Meet The Professor

Optimizing the Management of Chronic Lymphocytic Leukemia

Tuesday, September 17, 2024
5:00 PM – 6:00 PM ET

Faculty

Matthew S Davids, MD, MMSc

Moderator

Neil Love, MD

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Commercial Support

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Dr Love — Disclosures

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Dr Ujjani — Disclosures
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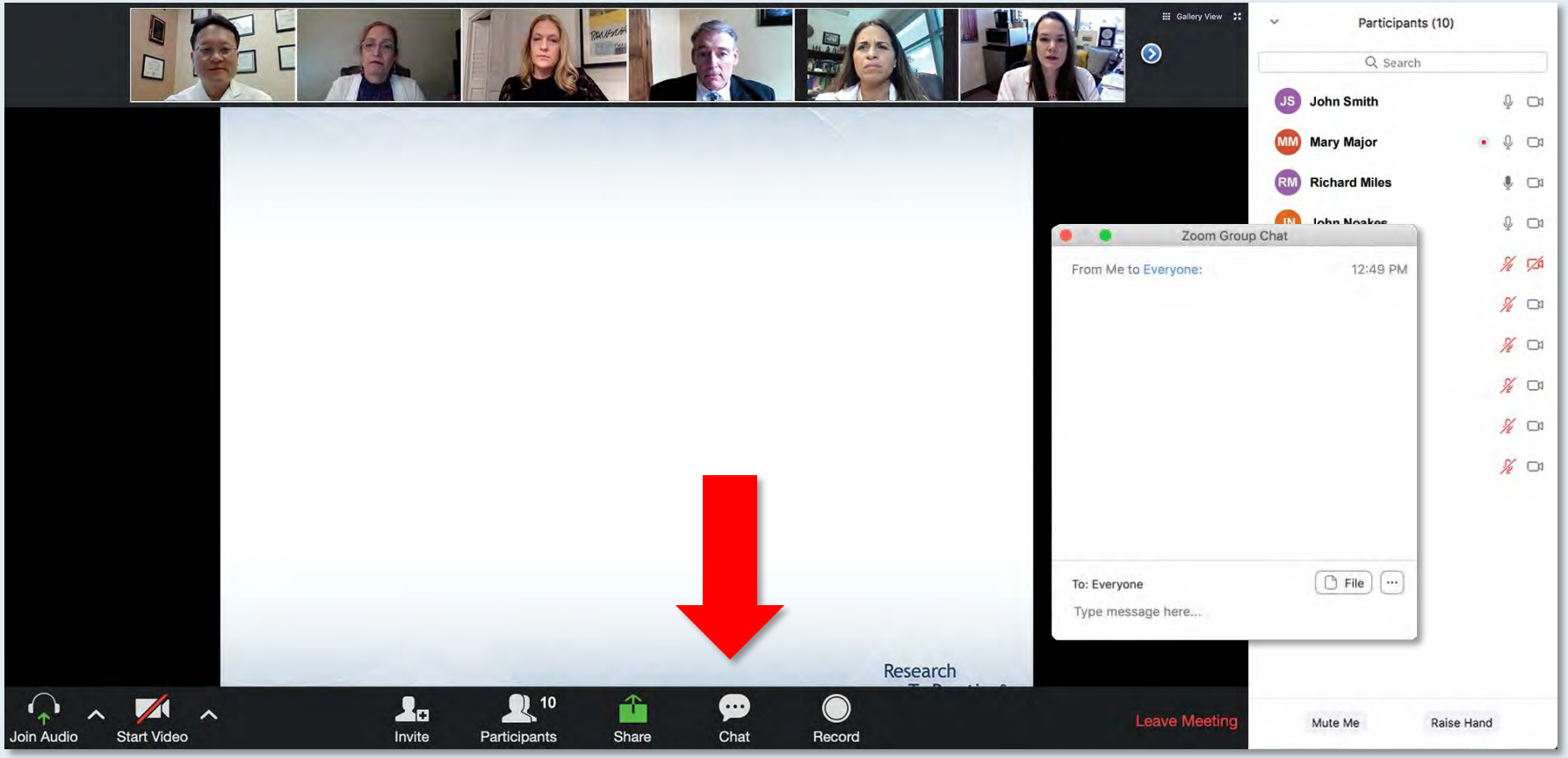

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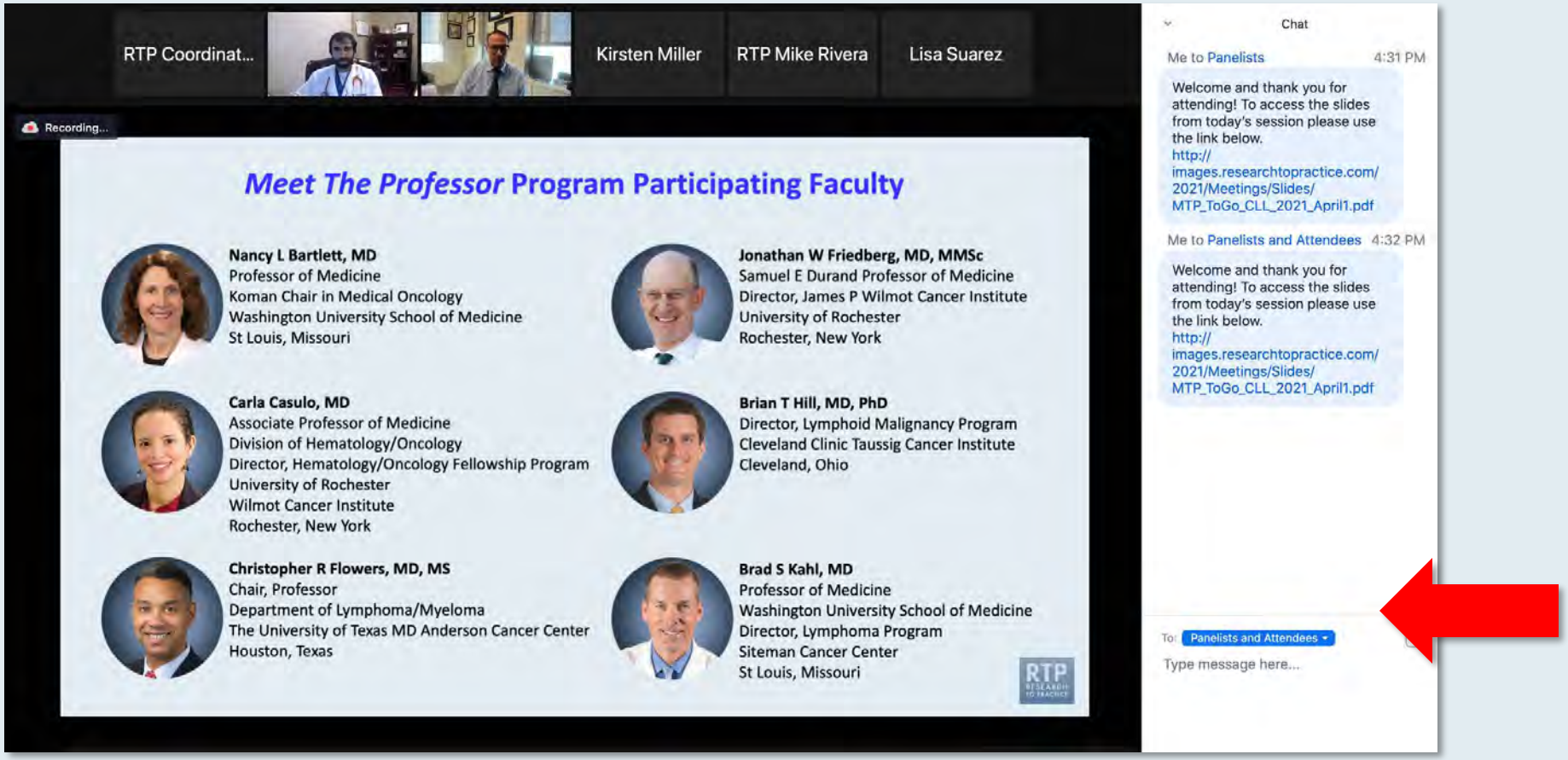

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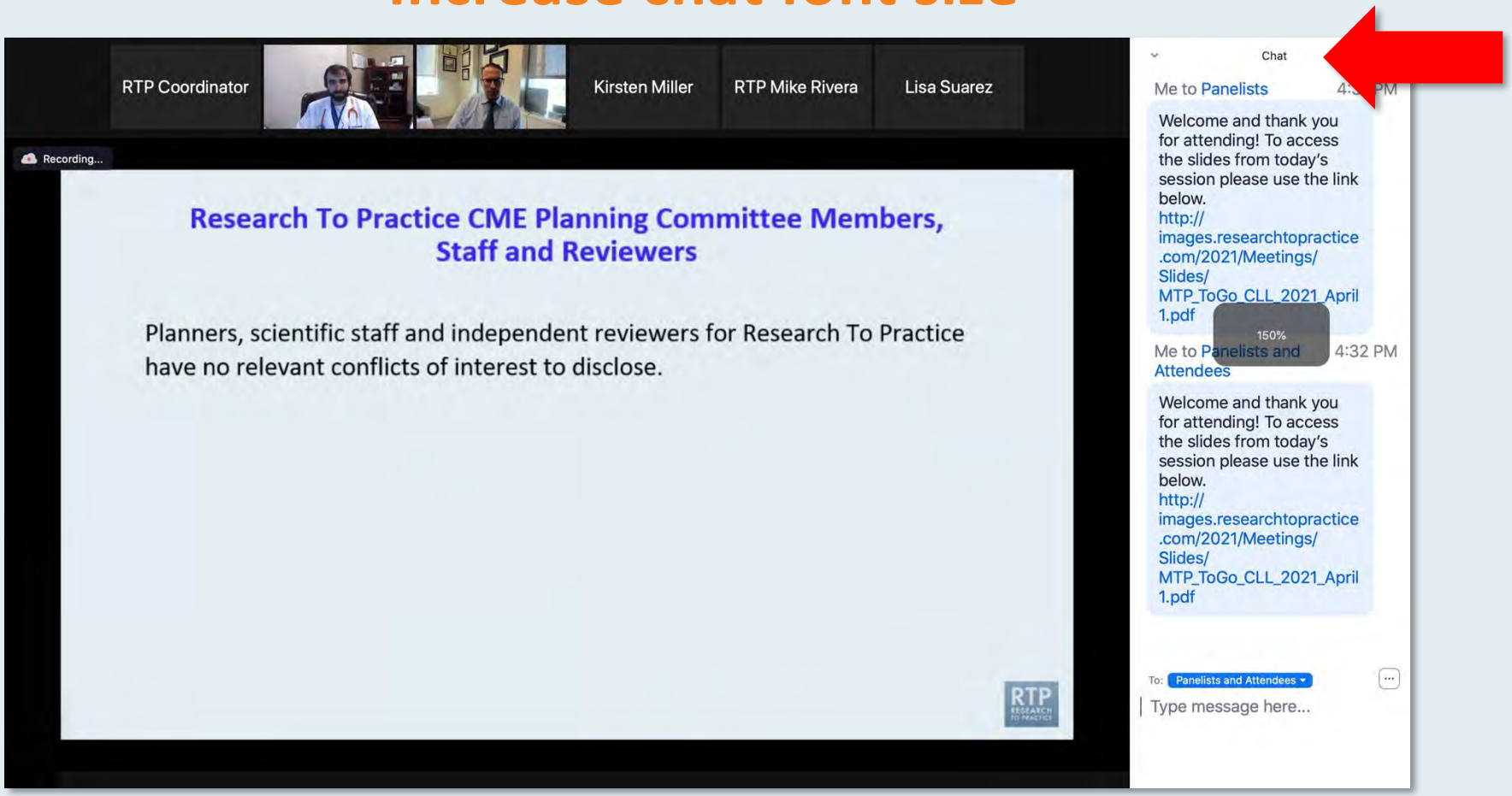

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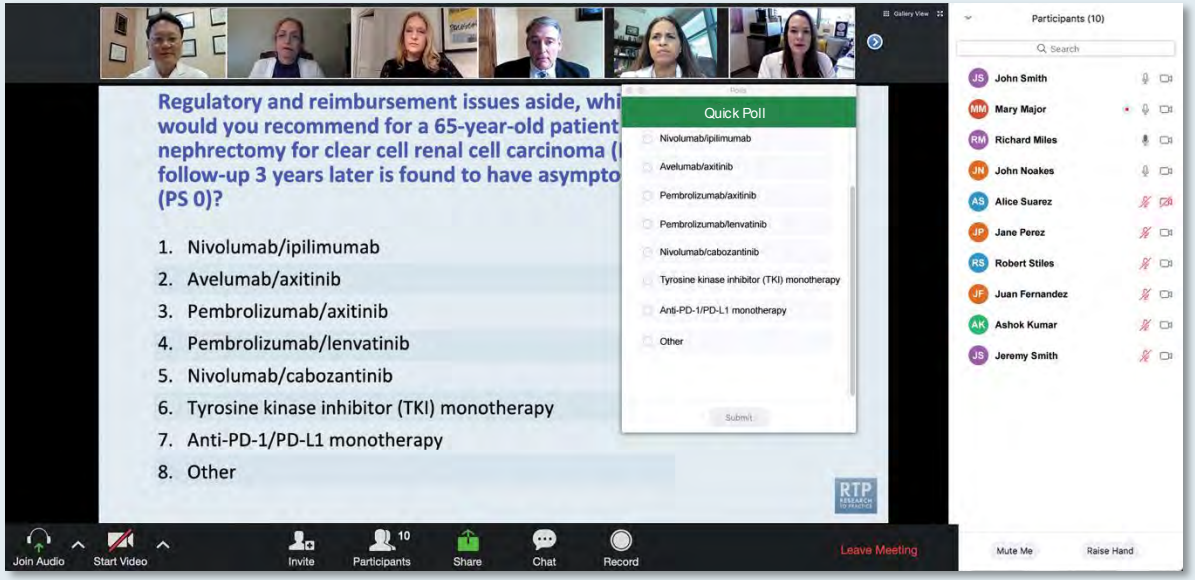

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Key Presentations on Chronic Lymphocytic Leukemia from Recent Major Conferences

DR BITA FAKHRI
STANFORD UNIVERSITY

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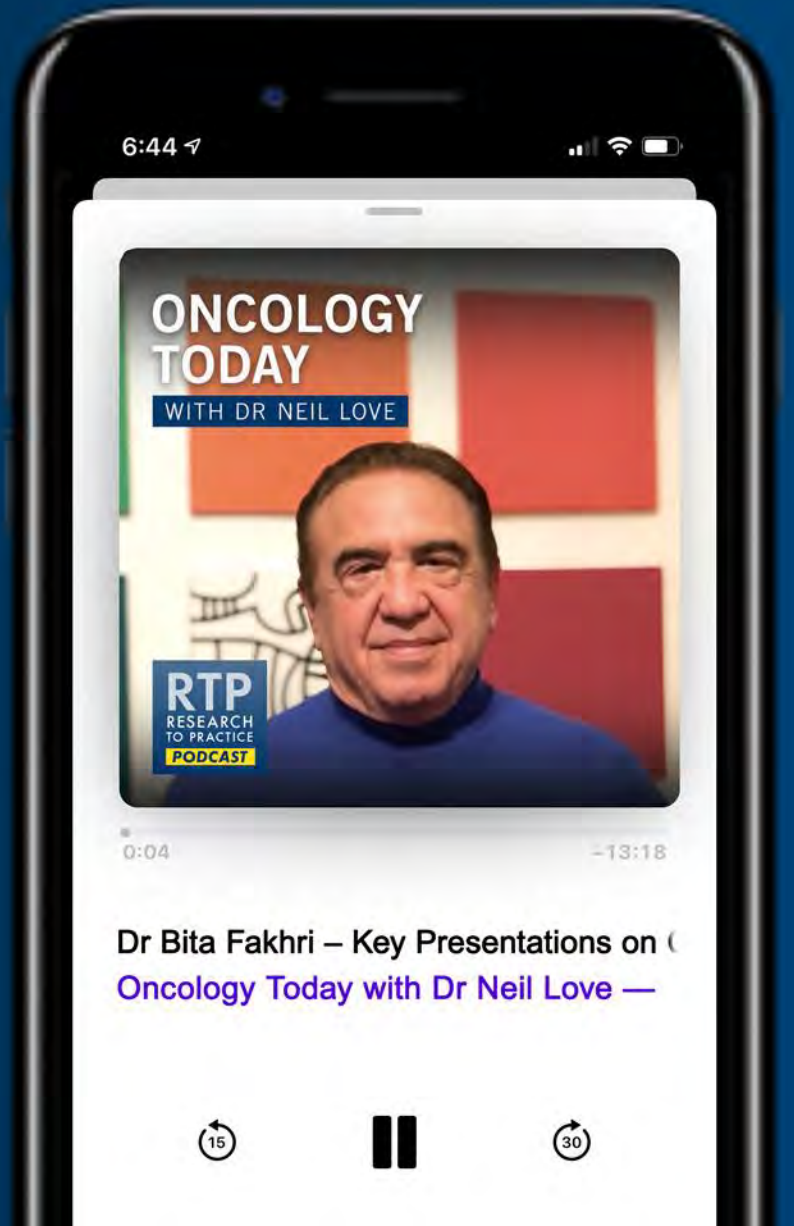

Practical Perspectives: Optimizing Diagnosis and Treatment for Patients with Desmoid Tumors

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Tuesday, September 24, 2024
5:00 PM – 6:00 PM ET

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Mrinal Gounder, MD

Moderator

Neil Love, MD

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Kevin Kalinsky, MD, MS

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Data + Perspectives: Clinical Investigators Explore the Application of Recent Datasets in Current Oncology Care

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Joshua K Sabari, MD

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Fontainebleau Hotel, Miami Beach, Florida

Moderated by Neil Love, MD

Thank you for joining us!

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MODERATOR
Neil Love, MD
Research To Practice
Miami, Florida

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Contributing Faculty

Catherine C Coombs, MD
Associate Clinical Professor
Division of Hematology/Oncology
Department of Medicine
UCI Health
Orange County, California

Adam Kittai, MD
Associate Professor
Division of Hematology and Medical Oncology
Assistant Director of Lymphoma Clinical Research
CLL Clinical Research Leader
Icahn School of Medicine at Mount Sinai Hospital
New York, New York

Nicole Lamanna, MD
Judy Horrigan Professor of Medicine
Director of the Chronic Lymphocytic Leukemia Program
Leukemia Service, Hematologic Malignancies Section
Herbert Irving Comprehensive Cancer Center
NewYork-Presbyterian/Columbia University
Medical Center
New York, New York

Chaitra Ujjani, MD
Clinical Director of Lymphoma
Fred Hutchinson Cancer Center
Clinical Professor
University of Washington
Seattle, Washington

Jennifer Woyach, MD
Professor
Division of Hematology
Department of Internal Medicine
The Ohio State University Comprehensive
Cancer Center
Columbus, Ohio

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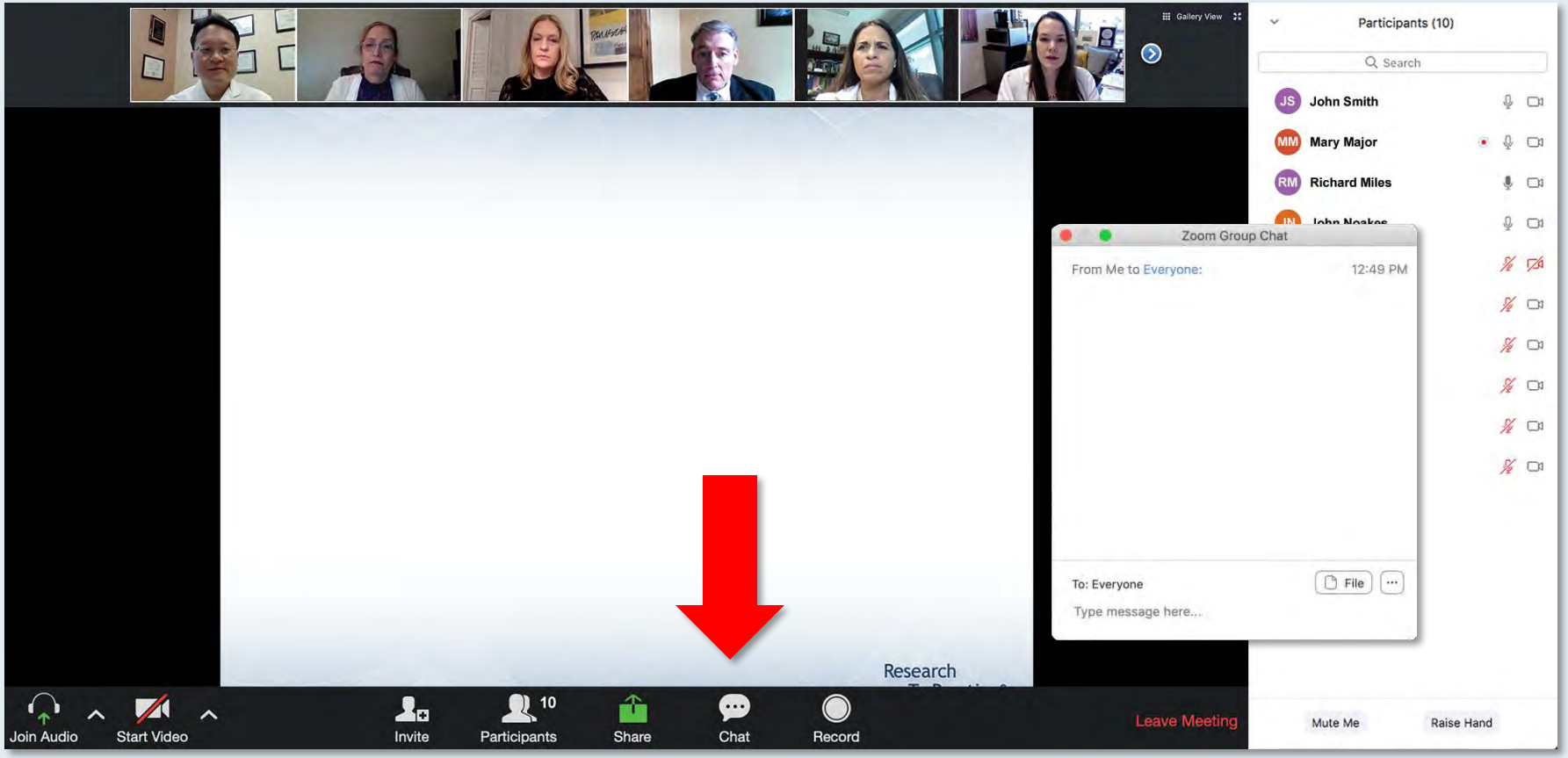

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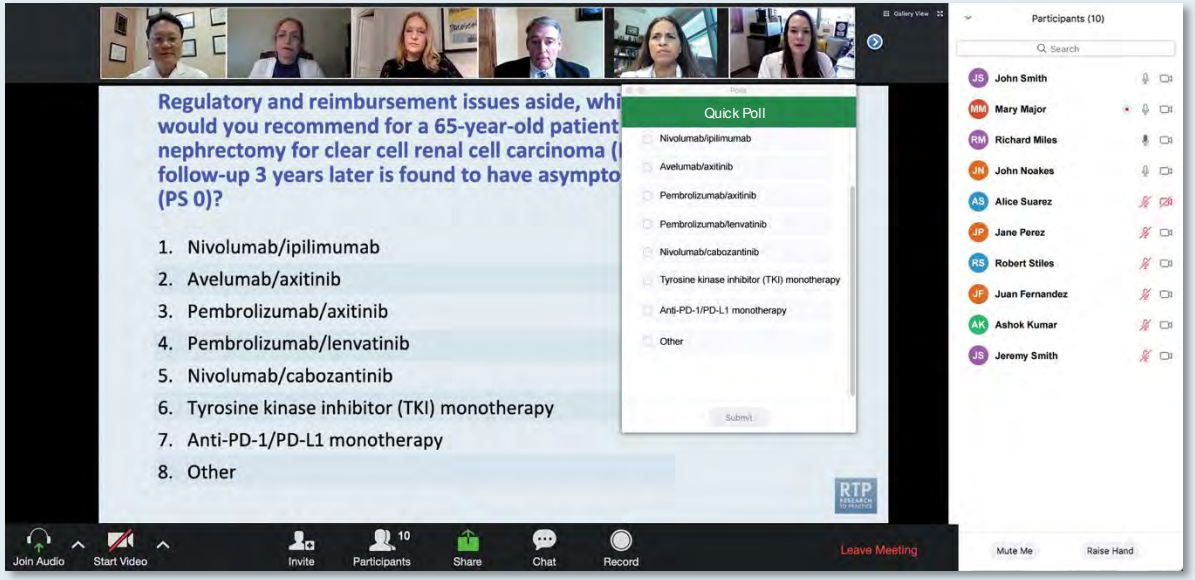

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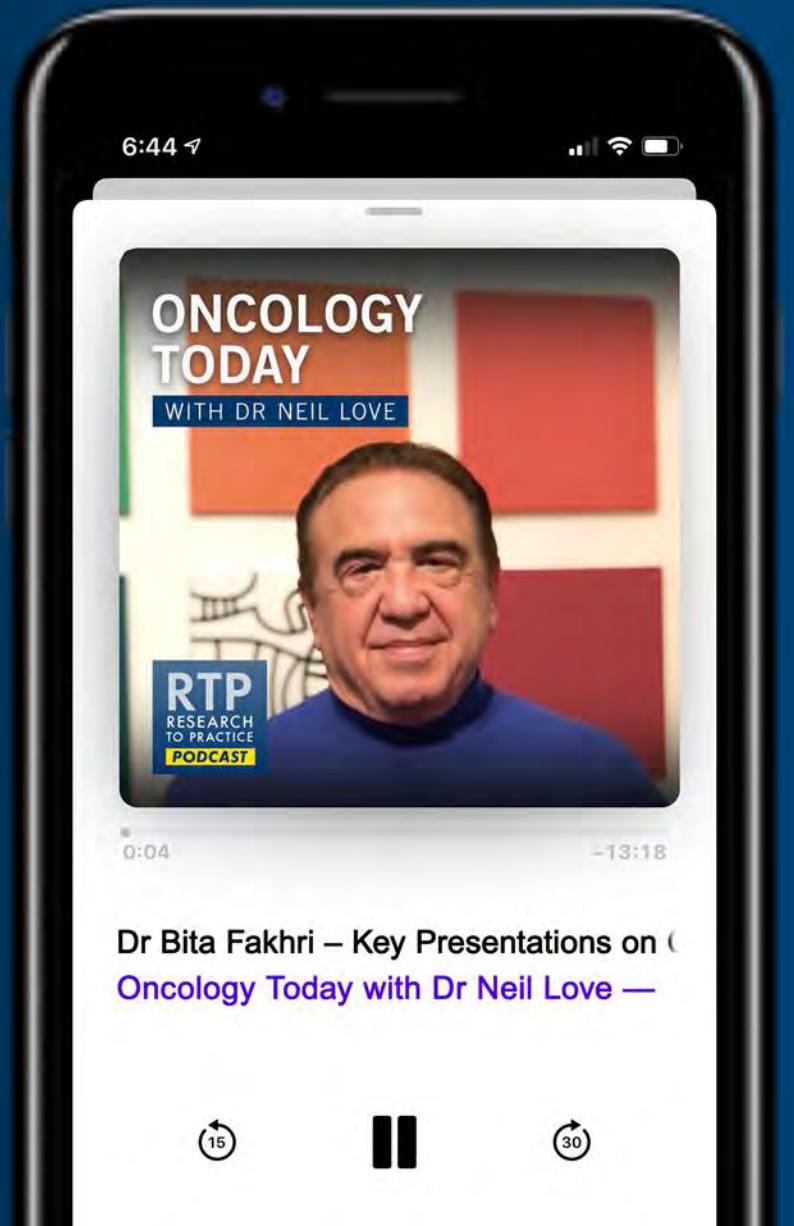

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Boca Raton, Florida

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

Bhavana (Tina) Bhatnagar, DO
WVU Cancer Institute
Wheeling, West Virginia

Erik Rupard, MD
Intermountain Health
St George, Utah

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Meet The Professor with Dr Davids

Introduction: Is CLL the New CML? Cases We Didn't Hear About Last Week

Module 1: Case Presentations

Module 2: Transformed CLL; CAR T-Cell Therapy

Module 3: Journal Club with Dr Davids

Module 4: Appendix

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Hagop M Kantarjian, MD

MD Anderson Cancer Center

Houston, Texas

RTP
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Practical Perspectives: Current Management of Chronic Myeloid Leukemia

Friday, August 30, 2024
12:00 PM – 2:15 PM ET

Faculty

Jorge Cortes, MD
Michael J Mauro, MD
Neil P Shah, MD, PhD

Case Presenters

Bhavana (Tina) Bhatnagar, DO
Amanda Blackmon, DO, MS

Moderator

Neil Love, MD

RTP RESEARCH TO PRACTICE

Questions and Comments: Integrating pirtobrutinib and CAR T-cell therapy into the CLL treatment algorithm

Dr Tina Bhatnagar (Wheeling, West Virginia)

Which third-line therapy would you generally prefer for a patient with double-refractory CLL?

 Dr Coombs	Pirtobrutinib
 Dr Davids	Pirtobrutinib
 Dr Kittai	Pirtobrutinib
 Dr Lamanna	Pirtobrutinib
 Dr Ujjani	Lisocabtagene maraleucel
 Dr Woyach	Pirtobrutinib

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

	Efficacy	Tolerability/toxicity
 Dr Coombs	There are not enough available data at this time	Pirtobrutinib has the least toxicity
 Dr Davids	About the same	Pirtobrutinib has the least toxicity
 Dr Kittai	There are not enough available data at this time	There are not enough available data at this time
 Dr Lamanna	There are not enough available data at this time	Pirtobrutinib has the least toxicity
 Dr Ujjani	There are not enough available data at this time	Pirtobrutinib has the least toxicity
 Dr Woyach	There are not enough available data at this time	Pirtobrutinib has the least toxicity

To approximately how many patients with CLL have you adminstered pirtobrutinib on or off protocol? Please describe the last patient with CLL to whom you administered pirtobrutinib.

	No. of patients	Most recent patient			
		Age	Response	Tolerance	Prior BTKi
 Dr Coombs	15	78	PR	Well tolerated	Ibrutinib
 Dr Davids	15	68	PR for 15 mo before PD	Very well tolerated	Ibrutinib
 Dr Kittai	5	77	Currently in PR	Well tolerated	Ibrutinib, acalabrutinib
 Dr Lamanna	>30	70s	PR	Well tolerated	None
 Dr Ujjani	5	80	PR	Well tolerated	Zanubrutinib
 Dr Woyach	60	68	PR	Very well tolerated	Ibrutinib

PR = partial response; PD = progression of disease

FDA Grants Accelerated Approval to Pirtobrutinib for CLL or Small Lymphocytic Lymphoma (SLL)

Press Release: December 1, 2023

"... the Food and Drug Administration granted accelerated approval to pirtobrutinib for adults with chronic lymphocytic leukemia or small lymphocytic lymphoma (CLL/SLL) who have received at least two prior lines of therapy, including a BTK inhibitor and a BCL-2 inhibitor.

Efficacy was evaluated in BRUIN (NCT03740529], an open-label, international, single-arm, multicohort trial that included 108 patients with CLL or SLL previously treated with at least two prior lines of therapy, including a BTK inhibitor and a BCL-2 inhibitor.

Pirtobrutinib was administered orally at 200 mg once daily and was continued until disease progression or unacceptable toxicity.

The main efficacy outcome measures were overall response rate (ORR) and duration of response (DOR), as assessed by an independent review committee using 2018 iwCLL criteria."

https://www.fda.gov/drugs/resources-information-approved-drugs/fda-grants-accelerated-approval-pirtobrutinib-chronic-lymphocytic-leukemia-and-small-lymphocytic.

The NEW ENGLAND JOURNAL of MEDICINE

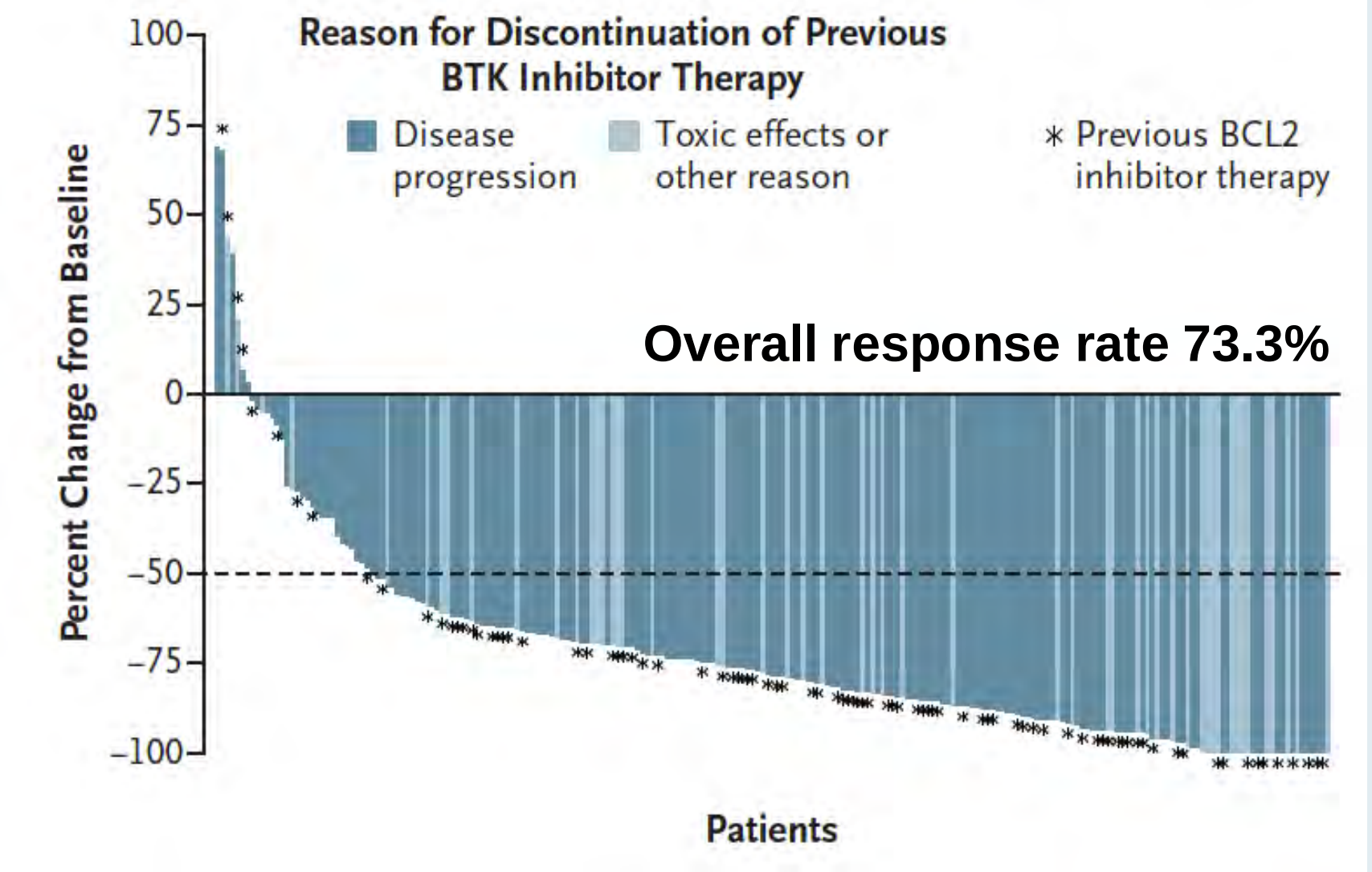
ORIGINAL ARTICLE

Pirtobrutinib after a Covalent BTK Inhibitor in Chronic Lymphocytic Leukemia

A.R. Mato, J.A. Woyach, J.R. Brown, P. Ghia, K. Patel, T.A. Eyre, T. Munir, E. Lech-Maranda, N. Lamanna, C.S. Tam, N.N. Shah, C.C. Coombs, C.S. Ujjani, B. Fakhri, C.Y. Cheah, M.R. Patel, A.J. Alencar, J.B. Cohen, J.N. Gerson, I.W. Flinn, S. Ma, D. Jagadeesh, J.M. Rhodes, F. Hernandez-Ilizaliturri, P.L. Zinzani, J.F. Seymour, M. Balbas, B. Nair, P. Abada, C. Wang, A.S. Ruppert, D. Wang, D.E. Tsai, W.G. Wierda, and W. Jurczak

2023;389:33-44.

BRUIN: Pirtobrutinib Efficacy in Patients with CLL or SLL Who Received Prior BTK Inhibitor Treatment



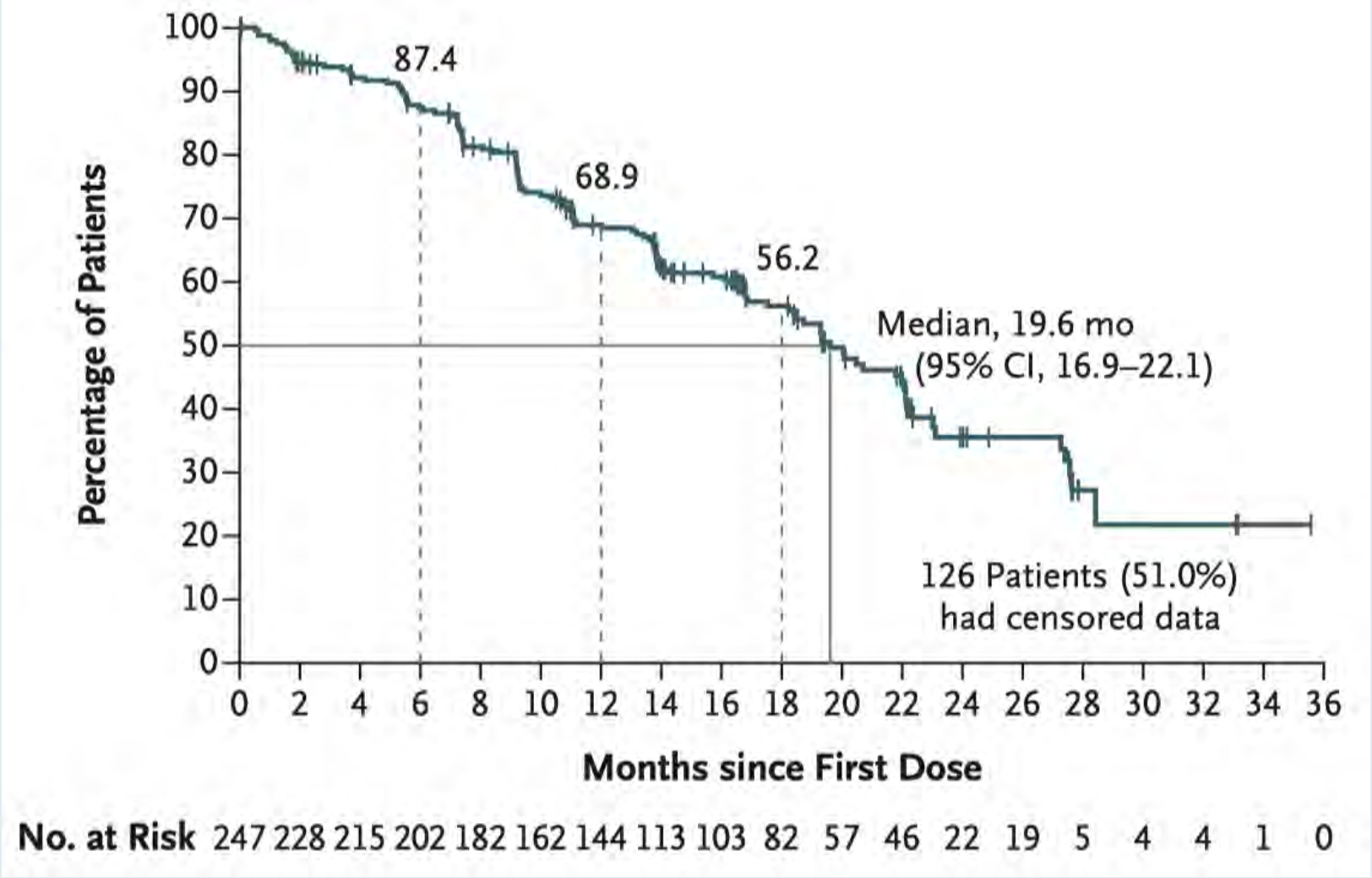
Mato et al. *N Engl J Med* 2023;389:33-44.

BRUIN: Responses

Variable	Previous BTK Inhibitor (N=247)	Previous BTK Inhibitor + BCL2 Inhibitor (N=100)
Overall response — % (95% CI)		
Including complete response, nodular partial response, or partial response	73.3 (67.3–78.7)	70.0 (60.0–78.8)
Including complete response, nodular partial response, partial response, or partial response with lymphocytosis	82.2 (76.8–86.7)	79.0 (69.7–86.5)
Best response — no. (%)		
Complete response	4 (1.6)	0
Nodular partial response	1 (0.4)	0
Partial response	176 (71.3)	70 (70.0)
Partial response with lymphocytosis	22 (8.9)	9 (9.0)
Stable disease	26 (10.5)	11 (11.0)

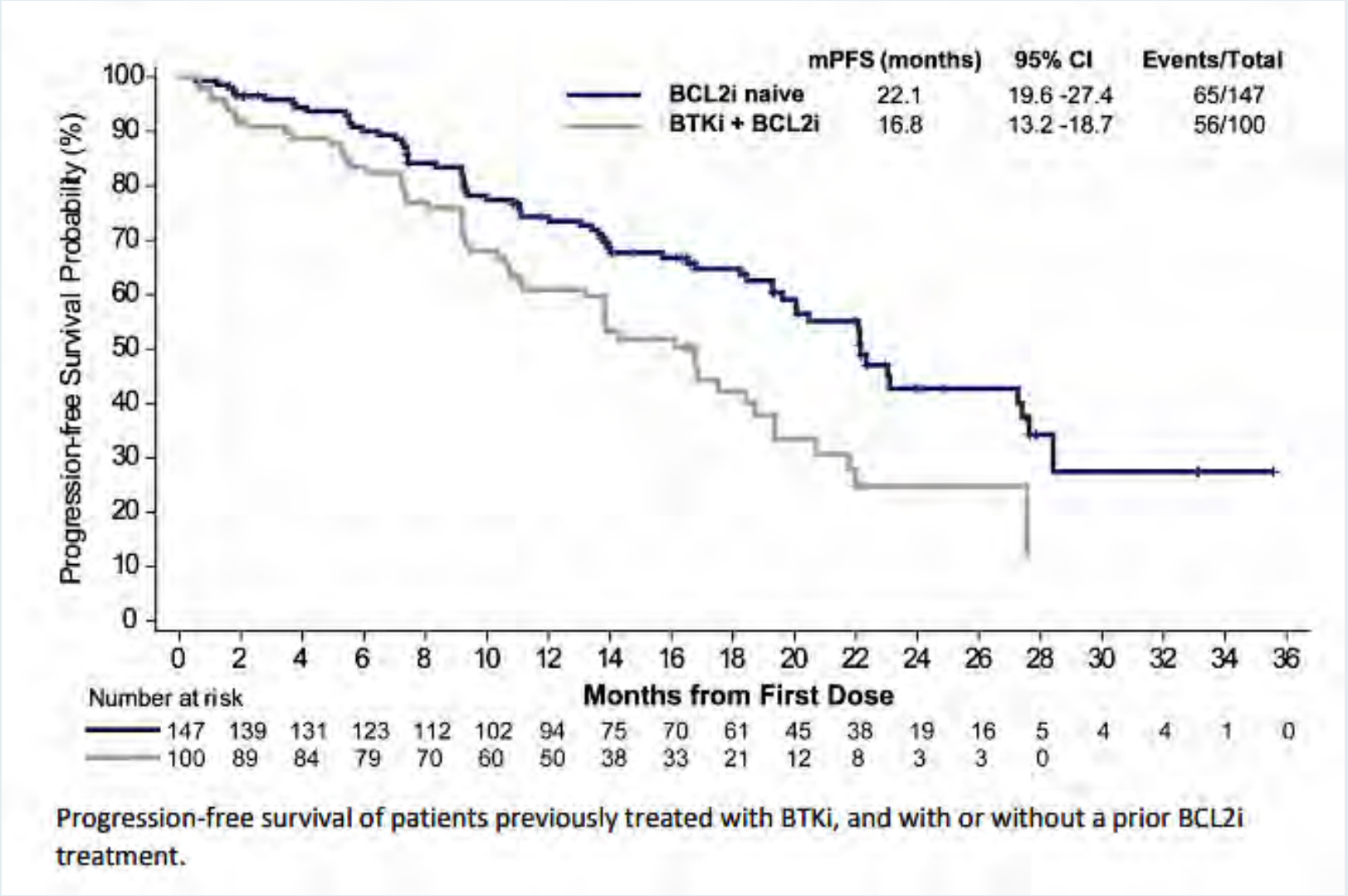
Mato et al. *N Engl J Med* 2023;389:33-44.

BRUIN: Progression-Free Survival in Overall Population



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

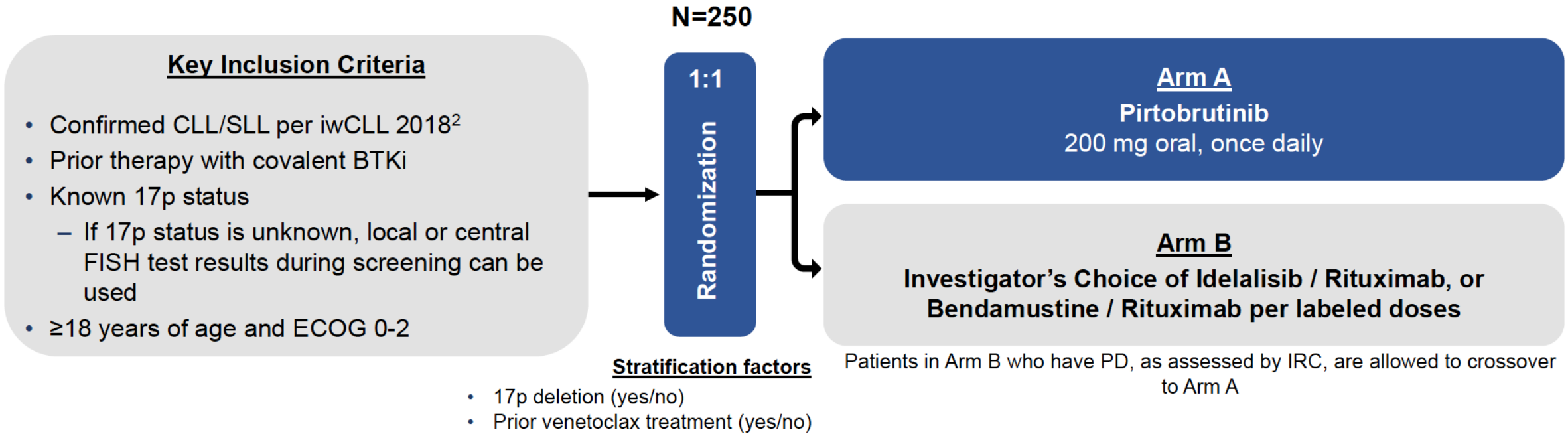
BRUIN: Progression-Free Survival in Patients Previously Treated with a BTK Inhibitor with or without a Prior Bcl-2 Inhibitor



Progression-free survival of patients previously treated with BTKi, and with or without a prior BCL2i treatment.

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

BRUIN CLL-321: An Ongoing Phase III Trial of Pirtobrutinib Monotherapy for Relapsed/Refractory CLL



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

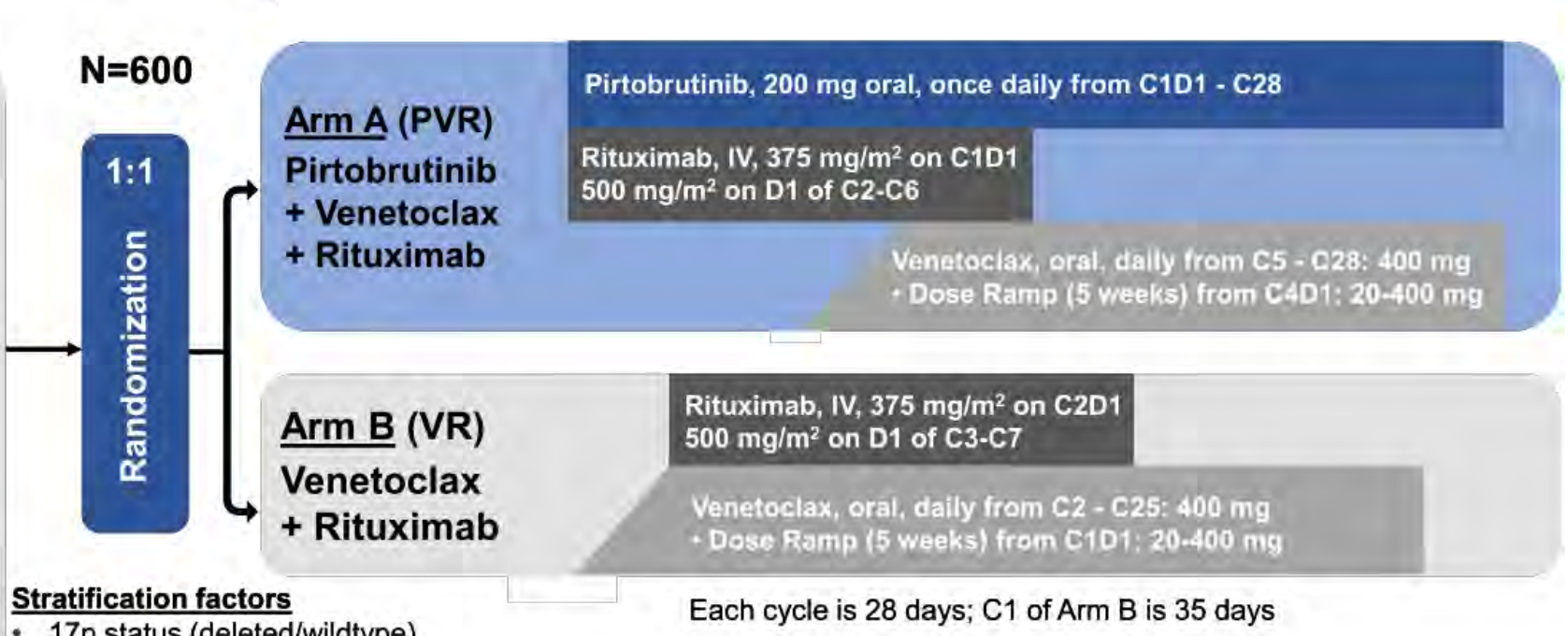
iwCLL = International Workshop on Chronic Lymphocytic Leukemia; IRC = independent review committee; FISH = fluorescence in situ hybridization; ECOG = Eastern Cooperative Oncology Group; PD = disease progression

Follows G et al. ASCO 2023;Abstract TPS7582. Hill M et al. SOHO 2022;Abstract CLL-114.

BRUIN CLL-322: An Ongoing Phase III Trial of Pirtobrutinib and Venetoclax/Rituximab for Relapsed/Refractory CLL

Key Inclusion Criteria

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



Stratification factors

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

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

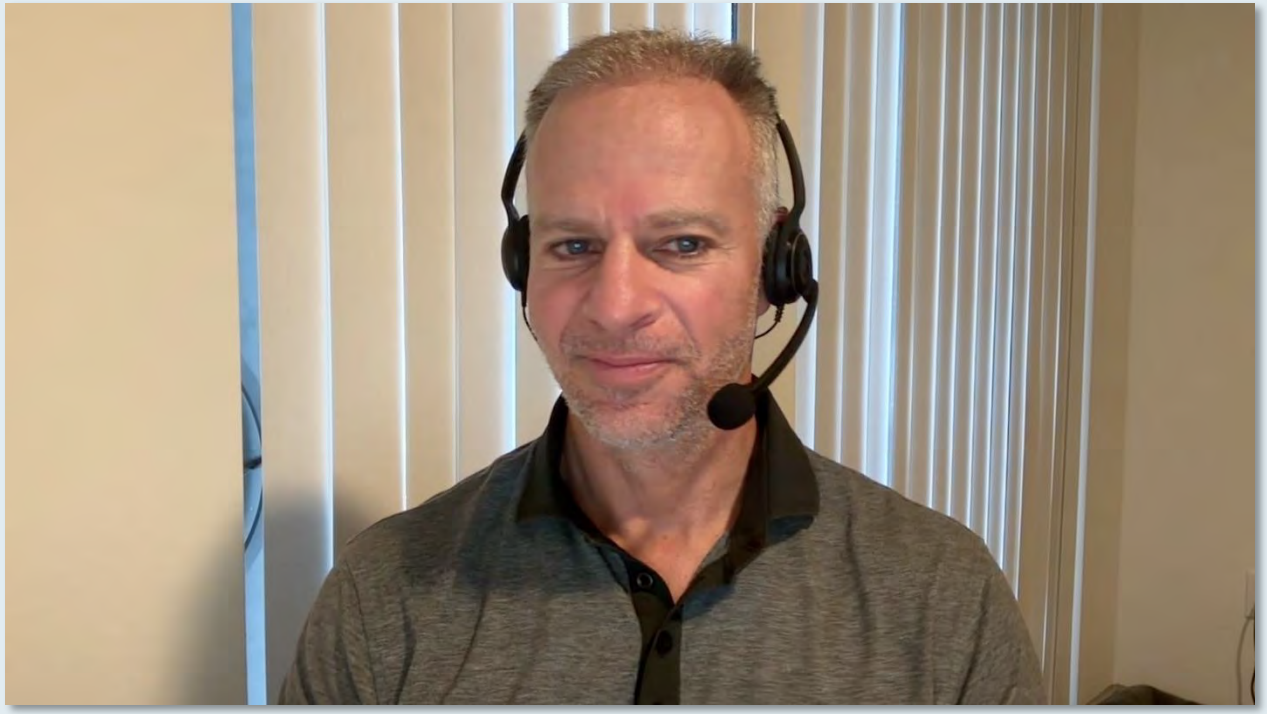
Eyre TA et al. ASCO 2023;Abstract TPS7583. Wierda WG et al. SOHO 2022;Abstract CLL-322.

Meet The Professor with Dr Davids

Module 1: Case Presentations

- Dr Brenner: A 70-year-old man with IGHV-unmutated CLL (trisomy 12, del[17p]) receives ibrutinib for several years and is switched to acalabrutinib to lower the risk of cardiotoxicity
- Dr Bhatnagar: A 76-year-old man with relapsed atypical del(17p) CLL who previously received ibrutinib receives venetoclax/obinutuzumab
- Dr Rupard: An 83-year-old woman with IGHV-mutated CLL begins treatment with zanubrutinib and 6 months later develops altered mental status due to cryptococcal meningitis
- Dr Bachow: An 82-year-old woman with relapsed CLL (del[17p]/TP53 mutation) develops Stevens-Johnson syndrome while receiving ibrutinib
- Dr Brenner: An 85-year-old woman with rising WBC counts and asymptomatic recurrence of CLL (trisomy 12) receives rituximab with subsequent addition of venetoclax
- Dr Rupard: A 94-year-old man with del(13q) CLL under observation for 12 years begins treatment with zanubrutinib and develops significant bruising/ecchymosis
- Dr Bhatnagar: A 79-year-old woman with relapsed del(13q) CLL receives acalabrutinib and develops hyperleukocytosis

Case Presentation: A 70-year-old man with IGHV-unmutated CLL (trisomy 12, del[17p]) receives ibrutinib for several years and is switched to acalabrutinib to lower the risk of cardiotoxicity



Dr Warren Brenner (Boca Raton, Florida)

Regulatory and reimbursement issues aside, what would be your preferred initial regimen for a 70-year-old patient with IGHV-unmutated CLL who requires treatment and has the mutation status described below?

	Without del(17p) or TP53 mutation	With del(17p) or TP53 mutation
 Dr Coombs	Venetoclax + obinutuzumab	Zanubrutinib
 Dr Davids	Venetoclax + obinutuzumab	Zanubrutinib
 Dr Kittai	Acalabrutinib	Acalabrutinib
 Dr Lamanna	Acalabrutinib or zanubrutinib or venetoclax/obinutuzumab	Acalabrutinib or zanubrutinib
 Dr Ujjani	Venetoclax + obinutuzumab	Zanubrutinib
 Dr Woyach	Venetoclax + obinutuzumab	Acalabrutinib or zanubrutinib

Regulatory and reimbursement issues aside, what would be your preferred initial regimen for a 70-year-old patient with IGHV-mutated CLL who requires treatment and has the mutation status described below?

	Without del(17p) or TP53 mutation	With del(17p) or TP53 mutation
 Dr Coombs	Venetoclax + obinutuzumab	Zanubrutinib
 Dr Davids	Venetoclax + obinutuzumab	Venetoclax + obinutuzumab
 Dr Kittai	Venetoclax + obinutuzumab	Acalabrutinib
 Dr Lamanna	Acalabrutinib or zanubrutinib or venetoclax/obinutuzumab	Acalabrutinib or zanubrutinib
 Dr Ujjani	Venetoclax + obinutuzumab	Zanubrutinib
 Dr Woyach	Venetoclax + obinutuzumab	Acalabrutinib or zanubrutinib

Approximately what proportion of your patients would prefer to receive continuous therapy with a BTK inhibitor?

	Younger patients (eg, age 60)	Older patients (eg, age 80)
 Dr Coombs	30%	80%
 Dr Davids	10%	80%
 Dr Kittai	20%	80%
 Dr Lamanna	20%	60%
 Dr Ujjani	10%	25%
 Dr Woyach	20%	60%

Case Presentation: A 76-year-old man with relapsed atypical del(17p) CLL who previously received ibrutinib receives venetoclax/obinutuzumab

Dr Tina Bhatnagar (Wheeling, West Virginia)

RTP RESEARCH TO PRACTICE

Regulatory and reimbursement issues aside, have you administered or would you administer the regimens below as first-line treatment for a patient with CLL?

	BTKi + venetoclax	BTKi + venetoclax + anti-CD20 antibody
 Dr Coombs	I have	I have not but would for the right patient
 Dr Davids	I have	I have not and would not
 Dr Kittai	I have not but would for the right patient	I have not and would not
 Dr Lamanna	I have	I have not and would not
 Dr Ujjani	I have	I have not and would not
 Dr Woyach	I have not but would for the right patient	I have not and would not

BTKi = BTK inhibitor

AMPLIFY: An Ongoing Phase III Trial of Fixed-Duration Acalabrutinib and Venetoclax with or without Obinutuzumab for Previously Untreated CLL without Del(17p) or TP53 Mutation

Trial identifier: NCT03836261 (active, not recruiting)
Estimated enrollment: 984

Eligibility

- Diagnosis of CLL requiring active treatment
- ECOG PS 0-2
- No detected del(17p) or TP53 mutation
- No prior CLL-specific therapies

R

Acalabrutinib + venetoclax

Acalabrutinib + venetoclax + obinutuzumab

Investigator choice of FCR or bendamustine/rituximab

FCR = fludarabine, cyclophosphamide and rituximab

Primary endpoint: Progression-free survival by independent central review

www.clinicaltrials.gov. Accessed August 2024.

Positive High-Level Results from the Phase III AMPLIFY Trial Announced

Press Release: July 29, 2024

"Positive high-level results from an interim analysis of the AMPLIFY Phase III trial showed a fixed duration of acalabrutinib in combination with venetoclax, with or without obinutuzumab, demonstrated a statistically significant and clinically meaningful improvement in progression-free survival (PFS) compared to standard-of-care chemoimmunotherapy in previously untreated adult patients with chronic lymphocytic leukemia (CLL).

For the secondary endpoint of overall survival (OS), a trend was observed in favour of acalabrutinib in combination with venetoclax, with or without obinutuzumab, versus standard-of-care chemoimmunotherapy. The OS data were not mature at the time of this analysis and the trial will continue to assess OS as a key secondary endpoint.

The safety and tolerability were consistent with the known safety profile of each medicine. No new safety signals were identified, with low rates of cardiac toxicity observed. The data will be presented at a forthcoming medical meeting and shared with global regulatory authorities."

https://www.astrazeneca.com/media-centre/press-releases/2024/calquence-fixed-duration-combo-improved-1l-cll-pfs.html

At what point in the treatment course are you referring patients with multiregimen-relapsed CLL for consultation regarding chimeric antigen receptor (CAR) T-cell therapy?

 Dr Coombs	At third relapse
 Dr Davids	After third relapse
 Dr Kittai	At or after third relapse
 Dr Lamanna	At or after third relapse (depending on patient comorbidities and discussions with patient)
 Dr Ujjani	At third relapse
 Dr Woyach	At second relapse

Case Presentation: An 83-year-old woman with IGHV-mutated CLL begins treatment with zanubrutinib and 6 months later develops altered mental status due to cryptococcal meningitis

Dr Erik Rupard (St George, Utah)

When you are going to administer a BTK inhibitor as initial treatment for a patient with CLL, which would you generally prefer?

 Dr Coombs	Zanubrutinib
 Dr Davids	Acalabrutinib
 Dr Kittai	Acalabrutinib
 Dr Lamanna	Acalabrutinib or zanubrutinib
 Dr Ujjani	Zanubrutinib
 Dr Woyach	Acalabrutinib or zanubrutinib

RTP
RESEARCH TO PRACTICE

Based on current clinical trial data and/or your personal experience, how would you compare the global efficacy and tolerability/toxicity of ibrutinib, acalabrutinib and zanubrutinib for patients with newly diagnosed CLL?

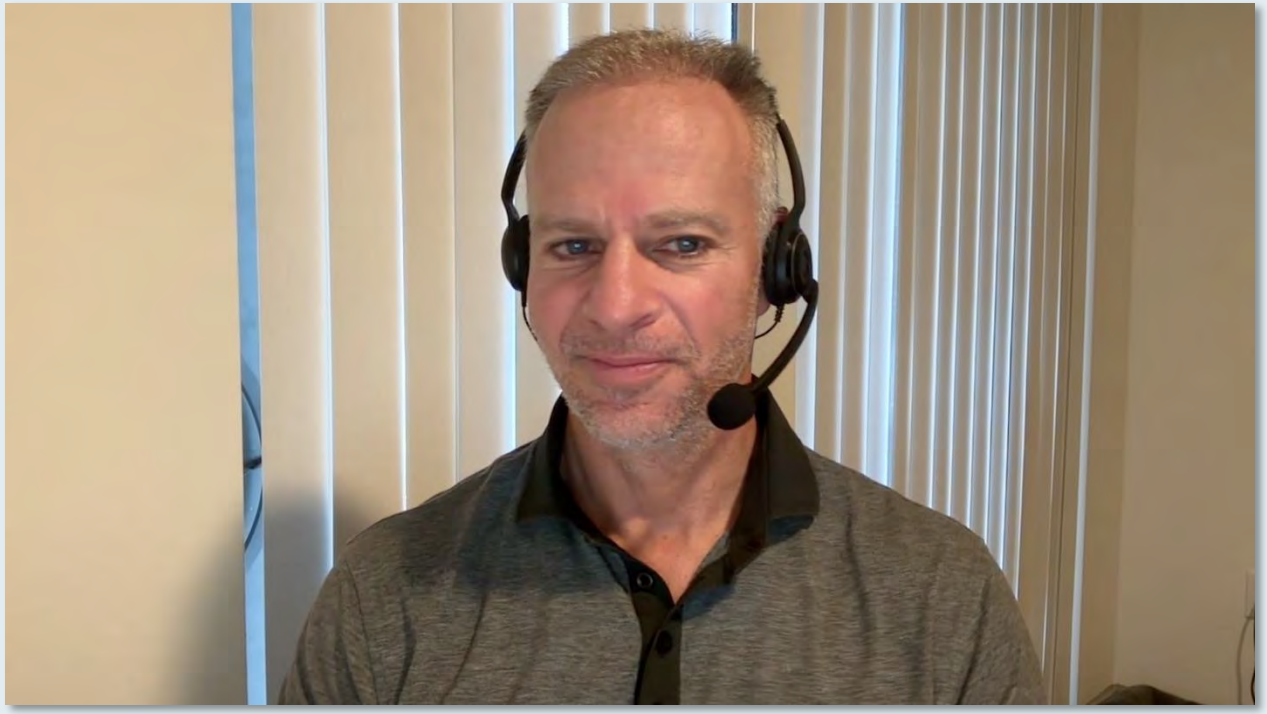
	Efficacy	Tolerability/toxicity
 Dr Coombs	About the same	Acalabrutinib has the least toxicity
 Dr Davids	Zanubrutinib is the most efficacious	Acalabrutinib has the least toxicity
 Dr Kittai	About the same	Acalabrutinib has the least toxicity
 Dr Lamanna	About the same	Toxicity profiles differ*
 Dr Ujjani	There are not enough available data at this time	Zanubrutinib has the least toxicity
 Dr Woyach	About the same	Acalabrutinib has the least toxicity

*Bruising is similar among all 3. Less cardiac toxicity with acalabrutinib and zanubrutinib. More headache with acalabrutinib, more myelosuppression with zanubrutinib

Case Presentation: An 82-year-old woman with relapsed CLL (del[17p]/TP53 mutation) develops Stevens-Johnson syndrome while receiving ibrutinib

Dr Spencer Bachow (Boca Raton, Florida)

Case Presentation: An 85-year-old woman with rising white blood cell counts and asymptomatic recurrence of CLL (trisomy 12) receives rituximab with subsequent addition of venetoclax



Dr Warren Brenner (Boca Raton, Florida)

RTP
RESEARCH TO PRACTICE

Case Presentation: A 94-year-old man with del(13q) CLL under observation for 12 years begins treatment with zanubrutinib and develops significant bruising/ecchymosis

Dr Erik Rupard (St George, Utah)

Case Presentation: A 79-year-old woman with relapsed del(13q) CLL receives acalabrutinib and develops hyperleukocytosis

Dr Tina Bhatnagar (Wheeling, West Virginia)

3m ago | All Rows | Time Mark

	2023 5/26/23 06:55	5/10/23 13:27	5/8/23 07:21	5/4/23 07:34	5/1/23 07:32	4/27/23 07:47	4/24/23 09:04
CBC							
WBC	344.8 ↑↑	15.1 ↑	26.5 ↑↑	23.7 ↑	32.1 ↑↑	24.9 ↑	29.0 ↑↑
HGB	6.6 ↓↓	8.3 ↓	8.4 ↓	9.1 ↓	8.8 ↓	8.6 ↓	8.7 ↓
HCT	21.4 ↓	25.6 ↓	24.6 ↓	26.7 ↓	26.3 ↓	25.2 ↓	25.9 ↓
PLATELET COUNT	22 ↓↓	27 ↓↓	32 ↓↓	34 ↓↓	31 ↓↓	31 ↓↓	31 ↓↓
RBC	1.99 ↓	2.41 ↓ 2.41 ↓	2.36 ↓	2.56 ↓	2.52 ↓	2.44 ↓	2.48 ↓
MCV	107.5 ↑	106.2 ↑	104.4 ↑	104.2 ↑	104.4 ↑	103.2 ↑	104.2 ↑
MCHC	31.0 ↓	32.6	34.1	34.0	33.6	34.0	33.7
MCH	33.3 ↑	34.6 ↑	35.5 ↑	35.4 ↑	35.1 ↑	35.1 ↑	35.1 ↑
RDW	19.0 ↑	19.5 ↑	18.8 ↑	19.8 ↑	19.0 ↑	18.9 ↑	18.8 ↑
RETICULOCYTE COUNT %		2.924 ↑					
MPV		8.8					

Meet The Professor with Dr Davids

Introduction: Is CLL the New CML? Cases We Didn't Hear About Last Week

Module 1: Case Presentations

Module 2: Transformed CLL; CAR T-Cell Therapy

Module 3: Journal Club with Dr Davids

Module 4: Appendix

Questions and Comments: Care of patients with Richter's transformation

Dr Erik Rupard (St George, Utah)

Regulatory and reimbursement issues aside, what treatment would you recommend for a 75-year-old patient with IGHV-unmutated CLL and a TP53 mutation who developed Richter's transformation?

 Dr Coombs	R-CHOP + venetoclax
 Dr Davids	R-CHOP + venetoclax
 Dr Kittai	R-CHOP + venetoclax
 Dr Lamanna	Pirtobrutinib
 Dr Ujjani	R-CHOP
 Dr Woyach	R-CHOP + venetoclax

RTP RESEARCH TO PRACTICE

CLL IN FOCUS

Current Developments in the Management of Chronic Lymphocytic Leukemia

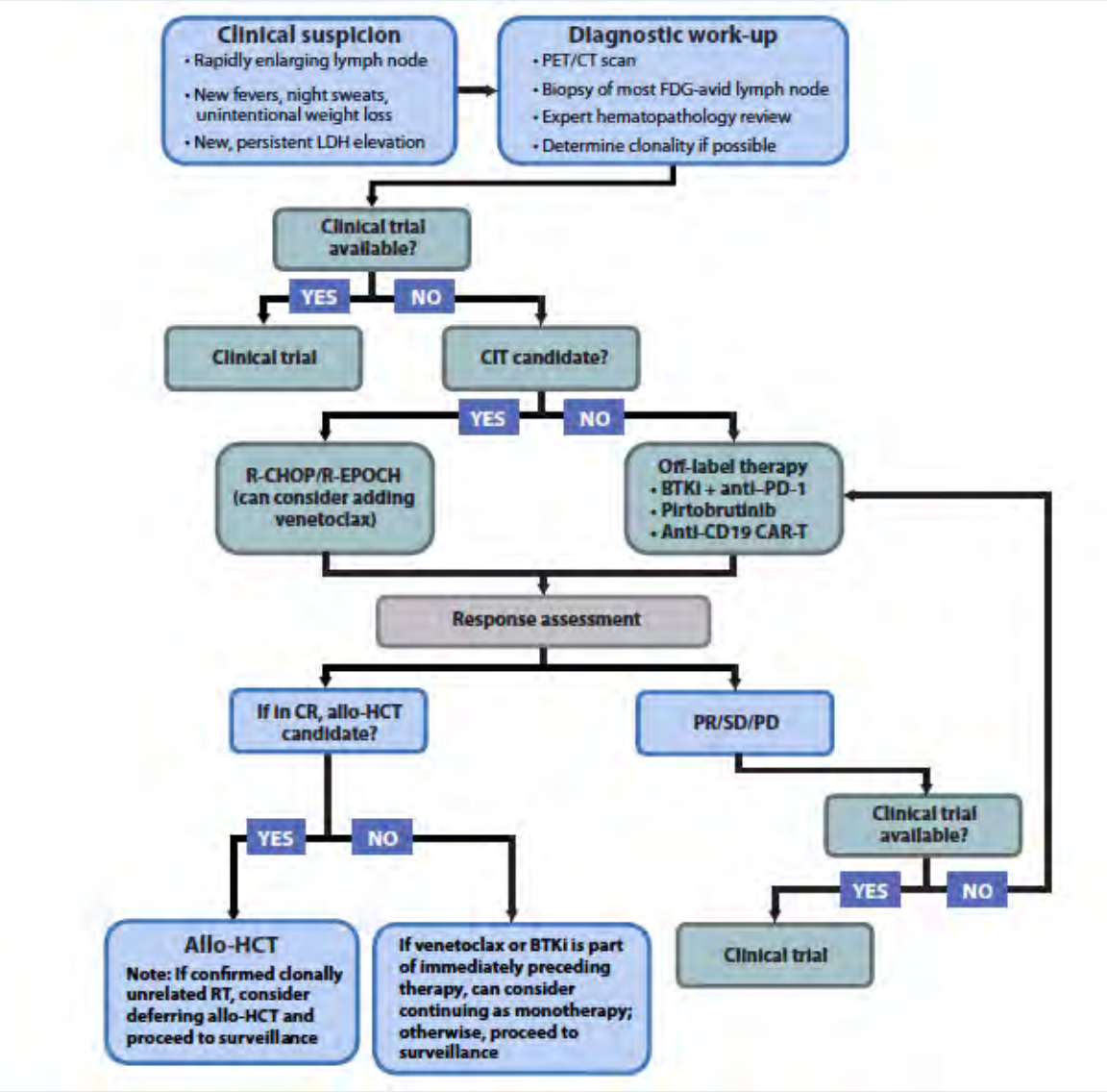
CLL

Management of Richter Transformation

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

***Clin Adv Hematol Oncol* 2023;21(8):449-51.**

Summary of the Practical Management of Richter's Transformation in 2023



Davids MS. *Clin Adv Hematol Oncol* 2023;21(8):449-51.

HEMATOLOGIC MALIGNANCIES

Practical Management of Richter Transformation in 2023 and Beyond

Christine E. Ryan, MD[1] and Matthew S. Davids, MD, MMSc[1]

Am Soc Clin Oncol Educ Book 2023;43:e390804.

Original Reports | Hematologic Malignancy

Anti-CD19 Chimeric Antigen Receptor T-Cell Therapy for Richter Transformation: An International, Multicenter, Retrospective Study

Adam S. Kittai, MD[1]; David Bond, MD[1]; Ying Huang, MA, MS[1]; Seema A. Bhat, MD[1]; Emily Blyth, B.Med(Hons), PhD, FRACP, FRCPA[2]; John C. Byrd, MD[3]; Julio C. Chavez, MD, MS[4]; Matthew S. Davids, MD, MMSc[5]; Jamie P. Dela Cruz, BS[5]; Mark R. Dowling, PhD, MBBS[6,7]; Caitlyn Duffy, BS[5]; Carrie Ho, MD[8]; Caron Jacobson, MD, MMSc[5]; Samantha Jaglowski, MD, MPH[1]; Nitin Jain, MD[9]; Kevin H. Lin, MD, PhD[5]; Cecelia Miller, PhD[10]; Christine McCarthy, BS[11]; Zulfa Omer, MD[3]; Erin Parry, MD, PhD[5]; Manoj Rai, MD[12]; Kerry A. Rogers, MD[1]; Aditi Saha, MBBS[4]; Levanto Schachter, DO, MS[12]; Hamish Scott, MD[6]; Jayastu Senapati, MD, DM, MBBS[9]; Mazyar Shadman, MD, MPH[7]; Tanya Siddiqi, MD[13]; Deborah M. Stephens, DO[14]; Vinay Vanguru, MBBS, FRACP, FRCPA[15]; William Wierda, MD, PhD[9]; Jennifer A. Woyach, MD[1]; and Philip A. Thompson, MBBS[6,7]

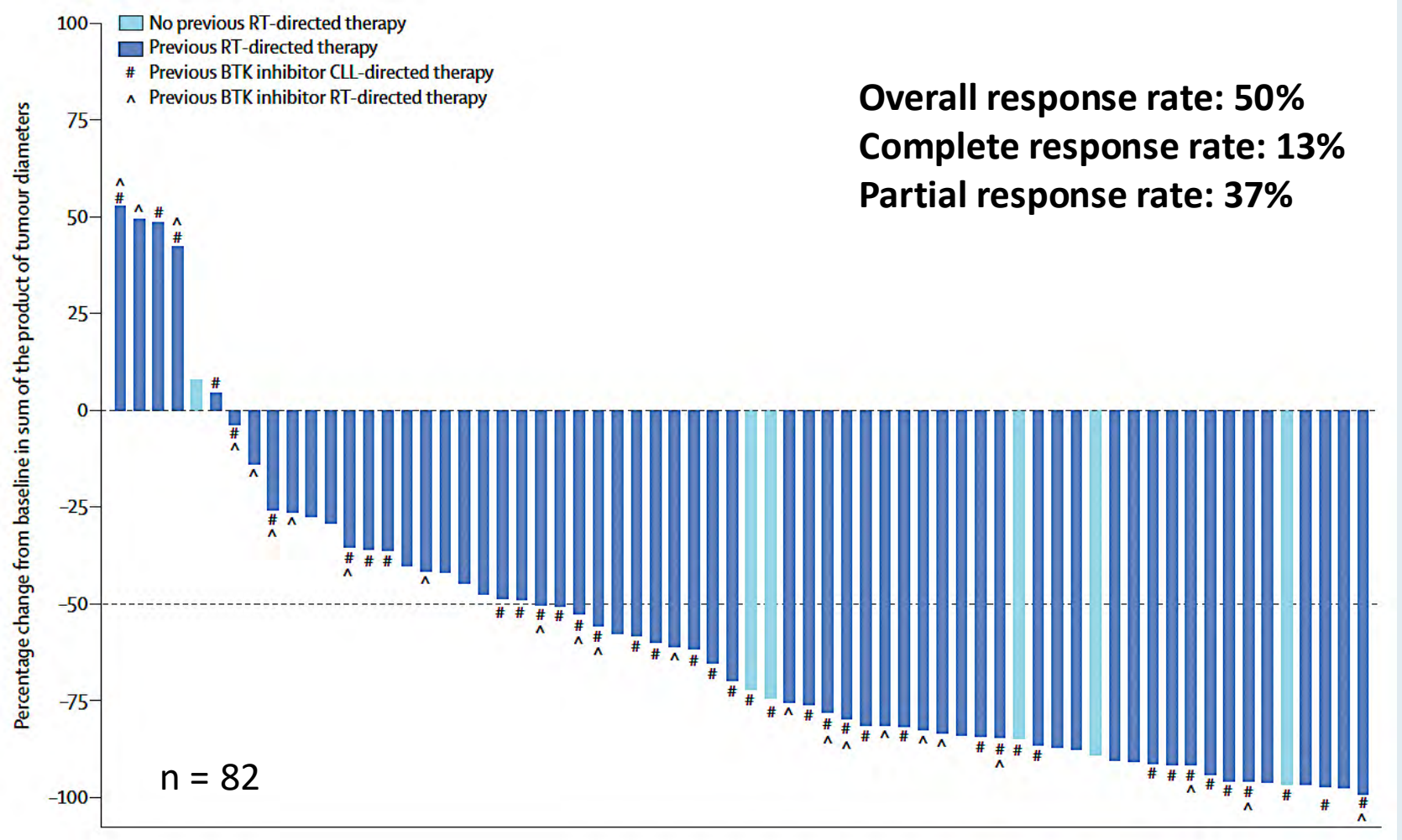
J Clin Oncol 2024;42(17):2071-9.

Pirtobrutinib, a highly selective, non-covalent (reversible) BTK inhibitor in patients with B-cell malignancies: analysis of the Richter transformation subgroup from the multicentre, open-label, phase 1/2 BRUIN study

William G Wierda, Nirav N Shah, Chan Y Cheah, David Lewis, Marc S Hoffmann, Catherine C Coombs, Nicole Lamanna, Shuo Ma, Deepa Jagadeesh, Talha Munir, Yucai Wang, Toby A Eyre, Joanna M Rhodes, Matthew McKinney, Ewa Lech-Maranda, Constantine S Tam, Wojciech Jurczak, Koji Izutsu, Alvaro J Alencar, Manish R Patel, John F Seymour, Jennifer A Woyach , Philip A Thompson, Paolo B Abada, Caleb Ho, Samuel C McNeely, Narasimha Marella, Bastien Nguyen, Chunxiao Wang, Amy S Ruppert, Binoj Nair, Hui Liu, Donald E Tsai, Lindsey E Roeker, Paolo Ghia

***Lancet Haematol* 2024 September;11(9):e682-92.**

BRUIN Subgroup Analysis: Activity of Pirtobrutinib in Patients with Richter's Transformation (RT)



- The most common grade 3 or worse adverse event was neutropenia (n = 19).

Wierda WG et al. *Lancet Haematol* 2024 September;11(9):e682-92.

FDA Grants Accelerated Approval to Lisocabtagene Maraleucel for Relapsed/Refractory (R/R) CLL or SLL

Press Release: March 14, 2024

"… the US Food and Drug Administration (FDA) has granted accelerated approval of lisocabtagene maraleucel (liso-cel), a CD19-directed chimeric antigen receptor (CAR) T cell therapy, for the treatment of adult patients with relapsed or refractory chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL) who have received at least two prior lines of therapy, including a Bruton tyrosine kinase (BTK) inhibitor and a B-cell lymphoma 2 (BCL-2) inhibitor. This indication is approved under accelerated approval based on response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trial(s). In R/R CLL or SLL, liso-cel is delivered through a treatment process which culminates in a one-time infusion with a single dose containing 90 to 110 x 10^6 CAR-positive viable T cells."

Accelerated approval was based on results from the Phase I/II open-label, single-arm TRANSCEND CLL 004 study for patients with R/R CLL or SLL.

https://news.bms.com/news/details/2024/U.S.-FDA-Approves-Bristol-Myers-Squibbs-Breyanzi--as-the-First-and-Only-CAR-T-Cell-Therapy-for-Adults-with-Relapsed-or-Refractory-Chronic-Lymphocytic-Leukemia-CLL-or-Small-Lymphocytic-Lymphoma-SLL/default.aspx

Lisocabtagene Maraleucel in Relapsed or Refractory Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma: 24-Month Median Follow-up of TRANSCEND CLL 004

Tanya Siddiqi,[1] David G. Maloney,[2] Saad S. Kenderian,[3] Danielle M. Brander,[4] Kathleen Dorritie,[5] Jacob Soumerai,[6] Peter A. Riedell,[7] Nirav N. Shah,[8] Rajneesh Nath,[9] Bita Fakhri,[10] Deborah M. Stephens,[11] Shuo Ma,[12] Tatyana Feldman,[13] Scott R. Solomon,[14] Stephen J. Schuster,[15] Serena K. Perna,[16] Sherilyn A. Tuazon,[17] San-San Ou,[17] Neha Rane,[16] William G. Wierda[18]

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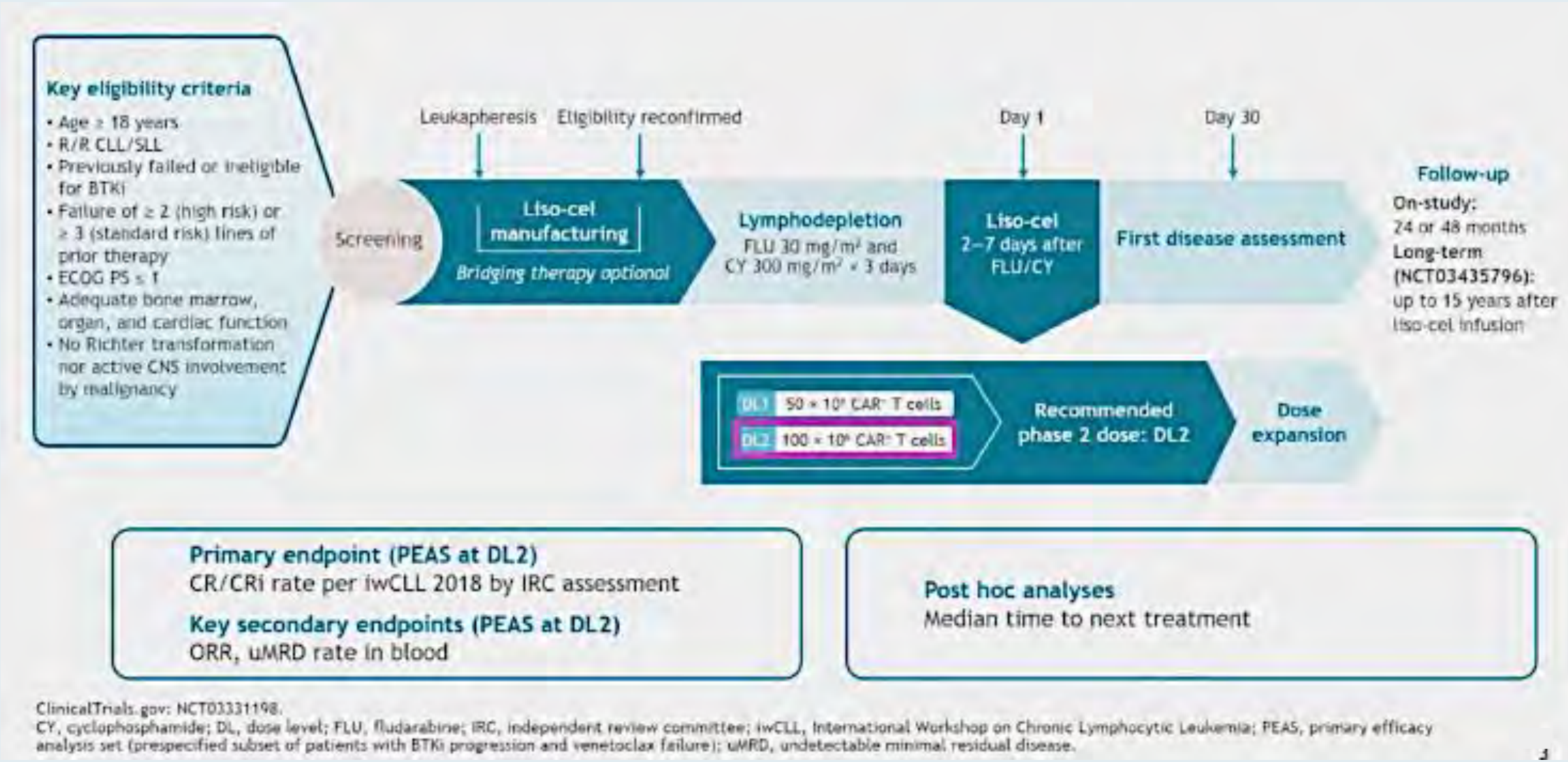
ASH 2023, Presentation 330

TRANSCEND CLL 004: An Open-Label Phase I/II Study Design



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

Siddiqi T et al. ASH 2023;Abstract 330.

TRANSCEND CLL 004 Efficacy Outcomes: Dose Level 2 (DL2) Only

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

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

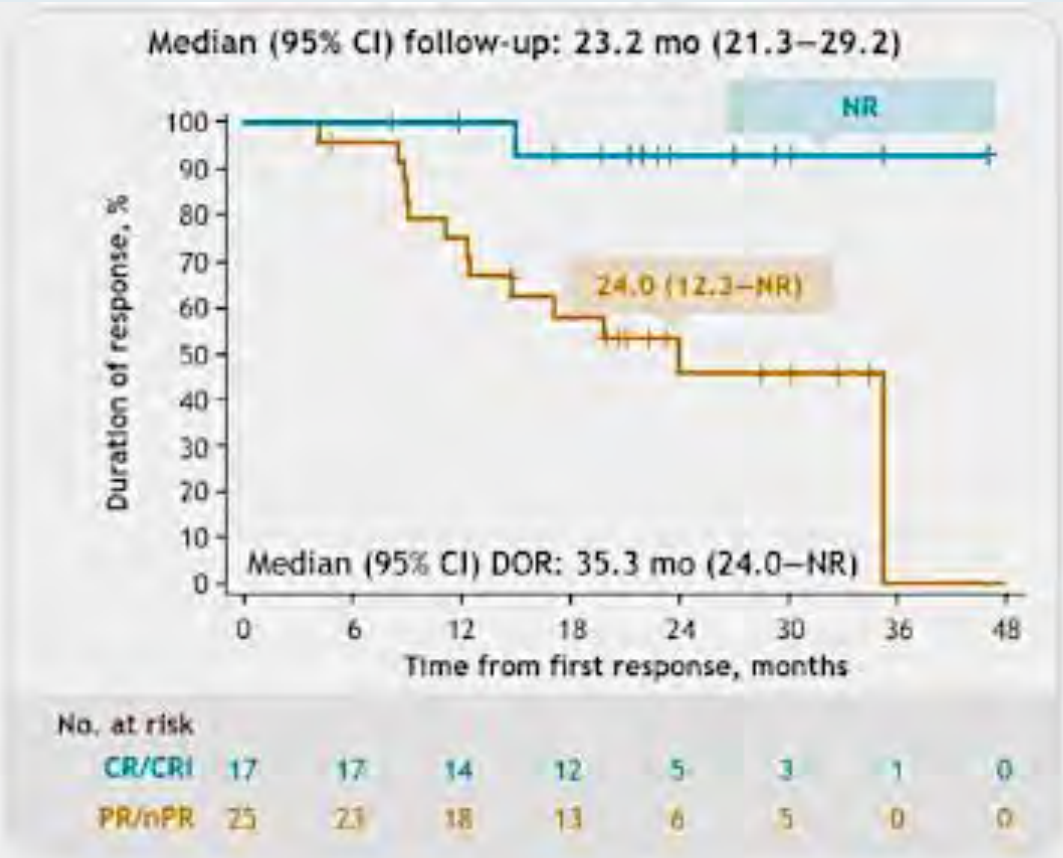
[a]One patient had an indeterminate status for MRD, which was considered positive as per FDA guidelines. SD, stable disease.

ORR = overall response rate

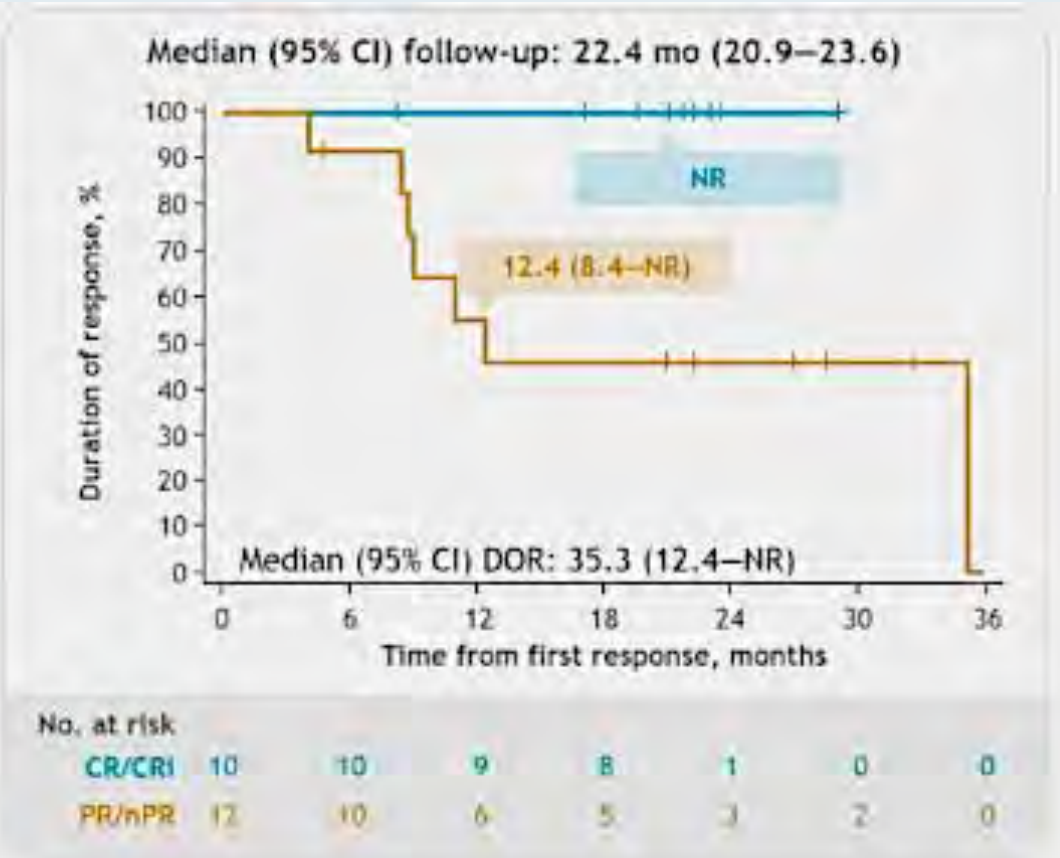
Siddiqi T et al. ASH 2023;Abstract 330.

TRANSCEND CLL 004: Duration of Response by Best Overall Response

Full Study Population at DL2 (n = 88)



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



Data on KM curves are expressed as median (95% CI, if available). DOR, duration of response; NR, not reached.

Siddiqi T et al. ASH 2023;Abstract 330.

TRANSCEND CLL 004: Cytokine Release Syndrome (CRS), Neurological Events and Other AESIs

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

Other AESIs, n (%)

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

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

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

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

Siddiqi T et al. ASH 2023;Abstract 330.

Meet The Professor with Dr Davids

Introduction: Is CLL the New CML? Cases We Didn't Hear About Last Week

Module 1: Case Presentations

Module 2: Transformed CLL; CAR T-Cell Therapy

Module 3: Journal Club with Dr Davids

Module 4: Appendix

RTP
RESEARCH TO PRACTICE

REGULAR ARTICLE

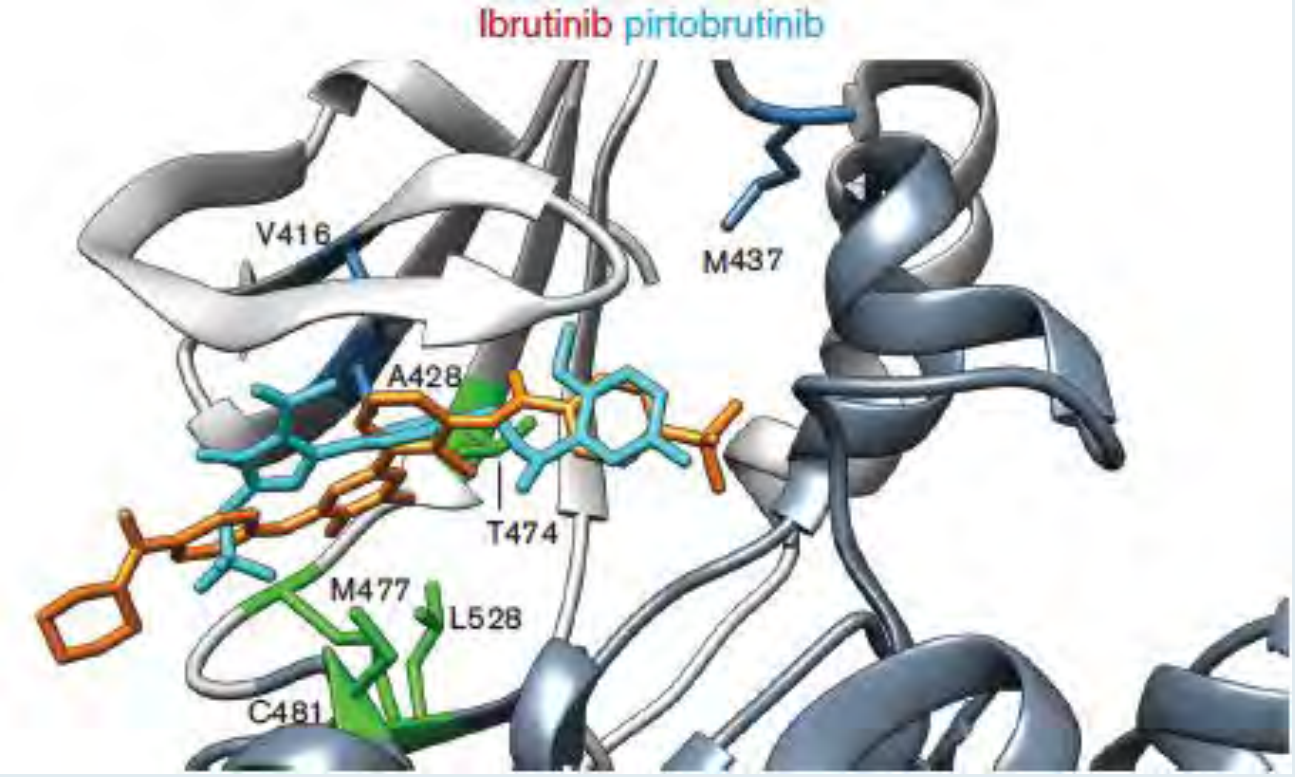
blood advances

Pirtobrutinib targets BTK C481S in ibrutinib-resistant CLL but second-site BTK mutations lead to resistance

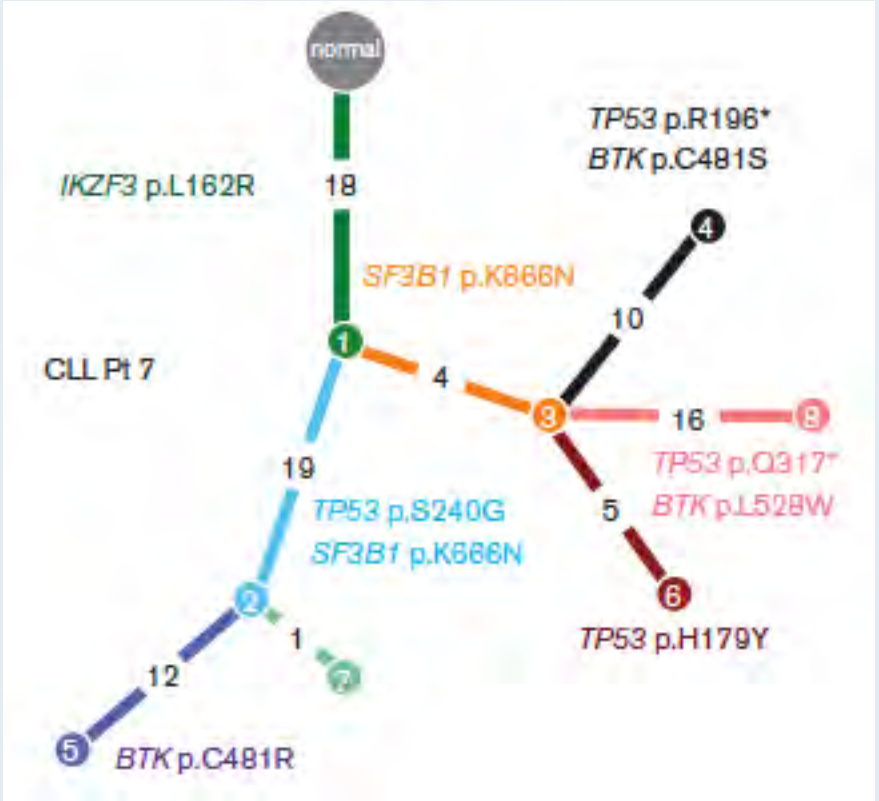
Aishath Naeem,[1,2] Filippo Utro,[3,†] Qing Wang,[4,†] Justin Cha,[2,†] Mauno Vihinen,[5] Stephen Martindale,[1] Yinglu Zhou,[6] Yue Ren,[6] Svitlana Tyekucheva,[6] Annette S. Kim,[7] Stacey M. Fernandes,[1] Gordon Saksena,[2] Kahn Rhrissorrakrai,[3] Chaya Levovitz,[3] Brian P. Danysh,[2] Kara Slowik,[2] Raquel A. Jacobs,[2] Matthew S. Davids,[1,8] James A. Lederer,[9] Rula Zain,[4,10,*] C. I. Edvard Smith,[4,*] Ignaty Leshchiner,[2,*] Laxmi Parida,[3,*] Gad Getz,[2,11,12,*] and Jennifer R. Brown[1,2,8,*]

2023;7(9):1929-43.

Docking of Pirtobrutinib to BTK and Second-Site BTK Mutations Are Associated with Resistance to Pirtobrutinib



Phylogenetic tree of clonal and subclonal architecture of somatic mutations in a patient with CLL and disease progression on pirtobrutinib



Naeem A et al. *Blood Adv* 2023;7(9):1929-43.

Dana-Farber Cancer Institute

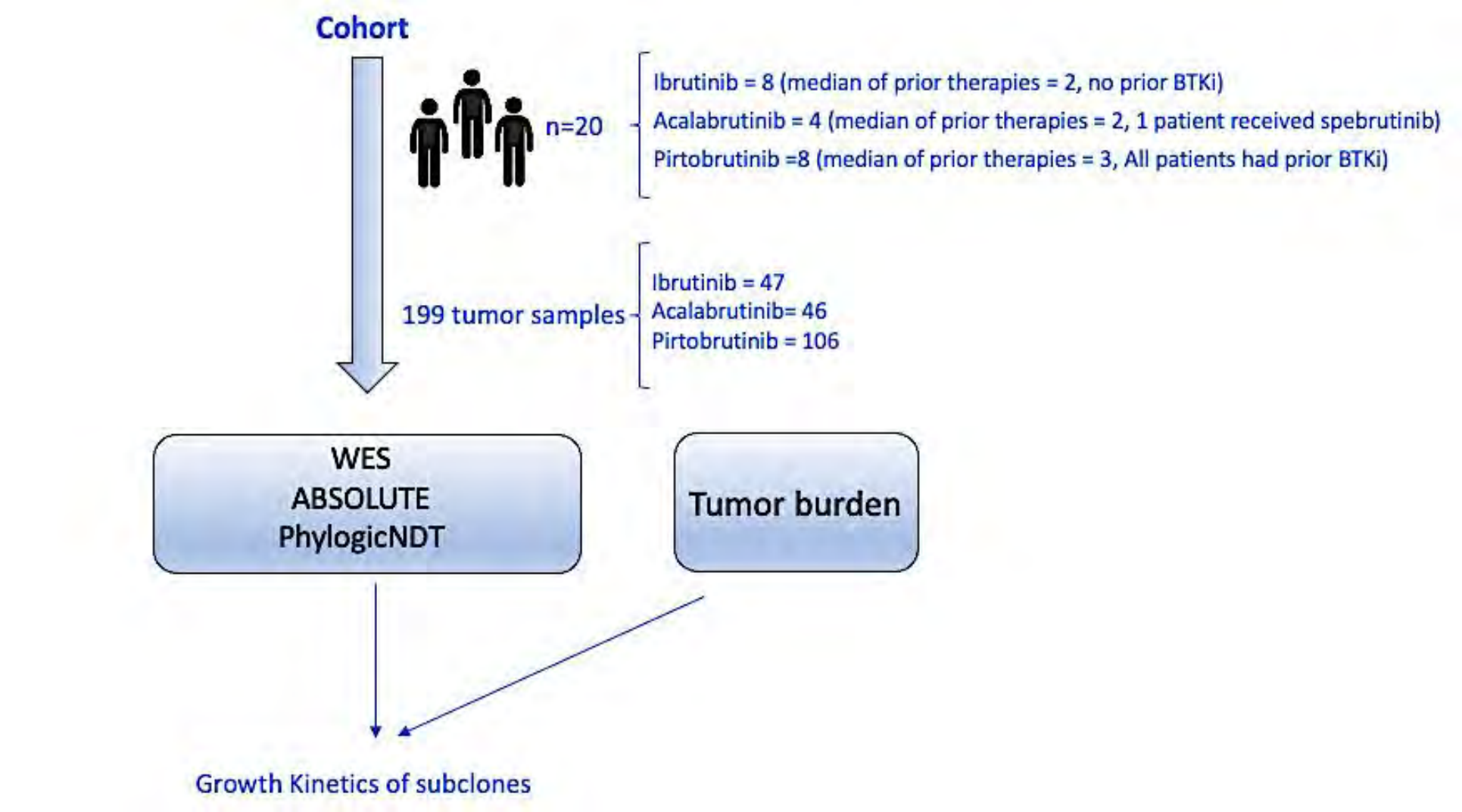
Understanding resistance mechanisms and growth kinetics of CLL treated with covalent and non-covalent BTK inhibitors

Aishath S. Naeem*[1,2], Liang Li*[2], Filippo Utro*[3], Justin Cha[2], Junko Tsuji[2], Stacey M. Fernandes[1], Roberta Santos Azevedo[1,4], Francesca Morelli[1,5], Zunqiu Wang[1], Kahn Rhrissorrakrai[3], Chaya Levovitz[3], Brian P. Danysh[2], Alexandria Kluge[2], Matthew S. Davids[1,6], Ignaty Leshchiner[2,7], Laxmi Parida[3], Gad Getz[2,8,9,10], Jennifer R. Brown[1,2,6]

[1]Department of Medical Oncology, Dana-Farber Cancer Institute, Harvard Medical School, Boston, Massachusetts, USA. [2]Cancer Program, Broad Institute of MIT and Harvard, Cambridge, Massachusetts, USA. [3]IBM Research, Yorktown Heights, New York, USA. [4]Department of Hematology, Hospital Nove de Julho, São Paulo, Brazil. [5]Department of Hematology, University of Florence, Florence, Italy. [6]Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA. [7]Department of Medicine, Section of Computational Biomedicine, Boston University School of Medicine, Boston, MA. [8]Cancer Center, Massachusetts General Hospital, Boston, MA USA. [9]Harvard Medical School, Boston, MA USA. [10]Department of Pathology, Massachusetts General Hospital, Boston, MA USA.

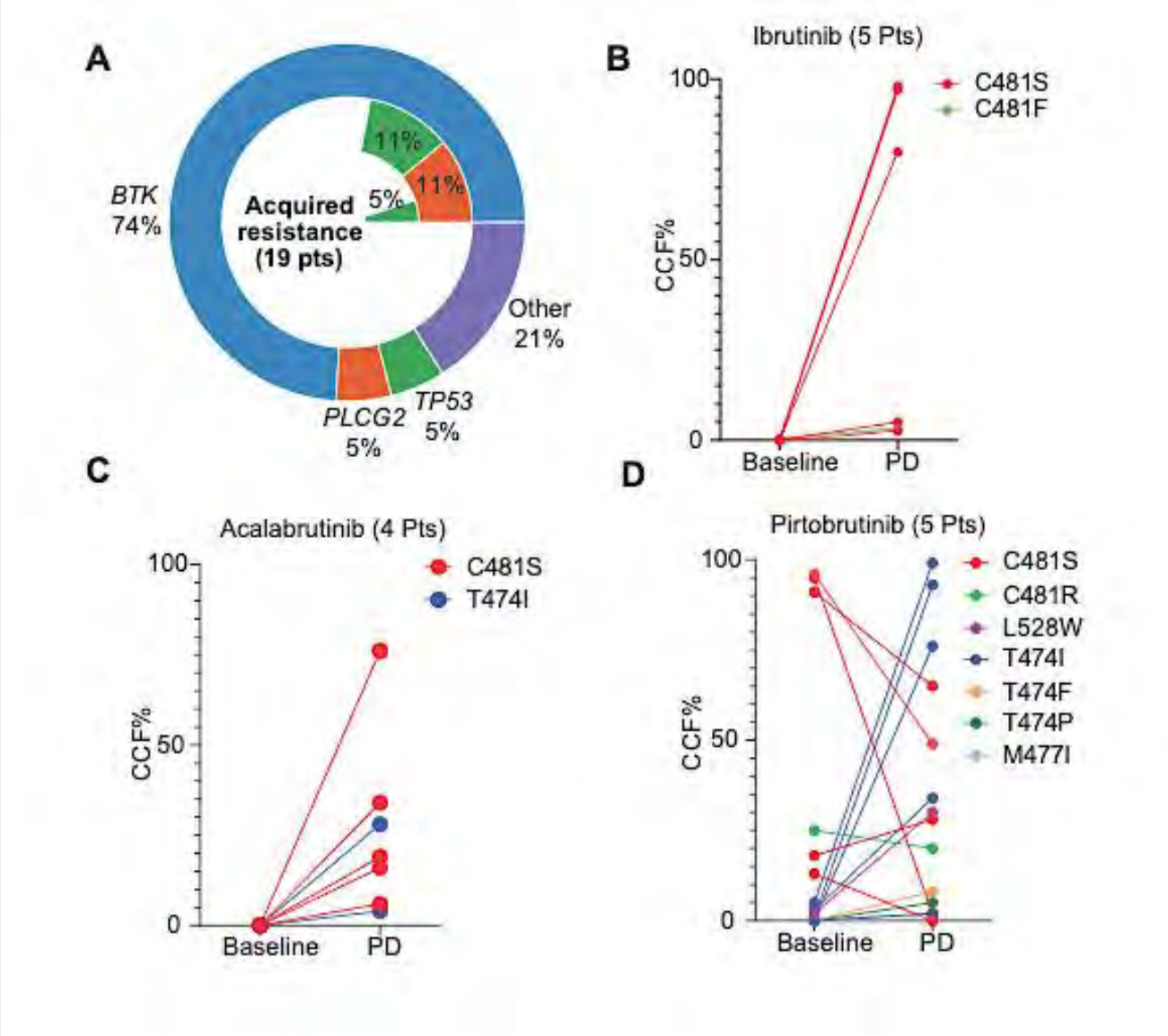
ASH 2023;Abstract 4623.

Our Approach



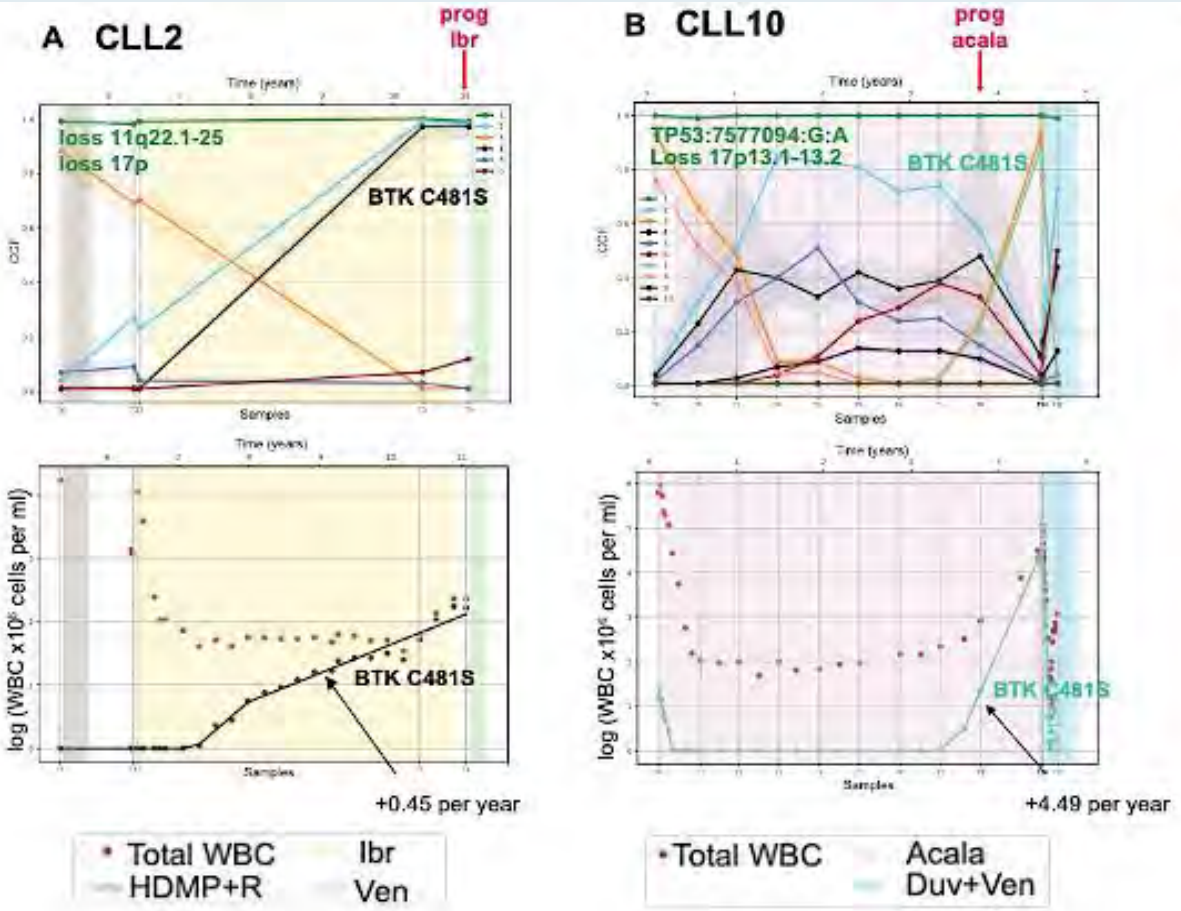
Naeem A et al. ASH 2023;Abstract 4623.

Characteristics of Acquired Resistance to BTK Inhibitors



Naeem A et al. ASH 2023;Abstract 4623.

C481S Clone Grows Slower on Ibrutinib Than on Acalabrutinib



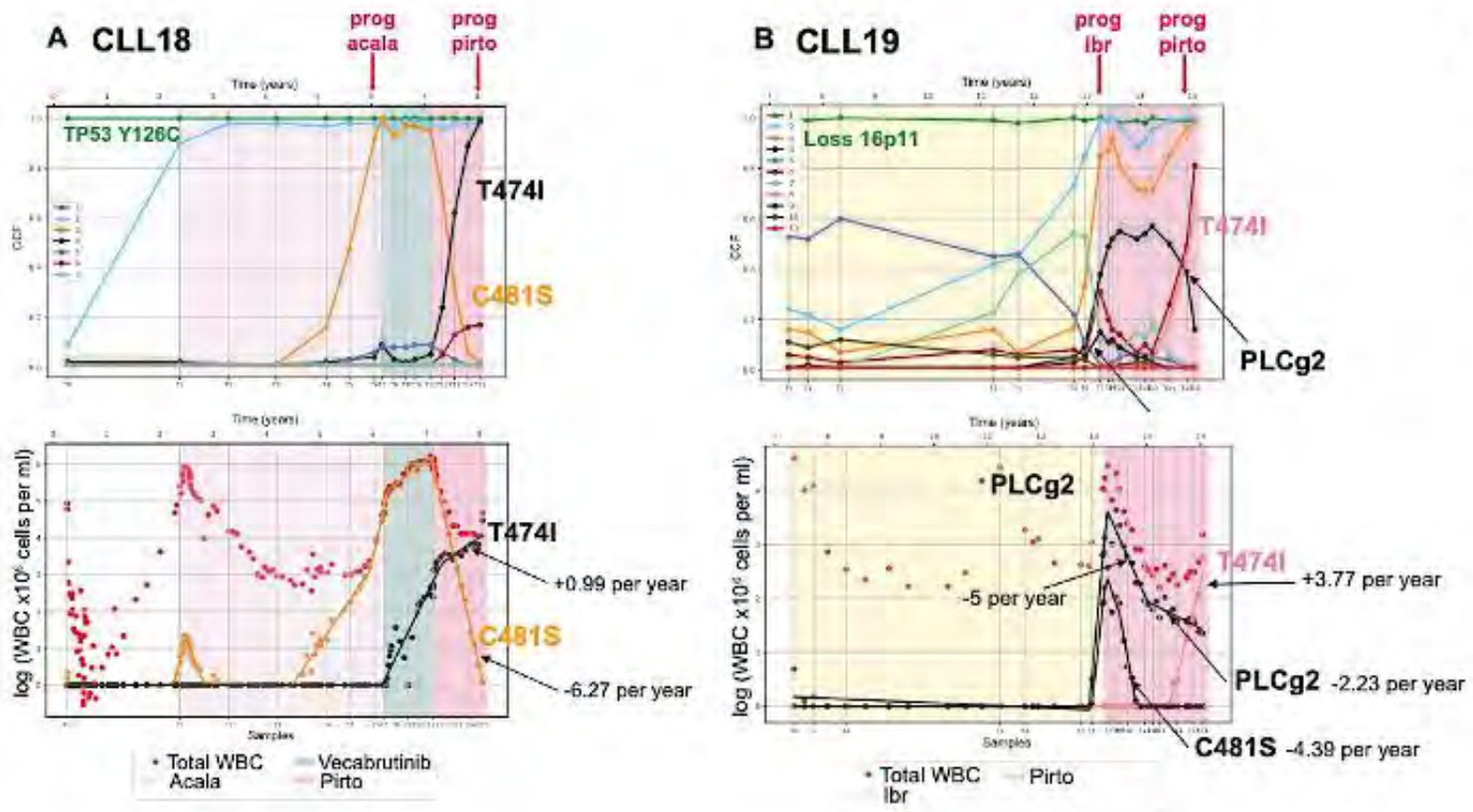
C

Cohort	Patient	Clone	Growth rate (per year)
Ibr	CLL2	*BTK* C481S	+0.45
	CLL5	*BTK* C481S	+2.12
Acala	CLL10	*BTK* C481S	+4.49
	CLL11	*BTK* C481S	+4.63
	CLL14	*BTK* C481S	+4.29
	CLL18	*BTK* C481S	+2.13

Liang Li, Getz Lab

Naeem A et al. ASH 2023;Abstract 4623.

Gatekeeper Mutation T474I Grows and C481S Declines During Pirtobrutinib Treatment



C

Cohort	Patient	Clone	Growth rate (per year)
Pirto	CLL18	*BTK* T474I	+ 0.99
		BTK C481S	- 6.27
	CLL19	*BTK* T474I	+3.77
		BTK C481S	-4.39
		PLCG2 L845F	-2.23, -5
	CLL20	*BTK* C481S	-2.71

Liang Li, Getz Lab

Naeem A et al. ASH 2023;Abstract 4623.

Conclusions

- At progression (PD), mutations in *BTK* C481S were found in 5/8 patients (55%) in the ibr cohort with CCF>80% in 3 patients. Two of these patients also have mutations in PLCG2 (CCF>30%). One patient in the cohort has an acquired PLCG2 mutation (D1140N) with CCF>70%, without *BTK* C481S
- All 4 patients that progressed on acala have resistant clones harboring *BTK* C481S (CCF 16-75%) mutations, with T474I mutations present in 2 patients (CCF 4% and 26%) at progression.
- All but one patient in the pirto cohort had developed PD on cBTKi and 71% (5/7) had *BTK* C481S mutations prior to starting pirto (CCF 26 - 99%). In 5 cases, the C481S clone declines on pirto and at PD is replaced by the *BTK* gatekeeper mutation T474I (CCF 76 - 99%) in 3 patients, the kinase-inactive mutation *BTK* L528W (CCF 30%) in 1 patient, and mutations in other driver genes (XPO1, MED12) in 1 patient.
- Rapid growth of C481S clone under acala is consistent with expected inactivity of the drug against the mutation.
- Growth of T474I and exponential decline of C481S clones observed at pirto progression.

Naeem A et al. ASH 2023;Abstract 4623.

Long-Term Safety with ≥12 Months of Pirtobrutinib in Relapsed/Refractory (R/R) B-Cell Malignancies

Wojciech Jurczak (Presenter)[1], Catherine C. Coombs[2], Nirav N. Shah[3], Jennifer Woyach[4], Chan Y. Cheah[5], Krish Patel[6], Kami Maddocks[4], Yucai Wang[7], Catherine E. Muehlenbein[8], Chunxiao Wang[9], Sarang Abhyankar[8], Donald E. Tsai[8], Toby A. Eyre[10]

[1]Maria Sklodowska-Curie National Research Institute of Oncology, Krakow, Poland; [2]UCI Health, Orange, CA, USA; [3]Medical College of Wisconsin, Milwaukee, WI, USA; [4]The Ohio State University Comprehensive Cancer Center, Columbus, USA; [5]Linear Clinical Research and Sir Charles Gairdner Hospital, Perth, Australia; [6]Center for Blood Disorders and Cellular Therapy, Swedish Cancer Institute, Seattle, WA, USA; [7]Division of Hematology, Mayo Clinic, Rochester, MN, USA; [8]Loxo@Lilly, Indianapolis, IN, USA; [9]Eli Lilly and Company, Indianapolis, IN, USA; [10]Oxford University Hospitals NHS Foundation Trust, Churchill Cancer Center, Oxford, United Kingdom

RTP RESEARCH TO PRACTICE

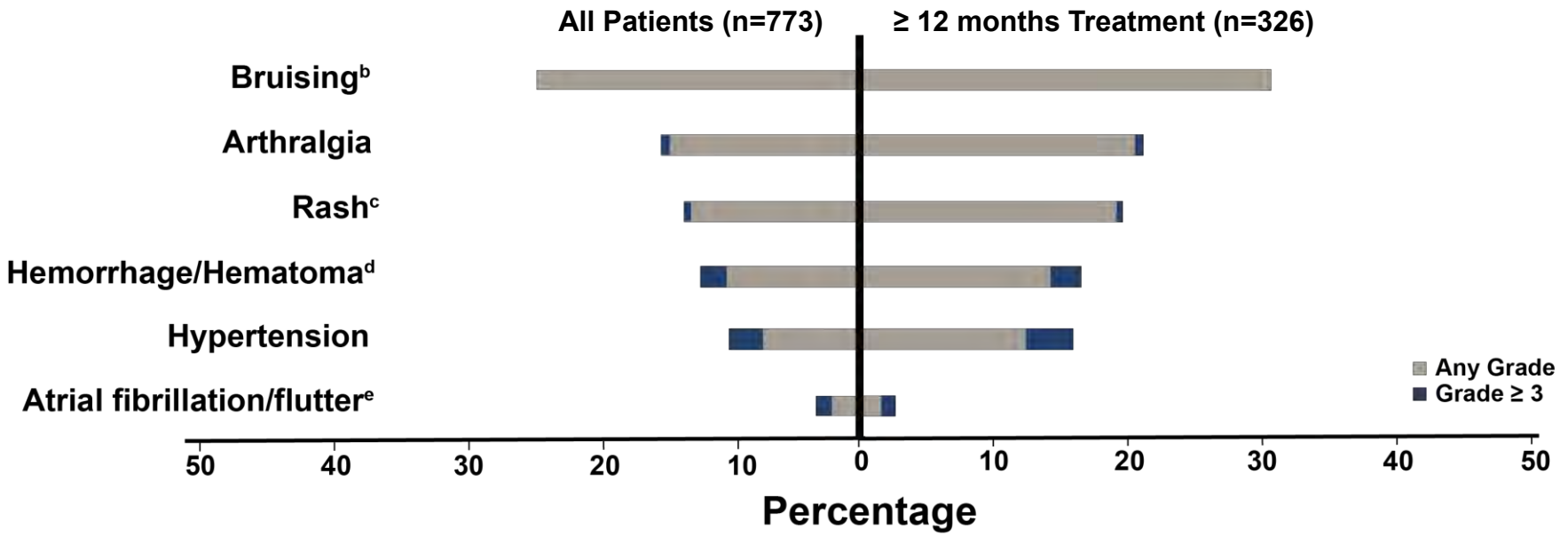
BRUIN: Pirtobrutinib Safety Profile in Patients with ≥12 Months Treatment and in the Overall Safety Population

Treatment Emergent AEs (≥15%)	≥12 Months Treatment (N=326)				All Patients (N=773)			
	Any Grade TEAE (%)	Grade ≥3 TEAE (%)	Leading to Dose Reduction (%)	Leading to Drug Discontinuation (%)	Any Grade TEAE (%)	Grade ≥3 TEAE (%)	Leading to Dose Reduction (%)	Leading to Drug Discontinuation (%)
Fatigue	32.2	1.2	0	0	28.7	2.1	0.4	0.3
Diarrhea	30.7	1.2	0.3	0	24.2	0.9	0.3	0
Neutropenia[a]	29.8	23.9	3.1	0.6	25.0	20.3	2.1	0.5
Covid-19	28.5	4.3	0.3	0	16.7	2.7	0.1	0.4
Contusion	25.8	0	0.3	0	19.4	0	0.1	0
Cough	24.5	0	0	0	17.5	0.1	0.1	0
Back Pain	20.9	0.9	0	0	12.7	0.5	0	0
Headache	18.4	0.6	0	0	13.1	0.5	0.1	0
Upper Respiratory Tract Infection	18.1	0	0	0	9.8	0.1	0	0
Nausea	17.5	0.3	0	0	16.2	0.1	0.1	0.1
Dyspnea	17.2	0.6	0.3	0	15.5	1.0	0.1	0.1
Abdominal Pain	16.3	0.9	0	0	13.1	1.0	0	0.1
Constipation	16.3	0	0	0	13.6	0.3	0	0
AEs of Special Interest[b]	**Any Grade TEAE (%)**	**Grade ≥3 TEAE (%)**	**Leading to Dose Reduction (%)**	**Leading to Drug Discontinuation (%)**	**Any Grade TEAE (%)**	**Grade ≥3 TEAE (%)**	**Leading to Dose Reduction (%)**	**Leading to Drug Discontinuation (%)**
Bruising[c]	30.7	0	0.3	0	23.7	0	0.1	0
Arthralgia	21.2	0.6	0	0	14.4	0.6	0	0
Rash[d]	19.6	0.3	0	0	12.7	0.5	0.3	0.1
Hemorrhage/ Hematoma[e]	16.6	2.1	0	0	11.4	1.8	0	0
Hypertension	16.0	3.4	0.3	0	9.2	2.3	0.1	0
Atrial fibrillation/ flutter[f]	2.8	0.9	0	0	2.8	1.2	0	0

Data cutoff date of 29 July 2022. [a]Aggregate of neutropenia and neutrophil count decreased. [b]AEs of special interest are those that were previously associated with covalent BTK inhibitors. [c]Aggregate of contusion, petechiae, ecchymosis, and increased tendency to bruise. [d]Aggregate of all preferred terms including rash. [e]Aggregate of all preferred terms including hematoma or hemorrhage. [f]Aggregate of atrial fibrillation and atrial flutter.

Jurczak W et al. EHA 2023;Abstract P618.

BRUIN: Selected Adverse Events (AEs) of Special Interest



Data cutoff date of 29 July 2022. [a]AEs of special interest are those that were previously associated with covalent BTK inhibitors. [b]Aggregate of contusion, petechiae, ecchymosis, and increased tendency to bruise. [c]Aggregate of all preferred terms including rash. [d]Aggregate of all preferred terms including hematoma or hemorrhage. [e]Aggregate of atrial fibrillation and atrial flutter.

Among the 326 patients who received ≥12 months treatment:

- Most TEAEs and AEs of special interest were low grade and did not lead to dose reduction or discontinuation
- 42% of the patients with treatment-emergent hypertension had a pre-existing medical history of hypertension
- In total, across all TEAEs, dose reduction or discontinuation occurred in 23 (7%) and 11 (3%) patients, respectively
- **With additional treatment, the rates of selected AEs of special interest did not show clinically meaningful increases, particularly Grade ≥3**

TEAEs = treatment-emergent adverse events

Jurczak W et al. EHA 2023;Abstract P618.

REGULAR ARTICLE

blood advances

Acalabrutinib-based regimens in frontline or relapsed/refractory higher-risk CLL: pooled analysis of 5 clinical trials

Matthew S. Davids,[1] Jeff P. Sharman,[2] Paolo Ghia,[3,4] Jennifer A. Woyach,[5] Toby A. Eyre,[6] Wojciech Jurczak,[7] Tanya Siddiqi,[8] Paulo Miranda,[9] Mina Shahkarami,[10] Anna Butturini,[10] Ugochinyere Emeribe,[9] and John C. Byrd[11]

Blood Adv 2024;8(13):3345-59.

REGULAR ARTICLE

blood advances

An indirect comparison of acalabrutinib with and without obinutuzumab vs zanubrutinib in treatment-naive CLL

Adam S. Kittai,[1,*] John N. Allan,[2,*] Dan James,[3] Helen Bridge,[4] Miguel Miranda,[4] Alan S. M. Yong,[5] Fady Fam,[4] Jack Roos,[5] Vikram Shetty,[5] Alan Skarbnik,[6,†] and Matthew S. Davids[7,†]

2024;8(11):2861-9.

Seminars in Hematology 61 (2024) 109–118

Contents lists available at ScienceDirect

Seminars in Hematology

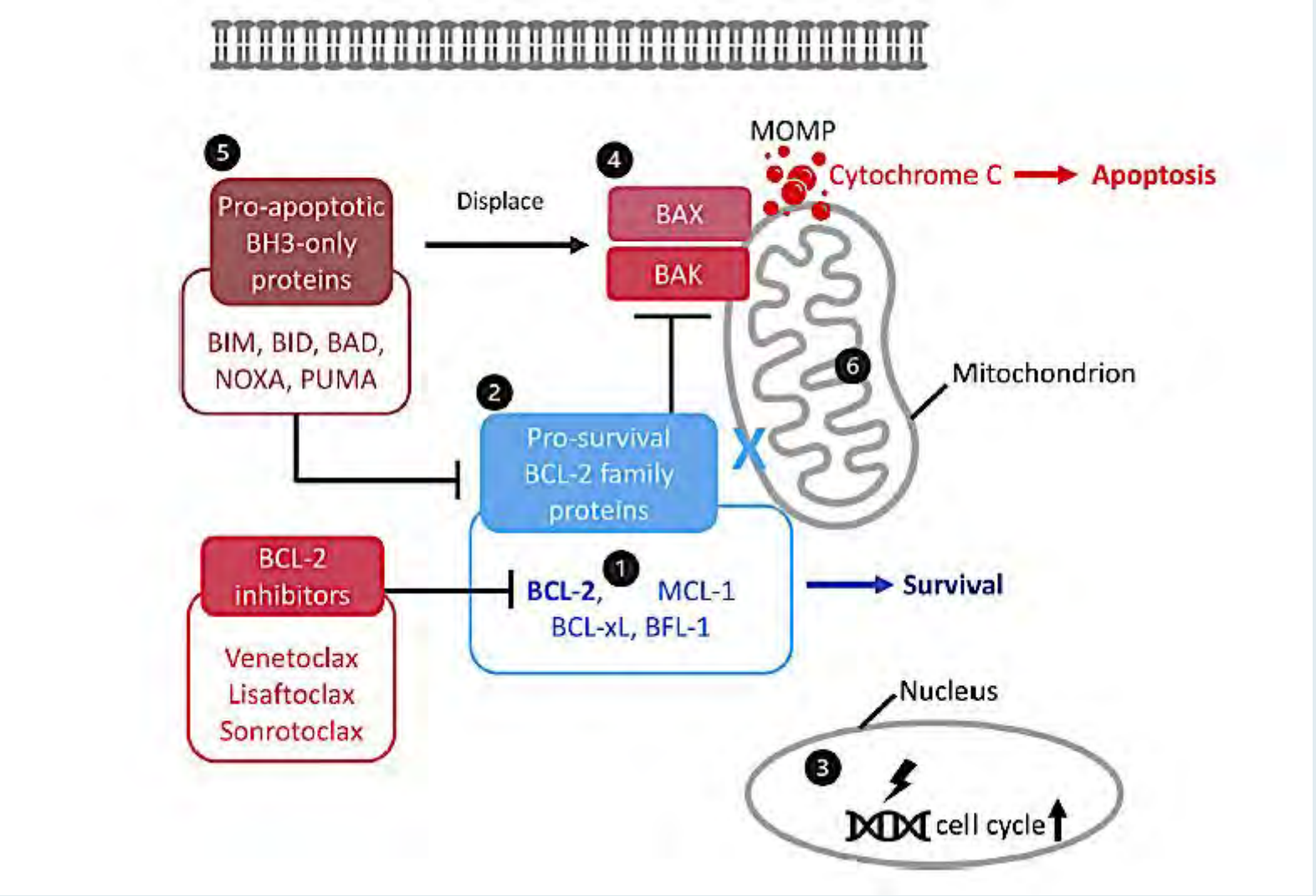
journal homepage: www.elsevier.com/locate/seminhematol

Therapeutic targeting of apoptosis in chronic lymphocytic leukemia ☆

Inhye E. Ahn, Matthew S. Davids*

Department of Medical Oncology, Dana-Farber Cancer Institute, Boston, MA

Therapeutic Targeting of Apoptosis and Mechanisms of Resistance to Bcl-2 Inhibition



Ahn IE, Davids MS. *Semin Hematol* 2024;61(2):109-18.

Clin Cancer Res. 2024 February 01; 30(3): 471–473. doi:10.1158/1078-0432.CCR-23-2872.

Overcoming Resistance in Chronic Lymphocytic Leukemia – Maybe Less is More?

Othman Al-Sawaf[1,2,3], **Matthew S. Davids**[4]

SAVE (Safe Accelerated Venetoclax Escalation): Initial Results of a Prospective, Phase Ib Study of Venetoclax with an Accelerated Dose Ramp-Up in Patients with CLL

Crombie JL et al.

ASCO 2023;Abstract 7512.

haematologica

Journal of the Ferrata Storti Foundation

LP-118 is a novel B-cell lymphoma 2/extra-large inhibitor that demonstrates efficacy in models of venetoclax-resistant chronic lymphocytic leukemia

by Janani Ravikrishnan, Daisy Y. Diaz-Rohena, Elizabeth Muhowski, Xiaokui Mo, Tzung-Huei Lai, Shrilekha Misra, Charmelle D. Williams, John Sanchez, Andrew Mitchell, Suresh Satpati, Elizabeth Perry, Tierney Kaufman, Chaomei Liu, Arletta Lozanski, Gerard Lozanski, Kerry A. Rogers, Adam S. Kittai, Seema A. Bhat, Mary C. Collins, Matthew S. Davids, Nitin Jain, William G. Wierda, Rosa Lapalombella, John C. Byrd, Fenlai Tan, Yi Chen, Yu Chen, Yue Shen, Stephen P. Anthony, Jennifer A. Woyach, and Deepa Sampath

2024 August 8;[Online ahead of print].

Meet The Professor with Dr Davids

Introduction: Is CLL the New CML? Cases We Didn't Hear About Last Week

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Module 4: Appendix

Selection of First-Line Therapy for Patients with Chronic Lymphocytic Leukemia (CLL)

Final Analysis of the RESONATE-2 Study: Up to 10 Years of Follow-Up of First-Line Ibrutinib Treatment in Patients with Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma

Burger J et al.

EHA 2024;Abstract P670.

Author Conclusions: *With the longest follow-up to date from a phase 3 study of any targeted therapy for CLL/SLL, this final analysis of the landmark RESONATE-2 study defines median PFS and demonstrates continued OS benefit of single-agent ibrutinib (Ibr) treatment for patients with previously untreated disease, including those with high-risk genomic features. Median PFS was significantly longer with Ibr versus chlorambucil, and responses to Ibr were sustained over time. At study completion, 27% of patients remained on Ibr, AE rates were stable, and no new safety signals emerged since the prior report. Sustained efficacy and tolerability of first-line Ibr treatment reinforces the favorable benefit-risk profile.*

Presentation #636

Acalabrutinib ± Obinutuzumab vs Obinutuzumab + Chlorambucil in Treatment-naive Chronic Lymphocytic Leukemia: 6-Year Follow-up of ELEVATE-TN

Jeff P. Sharman,[1] Miklos Egyed,[2] Wojciech Jurczak,[3] Alan Skarbnik,[4] Krish Patel,[5] Ian W. Flinn,[6] Manali Kamdar,[7] Talha Munir,[8] Renata Walewska,[9] Marie Hughes,[10] Laura Maria Fogliatto,[11] Yair Herishanu,[12] Versha Banerji,[13] George Follows,[14] Patricia Walker,[15] Karin Karlsson,[16] Paolo Ghia,[17] Ann Janssens,[18] Florence Cymbalista,[19] John C. Byrd,[20] Emmanuelle Ferrant,[21] Alessandra Ferrajoli,[22] William G. Wierda,[22] Veerendra Munugalavadla,[23] Catherine Wangui Wachira,[24] Chuan-Chuan Wun,[23] Jennifer A. Woyach[20]

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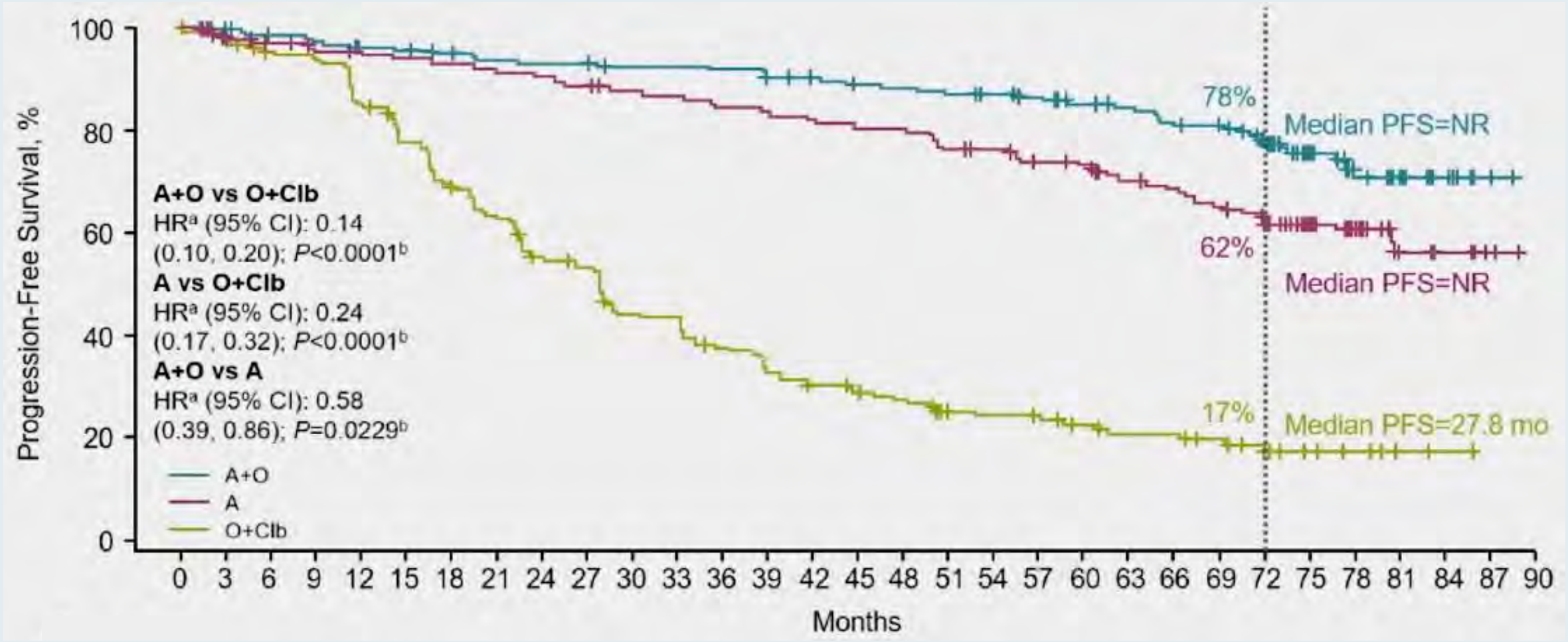
Presented at the American Society of Hematology (ASH) Annual Meeting; December 9–12, 2023

ELEVATE-TN 6-Year Follow-Up: Progression-Free Survival



Sharman JP et al. ASH 2023;Abstract 636.

ELEVATE-TN 6-Year Follow-Up: Author Conclusions

- With median follow-up at 74.5 months (~6 years), the efficacy and safety of A+O and A were maintained in patients with TN CLL
  - Median PFS was significantly longer for A-containing arms vs O+Clb
  - Median PFS was significantly longer in patients treated with A+O vs A
  - Addition of O to A resulted in higher complete response rates compared with A monotherapy
  - Patients treated with A±O who achieved a complete response had longer PFS than those who did not achieve a complete response
  - OS was not reached in any treatment arm and was longer with A+O vs O+Clb
- These benefits in outcomes were observed regardless of patients' genomic marker status
- Safety of A+O and A remained consistent with previously reported findings, with low incidences of some grade ≥3 AEs typically associated with BTKis

Sharman JP et al. ASH 2023;Abstract 636.

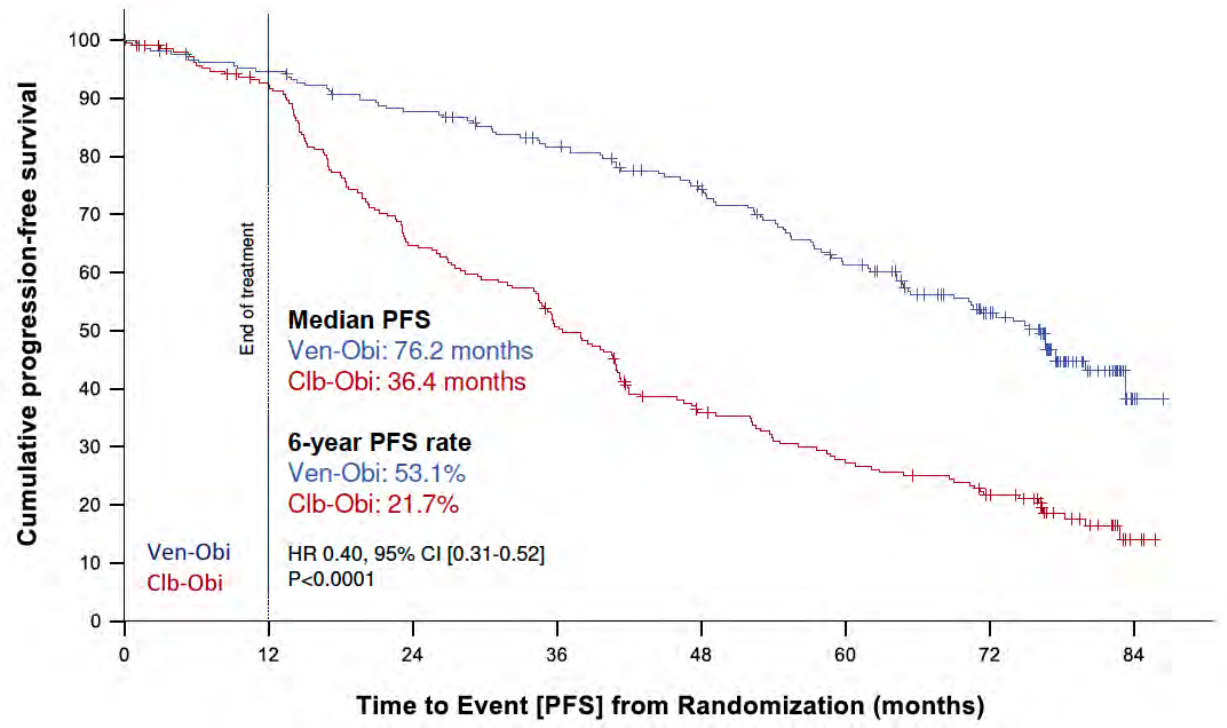
Venetoclax-Obinutuzumab for previously untreated chronic lymphocytic leukemia: 6-year results of the phase 3 CLL14 study

Othman Al-Sawaf, Sandra Robrecht, Can Zhang, Stefano Olivieri, Yi Meng Chang, Anna-Maria Fink, Eugen Tausch, Christof Schneider, Matthias Ritgen, Karl-Anton Kreuzer, Liliya Sivcheva, Carsten Utoft Niemann, Anthony P. Schwarer, Javier Loscertales, Robert Weinkove, Dirk Strumberg, Allanah Kilfoyle, Beenish S. Manzoor, Dureshahwar Jawaid, Nnadozie Emechebe, Jacob Devine, Michelle Boyer, Eva D Runkel, Barbara Eichhorst, Stephan Stilgenbauer, Yanwen Jiang, Michael J Hallek, Kirsten Fischer

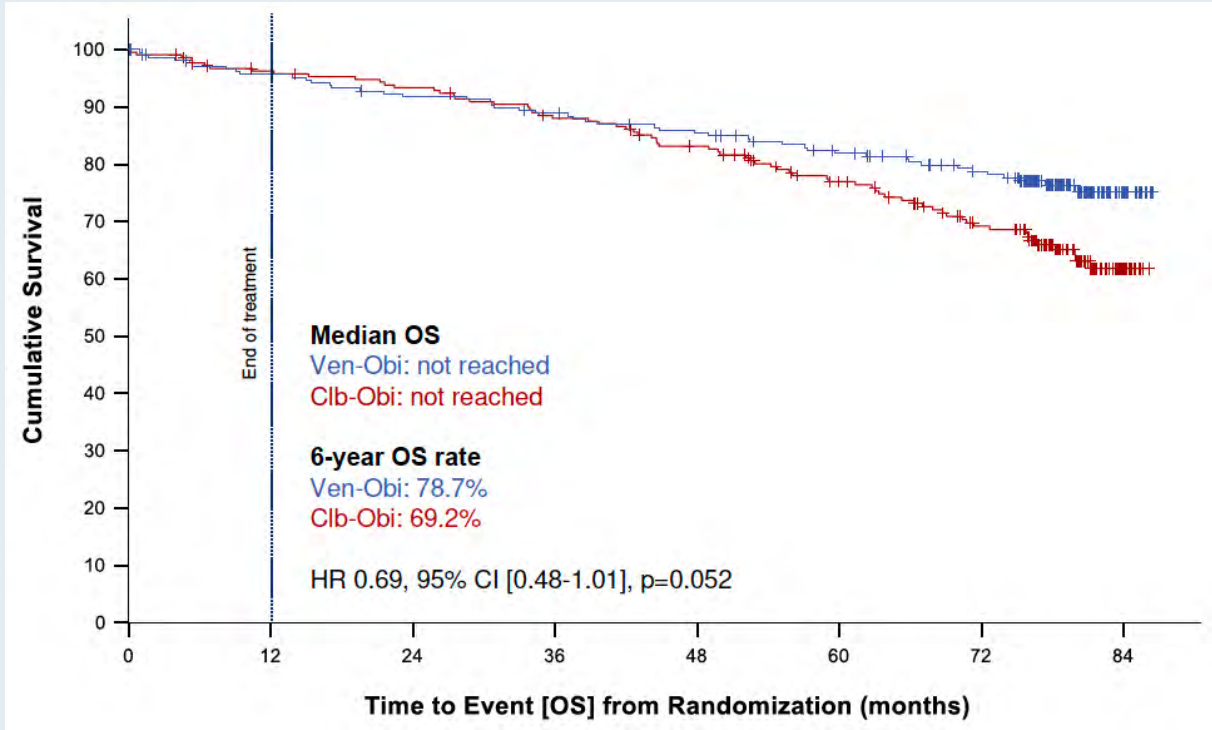
Blood **2024 July 10;[Online ahead of print].**

CLL14 6-Year Follow-Up: Survival

Progression-free survival



Overall survival



Al-Sawaf OA et al. *Blood* 2024 July 10;[Online ahead of print].

Abstract 634

First-Line Fixed-Duration Ibrutinib Plus Venetoclax (Ibr+Ven) Versus Chlorambucil Plus Obinutuzumab (Clb+O): Up to 5 Years' Follow-up From the GLOW Study

Carol Moreno,[1] Talha Munir,[2] Carolyn Owen,[3] George Follows,[4] José-Ángel Hernández-Rivas,[5] Ohad Benjamini,[6] Ann Janssens,[7] Mark-David Levin,[8] Tadeusz Robak,[9] Martin Simkovic,[10] Sergey Voloshin,[11] Vladimir Vorobyev,[12] Munci Yagci,[13] Loic Ysebaert,[14] Qianya Qi,[15] Emma Smith,[15] Srimathi Srinivasan,[16] Natasha Schuier,[15] Kurt Baeten,[17] Donne Bennett Caces,[15] Carsten U. Niemann,[18] Arnon P. Kater[19]

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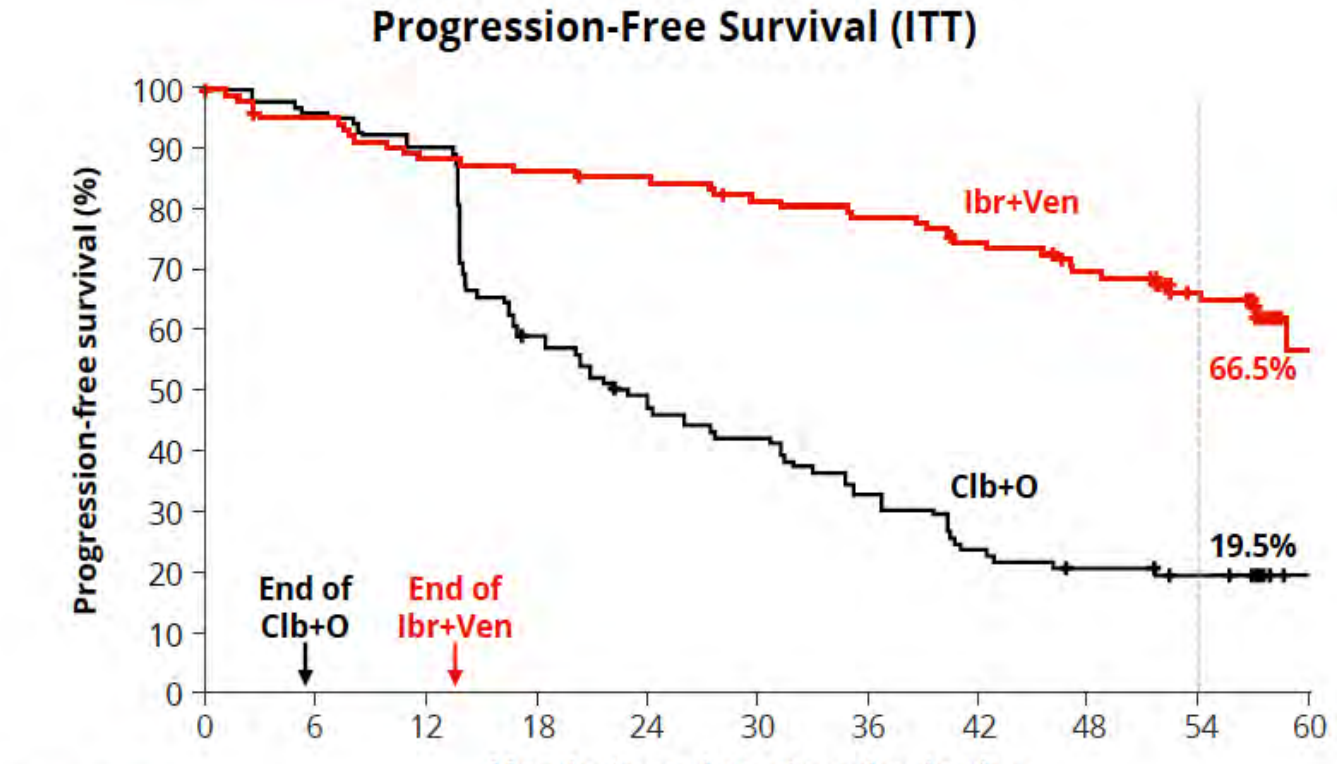
Presented at the 65th ASH Annual Meeting and Exposition; December 9-12, 2023; San Diego, CA, USA

GLOW: Investigator-Assessed PFS at 57 Months of Study Follow-Up

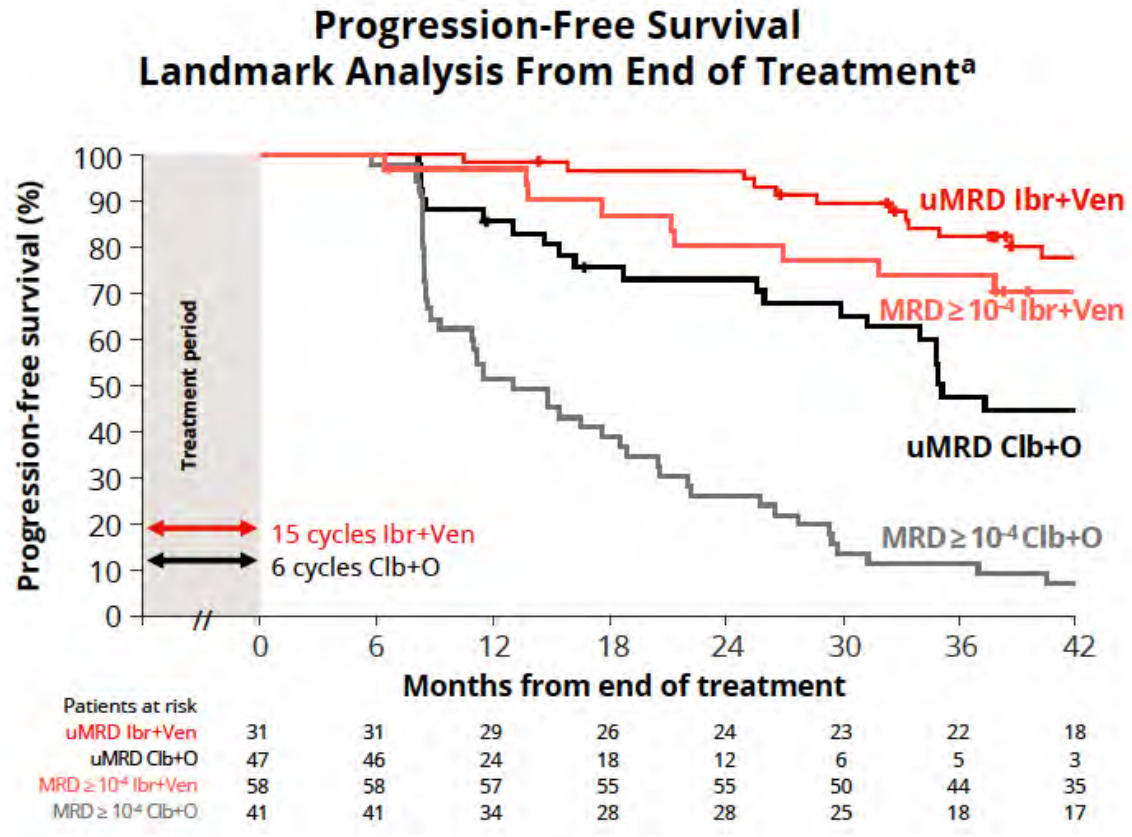


p value is nominal.
ITT, intention to treat.

- **Ibr+Ven reduced the risk of progression or death by 74%** versus Clb+O
  - HR 0.256 (95% CI, 0.172-0.382); $p < 0.0001$
- Estimated 54-month PFS rates at 57 months of follow-up:
  - **66.5%** for Ibr+Ven
  - **19.5%** for Clb+O

Moreno C et al. ASH 2023;Abstract 634.

GLOW: Investigator-Assessed PFS by Minimal Residual Disease (MRD) Status at 3 Months After End of Treatment (EOT+3)



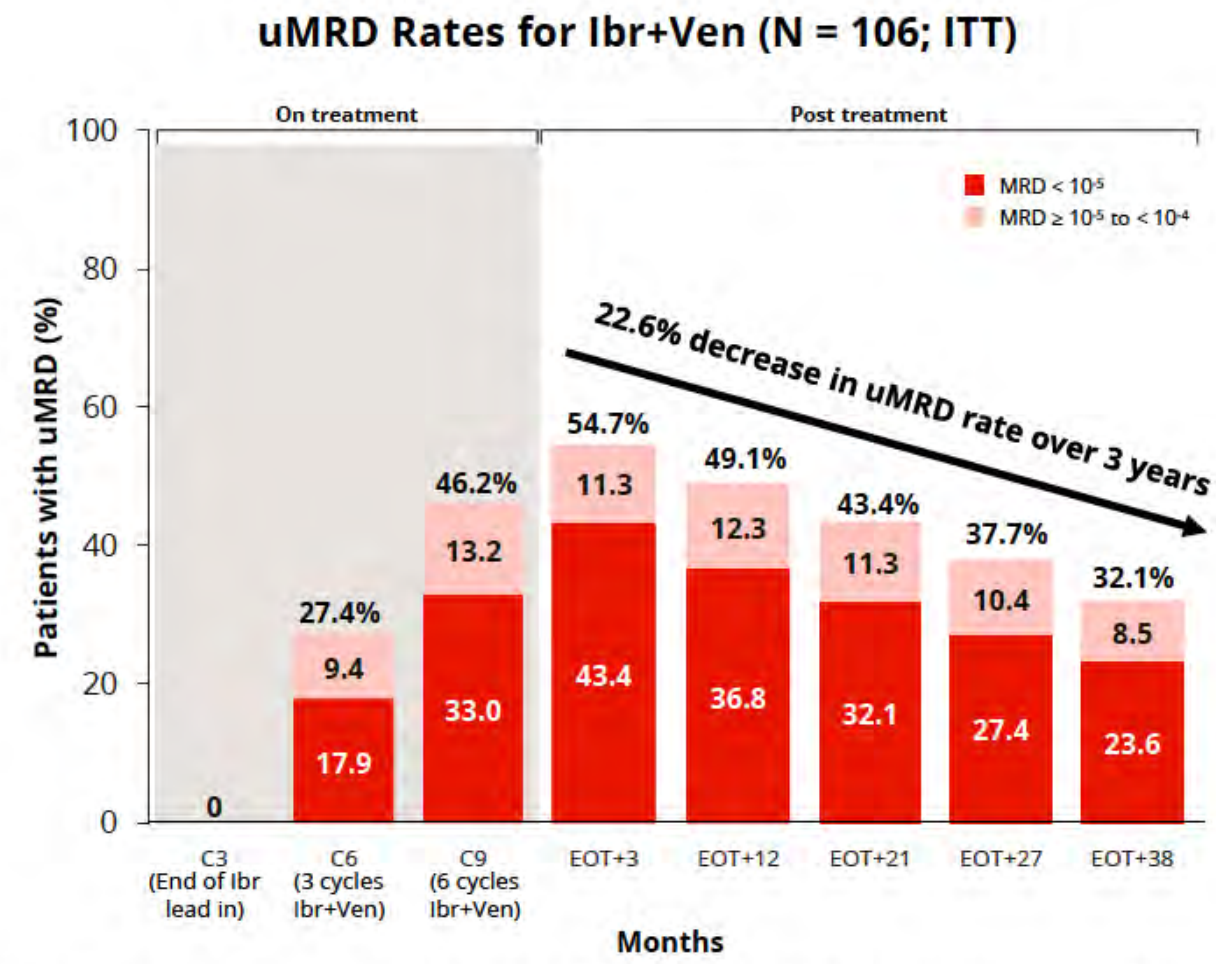
- Estimated PFS rates at 42 months post treatment:
  - **Ibr+Ven:**
    - 78% for patients with uMRD at EOT+3
    - 70% for patients with MRD ≥ 10^{-4} at EOT+3
  - **Clb+O:**
    - 44% for patients with uMRD at EOT+3
    - 6% for patients with MRD ≥ 10^{-4} at EOT+3

[a]Curves generated from EOT (C15 for Ibr+Ven, C6 for Clb+O),
All patients who had MRD outcome at EOT+3 were included in this analysis; uMRD was defined as < 1 CLL cell per 10,000 leukocytes (< 10^{-4}).
MRD, minimal residual disease.

- A similar high PFS rate was observed with Ibr + Ven for patients with unmutated IGHV who had uMRD at EOT+3, whereas those with MRD ≥10^{-4} had a lower PFS rate

Moreno C et al. ASH 2023;Abstract 634.

GLOW: Undetectable MRD Rates 3 Years After Treatment with Ibrutinib and Venetoclax

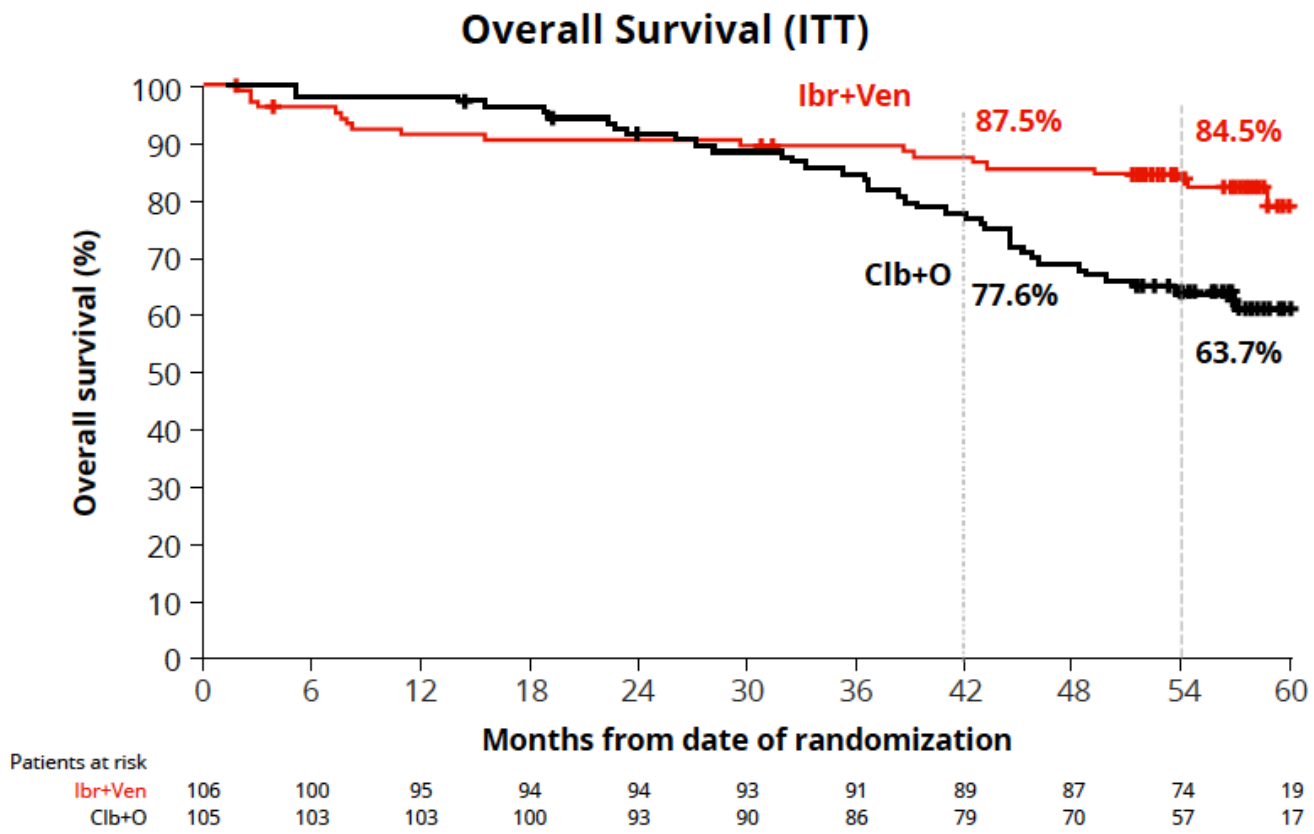


Numbers may not add up to exact total due to rounding. uMRD was defined as < 1 CLL cell per 10,000 leukocytes (< 10^{-4}).

- On treatment:
  - 47 (81%) of 58 patients who achieved uMRD by EOT+3 did so by C9 (ie, after 6 cycles of combined Ibr+Ven)
- 3 years post treatment:
  - uMRD responses in the Ibr+Ven arm had an annual decline of less than 10%

Moreno C et al. ASH 2023;Abstract 634.

GLOW: Overall Survival at 57 Months of Study Follow-Up



- **Ibr+Ven reduced the risk of death by 55%** versus Clb+O
  - HR 0.453 (95% CI, 0.261-0.785); $p = 0.0038$
- Estimated 54-month OS rates:
  - **84.5%** for patients treated with Ibr+Ven
  - **63.7%** for patients treated with Clb+O

Moreno C et al. ASH 2023;Abstract 634.

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

Incidence and Management Recommendations for Select BTK Inhibitor-Associated Cardiologic Adverse Events and Bleeding

Adverse event	BTK inhibitor	Incidence Any grade, Grade ≥3	Management
Atrial fibrillation	Ibrutinib	16%, 2%-5%	**A**void stroke; anticoagulation **B**etter symptom control: rate vs rhythm **C**ardiovascular and other comorbidity management
	Acalabrutinib	6%-9%, 1%-5%	
	Zanubrutinib	3%-6%, ≤1%	
	Pirtobrutinib	2.8%, 1.2%	
Hypertension	Ibrutinib	16%-23%, 8%-12%	Correct predisposing factors Antihypertensive therapy
	Acalabrutinib	7%-9%, 3%-4%	
	Zanubrutinib	14%-17%, 6%-15%	
	Pirtobrutinib	9.2%, 2.3%	
Bleeding	Ibrutinib	36%-51%, 3%-4%	Minor bleeding: no intervention Major bleeding: • Consider treatment discontinuation • Platelet transfusions regardless of platelet counts
	Acalabrutinib	36%-51%, 3%	
	Zanubrutinib	36%-45%, 3%	
	Pirtobrutinib	—	

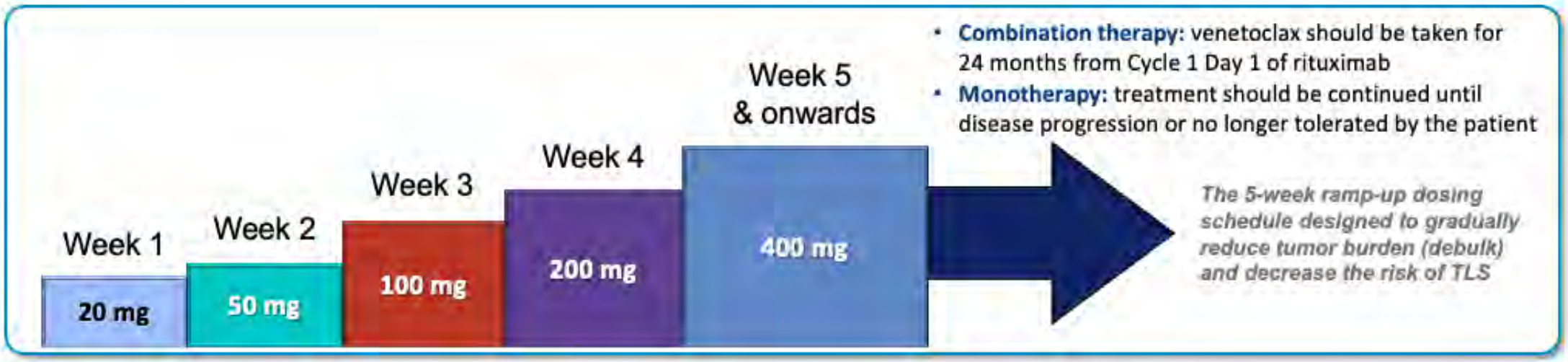
Galitzia A et al. *Cancers* 2024;16:1996; Jurczak W et al. EHA 2023;Abstract P618.

Incidence and Management Recommendations for Select BTK Inhibitor-Associated Noncardiovascular Adverse Events

Adverse event	BTK inhibitor	Incidence Any grade, Grade ≥3	Management
Neutropenia	Ibrutinib	25%-39%, 13%-31%	Growth factor support
	Acalabrutinib	21%-23%, 13%-19%	
	Zanubrutinib	37%-34%, 15%-19%	
	Pirtobrutinib	25%, 20.3%	
Diarrhea	Ibrutinib	22%-59%, <1%-4%	Symptomatic treatments and dose adjustments Dietary modifications, hydration, anti-diarrheal medications Probiotics
	Acalabrutinib	18%-39%, 1%-5%	
	Zanubrutinib	14%-18%, <1%-2%	
	Pirtobrutinib	24.2%, 0%-9%	
Headache	Ibrutinib	14%-18%, 1%-2%	Moderate dose of caffeine or acetaminophen
	Acalabrutinib	22%-39%, <1%	
	Zanubrutinib	11%-12%, 0%-1%	
	Pirtobrutinib	13.1%, 0.5%	

Galitzia A et al. *Cancers* 2024;16:1996; Jurczak W et al. EHA 2023;Abstract P618.

Venetoclax Dose Initiation



The 5-week dose-titration schedule is designed to gradually reduce tumour burden and decrease the risk of TLS

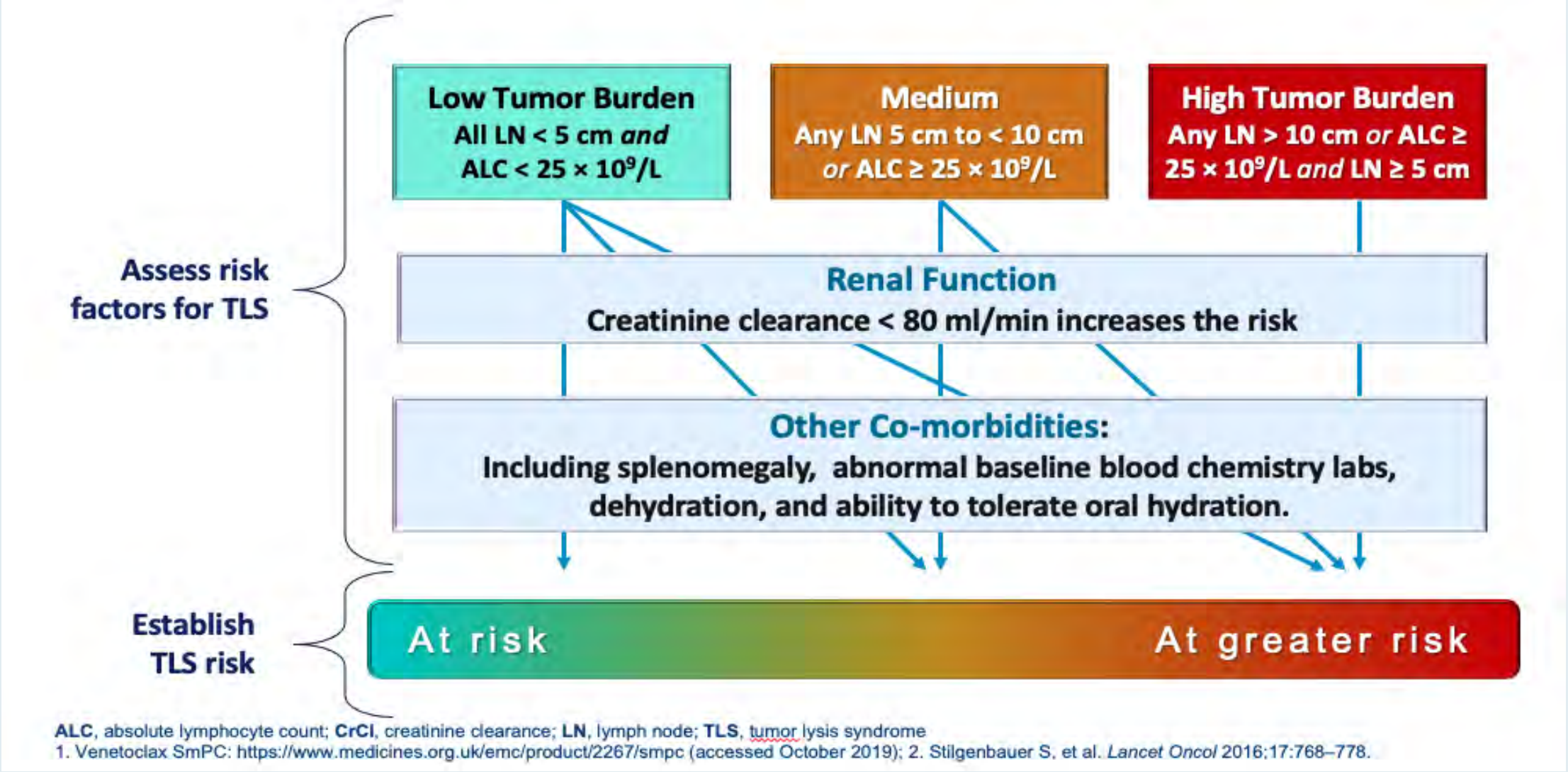
Combination therapy: recommended dose of venetoclax in combination with rituximab is 400 mg once daily; rituximab should be administered after the patient has completed the dose-titration schedule and has received the recommended daily dose of 400 mg venetoclax for 7 days.

Monotherapy: the recommended dose of venetoclax is 400 mg once daily.

Venetoclax SmPC: https://www.medicines.org.uk/emc/product/2267/smpc (accessed October 2019).

Courtesy of Matthew S Davids, MD, MMSc

TLS Risk with Venetoclax Is a Continuum Based on Multiple Factors



ALC, absolute lymphocyte count; **CrCl**, creatinine clearance; **LN**, lymph node; **TLS**, tumor lysis syndrome

1. Venetoclax SmPC: https://www.medicines.org.uk/emc/product/2267/smpc (accessed October 2019); 2. Stilgenbauer S, et al. *Lancet Oncol* 2016;17:768–778.

Courtesy of Matthew S Davids, MD, MMSc

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