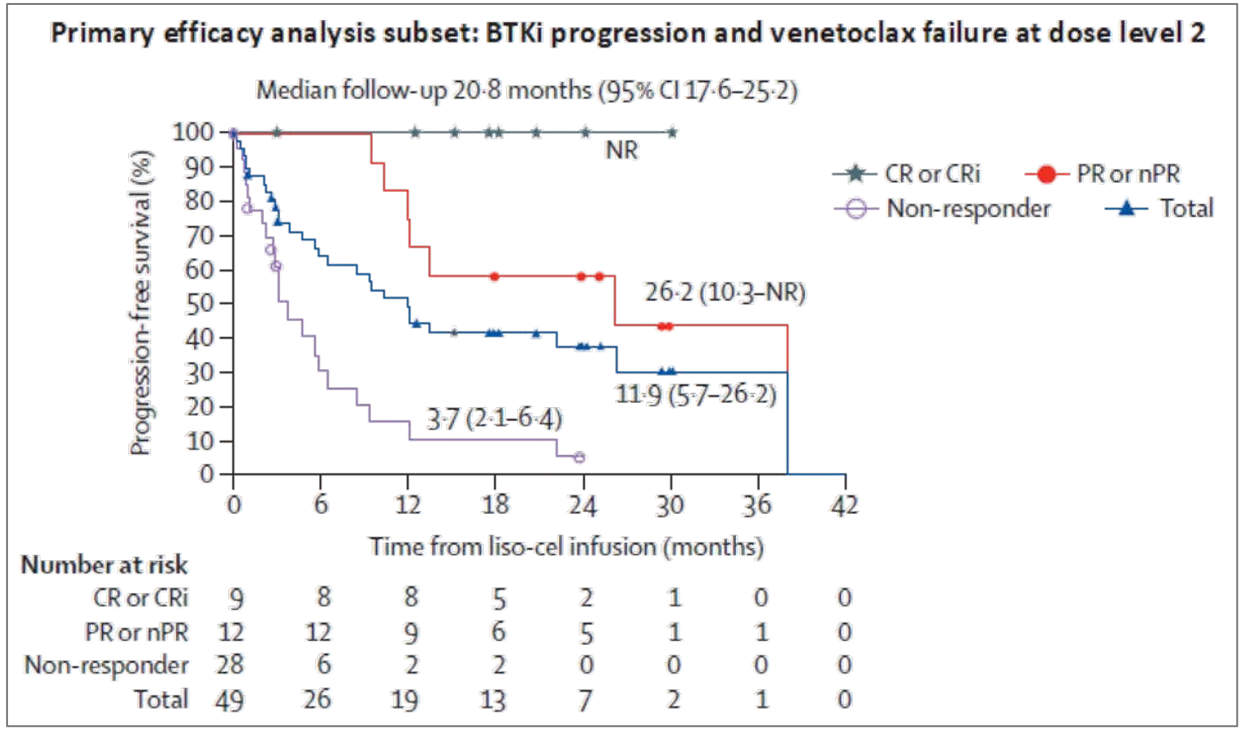
Multicenter Study (2018 – 2022)

All patients were BTKi treatment failures

Multicenter Study: ***all patients BTKi failures***

N = 117 (efficacy set, n = 96)
Best CR rate: **18%**
Best OR rate: **48%**
Median PFS: **18 months**
Median response duration: 35 months
Median response duration for CR: not reached

N = 49 (BTKi progression and venetoclax failure at DL2)
Best CR rate: **18%**
Best OR rate: **43%**
Median PFS: 12 months
Median response duration: 35 months
Median response duration for CR: not reached



Siddiqi, et al. The Lancet. 2023;402(10402):641-654.

Outcomes of CAR-T therapies in relapsed CLL

How can we do better?

Ibrutinib improves T cell number and function in CLL

Plenary Paper

LYMPHOID NEOPLASIA

Ibrutinib is an irreversible molecular inhibitor of ITK driving a Th1-selective pressure in T lymphocytes

Jason A. Dubovsky,[1] Kyle A. Beckwith,[1,2] Gayathri Natarajan,[3] Jennifer A. Woyach,[1] Samantha Jaglowski,[1] Yiming Zhong,[1] Joshua D. Hessler,[1] Ta-Ming Liu,[1] Betty Y. Chang,[4] Karilyn M. Larkin,[1] Matthew R. Stefanovski,[1] Danielle L. Chappell,[1] Frank W. Frissora,[1] Lisa L. Smith,[1] Kelly A. Smucker,[1] Joseph M. Flynn,[1] Jeffrey A. Jones,[1] Leslie A. Andritsos,[1] Kami Maddocks,[1] Amy M. Lehman,[5] Richard Furman,[6] Jeff Sharman,[7] Anjali Mishra,[1] Michael A. Caligiuri,[1] Abhay R. Satoskar,[8] Joseph J. Buggy,[4] Natarajan Muthusamy,[1] Amy J. Johnson,[1,9] and John C. Byrd[1,9]

[1]Department of Internal Medicine, Division of Hematology, [2]Medical Scientist Training Program, and [3]Department of Microbiology, The Ohio State University, Columbus, OH; [4]Pharmacyclics, Inc., Sunnyvale, CA; [5]Center for Biostatistics, The Ohio State University, Columbus, OH; [6]Department of Medicine, Division of Hematology-Oncology, Weill Cornell Medical College, New York, NY; [7]Willamette Valley Cancer Institute/US Oncology, Springfield, OR; and [8]Department of Pathology, and [9]Division of Medicinal Chemistry, College of Pharmacy, The Ohio State University, Columbus, OH

- **Ibrutinib is a clinically viable irreversible ITK inhibitor[1]**
- **Ibrutinib inhibits the formation of Th2 but not Th1 immunity[1]**

Regular Article

IMMUNOBIOLOGY

Ibrutinib enhances chimeric antigen receptor T-cell engraftment and efficacy in leukemia

Joseph A. Fraietta,[1,2,*] Kyle A. Beckwith,[3,*] Prachi R. Patel,[1,2] Marco Ruella,[1,2] Zhaohui Zheng,[1,2] David M. Barrett,[4] Simon F. Lacey,[1,2] Jan Joseph Melenhorst,[1,2] Shannon E. McGettigan,[1,2] Danielle R. Cook,[1,2] Changfeng Zhang,[1,2] Jun Xu,[1,2] Priscilla Do,[3] Jessica Hulitt,[4] Sagar B. Kudchodkar,[1,2] Alexandria P. Cogdill,[1,2] Saar Gill,[1,5] David L. Porter,[1,2,5] Jennifer A. Woyach,[3] Meixiao Long,[3] Amy J. Johnson,[3] Kami Maddocks,[3] Natarajan Muthusamy,[3] Bruce L. Levine,[1,2,6] Carl H. June,[1,2,6] John C. Byrd,[3,*] and Marcela V. Maus[7,*]

- **Ibrutinib treatment of CLL enhances the generation of CAR-T cells for adoptive immunotherapy[2]**
- **Concurrent ibrutinib therapy improves the engraftment and therapeutic efficacy of anti-CD19 CAR T cells in mouse models[2]**

[1]Dubovsky, *et al.* Blood. 2013;122:2539-2549; [2]Fraietta, *et al.* Blood. 2016;127(9):1117-1127.

Ibrutinib improves T cell number and function in CLL

CLINICAL MEDICINE

The Journal of Clinical Investigation

Ibrutinib treatment improves T cell number and function in CLL patients

Meixiao Long,[1,2] Kyle Beckwith,[1,2,3] Priscilla Do,[1,2,3] Bethany L. Mundy,[1,2] Amber Gordon,[1,2] Amy M. Lehman,[2,4] Kami J. Maddocks,[1,2] Carolyn Cheney,[2] Jeffrey A. Jones,[1,2] Joseph M. Flynn,[1] Leslie A. Andritsos,[1,2] Farrukh Awan,[1,2] Joseph A. Fraietta,[5] Carl H. June,[5] Marcela V. Maus,[6] Jennifer A. Woyach,[1,2] Michael A. Caligiuri,[1,2] Amy J. Johnson,[1,2] Natarajan Muthusamy,[1,2] and John C. Byrd[1,2]

Ibrutinib treatment:

- **increases *in vivo* persistence of activated CD4+ and CD8+ T cells, via diminished activation-induced cell death through ITK inhibition**
- **decreases the Treg/CD4+ T cell ratio**
- **diminishes the immune-suppressive properties of CLL cells through BTK-independent and BTK-dependent mechanisms:**
  1. ***decreased PD-1 expression by T cells***
  2. ***decreased CTLA-4 expression by T cells***
  3. ***decreased CD200 (OX-2) expression by CLL cells***
  4. ***decreased BTLA expression by CLL cells***
  5. ***decreased IL-10 production by CLL cells***

Long, *et al*. J Clin Invest. 2017;127:3052-3064.

Outcome of CAR-T with concurrent ibrutinib in r/r CLL

UPenn

- **Patients on ibrutinib for at least 6 months with best response to ibrutinib ≤ PR**
  - **3 patients had prior CAR T**

UPenn Study: CAR T cells with concurrent ibrutinib

N = 19

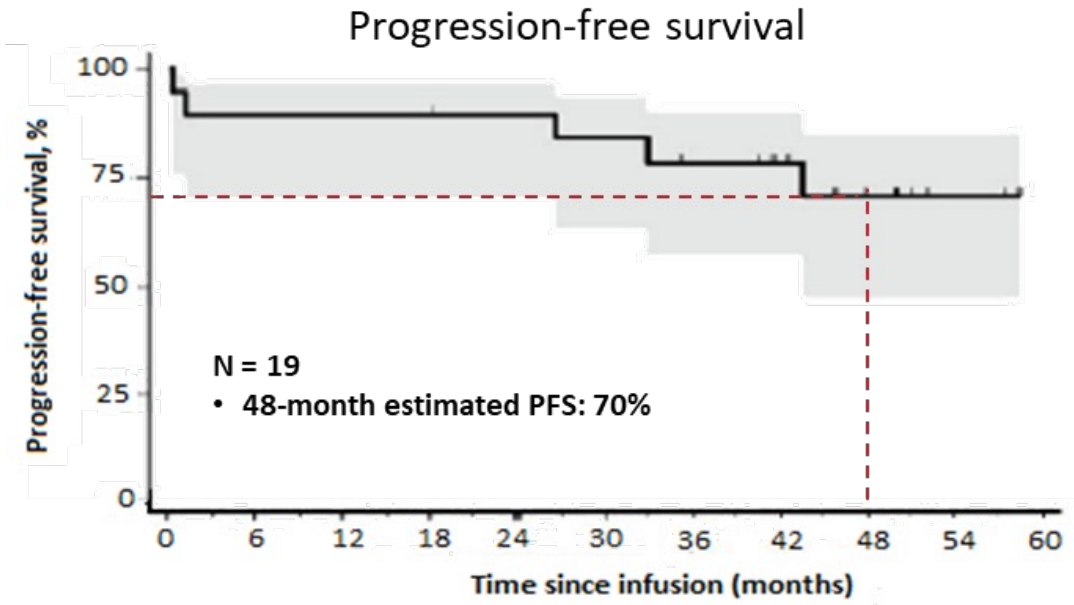
3-months CR rate: **44%** (90% CI 23 to 67)

Best CR rate: **53%** (72% MRD-)

OR rate: **68%**

Median PFS: **not reached**

48-month estimated PFS: 70%



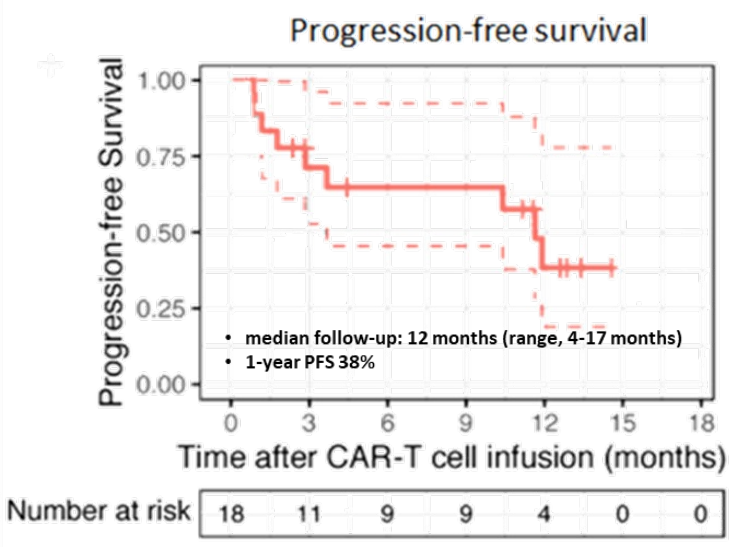
Gill, et al. Blood Adv. 2022;6(21):5774-5785.

Outcome of CAR-T with concurrent ibrutinib in r/r CLL

Fred Hutchinson CRC

- **Ibrutinib began ≥ 2 weeks before leukapheresis and continued for ≥ 3 months after CAR T-cell infusion**
  - **All patients had previously failed ibrutinib (PD, n = 18; SD, n = 1)**

FHCRC Study: CAR T cells with concurrent ibrutinib
N = 19
CR rate: **22%**
OR rate: **83%**
1-year PFS: 38%



Gauthier et al. Blood. 2020;135(19):1650-1660.

Multicenter Study (2018 -2021)

- **Ibrutinib began at enrollment, continued through leukapheresis and for 90 days after CAR T-cell infusion (liso-cel)**
  - **All patients were BTKi treatment failures**

Multicenter Study: CAR T cells with concurrent ibrutinib
N = 19
Median lines of prior therapy: 4
- refractory to Ibrutinib and venetoclax: 58%
CR/CRi rate: **63%** (89% blood and 79% marrow MRD-)
OR rate: **95%**
Ongoing responses at ≥ 6 months: 89%

Parameter	All Evaluable Patients (N=19)	DL1 (n=4)	DL2 (n=15)
Common grade 3/4 TEAEs, n (%)			
Neutropenia/neutrophil count decrease	17 (89)	3 (75)	14 (93)
Anemia	9 (47)	3 (75)	6 (40)
Febrile neutropenia	5 (26)	1 (25)	4 (27)
AEs of special interest			
Grade 3 CRS, n (%)	1 (5)	1 (25)	0
Time to CRS onset, median (range), days	6.5 (1–13)	8 (6–13)	5.5 (1–8)
Duration of CRS, median (range), days	6 (3–13)	6.5 (4–7)	5.5 (3–13)
Grade ≥3 NEs, n (%)	3 (16)	0	3 (20)
Time to NE onset, median (range), days	8 (5–12)	9 (6–12)	8 (5–10)
Duration of NE, median (range), days	6.5 (4–8)	8 (8–8)	5 (2.5–6.5)

AE, adverse event; CRS, cytokine release syndrome; DL, dose level; NE, neurological event; TEAE, treatment-emergent adverse event.

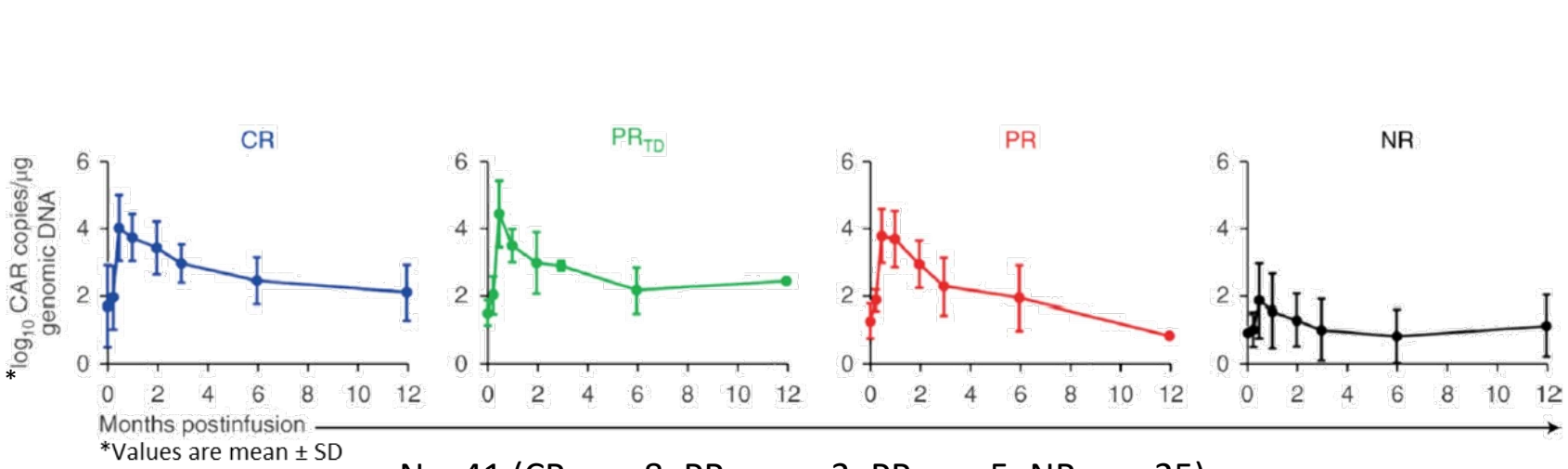
Wierda et al. ICML. 2021; abstract 1084088

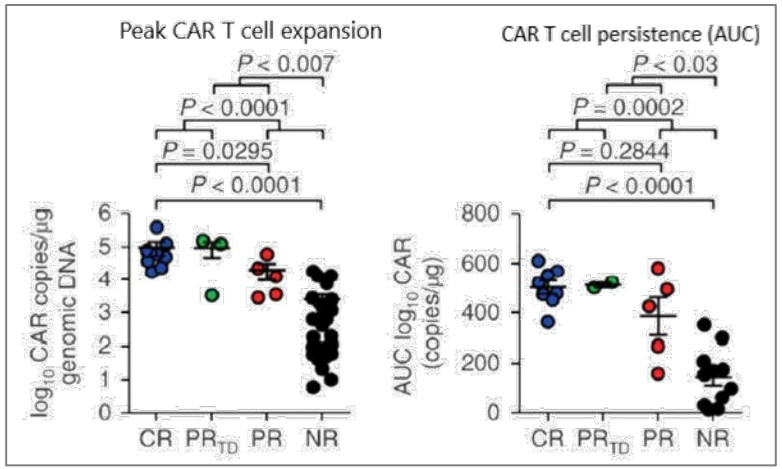
Outcomes of CAR-T therapies in relapsed CLL

What CAR T cell characteristics impact *initial response* and *duration of response* in CLL?

Functional T cell subsets may determine CAR-T cell responses

- **CAR-T cell expansion kinetics and response in CLL patients**





N = 41 (CR, n = 8; PR_{TD}, n = 3; PR, n = 5; NR, n = 25)

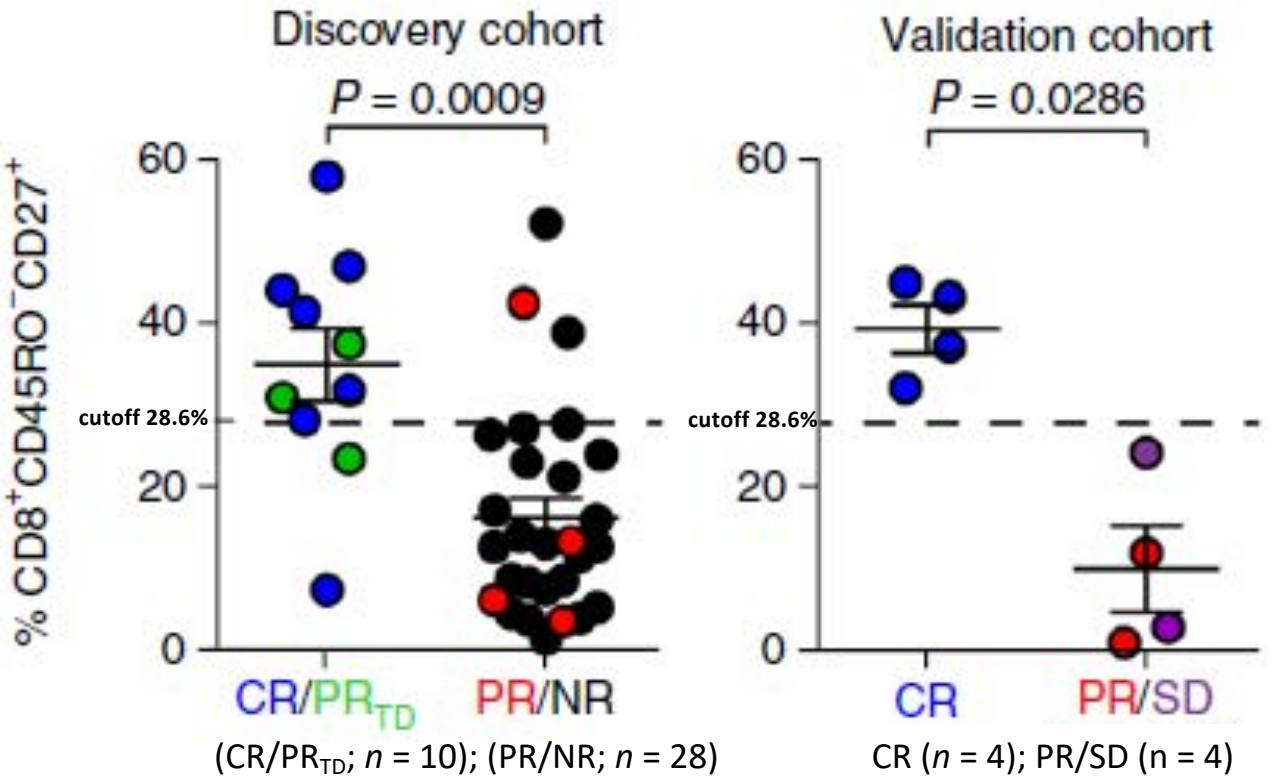
CR, complete remission; PR_{TD}, partial remission with late relapse of transformed disease; PR, partial response; NR, no response

Fraietta, *et al*. Nat Med 2018; 24:563–571.

Functional T cell subsets may determine CAR-T cell responses

- **$CD27^+$ $CD45RO^-$ (memory phenotype) $CD8^+$ T cell content in leukapheresis product and response**

Leukapheresis Products



(CR/PR_{TD}; *n* = 10); (PR/NR; *n* = 28)

CR (*n* = 4); PR/SD (n = 4)

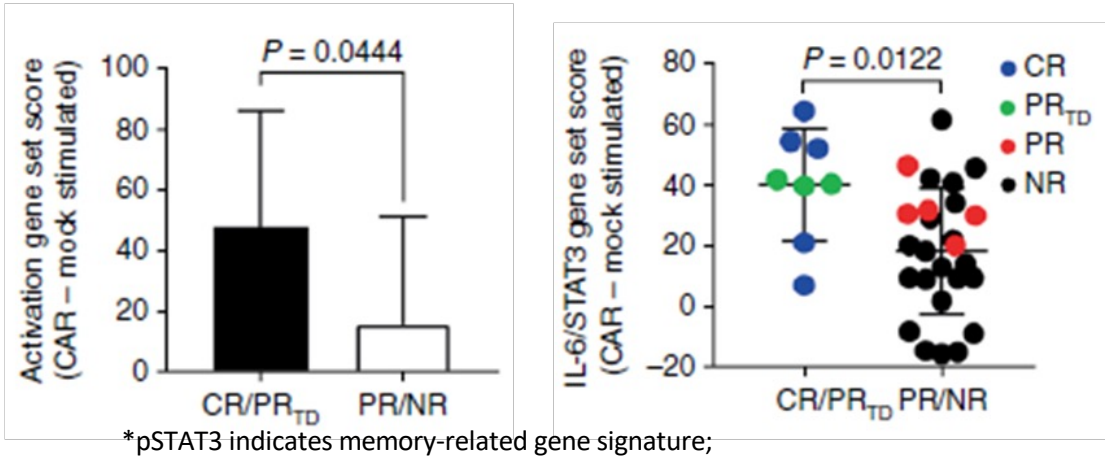
Leukapheresis biomarker ($CD8^+CD45RO^-CD27^+$)		
	Specificity	Sensitivity
Discovery	89%	80%
Validation	100%	100%

Fraietta, *et al*. Nat Med 2018; 24:563–571.

Functional T cell subsets may determine CAR-T cell responses

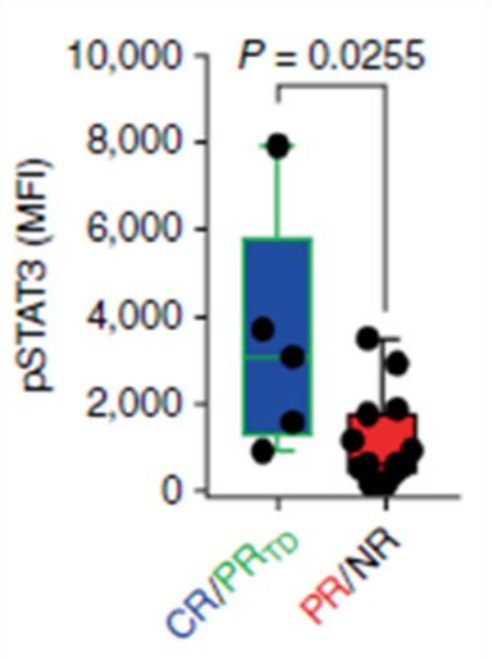
- **Genomic and phenotypic evaluation of CLL patient-derived CAR-T cells**

Change in expression of T cell–activation gene set signatures in pre-infusion CAR-T cells from CR and non-CR patients



*pSTAT3 indicates memory-related gene signature;
PR$_{TD}$, patients with PR that later relapsed with transformed disease

Change in pSTAT3 levels of pre-infusion CAR-T cells from CR and non-CR patients



→ **Responders upregulate T cell activation-related genes and IL-6/STAT3 signatures**

Fraietta, *et al*. Nat Med 2018; 24:563–571.

Functional T cell subsets may determine CAR-T cell responses

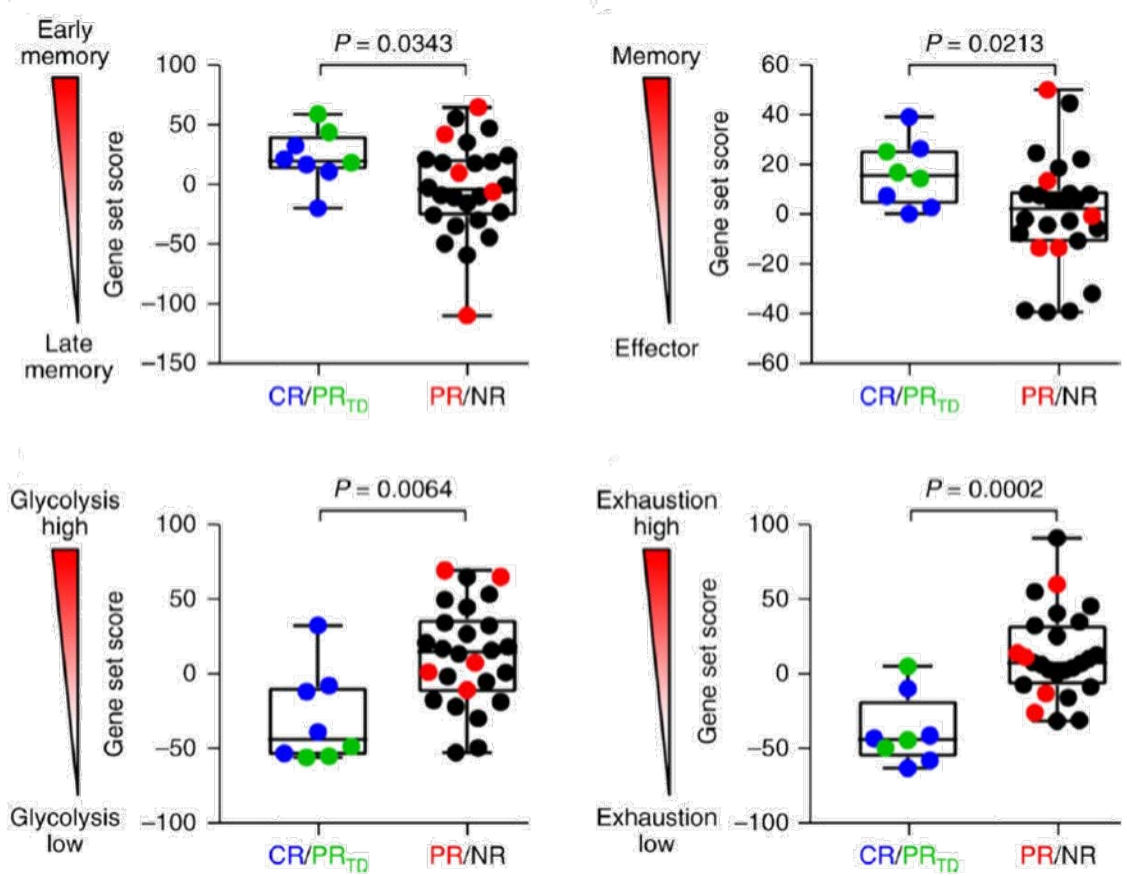
- **Genomic evaluation of CLL patient-derived CAR T cells**

Genes significantly up- or down-regulated

Early memory T cell
Nonexhausted T cell
Naive vs. activated T_H2 $Cd4^+$ T cell
Unstimulated vs. stimulated memory T cell
Resting vs. bystander activated $CD4^+$ T cel
Conventional vs. effector memory T cell
Multipotent vs. progenitor $CD4^+$ T cell
Memory vs. effector $CD8^+$ T cell
Exhausted vs. effector T cell
Exhausted T cell
Activated T_H2 vs. naive $CD4^+$ T cell
Stimulated vs. unstimulated memory T cell
Glycolysis
Hypoxia
Effector vs. memory $CD8^+$ T cell
Apoptosis

→ **Responders upregulate T cell memory-related gene sets**

→ **Non-responders upregulate programs involved in effector T-cell differentiation, glycolysis, exhaustion and apoptosis**



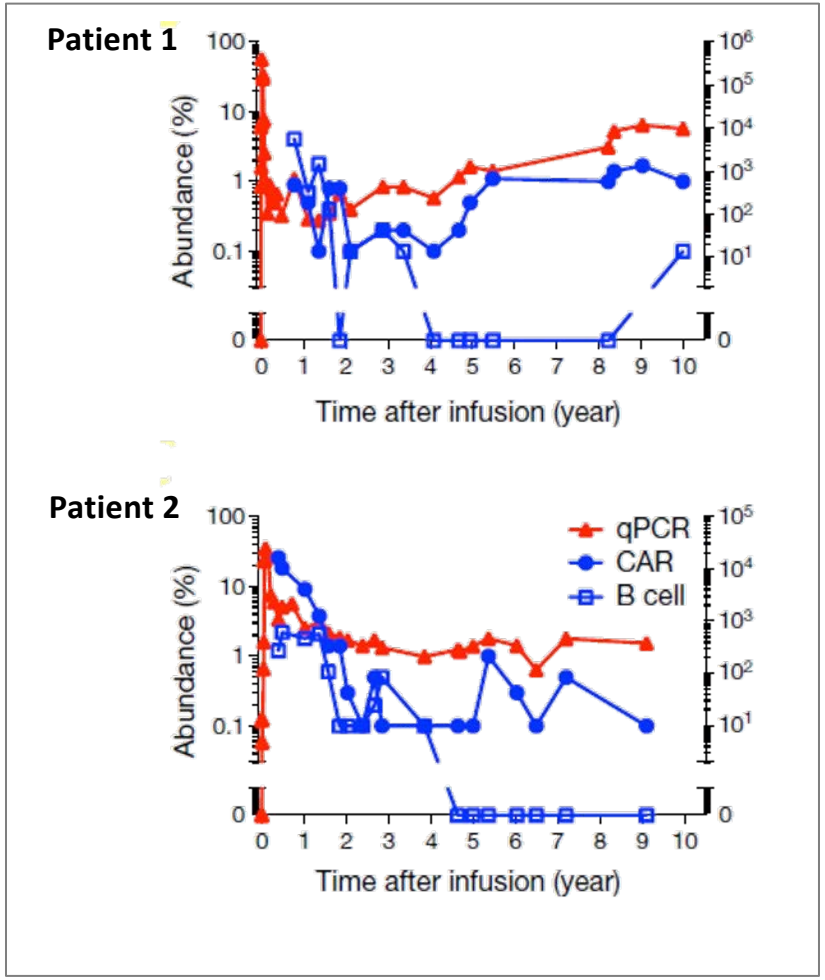
CR, complete remission; PR_{TD}, partial remission with late relapse of transformed disease; PR, partial response; NR, no response

Fraietta, *et al*. Nat Med 2018; 24:563–571.

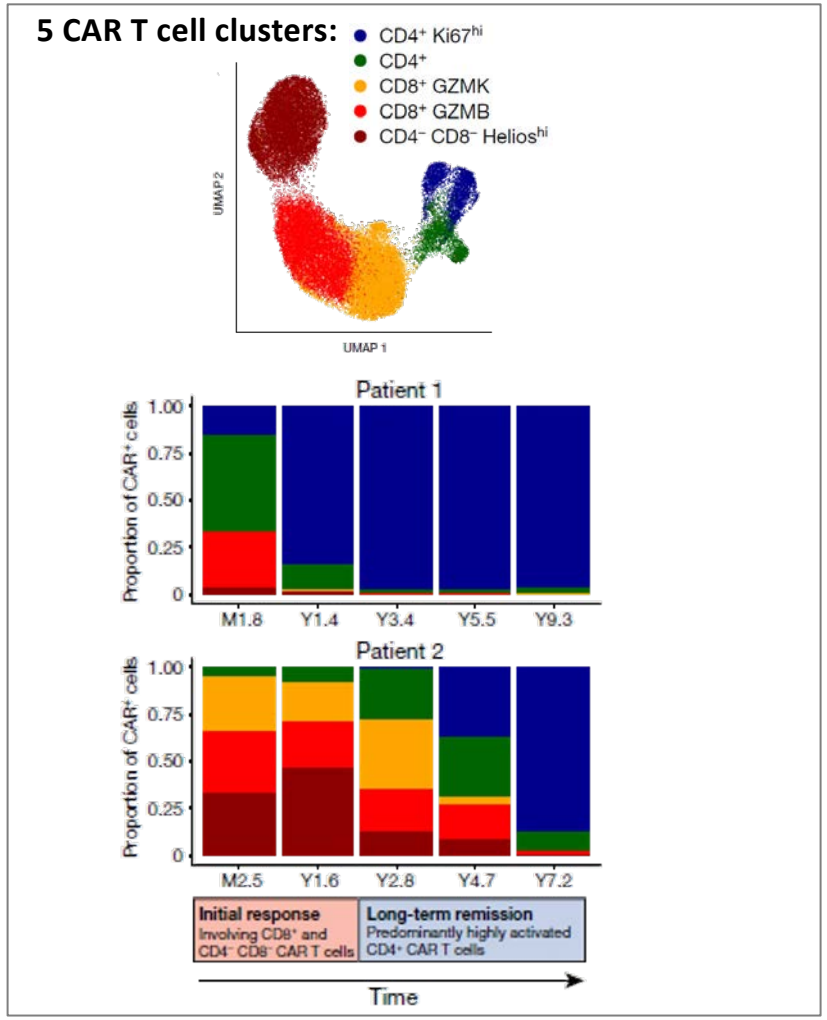
Decade-long remissions in CLL with persistence of CD4+ CAR-T cells

- **Studies of CAR T cells in 2 patients with CLL in complete remissions since 2010**

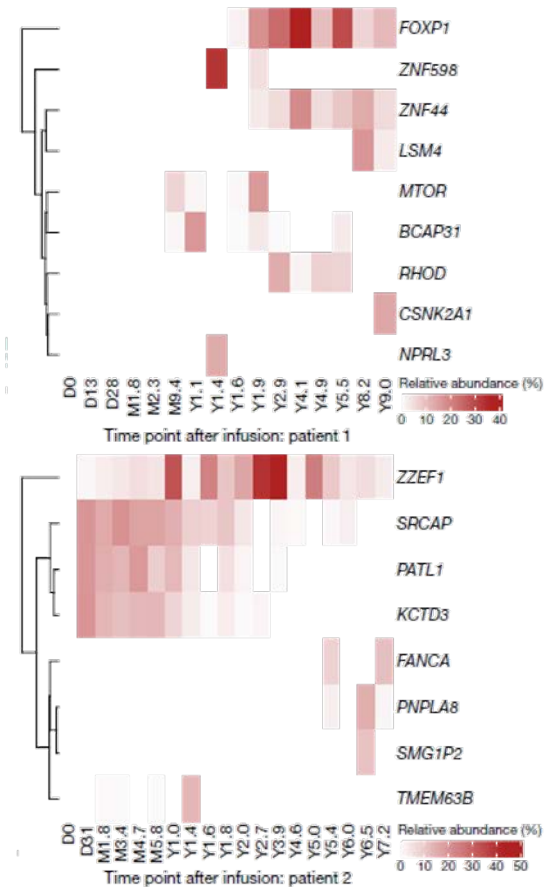
Kinetics of CAR T cell expansion and persistence



5 CAR T cell clusters:



Vector integration sites with abundance above 10% tracked over time



Melenhorst, et al. Nature. 2022;602(7897):503-509.

What CAR-T cell characteristics impact initial response and duration of response in CLL?

Initial Response[1,2]	Remission Duration[2,3]
• magnitude of CAR T cell expansion after infusion • high proportion of memory T cells in the pre-infusion apheresis product • limited CAR T cell conversion to an exhausted phenotype after infusion • CD8+ and/or γδ CAR T cell expansion mediate early cytotoxic response to CLL cells	• CAR transgene integration into specific genes that promote clonal expansion and/or cell survival has been observed (*e.g.,* TET2), but is not required • persistence of cytotoxic CD4+ CAR T cells

[1]Fraietta, *et al*. Nat Med. 2018;24:563–571.
[2]Melenhorst, et al. Nature. 2022;602(7897):503-509.
[3]Fraietta, et al. Nature. 2018;558,307–312.

CAR T-cell therapy for CLL: Where does it fit?

- **CAR-T cell therapy can achieve durable remissions in some patients with relapsed and/or refractory CLL.**

  - The safety profile is manageable.

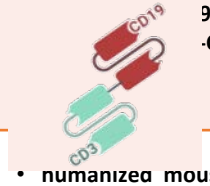
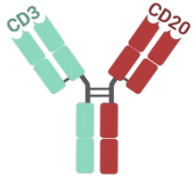
- **CAR-T cell therapy can be administered to CLL patients while on ibrutinib.**

  - Ibrutinib may facilitate CAR-T cell production and reduces severity of CRS.

- **Biologic features of patients' T cells and their CAR-T cell products may each, in part, determine the response of CLL to CAR-T cell therapy.**

- **CD19-directed CAR-T cell therapy of CLL should be integrated into our treatment approach to poor prognosis and relapsed or refractory CLL as additional data emerge.**

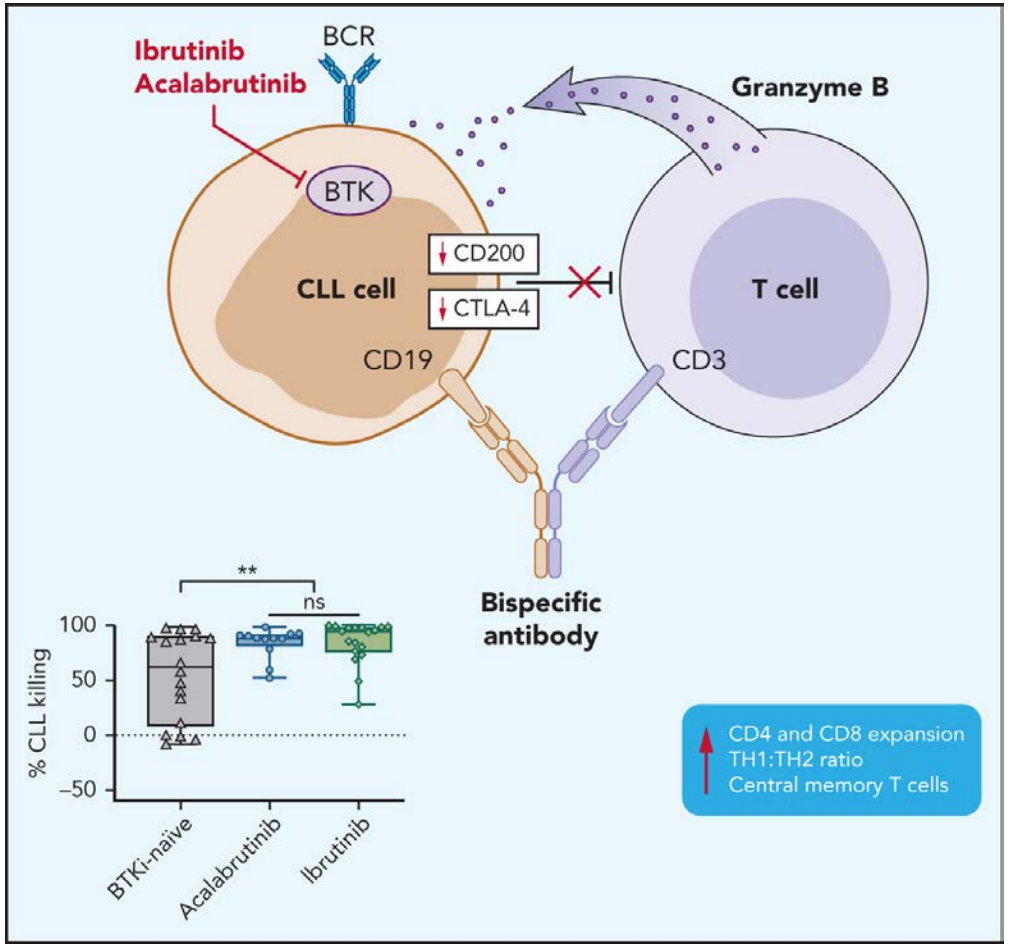
FDA-approved bispecific T-cell engaging antibodies for B-cell cancers

Bispecific antibody	Targets	Design	Ig Fragment Formats	Indication(s)	Ref.
blinatumomab	**CD19 x CD3**		• two murine scFv joined by a glycine-serine linker • 9 and monovalent CD3 binding • CD19 (clone HD37) and anti-CD3 (clone L2K-07)	• CD19-positive B-cell precursor ALL in 1st or 2nd CR with MRD ≥ 0.1% • relapsed or refractory CD19-positive B-cell precursor ALL	1, 2
mosunetuzumab	**CD20 x CD3**		• humanized mouse heterodimeric IgG1-based antibody • monovalent CD20 and monovalent CD3ε binding • modified Fc devoid of FcγR and complement binding	• relapsed/refractory FL after ≥ 2 lines of systemic therapy	3
glofitamab	**$(CD20)_2$ x CD3**		• humanized mouse IgG1-based antibody • bivalent CD20 and monovalent CD3ε binding • modified Fc devoid of FcγR and complement binding	• relapsed/refractory DLBCL NOS or LBCL arising from FL after ≥ 2 lines of systemic therapy	4
epcoritamab	**CD20 x CD3**		• humanized mouse IgG1-based heterodimeric antibody • monovalent CD20 and monovalent CD3 binding • Ig Fc modified to minimize Fc-dependent effector functions and to control Fab-arm exchange of mAb half-molecules, resulting in high bispecific product yield	• relapsed/refractory DLBCL NOS, LBCL arising from indolent lymphoma, or high-grade BCL after ≥ 2 lines of systemic therapy	5

Ig, immunoglobulin; scFv, single-chain variable fragment; mAb, monoclonal antibody; Fc, fragment crystallizable; FcγR, Fc gamma receptor; ALL, acute lymphoblastic leukemia; DLBCL, diffuse large B-cell lymphoma; LBCL, large B-cell lymphoma; FL, follicular lymphoma; BCL, B-cell lymphoma

[1]Dufner V, *et al.* Blood Adv 2019;3:2491; [2]Goebeler ME, *et al.* J Clin Oncol 2016; 34:1104; [3]Schuster SJ, *et al.* ASH 2019, Plenary Abstract 6; [4]Hutchings M, *et al.* ASH 2020, Abstract 403; [5]Hutchings M, *et al.* ASH 2020, Abstract 406.

BTK inhibitors increase CD19/CD3-bispecific antibody cytotoxicity against CLL cells *in vitro*

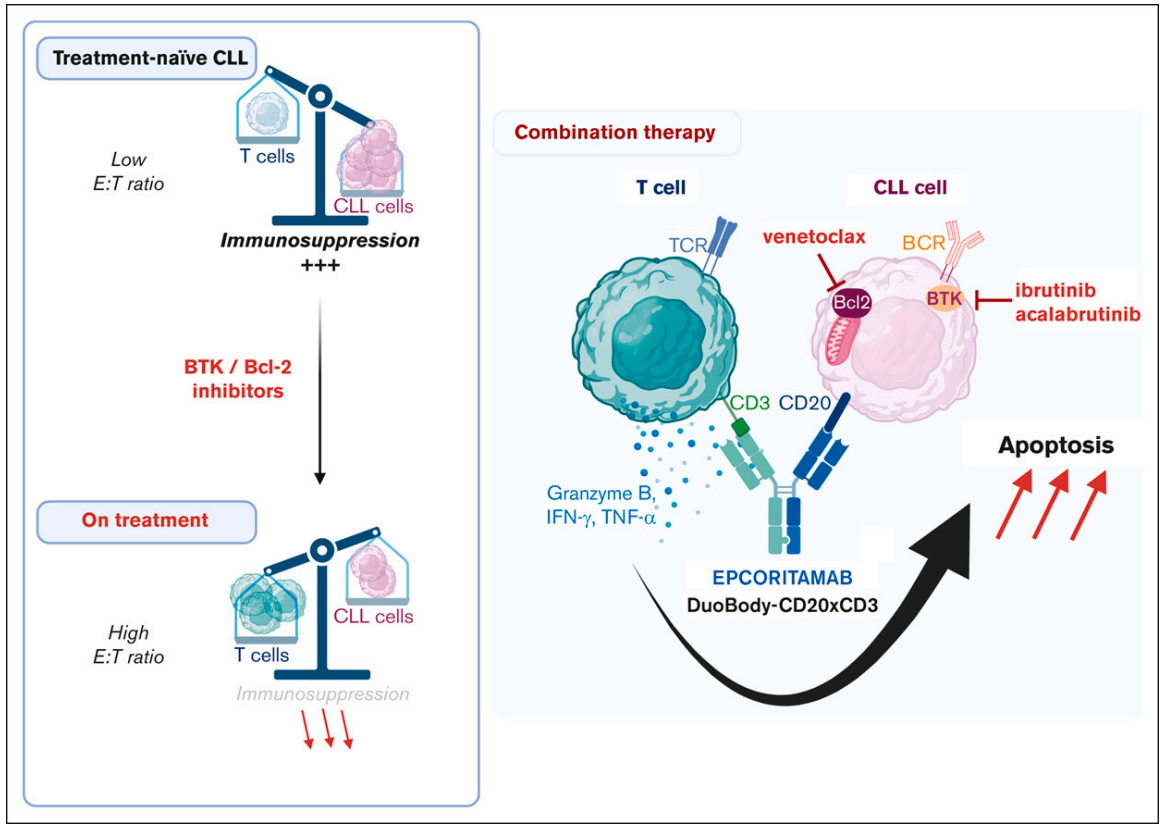


- BTK inhibitors, independent of ITK inhibition, downregulate immunosuppressive effectors in CLL cells
- CD19/CD3-bispecific antibody-induced cytotoxicity is enhanced in PBMCs from patients treated with BTK inhibitors

Mhibik, *et al.* Blood, 2021;138(19),1843-1854.

American Society of Hematology
Helping hematologists conquer blood diseases worldwide

In vitro cytotoxicity of epcoritamab (CD20xCD3-bispecific antibody) against CLL cells is increased by concurrent BTK or BCL-2 inhibition



- Epcoritamab-mediated killing of CLL cells by autologous T cells correlates with the effector-to-target ratio but not CD20 expression
- Epcoritamab efficacy is increased by concurrent use of a BTKi or venetoclax, supporting combination therapy

Mhibik, *et al.* Blood Adv. 2023;7(15),4089-4101.

American Society of Hematology
Helping hematologists conquer blood diseases worldwide

Promising Investigational Agents and Strategies for CLL

ASH | Annual Meeting & Exposition: Abstracts of interest

CAR-T cells

- Saturday, December 9, 2023, 5:15 PM (Oral): Liso-cel in R/R CLL/SLL: 24-Month Median Follow-up of TRANSCEND CLL 004 (abstract 330)
- Saturday, December 9, 2023, 10:45 AM (Oral): Anti-CD19 Chimeric Antigen Receptor T-Cell Therapy for Richter's Transformation: An International Multicenter Retrospective Study (abstract 108)
- Saturday, December 9, 2023, 5:30 PM-7:30 PM (Poster): Seven-Day Vein-to-Vein Point-of-Care Manufactured CD19 CAR T Cells (GLPG5201) in Relapsed/Refractory CLL/SLL Including Richter's Transformation: Results from the Phase 1 Euplagia-1 Trial (abstract 2112)
- Sunday, December 10, 2023, 6:00 PM-8:00 PM (Poster): Varnimcabtagene Autoleucel (ARI-0001) for Relapsed or Refractory Chronic Lymphocytic Leukemia and Richter Transformation (abstract 3483)
- Sunday, December 10, 2023, 6:00 PM-8:00 PM (Poster): Real-World Tisagenlecleucel Outcomes in Richter-Transformed Chronic Lymphocytic Leukemia: A Center for International Blood & Marrow Transplant Research (CIBMTR) Analysis (abstract 705)
- Monday, December 11, 2023, 6:00 PM-8:00 PM (Poster): A Compilation of Experiences in Utilizing CAR-T Cell Therapy for Richter's Transformation (abstract 4638)

Bispecific antibodies

- Saturday, December 9, 2023, 5:00 PM (Oral): Time Limited Exposure to a ROR1 Targeting Bispecific T Cell Engager (NVG-111) Leads to Durable Responses in Subjects with Relapsed Refractory Chronic Lymphocytic Leukemia and Mantle Cell Lymphoma (abstract 329)
- Saturday, December 9, 2023, 5:30 PM-7:30 PM (Poster): Fine Tuning Bispecific Activity in CLL: Harmonizing a CD19/20-T Cell Bispecific with a CD28 or 4-1BBL Costimulatory Bispecific (abstract 2058)

Beyond the Guidelines: Clinical Investigator Perspectives on the Management of Chronic Lymphocytic Leukemia (Part 3 of a 4-Part Series)

A CME Friday Satellite Symposium and Virtual Event Preceding the 65th ASH Annual Meeting

Friday, December 8, 2023

3:15 PM – 5:15 PM PT (6:15 PM – 8:15 PM ET)

Faculty

Farrukh T Awan, MD
Matthew S Davids, MD, MMSc
Stephen J Schuster, MD
William G Wierda, MD, PhD
Jennifer Woyach, MD

Moderator

Neil Love, MD

RTP RESEARCH TO PRACTICE

Beyond the Guidelines: Clinical Investigator Perspectives on the Management of Multiple Myeloma (Part 4 of a 4-Part Series)

A CME Friday Satellite Symposium and Virtual Event Preceding the 65th ASH Annual Meeting

Friday, December 8, 2023

7:00 PM – 9:00 PM PT (10:00 PM – 12:00 AM ET)

Faculty

Amrita Krishnan, MD
Sagar Lonial, MD
Robert Z Orlowski, MD, PhD
Noopur Raje, MD
Paul G Richardson, MD

Moderator

Neil Love, MD

RTP RESEARCH TO PRACTICE

Thank you for joining us!
Your feedback is very important to us.

Please complete the survey currently up on the iPads for attendees in the room and on Zoom for those attending virtually. The survey will remain open up to 5 minutes after the meeting ends.

How to Obtain CME Credit

In-person attendees: Please refer to the program syllabus for the CME credit link or QR code. You may also use the iPads available in the meeting room to complete the course evaluation.

Online/Zoom attendees: The CME credit link is posted in the chat room.

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