Meet The Professor

Current and Future Management of Chronic Lymphocytic Leukemia

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

RTP
RESEARCH
TO PRACTICE

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.

RTP
RESEARCH
TO PRACTICE

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, Elevation Oncology 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, Novartis Pharmaceuticals Corporation on behalf of Advanced Accelerator Applications, Novocure Inc, Oncopeptides, Pfizer Inc, Pharmacyclics LLC, an AbbVie Company, Puma Biotechnology Inc, Regeneron Pharmaceuticals Inc, 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 and Zymeworks Inc.

RTP
RESEARCH
TO PRACTICE

Research To Practice CME Planning Committee Members, Staff and Reviewers

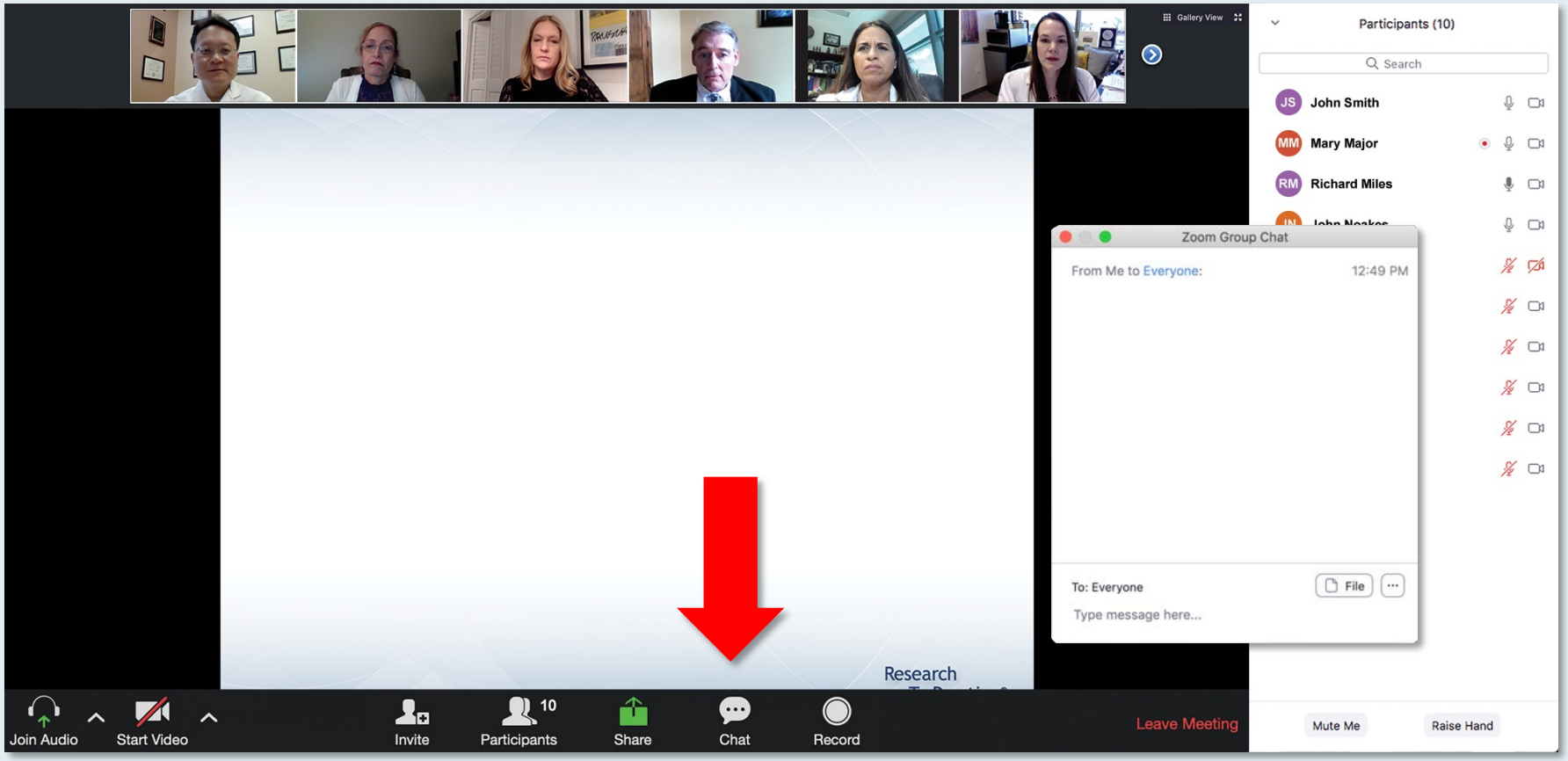
Planners, scientific staff and independent reviewers for Research To Practice have no relevant conflicts of interest to disclose.

Dr Sharman — Disclosures

Consulting Agreements	AbbVie Inc, AstraZeneca Pharmaceuticals LP, BeiGene Ltd, Bristol-Myers Squibb Company, Genentech, a member of the Roche Group, Merck, TG Therapeutics Inc
Research Funding	Celgene Corporation, Genentech, a member of the Roche Group, Gilead Sciences Inc, Merck, Takeda Pharmaceuticals USA Inc, TG Therapeutics Inc

RTP
RESEARCH
TO PRACTICE

We Encourage Clinicians in Practice to Submit Questions

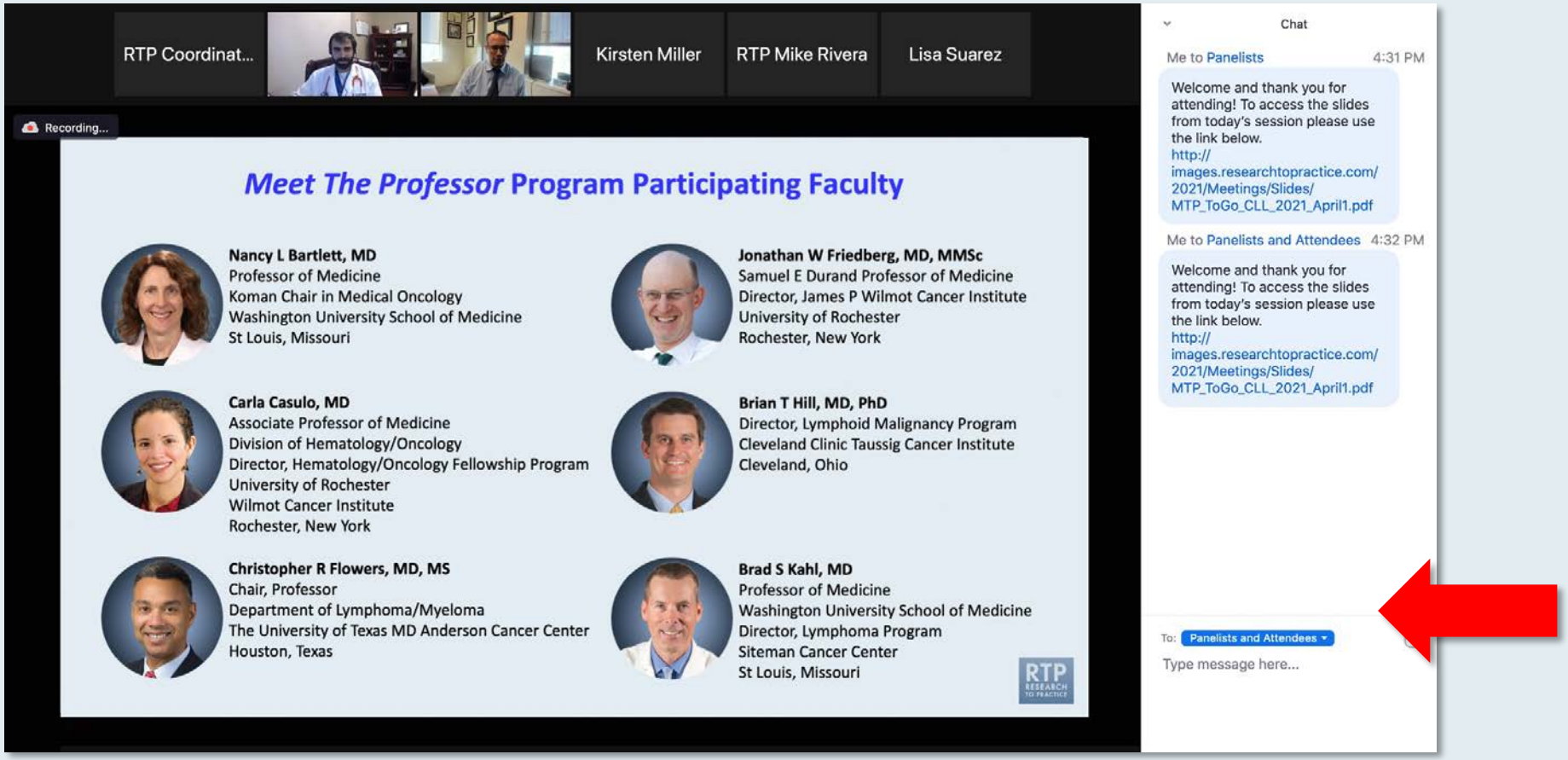


Feel free to submit questions now before the program begins and throughout the program.

RTP RESEARCH TO PRACTICE

Familiarizing Yourself with the Zoom Interface

Expand chat submission box

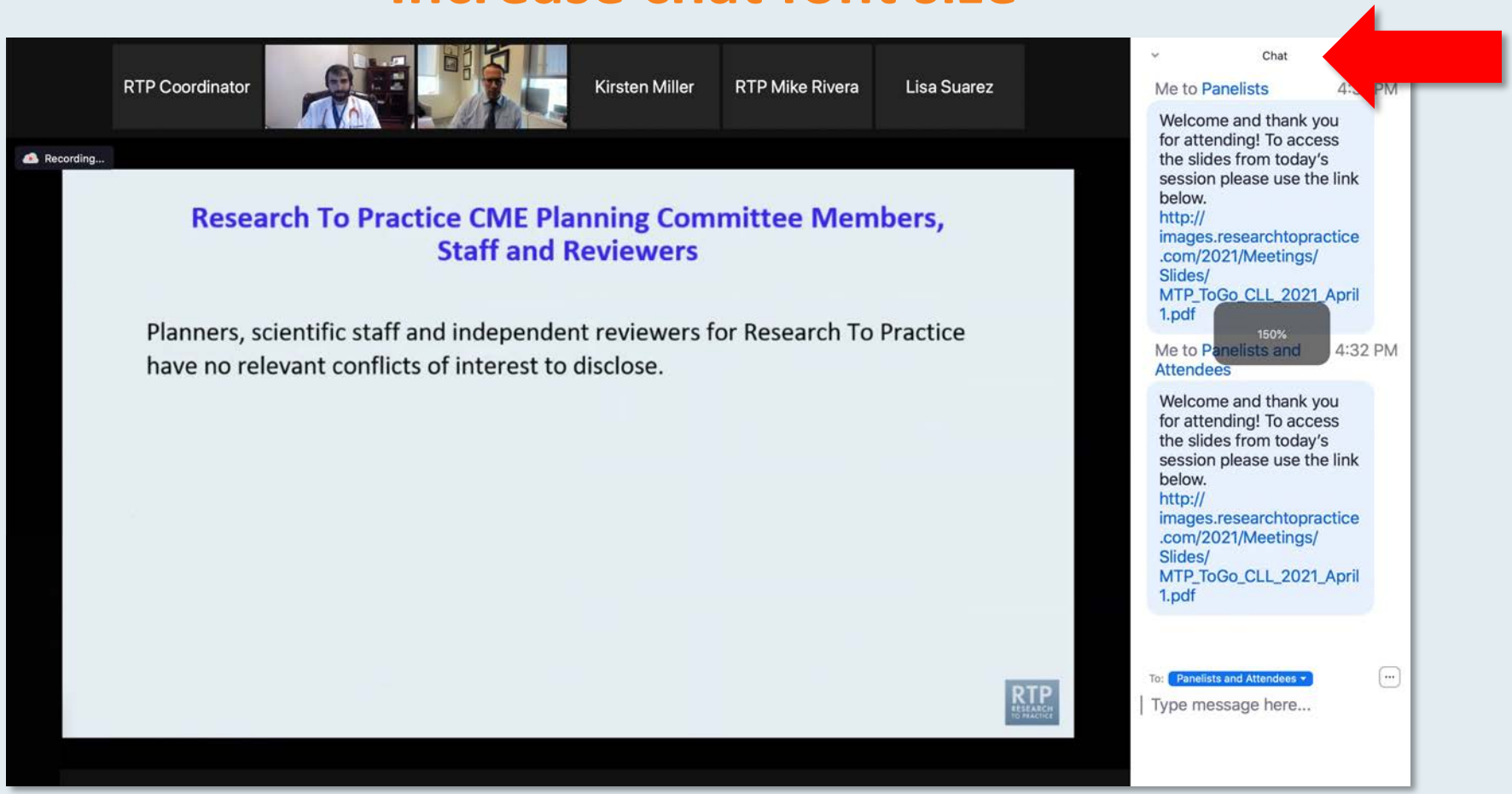


Drag the white line above the submission box up to create more space for your message.

RTP RESEARCH TO PRACTICE

Familiarizing Yourself with the Zoom Interface

Increase chat font size



Press Command (for Mac) or Control (for PC) and the + symbol.
You may do this as many times as you need for readability.

ONCOLOGY TODAY

WITH DR NEIL LOVE

Recent Advances in the Treatment of Chronic Lymphocytic Leukemia

DR PETER HILLMEN
UNIVERSITY OF LEEDS

Listen on Apple Podcasts

Spotify

Listen on Google Podcasts

Meet The Professor

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

Thursday, June 16, 2022
5:00 PM – 6:00 PM ET

Faculty

Melissa Johnson, MD

Moderator

Neil Love, MD

RTP
RESEARCH
TO PRACTICE

Meet The Professor

Optimizing the Management of Ovarian Cancer

Tuesday, June 21, 2022
5:00 PM – 6:00 PM ET

Faculty

Shannon N Westin, MD, MPH

Moderator

Neil Love, MD

RTP
RESEARCH
TO PRACTICE

Meet The Professor

Optimizing the Management of Gastroesophageal Cancers

Wednesday, June 22, 2022
5:00 PM – 6:00 PM ET

Faculty

Manish A Shah, MD

Moderator

Neil Love, MD

RTP
RESEARCH
TO PRACTICE

PARP Inhibition in the Management of Prostate Cancer — Where We Are and Where We're Headed

Thursday, June 23, 2022
5:00 PM – 6:00 PM ET

Faculty

Johann S de Bono, MB ChB, MSc, PhD, FMedSci
Fred Saad, MD

Moderator

Neil Love, MD

RTP RESEARCH TO PRACTICE

Meet The Professor

Optimizing the Management of Chronic Myeloid Leukemia

Tuesday, June 28, 2022
5:00 PM – 6:00 PM ET

Faculty

Jorge E Cortes, MD

Moderator

Neil Love, MD

RTP
RESEARCH
TO PRACTICE

Meet The Professor

Current and Future Management of Non-Small Cell Lung Cancer with an EGFR Mutation

Thursday, June 30, 2022
5:00 PM – 6:00 PM ET

Faculty

Joel W Neal, MD, PhD

Moderator

Neil Love, MD

RTP
RESEARCH
TO PRACTICE

Thank you for joining us!

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

RTP
RESEARCH
TO PRACTICE

Meet The Professor

Current and Future Management of Chronic Lymphocytic Leukemia

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

RTP
RESEARCH
TO PRACTICE

Meet The Professor Program Participating Faculty

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

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

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

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

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

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

RTP
RESEARCH TO PRACTICE

Meet The Professor Program Participating Faculty

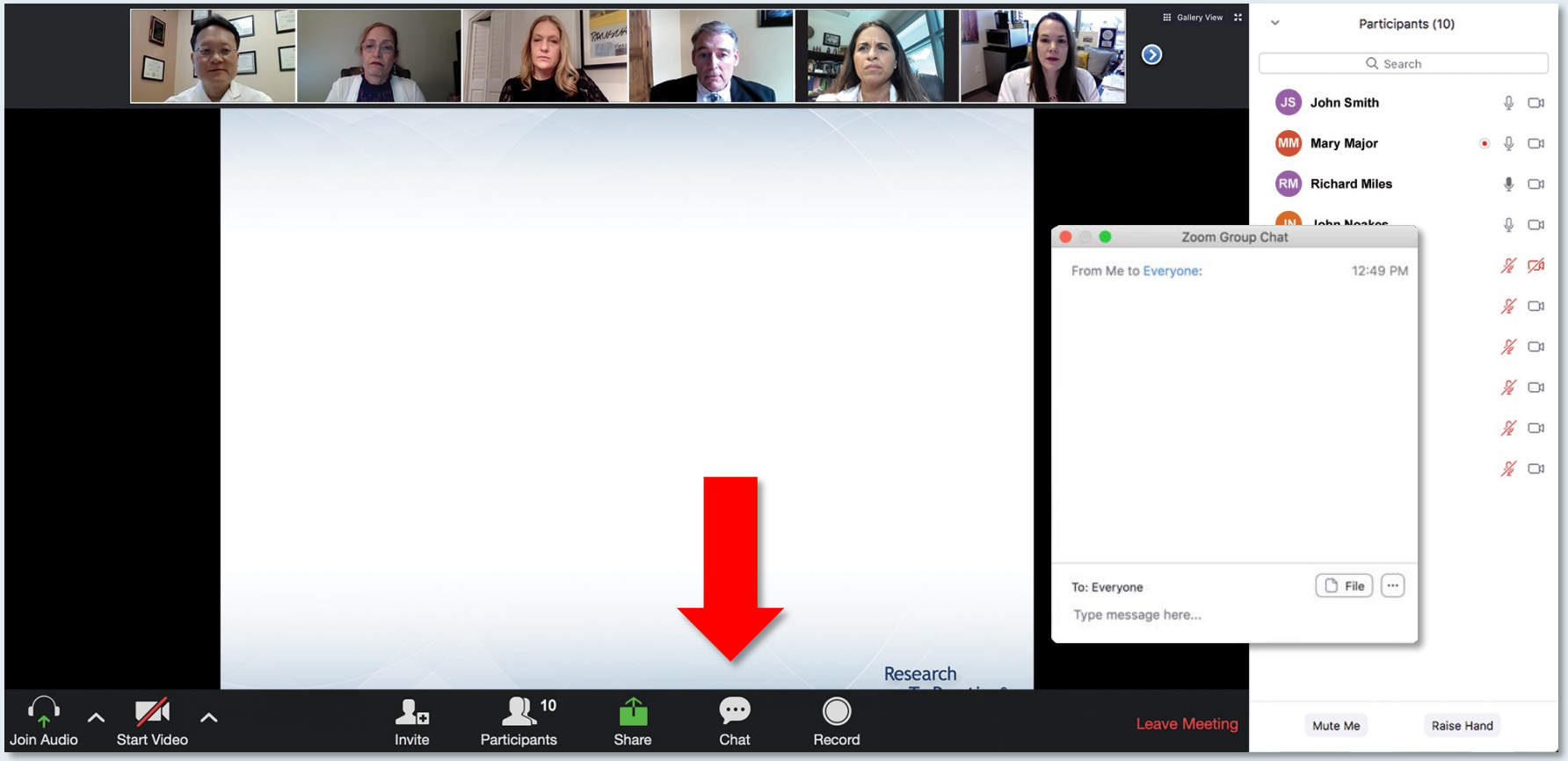
William G Wierda, MD, PhD
DB Lane Cancer Research Distinguished Professor
Section Chief, Chronic Lymphocytic Leukemia
Center Medical Director
Department of Leukemia, Division of Cancer Medicine
Executive Medical Director, Inpatient Medical Services
The University of Texas MD Anderson Cancer Center
Houston, Texas

Moderator

Neil Love, MD
Research To Practice

RTP
RESEARCH
TO PRACTICE

We Encourage Clinicians in Practice to Submit Questions



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

RTP RESEARCH TO PRACTICE

ONCOLOGY TODAY

WITH DR NEIL LOVE

Recent Advances in the Treatment of Chronic Lymphocytic Leukemia

DR PETER HILLMEN
UNIVERSITY OF LEEDS

Listen on Apple Podcasts

Spotify

Listen on Google Podcasts

Meet The Professor

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

Thursday, June 16, 2022
5:00 PM – 6:00 PM ET

Faculty

Melissa Johnson, MD

Moderator

Neil Love, MD

RTP
RESEARCH
TO PRACTICE

Meet The Professor

Optimizing the Management of Ovarian Cancer

Tuesday, June 21, 2022
5:00 PM – 6:00 PM ET

Faculty

Shannon N Westin, MD, MPH

Moderator

Neil Love, MD

RTP
RESEARCH
TO PRACTICE

Meet The Professor

Optimizing the Management of Gastroesophageal Cancers

Wednesday, June 22, 2022
5:00 PM – 6:00 PM ET

Faculty

Manish A Shah, MD

Moderator

Neil Love, MD

RTP
RESEARCH
TO PRACTICE

PARP Inhibition in the Management of Prostate Cancer — Where We Are and Where We're Headed

Thursday, June 23, 2022
5:00 PM – 6:00 PM ET

Faculty

Johann S de Bono, MB ChB, MSc, PhD, FMedSci
Fred Saad, MD

Moderator

Neil Love, MD

RTP RESEARCH TO PRACTICE

Meet The Professor

Optimizing the Management of Chronic Myeloid Leukemia

Tuesday, June 28, 2022
5:00 PM – 6:00 PM ET

Faculty

Jorge E Cortes, MD

Moderator

Neil Love, MD

RTP
RESEARCH
TO PRACTICE

Meet The Professor

Current and Future Management of Non-Small Cell Lung Cancer with an EGFR Mutation

Thursday, June 30, 2022
5:00 PM – 6:00 PM ET

Faculty

Joel W Neal, MD, PhD

Moderator

Neil Love, MD

RTP
RESEARCH
TO PRACTICE

Meet The Professor

Current and Future Management of Chronic Lymphocytic Leukemia

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

RTP
RESEARCH
TO PRACTICE

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.

Research To Practice CME Planning Committee Members, Staff and Reviewers

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

Dr Sharman — Disclosures

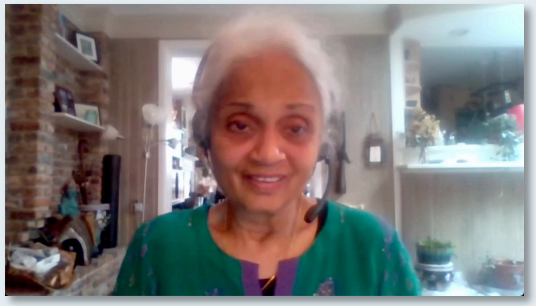
Consulting Agreements	AbbVie Inc, AstraZeneca Pharmaceuticals LP, BeiGene Ltd, Bristol-Myers Squibb Company, Genentech, a member of the Roche Group, Merck, TG Therapeutics Inc
Research Funding	Celgene Corporation, Genentech, a member of the Roche Group, Gilead Sciences Inc, Merck, Takeda Pharmaceuticals USA Inc, TG Therapeutics Inc

RTP
RESEARCH
TO PRACTICE

Spencer H Bachow, MD
Lynn Cancer Institute
Boca Raton, Florida

Shaachi Gupta, MD, MPH
Florida Cancer Specialists and Research Institute
Lake Worth, Florida

Philip L Brooks, MD
Northern Light Eastern Maine Medical Center and Lafayette Family Cancer Institute
Brewer, Maine



Rajalaxmi McKenna, MD
Southwest Medical Consultants SC
Willowbrook, Illinois

Shams Bufalino, MD
Advocate Aurora Health
Park Ridge, Illinois

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

RTP
RESEARCH
TO PRACTICE

Vignesh Narayanan, MD
Colorado Permanente Medical Group (CPMG)
Lone Tree, Colorado

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

Erik Rupard, MD
Drexel University College of Medicine
The Reading Hospital
West Reading, Pennsylvania

RTP
RESEARCH
TO PRACTICE

Meet The Professor with Dr Sharman

Introduction: Journal Club Part 1

MODULE 1: Case Presentations

- Dr Bufalino: A 58-year-old man with progressive SLL who developed acalabrutinib-associated rash
- Dr Gupta: A 69-year-old man with recurrent DVT who is receiving warfarin and is diagnosed with CLL requiring treatment
- Dr McKenna: A 72-year-old man with IGHV-unmutated CLL who has severe cardiac disease requiring a defibrillator
- Dr Brooks: A 70-year-old man with CLL who remains in remission after treatment with chlorambucil/obinutuzumab
- Dr Narayanan: A 51-year-old man with IGHV-unmutated CLL and del(17p) who developed atrial fibrillation on ibrutinib
- Dr Bachow: An 87-year-old woman with CLL transformed to Hodgkin lymphoma
- Dr Rupard: A 59-year-old man with relapsed IGHV-mutated CLL who experienced acalabrutinib-associated headache
- Dr Metzner-Sadurski: A 64-year-old woman with IGHV-unmutated CLL and hemolytic anemia
- Dr Polkinghorn: An 81-year-old man with recurrent CLL who discontinued ibrutinib due to atrial fibrillation

MODULE 2: Faculty Survey

MODULE 3: Journal Club Part 2

MODULE 4: Appendix of Key Recent Data Sets

RTP
RESEARCH
TO PRACTICE

Meet The Professor with Dr Sharman

Introduction: Journal Club Part 1

MODULE 1: Case Presentations

- Dr Bufalino: A 58-year-old man with progressive SLL who developed acalabrutinib-associated rash
- Dr Gupta: A 69-year-old man with recurrent DVT who is receiving warfarin and is diagnosed with CLL requiring treatment
- Dr McKenna: A 72-year-old man with IGHV-unmutated CLL who has severe cardiac disease requiring a defibrillator
- Dr Brooks: A 70-year-old man with CLL who remains in remission after treatment with chlorambucil/obinutuzumab
- Dr Narayanan: A 51-year-old man with IGHV-unmutated CLL and del(17p) who developed atrial fibrillation on ibrutinib
- Dr Bachow: An 87-year-old woman with CLL transformed to Hodgkin lymphoma
- Dr Rupard: A 59-year-old man with relapsed IGHV-mutated CLL who experienced acalabrutinib-associated headache
- Dr Metzner-Sadurski: A 64-year-old woman with IGHV-unmutated CLL and hemolytic anemia
- Dr Polkinghorn: An 81-year-old man with recurrent CLL who discontinued ibrutinib due to atrial fibrillation

MODULE 2: Faculty Survey

MODULE 3: Journal Club Part 2

MODULE 4: Appendix of Key Recent Data Sets

RTP RESEARCH TO PRACTICE

Blood Rev 2022 Apr 22;[Online ahead of print].

Contents lists available at ScienceDirect

Blood Reviews

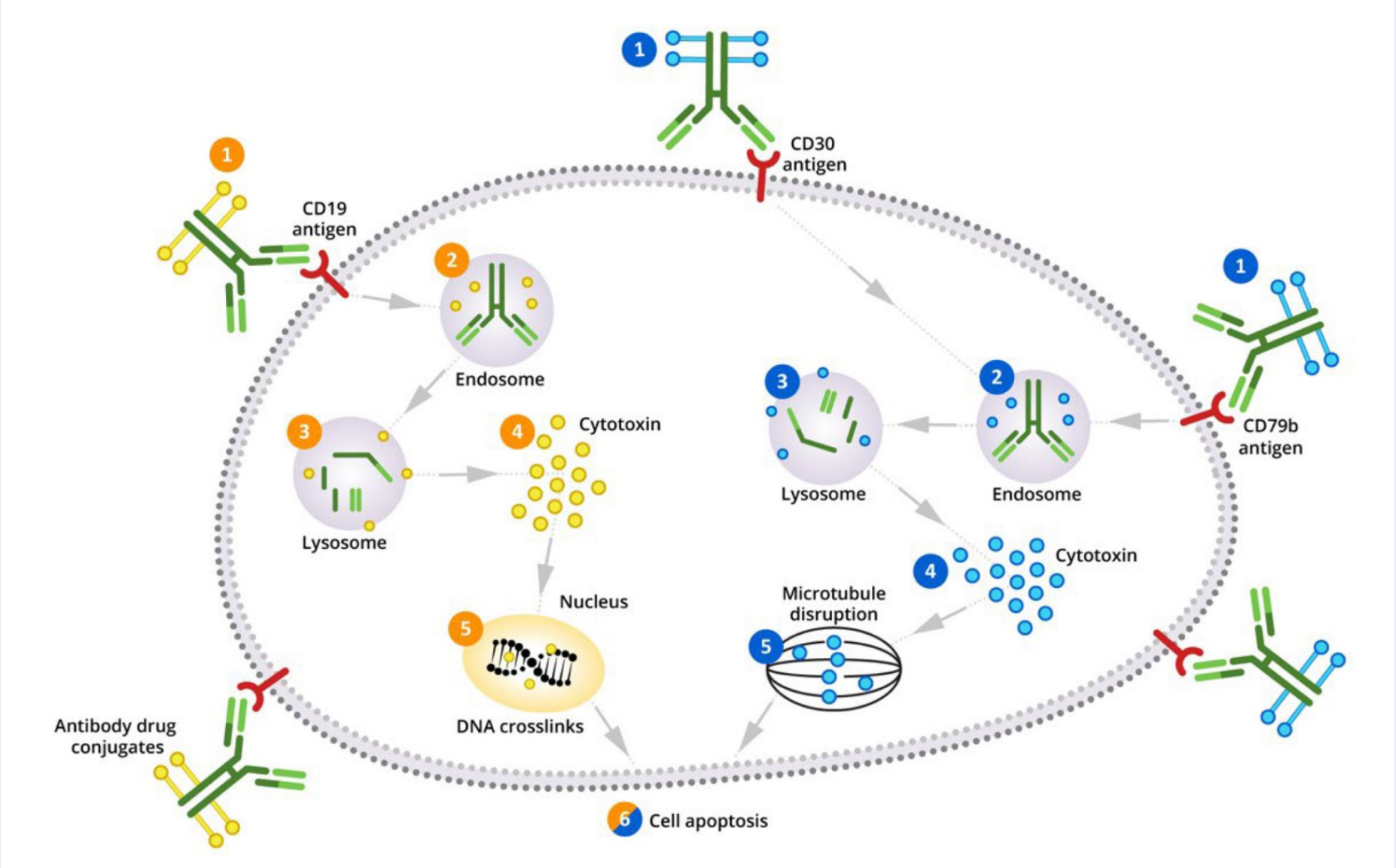
journal homepage: www.elsevier.com/locate/issn/0268960X

Review

ABCs of ADCs in management of relapsed/refractory diffuse large B-cell lymphoma

Juan Pablo Alderuccio [a,*], Jeff P. Sharman [b]

Antibody-Drug Conjugate Mechanism of Action in DLBCL



Alderuccio JP, Sharman JP. *Blood Rev* 2022;[Online ahead of print].

Meet The Professor with Dr Sharman

Introduction: Journal Club Part 1

MODULE 1: Case Presentations

- Dr Bufalino: A 58-year-old man with progressive SLL who developed acalabrutinib-associated rash
- Dr Gupta: A 69-year-old man with recurrent DVT who is receiving warfarin and is diagnosed with CLL requiring treatment
- Dr McKenna: A 72-year-old man with IGHV-unmutated CLL who has severe cardiac disease requiring a defibrillator
- Dr Brooks: A 70-year-old man with CLL who remains in remission after treatment with chlorambucil/obinutuzumab
- Dr Narayanan: A 51-year-old man with IGHV-unmutated CLL and del(17p) who developed atrial fibrillation on ibrutinib
- Dr Bachow: An 87-year-old woman with CLL transformed to Hodgkin lymphoma
- Dr Rupard: A 59-year-old man with relapsed IGHV-mutated CLL who experienced acalabrutinib-associated headache
- Dr Metzner-Sadurski: A 64-year-old woman with IGHV-unmutated CLL and hemolytic anemia
- Dr Polkinghorn: An 81-year-old man with recurrent CLL who discontinued ibrutinib due to atrial fibrillation

MODULE 2: Faculty Survey

MODULE 3: Journal Club Part 2

MODULE 4: Appendix of Key Recent Data Sets

RTP RESEARCH TO PRACTICE

Haematologica 2022;107(4):984-7.

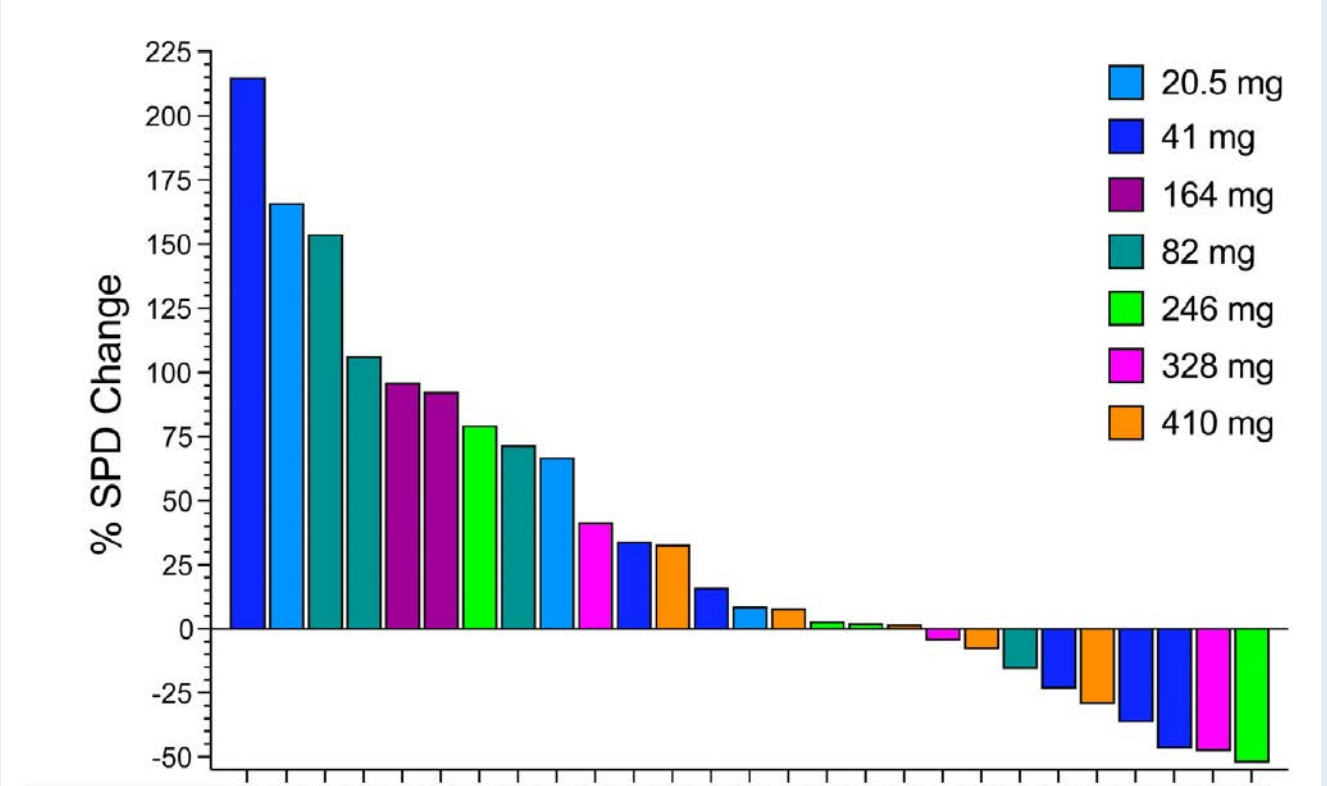
Letters to the Editor

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

John N. Allan,1 Javier Pinilla-Ibarz,2 Douglas E. Gladstone,3 Krish Patel,4 Jeff P. Sharman,5 William G. Wierda,6 Michael Y. Choi,7 Susan M. O'Brien,8 Mazyar Shadman,9 Matthew S. Davids,10 John M. Pagel,4 Habte A. Yimer,11 Renee Ward,12 Gary Acton,12 Pietro Taverna,12 Daniel L. Combs,13 Judith A. Fox,12 Richard R. Furman1 and Jennifer R. Brown10

JC JOURNAL CLUB RTP RESEARCH TO PRACTICE

Percent Change in Tumor Burden from Baseline with Vecabrutinib



Patient #	13	3	18	20	22	23	27	16	2	32	6	34	7	1	37	29	26	35	31	36	14	12	39	4	11	33	28
Disease	CLL	CLL	CLL	CLL	CLL	CLL	CLL	CLL	CLL	CLL	CLL	CLL	MCL	CLL	MCL	CLL	MZL	CLL	CLL	CLL	CLL	CLL	CLL	MCL	CLL	CLL	CLL
Dose mg BID	41	21	82	82	164	164	246	82	21	328	41	410	41	21	410	246	246	410	328	410	82	41	410	41	41	328	246
Response per investigator	PD	PD	PD	PD	PD	PD	PD	PD	PD	SD	PD	PD	PD	SD	SD	SD	SD	SD	SD	SD	SD	SD	SD	PD	SD	SD	PR
BTK C481X	S	S		P		S,T	S	R		S				S		S					S		S,F		S		
PLCγ2 mutation	✓				✓[a]					✓							✓		✓			✓	U		✓		
Complex karyotype	U		✓		✓		✓	✓	✓		U		U	✓			U				✓	U		U	✓		
TP53 mutation	✓	✓	✓	✓	✓	✓	✓	✓	✓			✓	✓	✓	✓	✓	✓				✓	✓	✓		✓		
Del(17p)		✓	✓		✓		✓	✓	✓		✓	✓	U				U					✓		U	✓		
# Prior regimens	4	3	4	4	3	4	2	7	5	8	6	3	7	5	3	4	9	2	3	3	2	2	6	2	4	7	2

[a]Known Plcγ2 activating mutation (functional impact of other Plcγ2 mutations is unknown).

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

Meet The Professor with Dr Sharman

Introduction: Journal Club Part 1

MODULE 1: Case Presentations

- Dr Bufalino: A 58-year-old man with progressive SLL who developed acalabrutinib-associated rash
- Dr Gupta: A 69-year-old man with recurrent DVT who is receiving warfarin and is diagnosed with CLL requiring treatment
- Dr McKenna: A 72-year-old man with IGHV-unmutated CLL who has severe cardiac disease requiring a defibrillator
- Dr Brooks: A 70-year-old man with CLL who remains in remission after treatment with chlorambucil/obinutuzumab
- Dr Narayanan: A 51-year-old man with IGHV-unmutated CLL and del(17p) who developed atrial fibrillation on ibrutinib
- Dr Bachow: An 87-year-old woman with CLL transformed to Hodgkin lymphoma
- Dr Rupard: A 59-year-old man with relapsed IGHV-mutated CLL who experienced acalabrutinib-associated headache
- Dr Metzner-Sadurski: A 64-year-old woman with IGHV-unmutated CLL and hemolytic anemia
- Dr Polkinghorn: An 81-year-old man with recurrent CLL who discontinued ibrutinib due to atrial fibrillation

MODULE 2: Faculty Survey

MODULE 3: Journal Club Part 2

MODULE 4: Appendix of Key Recent Data Sets

RTP RESEARCH TO PRACTICE

BRUIN CLL-321: A Phase 3 Open-Label, Randomized Study of Pirtobrutinib versus Investigator's Choice of Idelalisib plus Rituximab or Bendamustine plus Rituximab in BTK Inhibitor Pretreated Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma (Trial in Progress)

Sharman JP et al.

ASH 2021;Abstract 3736.

JC JOURNAL CLUB RTP RESEARCH TO PRACTICE

Majic: A Phase 3 Prospective, Multicenter, Randomized, Open-Label Trial of Acalabrutinib plus Venetoclax versus Venetoclax plus Obinutuzumab in Previously Untreated Chronic Lymphocytic Leukemia or Small Lymphocytic Lymphoma

Davids MS et al.

ASH 2021;Abstract 1553.

JC JOURNAL CLUB RTP RESEARCH TO PRACTICE

NEJM Evidence

Published May 13, 2022

DOI: 10.1056/EVIDoa2200006

ORIGINAL ARTICLE

Fixed-Duration Ibrutinib-Venetoclax in Patients with Chronic Lymphocytic Leukemia and Comorbidities

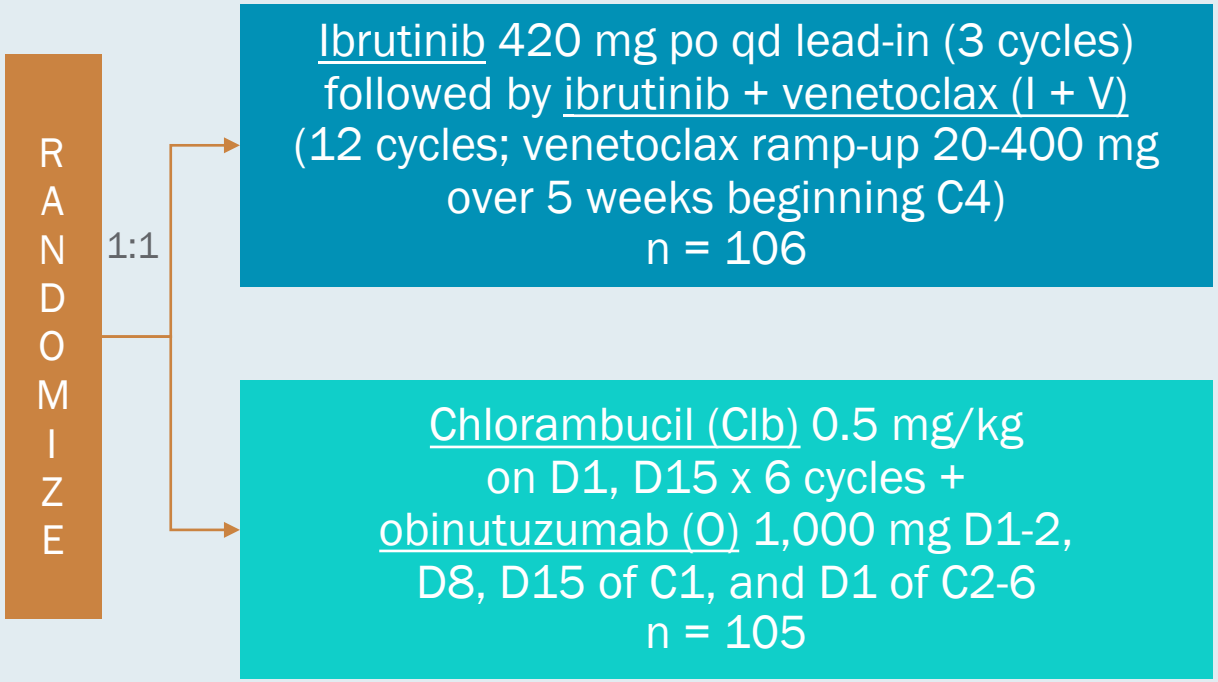
Arnon P. Kater, M.D., Ph.D.,[1] Carolyn Owen, M.D.,[2] Carol Moreno, M.D.,[3] George Follows, B.M.Bch., Ph.D.,[4] Talha Munir, M.B.B.S.,[5] Mark-David Levin, M.D.,[6] Ohad Benjamini, M.D.,[7] Ann Janssens, M.D., Ph.D.,[8] Anders Osterborg, M.D., Ph.D.,[9] Tadeusz Robak, M.D., Ph.D.,[10] Martin Simkovic, M.D., Ph.D.,[11] Don Stevens, M.D.,[12] Sergey Voloshin, M.D., Ph.D.,[13] Vladimir Vorobyev, Ph.D.,[14] Loic Ysebaert, M.D., Ph.D.,[15] Rui Qin, Ph.D.,[16] Andrew J. Steele, Ph.D.,[17] Natasha Schuier, M.D.,[18] Kurt Baeten, Ph.D.,[19] Donne Bennett Caces, M.D., Ph.D.,[16] and Carsten U. Niemann, M.D., Ph.D.,[20] for the GLOW Investigators*

RTP RESEARCH TO PRACTICE

GLOW Study in Older and/or Less Fit Patients with Treatment-Naïve CLL

Key Eligibility Criteria

- Previously untreated CLL
- ≥65 years of age or <65 years with CIRS >6 or CrCl <70 mL/min
- No del(17p) or known *TP53* mutation
- ECOG PS ≤2



Primary endpoint: IRC-assessed PFS

Current MRD analysis:

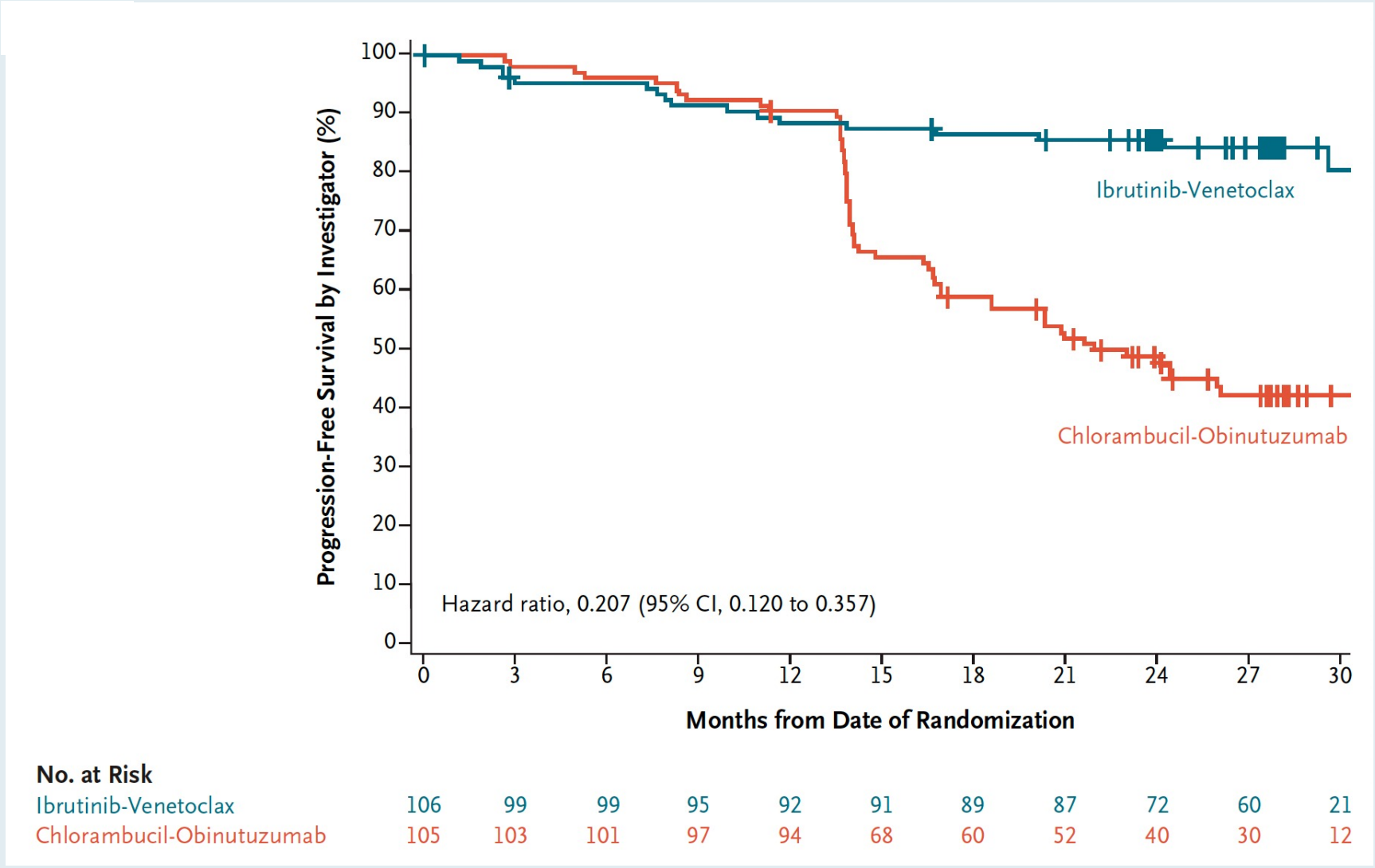
- MRD reported with cutoffs of $<10^{-4}$ and $<10^{-5}$
- PB/BM concordance calculated for patients with uMRD in PB at EOT+3 who had paired BM sample
- PFS results updated with 34.1 months of follow-up

CIRS = cumulative illness rating scale; CrCl = creatinine clearance; IRC = independent review committee; PFS = progression-free survival; MRD = minimal residual disease; PB = peripheral blood; BM = bone marrow; uMRD = undetectable MRD; EOT = end of treatment

Munir T et al. ASH 2021;Abstract 70. Kater A et al. EHA 2021;Abstract LB1902.

RTP RESEARCH TO PRACTICE

GLOW: Investigator-Assessed PFS for Older and/or Less Fit Patients with Treatment-Naïve CLL

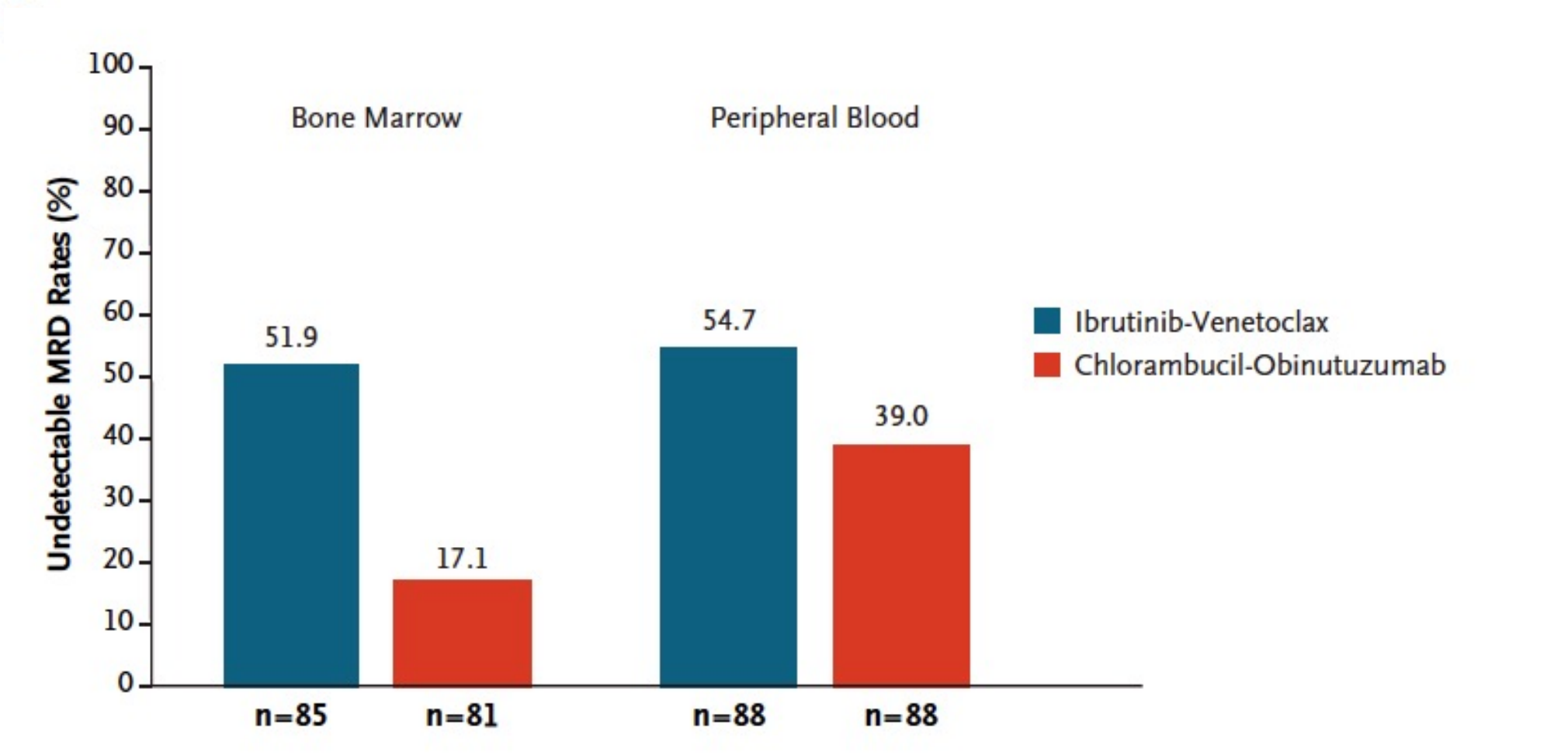


No. at Risk											
Ibrutinib-Venetoclax	106	99	99	95	92	91	89	87	72	60	21
Chlorambucil-Obinutuzumab	105	103	101	97	94	68	60	52	40	30	12

Kater AP et al. *NEJM Evidence* 2022;10.1056/EVIDoa2200006.

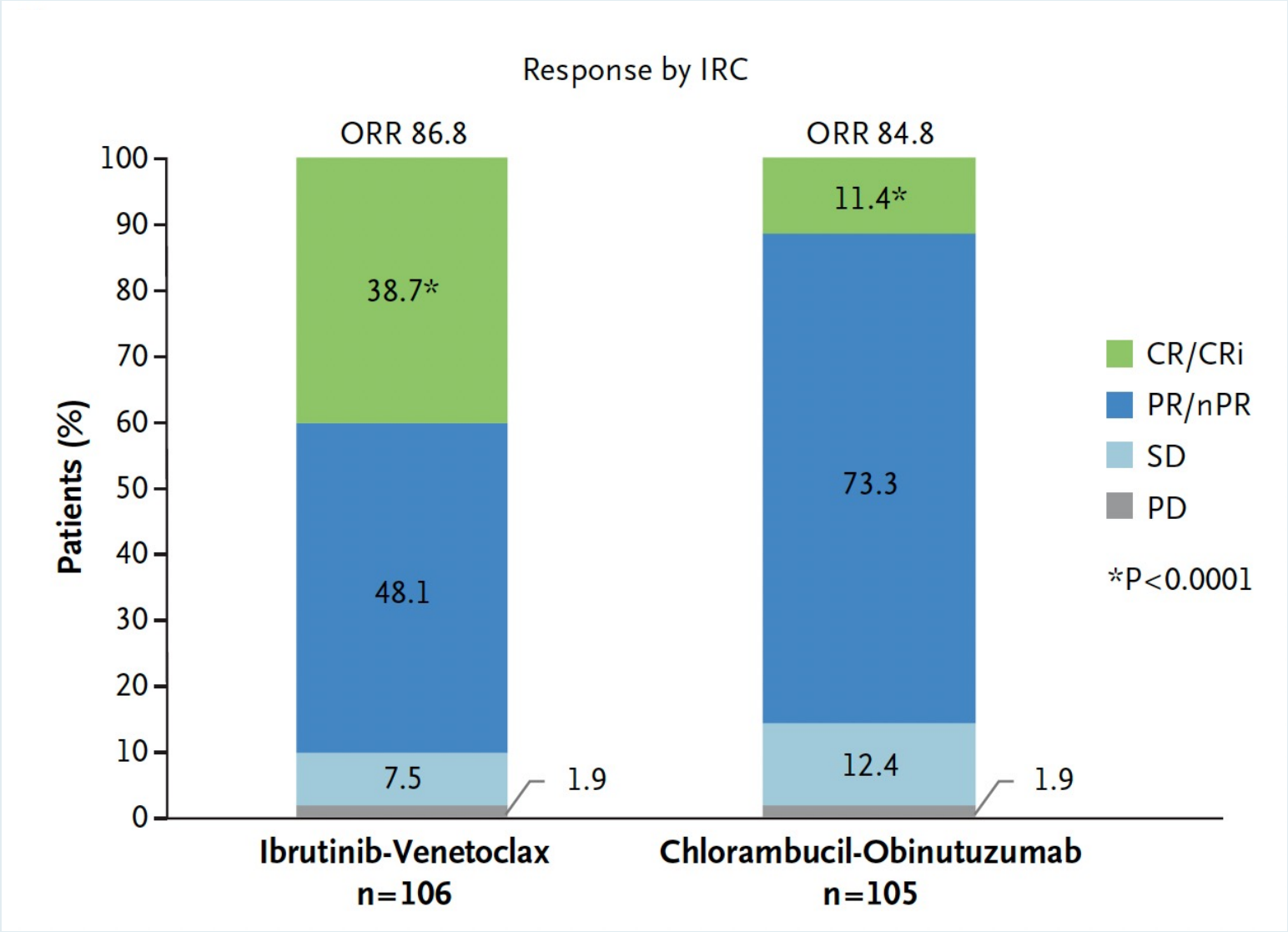
RTP RESEARCH TO PRACTICE

GLOW: MRD Rates at 3 Months After End of Treatment



Kater AP et al. *NEJM Evidence* 2022;10.1056/EVIDoa2200006.

GLOW: Independent Review Committee Tumor Response (ITT)



Kater AP et al. *NEJM Evidence* 2022;10.1056/EVIDoa2200006.

GLOW: Summary of Serious Adverse Events

Adverse Events* – n (%)	Ibrutinib-Venetoclax (n=106)	Chlorambucil-Obinutuzumab (n=105)
Any	49 (46.2)	29 (27.6)
Infections†	13 (12.3)	9 (8.6)
Atrial fibrillation	7 (6.6)	0
Anemia	3 (2.8)	2 (1.9)
Diarrhea	3 (2.8)	1 (1.0)
Cardiac failure	3 (2.8)	0
Febrile neutropenia	1 (0.9)	3 (2.9)
Infusion-related reaction	0	3 (2.9)
Tumor lysis syndrome	0	3 (2.9)

Kater AP et al. *NEJM Evidence* 2022;10.1056/EVIDoa2200006.

RTP RESEARCH TO PRACTICE

Meet The Professor with Dr Sharman

Introduction: Journal Club Part 1

MODULE 1: Case Presentations

- Dr Bufalino: A 58-year-old man with progressive SLL who developed acalabrutinib-associated rash
- Dr Gupta: A 69-year-old man with recurrent DVT who is receiving warfarin and is diagnosed with CLL requiring treatment
- Dr McKenna: A 72-year-old man with IGHV-unmutated CLL who has severe cardiac disease requiring a defibrillator
- Dr Brooks: A 70-year-old man with CLL who remains in remission after treatment with chlorambucil/obinutuzumab
- Dr Narayanan: A 51-year-old man with IGHV-unmutated CLL and del(17p) who developed atrial fibrillation on ibrutinib
- Dr Bachow: An 87-year-old woman with CLL transformed to Hodgkin lymphoma
- Dr Rupard: A 59-year-old man with relapsed IGHV-mutated CLL who experienced acalabrutinib-associated headache
- Dr Metzner-Sadurski: A 64-year-old woman with IGHV-unmutated CLL and hemolytic anemia
- Dr Polkinghorn: An 81-year-old man with recurrent CLL who discontinued ibrutinib due to atrial fibrillation

MODULE 2: Faculty Survey

MODULE 3: Journal Club Part 2

MODULE 4: Appendix of Key Recent Data Sets

RTP RESEARCH TO PRACTICE

SCIENCE IMMUNOLOGY | RESEARCH ARTICLE

CORONAVIRUS

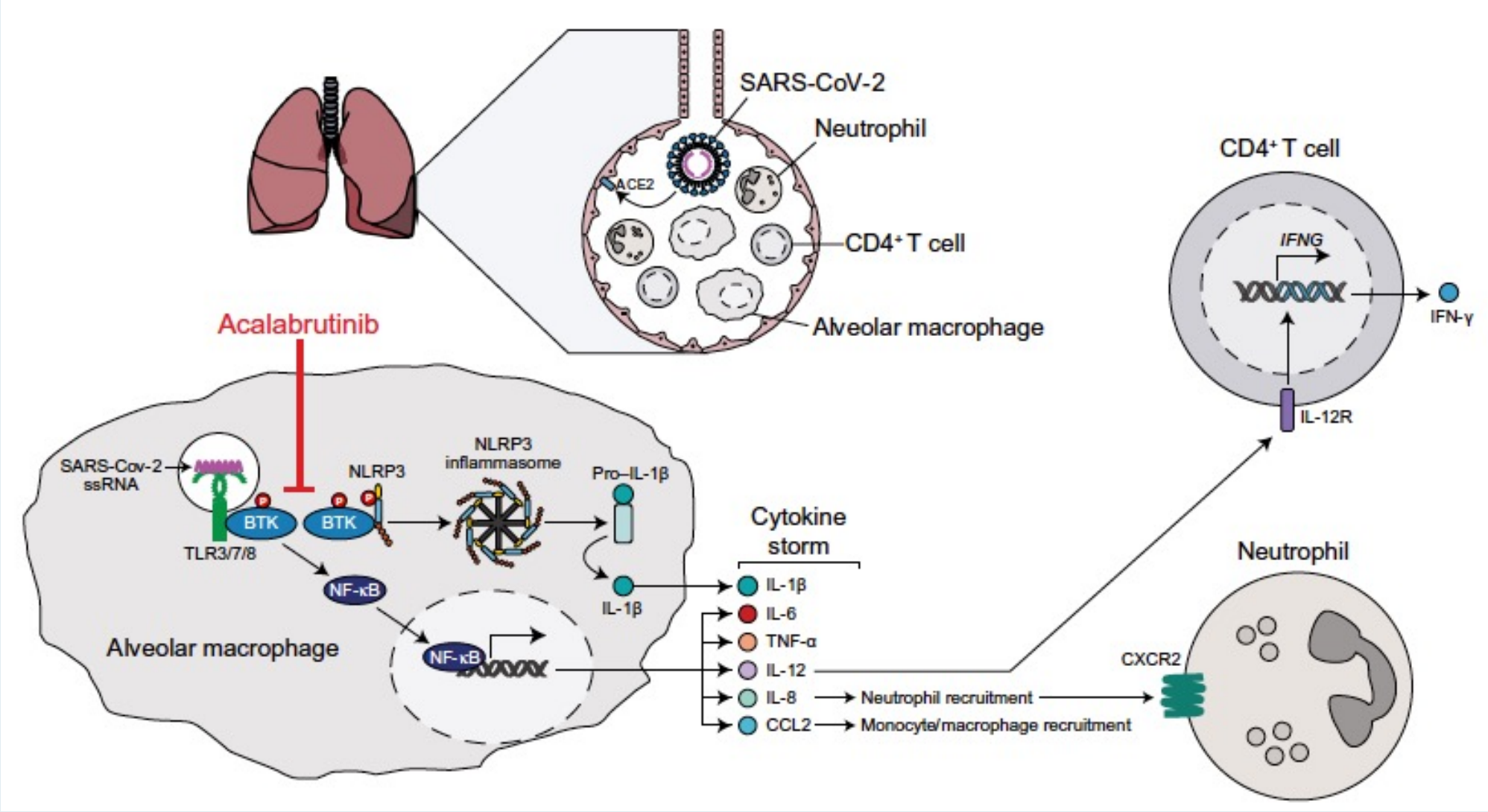
Inhibition of Bruton tyrosine kinase in patients with severe COVID-19

Mark Roschewski[1]*, Michail S. Lionakis[2]*, Jeff P. Sharman[3]*, Joseph Roswarski[4]*, Andre Goy[5], M. Andrew Monticelli[6], Michael Roshon[7,8], Stephen H. Wrzesinski[9], Jigar V. Desai[2], Marissa A. Zarakas[2], Jacob Collen[10], Keith M. Rose[5], Ahmed Hamdy[11], Raquel Izumi[11], George W. Wright[12], Kevin K. Chung[9], Jose Baselga[13], Louis M. Staudt[1†], Wyndham H. Wilson[1†‡]

Sci Immunol 2020;5(48):eabd0110.

RTP RESEARCH TO PRACTICE

Model of BTK-Dependent Hyperinflammation in Severe COVID-19



Roschewski M et al. *Sci Immunol* 2020;5(48):eabd0110.

RTP RESEARCH TO PRACTICE

Meet The Professor with Dr Sharman

Introduction: Journal Club Part 1

MODULE 1: Case Presentations

- Dr Bufalino: A 58-year-old man with progressive SLL who developed acalabrutinib-associated rash
- Dr Gupta: A 69-year-old man with recurrent DVT who is receiving warfarin and is diagnosed with CLL requiring treatment
- Dr McKenna: A 72-year-old man with IGHV-unmutated CLL who has severe cardiac disease requiring a defibrillator
- Dr Brooks: A 70-year-old man with CLL who remains in remission after treatment with chlorambucil/obinutuzumab
- Dr Narayanan: A 51-year-old man with IGHV-unmutated CLL and del(17p) who developed atrial fibrillation on ibrutinib
- Dr Bachow: An 87-year-old woman with CLL transformed to Hodgkin lymphoma
- Dr Rupard: A 59-year-old man with relapsed IGHV-mutated CLL who experienced acalabrutinib-associated headache
- Dr Metzner-Sadurski: A 64-year-old woman with IGHV-unmutated CLL and hemolytic anemia
- Dr Polkinghorn: An 81-year-old man with recurrent CLL who discontinued ibrutinib due to atrial fibrillation

MODULE 2: Faculty Survey

MODULE 3: Journal Club Part 2

MODULE 4: Appendix of Key Recent Data Sets

RTP
RESEARCH
TO PRACTICE

Case Presentation: A 58-year-old man with progressive SLL (small lymphocytic lymphoma) who developed acalabrutinib-associated rash

Dr Shams Bufalino (Park Ridge, Illinois)

RTP RESEARCH TO PRACTICE

Front Oncol 2021;11:720704.

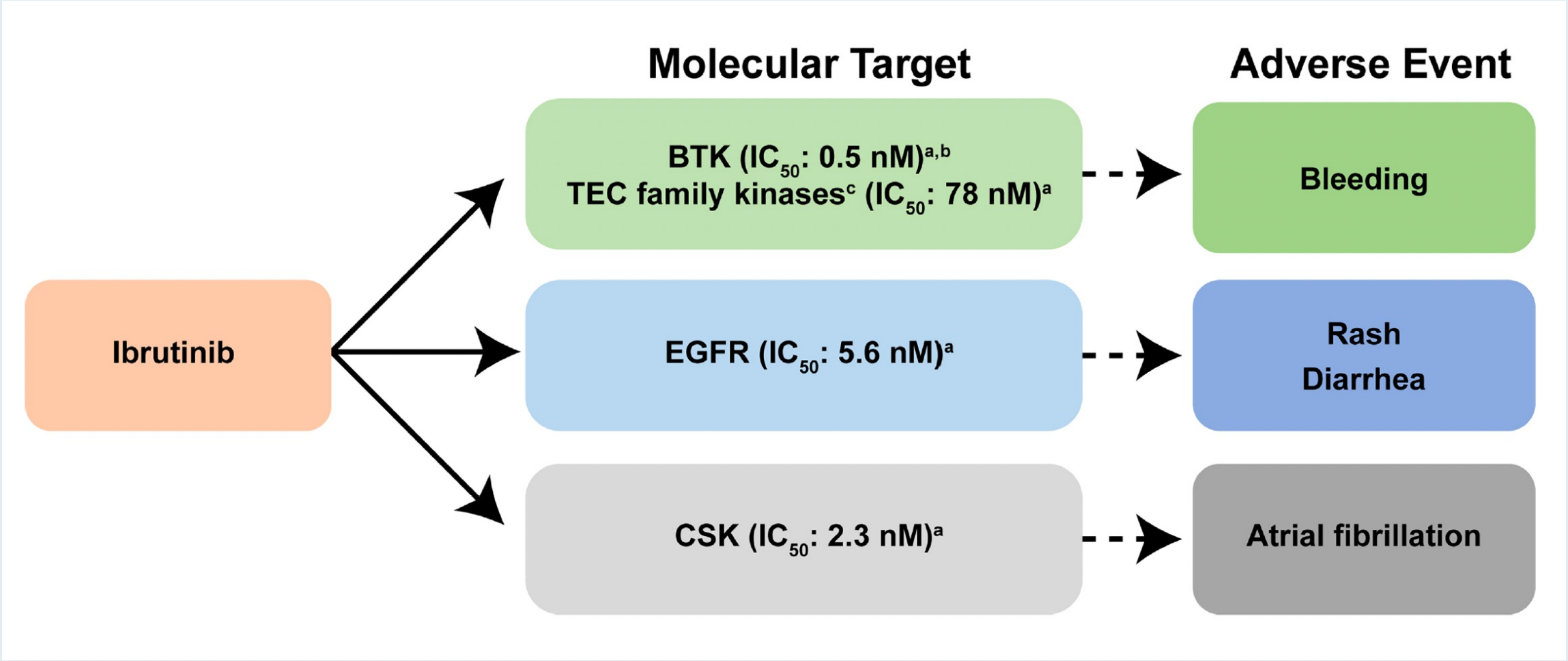
frontiers in Oncology

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]*

JC JOURNAL CLUB RTP RESEARCH TO PRACTICE

Reported Molecular Targets of Ibrutinib and Their Associated Adverse Events



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

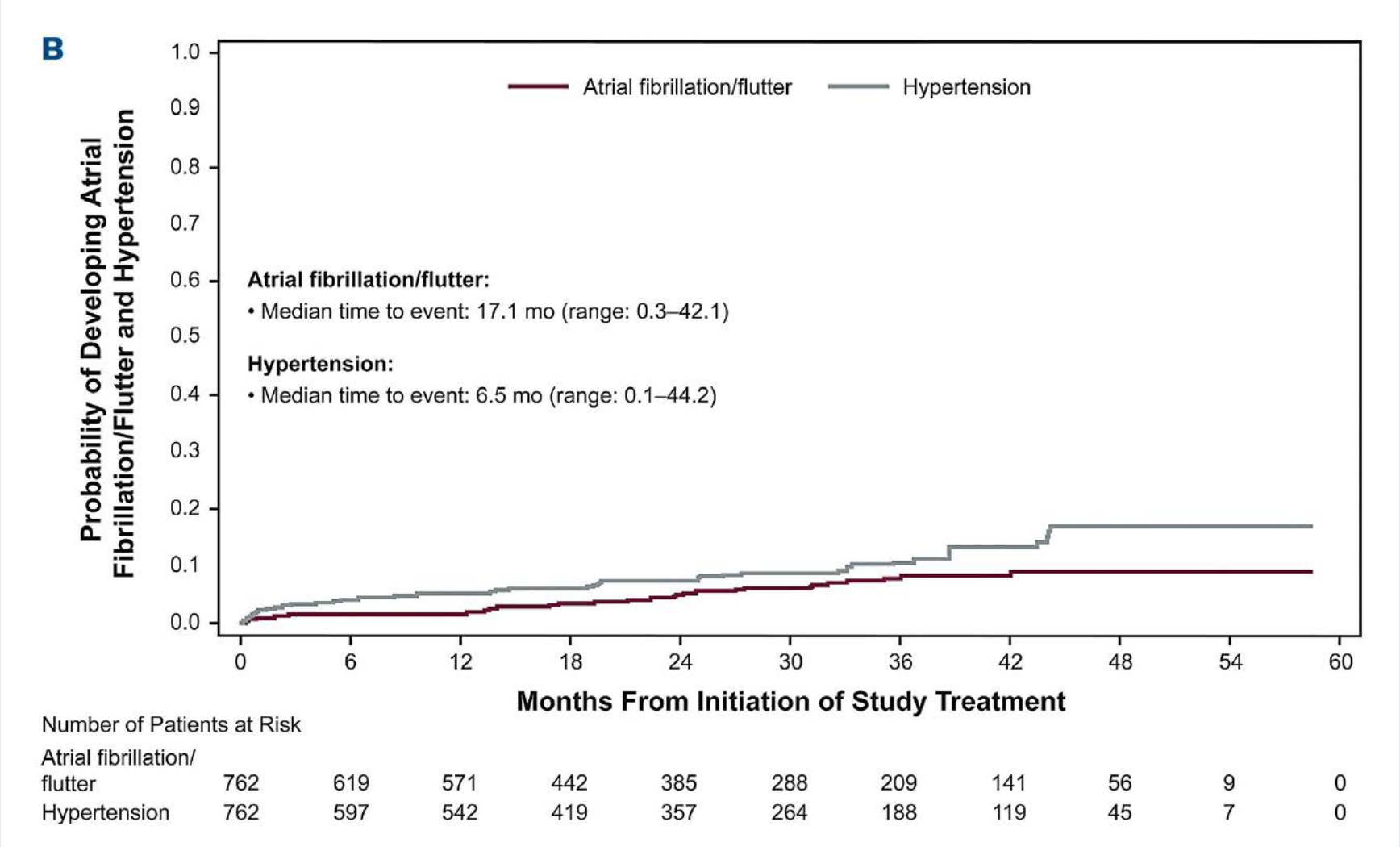
Haematologica 2022;107(6):1335-46.

Cardiovascular adverse events in patients with chronic lymphocytic leukemia receiving acalabrutinib monotherapy: pooled analysis of 762 patients

Jennifer R. Brown,[1] John C. Byrd,[2] Paolo Ghia,[3] Jeff P. Sharman,[4] Peter Hillmen,[5] Deborah M. Stephens,[6] Clare Sun,[7] Wojciech Jurczak,[8] John M. Pagel,[9] Alessandra Ferrajoli,[10] Priti Patel,[11] Lin Tao,[11] Nataliya Kuptsova-Clarkson,[12] Javid Moslehi[13] and Richard R. Furman[14]

JC JOURNAL CLUB RTP RESEARCH TO PRACTICE

Time to Onset of Atrial Fibrillation/Flutter and Hypertension Events



Brown JP et al. *Haematologica* 2022;107(6):1335-46.

Case Presentation: A 69-year-old man with recurrent DVT who is receiving warfarin and is diagnosed with CLL requiring treatment

Dr Shaachi Gupta (Lake Worth, Florida)

RTP
RESEARCH
TO PRACTICE

Debulking Before Initiation of Venetoclax Therapy in Untreated Patients with Chronic Lymphocytic Leukemia: Results from a Phase 3b Study

Flinn IW et al.

ASH 2021;Abstract 3725.

JC JOURNAL CLUB
RTP RESEARCH TO PRACTICE

Flinn IW et al. ASH 2021;Abstract 3725

#3725

Debulking Before Initiation of Venetoclax Therapy in Untreated Patients With Chronic Lymphocytic Leukemia: Results From a Phase 3b Study

Ian Flinn[1], David Andorsky[2], Jason Melear[3], Sudhir Manda[4], Bertrand Arz III[5], Habte Yimer[6], John M. Burke[7], Suzanne Fanning[8], Jay Courbright[8], Miguel Islas-Ohlmayer[8], Suman Kambhampati[9], Tamas Vizkelety[10], John Pesko[10], Brenda Chyla[10], Dingfeng Jiang[10], and Jeff P. Sharman[11]

[1]Sarah Cannon Research Institute-Tennessee Oncology, Nashville, TN, USA; [2]Rocky Mountain Cancer Centers, Boulder, CO, USA; [3]Texas Oncology-Austin Midtown, Austin, TX, USA; [4]Arizona Oncology Associates, PC-HOPE, Tucson, AZ, USA; [5]Renessaee Oncology Chattanooga, Chattanooga, TN, USA; [6]Texas Oncology-Tyler, Tyler, TX, USA; [7]Rocky Mountain Cancer Centers Aurora, Aurora, CO, USA; [8]Pharma Health, Greenville, SC, USA; [9]Texas Oncology-Dallas, Dallas, TX, USA; [10]Oncology Hematology Care, Inc., Cincinnati, OH, USA; [11]Sarah Cannon Cancer Institute, HCA Midwest Health, Research Medical Center, Kansas City, MO, USA; [12]AbbVie Inc., North Chicago, IL, USA; [13]Willamette Valley Cancer Institute and US Oncology Research, Eugene, OR, USA

OBJECTIVE

Establish the utility of a debulking strategy to facilitate venetoclax ramp-up in the outpatient setting by evaluating the reduction in tumor burden after debulking and assessing efficacy and safety outcomes with subsequent venetoclax + obinutuzumab therapy

CONCLUSIONS

- Most (91.6%) patients achieved low tumor burden after debulking with obinutuzumab ± bendamustine prior to venetoclax treatment
- The best rate of undetectable minimal residual disease ($<10^{-4}$) was 98.2% among evaluable patients in this frontline population with medium or high baseline tumor burden
- Overall, these results highlight the utility of obinutuzumab ± bendamustine as an effective debulking strategy that can facilitate venetoclax treatment initiation in the outpatient setting

For additional information or to obtain a PDF of this poster

Scan QR code to download an electronic version of this presentation and other AbbVie ASH 2021 scientific presentations.

QR Code expiration: December 1, 2022

To submit a medical question, please visit www.abbviemedinfo.com

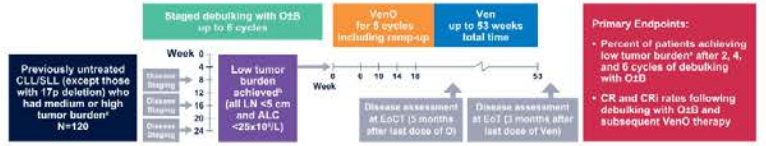
References

BACKGROUND

- Venetoclax (Ven), an oral B-cell lymphoma 2 inhibitor, is approved for use in adult patients with chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) in both the newly diagnosed and relapsed settings[1-3]
- As a targeted and highly active antitumor agent, Ven induces rapid and profound tumor reduction
- Inpatient monitoring for tumor lysis syndrome is recommended by US Prescribing Information during initial doses of Ven for patients with high tumor burden or medium tumor burden with reduced renal function[3]
- Treatment with other agents, such as obinutuzumab (O), bendamustine (B), or BTK inhibitors, help reduce tumor burden and may reduce the need for inpatient monitoring; however, more data are needed to conclusively determine the benefits of debulking regimens
- Tumor reduction data and outcomes with venetoclax + obinutuzumab (VenO) following debulking will help definitively establish the utility of a debulking strategy prior to Ven treatment to facilitate administration of Ven in the outpatient setting

METHODS

Study Design (NCT03406156)



RESULTS

Study Disposition and Baseline Patient Characteristics

Patient characteristics	Debulking With O (n=81)	Debulking With O+B (n=39)	Total[a] (N=120)
Sex, male, n (%)	54 (66.7)	28 (71.8)	82 (68.3)
Median age (range), years	66 (37–83)	59 (45–82)	64 (37–83)
Age ≥65 years, n (%)	47 (58.0)	12 (30.8)	59 (49.2)
IgVH, n (%)			
Mutated	36 (44.4)	13 (33.3)	49 (40.8)
Unmutated	41 (50.6)	25 (64.1)	66 (55.0)
11Q Deletion status, n (%)			
Deleted	10 (12.3)	12 (30.8)	22 (18.3)
Not deleted	66 (81.5)	26 (66.7)	92 (76.7)
ALC ≥25×10⁹/L, n (%)	74 (91.4)	25 (64.1)	99 (82.5)
LN size, n (%)			
≥5 cm	13 (16.0)	27 (69.2)	40 (33.3)
≥10 cm	1 (1.2)	10 (25.6)	11 (9.2)
Tumor burden[b], n (%)			
High	8 (9.9)	21 (53.8)	29 (24.2)
Medium	72 (88.9)	18 (46.2)	90 (75.0)
Low	1 (1.2)	0 (0.0)	1 (0.8)

- As of 13 May 2021, 2 patients remained on study treatment, 108 were in post-treatment follow-up, and not all had reached final assessment; 10[c] had discontinued the study for reasons including death (n=7), withdrawn consent (n=2), and COVID-19 infection (n=1)

Most Patients Achieved Low Tumor Burden[a] by the End of Debulking (n=119[b])

- Among patients receiving debulking with O (n=80[c])
  - Low tumor burden was achieved in 86.3% after 2 cycles and 95.0% by the end of debulking
- Among patients receiving debulking with O+B (n=39)
  - Low tumor burden was achieved in 74.4% after 2 cycles and 84.6% by the end of debulking
- Among all patients receiving debulking (n=119[b]), 10 did not achieve low tumor burden by the end of debulking
  - 1 had high tumor burden after debulking (with baseline LN ≥10 cm)
  - 6 had medium tumor burden after debulking (4 with baseline LN ≥10 cm; 2 with baseline LN 5 to <10 cm)
  - 3 had missing tumor burden after debulking
- Among all patients receiving debulking (N=120)
  - ALC reduction from ≥25×10⁹/L at baseline to <25×10⁹/L was achieved in 100.0% (99/99) of evaluable patients after 2 cycles
  - In evaluable patients, LN size reduction from ≥5 cm at baseline to <5 cm was achieved in 55.0% (22/40) after 2 cycles and 82.5% (33/40) by the end of debulking

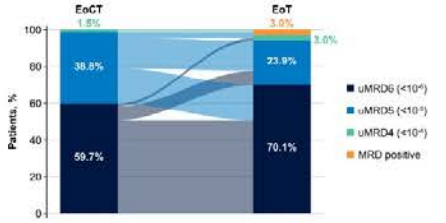
High Response Rates and uMRD Rates Were Observed in Patients Treated With VenO After Debulking

Best Overall Response	Patients With EoT Assessment (n=76)[a]	All Treated Patients (N=120)
ORR[b], n (%); [95% CI]	75[c] (98.7); [92.9–100.0]	108[d] (90.0); [83.2–94.7]
CR+CRi rate, n (%); [95% CI]	34 (44.7); [33.3–56.6]	43 (35.8); [27.3–45.1]

MRD Rates in Peripheral Blood[e] for Patients With Assessments, n/n (%); [95% CI]	MRD at EoT[f]	Best MRD Rate
uMRD4	68/70 (97.1); [90.1–99.7]	107/109 (98.2); [93.5–99.8]
uMRD6	48/70 (68.6); [56.4–79.1]	78/109 (71.6); [62.1–79.8]

- In patients with bone marrow MRD assessments[g], the best rate of uMRD4 and uMRD6 in bone marrow was 96.4% (53/55; 95% CI, 87.5–99.6) and 54.5% (30/55; 95% CI, 40.0–68.0), respectively
- The estimated progression-free survival at Month 18 was 94.1% [95% CI, 86.3–97.5]; no incidences of disease progression were reported

MRD Responses at EoCT and EoT (n=67)[a]



- In patients with assessments at both timepoints, 19.4% had a deepening of their MRD response from EoCT to EoT and 67.2% maintained the same MRD level

Overview of TEAEs and Deaths

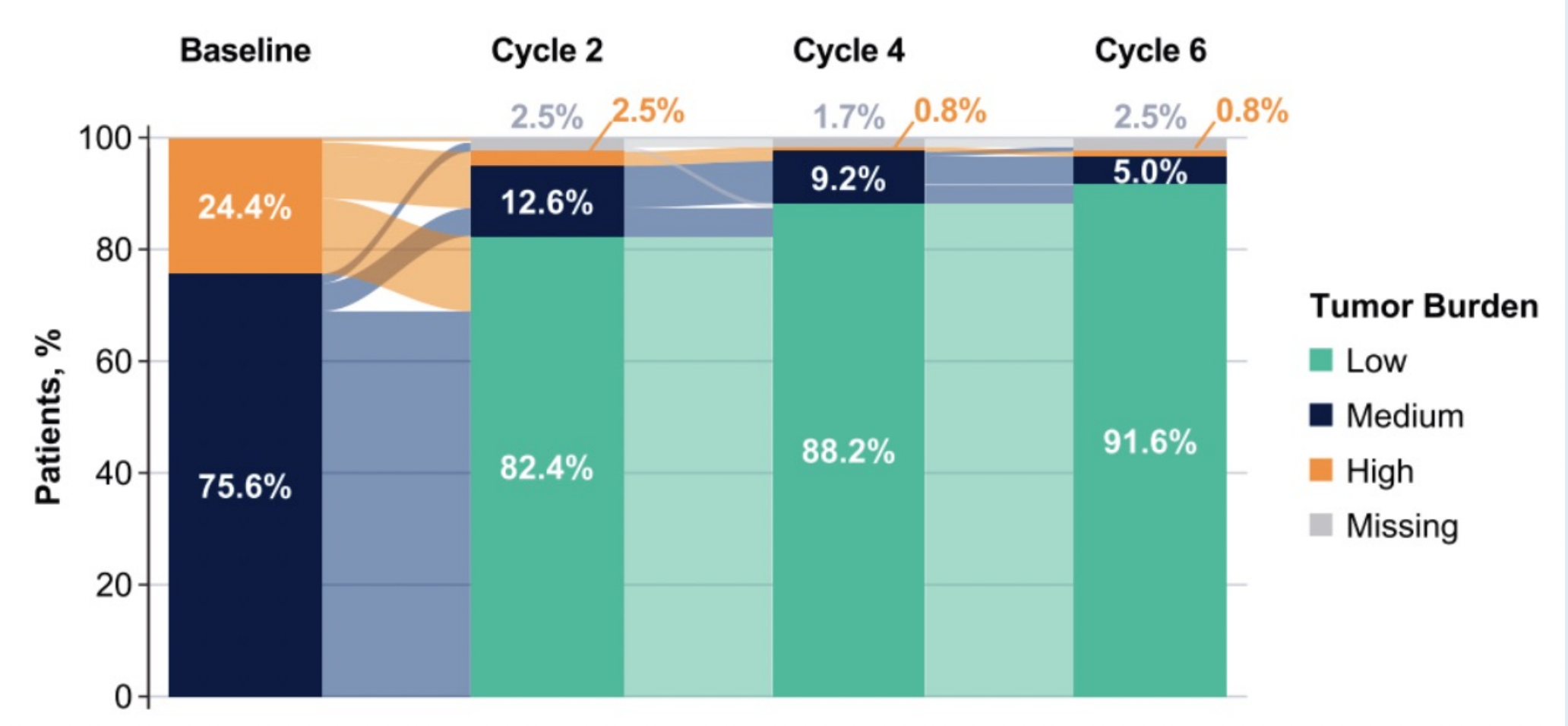
Patients With AEs, n (%)	Debulking With O (n=81)	Debulking With O+B (n=39)	Total (N=120)
Any TEAE	81 (100.0)	39 (100.0)	120 (100.0)
Grade ≥3 TEAE	58 (71.6)	33 (84.6)	91 (75.8)
Neutropenia or neutrophil count decreased[a]	41 (50.6)	26 (66.7)	67 (55.8)
Thrombocytopenia or platelet count decreased[a]	20 (24.7)	9 (23.1)	29 (24.2)
Leukopenia or WBC count decreased[a]	8 (9.9)	10 (25.6)	18 (15.0)
Serious TEAE[b]	19 (23.5)	7 (17.9)	26 (21.7)
TLS[c]	5 (6.2)	7 (17.9)	12 (10.0)

- After a median follow-up of 24 months, 7 deaths were reported (1 from cardiac complication after pancreatic mass resection)
  - 6 deaths were related to COVID-19 infection (5 patients received debulking with O, and 1 received debulking with O+B)
  - Vaccination records for these patients were not reported
- Preventive measures for COVID-19 should be continuously emphasized for patients with CLL

JC JOURNAL CLUB

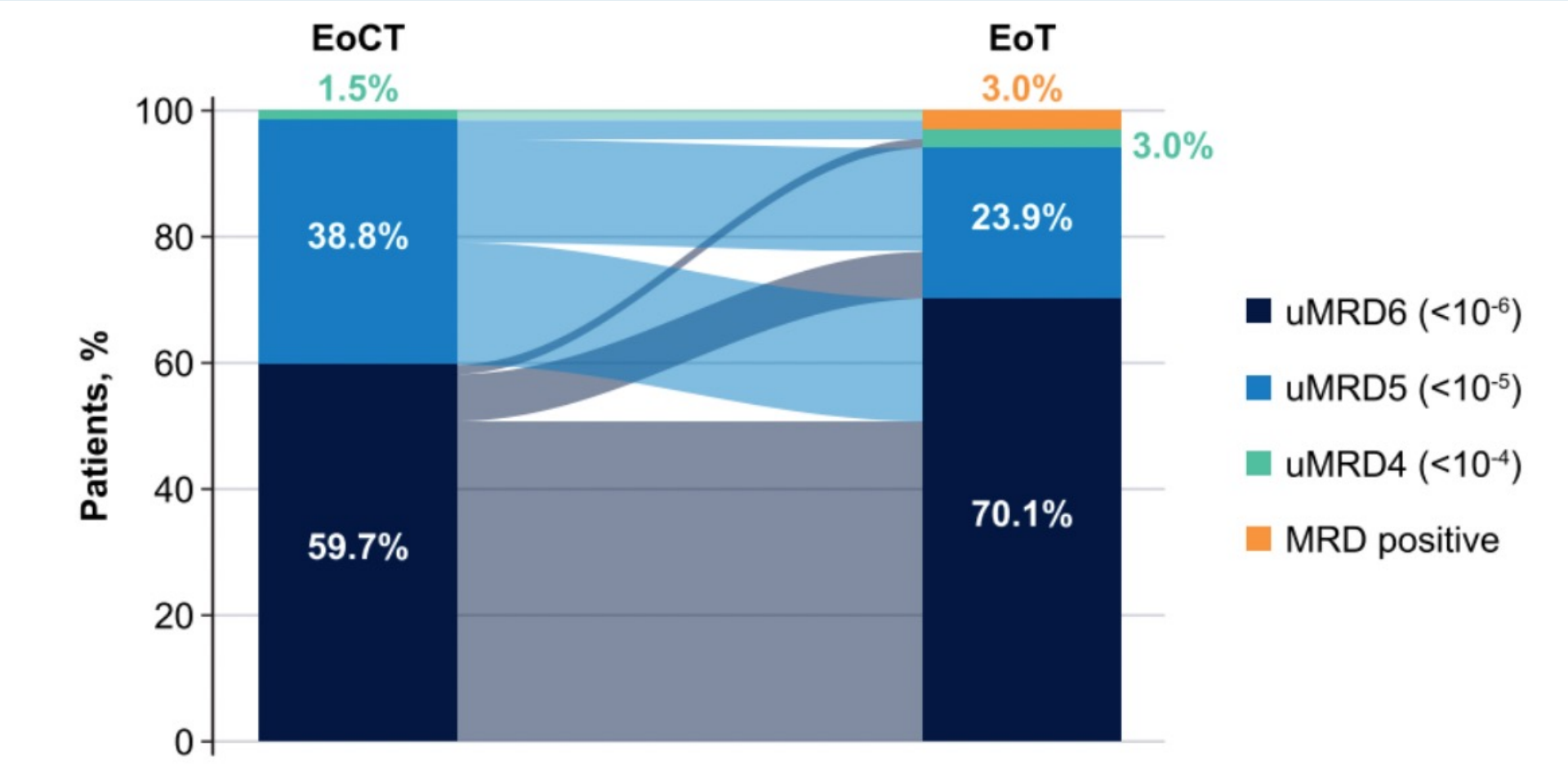
RTP RESEARCH TO PRACTICE

Most Patients Achieved Low Tumor Burden by the End of Debulking (n = 119)



Flinn IW et al. ASH 2021;Abstract 3725.

MRD Responses at End of Combination Therapy (EoCT) and End of Therapy (EoT); n = 67



Flinn IW et al. ASH 2021;Abstract 3725.

Case Presentation: A 72-year-old man with IGHV-unmutated CLL who has severe cardiac disease requiring a defibrillator

Dr Rajalaxmi McKenna (Willowbrook, Illinois)

RTP
RESEARCH
TO PRACTICE

Case Presentation: A 70-year-old man with CLL who remains in remission after treatment with chlorambucil/obinutuzumab

Dr Philip Brooks (Brewer, Maine)

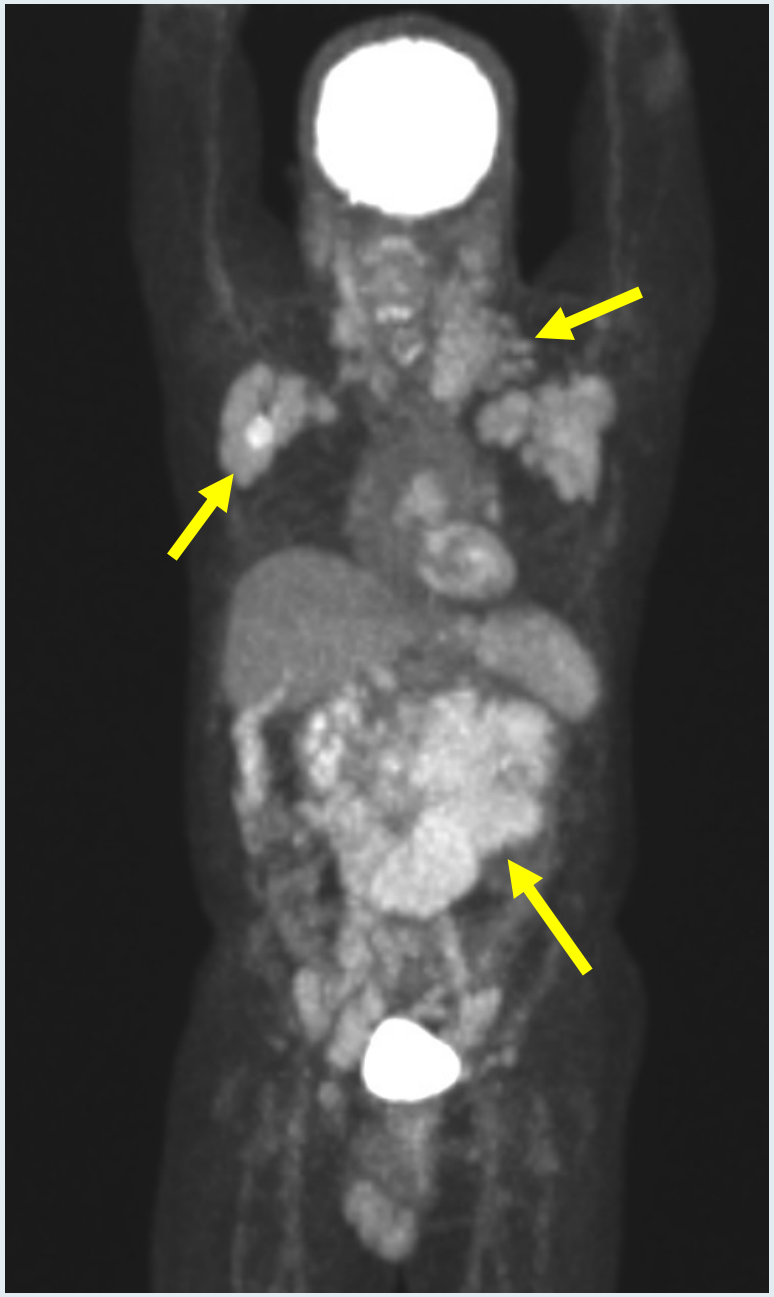
RTP
RESEARCH
TO PRACTICE

Case Presentation: A 51-year-old man with IGHV-unmutated CLL and del(17p) who developed atrial fibrillation on ibrutinib

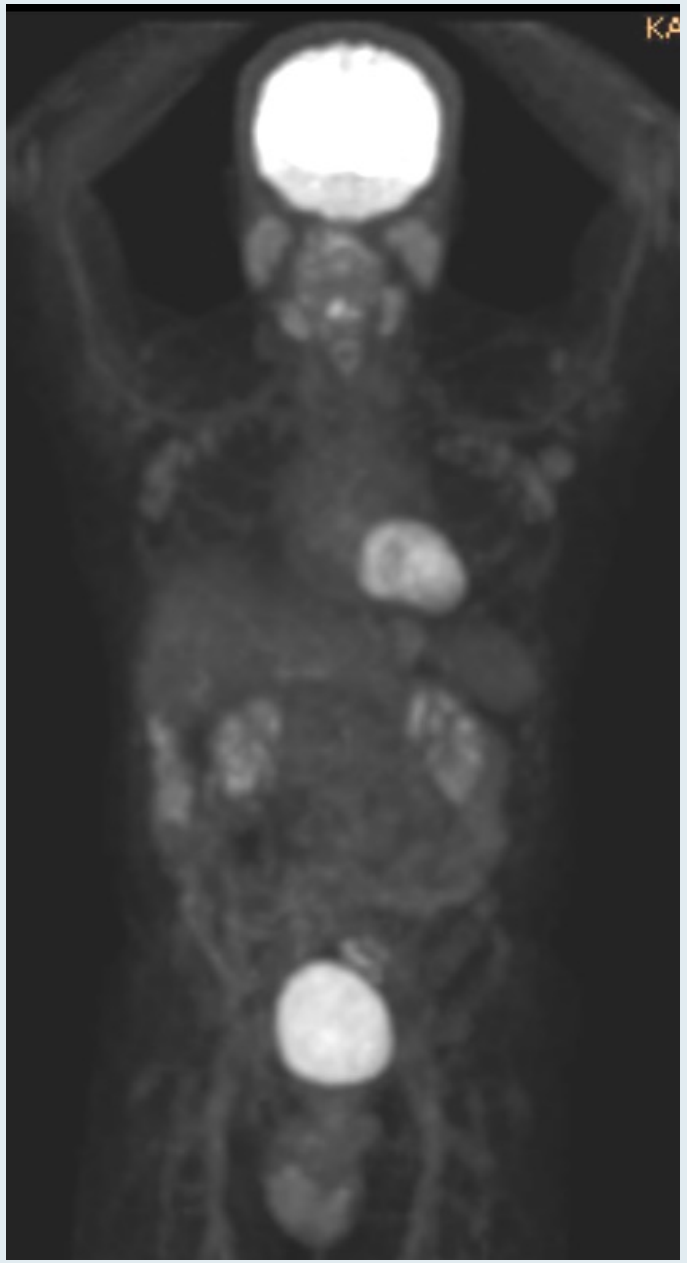
Dr Vignesh Narayanan (Lone Tree, Colorado)

RTP
RESEARCH
TO PRACTICE

PET scan before ibrutinib



PET scan after ibrutinib



RTP
RESEARCH
TO PRACTICE

Haematologica 2022;[Online ahead of print].

haematologica

Journal of The Ferrata Storti Foundation

A clinical practice comparison of patients with chronic lymphocytic leukemia with and without deletion 17p receiving first-line treatment with ibrutinib

by Anthony R. Mato, Boxiong Tang, Soraya Azmi, Keri Yang, Xiaojuan Zhang, Jennifer C. Stern, Eric Hedrick, Jane Huang, and Jeff P. Sharman

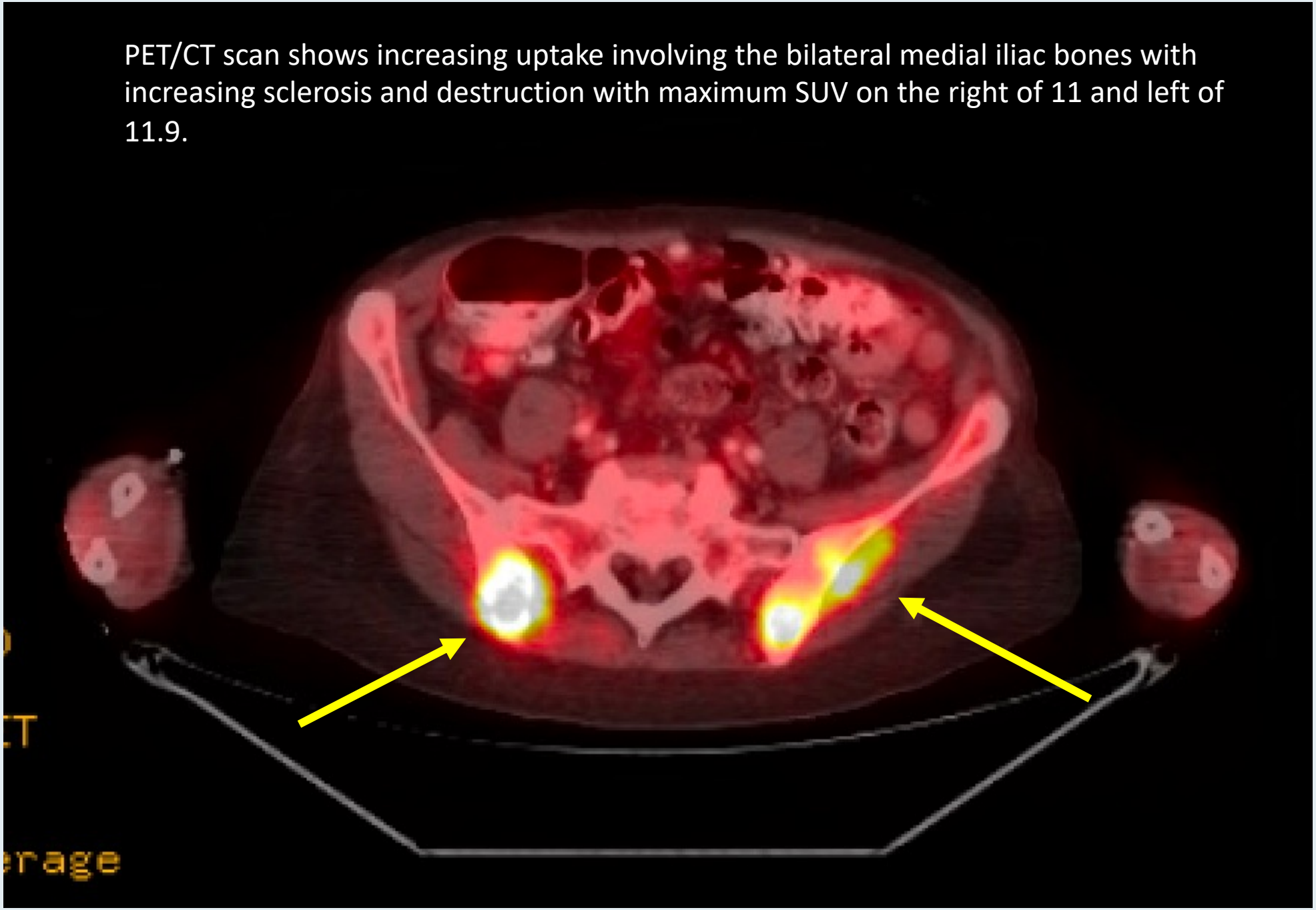
JC JOURNAL CLUB RTP RESEARCH TO PRACTICE

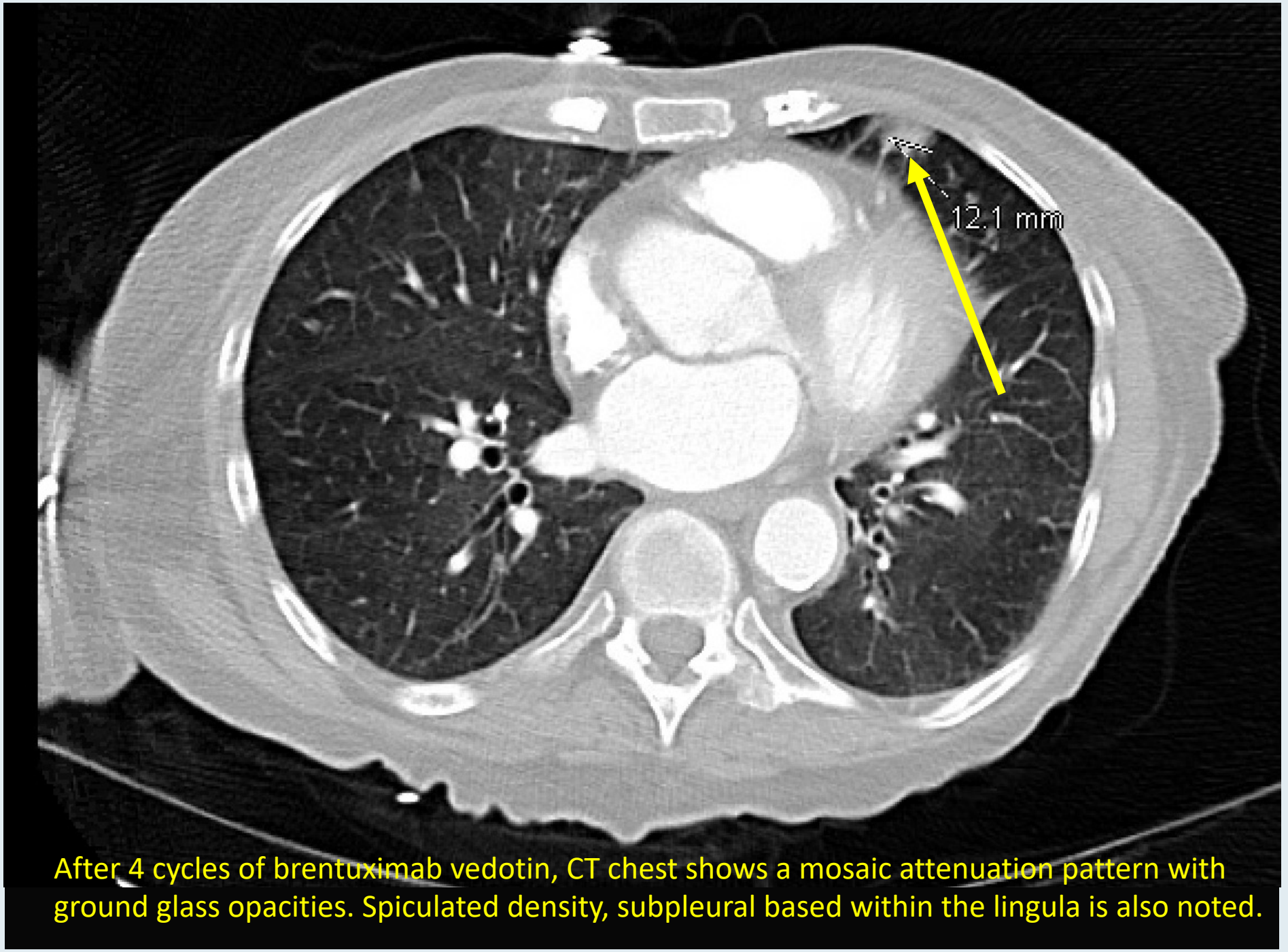
Case Presentation: An 87-year-old woman with CLL transformed to Hodgkin lymphoma

Dr Spencer Bachow (Boca Raton, Florida)

RTP RESEARCH TO PRACTICE

PET/CT scan shows increasing uptake involving the bilateral medial iliac bones with increasing sclerosis and destruction with maximum SUV on the right of 11 and left of 11.9.





After 4 cycles of brentuximab vedotin, CT chest shows a mosaic attenuation pattern with ground glass opacities. Spiculated density, subpleural based within the lingula is also noted.

RTP
RESEARCH
TO PRACTICE

Case Presentation: A 59-year-old man with relapsed IGHV-mutated CLL who experienced acalabrutinib-associated headache

Dr Erik Rupard (West Reading, Pennsylvania)

RTP
RESEARCH
TO PRACTICE

Case Presentation: A 64-year-old woman with IGHV-unmutated CLL and hemolytic anemia

Dr Joanna Metzner-Sadurski (Greenwood, South Carolina)

RTP RESEARCH TO PRACTICE

Case Presentation: An 81-year-old man with recurrent CLL who discontinued ibrutinib due to atrial fibrillation

Dr Richard Polkinghorn (Augusta, Maine)

RTP
RESEARCH
TO PRACTICE

Leukemia 2022;36(4):1171-5.

Leukemia

www.nature.com/leu

LETTER OPEN

CHRONIC LYMPHOCYTIC LEUKEMIA

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]

JC JOURNAL CLUB RTP RESEARCH TO PRACTICE

Acalabrutinib ± Obinutuzumab versus Obinutuzumab + Chlorambucil in Treatment-Naïve Chronic Lymphocytic Leukemia: Five-Year Follow-Up of ELEVATE-TN

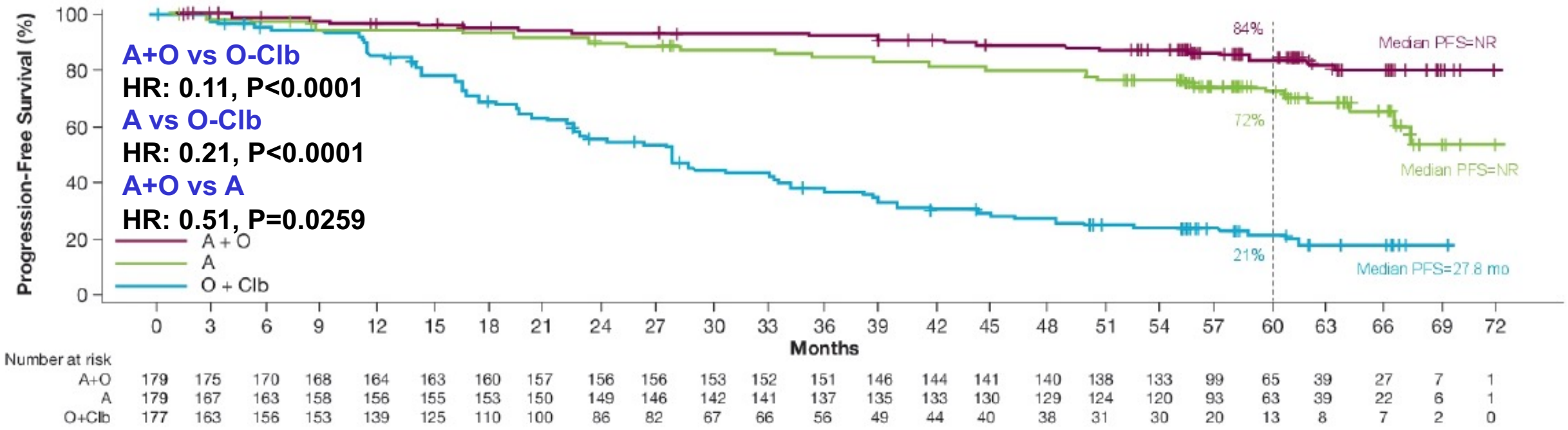
Sharman JP et al.

ASCO 2022;Abstract 7539.

RTP
RESEARCH
TO PRACTICE

ELEVATE-TN: Investigator-Assessed Progression-Free Survival (Overall)

5-Year Follow-Up

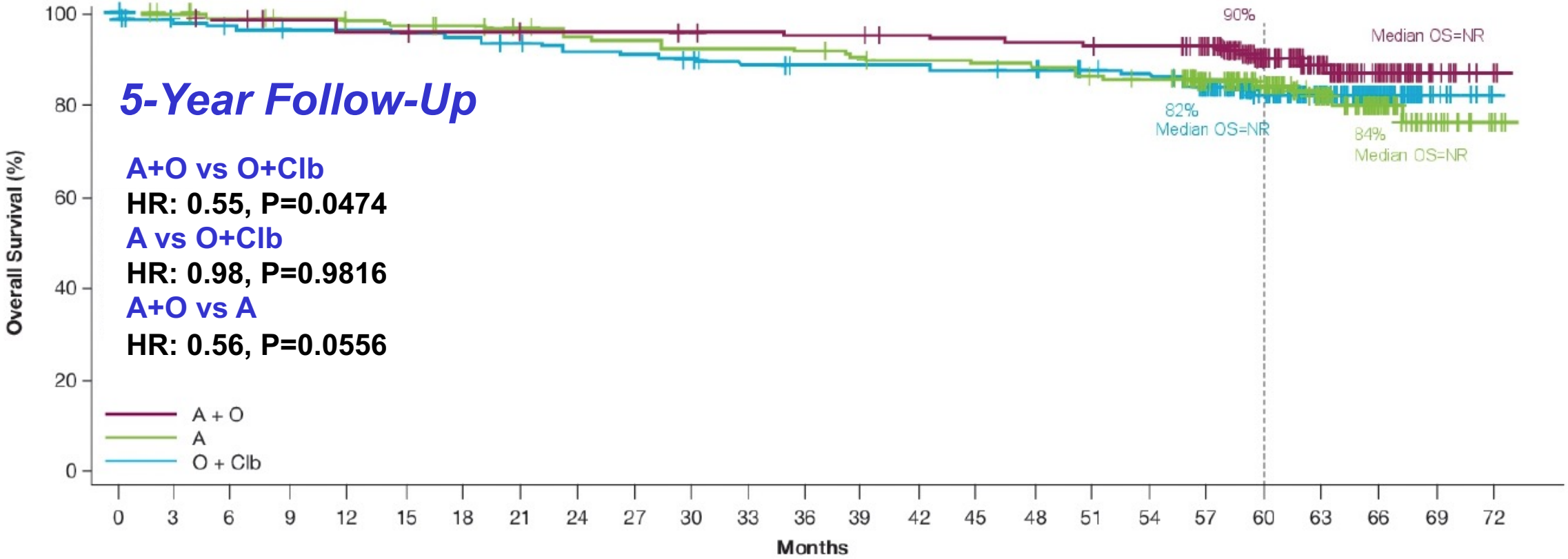


A = acalabrutinib; O = obinutuzumab; Clb = chlorambucil; HR = hazard ratio; CI = confidence interval

Sharman JP et al. ASCO 2022;Abstract 7539.

RTP RESEARCH TO PRACTICE

ELEVATE-TN: Overall Survival



A = acalabrutinib; O = obinutuzumab; Clb = chlorambucil; HR = hazard ratio; CI = confidence interval

Sharman JP et al. ASCO 2022;Abstract 7539.

RTP RESEARCH TO PRACTICE

Meet The Professor with Dr Sharman

Introduction: Journal Club Part 1

MODULE 1: Case Presentations

MODULE 2: Faculty Survey

MODULE 3: Journal Club Part 2

MODULE 4: Appendix of Key Recent Data Sets

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

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?

 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

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

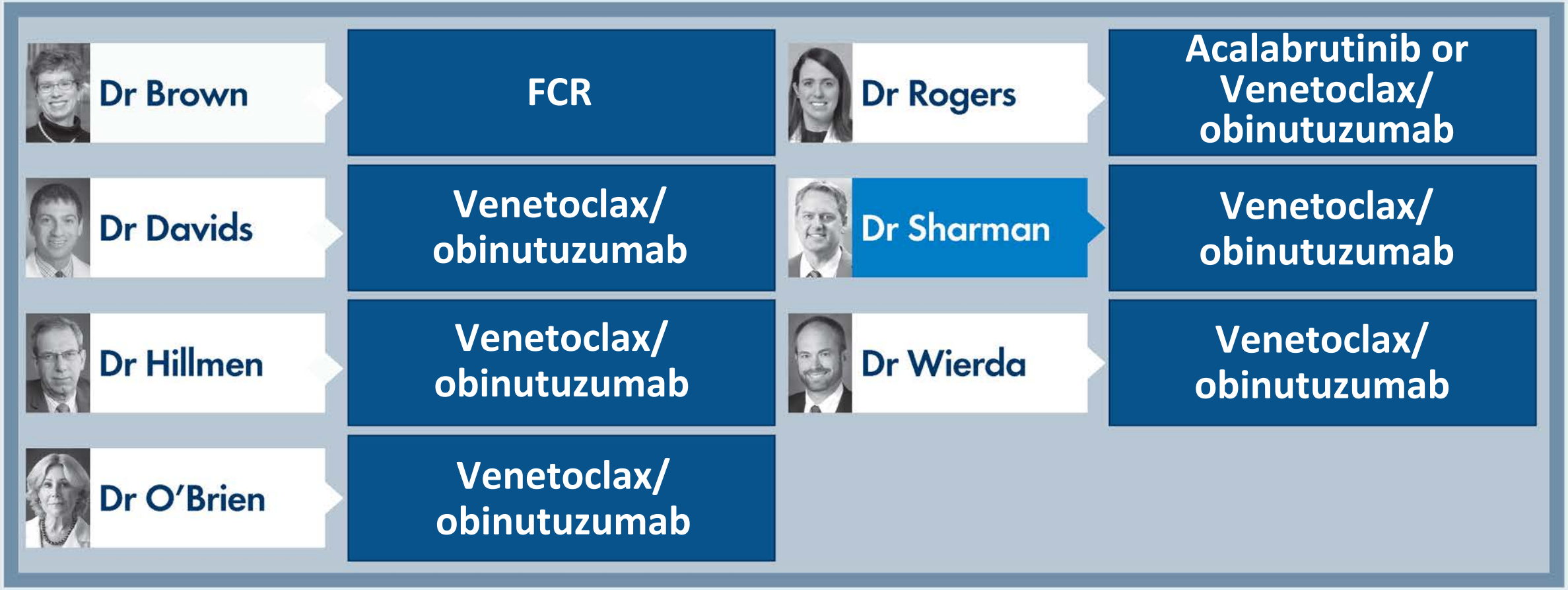
RTP
RESEARCH
TO PRACTICE

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 Davids	Venetoclax + obinutuzumab
 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 with IGHV mutation but no del(17p) or TP53 mutation who requires treatment?



FCR = fludarabine/cyclophosphamide/rituximab

RTP RESEARCH TO PRACTICE

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 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

Meet The Professor with Dr Sharman

Introduction: Journal Club Part 1

MODULE 1: Case Presentations

MODULE 2: Faculty Survey

MODULE 3: Journal Club Part 2

MODULE 4: Appendix of Key Recent Data Sets

RTP
RESEARCH
TO PRACTICE

ARTICLE

Ferrata Storti Foundation

Haematologica 2021
Volume 106(9):2364-2373

Phase II study of acalabrutinib in ibrutinib-intolerant patients with relapsed/refractory chronic lymphocytic leukemia

Kerry A. Rogers,[1] Philip A. Thompson,[2] John N. Allan,[3] Morton Coleman,[3] Jeff P. Sharman,[4] Bruce D. Cheson,[5] Daniel Jones,[1] Raquel Izumi,[6] Melanie M. Frigault,[6] Cheng Quah,[6] Rakesh K. Raman,[6] Priti Patel,[6] Min Hui Wang[6] and Thomas J. Kipps[7]

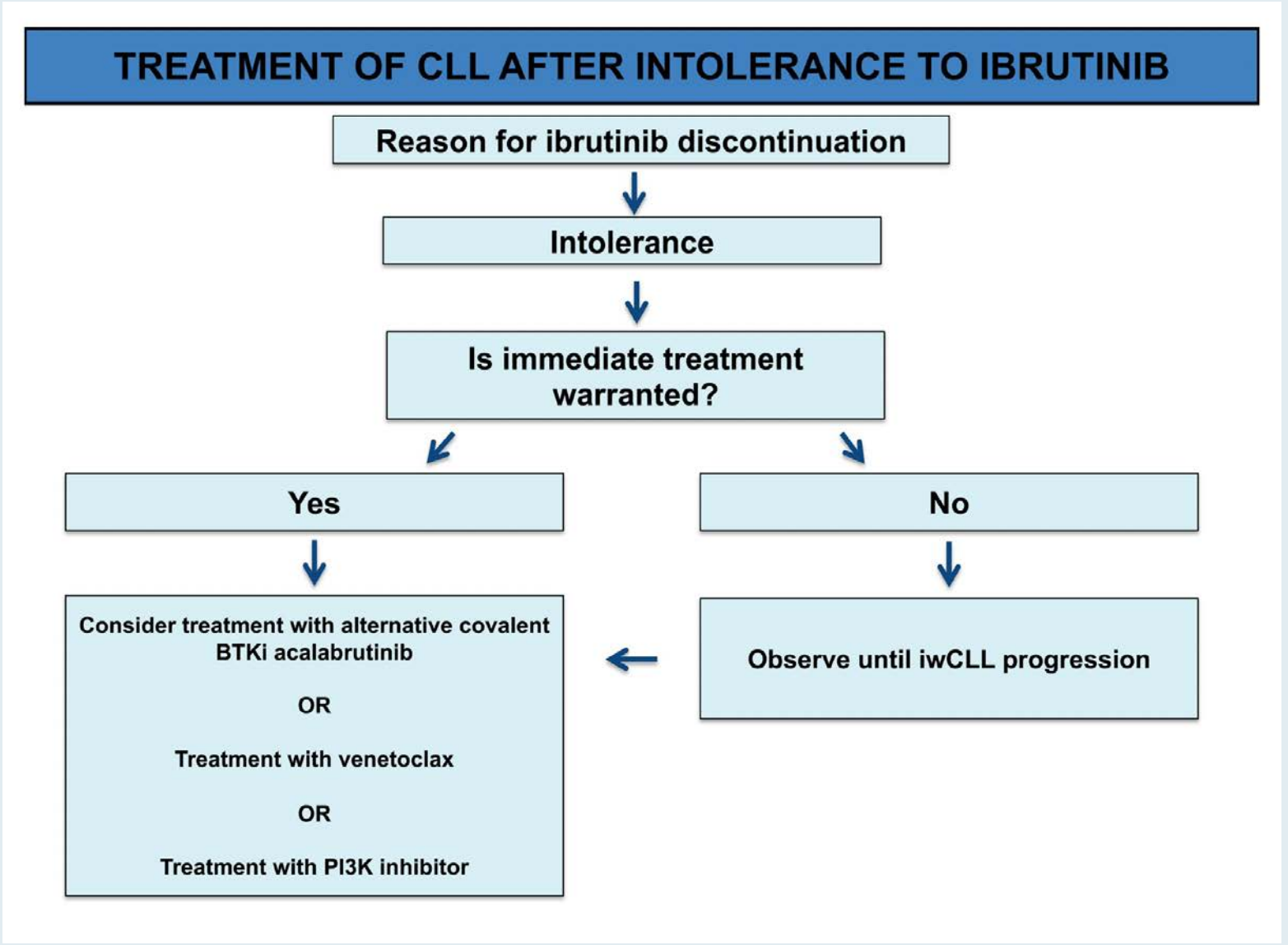
Haematologica 2021;106(9):2300-1.

All in the family: back-to-back kinase inhibitors for the treatment of chronic lymphocytic leukemia

Meghan C. Thompson, Lindsey E. Roeker and Anthony R. Mato

JC JOURNAL CLUB RTP RESEARCH TO PRACTICE

Proposed Sequencing Algorithm for Treatment of CLL After Discontinuation of Ibrutinib Due to Intolerance



Thompson MC et al. *Haematologica* 2021;106(9):2300-1.

ARTICLE

Ferrata Storti Foundation

The impact of early discontinuation/dose modification of venetoclax on outcomes in patients with relapsed/refractory chronic lymphocytic leukemia: *post-hoc* analyses from the phase III MURANO study

Anthony R. Mato,[1] Jeff P. Sharman,[2] Juliana M.L. Biondo,[3] Mei Wu,[3] Yong Mun,[3] Su Y. Kim,[4] Kathryn Humphrey,[5] Michelle Boyer,[5] Qian Zhu[3] and John F. Seymour[6]

Haematologica 2022
Volume 107(1):134-142

JC JOURNAL CLUB
RTP RESEARCH TO PRACTICE

Preliminary Results of the Phase 2 Study of Zanubrutinib in Patients with Previously Treated B-Cell Malignancies Intolerant to Ibrutinib and/or Acalabrutinib

Shadman M et al.

ASCO 2021;Abstract e19506.

JC JOURNAL CLUB
RTP RESEARCH TO PRACTICE

Meet The Professor with Dr Sharman

Introduction

MODULE 1: Case Presentations

MODULE 2: Journal Club with Dr Sharman

MODULE 3: Faculty Survey

MODULE 4: Appendix of Key Recent Data Sets

RTP
RESEARCH
TO PRACTICE

Minimal Residual Disease

RTP
RESEARCH
TO PRACTICE

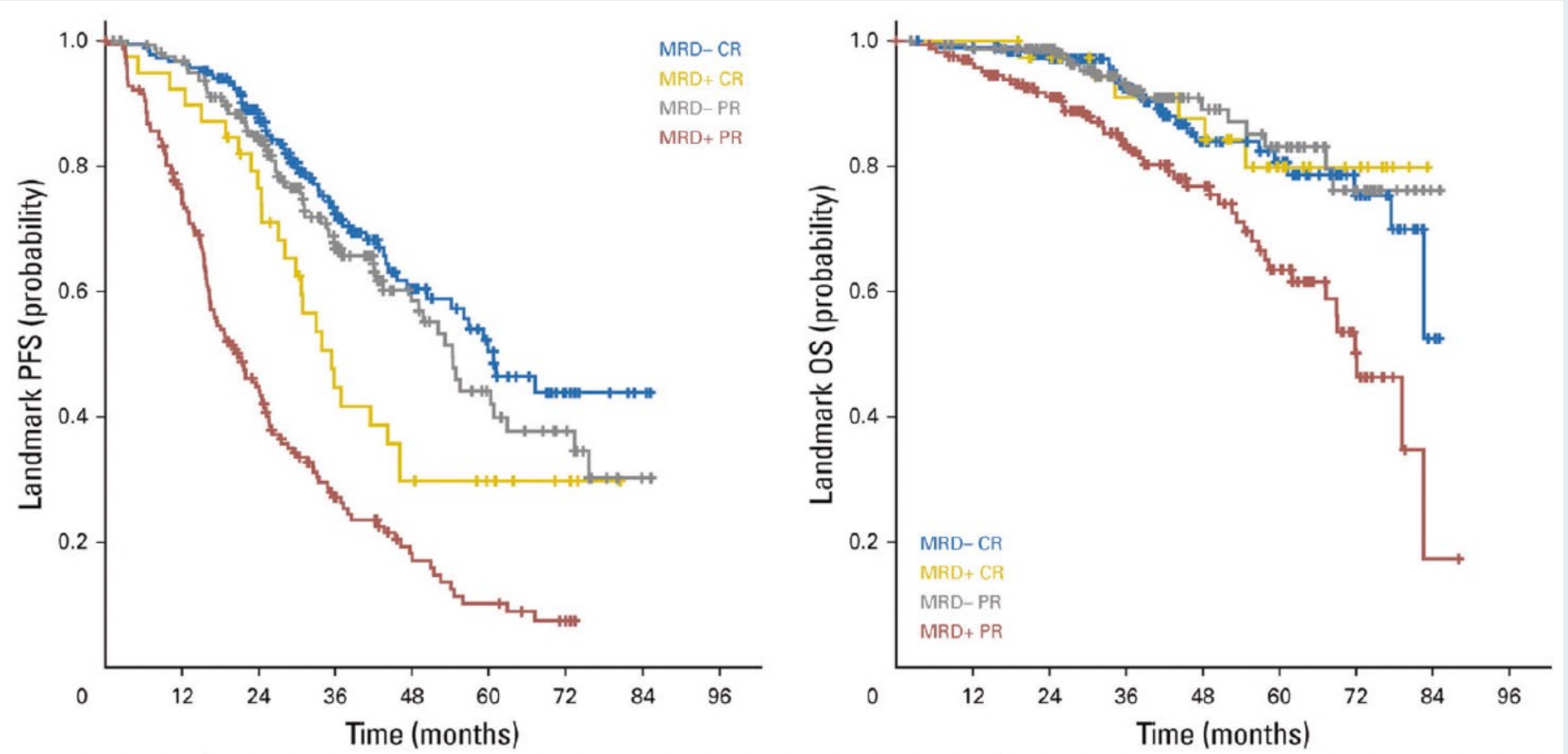
Currently Applied Methods for MRD Assessment

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.

RTP RESEARCH TO PRACTICE

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

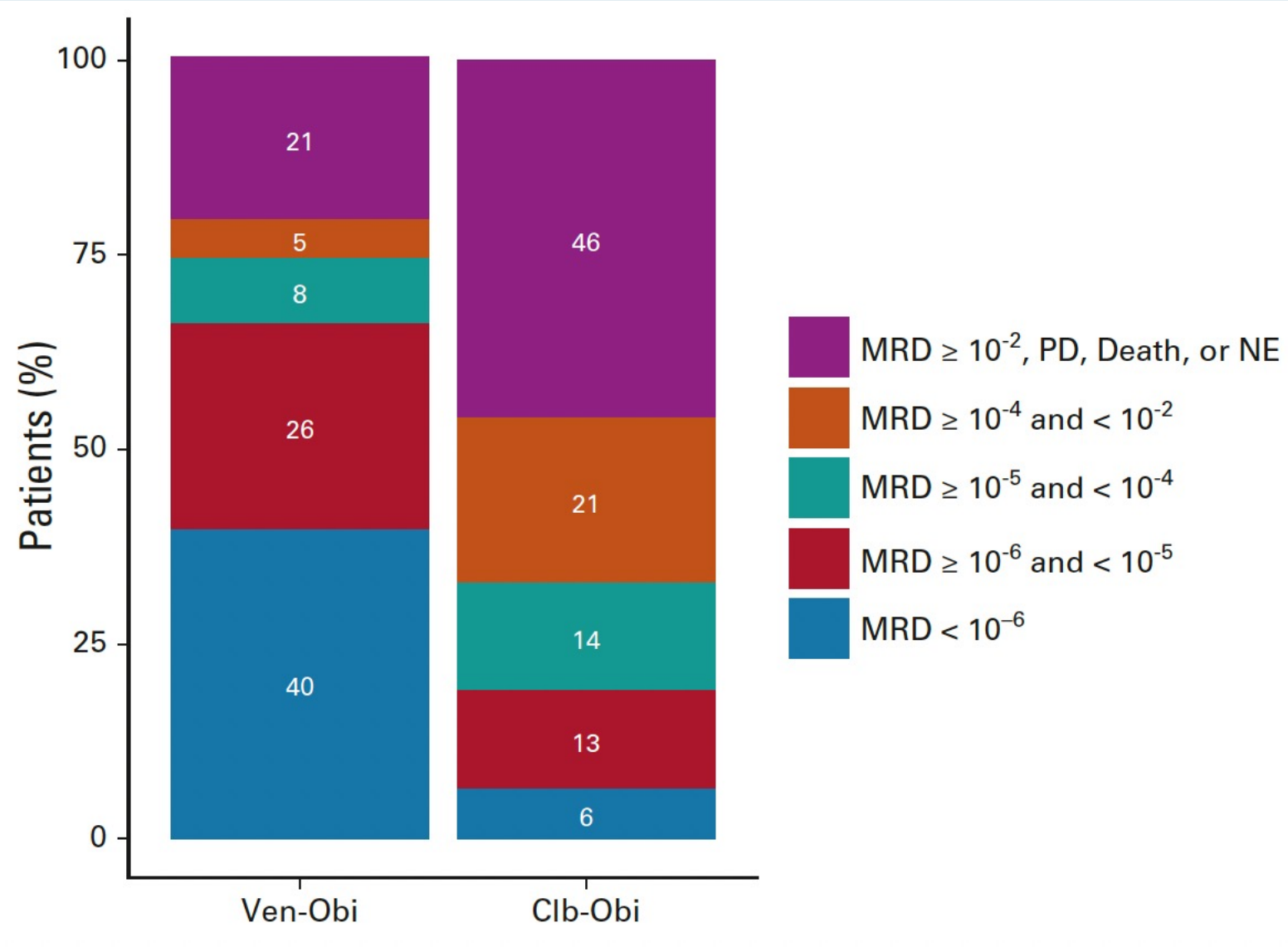
Minimal Residual Disease Dynamics after Venetoclax-Obinutuzumab Treatment: Extended Off-Treatment Follow-up From the Randomized CLL14 Study

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.

RTP RESEARCH TO PRACTICE

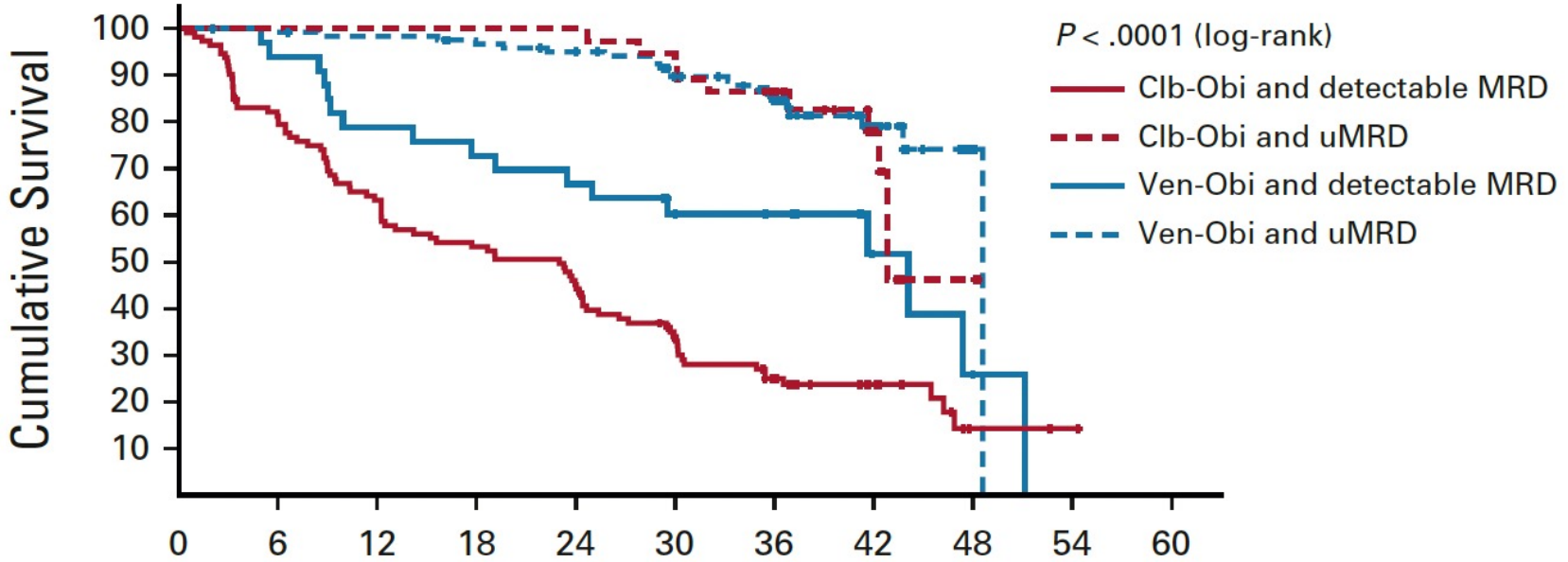
CLL14 Update: Minimum Residual Disease (MRD) Status by Next-Generation Sequencing 2 Months After Completion of Treatment



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

RTP RESEARCH TO PRACTICE

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

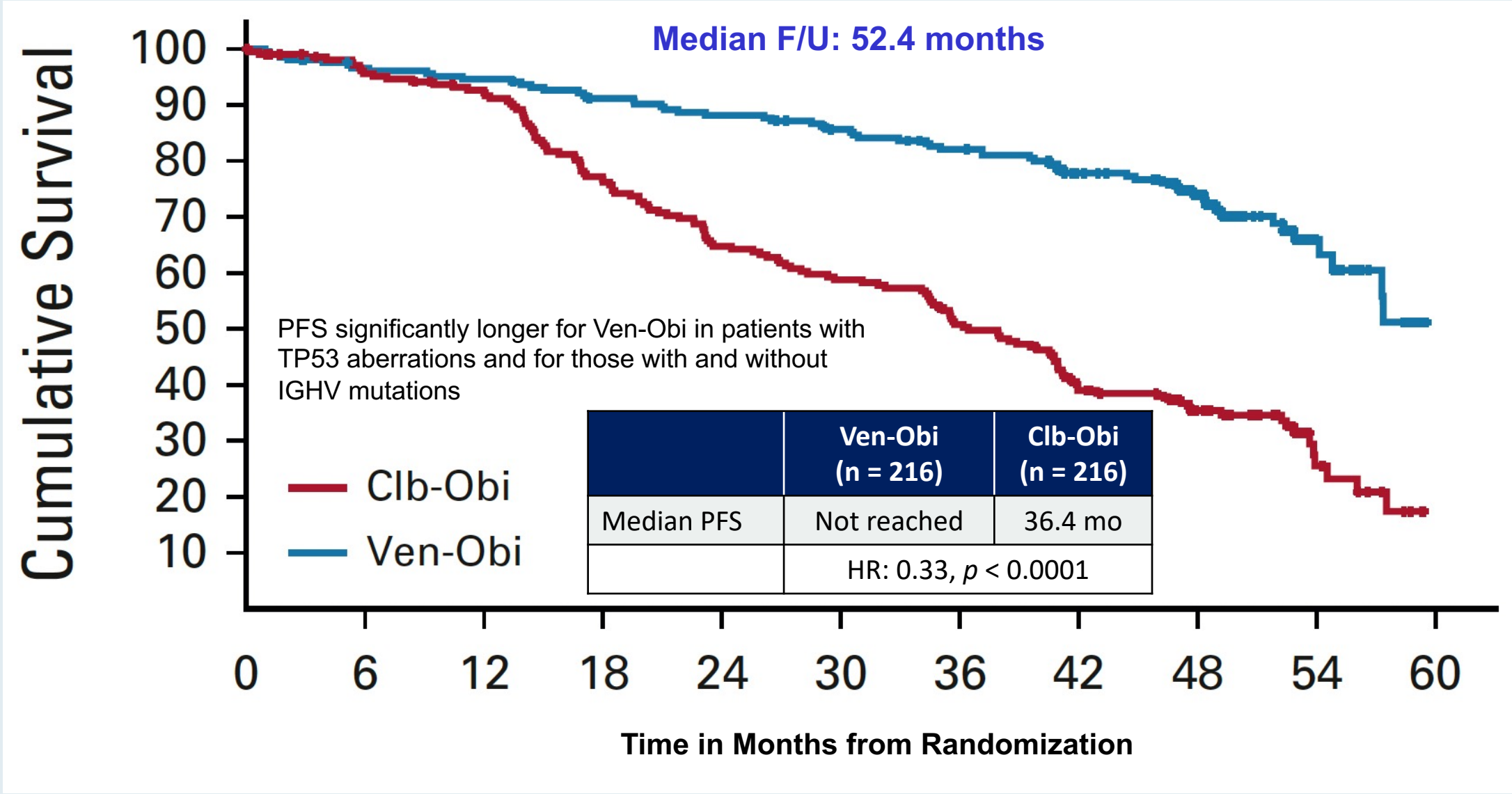
Al-Sawaf O et al. *J Clin Oncol* 2021;39(36):4049-60.

RTP RESEARCH TO PRACTICE

Current Approach to First-Line Treatment

RTP
RESEARCH
TO PRACTICE

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

Venetoclax-Obinutuzumab for Previously Untreated Chronic Lymphocytic Leukemia: 5-Year Results of the Randomized CLL14 Study

Al-Sawaf O et al.

EHA 2022;Abstract S148.

June 12, 2022

RTP
RESEARCH
TO PRACTICE

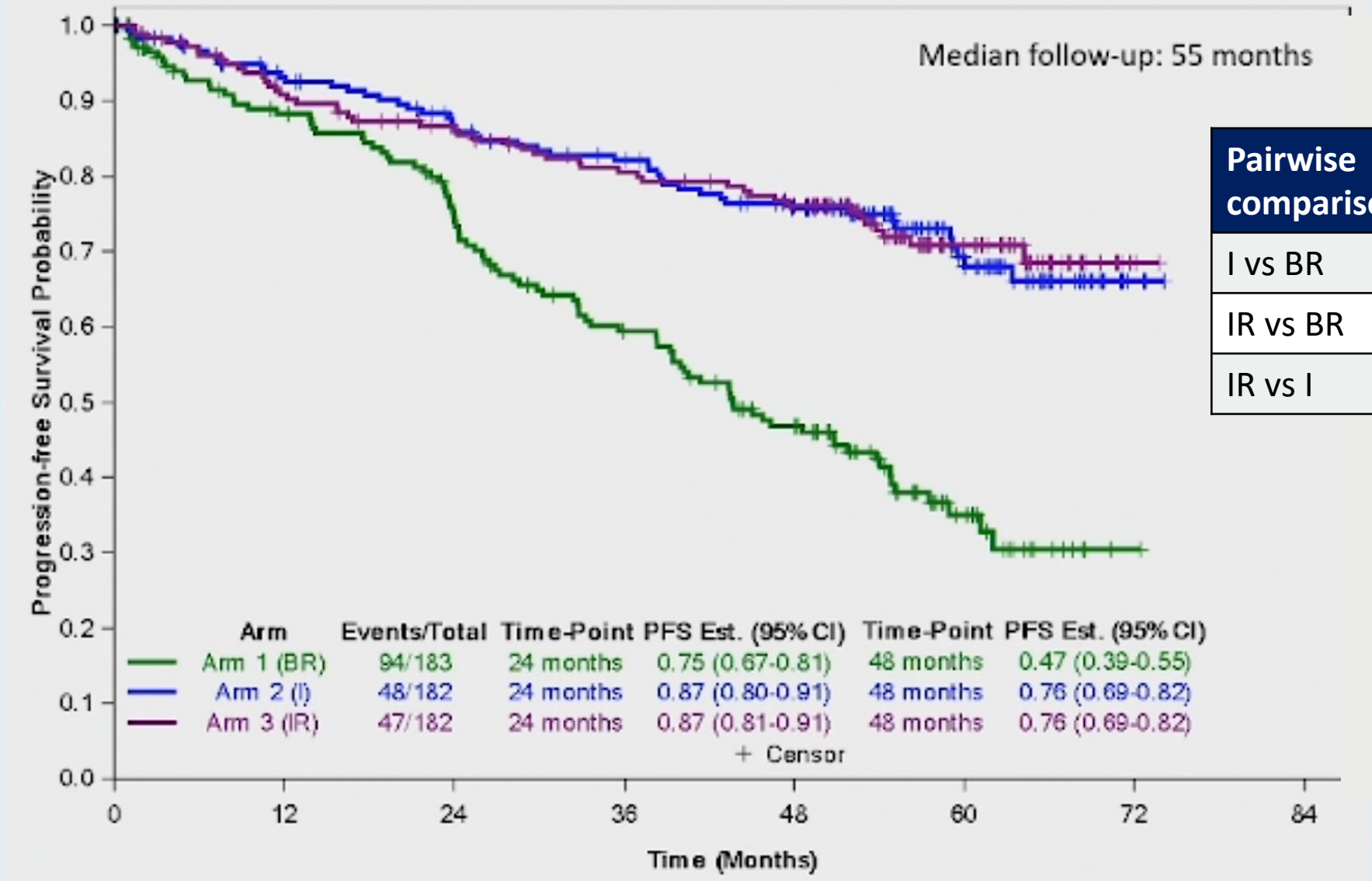
Long term results of A041202 show continued advantage of ibrutinib-based regimens compared with bendamustine plus rituximab chemoimmunotherapy

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

RTP
RESEARCH
TO PRACTICE

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.

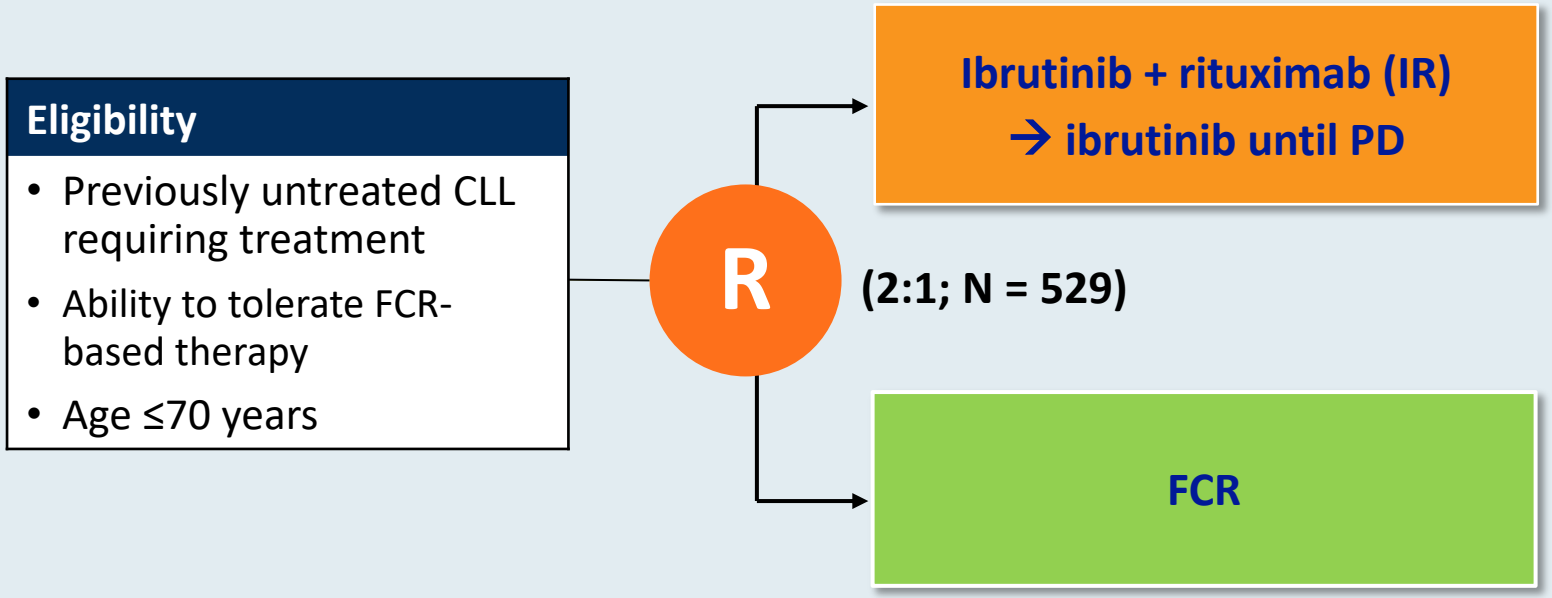
RTP RESEARCH TO PRACTICE

Blood 2022;[Online ahead of print].

Long-term Outcomes for Ibrutinib-Rituximab and Chemoimmunotherapy in CLL: Updated Results of the E1912 Trial

Tait D. Shanafelt, MD[1], Xin Victoria Wang, Ph.D.[2] , Curtis A. Hanson, M.D.[3], Elisabeth M. Paietta, M.D.[4], Susan O'Brien, M.D.[5], Jacqueline Barrientos, M.D.[6], Diane F. Jelinek, Ph.D.[3], Esteban Braggio, Ph.D.[3], Jose F. Leis, M.D., Ph.D.[3], Cong Christine Zhang, M.D.[7], Steven E. Coutre, M.D.[1], Paul M. Barr, M.D.[8], Amanda F. Cashen, M.D.[9], Anthony R. Mato, MSCE[10], Avina K. Singh, M.D.[11], Michael P. Mullane, M.D.[12], Richard F. Little, M.D. [13] , Harry Erba, M.D., Ph.D.[14], Richard M. Stone, M.D.[2], Mark Litzow, M.D.[3], Martin Tallman, M.D.[10], Neil E. Kay, M.D.[3]

Phase III ECOG-ACRIN E1912 Study Design

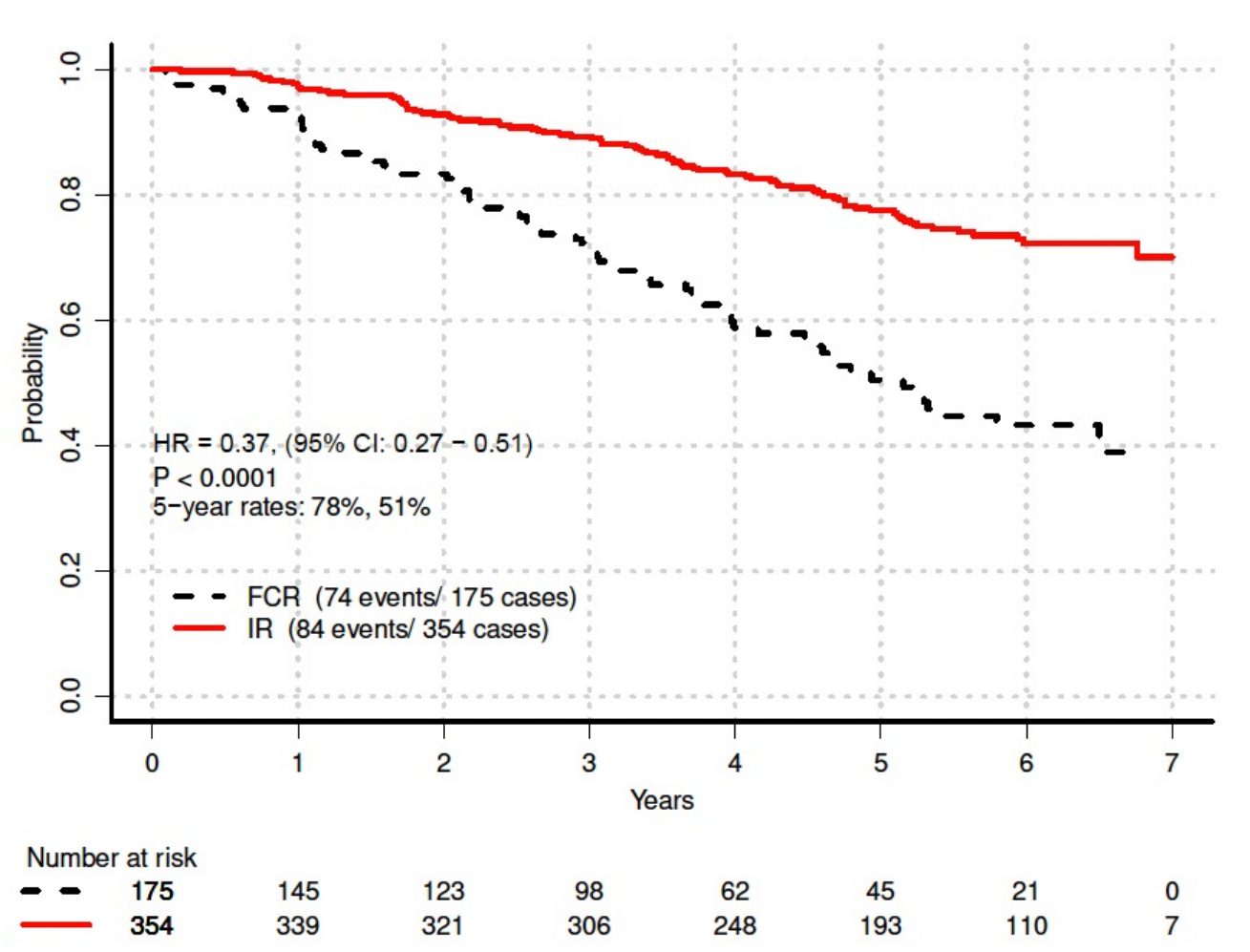


Primary endpoint: PFS
Secondary endpoints: OS, ORR, Toxicity and Tolerability

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

RTP RESEARCH TO PRACTICE

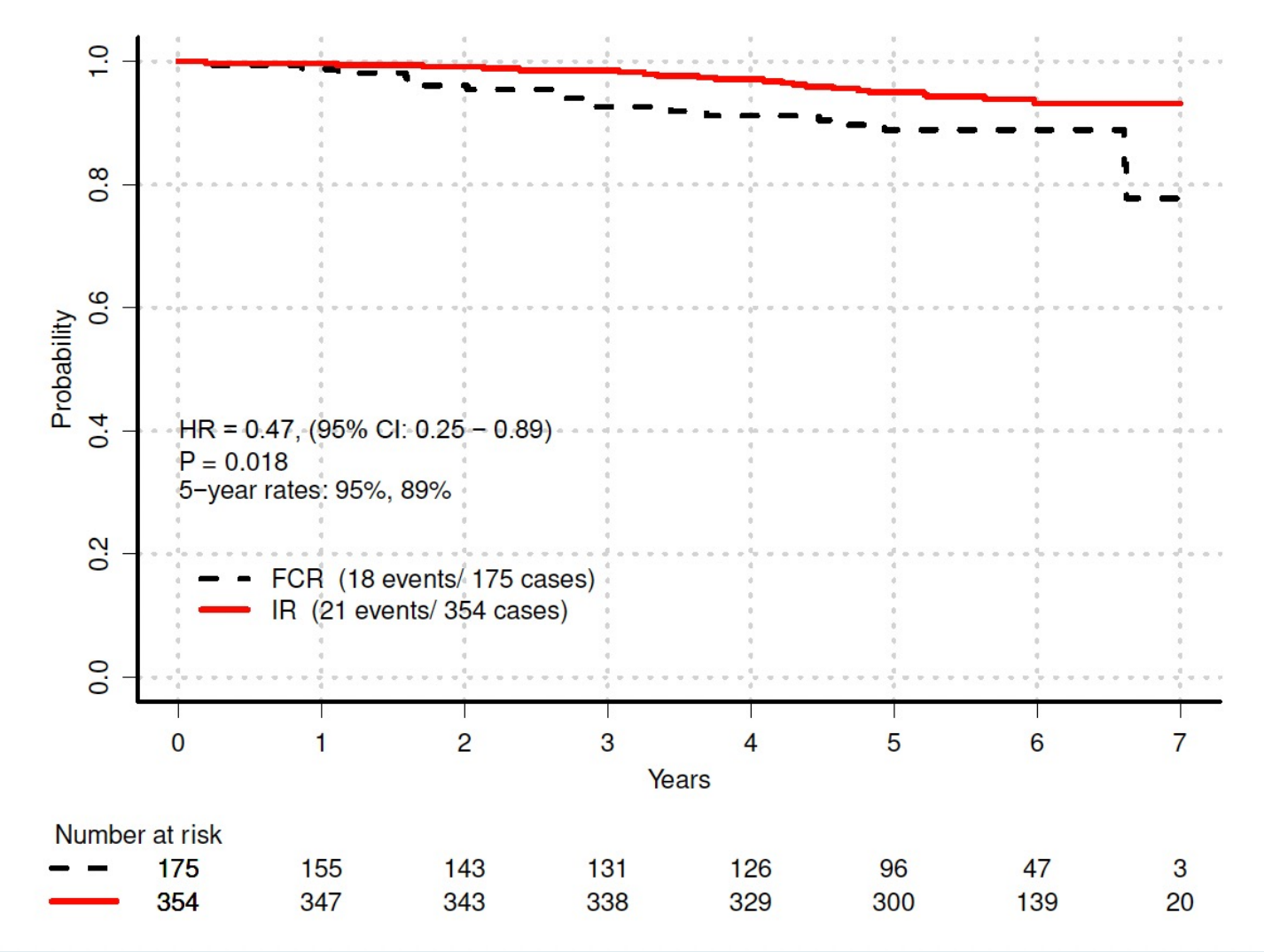
ECOG-ACRIN E1912 Extended Follow-Up: Progression-Free Survival (All Patients)



Shanafelt TD et al. *Blood* 2022;[Online ahead of print].

RTP RESEARCH TO PRACTICE

ECOG-ACRIN E1912 Extended Follow-Up: Overall Survival



Shanafelt TD et al. *Blood* 2022;[Online ahead of print].

RTP RESEARCH TO PRACTICE

The Combination of Ibrutinib plus Venetoclax Results in a High Rate of MRD Negativity in Previously Untreated CLL: The Results of the Planned Interim Analysis of the Phase III NCRI Flair Trial

Hillmen P et al.
EHA 2022;Abstract S145.

June 12, 2022

RTP
RESEARCH
TO PRACTICE

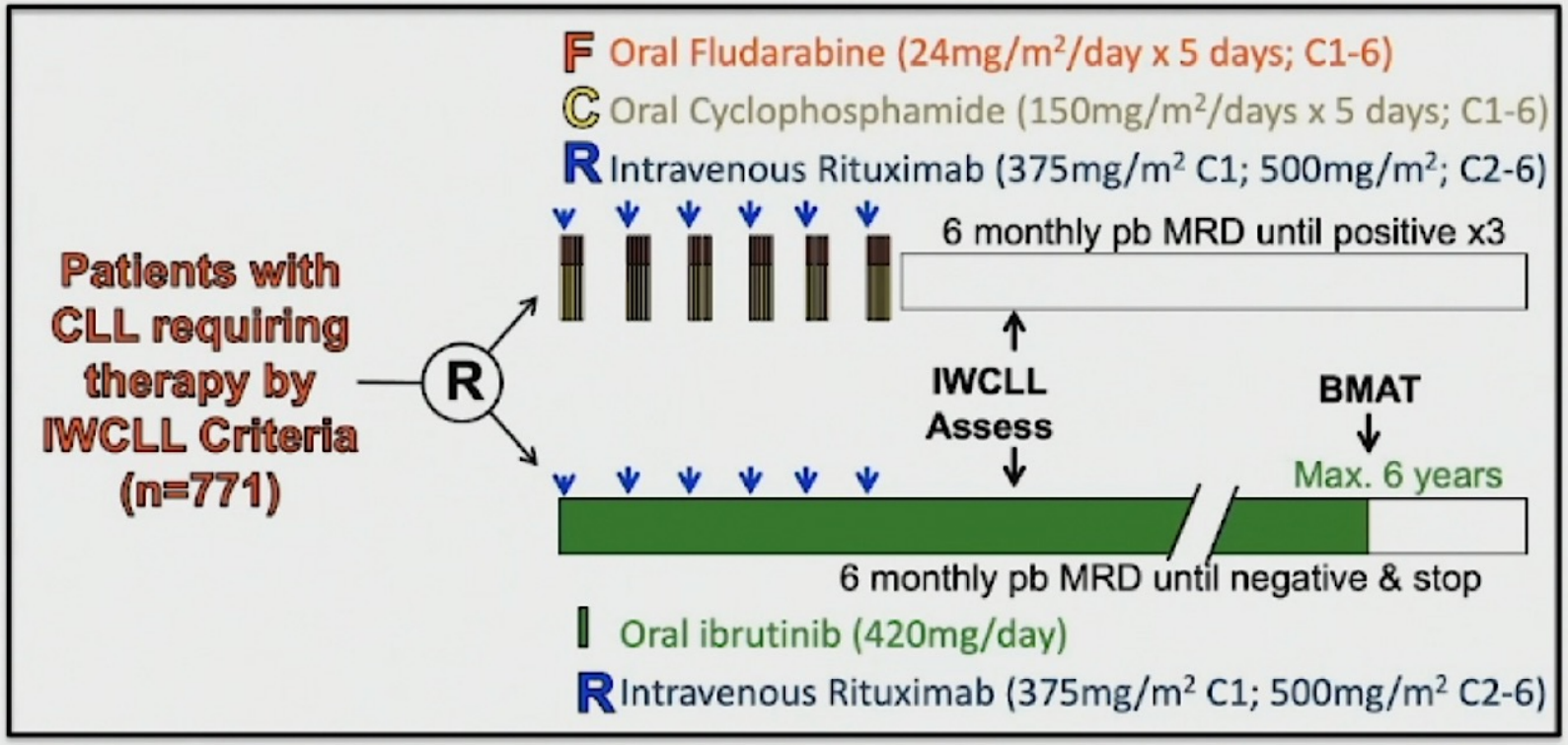
Ibrutinib plus Rituximab Is Superior to FCR in Previously Untreated CLL: Results of the Phase III NCRI FLAIR Trial

Hillmen P et al.

ASH 2021;Abstract 642.

RTP
RESEARCH
TO PRACTICE

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:

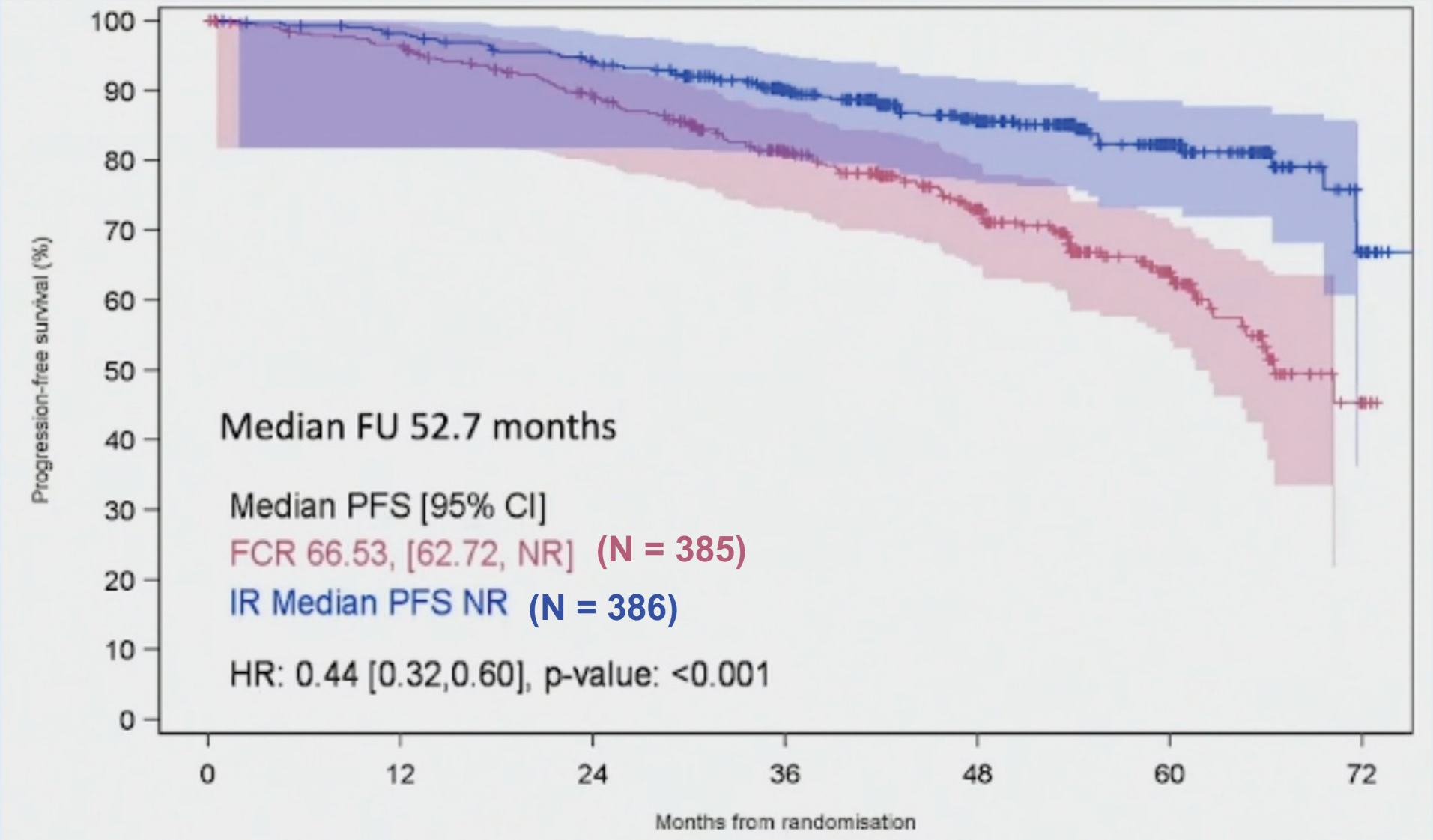
- Previously untreated CLL requiring therapy by IWCLL criteria
- Considered fit for FCR
- ≤75 years old

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

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

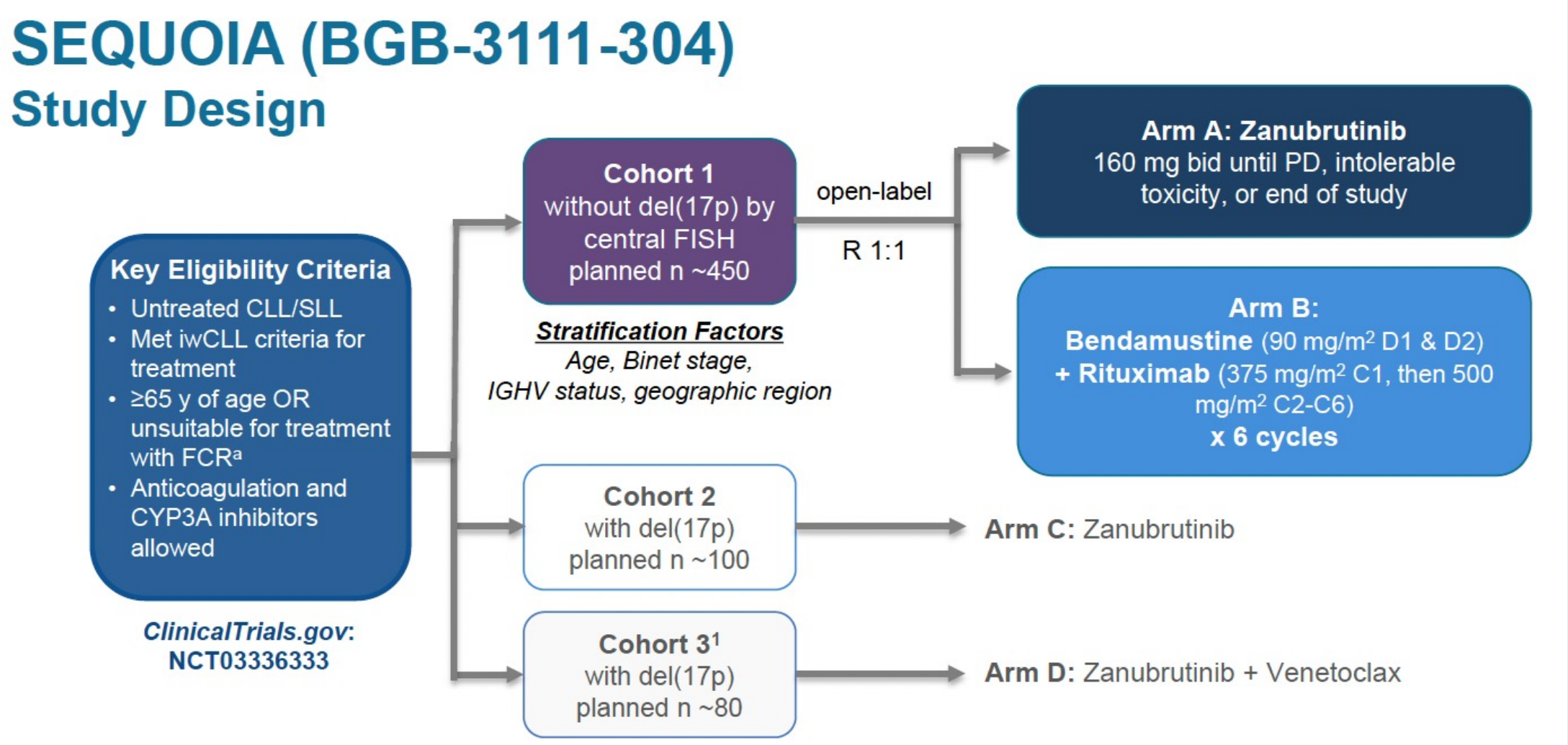
Constantine S. Tam, MBBS, MD[1,2,3,4]; Krzysztof Giannopoulos, MD, PhD[5,6]; Wojciech Jurczak, MD, PhD[7]; Martin Šimkovič, MD, PhD[8,9]; Mazyar Shadman, MD, MPH[10,11]; Anders Österborg, MD, PhD[12,13]; Luca Laurenti, MD[14]; Patricia Walker, MBBS, BMedSci, FRACP, FRCPA[15]; Stephen Opat, MBBS (Hons), 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

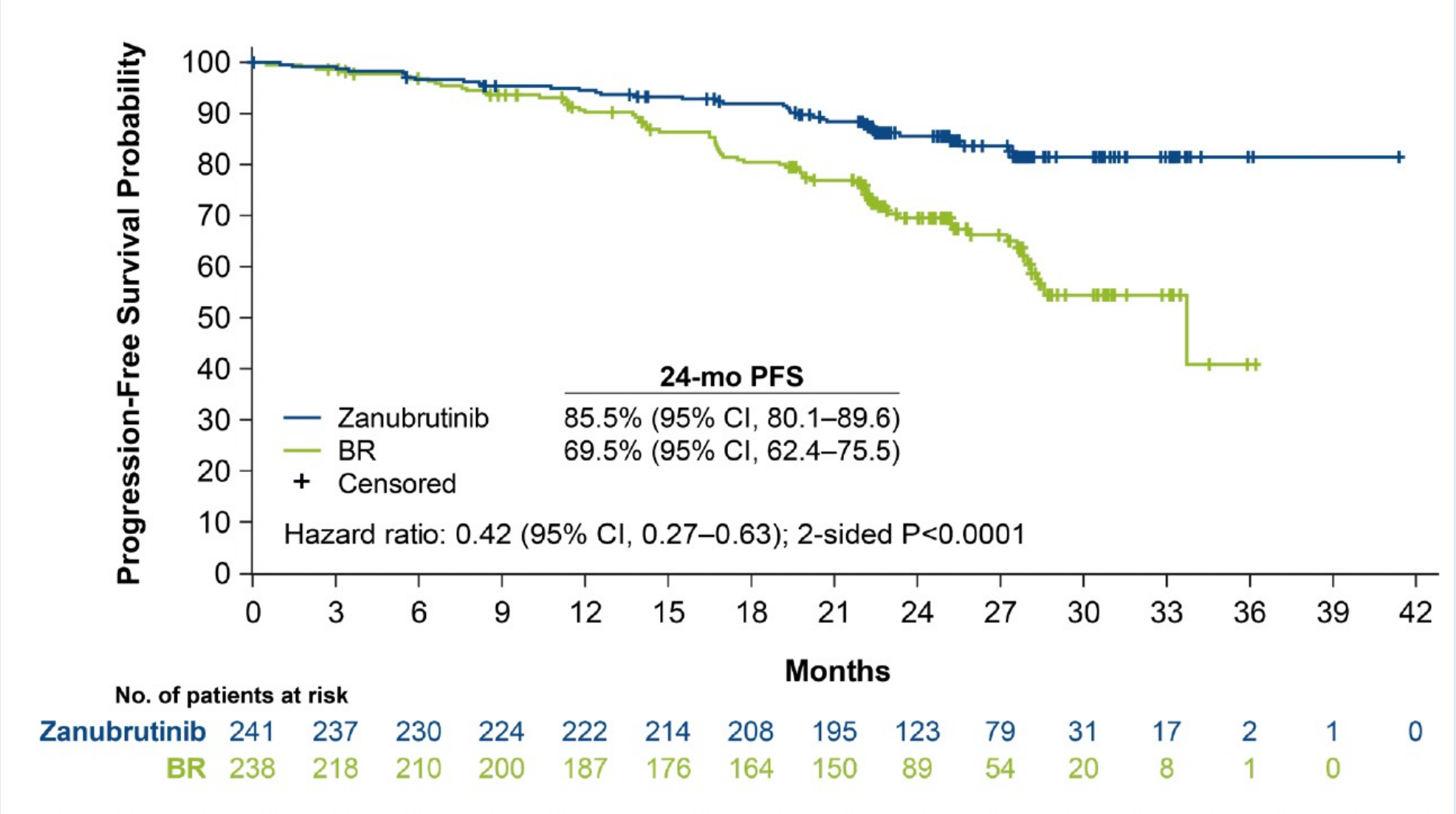
RTP RESEARCH TO PRACTICE

SEQUOIA Phase III Study Design



Tam CS et al. ASH 2021;Abstract 396.

SEQUOIA: Progression-Free Survival by IRC

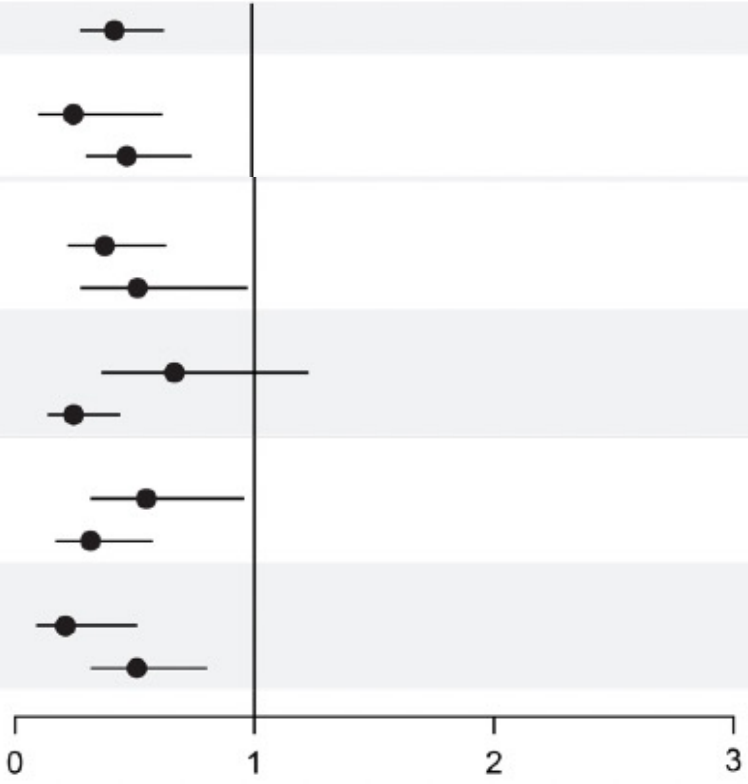


Tam CS et al. ASH 2021;Abstract 396.

RTP RESEARCH TO PRACTICE

SEQUOIA: Progression-Free Survival by Subgroups

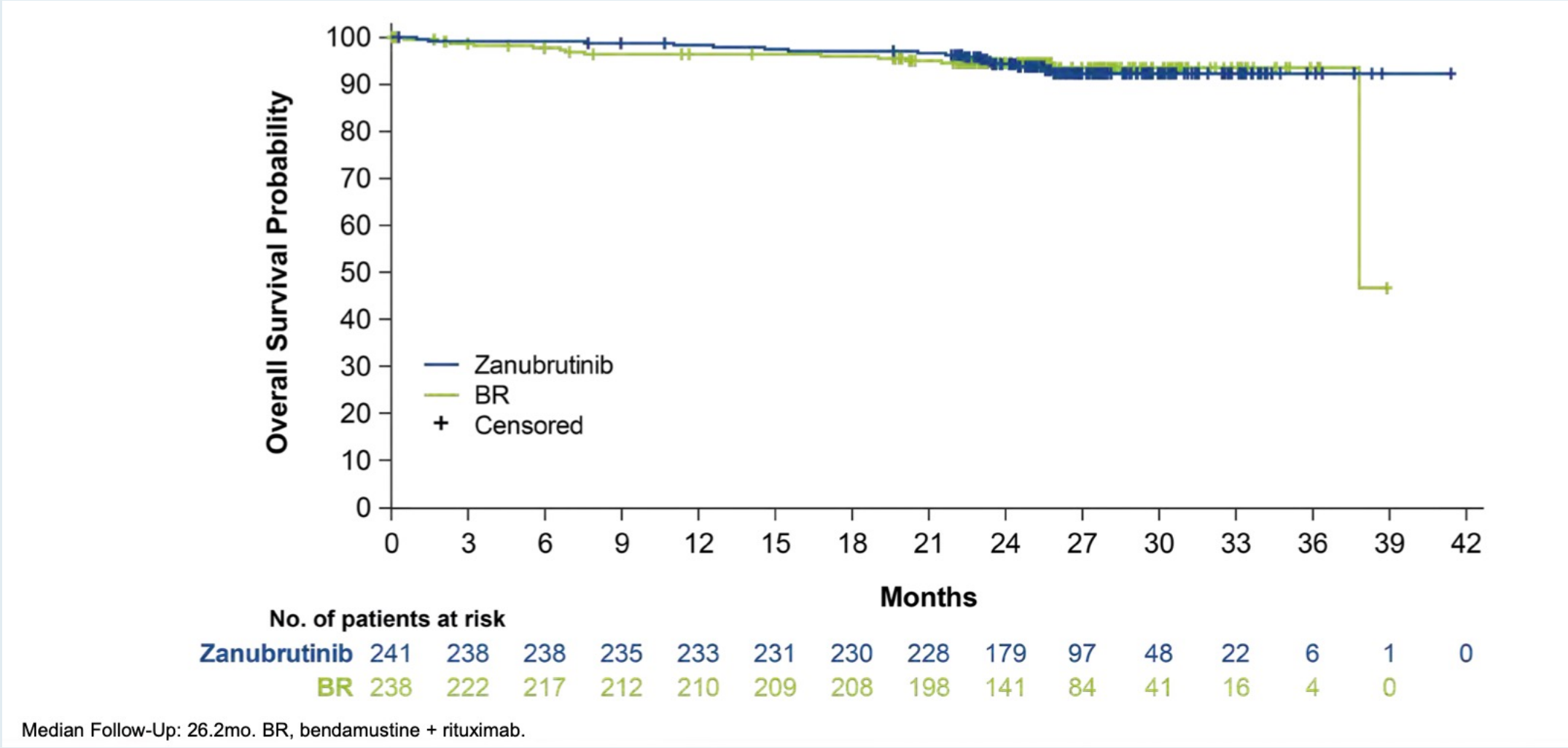
Subgroup	Event/Patient Zanubrutinib	Event/Patient BR	Hazard Ratio (95% CI), %[a]
All Patients	36/241	71/238	0.42 (0.28–0.63)
Age (years)			
<65	6/45	19/46	0.25 (0.10–0.62)
≥65	30/196	52/192	0.47 (0.30–0.74)
Bulky disease (LDi <5 cm vs ≥5 cm)			
<5 cm	21/172	44/165	0.37 (0.22–0.63)
≥5 cm	15/69	27/73	0.52 (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.

RTP RESEARCH TO PRACTICE

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.

RTP RESEARCH TO PRACTICE

Venetoclax Combination Regimens

RTP
RESEARCH
TO PRACTICE

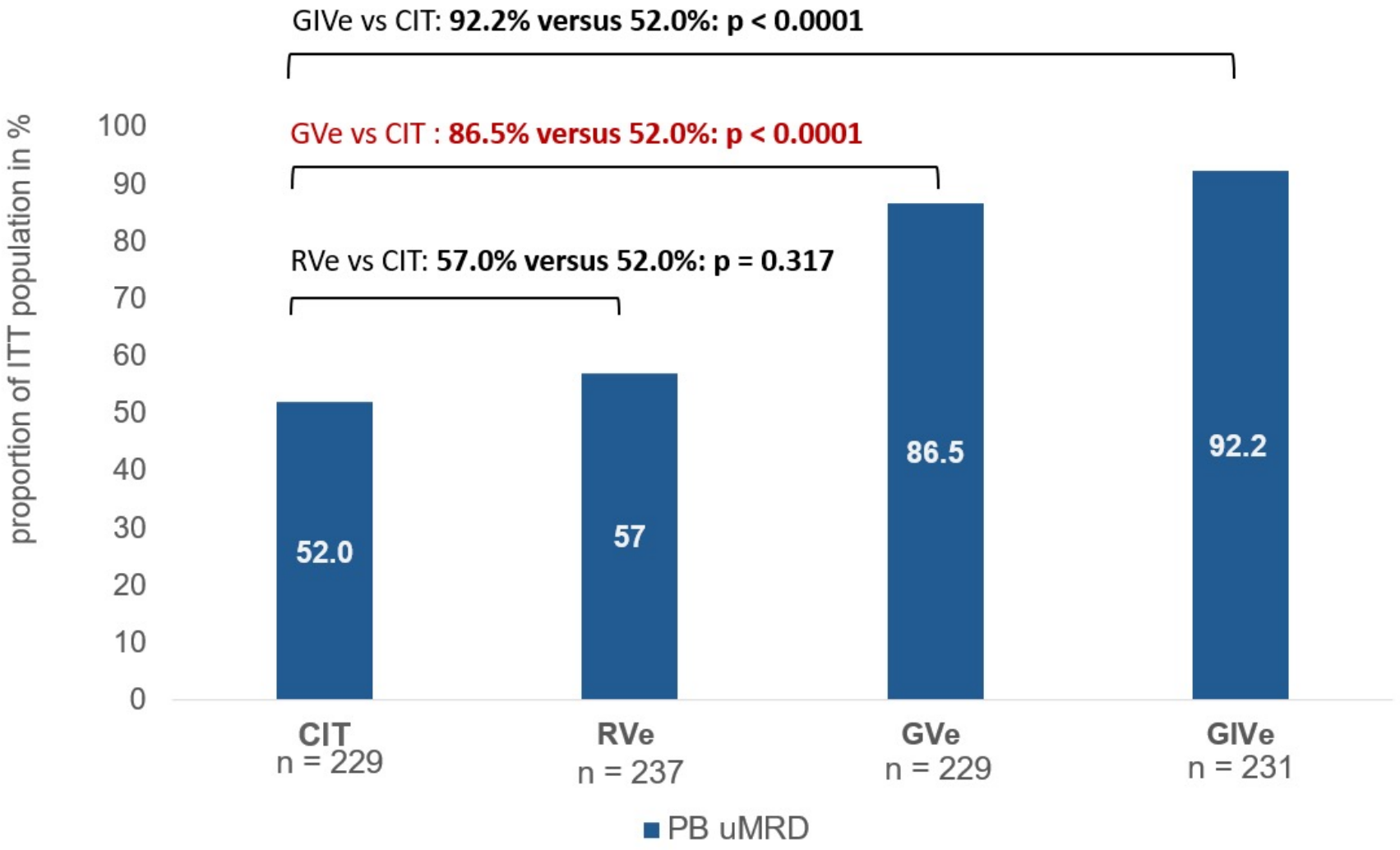
A Randomized Phase III Study of Venetoclax-Based Time-Limited Combination Treatments (RVe, GVe, GIVe) vs Standard Chemoimmunotherapy (CIT: FCR/BR) in Frontline Chronic Lymphocytic Leukemia (CLL) of Fit Patients: First Co-Primary Endpoint Analysis of the International Intergroup GAIA (CLL13) Trial

Eichhorst B et al.

ASH 2021;Abstract 71.

RTP
RESEARCH
TO PRACTICE

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.

ASCO 2022;Abstract 7519.

Fixed-duration (FD) ibrutinib + venetoclax for first-line treatment of chronic lymphocytic leukemia/small lymphocytic lymphoma: 3-year follow-up from the FD cohort of the phase 2 CAPTIVATE study

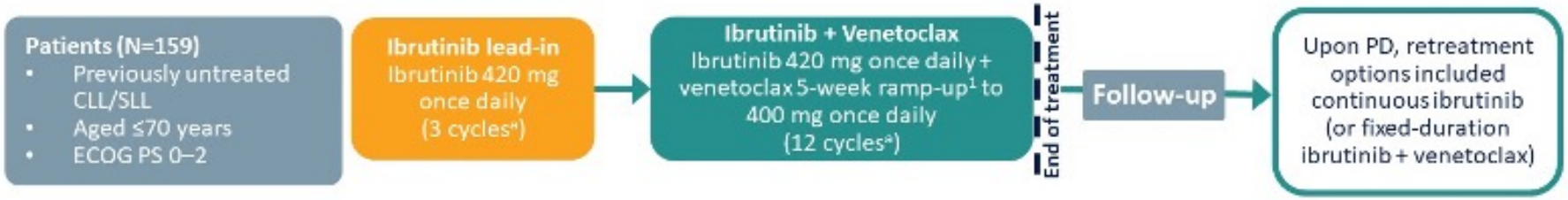
William G. Wierda, MD, PhD[1]; Paul M. Barr, MD[2]; Tanya Siddiqi, MD[3]; John N. Allan, MD[4]; Thomas J. Kipps, MD, PhD[5]; Livio Trentin, MD[6]; Ryan Jacobs, MD[7]; Sharon Jackson, MD[8]; Alessandra Tedeschi, MD[9]; Stephen Opat, FRACP, FRCPA, MBBS[10]; Rajat Bannerji, MD, PhD[11]; Bryone J. Kuss, MBBS, PhD, FRACP, FRCPA[12]; Carol Moreno, MD, PhD[13]; Lisa J. Croner[14, 15]; Edith Szafer-Glusman, PhD[14,15]; Cathy Zhou, MS[15]; Anita Szoke, MD[15]; James P. Dean, MD, PhD[15]; Paolo Ghia, MD, PhD[16]; Constantine S. Tam, MBBS, MD[17]

[1]Department of Leukemia, University of Texas MD Anderson Cancer Center, Houston, TX, USA; [2]Wilmot Cancer Institute, University of Rochester Medical Center, Rochester, NY, USA; [3]City of Hope National Medical Center, Duarte, CA, USA; [4]Weill Cornell Medicine, New York, NY, USA; [5]UCSD Moores Cancer Center, La Jolla, CA, USA; [6]University of Padova, Padova, Italy; [7]Levine Cancer Institute, Charlotte, NC, USA; [8]Middlemore Hospital, Auckland, New Zealand; [9]ASST Grande Ospedale Metropolitano Niguarda, Milan, Italy; [10]Monash University, Clayton, VIC, Australia; [11]Rutgers Cancer Institute of New Jersey, New Brunswick, NJ, USA; [12]Flinders University and Medical Center, Bedford Park, SA, Australia; [13]Hospital de la Santa Creu i Sant Pau, Autonomous University of Barcelona, Barcelona, Spain; [14]AbbVie Company, North Chicago, IL, USA; [15]Pharmacyclics LLC, an AbbVie Company, South San Francisco, CA, USA; [16]Università Vita-Salute San Raffaele and IRCCS Ospedale San Raffaele, Milan, Italy; [17]Peter MacCallum Cancer Center & St. Vincent's Hospital and the University of Melbourne, Melbourne, VIC, Australia

RTP RESEARCH TO PRACTICE

CAPTIVATE FD Cohort Study Design

- 3-year follow up data from the FD cohort of CAPTIVATE are presented. CAPTIVATE is an international, multicenter phase 2 study evaluating first-line treatment with 3 cycles of ibrutinib followed by 12 cycles of combined ibrutinib + venetoclax



- **Median time on study: 38.7 months (range, 0.8–41.4)**
  - 92% completed planned 12 cycles of combined ibrutinib + venetoclax[2]
  - Median treatment duration: 13.8 months (range, 0.5–24.9), equivalent to fifteen 28-day cycles[2]
- **Median of 25 months follow-up after completion of FD therapy**
- Baseline characteristics have been previously published[2]

Key Characteristics[2]	All treated patients N=159
Median age, years (range)	60 (33–71)
High-risk features, n (%)	
Unmutated IGHV	89 (56)
del(17p)/*TP53* mutation	27 (17)
del(17p)	20 (13)
del(11q)[b]	28 (18)
Complex karyotype[c]	31 (19)
Lymph node diameter ≥5 cm, n (%)	48 (30)
Median ALC × 10^9/L (range)	70 (1–503)
ALC ≥25 × 10^9/L, n (%)	120 (75)

ALC, absolute lymphocyte count; ECOG PS, Eastern Cooperative Oncology Group performance status; FD, fixed-duration; PD, progressive disease; SLL, small lymphocytic lymphoma.
[a]1 cycle = 28 days; [b]Without del(17p) per Dohner hierarchy; [c]Defined as ≥3 abnormalities by conventional CpG-stimulated cytogenetics.
1. VENCLEXTA (venetoclax tablets) for oral use [package insert]. South San Francisco, CA: Genentech USA Inc; 2021. 2. Tam CS et al. Blood. 2022; doi: 10.1182/blood.2021014488.

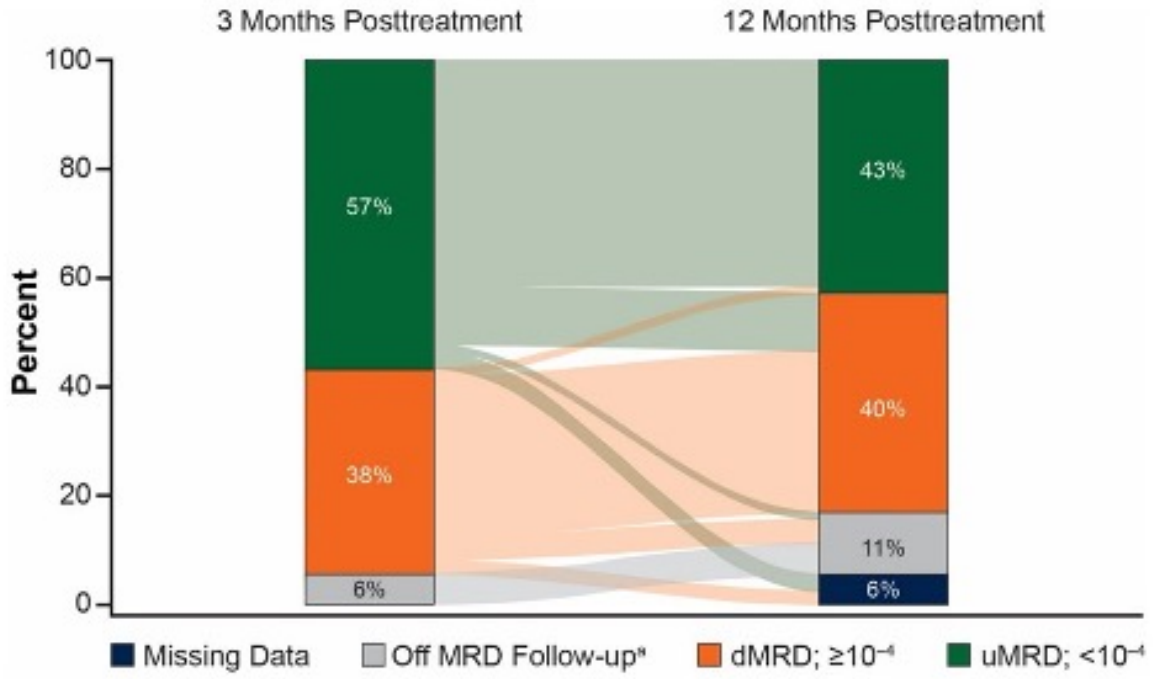
Wierda WG et al. ASCO 2022;Abstract 7519.

RTP RESEARCH TO PRACTICE

CAPTIVATE: Rates of Complete Response (CR) and Undetectable Minimal Residual Disease (uMRD)

- The CR rate in all treated patients increased from 55% (95% CI, 48–63) at primary analysis to 57% (95% CI, 50–65) with an additional year of follow-up off treatment
- 79% of patients (125/159) had a best response of uMRD in PB and/or BM

- Of patients with uMRD in PB at 3 months posttreatment, 78% (66/85) of evaluable patients maintained uMRD through 12 months posttreatment

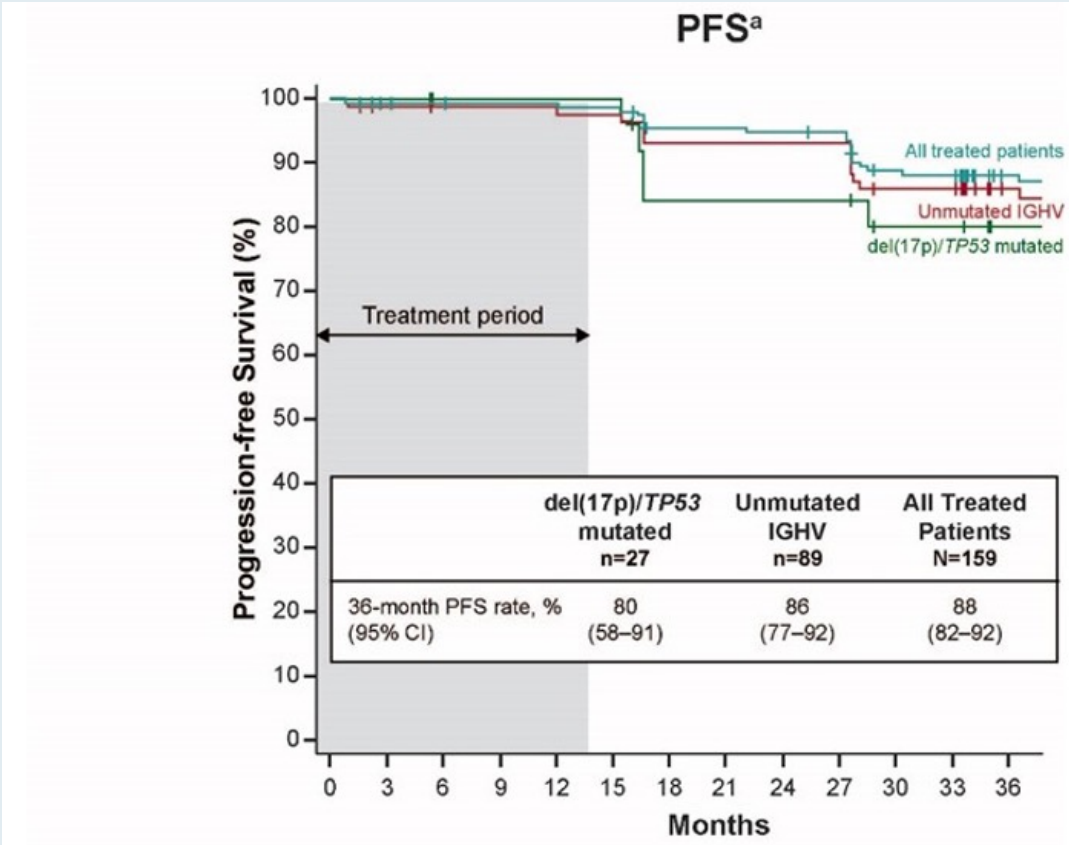


CI = confidence interval; PB = peripheral blood; BM = bone marrow

Wierda WG et al. ASCO 2022;Abstract 7519.

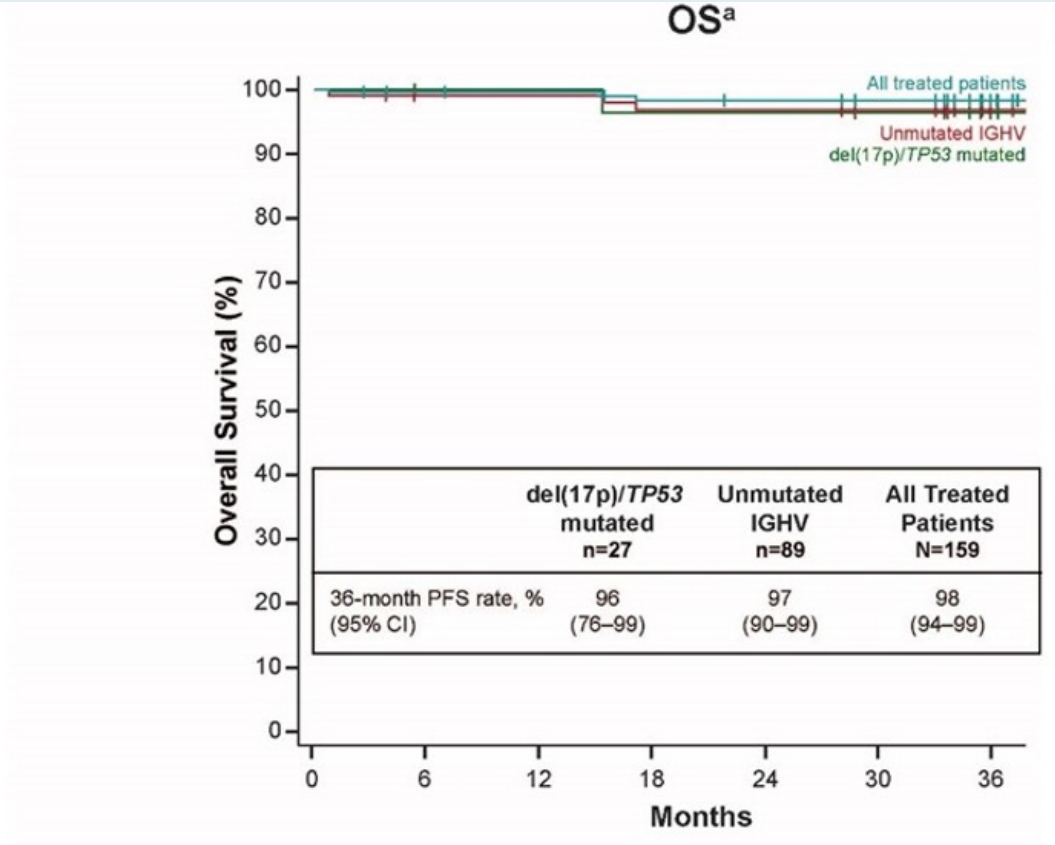
RTP RESEARCH TO PRACTICE

CAPTIVATE: Progression-Free and Overall Survival



	del(17p)/*TP53* mutated n=27	Unmutated IGHV n=89	All Treated Patients N=159
36-month PFS rate, % (95% CI)	80 (58–91)	86 (77–92)	88 (82–92)

Patients at Risk													
All treated patients	159	155	153	152	152	151	144	144	143	142	131	130	117
Unmutated IGHV	89	86	85	85	85	84	79	79	79	79	72	72	63
del(17p)/*TP53* mutated	27	27	26	26	26	26	21	21	21	21	18	18	15



	del(17p)/*TP53* mutated n=27	Unmutated IGHV n=89	All Treated Patients N=159
36-month PFS rate, % (95% CI)	96 (76–99)	97 (90–99)	98 (94–99)

Patients at Risk							
All treated patients	159	155	154	151	150	148	139
Unmutated IGHV	89	86	86	84	84	82	75
del(17p)/*TP53* mutated	27	26	26	25	25	24	20

[a]Due to rapid enrollment in the study, the number of patients at risk drops substantially between 36 and 39 months. The Kaplan-Meier curves have therefore been truncated at 38 months due to instability of the curves.

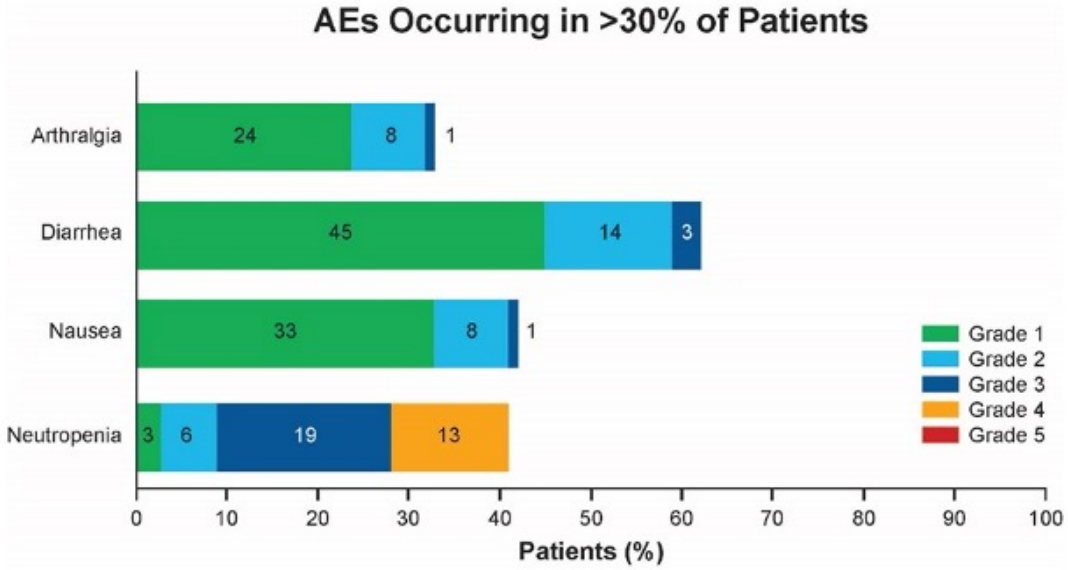
Wierda WG et al. ASCO 2022;Abstract 7519.

RTP RESEARCH TO PRACTICE

CAPTIVATE: Responses with Ibrutinib Re-treatment and Adverse Event (AE) Summary

- **Retreatment: 12 patients who progressed after FD treatment with ibrutinib + venetoclax have been retreated with single-agent ibrutinib, with duration of retreatment ranging from 6–32 months**
  - 11/12 patients were evaluable for response, with 9 achieving PR, 1 PR-L and 1 achieving SD

- **Most frequently occurring AEs (>30% of patients) were grade 1-2, occurred within 4 months of treatment initiation, and resolved**



AE (occurring in >30% of patients)	Median time to first onset (range), days	Median time from onset to resolution or improvement (range), days	Resolution rate (%)
Arthralgia	30 (1-449)	42.5 (1-1187)	87
Diarrhea	102 (1-475)	16.5 (1-587)	95
Nausea	100 (1-412)	40.5 (1-676)	96
Neutropenia	127 (21-338)	17 (1-757)	100

FD = fixed duration; PR = partial response; PR-L = PR with lymphocytosis; SD = stable disease

Wierda WG et al. ASCO 2022;Abstract 7519.

RTP RESEARCH TO PRACTICE

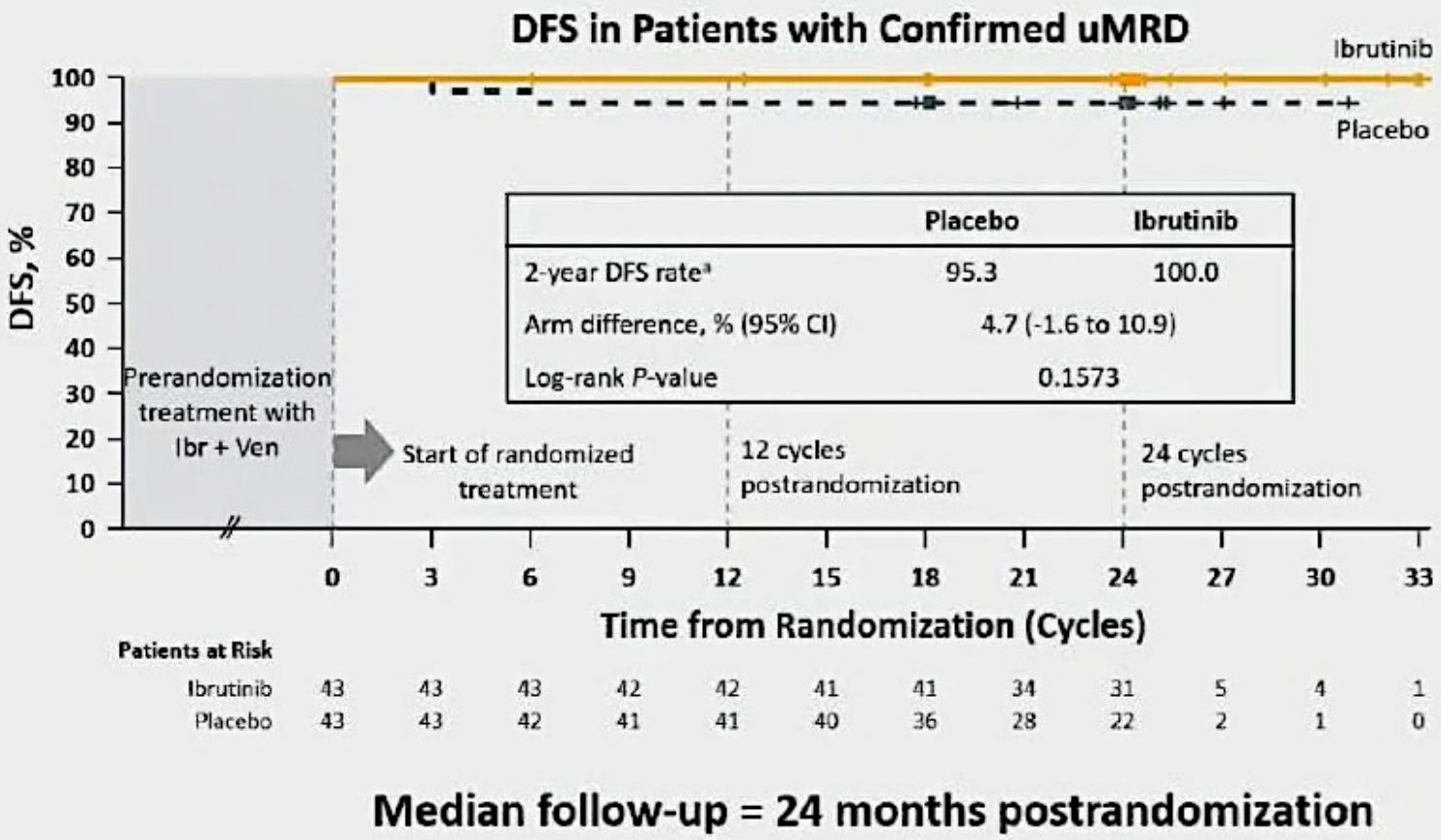
First-Line Treatment with Ibrutinib (Ibr) plus Venetoclax (Ven) for Chronic Lymphocytic Leukemia (CLL): 2-Year Post-Randomization Disease-Free Survival (DFS) Results from the Minimal Residual Disease (MRD) Cohort of the Phase 2 Captivate Study

Ghia P et al.

ASH 2021;Abstract 68.

RTP
RESEARCH
TO PRACTICE

CAPTIVATE MRD Cohort: DFS Events in Patients with Confirmed uMRD

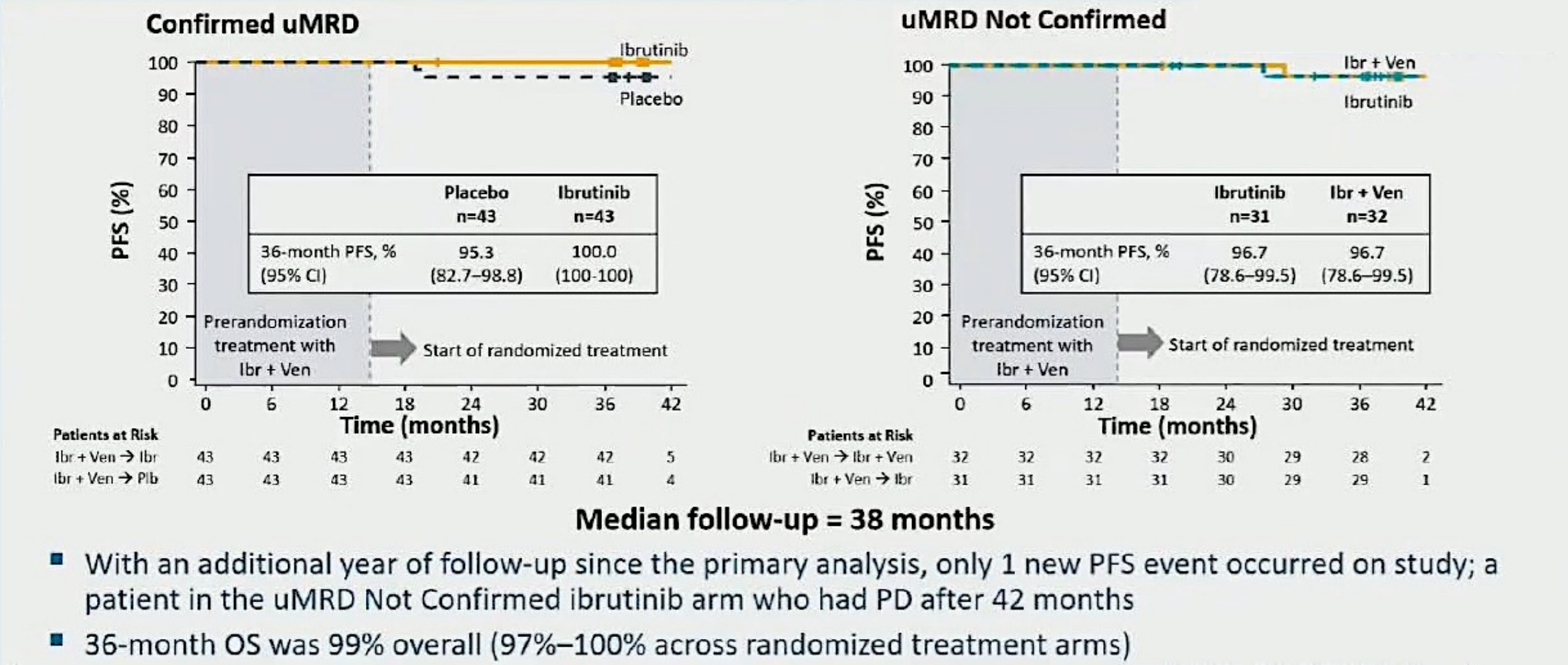


Median follow-up = 24 months postrandomization

- 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



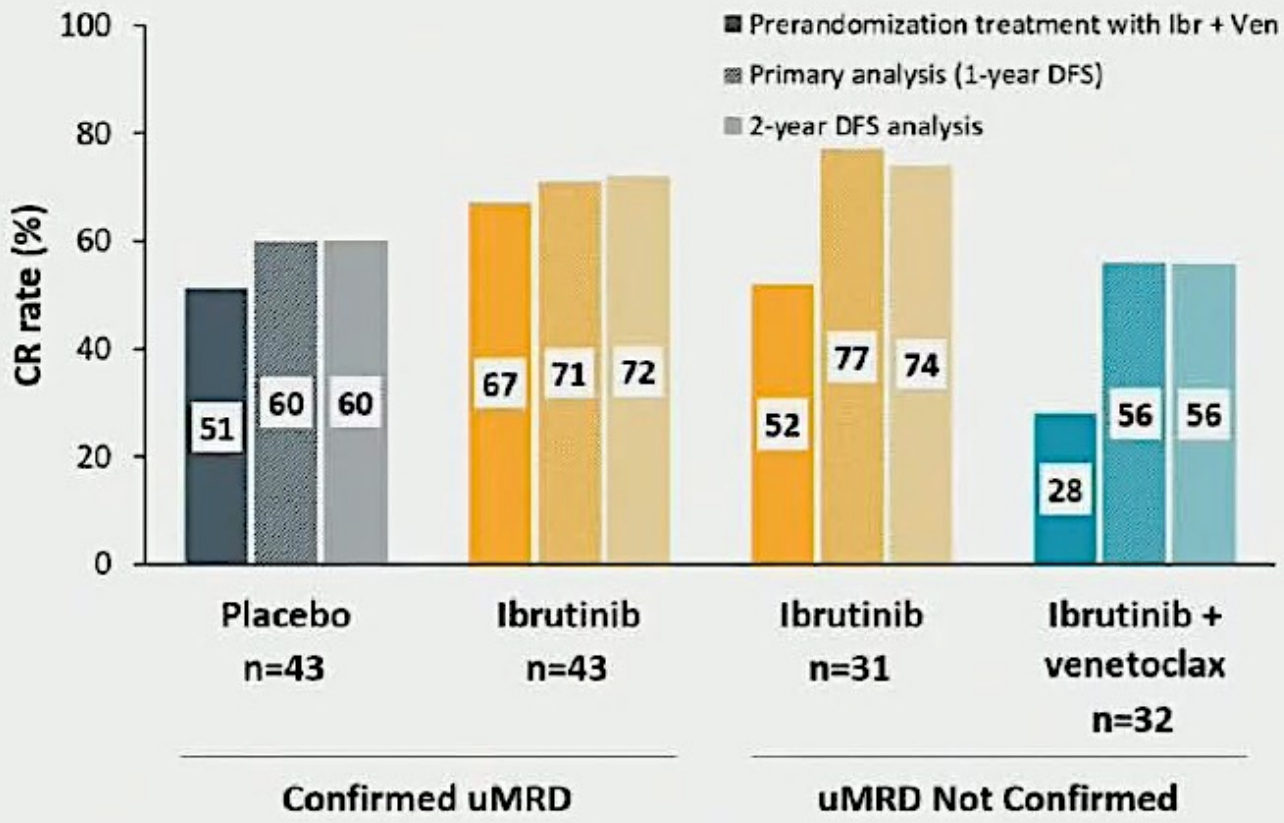
Median follow-up = 38 months

- 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.

RTP RESEARCH TO PRACTICE

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.

Immune Restoration and Synergistic Activity with First-Line (1L) Ibrutinib (Ibr) plus Venetoclax (Ven): Translational Analyses of CAPTIVATE Patients with CLL

Solman I et al.

EHA 2022;Abstract S144.

June 11, 2022

RTP
RESEARCH
TO PRACTICE

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

An electronic version of this presentation can be viewed by scanning the QR code or accessing this link https://www.oncologysciencehub.com/ASH2021/Ibrutinib/Kater/.
The QR code is intended to provide scientific information for individual reference and the content should not be altered or reproduced in any way.

ASH 2021;Abstract 70.

RTP RESEARCH TO PRACTICE

NEJM Evidence

Published May 13, 2022

DOI: 10.1056/EVIDoa2200006

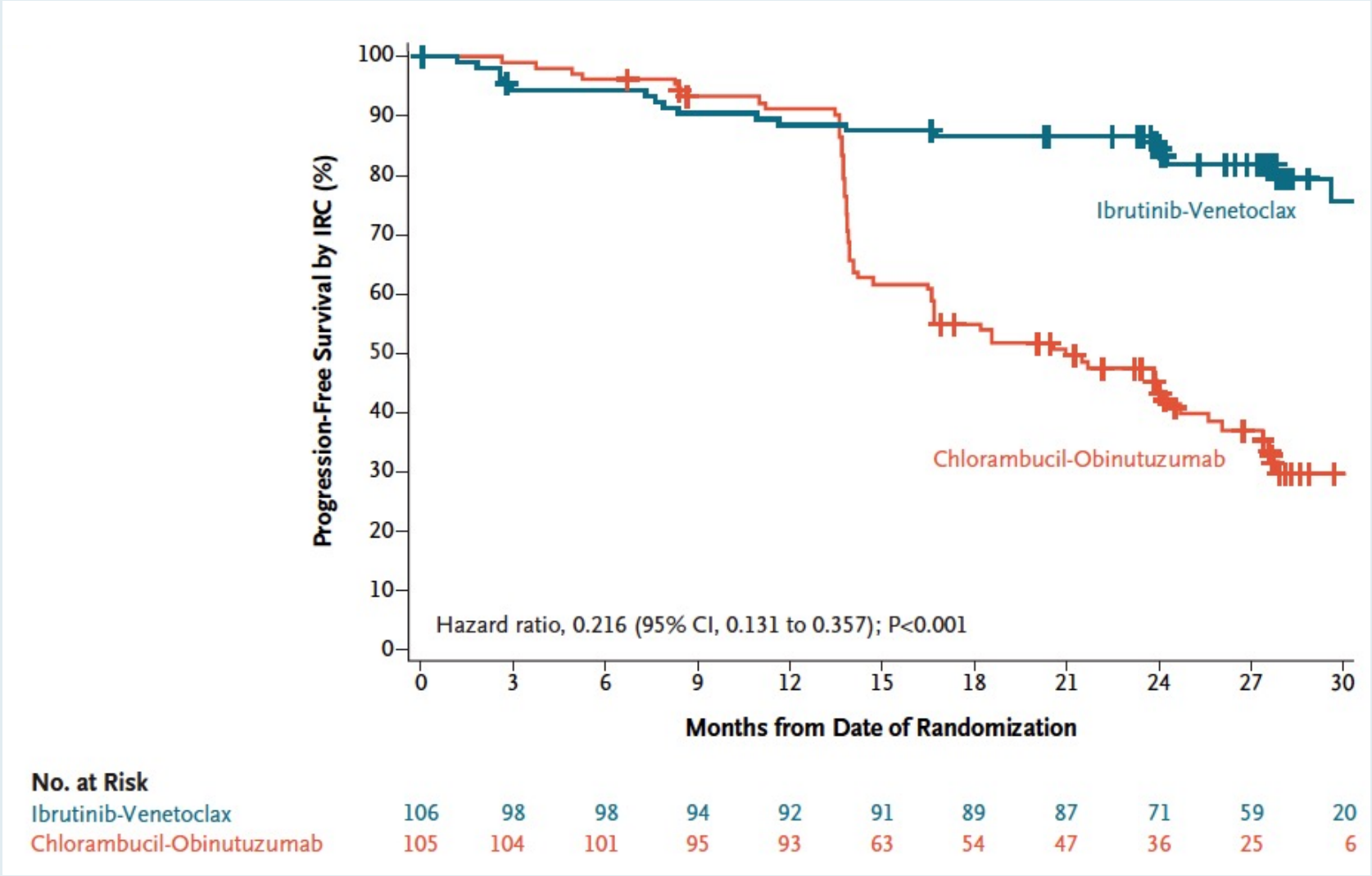
ORIGINAL ARTICLE

Fixed-Duration Ibrutinib-Venetoclax in Patients with Chronic Lymphocytic Leukemia and Comorbidities

Arnon P. Kater, M.D., Ph.D.,[1] Carolyn Owen, M.D.,[2] Carol Moreno, M.D.,[3] George Follows, B.M.Bch., Ph.D.,[4] Talha Munir, M.B.B.S.,[5] Mark-David Levin, M.D.,[6] Ohad Benjamini, M.D.,[7] Ann Janssens, M.D., Ph.D.,[8] Anders Osterborg, M.D., Ph.D.,[9] Tadeusz Robak, M.D., Ph.D.,[10] Martin Simkovic, M.D., Ph.D.,[11] Don Stevens, M.D.,[12] Sergey Voloshin, M.D., Ph.D.,[13] Vladimir Vorobyev, Ph.D.,[14] Loic Ysebaert, M.D., Ph.D.,[15] Rui Qin, Ph.D.,[16] Andrew J. Steele, Ph.D.,[17] Natasha Schuier, M.D.,[18] Kurt Baeten, Ph.D.,[19] Donne Bennett Caces, M.D., Ph.D.,[16] and Carsten U. Niemann, M.D., Ph.D.,[20] for the GLOW Investigators*

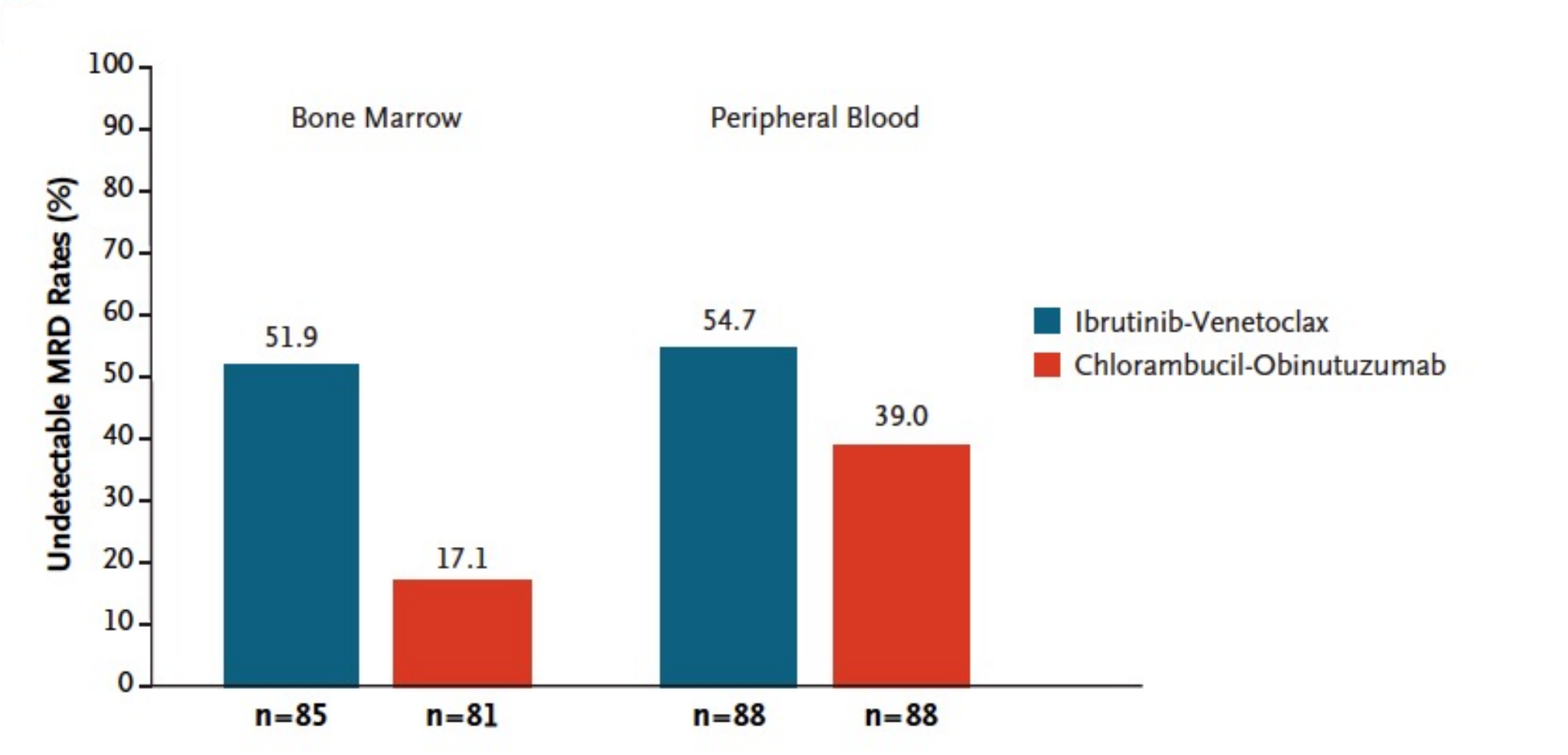
RTP RESEARCH TO PRACTICE

GLOW: Independent Review Committee (IRC)-Assessed PFS



Kater AP et al. *NEJM Evidence* 2022;10.1056/EVIDoa2200006.

GLOW: MRD Rates at 3 Months After End of Treatment



Kater AP et al. *NEJM Evidence* 2022;10.1056/EVIDoa2200006.

GLOW: Summary of Serious Adverse Events

Adverse Events* – n (%)	Ibrutinib-Venetoclax (n=106)	Chlorambucil-Obinutuzumab (n=105)
Any	49 (46.2)	29 (27.6)
Infections†	13 (12.3)	9 (8.6)
Atrial fibrillation	7 (6.6)	0
Anemia	3 (2.8)	2 (1.9)
Diarrhea	3 (2.8)	1 (1.0)
Cardiac failure	3 (2.8)	0
Febrile neutropenia	1 (0.9)	3 (2.9)
Infusion-related reaction	0	3 (2.9)
Tumor lysis syndrome	0	3 (2.9)

Kater AP et al. *NEJM Evidence* 2022;10.1056/EVIDoa2200006.

RTP RESEARCH TO PRACTICE

Lancet Oncol 2022;23(6):818-28.

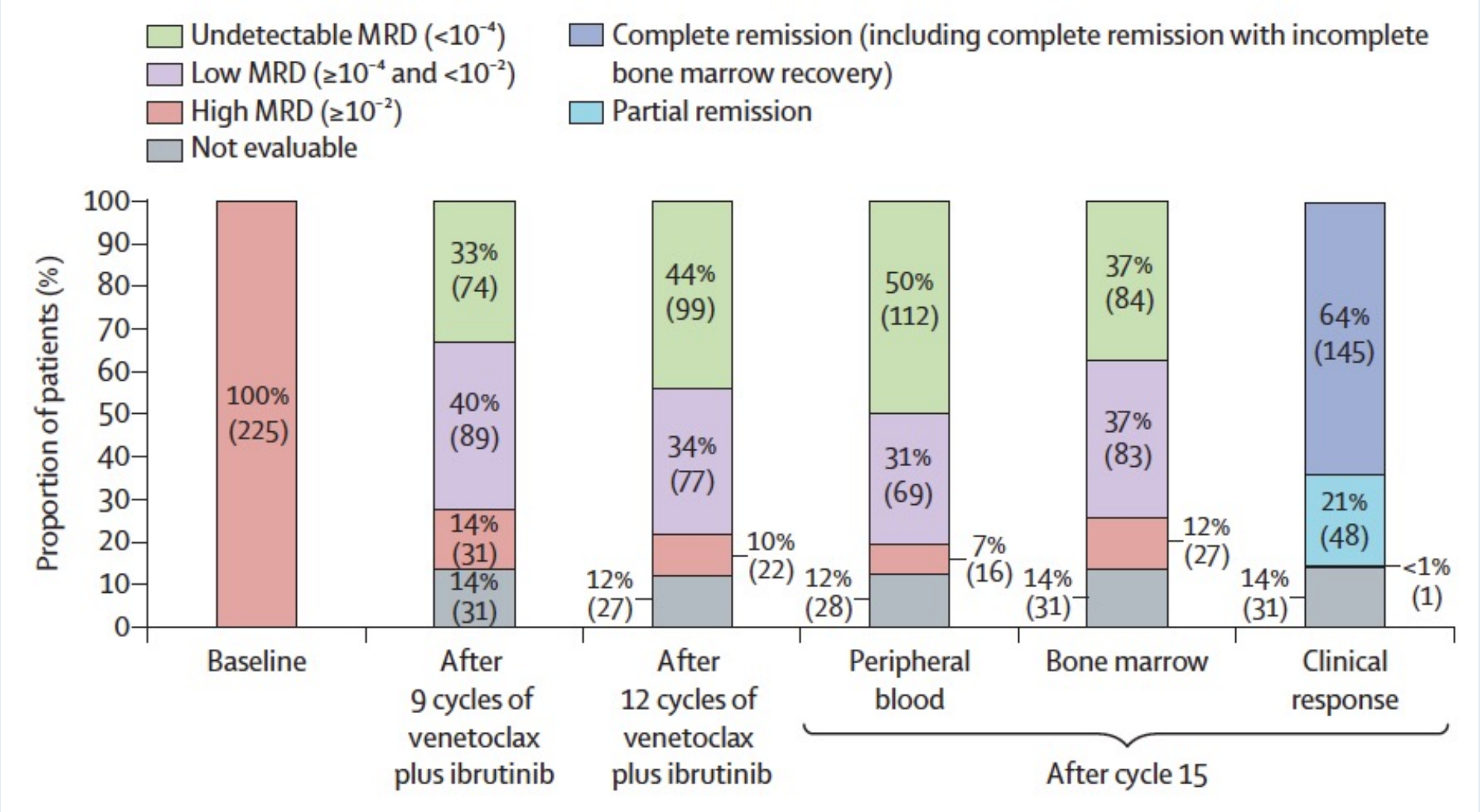
Articles

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

Arnon P Kater, Mark-David Levin, Julie Dubois, Sabina Kersting, Lisbeth Enggaard, Gerrit J Veldhuis, Rogier Mous, Clemens H M Mellink, Anne-Marie F van der Kevie-Kersemaekers, Johan A Dobber, Christian B Poulsen, Henrik Frederiksen, Ann Janssens, Ida Schjødt, Ellen C Dompeling, Juha Ranti, Christian Brieghel, Mattias Mattsson, Mar Bellido, Hoa T T Tran, Kazem Nasserinejad, Carsten U Niemann

RTP RESEARCH TO PRACTICE

VISION H0141: MRD and Responses in ITT Population

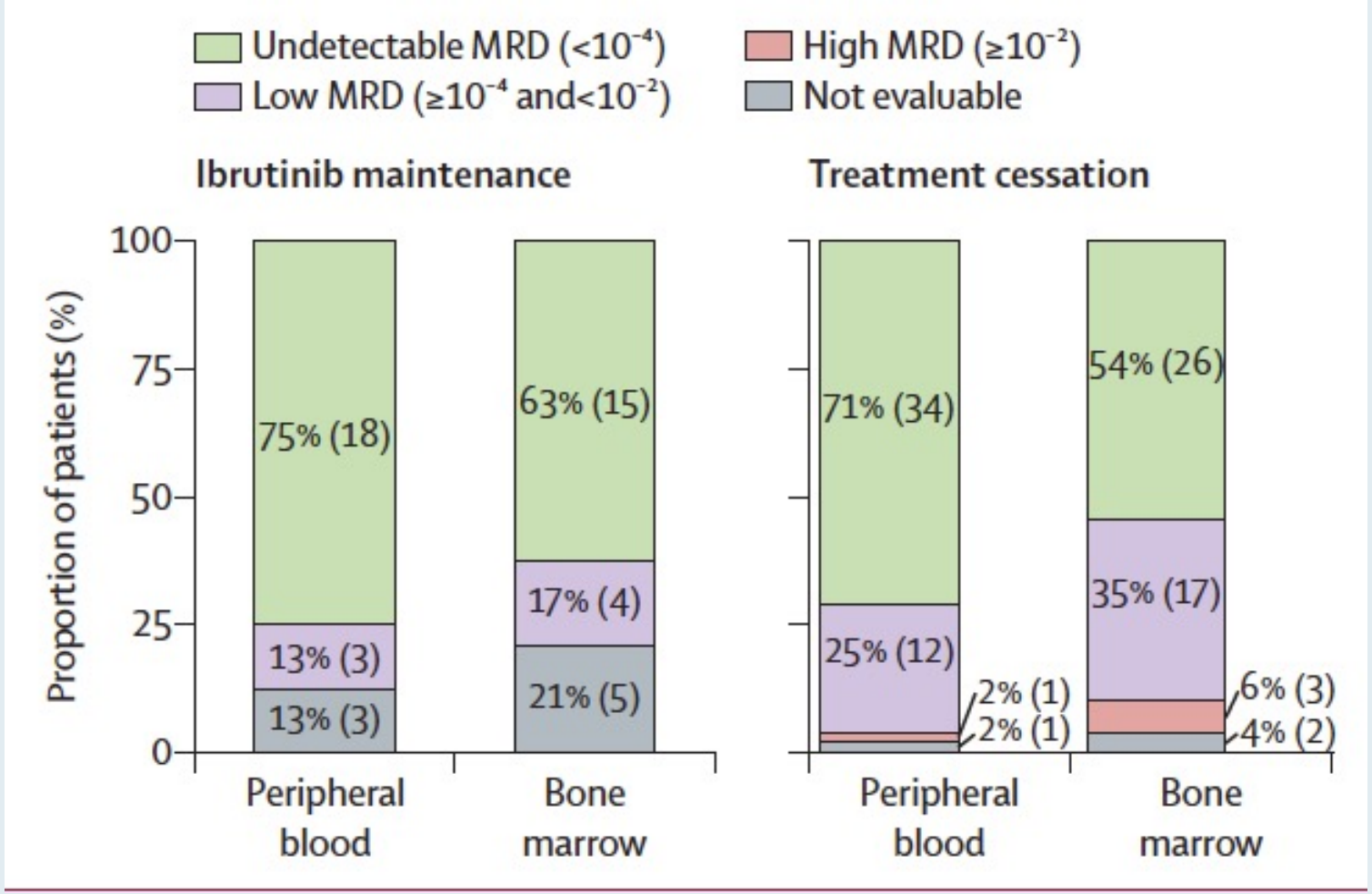


ITT = intention-to-treat

Kater AP et al. *Lancet Oncol* 2022;23(6):818-28

RTP RESEARCH TO PRACTICE

VISION H0141: MRD Rates at Month 27 After Treatment Start for Patients in the Ibrutinib Maintenance and Treatment Cessation Groups



Kater AP et al. *Lancet Oncol* 2022;23(6):818-28

RTP RESEARCH TO PRACTICE

VISION H0141: Summary of Treatment-Related Adverse Events After Cycle 15

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

Kater AP et al. *Lancet Oncol* 2022;23(6):818-28

RTP RESEARCH TO PRACTICE

Selection of BTK Inhibitor

RTP
RESEARCH
TO PRACTICE

original reports

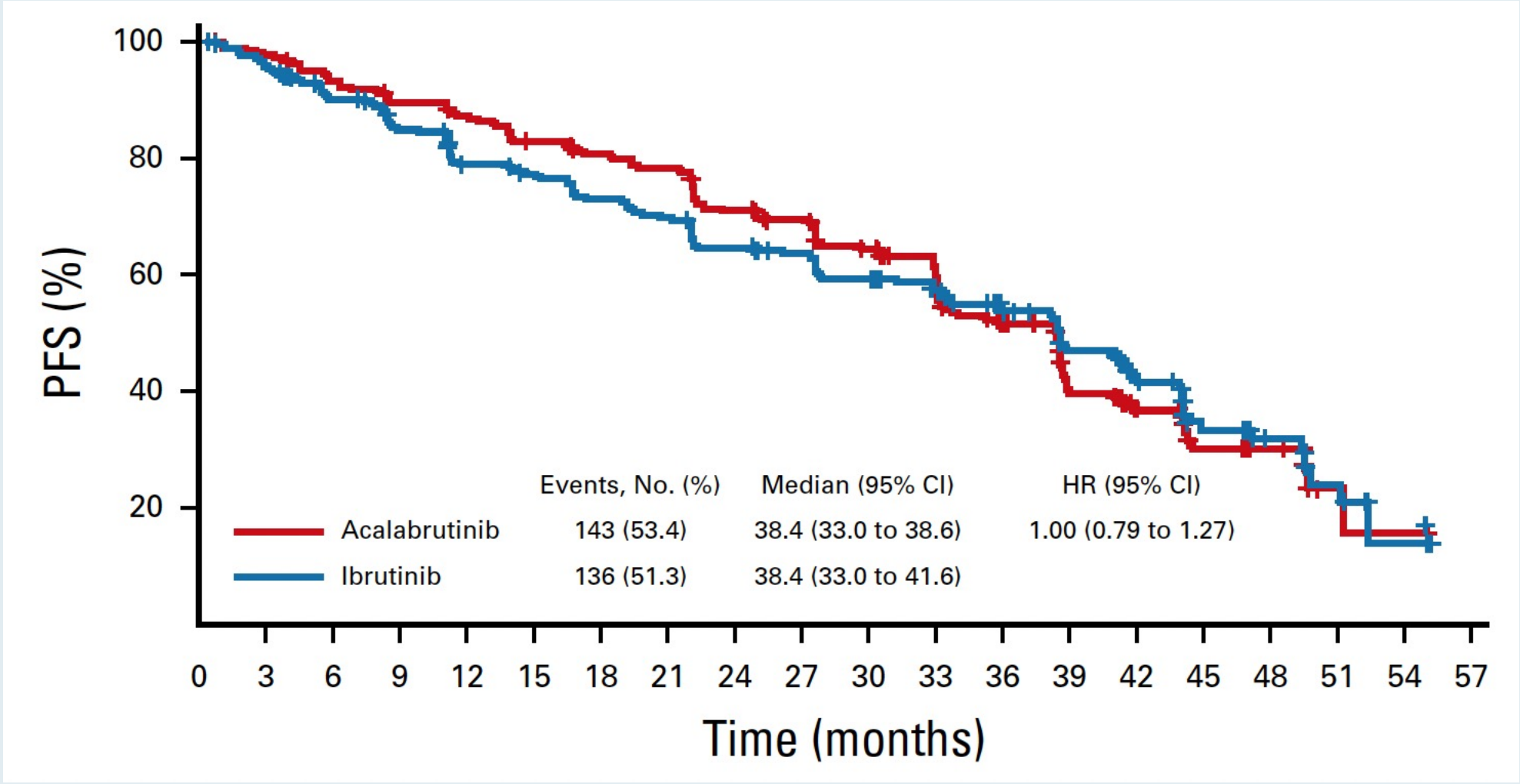
Acalabrutinib Versus Ibrutinib in Previously Treated Chronic Lymphocytic Leukemia: Results of the First Randomized Phase III Trial

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.

RTP RESEARCH TO PRACTICE

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.

RTP RESEARCH TO PRACTICE

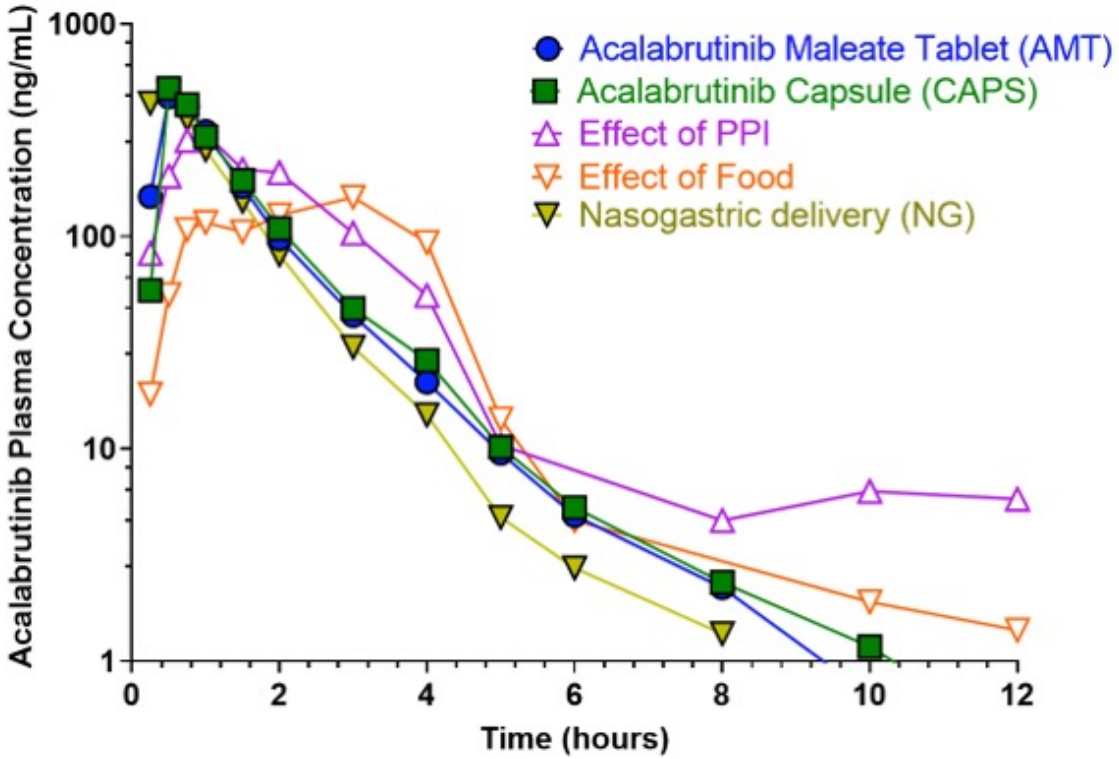
New Acalabrutinib Formulation Enables Co-Administration with Proton Pump Inhibitors and Dosing in Patients Unable to Swallow Capsules (ELEVATE-PLUS)

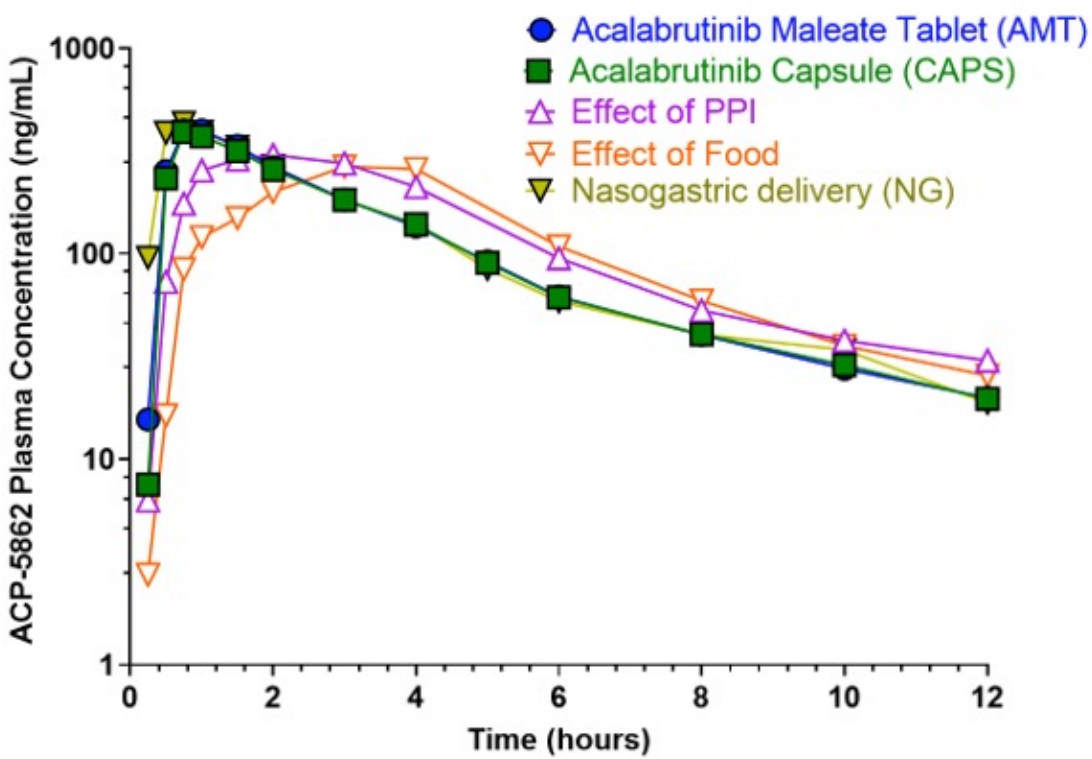
Sharma S et al. ASH 2021;Abstract 4365.

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.

RTP
RESEARCH
TO PRACTICE

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

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

RTP RESEARCH TO PRACTICE

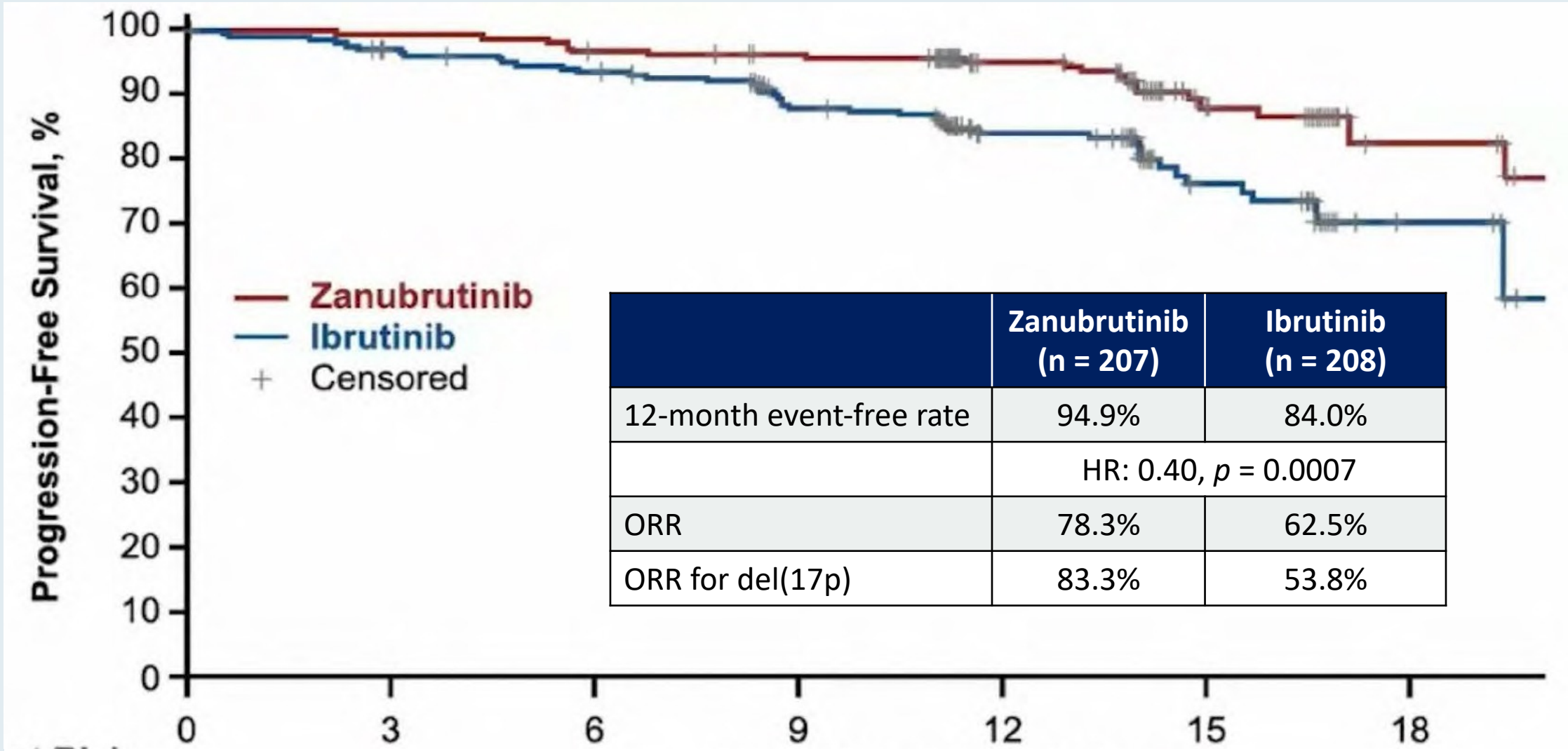
First Interim Analysis of ALPINE Study: Results of a Phase 3 Randomized Study of Zanubrutinib vs Ibrutinib in Patients with Relapsed/Refractory Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma

Hillmen P et al.

EHA 2021;Abstract LBA1900.

RTP
RESEARCH
TO PRACTICE

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.

RTP RESEARCH TO PRACTICE

N Engl J Med 2022;386:735-43.

The NEW ENGLAND JOURNAL of MEDICINE

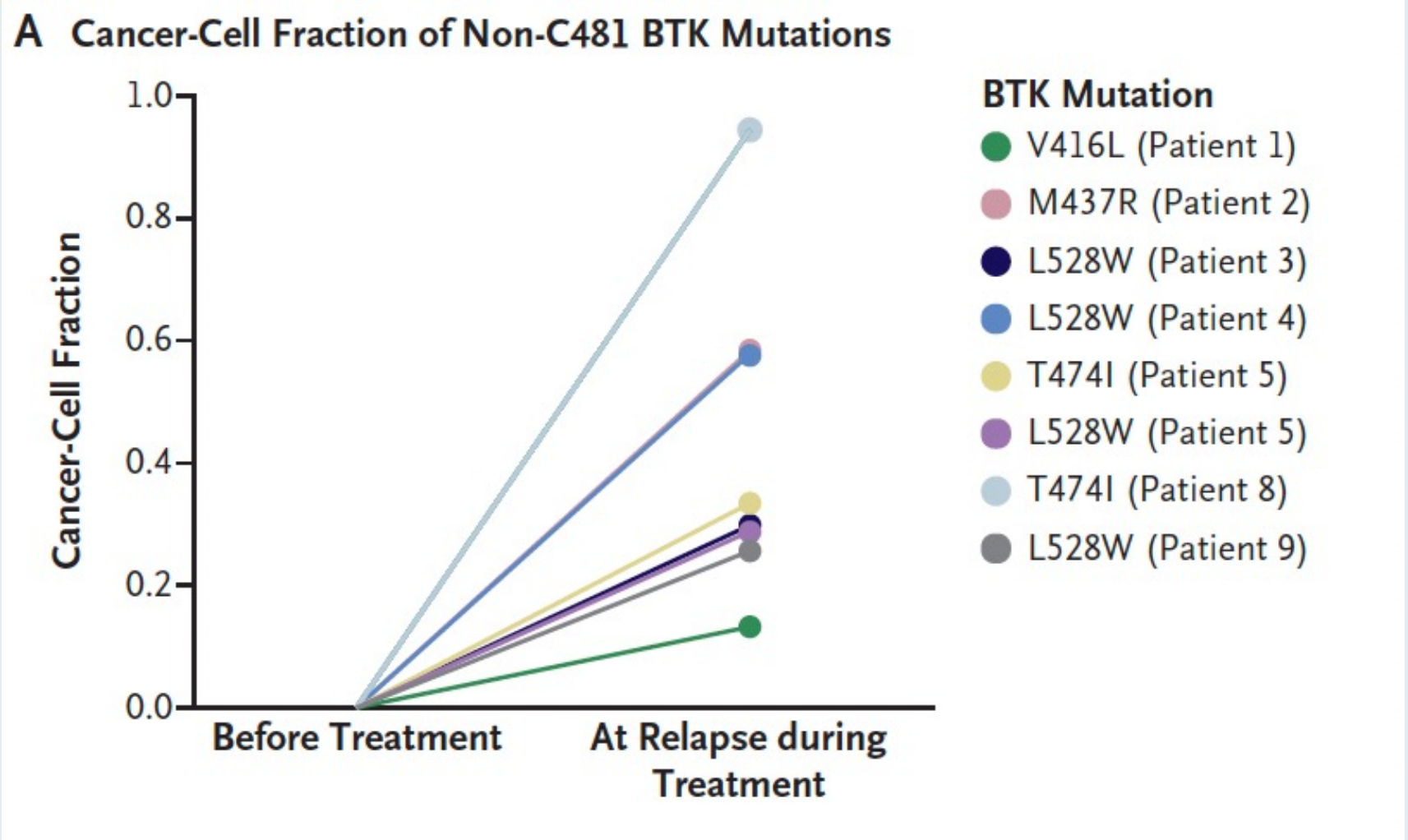
ORIGINAL ARTICLE

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.

RTP RESEARCH TO PRACTICE

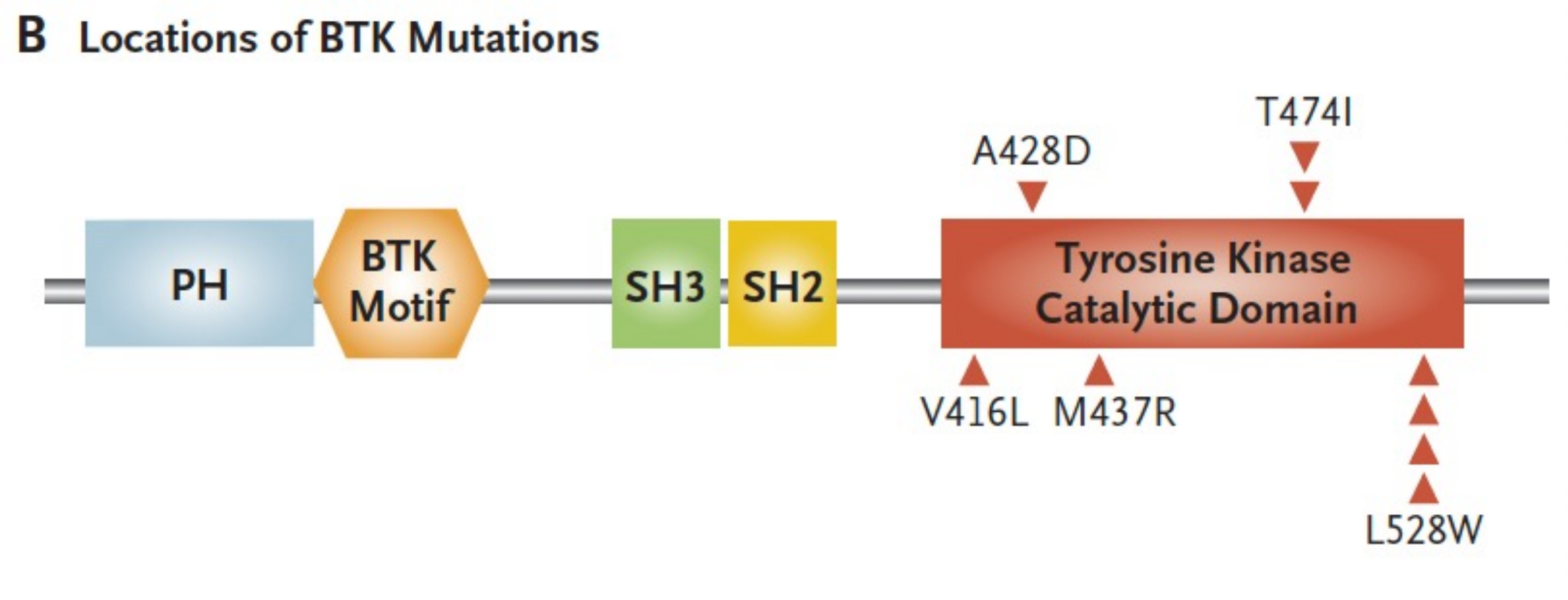
BTK Mutations in Patients with CLL with Acquired Resistance to Noncovalent BTK Inhibitors



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

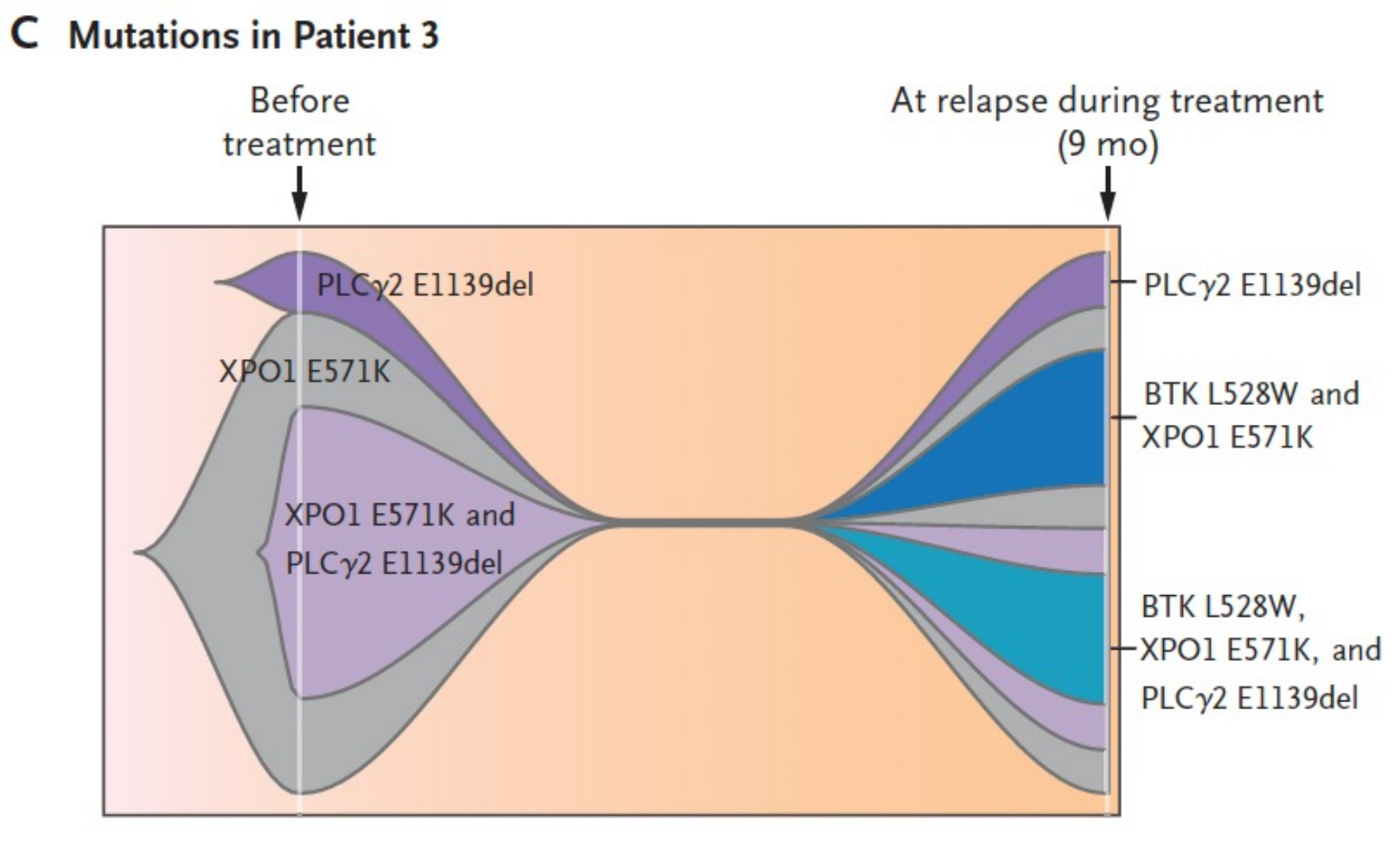
RTP RESEARCH TO PRACTICE

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.

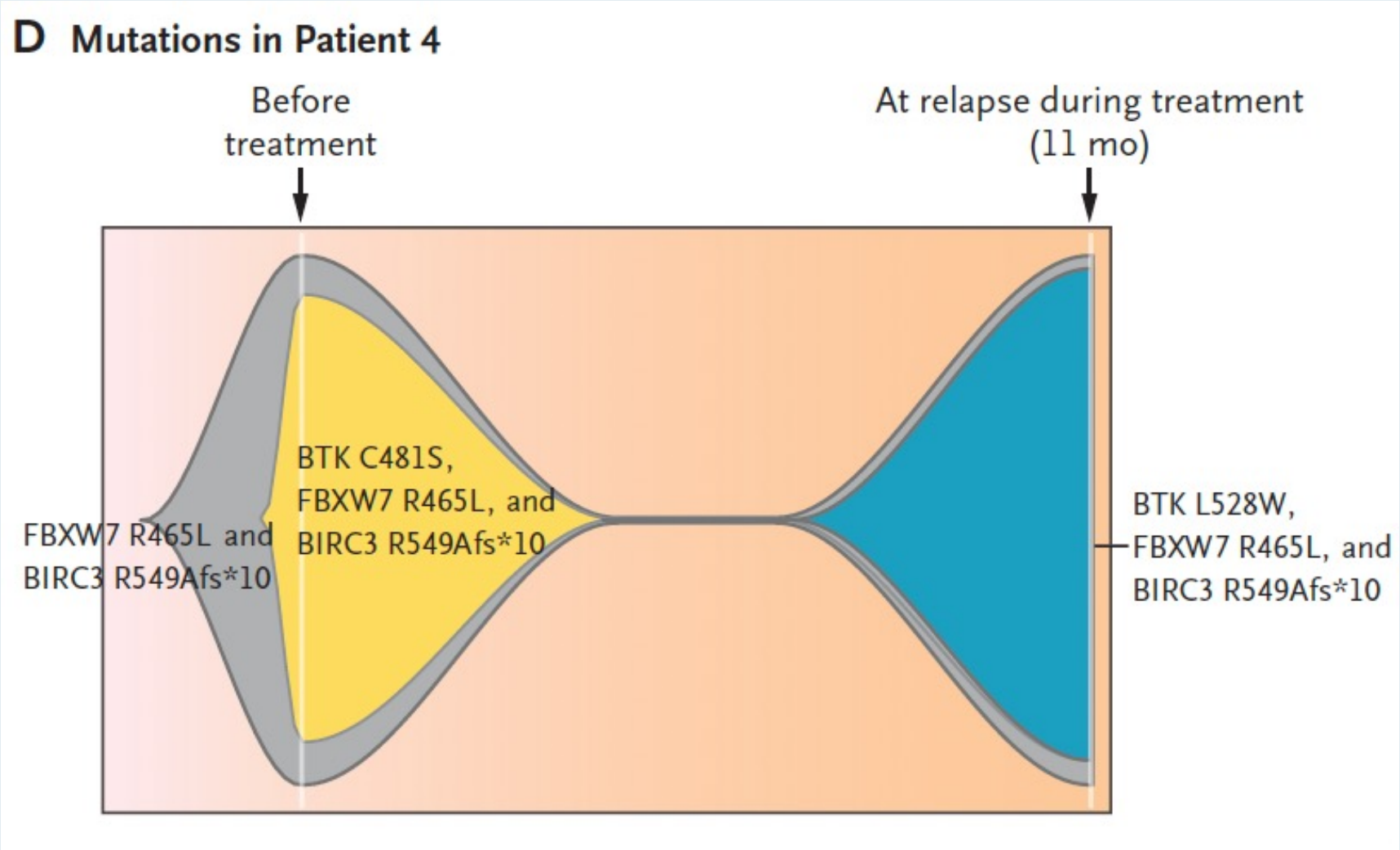
BTK Mutations in Patients with CLL with Acquired Resistance to Noncovalent BTK Inhibitors



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

RTP RESEARCH TO PRACTICE

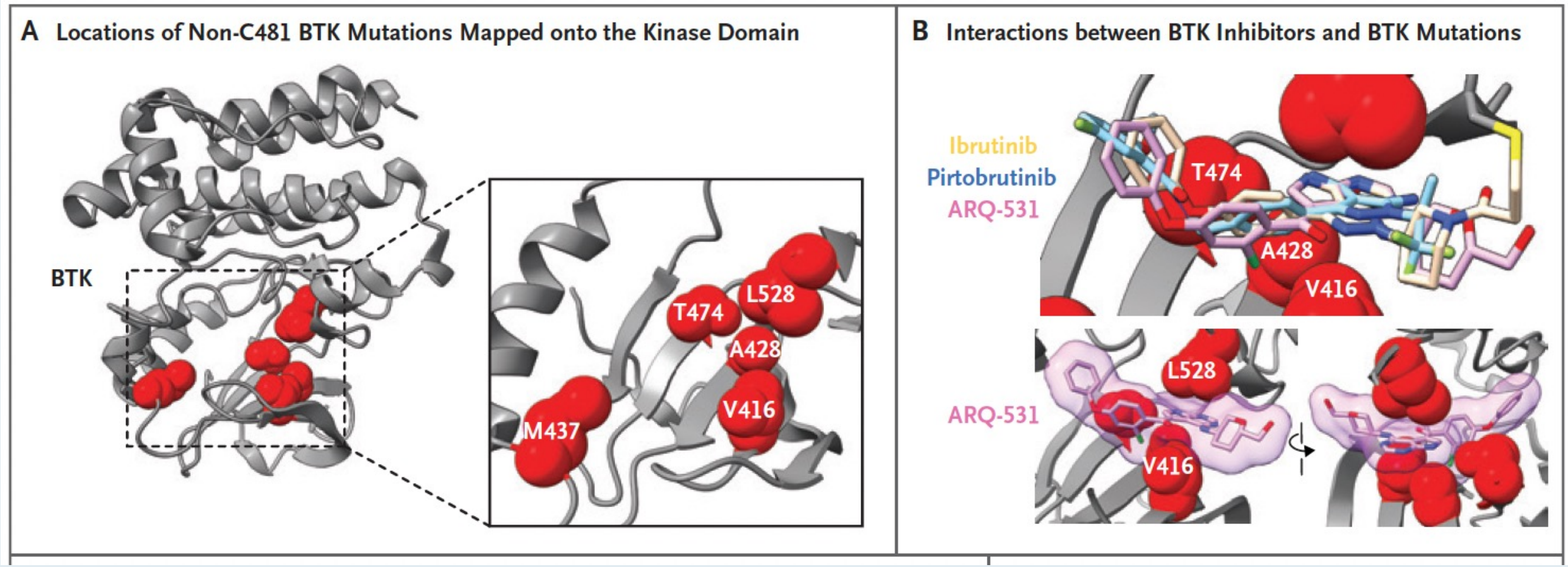
BTK Mutations in Patients with CLL with Acquired Resistance to Noncovalent BTK Inhibitors



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

RTP RESEARCH TO PRACTICE

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



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

RTP RESEARCH TO PRACTICE

Relapsed/Refractory CLL

RTP
RESEARCH
TO PRACTICE

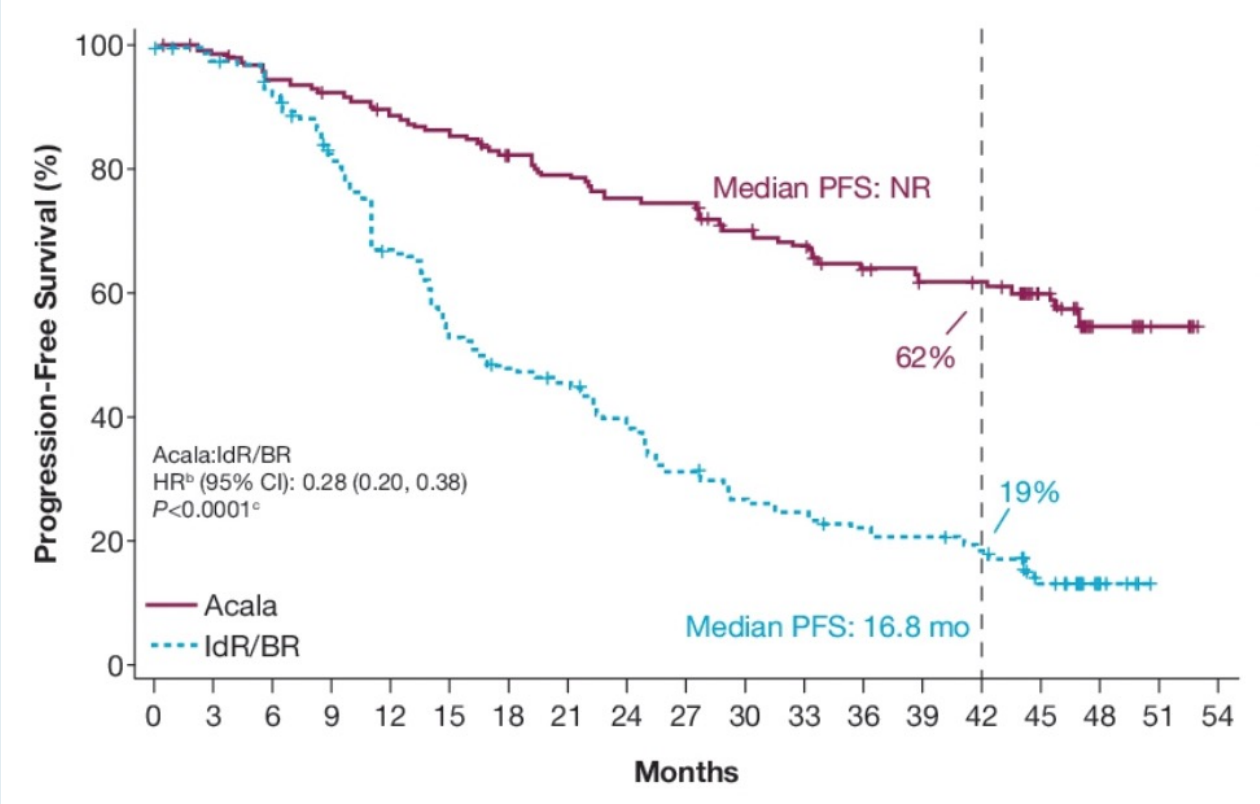
Acalabrutinib versus Rituximab plus Idelalisib or Bendamustine in Relapsed/Refractory Chronic Lymphocytic Leukemia: ASCEND Results at 4 Years of Follow-Up

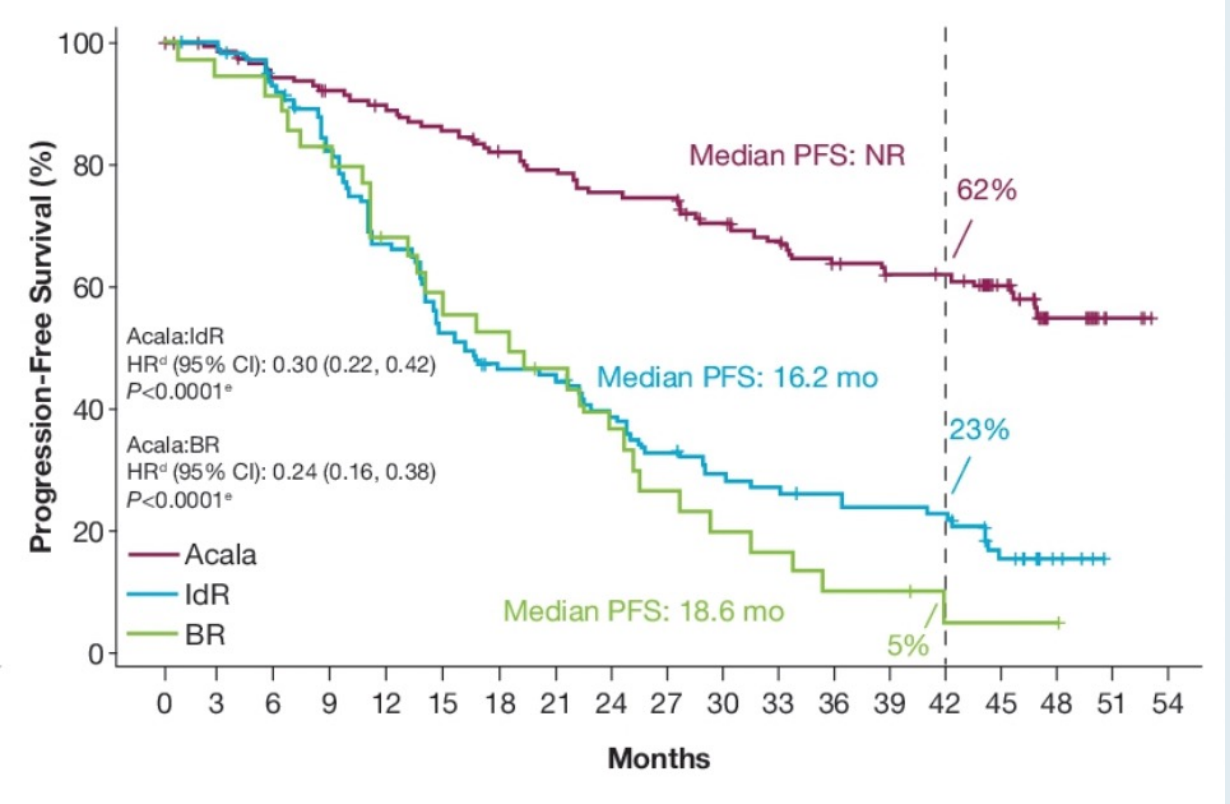
Jurczak W et al.

ASCO 2022;Abstract 7538.

RTP
RESEARCH
TO PRACTICE

ASCEND: Investigator-Assessed PFS



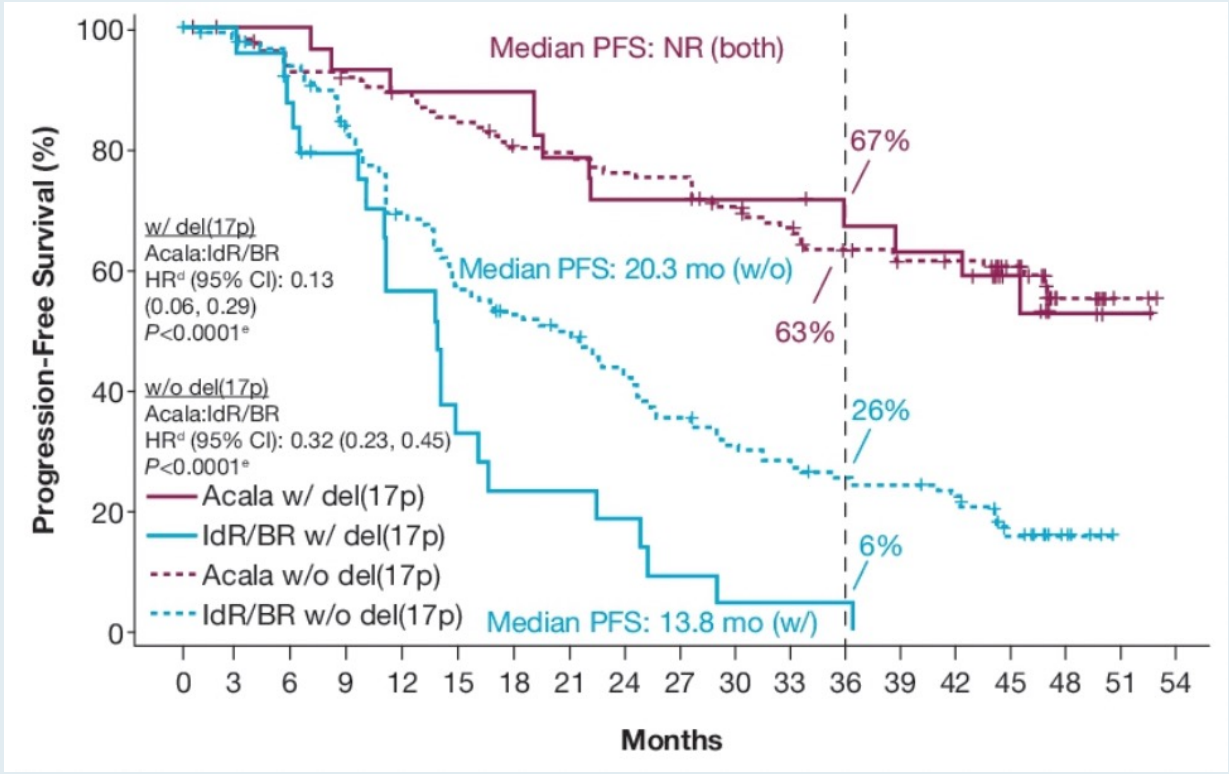


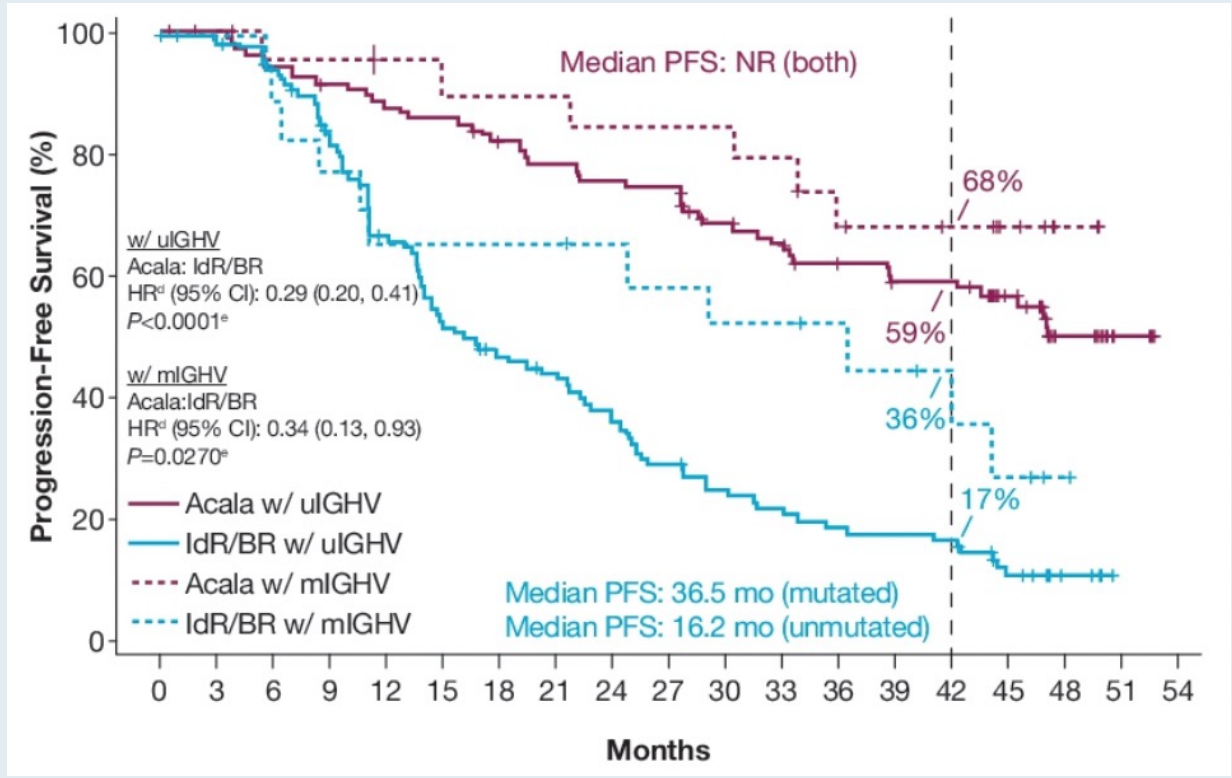
Acala = acalabrutinib; IdR = idelalisib and rituximab; BR = bendamustine and rituximab; NR = not reached

Jurczak W et al. ASCO 2022;Abstract 7538.

RTP RESEARCH TO PRACTICE

ASCEND: Investigator-Assessed PFS by Del(17p) and IGHV Mutation Status

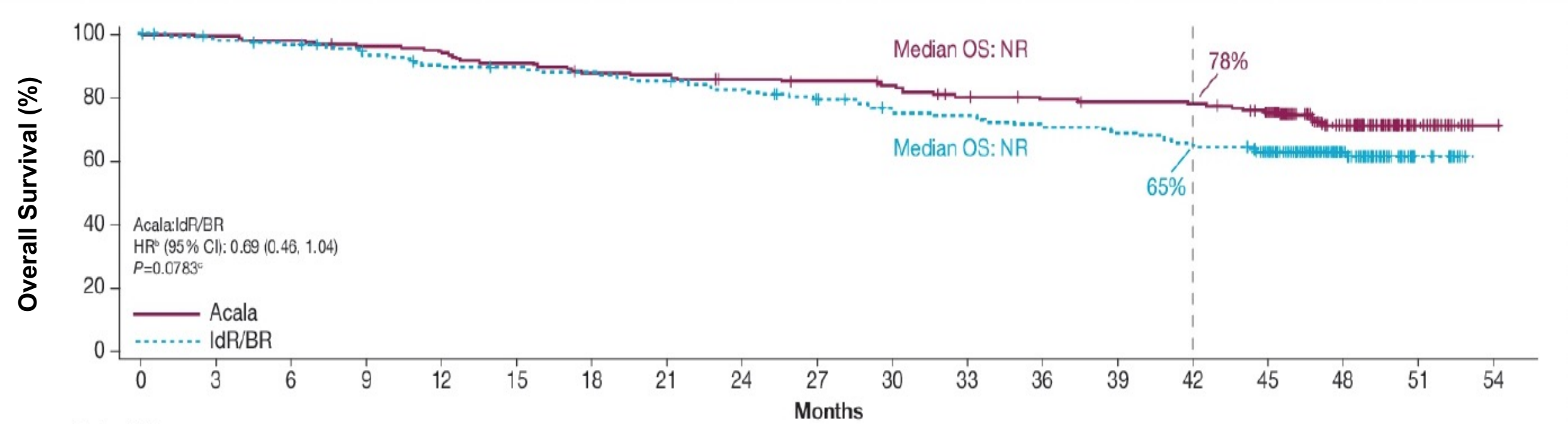




Acala = acalabrutinib; IdR = idelalisib and rituximab; BR = bendamustine and rituximab; NR = not reached

Jurczak W et al. ASCO 2022;Abstract 7538.

ASCEND: Overall Survival



Acala = acalabrutinib; IdR = idelalisib and rituximab; BR = bendamustine and rituximab; NR = not reached

Jurczak W et al. ASCO 2022;Abstract 7538.

RTP RESEARCH TO PRACTICE

ASCEND: Incidence of Adverse Events of Clinical Interest (ECI)

ECI, n (%)	Acala (n=154)		IdR (n=118)		BR (n=35)	
	Any	Grade ≥3	Any	Grade ≥3	Any	Grade ≥3
Atrial fibrillation	12 (8)	2 (1)	4 (3)	1 (1)	1 (3)	1 (3)
Hemorrhage	47 (31)	4 (3)	10 (8)	3 (3)	2 (6)	1 (3)
Major hemorrhage[a]	5 (3)	4 (3)[b]	3 (3)	3 (3)[c]	1 (3)	1 (3)[d]
Hypertension	12 (8)	7 (5)	7 (6)	1 (1)	0	0
Infections	105 (68)	45 (29)	86 (73)	40 (34)	17 (49)	4 (11)
Second primary malignancies excluding non-melanoma skin carcinomas	11 (7)	10 (6)	2 (2)	1 (1)	1 (3)	1 (3)
Tumor lysis syndrome	1 (1)	1 (1)	1 (1)	1 (1)	0	0

Acala = acalabrutinib; IdR = idelalisib and rituximab; BR = bendamustine and rituximab

Jurczak W et al. ASCO 2022;Abstract 7538.

RTP RESEARCH TO PRACTICE

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

Regular Article

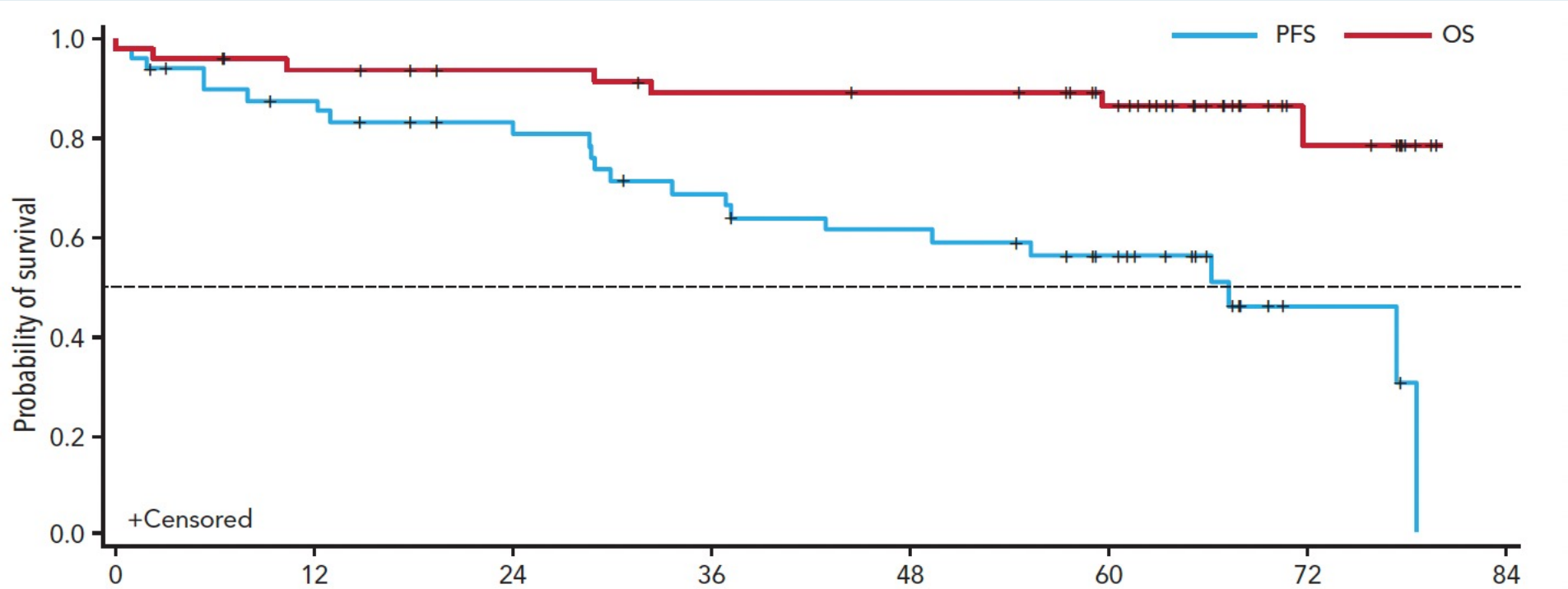
CLINICAL TRIALS AND OBSERVATIONS

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]

RTP RESEARCH TO PRACTICE

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.

RTP RESEARCH TO PRACTICE

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.

RTP RESEARCH TO PRACTICE

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.

RTP RESEARCH TO PRACTICE

Novel Strategies Under Investigation

RTP
RESEARCH
TO PRACTICE

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

Mato AR et al.

EHA 2022;Abstract S147.

June 12, 2022

RTP
RESEARCH
TO PRACTICE

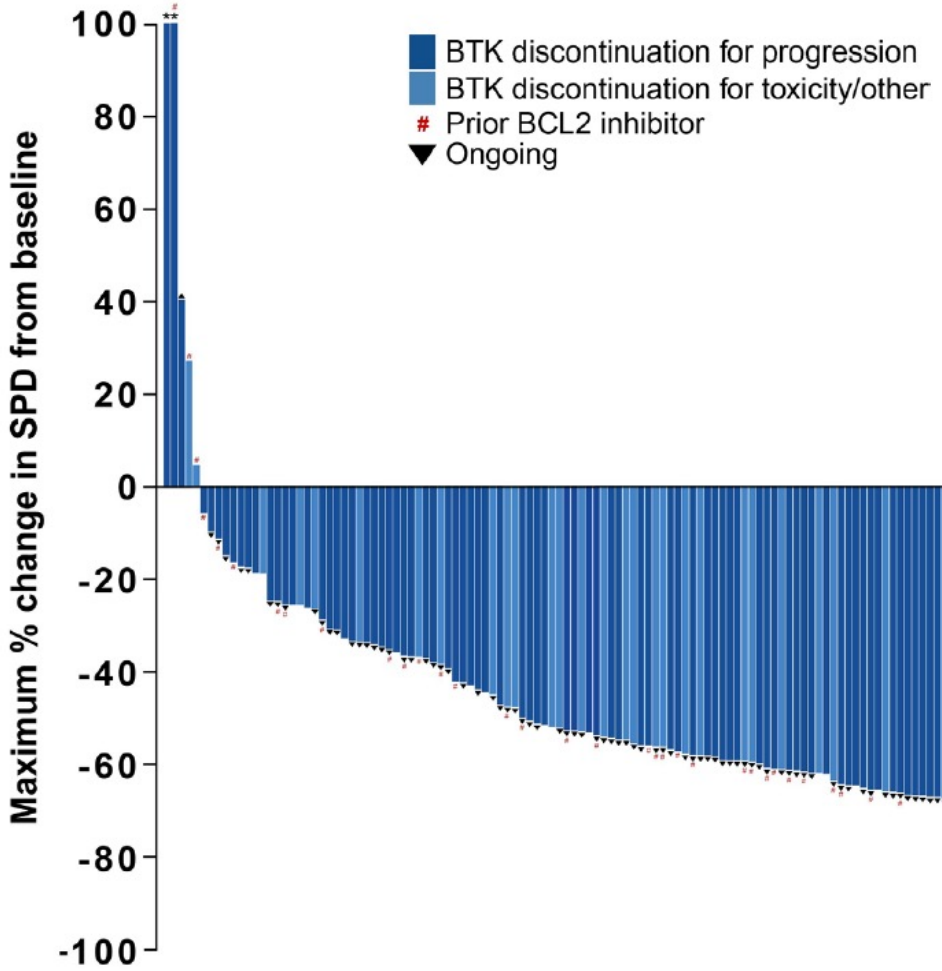
Pirtobrutinib, a Next Generation, Highly Selective, Non-Covalent BTK Inhibitor in Previously Treated CLL/SLL: Updated Results from the Phase 1/2 BRUIN Study

Mato AR et al.

ASH 2021;Abstract 391.

RTP
RESEARCH
TO PRACTICE

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.

RTP RESEARCH TO PRACTICE

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

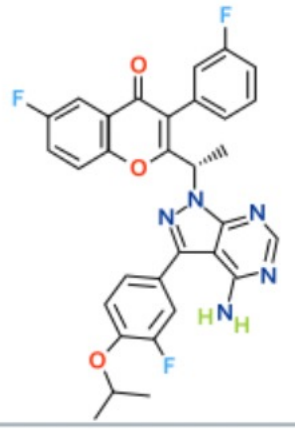
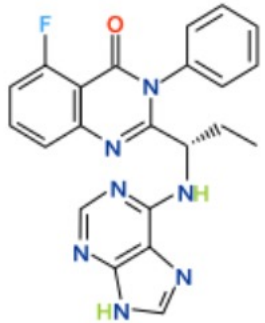
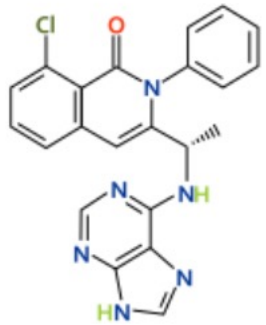
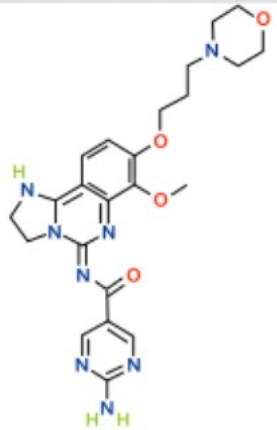
Efficacy and Safety of Ublituximab in Combination with Umbralisib (U2) in Patients with Chronic Lymphocytic Leukemia (CLL) by Treatment Status: A Sub-Analysis of the Phase 3 Unity-CLL Study

Jacobs R et al.

ASH 2021;Abstract 3726.

RTP
RESEARCH
TO PRACTICE

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**

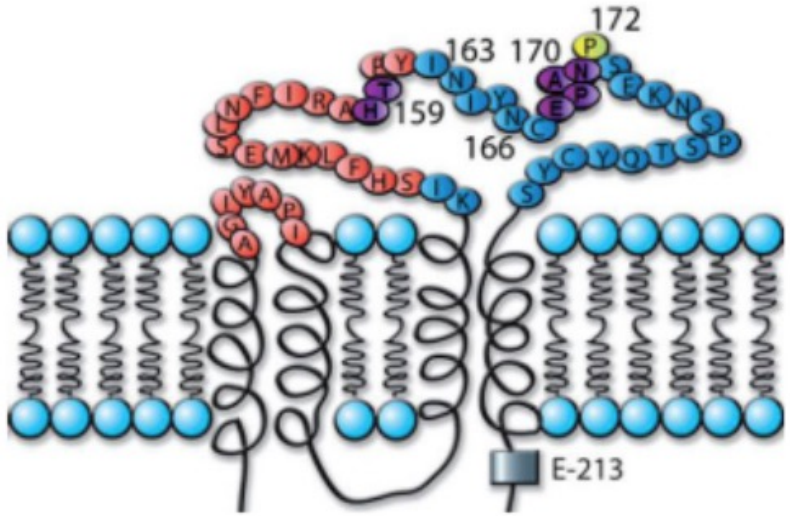
Jacobs R et al. ASH 2021;Abstract 3726.

RTP RESEARCH TO PRACTICE

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



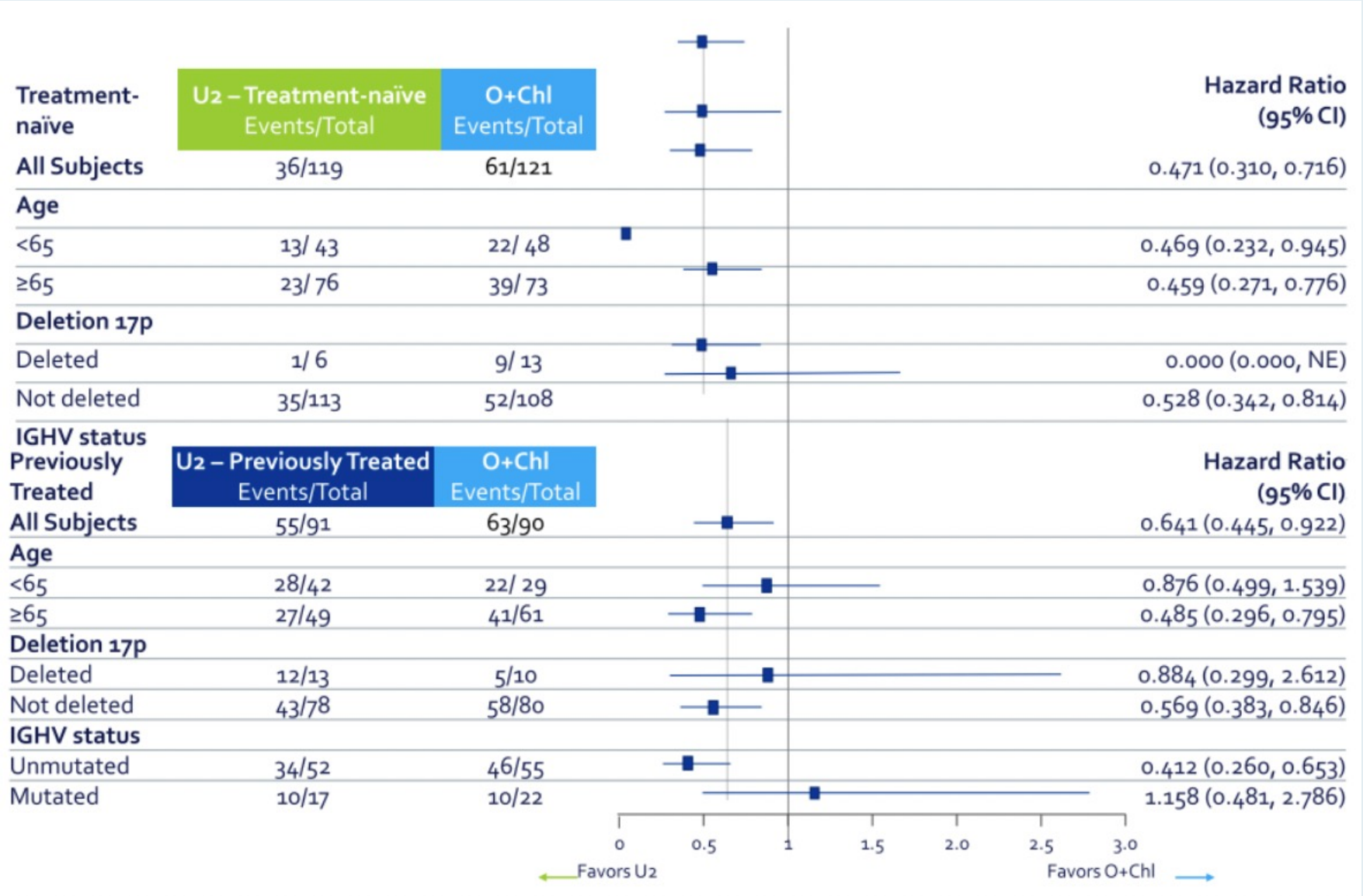
Red: Key ofatumumab epitope amino acids
Purple: Core amino acids of ublituximab epitope

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.

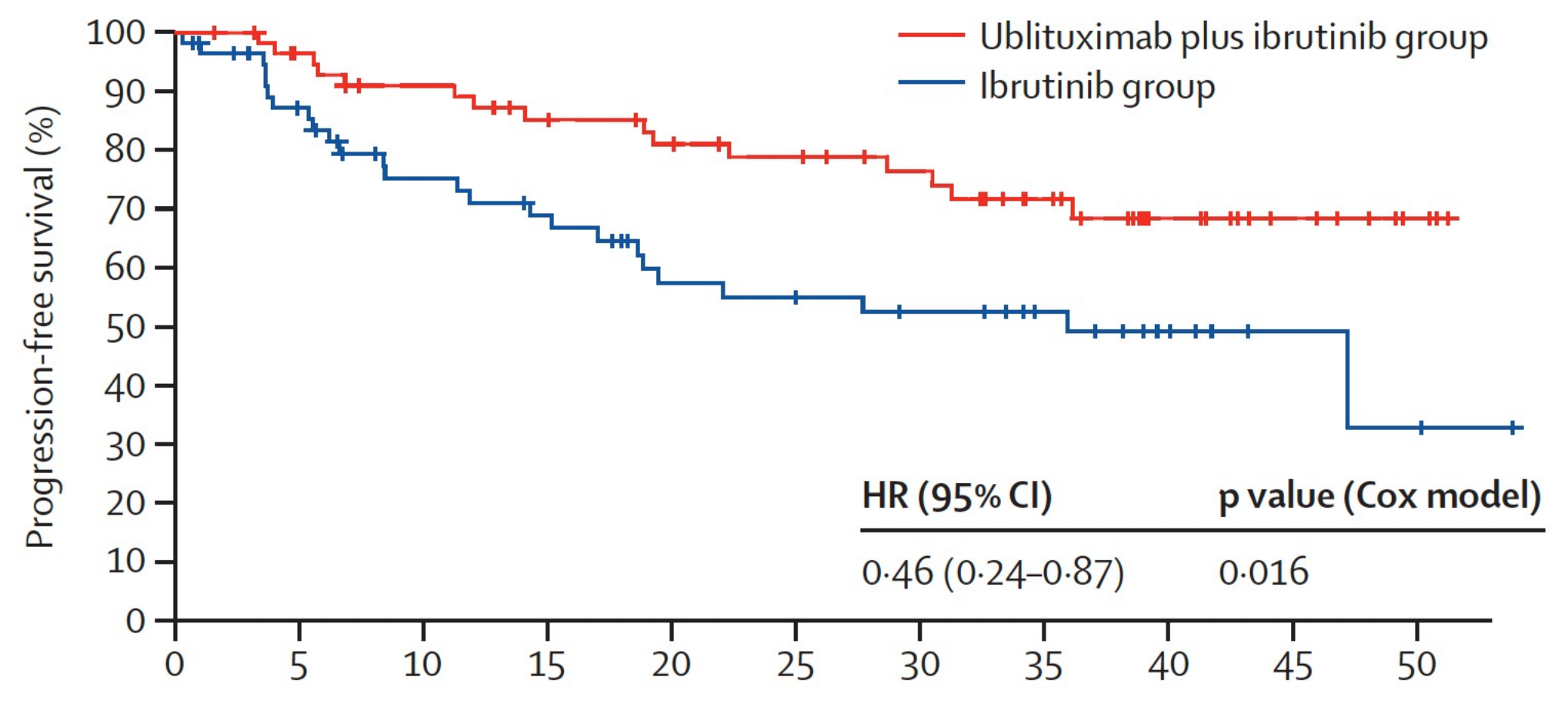
RTP RESEARCH TO PRACTICE

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

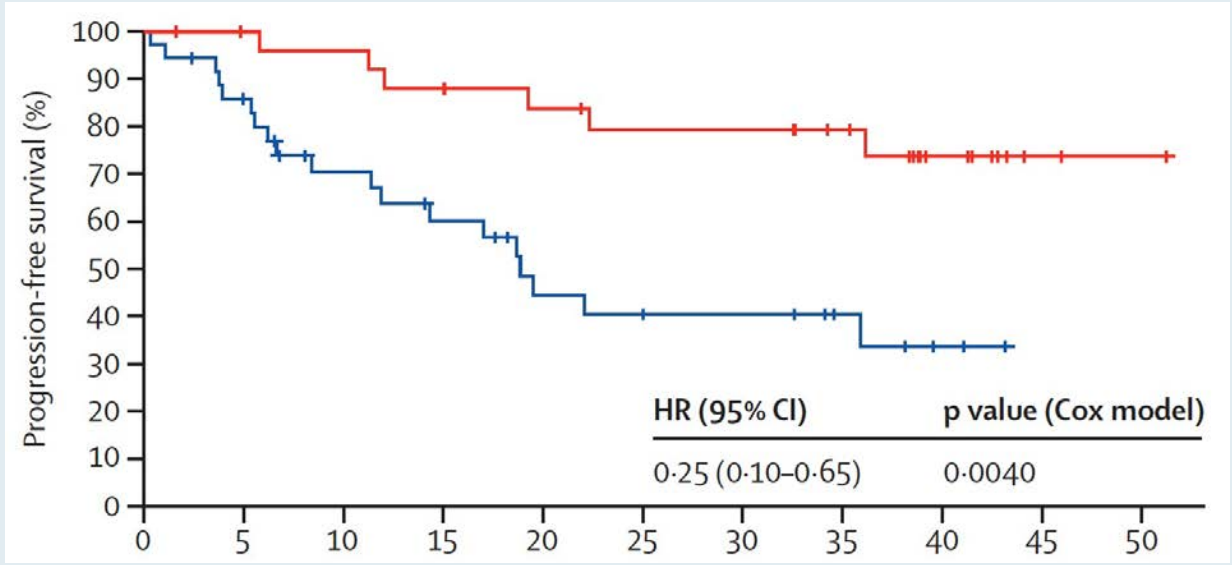
GENUINE: Progression-Free Survival (All Patients)



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

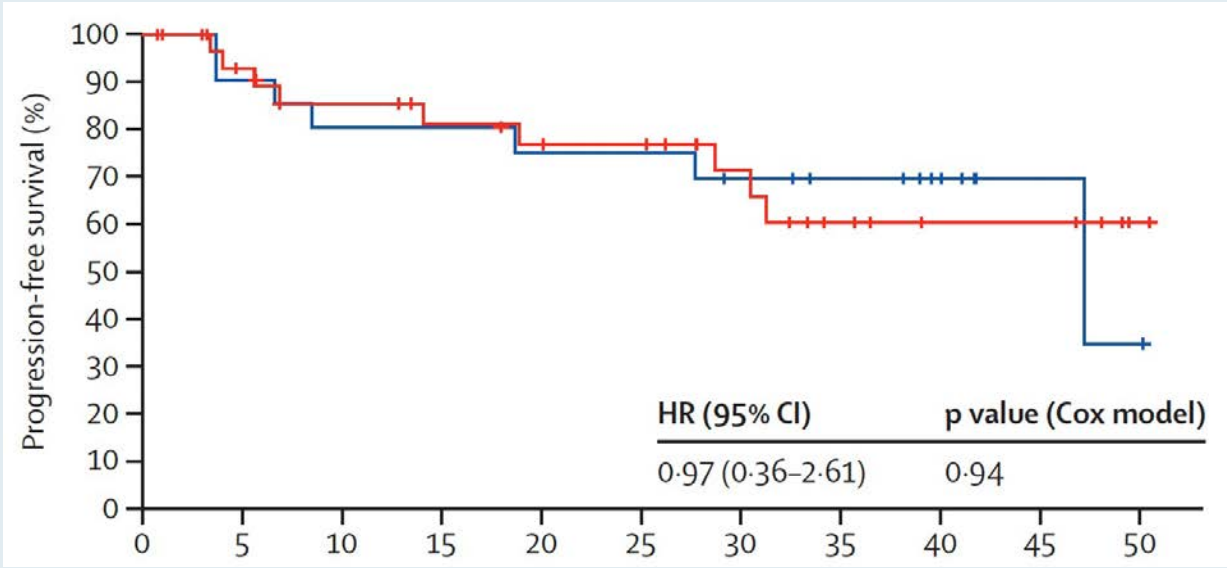
GENUINE: Progression-Free Survival in Subgroups

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

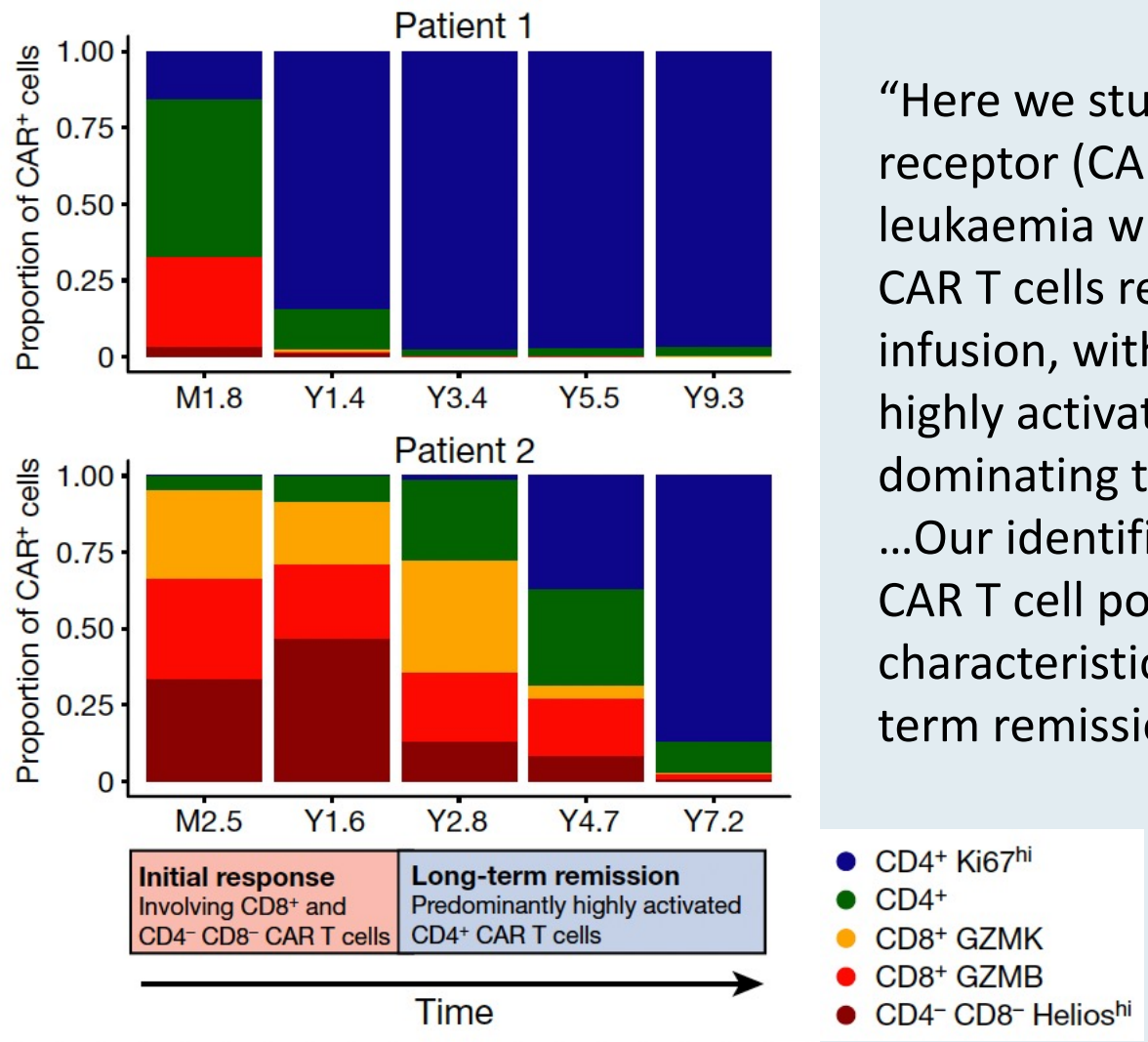
Accepted: 29 December 2021

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]✉

RTP RESEARCH TO PRACTICE

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].

RTP RESEARCH TO PRACTICE

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)

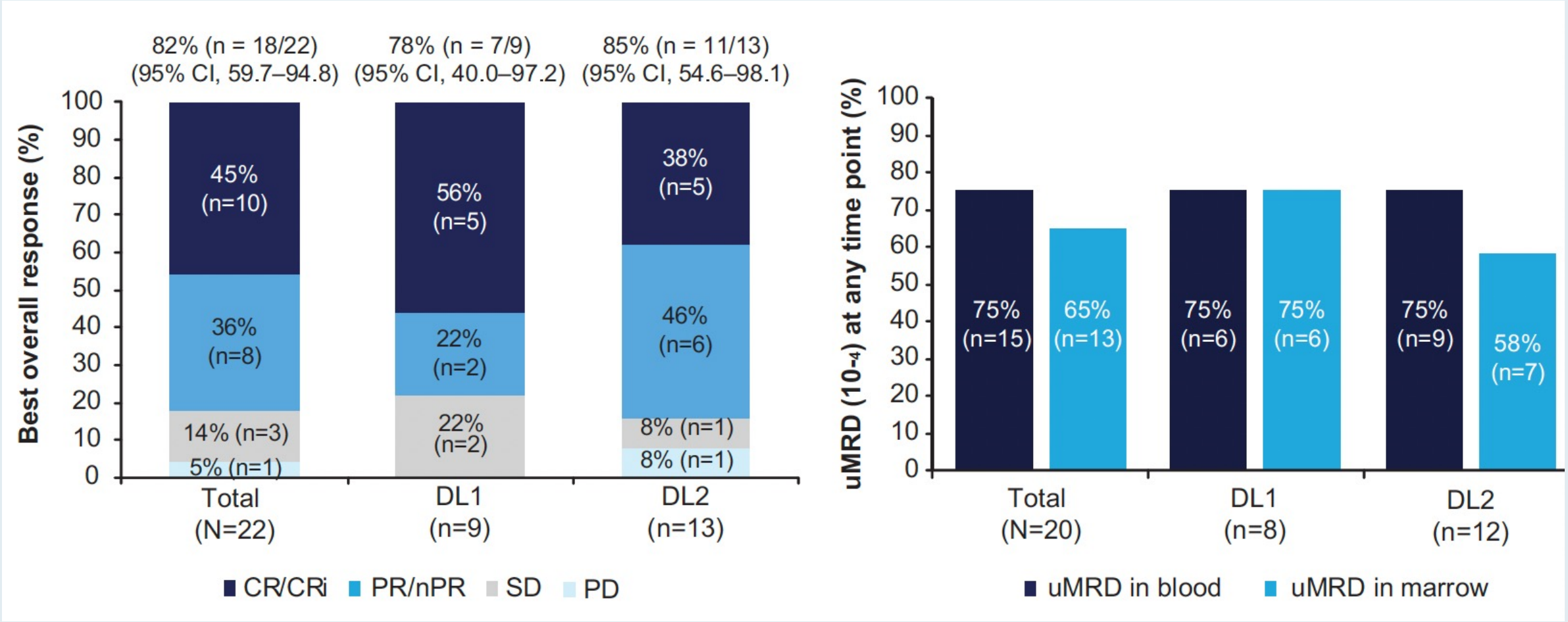
TRANSCEND CLL 004: Rates of Cytokine Release Syndrome (CRS), Neurologic Events (NE) and Rehospitalization After Liso-cel Infusion

	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].

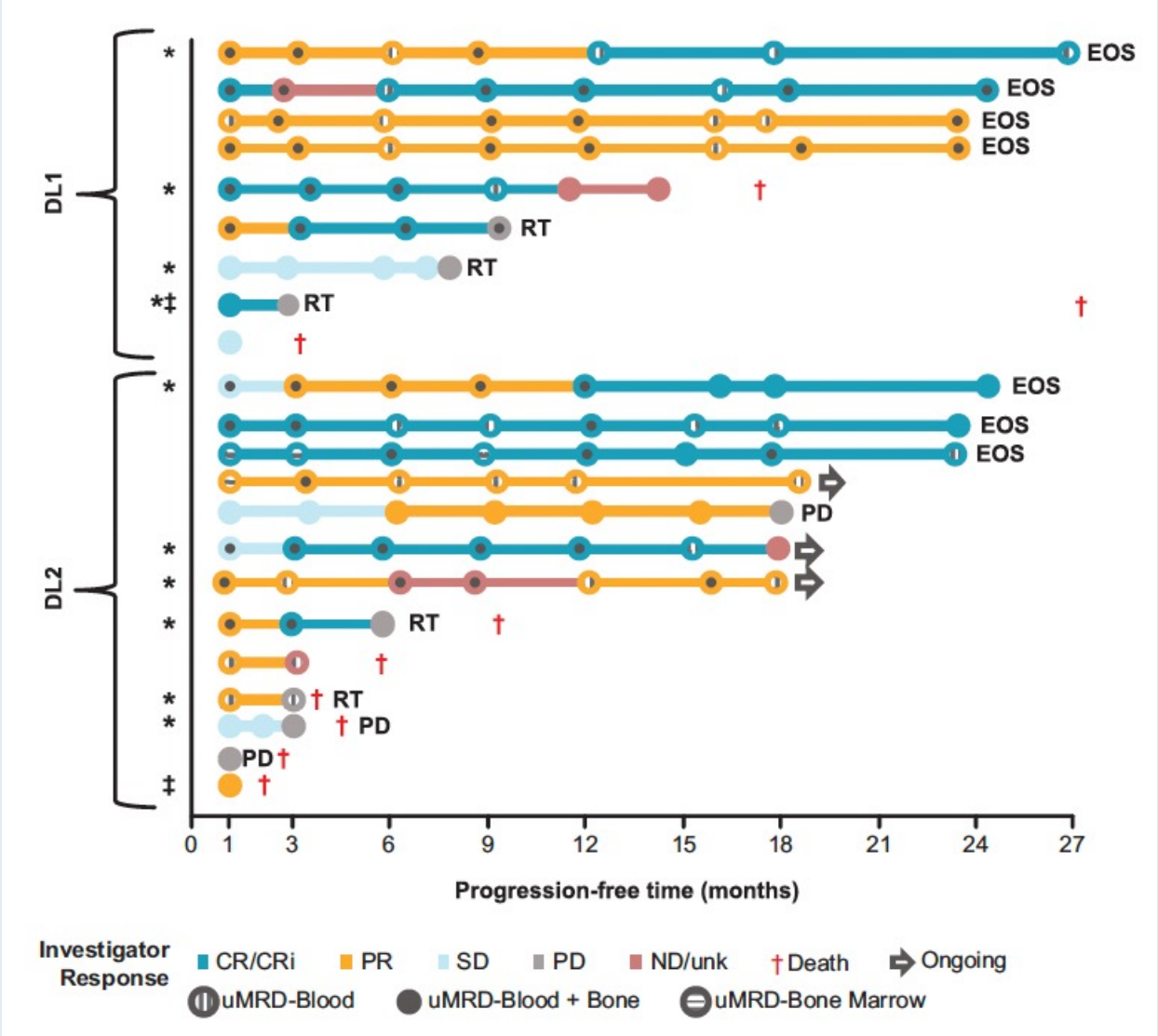
RTP RESEARCH TO PRACTICE

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

Thursday, June 16, 2022
5:00 PM – 6:00 PM ET

Faculty

Melissa Johnson, MD

Moderator

Neil Love, MD

RTP
RESEARCH
TO PRACTICE

Thank you for joining us!

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

RTP
RESEARCH
TO PRACTICE