Meet The Professor
Management of Chronic Lymphocytic Leukemia

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Division of Cancer Medicine
The University of Texas MD Anderson Cancer Center
Houston, Texas

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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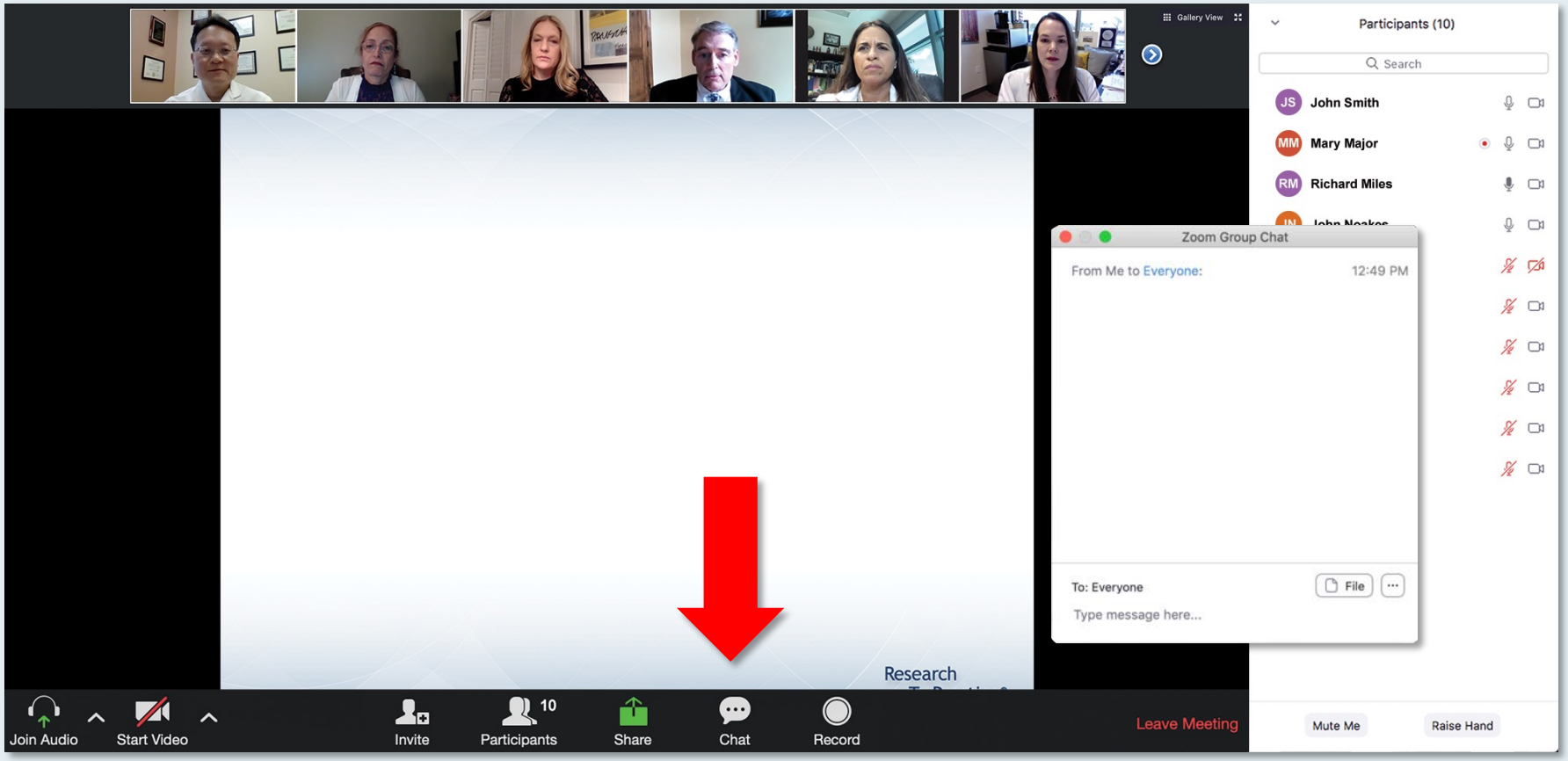
We Encourage Clinicians in Practice to Submit Questions



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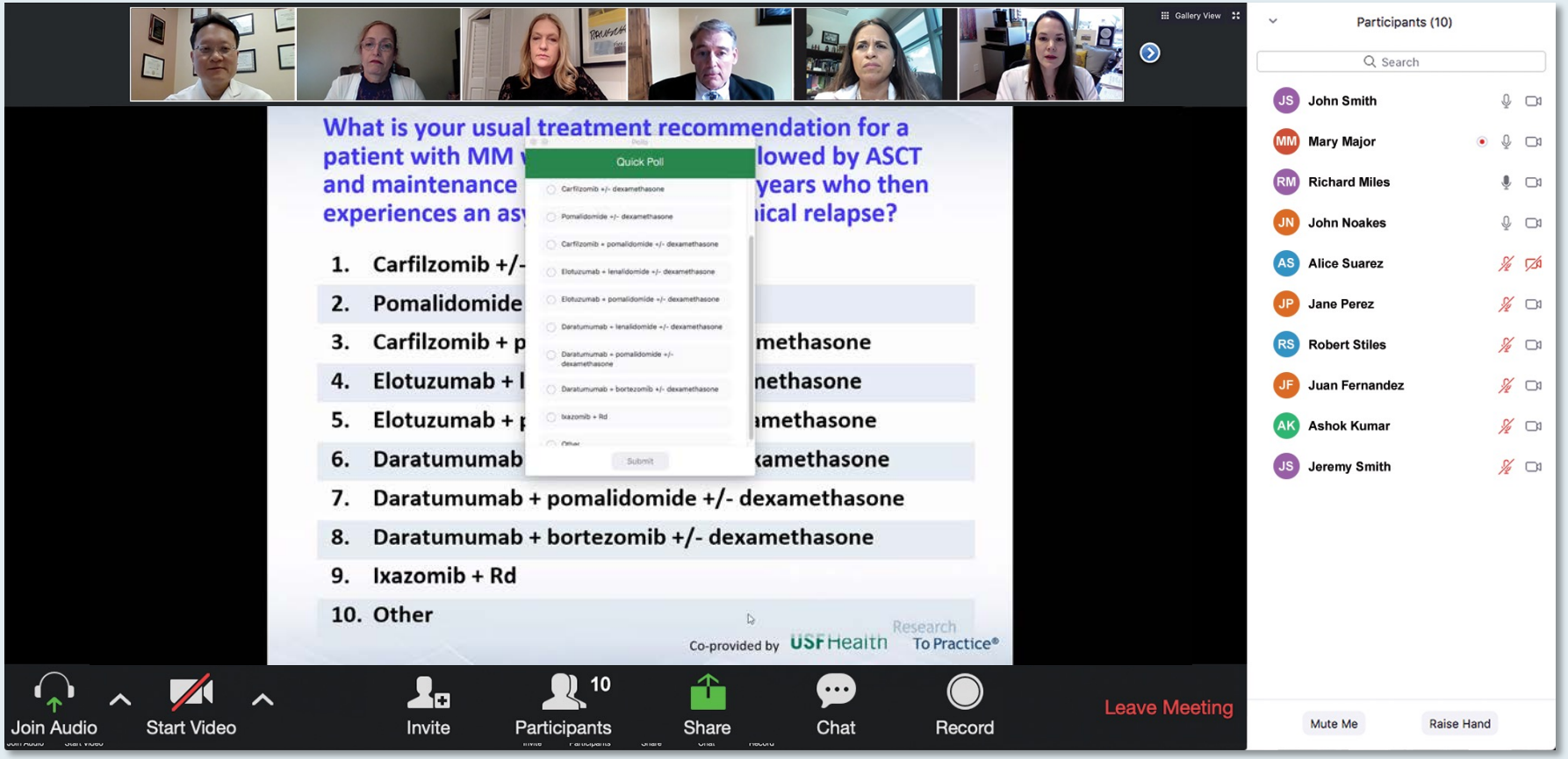

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WITH DR NEIL LOVE

Front-Line Treatment of Chronic Lymphocytic Leukemia

DR STEVEN COUTRE
STANFORD UNIVERSITY SCHOOL OF MEDICINE

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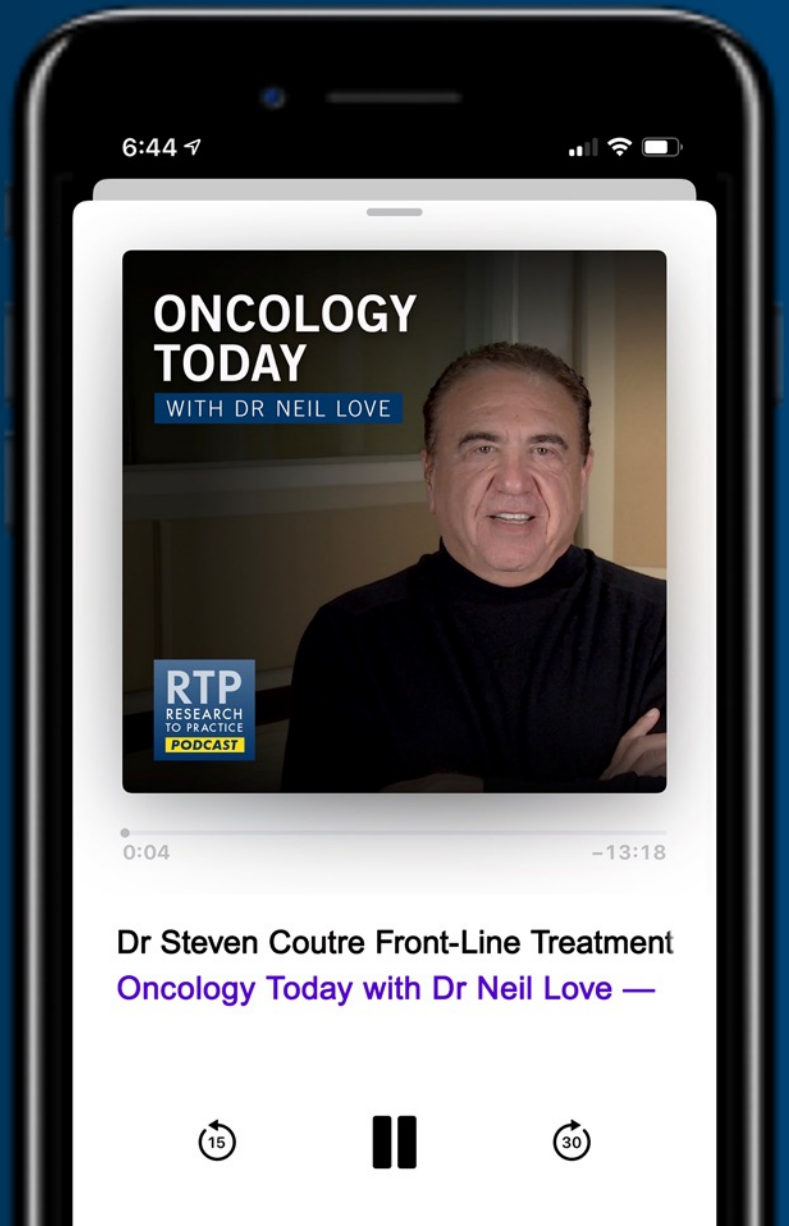

Meet The Professor

Immunotherapy and Novel Agents in Gynecologic Cancers

Monday, April 5, 2021
5:00 PM – 6:00 PM ET

Faculty

Bradley J Monk, MD

Moderator

Neil Love, MD

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Ask the Expert: Clinical Investigators Provide Perspectives on the Management of Renal Cell Carcinoma

Tuesday, April 6, 2021
12:00 PM – 1:00 PM ET

Faculty

Sumanta K Pal, MD

Moderator

Neil Love, MD

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Meet The Professor

Optimizing the Selection and Sequencing of Therapy for Patients with Advanced Gastrointestinal Cancers

Thursday, April 8, 2021
5:00 PM – 6:00 PM ET

Faculty

Dirk Arnold, MD, PhD

Moderator

Neil Love, MD

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Ask the Investigators: Applying Emerging Clinical Research to the Care of Patients with Gastroesophageal Cancers

Monday, April 12, 2021
6:30 PM – 7:30 PM ET

Faculty

Joseph Chao, MD
Yelena Y Janjigian, MD

Moderator

Neil Love, MD

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Meet The Professor

Management of Chronic Lymphocytic Leukemia

Thursday, April 15, 2021
5:00 PM – 6:00 PM ET

Faculty

John N Allan, MD

Moderator

Neil Love, MD

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Dissecting the Decision: Investigator Perspectives on Key Issues in the Management of Common Cancers

Breast Cancer

Tuesday, April 20, 2021
8:30 AM – 10:00 AM ET

Faculty

Carey K Anders, MD
Kathy D Miller, MD
Sara M Tolaney, MD, MPH

Moderator

Neil Love, MD

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Thank you for joining us!

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

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Meet The Professor
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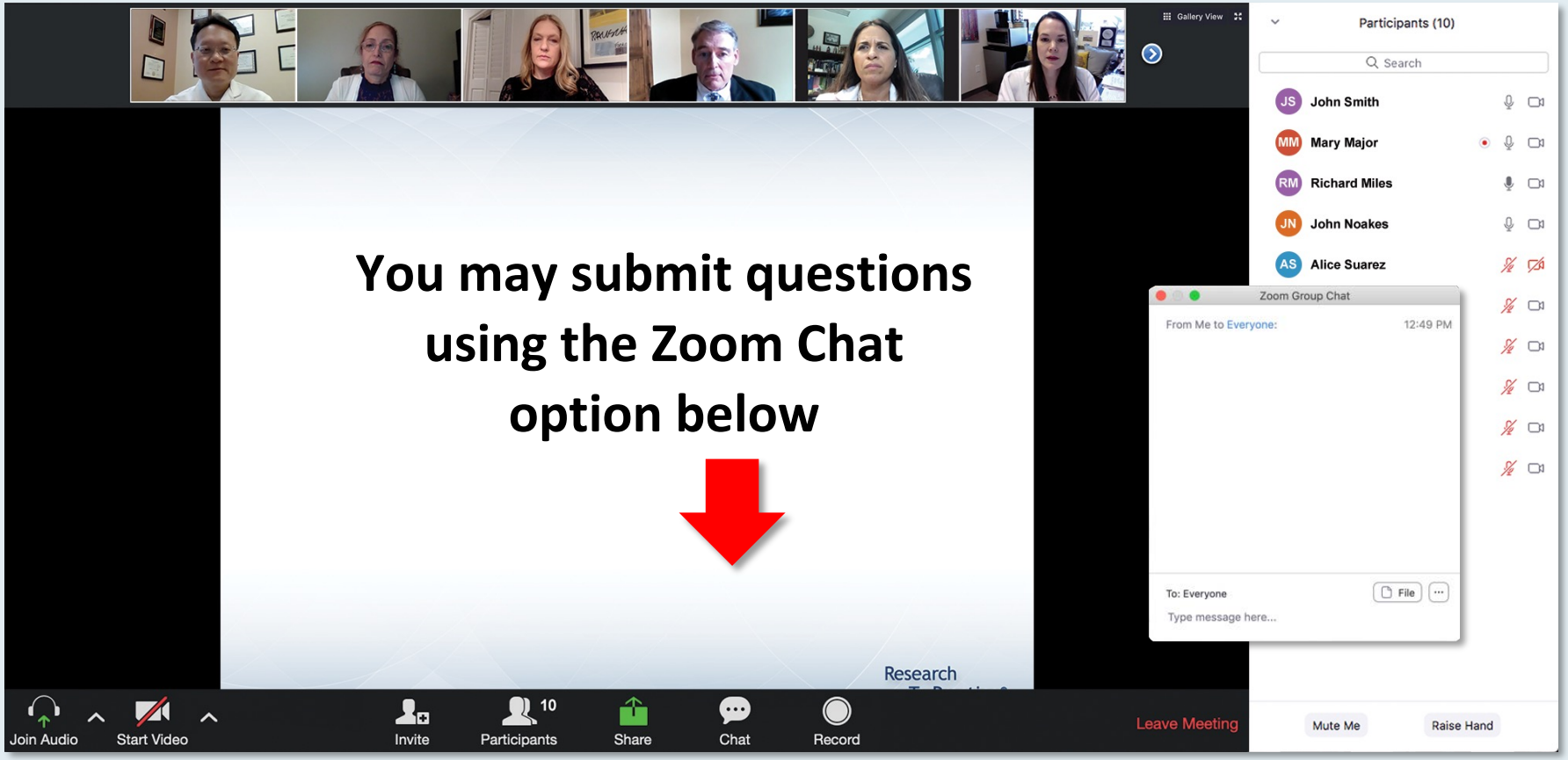

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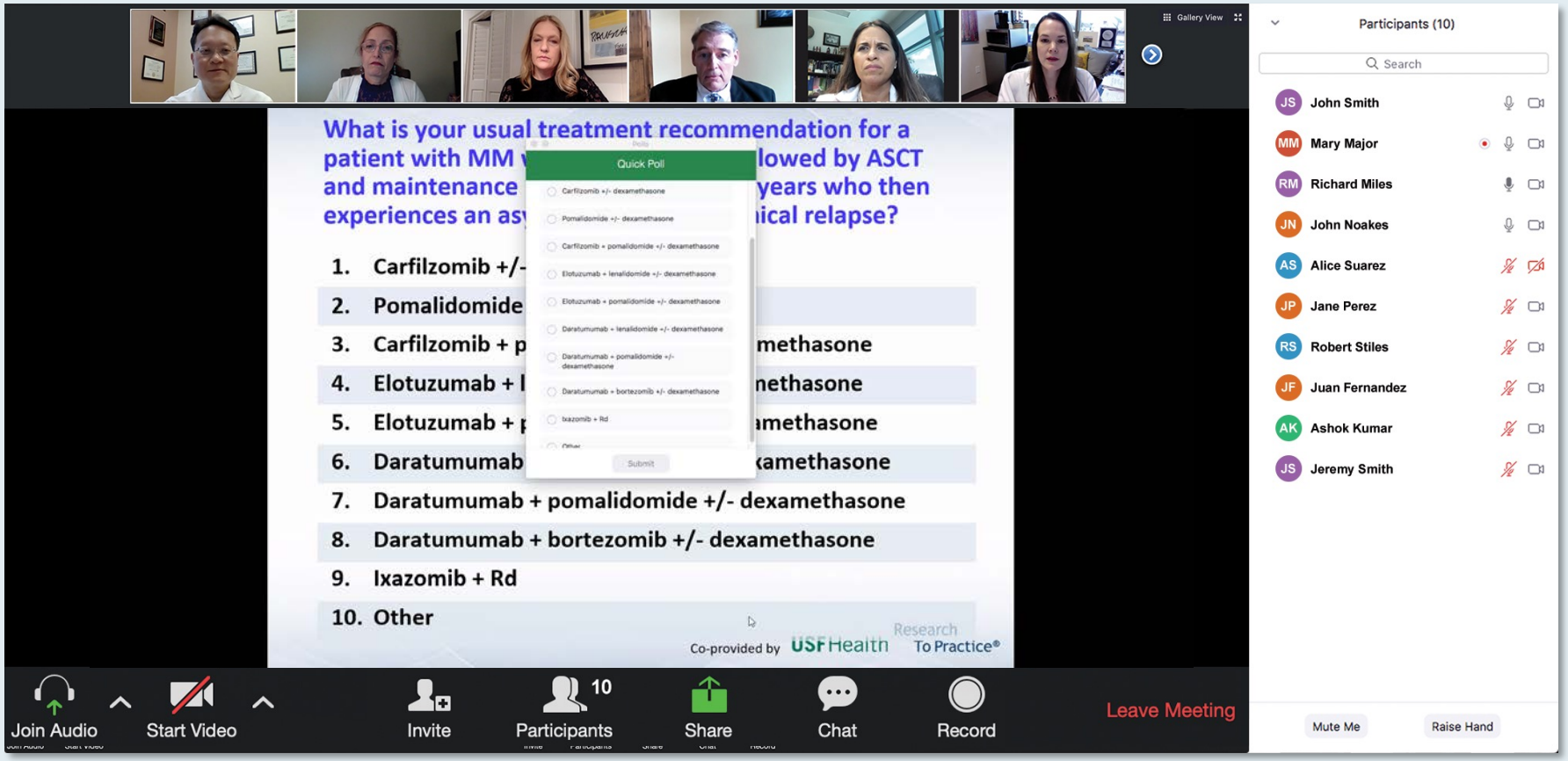

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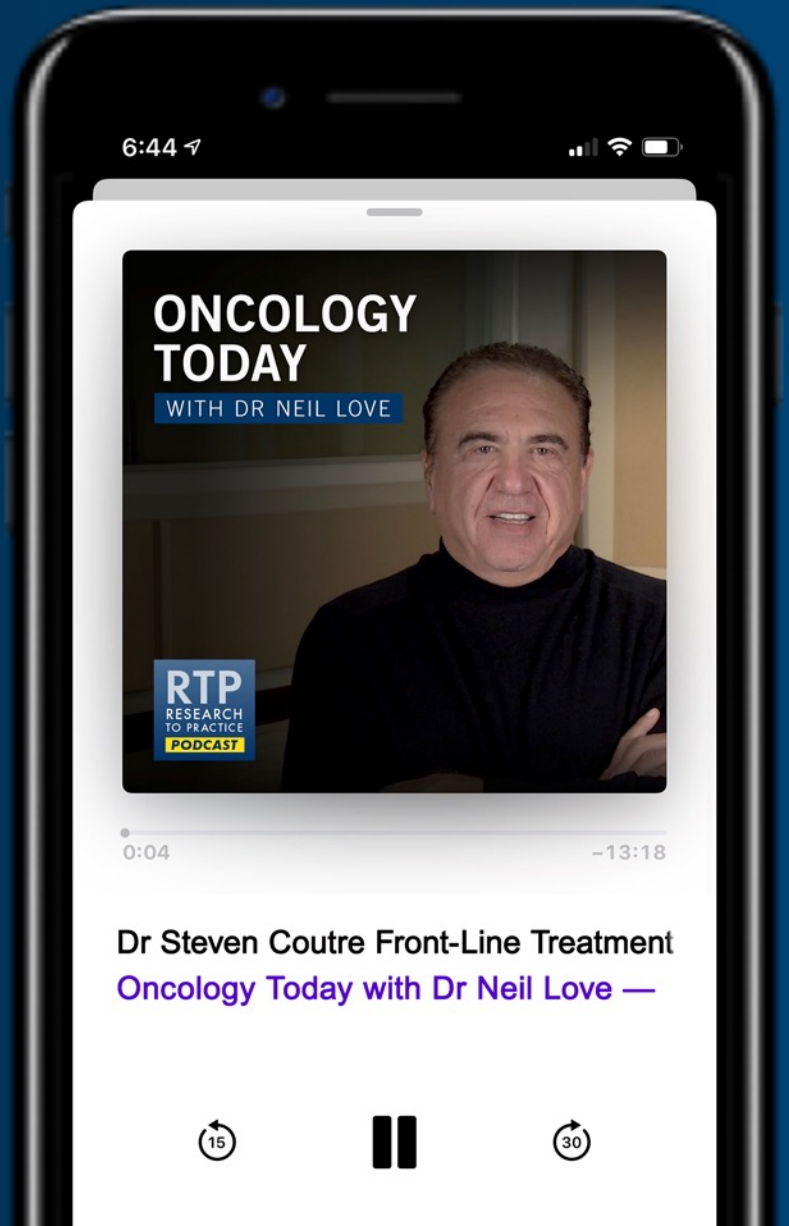

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Current Role of Minimal Residual Disease Assessment in the Management of Multiple Myeloma and Chronic Lymphocytic Leukemia with Drs Shaji Kumar and Philip Thompson

Episode 57 · March 1, 2021

https://oncologytoday.researchtopractice.com/57

Episode Host
Neil Love, MD

Dr Shaji Kumar
Mayo Clinic

Dr Philip Thompson
The University of Texas MD Anderson Cancer Center

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Meet The Professor with Dr Thompson

MODULE 1: Cases from Dr Allan

- A 79-year-old man with significant cardiac history and symptomatic CLL (Parts 1, 2 and 3)
- A 93-year-old woman with symptomatic disease progression after response to obinutuzumab (Parts 1, 2 and 3)
- A 65-year-old man with significant cardiac history, AIHA (Parts 1 and 2)
- An 86-year-old man with relapsed CLL treated with ibrutinib/venetoclax

MODULE 2: Beyond the Guidelines

MODULE 3: Journal Club with Dr Thompson

MODULE 4: Key Recent Data Sets

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A 79-year-old man with significant cardiac history and symptomatic CLL — Part 1

Dr John Allan

- PMH: CAD s/p STEMI 10/2018, multiple catheterizations, with > 5 DES stents placed, 2nd degree heart block; CVA in 2008
- 2016: Diagnosed with CLL
- 12/2018: Referred due to significant anemia (Hgb: 8), adenopathy
  - CLL work up: Unmutated IGHV, Del13q, NOTCH1, BCOR, MALT1, NF1, SAMHD1, TET2 mutations

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A 79-year-old man with significant cardiac history and symptomatic CLL — Part 2

Dr John Allan

- PMH: CAD s/p STEMI 10/2018, multiple catheterizations, with > 5 DES stents placed, 2nd degree heart block; CVA in 2008
- 2016: Diagnosed with CLL
- 12/2018: Referred due to significant anemia (Hgb: 8), adenopathy
  - CLL work up: Unmutated IGHV, Del13q, NOTCH1, BCOR, MALT1, NF1, SAMHD1, TET2 mutations
- ***2/2019: Obinutuzumab induction, with delayed venetoclax initiation until 5/2019 due to insurance***
  - ***8/2019: Essentially nCR, with one 2-cm residual node***
- ***7/2020: Peripheral blood MRD 0.03% → Treatment discontinued***
- ***10/2020: Diffuse adenopathy, worsening anemia, thrombocytopenia***

Questions

- ***What do you think has happened? What would you do at this point to manage this patient?***

A 79-year-old man with significant cardiac history and symptomatic CLL — Part 3

Dr John Allan

- PMH: CAD s/p STEMI 10/2018, multiple catheterizations, with > 5 DES stents placed, 2nd degree heart block; CVA in 2008
- 2016: Diagnosed with CLL
- 12/2018: Referred due to significant anemia (Hgb: 8), adenopathy
  - CLL work up: Unmutated IGHV, Del13q, NOTCH1, BCOR, MALT1, NF1, SAMHD1, TET2 mutations
- 2/2019: Obinutuzumab induction, with delayed venetoclax initiation until 5/2019 due to insurance
  - 8/2019: Essentially nCR, with one 2-cm residual node
- 7/2020: Peripheral blood MRD 0.03% → Treatment discontinued
- 10/2020: Diffuse adenopathy, worsening anemia ***(not transformed, no BCL mutation)***
- ***Venetoclax re-ramp from 100 mg to 400 mg, with resolution of adenopathy***

Questions

- ***Would you stop treatment if he continues venetoclax for another year or 2 years and achieves MRD negativity? If he is MRD-positive after that time, would you change treatment, or add another drug to venetoclax?***

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What is Minimal Residual Disease (MRD) in Hematologic Malignancies?

- Malignant cell populations present in low numbers, below the threshold for detection using standard morphologic techniques.
- “CR” in bone marrow in acute myeloid leukemia = <5% blasts: reduction from 10^{12} to <5 x 10^{10} leukemic cells.[1]
- “Minimal” may be a misnomer.

[1] Campana D. *Cytometry* 1999

Courtesy of Dr Philip A Thompson

Why measure MRD in CLL?

- If MRD present, in the absence of further therapy, relapse will occur.
- Accurate quantitation of residual disease:
    1. Accurately determines prognosis.
    2. May guide treatment decisions.

Courtesy of Dr Philip A Thompson

When could we measure MRD?

- At completion of therapy (best established role):
    1. Determine prognosis.
    2. Guide use of consolidation therapy (potentially).
- During therapy to allow modification of treatment strategy (work in progress).
- During observation after completion of therapy to detect early relapse that may have a specific intervention (best established after alloSCT).

Courtesy of Dr Philip A Thompson

Why is MRD such a useful prognostic marker?

- Predictive of PFS and OS independent of clinical response and treatment received.
- Quantitative and functions as a continuous variable.

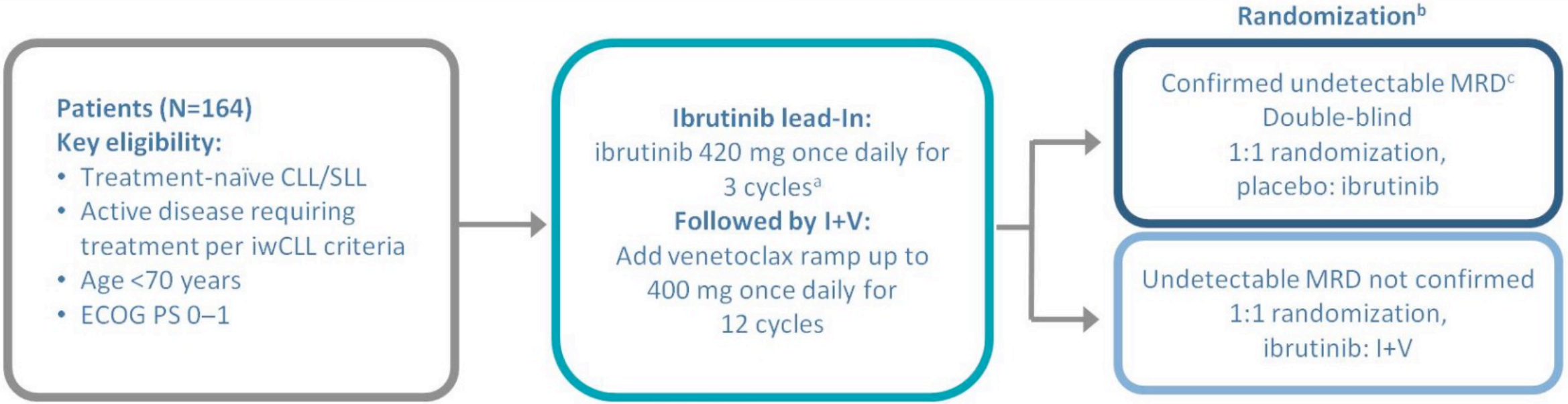
Courtesy of Dr Philip A Thompson

Conclusions from the 5-Year Analysis of MURANO

- Most patients who completed Ven monotherapy had uMRD at EOT and MRD status continued to be a robust predictor of outcomes.
  Patients in the VenR arm with uMRD at EOT had a 61.3% PFS rate at 36 months post-EOT.
- Median time to MRD conversion was 19 months and median time to PD from MRD conversion was a further 25 months for patients with uMRD at EOT. A significant proportion of patients remained with uMRD at this follow-up.
- Poor baseline characteristics are associated with faster MRD doubling rates.
- Deep and durable initial response alongside favorable baseline characteristics predict sensitivity to re-treatment.
- Sustained uMRD, PFS and OS benefits provide further support for the use of fixed duration VenR in patients with relapsed/refractory CLL.

Courtesy of Dr Philip A Thompson

Phase 2 CAPTIVATE Study Design (NCT02910583)



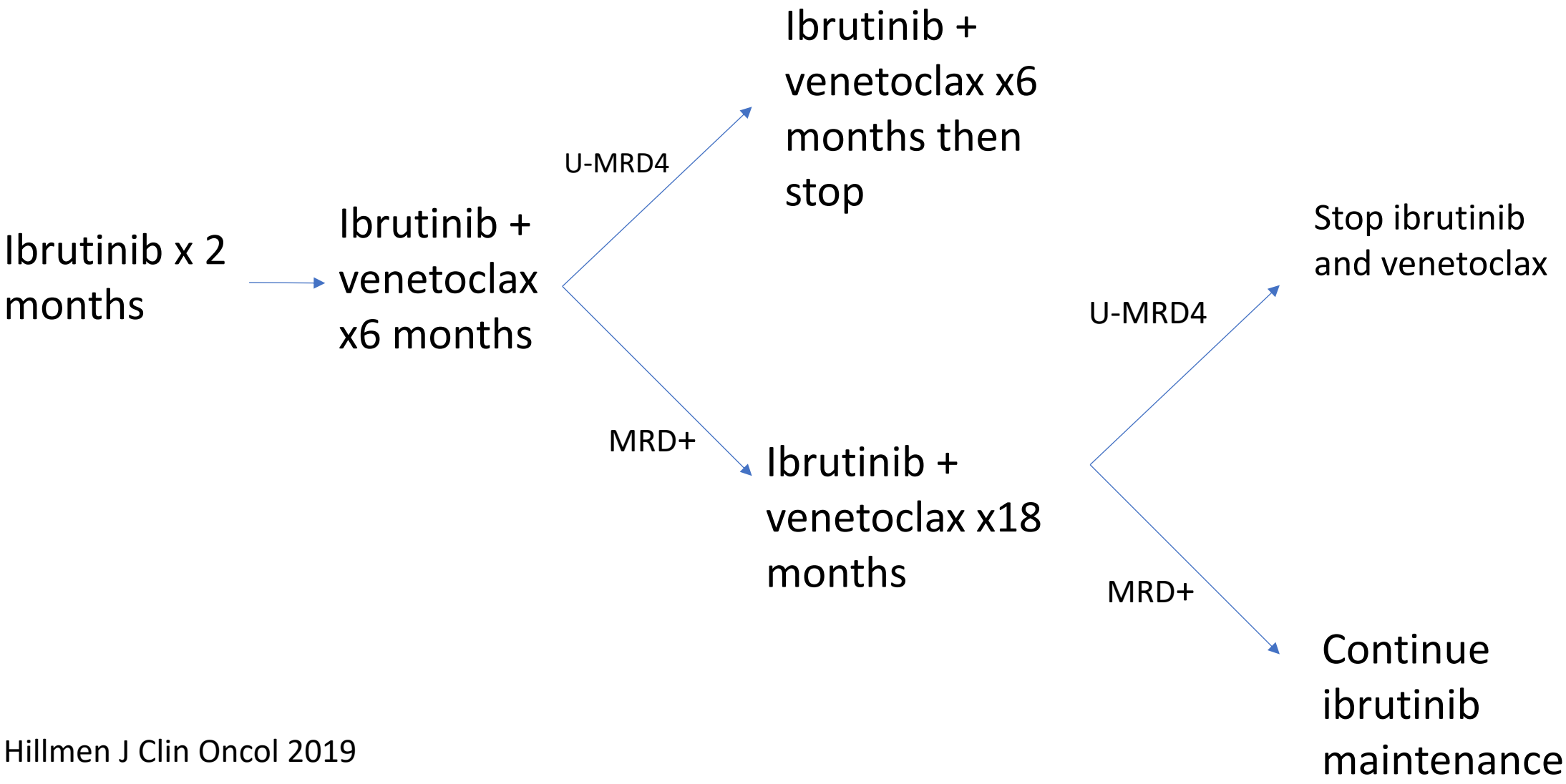
[a]1 cycle = 28 days.
[b]Stratified by *IGHV* mutation status.
[c]Confirmed undetectable MRD for randomization defined as undetectable MRD serially over at least 3 cycles in peripheral blood (PB), and undetectable MRD in both PB and BM.

Study Populations:

- MRD cohort (N=164): exposure and safety analysis
  - Safety Run-in: first 14 patients completed C15 treatment (12 cycles of I+V); no dose-limiting toxicities (DLT) or clinical TLS during first 6 weeks of I+V combination
  - Prespecified analysis of the first 30 patients who completed C9 treatment (6 cycles of I+V) for MRD evaluation
- Fixed Duration cohort (N=159): separate cohort; analysis not shown

Courtesy of Dr Philip A Thompson

CLARITY Study – relapsed CLL



Hillmen J Clin Oncol 2019

Courtesy of Dr Philip A Thompson

A 93-year-old woman with symptomatic disease progression after response to obinutuzumab — Part 1

Dr John Allan

- 2010: Diagnosed with SLL, based on lymph node biopsy
- 2016: Elevated WBC to 81K, with increased adenopathy

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A 93-year-old woman with symptomatic disease progression after response to obinutuzumab — Part 2

Dr John Allan

- 2010: Diagnosed with SLL, based on lymph node biopsy
- 2016: Elevated WBC to 81K, with increased adenopathy
- ***2017: Diagnosed with CLL del13q, unmutated IGHV (NGS not performed due to insurance coverage)***
- ***Obinutuzumab x 6 months, with normalization of blood counts, reduction in LAD, PR on imaging***
- ***8/2020: Increasing WBC to 43K, with increasing adenopathy***

Questions

- ***How are you managing these older and frailer patients? What options would you consider for a patient like this – obinutuzumab alone, chlorambucil? How do you view BTK inhibitors or venetoclax-based therapies for a patient like this woman?***
- ***When her WBC and adenopathy began increasing on obinutuzumab, what would you have done – another round of treatment, or go to targeted agents? Which targeted agent would you use?***

A 93-year-old woman with symptomatic disease progression after response to obinutuzumab — Part 3

Dr John Allan

- 2010: Diagnosed with SLL, based on lymph node biopsy
- 2016: Elevated WBC to 81K, with increased adenopathy
- 2017: Diagnosed with CLL del13q, unmutated IGHV (NGS not performed due to insurance coverage)
- Obinutuzumab x 6 months, with normalization of blood counts, reduction in LAD, PR on imaging
- 8/2020: Increasing WBC to 43K, with increasing adenopathy
- ***Acalabrutinib 100 mg BID***
  - ***9/2020: WBC 107K***
  - ***11/2020: WBC 63K, with decreasing adenopathy***

A 65-year-old man with significant cardiac history, AIHA — Part 1

Dr John Allan

- Admitted for elective heart catherization, DES stent (dual antiplatelet agents)
  - WBC: 88K, ALC: 60K
- Diagnosed with CLL, deletion 11q+, IGHV unmutated (adenopathy < 5 cm, spleen 22 cm)
- Brisk autoimmune hemolytic anemia (AIHA) → 6/2018: Obinutuzumab, with improvement

Questions

- Given the need for treatment and his brisk AIHA, what would be an appropriate approach for this patient at this time?

A 65-year-old man with significant cardiac history, AIHA — Part 2

Dr John Allan

- Admitted for elective heart catherization, DES stent (dual antiplatelet agents)
  - WBC: 88K, ALC: 60K
- Diagnosed with CLL, deletion 11q+, IGHV unmutated (adenopathy < 5 cm, spleen 22 cm)
- Brisk autoimmune hemolytic anemia (AIHA)
  - ***6/2018: Obinutuzumab, with rapid improvement in WBC over the first 3 weeks, hemolysis essentially stopped by week 3***
- ***Off protocol venetoclax initiated***
- ***6/2019 Bone marrow MRD: negative***
- ***10/2020 Peripheral blood MRD: negative***

Questions

- ***Given his cardiac history, would you have considered a BTK inhibitor or would you have taken the approach that was taken?***
- ***Are you following MRD in your clinical practice?***
- ***Have you followed rapid dose escalation of venetoclax for high-risk patients, who are progressing rapidly? Do you have any risk mitigation strategies that have been helpful?***

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An 86-year-old man with relapsed CLL treated with ibrutinib/venetoclax

Dr John Allan

- August 2015: Diagnosed at age 81, ibrutinib initiated due to rising WBC count and anemia; counts returned to normal
  - Full CLL workup not performed prior to treatment by outside physician
  - Bone marrow biopsy: Complex karyotype with monosomy 17
- 2018: Patient referred due to outside physician moving out of state
- August 2020: WBC counts begin to rise to 20K with mild anemia and thrombocytopenia
- CLL evaluation:
  - Complex karyotype with monosomy 17, unmutated IGHV V3-23
  - ARID1A, CCND3, TP53 mutated, no BTK mutation

Question

- How often are you assessing for BTK mutations? How often are you repeat testing -- FISH testing, mutational testing -- on your patients when they are progressing on targeted agents?
- How would you manage this patient?

Meet The Professor with Dr Thompson

MODULE 1: Cases from Dr Allan

MODULE 2: Beyond the Guidelines

MODULE 3: Journal Club with Dr Thompson

- Occupy BTK: The key to controlling CLL
- Acalabrutinib for patients with relapsed/refractory CLL intolerant to ibrutinib
- Ibrutinib induces durable remissions in patients with treatment-naïve CLL with 17p deletion/TP53 mutations
- Achieving complete remission with ibrutinib: Clinical significance and predictive factors
- Prognostic value of measurable residual disease after venetoclax and decitabine for AML
- A multicenter Phase II study of venetoclax with dose-adjusted R-EPOCH (VR-EPOCH) for Richter's syndrome
- Clinical and molecular characteristics and treatment patterns of adolescents and young adults with CLL

MODULE 4: Key Recent Data Sets

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

1. FCR (fludarabine/cyclosphosphamide/rituximab)
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?

 Dr Davids	Venetoclax + obinutuzumab	 Dr Mato	FCR
 Dr Flinn	Venetoclax + obinutuzumab	 Dr Pagel	Acalabrutinib
 Dr Hill	Venetoclax + obinutuzumab OR BR	 Dr Rogers	Ibrutinib or FCR
 Dr Jain	Venetoclax + obinutuzumab	 Dr Siddiqi	Venetoclax + obinutuzumab

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

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?

 Dr Davids	Venetoclax + obinutuzumab	 Dr Mato	Acalabrutinib
 Dr Flinn	Acalabrutinib	 Dr Pagel	Acalabrutinib
 Dr Hill	Obinutuzumab	 Dr Rogers	Acalabrutinib or venetoclax + obinutuzumab
 Dr Jain	Venetoclax + obinutuzumab	 Dr Siddiqi	Acalabrutinib + obinutuzumab

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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?

 Dr Davids	Venetoclax + obinutuzumab	 Dr Mato	Venetoclax + obinutuzumab
 Dr Flinn	Venetoclax + obinutuzumab	 Dr Pagel	Acalabrutinib
 Dr Hill	Venetoclax + obinutuzumab	 Dr Rogers	Acalabrutinib or venetoclax + obinutuzumab
 Dr Jain	Venetoclax + obinutuzumab	 Dr Siddiqi	Venetoclax + obinutuzumab

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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?

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?

 Dr Davids	Discontinue treatment	 Dr Mato	Continue treatment
 Dr Flinn	Discontinue treatment	 Dr Pagel	Continue treatment
 Dr Hill	Discontinue treatment	 Dr Rogers	Discontinue treatment
 Dr Jain	Continue treatment	 Dr Siddiqi	Continue treatment

RTP RESEARCH TO PRACTICE

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

 Dr Davids	Ibrutinib	 Dr Mato	Acalabrutinib
 Dr Flinn	Acalabrutinib	 Dr Pagel	Acalabrutinib
 Dr Hill	Acalabrutinib	 Dr Rogers	Ibrutinib
 Dr Jain	Acalabrutinib	 Dr Siddiqi	Acalabrutinib + obinutuzumab

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

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 ibrutinib and then experiences disease progression 3 years later?

 Dr Davids	Venetoclax + rituximab	 Dr Mato	Venetoclax + rituximab
 Dr Flinn	Venetoclax + obinutuzumab	 Dr Pagel	Venetoclax
 Dr Hill	Venetoclax + rituximab	 Dr Rogers	Venetoclax + rituximab
 Dr Jain	Venetoclax + obinutuzumab	 Dr Siddiqi	Ibrutinib + obinutzumab OR venetoclax + obinutuzumab

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?

 Dr Davids	Venetoclax + obinutuzumab	 Dr Mato	Venetoclax + rituximab
 Dr Flinn	Acalabrutinib	 Dr Pagel	Acalabrutinib
 Dr Hill	Acalabrutinib	 Dr Rogers	Ibrutinib
 Dr Jain	Acalabrutinib	 Dr Siddiqi	Acalabrutinib + obinutuzumab

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?

 Dr Davids	Admit to hospital	 Dr Mato	Admit to hospital
 Dr Flinn	Debulk with obinutuzumab	 Dr Pagel	Admit to hospital
 Dr Hill	Admit to hospital	 Dr Rogers	Admit to hospital
 Dr Jain	Admit to hospital	 Dr Siddiqi	Admit to hospital

RTP RESEARCH TO PRACTICE

Meet The Professor with Dr Thompson

MODULE 1: Cases from Dr Allan

MODULE 2: Beyond the Guidelines

MODULE 3: Journal Club with Dr Thompson

- Occupy BTK: The key to controlling CLL
- Acalabrutinib for patients with relapsed/refractory CLL intolerant to ibrutinib
- Ibrutinib induces durable remissions in patients with treatment-naïve CLL with 17p deletion/TP53 mutations
- Achieving complete remission with ibrutinib: Clinical significance and predictive factors
- Prognostic value of measurable residual disease after venetoclax and decitabine for AML
- A multicenter Phase II study of venetoclax with dose-adjusted R-EPOCH (VR-EPOCH) for Richter's syndrome
- Clinical and molecular characteristics and treatment patterns of adolescents and young adults with CLL

MODULE 4: Key Recent Data Sets

RTP
RESEARCH
TO PRACTICE

Comment on Sun et al, page 93

Occupy BTK: the key to controlling CLL

Philip A. Thompson | The University of Texas MD Anderson Cancer Center

In this issue of *Blood*, Sun and colleagues present results from a randomized, phase 2 study of acalabrutinib at either 100 mg twice daily or 200 mg daily in patients with treatment-naive or relapsed/refractory chronic lymphocytic leukemia (CLL).[1] As part of the study, they undertook a rigorous analysis of Bruton tyrosine kinase (BTK) occupancy and the resulting biologic consequences in different tissue compartments. They established that twice-daily dosing achieved higher BTK occupancy and resultant downstream pathway inhibition in lymph nodes than once-daily dosing and established the rate of BTK resynthesis in CLL cells.

***Blood* 2020;136(1):4-6**

Phase 2 Study of Acalabrutinib in Ibrutinib (IBR)-Intolerant Patients (pts) with Relapsed/Refractory (R/R) Chronic Lymphocytic Leukemia (CLL)

Rogers KA et al.

ASCO 2019;Abstract 7530.

Ibrutinib Induces Durable Remissions in Treatment-Naïve CLL Patients with 17p Deletion/TP53 Mutations: Five Year Follow-Up from a Phase 2 Study

Sivina M et al.

ASH 2020;Abstract 2218.

Blood 2020;135(7):510-3

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]

Prognostic Value of Measurable Residual Disease After Venetoclax and Decitabine in Acute Myeloid Leukemia

Maiti A et al.

ASH 2020;Abstract 276.

ASCO 2020;Abstract 8004

THE UNIVERSITY OF TEXAS MD Anderson Cancer Center

Dana-Farber Cancer Institute

The James The Ohio State University Comprehensive Cancer Center

A Multicenter Phase 2 Study of Venetoclax plus Dose-Adjusted R-EPOCH (VR-EPOCH) for Richter's Syndrome

Matthew S. Davids, MD, MMSc[1], Kerry A. Rogers, MD[2], Svitlana Tyekucheva, PhD[3], Samantha Pazienza, BS[1], Sarah K. Renner, RN[4], Josie Montegaard, NP[1], Michael Rocchio, BA[1], Udochukwu Ihuoma, BA[1], Caron A. Jacobson, MD, MMSc[1], David C. Fisher, MD[1], Jennifer R. Brown, MD, PhD[1], and Philip A. Thompson, MB, BS (Hons)[4]

[1]Department of Medical Oncology, Dana-Farber Cancer Institute, Boston, MA, USA
[2]Division of Hematology, The Ohio State University, Columbus, OH, USA
[3]Department of Data Sciences, Dana-Farber Cancer Institute, Boston, MA, USA
[4]Department of Leukemia, The University of Texas MD Anderson Cancer Center, Houston, TX, USA

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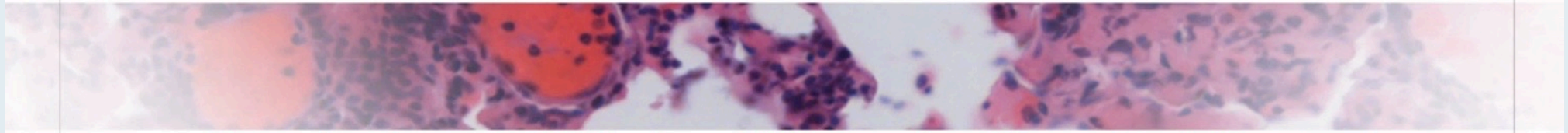

Examination of Clinical and Molecular Characteristics and Treatment Patterns of Adolescent and Young Adult (AYA) Patients with Chronic Lymphocytic Leukemia

Hua-Jay J Cherng, MD[1], Nadya Jammal, PharmD[2], Shilpa Paul, PharmD[2], Xuemei Wang, MS[3], Koji Sasaki, MD[1], Philip A. Thompson, MBBS[1], Jan A. Burger, MD PhD[1], Alessandra Ferrajoli, MD[1], Zeev E. Estrov, MD[1], Susan M. O'Brien, MD[4], Michael J. Keating, MBBS[1], William G. Wierda, MD PhD[1], Nitin Jain, MD[1]

[1]Department of Leukemia, The University of Texas MD Anderson Cancer Center, Houston, TX
[2]Department of Clinical Pharmacy, The University of Texas MD Anderson Cancer Center, Houston, TX
[3]Department of Biostatistics, The University of Texas MD Anderson Cancer Center, Houston, TX
[4]Chao Family Comprehensive Cancer Center, University of Irvine, Orange County, CA

2020 ASH Annual Meeting

Abstract #1301

Meet The Professor with Dr Thompson

MODULE 1: Cases from Dr Allan

MODULE 2: Beyond the Guidelines

MODULE 3: Journal Club with Dr Thompson

- Occupy BTK: The key to controlling CLL
- Acalabrutinib for patients with relapsed/refractory CLL intolerant to ibrutinib
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- Clinical and molecular characteristics and treatment patterns of adolescents and young adults with CLL

MODULE 4: Key Recent Data Sets

RTP RESEARCH TO PRACTICE

Optimal Integration of BTK Inhibitors and Venetoclax into First-Line Treatment

RTP
RESEARCH
TO PRACTICE

The NEW ENGLAND JOURNAL of MEDICINE

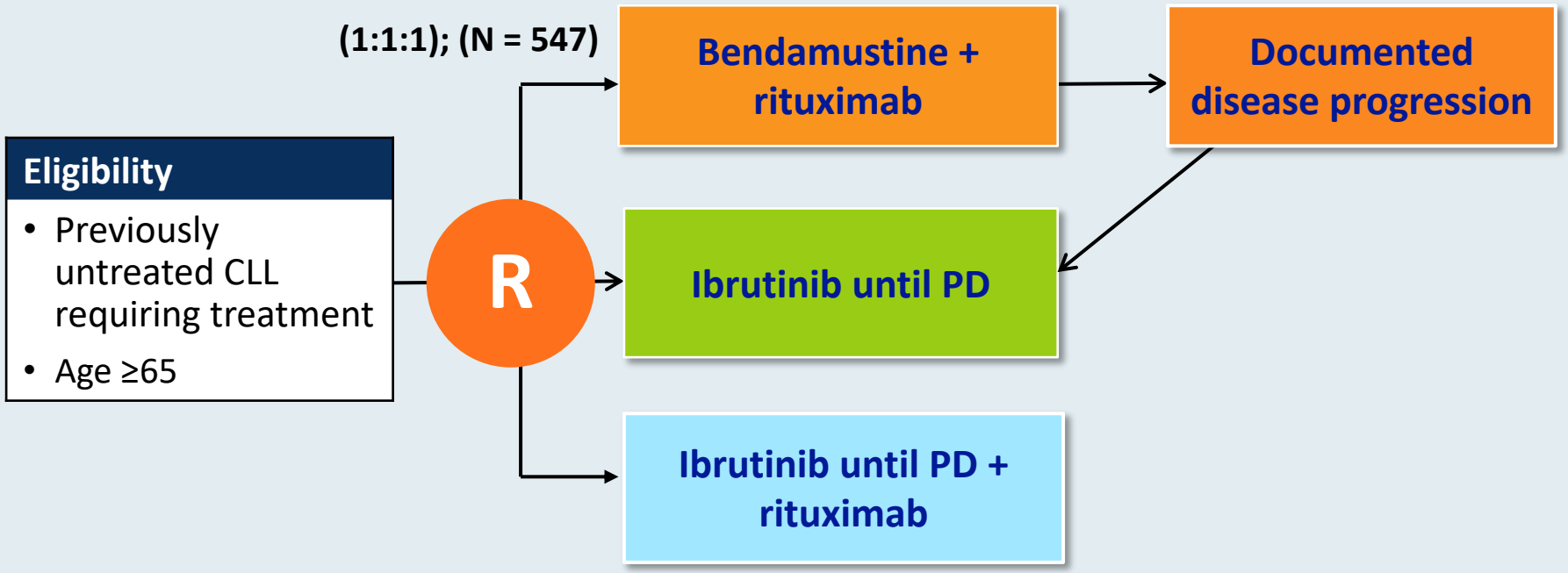
ORIGINAL ARTICLE

Ibrutinib Regimens versus Chemoimmunotherapy in Older Patients with Untreated CLL

J.A. Woyach, A.S. Ruppert, N.A. Heerema, W. Zhao, A.M. Booth, W. Ding, N.L. Bartlett, D.M. Brander, P.M. Barr, K.A. Rogers, S.A. Parikh, S. Coutre, A. Hurria,* J.R. Brown, G. Lozanski, J.S. Blachly, H.G. Ozer, B. Major-Elechi, B. Fruth, S. Nattam, R.A. Larson, H. Erba, M. Litzow, C. Owen, C. Kuzma, J.S. Abramson, R.F. Little, S.E. Smith, R.M. Stone, S.J. Mandrekar, and J.C. Byrd

N Engl J Med 2018;379(26):2517-28.

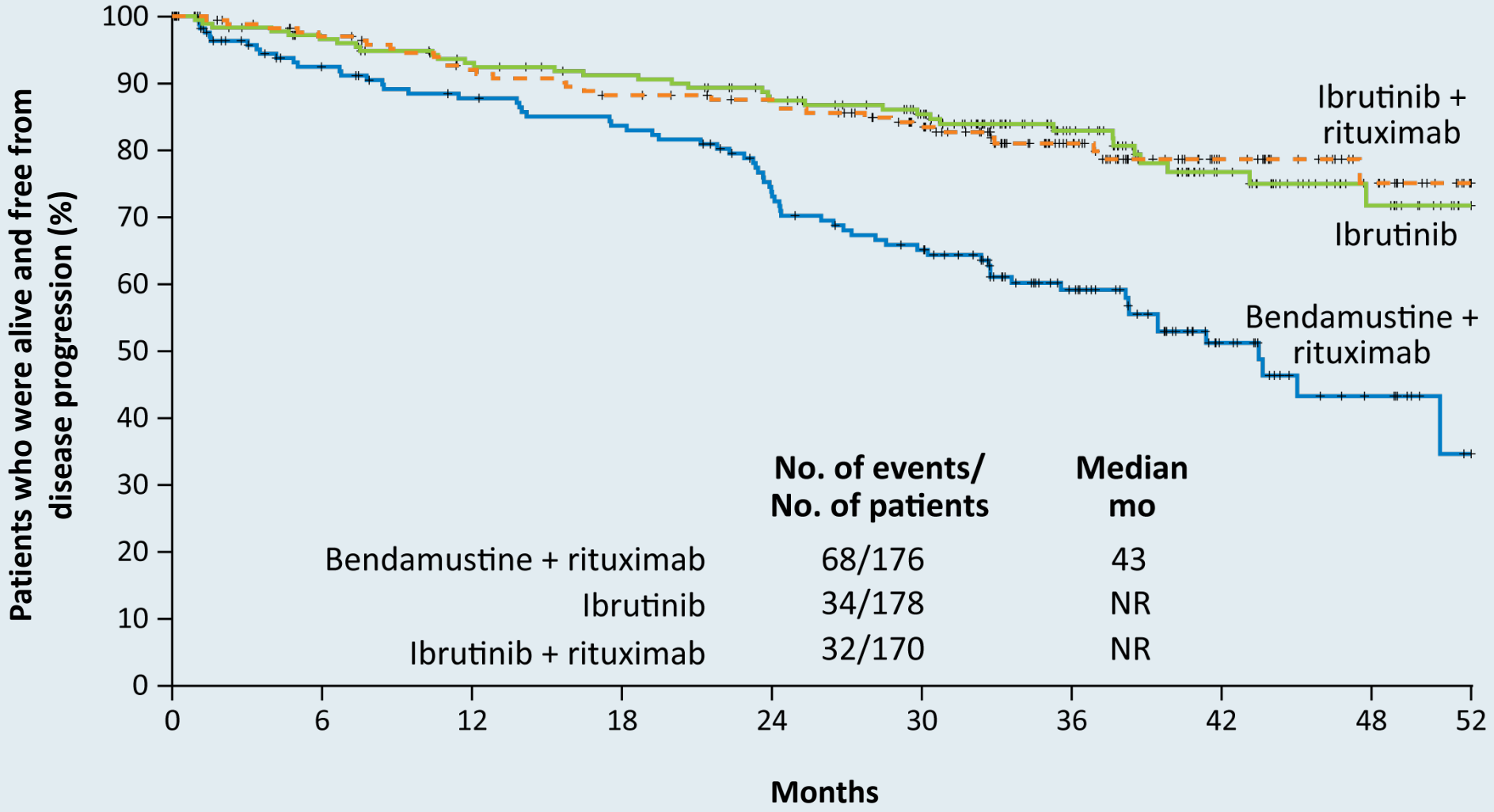
Phase III Alliance A041202 Study Design



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

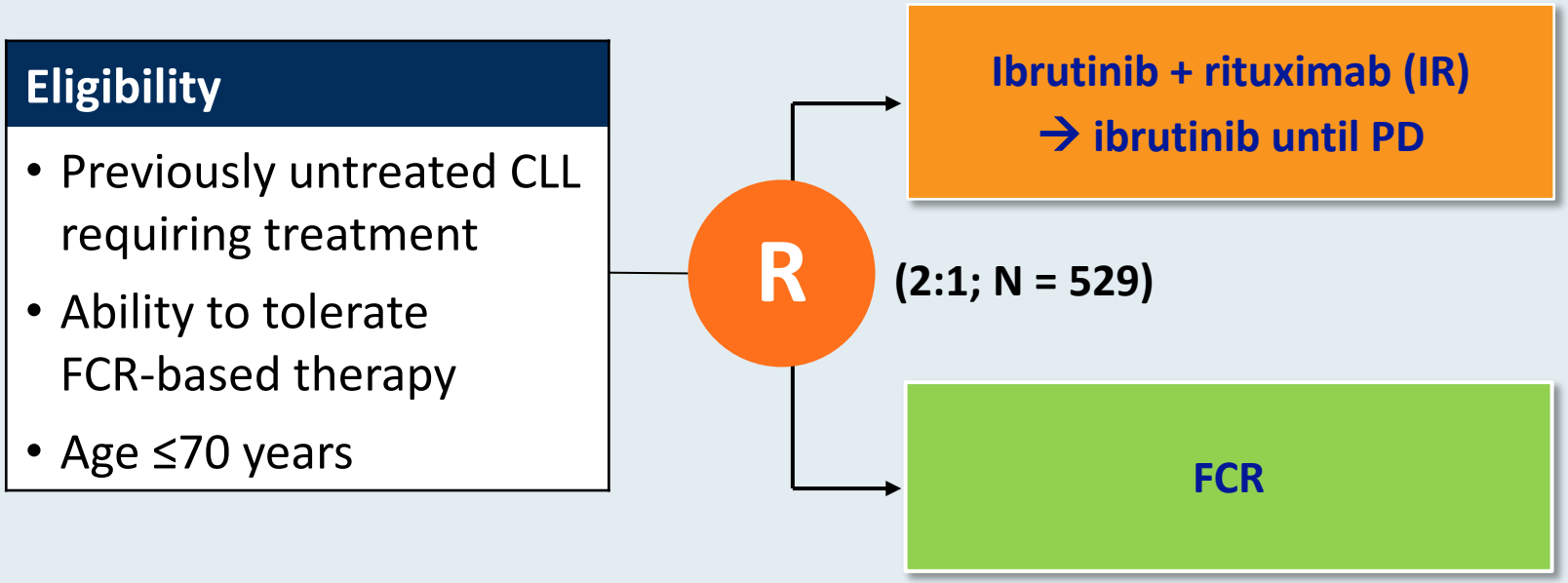
Woyach JA et al. *N Engl J Med* 2018;379(26):2517-28.

Ibrutinib and Rituximab Provides Superior Clinical Outcome Compared to FCR in Younger Patients with Chronic Lymphocytic Leukemia (CLL): Extended Follow-Up from the E1912 Trial

Shanafelt TD et al.

ASH 2019;Abstract 33.

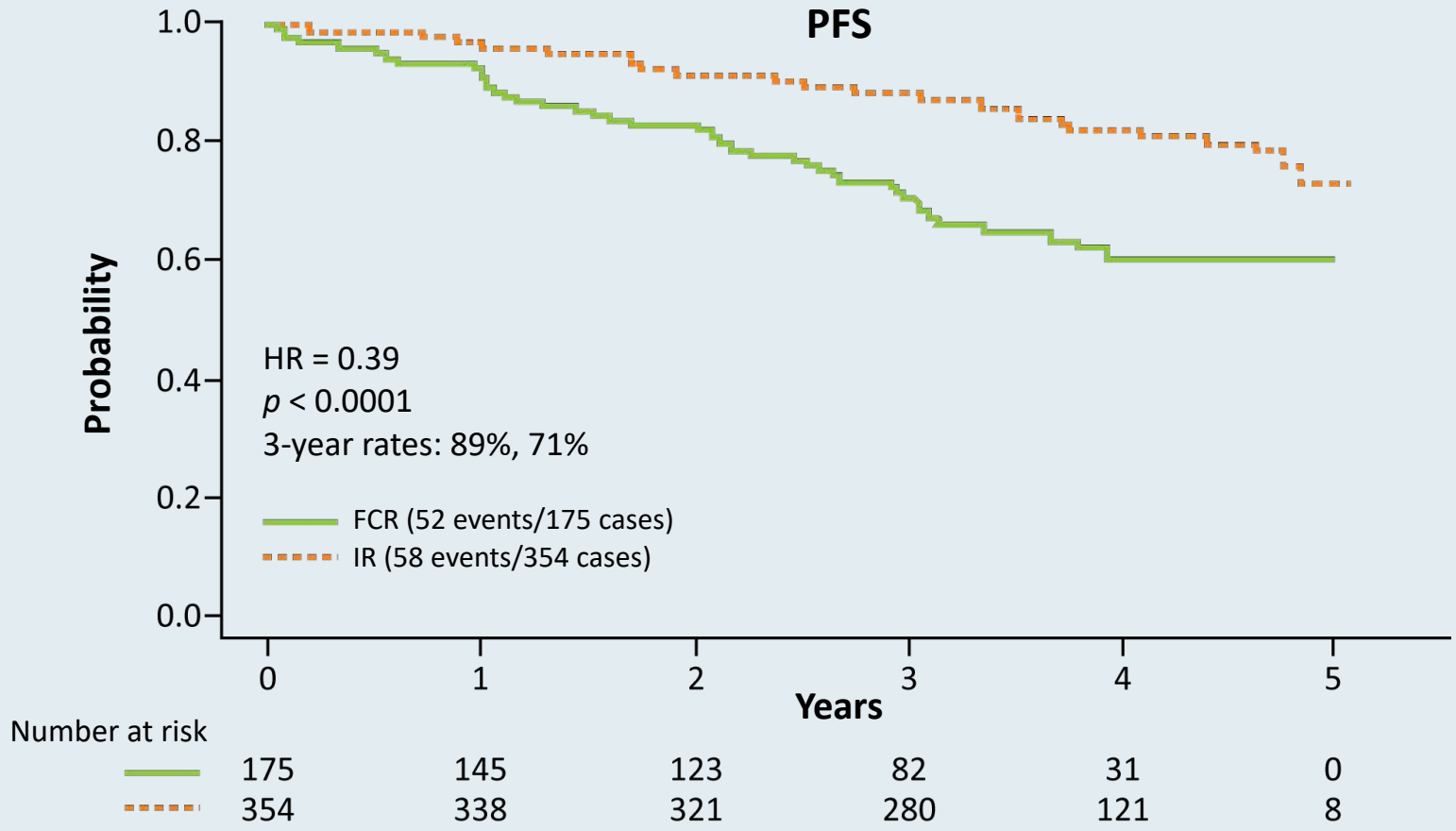
Phase III ECOG-ACRIN E1912 Study Design



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

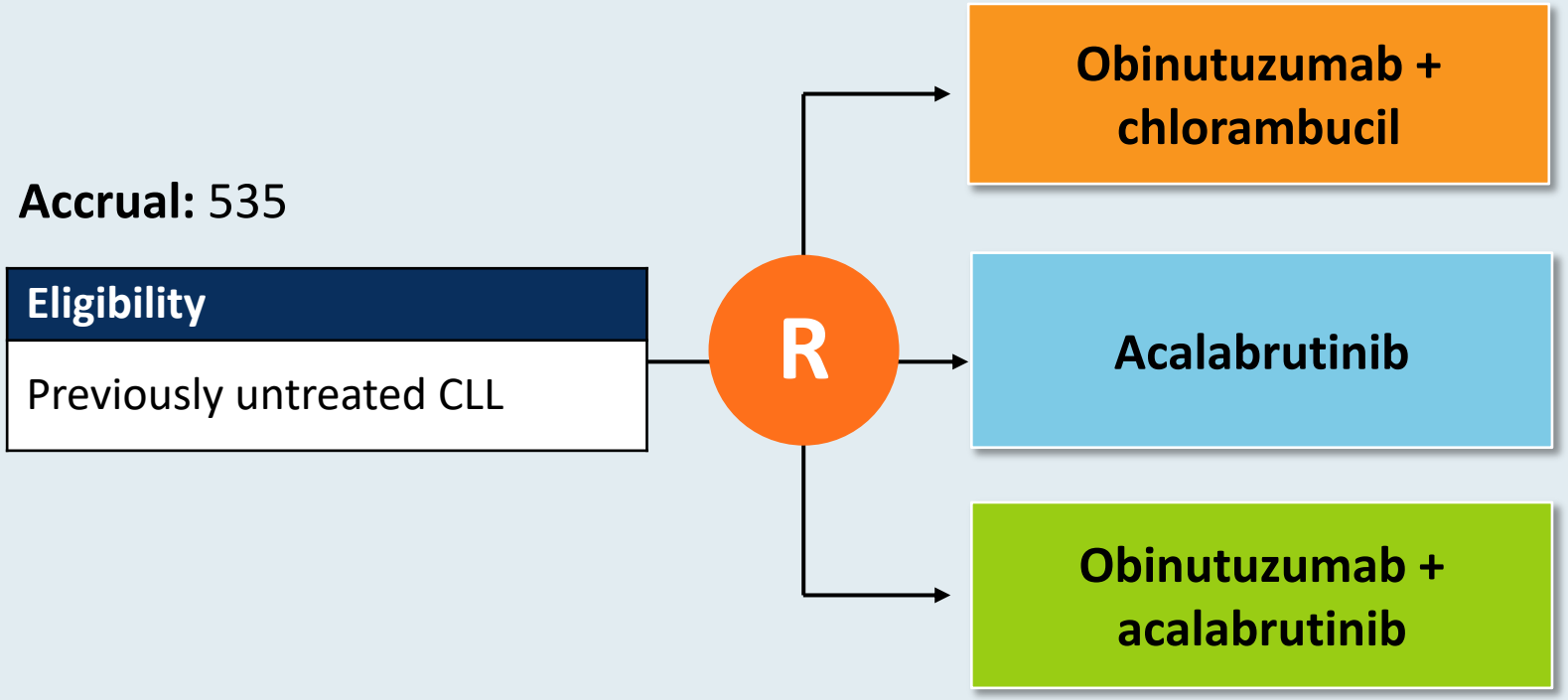
Articles

Acalabrutinib with or without obinutuzumab versus chlorambucil and obinutuzumab for treatment-naive chronic lymphocytic leukaemia (ELEVATE-TN): a randomised, controlled, phase 3 trial

Jeff P Sharman, Miklos Egyed, Wojciech Jurczak, Alan Skarbnik, John M Pagel, Ian W Flinn, Manali Kamdar, Talha Munir, Renata Walewska, Gillian Corbett, Laura Maria Fogliatto, Yair Herishanu, Versha Banerji, Steven Coutre, George Follows, Patricia Walker, Karin Karlsson, Paolo Ghia, Ann Janssens, Florence Cymbalista, Jennifer A Woyach, Gilles Salles, William G Wierda, Raquel Izumi, Veerendra Munugalavadla, Priti Patel, Min Hui Wang, Sofia Wong, John C Byrd

Lancet 2020;395(10232):1278-91.

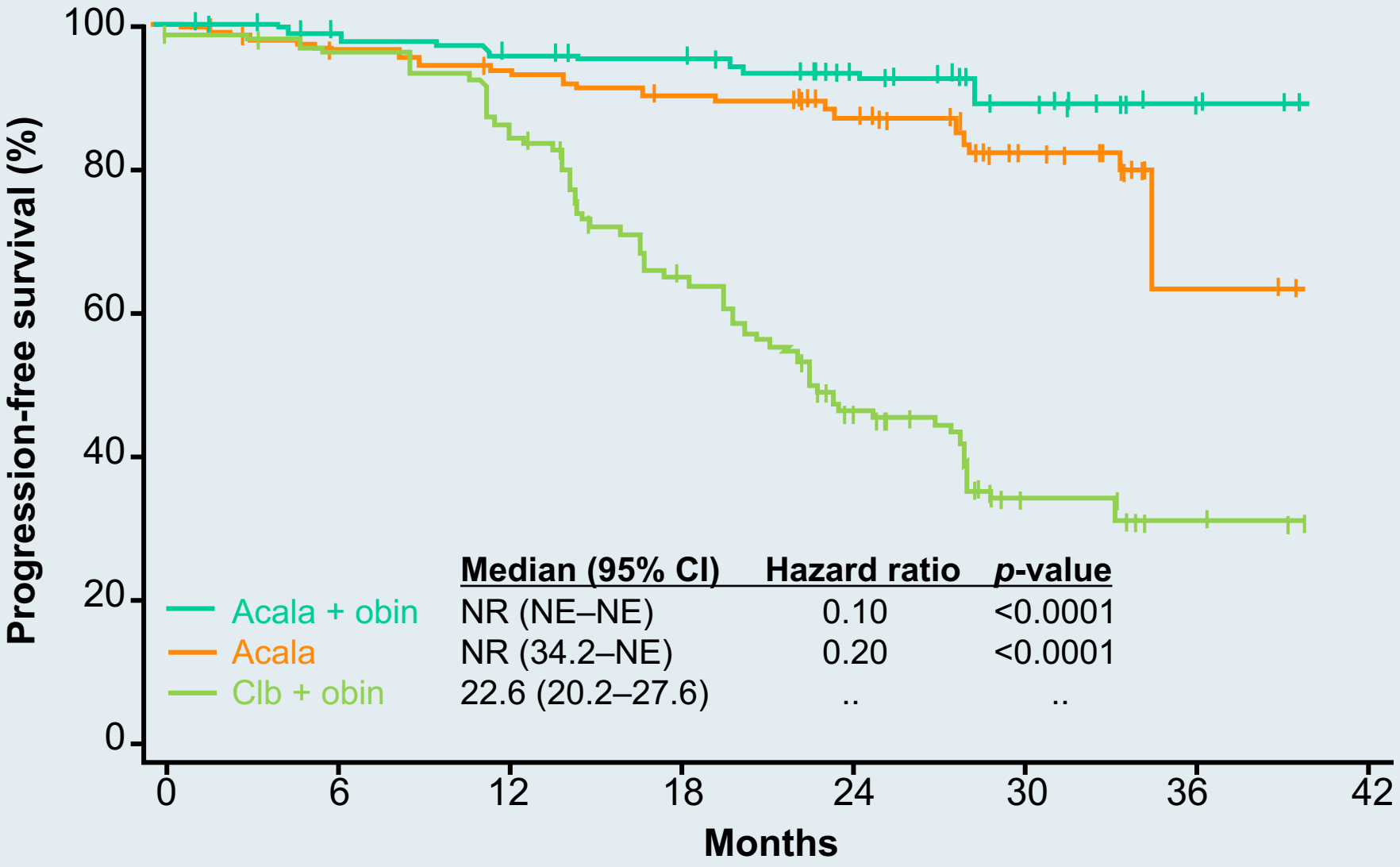
ELEVATE-TN Phase III Trial Schema



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.

Acalabrutinib Met Primary Efficacy Endpoint in Head-to-Head Trial Against Ibrutinib for Chronic Lymphocytic Leukemia

Press Release — January 25, 2021

"Positive high-level results from the ELEVATE-RR Phase III trial showed acalabrutinib met the primary endpoint demonstrating non-inferior progression-free survival (PFS) for adults with previously treated, high-risk chronic lymphocytic leukemia (CLL) compared to ibrutinib.

The trial also met a key secondary endpoint for safety, showing patients treated with acalabrutinib had statistically significantly lower incidence of atrial fibrillation compared to patients treated with ibrutinib. Atrial fibrillation is an irregular heart rate that can increase the risk of stroke, heart failure and other heart-related complications. Further hierarchical testing revealed no difference for Grade 3 or higher infections or Richter's transformation. There was a descriptive trend for numerically favorable overall survival. Overall, the safety and tolerability of acalabrutinib were consistent with the profile seen in the broader acalabrutinib clinical development program.

ELEVATE-RR is the first Phase III trial to compare two Bruton's tyrosine kinase (BTK) inhibitors in patients with CLL, the most common type of leukemia in adults."

https://www.astrazeneca.com/media-centre/press-releases/2021/calquence-met-primary-endpoint-against-ibrutinib.html

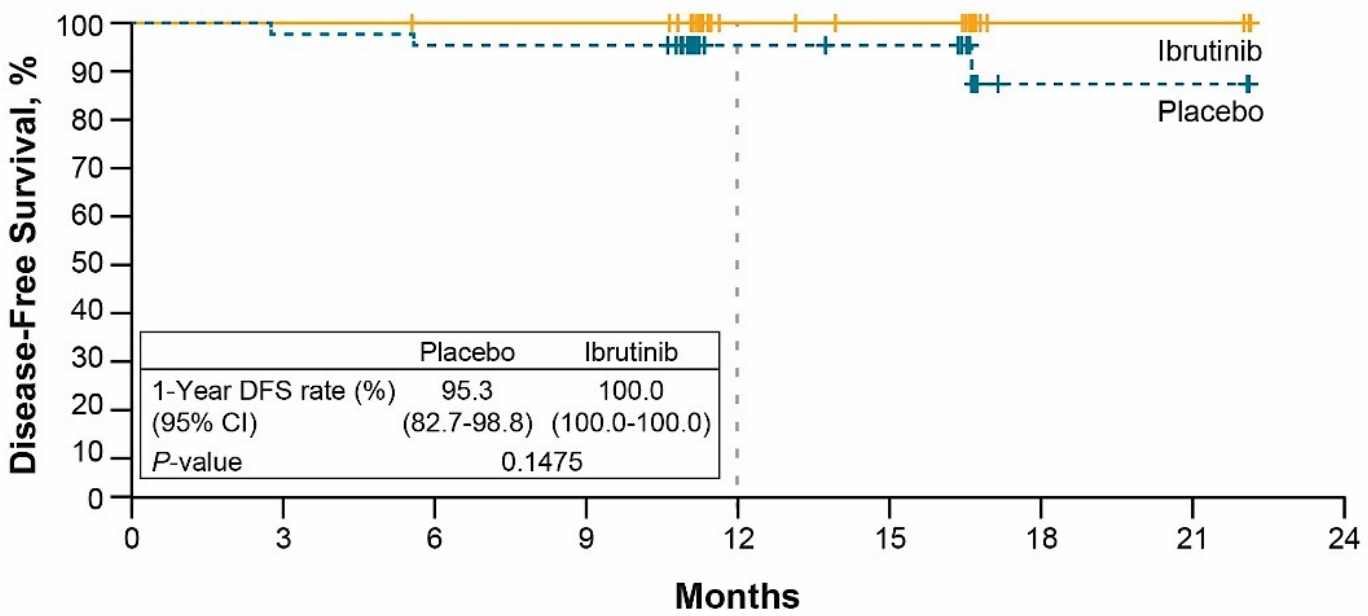
Ibrutinib (Ibr) plus Venetoclax (Ven) for First-Line Treatment of Chronic Lymphocytic Leukemia (CLL)/Small Lymphocytic Lymphoma (SLL): 1-Year Disease-Free Survival (DFS) Results from the MRD Cohort of the Phase 2 CAPTIVATE Study Trial

Wierda WG et al.

ASH 2020;Abstract 123.

CAPTIVATE Phase II Trial of First-Line Ibrutinib with Venetoclax for CLL: 1-Year DFS Results from the MRD Cohort

Figure. DFS by Randomized Treatment Arm in Confirmed uMRD Group[a]



Patients at Risk

Placebo	43	42	41	41	22	21	3	3	0
Ibrutinib	43	43	42	42	25	23	5	5	0

[a]The 3 DFS events in placebo arm were disease progression in 2 patients and MRD relapse in 1 patient.

<u>30 month PFS Rate:</u>

Confirmed uMRD:

- 95.3% placebo
- 100% ibrutinib

Without confirmed uMRD:

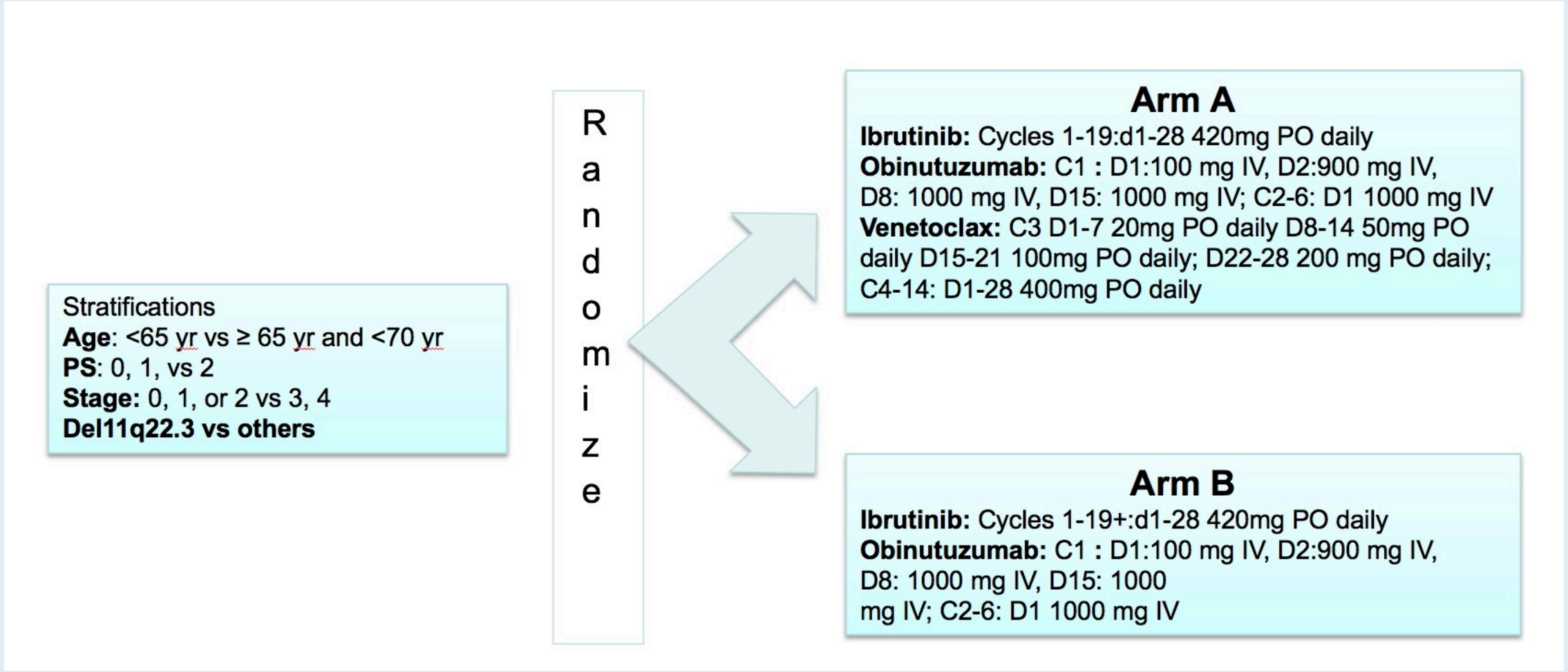
- 95.2% ibrutinib
- 96.7% ibr/ven

AEs were primarily Grade 1/2 and mostly occurred in early cycles of Ibr + Ven, with modest differences by randomized treatment arm.

Wierda WG et al. ASH 2020;Abstract 123.

RTP RESEARCH TO PRACTICE

Phase III EA9161 Schema



Clinicaltrials.gov/ct2/show/NCT03701282?term=EA9161&draw=2&rank=1, Accessed March 1, 2021

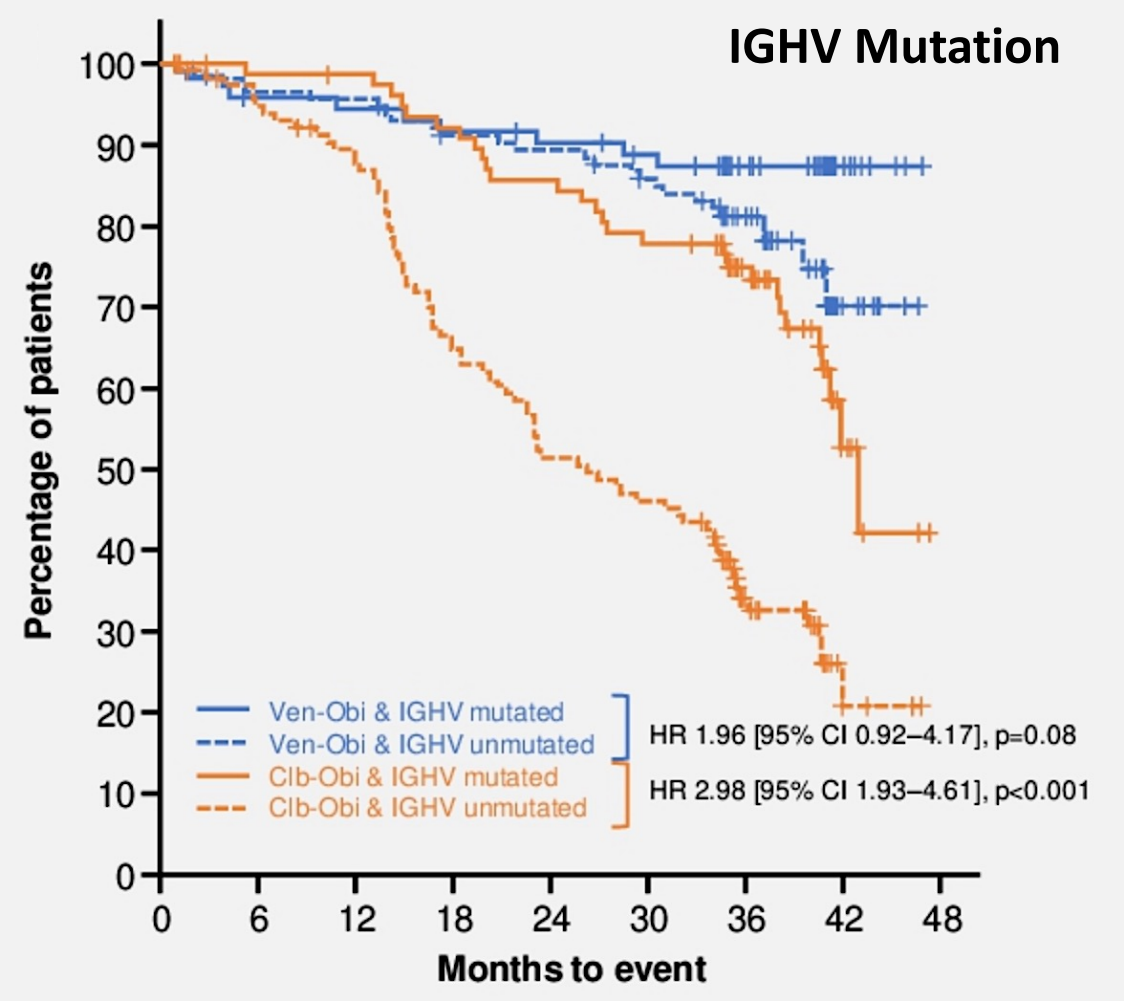
Articles

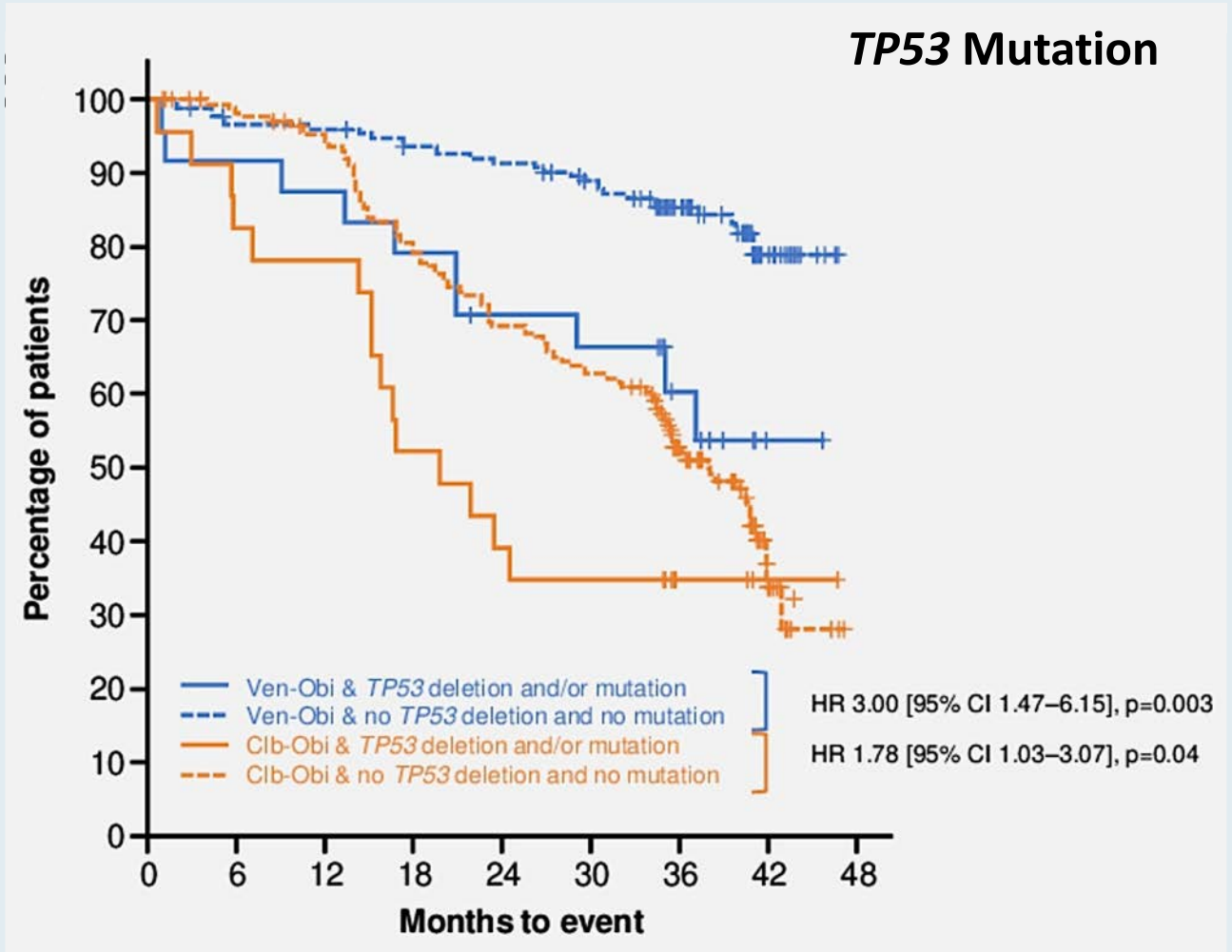
Venetoclax plus obinutuzumab versus chlorambucil plus obinutuzumab for previously untreated chronic lymphocytic leukaemia (CLL14): follow-up results from a multicentre, open-label, randomised, phase 3 trial

Othman Al-Sawaf, Can Zhang, Maneesh Tandon, Arijit Sinha, Anna-Maria Fink, Sandra Robrecht, Olga Samoylova, Anna M Liberati, Javier Pinilla-Ibarz, Stephen Opat, Liliya Sivcheva, Katell Le Dû, Laura M Fogliatto, Carsten U Niemann, Robert Weinkove, Sue Robinson, Thomas J Kipps, Eugen Tausch, William Schary, Matthias Ritgen, Clemens-Martin Wendtner, Karl-Anton Kreuzer, Barbara Eichhorst, Stephan Stilgenbauer, Michael Hallek, Kirsten Fischer**

Lancet Oncol 2020;21(9):1188-200.

CLL14: PFS by IGHV and TP53 Mutation Status

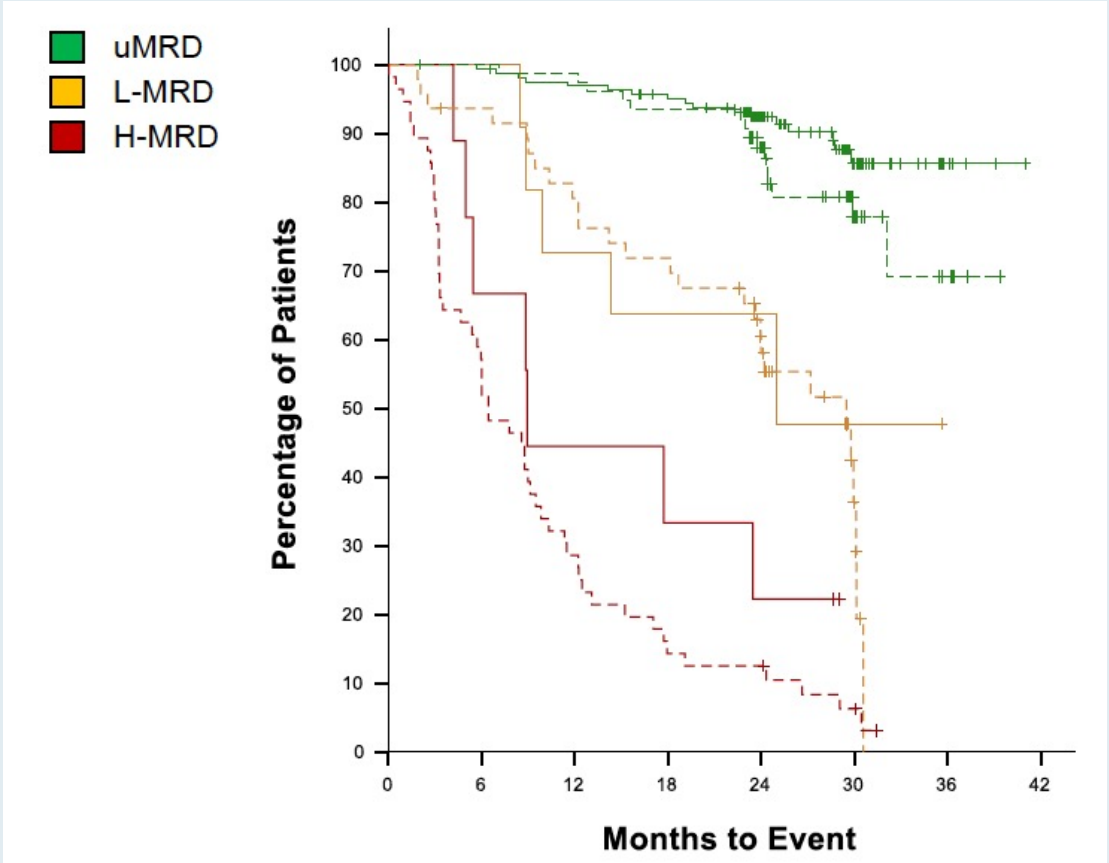




Al-Sawaf O et al. *Lancet Oncol* 2020;21(9):1188-200.

RTP RESEARCH TO PRACTICE

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



Patients at risk								
VEN-OBI & uMRD	163	161	156	150	91	34	5	0
VEN-OBI & L-MRD	11	11	8	7	4	1	0	0
VEN-OBI & H-MRD	9	6	4	3	2	0	0	0
CLB-OBI & uMRD	76	76	75	71	56	18	6	0
CLB-OBI & L-MRD	47	43	37	33	23	5	0	0
CLB-OBI & H-MRD	56	32	16	8	7	3	0	0

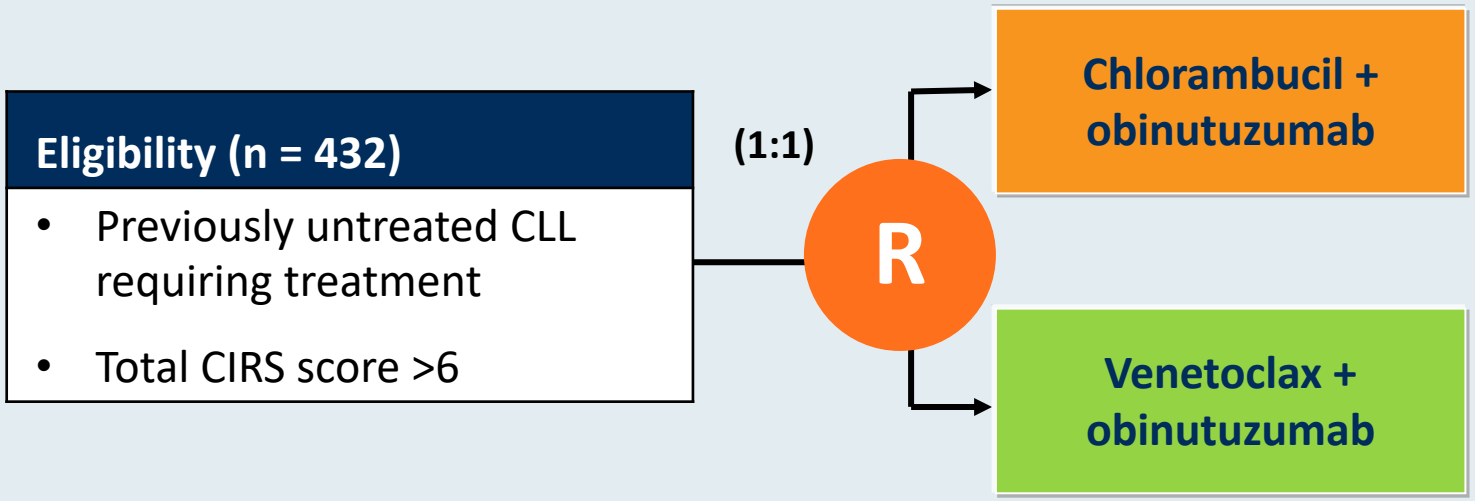
Al-Sawaf O et al. *Lancet Oncol* 2020;21(9):1188-200.

Clonal Dynamics After Venetoclax-Obinutuzumab Therapy: Novel Insights from the Randomized, Phase 3 CLL14 Trial

Al-Sawaf O et al.

ASH 2020;Abstract 127.

CLL14 Phase III Study Schema

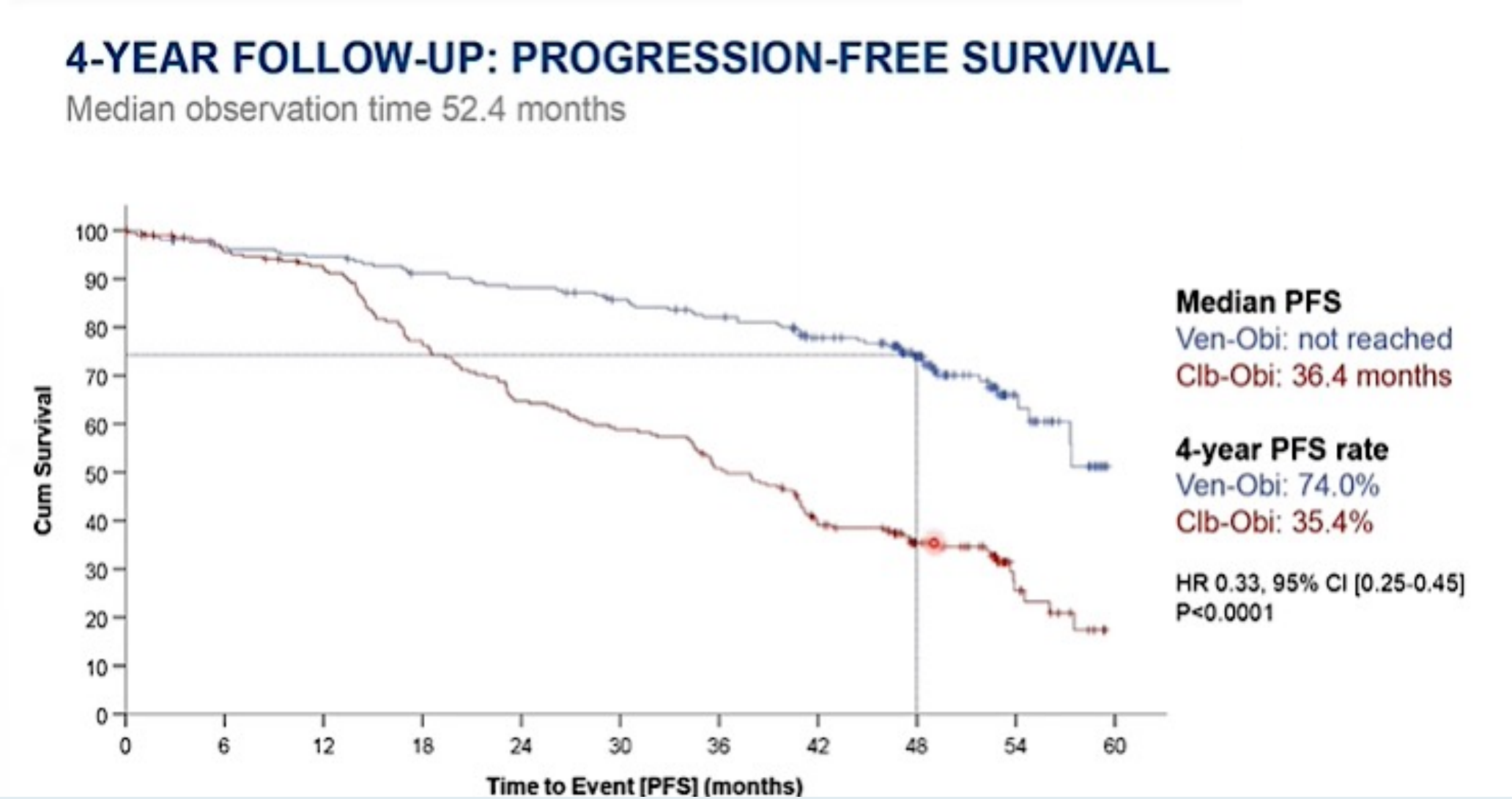


Primary endpoint: Progression-free survival

- 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: Updated 4-Year PFS



Al-Sawaf O et al. ASH 2020;Abstract 127 .

RTP RESEARCH TO PRACTICE

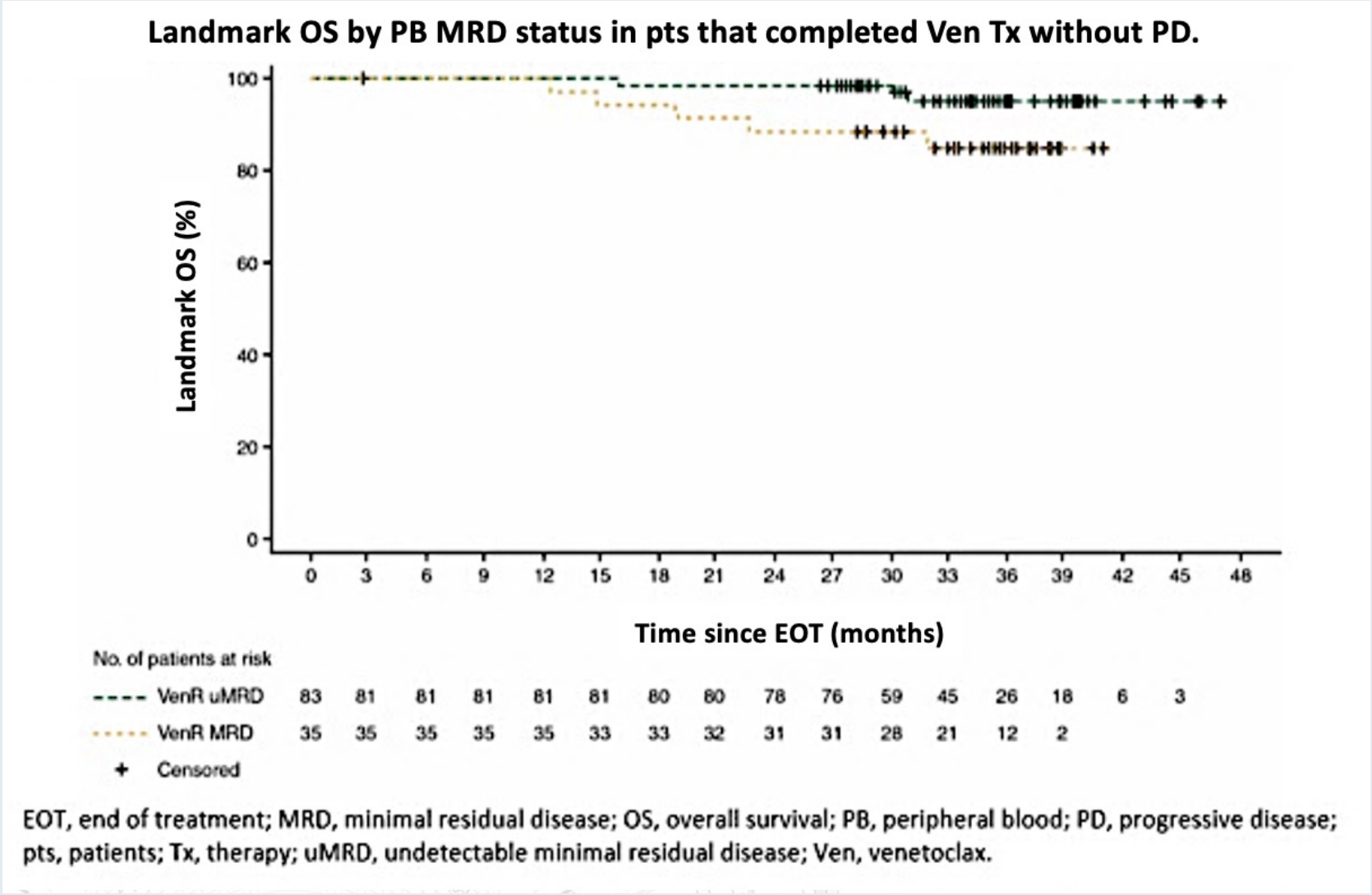
Management of Relapsed/Refractory CLL

Five-Year Analysis of Murano Study Demonstrates Enduring Undetectable Minimal Residual Disease (uMRD) in a Subset of Relapsed/Refractory Chronic Lymphocytic Leukemia (R/R CLL) Patients (Pts) Following Fixed-Duration Venetoclax-Rituximab (VenR) Therapy (Tx)

Kater AP et al.

ASH 2020;Abstract 125.

MURANO: 5-Year Follow-Up of Venetoclax/Rituximab (Ven/R) in R/R CLL



EOT, end of treatment; MRD, minimal residual disease; OS, overall survival; PB, peripheral blood; PD, progressive disease; pts, patients; Tx, therapy; uMRD, undetectable minimal residual disease; Ven, venetoclax.

- Median PFS for VenR: 53.6 mo
- 5 year OS rate: 82%
- Of 83 patients with uMRD at end of therapy, 38.5% remained uMRD
- 25 months was the average time from MRD conversion to requirement for therapy

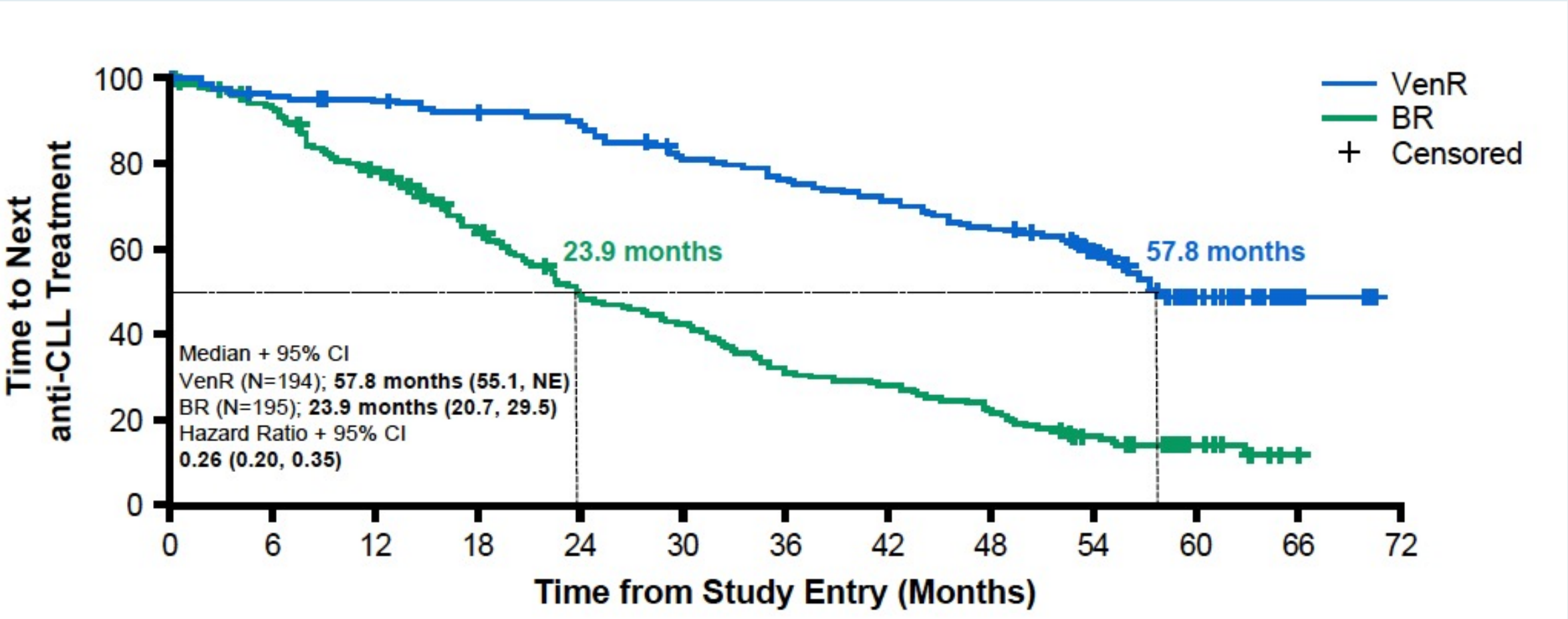
Kater AP et al. ASH 2020;Abstract 125.

RTP RESEARCH TO PRACTICE

Efficacy of Subsequent Novel Targeted Therapies, Including Repeated Venetoclax-Rituximab (VenR), in Patients with Relapsed/Refractory Chronic Lymphocytic Leukemia (R/R CLL) Previously Treated with Fixed-Duration VenR in the MURANO Study

Harrup R et al.
ASH 2020;Abstract 3139.

MURANO: TTNT with VenR versus BR



Harrup R et al. ASH 2020;Abstract 3139.

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Efficacy of Subsequent Novel Targeted Therapies in Patients Treated on the MURANO Trial: Conclusions

- 5-year follow-up data from the MURANO study demonstrated TTNT benefit with VenR versus BR.
- Initial VenR treatment was associated with improved time to second PFS event, indicating that early use of Ven over BR does not compromise efficacy of subsequent therapy.
- Response rates to subsequent BTKi therapy, re-treatment with Ven-based regimens or crossover to Ven-based regimens were high.
- Fixed-duration VenR is an effective approach in patients with R/R CLL and does not compromise response to subsequent therapy or OS.[1,2]

Harrup R et al. ASH 2020;Abstract 3139.

ASH Annual Meeting 2020 **Abstract Publication Number 3136**

Venetoclax Re-Treatment of Chronic Lymphocytic Leukemia Patients after a Previous Venetoclax-based Regimen

Meghan C. Thompson, MD[1], John N. Allan, MD[2], Kavita Sail, PhD[3], Beenish S. Manzoor, PhD, MPH[4], Jeffrey J. Pu, MD, PhD[5], Paul M. Barr, MD[6], Callie C. Coombs, MD[7], Stephen J. Schuster, MD[8], Alan Skarbnik, MD[9], Joanna M Rhodes, MD[10], Jacqueline C. Barrientos, MD[10], Lindsey E Roeker, MD[1], Lori A. Leslie, MD[11], Manali Kamdar, MD[12], Michael Y. Choi, MD[13], Martin Simkovic, MD, PhD[14], Frederick Lansigan, MD[15], Brittany Jane Hale, MD[15], Andrew D Zelenetz, MD, PhD[16], Alison J. Moskowitz, MD[1], Kurt S. Bantilan, MPH[1], Celina J. Komari, BS[1], Andre H. Goy, MD[1], Tatyana A. Feldman, MD[11], Richard R. Furman, MD[2] and Anthony R. Mato, MD[1]

Study Design and Endpoints

- Multicenter, retrospective study
- 13 centers and the CLL Collaborative Study of Real-World Evidence (CORE) database
- Eligibility:
  - CLL patients treated with Ven-based regimen (any line of therapy, Ven1)
  - Then re-treated with second Ven-based regimen (Ven2) in a later line of therapy
- Data collected by investigators at individual sites
  - Demographics, prognostic disease characteristics, tumor lysis syndrome risk and incidence, clinical response and reasons for treatment discontinuation

- Primary endpoint:
  - Investigator-assessed ORR
  - CR: complete response, PR: partial response, SD: stable disease, PD: progression of disease, iwCLL 2018
- PFS estimated by Kaplan-Maier method
- All other analyses descriptive

Memorial Sloan Kettering Cancer Center
Weill Cornell Medicine
UPSTATE CANCER CENTER
UC San Diego Health
University of Colorado
UR MEDICINE
UNC
Penn
Hackensack Meridian John Theurer Cancer Center
NOVANT HEALTH
Northwell Health
Dartmouth-Hitchcock NORRIS COTTON CANCER CENTER
FAKULTNÍ NEMOCNICE HRADEC KRÁLOVÉ

Thompson MC et al. ASH 2020;Abstract 3136.

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Conclusions

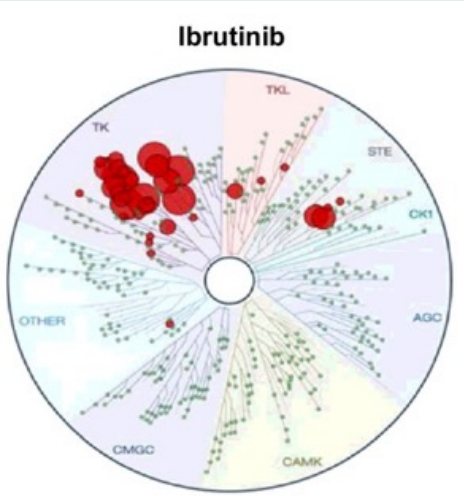
- **ORR:** High ORR of 72.2% for Ven re-treatment
- **Heavily pretreated population:** Cohort studied had median 2 prior therapies, majority R/R (88%), BTKi exposed (60%)
- **Safety:** TLS rare event and majority were able to tolerate 400 mg daily
- **Improved outcomes with time:** Patients with CR to Ven re-treatment had a longer median follow-up than PR or SD patients
  - Potential for better responses with longer time on therapy?
- **Next steps:** Longer follow-up and prospective validation of Ven re-treatment → potential role of Ven re-treatment in sequencing algorithms

Thompson MC et al. ASH 2020;Abstract 3136.

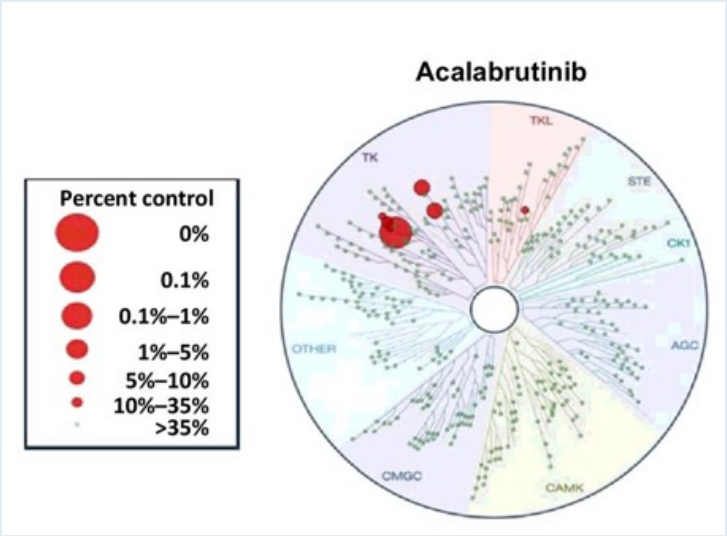
Overview of BTK Inhibitors in CLL

Irreversible

Ibrutinib



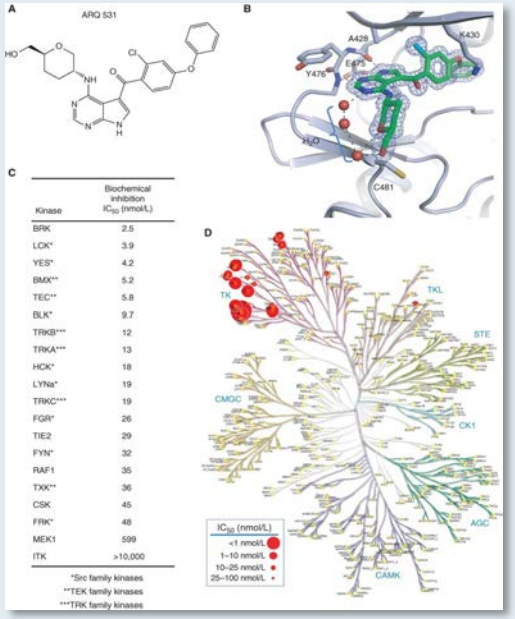
Acalabrutinib



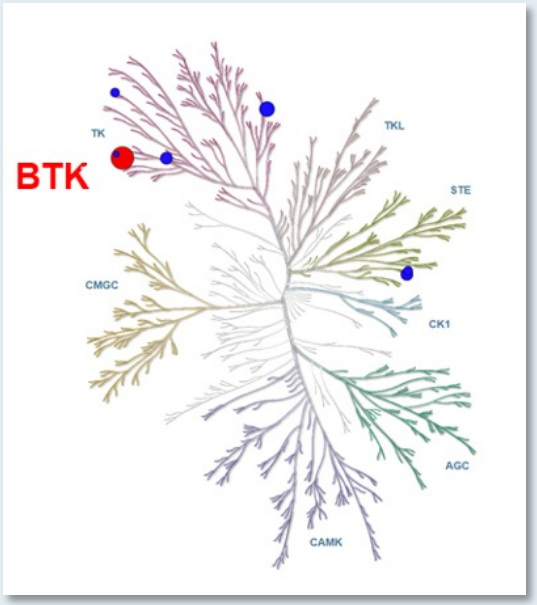
Zanubrutinib

Reversible

ARQ-531 (MK-1026)



LOXO-305



Courtesy of Matthew S Davids, MD, MMSc

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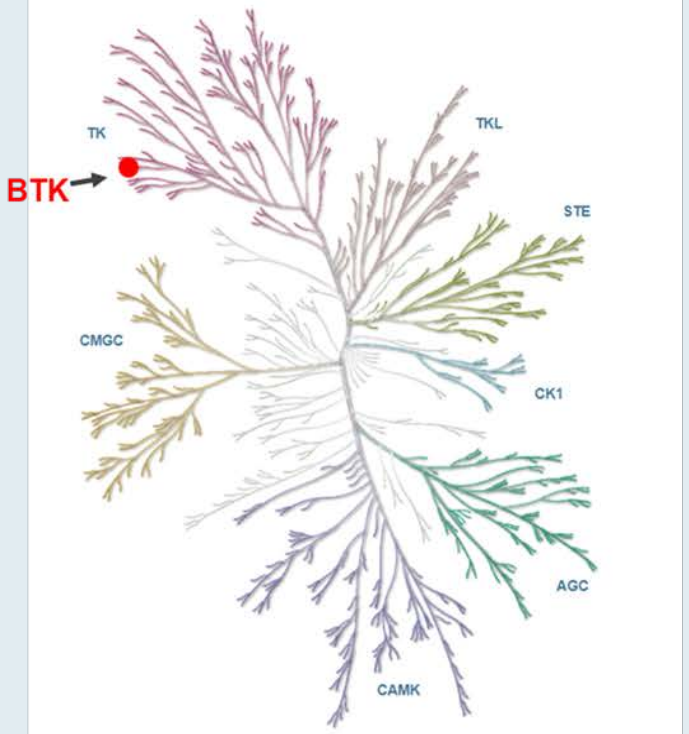
LOXO-305 is a Highly Potent and Selective Non-Covalent BTK Inhibitor

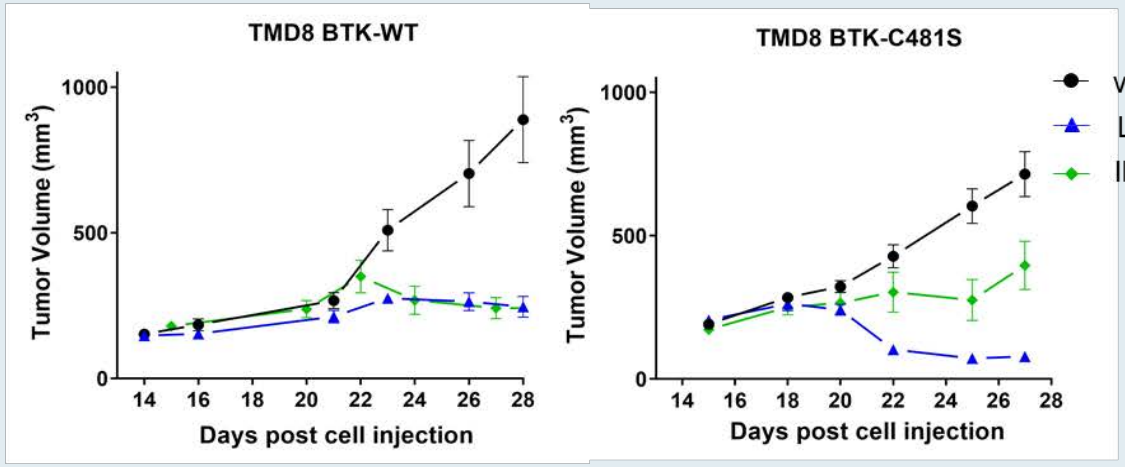
Kinome selectivity

Highly selective for BTK



Xenograft models

In vivo activity similarly efficacious as ibrutinib in WT; superior in C481S



- Nanomolar potency against WT & C481-mutant BTK in cell and enzyme assays[1,2]
- >300-fold selectivity for BTK vs 370 other kinases[1]
- Due to reversible binding mode, BTK inhibition not impacted by intrinsic rate of BTK turnover[1]
- Favorable pharmacologic properties allow sustained BTK inhibition throughout dosing interval[1]

BID, twice-daily; BTK, Bruton tyrosine kinase. Illustration reproduced courtesy of Cell Signaling Technology, Inc. (www.cellsignal.com). [1]Brandhuber et al. *Clin. Lymphoma Myeloma Leuk.* 2018;18:S216. [2]Mato et al. *Blood.* 2019:134 (Suppl 1):501.

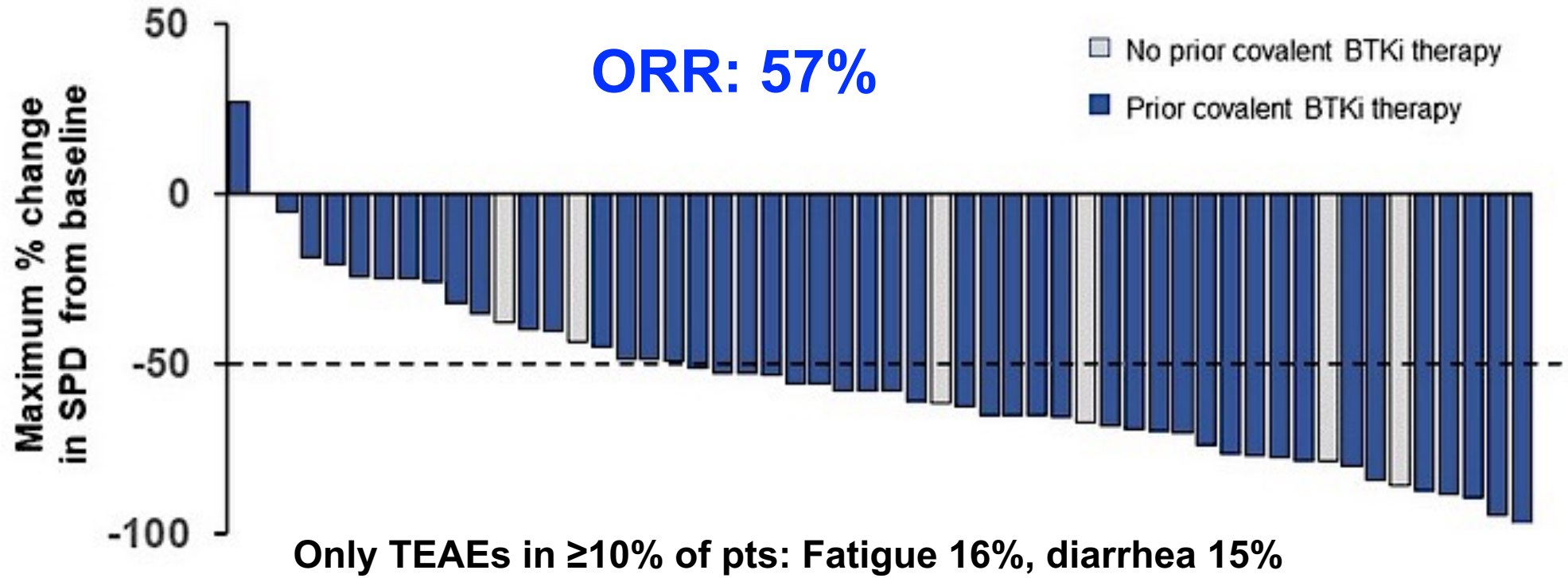
Mato AR et al. ASH 2020;Abstract 542.

LOXO-305, a Next Generation, Highly Selective, Non-Covalent BTK Inhibitor in Previously Treated CLL/SLL: Results from the Phase 1/2 BRUIN Study

Mato AR et al.

ASH 2020;Abstract 542.

BRUIN: LOXO-305 for Previously Treated CLL/SLL
(Median prior therapies: 4)



Only TEAEs in ≥10% of pts: Fatigue 16%, diarrhea 15%

* 11 efficacy-evaluable pts are not included in the waterfall plot, including 1 pt who discontinued prior to first response assessment, and 10 pts (4 pts with PR/PR-L and 6 pts with SD) with incomplete tumor lesion measurement data at the time of data cut

Mato AR et al. ASH 2020;Abstract 542.

BRUIN: Safety

Adverse Events, at All Doses and Patients (N=323), n (%)		Treatment-Emergent AEs, (≥10%)[a]				Treatment-Related AEs	
		Any Grade	Grade 1	Grade 2	Grade 3	Any Grade	Grade 3/4
Fatigue		65 (20)	40 (12)	22 (7)	3 (1)	27 (8)	2 (<1)
Diarrhea		55 (17)	45 (14)	10 (3)	-	28 (9)	-
Contusion		42 (13)	37 (12)	5 (2)	-	29 (9)	-
AEs of special interest, [b,c]	Bruising	53 (16)	48 (15)	5 (2)	-	37 (12)	-
	Rash	35 (11)	30 (9)	5 (2)	-	18 (6)	-
	Arthralgia	16 (5)	13 (4)	3 (1)	-	5 (2)	-
	Hemorrhage	15 (5)	10 (3)	4 (1)	1 (<1)[d]	5 (2)	-
	Hypertension	15 (5)	2 (<1)	9 (3)	4 (1)	4 (1)	-
	AFib/Flutter	2 (<1)	-	2 (<1)[e]	-	-	-

- No DLTs reported and MTD not reached
- 5 (1.5%) discontinued due to treatment-related AEs
- 200 mg QD selected as recommended phase 2 dose

Mato AR et al. ASH 2020. Abstract 542.

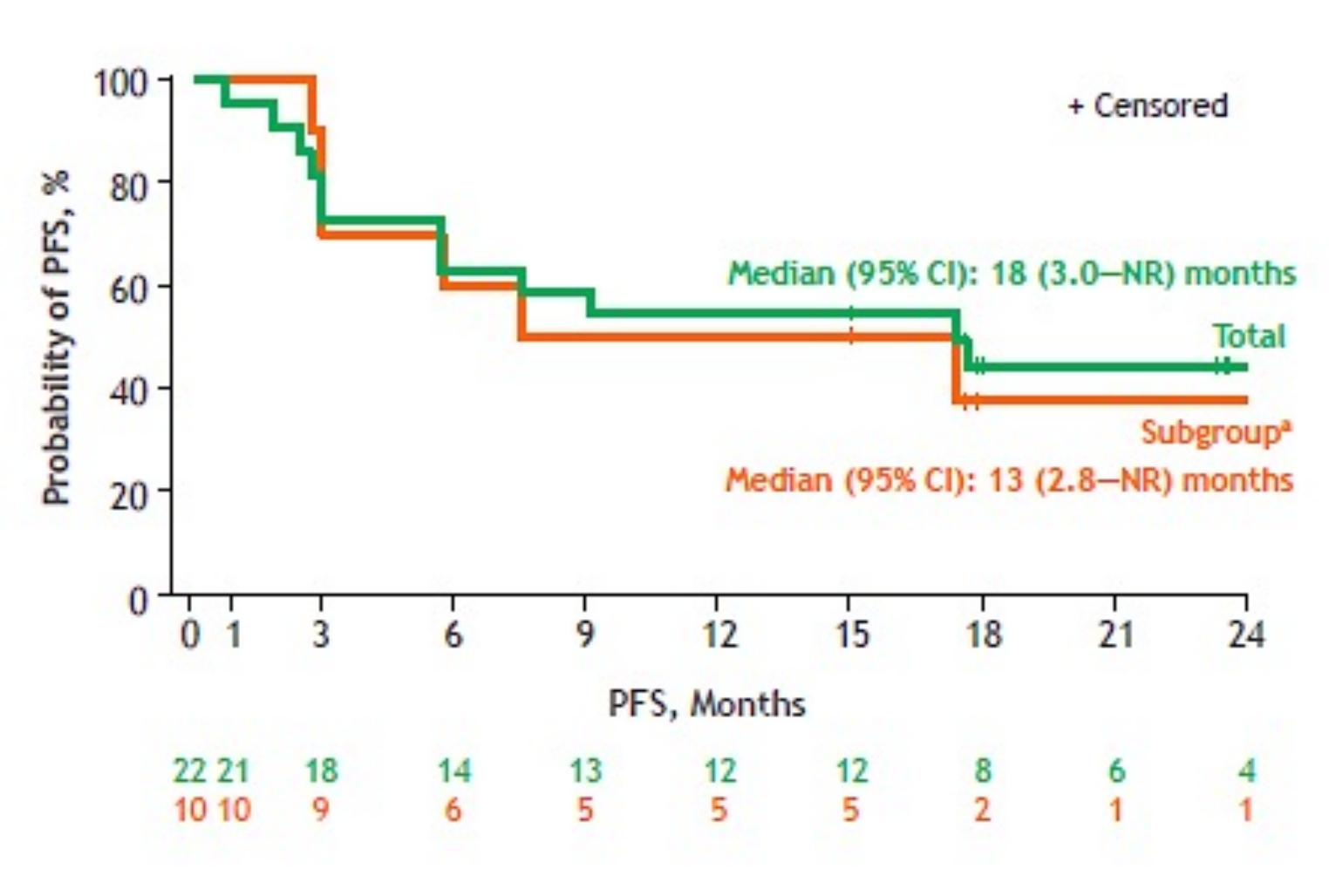
Courtesy of Matthew S Davids, MD, MMSc

Updated Follow-Up of Patients with Relapsed/Refractory Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma Treated with Lisocabtagene Maraleucel in the Phase 1 Monotherapy Cohort of Transcend CLL 004, Including High-Risk and Ibrutinib-Treated Patients

Siddiqi T et al.

ASH 2020;Abstract 546.

TRANSCEND CLL 04: Liso-cel Monotherapy Cohort



- ORR/CR = 82%/68%
- Median PFS 13 mo and DOR 50% at 12 mo
- Gr 3 CRS= 9% and NE 22% (No Grade 4/5)
- 4 of 6 progressions due to RT

Siddiqi T et al. ASH 2020;Abstract 546.

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Meet The Professor

Immunotherapy and Novel Agents in Gynecologic Cancers

Monday, April 5, 2021
5:00 PM – 6:00 PM ET

Faculty

Bradley J Monk, MD

Moderator

Neil Love, MD

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Thank you for joining us!

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

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