Meet The Professor
Management of Chronic Lymphocytic Leukemia

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Commercial Support

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Dr Love — Disclosures

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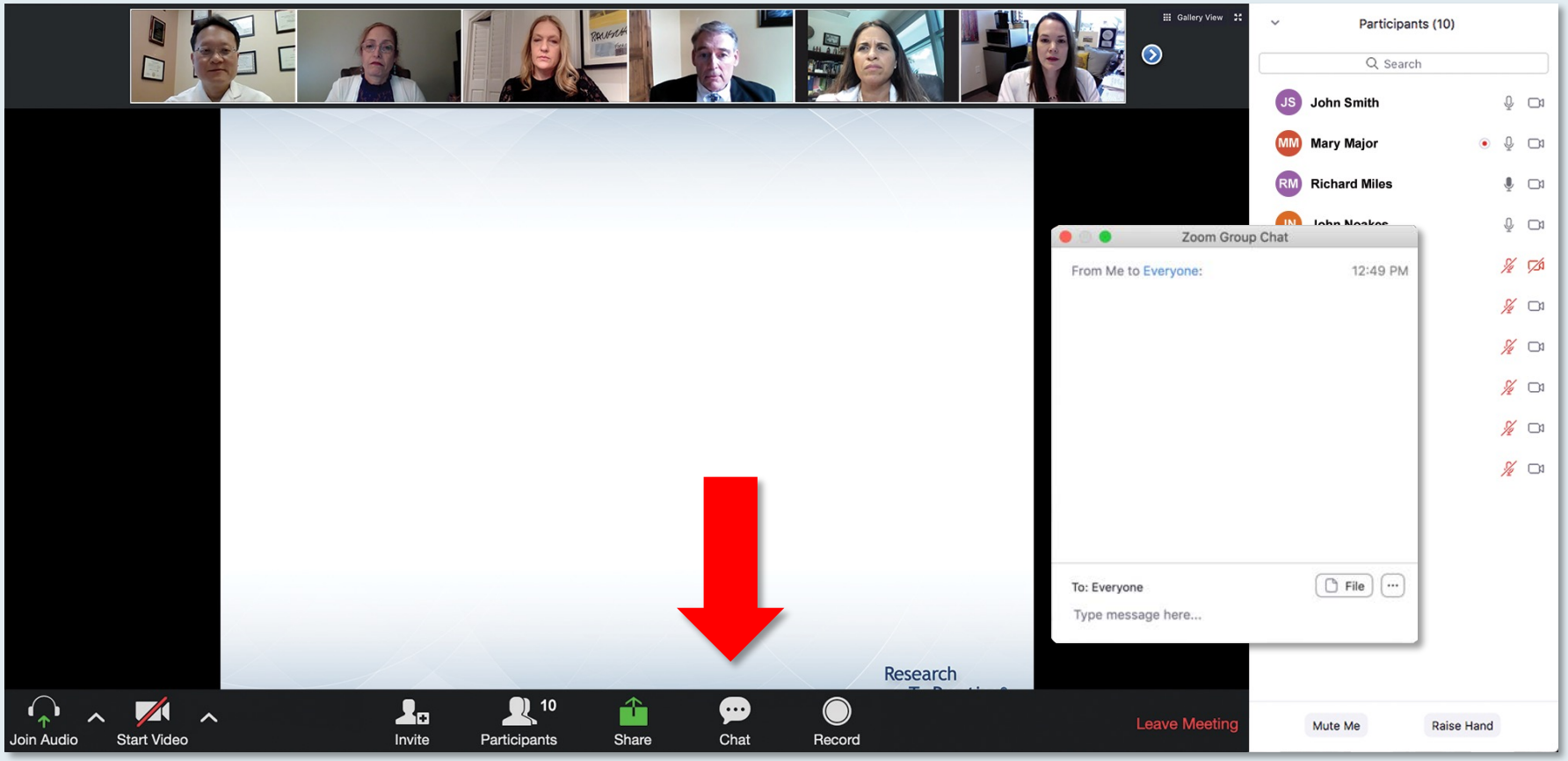

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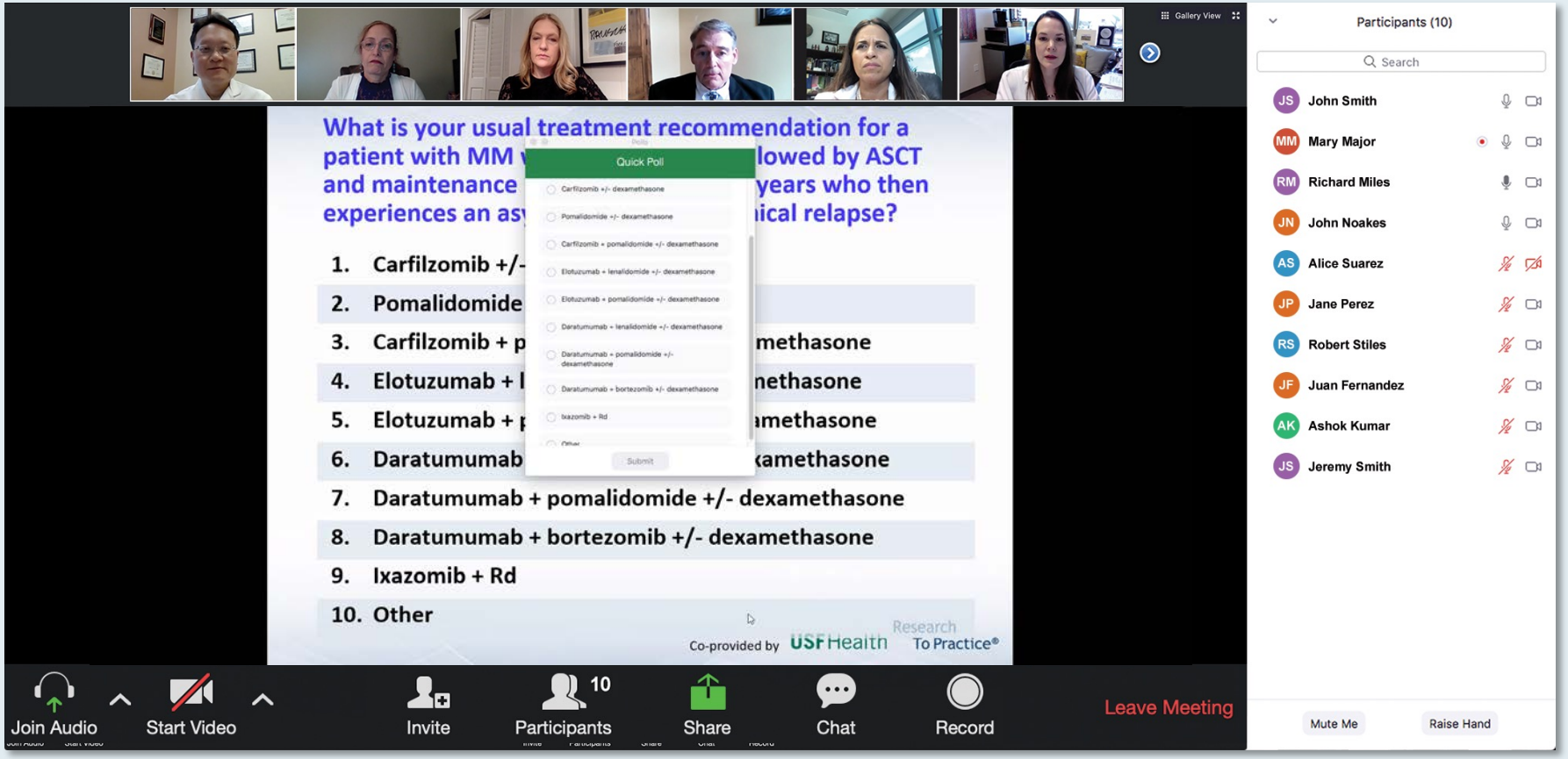

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Familiarizing Yourself with the Zoom Interface

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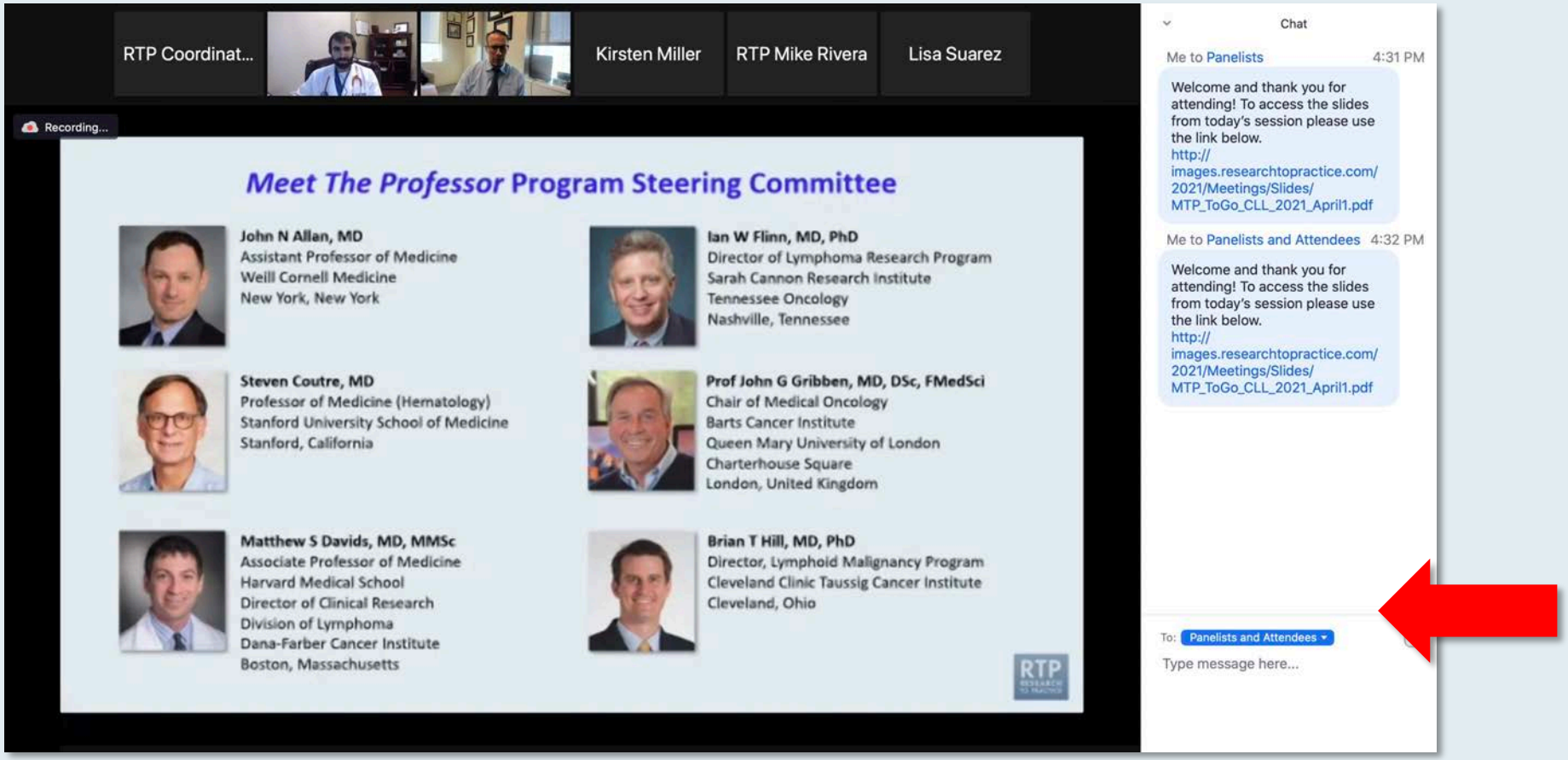

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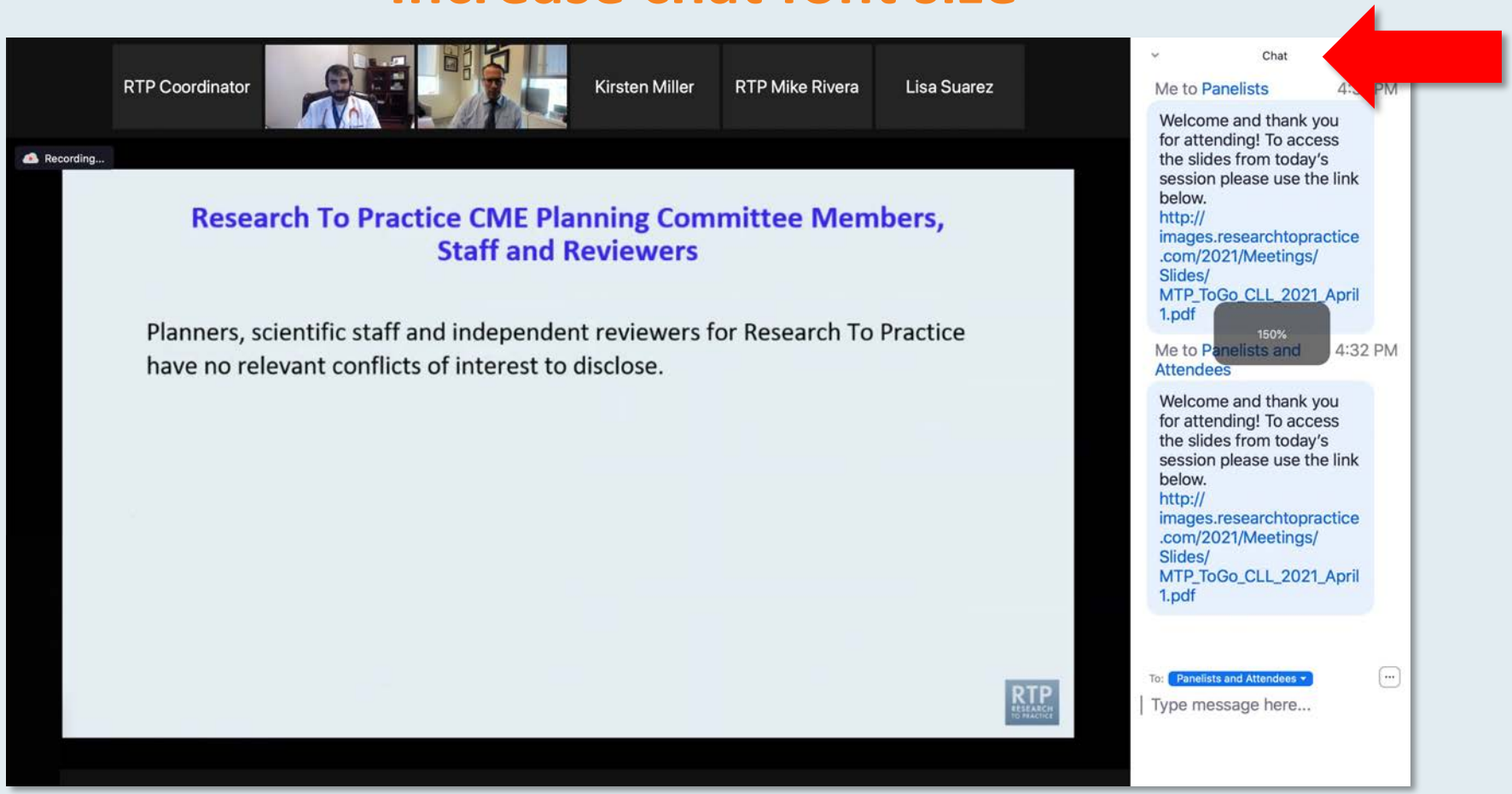

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DR ANN LACASCE

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BOSTON, MASSACHUSETTS

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Up for Debate: Oncology Investigators Provide Their Take on Current Controversies in Patient Care

A Daylong Multitumor Educational Webinar
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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 Program Participating Faculty

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Boston, Massachusetts

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Meet The Professor Program Participating Faculty

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Swedish Cancer Institute
Seattle, Washington

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Duarte, California

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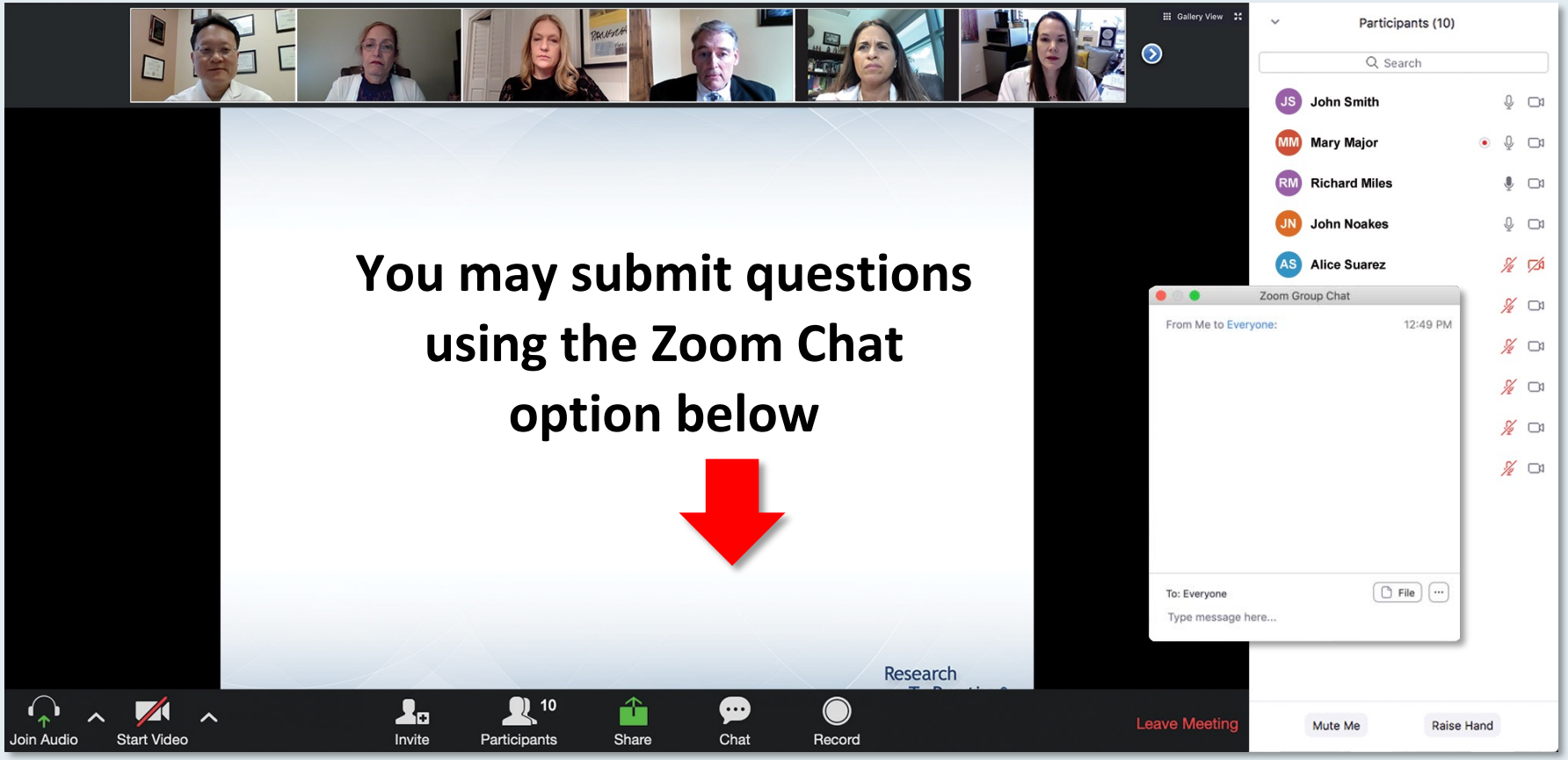

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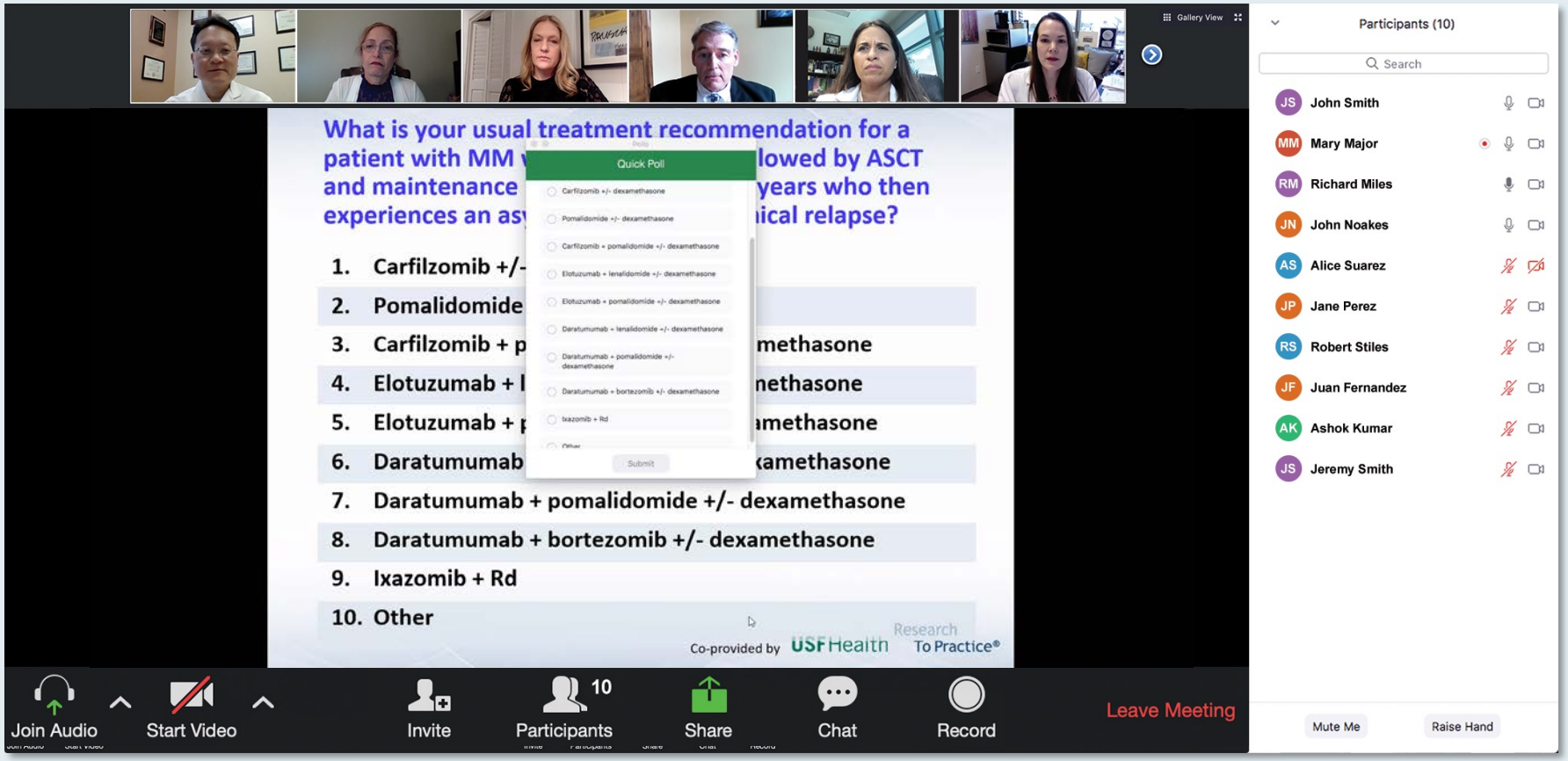

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Oncology Specialists of Charlotte
Charlotte, North Carolina

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

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

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 Objective Response Rate and Reduced Rates of Atrial Fibrillation or Flutter in Head-to-Head Trial Against Ibrutinib for CLL

Press Release: April 28, 2021

"Positive results [were announced] from a planned interim analysis of the Phase 3 ALPINE trial comparing zanubrutinib against ibrutinib in adults with relapsed or refractory (R/R) chronic lymphocytic leukemia (CLL) or small lymphocytic leukemia (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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First Results of a Head-to-Head Trial of Acalabrutinib versus Ibrutinib in Previously Treated Chronic Lymphocytic Leukemia

Byrd JC et al.

ASCO 2021;Abstract 7500

Oral Abstract Session: Monday, June 7, 2021, 11:30 AM – 2:30 PM EDT

ELEVATE-RR: Acalabrutinib versus Ibrutinib for Previously Treated CLL

Adverse events	Acalabrutinib (n = 266)		Ibrutinib (n = 263)	
	Any grade	Grade ≥3	Any grade	Grade ≥3
Cardiac events	24.1%	8.6%	30.0%	9.5%
Atrial fibrillation	9.4%	4.9%	16.0%	3.8%
Ventricular tachyarrhythmias	0	0	0.4%	0.4%
Hypertension	9.4%	4.1%	23.2%	9.1%
Bleeding events	38.0%	3.8%	51.3%	4.6%
Major bleeding events	4.5%	3.8%	5.3%	4.6%
Infections	78.2%	30.8%	81.4%	30.0%
SPMs	9.0%	6.0%	7.6%	5.3%

SPM = Second primary malignancies, excluding nonmelanoma skin cancers

- Median PFS: 38.4 months for both arms (HR 1.00)
- Median OS: Not reached in either arm (HR 0.82)

Byrd JC et al. ASCO 2021;Abstract 7500.

Meet The Professor with Dr Woyach

MODULE 1: Cases from Medical Oncology Practices

- Dr Favaro: A 63-year-old man with CLL and initial del(17p)
- Dr Flores: A 64-year-old man with CLL treated with obinutuzumab/venetoclax
- Dr Morganstein: A 79-year-old woman with CLL and asymptomatic, bulky nodal disease
- Dr Favaro: A 79-year-old man with CLL and secondary cancer and repeat infections

MODULE 2: Journal Club with Dr Woyach

MODULE 3: Beyond the Guidelines

MODULE 4: Key Recent Data Sets

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Case Presentation – Dr Favaro: A 63-year-old man with CLL and initial del(17p) (Part 1)

Dr Justin Favaro

- Diagnosed with CLL – FISH del(13q) 15%, FISH del(17p) 15% → Observed with minimal LAD x 4 years
- Worsening LAD, rising WBC to 60
  - FISH: del(13q), del(11q), no del(17p)
- Ibrutinib 420 mg daily, with rash and throat swelling → Acalabrutinib 100 mg BID
  - WBC normalized, LAD resolved
  - Occasional heart palpitations, on a heart monitor

Questions

- In asymptomatic patients with del(17p) at the beginning of their presentation, I still don't treat them. Do you agree with that decision? When they become symptomatic, having the presence of a 17p deletion, does that change your decision about what your first-line therapy would be?
- How often do you see the del(17p) disappear, and how does that influence the prognosis for these patients?

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Case Presentation – Dr Favaro: A 63-year-old man with CLL and initial del(17p) (Part 2)

Dr Justin Favaro

- Diagnosed with CLL del(13q), del(17p) → Observed with minimal LAD x 4 years
- Worsening LAD, rising WBC to 60
  - FISH: del(13q), del(11q), no del(17p)
- Ibrutinib 420 mg daily, with rash and throat swelling → Acalabrutinib 100 mg BID
  - WBC normalized, LAD resolved
  - Occasional heart palpitations, on a heart monitor
- ***Recently, he contracted COVID-19 and has been symptomatic the past 2 weeks***
  - ***Discontinued acalabrutinib and his COVID-19-related symptoms worsened***
  - ***Resumed acalabrutinib and his symptoms improved***

Questions

- ***Have you had a patient with CLL who is being treated with acalabrutinib contract COVID-19?***

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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?

Case Presentation – Dr Morganstein: A 79-year-old woman with CLL and asymptomatic, bulky nodal disease

Dr Neil Morganstein

- 2007: Diagnosed with CLL/SLL
  - FISH and cytogenetics: Negative
- Increasing LAD requiring treatment → Bendamustine/rituximab
- Recent PET/CT: Increasing LAD (largest nodal mass increased from 5.5 cm to > 10 cm in past 6 months)
  - Repeat biopsy: SLL, FISH: Negative
  - Patient is asymptomatic

Questions

- Does she currently need treatment? And if so, what is the appropriate second-line therapy?
- What is the best way to monitor patients with CLL? Is PET/CT the "go to," and what do you use and how often?
- In patients with bulky nodal disease, what's the best way to manage tumor lysis if venetoclax is the drug of choice? Can we give rasburicase and IV fluids as an outpatient? Is this a clear indication for admission? As our comfort with tumor lysis has evolved, how much have we switched from inpatient treatment to outpatient treatment?

Case Presentation – Dr Favaro: A 79-year-old man with CLL and secondary cancer and repeat infections

Dr Justin Favaro

- 2017: Presents with extensive LAD, 70% bone marrow involvement, and sepsis from cholecystitis
- CLL with trisomy 12 → Ibrutinib with monthly IVIG
- 1/2020: Developed squamous cell carcinoma of the right ear canal, with metastasis to the right parotid gland → Right parotid temporal bone tumor resection
  - Ibrutinib held and treated with cisplatin/RT
- Ibrutinib re-started, but developed MSSA sepsis from infected penile implant
  - Ibrutinib stopped, admitted to the hospital intensive care x 6 weeks
- LAD has not recurred, WBC: 6, HgB: 10, PLT: 200

Questions

- How often do you see secondary malignancies in the setting of CLL treatment?
- When would you start him back on treatment, and would re-starting him back on a BTK inhibitor put him at risk for any further malignancies?

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MODULE 1: Cases from General Medical Oncology Practices

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MODULE 2: Journal Club with Dr Woyach

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Journal Club with Dr Woyach

- Second cancer incidence in CLL patients receiving Bruton tyrosine kinase (BTK) inhibitors
- Natural history of noninfectious, ibrutinib-attributable adverse events in CLL
- Acalabrutinib in treatment-naïve CLL
- Safety of venetoclax rapid dose escalation in CLL previously treated with B-cell receptor signaling antagonists
- Novel Bcl-2 mutations in patients with venetoclax-resistant, ibrutinib-resistant CLL with BTK/PLCG2 mutations
- BRUIN study: Pirtobrutinib for relapsed or refractory B-cell cancers

Journal Club with Dr Woyach (Continued)

- BRUIN: LOXO-305, a next-generation, highly selective, noncovalent BTK inhibitor for previously treated CLL
- BRUIN: LOXO-305, a next-generation, highly selective, noncovalent BTK inhibitor for previously treated mantle cell lymphoma, Waldenström macroglobulinemia and other non-Hodgkin lymphomas
- Three-year follow-up from a Phase II study of combination obinutuzumab, ibrutinib and venetoclax for CLL
- Phase II study of combination obinutuzumab, ibrutinib and venetoclax for treatment-naïve and relapsed or refractory CLL
- Clinical activity of axicabtagene ciloleucel in adult patients with Richter syndrome
- BTK inhibitors and anti-CD20 monoclonal antibodies for older patients with treatment-naïve CLL

Published in final edited form as:
Leukemia. 2020 December ; 34(12): 3197–3205. doi:10.1038/s41375-020-0987-6.

Second Cancer Incidence in CLL Patients Receiving BTK Inhibitors

David A Bond[1,*], Ying Huang[1], James L Fisher[2], Amy S Ruppert[1], Dwight H Owen[3], Erin M Bertino[3], Kerry A Rogers[1], Seema A Bhat[1], Michael R Grever[1], Samantha M Jaglowski[1], Kami J Maddocks[1], John C Byrd[1], Jennifer A Woyach[1]

LEUKEMIA & LYMPHOMA
2021, VOL. 62, NO. 3, 716–721
https://doi.org/10.1080/10428194.2020.1838508

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LETTER TO THE EDITOR

Natural history of noninfectious, ibrutinib-attributable adverse events in patients with chronic lymphocytic leukemia

Soun Khountham[a]*, Polina Shindiapina[a]*, Xiaokui Mo[b], Curtis Lachowiez[c], Tracy Wiczer[d], Luay Mousa[a], Kerry A. Rogers[a], Leslie A. Andritsos[a], Jennifer A. Woyach[a], John C. Byrd[a], Stephen E. Spurgeon[c] and Farrukh T. Awan[e]

Blood 2021;[Online ahead of print].

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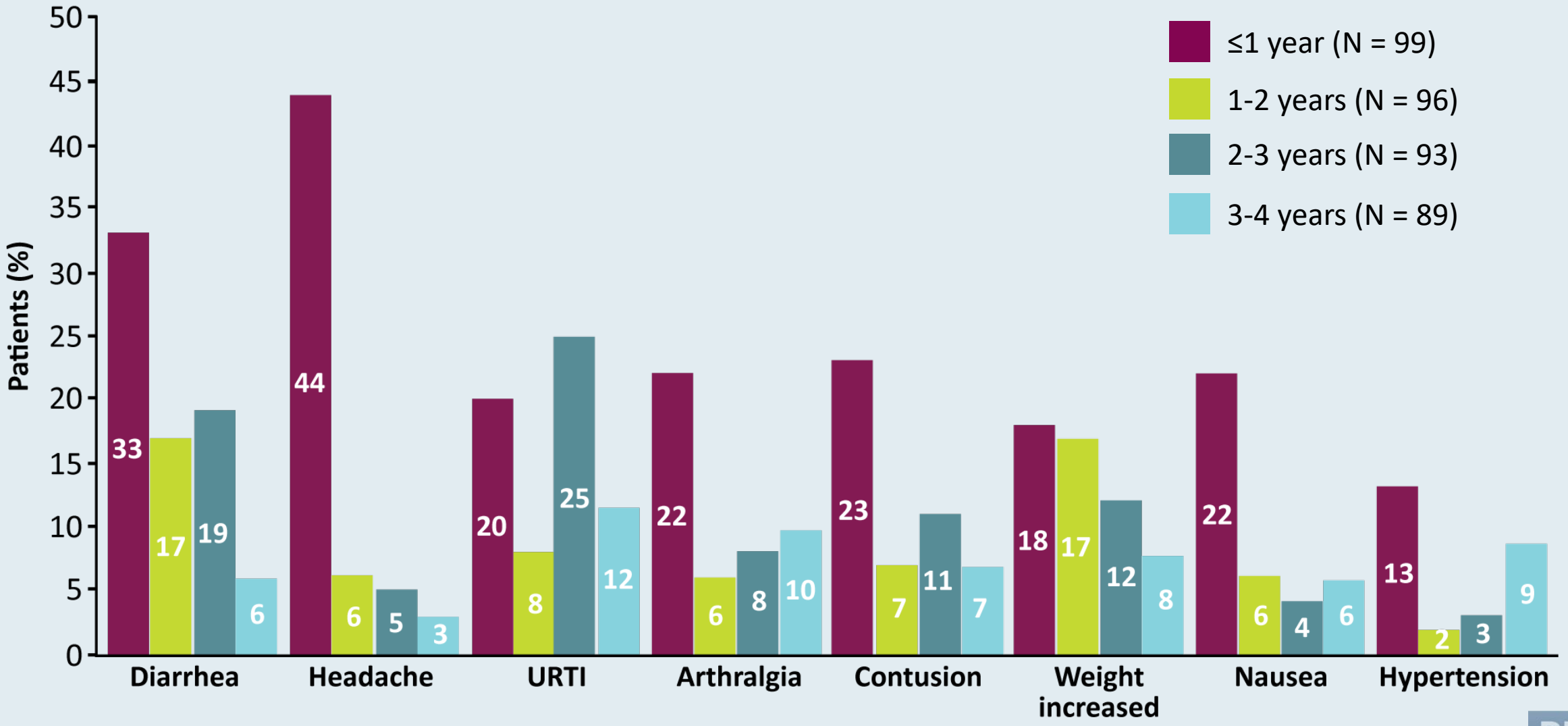
Acalabrutinib in Treatment-Naïve Chronic Lymphocytic Leukemia

Tracking no: BLD-2020-009617R1

John Byrd (Ohio State University, United States) Jennifer Woyach (The Ohio State University, United States) Richard Furman (Weill Medical College of Cornell University, United States) Peter Martin (Weill Cornell Medical College, United States) Susan O'Brien (Chao Family Comprehensive Cancer Center at UC Irvine Medical Center, United States) Jennifer Brown (DFCI / Harvard Medical School, United States) Deborah Stephens (University of Utah, United States) Jacqueline Barrientos (Zucker School of Medicine at Hofstra/Northwell, United States) Stephen Devereux (Kings College Hospital, United Kingdom) Peter Hillmen (The Leeds Teaching Hospitals, St. James Institute of Oncology, United Kingdom) John Pagel (Swedish Cancer Institute, United States) Ahmed Hamdy (Acerta Pharma, United States) Raquel Izumi (Acerta Pharma, United States) Priti Patel (Acerta Pharma, United States) Min Hui Wang (Acerta Pharma, United States) Nitin Jain (M.D. Anderson Cancer Ctr. University of Texas, United States) William Wierda (University of Texas M.D. Anderson Cancer Center, United States)

Incidence of Select Treatment-Emergent Adverse Events by Yearly Interval



Byrd JC et al. *Blood* 2021;[Online ahead of print].

RTP RESEARCH TO PRACTICE

REGULAR ARTICLE

blood advances

Safety of venetoclax rapid dose escalation in CLL patients previously treated with B-cell receptor signaling antagonists

Kristin L. Koenig,[1] Ying Huang,[1] Emily K. Dotson,[2] Shane Sheredy,[2] Seema A. Bhat,[1] John C. Byrd,[1] Emily Desmond,[1] Jill Ford,[1] Shauna Iarocci,[1] Jeffrey A. Jones,[1] Margaret S. Lucas,[1] Mollie E. Moran,[1] Tracy E. Wiczer,[2] Jennifer A. Woyach,[1] Farrukh T. Awan,[3,*] and Kerry A. Rogers[1,*]

Blood 2020;135(24):2192-5.

blood®

Letter to *Blood*

TO THE EDITOR:

Novel *BCL2* mutations in venetoclax-resistant, ibrutinib-resistant CLL patients with *BTK/PLCG2* mutations

Fabienne Lucas,[1,2] Karylin Larkin,[1,2] C. Thomas Gregory,[1,2] Shelley Orwick,[1,2] Tzyy-Jye Doong,[1,2] Arletta Lozanski,[1,2] Gerard Lozanski,[3] Shrilekha Misra,[1,2] Apollinaire Ngankeu,[1,2] Hatice Gulcin Ozer,[4] Deepa Sampath,[1,2] Shanmugapriya Thangavadivel,[1,2] Selen A. Yilmaz,[4] Kerry A. Rogers,[1,2] John C. Byrd,[1,2,5,6] Jennifer A. Woyach,[1,2,5,*] and James S. Blachly[1,2,4,*]

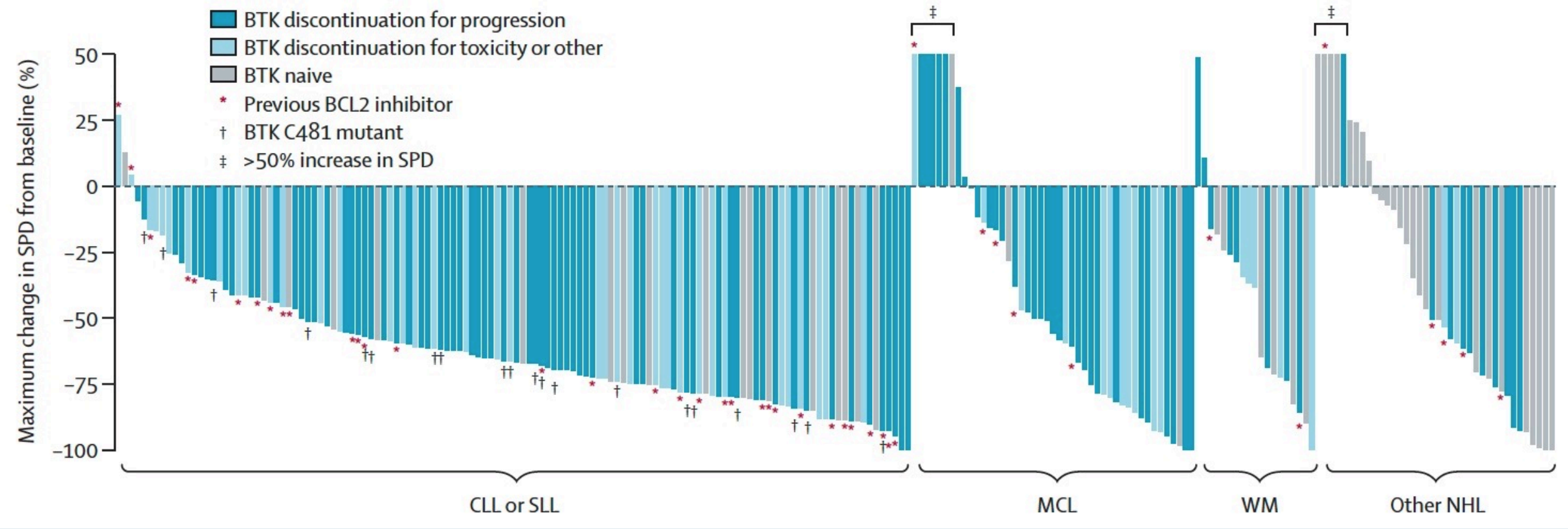
Lancet 2021;397:892-901.

Articles

Pirtobrutinib in relapsed or refractory B-cell malignancies (BRUIN): a phase 1/2 study

Anthony R Mato, Nirav N Shah, Wojciech Jurczak, Chan Y Cheah, John M Pagel, Jennifer A Woyach, Bita Fakhri, Toby A Eyre, Nicole Lamanna, Manish R Patel, Alvaro Alencar, Ewa Lech-Maranda, William G Wierda, Catherine C Coombs, James N Gerson, Paolo Ghia, Steven Le Gouill, David John Lewis, Suchitra Sundaram, Jonathon B Cohen, Ian W Flinn, Constantine S Tam, Minal A Barve, Bryone Kuss, Justin Taylor, Omar Abdel-Wahab, Stephen J Schuster, M Lia Palomba, Katharine L Lewis, Lindsey E Roeker, Matthew S Davids, Xuan Ni Tan, Timothy S Fenske, Johan Wallin, Donald E Tsai, Nora C Ku, Edward Zhu, Jessica Chen, Ming Yin, Binoj Nair, Kevin Ebata, Narasimha Marella, Jennifer R Brown, Michael Wang

Change in Tumor Burden from Baseline, Measured by Changes in the SPD on Axial CT Images of Index Lesions for Efficacy-Evaluable Patients with CLL or SLL, MCL and Other B-Cell Lymphomas



Mato AR et al. *Lancet* 2021;397(10277):892-901.

RTP RESEARCH TO PRACTICE

LOXO-305, A Next Generation, Highly Selective, Non-Covalent BTK Inhibitor In Previously Treated CLL/SLL: Results From The Phase 1/2 BRUIN Study

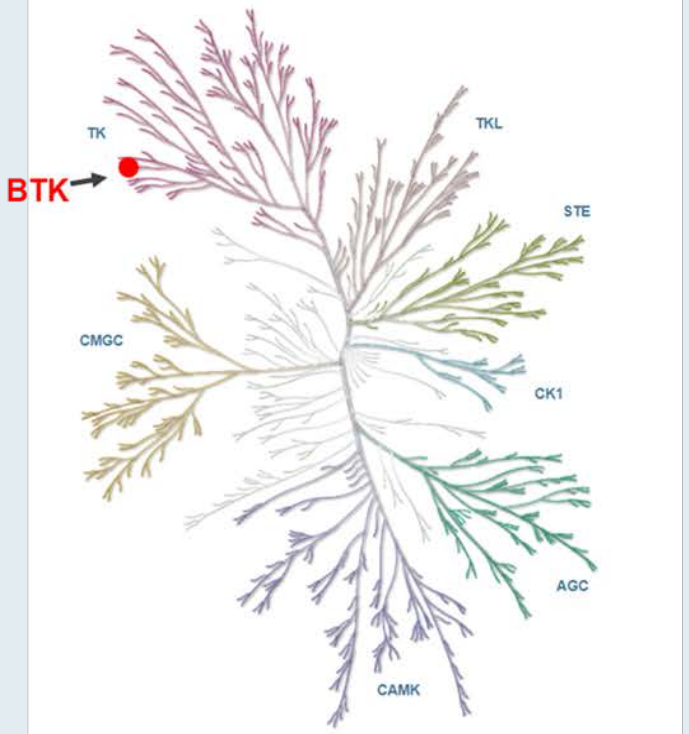
Anthony R. Mato[1], John M. Pagel[2], Catherine C. Coombs[3], Nirav N. Shah[4], Nicole Lamanna[5], Ewa Lech-Maranda[6], Toby A. Eyre[7], Jennifer A. Woyach[8], William G. Wierda[9], Chan Y. Cheah[10], Lindsey Roeker[1], Manish R. Patel[11], Bita Fakhri[12], Minal A. Barve[13], Constantine S. Tam[14], David Lewis[15], James N. Gerson[16], Alvaro Alencar[17], Justin Taylor[17], Omar Abdel-Wahab[1], Paolo Ghia[18], Stephen J. Schuster[16], Jessica Chen[19], Binoj Nair[20], Donald E. Tsai[20], Nora C. Ku[20], Matthew S. Davids[21], Jennifer R. Brown[21], Wojciech Jurczak[22]

ASH 2020;Abstract 542

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

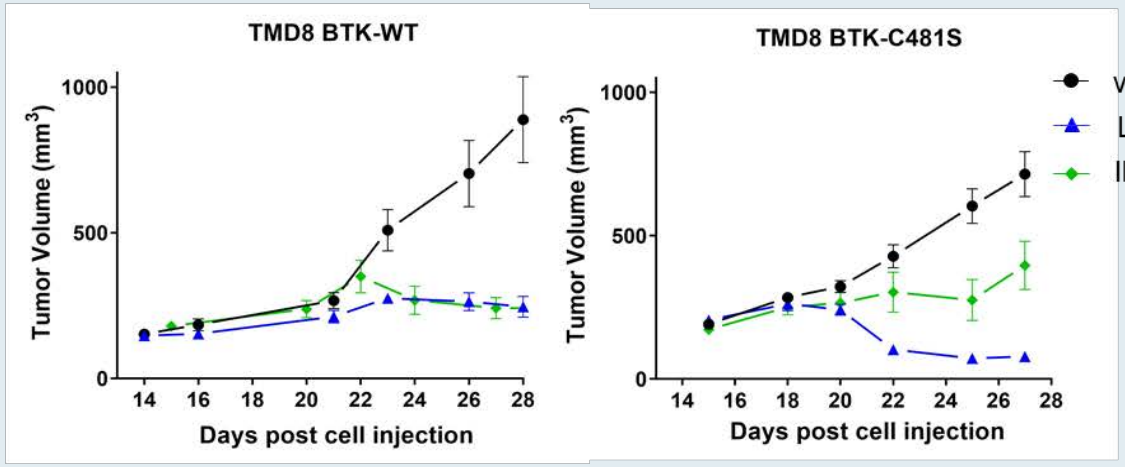
Kinome selectivity

Highly selective for BTK



Xenograft models

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



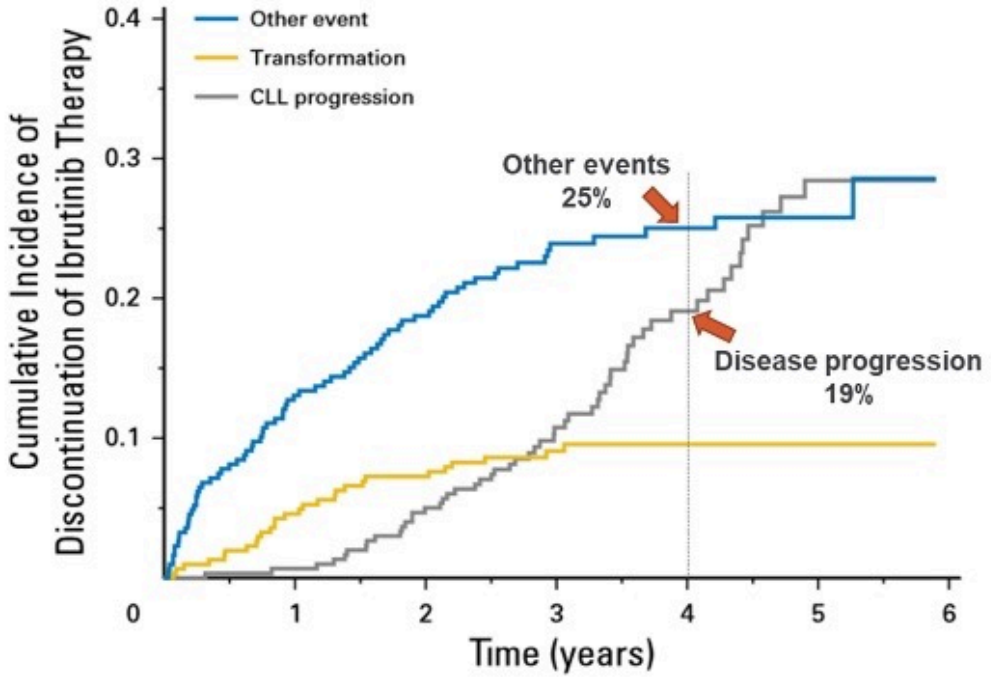
- Nanomolar potency against WT & C481-mutant BTK in cell and enzyme assays[1,2]
- >300-fold selectivity for BTK vs 370 other kinases[1]
- Due to reversible binding mode, BTK inhibition not impacted by intrinsic rate of BTK turnover[1]
- Favorable pharmacologic properties allow sustained BTK inhibition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

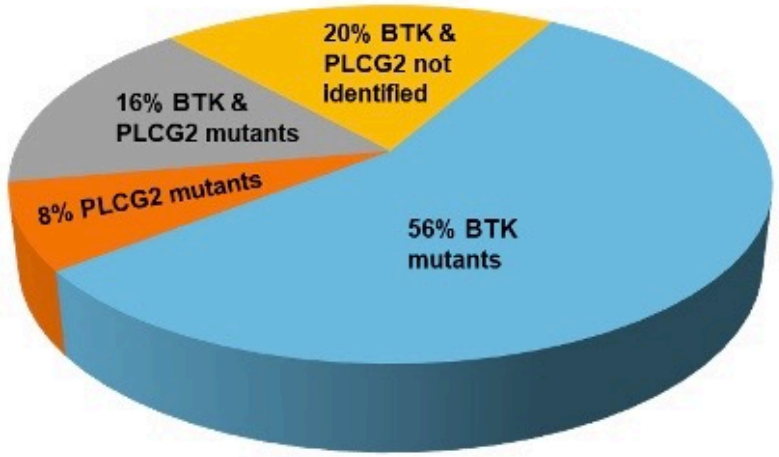
Resistance and Intolerance Limit Covalent BTK Inhibitor Outcomes

Ibrutinib discontinuation from 4 prospective studies[1]



- Ibrutinib discontinuation rates at 5 years
  - Front line = 41%[3]
  - Relapsed/refractory = 54%[1]

Ibrutinib acquired resistance in patients with progressive CLL[2]

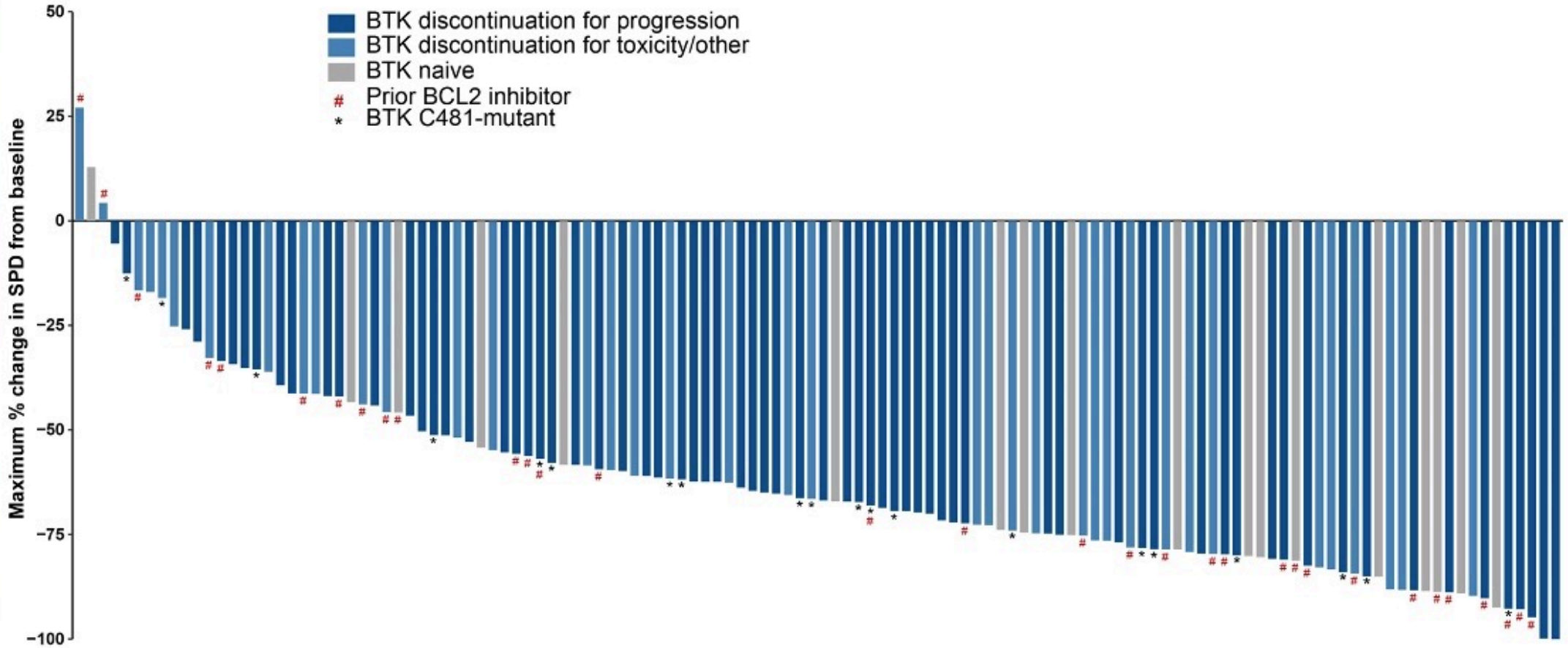


- BTK C481 mutations are the dominant reason for progressive CLL after covalent BTK inhibitors[1-8]
- BTK C481 mutations prevent covalent BTK inhibitors from effective target inhibition[1-6]

[1]Woyach et al. *J Clin Oncol.* 2017;35:1437-43. [2]Lampson et al. *Expert Rev Hematol.* 2018;11:185-94. [3]Burger et al. *Leukemia.* 2020;34:878-789. [4]Byrd et al. *N Engl J Med.* 2016;374:323-32. [5]Hershkovitz-Rokah et al. *Br J Haematol.* 2018;181:306-19. [6]Woyach et al. *N Engl J Med.* 2014;370:2286–94. [7]Woyach et al. *Blood.* 2019;134(Suppl 1):504. [8]Xu et al. *Blood.* 2017;129:2519–25.

Mato AR et al. ASH 2020;Abstract 542.

Efficacy of LOXO-305 in CLL/SLL



Data cutoff date of 27 September 2020. Total % may be different than the sum of the individual components due to rounding. Data for 13 CLL/SLL patients are not shown in the waterfall plot due to 4 having no target lesions identified at baseline, 5 with no/incomplete post-baseline lesion measurements, and 4 discontinued prior to first post-baseline disease assessment.

Mato AR et al. ASH 2020;Abstract 542.

LOXO-305, a Next Generation, Highly Selective, Non-Covalent BTK Inhibitor in Previously Treated Mantle Cell Lymphoma, Waldenström's Macroglobulinemia, and Other Non-Hodgkin Lymphomas: Results from the Phase 1/2 BRUIN Study

Michael L. Wang[1], Nirav N. Shah[2], Alvaro J. Alencar[3], James N. Gerson[4], Manish R. Patel[5], Bita Fakhri[6], Wojciech Jurczak[7], Xuan Tan[8], Katharine Lewis[8], Timothy Fenske[9], Catherine C. Coombs[10], Ian Flinn[11], David Lewis[12], Steven Le Gouill[13], M. Lia Palomba[14], Jennifer Woyach[15], John M. Pagel[16], Nicole Lamanna[17], Jonathon B. Cohen[18], Minal A. Barve[19], Paolo Ghia[20], Toby A. Eyre[21], Ming Yin[22], Binoj Nair[22], Donald E. Tsai[22], Nora C. Ku[22], Anthony R. Mato[14], Chan Y. Cheah[8]

ASH 2020;Abstract 117.

Three-Year Follow-Up from a Phase 2 Study of Combination Obinutuzumab, Ibrutinib, and Venetoclax in Chronic Lymphocytic Leukemia

Rogers KA et al.

ASH 2020;Abstract 1305.

original reports

Phase II Study of Combination Obinutuzumab, Ibrutinib, and Venetoclax in Treatment-Naïve and Relapsed or Refractory Chronic Lymphocytic Leukemia

Kerry A. Rogers, MD[1,2]; Ying Huang, MA, MS[1]; Amy S. Ruppert, PhD[1]; Lynne V. Abruzzo, MD, PhD[3]; Barbara L. Andersen, PhD[4]; Farrukh T. Awan, MBBS, MS[1]; Seema A. Bhat, MD[1]; Allison Dean, CNP[2]; Margaret Lucas, PA[2]; Christin Banks, BS[2]; Cara Grantier, APRN-CNP, MPH[2]; Nyla A. Heerema, PhD[3]; Gerard Lozanski, MD[3]; Kami J. Maddocks, MD[1]; Thomas R. Valentine, PhD[4]; David M. Weiss, PhD[4]; Jeffrey A. Jones, MD, MPH, MBA[1]; Jennifer A. Woyach, MD[1,2]; and John C. Byrd, MD[1,2]

J Clin Oncol 2020;38(31):3626-37.

RTP RESEARCH TO PRACTICE

COMMENTARY

blood advances

TO THE EDITOR:

Clinical activity of axicabtagene ciloleucel in adult patients with Richter syndrome

Adam S. Kittai,[1-3,*] David A. Bond,[1-3,*] Basem William,[1-3] Ayman Saad,[1-3] Sam Penza,[1-3] Yvonne Efebera,[1-3] Karilyn Larkin,[1-3] Sarah A. Wall,[1-3] Hannah K. Choe,[1-3] Bhavana Bhatnagar,[1-3] Sumithira Vasu,[1-3] Jonathan Brammer,[1-3] Polina Shindiapina,[1-3] Meixiao Long,[1-3] Alice Mims,[1-3] Lynn O'Donnell,[1-3] Seema A. Bhat,[1-3] Kerry A. Rogers,[1-3] Jennifer A. Woyach,[1-4] John C. Byrd,[1-4] and Samantha M. Jaglowski[1-3]

Therapeutic Advances in Hematology *Review*

BTK inhibitors and anti-CD20 monoclonal antibodies for treatment-naïve elderly patients with CLL

Ther Adv Hematol

2020, Vol. 11: 1–10

DOI: 10.1177/2040620720912990

Andrew Rogers and Jennifer A. Woyach

Meet The Professor with Dr Woyach

MODULE 1: Cases from Medical Oncology Practices

- Dr Favaro: A 63-year-old man with CLL and initial del(17p)
- Dr Flores: A 64-year-old man with CLL treated with obinutuzumab/venetoclax
- Dr Morganstein: A 79-year-old woman with CLL and asymptomatic, bulky nodal disease
- Dr Favaro: A 79-year-old man with CLL and secondary cancer and repeat infections

MODULE 2: Journal Club with Dr Woyach

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

Meet The Professor with Dr Woyach

MODULE 1: Cases from Medical Oncology Practices

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MODULE 2: Journal Club with Dr Woyach

MODULE 3: Beyond the Guidelines

MODULE 4: Key Recent Data Sets

RTP RESEARCH TO PRACTICE

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

RTP
RESEARCH
TO PRACTICE

The NEW ENGLAND JOURNAL of MEDICINE

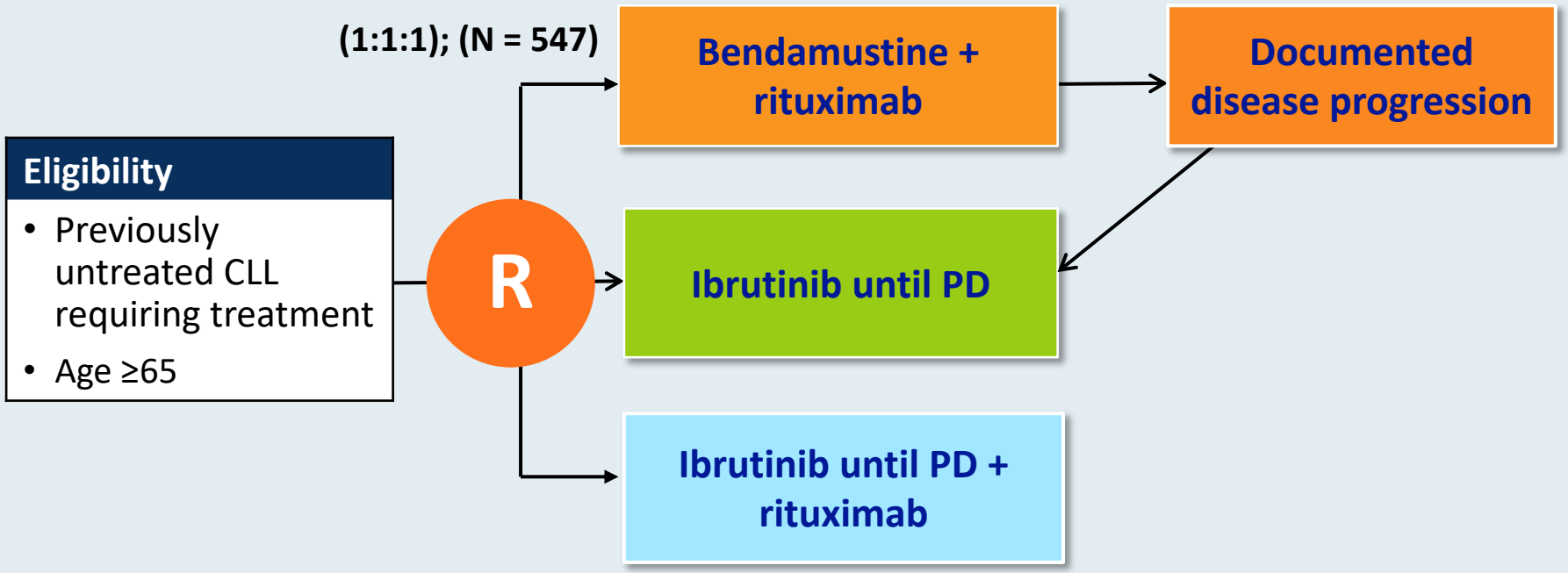
ORIGINAL ARTICLE

Ibrutinib Regimens versus Chemoimmunotherapy in Older Patients with Untreated CLL

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

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

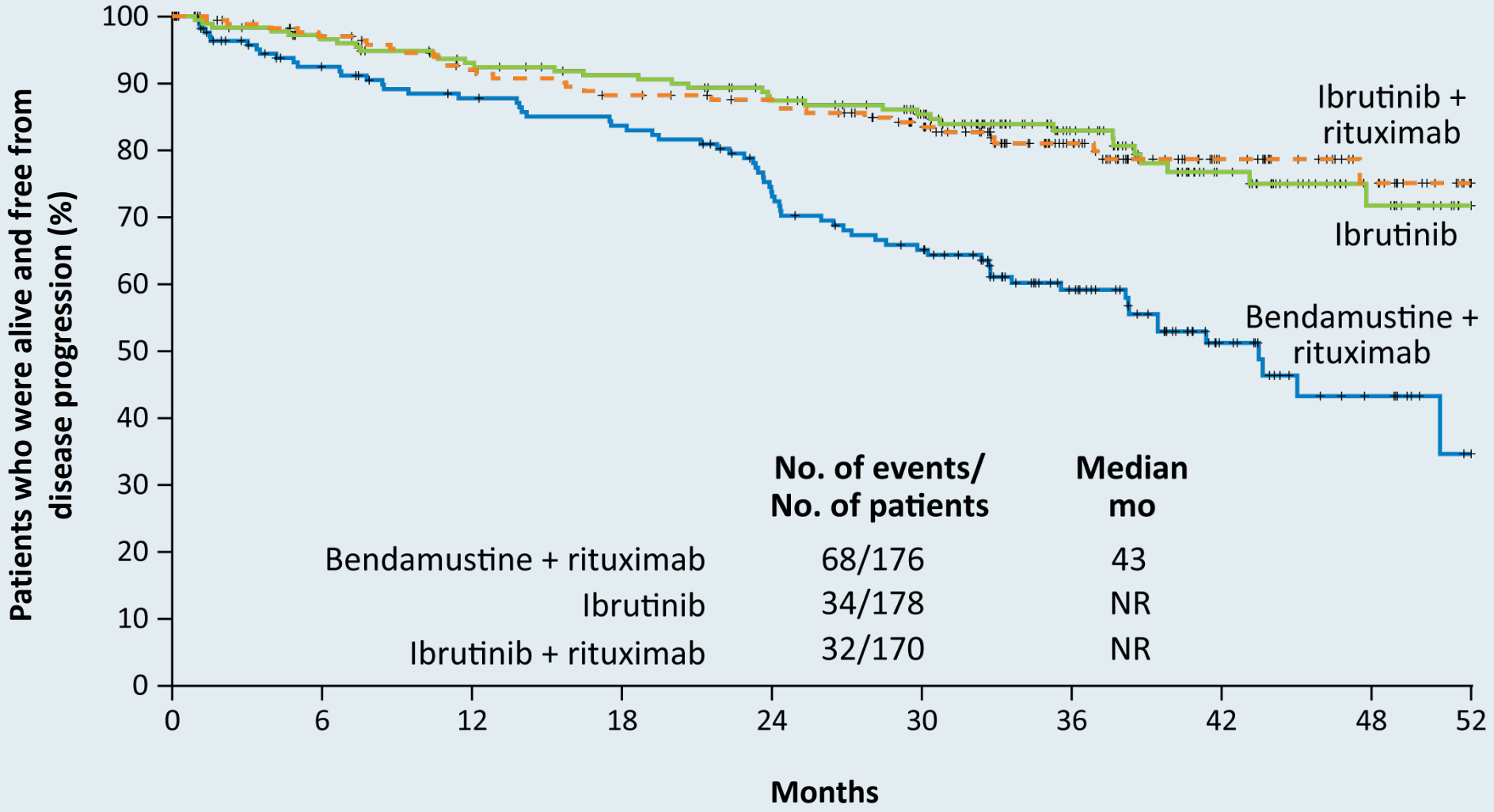
Phase III Alliance A041202 Study Design



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

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

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



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

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

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

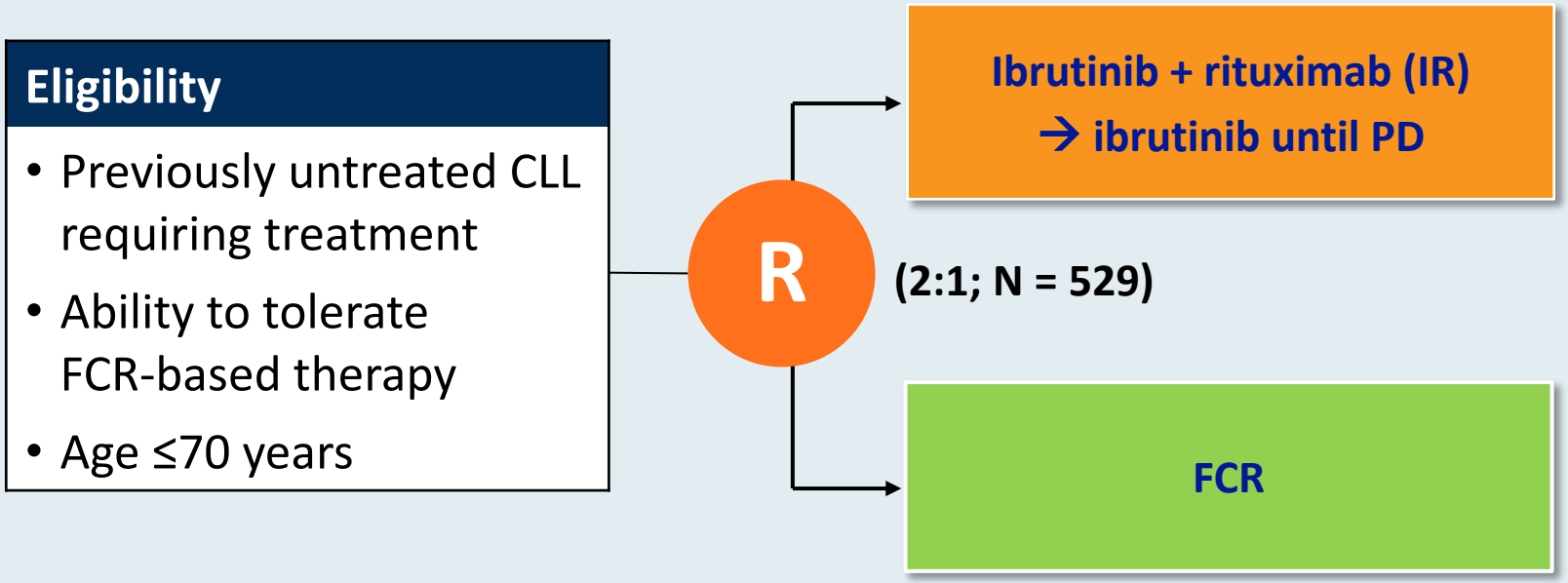
Woyach JA et al. *N Engl J Med* 2018;379(26):2517-28.

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

Shanafelt TD et al.

ASH 2019;Abstract 33.

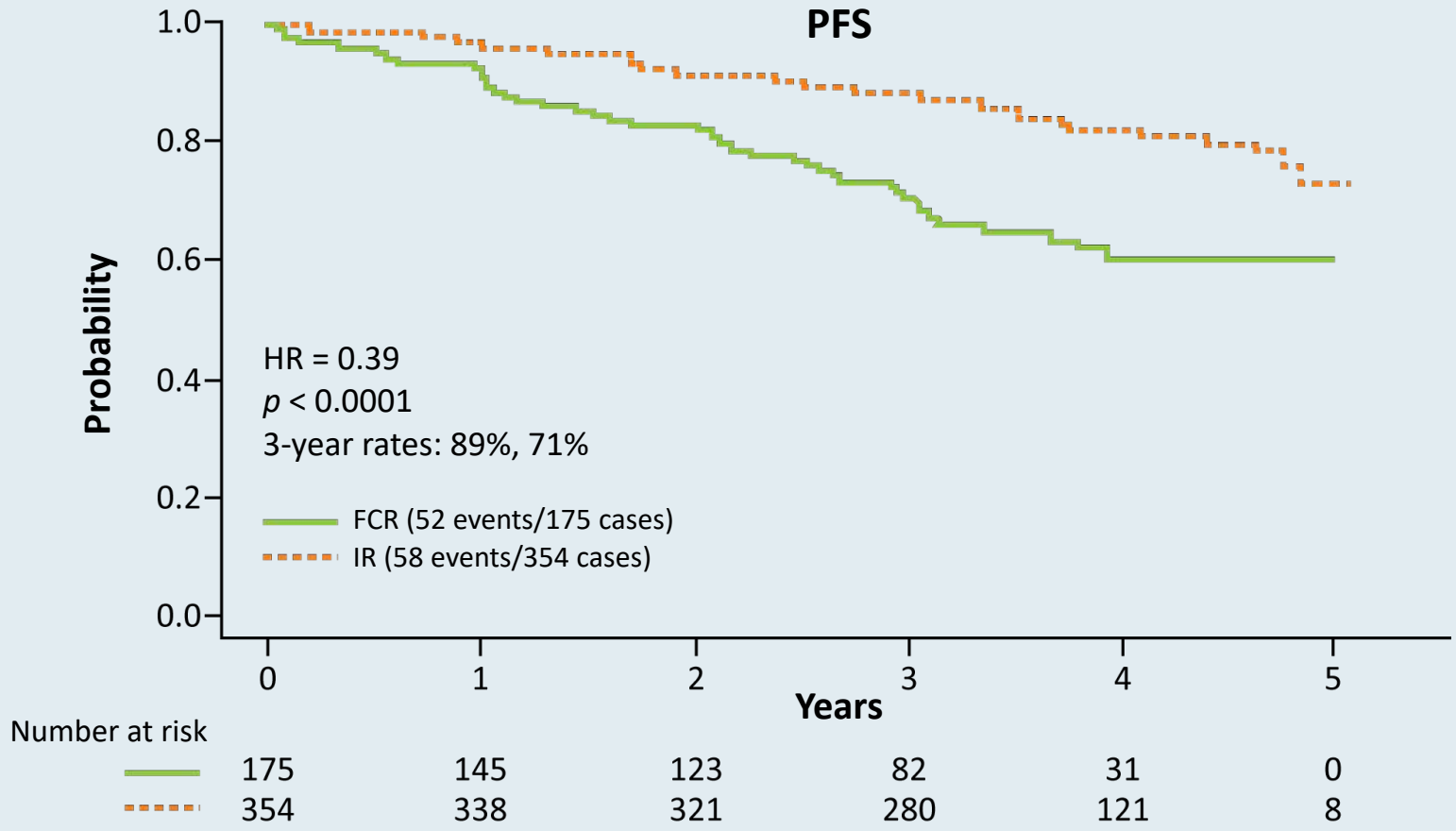
Phase III ECOG-ACRIN E1912 Study Design



Primary endpoint: PFS
Secondary endpoints: OS, ORR, Toxicity and Tolerability

ECOG-ACRIN E1912 Physician Fact Sheet, version 01/15/16;
www.clinicaltrials.gov (NCT02048813); Shanafelt TD et al. ASH 2018;Abstract LBA-4.

ECOG-ACRIN E1912 Extended Follow-Up: Up-Front IR Compared to FCR for Younger Patients with CLL



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

Shanafelt TD et al. ASH 2019;Abstract 33.

RTP RESEARCH TO PRACTICE

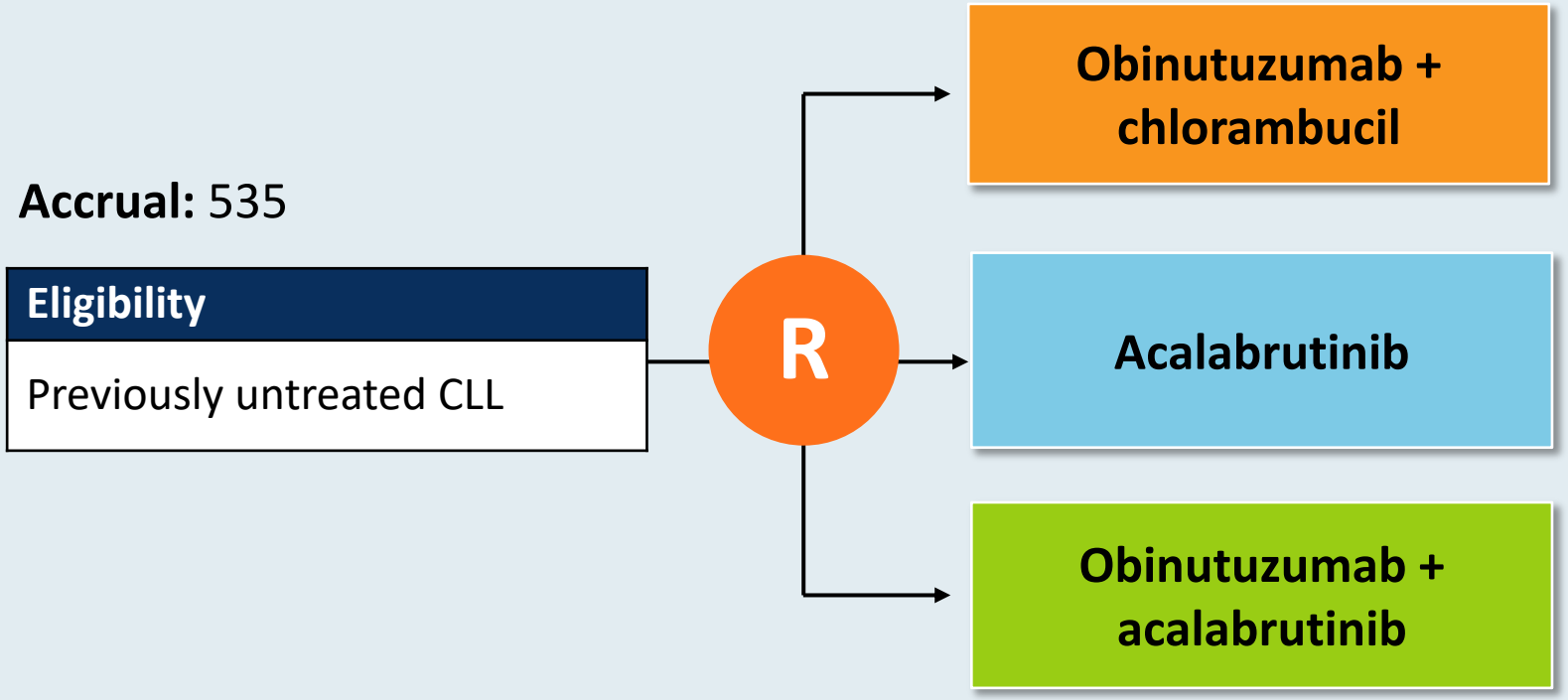
Articles

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

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

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

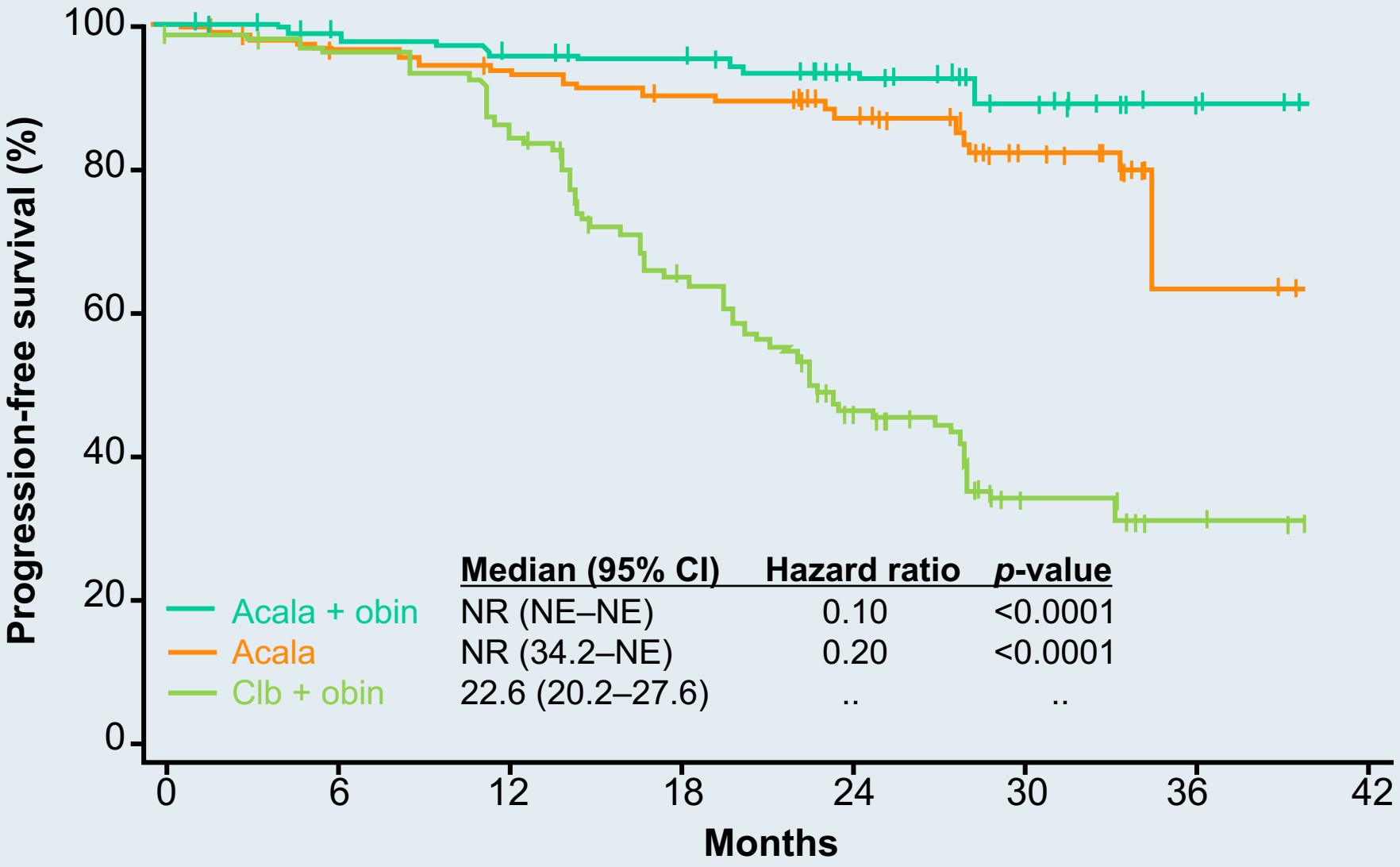
ELEVATE-TN Phase III Trial Schema



Primary endpoint: Progression-free survival

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

ELEVATE-TN: PFS (IRC)



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

ELEVATE-TN: Select Safety Parameters

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

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

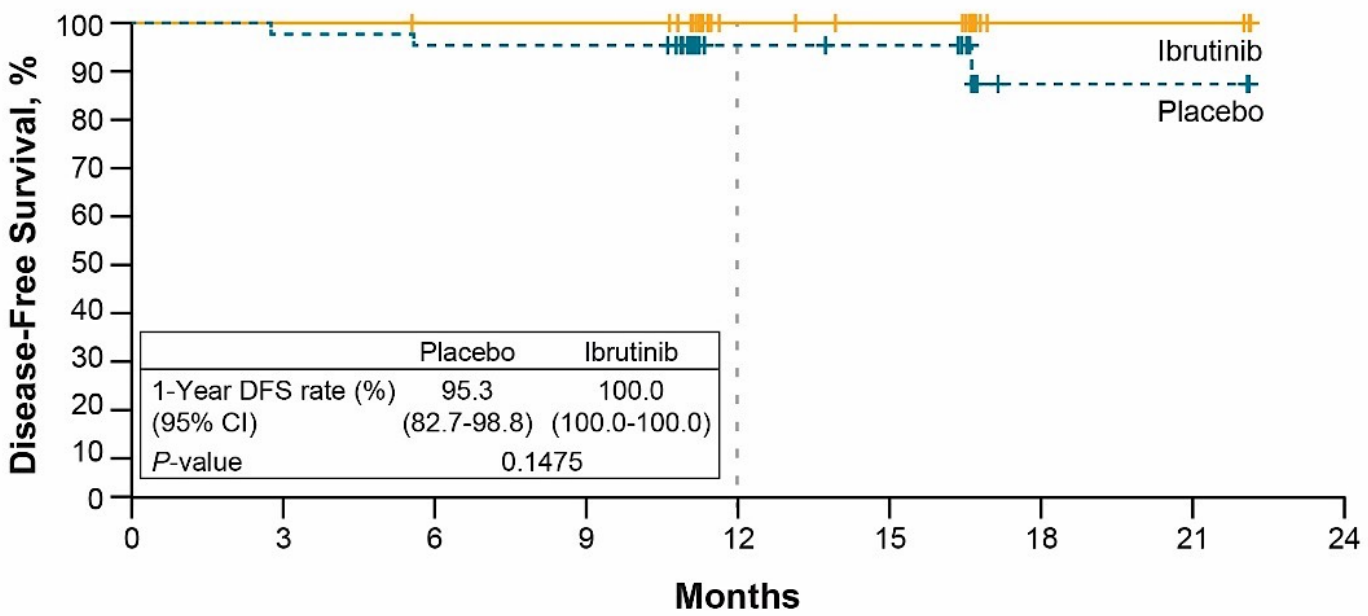
Ibrutinib (Ibr) plus Venetoclax (Ven) for First-Line Treatment of Chronic Lymphocytic Leukemia (CLL)/Small Lymphocytic Lymphoma (SLL): 1-Year Disease-Free Survival (DFS) Results from the MRD Cohort of the Phase 2 CAPTIVATE Study Trial

Wierda WG et al.

ASH 2020;Abstract 123.

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

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



Patients at Risk

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

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

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

Confirmed uMRD:

- 95.3% placebo
- 100% ibrutinib

Without confirmed uMRD:

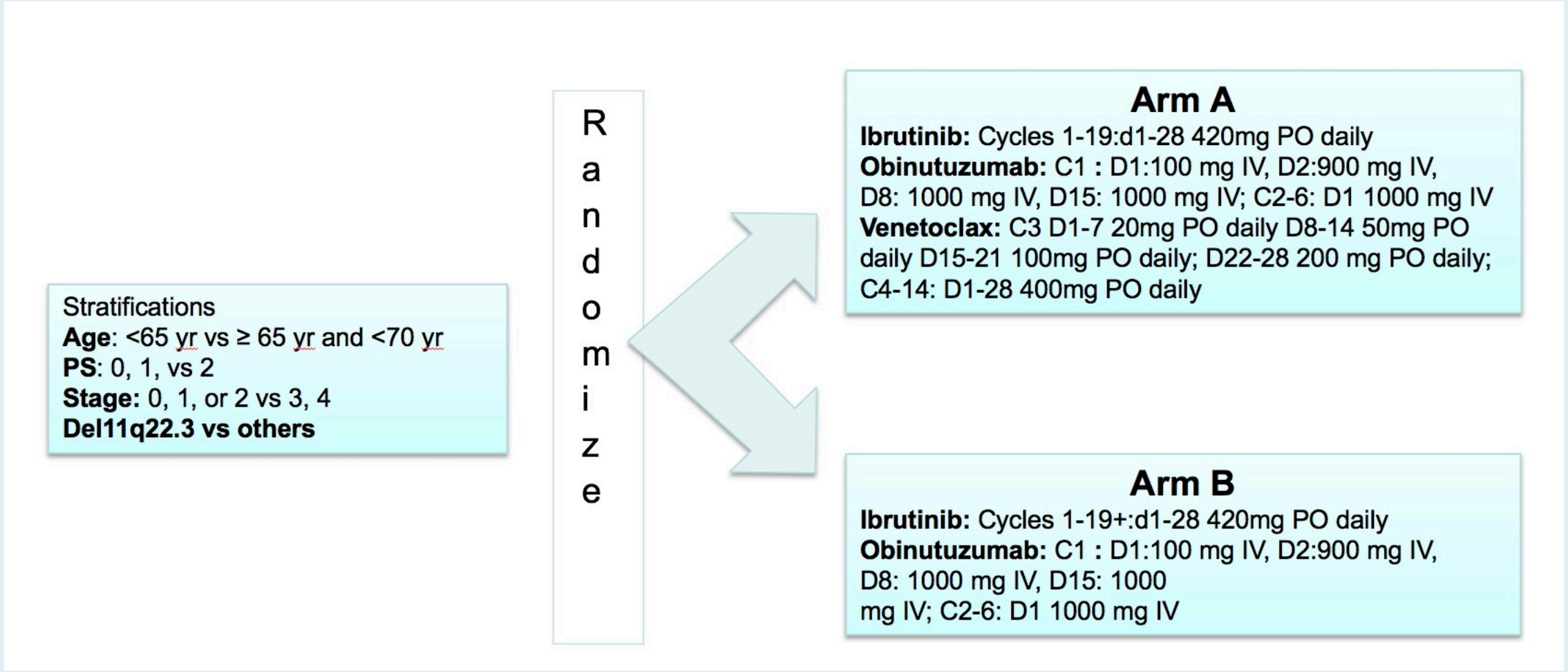
- 95.2% ibrutinib
- 96.7% ibr/ven

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

Wierda WG et al. ASH 2020;Abstract 123.

RTP RESEARCH TO PRACTICE

Phase III EA9161 Schema



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

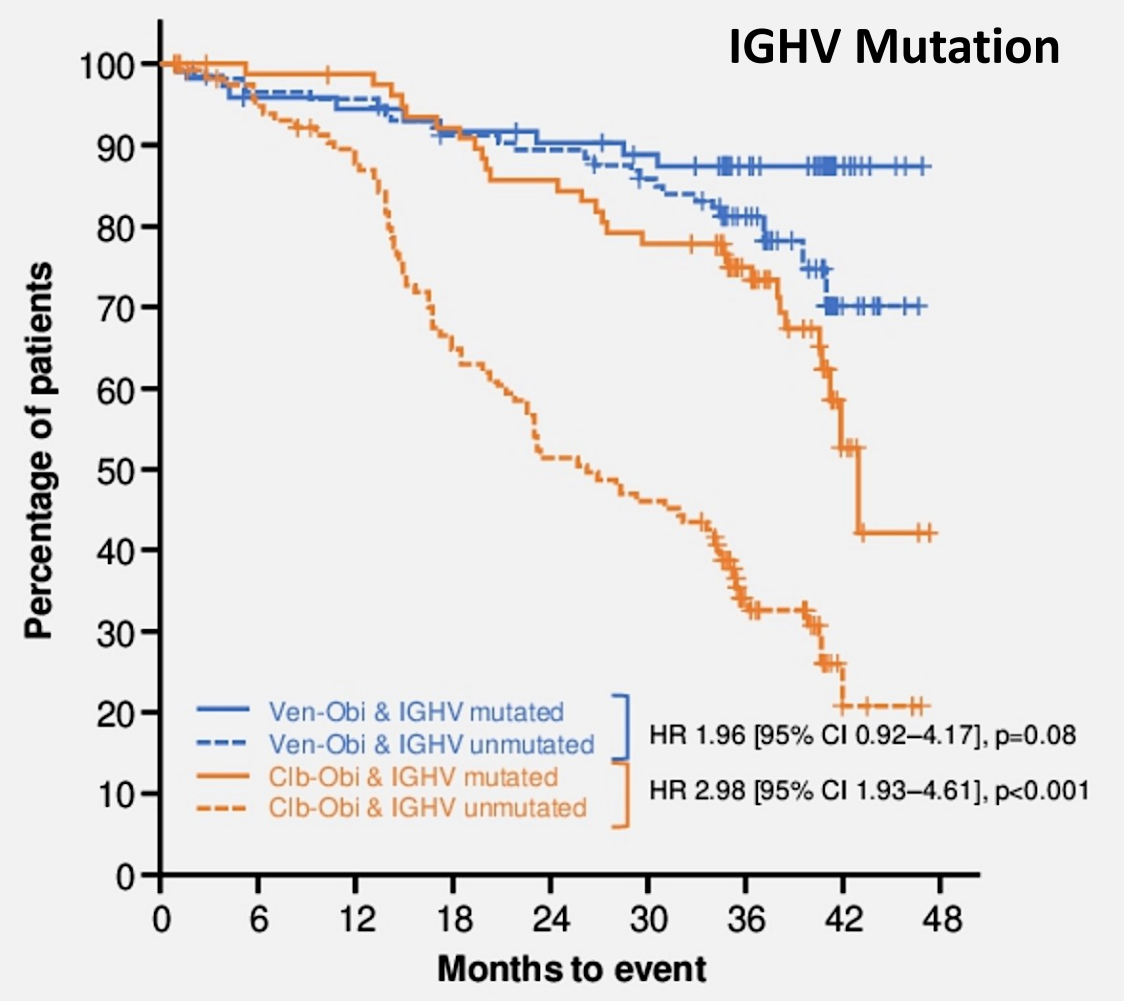
Articles

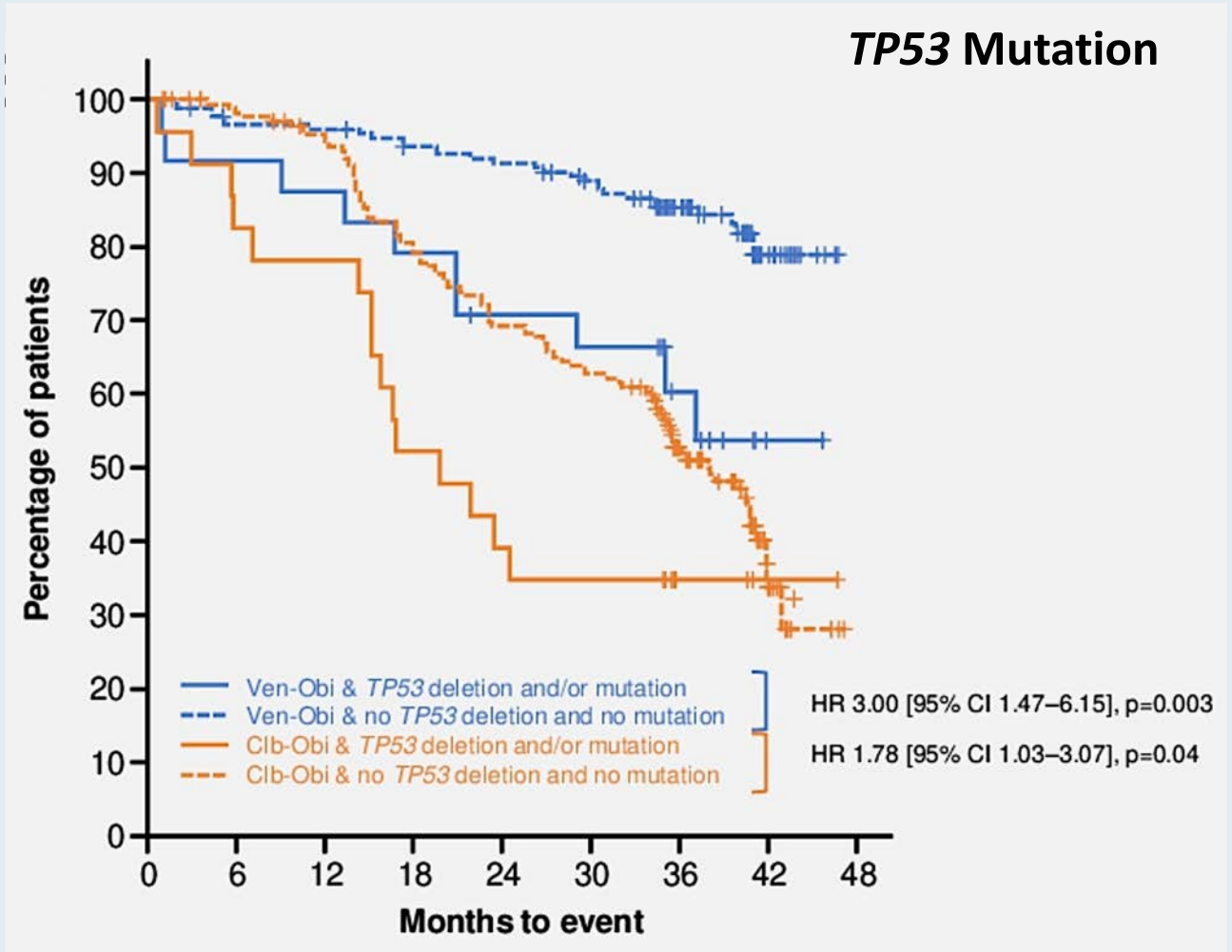
Venetoclax plus obinutuzumab versus chlorambucil plus obinutuzumab for previously untreated chronic lymphocytic leukaemia (CLL14): follow-up results from a multicentre, open-label, randomised, phase 3 trial

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

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

CLL14: PFS by IGHV and TP53 Mutation Status

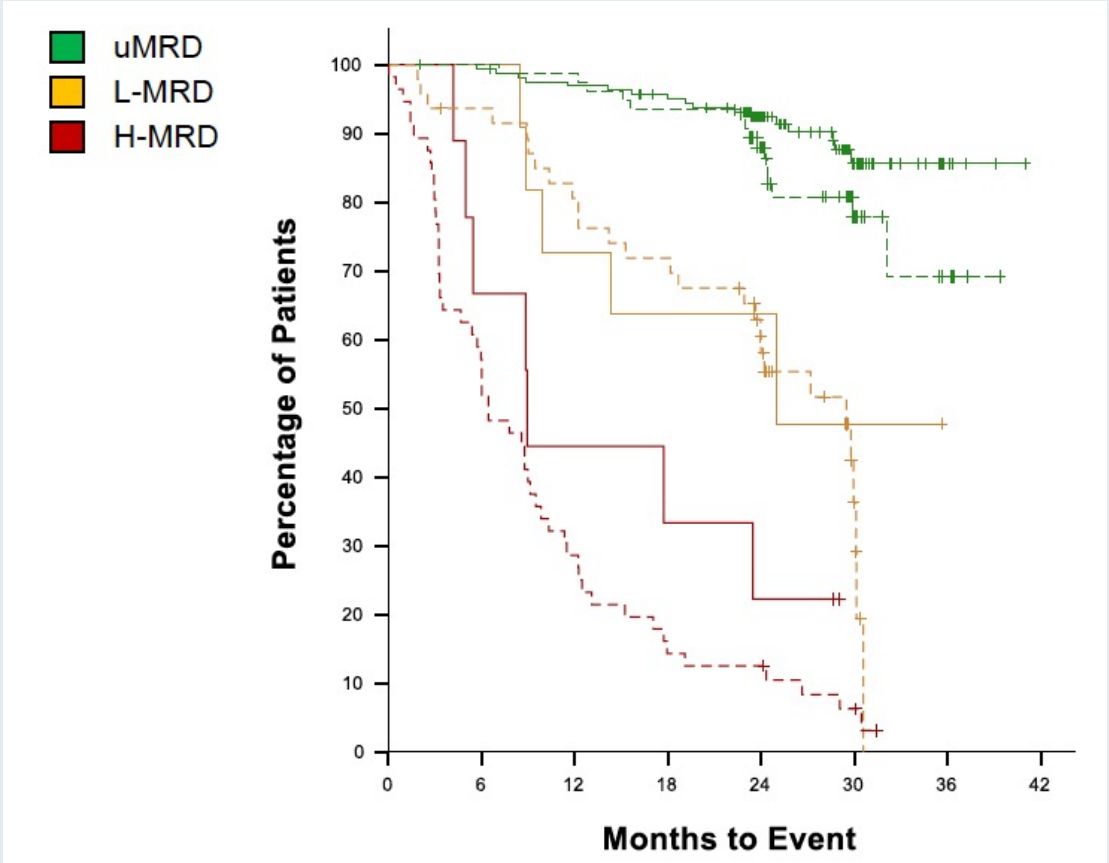




Al-Sawaf O et al. *Lancet Oncol* 2020;21(9):1188-200.

RTP RESEARCH TO PRACTICE

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



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

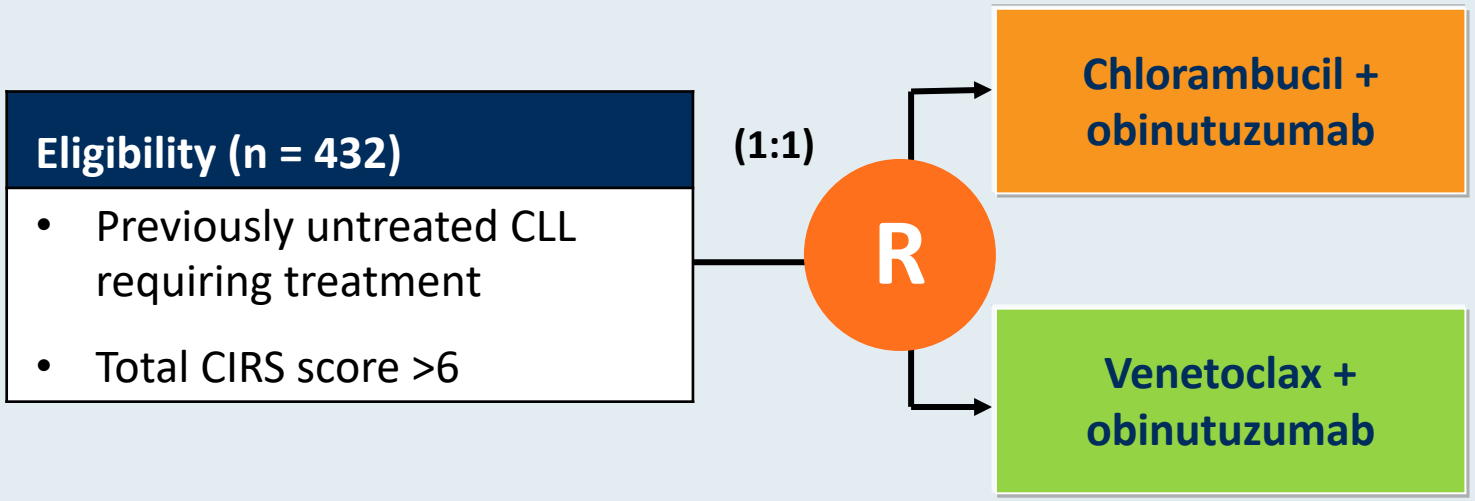
Al-Sawaf O et al. *Lancet Oncol* 2020;21(9):1188-200.

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

Al-Sawaf O et al.

ASH 2020;Abstract 127.

CLL14 Phase III Study Schema

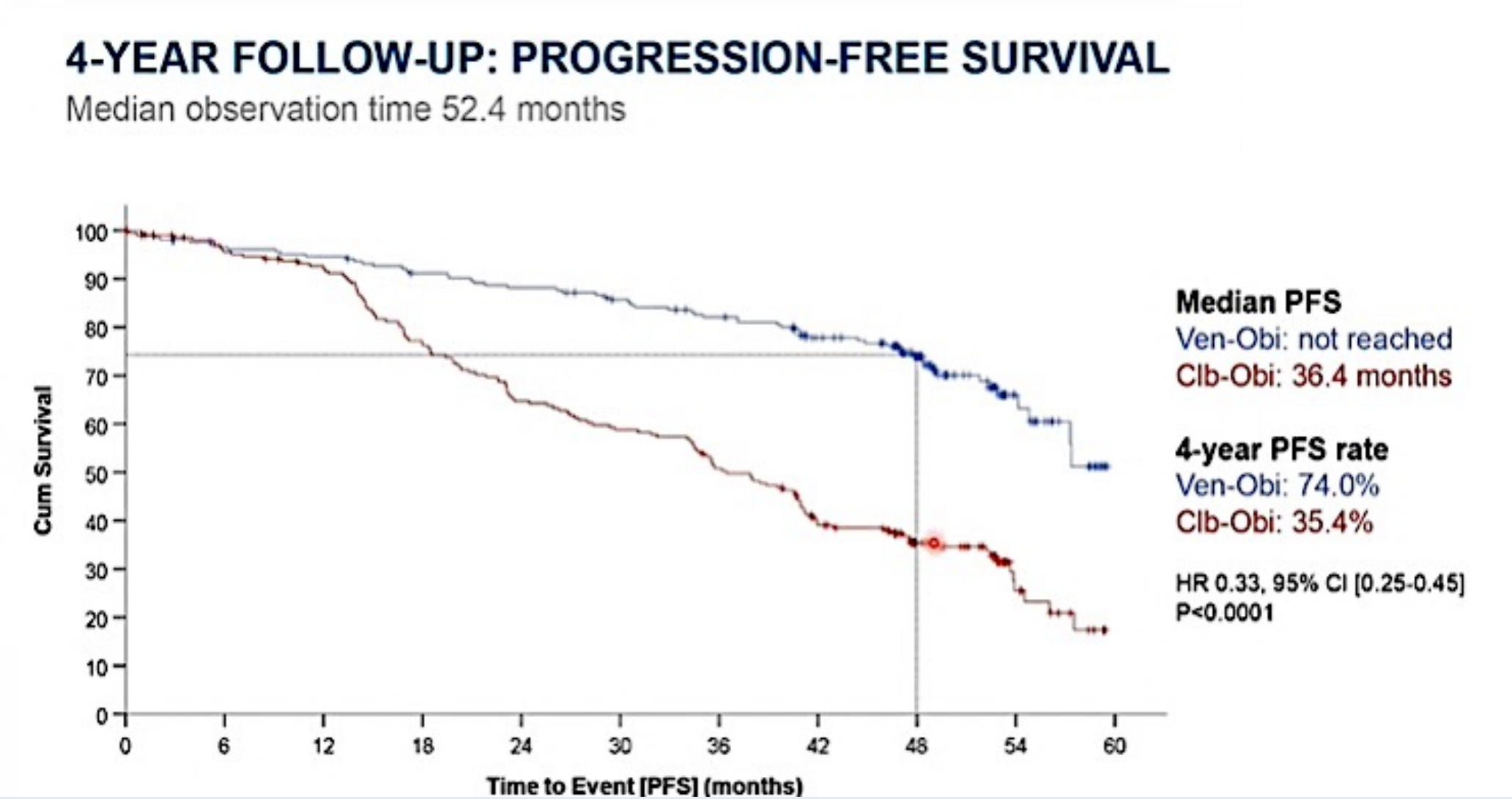


Primary endpoint: Progression-free survival

- Treatment duration in both groups: 12 cycles, 28 days each
- No crossover was allowed
- Daily oral venetoclax regimen:
  - Initiated on day 22 of cycle 1, starting with a 5-week dose ramp-up (1 week each of 20, 50, 100 and 200 mg, then 400 mg daily for 1 week)
  - Thereafter continuing at 400 mg daily until completion of cycle 12

www.clinicaltrials.gov (NCT02242942). Accessed August 2020.
Fischer K et al. *N Engl J Med* 2019;380(23):2225-36.

CLL14: Updated 4-Year PFS



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

RTP RESEARCH TO PRACTICE

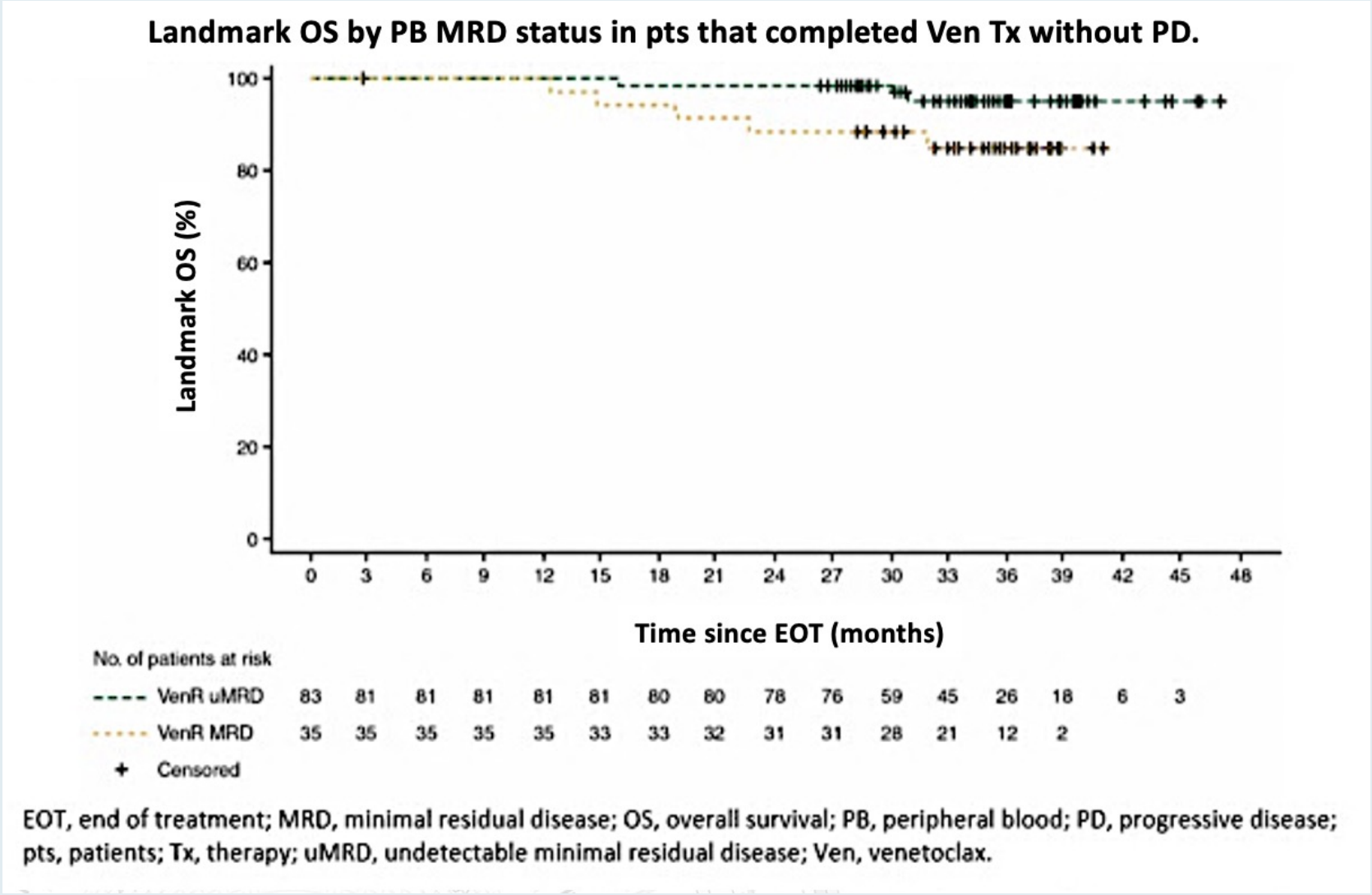
Management of Relapsed/Refractory CLL

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

Kater AP et al.

ASH 2020;Abstract 125.

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



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

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

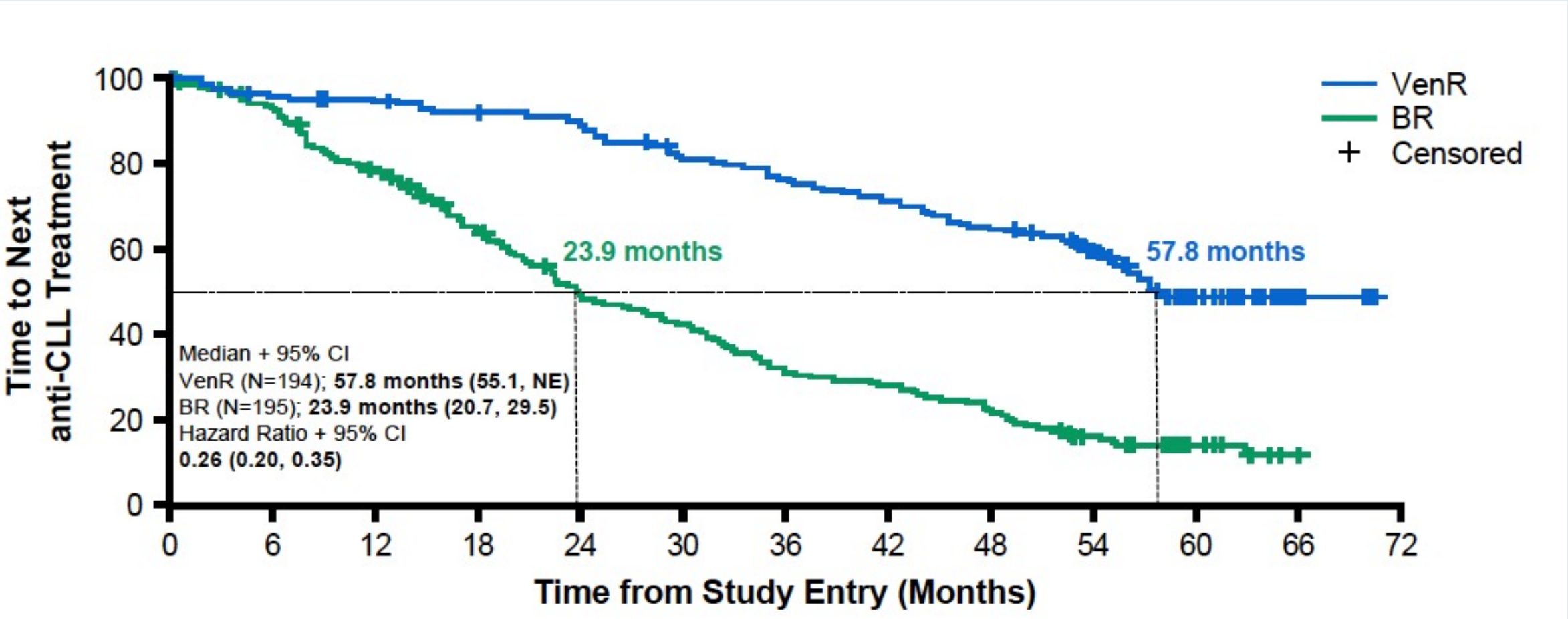
Kater AP et al. ASH 2020;Abstract 125.

RTP RESEARCH TO PRACTICE

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

Harrup R et al.
ASH 2020;Abstract 3139.

MURANO: TTNT with VenR versus BR



Harrup R et al. ASH 2020;Abstract 3139.

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

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

Harrup R et al. ASH 2020;Abstract 3139.

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

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

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

Study Design and Endpoints

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

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

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

Thompson MC et al. ASH 2020;Abstract 3136.

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Conclusions

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

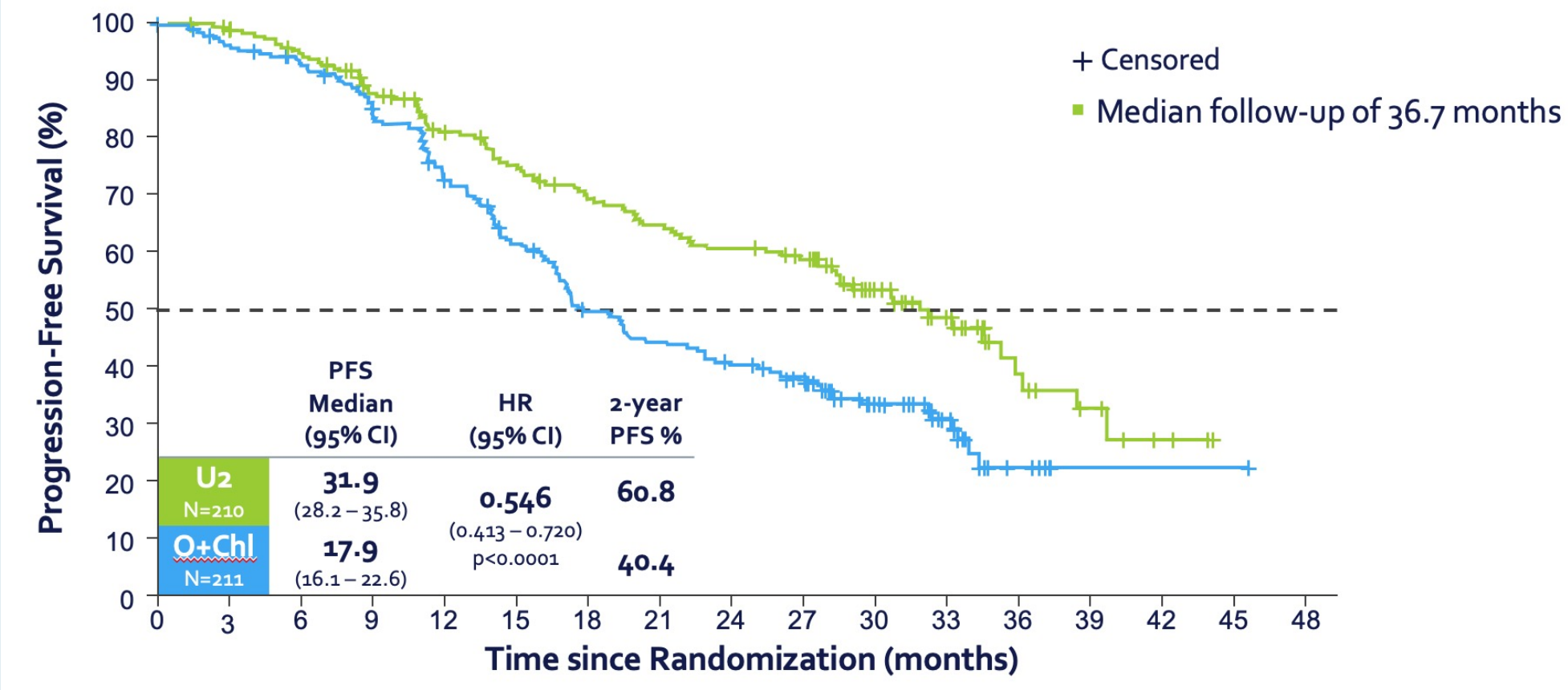
Thompson MC et al. ASH 2020;Abstract 3136.

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 543.

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%

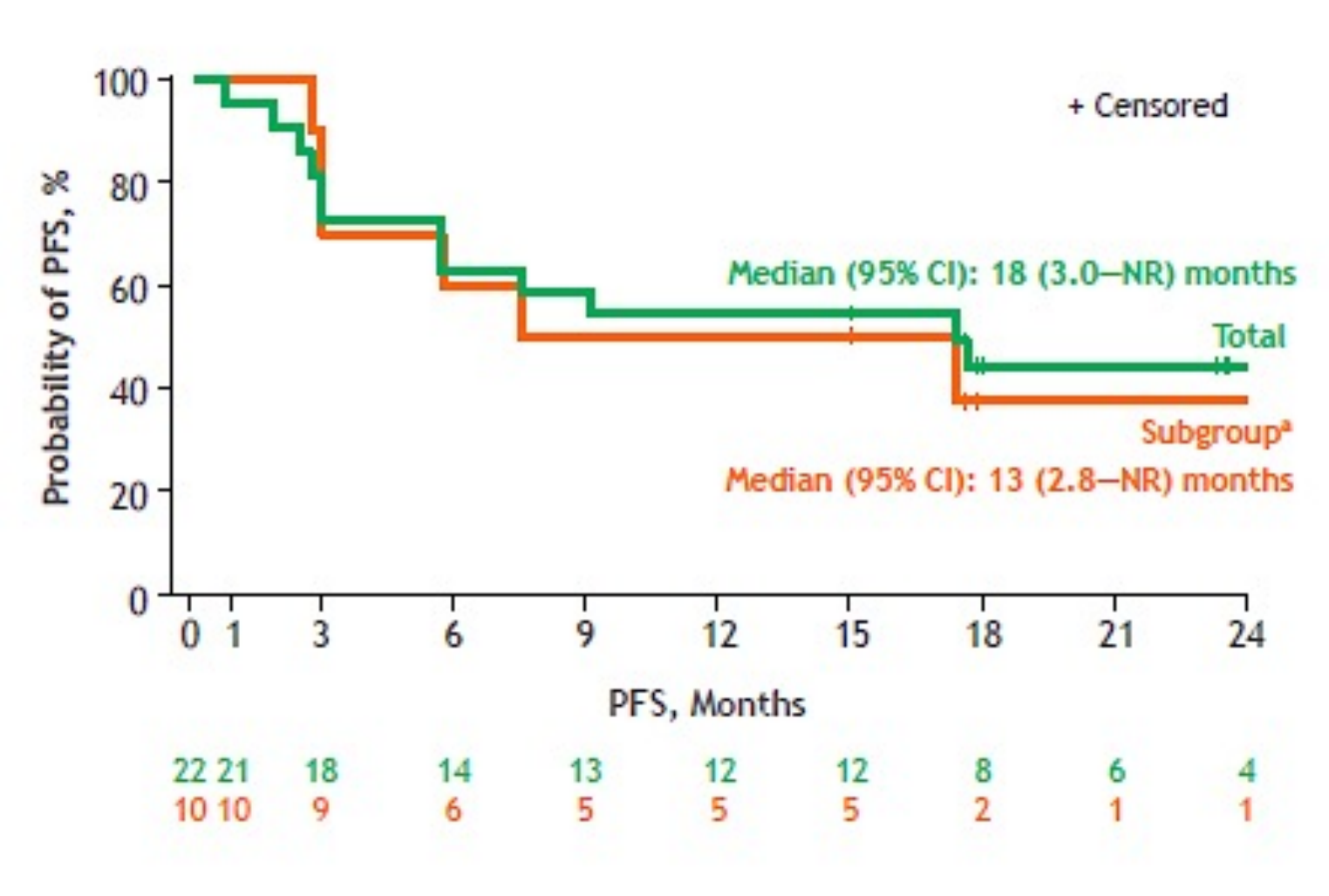
Gribben JG et al. ASH 2020;Abstract 543.

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.

RTP RESEARCH TO PRACTICE

Up for Debate: Oncology Investigators Provide Their Take on Current Controversies in Patient Care

A Daylong Multitumor Educational Webinar
in Partnership with Florida Cancer Specialists

Saturday, May 22, 2021
10:15 AM – 4:15 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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