Meet The Professor
Current and Future Management of Chronic Lymphocytic Leukemia

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

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

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 Company, Celgene Corporation, Clovis Oncology, Coherus BioSciences, CTI BioPharma Corp, Daiichi Sankyo Inc, Eisai Inc, EMD Serono Inc, Epizyme Inc, Exact Sciences, Exelixis Inc, Five Prime Therapeutics Inc, Foundation Medicine, G1 Therapeutics Inc, Genentech, a member of the Roche Group, Genmab, Gilead Sciences Inc, GlaxoSmithKline, Grail Inc, 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, Lilly, Loxo Oncology Inc, a wholly owned subsidiary of Eli Lilly & Company, Merck, Mersana Therapeutics Inc, Natera Inc, Novartis, Novocure Inc, Oncopeptides, Pfizer Inc, Pharmacyclics LLC, an AbbVie Company, Puma Biotechnology Inc, Regeneron Pharmaceuticals Inc, Sanofi Genzyme, Seagen Inc, Servier Pharmaceuticals LLC, Sumitomo Dainippon Pharma Oncology Inc, Taiho Oncology Inc, Takeda Pharmaceuticals USA Inc, Tesaro, A GSK Company, TG Therapeutics Inc, Turning Point Therapeutics Inc, Verastem Inc andZymeworks Inc.

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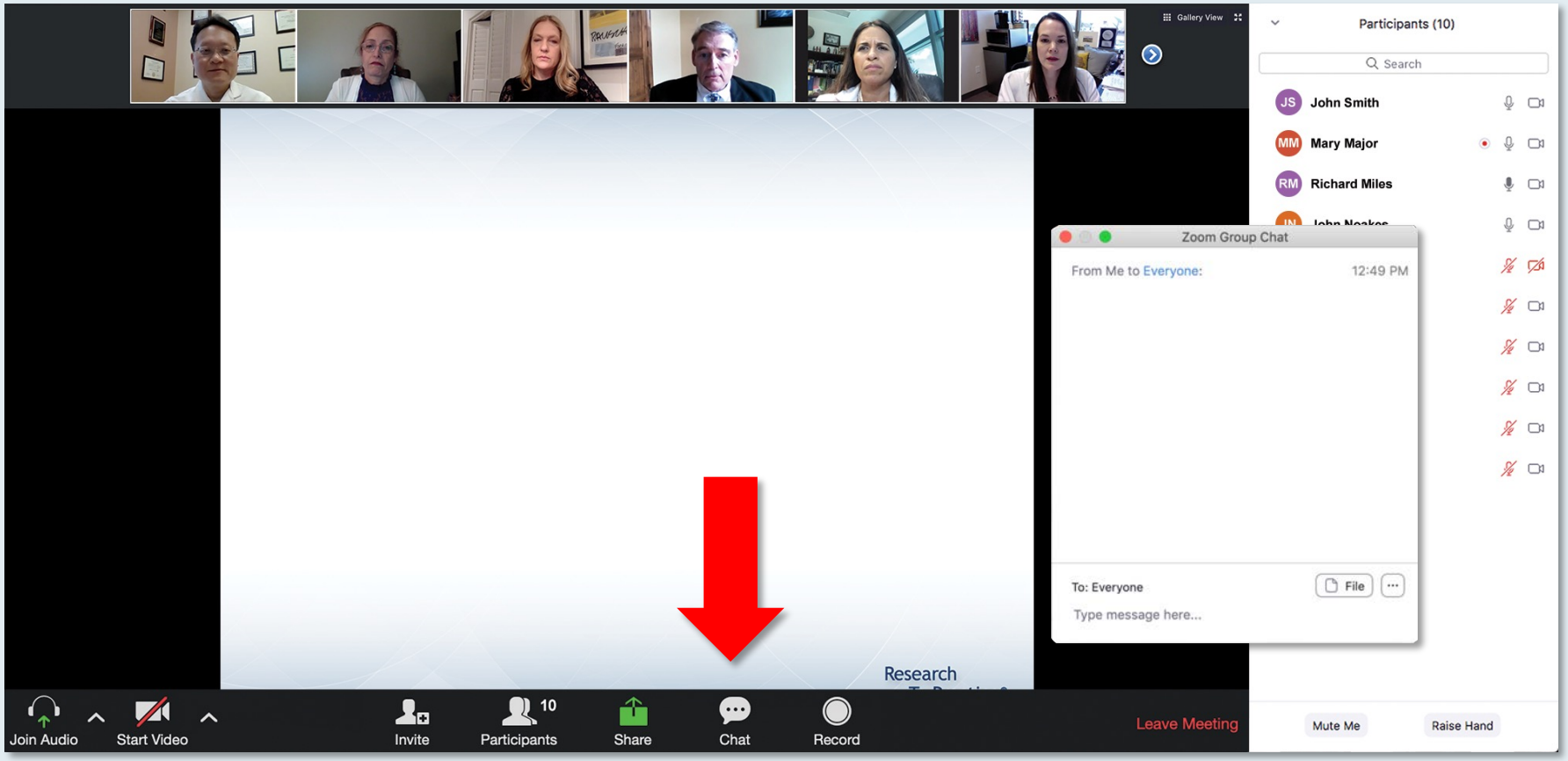

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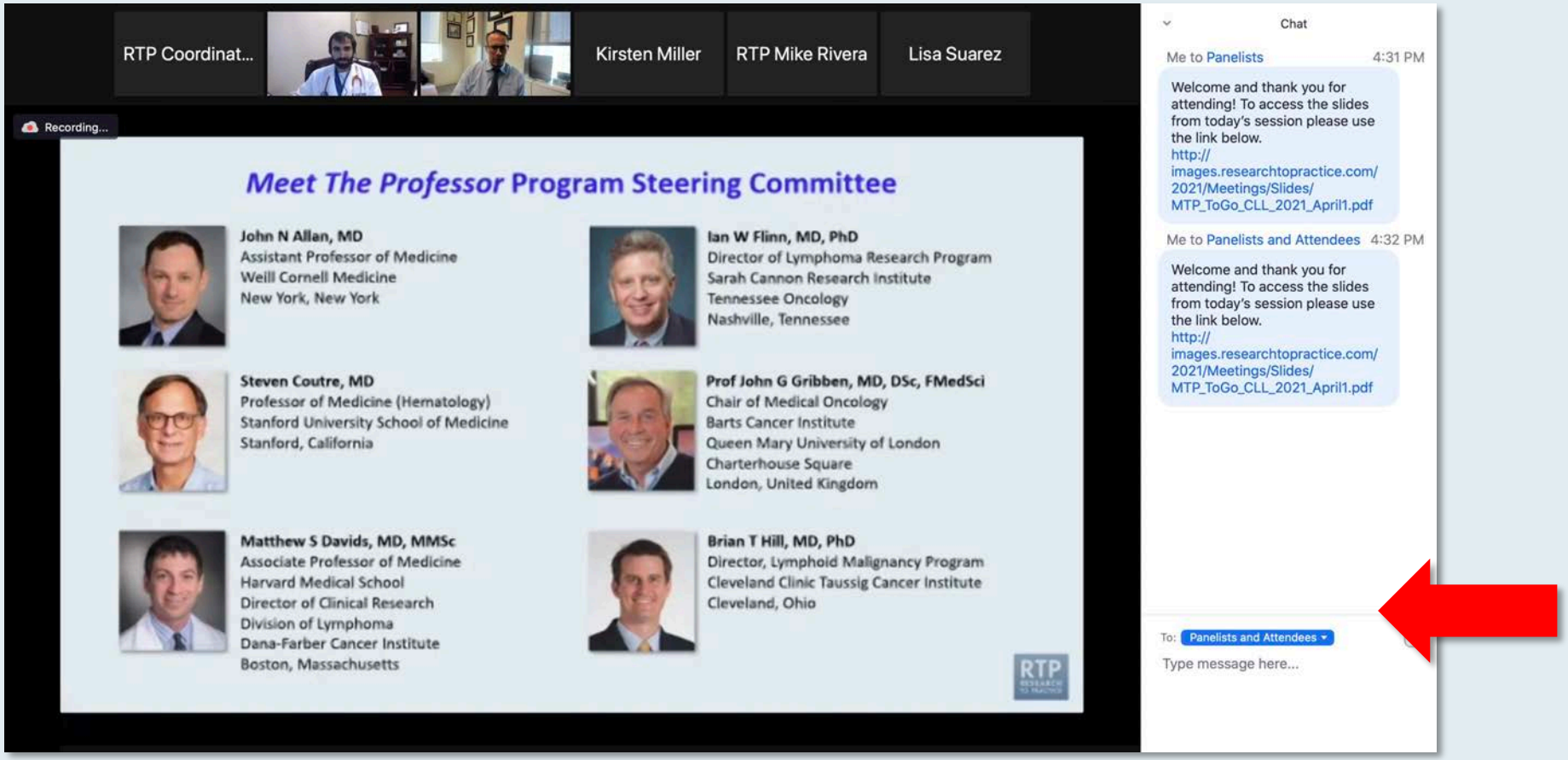

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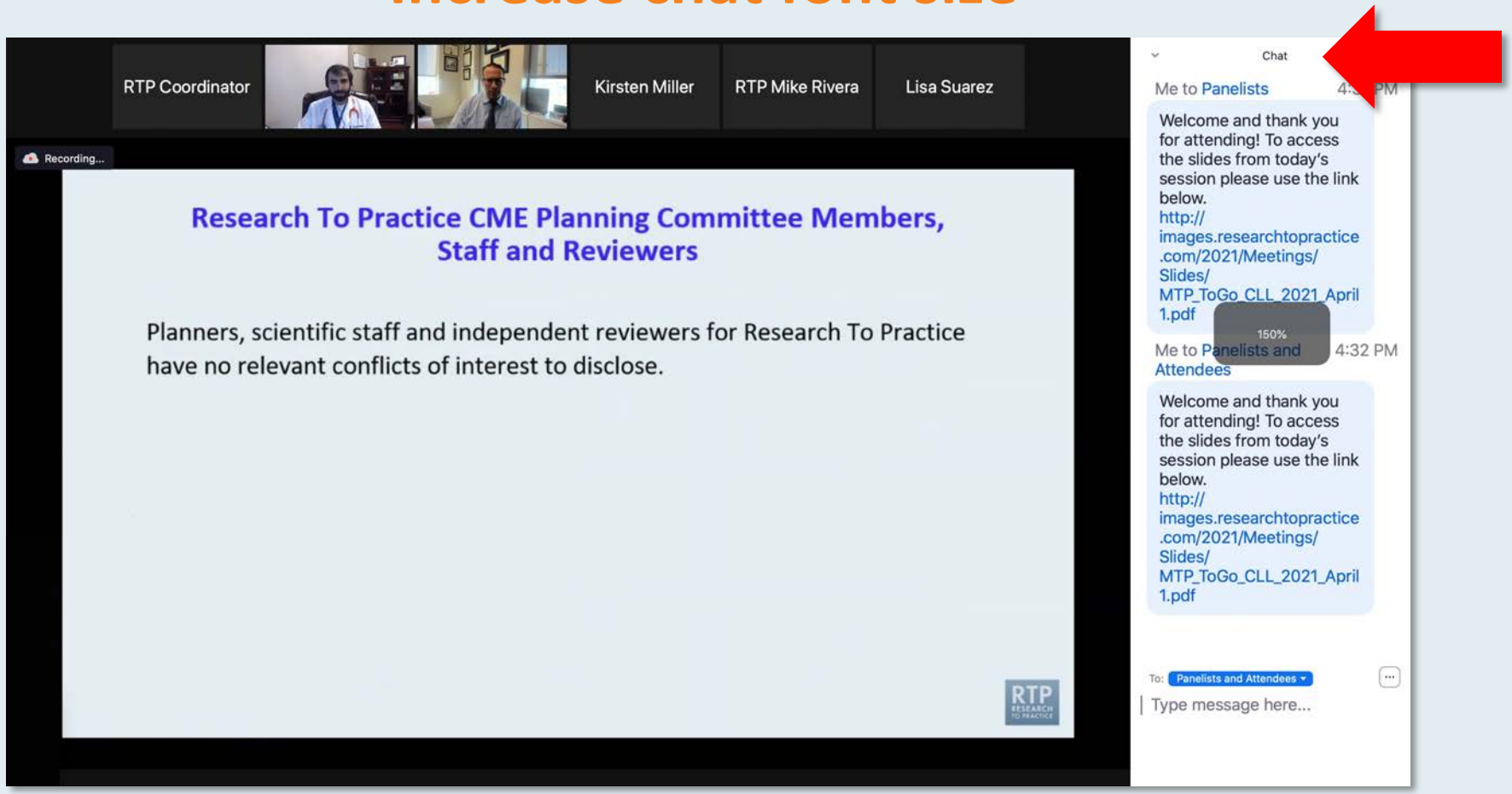

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WITH DR NEIL LOVE

Recent Advances in the Treatment of Chronic Lymphocytic Leukemia

DR PETER HILLMEN
UNIVERSITY OF LEEDS

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Meet The Professor

Current and Future Role of Immunotherapy in the Management of Lung Cancer

Monday, March 7, 2022
5:00 PM – 6:00 PM ET

Faculty

Charu Aggarwal, MD

Moderator

Neil Love, MD

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Year in Review:
Kidney and Bladder Cancer

Tuesday, March 8, 2022
5:00 PM – 6:00 PM ET

Faculty

Elizabeth R Plimack, MD, MS

Thomas Powles, MBBS, MRCP, MD

Moderator

Neil Love, MD

RTP Year in Review 2022

Meet The Professor

Optimizing the Management of Acute Myeloid Leukemia

Wednesday, March 9, 2022
5:00 PM – 6:00 PM ET

Faculty

Rebecca L Olin, MD, MSCE

Moderator

Neil Love, MD

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Meet The Professor

Current and Future Management of Myelofibrosis

Thursday, March 10, 2022
5:00 PM – 6:00 PM ET

Faculty

Srdan Verstovsek, MD, PhD

Moderator

Neil Love, MD

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Meet The Professor

Current and Future Management of Chronic Lymphocytic Leukemia

Thursday, March 17, 2022
5:00 PM – 6:00 PM ET

Faculty

Peter Hillmen, MB ChB, PhD

Moderator

Neil Love, MD

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Data + Perspectives: Clinical Investigators Discuss the Current and Future Management of Ovarian Cancer

Saturday, March 19, 2022

12:30 PM – 2:00 PM MT

Faculty

Mansoor Raza Mirza, MD
Kathleen N Moore, MD, MS
David M O'Malley, MD

Moderator

Robert L Coleman, 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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Department of Leukemia, Division of Cancer Medicine
Executive Medical Director, Inpatient Medical Services
The University of Texas
MD Anderson Cancer Center
Houston, Texas

Meet The Professor Program Participating Faculty

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

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

John C Byrd, MD
The Gordon and Helen Hughes Taylor Professor and Chair
Department of Internal Medicine
University of Cincinnati College of Medicine
Chief Medical Officer, Beat AML LLC
Leukemia and Lymphoma Society
Cincinnati, Ohio

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

Moderator

Neil Love, MD
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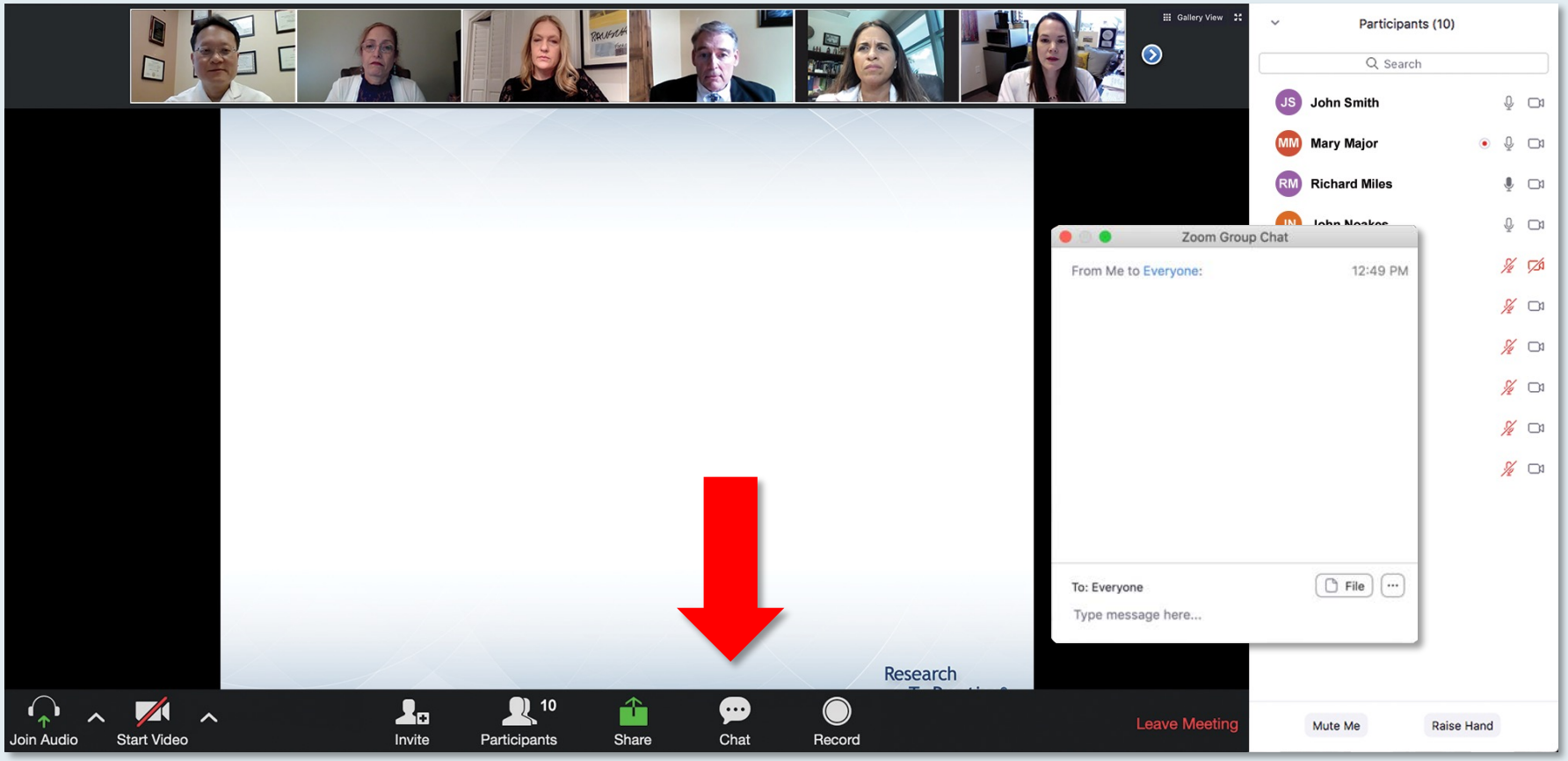

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Bhavana (Tina) Bhatnagar, DO
Schiffler Cancer Center
Wheeling, West Virginia

Jeanne Palmer, MD
Mayo Clinic
Phoenix, Arizona

Warren S Brenner, MD
Lynn Cancer Institute
Boca Raton, Florida

Mitchell R Smith, MD, PhD
George Washington University
Washington, DC

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

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Meet The Professor with Dr Wierda

MODULE 1: Case Presentations

- Dr Bhatnager: A 77-year-old man with chronic lymphocytic leukemia (CLL) and a TP53 mutation who experiences disease progression after observation
- Dr Brenner: A 69-year-old man with CLL and brawny type edema during treatment with ibrutinib
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MODULE 2: Faculty Survey

MODULE 3: Journal Club with Dr Wierda

MODULE 4: Key Recent Data Sets

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Case Presentation: A 77-year-old man with CLL and a TP53 mutation who experiences disease progression after observation

Dr Tina Bhatnagar (Wheeling, WV)

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Case Presentation: A 69-year-old man with CLL and brawny type edema during treatment with ibrutinib

Dr Warren Brenner (Boca Raton, FL)

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Case Presentation: A 76-year-old man with relapsed CLL after 3 years of second-line ibrutinib

Dr Jeanne Palmer (Phoenix, AZ)

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Case Presentation: A 60-year-old man with newly diagnosed CLL who received obinutuzumab/venetoclax

Dr Khuda Dad Kahn (Prospect, KY)

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Case Presentation: An 81-year-old man with CLL and bone marrow infiltrate consistent with Hodgkin Lymphoma

Dr Mitchell Smith (Washington, DC)

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Case Presentation: A 72-year-old man with CLL and significant cytopenias on acalabrutinib

Dr Tina Bhatnagar (Wheeling, WV)

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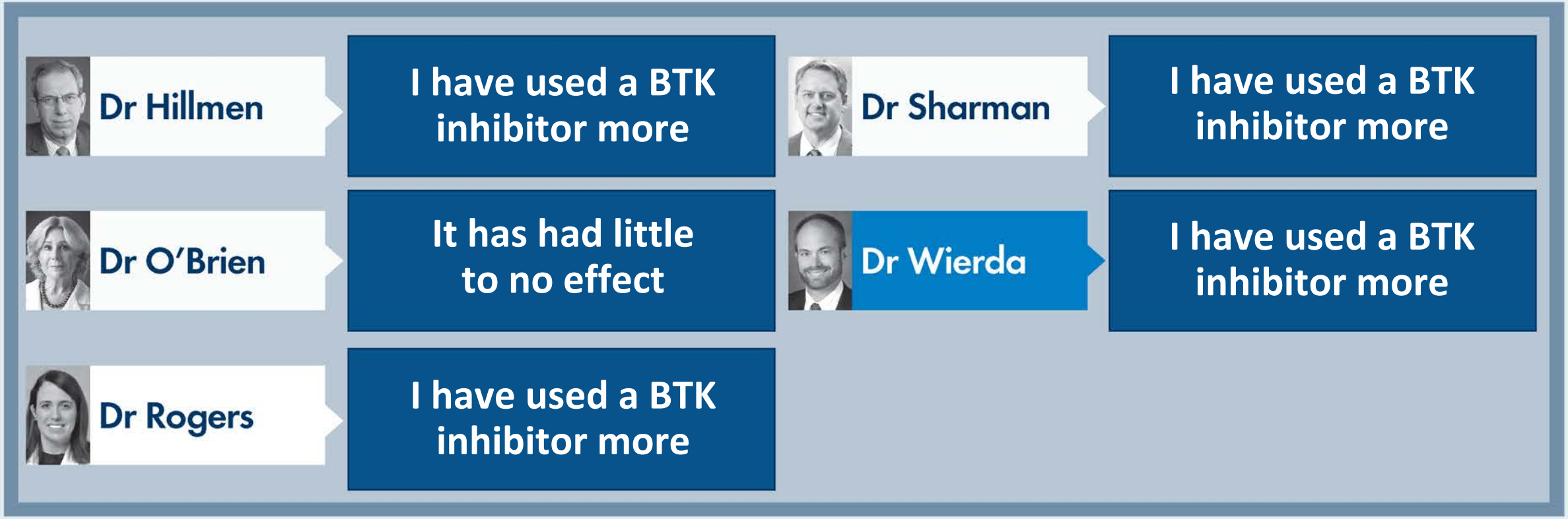
In general, how if at all has the COVID-19 pandemic affected your selection of first-line therapy for patients with chronic lymphocytic leukemia (CLL) who require treatment?



BTK = Bruton tyrosine kinase

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For which patients with CLL are you using Evusheld™ (tixagevimab copackaged with cilgavimab) as pre-exposure prophylaxis for COVID-19?

SLL = small lymphocytic lymphoma

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For patients with CLL who are receiving a BTK inhibitor and contract an asymptomatic COVID-19 infection, should the BTK inhibitor generally be continued or held?

1. BTK inhibitor should be continued
2. BTK inhibitor should be held
3. I’m not sure

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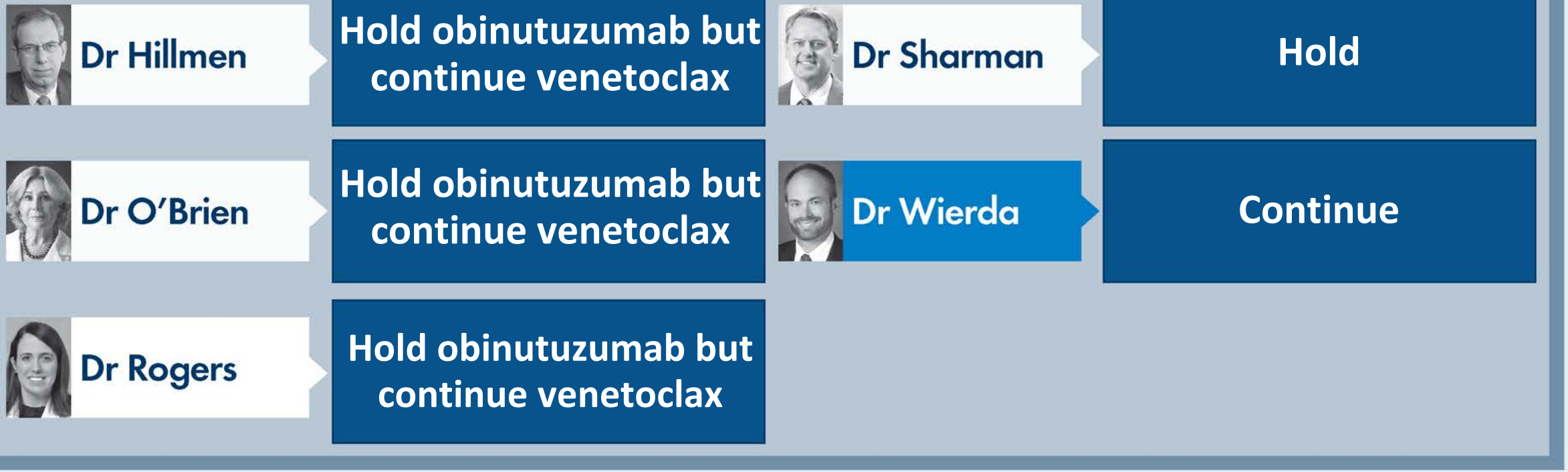
For patients with CLL who are receiving a BTK inhibitor and contract an asymptomatic COVID-19 infection, do you generally continue or hold the BTK inhibitor?

For patients with CLL who are receiving obinutuzumab/venetoclax and contract an asymptomatic COVID-19 infection, do you generally continue or hold the treatment?



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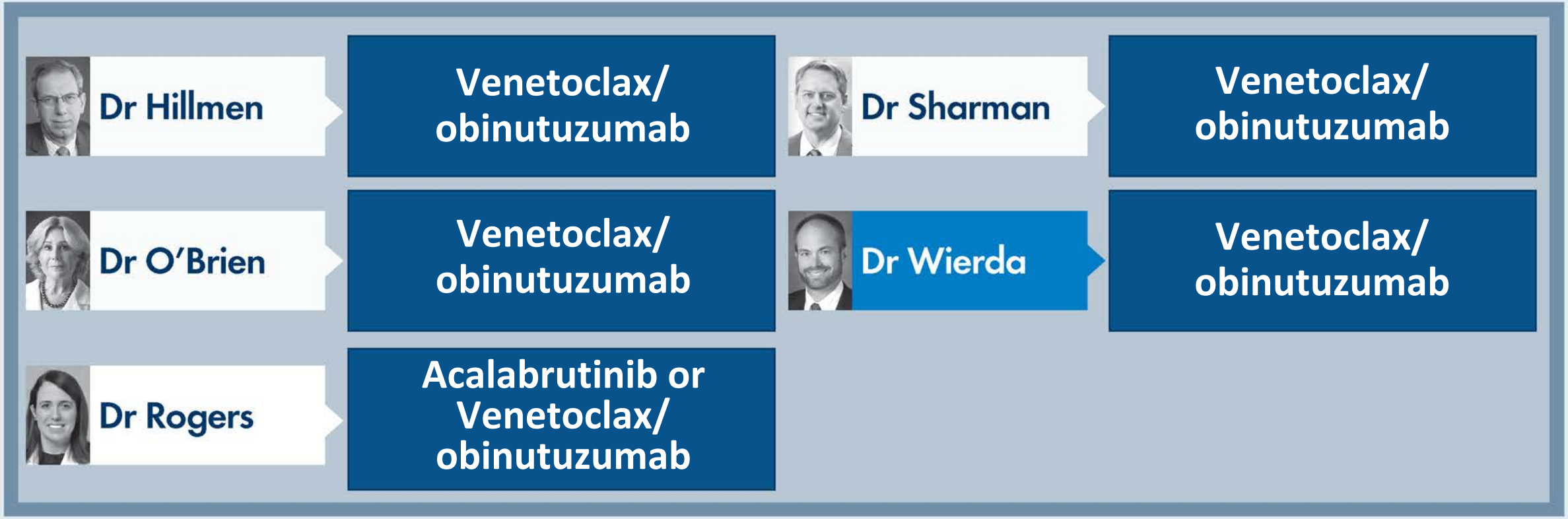
What is your usual preferred initial regimen for a 60-year-old patient with CLL with IGHV mutation but no del(17p) or TP53 mutation who requires treatment?

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?



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 Hillmen	Venetoclax/ibrutinib
 Dr O'Brien	Venetoclax/ibrutinib
 Dr Rogers	Acalabrutinib or Venetoclax/ obinutuzumab
 Dr Sharman	Venetoclax/ obinutuzumab
 Dr Wierda	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
2. BR
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8. Other

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

 Dr Hillmen	Acalabrutinib
 Dr O'Brien	Acalabrutinib
 Dr Rogers	Acalabrutinib
 Dr Sharman	Acalabrutinib
 Dr Wierda	Acalabrutinib

RTP RESEARCH TO PRACTICE

For patients with CLL who are receiving obinutuzumab/venetoclax as initial therapy, do you generally order a minimal residual disease (MRD) assay at the end of 12 months?

1. Yes
2. No

For patients with CLL who are receiving obinutuzumab/venetoclax as initial therapy, do you generally order a minimal residual disease (MRD) assay at the end of 12 months?

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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?

Should community-based medical oncologists/hematologists be ordering MRD assessment in any CLL clinical situations?

1. Yes
2. No

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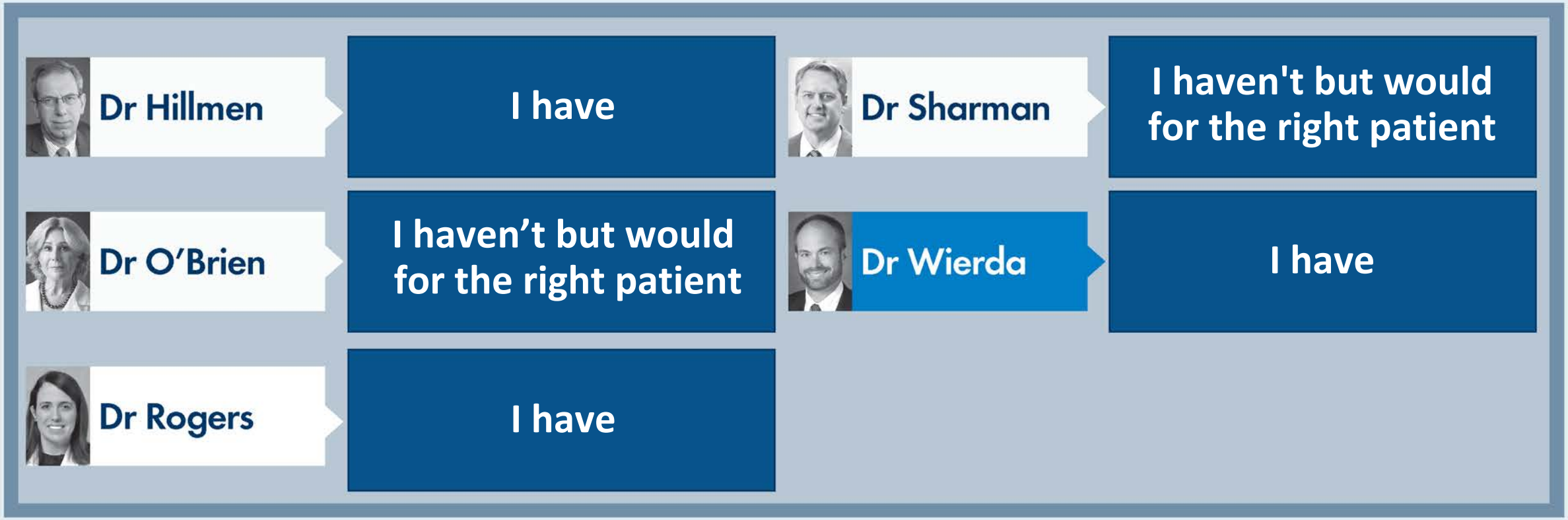
Should community-based medical oncologists/hematologists be ordering MRD assessment for patients with CLL in any clinical situations?

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

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



Based on current clinical trial data and your personal experience, how would you compare the global efficacy of zanubrutinib to that of ibrutinib and that of acalabrutinib in patients with relapsed/refractory CLL?

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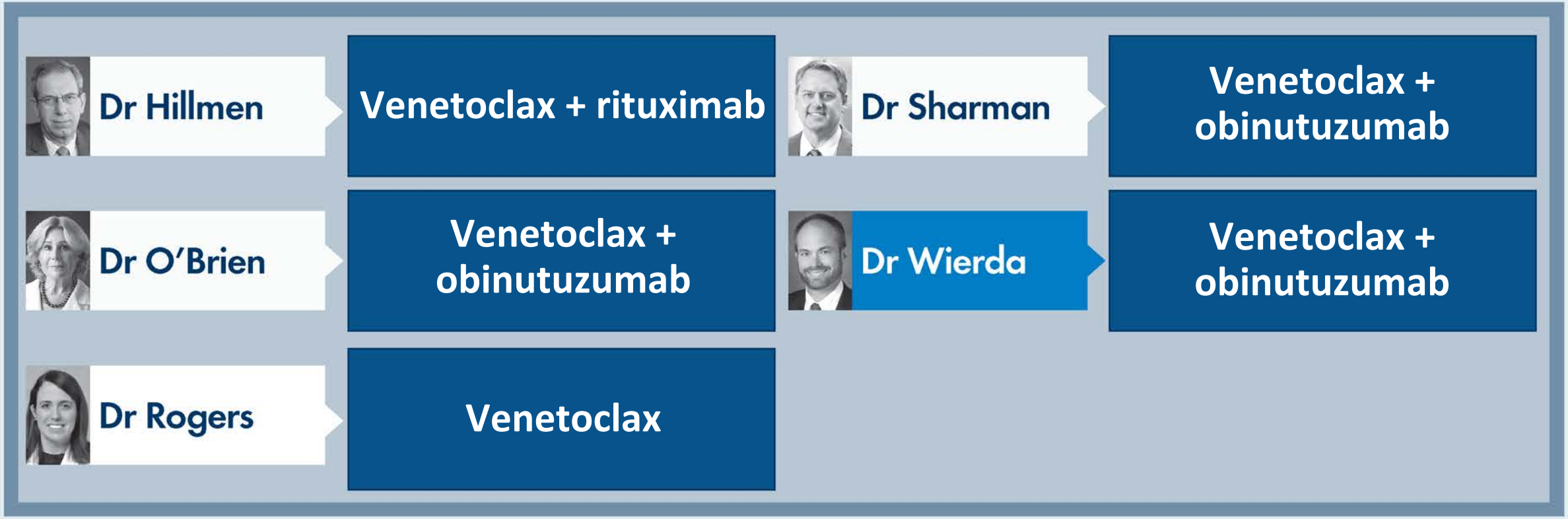
Which management strategy would you generally recommend for a patient experiencing acalabrutinib-associated headache?

RTP RESEARCH TO PRACTICE

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

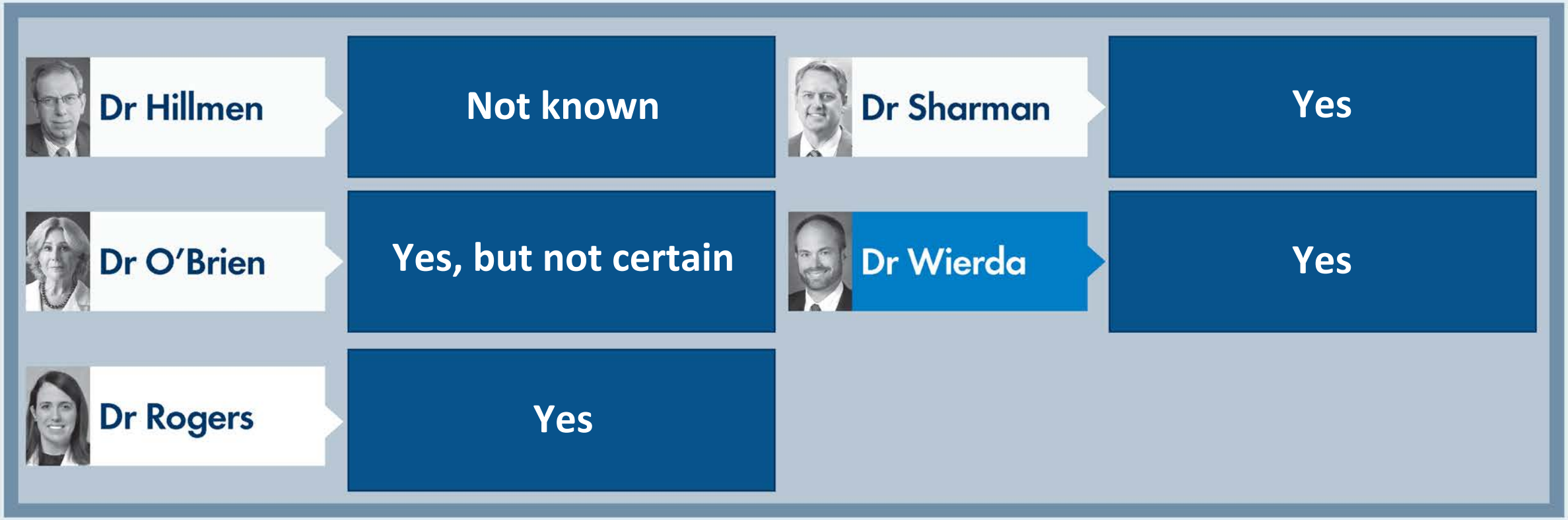
1. Acalabrutinib
2. Acalabrutinib + obinutuzumab
3. Venetoclax
4. Venetoclax + rituximab
5. Venetoclax + obinutuzumab
6. Idelalisib
7. Duvelisib
8. Other

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



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

Do you believe there is a benefit to administering a BTK inhibitor in combination with venetoclax as opposed to sequentially for patients with CLL?



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Based on current clinical trial data and your personal experience, how would you compare the global tolerability/toxicity of pirtobrutinib to that of ibrutinib, that of acalabrutinib and that of zanubrutinib in patients with relapsed/refractory CLL?

Dr Hillmen

Pirtobrutinib has the least toxicity

Dr O'Brien

Pirtobrutinib has the least toxicity

Dr Rogers

Pirtobrutinib has the least toxicity

Dr Sharman

Pirtobrutinib has the least toxicity

Dr Wierda

Pirtobrutinib has the least toxicity

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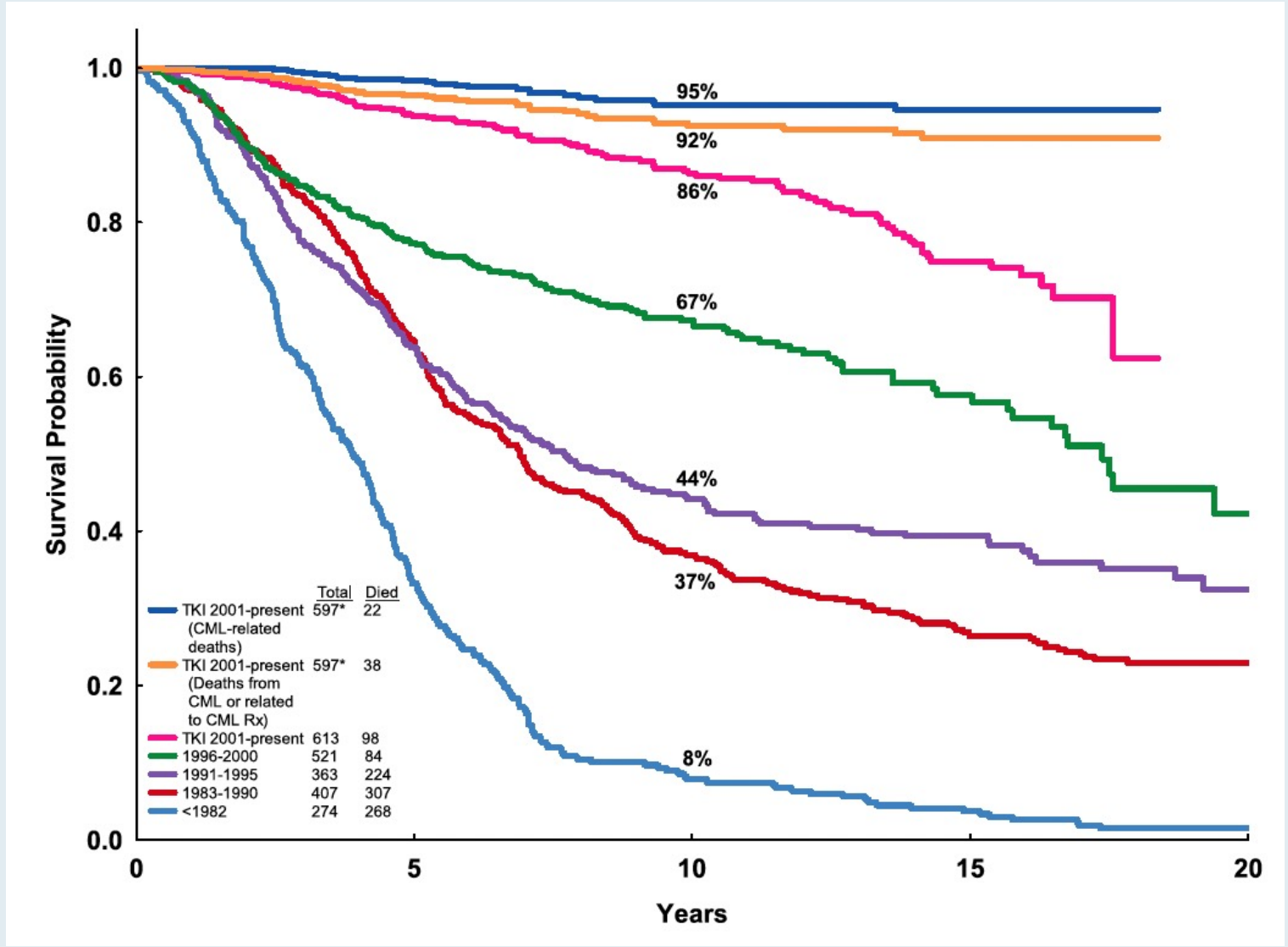
Cancer 2022;128(2):240-59.

Review Article

The Cure of Leukemia Through the Optimist's Prism

Hagop M. Kantarjian, MD ; Nitin Jain, MD; Guillermo Garcia-Manero, MD ; Mary Alma Welch, MMSC; Farhad Ravandi, MD; William G. Wierda, MD; and Elias J. Jabbour, MD

Survival in CML at the MD Anderson Cancer Center Over 5 Decades



Kantarjian HM et al. *Cancer* 2022;128(2):240-59.

Pharmaceutics 2021;13(12):2201.

pharmaceutics

MDPI

Review

The TKI Era in Chronic Leukemias

Danilo De Novellis [1,*], Fabiana Cacace [2], Valeria Caprioli [2], William G. Wierda [3], Kris M. Mahadeo [4] and Francesco Paolo Tambaro [2]

Journal of Experimental Pharmacology 2021;13:923-35

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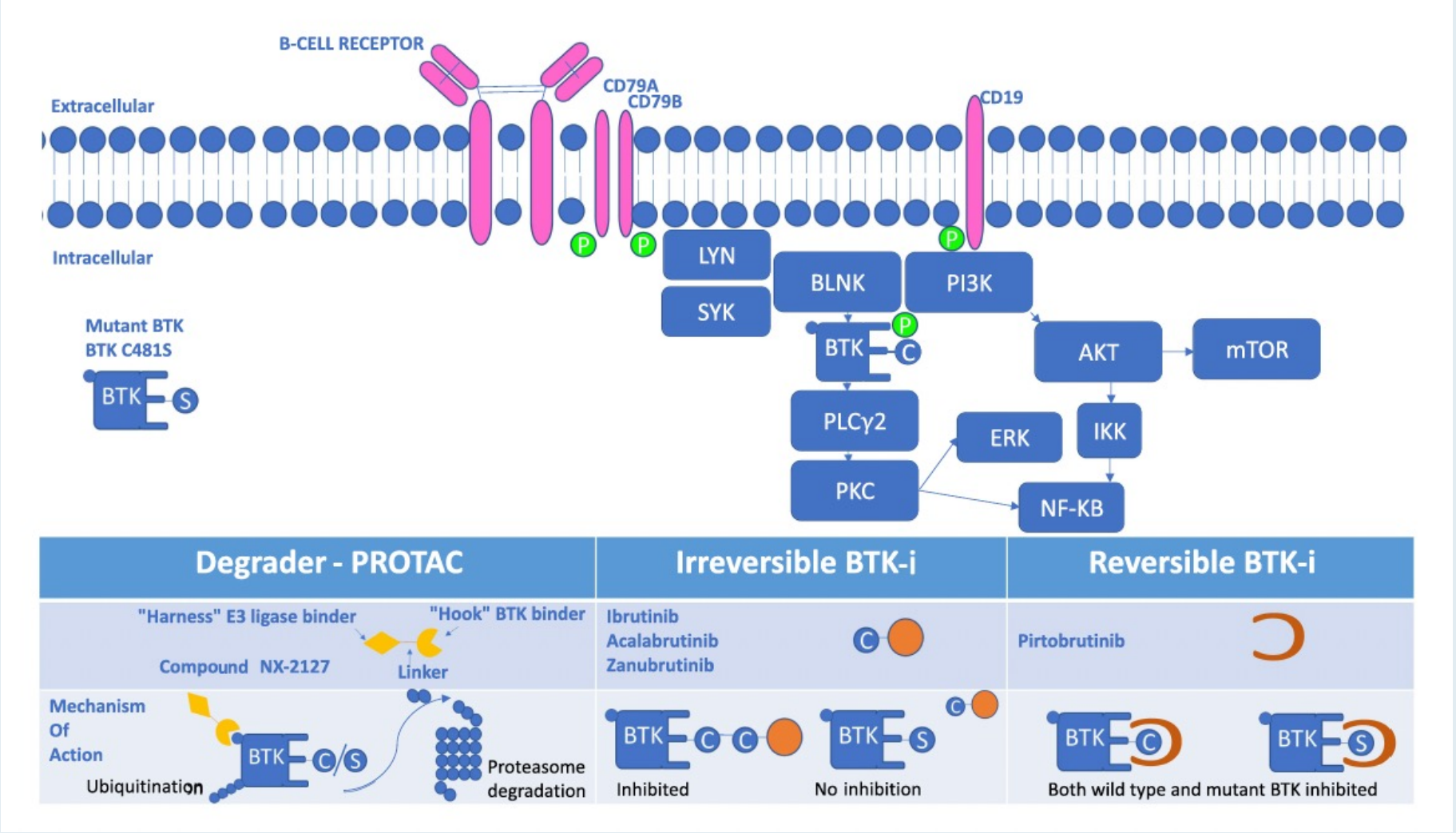
REVIEW

The Role of BTK Inhibition in the Treatment of Chronic Lymphocytic Leukemia: A Clinical View

Francesco Paolo Tambaro[1]
Danilo De Novellis[1,2]
William G Wierda[3]

B-Cell Receptor Signaling Pathway and Inhibition of Bruton Tyrosine Kinase (BTK)



Tambaro FP et al. *J Exp Pharmacol* 2021;13:923-35.

frontiers in Oncology

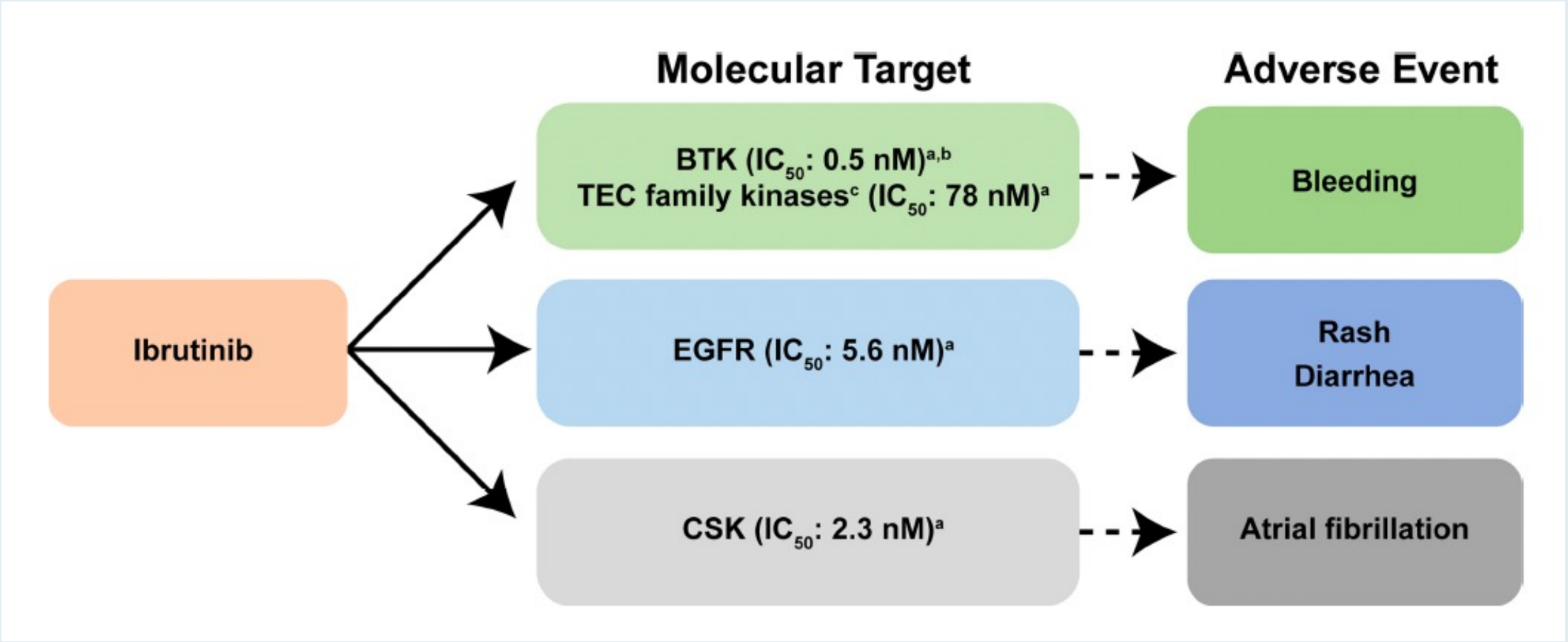
Front Oncol 2021;11:720704

PERSPECTIVE
published: 08 November 2021
doi: 10.3389/fonc.2021.720704

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.

frontiers in Oncology

Front Oncol 2021;11:668162

MINI REVIEW
published: 14 May 2021
doi: 10.3389/fonc.2021.668162

Acalabrutinib: A Selective Bruton Tyrosine Kinase Inhibitor for the Treatment of B-Cell Malignancies

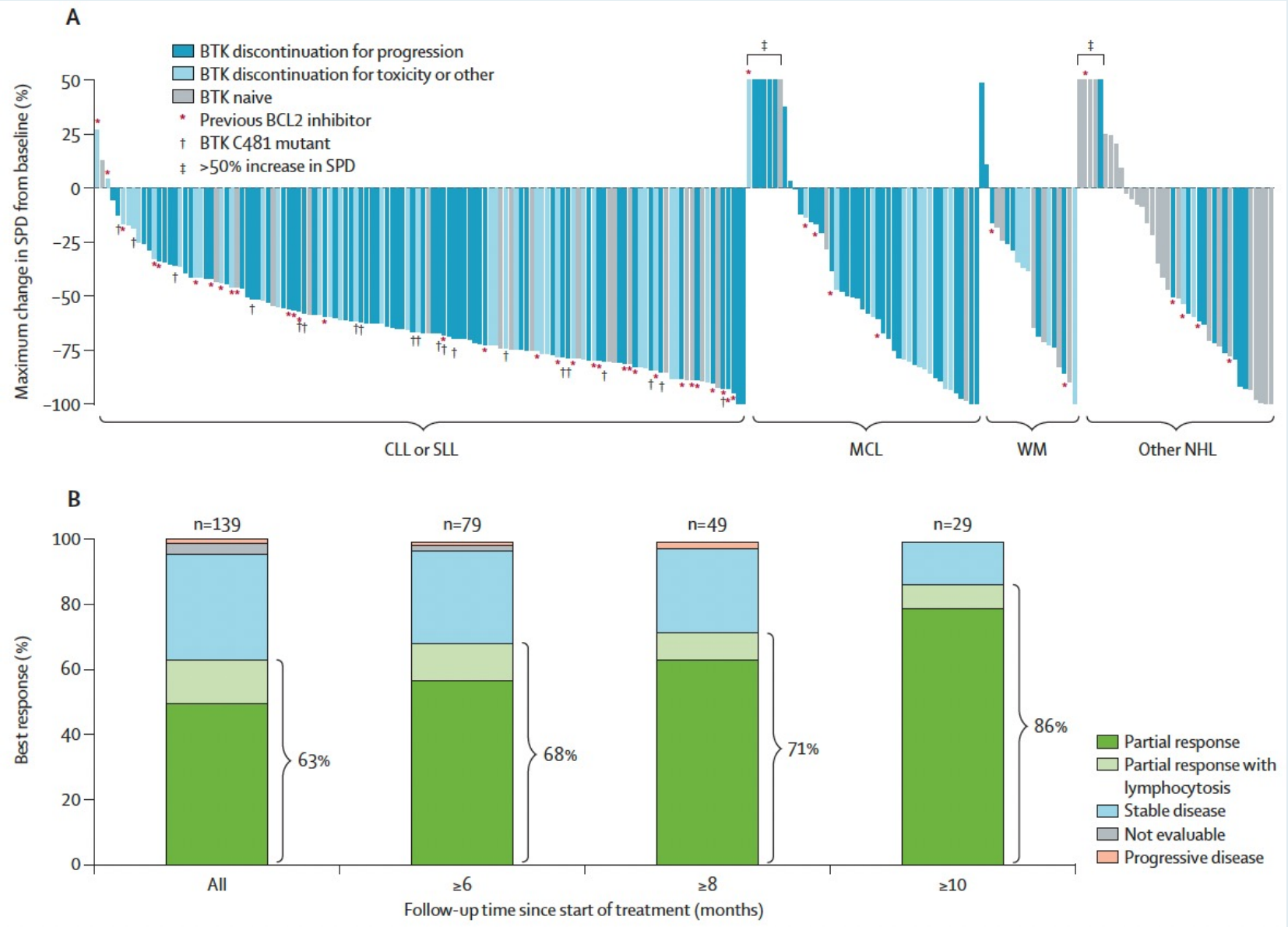
Hussein A. Abbas[1] *and William G. Wierda*[2*]

Lancet 2021;397:892-901

Pirtobrutinib in relapsed or refractory B-cell malignancies (BRUIN): a phase 1/2 study

Anthony R Mato, Nirav N Shah, Wojciech Jurczak, Chan Y Cheah, John M Pagel, Jennifer A Woyach, Bita Fakhri, Toby A Eyre, Nicole Lamanna, Manish R Patel, Alvaro Alencar, Ewa Lech-Maranda, William G Wierda, Catherine C Coombs, James N Gerson, Paolo Ghia, Steven Le Gouill, David John Lewis, Suchitra Sundaram, Jonathon B Cohen, Ian W Flinn, Constantine S Tam, Minal A Barve, Bryone Kuss, Justin Taylor, Omar Abdel-Wahab, Stephen J Schuster, M Lia Palomba, Katharine L Lewis, Lindsey E Roeker, Matthew S Davids, Xuan Ni Tan, Timothy S Fenske, Johan Wallin, Donald E Tsai, Nora C Ku, Edward Zhu, Jessica Chen, Ming Yin, Binoj Nair, Kevin Ebata, Narasimha Marella, Jennifer R Brown, Michael Wang

BRUIN: Efficacy of Pirtobrutinib



Mato AR et al. *Lancet* 2021;397:892-901.

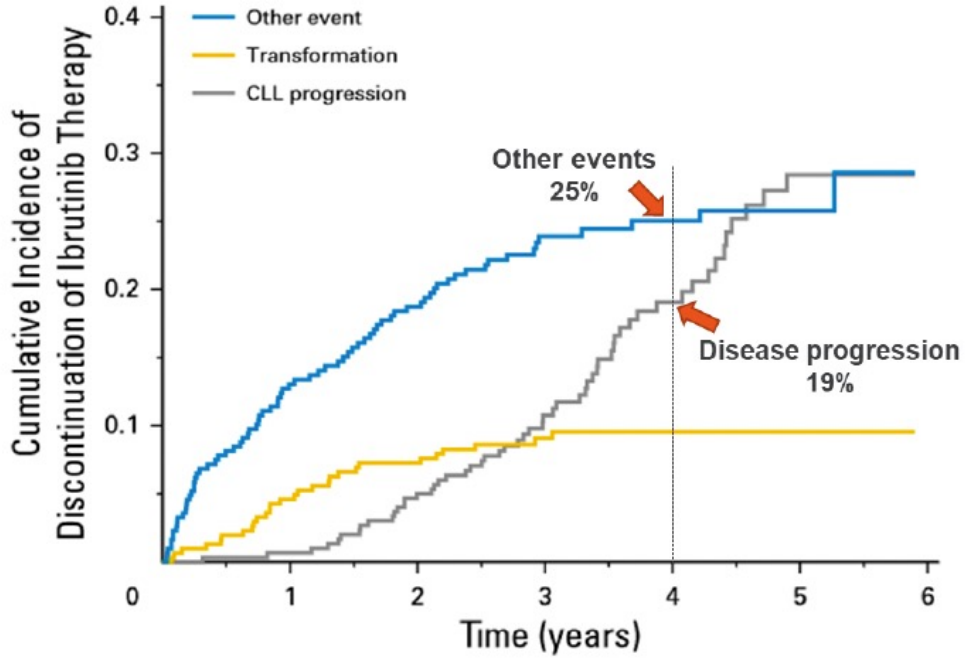
ASH 2021;Abstract 391

Pirtobrutinib, A Highly Selective, Non-covalent (Reversible) BTK Inhibitor In Previously Treated CLL/SLL: Updated Results From The Phase 1/2 BRUIN Study

Anthony R. Mato[1], John M. Pagel[2], Catherine C. Coombs[3], Nirav N. Shah[4], Nicole Lamanna[5], Talha Munir[6], Ewa Lech-Maranda[7], Toby A. Eyre[8], Jennifer A. Woyach[9], William G. Wierda[10], Chan Y. Cheah[11], Jonathan B. Cohen[12], Lindsey E. Roeker[1], Manish R. Patel[13], Bita Fakhri[14], Minal A. Barve[15], Constantine S. Tam[16], David J. Lewis[17], James N. Gerson[18], Alvaro J. Alencar[19], Chaitra S. Ujjani[20], Ian W. Flinn[21], Suchitra Sundaram[22], Shuo Ma[23], Deepa Jagadeesh[24], Joanna M. Rhodes[25], Justin Taylor[19], Omar Abdel-Wahab[1], Paolo Ghia[26], Stephen J. Schuster[18], Denise Wang[27], Binoj Nair[27], Edward Zhu[27], Donald E. Tsai[27], Matthew S. Davids[28], Jennifer R. Brown[28], Wojciech Jurczak[29]

Resistance and Intolerance Limit Covalent BTK Inhibitor Outcomes

Ibrutinib discontinuation from 4 prospective studies[1]



- Ibrutinib discontinuation rates at 5 years
  - Front line = 41%[1]
  - Relapsed/refractory = 54%[2]

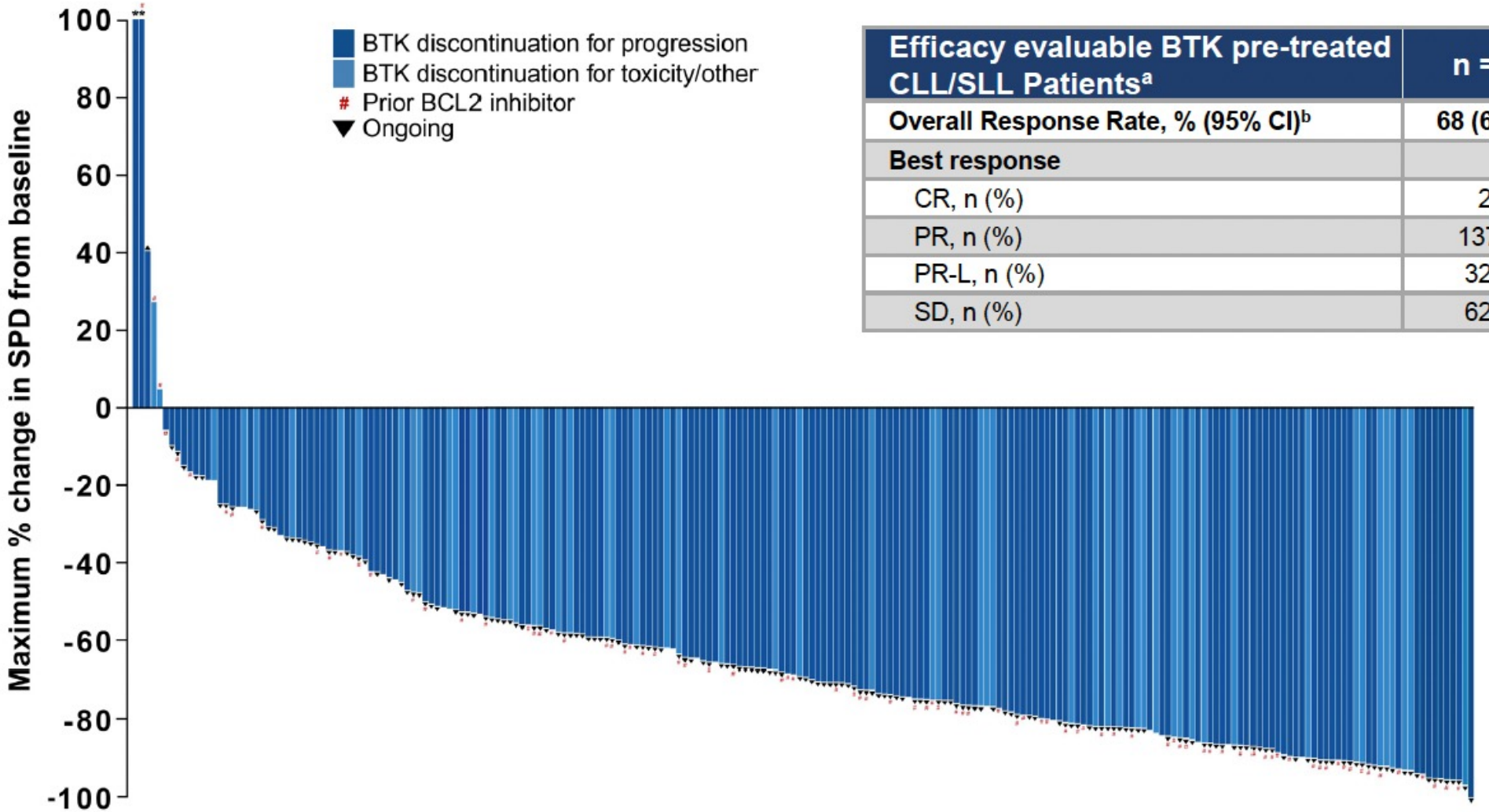
Available options following covalent BTK inhibitor treatment are limited:

- **Covalent BTK inhibitor retreatment**: Only effective in the context of covalent BTK intolerance, not progression
- **Venetoclax**: Efficacious, but complicated administration and not appropriate for all patients
- **PI3K Inhibitors**: Limited benefit in this population and significant toxicity burden
- **Chemoimmunotherapy**: Limited benefit in this population and most current patients have already received these regimens

[1]Woyach et al. *J Clin Oncol*. 2017; 35:1437–43. [2]Burger. *Leukemia*. 2020. 34:787–98.

Mato AR et al. ASH 2021;Abstract 391.

Pirtobrutinib Efficacy in BTK Pre-treated CLL/SLL Patients



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

Mato AR et al. ASH 2021;Abstract 391.

ASH 2021;Abstract 394

Retrospective Single-Institution Analysis of Patients with Chronic Lymphocytic Leukemia with *TP53* alterations Treated First-Line with Bruton's Tyrosine Kinase Inhibitor-Based Therapy

Hua-Jay J. Cherng[1], Raamis Khwaja[2], Rashmi Kanagal-Shamanna[3], Jan Burger[4], Philip Thompson[4], Alessandra Ferrajoli[4], Zeev Estrov[4], Koji Sasaki[4], Deepa Sampath[5], Guilin Tang[3], Xuemei Wang[6], Hagop Kantarjian[4], Michael Keating[4], William G. Wierda[4], Nitin Jain[4]

[1]Division of Cancer Medicine, The University of Texas MD Anderson Cancer Center, Houston, TX
[2]Department of Internal Medicine, The University of Texas Health Science Center at Houston, Houston, TX
[3]Department of Hematopathology, The University of Texas MD Anderson Cancer Center, Houston, TX
[4]Department of Leukemia, The University of Texas MD Anderson Cancer Center, Houston, TX
[5]Department of Hematopoietic Biology and Malignancy, The University of Texas MD Anderson Cancer Center, Houston, TX
[6]Department of Biostatistics, The University of Texas MD Anderson Cancer Center, Houston, TX

ASH, December 11-14, 2021 | Abstract #394

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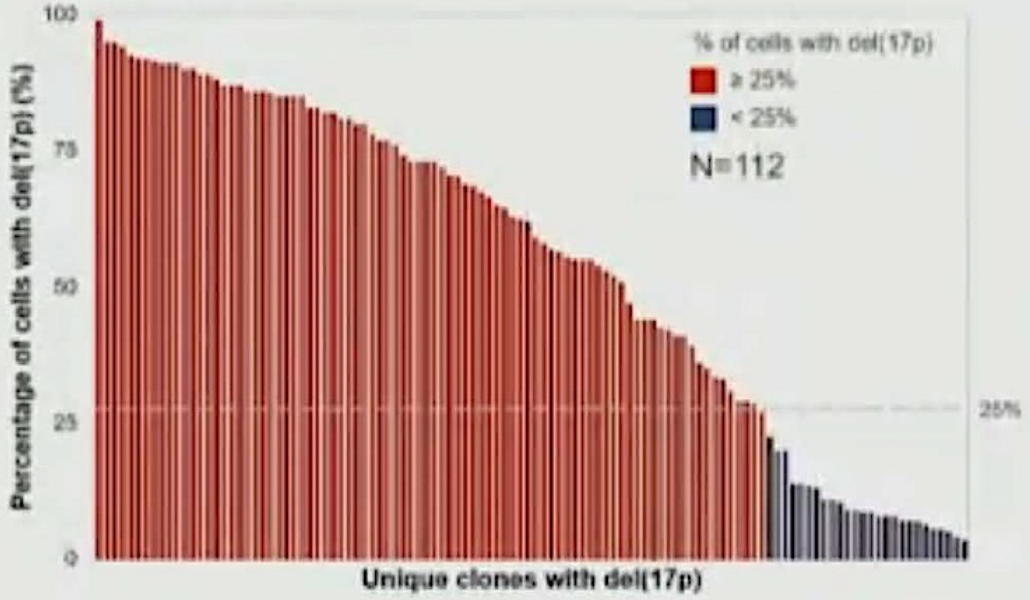
Profiling of *TP53* alterations

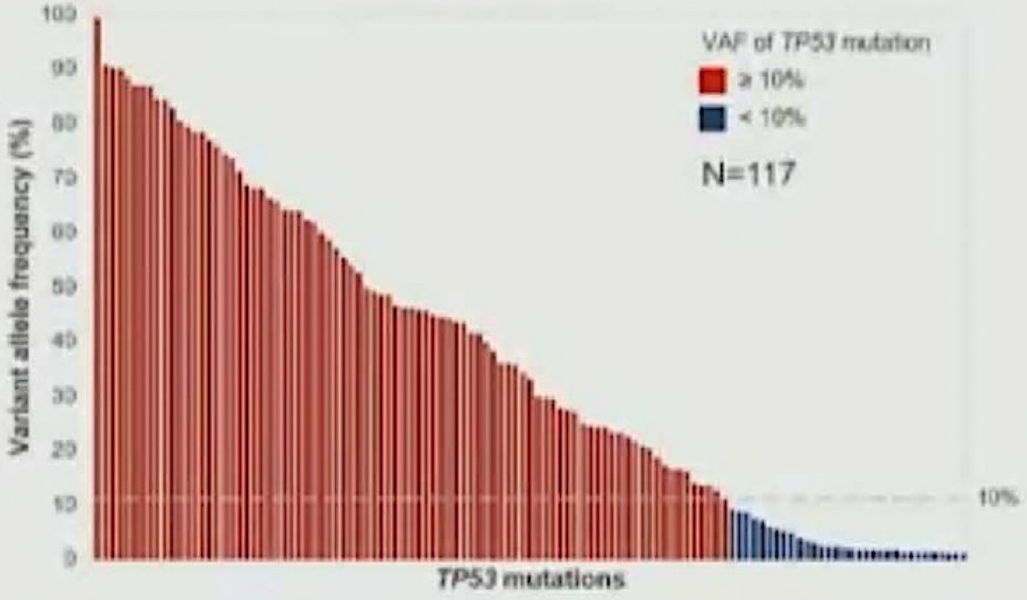
Del(17p)

- 112/140 (80%) patients affected
- Median % cells affected 60.5% and 26 (23%) patients had < 25% of cells affected

Mutated *TP53*

- 100/120 (83%) patients affected
- 122 unique *TP53* mutations (117 had an available VAF)
- Median VAF was 33% and 32 (27%) mutations were subclonal with VAF < 10%

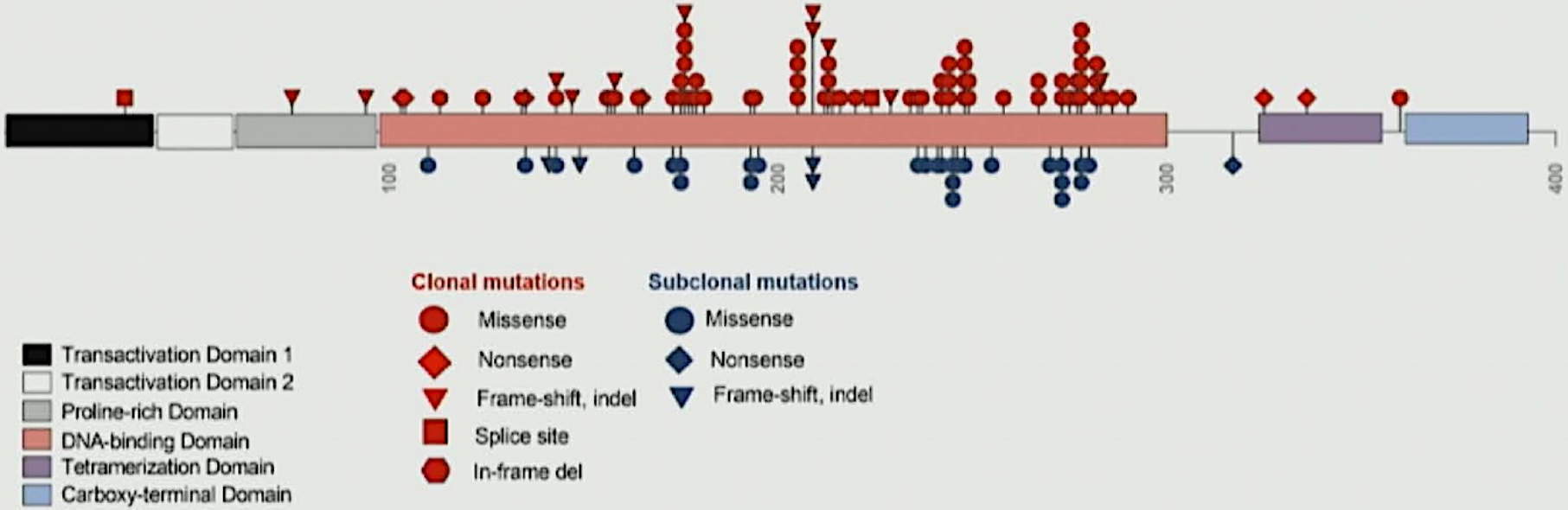




Cherng HJJ et al. ASH 2021;Abstract 394.

Position of unique *TP53* mutations

- **Missense mutations involving the DNA binding domain of TP53 protein were most common regardless VAF**



MD ANDERSON CANCER CENTER

Cherng HJJ et al. ASH 2021;Abstract 394.

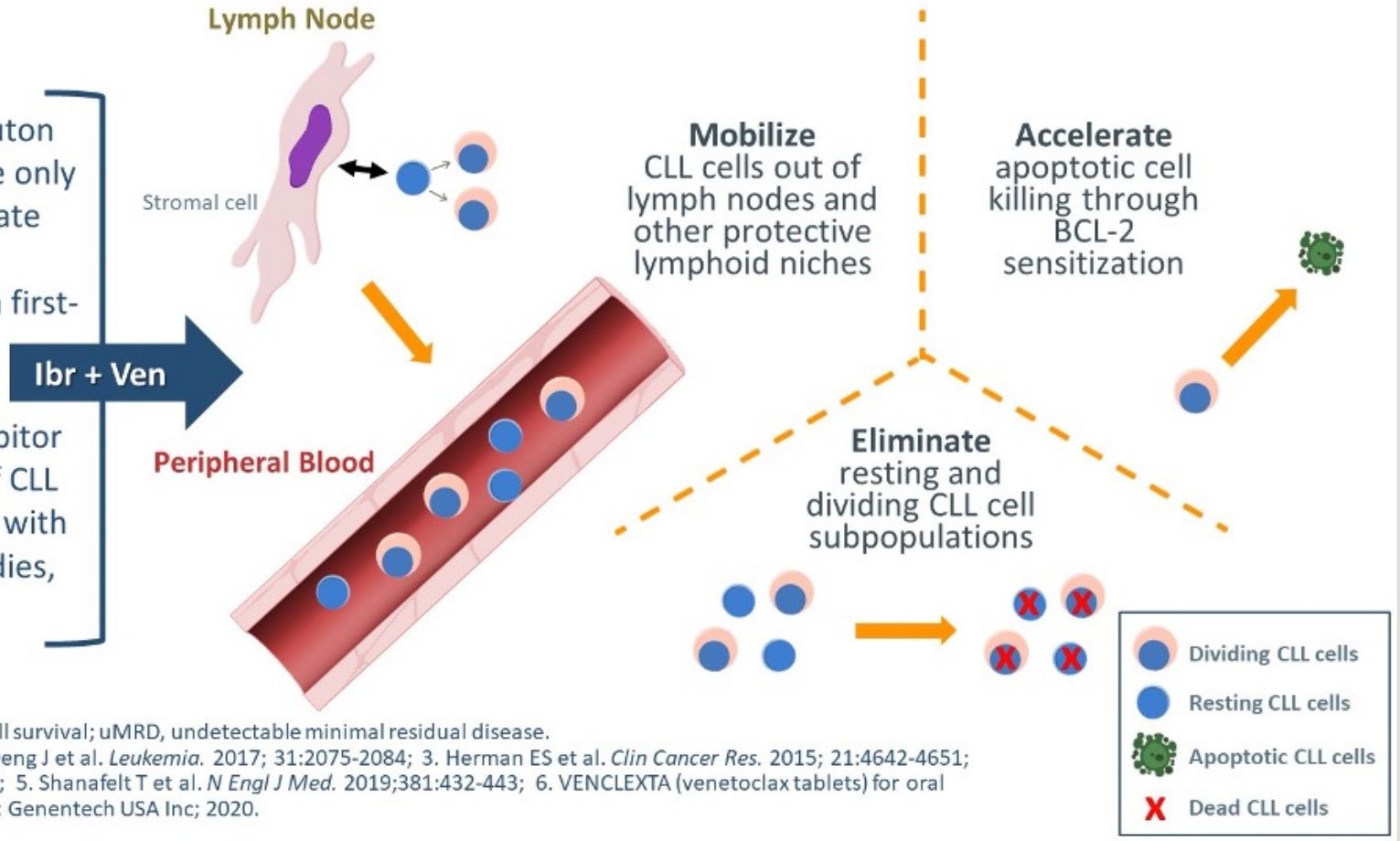
Fixed-Duration (FD) First-Line Treatment With Ibrutinib Plus Venetoclax for Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma: Primary Analysis of the FD Cohort of the Phase 2 CAPTIVATE Study

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

Rationale: Ibrutinib and Venetoclax Have Distinct and Complementary Modes of Action That Work Synergistically[1-3]

- Ibrutinib, a once-daily oral Bruton tyrosine kinase inhibitor, is the only targeted therapy to demonstrate significant OS benefit in randomized phase 3 studies in first-line CLL[4,5]
- Venetoclax, an oral BCL-2 inhibitor approved for the treatment of CLL as a single agent or combined with anti-CD20 monoclonal antibodies, achieves high rates of uMRD[6]



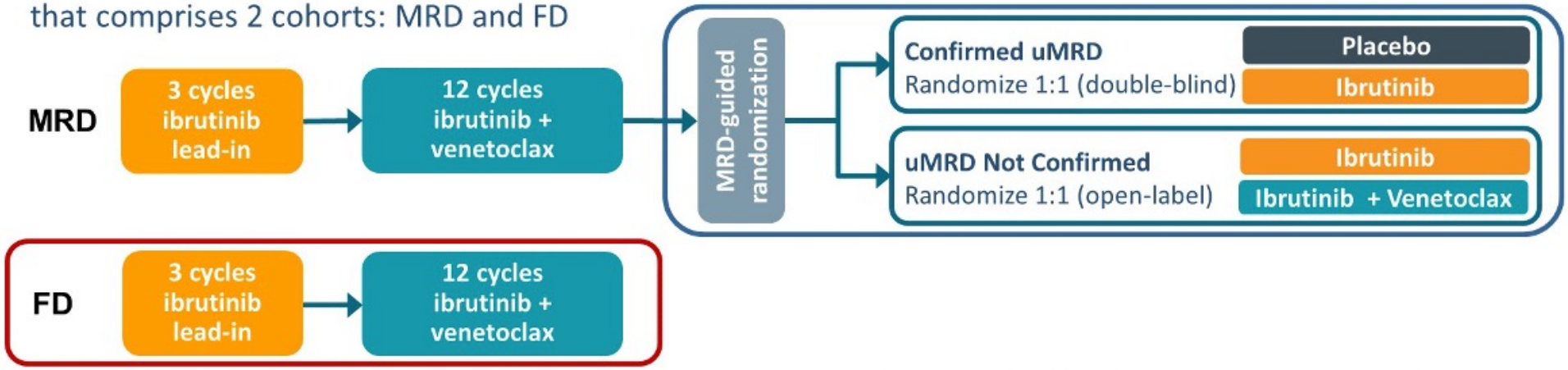
CLL, chronic lymphocytic leukemia; OS, overall survival; uMRD, undetectable minimal residual disease.

1. Lu P et al. *Blood Cancer J.* 2021; 11:39; 2. Deng J et al. *Leukemia.* 2017; 31:2075-2084; 3. Herman ES et al. *Clin Cancer Res.* 2015; 21:4642-4651; 4. Burger JA et al. *Leukemia.* 2020;34:787-798; 5. Shanafelt T et al. *N Engl J Med.* 2019;381:432-443; 6. VENCLEXTA (venetoclax tablets) for oral use [package insert]. South San Francisco, CA: Genentech USA Inc; 2020.

Ghia P et al. ASCO 2021;Abstract 7501.

Phase 2 CAPTIVATE Study

- 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]
- Primary analysis results from the FD cohort of CAPTIVATE are presented

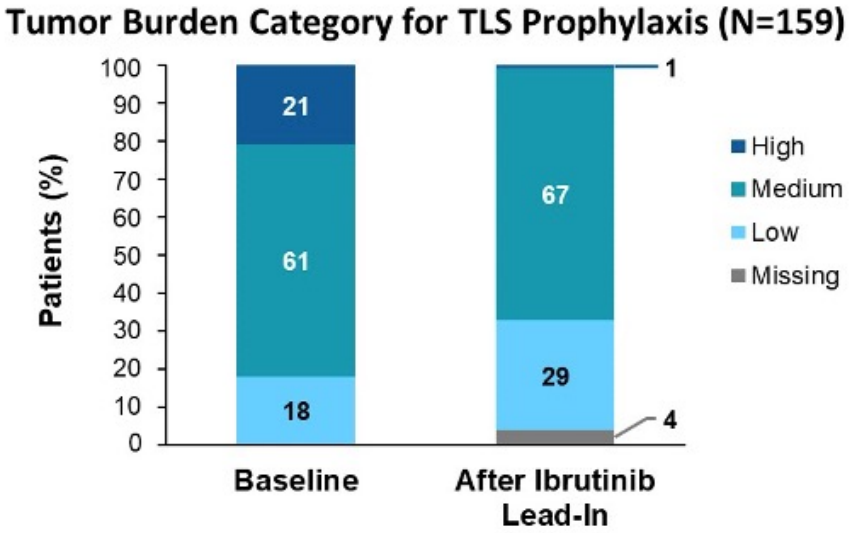
BM, bone marrow; MRD, minimal residual disease; FD, fixed-duration; PB, peripheral blood; PFS, progression-free survival.

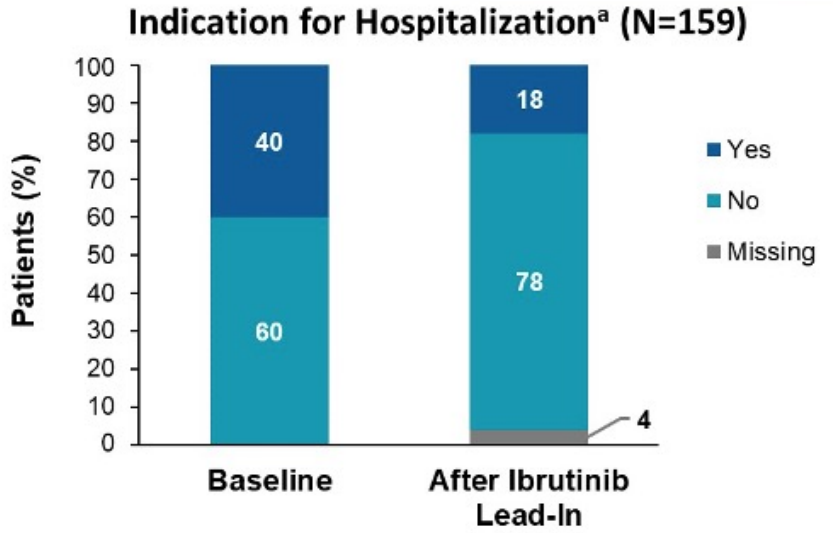
1. Wierda WG et al. ASH 2020, Abstract #123.

ASCO 2021, CAPTIVATE-FD; Ghia et al.

Ghia P et al. ASCO 2021;Abstract 7501.

Effective Debulking With 3 Cycles of Ibrutinib Lead-In Reduces Tumor Burden Category for TLS





- After ibrutinib lead-in
  - 94% (32/34) with baseline high tumor burden category for TLS shifted to medium or low
  - Fewer than 1 in 5 pts (18%) had an indication for hospitalization for TLS prophylaxis/monitoring
- No clinical TLS occurred, and no patient had laboratory TLS per Howard criteria

13 [a]Defined as patients in high-risk category for TLS or patients in medium-risk category with creatinine clearance <80 mL/min. ASCO 2021, CAPTIVATE-FD; Ghia et al.

Ghia P et al. ASCO 2021;Abstract 7501.

Conclusions

- Ibrutinib + venetoclax met the primary endpoint with a CR/CRi rate of 56%, with similarly high rates overall and in patients with high-risk features
  - High rates of uMRD; 2-year PFS and OS rates over 95%
- Favorable safety profile: 92% of patients completed the full fixed-duration regimen; 3 cycles of ibrutinib provided effective tumor debulking
- Results from the FD cohort are largely consistent with the MRD cohort,[1] for a total of 323 patients treated in the CAPTIVATE study
- Results support fixed-duration treatment with ibrutinib + venetoclax as an all-oral, once-daily, chemotherapy-free, fixed-duration regimen that drives deep, durable responses in patients with CLL/SLL
  - Deliverable in the outpatient setting for most young, fit patients with CLL/SLL
  - Regimen is currently being evaluated in older patients in the phase 3 GLOW study, with results anticipated soon

1. Wierda WG et al. ASH 2020, Abstract #123.

ASCO 2021, CAPTIVATE-FD; Ghia et al.

Ghia P et al. ASCO 2021;Abstract 7501.

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.

JAMA Oncol 2021;7(8):1213-19

Research

JAMA Oncology | Original Investigation

Ibrutinib Plus Venetoclax for First-line Treatment of Chronic Lymphocytic Leukemia
A Nonrandomized Phase 2 Trial

Nitin Jain, MD; Michael Keating, MD; Philip Thompson, MD; Alessandra Ferrajoli, MD; Jan A. Burger, MD, PhD; Gautam Borthakur, MD; Koichi Takahashi, MD, PhD; Zeev Estrov, MD; Koji Sasaki, MD; Nathan Fowler, MD; Tapan Kadia, MD; Marina Konopleva, MD, PhD; Yesid Alvarado, MD; Musa Yilmaz, MD; Courtney DiNardo, MD; Prithviraj Bose, MD; Maro Ohanian, DO; Naveen Pemmaraju, MD; Elias Jabbour, MD; Rashmi Kanagal-Shamanna, MD; Keyur Patel, MD, PhD; Wei Wang, MD, PhD; Jeffrey Jorgensen, MD, PhD; Sa A. Wang, MD; Naveen Garg, MD; Xuemei Wang, MS; Chongjuan Wei, PhD; Nichole Cruz, RN; Ana Ayala, RN; William Plunkett, PhD; Hagop Kantarjian, MD; Varsha Gandhi, PhD; William G. Wierda, MD, PhD

Venetoclax, Obinutuzumab and Atezolizumab (PD-L1 Checkpoint Inhibitor) for First-line Treatment for Patients with Chronic Lymphocytic Leukemia (CLL)

Nitin Jain, Alessandra Ferrajoli, Musa Yilmaz, Philip Thompson, Marina Konopleva, Michael Green, Deepa Sampath, Sattva Neelapu, Koichi Takahashi, Lucia Masarova, Jan Burger, Rashmi Kanagal-Shamanna, Joseph Khoury, Naveen Garg, Xiaoping Su, Xuemei Wang, Hinalben Patel, Ana Ayala, Hagop Kantarjian, Michael Keating, William Wierda

Department of Leukemia
The University of Texas MD Anderson Cancer Center
ASH 2021, Abstract 2626

American Society of Hematology
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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)

Blood 2021;138(24):2589-92.

Letter to *Blood*

TO THE EDITOR:

Ibrutinib induces durable remissions in treatment-naïve patients with CLL and 17p deletion and/or *TP53* mutations

Mariela Sivina, Ekaterina Kim, William G. Wierda, Alessandra Ferrajoli, Nitin Jain, Philip Thompson, Hagop Kantarjian, Michael Keating, and Jan A. Burger

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]

Meet The Professor with Dr Wierda

MODULE 1: Case Presentations

- Dr Bhatnager: A 77-year-old man with chronic lymphocytic leukemia (CLL) and a TP53 mutation who experiences disease progression after observation
- Dr Brenner: A 69-year-old man with CLL and brawny type edema during treatment with ibrutinib
- Dr Palmer: A 76-year-old man with relapsed CLL after 3 years of second-line ibrutinib
- Dr Khan: A 60-year-old man with newly diagnosed CLL who received obinutuzumab/venetoclax
- Dr Smith: An 81-year-old man with CLL and bone marrow infiltrate consistent with Hodgkin lymphoma
- Dr Bhatnagar: A 72-year-old man with CLL and significant cytopenias on acalabrutinib

MODULE 2: Faculty Survey

MODULE 3: Journal Club with Dr Wierda

MODULE 4: Key Recent Data Sets

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Minimal Residual Disease

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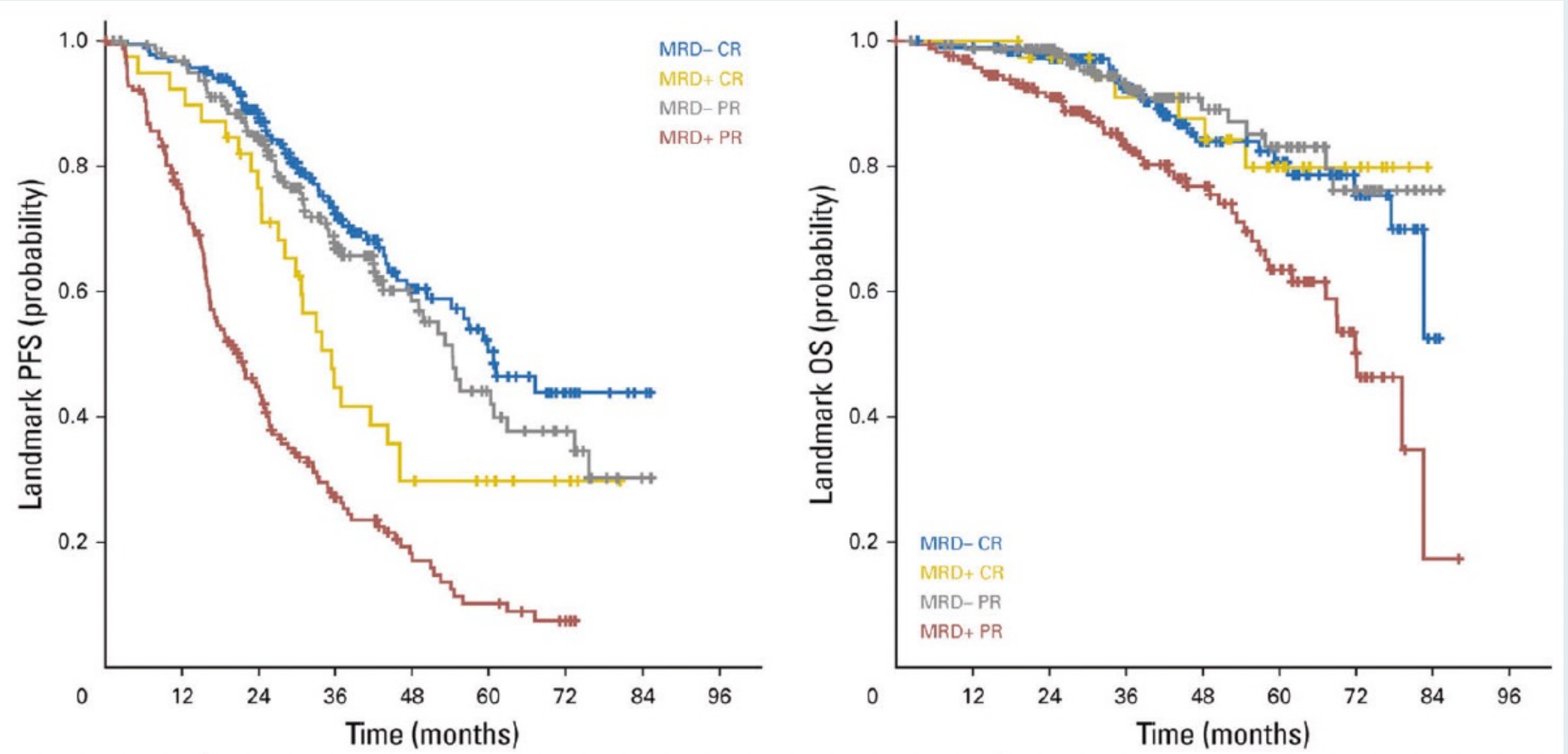
Currently Applied Methods for MRD Assessment

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

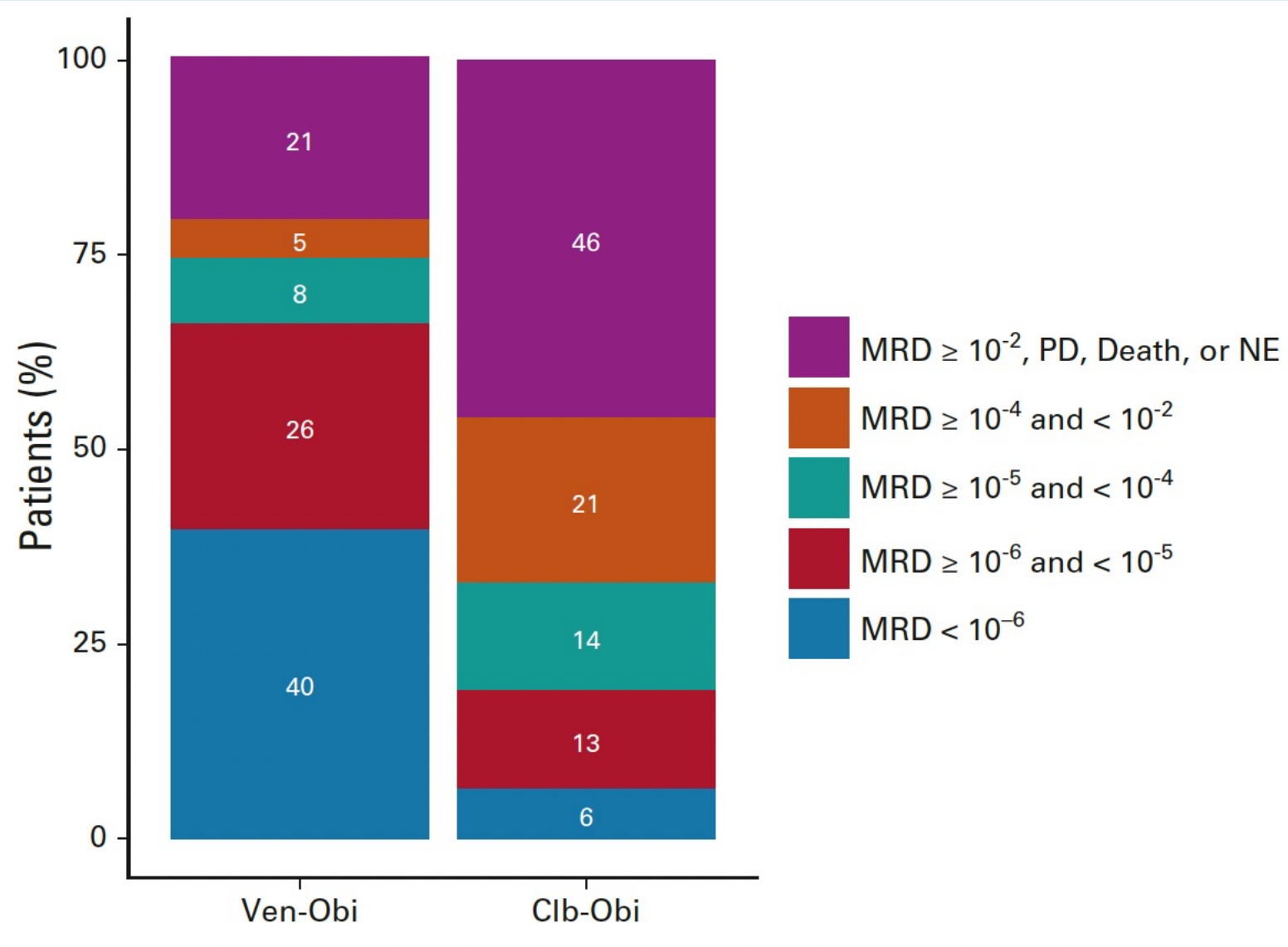
original reports

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]

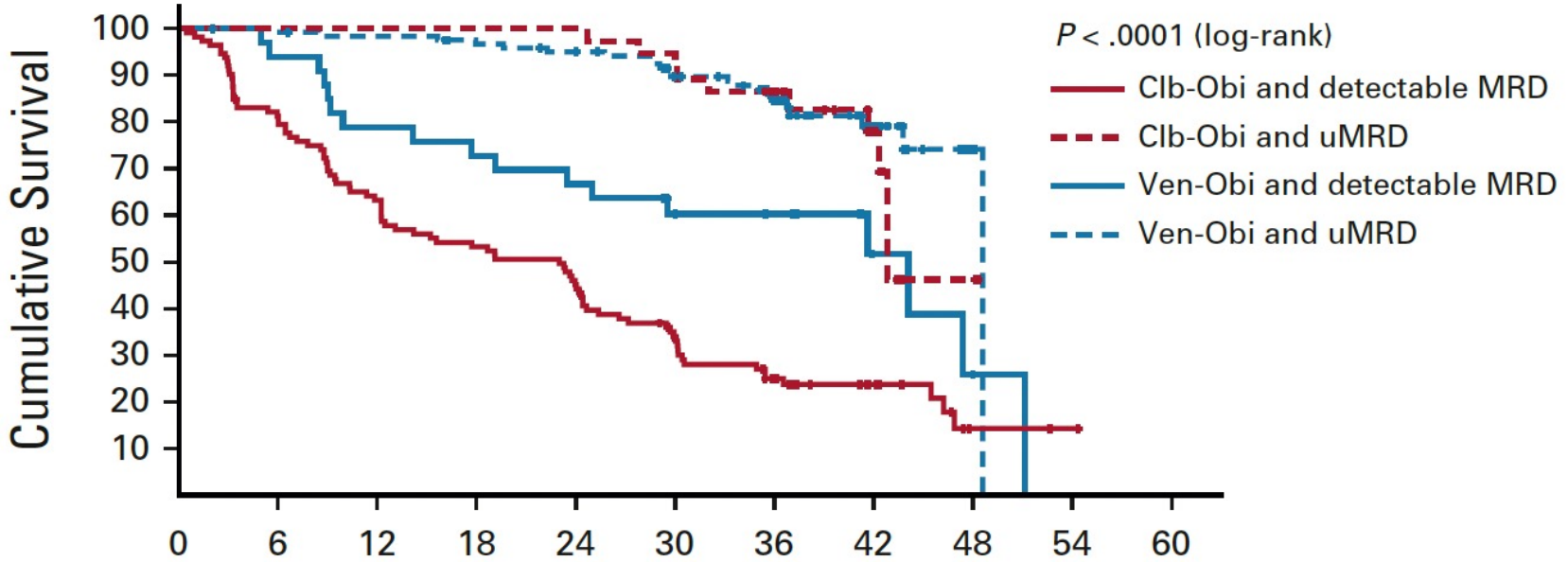
J Clin Oncol 2021;39(36):4049-60.

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



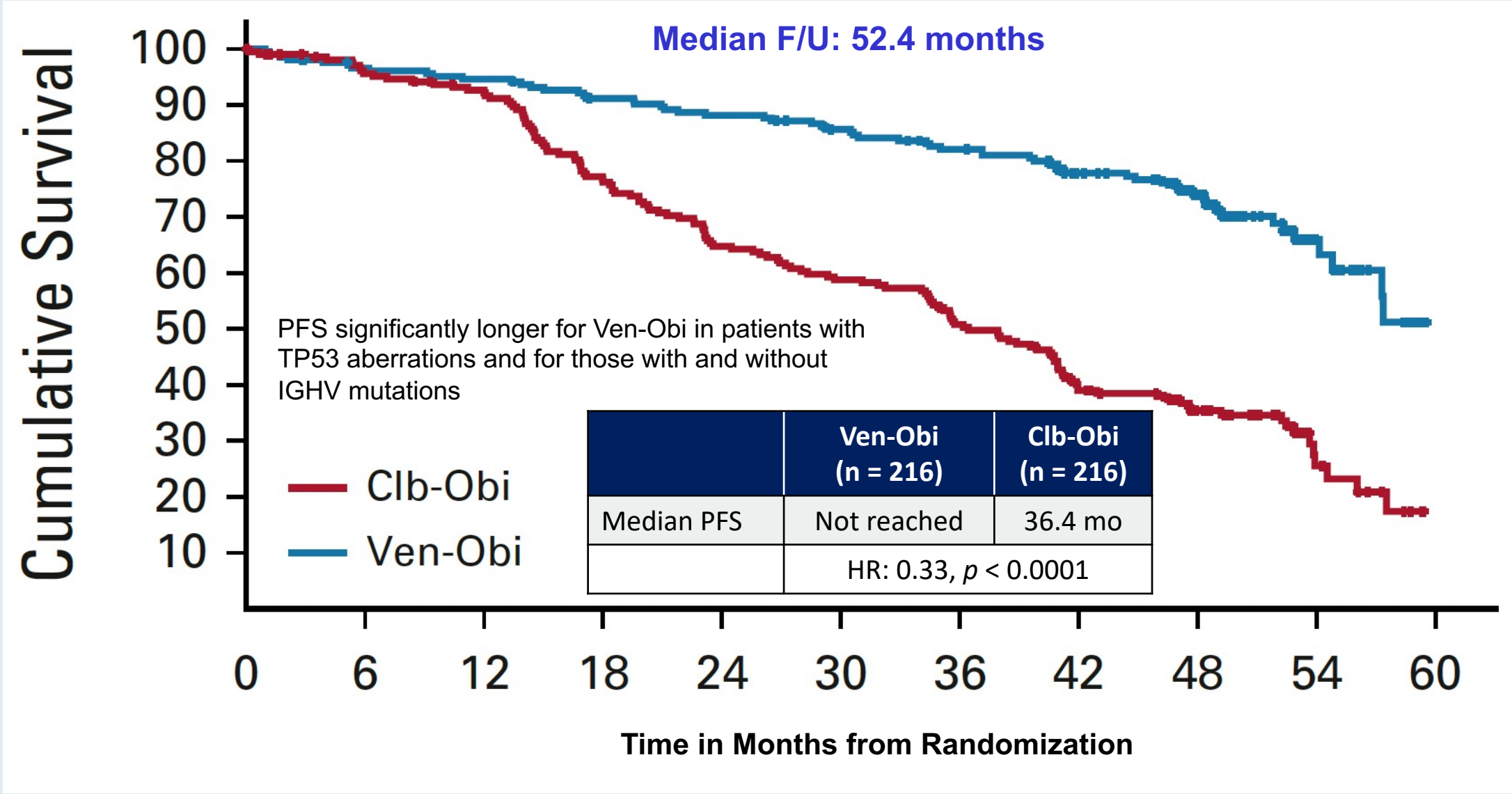
No. at risk:

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.

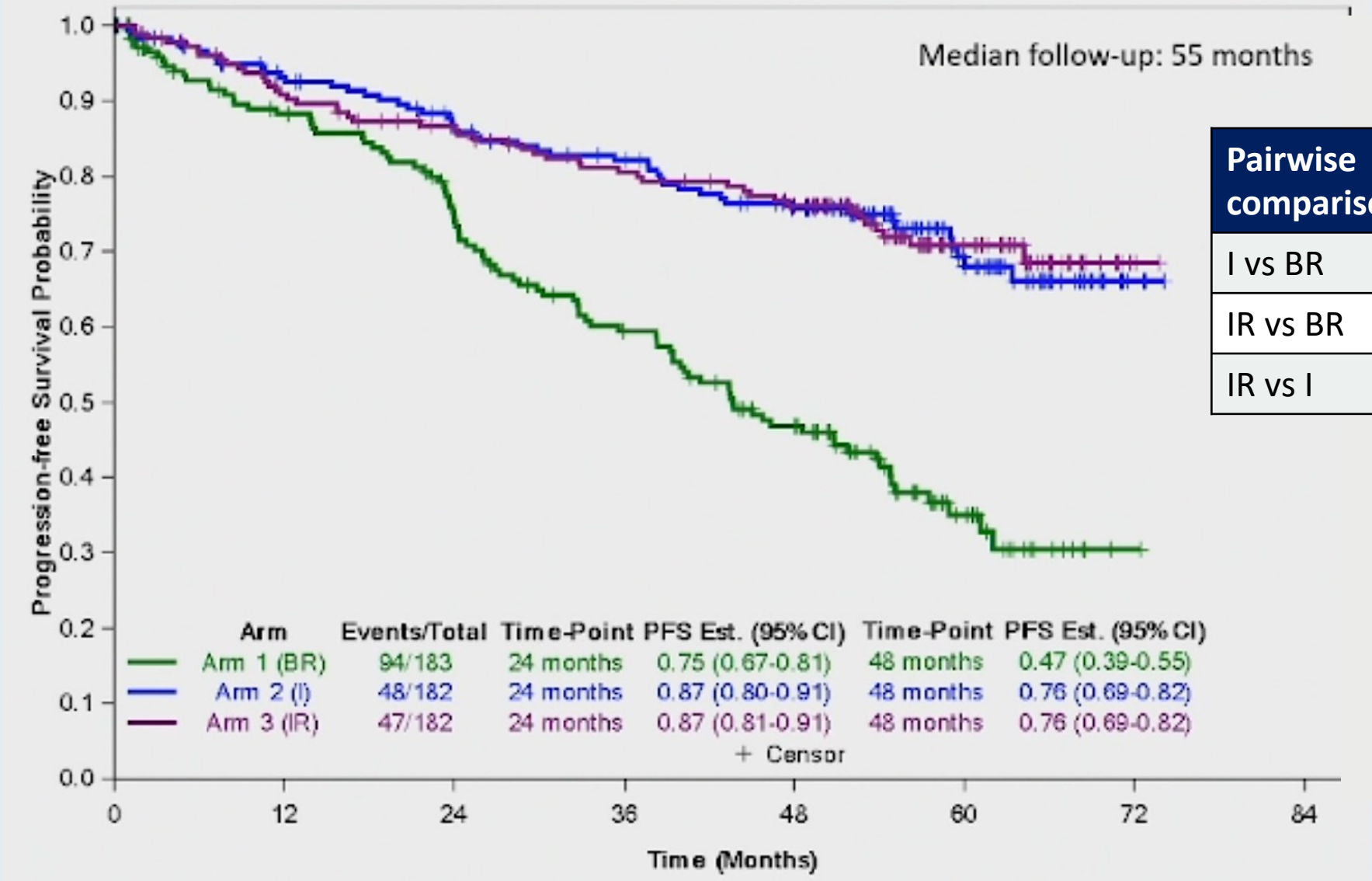
RTP RESEARCH TO PRACTICE

Long-Term Results of Alliance A041202 Show Continued Advantage of Ibrutinib-Based Regimens Compared with Bendamustine Plus Rituximab (BR) Chemoimmunotherapy

Woyach JA et al.

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.

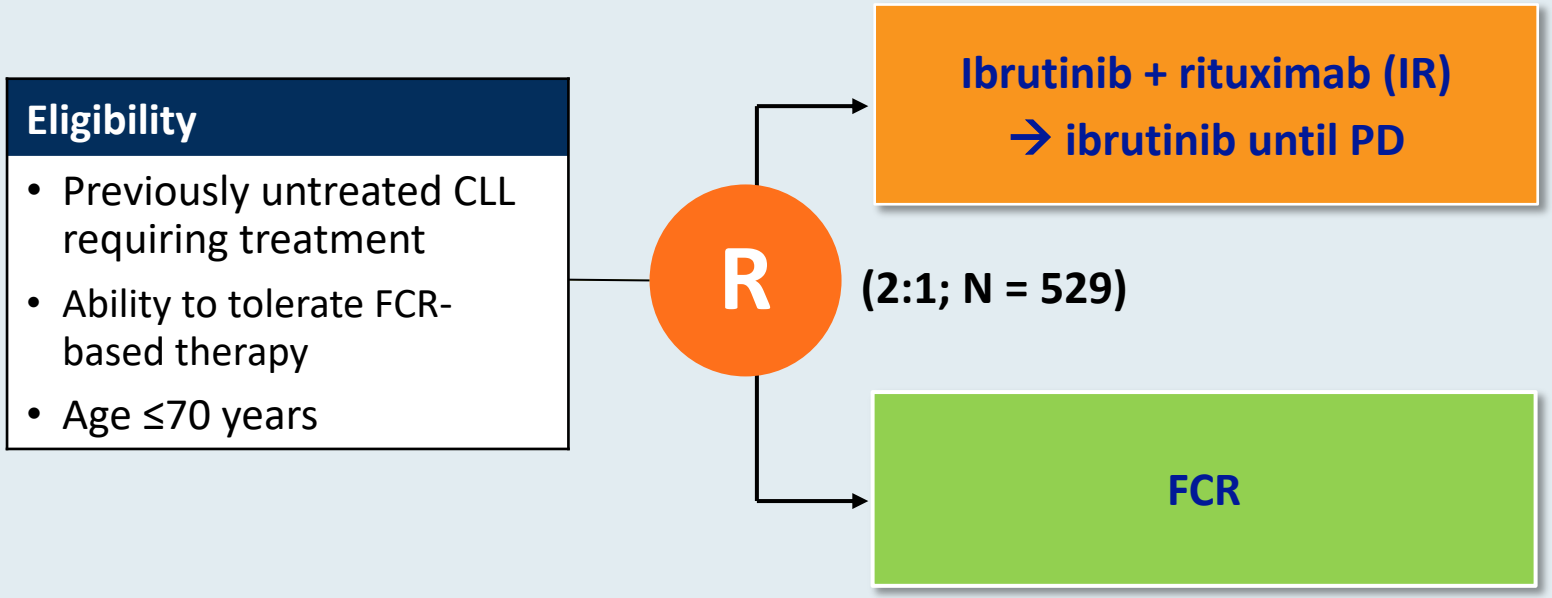
RTP RESEARCH TO PRACTICE

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.

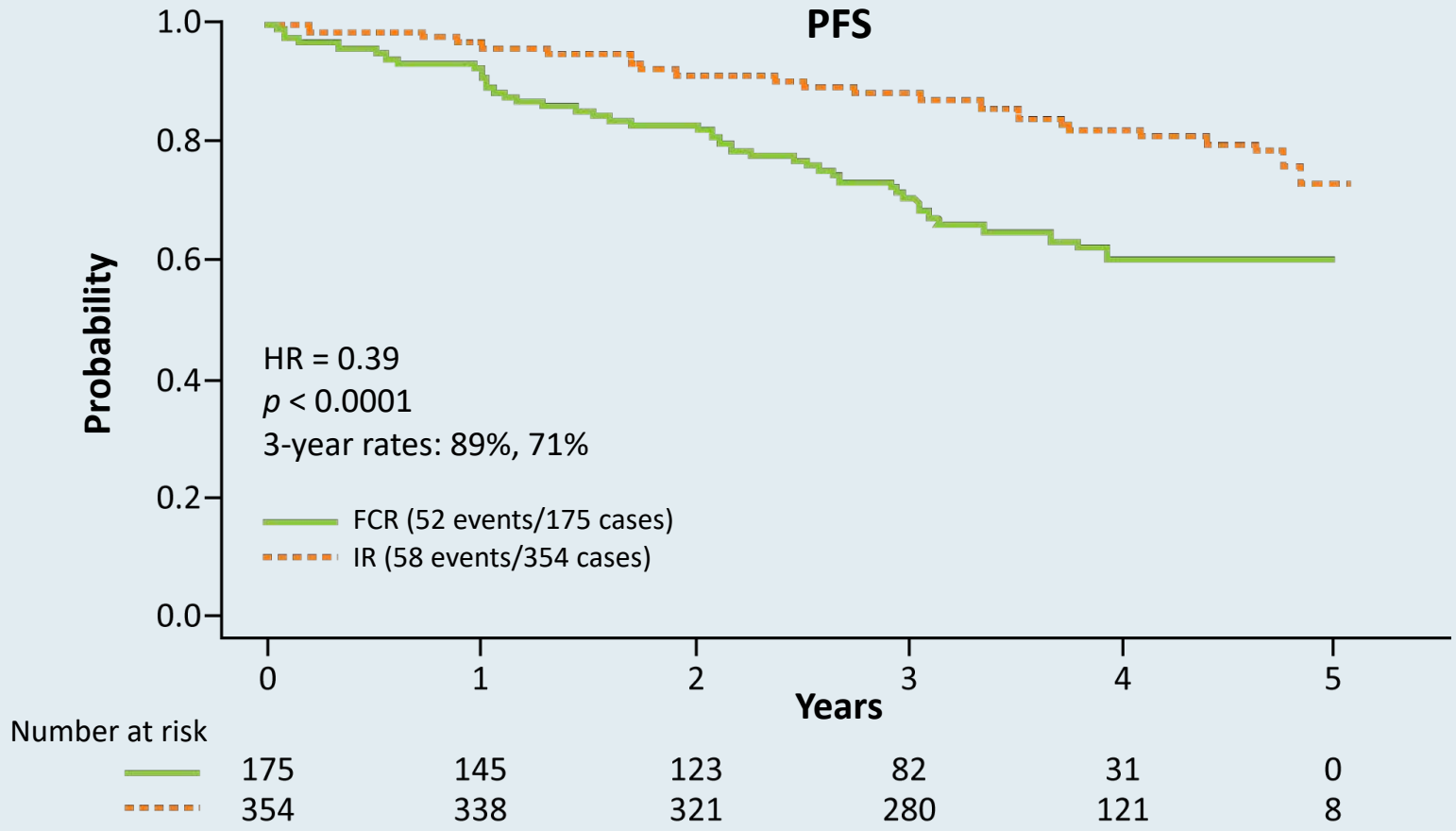
Phase III ECOG-ACRIN E1912 Study Design



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.

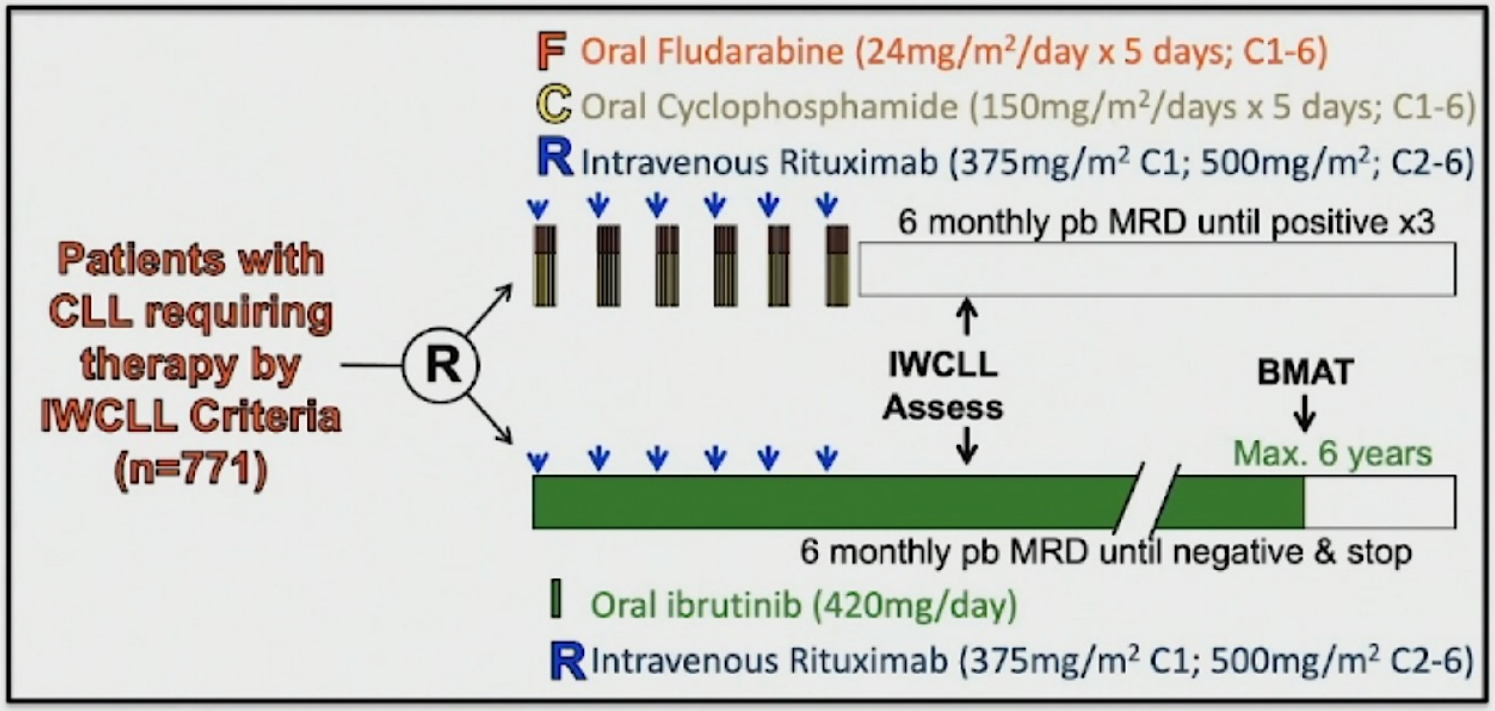
RTP RESEARCH TO PRACTICE

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:

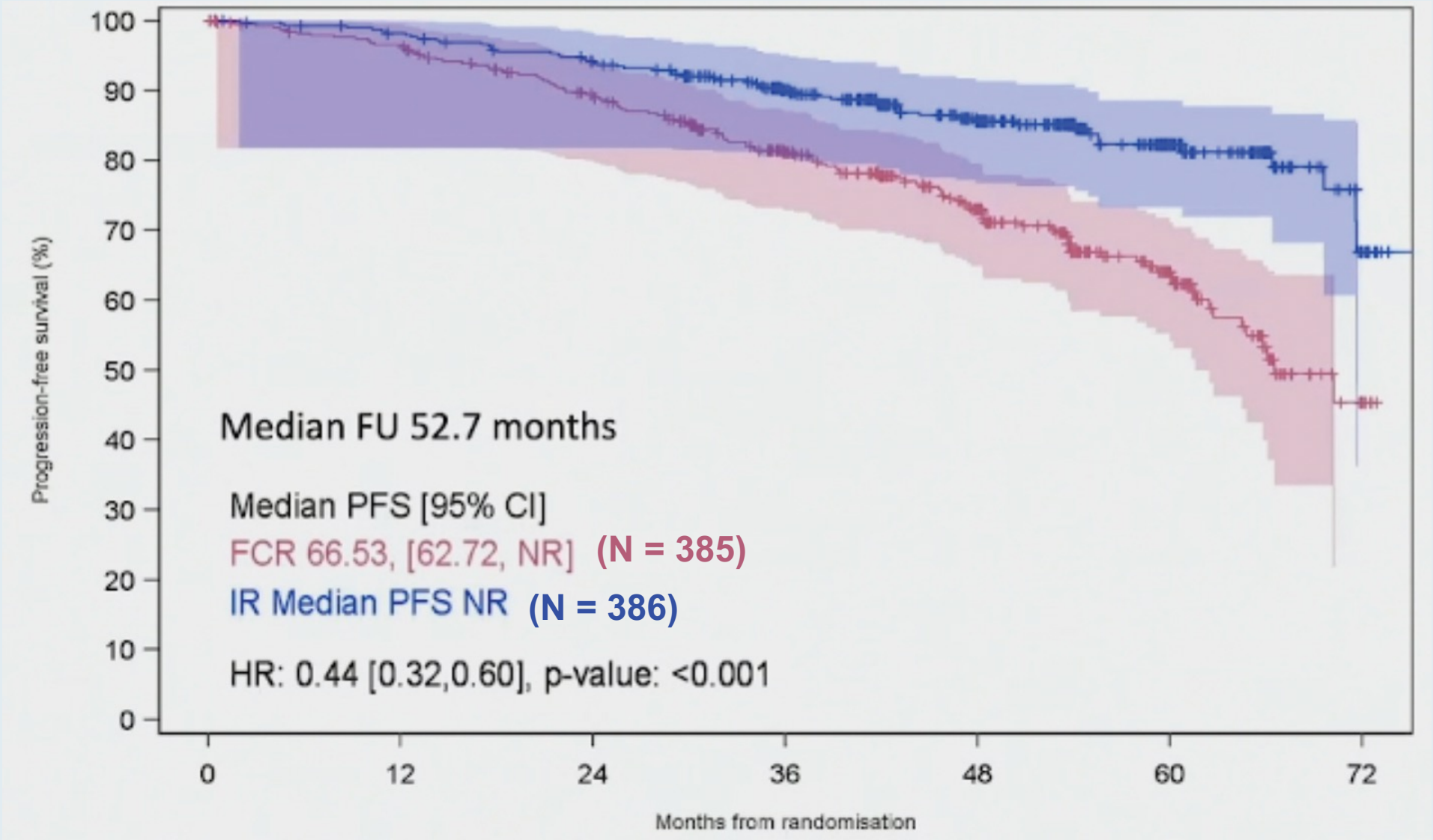
- Previously untreated CLL requiring therapy by IWCLL criteria
- Considered fit for FCR
- ≤75 years old

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

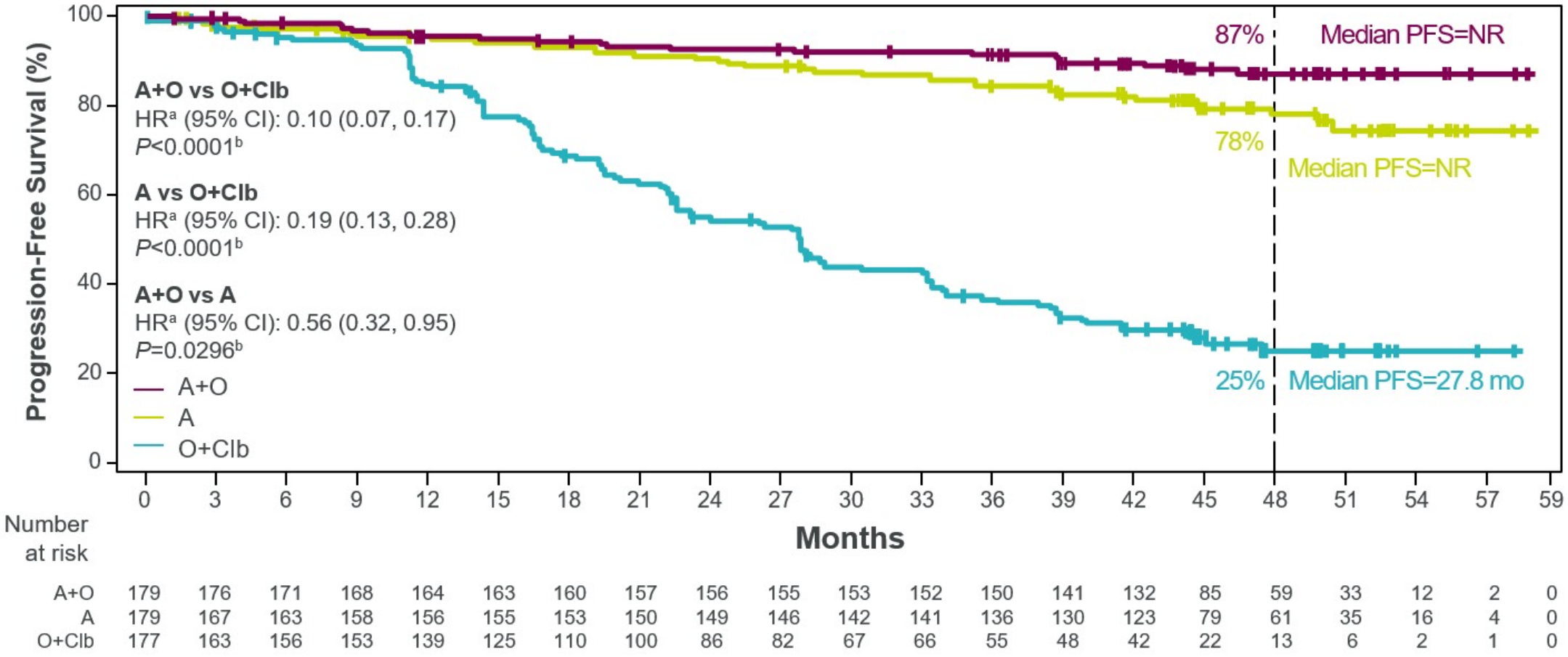
Leukemia 2022;[Online ahead of print].

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

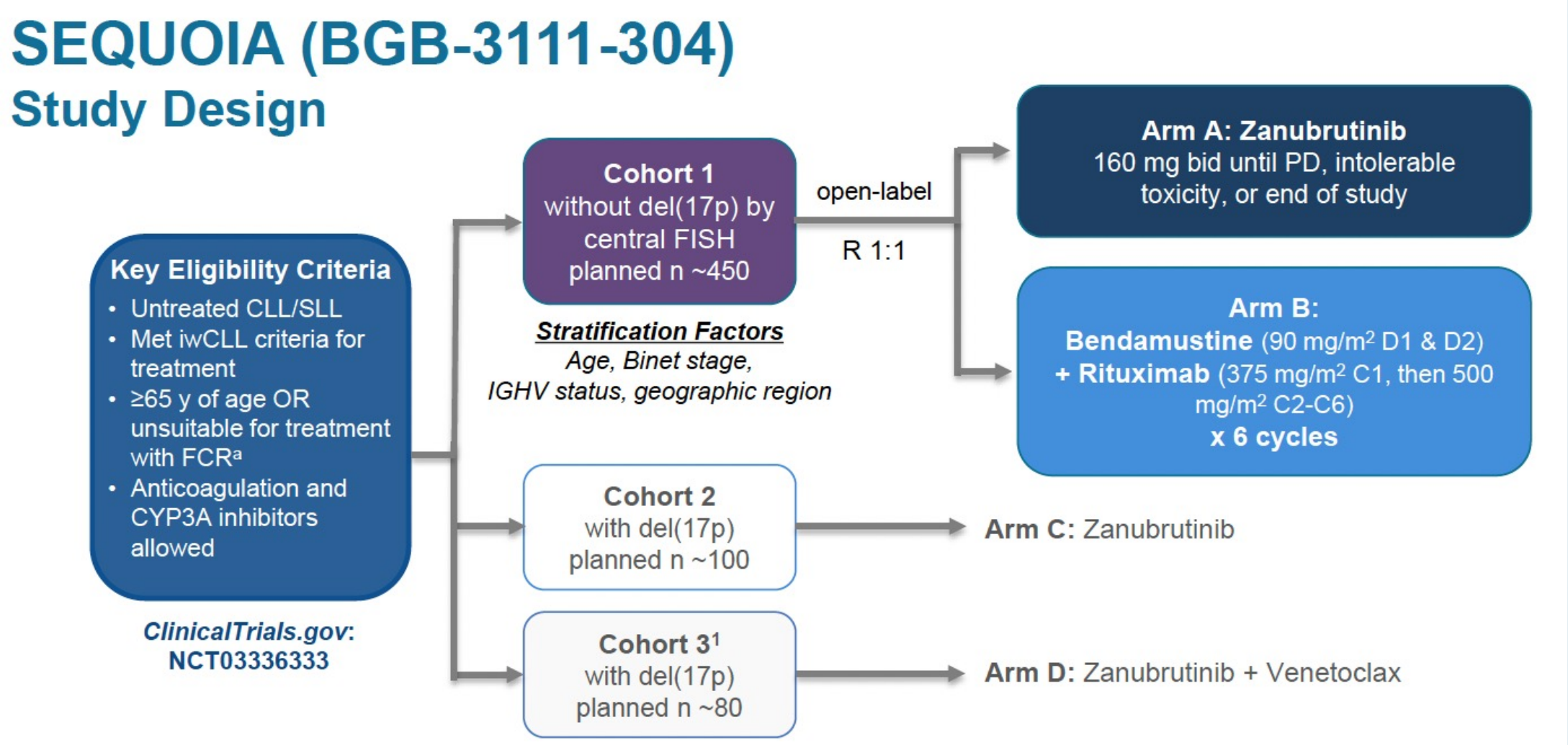
SEQUOIA: RESULTS OF A PHASE 3 RANDOMIZED STUDY OF ZANUBRUTINIB VERSUS BENDAMUSTINE + RITUXIMAB IN PATIENTS WITH TREATMENT-NAIVE CHRONIC LYMPHOCYTIC LEUKEMIA/SMALL LYMPHOCYTIC LYMPHOMA

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

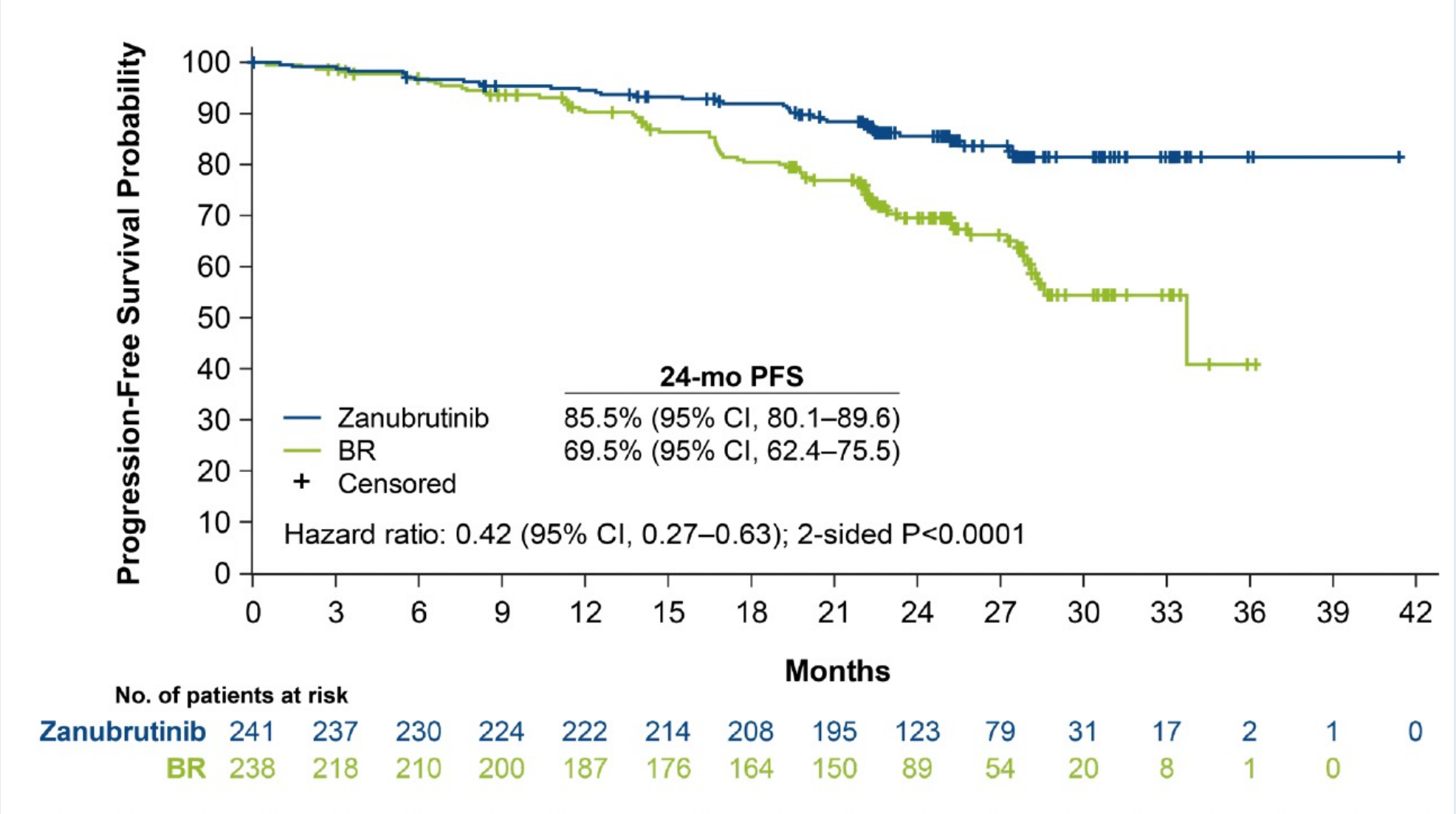
Sunday, December 12, 2021
642. Chronic Lymphocytic Leukemia: Clinical and Epidemiological I

SEQUOIA Phase III Study Design



Tam CS et al. ASH 2021;Abstract 396.

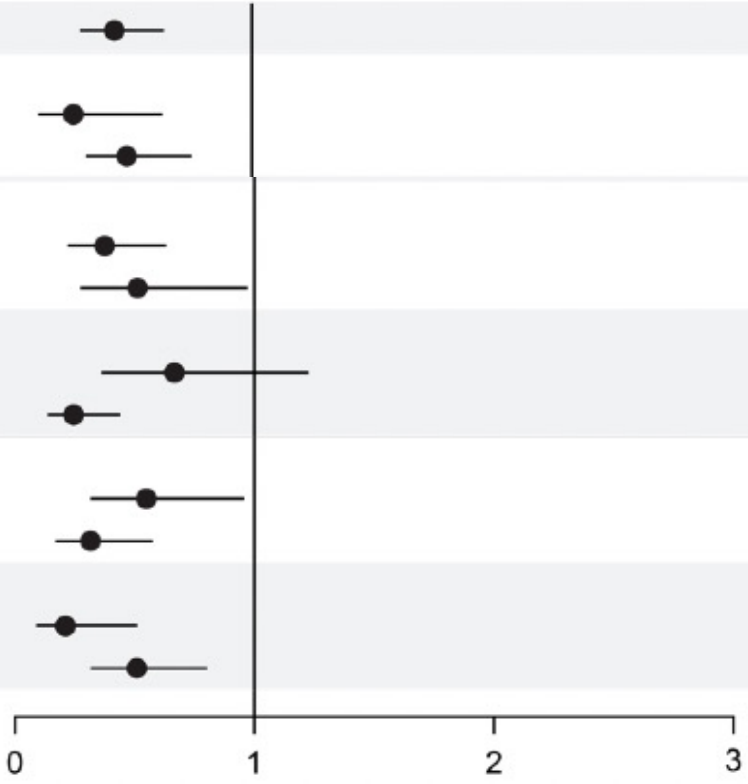
SEQUOIA: Progression-Free Survival by IRC



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: 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.

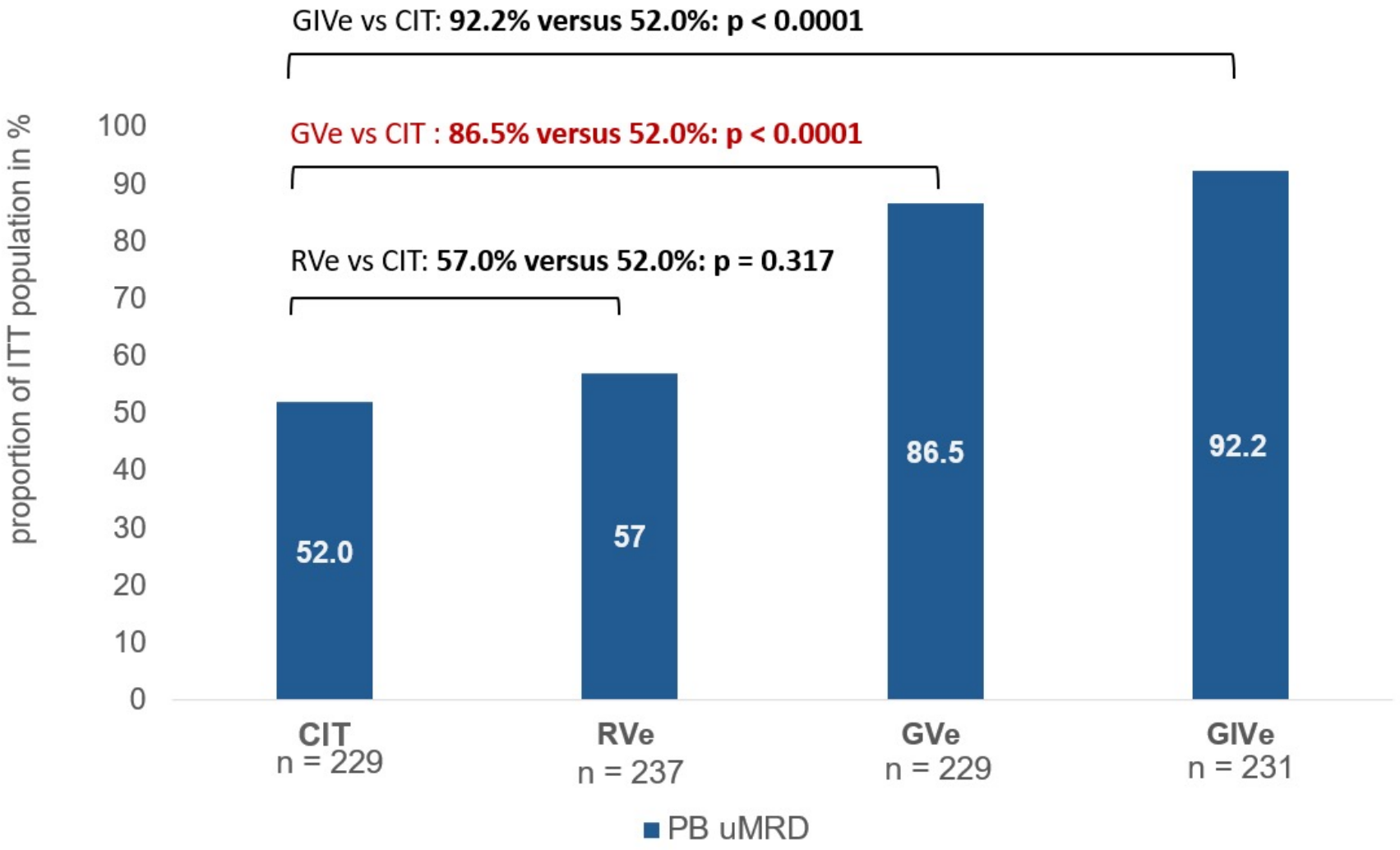
Venetoclax Combination Regimens

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.

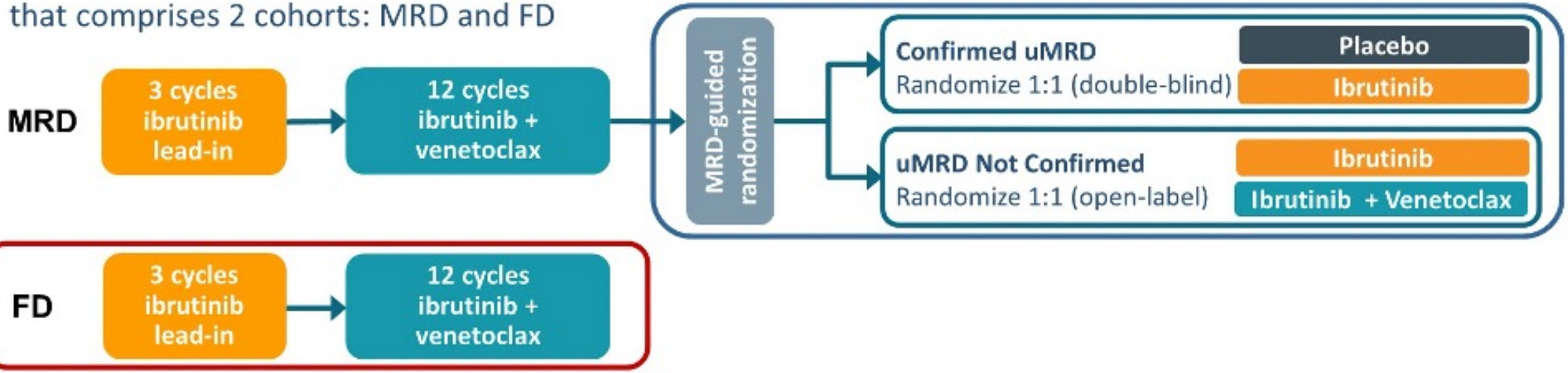
Fixed-Duration (FD) First-Line Treatment With Ibrutinib Plus Venetoclax for Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma: Primary Analysis of the FD Cohort of the Phase 2 CAPTIVATE Study

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

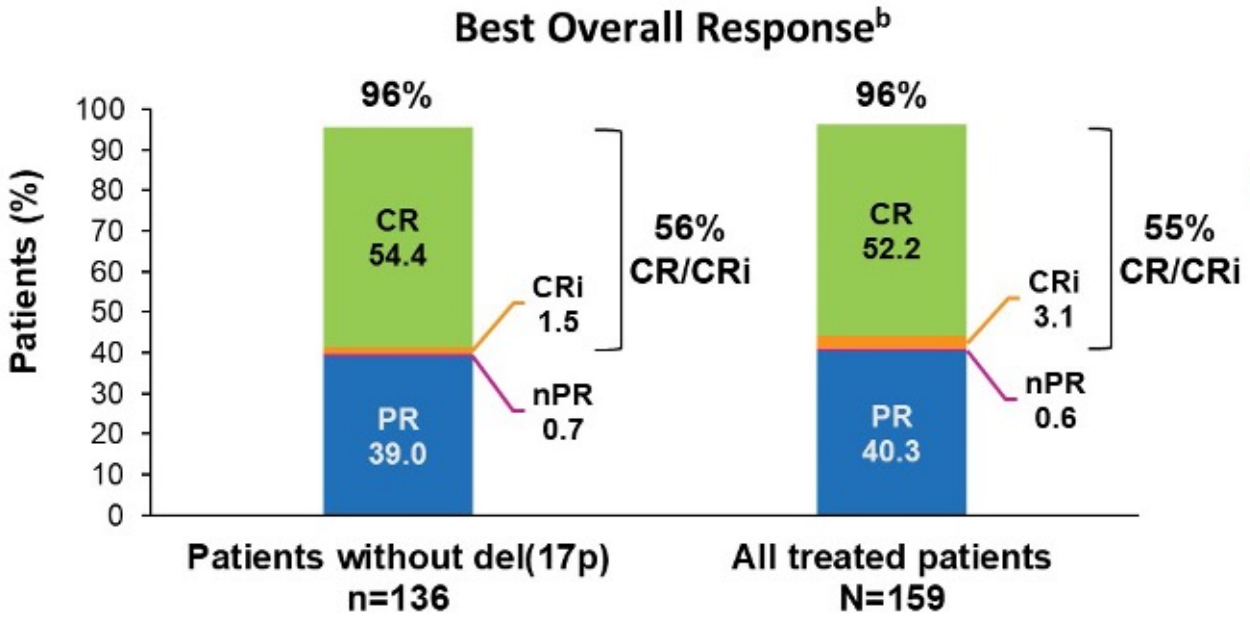
- CAPTIVATE (PCYC-1142) is an international, multicenter phase 2 study evaluating first-line treatment with 3 cycles of ibrutinib followed by 12 cycles of combined ibrutinib + venetoclax that comprises 2 cohorts: MRD and FD



- 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



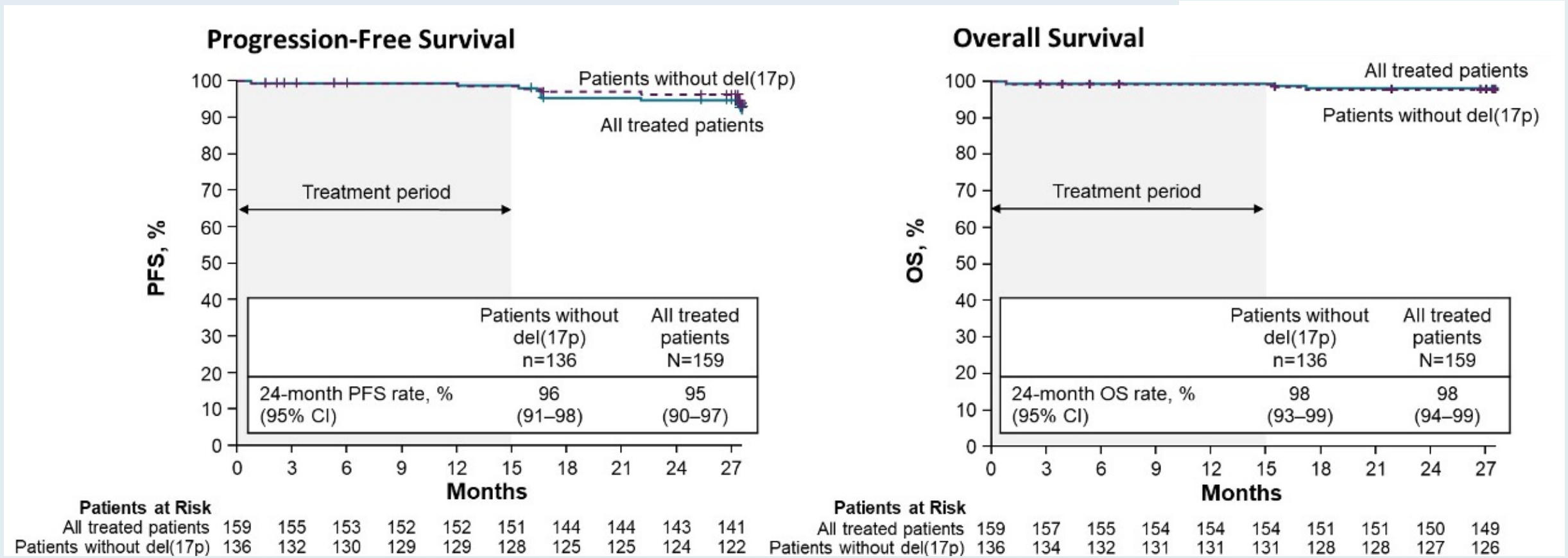
DOCR ≥12 cycles n/N (%)	66/76 (87)	78/88 (89)*

- 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.

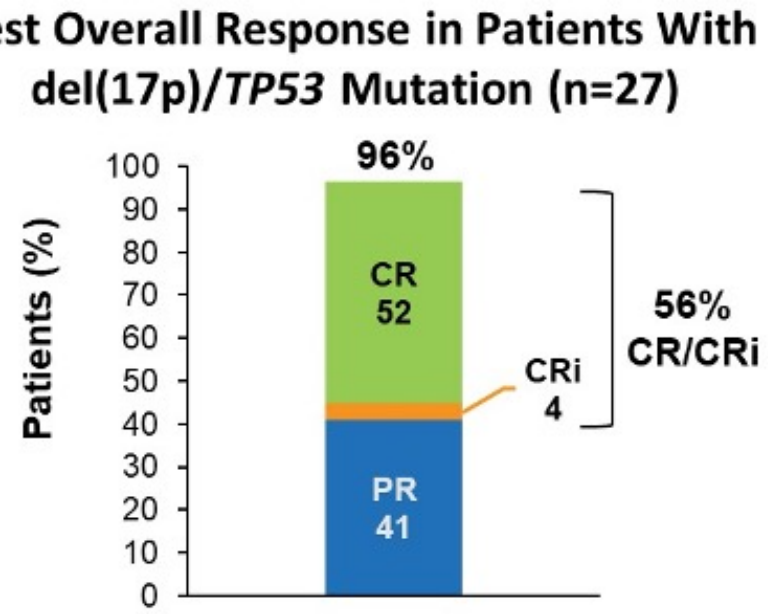
Ghia P et al. ASCO 2021;Abstract 7051.

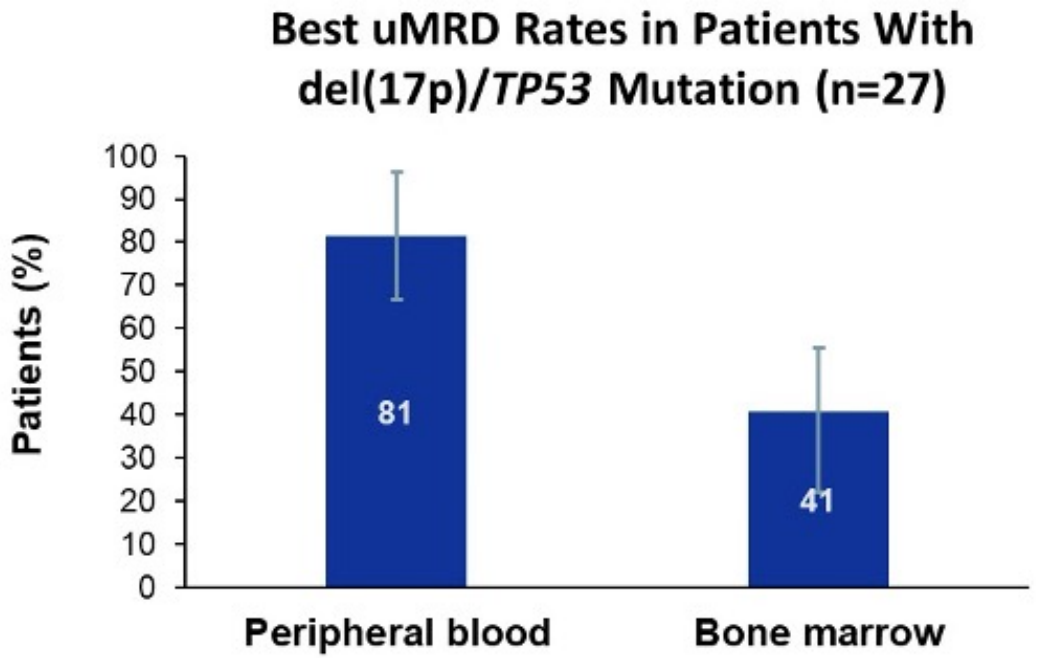
CAPTIVATE: Progression-Free and Overall Survival



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)

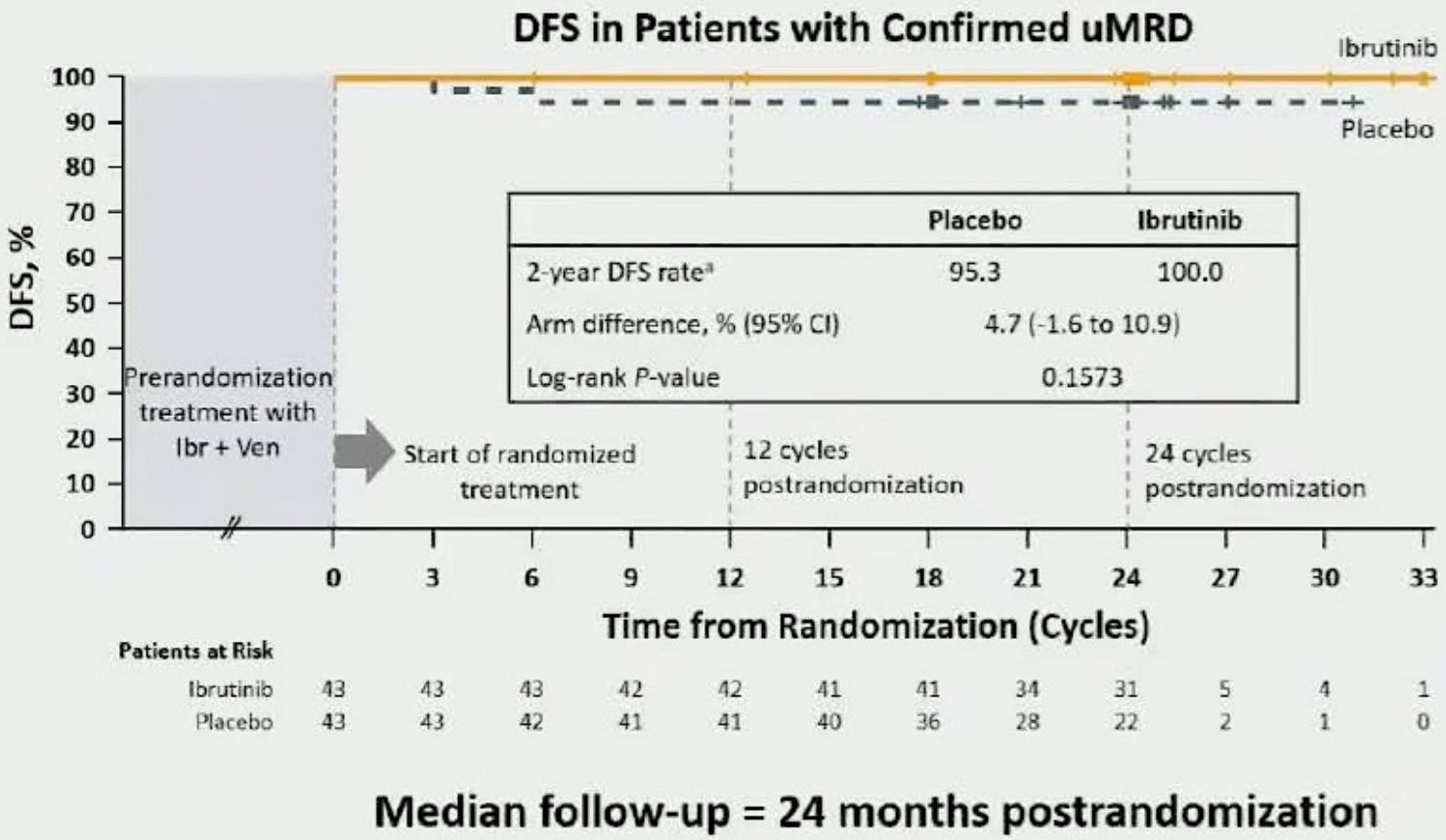
Ghia P et al. ASCO 2021;Abstract 7051.

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

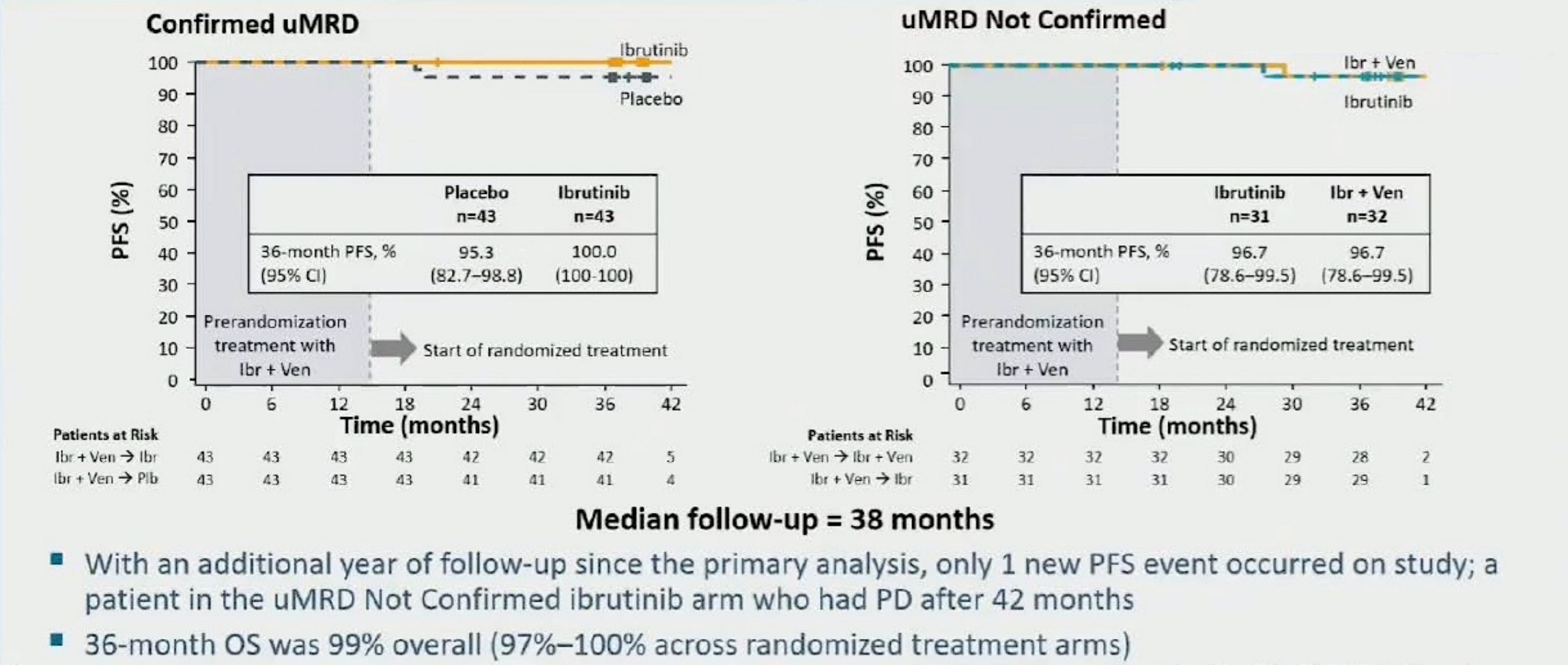


Median follow-up = 24 months postrandomization

- 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

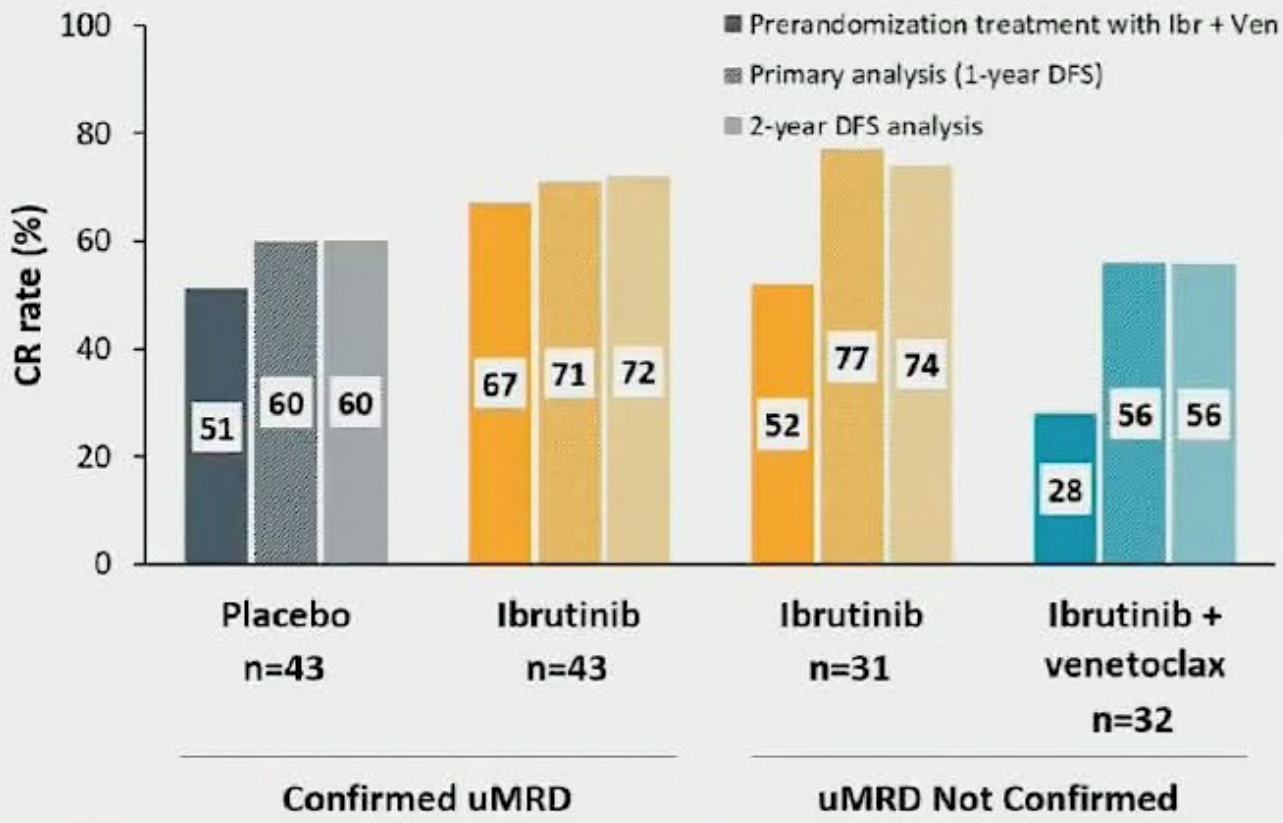


Median follow-up = 38 months

- 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.

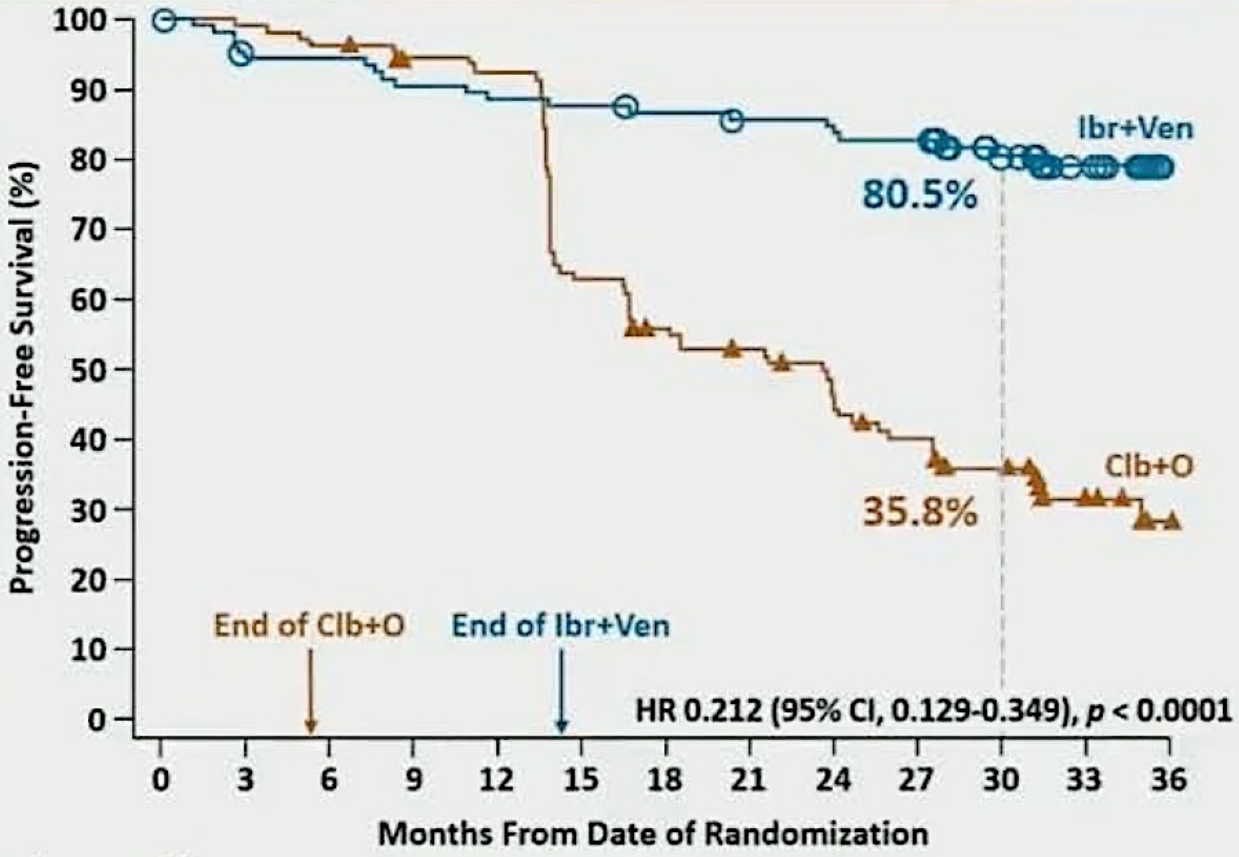
First Prospective Data on Minimal Residual Disease (MRD) Outcomes After Fixed-Duration Ibrutinib Plus Venetoclax (Ibr+Ven) Versus Chlorambucil Plus Obinutuzumab (Clb+O) for First-Line Treatment of CLL in Elderly or Unfit Patients: The GLOW Study

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.

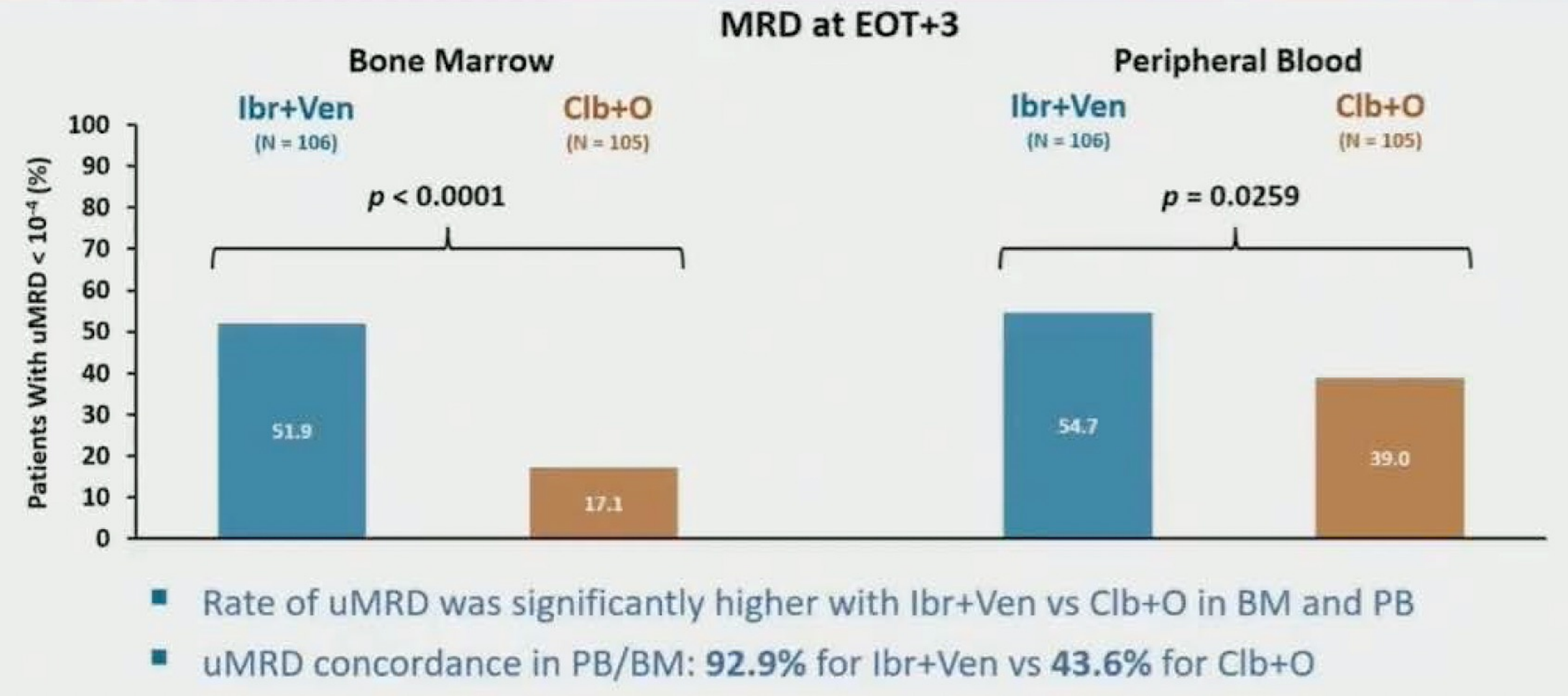
GLOW: Independent Review Committee (IRC)-Assessed PFS



- 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.

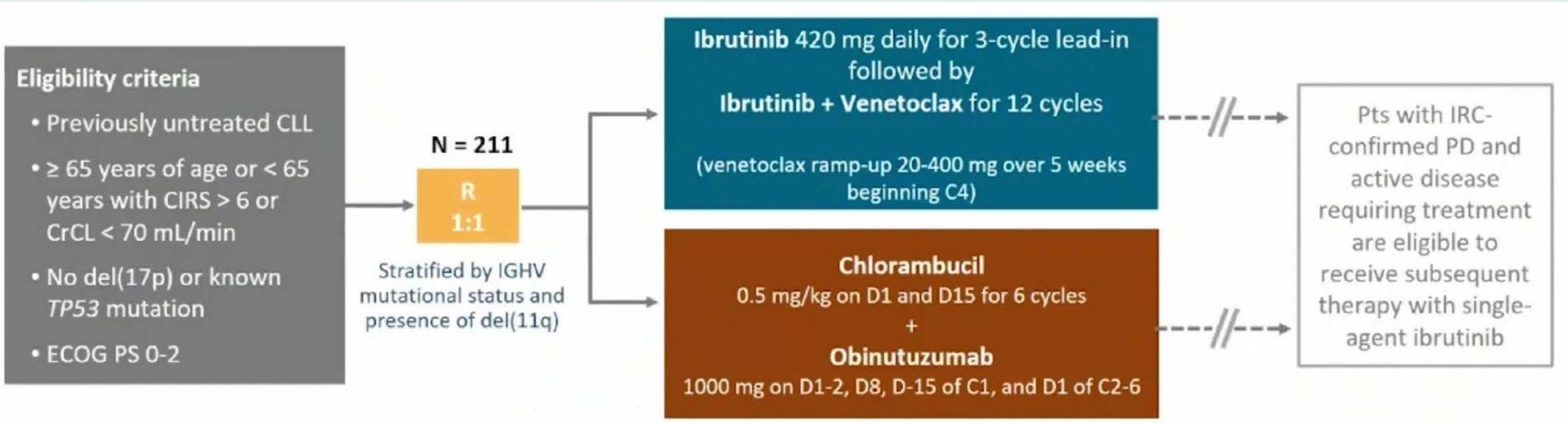
RTP RESEARCH TO PRACTICE

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



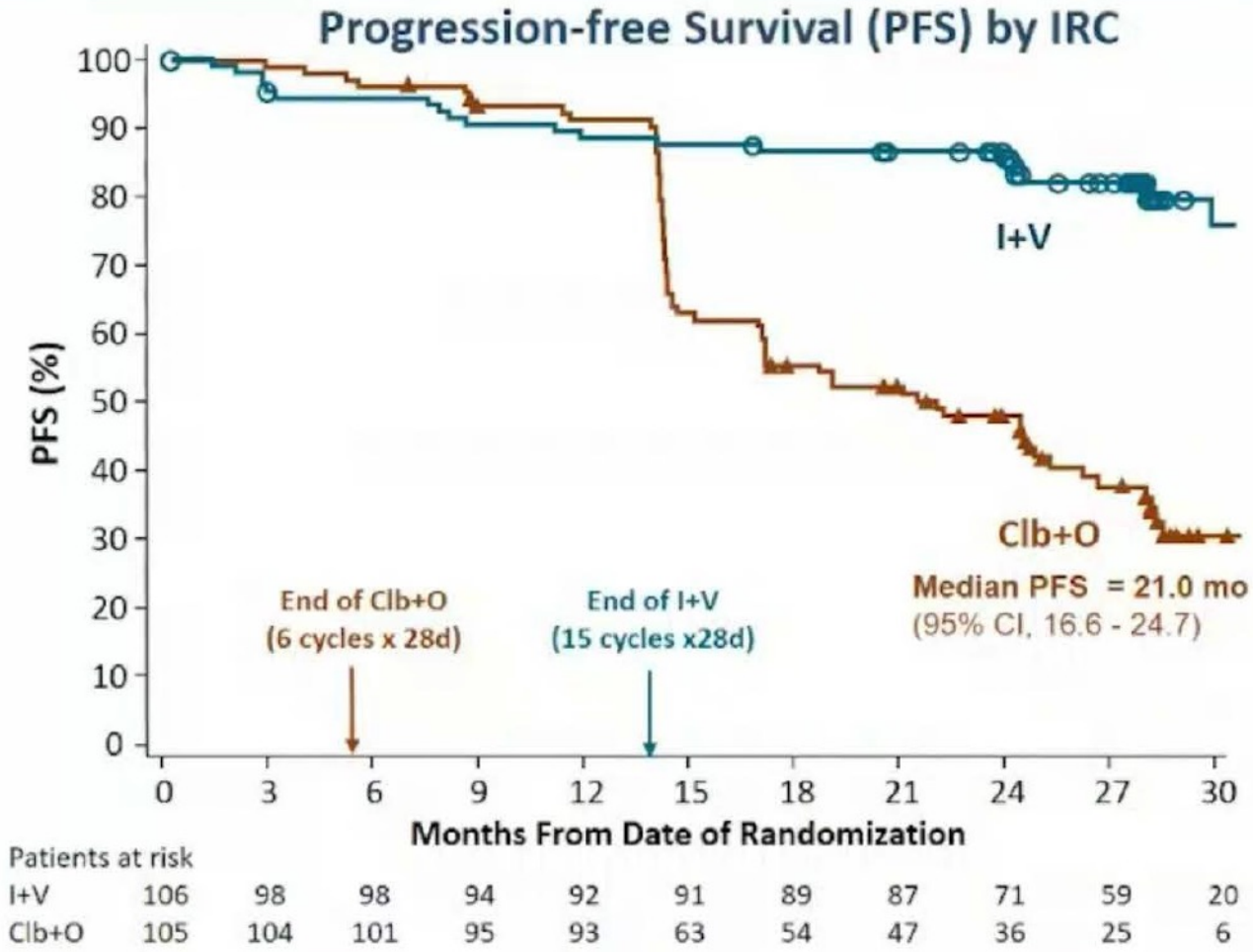
Primary end point: Progression-free survival by independent review committee (IRC)

- 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

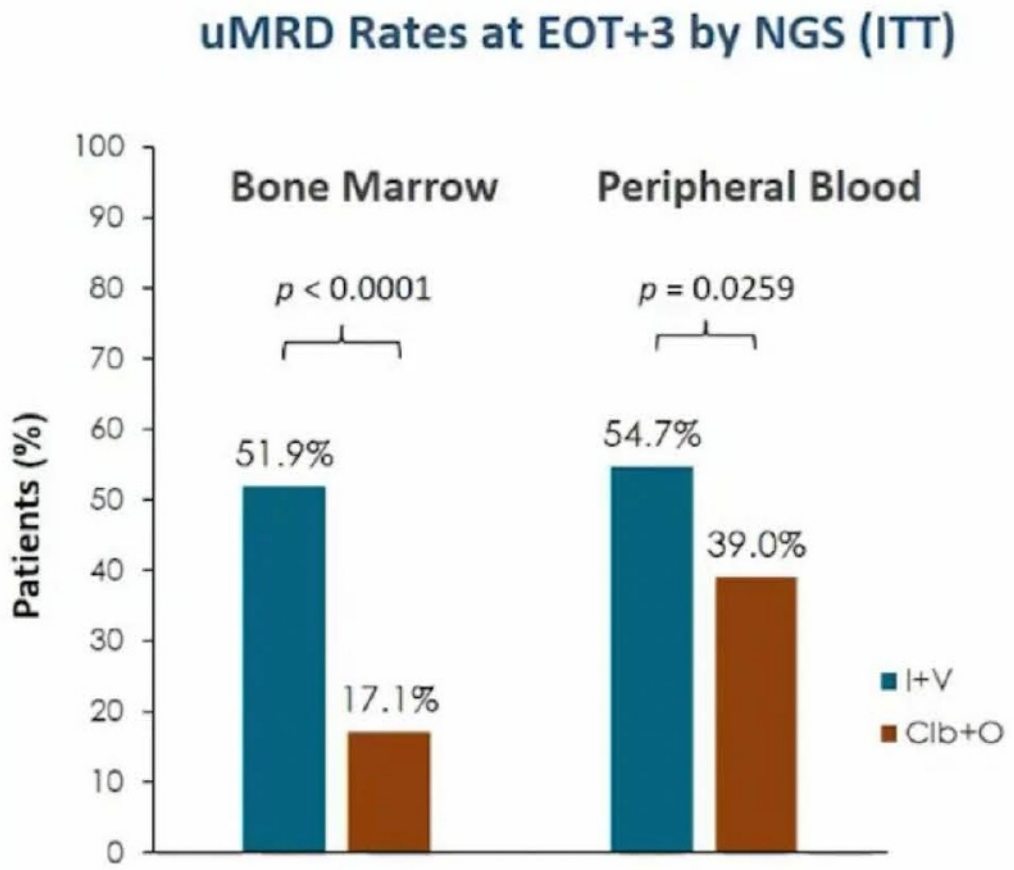


- **With a median follow up of 27.7 months, IRC-assessed PFS for I+V was superior to Clb+O**
- I+V reduced the risk of progression or death by 78% vs Clb+O
  - **HR 0.216** (95% CI, 0.131-0.357; p < 0.0001)
- PFS by INV assessment was consistent with IRC
  - **HR 0.207** (95% CI, 0.120, 0.357; p < 0.0001)

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%

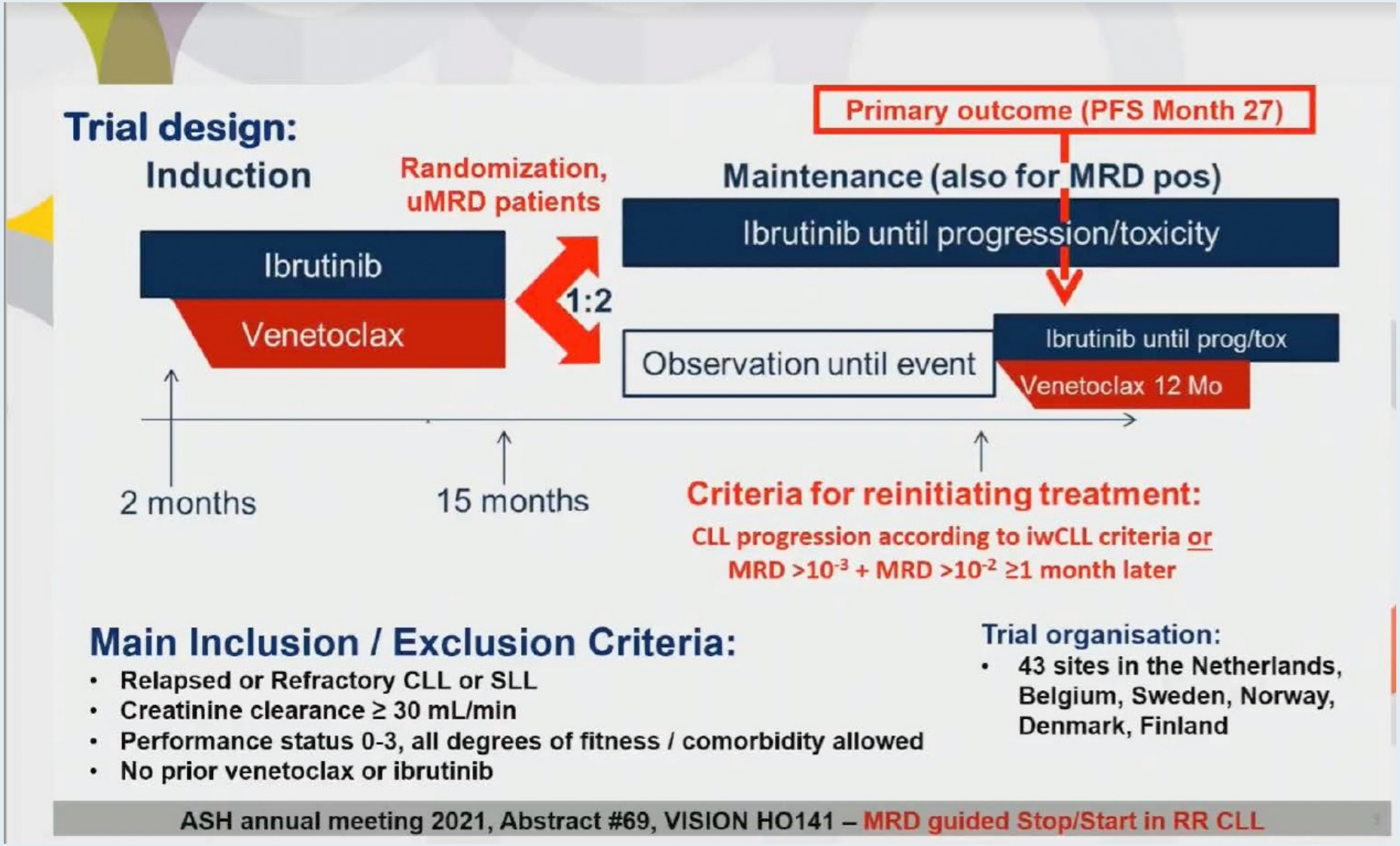
Kater A et al. EHA 2021;Abstract LB1902.

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

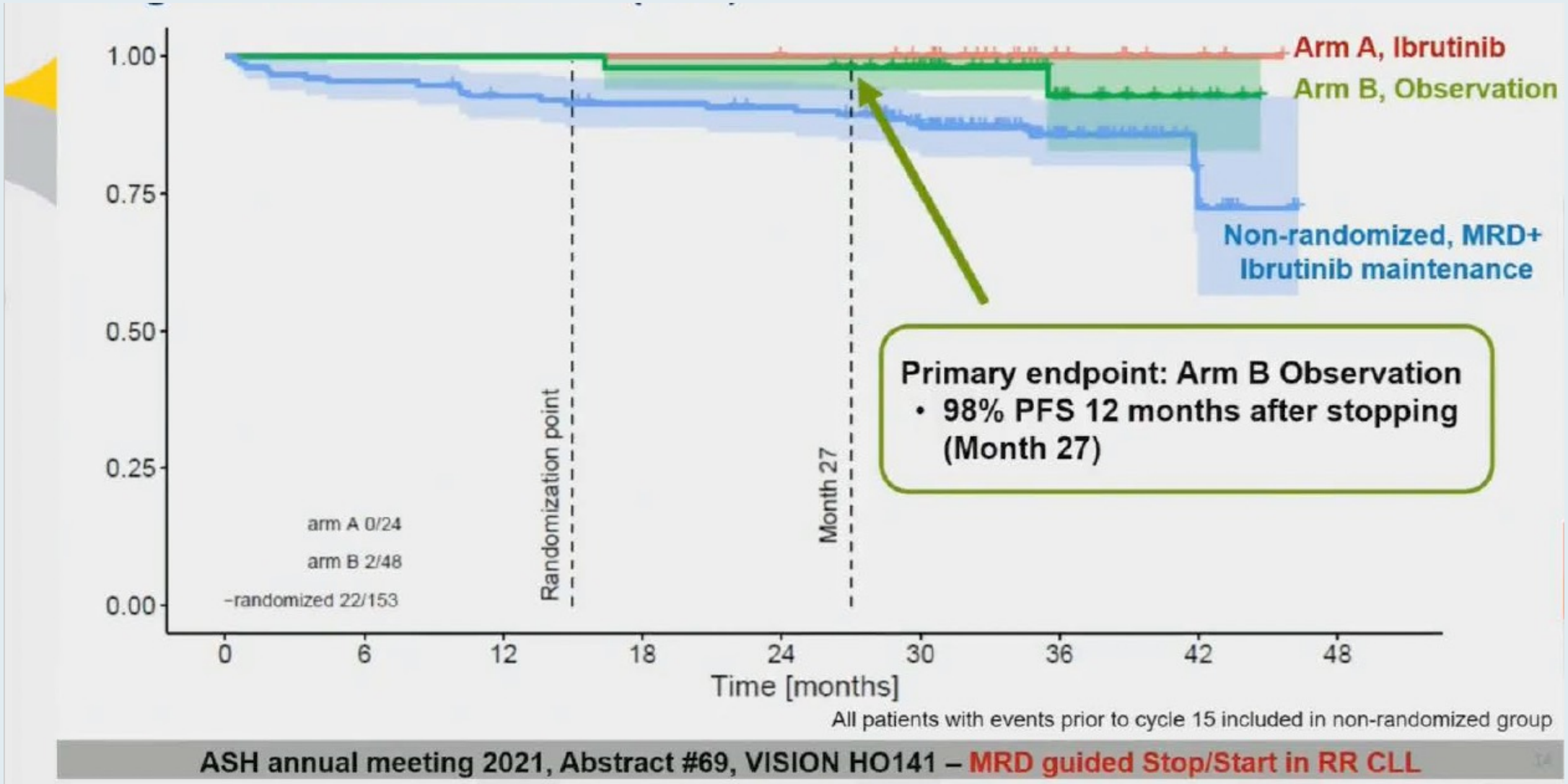
Carsten U Niemann, Julie Dubois, Christian Brieghel, Sabina Kersting, Lisbeth Enggaard, Gerrit J. Veldhuis, Rogier Mous, Clemens HM Mellink, Johan A Dobber, Christian B Poulsen, Henrik Frederiksen, Ann Janssens, Ida Schjødt, Ellen C Dompeling, Juha Ranti, Mattias Mattsson, Mar Bellido, Hoa TT Tran, Kazem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

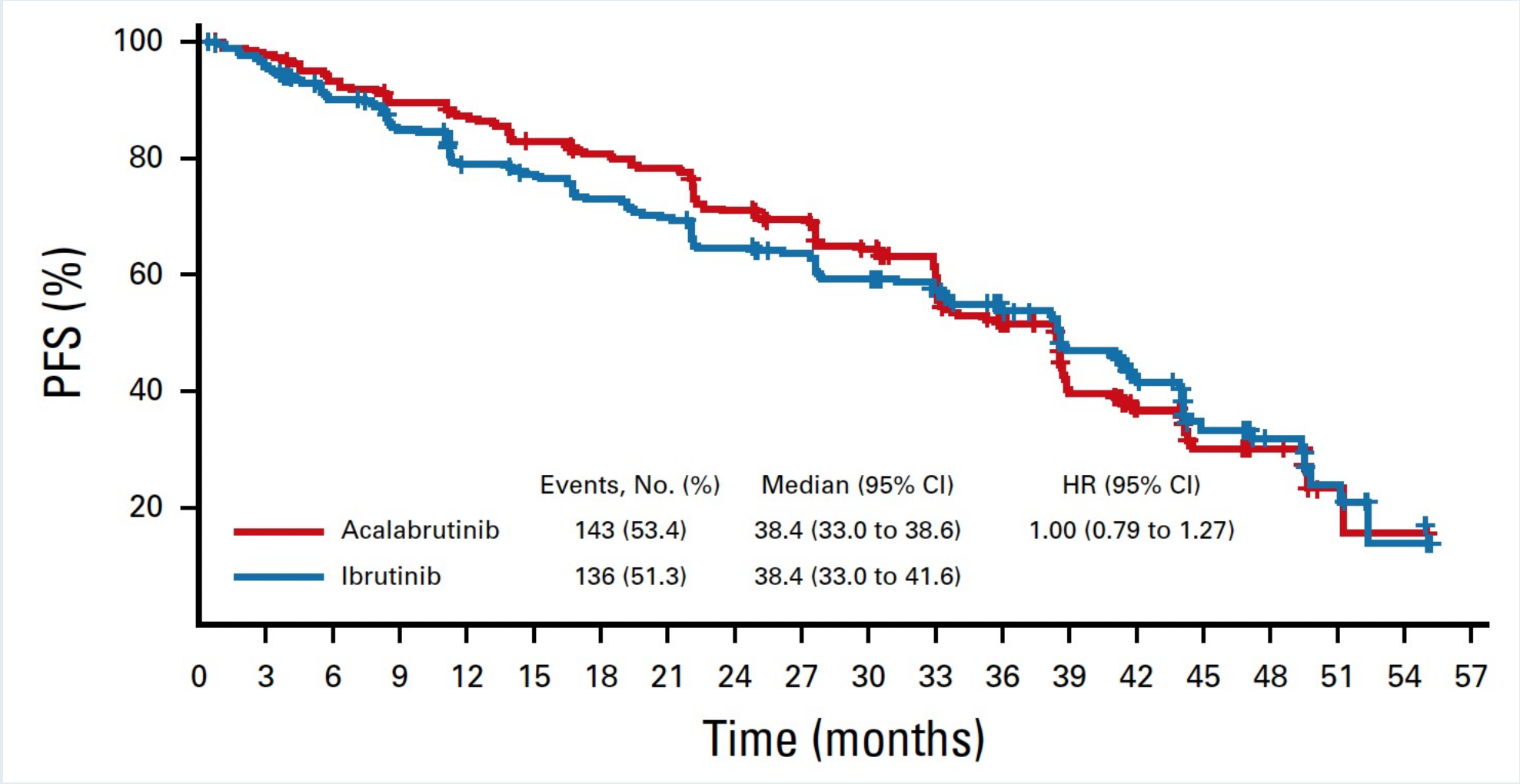
Acalabrutinib Versus Ibrutinib in Previously Treated Chronic Lymphocytic Leukemia: Results of the First Randomized Phase III Trial

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

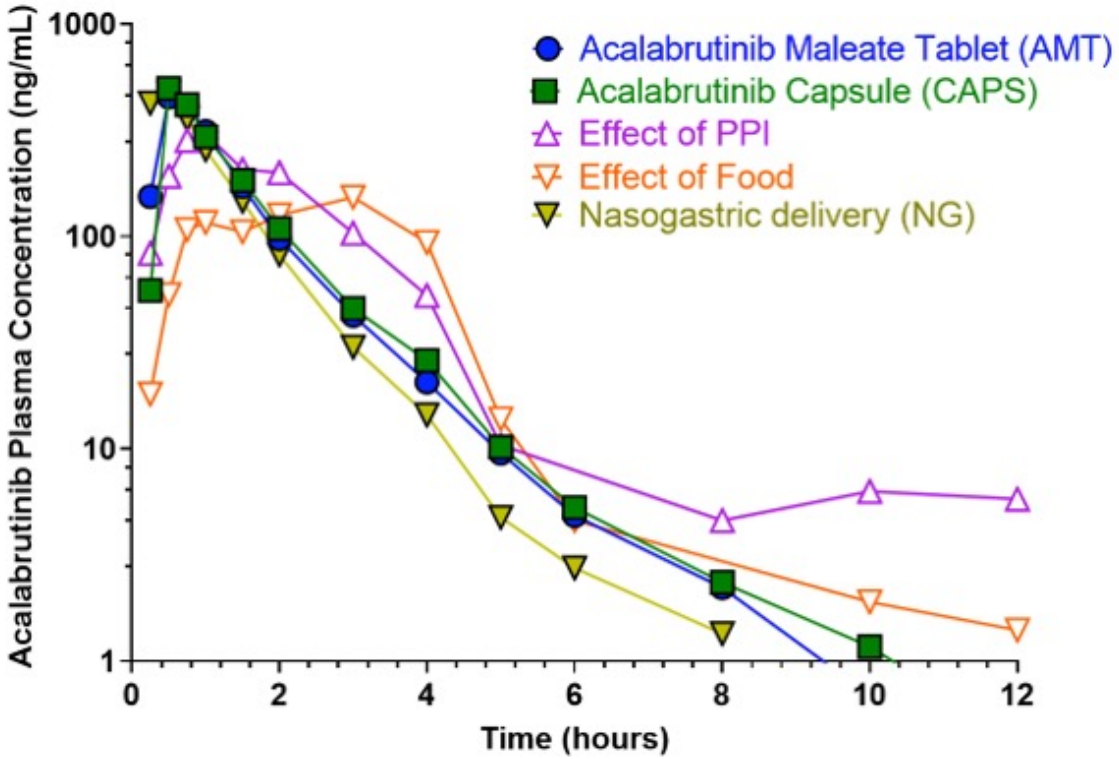
Seymour JF et al. ASH 2021;Abstract 3721.

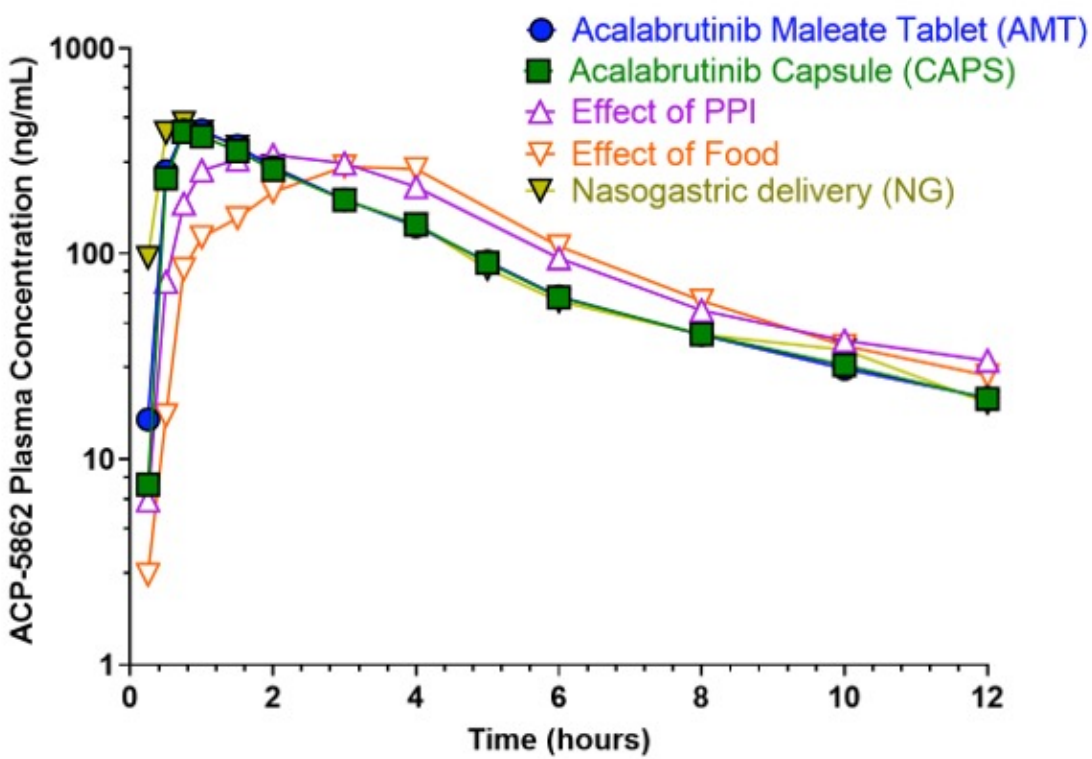
New Acalabrutinib Formulation Enables Co-Administration with Proton Pump Inhibitors and Dosing in Patients Unable to Swallow Capsules (ELEVATE-PLUS)

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.

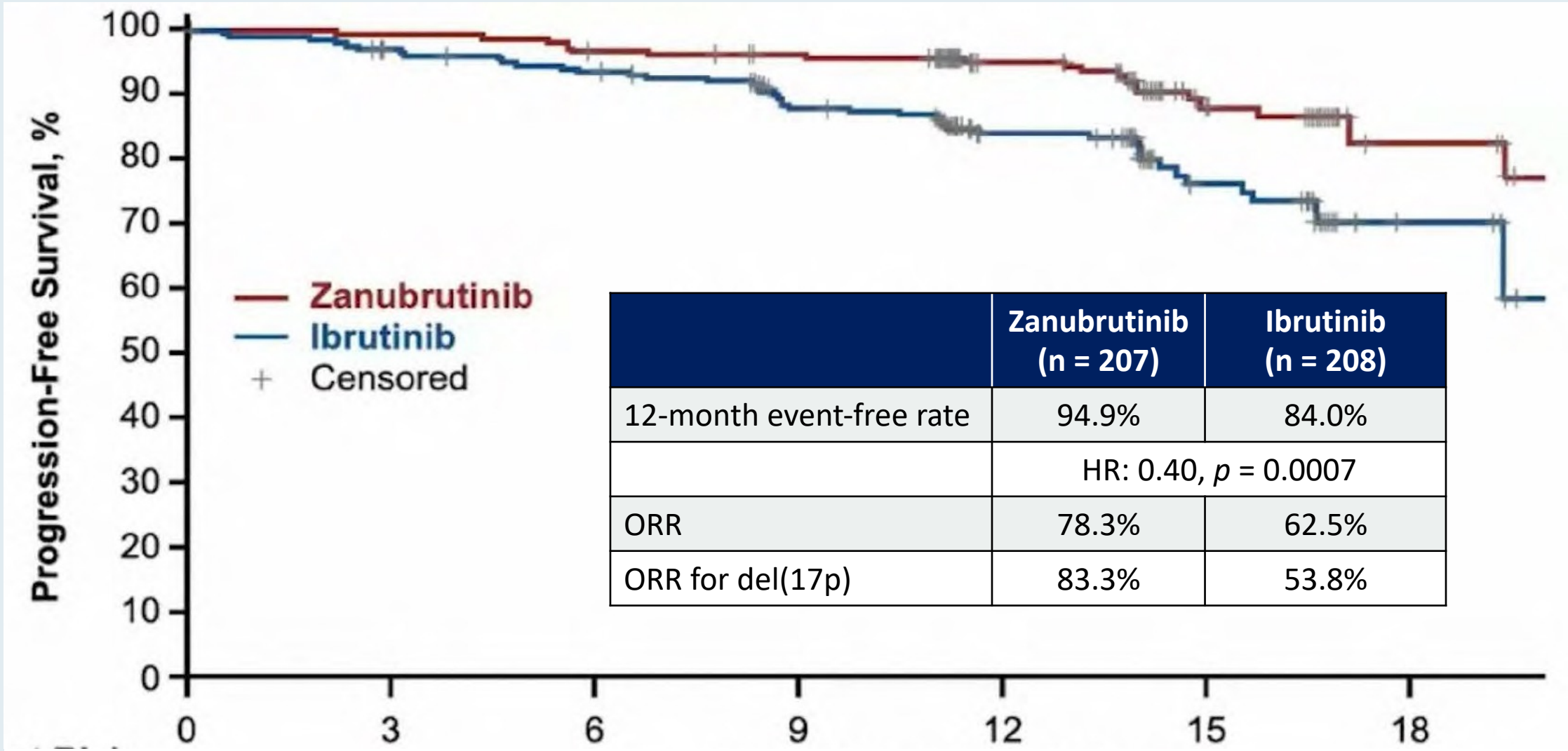
RTP RESEARCH TO PRACTICE

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.

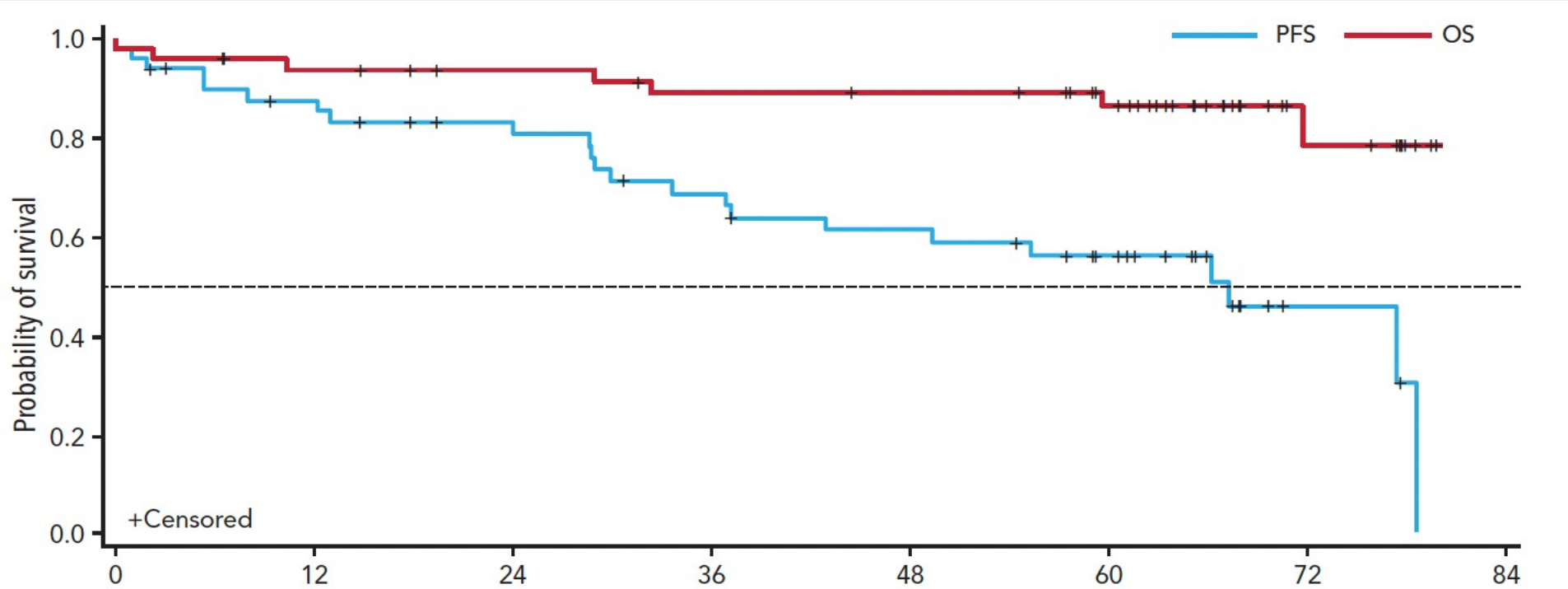
Regular Article

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.

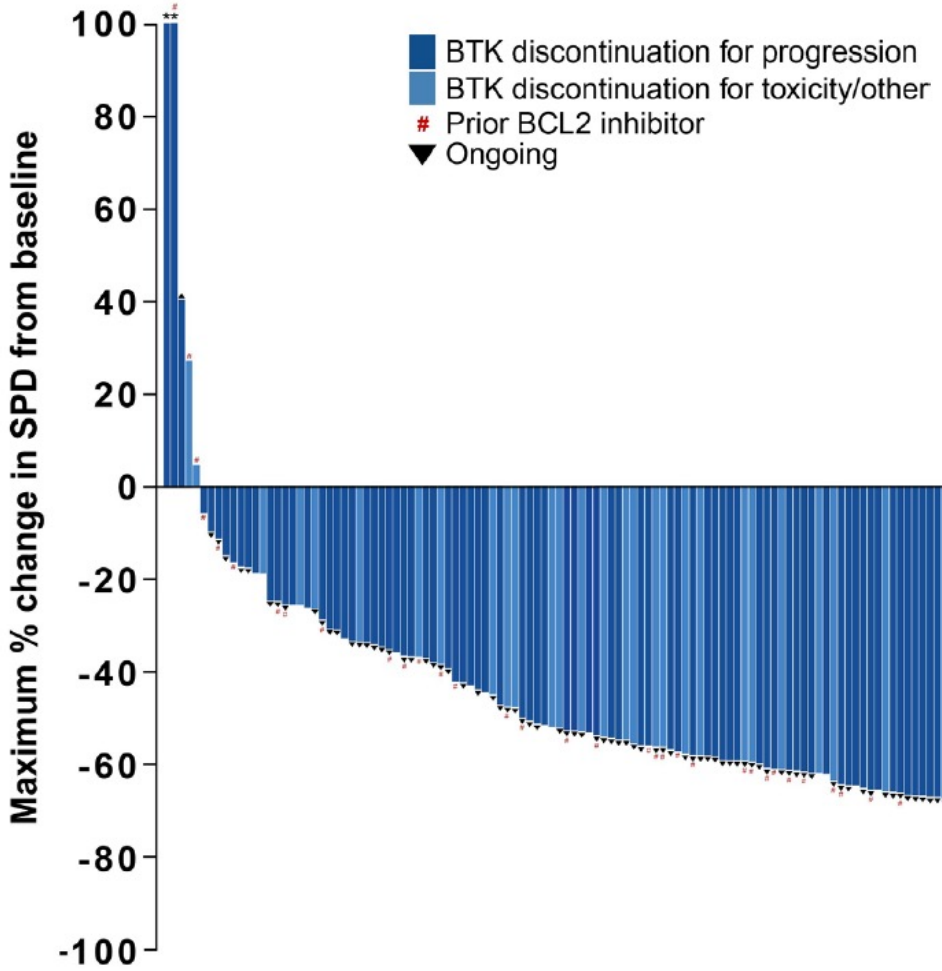
Novel Strategies Under Investigation

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

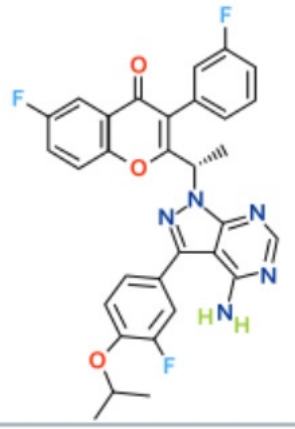
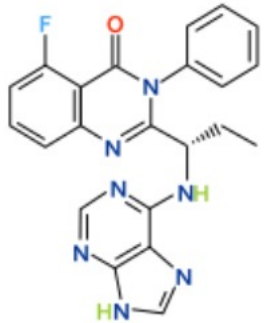
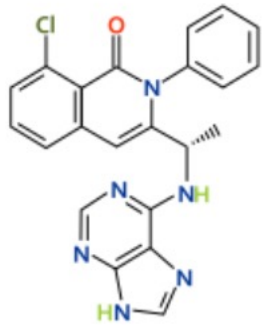
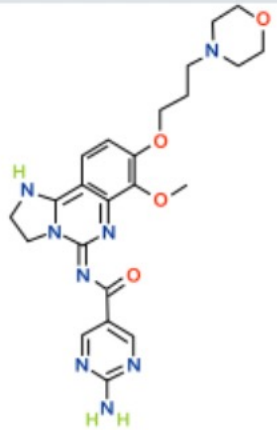
RTP RESEARCH TO PRACTICE

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

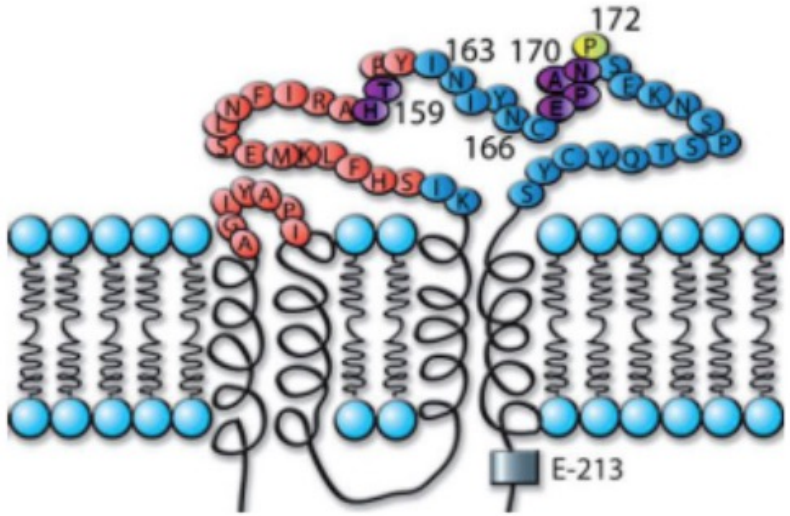
- Umbralisib is an oral, once daily, selective inhibitor of PI3Kδ and CK1ε
- Umbralisib has >1000-fold greater selectivity for PI3Kδ compared to α and β isoforms
- Umbralisib is also **>200-fold** more selective for PI3Kδ relative to **PI3Kγ**

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.

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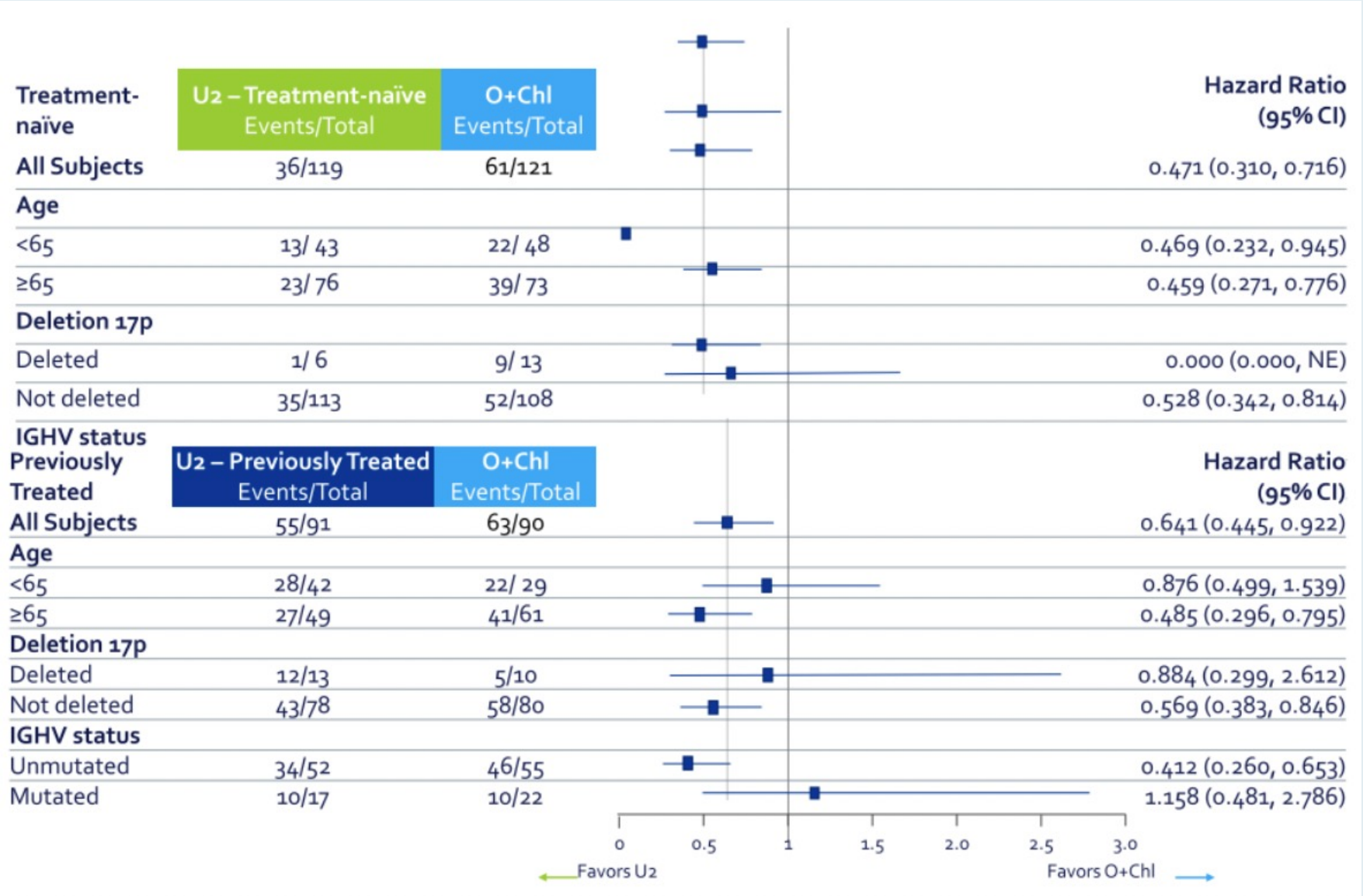
UNITY-CLL: IRC-Assessed PFS by Treatment Status



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)	-

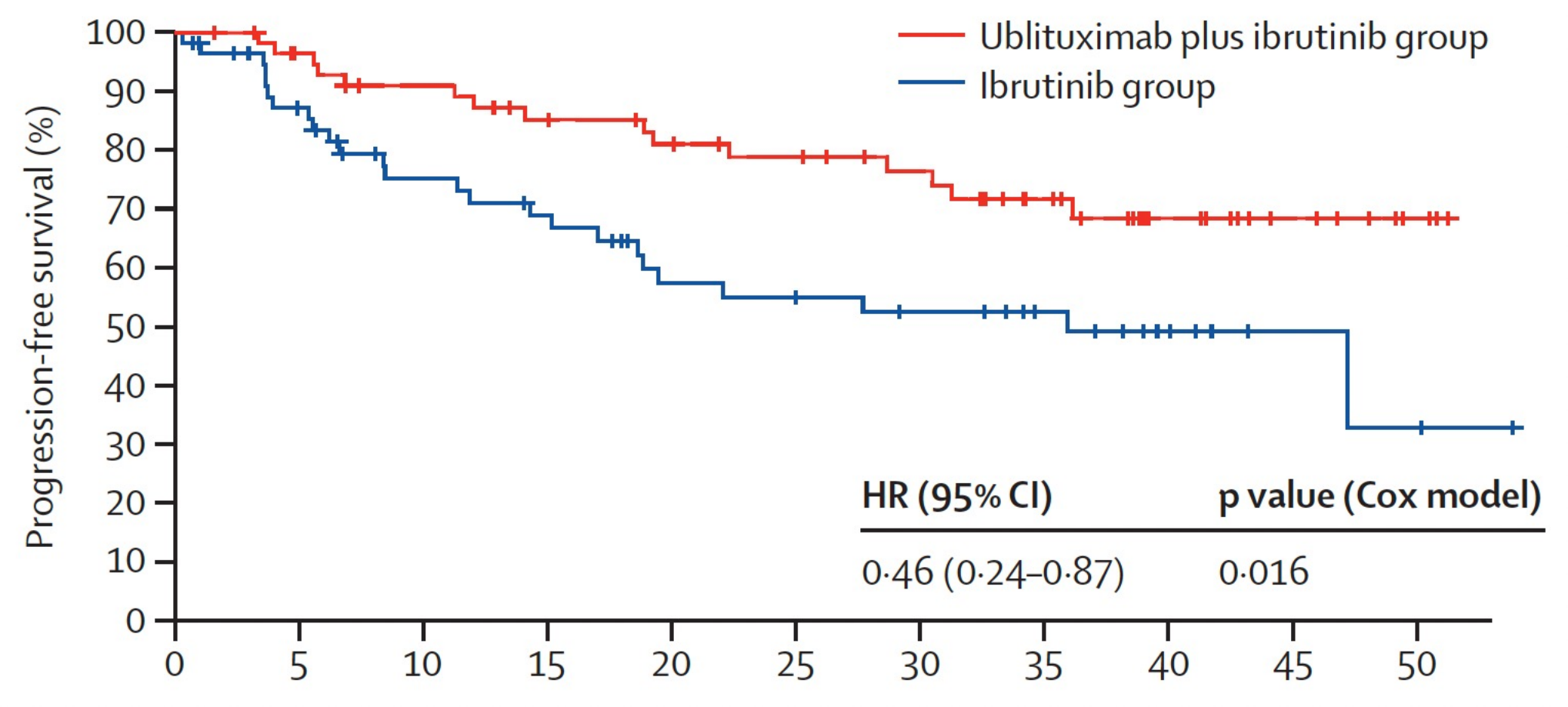
Jacobs R et al. ASH 2021;Abstract 3726.

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

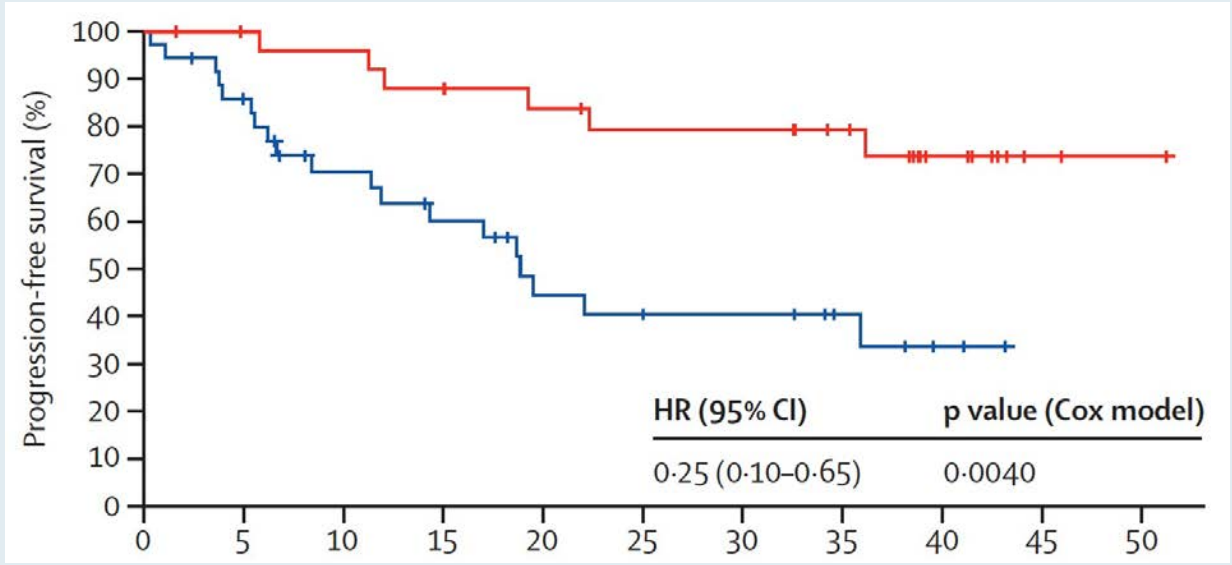
GENUINE: Progression-Free Survival (All Patients)



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

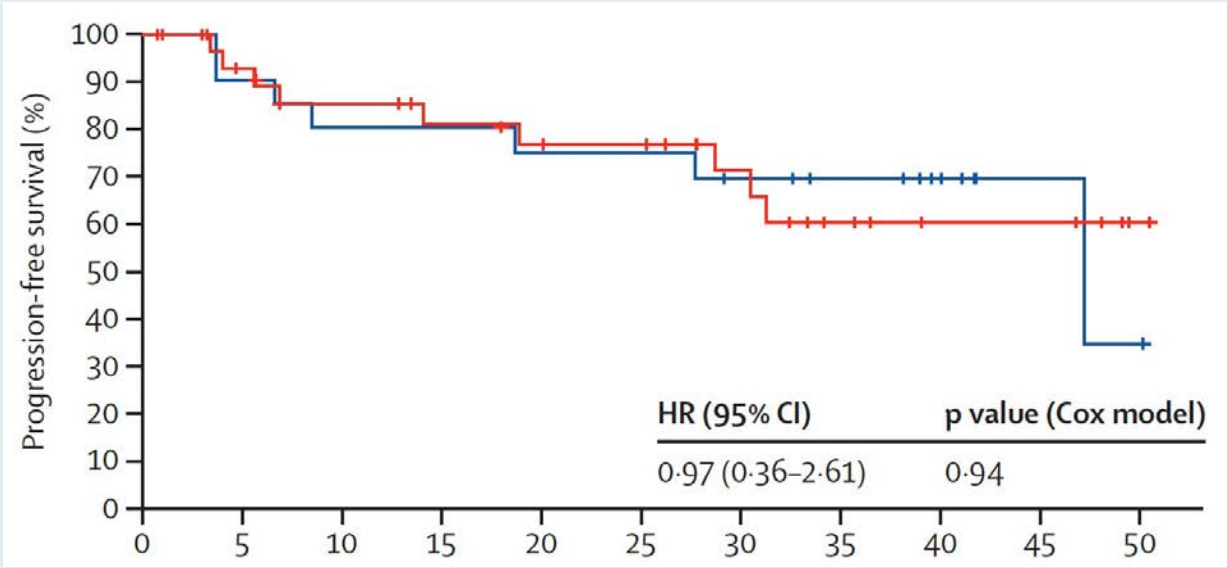
GENUINE: Progression-Free Survival in Subgroups

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.

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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

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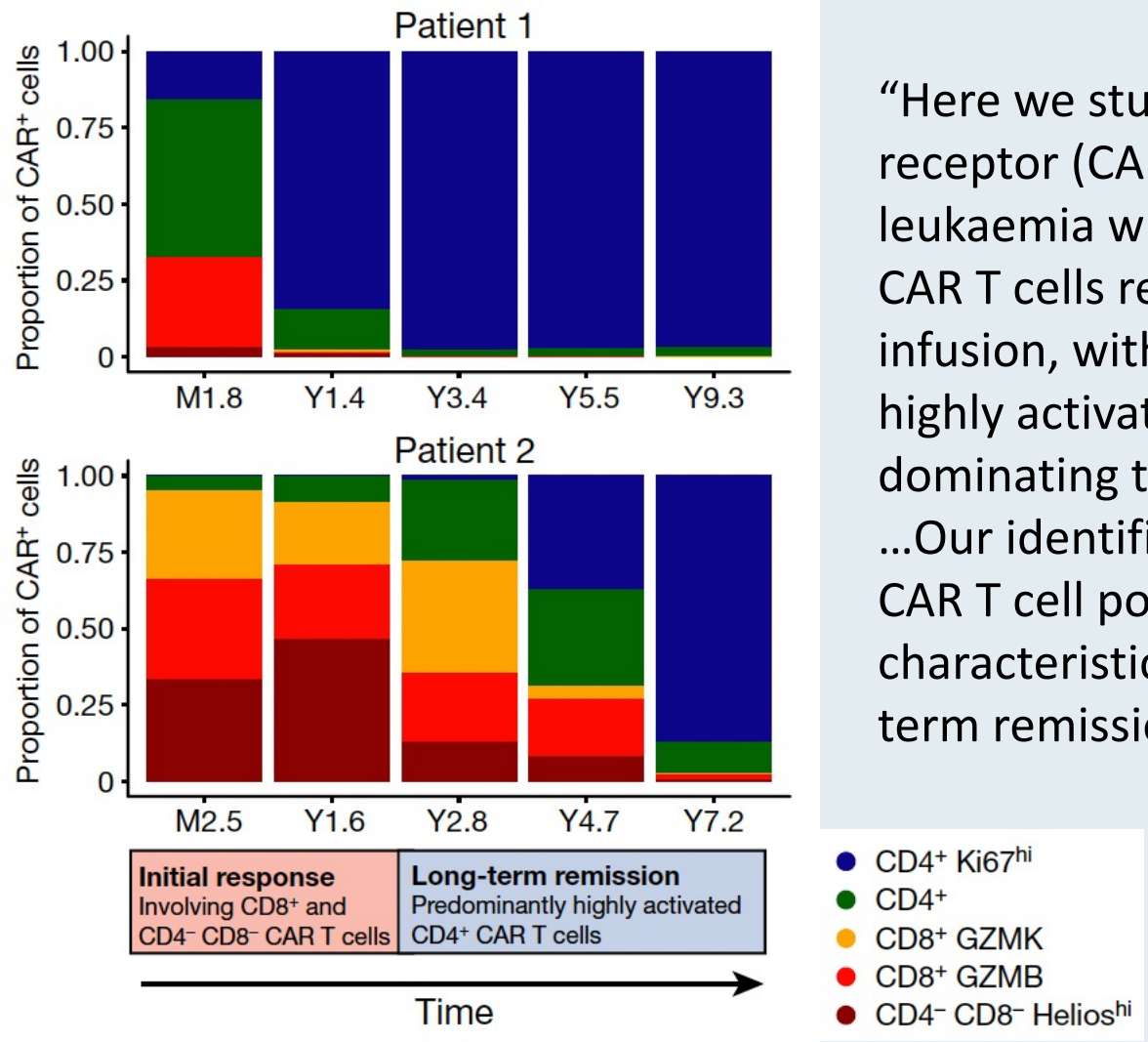
Analysis of CD3+ CAR+ T Cells Using CyTOF Across Multiple Time Points



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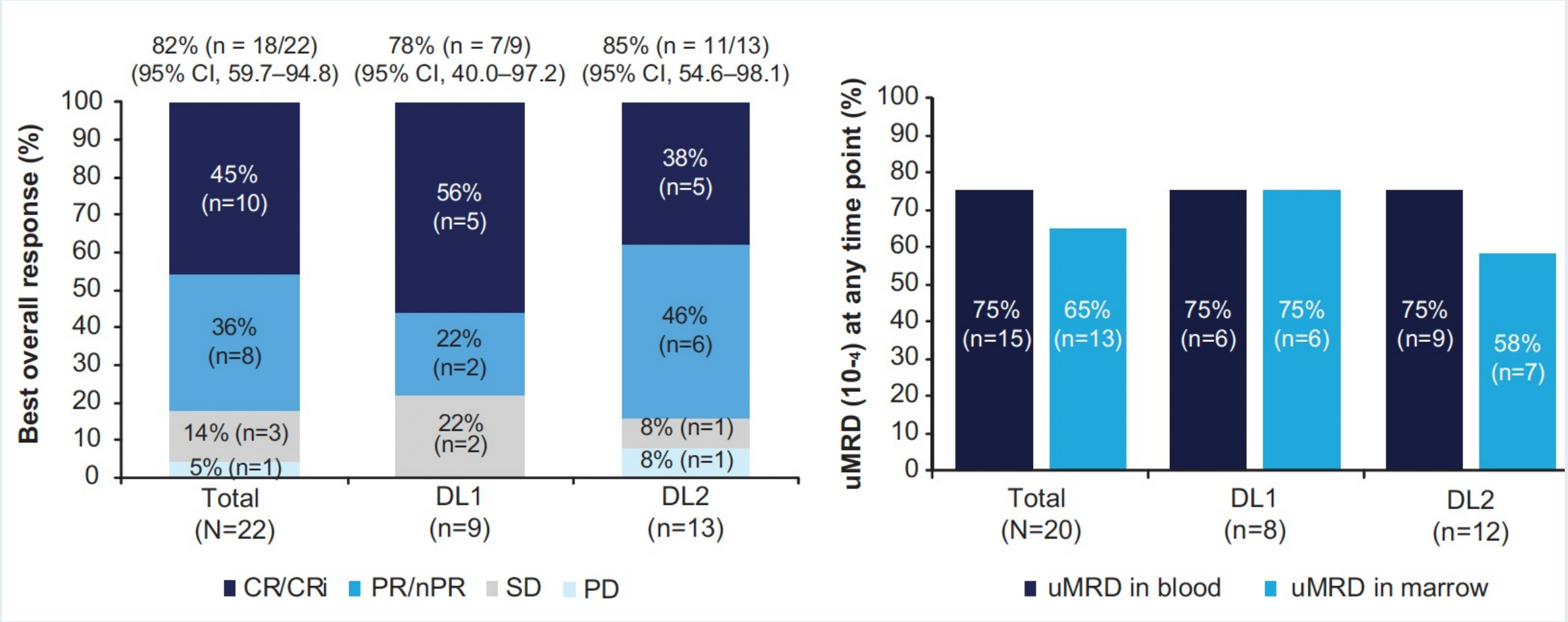
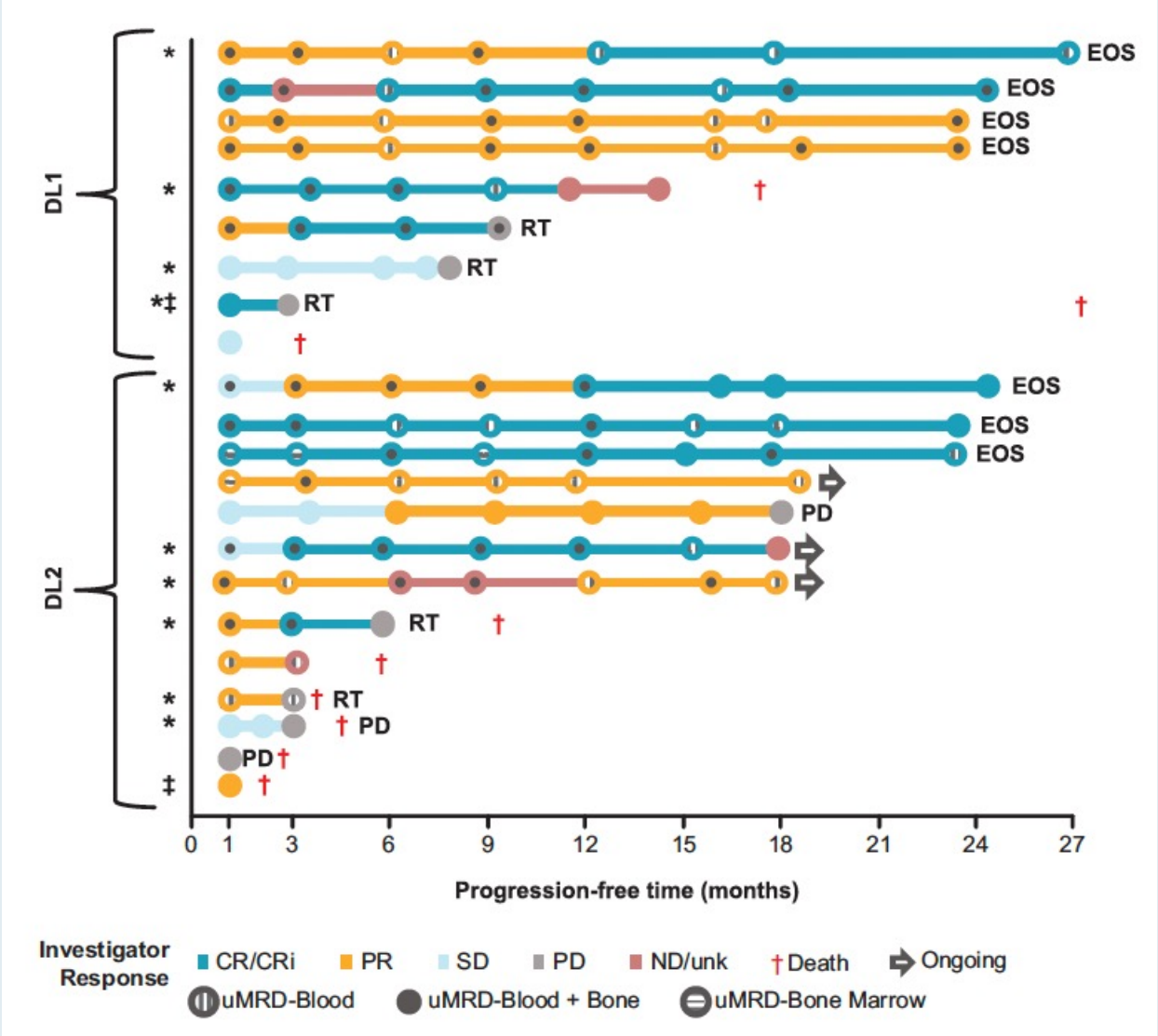
TRANSCEND CLL 004: Response and uMRD (10^{-4}) Rates



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

Current and Future Role of Immunotherapy in the Management of Lung Cancer

Monday, March 7, 2022
5:00 PM – 6:00 PM ET

Faculty

Charu Aggarwal, MD

Moderator

Neil Love, 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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