Meet The Professor
Management of Chronic Lymphocytic Leukemia

Jeremy Abramson, MD
Director, Center for Lymphoma
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Associate Professor of Medicine
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Boston, Massachusetts

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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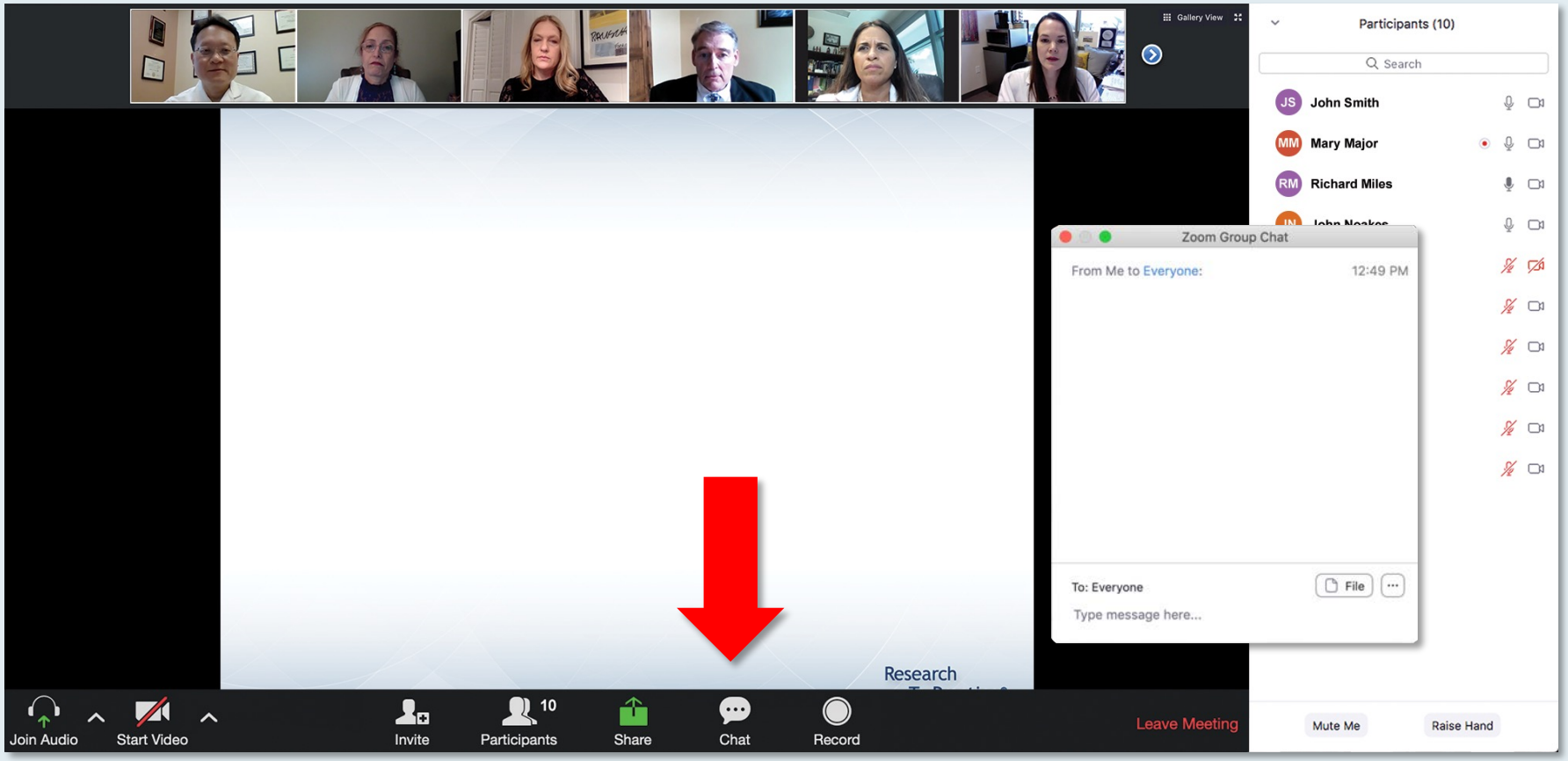
We Encourage Clinicians in Practice to Submit Questions



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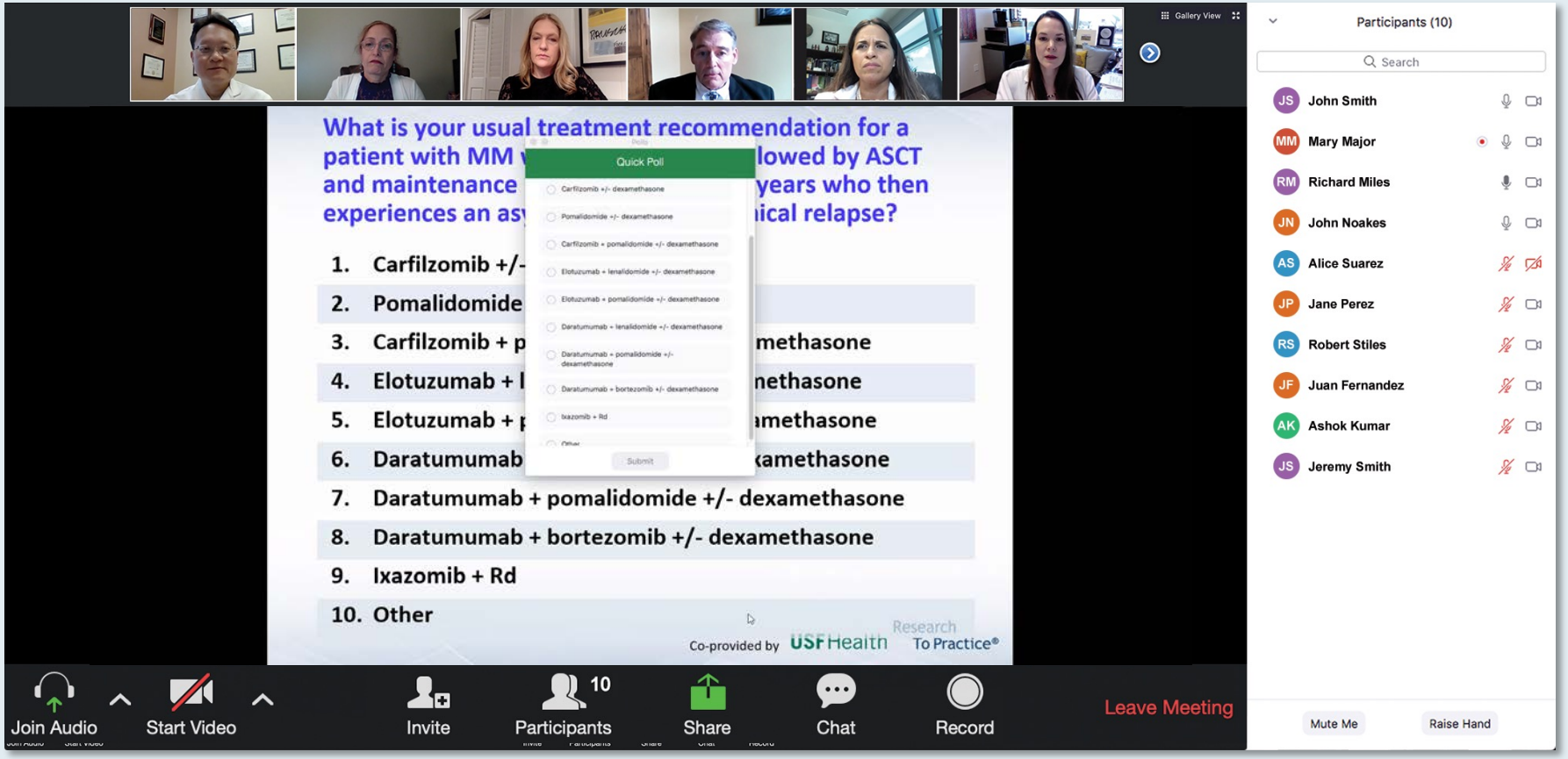

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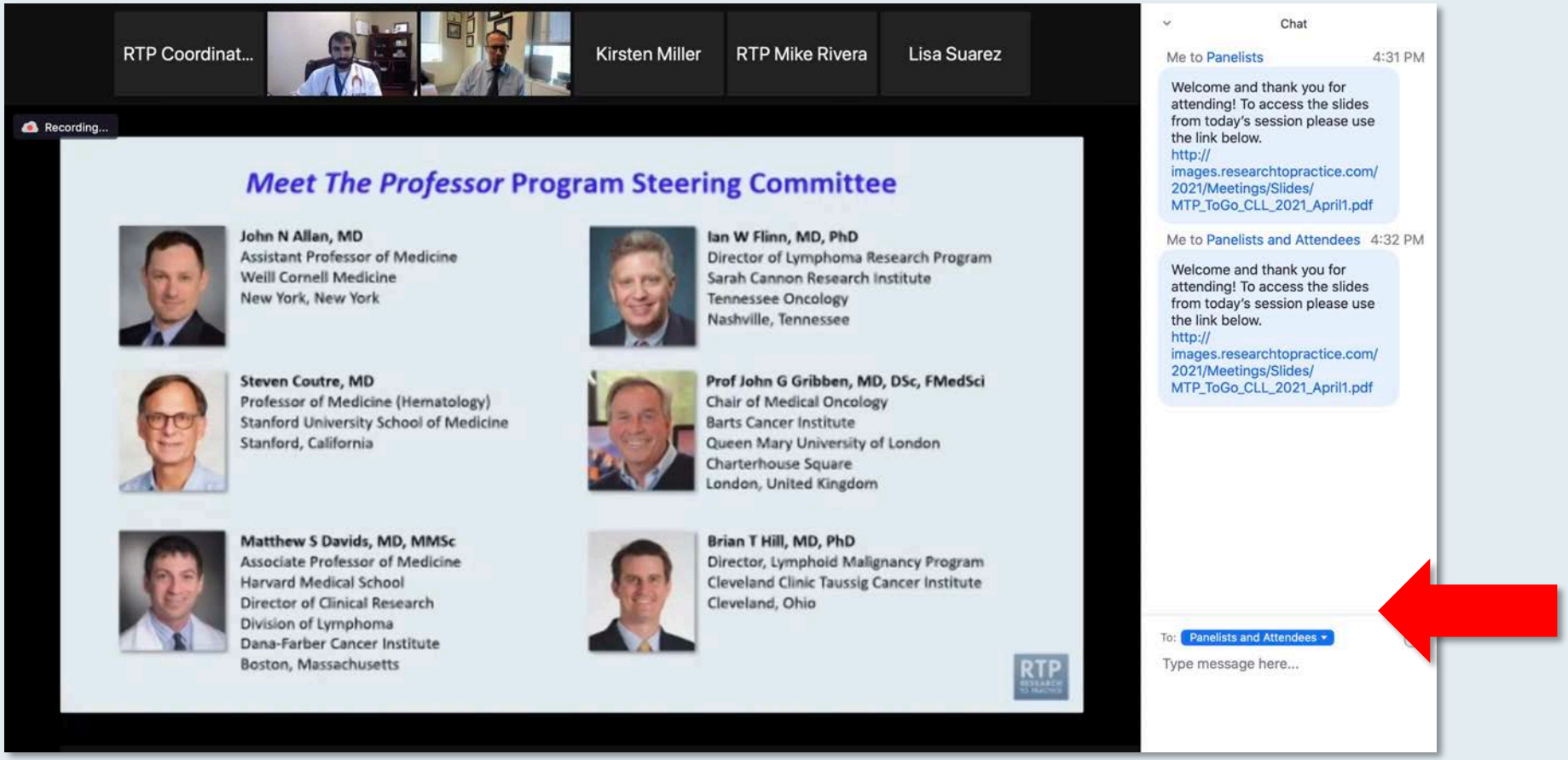

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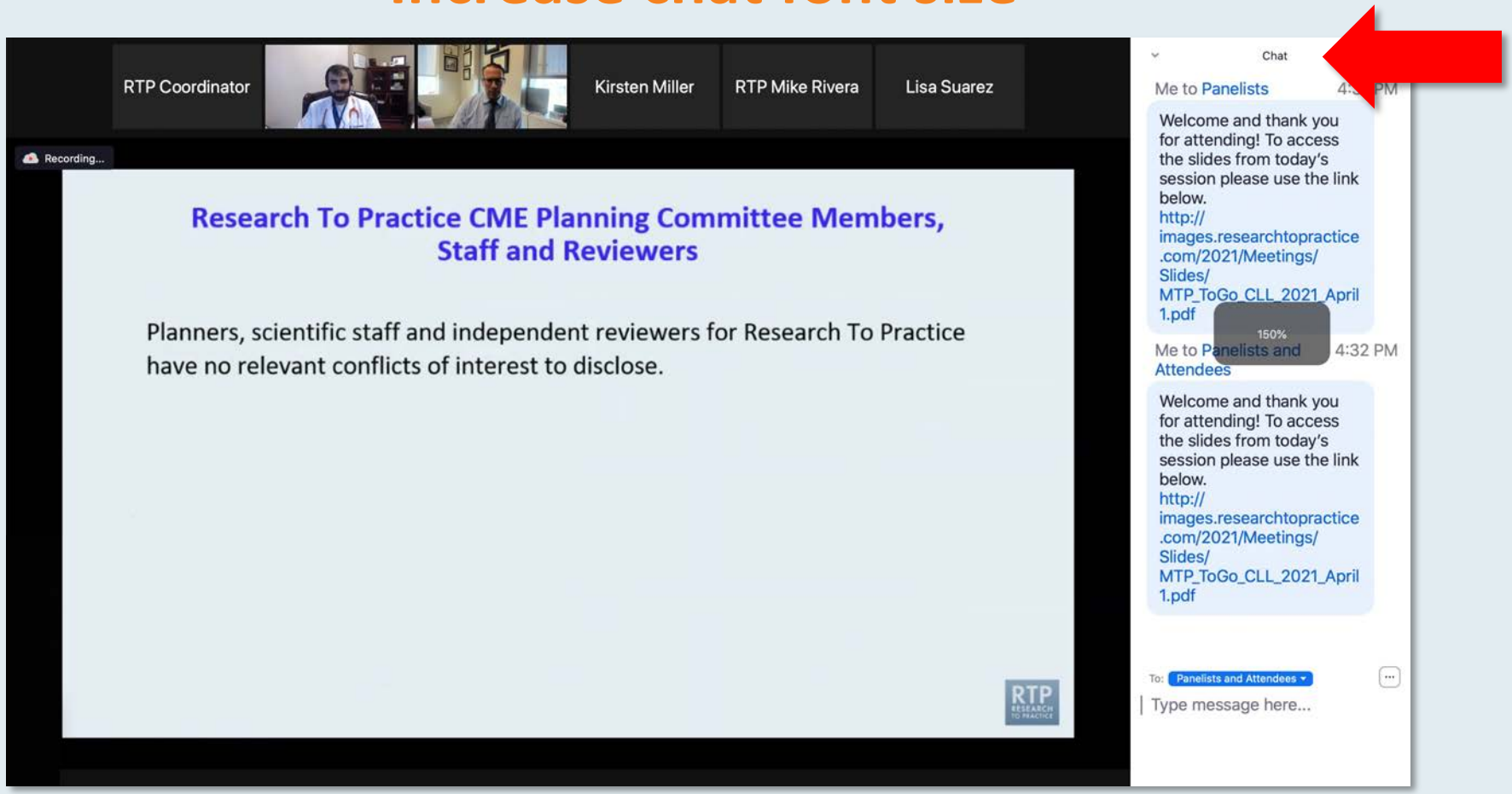

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You may do this as many times as you need for readability.

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Key Presentations on Chronic Lymphocytic Leukemia and Follicular Lymphoma from the 2020 ASH Annual Meeting

DR ANN LACASCE

DANA-FARBER CANCER INSTITUTE

BOSTON, MASSACHUSETTS

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Meet The Professor

Immunotherapy and Novel Agents in Gynecologic Cancers

Wednesday, May 12, 2021
5:00 PM – 6:00 PM ET

Faculty

Michael J Birrer, MD, PhD

Moderator

Neil Love, MD

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Current Concepts and Recent Advances in Oncology

A Daylong Clinical Summit Hosted in Partnership with Medical Oncology Association of Southern California (MOASC)

Saturday, May 15, 2021
10:30 AM – 6:30 PM ET

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Virginia Kaklamani, Nancy U Lin

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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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Meet The Professor Program Participating Faculty

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Associate Professor of Medicine
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Boston, Massachusetts

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Cell Transplantation
Swedish Cancer Institute
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Washington, DC

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Professor
Division of Hematology
Department of Internal Medicine
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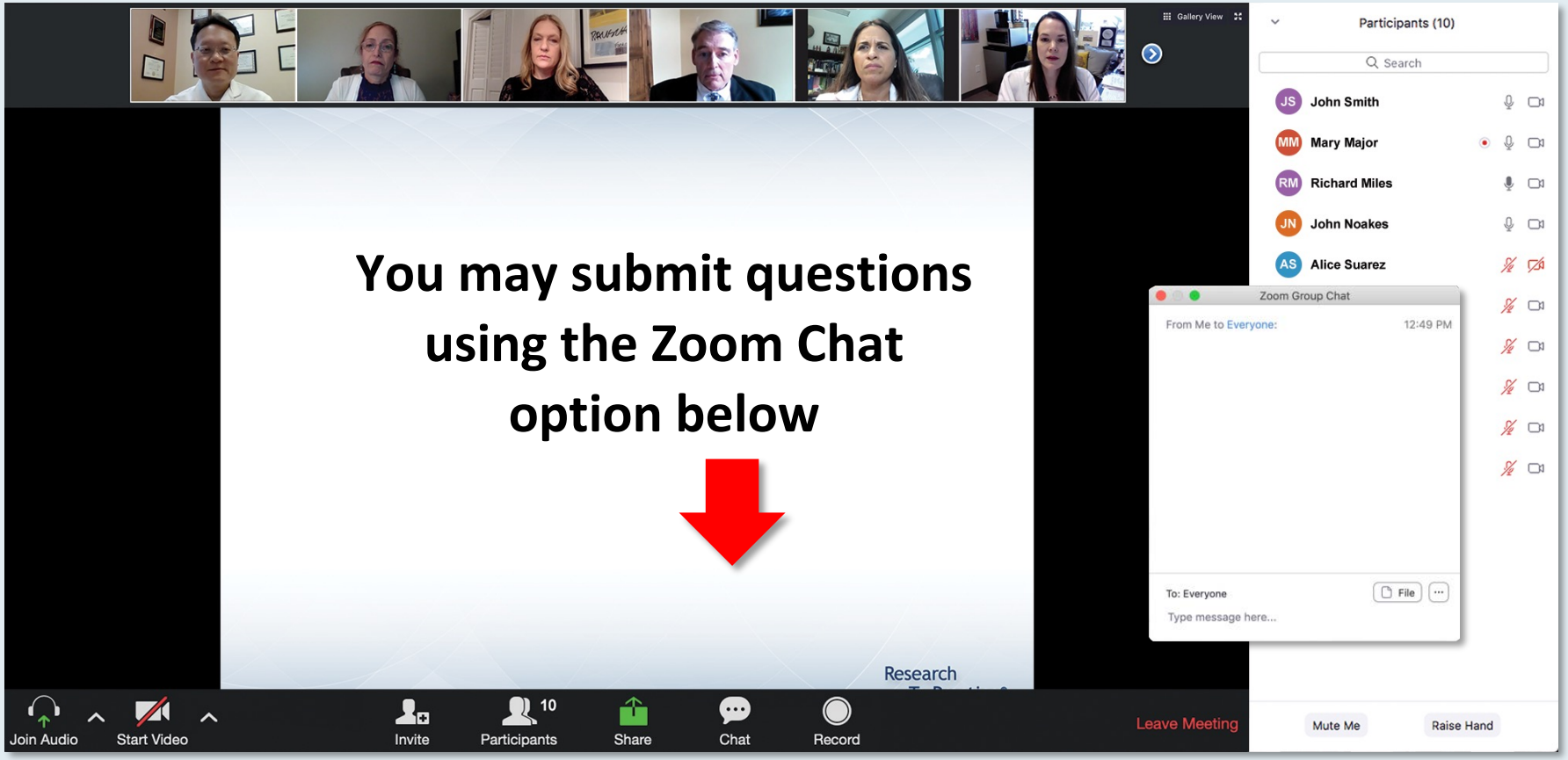

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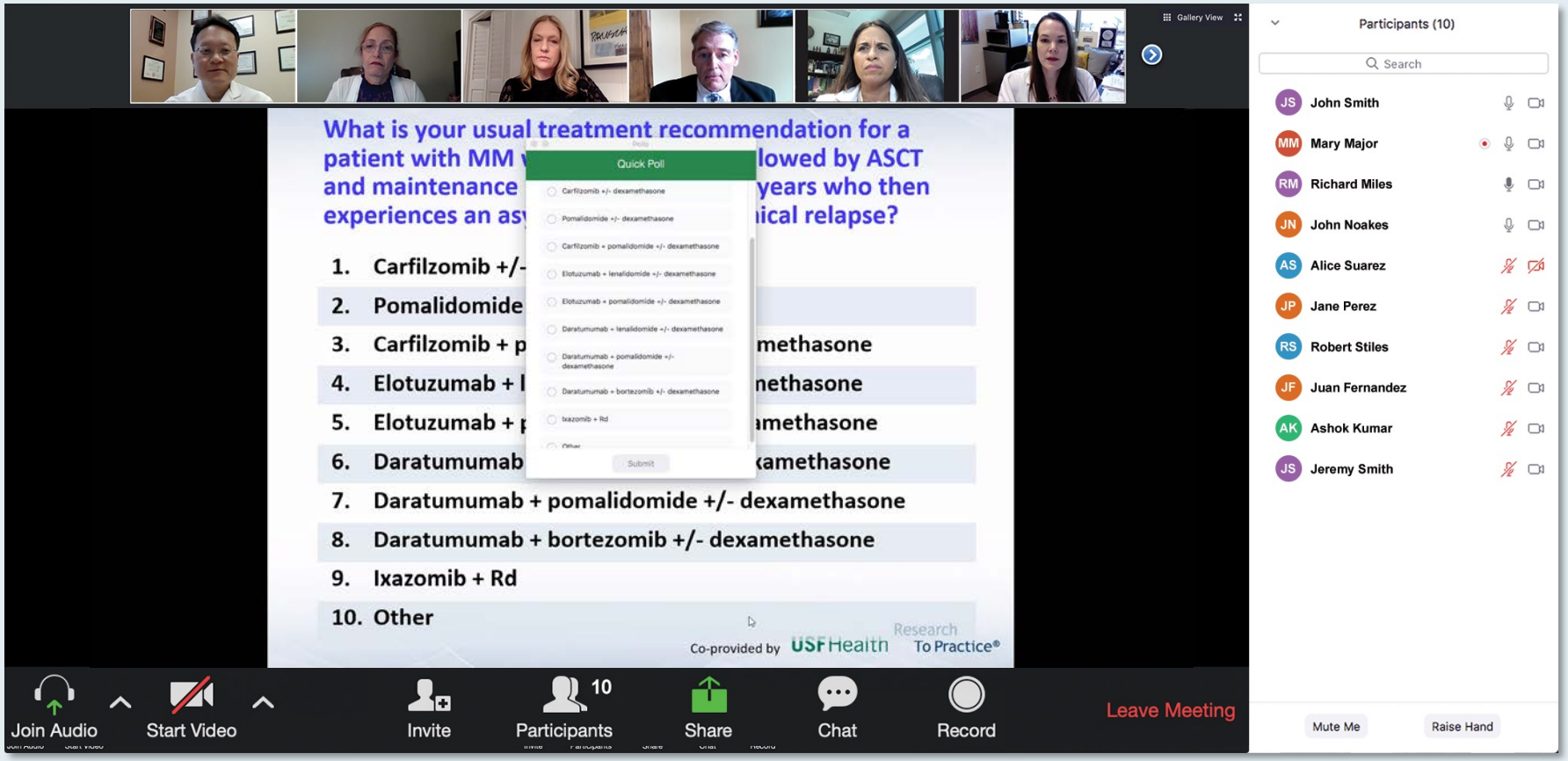

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Spencer Henick Bachow, MD
Hematologist/Oncologist at Lynn Cancer Institute
Affiliate Assistant Professor of Medicine
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Ranju Gupta, MD
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Co-Director, Cardio-Oncology Program
LVPG Hematology Oncology Associates
Lehigh Valley Health Network
Bethlehem, Pennsylvania

Maria Regina Flores, MD
Advent Health Orlando
Orlando Regional Hospital
HCA Oviedo Medical Center
UCF Lake Nona
Orlando, Florida

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

Zanubrutinib Demonstrates Superior ORR and Reduced Rates of Atrial Fibrillation or Flutter in Head-to-Head Trial Against Ibrutinib for CLL

Press Release: April 28, 2021

"Positive results from a planned interim analysis of the Phase 3 ALPINE trial comparing zanubrutinib against ibrutinib in adults with relapsed or refractory CLL or SLL.

Zanubrutinib met the primary endpoint of the trial, demonstrating non-inferiority in objective response rate (ORR) by both investigator and independent review committee (IRC) assessments ($p < 0.0001$). The interim analysis from this fully-enrolled, ongoing trial is based on 415 of 652 patients followed for a minimum of 12 months.

The trial also met a pre-specified secondary endpoint related to safety. Compared to ibrutinib, zanubrutinib demonstrated a statistically significant lower risk of atrial fibrillation or flutter…"

https://www.businesswire.com/news/home/20210428005360/en/BRUKINSA%C2%AE-Zanubrutinib-Demonstrates-Superior-Objective-Response-Rate-by-Investigator-Assessment-and-Reduced-Rates-of-Atrial-Fibrillation-or-Flutter-at-Interim-Analysis-in-Head-to-Head-Trial-Against-Ibrutinib-in-Chronic-Lymphocytic-Leukemia

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Meet The Professor with Dr Abramson

MODULE 1: Cases from Medical Oncology Practices

- Dr Rogers: An 83-year-old man with CLL faring well on acalabrutinib but wishes to discontinue (Parts 1 and 2)
- Dr Gupta: A 68-year-old man with CLL, cirrhosis and COVID-19 infection (Parts 1 and 2)
- Dr Bachow: A 67-year-old man with bulky CLL – del(17p), p53 mutation, IGHV unmutated
- Dr Flores: A 64-year-old man with CLL treated with obinutuzumab/venetoclax

MODULE 2: Journal Club with Dr Abramson

MODULE 3: Beyond the Guidelines

MODULE 4: Key Recent Data Sets

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Case Presentation – Dr Rogers: An 83-year-old man with CLL faring well on acalabrutinib but wishes to discontinue (Part 1)

Dr Kerry Rogers

- PMH: Severe but treated COPD
- 2017: Diagnosed with CLL after lymphocytosis noted → Observed
  - IGHV unmutated, del(13q)
- 2019: New fatigue, near syncope while golfing, 5 lbs weight loss, had to cut golfing to 9 holes
- Bone marrow biopsy to exclude ITP: 90% cellular with 90% CLL
- Patient wishes to avoid treatment visits and driving to the cancer center
- Acalabrutinib, with return to golfing 18 holes 3 days after starting treatment

Case Presentation – Dr Rogers: An 83-year-old man with CLL faring well on acalabrutinib but wishes to discontinue (Part 2)

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- Patient wishes to avoid treatment visits and driving to the cancer center
- Acalabrutinib, with return to golfing 18 holes 3 days after starting treatment
- ***2020 telehealth visit: Patient feels great with no new symptoms of CLL, except bruises more easily***
- ***Patient inquires about discontinuing treatment***

Questions

- ***If you have a patient who is motivated to stop the BTK inhibitor would you consider it and when?***
- ***What other treatments might you have offered to this patient other than acalabrutinib, ibrutinib and venetoclax/obinutuzumab?***

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Case Presentation – Dr Gupta: A 68-year-old man with CLL, cirrhosis and COVID-19 infection (Part 1)

Dr Ranju Gupta

- PMH: Cirrhosis secondary to hepatitis C, treated and in remission; Atrial fibrillation
- 2018: Diagnosed with standard-risk CLL → Observation
- Presently, worsening anemia, fatigue; WBC from 30K to 100K from June to November 2020
- Developed autoimmune hemolytic anemia (AIHA), which has improved, but now positive for COVID-19

Questions

- What would be the best treatment option in a patient with standard-risk CLL and cirrhosis who is also on anticoagulation? Any dose reductions in whatever treatment you would recommend, whether with venetoclax or the BTK inhibitors?

Case Presentation – Dr Gupta: A 68-year-old man with CLL, cirrhosis and COVID-19 infection (Part 2)

Dr Ranju Gupta

- PMH: Cirrhosis secondary to hepatitis C, treated and in remission; Atrial fibrillation
- 2018: Diagnosed with standard-risk CLL → Observation
- Presently, worsening anemia, fatigue; WBC from 30K to 100K from June to November 2020
- Developed autoimmune hemolytic anemia (AIHA), which has improved, but now positive for COVID-19

Questions

- ***Is he not clearing the COVID-19 infection due to his underlying CLL? Should I wait until he's cleared of the COVID-19 or should I start him on treatment now that it's already 3 weeks out and most of his symptoms have resolved?***
- ***And any concerns that even though his hepatitis C is treated that obinutuzumab will reactivate hepatitis C? Should I not give him obinutuzumab at all, and just manage him with venetoclax alone?***
- ***In what situations can we use or not use the COVID-19 vaccine in our patients with CLL?***

Case Presentation – Dr Bachow: A 67-year-old man with bulky CLL – del(17p), p53 mutation, IGHV unmutated

Dr Spencer Bachow

- History of trigeminal neuralgia
- Bulky neck, axillary and supraclavicular LAD; biopsy-proven CLL
- FISH peripheral blood: del(17p), p53 mutation, IGHV unmutated
- Acalabrutinib with resolution of LAD

Questions

- Does the presence of deletion 17p and/or a p53 mutation cause you to lean more towards using BTK inhibitor-based therapy or venetoclax-based therapy up front?
- For patients with CLL that require up-front therapy, and you plan to do acalabrutinib-based therapy, do you add the obinutuzumab, or do you tend to give the acalabrutinib as monotherapy?
- Now that we have multiple BTK inhibitors to use, both in the up-front setting and in the relapse setting, which one do you tend to choose?

Case Presentation – Dr Flores: A 64-year-old man with CLL treated with obinutuzumab/venetoclax

Dr Regina Flores

- PMH: Hypogammaglobulinemia, skin cancers
- CLL IGHV unmutated, no actionable mutations
- Observation until unexplained weight loss, worsening anemia and thrombocytopenia
- Obinutuzumab/venetoclax
  - Dose reduced venetoclax due to neutropenia, thrombocytopenia, then discontinued at 6 months
- Currently off treatment x 5 months with resolution of LAD and feeling great

Questions

- If he needs treatment again in the future, what regimen would you choose? Let's say he has a long disease-free interval, would you re-treat him with the same regimen? Would you choose something else?

Meet The Professor with Dr Abramson

MODULE 1: Cases from General Medical Oncology Practices

MODULE 2: Journal Club with Dr Abramson

- Management of BTK inhibitor-associated adverse events: Expert recommendations
- Alliance A041202: Toxicity burden in older patients with CLL receiving bendamustine with rituximab or ibrutinib
- MRD-driven time-limited therapy with zanubrutinib, obinutuzumab and venetoclax
- A virtual resiliency program for lymphoma survivors: Helping survivors cope with post-treatment challenges

MODULE 3: Beyond the Guidelines

MODULE 4: Key Recent Data Sets

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Management of BTK Inhibitor Associated Adverse Events: Current Practice Trends Among Healthcare Providers and Concordance with Expert Recommendations

Rosenthal K et al.

ASH 2020;Abstract 2501.

Toxicity Burden in Older Patients with Chronic Lymphocytic Leukemia (CLL) Receiving Bendamustine with Rituximab (BR) or Ibrutinib (IB) Regimens: Alliance A041202

Ruppert AS et al.
ASCO 2020;Abstract e20004.

American Society *of* Hematology

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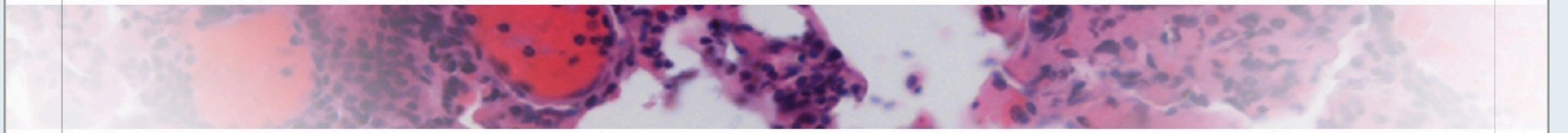


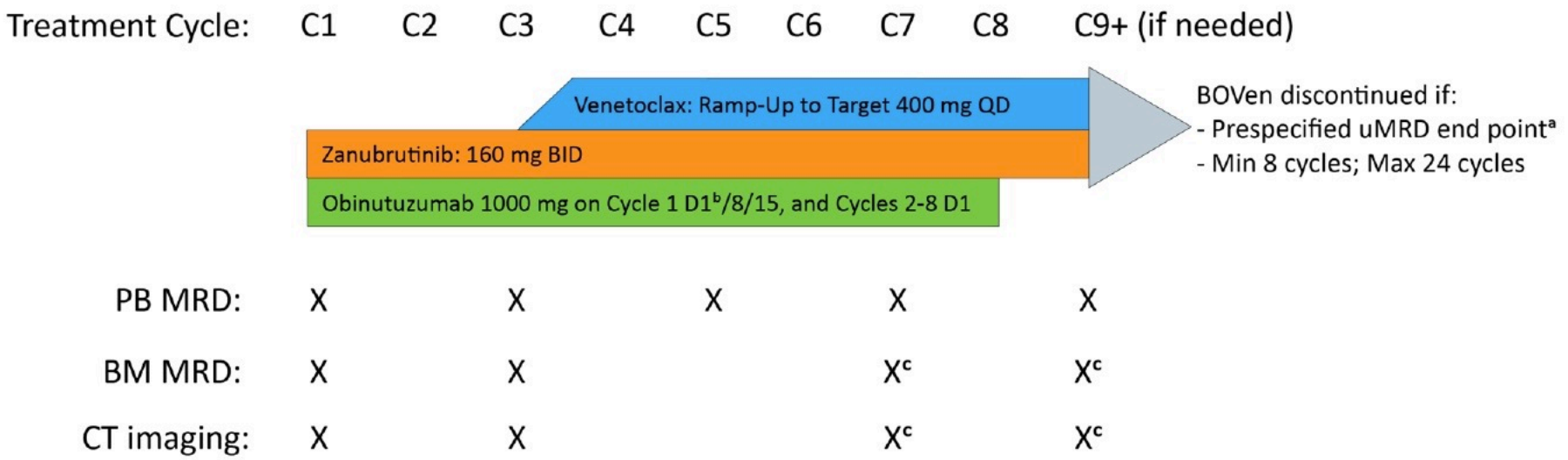
MRD-driven time-limited therapy with zanubrutinib, obinutuzumab, and venetoclax (BOVen) in previously untreated chronic lymphocytic leukemia

Jacob D. Soumerai[1], Anthony R. Mato[2], Jason Carter[2], Ahmet Dogan[2], Ephraim P Hochberg[1], Jeffrey A Barnes[1], Audrey Hamilton[2], Jeremy S. Abramson[1], Connie L. Batlevi[2], Erel Joffe[2], Matthew J. Matasar[2], Ariela Noy[2], Colette Owens[2], M. Lia Palomba[2], Tak Takvorian[1], Venkatraman Seshan[2], Kelsey Flaherty[2], Lauren Ramos[1], Morgan Choma[2], Chaya Friedman[2], Puja Chadha[2], Elizabeth Simkins[1], Daneal Portman[1], Neena Majahan[2], Rosalba Martignetti[1], Joanna Mi[2], Krista J Scorsune[1], Julia M. Lynch[1], Brianne McGree[1], Stephanie Y Hughes[2], Clare Grieve[2] , Lindsey E. Roeker[2], Omar Abdel-Wahab[2], and **Andrew D. Zelenetz**[2]

[1]Massachusetts General Hospital, Boston, MA; [2]Memorial-Sloan Kettering Cancer Center, New York, NY

ASH 2020;Abstract 1307.

BOVen treatment schema



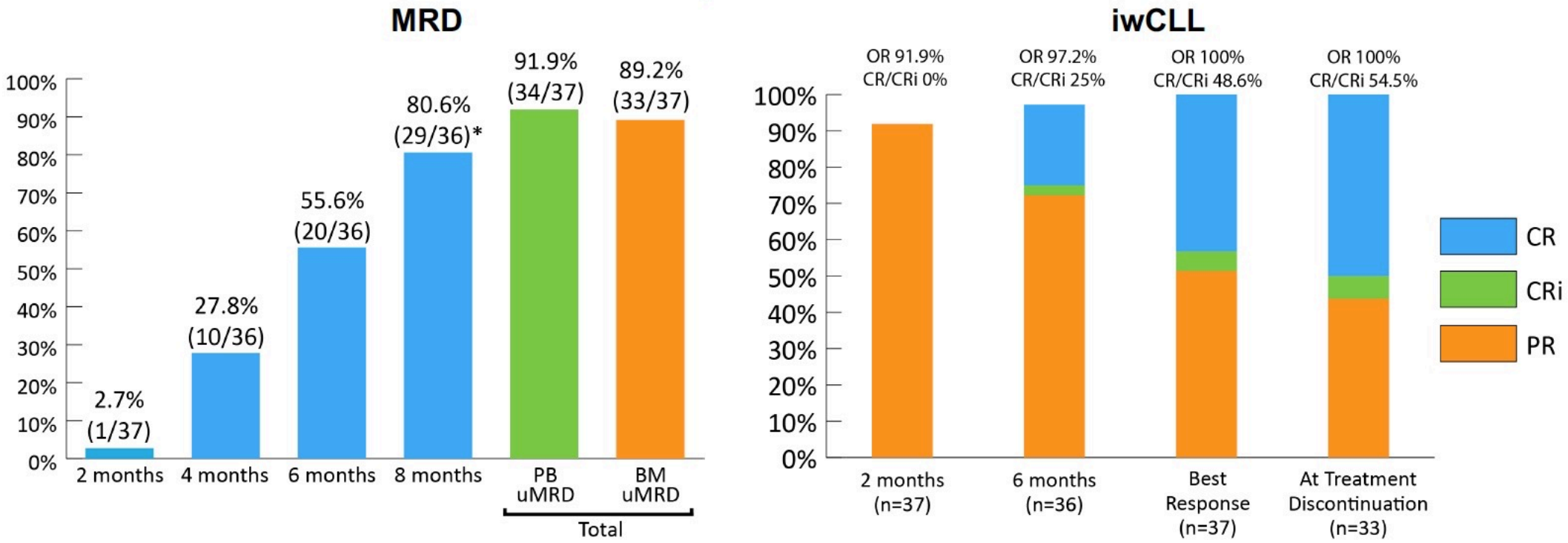
a- Once peripheral blood (PB) uMRD is determined and confirmed in bone marrow (BM), patients complete 2 additional cycles followed by confirmatory MRD peripheral blood testing; if PB uMRD x 2 and BM uMRD x 1, therapy is discontinued.

b- Obinutuzumab split over days 1-2 of cycle 1 if ALC >25,000.

c- BM biopsy obtained at Screening and C3D1; thereafter BM is only obtained if PB-uMRD.
CT imaging obtained at Screening, C3D1, C7D1, EOT, then every 6 months during post-treatment surveillance.

Soumerai JD et al. ASH 2020;Abstract 1307.

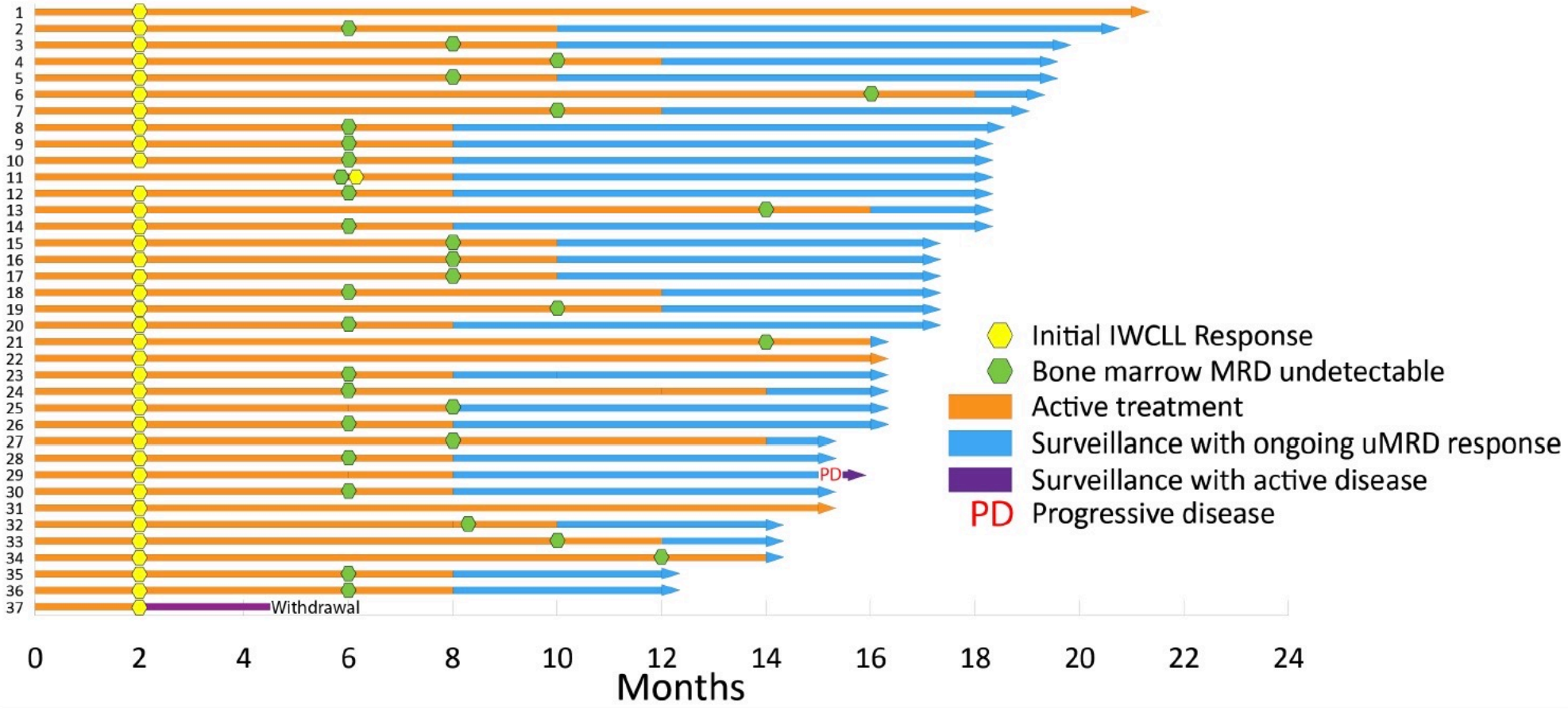
MRD and iwCLL response



- 89.2% (33/37) have achieved uMRD in peripheral blood and bone marrow and have stopped therapy after a median of 10 mo (8 mo of triplet)

Soumerai JD et al. ASH 2020;Abstract 1307.

Patient-level outcomes



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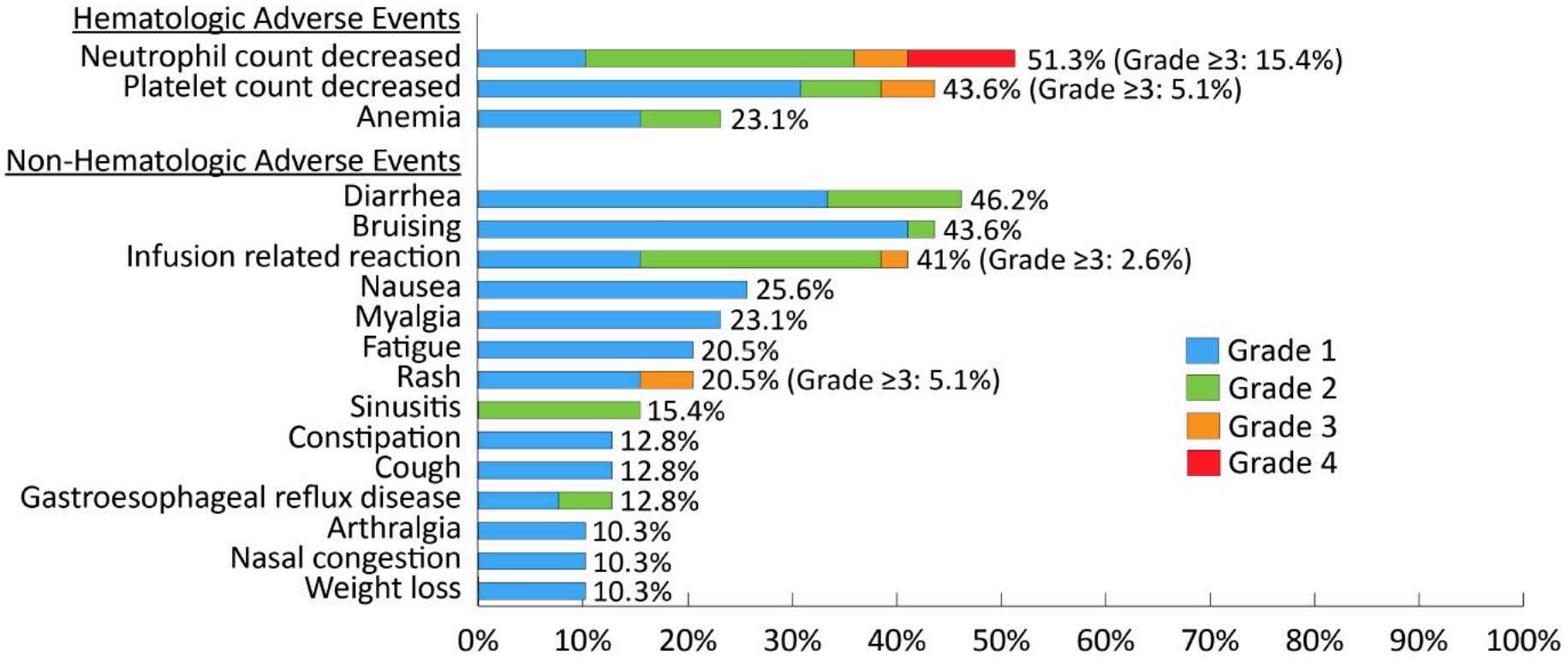
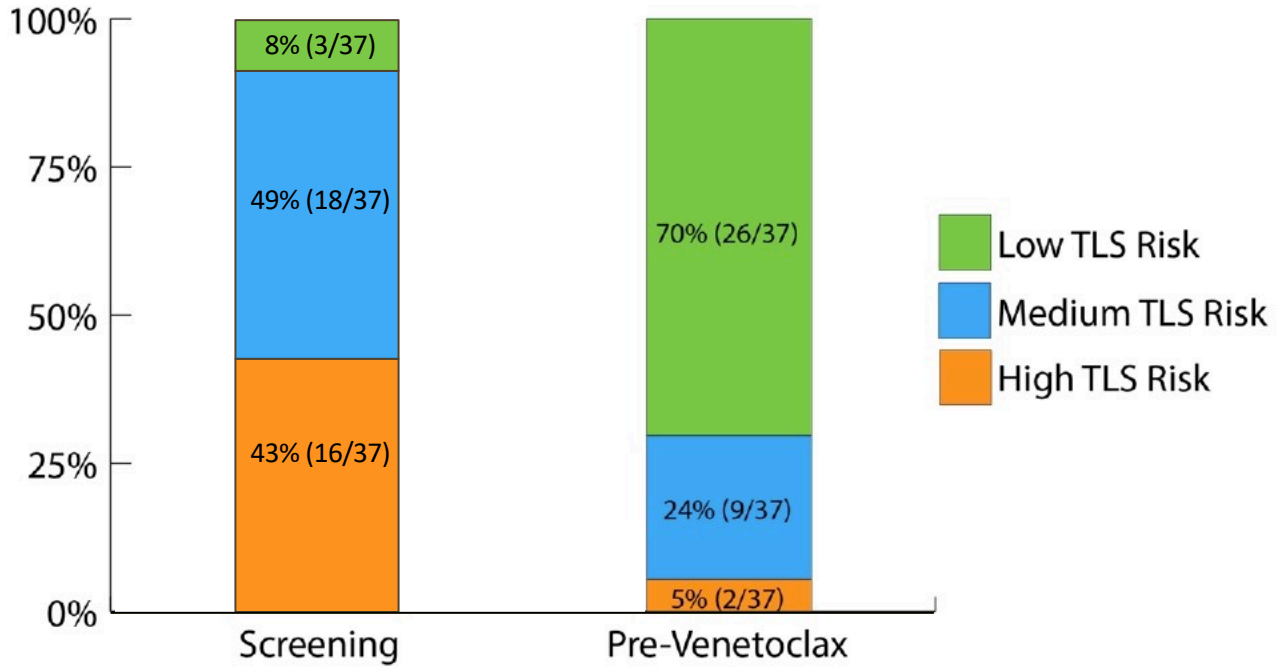
Treatment emergent adverse events



- One grade 5 ICH on cycle 1 day after initiating intravenous heparin for pulmonary emboli
- Atrial fibrillation occurred in 1 patient who had a history of prior paroxysmal atrial fibrillation

Soumerai JD et al. ASH 2020;Abstract 1307.

Reduction in TLS risk prior to venetoclax



Four patients initiated venetoclax ramp-up inpatient
No patients had laboratory or clinical TLS (Howard)

Soumerai JD et al. ASH 2020;Abstract 1307.

Detection of MRD by immunosequencing

	Detection by Flow Cytometry		Detection by Immunosequencing		
Population	**Timepoint**	**Compartment**	**$<10^{-4}$**	**$<10^{-5}$**	**$<10^{-6}$**
PB uMRD (n=34)	PB uMRD (Best)	Peripheral blood	100% (34/34)	97% (33/34)	17.2% (5/29)
BM uMRD (n=33)	Initial BM uMRD	Bone marrow	81% (25/31)	39% (12/31)	3.4% (1/29)
		Peripheral blood	97% (32/33)	58% (19/33)	3.8% (1/26)
	Confirmatory PB uMRD	Peripheral blood	100% (30/30)	87% (26/30)	5.6% (1/18)

- Among 34 pts who achieved uMRD in peripheral blood by flow (cutoff, $<10^{-4}$), 97% achieved uMRD by immunosequencing at a cutoff of $<10^{-5}$
- Among pts who reached uMRD in BM by flow (10^{-4}) and stopped therapy: MRD levels measured by immunosequencing continued to decline in final 2 cycles

Soumerai JD et al. ASH 2020;Abstract 1307.

ΔMRD400 may identify favorable patients

ΔMRD400 at C5D1 (after 2 mo triplet)	BM uMRD ≤8 mo	DC therapy ≤12 mo
≥400-fold reduction in 21/35 (60%)	100% (21/21)	95% (20/21)
<400-fold reduction in 14/35 (40%)	21% (3/14)	50% (7/14)

- Patients separated into two groups with discrete MRD kinetics
- *Post hoc* analysis to determine if **Δ**MRD measured by immunosequencing at cycle 5 day 1 (after 2 cycles of triplet) predicted early uMRD in bone marrow
- ≥400-fold reduction (2.6-log, **Δ**MRD400) was selected using the Youden Index, and was highly predictive of uMRD within six cycles of starting the BOVen triplet
  - Sensitivity of 88%, Specificity 100%, PPV 100%, NPV 79%

Soumerai JD et al. ASH 2020;Abstract 1307.

A virtual resiliency program for lymphoma survivors: helping survivors cope with post-treatment challenges

Giselle K. Perez[a,b], Emily A. Walsh[c], Kit Quain[d], Jeremy S. Abramson[a#] and Elyse R. Park[a,b#]

[a]Harvard Medical School, Massachusetts General Hospital, Boston, MA, USA; [b]Mongan Institute Health Policy Research Center, Massachusetts General Hospital, Boston, MA, USA; [c]Department of Psychology, University of Miami, Coral Gables, FL, USA; [d]Sidney Kimmel Medical College, Thomas Jefferson University, Philadelphia, PA, USA

Hematol Oncol 2021;39(2):185-95.

RTP RESEARCH TO PRACTICE

Meet The Professor with Dr Abramson

MODULE 1: Cases from Dr Allan

MODULE 2: Journal Club with Dr Abramson

MODULE 3: Beyond the Guidelines

MODULE 4: Key Recent Data Sets

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 (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

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?

 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

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 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

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

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RESEARCH
TO PRACTICE

The NEW ENGLAND JOURNAL of MEDICINE

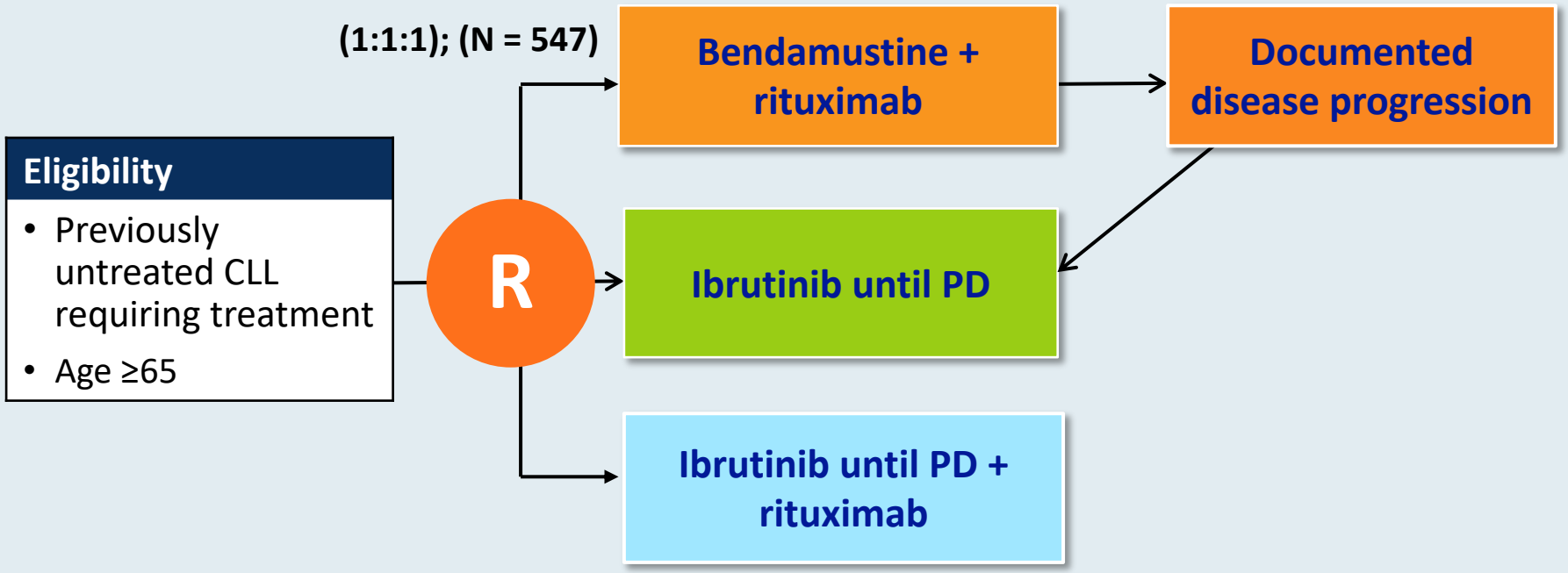
ORIGINAL ARTICLE

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.

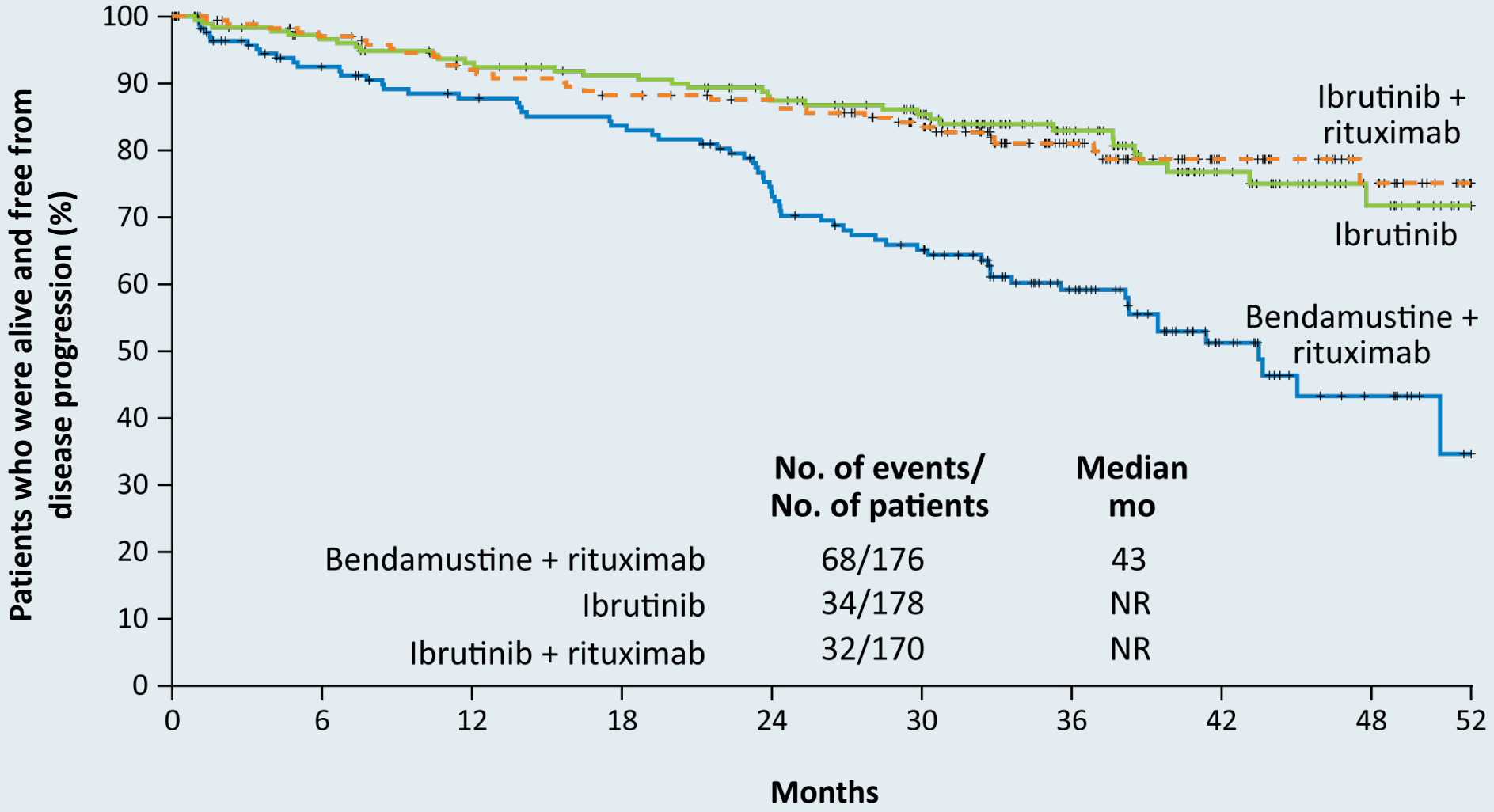
Phase III Alliance A041202 Study Design



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

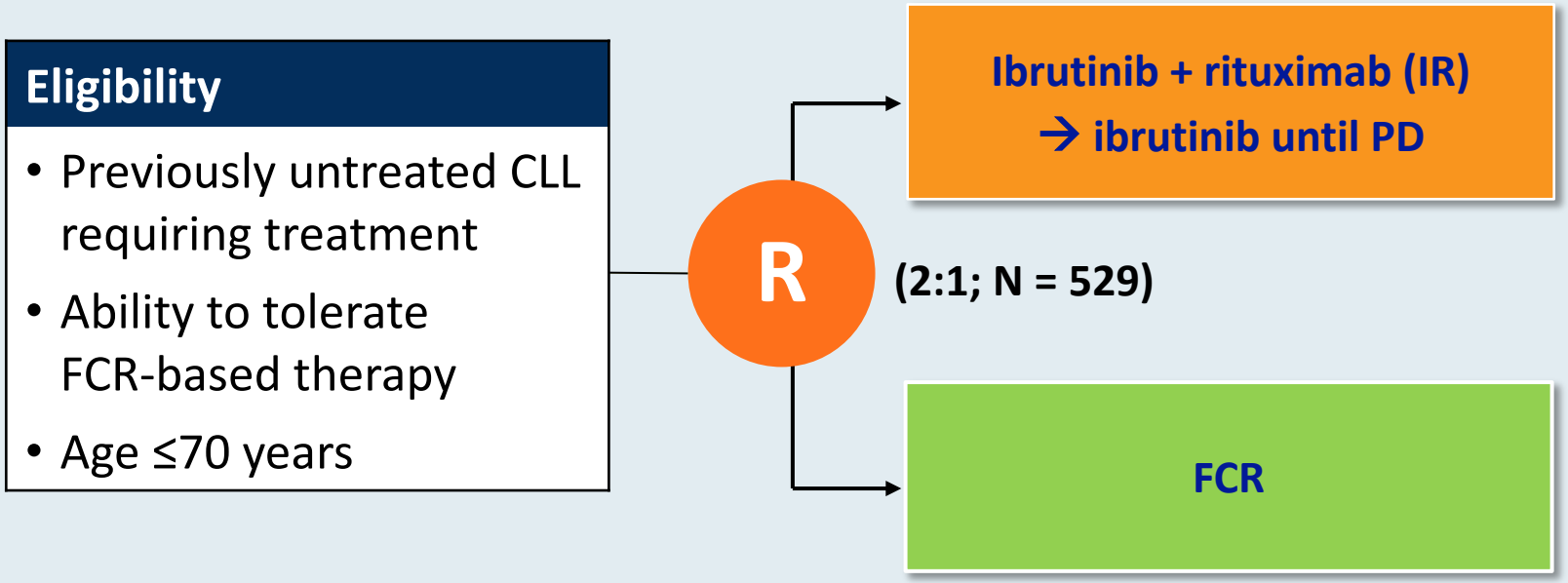
Woyach JA et al. *N Engl J Med* 2018;379(26):2517-28.

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.

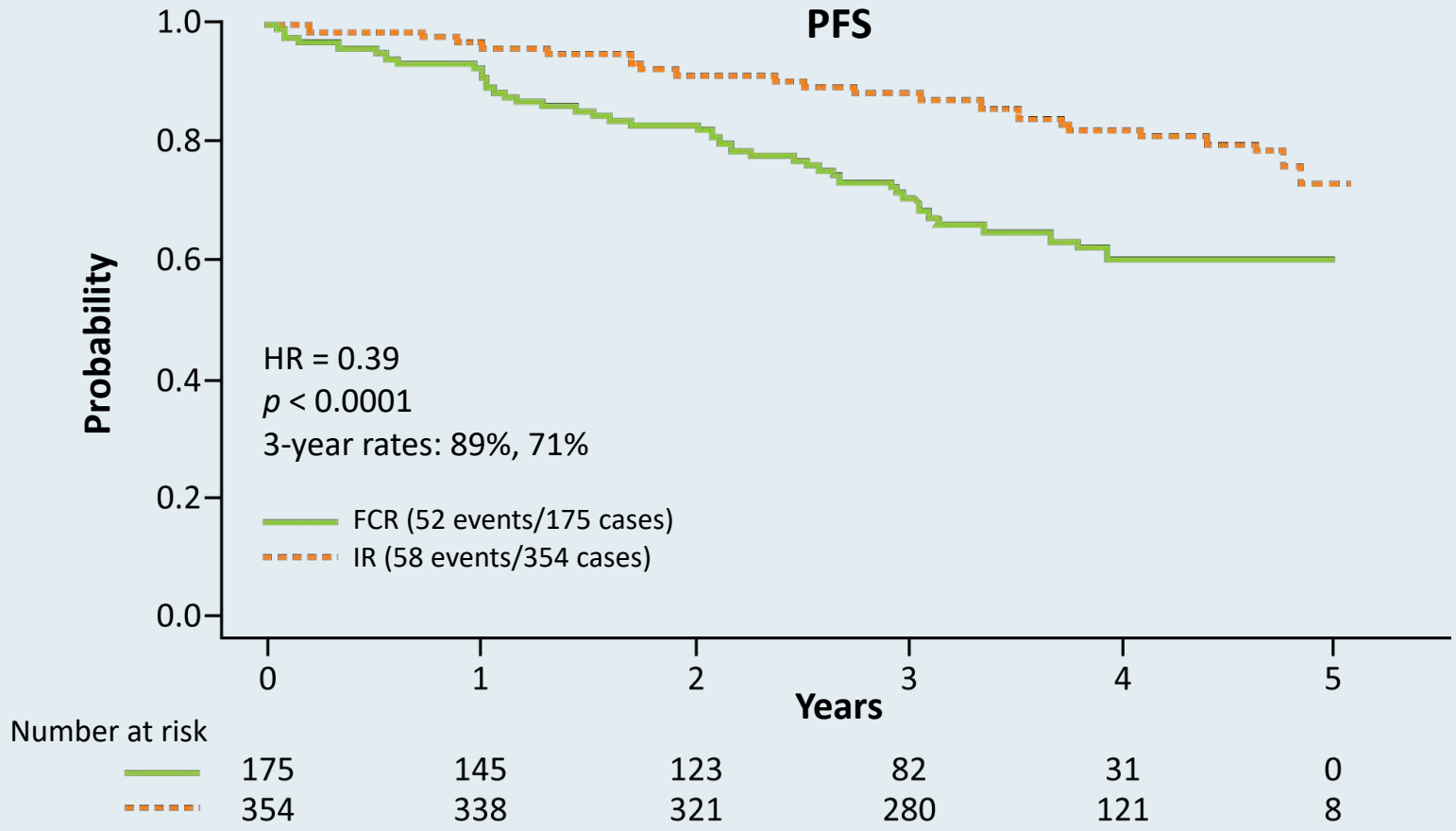
Phase III ECOG-ACRIN E1912 Study Design



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

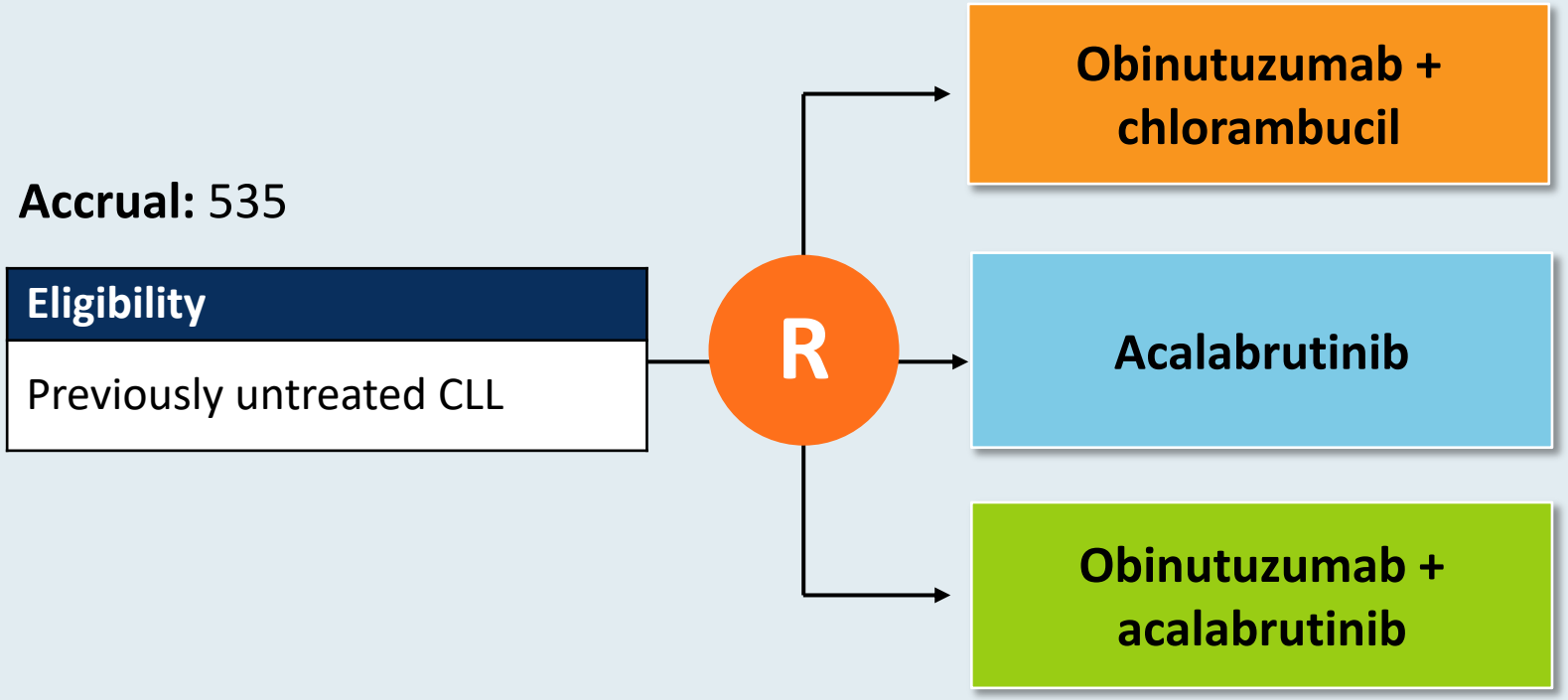
Articles

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.

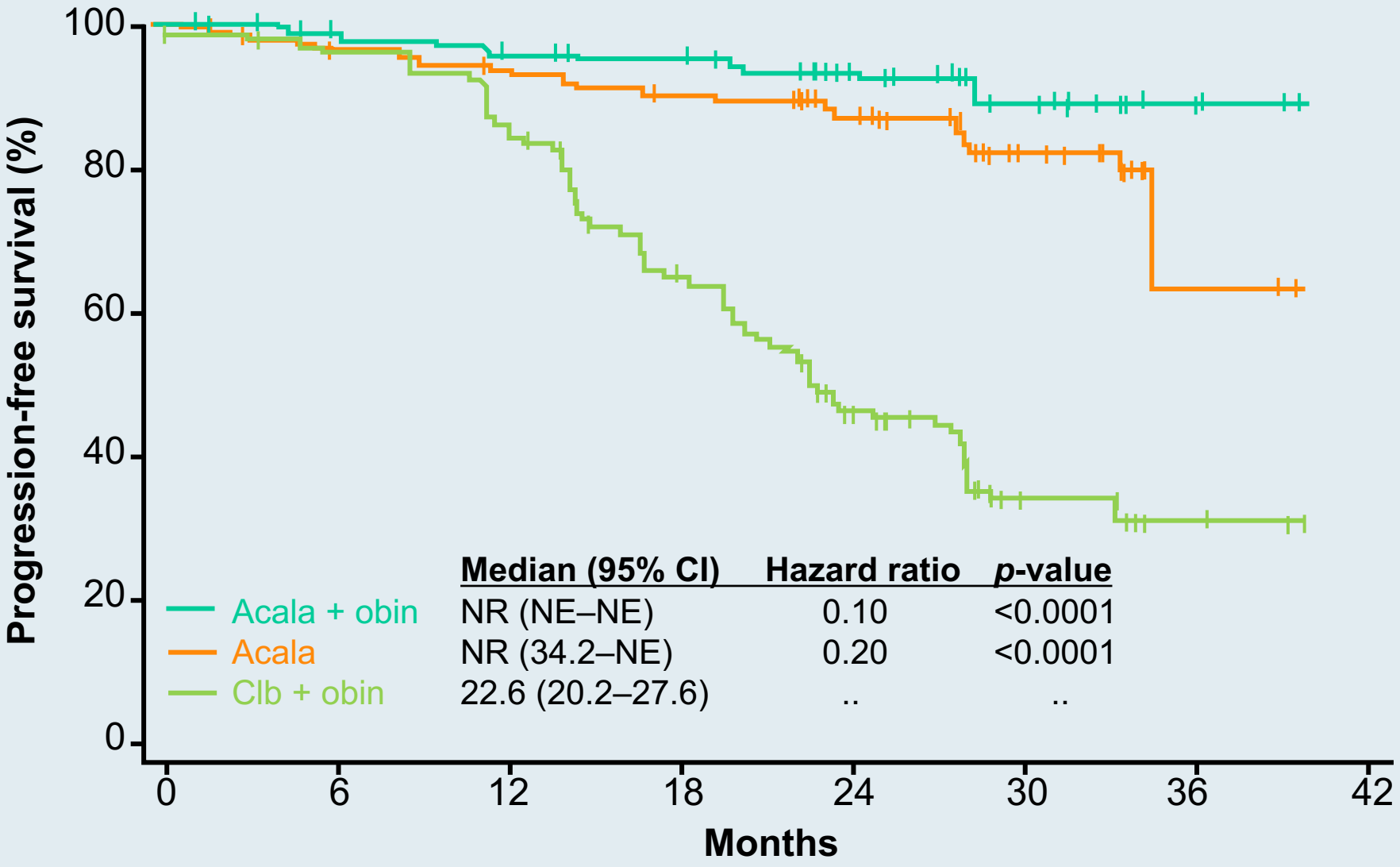
ELEVATE-TN Phase III Trial Schema



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.

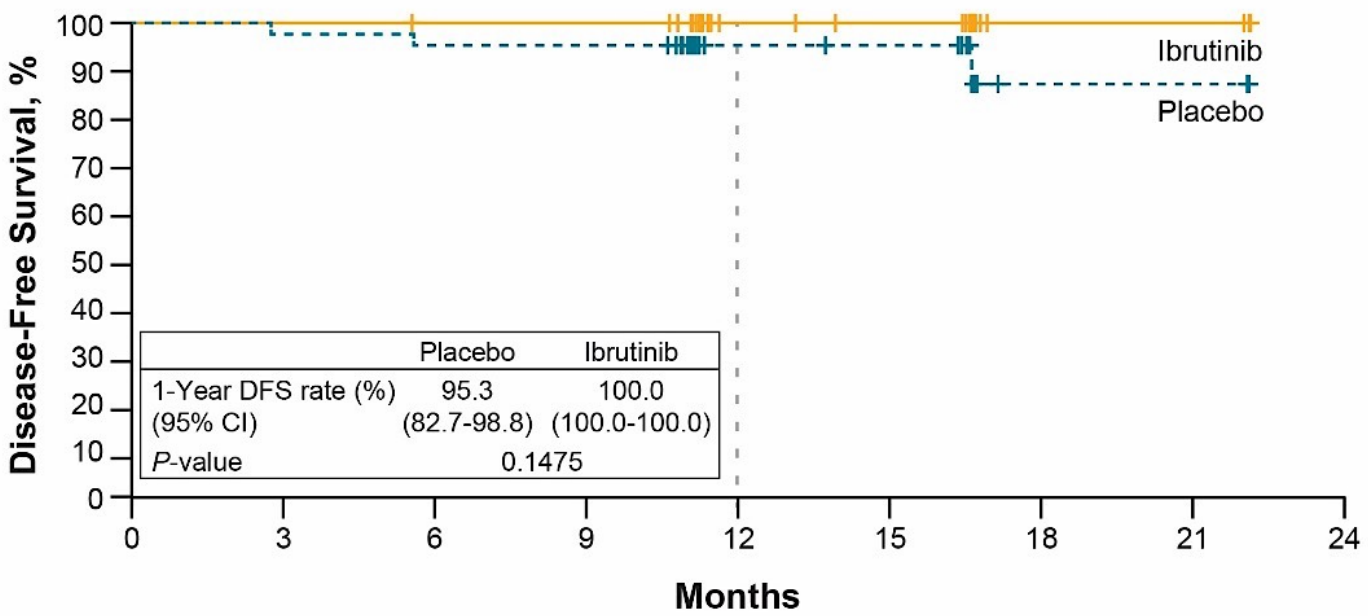
Ibrutinib (Ibr) plus Venetoclax (Ven) for First-Line Treatment of Chronic Lymphocytic Leukemia (CLL)/Small Lymphocytic Lymphoma (SLL): 1-Year Disease-Free Survival (DFS) Results from the MRD Cohort of the Phase 2 CAPTIVATE Study Trial

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:

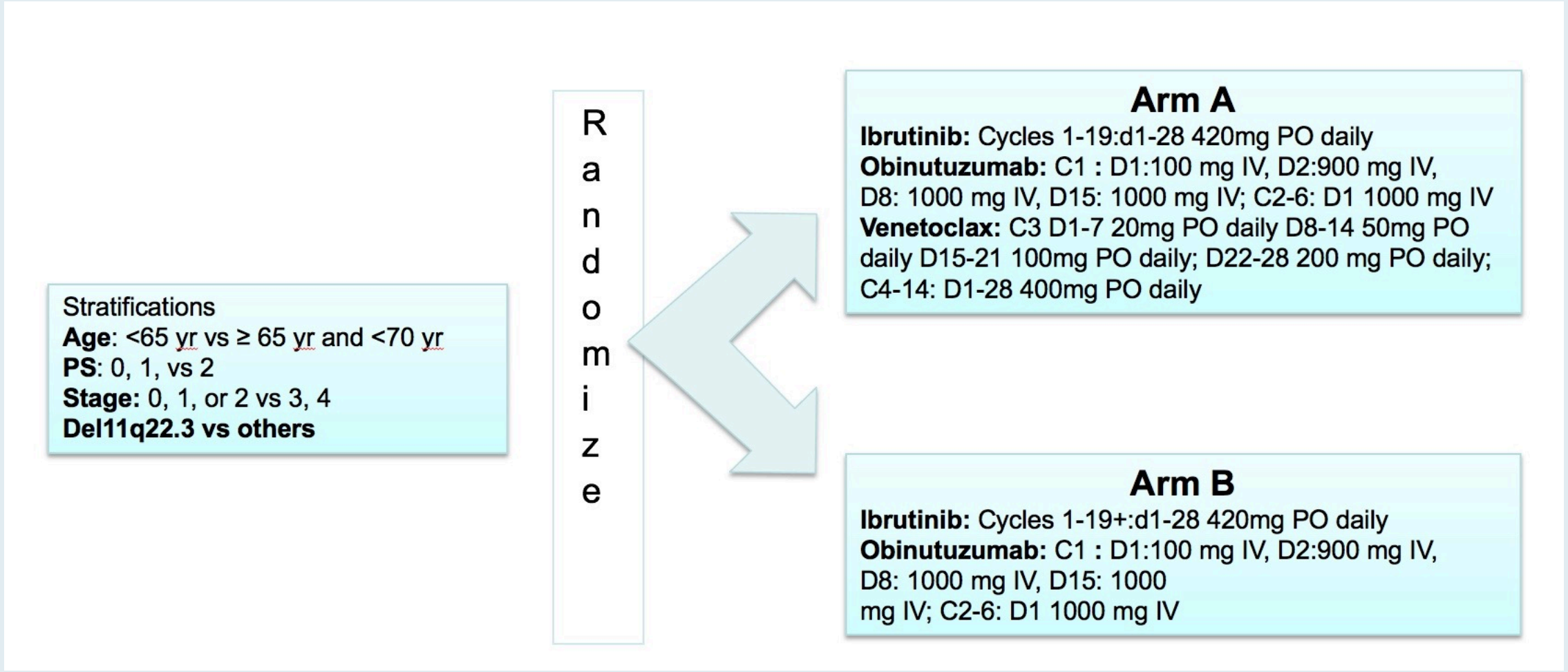
- 95.2% ibrutinib
- 96.7% ibr/ven

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

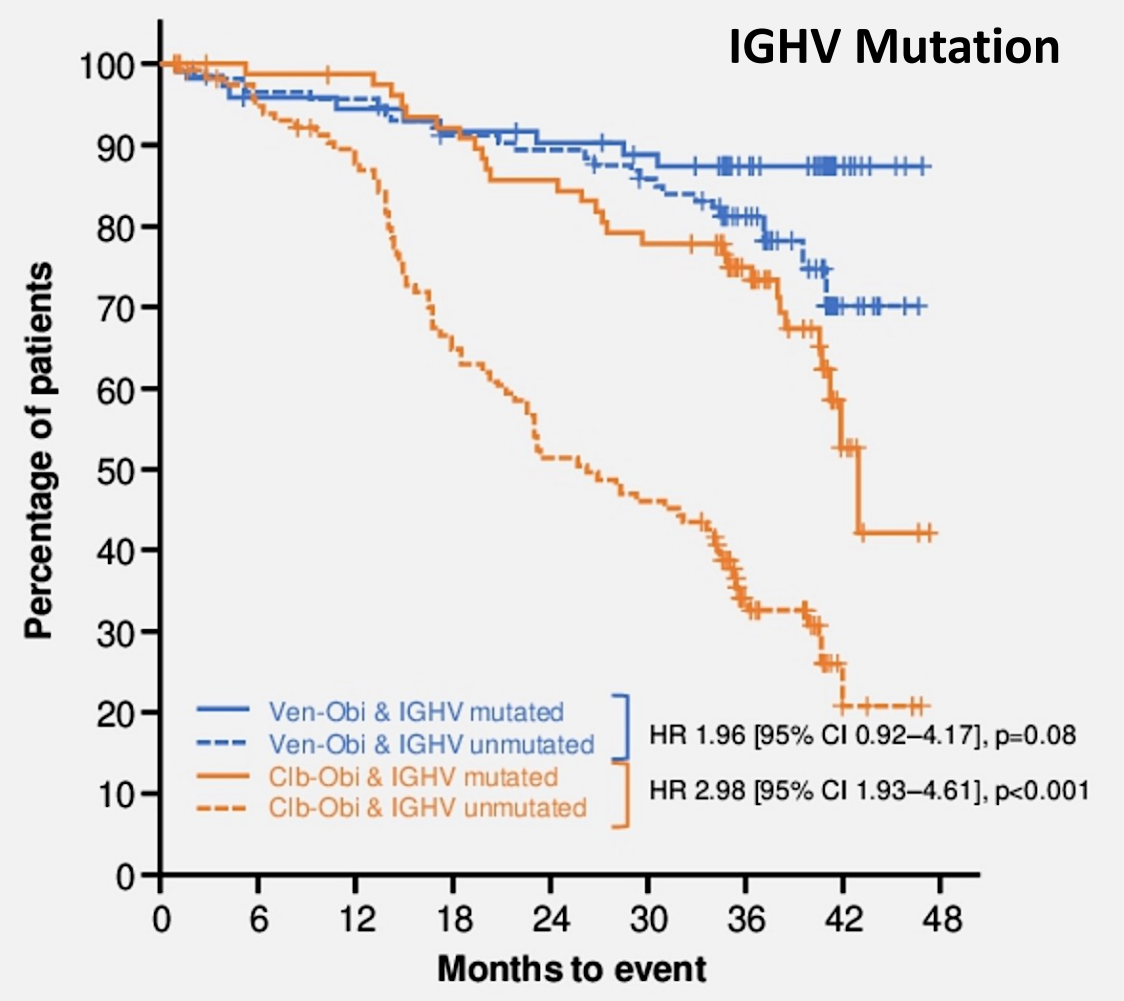
Articles

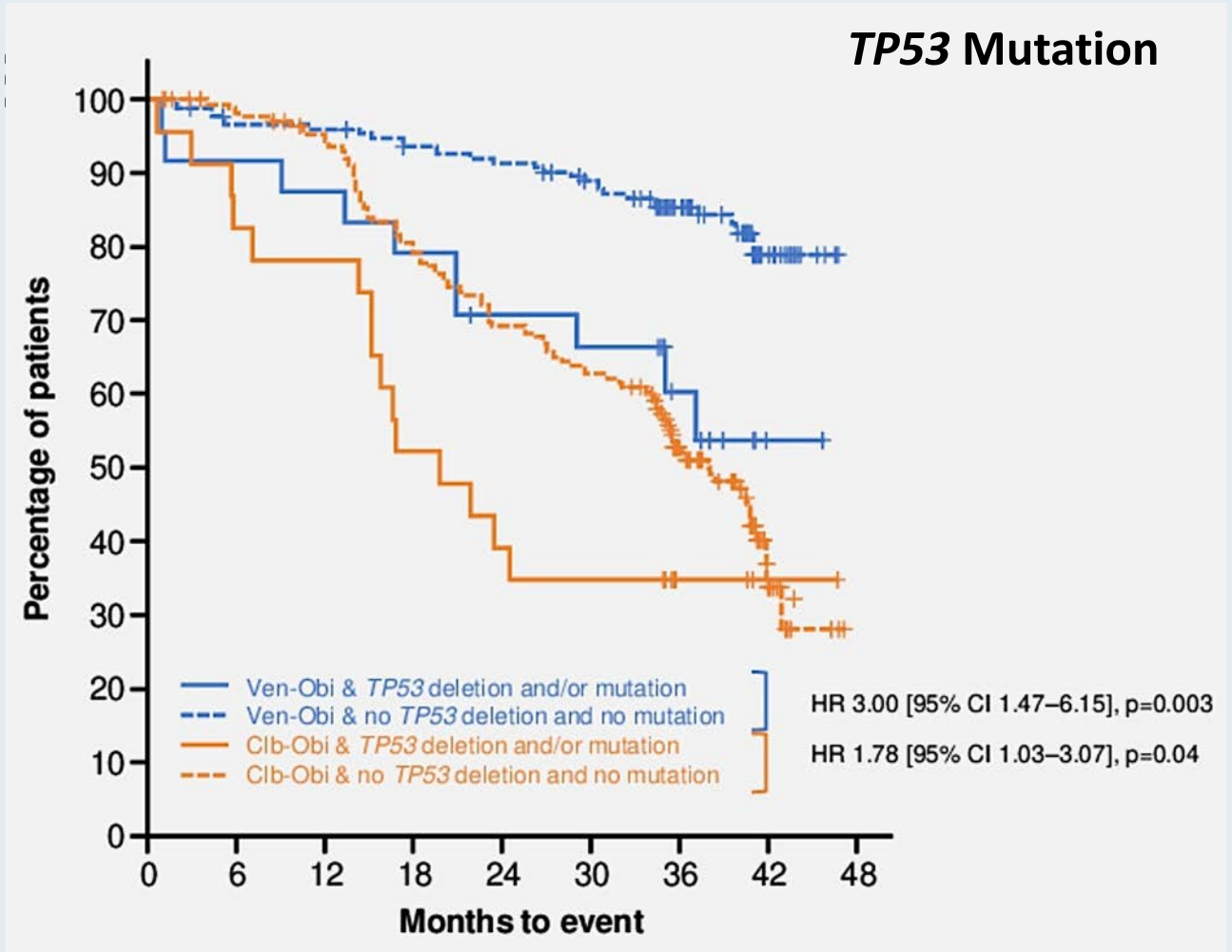
Venetoclax plus obinutuzumab versus chlorambucil plus obinutuzumab for previously untreated chronic lymphocytic leukaemia (CLL14): follow-up results from a multicentre, open-label, randomised, phase 3 trial

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

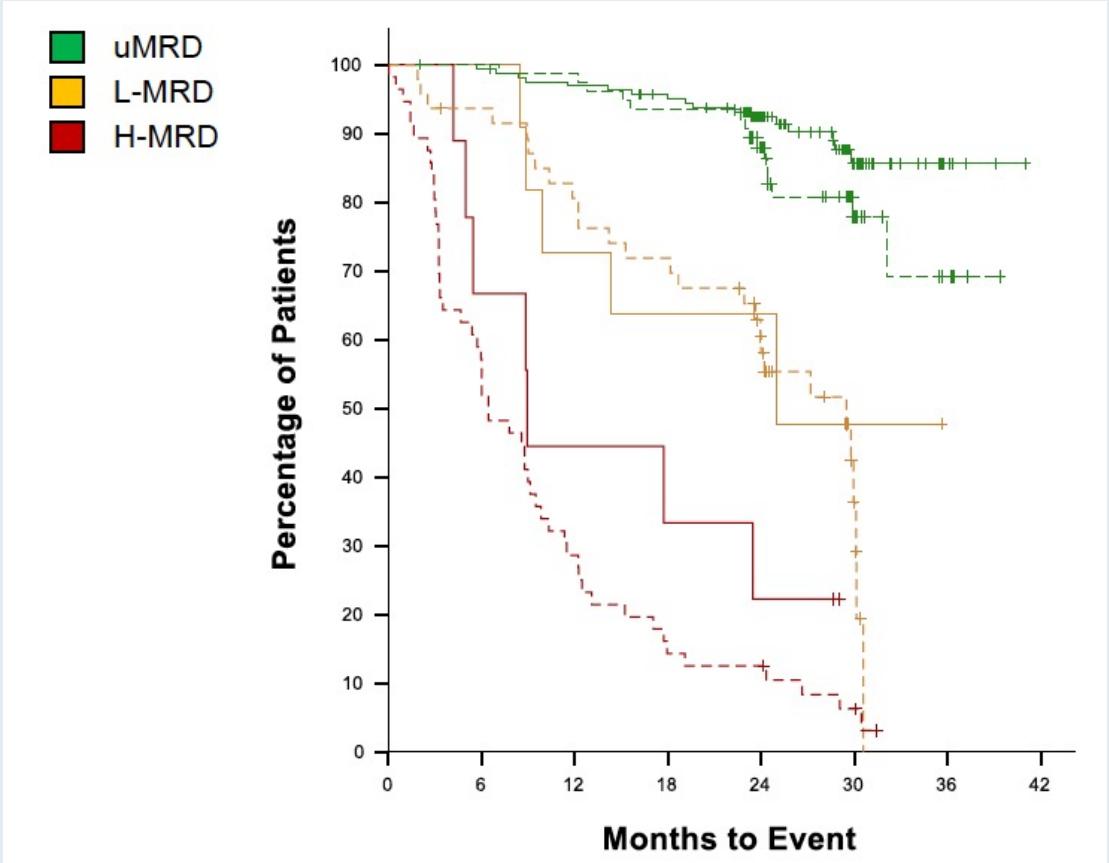




Al-Sawaf O et al. *Lancet Oncol* 2020;21(9):1188-200.

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

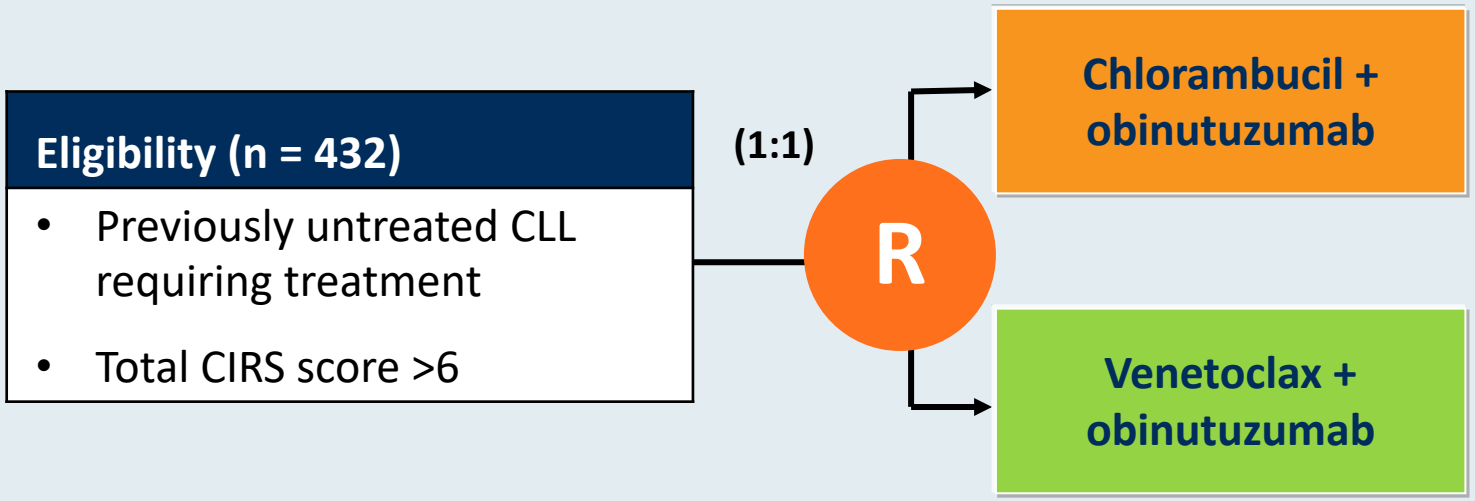
Al-Sawaf O et al. *Lancet Oncol* 2020;21(9):1188-200.

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

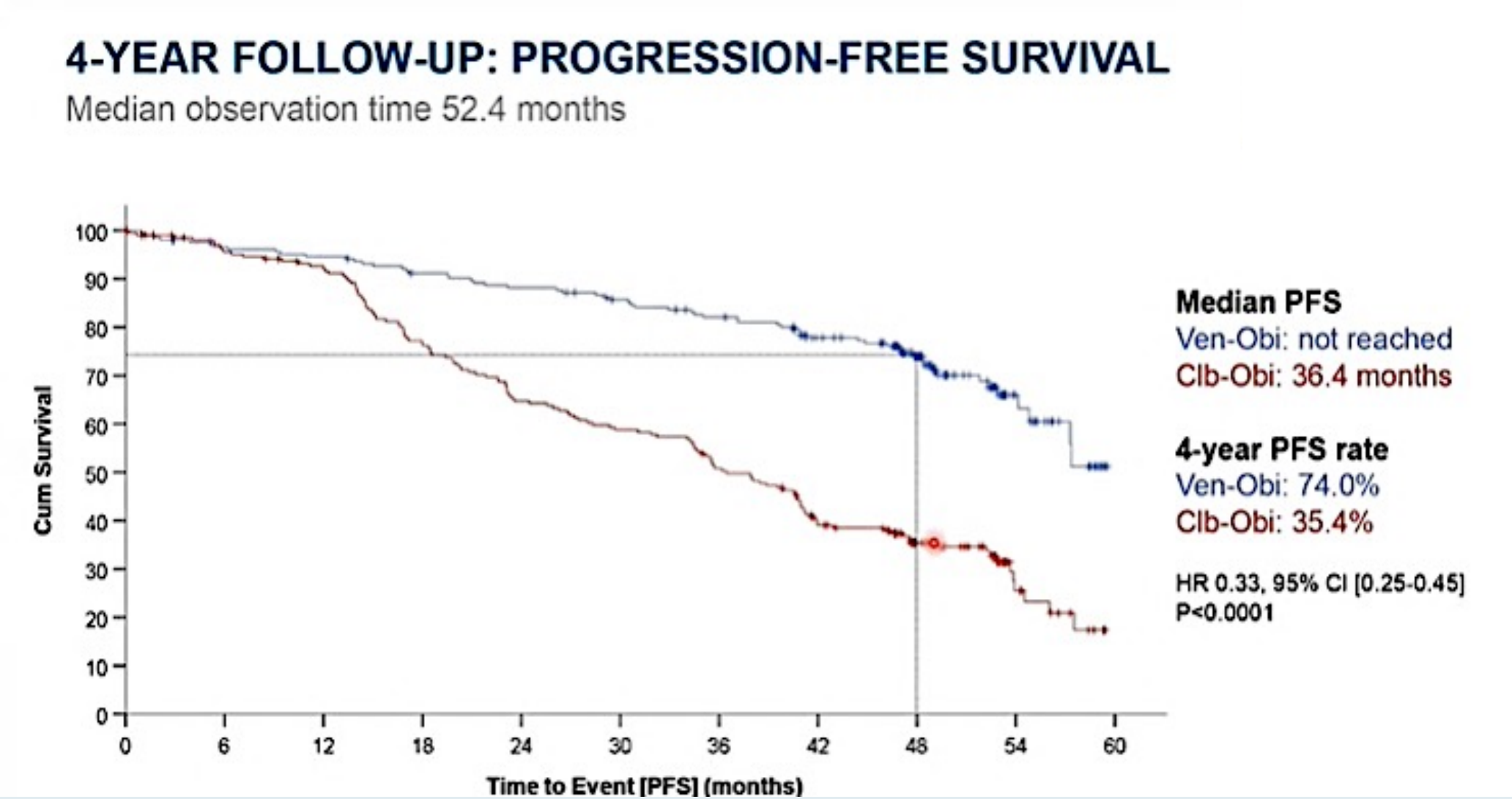


Primary endpoint: Progression-free survival

- 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

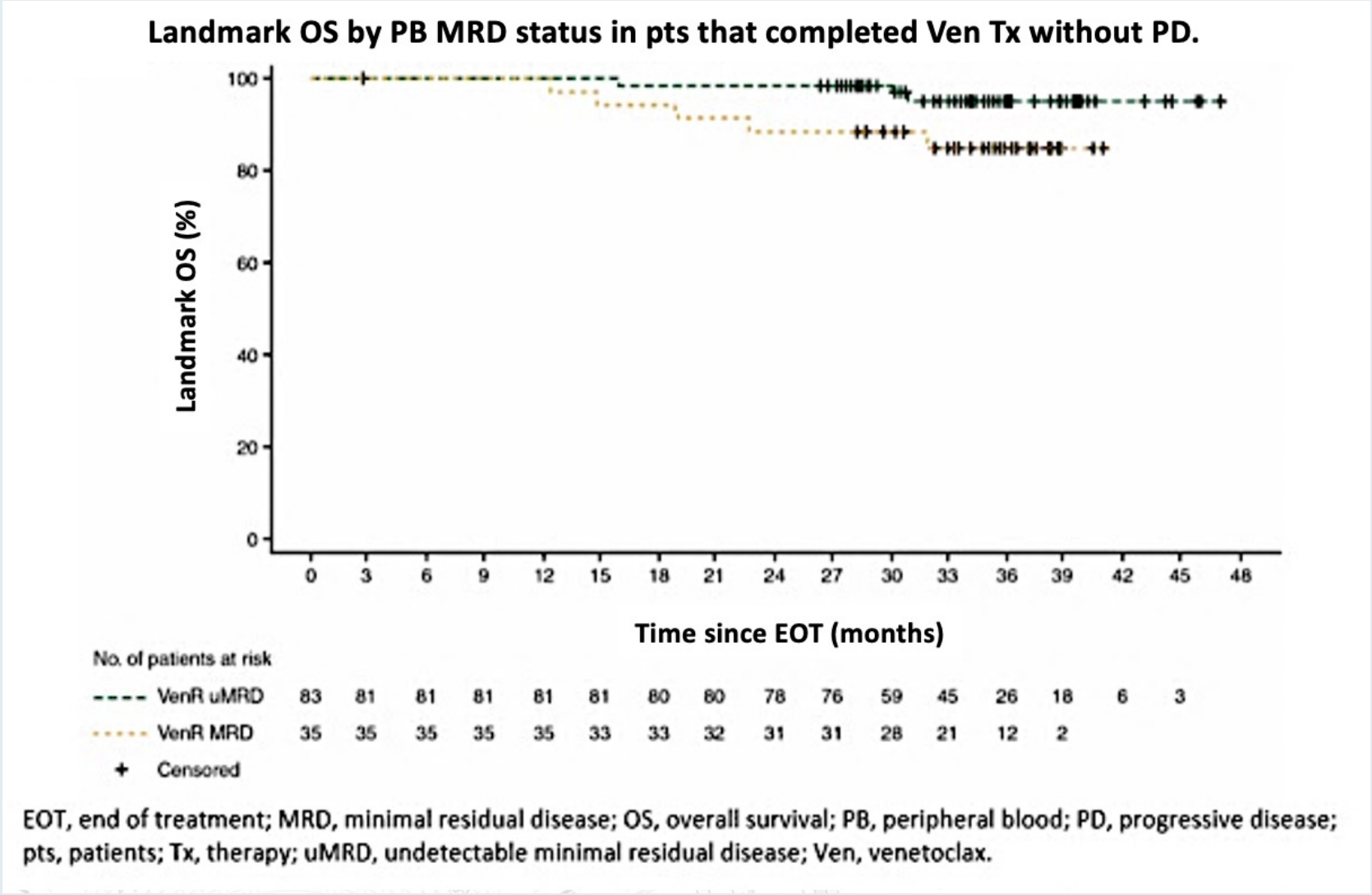
Management of Relapsed/Refractory CLL

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

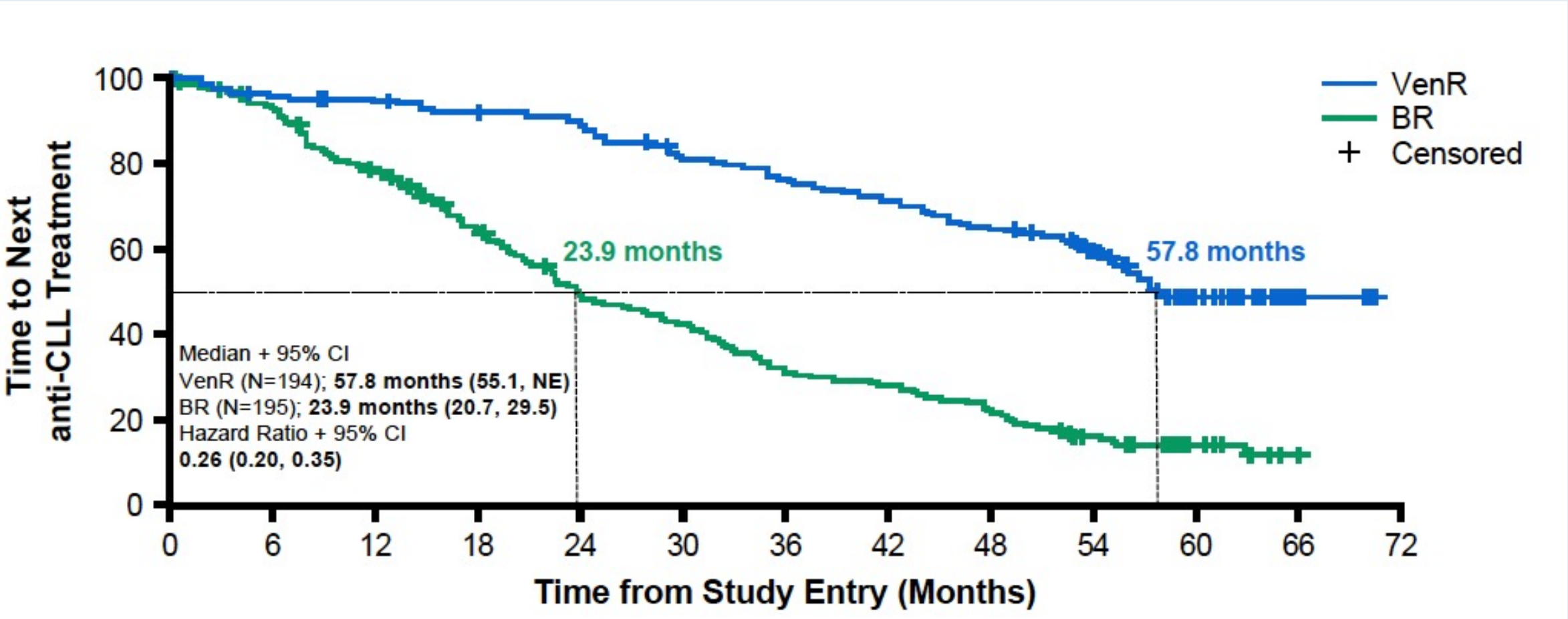
Kater AP et al. ASH 2020;Abstract 125.

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.

RTP RESEARCH TO PRACTICE

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

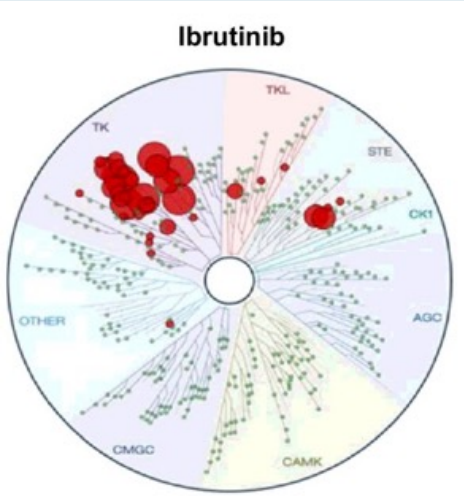
- **ORR:** High ORR of 72.2% for Ven re-treatment
- **Heavily pretreated population:** Cohort studied had median 2 prior therapies, majority R/R (88%), BTKi exposed (60%)
- **Safety:** TLS rare event and majority were able to tolerate 400 mg daily
- **Improved outcomes with time:** Patients with CR to 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.

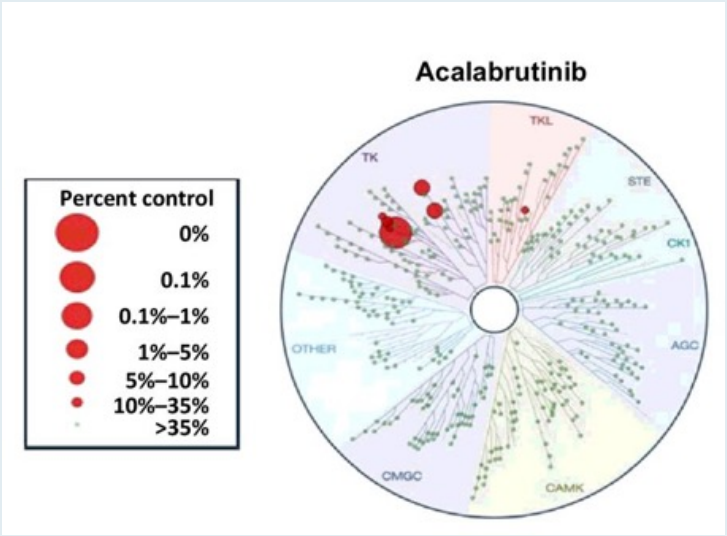
Overview of BTK Inhibitors in CLL

Irreversible

Ibrutinib



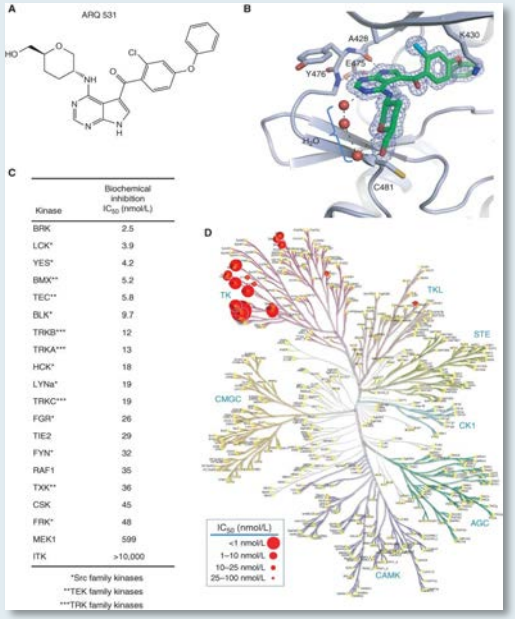
Acalabrutinib



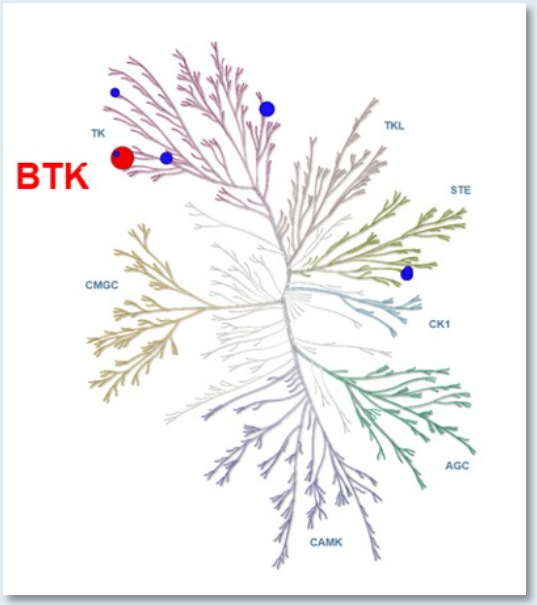
Zanubrutinib

Reversible

ARQ-531 (MK-1026)



LOXO-305



Courtesy of Matthew S Davids, MD, MMSc

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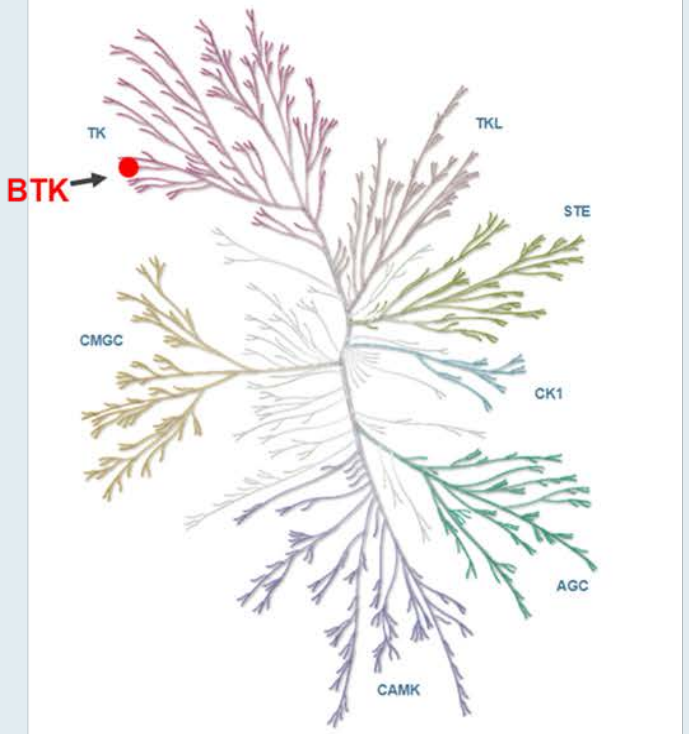
LOXO-305 is a Highly Potent and Selective Non-Covalent BTK Inhibitor

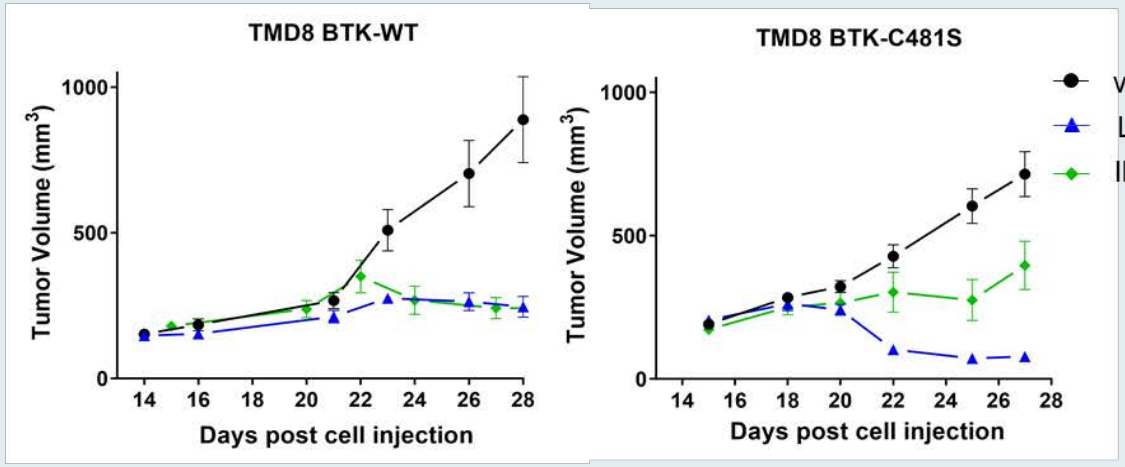
Kinome selectivity

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.

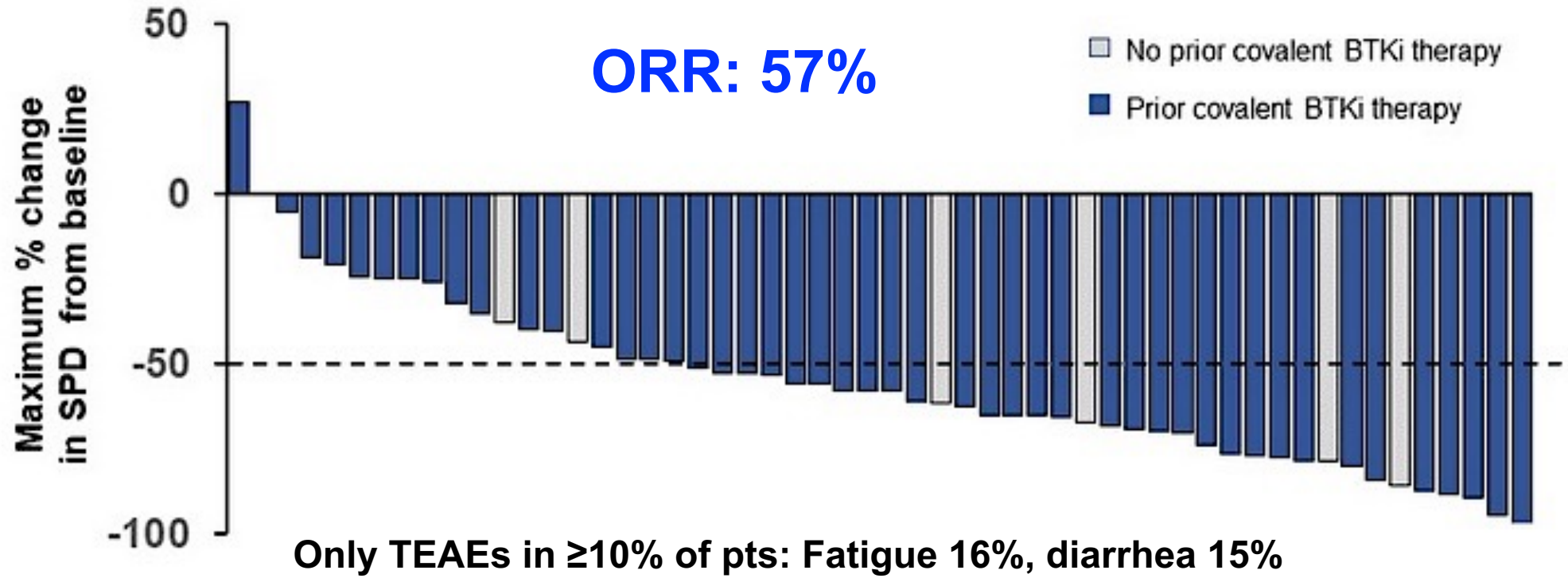
Mato AR et al. ASH 2020;Abstract 542.

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.

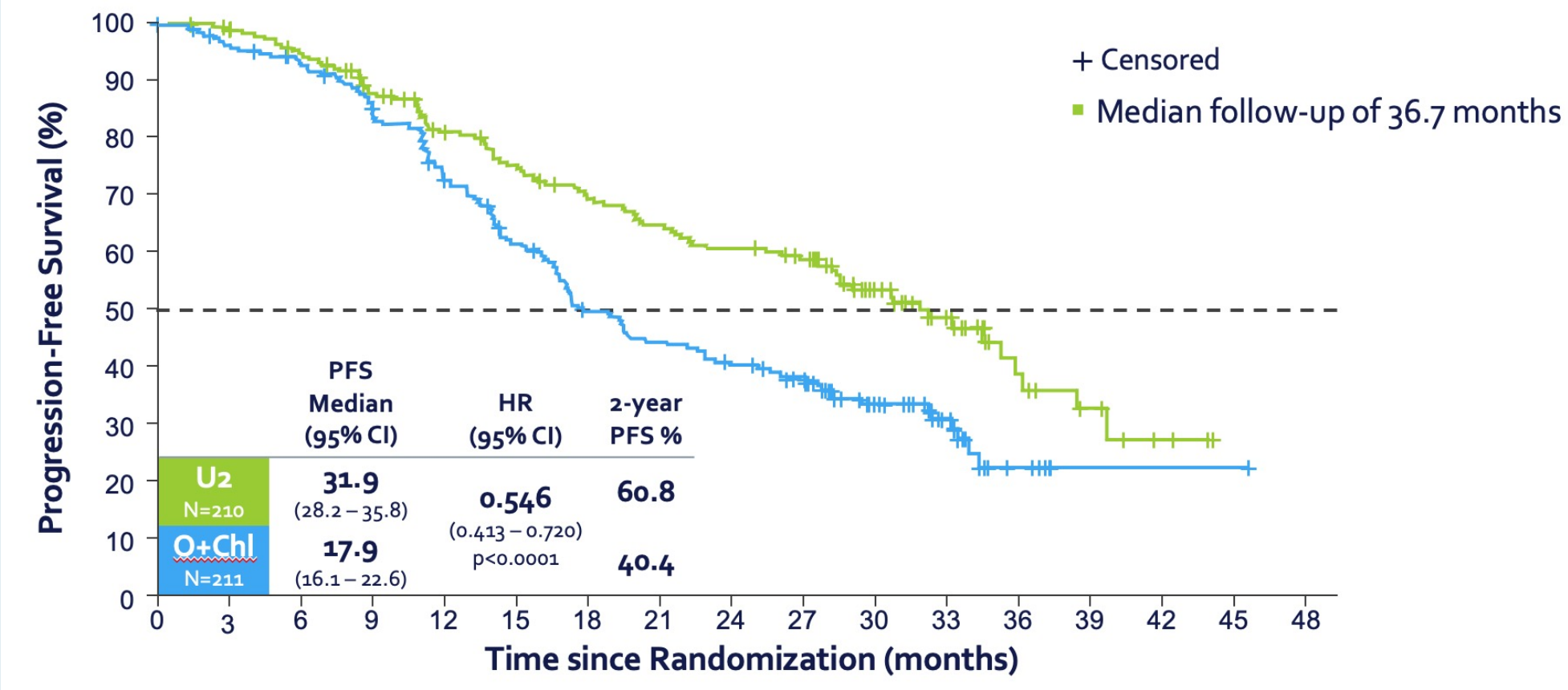
Courtesy of Matthew S Davids, MD, MMSc

Umbralisib plus Ublituximab (U2) Is Superior to Obinutuzumab plus Chlorambucil (O + Chl) in Patients with Treatment Naïve (TN) and Relapsed/Refractory (R/R) Chronic Lymphocytic Leukemia (CLL): Results from the Phase 3 Unity-CLL Study

Gribben JG et al.

ASH 2020;Abstract 542.

UNITY-CLL Phase III Trial of Umbralisib with Ublituximab (U2) versus Obinutuzumab with Chlorambucil in CLL



- PFS for patients with treatment-naïve CLL (U2 vs O + Chl): 38.5 vs 26.1 mo
- PFS for patients with R/R disease (U2 vs O + Chl): 19.5 vs 12.9 mo
- Grade 3+ colitis in 3.4%, Grade 3+ transaminitis in 8.3%, Grade 3+ pneumonitis in 2.9%

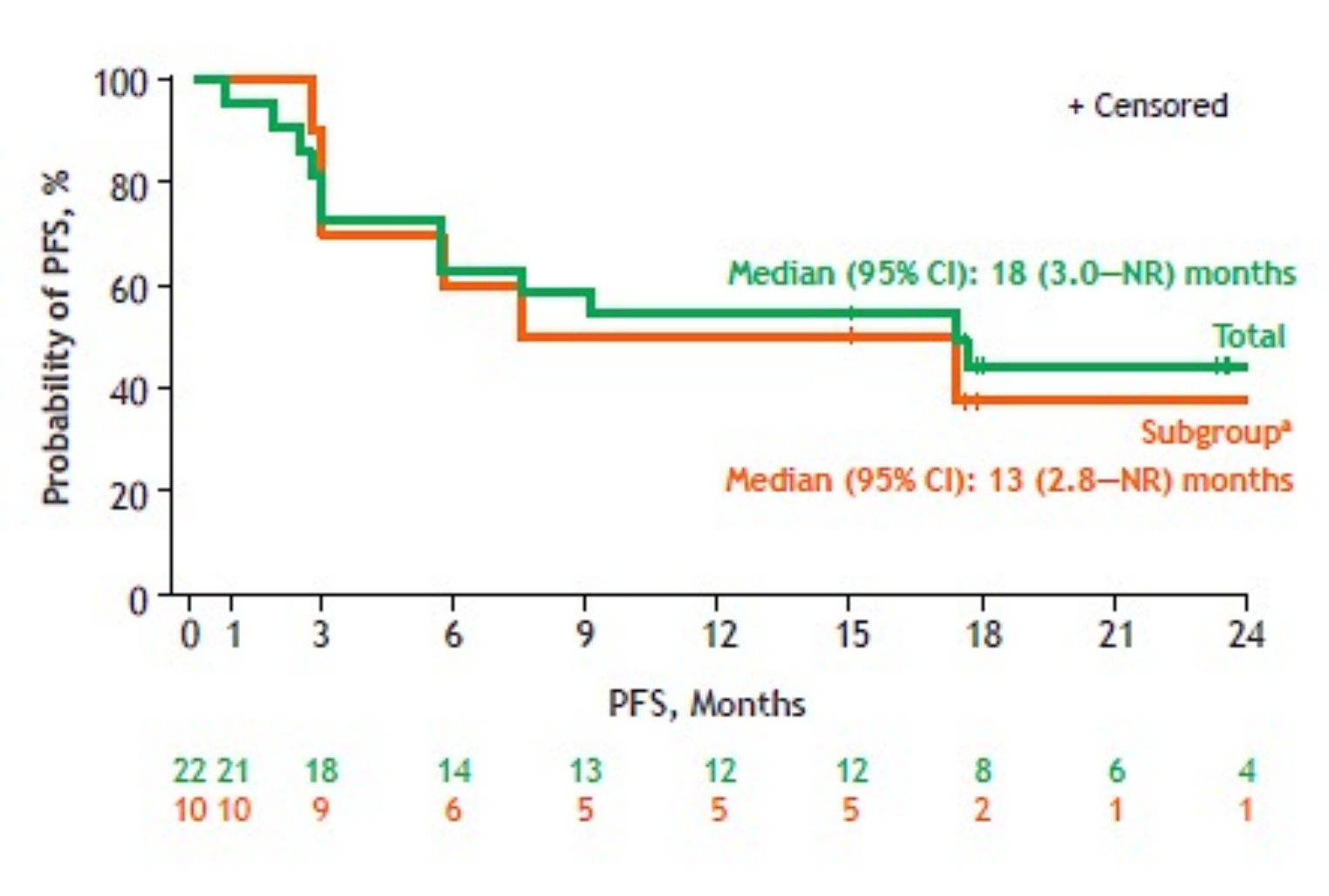
Gribben JG et al. ASH 2020;Abstract 543.

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

Wednesday, May 12, 2021
5:00 PM – 6:00 PM ET

Faculty

Michael J Birrer, MD, PhD

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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