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

A CME Friday Satellite Symposium Preceding the 66th ASH Annual Meeting

Friday, December 6, 2024

7:30 AM – 9:30 AM PT (10:30 AM – 12:30 PM ET)

Faculty

Farrukh T Awan, MD
Bita Fakhri, MD, MPH
Kerry A Rogers, MD
William G Wierda, MD, PhD

Moderator

Jeff Sharman, MD

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Faculty

Farrukh T Awan, MD
Professor of Internal Medicine
Director of Lymphoid Malignancies Program
Harold C Simmons Comprehensive Cancer Center
The University of Texas
Southwestern Medical Center
Dallas, Texas

Bita Fakhri, MD, MPH
Assistant Professor of Medicine (Hematology)
Stanford University School of Medicine
Stanford, California

Kerry A Rogers, MD
Associate Professor
Division of Hematology
The Ohio State University
Columbus, Ohio

William G Wierda, MD, PhD
Jane and John Justin Distinguished Chair
in Leukemia Research in Honor of Dr Elihu Estey
Section Chief, Chronic Lymphocytic Leukemia
Center Medical Director
Department of Leukemia
Division of Cancer Medicine
Executive Medical Director
Inpatient Medical Services
The University of Texas MD Anderson Cancer Center
Houston, Texas

Moderator

Jeff Sharman, MD
Medical Director of Hematology Research
US Oncology/Sarah Cannon Research Institute
Willamette Valley Cancer Center
Eugene, Oregon

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Dr Awan — Disclosures
Faculty

Consulting Agreements	AbbVie Inc, Adaptive Biotechnologies Corporation, ADC Therapeutics, AstraZeneca Pharmaceuticals LP, BeiGene Ltd, Bristol Myers Squibb, Caribou Biosciences Inc, DAVA Oncology, Genmab US Inc, Incyte Corporation, Kite, A Gilead Company, Loxo Oncology Inc, a wholly owned subsidiary of Eli Lilly & Company
Contracted Research	Pharmacyclics LLC, an AbbVie Company
Data and Safety Monitoring Boards/Committees	Ascentage Pharma, AstraZeneca Pharmaceuticals LP

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Dr Fakhri — Disclosures
Faculty

Advisory Committees	AbbVie Inc, AstraZeneca Pharmaceuticals LP, BeiGene Ltd, Bristol Myers Squibb, Genentech, a member of the Roche Group, Janssen Biotech Inc, Loxo Oncology Inc, a wholly owned subsidiary of Eli Lilly & Company, Pharmacyclics LLC, an AbbVie Company
Contracted Research	AbbVie Inc, BeiGene Ltd, Genmab US Inc, Loxo Oncology Inc, a wholly owned subsidiary of Eli Lilly & Company
Speakers Bureaus	AbbVie Inc, Loxo Oncology Inc, a wholly owned subsidiary of Eli Lilly & Company

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Dr Rogers — Disclosures
Faculty

Advisory Committees	AstraZeneca Pharmaceuticals LP, Janssen Biotech Inc
Consulting Agreements	AbbVie Inc, Alpine Immune Sciences, BeiGene Ltd, Genentech, a member of the Roche Group, Loxo Oncology Inc, a wholly owned subsidiary of Eli Lilly & Company, Pharmacyclics LLC, an AbbVie Company
Contracted Research	AbbVie Inc, AstraZeneca Pharmaceuticals LP, Genentech, a member of the Roche Group, Loxo Oncology Inc, a wholly owned subsidiary of Eli Lilly & Company, Novartis

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Dr Wierda — Disclosures
Faculty

Consulting Agreements	BeiGene Ltd, Numab Therapeutics AG
Contracted Research	AbbVie Inc, Acerta Pharma — A member of the AstraZeneca Group, Bristol Myers Squibb, Cyclacel Pharmaceuticals Inc, Genentech, a member of the Roche Group, Gilead Sciences Inc, GSK, Janssen Biotech Inc, Juno Therapeutics, a Celgene Company, Kite, A Gilead Company, Loxo Oncology Inc, a wholly owned subsidiary of Eli Lilly & Company, Novartis, Nurix Therapeutics Inc, Oncternal Therapeutics, Pharmacyclics LLC, an AbbVie Company
Nonrelevant Financial Relationships	National Comprehensive Cancer Network (Chair, CLL), Support by the NIH/NCI under award number P30 CA016672 and use of MD Anderson Cancer Center Support Grant (CCSG) shared resources

Dr Sharman — Disclosures
Moderator

Consulting Agreements	AbbVie Inc, AstraZeneca Pharmaceuticals LP, BeiGene Ltd, Bristol Myers Squibb, Genentech, a member of the Roche Group, Merck, Novartis, Pharmacyclics LLC, an AbbVie Company

Commercial Support

This activity is supported by educational grants from AstraZeneca Pharmaceuticals LP, BeiGene Ltd, and Lilly.

Research To Practice CME Planning Committee Members, Staff and Reviewers

Planners, scientific staff and independent reviewers for Research To Practice have no relevant conflicts of interest to disclose.

This educational activity contains discussion of non-FDA-approved uses of agents and regimens. Please refer to official prescribing information for each product for approved indications.

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What Clinicians Want to Know: Addressing Current Questions and Controversies Regarding the Role of CAR T-Cell Therapy and Bispecific Antibodies in the Management of Lymphoma

A CME Friday Satellite Symposium and Webcast Preceding the 66th ASH Annual Meeting

Friday, December 6, 2024

11:30 AM – 1:30 PM PT (2:30 PM – 4:30 PM ET)

Faculty

Jennifer Crombie, MD

Martin Hutchings, MD, PhD

Matthew Lunning, DO

Tycel Phillips, MD

Moderator

Jeremy S Abramson, MD, MMSc

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What Clinicians Want to Know: Addressing Current Questions and Controversies in the Management of Myelofibrosis

A CME Friday Satellite Symposium and Webcast Preceding the 66th ASH Annual Meeting

Friday, December 6, 2024

11:30 AM – 1:30 PM PT (2:30 PM – 4:30 PM ET)

Faculty

Prithviraj Bose, MD

Angela G Fleischman, MD, PhD

Abdulraheem Yacoub, MD

Moderator

Andrew T Kuykendall, MD

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What Clinicians Want to Know: Addressing Current Questions and Controversies in the Management of Acute Myeloid Leukemia

A CME Friday Satellite Symposium and Webcast Preceding the 66th ASH Annual Meeting

Friday, December 6, 2024

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

Faculty

Alexander Perl, MD

Richard M Stone, MD

Eunice S Wang, MD

Andrew H Wei, MBBS, PhD

Moderator

Eytan M Stein, MD

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TO PRACTICE

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

A CME Friday Satellite Symposium and Webcast Preceding the 66th ASH Annual Meeting

Friday, December 6, 2024

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

Faculty

Professor Philippe Moreau, MD

Robert Z Orlowski, MD, PhD

Noopur Raje, MD

Paul G Richardson, MD

Moderator

Sagar Lonial, MD

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Rounds with the Investigators: Compelling Teaching Cases Focused on the Management of Breast Cancer

A 3-Part CME Hybrid Satellite Symposium Series in Partnership with the 2024 San Antonio Breast Cancer Symposium®

HER2-Low and HER2-Ultralow Breast Cancer

Tuesday, December 10, 2024

7:15 PM – 8:45 PM CT

New Developments in Endocrine Treatment for Breast Cancer

Wednesday, December 11, 2024

7:15 PM – 9:15 PM CT

Management of Metastatic Breast Cancer

Thursday, December 12, 2024

7:00 PM – 9:00 PM CT

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Save The Date

Fourth Annual
National General Medical Oncology Summit

A Multitumor CME/MOC-, NCPD- and ACPE-Accredited Educational Conference Developed in Partnership with Florida Cancer Specialists & Research Institute

Friday to Sunday, February 28 to March 2, 2025

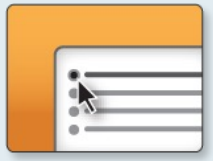
Fontainebleau Hotel, Miami Beach, Florida

Moderated by Neil Love, MD

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.

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

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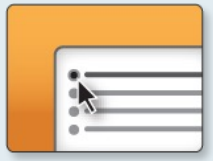
Clinicians Attending via Zoom

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

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Survey of General Medical Oncologists: November 22nd – December 5th

Results available on iPads and Zoom chat room

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Agenda

Module 1: Optimizing First-Line Therapy for Chronic Lymphocytic Leukemia (CLL) — Dr Sharman

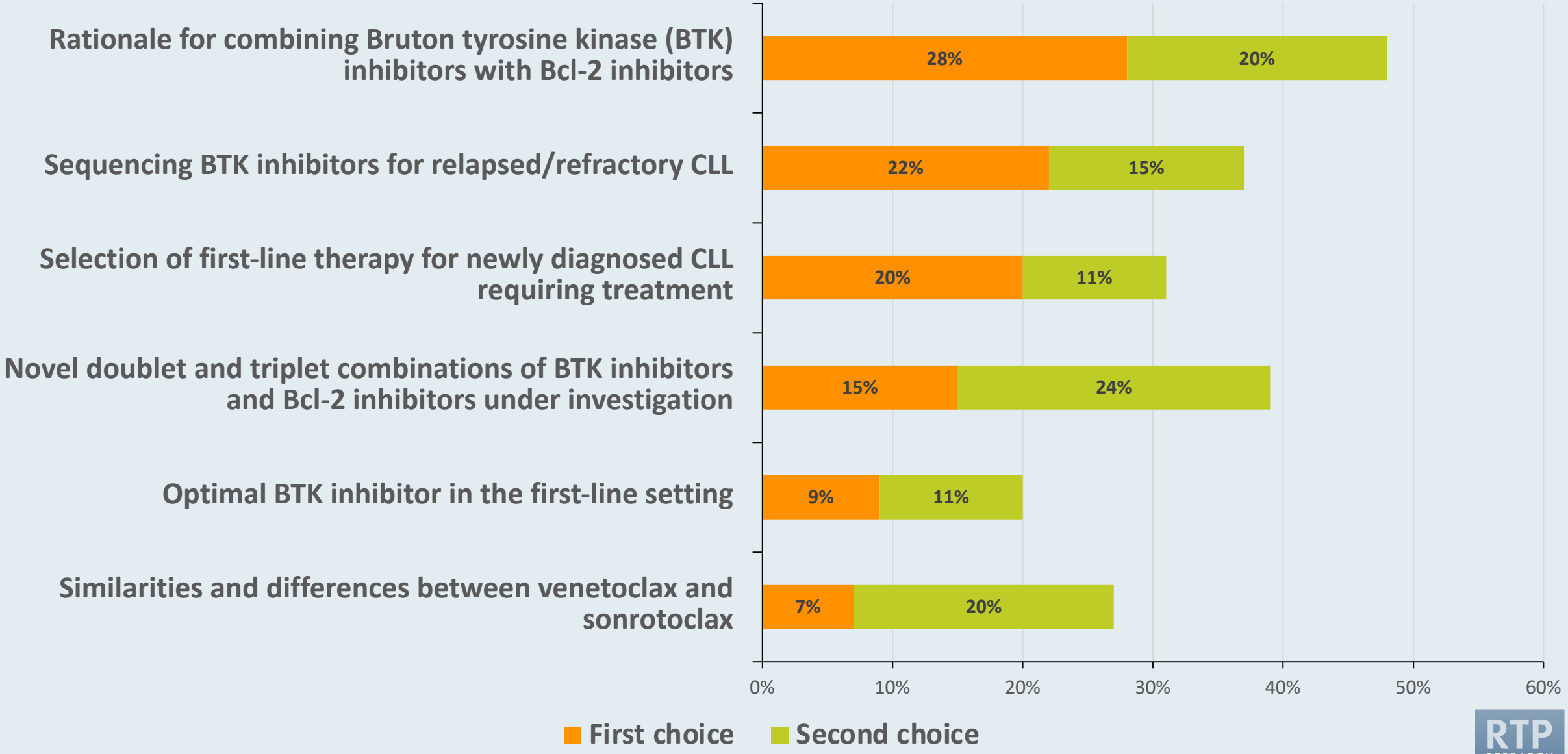
Module 2: Emerging Role of Bruton Tyrosine Kinase (BTK) Inhibitors in Combination with Bcl-2 Inhibitors — Dr Rogers

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

Module 4: Integration of Noncovalent BTK Inhibitors into the Management of Relapsed/Refractory CLL — Dr Fakhri

Module 5: Chimeric Antigen Receptor T-Cell Therapy and Other Novel Strategies for CLL — Dr Wierda

Topics of Interest for Future CME Programs



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Agenda

Module 1: Optimizing First-Line Therapy for Chronic Lymphocytic Leukemia (CLL) — Dr Sharman

Module 2: Emerging Role of Bruton Tyrosine Kinase (BTK) Inhibitors in Combination with Bcl-2 Inhibitors — Dr Rogers

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

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Module 5: Chimeric Antigen Receptor T-Cell Therapy and Other Novel Strategies for CLL — Dr Wierda

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Considerations in Frontline CLL

Jeff Sharman M.D.
Willamette Valley Cancer Institute
Medical Director of Hematology Research
Sarah Cannon Research

iwCLL guidelines for diagnosis, indications for treatment, response assessment, and supportive management of CLL

Active disease should be clearly documented to initiate therapy. At least 1 of the following criteria should be met.

1. Evidence of progressive marrow failure as manifested by the development of, or worsening of, anemia and/or thrombocytopenia. Cutoff levels of Hb <10 g/dL or platelet counts $<100 \times 10^9$/L are generally regarded as indication for treatment. However, in some patients, platelet counts $<100 \times 10^9$/L may remain stable over a long period; this situation does not automatically require therapeutic intervention.
2. Massive (ie, ≥6 cm below the left costal margin) or progressive or symptomatic splenomegaly.
3. Massive nodes (ie, ≥10 cm in longest diameter) or progressive or symptomatic lymphadenopathy.
4. Progressive lymphocytosis with an increase of ≥50% over a 2-month period, or lymphocyte doubling time (LDT) <6 months. LDT can be obtained by linear regression extrapolation of absolute lymphocyte counts obtained at intervals of 2 weeks over an observation period of 2 to 3 months; patients with initial blood lymphocyte counts $<30 \times 10^9$/L may require a longer observation period to determine the LDT. Factors contributing to lymphocytosis other than CLL (eg, infections, steroid administration) should be excluded.
5. Autoimmune complications including anemia or thrombocytopenia poorly responsive to corticosteroids.
6. Symptomatic or functional extranodal involvement (eg, skin, kidney, lung, spine).
7. Disease-related symptoms as defined by any of the following:
   a. Unintentional weight loss ≥10% within the previous 6 months.
   b. Significant fatigue (ie, ECOG performance scale 2 or worse; cannot work or unable to perform usual activities).
   c. Fevers ≥100.5°F or 38.0°C for 2 or more weeks without evidence of infection.
   d. Night sweats for ≥1 month without evidence of infection.

1998: NEJM
Chlorambucil vs Watch and Wait

2017: Leukemia
CLL1
Fludarabine vs Watch and Wait

2020: Leukemia
CLL7
FCR vs Watch and Wait

The New England Journal of Medicine

CHLORAMBUCIL IN INDOLENT CHRONIC LYMPHOCYTIC LEUKEMIA

Guillaume Dighiero, M.D., Ph.D., Karim Maloum, M.D., Ph.D., Bernard Desablens, M.D., Bruno Cazin, M.D., Maurice Navarro, M.D., Robert Leblay, M.D., Michel Leporrier, M.D., Jérome Jaubert, M.D., Gérard Lepeu, M.D., Brigitte Dreyfus, M.D., Jacques-Louis Binet, M.D., and Philippe Travade, M.D., for the French Cooperative Group on Chronic Lymphocytic Leukemia

› Leukemia. 2017 Dec;31(12):2833-2837. doi: 10.1038/leu.2017.246. Epub 2017 Aug 14.

Early, risk-adapted treatment with fludarabine in Binet stage A chronic lymphocytic leukemia patients: results of the CLL1 trial of the German CLL study group

Leukemia (2020) 34:2038–2050
https://doi.org/10.1038/s41375-020-0747-7

ARTICLE

Chronic lymphocytic leukemia

Early treatment with FCR versus watch and wait in patients with stage Binet A high-risk chronic lymphocytic leukemia (CLL): a randomized phase 3 trial

10 years of oral targeted Rx approval in CLL

CENTER FOR DRUG EVALUATION AND RESEARCH

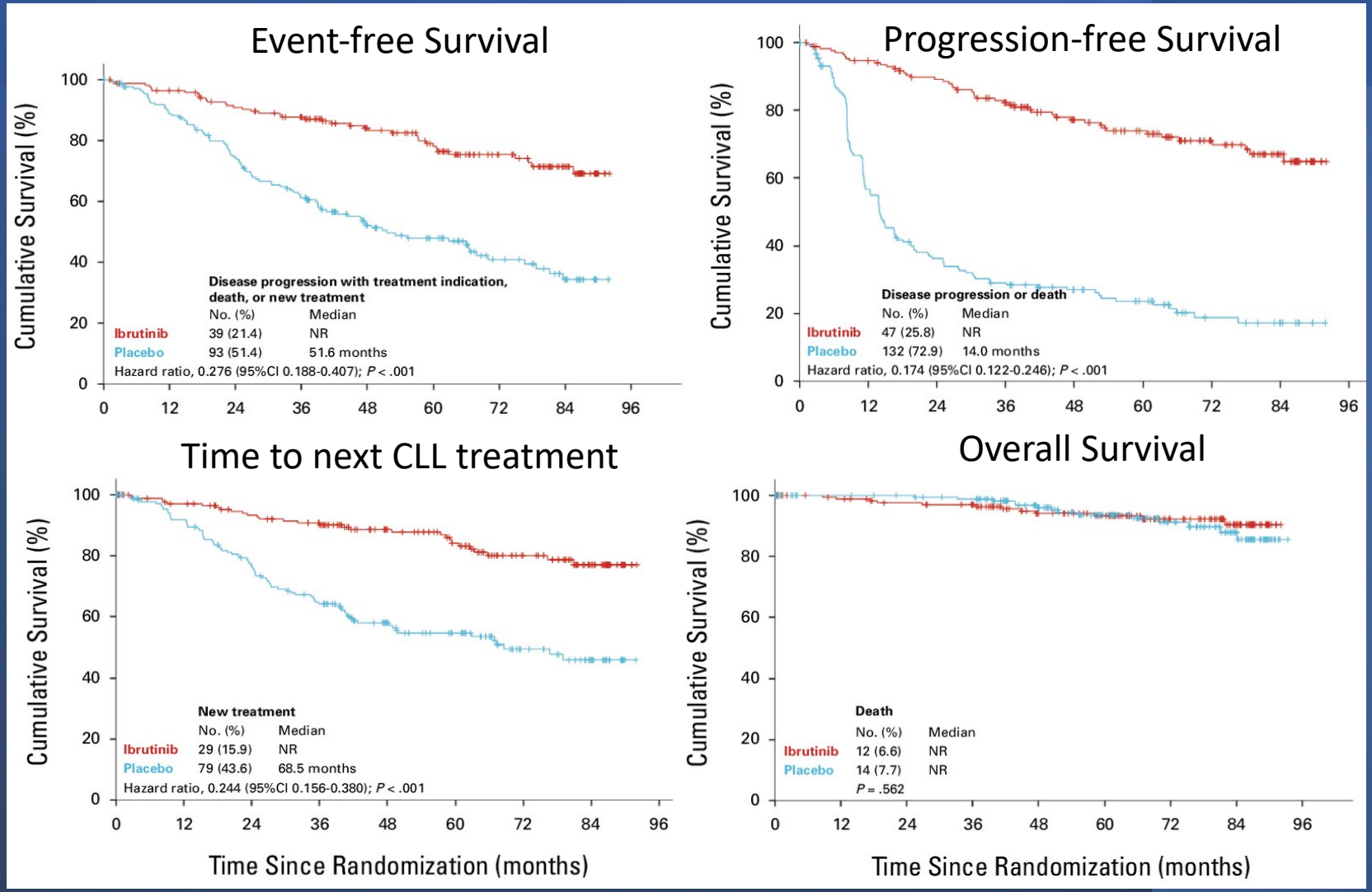
Approval Package for:

APPLICATION NUMBER:

205552Orig2s000

Trade Name:	Imbruvica
Generic Name:	Ibrutinib capsules, 140 mg
Sponsor:	Pharmacyclics, Inc.
Approval Date:	February 12, 2014
Indications:	For the treatment of patients with Chronic Lymphocytic Leukemia (CLL) who have received at least one prior therapy.

Ibrutinib in Early-Stage Chronic Lymphocytic Leukemia: The Randomized, Placebo-Controlled, Double-Blind, Phase III CLL12 Trial



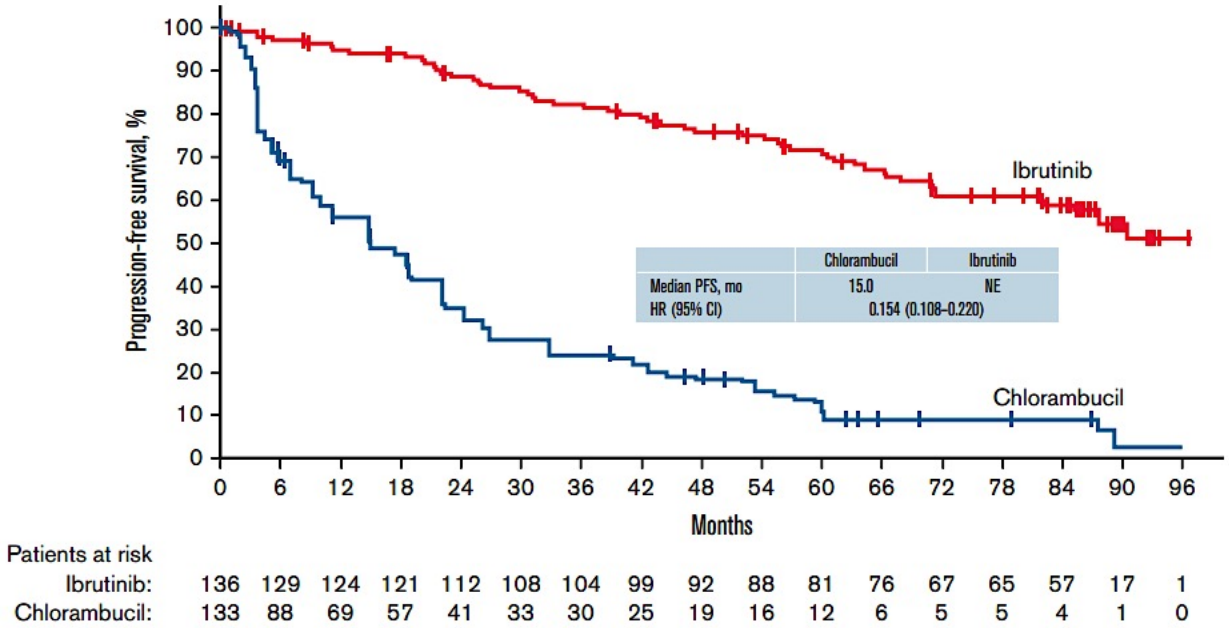
Langerbeins P et al. J Clin Oncol. 2024 Nov 27:JCO2400975

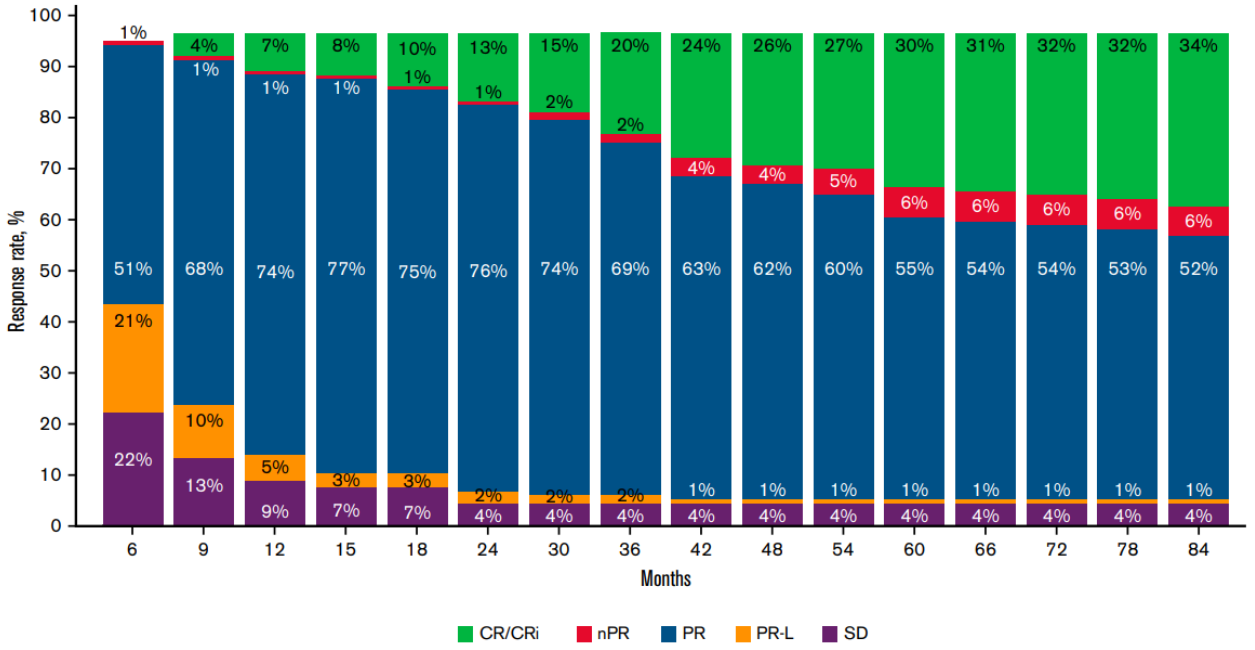
Adverse Event and Serious Adverse Event	Ibrutinib Group (n = 170)	Placebo Group (n = 168)
Adverse events, No. (%)		
Adverse events reported in >15% of patients in either group		
Arthralgia	30 (17.6)	15 (8.9)
Atrial fibrillation	27 (15.9)	5 (3.0)
Bronchitis	27 (15.9)	20 (11.9)
Diarrhea	58 (34.1)	31 (18.5)
Dizziness	26 (15.3)	11 (6.5)
Dyspepsia	27 (15.9)	6 (3.6)
Fatigue	47 (27.6)	35 (20.8)
Hematoma	30 (17.6)	9 (5.4)
Headache	30 (17.6)	20 (11.9)
Hypertension	31 (18.2)	13 (7.7)
Nasopharyngitis	51 (30.0)	72 (42.9)
Nausea	32 (18.8)	20 (11.9)
Rash	33 (19.4)	11 (6.5)
Grade ≥3 adverse event	122 (71.8)	111 (66.1)
Grade ≥3 adverse event reported in ≥3% of the patients in either group		
Acute myocardial infarction	2 (1.2)	5 (3.0)
Atrial fibrillation	15 (8.8)	4 (2.4)
Basal cell carcinoma	4 (2.4)	12 (7.1)
Coronary artery disease	6 (3.5)	5 (3.0)
Hypertension	8 (4.7)	5 (3.0)
Pneumonia	8 (4.7)	11 (6.5)
Rash	6 (3.5)	0
Richter transformation	0	5 (3.0)

Langerbeins P et al. J Clin Oncol. 2024 Nov 27:JCO2400975

Frontline BTK Options

Up to 8-year follow-up from RESONATE-2: first-line ibrutinib treatment for patients with chronic lymphocytic leukemia

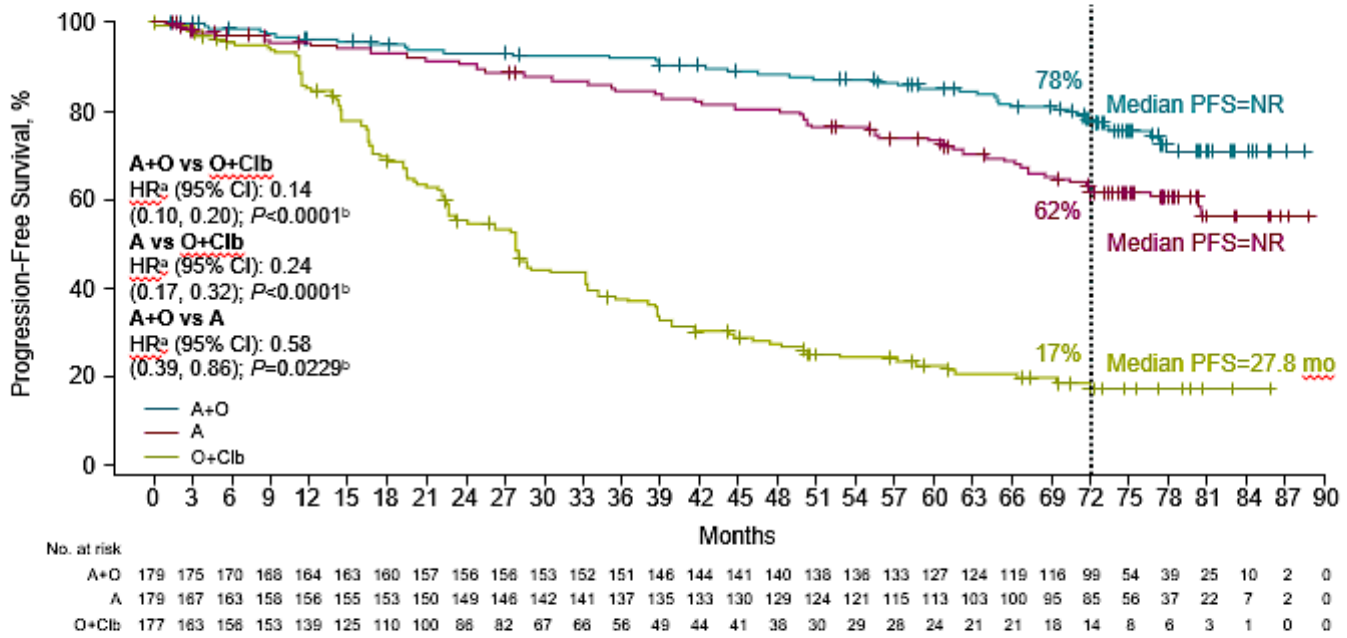




Barr PM et al. *Blood Adv* (2022) 6 (11): 3440–3450.

Acalabrutinib: ELEVATE-TN

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



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

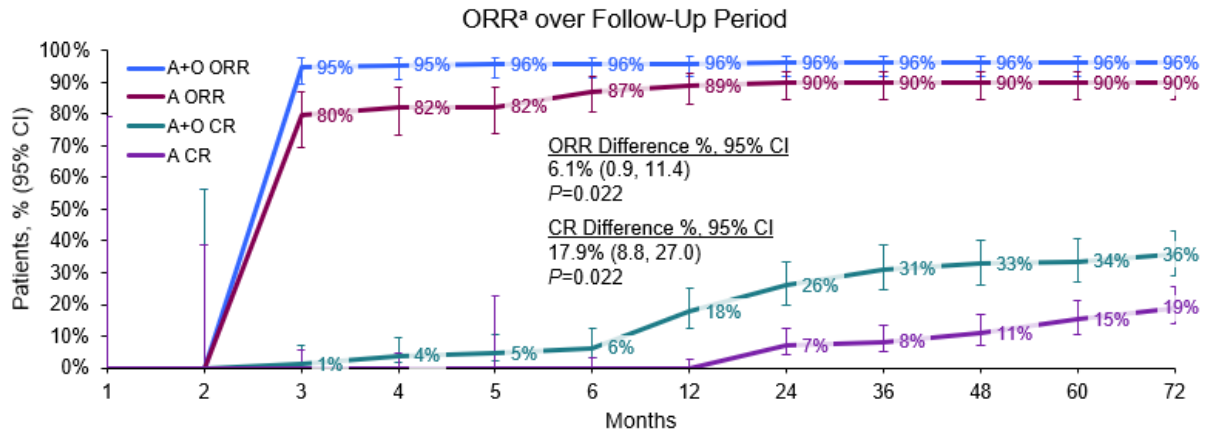
[a]Hazard ratio based on stratified Cox proportional-hazards model.
[b]*P*-value based on stratified log-rank test.

ELEVATE-TN 6 Year Update

Sharman JP et al. ASH 2023; Abstract 636

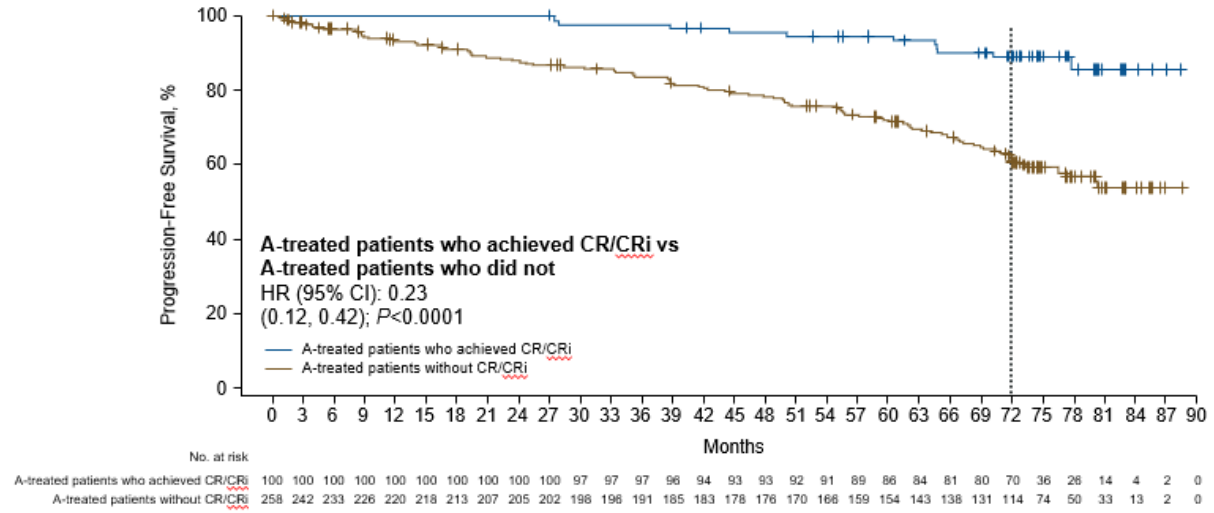
Should Obinutuzumab be included?

ORR improves over time in acalabrutinib-containing arms



- ORR and CR/CRi rates were significantly higher with A+O and A vs O+Clb ($P \leq 0.0499$ for both arms of the analyses)
- ORR and CR/CRi rates were significantly higher with A+O vs A ($P=0.022$ for both comparisons)

Acalabrutinib-treated patients who achieved CR/CRi had longer PFS



Sharman JP et al. ASH 2023; Abstract 636

ASH 2024

1868 A Phase II Study of Time-Limited Treatment with Acalabrutinib Plus Obinutuzumab in Patients with Treatment-Naïve Chronic Lymphocytic Leukemia

Program: Oral and Poster Abstracts

Session: 642. Chronic Lymphocytic Leukemia: Clinical and Epidemiological: Poster I

Hematology Disease Topics & Pathways:

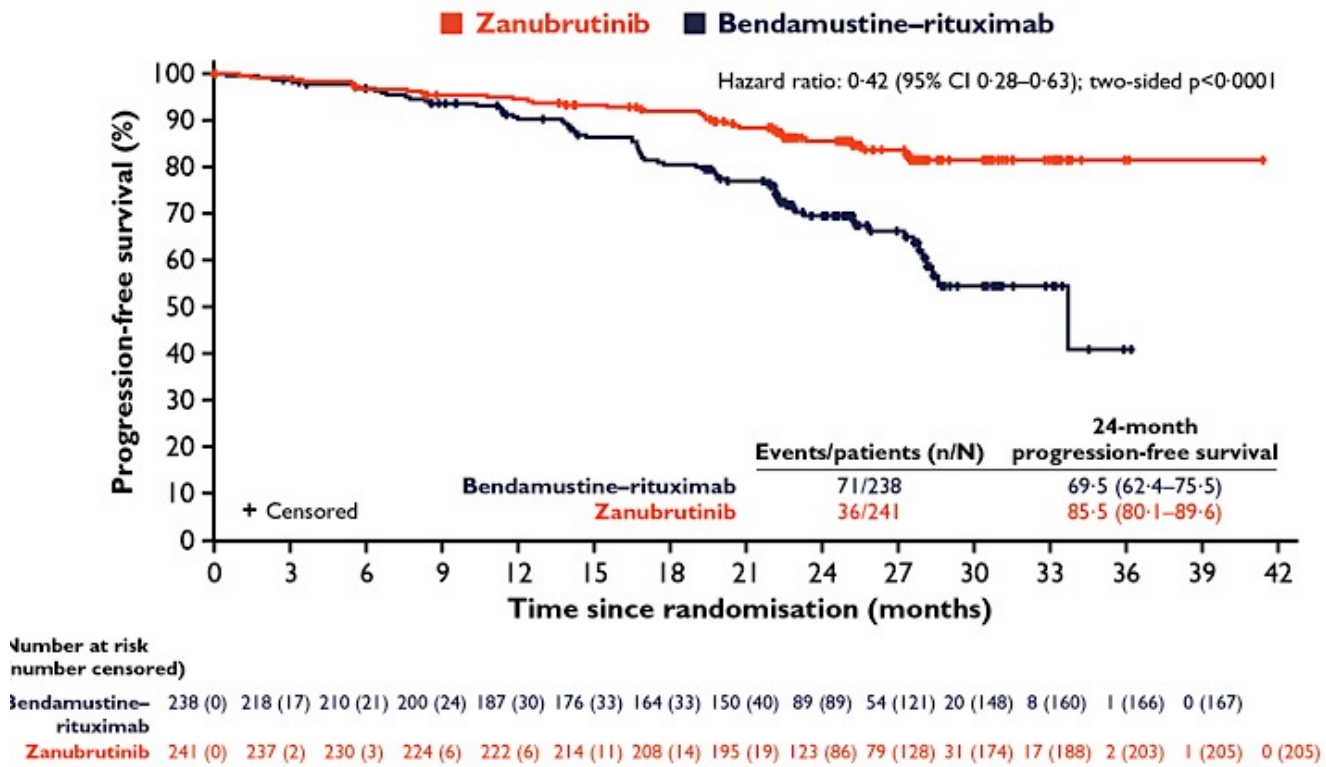
Lymphoid Leukemias, Combination therapy, CLL, Diseases, Treatment Considerations, Lymphoid Malignancies, Measurable Residual Disease

Saturday, December 7, 2024, 5:30 PM-7:30 PM

Jan A. Burger, MD, PhD [1], *Ekaterina Kim, PhD, MS*[1*], *Gitanjali Jayachandran, PhD*[2*], *Wanda Lopez, RN*[1*], *Ghayas C. Issa, MD*[1], *Musa Yilmaz, MD*[1*], *Mahesh Swaminathan, MD*[1], *Jo Ishizawa, MD, PhD*[1], *Alexandre Bazinet, MD*[1*], *Yesid Alvarado Valero, MD*[1], *Nitin Jain, MD*[1], *William G. Wierda*[1] *and Alessandra Ferrajoli, MD*[1]

Zanubrutinib

SEQUOIA – Arms A & B



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

Zanubrutinib

3249 Sustained Superiority of Zanubrutinib vs Bendamustine + Rituximab in Treatment-Naive Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma (TN CLL): 5-Year Follow-Up of Cohort 1 from the SEQUOIA Study

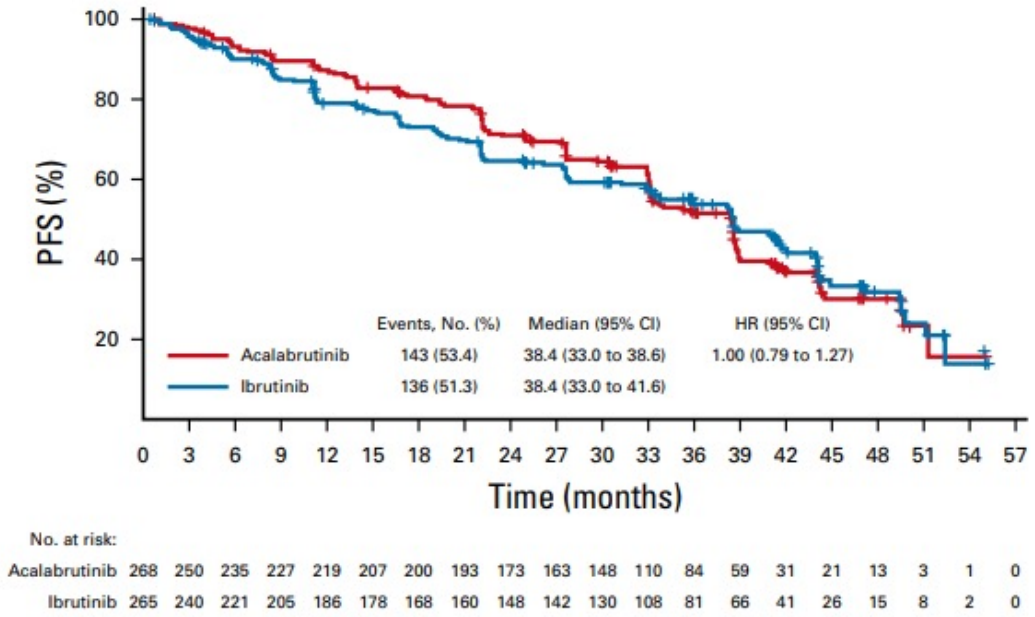
Program: Oral and Poster Abstracts
Session: 642. Chronic Lymphocytic Leukemia: Clinical and Epidemiological: Poster II
Hematology Disease Topics & Pathways:
Lymphoid Leukemias, Diseases, Lymphoid Malignancies

Sunday, December 8, 2024, 6:00 PM-8:00 PM

Mazyar Shadman, MD, MPH[1,2], *Talha Munir, MBBS, PhD*[3], *Tadeusz Robak*[4*], *Jennifer R. Brown, MD, PhD*[5], *Brad S. Kahl, MD*[6], *Paolo Ghia, MD, PhD*[7,8], *Tian Tian, PhD*[9*], *Andy Szeto*[9*], *Roman Korolkiewicz*[10*], *Constantine S. Tam*[11*] *and Wojciech Jurczak, MD, PhD*[12]

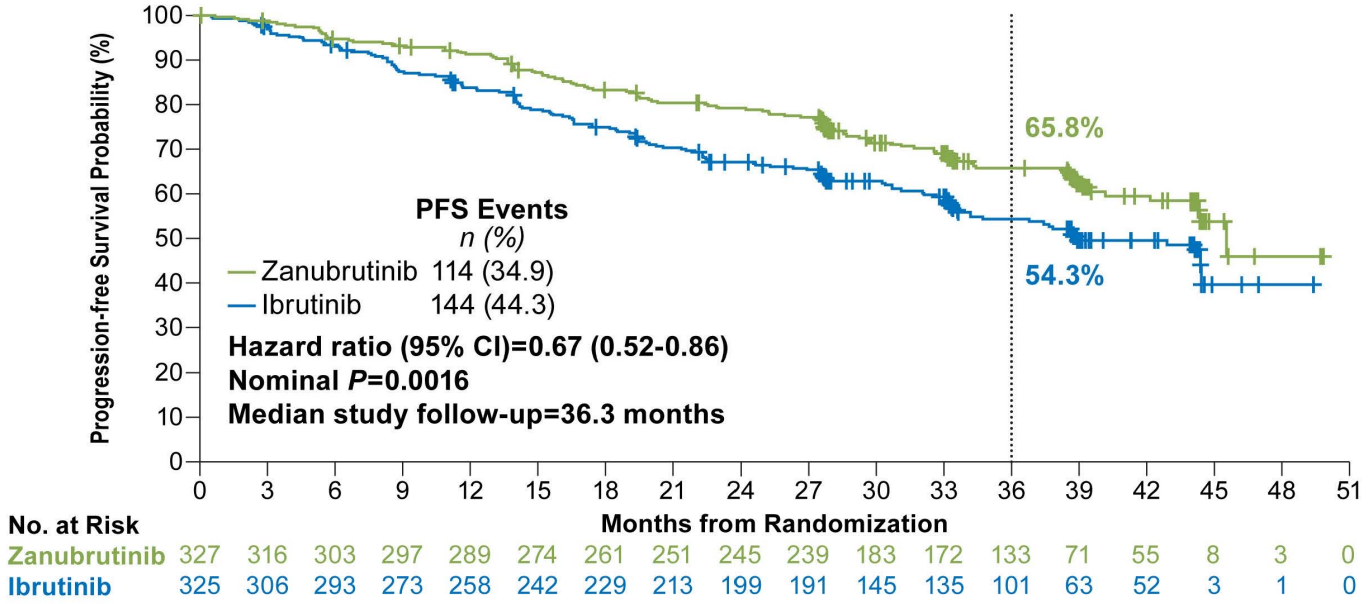
Selecting BTK agent

Acalabrutinib Versus Ibrutinib in Previously Treated Chronic Lymphocytic Leukemia: Results of the First Randomized Phase III Trial



Extended Follow-up of ALPINE Randomized Phase 3 Study Confirms Sustained Superior Progression-Free Survival of Zanubrutinib Versus Ibrutinib for Treatment of Relapsed/Refractory Chronic Lymphocytic Leukemia and Small Lymphocytic Lymphoma (R/R CLL/SLL)

Figure 1. Investigator-Assessed Progression-Free Survival (ITT Population)



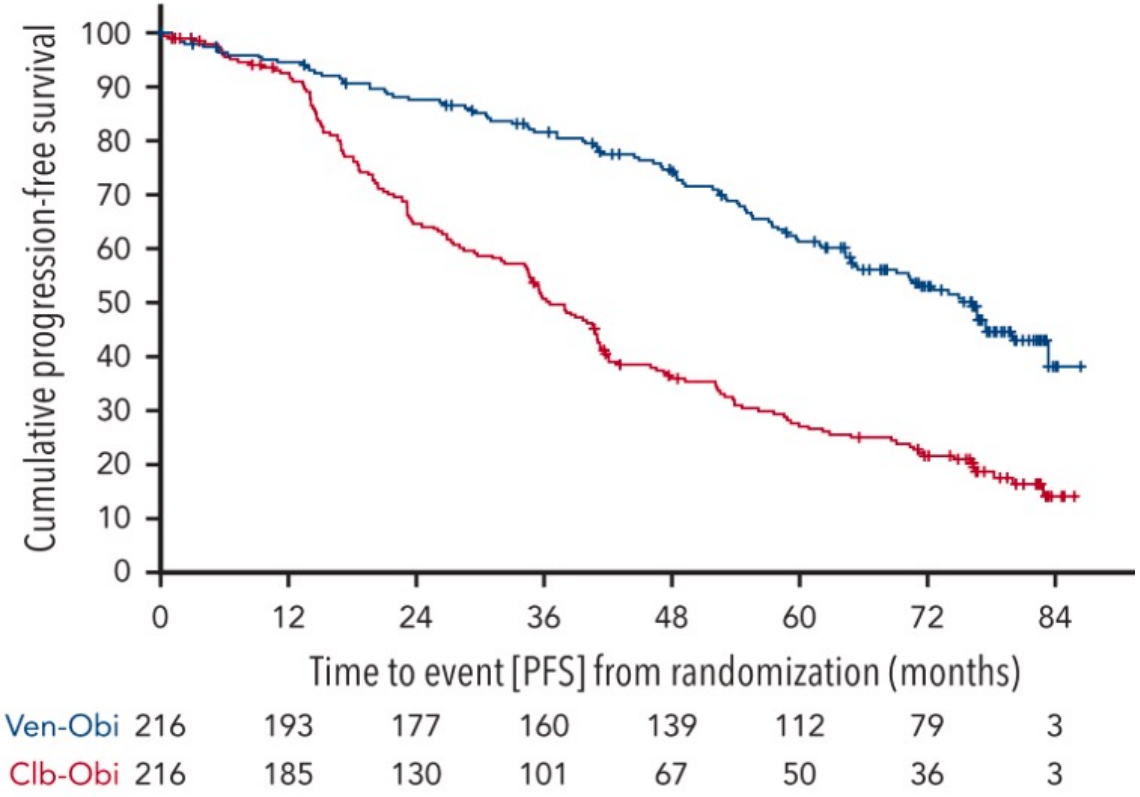
Byrd JC et al. *JCO* **39**, 3441-3452(2021).
Brown JR et al. ASH 2023; Abstract 202

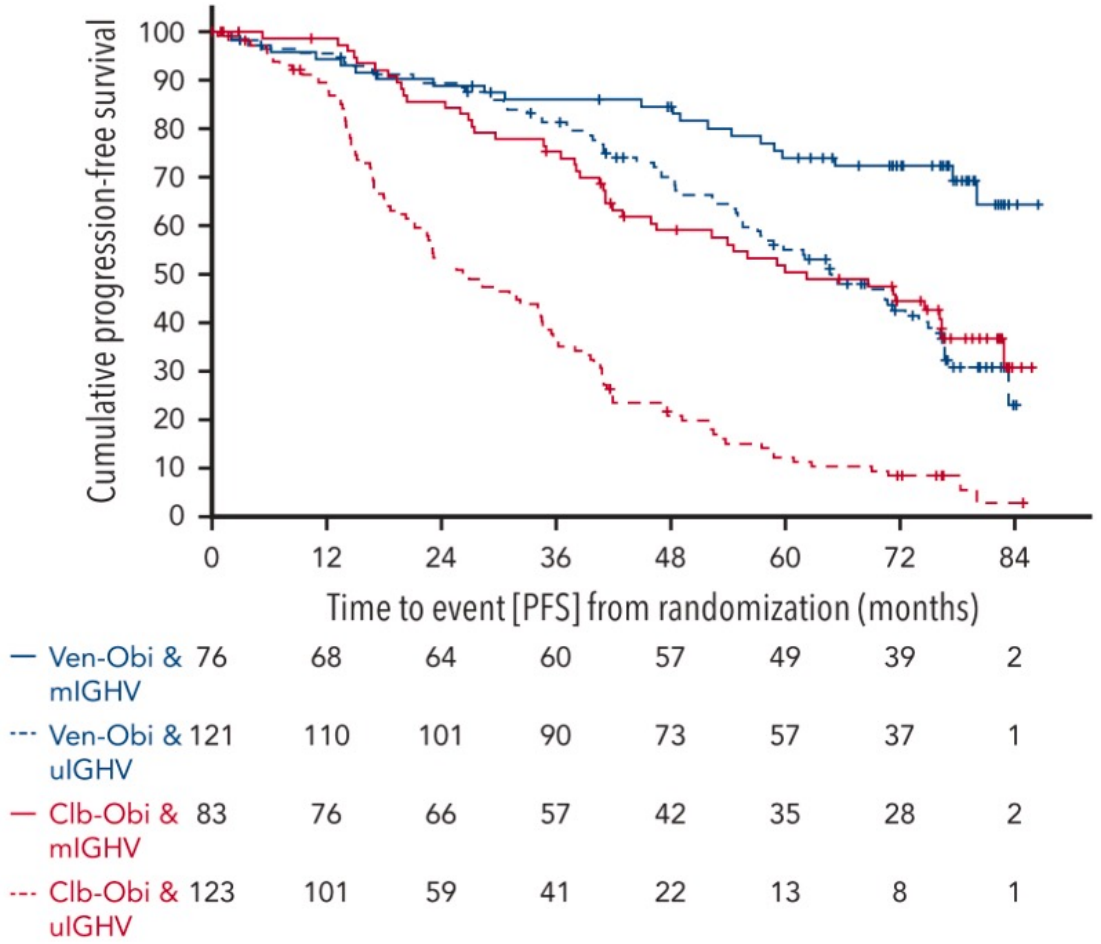
SUGGESTED TREATMENT REGIMENS[a,b,c,d]
CLL/SLL Without del(17p)/*TP53* Mutation
(alphabetical by category)

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

BCL-2 in Frontline CLL

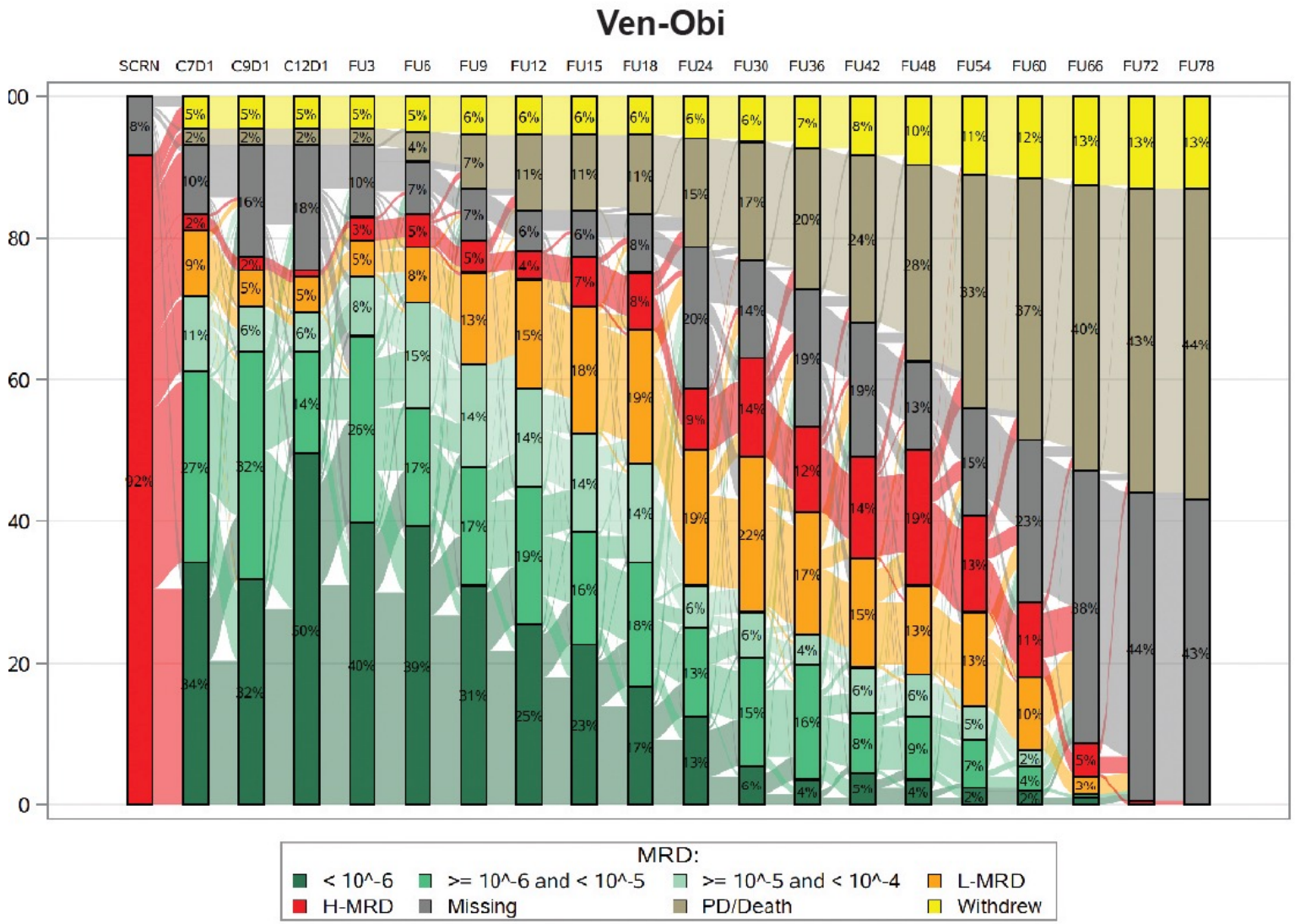
CLL-14 Study
Obi-Ven vs Obi-Clb





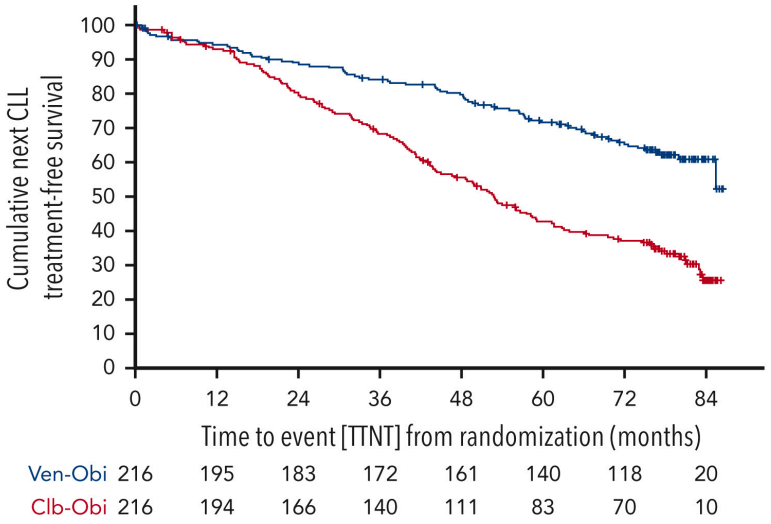
Al-Sawaf O et al. *Blood* (2024) 144 (18): 1924–1935.

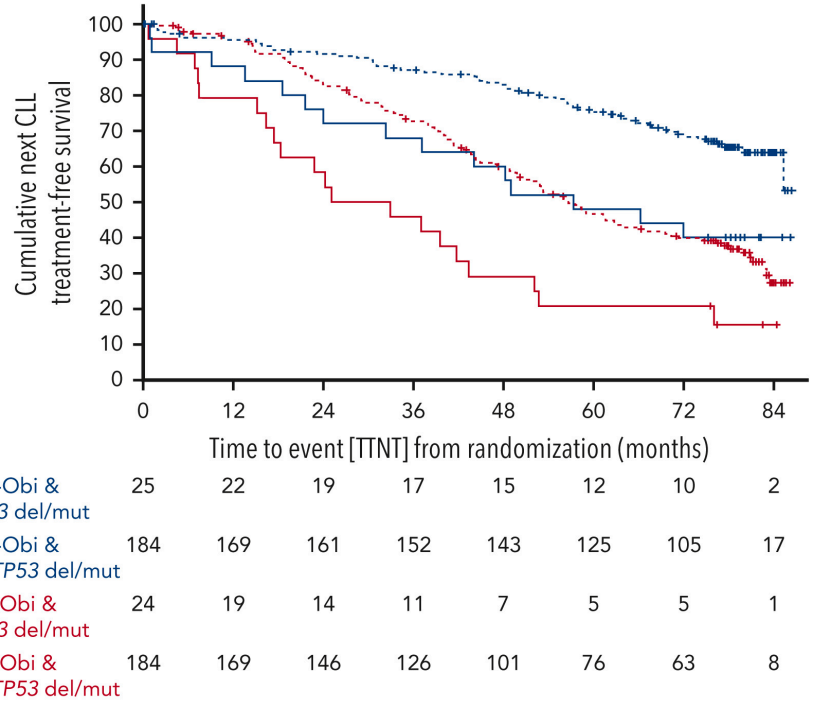
MRD following Obi-Ven



Al-Sawaf O et al. *Blood* (2024) 144 (18): 1924–1935.

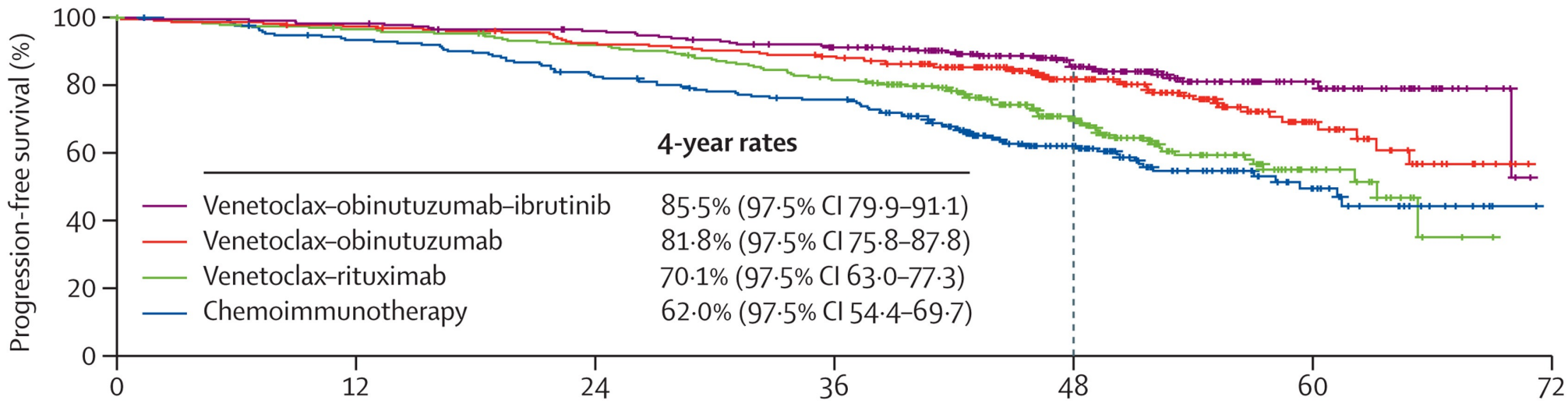
TTNT: Capturing the full benefit





Al-Sawaf O et al. *Blood* (2024) 144 (18): 1924–1935.

CLL-13: Young/Fit vs Intensive CIT



Number at risk (number censored)							
Chemoimmunotherapy	229 (0)	197 (18)	173 (19)	156 (22)	84 (68)	24 (117)	.. (..)
Venetoclax–rituximab	237 (0)	227 (2)	214 (4)	188 (6)	106 (67)	21 (135)	.. (..)
Venetoclax–obinutuzumab	229 (0)	222 (1)	209 (3)	198 (5)	121 (69)	32 (146)	.. (..)
Venetoclax–obinutuzumab–ibrutinib	231 (0)	227 (0)	218 (4)	201 (10)	130 (71)	44 (152)	.. (..)

Fürstenau M et al. Lancet Oncol. 2024 Jun;25(6):744-759.

Additional ASH 2024 Updates

3237 CRISTALLO: Results from a Phase III Trial of Venetoclax–Obinutuzumab Versus Fludarabine, Cyclophosphamide and Rituximab or Bendamustine–Rituximab in Patients with Untreated Chronic Lymphocytic Leukemia without Del(17p) or *TP53* Mutations

Program: Oral and Poster Abstracts
Session: 642. Chronic Lymphocytic Leukemia: Clinical and Epidemiological: Poster II
Hematology Disease Topics & Pathways:
Research, Lymphoid Leukemias, CLL, Clinical Research, Chronic Myeloid Malignancies, Diseases, Lymphoid Malignancies, Measurable Residual Disease

Sunday, December 8, 2024, 6:00 PM-8:00 PM

Jeff P. Sharman, MD[1], *Luca Laurenti, MD*[2*], *Emmanuelle Ferrant*[3*], *Luis Felipe Casado Montero*[4*], *Stephen P Mulligan*[5*], *Rosemary Harrup*[6*], *Stephen Opat*[7*], *Adalberto Ibatici*[8*], *Roberto Marasca*[9], *Paolo Sportoletti*[10*], *Marcus Lefebure*[11*], *Michelle Boyer*[12*], *Yanwen Jiang*[12*], *Simona Barlera*[13*], *Oscar Cazares*[12*] *and Franck Morschhauser, MD, PhD*[14]

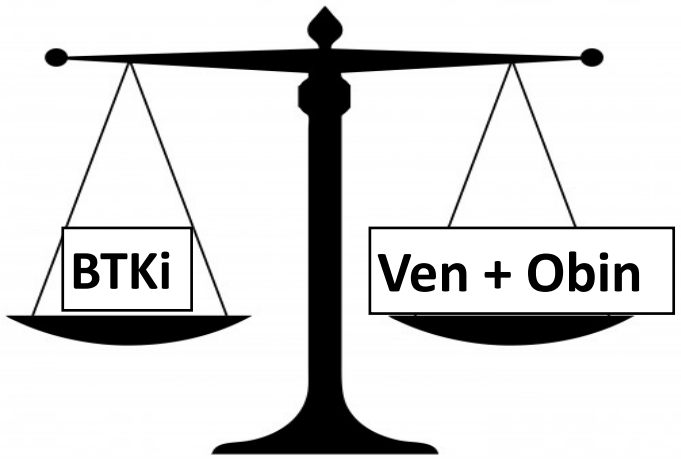
1010 Minimal Residual Disease (MRD)-Adapted Duration of Front-Line Venetoclax and Obinutuzumab Treatment for Fit Patients with Chronic Lymphocytic Leukemia (CLL)

Program: Oral and Poster Abstracts
Type: Oral
Session: 642. Chronic Lymphocytic Leukemia: Clinical and Epidemiological: Frontline Targeted Therapy Combinations
Hematology Disease Topics & Pathways:
Research, Clinical trials, Lymphoid Leukemias, Combination therapy, Adult, CLL, Clinical Research, Diseases, Treatment Considerations, Lymphoid Malignancies, Study Population, Human, Measurable Residual Disease

Monday, December 9, 2024: 4:45 PM

Lindsey Roeker, MD[1], *Anthony R. Mato, MD*[2*], *Andrew D. Zelenetz, MD, PhD*[3], *Jae H. Park, MD*[4], *Mark Blaine Geyer, MD*[1], *Andriy Derkach, PhD*[5*], *David Nemirovsky*[5*], *Prioty Islam, MD*[1*], *Lorenzo Falchi, MD*[6], *Maria Lia Palomba, MD*[3], *Anita Kumar, MD*[3], *Gilles Salles, MD, PhD*[3], *Jennifer Kimberly Lue, MD*[3], *Aaron D. Goldberg*[7], *Deborah M. Stephens, DO*[8], *Victoria Duffy*[6*], *Gail Panton*[6*], *Dianna Tyznar*[6*], *Colleen Dorsey*[6*], *Dhara Soni*[5*], *Claire Hutzler*[6*], *Lauren Nogan*[6*], *Alexandra Allen*[6*], *Tenzin Nyima*[6*], *Thu Quynh Nguyen, BSc*[9*], *Monica Shah, BA*[10*], *Tamotha R Cook*[8*], *Jennifer Abillar-Wright*[5*], *Jamila Brutus, NP*[6*], *Carissa Laudati, NP*[6*], *Bejal Kikani*[11*], *Catherine C Coombs, MD*[12*], *Michael R. Silvestrone*[6*], *Christopher E. Jensen*[8*], *Bita Fakhri, MD, MPH*[13] *and* ***Meghan C. Thompson, MD***[1]

Frontline BTKi vs. Ven + Obinutuzumab: Factors to Consider



- Convenience (no infusions, TLS monitoring)
- Long term efficacy data
- Phase 3 data compared to FCR and BR
- More data for efficacy of ven at time of ibrutinib progression

- Potential for 1-year time-limited therapy
- No known cardiac or bleeding risks
- Less concern for long term adherence
- Potential for cost-saving if 1-year of therapy is durable

Questions from General Medical Oncologists

- What would be your preferred initial regimen for an 80-year-old patient with IGHV-unmutated CLL and a TP53 mutation? What if the patient were 55 years old?
- How do you pick between zanubrutinib vs acalabrutinib?
- Is there a need for CD20 antibody with BTKi?
- Any reason to switch from ibrutinib in a responding patient?
- When should you expect normalization of lymphocytosis? If not normalized, any changes to treatment?

Questions from General Medical Oncologists

- 56 yo woman on acalabrutinib. Patient concerned about tripling of lymphocyte count. Is there a lymphocyte count that should not be exceeded?
- 68 yo man on ven/obin with CR. Is there a role for MRD evaluation at end of treatment? Can it be done with peripheral blood, or does it require bone marrow? Should it lead to treatment escalation/extension of treatment duration if positive?

Questions from General Medical Oncologists

- **Patient with CLL and hemolytic anemia and thrombocytopenia — rx with rituximab, relapsed and couldn't tolerate Ven+obin. Patient had cardiac comorbidities of Afib requiring anticoagulation. Started her on zanubrutinib with improvement in anemia. Do you normally use once-daily dosing or twice-daily dosing with zanubrutinib?**

Agenda

Module 1: Optimizing First-Line Therapy for Chronic Lymphocytic Leukemia (CLL) — Dr Sharman

Module 2: Emerging Role of Bruton Tyrosine Kinase (BTK) Inhibitors in Combination with Bcl-2 Inhibitors — Dr Rogers

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

Module 4: Integration of Noncovalent BTK Inhibitors into the Management of Relapsed/Refractory CLL — Dr Fakhri

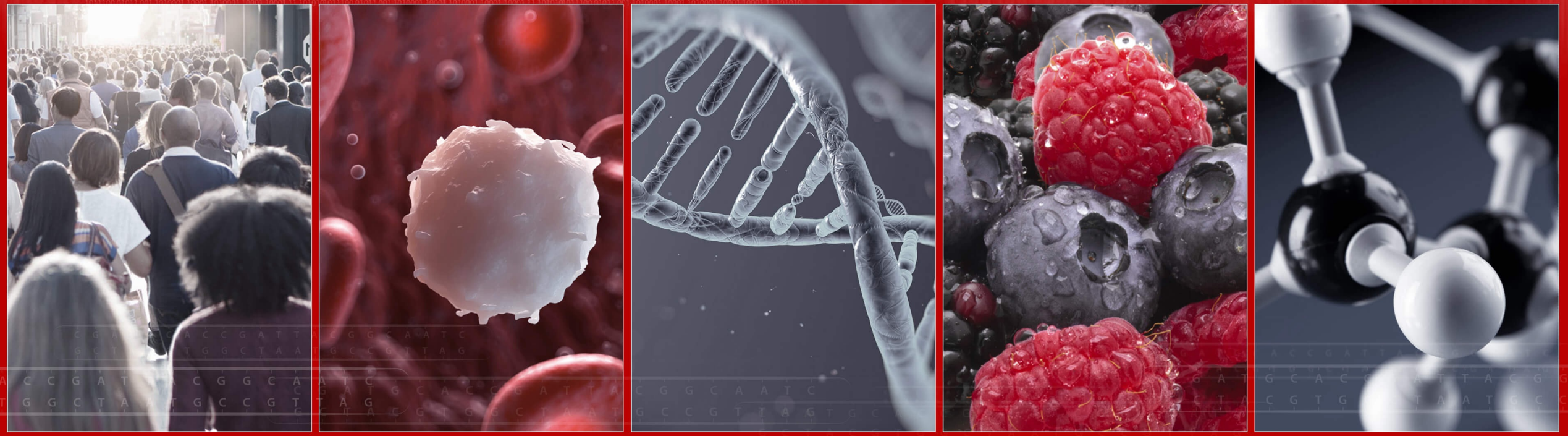
Module 5: Chimeric Antigen Receptor T-Cell Therapy and Other Novel Strategies for CLL — Dr Wierda

RTP
RESEARCH
TO PRACTICE

Emerging Role of BTK Inhibitors in Combination with BCL2 Inhibitors

Kerry A Rogers, MD
The Ohio State University

The James
THE OHIO STATE UNIVERSITY
COMPREHENSIVE CANCER CENTER



Rationale for Combining BTK and BCL2 Inhibitors

1. BTK inhibition sensitizes CLL cells to BCL2 inhibition by decreasing MCL1 and BCL-xL levels
2. Mitochondrial BCL2 dependence increases after BTK inhibitor treatment sensitizing CLL cells to BCL2 inhibition
3. Ibrutinib targets dividing cells and venetoclax targets resting cells, therefore the combination kills both CLL populations

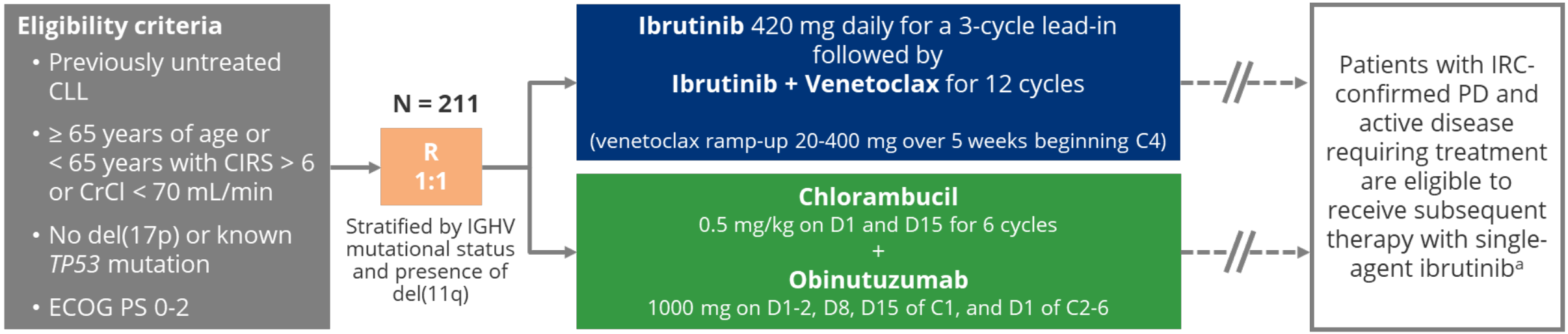
Based on this rationale combination studies were undertaken in CLL with high efficacy and safety

Anti-CD20 antibodies enhance efficacy when combined with other CLL therapies and therefore should be added too!

Cervantes-Gomez et at., CCR 2015; Deng et al., Leukemia 2017; Lu et al., Blood Ca Journal 2021

GLOW: Ibrutinib and Venetoclax (IV)

- Randomized phase 3 frontline trial in older or less fit patients
- Ibrutinib started for 3 cycles then venetoclax added for 12 more

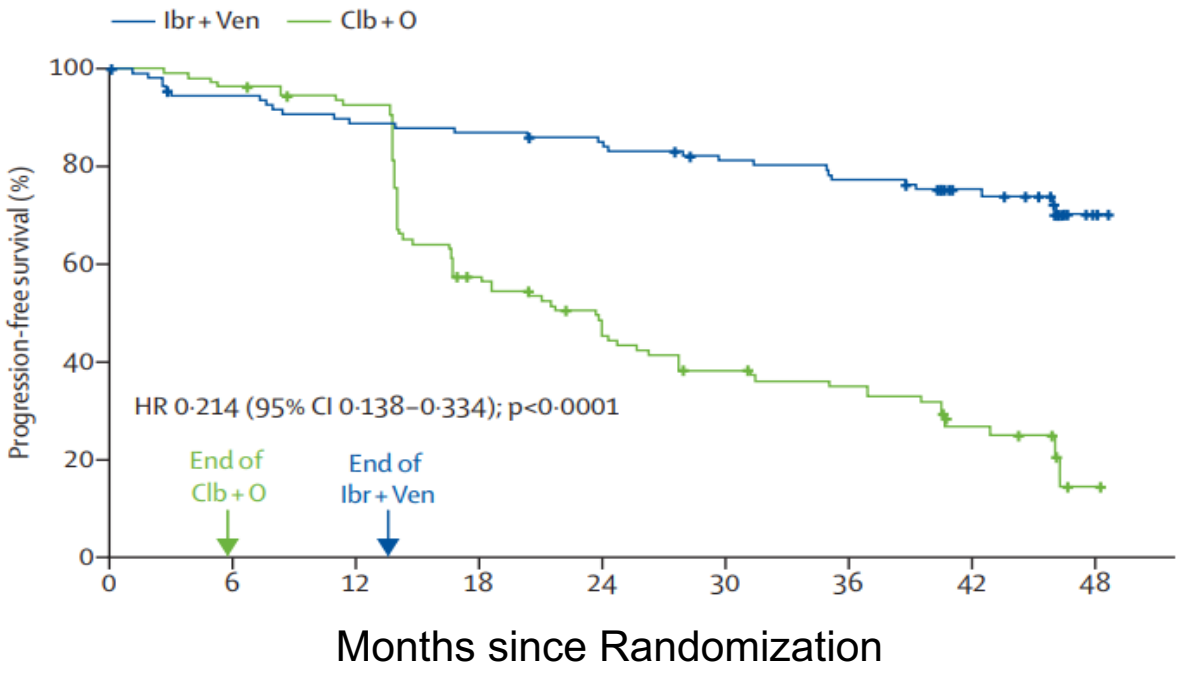


Niemann et al., ASH 2022

PFS with Ibrutinib and Venetoclax (IV) (GLOW)

- 60-month PFS for IV was 59.9% (median follow up of 54 months)
- PFS remains improved with IV vs O-Clb (HR 0.27, p < 0.0001)

Progression-Free Survival in GLOW



Niemann et al., Lancet Onc 2023, Niemann et al. ASH 2024 Abstract 1871 (Saturday, December 7, 2024, 5:30 PM-7:30 PM)

Ibrutinib, Venetoclax, and Obinutuzumab (IVO)

- Phase 2 study combining ibrutinib, venetoclax, and obinutuzumab
- Cohorts of treatment-naïve and relapsed/refractory CLL patients

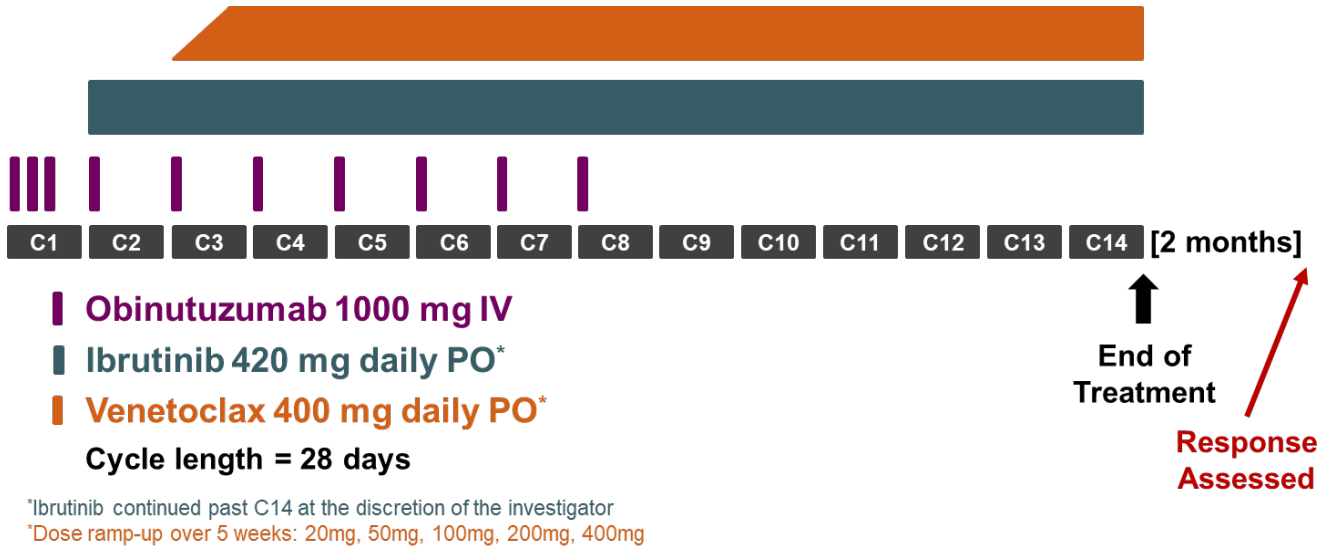
Cohorts

TN1: Phase 2 Treatment Naïve (n=25)
Completed accrual: November 16th, 2016
Median follow-up: 85.6 (10.3-91.1) months

RR: Phase 2 Relapsed/Refractory (n=25)
Completed accrual: April 5th, 2017
Median follow-up: 83.0 (0.2-89.7) months

TN2: Phase 2 Treatment Naïve (n=25)
Completed accrual: October 14th, 2019
Median follow-up: 51.7 (35.8-57.3) months

Study Treatment

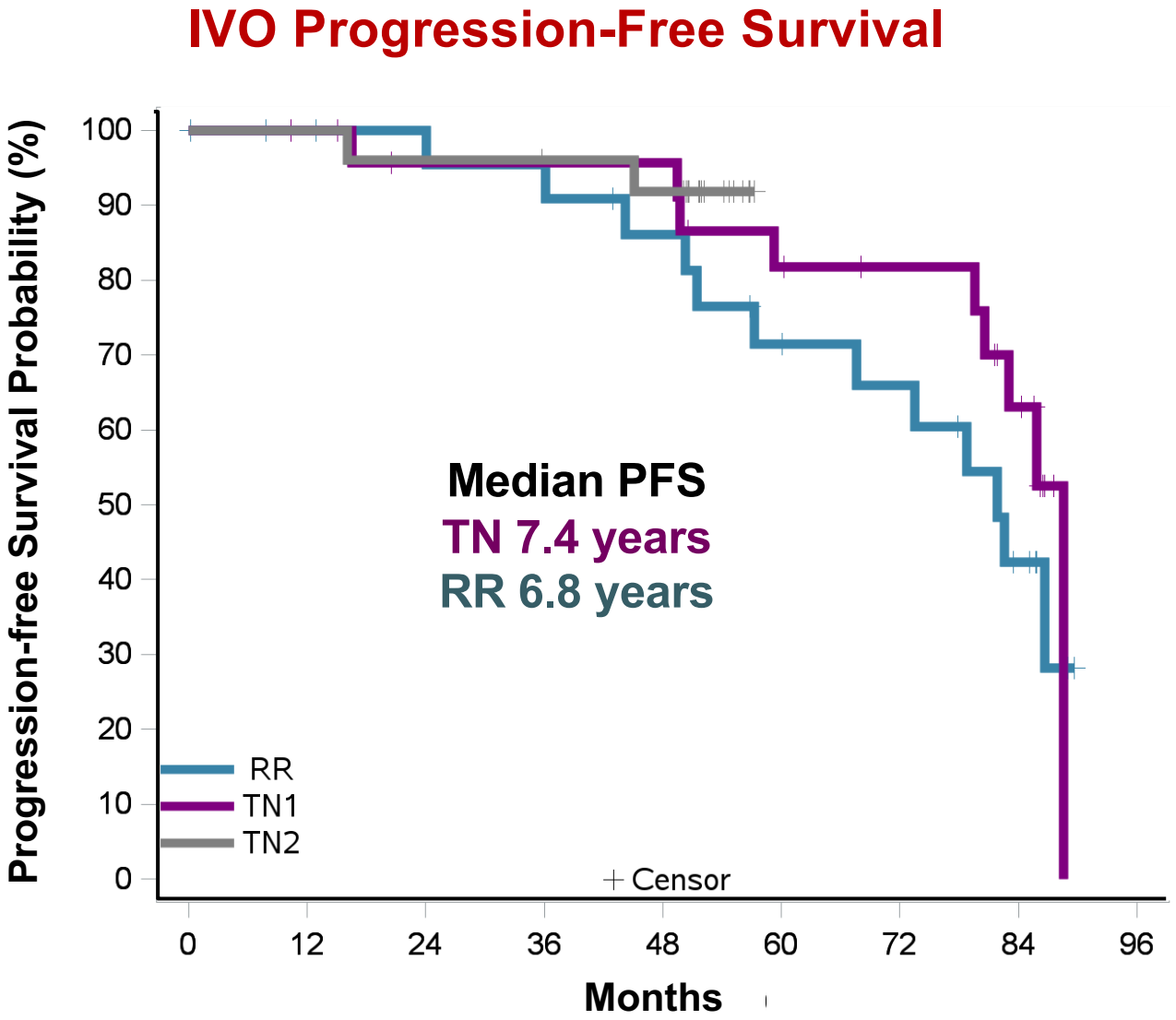


*Ibrutinib continued past C14 at the discretion of the investigator
*Dose ramp-up over 5 weeks: 20mg, 50mg, 100mg, 200mg, 400mg

Rogers et al., EHA 2024

PFS after IVO in a Phase 2 Study

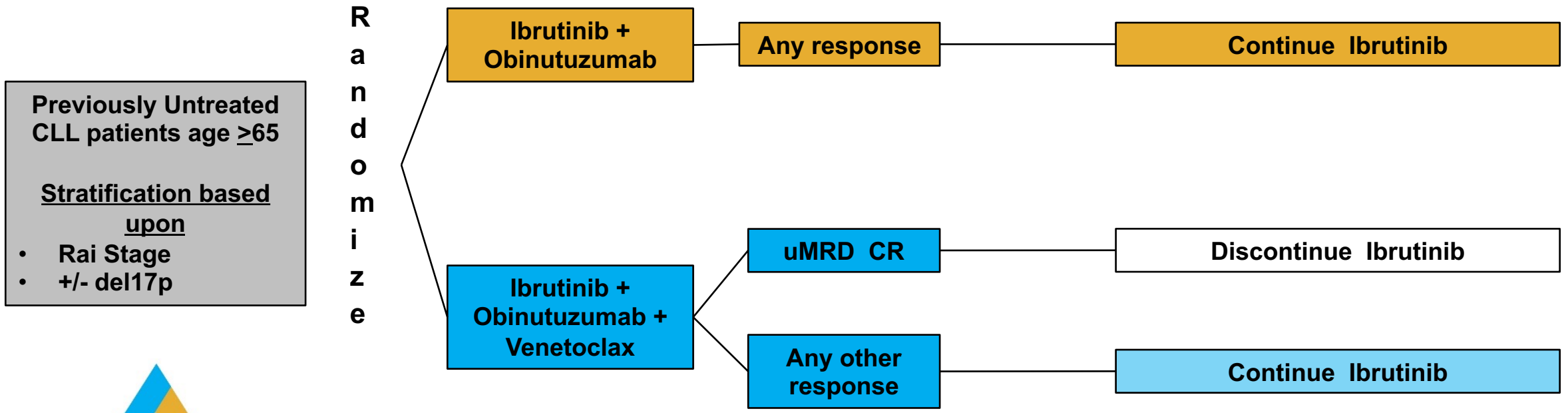
- Median PFS for **TN1** was **88.5 months** (95% CI 80.6-NR)
- Median PFS for **RR** was **81.8 months** (95% CI 57.3-NR)
- For **TN2** the median PFS was **not reached**



Rogers et al., EHA 2024

A041702: Phase 3 Study of IO vs IVO

- Cooperative group study in older CLL patients
- Primary endpoint is PFS and powered for superiority



ALLIANCE FOR CLINICAL TRIALS IN ONCOLOGY

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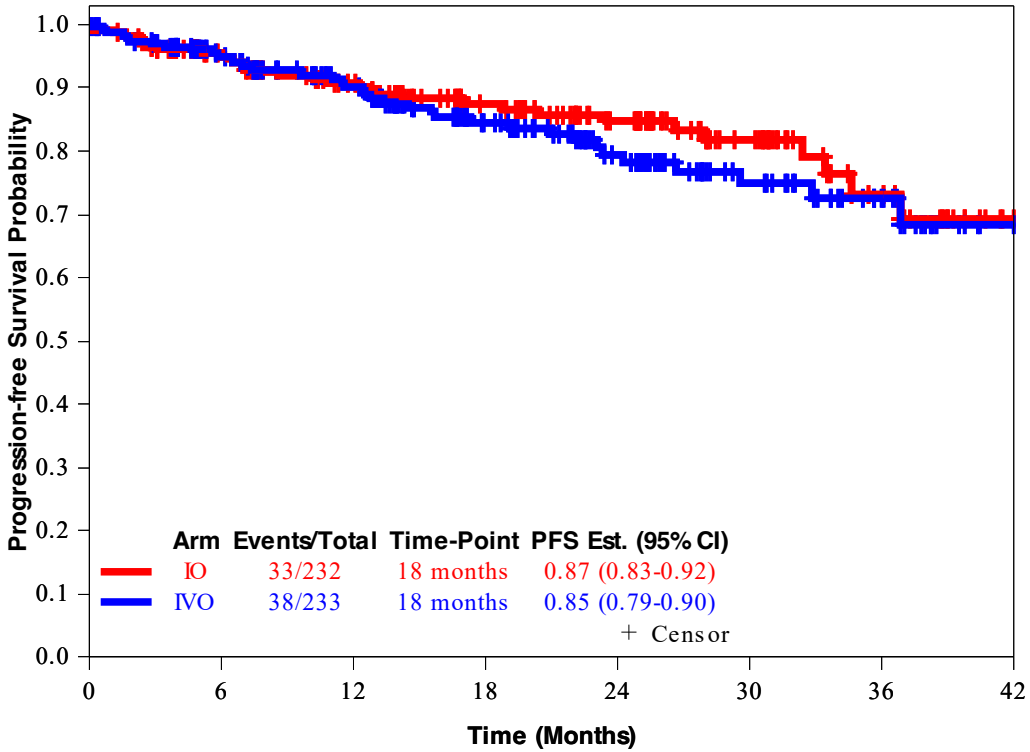
Woyach et al., ASCO 2023

PFS with IVO vs IO (A041702)

- Study reached futility for the primary endpoint of PFS (superiority)
- A similar study in younger patients is ongoing (EA9161)

PFS: IO vs IVO



IVO vs I0:
Hazard Ratio 1.12
95% CI: 0.70-1.79

Woyach et al., ASCO 2023

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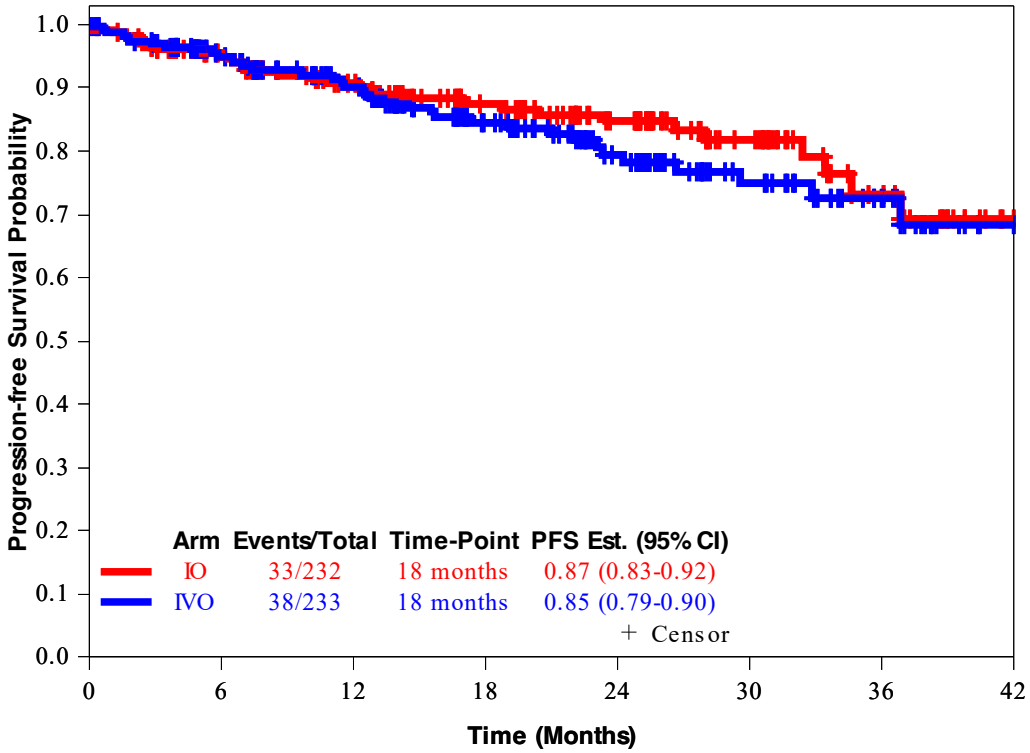
Comprehensive Cancer Center

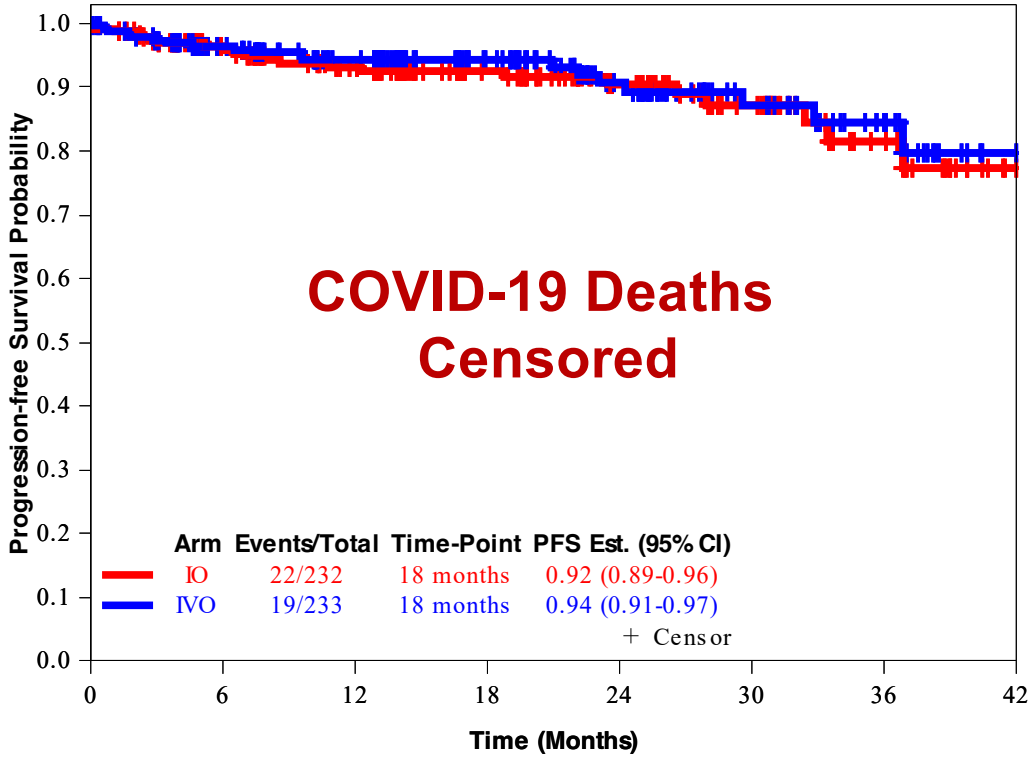
PFS with IVO vs IO Censoring COVID-19 Deaths

- PFS curves are closer after censoring of COVID-19 deaths
- COVID may have had a bigger impact on older patients

PFS: IO vs IVO



PFS: IO vs IVO

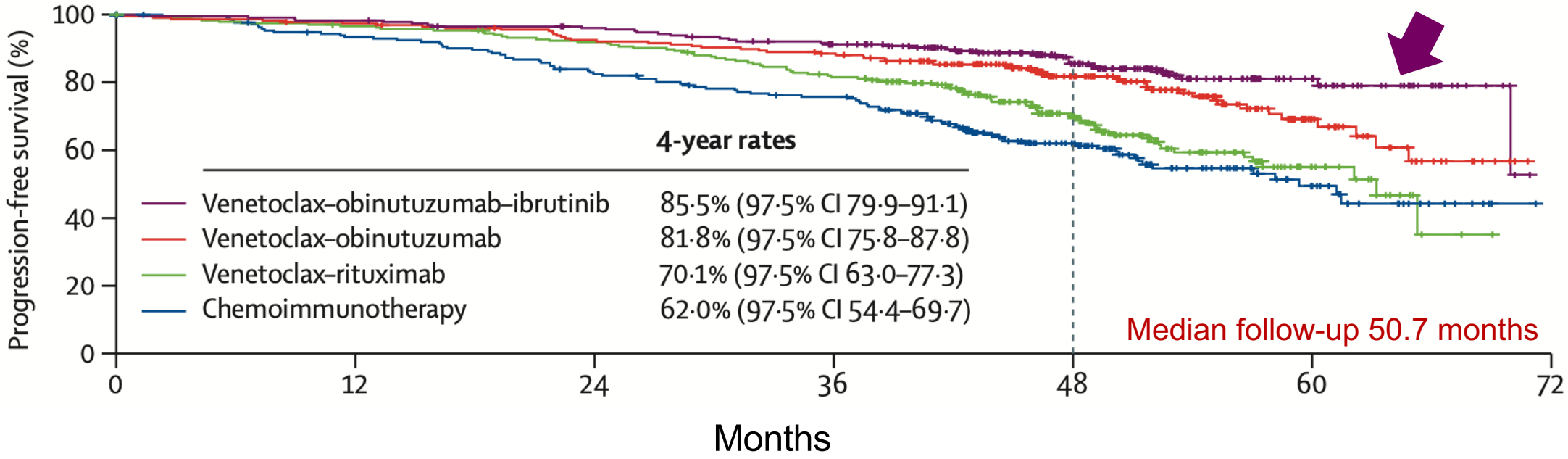


Woyach et al., ASCO 2023

Venetoclax Regimens in Fit Patients (CLL13)

- VO and IVO had better PFS than CIT
- IGHV unmutated CLL patients had a significantly longer PFS with IVO compared to VO (HR 0.58, p=0.025)

PFS with Venetoclax Combinations vs CIT (FCR/BR)



Furstenau et al., Lancet Onc 2024

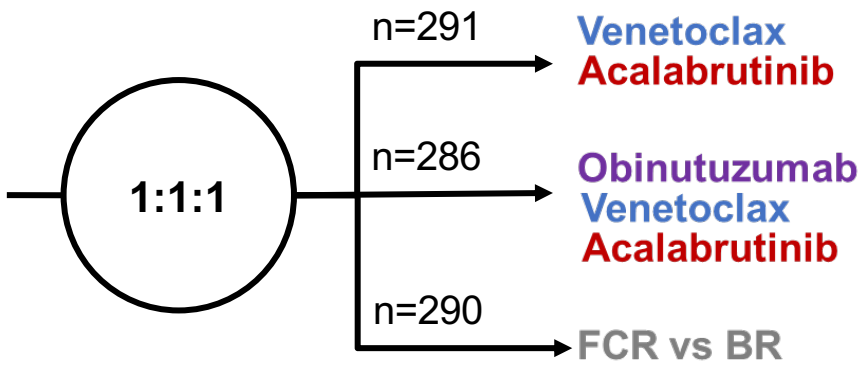
Phase 3 Study of FCR/BR vs AV vs AVO (AMPLIFY)

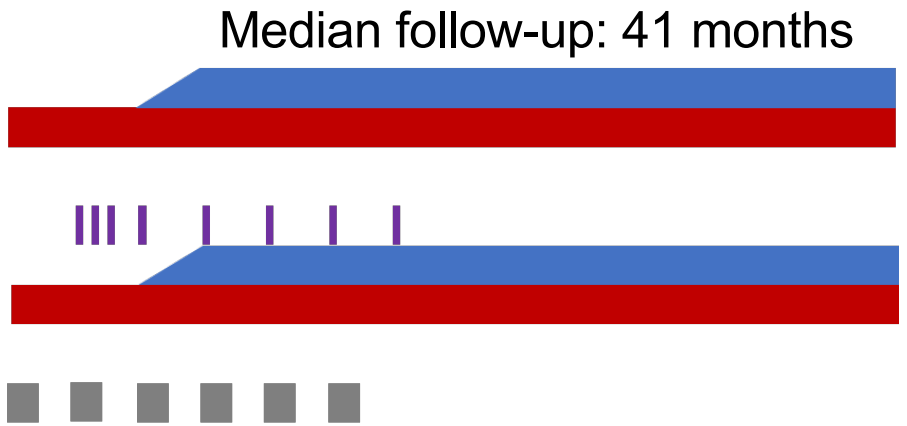
- Randomized phase 3 study comparing acalabrutinib + venetoclax +/- obinutuzumab to investigators choice of FCR or BR
- Primary endpoint: PFS of AV vs FCR/BR
- Secondary Endpoints: PFS of AVO vs FCR/BR, uMRD (10^{-4} cutoff) rate assessed in peripheral blood, and overall survival

Patients with TN CLL (n=867)

- Median age: 61
- Men: 64.5%
- IGHV unmutated: 58.6%

(with and without del(17p) and TP53 mutation allowed)





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Brown et al., ASH 2024 Abstract 1009. (Monday, December 9, 2024: 4:30 PM)

Phase 3 Study of FCR/BR vs AV vs AVO (AMPLIFY)

- PFS was improved with AV (HR 0.65, p=0.0038) and AVO (0.42, p<0.0001) compared to FCR/BR
- AVO may result in improved disease control over AV, but this must be weighted against increased toxicity

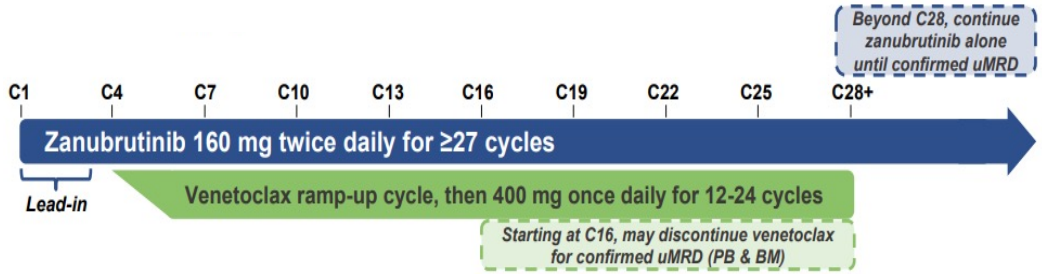
Treatment Arm	Median PFS	Est. 36-month PFS	Overall Response Rate	Deaths	COVID Deaths	Grade ≥3 Neutropenia
AV	Not reached	76.5%	92.8%	18	10	26.8%
AVO	Not reached	83.1%	92.7%	37	25	35.2%
FCR/BR	47.6 months	66.5%	75.2%	42	21	32.4%

Brown et al., ASH 2024 Abstract 1009. (Monday, December 9, 2024: 4:30 PM)

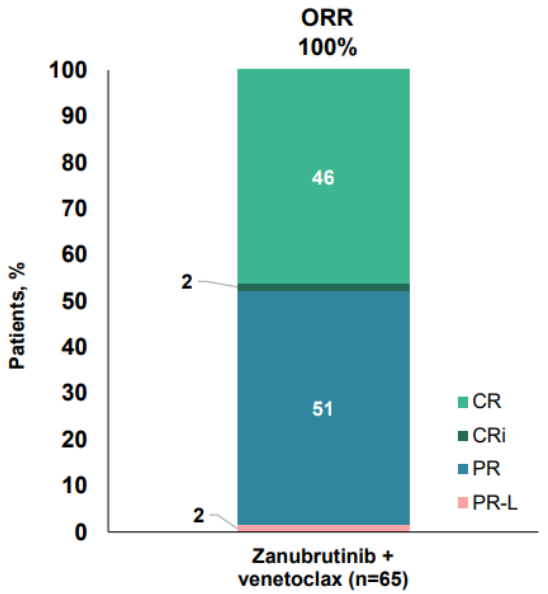
Zanubrutinib and Venetoclax (ZV) (SEQUOIA arm D)

- Non-randomized arm of a phase 3 study for treatment-naïve patients with del(17p) and/or TP53 mutations (n=66)
- The ORR was 100% with a best uMRD rate of 59% in the blood
- The estimated 24-month PFS was 94%

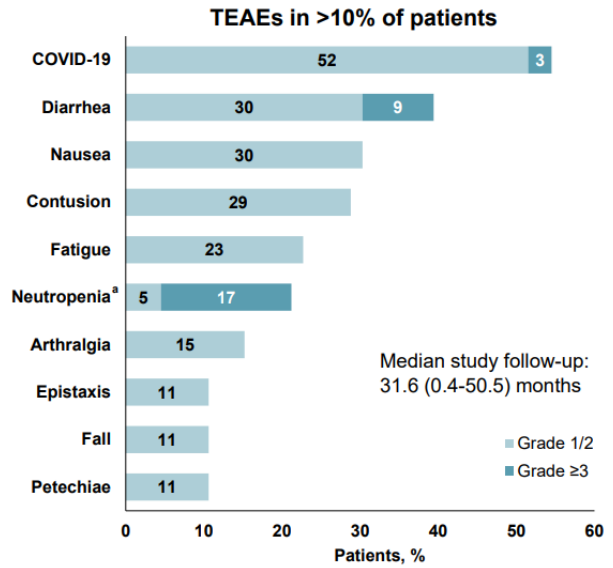
Study Treatment



Overall Responses



TEAEs (in >10%)



[a] Neutropenia combines preferred terms *neutrophil count decreased* and *neutropenia*.

Ma et al., EHA 2024

Zanubrutinib and Venetoclax (ZV) in RR CLL

- Study of ZV in different populations of previously treated CLL patients based on exposure and resistance
- Median follow up of 9 months for 26 patients showed a response rate of 95% with no difference across cohorts

Study Cohorts

Cohort A:
BTK and BCL2 Inhibitor Naïve
(n=13)

Cohort B:
BTK and/or BCL2 Inhibitor Exposed
(n=12)

Cohort C:
Progressed on covalent BTK inhibitor
(n=1)

Study Treatment

- Fixed-duration of 15 cycles of ZV
  - Zanubrutinib 160 mg BID began on C1D1
  - Venetoclax with standard 5-week dose ramp-up starting on C4D1 for Cohorts A and B and on C2D1 for Cohort C
- ZV stopped ZV after C15 regardless of clinical response or MRD

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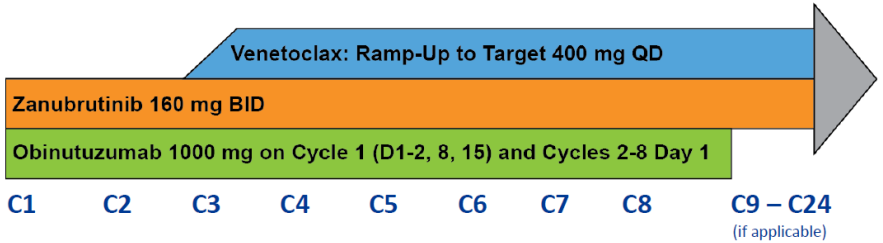
Ahn et al., ASH 2024 Abstract 1874. (Saturday, December 7, 2024, 5:30 PM-7:30 PM)

BOVen: Phase 2 Study of ZVO

- Treatment-naïve CLL patients (n=52) with provision for re-treatment
- At a median follow up of 57 months, 46 patients met criteria to stop treatment and median MRD-free survival was 34 months
- 12 patients were re-treated for progression with an ORR of 92%

BOVen Study Diagram

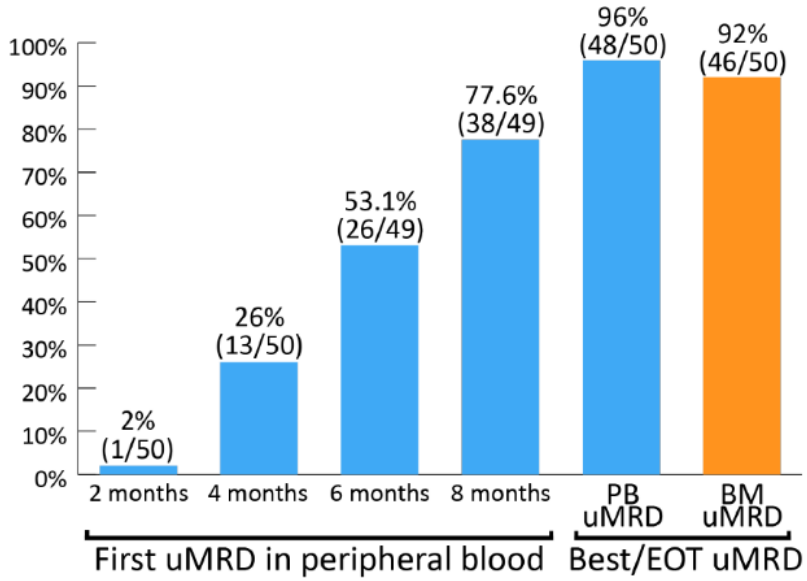
Key eligibility criteria
Previously untreated CLL/SLL
Requires treatment (iwCLL guidelines)
ECOG 0-2
ANC ≥1,000, PLT count ≥75 (unless due to CLL)
Warfarin and dual antiplatelet excluded



Treatment duration / MRD-directed treatment discontinuation criteria

- Treatment duration: Min 8 months to Max 24 months (including 2-month doublet lead-in prior to venetoclax)
- Peripheral blood MRD (flow cytometry) assessed every 2 cycles
  - If PB uMRD $<10^{-4}$ (flow), then BM MRD assessment within 14 days
  - If PB and BM uMRD $<10^{-4}$ (flow), then repeat PB MRD assessment after 2 additional cycles
  - If PB x 2 (consecutively) and BM uMRD $<10^{-4}$ (primary endpoint), treatment is discontinued

BOVen MRD Outcomes

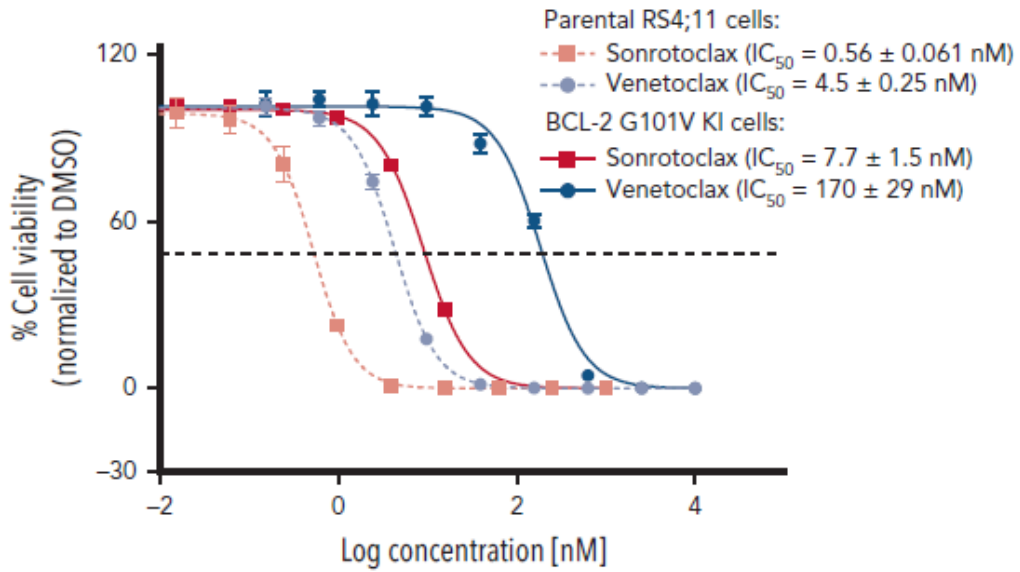


Soumerai et al., ICML 2023; Soumerai et al., ASH 2024 Abstract 1867.
(Saturday, December 7, 2024, 5:30 PM-7:30 PM)

The BCL2 Inhibitor Sonrotoclax

- Potent and selective BCL2 inhibitor with activity against BCL-xL
- Effective in cells with venetoclax resistance (BCL2 G101V)

Viability in the parental RS4;11 and G101V KI Cells



Measured IC50 values

Protein	BCL2	BCL-xL
IC_{50} (nM) of sonrotoclax	0.014 ± 0.0021	28 ± 3.6
IC_{50} (nM) of venetoclax	0.20 ± 0.015	65 ± 9.1

Liu et al., Blood 2024

Phase 1/1b of Zanubrutinib and Sonrotoclax (ZS)

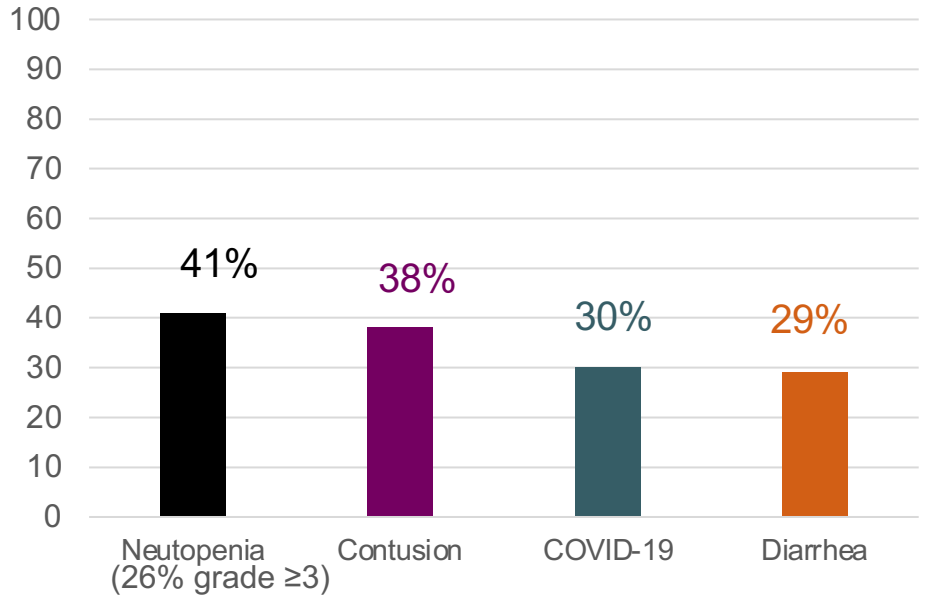
- Treatment-naïve patients received zanubrutinib for 8-12 weeks then sonrotoclax with ramp-up to 160 mg or 320 mg daily
- At 18.3 months median follow up there was 1 PFS event (160 mg)

Efficacy Measures

Sonrotoclax Dose	Complete Remission[1]	uMRD at 24 months[2]	uMRD at 48 months[2]
160 mg (n=51)	41%	61% (31/51)	79% (27/34)
320 mg (n=61)	42%	77% (43/56)	90% (43/48)

[1]ORR was 100% (n=108 evaluable) [2]uMRD at $1x10^{-4}$
Median follow-up = 18.3 months.

Most Frequent Adverse Events



Soumerai et al., ASH 2024 Abstract 1012. (Monday, December 9, 2024: 5:15 PM)

Phase 3 BTK and BCL2 Inhibitor Studies (Unreported)

Study	Regimens Compared	Patient Population	Primary Endpoint
NCT03701282 EA9161	• Ibrutinib + Obinutuzumab (IO) • Ibrutinib + Venetoclax + Obinutuzumab (IVO)	• Treatment-naïve CLL • Age <70 years-old	PFS
NCT04608318 CLL17	• Ibrutinib (I) • Venetoclax + Obinutuzumab (IO) • Ibrutinib + Venetoclax (IV)	• Treatment-naïve CLL	PFS
NCT05057494 MAJIC	• Acalabrutinib + Venetoclax (AV) • Acalabrutinib + Obinutuzumab (AO)	• Treatment-naïve CLL	PFS
NCT05197192	• Acalabrutinib + Venetoclax + Obinutuzumab (AVO) • Venetoclax + Obinutuzumab (VO)	• Treatment-Naïve CLL • TP53 aberration or CK	PFS
NCT06319456	• Acalabrutinib + Lisaftoclax (AL) • Chemoimmunotherapy (CIT)	• Treatment-naïve CLL	PFS
NCT06073821 CELESTIAL-TNCLL	• Zanubrutinib + Sonrotoclax (ZS) • Venetoclax + Obinutuzumab (VO)	• Treatment-naïve CLL	PFS
NCT04965493 BRUIN CLL-322	• Pirtobrutinib + Venetoclax + Rituximab (PVR) • Venetoclax + Rituximab (VR)	• Relapsed/Refractory CLL	PFS
NCT05947851 BELLWAVE-010	• Nemtabrutinib + Venetoclax (NV) • Venetoclax + Rituximab (VR)	• Relapsed/Refractory CLL	PFS

Clinicaltrials.gov

Questions from General Medical Oncologists

- What would you most likely recommend for a patient with newly diagnosed IGHV-unmutated CLL with normal cytogenetics who prefers time-limited treatment? What if the patient had IGHV-mutated disease? How would patient age affect this decision?
- If you could access first-line acalabrutinib and venetoclax (as per the Phase III AMPLIFY trial), for which patients would you most likely use it? In which situations, if any, would you also add obinutuzumab?

Questions from General Medical Oncologists

- A 63-year-old woman with trisomy 12, unmutated IGHV, bulky nodes up to 20 cm in the abdomen, WBC 22K, started acalabrutinib for 3 months with intent to add venetoclax, but she is in CR even as early as 1 month on acalabrutinib. What are the panel's thoughts?
- How often do patients develop resistance mutations on combination regimens? Can we re-use the same or other drugs in the class in a later line of therapy?

Agenda

Module 1: Optimizing First-Line Therapy for Chronic Lymphocytic Leukemia (CLL) — Dr Sharman

Module 2: Emerging Role of Bruton Tyrosine Kinase (BTK) Inhibitors in Combination with Bcl-2 Inhibitors — Dr Rogers

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

Module 4: Integration of Noncovalent BTK Inhibitors into the Management of Relapsed/Refractory CLL — Dr Fakhri

Module 5: Chimeric Antigen Receptor T-Cell Therapy and Other Novel Strategies for CLL — Dr Wierda

RTP
RESEARCH
TO PRACTICE

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

UT Southwestern
Harold C. Simmons
Comprehensive Cancer Center

Safety Issues

BTK Inhibitors

Ibrutinib/BTKi related toxicities of interest

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

Shanafelt TD et al. Blood. 2022;140:112

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

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

TRAEs = Treatment related adverse events

1. Shanafelt TD et al. Blood. 2022;140:112.
2. Woyach JA et al. NEJM. 2018;379:2517.

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

ELEVATE-TN – Safety Analysis

5- Year Follow-Up

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

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

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

Sharman JP et al, Lancet. 2020:395:1278-91

SEQUOIA – Safety Analysis

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

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

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

Safety Profile of Pirtobrutinib in Patients With CLL/SLL (AEs of Special Interest)

Event	Adverse Events (n = 317)		Treatment-Related Adverse Events (n = 317)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
	Number of patients, %			
Atrial fibrillation or flutter	12 (3.8)	4 (1.3)	4 (1.3)	1 (0.3)
Bleeding	135 (42.6)	7 (2.2)	75 (23.7)	3 (0.9)
Bruising	96 (30.3)	0	62 (19.6)	0
Hemorrhage	67 (21.1)	7 (2.2)	22 (6.9)	3 (0.9)
Hypertension	45 (14.2)	11 (3.5)	12 (3.8)	1 (0.3)
Infections	225 (71)	89 (28.1)	39 (12.3)	12 (3.8)
Neutropenia	103 (32.5)	85 (26.8)	62 (19.6)	47 (14.8)

ncBTKi = non-covalent BTK inhibitor.

1. Mato A et al. *N Engl J Med.* 2023;389:33-44.

Safety Profile of Nemtabrutinib in Patients With CLL/SLL (AEs of Special Interest)

AEs of Special Interest in ≥5 Patients	All Patients at 65 mg Every Day (N = 112)
Hypertension	34 (30)
Arthralgia	22 (20)
Rash maculopapular	16 (14)
Pneumonia	16 (14)
Rash	14 (13)
Upper respiratory tract infection	13 (12)
Cellulitis	8 (7)
Urinary tract infection	8 (7)
Sinusitis	8 (7)
Sepsis	6 (5)
Atrial fibrillation	5 (4)
COVID-19	5 (4)
Oral candidiasis	5 (4)
Rhinovirus infection	5 (4)

1. Woyach J et al. EHA 2023. Abstract P628.

ELEVATE-RR: Acalabrutinib vs Ibrutinib

Comparison of Adverse Events

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

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

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

ALPINE: Events of Clinical Toxicity Interest

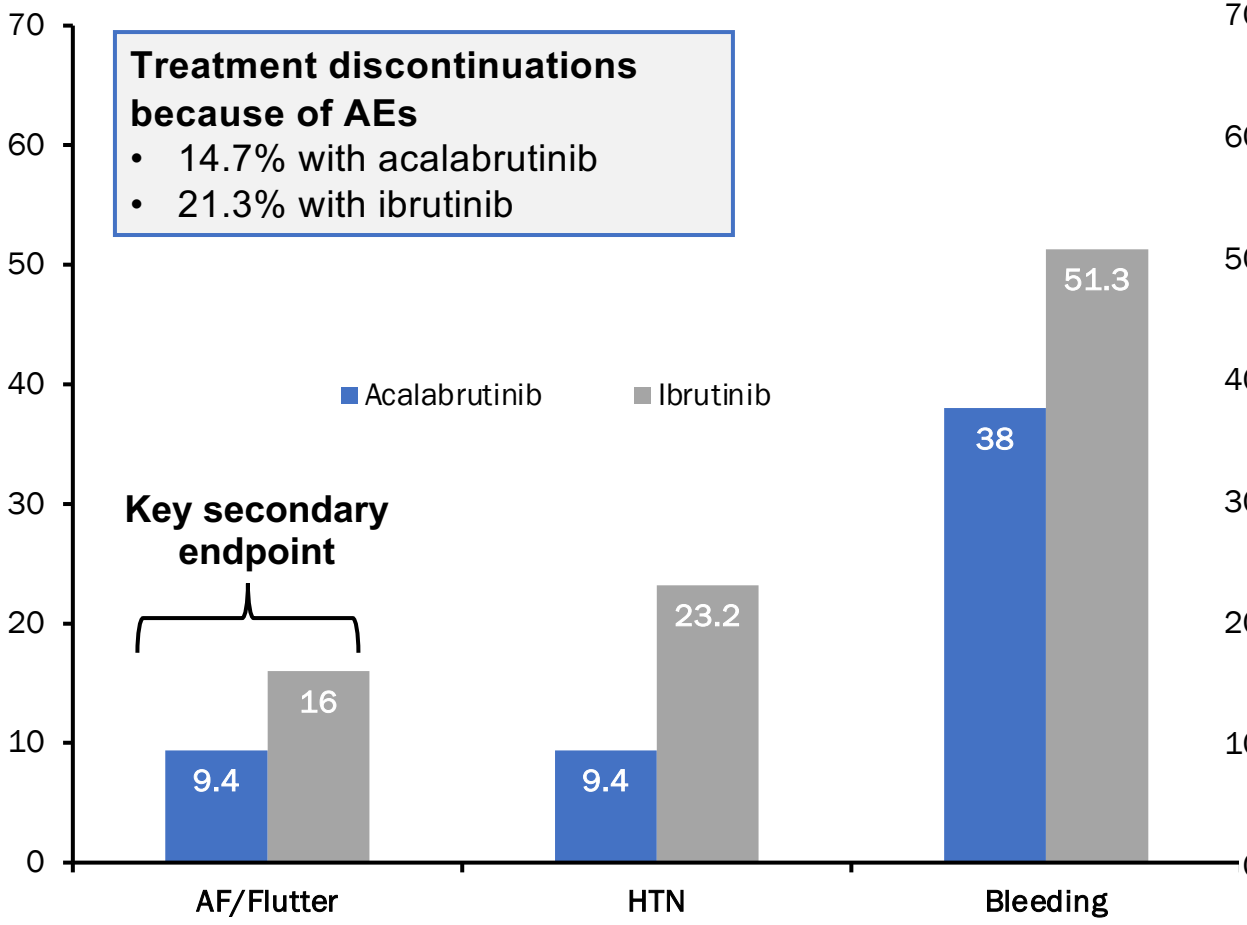
Safety analysis population	Zanubrutinib (n=324), n (%)		Ibrutinib (n=324), n (%)	
	Any grade	Grade ≥ 3	Any grade	Grade ≥ 3
Cardiac disorders[a]	1 (0.3)		14 (4.3)	
Atrial fibrillation and flutter (key 2º endpoint)	**17 (5.2)**	**8 (2.5)**	**43 (13.3)**	**13 (4.0)**
Hemorrhage Major hemorrhage[b]	137 (42.3)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

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

Acalabrutinib vs. Zanubrutinib

After median follow-up of 40.9 months

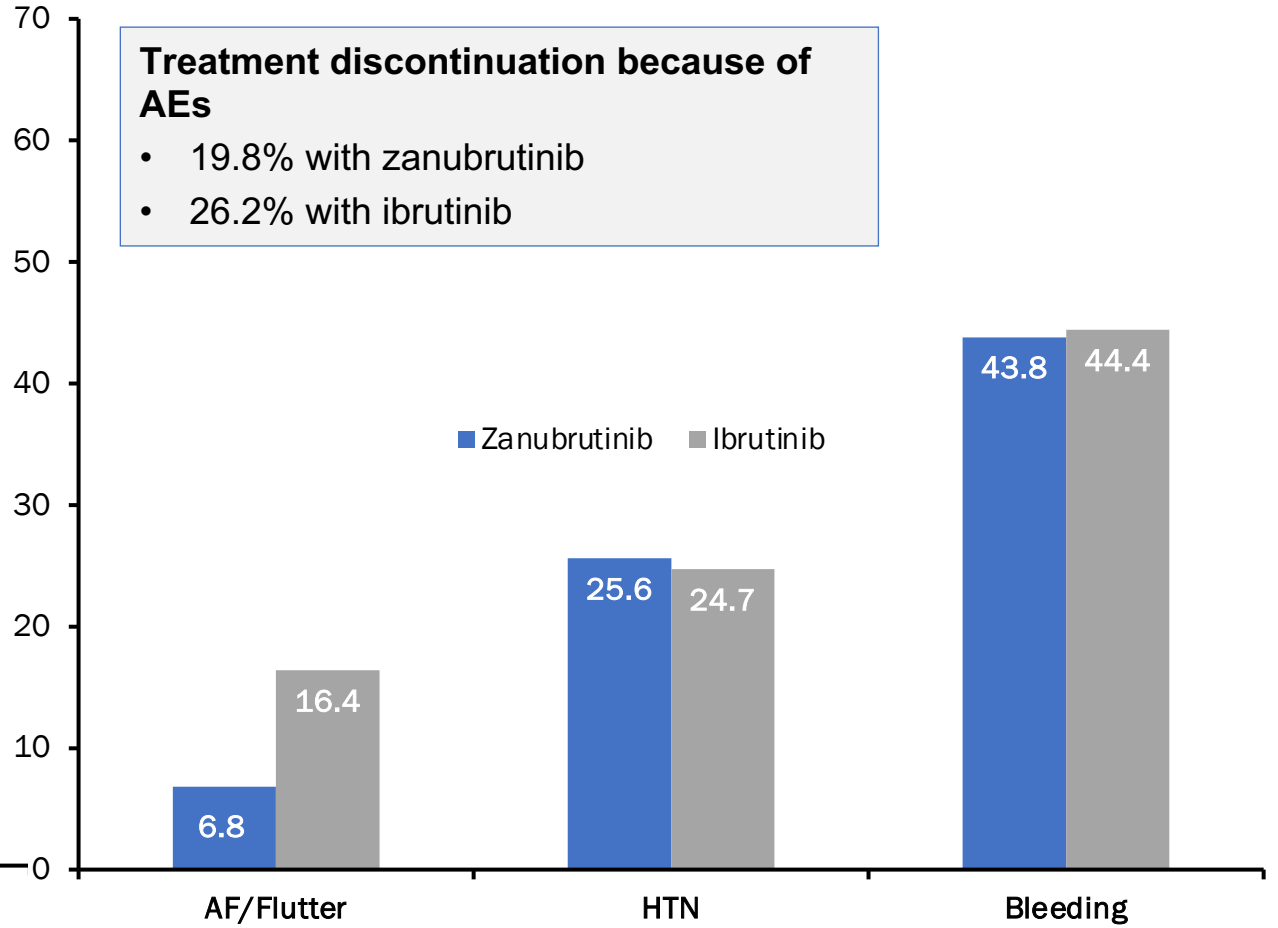
Treatment discontinuations because of AEs
- 14.7% with acalabrutinib
- 21.3% with ibrutinib



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

After a Median Follow-Up of 39.0 months

Treatment discontinuation because of AEs
- 19.8% with zanubrutinib
- 26.2% with ibrutinib



1. Brown J et al. ASH 2023. Abstract 202.

Adverse Events of Clinical Interest in H2H studies

In my opinion worth considering with each patient…

All grades	Ibrutinib ELEVATE-RR % (n=263)	Acalabrutinib ELEVATE-RR % (n=266)	Ibrutinib ALPINE % (n=324)	Zanubrutinib ALPINE % (n=324)
Atrial fib/flutter	15.6	9.0	13.3	5.2
Hypertension	22.8	8.6	22.8	23.5
Bleeding events	51.3	38.0	41.1	42.3
Neutropenia	24.7	21.1	24.4	29.3

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

Newer BTKi Preferred in CLL When Safety Concerns/CV Risk Factors Are Present

Initial Workup

Comprehensive patient history

- Blood pressure measurement
- Electrocardiogram
- Concomitant medications
- CV risk factor assessment: presence of diabetes, obesity, hypertension, dyslipidemia, or chronic renal disease
- History of valvular heart disease
- History of arrhythmias, heart failure, or left ventricular dysfunction/reduced ejection fraction
- History of ischemic heart disease

For patients with high CV risk or established CV disease

- Echocardiogram
- Baseline cardiac biomarkers
- Consider using FRS-CVD score for stratification

Conclusions based on an international consensus publication in 2022

Treatment Selection

Patients with no CV risk factors

- Any approved BTKi
- If there are other safety concerns, favor more selective drugs (acalabrutinib or zanubrutinib) or a BCL2 inhibitor

Patients with CV risk (eg, well-controlled AF, HTN, heart failure, or valvular heart disease)

- Consider newer BTKi (acalabrutinib or zanubrutinib)

1. Awan F et al. *Blood Adv*. 2022;6:5516-5525.

Recommendations for the Management of Bleeding and Cardiovascular Issues – BTKi

- Consider discontinuation of anti-platelet and anti-coagulants prior to starting
- Watch for bleeding closely – especially early in the disease course
- Do not give concomitantly with warfarin
- Hold BTKi for 3-7 days prior to minor and major procedures
- Watch for signs and symptoms of cardiac arrhythmias
- Work closely with Cardio-Oncology colleagues
- Control hypertension aggressively
- Avoid the use of medications that impact drug concentrations

BTK Inhibitors: Cardiovascular Adverse Event Management

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

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

Ibrutinib PI. Acalabrutinib PI. Zanubrutinib PI. Rogers. J Adv Pract Oncol. 2017;8:97. Dickerson T et al. Blood (2019) 134 (22): 1919–1928.
NCCN Guidelines®. Version 2.2022, 01/18/22 © 2022 National Comprehensive Cancer Network® (NCCN®).

BTKi: Management of Other Adverse Events

- Acalabrutinib: manage headache with acetaminophen + caffeine
- Zanubrutinib: neutropenia; for first occurrence, dose interruption is recommended (growth factor support for more severe manifestations)
- Consider sequencing

Bcl-2 Antagonists

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

Grade ≥3 Adverse Event, %	Venetoclax + Obinutuzumab (n = 212)		Chlorambucil + Obinutuzumab (n = 214)	
	During Treatment	After Treatment	During Treatment	After Treatment
Neutropenia	51.9	4.0	47.2	1.9
Thrombocytopenia	14.2	0.5	15.0	0
Anemia	7.5	2.0	6.1	0.5
Febrile neutropenia	4.2	1.0	3.3	0.5
Leukopenia	2.4	0	4.7	0
Pneumonia	3.8	3.0	3.3	1.4
Infusion-related reaction	9.0	0	9.8	0.5
Tumour lysis syndrome	1.4	0	3.3	0

Al-Sawaf O et al. EHA 2022. Abstr S148.
Al-Sawaf O et al, Lancet Oncol. 2020:21:1188-1200

CLL11: Overview of Adverse Events

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

Goede V et al. EHA 2018. Abstr S151.

Management of Venetoclax-Associated Toxicities

Toxicity Management

Tumor Lysis Syndrome

Laboratory TLS

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

Clinical TLS

- Creatinine ↑, cardiac arrythmia, seizure

Debulking Strategies

Prior to venetoclax ramp-up

- Chemotherapy (eg, 2x bendamustine)

  OR

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

  OR

- BTK inhibitor (eg, ibrutinib for 3 mo)

Neutropenia

In cases of grade 3/4 neutropenia or febrile neutropenia

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

Risk Assessment

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

Risk Mitigation

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

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

Conclusions

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

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

Questions from General Medical Oncologists

- What would be your preferred initial regimen for a 70-year-old patient with IGHV-mutated CLL and a history of renal insufficiency (creatinine 2.0 mg/dL)?
- When you are going to administer a BTK inhibitor to a patient with CLL and a history of difficult-to-control hypertension, which would you prefer? What if the patient had a history of migraine headache?
- What remedies are recommended for acalabrutinib headache management?

Questions from General Medical Oncologists

- 72 yo woman responding to acalabrutinib but has new onset, symptomatic pneumonitis. Have you seen drug-induced pneumonitis on acala or zanu? Had symptomatic response to high-dose steroids; however, no radiographic resolution of GGO. Getting additional workup with pulmonologist at the present time.
- How to manage bleeding side effects (eg, frequent and prolonged nosebleed)?
- What cardiac condition would preclude use of BTKi?

Questions from General Medical Oncologists

- Among patients with cardiovascular comorbidities/ underlying arrhythmias, how do you choose between the various available BTKi other than ibrutinib? How do you manage recurrent Afib on BTKi? Will you switch BTKi for new-onset grade 1/2 Afib?
- Do you use frequent EKG with acala or zanu?
- For the management of fatigue, how do you dose adjust the BTK inhibitors?

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Integration of Noncovalent BTK Inhibitors into the Management of R/R CLL

Bita Fakhri, MD, MPH

Stanford University School of Medicine

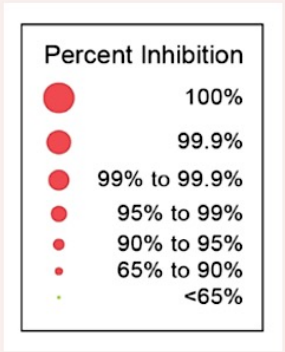
December 6, 2024

Deciding Factors in Treatment of Patients with Double Refractory CLL

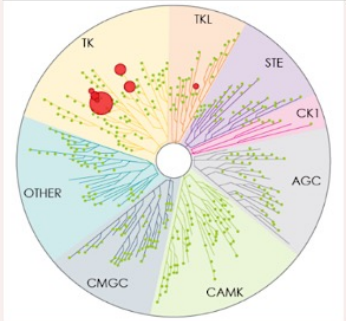
Patient specific	Disease specific	Therapeutic specific
Age Comorbidities Personal preferences	Del(17p) and/or TP53 mutation IGHV mutation status Disease bulk	Side effect profile Route of administration

Several Covalent BTKi Options to Consider With Differences in BTKi Specificity, MOA, and Potential for Off-Target Effects

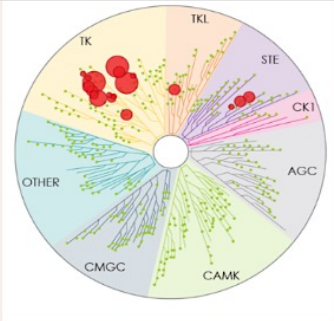
Covalent



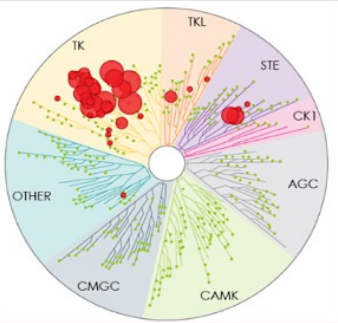
Acalabrutinib[1]



Zanubrutinib[1]

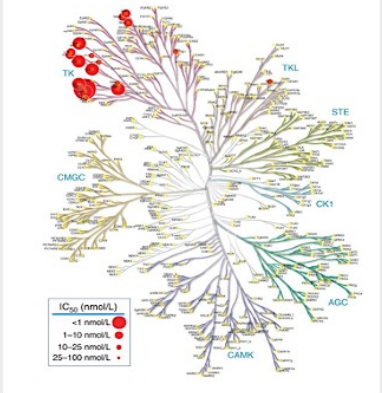


Ibrutinib[1]

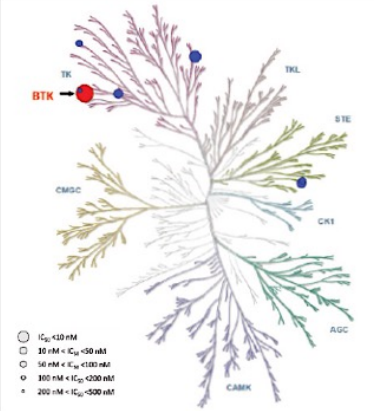


Noncovalent

Nemtabrutinib[2]



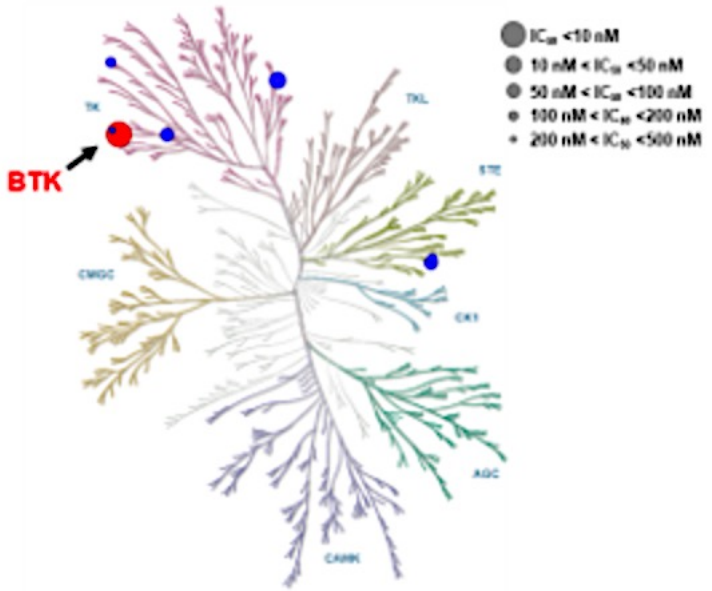
Pirtobrutinib[3]



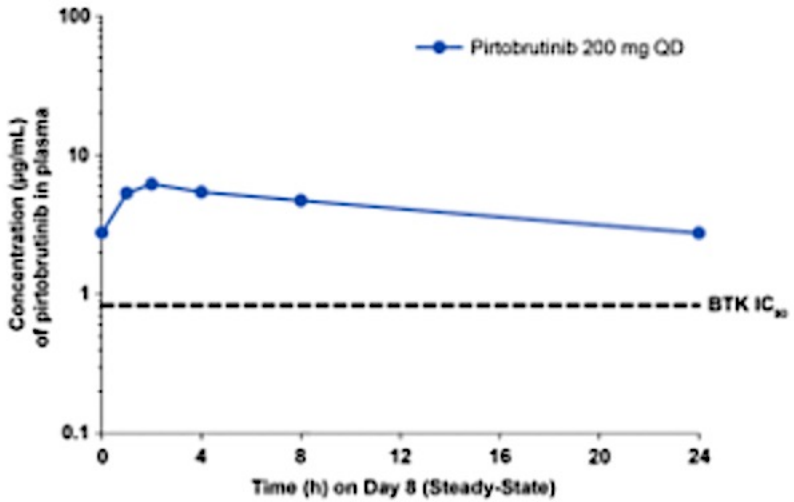
1. Kaptein A, et al. *Blood*. 2018;132(Suppl 1):1871. **2.** Reiff SD, et al. *Cancer Discov*. 2018;8(10):1300-1315. **3.** Brandhuber B, et al. SOHO 2018. Abstract CLL-200.

Pirtobrutinib is a Highly Selective, Non-Covalent (Reversible) BTK Inhibitor

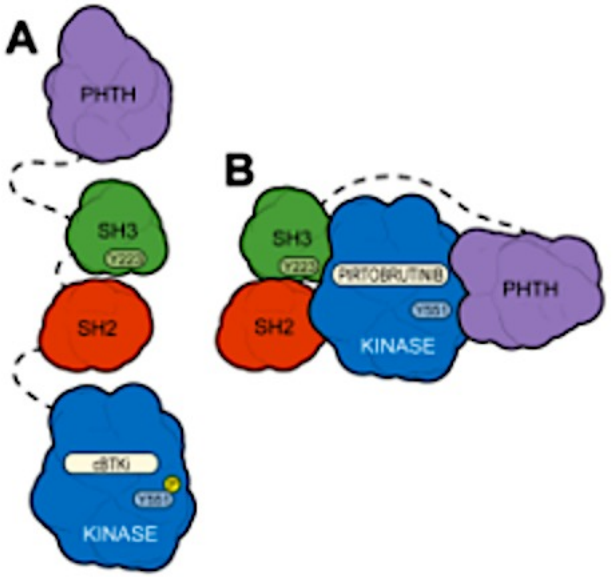
Highly selective for BTK[5,6]



Plasma exposures exceeded BTK IC_{90} throughout dosing interval



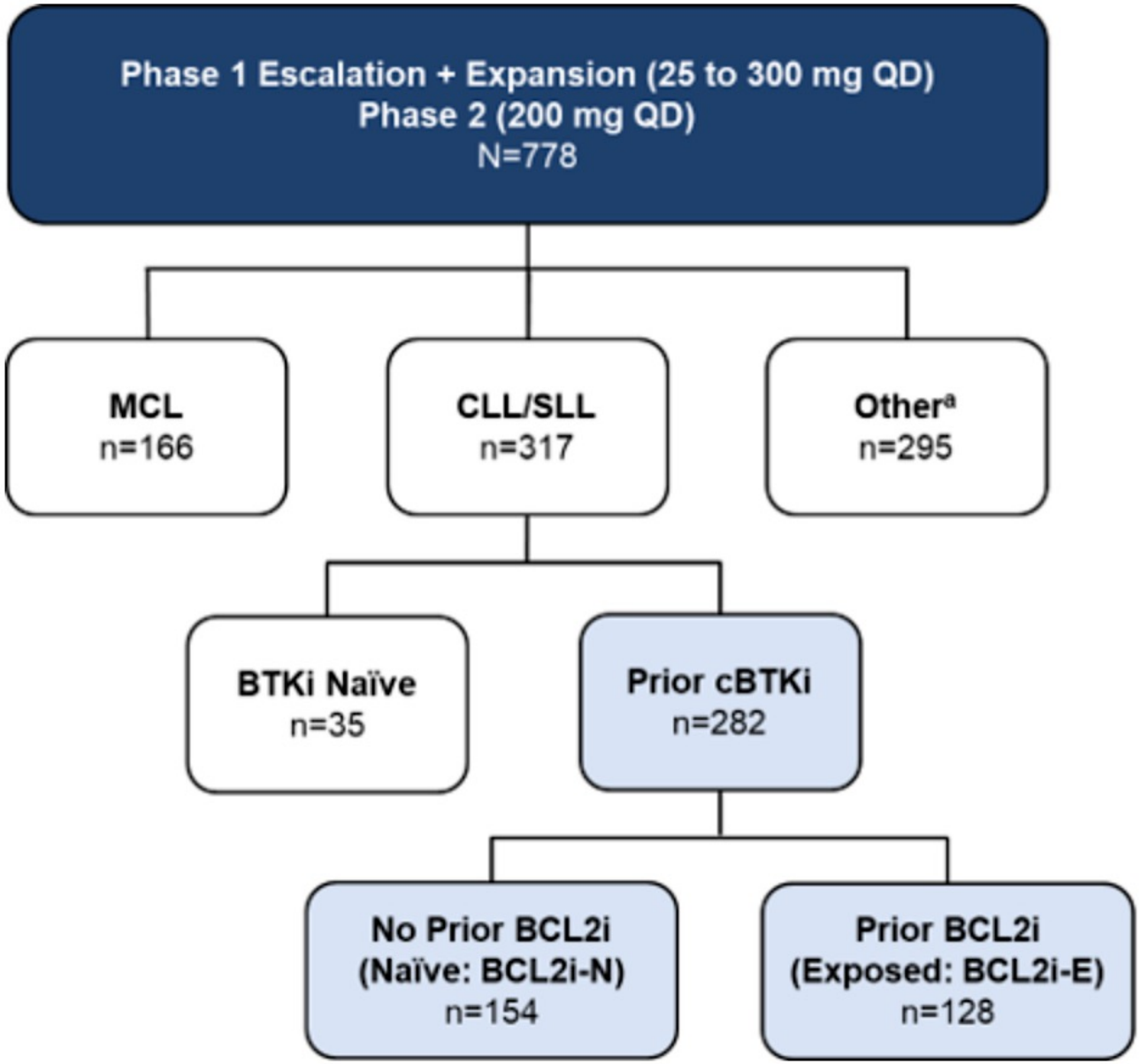
Pirtobrutinib may stabilize/maintain BTK in a closed inactive conformation[7]



- Inhibits both WT and C481-mutant BTK with equal low nM potency[7]
- Steady state plasma exposure corresponding to 96% BTK target inhibition and a half-life of about 20 hours[7]
- In contrast to cBTKi (A), pirtobrutinib (B) appears to stabilize BTK in a closed, inactive conformation, blocking access to upstream kinases and phosphorylation of Y551, thus inhibiting scaffolding interactions that support kinase-independent BTK signaling[7]

Woyach et al; ASH 2023

Phase 1/2 BRUIN Study: Design, Eligibility and Enrollment



Phase 1 3+3 design

- 28-day cycles
- Intra-patient dose escalation allowed
- Cohort expansion permitted at doses deemed safe

Eligibility

- Age ≥18
- ECOG PS 0-2
- Active disease and in need of treatment
- Previously treated

Key endpoints

- Safety/tolerability
- Determine MTD and RP2D
- Pharmacokinetics
- Efficacy (ORR according to iwCLL 2018 criteria, DoR, PFS, and OS)

Woyach et al; ASH 2023

Baseline Characteristics of Patients with CLL/SLL who Received Prior cBTKi

Characteristics	Prior cBTKi (n=282)	BCL2i-N (n=154)	BCL2i-E (n=128)
Median age, years (range)	69 (36-88)	69 (36-87)	68 (41-88)
Male, n (%)	192 (68)	106 (69)	86 (67)
Rai staging, n (%)			
0-II	147 (52)	94 (61)	53 (41)
III-IV	120 (43)	58 (38)	62 (48)
Missing	15 (5)	2 (1)	13 (10)
Bulky Lymphadenopathy ≥5 cm, n (%)	88 (31)	42 (27)	46 (36)
ECOG PS, n (%)			
0	144 (51)	89 (58)	55 (43)
1	118 (42)	56 (36)	62 (48)
2	20 (7)	9 (6)	11 (9)
Median number of prior lines of systemic therapy, (range)	4 (1-11)	3 (1-9)	5 (1-11)
Prior therapy, n (%)			
BTK inhibitor	282 (100)	154 (100)	128 (100)
Anti-CD20 antibody	251 (89)	127 (83)	124 (97)
Chemotherapy	228 (81)	114 (74)	114 (89)
BCL2 inhibitor	128 (45)	0 (0)	128 (100)
PI3K inhibitor	71 (25)	17 (11)	54 (42)
CAR-T	17 (6)	2 (1)	15 (12)
Allogeneic stem cell transplant	7 (3)	1 (1)	6 (5)

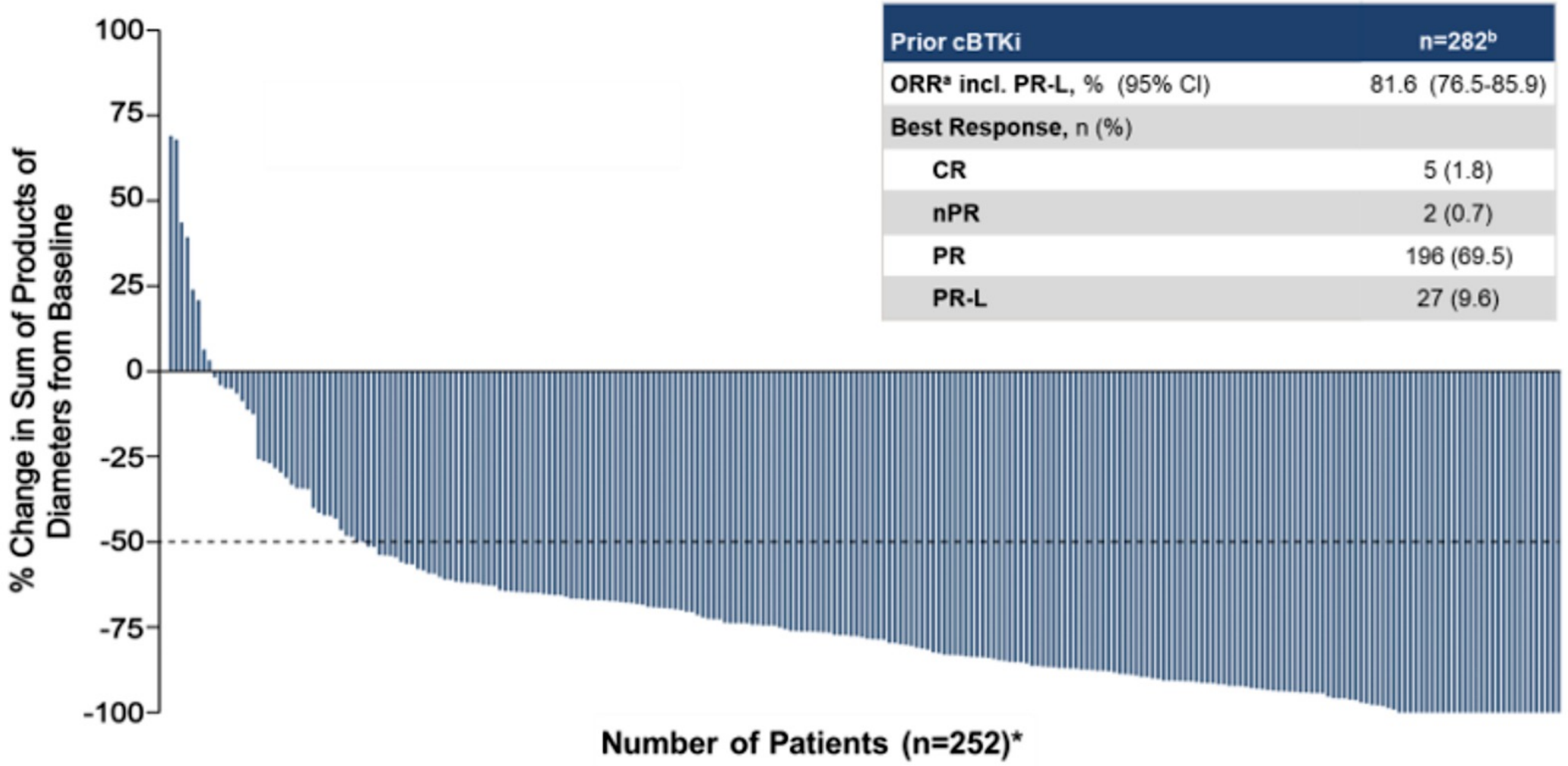
Characteristics	Prior cBTKi (n=282)	BCL2i-N (n=154)	BCL2i-E (n=128)
Median time from diagnosis to first dose, years (IQR)	11 (8-15)	11 (7-15)	12 (8-15)
Reason for any prior BTKi discontinuation[a], n (%)			
Progressive disease	217 (77)	110 (71)	107 (84)
Toxicity/Other	64 (23)	43 (28)	21 (16)

Baseline Molecular Characteristics[b]	Prior cBTKi (n=282)	BCL2i-N (n=154)	BCL2i-E (n=128)
Mutation status, n/n available (%)			
BCL2 mutated	19/246 (8)	0/133 (0)	19/113 (17)
BTK C481-mutant	96/245 (39)	57/138 (41)	39/107 (36)
PLCG2-mutant	18/245 (7)	10/138 (7)	8/107 (8)
High Risk Molecular Features, n/n available (%)			
17p deletion and/or TP53 mutation	104/217 (48)	57/123 (46)	47/94 (50)
IGHV unmutated	193/225 (86)	100/125 (80)	93/100 (93)
Complex Karyotype	33/73 (45)	17/41 (42)	16/32 (50)
11q deletion	47/202 (23)	28/115 (24)	19/87 (22)

Woyach et al; ASH 2023

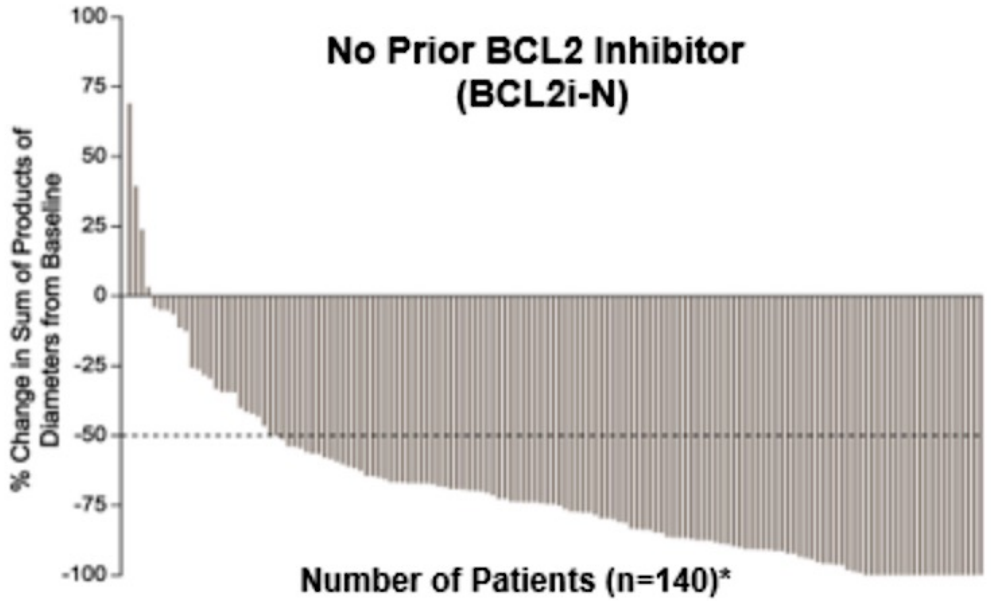
Pirtobrutinib Efficacy in All Patients with CLL/SLL who Received Prior cBTKi

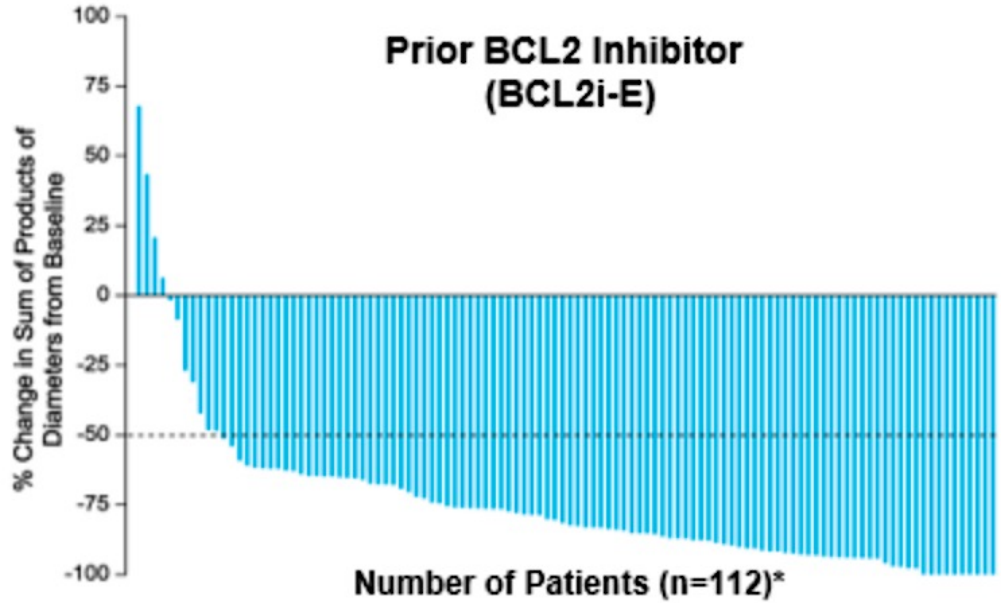
Prior cBTKi	n=282[b]
ORR[a] incl. PR-L, % (95% CI)	81.6 (76.5-85.9)
Best Response, n (%)	
CR	5 (1.8)
nPR	2 (0.7)
PR	196 (69.5)
PR-L	27 (9.6)



Woyach et al; ASH 2023

Pirtobrutinib Efficacy in Patients who Received Prior cBTKi, with or without Prior BCL2i



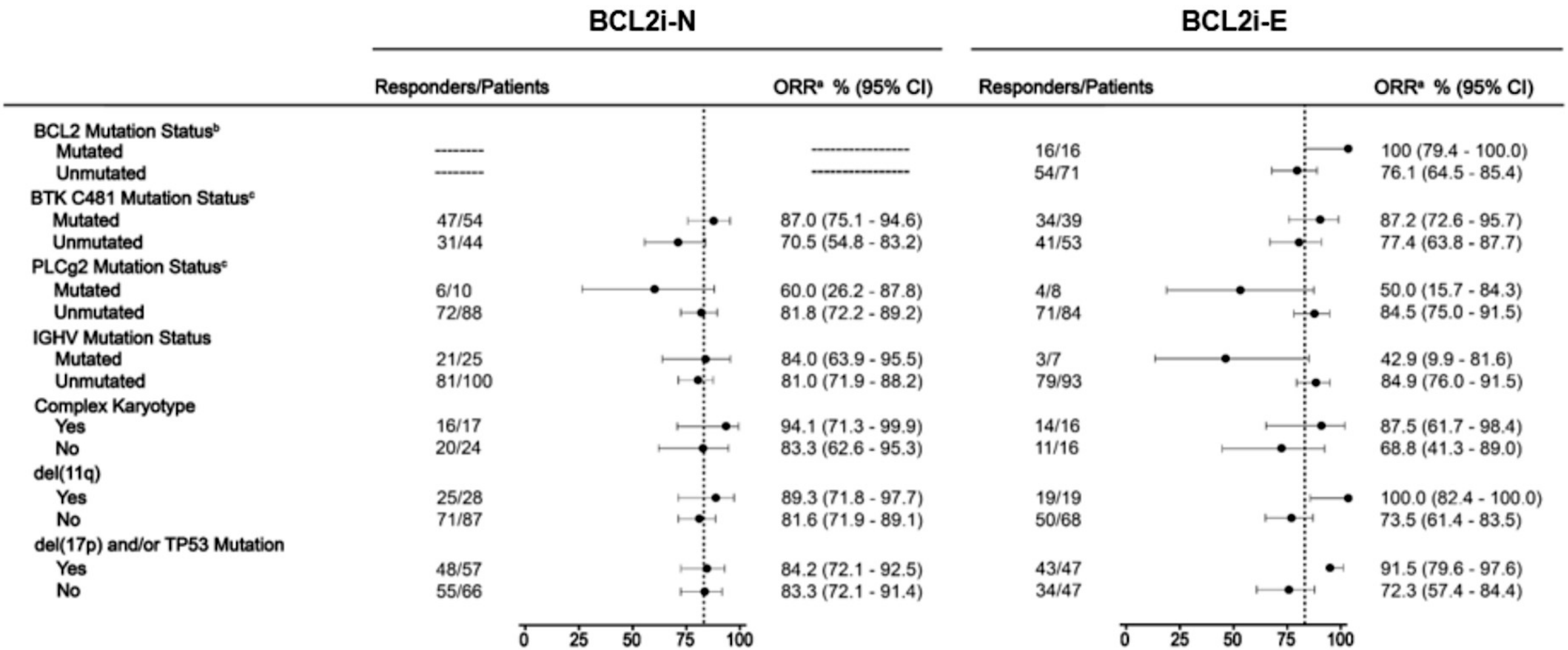


BCL2i-N	(n=154)[b]
ORR[a] incl. PR-L, % (95% CI)	83.1 (76.2-88.7)
Best Response, n (%)	
CR	5 (3.2)
nPR	2 (1.3)
PR	108 (70.1)
PR-L	13 (8.4)

BCL2i-E	(n=128)[c]
ORR[a] incl. PR-L, % (95% CI)	79.7 (71.7-86.3)
Best Response, n (%)	
CR	0 (0)
nPR	0 (0)
PR	88 (68.8)
PR-L	14 (10.9)

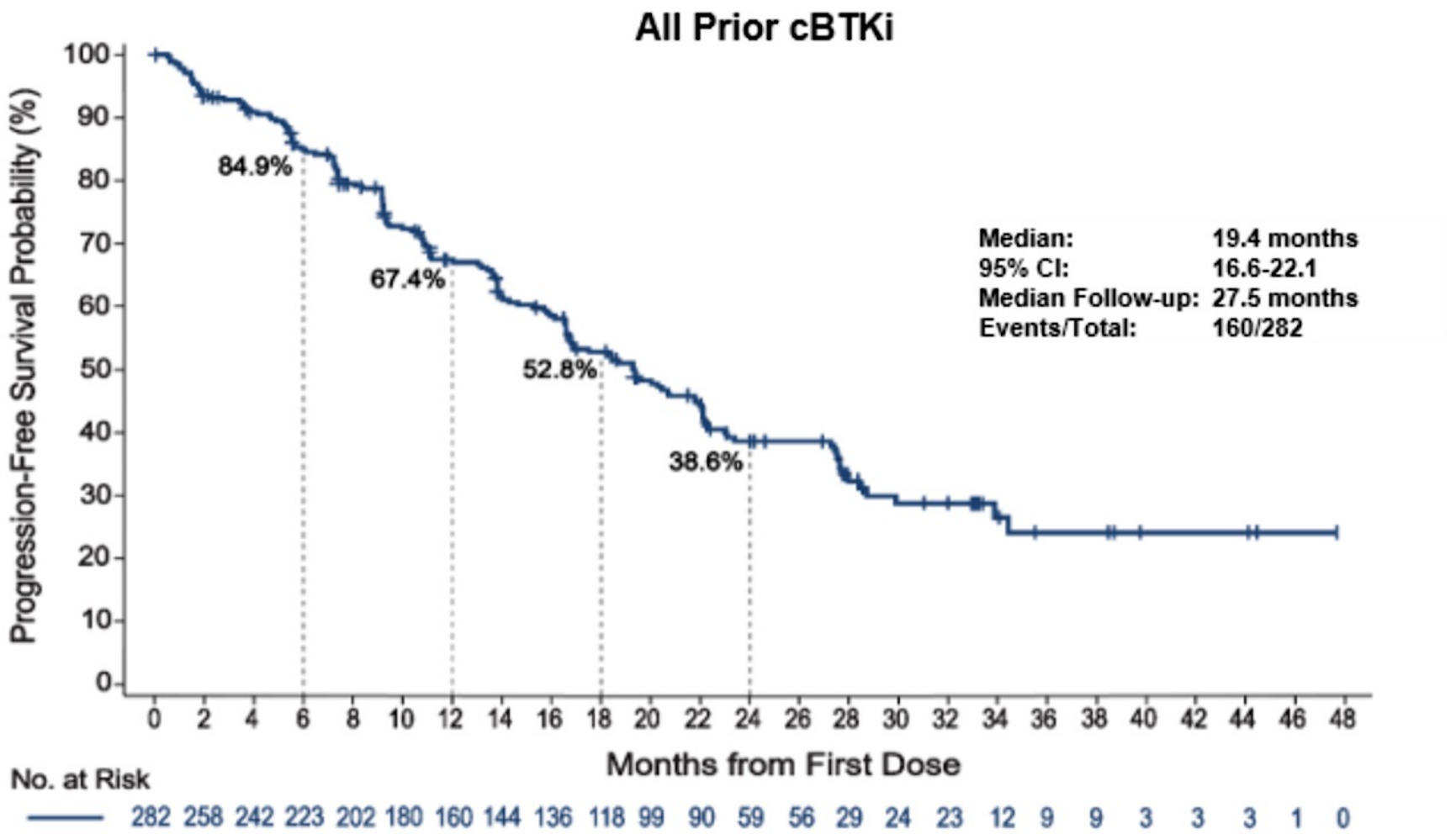
Woyach et al; ASH 2023

Pirtobrutinib Overall Response Rate in Patients who Received Prior cBTKi, with or without Prior BCL2i: Molecular Characteristics



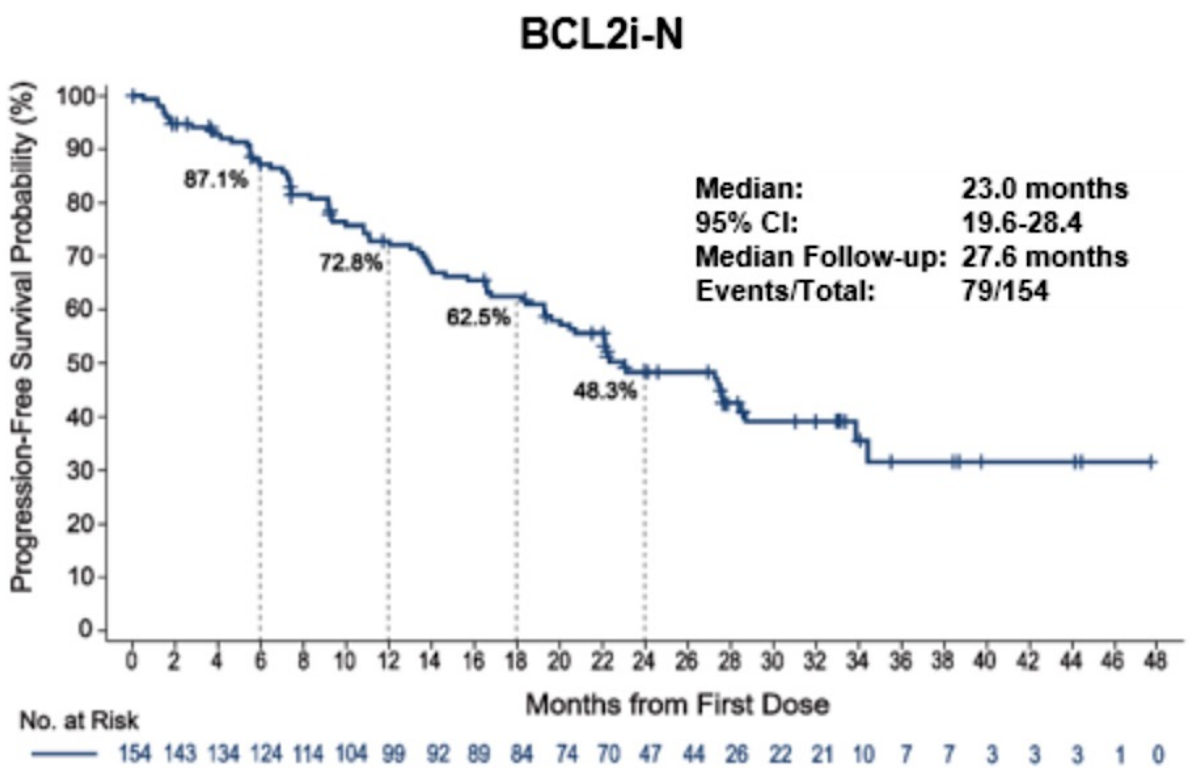
Woyach et al; ASH 2023

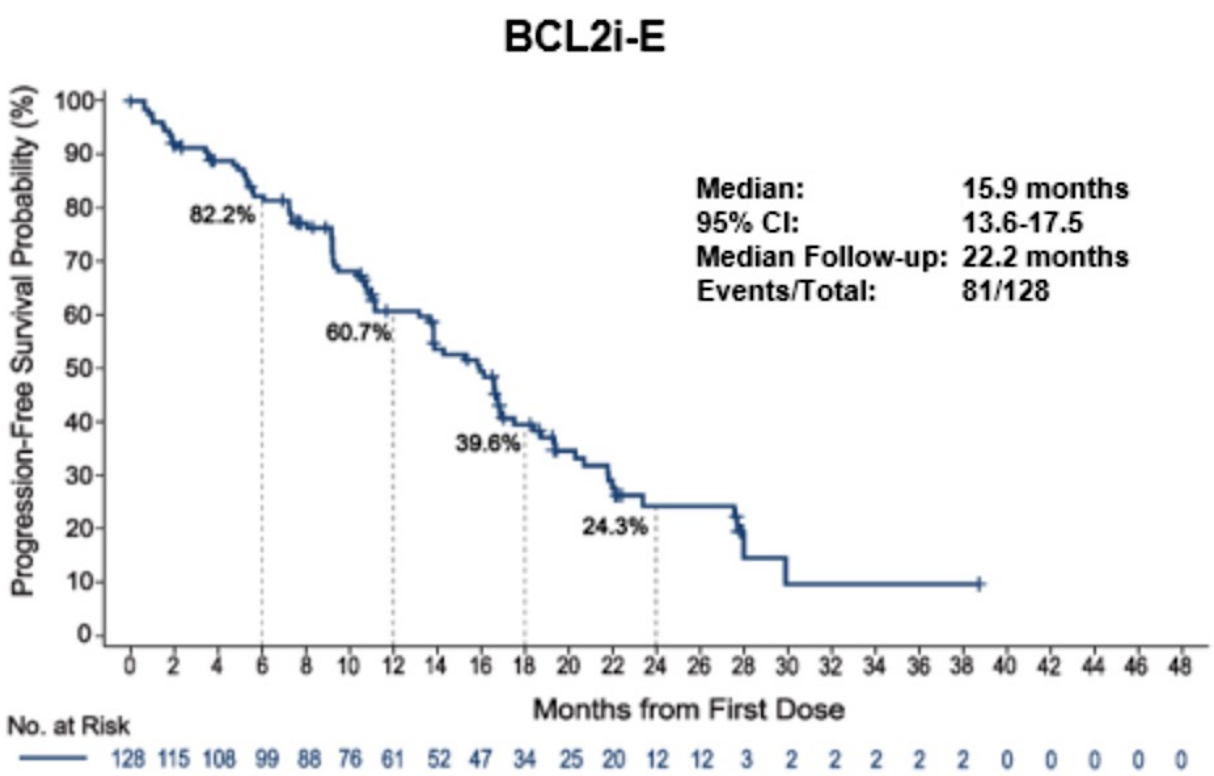
Pirtobrutinib Progression-Free Survival in Patients with Prior cBTKi



Woyach et al; ASH 2023

Pirtobrutinib Progression-Free Survival with Prior cBTKi, with or without Prior BCL2i





Woyach et al; ASH 2023

Pirtobrutinib Safety Profile of Patients who Received Prior cBTKi

	Treatment-Emergent AEs in Patients with CLL/SLL (n=282)			
	All Cause AEs, (≥20%), %		Treatment-Related AEs, %	
Adverse Event	**Any Grade**	**Grade ≥3**	**Any Grade**	**Grade ≥3**
Fatigue	36.9	1.8	3.5	0.0
Neutropenia[b,c]	34.4	28.4	19.5	15.2
Diarrhea	28.4	0.4	7.8	0.0
Cough	27.3	0.0	1.8	0.0
Contusion	26.2	0.0	17.4	0.0
Covid-19	25.9	4.6	0.7	0.0
Dyspnea	22.3	2.1	0.7	0.4
Nausea	22.0	0.0	3.5	0.0
Abdominal pain	21.3	1.8	2.1	0.4
AEs of Interest[a]	**Any Grade**	**Grade ≥3**	**Any Grade**	**Grade ≥3**
Infections[d]	74.1	30.9	12.8	4.3
Bruising[e]	30.1	0.0	19.1	0.0
Rash[f]	24.5	1.1	5.7	0.4
Arthralgia	22.7	1.4	4.3	0.0
Hemorrhage[g]	13.5	2.1	4.6	1.1
Hypertension	14.2	4.3	3.5	0.4
Atrial Fibrillation/Flutter[h,i]	4.6	1.8	1.4	0.7

Median time on treatment was 18.7 months (prior cBTKi), 24.3 months (BCL2i-N) and 15.3 months (BCL2i-E)
11 (3.9%; 9 BCL2i-N, 2 BCL2i-E) patients had Treatment-Related AEs leading to pirtobrutinib dose reduction
7 (2.5%; 4 BCL2i-N, 3 BCL2i-E) patients had Treatment-Related AEs leading to pirtobrutinib discontinuation
Safety profiles of BCL2i-N and BCL2i-E subgroups were similar

Woyach et al; ASH 2023

Conclusions

- With median follow-up of 30 months, pirtobrutinib continues to demonstrate clinically meaningful and durable efficacy in heavily pretreated patients with CLL/SLL who received prior covalent BTK inhibitor
  - ORR including PR-L was ~80% regardless of prior BCL2 inhibitor exposure
  - Median PFS was 19.4 months overall, with 23.0 months for BCL2i-N patients and 15.9 months for BCL2i-E patients
- Pirtobrutinib was well-tolerated with low-rates of discontinuation due to drug-related toxicity among both BCL2i-N and BCL2i-E patients
- These results suggest that continuation of BTK pathway inhibition may be an important sequencing approach to consider in the treatment of CLL/SLL
- On December 1, 2023, the FDA granted accelerated approval to pirtobrutinib for adults with CLL/SLL who have received at least two prior lines of therapy, including a BTK inhibitor and a BCL2 inhibitor*

Woyach et al; ASH 2023

Pirtobrutinib Clinical Development Plan in CLL

Previously Treated CLL/SLL or NHL	Previously Treated CLL/SLL	BTKi-Naïve CLL/SLL
Phase 1/2: BRUIN **Previously Treated CLL/SLL or NHL** **Pirtobrutinib Monotherapy (Ph 1/2)** **Pirtobrutinib + Venetoclax +/- Rituximab (Ph 1b)** • Estimated Enrollment: 860 • Identifier: NCT03740529	**Phase 3: BRUIN CLL-321** **Previously Treated (must include BTKi) CLL/SLL** **Pirtobrutinib vs. Investigator's Choice of Idelalisib + Rituximab or Bendamustine + Rituximab (Optional Crossover)** • Estimated Enrollment: 250 • Identifier: NCT04666038	**Phase 3: BRUIN CLL-313** **Previously Untreated CLL/SLL** **Pirtobrutinib vs. Bendamustine + Rituximab (Optional Crossover)** • Estimated Enrollment: 250 • Identifier: NCT05023980
	Phase 3: BRUIN CLL-322 **Previously Treated (may include BTKi) CLL/SLL** **Fixed Duration Pirtobrutinib + Venetoclax + Rituximab vs. Venetoclax + Rituximab** • Estimated Enrollment: 600 • Identifier: NCT04965493	**Phase 3: BRUIN CLL-314** **Previously Untreated or Previously Treated (non-BTKi) CLL/SLL** **Pirtobrutinib vs. Ibrutinib** • Estimated Enrollment: 650 • Identifier: NCT05254743

BTKi=Bruton tyrosine kinase inhibitor; CLL=chronic lymphocytic leukemia; NHL=non-Hodgkin lymphoma; Ph=phase; SLL= small lymphocytic lymphoma.

1. ClinicalTrials.gov identifier: NCT03740529. https://www.clinicaltrials.gov/ct2/show/NCT03740529.
2. ClinicalTrials.gov identifier: NCT04666038. https://www.clinicaltrials.gov/ct2/show/NCT04666038.
3. ClinicalTrials.gov identifier: NCT04965493. https://www.clinicaltrials.gov/ct2/show/NCT04965493.
4. ClinicalTrials.gov identifier: NCT04662255. https://www.clinicaltrials.gov/ct2/show/NCT04662255.
5. ClinicalTrials.gov identifier: NCT05023980. https://www.clinicaltrials.gov/ct2/show/NCT05023980.
6. ClinicalTrials.gov identifier: NCT05254743. https://www.clinicaltrials.gov/ct2/show/NCT05254743.

Please note that BRUIN CLL-321 data will be presented at ASH with the details below!

- BRUIN CLL-321: Randomized Phase III Trial of Pirtobrutinib Versus Idelalisib Plus Rituximab (IdelaR) or Bendamustine Plus Rituximab (BR) in BTK Inhibitor Pretreated Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma
- Accepted as oral presentation (Pub#886)
- **Presenting Author**: Jeff P Sharman
- **Session Name**: 642. Chronic Lymphocytic Leukemia: Clinical and Epidemiological: Treating Refractory Disease-Novel Agents and Quality-of-Life
- **Session Date**: Monday, December 9, 2024. 2:45 PM - 4:15 PM (PT)
- **Presentation Time**: 3:30 PM (PT)
- **Room**: Marriott Marquis San Diego Marina, Marriott Grand Ballroom 5-6

Nemtabrutinib

- MK-1026 (formerly ARQ-531) is an investigational noncovalent BTK inhibitor
  - Active against wild-type and *C481S*-mutated BTK
  - RP2D defined as 65 mg QD in phase I/II trial in hematologic malignancies
- Data from CLL/SLL cohorts of ongoing phase II study of MK-1026 in patients with R/R CLL/SLL, B-cell NHL, and WM

MK-1026-001: Study Design

- Multicenter, open-label, single-arm, dose-expansion phase II trial

Adults with symptomatic R/R CLL/SLL and ECOG PS 0-2

Adults with measurable B-cell NHL or WM and ECOG PS 0-2

MK-1026 65 mg QD
Cohort A: with *C481S* mutation

MK-1026 65 mg QD
Cohort B: no *C481S* mutation

MK-1026 65 mg QD
Cohort C-H: B-cell NHL and WM

- Primary endpoint: ORR per iwCLL criteria
- Secondary endpoints: DoR, safety, tolerability

Woyach. ASH 2021. Abstr 392.

MK-1026-001: Baseline Characteristics

Characteristic	Overall Population (N = 118)
Median age, yr (range)	66.6 (38-86)
Male, n (%)	91 (77.1)
White, n (%)	105 (89.0)
CLL/SLL, n (%)	68 (57.6)
WM, n (%)	4 (3.4)
B-cell NHL,* n (%)	44 (37.3)
MK-1026 65 mg QD, n (%)	94 (79.7)

*DLBCL, FL, high-grade BCL, MCL, MZL, RT.

Characteristic	CLL/SLL 65 mg QD (n = 51)
Median prior therapy lines, n (range)	4 (1-18)
Prior BTK inhibitor, n (%)	43 (84.3)
ECOG PS, n (%) ▪ 0/1/2	14 (27.5)/32 (62.7)/5 (9.8)
IGHV unmutated, n (%) ▪ Mutated ▪ Unknown	30 (58.8) 2 (3.9) 19 (37.3)
Del(17p) present, n (%) ▪ Absent ▪ Missing	12 (23.5) 33 (64.7) 6 (11.8)
BTK *C481S* present, n (%) ▪ Absent ▪ Missing	32 (62.7) 12 (23.5) 7 (13.7)

Woyach et al; ASH 2021; *Cancer Discov* 2024;14(1):66-75.

MK-1026-001: Response

Response, n (%) (95% CI)	CLL/SLL 65 mg QD (n = 38)
ORR	22 (57.9) (40.8-73.6)
CR	1 (2.6) (0.0-13.8)
PR	12 (31.6) (17.5-48.6)
PR-L	9 (23.7) (11.4-40.2)
SD	15 (39.5)

- Median DoR, mo: NE (95% CI: 8.3-NE)
- SPD decrease observed in 93.9%, ≥50% decrease in 69.7% (n = 33)

Woyach et al; ASH 2021; *Cancer Discov* 2024;14(1):66-75.

MK-1026-001: Treatment-Emergent Adverse Events

TEAEs, n (%)	All Patients (N = 118)
Any TEAE	114 (96.6)
Grade ≥3	80 (68.0)
MK-1026 related	78 (66.1)
Grade ≥3 related	31 (26.3)
Leading to d/c	9 (7.6)

Common TEAEs Occurring in ≥20%, %	All Patients (N = 118)	
	Any Grade	Grade ≥3
Fatigue	33.1	3.4
Constipation	31.4	0.8
Dysgeusia	28.0	0
Cough	24.6	0
Nausea	24.6	0.8
Pyrexia	24.6	0
Dizziness	22.9	0
Hypertension	22.9	9.3
Peripheral edema	22.0	0
Diarrhea	21.2	0.8
Arthralgia	20.3	0

Woyach et al; ASH 2021; *Cancer Discov* 2024;14(1):66-75.

Nemtabrutinib: Investigators' Conclusions

- In patients with R/R CLL/SLL, the BTK inhibitor MK-1026 was active and tolerable when dosed at 65 mg QD, the RP2D
  - ORR: 57.9%
  - DoR: NE
- Patients were heavily treatment experienced, including patients with prior disease progression on BTK inhibitors
- MK-1026 continues to be evaluated in patients with B-cell malignancies at 65 mg QD and higher doses

Woyach et al; ASH 2021

In the 3rd Relapse Setting (Double Refractory/Exposed)

FDA Approved	Investigational
Nc-BTKi CD19 CAR T therapy	BTK degraders Bispecific T cell engagers Allogeneic CAR T therapy

Questions from General Medical Oncologists

- **Which third-line therapy would you prefer for a 60-year-old patient with CLL that is refractory to a BTK inhibitor and a Bcl-2 inhibitor? What if the patient were 80 years old?**
- **How would you compare the global tolerability/ toxicity of pirtobrutinib to that of available second-generation covalent BTK inhibitors for patients with relapsed/refractory CLL?**

Questions from General Medical Oncologists

- If a patient already received CD20 + ven, is there a role for combination BTK + XYZ (usually CD20 or ven) or is that a moot point since they were already exposed/refractory to those agents? Right now, I'd use BTKi monotherapy.
- Should pirtobrutinib be moved to first line therapy considering its superior efficacy and very favorable toxicity profile?
- Would you switch a responding patient from Zanu to Pirto or an alternate BTKi for poorly controlled HTN in spite of multidrug therapies?

Questions from General Medical Oncologists

- **Should I perform resistance testing to determine whether to use pirtobrutinib next?**
- **Would you skip directly to pirtobrutinib after progression on a covalent BTK inhibitor in a patient who hadn't been exposed to venetoclax but preferred oral therapy?**

Agenda

Module 1: Optimizing First-Line Therapy for Chronic Lymphocytic Leukemia (CLL) — Dr Sharman

Module 2: Emerging Role of Bruton Tyrosine Kinase (BTK) Inhibitors in Combination with Bcl-2 Inhibitors — Dr Rogers

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

Module 4: Integration of Noncovalent BTK Inhibitors into the Management of Relapsed/Refractory CLL — Dr Fakhri

Module 5: Chimeric Antigen Receptor T-Cell Therapy and Other Novel Strategies for CLL — Dr Wierda

RTP RESEARCH TO PRACTICE

THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center
Making Cancer History®

CD19 Chimeric Antigen Receptor (CAR) T-Cell Therapy and Other Novel Strategies for CLL

William G. Wierda MD, PhD

Professor of Medicine

Section Head, CLL

Department of Leukemia

U.T. M.D. Anderson Cancer Center

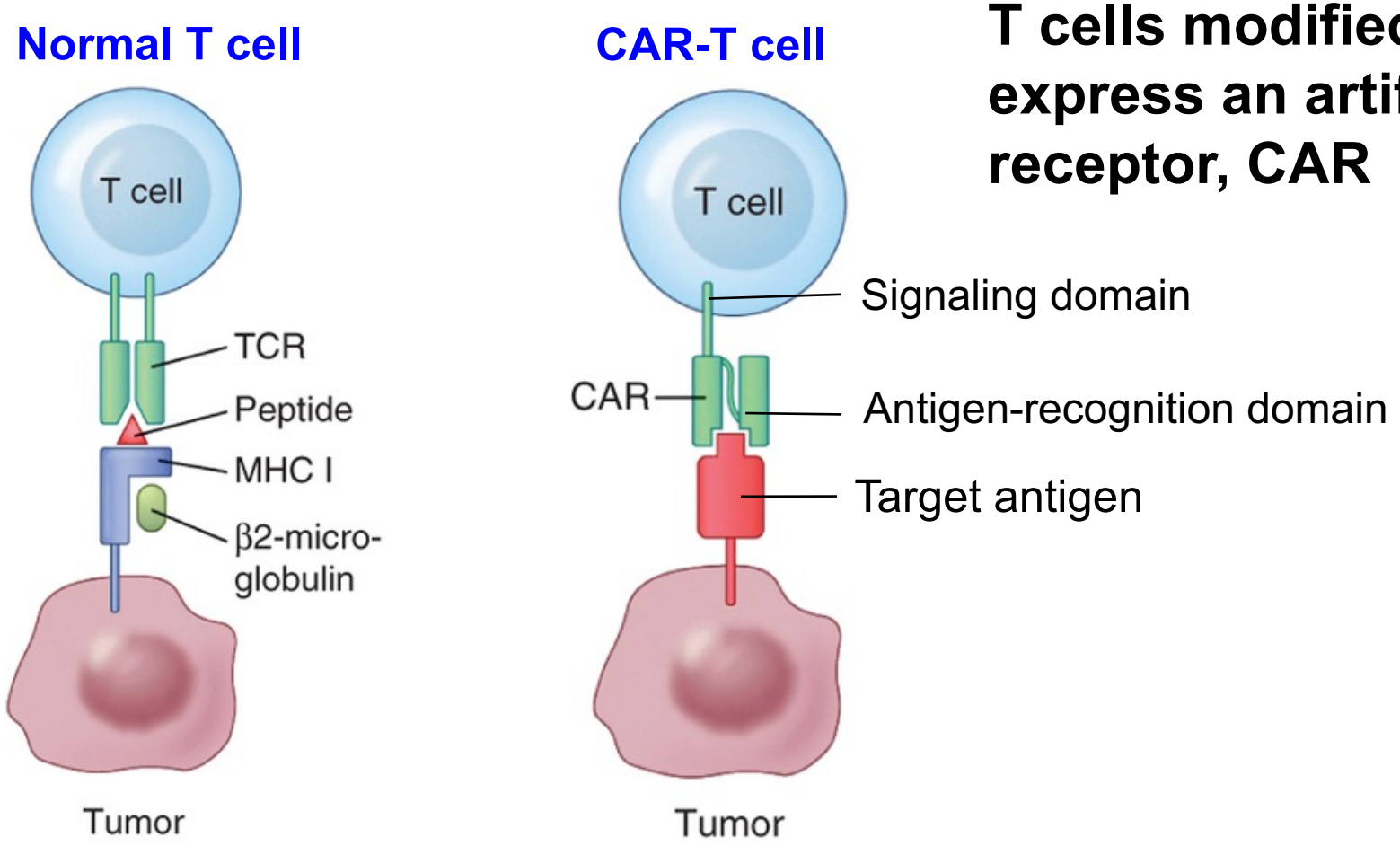
Houston, TX USA

New Agents for Relapsed / Refractory CLL

- **Old targets:**
  - **BTK degrader (NX-5948; ABBV-101; BGB-16673)**
  - ncBTKi (nemtabrutinib; TT-01488; LP-168; AS-1763)
  - ngBCL2i (lisaftoclax; sonrotoclax; ABBV-453)
  - **CD20xCD3 bispecifics (mosunetuzumab; epcoritamab; glofitamab)**
  - **CD19 (liso-cel CD19-CAR-T cells)**
- **New targets:**
  - BCLxL/BCL2 – (LP-118)
  - PKCβ inhibitor – (MS-553)
  - MALT1 (ABBV-525)
  - ROR1 (xCD3 bispecific; CAR-T cells)
  - MCL-1/CDK9

Chimeric Antigen Receptor (CAR) Modified T Cells

Genetically engineered T cells modified to express an artificial receptor, CAR

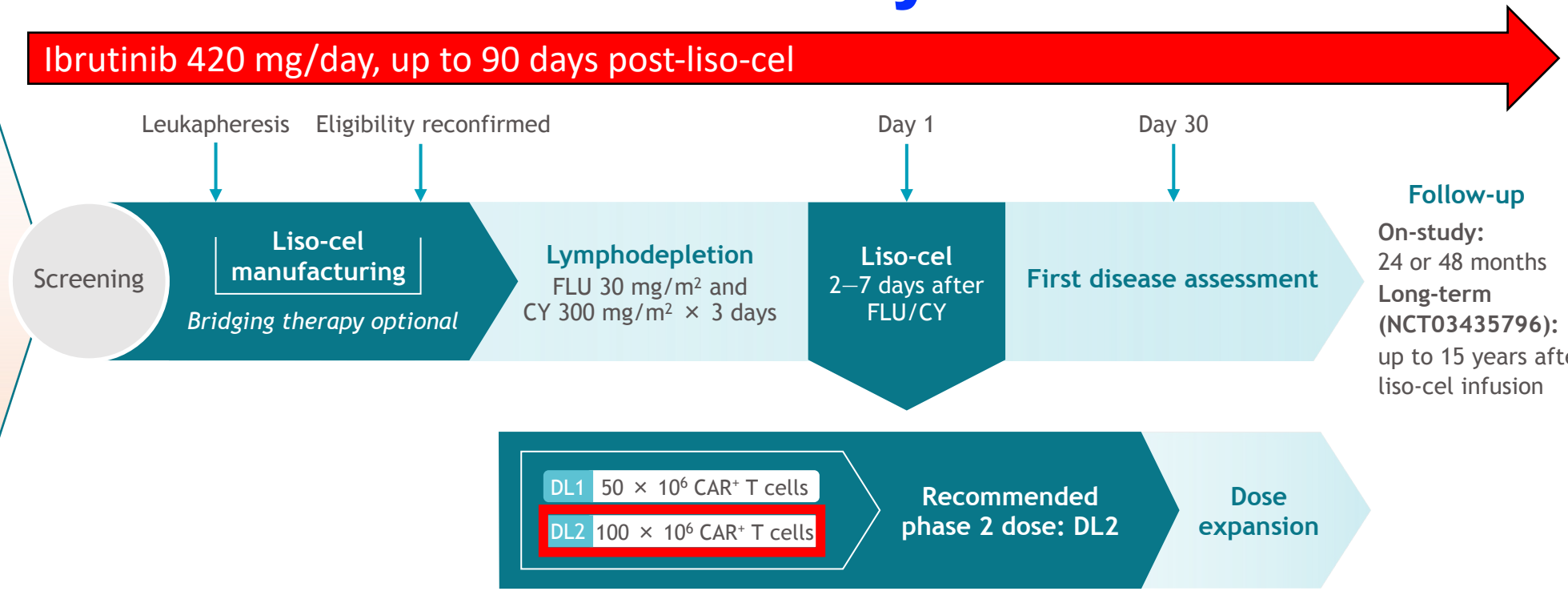


Adapted from Hinrichs & Restifo. Nat Biotech 2013

TRANSCEND CLL 004: phase 1/2, open-label, multicenter study

Key eligibility criteria

- Age ≥ 18 years
- R/R CLL/SLL
- Previously failed or ineligible for BTKi
- Failure of ≥ 2 (high risk) or ≥ 3 (standard risk) lines of prior therapy
- ECOG PS ≤ 1
- Adequate bone marrow, organ, and cardiac function
- No Richter transformation nor active CNS involvement by malignancy



Follow-up

On-study: 24 or 48 months
Long-term (NCT03435796): up to 15 years after liso-cel infusion

Primary endpoint (PEAS at DL2)
CR/CRi rate per iwCLL 2018 by IRC assessment

Key secondary endpoints (PEAS at DL2)
ORR, uMRD rate in blood

Post hoc analyses
Median time to next treatment

ClinicalTrials.gov: NCT03331198.
CY, cyclophosphamide; DL, dose level; FLU, fludarabine; IRC, independent review committee; iwCLL, International Workshop on Chronic Lymphocytic Leukemia; PEAS, primary efficacy analysis set (prespecified subset of patients with BTKi progression and venetoclax failure); uMRD, undetectable minimal residual disease.

Siddiqi T, et al. ASH 2023 [Presentation #330]

Demographics and baseline characteristics (Mono)

	Full study population (n = 118)	BTKi progression/venetoclax failure subset (n = 71)
Median (range) age, y	65.0 (49—82)	66.0 (49—78)
Median (range) prior lines of systemic therapy	5 (2—14)	5 (2—14)
Bulky lymph nodes,[a] n (%)		
Yes	53 (45)	33 (46)
Unknown	9 (8)	8 (11)
High-risk cytogenetics,[b] n (%)	98 (83)	61 (86)
Prior BTKi, n (%)	118 (100)	71 (100)
BTKi refractory[c]	104 (88)	71 (100)
BTKi relapsed[d]	2 (2)	0
BTKi intolerant only	12 (10)	0
Prior venetoclax, n (%)	95 (81)	71 (100)
Venetoclax refractory	90 (76)	68 (96)
Venetoclax relapsed[d]	0	0
Venetoclax intolerant only	4 (3)	3 (4)
Prior BTKi and venetoclax, n (%)	95 (81)	71 (100)
BTKi progression/venetoclax failure,[e] n (%)	71 (60)	71 (100)
Received bridging therapy, n (%)	90 (76)	56 (79)

[a]Defined as ≥ 1 lesion with the longest diameter of ≥ 5 cm; [b]Includes del(17p), *TP53* mutation, unmutated immunoglobulin heavy-chain variable region, and complex cytogenetics; [c]Defined as no response or progression ≤ 6 months from last dose of therapy; [d]Defined as disease progression in a patient who previously had CR/CRi or PR/nPR for ≥ 6 months; [e]Including patients who progressed on a BTKi and met one of the following: (1) discontinued venetoclax due to disease progression or intolerability and patient's disease met indications for further therapy per iwCLL 2018, or (2) failed to achieve an objective response ≤ 3 months of initiating therapy.
nPR, nodular partial response/remission.

Siddiqi T, et al. ASH 2023 [Presentation #330]

Efficacy outcomes: DL2 only (Mono)

	Full study population at DL2 (n = 88)	BTKi progression/venetoclax failure subset at DL2 (n = 50)
Primary endpoint: IRC-assessed CR/CRi rate per iwCLL 2018, n (%) [95% CI]	17 (19) [12—29]	10 (20) [10—34]
Key secondary endpoints		
IRC-assessed ORR, n (%) [95% CI]	42 (48) [37—59]	22 (44) [30—59]
uMRD rate in blood, n (%) [95% CI]	58 (66) [55—76]	32 (64) [49—77]
Exploratory endpoint: uMRD rate in marrow, n (%) [95% CI]	53 (60) [49—71]	30 (60) [45—74]
Other secondary endpoints		
Best overall response, n (%)		
CR/CRi	17 (19)	10 (20)
PR/nPR	25 (28)	12 (24)
SD	34 (39)	21 (42)
PD	6 (7)	4 (8)
Not evaluable	6 (7)	3 (6)
Time to first response, months, median (range)	1.3 (0.8—17.4)	1.1 (0.8—17.4)
Time to first CR/CRi, months, median (range)	5.5 (0.8—18.0)	2.1 (0.8—18.0)

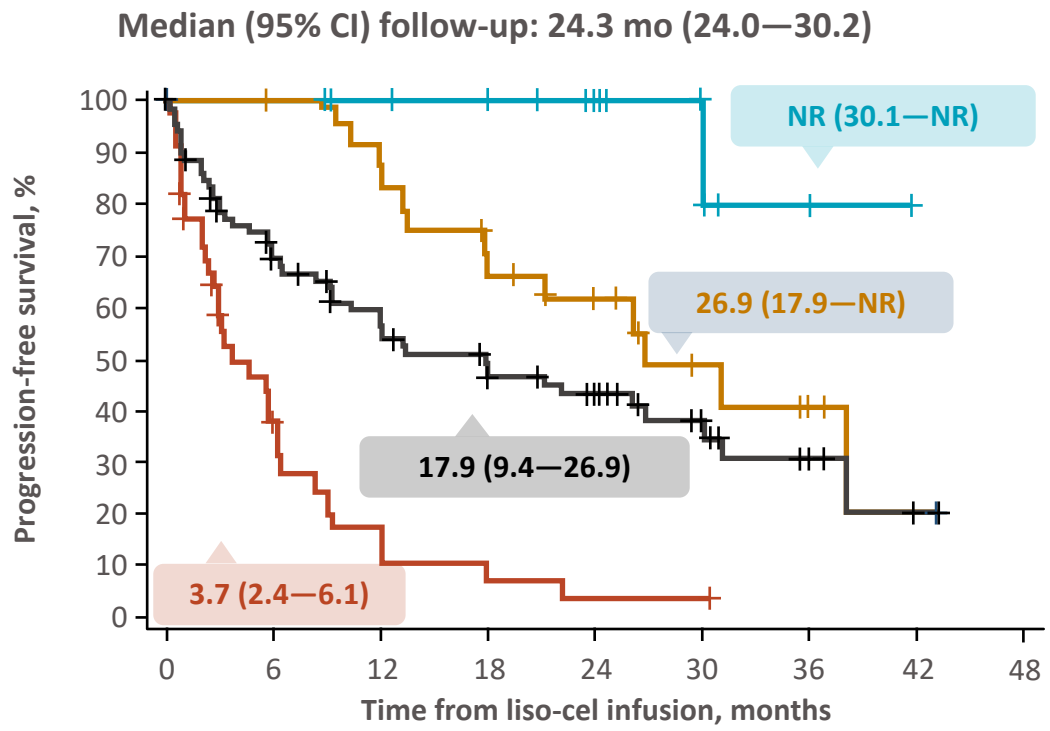
- **uMRD was achieved in MRD-evaluable patients in the full population at DL2 by:**
  - **15/15 (100%) patients with CR/CRi in blood and 15[a]/16 (94%) in marrow**
  - 24/24 (100%) patients with PR/nPR in blood and 23/23 (100%) in marrow
  - 19/32 (59%) patients with SD in blood and 15/32 (47%) in marrow

[a]One patient had an indeterminate status for MRD, which was considered positive as per FDA guidelines. SD, stable disease.

Siddiqi T, et al. ASH 2023 [Presentation #330]

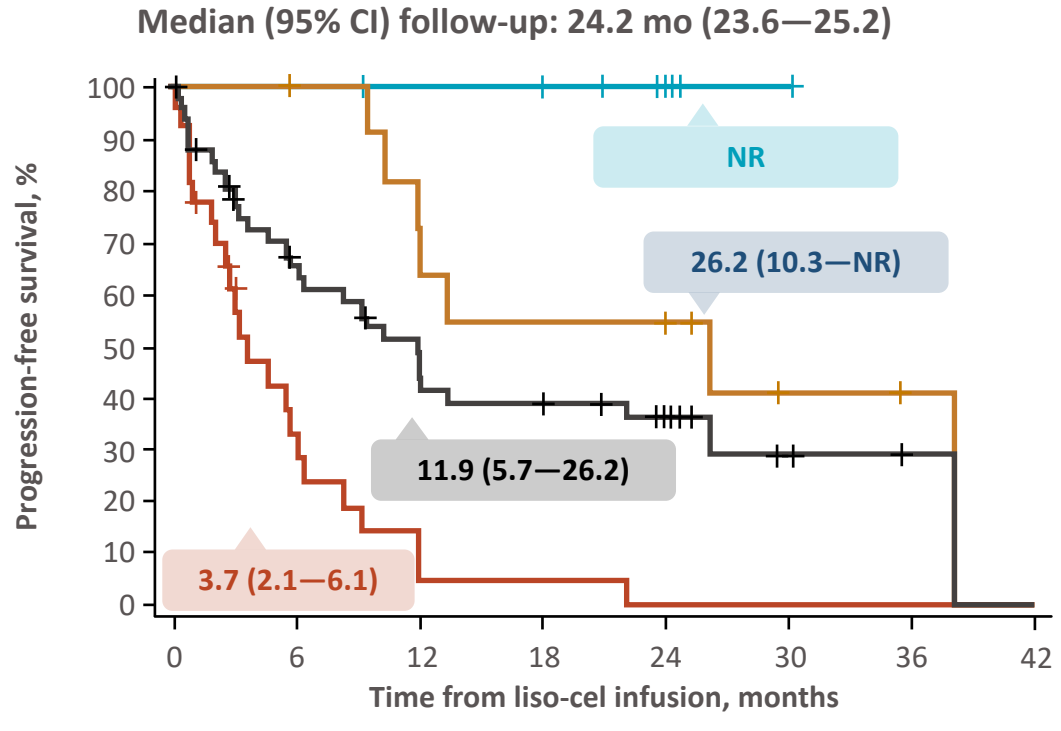
PFS by best overall response (Mono)

(A) Full study population at DL2 (n = 88)



No. at risk									
CR/CRi	17	17	15	14	10	5	2	0	0
PR/nPR	25	24	21	15	11	6	3	1	0
Nonresponder	46	12	4	2	1	1	0	0	0
Total	88	53	40	31	22	12	5	1	0

(B) PEAS (BTKi progression/venetoclax failure subset) at DL2 (n = 50)



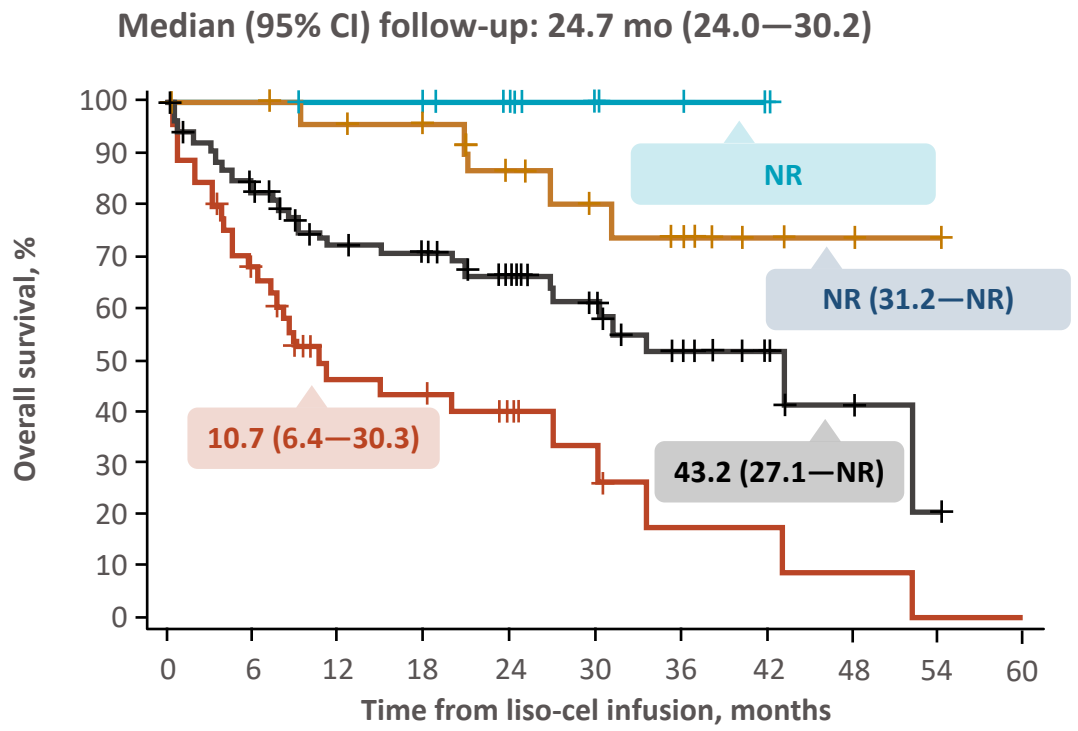
No. at risk									
CR/CRi	10	10	9	9	5	1	0	0	
PR/nPR	12	11	8	6	5	2	1	0	
Nonresponder	28	7	2	1	0	0	0	0	
Total	50	28	19	16	10	3	1	0	

Data on KM curves are expressed as median (95% CI, if available).

Siddiqi T, et al. ASH 2023 [Presentation #330]

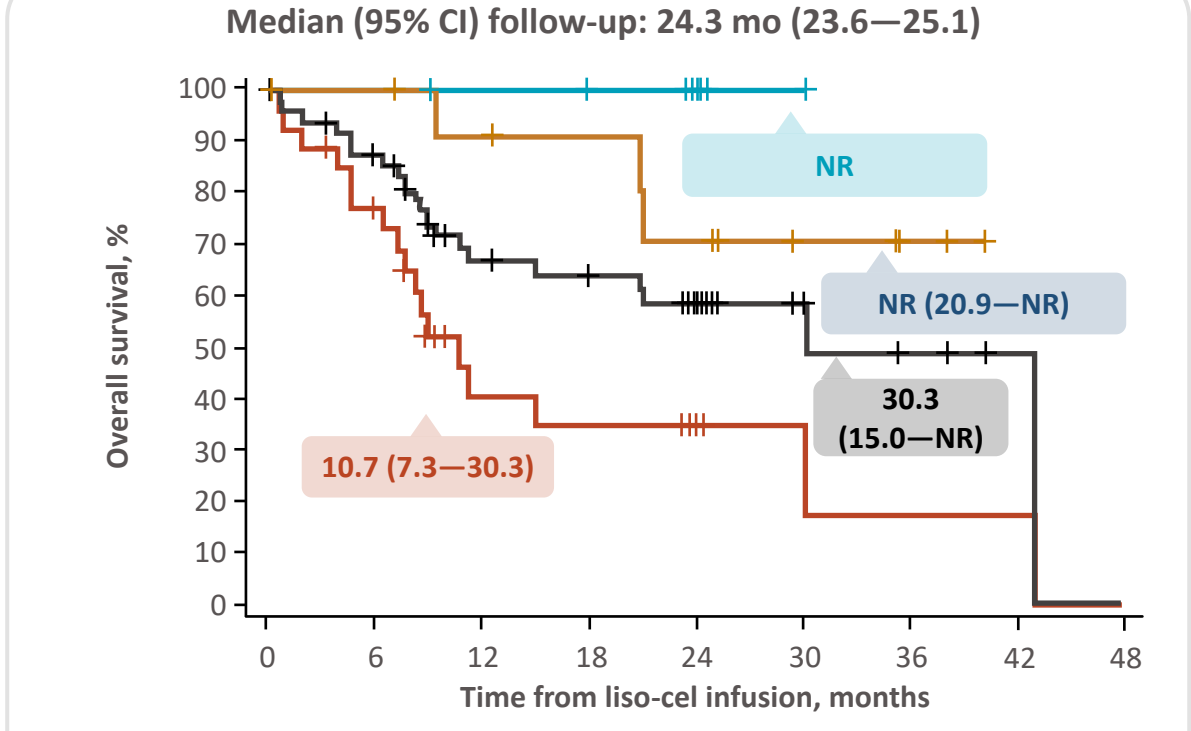
Overall survival by best overall response (Mono)

(A) Full study population at DL2 (n = 88)



No. at risk											
CR/CRi	17	17	16	16	12	6	3	1	0	0	0
PR/nPR	25	25	23	21	16	12	7	3	2	1	0
Nonresponder	46	27	15	14	8	5	2	2	1	0	0
Total	88	69	54	51	36	23	12	6	3	1	0

(B) PEAS (BTKi progression/venetoclax failure subset) at DL2 (n = 50)

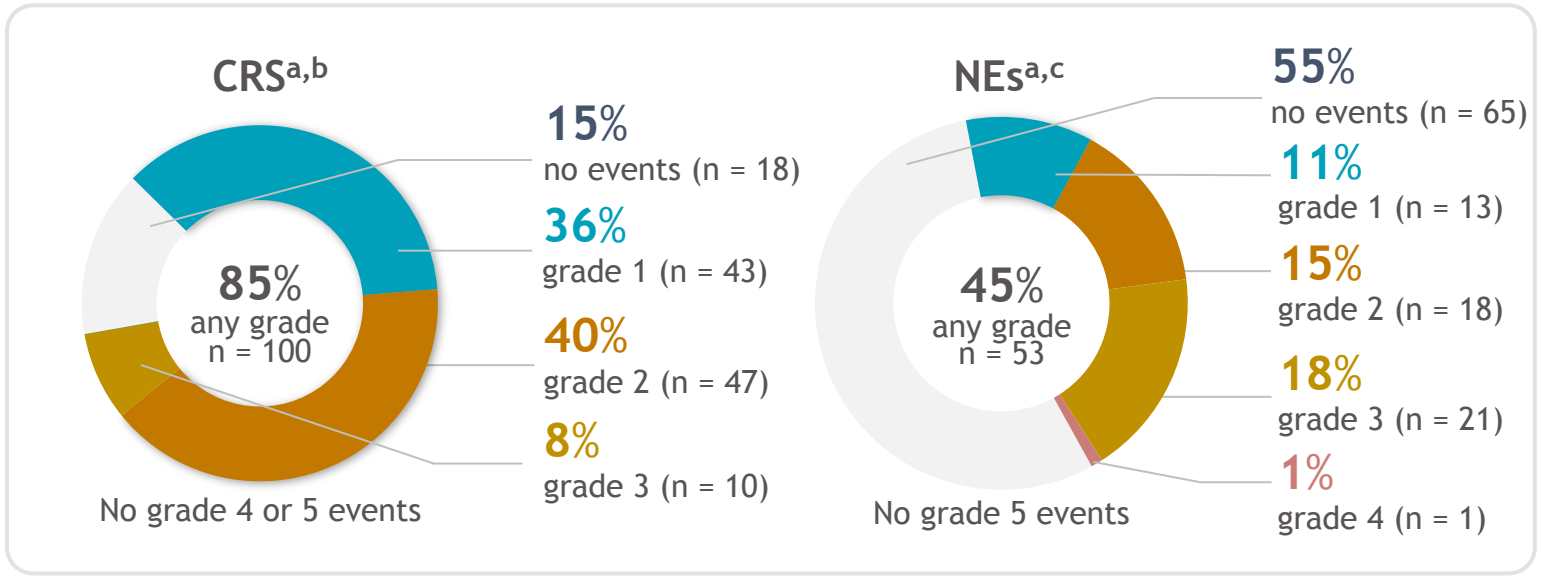


No. at risk									
CR/CRi	10	10	9	9	6	1	0	0	0
PR/nPR	12	12	10	9	7	4	2	0	0
Nonresponder	28	19	7	6	4	2	1	1	0
Total	50	41	26	24	17	7	3	1	0

Data on KM curves are expressed as median (95% CI, if available).

Siddiqi T, et al. ASH 2023 [Presentation #330]

Safety: full study population (n = 118) (Mono)



	Total (n = 118)	
	CRS	NE
Patients with an event, n (%)	100 (85)	53 (45)
Median (range) time to onset, days	4 (1—18)	7 (1—21)
Median (range) time to resolution, days	6 (2—37)	7 (1—83)
Received tocilizumab and/or corticosteroids for CRS and/or NE	82 (69)	

Other AESIs, n (%)

- Prolonged cytopenias[d]: 64 (54%)
- Grade ≥ 3 infections[e]: 21 (18%)
- Hypogammaglobulinemia[f]: 18 (15%)
- Tumor lysis syndrome: 13 (11%)
- SPM[f]: 11 (9%)
- MAS: 4 (3%)

Deaths due to TEAEs, n = 5 (4%)

- 4 (3%) considered unrelated to liso-cel by investigators (respiratory failure, sepsis, *Escherichia coli* infection, and invasive aspergillosis)
- 1 (1%) considered related to liso-cel by investigators (MAS)

[a]Summed percentages for grouped grades within each graph may not equal the any-grade percentage due to rounding; [b]CRS was graded based on the Lee 2014 criteria; [c]NEs were defined as investigator-identified neurological AEs related to liso-cel; [d]Defined as grade ≥ 3 laboratory abnormalities of neutropenia, anemia, or thrombocytopenia at Day 30 after liso-cel infusion; [e]Includes grade ≥ 3 TEAEs from infections and infestations (System Organ Class) by AE high-level group term; [f]AEs from the 90-day treatment-emergent period, posttreatment-emergent period, and long-term follow-up were included.

AESI, adverse event of special interest; MAS, macrophage activation syndrome; NE, neurological event; SPM, second primary malignancy.

Siddiqi T, et al. ASH 2023 [Presentation #330]

TRANSCEND CLL 004: Response in patients with high-risk genomic features (Mono)

Characteristic	OR rate	CR rate
Unmutated IGHV at screening		
Yes (n = 41) vs No (n = 19), %	41.5 vs 63.2	22.0 vs 21.1
Odds ratio (95% CI)	0.41 (0.13—1.27)	1.05 (0.28—3.98)
Del(17p) status at screening		
Yes (n = 34) vs No (n = 51), %	47.1 vs 45.1	26.5 vs 13.7
Odds ratio (95% CI)	1.08 (0.45—2.58)	2.26 (0.75—6.82)
***TP53* mutation at screening**		
Yes (n = 36) vs No (n = 50), %	41.7 vs 50.0	22.2 vs 16.0
Odds ratio (95% CI)	0.71 (0.30—1.69)	1.50 (0.50—4.46)
Del(17p) AND *TP53* mutation at screening		
Yes (n = 25) vs No (n = 60), %	44.0 vs 46.7	28.0 vs 15.0
Odds ratio (95% CI)	0.90 (0.35—2.30)	2.20 (0.72—6.78)
Complex karyotype at screening[a]		
Yes (n = 52) vs No (n = 34), %	44.2 vs 52.9	19.2 vs 17.6
Odds ratio (95% CI)	0.70 (0.30—1.68)	1.11 (0.36—3.40)

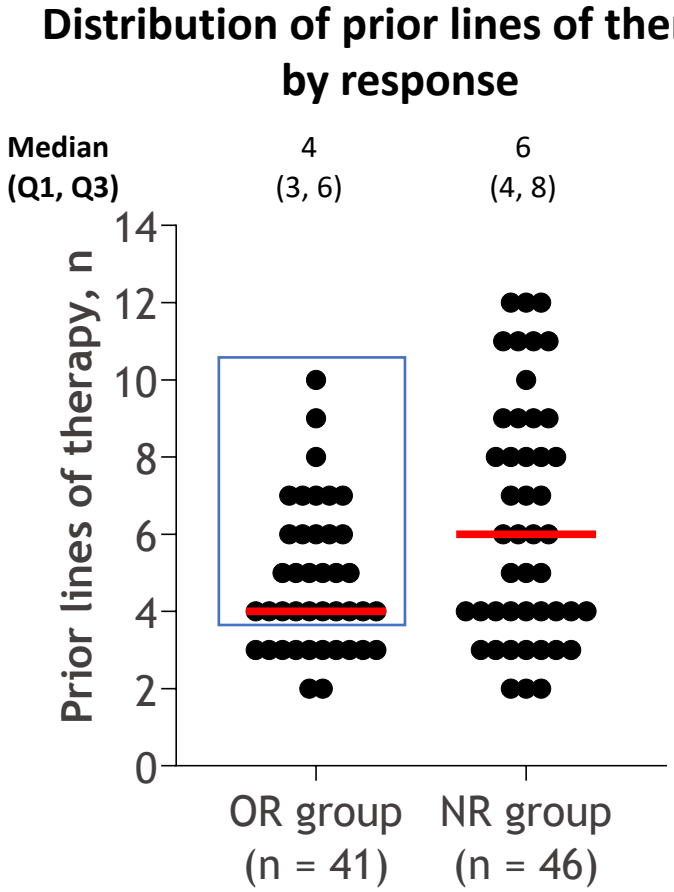
- Age was also not correlated with response

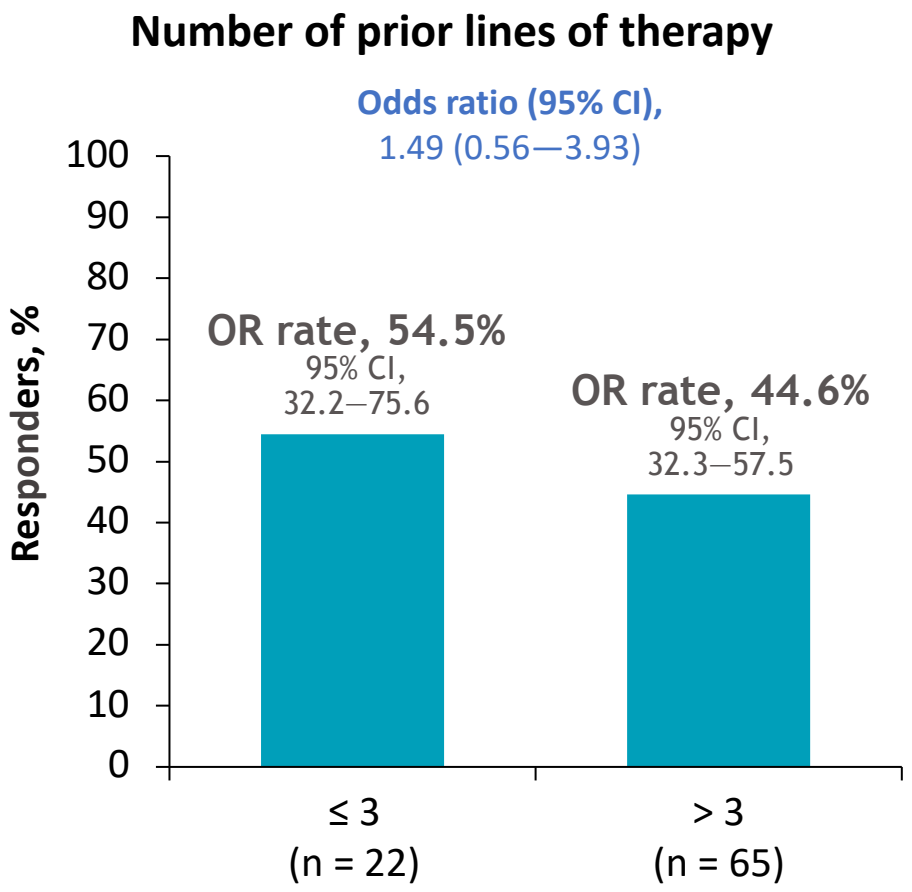
[a]Defined as the presence of ≥ 3 chromosomal aberrations.

Wierda, et al., EHA 2024; Abstract number S158

TRANSCEND CLL 004: Number of prior lines of therapy and overall response (Mono)

- Patients in TRANSCEND CLL 004 had heavily pretreated disease with a median of 5 prior lines of therapy, and responses were observed in patients with multiple prior treatments
- OR rate was numerically higher in patients who received ≤ 3 versus > 3 prior lines of therapy



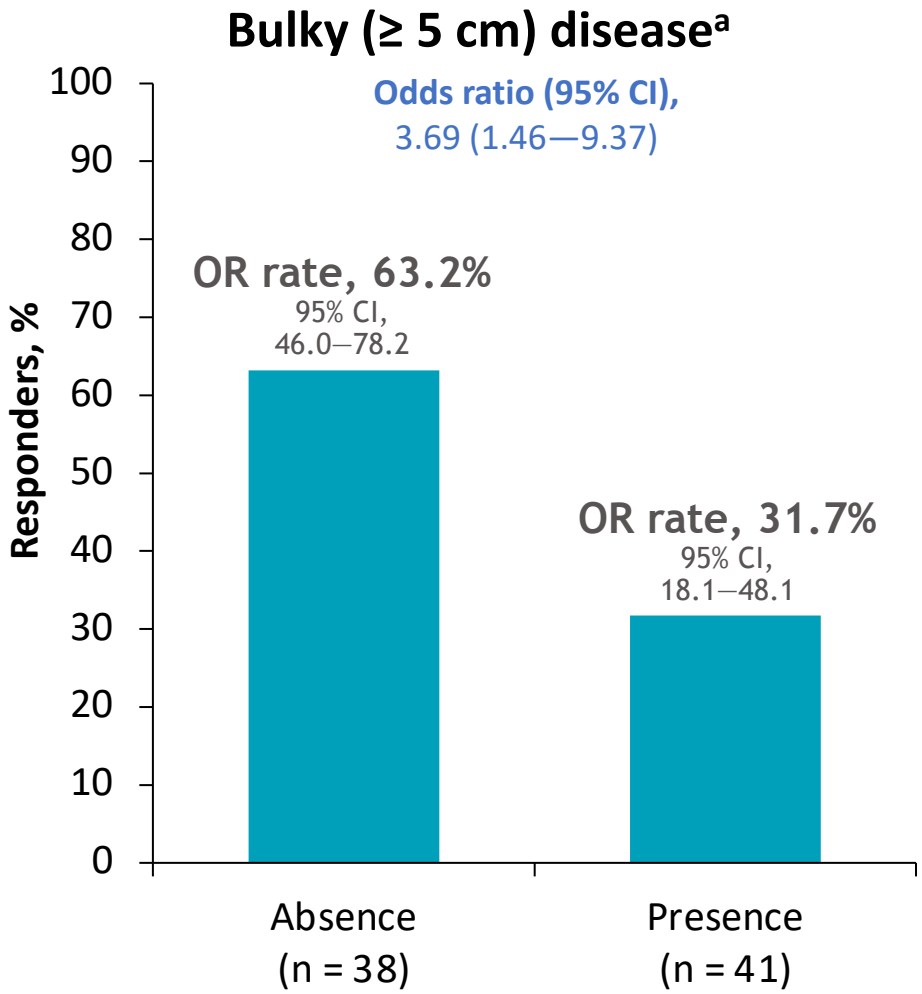


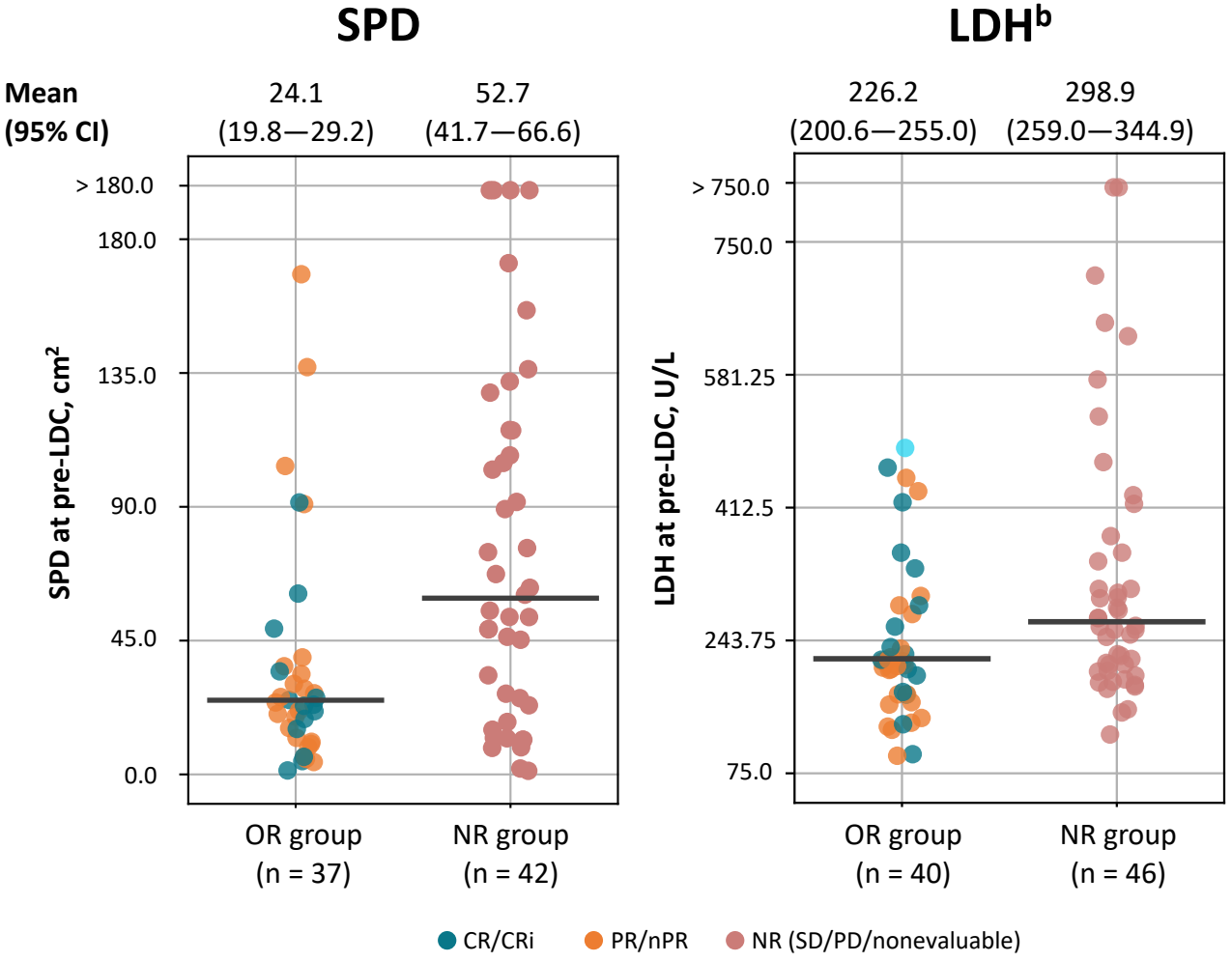
Wierda, et al., EHA 2024; Abstract number S158

Red lines indicate the median number of prior lines of therapy for each group.

TRANSCEND CLL 004: Tumor burden correlation with overall response (Mono)

- Lower tumor burden was correlated with overall response





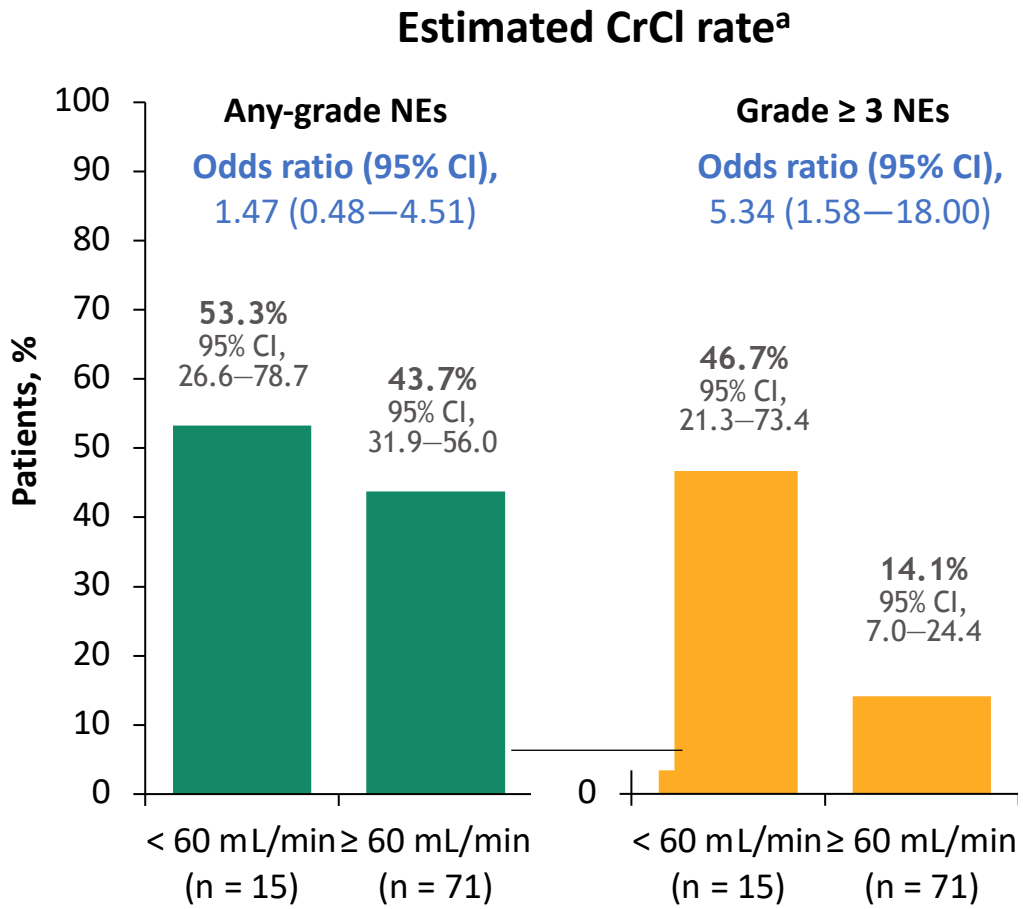
All characteristics were collected at the prelymphodepletion study visit unless otherwise specified. [a]Defined as ≥ 1 lesion with the longest diameter of ≥ 5 cm; [b]LDH was also associated with OR when treated as a discrete variable ≤ ULN.

Wierda, et al., EHA 2024; Abstract number S158

TRANSCEND CLL 004: Baseline inflammation, SPD, and renal insufficiency correlation with NEs (Mono)

- Inflammatory markers, bulky disease, and lower estimated CrCl rate may be associated with an increased risk of neurological events

Characteristic, mean (95% CI)	Any NE	No NE	Grade ≥ 3 NE	No grade ≥ 3 NE
SPD, cm^2	49.1 (40.7—59.2) n = 38	27.7 (21.6—35.7) n = 41	45.4 (33.4—61.7) n = 17	34.4 (28.4—41.6) n = 62
CRP, mg/L	16.6 (9.6—28.5) n = 38	5.1 (3.5—7.5) n = 47	22.5 (9.4—53.6) n = 16	6.9 (4.8—9.9) n = 69
Ferritin, pmol/L	457.0 (293.9—710.6) n = 38	275.5 (186.1—407.7) n = 47	278.5 (226.4—342.6) n = 16	258.8 (231.3—289.5) n = 69



All characteristics were collected at the prelymphodepletion study visit unless otherwise specified. [a]Calculated using Cockcroft-Gault equation; inclusion in the TRANSCEND CLL 004 study required serum creatinine ≤ 1.5 × age-adjusted ULN or calculated CrCl rate > 30 mL/min. CRP, C-reactive protein.

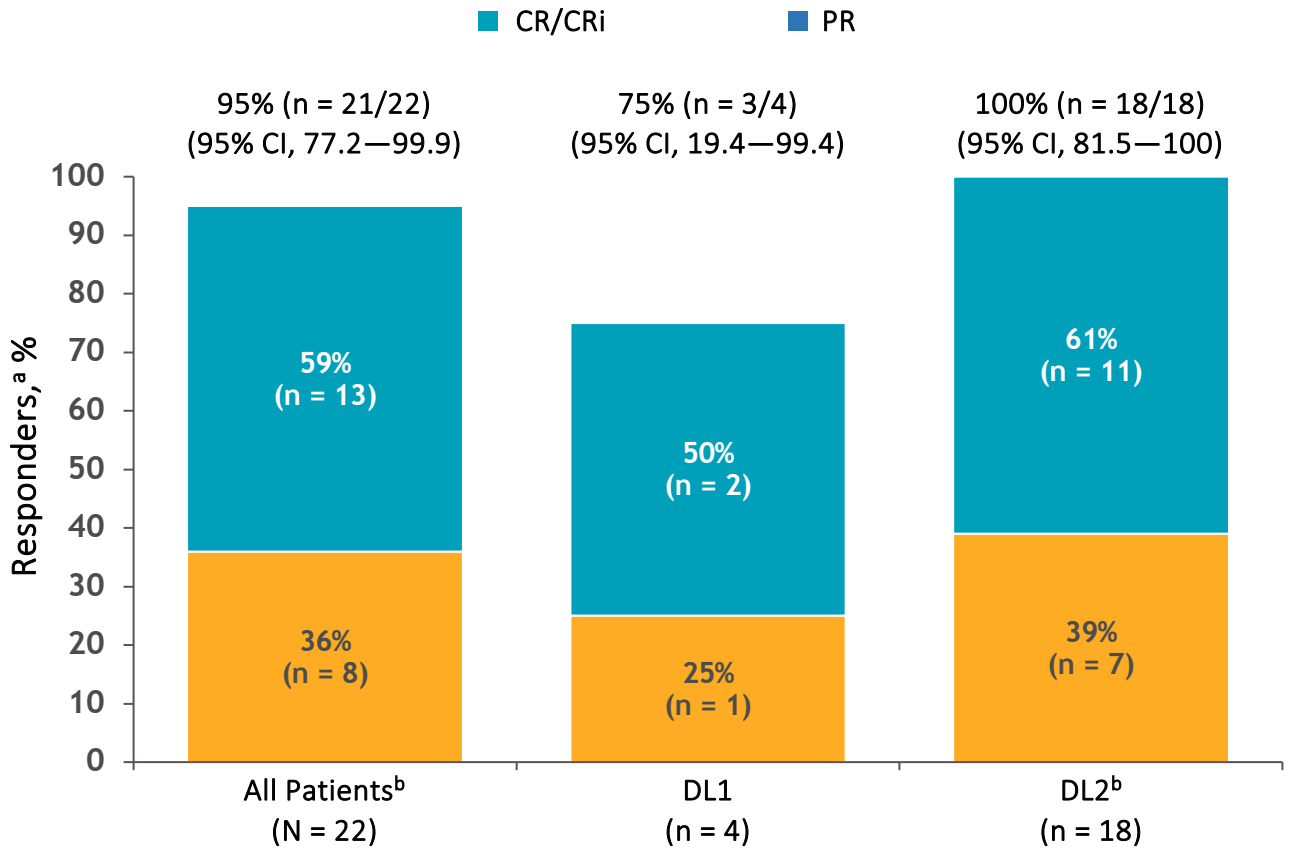
Wierda, et al., EHA 2024; Abstract number S158

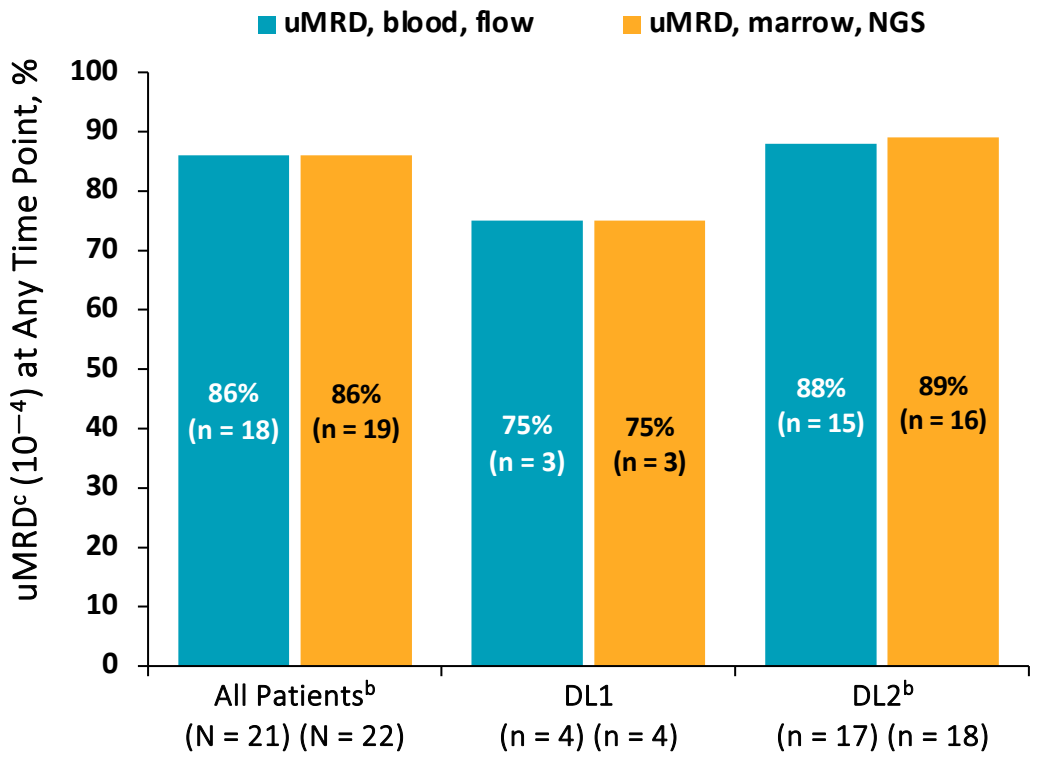
Demographic and Baseline Disease Characteristics (Combo)

Characteristic	All Patients (N = 23)	DL1 + Ibrutinib (n = 4)	DL2 + Ibrutinib (n = 19)
Median age, y (range)	61 (50–77)	58 (50–70)	62 (51–77)
Male, n (%)	16 (70)	2 (50)	14 (74)
Median time since diagnosis, mo (range)	121 (21–281)	84 (31–176)	127 (21–281)
Bulky disease ≥5 cm, n (%)[a]	6 (26)	0	6 (32)
Median SPD, cm^2 (range)	25 (2–193)	27 (2–55)	22 (3–193)
Median BALL risk score[1] (range)	1 (0–3)	1.5 (1–2)	1 (0–3)
Median LDH, U/L (range)	182 (104–604)	182.5 (104–428)	182 (106–604)
Stage, n (%)			
Rai stage III/IV	10 (43)	2 (50)	8 (42)
Binet stage C	10 (43)	2 (50)	8 (42)
High-risk feature (any), n (%)	22 (96)	4 (100)	18 (95)
del(17p)	9 (39)	2 (50)	7 (37)
TP53 mutated	8 (35)	1 (25)	7 (37)
Complex karyotype[b]	10 (43)	3 (75)	7 (37)
Median no. of lines of prior therapy (range)	4 (1–10)	4.5 (1–5)	3 (1–10)
Prior ibrutinib, n (%)	23 (100)	4 (100)	19 (100)
Ibrutinib relapsed or refractory, n (%)	23 (100)	4 (100)	19 (100)
Prior BTKi and venetoclax, n (%)	12 (52)	2 (50)	10 (53)
Received additional bridging therapy, n (%)	9 (39)	2 (50)	7 (37)

[a]Bulky disease defined as ≥1 lesion with longest diameter of ≥5 cm; [b]At least 3 chromosomal aberrations.
BALL, β_2 macroglobulin, anemia, LDH, and time from last therapy; BTKi, Bruton tyrosine kinase inhibitor; SPD, sum of the product of perpendicular diameters.
1. Soumerai JD, et al. *Lancet Haematol*. 2019;6:e366-e374.

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





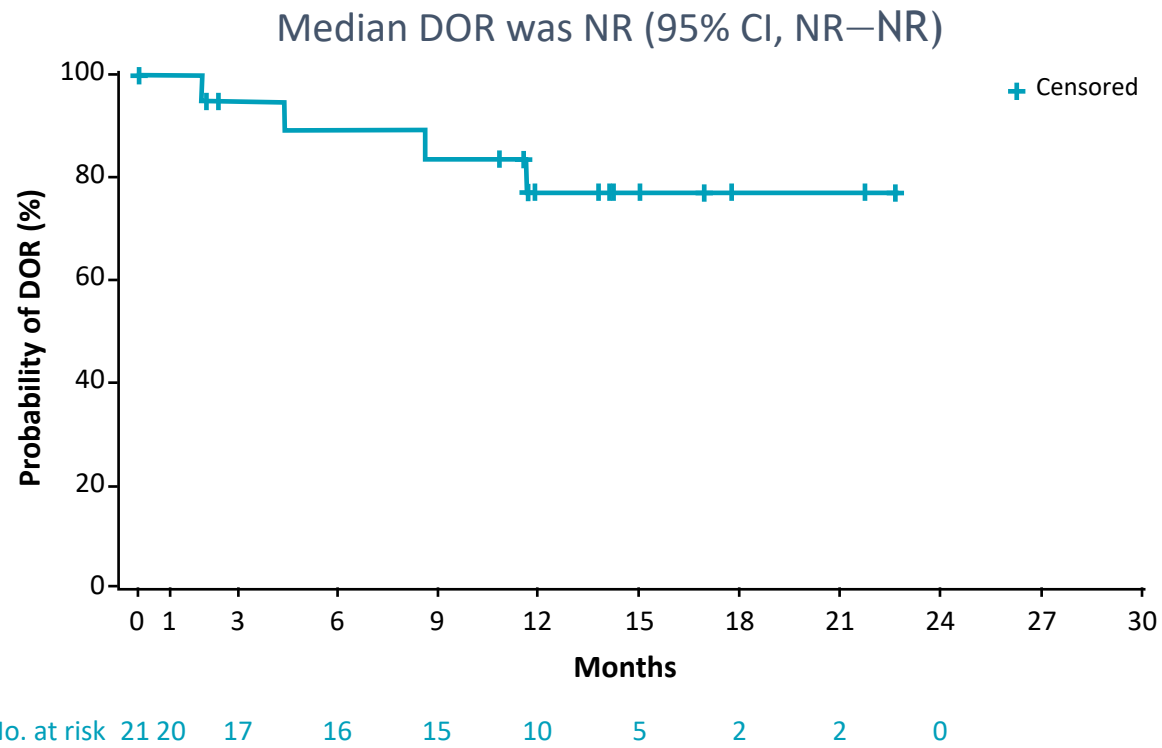
- No patients had PD during the first month after liso-cel
- One patient at DL1 had SD for 6 months but later progressed

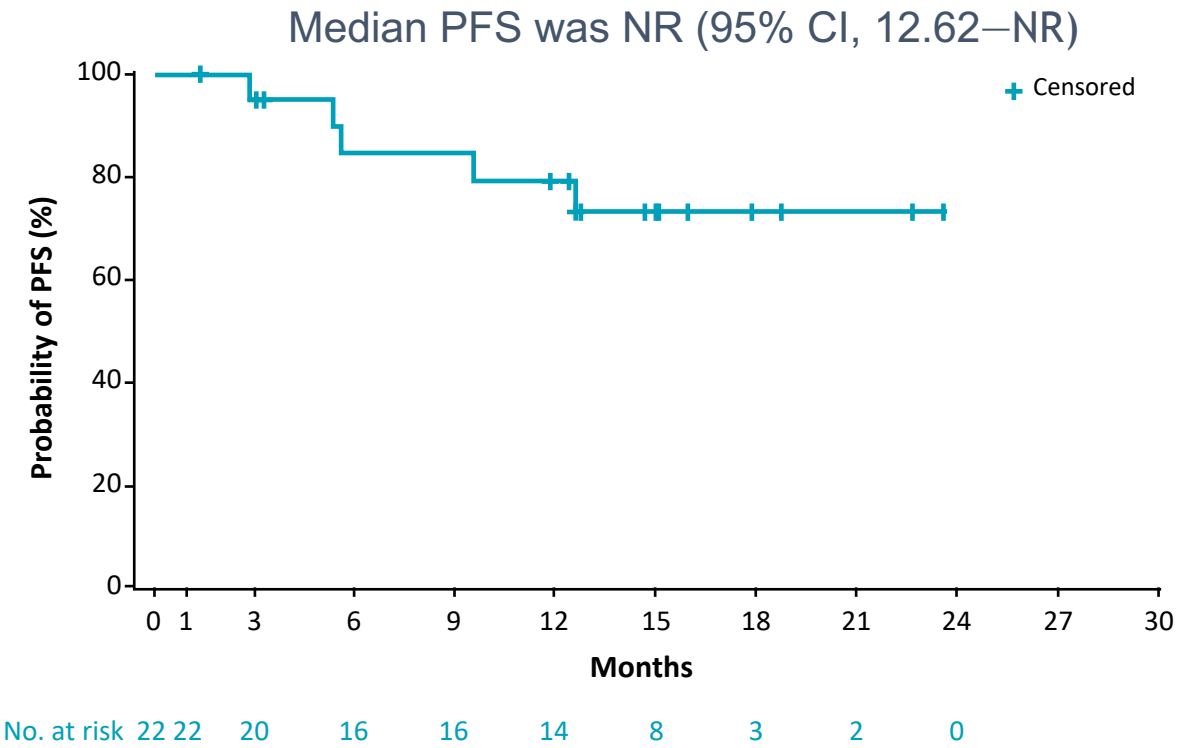
[a]Evaluated according to iwCLL 2018 criteria; [b]At the time of this data cut, 1 patient had only 11 days of follow-up after liso-cel infusion and was not yet evaluable for response;
[c]Assessed in blood by flow cytometry and/or in bone marrow by NGS.
CRi, CR with incomplete blood count recovery; NGS, next-generation sequencing.

ICML, 2021; Presentation Number 86

PFS and Duration of Response (Combo)

- The median follow-up for all patients was 17 months





DOR, duration of response; NR, not reached; PFS, progression-free survival.

ICML, 2021; Presentation Number 86

Treatment-Emergent AEs, Cytokine Release Syndrome, and Neurological Events (Combo)

- 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)

[a]Based on Lee criteria (Lee DW, et al. *Blood.* 2014;124:188–195); [b]NEs were not mutually exclusive: aphasia (n = 2), agitation (n = 1), ataxia (n = 1), confusional state (n = 1), and encephalopathy (n = 1).

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Ibrutinib-Related Treatment-Emergent AEs Infrequently Resulted in Dose Reduction or Discontinuation (Combo)

Parameter	All Patients (N = 23)	DL1 + Ibrutinib (n = 4)	DL2 + Ibrutinib (n = 19)
Ibrutinib-related TEAEs, n (%)	19 (83)	4 (100)	15 (79)
Grade 3/4 ibrutinib-related TEAEs	9 (39)	3 (75)	6 (32)
Ibrutinib dose reduced due to TEAE, n (%)	2 (9)	0	2 (11)
Ibrutinib discontinued due to TEAE, n (%)	4 (17)	1 (25)	3 (16)
Received ≥90 days of ibrutinib after liso-cel,[a] n (%)	17 (74)	4 (100)	13 (68)
Median total duration of ibrutinib therapy, days (range)	141 (45—629)	161.5 (94—285)	141 (45—629)
Median duration of ibrutinib therapy after liso-cel infusion, days (range)	97 (9—584)	132 (59—197)	97 (9—584)

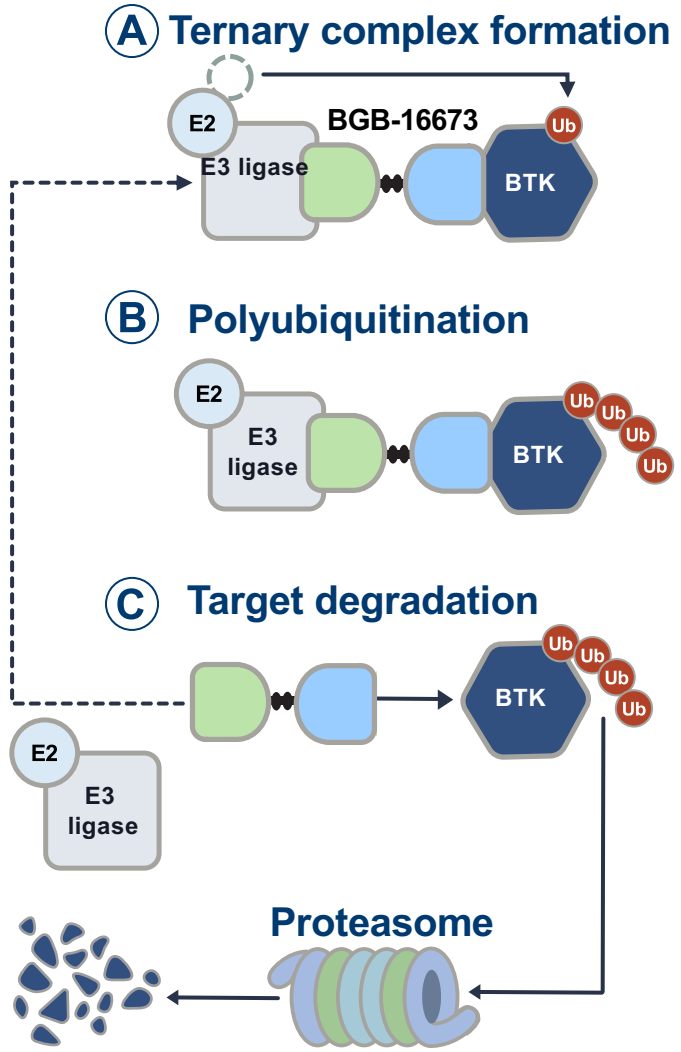
- Grade 3/4 ibrutinib-related TEAEs included neutropenia/neutrophil count decrease (n = 6), anemia (n = 4), thrombocytopenia (n = 2), atrial fibrillation (n = 1), hypertension (n = 1), lung infection (n = 1), and staphylococcal infection (n = 1)
- TEAEs/toxicities leading to ibrutinib dose reduction (all resolved):
  - Grade 2 atrial fibrillation and grade 2 fatigue
- TEAEs leading to ibrutinib discontinuation (all resolved):
  - Grade 3 atrial fibrillation, grade 2 red blood cell aplasia (related to liso-cel), grade 2 fatigue, and grade 1 palpitations

[a]Five patients were still receiving ibrutinib.

ICML, 2021; Presentation Number 86

BGB-16673: A Chimeric Degradation Activating Compound (CDAC)

- Many patients with CLL/SLL experience disease progression after BTK inhibitors[1-3]
- BGB-16673, a CDAC, is a bivalent molecule comprising a BTK-binding moiety + linker + E3 ligase binder that induces BTK degradation via polyubiquitination[4]
- In preclinical models, BGB-16673 degraded both wild-type and mutant BTK resistant to covalent and noncovalent BTK inhibitors,[a] leading to tumor suppression[4,5]
- BGB-16673 led to substantial reductions in BTK protein levels in peripheral blood and tumor tissue in the first-in-human study[6]
- Here, the updated safety and efficacy results are presented from patients with R/R CLL/SLL in the ongoing CaDAnCe-101 study



Parrondo, et al. EHA 2024, Abstract S157

[a] Covalent BTK inhibitor–resistant mutations including C481S, C481F, C481Y, L528W, and T474I; non-covalent BTK inhibitor–resistant mutations including V416L, M437R, T474I, and L528W. CDAC, chimeric degradation activating compound; ub, ubiquitin.

1. Tam CS, et al. *Blood Cancer J*. 2023;13(1):141-413; 2. Woyach JA, et al. *N Engl J Med*. 2014;370:2286-2294; 3. Wang E, et al. *N Engl J Med.* 2022;386:735-743; 4. Feng X, et al. EHA 2023. Abstract P1239; 5. Wang H, et al. EHA 2023. Abstract P1219; 6. Seymour JF, et al. ASH 2023; Abstract 4401.

BGB-16673: Study Design

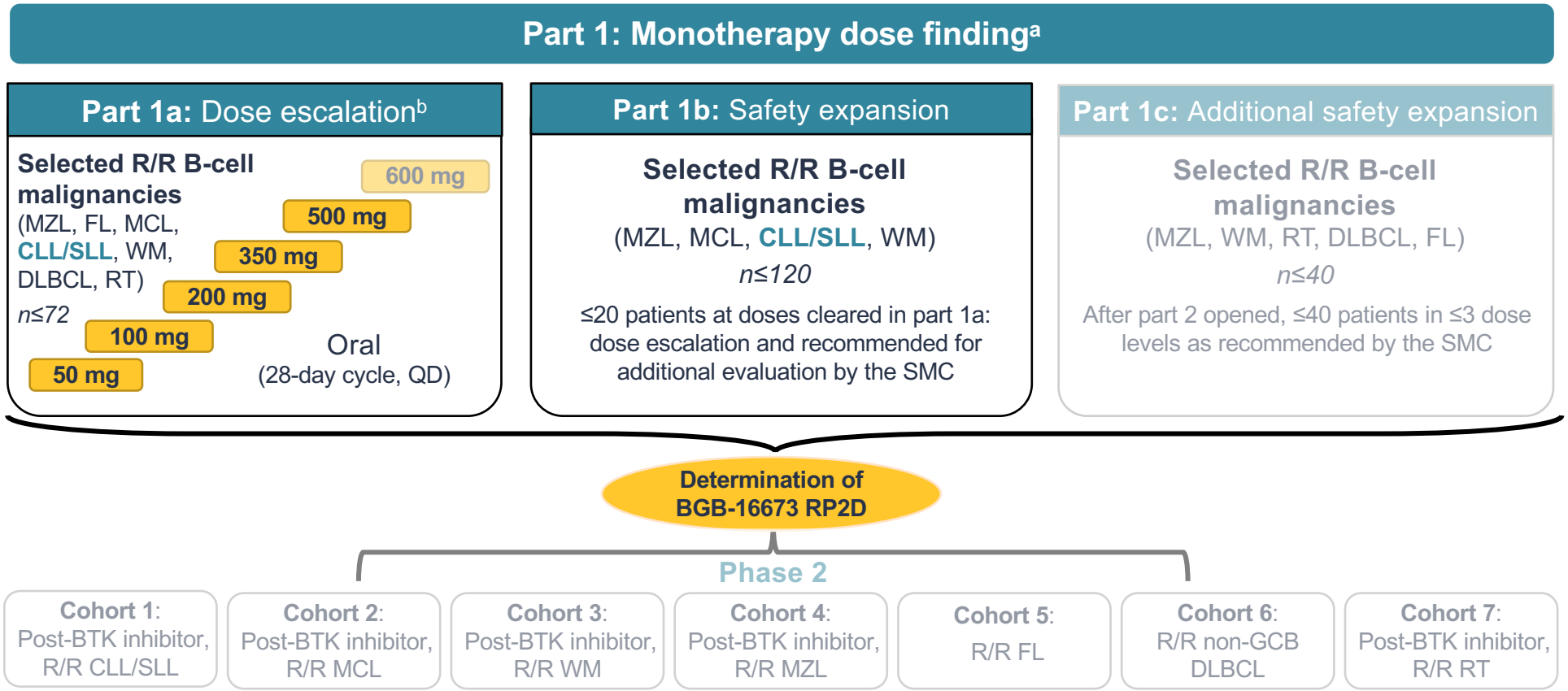
- CaDAnCe-101 (BGB-16673-101, NCT05006716) is a phase 1/2, open-label, dose-escalation and dose-expansion study evaluating BGB-16673 in adults with R/R B-cell malignancies

Key eligibility criteria for CLL/SLL

- Meets iwCLL 2018 criteria for treatment
- ≥2 prior therapies, including cBTKi if approved for disease
- ECOG PS 0-2 & adequate end-organ function

Key study objectives for part 1

- **Primary:** safety[c] and tolerability, MTD, and RP2D
- **Secondary:** PK, PD, and preliminary antitumor activity[d]



[a] Data from grey portions of figure are not included in this presentation. [b] Bayesian optimal interval design with 6 dose levels (50-600 mg orally QD). [c] Safety was assessed according to CTCAE v5.0 in all patients and iwCLL hematologic toxicity criteria in patients with CLL; DLTs were assessed during the first 4 weeks. [d] Response was assessed per iwCLL 2018 criteria after 12 weeks for patients with CLL.[1]

GCB, germinal center B-cell; RT, Richter transformation. 1. Hallek M, et al. *Blood.* 2018;131:2745-2760.

Parrondo, et al. EHA 2024, Abstract S157

BGB-16673: Most Frequent Adverse Events

Patients, n (%)	Total (N=49)[a]	
	All Grade	Grade ≥3
Fatigue	16 (33)	1 (2)
Contusion	14 (29)	0
Anemia	11 (22)	1 (2)
Diarrhea	11 (22)	0
Neutropenia/neutrophil count decreased	11 (22)	10 (20)
Pneumonia	8 (16)	6 (12)
COVID-19	7 (14)	0
Cough	7 (14)	0
Dyspnea	7 (14)	0
Amylase increased[b]	6 (12)	0
Lipase increased[b]	6 (12)	1 (2)
Pyrexia	6 (12)	0
Thrombocytopenia/platelet count decreased	6 (12)	0
Arthralgia	5 (10)	0
Decreased appetite	5 (10)	0
Nausea	5 (10)	0

No cases of atrial fibrillation or grade ≥3 hypertension were reported

[a] All grade TEAEs in ≥10% of patients. [b] All events were lab findings and were transient, mostly occurring during the first 1-3 cycles of treatment, with no clinical pancreatitis.

BGB-16673: Responses to Treatment

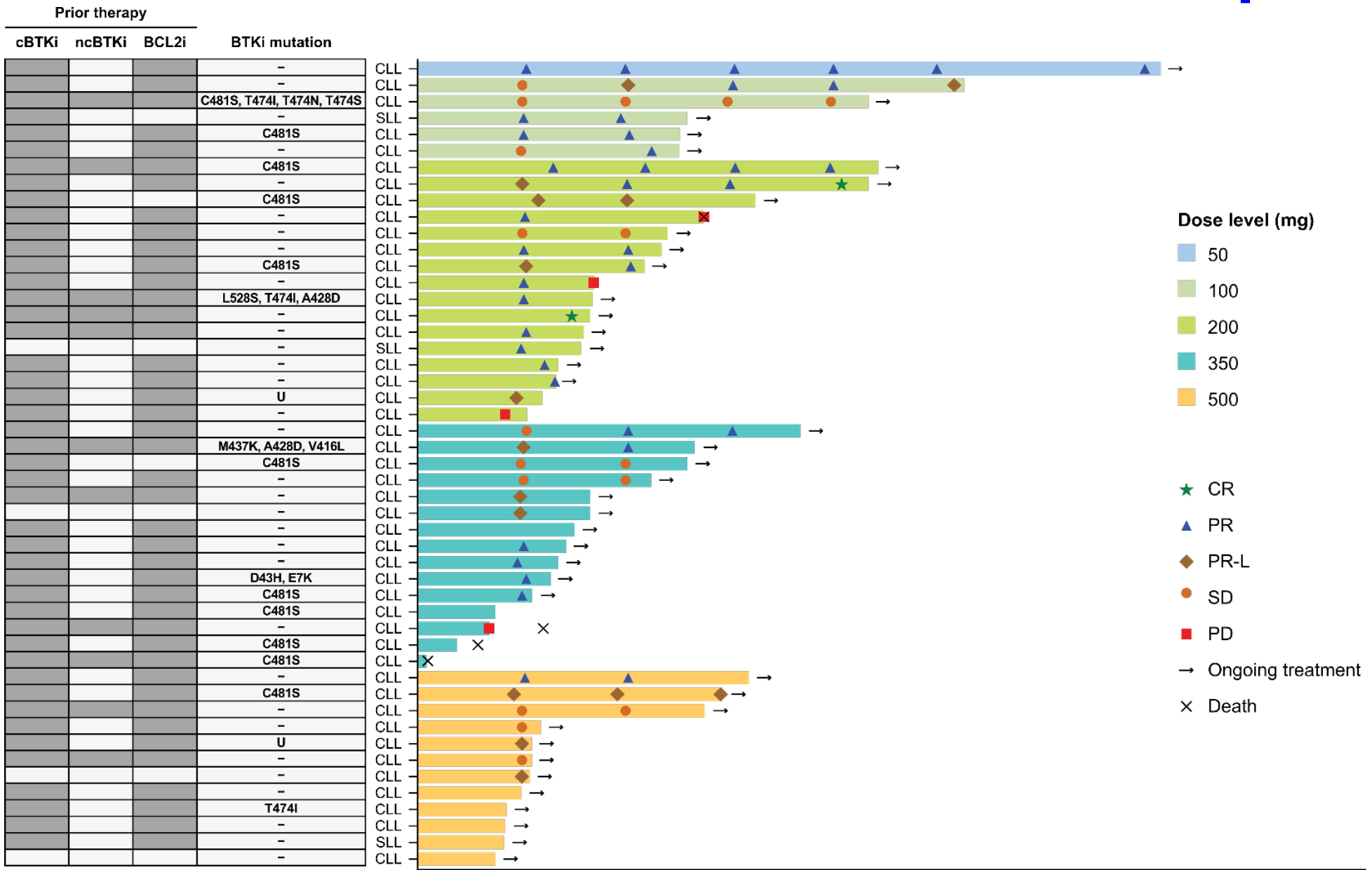
- The ORR was 72% (31/43) in response-evaluable patients with CLL/SLL
- The ORR for the 200-mg group was 88%, with 2 patients achieving CR

	50 mg (n=1)	100 mg (n=5)	200 mg (n=16)	350 mg (n=14)	500 mg (n=7)	Total (N=43)
Best overall response, n (%)[a]						
CR	0	0	2 (13)	0	0	**2 (5)**
PR	1 (100)	4 (80)	10 (63)	6 (43)	1 (14)	**22 (51)**
PR-L	0	0	2 (13)	2 (14)	3 (43)	**7 (16)**
SD	0	1 (20)	1 (6)	2 (14)	3 (43)	**7 (16)**
PD	0	0	1 (6)	1 (7)	0	**2 (5)**
Discontinued prior to first assessment	0	0	0	3 (21)	0	**3 (7)**
ORR, n (%)[b]	**1 (100)**	**4 (80)**	**14 (88)[c]**	**8 (57)**	**4 (57)**	**31 (72)**
Disease control rate, n (%)[d]	1 (100)	5 (100)	15 (94)	10 (71)	7 (100)	**38 (88)**
Follow-up time, median, months	19.8	7.2	6.3	3.9	3.3	**4.6[e]**
Time to first response, median (range), months[f]	2.9 (2.9-2.9)	4.2 (2.8-6.2)	2.8 (2.6-4.1)	2.8 (2.6-5.6)	2.8 (2.6-2.8)	**2.8 (2.6-6.2)**

[a] Percentages may not sum to 100 due to rounding. [b] Proportion of patients who achieved a best overall response of PR-L or better. [c] One additional patient reported response after the February 14, 2024 data cut, indicating a 94% ORR (15/16 patients) in the 200-mg dose group. [d] Proportion of patients who achieved a best overall response of SD or better. [e] Study follow-up enrolled set N=49. [f] Time to first qualifying response in patients with a best overall response better than SD. PR-L, partial response with lymphocytosis.

Parrondo, et al. EHA 2024, Abstract S157

BGB-16673: Treatment Duration and Response



BTK mutation status listed or was absent (-) or unknown (U).

PR-L, partial response with lymphocytosis.

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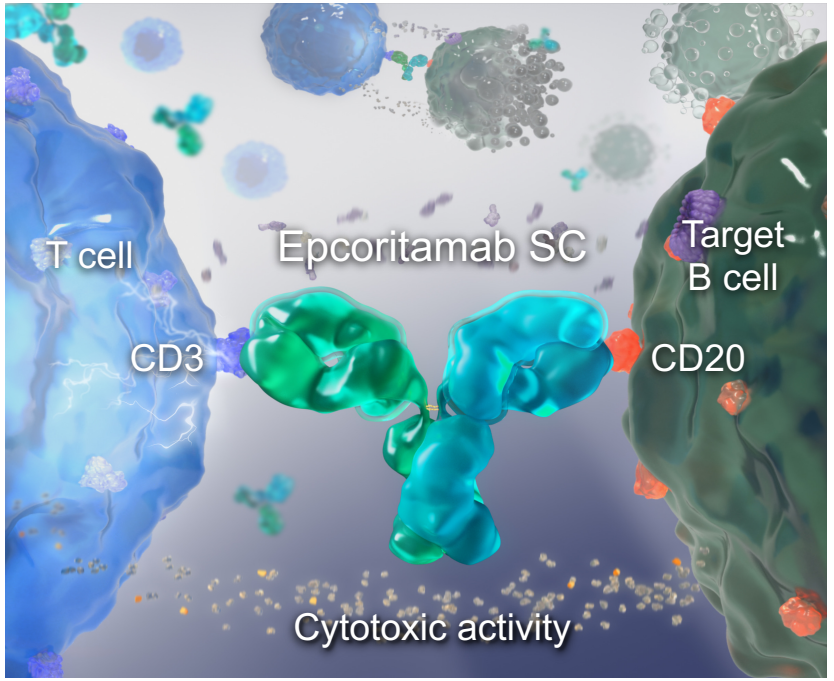
Novel Treatment Options for Patients With R/R CLL

- Bruton tyrosine kinase (BTK) and B-cell lymphoma 2 (Bcl-2) inhibitors have improved outcomes in R/R CLL; however, they are not considered curative[1,2]
- An increasing number of patients with R/R CLL are double-refractory to these agents, and there is a lack of effective salvage options, leading to very poor outcomes[3]
- Novel, efficacious therapies are needed for these patients, who often have poor prognostic factors, including genomic aberrations[1,2]



Epcoritamab is a novel CD3xCD20 bispecific antibody

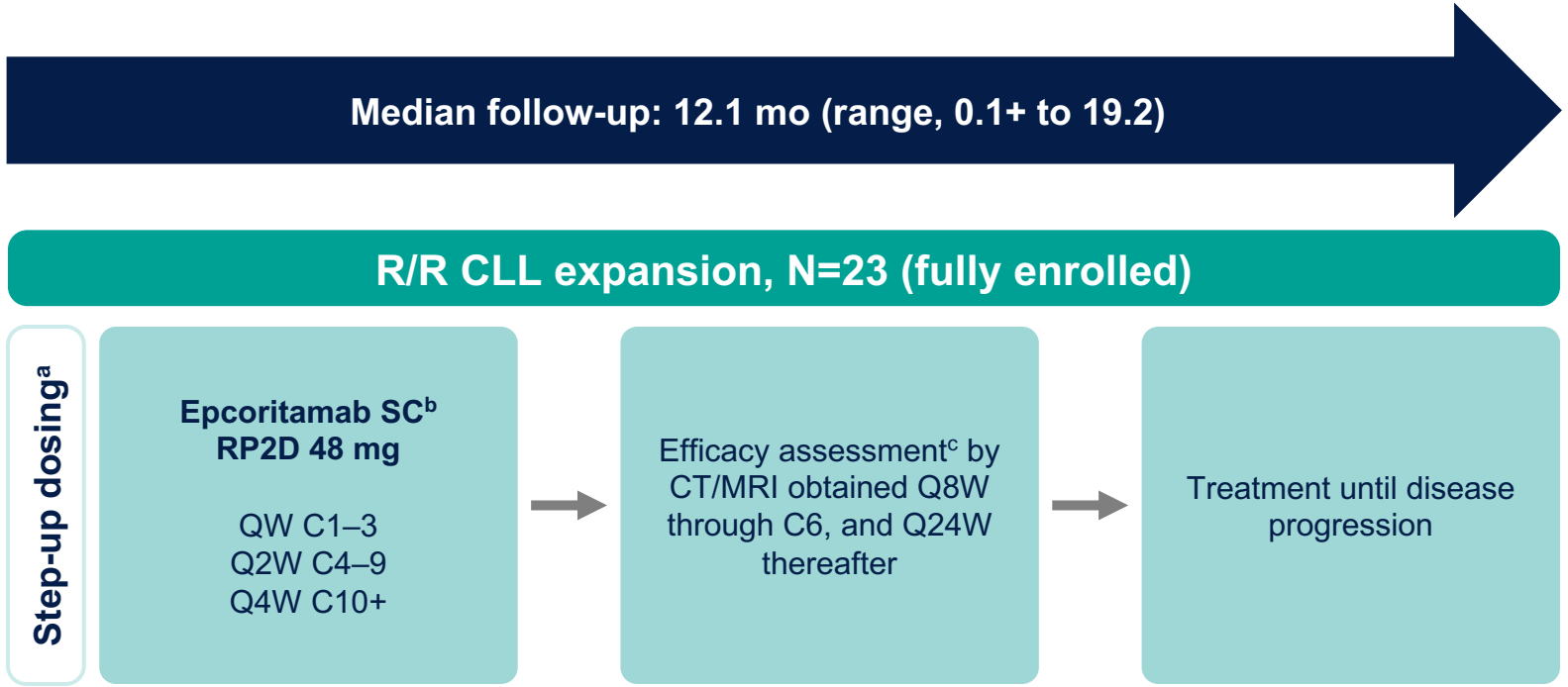
- Approved by the US FDA for the treatment of adults with R/R DLBCL, not otherwise specified, including DLBCL arising from indolent lymphoma, and HGBCL after ≥2 lines of systemic therapy[4]; also approved by the EMA[a,5] and the Japan PMDA[b,6]
- Previous reports from EPCORE CLL-1 showed encouraging efficacy and manageable safety in R/R CLL (dose escalation) and Richter's transformation (dose expansion)[7,8]

[a]Approved in Europe for the treatment of adults with R/R DLBCL after ≥2 lines of systemic therapy. [b]Approved in Japan for the treatment of adults with the following R/R LBCL: DLBCL, HGBCL, PMBCL, and FL G3B after ≥2 lines of systemic therapy. **1.** Hallek M, et al. *Lancet*. 2018;391:1524-37. **2.** Dreger P, et al. *Blood*. 2018;132:892-902. **3.** Martens AWJ, et al. *Leukemia*. 2023;37:606-16. **4.** EPKINLY [prescribing information]. Plainsboro, NJ: Genmab US, Inc.; 2023. **5.** Tepkinly [summary of product characteristics]. Ludwigshafen, Germany: AbbVie Deutschland GmbH & Co. KG; 2023. **6.** EPKINLY [prescribing information]. Tokyo, Japan: Genmab K.K.; 2023. **7.** Kater AP, et al. ASH 2021. Abstract 2627. **8.** Kater AP, et al. ASH 2022. Abstract 348.

Study Design: EPCORE CLL-1 Expansion Cohort

Key inclusion criteria

- CD20^{+} R/R CLL
- ≥2 prior lines of systemic therapy, including treatment with or intolerance to a BTK inhibitor
- ECOG PS 0–2
- Requiring treatment per iwCLL criteria
- Measurable disease with ≥5×10^{9}/L B lymphocytes or measurable lymphadenopathy or organomegaly
- No minimum life expectancy required



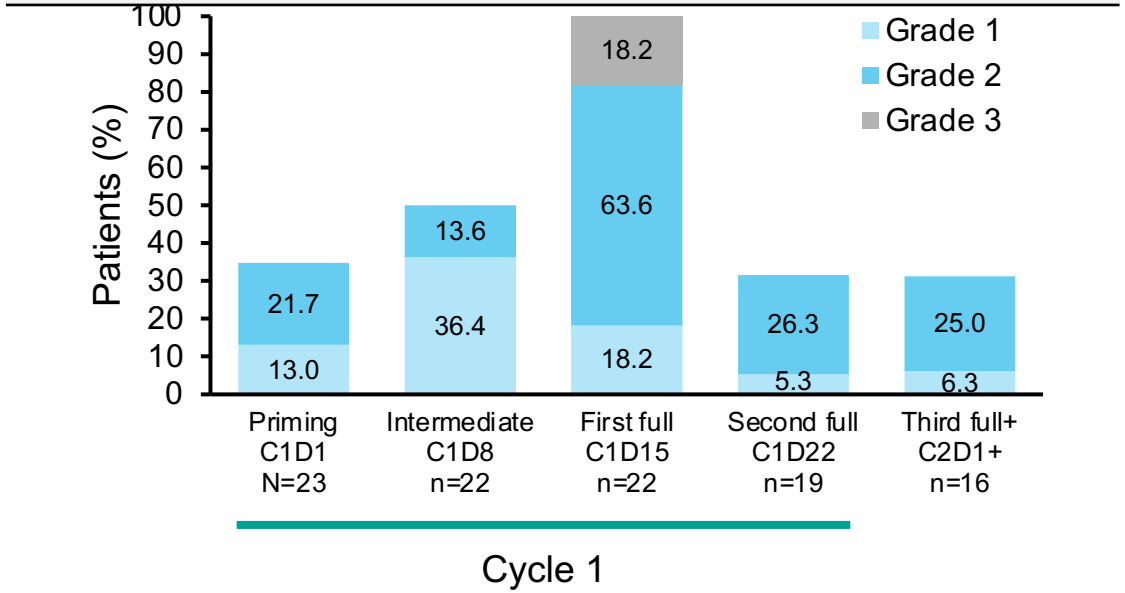
- **Primary endpoint:** Overall response rate (ORR)
- **Key secondary endpoints:** Complete response (CR) rate, time to response, safety/tolerability, and measurable residual disease (MRD) in PBMCs using the clonoSEQ next-generation sequencing (NGS) assay

Data cutoff: July 5, 2023. Epcoritamab was administered in 28-d cycles. [a]Patients received epcoritamab SC with step-up dosing (ie, 0.16 mg priming and 0.8 mg intermediate doses before first full dose) and corticosteroid prophylaxis as previously described to mitigate CRS. [b]To ensure patient safety and better characterize CRS, inpatient monitoring was required for the first 4 doses of epcoritamab. [c]Based on iwCLL guidelines. PBMCs, peripheral blood mononuclear cells.

Kater, et al., iwCLL 2023

AEs of Special Interest

CRS[a]	Total, N=23
Median time to onset after first full dose, h (range)	7.3 (1–99)
Median time to resolution, d (range)[b]	3 (1–16)
Treated with tocilizumab, n (%)	19 (83)
CRS resolution, n/n (%)	22/22 (100)



[a]Graded by Lee et al 2019 criteria. [b]Median is Kaplan–Meier estimate based on longest CRS duration in patients with CRS. [c]All ICANS events occurred with grade 2 CRS.

ICANS & Clinical Tumor Lysis Syndrome	Total, N=23
ICANS, n (%)[c]	**3 (13)**
Grade 1	1 (4)
Grade 2	2 (9)
Median time to resolution, d (range)	3 (3–4)
ICANS resolution, n/n (%)	3/3 (100)
Tumor lysis syndrome, n (%)	**1 (4)**
Laboratory only	0
Clinical – grade 2	1 (4)
Time to resolution, d	11
Clinical tumor lysis syndrome resolution, n/n (%)	1/1 (100)

- CRS occurrence was predictable, with most cases following the first full dose
- No AEs of special interest led to discontinuation, and all resolved

Kater, et al., iwCLL 2023

High Overall and Complete Response Rates

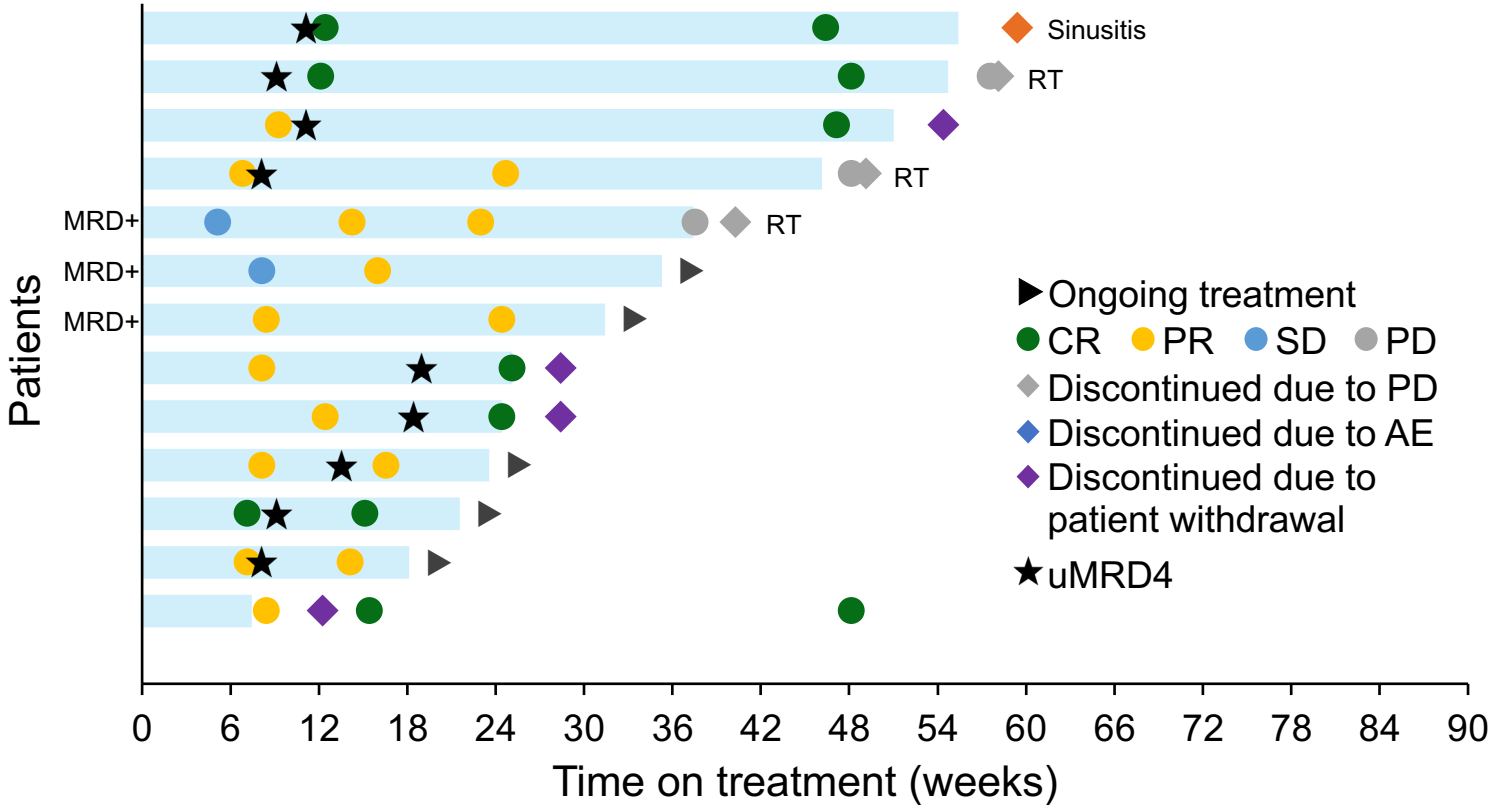
Response, n (%)[a]	Total Efficacy Evaluable n=21	*TP53* Aberration n=14	Double-Exposed[b] n=17	*IGHV* Unmutated n=15
Overall response[c]	**13 (62)**	**9 (64)**	**9 (53)**	**9 (60)**
Complete response	7 (33)	4 (29)	5 (29)	6 (40)
Partial response	6 (29)	5 (36)	4 (24)	3 (20)
Stable disease	4 (19)	2 (14)	4 (24)	3 (20)
Progressive disease	1 (5)	1 (7)	1 (6)	1 (7)

Encouraging overall and complete response rates observed, including in difficult-to-treat, high-risk R/R CLL patients

Three patients were not evaluable or had no assessment, including 2 patients who died without postbaseline assessment. [a]Based on response-evaluable population, defined as patients who received ≥1 full dose of epcoritamab, had ≥1 postbaseline response evaluation, or died within 60 d of first dose. [b]Patients previously treated with both a BTK inhibitor and a Bcl-2 inhibitor. [c]Response assessment according to iwCLL criteria.

Kater, et al., iwCLL 2023

Depth and Duration of Response



	Assessed for MRD n=12
Patients with uMRD4,[a,b] n/n (%)	9/12 (75)
CR with uMRD4	6/6
PR with uMRD4	3/6
MRD-positive patients,[a] n/n (%)	3/12 (25)
> uMRD4 to uMRD2	1/3
MRD > uMRD2	2/3

MRD was evaluated in PBMCs using the clonoSEQ next-generation sequencing assay. [a]Among responders who were tested for MRD. [b]Eight of 12 patients had uMRD6.

uMRD4 was achieved by most responders, including all patients with CR who were tested for MRD

Median follow-up, mo (range): 12.1 (0.1+ to 19.2). Median number of treatment cycles initiated (range): 5 (1–14). Median duration of treatment, mo (range): 5.0 (0.03–12.7). RT, Richter's transformation; uMRD, undetectable MRD.

Kater, et al., iwCLL 2023

Summary

- A single administration of liso-cel monotherapy demonstrated rapid, deep, and durable responses in patients with R/R CLL/SLL, with median follow-up 23.5 mos
- Safety data demonstrated that safety was manageable, with low rates of grade ≥ 3 CRS and NEs, and no notable safety signals
- Post hoc exploratory univariable analyses indicated that responses to liso-cel monotherapy are consistent in patients with R/R CLL/SLL regardless of high-risk genomic features, including unmutated IGHV, del(17p), *TP53* mutation, and complex karyotype
  - Lower baseline tumor burden and fewer lines of prior systemic therapy appear to be associated with increased likelihood of achieving response
- Higher baseline levels of inflammation markers (including CRP and ferritin) and renal insufficiency, in addition to high tumor burden, may be associated with an increased risk of NEs
- Preliminary data show that liso-cel combined with ibrutinib was well tolerated, with a low incidence of grade 3 CRS/NEs and no grade 4 or 5 CRS/NEs

Questions from General Medical Oncologists

- **I have a young man who had p53 at diagnosis with his hemolytic anemia. Promptly resolved with steroids. Symptomatic 8 years later. Progressed on ven/obin and zanubrutinib. p53 still 10%. Should he be sent for transplant? He is asking about CAR-T. Where is the data on that? How often should I check his p53 even if he is asymptomatic?**

Questions from General Medical Oncologists

- **Do you think CAR-T might be more effective in the contemporary population than it was in the trial? Our patients with a more recent diagnosis have not seen chemoimmunotherapy in the past and have less T-cell exhaustion. Could this impact on efficacy?**
- **Is there a bridging therapy you prefer for patients while they wait for access to CAR T cells? Should we be using pirtobrutinib as a bridge to CAR-T, or should we wait for patients to relapse on that agent before starting the collection/manufacturing process?**

Questions from General Medical Oncologists

- **What should we be thinking about next for patients who don't benefit from CAR T-cell therapy? Any experimental strategies you're excited about?**

What Clinicians Want to Know: Addressing Current Questions and Controversies Regarding the Role of CAR T-Cell Therapy and Bispecific Antibodies in the Management of Lymphoma

A CME Friday Satellite Symposium and Webcast Preceding the 66th ASH Annual Meeting

Friday, December 6, 2024

11:30 AM – 1:30 PM PT (2:30 PM – 4:30 PM ET)

Faculty

Jennifer Crombie, MD

Martin Hutchings, MD, PhD

Matthew Lunning, DO

Tycel Phillips, MD

Moderator

Jeremy S Abramson, MD, MMSc

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What Clinicians Want to Know: Addressing Current Questions and Controversies in the Management of Myelofibrosis

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Moderator

Andrew T Kuykendall, MD

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