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

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

A Meet The Professor Series

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

Commercial Support

These activities are supported by educational grants from AbbVie Inc and AstraZeneca Pharmaceuticals LP.

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Dr Love — Disclosures

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Dr Flinn — Disclosures

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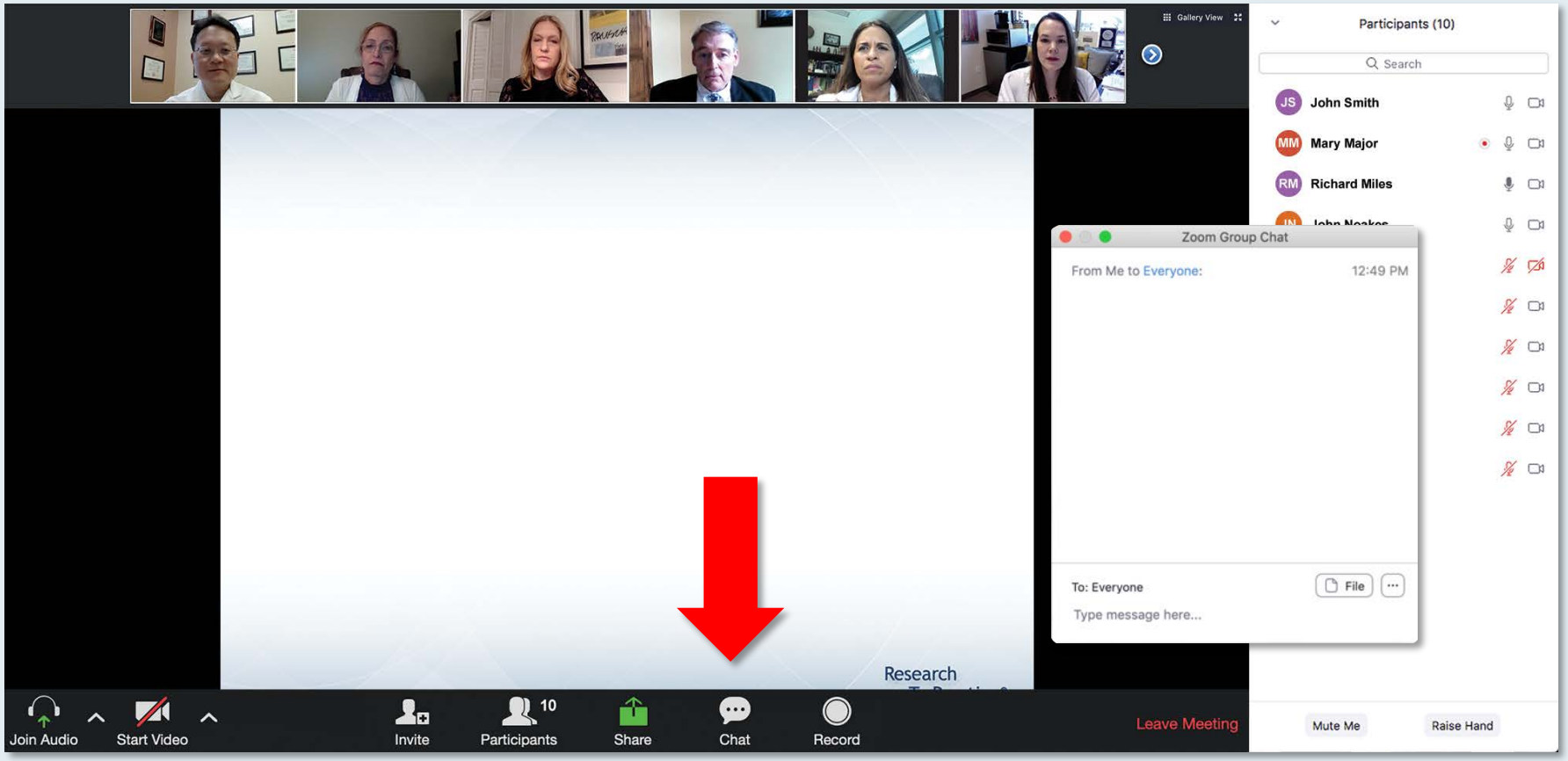
We Encourage Clinicians in Practice to Submit Questions



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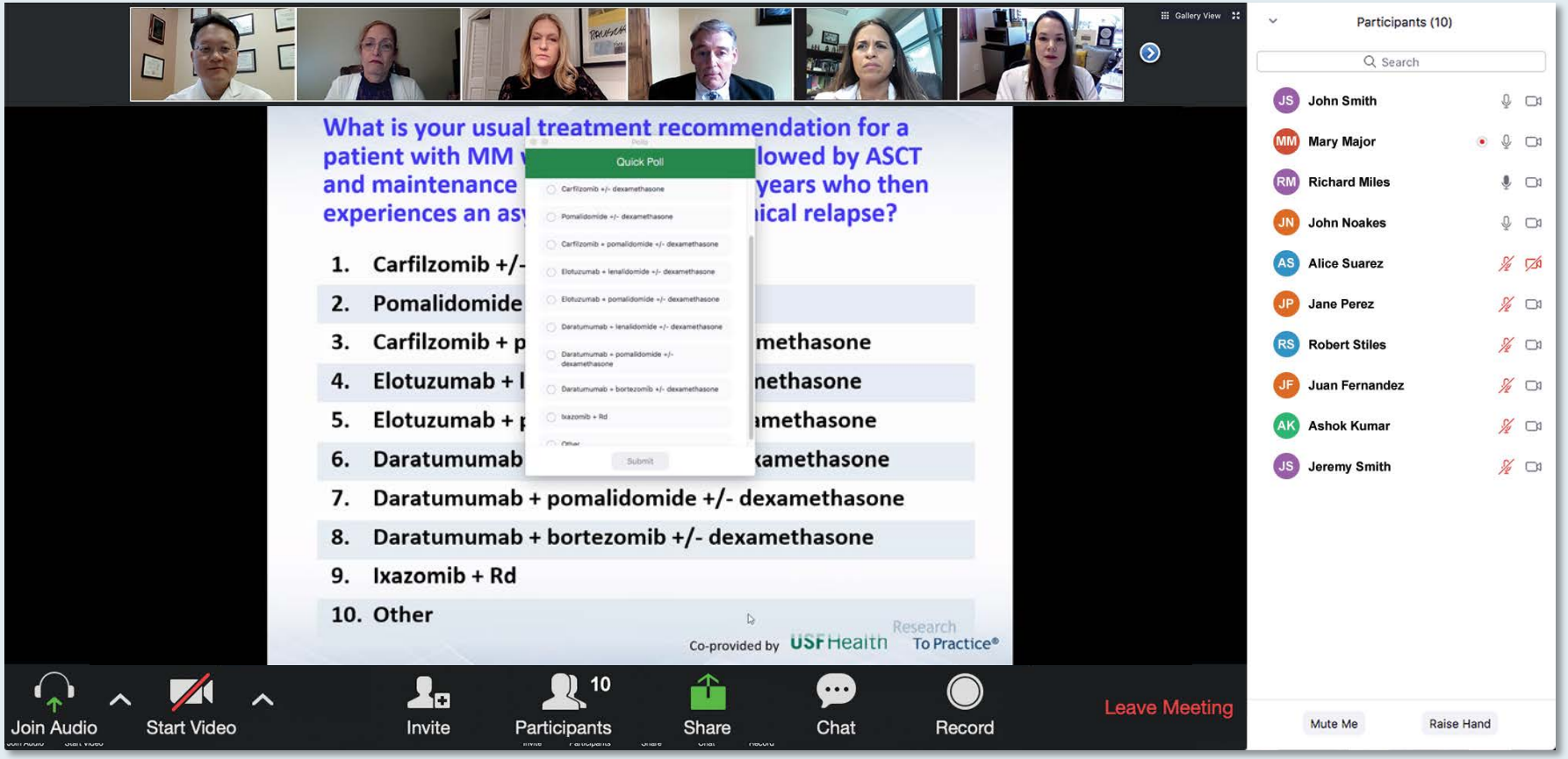
RTP RESEARCH TO PRACTICE

Familiarizing Yourself with the Zoom Interface

How to answer poll questions



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RTP RESEARCH TO PRACTICE

Upcoming Live Webinars

Wednesday, September 16, 2020
12:00 PM – 1:00 PM ET

Clinical Investigator Perspectives on the Current and Future Management of Multiple Myeloma

Faculty
Jonathan L Kaufman, MD

Moderator
Neil Love, MD

Friday, September 18, 2020
12:00 PM – 1:00 PM ET

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

Faculty
Matthew S Davids, MD, MMSc

Moderator
Neil Love, MD

Thank you for joining us!

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

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WITH DR NEIL LOVE

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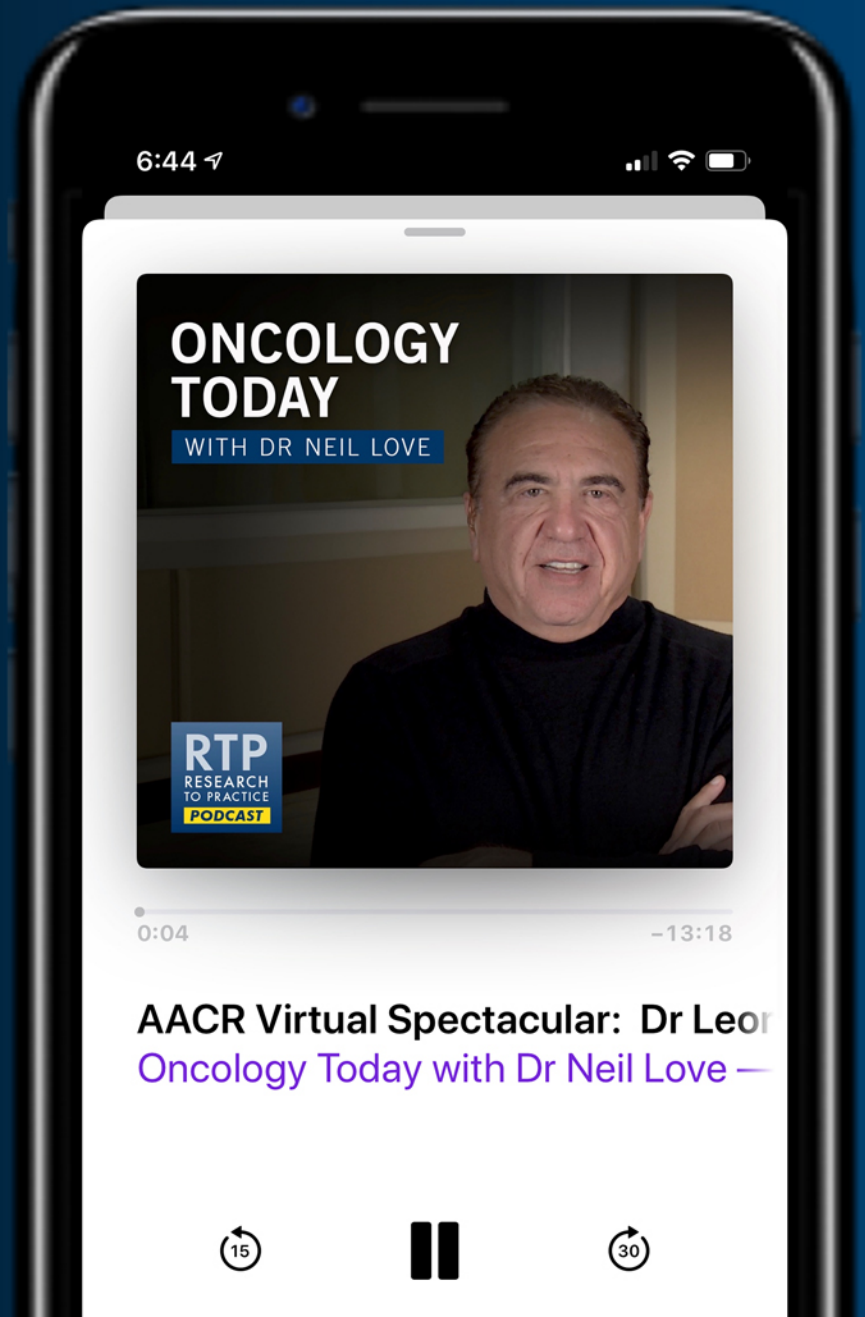

Optimizing the Selection and Sequencing of Therapy for Patients with Chronic Lymphocytic Leukemia

A Meet The Professor Series

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

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
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Sarah Cannon Research Institute
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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

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

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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
Professor
Division of Hematology
Department of Internal Medicine
The Ohio State University
Comprehensive Cancer Center
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DB Lane Cancer Research
Distinguished Professor
Department of Leukemia
Division of Cancer Medicine
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MD Anderson Cancer Center
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Project Chair
Neil Love, MD
Research To Practice
Miami, Florida

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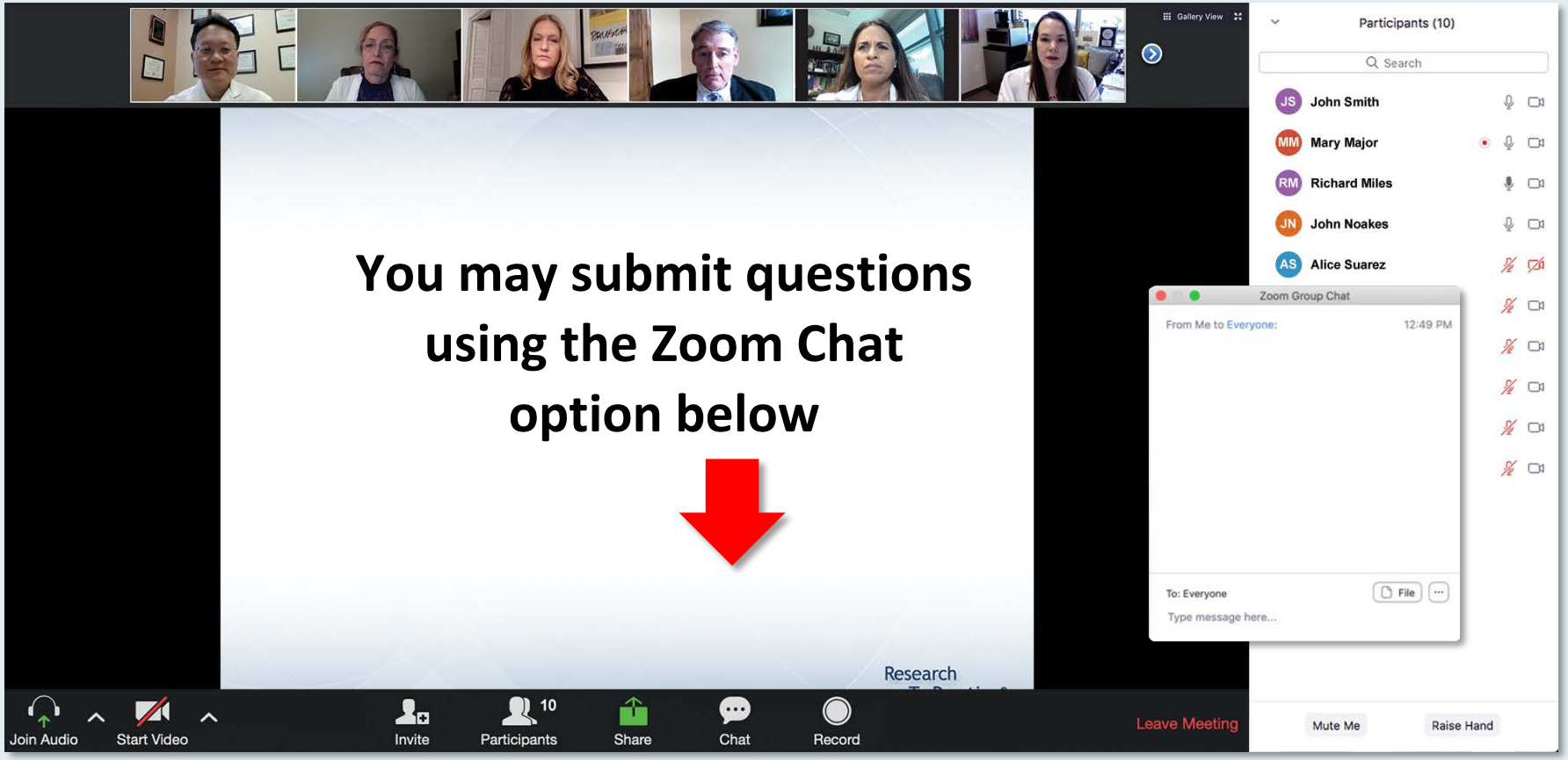

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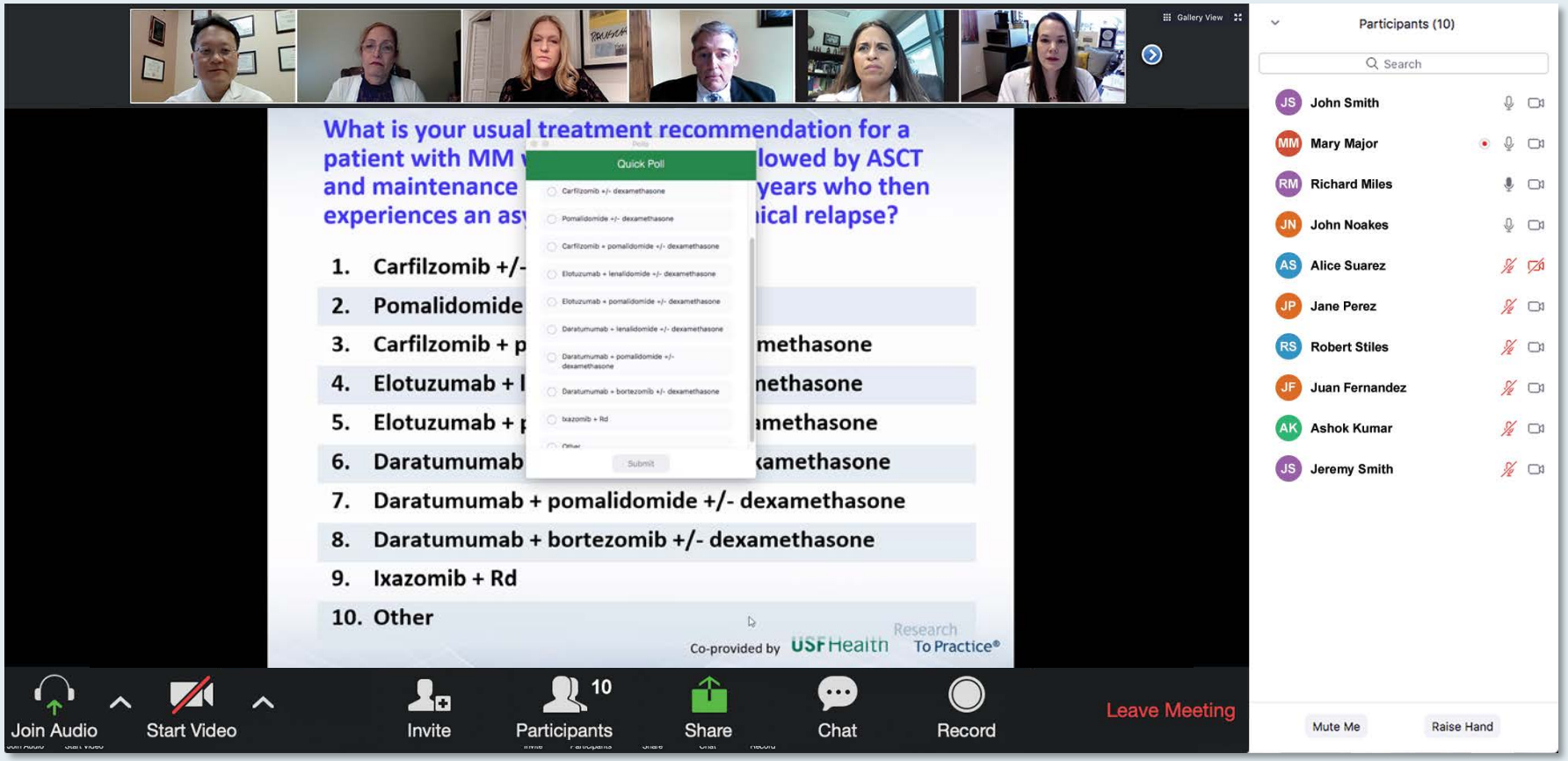

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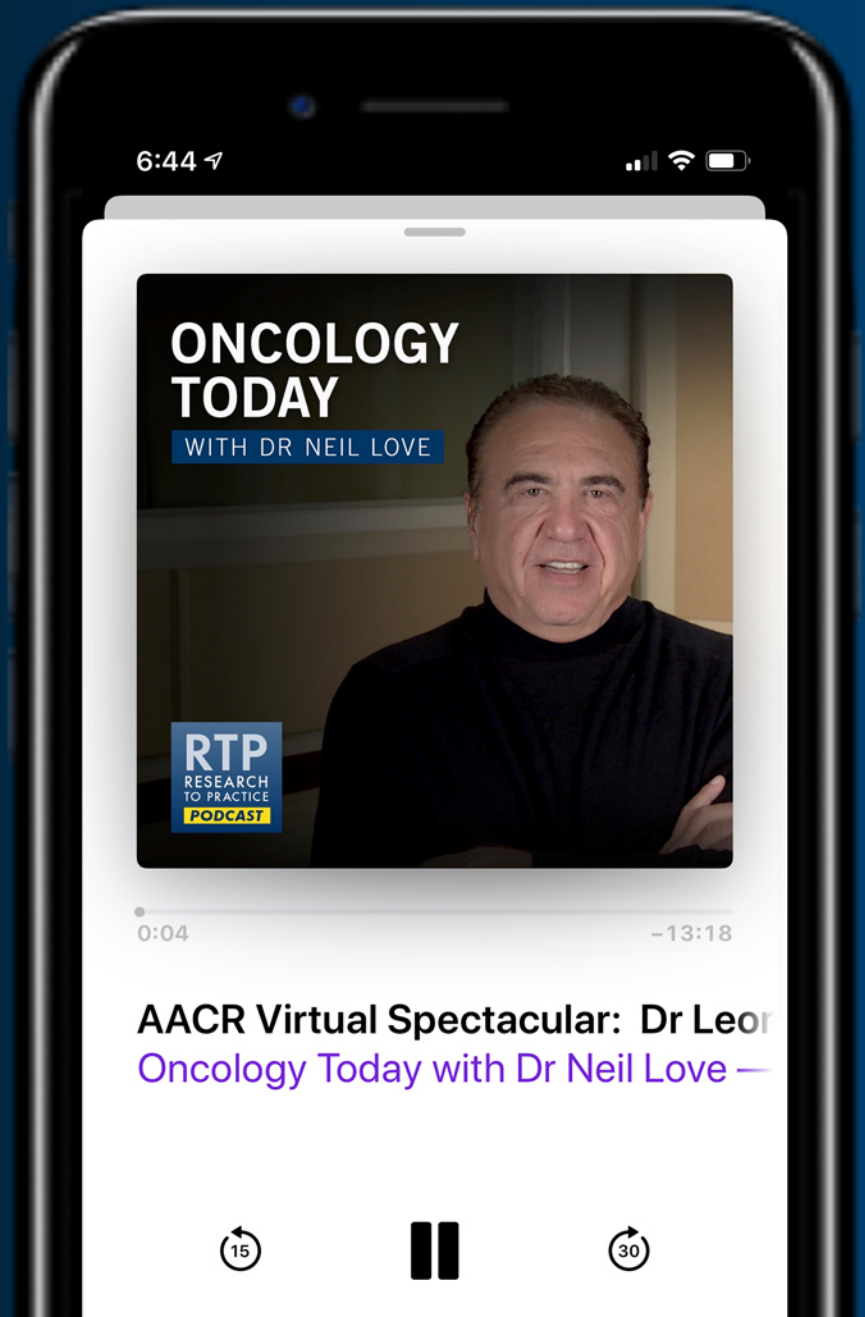

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Wednesday, September 16, 2020
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Ian W Flinn, MD, PhD
Director of Lymphoma Research Program
Sarah Cannon Research Institute
Tennessee Oncology
Nashville, Tennessee

Ranju Gupta, MD
Attending Physician
Co-Director, Cardio-Oncology program
LVPG Hematology Oncology Associates
Lehigh Valley Health Network
Bethlehem, Pennsylvania

Meet The Professor with Dr Flinn

MODULE 1: Cases from the Community – Dr Gupta

- A 79-year-old man with relapsed CLL – Part 1
- A 79-year-old man with relapsed CLL – Part 2
- A 79-year-old man with relapsed CLL – Part 3
- A 55-year-old man with relapsed CLL
- A fit 75-year-old man with relapsed CLL – Part 1
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MODULE 2: Beyond the Guidelines – Clinical Investigator Approaches to Common Clinical Scenarios

MODULE 3: Key Recent Data Sets

- PFS and rate and duration of MRD negativity with venetoclax/obinutuzumab (CLL14 trial)
- FDA approval of acalabrutinib (ELEVATE-TN trial)
- Ibrutinib/rituximab in older (Alliance A041202 trial) and younger (ECOG-E1912 trial) patients
- CAPTIVATE MRD cohort
- Available data and current clinical role of ibrutinib/obinutuzumab (iLLUMINATE trial)
- Venetoclax/rituximab (MURANO trial)
- Acalabrutinib (ASCEND trial)
- Side effects associated with BTK inhibitors and venetoclax-associated toxicities

RTP RESEARCH TO PRACTICE

Case Presentation – Dr Gupta: A 79-year-old man with relapsed CLL

Dr Ranju Gupta

- 2012: Stage IIIA CLL/SLL with extensive bone marrow involvement
  - Bendamustine/rituximab x 4, with excellent response
- Prior medical history: HTN and Parkinson's disease
- 2014: Relapse → Ibrutinib
- FISH: Normal
- June 2018: Progression of disease, with symptomatic worsening adenopathy
- Venetoclax/rituximab
  - Venetoclax initiated per package insert as inpatient
  - Rituximab given for 6 months then discontinued
- August 2020 scan: No adenopathy

Questions

- Should I discontinue venetoclax after 2 years, per MURANO, even though he has had no side effects? If continued, should I reduce the dose?
- If I stop venetoclax and he has POD, should I re-start venetoclax? Venetoclax/obinutuzumab?

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Comments and Questions: Duration of venetoclax

Dr Ranju Gupta

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Comments and Questions: Considerations during initiation of venetoclax for CLL

Dr Ranju Gupta

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Case Presentation – Dr Gupta: A 55-year-old man with relapsed CLL

Dr Ranju Gupta

- 2019: Presented to ER with spleen laceration due to motorcycle accident
  - Work up: Abdominal adenopathy and splenomegaly
- Stage IIa, IGVH unmutated CLL, with homozygous deletion of 13q14; Asymptomatic
- Baseline Hgb, plt: Normal, WBC: ~65-70k
- Observation
- June 2020: Admitted with abdominal pain, fatigue, and new skin nodules
  - Hgb: 9, Plt: 78, WBC: 98k; CT: Progressive adenopathy, possible spleen rupture
- Planned to initiate ibrutinib/obinutuzumab, but WBC doubled from 98k to 180k in 4 days with worsening anemia and could not get ibrutinib quickly enough
- Admitted, administered bendamustine → Well tolerated; No TLS; Cervical adenopathy decreased
- Just initiated obinutuzumab and plan to start ibrutinib in 3-4 weeks once counts recover

Questions

- How would you have treated this patient – ibrutinib/obinutuzumab, ibrutinib/venetoclax, venetoclax/obinutuzumab?
- When admitted, with rapid doubling of WBC, would you have approached treatment differently?

RTP RESEARCH TO PRACTICE

Case Presentation – Dr Gupta: A fit 75-year-old man with relapsed CLL

Dr Ranju Gupta

- 2015: Stage IV CLL, presenting with anemia, thrombocytopenia (TTP), and mild adenopathy
  - FISH: Abnormal signal pattern for heterozygous deletion of 13q14
- Prior medical history: PS 0, HTN, prostate cancer well controlled on leuprolide alone
- Recurrent episode of autoimmune hemolytic anemia (AIHA) and autoimmune thrombocytopenia
- 2016: Completed BR x 6, with excellent response
- 2020: Worsening adenopathy, AIHA, appetite and weight loss, doubling of WBC in <3 months, mild TTP
- Venetoclax/obinutuzumab
  - Day 1: Obinutuzumab: WBC: 60-70K → neutropenic; Plt: 80K, Hgb: 11 → 9.2
  - Day 2: WBC: 3.4K, Plt: 100K, ANC: 1.7, Hgb: 9.8 → administered venetoclax, obinutuzumab
  - Next visit: Uric acid 3.2 → 7.8, LDH: 250 → 1500 → rasburicase, hold venetoclax
  - Next visit: Uric acid 3.4, WBC: 3.8K, Plt: 100K, ANC: ~2 → proceed with venetoclax, obinutuzumab

Questions

- What is the optimal treatment choice, and why, for patients with standard-risk CLL (patient prefers not to be on life-long medication if possible)?

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Comments and Questions: Venetoclax/obinutuzumab and TLS: Determining when to hold venetoclax or obinutuzumab

Dr Ranju Gupta

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Meet The Professor with Dr Flinn

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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 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?

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

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

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
 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

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

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

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

Meet The Professor with Dr Flinn

MODULE 1: Cases from the Community – Dr Gupta

- A 79-year-old man with relapsed CLL – Part 1
- A 79-year-old man with relapsed CLL – Part 2
- A 79-year-old man with relapsed CLL – Part 3
- A 55-year-old man with relapsed CLL
- A fit 75-year-old man with relapsed CLL – Part 1
- A fit 75-year-old man with relapsed CLL – Part 2

MODULE 2: Beyond the Guidelines – Clinical Investigator Approaches to Common Clinical Scenarios

MODULE 3: Key Recent Data Sets

- PFS and rate and duration of MRD negativity with venetoclax/obinutuzumab (CLL14 trial)
- FDA approval of acalabrutinib (ELEVATE-TN trial)
- Ibrutinib/rituximab in older (Alliance A041202 trial) and younger (ECOG-E1912 trial) patients
- CAPTIVATE MRD cohort
- Available data and current clinical role of ibrutinib/obinutuzumab (iLLUMINATE trial)
- Venetoclax/rituximab (MURANO trial)
- Acalabrutinib (ASCEND trial)
- Side effects associated with BTK inhibitors and venetoclax-associated toxicities

RTP RESEARCH TO PRACTICE

bjh emergencies in haematology

Practical management of tumour lysis syndrome in venetoclax-treated patients with chronic lymphocytic leukaemia

John G. Gribben

Barts Cancer Institute, St. Bartholomew's Hospital, Queen Mary University of London, London, UK

***British Journal of Haematology* 2020;188:844-51.**

blood®

How I Treat

How I manage ibrutinib intolerance and complications in patients with chronic lymphocytic leukemia

Deborah M. Stephens[1] and John C. Byrd[2-4]

blood® 21 MARCH 2019 | VOLUME 133, NUMBER 12

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

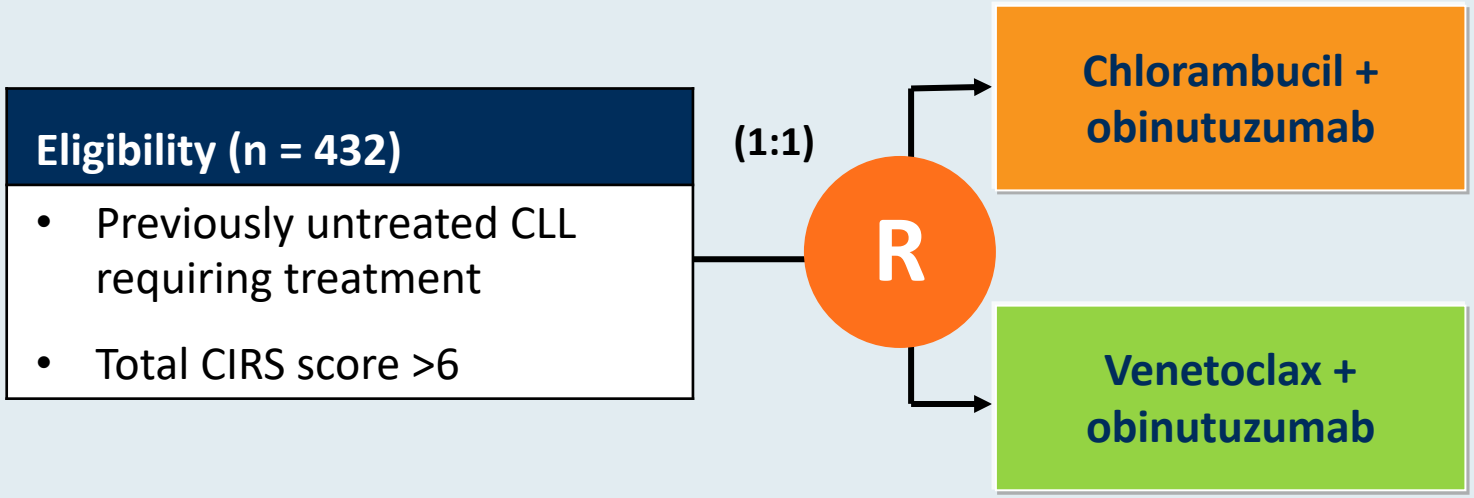
- 72 yo man with CLL requiring treatment.
- 17p deletion by FISH

- BTKi plus obinutuzumab

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

Courtesy of Brad Kahl, MD

CLL14 Phase III Study Schema

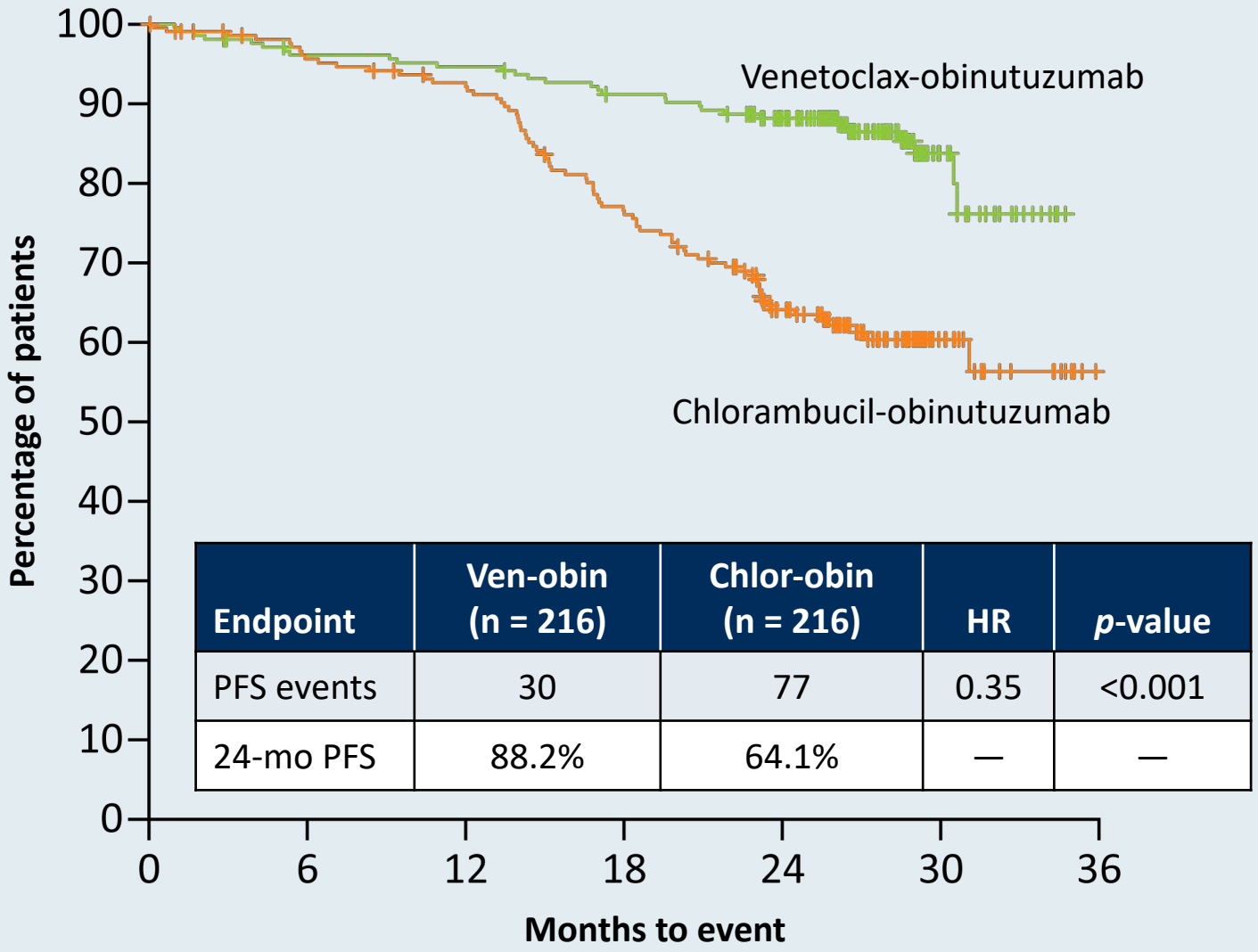


Primary endpoint: Progression-free survival

- 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.

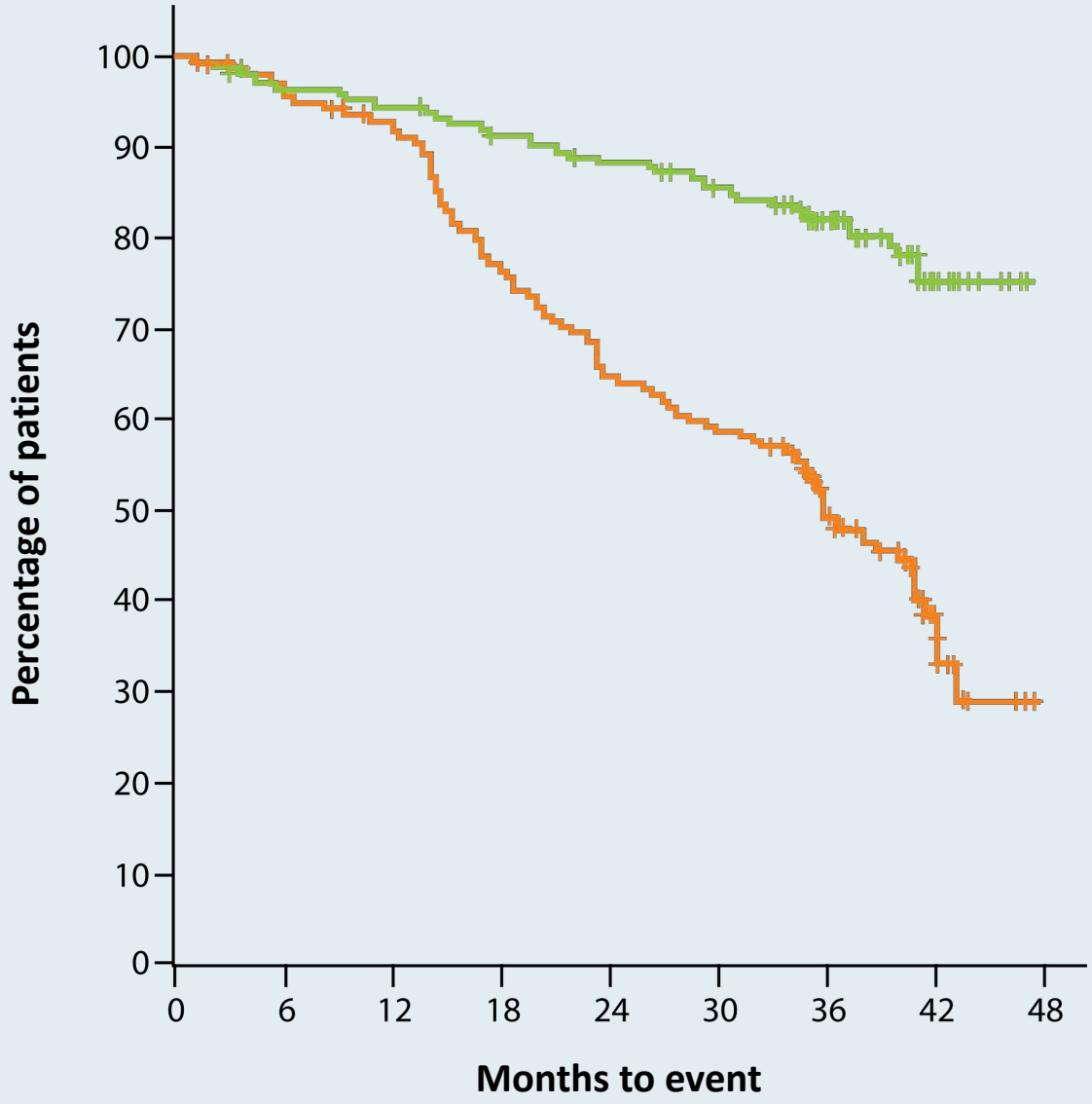
CLL14: Investigator-Assessed Progression-Free Survival



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%

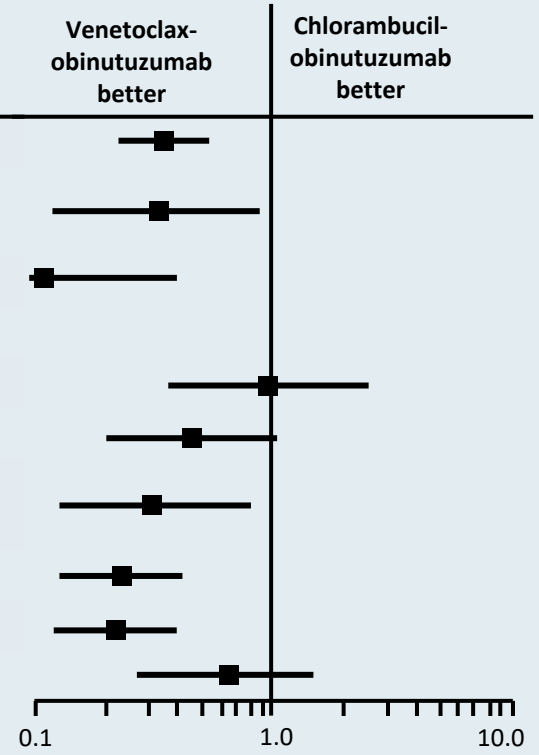
HR 0.31, 95% CI [0.22-0.44]

$p < 0.0001$

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

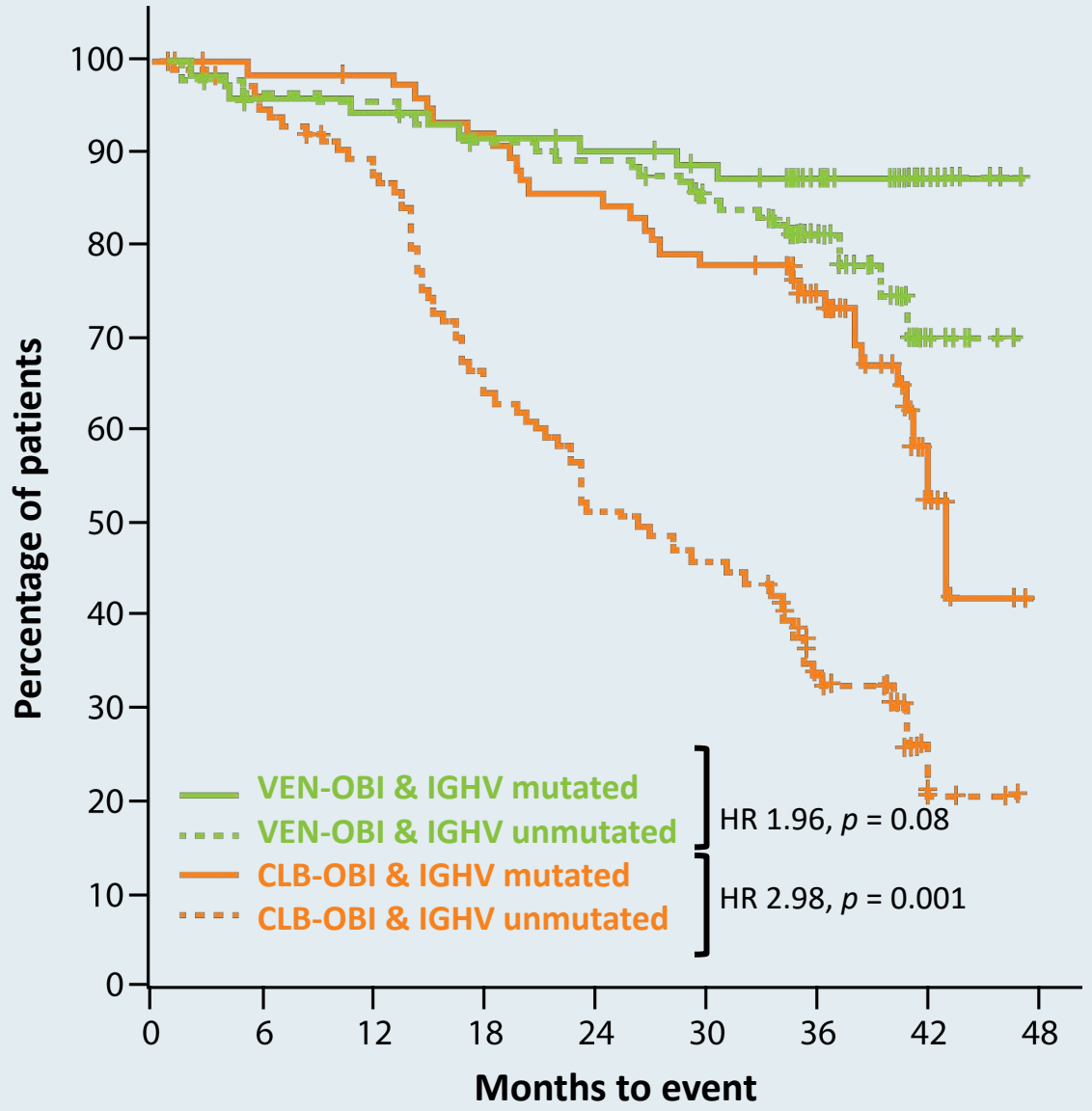
CLL14: Investigator-Assessed Progression-Free Survival by Prognostic Subgroup

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.

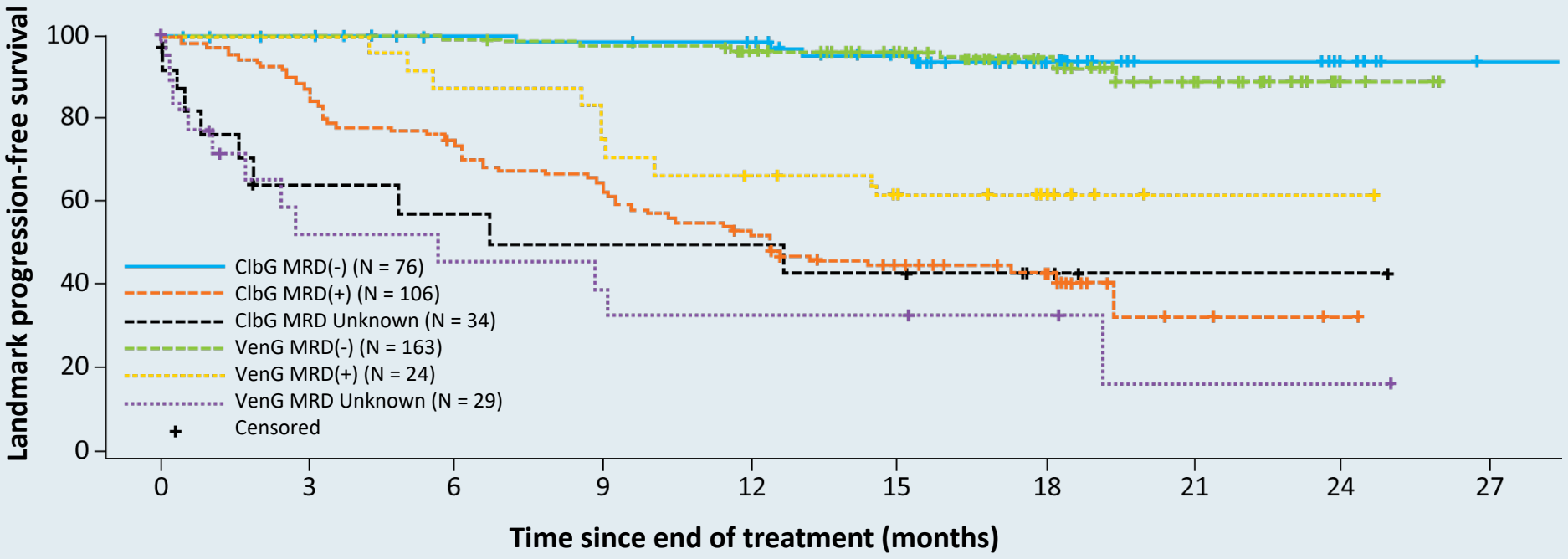
RTP RESEARCH TO PRACTICE

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.

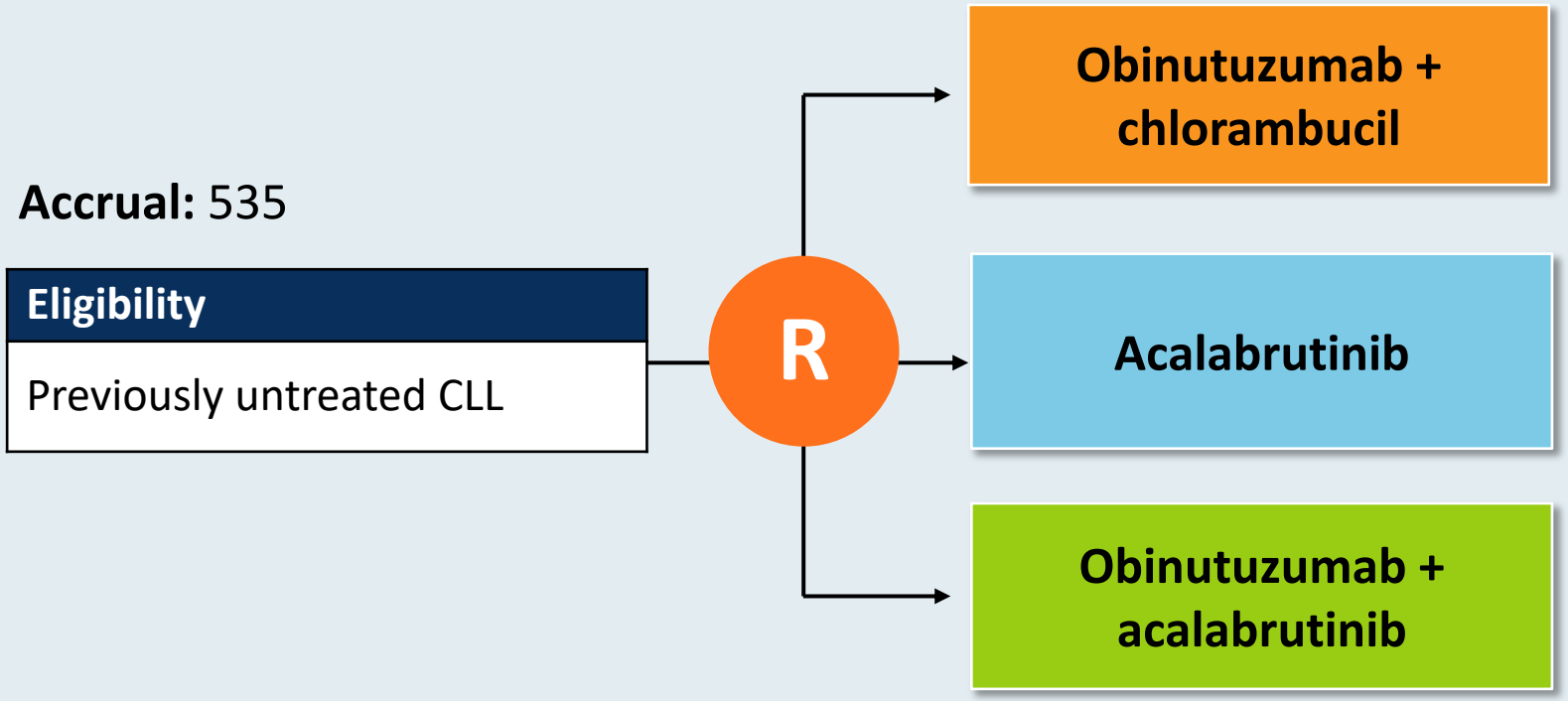
CLL14: Landmark Analysis from End of Therapy PFS by MRD Group



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.

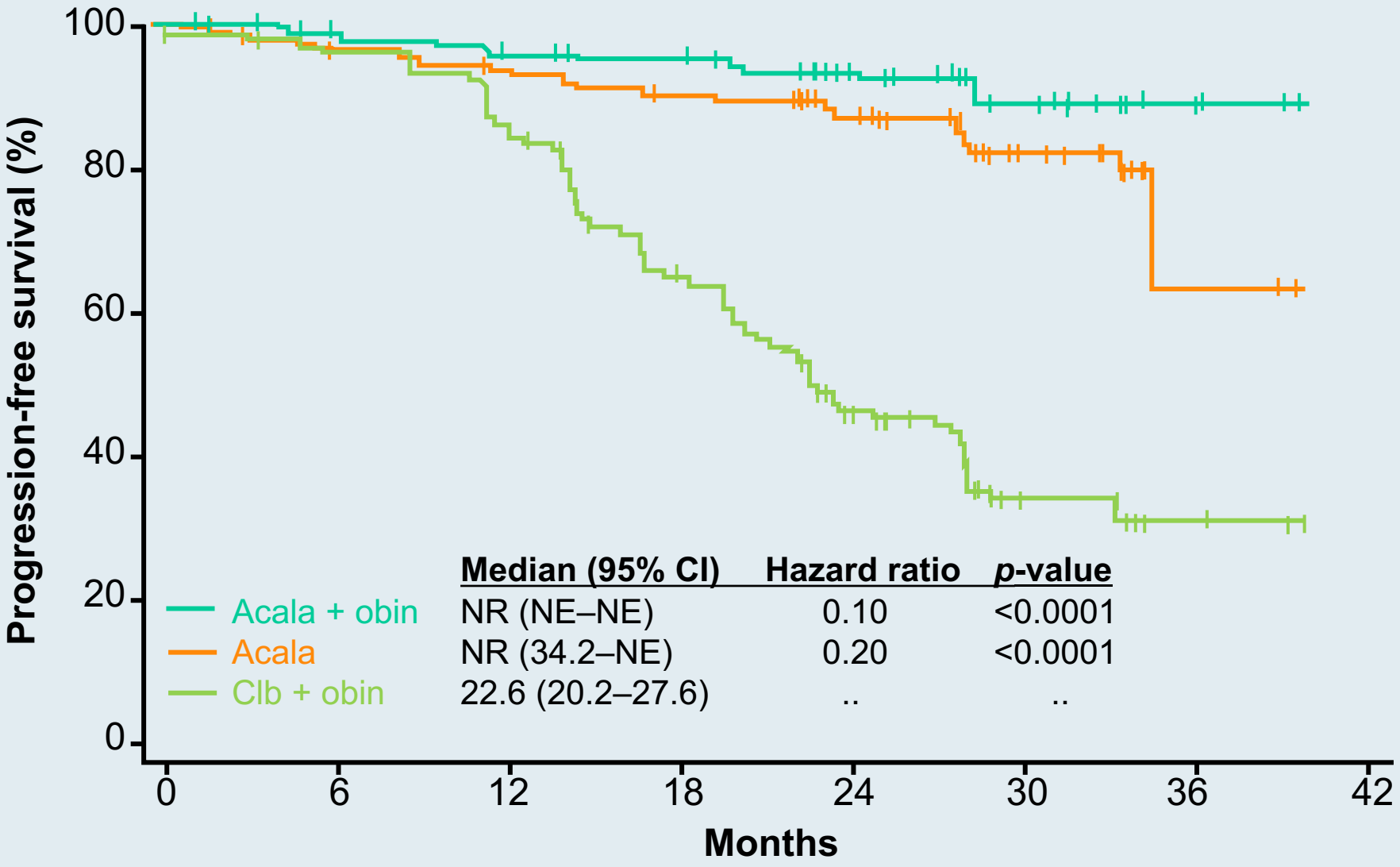
ELEVATE-TN Phase III Trial Schema



Primary endpoint: Progression-free survival

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

ELEVATE-TN: PFS (IRC)



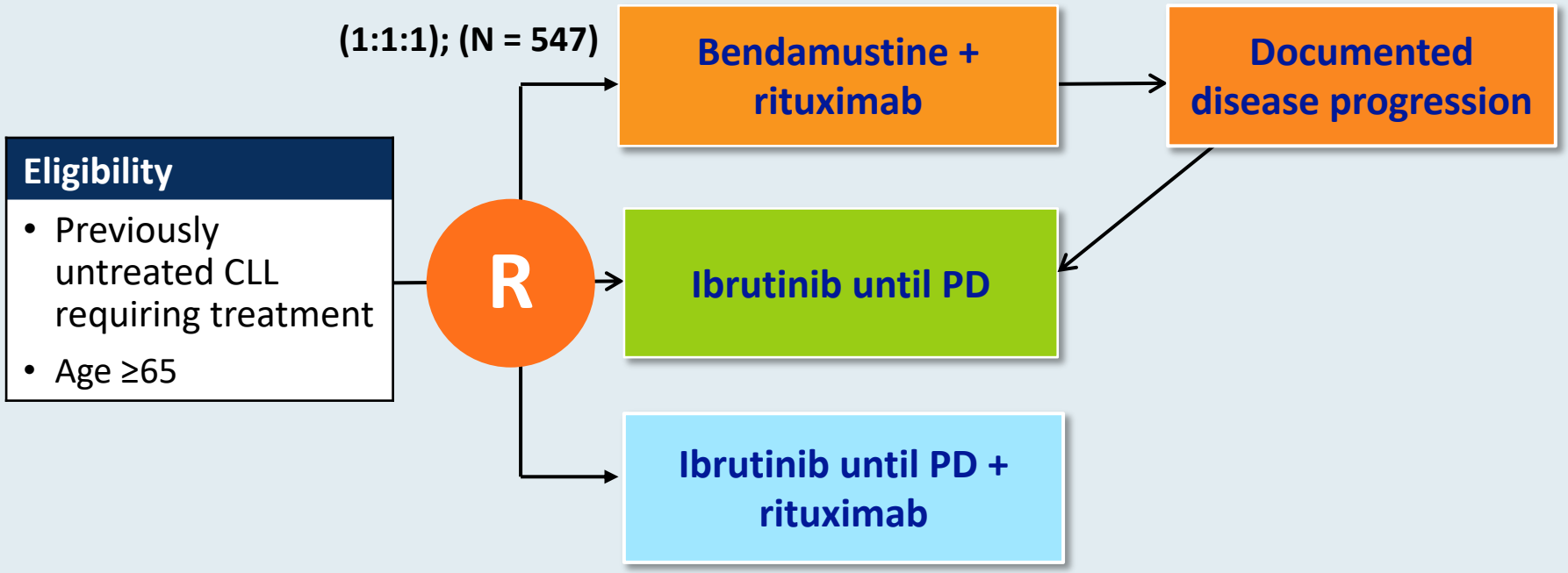
Sharman JP et al. *Lancet* 2020;395:1278-91.

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.

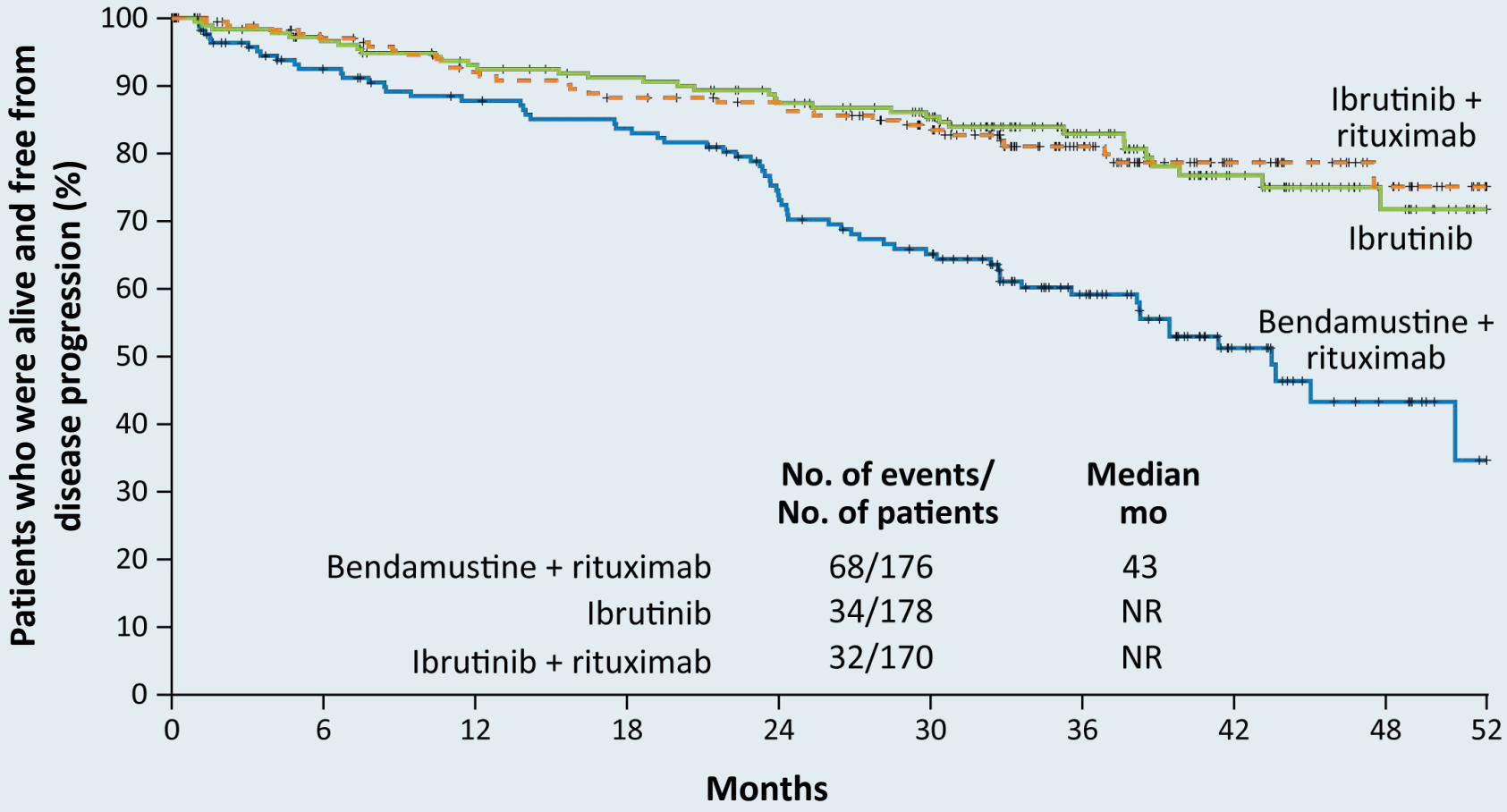
Phase III Alliance A041202 Study Design



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

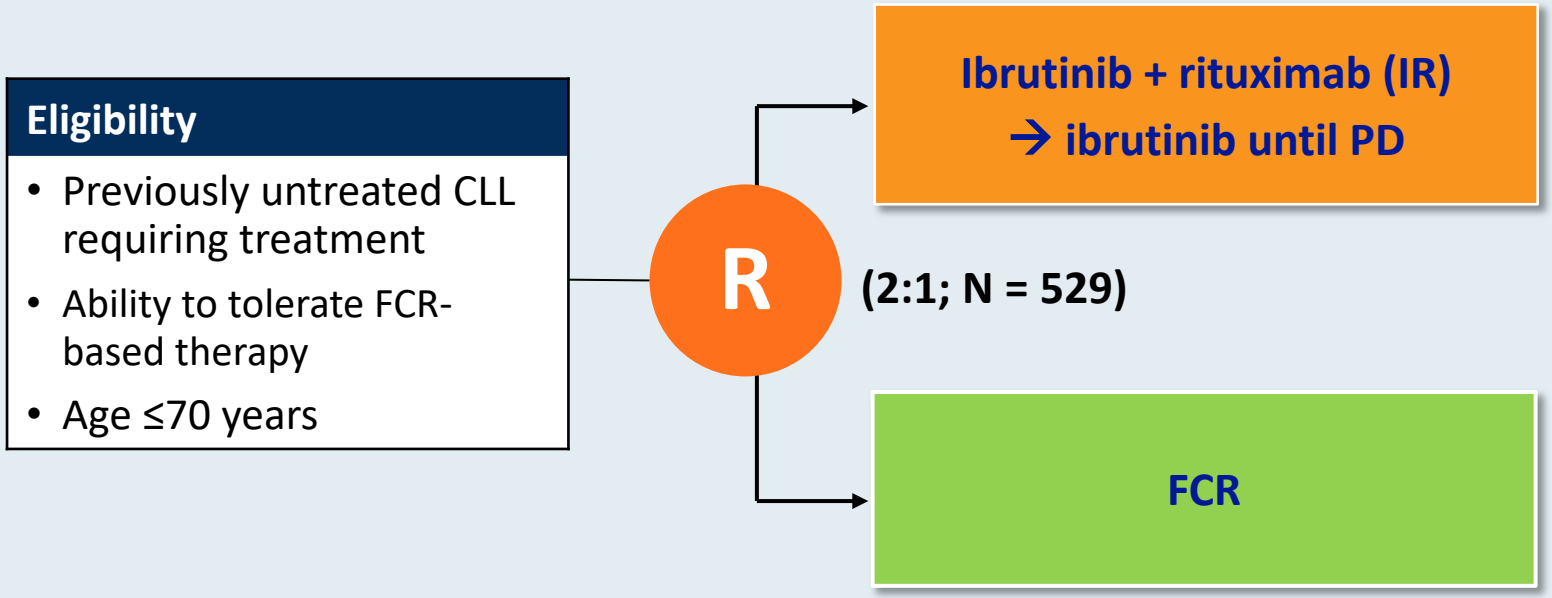
Press Release – April 21, 2020

"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

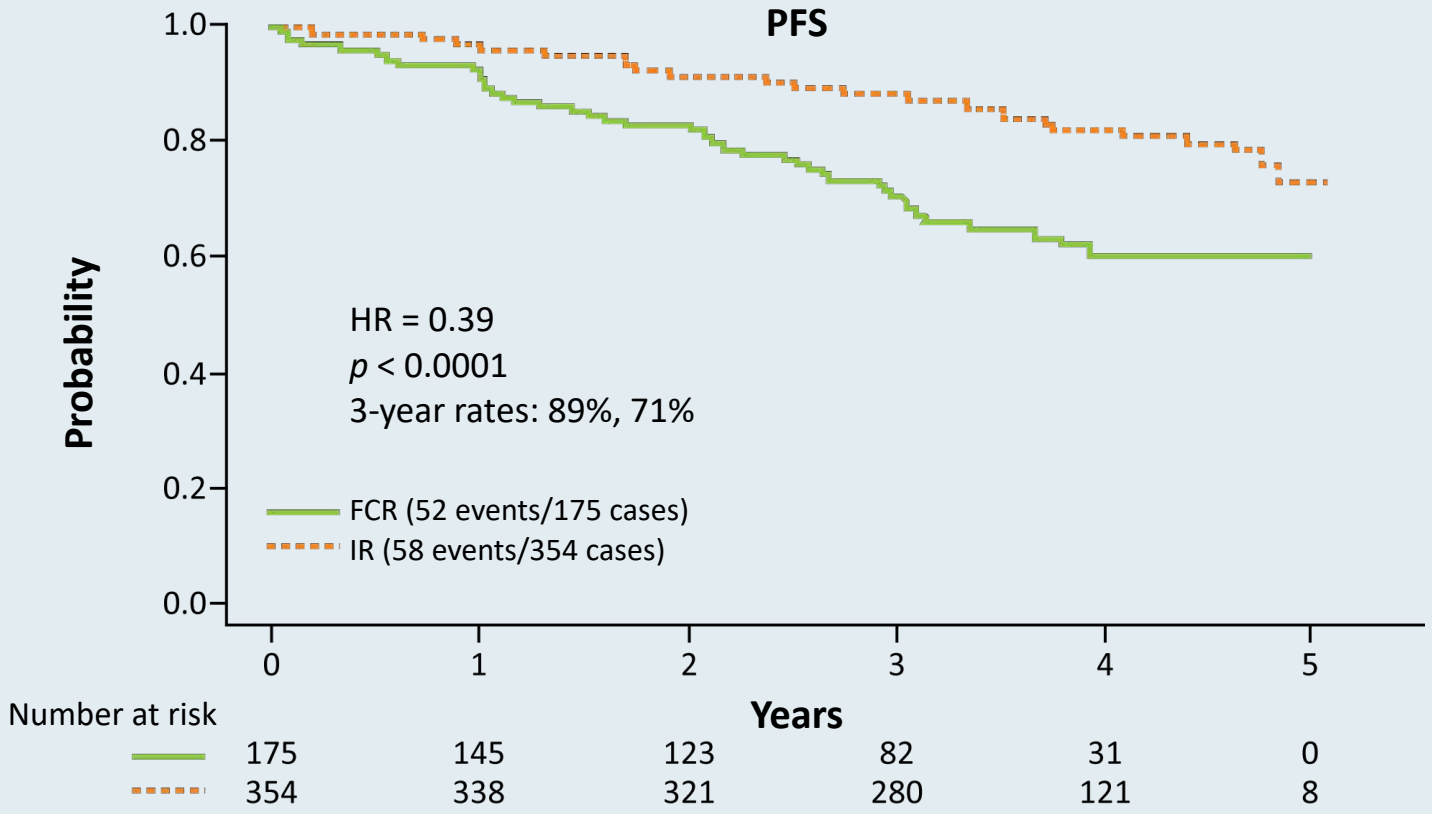
Phase III ECOG-ACRIN E1912 Study Design



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

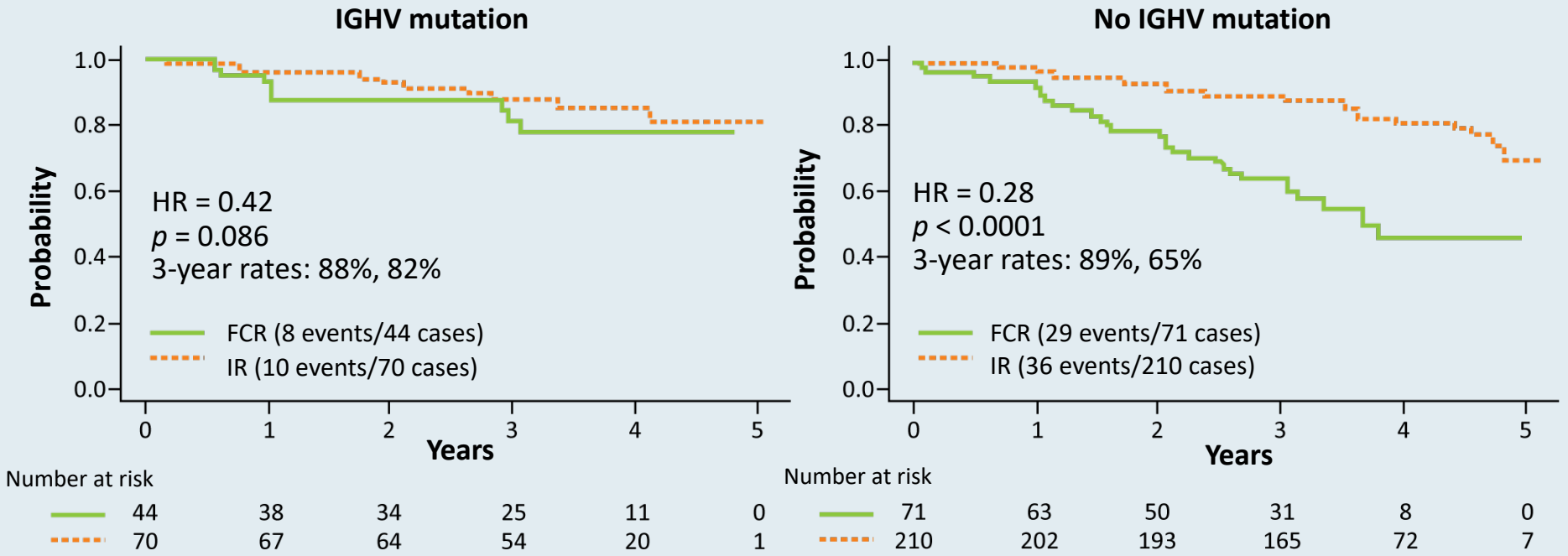


- Grade ≥3 treatment-related AEs were reported in 70% of patients receiving IR and 80% of patients receiving FCR (odds ratio = 0.56; $p = 0.013$).
- Among the 95 patients who discontinued ibrutinib, the most common cause was AE or complication.

Shanafelt TD et al. ASH 2019;Abstract 33.

RTP RESEARCH TO PRACTICE

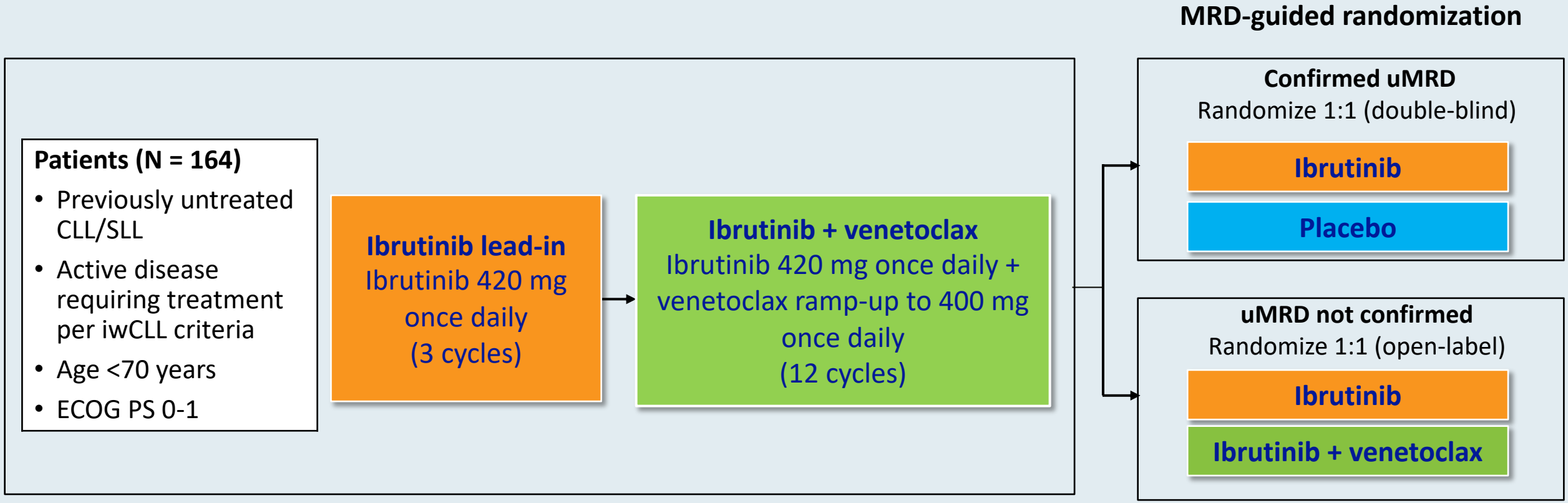
ECOG-ACRIN E1912 Extended Follow-Up: PFS by IGHV Mutation Status



- 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.

CAPTIVATE MRD Cohort: Study Design

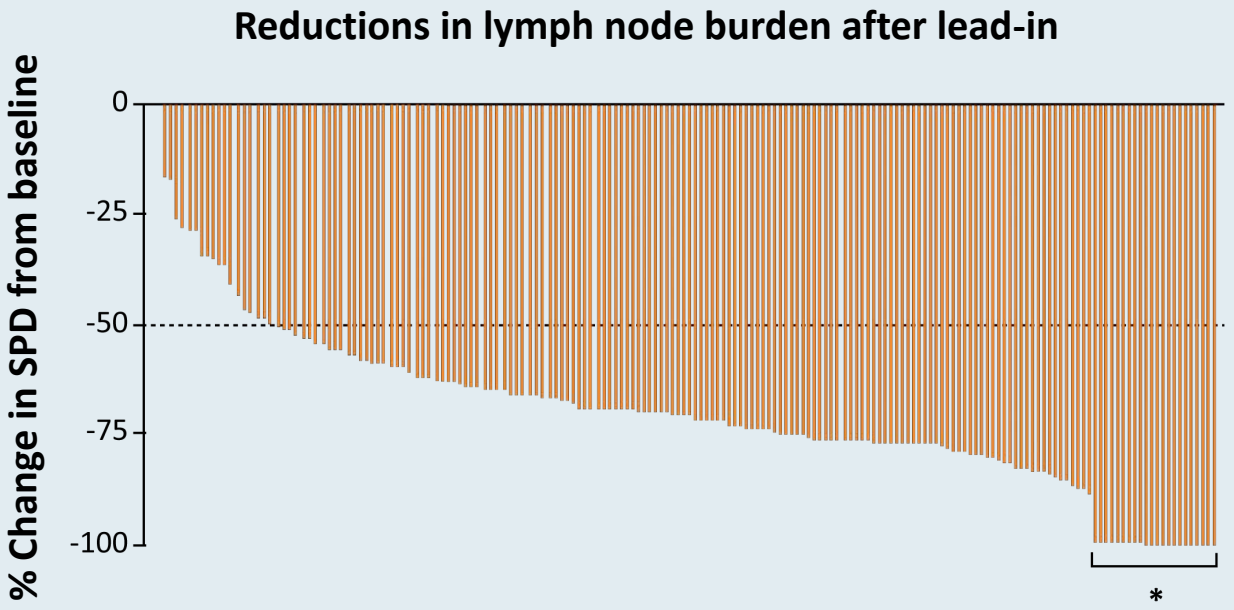


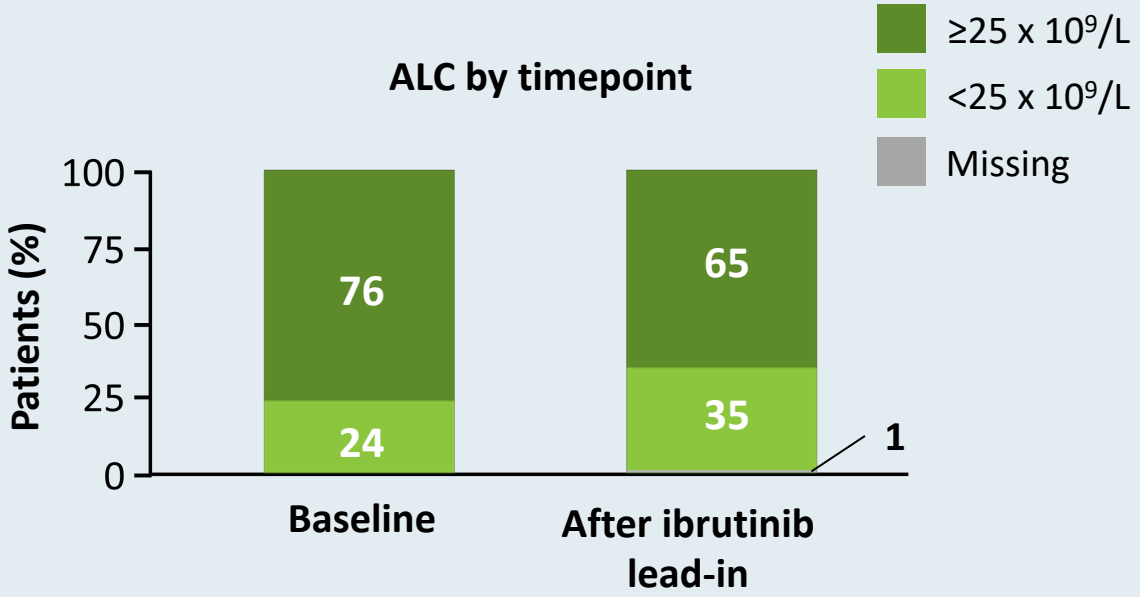
uMRD = undetectable minimal residual disease

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.

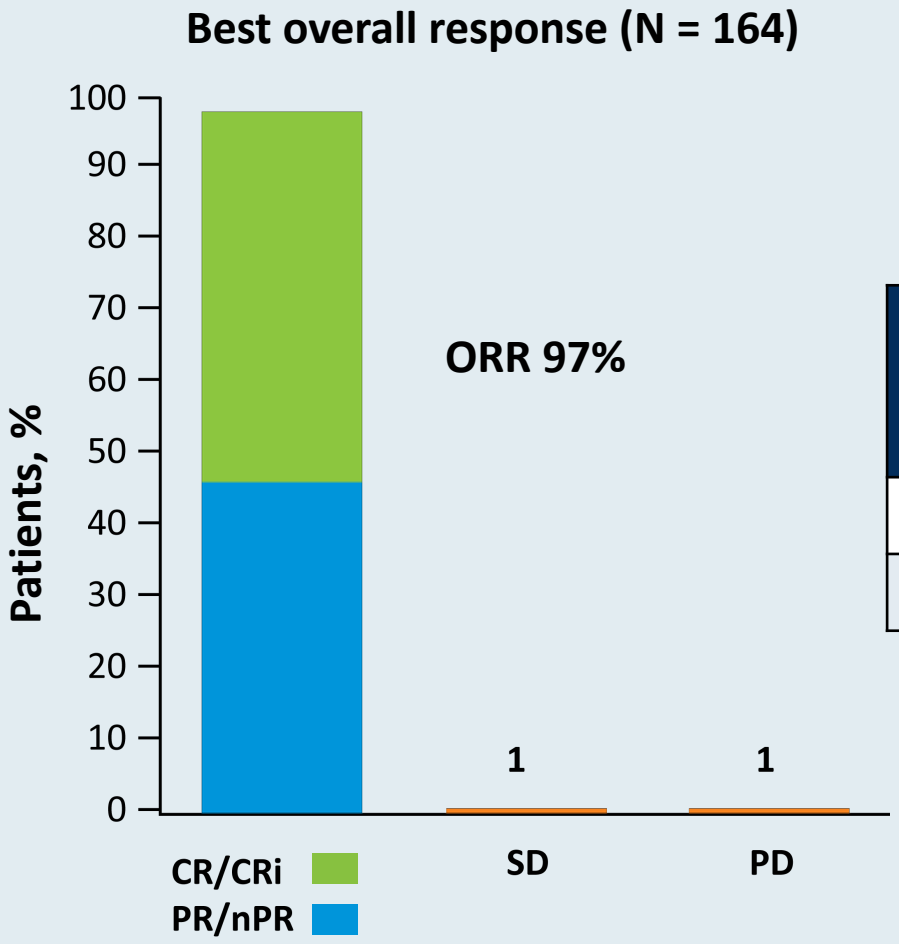
CAPTIVATE MRD Cohort: Undetectable MRD Rate

	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.

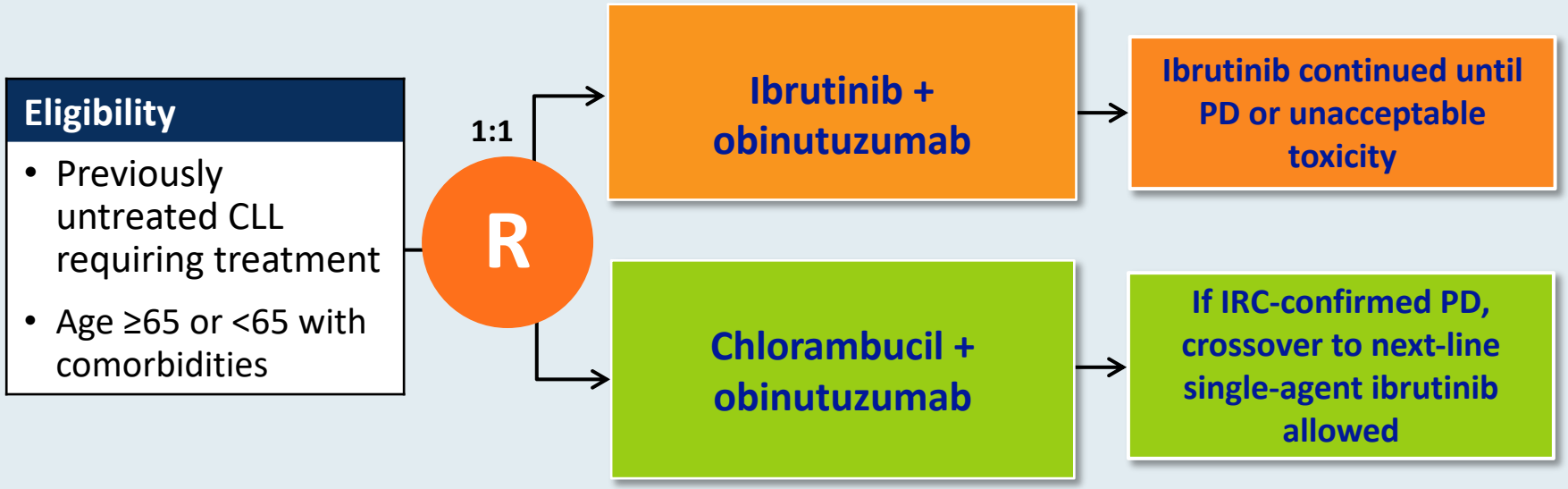
CAPTIVATE MRD Cohort: Summary of Grade 3 and 4 AEs of Interest

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.

Phase III iLLUMINATE Study Design



Stratification

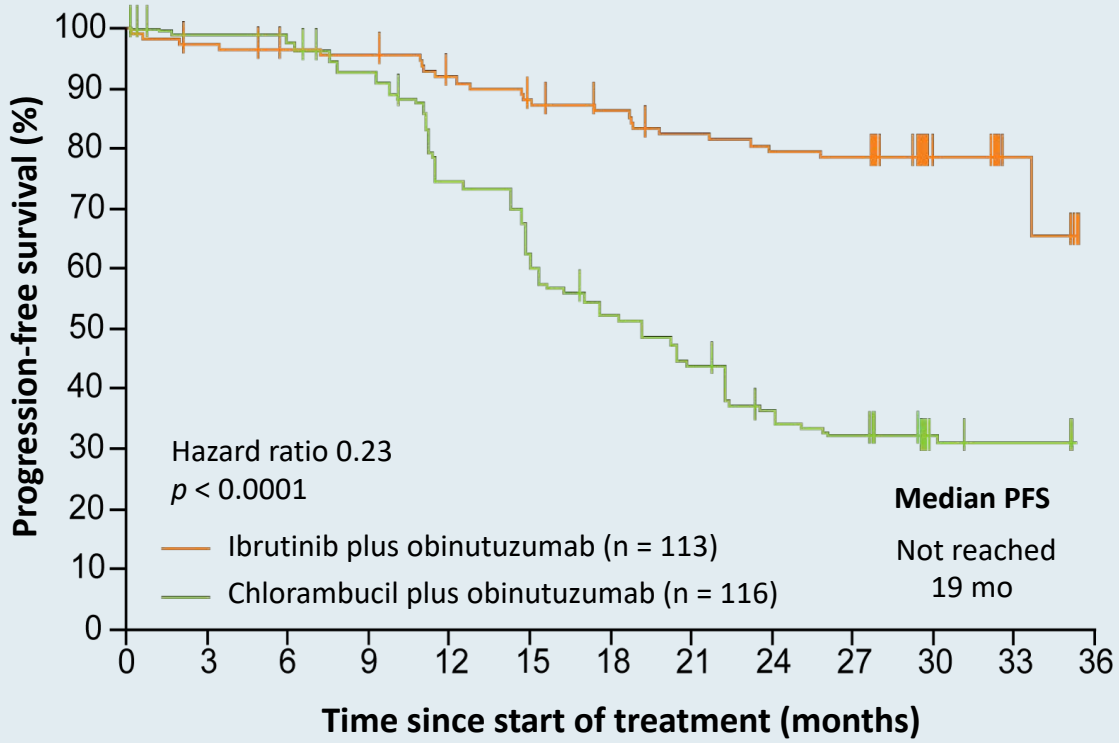
- ECOG PS (0-1 vs 2)
- Del(17p)/del(11q) (+/+ vs +/- vs -/+ vs -/-)

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.

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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

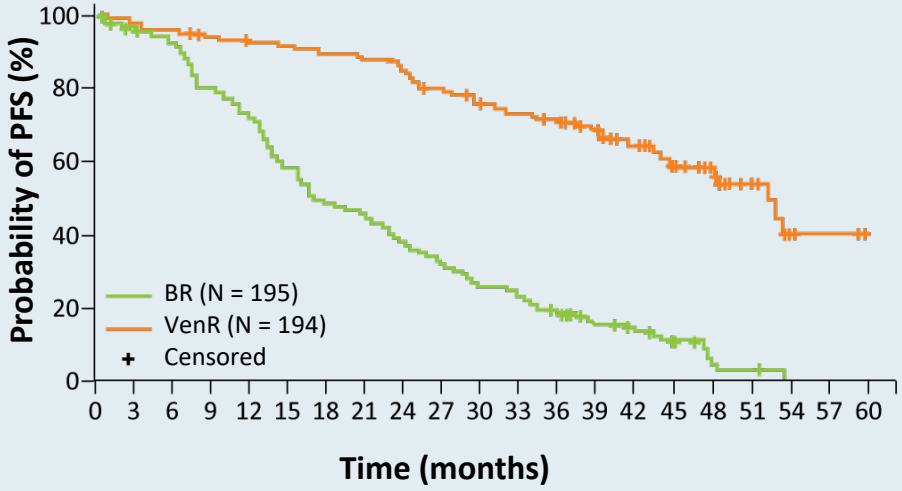
Arm B
Ibrutinib: Cycles 1-19+:d1-28 420mg PO daily
Obinutuzumab: C1 **:** D1:100 mg IV, D2:900 mg IV, D8: 1000 mg IV, D15: 1000 mg IV; C2-6: D1 1000 mg IV

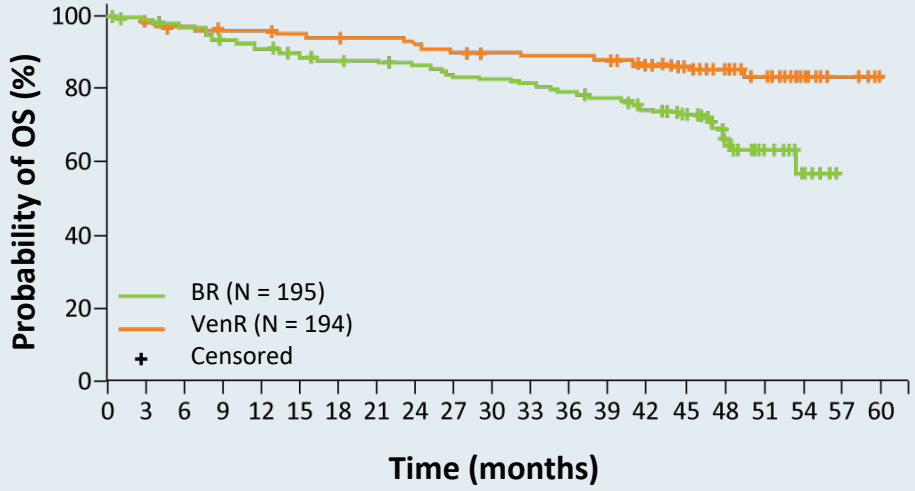
Courtesy of Brad Kahl, MD

Relapsed/Refractory Disease

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

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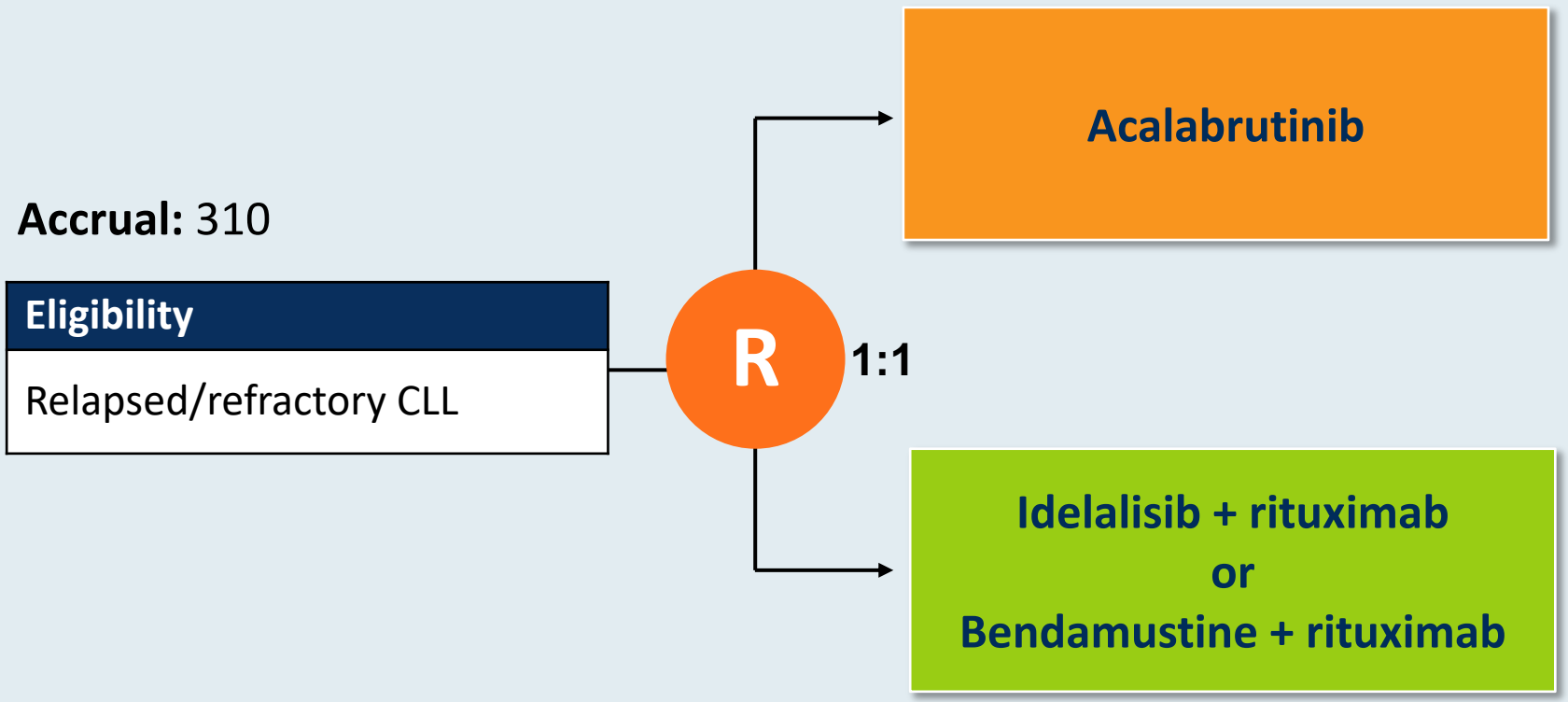
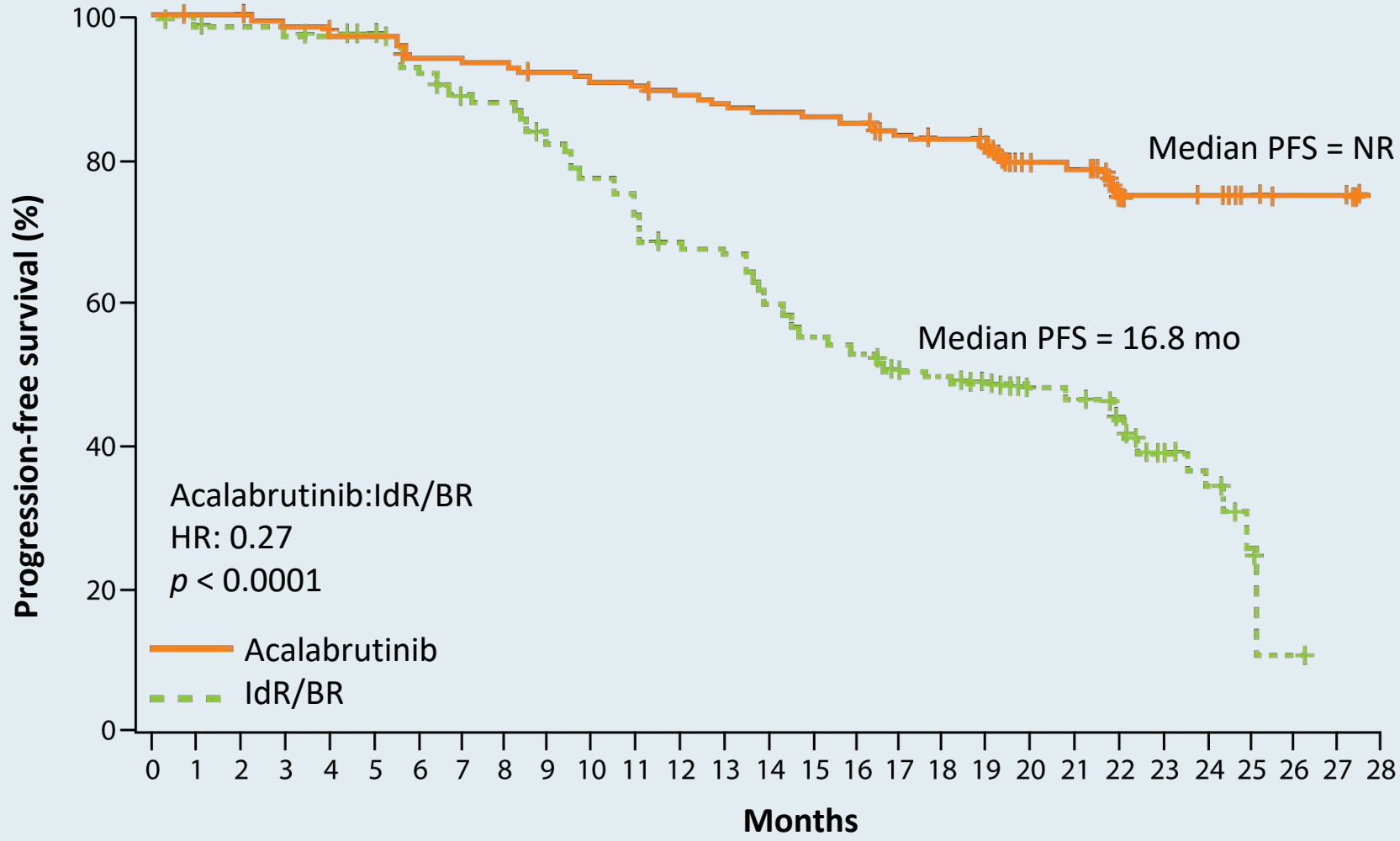
ASCEND Phase III Trial Schema



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 nonmelanoma skin carcinomas	5%	4%	2%	1%
Tumor lysis syndrome	1%	1%	1%	1%

IdR = rituximab/idelalisib

Ghia P et al. EHA 2020;Abstract S159.

Clinical Investigator Perspectives on the Current and Future Management of Multiple Myeloma

A Meet The Professor Series

Wednesday, September 16, 2020
12:00 PM – 1:00 PM ET

Faculty

Jonathan L Kaufman, MD

Moderator

Neil Love, MD

Co-provided by USF Health

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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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