Thank you for joining us.
The program will commence momentarily.

Optimizing the Selection and Sequencing of Therapy for Patients with Chronic Lymphocytic Leukemia

A Meet The Professor Series

Brad S Kahl, MD
Professor of Medicine
Washington University School of Medicine
Director, Lymphoma Program
Siteman Cancer Center
St Louis, Missouri

Commercial Support

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Upcoming Live Webinars

Tuesday, August 25, 2020
5:00 PM – 6:00 PM ET

Optimizing the Selection and Sequencing of Therapy for Patients with Chronic Lymphocytic Leukemia

Faculty
Anthony R Mato, MD, MSCE

Moderator
Neil Love, MD

Wednesday, August 26, 2020
12:00 PM – 1:00 PM ET

Current Questions and Controversies in the Management of Lung Cancer

Faculty
Lecia V Sequist, MD, MPH

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Faculty
Michael J Birrer, MD, PhD

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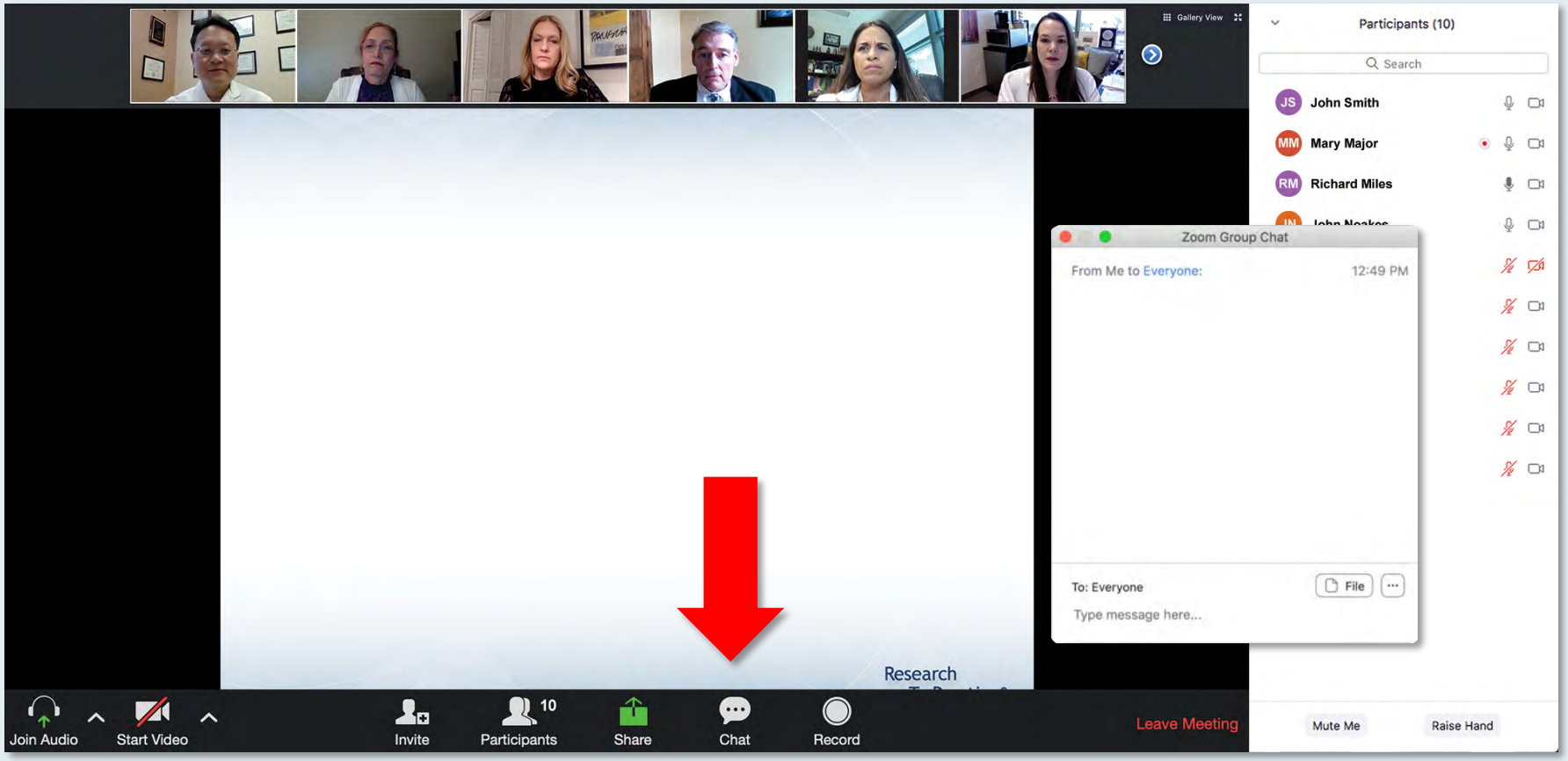
We Encourage Clinicians in Practice to Submit Questions



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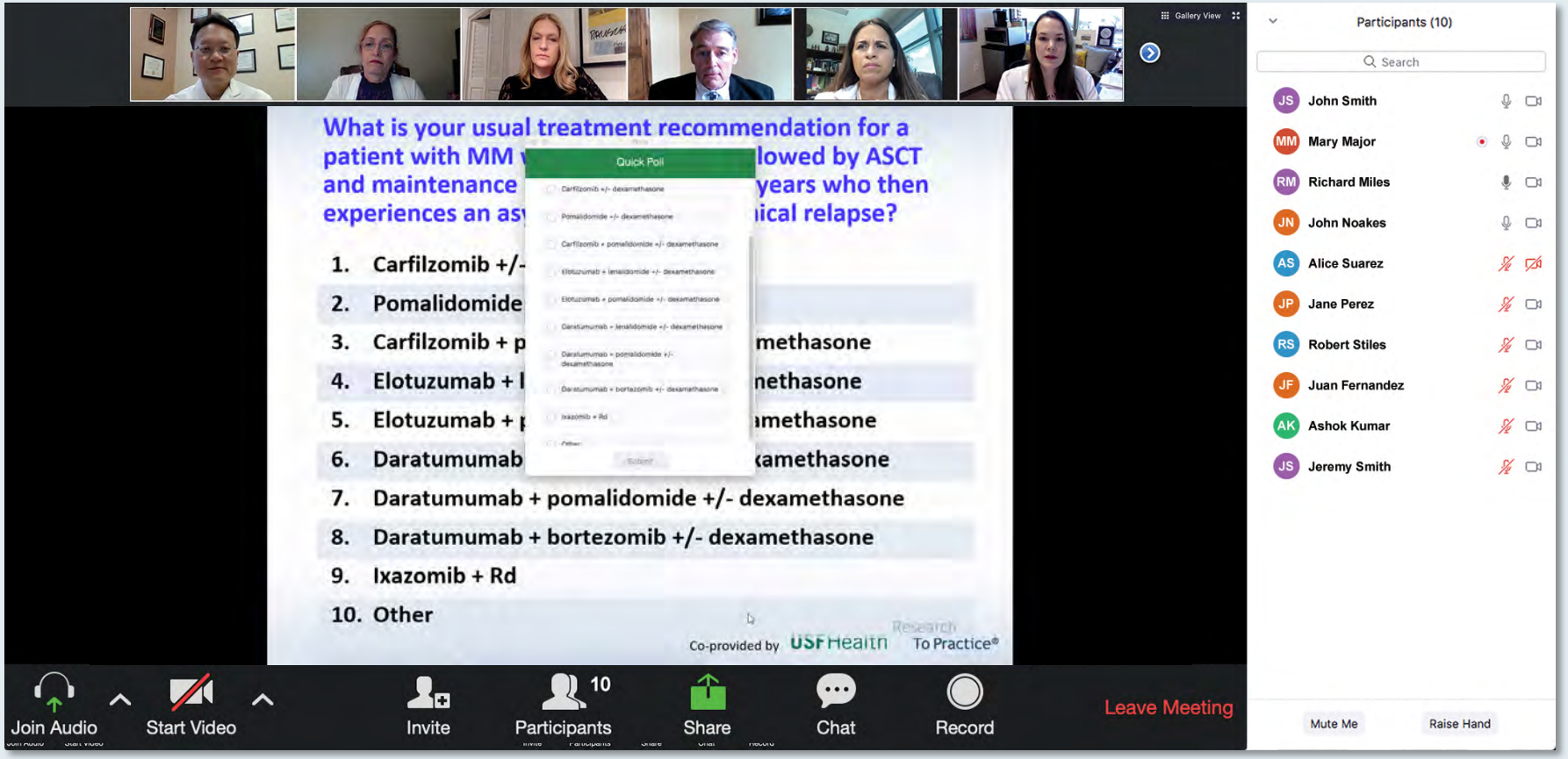
Familiarizing yourself with the Zoom interface

How to answer poll questions



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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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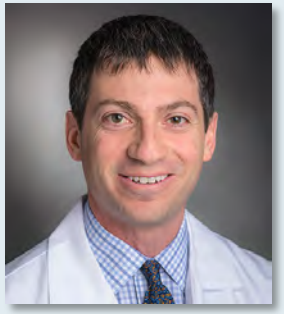
Meet The Professor Program Participating Faculty



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

Brian T Hill, MD, PhD
Director, Lymphoid Malignancy Program
Cleveland Clinic Taussig Cancer Institute
Cleveland, Ohio

Ian W Flinn, MD, PhD
Director of Lymphoma Research Program
Sarah Cannon Research Institute
Tennessee Oncology
Nashville, Tennessee

Brad S Kahl, MD
Professor of Medicine
Washington University School of Medicine
Director, Lymphoma Program
Siteman Cancer Center
St Louis, Missouri

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Meet The Professor Program Participating Faculty

Anthony R Mato, MD, MSCE
Associate Attending
Director, Chronic Lymphocytic Leukemia Program
Memorial Sloan Kettering Cancer Center
New York, New York

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

John M Pagel, MD, PhD
Chief of Hematologic Malignancies
Center for Blood Disorders and Stem Cell Transplantation
Swedish Cancer Institute
Seattle, Washington

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

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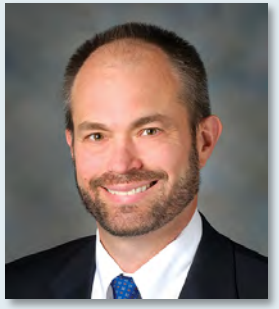
Meet The Professor Program Participating Faculty

Mitchell R Smith, MD, PhD
Professor of Medicine
Associate Center Director for Clinical Investigations
Director, Division of Hematology and Oncology
GW Cancer Center
Washington, DC

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



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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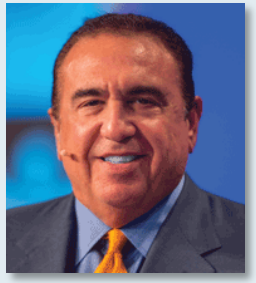
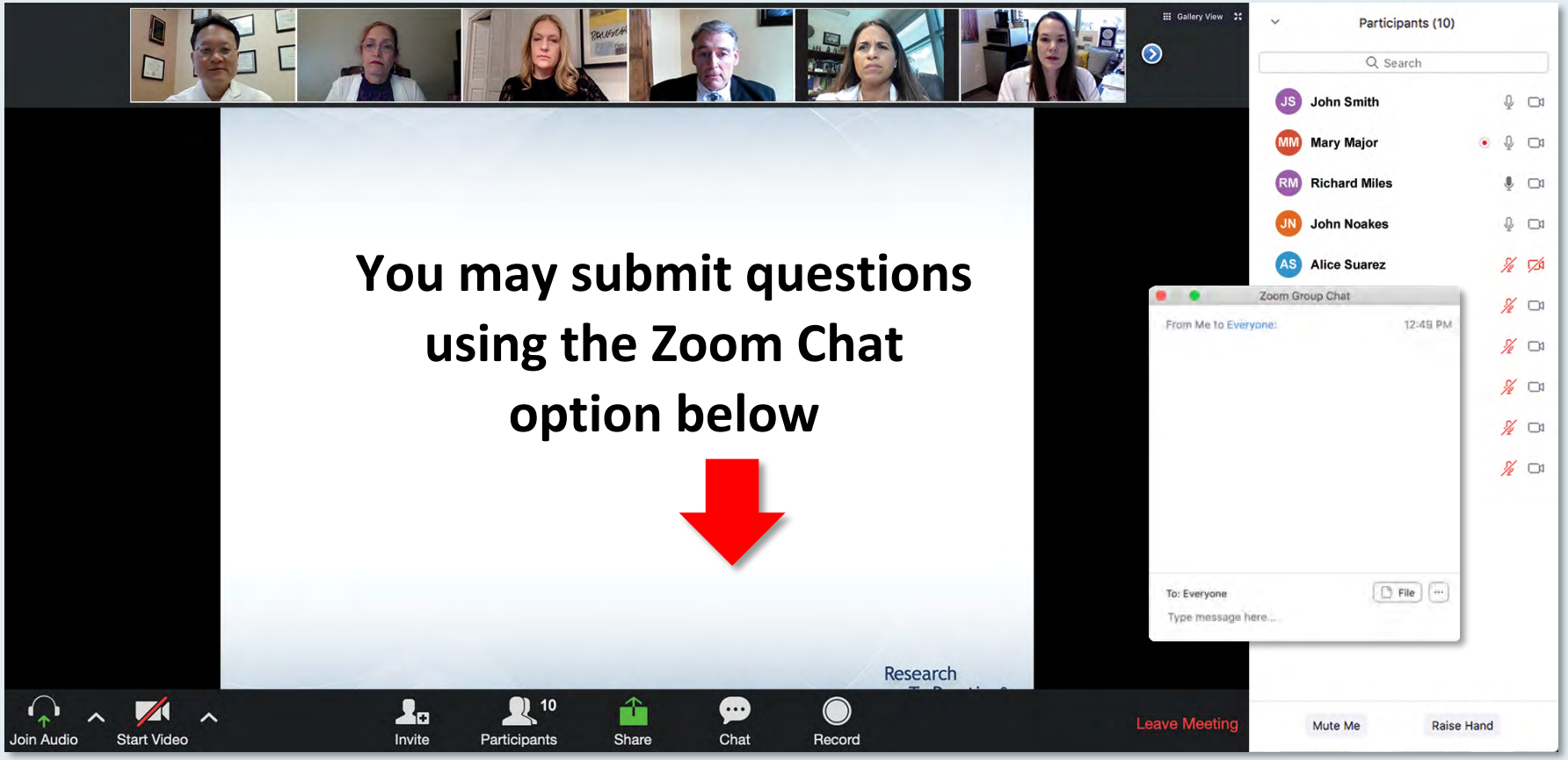
Meet The Professor Program Moderator



Project Chair
Neil Love, MD
Research To Practice
Miami, Florida

We Encourage Clinicians in Practice to Submit Questions



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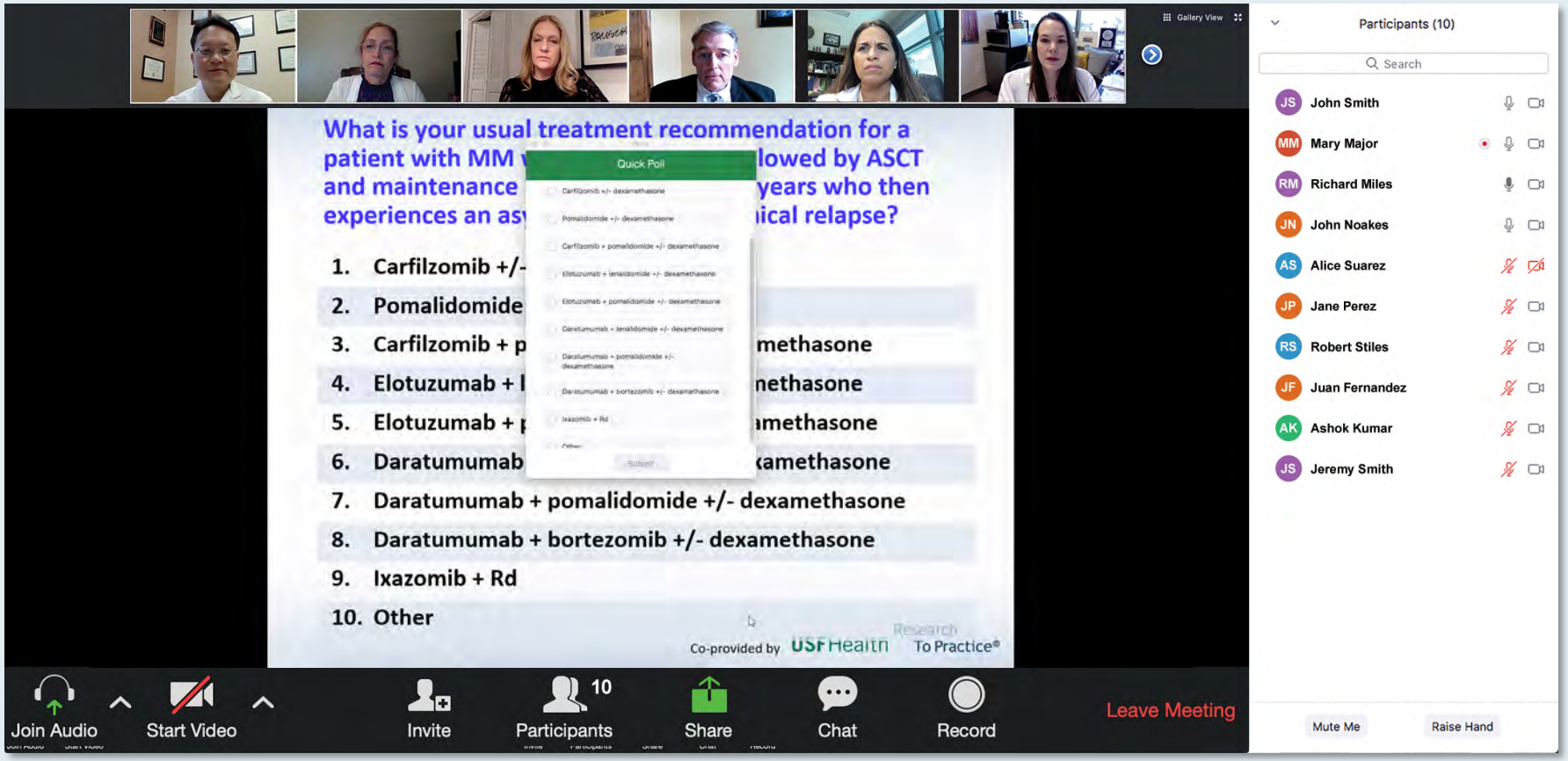

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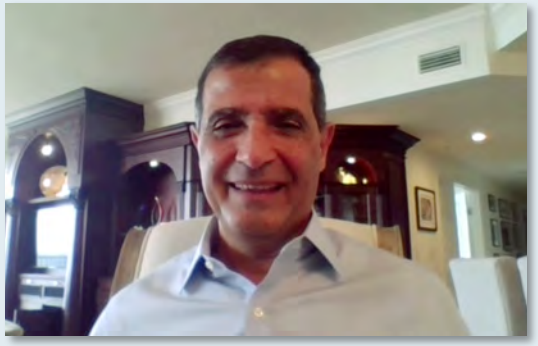

Atif Hussein, MD, MMM
Florida International University
Herbert Wertheim College of Medicine
Hollywood, Florida

Neil Morganstein, MD
Hematology Oncology
Atlantic Health System
Summit, New Jersey

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Meet The Professor with Dr Kahl

MODULE 1: Optimal Integration of Venetoclax and BTK Inhibitors into the Front-Line Setting

- Case presentations
- Ibrutinib/rituximab in younger (ECOG-E1912 trial) and older patients (Alliance A041202 trial)
- Available data and current clinical role of ibrutinib/obinutuzumab (iLLUMINATE trial)
- FDA approval of acalabrutinib (ELEVATE-TN trial)
- PFS and rate and duration of MRD negativity with venetoclax/obinutuzumab (CLL14 trial)
- Optimal MRD testing methodology and current role, if any, in clinical practice

MODULE 2: Management of Relapsed/Refractory Chronic Lymphocytic Leukemia (CLL)

- Case presentations
- Venetoclax/rituximab (MURANO trial)
- Acalabrutinib (ASCEND trial)
- Spectrum, frequency and severity of side effects with BTK inhibitors alone versus combined with an anti-CD20 antibody
- Spectrum, incidence, severity and management of venetoclax-associated toxicities, including tumor lysis syndrome

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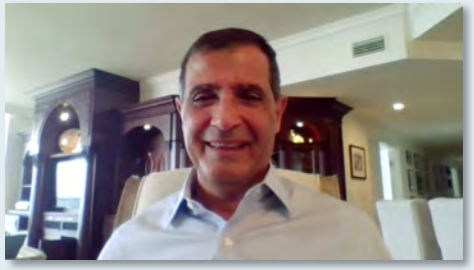
Case Presentation – Dr Hussein: 71-year-old man with Stage IV CLL



Atif Hussein, MD, MMM

- Chronic renal insufficiency secondary to longstanding diabetes mellitus and hypertension
  - Well controlled ventricular rate atrial fibrillation on oral anticoagulation
- Imaging studies: Diffuse adenopathy
- Peripheral blood flow cytometry: Diagnostic of CLL
  - Peripheral blood karyotype: Normal, but FISH testing: 11q deletion, IgHV unmutated
  - WBC of 90,000/cu mm with 89% lymphocytes, hemoglobin of 10.1 g/dL, platelets 90,000/cu mm, serum creatinine of 1.9 mg/dL
- Patient desires the most effective fixed duration therapy

Questions

- In this patient who needs treatment but with compromised renal function from diabetes and hypertension, what front-line therapy would you give him? If you choose to use a BTK inhibitor with his well-controlled atrial fibrillation, which one?
- Do you give him a BTK inhibitor or do you give him fixed-dose venetoclax/obinutuzumab?

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Case Presentation – Dr Morganstein: 72-year-old man

Neil Morganstein, MD

- Stage 1 CLL with rapid doubling time, FISH with no high-risk features, IGHV mutated
- Acalabrutinib
  - Tumor lysis syndrome, increased creatinine

Questions

- What is the risk of tumor lysis syndrome with BTK inhibitors?
- In patients with very high white counts, what TLS prophylaxis is appropriate?
- Is there any role to try to quiet these people down with either steroids or other induction therapies, either with anti-CD20 antibodies or maybe even chemotherapy?

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Brief Report

LYMPHOID NEOPLASIA

BTK inhibitor therapy is effective in patients with CLL resistant to venetoclax

Victor S. Lin,[1-3,*] Thomas E. Lew,[1,3,*] Sasanka M. Handunnetti,[1] Piers Blombery,[1,2,4] Tamia Nguyen,[4] David A. Westerman,[1,2,4] Bryone J. Kuss,[5] Constantine S. Tam,[1,2,6] Andrew W. Roberts,[1-3] John F. Seymour,[1,2] and Mary Ann Anderson[1,3]

[1]Department of Clinical Haematology, Royal Melbourne Hospital and Peter MacCallum Cancer Centre, Melbourne, VIC, Australia; [2]Faculty of Medicine, Dentistry and Health Sciences, University of Melbourne, Parkville, VIC, Australia; [3]Blood Cells and Blood Cancer Division, Walter and Eliza Hall Institute of Medical Research, Parkville, VIC, Australia; [4]Department of Pathology, Peter MacCallum Cancer Centre, Melbourne, VIC, Australia; [5]Department of Haematology and Genetic Pathology, Flinders University, Adelaide, SA, Australia; and [6]Department of Haematology, St Vincent's Hospital Melbourne, Fitzroy, VIC, Australia

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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]

[1]Department of Lymphoma and Myeloma, [2]Department of Hematopathology, [3]Department of Translational Pathology, and [4]Department of Leukemia, MD Anderson Cancer Center, The University of Texas, Houston, TX

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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

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Strategy for Selecting First-Line CLL Treatment

TP53 status (del(17p)/*TP53* mutation)	Age/ fitness	IGHV MS	First-line treatment (in order of authors' preference)
TP53 intact	Younger/ fit	Mutated	(1) FCR (fixed duration), (2) VEN + OBIN (fixed duration), (3) BTKi ± OBIN (continuous)
		Unmutated	(1) VEN + OBIN (fixed-duration), (2) BTKi ± OBIN (continuous)
	Older/ unfit	Mutated	(1) VEN + OBIN (fixed duration), (2) BTKi ± OBIN (continuous)
		Unmutated	(1) BTKi ± OBIN (continuous), (2) VEN + OBIN (fixed-duration)

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 ± OBIN (continuous), (2) VEN + OBIN (fixed duration), no CIT

Wierda WG, Tambaro FP. Blood 2020;135(17):1421-27.

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Strategy for Selecting Treatment of R/R CLL

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

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

Allo-SCT, allogeneic stem cell transplant; BCL2i, BCL2 inhibitor; mAb, monoclonal antibody; PI3Ki, PI3K inhibitor.

Wierda WG, Tambaro FP. Blood 2020;135(17):1421-27.

How to select a treatment for an individual patient?

Menu

- Immunochemotherapy
  - FCR
  - BR
  - Chlorambucil/Obinutuzumab
- Novel Agents
  - Ibrutinib ± obinutuzumab
  - Acalabrutinib ± obinutuzumab
  - Venetoclax + Obinutuzumab

Considerations

- If deletion 17p or p53 mutation
  - Chemo not very effective, better off with novel agents
- If IgHV unmutated
  - Chemo less effective than novel agents
- If IgHV mutated
  - Chemo and novels agents are similarly effective

Courtesy of Brad Kahl, MD

Scenario #1

- 52 yo man with CLL requiring treatment.
  - No p53 mutation or 17p deletion.
  - IgHV unmutated.

- Best options include
  1. Venetoclax plus obinutuzumab
  2. BTKi plus obinutuzumab

- Pro's and Con's to each

Courtesy of Brad Kahl, MD

Scenario #2

- 52 yo man with CLL requiring treatment.
  - No p53 mutation by sequencing
  - No 17p deletion or 11q deletion by FISH.
  - IgHV mutated.

- Best options include
  1. FCR
  2. Venetoclax plus obinutuzumab
  3. BTKi plus obinutuzumab
- Pro's and Con's to each

Courtesy of Brad Kahl, MD

Scenario #3

- 72 yo man with CLL requiring treatment.
  - No p53 mutation.
  - No 17p deletion or 11q deletion.
  - IgHV unmutated.

- Best options include
  1. Venetoclax plus obinutuzumab
  2. BTKi

- Pro's and Con's to each.

Courtesy of Brad Kahl, MD

Scenario #4

- 72 yo man with CLL requiring treatment.
  - No p53 mutation or 17p deletion.
  - IgHV mutated.

- Best options include
  1. Venetoclax plus obinutuzumab
  2. BR
  3. BTKi

- Pro's and Con's to each.

Courtesy of Brad Kahl, MD

Scenario #5

- 72 yo man with CLL requiring treatment.
- 17p deletion by FISH

- BTKi plus obinutuzumab

- This is the one scenario where I favor indefinite therapy over time limited therapy

Courtesy of Brad Kahl, MD

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

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7. Venetoclax + obinutuzumab
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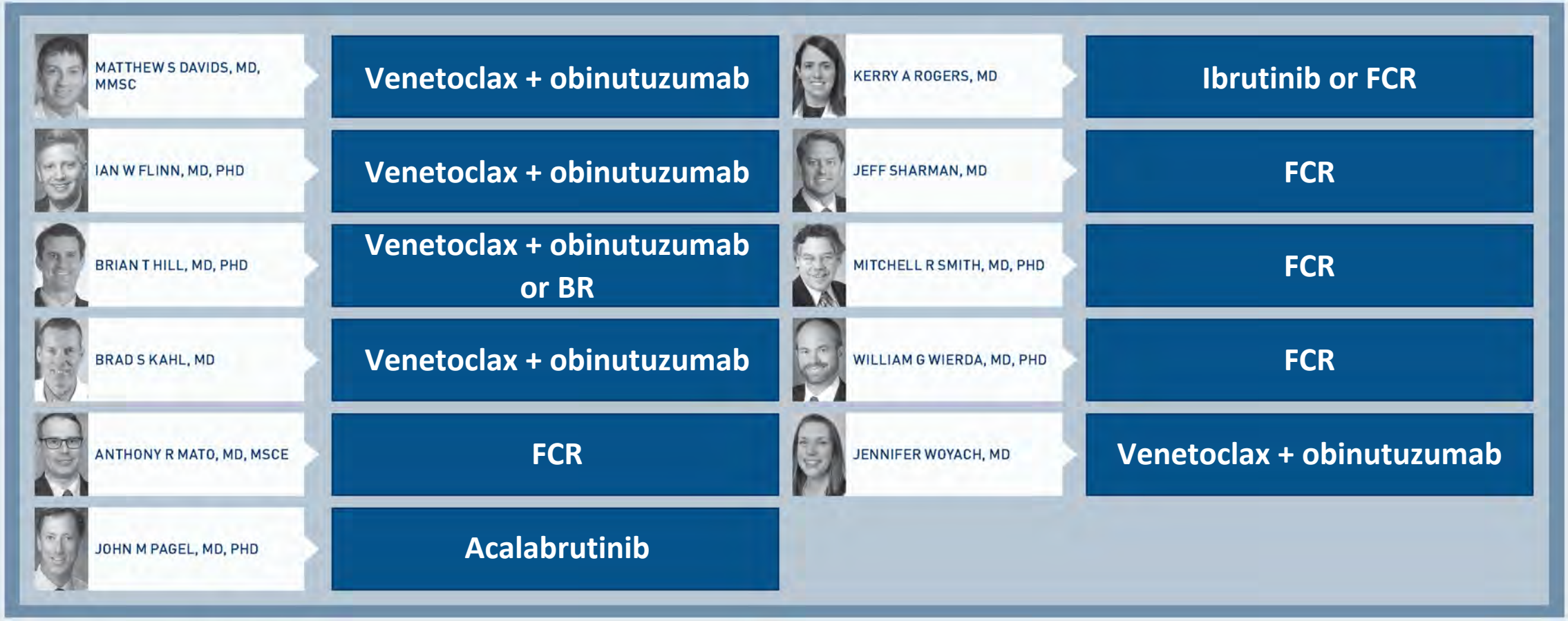

BR = bendamustine/rituximab; FCR = fludarabine/cyclosphosphamide/rituximab (FCR)

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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 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
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 WILLIAM G WIERDA, MD, PHD	Acalabrutinib
 JENNIFER WOYACH, MD	Ibrutinib

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Based on current clinical trial data and your personal experience, how would you compare the global efficacy of acalabrutinib to that of ibrutinib for CLL?

 MATTHEW S DAVIDS, MD, MMSC	About the same
 IAN W FLINN, MD, PHD	About the same
 BRIAN T HILL, MD, PHD	About the same
 BRAD S KAHL, MD	About the same
 ANTHONY R MATO, MD, MSCE	About the same
 JOHN M PAGEL, MD, PHD	About the same
 KERRY A ROGERS, MD	About the same
 JEFF SHARMAN, MD	Not enough data are currently available
 MITCHELL R SMITH, MD, PHD	About the same
 WILLIAM G WIERDA, MD, PHD	About the same
 JENNIFER WOYACH, MD	About the same

RTP RESEARCH TO PRACTICE

Based on current clinical trial data and your personal experience, how would you compare the global efficacy of a single-agent Bruton tyrosine kinase (BTK) inhibitor to that of venetoclax/obinutuzumab for CLL?

 MATTHEW S DAVIDS, MD, MMSC	Not enough data are currently available
 IAN W FLINN, MD, PHD	About the same
 BRIAN T HILL, MD, PHD	A single-agent BTK inhibitor is more efficacious
 BRAD S KAHL, MD	About the same
 ANTHONY R MATO, MD, MSCE	About the same
 JOHN M PAGEL, MD, PHD	Venetoclax/obinutuzumab is more efficacious
 KERRY A ROGERS, MD	Not enough data are currently available
 JEFF SHARMAN, MD	A single-agent BTK inhibitor is more efficacious
 MITCHELL R SMITH, MD, PHD	Not enough data are currently available
 WILLIAM G WIERDA, MD, PHD	I don't know
 JENNIFER WOYACH, MD	Not enough data are currently available

RTP RESEARCH TO PRACTICE

Case Presentation – Dr Morganstein: 65-year-old man

Neil Morganstein, MD

- CLL with del(17p)
- Venetoclax and obinutuzumab x 2 years
  - No side effects
  - Hematologic complete response

Questions

- How long should venetoclax be continued?
- What is the role of MRD in clinical practice and what is the best way to test?

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

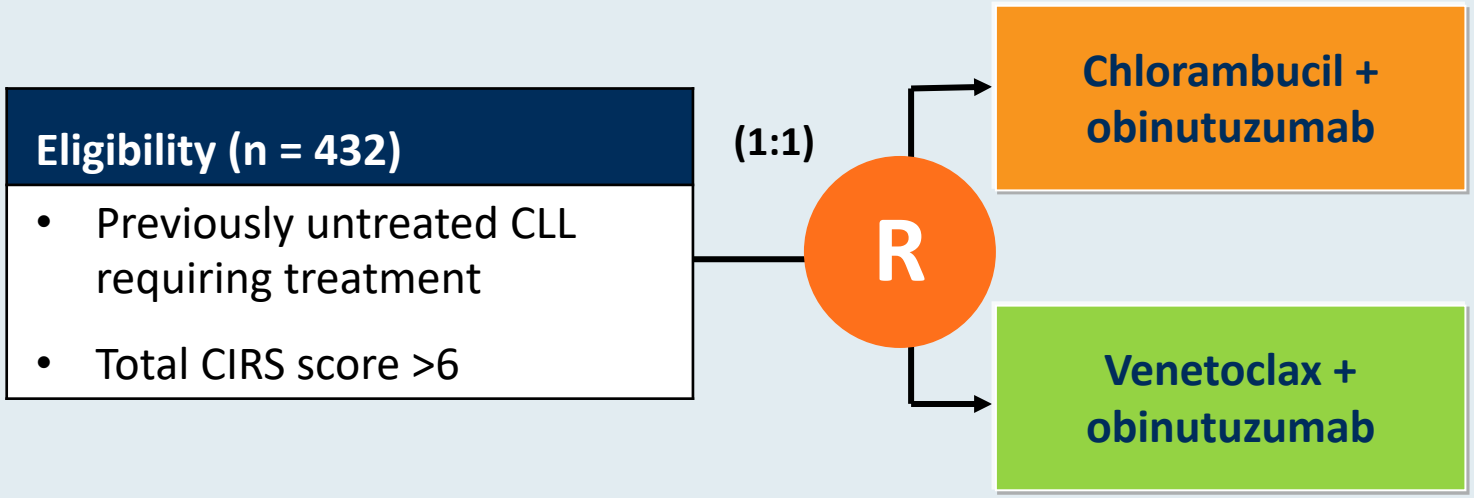
What would be your most likely approach for a patient with newly diagnosed CLL to whom you administer up-front venetoclax/obinutuzumab who has achieved undetectable MRD status after 1 year of treatment?

 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

Recent Relevant Data Sets

CLL14 Phase III Study Schema

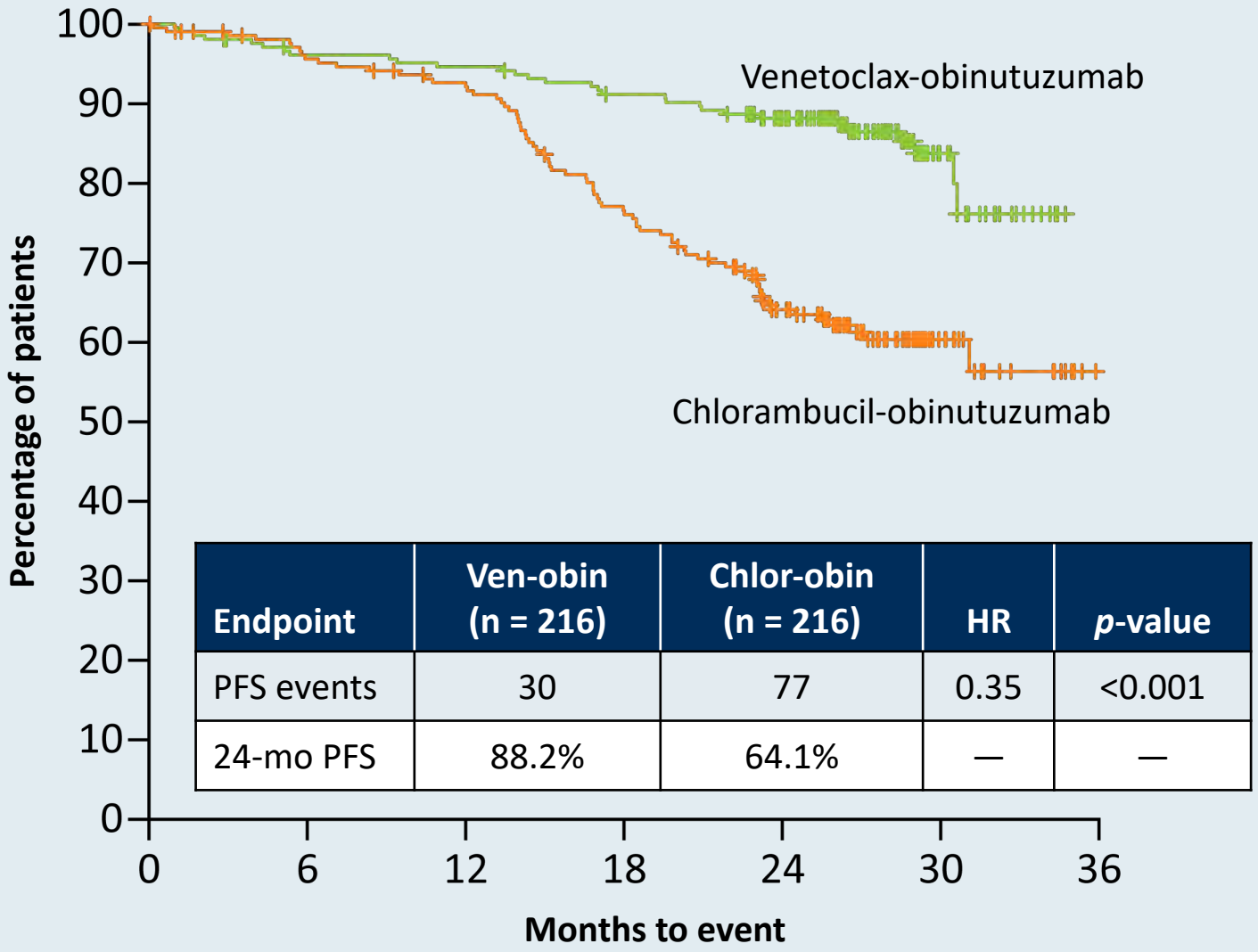


Primary endpoint: Progression-free survival

- 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.

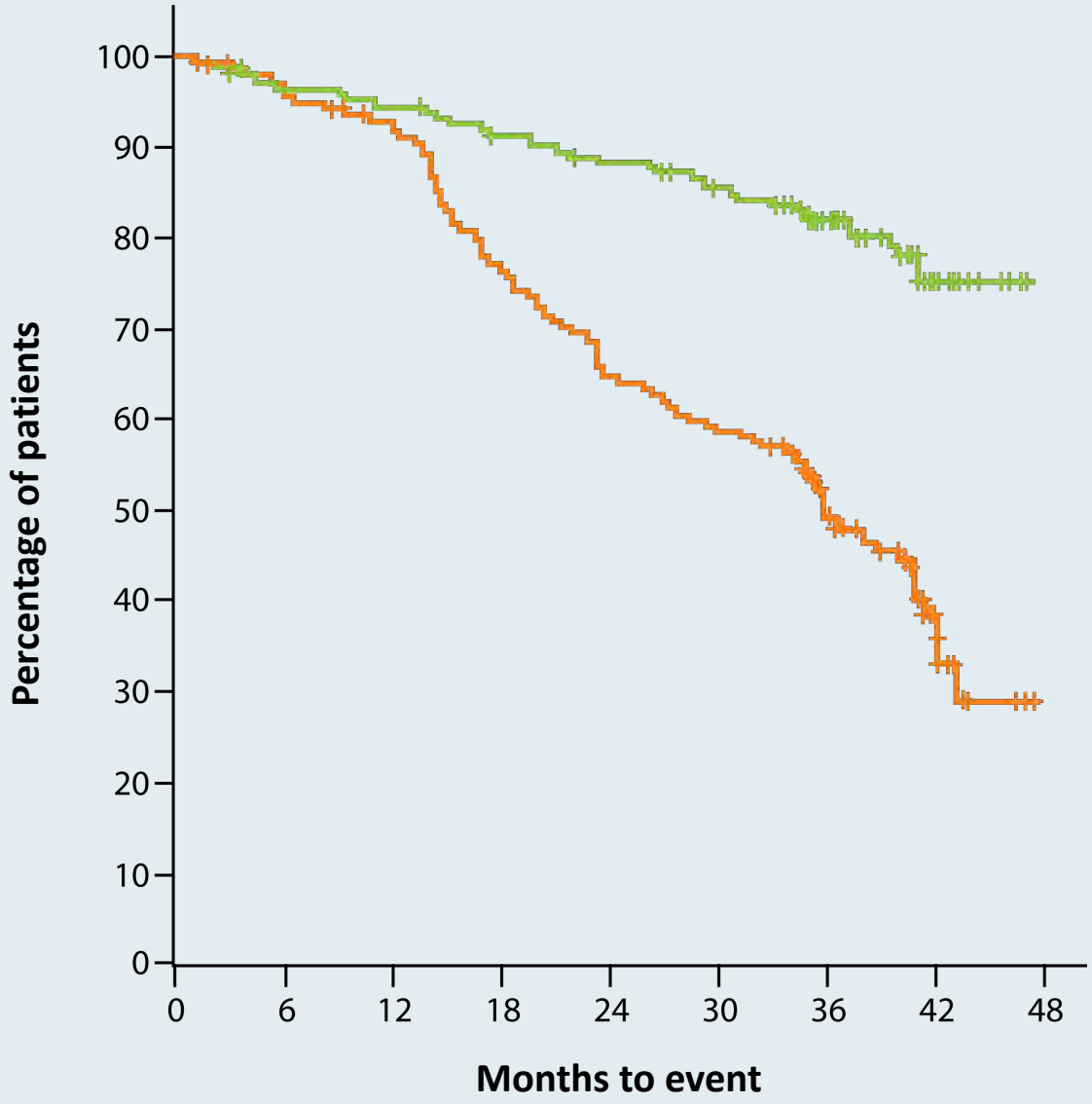
CLL14: Investigator-Assessed Progression-Free Survival



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: Updated 3-Year PFS



Median PFS

Ven-Obi: not reached

Clb-Obi: 35.6 months

3-year PFS rate

Ven-Obi: 81.9%

Clb-Obi: 49.5%

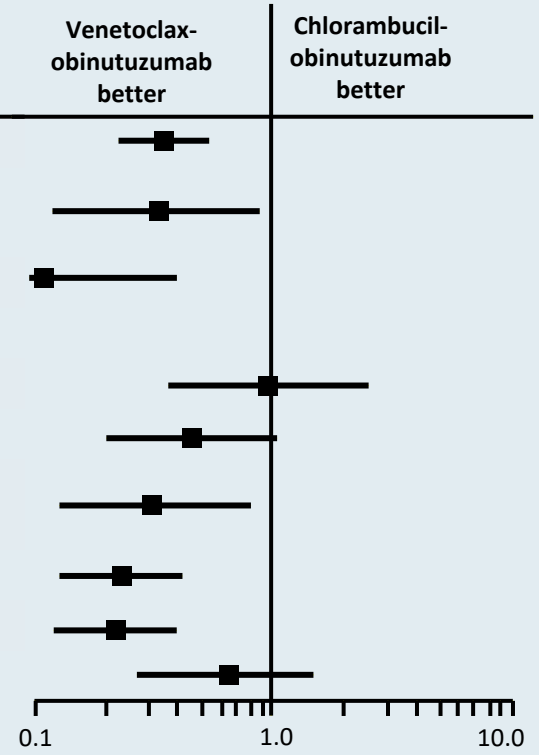
HR 0.31, 95% CI [0.22-0.44]

$p < 0.0001$

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

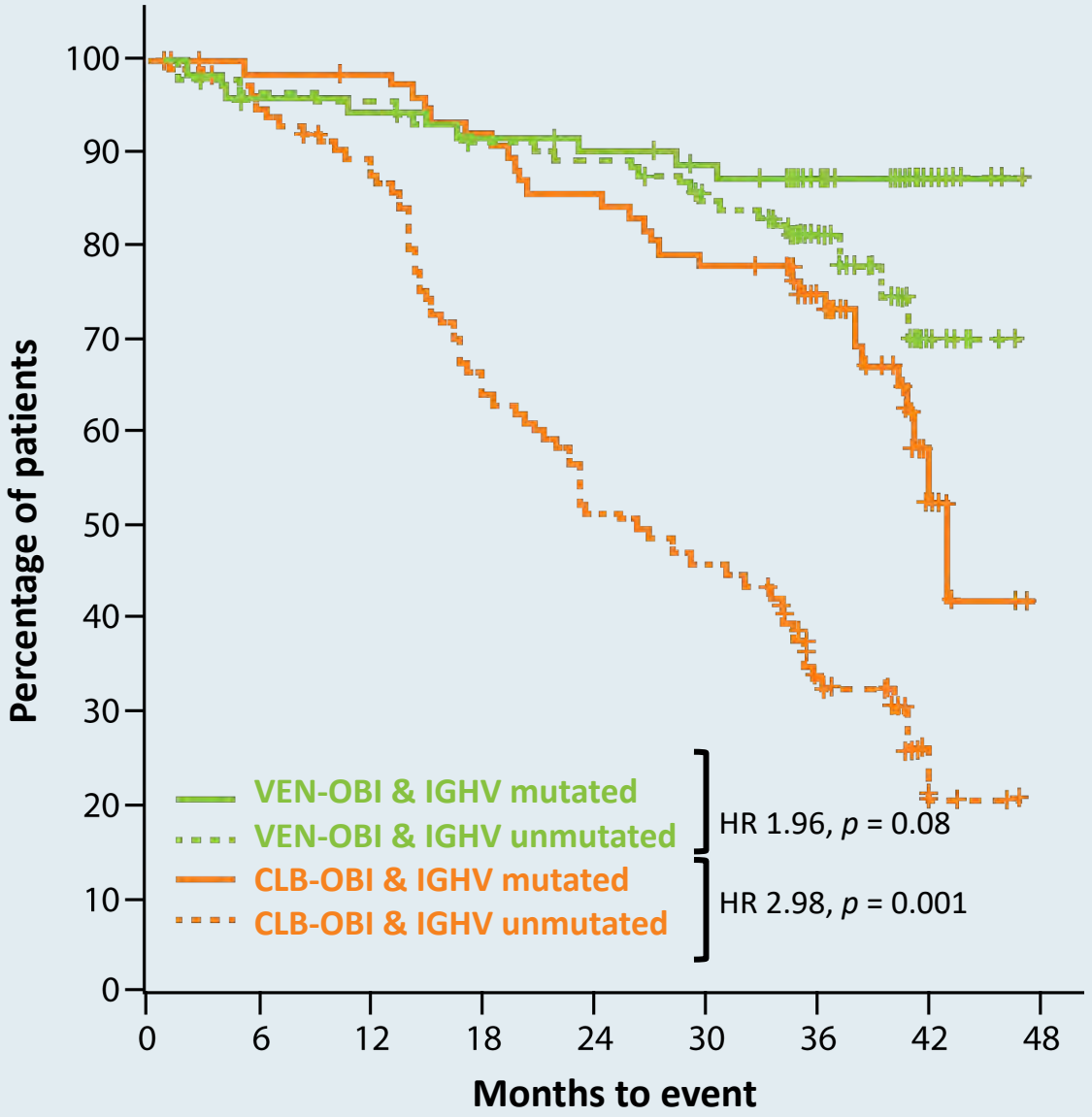
CLL14: Investigator-Assessed Progression-Free Survival by Prognostic Subgroup

Category	Subgroup	Total n	Chlorambucil-obinutuzumab n	Chlorambucil-obinutuzumab PFS rate month 24 (%)	Venetoclax-obinutuzumab n	Venetoclax-obinutuzumab PFS rate month 24 (%)	Hazard ratio
All		432	216	64.1	216	88.1	0.34
Cytogenetic subgroups as per hierarchy	del(17p)	31	14	23.1	17	64.7	0.33
	del(11q)	74	38	41.3	36	91.2	0.11
	Trisomy 12	76	40	55.6	36	100.0	NE
	No abnormalities	92	42	82.1	50	87.2	0.93
	del(13q)	120	59	78.3	61	88.1	0.45
TP53 deletion and/or mutation	Present	46	22	32.7	24	73.9	0.31
	Not present	287	139	65.0	148	92.1	0.23
IGHV mutation status	Unmutated	244	123	51.0	121	89.4	0.22
	Mutated	159	83	85.6	76	90.3	0.64



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

CLL14: PFS by IGHV Mutation and TP53 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.

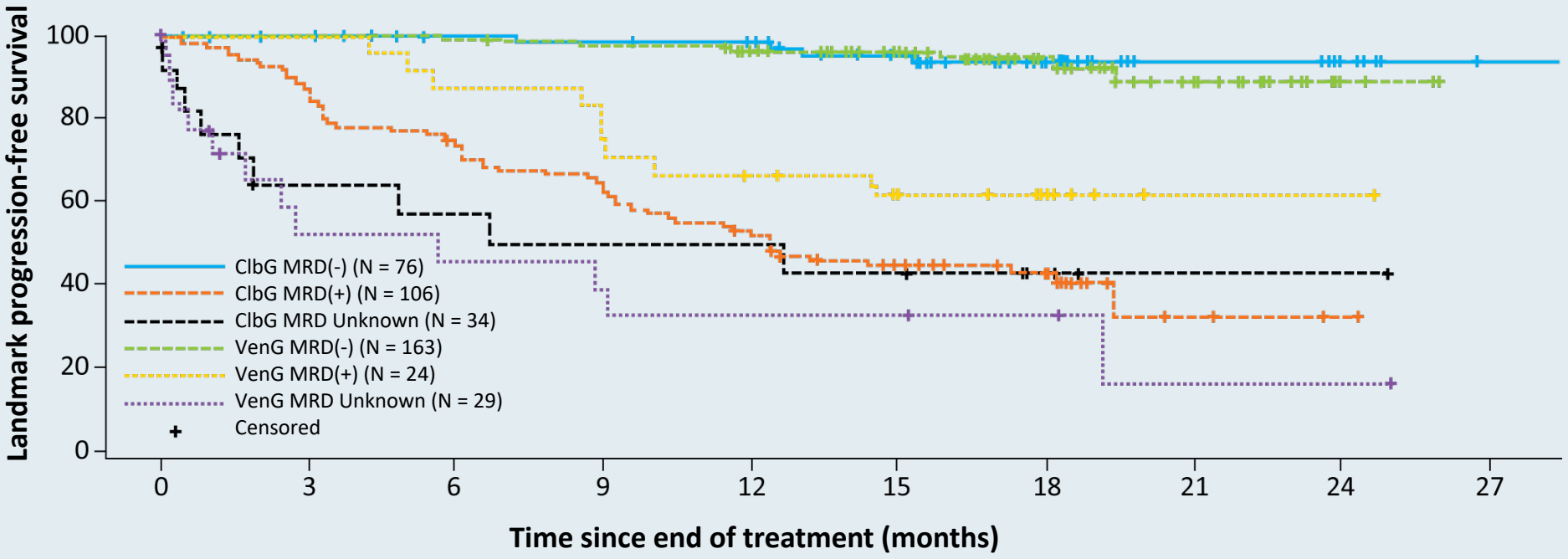
RTP RESEARCH TO PRACTICE

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

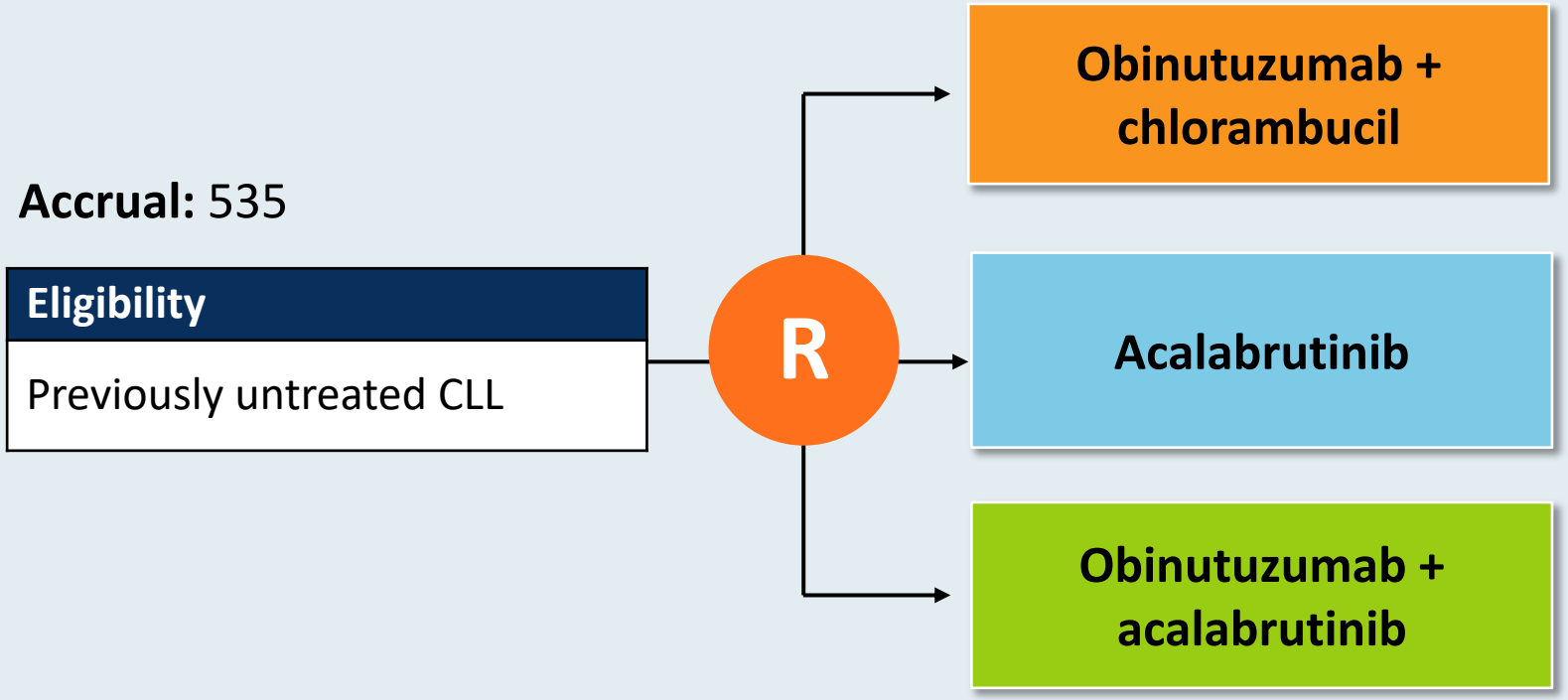


Further landmark analysis of PFS by MRD status showed that undetectable MRD translated into improved PFS regardless of the clinical response status at end of therapy.

Fischer K et al. ASH 2019;Abstract 36.

RTP RESEARCH TO PRACTICE

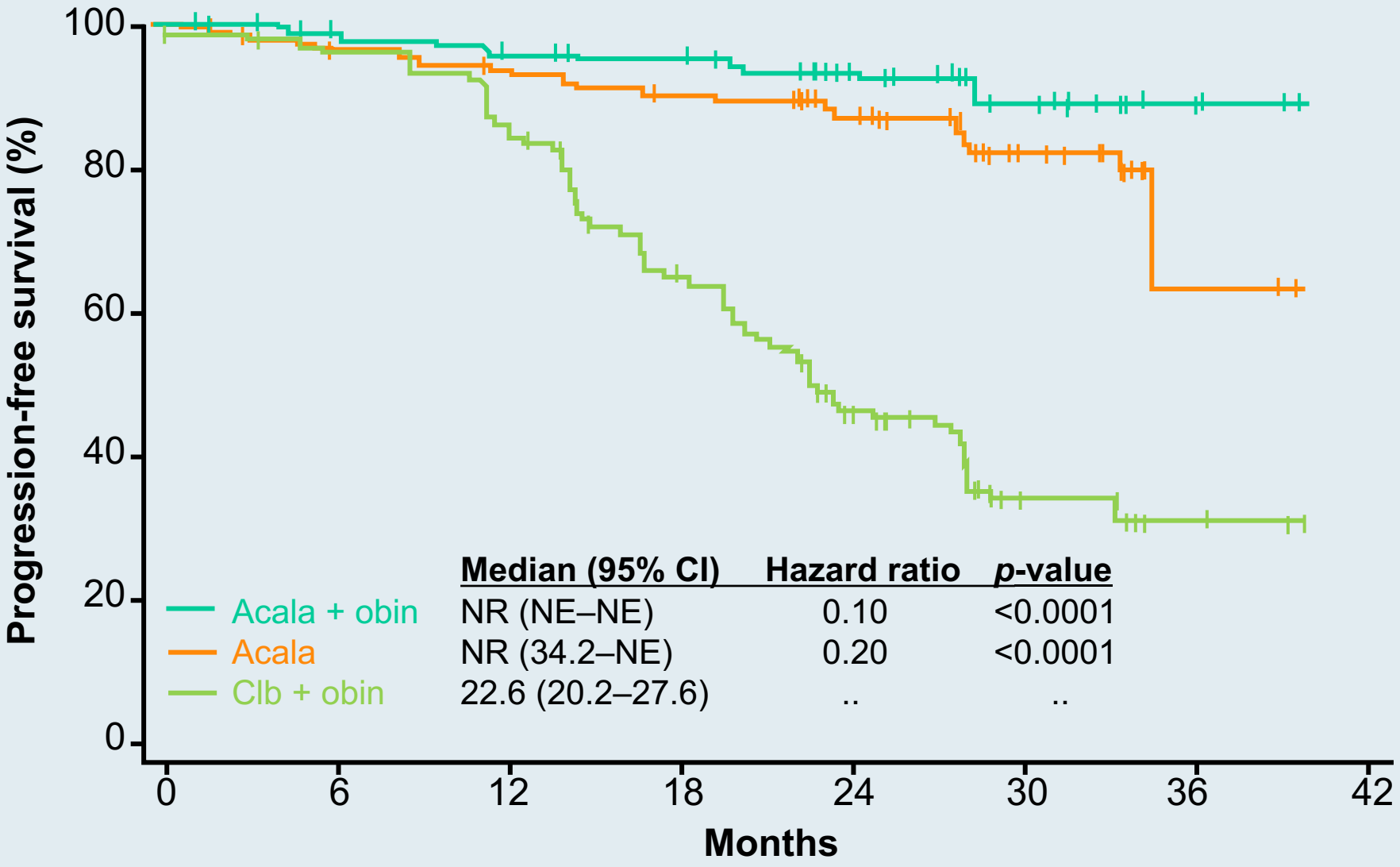
ELEVATE-TN Phase III Trial Schema



Primary endpoint: Progression-free survival

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

ELEVATE-TN: PFS (IRC)



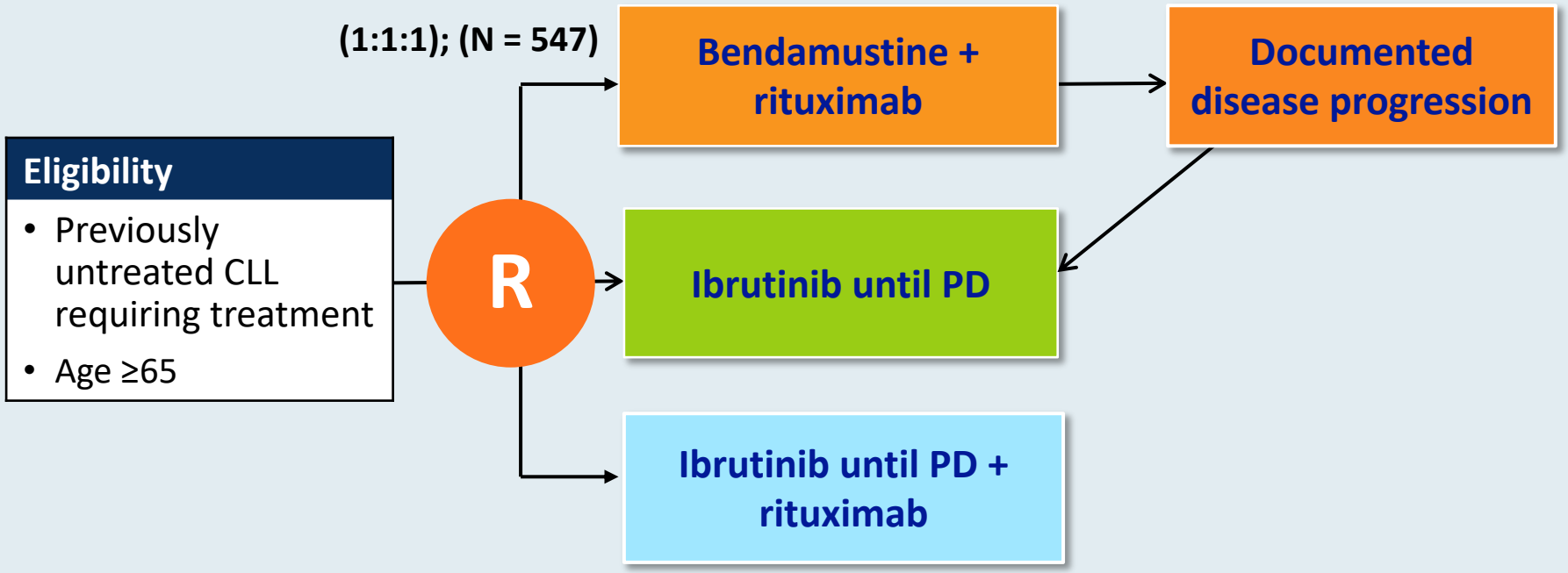
Sharman JP et al. *Lancet* 2020;395:1278-91.

ELEVATE-TN: Select Safety Parameters

	Acalabrutinib/obinutuzumab (n = 178)		Acalabrutinib (n = 179)		Obinutuzumab/chlorambucil (n = 169)	
	Grade 1-2	Grade ≥3	Grade 1-2	Grade ≥3	Grade 1-2	Grade ≥3
Any AE	26%	70%	45%	50%	29%	70%
Serious AE	6%	33%	2%	30%	2%	20%
AE leading to drug discontinuation	11%		9%		14%	
Neutropenia	2%	30%	1%	10%	4%	41%
Grade ≥3 infections						
Infusion-related reactions	11%	2%	0	0	34%	5%

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

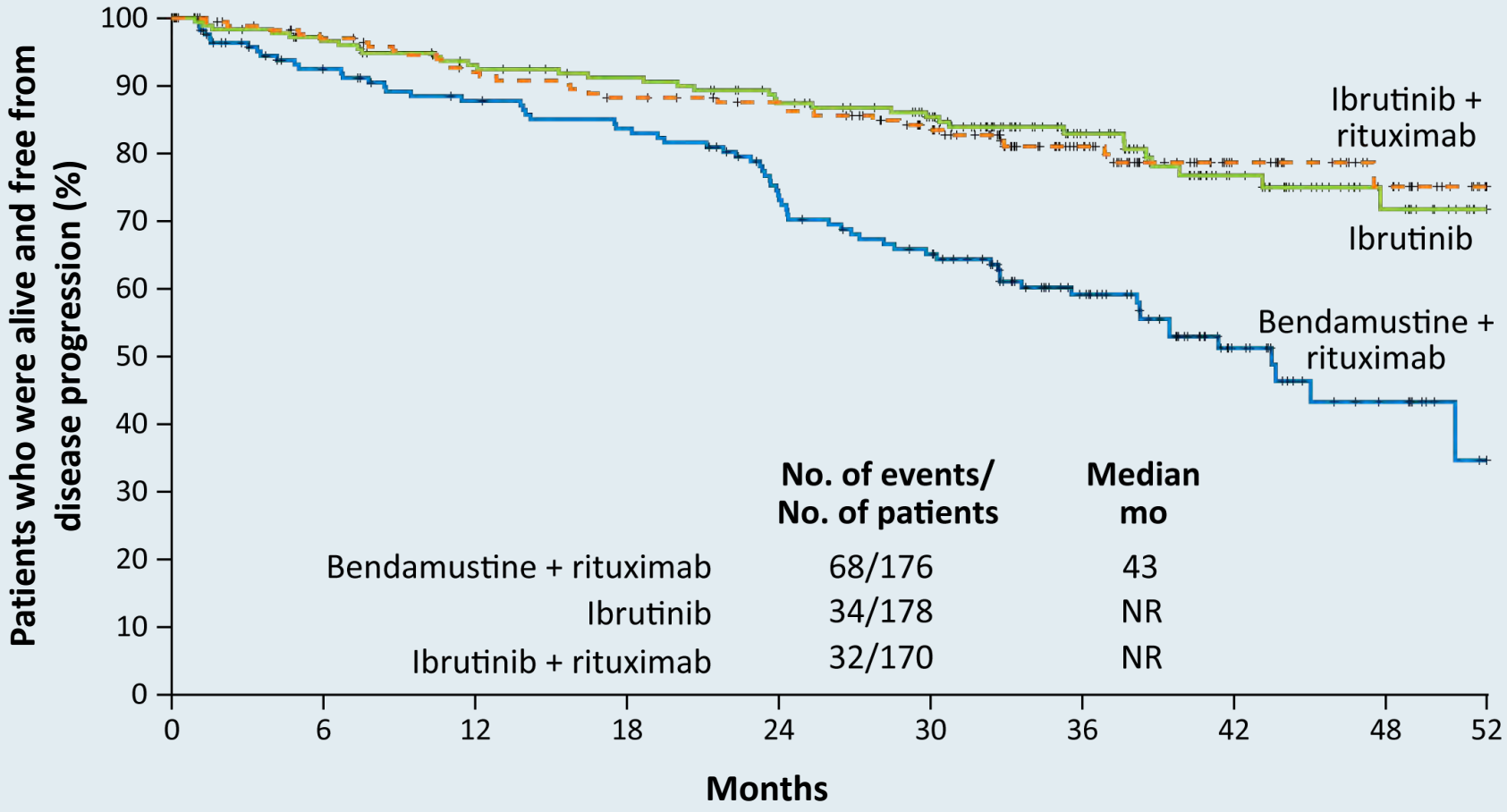
Phase III Alliance A041202 Study Design



Primary endpoint: Progression-free survival (PFS)
Secondary endpoints: OS, ORR, Impact of MRD on PFS and OS, Duration of response, Toxicity and Tolerability

Woyach JA et al. *N Engl J Med* 2018;379(26):2517-28.
Woyach J et al. Alliance Fall Group Meeting, November 5, 2015.

Alliance A041202: Efficacy with Ibrutinib Alone or in Combination with Rituximab Compared to Bendamustine/Rituximab



Woyach JA et al. *N Engl J Med* 2018;379(26):2517-28.

Alliance A041202: Grade 3 to 5 Adverse Events of Special Interest

Adverse event	Bendamustine + rituximab (N = 176)	Ibrutinib (N = 180)	Ibrutinib + rituximab (N = 181)	*p*-value
Hematologic – Any Grade 3-4	**61%**	**41%**	**39%**	**<0.001**
Anemia	12%	12%	6%	0.09
Decreased neutrophil count	40%	15%	21%	<0.001
Decreased platelet count	15%	7%	5%	0.008
Nonhematologic – Any Grade 3-5	**63%**	**74%**	**74%**	**0.04**
Bleeding	0	2%	3%	0.46
Infections	15%	20%	21%	0.62
Febrile neutropenia	7%	2%	1%	<0.001
Atrial fibrillation	3%	9%	6%	0.05
Hypertension	15%	29%	34%	<0.001

Woyach JA et al. *N Engl J Med* 2018;379(26):2517-28.

FDA Approval of Ibrutinib with Rituximab for Chronic Lymphocytic Leukemia or Small Lymphocytic Lymphoma

Press Release – April 21, 2020

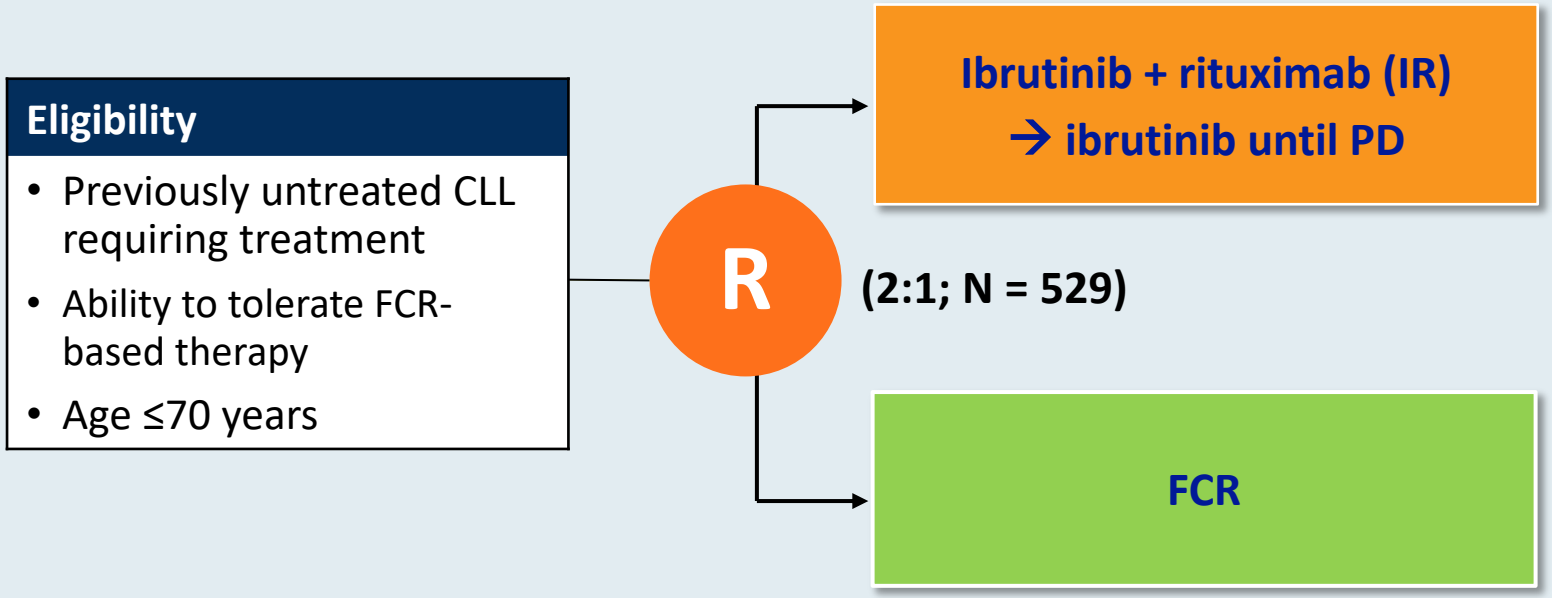
"The Food and Drug Administration expanded the indication of ibrutinib to include its combination with rituximab for the initial treatment of adult patients with chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL).

Approval was based on the E1912 trial (NCT02048813), a 2:1 randomized, multicenter, open-label, actively controlled trial of ibrutinib with rituximab compared to fludarabine, cyclophosphamide, and rituximab (FCR) in 529 adult patients 70 years or younger with previously untreated CLL or SLL requiring systemic therapy. Patients with 17p deletion were excluded. Ibrutinib was administered at 420 mg daily until disease progression or unacceptable toxicity."

https://www.fda.gov/drugs/drug-approvals-and-databases/fda-approves-ibrutinib-plus-rituximab-chronic-lymphocytic-leukemia

RTP RESEARCH TO PRACTICE

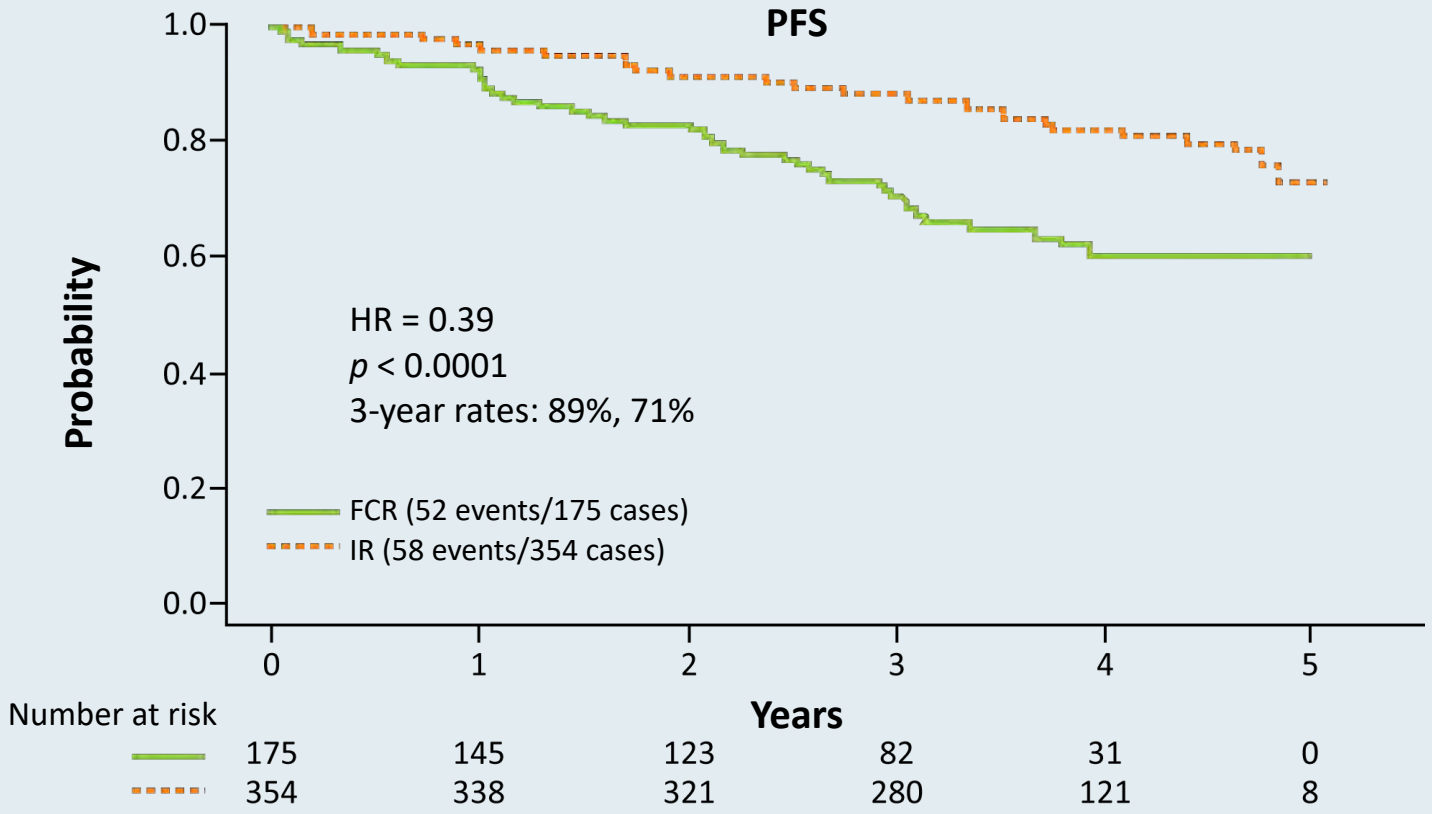
Phase III ECOG-ACRIN E1912 Study Design



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

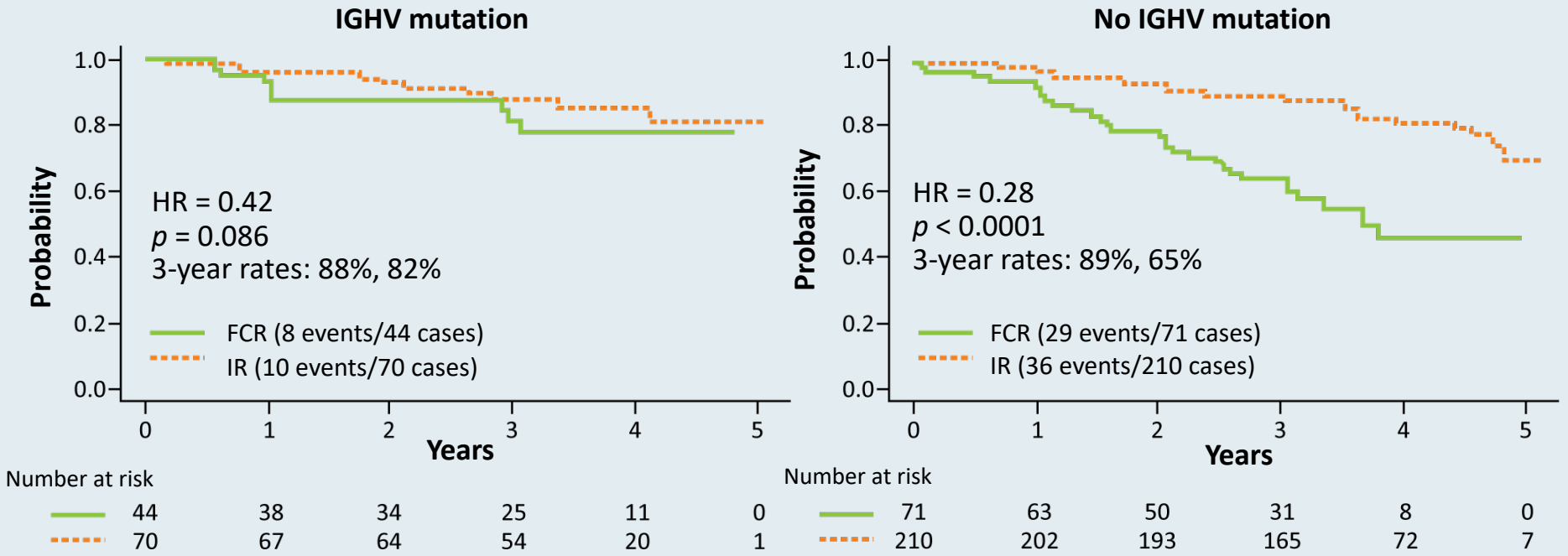


- Grade ≥3 treatment-related AEs were reported in 70% of patients receiving IR and 80% of patients receiving FCR (odds ratio = 0.56; $p = 0.013$).
- Among the 95 patients who discontinued ibrutinib, the most common cause was AE or complication.

Shanafelt TD et al. ASH 2019;Abstract 33.

RTP RESEARCH TO PRACTICE

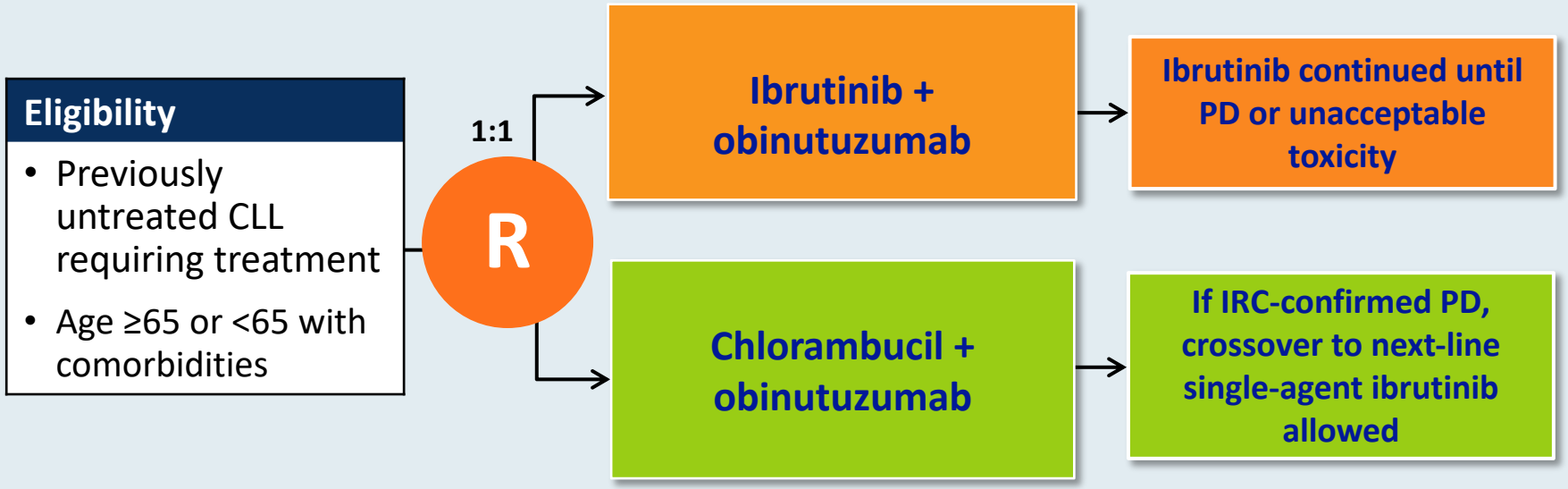
ECOG-ACRIN E1912 Extended Follow-Up: PFS by IGHV Mutation Status



- 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.

Phase III iLLUMINATE Study Design



Stratification

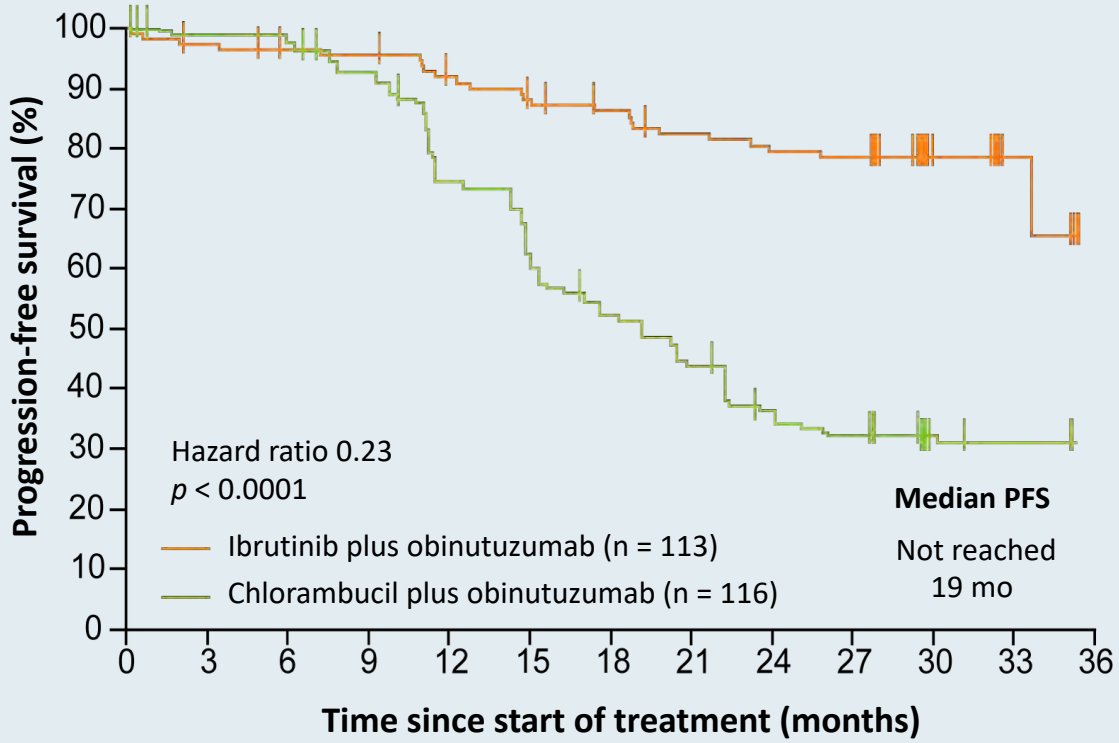
- ECOG PS (0-1 vs 2)
- Del(17p)/del(11q) (+/+ vs +/- vs -/+ vs -/-)

Primary endpoint: PFS by IRC in ITT

Secondary endpoints: PFS for patients at high risk (positive for del(17p) or TP53 mutation, del(11q), or no IGHV mutation), MRD, ORR, OS, IRRs, safety

Moreno C et al. *Lancet Oncol* 2019;20(1):43-56.

iLLUMINATE: A Phase III Trial of Ibrutinib and Obinutuzumab as First-Line Therapy for CLL



Most common Grade 3 or 4 AEs

- Neutropenia
- Thrombocytopenia

Serious AEs

- Ibrutinib/obinutuzumab: 58%
- Chlorambucil/obinutuzumab: 35%

Moreno C et al. *Lancet Oncol* 2019;20(1):43-56.

RTP RESEARCH TO PRACTICE

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

Meet The Professor with Dr Kahl

MODULE 1: Optimal Integration of Venetoclax and BTK Inhibitors into the Front-Line Setting

- Case presentations
- Ibrutinib/rituximab in younger (ECOG-E1912 trial) and older patients (Alliance A041202 trial)
- Available data and current clinical role of ibrutinib/obinutuzumab (iLLUMINATE trial)
- FDA approval of acalabrutinib (ELEVATE-TN trial)
- PFS and rate and duration of MRD negativity with venetoclax/obinutuzumab (CLL14 trial)
- Optimal MRD testing methodology and current role, if any, in clinical practice

MODULE 2: Management of Relapsed/Refractory CLL

- Case presentations
- Venetoclax/rituximab (MURANO trial)
- Acalabrutinib (ASCEND trial)
- Spectrum, frequency and severity of side effects with BTK inhibitors alone versus combined with an anti-CD20 antibody
- Spectrum, incidence, severity and management of venetoclax-associated toxicities, including tumor lysis syndrome

RTP RESEARCH TO PRACTICE

Case Presentation – Dr Morganstein: 78-year-old man with transformation

Neil Morganstein, MD

- CLL with 17p deletion treated over the past 12-13 years
- Treated with multiple agents
- More recently, doing well on ibrutinib, but developed transformation
  - Unable to salvage
  - Unable to enroll on CAR-T trials

Questions

- How often are we seeing transformation in CLL? If you see a new patient right now, how would you counsel the patient about the risk of transformation? And then, what is the current care for that?

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

Based on current clinical trial data and your personal experience, how would you compare the tolerability/toxicity of acalabrutinib to that of ibrutinib for CLL?

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

RTP RESEARCH TO PRACTICE

Based on current clinical trial data and your personal experience, how would you compare the tolerability/toxicity of a single-agent BTK inhibitor to that of venetoclax/obinutuzumab for CLL?

 MATTHEW S DAVIDS, MD, MMSC	Venetoclax/obinutuzumab has less toxicity
 IAN W FLINN, MD, PHD	Venetoclax/obinutuzumab has less toxicity
 BRIAN T HILL, MD, PHD	Venetoclax/obinutuzumab has less toxicity
 BRAD S KAHL, MD	Venetoclax/obinutuzumab has less toxicity
 ANTHONY R MATO, MD, MSCE	Venetoclax/obinutuzumab has less toxicity
 JOHN M PAGEL, MD, PHD	About the same
 KERRY A ROGERS, MD	Venetoclax/obinutuzumab has less toxicity
 JEFF SHARMAN, MD	Venetoclax/obinutuzumab has less toxicity
 MITCHELL R SMITH, MD, PHD	A single-agent BTK inhibitor has less toxicity
 WILLIAM G WIERDA, MD, PHD	Venetoclax/obinutuzumab has less toxicity
 JENNIFER WOYACH, MD	About the same

RTP RESEARCH TO PRACTICE

Case Presentation – Dr Morganstein: 84-year-old man with a long history of CLL treated with FR in the past

Neil Morganstein, MD

- Presents with worsening anemia, thrombocytopenia and rapidly rising lymphocyte count
- Acalabrutinib, with no response for 3 months
  - FISH: del (13q), No del(17p)
  - Could not order TP53 mutation because of insurance
- Eventually, low-dose bendamustine, with rapid improvement in counts
- Currently, on acalabrutinib (due to insurance issues)

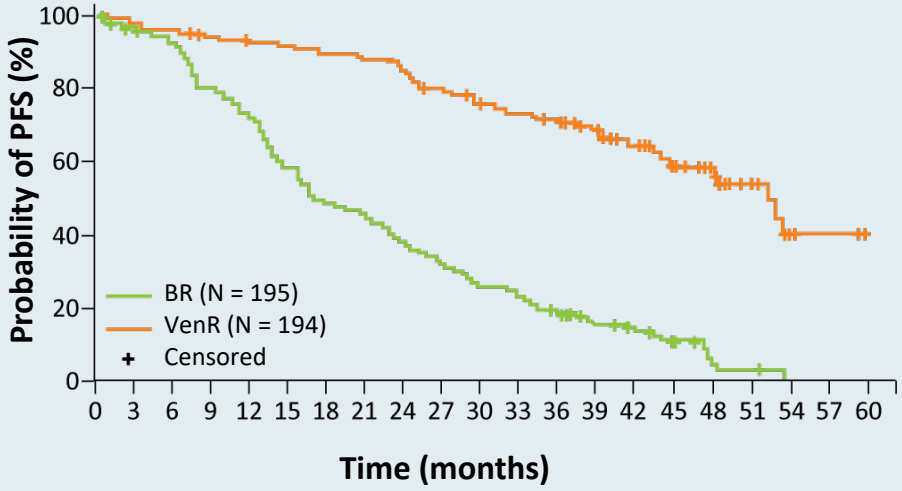
Questions

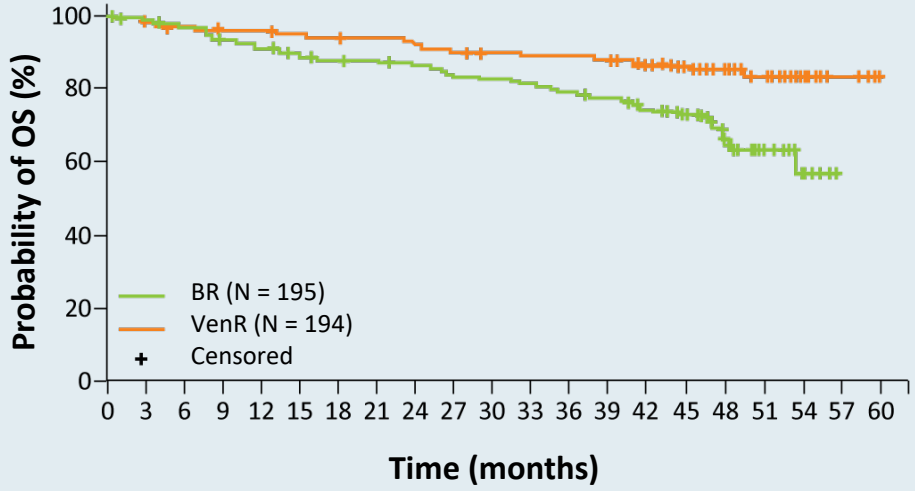
- For elderly patients with comorbidities and elevated WBC > 100,000, what is the optimal first-line therapy – ibrutinib, acalabrutinib or venetoclax? And should they be used in combination with anti-CD20 antibodies, or alone?
- Would it change if they were pretreated in the past with chemo or other first line treatments?

Recent Relevant Data Sets

MURANO Trial: Survival Analyses with Venetoclax/ Rituximab for R/R CLL (48-Month Median Follow-Up)

	VenR (n = 194)	BR (n = 195)	Hazard ratio	*p*-value
Four-year PFS	57.3%	4.6%	0.19	<0.0001
Four-year OS	85.3%	66.8%	0.41	<0.0001





Seymour JF et al. ASH 2019;Abstract 355.

FDA Approval of Acalabrutinib for Chronic Lymphocytic Leukemia or Small Lymphocytic Lymphoma

Press Release – November 21, 2019

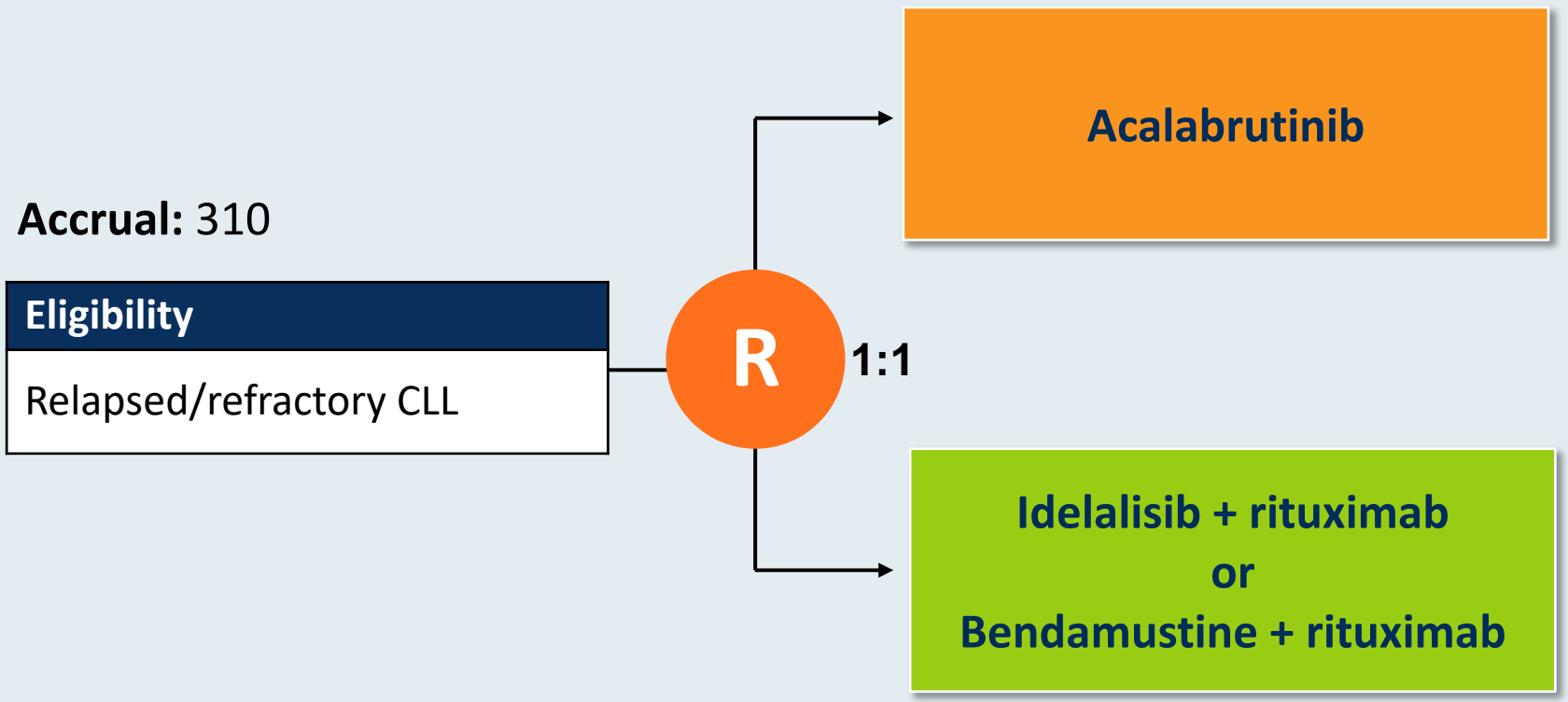
"The Food and Drug Administration approved acalabrutinib for adults with chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL). This review was conducted under Project Orbis, an initiative of the FDA Oncology Center of Excellence. Project Orbis provides a framework for concurrent submission and review of oncology drugs among international partners.

Approval was based on two randomized, actively controlled trials in patients with CLL: ELEVATE-TN (NCT02475681) and ASCEND (NCT02970318). Efficacy in both trials was based on progression-free survival (PFS) as assessed by independent review. The recommended dose is 100 mg orally every 12 hours."

https://www.fda.gov/drugs/resources-information-approved-drugs/project-orbis-fda-approves-acalabrutinib-cll-and-sll

RTP RESEARCH TO PRACTICE

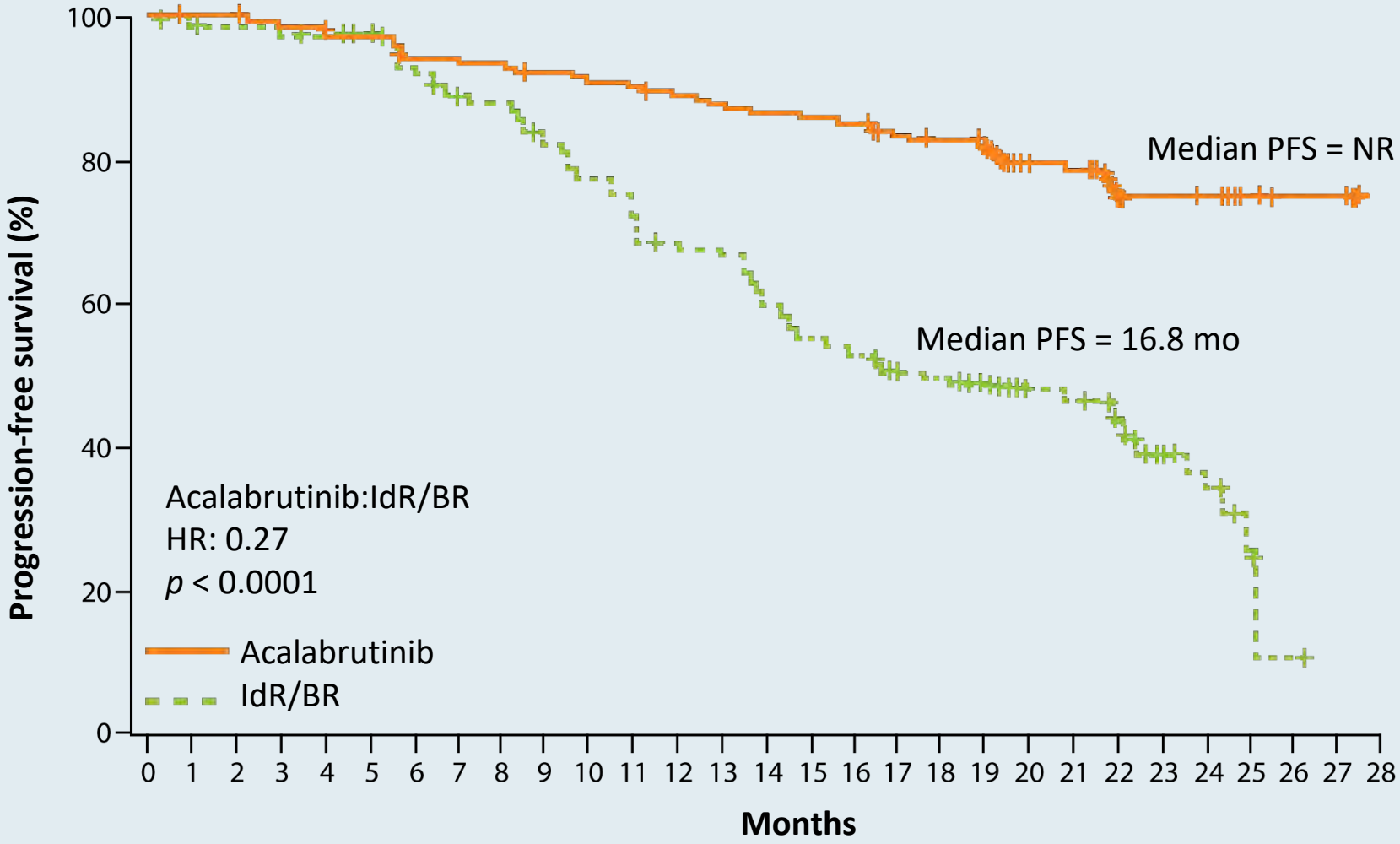
ASCEND Phase III Trial Schema



Primary endpoint: Progression-free survival by IRC

Ghia P et al. EHA 2019;Abstract LBA 2606.
www.clinicaltrials.gov (NCT02970318). Accessed August 2020.

ASCEND: Final Analysis of Investigator-Assessed PFS



After a median of 22 months, acalabrutinib prolonged PFS vs investigator's choice of therapy (estimated 18-mo PFS: 82% and 48%, respectively)

Ghia P et al. EHA 2020;Abstract S159.

ASCEND: Adverse Events of Clinical Interest

Adverse event	Acalabrutinib (n = 154)		IdR (n = 118)	
	Any grade	Grade ≥3	Any grade	Grade ≥3
Atrial fibrillation	6%	1%	3%	1%
Hemorrhage	29%	3%	8%	3%
Major hemorrhage	3%	3%	3%	3%
Hypertension	5%	3%	4%	1%
Infections	63%	20%	65%	25%
Second primary cancer, excluding non-melanoma skin carcinomas	5%	4%	2%	1%
Tumor lysis syndrome	1%	1%	1%	1%

IdR = rituximab/idelalisib

Ghia P et al. EHA 2020;Abstract S159.

Optimizing the Selection and Sequencing of Therapy for Patients with Chronic Lymphocytic Leukemia

A Meet The Professor Series

Tuesday, August 25, 2020
5:00 PM – 6:00 PM ET

Faculty

Anthony R Mato, MD, MSCE

Moderator

Neil Love, MD

RTP RESEARCH TO PRACTICE

Thank you for joining us!

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