Meet The Professor
Management of Chronic Lymphocytic Leukemia

William G Wierda, MD, PhD
DB Lane Cancer Research Distinguished Professor
Department of Leukemia
Division of Cancer Medicine
The University of Texas MD Anderson Cancer Center
Houston, Texas

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Commercial Support

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Dr Love — Disclosures

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Dr Wierda — Disclosures

No financial interests or affiliations to disclose

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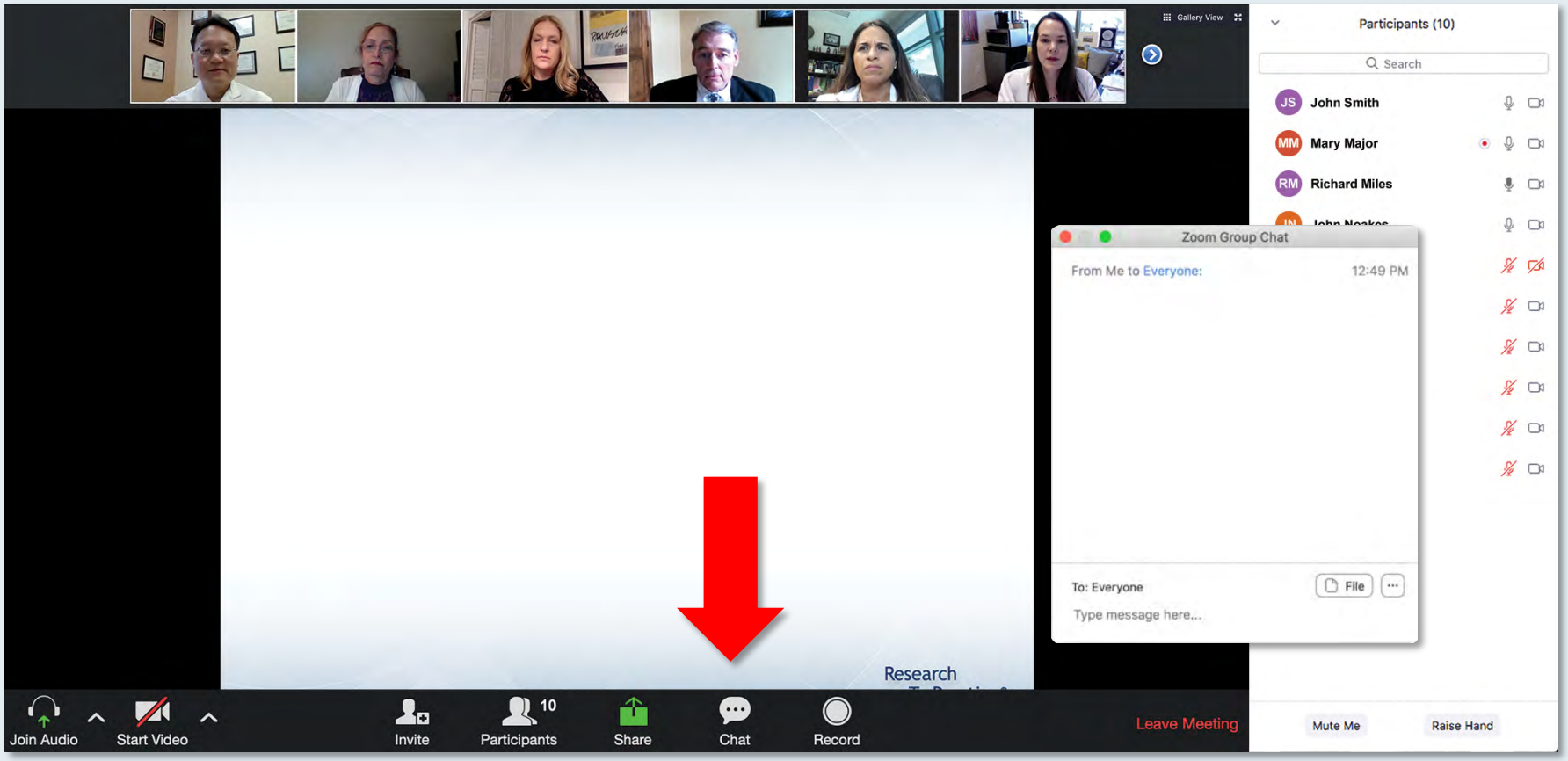

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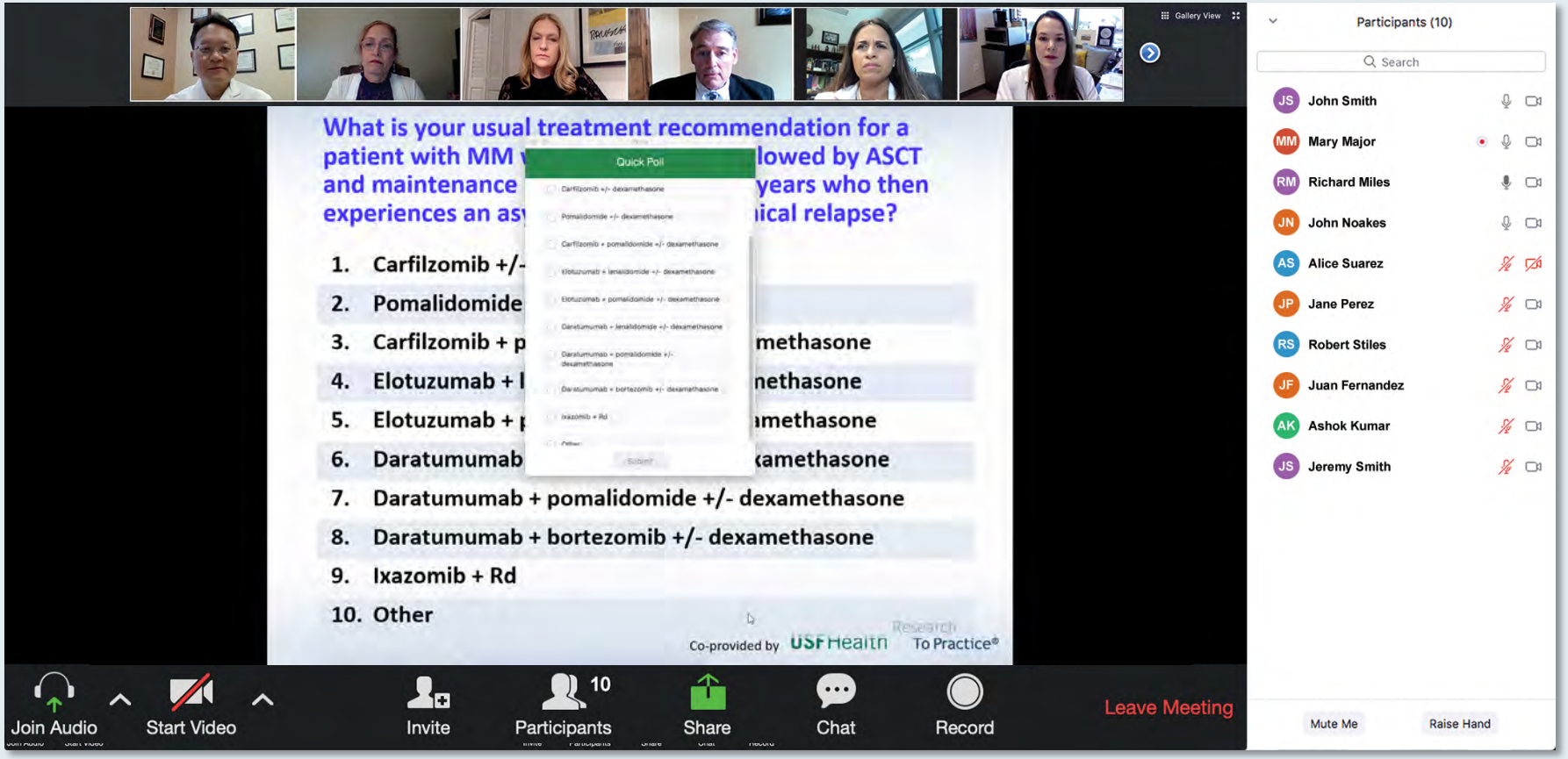

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Upcoming Live Webinars

Monday, October 5, 2020
12:00 PM – 1:00 PM ET

Meet The Professor: Management of Lung Cancer

Faculty
Professor Tony SK Mok, MD

Moderator
Neil Love, MD

Wednesday, October 7, 2020
12:00 PM – 1:00 PM ET

Meet The Professor: Management of Chronic Lymphocytic Leukemia

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Mitchell R Smith, MD, PhD

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Meet The Professor: Immunotherapy and Novel Agents in Gynecologic Cancers

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Thank you for joining us!

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

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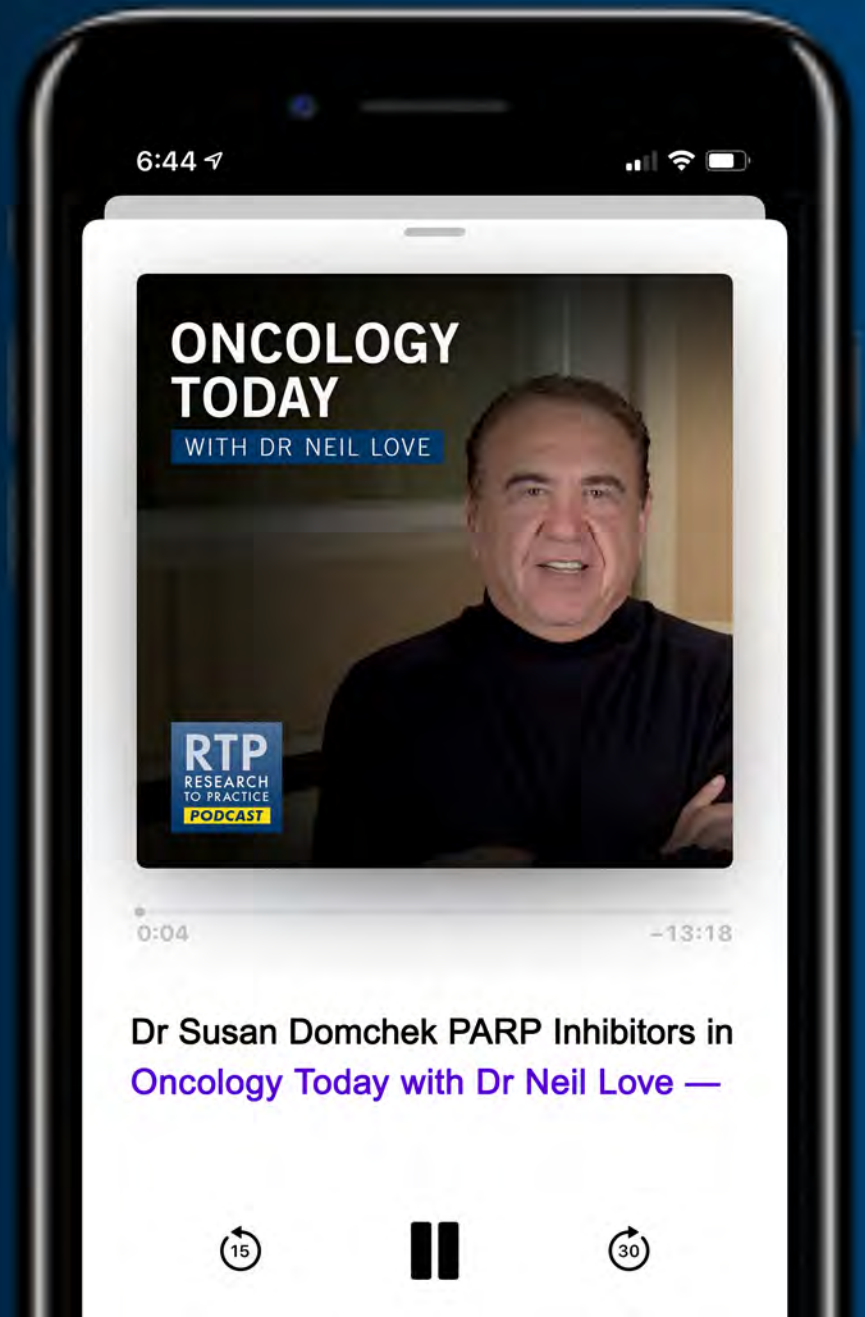

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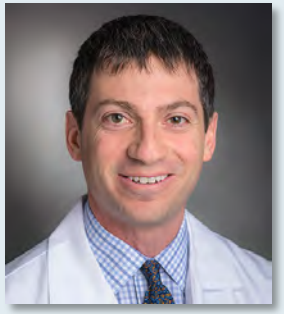
Meet The Professor Program Participating Faculty



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Willamette Valley Cancer Institute and Research Center
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Associate Center Director for Clinical Investigations
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Jennifer Woyach, MD
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Division of Hematology
Department of Internal Medicine
The Ohio State University
Comprehensive Cancer Center
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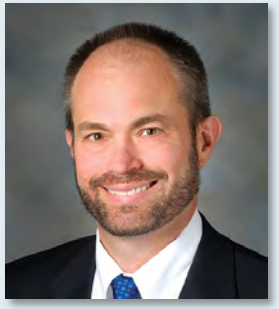

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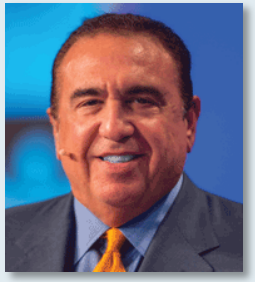

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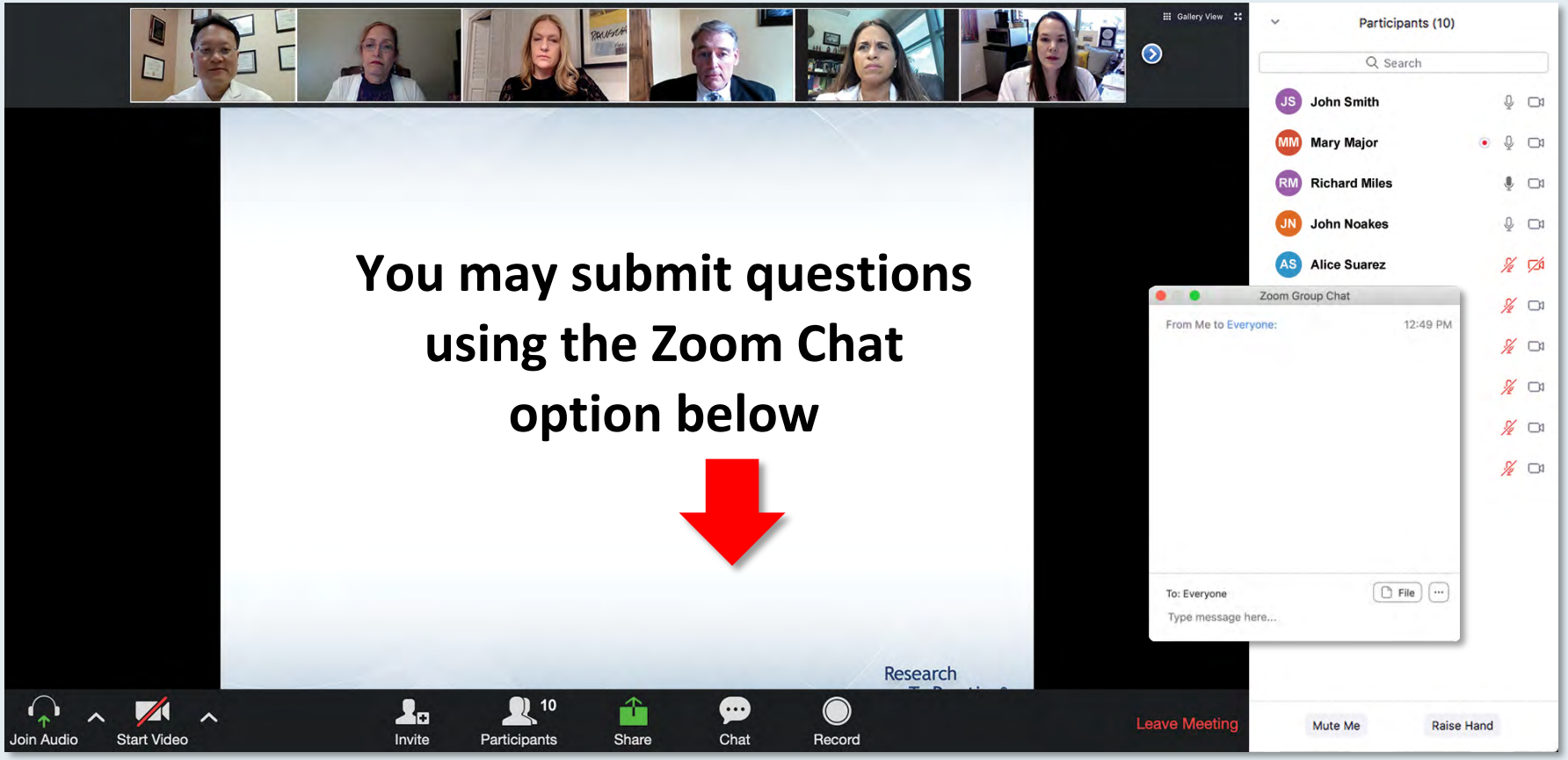

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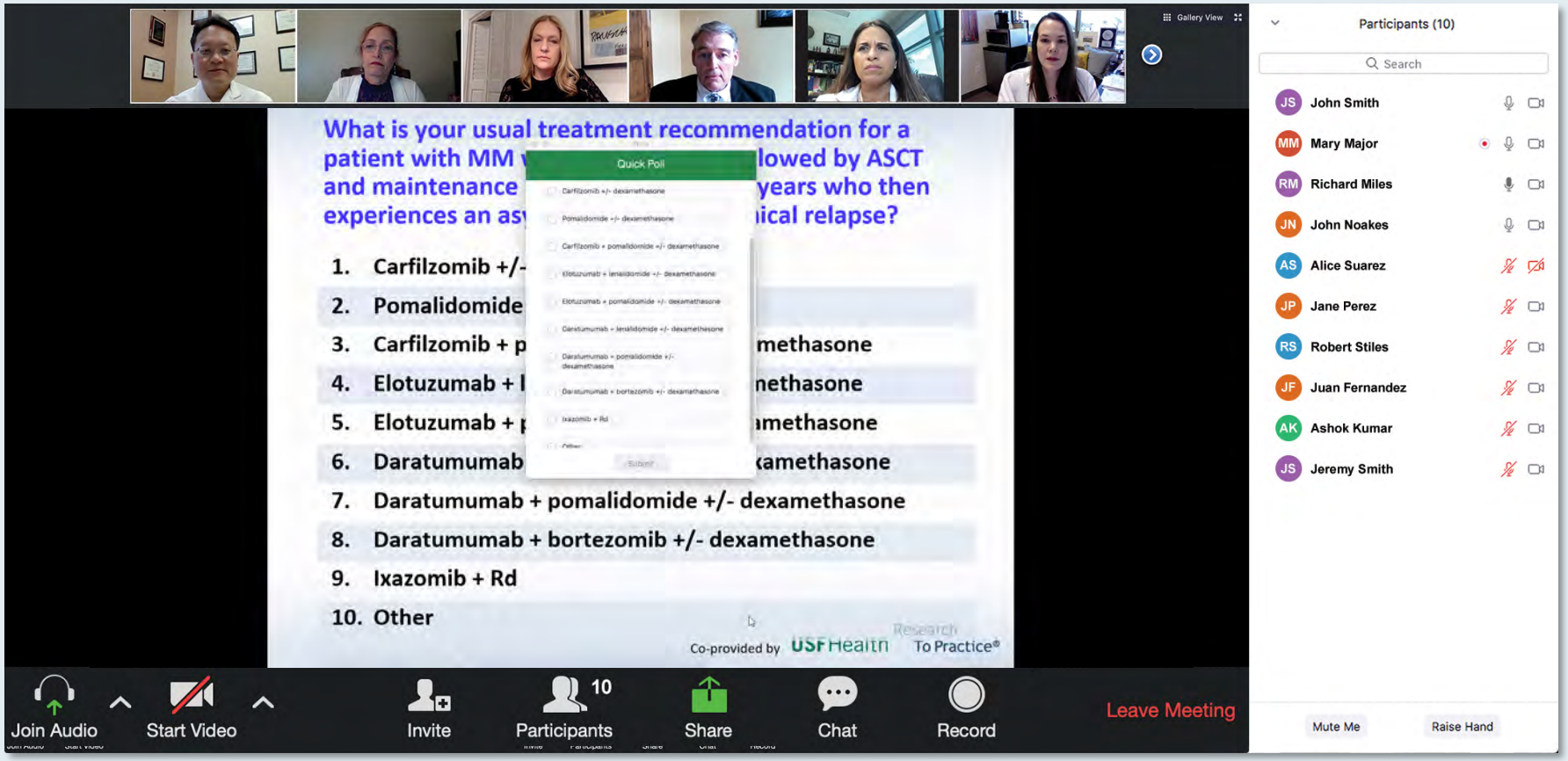

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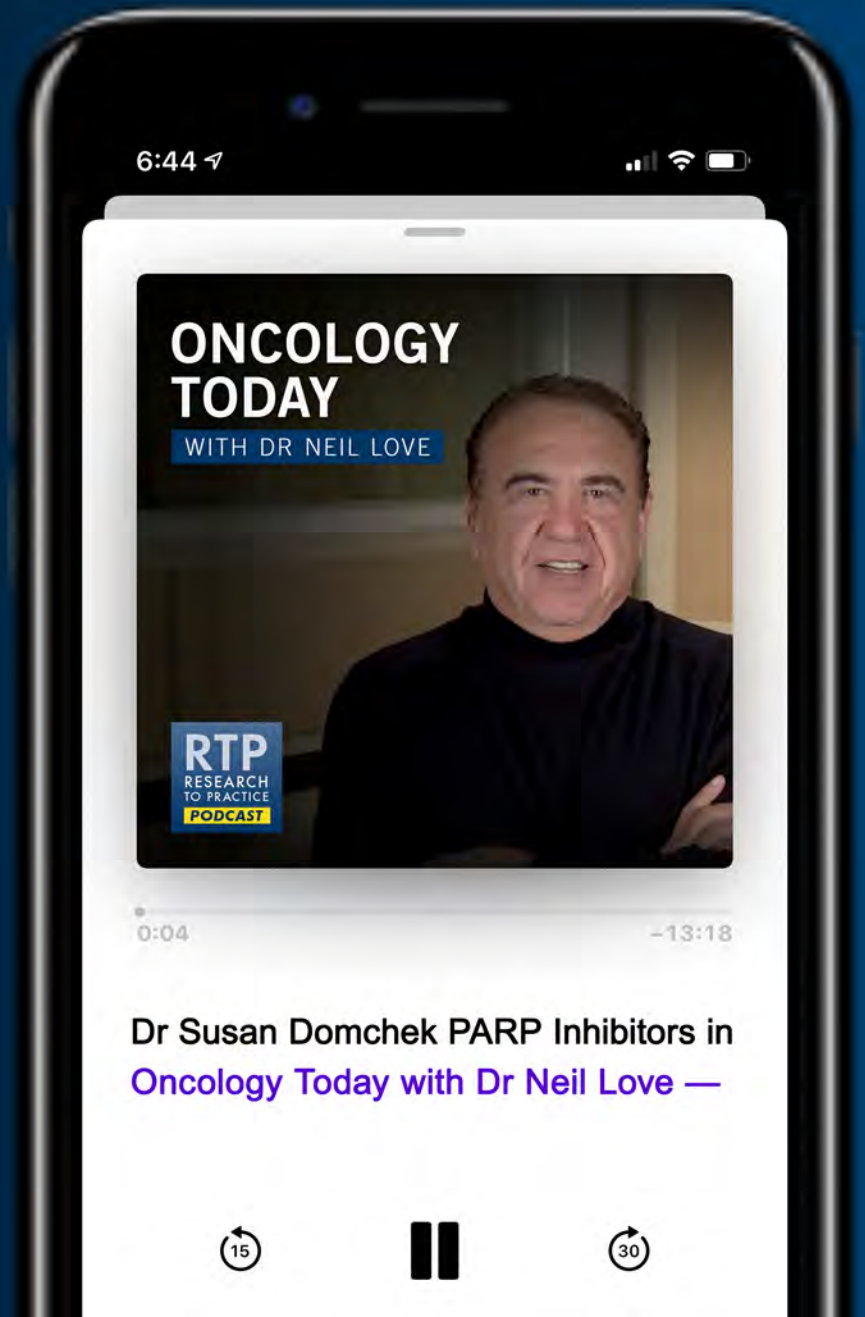

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Immunotherapy and Novel Agents in Gynecologic Cancers

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Erik J Rupard, MD
Chief, Section of Hematology-Oncology
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Reading Hospital and Medical Center
West Reading, Pennsylvania

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How I Treat

How I manage CLL with venetoclax-based treatments

William G. Wierda[1] and Francesco Paolo Tambaro[2]

[1]Department of Leukemia, The University of Texas MD Anderson Cancer Center, Houston, TX; and [2]Unità Operativa di Trapianto di Midollo Osseo e Servizio Trasfusionale, Azienda Ospedaliera di Rilievo Nazionale Santobono-Pausilipon, Napoli, Italy

Blood 2020;135(17):1421-27

Selecting First-Line CLL Treatment

TP53 status (del(17p)/*TP53* mutation)	Age/ fitness	IGHV MS	First-line treatment (in order of authors' preference)
TP53 deleted and/ or mutated	All	Either	(1) BTKi 6 OBIN (continuous), (2) VEN 1 OBIN (fixed duration), no CIT
TP53 intact	Younger/ fit	Mutated	(1) FCR (fixed duration), (2) VEN 1 OBIN (fixed duration), (3) BTKi 6 OBIN (continuous)
		Unmutated	(1) VEN 1 OBIN (fixed-duration), (2) BTKi 6 OBIN (continuous)
	Older/ unfit	Mutated	(1) VEN 1 OBIN (fixed duration), (2) BTKi 6 OBIN (continuous)
		Unmutated	(1) BTKi 6 OBIN (continuous), (2) VEN 1 OBIN (fixed-duration)

Selecting Treatment for Relapsed/Refractory CLL

Prior treatment			Recommendation for nexttreatment	Allo-SCT planning
CIT	BCL2i	BTKi		
Yes	No	No	VEN 1 RIT (fixed duration) or BTKi (continuous)	No
		Yes (intolerant)	Alternative BTKi (continuous) or PI3Ki 6 CD20 mAb (continuous)	No
		Yes (refractory)	VEN 1 RIT	Short-term
	Yes	No	BTKi (continuous)	Yes
		Yes (intolerant)	Alternative BTKi (continuous) or PI3Ki 6 CD20 mAb (continuous)	Yes
		Yes (refractory)	Clinical trial CIT if no TP53 abnormality to debulk	Immediate
No	No	Yes (intolerant)	Alternative BTKi (continuous) or PI3Ki 6 CD20 mAb (continuous)	No
		Yes (refractory)	VEN 1 RIT (fixed duration)	Yes
	Yes	No	BTKi (continuous)	No
		Yes (intolerant)	Alternative BTKi (continuous) or PI3Ki 6 CD20 mAb (continuous)	No
		Yes (refractory)	Clinical trial CIT if no TP53 abnormality to debulk	Immediate

Wierda *Blood* 2020

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Viewpoint

Tumour lysis syndrome in patients with chronic lymphocytic leukaemia treated with BCL-2 inhibitors: risk factors, prophylaxis, and treatment recommendations

Francesco Paolo Tambaro, William G Wierda

***Lancet Haematol* 2020;7(2):e168-76**

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Meet The Professor with Dr Wierda

MODULE 1: Cases from the Community (Drs Lamar, Morganstein and Rupard)

- Dr Lamar: An asymptomatic 81-year-old man with newly diagnosed CLL
- Questions and Comments: First-line treatment of CLL
- Questions and Comments: Relevance of TP53 mutation testing in CLL prognostication
- Questions and Comments: First-line therapy for older patients with comorbidities
- Questions and Comments: Current role of up-front chemotherapy
- Dr Rupard: A 94-year-old man with CLL and Merkel cell carcinoma

MODULE 2: CLL Journal Club with Dr Wierda

MODULE 3: Beyond the Guidelines – Clinical Investigator Approaches to Common Clinical Scenarios

MODULE 4: Key Recent Data Sets

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Case Presentation – Dr Lamar: An asymptomatic 81-year-old man with newly diagnosed CLL

Dr Zanetta Lamar

- December 2019: Presents with elevated white blood cell count found on routine blood work
- Flow cytometry: CD5+, CD23+, CD38-, ZAP70-, IGHV mutated
- FISH: del17p negative
- CT scan shows splenomegaly, 17 cm
- Observation recommended; atient obtained second opinion at academic center that recommended treatment with obinutuzumab/venetoclax

Questions

- Do you routinely use asymptomatic splenomegaly or nodal enlargement alone as treatment indications? If so, do you have any data? Could you expound on why this was changed in the most recent guidelines update?
- Do you incorporate MRD testing in your management of patients with CLL?

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Special Report

iwCLL guidelines for diagnosis, indications for treatment, response assessment, and supportive management of CLL

Michael Hallek,[1,2] Bruce D. Cheson,[3] Daniel Catovsky,[4] Federico Caligaris-Cappio,[5] Guillermo Dighiero,[6] Hartmut Döhner,[7] Peter Hillmen,[8] Michael Keating,[9] Emili Montserrat,[10] Nicholas Chiorazzi,[11] Stephan Stilgenbauer,[7] Kanti R. Rai,[11] John C. Byrd,[12] Barbara Eichhorst,[1] Susan O'Brien,[13] Tadeusz Robak,[14] John F. Seymour,[15] and Thomas J. Kipps[16]

Blood 2019;131(25):2745-60

Questions and Comments: First-line treatment of CLL

Dr Zanetta Lamar

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Questions and Comments: Relevance of TP53 mutation testing in CLL prognostication

Dr Neil Morganstein

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Questions and Comments: First-line therapy for older patients with comorbidities

Dr Neil Morganstein

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Questions and Comments: Current role of up-front chemotherapy

Dr Neil Morganstein

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Case Presentation – Dr Rupard: A 94-year-old man with CLL and Merkel cell carcinoma

Dr Eric Rupard

- Active farmer presents in emergency department with a “scalp lesion”
- White blood cell count: 84,000
  - 90% lymphocytes
  - No anemia or thrombocytopenia
- Lymph node positive
- Biopsy of scalp lesion: Merkel cell carcinoma
- Did not require treatment for CLL

Questions

- How often do you see Merkel cell carcinoma in patients with CLL? How often do you see other skin tumors in patients with CLL?

Meet The Professor with Dr Wierda

MODULE 1: Cases from the Community (Drs Lamar, Morganstein and Rupard)

MODULE 2: CLL Journal Club with Dr Wierda

- Management of leukemia in the era of COVID-19
- Adverse events associated with novel therapies for hematologic cancers
- Mature results from a Phase II study of acalabrutinib for treatment-naïve CLL
- Fungal infections in patients with CLL receiving ibrutinib
- Richter's transformation in patients with CLL during interruption of ibrutinib treatment
- Clinical significance and predictive factors associated with achieving complete remission with ibrutinib
- Mechanistic model of minimal residual disease (MRD) kinetics with venetoclax
- CAPTIVATE trial: Ibrutinib with venetoclax as first-line therapy for CLL in MRD cohort
- Ibrutinib with venetoclax in high-risk CLL
- CAR T-cell therapy for CD19-positive lymphoid tumors

MODULE 3: Beyond the Guidelines – Clinical Investigator Approaches to Common Clinical Scenarios

MODULE 4: Key Recent Data Sets

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Review

Acta Hæmatologica

Acta Haematol
DOI: 10.1159/000508199

Received: April 24, 2020
Accepted: April 26, 2020
Published online: May 11, 2020

Treating Leukemia in the Time of COVID-19

Shilpa Paul[a] Caitlin R. Rausch[a] Nitin Jain[b] Tapan Kadia[b] Farhad Ravandi[b]
Courtney D. DiNardo[b] Mary Alma Welch[b] Bouthaina S. Dabaja[c] Naval Daver[b]
Guillermo Garcia-Manero[b] William Wierda[b] Naveen Pemmaraju[b]
Guillermo Montalban Bravo[b] Philip Thompson[b] Srdan Verstovsek[b]
Marina Konopleva[b] Hagop Kantarjian[b] Elias Jabbour[b]

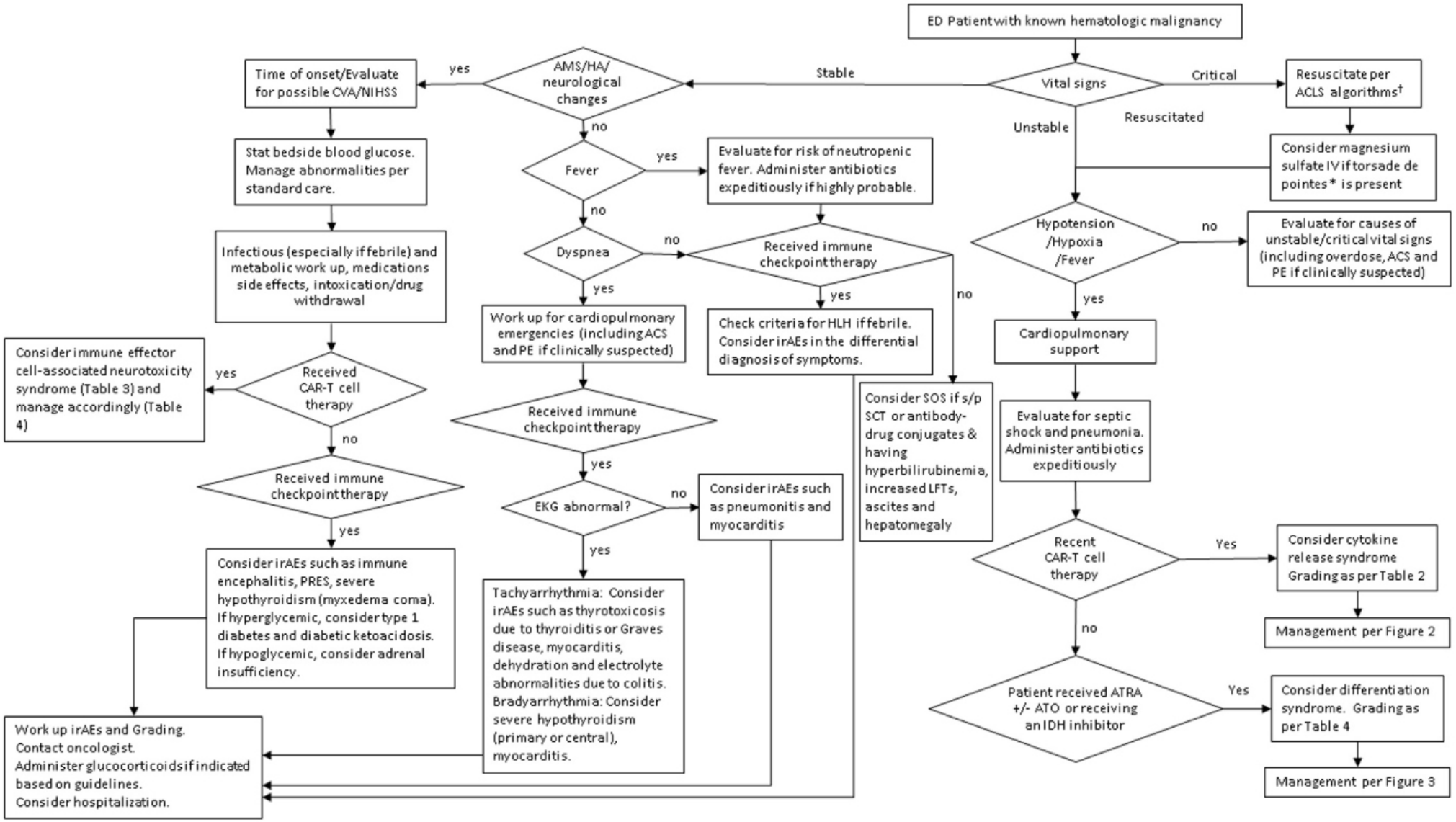
Acta Haematol 2020;11:1-13

GENERAL MEDICINE/REVIEW ARTICLE

Adverse Events of Novel Therapies for Hematologic Malignancies: What Emergency Physicians Should Know

Mohsin Shah, MD; Eva Rajha, MD; Courtney DiNardo, MD, MSCE; Erin Muckey, MD, MBA; William G. Wierda, MD, PhD; Sai-Ching J. Yeung, MD, PhD*

Ann Emerg Med 2020;75(2):264-86



Shah *Ann Emerg Med* 2020

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Acalabrutinib in Treatment-Naïve Chronic Lymphocytic Leukemia: Mature Results from Phase II Study Demonstrating Durable Remissions and Long-Term Tolerability

Byrd JC et al.

ASCO 2020;Abstract 8024.

Leukemia & Lymphoma

ISSN: 1042-8194 (Print) 1029-2403 (Online) Journal homepage: https://www.tandfonline.com/loi/ilal20

Incidence and characterization of fungal infections in chronic lymphocytic leukemia patients receiving ibrutinib

Michael Frei, Samuel L. Aitken, Nitin Jain, Philip Thompson, William Wierda, Dimitrios P. Kontoyiannis & Adam J. DiPippo

Leuk Lymphoma 2020;61(10):2488-91

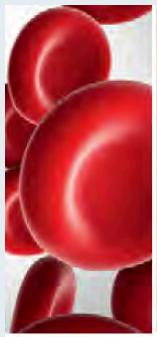
STIMULUS REPORT

blood advances

Incidental Richter transformation in chronic lymphocytic leukemia patients during temporary interruption of ibrutinib

Paul J. Hampel,[1,*] Hua-Jay J. Cherng,[2,*] Timothy G. Call,[1] Wei Ding,[1] Mahsa Khanlari,[3] Ellen D. McPhail,[4] Roberto N. Miranda,[3] Pei Lin,[3] Hussein A. Tawbi,[5] Alessandra Ferrajoli,[2] William G. Wierda,[2] Nitin Jain,[2] and Sameer A. Parikh[1]

Blood Adv 2020;4(18):4508-11



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Letter to *Blood*

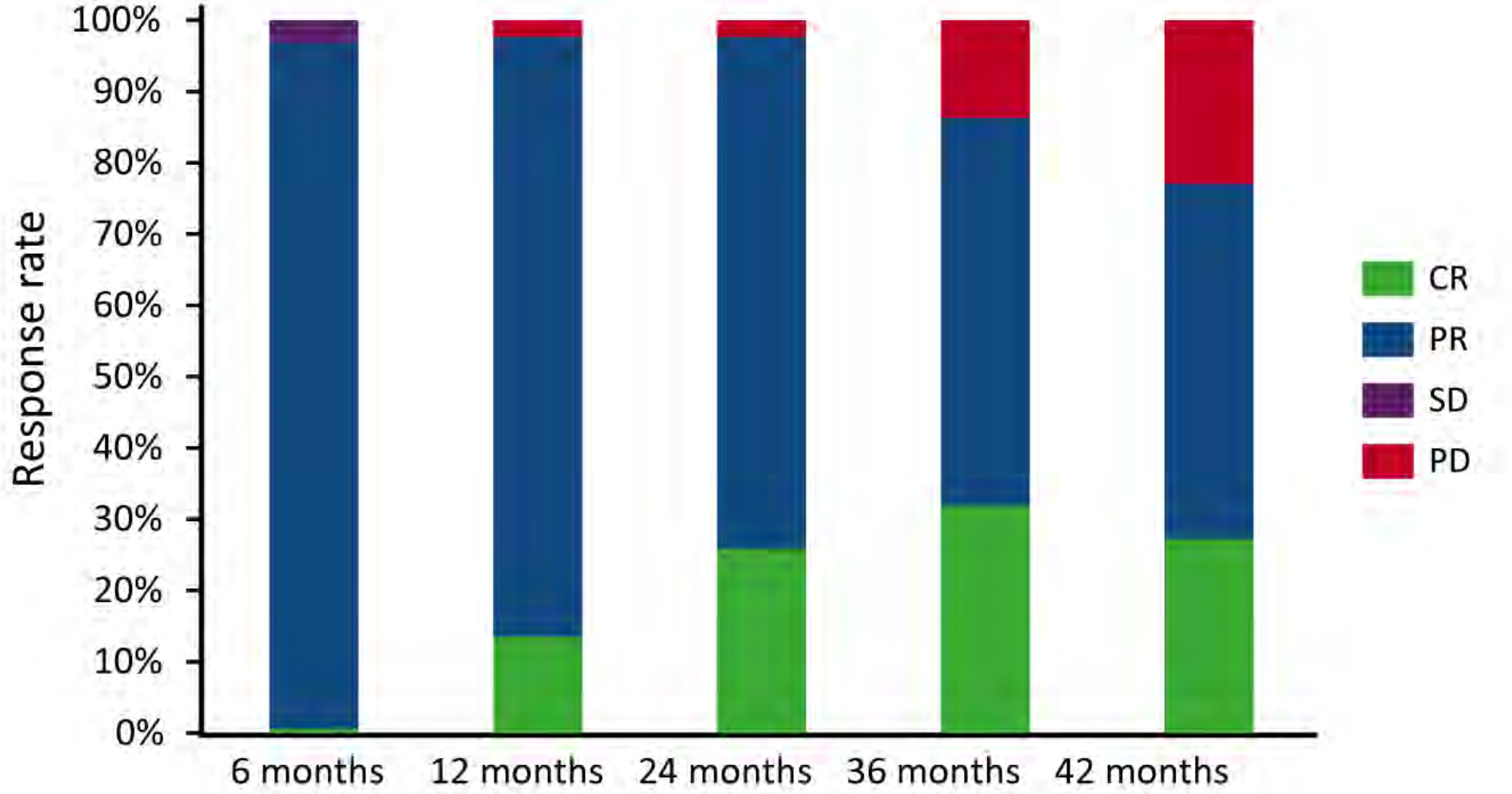
TO THE EDITOR:

Achieving complete remission in CLL patients treated with ibrutinib: clinical significance and predictive factors

Paolo Strati,[1] Ellen J. Schlette,[2] Luisa M. Solis Soto,[3] Daniela E. Duenas,[3] Mariela Sivina,[4] Ekaterina Kim,[4] Michael J. Keating,[4] William G. Wierda,[4] Alessandra Ferrajoli,[4] Hagop Kantarjian,[4] Zeev Estrov,[4] Nitin Jain,[4] Philip A. Thompson,[4] Ignacio I. Wistuba,[3] and Jan A. Burger[4]

***Blood* 2020;135(7):510-13**

Response Rate Over Time with Ibrutinib



Strati *Blood* 2020

Integrated Mechanistic Model of Minimal Residual Disease Kinetics With Venetoclax Therapy in Chronic Lymphocytic Leukemia

Sathej Gopalakrishnan[1,*], William Wierda[2], Brenda Chyla[3], Rajeev Menon[1], Dale Miles[4], Rod Humerickhouse[5], Walid Awni[1], Ahmed Hamed Salem[1,6], Sven Mensing[1] and Kevin J. Freise[1]

Clin Pharmacol Ther 2020;[Online ahead of print]

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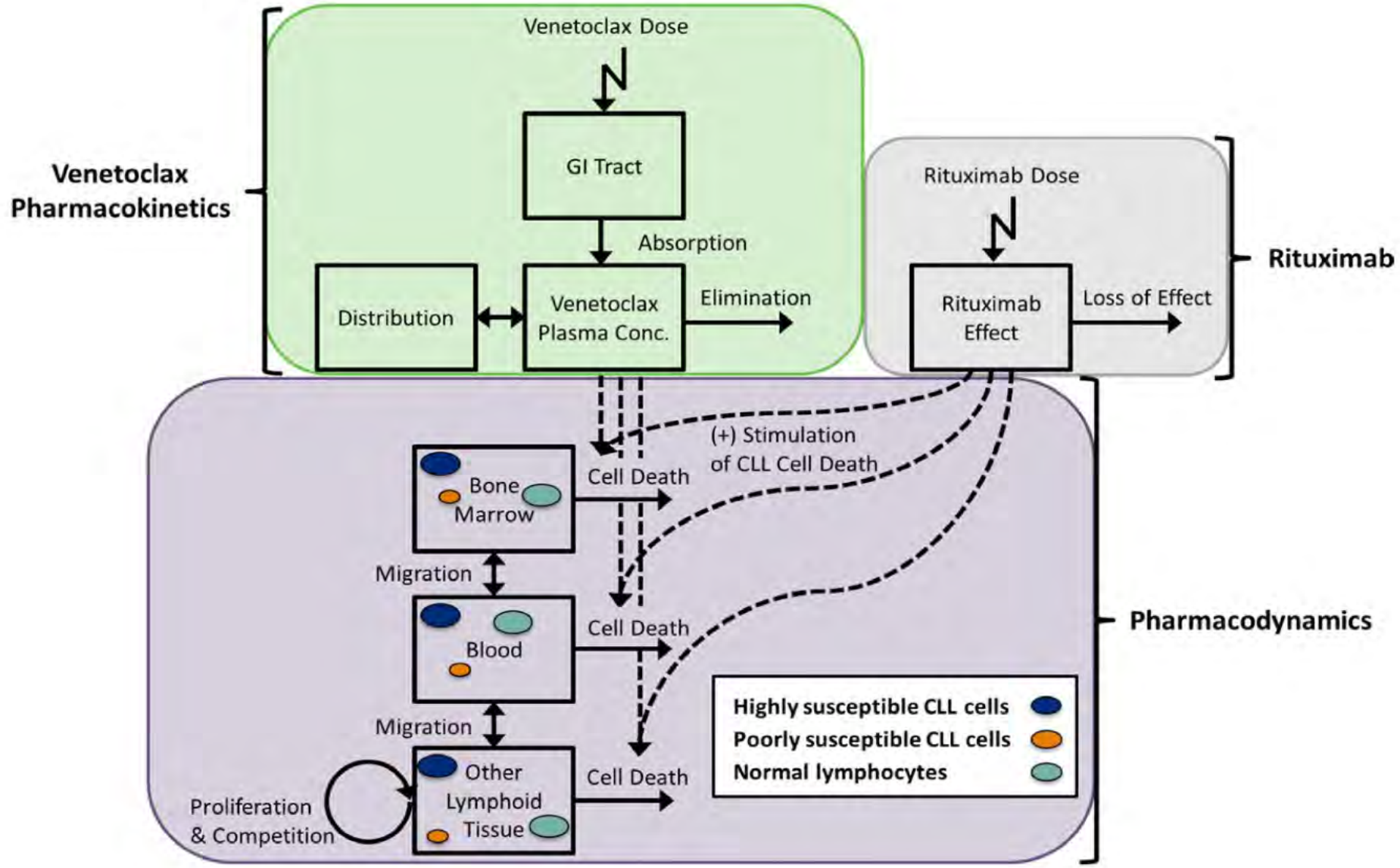
Integrated Mechanistic MRD Model



Gopalakrishnan *Clin Pharmacol Ther* 2020

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Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

☑ Venetoclax administered in combination with the CD20-targeting monoclonal antibody rituximab in relapsed or refractory chronic lymphocytic leukemia (CLL) results in a large proportion of patients achieving negative minimal residual disease (MRD) status ($< 10^{-4}$) in the bone marrow (BM).

WHAT QUESTION DID THIS STUDY ADDRESS?

☑ The objective of this research was to develop an integrated mechanistic model of the kinetics of MRD response to treatment in CLL in order to evaluate the impact of venetoclax and rituximab combination therapy duration on MRD.

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

☑ The integrated mechanistic model was validated with internal and external data and simulations indicated an MRD-negative ($< 10^{-4}$) rate of 63% (59–67%) in the BM in 2 years.

HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?

☑ The work provides an example of how modeling and simulation can be effectively used to evaluate different treatment durations in oncology.

Gopalakrishnan *Clin Pharmacol Ther* 2020

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Ibrutinib (Ibr) plus Venetoclax (Ven) for First-Line Treatment of Chronic Lymphocytic Leukemia (CLL)/Small Lymphocytic Lymphoma (SLL): Results from the MRD Cohort of the Phase 2 CAPTIVATE Study

Tam CS et al.

ASH 2019;Abstract 35.

Venetoclax Added to Ibrutinib in High-Risk CLL Achieves a High Rate of Undetectable Minimal Residual Disease

Thompson PA et al.

ASH 2019;Abstract 358.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Use of CAR-Transduced Natural Killer Cells in CD19-Positive Lymphoid Tumors

Enli Liu, M.D., David Marin, M.D., Pinaki Banerjee, Ph.D., Homer A. Macapinlac, M.D., Philip Thompson, M.B., B.S., Rafet Basar, M.D., Lucila Nassif Kerbauy, M.D., Bethany Overman, B.S.N., Peter Thall, Ph.D., Mecit Kaplan, M.S., Vandana Nandivada, M.S., Indresh Kaur, Ph.D., Ana Nunez Cortes, M.D., Kai Cao, M.D., May Daher, M.D., Chitra Hosing, M.D., Evan N. Cohen, Ph.D., Partow Kebriaei, M.D., Rohtesh Mehta, M.D., Sattva Neelapu, M.D., Yago Nieto, M.D., Ph.D., Michael Wang, M.D., William Wierda, M.D., Ph.D., Michael Keating, M.D., Richard Champlin, M.D., Elizabeth J. Shpall, M.D., and Katayoun Rezvani, M.D., Ph.D.

N Engl J Med 2020;382(6):545-53

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MODULE 2: CLL Journal Club with Dr Wierda

MODULE 3: Beyond the Guidelines – Clinical Investigator Approaches to Common Clinical Scenarios

MODULE 4: Key Recent Data Sets

- PFS and rate and duration of MRD negativity with venetoclax/obinutuzumab (CLL14 trial)
- Acalabrutinib for previously untreated CLL (ELEVATE-TN trial)
- Extended follow-up results with ibrutinib/rituximab in younger patients (ECOG-E1912 trial)
- CAPTIVATE MRD cohort: Efficacy and safety results with ibrutinib lead-in and ibrutinib/venetoclax combination

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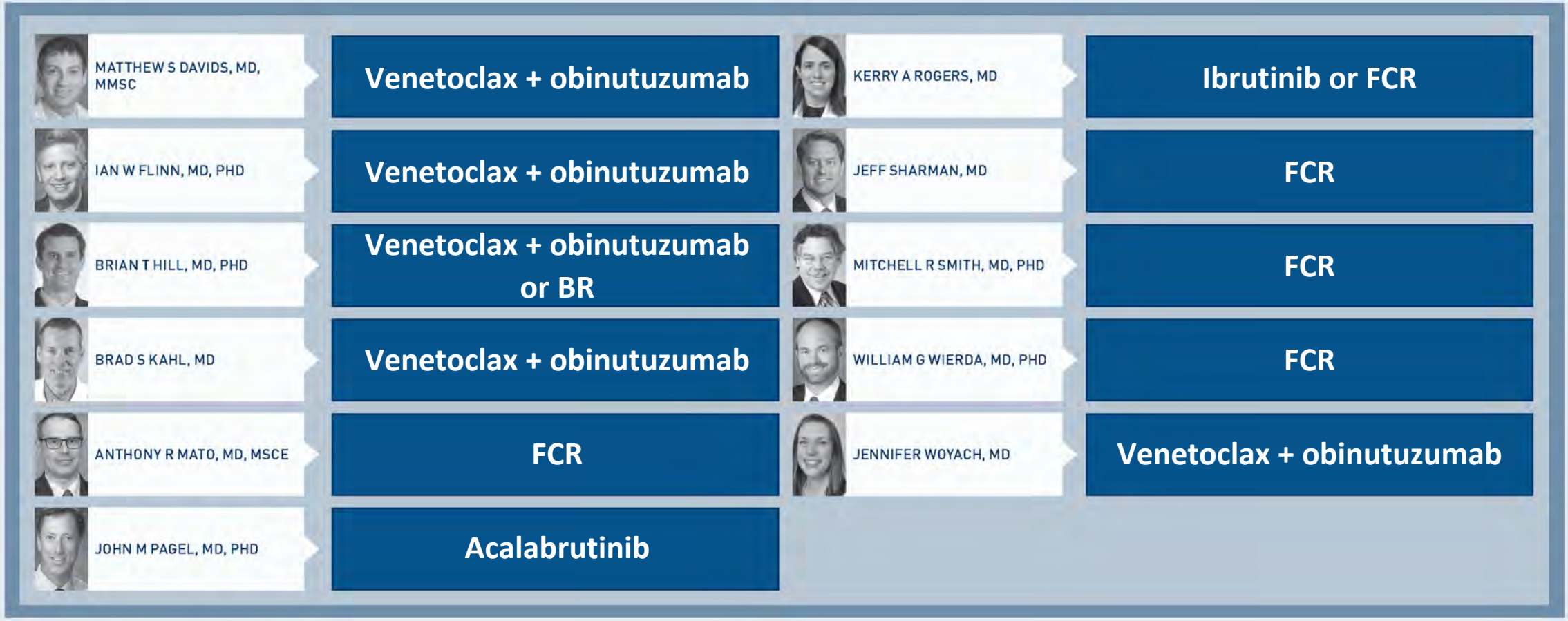
What is your usual preferred initial regimen for a 60-year-old patient with CLL with IGHV mutation but no del(17p) or TP53 mutation who requires treatment?

1. FCR
2. Ibrutinib
3. Ibrutinib + rituximab
4. Ibrutinib + obinutuzumab
5. Acalabrutinib
6. Acalabrutinib + obinutuzumab
7. Venetoclax + obinutuzumab
8. Other

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



BR = bendamustine/rituximab; FCR = fludarabine/cyclosphosphamide/rituximab (FCR)

RTP RESEARCH TO PRACTICE

What is your usual preferred initial regimen for a 75-year-old patient with CLL with IGHV mutation but no del(17p) or TP53 mutation who requires treatment?

 MATTHEW S DAVIDS, MD, MMSC	Venetoclax + obinutuzumab
 IAN W FLINN, MD, PHD	Acalabrutinib
 BRIAN T HILL, MD, PHD	Obinutuzumab
 BRAD S KAHL, MD	Venetoclax + obinutuzumab
 ANTHONY R MATO, MD, MSCE	Acalabrutinib
 JOHN M PAGEL, MD, PHD	Acalabrutinib
 KERRY A ROGERS, MD	Acalabrutinib or venetoclax + obinutuzumab
 JEFF SHARMAN, MD	Venetoclax + obinutuzumab
 MITCHELL R SMITH, MD, PHD	Ibrutinib
 WILLIAM G WIERDA, MD, PHD	Venetoclax + obinutuzumab
 JENNIFER WOYACH, MD	Ibrutinib

RTP RESEARCH TO PRACTICE

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

1. FCR
2. Ibrutinib
3. Ibrutinib + rituximab
4. Ibrutinib + obinutuzumab
5. Acalabrutinib
6. Acalabrutinib + obinutuzumab
7. Venetoclax + obinutuzumab
8. Other

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

 MATTHEW S DAVIDS, MD, MMSC	Venetoclax + obinutuzumab
 IAN W FLINN, MD, PHD	Venetoclax + obinutuzumab
 BRIAN T HILL, MD, PHD	Venetoclax + obinutuzumab
 BRAD S KAHL, MD	Venetoclax + obinutuzumab
 ANTHONY R MATO, MD, MSCE	Venetoclax + obinutuzumab
 JOHN M PAGEL, MD, PHD	Acalabrutinib
 KERRY A ROGERS, MD	Acalabrutinib or venetoclax + obinutuzumab
 JEFF SHARMAN, MD	Acalabrutinib
 MITCHELL R SMITH, MD, PHD	Venetoclax + obinutuzumab
 WILLIAM G WIERDA, MD, PHD	Venetoclax + obinutuzumab
 JENNIFER WOYACH, MD	Ibrutinib

RTP RESEARCH TO PRACTICE

What is your usual preferred initial regimen for a 75-year-old patient with CLL with unmutated IGHV and no del(17p) or TP53 mutation who requires treatment?

 MATTHEW S DAVIDS, MD, MMSC	Venetoclax + obinutuzumab
 IAN W FLINN, MD, PHD	Acalabrutinib
 BRIAN T HILL, MD, PHD	Venetoclax + obinutuzumab
 BRAD S KAHL, MD	Venetoclax + obinutuzumab
 ANTHONY R MATO, MD, MSCE	Acalabrutinib
 JOHN M PAGEL, MD, PHD	Acalabrutinib
 KERRY A ROGERS, MD	Acalabrutinib or venetoclax + obinutuzumab
 JEFF SHARMAN, MD	Acalabrutinib
 MITCHELL R SMITH, MD, PHD	Ibrutinib
 WILLIAM G WIERDA, MD, PHD	Acalabrutinib
 JENNIFER WOYACH, MD	Ibrutinib

RTP RESEARCH TO PRACTICE

What is your usual preferred initial regimen for a 75-year-old patient with CLL with unmutated IGHV and no del(17p) or TP53 mutation who requires treatment and has bulky disease?

 MATTHEW S DAVIDS, MD, MMSC	Venetoclax + obinutuzumab
 IAN W FLINN, MD, PHD	Acalabrutinib
 BRIAN T HILL, MD, PHD	Venetoclax + obinutuzumab
 BRAD S KAHL, MD	Venetoclax + obinutuzumab
 ANTHONY R MATO, MD, MSCE	Acalabrutinib + obinutuzumab
 JOHN M PAGEL, MD, PHD	Acalabrutinib
 KERRY A ROGERS, MD	Acalabrutinib
 JEFF SHARMAN, MD	Acalabrutinib
 MITCHELL R SMITH, MD, PHD	Venetoclax + obinutuzumab
 WILLIAM G WIERDA, MD, PHD	Acalabrutinib
 JENNIFER WOYACH, MD	Ibrutinib

RTP RESEARCH TO PRACTICE

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

 MATTHEW S DAVIDS, MD, MMSC	Ibrutinib
 IAN W FLINN, MD, PHD	Acalabrutinib
 BRIAN T HILL, MD, PHD	Acalabrutinib
 BRAD S KAHL, MD	Acalabrutinib + obinutuzumab
 ANTHONY R MATO, MD, MSCE	Acalabrutinib
 JOHN M PAGEL, MD, PHD	Acalabrutinib
 KERRY A ROGERS, MD	Ibrutnib
 JEFF SHARMAN, MD	Acalabrutinib
 MITCHELL R SMITH, MD, PHD	Venetoclax + obinutuzumab
 WILLIAM G WIERDA, MD, PHD	Acalabrutinib
 JENNIFER WOYACH, MD	Ibrutinib

RTP RESEARCH TO PRACTICE

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

1. Continue treatment
2. Discontinue treatment

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

 MATTHEW S DAVIDS, MD, MMSC	Discontinue treatment
 IAN W FLINN, MD, PHD	Discontinue treatment
 BRIAN T HILL, MD, PHD	Discontinue treatment
 BRAD S KAHL, MD	Discontinue treatment
 ANTHONY R MATO, MD, MSCE	Continue treatment
 JOHN M PAGEL, MD, PHD	Continue treatment
 KERRY A ROGERS, MD	Discontinue treatment
 JEFF SHARMAN, MD	Discontinue treatment
 MITCHELL R SMITH, MD, PHD	Discontinue treatment
 WILLIAM G WIERDA, MD, PHD	Continue treatment
 JENNIFER WOYACH, MD	Discontinue treatment

RTP RESEARCH TO PRACTICE

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

 MATTHEW S DAVIDS, MD, MMSC	Discontinue treatment
 IAN W FLINN, MD, PHD	Discontinue treatment
 BRIAN T HILL, MD, PHD	Discontinue treatment
 BRAD S KAHL, MD	Discontinue treatment
 ANTHONY R MATO, MD, MSCE	Discontinue treatment
 JOHN M PAGEL, MD, PHD	Discontinue treatment
 KERRY A ROGERS, MD	Discontinue treatment
 JEFF SHARMAN, MD	Discontinue treatment
 MITCHELL R SMITH, MD, PHD	Discontinue treatment
 WILLIAM G WIERDA, MD, PHD	Discontinue treatment
 JENNIFER WOYACH, MD	Discontinue treatment

RTP RESEARCH TO PRACTICE

Which second-line systemic therapy would you recommend for a 60-year-old patient with CLL with no IGHV mutation and no del(17p) or TP53 mutation who responds to ibrutinib and then experiences disease progression 3 years later?

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

Which second-line systemic therapy would you recommend for a 60-year-old patient with CLL with unmutated IGHV and no del(17p) or TP53 mutation who responds to ibrutinib and then experiences disease progression 3 years later?

 MATTHEW S DAVIDS, MD, MMSC	Venetoclax + rituximab
 IAN W FLINN, MD, PHD	Venetoclax + obinutuzumab
 BRIAN T HILL, MD, PHD	Venetoclax + rituximab
 BRAD S KAHL, MD	Venetoclax + rituximab
 ANTHONY R MATO, MD, MSCE	Venetoclax + rituximab
 JOHN M PAGEL, MD, PHD	Venetoclax
 KERRY A ROGERS, MD	Venetoclax + rituximab
 JEFF SHARMAN, MD	Venetoclax + rituximab
 MITCHELL R SMITH, MD, PHD	Venetoclax + obinutuzumab
 WILLIAM G WIERDA, MD, PHD	Venetoclax + rituximab
 JENNIFER WOYACH, MD	Venetoclax + rituximab

RTP RESEARCH TO PRACTICE

Which second-line systemic therapy would you recommend for a 60-year-old patient with CLL with no IGHV mutation and no del(17p) or TP53 mutation who responds to venetoclax/obinutuzumab and then experiences disease progression 3 years later?

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

RTP RESEARCH TO PRACTICE

Which second-line systemic therapy would you recommend for a 60-year-old patient with CLL with unmutated IGHV and no del(17p) or TP53 mutation who responds to venetoclax/obinutuzumab and then experiences disease progression 3 years later?

 MATTHEW S DAVIDS, MD, MMSC	Venetoclax + obinutuzumab
 IAN W FLINN, MD, PHD	Acalabrutinib
 BRIAN T HILL, MD, PHD	Acalabrutinib
 BRAD S KAHL, MD	Acalabrutinib
 ANTHONY R MATO, MD, MSCE	Venetoclax + rituximab
 JOHN M PAGEL, MD, PHD	Acalabrutinib
 KERRY A ROGERS, MD	Ibrutinib
 JEFF SHARMAN, MD	Acalabrutinib
 MITCHELL R SMITH, MD, PHD	Ibrutinib
 WILLIAM G WIERDA, MD, PHD	Venetoclax + rituximab
 JENNIFER WOYACH, MD	Ibrutinib

RTP RESEARCH TO PRACTICE

A 60-year-old patient with CLL, an absolute lymphocyte count of 20,000 and several involved lymph nodes that are smaller than 2 centimeters is about to receive venetoclax. What preemptive measures, if any, would you take to address tumor lysis syndrome prior to the initiation of therapy?

 MATTHEW S DAVIDS, MD, MMSC	Encourage oral hydration and allopurinol
 IAN W FLINN, MD, PHD	IV hydration and allopurinol
 BRIAN T HILL, MD, PHD	Encourage oral hydration and allopurinol
 BRAD S KAHL, MD	Encourage oral hydration and allopurinol
 ANTHONY R MATO, MD, MSCE	IV hydration and allopurinol
 JOHN M PAGEL, MD, PHD	Encourage oral hydration and allopurinol
 KERRY A ROGERS, MD	Encourage oral hydration and allopurinol
 JEFF SHARMAN, MD	Give the obinutuzumab first to debulk, then after 1 month can start as outpatient with hydration and allopurinol
 MITCHELL R SMITH, MD, PHD	Encourage oral hydration and allopurinol
 WILLIAM G WIERDA, MD, PHD	Encourage oral hydration and allopurinol
 JENNIFER WOYACH, MD	Encourage oral hydration and allopurinol

RTP RESEARCH TO PRACTICE

A 60-year-old patient with CLL, an absolute lymphocyte count of 80,000 and several involved lymph nodes that are larger than 5 centimeters is about to receive venetoclax. What preemptive measures, if any, would you take to address tumor lysis syndrome prior to the initiation of therapy?

 MATTHEW S DAVIDS, MD, MMSC	Admit to hospital
 IAN W FLINN, MD, PHD	Debulk with obinutuzumab
 BRIAN T HILL, MD, PHD	Admit to hospital
 BRAD S KAHL, MD	Admit to hospital
 ANTHONY R MATO, MD, MSCE	Admit to hospital
 JOHN M PAGEL, MD, PHD	Admit to hospital
 KERRY A ROGERS, MD	Admit to hospital
 JEFF SHARMAN, MD	Obinutuzumab for 1 month to lower patient risk, then outpatient hydration and allopurinol
 MITCHELL R SMITH, MD, PHD	Admit to hospital
 WILLIAM G WIERDA, MD, PHD	Admit to hospital
 JENNIFER WOYACH, MD	IV hydration and allopurinol

RTP RESEARCH TO PRACTICE

For your patients with CLL whom you admit to the hospital to receive venetoclax, for how long do you typically admit them?

 MATTHEW S DAVIDS, MD, MMSC	8 days
 IAN W FLINN, MD, PHD	2 days
 BRIAN T HILL, MD, PHD	2 days (<48 hours)
 BRAD S KAHL, MD	2 days
 ANTHONY R MATO, MD, MSCE	2-3 days
 JOHN M PAGEL, MD, PHD	1 day
 KERRY A ROGERS, MD	2 nights for each dose escalation
 JEFF SHARMAN, MD	2 days
 MITCHELL R SMITH, MD, PHD	1- 2 days
 WILLIAM G WIERDA, MD, PHD	2 days
 JENNIFER WOYACH, MD	2 days or rapid escalation to full dose over 5 days

RTP RESEARCH TO PRACTICE

Meet The Professor with Dr Wierda

MODULE 1: Cases from the Community (Drs Lamar, Morganstein, and Rupard)

MODULE 2: CLL Journal Club with Dr Wierda

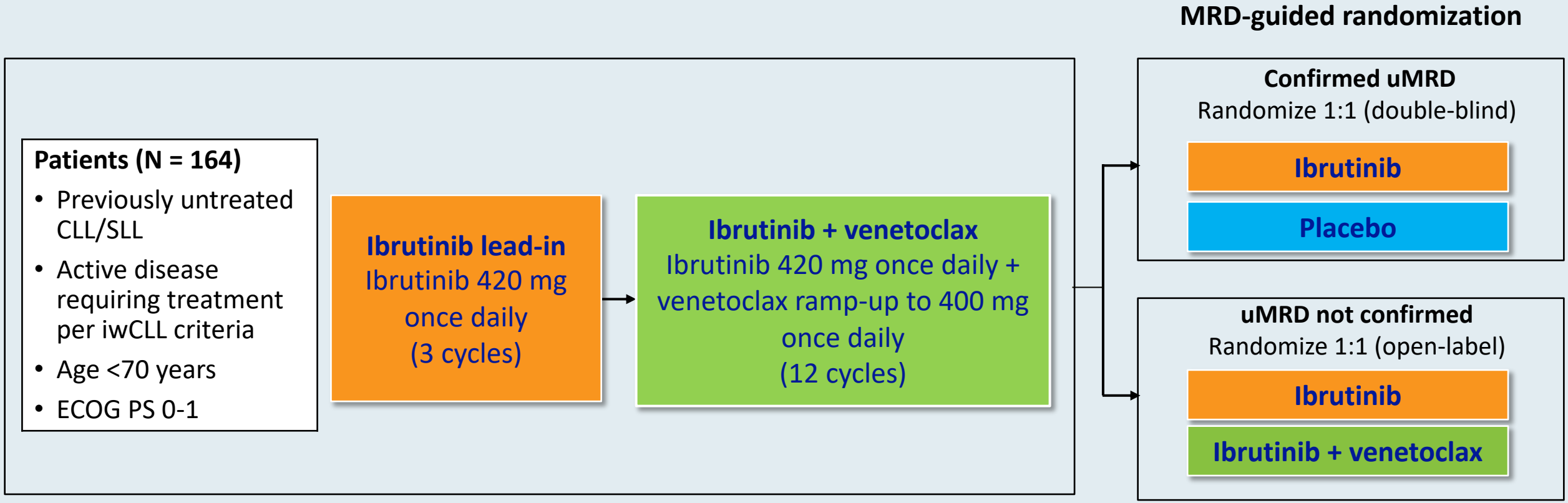
MODULE 3: Beyond the Guidelines – Clinical Investigator Approaches to Common Clinical Scenarios

MODULE 4: Key Recent Data Sets

- CAPTIVATE MRD cohort: Efficacy and safety results with ibrutinib lead-in and ibrutinib/venetoclax combination
- PFS and rate and duration of MRD negativity with venetoclax/obinutuzumab (CLL14 trial)
- Acalabrutinib for previously untreated CLL (ELEVATE-TN trial)
- Extended follow-up results with ibrutinib/rituximab in younger patients (ECOG-E1912 trial)

RTP
RESEARCH
TO PRACTICE

CAPTIVATE MRD Cohort: Study Design

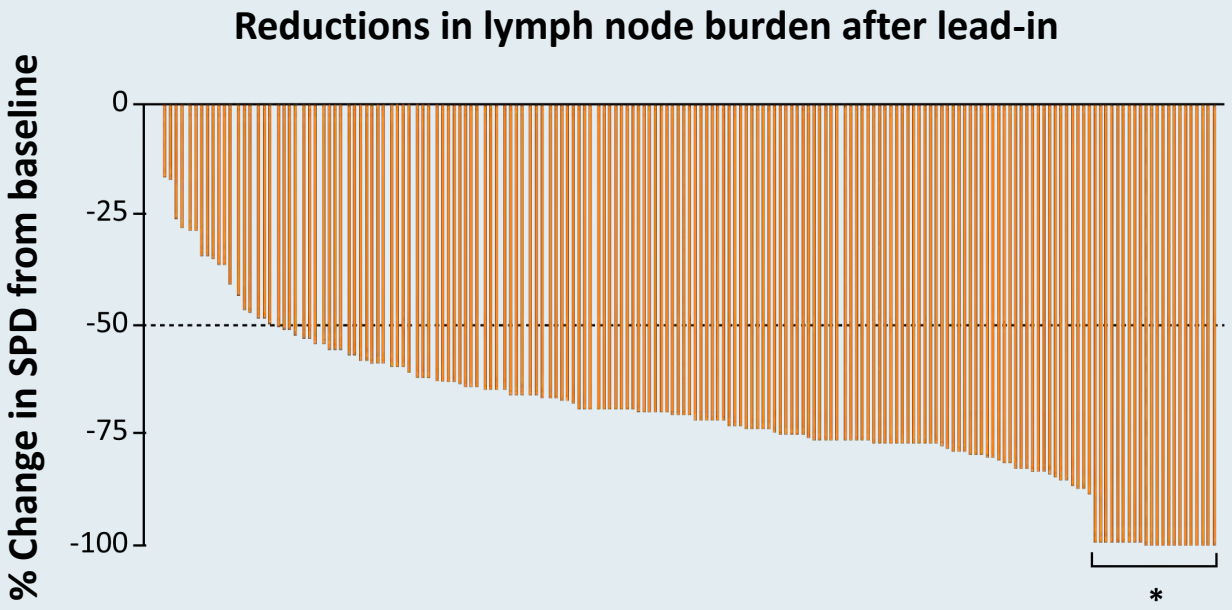


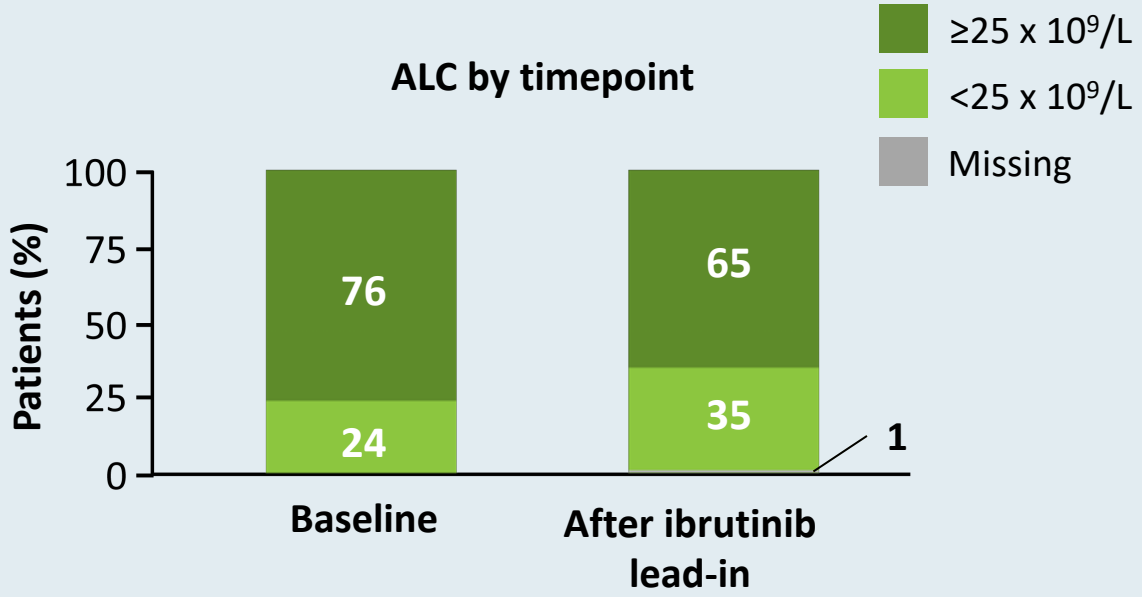
uMRD = undetectable minimal residual disease

Results presented for prerandomization phase of the MRD cohort (n = 164) with 12 cycles of ibrutinib + venetoclax prior to MRD-guided randomization

Siddiqi S et al. EHA 2020;Abstract S158.

CAPTIVATE MRD Cohort: 3 Cycles of Ibrutinib Lead-In





Three cycles of ibrutinib lead-in reduces TLS risk and indication for hospitalization

Siddiqi S et al. EHA 2020;Abstract S158.

RTP RESEARCH TO PRACTICE

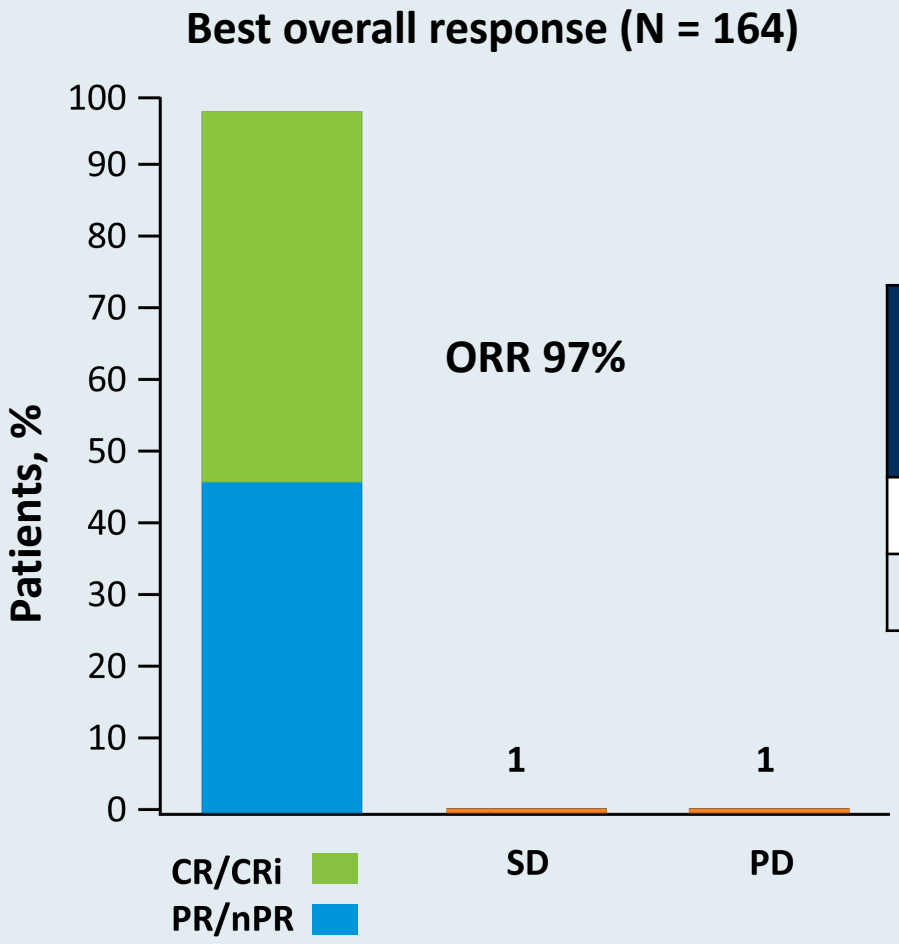
CAPTIVATE MRD Cohort: Undetectable MRD Rate

	Peripheral blood n = 163	Bone marrow n = 155
Best response of undetectable MRD in evaluable patients (95% CI)	**75%** (68-82)	**72%** (64-79)

- Rates of undetectable MRD in peripheral blood and bone marrow were highly concordant at Cycle 16 (91%)
- In the all-treated population (N = 164), undetectable MRD was achieved in 75% of patients in peripheral blood and in 68% of patients in bone marrow with up to 12 cycles of combination ibrutinib/venetoclax

Siddiqi S et al. EHA 2020;Abstract S158.

CAPTIVATE MRD Cohort: Undetectable MRD in Patients with CR/PR



Best overall response (up to Cycle 16)	CR n = 84	PR n = 75	ORR (CR + PR) n = 159
Undetectable MRD in PB, n (%)	71 (85)	52 (69)	123 (77)
Undetectable MRD in BM, n (%)	67 (80)	44 (59)	111 (70)

At 15 months, 98% of patients were progression free with no deaths

Siddiqi S et al. EHA 2020;Abstract S158.

CAPTIVATE MRD Cohort: Summary of Grade 3 and 4 AEs of Interest

AEs, n (%)	Ibrutinib lead-in (3 cycles) N = 164		Ibrutinib + venetoclax combination (12 cycles) N = 159		Overall (15 cycles) N = 164
	Grade 3	Grade 4	Grade 3	Grade 4	Grade 3-4
Atrial fibrillation	2 (1)	0	1 (1)	0	3 (2)
Major hemorrhage	0	0	1 (1)	0	1 (1)
Infections	4 (2)	0	10 (6)	0	14 (9)
Neutropenia	4 (2)	7 (4)	27 (17)	26 (16)	58 (35)
Febrile neutropenia	1 (1)	0	2 (1)	0	3 (2)
Laboratory TLS	0	0	2 (1)	0	2 (1)

- Low rates of Grade 3 atrial fibrillation, major hemorrhage, infections, febrile neutropenia and laboratory TLS (no Grade 4 event)
- No patients developed clinical TLS
  - Laboratory TLS reported as AE in 3 patients (only 1 met Howard criteria)
- No fatal AEs

Siddiqi S et al. EHA 2020;Abstract S158.

Ongoing Phase III EA9161 Trial Schema

Stratifications
Age: <65 yr vs ≥ 65 yr and <70 yr
PS: 0, 1, vs 2
Stage: 0, 1, or 2 vs 3, 4
Del11q22.3 vs others

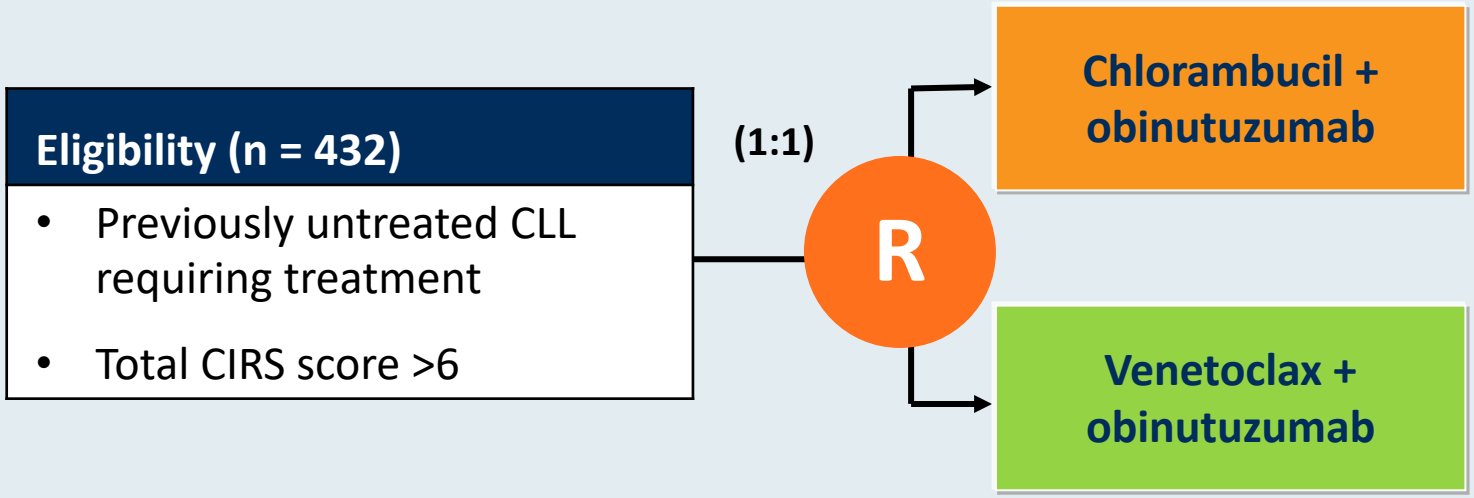
Randomize

Arm A
Ibrutinib: Cycles 1-19:d1-28 420mg PO daily
Obinutuzumab: C1 **:** D1:100 mg IV, D2:900 mg IV, D8: 1000 mg IV, D15: 1000 mg IV; C2-6: D1 1000 mg IV
Venetoclax: C3 D1-7 20mg PO daily D8-14 50mg PO daily D15-21 100mg PO daily; D22-28 200 mg PO daily; C4-14: D1-28 400mg PO daily

Arm B
Ibrutinib: Cycles 1-19+:d1-28 420mg PO daily
Obinutuzumab: C1 **:** D1:100 mg IV, D2:900 mg IV, D8: 1000 mg IV, D15: 1000 mg IV; C2-6: D1 1000 mg IV

Courtesy of Brad Kahl, MD

CLL14 Phase III Study Schema

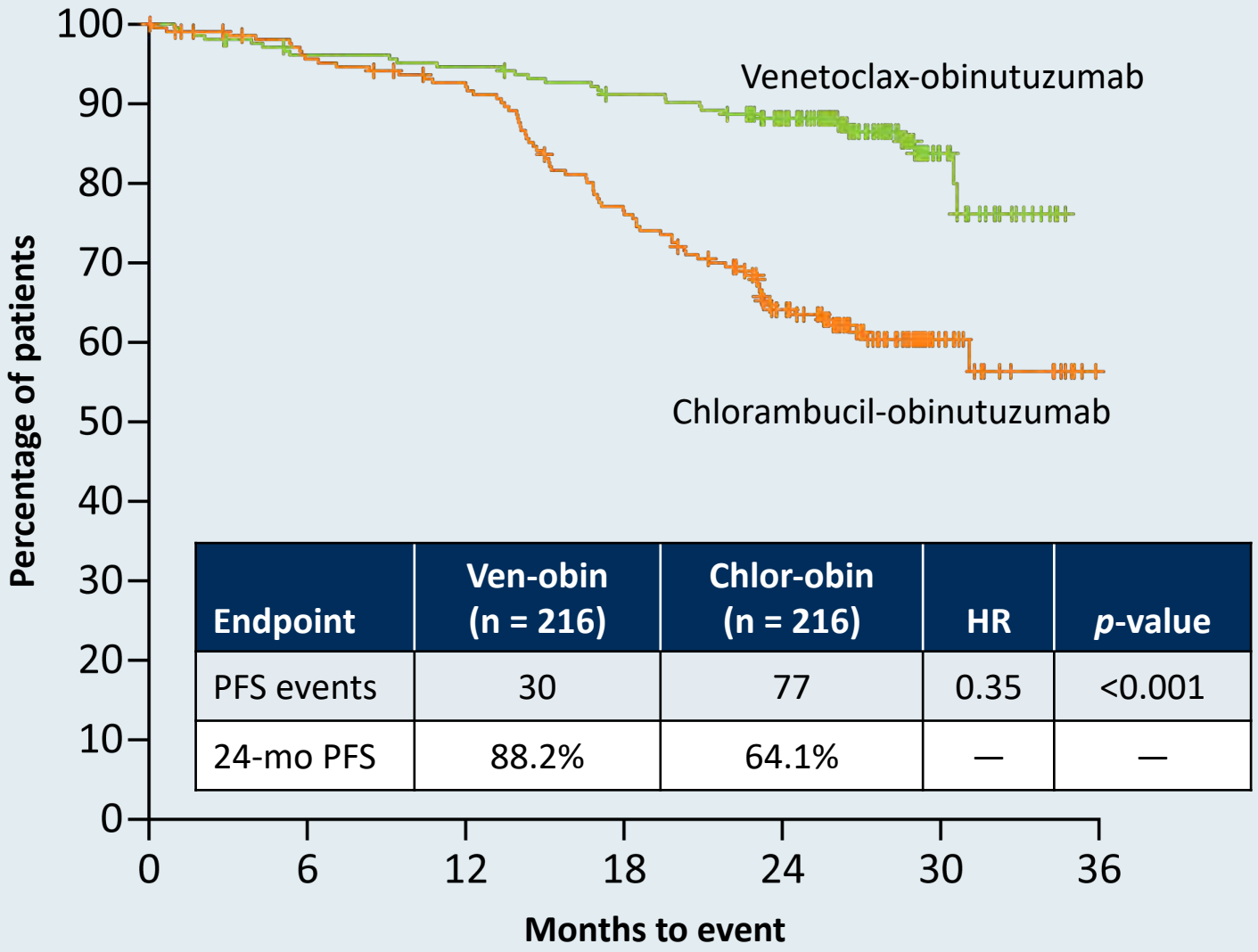


Primary endpoint: Progression-free survival

- Treatment duration in both groups: 12 cycles, 28 days each
- No crossover was allowed
- Daily oral venetoclax regimen:
  - Initiated on day 22 of cycle 1, starting with a 5-week dose ramp-up (1 week each of 20, 50, 100 and 200 mg, then 400 mg daily for 1 week)
  - Thereafter continuing at 400 mg daily until completion of cycle 12

www.clinicaltrials.gov (NCT02242942). Accessed August 2020.
Fischer K et al. *N Engl J Med* 2019;380(23):2225-36.

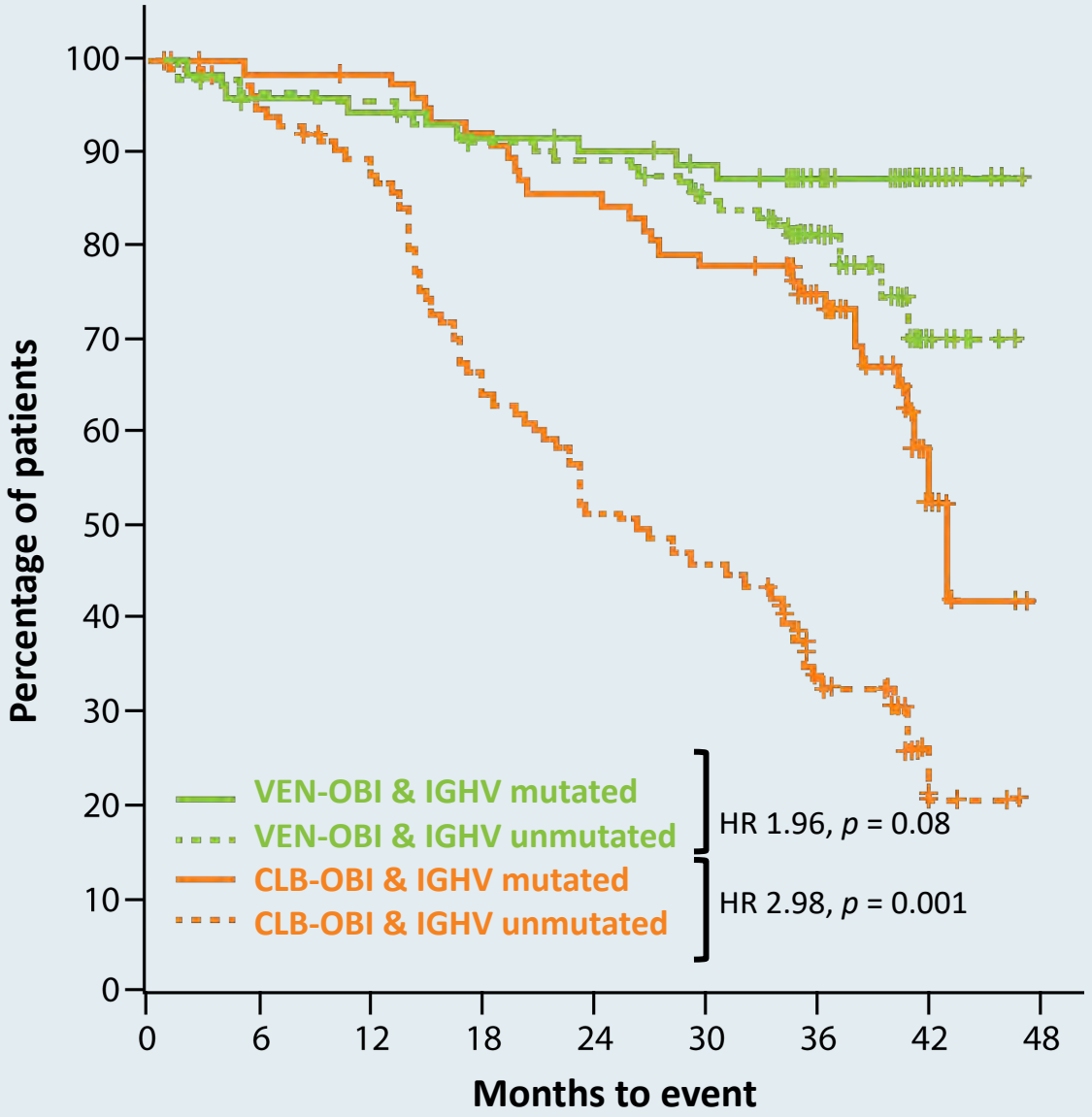
CLL14: Investigator-Assessed Progression-Free Survival



Endpoint	Ven-obin (n = 216)	Chlor-obin (n = 216)	HR	*p*-value
PFS events	30	77	0.35	<0.001
24-mo PFS	88.2%	64.1%	—	—

Fischer K et al. *N Engl J Med* 2019;380(23):2225-36.

CLL14: PFS by IGHV Mutation Status



Median PFS

Ven-Obi & IGHVmut: not reached

Ven-Obi & IGHVunmut: not reached

Clb-Obi & IGHVmut: 42.9 months

Clb-Obi & IGHVunmut: 26.3 months

Al-Sawaf O et al. EHA 2020;Abstract S155.

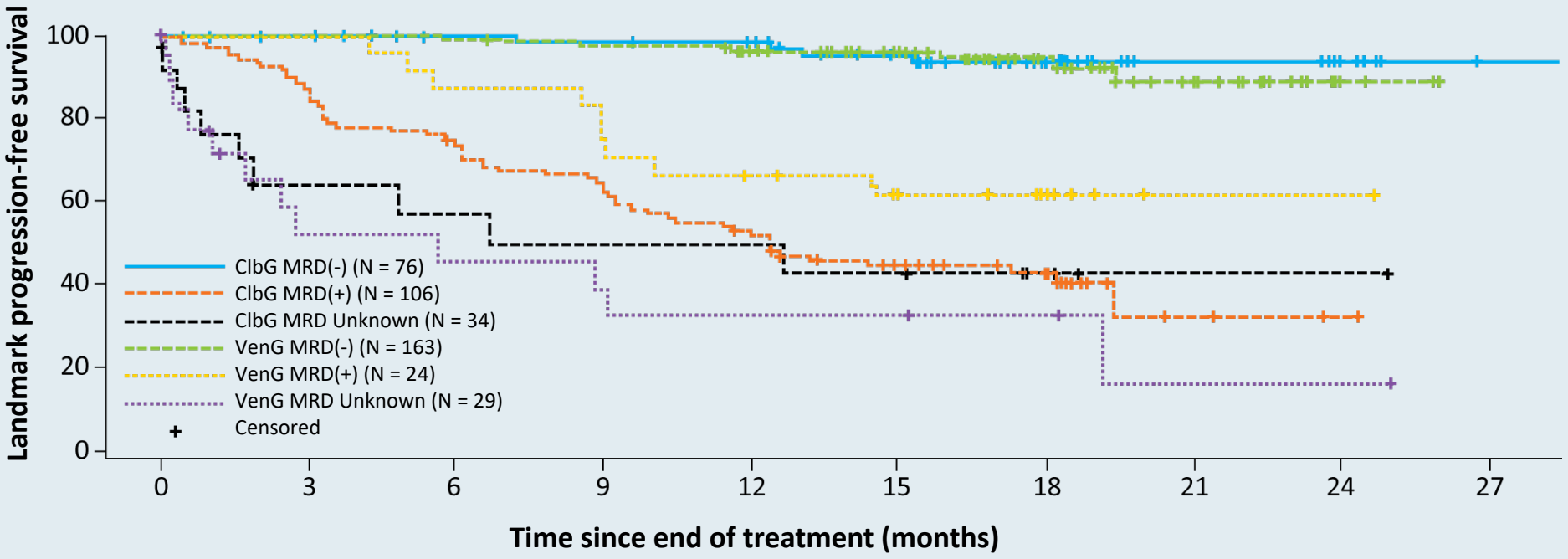
RTP RESEARCH TO PRACTICE

CLL14: Minimal Residual Disease 3 Months After Treatment

MRD 3 months after treatment	MRD-negative		MRD responders	
	Veneto/obin (N = 216)	Chloram/obin (N = 216)	Veneto/obin (N = 216)	Chloram/obin (N = 216)
MRD in bone marrow	56.9%	17.1%	33.8%	10.6%
Odds ratio, *p*-value	OR 6.4, $p < 0.0001$		OR 4.3, $p < 0.0001$	
MRD in peripheral blood	75.7%	35.2%	42.1%	14.4%
Odds ratio, *p*-value	OR 5.7, $p < 0.0001$		OR 4.3, $p < 0.0001$	

Fischer K et al. *N Engl J Med* 2019;380(23):2225-36.

CLL14: Landmark Analysis from End of Therapy PFS by MRD Group

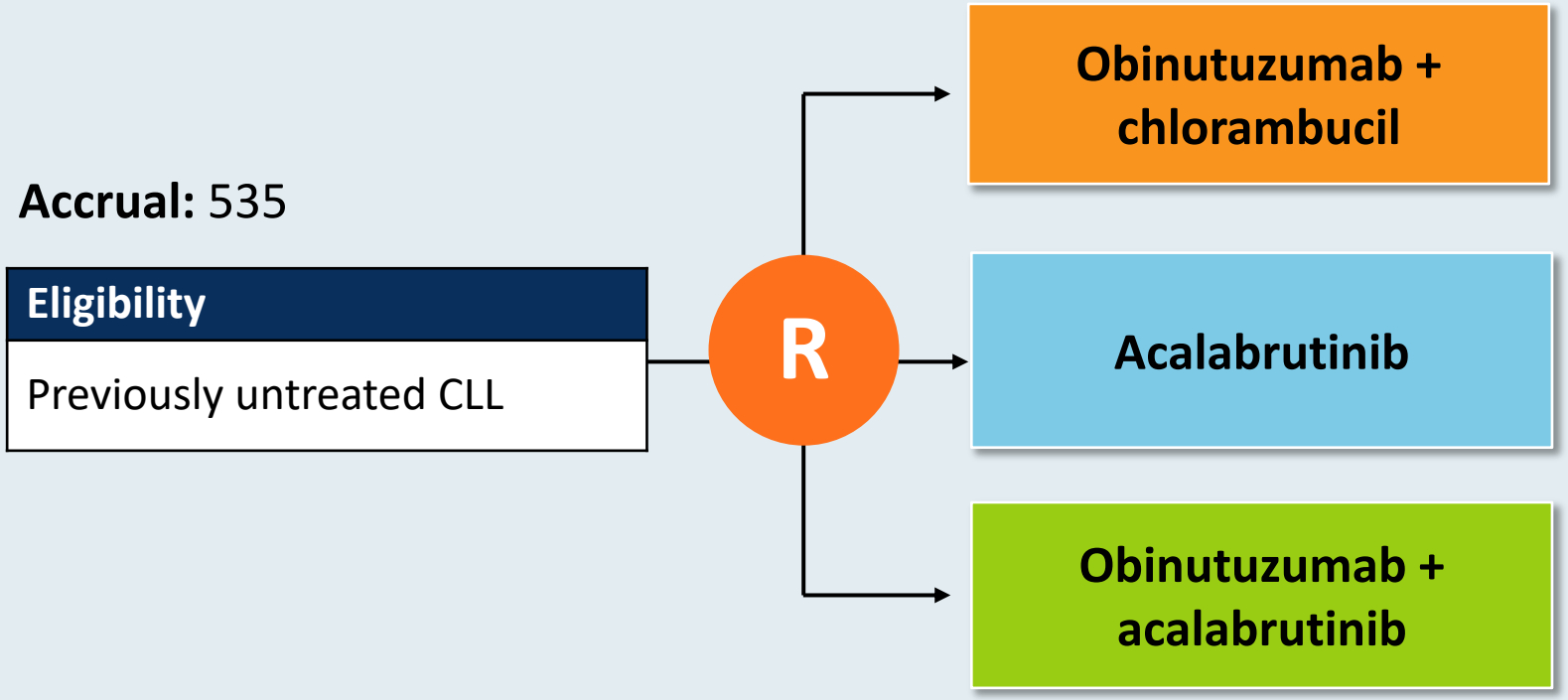


Further landmark analysis of PFS by MRD status showed that undetectable MRD translated into improved PFS regardless of the clinical response status at end of therapy.

Fischer K et al. ASH 2019;Abstract 36.

RTP RESEARCH TO PRACTICE

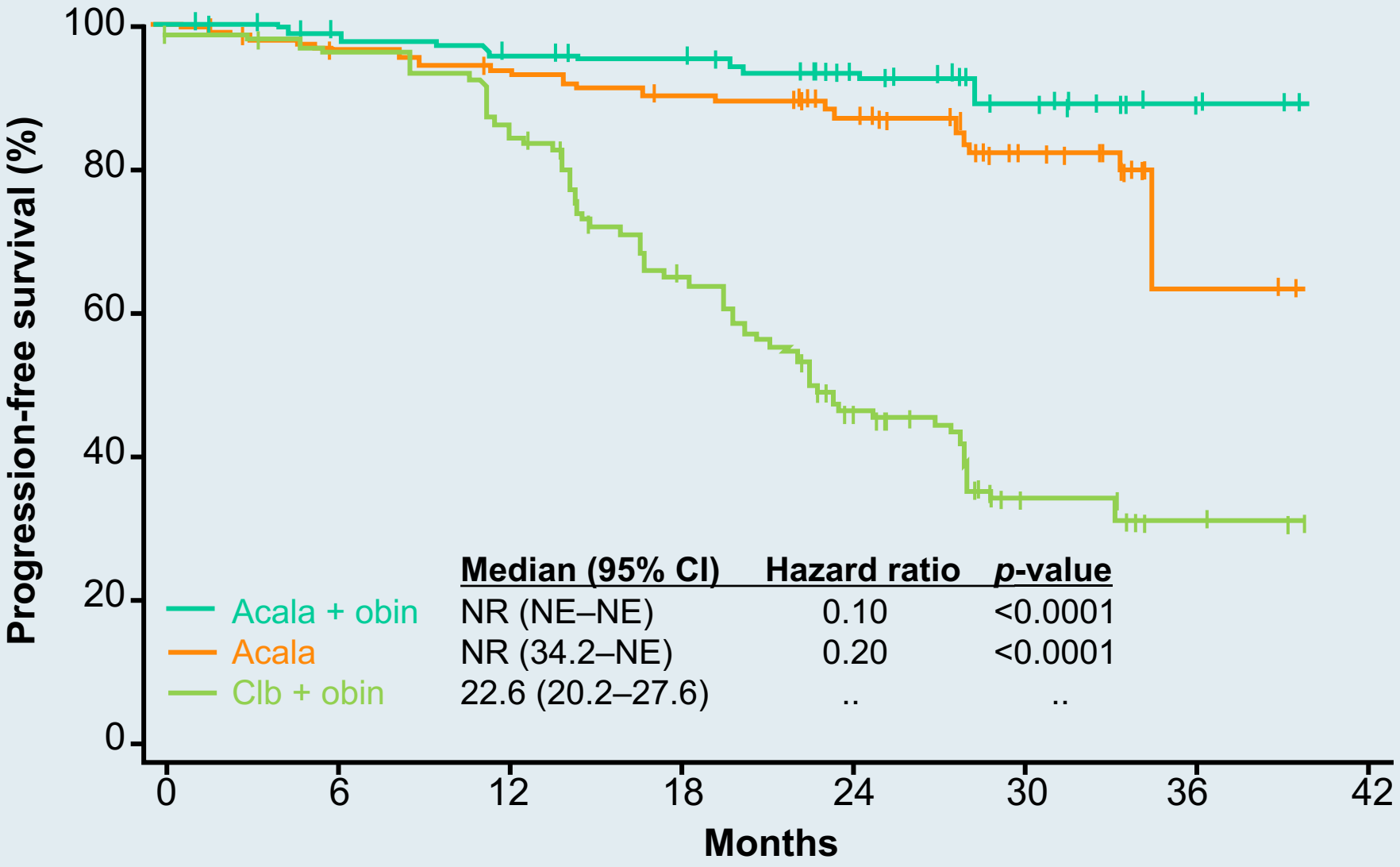
ELEVATE-TN Phase III Trial Schema



Primary endpoint: Progression-free survival

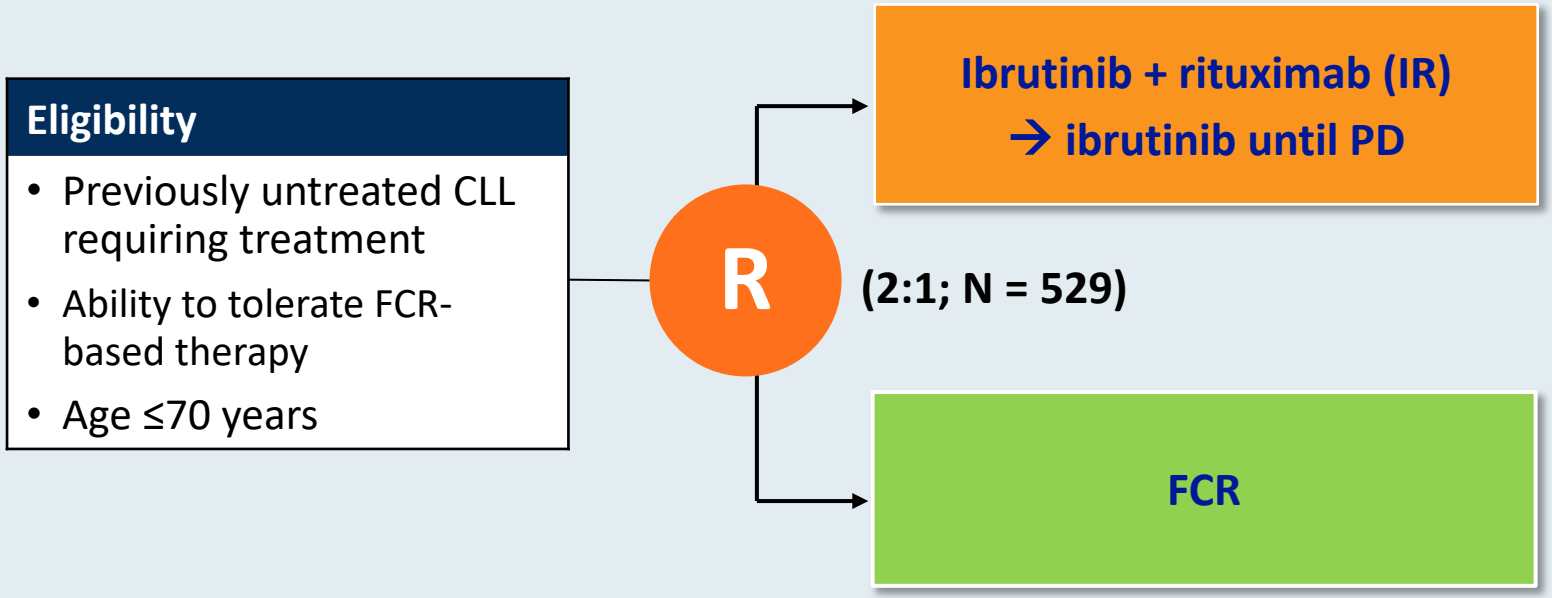
www.clinicaltrials.gov (NCT02475681). Accessed August 2020.

ELEVATE-TN: PFS (IRC)



Sharman JP et al. *Lancet* 2020;395:1278-91.

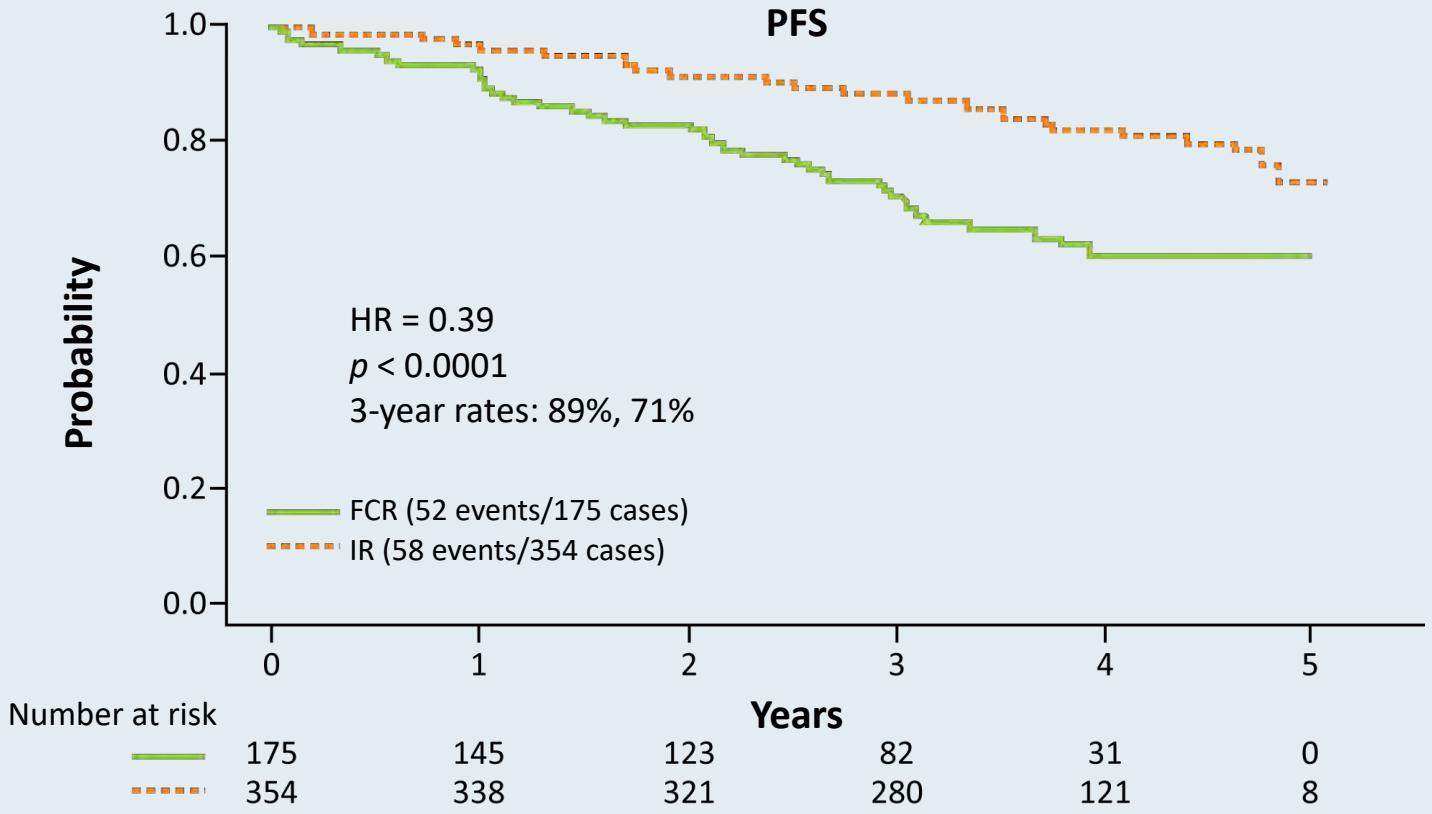
Phase III ECOG-ACRIN E1912 Study Design



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

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

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

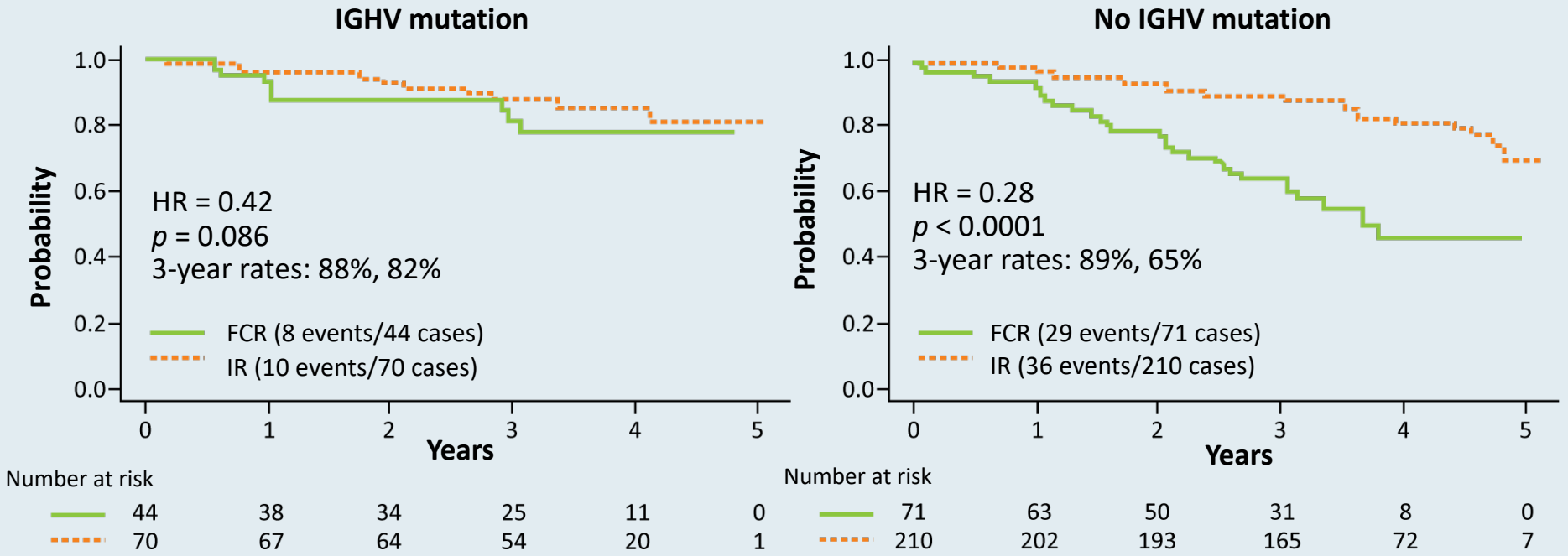


- Grade ≥3 treatment-related AEs were reported in 70% of patients receiving IR and 80% of patients receiving FCR (odds ratio = 0.56; $p = 0.013$).
- Among the 95 patients who discontinued ibrutinib, the most common cause was AE or complication.

Shanafelt TD et al. ASH 2019;Abstract 33.

RTP RESEARCH TO PRACTICE

ECOG-ACRIN E1912 Extended Follow-Up: PFS by IGHV Mutation Status



- On subgroup analysis by IGHV mutation status, IR was superior to FCR for CLL with no IGHV mutation (HR = 0.28; $p < 0.0001$).
- With current follow-up the difference between IR and FCR is not significant for CLL with IGHV mutation (HR = 0.42; $p = 0.086$).

Shanafelt TD et al. ASH 2019;Abstract 33.

Meet The Professor
Management of Lung Cancer

Monday, October 5, 2020
12:00 PM – 1:00 PM ET

Faculty

Professor Tony SK Mok, MD

Moderator

Neil Love, MD

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RESEARCH
TO PRACTICE

Thank you for joining us!

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