Addressing Current Questions and Controversies in the Management of Chronic Lymphocytic Leukemia — What Clinicians Want to Know

Part 1 of a 3-Part CME Friday Satellite Symposium and Virtual Event Series
Preceding the 64th ASH Annual Meeting

Friday, December 9, 2022
11:30 AM – 1:30 PM CT

Faculty

Alexey V Danilov, MD, PhD
Matthew S Davids, MD, MMSc
Professor Dr Arnon P Kater, MD, PhD
Lindsey Roeker, MD
Philip A Thompson, MB, BS

Moderator

Neil Love, MD

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Faculty

Alexey V Danilov, MD, PhD
Professor, Department of Hematology
and Transplantation
Co-Director, Toni Stephenson Lymphoma Center
City of Hope National Medical Center
Duarte, California

Lindsey Roeker, MD
Assistant Attending Physician
Memorial Sloan Kettering Cancer Center
New York, New York

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

Philip A Thompson, MB, BS
Associate Professor
Department of Leukemia
Division of Cancer Medicine
The University of Texas
MD Anderson Cancer Center
Houston, Texas

Professor Dr Arnon P Kater, MD, PhD
Department of Hematology, Cancer Center
Amsterdam University Medical Centers
University of Amsterdam
Amsterdam, Netherlands

Moderator
Neil Love, MD
Research To Practice

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Clinicians in the Meeting Room

Networked iPads are available.

Review Program Slides: Tap the Program Slides button to review speaker presentations and other program content.

Answer Survey Questions: Complete the pre- and postmeeting surveys.

Ask a Question: Tap Ask a Question to submit a challenging case or question for discussion. We will aim to address as many questions as possible during the program.

Complete Your Evaluation: Tap the CME Evaluation button to complete your evaluation electronically to receive credit for your participation.

For assistance, please raise your hand. Devices will be collected at the conclusion of the activity.

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Clinicians Attending via Zoom

Review Program Slides: A link to the program slides will be posted in the chat room at the start of the program.

Answer Survey Questions: Complete the pre- and postmeeting surveys.

Ask a Question: Submit a challenging case or question for discussion using the Zoom chat room.

Get CME Credit: A CME credit link will be provided in the chat room at the conclusion of the program.

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About the Enduring Program

- The live meeting is being video and audio recorded.
- The proceedings from today will be edited and developed into an enduring web-based video/PowerPoint program.
  An email will be sent to all attendees when the activity is available.
- To learn more about our education programs, visit our website, **www.ResearchToPractice.com**

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Addressing Current Questions and Controversies in the Management of Hodgkin and Non-Hodgkin Lymphoma — What Clinicians Want to Know

Part 2 of a 3-Part CME Friday Satellite Symposium and Virtual Event Series
Preceding the 64th ASH Annual Meeting

Friday, December 9, 2022
3:15 PM – 5:15 PM CT (4:15 PM – 6:15 PM ET)

Faculty

Jonathan W Friedberg, MD, MMSc
Brad S Kahl, MD
David G Maloney, MD, PhD
Loretta J Nastoupil, MD
Sonali M Smith, MD

Moderator

Neil Love, MD

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Addressing Current Questions and Controversies in the Management of Multiple Myeloma — What Clinicians Want to Know

Part 3 of a 3-Part CME Friday Satellite Symposium and Virtual Event Series
Preceding the 64th ASH Annual Meeting

Friday, December 9, 2022
7:00 PM – 9:00 PM CT (8:00 PM – 10:00 PM ET)

Faculty

Jesús G Berdeja, MD
Rafael Fonseca, MD
Sagar Lonial, MD
Robert Z Orlowski, MD, PhD
Noopur Raje, MD

Moderator

Neil Love, MD

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Spencer Henick Bachow, MD
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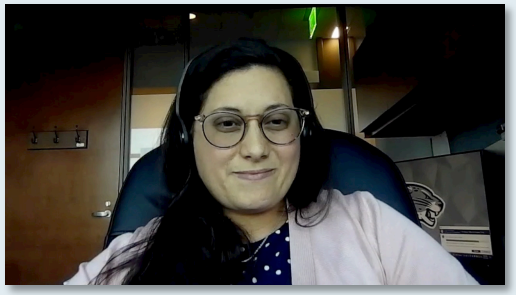
WVU Cancer Institute
Wheeling, West Virginia

Jennifer L Dallas, MD
Oncology Specialists of Charlotte
Charlotte, North Carolina

Justin Peter Favaro, MD, PhD
Oncology Specialists of Charlotte
Charlotte, North Carolina



Amany R Keruakous, MD, MS
Georgia Cancer Center
Augusta University
Augusta, Georgia

Henna Malik, MD
Texas Oncology
North Houston, Willowbrook/Cypress
Houston, Texas

Syed Farhan Zafar, MD
Florida Cancer Specialists
Fort Myers, Florida

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Speakers Bureau	AbbVie Inc

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Speaking Engagements	Curio Bioscience, DAVA Oncology
Travel Support	Loxo Oncology Inc, a wholly owned subsidiary of Eli Lilly & Company

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Contracted Research	AbbVie Inc, Adaptive Biotechnologies Corporation, AstraZeneca Pharmaceuticals LP, Lilly

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Moderator

Neil Love, MD

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Agenda

Module 1: Front-Line Treatment of Chronic Lymphocytic Leukemia (CLL) — Dr Danilov

Module 2: Novel Strategies Combining Bruton Tyrosine Kinase (BTK) and Bcl-2 Inhibitors for CLL — Prof Kater

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

Module 4: Selection and Sequencing of Available Therapies for Relapsed/Refractory Disease — Dr Thompson

Module 5: Promising Investigational Agents and Strategies — Dr Roeker

Agenda

Module 1: Front-Line Treatment of Chronic Lymphocytic Leukemia (CLL) — Dr Danilov

▸ *Real World Cases and Questions*

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▸ *Real World Cases and Questions*

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▸ *Real World Cases and Questions*

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Module 1: Front-Line Treatment of Chronic Lymphocytic Leukemia (CLL) — Dr Danilov

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Dr Tina Bhatnagar
(Wheeling, West Virginia)

Case Presentation: 91-year-old man with Rai Stage 0 CLL underwent surveillance x 5 years and now develops cytopenias and transfusion-dependent anemia

Dr Jennifer Dallas
(Charlotte, North Carolina)

Case Presentation: 67-year-old woman with IGHV-unmutated CLL develops night sweats, rapid doubling time of ALC

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Case Presentation: 54-year-old man with relapsed CLL s/p ibrutinib x 5 years now with disease progression

Dr Amany Keruakous (Augusta, Georgia)

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Front-Line Treatment of Chronic Lymphocytic Leukemia

Alexey Danilov, MD, PhD

Co-Director, Toni Stephenson Lymphoma Center

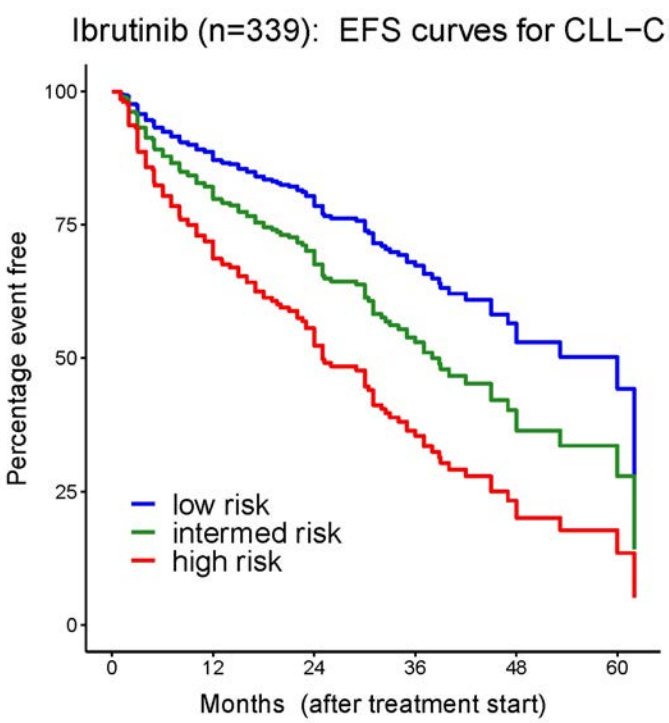
Professor, Department of Hematology & Hematopoietic Cell Transplantation

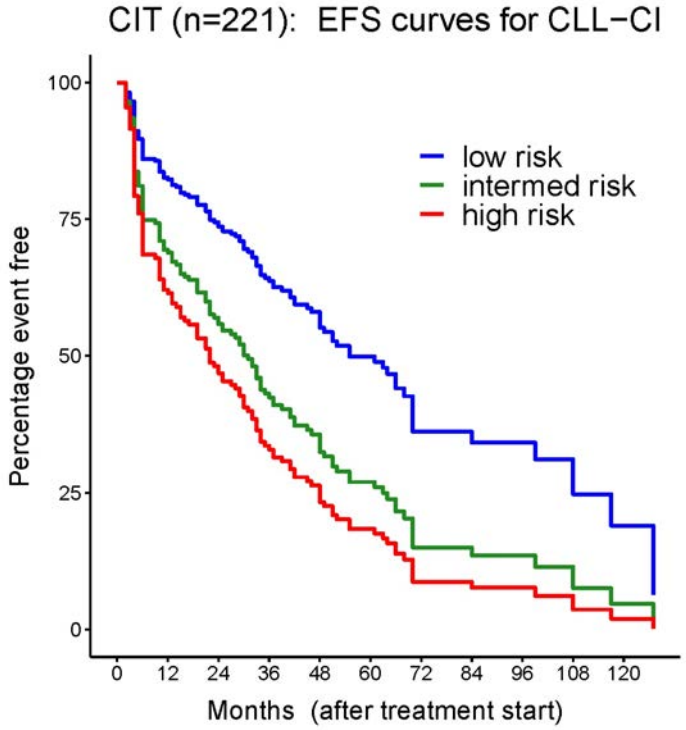
City of Hope Comprehensive Cancer Center

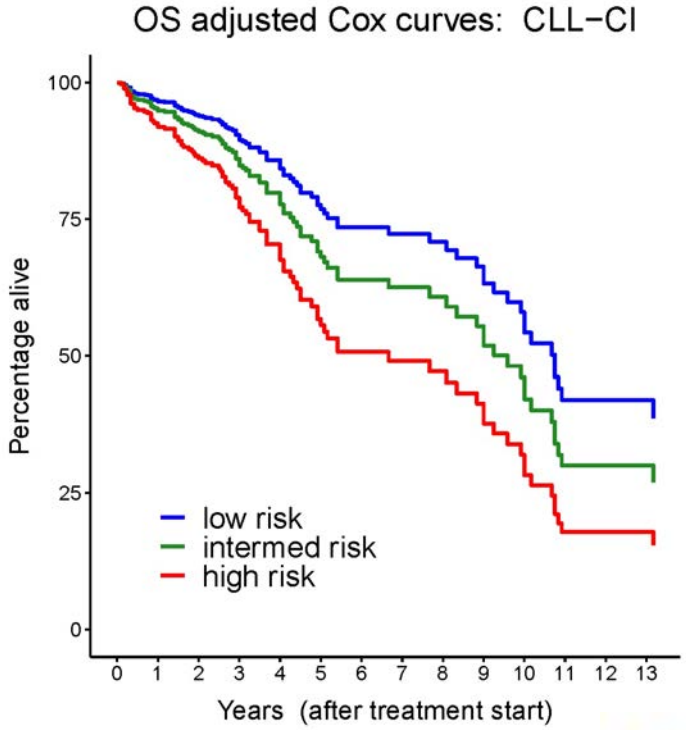
City of Hope.

Factors to Consider when Selecting Treatment for CLL

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







Gordon et al, 2021

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Frontline Phase III Randomized Trials in CLL

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

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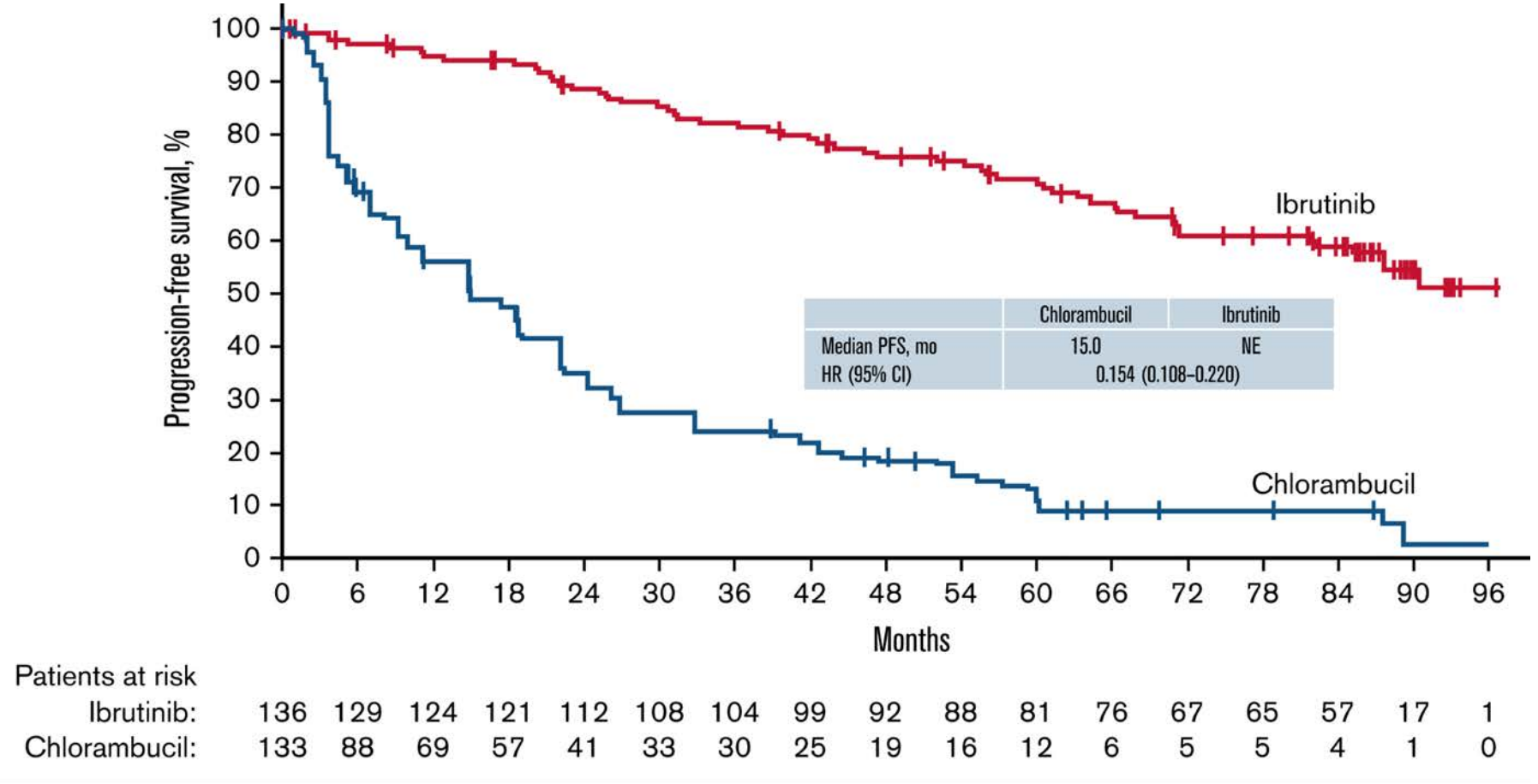
RESONATE-2: PFS after 8-year follow-up



Barr et al 2022

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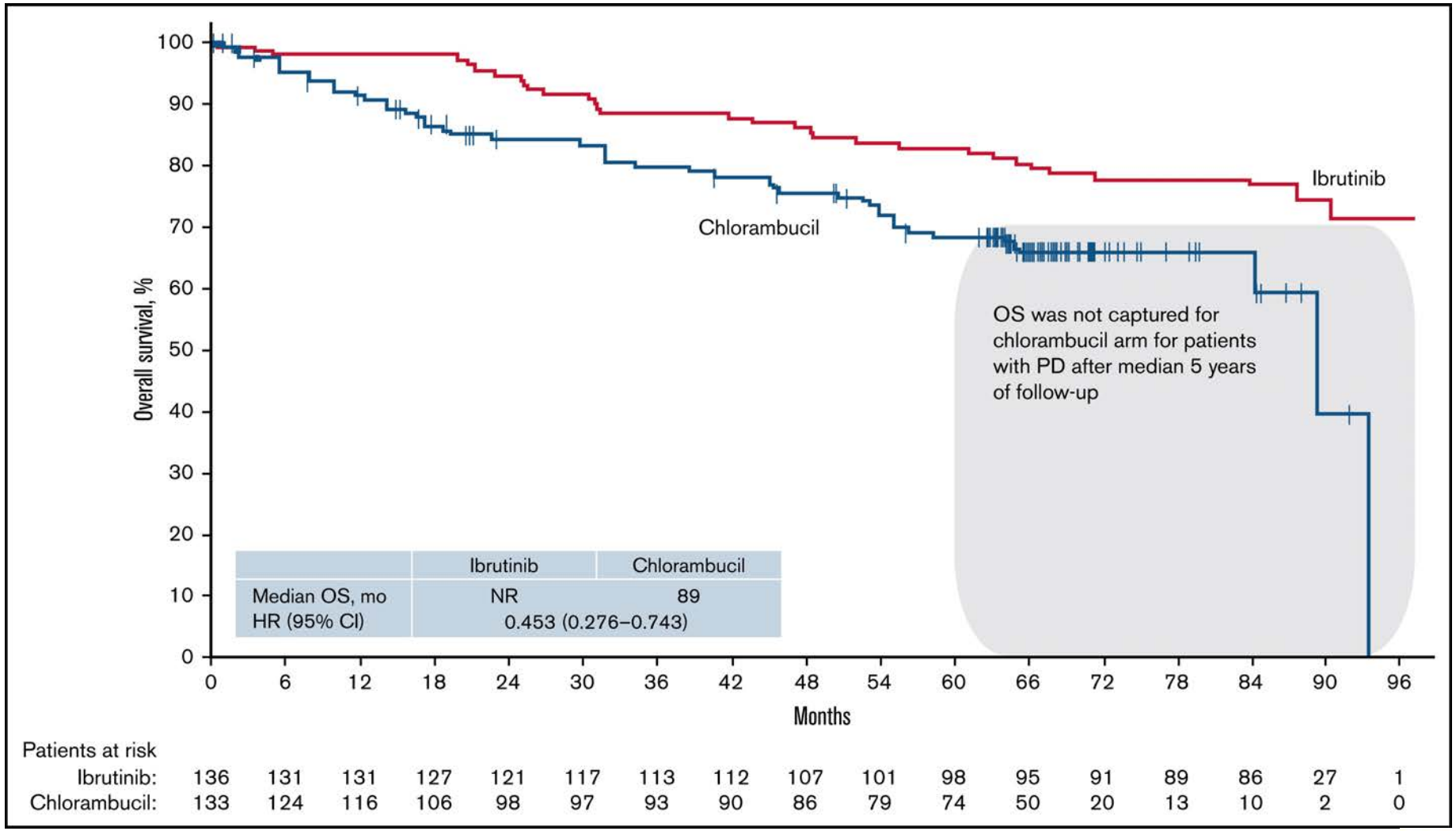
RESONATE-2: OS after 8-year follow-up



Barr et al 2022

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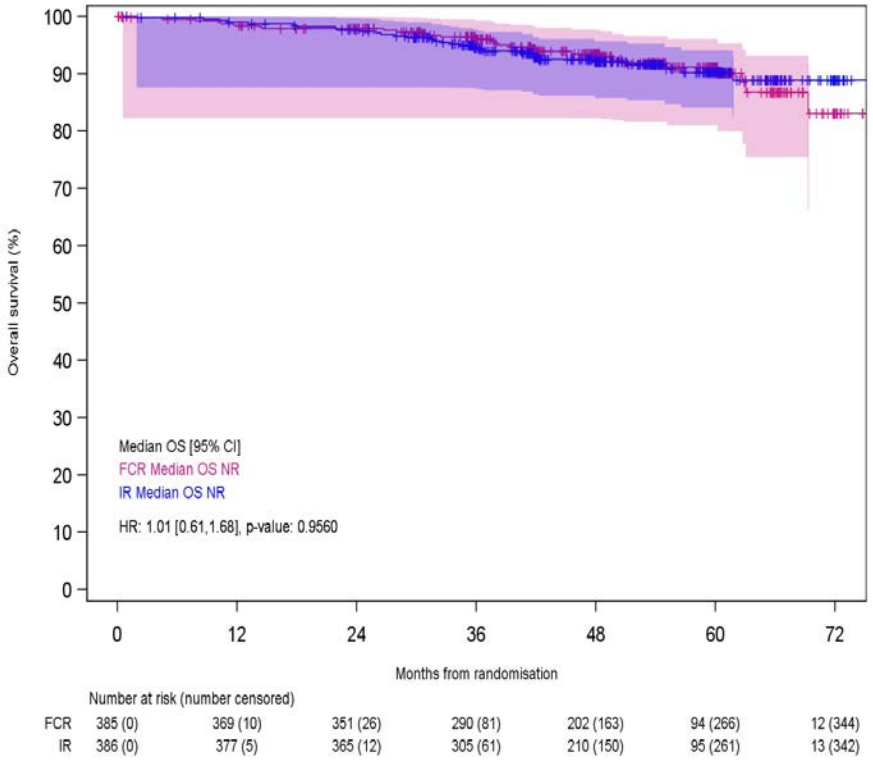
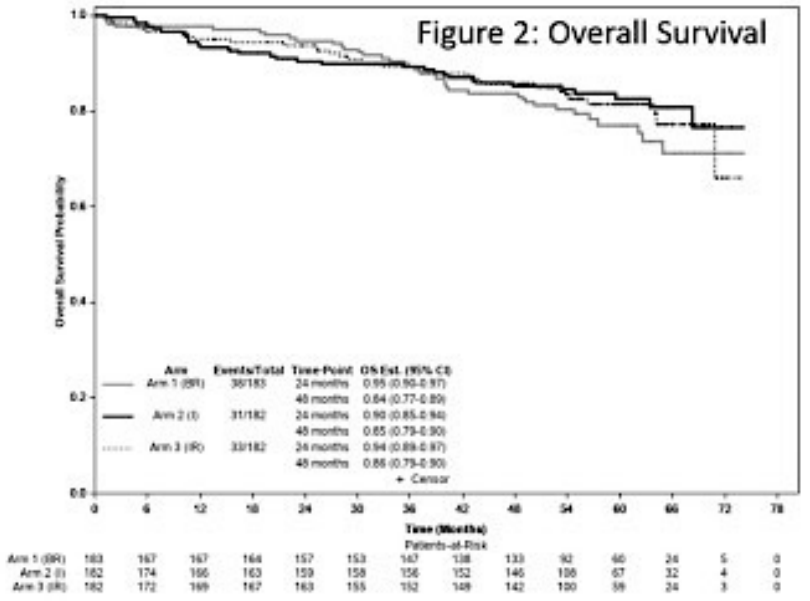
OS across frontline Phase III ibrutinib *vs* chemo studies

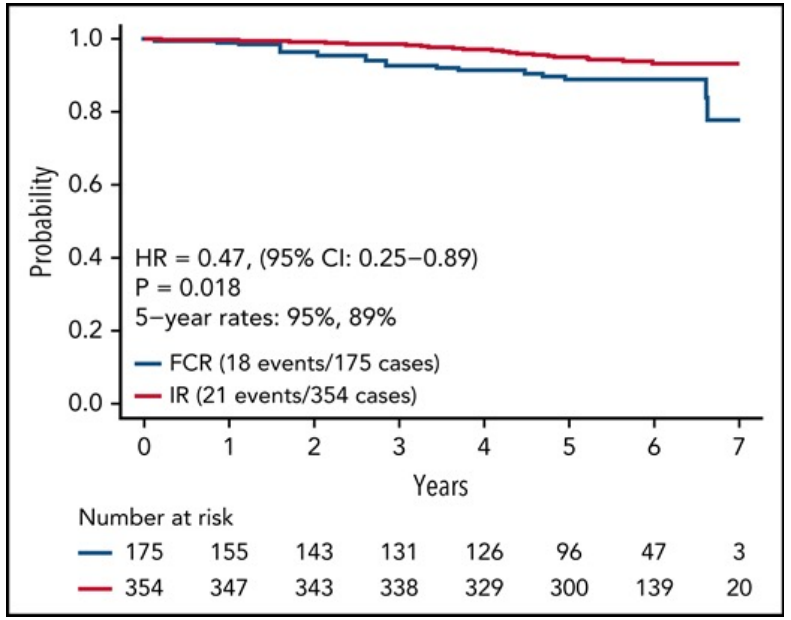
FLAIR (Hillmen, 2021)



Alliance (Woyach, 2021)



ECOG1912 (Shanafelt, 2022)



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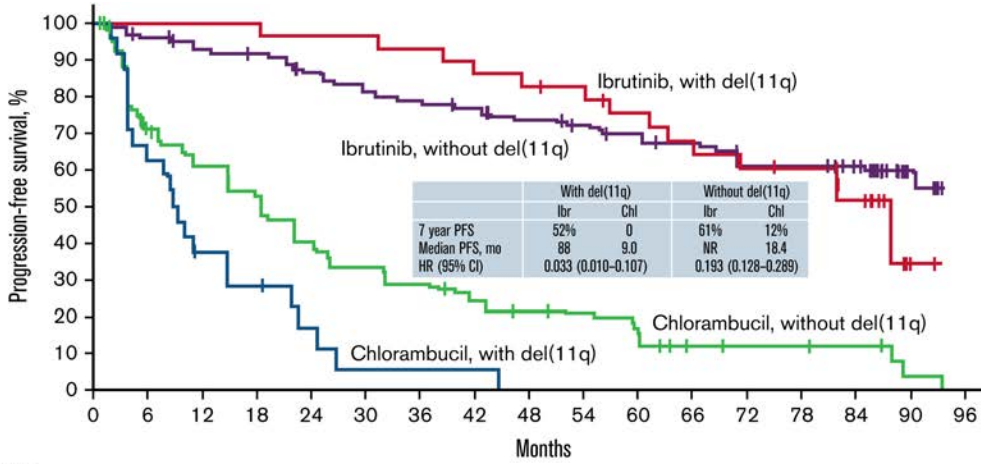
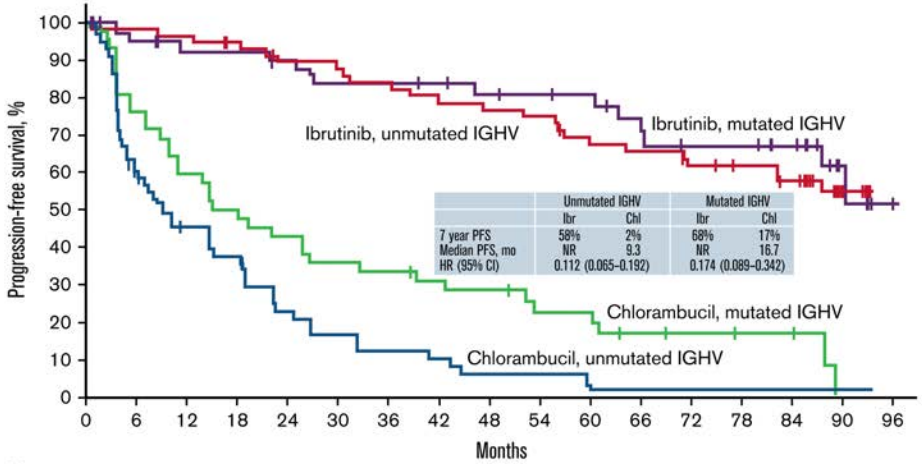
Ibrutinib Overcomes del(11q) and U-*IGHV* in RESONATE-2



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



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

Barr et al 2022

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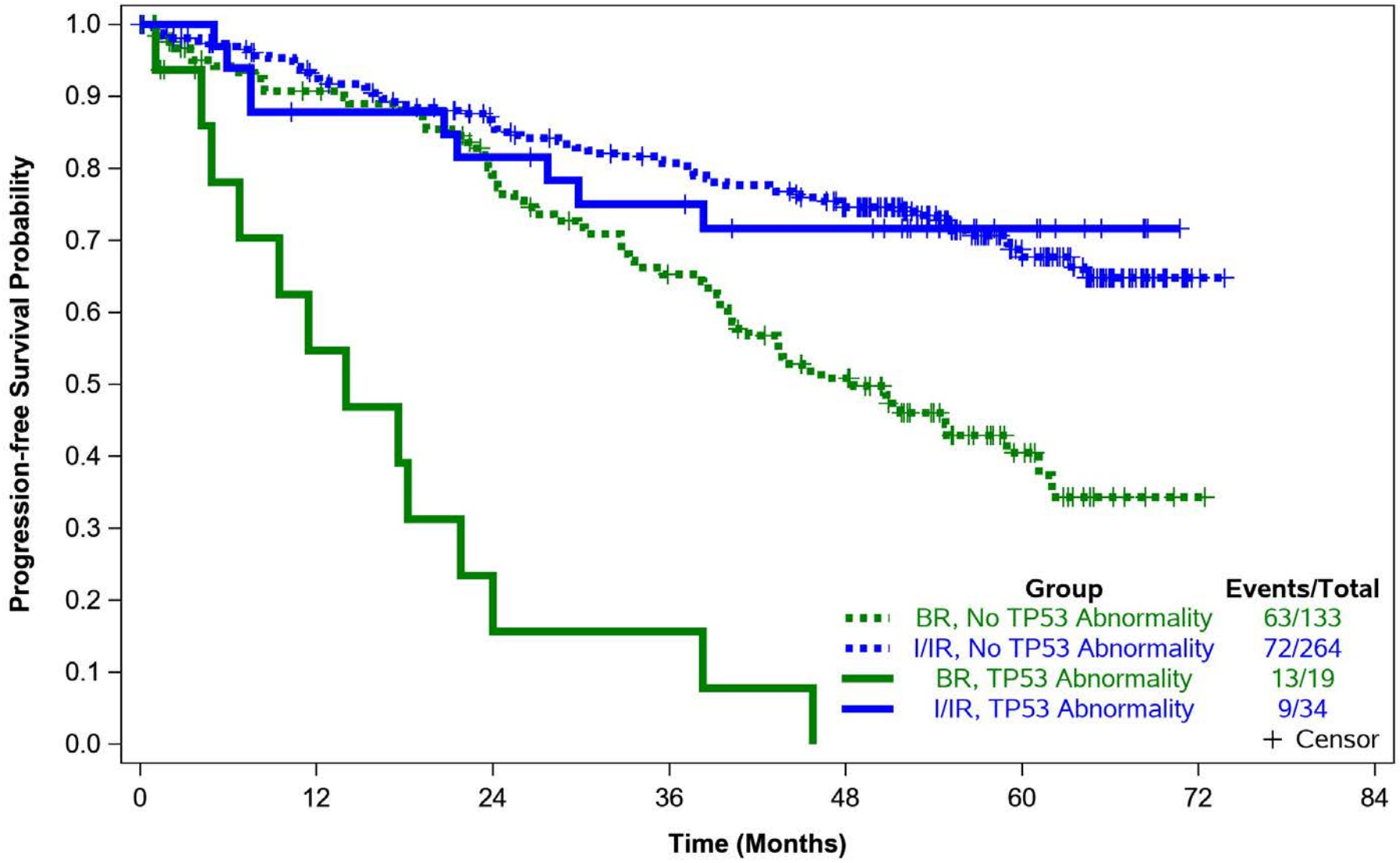
Ibrutinib and TP53 abnormalities: Alliance study



Treatment Effect
I/IR vs BR

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

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

Interaction P = 0.0006

Woyach, et al. 2021

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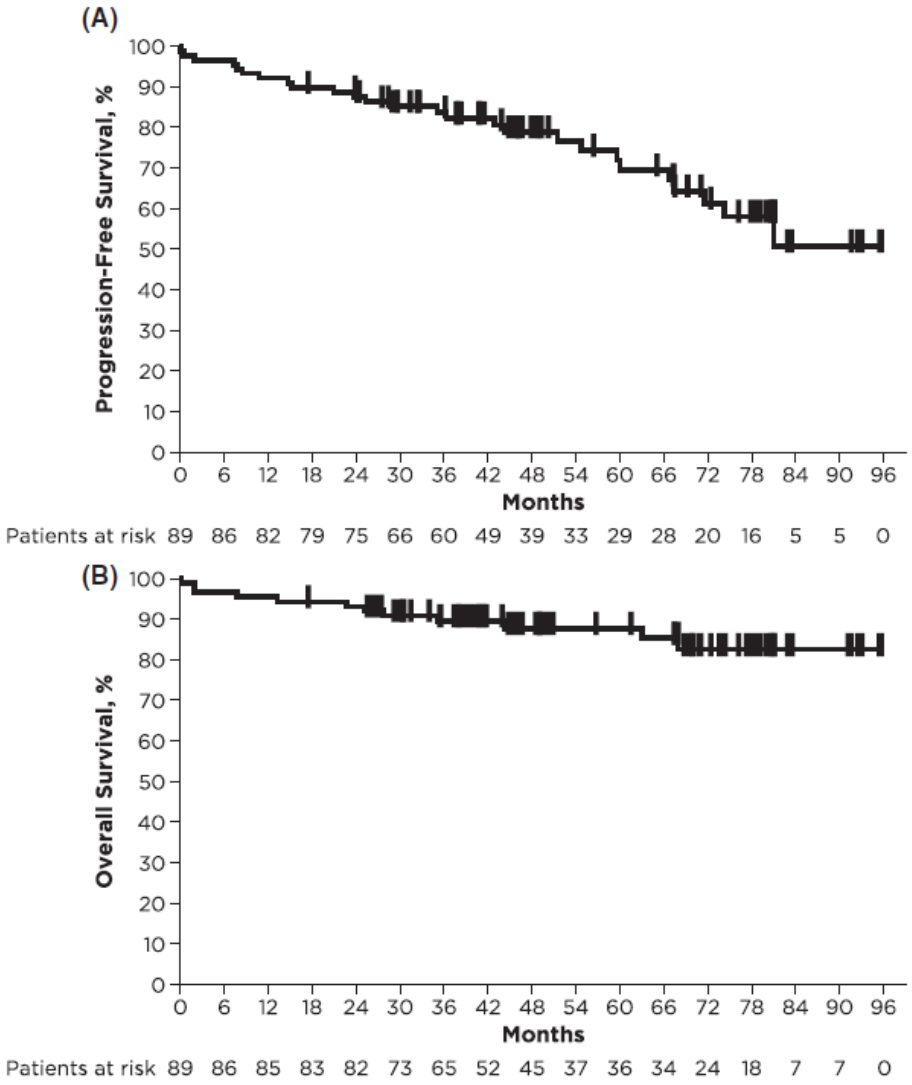
Pooled analysis of ibrutinib in TN *TP53*^{mut} CLL



4-year PFS – 80%

4-year OS – 88%

Allan et al., 2022

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Cardiac toxicity with ibrutinib

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

Meta-analysis

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

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

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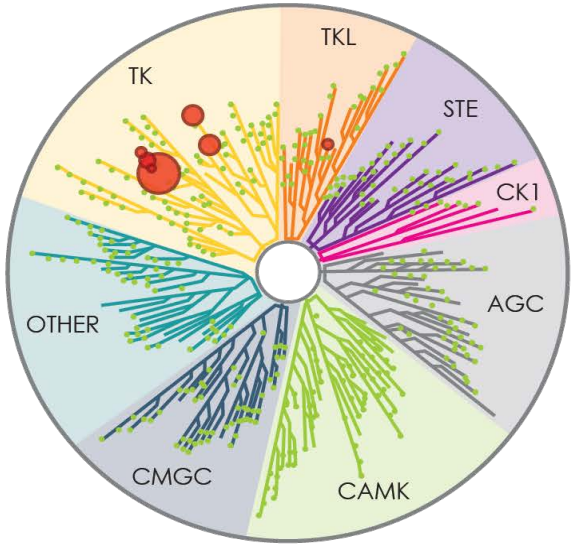
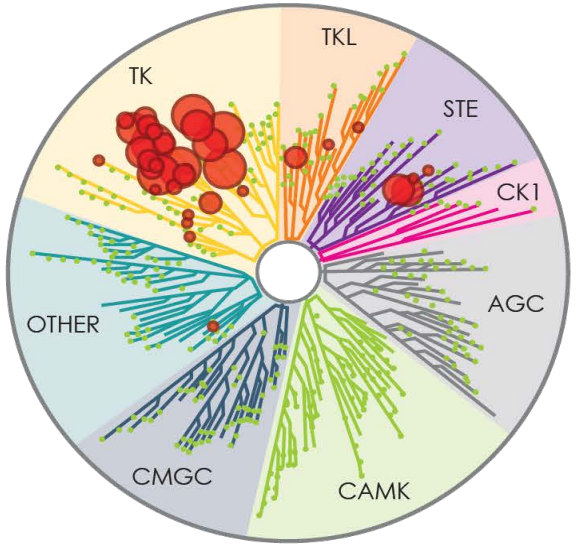
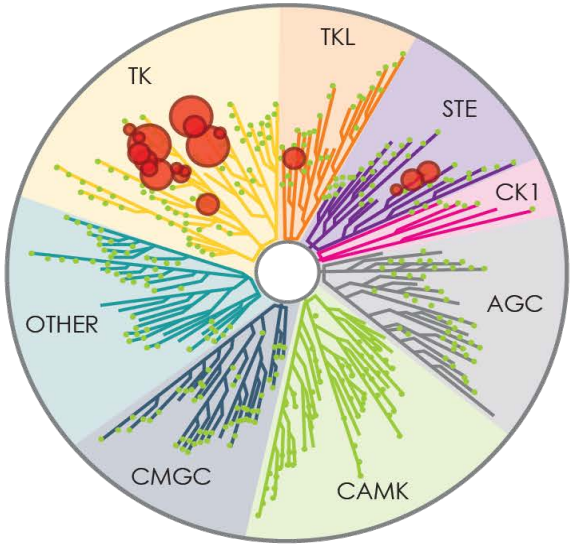
BTKI's: Kinase Selectivity



Acalabrutinib



Ibrutinib



Zanubrutinib

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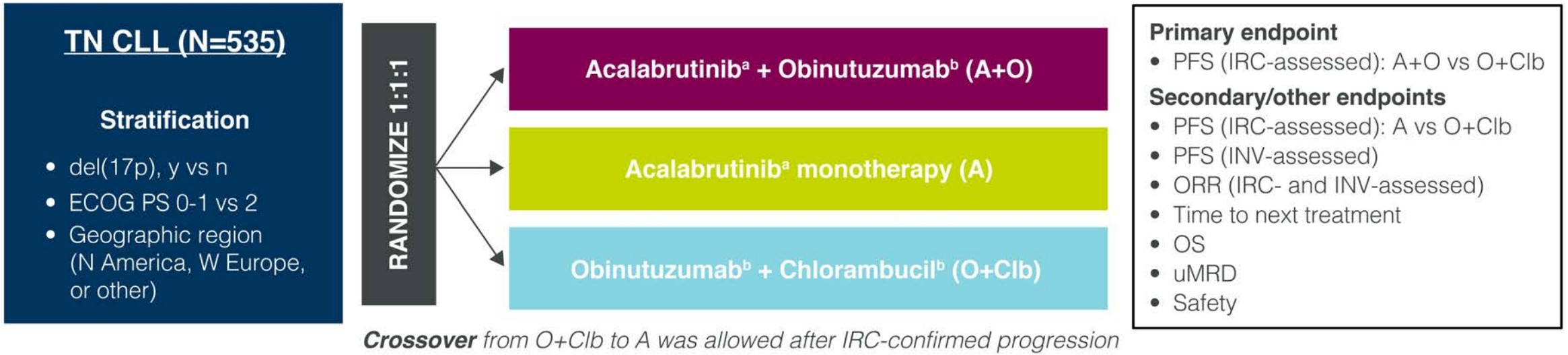
Acalabrutinib in frontline CLL: ELEVATE-TN



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

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

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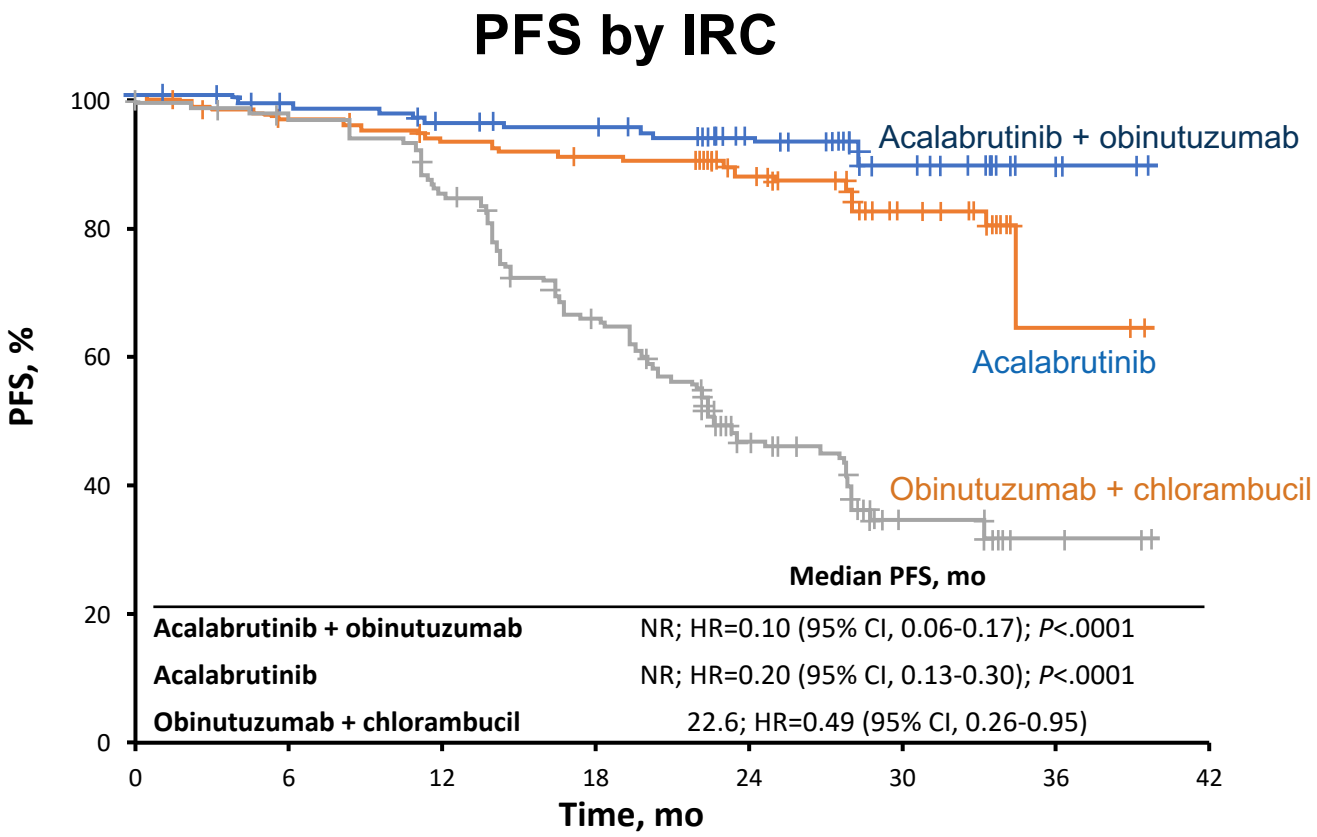
ELEVATE-TN: PFS (Primary Endpoint)



Estimated PFS at 24 months

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

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

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

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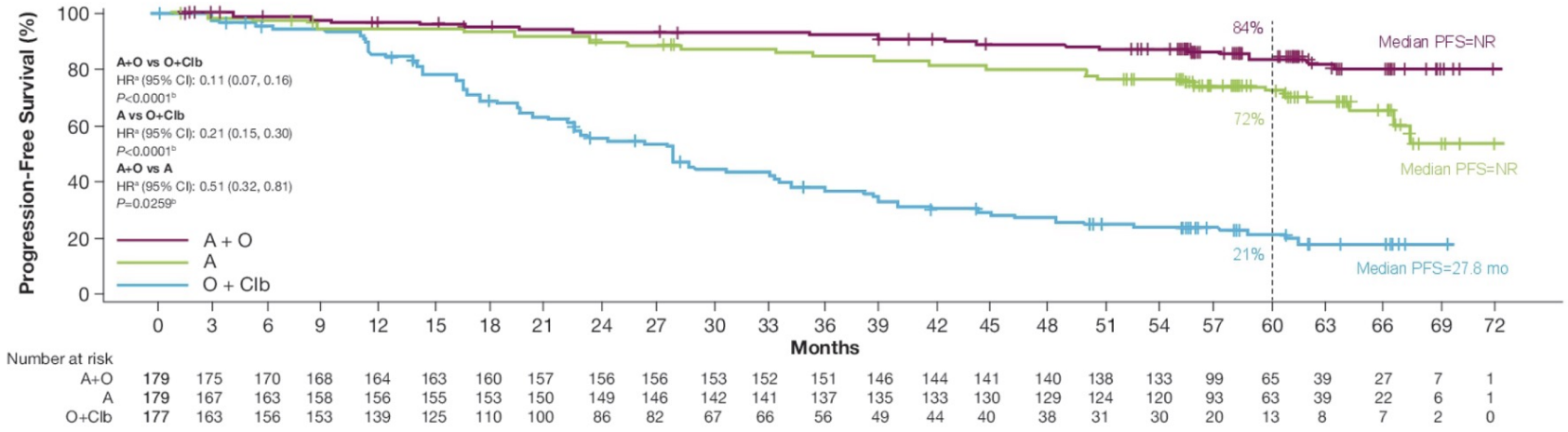
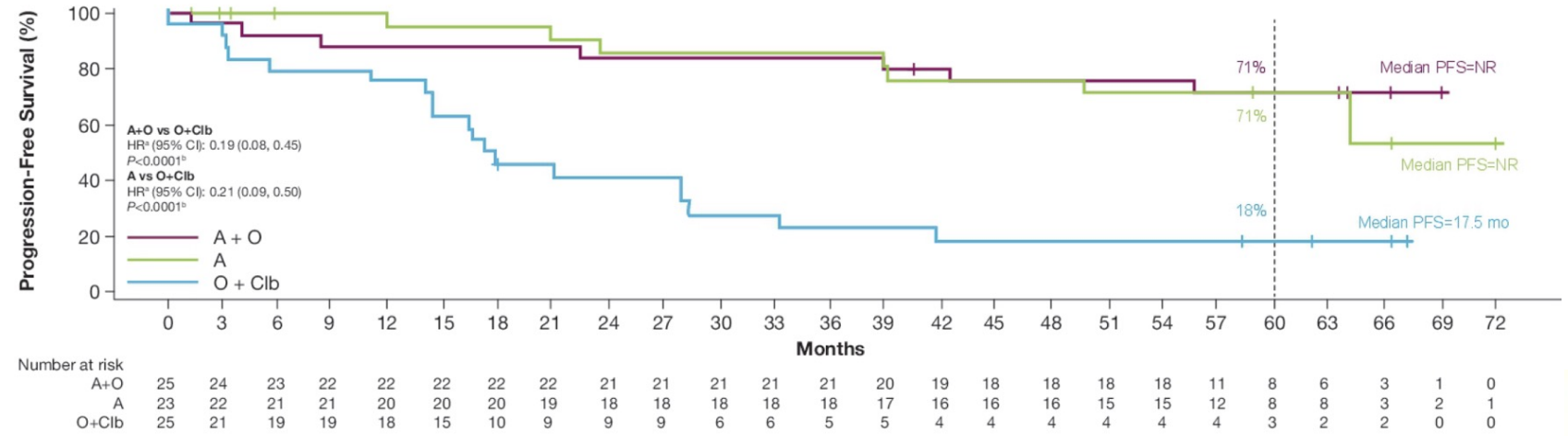
5-Year Follow-Up of the ELEVATE-TN Phase 3 Study: PFS

INV-Assessed PFS



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



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

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

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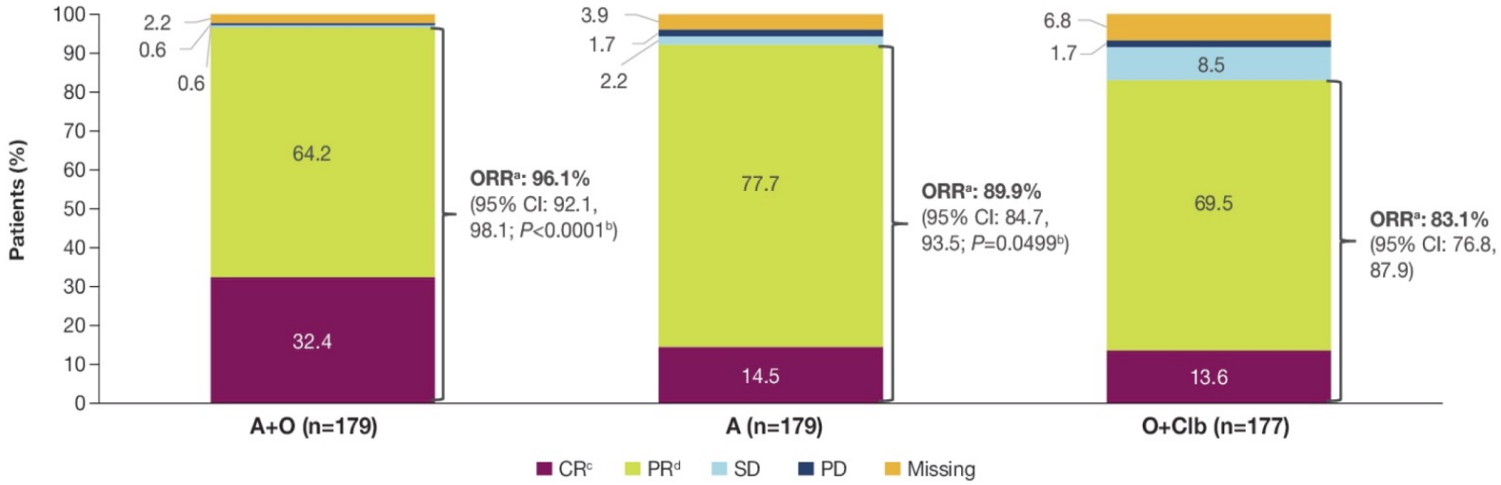
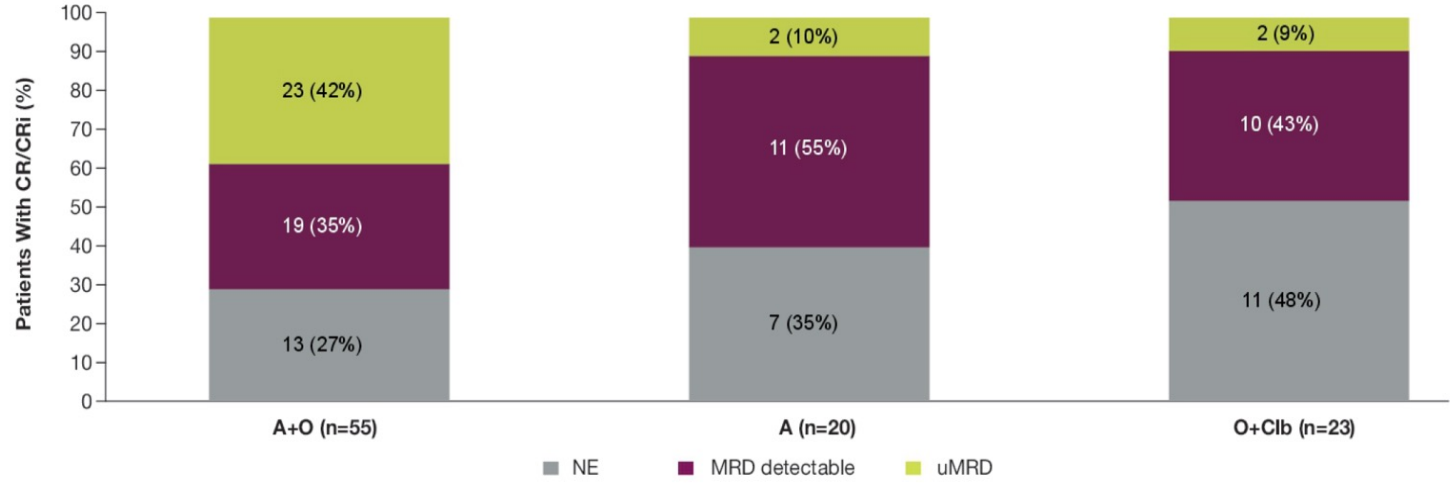
5-Year Follow-Up of the ELEVATE-TN Phase 3 Study: ORR and uMRD

INV-Assessed ORR



MRD Status in Patients With CR/CRi



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

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

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

Patient Disposition

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

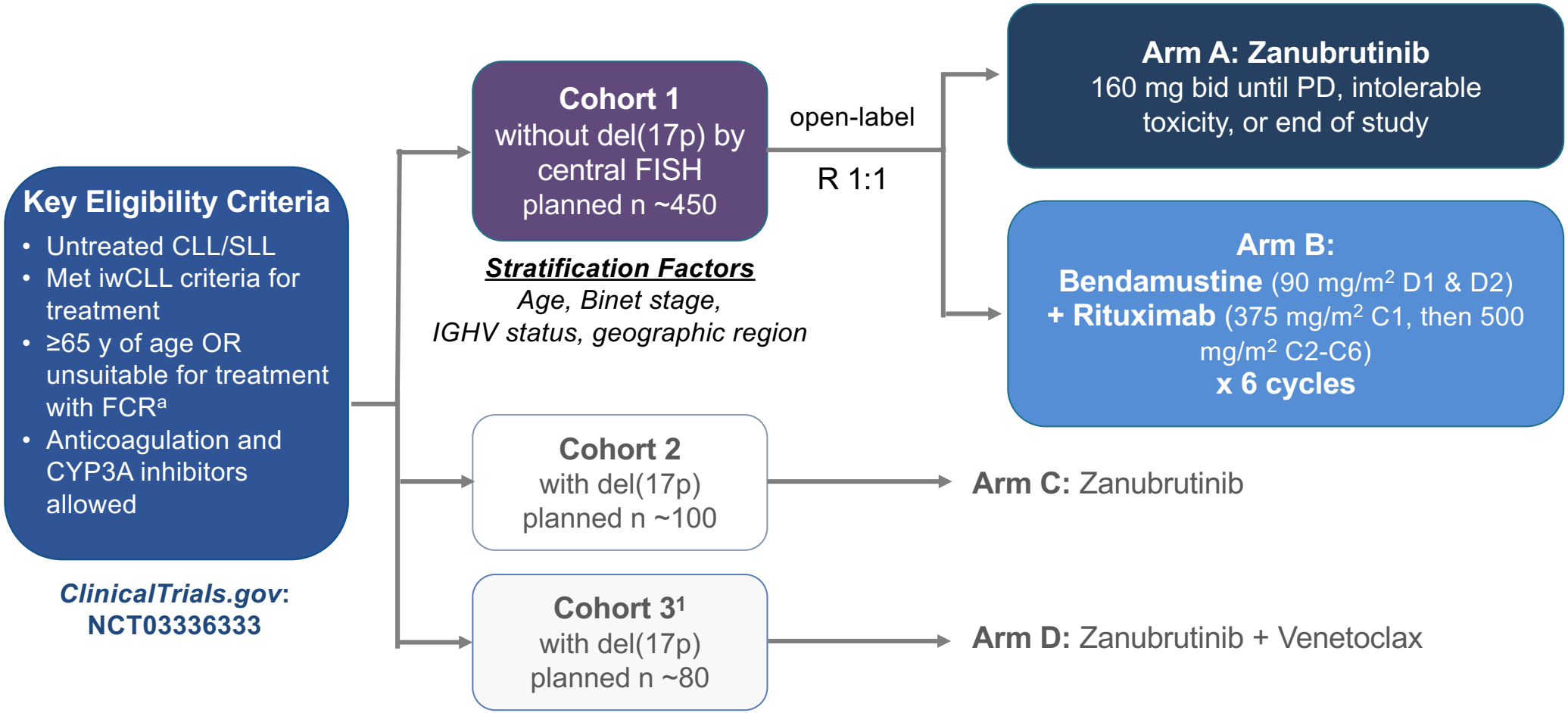
Safety

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

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

City of Hope.

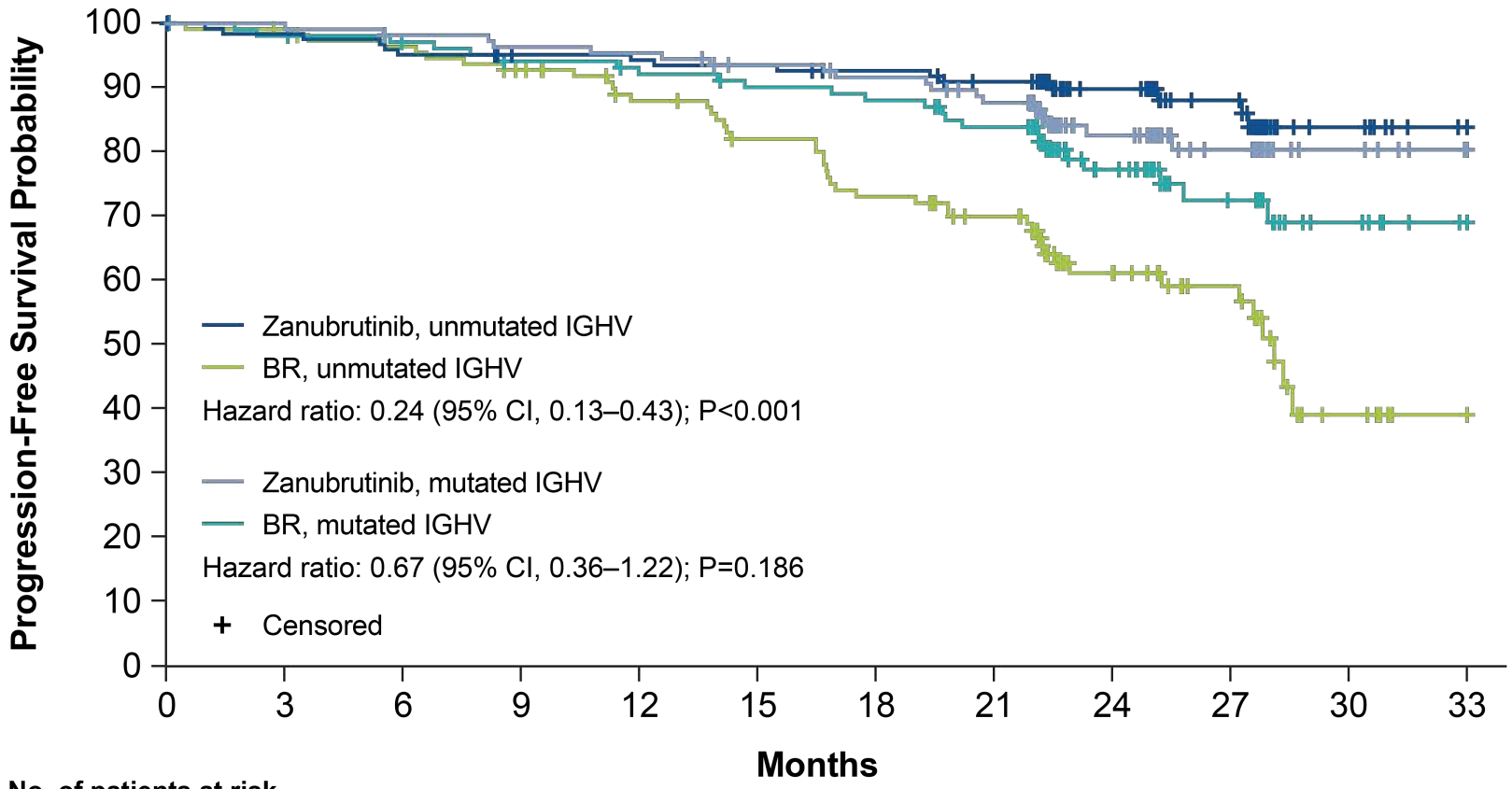
SEQUOIA (BGB-3111-304)
Study Design



[a]Defined as Cumulative Illness Rating Scale >6, creatinine clearance <70 mL/min, or a history of previous severe infection or multiple infections within the last 2 years.
C, cycle; CLL/SLL, chronic lymphocytic leukemia/small lymphocytic lymphoma; CYP3A, cytochrome P450, family 3, subfamily A; D, day; del(17p), chromosome 17p deletion; FCR, fludarabine, cyclophosphamide, and rituximab; FISH, fluorescence in-situ hybridization; IRC, independent review committee; IGHV, gene encoding the immunoglobulin heavy chain variable region; iwCLL, International Workshop on CLL; ORR, overall response rate; PD, progressive disease; R, randomized.
1. Tedeschi A, et al. ASH 2021. Abstract 67.

Tam, et al. ASH 2021, Abstract #396

Progression-Free Survival Per IRC Assessment by IGHV Status



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

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

Tam, et al. ASH 2021, Abstract #396

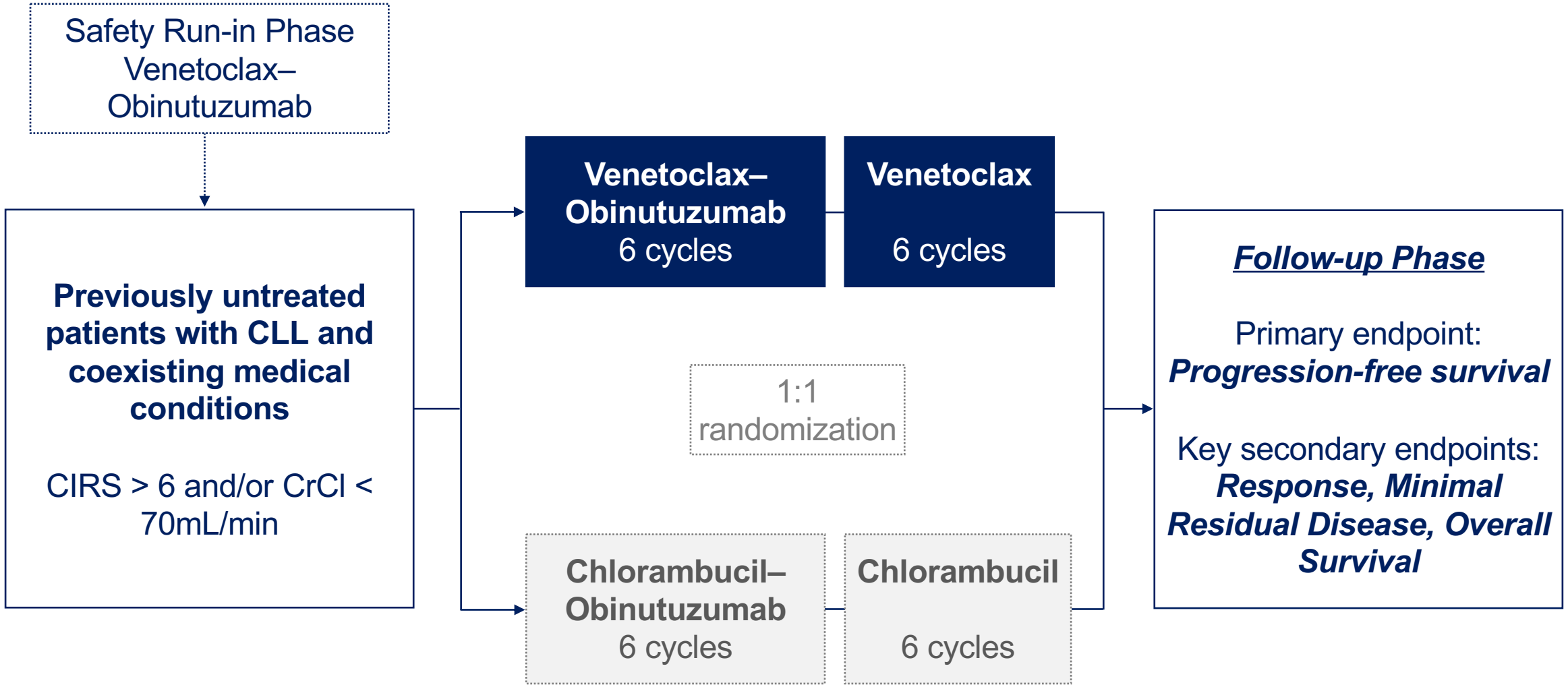
Adverse Events of Interest

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

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

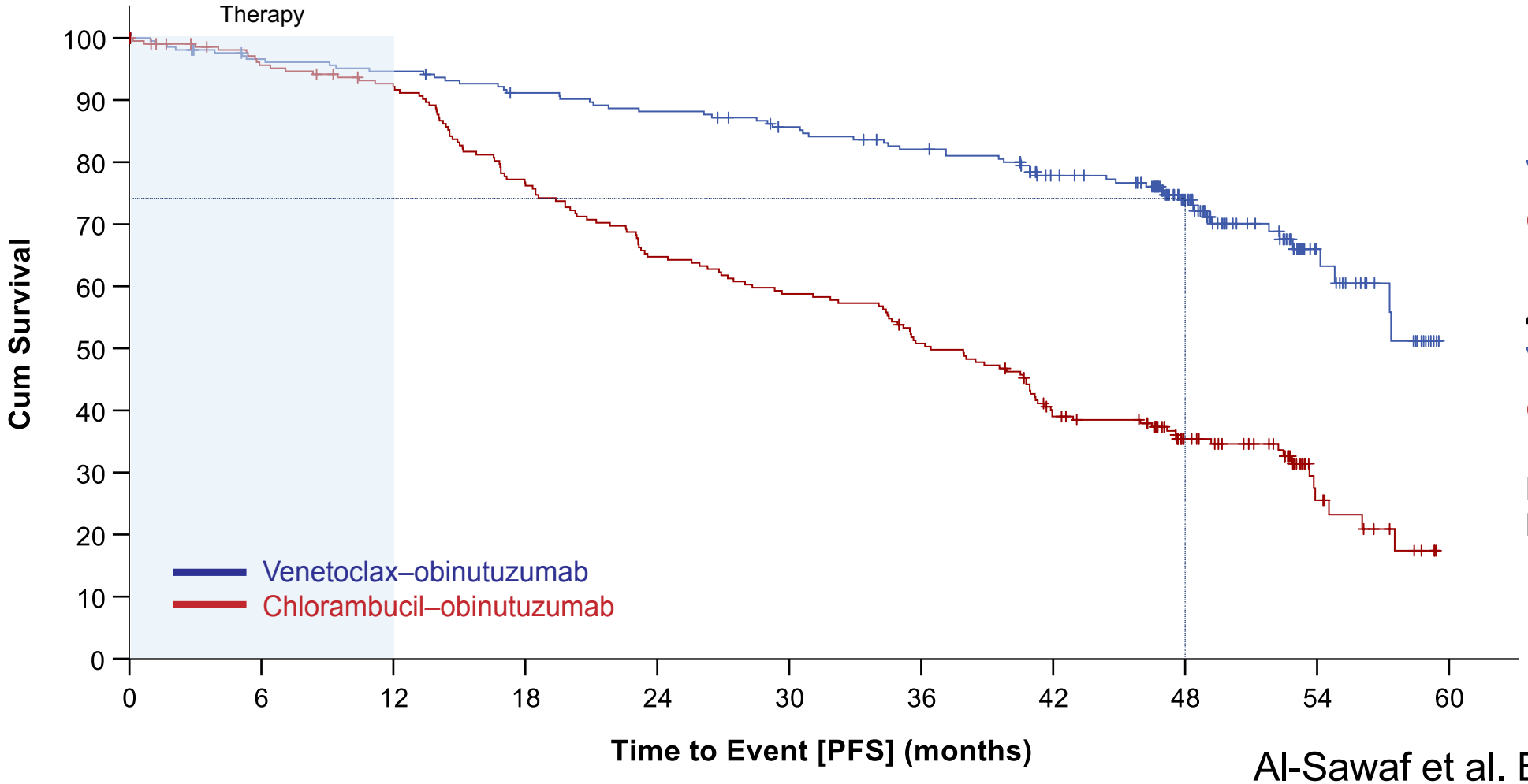
Tam, et al. ASH 2021, Abstract #396

CLL14: Trial Design



Progression-free Survival

Median observation time 52.4 months



Median PFS

Ven-Obi: not reached

Clb-Obi: 36.4 months

4-year PFS rate

Ven-Obi: 74.0%

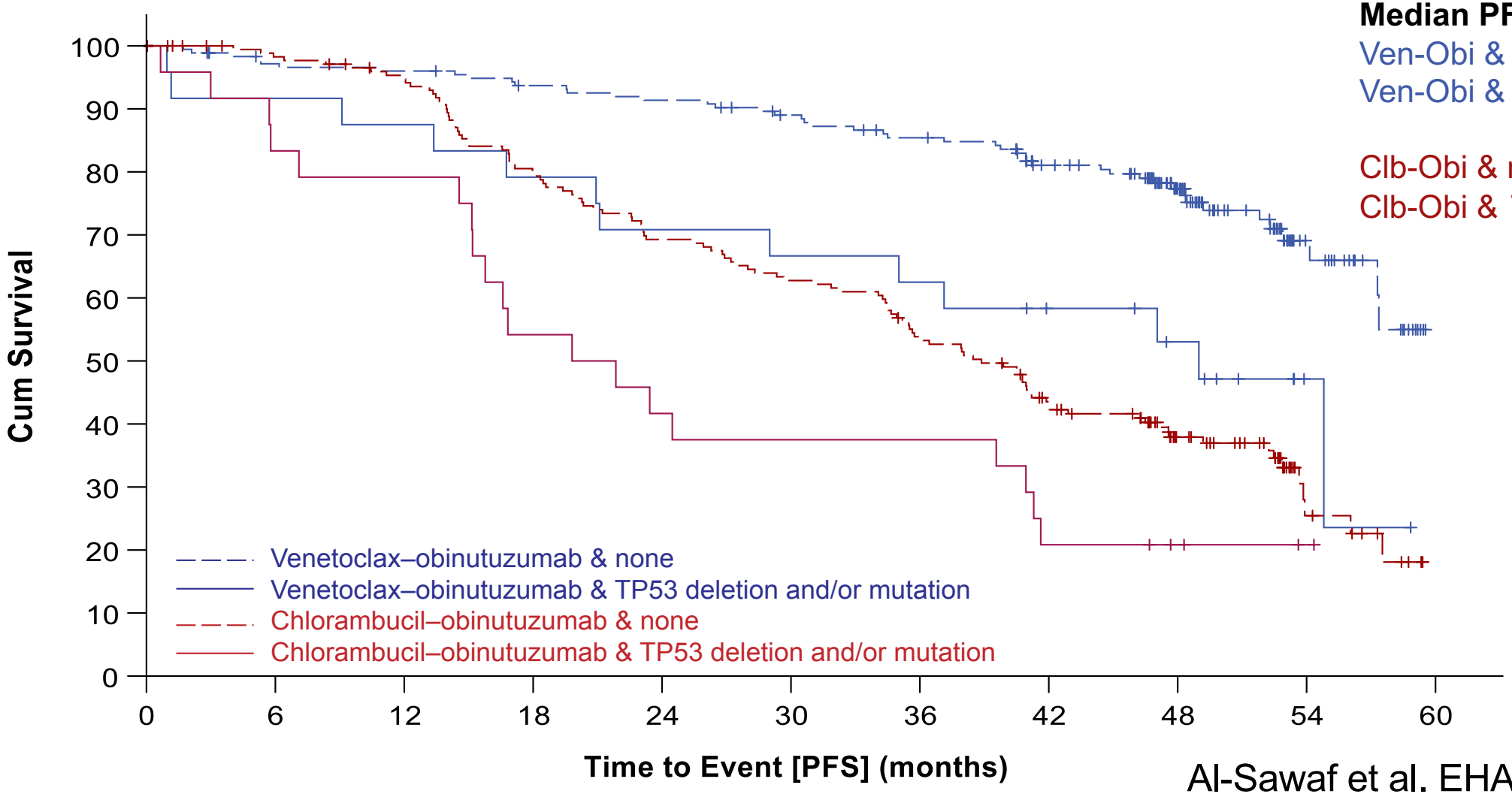
Clb-Obi: 35.4%

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

Al-Sawaf et al. EHA 2021, Abstract S146

Progression-free Survival – *TP53* Status

Median observation time 52.4 months



Median PFS

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

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

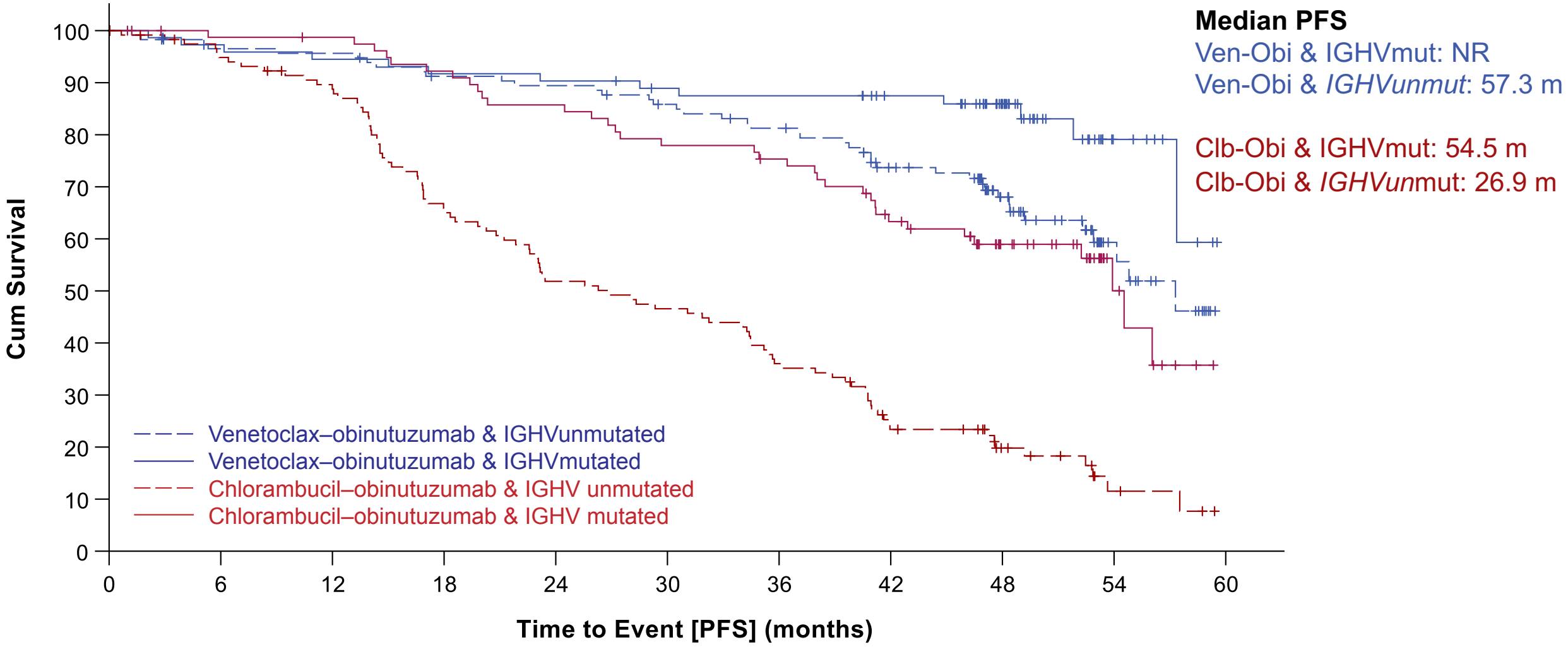
Clb-Obi & no *TP53*del/mut: 38.9 m

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

Al-Sawaf et al. EHA 2021, Abstract S146

Progression-free Survival – IGHV Status

Median observation time 52.4 months

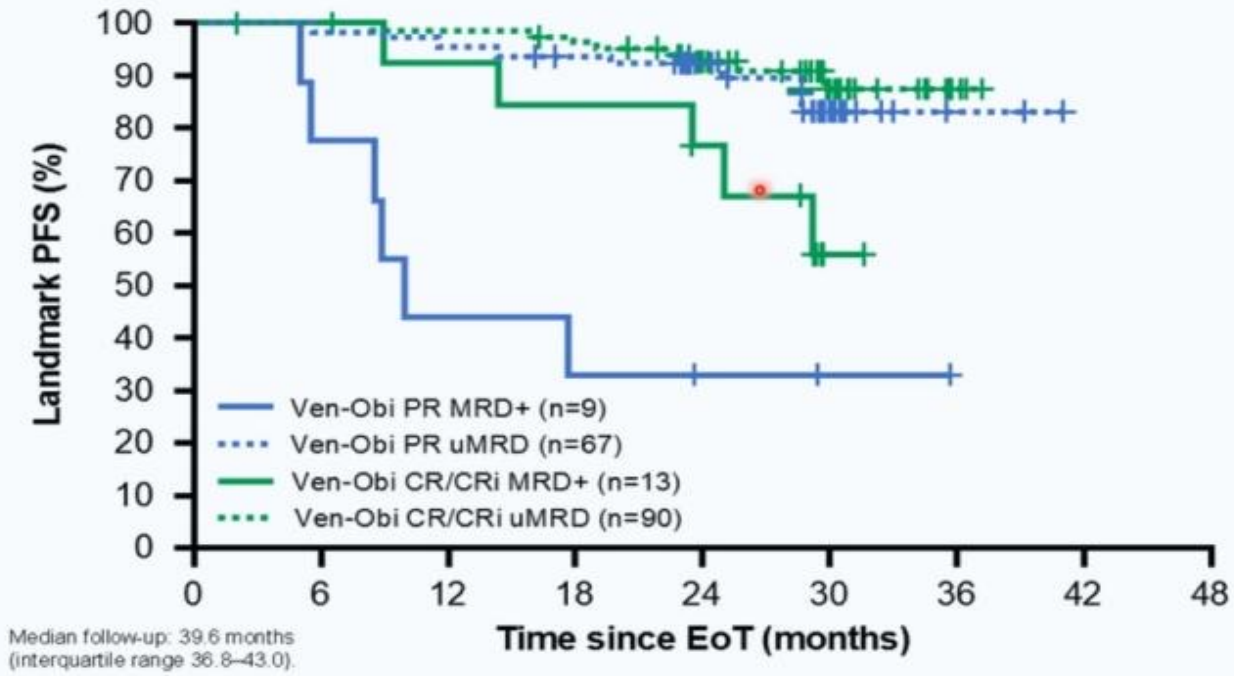


Al-Sawaf et al. EHA 2021, Abstract S146

uMRD associated with improved responses

CLL

LANDMARK PFS BY MRD/CLINICAL RESPONSE



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

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

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

Venetoclax vs Ibrutinib: Grade 3-4 events

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

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

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

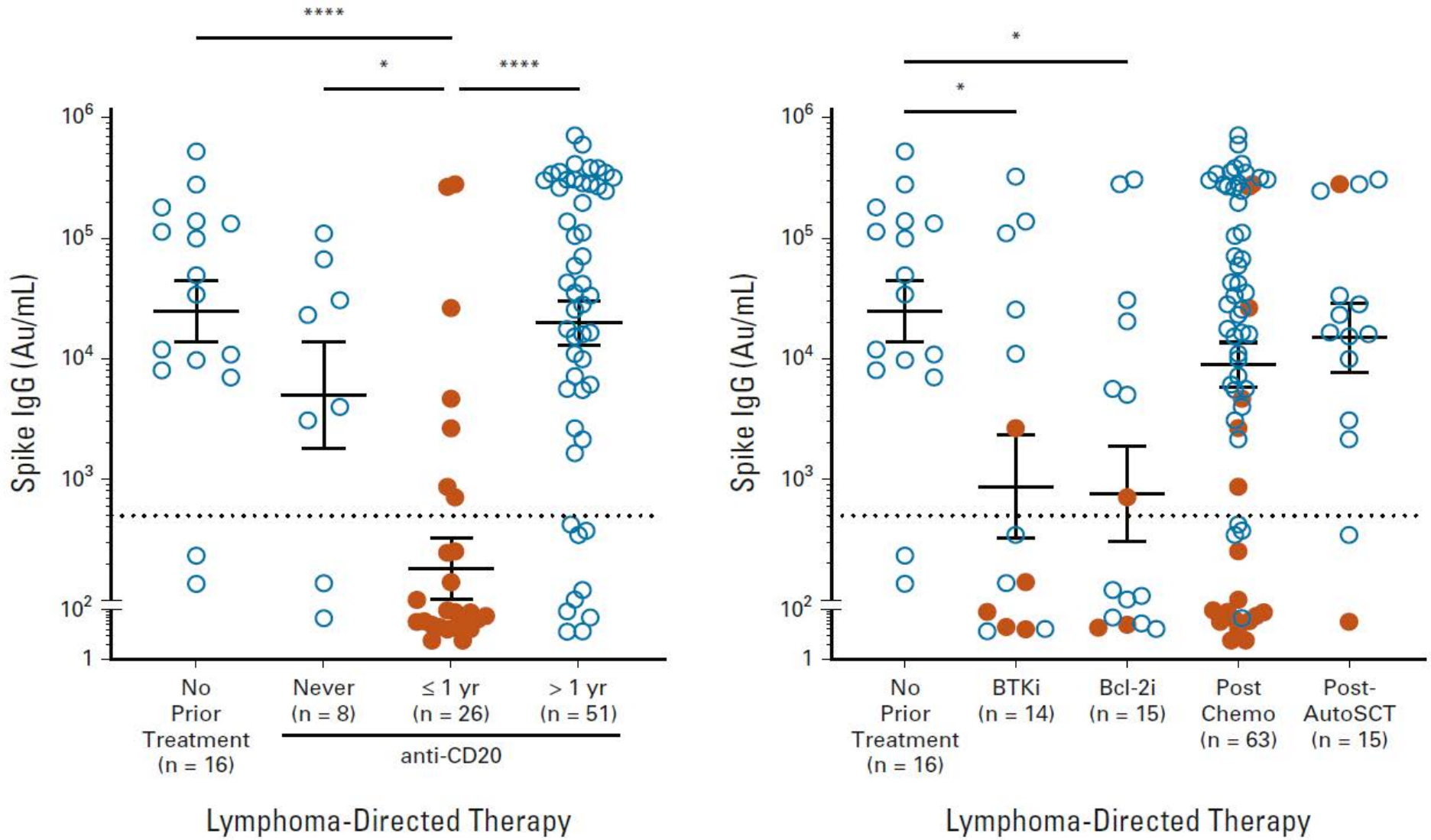
BTK Inhibitor

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

BCL-2 Inhibitor

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

COVID Vaccination Efficacy



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

Module 2: Novel Strategies Combining Bruton Tyrosine Kinase (BTK) and Bcl-2 Inhibitors for CLL — Prof Kater

RTP
RESEARCH
TO PRACTICE

Case Presentation: 79-year-old man with IGHV-unmutated CLL under observation for many years develops B symptoms, cytopenias and lymphadenopathy

Dr Henna Malik (Houston, Texas)

RTP
RESEARCH
TO PRACTICE

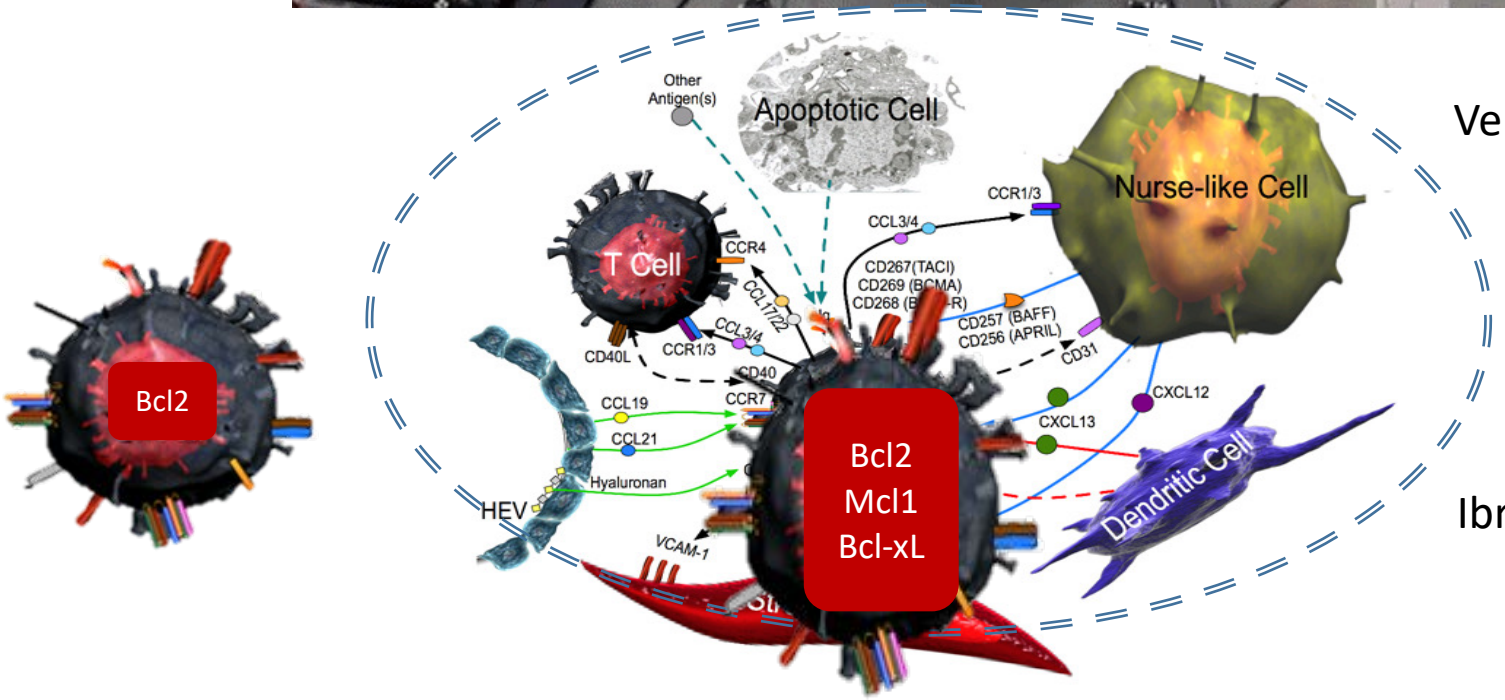
Novel Strategies Combining Bruton Tyrosine Kinase (BTK) and Bcl-2 Inhibitors for CLL

Arnon Kater

Amsterdam University Medical Centers

Chairman Hovon CLL study group

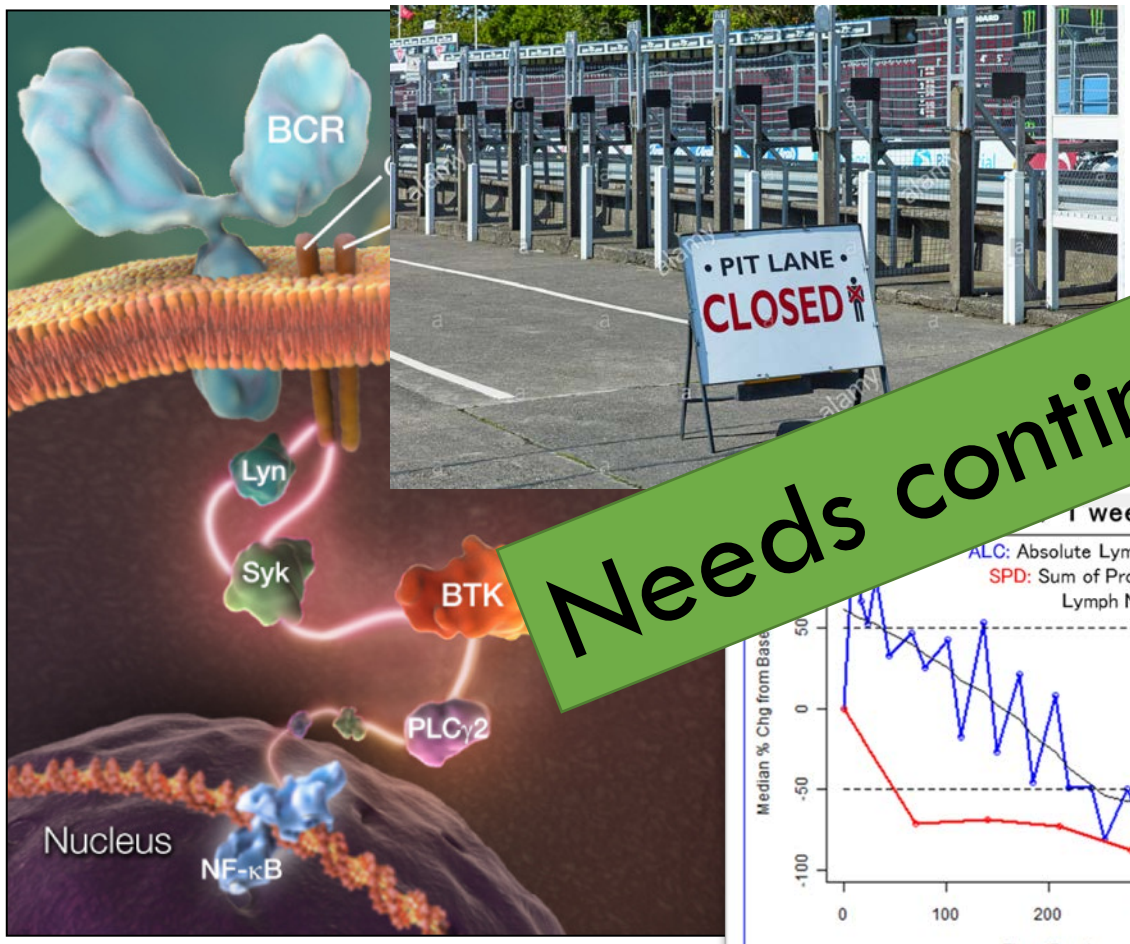
The key role of the TME



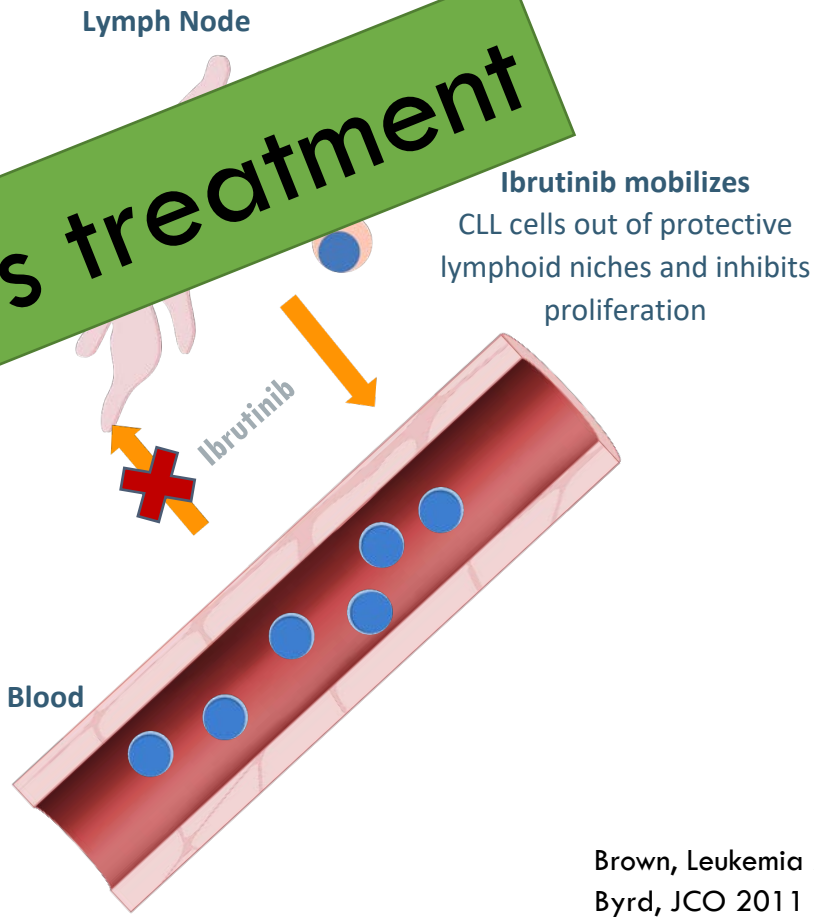
Venetoclax active in blood, less in LNN

Ibrutinib active in LNN, less in marrow

BTK-inhibition targets adhesion and homing to lymph node

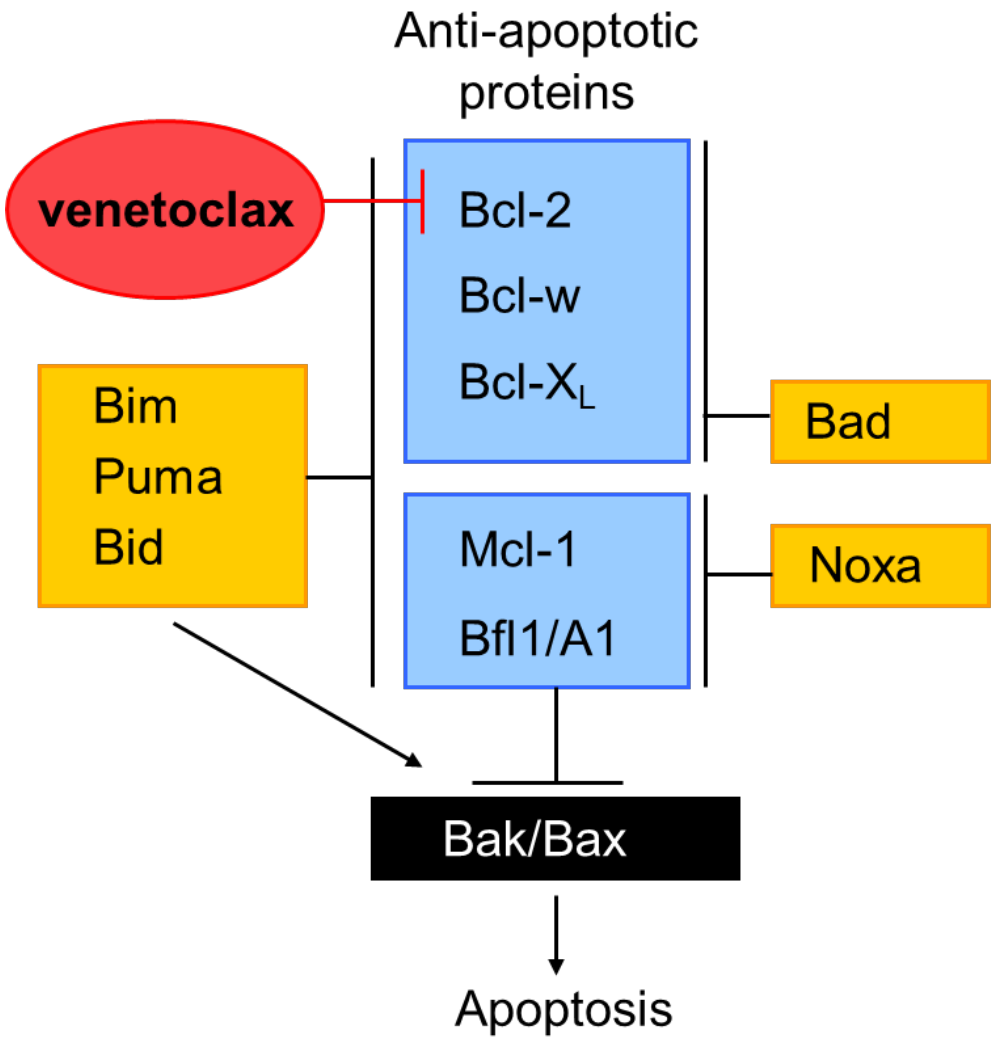


Needs continuous treatment



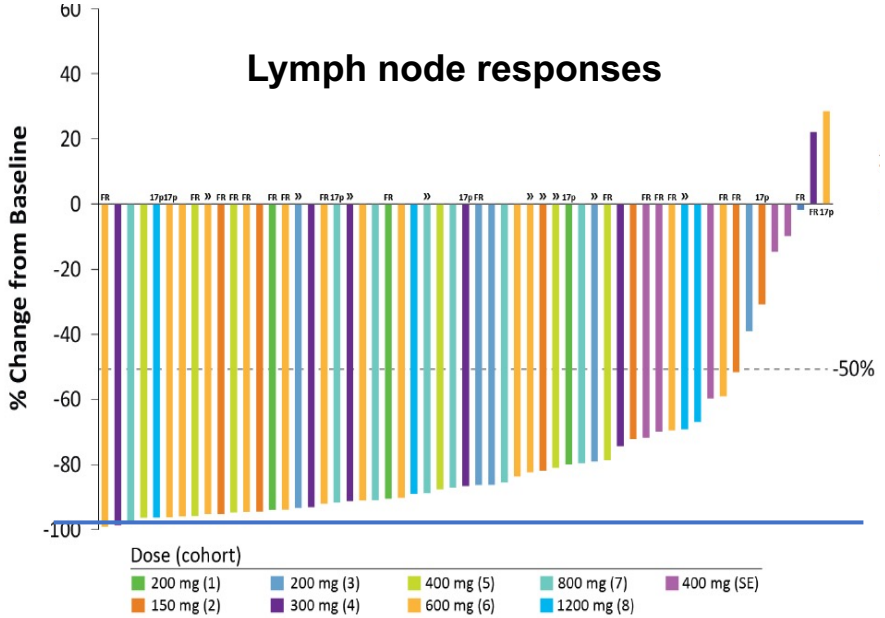
Brown, Leukemia 2018
Byrd, JCO 2011

Venetoclax sensitivity differs between compartments

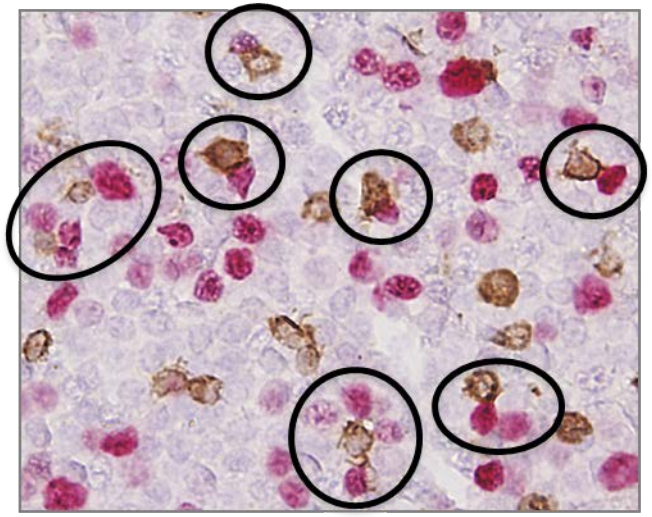


Blood responses

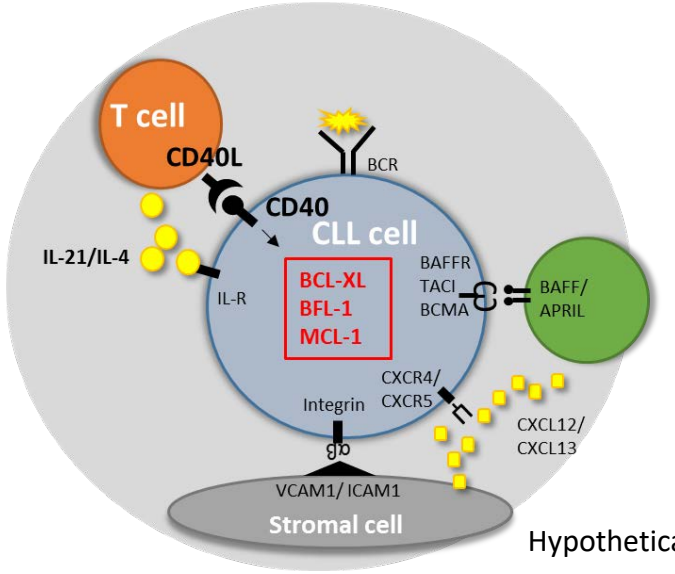
Lymph node responses



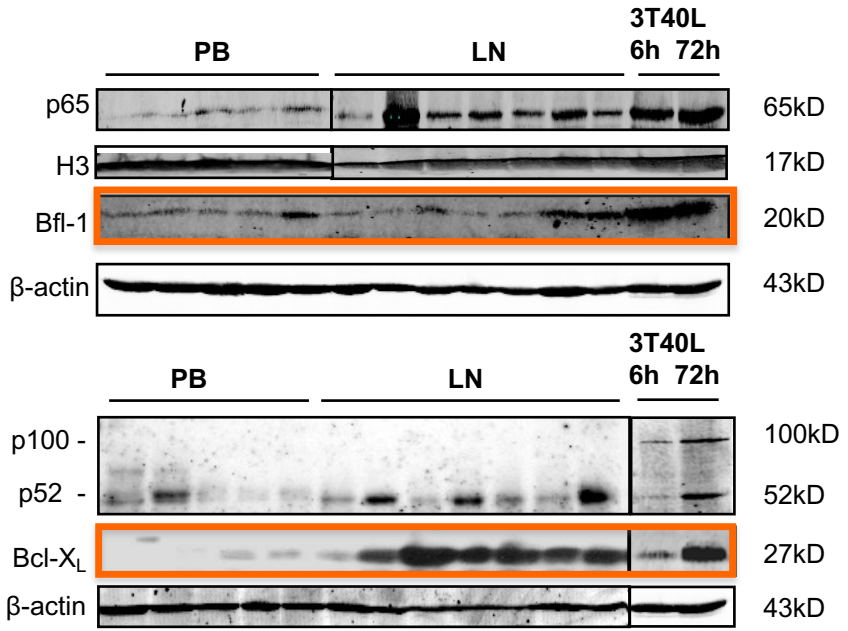
Bfl-1, Bcl-XL and Mcl-1 expression increased in CLL LN

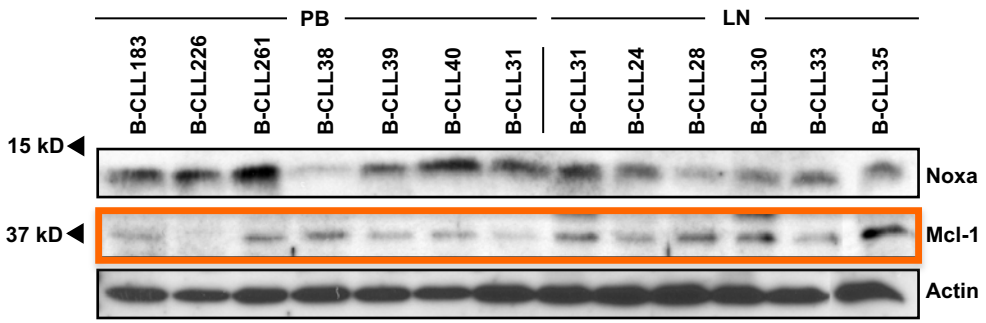


Many Ki67+ CLL cells are in close contact with CD3+ T cells.



Hypothetical Lymph node environment

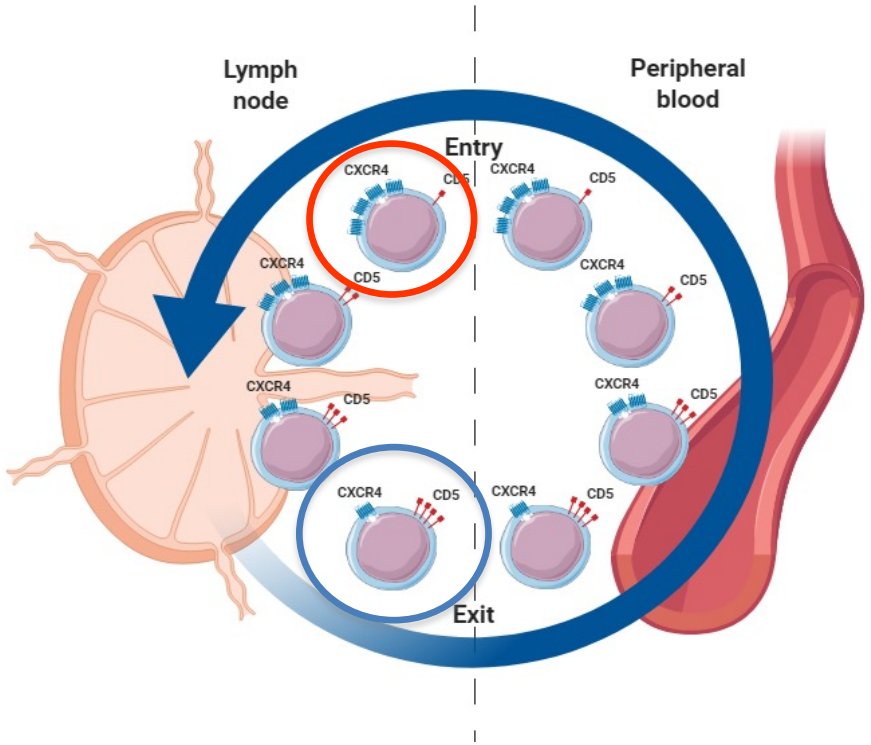




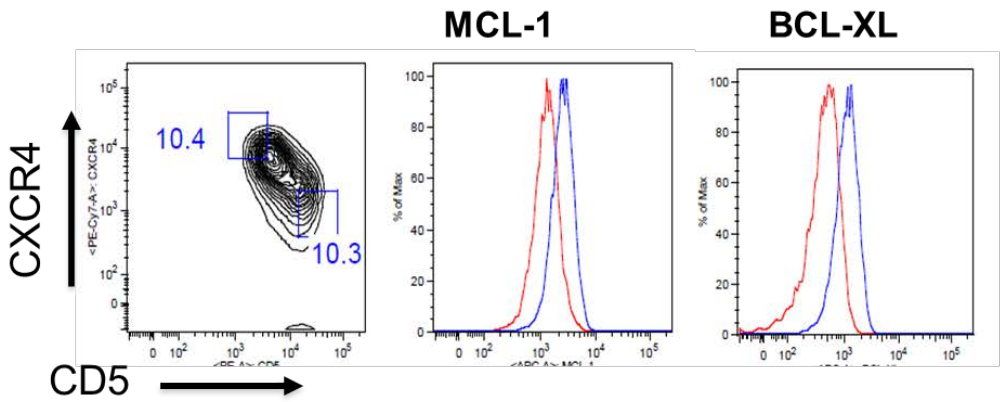
Noxa/Mcl1 balance altered in CLL LN
Smit LA et al, Blood 109: 1660, 2007.

Tromp J et al Oncogene 29: 5071, 2010

Using a FACS trick to explore expression levels of anti-apoptotic proteins in the lymph node



(Calissano etal. Mol Med. 2011)



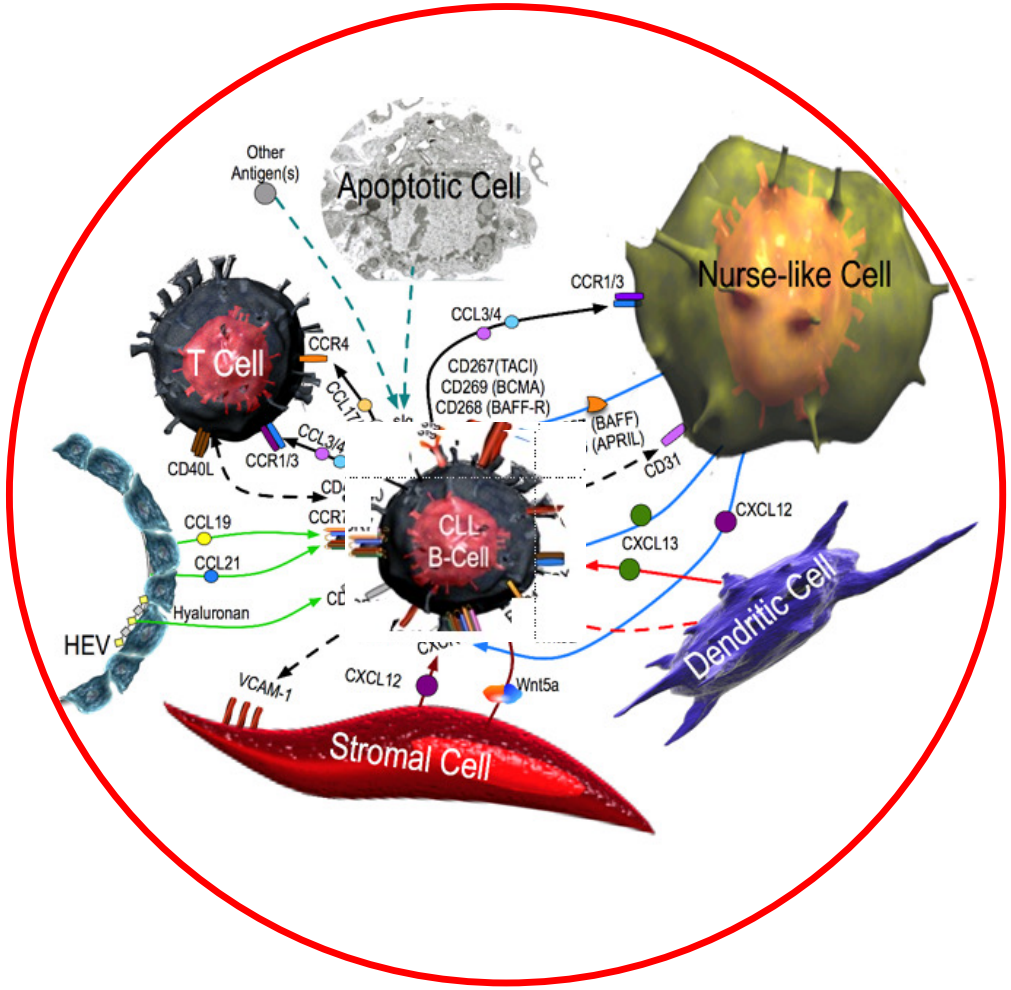
CXCR4^{high}CD5^{dim} 'old' CLL cells

CXCR4^{dim}CD5^{high} LN emigrant CLL cells

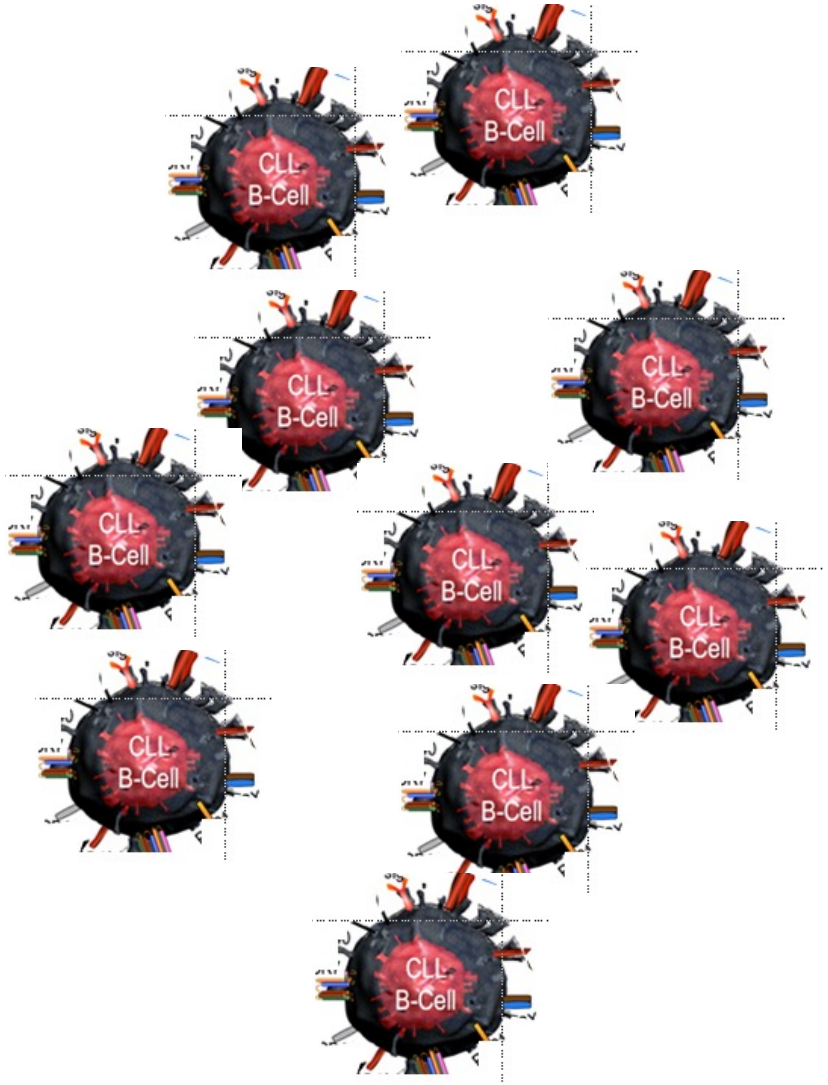
Differences in Mcl-1 & Bcl-XL in recent LN emigrants and 'old' returning cells

Haselager Blood 2021

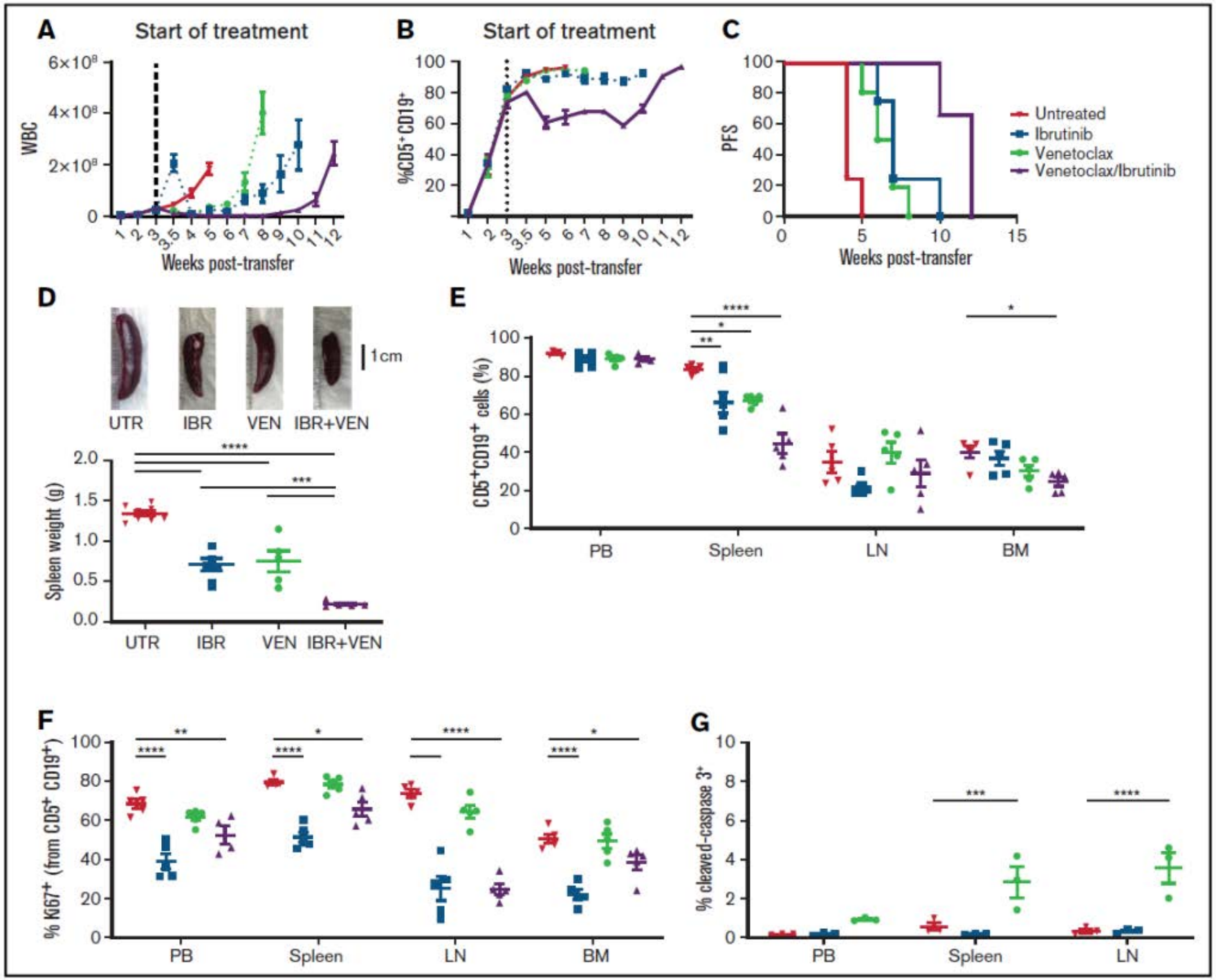
Combining Venetoclax with……



BTK-i



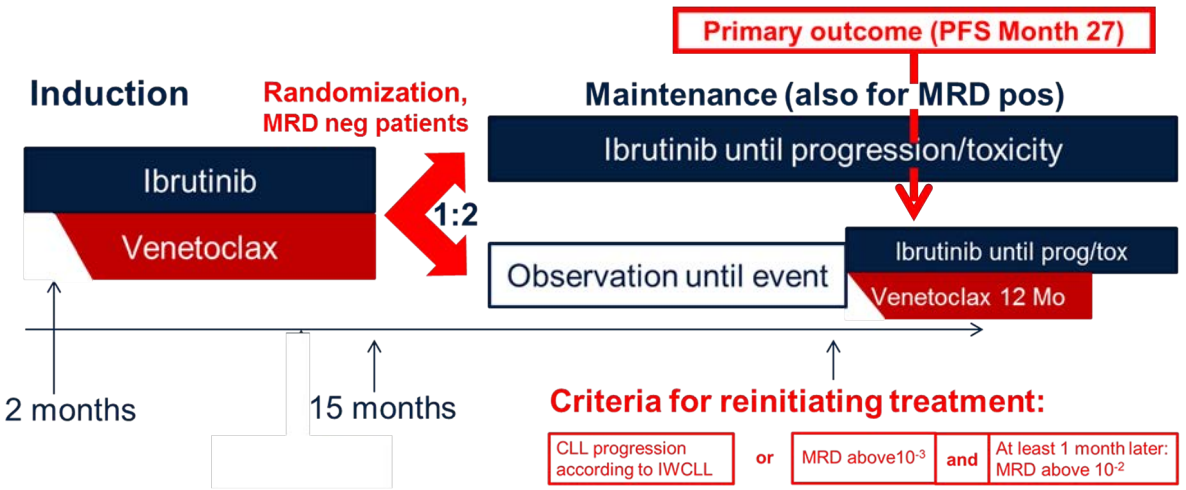
Venetoclax

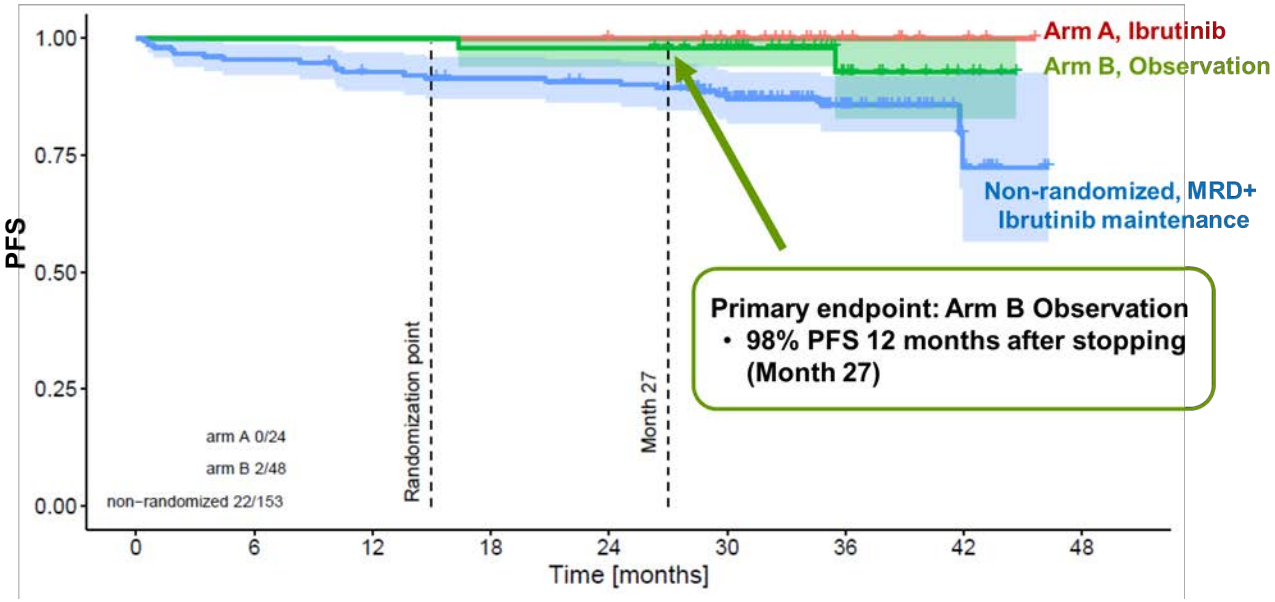


Kater, Blood Adv. 2022

Efficacy data

Minimal residual disease-guided stop and start of venetoclax plus ibrutinib for patients with relapsed or refractory chronic lymphocytic leukaemia (HOVON141/VISION): primary analysis of an open-label, randomised, phase 2 trial





	N
Non-randomized Ibrutinib	153
Arm A Ibrutinib	24
Arm B Observation	48

- **7 patients reinitiated ibrutinib-venetoclax during observation due to MRD+**
- **6 of 7 achieved de novo CR within 3 cycles**
- **7th patient awaits evaluation**

HOVON

Nordic CLL Study Group

Kater AP *Lancet Oncol* 2022; 23: 818–28

Clinical evidence of Ven+Ibr fixed duration 1st-line

Phase 2 CAPTIVATE

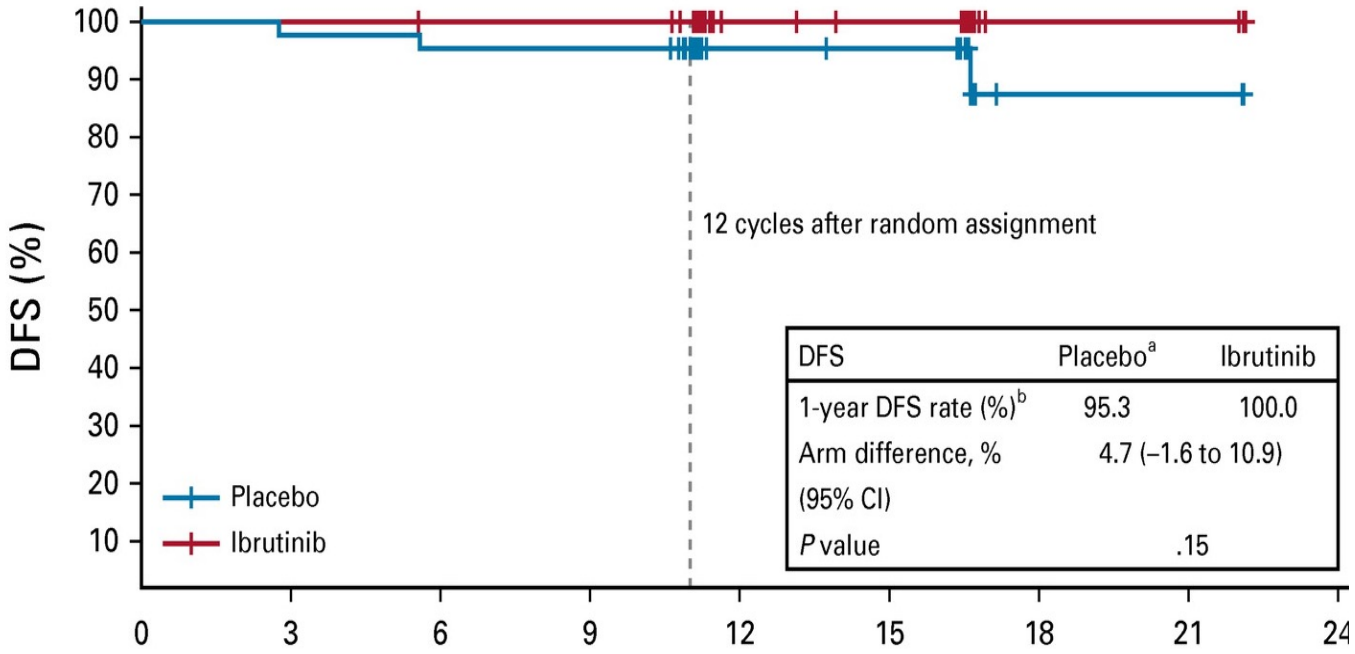
Patients (N=159)
- Previously untreated CLL/SLL
- Active disease requiring treatment per iwCLL criteria[1]
- Aged ≤70 years
- ECOG PS 0–2

Ibrutinib lead-in
Ibrutinib 420 mg once daily (3 cycles[a])

Ibrutinib + Venetoclax
Ibrutinib 420 mg once daily + venetoclax 400 mg once daily (12 cycles[a])

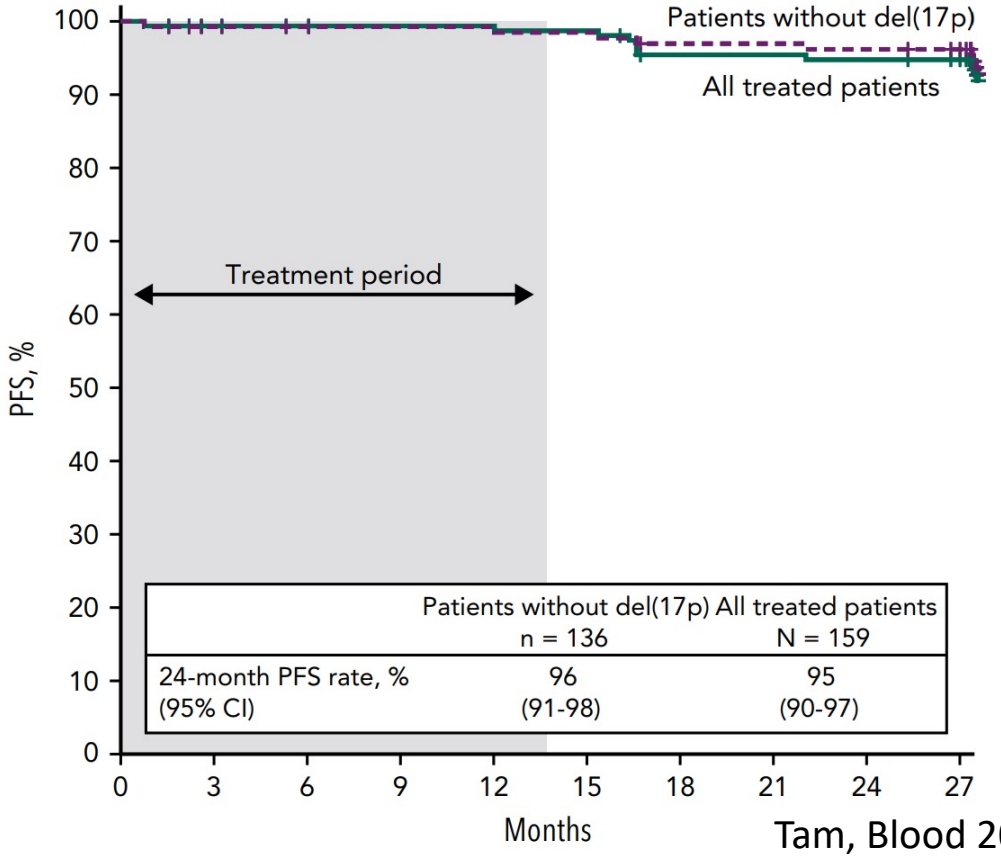
MRD-guided discontinuation

Follow-up



DFS	Placebo[a]	Ibrutinib
1-year DFS rate (%)[b]	95.3	100.0
Arm difference, % (95% CI)	4.7 (–1.6 to 10.9)	
P value	.15	

Wierda, JCO 2021



	Patients without del(17p) n = 136	All treated patients N = 159
24-month PFS rate, % (95% CI)	96 (91-98)	95 (90-97)

Tam, Blood 2022

Clinical evidence of Ven+Ibr fixed duration 1st-line

Phase 3 GLOW

Patients (N=106)
- Previously untreated CLL/SLL
- ≥ 65 years of age or < 65 years with CIRS > 6 or CrCL < 70 mL/min

Ibrutinib lead-in
Ibrutinib 420 mg once daily (3 cycles[a])

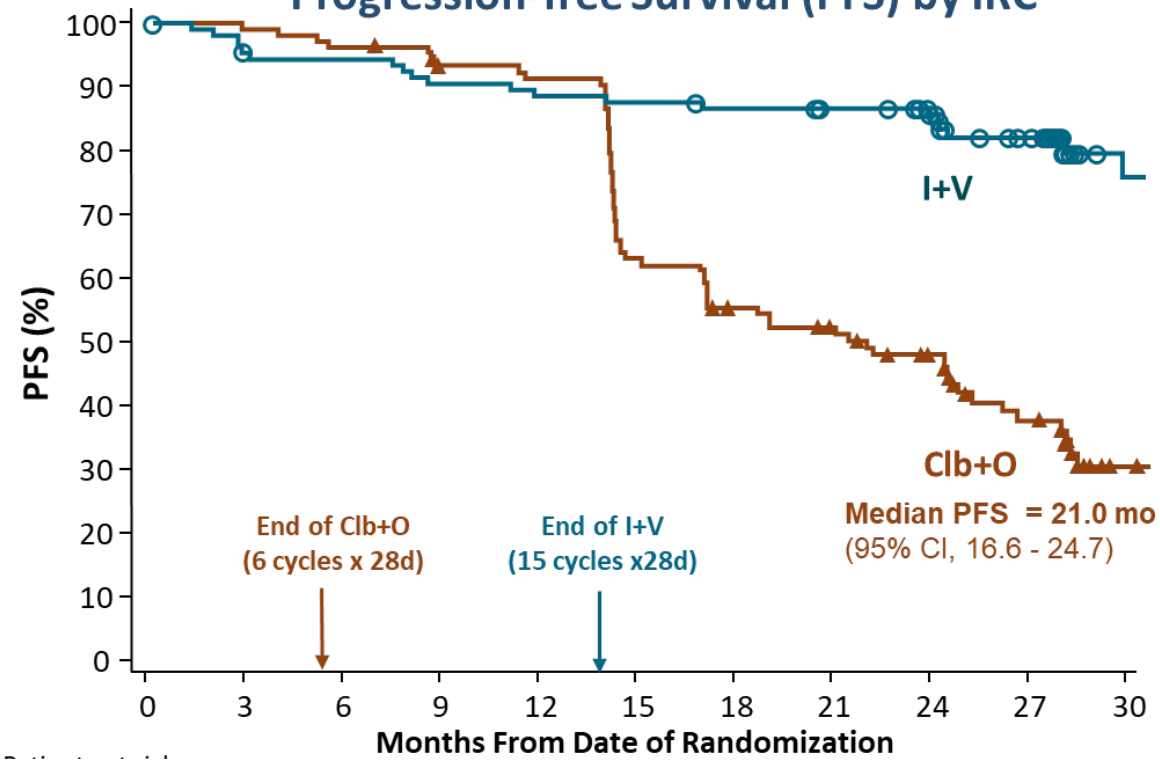
→

Ibrutinib + Venetoclax
Ibrutinib 420 mg once daily + venetoclax 400 mg once daily (12 cycles[a])

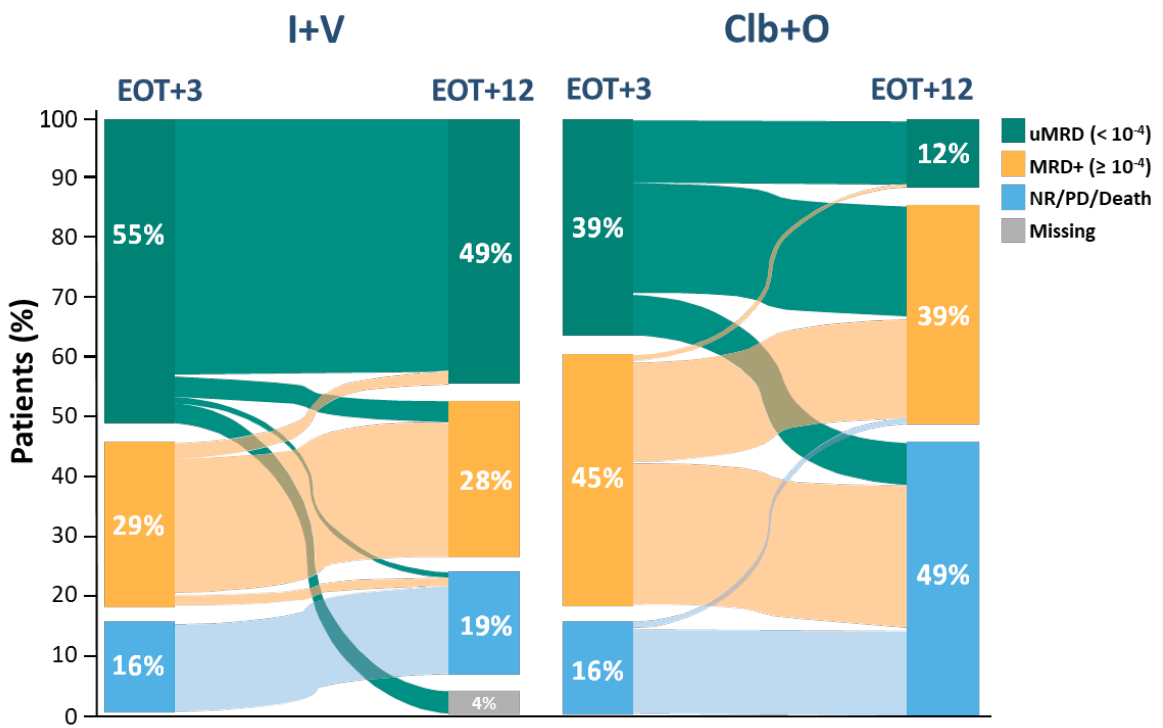
→ **Follow-up**

Responses (ITT):
- CR: 39%
- uMRD: PB 55% / BM 52%

Progression-free Survival (PFS) by IRC



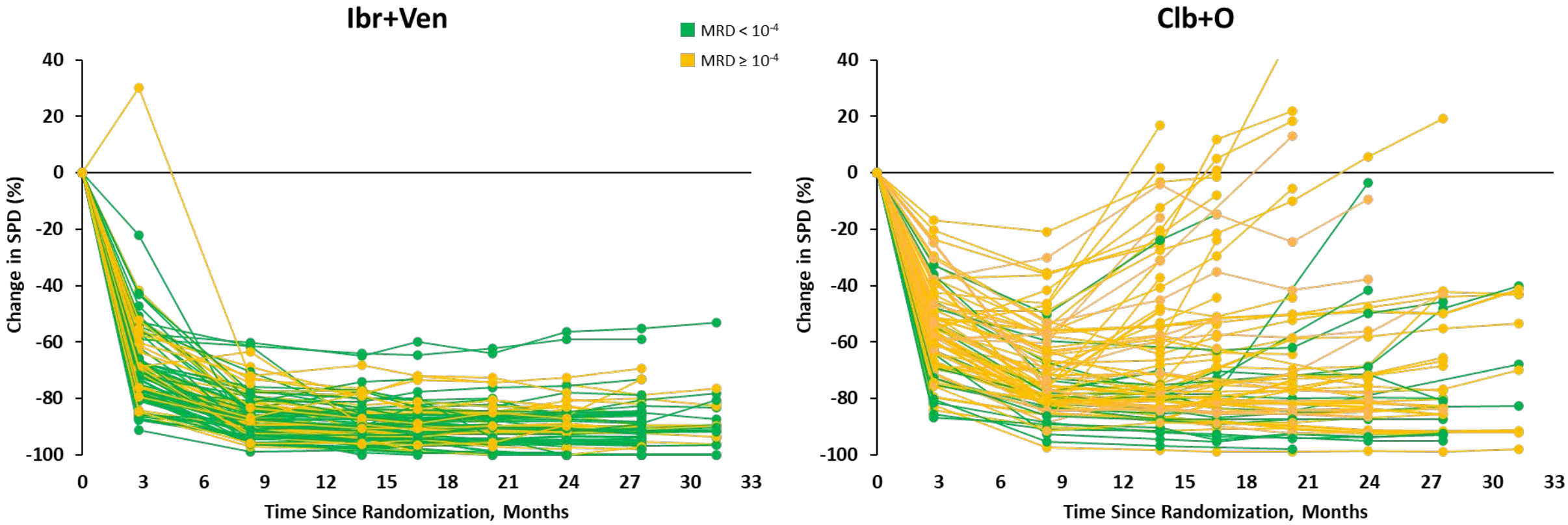
Peripheral Blood MRD (NGS)



Sustained MRD responses

Kater, NEJMe 2022

Lymph Node Responses Were Better Maintained Over Time With Ibr+Ven vs Clb+O in Patients With Detectable BM MRD

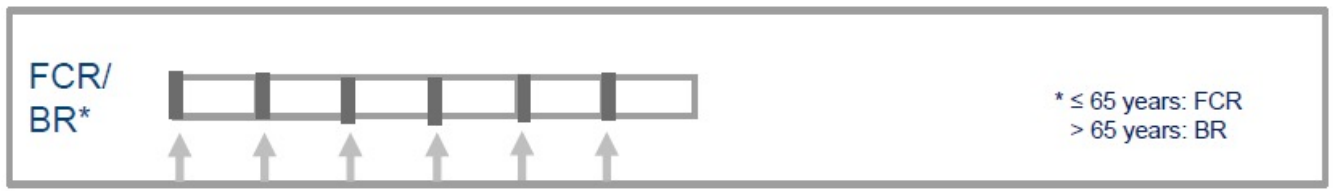
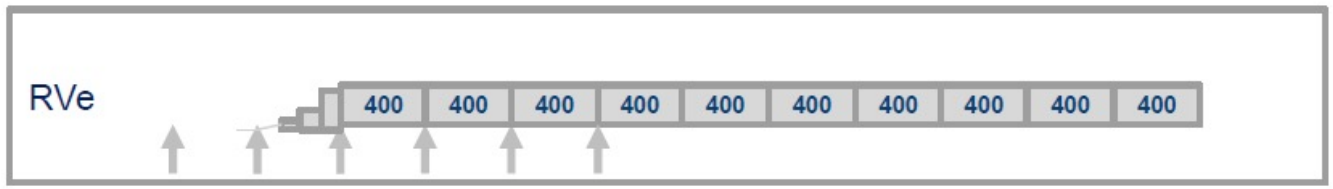
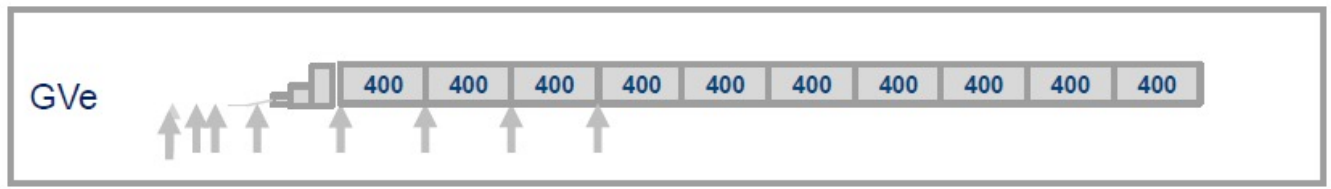
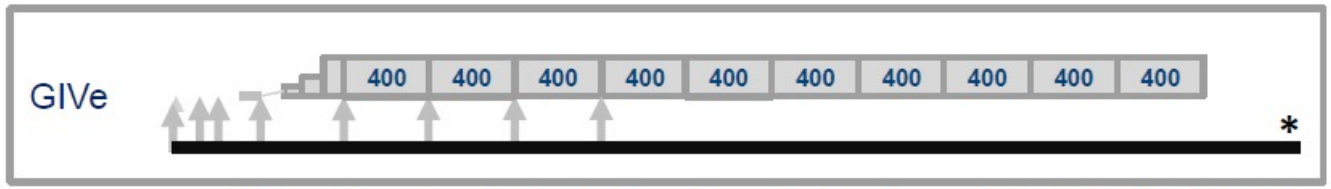


[a] < 10^{-4} at EOT+3.
BM, bone marrow; EOT, end of treatment; SPD, sum of the product of perpendicular dimensions.

Kater, NEJMe 2022

GAIA/CLL13 Study : Treatment regimen

Treatment regimen in 28 days (D) interval cycles (C)

FCR/BR*		Fludarabine 25mg/m² d1-3 iv Cyclophosphamide 250mg/m² d1-3 iv Rituximab 375/500mg/m² d1 iv Bendamustine 90mg/m² d1+2 iv Rituximab 375/500mg/m² d1iv
RVe		Venetoclax ramp up 20 – 400mg po Venetoclax 400mg po C3-C12 Rituximab 375/500mg/m² d1 iv
GVe		Venetoclax ramp up 20 – 400mg po Venetoclax 400mg po C3-C12 Obinutuzumab 1000mg/m² iv d1+8+15 during C1, d1 C2-C6
GIVe		Ibrutinib 420mg po from d1 C1 Venetoclax ramp up 20 – 400mg po Venetoclax 400mg po C3-C12 Obinutuzumab 1000mg/m² iv d1+8+15 during C1, d1 C2-C6

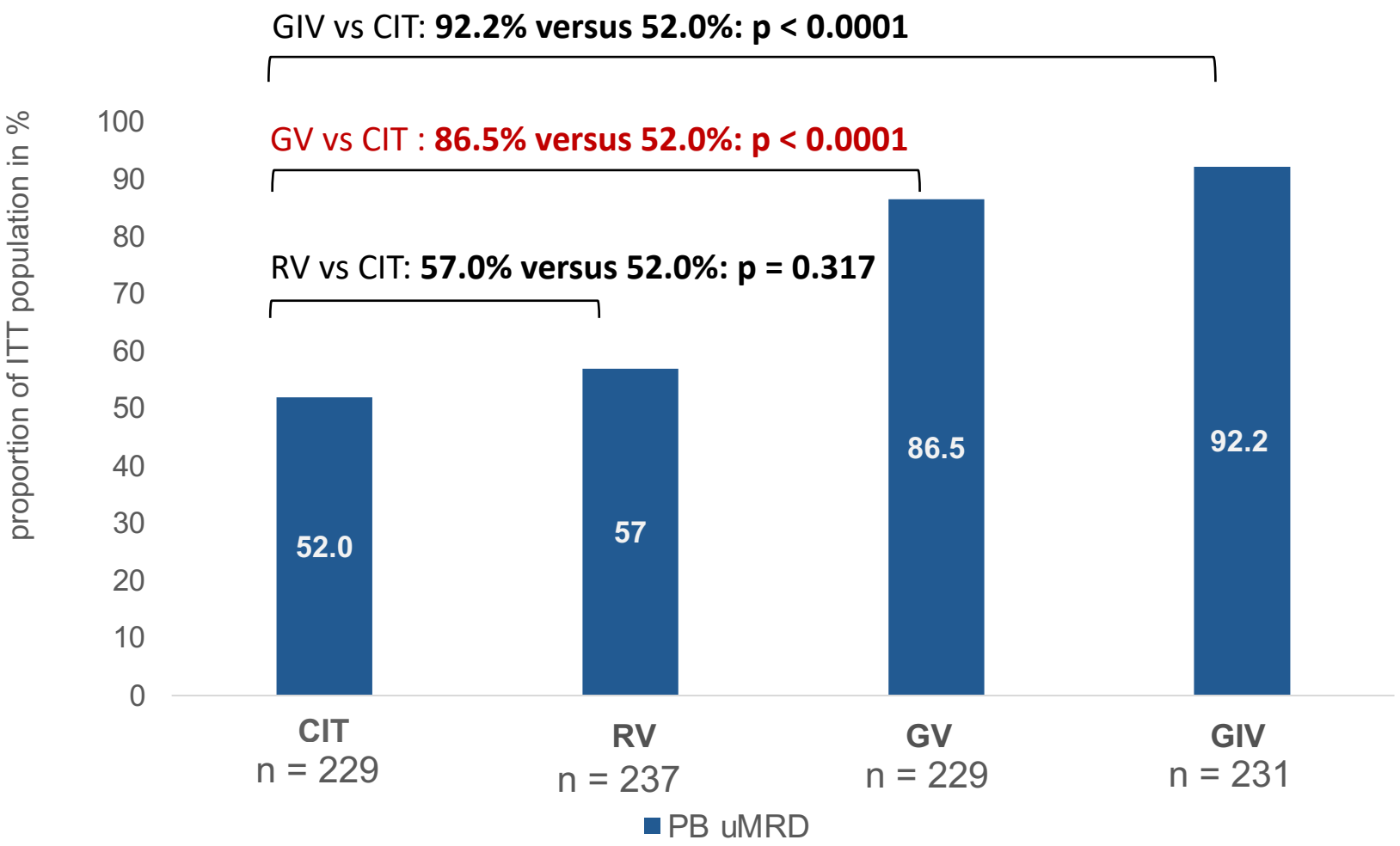
* Continuation of ibrutinib up to cycle 36 allowed, if MRD still detectable

Chemotherapy | CD20-antibody | 400 Venetoclax (V) | Ramp-Up | Ibrutinib (I)

Eichhorst EHA 2022

Results of coprimary endpoint rate of undetectable minimal residual disease

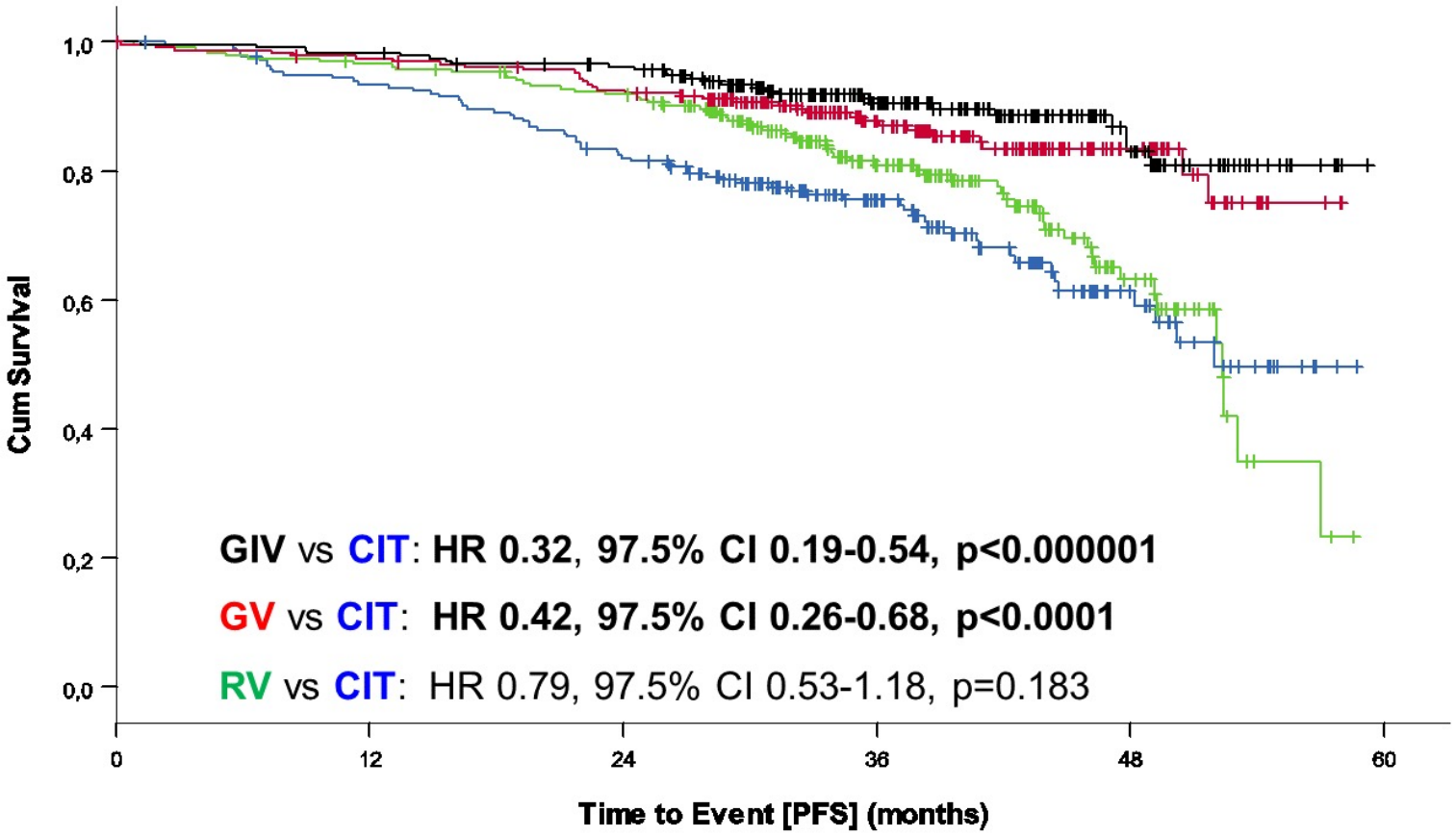
Coprimary endpoint: uMRD (< 10^{-4}) at Mo15 in PB by 4-colour-flow



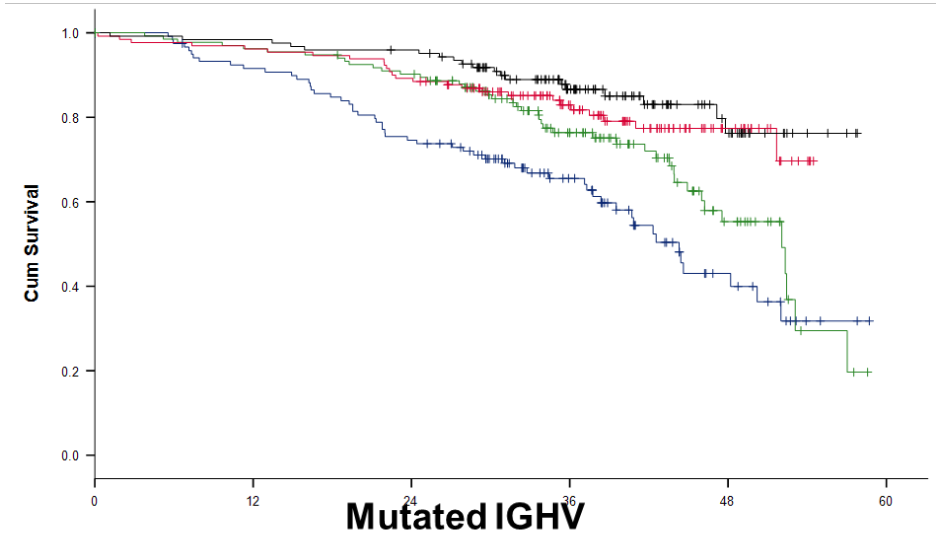
	uMRD%	97.5% CI
GIV	92.2	87.3 – 95.7
GV	86.5	80.6 – 91.1
RV	57.0	49.5 – 64.2
CIT	52.0	44.4 – 59.5

Eichhorst B. et al., ASH 2021: abstract 72

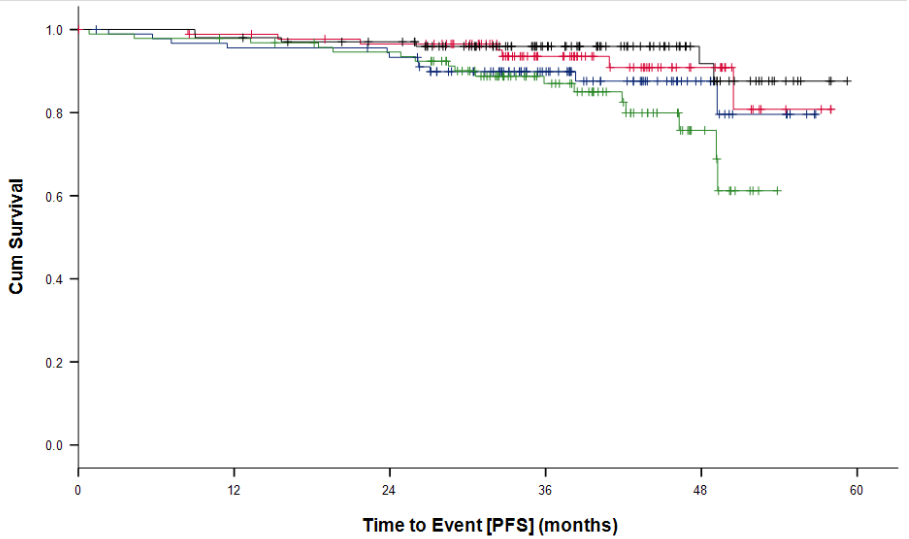
Results of the coprimary endpoint progression-free survival (PFS)



Unmutated IGHV



Mutated IGHV



Eichhorst EHA 2022

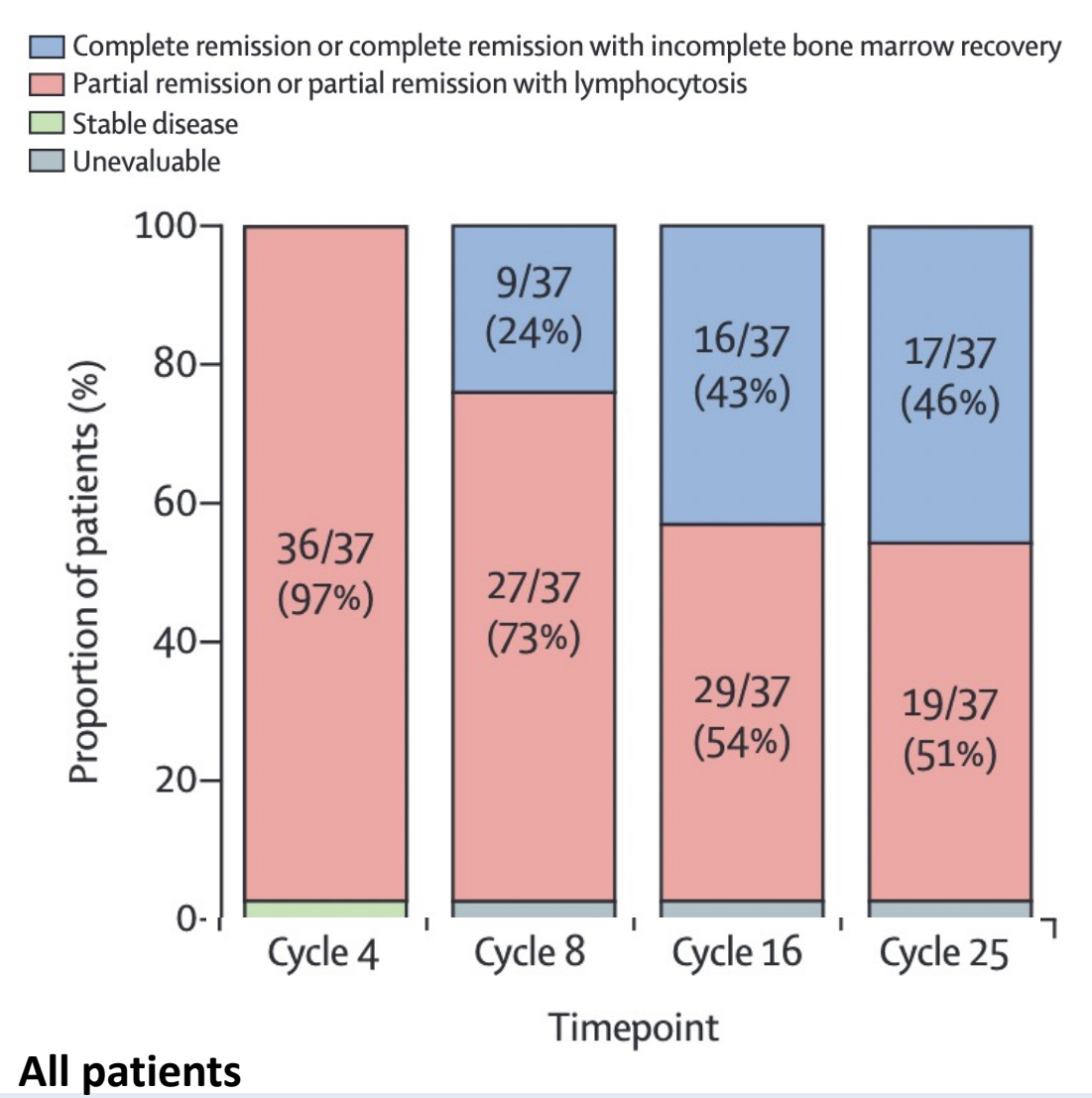
Articles

Acalabrutinib, venetoclax, and obinutuzumab as frontline treatment for chronic lymphocytic leukaemia: a single-arm, open-label, phase 2 study

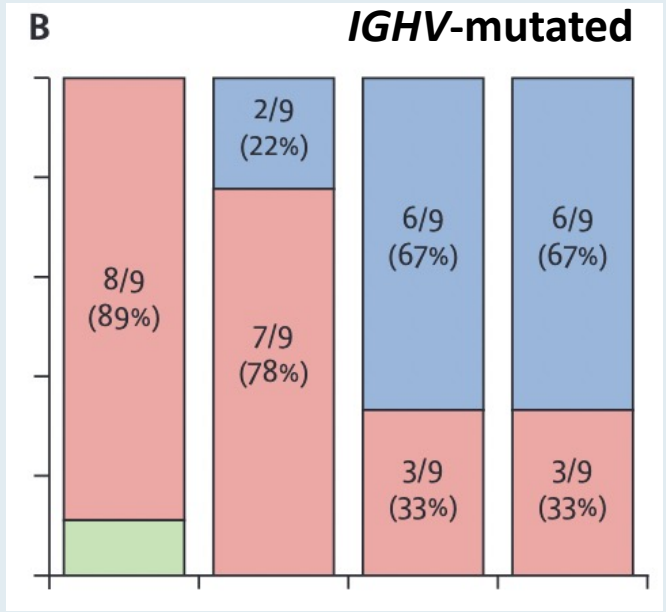
Matthew S Davids, Benjamin L Lampson*, Svitlana Tyekucheva, Zixu Wang, Jessica C Lowney, Samantha Pazienza, Josie Montegaard, Victoria Patterson, Matthew Weinstock, Jennifer L Crombie, Samuel Y Ng, Austin I Kim, Caron A Jacobson, Ann S LaCasce, Philippe Armand, Jon E Arnason, David C Fisher, Jennifer R Brown*

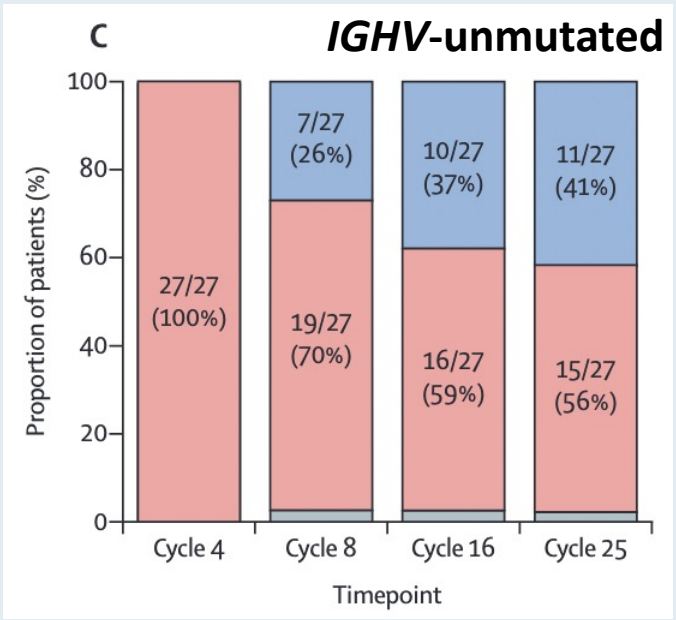
Davids MS et al. *Lancet Oncol* 2021;22(10):1391-402.

Acalabrutinib, venetoclax and obinutuzumab: Response rates at the start of indicated cycles



All patients





Davids MS et al. *Lancet Oncol* 2021;22(10):1391-402.

RTP RESEARCH TO PRACTICE

Updated Results from a Multicenter, Phase 2 Study of Acalabrutinib, Venetoclax, Obinutuzumab (AVO) in a Population of Previously Untreated Patients with CLL Enriched for High-Risk Disease

Ryan C et. al.

ASH 2022; Abstract 344
Saturday, December 10, 2022, 4:15 PM

Toxicity data

Serious toxicity GLOW >> CAPTIVATE

- HR (95% CI) for overall survival: 1.048 (0.454, 2.419), with 11 deaths in I+V arm and 12 in Clb+O arm (Table)
- Causes of death were generally similar in nature for both study arms, with infections (including COVID-19-related pneumonia) and cardiac events most common

Death from Any Cause	During Treatment			During Follow-up	
	I+V (N=106)		Clb+O (N=105)	I+V (N=106)	Clb+O (N=105)
	Ibr lead-in	I+V			
Total, n	**4**	**3**	**2**	**4**	**10**
Infections and Infestations	1	-	1	2	6
Cardiac Disorders	2[a]	-	-	-	2
General Disorders (Sudden Death)	-	2	-	1	-
Neoplasm	1	-	-	-	-
Nervous System Disorders	-	1	-	-	1
Hepatobiliary Disorders	-	-	1	-	-
Respiratory, Thoracic, Mediastinal Dis.	-	-	-	-	1
Progressive Disease/Richter Transform.	-	-	-	1	-

(sudden) cardiac deaths:

- CIRS score ≥ 10
- History of hypertension, cardiovascular disease, and/or diabetes

Treatment cessation mitigates treatment-related toxicities
Ho141/VISION trial in R/R CLL

	Ibrutinib continuation group (n=24)			Treatment cessation group (n=48)			Patients not randomly assigned (n=116)			
	Grade 2	Grade 3	Grade 4	Grade 2	Grade 3	Grade 4	Grade 2	Grade 3	Grade 4	Grade 5
Patients with any adverse event, highest grade only	9 (38%)	7 (29%)	2 (8%)	7 (15%)	7 (15%)	0	37 (32%)	40 (34%)	7 (6%)	1 (1%)
Infections	9 (38%)	5 (21%)	0	5 (10%)	2 (4%)	0	31 (27%)	14 (12%)	2 (2%)	1 (1%)
Neutropenia	0	0	0	0	2 (4%)	0	2 (2%)	2 (2%)	2 (2%)	0
Diarrhoea, abdominal discomfort	2 (8%)	0	0	1 (2%)	0	0	7 (6%)	0	0	0
Bleeding	1 (4%)	1 (4%)	0	0	0	0	10 (9%)	0	0	0
Arthralgia, muscle pain	1 (4%)	0	0	1 (2%)	0	0	3 (3%)	0	0	0
Atrial fibrillation	1 (4%)	0	0	0	0	0	3 (3%)	0	0	0
Malignancies, neoplasm	0	1 (4%)	1 (4%)	3 (6%)	1 (2%)	0	4 (3%)	7 (6%)	0	0
Hypertension	2 (8%)	1 (4%)	0	0	0	0	5 (4%)	2 (2%)	0	0
Headache	0	0	0	2 (4%)	0	0	0	0	0	0
Nail changes	0	0	0	0	0	0	1 (1%)	0	0	0
Other	6 (25%)	2 (8%)	1 (4%)	5 (10%)	3 (6%)	0	30 (26%)	19 (16%)	3 (3%)	0

Grade 1 adverse events were not collected.

Table 2: Summary of treatment-related adverse events after cycle 15

Venetoclax + BTKi Based Combinations
Conclusions

- Strong rationale for combination: sensitize to Bcl-2 dependency by inhibition of lymph node migration
- High response rates are sustained after treatment cessation
- MRD is less of a predictive marker for fixed duration venetoclax + BTK-i
- Toxicities similar to single agents
  - Cardiac toxicity of concern in population at-risk

CLL17

Patients with previously untreated CLL

Incl. fit and unfit pts
Incl. pts with del17p/TP53 mut

Stratification according to
fitness, del17p/TP53, IGHV, region

R

1:1:1

294 pts
Ibrutinib monotherapy
Ibrutinib until non-tolerance or PD

294 pts
Venetoclax + Obinutuzumab
6x Ven+Ob, 6x Ven

294 pts
Venetoclax + Ibrutinib
3x Ibrutinib, 12x Ven+Ibrutinib

Total 882 pts

Primary endpoint:
Progression-free survival

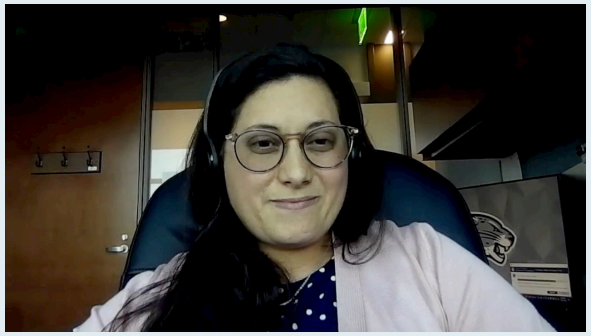
Key secondary endpoints:
Response, minimal residual disease, overall survival

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

Case Presentation: 70-year-old man with multiple musculoskeletal comorbidities and transportation limitations develops symptomatic IGHV-mutated CLL with cytopenias

Dr Syed Zafar (Fort Myers, Florida)

RTP
RESEARCH
TO PRACTICE

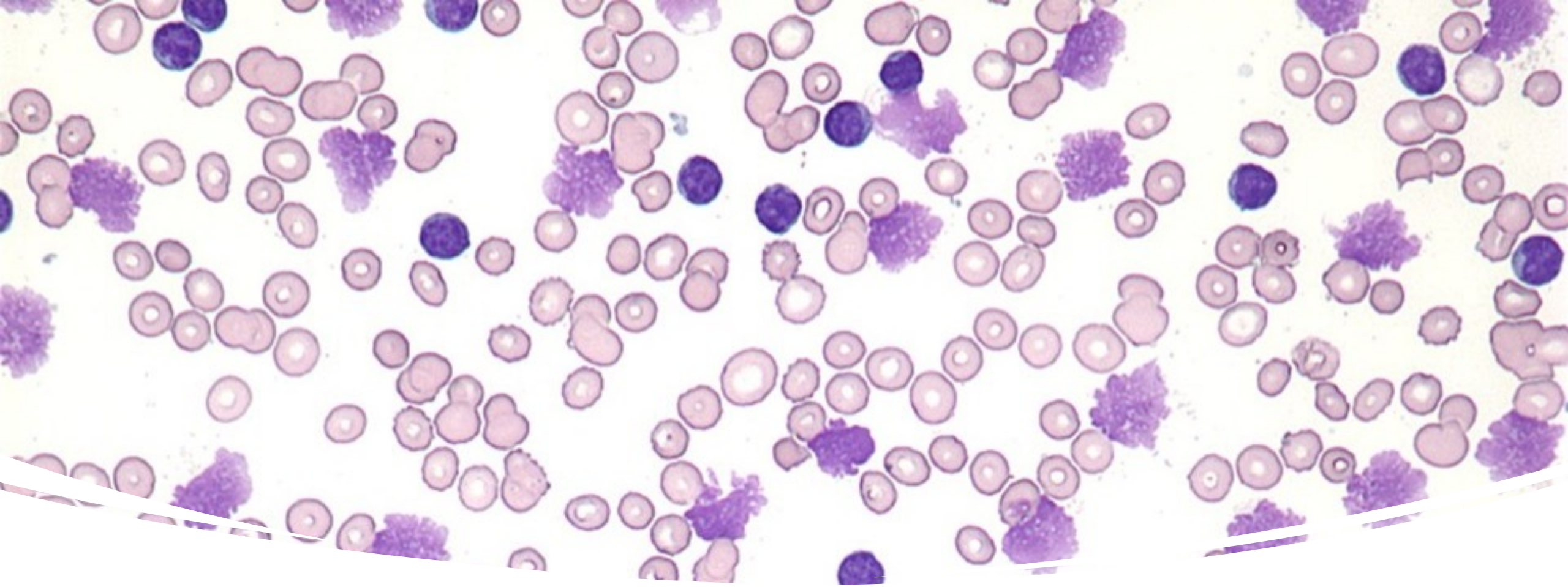


Dr Amany Keruakous
(Augusta, Georgia)

Case Presentation: 55-year-old man with del(17p) CLL and significant lymphadenopathy and B symptoms receives acalabrutinib

Dr Spencer Bachow
(Boca Raton, Florida)

Case Presentation: 72-year-old woman with IGHV-mutated CLL and a complex karyotype



Optimal Management of Adverse Events with BTK and Bcl-2 Inhibitors: Considerations for Special Patient Populations

Matthew S. Davids, MD, MMSc

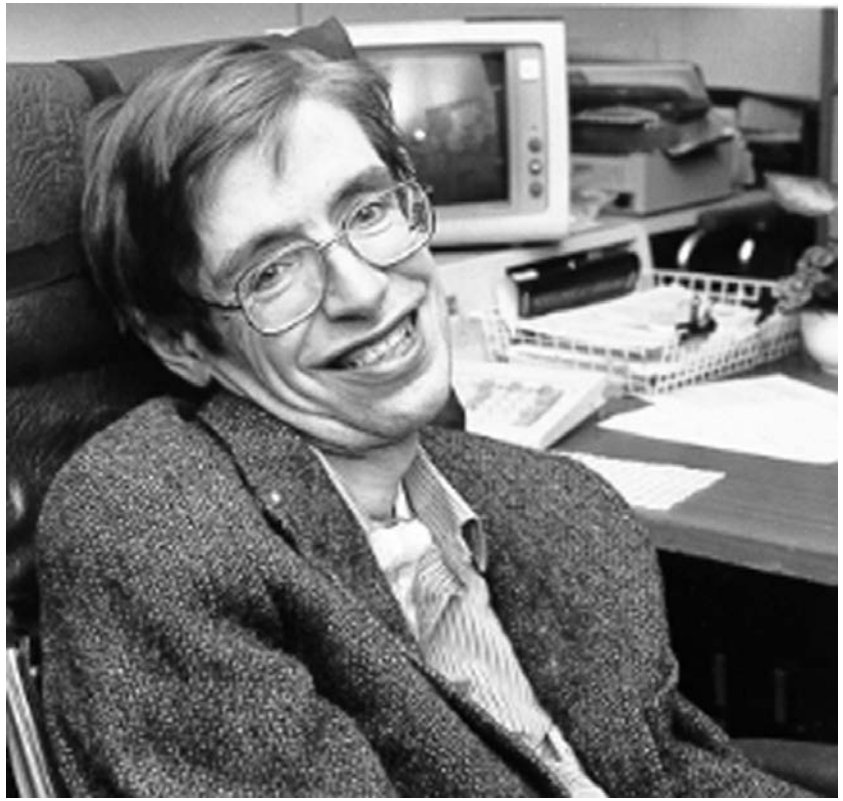
Dana-Farber Cancer Institute | Harvard Medical School

2022 ASH CLL Satellite Symposium | Research To Practice

December 9, 2022

Dana-Farber Cancer Institute

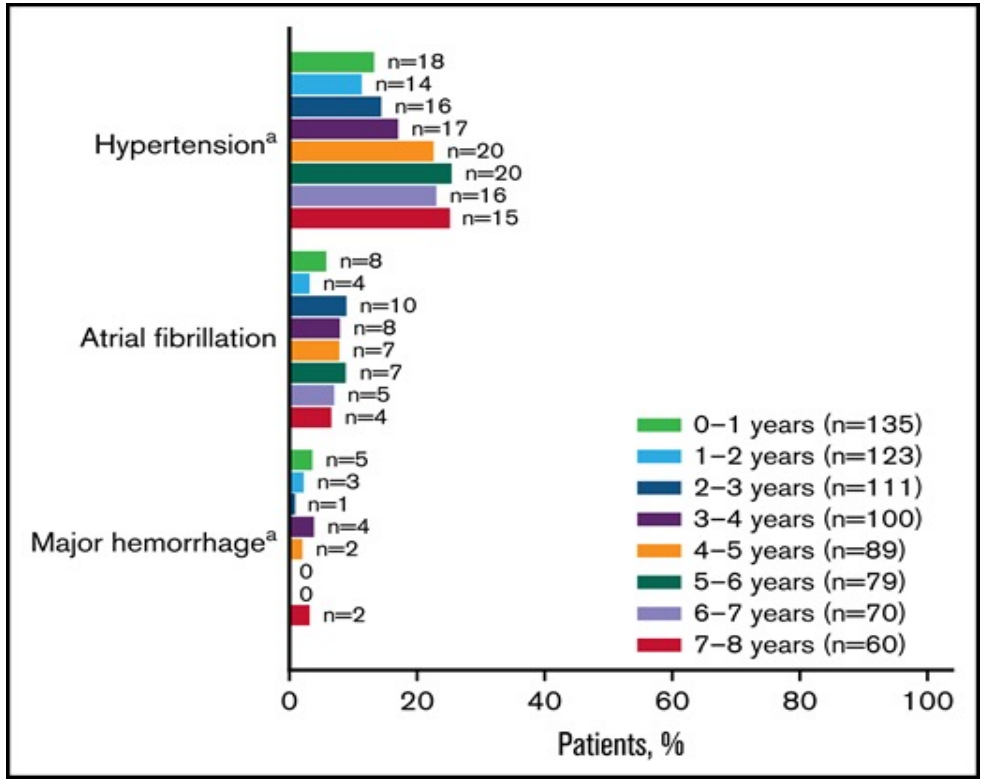
Harvard Medical School

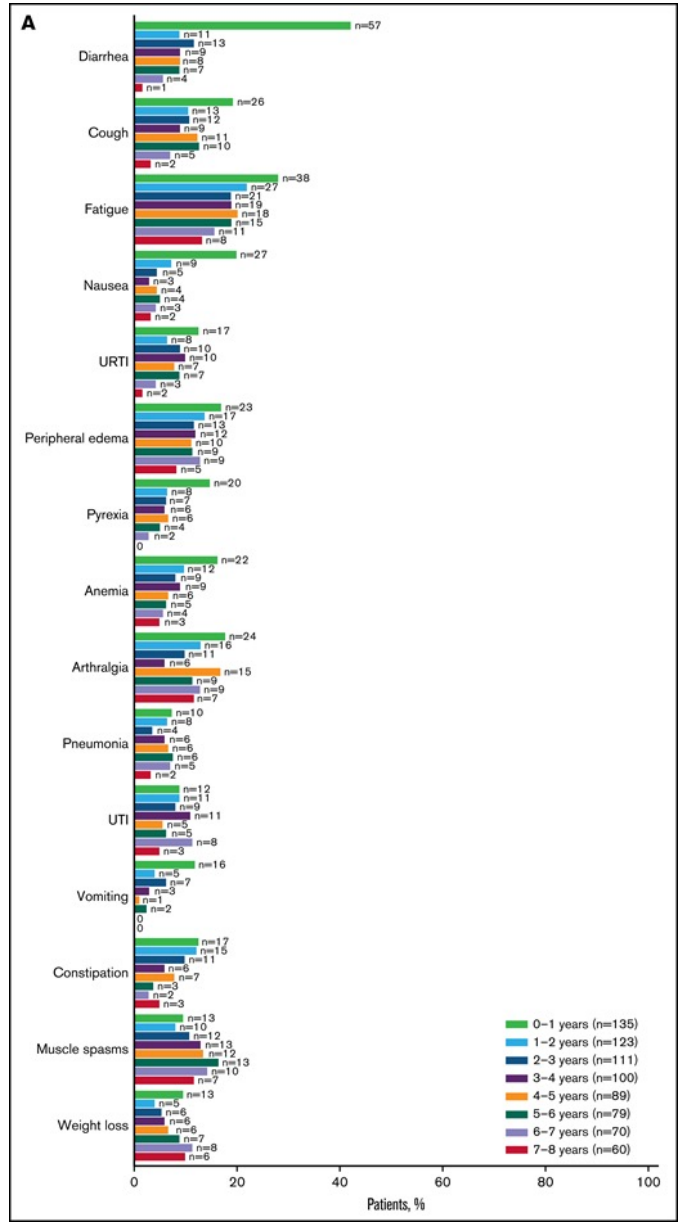


"One of the basic rules of the universe is that nothing is perfect."

Stephen Hawking

RESONATE-2: Discontinuation Rates With Ibrutinib Are High, and Are Due Mostly to AEs





- 42% of patients still on ibrutinib at 8 years
- Most common reason for discontinuation was AEs (24%)

Barr, et al. *Blood Adv.* 2022;6(11):3440-3450

US cooperative group studies suggest Gr 3/4 ibrutinib toxicities may be less in younger patients

Adverse event	IR Arm Alliance n=181	IR Arm E1912 N=352
Median Age Age range	71 yrs 65 – 86	57 yrs 31 - 70
Infection	19%	5%
Atrial fibrillation	6%	3%
Bleeding	4%	1%
Hypertension	34%	7%
Deaths during active treatment +30 days	**7%***	**1%**

*including patients with presumed sudden cardiac death

Adapted from Shanafelt et al., ASH, 2018

Reasons for Ibrutinib Discontinuation Outside of Clinical Trials

Most Common Ibrutinib-related Toxicities as Reasons for Discontinuation	
Relapsed CLL (%)	**Front-line CLL (%)**
Atrial fibrillation (12.3)	Arthralgia (41.6)
Infection (10.7)	Atrial fibrillation (25)
Pneumonitis (9.9)	Rash (16.7)
Bleeding (9)	
Diarrhea (6.6)	

Median Times to Ibrutinib Discontinuation Stratified by Toxicity	
Bleeding	8 months
Diarrhea	7.5 months
Atrial fibrillation	7 months
Infection	6 months
Arthralgia	5 months
Pneumonitis	4.5 months
Rash	3.5 months

Mato, et al. *Blood.* 2016;128 (22): 3222

- Ibrutinib discontinuation due to AEs is common in the real-world setting (41% discontinuation at median of 17 mo.)

Mato et al., *Haematologica*, 2018

CLL12: CLL patients commonly have symptoms and complications

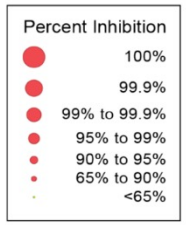
DEUTSCHE STUDIENGRUPPE

	Ibrutinib (n = 158)			Placebo (n = 155)		
	Any grade	Grade 1-2	Grade ≥3	Any grade	Grade 1-2	Grade ≥3
Total no. of events	1593	1426	167	1015*	885	129
Any AE, n (%)	150 (94.9)	70 (44.3)	80 (50.6)	147 (94.8)	80 (51.6)	67 (43.2)
Most common AEs occurring in ≥0% of patients in any treatment group, n (%)†						
Atrial fibrillation	19 (12.0)	9 (5.7)	10 (6.3)	2 (1.3)		2 (1.3)
Diarrhea	50 (31.6)	48 (30.4)	2 (1.3)	28 (18.1)	27 (17.4)	1 (0.6)
Dyspepsia	23 (14.6)	23 (14.6)		4 (2.6)	4 (2.6)	
Nausea	26 (16.5)	26 (16.5)		15 (9.7)	15 (9.7)	
Fatigue	40 (25.3)	39 (24.7)	1 (0.6)	32 (20.6)	31 (20.0)	1 (0.6)
Nasopharyngitis	42 (26.6)	41 (25.9)	1 (0.6)	51 (32.9)	51 (32.9)	
Upper respiratory tract infection	16 (10.1)	15 (9.5)	1 (0.6)	11 (7.1)	11 (7.1)	
Arthralgia	19 (12.0)	18 (11.4)	1 (0.6)	14 (9.0)	13 (8.4)	1 (0.6)
Back pain	16 (10.1)	14 (8.9)	2 (1.3)	17 (11.0)	15 (9.7)	2 (1.3)
Muscle spasms	22 (13.9)			6 (3.9)		
Dizziness	22 (13.9)	20 (12.7)	2 (1.3)	8 (5.2)	8 (5.2)	
Headache	28 (17.7)	28 (17.7)		17 (11.0)	17 (11.0)	
Rash	29 (18.4)	24 (15.2)	5 (3.2)	8 (5.2)	8 (5.2)	
Hematoma	22 (13.9)	20 (12.7)	2 (1.3)	6 (3.9)	6 (3.9)	
Hypertension	16 (10.1)	14 (8.8)	2 (1.3)	7 (4.5)	4 (2.6)	3 (1.9)

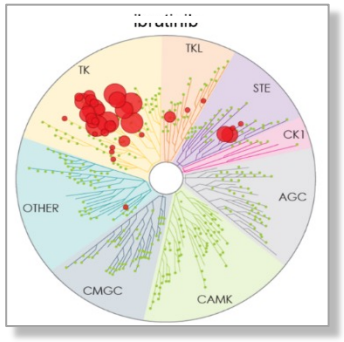
Langerbeins et al., *Blood*, 2022

BTK Inhibitors Exhibit Differences in Kinase Selectivity

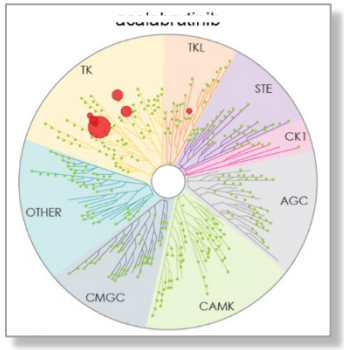
Irreversible



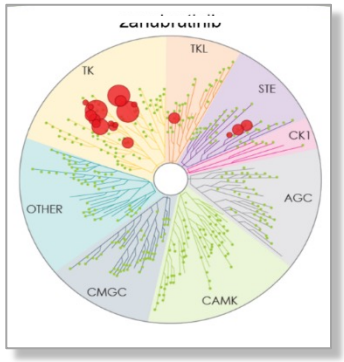
Ibrutinib



Acalabrutinib

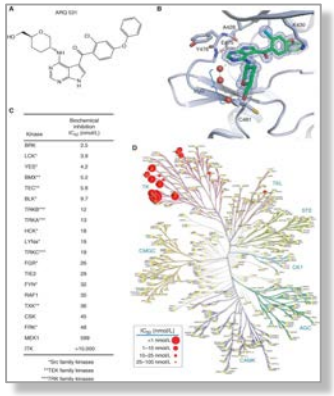


Zanubrutinib

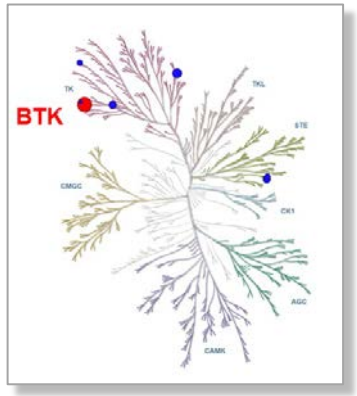


Reversible

Nemtabrutinib



Pirtobrutinib



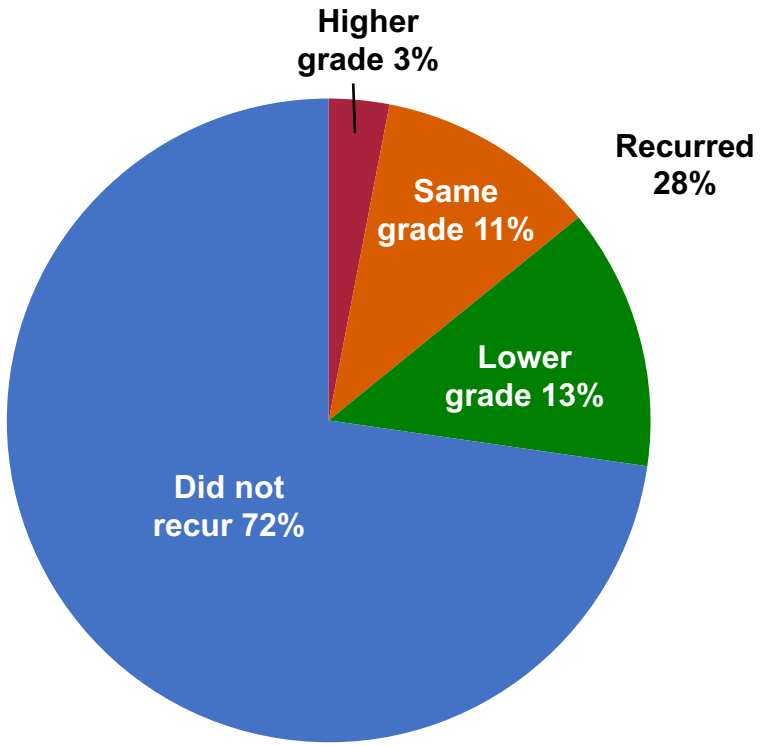
Do differences in binding and selectivity impact treatment efficacy and risk of adverse events?

.

Kaptein A, de Bruin G, Emmelot-van Hoek M, et al. *Blood*. 2018;132(Suppl 1):1871.

Acalabrutinib can be well-tolerated in ibrutinib-intolerant patients

Subset analysis of patients with ibrutinib intolerance enrolled in phase 1/2 ACE-CL-001 (n = 33)



Recurrence of Ibrutinib-Related Adverse Events (n=61)
During Acalabrutinib Treatment

- ~70% of patients remained on acalabrutinib after a median of 19 months
  - 3 patients had discontinued acalabrutinib due to AEs; 4 patients discontinued due to progressive disease

Awan FT, et al. *Blood.* 2019;3(9):1553-1562.

Phase 2 Trial of Acalabrutinib in Ibrutinib-Intolerant Patients

- Standard-dose acalabrutinib in 60 patients with R/R CLL who were ibrutinib-intolerant
  - Ibrutinib was the most recent systemic therapy for all patients
  - All patients met iwCLL criteria for treatment

	Acalabrutinib (N=60)
ORR	73%
CR	5%
mPFS	NR
24-month PFS	72%
mOS	NR
24-month OS	81%

	Acalabrutinib (N=60)
Most frequent AEs	
Diarrhea	53%
Headache	42%
Contusion	40%
Dizziness	33%
Upper RTI	33%
Cough	30%
AEs leading to discontinuation*	17%

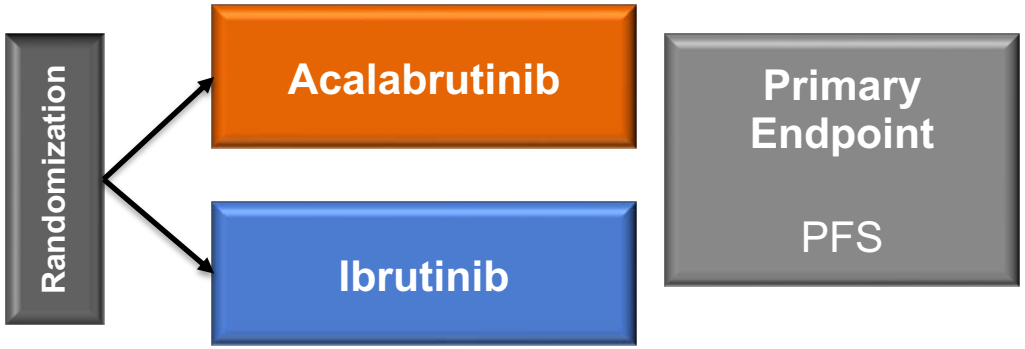
*1 patient discontinued acalabrutinib for the same toxicity (diarrhea) that led to ibrutinib discontinuation

Rogers KA, et al. *Haematologica*. 2021;106(9):2364-2373.

Phase 3 ELEVATE-CLL R/R: Acalabrutinib vs Ibrutinib in R/R High-risk CLL

R/R High-risk CLL
N=533

- ≥ 1 prior therapies for CLL
- ECOG of 0-2; Active disease meeting ≥1 of the IWCLL 2008 criteria for requiring treatment; Must have ≥ 1 high-risk prognostic factors (17p del and/or 11q del by central laboratory)
- No prior exposure to ibrutinib or to a BCR inhibitor or a BCL-2 inhibitor



- **Primary Endpoint:**
  - **Acalabrutinib demonstrated noninferiority to ibrutinib** (PFS)
    - At a median follow-up of 40.9 months (range, 0.0-59.1), the mPFS was 38.4 months for both acalabrutinib and ibrutinib (HR, 1.00; 95% CI, 0.79-1.27).

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

ELEVATE-R/R: Lower Incidence of Any Grade A-fib/Flutter, Hypertension, Bleeding With Acalabrutinib vs Ibrutinib[1]

Events, n (%)	Acalabrutinib (n = 266)		Ibrutinib (n = 263)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Cardiac events	64 (24.1)	23 (8.6)	79 (30.0)	25 (9.5)
A-fib[a]	**25 (9.4)**	13 (4.9)	**42 (16.0)**	10 (3.8)
Ventricular tachyarrhythmias	0	0	1 (0.4)	1 (0.4)
Hypertension[b]	**25 (9.4)**	11 (4.1)	**61 (23.2)**	24 (9.1)
Bleeding events	**101 (38.0)**	10 (3.8)	**135 (51.3)**	12 (4.6)
Major bleeding events[a]	12 (4.5)	10 (3.8)	14 (5.3)	12 (4.6)
Infections	208 (78.2)	82 (30.8)	214 (81.4)	79 (30.0)

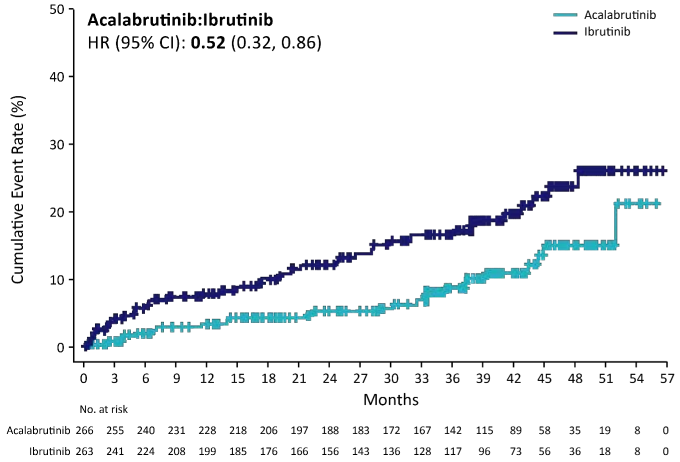
- AEs led to discontinuation in 14.7% of acalabrutinib-treated pts vs 21.3% of ibrutinib-treated pts

[a] Includes A-fib/flutter. [b] Includes hypertension, blood pressure increased, and blood pressure systolic increased.

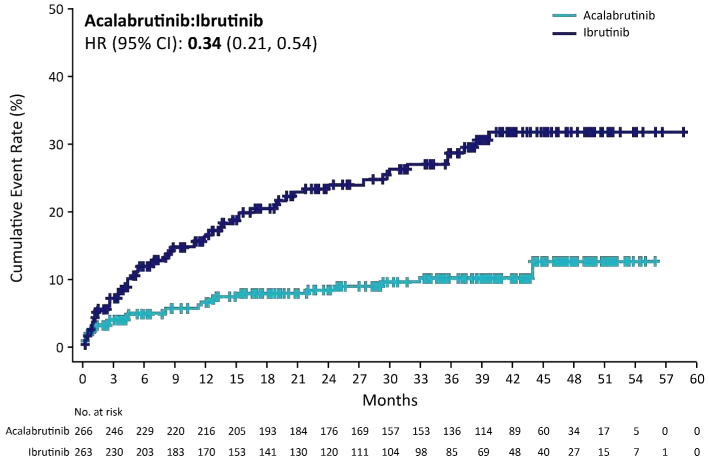
1. Byrd JC et al. *J Clin Oncol*. 2021;39:3441-3452.

Acalabrutinib has an improved AE profile compared to ibrutinib, but toxicities are still common

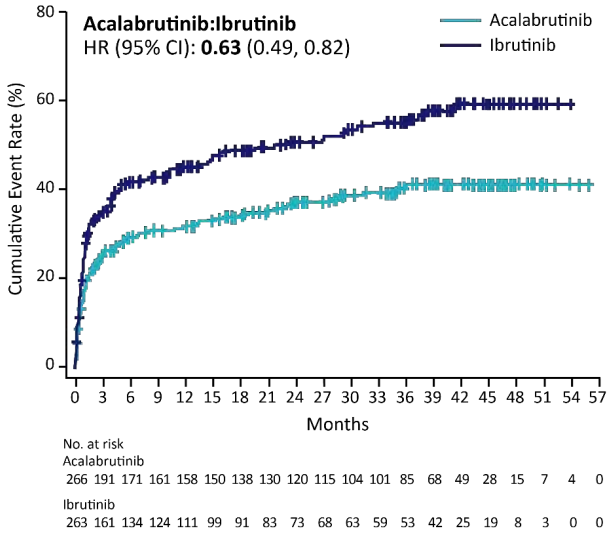
Afib/Flutter



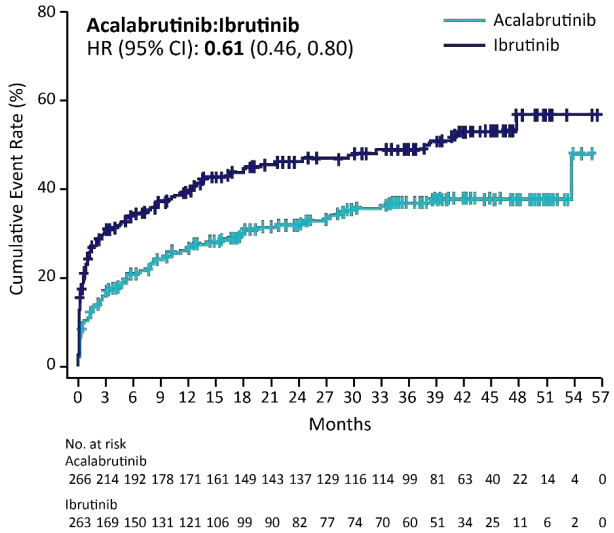
Hypertension



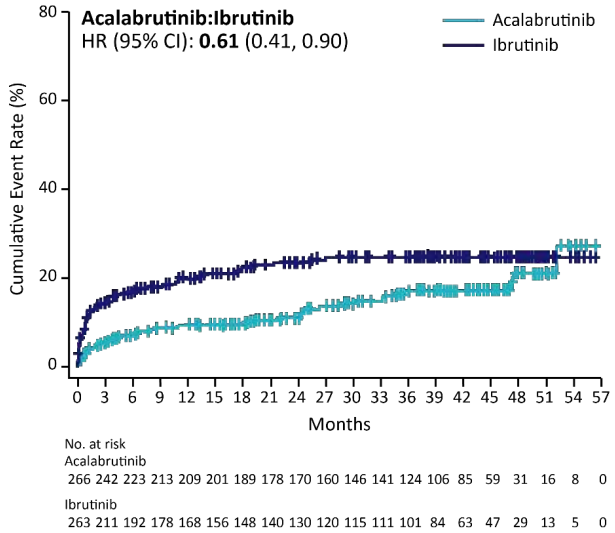
Bleeding Events



Diarrhea



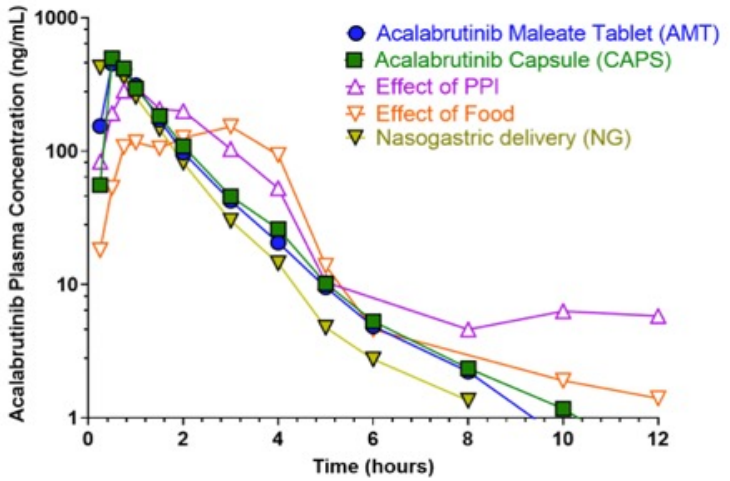
Arthralgia

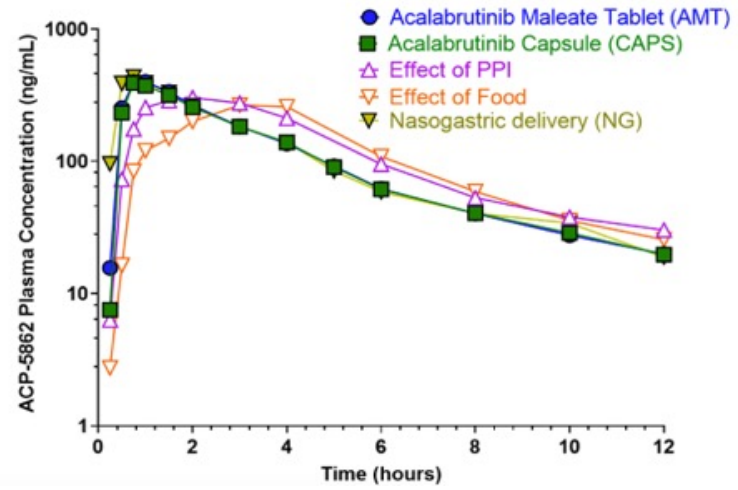


ELEVATE-PLUS: Acalabrutinib Maleate Tablet (AMT) Formulation Allowing Co-administration With PPI and Dosing in Patients Unable to Swallow

- **Three Phase 1, open-label, single-dose, cross-over studies conducted in healthy subjects demonstrated**
  - Similar systemic exposure between AMT and acalabrutinib capsules
  - No clinically relevant differences in acalabrutinib and ACP-5862 exposures was observed following administration of AMT +/- PPI
  - No clinically relevant impact of food on exposures
  - Similar BTK target occupancy
  - No new safety concerns with the AMT

PK Profiles of Acalabrutinib/ACP-5862





ACP-5862, major pharmacologically active metabolite of acalabrutinib.
Sharma S, et al. ASH 2021. Abstract 4365

ALPINE: Phase 3, Randomized Study of Zanubrutinib vs Ibrutinib in Patients With Relapsed/Refractory CLL or SLL

R/R CLL/SLL with ≥ 1 prior treatment
(Planned N=600, Actual N=652)

Key Inclusion Criteria

- R/R to ≥1 prior systemic therapy for CLL/SLL
- Measurable lymphadenopathy by CT or MRI

Key Exclusion Criteria

- Current or past Richter's transformation
- Prior BTK inhibitor therapy
- Treatment with warfarin or other vitamin K antagonists

R
1:1

Arm A
Zanubrutinib 160 mg BID

Arm B
Ibrutinib 420 mg QD

Stratification Factors

- Age
- Geographic region
- Refractory status
- Del(17p)/*TP53* mutation status

Primary endpoint: ORR

BID, twice daily; BTK, Bruton tyrosine kinase CLL, chronic lymphocytic leukemia; CT, computed tomography; MRI, magnetic resonance imaging; QD, once daily; R, randomized; R/R, relapsed/refractory; SLL, small lymphocytic lymphoma.

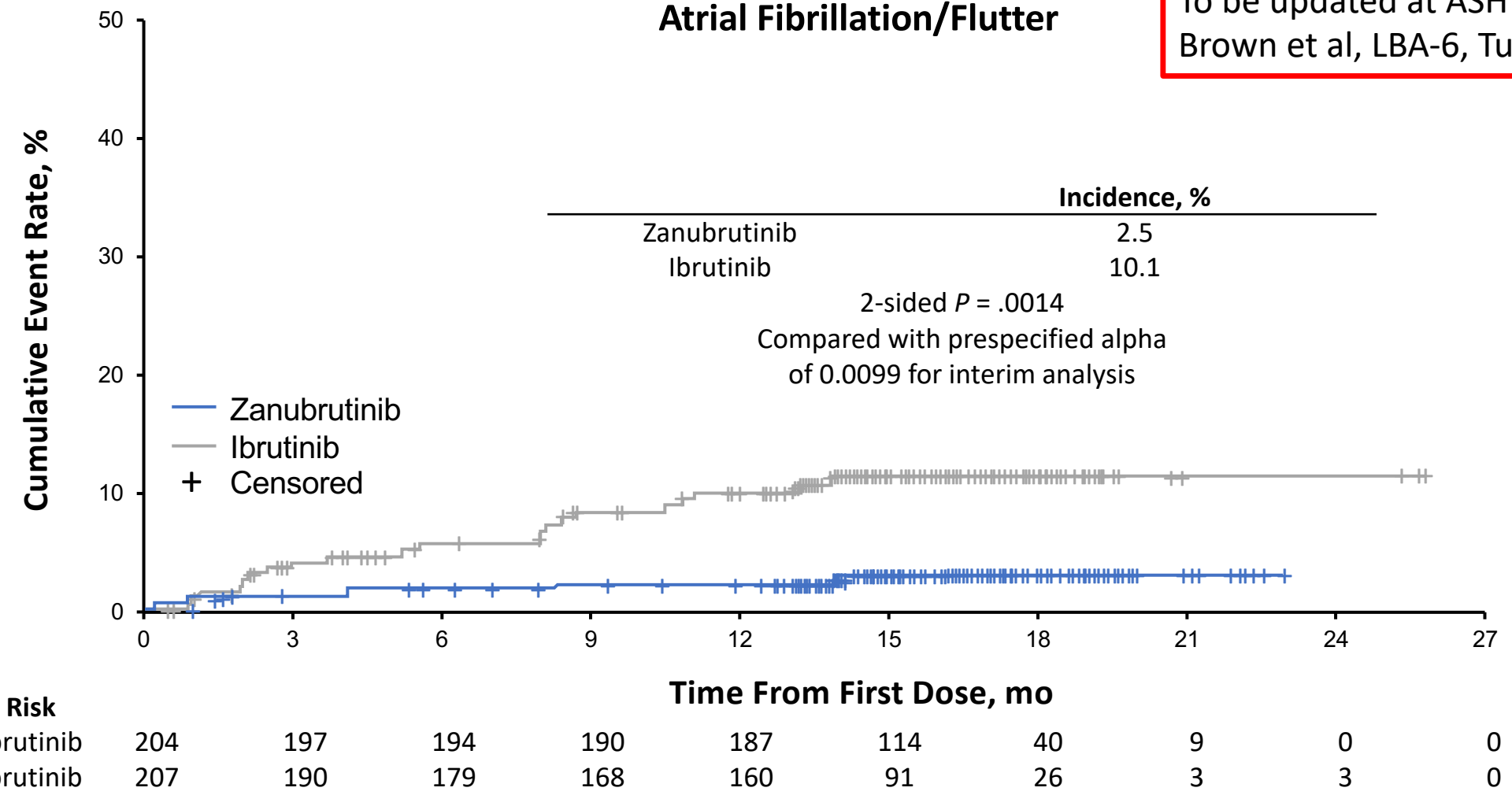
Additional AEs of Special Interest

Safety Analysis Population	Zanubrutinib (n=204), n (%)		Ibrutinib (n=207), n (%)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Cardiac disorders[a]	28 (13.7)	5 (2.5)	52 (25.1)	14 (6.8)
Atrial fibrillation and flutter (key 2º endpoint)	**5 (2.5)**	**2 (1.0)**	**21 (10.1)**	**4 (1.9)**
Hemorrhage	73 (35.8)	6 (2.9)	75 (36.2)	6 (2.9)
Major hemorrhage[b]	6 (2.9)	6 (2.9)	8 (3.9)	6 (2.9)
Hypertension	34 (16.7)	22 (10.8)	34 (16.4)	22 (10.6)
Infections	122 (59.8)	26 (12.7)	131 (63.3)	37 (17.9)
Neutropenia[c]	58 (28.4)	38 (18.6)	45 (21.7)	31 (15.0)
Thrombocytopenia[c]	19 (9.3)	7 (3.4)	26 (12.6)	7 (3.4)
Secondary primary malignancies	17 (8.3)	10 (4.9)	13 (6.3)	4 (1.9)
Skin cancers	7 (3.4)	3 (1.5)	10 (4.8)	2 (1.0)

AE, adverse events. All events are of any grade unless otherwise specified.
[a] Cardiac disorders leading to treatment discontinuation: zanubrutinib 0 patients and ibrutinib 7 (3.4%) patients.
[b] Includes hemorrhages that were serious or grade ≥3 or CNS hemorrhages of all grades.
[c] Pooled terms including neutropenia, neutrophil count decreased, and febrile neutropenia; thrombocytopenia and platelet count decreased.

ALPINE: Safety Analysis with Lower Rates of A-fib/Flutter With Zanubrutinib

To be updated at ASH 2022:
Brown et al, LBA-6, Tues AM Dec. 13

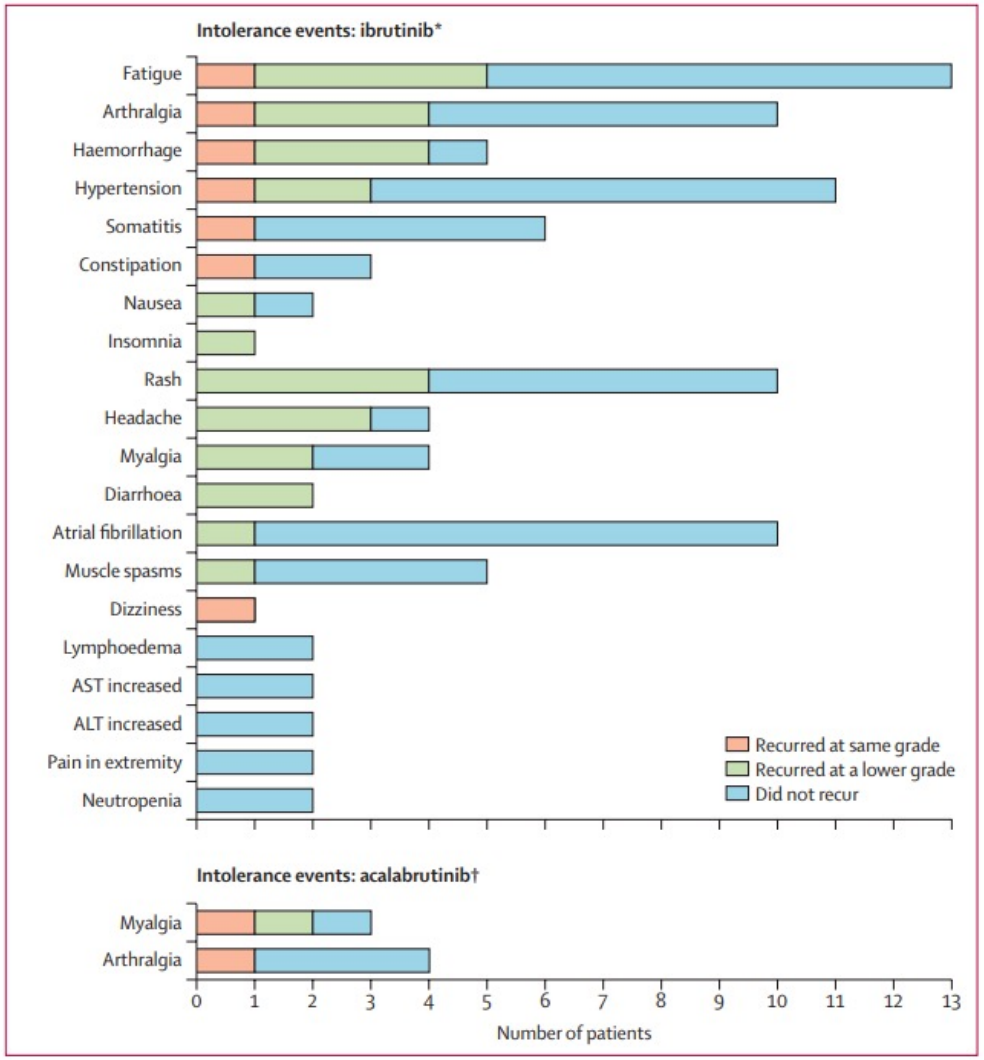


Overall AEs leading to treatment discontinuation: 16 in zanubrutinib group (8%) vs 27 for ibrutinib (13%)

Hillmen P et al. EHA 2021. Abstract LB1900.

A phase 2 study of zanubrutinib in patients with previously treated B-cell malignancies intolerant of previous BTKi

Recurrence and change in severity of ibrutinib and acalabrutinib intolerance events during treatment with zanubrutinib



Shadman et al., *Lancet Haem*, 2022

Tips for BTKi toxicity management[1]

- Avoid warfarin when anticoagulation needed
- Hypertension: proactively manage with antihypertensives
- Monitor for and manage cardiac arrhythmia/a-fib; treat appropriately
- Monitor patients for signs of bleeding

- Headaches commonly occur early in therapy with acalabrutinib and typically resolved in 1-2 months (manage with acetaminophen + caffeine)
- Monitor for neutropenia (particularly with zanubrutinib), use GCSF prn
- Monitor for infections and secondary malignancies
- Hold perioperatively depending on how significant the procedure is

1. NCCN Clinical Practice Guidelines in Oncology. Chronic Lymphocytic Leukemia. Version 2.2022. https://www.nccn.org/professionals/physician_gls/pdf/cll.pdf.

Venetoclax was generally well tolerated in phase 1, although specific toxicities were noted

Adverse events, serious adverse events and toxicity in the 116 study patients

Adverse event*	Any Grade [n (%)]	Grade 3 or 4 [n (%)]
Any	**115** (99)	**96** (83)
Diarrhea	**60** (52)	**2** (2)
Upper respiratory tract infection	**56** (48)	**1** (1)
Nausea	**55** (47)	**2** (2)
Neutropenia	**52** (45)	**48** (41)
Fatigue	**46** (40)	**4** (3)
Cough	**35** (30)	**0**
Pyrexia	**30** (26)	**1** (1)
Anemia	**29** (25)	**14** (12)
Headache	**28** (24)	**1** (1)
Constipation	**24** (21)	**1** (1)
Thrombocytopenia	**21** (18)	**14** (12)
Arthralgia	**21** (18)	**1** (1)
Vomiting	**21** (18)	**2** (2)
Peripheral oedema	**18** (16)	**0**
Pyrexia	**17** (15)	**10** (9)

Serious adverse event†	Any Grade [n (%)]	Grade 3 or 4 [n (%)]
Any	**52** (45)	
Febrile neutropenia	**7** (6)	
Pneumonia	**5** (4)	
Upper respiratory tract infection	**4** (3)	
Immune thrombocytopenia	**3** (3)	
Tumor lysis syndrome	**3** (3)	
Diarrhea	**2** (2)	
Fluid overload	**2** (2)	
Hyperglycaemia	**2** (2)	
Prostate cancer	**2** (2)	
Pyrexia	**2** (2)	

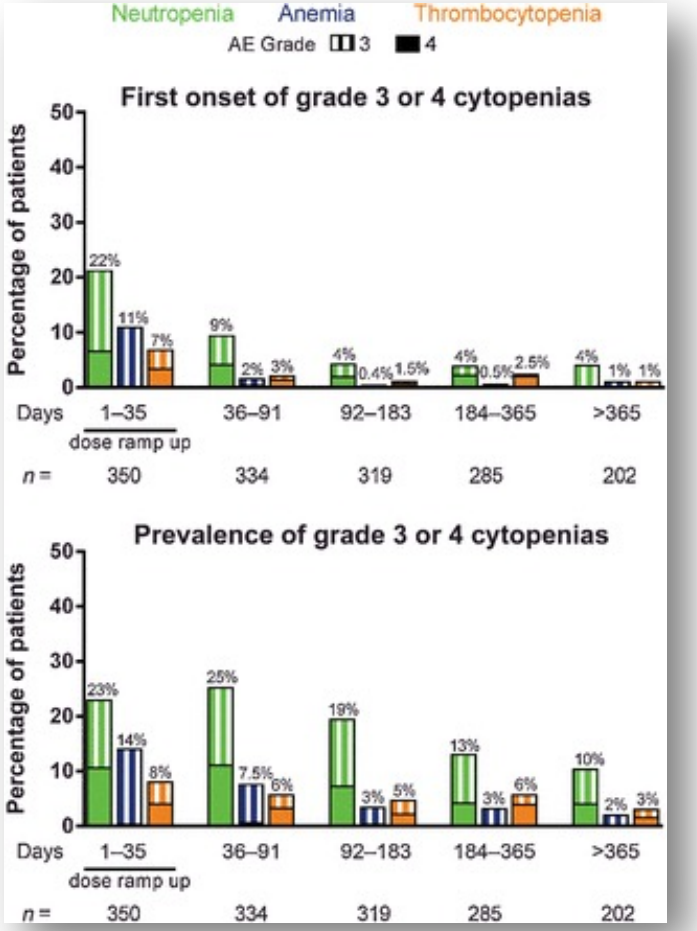
Toxicity	Any Grade (%)	Grade 3 or 4 (%)
Neutropenia	**45**	**41**
GI	**52**	**2**
TLS	**3**	**3**

*Listed are adverse events that were reported in at least 15% patients. Preexisting grade 1/2 abnormalities not reported, unless grade increased during the study.
†Listed are serious adverse events that were reported in at least two patients. Excluded are serious adverse events that were related to disease progression in two patients.

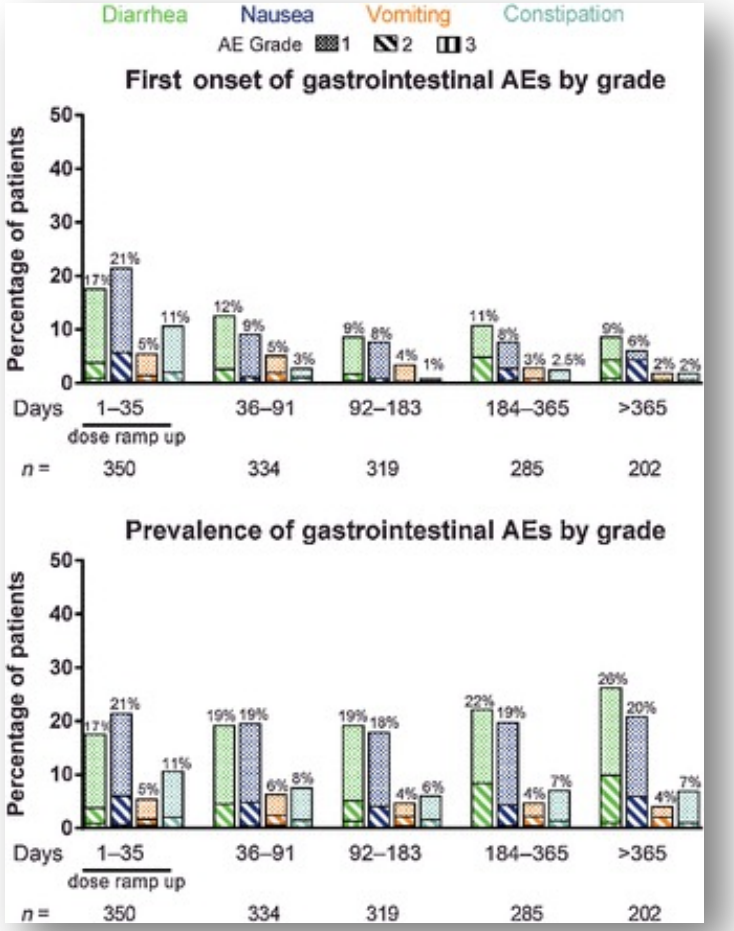
Roberts AW, Davids MS, et al. *N Engl J Med* 2016;374:311–322.

Venetoclax risks tend to decrease over time

Cytopenias



GI Toxicities



- **2/166 (1.4%) of patients treated with current dosing algorithm had biochemical laboratory changes in TLS parameters, but none had clinical TLS**

Davids MS et al., *Clin Cancer Res*, 2018

Phase 3 CLL14 study: Safety profile of ven + obin was favorable, especially after completion of therapy

Most frequent ≥ grade 3 adverse events	Venetoclax-obinutuzumab (N=212)	
	During Treatment	After Treatment
Neutropenia	51.9%	4.0%
Thrombocytopenia	13.7%	0.5%
Anemia	7.5%	1.5%
Febrile neutropenia	4.2%	1.0%
Infusion-related reaction	9.0%	0.0%
Tumor lysis syndrome	1.4%	0.0%
Neoplasms	1.4%	6.4%

Al-Sawaf et al, EHA 2020

Tips for venetoclax toxicity management

- For neutropenia (e.g. ANC <1,000), it is helpful to give growth factor support (pegfilgrastim when available) and continue venetoclax
  - Individualized frequency based on patient response
- For diarrhea, infectious etiologies should be ruled out and then anti-diarrheals can be used while continuing venetoclax
- For nausea: adjust dose timing and use antiemetics
- Dose interruption and dose reduction can be used for persistent toxicities despite the above measures
- Does **not** need to be held perioperatively

Davids MS. *Blood* 2017;130:1081–1088

CAPTIVATE-FD Cohort: Ibrut + Ven well-tolerated in a young, fit population

Median Age = 60

Treatment-Emergent 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

GLOW: Ibrut + Ven had more toxicities in an older, more comorbid population

Median Age = 71

Treatment exposure — mo, median (range)	**13.8 (0.7–19.5)**	
Adverse events — n (%)	Grade 3/4	Grade 5
Patients with ≥1 adverse events	73 (68.9)	7 (6.6)
Neutropenia	37 (34.9)	0
Infections and infestations	16 (15.1)	2 (1.9)
Diarrhea	11 (10.4)	0
Hypertension	8 (7.5)	0
Atrial fibrillation	7 (6.6)	0
Thrombocytopenia	6 (5.7)	0
Hyponatremia	6 (5.7)	0
Cardiac failure	3 (2.8)	1 (0.9)
Sinus node dysfunction	1 (0.9)	1 (0.9)
Cholestasis	1 (0.9)	0
Sudden death	0	2 (1.9)
Ischemic stroke	0	1 (0.9)
Malignant neoplasm	0	1 (0.9)
Cardiac arrest	0	1 (0.9)
Tumor lysis syndrome	0	0

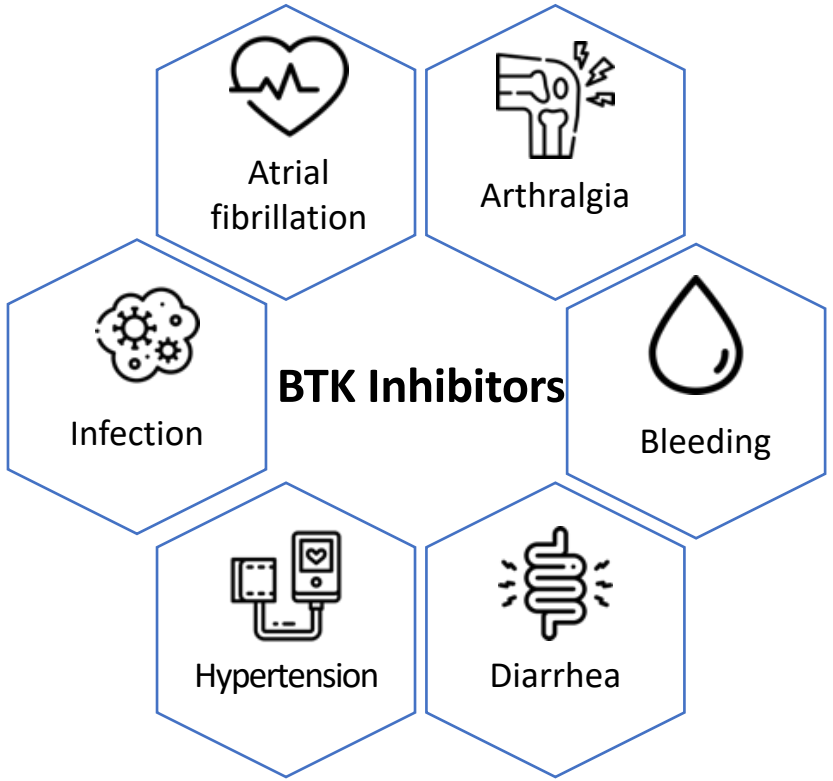
Kater et al., *NEJM Evid*, 2022

General tips for AE Management in CLL

- In the setting of active infection it is generally best to hold drug at least until seeing signs of clinical improvement (possible exception of mild COVID-19)
- For most toxicities requiring drug hold, it is preferable to either re-challenge with full dose or to start back at dose reduction but then get back to full dose
- I am more hesitant to hold drug soon after starting a novel agent or in a patient who is progressing on a novel agent
- I am less concerned about stopping drug in patients who have been on novel agents for at least a few months and are in a good clinical response
- It is generally safe to give growth factor support concomitantly with novel agents
- Patients who have to permanently discontinue a novel agent due to toxicity do not necessarily need to immediately start on a new therapy

Summary of AEs with Targeted Agents in CLL

AEs With BTKi



Additional important AEs: dermatologic changes, fatigue, cytopenias, and ventricular arrhythmias

AEs With Venetoclax

- **TLS**
- **GI events**
- **Infections**
- **Myelosuppression**

Module 4: Selection and Sequencing of Available Therapies for Relapsed/Refractory Disease — Dr Thompson

RTP
RESEARCH
TO PRACTICE

Case Presentation: 74-year-old man with relapsed del(17p) CLL s/p ibrutinib with multiple chronic low-grade toxicities

Dr Tina Bhatnagar (Wheeling, West Virginia)

RTP
RESEARCH
TO PRACTICE

Selection and Sequencing of Available Therapies for Relapsed/Refractory (R/R) CLL

Dr. Philip Thompson

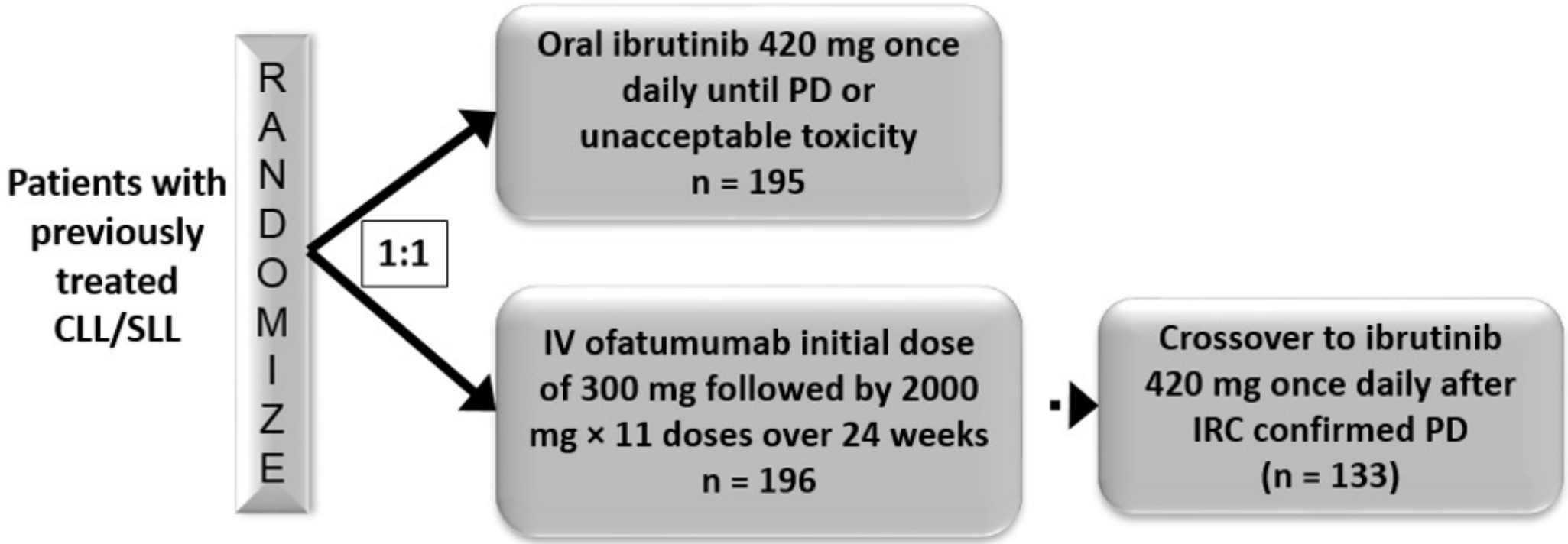
Associate Professor

The University of Texas M.D. Anderson Cancer Center

Topics

- Long-term follow-up data from phase III studies in R/R CLL.
- How I think about sequencing therapies.
- Role for PI3K inhibitors in CLL.
- Novel approaches to CLL and RS.

RESONATE Phase III Study Design

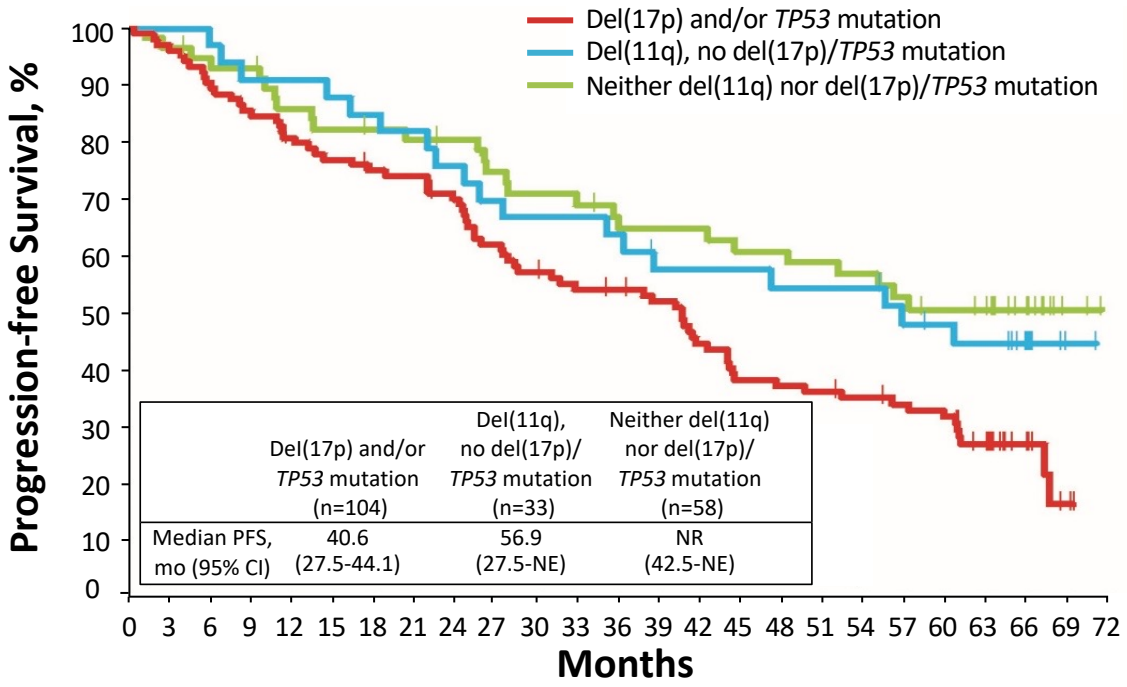


- Primary endpoint: PFS
- Median # therapies in ibrutinib arm = 3.
- In ibrutinib arm, 32% had del(17p) and 32% del(11q).

Byrd J et al. N Engl J Med. 2014;371(3):213-23

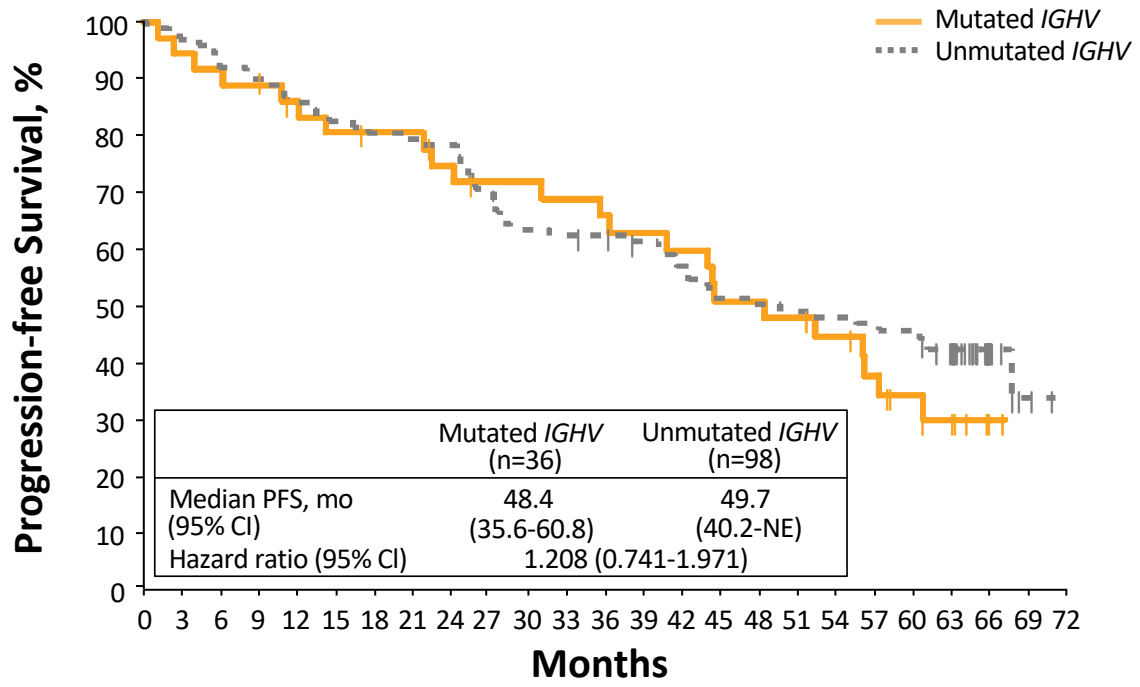
RESONATE: Long-term PFS Benefit With Ibrutinib Across Subgroups by Del(17p)/*TP53* Mutation, Del(11q), and *IGHV* Mutation Status

By Del(17p)/*TP53* Mutation and Del(11q)[a]



	Del(17p) and/or *TP53* mutation (n=104)	Del(11q), no del(17p)/ *TP53* mutation (n=33)	Neither del(11q) nor del(17p)/ *TP53* mutation (n=58)
Median PFS, mo (95% CI)	40.6 (27.5-44.1)	56.9 (27.5-NE)	NR (42.5-NE)

By *IGHV* Mutation



	Mutated *IGHV* (n=36)	Unmutated *IGHV* (n=98)
Median PFS, mo (95% CI)	48.4 (35.6-60.8)	49.7 (40.2-NE)
Hazard ratio (95% CI)	1.208 (0.741-1.971)	

- In ibrutinib-treated patients, median PFS was shorter for patients with del(17p) and/or *TP53* mutation (41 months) than in patients with del(11q) (57 months) or those without any of these abnormalities (not reached)
- PFS with ibrutinib was similar irrespective of *IGHV* mutation status

NE, not estimable; NR, not reached.

[a]Genomic abnormalities by fluorescence in situ hybridization cytogenetics were categorized according to Döhner hierarchical classification.

Blood 2019, RESONATE PCYC-1112; Mulligan et al.

ELEVATE-RR:
Phase 3 Randomized Non-inferiority Open-Label Trial

Patients (N=533)

Key Inclusion Criteria

- Adults with previously treated CLL requiring therapy (iwCLL 2008 criteria[1])
- Presence of del(17p) or del(11q)[a]
- ECOG PS of ≤2

Stratification

- del(17p) status (yes or no)
- ECOG PS (2 vs ≤1)
- No. prior therapies (1–3 vs ≥4)

RANDOMIZE 1:1

Acalabrutinib[b]
100 mg PO BID

Ibrutinib[b]
420 mg PO QD

Primary endpoint

- Non-inferiority on IRC-assessed PFS[c]

Secondary endpoints (hierarchical order):

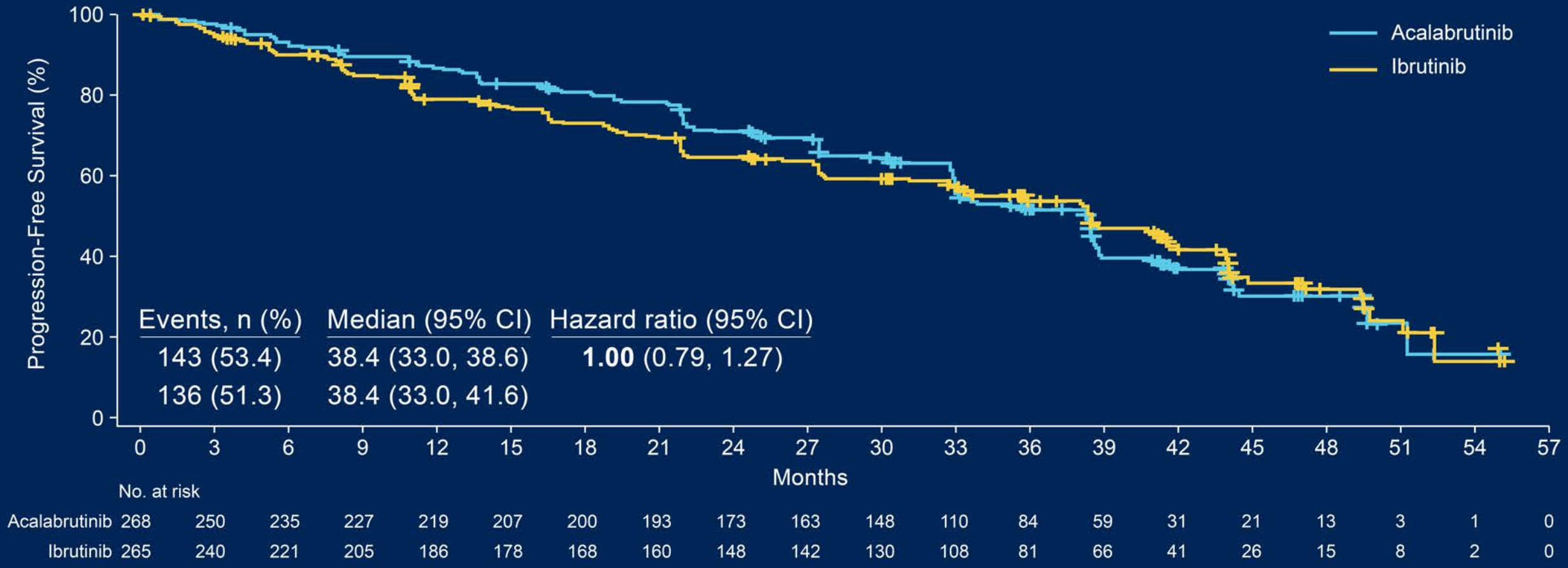
- Incidence of any grade atrial fibrillation/flutter
- Incidence of grade ≥3 infection
- Incidence of Richter transformation
- Overall survival

Key exclusion criteria: Significant CV disease; concomitant treatment with warfarin or equivalent vitamin K antagonist; prior treatment with ibrutinib, a BCR inhibitor (eg, BTK , PI3K, or Syk inhibitors), or a BCL-2 inhibitor (eg, venetoclax)

NCT02477696 (ACE-CL-006).
[a]By central laboratory testing; [b]continued until disease progression or unacceptable toxicity; [c]conducted after enrollment completion and accrual of ~250 IRC-assessed PFS events.
Afib/flutter, atrial fibrillation/flutter; BCL-2, B-cell leukemia/lymphoma-2; BCR, B-cell receptor; BID, twice daily; BTK, Bruton tyrosine kinase; CLL, chronic lymphocytic leukemia; CV, cardiovascular; ECOG PS, Eastern Cooperative Oncology Group performance status; IRC, independent review committee; iwCLL, International Workshop on CLL; PFS, progression-free survival; PI3K, phosphatidylinositol 3-kinase; PO, orally; QD, once daily.

1. Hallek M, et al. *Blood*. 2008;111:5446-56.

Primary Endpoint: Non-inferiority Met on IRC-Assessed PFS



Median follow-up: 40.9 months (range, 0.0–59.1).

CI, confidence interval; IRC, independent review committee; PFS, progression-free survival.

Events of Clinical Interest

Events, n (%)	Any grade		Grade ≥3	
	Acalabrutinib (n=266)	Ibrutinib (n=263)	Acalabrutinib (n=266)	Ibrutinib (n=263)
Cardiac events	64 (24.1)	79 (30.0)	23 (8.6)	25 (9.5)
Atrial fibrillation[a]*	25 (9.4)	**42 (16.0)**	13 (4.9)	10 (3.8)
Ventricular arrhythmias[b]	0	3 (1.1)	0	1 (0.4)
Bleeding events*	101 (38.0)	**135 (51.3)**	10 (3.8)	12 (4.6)
Major bleeding events[c]	12 (4.5)	14 (5.3)	10 (3.8)	12 (4.6)
Hypertension[d]*	25 (9.4)	**61 (23.2)**	11 (4.1)	**24 (9.1)**
Infections[e]	208 (78.2)	214 (81.4)	82 (30.8)	79 (30.0)
ILD/pneumonitis*	7 (2.6)	**17 (6.5)**	1 (0.4)	2 (0.8)
SPMs excluding NMSC	24 (9.0)	20 (7.6)	16 (6.0)	14 (5.3)

Higher incidence indicated in **bold yellow** for terms with statistical differences.
*Two-sided P-value for event comparisons <0.05 without multiplicity adjustment.
[a]Includes events with preferred terms atrial fibrillation and atrial flutter.
[b]Includes events with preferred terms torsade de pointes, ventricular arrhythmia, ventricular extrasystoles, ventricular fibrillation, ventricular flutter, ventricular tachyarrhythmia, and ventricular tachycardia.
[c]Defined as any hemorrhagic event that was serious, grade ≥3 in severity, or a central nervous system hemorrhage (any severity grade).
[d]Included events with the preferred terms of hypertension, blood pressure increased, and blood pressure systolic increased.
[e]Most common grade ≥3 infections were pneumonia (acalabrutinib, 10.5%; ibrutinib, 8.7%), sepsis (1.5% vs 2.7%, respectively), and UTI (1.1% vs 2.3%).
ILD, interstitial lung disease; NMSC, nonmelanoma skin cancer; SPMs, second primary malignancies; UTI, urinary tract infection.

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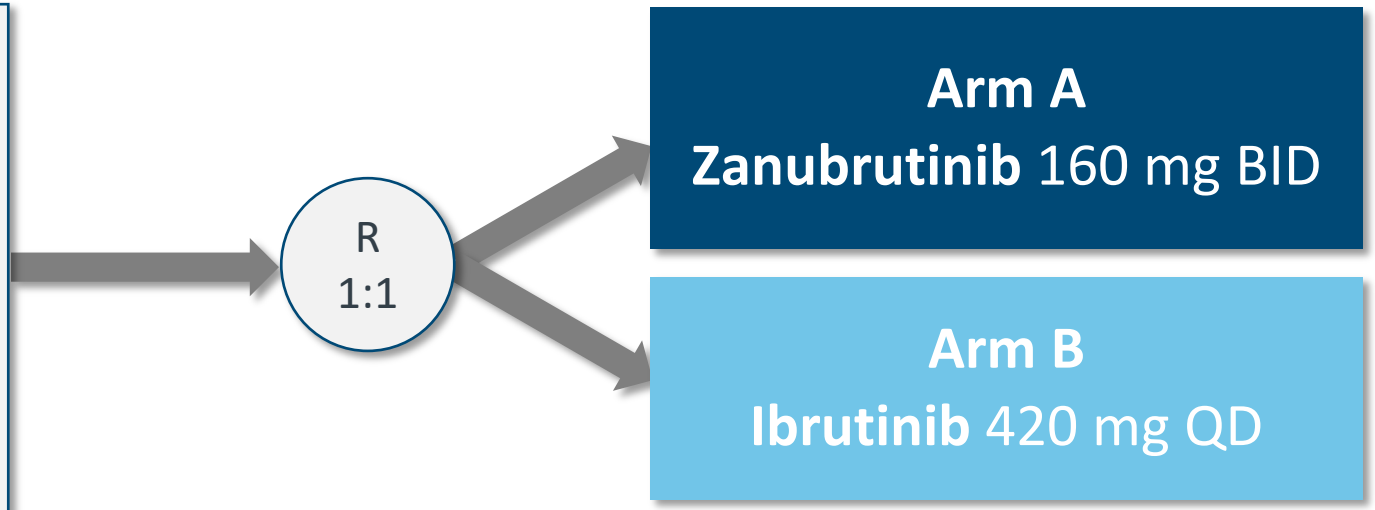
R/R CLL/SLL with ≥ 1 prior treatment
(Planned N=600, Actual N=652)

Key Inclusion Criteria

- R/R to ≥1 prior systemic therapy for CLL/SLL
- Measurable lymphadenopathy by CT or MRI

Key Exclusion Criteria

- Current or past Richter's transformation
- Prior BTK inhibitor therapy
- Treatment with warfarin or other vitamin K antagonists



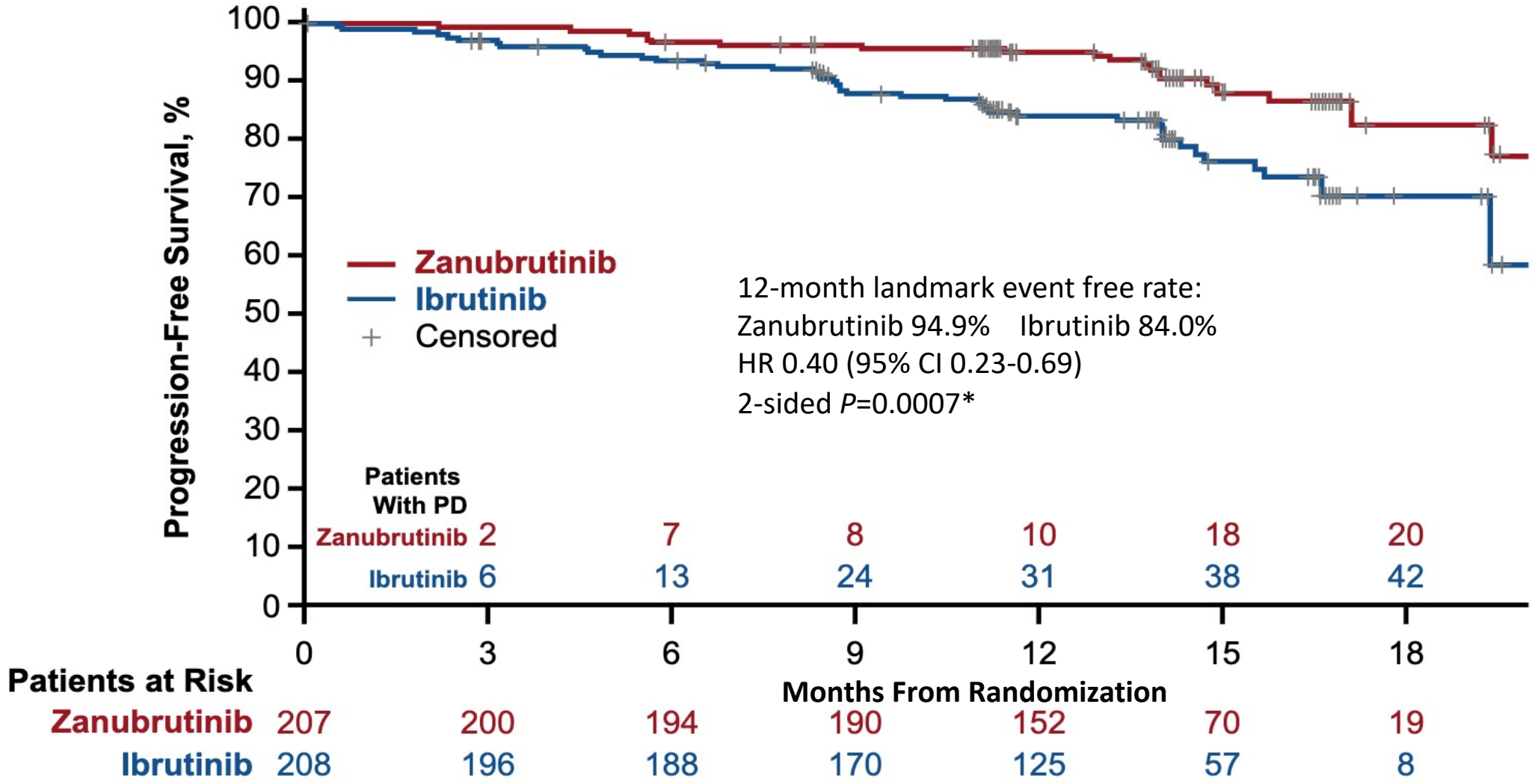
Stratification Factors

- Age
- Geographic region
- Refractory status
- Del(17p)/*TP53* mutation status

Hillmen et al, EHA 2021

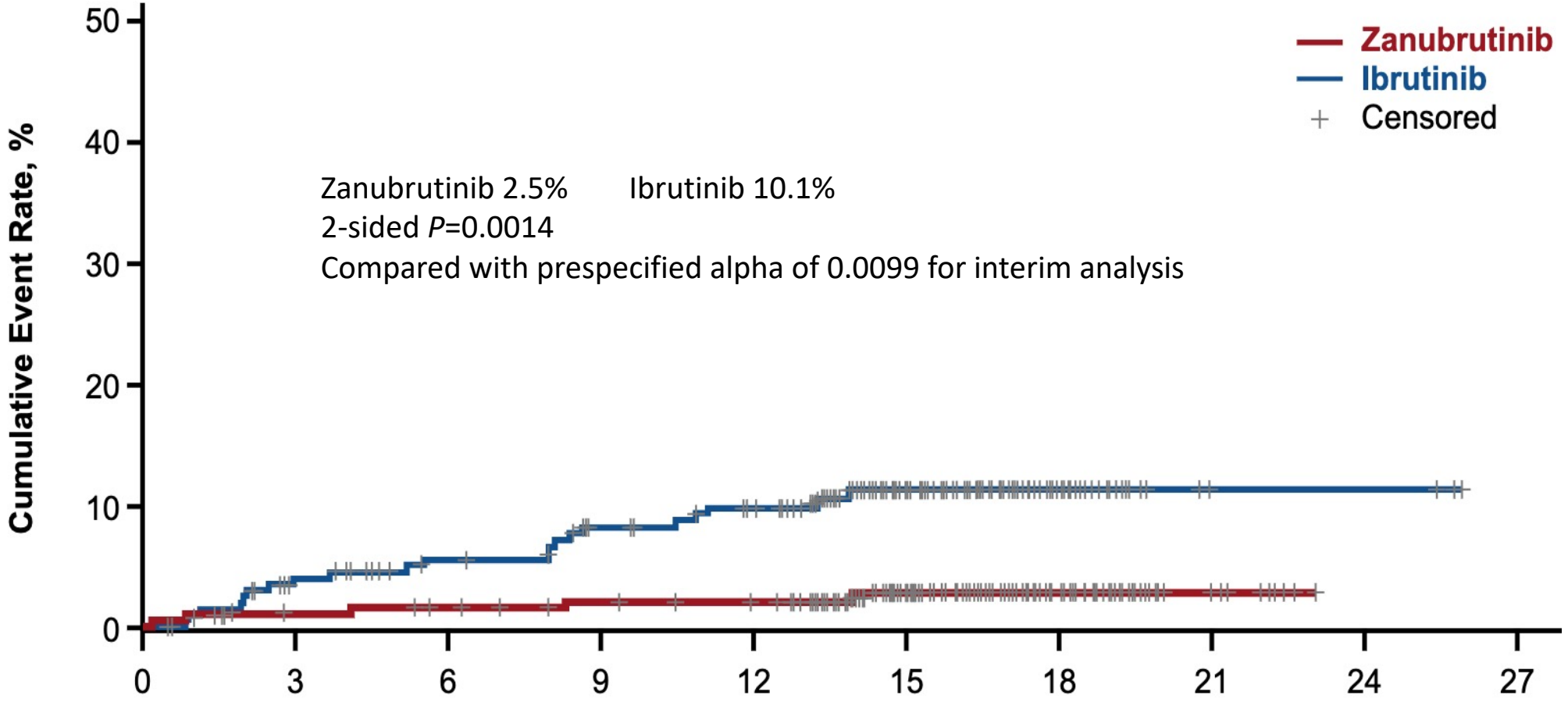
BID, twice daily; BTK, Bruton tyrosine kinase' CLL, chronic lymphocytic leukemia; CT, computed tomography; MRI, magnetic resonance imaging; QD, once daily; R, randomized; R/R, relapsed/refractory; SLL, small lymphocytic lymphoma.

PFS by Investigator Assessment



*Not a prespecified analysis; formal analysis of PFS will be based on all patients when the target number of events are reached.
Median PFS follow-up was 14.0 months for both zanubrutinib and ibrutinib arms by reverse KM method.
PFS, progression-free survival.

Atrial Fibrillation/Flutter



Patients at Risk										
Zanubrutinib	204	197	194	190	187	114	40	9	0	0
Ibrutinib	207	190	179	168	160	91	26	3	3	0

2nd Generation BTKi after ibrutinib intolerance

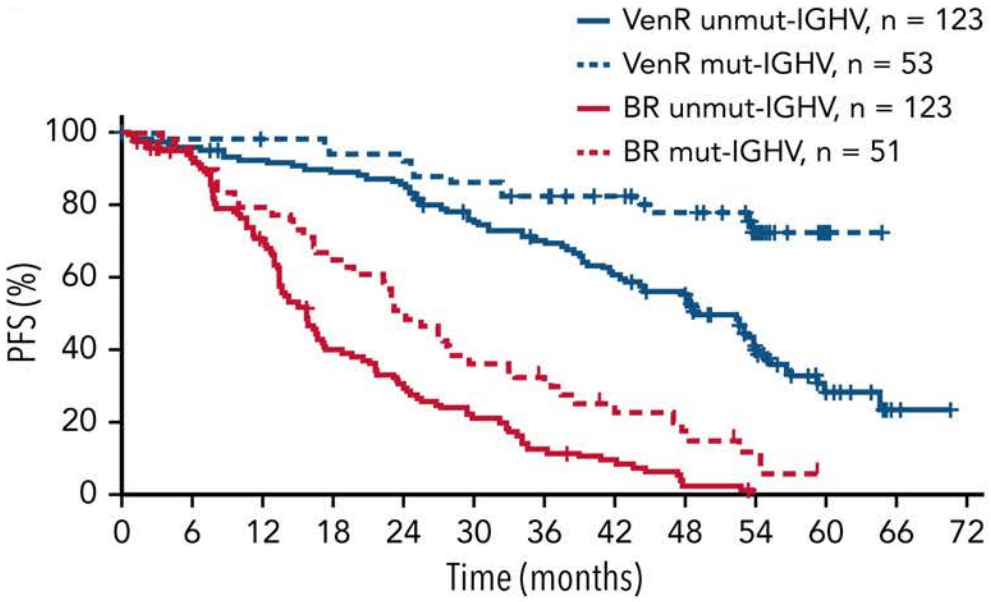
- 83% of patients treated with acalabrutinib after ibrutinib intolerance tolerate acalabrutinib, with 2y PFS of 72%.[1]
- 60% of patients treated with zanubrutinib after ibrutinib intolerance did not have recurrence of the intolerance event and recurrent AEs were of similar or lesser severity, leading to no discontinuations for intolerance.[2]

[1]Rogers et al. *Haematologica* 2021 Vol. 106 No. 9 (2021): September, 2021;
[2]Shadman et al. *Lancet Haematology* 2022

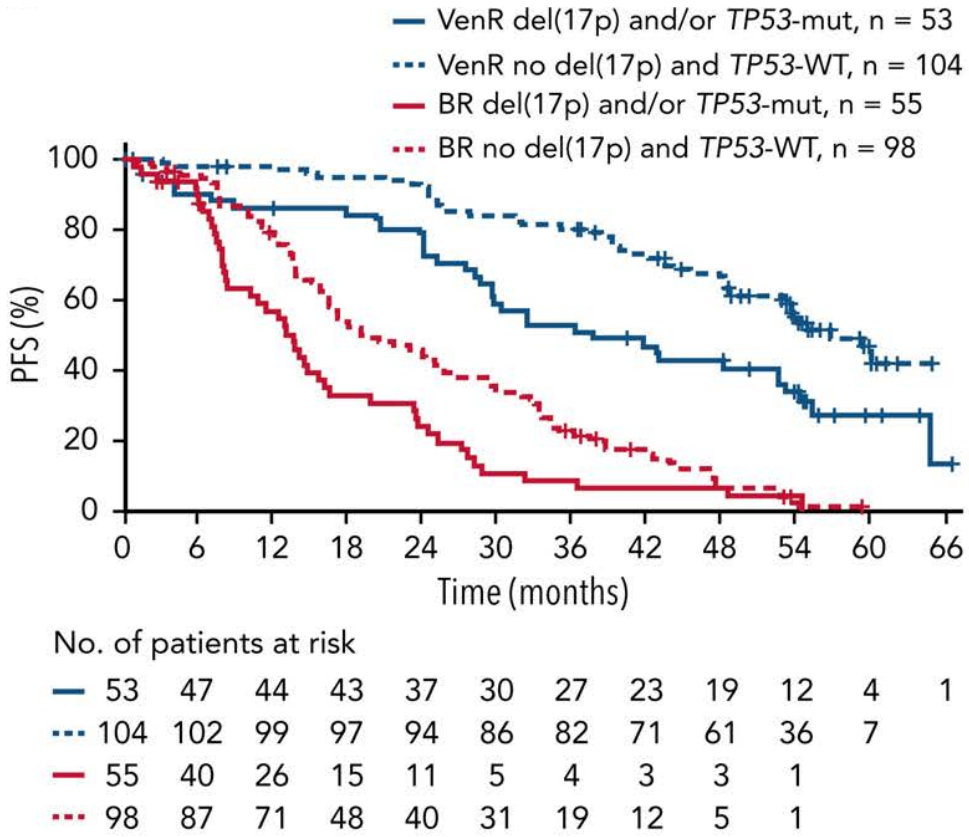
Summary

- BTK inhibitors are efficacious in R/R CLL.
- Overcome negative prognostic impact of del(11q) and unmutated *IGHV.* Del(17p) remains a high risk feature.
- 2nd generation covalent BTK inhibitors (acalabrutinib and zanubrutinib) have at least equivalent efficacy with more favorable AE profile.

MURANO: Enduring undetectable MRD and updated outcomes in relapsed/refractory CLL after fixed-duration venetoclax-rituximab



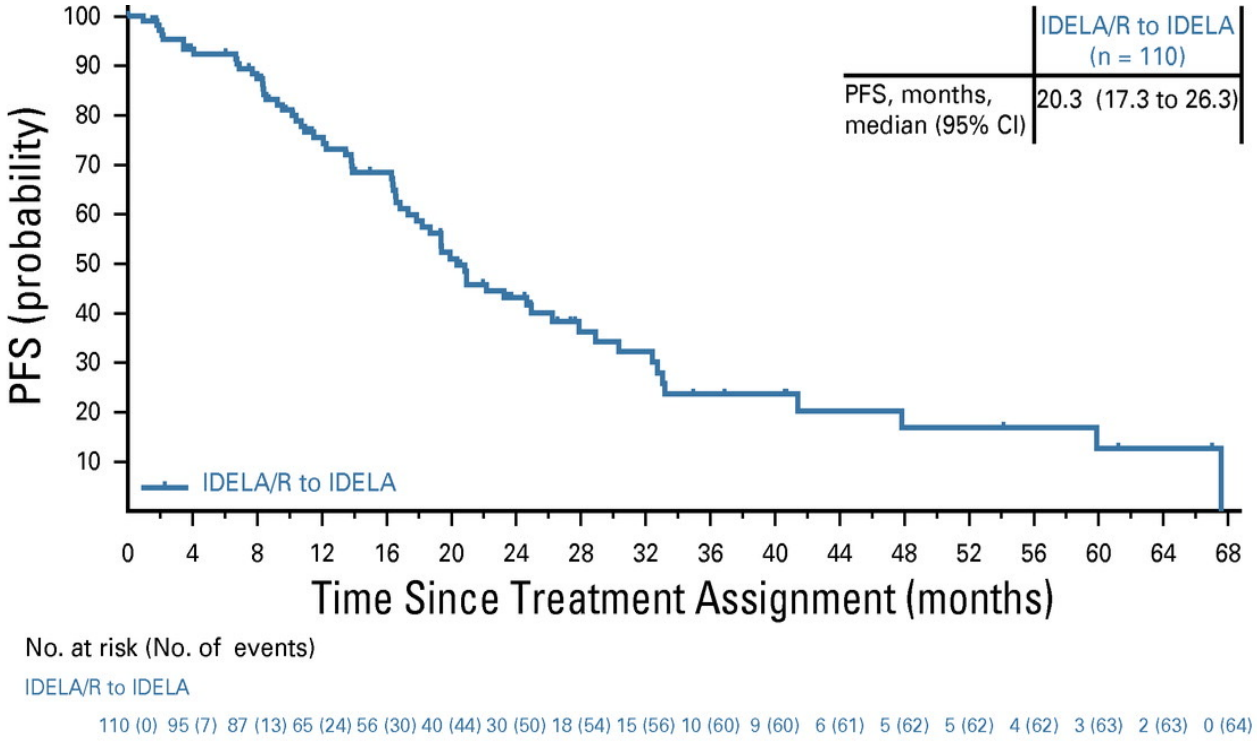
Category		Median PFS, months (95% CI)	HR (95% CI); *P* value†	5-year PFS, % (95% CI)
VenR	unmut-IGHV	52.2 (44.1, 53.8)	2.96 (1.64, 5.34);	28.7 (18.5, 38.9)
	mut-IGHV	NE	.0002	72.7 (59.7, 85.6)
BR	unmut-IGHV	15.7 (13.4, 17.3)	1.79 (1.24, 2.58);	NE
	mut-IGHV	24.2 (18.6, 32.8)	.0015	NE

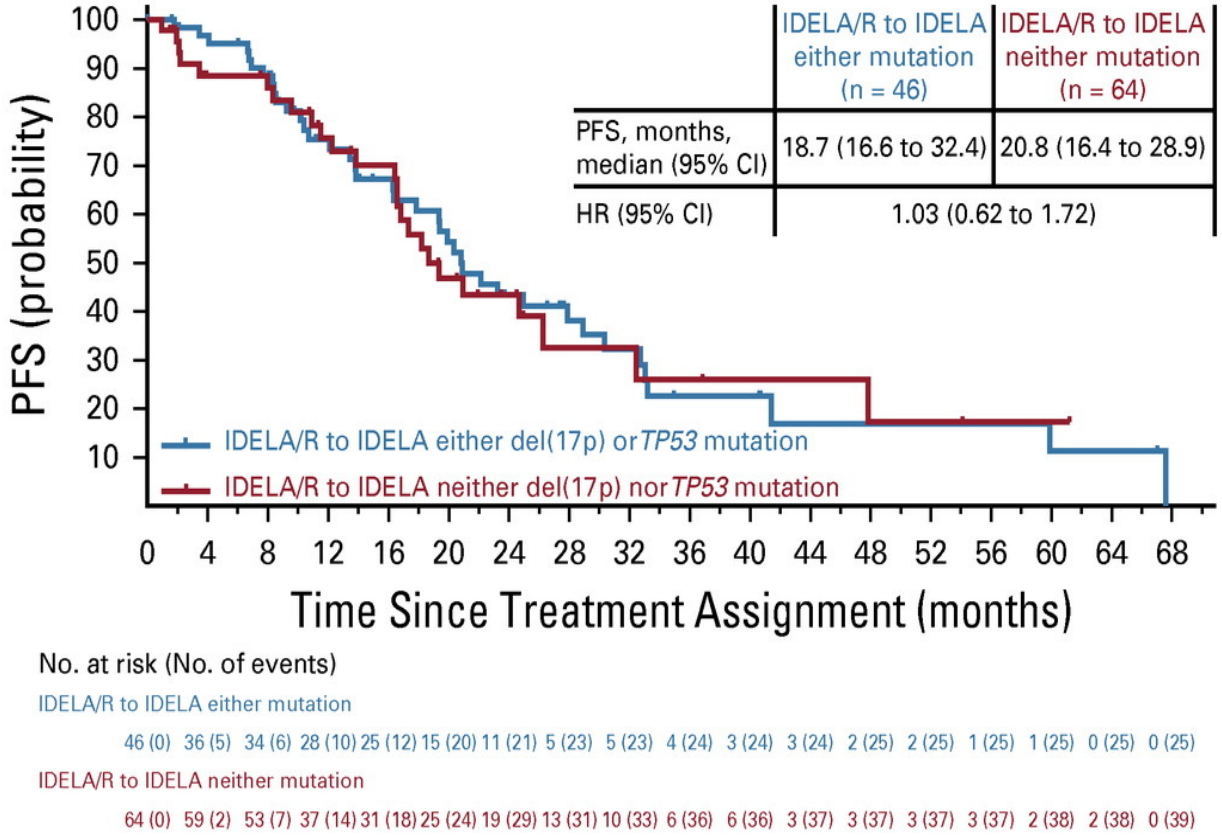


Category		Median PFS, months (95% CI)	HR (95% CI); *P* value†	5-year PFS, % (95% CI)
VenR	del(17p) and/or *TP53*-mut	37.4 (29.4, 52.3)	2.04 (1.32, 3.15);	27.3 (13.6, 41.0)
	No del(17p) and *TP53*-WT	56.6 (53.0, NE)	.0010	42.5 (28.9, 56.0)
BR	del(17p) and/or *TP53*-mut	13.4 (8.0, 15.8)	1.67 (1.15, 2.40);	NE
	No del(17p) and *TP53*-WT	19.6 (16.4, 25.4)	.0059	NE

Seymour et al. Blood 2022

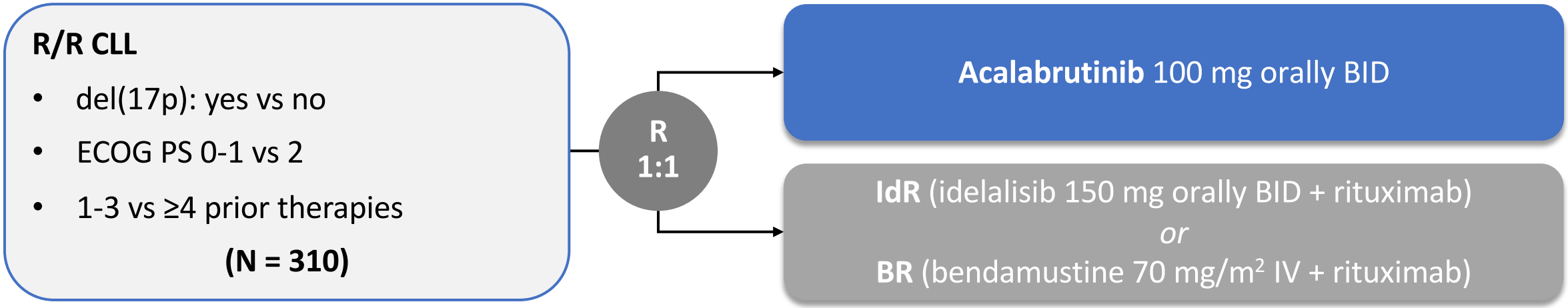
Idelalisib + Rituximab PFS





Sharman et al. *Journal of Clinical Oncology* 37, no. 16 (June 01, 2019) 1391-1402.

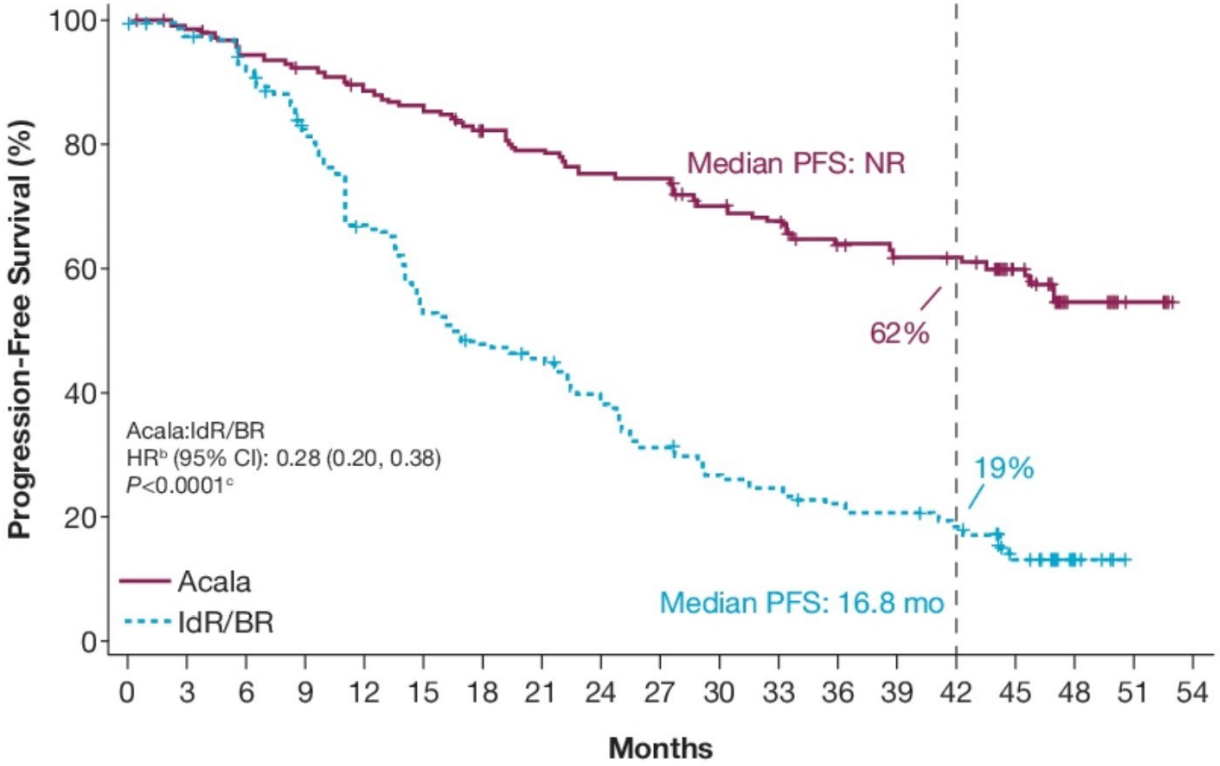
Phase 3 ACE-CL-309/ASCEND: Acalabrutinib Versus IdR or BR in R/R CLL[1]

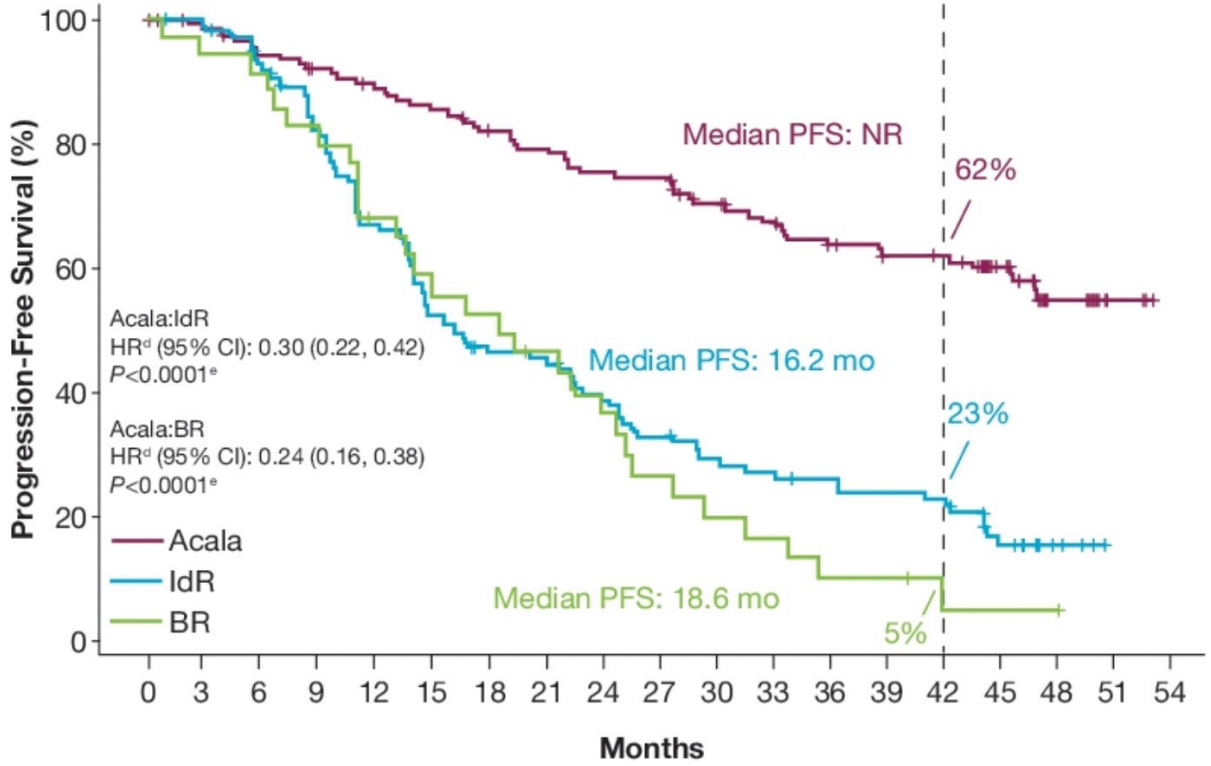


- Crossover from IdR/BR arm allowed after confirmed disease progression
- Interim analysis was planned after occurrence of ~79 PFS events (2/3 of primary event goal)
- **Primary endpoint:** PFS (assessed by IRC)
- **Key secondary endpoints:** ORR (assessed by IRC and investigator), duration of response, PFS (assessed by investigator), OS

1. Ghia P et al. ASCO 2020. Abstract 8015.

ASCEND: Superior PFS for acalabrutinib





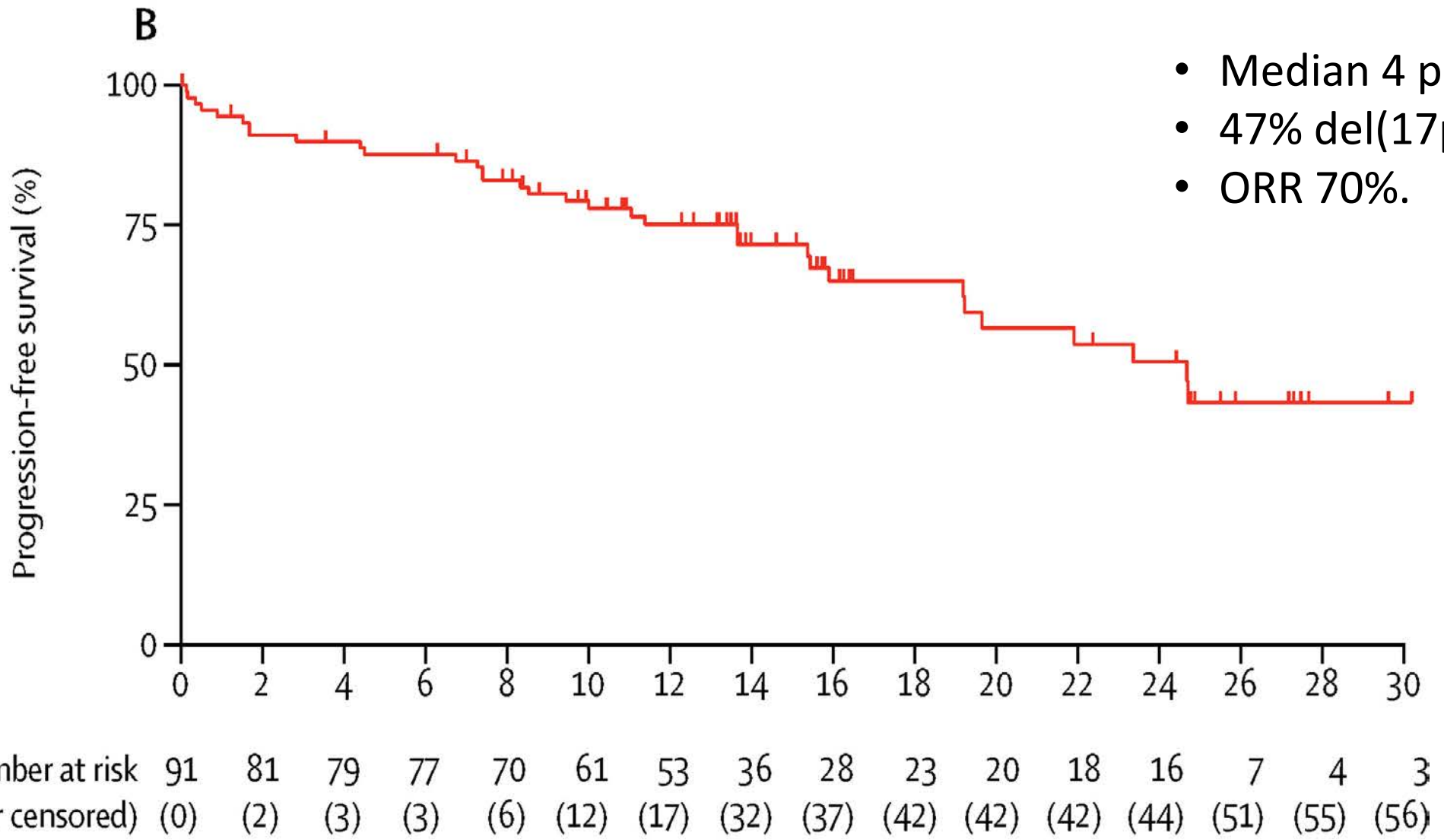
Jurczak W et al. ASCO 2022;Abstract 7538.

Summary – PI3K-delta inhibitors

- Idelalisib 150mg BID + rituximab remains approved for R/R CLL.
- Duvelisib withdrawn, umbralisib + ublituximab application for approval withdrawn.
- Tricky to use – close monitoring for immune transaminitis, colitis, opportunistic infections (PJP, CMV).
- Inferior PFS compared to acalabrutinib in head-to-head data.
- May have a role after failure/unavailability of both BTKi + ven, but extremely limited data for efficacy in this setting (and prefer clinical trials for such patients).

Treatment after failure of a targeted agent

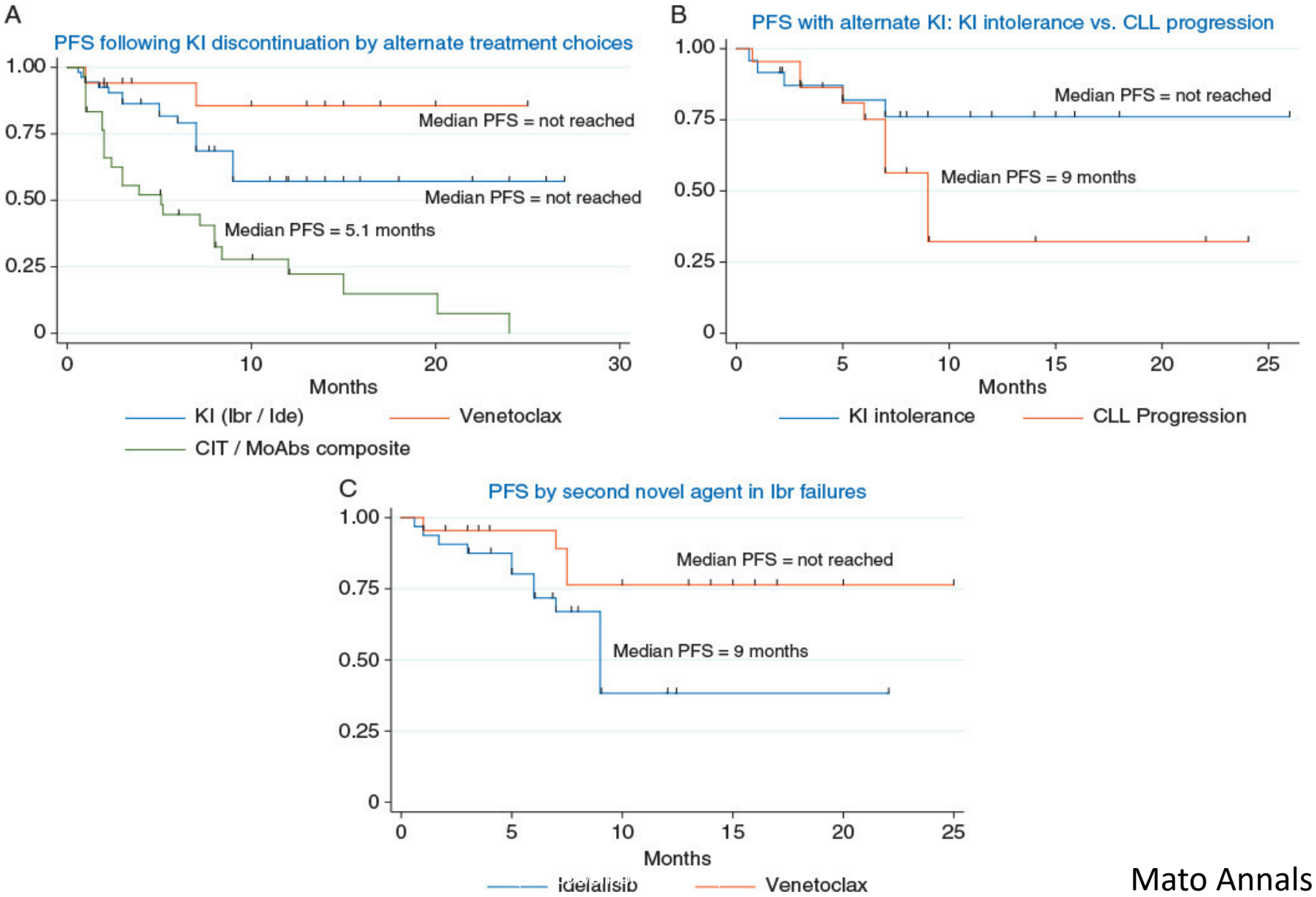
Venetoclax in ibrutinib refractoriness/intolerance



- Median 4 prior therapies.
- 47% del(17p)
- ORR 70%.

Jones et al. *Lancet Oncol* 2018

Treatment after kinase inhibitor failure – Real World data



Mato Annals of Oncology 2017

Treatment after time-limited venetoclax

- Venetoclax + Rituximab:

1. 72% ORR in 32 patients (5.6% CR) with venetoclax re-treatment.
2. Reasonable option, especially if U-MRD with first venetoclax therapy and long duration of off-treatment remission.

- Ibrutinib treatment after ven-R (n=18) showed 100% ORR.
- After ibrutinib + venetoclax:

1. 9 patients on CAPTIVATE Fixed duration cohort re-treated with ibrutinib monotherapy. 7 responded, 2 too early.[2]

[1]Seymour et al. *Blood* 2022 [2] Tam *Blood* (2022) 139 (22): 3278–3289)

Selecting 2nd line therapy

- No data based on long term efficacy to decide between BTKi/ven
- Key determinants: what 1L therapy was received; comorbidities and AE profile; desire for time-limited therapy:

1. Chemoimmunotherapy 1L → BTKi or venetoclax.
2. Venetoclax + Obinutuzumab 1L → BTKi or venetoclax if prolonged remission and deep initial response (ideally on clinical trial).
3. BTKi 1L →:
   - Intolerance → trial of alternative BTKi or venetoclax +/- rituximab.
   - Resistance → venetoclax +/- rituximab.

Double-refractory CLL

- Non-covalent BTKi – pirtobrutinib, nemtabrutinib.
- CAR-T – lisocabtagene ciloleucel. Others.
- Bi-specific antibodies – studies of epcoritamab in CLL/RS and mosunetuzumab

Efficacy of Pirtobrutinib, a Highly Selective, Non- Covalent (Reversible) BTK Inhibitor in Richter Transformation: Results from the Phase 1/2 BRUIN Study

- 57 patients, 50 evaluable.
- Heavily pre-treated. Median 2 prior therapies for RT. Most had had prior covalent BTKi.
- 50 evaluable, 54% ORR (10% CR).
- Median DOR 8.6mo.

Wierda WG et al. ASH 2022; Abstract 347.

Subcutaneous Epcoritamab in Patients with Richter's Syndrome: Early Results from Phase Ib/2 Trial

- CD3x20 bi-specific antibody.
- Phase I study in CLL R/R CLL.
- 10 patients with Richter's Syndrome (1L therapy for RS in 6/10).
- Manageable toxicity (low-grade CRS in 90%).
- ORR 60%. 50% CR.

Kater AP et al. ASH 2022. Abstract 348

Module 5: Promising Investigational Agents and Strategies — Dr Roeker

RTP
RESEARCH
TO PRACTICE

Case Presentation: 77-year-old woman with CLL (p53, 11q, 13q mutations) and disease progression on ibrutinib; repeat mutation testing detects a BTK C481S mutation

Dr Spencer Bachow (Boca Raton, Florida)

RTP
RESEARCH
TO PRACTICE

Case Presentation: 79-year-old man develops Richter's transformation while receiving obinutuzumab/venetoclax for CLL

Dr Justin Favaro (Charlotte, North Carolina)

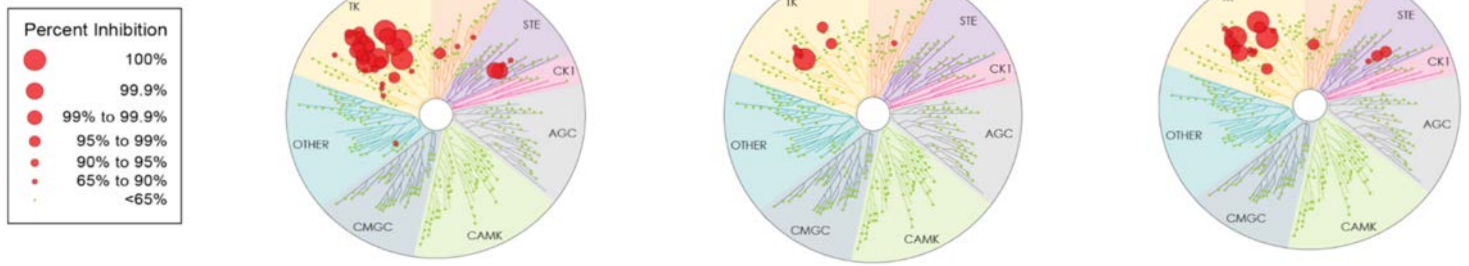
RTP
RESEARCH
TO PRACTICE

Promising Investigational Agents and Strategies

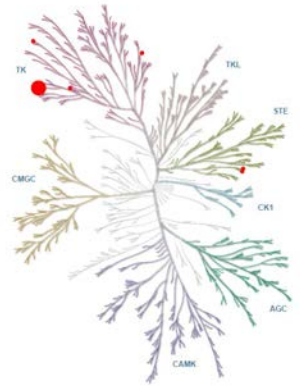
Lindsey Roeker, MD
Assistant Attending L1
Memorial Sloan Kettering Cancer Center
New York, NY

BTK inhibitors: comparing kinome selectivity and *in vivo* activity

Covalent

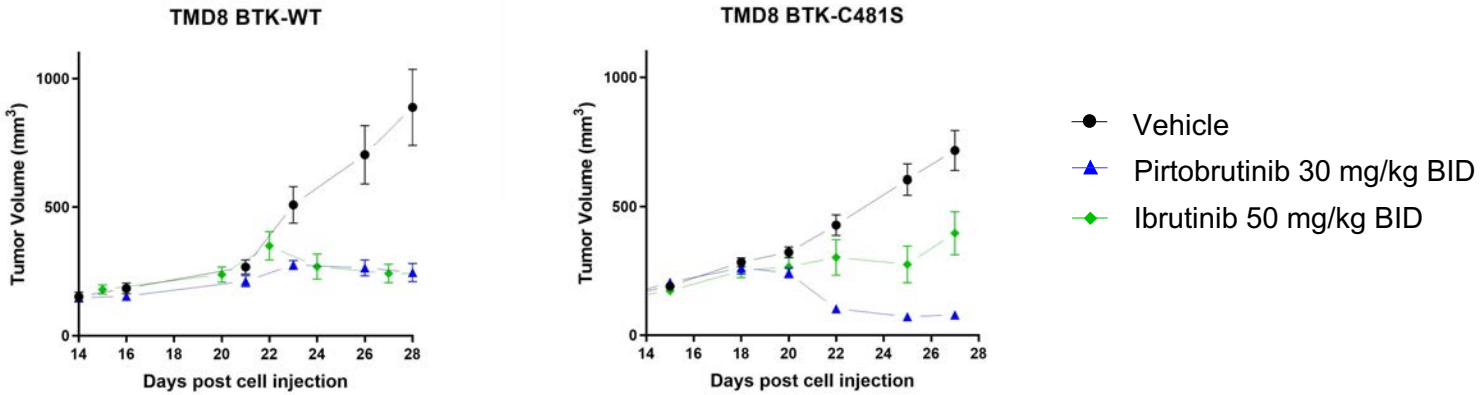


Non-Covalent



Xenograft models

In vivo activity similarly efficacious as ibrutinib in WT; superior in C481S



Pirtobrutinib

- >300-fold selectivity for BTK vs 370 other kinases
- Favorable pharmacologic properties allow sustained BTK inhibition throughout dosing interval
- Nanomolar potency against WT & C481-mutant BTK in cell and enzyme assays
- Due to reversible binding mode, BTK inhibition not impacted by a high intrinsic rate of BTK turnover

Kaptein A, et al. *Blood.* 2018;132(Supplement 1):1871. Mato et al, *Lancet*, 2021:397:892-901. Brandhuber BJ, et al. *Clin. Lymphoma Myeloma Leuk*. 2018.18:S216

BRUIN: phase I/II study of Pirtobrutinib

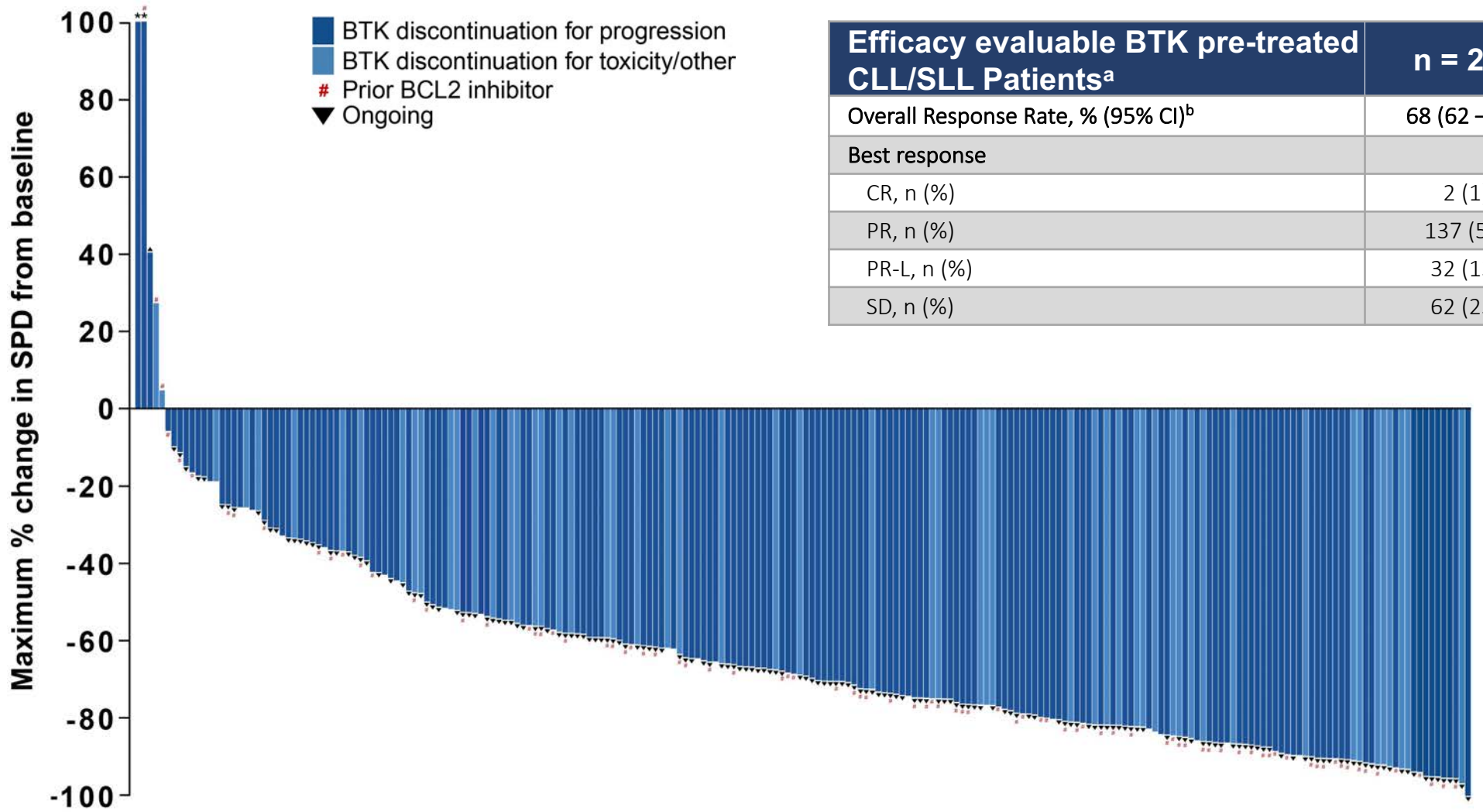
The most recent clinical update focused on CLL/SLL patients previously treated with BTK inhibitor

Characteristics	N = 261
Median age, years (range)	69 (36-88)
Female, n (%)	84 (32)
Male, n (%)	177 (68)
ECOG PS[a], n (%)	
0	138 (53)
1	104 (40)
2	19 (7)
Median number of prior lines of systemic therapy (range)	3 (1-11)
Prior therapy, n (%)	
BTK inhibitor	261 (100)
Anti-CD20 antibody	230 (88)
Chemotherapy	207 (79)
BCL2 inhibitor	108 (41)
PI3K inhibitor	51 (20)
CAR-T	15 (6)
Stem cell transplant	6 (2)
Allogeneic stem cell transplant	5 (2)
Autologous stem cell transplant	1 (<1)
Reason discontinued prior BTKi, n (%)	
Progressive disease	196 (75)
Toxicity/Other	65 (25)

Baseline Molecular Characteristics	
Mutation status, n (%)	
BTK C481-mutant	89 (43)
BTK C481-wildtype	118 (57)
PLCG2-mutant	33 (16)
High Risk Molecular Features, n (%)	
17p deletion	51 (28)
TP53 mutation	64 (37)
17p deletion or TP53 mutation	77 (36)
Both 17p deletion and TP53 mutation	38 (27)
IGHV unmutated	168 (84)
11q deletion	45 (25)

Mato A, et al. *Blood*. 2021;136(Supplement 1):35-37

Pirtobrutinib efficacy in BTK pre-treated CLL/SLL patients

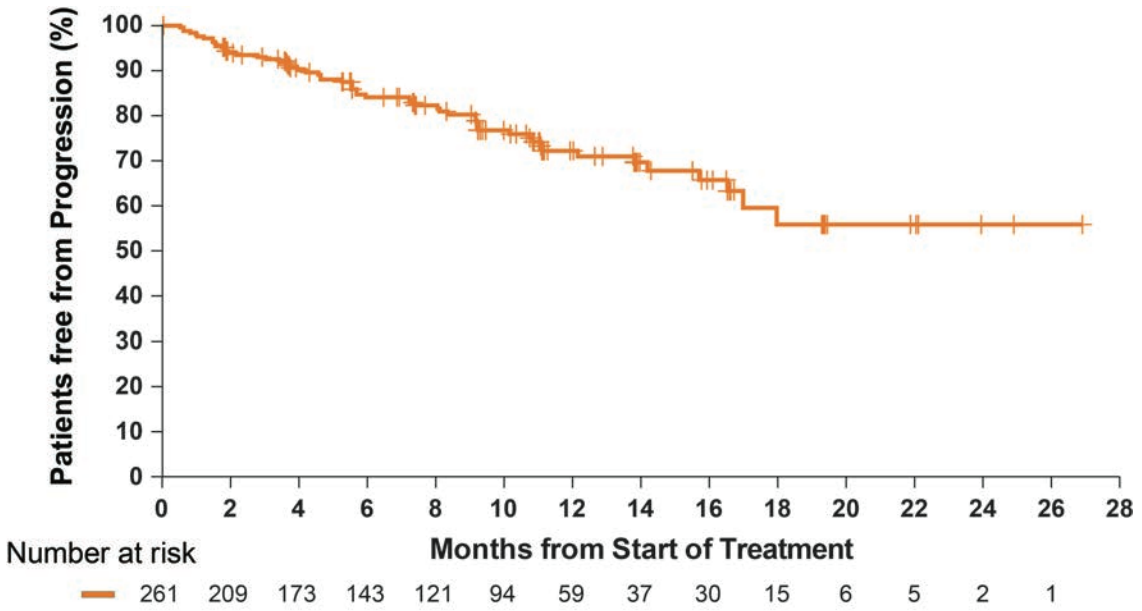


Efficacy evaluable BTK pre-treated CLL/SLL Patients[a]	n = 252
Overall Response Rate, % (95% CI)[b]	68 (62 – 74)
Best response	
CR, n (%)	2 (1)
PR, n (%)	137 (54)
PR-L, n (%)	32 (13)
SD, n (%)	62 (25)

Mato A, et al. *Blood*. 2021;136(Supplement 1):35-37; Mato AR et al. EHA 2022; Abstract S147.

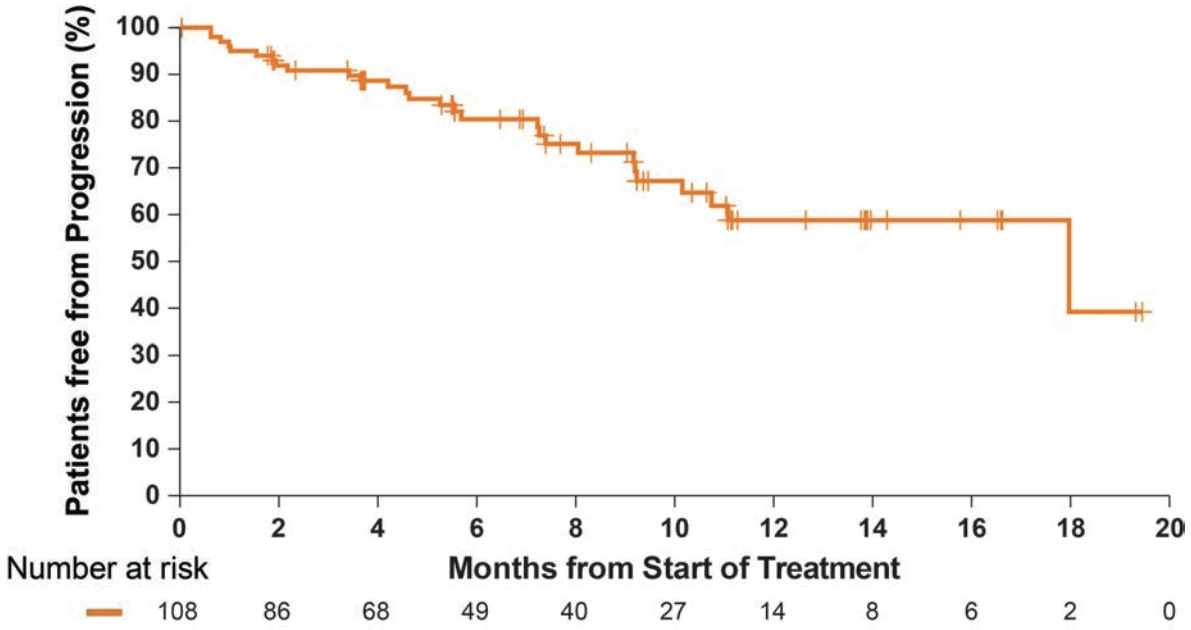
Progression-free survival in BTK pre-treated CLL/SLL patients

PFS in at least BTK pre-treated patients
Median prior lines = 3



Median PFS: Not Estimable (95% CI: 17.0 months – Not Estimable)

PFS in at least BTK and BCL2 pre-treated patients
Median prior lines = 5

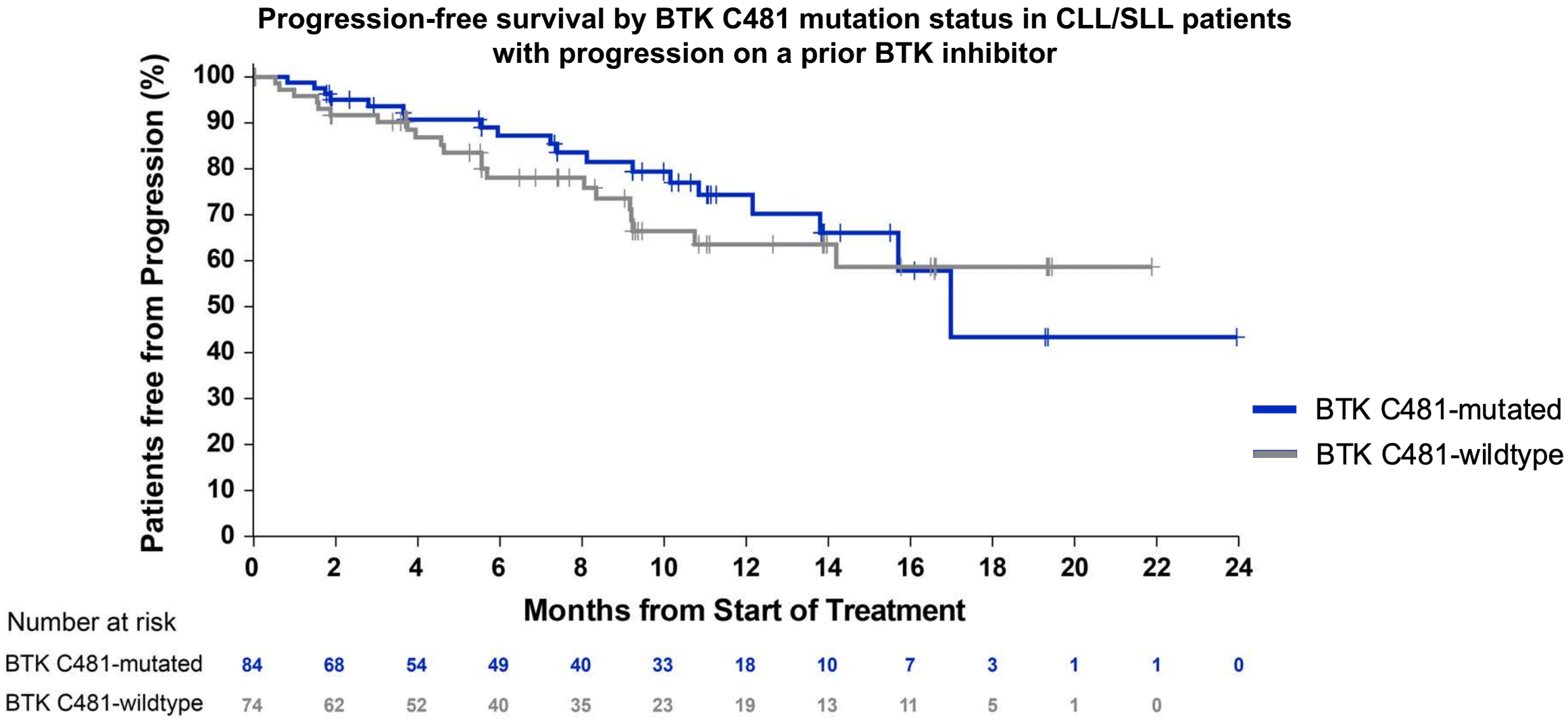


Median PFS: 18 months (95% CI: 10.7 months – Not Estimable)

- 74% (194/261) of BTK pre-treated patients remain on pirtobrutinib
- Median follow-up of 9.4 months (range, 0.3 – 27.4) for all BTK pre-treated patients

Mato A, et al. *Blood*. 2021;136(Supplement 1):35-37; Mato AR et al. EHA 2022; Abstract S147.

BTK C481 mutation status is not predictive of Pirtobrutinib benefit



Mato A, et al. *Blood*. 2021;136(Supplement 1):35-37; Mato AR et al. EHA 2022; Abstract S147.

Pirtobrutinib safety profile

All doses and patients (n=618)							
	Treatment-emergent AEs, (≥15%), %					Treatment-related AEs, %	
Adverse Event	Grade 1	Grade 2	Grade 3	Grade 4	Any Grade	Grades 3/4	Any Grade
Fatigue	13%	8%	1%	-	23%	1%	9%
Diarrhea	15%	4%	<1%	<1%	19%	<1%	8%
Neutropenia	1%	2%	8%	6%	18%	8%	10%
Contusion	15%	2%	-	-	17%	-	12%
AEs of special interest							
Bruising	20%	2%	-	-	22%	-	15%
Rash	9%	2%	<1%	-	11%	<1%	5%
Arthralgia	8%	3%	<1%	-	11%	-	3%
Hemorrhage	5%	2%	1%[g]	-	8%	<1%	2%
Hypertension	1%	4%	2%	-	7%	<1%	2%
Atrial fibrillation/flutter	-	1%	<1%	<1%	2%[h]	-	<1%

No DLTs reported and MTD not reached
96% of patients received ≥1 pirtobrutinib dose at or above RP2D of 200 mg daily
1% (n=6) of patients permanently discontinued due to treatment-related AEs

Mato A, et al. *Blood*. 2021;136(Supplement 1):35-37; Mato AR et al. EHA 2022; Abstract S147.

ASH 2022: Pirtobrutinib in CLL

Saturday, 4:00 – 5:30 PM

347 (Oral). Efficacy of Pirtobrutinib, a Highly Selective, Non-Covalent (Reversible) BTK Inhibitor in Richter Transformation: Results from the Phase 1/2 BRUIN Study

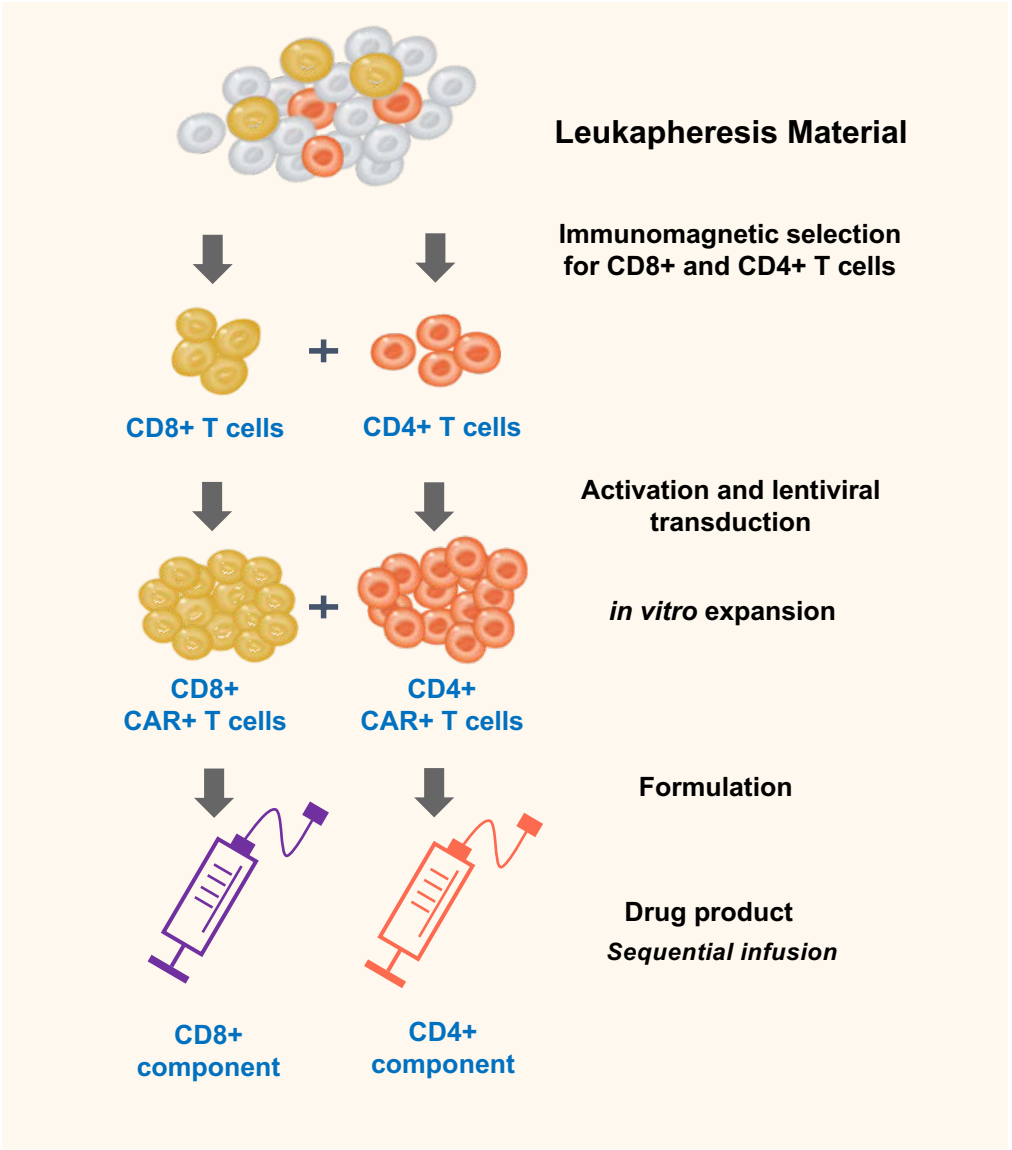
Saturday, 5:30 – 7:30 PM

1797 (Poster). Safety and Tolerability of Pirtobrutinib Monotherapy in Patients with B-Cell Malignancies Who Were Previously Intolerant to a Covalent BTK Inhibitor: Results from the Phase 1/2 BRUIN Study

Monday, 4:30 – 6:30 PM

961 (Oral). Efficacy of Pirtobrutinib in Covalent BTK-Inhibitor Pre-Treated Relapsed / Refractory CLL/SLL: Additional Patients and Extended Follow-up from the Phase 1/2 BRUIN Study

TRANSCEND CLL 004: Liso-Cel in CLL



CD19-Directed, Defined Composition, 4-1BB CAR T Cell Product

CD8+ and CD4+ CAR+ T cell components are administered separately at equal target doses of CD8+ and CD4+ CAR+ T cells

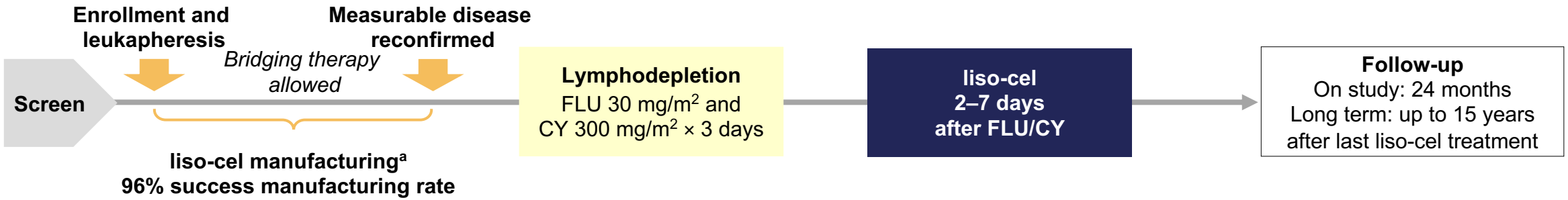
The defined composition of liso-cel results in:

- Consistent administered CD8+ and CD4+ CAR+ T cell dose
- Low variability in the CD8+/CD4+ ratio

Dose and ratio of CD8+ and CD4+ CAR+ T cells may influence the incidence and severity of CRS and neurological events

Siddiqi T, et al. *Blood*. 2019;134(Supplement 1):503. Turtle CJ, et al. *Sci Transl Med*. 2016;8(355):355ra116. DeAngelo DJ, et al. *J Immunother Cancer*. 2017;5(Suppl 2):116: Abstract P217. Neelapu SS, et al. *N Engl J Med*. 2017;377:2531–2544.

TRANSCEND CLL 004 Study Design



Key Eligibility

- Relapsed/refractory CLL/SLL
- Failed or ineligible for BTKi[b]
- High-risk disease[c]: failed ≥2 prior therapies
- Standard-risk disease: failed ≥3 prior therapies
- ECOG PS of 0–1

Dose Escalation: mTPI-2 Design[d]

28-day DLT period

Primary Objectives

- Safety
- Determine recommended dose

Exploratory Objectives

- Antitumor activity
- Pharmacokinetic profile

Dose Level	Dose	Evaluable (N=23)
1	50 × 10^6 CAR+ T cells	9
2	100 × 10^6 CAR+ T cells	14

ClinicalTrials.gov identifier: NCT03331198.

[a]One patient received nonconforming product. [b]Failure defined as SD or PD as best response, or PD after previous response, or discontinuation due to intolerance (unmanageable toxicity). Ineligibility defined as requirement for full-dose anticoagulation or history of arrhythmia. [c]Complex cytogenetic abnormalities, del(17p), *TP53* mutation, or unmutated IGHV. [d]Guo W, et al. *Contemp Clin Trials.* 2017;58:23-33.

BTKi, Bruton tyrosine kinase inhibitor; CAR, chimeric antigen receptor; CLL, chronic lymphocytic leukemia; CY, cyclophosphamide; DLT, dose-limiting toxicity; ECOG PS, Eastern Cooperative Oncology Group performance status; FLU, fludarabine; IGHV, immunoglobulin heavy-chain variable region; mTPI, modified toxicity probability interval for dose escalation; PD, progressive disease; SD, stable disease; SLL, small lymphocytic lymphoma.

Siddiqi T, et al. *Blood*. 2019;134(Supplement 1):503.

Baseline Characteristics

	All Patients (N=23)	Failed BTKi and Venetoclax (n=9)
Age, years, median (range)	66 (49–79)	68 (59–76)
Male, n (%)	11 (48)	4 (44)
Time from diagnosis, months, median (range)	87.5 (30–209)	145 (30–209)
Bulky disease >5 cm, n (%)[a]	8 (35)	4 (44)
BALL risk score,[1] median (range)	2 (0–3)	2 (0–3)
SPD, cm^2, median (range)	25 (2–197)	46 (2–197)
LDH, U/L, median (range)	243 (119–634)	245 (119–634)
Received bridging therapy, n (%)	17 (74)	7 (78)
Stage, n (%)		
Rai stage III/IV	15 (65)	7 (78)
Binet stage C	16 (70)	7 (78)
High-risk features (any), n (%)	19 (83)	8 (89)
Del(17p)	8 (35)	2 (22)
TP53 mutation	14 (61)	6 (67)
Complex karyotype[b]	11 (48)	3 (33)
Lines of prior therapy, median (range)	5 (2–11)	6 (5–10)
Prior ibrutinib, n (%)	23 (100)	9 (100)
Ibrutinib refractory/relapsed, n (%)	21 (91)	9 (100)
BTKi progression and failed venetoclax,[c] n (%)	9 (39)	9 (100)

Siddiqi T, et al. *Blood*. 2019;134(Supplement 1):503.

Treatment emergent AEs (≥20% all grades)

	Any grade	Grade ≥3		
	Total (n = 23)	**Total (n = 23)**	**Dose level 1 (n = 9)**	**Dose level 2 (n = 14)**
Patients with any TEAE	23 (100)	22 (96)	8 (89)	14 (100)
Anemia	19 (83)	17 (74)	6 (67)	11 (79)
Cytokine release syndrome	17 (74)	2 (9)	0	2 (14)
Thrombocytopenia	17 (74)	16 (70)	4 (44)	12 (86)
Neutropenia/Neutrophil count decrease	16 (70)	16 (70)	5 (56)	11 (79)
Leukopenia	11 (48)	10 (43)	4 (44)	6 (43)
Pyrexia	10 (43)	0	0	0
Hypokalemia	9 (39)	0	0	0
Diarrhea	8 (35)	0	0	0
Hypophosphatemia	8 (35)	5 (22)	0	5 (36)
Nausea	8 (35)	0	0	0
Chills	7 (30)	0	0	0
Headache	7 (30)	0	0	0
Tremor	7 (30)	0	0	0
Acute kidney injury	6 (26)	1 (4)	1 (11)	0
Decreased appetite	6 (26)	0	0	0
Febrile neutropenia	6 (26)	6 (26)	0	6 (43)
Hypomagnesemia	6 (26)	0	0	0
Hyponatremia	6 (26)	0	0	0
Lymphopenia	6 (26)	6 (26)	2 (22)	4 (29)
Confusional state	5 (22)	2 (9)	0	2 (14)
Encephalopathy	5 (22)	4 (17)	1 (11)	3 (21)
Hypogammaglobulinemia	5 (22)	0	0	0
Insomnia	5 (22)	0	0	0

DLTs occurred in 2 patients receiving liso-cel at DL2

- Patient 1: grade 4 hypertension
- Patient 2: grade 3 encephalopathy, grade 3 muscle weakness, and grade 4 TLS

Nine deaths occurred

- 7 due to PD
- 1 patient with pneumonia, respiratory failure (2.5 mo after liso-cel)
- 1 patient with septic shock (>90 days after liso-cell)
- No deaths within 30 days of liso-cel administration

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

CRS and neurologic events

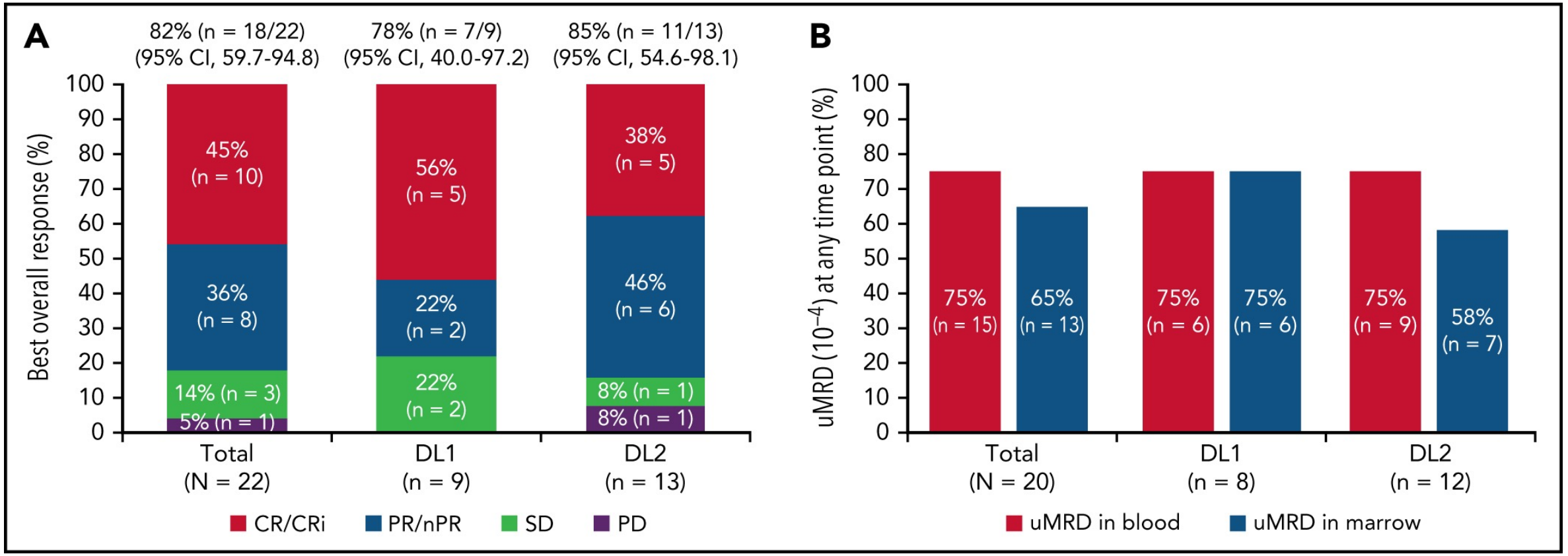
	All Patients (N=23)	Dose level 1 (n = 9)	Dose level 2 (n = 14)
CRS—any grade, n (%)	17 (74)	7 (78)	10 (71)
Median time to onset, days (range)	3 (1-10)	7 (1-10)	2 (1-10)
Median time to resolution, days (range)	12 (2-50)	6 (2-30)	12.5 (2-50)
Grade 3, n (%)	2 (9)	0	2 (14)
NE[a]—any grade, n (%)	9 (39)	2 (22)	7 (50)
Median time to onset, days (range)	4 (2-21)	16 (11-21)	4 (2-11)
Median time to resolution, days (range)	20.5 (6-50)	8.5 (6-11)	29.5 (9-50)
Grade ≥3,[a] n (%)	5 (22)	2 (22)	3 (21)
Any CRS or NE, n (%)	18 (78)	7 (78)	11 (79)
CRS only, n (%)	9 (39)	5 (56)	4 (29)
NE only, n (%)	1 (4)	0	1 (7)
Tocilizumab and/or steroid use			
Tocilizumab only	6 (26)	3 (33)	3 (21)
Corticosteroids only	1 (4)	0	1 (7)
Both tocilizumab and corticosteroids	8 (35)	2 (22)	6 (43)
Tocilizumab and/or corticosteroids	15 (65)	5 (56)	10 (71)

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

Best overall response and undetectable MRD

Best Overall Response (n = 22 evaluable for efficacy)

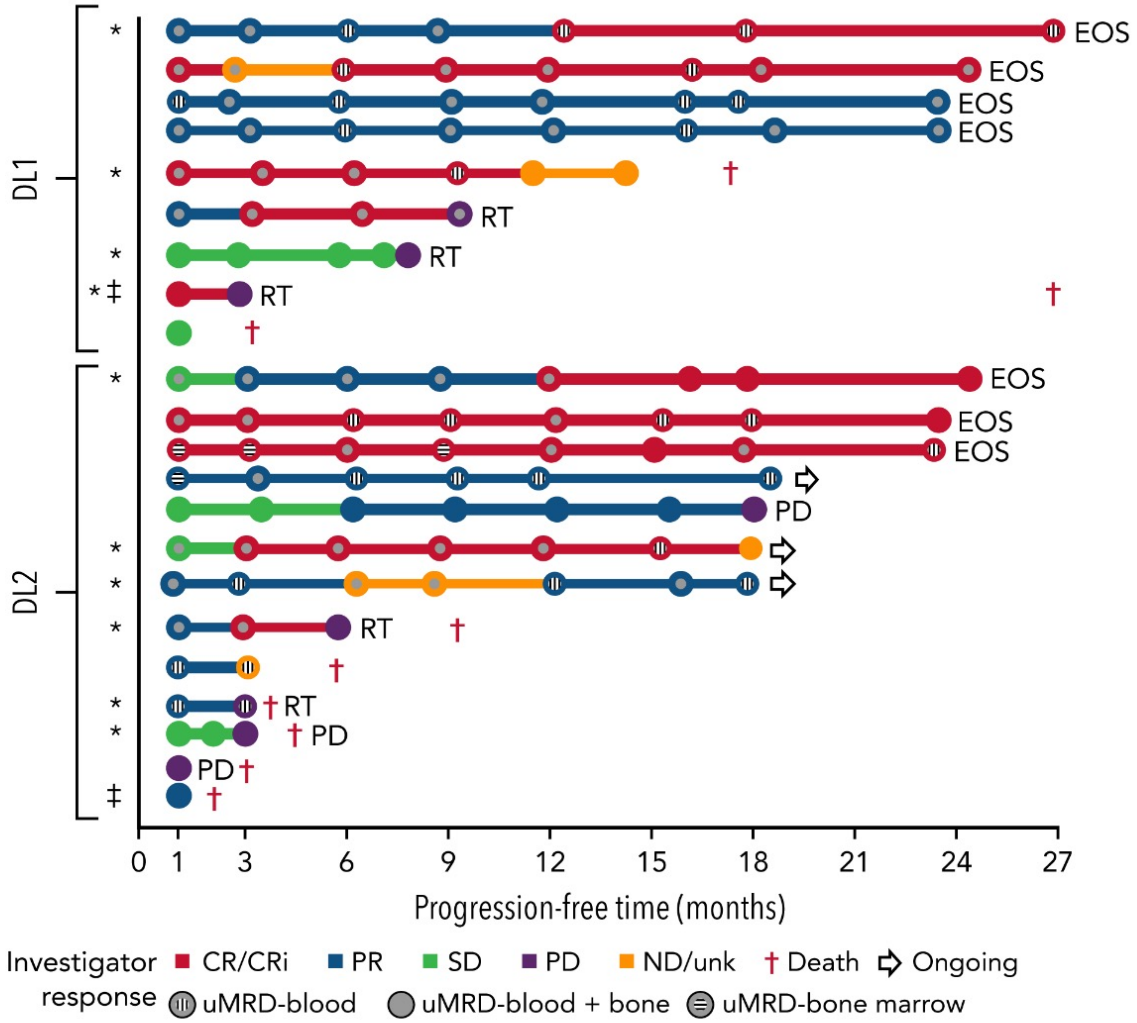
uMRD (n = 20 evaluable for MRD)



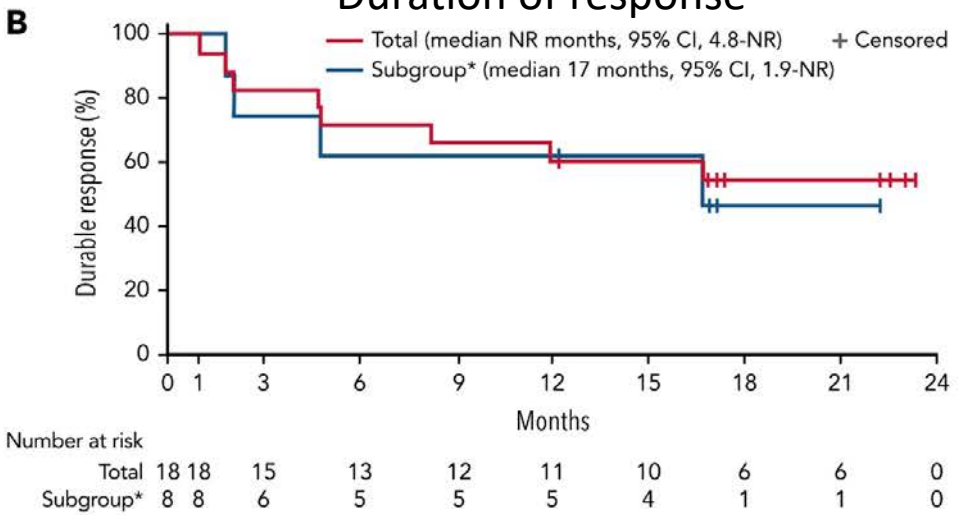
Median follow up = 24 months

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

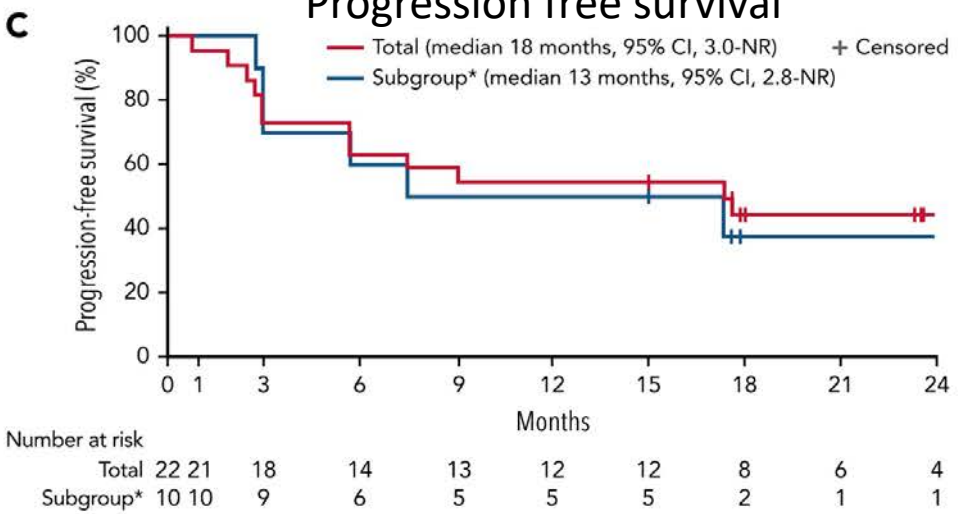
Individual patient efficacy, duration of response, and progression free survival



Duration of response

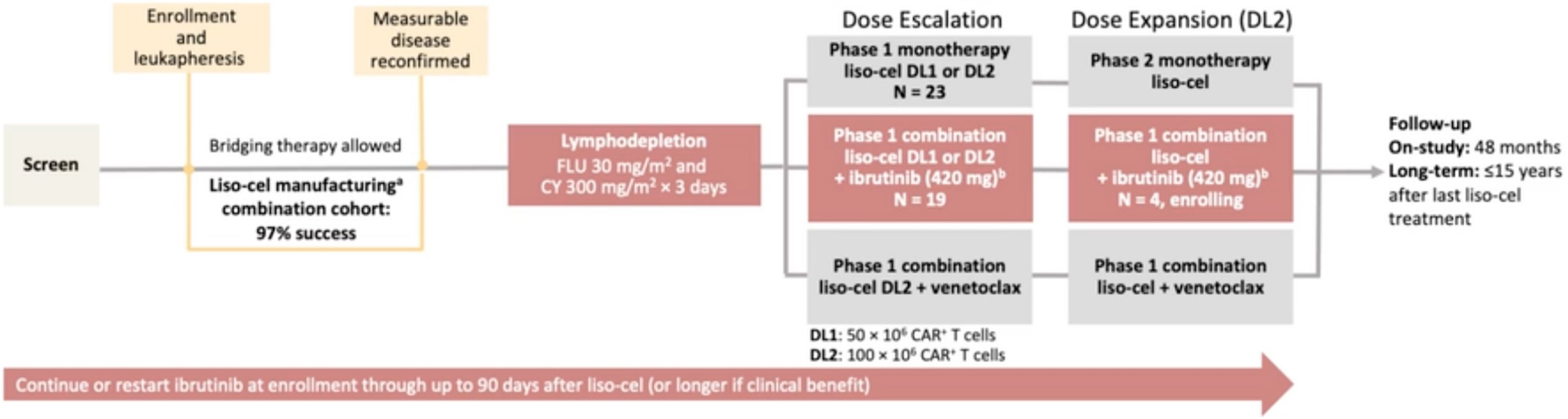


Progression free survival



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

TRANSCEND CLL 004: Liso-cel + Ibrutinib



Patients were eligible if they had 1 or more:

- received ibrutinib and progressed at time of study enrollment
- high-risk features and received ibrutinib for ≥6 months with less than a complete response
- *BTK* or *PLCγ2* gene mutation, with or without progression on ibrutinib
- received prior ibrutinib with no contraindication to reinitiating ibrutinib

Baseline Characteristics	N = 23
Age, median (range)	61 (50 – 77)
High risk features	
del17p	9 (39%)
TP53 mutation	8 (35%)
complex karyotype	10 (43%)
Prior lines of therapy, median (range)	4 (1-10)
Ibrutinib refractory	23 (100%)
Venetoclax refractory	12 (53%)

Weirda B, et al. iwCLL 2021.

Liso-cel + Ibrutinib Safety

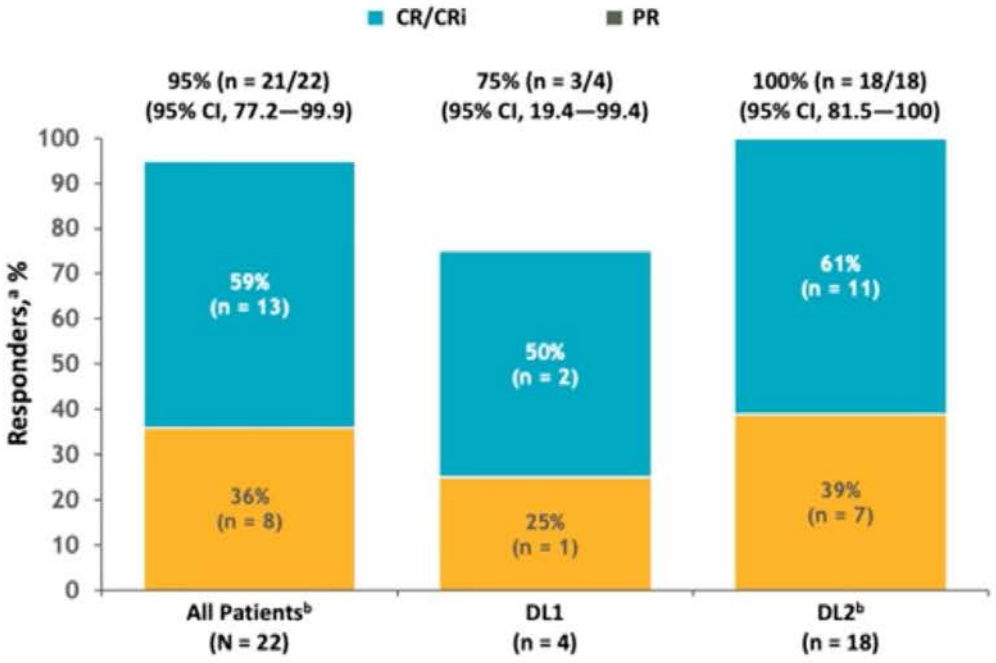
- The combination of liso-cel and ibrutinib was well tolerated, with no reported dose-limiting toxicities
- No grade 5 AEs or grade 4 or 5 cytokine release syndrome (CRS) or neurological events (NE) were reported

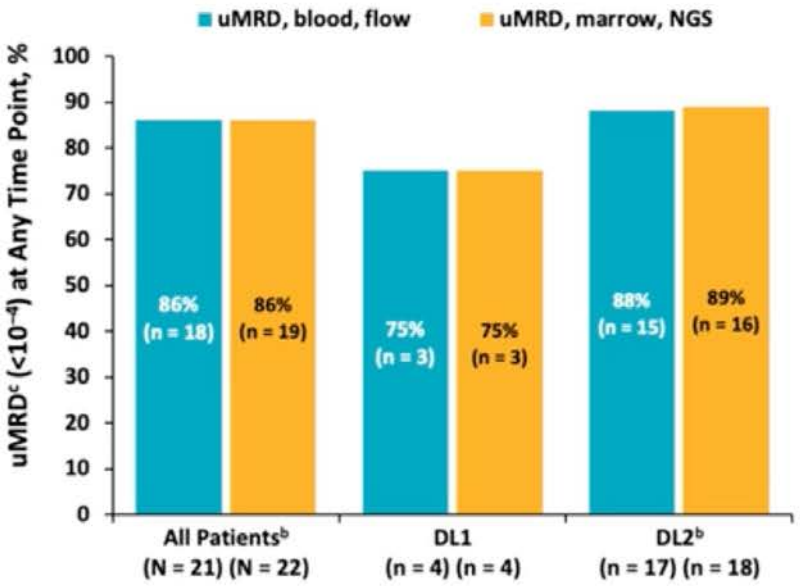
Parameter	All Patients (N = 23)	DL1 + Ibrutinib (n = 4)	DL2 + Ibrutinib (n = 19)
Common grade 3/4 treatment-emergent AEs (TEAEs), n (%)	22 (96)	4 (100)	18 (95)
Neutropenia/neutrophil count decrease	20 (87)	3 (75)	17 (89)
Anemia	10 (43)	3 (75)	7 (37)
Febrile neutropenia	7 (30)	1 (25)	6 (32)
CRS[a]			
All-grade CRS, n (%)	18 (78)	4 (100)	14 (74)
Median time to CRS onset, days (range)	7 (1—13)	8 (6—13)	6.5 (1—11)
Median duration of CRS, days (range)	5.5 (3—13)	6.5 (4—7)	5 (3—13)
Grades 1—2 CRS, n (%)	17 (74)	3 (75)	14 (74)
Grade 3 CRS, n (%)	1 (4)	1 (25)	0
NEs			
All-grade NEs, n (%)	7 (30)	2 (50)	5 (26)
Median time to NE onset, days (range)	9 (5—13)	9 (6—12)	9 (5—13)
Median duration of NE, days (range)	7 (1—10)	8 (8—8)	6 (1—10)
Grades 1—2 NEs, n (%)	3 (13)	2 (50)	1 (5)
Grade 3 NEs,[b] n (%)	4 (17)	0	4 (21)
Management of CRS and/or NEs, n (%)			
Tocilizumab only	3 (13)	0	3 (16)
Corticosteroids only	3 (13)	2 (50)	1 (5)
Tocilizumab and corticosteroids	5 (22)	1 (25)	4 (21)

Weirda B, et al. iwCLL 2021.

Liso-cel + Ibrutinib Efficacy

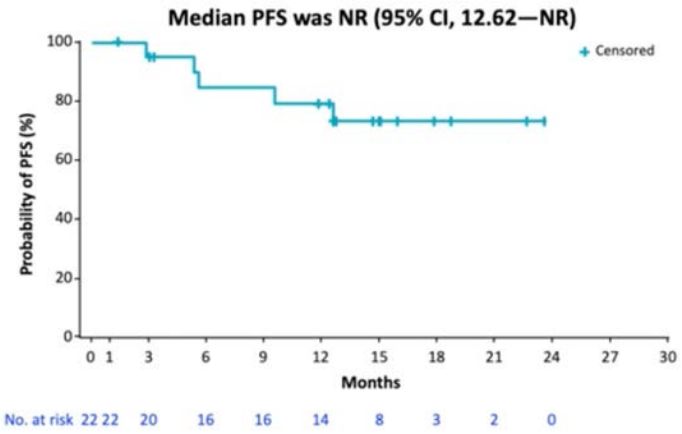
Best Objective Response by iwCLL and uMRD ($<10^{-4}$)





Progression Free Survival

Median follow up = 17 months



- No patients had PD during the first month after liso-cel
- One patient at DL1 had SD for 6 months but later progressed

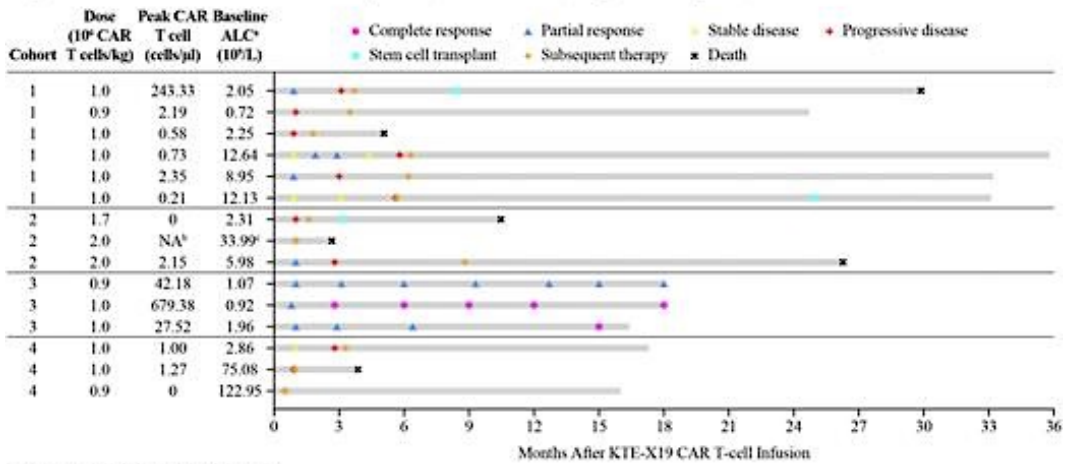
Weirda B, et al. iwCLL 2021.

ZUMA-8: To be presented at ASH 2022 (Sunday, 6 – 8 PM, abstract 3319)

Study Design:

- Brexucabtagene autoleucel: CD-19 Autologous CAR T-cell
- Patients with relapsed/refractory CLL
  - ≥2 prior lines of therapy
  - Including a BTK inhibitor
- Conditioning: Fludarabine / Cyclophosphamide
- 2 dose levels
  - DL1: 1×10^6 CAR T cells/kg
  - DL2: 2×10^6 CAR T cells/kg

Figure: Patient-level Peak CAR T-cell Expansion, Baseline ALC, Objective Response, and Survival Over Time.



Gray bars indicate duration of follow-up.
*Baseline ALC data were based on central assessment, except for 1 patient in Cohort 2. †Peak CAR T-cell data were not available. ‡Based on local assessment.
ALC, absolute lymphocyte count; CAR, chimeric antigen receptor; NA, not available.

Table: ZUMA-8 Patient Characteristics and AE Summary.

	Cohort 1 (low dose) n=6	Cohort 2 (high dose) n=3	Cohort 3 (low tumor burden) n=3	Cohort 4 (post ibrutinib) n=3	Overall N=15
Median follow-up duration, months (range)	35.8 (33.6–40.4)	30.3 (29.9–30.6)	18.2 (18.2–18.4)	17.05 (15.5–17.9)	30.3 (15.5–40.4)
Baseline Characteristics					
Median age, years (range)	60.5 (53–68)	61.0 (52–63)	69.0 (56–79)	67.0 (53–70)	63.0 (52–79)
Male, n (%)	3 (50)	2 (67)	3 (100)	2 (67)	10 (67)
ECOG PS 1, n (%)	4 (67)	1 (33)	1 (33)	2 (67)	8 (53)
>3 prior therapy lines, n (%)	6 (100)	3 (100)	1 (33)	2 (67)	12 (80)
17p deletion, n (%)	1 (17)	1 (33)	0	2 (67)	4 (27)
Complex karyotype, n (%)[a]	3 (50)	3 (100)	1 (33)	0	7 (47)
Median tumor burden, mm^2 (range)	7,026.0 (464.0–26,688.3)	7,458.1 (2,140.4–9,715.0)	625.0 (614.0–2,472.0)	1,434.0 (786.0–2,308.5)	2,308.50 (464.0–26,688.3)
Median CLL lymphocytes in bone marrow aspirate, % (range)[b]	75.0 (0.1–93.5)	86.4 (16.0–97.0)	30.0 (5.0–40.0)	91.0 (33.0–96.0)	75.0 (0.1–97.0)
AE Summary					
Grade ≥3 AE, n (%)					
Any	6 (100)	3 (100)	3 (100)	3 (100)	15 (100)
Treatment related	4 (67)	2 (67)	2 (67)	1 (33)	9 (60)
CRS					
Any	5 (83)	2 (67)	3 (100)	2 (67)	12 (80)
Grade ≥3	0	0	1 (33)	0	1 (7)
NE					
Any	6 (100)	1 (33)	3 (100)	1 (33)	11 (73)
Grade ≥3	2 (33)	0	1 (33)	0	3 (20)

Davids M, et al. *Blood*. 2022;140(Supplement 1):7454-7456

ASH 2022: Promising investigational agents in CLL

- **BTK Degraders**
  - 965. NX-2127-001, a First-in-Human Trial of **NX-2127**, a Bruton's Tyrosine Kinase-Targeted Protein Degrader, in Patients with Relapsed or Refractory Chronic Lymphocytic Leukemia and B-Cell Malignancies
- **Bispecific T cell Engagers**
  - 348. Subcutaneous **Epcoritamab** in Patients with Richter's Syndrome: Early Results from Phase 1b/2 Trial (EPCORE CLL-1)
- **Protein Kinase C β Inhibitor**
  - 963. Initial Results from a Phase 1/2 Dose Escalation and Expansion Study Evaluating **MS-553**, a Novel and Selective PKCβ Inhibitor, in Patients with CLL/SLL
- **ROR1**
  - 1810. First-in-Human Phase I Trial of a ROR1 Targeting Bispecific T Cell Engager (**NVG-111**) in Combination with Ibrutinib or As Monotherapy in Subjects with Relapsed Refractory Chronic Lymphocytic Leukaemia (CLL) and Mantle Cell Lymphoma (MCL)
- **New BCL2i**
  - 962. A Phase 1 Study with the Novel B-Cell Lymphoma 2 (Bcl-2) Inhibitor **Bgb-11417** As Monotherapy or in Combination with Zanubrutinib (ZANU) in Patients (Pts) with CLL/SLL: Preliminary Data
  - 964. **Lisaftoclax** (APG-2575) Safety and Activity As Monotherapy or Combined with Acalabrutinib or Rituximab in Patients (pts) with Treatment-Naïve, Relapsed or Refractory Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma (R/R CLL/SLL): Initial Data from a Phase 2 Global Study

Addressing Current Questions and Controversies in the Management of Hodgkin and Non-Hodgkin Lymphoma — What Clinicians Want to Know

Part 2 of a 3-Part CME Friday Satellite Symposium and Virtual Event Series
Preceding the 64th ASH Annual Meeting

Friday, December 9, 2022
3:15 PM – 5:15 PM CT

Faculty

Jonathan W Friedberg, MD, MMSc
Brad S Kahl, MD
David G Maloney, MD, PhD
Loretta J Nastoupil, MD
Sonali M Smith, MD

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