Meet The Professor
Management of Chronic Lymphocytic Leukemia

John N Allan, MD
Assistant Professor of Medicine
Weill Cornell Medicine
New York, New York

Commercial Support

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

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Dr Love — Disclosures

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Dr Allan — Disclosures

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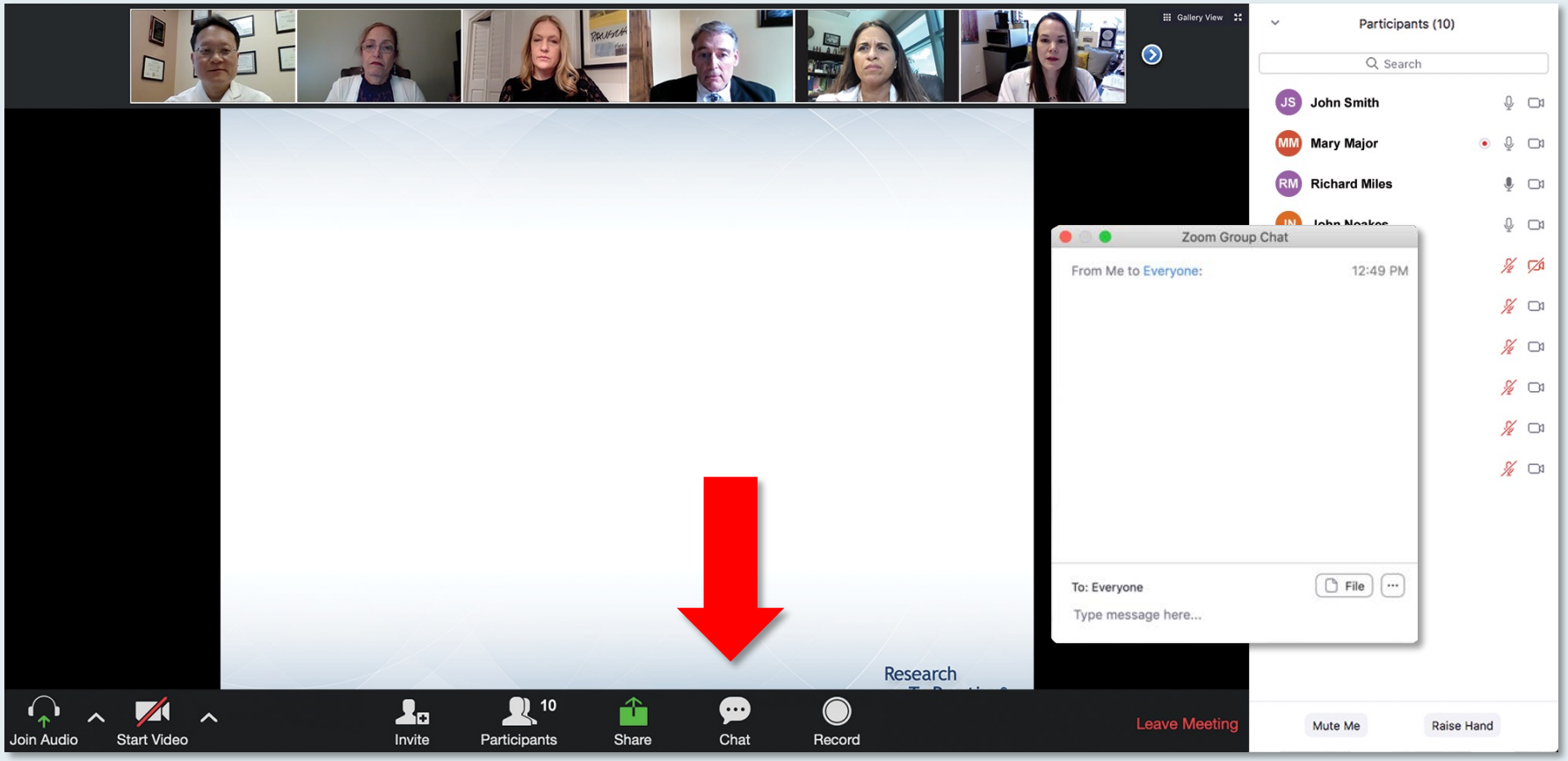
We Encourage Clinicians in Practice to Submit Questions



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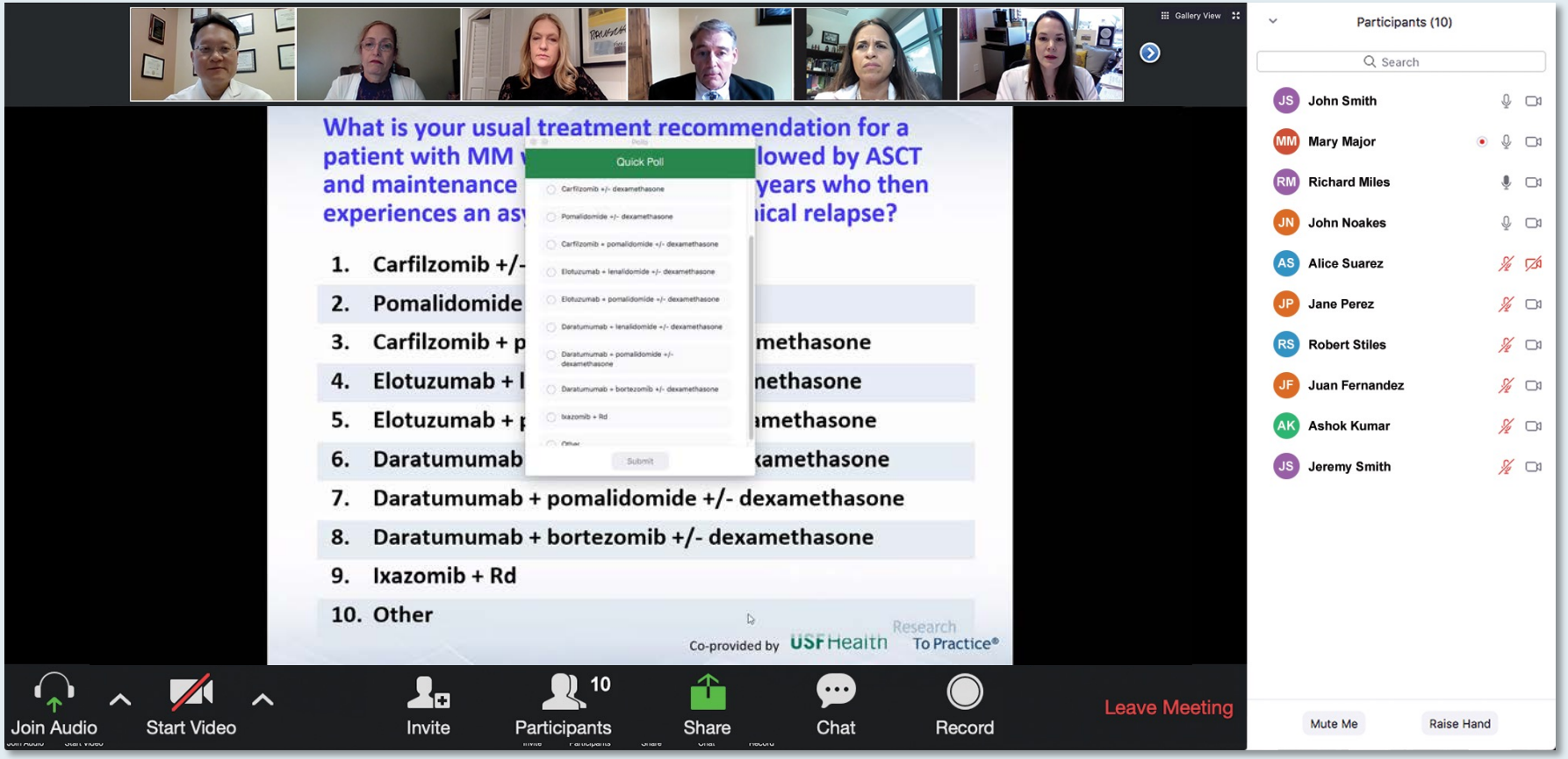

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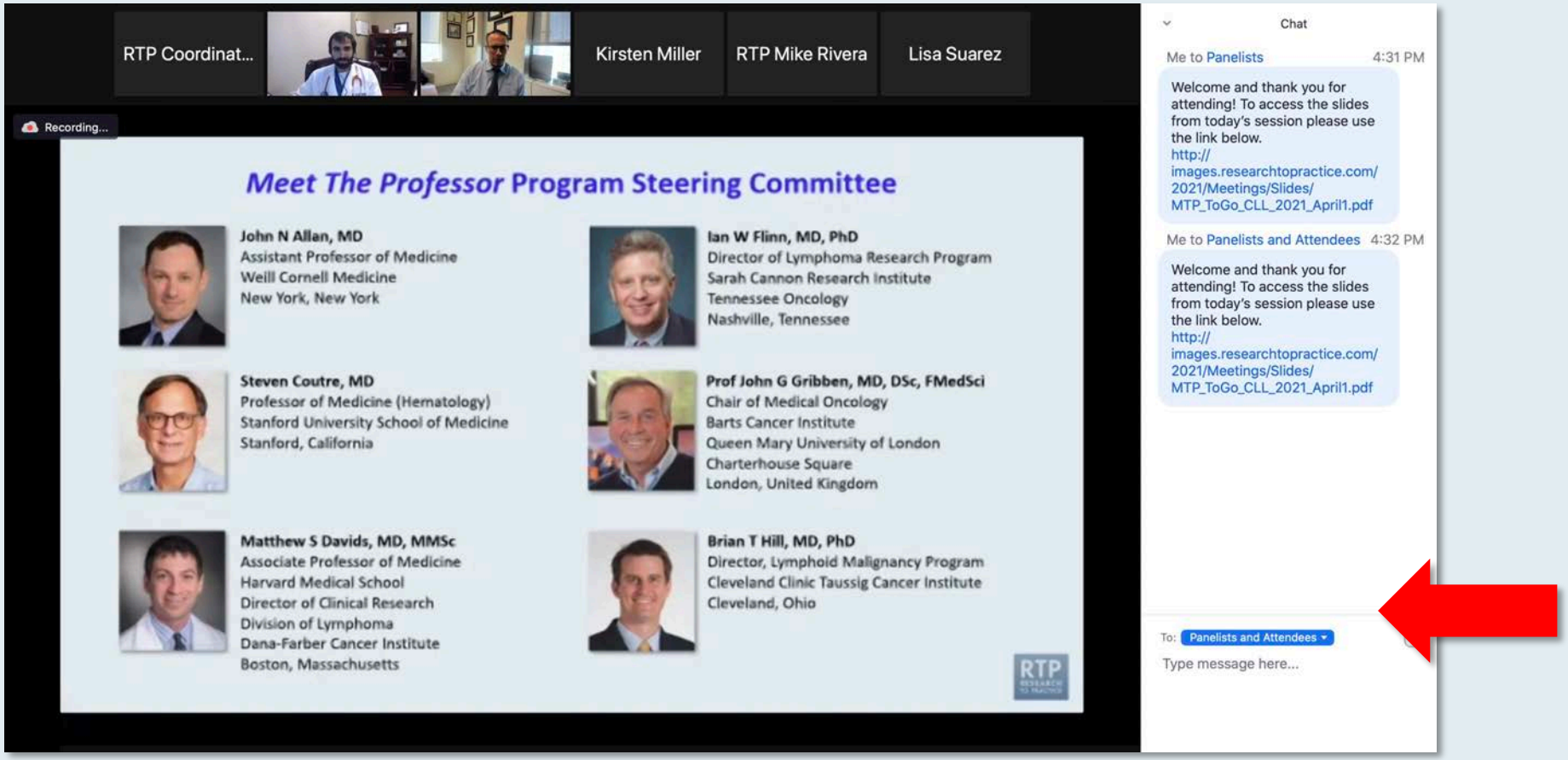
Familiarizing Yourself with the Zoom Interface

Expand chat submission box



Drag the white line above the submission box up to create more space for your message.

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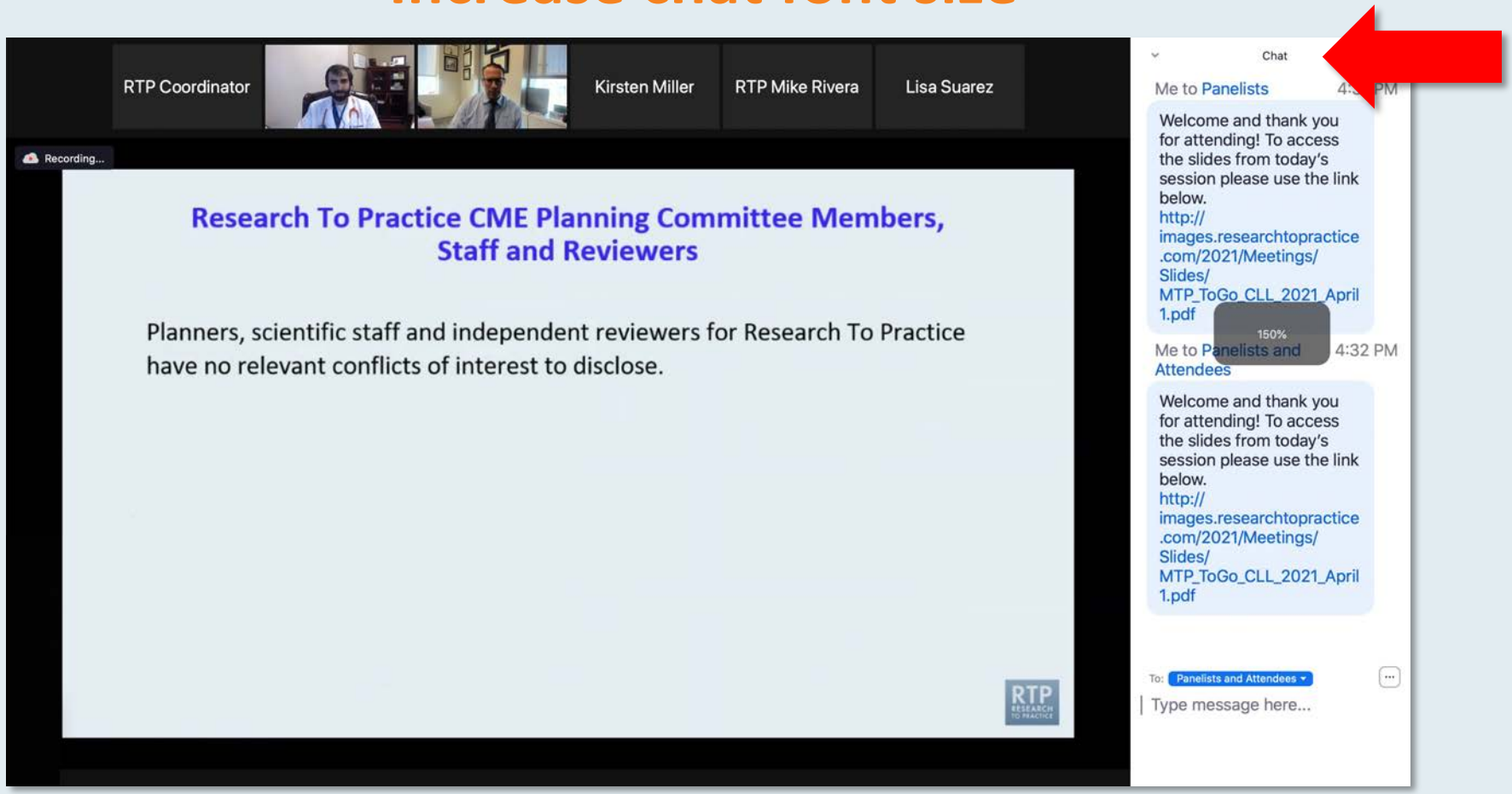
Increase chat font size



Press Command (for Mac) or Control (for PC) and the + symbol.
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

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

A Complimentary NCPD Live Webinar Series Hosted in Conjunction with the 46th Annual ONS Congress

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Chung-Han Lee, MD, PhD

Moderator

Neil Love, MD

Current Concepts and Recent Advances in Oncology

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

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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

John N Allan, MD
Assistant Professor of Medicine
Weill Cornell Medicine
New York, New York

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Cleveland, Ohio

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Meet The Professor Program Participating Faculty

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Director, Division of Hematology and Oncology
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Houston, Texas

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Department of Leukemia
Division of Cancer Medicine
The University of Texas
MD Anderson Cancer Center
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Professor
Division of Hematology
Department of Internal Medicine
The Ohio State University
Comprehensive Cancer Center
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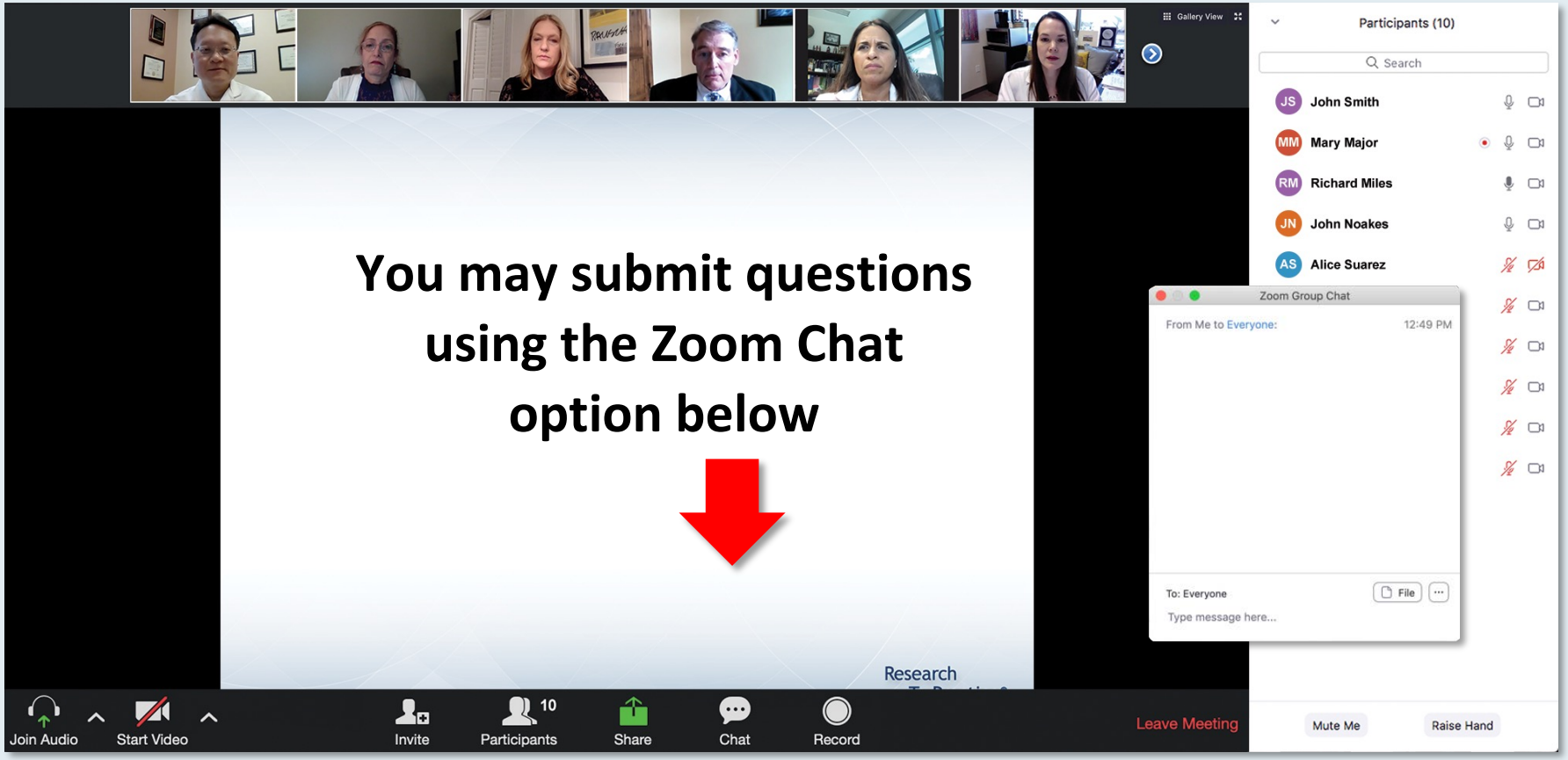

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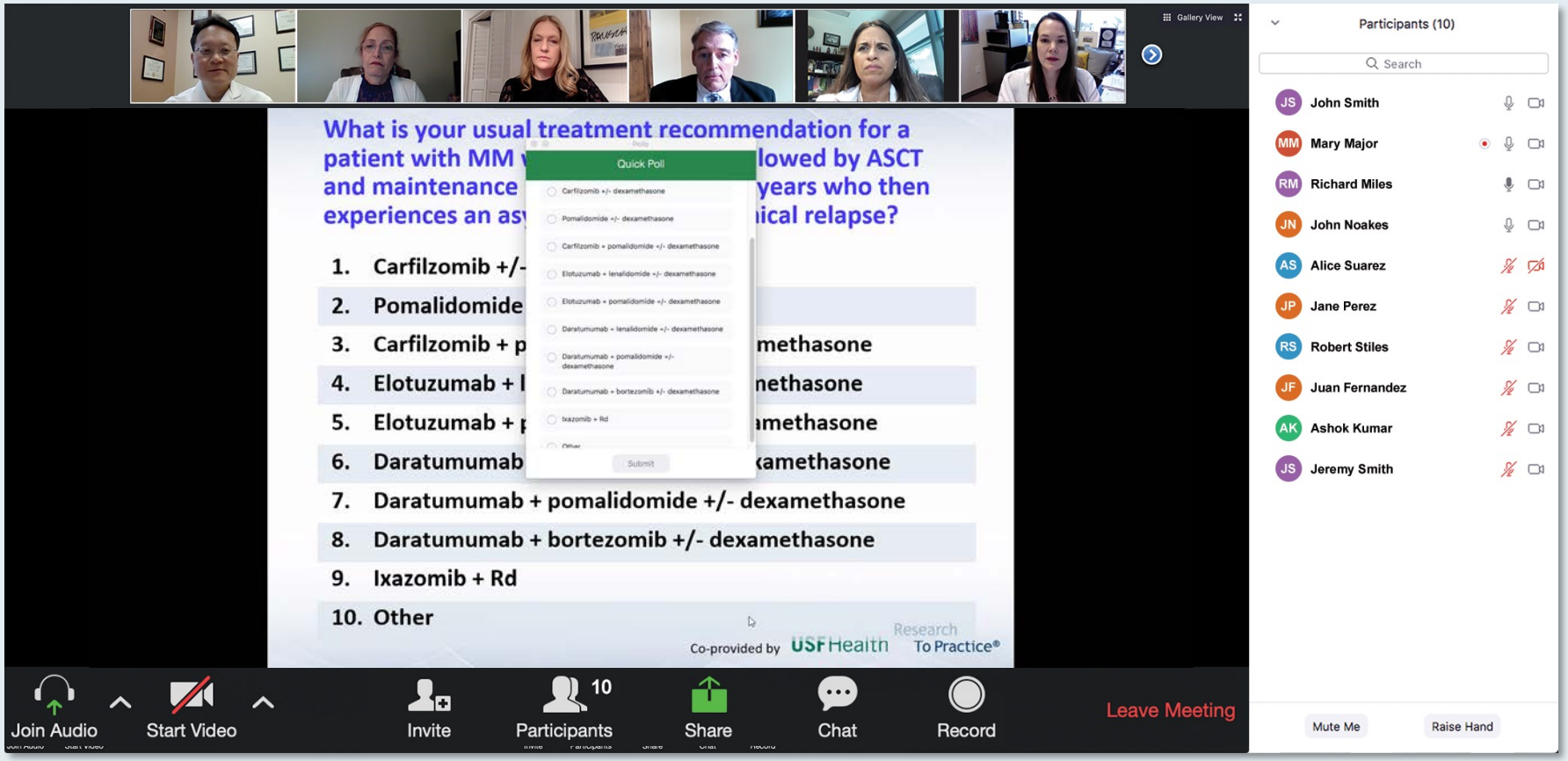

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Boca Raton, Florida

Lyle Feinstein, MD
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Miami, Florida

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

Shachar Peles, MD
Florida Cancer Specialists and Research Institute
Lake Worth, Florida

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Philip A Thompson, MB, BS
Assistant Professor, Department of Leukemia
Division of Cancer Medicine
The University of Texas MD Anderson Cancer Center
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New York, New York

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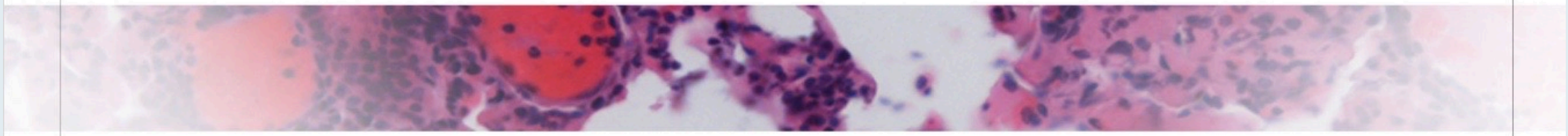
American Society *of* Hematology
Helping hematologists conquer blood diseases worldwide



Odronextamab (REGN1979), a human CD20 x CD3 bispecific antibody, induces durable, complete responses in patients with highly refractory B-cell non-Hodgkin lymphoma, including patients refractory to CAR T therapy

Rajat Bannerji MD, PhD[1], John N. Allan, MD[2], Jon E. Arnason, MD[3], Jennifer R. Brown, MD, PhD[4], Ranjana H. Advani, MD[5], Stephen M. Ansell, MD, PhD[6], Susan M. O'Brien, MD[7], Johannes Duell, MD[8], Jennifer L. Crombie, MD[4], Peter Martin, FRCPC, MD, MS[2], Robin M. Joyce, MD[3], Jingjin Li, PhD[9], Dina M. Flink, PhD[9], Min Zhu, PhD[9], Andres Sirulnik, MD, PhD[9], David M. Weinreich, MD[9], George D. Yancopoulos, MD, PhD[9], Israel Lowy, MD, PhD[9], Aafia Chaudhry, MD, MBA, MS[9], Srikanth R. Ambati, MBBS, MD[9], Max S. Topp, MD[8]

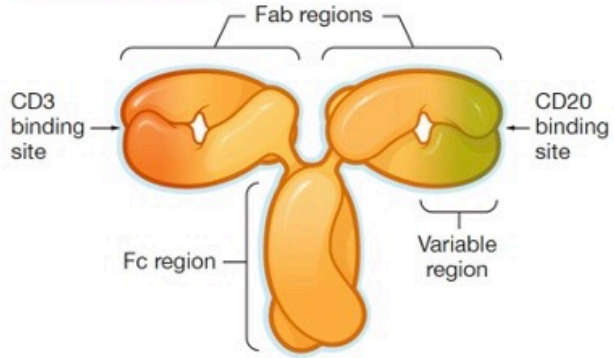
[1]Rutgers Cancer Institute of New Jersey, New Brunswick, NJ, USA; [2]Weill Cornell Medicine, New York, NY, USA; [3]Beth Israel Deaconess Medical Center, Boston, MA, USA; [4]Dana-Farber Cancer Institute, Boston, MA, USA; [5]Stanford University, Stanford, CA, USA; [6]Mayo Clinic, Rochester, MN, USA; [7]Chao Family Comprehensive Cancer Center, University of California, Irvine, Orange, CA, USA; [8]Universitätsklinikum Würzburg, Würzburg, Germany; [9]Regeneron Pharmaceuticals, Inc., Tarrytown, NY, USA

ClinicalTrials.gov ID: NCT02290951; this study was funded by Regeneron Pharmaceuticals, Inc.
Medical writing support: Paul Scutt, PhD, and Ben Caldwell, BSc, of Axis, a division of Spirit Medical Communications Ltd, funded by Regeneron Pharmaceuticals, Inc.
Presented at the 62nd ASH Annual Meeting and Exposition Virtual Event, December 5–8, 2020

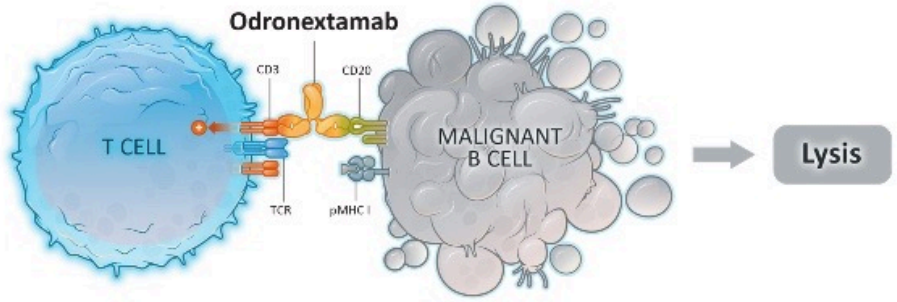
Abstract #400

Odronextamab: directing T cells to CD20(+) cells

Odronextamab bispecific antibody structure



Odronextamab mechanism of action



- Odronextamab (REGN1979) is a CD20 x CD3 bispecific antibody:
  - Binds to CD3 on T cells and CD20 on malignant B cells, triggering T-cell-mediated cytotoxicity independent of T-cell receptor recognition[1,2]
- Off-the-shelf treatment for IV infusion
- We report updated safety and efficacy data, with longer follow up, from a previously reported[3] Phase 1 study of odronextamab in patients with R/R B-NHL

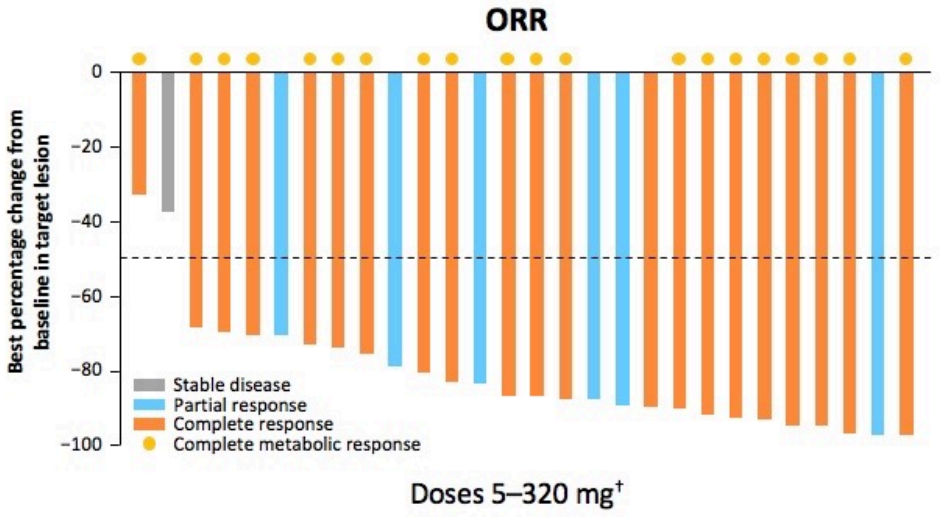
NCT02290951.
B-NHL, B-cell non-Hodgkin lymphoma; IV, intravenous; R/R, relapsed/refractory.

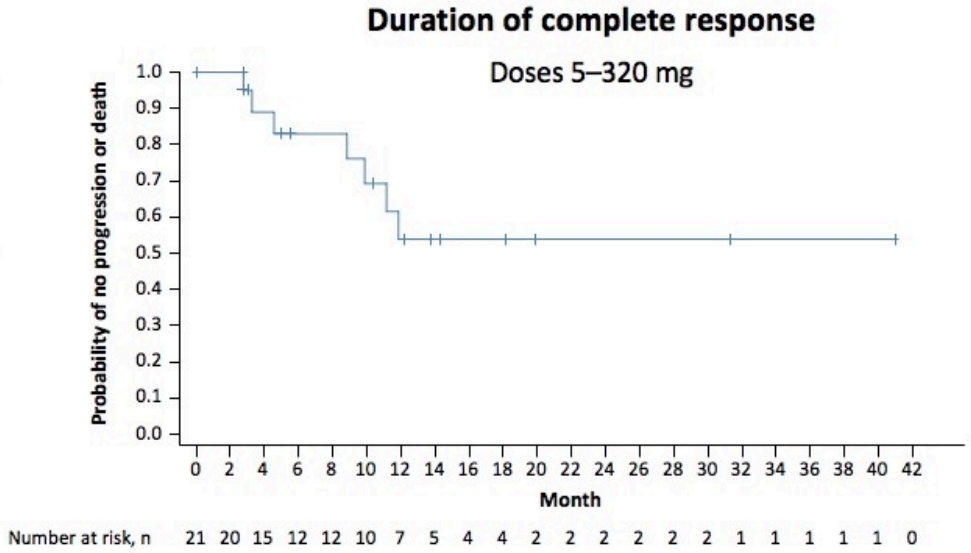
1. Smith EJ, et al. *Sci Rep*. 2015;5:17943;
2. Choi BD, et al. *Expert Opin Biol Ther*. 2011;11:843–53;
3. Bannerji R, et al. *Blood*. 2019;134(Supplement_1):762.

Bannerji R et al. ASH 2020; Abstract 400.

Odronextamab antitumor activity in R/R follicular lymphoma

ORR: **90%** (n=27/30); **CR rate**: **70%** (n=21/30)
CRs appear durable; median DoCR not reached
- **81%** of CRs were durable,* and are ongoing for up to **41 months**





Data cut-off: Oct 14, 2020.
Response per investigator assessment according to Lugano criteria. Median duration of follow up is 9 months (range, 1–44).
*Defined as a CR lasting at least 3 months; †Two patients with missing tumor assessments are not presented.
CR, complete response; DoCR, duration of complete response; ORR, objective response rate; R/R, relapsed/refractory.

Bannerji R et al. ASH 2020; Abstract 400.

Meet The Professor with Dr Allan

MODULE 1: Cases from Medical Oncology Practices

- Dr Peles: A 64-year-old man with significant ibrutinib-associated ecchymoses (Parts 1 and 2)
- Dr Brenner: A 74-year-old woman with CLL treated with acalabrutinib
- Dr Flores: A 78-year-old woman with transient atrial fibrillation while receiving ibrutinib
- Dr Feinstein: A 66-year-old man with newly diagnosed CLL who completes obinutuzumab/venetoclax
- Dr Peles: A 66-year-old man with Richter's transformation to large cell lymphoma (Parts 1 and 2)

MODULE 2: Journal Club with Dr Allan

MODULE 3: Beyond the Guidelines

MODULE 4: Key Recent Data Sets

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Case Presentation – Dr Peles: A 64-year-old man with significant ibrutinib-associated ecchymoses – Part 1

Dr Shachar Peles

- 2005: Diagnosed with Rai Stage II CLL
  - ZAP 70, CD38 negative, Biallelic 13q14 deletion, Unmutated IGHV
  - WBC: 29.4, ANC: 3.0, Hgb: 16.8, HCT: 48.9, MCV: 95.6, Plat: 129
  - Fatigue, weight loss, progressive cervical adenopathy
  - Extensive adenopathy throughout the neck, chest, abdomen and pelvis; Spleen: 18.5 cm
- Ibrutinib 420 mg daily
  - Improvement in adenopathy, splenomegaly and systemic symptoms, but spontaneous ecchymoses on extremities and trunk

Case Presentation – Dr Peles: A 64-year-old man with significant ibrutinib-associated ecchymoses – Part 2

Dr Shachar Peles

- 2005: Diagnosed with Rai Stage II CLL
  - ZAP 70, CD38 negative, Biallelic 13q14 deletion, Unmutated IGHV
  - WBC: 29.4, ANC: 3.0, Hgb: 16.8, HCT: 48.9, MCV: 95.6, Plat: 129
  - Fatigue, weight loss, progressive cervical adenopathy
  - Extensive adenopathy throughout the neck, chest, abdomen and pelvis; Spleen: 18.5 cm
- Ibrutinib 420 mg daily
  - Improvement in adenopathy, splenomegaly and systemic symptoms, but spontaneous ecchymoses on extremities and trunk
  - **Dose reduced to 280 mg daily with improvement in bruising**

Questions

- ***What do we know about bleeding risk with ibrutinib and how it interferes with coagulation?***
- ***Is there any evidence that dose reduction is beneficial in patients with extensive bruising or bleeding? How does the risk of bleeding with ibrutinib compare to acalabrutinib?***
- ***Do you feel comfortable with BTK inhibitors in patients who are already on anti-coagulants — for example, patients who have a history of a DVT or those with pre-existing atrial fibrillation?***

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Case Presentation – Dr Brenner: A 74-year-old woman with CLL treated with acalabrutinib

Dr Warren Brenner

- 6/2018: Diagnosed with Stage I CLL, del(13q), IGHV mutated → Observation
- 10/2020: Rising WBC, progressive anemia → Acalabrutinib
- Weeks later, presents with right visual loss
  - Papilledema and raised intracranial pressure thought to be related to pseudotumor cerebri
  - Placement of ventriculoperitoneal shunt
- 11-12/2020: Readmitted with subdural hemorrhage requiring revision of ventriculoperitoneal shunt, drainage of new subdural hemorrhage

Questions

- Have you ever seen a complication like this from BTK inhibitor therapy?
- Would you ever rechallenge a patient like this who's had a bleeding complication that is probably not related to acalabrutinib, but rather to a surgical procedure?
- Do you have a preference for ibrutinib or acalabrutinib, and if so, why?
- If you initiate front-line therapy with acalabrutinib, do you add a monoclonal antibody?

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Case Presentation – Dr Flores: A 78-year-old woman with transient atrial fibrillation while receiving ibrutinib

Dr Regina Flores

- PMH: Chronic kidney disease, hypogammaglobulinemia, depression, severe arthritis
- 2017: Diagnosed with symptomatic CLL, IGHV mutated, 13q14 deletion
  - Fevers, night sweats, anemia, recurrent infections
- Ibrutinib
- 2020: Suffered a fall with a knee fracture, transiently off IVIG while in rehabilitation
- Developed pneumonia with pericardial effusion and atrial fibrillation, which resolved after a pericardial window
- Currently, her disease is stable and she is not on anti-coagulants

Questions

- Would you stop the ibrutinib? Would you give her a drug holiday, and if so, for how long?
- Would you change the treatment because she had atrial fibrillation, or stay with it, since the atrial fibrillation was transient?

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Case Presentation – Dr Feinstein: A 66-year-old man with newly diagnosed CLL who completes obinutuzumab/venetoclax

Dr Lyle Feinstein

- Presents with fatigue, dyspnea on exertion, no B symptoms
- Diagnosed with CLL, trisomy 12, IGHV mutated
  - WBC: 62,900, ALC: 60,400, Hgb: 7.8, PLT: 64,600, LDH: 302
  - Enlarged lymph nodes (none >3 cm) with mild hypermetabolic activity above and below the diaphragm; Spleen: 17.8 cm, with mild hypermetabolic activity
- Patient desires limited duration therapy
- Obinutuzumab/venetoclax

Questions

- How do you use MRD following completion of treatment?
- What do you do if you start seeing rising MRD without evidence of disease progression based on a patient's counts or imaging?

RTP RESEARCH TO PRACTICE

Case Presentation – Dr Peles: A 66-year-old man with Richter's transformation to large cell lymphoma – Part 1

Dr Shachar Peles

- Diagnosed with SLL
- 5 years later, admitted to the hospital with abdominal pain
  - Imaging: Increase in size of abdominal lymph node
  - Biopsy: Large cell lymphoma
- RT of abdominal node, R-CHOP x 6

RTP RESEARCH TO PRACTICE

Case Presentation – Dr Peles: A 66-year-old man with Richter's transformation to large cell lymphoma – Part 2

Dr Shachar Peles

- Diagnosed with SLL
- 5 years later, admitted to the hospital with abdominal pain
  - Imaging: Increase in size of abdominal lymph node
  - Biopsy: Large cell lymphoma
- RT of abdominal node, R-CHOP x 6
- ***In the past year: Asymptomatic, but slowly enlarging intra-abdominal adenopathy, LDH normal***
  - ***Difficult to biopsy due to size and location of nodes***
  - ***PET: Hypermetabolic activity in the nodes***

RTP RESEARCH TO PRACTICE

Meet The Professor with Dr Allan

MODULE 1: Cases from General Medical Oncology Practices

MODULE 2: Journal Club with Dr Allan – Part 1

- Long-term efficacy of first-line ibrutinib for CLL with TP53 aberrations (17p deletion or TP53 mutation)
- Comparative analysis of targeted novel therapies for relapsed/refractory (R/R) CLL
- Odronextamab, a human CD20 x CD3 bispecific antibody: Durable CRs in highly refractory B-cell NHL
- Efficacy of bendamustine and rituximab in unfit patients with previously untreated CLL: Indirect comparison with ibrutinib in a real-world setting
- Venetoclax in elderly patients with R/R CLL
- Outcomes among patients with CLL with NOTCH1 regulatory pathway mutations
- CLL with TP53 gene alterations: A detailed clinicopathologic analysis

RTP
RESEARCH
TO PRACTICE

Meet The Professor with Dr Allan

MODULE 2: Journal Club with Dr Allan – Part 2

- Venetoclax alone or in combination with an anti-CD20 monoclonal antibody for R/R CLL
- Efficacy of therapies for CLL after venetoclax discontinuation: BTK inhibition as an effective strategy
- Recurrent gastrointestinal near-tetraploid DLBCL causing intussusception and ileal ulceration
- Phase II study of acalabrutinib for ibrutinib-intolerant patients with R/R CLL
- Worldwide examination of patients with CLL hospitalized for COVID-19
- Venetoclax re-treatment of CLL after a venetoclax-based regimen
- Age and survival among CLL patients receiving ibrutinib as initial therapy
- CAPTIVATE trial: Ibrutinib with venetoclax for first-line treatment of CLL and SLL
- Outcomes of COVID-19 in patients with CLL: A multicenter international experience

MODULE 3: Beyond the Guidelines

MODULE 4: Key Recent Data Sets

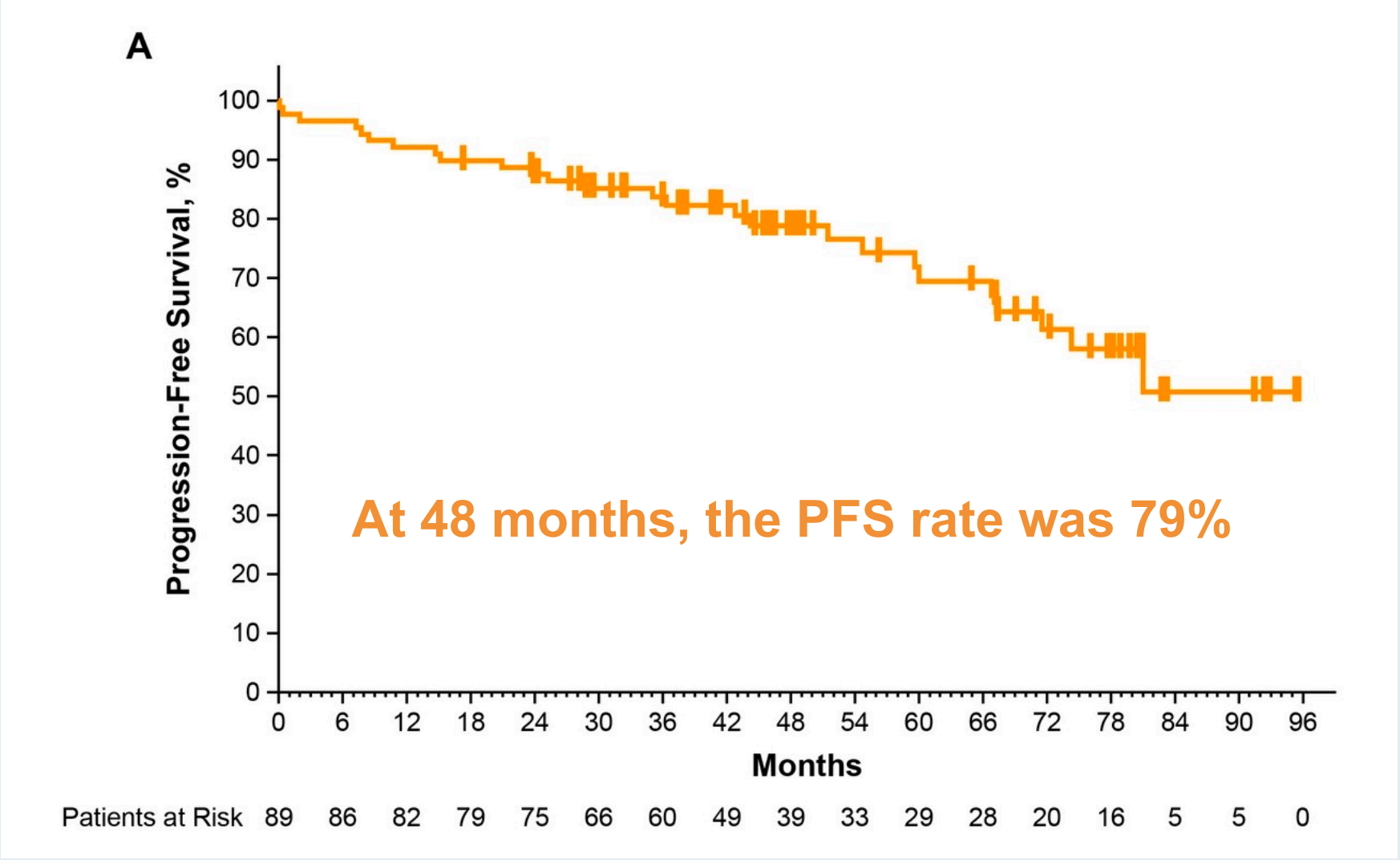
RTP
RESEARCH
TO PRACTICE

Long-Term Efficacy of First-Line Ibrutinib Treatment for Chronic Lymphocytic Leukemia (CLL) with 4 Years of Follow-Up in Patients with *TP53* Aberrations (del(17p) or *TP53* Mutation): A Pooled Analysis from 4 Clinical Trials

Allan JN et al.

ASH 2020;Abstract 2219.

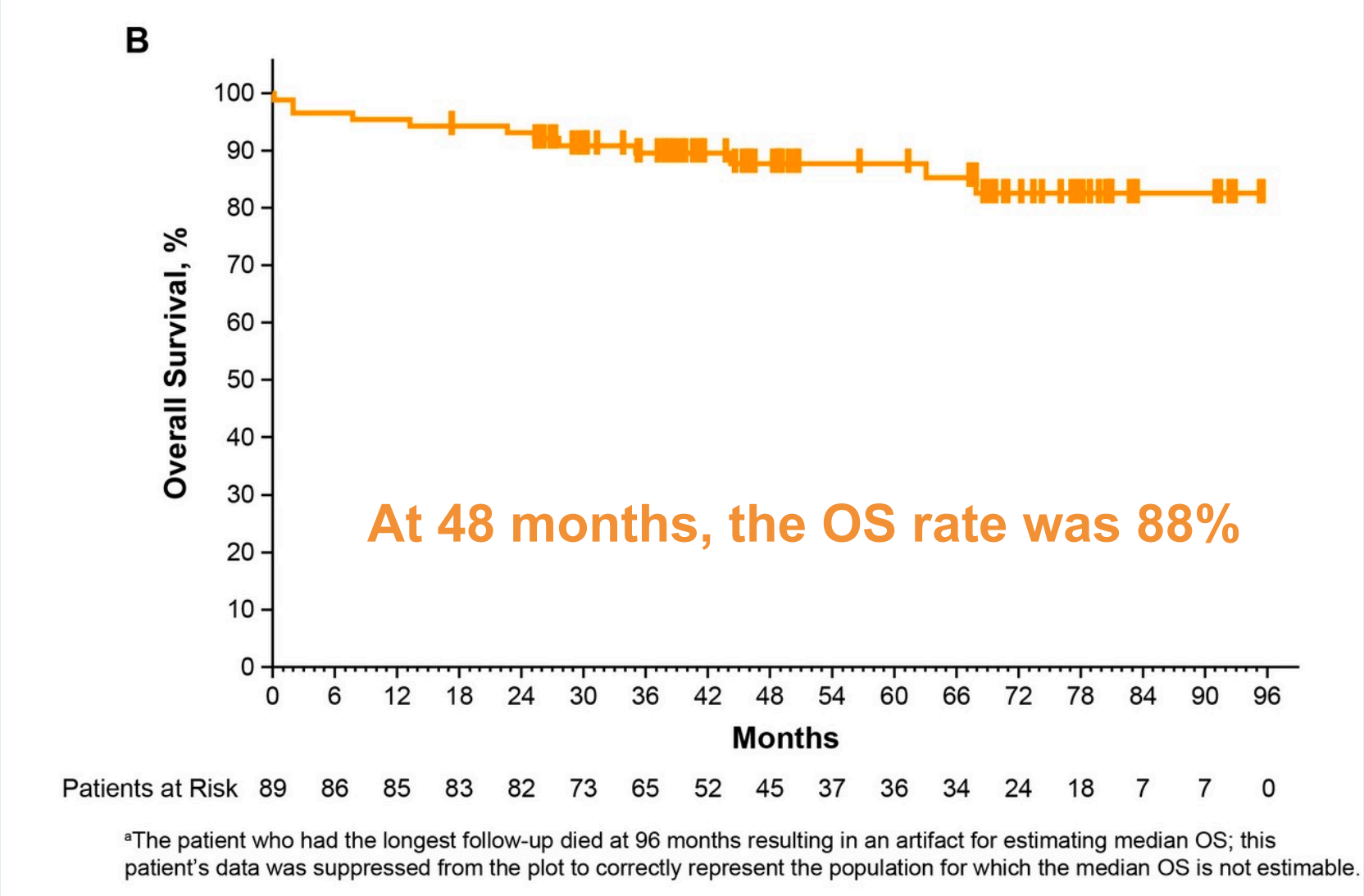
Progression-Free Survival for Patients with TP53 Aberrations Receiving First-Line Ibrutinib



Allan JN et al. ASH 2020;Abstract 2219.

RTP RESEARCH TO PRACTICE

Overall Survival for Patients with TP53 Aberrations Receiving First-Line Ibrutinib



[a]The patient who had the longest follow-up died at 96 months resulting in an artifact for estimating median OS; this patient's data was suppressed from the plot to correctly represent the population for which the median OS is not estimable.

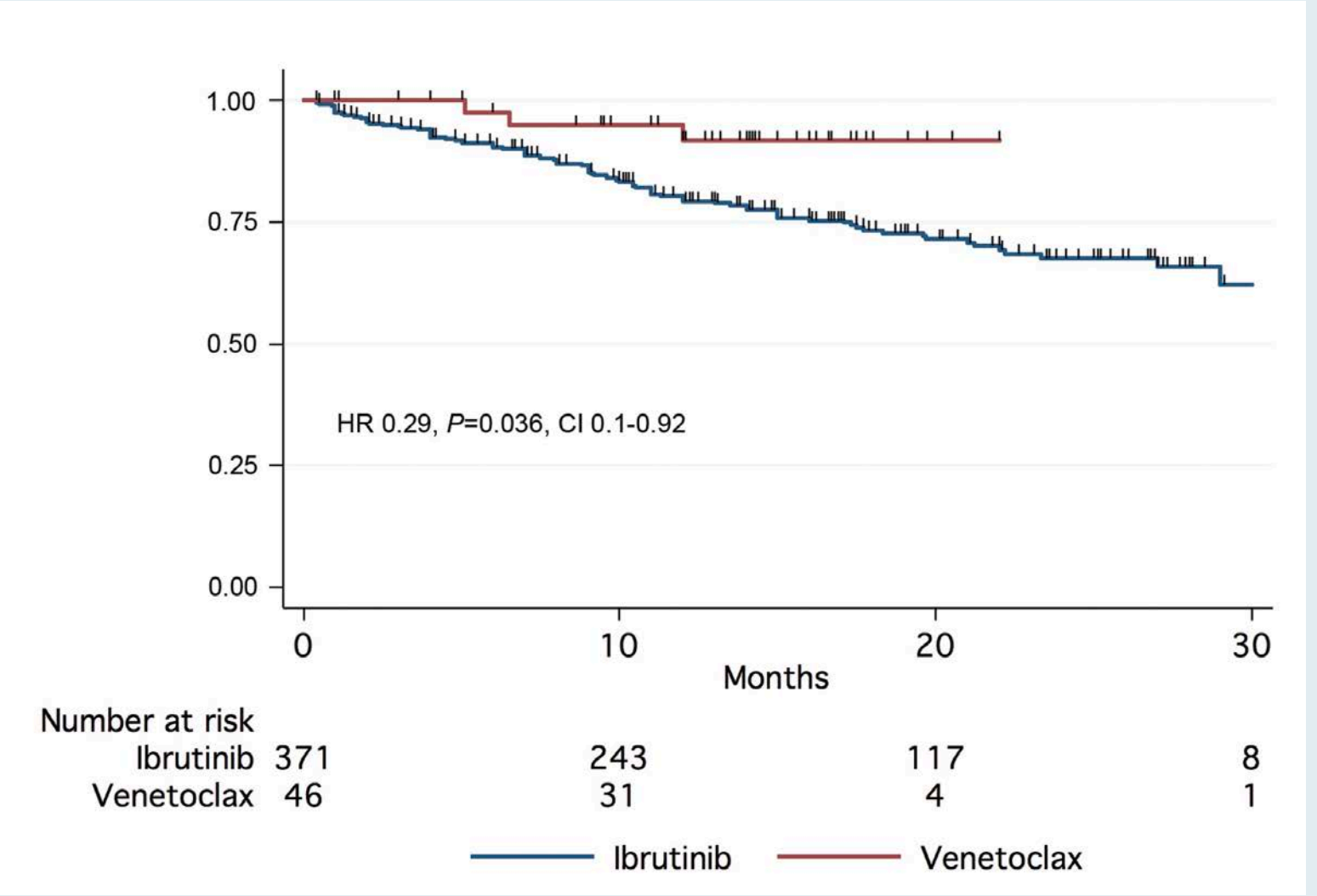
Allan JN et al. ASH 2020;Abstract 2219.

Eyre TA et al. *Haematologica* 2021;106(1):284-7.

Letters to the Editor

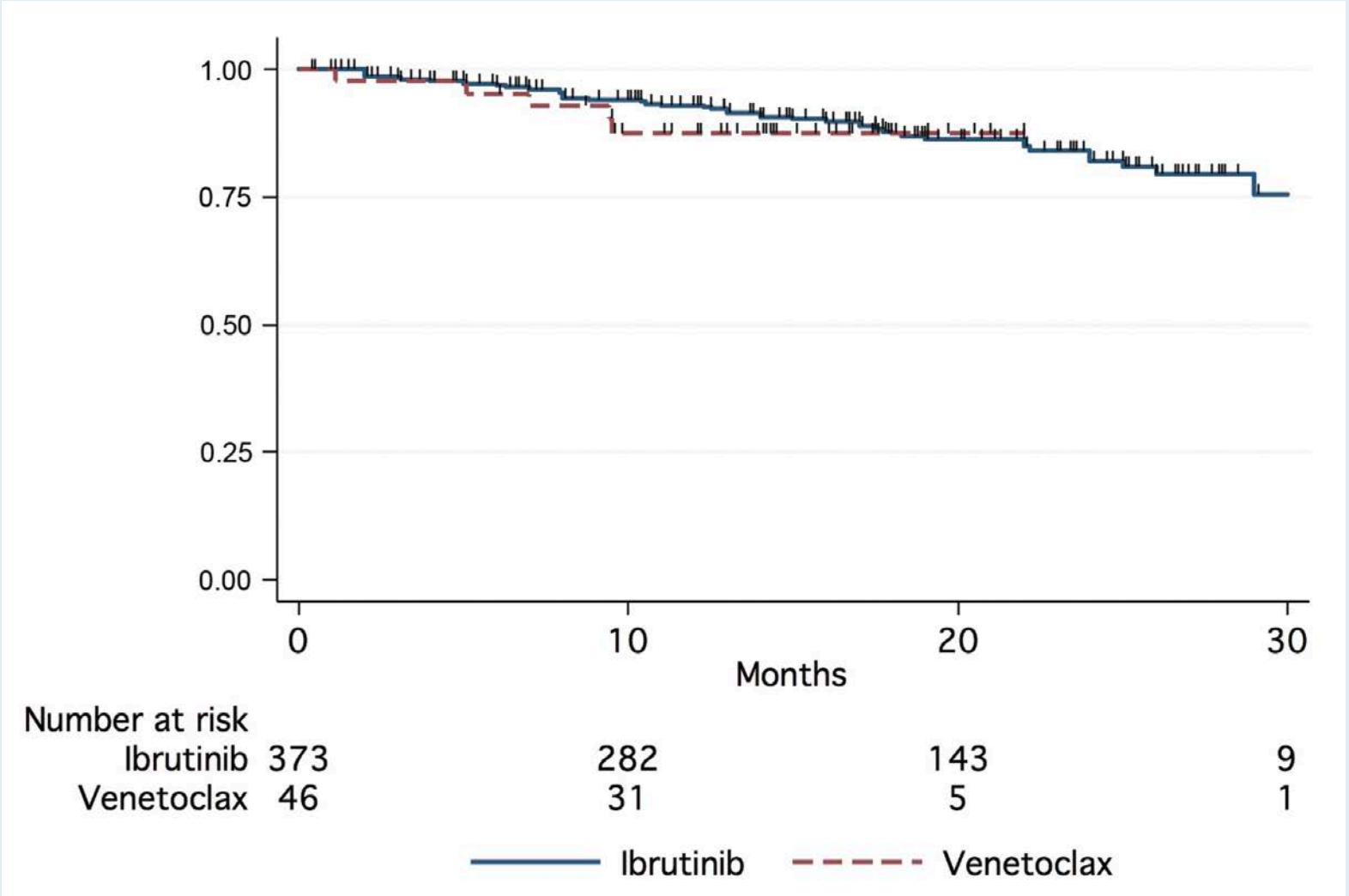
Comparative analysis of targeted novel therapies in relapsed, refractory chronic lymphocytic leukemia

Progression-Free Survival According to Novel Targeted Agent



Eyre TA et al. *Haematologica* 2021;106(1):284-7.

Overall Survival According to Novel Targeted Agent



Eyre TA et al. *Haematologica* 2021;106(1):284-7.

RTP RESEARCH TO PRACTICE

Cancer Med 2020;9(22):8468-79.

Received: 30 March 2020 | Revised: 28 August 2020 | Accepted: 2 September 2020

DOI: 10.1002/cam4.3470

ORIGINAL RESEARCH

Cancer Medicine Open Access WILEY

Efficacy of bendamustine and rituximab in unfit patients with previously untreated chronic lymphocytic leukemia. Indirect comparison with ibrutinib in a real-world setting. A GIMEMA-ERIC and US study

Antonio Cuneo[1] | Anthony R. Mato[2] | Gian Matteo Rigolin[1]* | Alfonso Piciocchi[3] | Massimo Gentile[4] | Luca Laurenti[5] | John N. Allan[6] | John M. Pagel[7] | Danielle M. Brander[8] | Brian T. Hill[9] | Allison Winter[9] | Nicole Lamanna[10] | Constantine S. Tam[11] | Ryan Jacobs[12] | Frederick Lansigan[13] | Paul M. Barr[14] | Mazyar Shadman[15] | Alan P. Skarbnik[16] | Jeffrey J. Pu[17] | Alison R. Sehgal[18] | Stephen J. Schuster[19] | Nirav N. Shah[20] | Chaitra S. Ujjani[15] | Lindsey Roeker[2] | Ester Maria Orlandi[21] | Atto Billio[22] | Livio Trentin[23] | Martin Spacek[24] | Monia Marchetti[25] | Alessandra Tedeschi[26] | Fiorella Ilariucci[27] | Gianluca Gaidano[28] | Michael Doubek[29] | Lucia Farina[30] | Stefano Molica[31] | Francesco Di Raimondo[32] | Marta Coscia[33] | Francesca Romana Mauro[34] | Javier de la Serna[35] | Angeles Medina Perez[36] | Isacco Ferrarini[37] | Giuseppe Cimino[38] | Maurizio Cavallari[1] | Rosalba Cucci[3] | Marco Vignetti[3] | Robin Foà[34] | Paolo Ghia[39] | the GIMEMA, European Research Initiative (ERIC) on CLL, US study group

Br J Haematol 2020;188(6):918-23.

bjh short report

The efficacy and safety of venetoclax therapy in elderly patients with relapsed, refractory chronic lymphocytic leukaemia

Toby A. Eyre,[1,†] Lindsey E. Roeker,[2,†] Christopher P. Fox,[3] Satyen H. Gohill,[4] Renata Walewska,[5] Harriet S. Walter,[6] Francesco Forconi,[7,8] Angus Broom,[9] Arvind Arumainathan,[10] Danielle M. Brander,[11] John N. Allan,[12] Stephen J. Schuster,[13] Brian T. Hill,[14] Frederick Lansigan,[15] Bruce D. Cheson,[16] Nicole Lamanna,[17] Catherine C. Coombs,[18] Paul M. Barr,[19] Alan P. Skarbnik,[20] Mazyar Shadman,[21] Chaitra S. Ujjani,[21] Laurie Pearson,[22] John M. Pagel,[23] Ryan Jacobs[24] and Anthony R. Mato[2]

Summary

Elderly chronic lymphocytic leukaemia (CLL) patients treated outside of trials have notably greater toxicity with the Bruton's tyrosine kinase inhibitor ibrutinib compared to younger patients. It is not known whether the same holds true for the B-cell lymphoma 2 inhibitor venetoclax. We provide a comprehensive analysis of key safety measures and efficacy in 342 patients comparing age categories ≥75 and <75 years treated in the relapsed, refractory non-trial setting. We demonstrate that venetoclax has equivalent efficacy and safety in relapsed/refractory CLL patients who are elderly, the majority of whom are previous ibrutinib-exposed and therefore may otherwise have few clear therapeutic options.

Keywords: chronic lymphocytic leukaemia, venetoclax, elderly, BCL2.

Received: 10 December 2020 | Revised: 22 February 2021 | Accepted: 23 February 2021

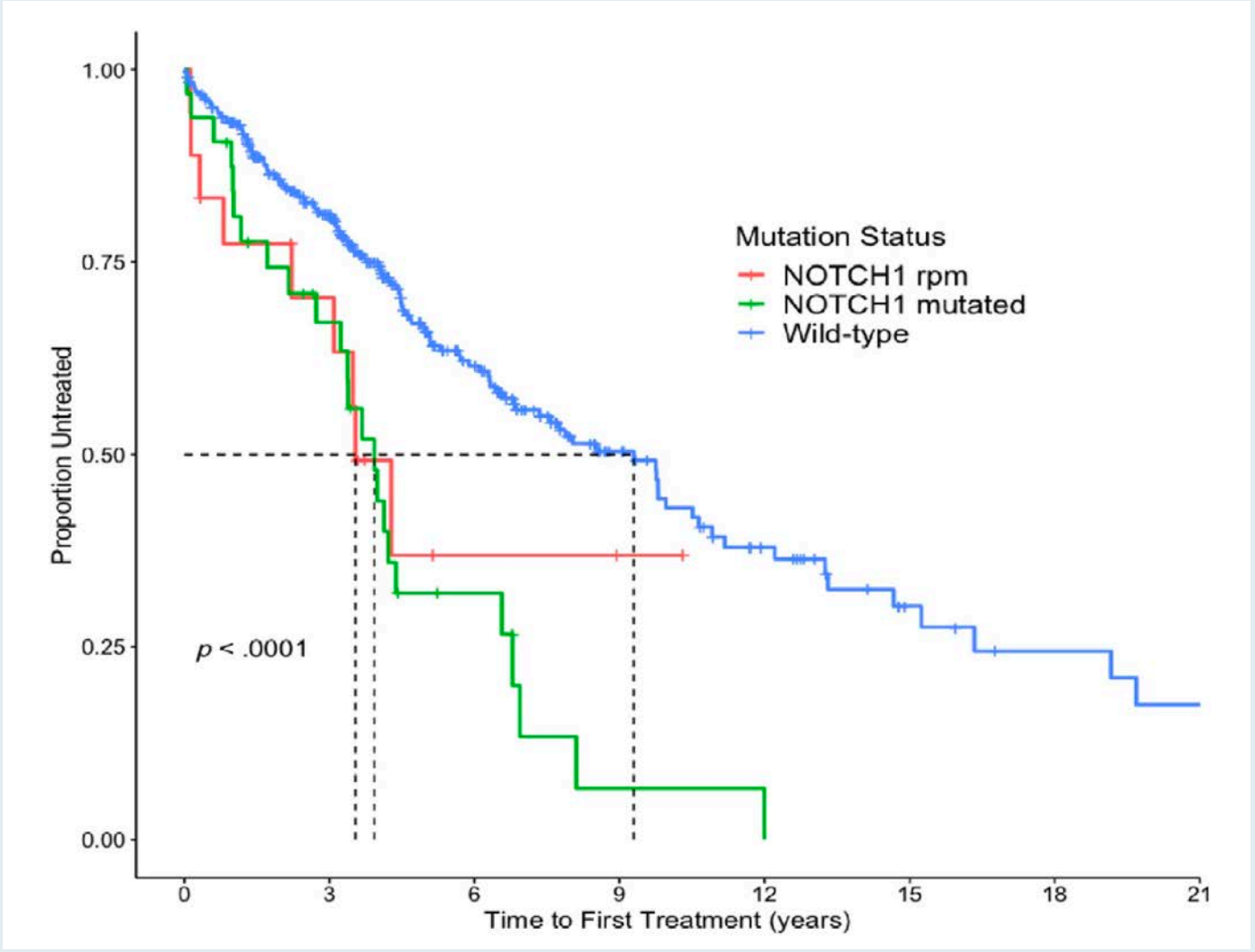
DOI: 10.1002/ajh.26140

CORRESPONDENCE

Outcomes in CLL patients with *NOTCH1* regulatory pathway mutations

Helbig DR et al. *Am J Hematol* 2021;[Online ahead of print].

Kaplan-Meier Curve of Time to First Treatment for Patients with NOTCH1 Regulatory Pathway Mutations, NOTCH1 Mutations and NOTCH1 Wild-Type Status



Helbig DR et al. *Am J Hematol* 2021;[Online ahead of print].

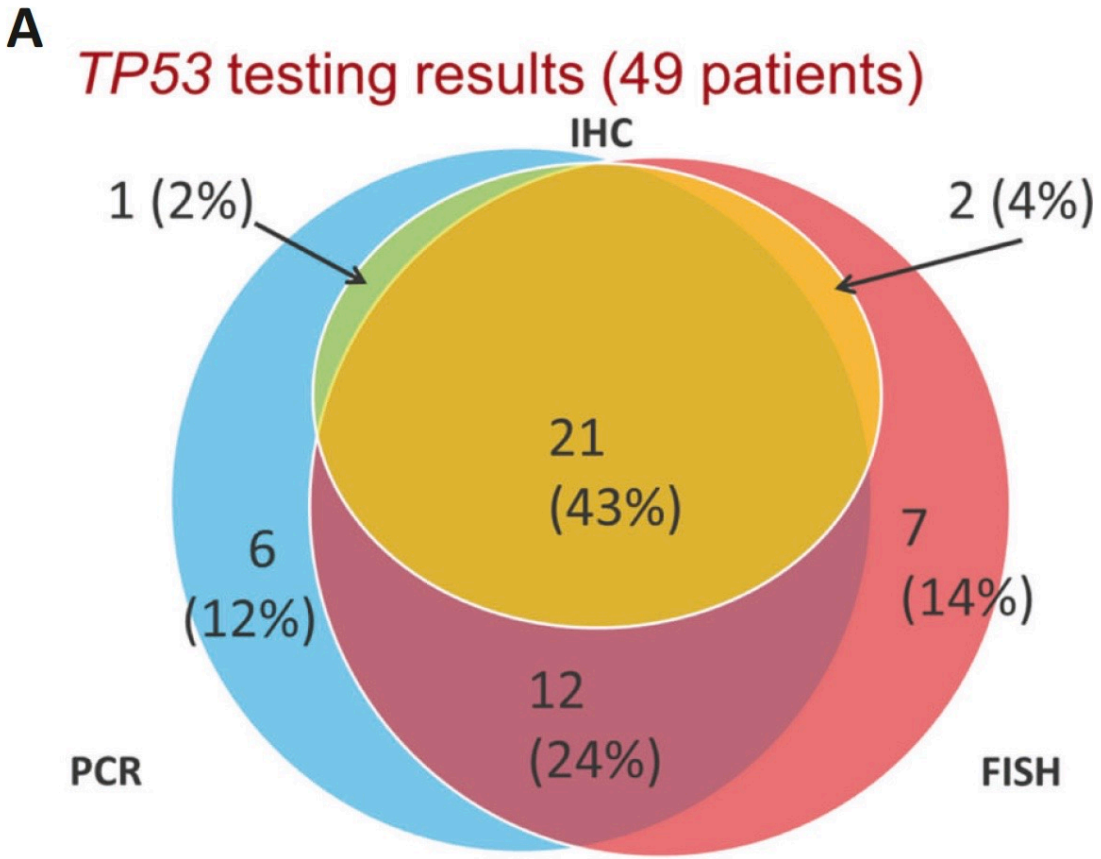
Modern Pathology (2020) 33:344–353
https://doi.org/10.1038/s41379-019-0356-z

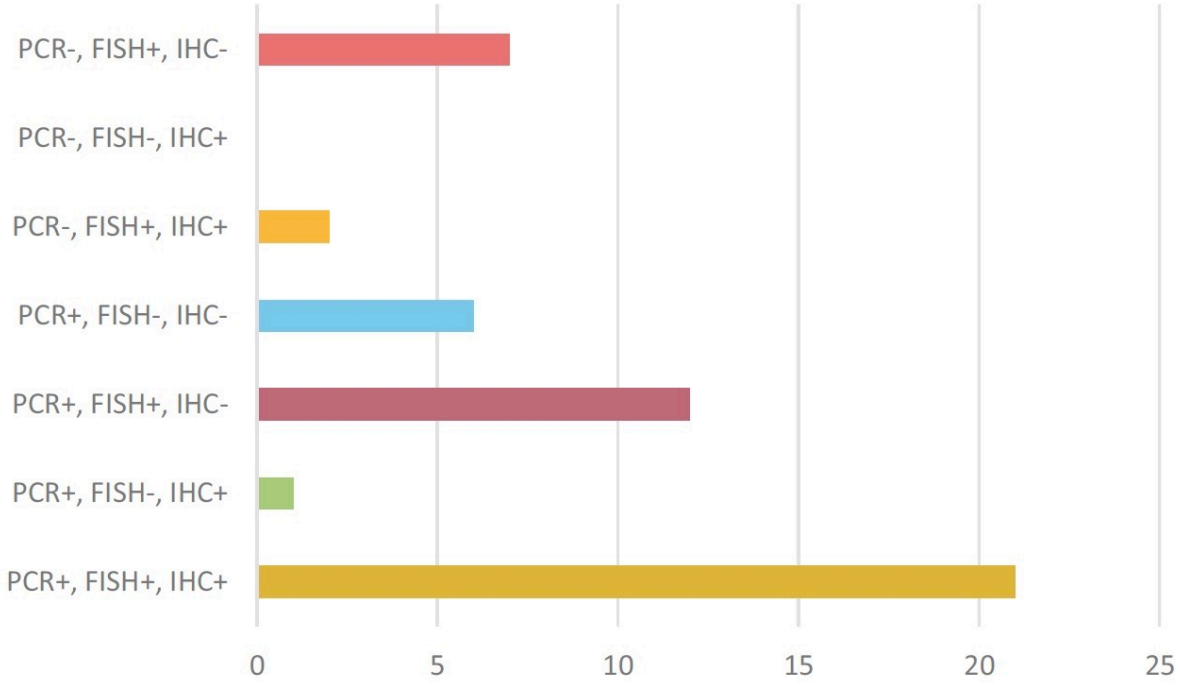
ARTICLE

Chronic lymphocytic leukemia with *TP53* gene alterations: a detailed clinicopathologic analysis

Yen-Chun Liu[1] · Elizabeth Margolskee[2] · John N. Allan[3] · Susan Mathew[2] · Erica Bhavsar[3] · Joseph Casano[2] · Attilio Orazi[4] · Richard R. Furman[3] · Julia T. Geyer[2]

Venn Diagram Demonstrating the Relationships Between Positive FISH, Sequencing and Immunohistochemical Evaluation Among Patients Tested by All 3 Modalities

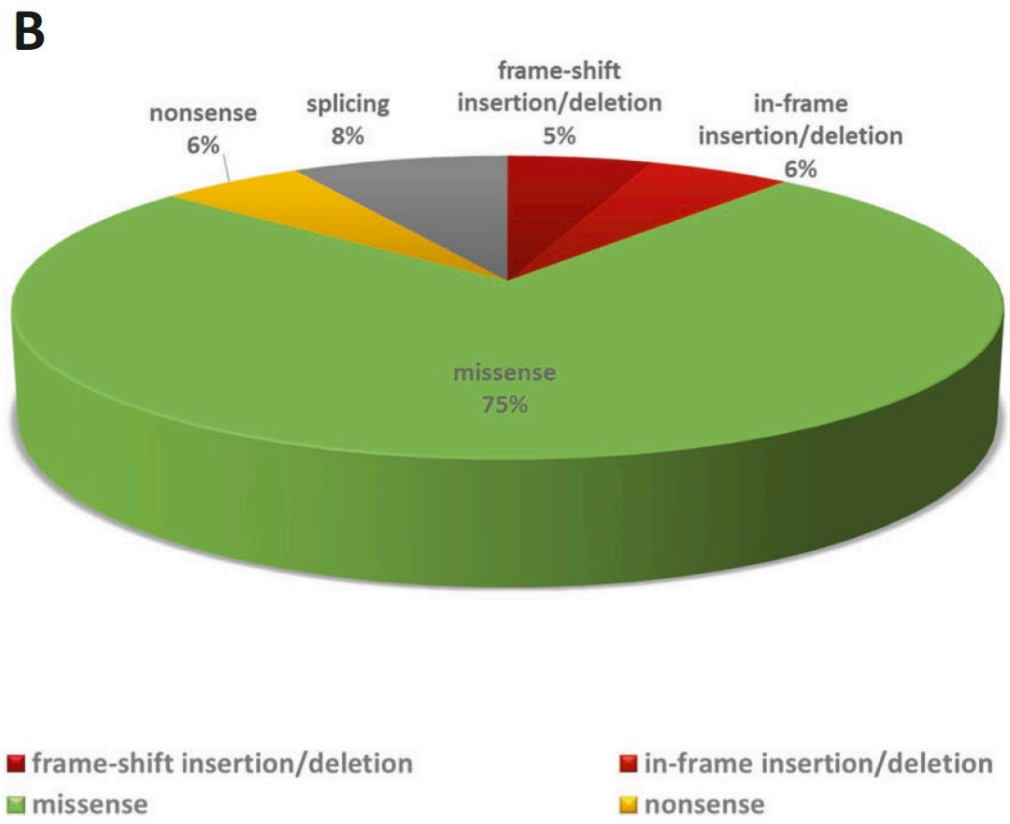


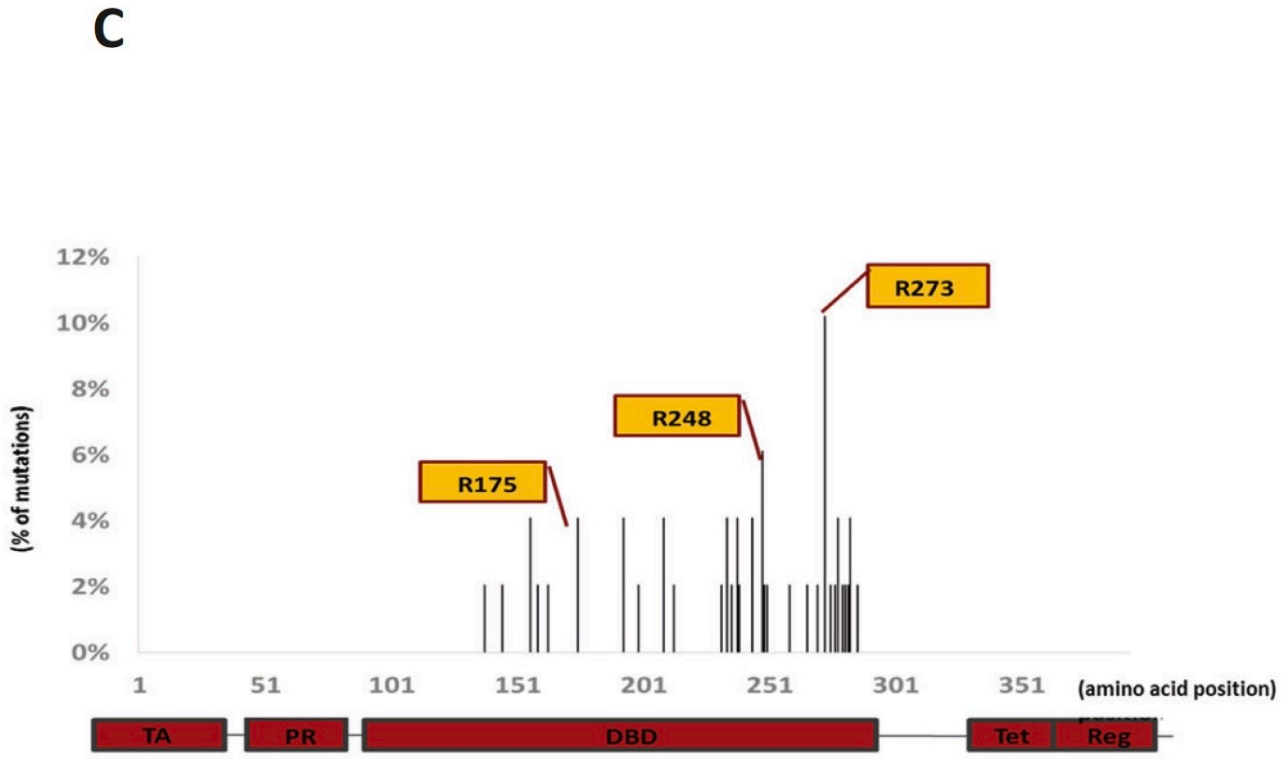


Liu YC et al. *Mod Pathol* 2020;33(3):344-53.

RTP RESEARCH TO PRACTICE

TP53 Mutations Identified by Sanger Sequencing





Liu YC et al. *Mod Pathol* 2020;33(3):344-53.

RTP RESEARCH TO PRACTICE

Blood Adv 2019;3(10):1568-73.

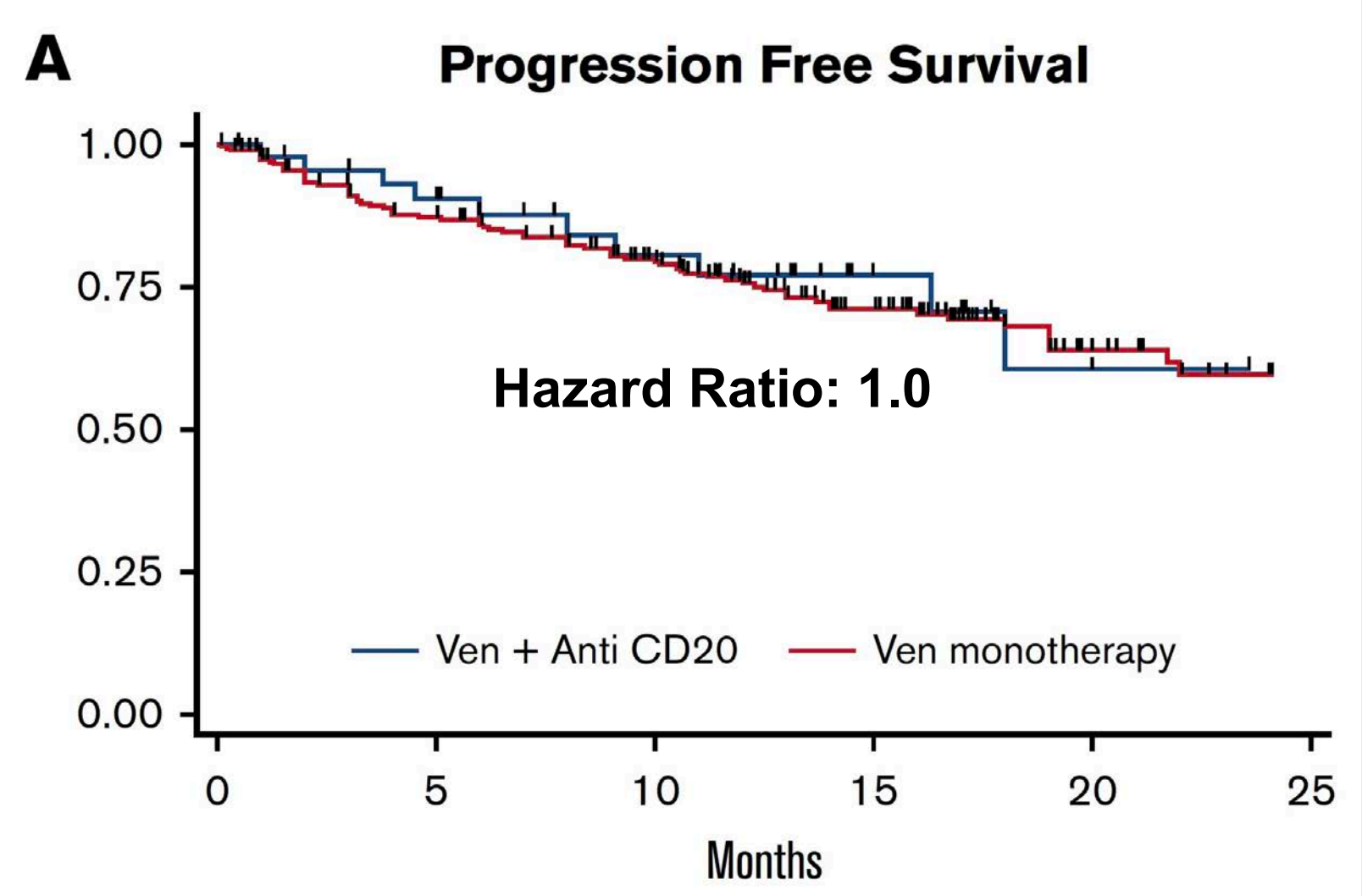
REGULAR ARTICLE

blood advances

A retrospective comparison of venetoclax alone or in combination with an anti-CD20 monoclonal antibody in R/R CLL

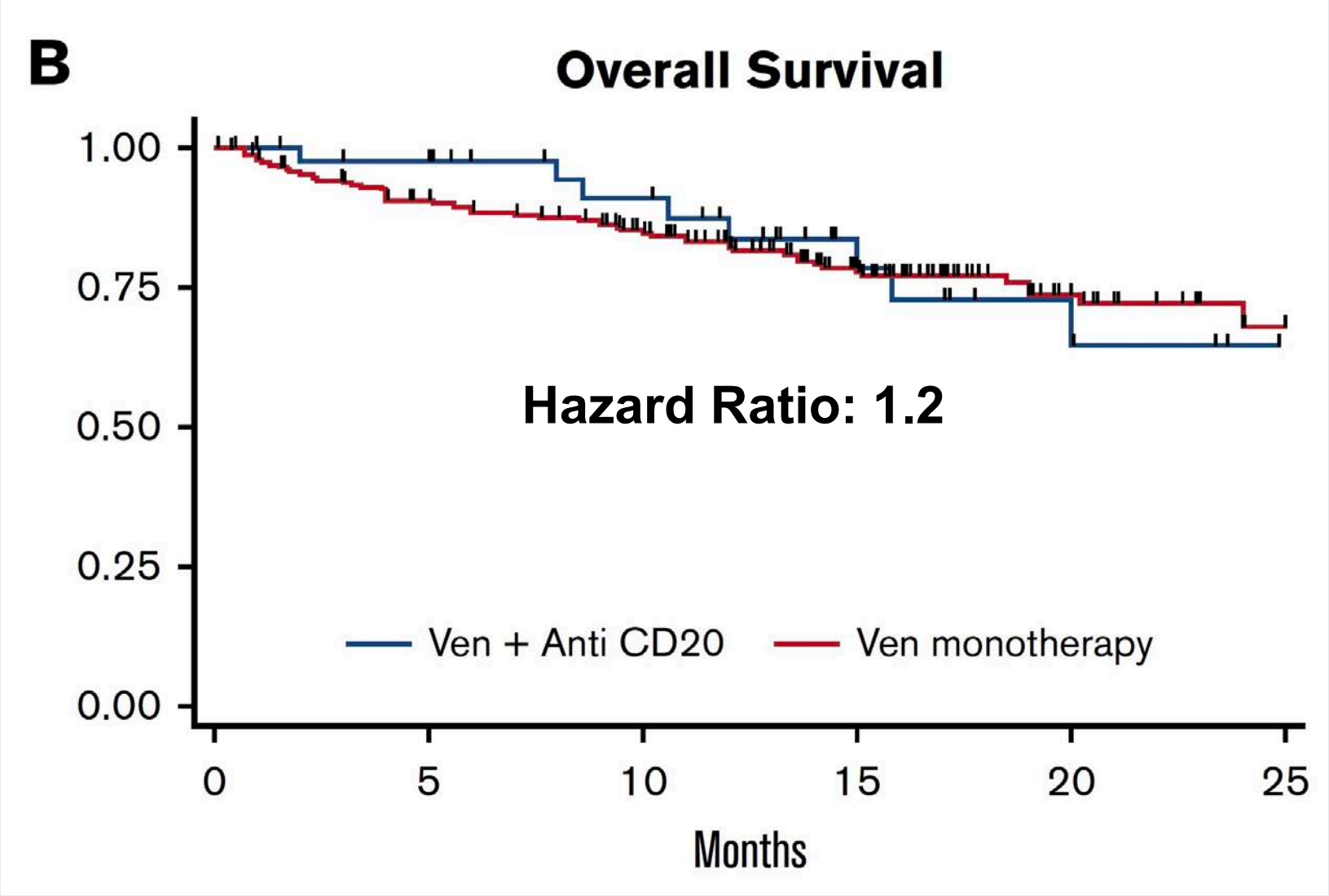
Anthony R. Mato,[1,*] Lindsey E. Roeker,[1,*] Toby A. Eyre,[2] Chadi Nabhan,[3] Nicole Lamanna,[4] Brian T. Hill,[5] Danielle M. Brander,[6] Paul M. Barr,[7] Frederick Lansigan,[8] Bruce D. Cheson,[9] Arun K. Singavi,[10] Maryam Sarraf Yazdy,[9] Nirav N. Shah,[10] John N. Allan,[11] Erica B. Bhavsar,[11] Joanna Rhodes,[12] Kaitlin Kennard,[12] Stephen J. Schuster,[12] AnnaLynn M. Williams,[7] Alan P. Skarbnik,[13] Andre H. Goy,[13] Julie M. Goodfriend,[1] Colleen Dorsey,[1] Catherine C. Coombs,[14] Hande Tuncer,[15] Chaitra S. Ujjani,[16] Ryan Jacobs,[17] Allison M. Winter,[5] John M. Pagel,[18] Neil Bailey,[18] Anna Schuh,[2] Mazyar Shadman,[16] Andrea Sitlinger,[6] Hanna Weissbrot,[4] Sivraj Muralikrishnan,[8] Andrew Zelenetz,[1] Amy A. Kirkwood,[19] and Christopher P. Fox[20]

PFS Stratified by Venetoclax Monotherapy and Ven with Anti-CD20 for R/R CLL



Mato AR et al. *Blood Adv* 2019;3(10):1568-73.

OS Stratified by Venetoclax Monotherapy and Ven with Anti-CD20 for R/R CLL



Mato AR et al. *Blood Adv* 2019;3(10):1568-73.

CLINICAL CANCER RESEARCH | CLINICAL TRIALS: TARGETED THERAPY

Assessment of the Efficacy of Therapies Following Venetoclax Discontinuation in CLL Reveals BTK Inhibition as an Effective Strategy

Anthony R. Mato[1], Lindsey E. Roeker[1], Ryan Jacobs[2], Brian T. Hill[3], Nicole Lamanna[4], Danielle Brander[5], Mazyar Shadman[6], Chaitra S. Ujjani[7], Maryam Sarraf Yazdy[8], Guilherme Fleury Perini[9], Javier A. Pinilla-Ibarz[10], Jacqueline Barrientos[11], Alan P. Skarbnik[12], Pallawi Torka[13], Jeffrey J. Pu[14], John M. Pagel[15], Satyen Gohil[16], Bita Fakhri[17], Michael Choi[18], Catherine C. Coombs[19], Joanna Rhodes[20], Paul M. Barr[21], Craig A. Portell[22], Helen Parry[23], Christine A. Garcia[24], Kate J. Whitaker[1], Allison M. Winter[25], Andrea Sitlinger[26], Sirin Khajavian[6], Ariel F. Grajales-Cruz[10], Krista M. Isaac[22], Pratik Shah[27], Othman S. Akhtar[28], Rachael Pocock[29], Kentson Lam[18], Timothy J Voorhees[19], Stephen J. Schuster[20], Thomas D. Rodgers[30], Christopher P. Fox[31], Nicolas Martinez-Calle[32], Talha Munir[33], Erica B. Bhavsar[34], Neil Bailey[15], Jason C. Lee[4], Hanna B. Weissbrot[4], Chadi Nabhan[35], Julie M. Goodfriend[1], Amber C. King[36], Andrew D. Zelenetz[37], Colleen Dorsey[1], Kayla Bigelow[1], Bruce D. Cheson[8], John N. Allan[34], and Toby A. Eyre[38]

***Clin Cancer Res* 2020;26(14):3589-96.**

ACG Case Rep J 2019;6(7):e00131

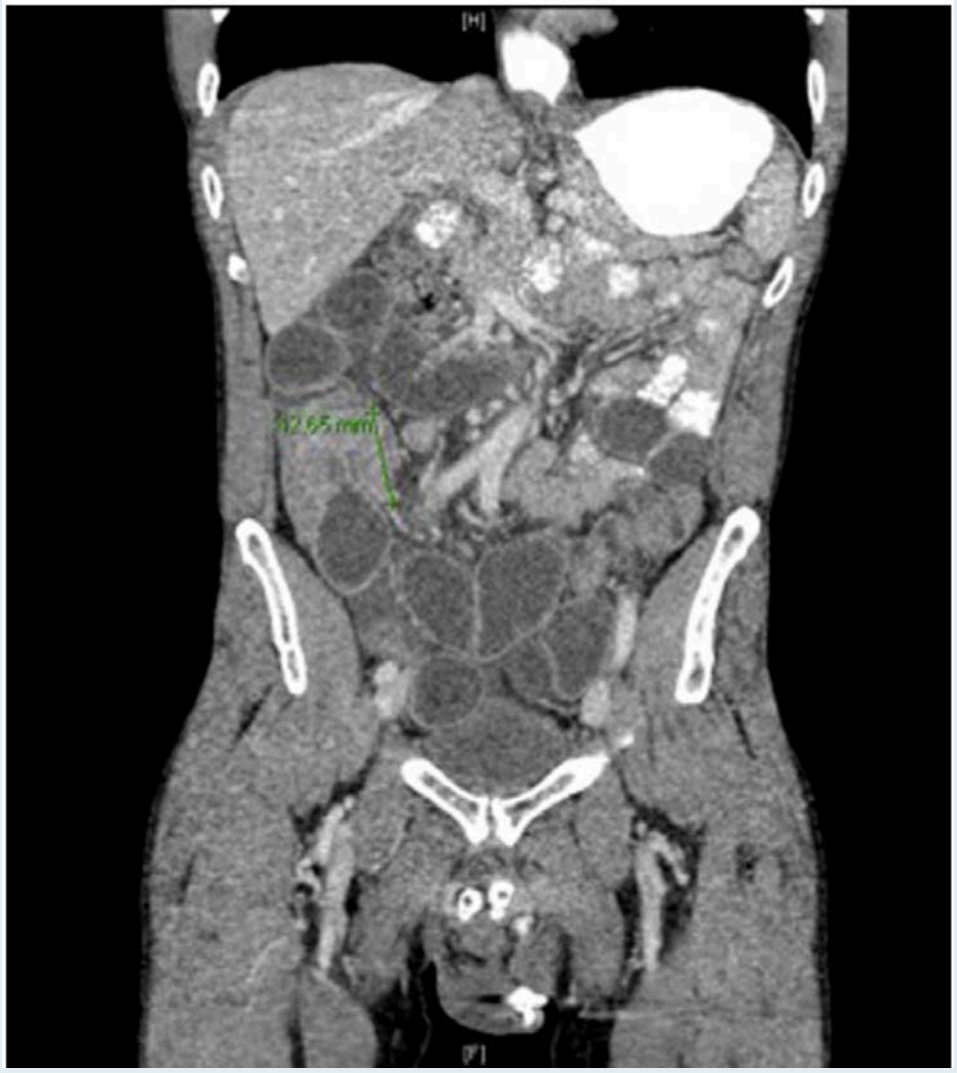
ACG CASE REPORTS JOURNAL

CASE REPORT | SMALL BOWEL

Recurrent Gastrointestinal Near-Tetraploid Diffuse Large B-Cell Lymphoma Causing Intussusception and Ileal Ulceration

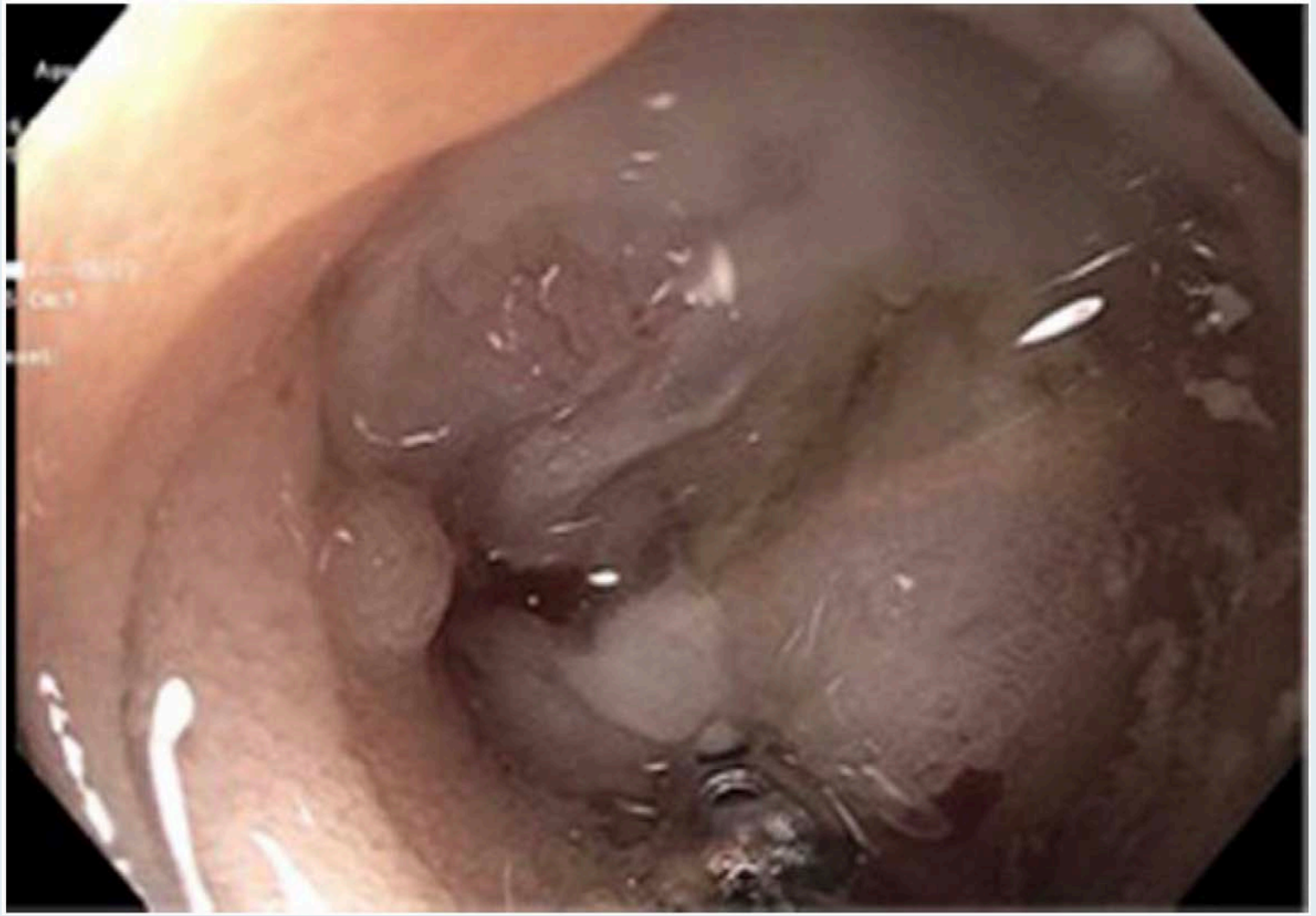
Steven N. Mathews, MD[1], Rachel Niec, MD, PhD[1], Susan Mathew, PhD[2], John N. Allan, MD[3], and Carl V. Crawford, MD[1]

Computed Tomography Scan Showing 4 cm of Intussusception of the Terminal Ileum into the Colon



Mathews SN et al. *ACG Case Rep J* 2019;6(7):e00131.

Colonoscopic View of the Solitary Ulcerated Ileal Polyp Confirmed to be Recurrent Diffuse Large B-Cell Lymphoma



Mathews SN et al. *ACG Case Rep J* 2019;6(7):e00131.

Haematologica 2021;[Online ahead of print]

Phase 2 study of acalabrutinib in ibrutinib-intolerant patients with relapsed/refractory chronic lymphocytic leukemia

by Kerry A. Rogers, Philip A. Thompson, John N. Allan, Morton Coleman, Jeff P. Sharman, Bruce D. Cheson, Daniel Jones, Raquel Izumi, Melanie M. Frigault, Cheng Quah, Rakesh K. Raman, Priti Patel, Min Hui Wang, and Thomas J. Kipps

Worldwide Examination of Patients with CLL Hospitalized for COVID-19

Roeker LE et al.

ASH 2020;Abstract 1590.

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

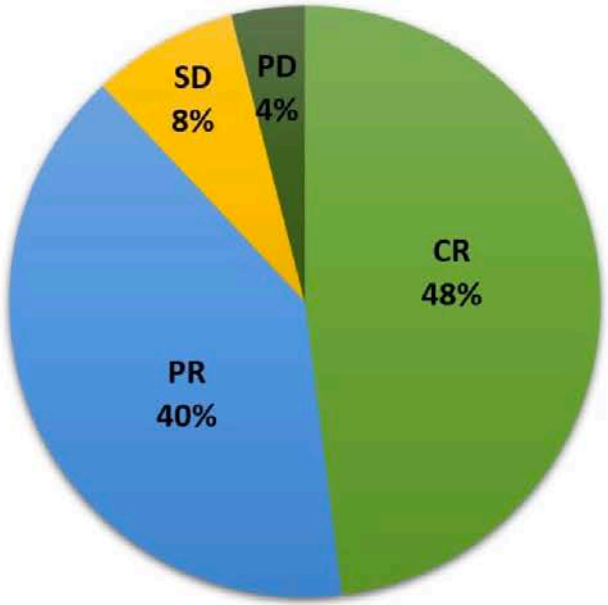
Venetoclax Re-Treatment of Chronic Lymphocytic Leukemia Patients after a Previous Venetoclax-based Regimen

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]

1. Memorial Sloan Kettering Cancer Center, New York, NY; 2. Weill Cornell Medicine, New York, NY; 3. AbbVie, Inc., North Chicago, IL; 4. AbbVie Inc., North Chicago, IL; 5. SUNY Upstate Medical University Cancer Center, Syracuse, NY; 6. Wilmot Cancer Institute, University of Rochester Medical Center, Rochester, NY; 7. UNC Health Care, Chapel Hill, NC; 8. University of Pennsylvania, Philadelphia, PA; 9. Novant Health, Charlotte, NC; 10. Northwell Health Cancer Institute, Lake Success, NY; 11. Hackensack University Medical Center, Hackensack, NJ; Division of Hematology, Hematologic Malignancies and Stem Cell Transplantation, 12. University of Colorado Cancer Center, Denver, CO; 13. University of California-San Diego, San Diego, CA; 14. University Hospital Hradec Kralove, Charles University, Hradec Kralove, Czech Republic; 15. Dartmouth-Hitchcock Medical Center, Lebanon, NH; 16. Department of Medicine, Lymphoma Service, Memorial Sloan Kettering Cancer Center, New York, NY

Results: Initial Ven (Ven1)

Initial Ven (n=25)



ORR 88%

Median duration of exposure Ven1: 15 months (64% pts > 12 months)

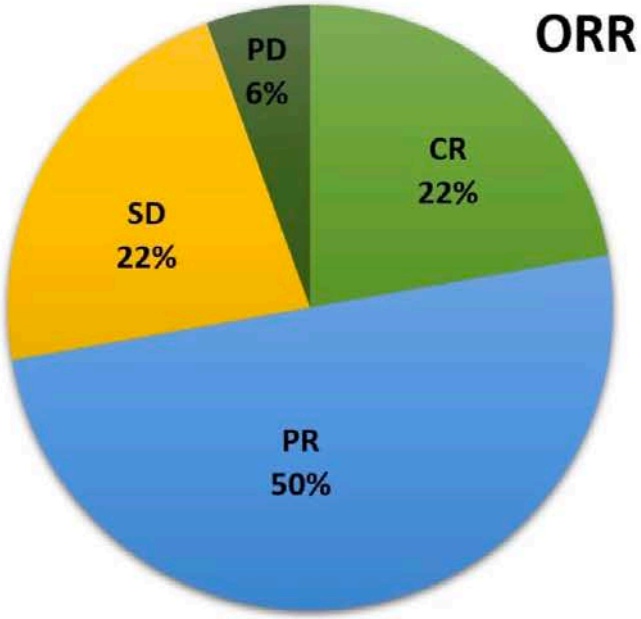
- 8 of 10 pts (80%) undetectable MRD (flow cytometry, $<10^{-4}$)
- Reasons for Ven1 discontinuation:
  - Toxicity: 28%
  - Completion of planned therapy: 24%
  - MD/patient preference: 24%
  - Other: 12%
  - Allogeneic stem cell transplant: 4%
  - Cost: 4%

Abbreviations: CR: complete response, PR: partial response, SD: stable disease, PD: progression of disease

Thompson MC et al. ASH 2020;Abstract 3136.

Results: Ven re-treatment (Ven2)

Ven re-treatment (n=18)



ORR 72.2%

Median time from Ven2 to progression or last follow up: 8 months (0.2-29 months)

- Median of 8.7 months (36% >12 mos) between Ven1 and Ven2
- 88% pts did not have another line of therapy between Ven1 and Ven2
- Reason for Ven2 initiation:
  - CLL progression: 87.5%
  - MRD-positive relapse: 12.5%

- Median PFS: not reached
- Estimated 12 month PFS: 69.1%
- Median follow up for CR pts: 14.5 months
- Median follow up for PR or SD pts: 7 months
- 68% of pts remain on Ven2
- 32% discontinued Ven2:
  - CLL progression: n=4, completion of planned therapy: n=1, unrelated death: n=1, MD/patient preference: n=1

Thompson MC et al. ASH 2020;Abstract 3136.

Blood Lymphat Cancer 2020;10:1-5.

Blood and Lymphatic Cancer: Targets and Therapy

Dovepress

open access to scientific and medical research

Open Access Full Text Article

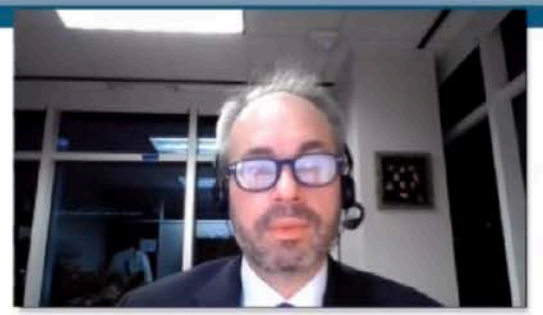
ORIGINAL RESEARCH

The Impact of Age on Survival in CLL Patients Receiving Ibrutinib as Initial Therapy

This article was published in the following Dove Press journal:
Blood and Lymphatic Cancer: Targets and Therapy

Chaitra Ujjani,[1] Anthony Mato,[2] Brian T Hill,[3] John N Allan,[4] Frederick Lansigan,[5] Ryan Jacobs,[6] Alan Skarbnik,[7] Hande Tuncer,[8] John Pagel,[9] Danielle Brander,[10] Bruce Cheson,[11] Paul Barr,[12] Lindsey E Roeker,[2] Jeffrey Pu,[13] Nirav N Shah,[14] Andre Goy,[15] Stephen J Schuster,[16] Nicole Lamanna,[17] Alison Sehgal,[18] Constantine S Tam,[19] Mazyar Shadman[1]

Ibrutinib Plus Venetoclax for First-Line Treatment of Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma: 1-Year Disease-Free Survival Results From the MRD Cohort of the Phase 2 CAPTIVATE Study

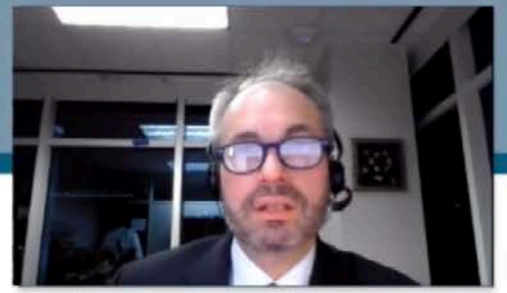


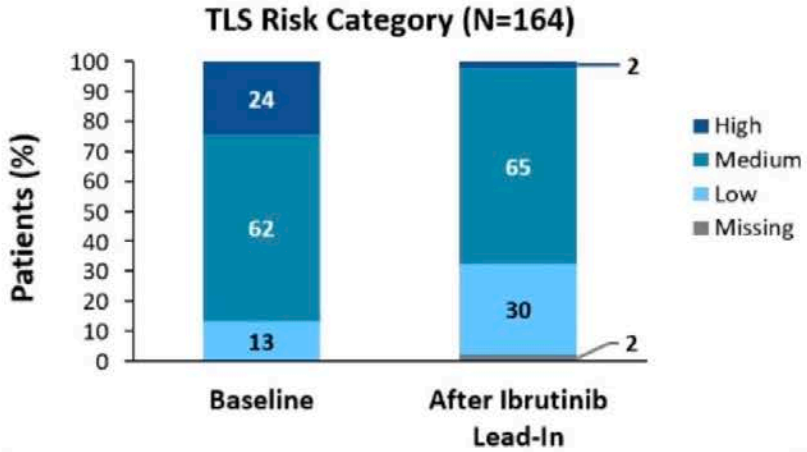
William G. Wierda, MD, PhD[1]; Constantine S. Tam, MBBS, MD[2]; John N. Allan, MD[3]; Tanya Siddiqi, MD[4]; Thomas J. Kipps, MD, PhD[5]; Stephan Opat, FRACP, FRCPA, MBBS[6]; Alessandra Tedeschi, MD[7]; Xavier C. Badoux, MBBS, FRACP, FRCPA[8]; Bryone J. Kuss, MBBS, PhD, FRACP, FRCPA[9]; Sharon Jackson, MD[10]; Carol Moreno, MD, PhD[11]; Ryan Jacobs, MD[12]; John M. Pagel, MD, PhD[13]; Ian Flinn, MD, PhD[14]; Cathy Zhou, MS[15]; Edith Szafer-Glusman, PhD[15]; Joi Ninomoto, PharmD[15]; James P. Dean, MD, PhD[15]; Danelle F. James, MD, MAS[15]; Paolo Ghia, MD, PhD[16]

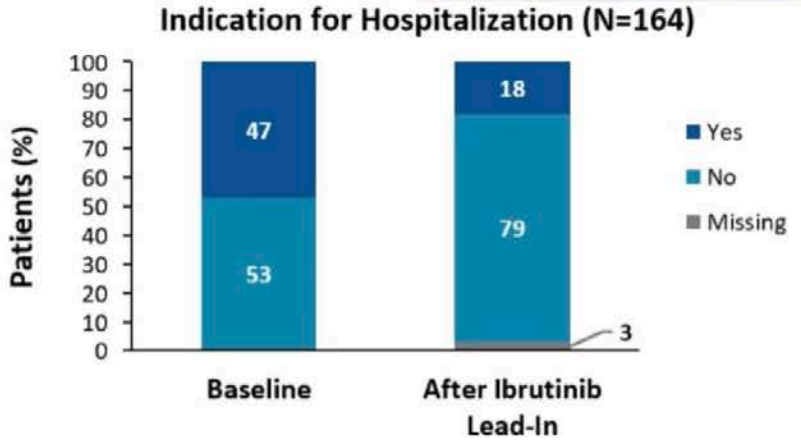
[1]Department of Leukemia, University of Texas MD Anderson Cancer Center, Houston, TX, USA; [2]Peter MacCallum Cancer Center & St. Vincent's Hospital and the University of Melbourne, Melbourne, VIC, Australia; [3]Weill Cornell Medicine, New York, NY, USA; [4]City of Hope National Medical Center, Duarte, CA, USA; [5]UCSD Moores Cancer Center, San Diego, CA, USA; [6]Monash University, Clayton, VIC, Australia; [7]ASST Grande Ospedale Metropolitano Niguarda, Milano, Italy; [8]Ministry of Health, Kogarah, NSW, Australia; [9]Flinders University and Medical Centre, Bedford Park, SA, Australia; [10]Middlemore Hospital, Auckland, New Zealand; [11]Hospital de la Santa Creu I Sant Pau, Autonomous University of Barcelona, Barcelona, Spain; [12]Levine Cancer Institute, Charlotte, NC, USA; [13]Swedish Cancer Institute Hematologic Malignancies Program, Seattle, WA, USA;
[14]Sarah Cannon Research Institute/Tennessee Oncology, Nashville, TN, USA; [15]Pharmacyclics LLC, an AbbVie Company, Sunnyvale, CA, USA; [16]Università Vita-Salute San Raffaele and IRCCS Ospedale San Raffaele, Milano, Italy

ASH 2020;Abstract 123

3 Cycles of Ibrutinib Lead-In Reduces TLS Risk and Hospitalization







- After ibrutinib lead-in, 90% of patients with baseline high TLS risk shifted to medium or low TLS risk categories[1]
- Among 77 patients for whom hospitalization would have been indicated[a] with venetoclax initiation, hospitalization was no longer indicated in 51 patients (66%) after ibrutinib lead-in
- Overall, 131/159 patients (82%) initiated venetoclax post-ibrutinib lead-in without hospitalization

TLS, tumor lysis syndrome.
[a]Defined as patients with high TLS risk or patients with medium TLS risk and CrCl <80 mL/min at baseline.

1. Siddiqi T et al. EHA 2020, Abstract #S158.

ASH 2020, CAPTIVATE-MRD; Wierda et al.

Wierda WG et al. ASH 2020;Abstract 123.

Blood 2020;136(10):1134-43.

blood®

Regular Article

CLINICAL TRIALS AND OBSERVATIONS

Outcomes of COVID-19 in patients with CLL: a multicenter international experience

Anthony R. Mato,[1,*] Lindsey E. Roeker,[1,*] Nicole Lamanna,[2] John N. Allan,[3] Lori Leslie,[4] John M. Pagel,[5] Krish Patel,[5] Anders Osterborg,[6] Daniel Wojenski,[7] Manali Kamdar,[8] Scott F. Huntington,[9] Matthew S. Davids,[10] Jennifer R. Brown,[10] Darko Antic,[11] Ryan Jacobs,[12] Inhye E. Ahn,[13] Jeffrey Pu,[14] Krista M. Isaac,[15] Paul M. Barr,[16] Chaitra S. Ujjani,[17] Mark B. Geyer,[1] Ellin Berman,[1] Andrew D. Zelenetz,[1] Nikita Malakhov,[3] Richard R. Furman,[3] Michael Koropsak,[4] Neil Bailey,[5] Lotta Hanson,[6] Guilherme F. Perini,[18] Shuo Ma,[7] Christine E. Ryan,[10] Adrian Wiestner,[13] Craig A. Portell,[15] Mazyar Shadman,[17] Elise A. Chong,[19] Danielle M. Brander,[20] Suchitra Sundaram,[21] Amanda N. Seddon,[22] Erlene Seymour,[23] Meera Patel,[23] Nicolas Martinez-Calle,[24] Talha Munir,[25] Renata Walewska,[26] Angus Broom,[27] Harriet Walter,[28] Dima El-Sharkawi,[29] Helen Parry,[30] Matthew R. Wilson,[31] Piers E. M. Patten,[32] José-Ángel Hernández-Rivas,[33] Fatima Miras,[34] Noemi Fernández Escalada,[35] Paola Ghione,[1] Chadi Nabhan,[36] Sonia Lebowitz,[1] Erica Bhavsar,[3] Javier López-Jiménez,[37] Daniel Naya,[38] Jose Antonio Garcia-Marco,[39] Sigrid S. Skånland,[40] Raul Cordoba,[41,†] and Toby A. Eyre[42,†]

CLL-Directed Therapy at Time of COVID-19 Diagnosis

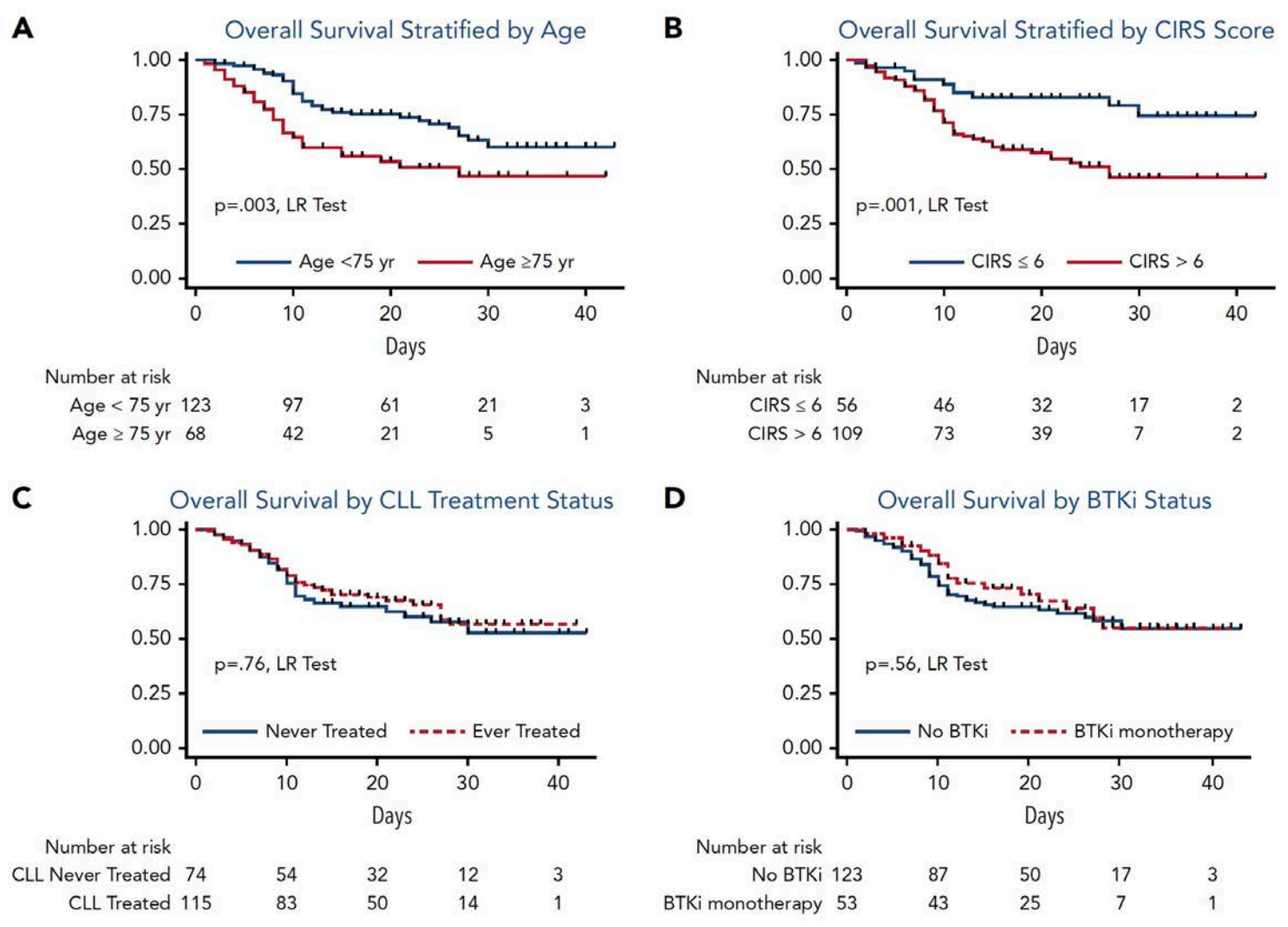
Current therapy	Patients receiving therapy
Total	90
BTKi	
Ibrutinib monotherapy	43
Acalabrutinib monotherapy	9
Zanubrutinib monotherapy	2
Ibrutinib + anti-CD20 mAb	6
Acalabrutinib + anti-CD20 mAb	1
Venetoclax	
Venetoclax monotherapy	7
Venetoclax + anti-CD20 mAb	7
PI3K inhibitor	
Idelalisib	1
Umbralisib	1

Current therapy	Patients receiving therapy
Anti-CD20 mAb	
Rituximab	1
Obinutuzumab	1
Novel drug combination therapy	
BTKi + venetoclax	2
BTKi + venetoclax + anti-CD20 mAb	1
BTKi + PI3Ki + anti-CD20 mAb	3
Venetoclax + PI3Ki + anti-CD20 mAb	1
BTKi + fludarabine + pembrolizumab	1
Bendamustine + rituximab	1
Other	2

Mato AR et al. *Blood* 2020;136(10):1134-43.

RTP RESEARCH TO PRACTICE

OS from Time of COVID-19 Diagnosis Stratified by Age, CIRS Score, Treatment History and Use of BTKi at Time of COVID-19 Diagnosis



Mato AR et al. *Blood* 2020;136(10):1134-43.

RTP RESEARCH TO PRACTICE

Meet The Professor with Dr Allan

MODULE 1: Cases from Dr Allan

MODULE 2: Journal Club with Dr Allan

MODULE 3: Beyond the Guidelines

MODULE 4: Key Recent Data Sets

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

RTP
RESEARCH
TO PRACTICE

The NEW ENGLAND JOURNAL of MEDICINE

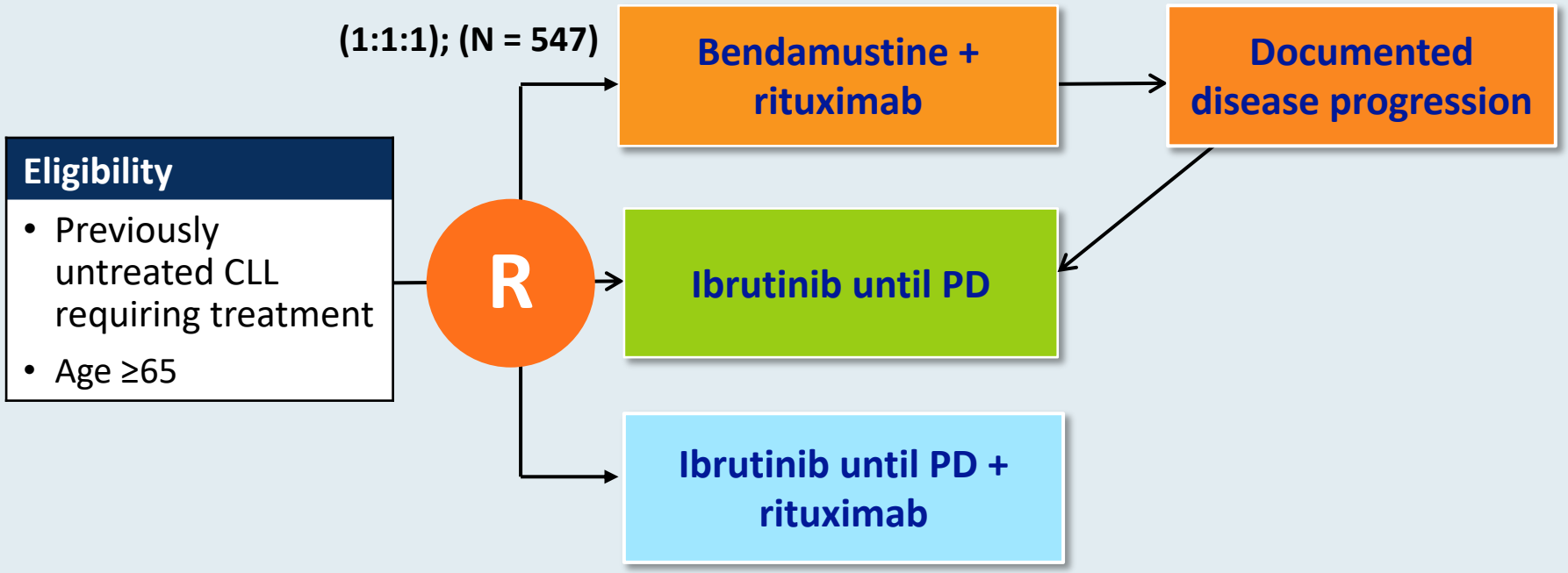
ORIGINAL ARTICLE

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.

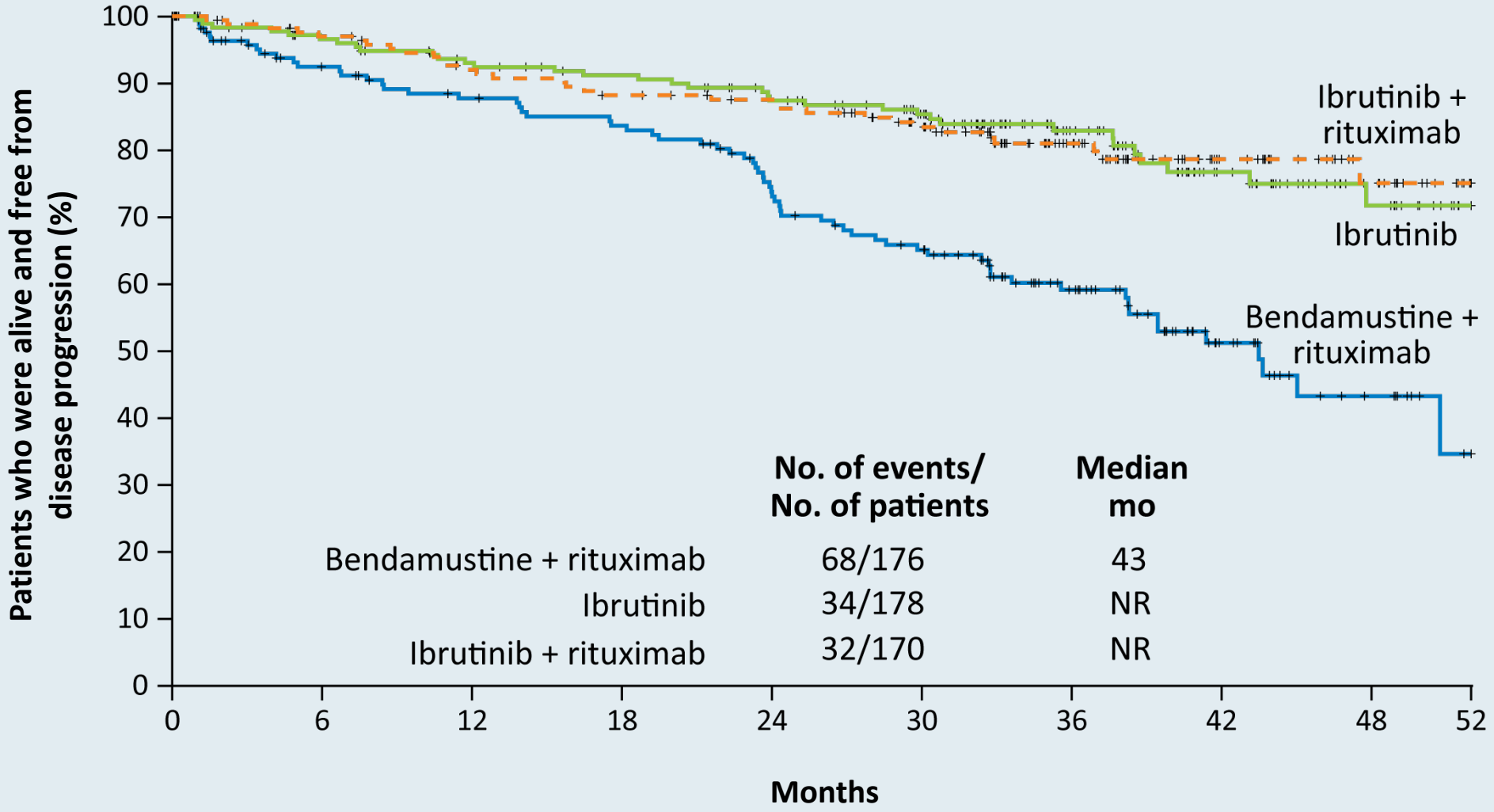
Phase III Alliance A041202 Study Design



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

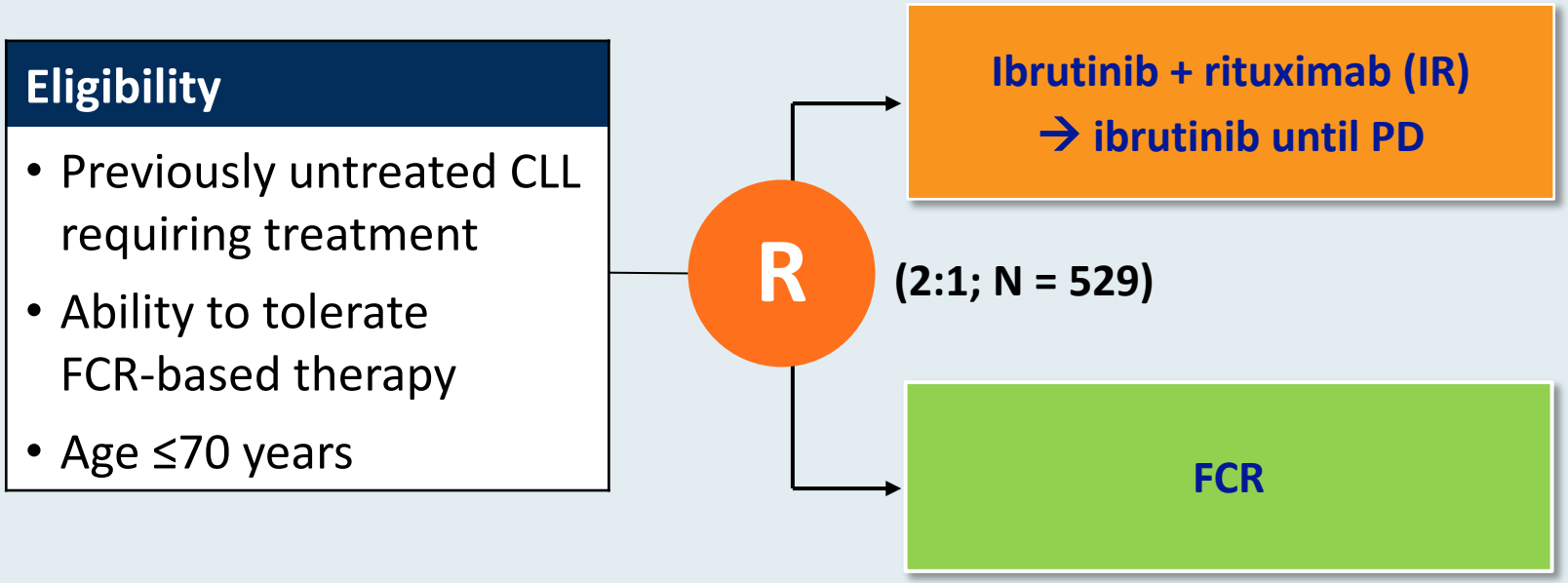
Woyach JA et al. *N Engl J Med* 2018;379(26):2517-28.

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.

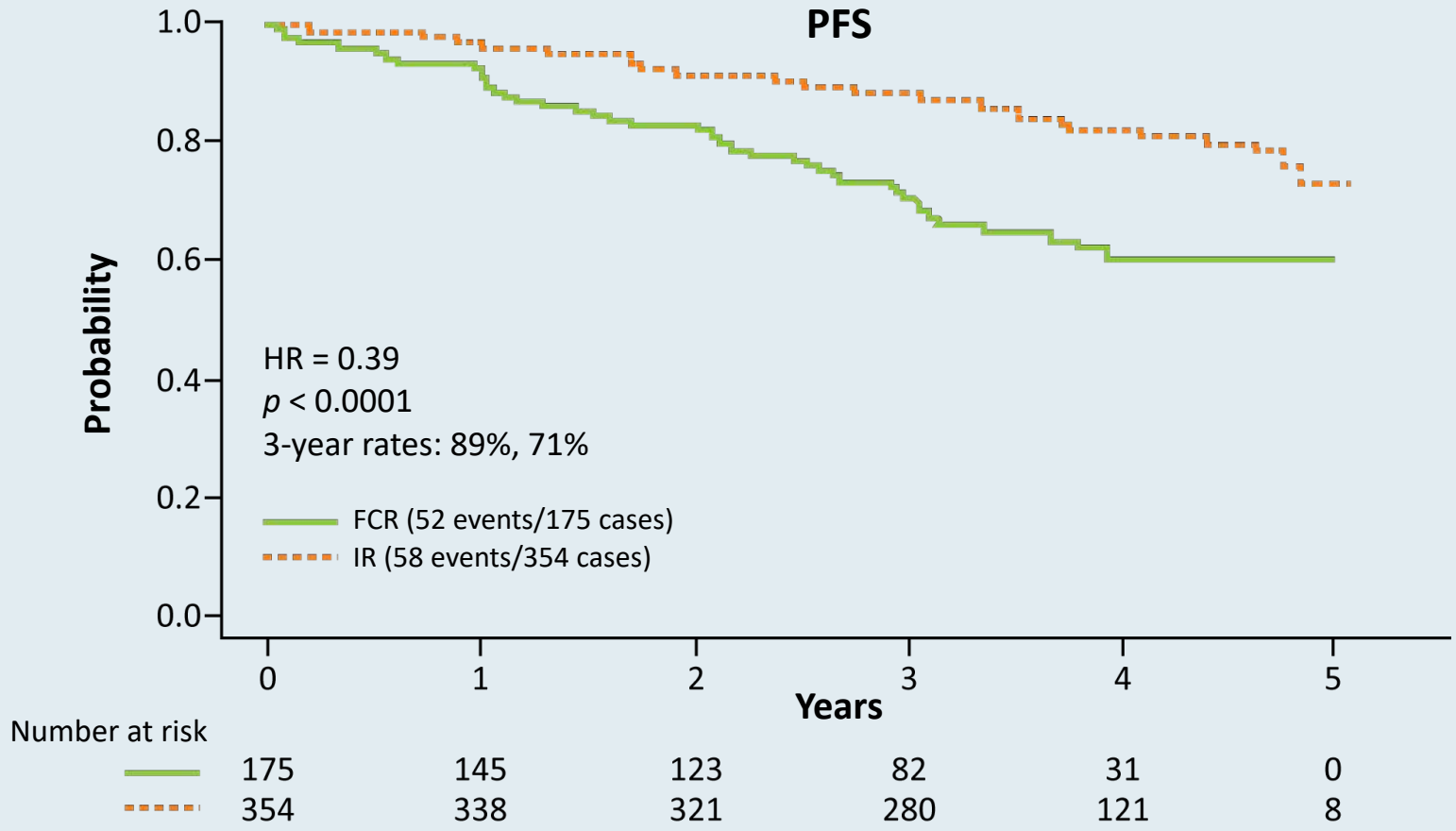
Phase III ECOG-ACRIN E1912 Study Design



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

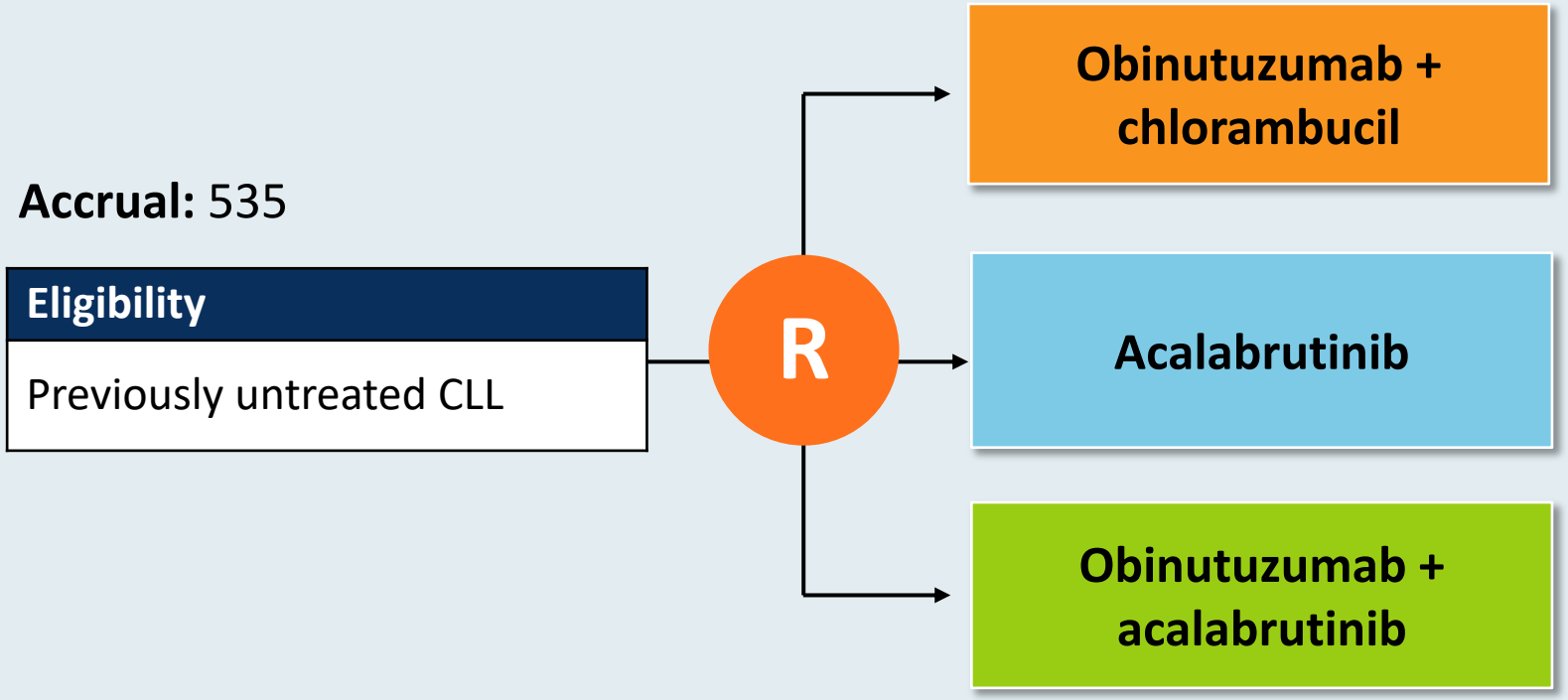
Articles

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.

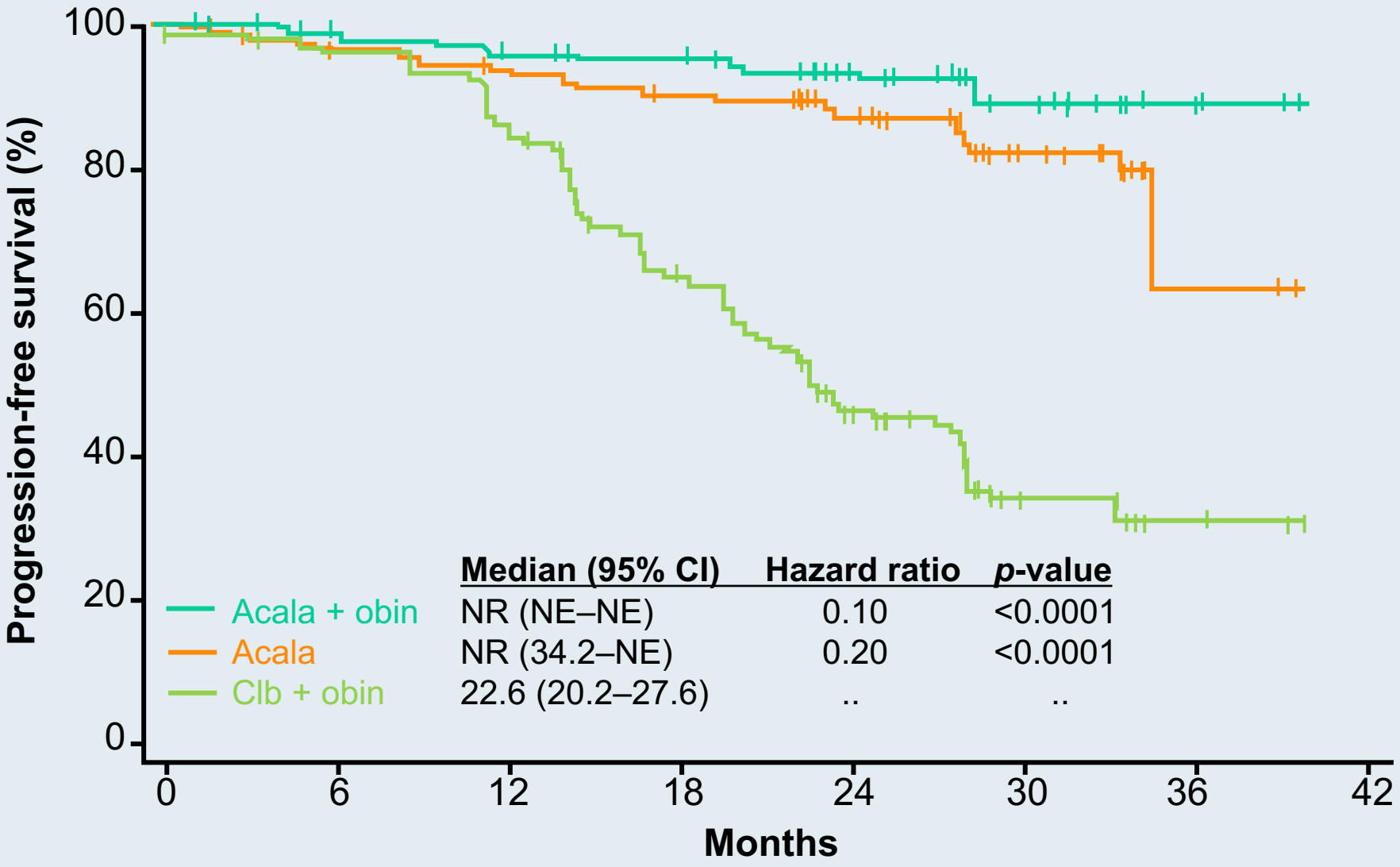
ELEVATE-TN Phase III Trial Schema



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

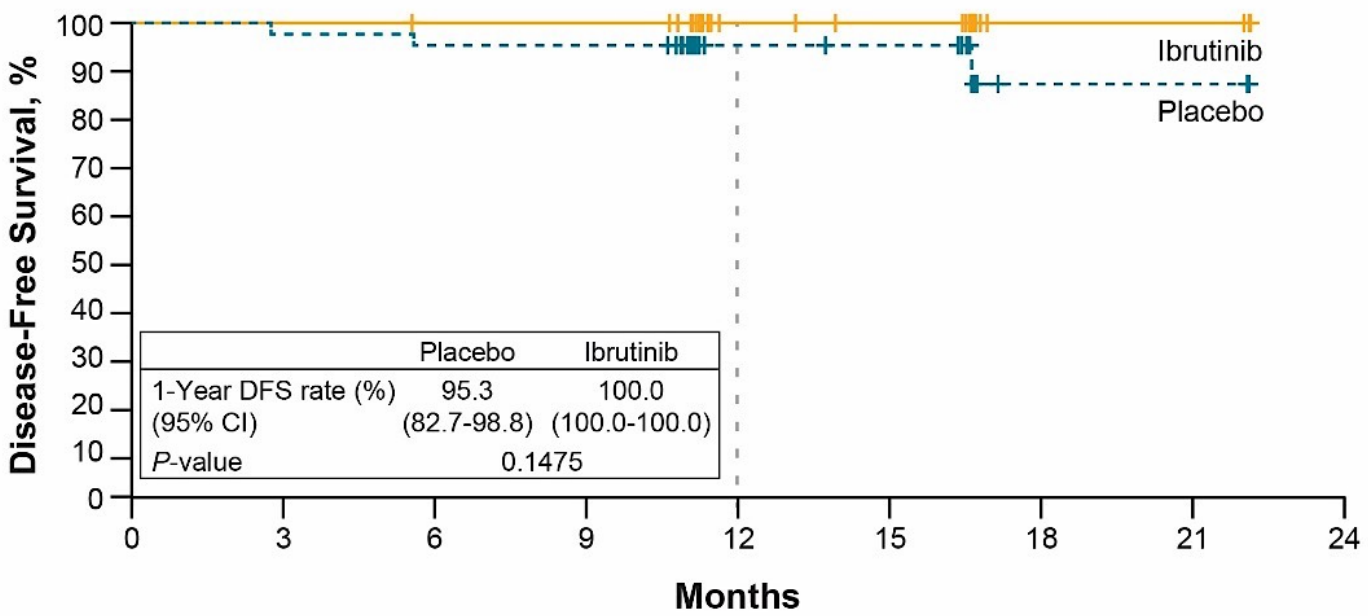
Ibrutinib (Ibr) plus Venetoclax (Ven) for First-Line Treatment of Chronic Lymphocytic Leukemia (CLL)/Small Lymphocytic Lymphoma (SLL): 1-Year Disease-Free Survival (DFS) Results from the MRD Cohort of the Phase 2 CAPTIVATE Study Trial

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:

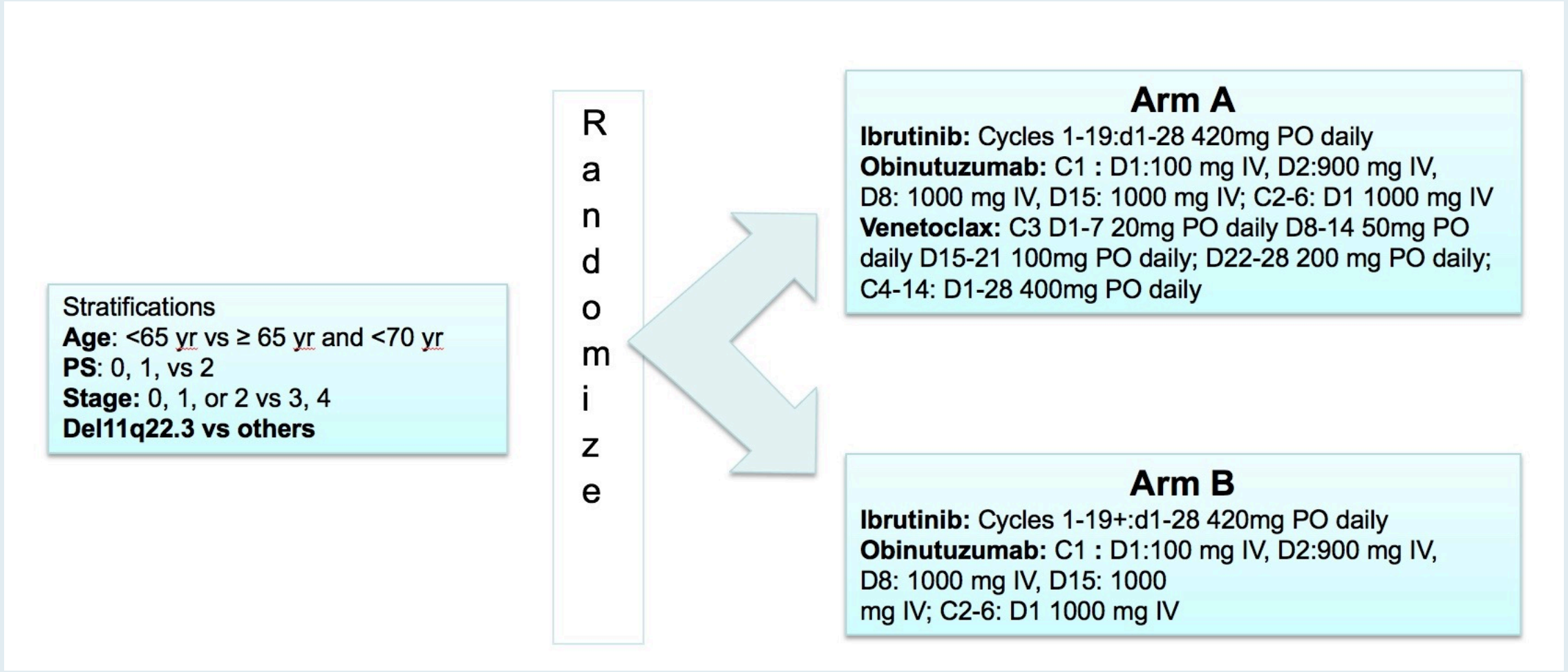
- 95.2% ibrutinib
- 96.7% ibr/ven

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

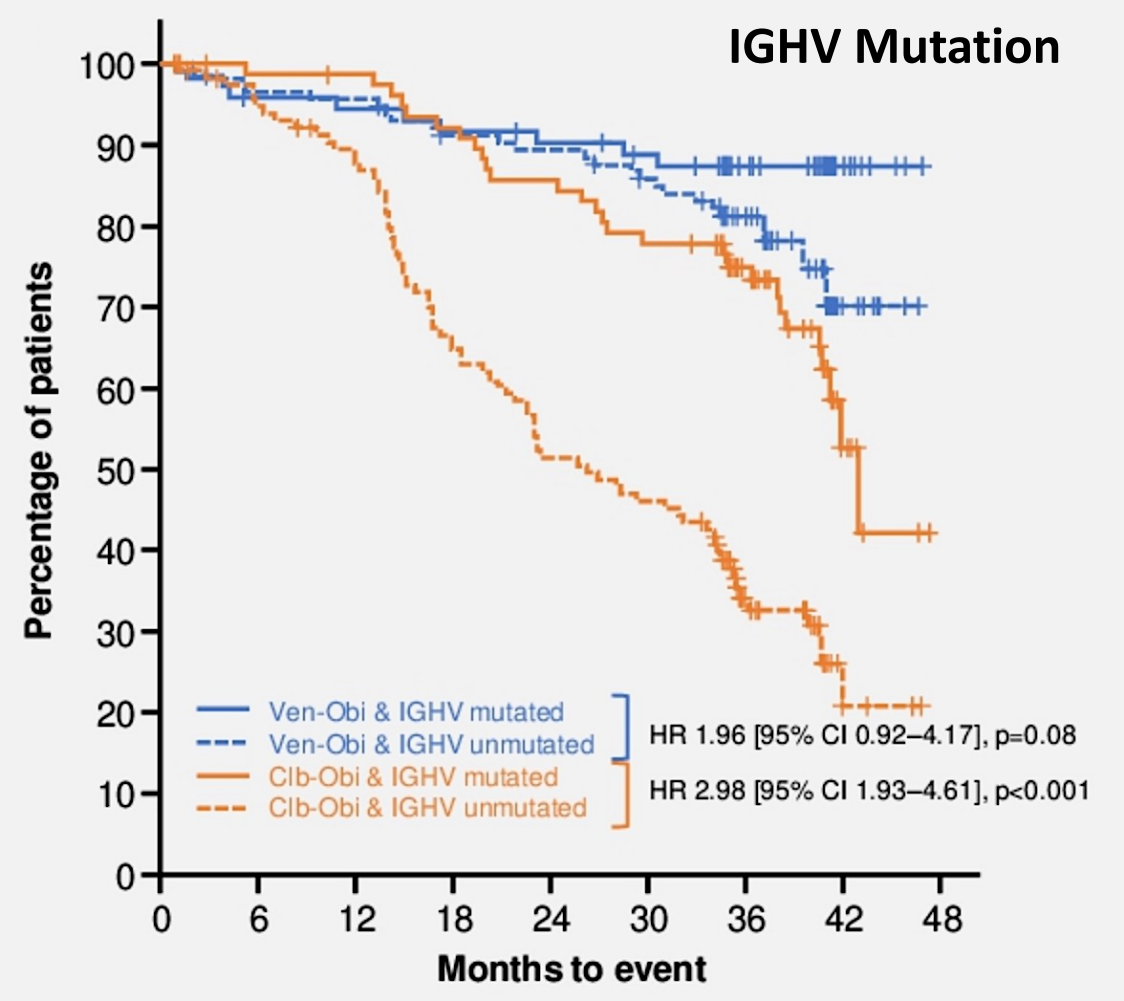
Articles

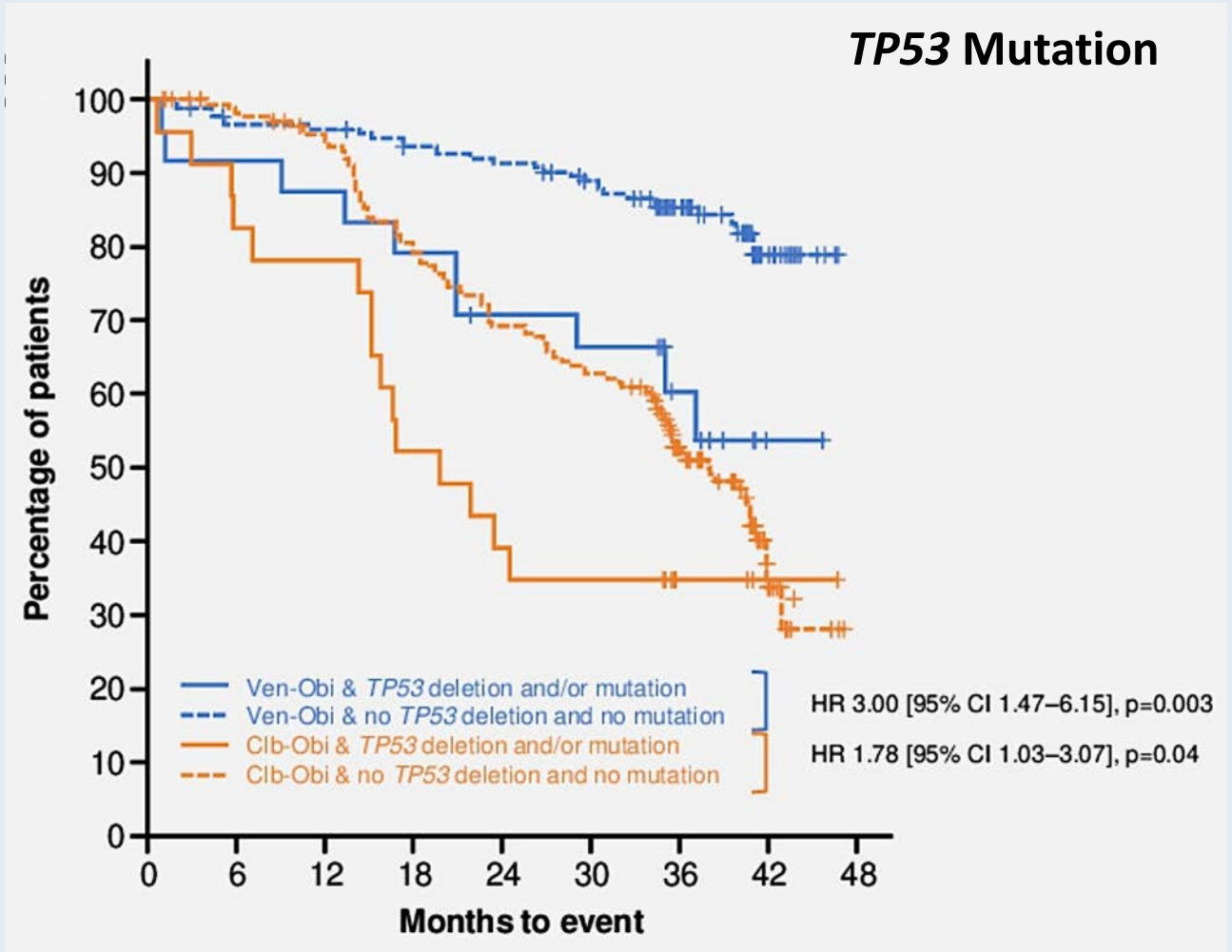
Venetoclax plus obinutuzumab versus chlorambucil plus obinutuzumab for previously untreated chronic lymphocytic leukaemia (CLL14): follow-up results from a multicentre, open-label, randomised, phase 3 trial

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

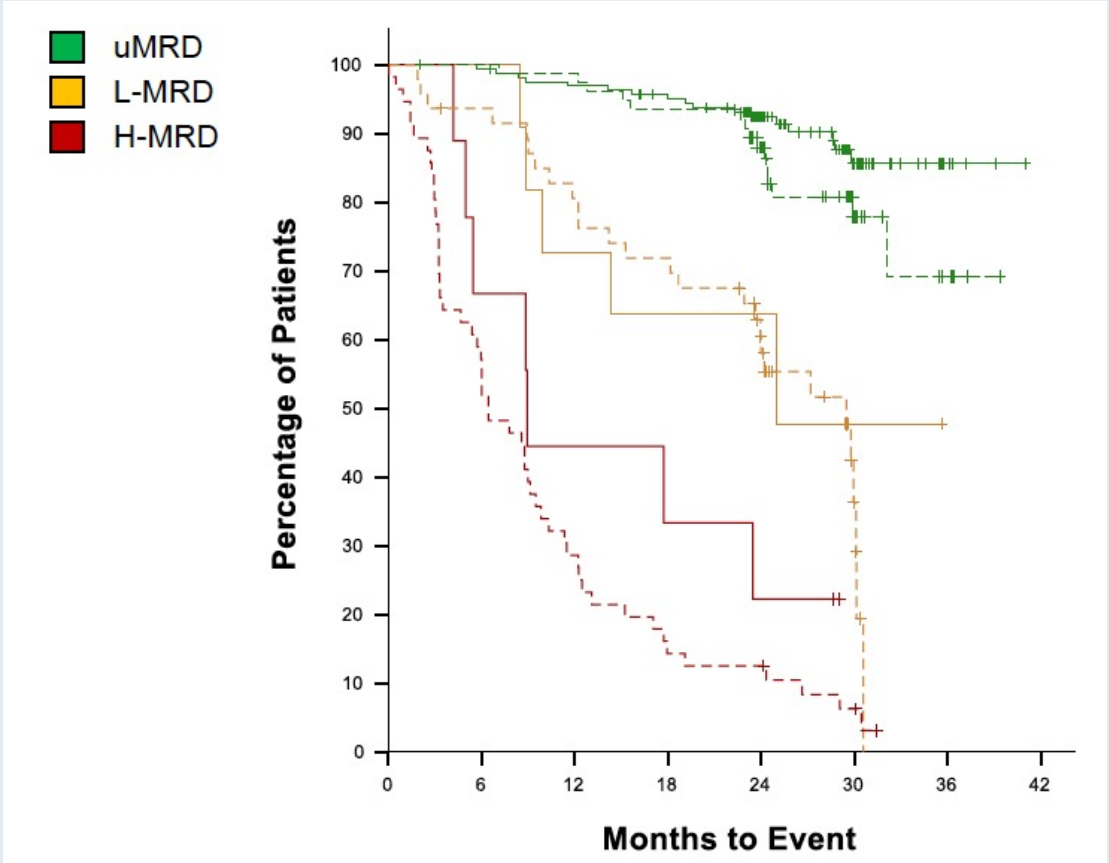




Al-Sawaf O et al. *Lancet Oncol* 2020;21(9):1188-200.

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

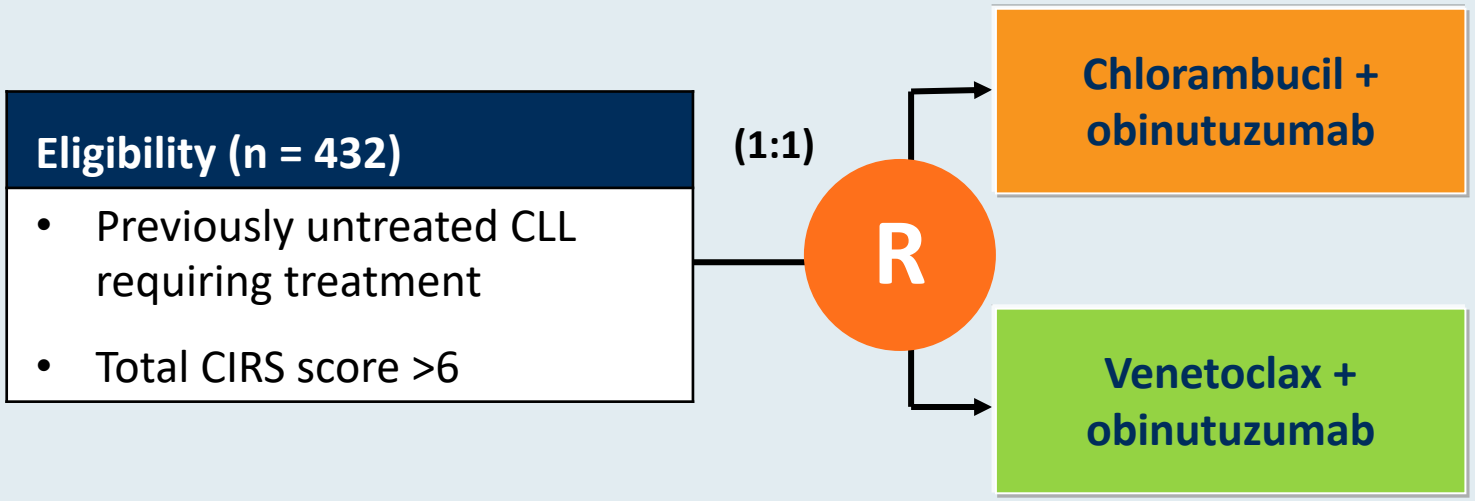
Al-Sawaf O et al. *Lancet Oncol* 2020;21(9):1188-200.

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

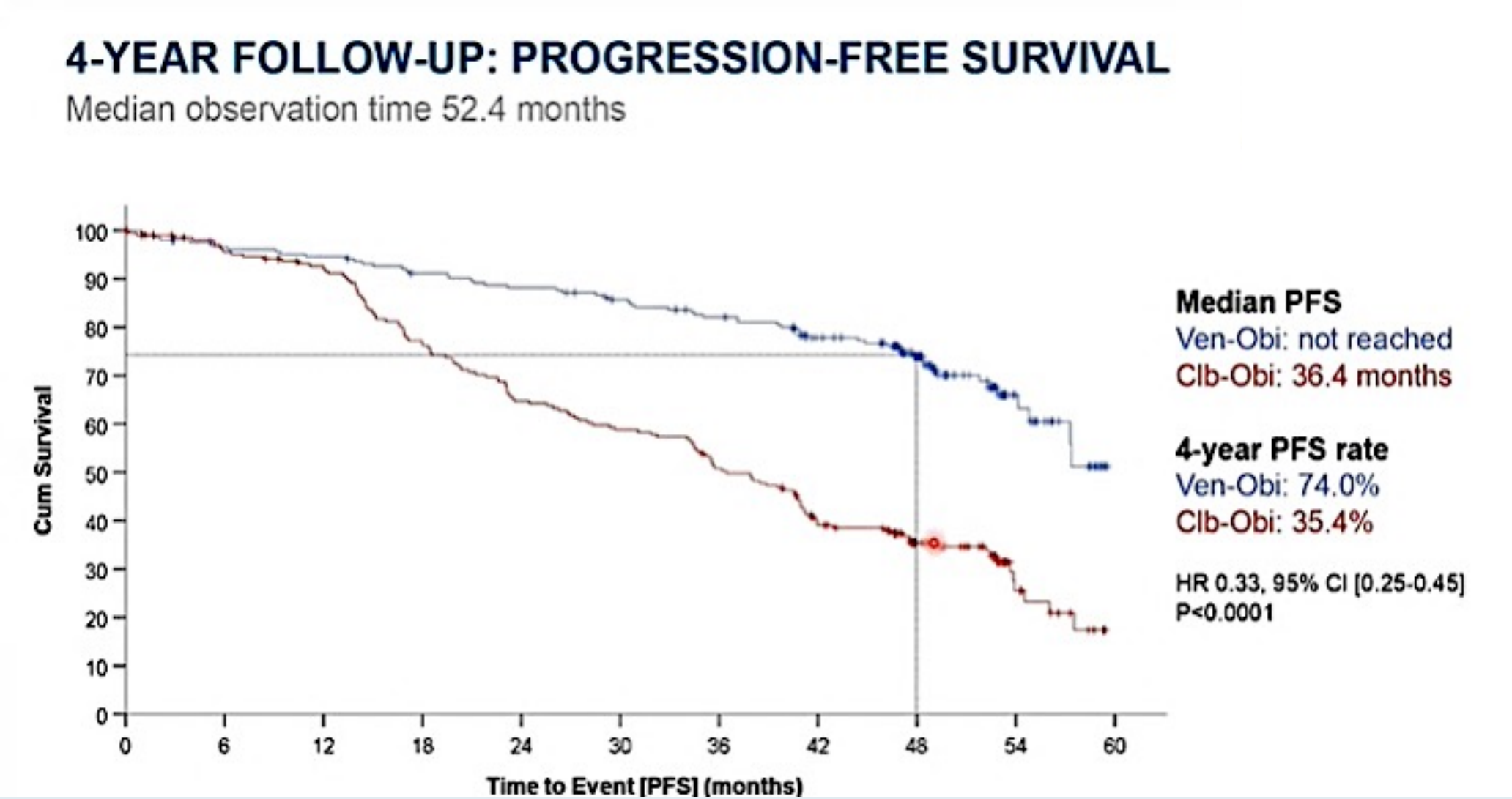


Primary endpoint: Progression-free survival

- 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

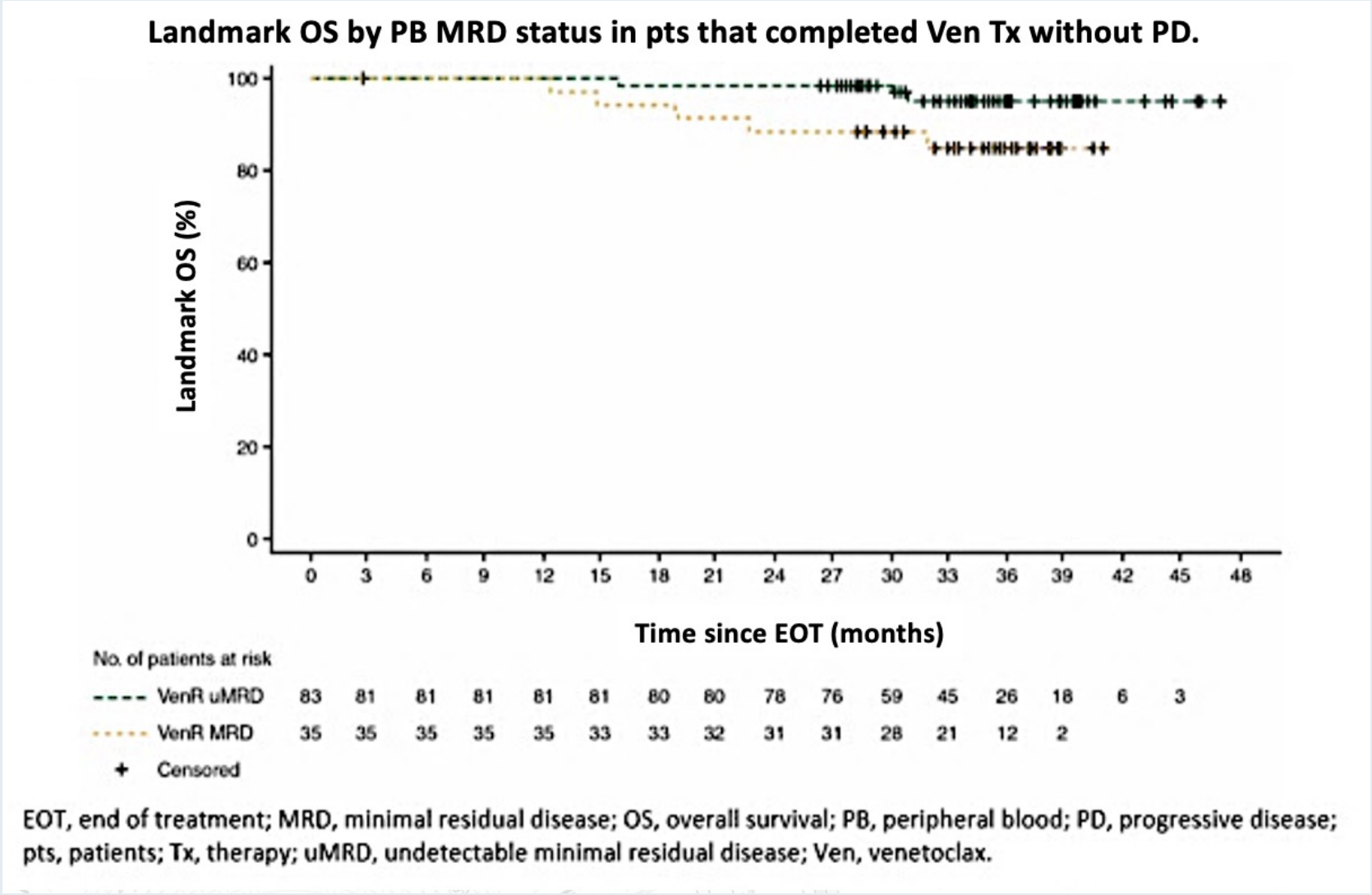
Management of Relapsed/Refractory CLL

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

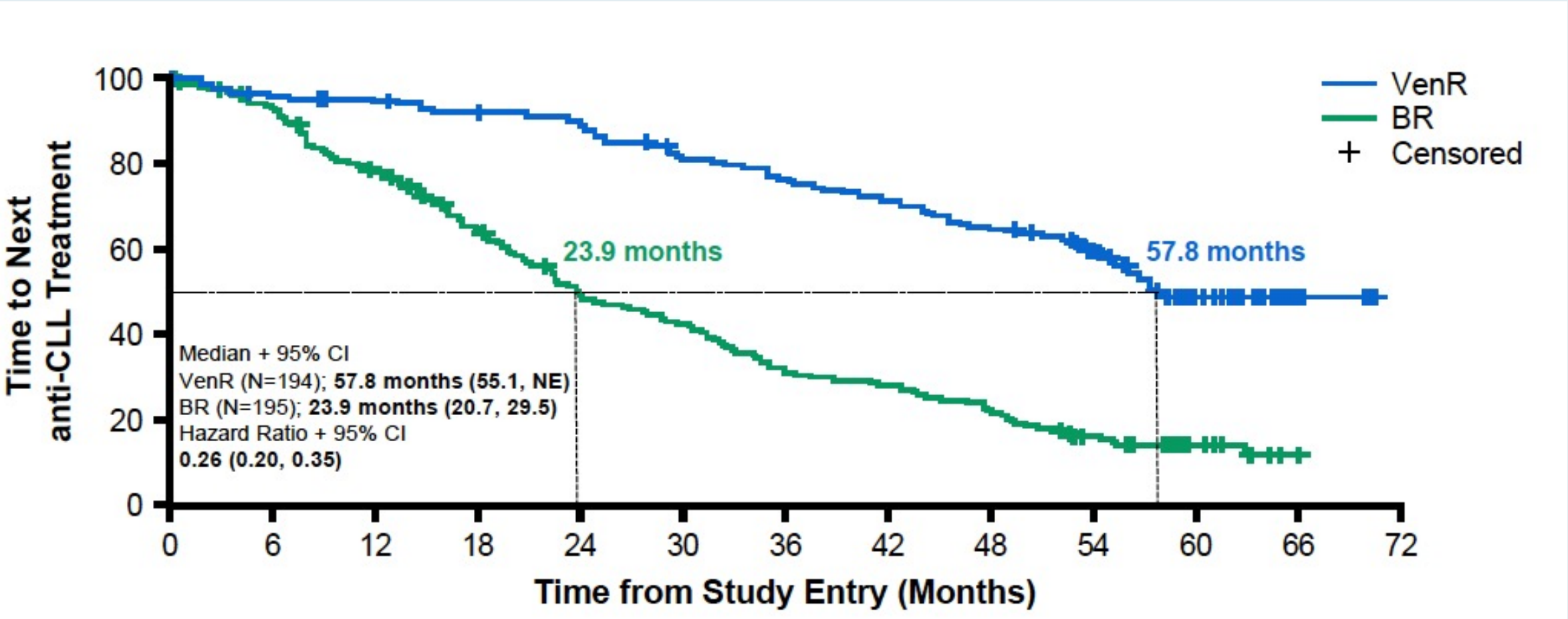
Kater AP et al. ASH 2020;Abstract 125.

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.

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.

RTP RESEARCH TO PRACTICE

Conclusions

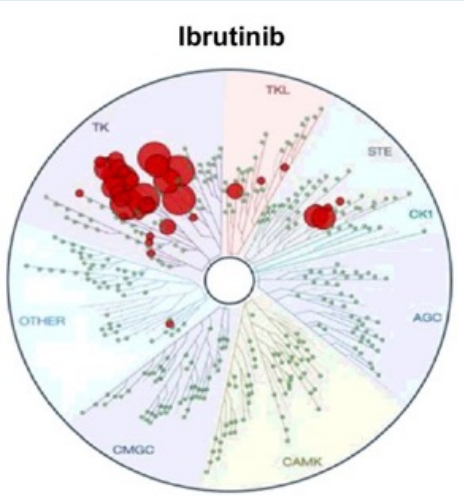
- **ORR:** High ORR of 72.2% for Ven re-treatment
- **Heavily pretreated population:** Cohort studied had median 2 prior therapies, majority R/R (88%), BTKi exposed (60%)
- **Safety:** TLS rare event and majority were able to tolerate 400 mg daily
- **Improved outcomes with time:** Patients with CR to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

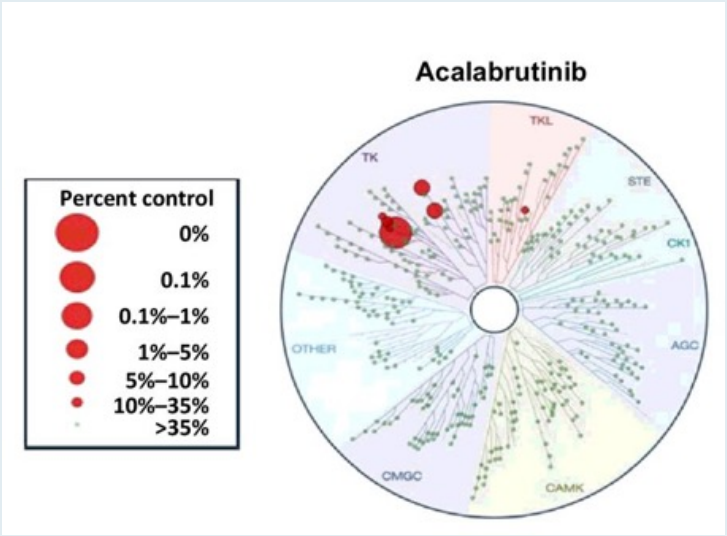
Overview of BTK Inhibitors in CLL

Irreversible

Ibrutinib



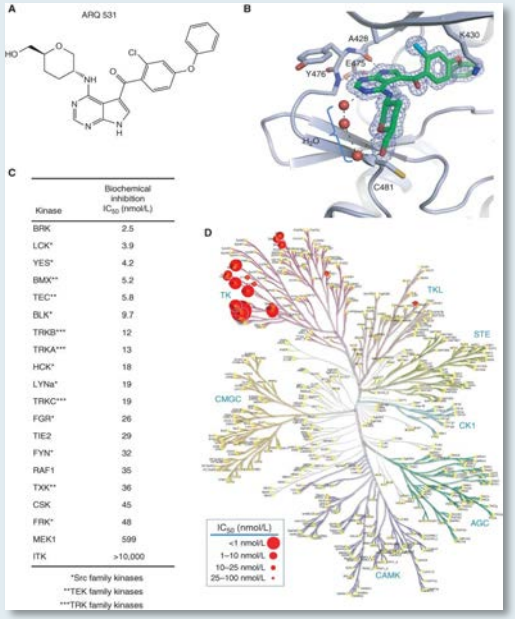
Acalabrutinib



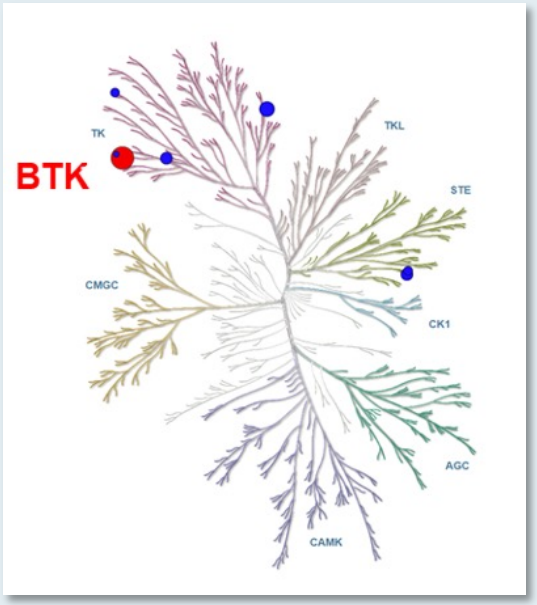
Zanubrutinib

Reversible

ARQ-531 (MK-1026)



LOXO-305



Courtesy of Matthew S Davids, MD, MMSc

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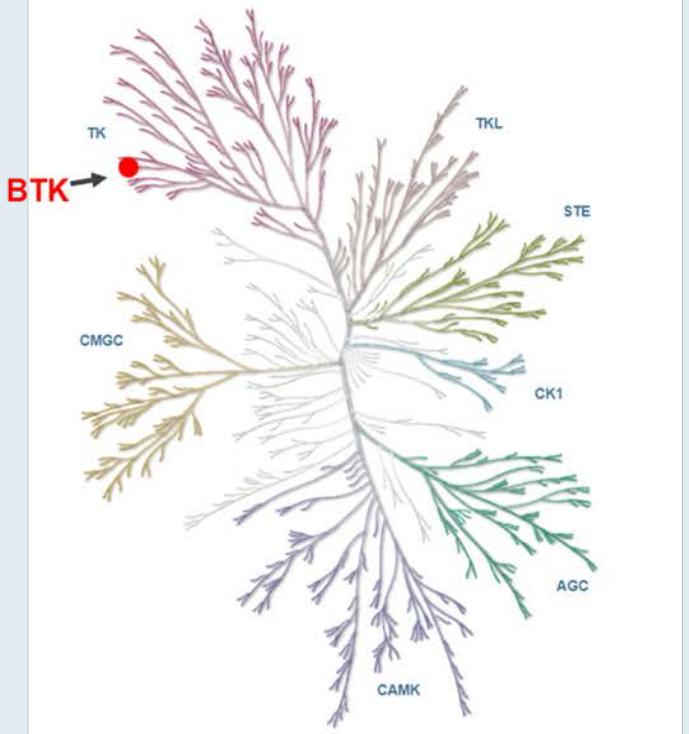
LOXO-305 is a Highly Potent and Selective Non-Covalent BTK Inhibitor

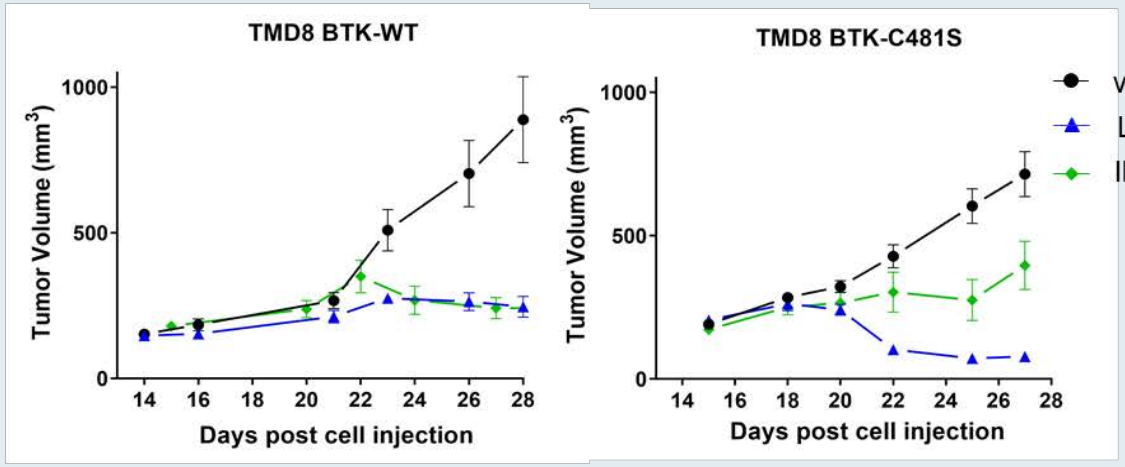
Kinome selectivity

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.

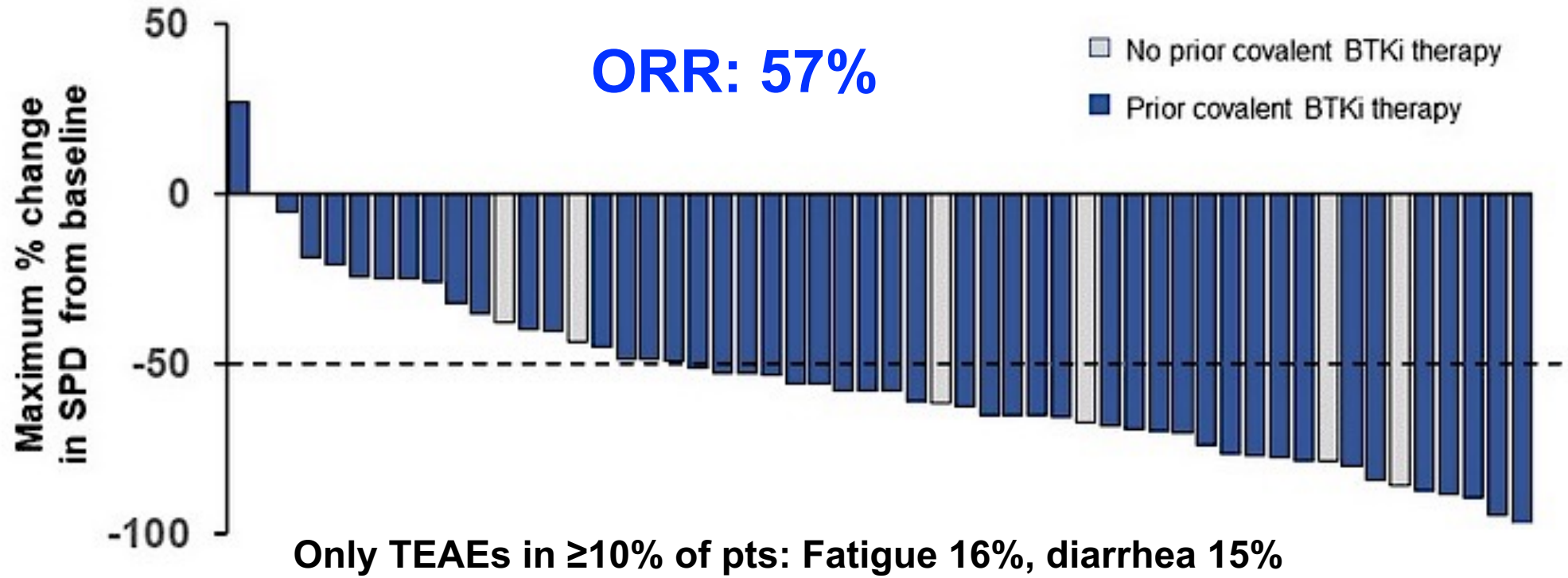
Mato AR et al. ASH 2020;Abstract 542.

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.

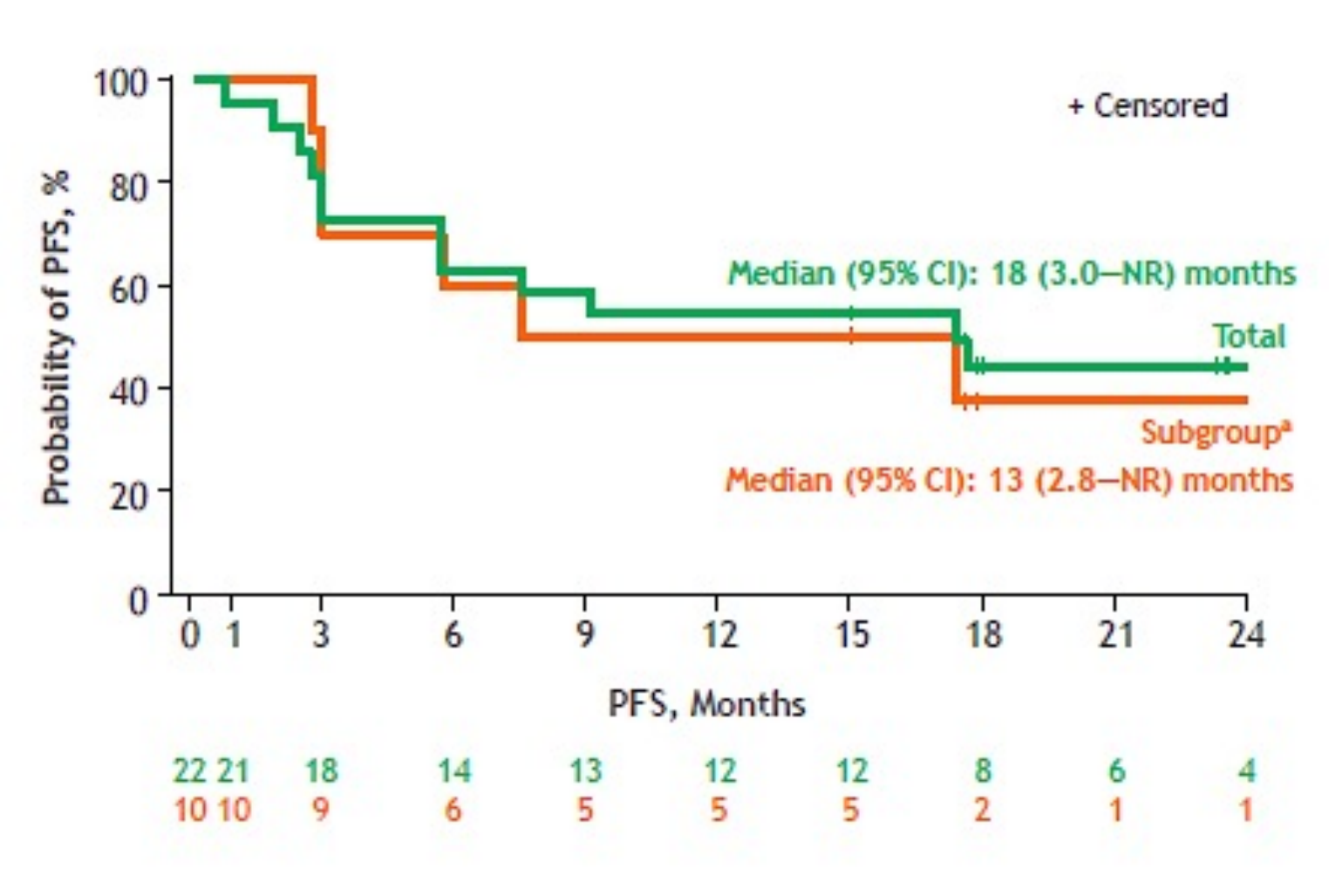
Courtesy of Matthew S Davids, MD, MMSc

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.

RTP RESEARCH TO PRACTICE

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

A Complimentary NCPD Live Webinar Series Hosted in Conjunction with the 46th Annual ONS Congress

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

Non-Small Cell Lung Cancer
Tuesday, April 20, 2021
5:00 PM – 6:30 PM ET

Acute Myeloid Leukemia
Wednesday, April 21, 2021
12:00 PM – 1:00 PM ET

Colorectal and Gastroesophageal Cancers
Wednesday, April 21, 2021
4:45 PM – 5:45 PM ET

Prostate Cancer
Thursday, April 22, 2021
8:30 AM – 10:00 AM ET

Hodgkin and Non-Hodgkin Lymphomas
Thursday, April 22, 2021
5:00 PM – 6:30 PM ET

Multiple Myeloma
Tuesday, April 27, 2021
8:30 AM – 10:00 AM ET

Gynecologic Cancers
Tuesday, April 27, 2021
5:00 PM – 6:30 PM ET

Urothelial Bladder Carcinoma
Wednesday, April 28, 2021
12:00 PM – 1:00 PM ET

Chronic Lymphocytic Lymphoma
Thursday, April 29, 2021
8:30 AM – 10:00 AM ET

Chimeric Antigen Receptor T-Cell Therapy
Thursday, April 29, 2021
5:00 PM – 6:30 PM ET

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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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