Meet The Professor

Current and Future Management of Chronic Lymphocytic Leukemia

Jennifer R Brown, MD, PhD
CLL Center Director and Institute Physician
Dana-Farber Cancer Institute
Worthington and Margaret Collette Professor of Medicine in the Field of Hematologic Oncology
Harvard Medical School
Boston, Massachusetts

Commercial Support

This activity is supported by educational grants from AstraZeneca Pharmaceuticals LP, Genentech, a member of the Roche Group, and Pharmacyclics LLC, an AbbVie Company and Janssen Biotech Inc, administered by Janssen Scientific Affairs LLC.

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Dr Love — Disclosures

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

Dr Brown — Disclosures

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Contracted Research	Gilead Sciences Inc, Loxo Oncology Inc, a wholly owned subsidiary of Eli Lilly & Company, Secura Bio, Sun Pharmaceutical Industries Ltd, TG Therapeutics Inc

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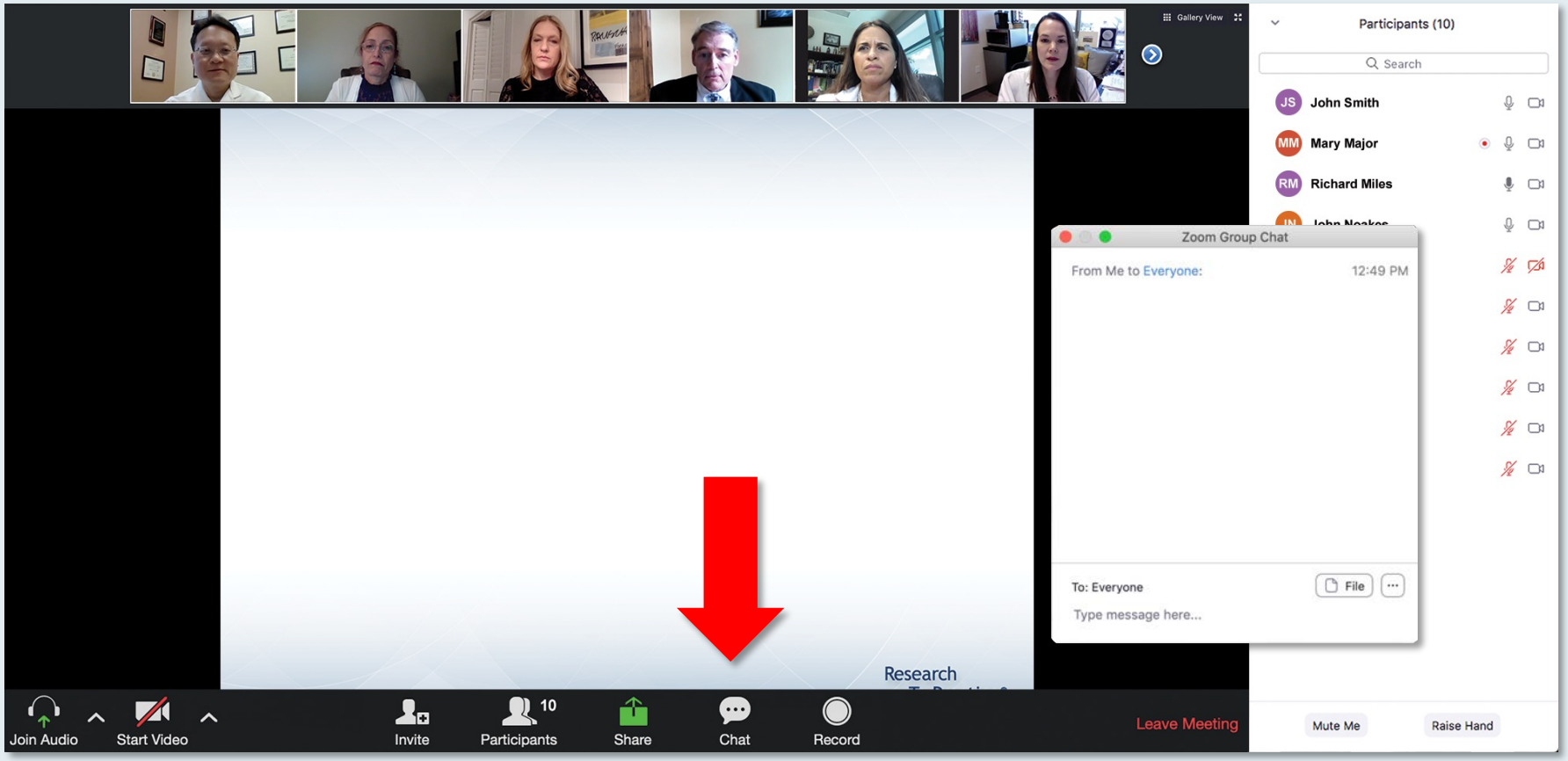
We Encourage Clinicians in Practice to Submit Questions



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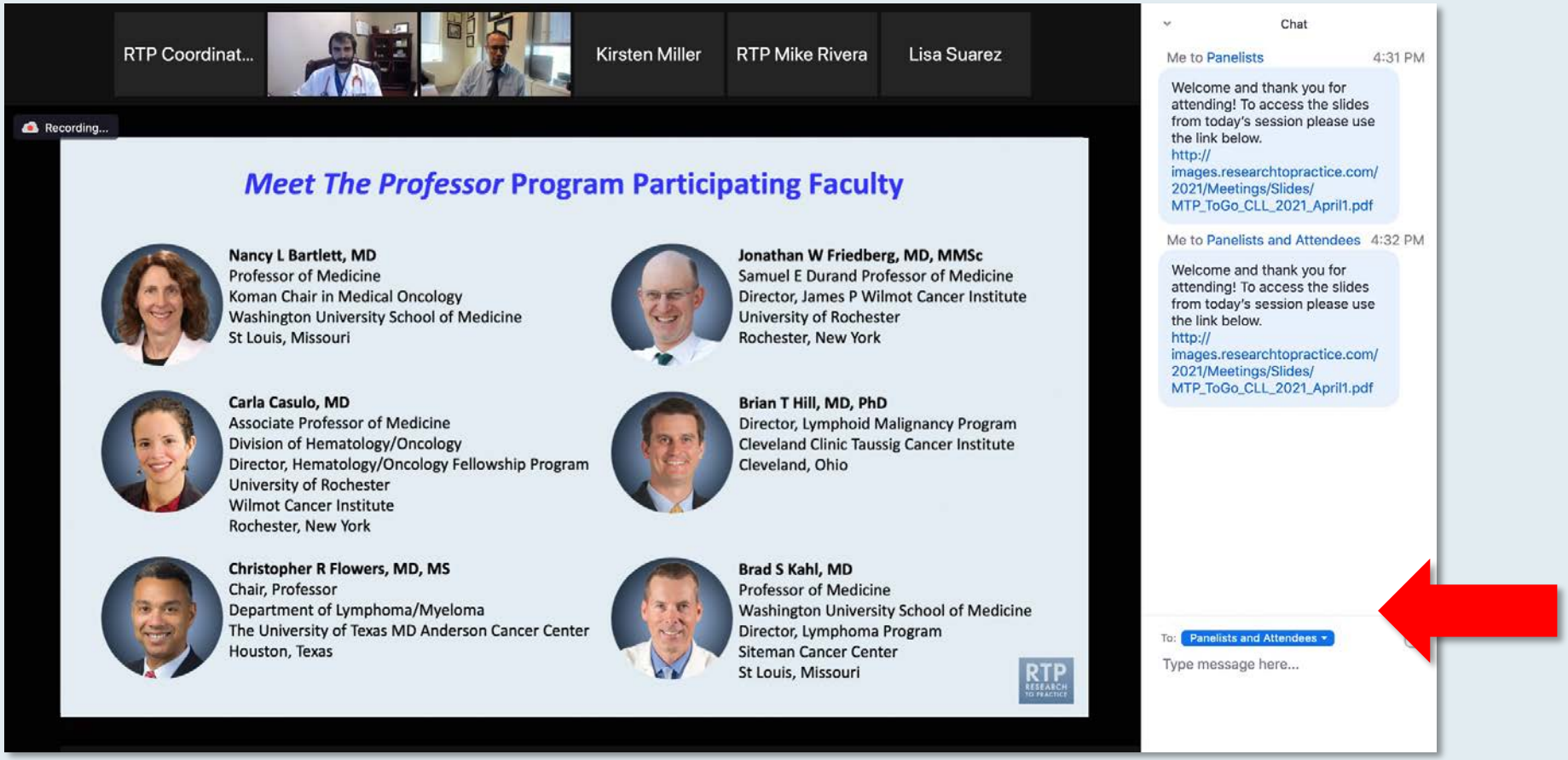

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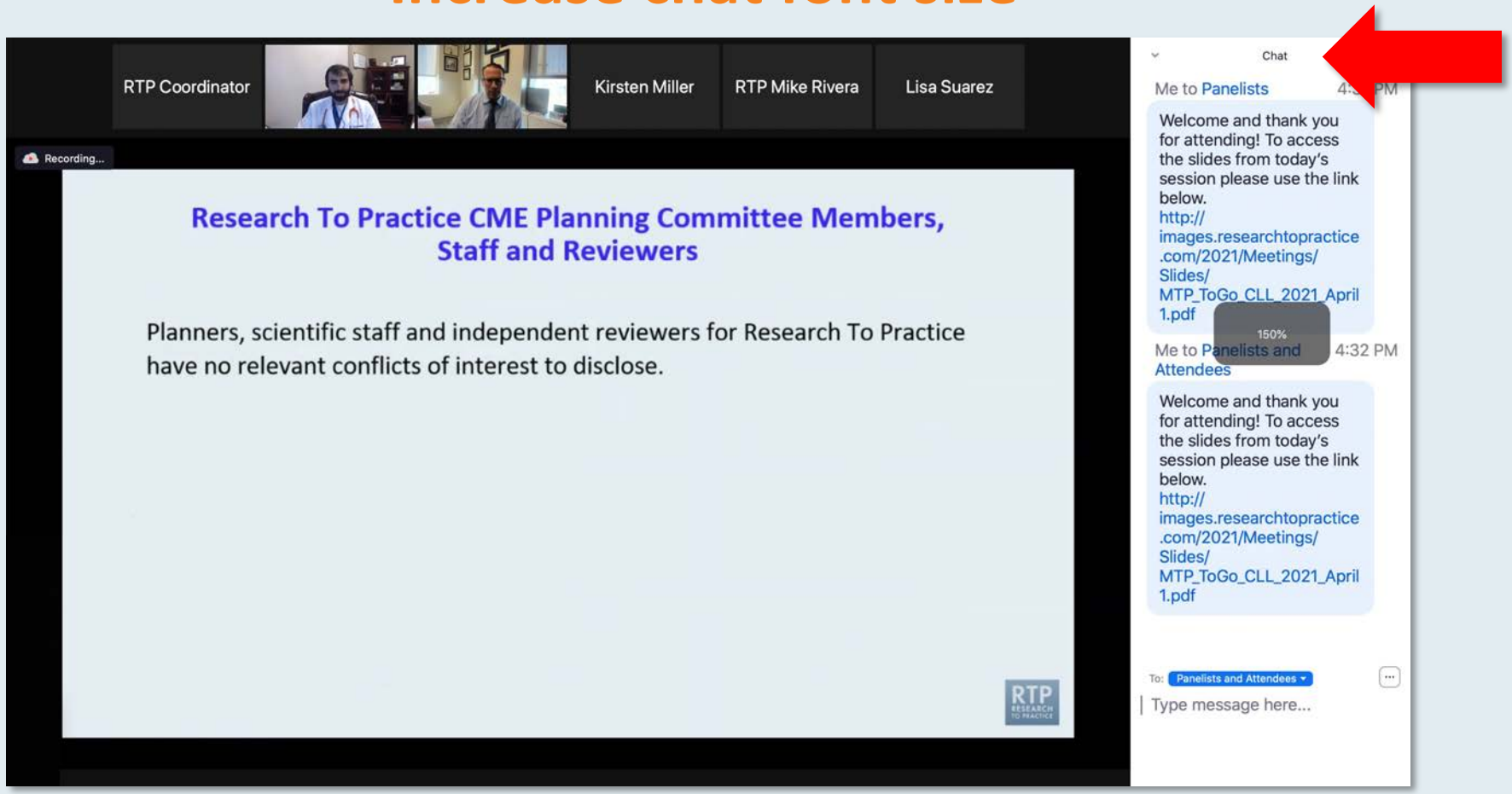

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ONCOLOGY TODAY

WITH DR NEIL LOVE

Recent Advances in the Treatment of Chronic Lymphocytic Leukemia

DR PETER HILLMEN
UNIVERSITY OF LEEDS

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Meet The Professor

Non-Small Cell Lung Cancer with an Actionable Target Beyond EGFR

Monday, April 18, 2022
5:00 PM – 6:00 PM ET

Faculty

D Ross Camidge, MD, PhD

Special Topics

- **ALK+ NSCLC: First-line treatment, resistance mutations**

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What I Tell My Patients: Expert Insights into Patient Education on New Treatments and Clinical Trial Participation

A Complimentary NCPD Hybrid Symposium Series Held During the 47th Annual ONS Congress

Prostate Cancer

Thursday, April 28, 2022
6:00 AM – 7:30 AM PT (9:00 AM – 10:30 AM ET)

Faculty
Kathy D Burns, RN, MSN, AGACNP-BC, OCN
Robert Dreicer, MD, MS
Sandy Srinivas, MD
Ronald Stein, JD, MSN, NP-C, AOCNP

Non-Small Cell Lung Cancer

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Kelly EH Goodwin, MSN, RN, ANP-BC
Tara Plues, APRN, MSN
Anne S Tsao, MD, MBA

Ovarian Cancer

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Kathleen N Moore, MD, MS
Krishnansu S Tewari, MD
Deborah Wright, MSN, APRN, AGCNS-BC

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Amanda K Wagner, APRN-CNP, AOCNP

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Matthew Gubens, MD, MS
Lowell L Hart, MD
Chaely J Medley, MSN, AGNP

Breast Cancer

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Sara A Hurvitz, MD
Kelly Leonard, MSN, FNP-BC
Hope S Rugo, MD

Chronic Lymphocytic Leukemia

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Amy Goodrich, CRNP
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Faculty
Monica Averia, MSN, AOCNP, NP-C
Shilpa Gupta, MD
Brenda Martone, MSN, NP-BC, AOCNP
Sumanta Kumar Pal, MD

Meet The Professor

Optimizing the Management of Gastroesophageal Cancers

Thursday, May 5, 2022
5:00 PM – 6:00 PM ET

Faculty

Yelena Y Janjigian, MD

Moderator

Neil Love, MD

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Cases from the Community: Urologic Oncology Investigators Provide Perspectives on the Optimal Management of Prostate Cancer

Friday, May 13, 2022

8:00 AM – 10:00 AM CT (9:00 AM – 11:00 AM ET)

Faculty

Fred Saad, MD

Matthew R Smith, MD, PhD

Additional faculty to be announced.

Moderator

Emmanuel S Antonarakis, MD

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Cases from the Community: Urologic Oncology Investigators Provide Perspectives on the Optimal Management of Urothelial Bladder Cancer

Friday, May 13, 2022

6:00 PM – 8:00 PM CT (7:00 PM – 9:00 PM ET)

Faculty

Matthew D Galsky, MD
Ashish M Kamat, MD, MBBS
Stephen B Williams, MD, MBA, MS

Moderator

Sumanta Kumar Pal, MD

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Thank you for joining us!

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

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Harvard Medical School
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Peter Hillmen, MB ChB, PhD
Professor of Experimental Haematology
University of Leeds
Honorary Consultant Haematologist
Leeds Teaching Hospitals NHS Trust
Leeds, United Kingdom

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

Susan O'Brien, MD
Professor, Division of Hematology/Oncology
School of Medicine
UCI Chao Family Comprehensive Cancer Center
Orange, California

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Meet The Professor Program Participating Faculty

Kerry Rogers, MD
Assistant Professor in the Division of Hematology
The Ohio State University
Columbus, Ohio

William G Wierda, MD, PhD
DB Lane Cancer Research Distinguished Professor
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

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

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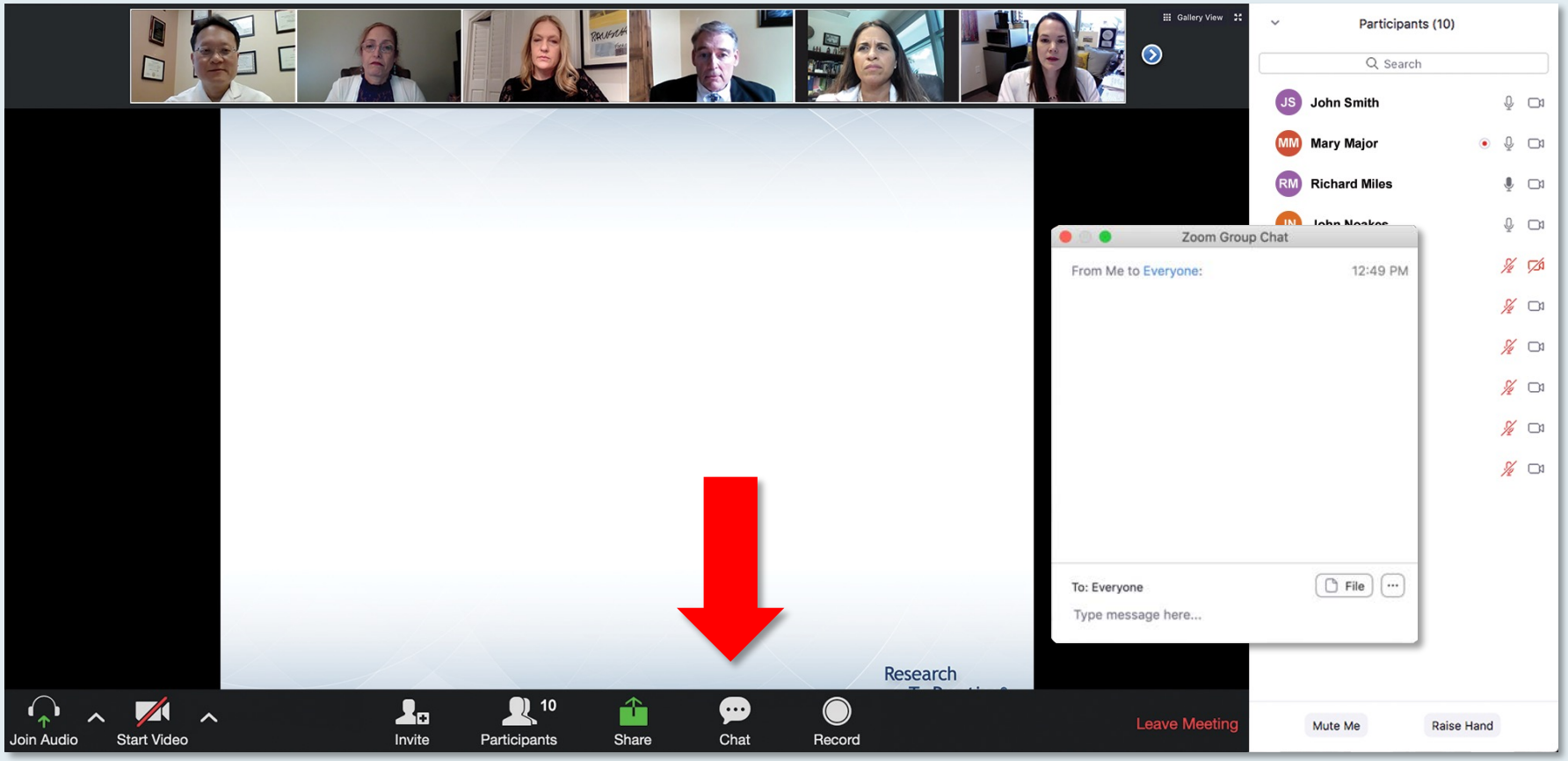

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Moderator

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RTP RESEARCH TO PRACTICE

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Stephen B Williams, MD, MBA, MS

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Contracted Research	Gilead Sciences Inc, Loxo Oncology Inc, a wholly owned subsidiary of Eli Lilly & Company, Secura Bio, Sun Pharmaceutical Industries Ltd, TG Therapeutics Inc

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Bhavana (Tina) Bhatnagar, DO
West Virginia University Cancer Institute Schiffler Cancer Center
Wheeling, West Virginia

G Richard Polkinghorn, MD
Harold Alfond Center for Cancer Care
MaineGeneral Medical Center
Augusta, Maine

Gurveen Kaur, MD
WVU Medicine Wheeling Hospital
Wheeling, West Virginia

Rajni Sinha, MD, MRCP
Piedmont Cancer Institute
Atlanta, Georgia

Khuda Dad Khan, MD, PhD
Norton Cancer Institute
Prospect, Kentucky

Raman Sood, MD
Brooks Memorial Hospital
Dunkirk, New York

Joanna Metzner-Sadurski, MD
Self Regional Healthcare Cancer Center
Greenwood, South Carolina

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Meet The Professor with Dr Brown

MODULE 1: Case Presentations

- Dr Polkinghorn: A 68-year-old man with chronic lymphocytic leukemia (CLL) on observation for 10 years who develops angioedema
- Dr Sinha: A 60-year-old woman with SLL and Bruton tyrosine kinase (BTK)-related arthralgia
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MODULE 2: Journal Club with Dr Brown

MODULE 3: Faculty Survey

MODULE 4: Appendix of Key Recent Data Sets

N Engl J Med 2022;386:735-43

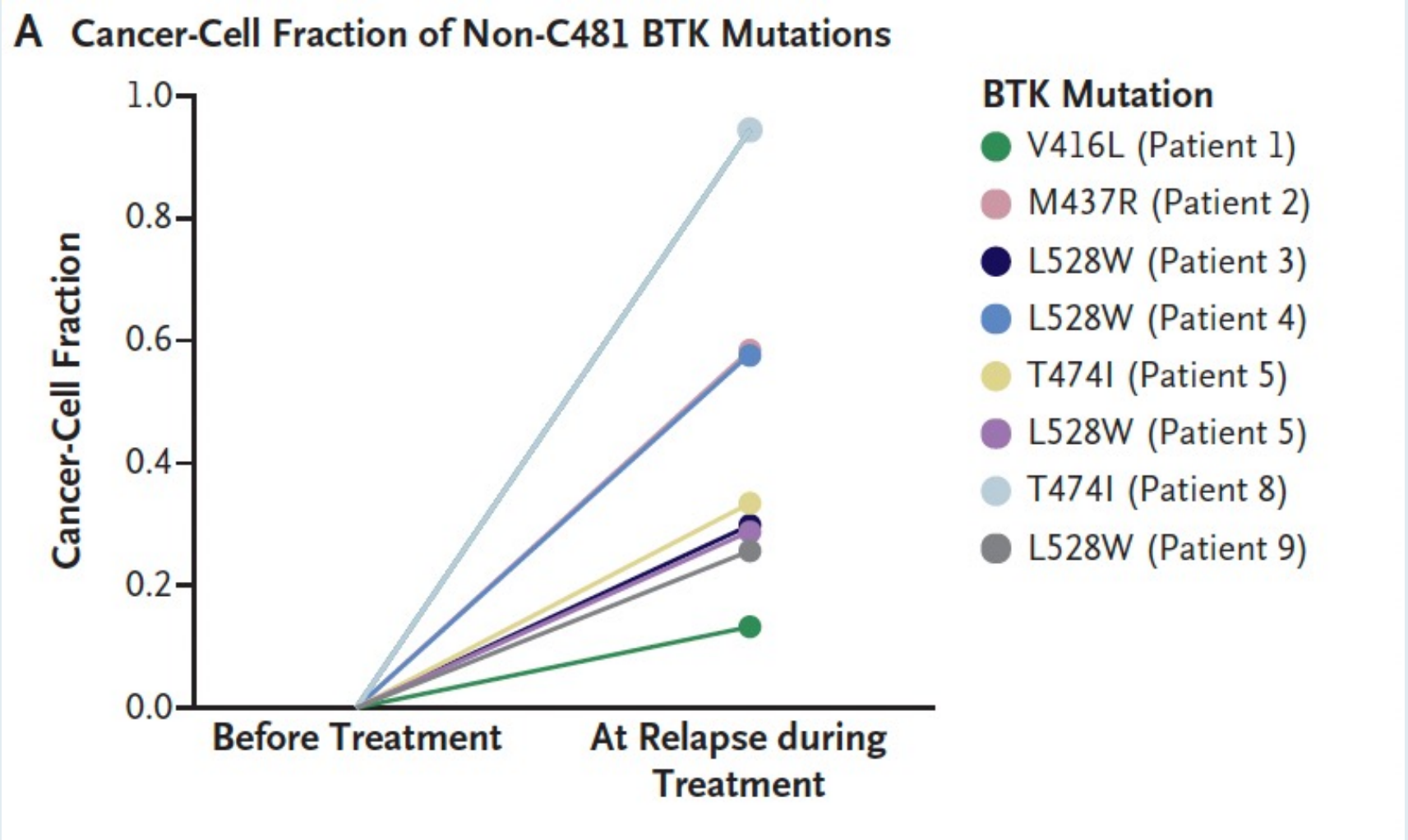
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Mechanisms of Resistance to Noncovalent Bruton's Tyrosine Kinase Inhibitors

Eric Wang, Ph.D., Xiaoli Mi, M.D., Meghan C. Thompson, M.D., Skye Montoya, B.Sc., Ryan Q. Notti, M.D., Ph.D., Jumana Afaghani, B.Sc., Benjamin H. Durham, M.D., Alex Penson, Ph.D., Matthew T. Witkowski, Ph.D., Sydney X. Lu, M.D., Ph.D., Jessie Bourcier, M.D., Simon J. Hogg, Ph.D., Caroline Erickson, B.Sc., Dan Cui, B.Sc., Hana Cho, B.Sc., Michael Singer, B.Sc., Tulasigeri M. Totiger, Ph.D., Sana Chaudhry, B.Sc., Mark Geyer, M.D., Alvaro Alencar, M.D., Adam J. Linley, Ph.D., M. Lia Palomba, M.D., Catherine C. Coombs, M.D., Jae H. Park, M.D., Andrew Zelenetz, M.D., Ph.D., Lindsey Roeker, M.D., Mary Rosendahl, Ph.D., Donald E. Tsai, M.D., Ph.D., Kevin Ebata, Ph.D., Barbara Brandhuber, Ph.D., David M. Hyman, M.D., Iannis Aifantis, Ph.D., Anthony Mato, M.D., M.S.C.E., Justin Taylor, M.D., and Omar Abdel-Wahab, M.D.

BTK Mutations in Patients with CLL with Acquired Resistance to Noncovalent BTK Inhibitors



Wang E et al. *N Engl J Med* 2022;386:735-43.

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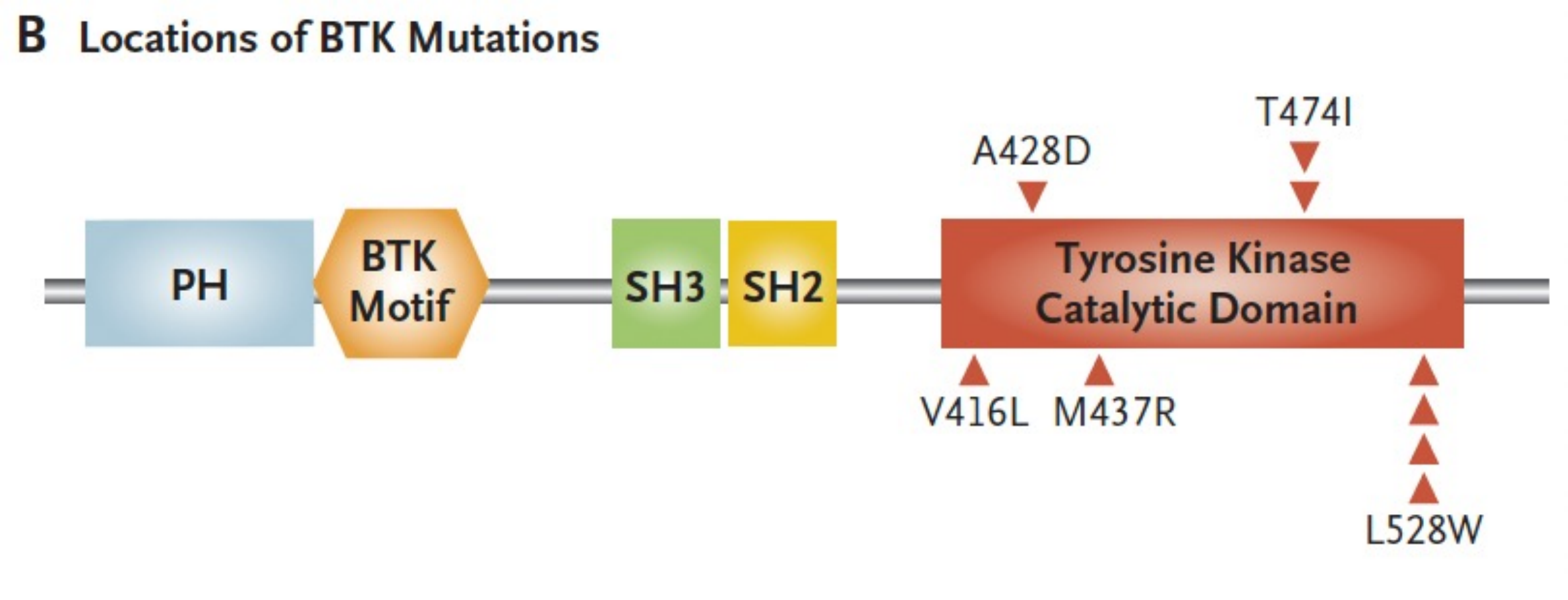

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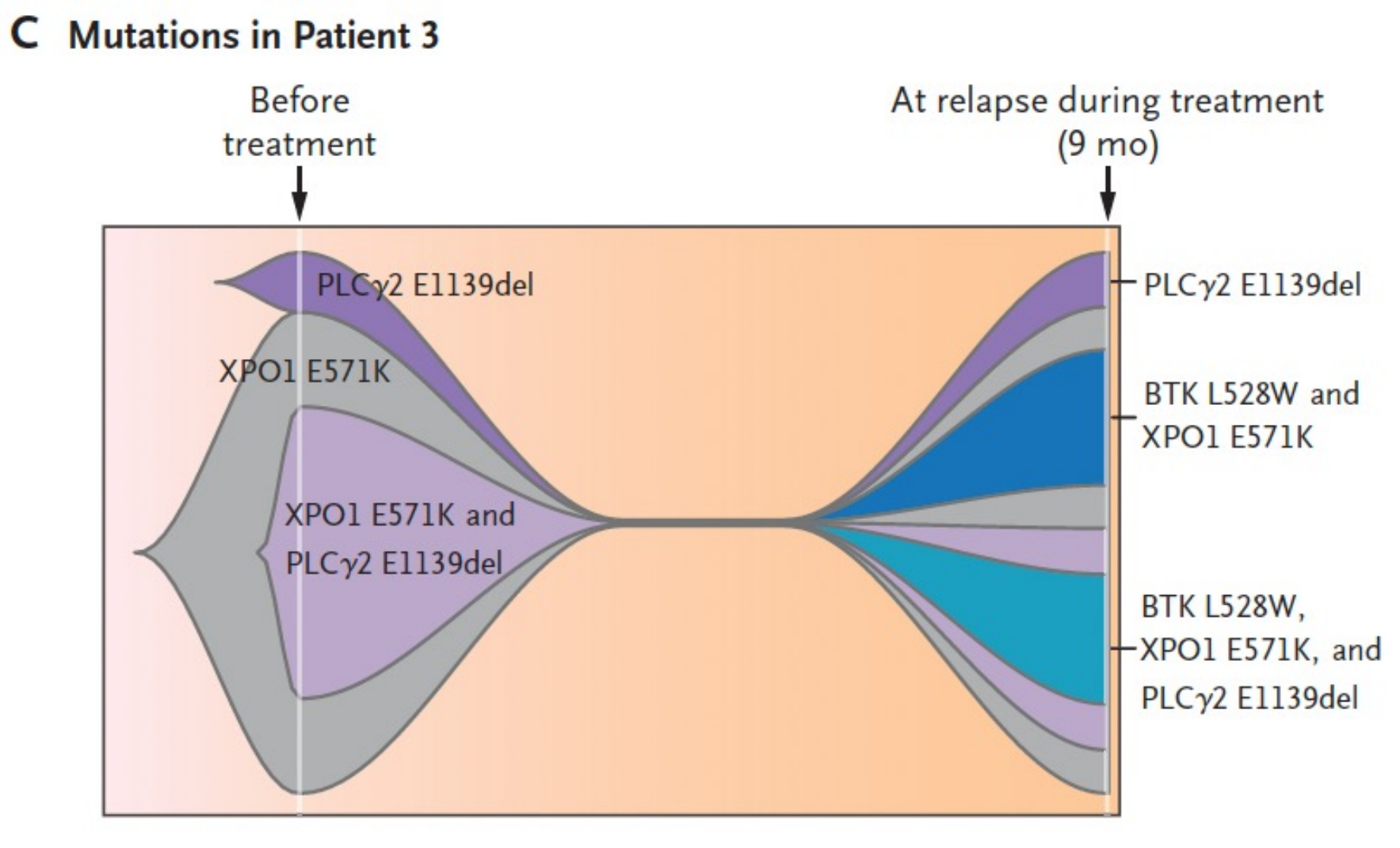

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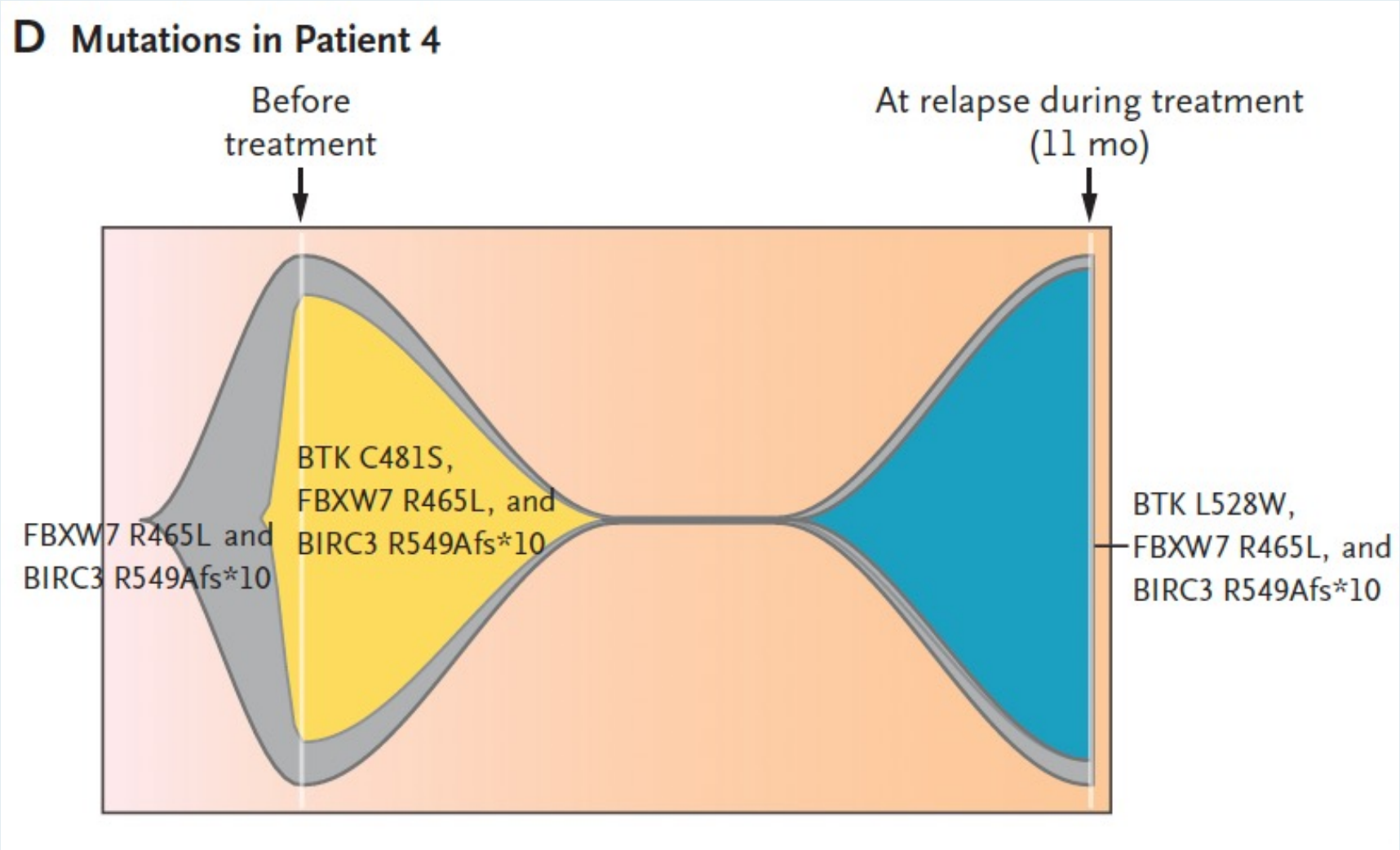

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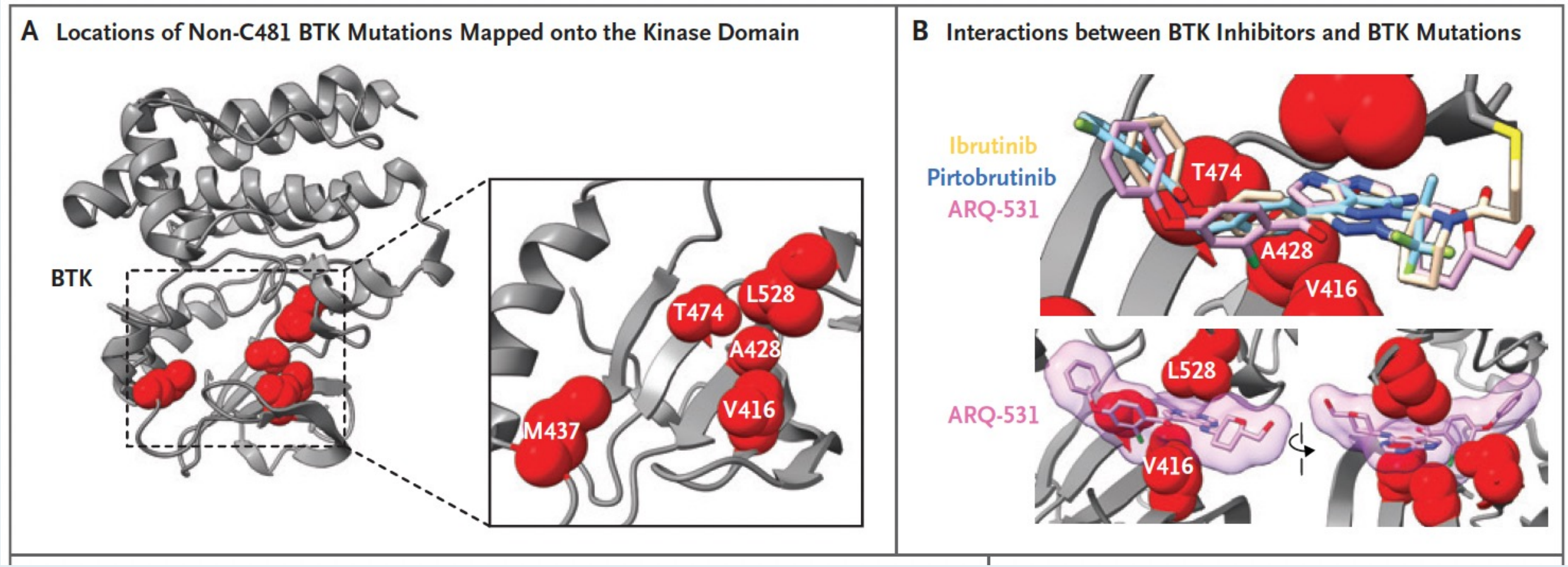
Resistance to BTK Inhibitors Conferred by BTK Mutations Outside the C481 Residue



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- Dr Bhatnagar: A 70-year-old man with CLL, thrombocytopenia and possible underlying plasma cell dyscrasia
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Case Presentation: A 68-year-old man with CLL on observation for 10 years who develops angioedema

Dr G Richard Polkinghorn (Augusta, Maine)

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Case Presentation: A 60-year-old woman with SLL and BTK-related arthralgia

Dr Rajni Sinha (Atlanta, Georgia)

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Case Presentation: A 60-year-old woman with SLL and BTK-related arthralgia (continued)

Dr Rajni Sinha (Atlanta, Georgia)

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Dr Khuda Dad Khan (Prospect, Kentucky)

Case Presentation: A 65-year-old man with CLL who receives obinutuzumab and venetoclax

Dr Raman Sood (Dunkirk, New York)

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Dr Gurveen Kaur (Wheeling, West Virginia)

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Dr Tina Bhatnagar (Wheeling, West Virginia)

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Dr Joanna Metzner-Sadurski (Greenwood, South Carolina)

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MODULE 2: Journal Club with Dr Brown

MODULE 3: Faculty Survey

MODULE 4: Appendix of Key Recent Data Sets

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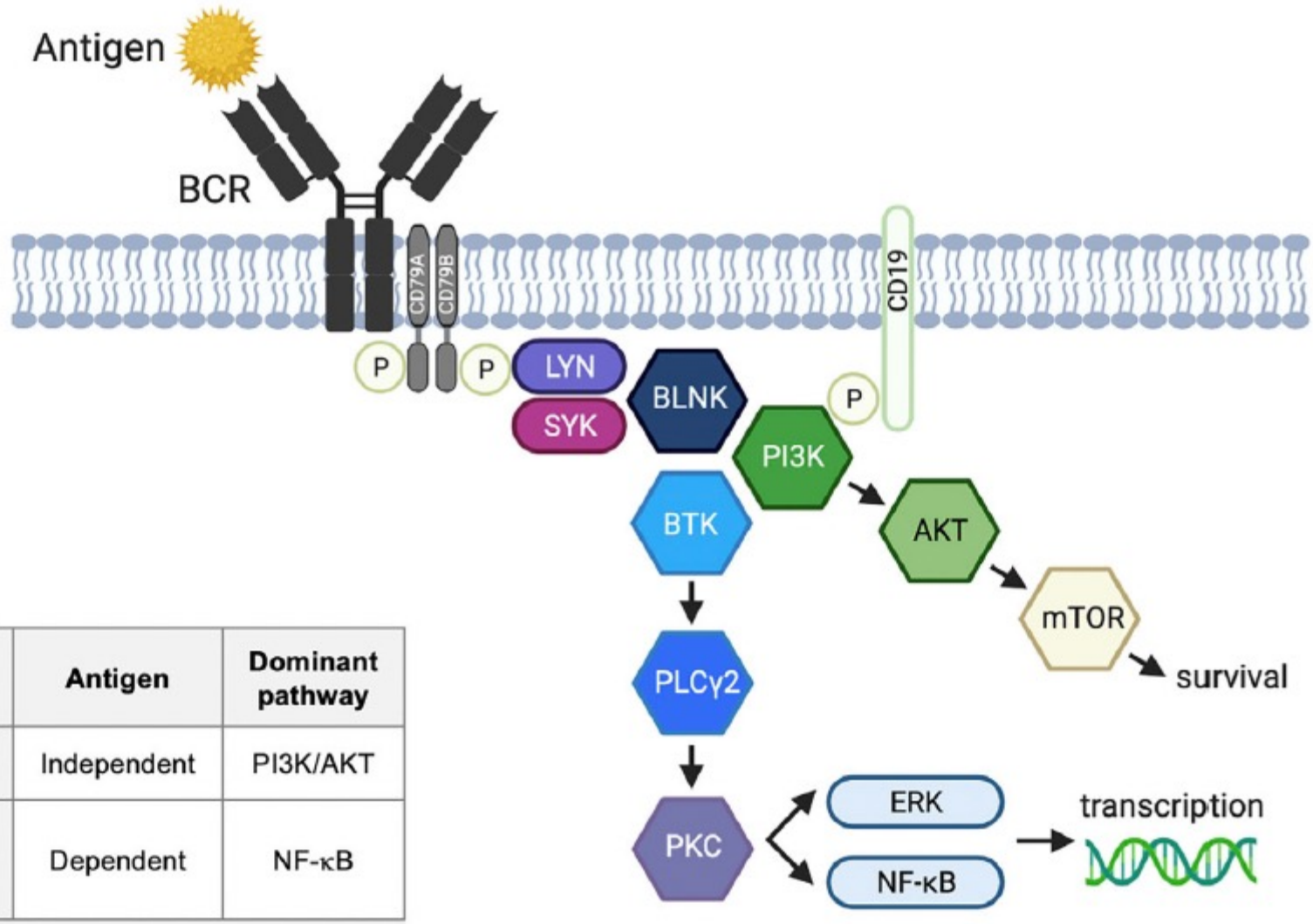
Front Immunol 2021;12:687458.

frontiers in Immunology

Targeting Bruton's Tyrosine Kinase in CLL

Inhye E. Ahn[1] *and Jennifer R. Brown*[2*]

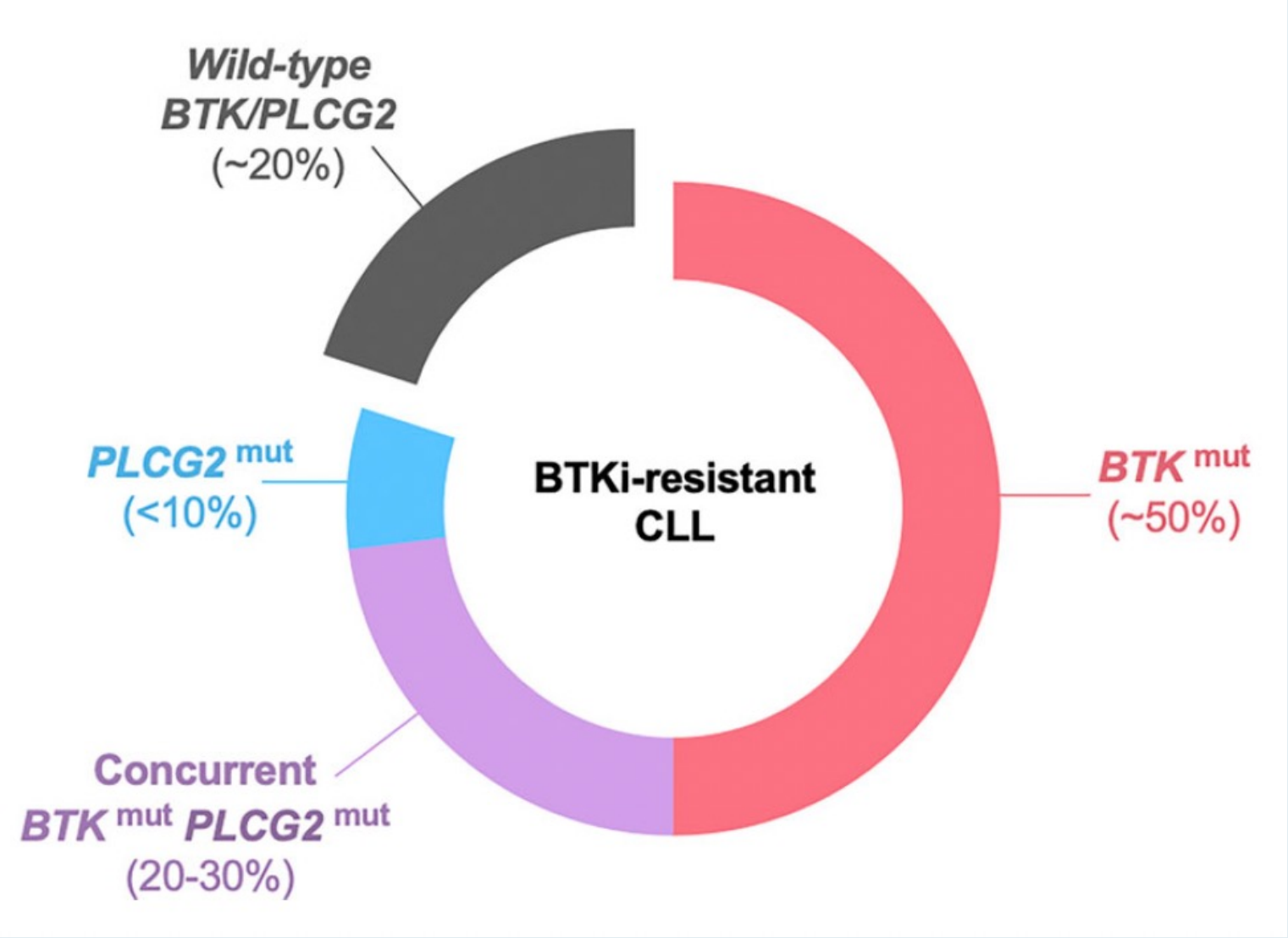
B-Cell Receptor Signaling Pathway



BCR signaling	Antigen	Dominant pathway
Tonic	Independent	PI3K/AKT
Chronic activated	Dependent	NF-κB

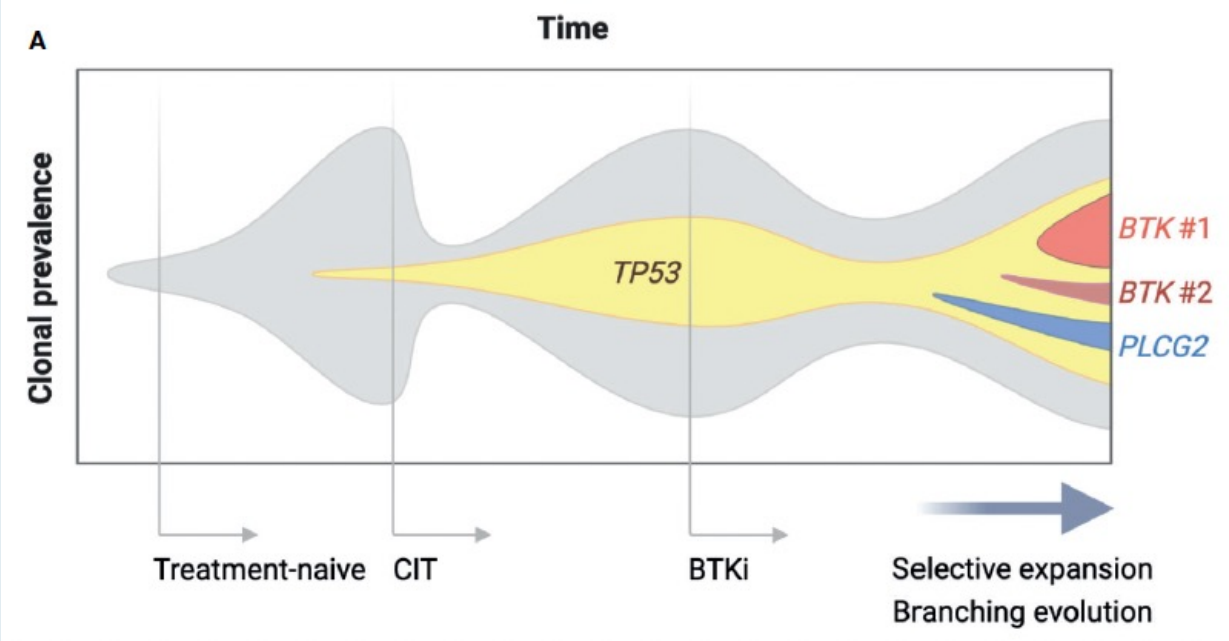
Ahn IE, Brown JR. *Front Immunol* 2021;12:687458.

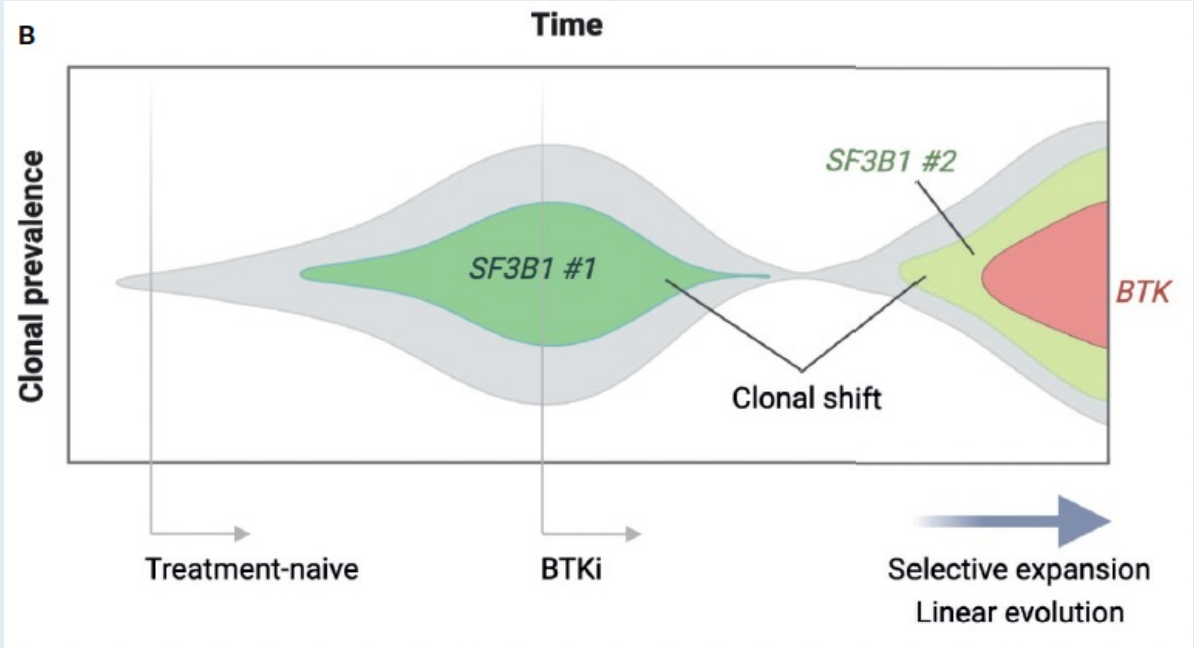
Bruton Tyrosine Kinase (BTK) and PLCG2 Mutations in BTK inhibitor (BTKi)-Resistant CLL



Ahn IE, Brown JR. *Front Immunol* 2021;12:687458.

Clonal Evolution of BTKi-Resistant CLL





Ahn IE, Brown JR. *Front Immunol* 2021;12:687458.

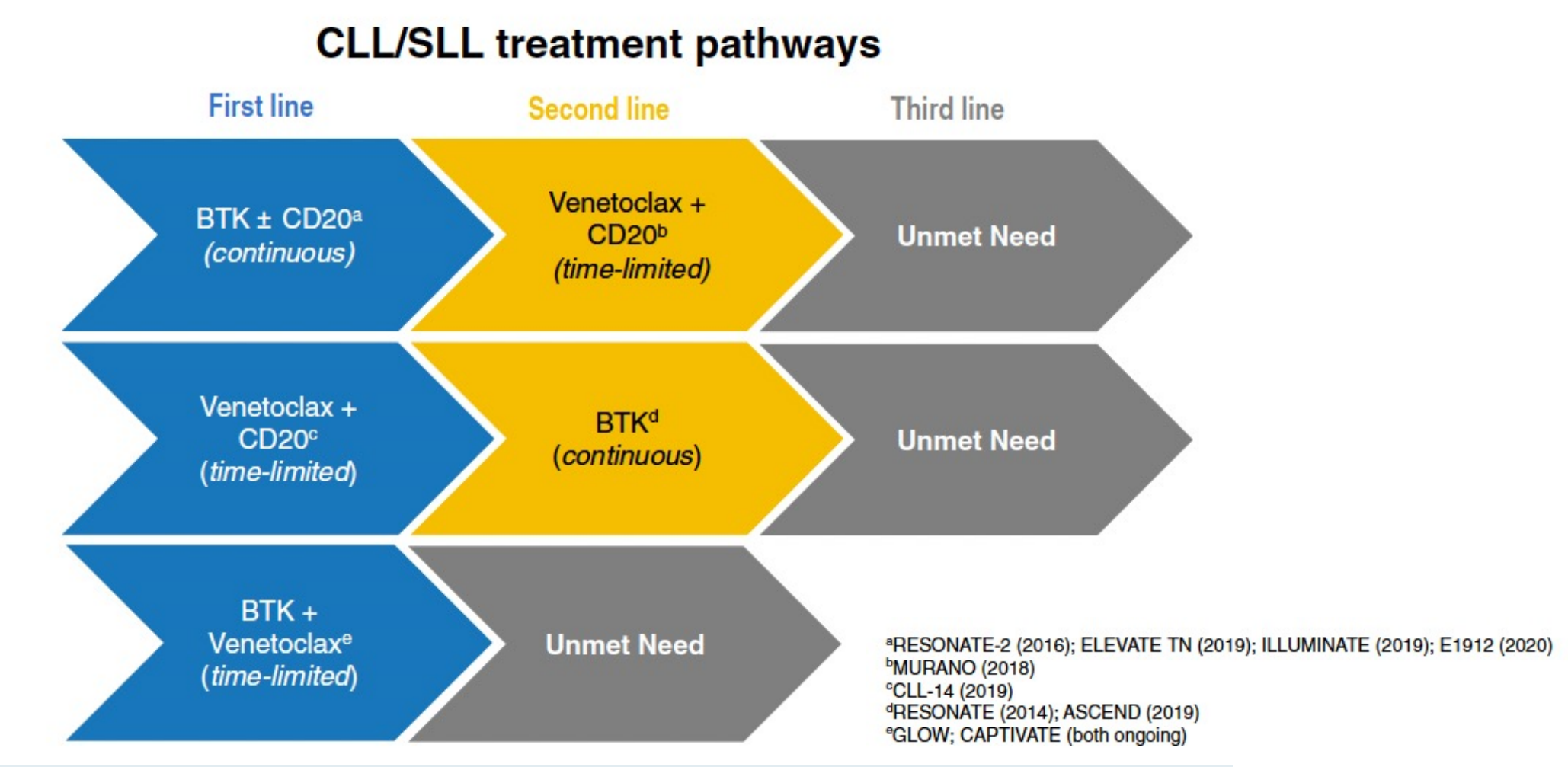
Clin Cancer Res 2022;28(4):603-8.

CLINICAL CANCER RESEARCH | PERSPECTIVES

Recognizing Unmet Need in the Era of Targeted Therapy for CLL/SLL: "What's Past Is Prologue" (Shakespeare)

Anthony R. Mato[1], Matthew S. Davids[2], Jeff Sharman[3], Lindsey E. Roeker[1], Neil Kay[4], Arnon P. Kater[5], Kerry Rogers[6], Meghan C. Thompson[1], Joanna Rhodes[7], Andre Goy[8], Alan Skarbnik[9], Stephen J. Schuster[7], Constantine S. Tam[10], Toby A. Eyre[11], Susan O'Brien[12], Chadi Nabhan[13], Nicole Lamanna[14], Clare Sun[15], Mazyar Shadman[16], John M. Pagel[17], Chaitra Ujjani[16], Danielle Brander[18], Catherine C. Coombs[19], Nitin Jain[8], Chan Y. Cheah[20], Jennifer R. Brown[2], John F. Seymour[10], and Jennifer A. Woyach[6]

Chemotherapy-Free Sequencing Algorithms for CLL/SLL: Unmet Needs in Modern Clinical Practice



Mato AR et al. *Clin Cancer Res* 2022;28(4):603-8.

Add to My Itinerary

Session PO.CT01.01 - Phase I Clinical Trials 1

CT138 / 5 - Pirtobrutinib, a highly selective, non-covalent (reversible) BTK inhibitor in combination with venetoclax ± rituximab in relapsed/refractory chronic lymphocytic leukemia: Results from the BRUIN phase 1b study

April 11, 2022, 1:30 PM - 5:00 PM | Section 35

Presenter/Authors

Lindsey E. Roeker, Anthony R. Mato, Jennifer R. Brown, Catherine C. Coombs, Nirav N. Shah, William G. Wierda, Manish R. Patel, Katharine L. Lewis, Minna Balbas, Junjie Zhao, Nora C. Ku, Jennifer F. Kherani, Donald E. Tsai, Binoj Nair, Chan Y. Cheah.

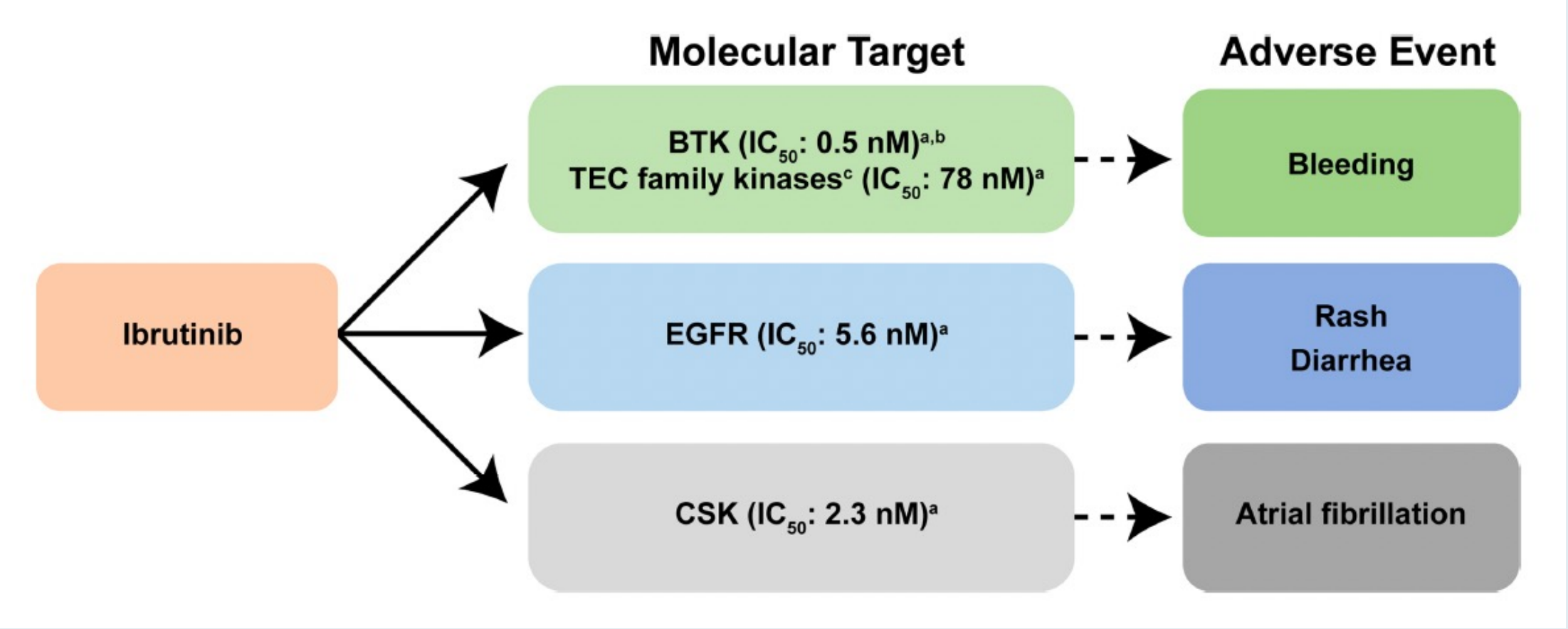
Front Oncol 2021;11:720704

frontiers in Oncology

Monitoring and Managing BTK Inhibitor Treatment-Related Adverse Events in Clinical Practice

Susan M. O'Brien[1], Jennifer R. Brown[2], John C. Byrd[3], Richard R. Furman[4], Paolo Ghia[5], Jeff P. Sharman[6] and William G. Wierda[7]*

Reported Molecular Targets of Ibrutinib and Their Associated Adverse Events



O'Brien SM et al. *Front Oncol* 2021;11:720704.

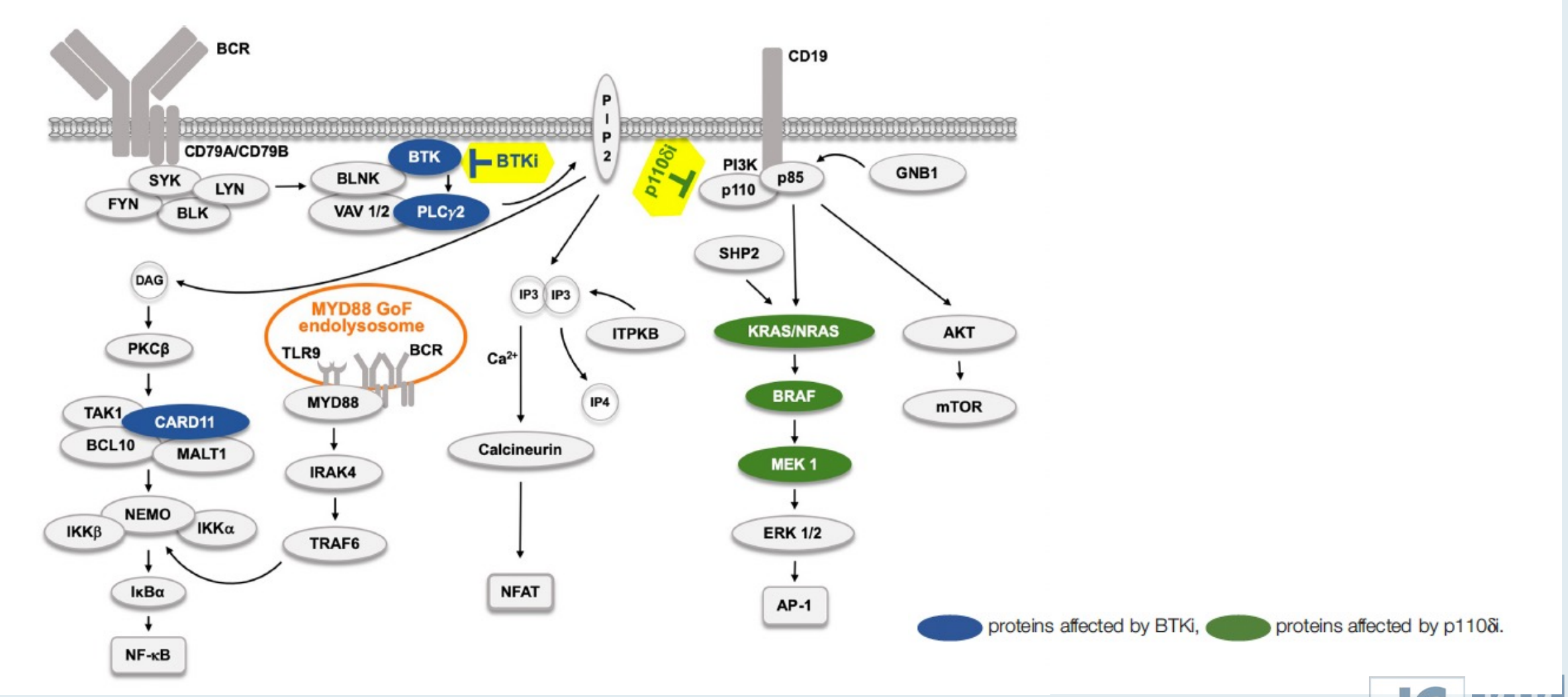
Front Immunol 2021;12:804735.

frontiers in Immunology

Editorial: New Insights on Bruton's Tyrosine Kinase Inhibitors

C. I. Edvard Smith [1], Jennifer R. Brown [2] and Rula Zain [1,3]*

The B-Cell Receptor (BCR) Signaling Pathway and the Effect of Kinase Inhibitors

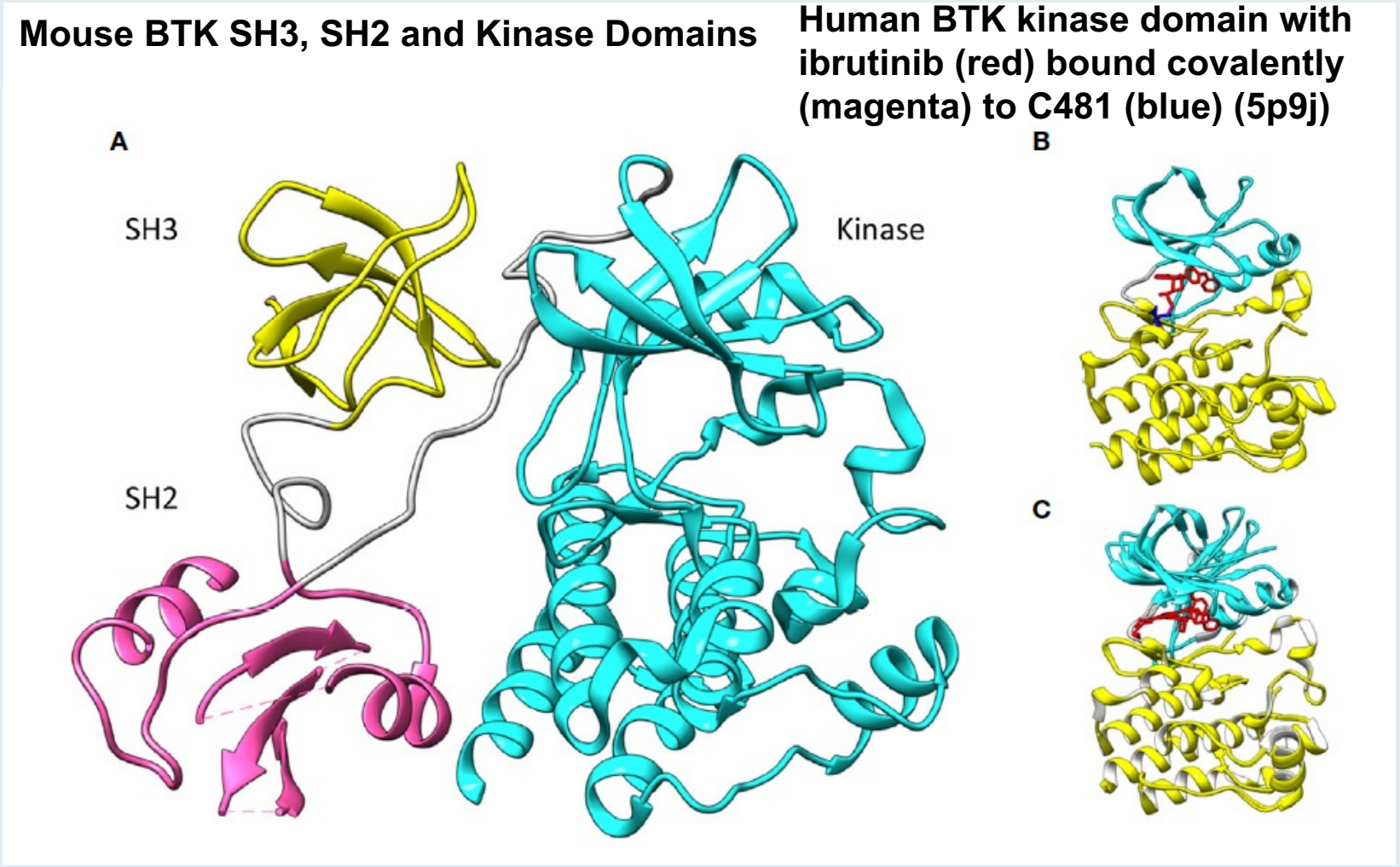


Smith CIE et al. *Front Immunol* 2021;12:804735.

Spatial Organization of the BTK Kinase Domains

Mouse BTK SH3, SH2 and Kinase Domains

Human BTK kinase domain with ibrutinib (red) bound covalently (magenta) to C481 (blue) (5p9j)



Zain R, Vihinen M. *Front Immunol* 2021;12:694853.

IRC Determines That Zanubrutinib Demonstrates Superior Overall Response Rate versus Ibrutinib in Final Response Analysis of ALPINE Trial for CLL

Press Release: April 11, 2022

"…Results from the Phase 3 ALPINE trial [were announced] showing BTK inhibitor zanubrutinib demonstrated superiority versus ibrutinib in overall response rate (ORR) as assessed by an Independent Review Committee (IRC) in adult patients with relapsed or refractory (R/R) chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL).

After achieving superiority in the primary endpoint of investigator-assessed overall response rate at the interim analysis, in this final response analysis, zanubrutinib met the primary endpoint of superiority over ibrutinib in ORR as determined by IRC, with a response rate of 80.4% versus 72.9% (2-sided p = 0.0264). ORR is defined as the combined rate of complete responses (CR) and partial responses (PR). A total of 652 patients were enrolled in the ALPINE trial across Europe (60%), the United States (17%), China (14%), New Zealand and Australia (9%) and were followed for a median of 24.2 months. The next planned analysis of ALPINE data will be the PFS final analysis."

https://www.businesswire.com/news/home/20220411005299/en/IRC-Determines-BRUKINSA%C2%AE-Zanubrutinib-Demonstrates-Superior-Overall-Response-Rate-Versus-Ibrutinib-in-Final-Response-Analysis-of-ALPINE-Trial-in-Chronic-Lymphocytic-Leukemia

American Society of Hematology
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SEQUOIA: RESULTS OF A PHASE 3 RANDOMIZED STUDY OF ZANUBRUTINIB VERSUS BENDAMUSTINE + RITUXIMAB IN PATIENTS WITH TREATMENT-NAIVE CHRONIC LYMPHOCYTIC LEUKEMIA/SMALL LYMPHOCYTIC LYMPHOMA

Constantine S. Tam, MBBS, MD[1,2,3,4]; Krzysztof Giannopoulos, MD, PhD[5,6]; Wojciech Jurczak, MD, PhD[7]; Martin Šimkovič, MD, PhD[8,9]; Mazyar Shadman, MD, MPH[10,11]; Anders Österborg, MD, PhD[12,13]; Luca Laurenti, MD[14]; Patricia Walker, MBBS, BMedSci, FRACP, FRCPA[15]; Stephen Opat, MBBS (Hons), FRACP, FRCPA[16,17]; Henry Chan, MBChB, FRACP, FRCPA[18]; Hanna Ciepluch, MD, PhD[19]; Richard Greil, MD[20,21,22]; Monica Tani, MD[23]; Marek Trněný, MD[24]; Danielle M. Brander, MD[25]; Ian W. Flinn, MD, PhD[26]; Sebastian Grosicki, MD, PhD[27]; Emma Verner, MBBS, BMedSci, FRCPA, FRACP[28,29]; Jennifer R. Brown MD, PhD[30]; Brad S. Kahl, MD[31]; Paolo Ghia, MD, PhD[32]; Jianyong Li, MD, PhD[33]; Tian Tian, PhD[34]; Lei Zhou, MD[34]; Carol Marimpietri[34]; Jason C. Paik, MD, PhD[34]; Aileen Cohen, MD, PhD[34]; Jane Huang, MD[34]; Tadeusz Robak, MD, PhD[35]; and Peter Hillmen, MBChB, PhD[36]

[1]Peter MacCallum Cancer Centre, Melbourne, Victoria, Australia; [2]University of Melbourne, Parkville, Victoria, Australia; [3]St Vincent's Hospital Melbourne, Fitzroy, Victoria, Australia; [4]Royal Melbourne Hospital, Parkville, Victoria, Australia; [5]Experimental Hematooncology Department, Medical University of Lublin, Lublin, Poland; [6]Hematology Department, St. John's Cancer Centre, Lublin, Poland; [7]Maria Sklodowska-Curie National Research Institute of Oncology, Krakow, Poland; [8]Fourth Department of Internal Medicine - Haematology, University Hospital, Hradec Kralove, Czech Republic; [9]Faculty of Medicine, Charles University, Prague, Czech Republic; [10]Fred Hutchinson Cancer Research Center, Seattle, WA, USA; [11]Department of Medicine, University of Washington, Seattle, WA, USA; [12]Department of Oncology-Pathology, Karolinska Institutet, Stockholm, Sweden; [13]Department of Hematology, Karolinska University Hospital, Stockholm, Sweden; [14]Fondazione Policlinico Universitario A Gemelli UCSC, Rome, Italy; [15]Peninsula Private Hospital, Frankston, Victoria, Australia; [16]Monash Health, Clayton, Victoria, Australia; [17]Monash University, Clayton, Victoria, Australia; [18]North Shore Hospital, Auckland, New Zealand; [19]Copernicus Regional Oncology Center, Gdansk, Poland; [20]Third Medical Department with Hematology, Medical Oncology, Rheumatology and Infectiology, Paracelsus Medical University, Salzburg, Austria; [21]Salzburg Cancer Research Institute (SCRI) Center for Clinical Cancer and Immunology Trials (CCCIT), Salzburg, Austria; [22]Cancer Cluster Salzburg (CCS), Salzburg, Austria; [23]Hematology Unit, Santa Maria delle Croci Hospital, Ravenna, Italy; [24]First Department of Medicine, First Faculty of Medicine, Charles University, General Hospital, Prague, Czech Republic; [25]Hematologic Malignancies and Cellular Therapy, Duke University School of Medicine, Durham, NC, USA; [26]Sarah Cannon Research Institute/Tennessee Oncology, Nashville, TN, USA; [27]Department of Hematology and Cancer Prevention, Health Sciences Faculty, Medical University of Silesia, Katowice, Poland; [28]Concord Repatriation General Hospital, Concord, New South Wales, Australia; [29]University of Sydney, Sydney, New South Wales, Australia; [30]Dana-Farber Cancer Institute, Boston, MA, USA; [31]Washington University School of Medicine, St Louis, MO, USA; [32]Università Vita-Salute San Raffaele and IRCCS Ospedale San Raffaele, Milano, Italy; [33]Department of Hematology, The First Affiliated Hospital of Nanjing Medical University, Jiansu Province Hospital, Nanjing, China; [34]BeiGene (Beijing) Co., Ltd., Beijing, China and BeiGene USA, Inc., San Mateo, CA, USA; [35]Medical University of Lodz, Lodz, Poland; and [36]St James's University Hospital, Leeds, United Kingdom

Sunday, December 12, 2021
642. Chronic Lymphocytic Leukemia: Clinical and Epidemiological I

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ZANUBRUTINIB IN COMBINATION WITH VENETOCLAX FOR PATIENTS WITH TREATMENT-NAIVE CHRONIC LYMPHOCYTIC LEUKEMIA OR SMALL LYMPHOCYTIC LYMPHOMA WITH DEL(17P): EARLY RESULTS FROM ARM D OF THE SEQUOIA (BGB-3111-304) TRIAL

Alessandra Tedeschi, MD[1]; Emmanuelle Ferrant, MD[2]; Ian Flinn MD, PhD[3]; Constantine S. Tam MBBS, MD[4,5,6,7]; Paolo Ghia, MD, PhD[8]; Tadeusz Robak, MD, PhD[9]; Jennifer R. Brown, MD, PhD[10]; Vanitha Ramakrishnan, PhD[11]; Tian Tian, PhD[11]; Sowmya B. Kuwahara, PharmD[11]; Fangfang Yin, PhD[11]; Jason C. Paik, MD, PhD[11]; Aileen Cohen, MD, PhD[11]; Jane Huang, MD[11]; and Peter Hillmen, MBChB, PhD[12]

[1]ASST Grande Ospedale Metropolitano Niguarda, Milan, Italy; [2]Centre Hospitalier Lyon-Sud, University Claude Bernard Lyon 1, Pierre-Bénite, France; [3]Sarah Cannon Research Institute/Tennessee Oncology, Nashville, TN, USA; [4]Peter MacCallum Cancer Centre, Melbourne, Victoria, Australia; [5]University of Melbourne, Parkville, Victoria, Australia; [6]St Vincent's Hospital, Fitzroy, Victoria, Australia; [7]Royal Melbourne Hospital, Parkville, Victoria, Australia; [8]Università Vita-Salute San Raffaele and IRCCS Ospedale San Raffaele, Milano, Italy; [9]Medical University of Lodz, Lodz, Poland; [10]Dana-Farber Cancer Institute, Boston, MA, USA; [11]BeiGene (Beijing) Co., Ltd., Beijing, China and BeiGene USA, Inc., San Mateo, CA, USA; [12]Saint James's University Hospital, Leeds, UK

Saturday, December 11, 2021
642. Chronic Lymphocytic Leukemia: Clinical and Epidemiological: Combination Small Molecules

AACR American Association for Cancer Research ANNUAL MEETING 2022 New Orleans

JOIN US APRIL 8-13!

Add to My Itinerary

Session PO.ET04.03 - Molecular Classification of Tumors

4007 / 1 - Evolutionary history of transformation from chronic lymphocytic leukemia to Richter's syndrome

April 13, 2022, 9:00 AM - 12:30 PM | Section 25

Presenter/Authors

Erin M. Parry, Ignaty Leshchiner, Romain Guièze, Connor Johnson, Eugen Tausch, Sameer Parikh, Camilla Lemvigh, Conor Messer, Daniel Rosebrock, Filippo Utro, Chaya Levovitz, Kahn Rhrissorrakrai, Matthew S. Davids, Raquel A. Jacobs, Kara Slowik, Julien Broseus, Shanye Yin, Shuqiang Li, Geoff Fell, Ziao Lin, Binyamin A. Knisbacher, Neil Ruthen, Dimitri Livitz, Christof Schneider, Jialin Ma, Julian Hess, Laura Z. Rassenti, Thomas J. Kipps, Nitin Jain, William Wierda, Florence Cymbalista, Neil E. Kay, Kenneth J. Livak, Brian P. Danysh, Chip Stewart, Donna Neuberg, Jennifer R. Brown, Laxmi Parida, Stephan Stilgenbauer, Gad Getz, Catherine J. Wu.

Leukemia (2021) 35:3059–3072
https://doi.org/10.1038/s41375-021-01241-1

REVIEW ARTICLE

Chronic lymphocytic leukemia

Measurable residual disease in chronic lymphocytic leukemia: expert review and consensus recommendations

William G. Wierda[1] · Andrew Rawstron[2] · Florence Cymbalista[3] · Xavier Badoux[4] · Davide Rossi[5] · Jennifer R. Brown[6] · Alexander Egle[7] · Virginia Abello[8] · Eduardo Cervera Ceballos[9] · Yair Herishanu[10] · Stephen P. Mulligan[11] · Carsten U. Niemann[12] · Colin P. Diong[13] · Teoman Soysal[14] · Ritsuro Suzuki[15] · Hoa T. T. Tran[16] · Shang-Ju Wu[17] · Carolyn Owen[18] · Stephan Stilgenbauer[19] · Paolo Ghia[20] · Peter Hillmen[21]

Allan JN et al. *Haematologica* 2022;107(4):984-7.

Letters to the Editor

Phase Ib dose-escalation study of the selective, non-covalent, reversible Bruton's tyrosine kinase inhibitor vecabrutinib in B-cell malignancies

Blood 2022;139(5):686-9.

blood®

Brief Report

CLINICAL TRIALS AND OBSERVATIONS

Venetoclax plus dose-adjusted R-EPOCH for Richter syndrome

Matthew S. Davids,[1,*] Kerry A. Rogers,[2,*] Svitlana Tyekucheva,[3] Zixu Wang,[3] Samantha Pazienza,[1] Sarah K. Renner,[4] Josie Montegaard,[1] Udochukwu Ihuoma,[1] Timothy Z. Lehmberg,[1] Erin M. Parry,[1] Catherine J. Wu,[1,5] Caron A. Jacobson,[1] David C. Fisher,[1] Philip A. Thompson,[4,†] and Jennifer R. Brown[1,†]

Leukemia 2022;36(3):723-32.

ARTICLE

CHRONIC LYMPHOCYTIC LEUKEMIA

A T cell inflammatory phenotype is associated with autoimmune toxicity of the PI3K inhibitor duvelisib in chronic lymphocytic leukemia

Deepti Gadi[1,2,6], Alec Griffith[3,6], Svitlana Tyekucheva[4], Zixu Wang[4], Vanessa Rai[1,2], Alexander Vartanov[1], Emily Thrash[1,2], Stacey M. Fernandes[1,2], Timothy Z. Lehmberg[1], Brandon Lee[1], Stephen P. Martindale[1,2], John-Hanson Machado[1,2], Oreofe Odejide[1,2], Philippe Armand[1,2], David C. Fisher[1,2], Jon Arnason[5], Matthew S. Davids[1,2], James A. Lederer[3] and Jennifer R. Brown[1,2]✉

Meet The Professor with Dr Brown

MODULE 1: Case Presentations

- Dr Polkinghorn: A 68-year-old man with CLL on observation for 10 years who develops angioedema
- Dr Sinha: A 60-year-old woman with SLL and BTK-related arthralgia
- Dr Khan: A 69-year-old man with CLL and hypertension, CAD, GERD and atrial fibrillation
- Dr Sood: A 65-year-old man with CLL who receives obinutuzumab and venetoclax
- Dr Kaur: A 70-year-old man with IGHV-mutated CLL
- Dr Bhatnagar: A 70-year-old man with CLL, thrombocytopenia and possible underlying plasma cell dyscrasia
- Dr Metzner-Sadurski: A 64-year-old woman with IGHV-unmutated CLL and hemolytic anemia

MODULE 2: Journal Club with Dr Brown

MODULE 3: Faculty Survey

MODULE 4: Appendix of Key Recent Data Sets

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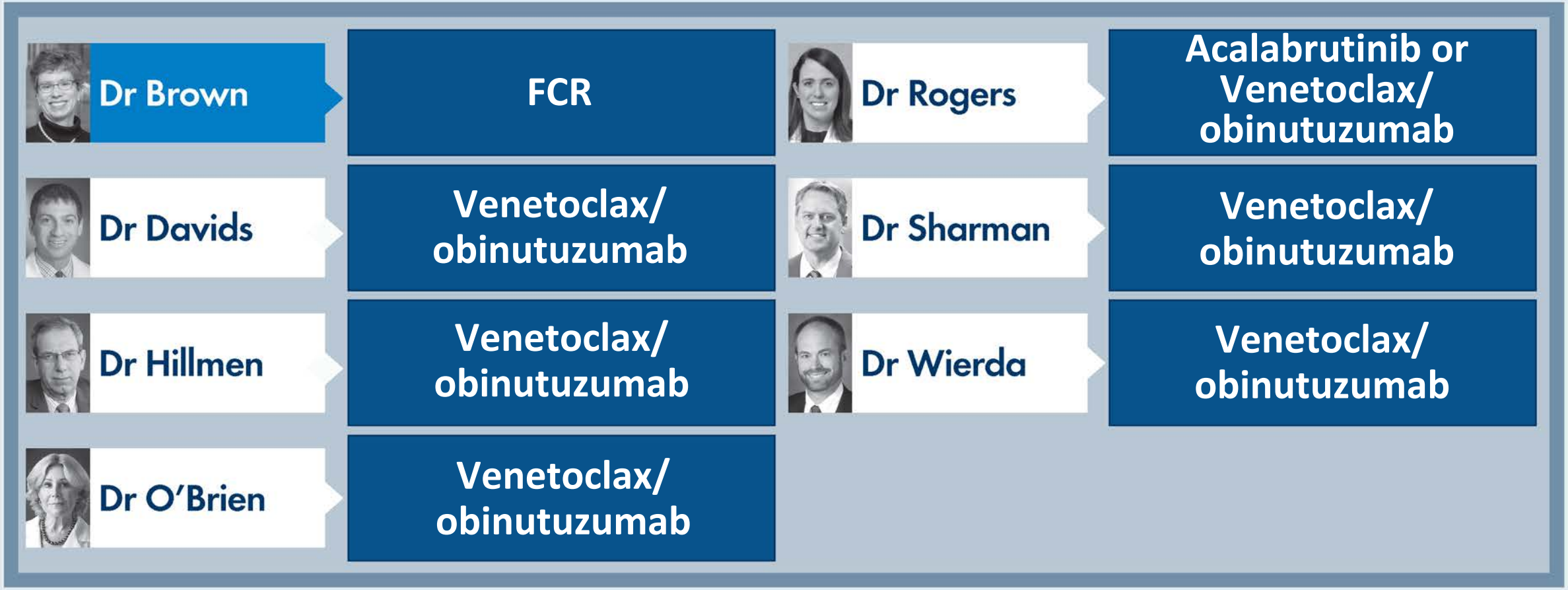
What is your usual preferred initial regimen for a 60-year-old patient with CLL with IGHV mutation but no del(17p) or TP53 mutation who requires treatment?

1. FCR
2. BR (bendamustine/rituximab)
3. Ibrutinib
4. Ibrutinib + anti-CD20 antibody
5. Acalabrutinib
6. Acalabrutinib + obinutuzumab
7. Venetoclax + obinutuzumab
8. Other

What is your usual preferred initial regimen for a 60-year-old patient with CLL with IGHV mutation but no del(17p) or TP53 mutation who requires treatment?



FCR = fludarabine/cyclophosphamide/rituximab

RTP RESEARCH TO PRACTICE

Regulatory and reimbursement issues aside, what is your usual preferred initial regimen for a 60-year-old patient with CLL, unmutated IGHV and no del(17p) or TP53 mutation who requires treatment?

1. Ibrutinib
2. Ibrutinib + anti-CD20 antibody
3. Acalabrutinib
4. Acalabrutinib + obinutuzumab
5. Zanubrutinib
6. Venetoclax + obinutuzumab
7. Venetoclax + ibrutinib
8. Other

Regulatory and reimbursement issues aside, what would be your preferred initial regimen for a 60-year-old patient with CLL, unmutated IGHV and no del(17p) or TP53 mutation who required treatment?

 Dr Brown	Venetoclax + obinutuzumab	 Dr Rogers	Acalabrutinib or Venetoclax/ obinutuzumab
 Dr Davids	Venetoclax + obinutuzumab	 Dr Sharman	Venetoclax/ obinutuzumab
 Dr Hillmen	Venetoclax/ibrutinib	 Dr Wierda	Venetoclax/ibrutinib
 Dr O'Brien	Venetoclax/ibrutinib		

RTP RESEARCH TO PRACTICE

What is your usual preferred initial regimen for a 60-year-old patient with CLL, IGHV mutation and del(17p) or TP53 mutation who requires treatment?

1. FCR
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4. Ibrutinib + anti-CD20 antibody
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7. Venetoclax + obinutuzumab
8. Other

What is your usual preferred initial regimen for a 60-year-old patient with CLL, IGHV mutation and del(17p) or TP53 mutation who requires treatment?

 Dr Brown	Acalabrutinib + obinutuzumab
 Dr Davids	Acalabrutinib
 Dr Hillmen	Acalabrutinib
 Dr O'Brien	Acalabrutinib
 Dr Rogers	Acalabrutinib
 Dr Sharman	Acalabrutinib
 Dr Wierda	Acalabrutinib

RTP RESEARCH TO PRACTICE

What would be your most likely approach for a patient with newly diagnosed CLL to whom you decide to administer up-front venetoclax/obinutuzumab who has detectable MRD after completing 1 year of treatment?

1. Continue treatment
2. Discontinue treatment

What would be your most likely approach for a patient with newly diagnosed CLL to whom you decide to administer up-front venetoclax/obinutuzumab who has detectable MRD after completing 1 year of treatment?

 Dr Brown	Discontinue treatment
 Dr Davids	Discontinue treatment
 Dr Hillmen	Discontinue treatment
 Dr O'Brien	Continue treatment
 Dr Rogers	Discontinue treatment
 Dr Sharman	Discontinue treatment
 Dr Wierda	Continue treatment

RTP RESEARCH TO PRACTICE

Meet The Professor with Dr Brown

MODULE 1: Case Presentations

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MODULE 2: Journal Club with Dr Brown

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Minimal Residual Disease

RTP
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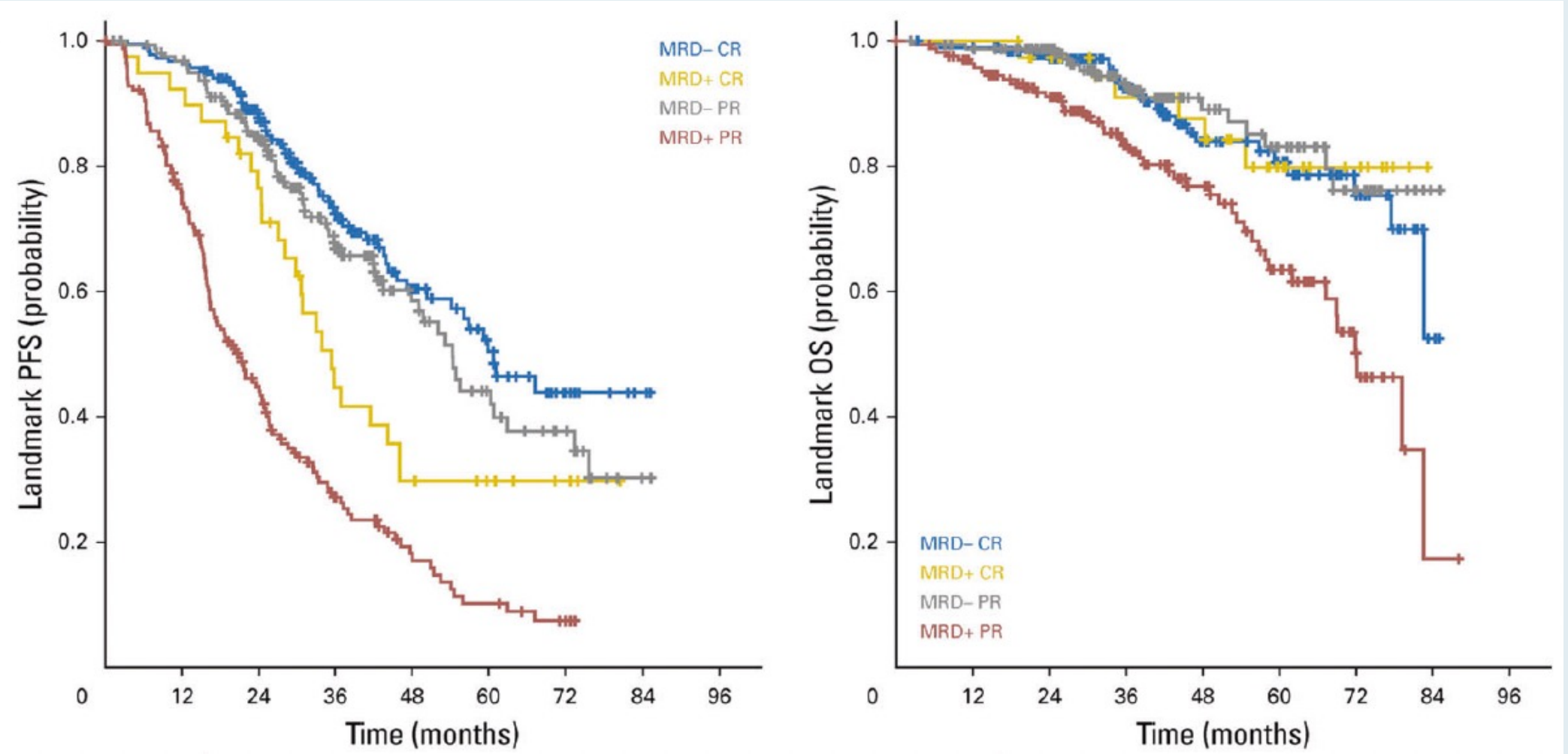
TO PRACTICE

Currently Applied Methods for MRD Assessment

Method	Sensitivity	Features	Advantages	Disadvantages
Flow cytometry				
4-color flow	10^{-4}	Detection of surface markers by established antibody panels	ERIC consensus guidelines available, widely accessible, relatively affordable, quantitative results relatively quick	Fresh (<48 h) PB or BM samples necessary, sufficient number of cells required to achieve sensitivity
≥6-color flow	10^{-5}			
8-color flow	10^{-6}			
10-color flow	10^{-5}			
Polymerase chain reaction (PCR)				
ASO PCR	10^{-5}	Quantification based on allele- and pt-specific primers for hypervariable CDR3 of IgH	Good sensitivity, use of DNA (instead of fresh material), quantitative results	Pt-specific primers required, baseline reference sample necessary, relatively time and labor intensive
Next-generation sequencing				
ClonoSEQ®	10^{-6}	Measurement of CLL-specific IgH sequences based on consensus primers	High sensitivity, use of DNA, tracking of clones possible, quantitative results	Relatively expensive, baseline reference sample necessary, not widely used yet

Al-Sawaf O et al. *Hematol Oncol Clin N Am* 2021;35(4):775-91. Wierda WG et al. *Leukemia* 2021;35:3059-72.

Landmark Analysis in the CLL8 and CLL10 Trials of Chemoimmunotherapy for CLL: Survival According to MRD Status



Wierda WG et al. *Leukemia* 2021;35:3059-72.

RTP RESEARCH TO PRACTICE

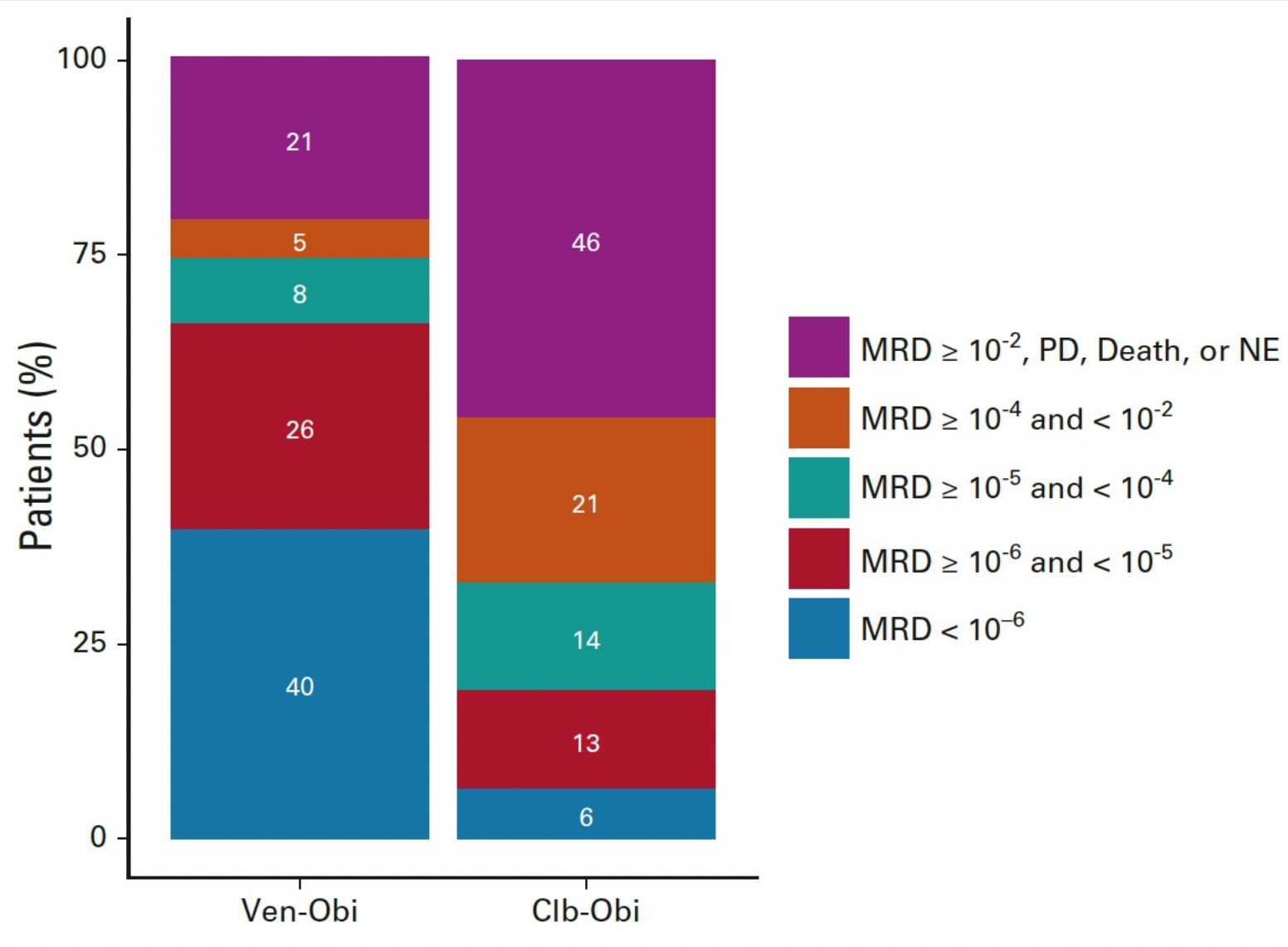
original reports

Minimal Residual Disease Dynamics after Venetoclax-Obinutuzumab Treatment: Extended Off-Treatment Follow-up From the Randomized CLL14 Study

Othman Al-Sawaf, MD[1,2,3]; Can Zhang, PhD[1]; Tong Lu, PhD[4]; Michael Z. Liao, PhD[4]; Anesh Panchal, MSc[5]; Sandra Robrecht, PhD[1]; Travers Ching, PhD[6]; Maneesh Tandon, MBChB[5]; Anna-Maria Fink, MD[1]; Eugen Tausch, MD[7]; Christof Schneider, MD[7]; Matthias Ritgen, MD[8]; Sebastian Böttcher, MD[9]; Karl-Anton Kreuzer, MD[1]; Brenda Chyla, PhD[10]; Dale Miles, PhD[4]; Clemens-Martin Wendtner, MD[11]; Barbara Eichhorst, MD[1]; Stephan Stilgenbauer, MD[7,12]; Yanwen Jiang, PhD[4]; Michael Hallek, MD[1]; and Kirsten Fischer, MD[1]

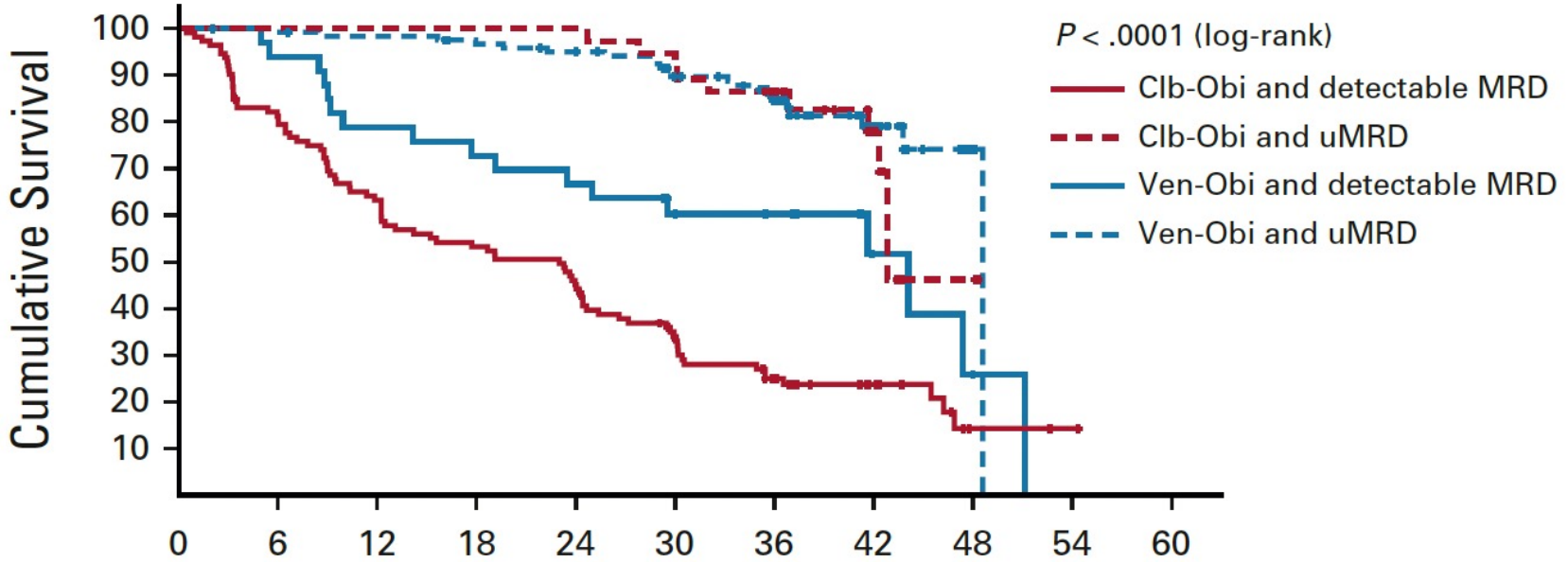
J Clin Oncol 2021;39(36):4049-60.

CLL14 Update: Minimum Residual Disease (MRD) Status by Next-Generation Sequencing 2 Months After Completion of Treatment



Al-Sawaf O et al. *J Clin Oncol* 2021;39(36):4049-60.

CLL14: PFS According to Bone Marrow MRD Status, from Last Treatment Exposure



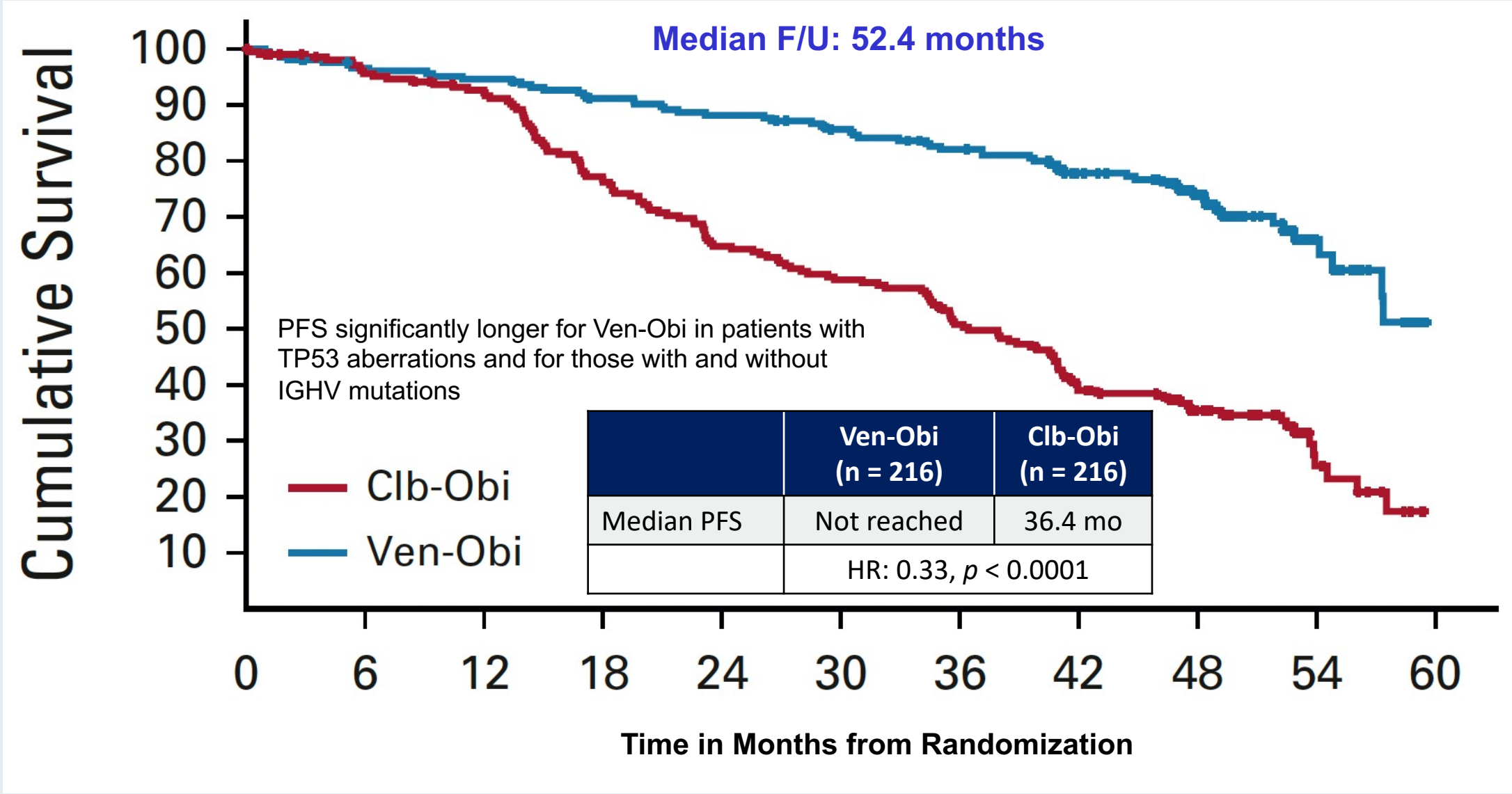
No. at risk:

Ven-Obi & uMRD	123	121	119	115	111	96	66	25	3	0	0
Ven-Obi & detectable MRD	33	31	26	24	22	18	12	4	2	0	0
Clb-Obi & uMRD	37	37	37	37	37	34	27	12	2	0	0
Clb-Obi & detectable MRD	112	90	70	59	50	34	22	12	2	1	0

Al-Sawaf O et al. *J Clin Oncol* 2021;39(36):4049-60.

Current Approach to First-Line Treatment

CLL14 Update: Progression-Free Survival



	Ven-Obi (n = 216)	Clb-Obi (n = 216)
Median PFS	Not reached	36.4 mo
	HR: 0.33, $p < 0.0001$	

Al-Sawaf O et al. *J Clin Oncol* 2021;39(36):4049-60.

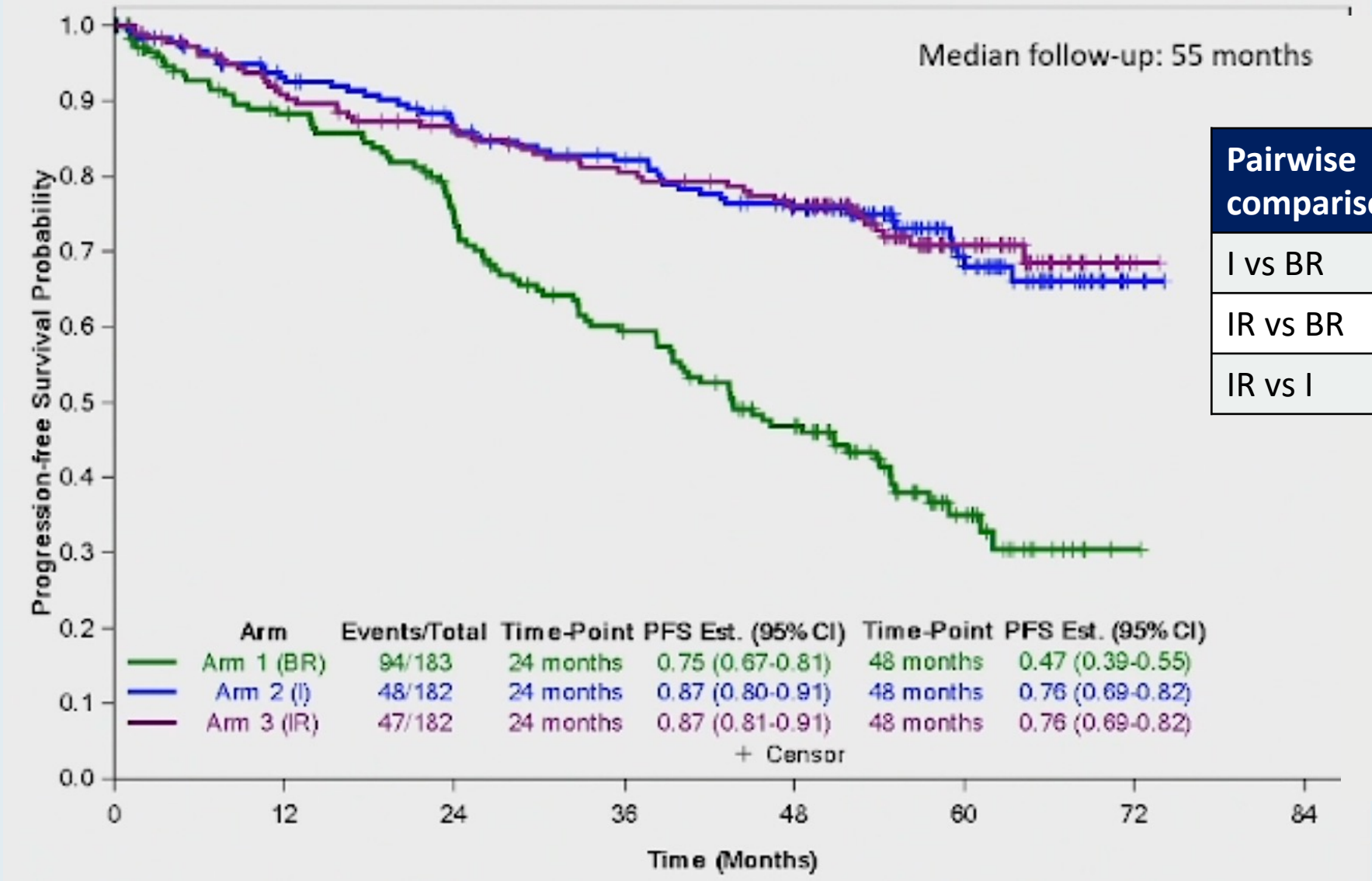
RTP RESEARCH TO PRACTICE

Long term results of A041202 show continued advantage of ibrutinib-based regimens compared with bendamustine plus rituximab chemoimmunotherapy

Jennifer A. Woyach, Amy S. Ruppert, Nyla Heerema, Weiqiang Zhao, Allison M Booth, Wei Ding, Nancy L. Bartlett, Danielle M Brander, Paul M Barr, Kerry A Rogers, Sameer Parikh, Steven Coutre, Arti Hurria, Gerard Lozanski, Sreenivasa Nattam, Richard A. Larson, Harry Erba, Mark Litzow, Carolyn Owen, James Atkins, Jeremy Abramson, Rich Little, Scott E. Smith, Richard M. Stone, Sumithra Mandrekar, John C. Byrd

ASH 2021;Abstract 639

Alliance A041202: Progression-Free Survival



Pairwise comparisons	Hazard ratio	*p*-value
I vs BR	0.36	<0.0001
IR vs BR	0.36	<0.001
IR vs I	0.99	0.96

Woyach JA et al. ASH 2021;Abstract 639.

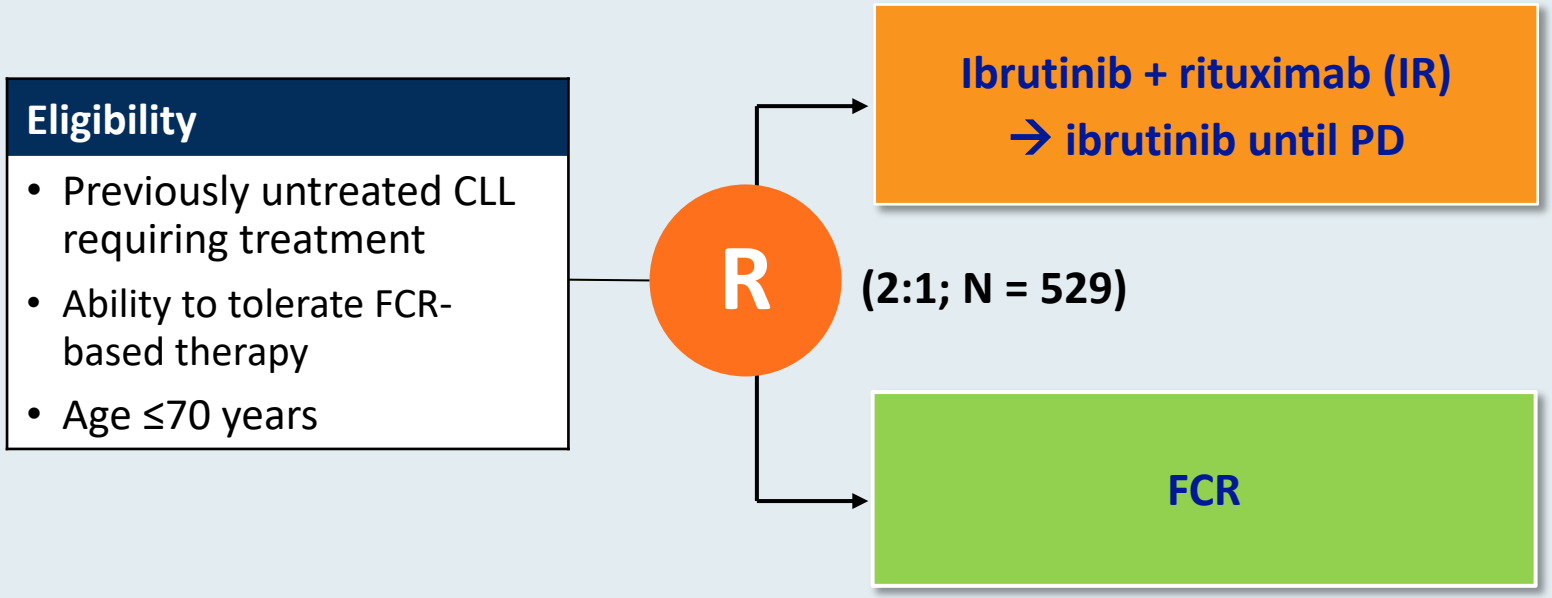
RTP RESEARCH TO PRACTICE

Ibrutinib and Rituximab Provides Superior Clinical Outcome Compared to FCR in Younger Patients with Chronic Lymphocytic Leukemia (CLL): Extended Follow-Up from the E1912 Trial

Shanafelt TD et al.

ASH 2019;Abstract 33.

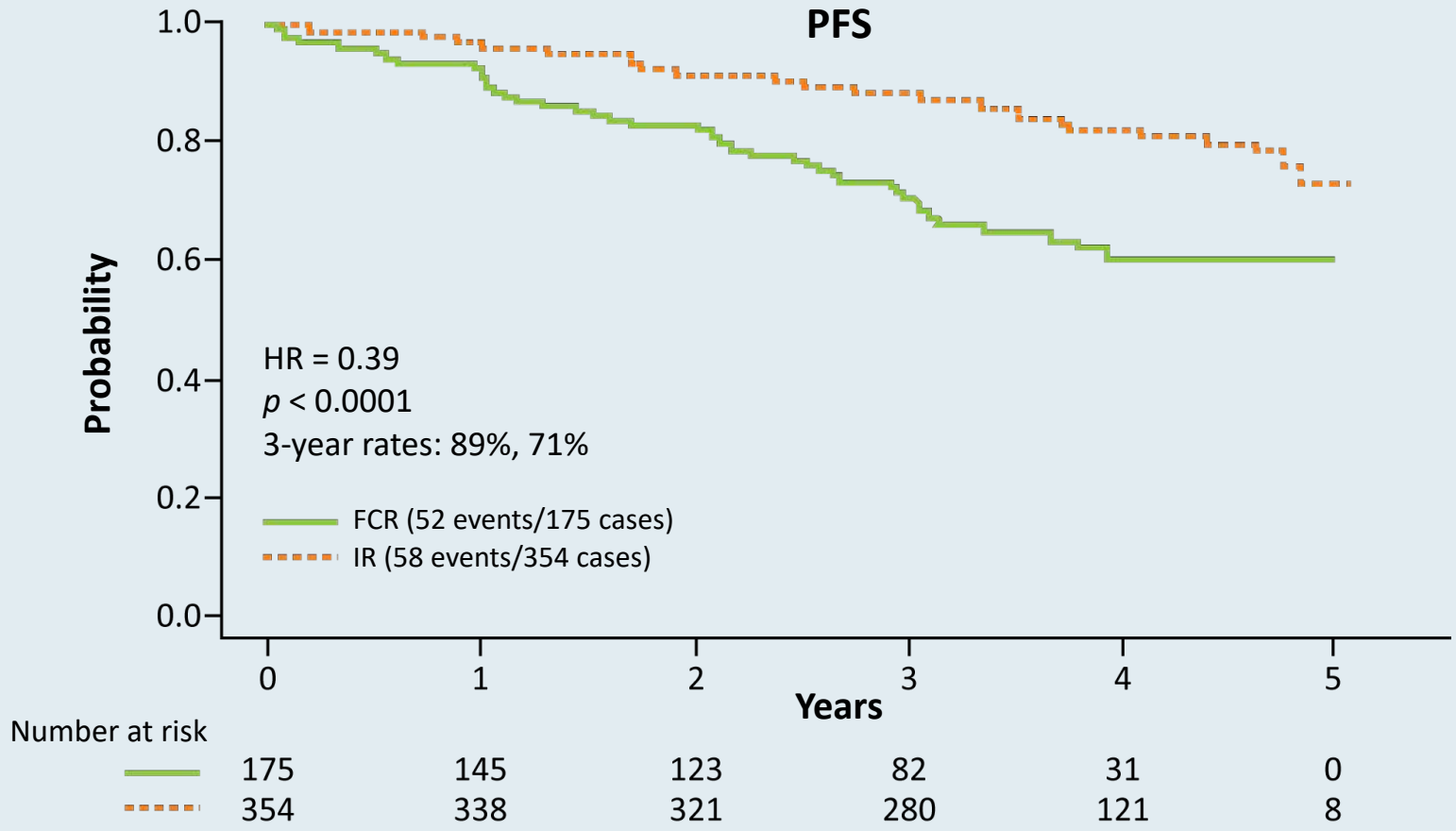
Phase III ECOG-ACRIN E1912 Study Design



Primary endpoint: PFS
Secondary endpoints: OS, ORR, Toxicity and Tolerability

ECOG-ACRIN E1912 Physician Fact Sheet, version 01/15/16;
www.clinicaltrials.gov (NCT02048813); Shanafelt TD et al. ASH 2018;Abstract LBA-4.

ECOG-ACRIN E1912 Extended Follow-Up: Up-Front IR Compared to FCR for Younger Patients with CLL



- Grade ≥3 treatment-related AEs were reported in 70% of patients receiving IR and 80% of patients receiving FCR (odds ratio = 0.56; $p = 0.013$).
- Among the 95 patients who discontinued ibrutinib, the most common cause was AE or complication.

Shanafelt TD et al. ASH 2019;Abstract 33.

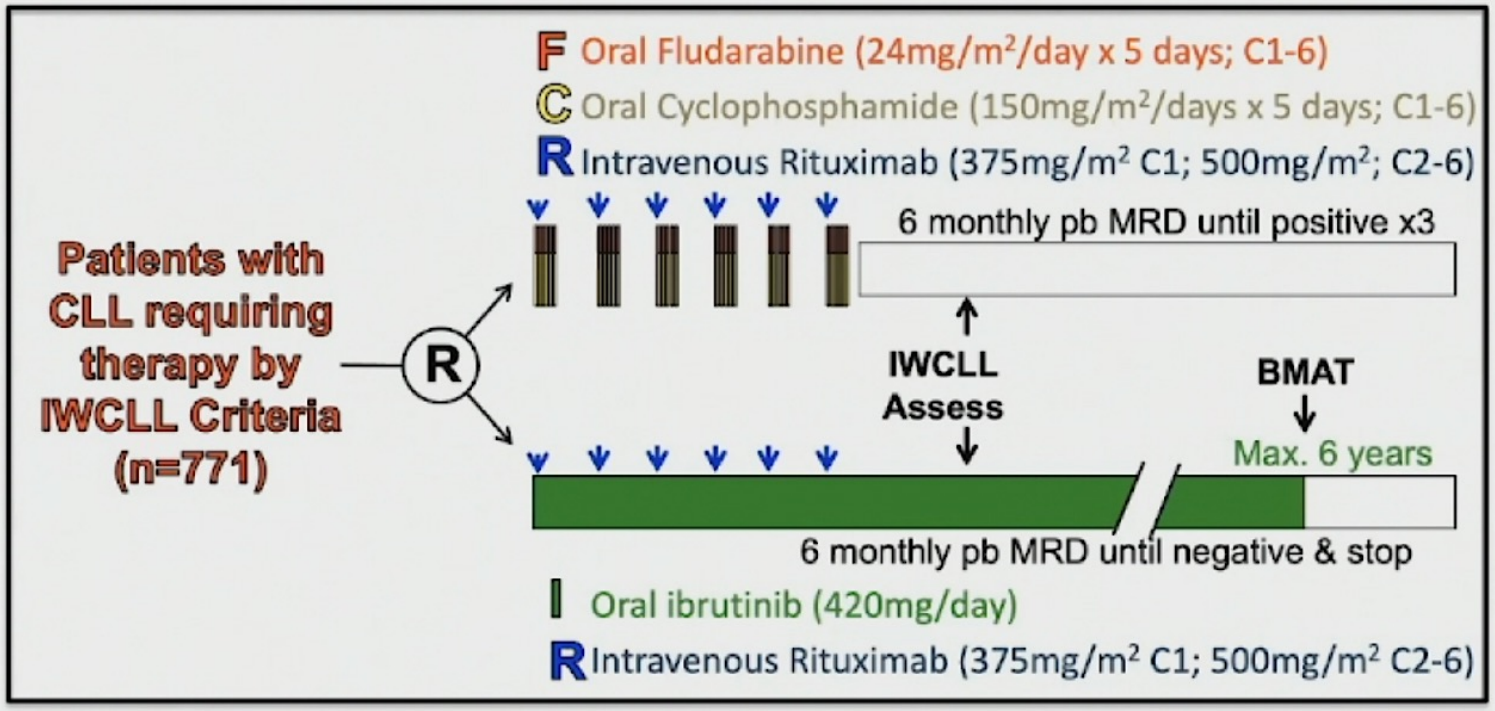
RTP RESEARCH TO PRACTICE

Ibrutinib plus Rituximab Is Superior to FCR in Previously Untreated CLL: Results of the Phase III NCRI FLAIR Trial

Hillmen P et al.

ASH 2021;Abstract 642.

NCRI FLAIR Study Design



Primary end-point:
To assess whether IR is superior to FCR in terms of PFS

Key secondary end-points:
Overall survival
Response including MRD
Safety and toxicity

Key Inclusion Criteria:

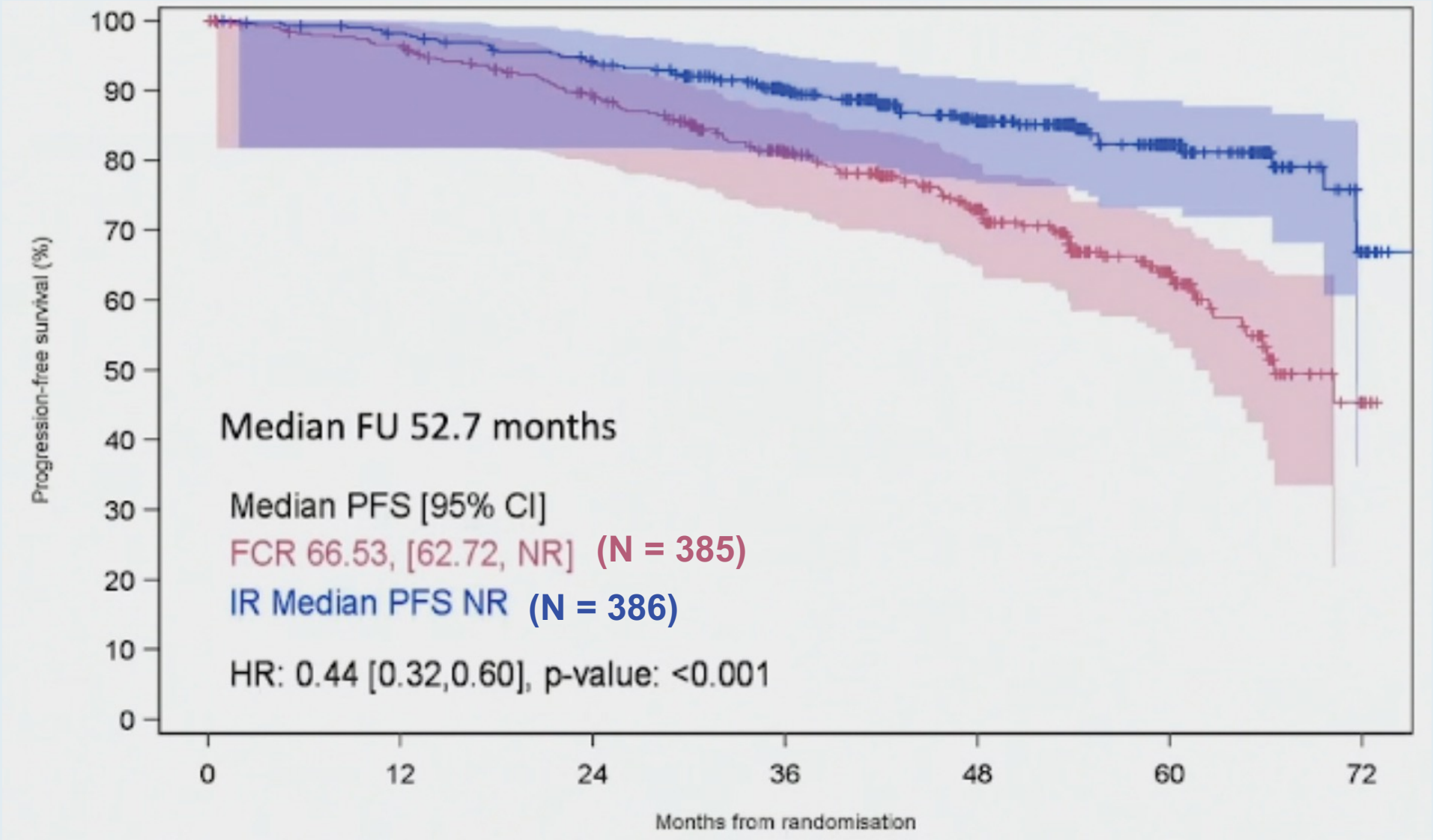
- Previously untreated CLL requiring therapy by IWCLL criteria
- Considered fit for FCR
- ≤75 years old

Key Exclusion Criteria:
Prior therapy for CLL; History of Richter's transformation; >20% TP53 deletion by FISH; Concomitant warfarin (or equivalent) Symptomatic cardiac failure or angina

Hillmen *et al.*, Abstract 642, ASH 2021

Hillmen P et al. ASH 2021;Abstract 642.

NCRI FLAIR: Progression-Free Survival



Hillmen P et al. ASH 2021;Abstract 642.

RTP RESEARCH TO PRACTICE

CHRONIC LYMPHOCYTIC LEUKEMIA

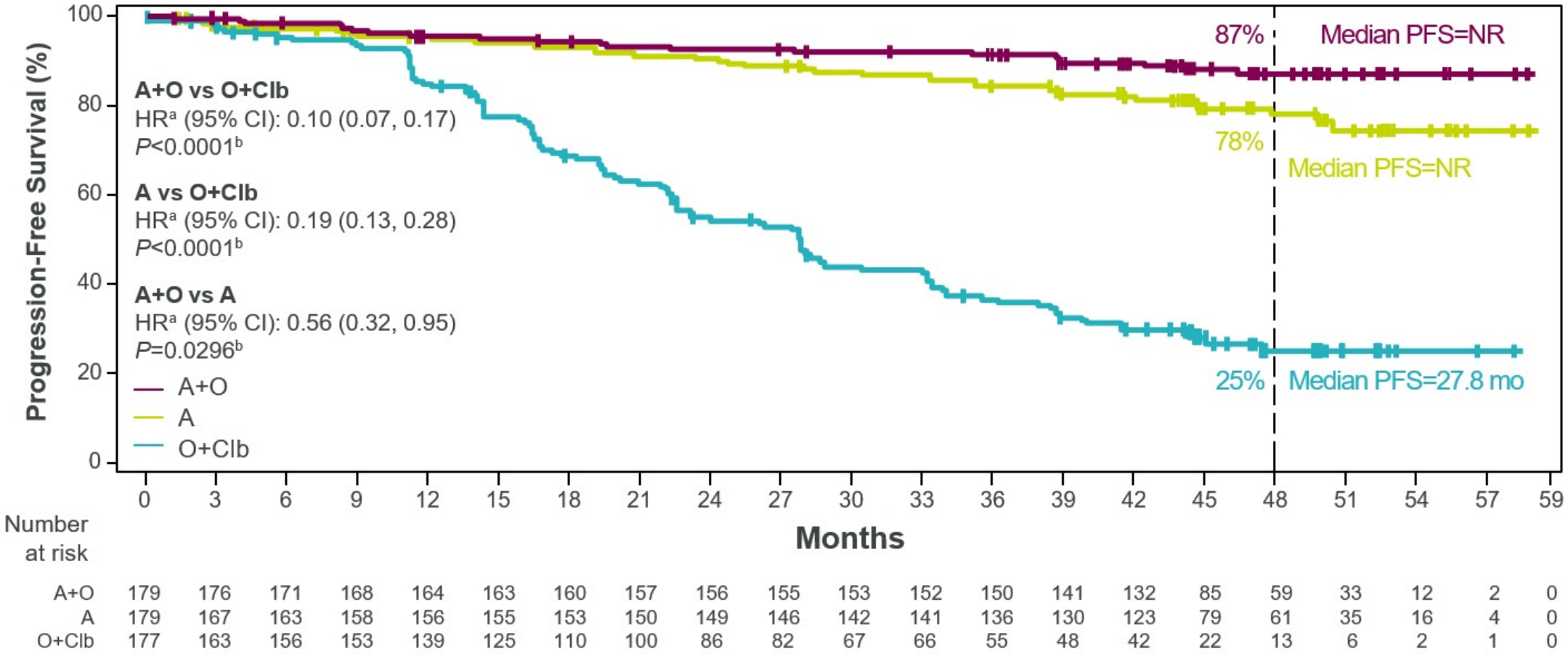
Leukemia 2022;[Online ahead of print].

Efficacy and safety in a 4-year follow-up of the ELEVATE-TN study comparing acalabrutinib with or without obinutuzumab versus obinutuzumab plus chlorambucil in treatment-naïve chronic lymphocytic leukemia

Jeff P. Sharman[1]✉, Miklos Egyed[2], Wojciech Jurczak[3], Alan Skarbnik[4], John M. Pagel[5], Ian W. Flinn[6], Manali Kamdar[7], Talha Munir[8], Renata Walewska[9], Gillian Corbett[10], Laura Maria Fogliatto[11], Yair Herishanu[12], Versha Banerji[13], Steven Coutre[14], George Follows[15], Patricia Walker[16], Karin Karlsson[17], Paolo Ghia[18], Ann Janssens[19], Florence Cymbalista[20], Jennifer A. Woyach[21], Emmanuelle Ferrant[22], William G. Wierda[23], Veerendra Munugalavadla[24], Ting Yu[24], Min Hui Wang[24] and John C. Byrd[21]

ELEVATE-TN: Investigator-Assessed PFS (Overall)

4-Year Follow-Up



Sharman JP et al. *Leukemia* 2022;[Online ahead of print].

RTP RESEARCH TO PRACTICE

American Society of Hematology
Helping hematologists conquer blood diseases worldwide

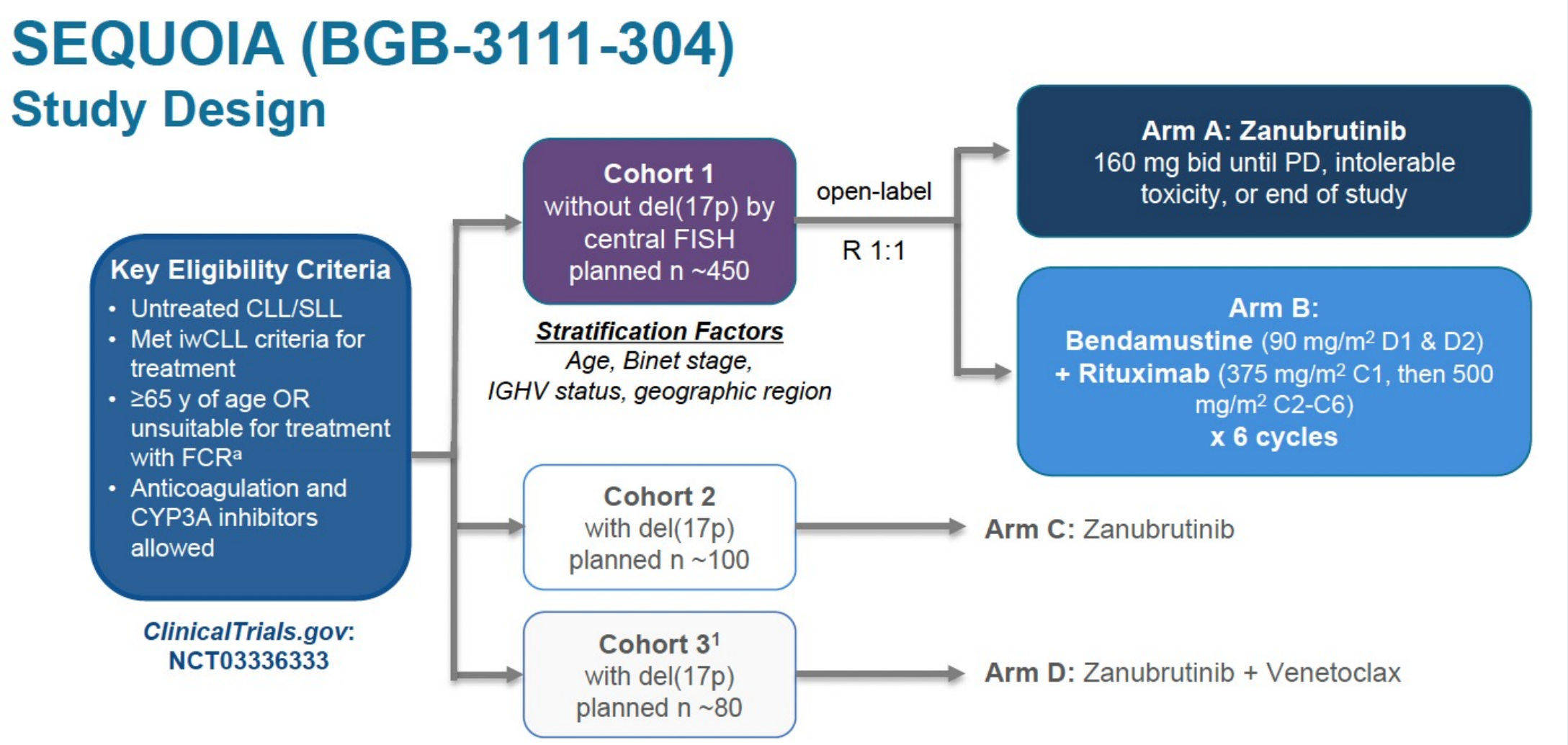
SEQUOIA: RESULTS OF A PHASE 3 RANDOMIZED STUDY OF ZANUBRUTINIB VERSUS BENDAMUSTINE + RITUXIMAB IN PATIENTS WITH TREATMENT-NAIVE CHRONIC LYMPHOCYTIC LEUKEMIA/SMALL LYMPHOCYTIC LYMPHOMA

Constantine S. Tam, MBBS, MD[1,2,3,4]; Krzysztof Giannopoulos, MD, PhD[5,6]; Wojciech Jurczak, MD, PhD[7]; Martin Šimkovič, MD, PhD[8,9]; Mazyar Shadman, MD, MPH[10,11]; Anders Österborg, MD, PhD[12,13]; Luca Laurenti, MD[14]; Patricia Walker, MBBS, BMedSci, FRACP, FRCPA[15]; Stephen Opat, MBBS (Hons), FRACP, FRCPA[16,17]; Henry Chan, MBChB, FRACP, FRCPA[18]; Hanna Ciepluch, MD, PhD[19]; Richard Greil, MD[20,21,22]; Monica Tani, MD[23]; Marek Trněný, MD[24]; Danielle M. Brander, MD[25]; Ian W. Flinn, MD, PhD[26]; Sebastian Grosicki, MD, PhD[27]; Emma Verner, MBBS, BMedSci, FRCPA, FRACP[28,29]; Jennifer R. Brown MD, PhD[30]; Brad S. Kahl, MD[31]; Paolo Ghia, MD, PhD[32]; Jianyong Li, MD, PhD[33]; Tian Tian, PhD[34]; Lei Zhou, MD[34]; Carol Marimpietri[34]; Jason C. Paik, MD, PhD[34]; Aileen Cohen, MD, PhD[34]; Jane Huang, MD[34]; Tadeusz Robak, MD, PhD[35]; and Peter Hillmen, MBChB, PhD[36]

[1]Peter MacCallum Cancer Centre, Melbourne, Victoria, Australia; [2]University of Melbourne, Parkville, Victoria, Australia; [3]St Vincent's Hospital Melbourne, Fitzroy, Victoria, Australia; [4]Royal Melbourne Hospital, Parkville, Victoria, Australia; [5]Experimental Hematooncology Department, Medical University of Lublin, Lublin, Poland; [6]Hematology Department, St. John's Cancer Centre, Lublin, Poland; [7]Maria Sklodowska-Curie National Research Institute of Oncology, Krakow, Poland; [8]Fourth Department of Internal Medicine - Haematology, University Hospital, Hradec Kralove, Czech Republic; [9]Faculty of Medicine, Charles University, Prague, Czech Republic; [10]Fred Hutchinson Cancer Research Center, Seattle, WA, USA; [11]Department of Medicine, University of Washington, Seattle, WA, USA; [12]Department of Oncology-Pathology, Karolinska Institutet, Stockholm, Sweden; [13]Department of Hematology, Karolinska University Hospital, Stockholm, Sweden; [14]Fondazione Policlinico Universitario A Gemelli UCSC, Rome, Italy; [15]Peninsula Private Hospital, Frankston, Victoria, Australia; [16]Monash Health, Clayton, Victoria, Australia; [17]Monash University, Clayton, Victoria, Australia; [18]North Shore Hospital, Auckland, New Zealand; [19]Copernicus Regional Oncology Center, Gdansk, Poland; [20]Third Medical Department with Hematology, Medical Oncology, Rheumatology and Infectiology, Paracelsus Medical University, Salzburg, Austria; [21]Salzburg Cancer Research Institute (SCRI) Center for Clinical Cancer and Immunology Trials (CCCIT), Salzburg, Austria; [22]Cancer Cluster Salzburg (CCS), Salzburg, Austria; [23]Hematology Unit, Santa Maria delle Croci Hospital, Ravenna, Italy; [24]First Department of Medicine, First Faculty of Medicine, Charles University, General Hospital, Prague, Czech Republic; [25]Hematologic Malignancies and Cellular Therapy, Duke University School of Medicine, Durham, NC, USA; [26]Sarah Cannon Research Institute/Tennessee Oncology, Nashville, TN, USA; [27]Department of Hematology and Cancer Prevention, Health Sciences Faculty, Medical University of Silesia, Katowice, Poland; [28]Concord Repatriation General Hospital, Concord, New South Wales, Australia; [29]University of Sydney, Sydney, New South Wales, Australia; [30]Dana-Farber Cancer Institute, Boston, MA, USA; [31]Washington University School of Medicine, St Louis, MO, USA; [32]Università Vita-Salute San Raffaele and IRCCS Ospedale San Raffaele, Milano, Italy; [33]Department of Hematology, The First Affiliated Hospital of Nanjing Medical University, Jiansu Province Hospital, Nanjing, China; [34]BeiGene (Beijing) Co., Ltd., Beijing, China and BeiGene USA, Inc., San Mateo, CA, USA; [35]Medical University of Lodz, Lodz, Poland; and [36]St James's University Hospital, Leeds, United Kingdom

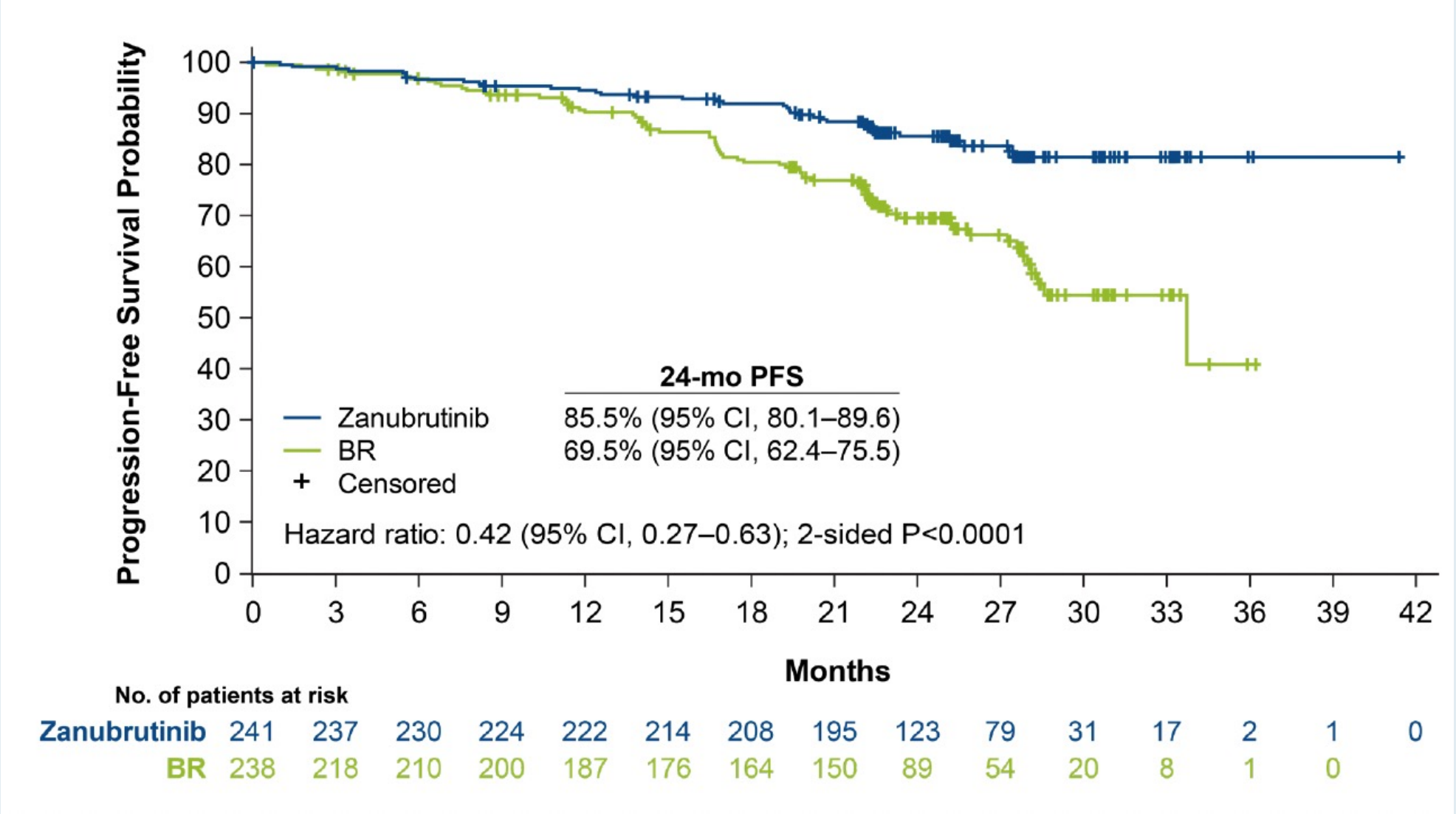
Sunday, December 12, 2021
642. Chronic Lymphocytic Leukemia: Clinical and Epidemiological I

SEQUOIA Phase III Study Design



Tam CS et al. ASH 2021;Abstract 396.

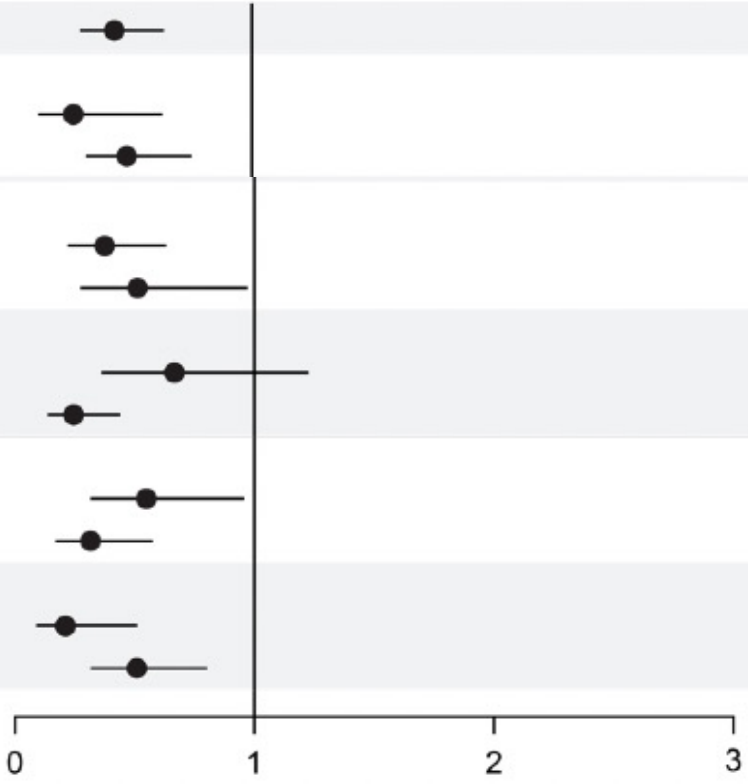
SEQUOIA: Progression-Free Survival by IRC



Tam CS et al. ASH 2021;Abstract 396.

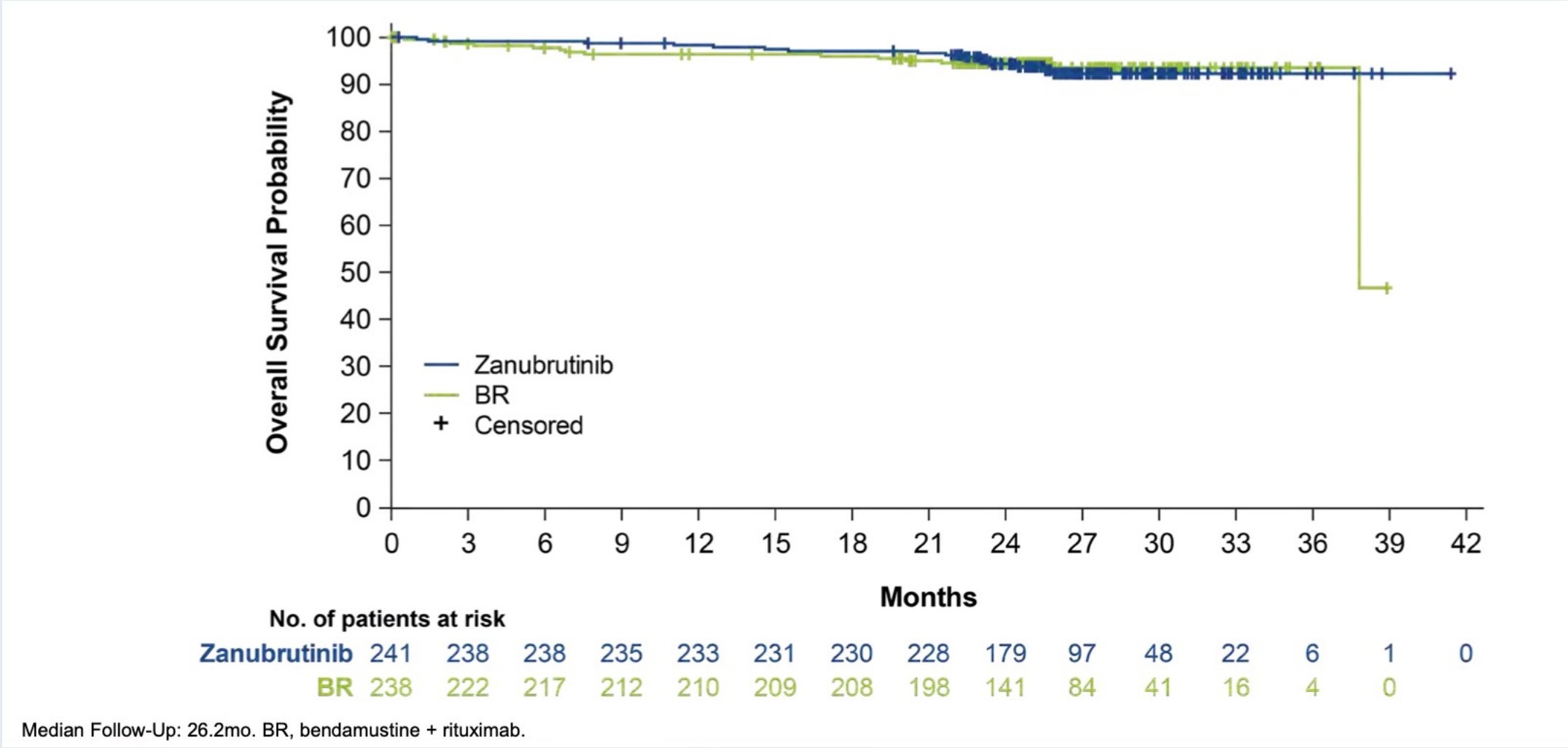
SEQUOIA: Progression-Free Survival by Subgroups

Subgroup	Event/Patient Zanubrutinib	Event/Patient BR	Hazard Ratio (95% CI), %[a]
All Patients	36/241	71/238	0.42 (0.28–0.63)
Age (years)			
<65	6/45	19/46	0.25 (0.10–0.62)
≥65	30/196	52/192	0.47 (0.30–0.74)
Bulky disease (LDi <5 cm vs ≥5 cm)			
<5 cm	21/172	44/165	0.37 (0.22–0.63)
≥5 cm	15/69	27/73	0.52 (0.27–0.97)
IGHV mutational status			
Mutated	18/109	25/110	0.67 (0.36–1.22)
Unmutated	15/125	45/121	0.24 (0.13–0.43)
Cytopenias at baseline[b]			
Yes	21/102	34/109	0.55 (0.32–0.95)
No	15/139	37/129	0.31 (0.17–0.57)
Chromosome 11q deletion			
Yes	7/43	22/46	0.21 (0.09–0.50)
No	29/198	49/192	0.50 (0.32–0.80)



Tam CS et al. ASH 2021;Abstract 396.

SEQUOIA: Overall Survival



Median Follow-Up: 26.2mo. BR, bendamustine + rituximab.

Tam CS et al. ASH 2021;Abstract 396.

SEQUOIA: Adverse Events of Interest

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

Tam CS et al. ASH 2021;Abstract 396.

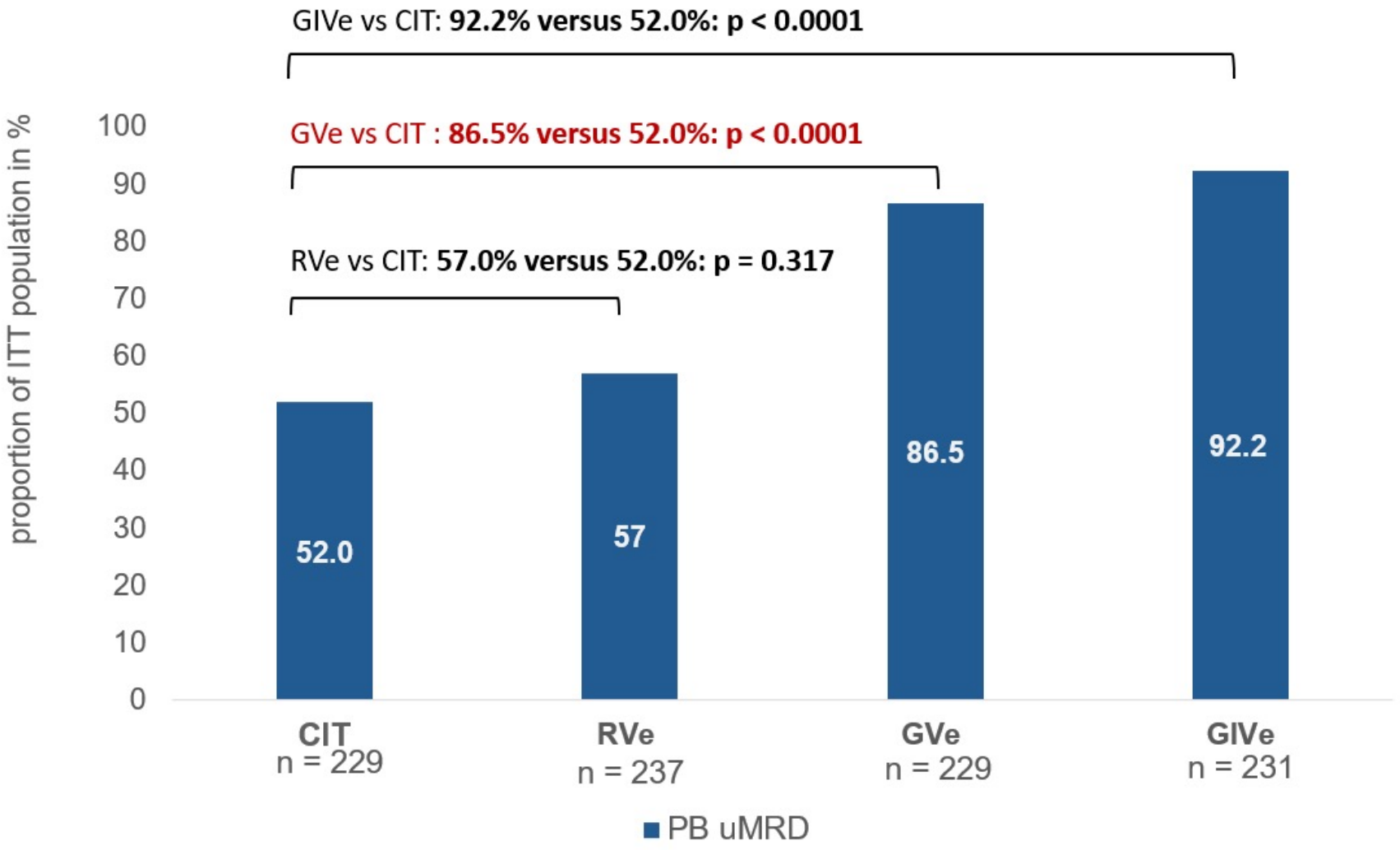
Venetoclax Combination Regimens

A Randomized Phase III Study of Venetoclax-Based Time-Limited Combination Treatments (RVe, GVe, GIVe) vs Standard Chemoimmunotherapy (CIT: FCR/BR) in Frontline Chronic Lymphocytic Leukemia (CLL) of Fit Patients: First Co-Primary Endpoint Analysis of the International Intergroup GAIA (CLL13) Trial

Eichhorst B et al.

ASH 2021;Abstract 71.

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



CIT
- BR >65
- ≤FCR 65

RVe
Rituximab/venetoclax

GVe
Obinutuzumab/venetoclax

GIVe
Obinutuzumab/ibrutinib/venetoclax

Eichhorst B et al. ASH 2021;Abstract 71.

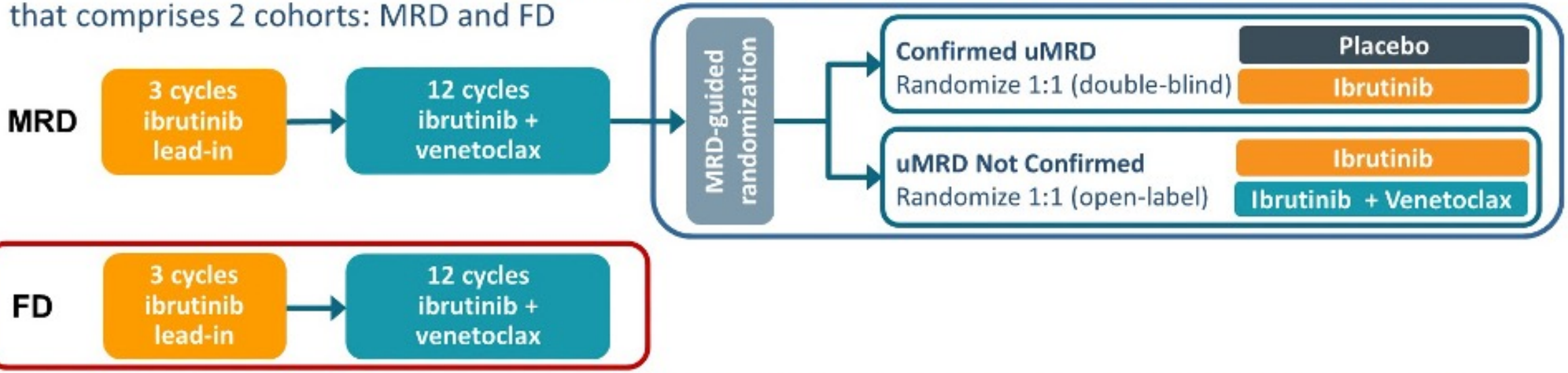
Fixed-Duration (FD) First-Line Treatment With Ibrutinib Plus Venetoclax for Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma: Primary Analysis of the FD Cohort of the Phase 2 CAPTIVATE Study

Paolo Ghia, MD, PhD[1]; John N. Allan, MD[2]; Tanya Siddiqi, MD[3]; Thomas J. Kipps, MD, PhD[4]; Ryan Jacobs, MD[5]; Stephen Opat, FRACP, FRCPA, MBBS[6]; Paul M. Barr, MD[7]; Alessandra Tedeschi, MD[8]; Livio Trentin, MD[9]; Rajat Bannerji, MD, PhD[10]; Sharon Jackson, MD[11]; Bryone Kuss, MBBS, PhD, FRACP, FRCPA[12]; Carol Moreno, MD, PhD[13]; Edith Szafer-Glusman, PhD[14]; Kristin Russell, BS[14]; Cathy Zhou, MS[14]; Joi Ninomoto, PharmD[14]; James P. Dean, MD, PhD[14]; William G. Wierda, MD, PhD[15]; Constantine Tam, MBBS, MD[16]

[1]Division of Experimental Oncology, Università Vita-Salute San Raffaele and IRCCS Ospedale San Raffaele, Milan, Italy; [2]Weill Cornell Medicine, New York, NY, USA; [3]City of Hope National Medical Center, Duarte, CA, USA; [4]UCSD Moores Cancer Center, San Diego, CA, USA; [5]Levine Cancer Institute, Charlotte, NC, USA; [6]Monash University, Clayton, VIC, Australia; [7]Wilmot Cancer Institute, University of Rochester Medical Center, Rochester, NY, USA; [8]ASST Grande Ospedale Metropolitano Niguarda, Milan, Italy; [9]Hematology and Clinical Immunology Unit, Department of Medicine, University of Padova, Padova, Italy; [10]Rutgers Cancer Institute of New Jersey, New Brunswick, NJ, USA; [11]Middlemore Hospital, Auckland, New Zealand; [12]Flinders University and Medical Centre, Bedford Park, SA, Australia; [13]Hospital de la Santa Creu i Sant Pau, Autonomous University of Barcelona, Barcelona, Spain; [14]Pharmacyclics LLC, an AbbVie Company, Sunnyvale, CA, USA; [15]Department of Leukemia, University of Texas MD Anderson Cancer Center, Houston, TX, USA; [16]Peter MacCallum Cancer Center & St. Vincent's Hospital and the University of Melbourne, Melbourne, VIC, Australia

CAPTIVATE Study Design

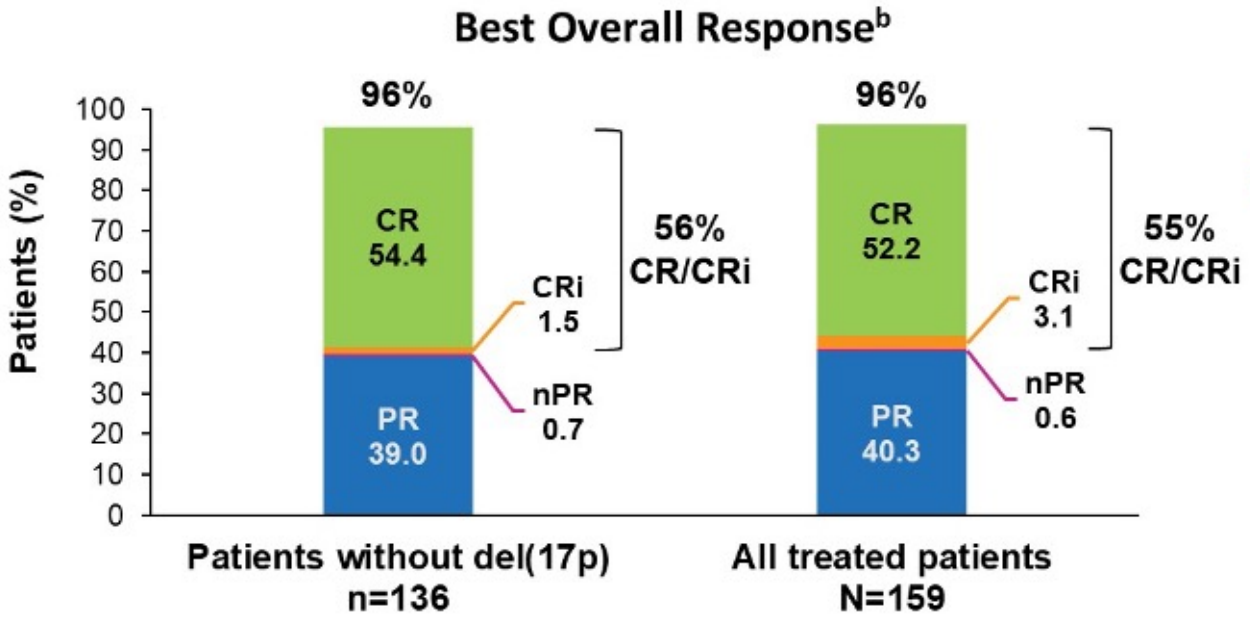
- CAPTIVATE (PCYC-1142) is an international, multicenter phase 2 study evaluating first-line treatment with 3 cycles of ibrutinib followed by 12 cycles of combined ibrutinib + venetoclax that comprises 2 cohorts: MRD and FD



- Results from the MRD cohort demonstrated uMRD in more than two-thirds of patients treated with 12 cycles of ibrutinib + venetoclax (PB, 75%; BM, 68%), and 30-month PFS rates of ≥95% irrespective of subsequent MRD-guided randomized treatment[1]

Ghia P et al. ASCO 2021;Abstract 7051.

CAPTIVATE: Response



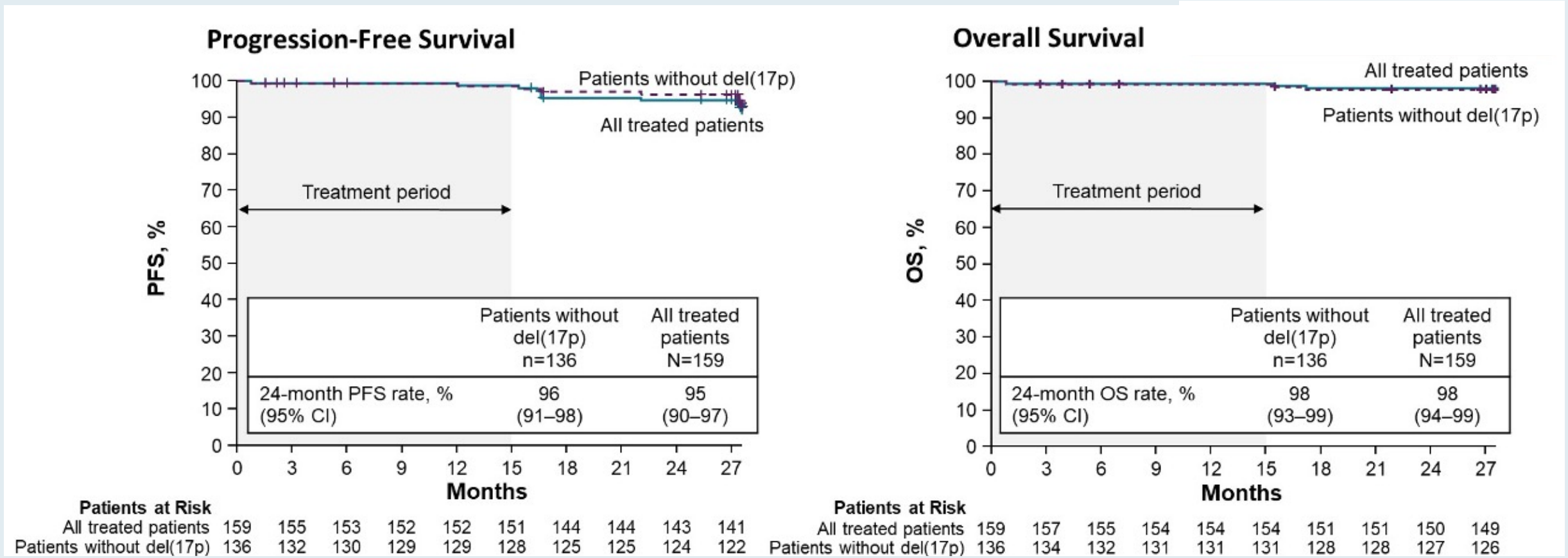
DOCR ≥12 cycles n/N (%)	66/76 (87)	78/88 (89)*

- Primary endpoint was met: 56% (95% CI, 48–64) CR rate[a] in patients without del(17p)
  - Significantly excludes 37% minimum rate ($P<0.0001$)
  - Meaningful improvement over 40% rate of historical comparator of FCR in CLL10[1]

*After achieving CR[a], 9 patients with <1 year of follow-up were not evaluable; 1 patient died 7 months after CR and completion of therapy.

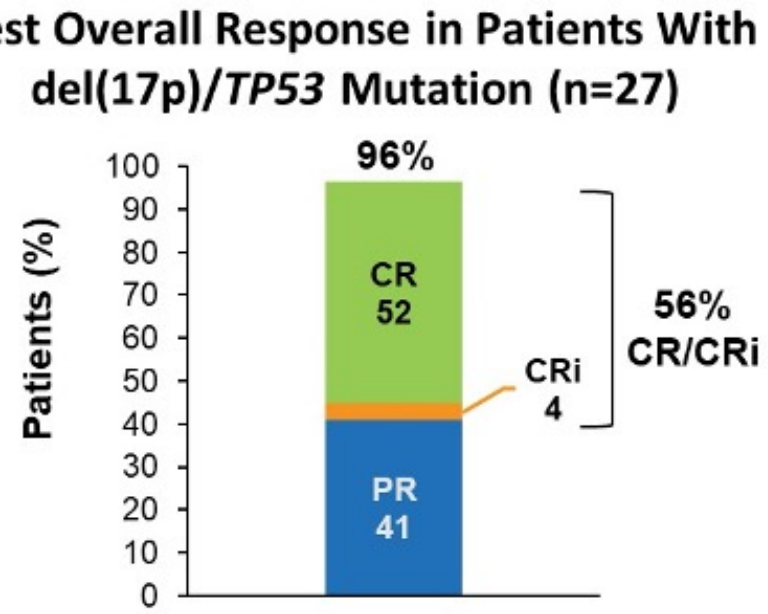
Ghia P et al. ASCO 2021;Abstract 7051.

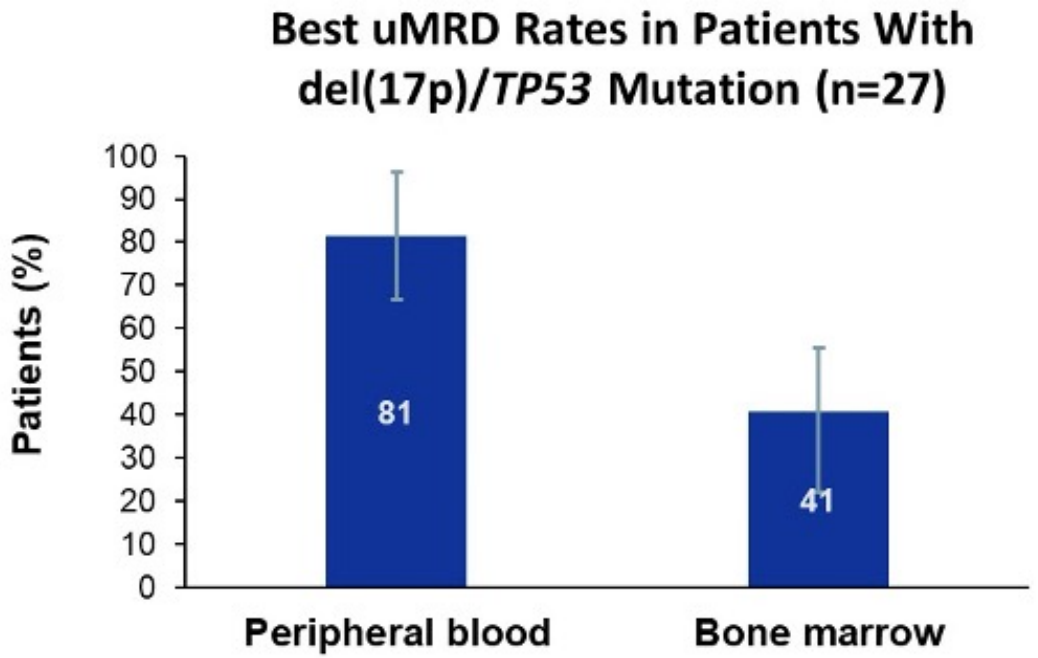
CAPTIVATE: Progression-Free and Overall Survival



Ghia P et al. ASCO 2021;Abstract 7051.

CAPTIVATE: Efficacy Outcomes for Patients with Del(17p)/TP53 Mutation





- Patients with DOCR ≥12 cycles was 87% (13/15)
- Estimated 24-month PFS rate was 84% (95% CI, 63–94)
- Estimated 24-month OS rate was 96% (95% CI, 76–99)

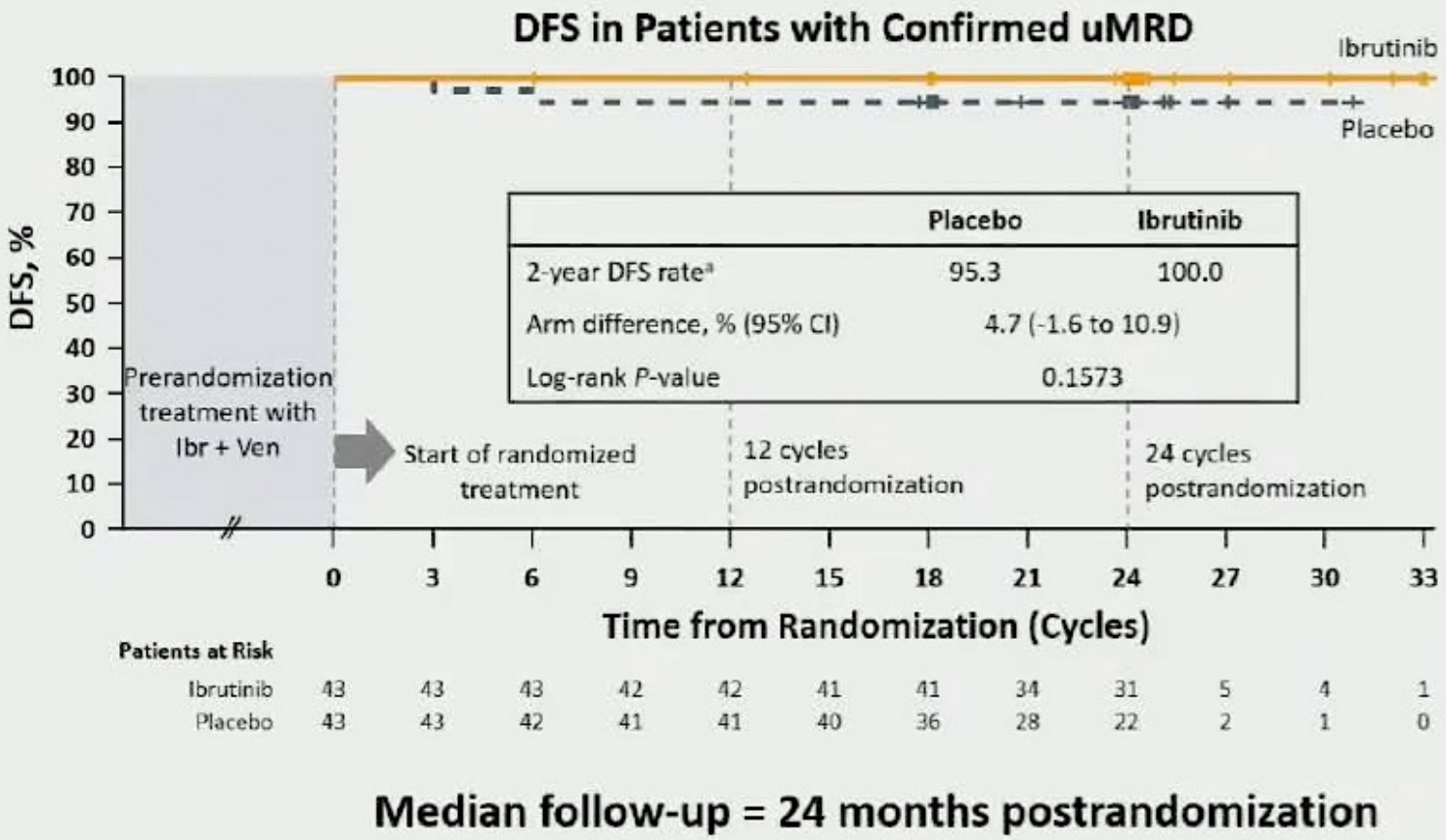
Ghia P et al. ASCO 2021;Abstract 7051.

First-Line Treatment with Ibrutinib (Ibr) plus Venetoclax (Ven) for Chronic Lymphocytic Leukemia (CLL): 2-Year Post-Randomization Disease-Free Survival (DFS) Results from the Minimal Residual Disease (MRD) Cohort of the Phase 2 Captivate Study

Ghia P et al.

ASH 2021;Abstract 68.

CAPTIVATE MRD Cohort: DFS Events in Patients with Confirmed uMRD

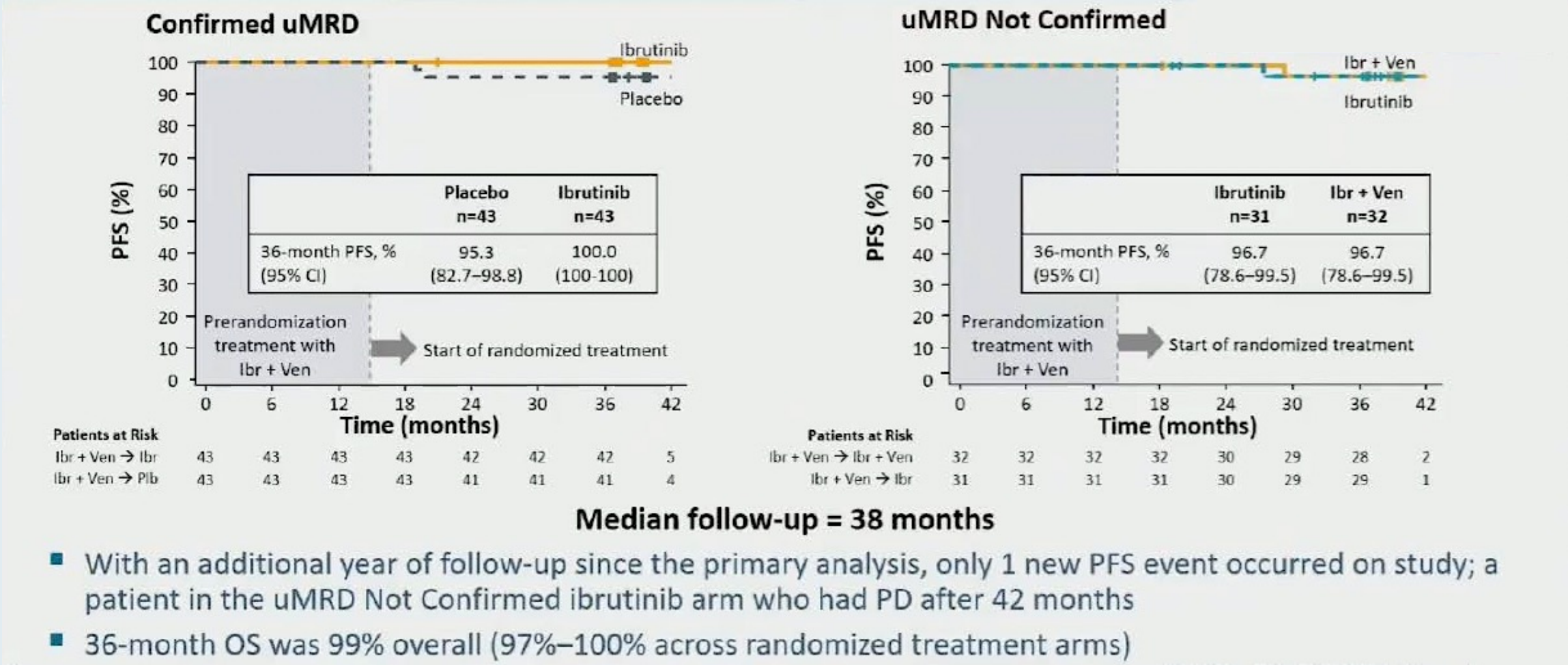


Median follow-up = 24 months postrandomization

- DFS was defined as freedom from MRD relapse ($\geq 10^{-2}$ confirmed on 2 separate occasions) and without PD or death starting from randomization after 15 cycles of treatment
- In the additional year of follow-up since the 1-year DFS primary analysis, no new MRD relapses, PD, or deaths occurred in patients with Confirmed uMRD randomized to ibrutinib or placebo

Ghia P et al. ASH 2021;Abstract 68.

CAPTIVATE MRD Cohort: Three-Year PFS Rates

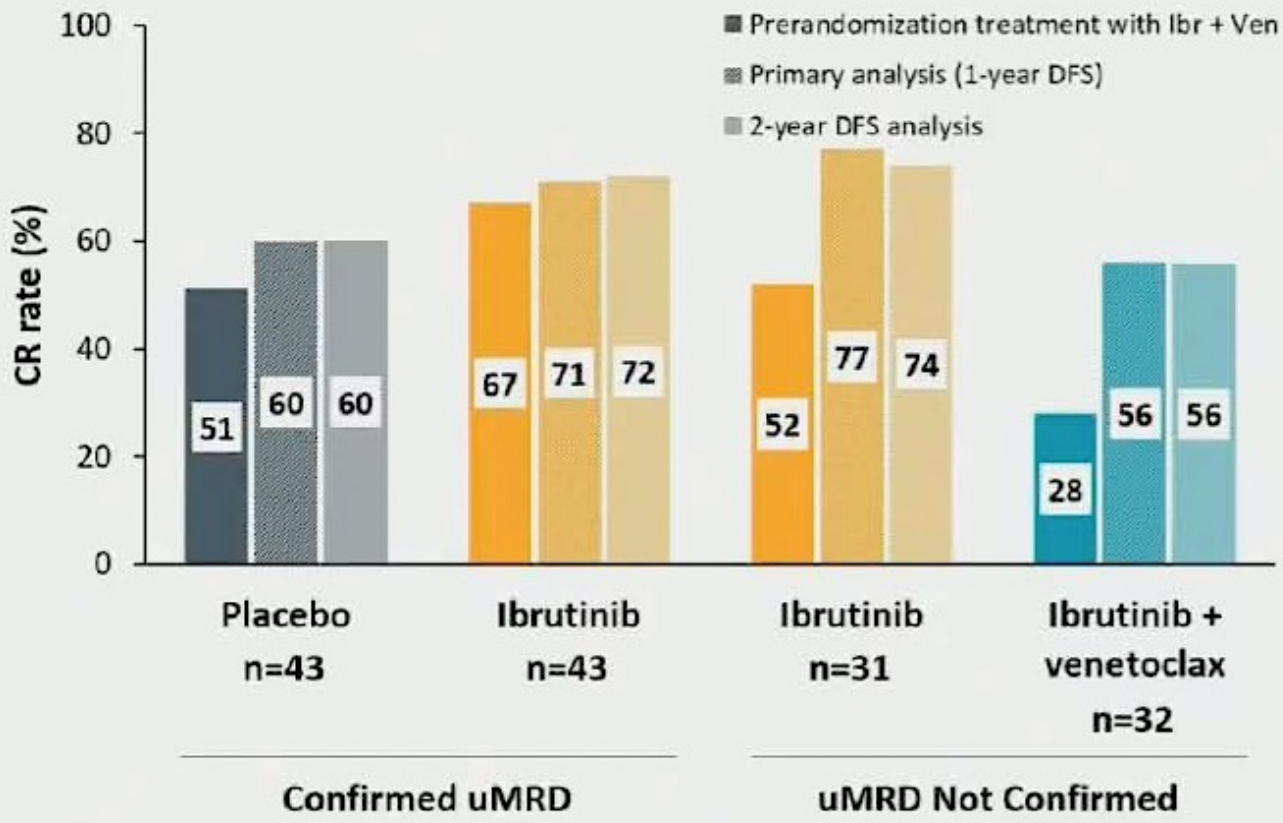


Median follow-up = 38 months

- With an additional year of follow-up since the primary analysis, only 1 new PFS event occurred on study; a patient in the uMRD Not Confirmed ibrutinib arm who had PD after 42 months
- 36-month OS was 99% overall (97%–100% across randomized treatment arms)

Ghia P et al. ASH 2021;Abstract 68.

CAPTIVATE MRD Cohort: CR Rates with 24 Months Postrandomization Follow-Up



- Greatest CR rate[a] improvements occurred during the first year of randomized treatment
  - Modest improvements observed in patients with Confirmed uMRD[b] randomized to placebo or ibrutinib
  - Improvements in CR rates[a] were similar with ibrutinib + venetoclax and ibrutinib in patients with uMRD Not Confirmed[b]

Ghia P et al. ASH 2021;Abstract 68.

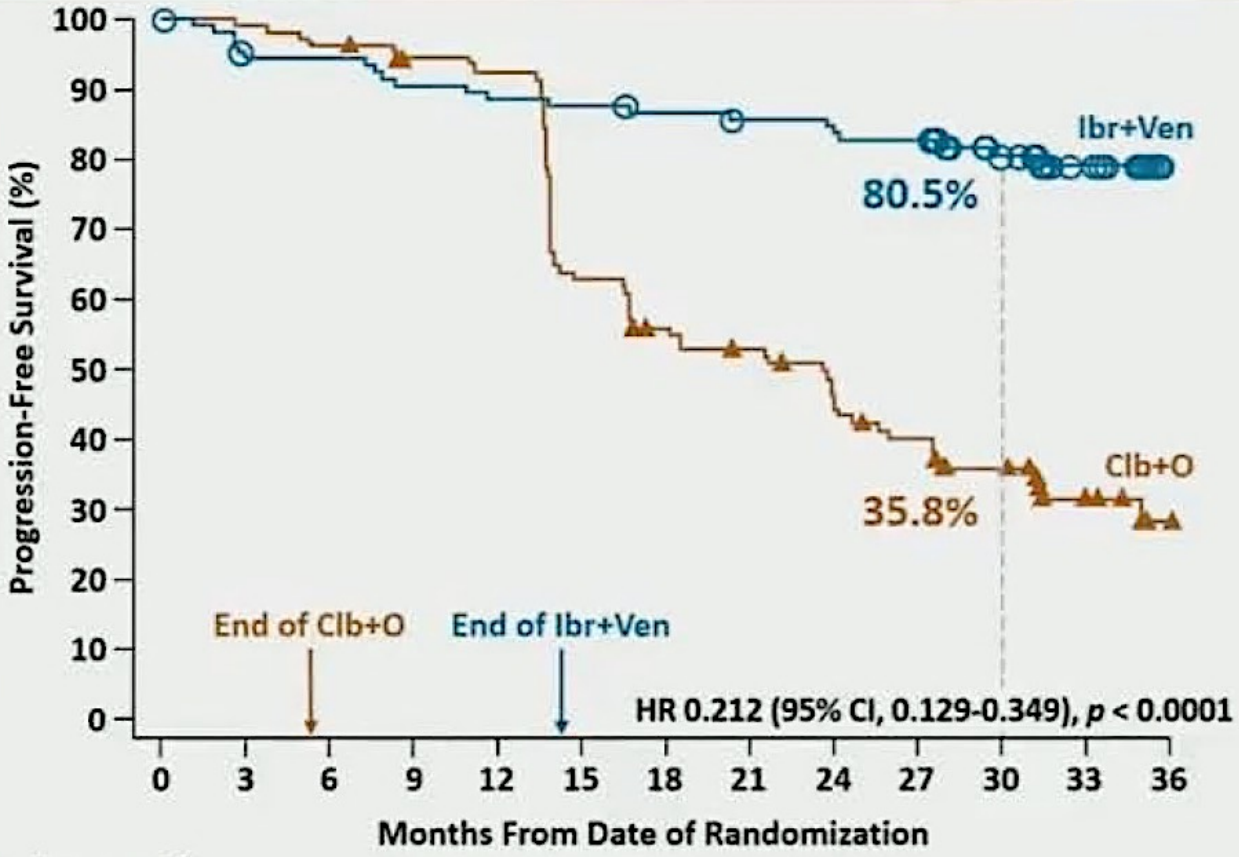
First Prospective Data on Minimal Residual Disease (MRD) Outcomes After Fixed-Duration Ibrutinib Plus Venetoclax (Ibr+Ven) Versus Chlorambucil Plus Obinutuzumab (Clb+O) for First-Line Treatment of CLL in Elderly or Unfit Patients: The GLOW Study

Talha Munir,[1] Carol Moreno,[2] Carolyn Owen,[3] George Follows,[4] Ohad Benjamini,[5] Ann Janssens,[6] Mark-David Levin,[7] Anders Osterborg,[8] Tadeusz Robak,[9] Martin Simkovic,[10] Don Stevens,[11] Sergey Voloshin,[12] Vladimir Vorobyev,[13] Munci Yagci,[14] Loic Ysebaert,[15] Qianya Qi,[16] Andrew J. Steele,[17] Natasha Schuier,[18] Kurt Baeten,[19] Donne Bennett Caces,[16] Carsten U. Niemann,[20] Arnon P. Kater[21]

[1]St James's Hospital, Leeds, UK; [2]Hospital de la Santa Creu i Sant Pau, Autonomous University of Barcelona, Spain; [3]Tom Baker Cancer Centre, Calgary, Canada; [4]Addenbrookes Hospital, Cambridge, UK; [5]Sheba Medical Center, Ramat Gan, Israel; [6]UZ Leuven Gasthuisberg, Leuven, Belgium; [7]Albert Schweitzer Hospital, Dordrecht, Netherlands; [8]Karolinska University Hospital, Stockholm, Sweden; [9]Medical University of Lodz, Copernicus Memorial Hospital, Lodz, Poland; [10]University Hospital Hradec Kralove, Hradec Kralove, Czech Republic; [11]Norton Cancer Institute, Louisville, KY, USA; [12]Russian Scientific and Research Institute of Hematology and Transfusiology, St. Petersburg, Russia; [13]S.P. Botkin Moscow City Clinical Hospital, Moscow, Russia; [14]Gazi Universitesi Tip Fakultesi, Ankara, Turkey; [15]Institut Universitaire du Cancer Toulouse Oncopole, Toulouse, France; [16]Janssen Research & Development, Raritan, NJ, USA; [17]Janssen Research & Development, Spring House, PA, USA; [18]Janssen Research & Development, Düsseldorf, Germany; [19]Janssen Research & Development, Beerse, Belgium; [20]Rigshospitalet Copenhagen University Hospital, Copenhagen, Denmark; [21]Amsterdam University Medical Centers, Cancer Center Amsterdam, University of Amsterdam, Netherlands

ASH 2021;Abstract 70.

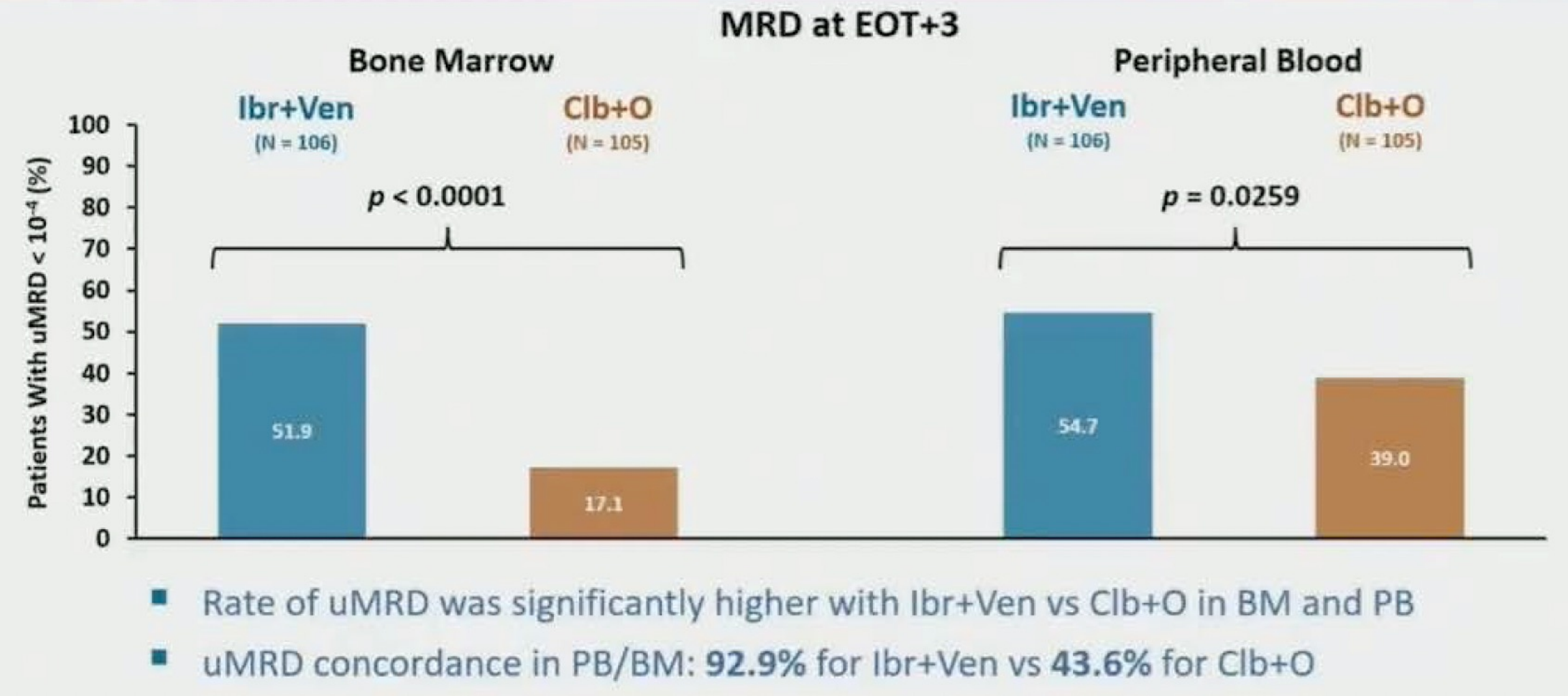
GLOW: Independent Review Committee (IRC)-Assessed PFS



- IRC-assessed PFS for Ibr+Ven was superior to Clb+O at primary analysis (median 27.7 months of follow-up)
  - HR 0.216 (95% CI, 0.131-0.357; $p < 0.0001$)
- **With median follow-up of 34.1 months:**
  - IRC-assessed PFS remained superior for Ibr+Ven (HR 0.212, 95% CI, 0.129-0.349; $p < 0.0001$)
  - 30-month PFS: 80.5% for Ibr+Ven vs 35.8% for Clb+O
  - Overall survival HR 0.76 (95% CI, 0.35-1.64), with 11 deaths for Ibr+Ven vs 16 for Clb+O

Munir T et al. ASH 2021;Abstract 70.

GLOW: uMRD <10^{-4} Rate



- Rate of uMRD was significantly higher with Ibr+Ven vs Clb+O in BM and PB
- uMRD concordance in PB/BM: **92.9%** for Ibr+Ven vs **43.6%** for Clb+O

Munir T et al. ASH 2021;Abstract 70.

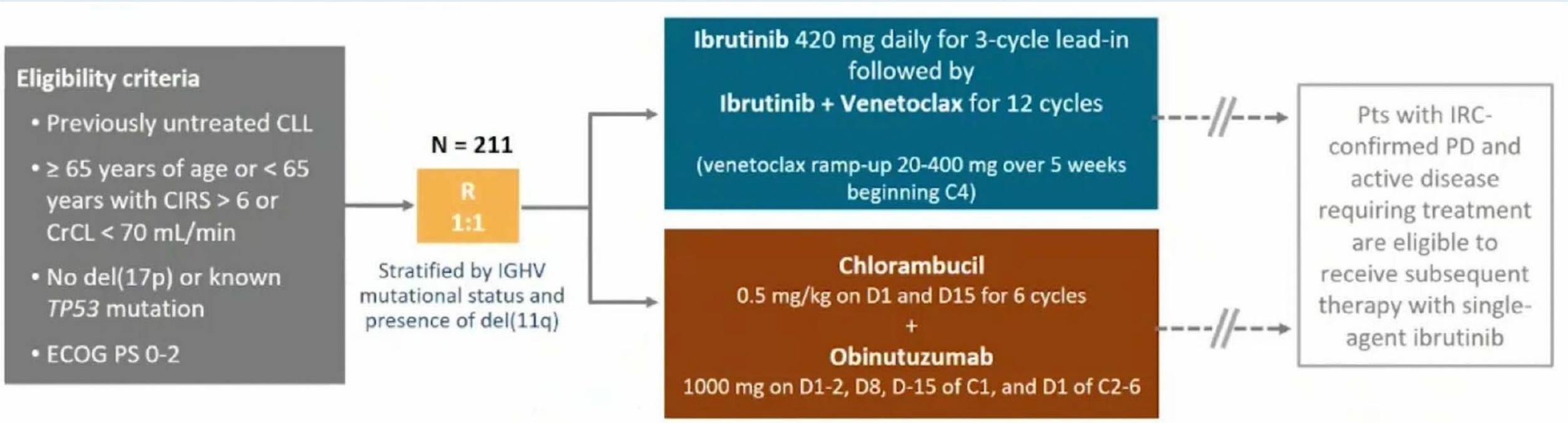
RTP RESEARCH TO PRACTICE

Fixed-Duration Ibrutinib and Venetoclax (I + V) versus Chlorambucil plus Obinutuzumab (Clb + O) for First-Line (1L) Chronic Lymphocytic Leukemia (CLL): Primary Analysis of the Phase 3 GLOW Study

Kater A et al.

EHA 2021;Abstract LB1902.

GLOW: Study Design and Endpoints



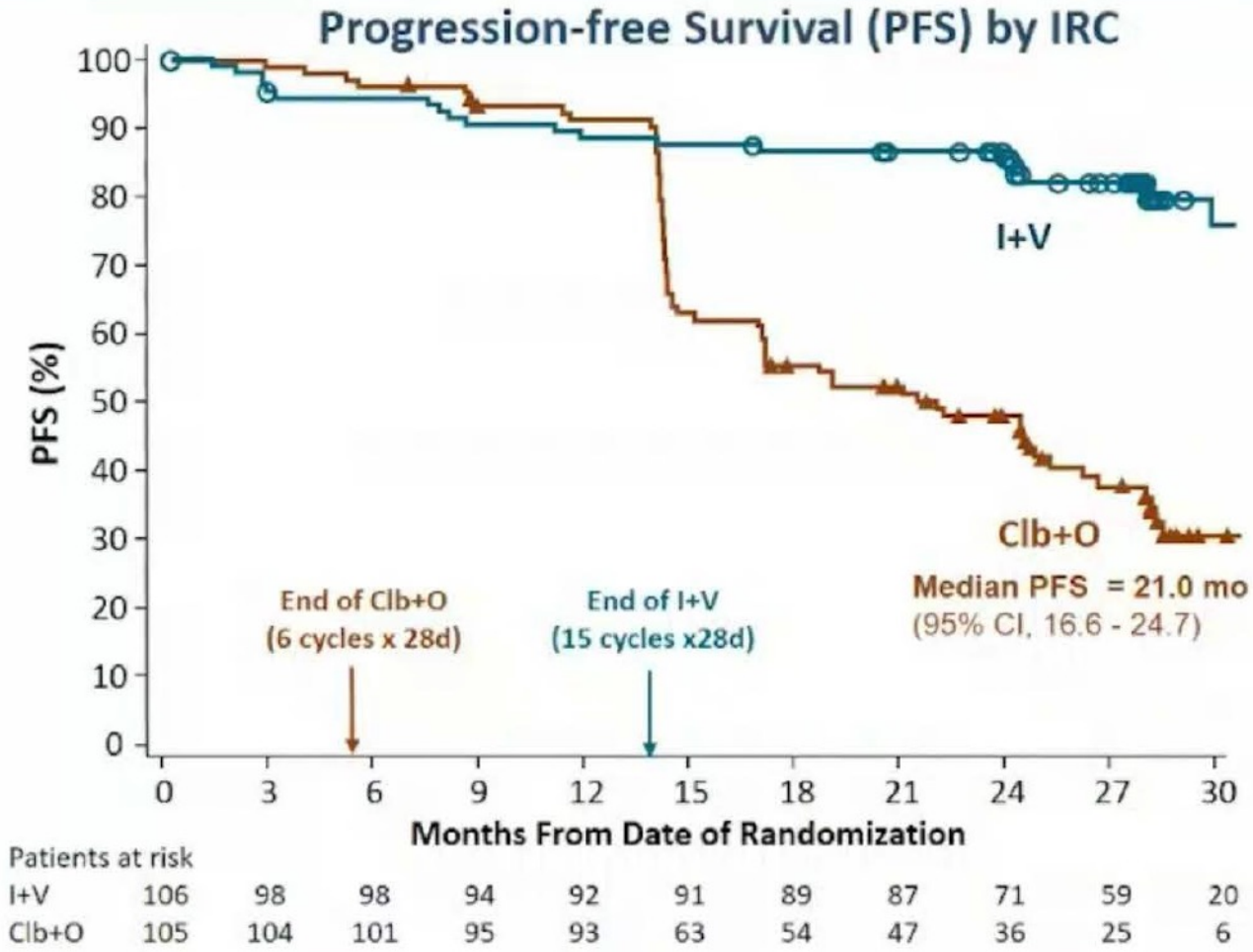
Primary end point: Progression-free survival by independent review committee (IRC)

- 71 PFS events to detect an effect size with an HR = 0.5 (80% power at a 2-sided significance level of 0.05)

Key secondary end points: Undetectable MRD in BM, CR rate (IRC), ORR (IRC), OS; safety was also evaluated.

Kater A et al. EHA 2021;Abstract LB1902.

GLOW: Progression-Free Survival

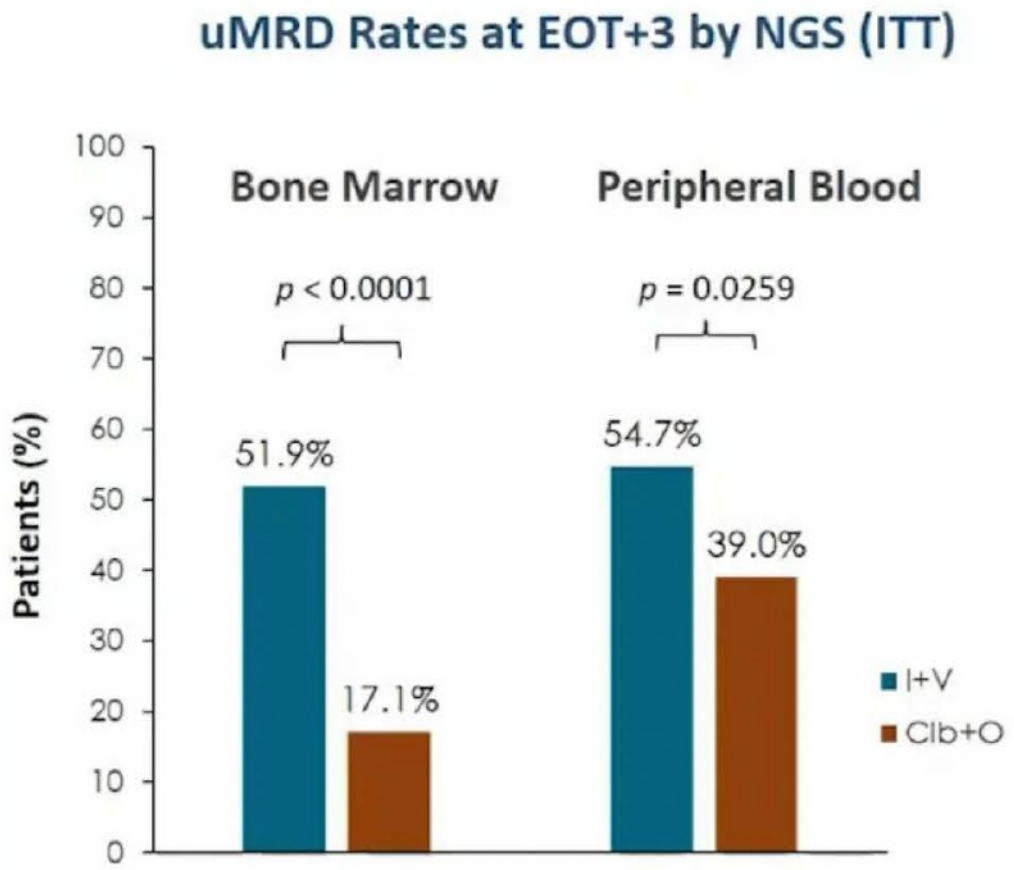


- **With a median follow up of 27.7 months, IRC-assessed PFS for I+V was superior to Clb+O**
- I+V reduced the risk of progression or death by 78% vs Clb+O
  - **HR 0.216** (95% CI, 0.131-0.357; p < 0.0001)
- PFS by INV assessment was consistent with IRC
  - **HR 0.207** (95% CI, 0.120, 0.357; p < 0.0001)

Kater A et al. EHA 2021;Abstract LB1902.

RTP RESEARCH TO PRACTICE

GLOW: Undetectable MRD Rate



- Rate of uMRD at EOT+3 was significantly higher for I+V vs Clb+O, irrespective of compartment
- With I+V, PB/BM uMRD concordance[b] was 92.9% (52/56)
  - Versus 43.6% (17/39) for Clb+O
- Best uMRD rates were higher for I+V (by flow cytometry)
  - I+V: 67.9% (BM) and 80.2% (PB)
  - Clb+O: 22.9% (BM) and 46.7% (PB)

Kater A et al. EHA 2021;Abstract LB1902.

GLOW: Safety

	I+V (N = 106)	Clb+O (N = 105)
Median exposure, mos (range)	13.8 (0.7-19.5)	5.1 (1.8-7.9)
Any, %	75.5	69.5
Neutropenia[a]	34.9	49.5
Infections[b]	17.0	11.4
Thrombocytopenia	5.7	20.0
Diarrhea	10.4	1.0
Hypertension	7.5	1.9
Atrial fibrillation	6.6	0
Hyponatremia	5.7	0
TLS	0	5.7

[a]Includes 'neutrophil count decreased'; grade ≥3 febrile neutropenia: 1.9% for I+V vs 2.9% for Clb+O

[b]Includes multiple preferred terms

- After 3 cycles of ibrutinib lead-in, <2% of patients remained at risk for TLS based on high tumor burden
- 2 (1.9%) patients in I+V arm discontinued ibrutinib due to atrial fibrillation
- SAEs in ≥5% of patients for I+V vs Clb+O: Infections (12.3% vs 8.6%) and atrial fibrillation (6.6% vs 0%)
- Rate of secondary malignancies at time of analysis: 8.5% for I+V vs 10.5% for Clb+O
  - NMSC: 3.8% vs 1.9%
  - Other: 4.7% vs 8.6%

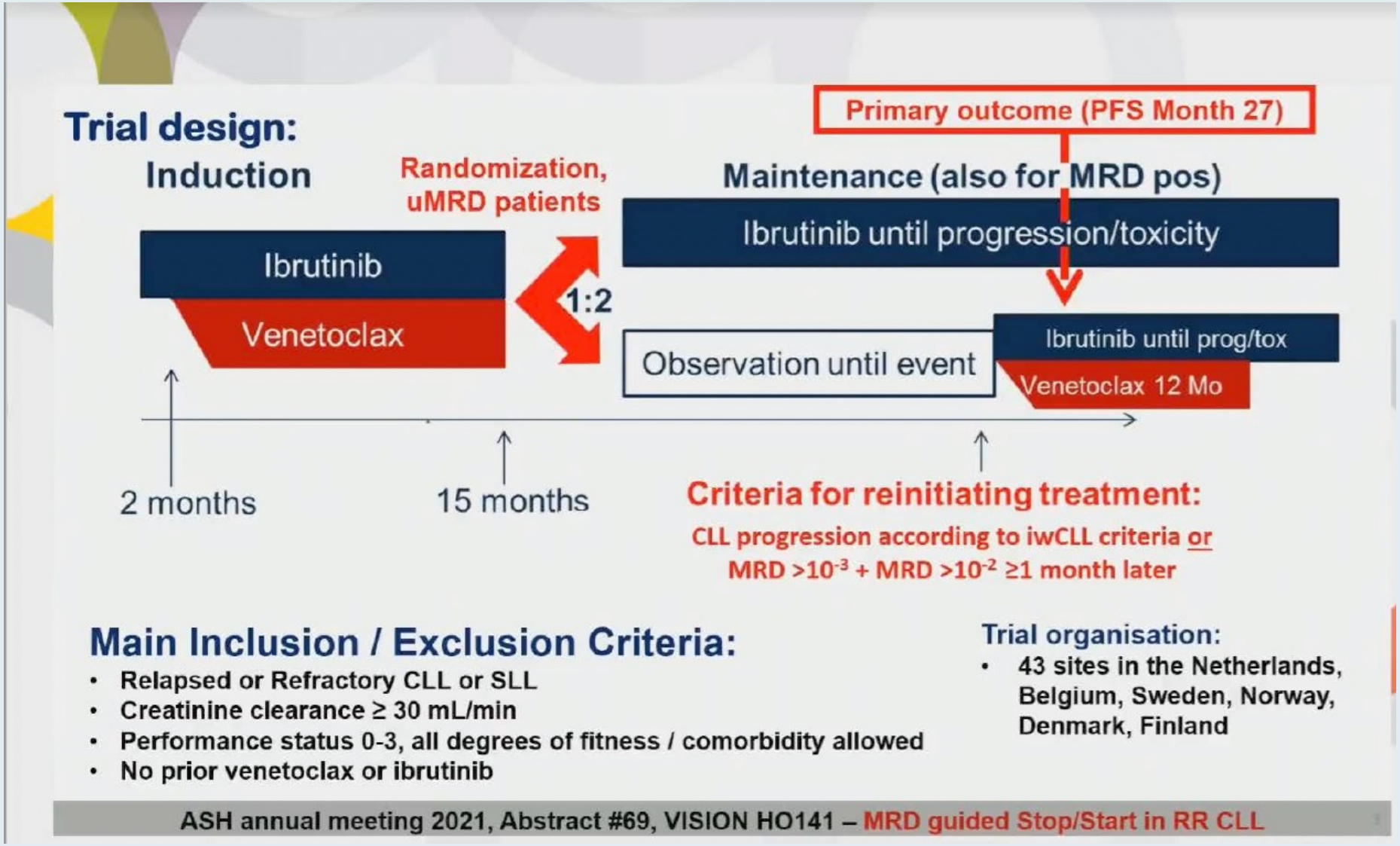
Kater A et al. EHA 2021;Abstract LB1902.

Time-limited Venetoclax and Ibrutinib for Patients with Relapsed/Refractory Chronic Lymphocytic Leukemia (RR CLL) who have Undetectable Minimal Residual Disease (uMRD) – Primary Analysis from the Randomized Phase 2 VISION HO141 Trial

MRD guided Stop / Start in RR CLL

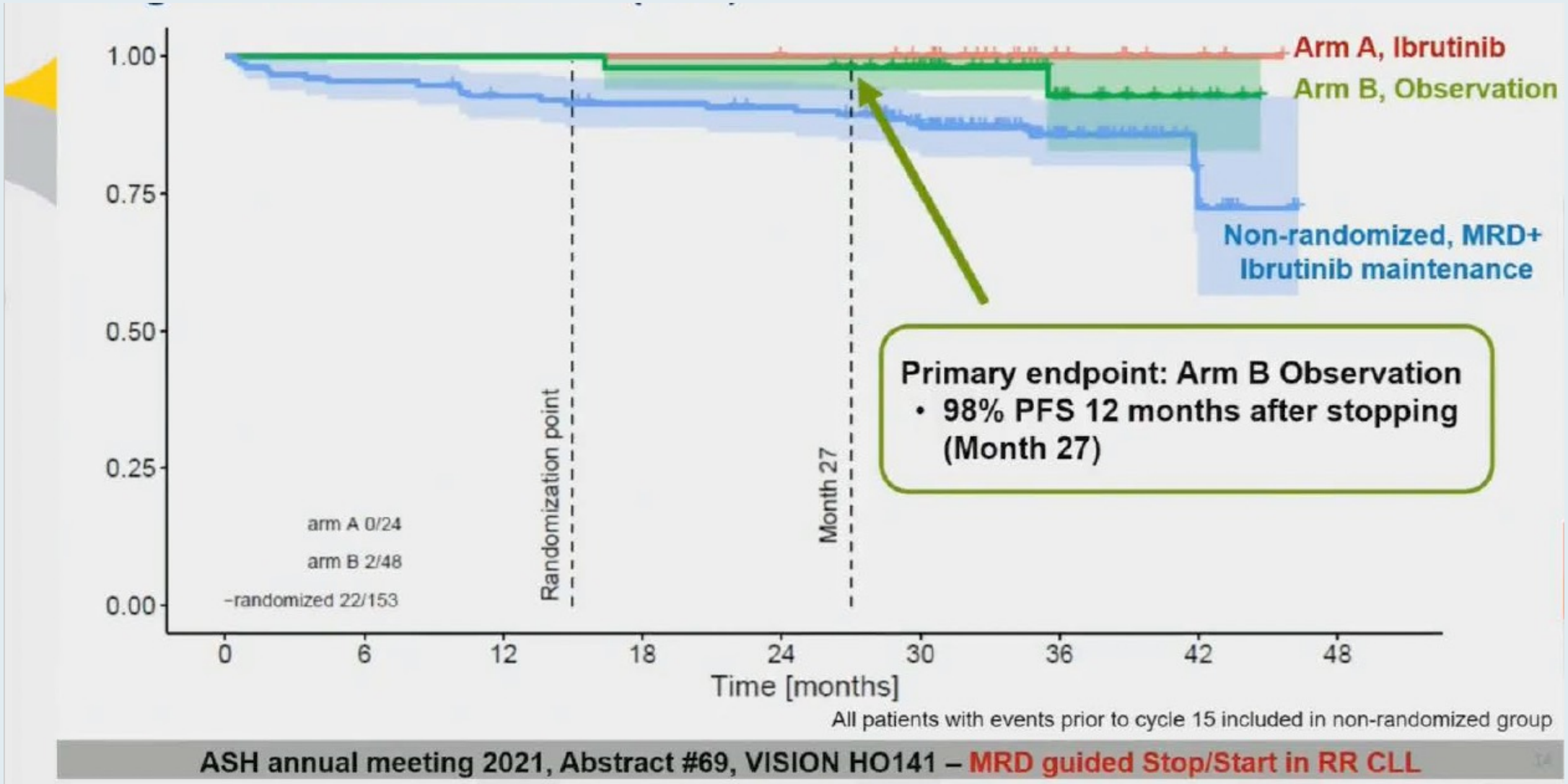
Carsten U Niemann, Julie Dubois, Christian Brieghel, Sabina Kersting, Lisbeth Enggaard, Gerrit J. Veldhuis, Rogier Mous, Clemens HM Mellink, Johan A Dobber, Christian B Poulsen, Henrik Frederiksen, Ann Janssens, Ida Schjødt, Ellen C Dompeling, Juha Ranti, Mattias Mattsson, Mar Bellido, Hoa TT Tran, Kazem Nasserinejad, Mark-David Levin, **Arnon P Kater**

VISION H0141 Study Schema



Niemann CU et al. ASH 2021;Abstract 69.

VISION H0141: Progression-Free Survival



ASH annual meeting 2021, Abstract #69, VISION HO141 – MRD guided Stop/Start in RR CLL

Selection of BTK Inhibitor

original reports

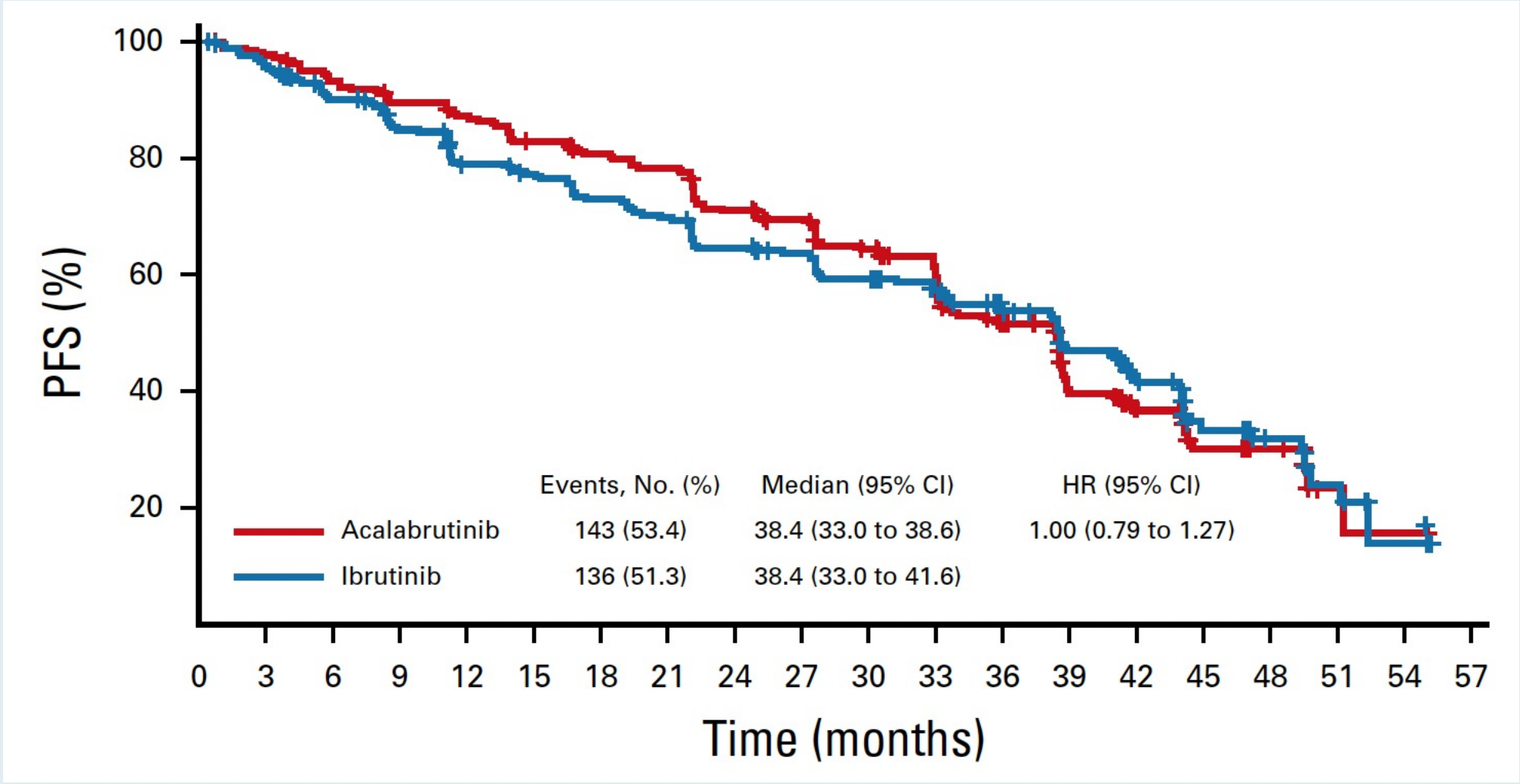
Acalabrutinib Versus Ibrutinib in Previously Treated Chronic Lymphocytic Leukemia: Results of the First Randomized Phase III Trial

John C. Byrd, MD[1]; Peter Hillmen, MD, MBChB, PhD[2]; Paolo Ghia, MD, PhD[3,4]; Arnon P. Kater, MD, PhD[5]; Asher Chanan-Khan, MD[6]; Richard R. Furman, MD[7]; Susan O'Brien, MD[8]; Mustafa Nuri Yenerel, MD[9]; Arpad Illés, MD[10]; Neil Kay, MD[11]; Jose A. Garcia-Marco, MD, PhD[12]; Anthony Mato, MD[13]; Javier Pinilla-Ibarz, MD, PhD[14]; John F. Seymour, PhD[15]; Stephane Lepretre, MD[16,17]; Stephan Stilgenbauer, MD[18]; Tadeusz Robak, PhD[19]; Wayne Rothbaum, MS[20]; Raquel Izumi, PhD[20]; Ahmed Hamdy, MD[20]; Priti Patel, MD[21]; Kara Higgins, MS[21]; Sophia Sohoni, MD[21]; and Wojciech Jurczak, MD, PhD[22]

J Clin Oncol 2021;39(31):3441-52.

RTP RESEARCH TO PRACTICE

ELEVATE-RR: Independent Review Committee-Assessed PFS



Byrd JC et al. *J Clin Oncol* 2021;39(31):3441-52.

ELEVATE-RR: Characterization of Adverse Events with Acalabrutinib versus Ibrutinib

	Incidence, %				Exposure-Adjusted Incidence[b]				Exposure-Adjusted Time With Event[c]			
	Any grade		Grade ≥3		Any grade		Grade ≥3		Any grade		Grade ≥3	
	Acala[d]	Ibru[e]	Acala[d]	Ibru[e]	Acala[d]	Ibru[e]	Acala[d]	Ibru[e]	Acala[d]	Ibru[e]	Acala[d]	Ibru[e]
ECIs												
Cardiac events	24%	30%	9%	10%	1.2	1.9	0.4	0.5	7.1	13.0	0.4	0.2
Afib/flutter	9%	**16%***	5%	4%	0.4	0.7	0.2	0.1	1.3	3.8	0.3	0.1
HTN[f]	9%	**23%***	4%	**9%***	0.4	1.2	0.1	0.4	4.1	15.0	1.6	4.0
Bleeding events[g]	38%	**51%***	4%	5%	2.4	3.8	0.1	0.2	13.7	24.6	0.1	0.1
Major bleeding events[h]	5%[i]	5%[j]	4%	5%	0.2	0.2	0.1	0.2	0.1	0.3	0.1	0.1
Infections[k]	78%	81%	31%	30%	8.9	10.4	1.6	2.0	14.6	15.6	1.5	1.1
Selected Common AEs (preferred term)												
Diarrhea	35%	**46%***	1%	**5%***	1.9	2.8	<0.1	0.2	6.7	9.6	<0.1	0.1
Headache	**35%***	20%	**2%***	0	1.8	1.1	<0.1	0	7.8	5.4	<0.1	0
Cough	**29%***	21%	1%	<1%	1.3	1.1	<0.1	<0.1	5.6	4.9	<0.1	<0.1
Fatigue	20%	17%	**3%***	0%	0.9	0.9	0.1	0	7.4	7.0	0.6	0
Arthralgia	16%	**23%***	0	1%	0.6	1.3	0	<0.1	7.5	10.4	0	<0.1
Back pain	8%	**13%***	0	1%	0.3	0.5	0	<0.1	1.9	3.2	0	0.1
Muscle spasms	6%	**13%***	0	1%	0.2	0.7	0	<0.1	0.8	10.0	0	0.1
Dyspepsia	4%	**12%***	0	0	0.1	0.5	0	0	1.0	2.4	0	0

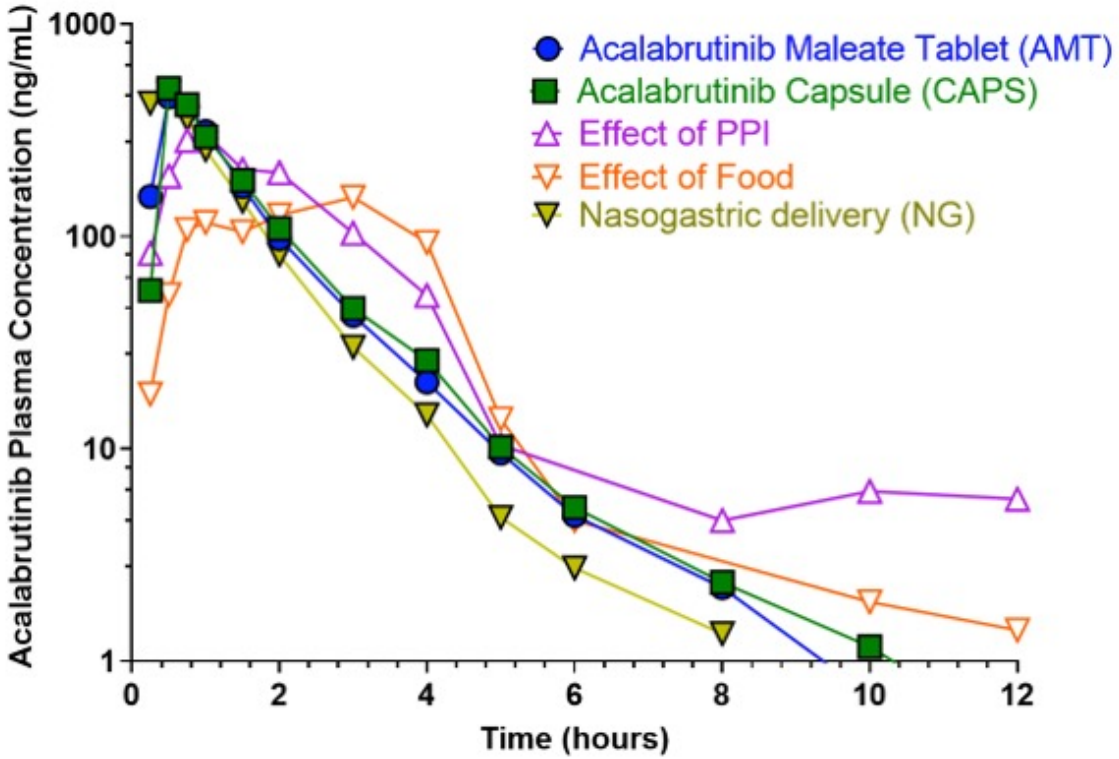
Seymour JF et al. ASH 2021;Abstract 3721.

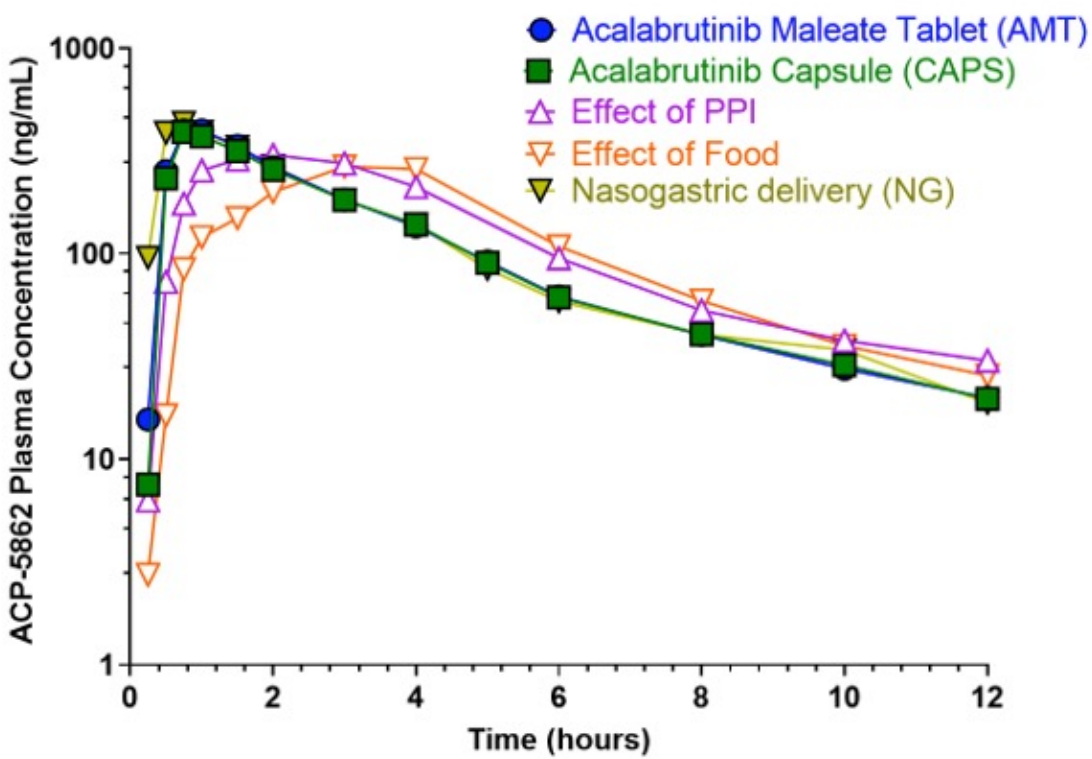
New Acalabrutinib Formulation Enables Co-Administration with Proton Pump Inhibitors and Dosing in Patients Unable to Swallow Capsules (ELEVATE-PLUS)

Sharma S et al. ASH 2021;Abstract 4365.

Author Conclusions: Acalabrutinib maleate, administered as a tablet or suspension, is safe and well tolerated. Based on the PK (and associated variability), BTK-TO, and established exposure-efficacy/safety relationship, AMT clinical effect is expected to be comparable to acalabrutinib capsules at the approved 100-mg BID dosing, regardless of use of PPIs and ingestion of food. Additionally, AMT improves swallowing ability given the film coating and a 50% reduced volume compared with the capsule, and can be easily suspended in a small amount of water to allow dosing in patients unable to swallow tablets.

ELEVATE-PLUS: Pharmacokinetic Profiles of Acalabrutinib and Its Major Pharmacologically Active Metabolite Across 3 Clinical Trials





Sharma S et al. ASH 2021;Abstract 4365.

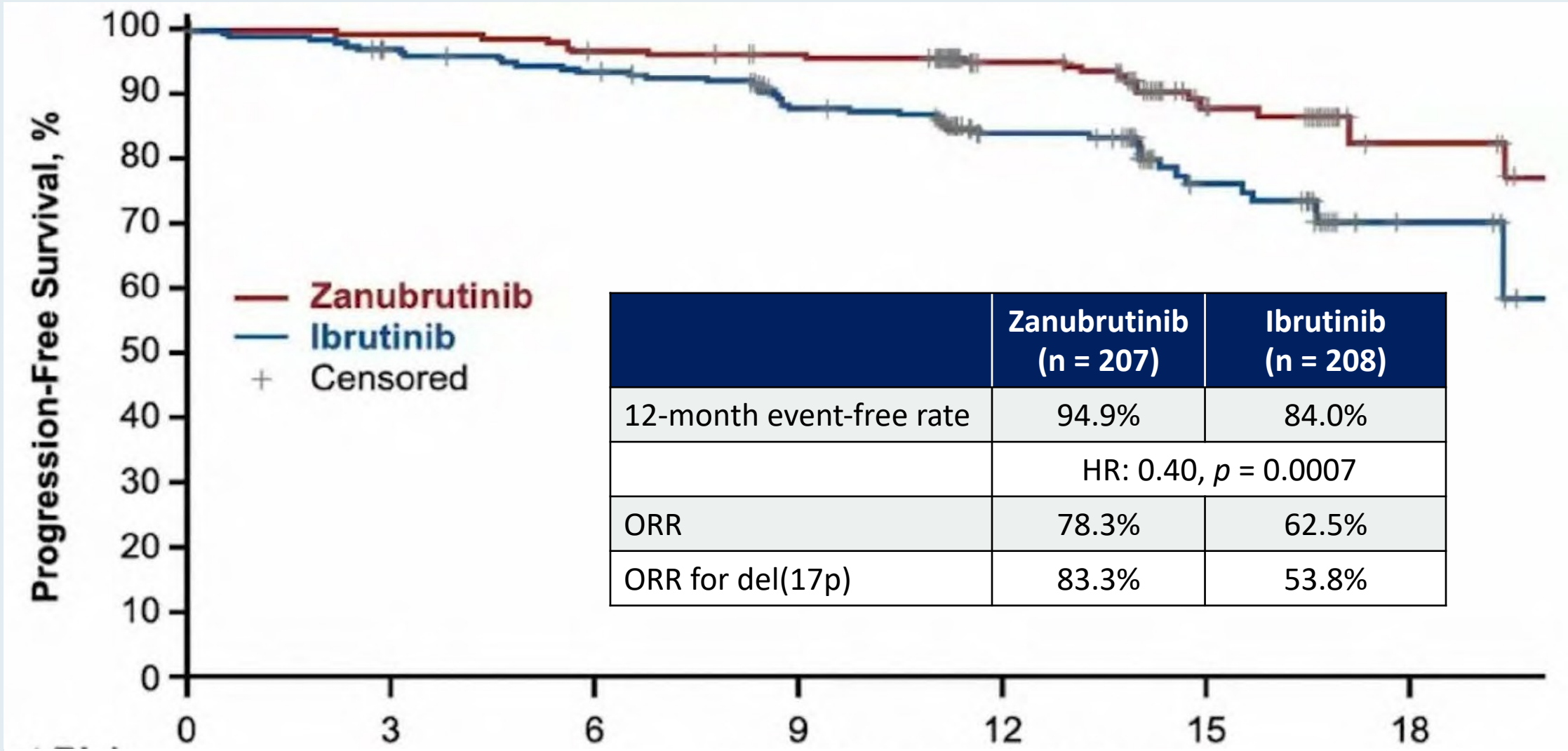
RTP RESEARCH TO PRACTICE

First Interim Analysis of ALPINE Study: Results of a Phase 3 Randomized Study of Zanubrutinib vs Ibrutinib in Patients with Relapsed/Refractory Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma

Hillmen P et al.

EHA 2021;Abstract LBA1900.

ALPINE: Response and Investigator-Assessed PFS



	Zanubrutinib (n = 207)	Ibrutinib (n = 208)
12-month event-free rate	94.9%	84.0%
	HR: 0.40, *p* = 0.0007	
ORR	78.3%	62.5%
ORR for del(17p)	83.3%	53.8%

Hillmen P et al. EHA 2021;Abstract LBA1900.

ALPINE: Adverse Events of Special Interest

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

Hillmen P et al. EHA 2021;Abstract LBA1900.

Relapsed/Refractory CLL

Blood 2021;138(10):836-46.

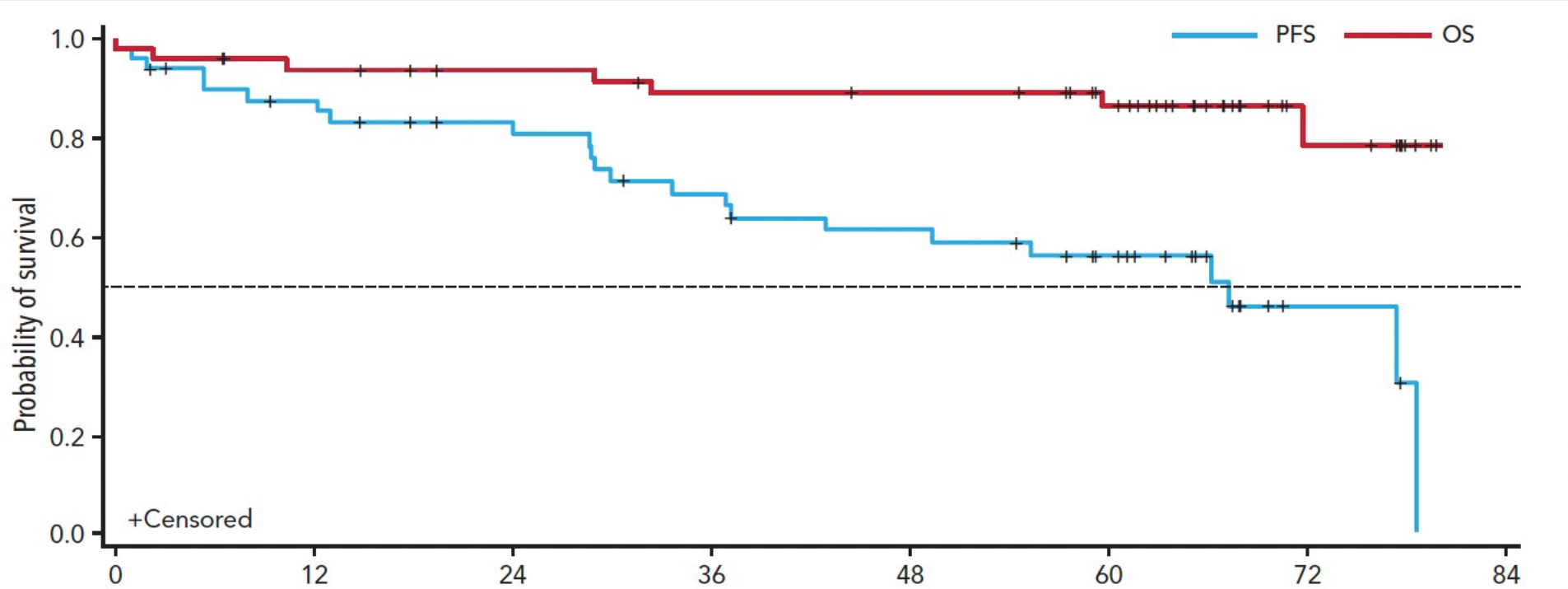
Regular Article

CLINICAL TRIALS AND OBSERVATIONS

Efficacy of venetoclax plus rituximab for relapsed CLL: 5-year follow-up of continuous or limited-duration therapy

Shuo Ma,[1,*] John F. Seymour,[2,3,*] Danielle M. Brander,[4] Thomas J. Kipps,[5] Michael Y. Choi,[5] Mary Ann Anderson,[2,3,6] Kathryn Humphrey,[7] Abdullah Al Masud,[8] John Pesko,[8] Ruby Nandam,[8] Ahmed Hamed Salem,[8,9] Brenda Chyla,[8] Jennifer Arzt,[8] Amanda Jacobson,[8] Su Young Kim,[8] and Andrew W. Roberts[2,3,6]

MURANO 5-Year Follow-Up: Overall and Progression-Free Survival (All Patients)



Patients at risk

PFS	49	40	34	28	24	18	3	0
OS	49	44	41	38	37	31	10	0

Survival estimate (95% CI)

	Events	Month 24	Month 36	Month 60	Month 72	Median months (95% CI)
PFS (N = 49)	23	80.7% (66.2–89.5)	68.8% (52.9–80.3)	56.1% (39.9–69.5)	45.9% (27.8–62.2)	67.3 (37.1–78.6)
OS (N = 49)	7	93.8% (82.0–98.0)	89.2% (75.8–95.3)	86.4% (71.9–93.7)	78.5% (54.7–90.8)	NR (NR–NR)

Ma S et al. *Blood* 2021;138(10):836-46.

RTP RESEARCH TO PRACTICE

MURANO 5-Year Follow-Up: Durability of Benefit in Deep Responders (CR or uMRD Response)

	Continuous Ven (n = 14)	Limited-duration Ven* (n = 19)	All deep responders (n = 33)
Median time on Ven, y (range)	5.6 (2.4-6.6)	1.4 (0.4-4.2)	3.1 (0.5-6.6)
PFS†			
Median, y (95% CI)	6.6 (4.6-6.6)	6.5 (3.6-6.5)	6.5 (5.5-6.6)
3-y estimate (95% CI)	92.9% (59.1-99.0)	87.1% (57.3-96.6)	89.9% (71.8-96.6)
5-y estimate (95% CI)	78.6% (47.2-92.5)	79.8% (49.4-93.0)	79.1% (59.1-90.0)
Duration of response†			
Median, y (95% CI)	6.3 (4.4-6.3)	6.2 (3.4-6.2)	6.2 (5.4-6.3)
3-y estimate (95% CI)	85.7% (53.9-96.2)	86.7% (56.4-96.5)	86.2% (67.2-94.6)
5-y estimate (95% CI)	70.7% (39.4-87.9)	79.4% (48.8-92.9)	73.9% (52.4-86.8)

CR = complete response; uMRD = undetectable minimal residual disease

Ma S et al. *Blood* 2021;138(10):836-46.

MURANO: Grade 3 or 4 Treatment-Emergent Adverse Events (AEs) Within and Beyond 2 Years of Treatment

AE preferred term	Within the first 2 y of treatment; all patients, N = 49*	After 2 y of treatment; all patients n = 21†
Grade 3/4 (≥5% of total patients), n (%)	40 (82)	11 (52)
Neutropenia	26 (53)	4 (19)‡
Thrombocytopenia	8 (16)	1 (5)
Anemia	7 (14)	0
Leukopenia	7 (14)	3 (14)
Febrile neutropenia	5 (10)	0
Decreased neutrophil count	4 (8)	0
Lower respiratory tract infection	3 (6)	1 (5)
Lymphopenia	3 (6)	0
Pneumonia	3 (6)	1 (5)
Pyrexia	3 (6)	1 (5)

Ma S et al. *Blood* 2021;138(10):836-46.

MURANO: Serious AEs Within and Beyond 2 Years of Treatment

AE preferred term	Within the first 2 y of treatment; all patients, N = 49*	After 2 y of treatment; all patients n = 21†
SAEs (>2% of total patients), n (%)	28 (57)	9 (43)
Pyrexia	5 (10)	1 (5)
Febrile neutropenia	4 (8)	0
Pneumonia	4 (8)	2 (10)
Lower respiratory tract infection	3 (6)	1 (5)
Diarrhea	2 (4)	1 (5)
Infusion-related reaction	2 (4)	0
Osteoarthritis	2 (4)	2 (10)
Tumor lysis syndrome	2 (4)	0

Ma S et al. *Blood* 2021;138(10):836-46.

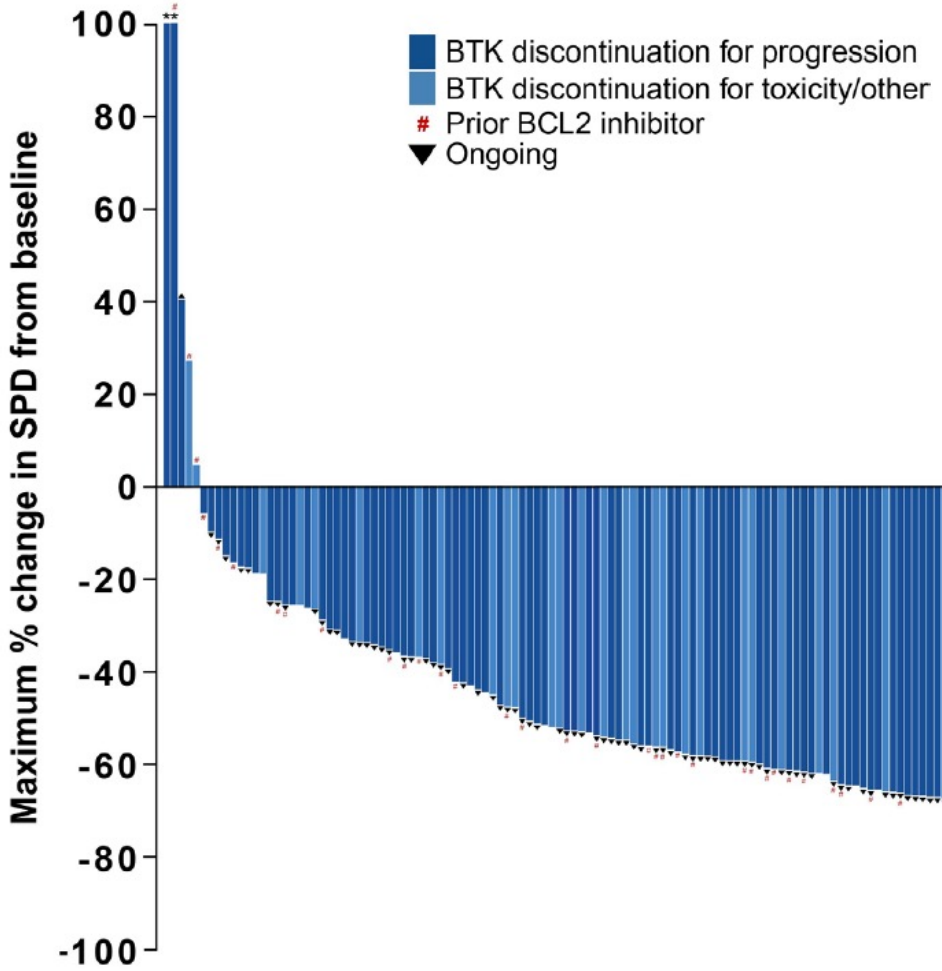
Novel Strategies Under Investigation

Pirtobrutinib, a Next Generation, Highly Selective, Non-Covalent BTK Inhibitor in Previously Treated CLL/SLL: Updated Results from the Phase 1/2 BRUIN Study

Mato AR et al.

ASH 2021;Abstract 391.

BRUIN: Pirtobrutinib Efficacy in Patients with BTK-Pretreated CLL or Small Lymphocytic Lymphoma (SLL)



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

Mato AR et al. ASH 2021;Abstract 391.

RTP RESEARCH TO PRACTICE

BRUIN: Pirtobrutinib Safety Profile

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

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

Mato AR et al. ASH 2021;Abstract 391.

FDA Has Placed a Partial Clinical Hold on Some Combination Candidate Studies for Leukemia and Lymphoma

Press Release: January 27, 2022

The FDA placed partial holds on studies of the U2 combination umbralisib and ublituximab for chronic lymphocytic leukemia (CLL) and non-Hodgkin lymphoma (NHL).

The updated overall survival (OS) preliminary results from the UNITY-CLL study showed improvement. The OS hazard ratio was 1.23, and, including COVID-19-related deaths, the ratio reached 1.04.

An OS hazard ratio above 1.00 implies a risk that the investigational therapy might be causing harm.

No new patients can be enrolled in some CLL and NHL trials, but those deriving a benefit may continue with consent.

https://www.yahoo.com/now/tg-therapeutics-falls-30-ceo-173034141.html

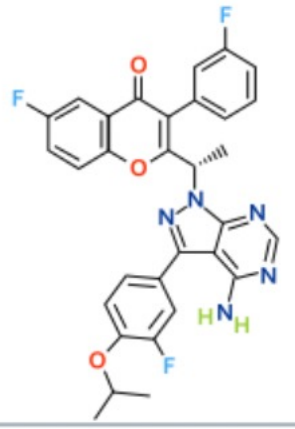
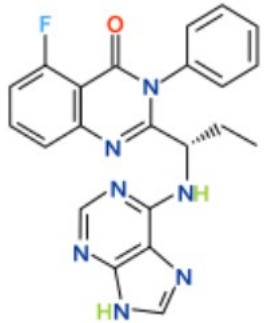
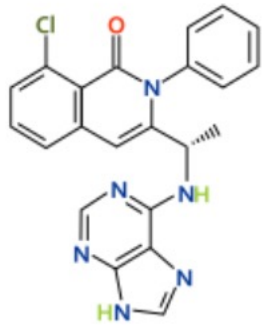
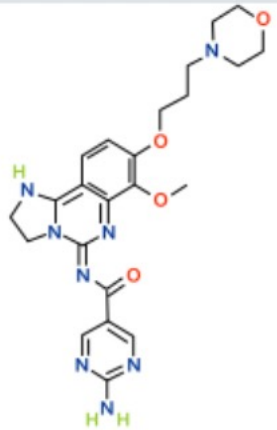
RTP RESEARCH TO PRACTICE

Efficacy and Safety of Ublituximab in Combination with Umbralisib (U2) in Patients with Chronic Lymphocytic Leukemia (CLL) By Treatment Status: A Sub-Analysis of the Phase 3 Unity-CLL Study

Jacobs R et al.

ASH 2021;Abstract 3726.

Umbralisib: A Selective Inhibitor of PI3Kδ and CK1ε

	Umbralisib[1]	Idelalisib[1]	Duvelisib[1]	Copanlisib[2]
				
Isoform	**K_d (nM)**			
PI3kα	>10000	600	40	0.04
PI3Kβ	>10000	19	0.89	1.5
PI3Kγ	1400	9.1	0.21	0.31
PI3Kδ	6.2	1.2	0.047	0.068
CK1ε	180	>30,000	>30,000	>6,000

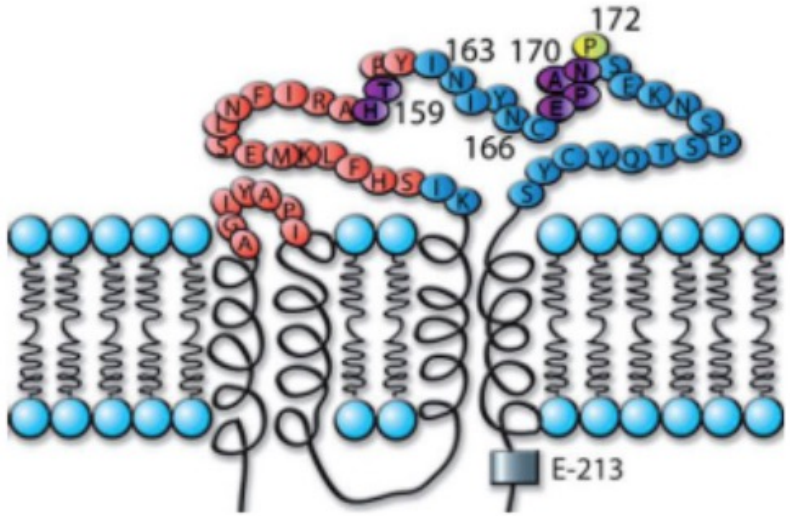
- Umbralisib is an oral, once daily, selective inhibitor of PI3Kδ and CK1ε
- Umbralisib has >1000-fold greater selectivity for PI3Kδ compared to α and β isoforms
- Umbralisib is also **>200-fold** more selective for PI3Kδ relative to **PI3Kγ**

Jacobs R et al. ASH 2021;Abstract 3726.

Ublituximab: A Novel Glycoengineered Anti-CD20 Monoclonal Antibody

- Ublituximab (TG-1101, UTX) is a novel, glycoengineered, Type I, anti-CD20 monoclonal antibody with several defining features:
  - Targets a unique epitope on the CD20 antigen
  - Type I maintains complement-dependent cytotoxicity (CDC)
  - Glycoengineered to enhance affinity for all variants of FcγRIIIa receptors, thereby demonstrating greater antibody-dependent cellular cytotoxicity (ADCC) activity than rituximab and ofatumumab, including in 17p deleted CLL cells[1]

Ublituximab



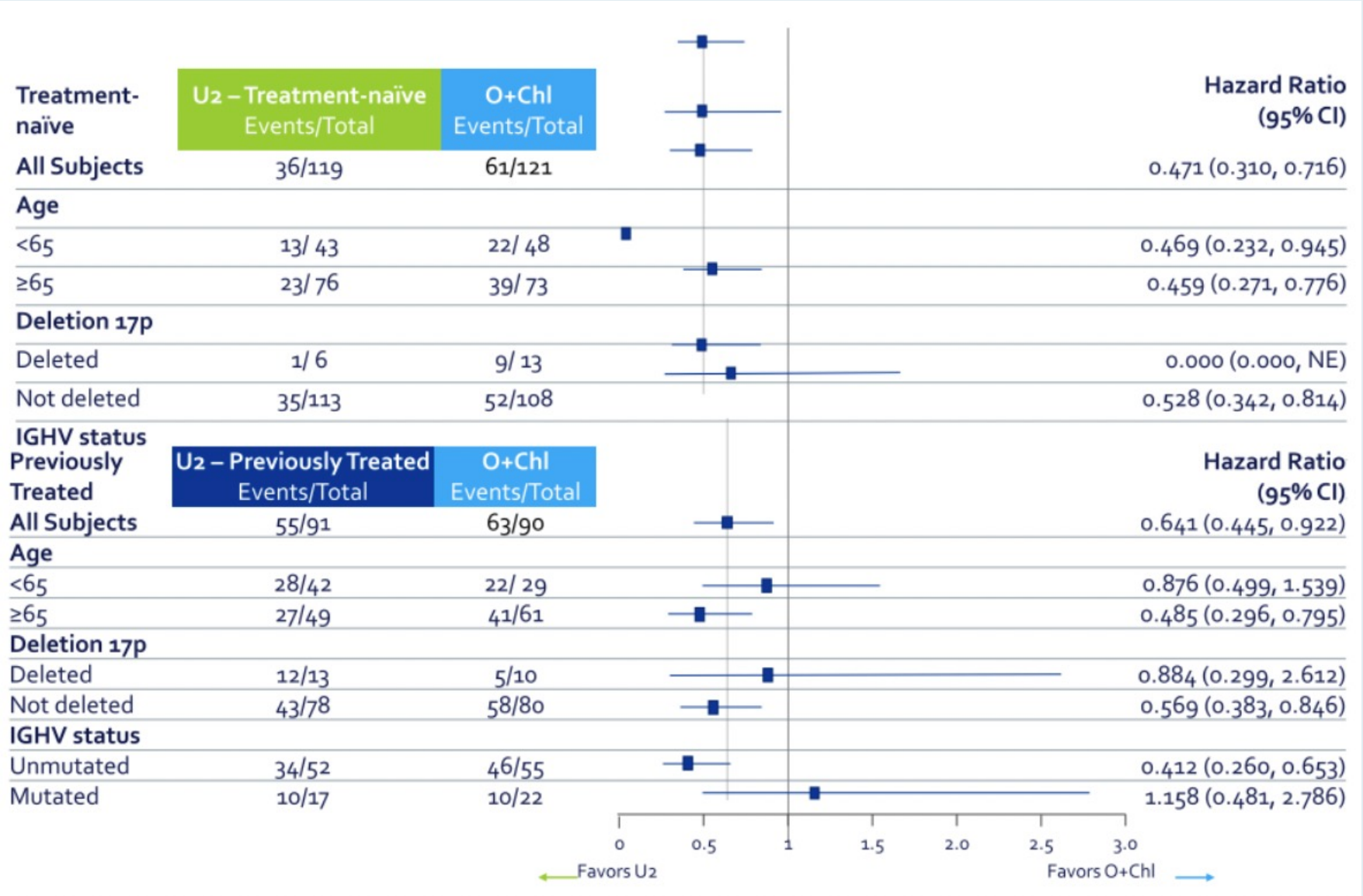
Red: Key ofatumumab epitope amino acids
Purple: Core amino acids of ublituximab epitope

Figure adapted from Ruuls et al, 2008[2]

Jacobs R et al. ASH 2021;Abstract 3726.

RTP RESEARCH TO PRACTICE

UNITY-CLL: IRC-Assessed PFS by Treatment Status



Jacobs R et al. ASH 2021;Abstract 3726.

UNITY-CLL: Adverse Events (AEs) of Clinical Interest

AEs, n (%)	Treatment-naïve N=116			Previously Treated N=90		
	Any	Grade ≥3	Discontinued U2[b]	Any	Grade ≥3	Discontinued U2[b]
ALT elevation	27 (23)	14 (12)	3 (3)	8 (9)	3 (3)	-
AST elevation	21 (18)	9 (8)	3 (3)	7 (8)	2 (2)	-
Rash[a]	17 (15)	4 (3)	1 (1)	9 (10)	1 (1)	1 (1)
Pneumonia	14 (12)	8 (7)	1 (1)	18 (20)	10 (11)	1 (1)
Colitis (non-infectious)[a]	8 (7)	3 (3)	-	2 (2)	1 (1)	1 (1)
Pneumonitis	4 (3)	1 (1)	2 (2)	2 (2)	-	1 (1)
Opportunistic infections[a]	3 (3)	1 (1)	1 (1)	3 (3)	1 (1)	-

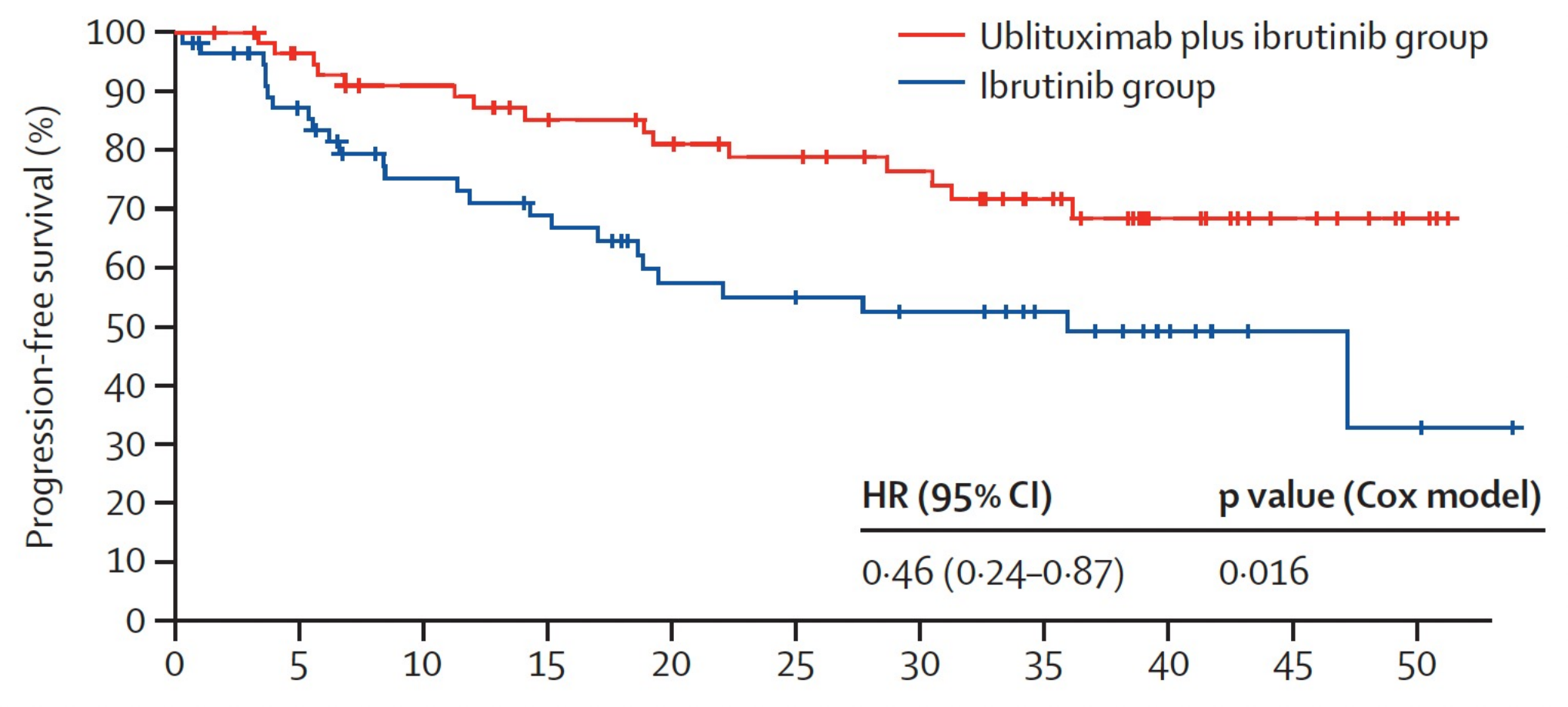
Jacobs R et al. ASH 2021;Abstract 3726.

Lancet Haematol 2021;8:e254-66.

Ublituximab plus ibrutinib versus ibrutinib alone for patients with relapsed or refractory high-risk chronic lymphocytic leukaemia (GENUINE): a phase 3, multicentre, open-label, randomised trial

Jeff P Sharman, Danielle M Brander, Anthony R Mato, Nilanjan Ghosh, Stephen J Schuster, Suman Kambhampati, John M Burke, Frederick Lansigan, Marshall T Schreeder, Scott D Lunin, Alexander Zweibach, Mikhail Shtivelband, Patrick M Travis, Jason C Chandler, Kathryn S Kolibaba, Peter Sportelli, Hari P Miskin, Michael S Weiss, Ian W Flinn

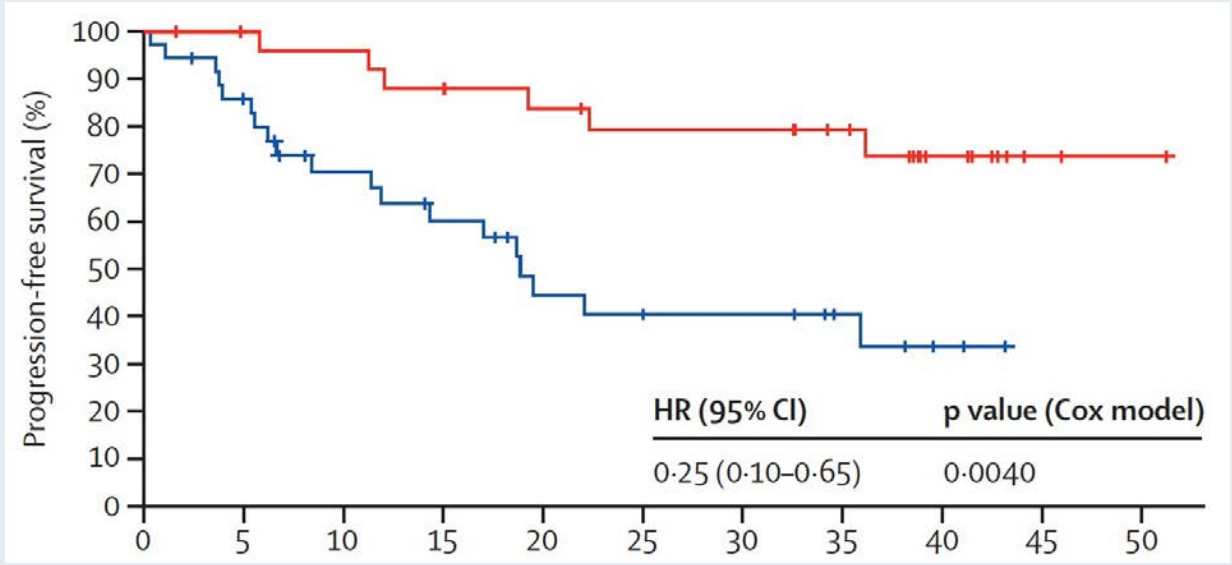
GENUINE: Progression-Free Survival (All Patients)



Sharman JP et al. *Lancet Haematol* 2021;8:e254-56.

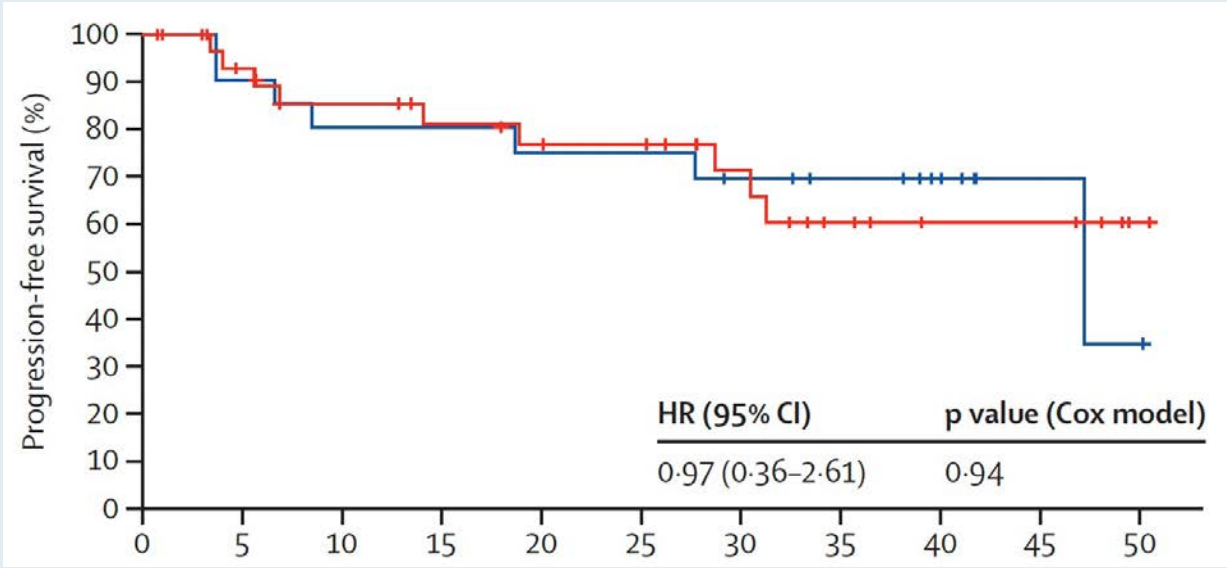
GENUINE: Progression-Free Survival in Subgroups

Patients with 17p deletion, *TP* mutation, or both



Time since randomization (months)

Patients with 11q deletion



Time since randomization (months)

Sharman JP et al. *Lancet Haematol* 2021;8:e254-56.

RTP RESEARCH TO PRACTICE

Nature 2022;[Online ahead of print].

Article

Decade-long leukaemia remissions with persistence of CD4$^+$ CAR T cells

https://doi.org/10.1038/s41586-021-04390-6

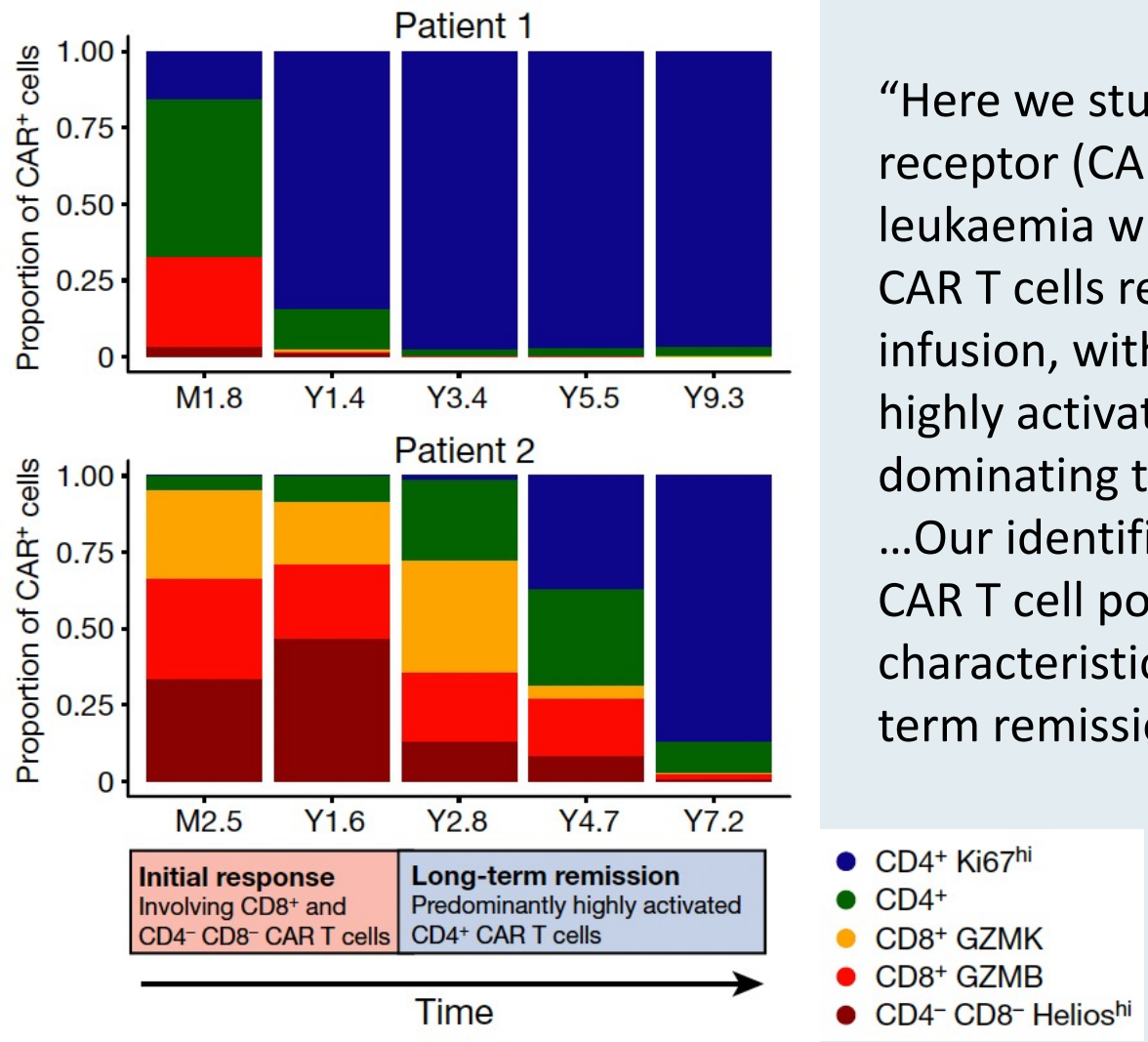
Received: 7 May 2021

Accepted: 29 December 2021

Published online: 02 February 2022

J. Joseph Melenhorst[1,2,3,4,5,15,16]✉, Gregory M. Chen[6,15], Meng Wang[1,2,3,14], David L. Porter[3,7,15], Changya Chen[8,9], McKensie A. Collins[1,2,3,10], Peng Gao[8,9], Shovik Bandyopadhyay[10], Hongxing Sun[1,2,3], Ziran Zhao[1,2,3], Stefan Lundh[1,2,3], Iulian Pruteanu-Malinici[11], Christopher L. Nobles[12], Sayantan Maji[1,2,3], Noelle V. Frey[3], Saar I. Gill[3], Lifeng Tian[1,3], Irina Kulikovskaya[1,2,3], Minnal Gupta[1,2,3], David E. Ambrose[1,2,3], Megan M. Davis[1,2,3], Joseph A. Fraietta[1,2,3,12], Jennifer L. Brogdon[11], Regina M. Young[1,2,3], Anne Chew[1,2,3], Bruce L. Levine[1,2,3], Donald L. Siegel[1,2,13], Cécile Alanio[4,5,14], E. John Wherry[4,5,14], Frederic D. Bushman[12], Simon F. Lacey[1,2,3], Kai Tan[2,4,6,9,10,16]✉ & Carl H. June[1,2,3,4,5,16]✉

Analysis of CD3+ CAR+ T Cells Using CyTOF Across Multiple Time Points



"Here we studied long-lasting CD19-redirected chimeric antigen receptor (CAR) T cells in two patients with chronic lymphocytic leukaemia who achieved a complete remission in 2010. CAR T cells remained detectable more than ten years after infusion, with sustained remission in both patients. Notably, a highly activated CD4+ population emerged in both patients, dominating the CAR T cell population at the later time points… …Our identification and characterization of these unexpected CAR T cell populations provide novel insight into the CAR T cell characteristics associated with anti-cancer response and long-term remission in leukaemia."

Melenhorst JJ et al. *Nature* 2022;[Online ahead of print].

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American Society of Hematology
2021 L Street NW, Suite 900,
Washington, DC 20036
Phone: 202-776-0544 | Fax 202-776-0545
editorial@hematology.org

Blood 2021;[Online ahead of print].

Phase 1 TRANSCEND CLL 004 study of lisocabtagene maraleucel in patients with relapsed/refractory CLL or SLL

Tracking no: BLD-2021-011895R2

Tanya Siddiqi (City of Hope Medical Center, United States) Jacob Soumerai (Massachusetts General Hospital Cancer Center, United States) Kathleen Dorritie (UPMC, United States) Deborah Stephens (University of Utah, United States) Peter Riedell (University of Chicago, United States) Jon Arnason (BIDMC, United States) Thomas Kipps (University of California-San Diego School of Medicine, United States) Heidi Gillenwater (Bristol Myers Squibb, United States) Lucy Gong (Bristol Myers Squibb, United States) Lin Yang (Bristol Myers Squibb, United States) Ken Ogasawara (Bristol Myers Squibb, United States) Jerill Thorpe (Bristol Myers Squibb, United States) William Wierda (University of Texas M.D. Anderson Cancer Center, United States)

TRANSCEND CLL 004: Rates of Cytokine Release Syndrome (CRS), Neurologic Events (NE) and Rehospitalization After Liso-cel Infusion

	All patients (N = 23)	Dose level 1 50×10^6 (n = 9)	Dose level 2 100×10^6 (n = 14)
CRS any grade	17 (74%)	7 (78%)	10 (71%)
CRS Grade ≥3	2 (9%)	0	2 (14%)
NE any grade	9 (39%)	2 (22%)	7 (50%)
NE Grade ≥3	5 (21%)	2 (22%)	2 (14%)
Reasons for patient rehospitalization			
Adverse events	11 (48%)	3 (33%)	8 (57%)
CRS and/or NE	5 (22%)	1 (11%)	4 (29%)
CRS and NE	2 (9%)	0	2 (14%)
NE only	3 (13%)	1 (11%)	2 (14%)

Siddiqi T et al. *Blood* 2021;[Online ahead of print].

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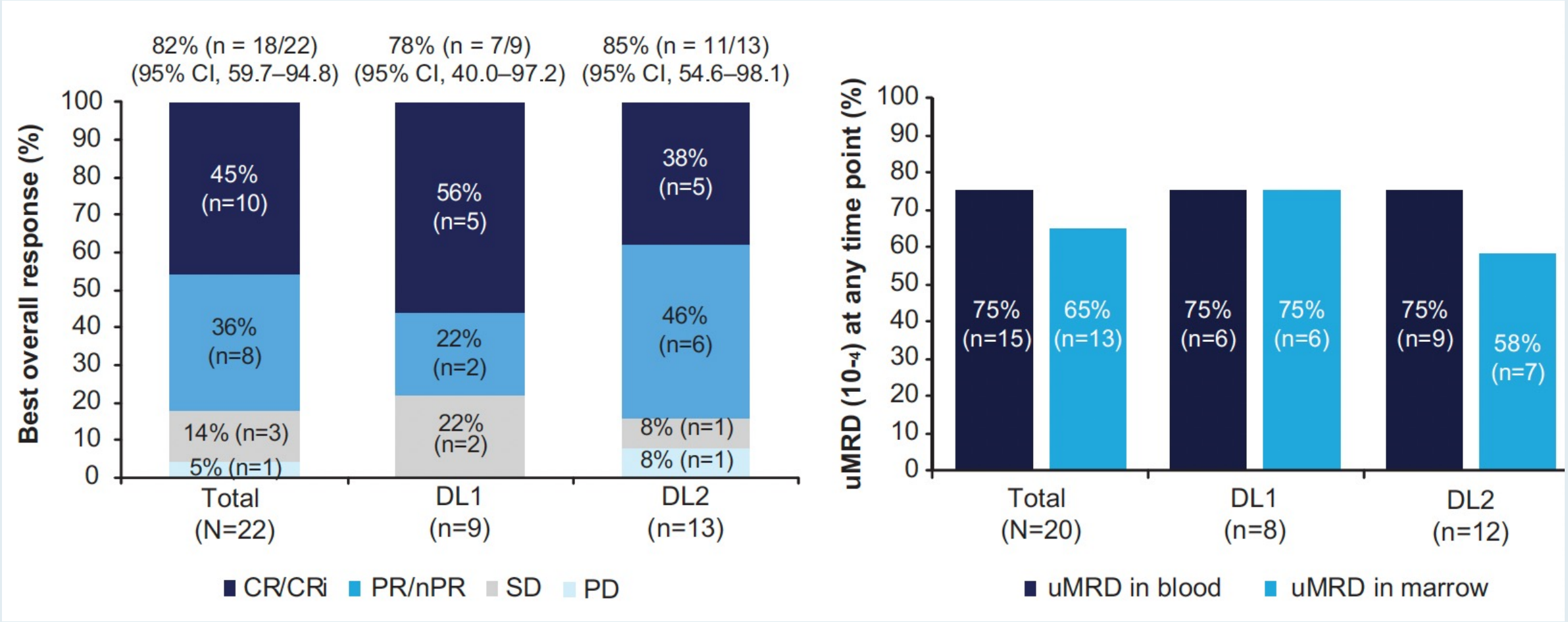
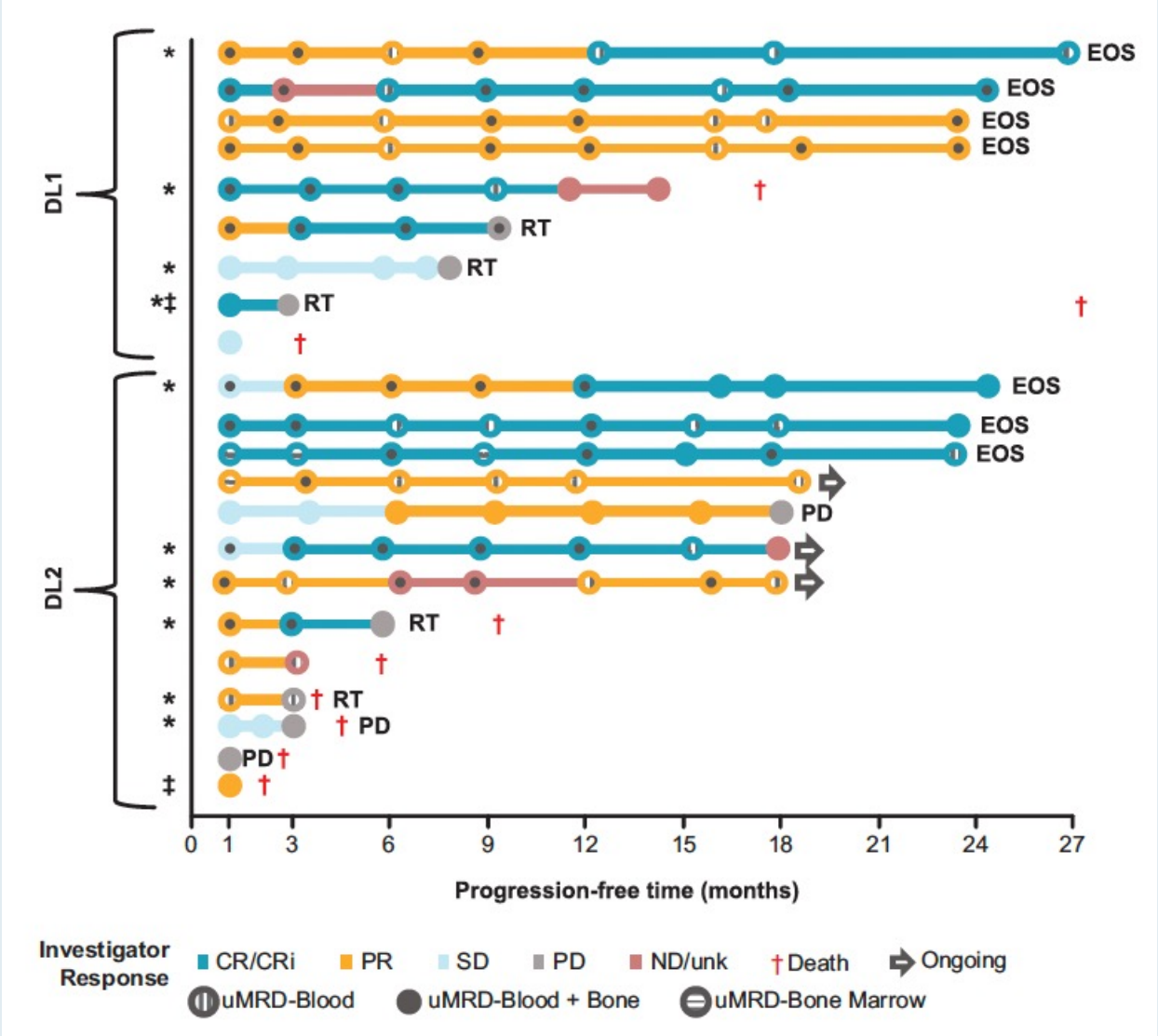
TRANSCEND CLL 004: Response and uMRD (10^{-4}) Rates



Siddiqi T et al. *Blood* 2021;[Online ahead of print].

TRANSCEND CLL 004: Swim Lane Plot, Duration of Response and PFS



Siddiqi T et al. *Blood* 2021;[Online ahead of print].

Meet The Professor

Non-Small Cell Lung Cancer with an Actionable Target Beyond EGFR

Monday, April 18, 2022
5:00 PM – 6:00 PM ET

Faculty

D Ross Camidge, MD, PhD

Special Topics

- **ALK+ NSCLC: First-line treatment, resistance mutations**

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RESEARCH
TO PRACTICE

What I Tell My Patients: Expert Insights into Patient Education on New Treatments and Clinical Trial Participation

A Complimentary NCPD Hybrid Symposium Series Held During the 47th Annual ONS Congress

Prostate Cancer

Thursday, April 28, 2022
6:00 AM – 7:30 AM PT (9:00 AM – 10:30 AM ET)

Faculty
Kathy D Burns, RN, MSN, AGACNP-BC, OCN
Robert Dreicer, MD, MS
Sandy Srinivas, MD
Ronald Stein, JD, MSN, NP-C, AOCNP

Non-Small Cell Lung Cancer

Thursday, April 28, 2022
6:00 PM – 8:00 PM PT (9:00 PM – 11:00 PM ET)

Faculty
Edward B Garon, MD, MS
Kelly EH Goodwin, MSN, RN, ANP-BC
Tara Plues, APRN, MSN
Anne S Tsao, MD, MBA

Ovarian Cancer

Thursday, April 28, 2022
12:15 PM – 1:45 PM PT (3:15 PM – 4:45 PM ET)

Faculty
Jennifer Filipi, MSN, NP
Kathleen N Moore, MD, MS
Krishnansu S Tewari, MD
Deborah Wright, MSN, APRN, AGCNS-BC

Hepatobiliary Cancers

Thursday, April 28, 2022
8:20 PM – 9:20 PM PT (11:20 PM – 12:20 AM ET)

Faculty
Richard S Finn, MD
Amanda K Wagner, APRN-CNP, AOCNP

What I Tell My Patients: Expert Insights into Patient Education on New Treatments and Clinical Trial Participation

A Complimentary NCPD Hybrid Symposium Series Held During the 47th Annual ONS Congress

Small Cell Lung Cancer

Friday, April 29, 2022
6:00 AM – 7:30 AM PT (9:00 AM – 10:30 AM ET)

Faculty
Marianne J Davies, DNP, MSN, RN, APRN
Matthew Gubens, MD, MS
Lowell L Hart, MD
Chaely J Medley, MSN, AGNP

Breast Cancer

Friday, April 29, 2022
6:00 PM – 8:00 PM PT (9:00 PM – 11:00 PM ET)

Faculty
Jamie Carroll, APRN, MSN, CNP
Sara A Hurvitz, MD
Kelly Leonard, MSN, FNP-BC
Hope S Rugo, MD

Chronic Lymphocytic Leukemia

Friday, April 29, 2022
12:15 PM – 1:45 PM PT (3:15 PM – 4:45 PM ET)

Faculty
Lesley Camille Ballance, MSN, FNP-BC
Amy Goodrich, CRNP
Anthony R Mato, MD, MSCE
Susan O'Brien, MD

Acute Myeloid Leukemia and Myelodysplastic Syndromes

Friday, April 29, 2022
8:20 PM – 9:20 PM PT (11:20 PM – 12:20 AM ET)

Faculty
Ilene Galinsky, NP
Eunice S Wang, MD

What I Tell My Patients: Expert Insights into Patient Education on New Treatments and Clinical Trial Participation

A Complimentary NCPD Hybrid Symposium Series Held During the 47th Annual ONS Congress

Cervical and Endometrial Cancer

Saturday, April 30, 2022
6:00 AM – 7:30 AM PT (9:00 AM – 10:30 AM ET)

Faculty
Paula J Anastasia, MN, RN, AOCN
Robert L Coleman, MD
David M O'Malley, MD
Jaclyn Shaver, MS, APRN, CNP, WHNP

Bladder Cancer

Saturday, April 30, 2022
12:15 PM – 1:45 PM PT (3:15 PM – 4:45 PM ET)

Faculty
Monica Averia, MSN, AOCNP, NP-C
Shilpa Gupta, MD
Brenda Martone, MSN, NP-BC, AOCNP
Sumanta Kumar Pal, MD

Thank you for joining us!

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

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