Meet The Professor
Management of Chronic Lymphocytic Leukemia

Brian T Hill, MD, PhD
Director, Lymphoid Malignancy Program
Cleveland Clinic Taussig Cancer Institute
Cleveland, Ohio

Commercial Support

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

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Dr Love — Disclosures

Dr Love is president and CEO of Research To Practice. Research To Practice receives funds in the form of educational grants to develop CME activities from the following commercial interests: AbbVie Inc, Acerta Pharma — A member of the AstraZeneca Group, Adaptive Biotechnologies Corporation, Agendia Inc, Agios Pharmaceuticals Inc, Amgen Inc, Array BioPharma Inc, a subsidiary of Pfizer Inc, Astellas, AstraZeneca Pharmaceuticals LP, Bayer HealthCare Pharmaceuticals, Biodesix Inc, bioTheranostics Inc, Blueprint Medicines, Boehringer Ingelheim Pharmaceuticals Inc, Bristol-Myers Squibb Company, Celgene Corporation, Clovis Oncology, Daiichi Sankyo Inc, Dendreon Pharmaceuticals Inc, Eisai Inc, EMD Serono Inc, Epizyme Inc, Exelixis Inc, Foundation Medicine, Genentech, a member of the Roche Group, Genmab, Genomic Health Inc, Gilead Sciences Inc, GlaxoSmithKline, Grail Inc, Guardant Health, Halozyme Inc, Helsinn Healthcare SA, ImmunoGen Inc, Incyte Corporation, Infinity Pharmaceuticals Inc, Ipsen Biopharmaceuticals Inc, Janssen Biotech Inc, administered by Janssen Scientific Affairs LLC, Jazz Pharmaceuticals Inc, Karyopharm Therapeutics, Kite, A Gilead Company, Lexicon Pharmaceuticals Inc, Lilly, Loxo Oncology Inc, a wholly owned subsidiary of Eli Lilly & Company, Merck, Merrimack Pharmaceuticals Inc, Myriad Genetic Laboratories Inc, Natera Inc, Novartis, Oncopeptides, Pfizer Inc, Pharmacyclics LLC, an AbbVie Company, Prometheus Laboratories Inc, Puma Biotechnology Inc, Regeneron Pharmaceuticals Inc, Sandoz Inc, a Novartis Division, Sanofi Genzyme, Seagen Inc, Sirtex Medical Ltd, Spectrum Pharmaceuticals Inc, Sumitomo Dainippon Pharma Oncology Inc, Taiho Oncology Inc, Takeda Oncology, Tesaro, A GSK Company, Teva Oncology, Tokai Pharmaceuticals Inc and Verastem Inc.

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Research To Practice CME Planning Committee Members, Staff and Reviewers

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Dr Hill — Disclosures

Advisory Committee and Consulting Agreements	AbbVie Inc, AstraZeneca Pharmaceuticals LP, Bayer HealthCare Pharmaceuticals, Celgene Corporation, Genentech, a member of the Roche Group, Kite, A Gilead Company, Novartis
Contracted Research	AbbVie Inc, Celgene Corporation, Genentech, a member of the Roche Group, Kite, A Gilead Company, Takeda Oncology

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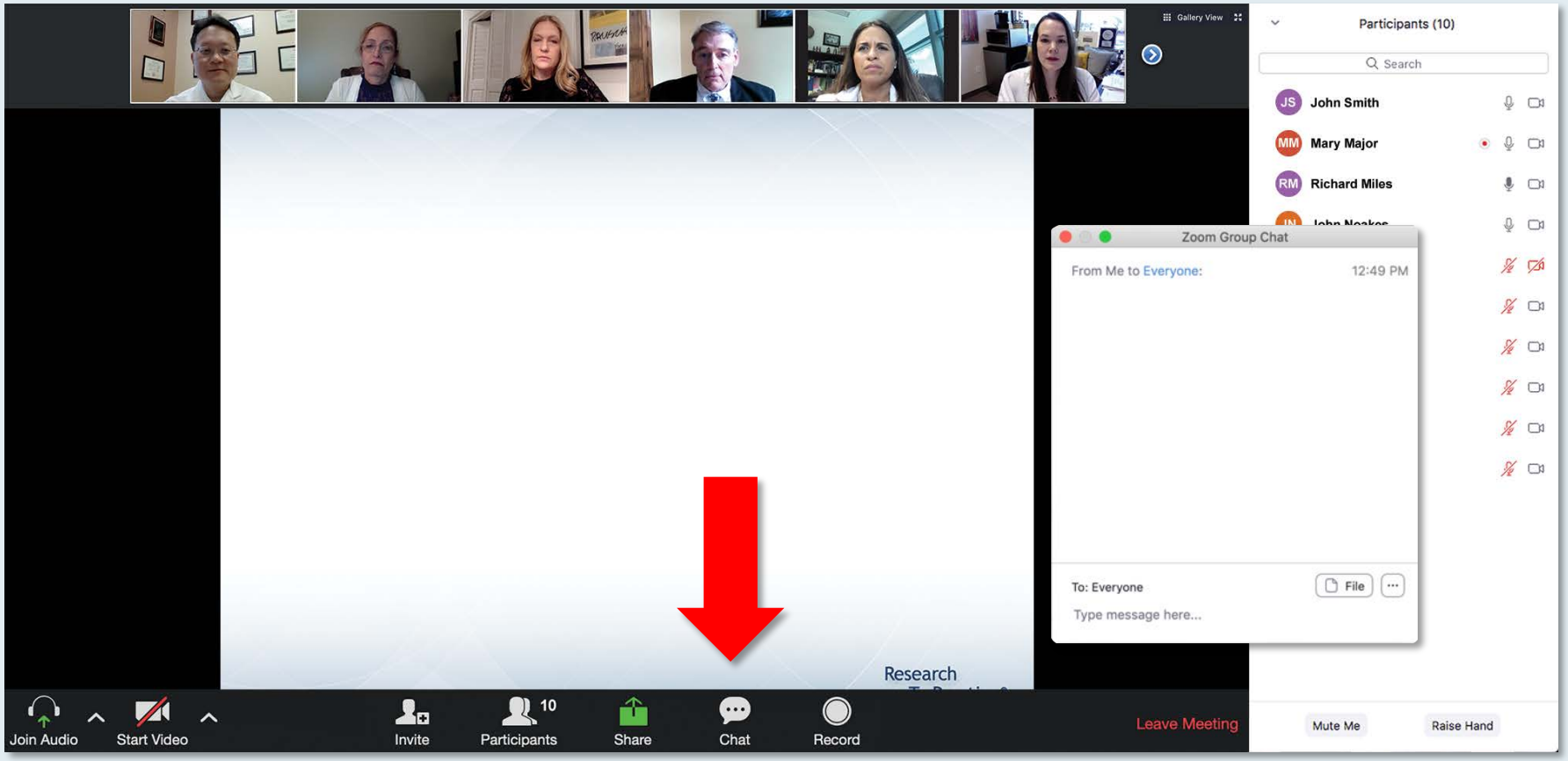

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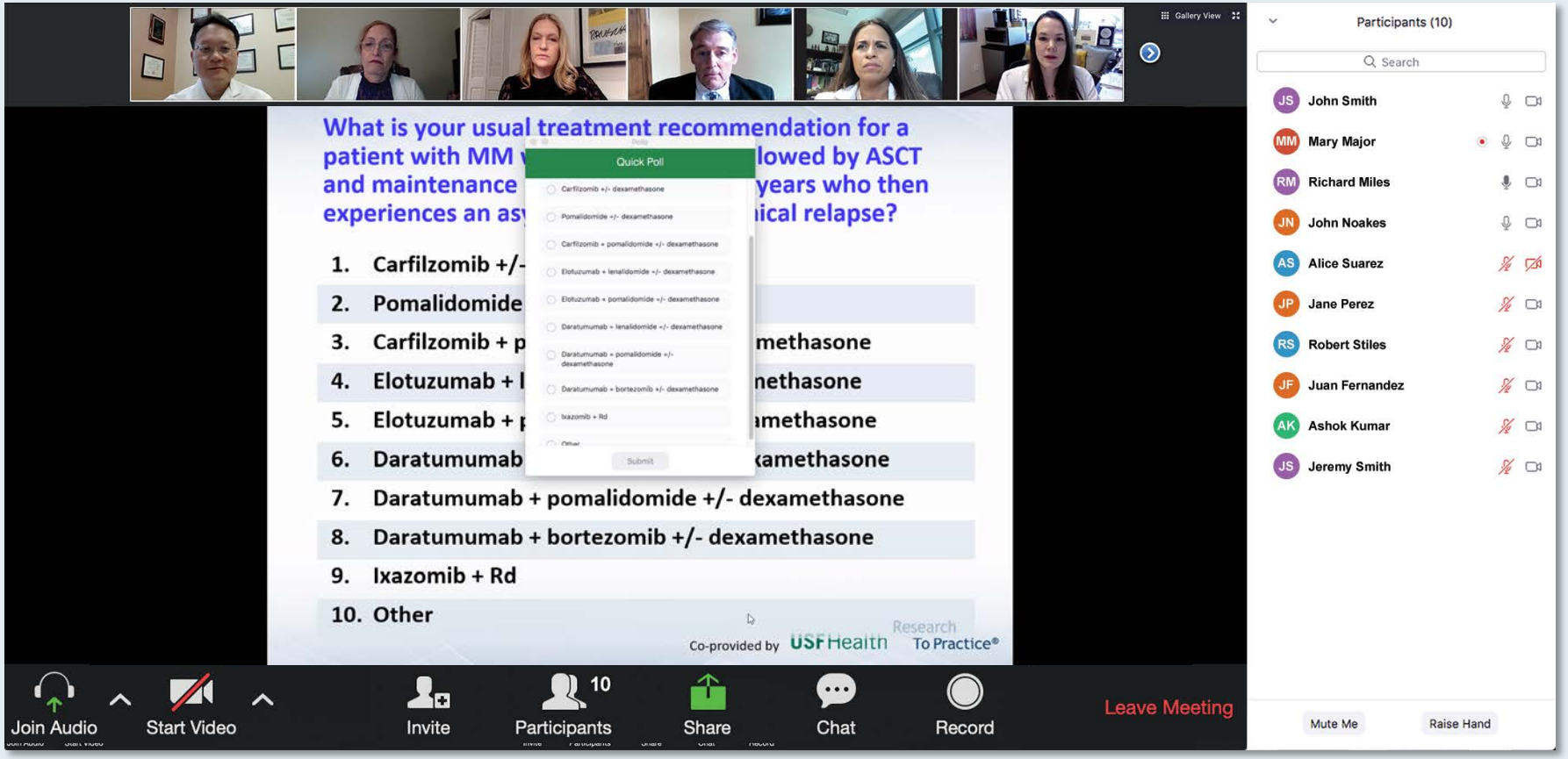
How to answer poll questions



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Upcoming Webinars

Wednesday, October 28, 2020
12:00 PM – 1:00 PM ET

Meet The Professor: Management of Lung Cancer

Faculty
Professor Solange Peters, MD, PhD

Moderator
Neil Love, MD

Friday, October 30, 2020
12:30 PM – 1:30 PM ET

Meet The Professor: Immunotherapy and Novel Agents in Gynecologic Cancers

Faculty
Richard T Penson, MD, MRCP

Moderator
Neil Love, MD

Upcoming Webinars

Friday, November 6, 2020
12:00 PM – 1:00 PM ET

Meet The Professor: Management of Ovarian Cancer

Faculty
Mansoor Raza Mirza, MD

Moderator
Neil Love, MD

Thank you for joining us!

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

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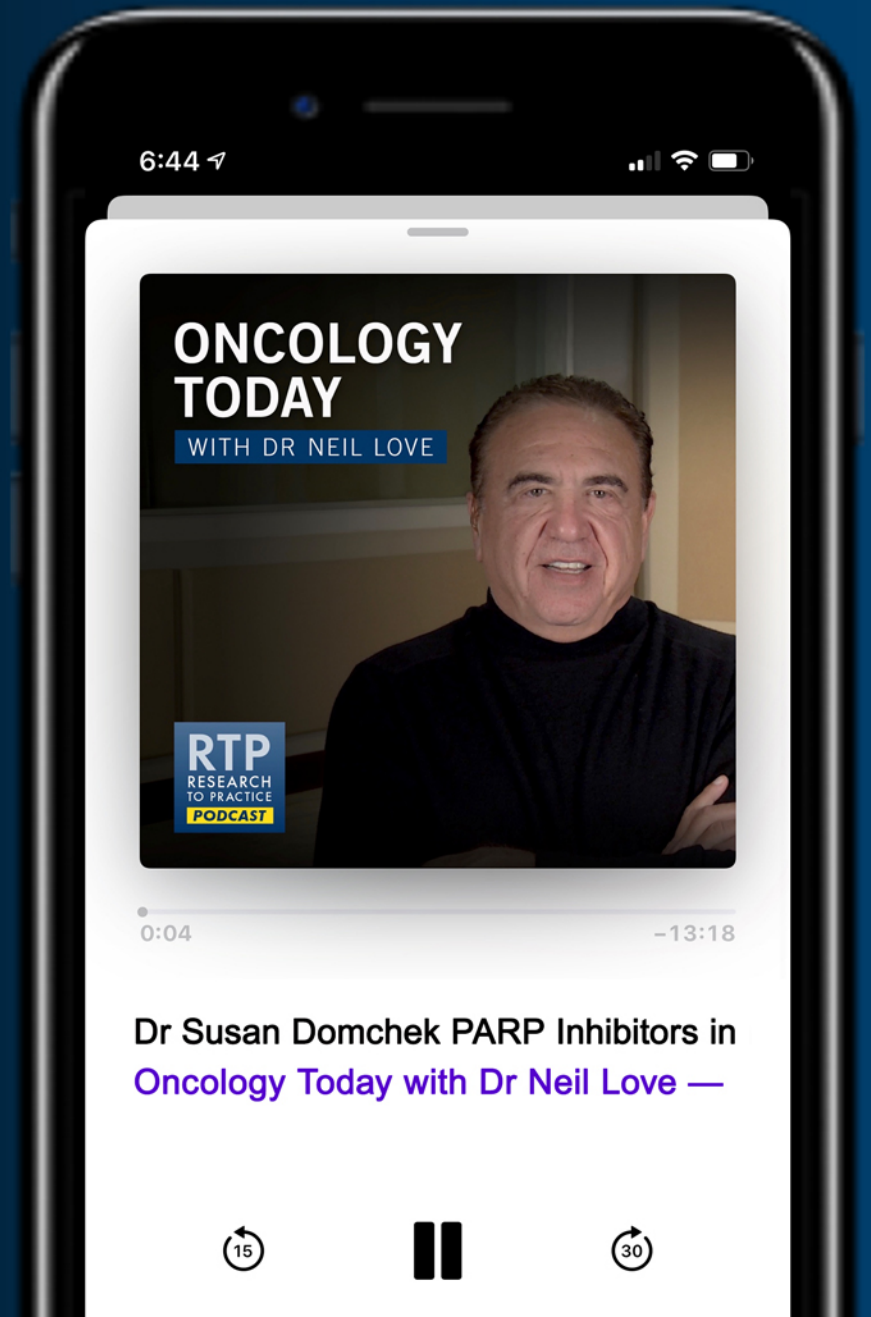

Meet The Professor
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Cleveland, Ohio

Meet The Professor Program Participating Faculty

Matthew S Davids, MD, MMSc
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Harvard Medical School
Director of Clinical Research
Division of Lymphoma
Dana-Farber Cancer Institute
Boston, Massachusetts

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Professor of Medicine
Washington University School of Medicine
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Siteman Cancer Center
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Meet The Professor Program Participating Faculty

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John M Pagel, MD, PhD
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Center for Blood Disorders and Stem Cell Transplantation
Swedish Cancer Institute
Seattle, Washington

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

Jeff Sharman, MD
Willamette Valley Cancer Institute and Research Center
Medical Director of Hematology Research
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Eugene, Oregon

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Duarte, California

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Meet The Professor Program Participating Faculty

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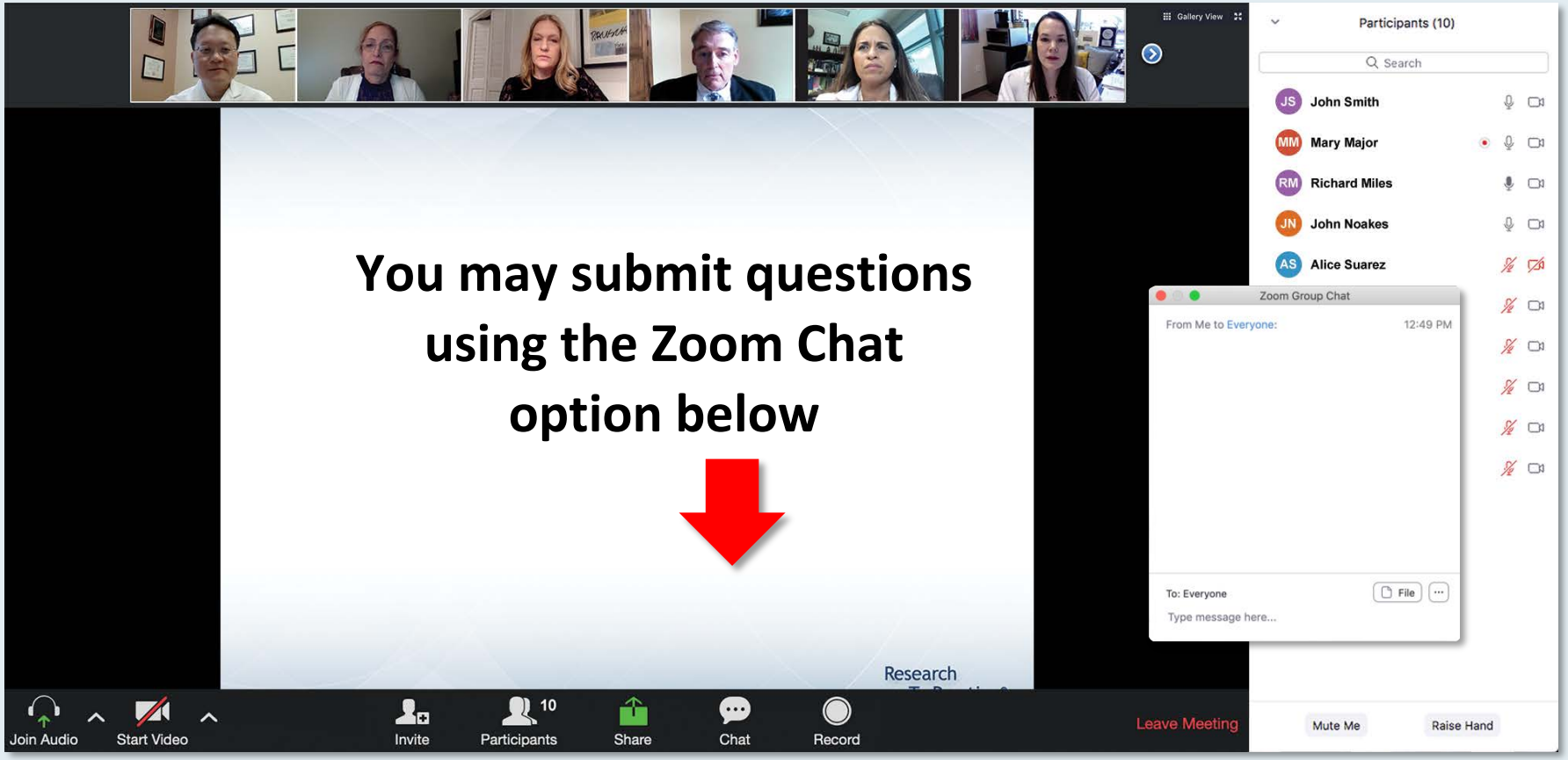

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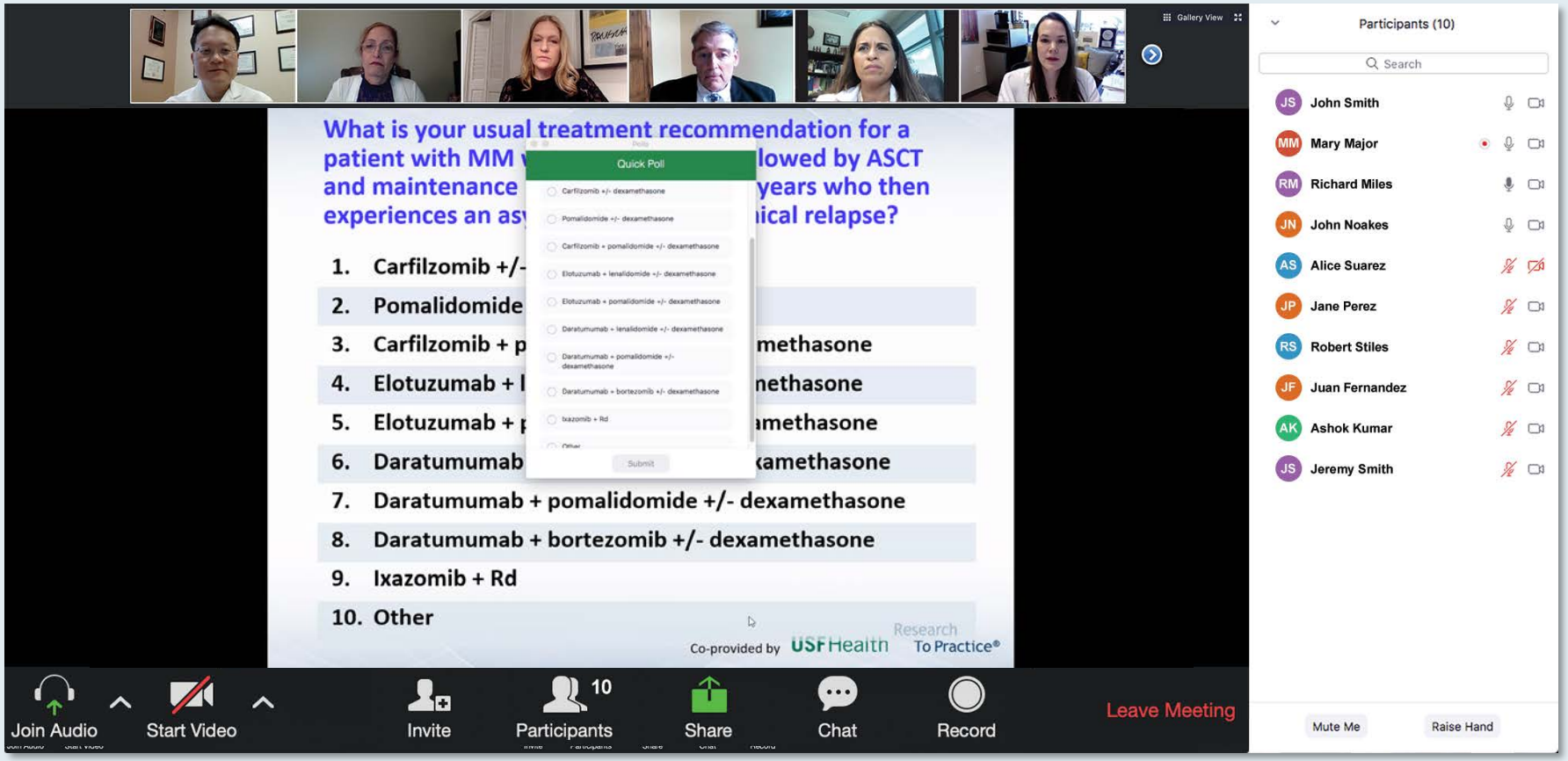

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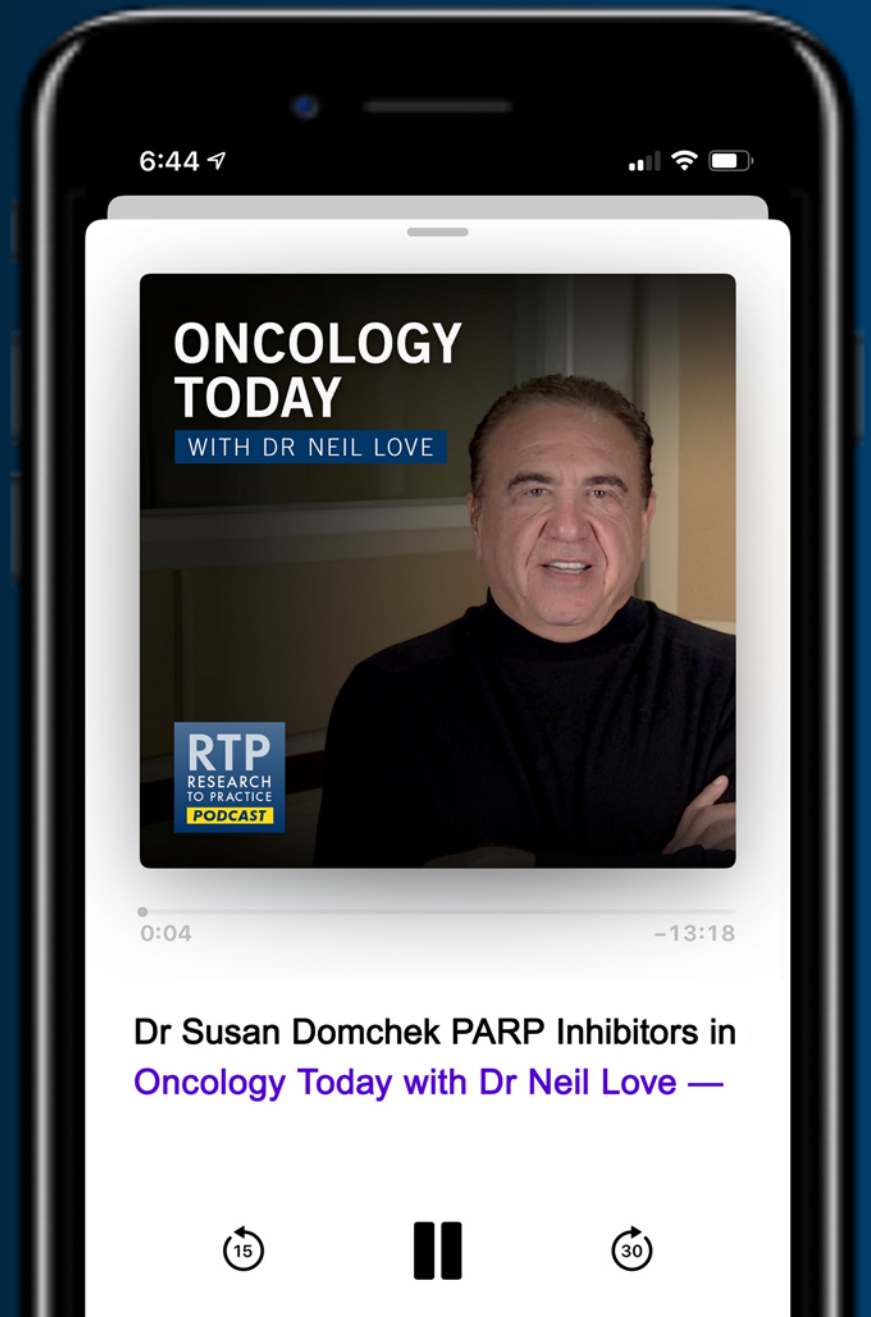

Meet The Professor
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Moderator

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Matthew S Davids, MD, MMSc
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Director of Clinical Research, Division of Lymphoma
Dana-Farber Cancer Institute
Boston, Massachusetts

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Allan Freedman, MD
Physician with Suburban Hematology-Oncology Associates
Snellville, Georgia

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Clinical Adjunct Professor, University of Wisconsin Madison
Madison, Wisconsin

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Meet The Professor with Dr Hill

MODULE 1: Cases from Drs Davids, Freedman and Parsons

- Dr Parsons: A 79-year-old man with significant coronary disease and newly diagnosed standard-risk CLL
- Questions and Comments: Sequencing of available up-front therapies; insights on novel triplet combinations and MRD-negative remission
- Dr Parsons: A 65-year-old man with newly diagnosed CLL and a rare Bcl-3 mutation
- Dr Freedman: A 79-year-old man with relapsed CLL and a BTK mutation
- Dr Davids: A 73-year-old man with newly diagnosed CLL and ibrutinib-related atrial fibrillation

MODULE 2: CLL Journal Club with Dr Hill

MODULE 3: Beyond the Guidelines – Clinical Investigator Approaches to Common Clinical Scenarios

MODULE 4: Key Recent Data Sets

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Case Presentation – Dr Parsons: A 79-year-old man with significant coronary disease and newly diagnosed standard-risk CLL

Dr Benjamin Parsons

- August 2020: presents with STEMI and thrombocytopenia, anemia, and mild lymphocytosis detected after workup for post-catheterization hematoma; diagnosed with CLL
  - Past medical history: STEMI in 2008 treated with medical management; hypertension, ascending aortic dilation, obesity, hyperlipidemia, CKD 3, BPH, and arthritis
- Bone marrow biopsy: 90% marrow involvement
- Cytogenetics: trisomy 12, *TP53* wildtype, unmutated IGHV

Questions

- What kind of treatment recommendations might you consider in the upfront setting for a patient with standard-risk CLL?

Case Presentation – Dr Parsons: A 79-year-old man with significant coronary disease and newly diagnosed standard-risk CLL (continued)

Dr Benjamin Parsons

- August 2020: presents with STEMI and thrombocytopenia, anemia, and mild lymphocytosis detected after workup for post-catheterization hematoma; diagnosed with CLL
  - Past medical history: STEMI in 2008 treated with medical management; hypertension, ascending aortic dilation, obesity, hyperlipidemia, CKD 3, BPH, and arthritis
- Bone marrow biopsy: 90% marrow involvement
- Cytogenetics: trisomy 12, *TP53* wildtype, unmutated IGHV
- **Concerned regarding infusion reactions given patient's cardiomyopathy**
- **Acalabrutinib initiated**

Questions and Comments: Sequencing of available up-front therapies; insights on novel triplet combinations and MRD-negative remission

Dr Benjamin Parsons

Case Presentation – Dr Parsons: A 65-year-old man with newly diagnosed CLL and a rare Bcl-3 mutation

Dr Benjamin Parsons

- 2016: Diagnosed with Rai stage II CLL
  - Cytogenetics: unmutated IGHV, trisomy 12, complex karyotype 45 XY-, -6(6:17)
    - t(14;19) translocation of Ig heavy chain and BCL3 genes
  - Bone marrow biopsy: 90% marrow involvement
- BR x 6 cycles → CR

Questions

- What are your thoughts on the biology of CLL positive for a BCL3 mutation?
- What would you recommend as second-line therapy for this patient should he progress?
- Is there still a role for IGHV mutation testing in aiding treatment selection? Are there certain tests that clinicians may omit as part of a patient's diagnostic workup for CLL?

Case Presentation – Dr Freedman: A 79-year-old man with relapsed CLL and a BTK mutation

Dr Allan Freedman

- 2010: Diagnosed with Rai Stage II CLL; del13q and unmutated IGHV
- BR x 6 cycles → CR
- Within 4 years fatigue, splenomegaly, and rapid doubling time of ALC
- March 2015: Ibrutinib initiated
- 2020: ALC quadrupled over 6 weeks and he developed mild anemia and thrombocytopenia; no bulky adenopathy on imaging
  - Genetic analysis: BTK C481Y mutation, PLCG2 mutation
- March 2020: Obinutuzumab + venetoclax initiated → clinical, hematological, and radiographic remission

Questions

- Do you have a preference in terms of sequencing a second-line CD20 agent in cases like this?

Case Presentation – Dr Davids: A 73-year-old man with newly diagnosed CLL and ibrutinib-related atrial fibrillation

Dr Matthew S Davids

- Diagnosed with Rai Stage IV CLL; del11q and unmutated IGHV, *TP53* wildtype
- Ibrutinib initiated
- After 10 weeks, patient's disease was responding to ibrutinib, but atrial fibrillation detected on routine office visit
- Ibrutinib held
- Patient met criteria for anticoagulation therapy per CHADS VASc criteria

Questions

- What would be the optimal next steps in the management of this patient's disease?

Case Presentation – Dr Davids: A 73-year-old man with newly diagnosed CLL and ibrutinib-related atrial fibrillation (continued)

Dr Matthew S Davids

- Diagnosed with Rai Stage IV CLL; del11q and unmutated IGHV, *TP53* wildtype
- Ibrutinib initiated
- After 10 weeks, patient's disease was responding to ibrutinib, but atrial fibrillation detected on routine office visit
- Ibrutinib held
- Patient met criteria for anticoagulation therapy per CHADS VASc criteria
- **Response of disease to ibrutinib was encouraging, but concerned regarding the development of atrial fibrillation early in the treatment course and bleeding risks due to coagulation therapy**
- **Treatment changed to acalabrutinib**
- **No disease recurrence or development of atrial fibrillation**

Meet The Professor with Dr Hill

MODULE 1: Cases from Drs Davids, Freedman and Parsons

MODULE 2: CLL Journal Club with Dr Hill

- Purine nucleoside analogue alone or with rituximab for hairy cell leukemia
- GIMEMA-ERIC and US indirect comparison of bendamustine/rituximab and ibrutinib in a real-world setting
- Preventing FOXO3a nuclear export and PI3K/AKT activation to overcome resistance to ibrutinib
- Venetoclax combined with anti-CD20 monoclonal antibody therapy for elderly patients with R/R CLL
- Real world treatment discontinuation patterns among patients with CLL
- Efficacy of therapies after venetoclax in CLL
- Treatment sequences and outcomes in patients with CLL treated with venetoclax and other novel agents
- Tumor lysis, adverse events and dose adjustments in patients with CLL treated with venetoclax
- Ibrutinib-associated invasive fungal diseases
- Umbralisib, ublituximab and venetoclax for R/R CLL
- Effect of age on survival for patients receiving ibrutinib as initial therapy for CLL

MODULE 3: Beyond the Guidelines – Clinical Investigator Approaches to Common Clinical Scenarios

MODULE 4: Key Recent Data Sets

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Treatment Outcomes with Purine Nucleoside Analog Alone or with Rituximab for Hairy Cell Leukemia Patients at First Relapse: A Multi-Center Outcomes Analysis

Hu R et al.

ASH 2019;Abstract 4004.

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

Cancer Med 2020;[Online ahead of print].

ARTICLE Open Access

Resistance to BTK inhibition by ibrutinib can be overcome by preventing FOXO3a nuclear export and PI3K/AKT activation in B-cell lymphoid malignancies

Isha Kapoor[1], Yue Li[2], Arishya Sharma[1], Huayuan Zhu[2], Juraj Bodo[3], Wei Xu[2], Eric D. Hsi[3], Brian T. Hill[4] and Alexandru Almasan[1,5,6]

Cell Death Dis 2019;10(12):924.

REGULAR ARTICLE

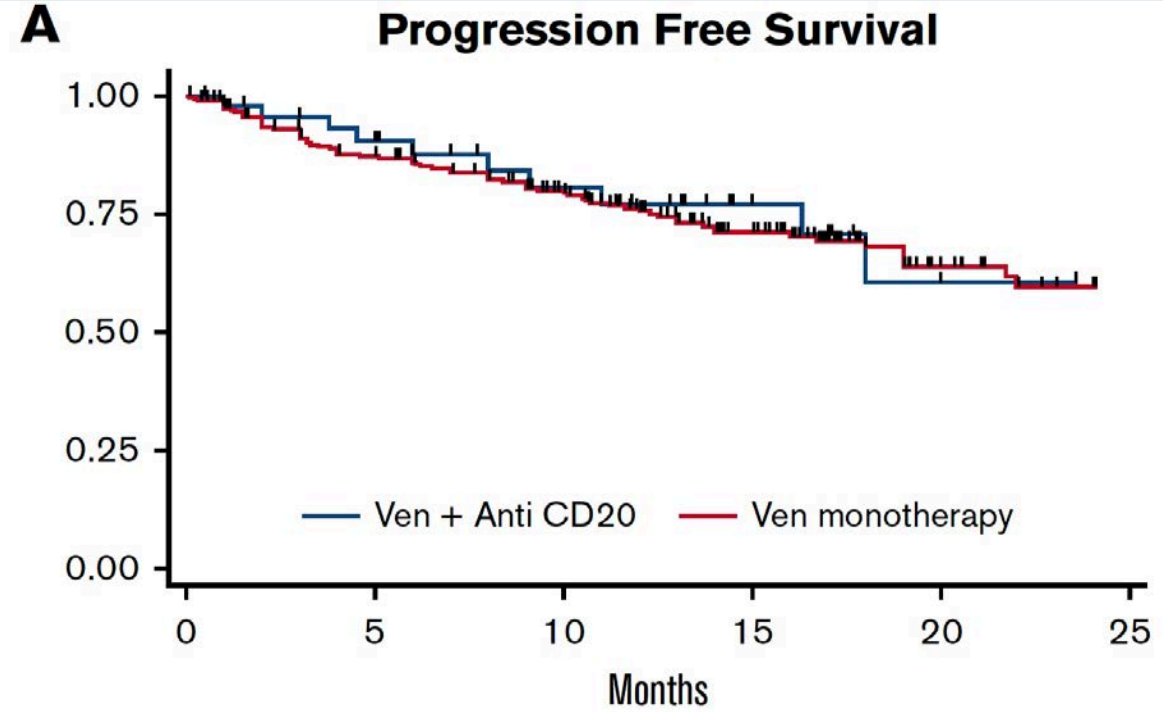
blood advances

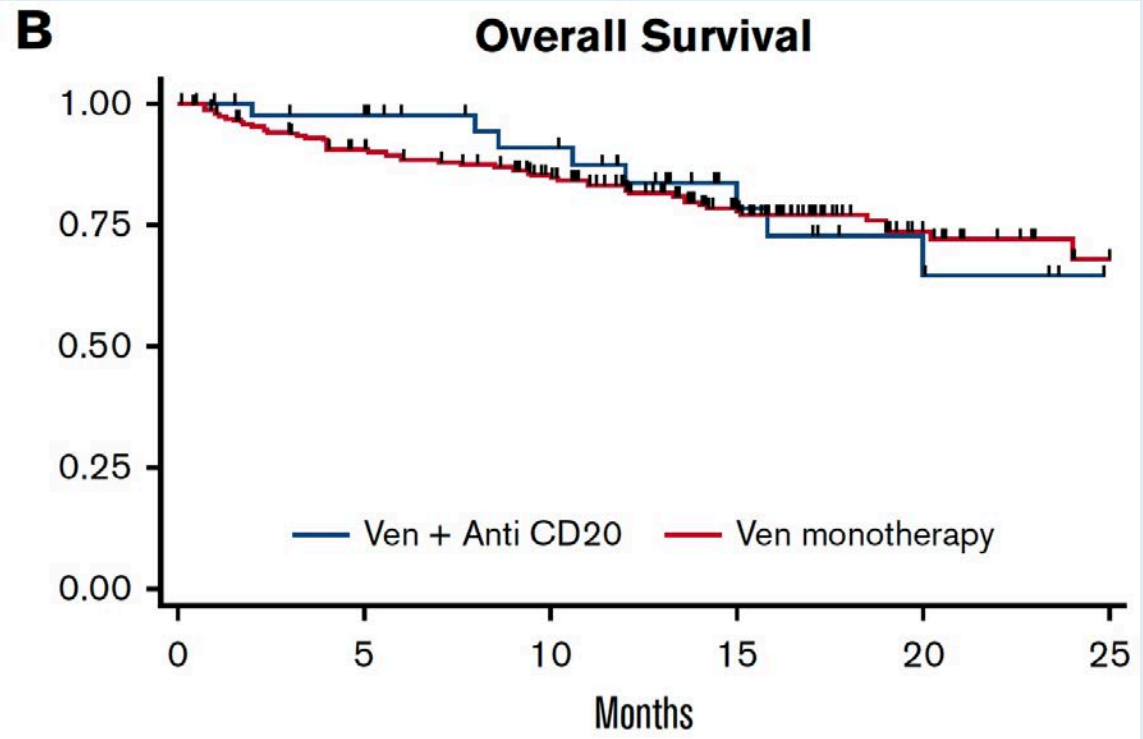
A retrospective comparison of venetoclax alone or in combination with an anti-CD20 monoclonal antibody in R/R CLL

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]

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

PFS (A) and OS (B) Stratified by Venetoclax Monotherapy and Venetoclax with Anti-CD20 Therapy for R/R CLL





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

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

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], Anthony R. Mato[2]

Treatment Discontinuation Patterns for Patients with CLL in the Real-World Settings: Results from a Multi-Center Study

Shadman M et al.

ASH 2019;Abstract 3048.

CLINICAL CANCER RESEARCH | PRECISION MEDICINE AND IMAGING

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.

Efficacy of Therapies Following Venetoclax Discontinuation in CLL: Focus on B-Cell Receptor Signal Transduction Inhibitors and Cellular Therapies

Mato AR et al.

ASH 2019;Abstract 502.

Treatment Sequences and Outcomes of Patients with CLL Treated with Venetoclax and Other Novel Agents Post Introduction of Novel Therapies

Mato AR et al.

ASH 2019;Abstract 1756.

Precision Medicine and Imaging

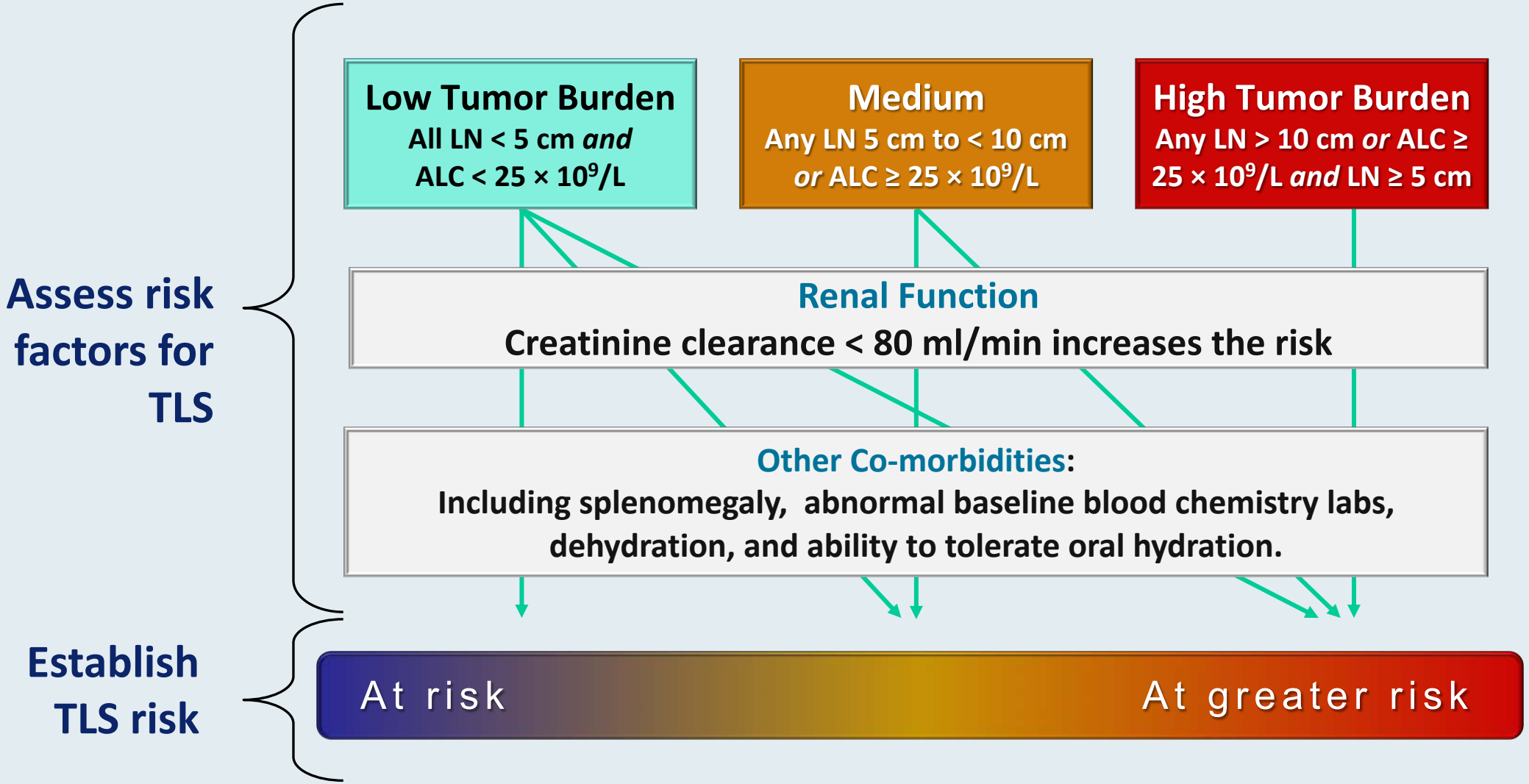
Clinical Cancer Research

Tumor Lysis, Adverse Events, and Dose Adjustments in 297 Venetoclax-Treated CLL Patients in Routine Clinical Practice

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

Clin Cancer Res 2019;25(14):4264-70.

TLS Risk with Venetoclax Is a Continuum Based on Multiple Factors



ALC, absolute lymphocyte count; **CrCl**, creatinine clearance; **LN**, lymph node; **TLS**, tumor lysis syndrome 1. Venetoclax SmPC: https://www.medicines.org.uk/emc/product/2267/smpc (accessed October 2019); 2. Stilgenbauer S, et al. *Lancet Oncol* 2016;17:768–778.

Courtesy of Matthew S Davids, MD MSSc

RTP RESEARCH TO PRACTICE

ORIGINAL ARTICLE

mycoses Diagnosis, Therapy and Prophylaxis of Fungal Diseases | WILEY

Mycoses 2019;62(12):1140-7.

Ibrutinib-associated invasive fungal diseases in patients with chronic lymphocytic leukaemia and non-Hodgkin lymphoma: An observational study

Rosa Ruchlemer[1] | Ronen Ben-Ami[2] | Maskit Bar-Meir[3] | Jennifer R. Brown[4] | Marion Malphettes[5] | Rogier Mous[6] | Sanne H. Tonino[7] | Carole Soussain[8] | Noelie Barzic[9] | Julia A. Messina[10] | Preetesh Jain[11] | Regev Cohen[12] | Brian Hill[13] | Stephen P. Mulligan[14] | Marcel Nijland[15] | Yair Herishanu[16] | Ohad Benjamini[17] | Tamar Tadmor[18] | Koh Okamoto[19] | Benjamin Arthurs[20] | Batsheva Gottesman[21] | Arnon P. Kater[7] | Munir Talha[22] | Barbara Eichhorst[23] | Maya Korem[24] | Naama Bogot[25] | Fransien De Boer[26] | Jacob M. Rowe[27] | Tamar Lachish[28]

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

Blood Lymphat Cancer 2020;10:1-5.

A Phase 1/2 Study of Umbralisib Ublituximab and Venetoclax in Patients with Relapsed or Refractory Chronic Lymphocytic Leukemia (CLL)

Barr PM et al.

ASH 2019;Abstract 360.

Meet The Professor with Dr Hill

MODULE 1: Cases from Drs Davids, Freedman and Parsons

MODULE 2: CLL Journal Club with Dr Hill

- Purine nucleoside analogue alone or with rituximab for hairy cell leukemia
- GIMEMA-ERIC and US indirect comparison of bendamustine/rituximab and ibrutinib in a real-world setting
- Preventing FOXO3a nuclear export and PI3K/AKT activation to overcome resistance to ibrutinib
- Venetoclax combined with anti-CD20 monoclonal antibody therapy for elderly patients with R/R CLL
- Real world treatment discontinuation patterns among patients with CLL
- Efficacy of therapies after venetoclax in CLL
- Treatment sequences and outcomes in patients with CLL treated with venetoclax and other novel agents
- Tumor lysis, adverse events and dose adjustments in patients with CLL treated with venetoclax
- Ibrutinib-associated invasive fungal diseases
- Umbralisib, ublituximab and venetoclax for R/R CLL
- Effect of age on survival for patients receiving ibrutinib as initial therapy for CLL

MODULE 3: Beyond the Guidelines – Clinical Investigator Approaches to Common Clinical Scenarios

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
2. Ibrutinib
3. Ibrutinib + rituximab
4. Ibrutinib + obinutuzumab
5. Acalabrutinib
6. Acalabrutinib + obinutuzumab
7. Venetoclax + obinutuzumab
8. Other

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

 MATTHEW S DAVIDS, MD, MMSC	Venetoclax + obinutuzumab
 IAN W FLINN, MD, PHD	Venetoclax + obinutuzumab
 BRIAN T HILL, MD, PHD	Venetoclax + obinutuzumab or BR
 BRAD S KAHL, MD	Venetoclax + obinutuzumab
 ANTHONY R MATO, MD, MSCE	FCR
 JOHN M PAGEL, MD, PHD	Acalabrutinib

 KERRY A ROGERS, MD	Ibrutinib or FCR
 JEFF SHARMAN, MD	FCR
 TANYA SIDDIQI, MD	Venetoclax + obinutuzumab
 MITCHELL R SMITH, MD, PHD	FCR
 WILLIAM G WIERDA, MD, PHD	FCR
 JENNIFER WOYACH, MD	Venetoclax + obinutuzumab

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

RTP RESEARCH TO PRACTICE

What is your usual preferred initial regimen for a 75-year-old patient with CLL with IGHV mutation but no del(17p) or TP53 mutation who requires treatment?

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

RTP RESEARCH TO PRACTICE

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

1. FCR
2. Ibrutinib
3. Ibrutinib + rituximab
4. Ibrutinib + obinutuzumab
5. Acalabrutinib
6. Acalabrutinib + obinutuzumab
7. Venetoclax + obinutuzumab
8. Other

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

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

RTP RESEARCH TO PRACTICE

What is your usual preferred initial regimen for a 75-year-old patient with CLL with unmutated IGHV and no del(17p) or TP53 mutation who requires treatment?

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

RTP RESEARCH TO PRACTICE

What is your usual preferred initial regimen for a 75-year-old patient with CLL with unmutated IGHV and no del(17p) or TP53 mutation who requires treatment and has bulky disease?

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

RTP RESEARCH TO PRACTICE

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

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

RTP RESEARCH TO PRACTICE

What would be your most likely approach for a patient with newly diagnosed CLL to whom you administer up-front venetoclax/obinutuzumab who has detectable MRD after 1 year of treatment?

1. Continue treatment
2. Discontinue treatment

What would be your most likely approach for a patient with newly diagnosed CLL to whom you administer up-front venetoclax/obinutuzumab who has detectable minimal residual disease (MRD) after 1 year of treatment?

 MATTHEW S DAVIDS, MD, MMSC	Discontinue treatment
 IAN W FLINN, MD, PHD	Discontinue treatment
 BRIAN T HILL, MD, PHD	Discontinue treatment
 BRAD S KAHL, MD	Discontinue treatment
 ANTHONY R MATO, MD, MSCE	Continue treatment
 JOHN M PAGEL, MD, PHD	Continue treatment
 KERRY A ROGERS, MD	Discontinue treatment
 JEFF SHARMAN, MD	Discontinue treatment
 TANYA SIDDIQI, MD	Continue treatment
 MITCHELL R SMITH, MD, PHD	Discontinue treatment
 WILLIAM G WIERDA, MD, PHD	Continue treatment
 JENNIFER WOYACH, MD	Discontinue treatment

RTP RESEARCH TO PRACTICE

What would be your most likely approach for a patient with newly diagnosed CLL to whom you administer up-front venetoclax/obinutuzumab who has achieved undetectable MRD status after 1 year of treatment?

 MATTHEW S DAVIDS, MD, MMSC	Discontinue treatment	 KERRY A ROGERS, MD	Discontinue treatment
 IAN W FLINN, MD, PHD	Discontinue treatment	 JEFF SHARMAN, MD	Discontinue treatment
 BRIAN T HILL, MD, PHD	Discontinue treatment	 TANYA SIDDIQI, MD	Discontinue treatment
 BRAD S KAHL, MD	Discontinue treatment	 MITCHELL R SMITH, MD, PHD	Discontinue treatment
 ANTHONY R MATO, MD, MSCE	Discontinue treatment	 WILLIAM G WIERDA, MD, PHD	Discontinue treatment
 JOHN M PAGEL, MD, PHD	Discontinue treatment	 JENNIFER WOYACH, MD	Discontinue treatment

RTP RESEARCH TO PRACTICE

Which second-line systemic therapy would you recommend for a 60-year-old patient with CLL with no IGHV mutation and no del(17p) or TP53 mutation who responds to ibrutinib and then experiences disease progression 3 years later?

1. Acalabrutinib
2. Acalabrutinib + obinutuzumab
3. Venetoclax
4. Venetoclax + rituximab
5. Venetoclax + obinutuzumab
6. Idelalisib
7. Duvelisib
8. Other

Which second-line systemic therapy would you recommend for a 60-year-old patient with CLL with unmutated IGHV and no del(17p) or TP53 mutation who responds to ibrutinib and then experiences disease progression 3 years later?

 MATTHEW S DAVIDS, MD, MMSC	Venetoclax + rituximab	 KERRY A ROGERS, MD	Venetoclax + rituximab
 IAN W FLINN, MD, PHD	Venetoclax + obinutuzumab	 JEFF SHARMAN, MD	Venetoclax + rituximab
 BRIAN T HILL, MD, PHD	Venetoclax + rituximab	 TANYA SIDDIQI, MD	Ibrutinib + obinutzumab OR venetoclax + obinutuzumab
 BRAD S KAHL, MD	Venetoclax + rituximab	 MITCHELL R SMITH, MD, PHD	Venetoclax + obinutuzumab
 ANTHONY R MATO, MD, MSCE	Venetoclax + rituximab	 WILLIAM G WIERDA, MD, PHD	Venetoclax + rituximab
 JOHN M PAGEL, MD, PHD	Venetoclax	 JENNIFER WOYACH, MD	Venetoclax + rituximab

RTP RESEARCH TO PRACTICE

Which second-line systemic therapy would you recommend for a 60-year-old patient with CLL with no IGHV mutation and no del(17p) or TP53 mutation who responds to venetoclax/obinutuzumab and then experiences disease progression 3 years later?

1. Ibrutinib
2. Ibrutinib + rituximab
3. Ibrutinib + obinutuzumab
4. Acalabrutinib
5. Acalabrutinib + obinutuzumab
6. Idelalisib
7. Duvelisib
8. Other

Which second-line systemic therapy would you recommend for a 60-year-old patient with CLL with unmutated IGHV and no del(17p) or TP53 mutation who responds to venetoclax/obinutuzumab and then experiences disease progression 3 years later?

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

RTP RESEARCH TO PRACTICE

A 60-year-old patient with CLL, an absolute lymphocyte count of 20,000 and several involved lymph nodes that are smaller than 2 centimeters is about to receive venetoclax. What preemptive measures, if any, would you take to address tumor lysis syndrome prior to the initiation of therapy?

 MATTHEW S DAVIDS, MD, MMSC	Encourage oral hydration and allopurinol	 KERRY A ROGERS, MD	Encourage oral hydration and allopurinol
 IAN W FLINN, MD, PHD	IV hydration and allopurinol	 JEFF SHARMAN, MD	Give the obinutuzumab first to debulk, then after 1 month can start as outpatient with hydration and allopurinol
 BRIAN T HILL, MD, PHD	Encourage oral hydration and allopurinol	 TANYA SIDDIQI, MD	Encourage oral hydration and allopurinol
 BRAD S KAHL, MD	Encourage oral hydration and allopurinol	 MITCHELL R SMITH, MD, PHD	Encourage oral hydration and allopurinol
 ANTHONY R MATO, MD, MSCE	IV hydration and allopurinol	 WILLIAM G WIERDA, MD, PHD	Encourage oral hydration and allopurinol
 JOHN M PAGEL, MD, PHD	Encourage oral hydration and allopurinol	 JENNIFER WOYACH, MD	Encourage oral hydration and allopurinol

RTP RESEARCH TO PRACTICE

A 60-year-old patient with CLL, an absolute lymphocyte count of 80,000 and several involved lymph nodes that are larger than 5 centimeters is about to receive venetoclax. What preemptive measures, if any, would you take to address tumor lysis syndrome prior to the initiation of therapy?

 MATTHEW S DAVIDS, MD, MMSC	Admit to hospital	 KERRY A ROGERS, MD	Admit to hospital
 IAN W FLINN, MD, PHD	Debulk with obinutuzumab	 JEFF SHARMAN, MD	Obinutuzumab for 1 month to lower patient risk, then outpatient hydration and allopurinol
 BRIAN T HILL, MD, PHD	Admit to hospital	 TANYA SIDDIQI, MD	Admit to hospital
 BRAD S KAHL, MD	Admit to hospital	 MITCHELL R SMITH, MD, PHD	Admit to hospital
 ANTHONY R MATO, MD, MSCE	Admit to hospital	 WILLIAM G WIERDA, MD, PHD	Admit to hospital
 JOHN M PAGEL, MD, PHD	Admit to hospital	 JENNIFER WOYACH, MD	IV hydration and allopurinol

RTP RESEARCH TO PRACTICE

For your patients with CLL whom you admit to the hospital to receive venetoclax, for how long do you typically admit them?

 MATTHEW S DAVIDS, MD, MMSC	8 days
 IAN W FLINN, MD, PHD	2 days
 BRIAN T HILL, MD, PHD	2 days (<48 hours)
 BRAD S KAHL, MD	2 days
 ANTHONY R MATO, MD, MSCE	2-3 days
 JOHN M PAGEL, MD, PHD	1 day
 KERRY A ROGERS, MD	2 nights for each dose escalation
 JEFF SHARMAN, MD	2 days
 TANYA SIDDIQI, MD	1-2 days each week during early ramp-up
 MITCHELL R SMITH, MD, PHD	1- 2 days
 WILLIAM G WIERDA, MD, PHD	2 days
 JENNIFER WOYACH, MD	2 days or rapid escalation to full dose over 5 days

RTP RESEARCH TO PRACTICE

Meet The Professor with Dr Hill

MODULE 1: Cases from Drs Davids, Freedman and Parsons

MODULE 2: CLL Journal Club with Dr Hill

- Purine nucleoside analogue alone or with rituximab for hairy cell leukemia
- GIMEMA-ERIC and US indirect comparison of bendamustine/rituximab and ibrutinib in a real-world setting
- Preventing FOXO3a nuclear export and PI3K/AKT activation to overcome resistance to ibrutinib
- Venetoclax combined with anti-CD20 monoclonal antibody therapy for elderly patients with R/R CLL
- Real world treatment discontinuation patterns among patients with CLL
- Efficacy of therapies after venetoclax in CLL
- Treatment sequences and outcomes in patients with CLL treated with venetoclax and other novel agents
- Tumor lysis, adverse events and dose adjustments in patients with CLL treated with venetoclax
- Ibrutinib-associated invasive fungal diseases
- Umbralisib, ublituximab and venetoclax for R/R CLL
- Effect of age on survival for patients receiving ibrutinib as initial therapy for CLL

MODULE 3: Beyond the Guidelines – Clinical Investigator Approaches to Common Clinical Scenarios

MODULE 4: Key Recent Data Sets

RTP
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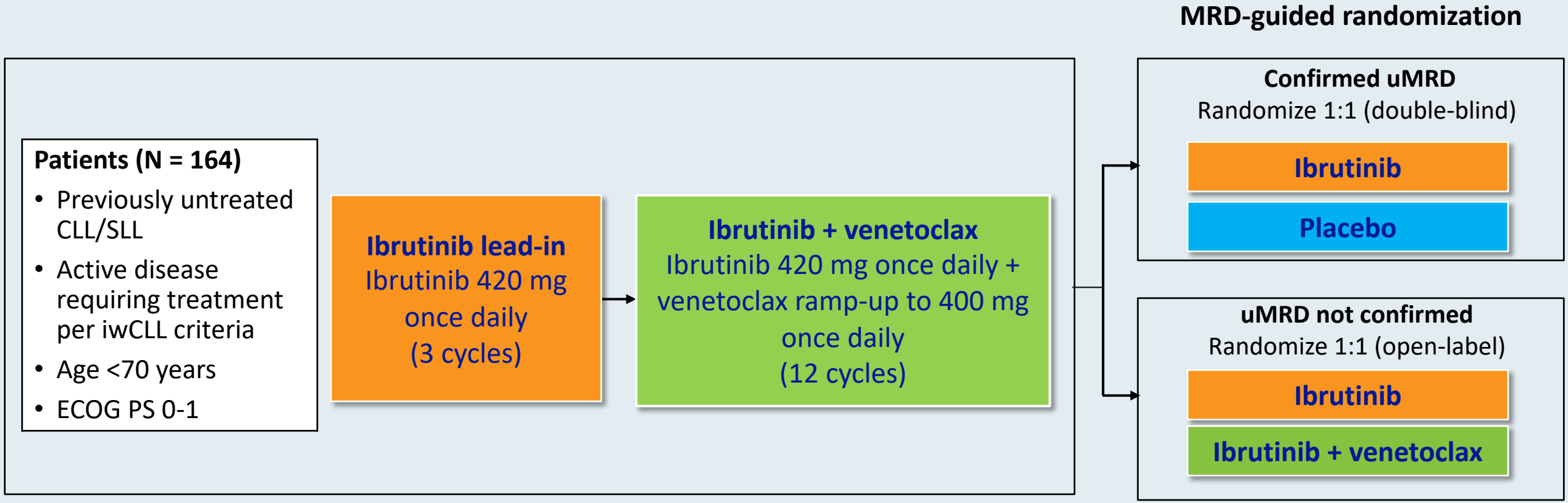
TO PRACTICE

CAPTIVATE MRD Cohort: Study Design

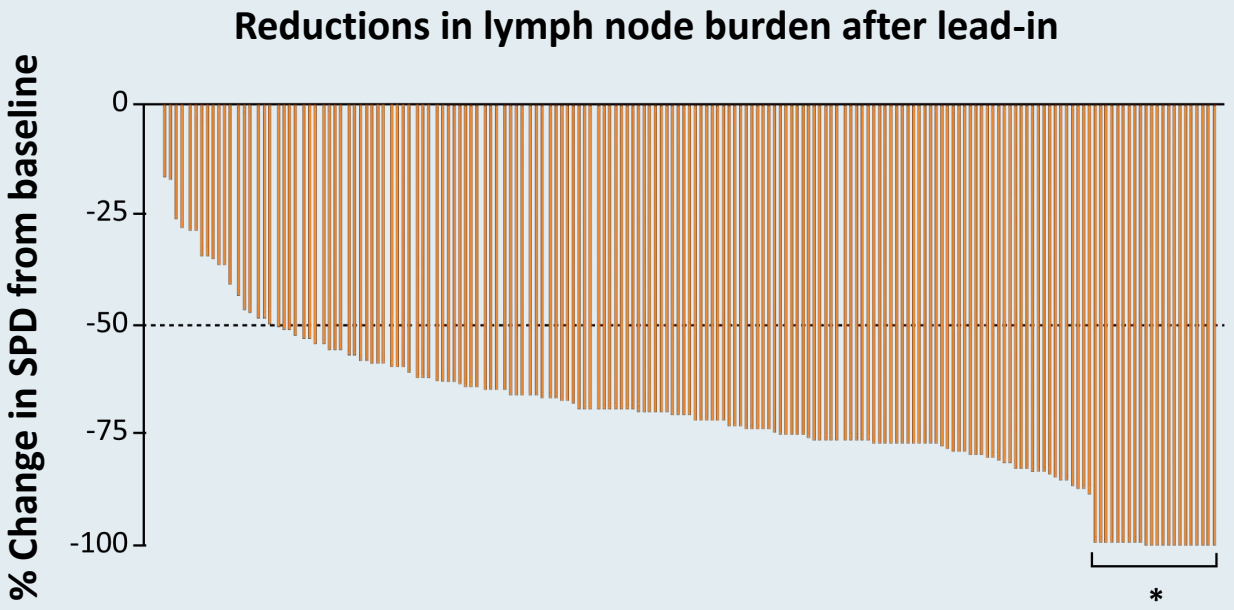


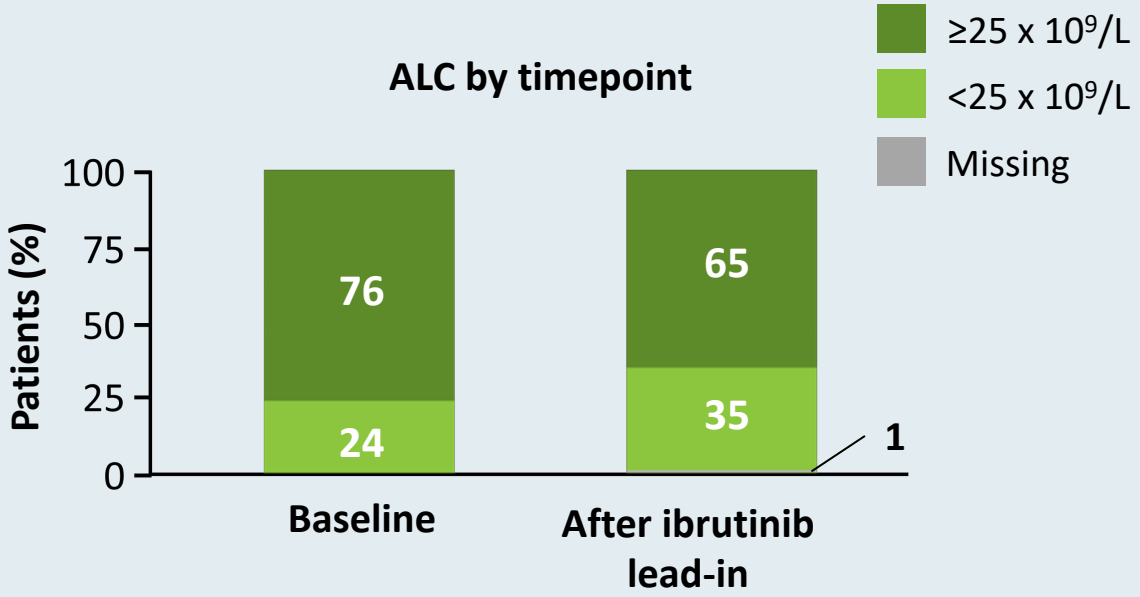
uMRD = undetectable minimal residual disease

Results presented for prerandomization phase of the MRD cohort (n = 164) with 12 cycles of ibrutinib + venetoclax prior to MRD-guided randomization

Siddiqi S et al. EHA 2020;Abstract S158.

CAPTIVATE MRD Cohort: 3 Cycles of Ibrutinib Lead-In





Three cycles of ibrutinib lead-in reduces TLS risk and indication for hospitalization

Siddiqi S et al. EHA 2020;Abstract S158.

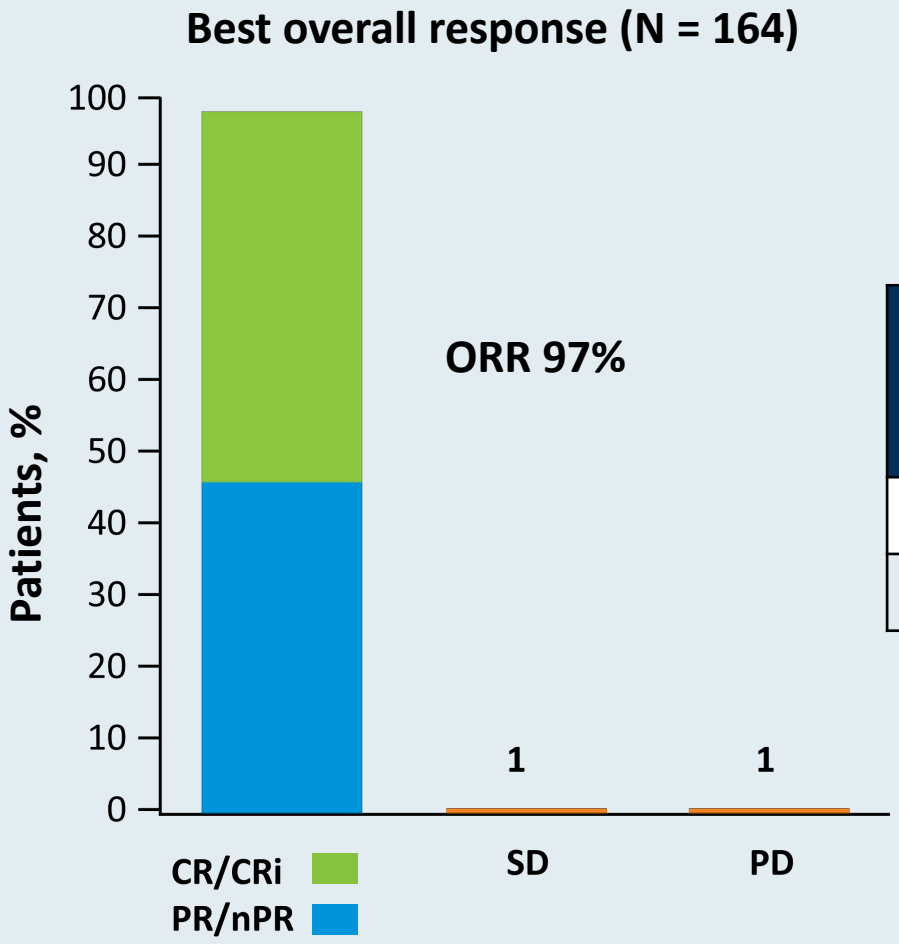
CAPTIVATE MRD Cohort: Undetectable MRD Rate

	Peripheral blood n = 163	Bone marrow n = 155
Best response of undetectable MRD in evaluable patients (95% CI)	**75%** (68-82)	**72%** (64-79)

- Rates of undetectable MRD in peripheral blood and bone marrow were highly concordant at Cycle 16 (91%)
- In the all-treated population (N = 164), undetectable MRD was achieved in 75% of patients in peripheral blood and in 68% of patients in bone marrow with up to 12 cycles of combination ibrutinib/venetoclax

Siddiqi S et al. EHA 2020;Abstract S158.

CAPTIVATE MRD Cohort: Undetectable MRD in Patients with CR/PR



Best overall response (up to Cycle 16)	CR n = 84	PR n = 75	ORR (CR + PR) n = 159
Undetectable MRD in PB, n (%)	71 (85)	52 (69)	123 (77)
Undetectable MRD in BM, n (%)	67 (80)	44 (59)	111 (70)

At 15 months, 98% of patients were progression free with no deaths

Siddiqi S et al. EHA 2020;Abstract S158.

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

AEs, n (%)	Ibrutinib lead-in (3 cycles) N = 164		Ibrutinib + venetoclax combination (12 cycles) N = 159		Overall (15 cycles) N = 164
	Grade 3	Grade 4	Grade 3	Grade 4	Grade 3-4
Atrial fibrillation	2 (1)	0	1 (1)	0	3 (2)
Major hemorrhage	0	0	1 (1)	0	1 (1)
Infections	4 (2)	0	10 (6)	0	14 (9)
Neutropenia	4 (2)	7 (4)	27 (17)	26 (16)	58 (35)
Febrile neutropenia	1 (1)	0	2 (1)	0	3 (2)
Laboratory TLS	0	0	2 (1)	0	2 (1)

- Low rates of Grade 3 atrial fibrillation, major hemorrhage, infections, febrile neutropenia and laboratory TLS (no Grade 4 event)
- No patients developed clinical TLS
  - Laboratory TLS reported as AE in 3 patients (only 1 met Howard criteria)
- No fatal AEs

Siddiqi S et al. EHA 2020;Abstract S158.

Ongoing Phase III EA9161 Trial Schema

Stratifications
Age: <65 yr vs ≥ 65 yr and <70 yr
PS: 0, 1, vs 2
Stage: 0, 1, or 2 vs 3, 4
Del11q22.3 vs others

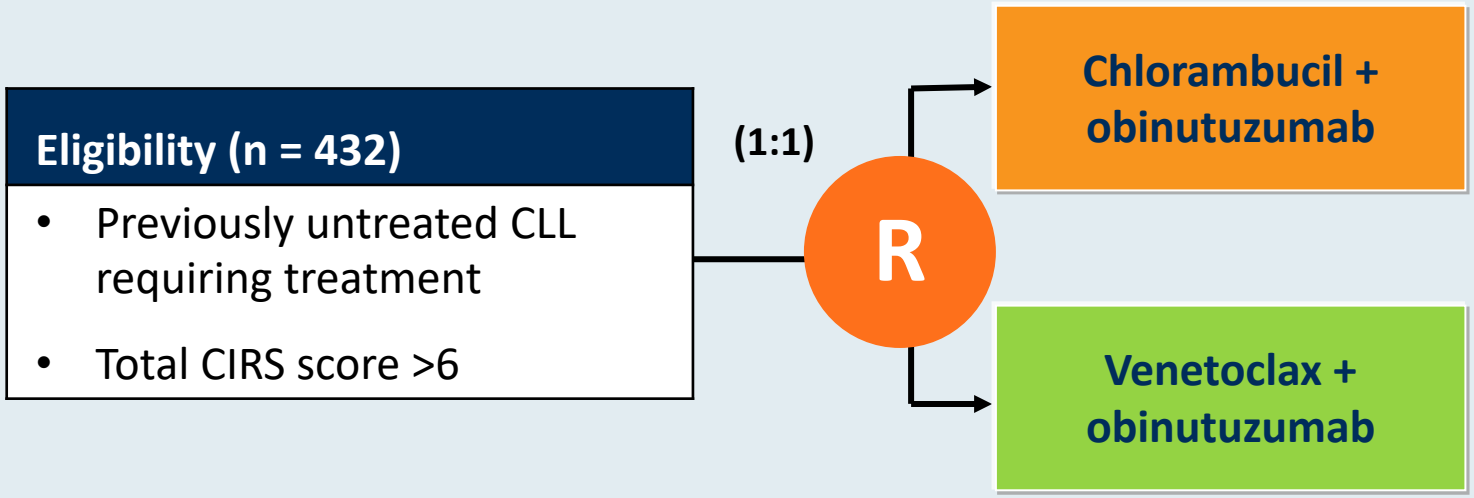
Randomize

Arm A
Ibrutinib: Cycles 1-19:d1-28 420mg PO daily
Obinutuzumab: C1 **:** D1:100 mg IV, D2:900 mg IV, D8: 1000 mg IV, D15: 1000 mg IV; C2-6: D1 1000 mg IV
Venetoclax: C3 D1-7 20mg PO daily D8-14 50mg PO daily D15-21 100mg PO daily; D22-28 200 mg PO daily; C4-14: D1-28 400mg PO daily

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

Courtesy of Brad Kahl, MD

CLL14 Phase III Study Schema

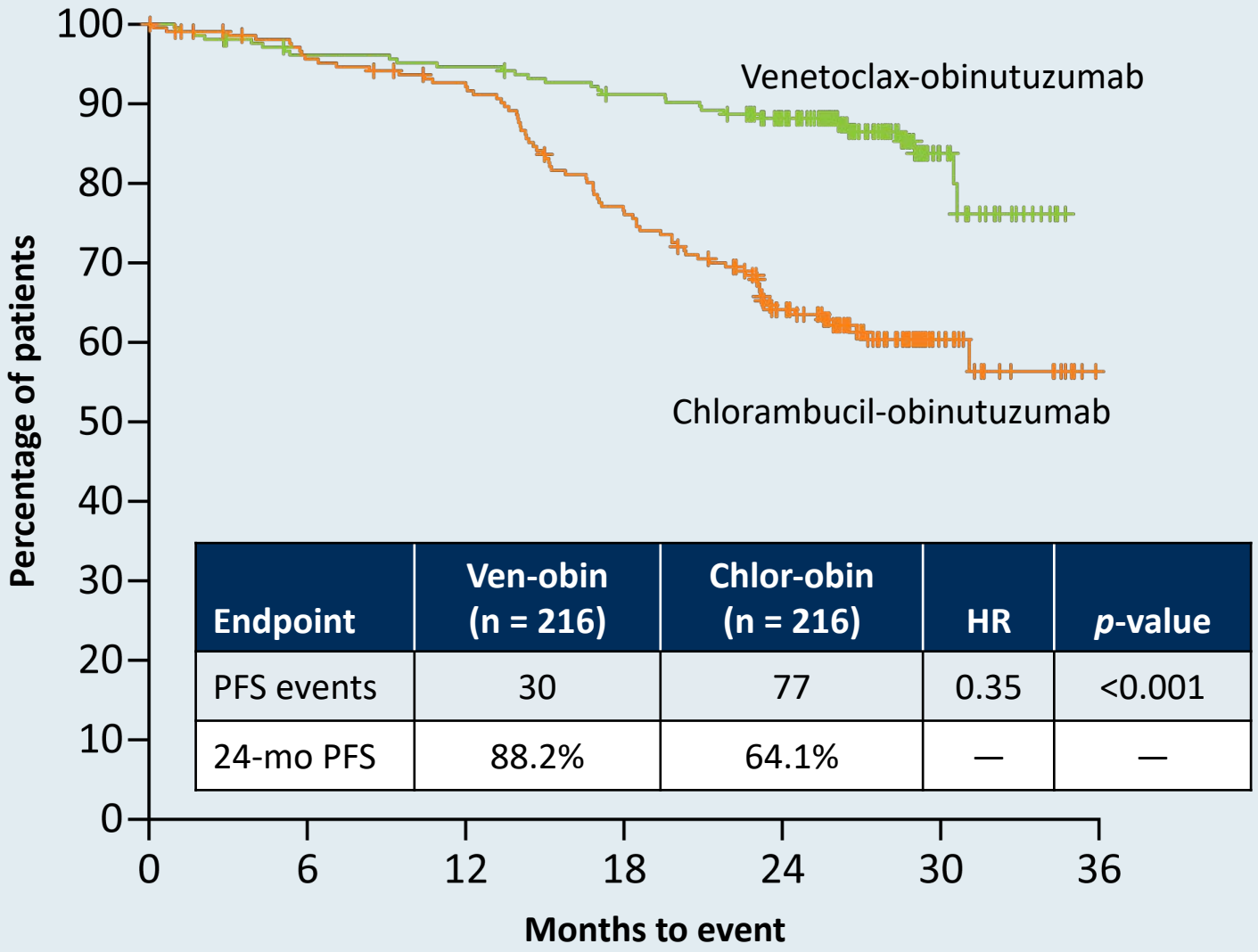


Primary endpoint: Progression-free survival

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

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

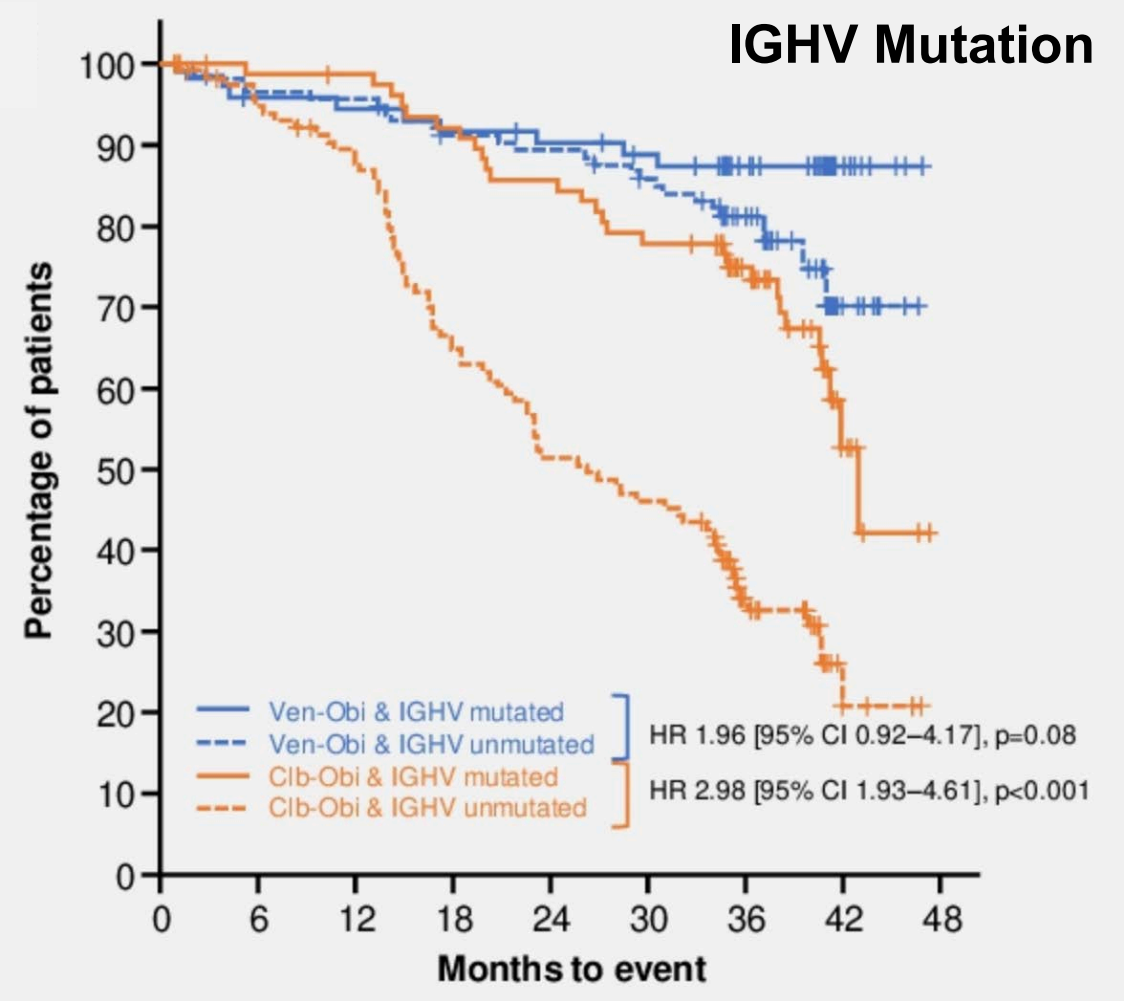
CLL14: Investigator-Assessed Progression-Free Survival

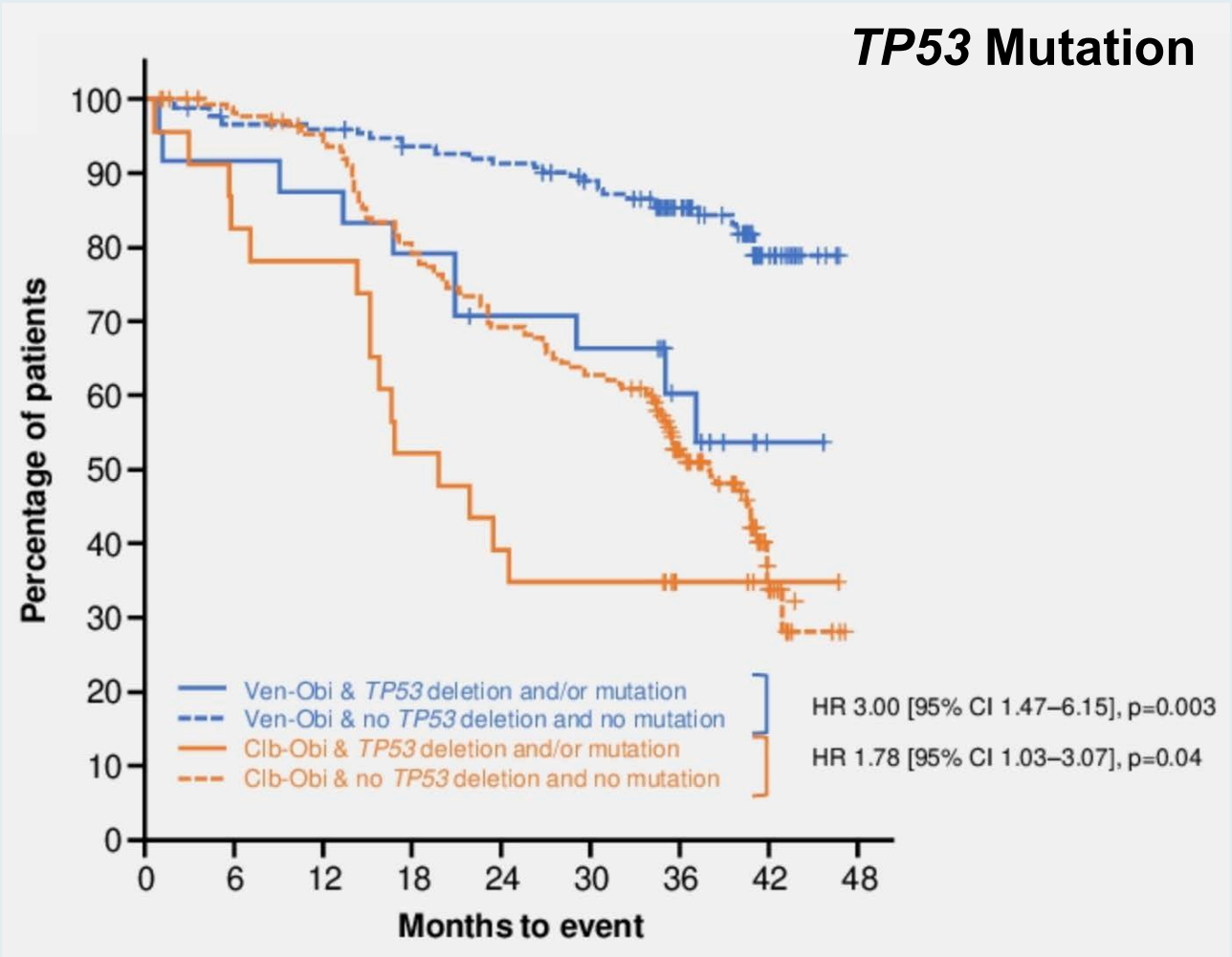


Endpoint	Ven-obin (n = 216)	Chlor-obin (n = 216)	HR	*p*-value
PFS events	30	77	0.35	<0.001
24-mo PFS	88.2%	64.1%	—	—

Fischer K et al. *N Engl J Med* 2019;380(23):2225-36.

CLL14: PFS by IGHV and TP53 Mutation Status





Al-Sawaf O et al. ASCO 2020;Abstract 8027.

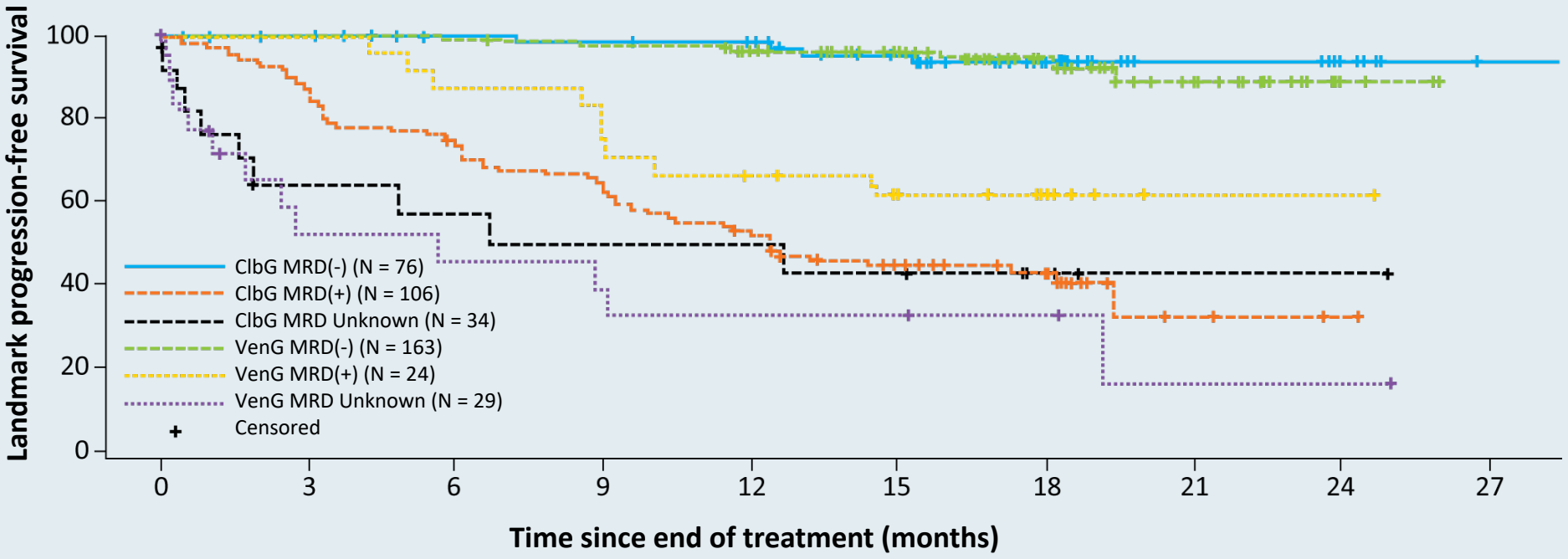
RTP RESEARCH TO PRACTICE

CLL14: Minimal Residual Disease 3 Months After Treatment

MRD 3 months after treatment	MRD-negative		MRD responders	
	Veneto/obin (N = 216)	Chloram/obin (N = 216)	Veneto/obin (N = 216)	Chloram/obin (N = 216)
MRD in bone marrow	56.9%	17.1%	33.8%	10.6%
Odds ratio, *p*-value	OR 6.4, $p < 0.0001$		OR 4.3, $p < 0.0001$	
MRD in peripheral blood	75.7%	35.2%	42.1%	14.4%
Odds ratio, *p*-value	OR 5.7, $p < 0.0001$		OR 4.3, $p < 0.0001$	

Fischer K et al. *N Engl J Med* 2019;380(23):2225-36.

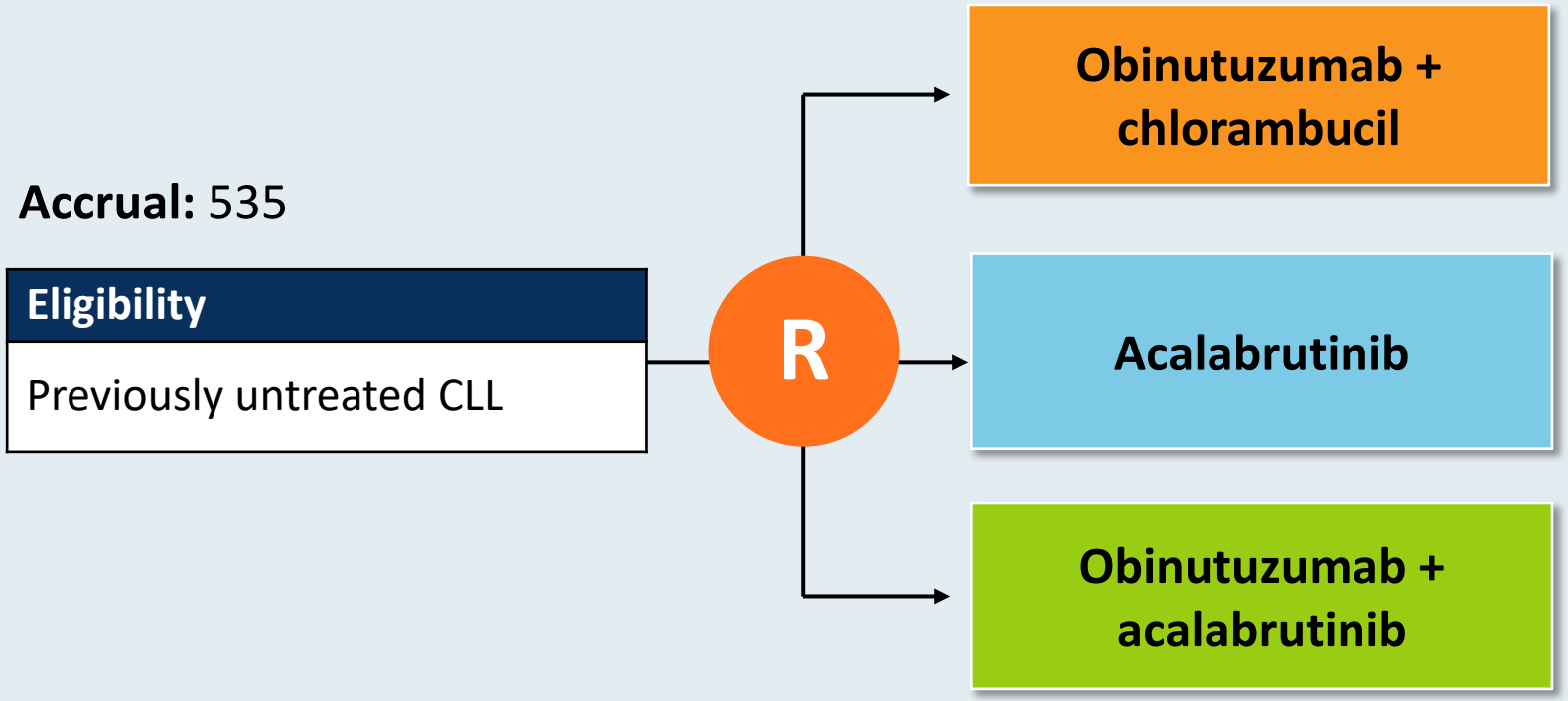
CLL14: Landmark Analysis from End of Therapy PFS by MRD Group



Further landmark analysis of PFS by MRD status showed that undetectable MRD translated into improved PFS regardless of the clinical response status at end of therapy.

Fischer K et al. ASH 2019;Abstract 36.

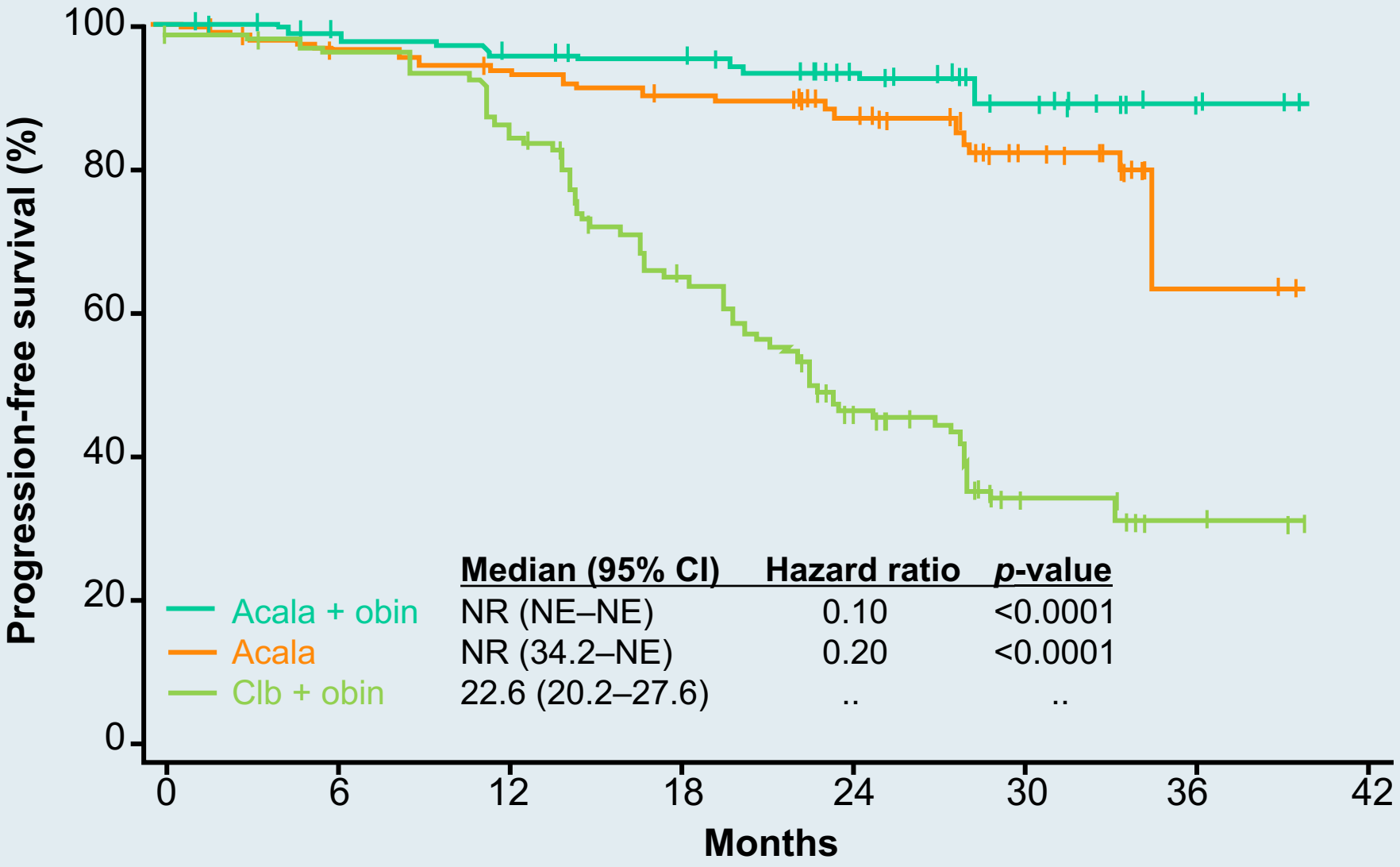
ELEVATE-TN Phase III Trial Schema



Primary endpoint: Progression-free survival

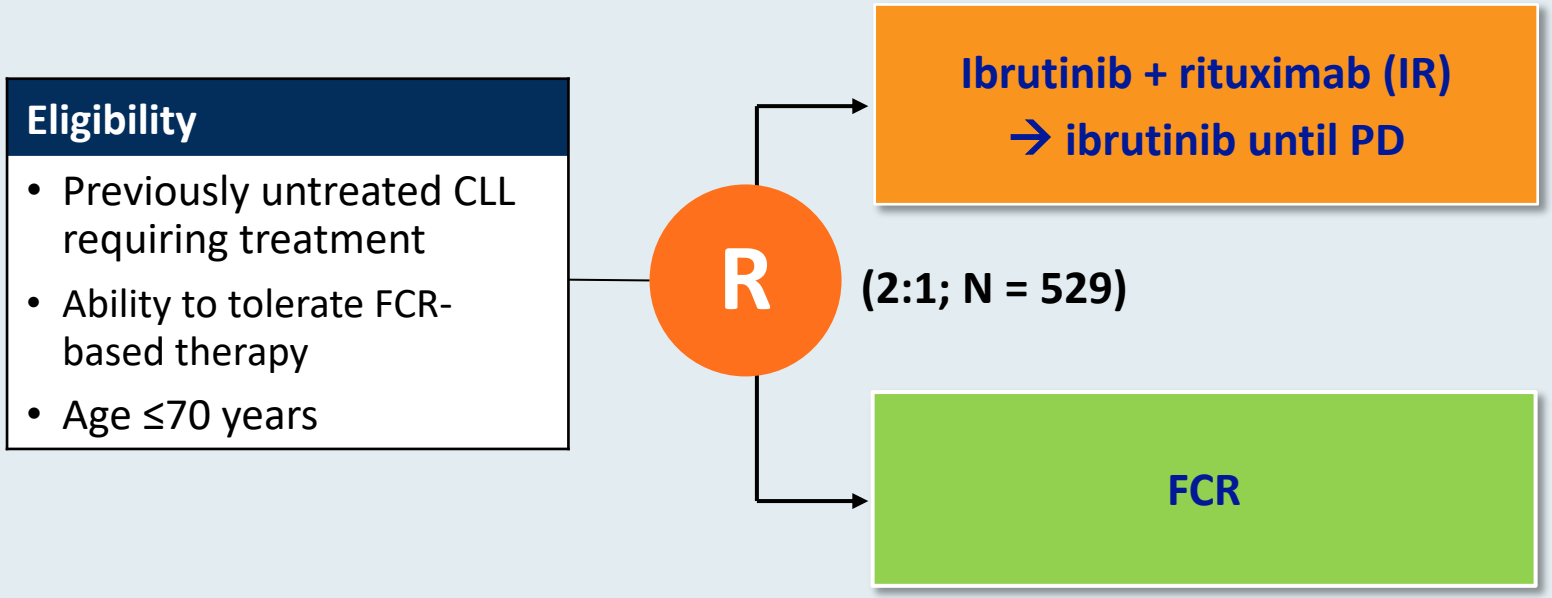
www.clinicaltrials.gov (NCT02475681). Accessed August 2020.

ELEVATE-TN: PFS (IRC)



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

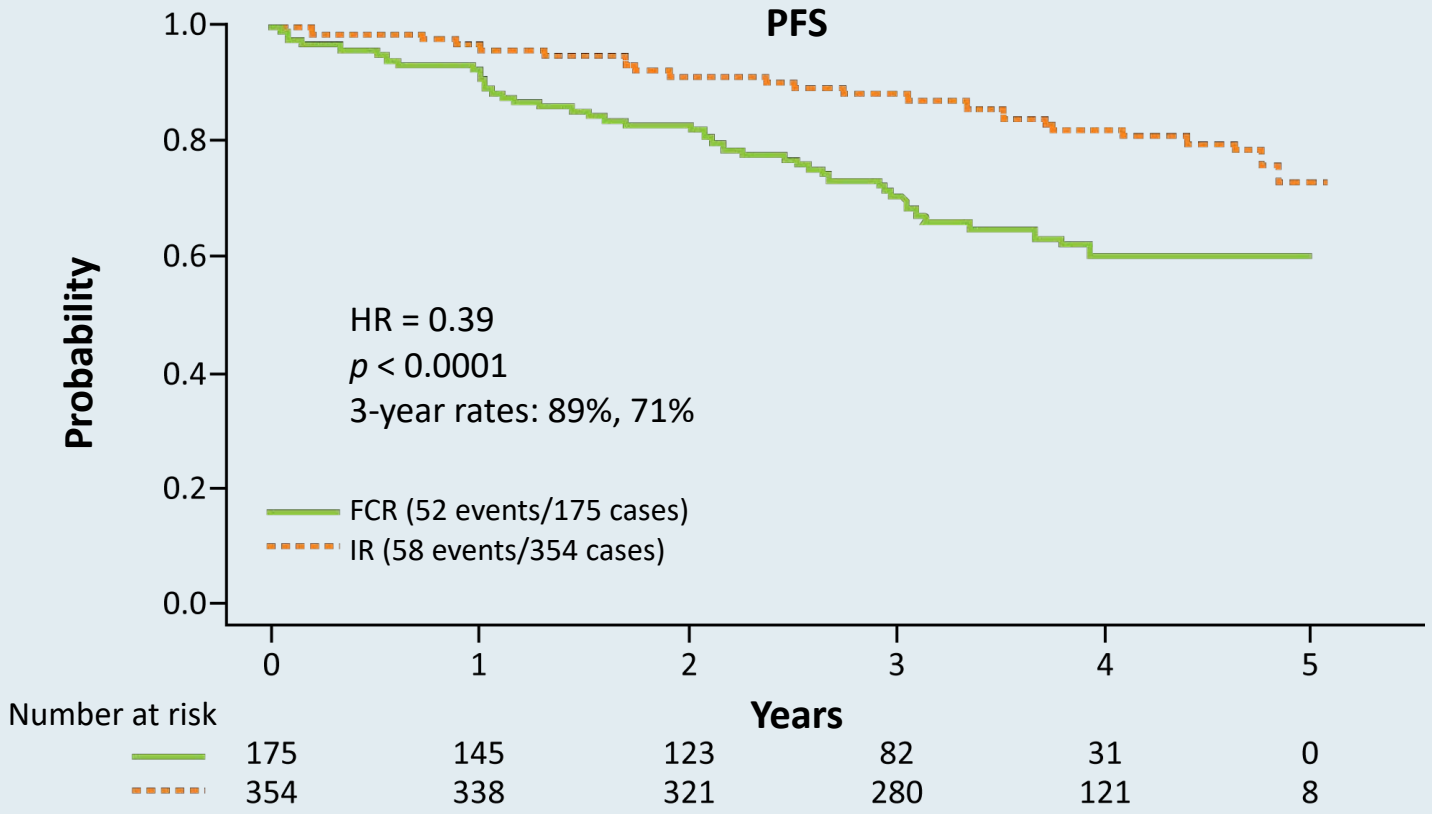
Phase III ECOG-ACRIN E1912 Study Design



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.

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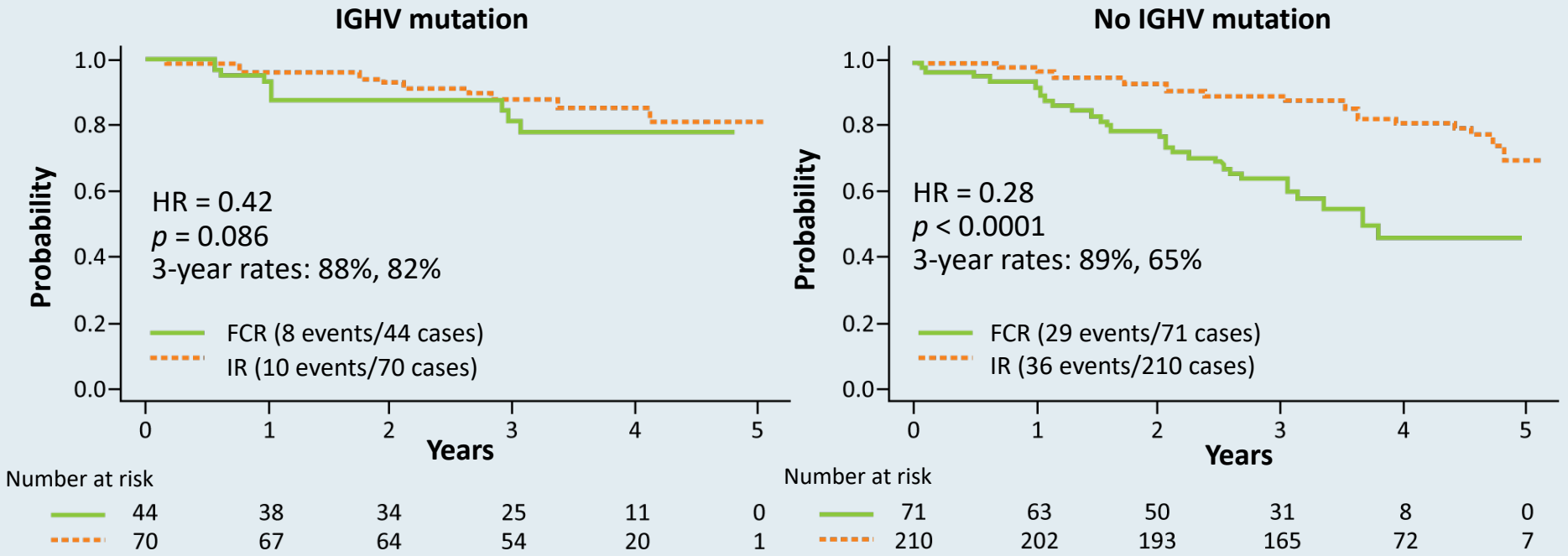
ECOG-ACRIN E1912 Extended Follow-Up: PFS by IGHV Mutation Status



- On subgroup analysis by IGHV mutation status, IR was superior to FCR for CLL with no IGHV mutation (HR = 0.28; $p < 0.0001$).
- With current follow-up the difference between IR and FCR is not significant for CLL with IGHV mutation (HR = 0.42; $p = 0.086$).

Shanafelt TD et al. ASH 2019;Abstract 33.

Meet The Professor
Management of Lung Cancer

Wednesday, October 28, 2020
12:00 PM – 1:00 PM ET

Faculty

Professor Solange Peters, MD, PhD

Moderator

Neil Love, MD

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Thank you for joining us!

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

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