Year in Review: Clinical Investigator Perspectives on the Most Relevant New Data Sets and Advances in Oncology

A Multitumor CME/MOC-Accredited Live Webinar Series

Chronic Lymphocytic Leukemia

Tuesday, February 6, 2024
5:00 PM – 6:00 PM ET

Faculty

Lindsey Roeker, MD

Jeff Sharman, MD

Moderator

Neil Love, MD

RTP Year in Review 2024

Faculty

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

MODERATOR
Neil Love, MD
Research To Practice
Miami, Florida

Jeff Sharman, MD
Medical Director of Hematology Research
US Oncology Network
Willamette Valley Cancer Institute and Research Center
Eugene, Oregon

RTP Year in Review 2024

Commercial Support

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

Dr Love — Disclosures

Dr Love is president and CEO of Research To Practice. Research To Practice receives funds in the form of educational grants to develop CME activities from the following companies: AbbVie Inc, Adaptive Biotechnologies Corporation, ADC Therapeutics, Agios Pharmaceuticals Inc, Alexion Pharmaceuticals, Amgen Inc, Array BioPharma Inc, a subsidiary of Pfizer Inc, Astellas, AstraZeneca Pharmaceuticals LP, Aveo Pharmaceuticals, Bayer HealthCare Pharmaceuticals, BeiGene Ltd, BeyondSpring Pharmaceuticals Inc, Blueprint Medicines, Boehringer Ingelheim Pharmaceuticals Inc, Bristol Myers Squibb, Celgene Corporation, Clovis Oncology, Coherus BioSciences, CTI Biopharma, a Sobi company, Daiichi Sankyo Inc, Eisai Inc, Elevation Oncology Inc, EMD Serono Inc, Epizyme Inc, Exact Sciences Corporation, Exelixis Inc, Five Prime Therapeutics Inc, Foundation Medicine, G1 Therapeutics Inc, Genentech, a member of the Roche Group, Genmab US Inc, Gilead Sciences Inc, Grail Inc, GSK, Halozyme Inc, Helsinn Healthcare SA, ImmunoGen Inc, Incyte Corporation, Ipsen Biopharmaceuticals Inc, Janssen Biotech Inc, administered by Janssen Scientific Affairs LLC, Jazz Pharmaceuticals Inc, Karyopharm Therapeutics, Kite, A Gilead Company, Kronos Bio Inc, Legend Biotech, Lilly, Loxo Oncology Inc, a wholly owned subsidiary of Eli Lilly & Company, MEI Pharma Inc, Merck, Mersana Therapeutics Inc, Mirati Therapeutics Inc, Natera Inc, Novartis, Novartis Pharmaceuticals Corporation on behalf of Advanced Accelerator Applications, Novocure Inc, Oncopeptides, Pfizer Inc, Pharmacyclics LLC, an AbbVie Company, Puma Biotechnology Inc, Regeneron Pharmaceuticals Inc, R-Pharm US, Sanofi, Seagen Inc, Servier Pharmaceuticals LLC, SpringWorks Therapeutics Inc, Stemline Therapeutics Inc, Sumitomo Dainippon Pharma Oncology Inc, Taiho Oncology Inc, Takeda Pharmaceuticals USA Inc, TerSera Therapeutics LLC, Tesaro, A GSK Company, TG Therapeutics Inc, Turning Point Therapeutics Inc, Verastem Inc, and Zymeworks Inc.

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.

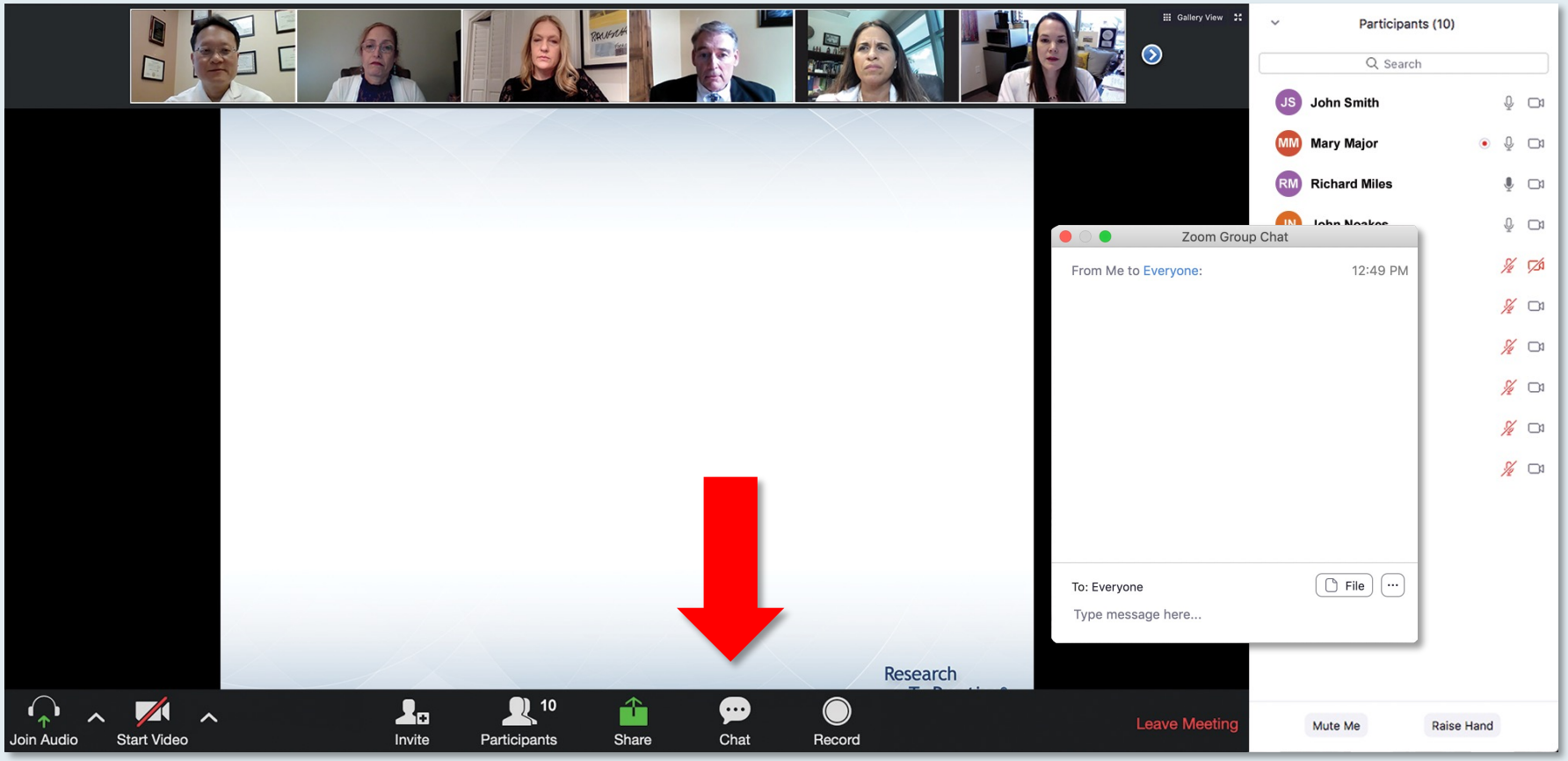
Dr Roeker — Disclosures

Advisory Committees	AbbVie Inc, Ascentage Pharma, AstraZeneca Pharmaceuticals LP, BeiGene Ltd, Janssen Biotech Inc, Loxo Oncology Inc, a wholly owned subsidiary of Eli Lilly & Company, TG Therapeutics Inc
CME Speaker	Curio Science, DAVA Oncology
Consulting Agreements	AbbVie Inc, Ascentage Pharma, AstraZeneca Pharmaceuticals LP, BeiGene Ltd, Janssen Biotech Inc, Loxo Oncology Inc, a wholly owned subsidiary of Eli Lilly & Company, Pfizer Inc, Pharmacyclics LLC, an AbbVie Company, TG Therapeutics Inc
Contracted Research	AbbVie Inc, Adaptive Biotechnologies Corporation, Aptose Biosciences Inc, AstraZeneca Pharmaceuticals LP, Dren Bio, Genentech, a member of the Roche Group, Loxo Oncology Inc, a wholly owned subsidiary of Eli Lilly & Company, Pfizer Inc, Sound Biologics
Stock Options/Stock — Public Company	Abbott Laboratories
Nonrelevant Financial Relationships	Medscape, PeerView

Dr Sharman — Disclosures

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

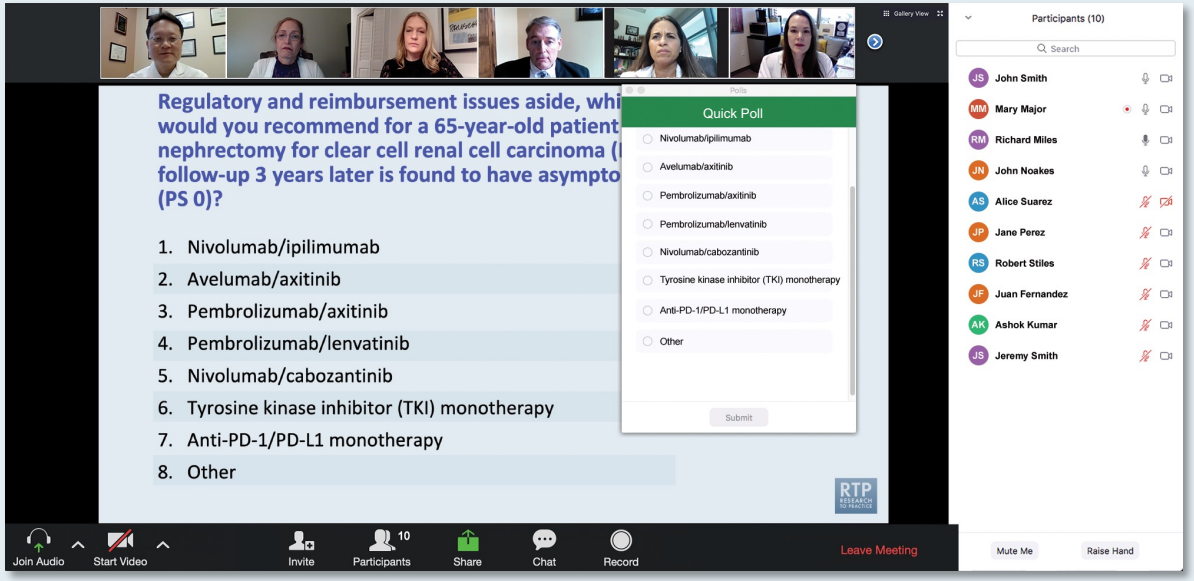
We Encourage Clinicians in Practice to Submit Questions



Feel free to submit questions now before the program begins and throughout the program.

RTP RESEARCH TO PRACTICE

Clinicians in the Audience, Please Complete the Pre- and Postmeeting Surveys



ONCOLOGY TODAY

WITH DR NEIL LOVE

Special Edition — Key Presentations on Chronic Lymphocytic Leukemia and Lymphoma from Recent Major Oncology/Hematology Conferences

DR JEREMY ABRAMSON
MASSACHUSETTS GENERAL HOSPITAL

Listen on Apple Podcasts

Spotify

Listen on Google Podcasts

Year in Review: Clinical Investigator Perspectives on the Most Relevant New Data Sets and Advances in Oncology

A Multitumor CME/MOC-Accredited Live Webinar Series

Gastroesophageal Cancers

Thursday, February 8, 2024
5:00 PM – 6:00 PM ET

Faculty

Yelena Y Janjigian, MD

Zev Wainberg, MD, MSc

Moderator

Neil Love, MD

RTP Year in Review 2024

Year in Review: Clinical Investigator Perspectives on the Most Relevant New Data Sets and Advances in Oncology

A Multitumor CME/MOC-Accredited Live Webinar Series

Lymphoma

Tuesday, February 13, 2024
5:00 PM – 6:00 PM ET

Faculty

Andrew M Evens, DO, MBA, MSc
Sonali M Smith, MD

Moderator

Neil Love, MD

RTP Year in Review 2024

Consensus or Controversy? Investigator Perspectives on the Current and Future Role of Immune Checkpoint Inhibitors in the Management of Hepatobiliary Cancers — A 2024 Post-ASCO Gastrointestinal Cancers Symposium Review

A CME-Accredited Virtual Event

Thursday, February 15, 2024
5:00 PM – 6:00 PM ET

Faculty

Robin (Katie) Kelley, MD
Mark Yarchoan, MD

Moderator

Neil Love, MD

RTP
RESEARCH
TO PRACTICE

Year in Review: Clinical Investigator Perspectives on the Most Relevant New Data Sets and Advances in Oncology

A Multitumor CME/MOC-Accredited Live Webinar Series

Urothelial Bladder Cancer

Thursday, February 22, 2024
5:00 PM – 6:00 PM ET

Faculty

Shilpa Gupta, MD

Thomas Powles, MBBS, MRCP, MD

Moderator

Neil Love, MD

RTP Year in Review 2024

JOIN US IN MARCH FOR THE RETURN OF

The Annual National General Medical Oncology Summit

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

MARCH 22-24, 2024

JW Marriott Miami Turnberry

To Learn More or to Register, Visit
www.ResearchToPractice.com/Meetings/GMO2024

Agenda

INTRODUCTION: An Audio Depiction of Mechanisms of Action of Bcl-2 Inhibitors, Anti-CD20 Antibodies and Covalent and Noncovalent BTK Inhibitors; Mechanisms of Resistance

MODULE 1: Current Management Approaches for Patients with Chronic Lymphocyctic Leukemia (CLL) — Dr Sharman

MODULE 2: Top 10 Questions — Part 1

MODULE 3: Future Directions in the Care of Patients with CLL — Dr Roeker

MODULE 4: Top 10 Questions — Part 2

Thank you for joining us!

CME and MOC credit information will be emailed to each participant within 5 business days.

RTP Year in Review 2024

Year in Review: Clinical Investigator Perspectives on the Most Relevant New Data Sets and Advances in Oncology

A Multitumor CME/MOC-Accredited Live Webinar Series

Chronic Lymphocytic Leukemia

Tuesday, February 6, 2024
5:00 PM – 6:00 PM ET

Faculty

Lindsey Roeker, MD

Jeff Sharman, MD

Moderator

Neil Love, MD

RTP Year in Review 2024

Faculty

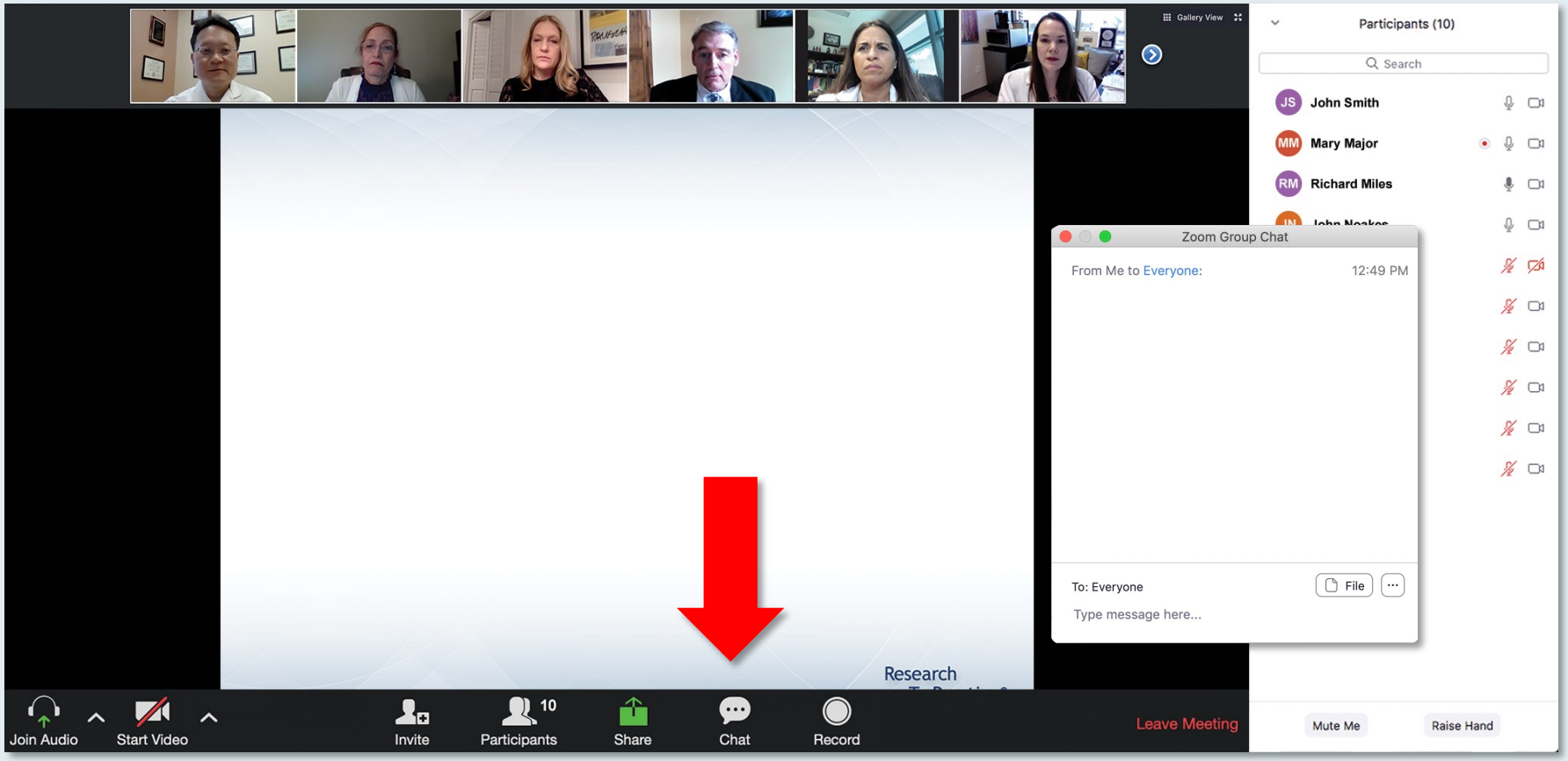
Lindsey Roeker, MD
Assistant Attending Physician
Memorial Sloan Kettering Cancer Center
New York, New York

MODERATOR
Neil Love, MD
Research To Practice
Miami, Florida

Jeff Sharman, MD
Medical Director of Hematology Research
US Oncology Network
Willamette Valley Cancer Institute and Research Center
Eugene, Oregon

RTP Year in Review 2024

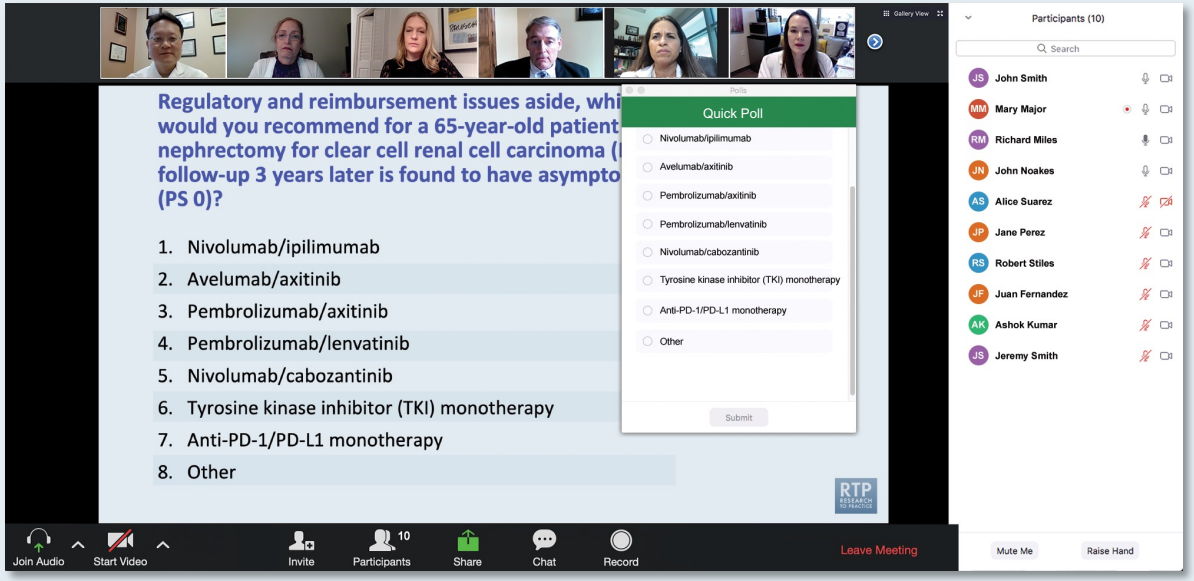
We Encourage Clinicians in Practice to Submit Questions



Feel free to submit questions now before the program begins and throughout the program.

RTP RESEARCH TO PRACTICE

Clinicians in the Audience, Please Complete the Pre- and Postmeeting Surveys



ONCOLOGY TODAY

WITH DR NEIL LOVE

Special Edition — Key Presentations on Chronic Lymphocytic Leukemia and Lymphoma from Recent Major Oncology/Hematology Conferences

DR JEREMY ABRAMSON
MASSACHUSETTS GENERAL HOSPITAL

Listen on Apple Podcasts

Spotify

Listen on Google Podcasts

Year in Review: Clinical Investigator Perspectives on the Most Relevant New Data Sets and Advances in Oncology

A Multitumor CME/MOC-Accredited Live Webinar Series

Gastroesophageal Cancers

Thursday, February 8, 2024
5:00 PM – 6:00 PM ET

Faculty

Yelena Y Janjigian, MD

Zev Wainberg, MD, MSc

Moderator

Neil Love, MD

RTP Year in Review 2024

Year in Review: Clinical Investigator Perspectives on the Most Relevant New Data Sets and Advances in Oncology

A Multitumor CME/MOC-Accredited Live Webinar Series

Lymphoma

Tuesday, February 13, 2024
5:00 PM – 6:00 PM ET

Faculty

Andrew M Evens, DO, MBA, MSc
Sonali M Smith, MD

Moderator

Neil Love, MD

RTP Year in Review 2024

Consensus or Controversy? Investigator Perspectives on the Current and Future Role of Immune Checkpoint Inhibitors in the Management of Hepatobiliary Cancers — A 2024 Post-ASCO Gastrointestinal Cancers Symposium Review

A CME-Accredited Virtual Event

Thursday, February 15, 2024
5:00 PM – 6:00 PM ET

Faculty

Robin (Katie) Kelley, MD
Mark Yarchoan, MD

Moderator

Neil Love, MD

RTP
RESEARCH
TO PRACTICE

Year in Review: Clinical Investigator Perspectives on the Most Relevant New Data Sets and Advances in Oncology

A Multitumor CME/MOC-Accredited Live Webinar Series

Urothelial Bladder Cancer

Thursday, February 22, 2024
5:00 PM – 6:00 PM ET

Faculty

Shilpa Gupta, MD

Thomas Powles, MBBS, MRCP, MD

Moderator

Neil Love, MD

RTP Year in Review 2024

JOIN US IN MARCH FOR THE RETURN OF

The Annual National General Medical Oncology Summit

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

MARCH 22-24, 2024

JW Marriott Miami Turnberry

To Learn More or to Register, Visit
www.ResearchToPractice.com/Meetings/GMO2024

Third Annual **National General Medical Oncology Summit**

Friday, March 22, 2024

6:30 PM – 7:00 PM

Welcome Reception

7:00 PM – 9:00 PM

Keynote Session: ER-Positive Metastatic Breast Cancer

Erika Hamilton, MD
Kevin Kalinsky, MD, MS
Joyce O'Shaughnessy, MD
Hope S Rugo, MD

Special Feature: Clinicians with Breast Cancer

Third Annual **National General Medical Oncology Summit**

Saturday, March 23, 2024

7:30 AM – 9:10 AM

Hodgkin and Non-Hodgkin Lymphoma

Ann S LaCasce, MD, MMSc
Matthew Lunning, DO
Kami Maddocks, MD
Andrew D Zelenetz, MD, PhD

9:30 AM – 10:20 AM

Gynecologic Cancers

Bradley J Monk, MD
David M O'Malley, MD

10:20 AM – 11:10 AM

Localized Breast Cancer; SABCS 2023 Review

Virginia Kaklamani, MD, DSc
Kevin Kalinsky, MD, MS
Joyce O'Shaughnessy, MD

11:10 AM – 12:00 PM

Metastatic Breast Cancer, Triple-Negative Breast Cancer, HER2-Positive Breast Cancer; SABCS 2023 Review

Erika Hamilton, MD
Virginia Kaklamani, MD, DSc
Hope S Rugo, MD

Third Annual **National General Medical Oncology Summit**

Saturday, March 23, 2024

12:30 PM – 1:20 PM

Prostate Cancer

Emmanuel S Antonarakis, MD
Rana R McKay, MD

1:20 PM – 2:10 PM

Urothelial Bladder Cancer

Matthew D Galsky, MD
Jonathan E Rosenberg, MD

2:10 PM – 3:00 PM

Renal Cell Carcinoma

Eric Jonasch, MD
Brian Rini, MD

3:20 PM – 4:10 PM

Targeted Therapy for Non-Small Cell Lung Cancer

Ibiayi Dagogo-Jack, MD
Helena Yu, MD

4:10 PM – 5:00 PM

Nontargeted Treatments for Lung Cancer

Edward B Garon, MD, MS
Corey J Langer, MD

Third Annual **National General Medical Oncology Summit**

Sunday, March 24, 2024

7:30 AM – 8:20 AM

Multiple Myeloma

Natalie S Callander, MD
Paul G Richardson, MD

8:20 AM – 9:10 AM

Gastroesophageal Cancers

Yelena Y Janjigian, MD
Samuel J Klempner, MD

9:30 AM – 10:20 AM

Hepatobiliary Cancers

Ghassan Abou-Alfa, MD, MBA
Richard S Finn, MD

10:20 AM – 11:10 AM

Colorectal Cancer

Kristen K Ciombor, MD, MSCI
John Strickler, MD

11:10 AM – 12:00 PM

Pancreatic Cancer

Andrew Ko, MD
Eileen M O'Reilly, MD

Year in Review: Clinical Investigator Perspectives on the Most Relevant New Data Sets and Advances in Oncology

A Multitumor CME/MOC-Accredited Live Webinar Series

Chronic Lymphocytic Leukemia

Tuesday, February 6, 2024
5:00 PM – 6:00 PM ET

Faculty

Lindsey Roeker, MD

Jeff Sharman, MD

Moderator

Neil Love, MD

RTP Year in Review 2024

Commercial Support

This activity is supported by educational grants from AstraZeneca Pharmaceuticals LP 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.

Dr Roeker — Disclosures

Advisory Committees	AbbVie Inc, Ascentage Pharma, AstraZeneca Pharmaceuticals LP, BeiGene Ltd, Janssen Biotech Inc, Loxo Oncology Inc, a wholly owned subsidiary of Eli Lilly & Company, TG Therapeutics Inc
CME Speaker	Curio Science, DAVA Oncology
Consulting Agreements	AbbVie Inc, Ascentage Pharma, AstraZeneca Pharmaceuticals LP, BeiGene Ltd, Janssen Biotech Inc, Loxo Oncology Inc, a wholly owned subsidiary of Eli Lilly & Company, Pfizer Inc, Pharmacyclics LLC, an AbbVie Company, TG Therapeutics Inc
Contracted Research	AbbVie Inc, Adaptive Biotechnologies Corporation, Aptose Biosciences Inc, AstraZeneca Pharmaceuticals LP, Dren Bio, Genentech, a member of the Roche Group, Loxo Oncology Inc, a wholly owned subsidiary of Eli Lilly & Company, Pfizer Inc, Sound Biologics
Stock Options/Stock — Public Company	Abbott Laboratories
Nonrelevant Financial Relationships	Medscape, PeerView

Dr Sharman — Disclosures

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

Year in Review
Chronic Lymphocytic Leukemia

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

Future Directions in the Care of Patients with CLL

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

RTP Year in Review 2024

Key Data Sets

Jeff Sharman, MD

- Langerbeins P et al. **Ibrutinib** versus placebo in patients with **asymptomatic, treatment-naïve early stage** chronic lymphocytic leukemia (CLL): **Final results** of the **Phase 3**, double-blind, placebo-controlled **CLL12 trial**. EHA 2023;Abstract S200.
- Wiestner A et al. **Long-term outcomes** in chronic lymphocytic leukemia treated with **ibrutinib**: **10-year follow-up** of a Phase 2 study. ASH 2023;Abstract 201.
- Hillmen P et al. **Ibrutinib and rituximab** versus **fludarabine, cyclophosphamide, and rituximab** for patients with previously untreated chronic lymphocytic leukaemia **(FLAIR)**: **Interim analysis** of a multicentre, open-label, randomised, **phase 3** trial. *Lancet Oncol* 2023;24(5):535-52.
- Sharman JP et al. **Acalabrutinib ± obinutuzumab** vs **obinutuzumab + chlorambucil** in **treatment-naive** chronic lymphocytic leukemia: **6-year follow-up** of **Elevate-TN**. ASH 2023;Abstract 636.
- Seymour JF et al. Detailed safety profile of **acalabrutinib vs ibrutinib** in **previously treated** chronic lymphocytic leukemia in the **ELEVATE-RR** trial. *Blood* 2023;142(8):687-99.

Key Data Sets

Jeff Sharman, MD (continued)

- Xu L et al. Broad superiority of **zanubrutinib** (zanu) over **bendamustine + rituximab** (BR) across multiple high-risk factors: Biomarker subgroup analysis in the **Phase 3 SEQUOIA** study in patients with **treatment-naive** (TN) chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL) **without del(17p).** ASH 2023;Abstract 1902.
- Brown J et al. 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). ASH 2023;Abstract 202.
- Fürstenau M et al. **First-line venetoclax combinations** in fit patients with CLL: **4-year follow-up** and NGS-based MRD analysis from the **Phase 3 GAIA/CLL13** trial. ASH 2023;Abstract 635.
- Al-Sawaf O et al. **Venetoclax-obinutuzumab** for **previously untreated** chronic lymphocytic leukemia: **6-year results** of the randomized **CLL14** study. EHA 2023;Abstract S145.

Key Data Sets

Jeff Sharman, MD (continued)

- Kater A et al. **Final 7-year follow up** and **retreatment** substudy analysis of **MURANO**: **Venetoclax-rituximab** (VenR)-treated patients with **relapsed/refractory** chronic lymphocytic leukemia (R/R CLL). EHA 2023;Abstract S201.
- Crombie JL et al. **SAVE (Safe Accelerated Venetoclax Escalation)**: Initial results of a prospective, phase Ib study of venetoclax with an accelerated dose ramp-up in patients with CLL. ASCO 2023;Abstract 7512.
- Woyach JA et al. **Pirtobrutinib** in **post-cBTKi** CLL/SLL: ~30 months follow-up and subgroup analysis with/without prior BCL2i from the Phase 1/2 **BRUIN** study. ASH 2023;Abstract 325.
- Brown J et al. Genomic **evolution** and **resistance** during **pirtobrutinib** therapy in covalent BTK-inhibitor (cBTKi) pre-treated chronic lymphocytic leukemia patients: Updated analysis from the **BRUIN** study. ASH 2023;Abstract 326.

Key Data Sets

Lindsey Roeker, MD

- Ghia P et al. Relapse after **first-line fixed duration ibrutinib + venetoclax**: High response rates to ibrutinib retreatment and absence of BTK mutations in patients with chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL) with up to **5 years of follow-up** in the **Phase 2 Captivate** study. ASH 2023;Abstract 633.
- Kater A et al. Time-limited **venetoclax and ibrutinib** for patients with **relapsed/refractory** CLL who have undetectable MRD – 4-year follow up from the randomized **Phase II VISION/HO141** trial. EHA 2023;Abstract S148.
- Hillmen P et al. **Ibrutinib plus venetoclax** with MRD-directed duration of treatment is superior to FCR and is a new standard of care for **previously untreated** CLL: Report of the **Phase III UK NCRI FLAIR** study. ASH 2023;Abstract 631.
- Woyach JA et al. Results of a **phase 3** study of **IVO vs IO** for **previously untreated** older patients (pts) with chronic lymphocytic leukemia (CLL) and impact of COVID-19 (Alliance). ASCO 2023;Abstract 7500.

Key Data Sets

Lindsey Roeker, MD (continued)

- Follows G et al. **First-line fixed-duration ibrutinib plus venetoclax** (Ibr + Ven) versus chlorambucil plus obinutuzumab (Clb + O): **55-month follow-up** from the **Glow** study. ASH 2023;Abstract 634.
- Furstenau M et al. Long-term remissions with MRD-guided **acalabrutinib, venetoclax and obinutuzumab** in **relapsed/refractory** CLL: Follow-up efficacy and circulating tumor DNA analysis of the CLL2-Baag trial. ASH 2023;Abstract 203.
- Allan J et al. **Zanubrutinib and venetoclax** as **initial therapy** for CLL/SLL with **obinutuzumab triplet consolidation** in patients with minimal residual disease positivity **(BruVenG)**. ASH 2023;Abstract 3285.
- Roeker L et al. **Fixed-duration pirtobrutinib** combined with **venetoclax ± rituximab** in **relapsed/refractory** chronic lymphocytic leukemia: Updated results, including MRD data, from the **BRUIN** Phase 1b study. ASH 2023;Abstract 3269.
- Woyach JA et al. First-in-human study of the **reversible BTK inhibitor nemtabrutinib** in patients with **relapsed/refractory** chronic lymphocytic leukemia and B-cell non-Hodgkin lymphoma. *Cancer Discov* 2024;14(1):66-75.

Key Data Sets

Lindsey Roeker, MD (continued)

- Siddiqi T et al. **Lisocabtagene maraleucel** (liso-cel) in R/R CLL/SLL: 24-month median follow-up of **TRANSCEND CLL 004**. ASH 2023;Abstract 330.
- Tam C et al. Combination treatment with **sonrotoclax (BGB-11417), a second-generation BCL2 inhibitor, and zanubrutinib**, a Bruton tyrosine kinase (BTK) inhibitor, is well tolerated and achieves deep responses in patients with **treatment-naïve** chronic lymphocytic leukemia/small lymphocytic lymphoma (TN-CLL/SLL): Data from an ongoing Phase 1/2 study. ASH 2023;Abstract 327.
- Frustaci AM et al. Results of **MOLTO**, a multicenter, open label, phase II clinical trial evaluating **venetoclax, atezolizumab and obinutuzumab** combination in **Richter syndrome**. ASCO 2023;Abstract 7502.
- Al-Sawaf O et al. **Tislelizumab plus zanubrutinib** in patients with **Richter transformation**: Primary endpoint analysis of the prospective, multi-center, **Phase-II RT1** trial of the German CLL Study Group. ASH 2023;Abstract 204.
- Wierda W et al. **Pirtobrutinib** in **Richter transformation**: Updated efficacy and safety results with 18-month median survival follow-up from the Phase 1/2 **BRUIN** study. ASH 2023;Abstract 1737.

Agenda

INTRODUCTION: An Audio Depiction of Mechanisms of Action of Bcl-2 Inhibitors, Anti-CD20 Antibodies and Covalent and Noncovalent BTK Inhibitors; Mechanisms of Resistance

MODULE 1: Current Management Approaches for Patients with Chronic Lymphocyctic Leukemia (CLL) — Dr Sharman

MODULE 2: Top 10 Questions — Part 1

MODULE 3: Future Directions in the Care of Patients with CLL — Dr Roeker

MODULE 4: Top 10 Questions — Part 2

Agenda

INTRODUCTION: An Audio Depiction of Mechanisms of Action of Bcl-2 Inhibitors, Anti-CD20 Antibodies and Covalent and Noncovalent BTK Inhibitors; Mechanisms of Resistance

MODULE 1: Current Management Approaches for Patients with Chronic Lymphocyctic Leukemia (CLL) — Dr Sharman

MODULE 2: Top 10 Questions — Part 1

MODULE 3: Future Directions in the Care of Patients with CLL — Dr Roeker

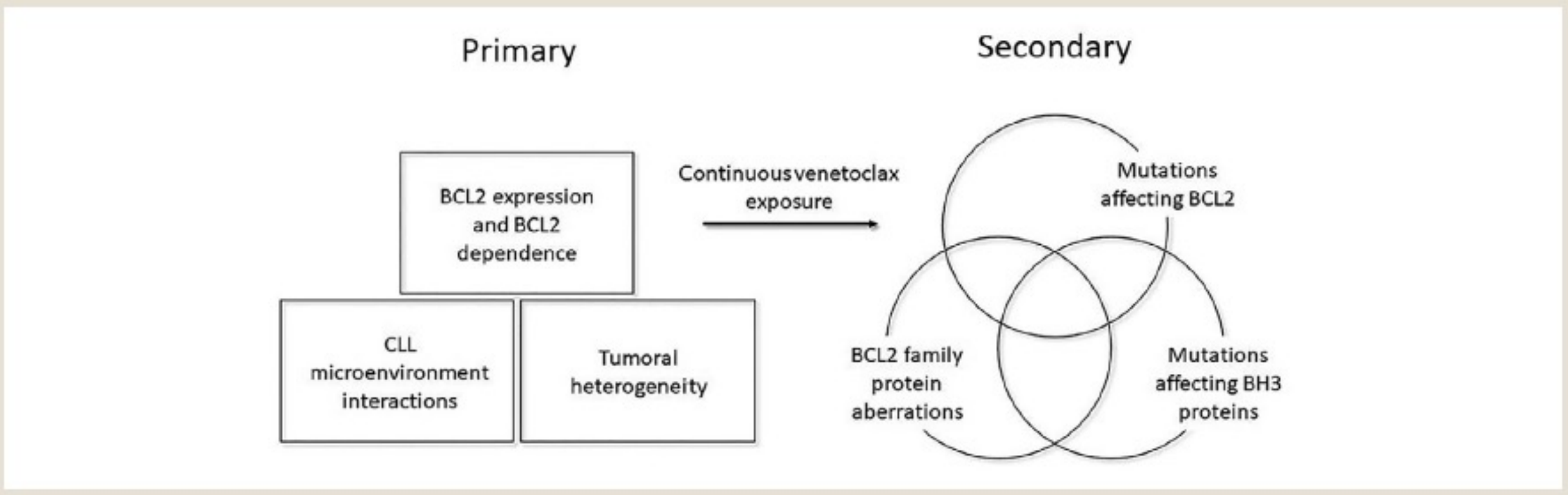
MODULE 4: Top 10 Questions — Part 2

SOHO State of the Art Updates and Next Questions | Mechanisms of Resistance to BCL2 Inhibitor Therapy in Chronic Lymphocytic Leukemia and Potential Future Therapeutic Directions

Rory Bennett,[1] Ella Thompson,[1,2] Constantine Tam[3]

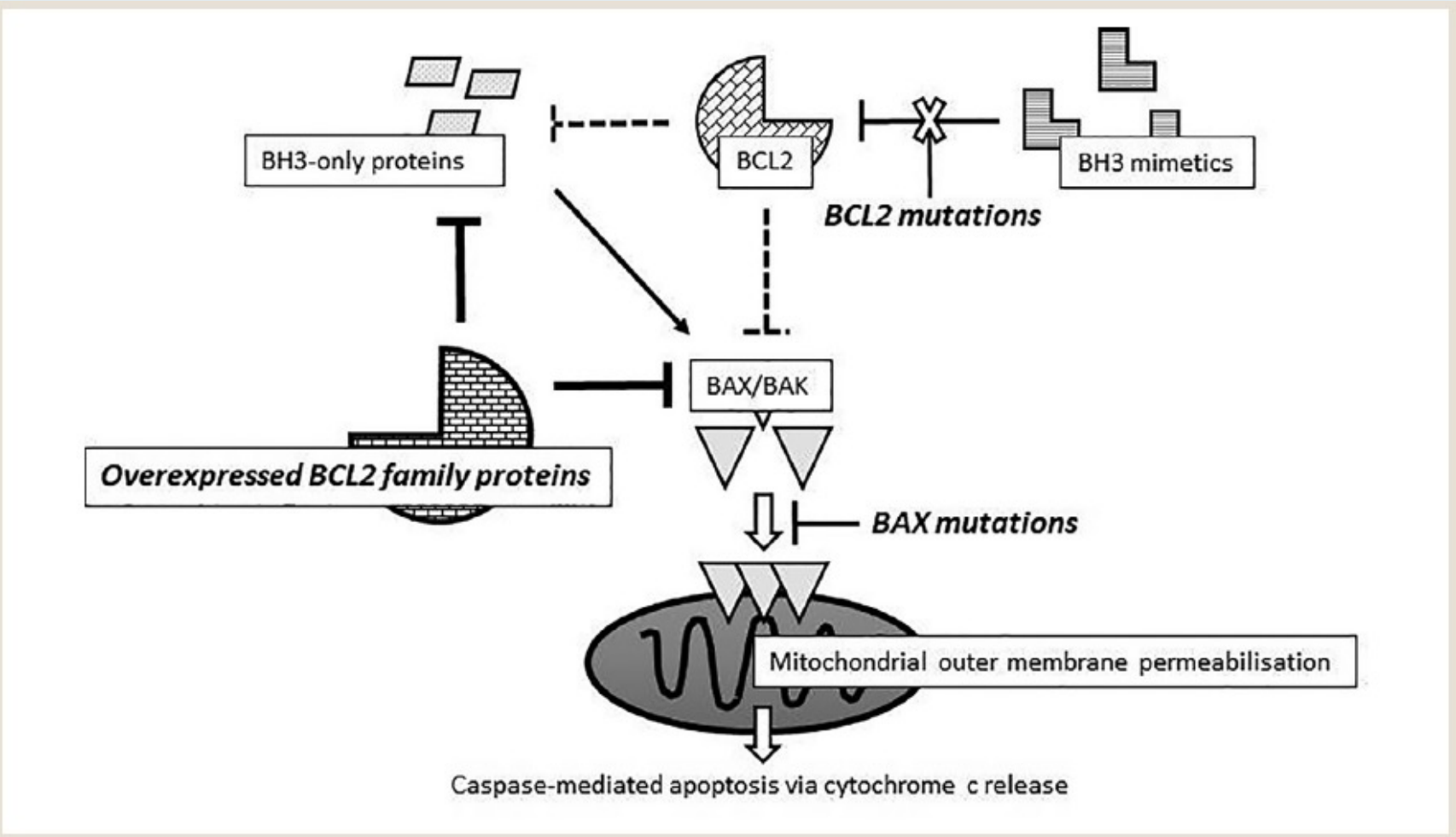
Clin Lymphoma Myeloma Leuk 2022;22(11):795-804.

Summary of Known Factors Affecting Primary Resistance to Venetoclax and Resistance Mechanisms Acquired After Continuous Venetoclax Exposure in CLL



Bennett R et al. *Clin Lymphoma Myeloma Leuk* 2022;22(11):795-804.

Mechanisms of Secondary Resistance to Bcl-2 Inhibition by BH3 Mimetics Such as Venetoclax



Bennett R et al. *Clin Lymphoma Myeloma Leuk* 2022;22(11):795-804.

Reyes *et al. Cancer Drug Resist* 2023;6:828-37
DOI: 10.20517/cdr.2023.97

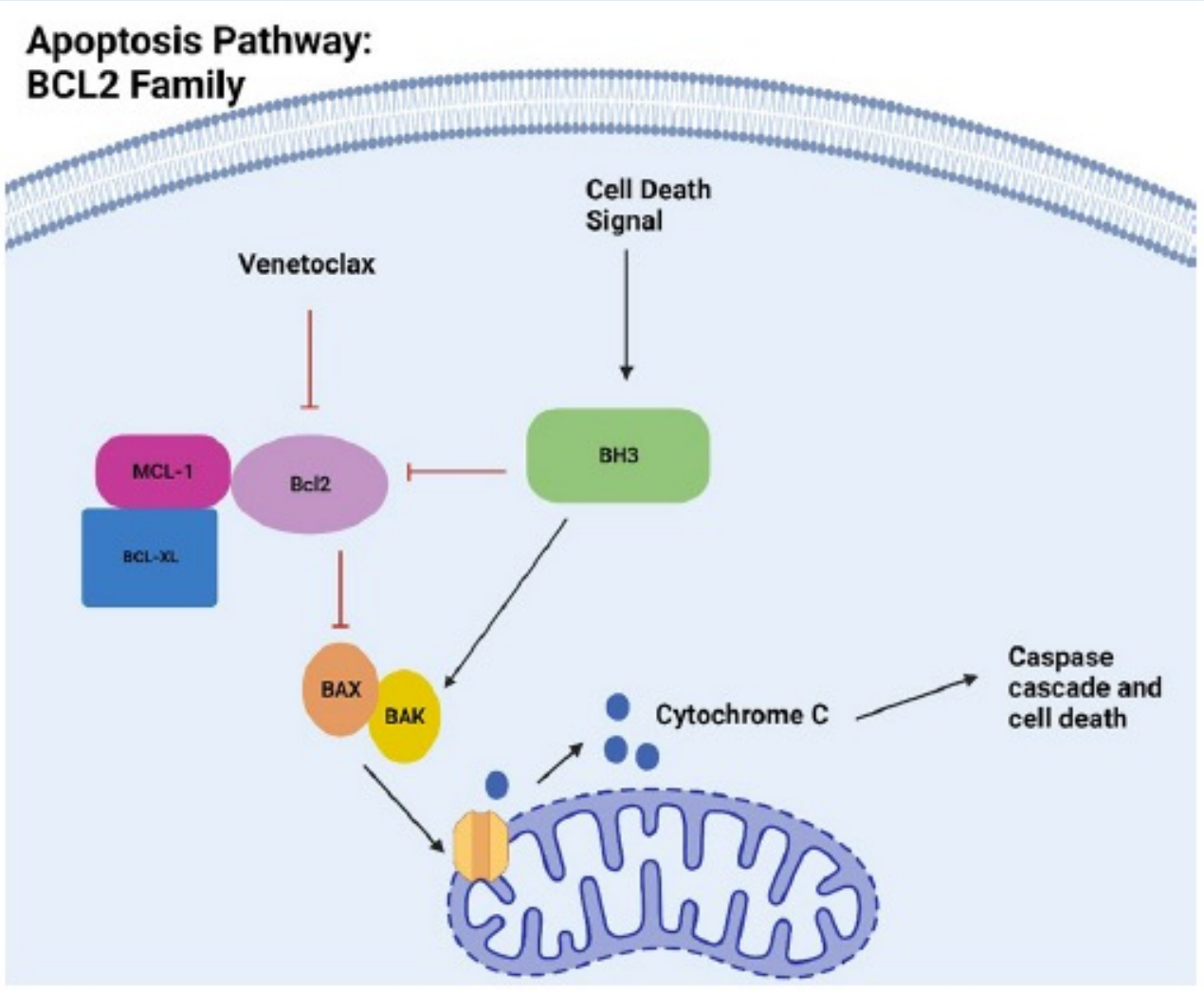
Cancer
Drug Resistance

Review

Targeting BCL2 pathways in CLL: a story of resistance and ingenuity

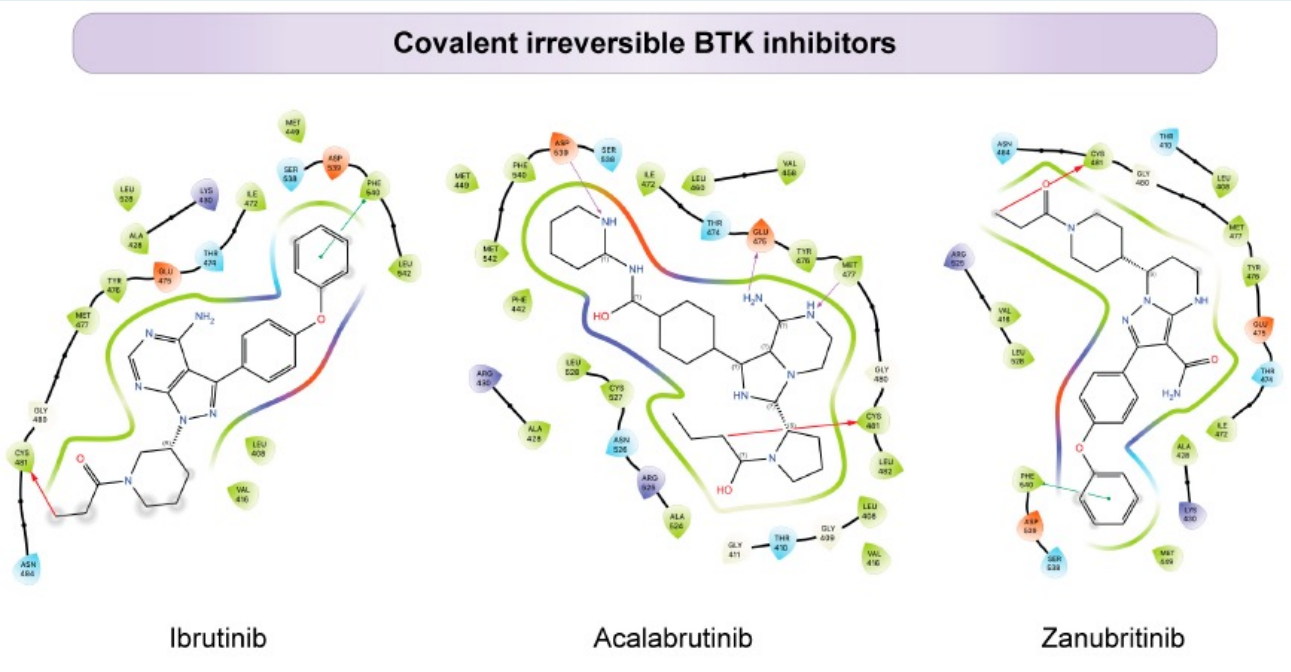
Amanda Reyes[1], Tanya Siddiqi[2]

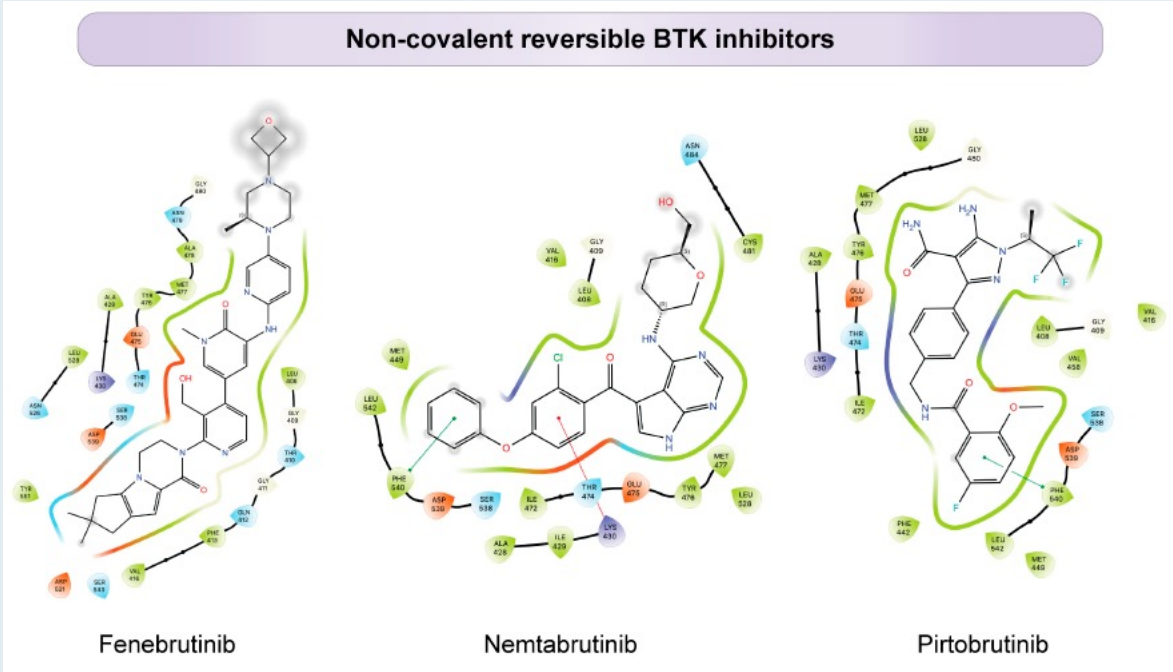
Apoptosis Pathway: Bcl-2 Proteins

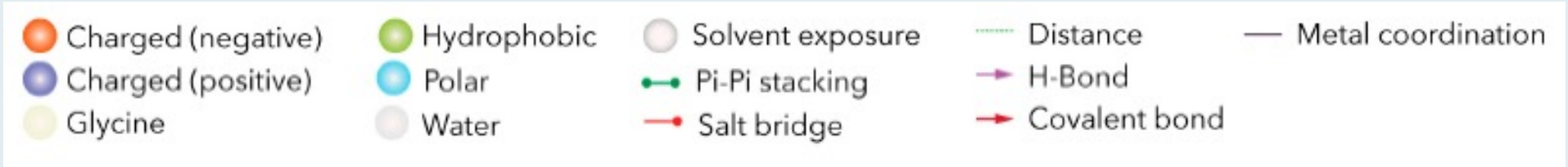


Reyes A, Siddiqi T. *Cancer Drug Resist* 2023;6(4):828-37.

Differential Binding of Bruton Tyrosine Kinase (BTK) Inhibitors







Chirino A et al. *Genes (Basel)* 2023 December 6;14(12):2182.

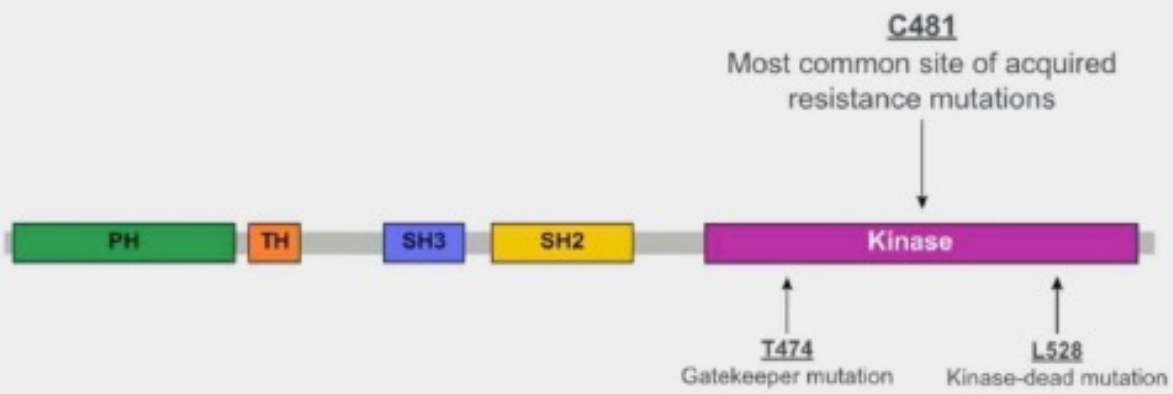
Genomic Evolution and Resistance during Pirtobrutinib Therapy in Covalent BTK-Inhibitor (cBTKi) Pre-Treated Chronic Lymphocytic Leukemia Patients: Updated Analysis from the BRUIN Study

Brown JR et al.

ASH 2023;Abstract 326.

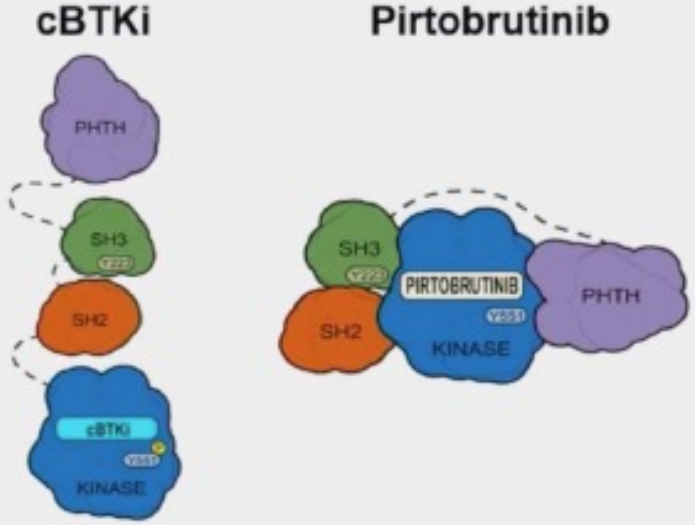
BTK Sites with Known Covalent BTK Inhibitor Resistance Mutations

BTK sites with known cBTKi resistance mutations



- The majority of patients discontinue covalent BTK inhibitors (cBTKi) due to intolerance or progression[1,2,3]
- BTK C481 substitutions are the most common resistance mechanism to cBTKi[4,5,6]
- Acquired mutations have been identified in a limited number of patients treated with pirtobrutinib[7,8]

Pirtobrutinib may stabilize BTK in a closed inactive conformation[9]



Inactive conformation of BTK by pirtobrutinib:

- blocks access to upstream kinases and phosphorylation of Y551
- inhibits both WT and C481-mutant BTK with equal low nM potency[7,9]
- may inhibit kinase-independent BTK signaling[9]

Brown J et al. ASH 2023;Abstract 326.

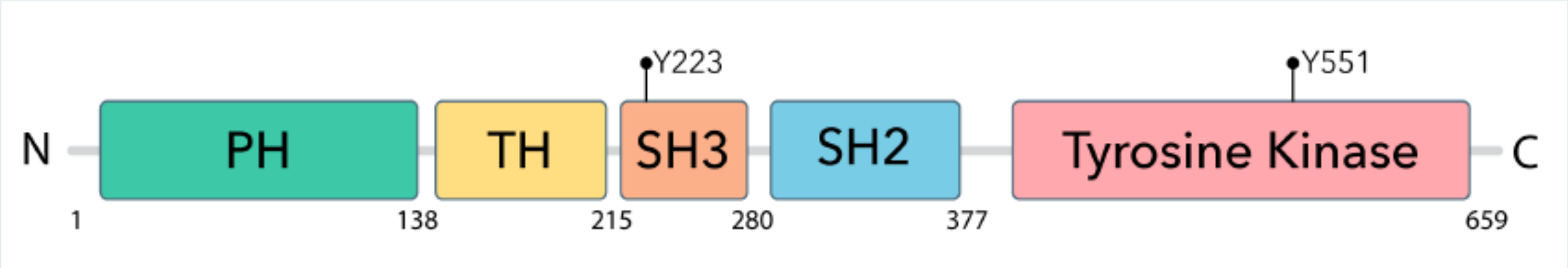
Review

Resisting the Resistance: Navigating BTK Mutations in Chronic Lymphocytic Leukemia (CLL)

Alexandra Chirino †, Skye Montoya †, Anita Safronenka and Justin Taylor *

Genes (Basel) **2023 December 6;14(12):2182**

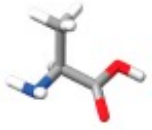
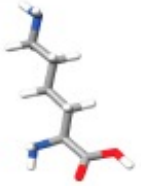
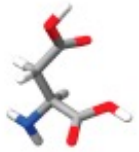
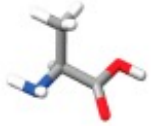
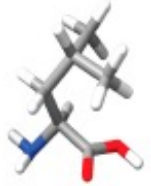
BTK Domains and Activating Tyrosine Phosphorylation Sites



Map of the domains found in BTK starting at the N terminal: BTK is made up of 5 different domains: the pleckstrin homology (PH), proline-rich TEC homology (TH), SRC homology 3 (SH3), SRC homology 2 (SH2), and a catalytic (kinase) domain ending with the C terminal, totaling 659 amino acids in length.

Chirino A et al. *Genes (Basel)* 2023 December 6;14(12):2182.

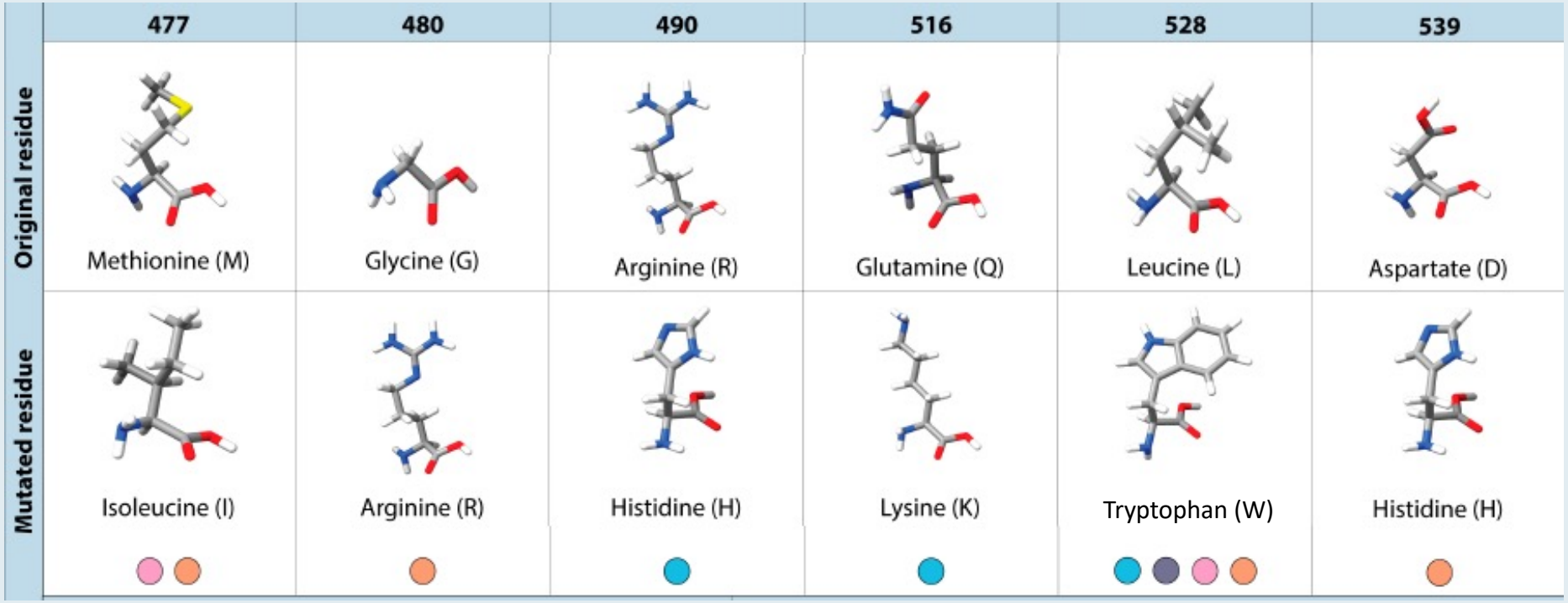
Observed Amino Acid Mutations and Their Corresponding Resistance to Covalent and Noncovalent BTK Inhibitors in Patients with CLL (1)

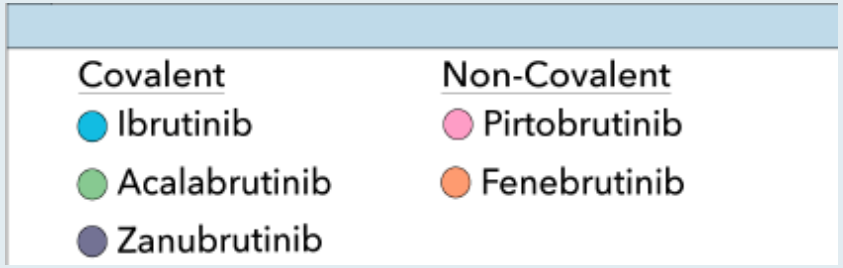
	28	41	164	316	416	428	437
Original residue	 Arginine (R)	 Glutamate (E)	 Glycine (G)	 Threonine (T)	 Valine (V)	 Alanine (A)	 Methionine (M)
Mutated residue	 Serine (S)	 Lysine (K)	 Aspartate (D)	 Alanine (A)	 Leucine (L)	 Aspartate (D)	 Arginine (R)
							

Covalent	Non-Covalent
Ibrutinib	Pirtobrutinib
Acalabrutinib	Fenebrutinib
Zanubrutinib	

Chirino A et al. *Genes (Basel)* 2023 December 6;14(12):2182.

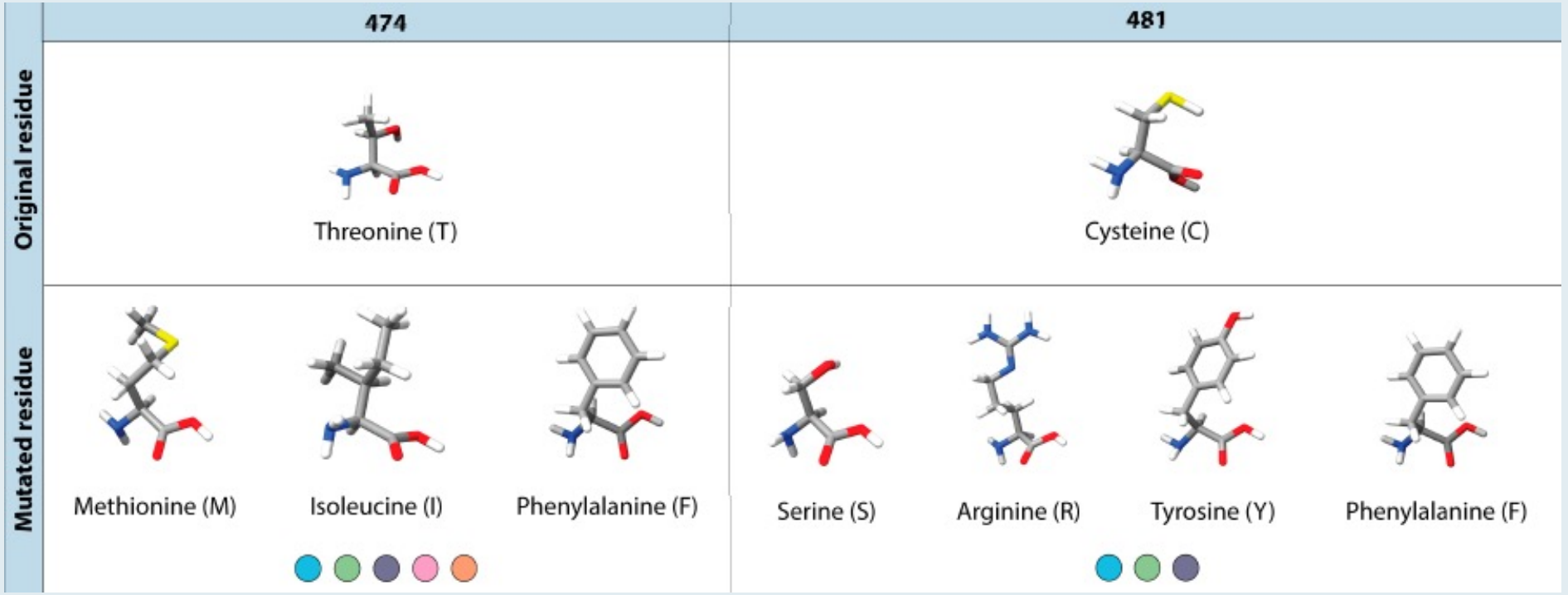
Observed Amino Acid Mutations and Their Corresponding Resistance to Covalent and Noncovalent BTK Inhibitors in Patients with CLL (2)





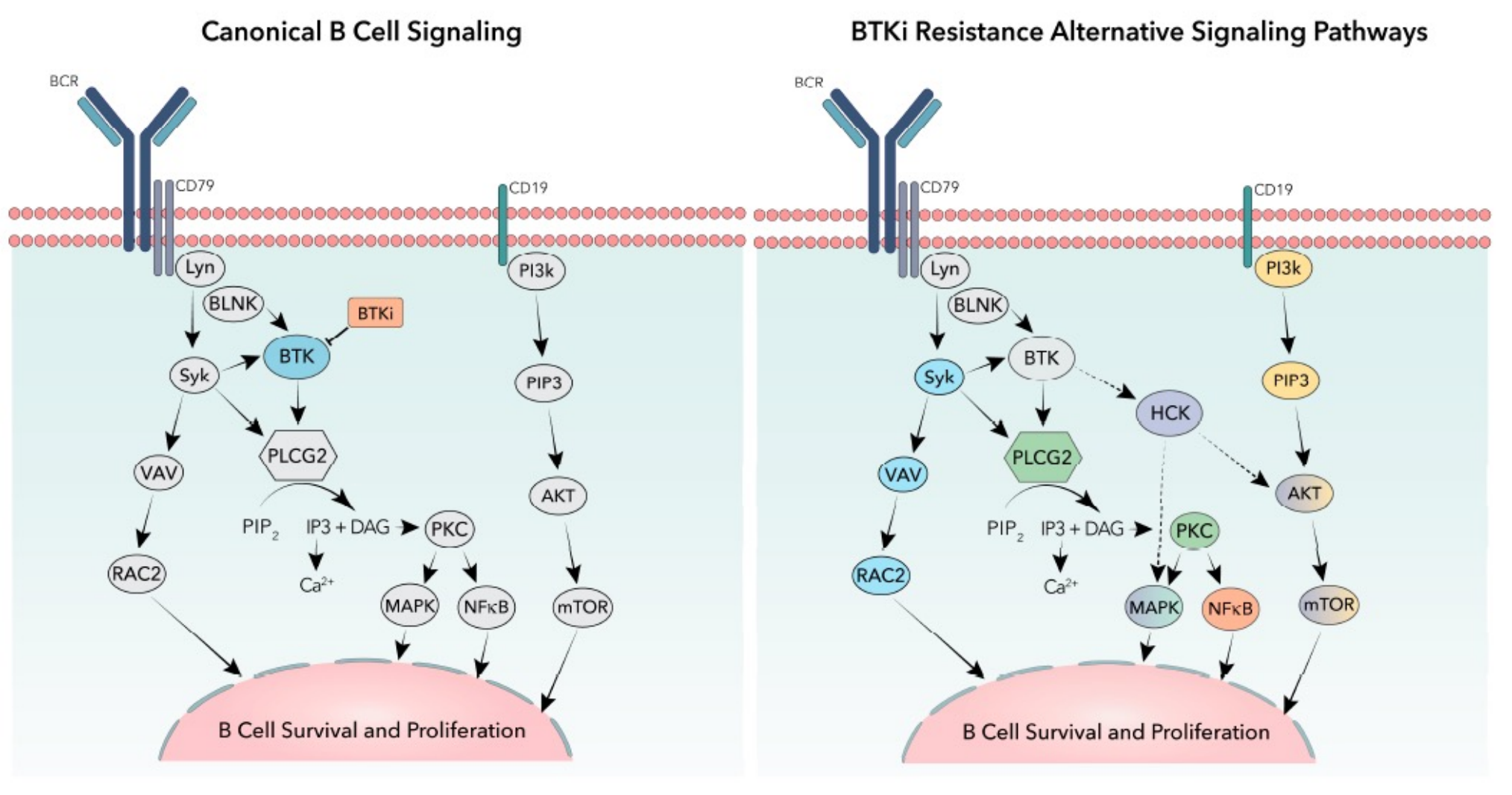
Chirino A et al. *Genes (Basel)* 2023 December 6;14(12):2182.

Observed Amino Acid Mutations and Their Corresponding Resistance to Covalent and Noncovalent BTK Inhibitors in Patients with CLL (3)



Chirino A et al. *Genes (Basel)* 2023 December 6;14(12):2182.

Canonical and Alternative Signaling Pathways in B Cells



Chirino A et al. *Genes (Basel)* 2023 December 6;14(12):2182.

2023;15(14):3648

cancers

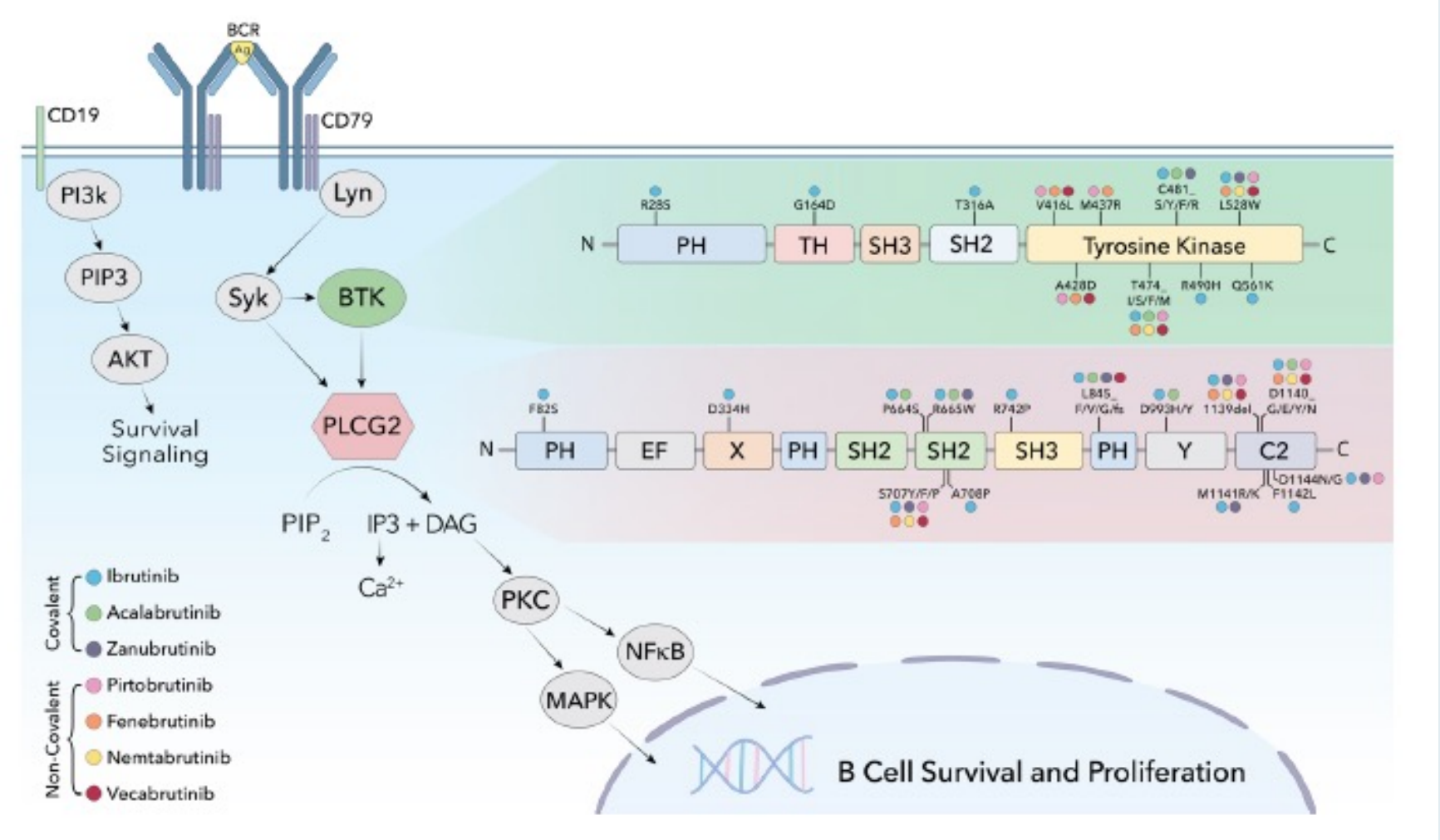
MDPI

Review

Non-Covalent Bruton's Tyrosine Kinase Inhibitors in the Treatment of Chronic Lymphocytic Leukemia

Skye Montoya [1] and Meghan C. Thompson [2,*]

B-Cell Receptor Mediated Signaling, Highlighting Resistance-Causing Mutations in BTK and PLCG2 Kinases



Montoya S, Thompson MC. *Cancers (Basel)* 2023;15(14):3648.

2023;15(5):1583

cancers

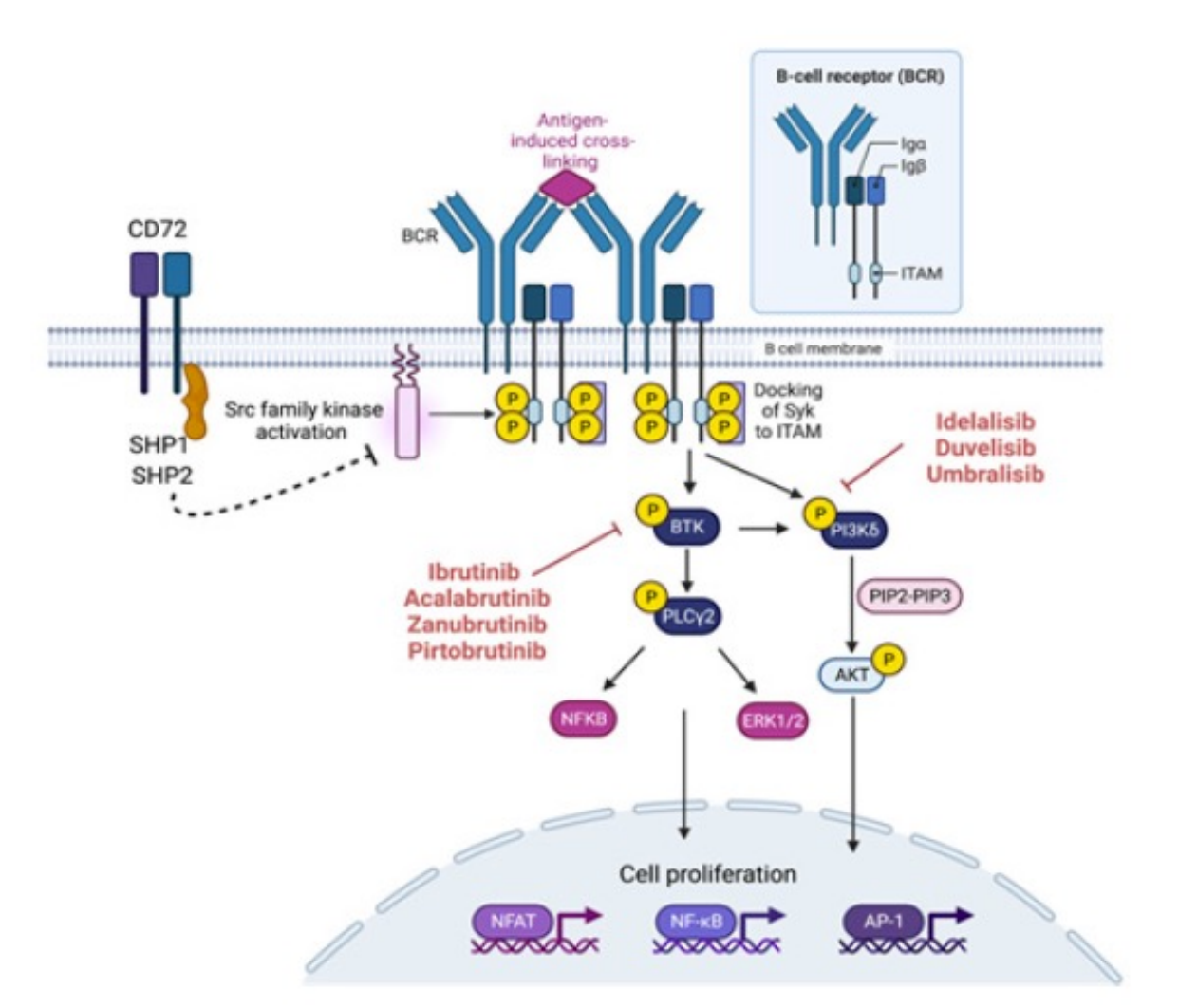
MDPI

Review

Emerging Therapies in CLL in the Era of Precision Medicine

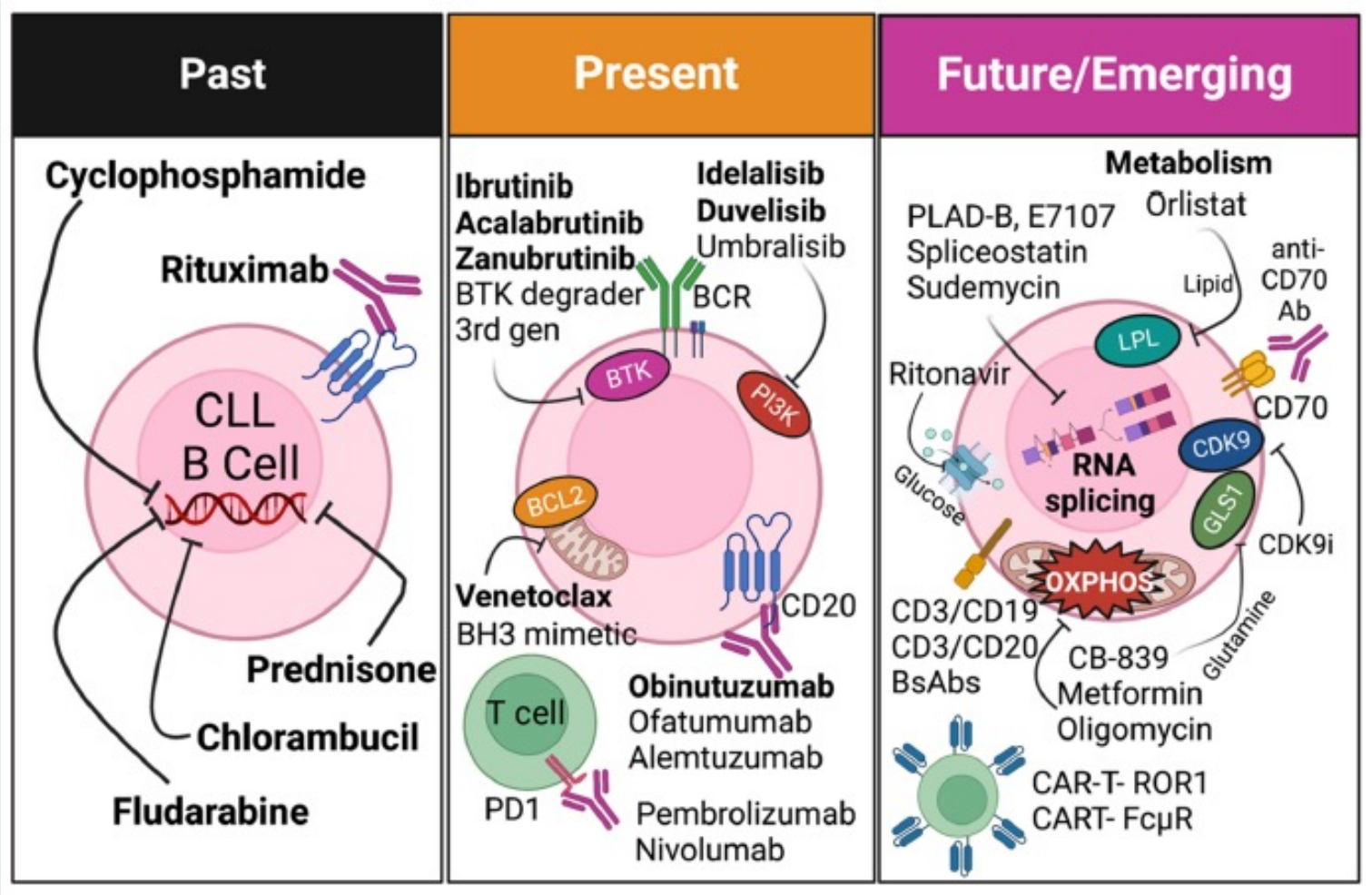
Prajish Iyer [1] and Lili Wang [1,2,*]

BCR Signaling and Targeting Agents



Iyer P, Wang L. *Cancers (Basel)* 2023;15(5):1583.

Summary of Past, Present and Emerging Treatments for CLL



Iyer P, Wang L. *Cancers (Basel)* 2023;15(5):1583.

Br J Haematol. 2023 January ; 200(2): 137–149. doi:10.1111/bjh.18418.

Resistance to BTK inhibition in CLL and non-Hodgkin lymphoma

Shazia Nakhoda[1], **Aldana Vistarop**[2,3], **Y. Lynn Wang**[2,3]

[1]Department of Hematology, Fox Chase Cancer Center, Philadelphia, USA

[2]Department of Pathology, Fox Chase Cancer Center, Philadelphia, USA

[3]Blood Cell Development and Function Program, Fox Chase Cancer Center, Philadelphia, USA

Zhang *et al. Biomarker Research* (2022) 10:17
https://doi.org/10.1186/s40364-022-00357-5

Biomarker Research

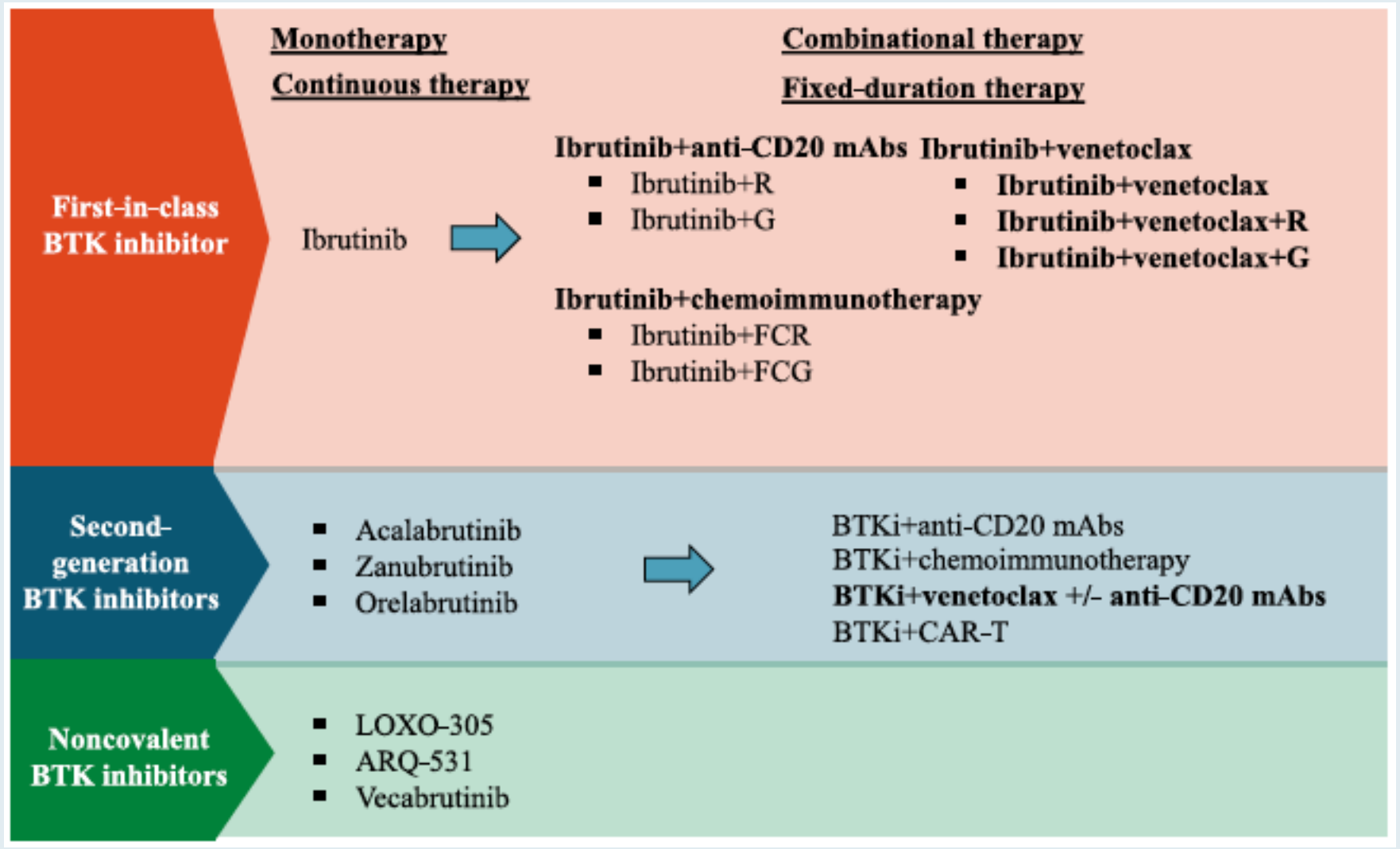
REVIEW

Open Access

Combining BTK inhibitors with BCL2 inhibitors for treating chronic lymphocytic leukemia and mantle cell lymphoma

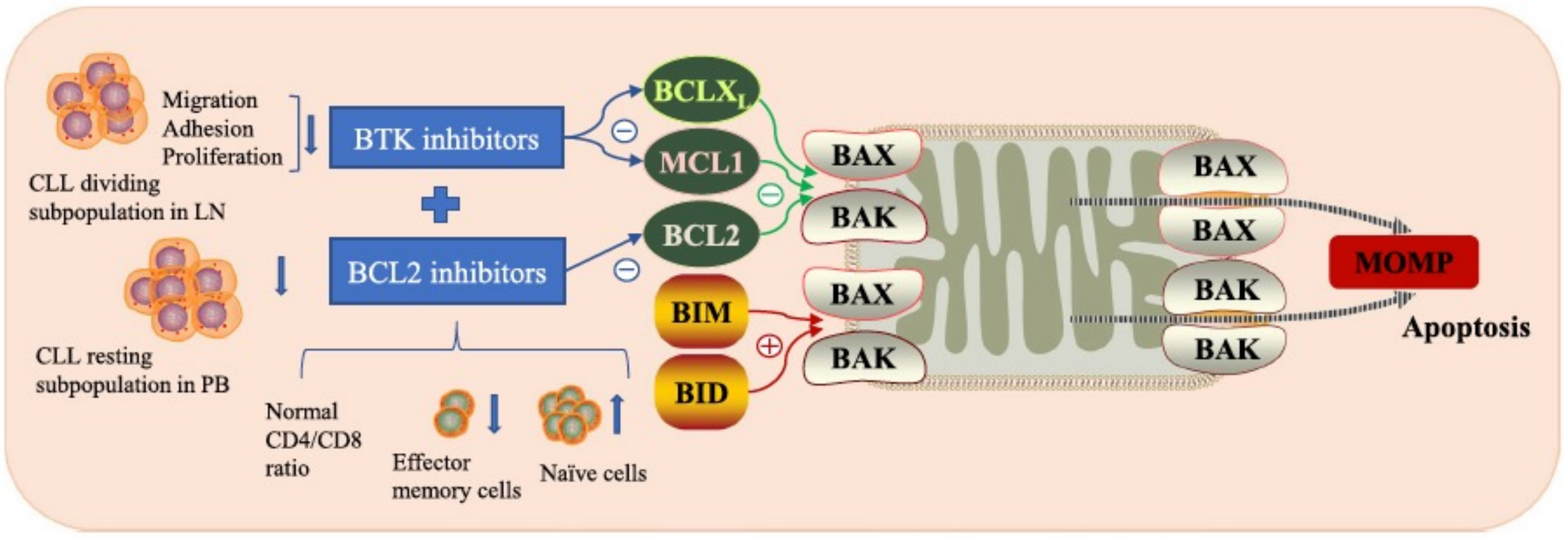
Jing Zhang[1,2†], Xueying Lu[1,2†], Jianyong Li[1,2,3,4*] and Yi Miao[1,2,3*]

Covalent and Noncovalent BTK Inhibitors



Zhang J et al. *Biomark Res* 2022;10(1):17.

Mechanisms of Action of BTK Inhibitors and Bcl-2 Inhibitors



Zhang J et al. *Biomark Res* 2022;10(1):17.

Agenda

INTRODUCTION: An Audio Depiction of Mechanisms of Action of Bcl-2 Inhibitors, Anti-CD20 Antibodies and Covalent and Noncovalent BTK Inhibitors; Mechanisms of Resistance

MODULE 1: Current Management Approaches for Patients with Chronic Lymphocyctic Leukemia (CLL) — Dr Sharman

MODULE 2: Top 10 Questions — Part 1

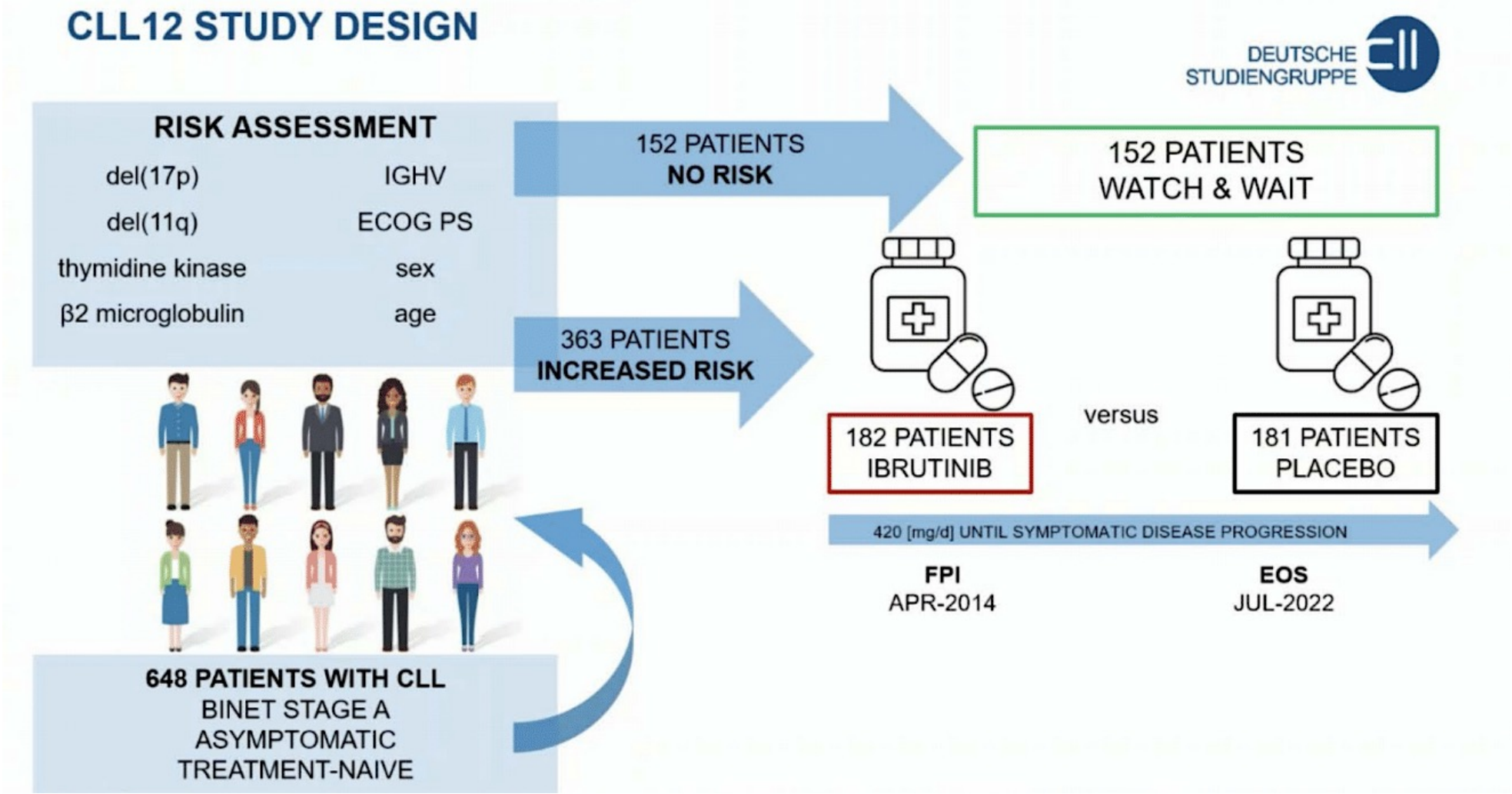
MODULE 3: Future Directions in the Care of Patients with CLL — Dr Roeker

MODULE 4: Top 10 Questions — Part 2

Front-Line Ibrutinib

- Langerbeins P et al. **Ibrutinib** versus placebo in patients with **asymptomatic, treatment-naïve early stage** chronic lymphocytic leukemia (CLL): **Final results** of the **Phase 3**, double-blind, placebo-controlled **CLL12 trial**. EHA 2023;Abstract S200.
- Wiestner A et al. **Long-term outcomes** in chronic lymphocytic leukemia treated with **ibrutinib**: **10-year follow-up** of a Phase 2 study. ASH 2023;Abstract 201.
- Hillmen P et al. **Ibrutinib and rituximab** versus **fludarabine, cyclophosphamide, and rituximab** for patients with previously untreated chronic lymphocytic leukaemia **(FLAIR)**: **Interim analysis** of a multicentre, open-label, randomised, **phase 3** trial. *Lancet Oncol* 2023;24(5):535-52.

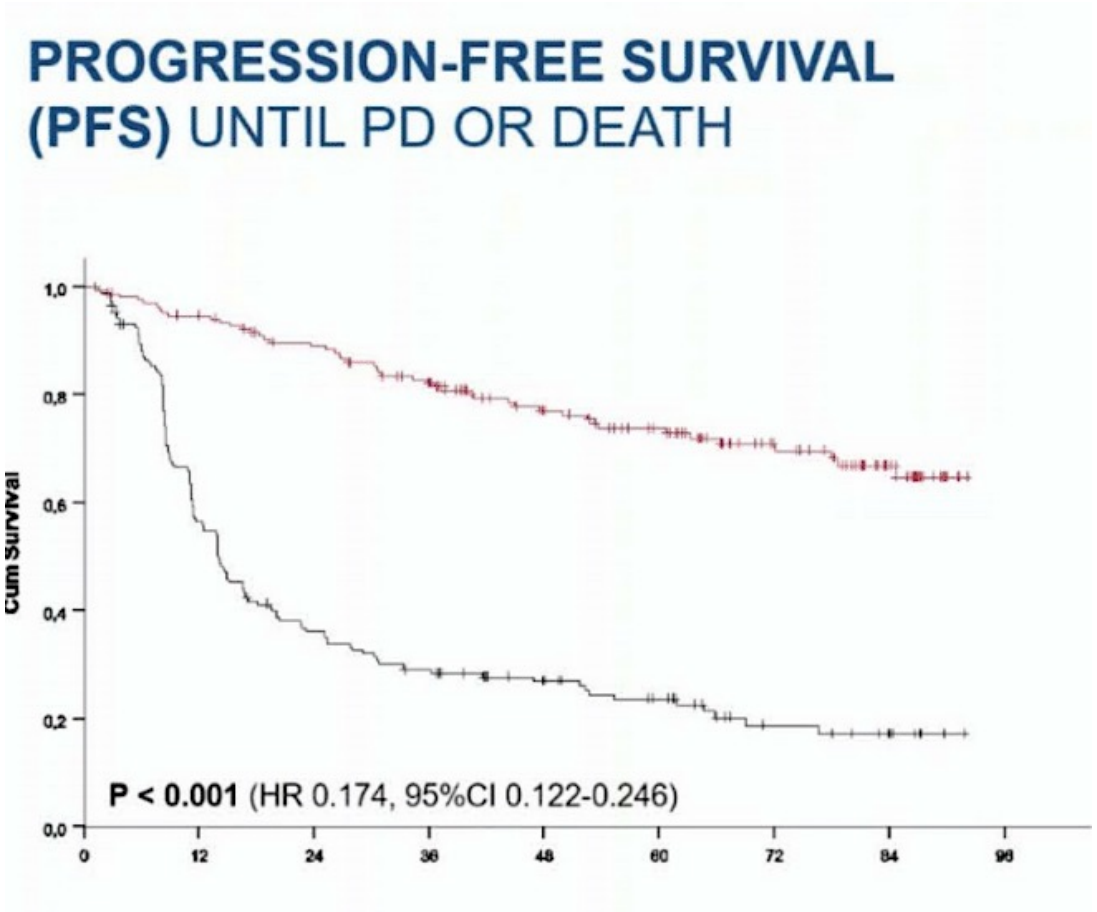
CLL12: Ibrutinib vs Watch and Wait

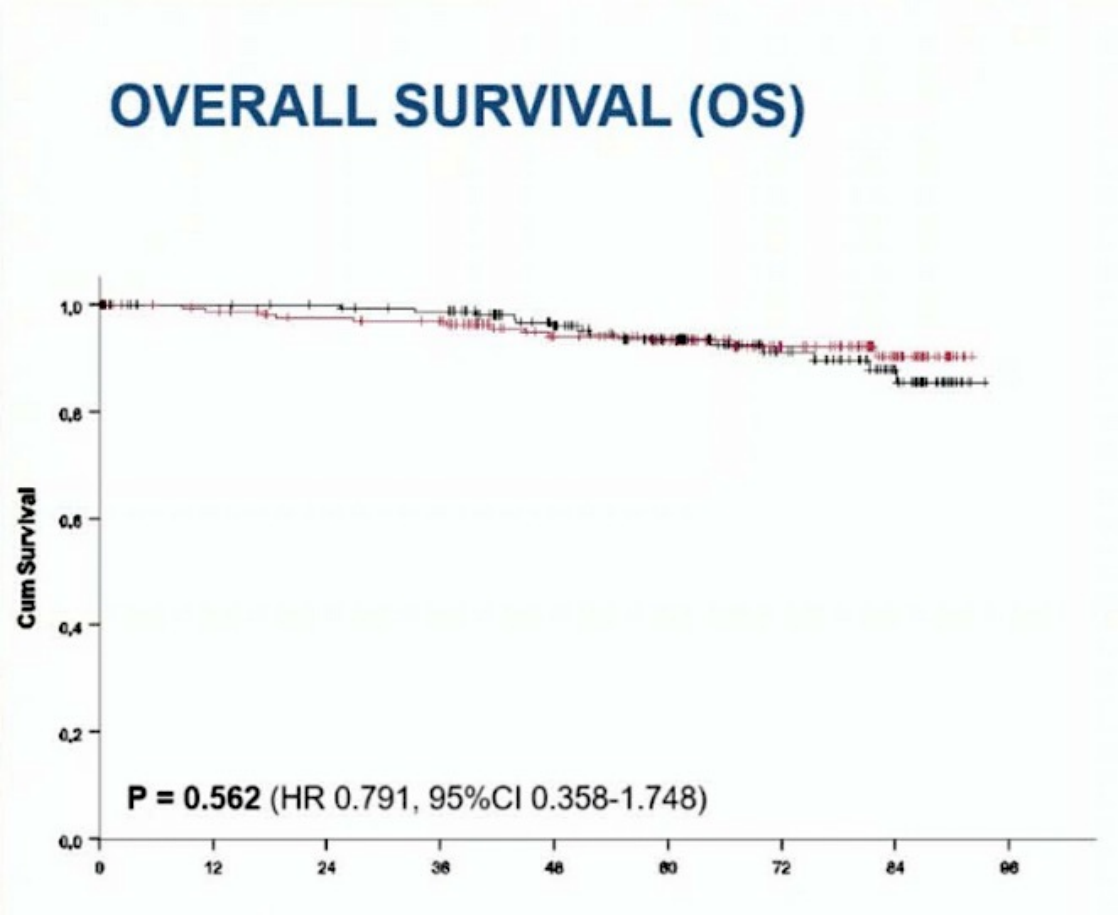


Langerbeins P et al. EHA 2023;Abstract S200.

Courtesy of Jeff Sharman, MD

CLL12: Treatment improves PFS but no OS impact of early therapy





Langerbeins P et al. EHA 2023;Abstract S200.

Courtesy of Jeff Sharman, MD

CLL12: Adverse Events (Patient Level)

	Ibrutinib N=170	Placebo N=168	Watch & wait N=152
Max. CTC grade, N (%)			
CTC grades 1 – 5	169 (99.4)	167 (99.4)	-
CTC grades 3 – 5	122 (71.8)	111 (66.1)	-
Marked as serious AE, N (%)	241 (9.9)	222 (14.9)	-
Second malignancy, N (%)			
CTC grades 1 – 5	22 (12.9)	36 (21.4)	15 (9.9)
CTC grade 5	2 (1.2)	5 (3)	2 (1.3)

Langerbeins P et al. EHA 2023;Abstract S200.

Courtesy of Jeff Sharman, MD

CLL12: AEs of Clinical Interest (Patient Level)

	Ibrutinib N=170	Placebo N=168
Max. CTC grade, N (%)		
CTC grades 1 – 5	136 (80)	88 (52.4)
CTC grade 5	4 (2.4)	1 (0.6)
Bleeding	62 (36.5)	25 (14.9)
Cardiac arrhythmias	38 (22.4)	16 (9.5)
Cardiac event other than arrhythmia	30 (17.6)	26 (15.5)
Diarrhea	69 (40.6)	48 (28.6)
Hypertensive disorders	33 (19.4)	14 (8.3)

Langerbeins P et al. EHA 2023;Abstract S200.

Courtesy of Jeff Sharman, MD

Frontline Ibrutinib Conclusions

- Early treatment of high risk CLL has not replaced watch and wait
- Placebo side effects considerable relative to ibrutinib
- TP53 mut/del reduces efficacy of ibrutinib but earlier use remains highly effective
- Ibrutinib superior to FCR in fit patients with variable impact on OS

Courtesy of Jeff Sharman, MD

Second-Generation BTK Inhibitors

- Sharman JP et al. **Acalabrutinib ± obinutuzumab** vs **obinutuzumab + chlorambucil** in **treatment-naive** chronic lymphocytic leukemia: **6-year follow-up** of **Elevate-TN**. ASH 2023;Abstract 636.
- Seymour JF et al. Detailed safety profile of **acalabrutinib vs ibrutinib** in **previously treated** chronic lymphocytic leukemia in the **ELEVATE-RR** trial. *Blood* 2023;142(8):687-99.
- Xu L et al. Broad superiority of **zanubrutinib** (zanu) over **bendamustine + rituximab** (BR) across multiple high-risk factors: Biomarker subgroup analysis in the **Phase 3 SEQUOIA** study in patients with **treatment-naive** (TN) chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL) **without del(17p).** ASH 2023;Abstract 1902.
- Brown J et al. 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). ASH 2023;Abstract 202.

BTK/CD20

ELEVATE-TN study design

TN CLL (N=535)

Key inclusion criteria

- Age ≥65 years, or >18 to <65 years with:
  - Creatinine clearance 30–69 mL/min (by Cockcroft-Gault equation)
  - CIRS-G score >6
- TN CLL requiring treatment per iwCLL 2008 criteria[6]
- ECOG PS ≤2

Key exclusion criteria

- Significant cardiovascular disease

Stratification

- del(17p), yes vs no
- ECOG PS 0–1 vs 2
- Geographic region

RANDOMIZE 1:1:1

- A[a] + O[b]
- A[a]
- O[b] + Clb[b]

Primary endpoint

- PFS (IRC-assessed): A+O vs O+Clb

Secondary/other endpoints

- PFS (IRC-assessed): A vs O+Clb
- PFS (INV-assessed)
- ORR (IRC- and INV-assessed)
- TTNT
- OS
- uMRD
- Safety

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

Note: After interim analysis, PFS assessments were by investigator only.[3]
All analyses are ad-hoc and *P*-values are descriptive.

NCT02475681. Data cutoff: March 3, 2023. Patients were enrolled between September 2015 and February 2017.
[a]Continued until disease progression or unacceptable toxicity at 100 mg PO BID.
[b]Treatments were fixed duration and administered for 6 cycles.

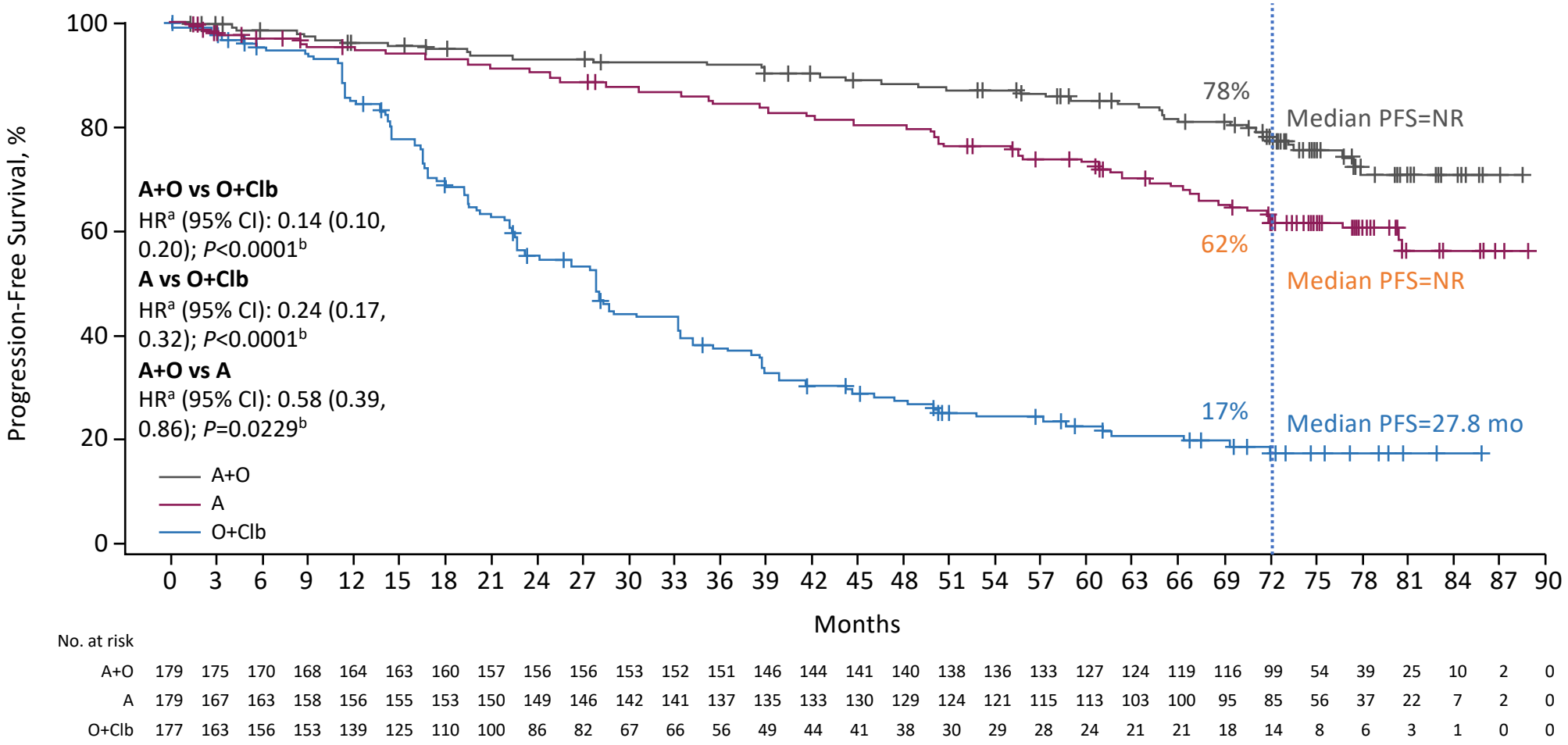
3

ELEVATE-TN 6 Year Update

Sharman 2023

Courtesy of Jeff Sharman, MD

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



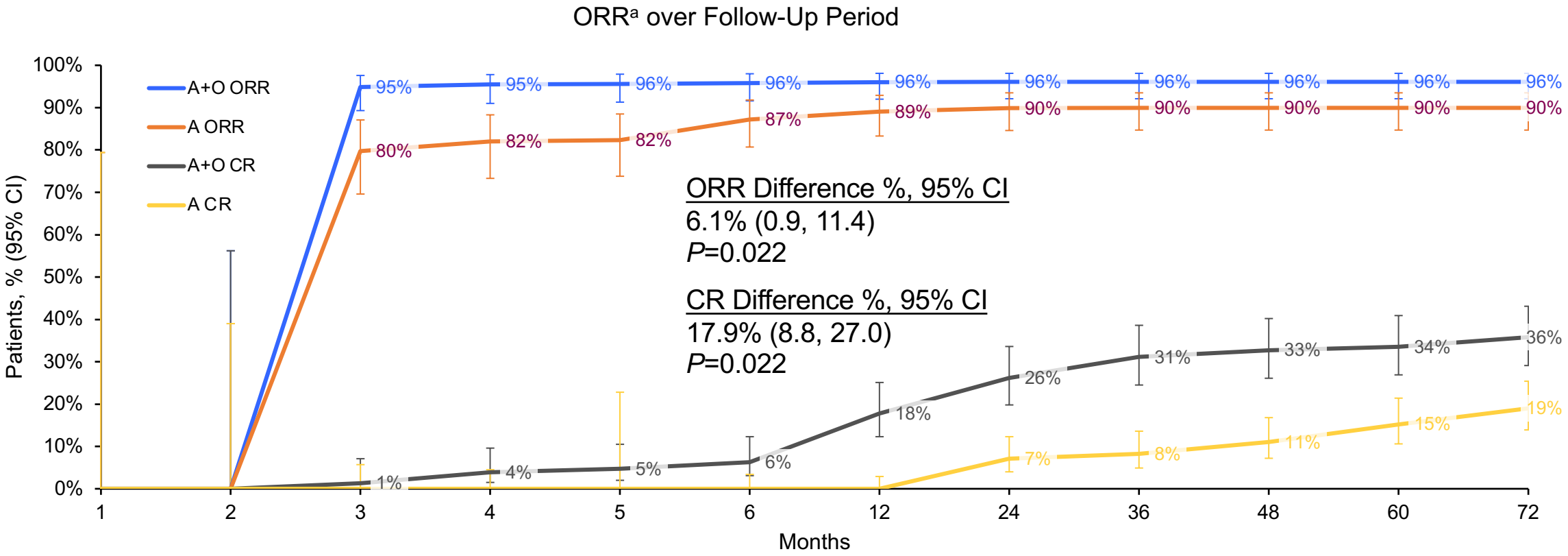
- Median PFS was significantly higher for A+O vs A

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

Sharman J et al. ASH 2023;Abstract 636.

Courtesy of Jeff Sharman, MD

ELEVATE-TN: ORR improves over time in acalabrutinib-containing arms



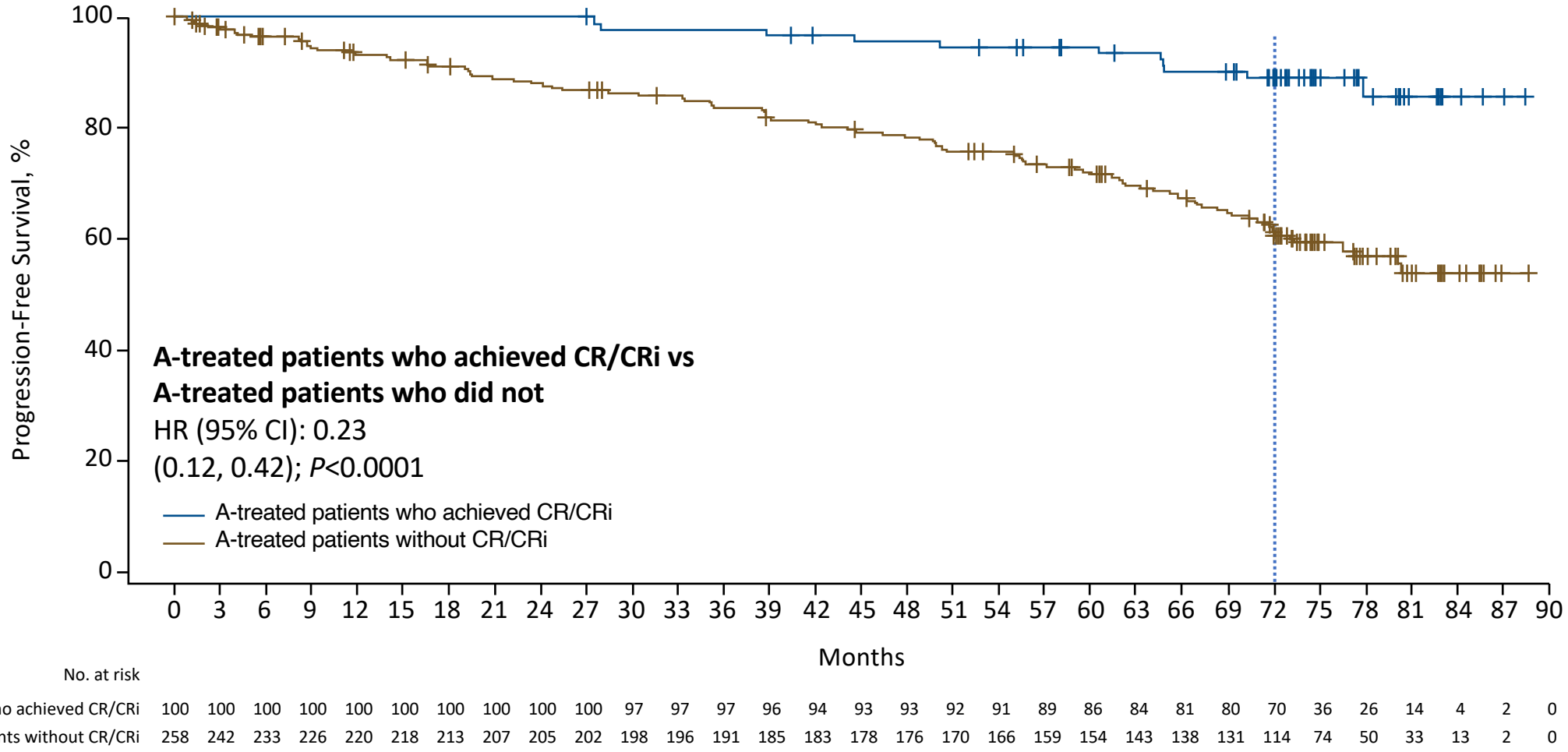
- ORR and CR/CRi rates were significantly higher with A+O and A vs O+Clb ($P \leq 0.0499$ for both arms of the analyses)
- ORR and CR/CRi rates were significantly higher with A+O vs A ($P=0.022$ for both comparisons)

[a]ORR is defined as achieving CR, CRi, nPR, or PR per the investigator per iwCLL 2008 criteria[6] at or before initiation of subsequent anticancer therapy. ORR does not include PRL.

Sharman J et al. ASH 2023;Abstract 636.

Courtesy of Jeff Sharman, MD

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



No. at risk																													
A-treated patients who achieved CR/CRi	100	100	100	100	100	100	100	100	100	100	97	97	97	96	94	93	93	92	91	89	86	84	81	80	70	36	26	14	4	2	0
A-treated patients without CR/CRi	258	242	233	226	220	218	213	207	205	202	198	196	191	185	183	178	176	170	166	159	154	143	138	131	114	74	50	33	13	2	0

Sharman J et al. ASH 2023;Abstract 636.

Courtesy of Jeff Sharman, MD

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)

Jennifer R. Brown, MD, PhD[1]; Barbara Eichhorst, MD[2]; Nicole Lamanna, MD[3]; Susan M. O'Brien, MD[4]; Constantine S. Tam, MBBS, MD[5,6]; Lugui Qiu,

ALPINE Study Design (NCT03734016)

R/R CLL/SLL with ≥1 prior treatment
(N=652)

Key Inclusion Criteria

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

Key Exclusion Criteria

- Prior BTK inhibitor therapy
- Treatment with warfarin or other vitamin K antagonists

R 1:1

Stratification factors:
Age, geographic region, refractoriness, del(17p)/*TP53*

Zanubrutinib 160 mg BID

Ibrutinib 420 mg QD

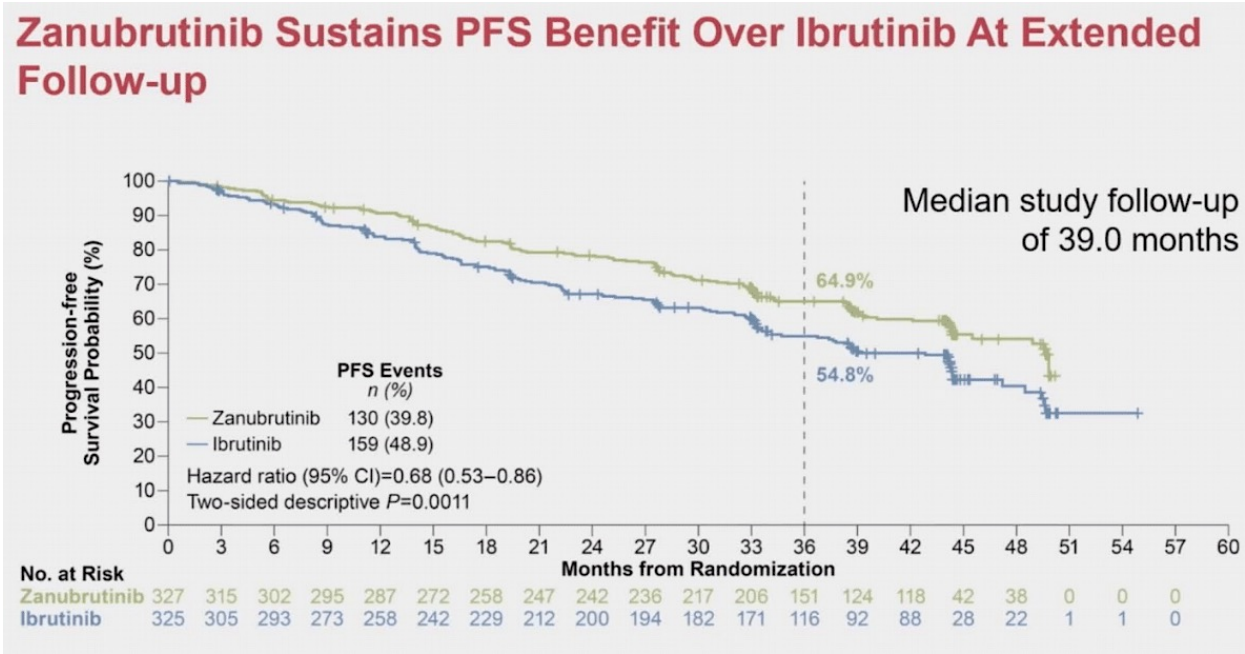
Treatment until disease progression or unacceptable toxicity

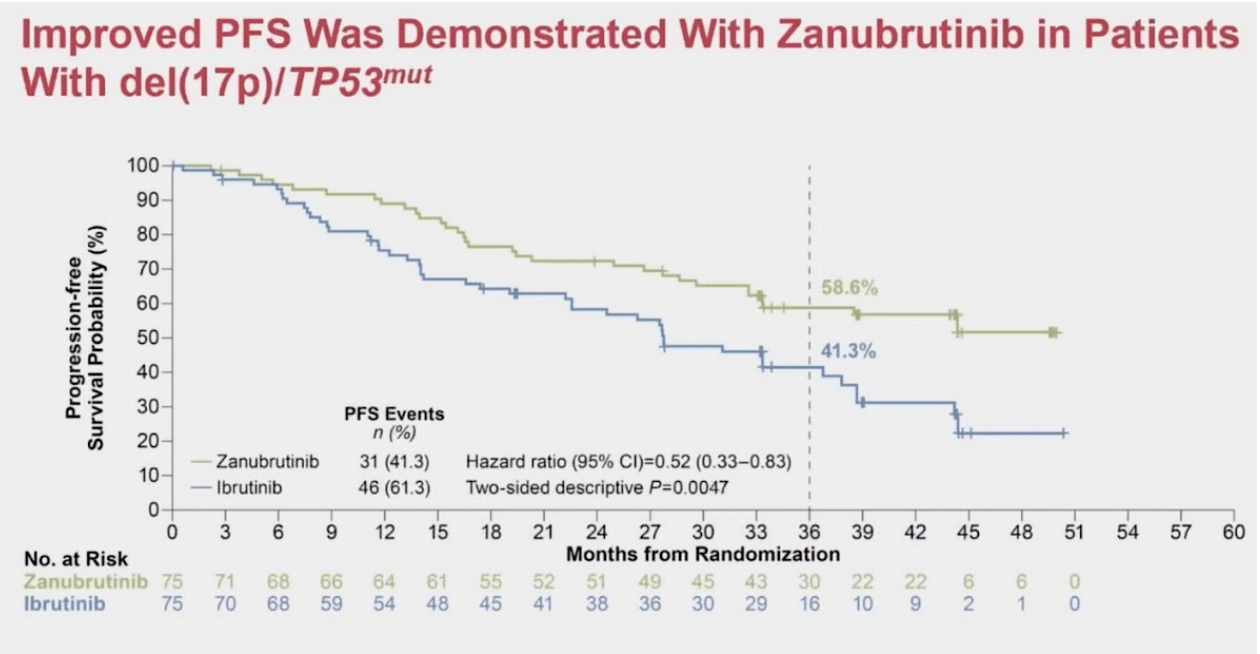
Brown JR, Eichhorst B, Hillmen P, et al. *N Engl J Med.* 2023;388:319-332.

Brown J et al. ASH 2023;Abstract 202.

Courtesy of Jeff Sharman, MD

ALPINE: Zanu vs Ibrutinib

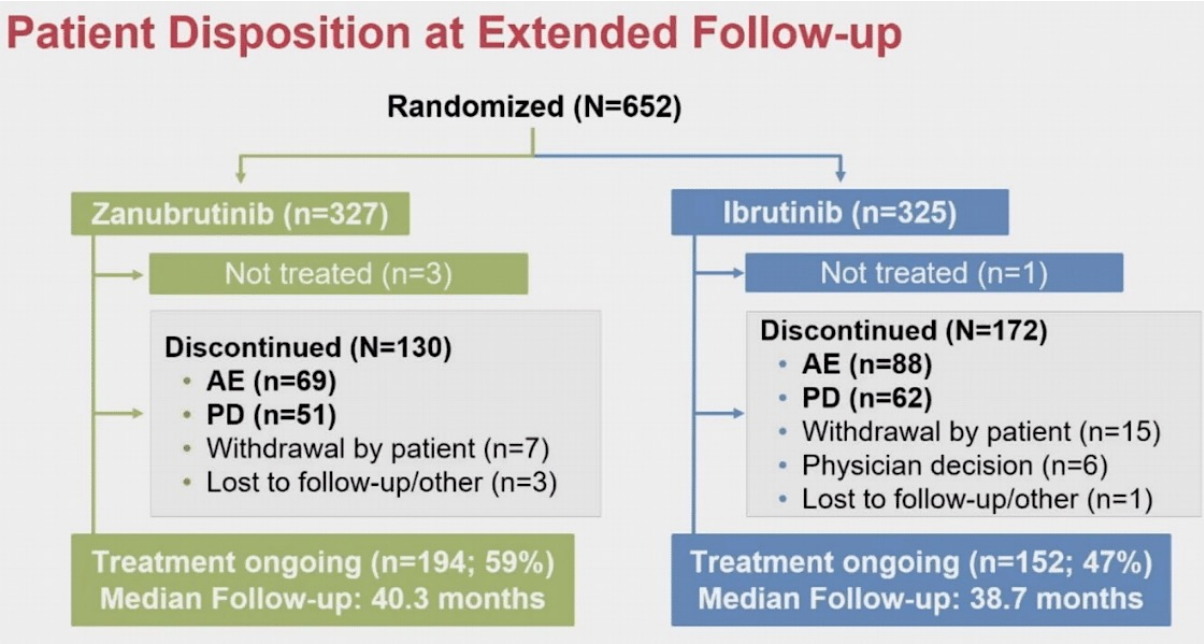


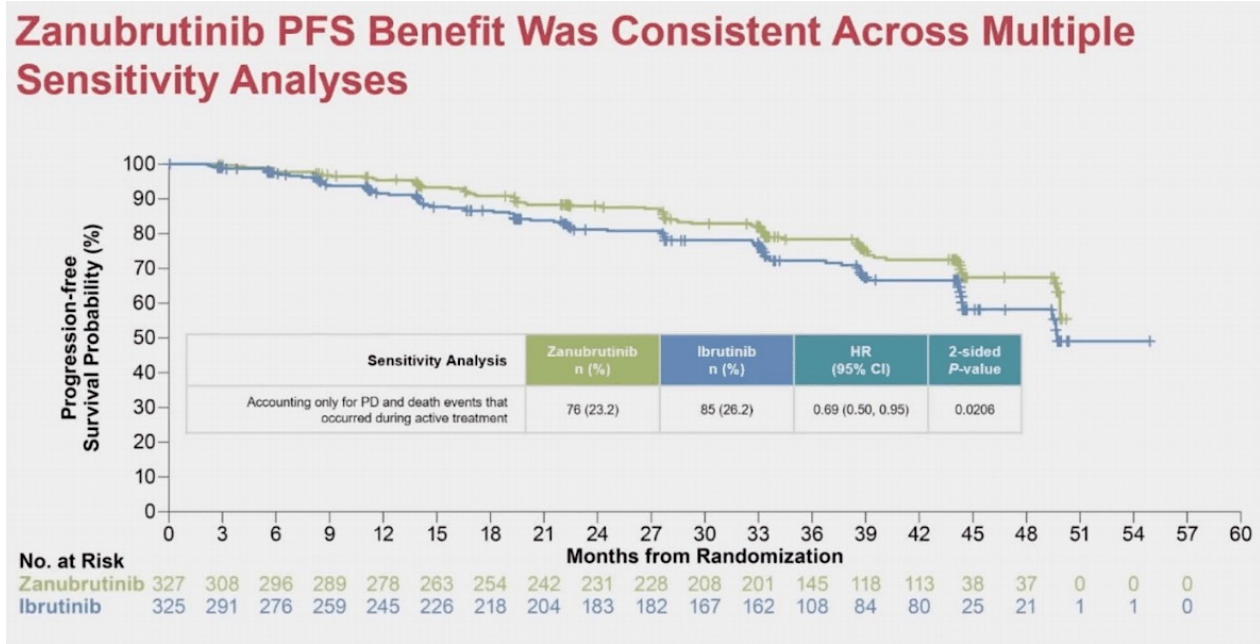


Brown J et al. ASH 2023;Abstract 202.

Courtesy of Jeff Sharman, MD

ALPINE: Zanu vs Ibrutinib





Brown J et al. ASH 2023;Abstract 202.

Courtesy of Jeff Sharman, MD

Second Generation BTK Conclusions

- Adding Obinutuzumab to acalabrutinib results in deeper responses and longer disease control
- Patients discontinue ibrutinib earlier than second generation BTK inhibitors and side effect profiles favor second generation agents
- Zanubrutinib beats BR in untreated CLL, study serves regulatory purpose if not clinical purpose

Courtesy of Jeff Sharman, MD

Venetoclax Combinations

- Fürstenau M et al. **First-line venetoclax combinations** in fit patients with CLL: **4-year follow-up** and NGS-based MRD analysis from the **Phase 3 GAIA/CLL13** trial. ASH 2023;Abstract 635.
- Al-Sawaf O et al. **Venetoclax-obinutuzumab** for **previously untreated** chronic lymphocytic leukemia: **6-year results** of the randomized **CLL14** study. EHA 2023;Abstract S145.
- Kater A et al. **Final 7-year follow up** and **retreatment** substudy analysis of **MURANO**: **Venetoclax-rituximab** (VenR)-treated patients with **relapsed/refractory** chronic lymphocytic leukemia (R/R CLL). EHA 2023;Abstract S201.
- Crombie JL et al. **SAVE (Safe Accelerated Venetoclax Escalation)**: Initial results of a prospective, phase Ib study of venetoclax with an accelerated dose ramp-up in patients with CLL. ASCO 2023;Abstract 7512.

Venetoclax Conclusions

- Obinutuzumab with venetoclax offers fixed duration therapy yielding impressive duration of disease control
- Bulky disease has lower PFS along with IgHV and TP53
- Obinutuzumab better than rituximab when combined with venetoclax
- Any advantage of triplet therapy emerges late
- Obi-ven can be given in both young/fit, and older/comorbid patients with similar efficacy
- Retreatment feasible
- Accelerating ramp up schedules remain a consideration

Courtesy of Jeff Sharman, MD

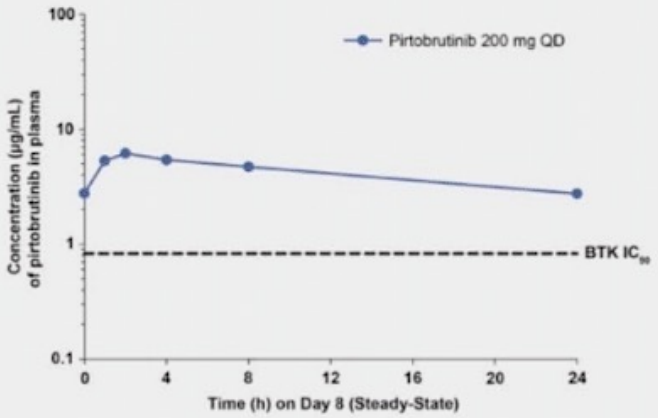
Pirtobrutinib

- Woyach JA et al. **Pirtobrutinib** in **post-cBTKi** CLL/SLL: ~30 months follow-up and subgroup analysis with/without prior BCL2i from the Phase 1/2 **BRUIN** study. ASH 2023;Abstract 325.
- Brown J et al. Genomic **evolution** and **resistance** during **pirtobrutinib** therapy in covalent BTK-inhibitor (cBTKi) pre-treated chronic lymphocytic leukemia patients: Updated analysis from the **BRUIN** study. ASH 2023;Abstract 326.

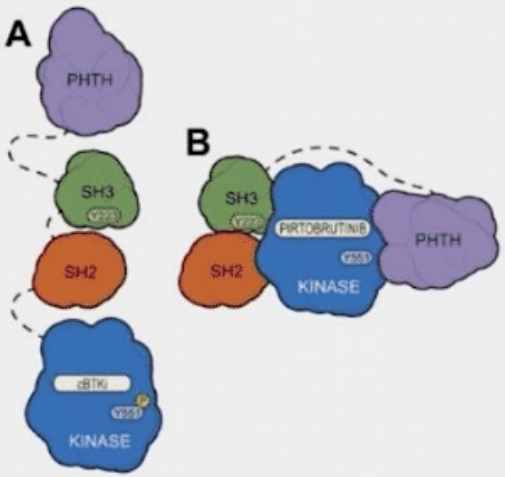
Pirtobrutinib in Post-cBTKi CLL/SLL: ~30 Months Follow-Up and Subgroup Analysis with/without Prior BCL2i from the Phase 1/2 BRUIN Study

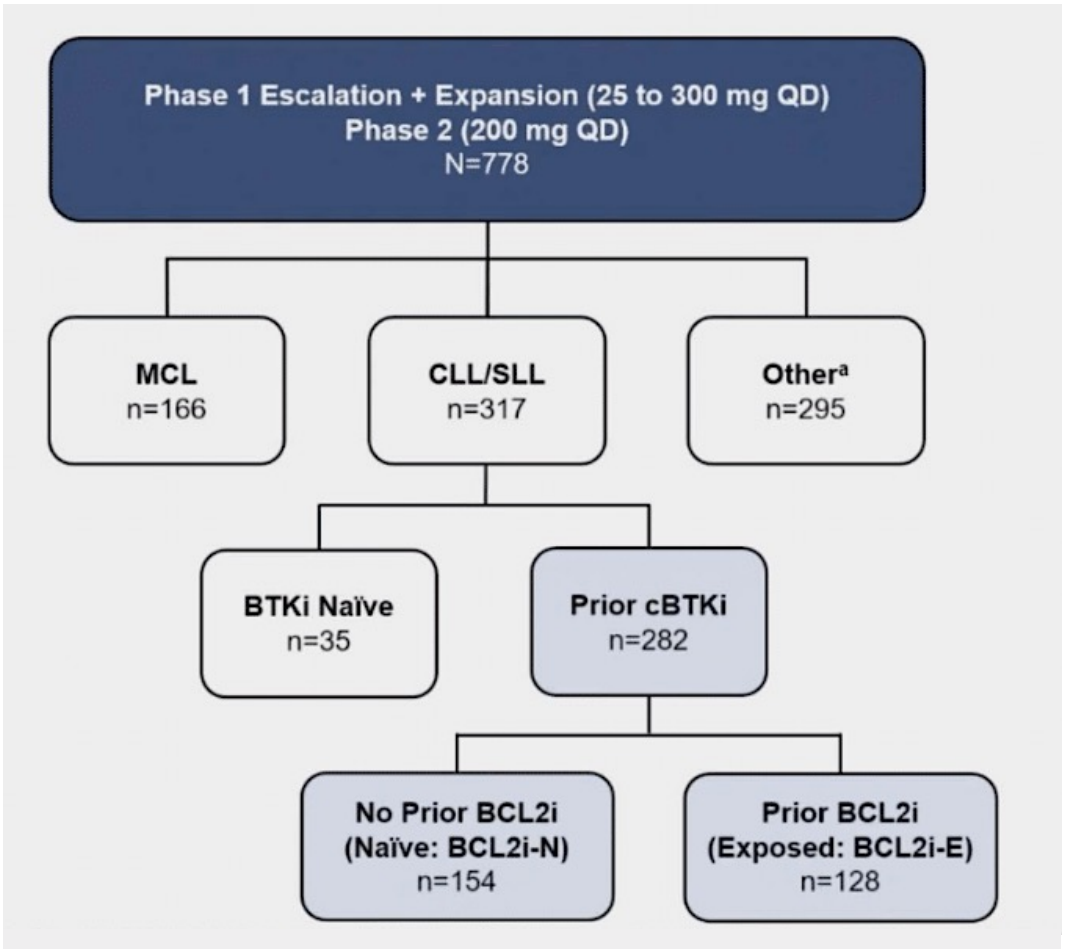
Jennifer A. Woyach[1], Jennifer R. Brown[2], Paolo Ghia[3], Lindsey E. Roeker[4], Krish Patel[5], Toby A. Eyre[6], Talha

Plasma exposures exceeded BTK IC_{90} throughout dosing interval



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



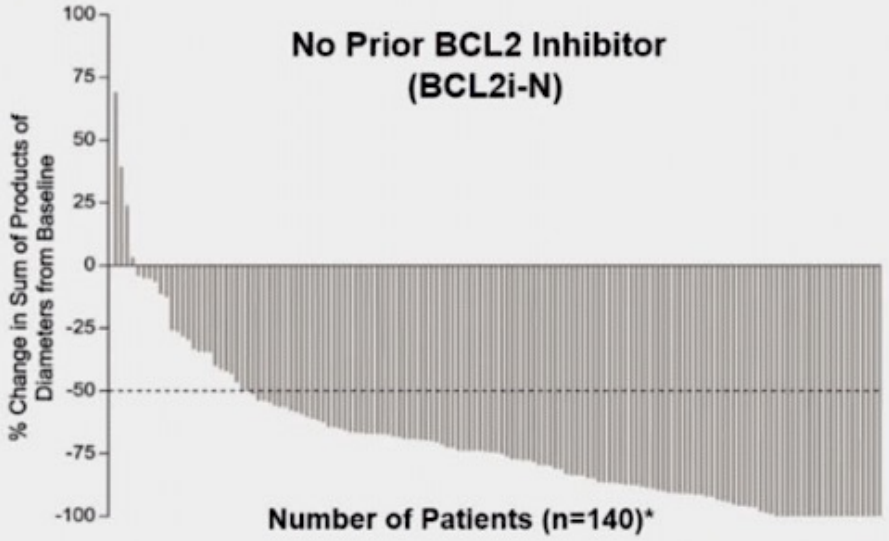


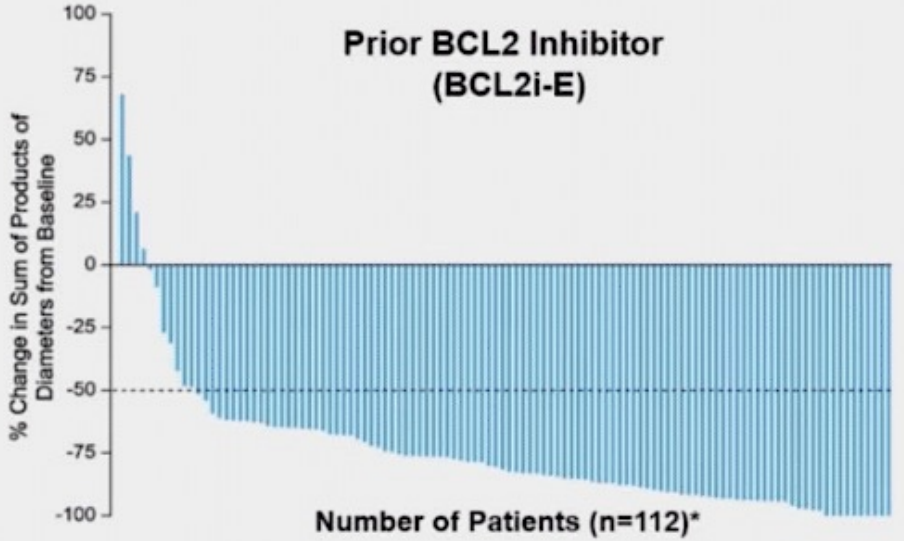
Woyach JA et al. ASH 2023;Abstract 325.

Courtesy of Jeff Sharman, MD

BRUIN: ORR Similar Between BCL-2 Exposed/Naive

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





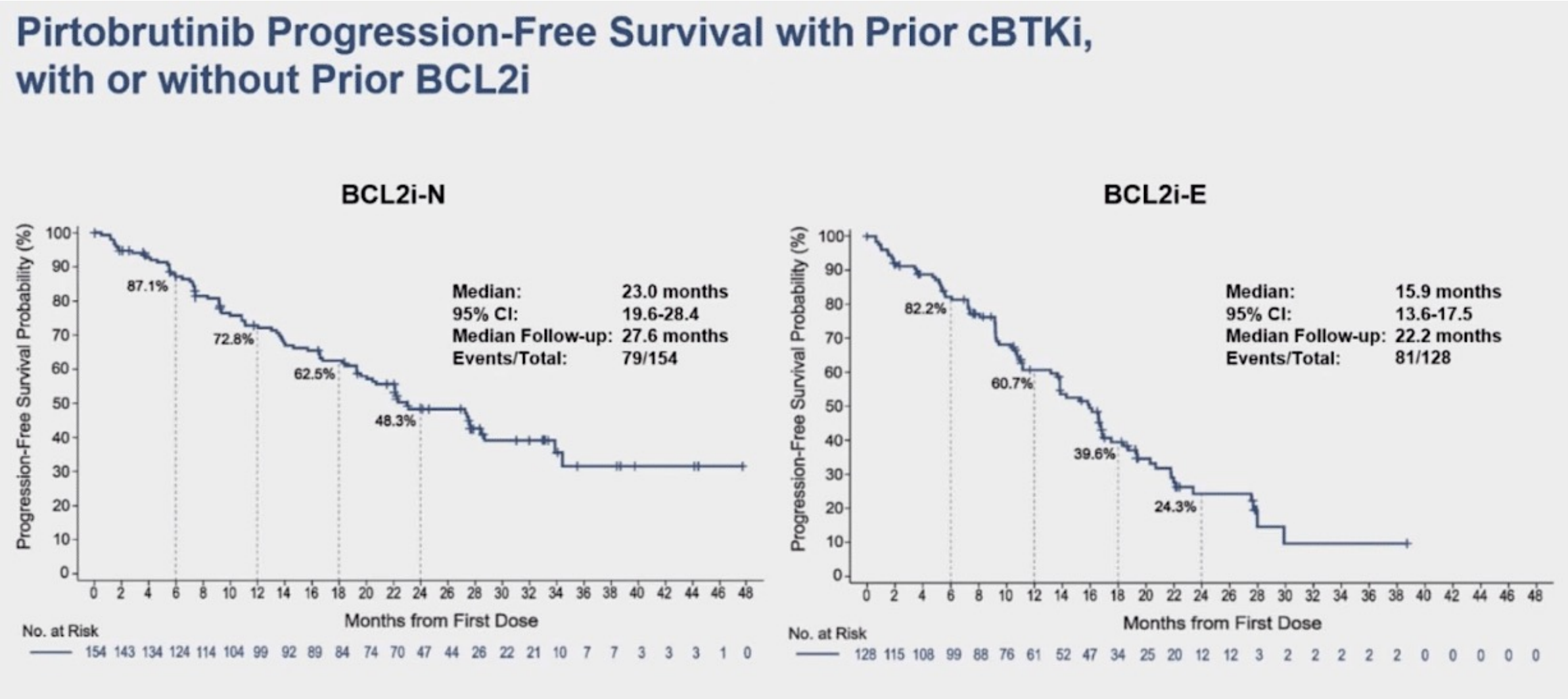
BCL2i-N	(n=154)[b]
ORR[a] incl. PR-L, % (95% CI)	83.1 (76.2-88.7)
Best Response, n (%)	
CR	5 (3.2)
nPR	2 (1.3)
PR	108 (70.1)
PR-L	13 (8.4)

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 JA et al. ASH 2023;Abstract 325.

Courtesy of Jeff Sharman, MD

BRUIN: PFS Varied based upon prior BCL2 exposure

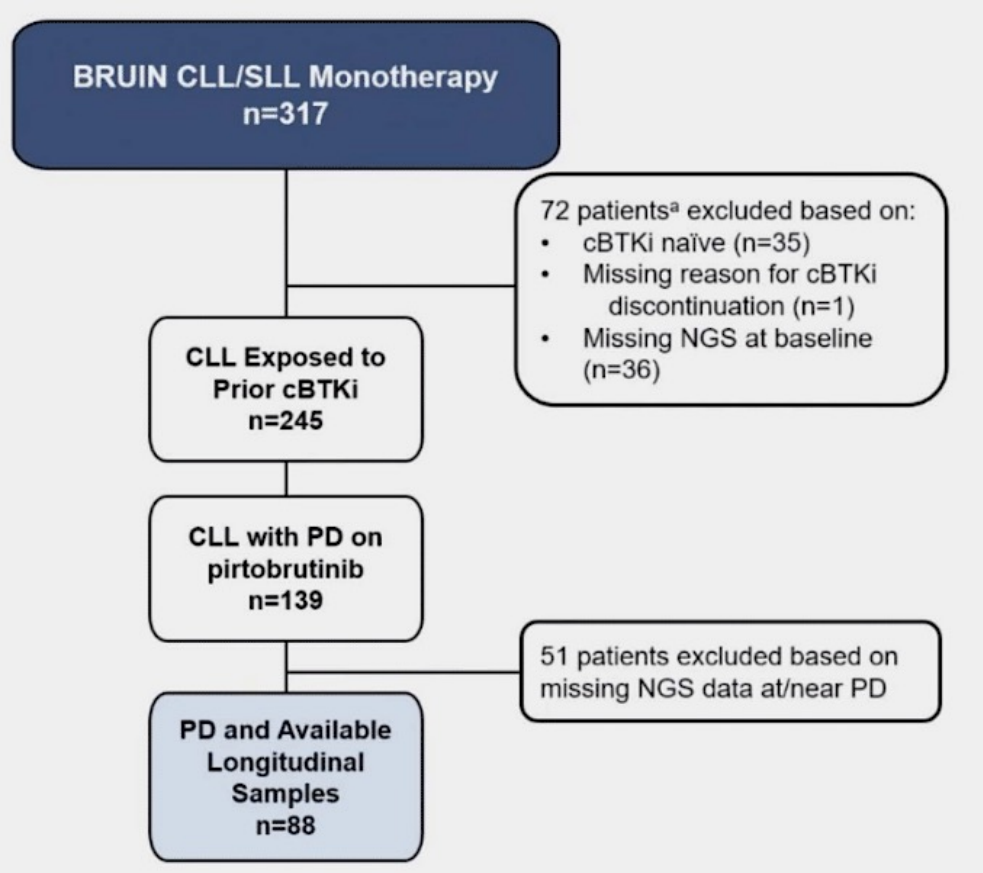


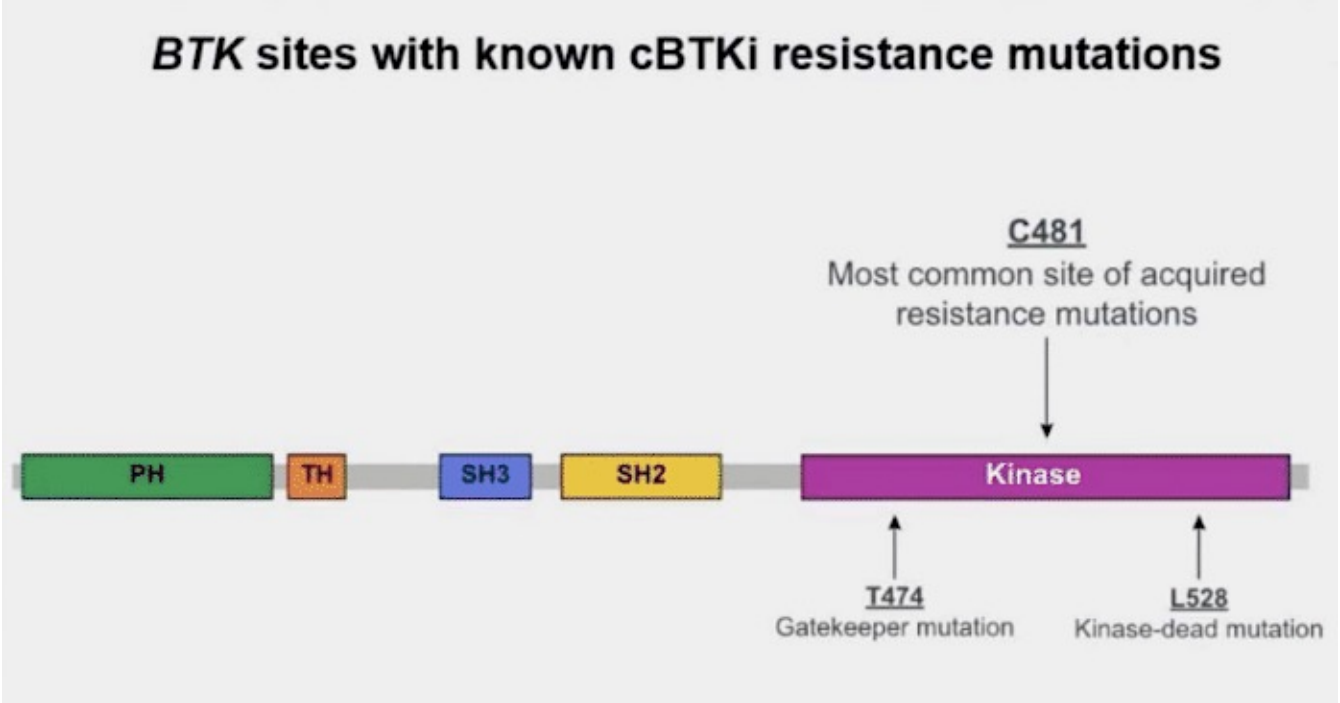
Woyach JA et al. ASH 2023;Abstract 325.

Courtesy of Jeff Sharman, MD

Genomic Evolution and Resistance during Pirtobrutinib Therapy in Covalent BTK-Inhibitor (cBTKi) Pre-treated Chronic Lymphocytic Leukemia Patients: Updated Analysis from the BRUIN Study

Jennifer R. Brown[1], Sai Prasad Desikan[2], Bastien Nguyen[3], Helen Won[3], Shady I. Tantawy[2], Samuel C.

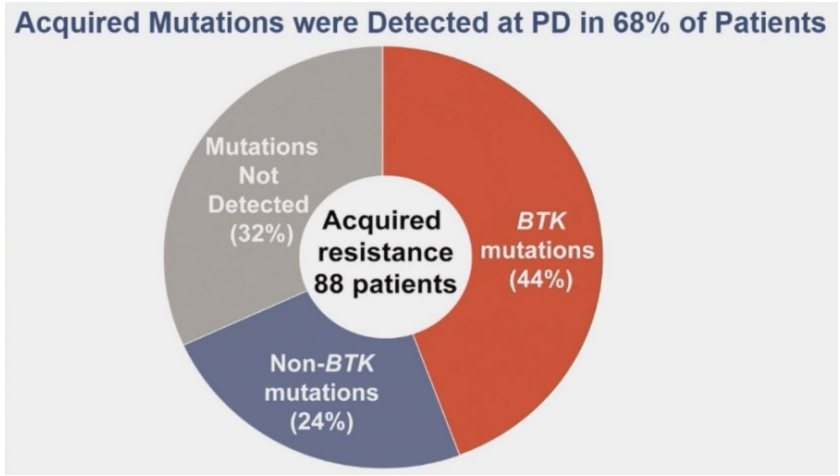


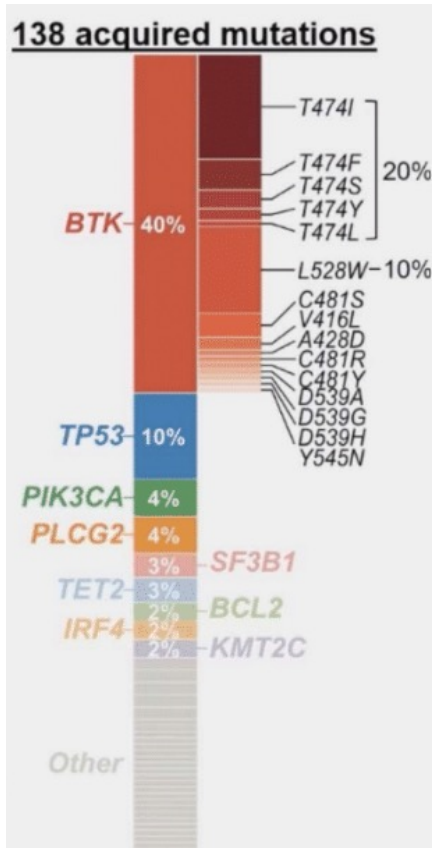


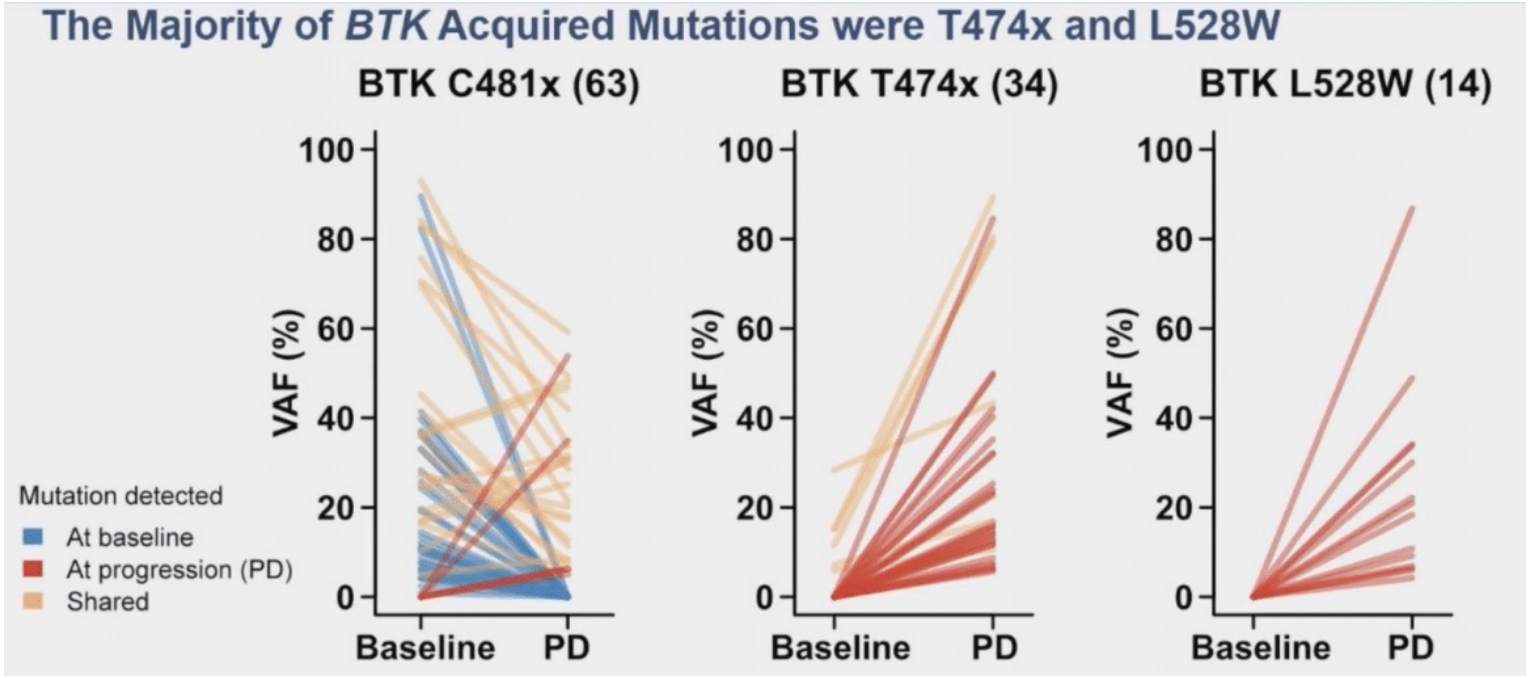
Brown J et al. ASH 2023;Abstract 326.

Courtesy of Jeff Sharman, MD

Mutation Profile Evolves on Pirtobrutinib







Brown J et al. ASH 2023;Abstract 326.

Courtesy of Jeff Sharman, MD

Pirtobrutinib conclusions

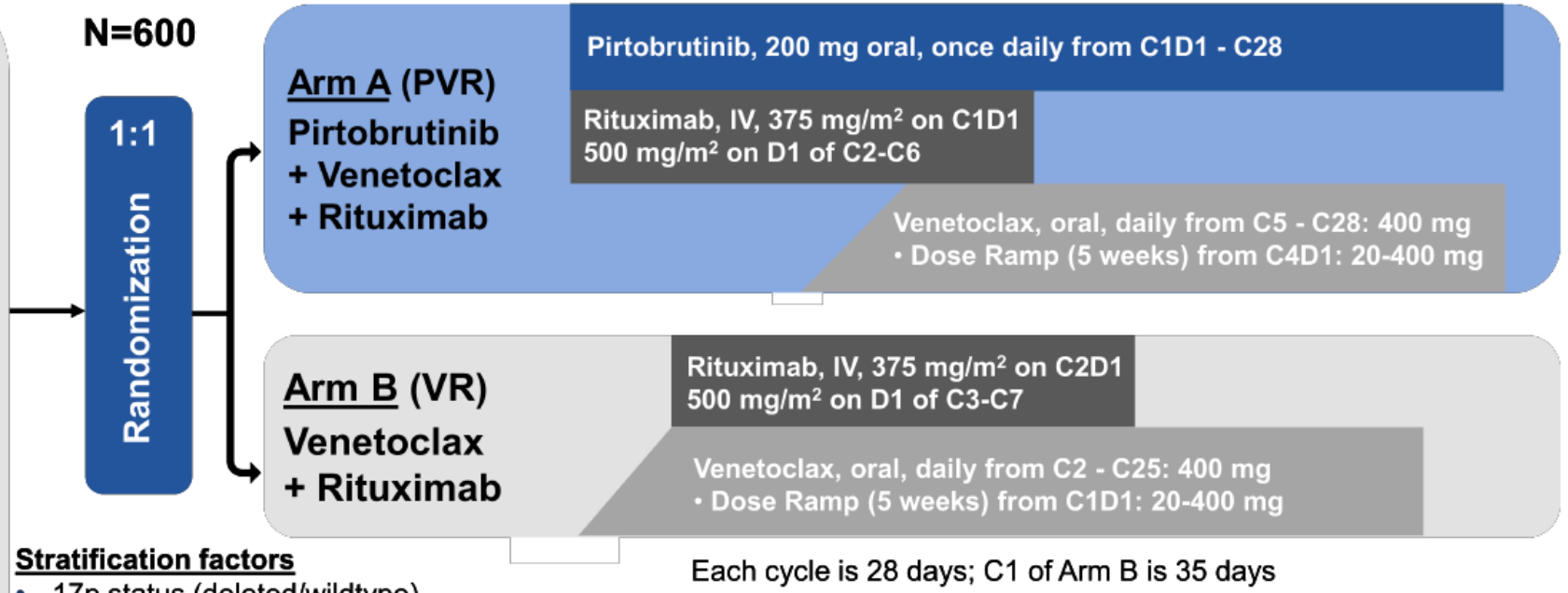
- Pirtobrutinib offers high response rates but modest PFS and significantly impacted by prior BCL2 use
- BTK resistance is an evolving story and clonal dynamics evolve quickly

Courtesy of Jeff Sharman, MD

BRUIN CLL-322: Phase III Trial Design

Key Inclusion Criteria

- Confirmed CLL/SLL per iwCLL 2018[3]
- Previously treated CLL/SLL (including a covalent BTKi or covalent BTKi naïve [limited to 20% of total enrollment])
- Known 17p status
  - If 17p status is unknown, local or central FISH test results during screening can be used
- No prior venetoclax
- ≥18 years of age and ECOG 0-2



Stratification factors

- 17p status (deleted/wildtype)
- Prior experience of BTKi (discontinuation due to PD or other vs no prior BTKi)

Primary endpoint: Progression-free survival per iwCLL 2018 by IRC

June 2023: Enrollment ongoing for patients who previously received cBTKi, complete for cBTKi-naïve disease

Eyre TA et al. ASCO 2023;Abstract TPS7583. Wierda WG et al. SOHO 2022;Abstract CLL-322.

Ongoing Phase III Trials Evaluating Pirtobrutinib

Trial	Population	Experimental Arm	Control Arm
NCT05023980, phase 3	Untreated CLL/SLL	Pirtobrutinib	Bendamustine + Rituximab
NCT04965493, phase 3	Previously treated CLL/SLL	Pirtobrutinib + Venetoclax + Rituximab	Venetoclax + Rituximab
NCT04666038, phase 3	BTK inhibitor pre-treated CLL/SLL	Pirtobrutinib	Investigator's choice of Idelalisib + Rituximab or Bendamustine + Rituximab
NCT04662255, phase 3	Previously treated, BTK inhibitor naïve MCL	Pirtobrutinib	Investigator choice of covalent BTK Inhibitor

BTK, Bruton's tyrosine kinase; CLL/SLL, chronic lymphocytic leukemia/small lymphocytic lymphoma; MCL, mantle cell lymphoma.

Jensen JL et al. *Ther Adv Hematol* 2022;13:20406207221101697.

Agenda

INTRODUCTION: An Audio Depiction of Mechanisms of Action of Bcl-2 Inhibitors, Anti-CD20 Antibodies and Covalent and Noncovalent BTK Inhibitors; Mechanisms of Resistance

MODULE 1: Current Management Approaches for Patients with Chronic Lymphocyctic Leukemia (CLL) — Dr Sharman

MODULE 2: Top 10 Questions — Part 1

MODULE 3: Future Directions in the Care of Patients with CLL — Dr Roeker

MODULE 4: Top 10 Questions — Part 2

Top 10 Questions — Part 1

What is your approach to the selection of a first-line BTK inhibitor for patients requiring treatment?

Top 10 Questions — Part 1

How would you compare the efficacy of zanubrutinib to that of acalabrutinib monotherapy and/or acalabrutinib/obinutuzumab?

Top 10 Questions — Part 1

How do you approach first-line treatment for patients with high-risk disease (del(17p), TP53, IGHV unmutated)? What about asymptomatic patients?

Top 10 Questions — Part 1

How do you approach the use of venetoclax as first-line treatment?

Do you always use it in combination with anti-CD20 therapy; which anti-CD20 and which do you administer first?

Top 10 Questions — Part 1

How do you approach the use of a BTK inhibitor for a patient requiring anticoagulation?

Agenda

INTRODUCTION: An Audio Depiction of Mechanisms of Action of Bcl-2 Inhibitors, Anti-CD20 Antibodies and Covalent and Noncovalent BTK Inhibitors; Mechanisms of Resistance

MODULE 1: Current Management Approaches for Patients with Chronic Lymphocyctic Leukemia (CLL) — Dr Sharman

MODULE 2: Top 10 Questions — Part 1

MODULE 3: Future Directions in the Care of Patients with CLL — Dr Roeker

MODULE 4: Top 10 Questions — Part 2

Fixed-Duration Ibrutinib/Venetoclax

- Ghia P et al. Relapse after **first-line fixed duration ibrutinib + venetoclax**: High response rates to ibrutinib retreatment and absence of BTK mutations in patients with chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL) with up to **5 years of follow-up** in the **Phase 2 Captivate** study. ASH 2023;Abstract 633.
- Kater A et al. Time-limited **venetoclax and ibrutinib** for patients with **relapsed/refractory** CLL who have undetectable MRD – 4-year follow up from the randomized **Phase II VISION/HO141** trial. EHA 2023;Abstract S148.
- Hillmen P et al. **Ibrutinib plus venetoclax** with MRD-directed duration of treatment is superior to FCR and is a new standard of care for **previously untreated** CLL: Report of the **Phase III UK NCRI FLAIR** study. ASH 2023;Abstract 631.
- Woyach JA et al. Results of a **phase 3** study of **IVO vs IO** for **previously untreated** older patients (pts) with chronic lymphocytic leukemia (CLL) and impact of COVID-19 (Alliance). ASCO 2023;Abstract 7500.
- Follows G et al. **First-line fixed-duration ibrutinib plus venetoclax** (Ibr + Ven) versus chlorambucil plus obinutuzumab (Clb + O): **55-month follow-up** from the **Glow** study. ASH 2023;Abstract 634.

Ibrutinib plus venetoclax with MRD-directed duration of treatment is superior to FCR and is a new standard of care for previously untreated CLL: Report of the Phase III UK NCRI FLAIR study

I+V improves progression free and overall survival compared to FCR (a real control arm!), especially in uIGHV and regardless of cytogenetics

Hillmen, et al. ASH 2023; Abstract 631.

Courtesy of Lindsey Roeker, MD

Relapse after first-line fixed duration ibrutinib + venetoclax: High response rates to ibrutinib retreatment and absence of BTK mutations in patients with chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL) with up to 5 years of follow-up in the Phase 2 CAPTIVATE study

Fixed duration I+V may mitigate risk of developing resistance mutations

Patients can successfully be retreated with ibrutinib-based therapy

Ghia, et al. ASH 2023; Abstract 633.

Courtesy of Lindsey Roeker, MD

First-line fixed-duration ibrutinib plus venetoclax (Ibr+Ven) versus chlorambucil plus obinutuzumab (Clb+O): 55-month follow-up from the GLOW study

MRD status at end of treatment predicts PFS, especially for uIGHV (less significant for mIGHV)

I+V improves TTNT for uIGHV vs. Chlorambucil/Obin

Follows, et al. ASH 2023; Abstract 634.

Courtesy of Lindsey Roeker, MD

Time-limited venetoclax and ibrutinib for patients with relapsed/refractory CLL who have undetectable MRD – 4-year follow up from the randomized Phase II VISION/HO141 trial

Patients who achieve uMRD and stop therapy
can be successfully retreated upon MRD progression

Kater, et al. EHA 2023; Abstract S148.

Courtesy of Lindsey Roeker, MD

Results of a phase 3 study of IVO vs IO for previously untreated older patients (pts) with chronic lymphocytic leukemia (CLL) and impact of COVID-19 (Alliance)

IVO is not superior to IO in older adults

Excess COVID-related deaths for those who received IVO

Woyach, et al. ASCO 2023; Abstract 7500.

Courtesy of Lindsey Roeker, MD

Second-Generation BTK Inhibitors in Combination with Venetoclax

- Furstenau M et al. Long-term remissions with MRD-guided **acalabrutinib, venetoclax and obinutuzumab** in **relapsed/refractory** CLL: Follow-up efficacy and circulating tumor DNA analysis of the CLL2-Baag trial. ASH 2023;Abstract 203.
- Allan J et al. **Zanubrutinib and venetoclax** as **initial therapy** for CLL/SLL with **obinutuzumab triplet consolidation** in patients with minimal residual disease positivity **(BruVenG)**. ASH 2023;Abstract 3285.

Long-term remissions with MRD-guided acalabrutinib, venetoclax and obinutuzumab in relapsed/refractory CLL: Follow-up efficacy and circulating tumor DNA analysis of the CLL2-BAAG trial

Treatment with AVO in a R/R population achieves high levels of uMRD

ctDNA enhances ability to detect early molecular relapse

Furstenau, et al. ASH 2023; Abstract 203.

Courtesy of Lindsey Roeker, MD

Pirtobrutinib in Combination with Venetoclax/Rituximab

- Roeker L et al. **Fixed-duration pirtobrutinib** combined with **venetoclax ± rituximab** in **relapsed/refractory** chronic lymphocytic leukemia: Updated results, including MRD data, from the **BRUIN** Phase 1b study. ASH 2023;Abstract 3269.

Fixed-duration pirtobrutinib combined with venetoclax ± rituximab in relapsed/refractory chronic lymphocytic leukemia: Updated results, including MRD data, from the BRUIN Phase 1b study

Pirtobrutinib / Venetoclax ± Rituximab is effective (achieves high ORR) in R/R population

No DLTs observed, combination being explored in Ph3 study

Roeker, et al. ASH 2023; Abstract 3269.

Courtesy of Lindsey Roeker, MD

Novel Agents and Strategies

- Woyach JA et al. First-in-human study of the **reversible BTK inhibitor nemtabrutinib** in patients with **relapsed/refractory** chronic lymphocytic leukemia and B-cell non-Hodgkin lymphoma. *Cancer Discov* 2024;14(1):66-75.
- Siddiqi T et al. **Lisocabtagene maraleucel** (liso-cel) in R/R CLL/SLL: 24-month median follow-up of **TRANSCEND CLL 004**. ASH 2023;Abstract 330.
- Tam C et al. Combination treatment with **sonrotoclax (BGB-11417), a second-generation BCL2 inhibitor, and zanubrutinib**, a Bruton tyrosine kinase (BTK) inhibitor, is well tolerated and achieves deep responses in patients with **treatment-naïve** chronic lymphocytic leukemia/small lymphocytic lymphoma (TN-CLL/SLL): Data from an ongoing Phase 1/2 study. ASH 2023;Abstract 327.

New Agents

First-in-human study of the reversible BTK inhibitor nemtabrutinib in patients with relapsed/refractory chronic lymphocytic leukemia and B-cell non-Hodgkin lymphoma

Nemtabrutinib is a noncovalent BTKi with activity in CLL (regardless of C481 status) and NHL

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

Courtesy of Lindsey Roeker, MD

Lisocabtagene maraleucel (liso-cel) in R/R CLL/SLL: 24-month median follow-up of TRANSCEND CLL 004

For responders, Liso-cel achieves durable remissions, even for those with double refractory disease

Siddiqi, et al. ASH 2023; Abstract 330.

Courtesy of Lindsey Roeker, MD

Combination treatment with sonrotoclax (BGB-11417), a second-generation BCL2 inhibitor, and zanubrutinib, a Bruton tyrosine kinase (BTK) inhibitor, is well tolerated and achieves deep responses in patients with treatment-naïve chronic lymphocytic leukemia/small lymphocytic lymphoma (TN-CLL/SLL): Data from an ongoing Phase 1/2 study

Sonrotoclax and Zanubrutinib is a well tolerated and effective (ORR 100%, though follow up is currently limited) combination

Tam, et al. ASH 2023; Abstract 327.

Courtesy of Lindsey Roeker, MD

Richter's Transformation

- Frustaci AM et al. Results of **MOLTO**, a multicenter, open label, phase II clinical trial evaluating **venetoclax, atezolizumab and obinutuzumab** combination in **Richter syndrome**. ASCO 2023;Abstract 7502.
- Al-Sawaf O et al. **Tislelizumab plus zanubrutinib** in patients with **Richter transformation**: Primary endpoint analysis of the prospective, multi-center, **Phase-II RT1** trial of the German CLL Study Group. ASH 2023;Abstract 204.
- Wierda W et al. **Pirtobrutinib** in **Richter transformation**: Updated efficacy and safety results with 18-month median survival follow-up from the Phase 1/2 **BRUIN** study. ASH 2023;Abstract 1737.

Richter’s Transformation

Results of MOLTO, a multicenter, open label, phase II clinical trial evaluating venetoclax, atezolizumab and obinutuzumab combination in Richter syndrome

Obin / Atezo / Ven has activity in untreated Richter's transformation with ORR of 68%, median PFS of 16 months (compares favorably to CIT)

Frustaci, et al. ASCO 2023; Abstract 7502.

Courtesy of Lindsey Roeker, MD

Tislelizumab plus zanubrutinib in patients with Richter transformation: Primary endpoint analysis of the prospective, multi-center, Phase-II RT1 trial of the German CLL Study Group

Tislelizumab / Zanubrutinib has activity in Richter's transformation (≤1 prior line) with ORR 58%, median PFS 10 months

Al-Sawaf, et al. ASH 2023; Abstract 204.

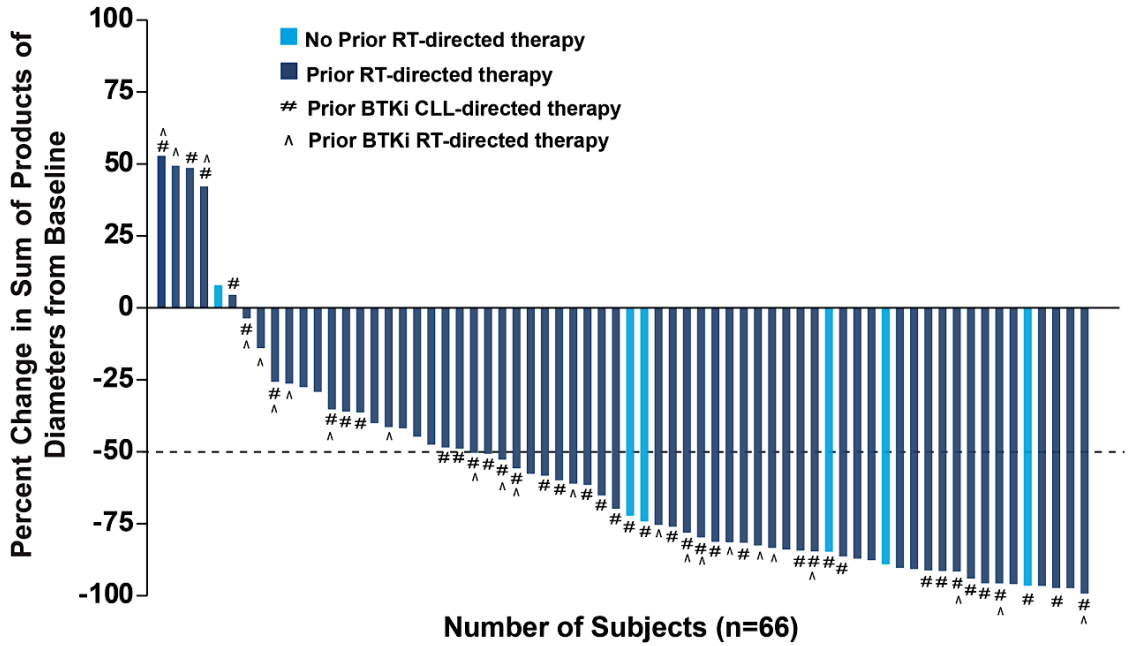
Courtesy of Lindsey Roeker, MD

Pirtobrutinib in Richter transformation: Updated efficacy and safety results with 18-month median survival follow-up from the Phase 1/2 BRUIN study

Characteristics	Overall n=82
Median Age, years (range)	67 (26-95)
Male, n (%)	55 (67)
ECOG PS, n (%)	
0	32 (39)
1	38 (46)
2	12 (15)
Ann Arbor Stage, n (%)	
Stage I-II	8 (10)
Stage III-IV	57 (70)
Missing	17 (21)
Tumor Bulk (cm), n (%)	
<5	39 (48)
≥5	36 (44)
No Measurable Lymph Node	7 (9)
Elevated LDH, n (%)	
Yes	66 (81)
No	16 (20)
Median Time, months (IQR)	
From Initial CLL Diagnosis to RT Presentation	61 (17-102)
From Transformation to First Pirtobrutinib Dose	5 (2-13)
Median Number of Prior Lines of, (range)	
CLL Therapy	2 (0-13)
RT Therapy	2 (0-8)
CLL and RT Therapy	4 (0-13)

Prior Therapies	Any	RT-Directed	CLL-Directed
Number of Patients, n/n (%)	81/82 (99)	74/82 (90)	65/82 (79)

	All n=82	Prior RT Therapy n=74
Overall Response Rate[a], % (95% CI)	50.0 (38.7-61.3)	48.6 (36.9-60.6)
Best Response,n (%)		
CR	11 (13.4)	9 (12.2)
PR	30 (36.6)	27 (36.5)



Median DOR = 7.4 months (9.7 mo f/u)
Median PFS = 3.7 months (13.8 mo f/u)

Wierda, et al. ASH 2023; Abstract 1737.

Courtesy of Lindsey Roeker, MD

Pirtobrutinib in Richter transformation: Updated efficacy and safety results with 18-month median survival follow-up from the Phase 1/2 BRUIN study

Pirtobrutinib has single agent activity in R/R Richter's with ORR of 50%

Wierda, et al. ASH 2023; Abstract 1737.

Courtesy of Lindsey Roeker, MD

Agenda

INTRODUCTION: An Audio Depiction of Mechanisms of Action of Bcl-2 Inhibitors, Anti-CD20 Antibodies and Covalent and Noncovalent BTK Inhibitors; Mechanisms of Resistance

MODULE 1: Current Management Approaches for Patients with Chronic Lymphocyctic Leukemia (CLL) — Dr Sharman

MODULE 2: Top 10 Questions — Part 1

MODULE 3: Future Directions in the Care of Patients with CLL — Dr Roeker

MODULE 4: Top 10 Questions — Part 2

Top 10 Questions — Part 2

Regulatory and reimbursement issues aside, in what situations, if any, do you believe a first-line combination of a BTKi and venetoclax (with or without an anti-CD20 antibody) is a reasonable choice for CLL?

Top 10 Questions — Part 2

Globally, how would you evaluate the efficacy and tolerability/convenience of a first-line combination of a BTKi and venetoclax (with or without an anti-CD20 antibody) versus a BTKi or venetoclax/obinutuzumab?

Top 10 Questions — Part 2

In what situations are you currently considering pirtobrutinib for CLL?

Globally, how would you evaluate the tolerability of pirtobrutinib versus acalabrutinib and zanubrutinib?

Any thoughts on the use of pirtobrutinib with venetoclax?

Top 10 Questions — Part 2

What are your thoughts on some of the promising therapeutic developments beyond R-CHOP for patients with Richter's transformation (Pirtobrutinib, CAR T-cell therapy)?

Top 10 Questions — Part 2

What are your thoughts on other new strategies and agents for patients with CLL or Richter's transformation (BTK degraders, CAR-T, bispecifics)?

Year in Review: Clinical Investigator Perspectives on the Most Relevant New Data Sets and Advances in Oncology

A Multitumor CME/MOC-Accredited Live Webinar Series

Gastroesophageal Cancers

Thursday, February 8, 2024
5:00 PM – 6:00 PM ET

Faculty

Yelena Y Janjigian, MD

Zev Wainberg, MD, MSc

Moderator

Neil Love, MD

RTP Year in Review 2024

Thank you for joining us!

CME and MOC credit information will be emailed to each participant within 5 business days.

RTP Year in Review 2024