# *Meet The Professor*
# Management of Chronic Lymphocytic Leukemia

**Steven Coutre, MD**
Professor of Medicine (Hematology)
Stanford University School of Medicine
Stanford, California

# Commercial Support

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# Dr Love — Disclosures

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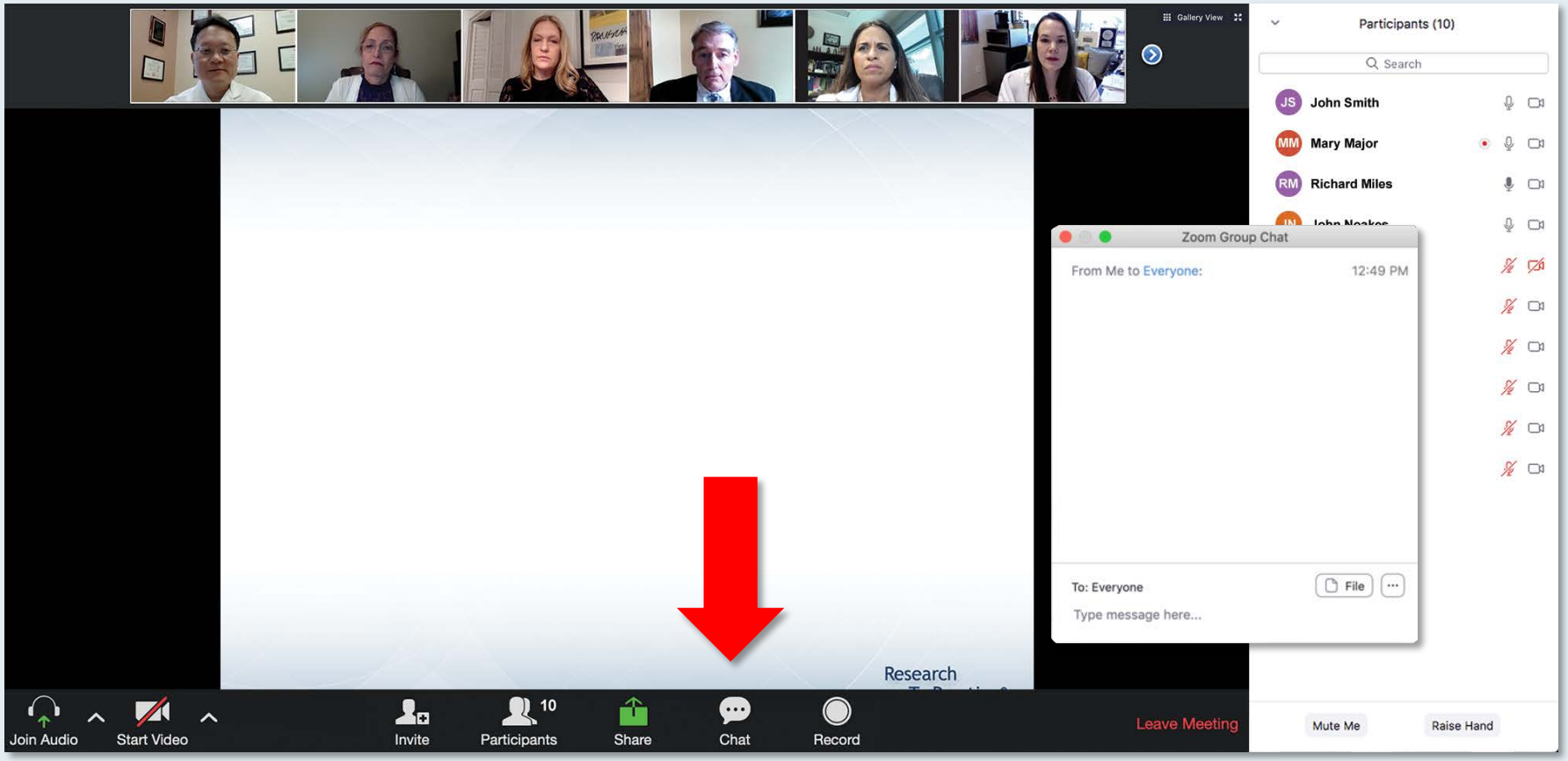


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# Familiarizing Yourself with the Zoom Interface

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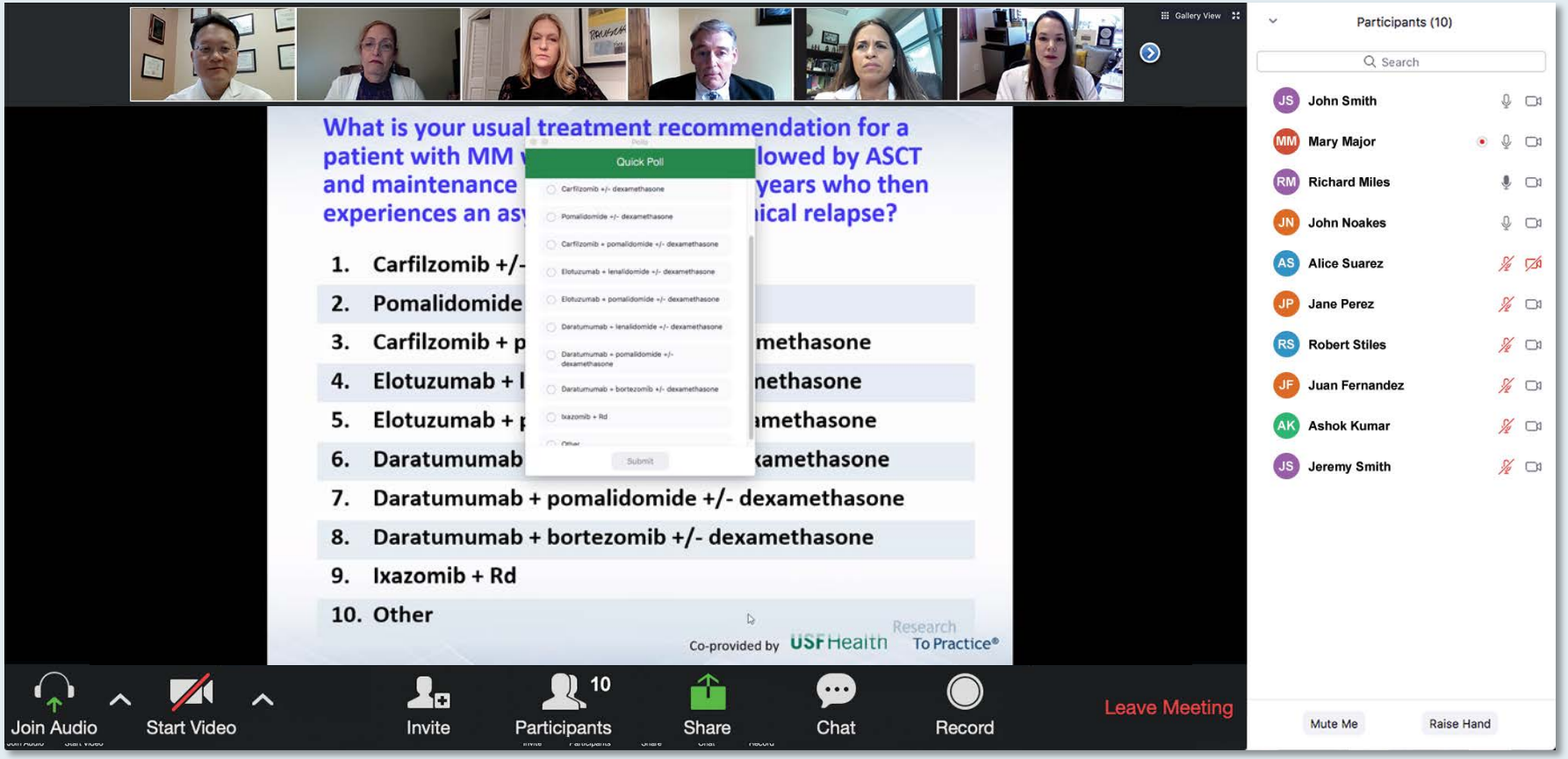


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## Front-Line Treatment of Chronic Lymphocytic Leukemia

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# Dissecting the Decision: Clinical and Nursing Investigators Provide Practical Perspectives on Key Issues in Cancer Care

# Part 1 — Acute Myeloid Leukemia

**Tuesday, March 16, 2021**
**5:00 PM – 6:00 PM ET**

## Faculty

**Rhonda Hewitt, MSN, ANP, AOCNP**
**Mark Levis, MD, PhD**

## Moderator

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**Sara Hurvitz, MD**

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**Shannon N Westin, MD, MPH**

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# Optimizing the Selection and Sequencing of Therapy for Patients with Renal Cell Carcinoma

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## Faculty

**Robert J Motzer, MD**

## Moderator

**Neil Love, MD**

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# *Meet The Professor*

# Management of Chronic Lymphocytic Leukemia

**Monday, March 29, 2021**
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# *Meet The Professor* Program Participating Faculty

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Weill Cornell Medicine
New York, New York

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Sarah Cannon Research Institute
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Stanford, California

**Prof John G Gribben, MD, DSc, FMedSci**
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Associate Professor of Medicine
Harvard Medical School
Director of Clinical Research
Division of Lymphoma
Dana-Farber Cancer Institute
Boston, Massachusetts

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

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# *Meet The Professor* Program Participating Faculty

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Department of Leukemia
The University of Texas
MD Anderson Cancer Center
Houston, Texas

**John M Pagel, MD, PhD**
Chief of Hematologic Malignancies
Center for Blood Disorders and Stem Cell Transplantation
Swedish Cancer Institute
Seattle, Washington

**Brad S Kahl, MD**
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Washington University School of Medicine
Director, Lymphoma Program
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St Louis, Missouri

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

**Anthony R Mato, MD, MSCE**
Associate Attending
Director, Chronic Lymphocytic Leukemia Program
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**Jeff Sharman, MD**
Willamette Valley Cancer Institute and Research Center
Medical Director of Hematology Research
US Oncology
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Department of Hematology and Hematopoietic Cell Transplantation
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**William G Wierda, MD, PhD**
DB Lane Cancer Research Distinguished Professor
Department of Leukemia
Division of Cancer Medicine
The University of Texas
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**Mitchell R Smith, MD, PhD**
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GW Cancer Center
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**Jennifer Woyach, MD**
Professor
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Department of Internal Medicine
The Ohio State University
Comprehensive Cancer Center
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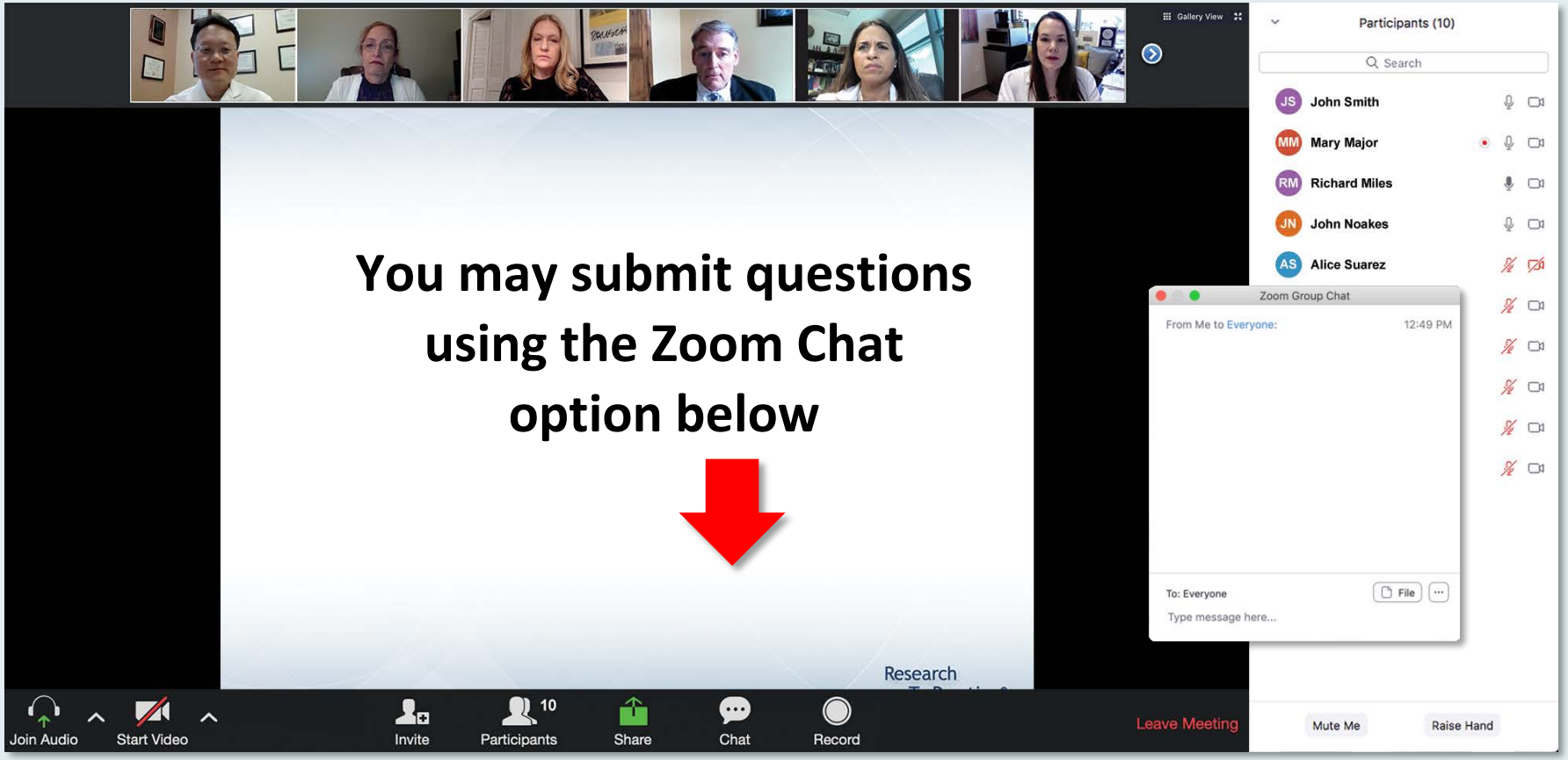


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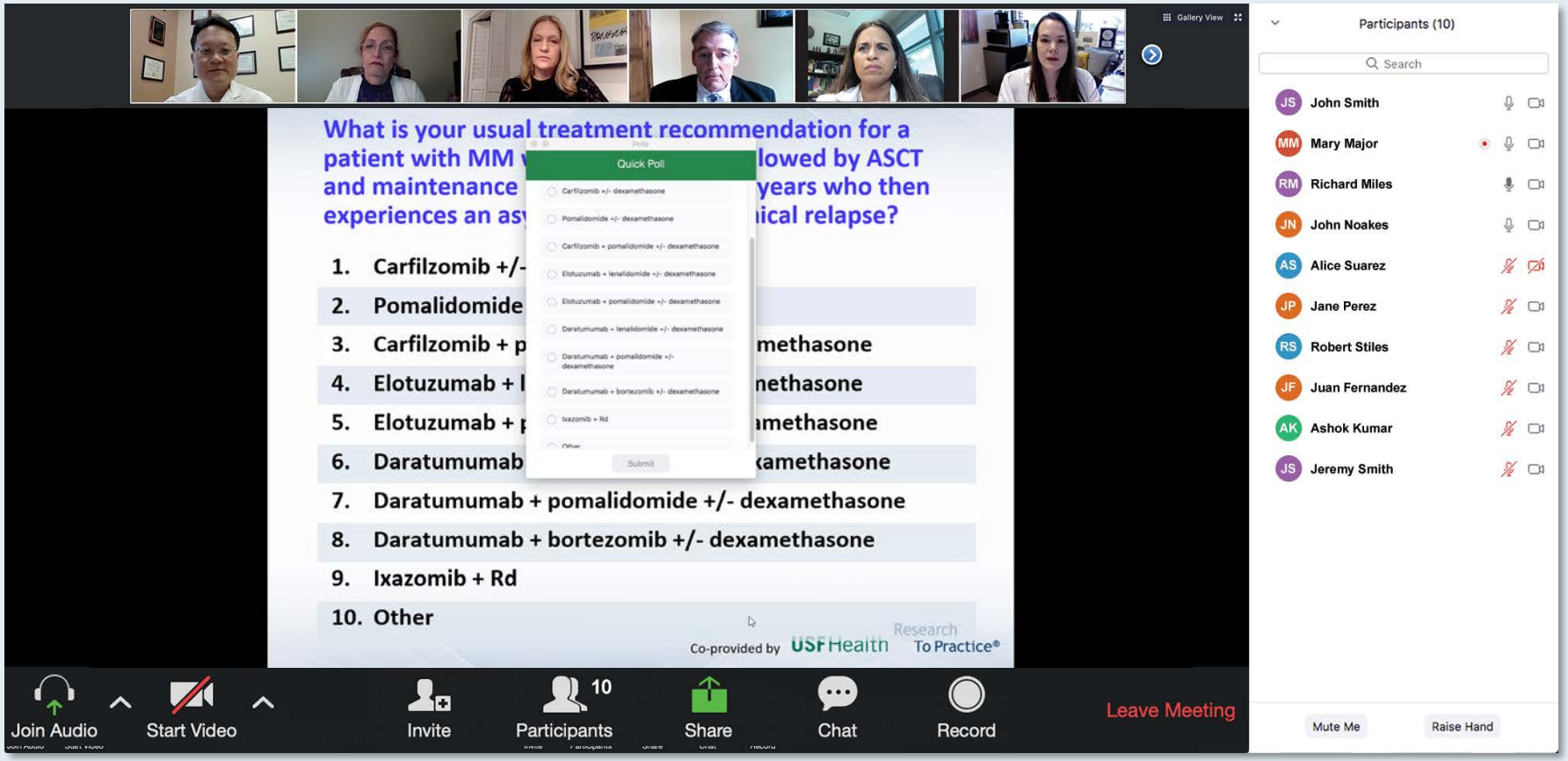


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**Spencer Henick Bachow, MD**
Hematologist/Oncologist at Lynn Cancer Institute
Affiliate Assistant Professor of Medicine at FAU Schmidt College of Medicine
Boca Raton, Florida

**Mamta Choksi, MD**
Florida Cancer Specialists and Research Institute
New Port Richey, Florida

**Justin Peter Favaro, MD, PhD**
Oncology Specialists of Charlotte
Charlotte, North Carolina

**Lyle Feinstein, MD**
Attending Physician, Malignant Hematology and Bone Marrow Transplant
Miami Cancer Institute
Miami, Florida

**Maria Regina Flores, MD**
Physician Partner for Florida Cancer Specialists and Research Institute
Orlando, Florida

**Ranju Gupta, MD**
Attending Physician
Co-Director, Cardio-Oncology Program
LVPG Hematology Oncology Associates
Lehigh Valley Health Network
Bethlehem, Pennsylvania

**Shachar Peles, MD**
Florida Cancer Specialists and Research Institute
Atlantis, Florida

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# Meet The Professor with Dr Coutre

## MODULE 1: Cases from Drs Favaro, Flores and Feinstein

- Dr Favaro: A 69-year-old physician with CLL who received rituximab/venetoclax
- Dr Flores: A very active 75-year-old man with asymptomatic CLL and a WBC count of 188k
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# Case Presentation – Dr Favaro: A 69-year-old physician with CLL who received rituximab/venetoclax

**Dr Justin Favaro**

- Presents with extensive LAD and del(13) CLL
- Rituximab/cyclophosphamide/vincristine
- Develops acquired von Willebrand's disease
  - Treated with IVIG monthly to keep factor VIII levels in normal range
- Two years later: Small bowel obstruction secondary to mesenteric adenopathy
- Rituximab/venetoclax, with complete resolution of LAD
  - After 2 years, flow cytometry: 0.02% abnormal B-cell population consistent with residual CLL
  - Continues venetoclax 200 mg daily, IVIG monthly

**Questions**

- After 2 years on venetoclax, with the flow cytometry still being positive, would you continue venetoclax therapy? What is the best way to measure minimal residual disease in patients with CLL?
- In our patients with CLL does rituximab influence the efficacy of any vaccine, including the COVID-19 vaccine?

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# Case Presentation – Dr Flores: A very active 75-year-old man with asymptomatic CLL and a WBC count of 188k

**Dr Maria Flores**

- PMH: HTN, hyperlipidemia but plays tennis daily
- 6/2017: Diagnosed with Stage I CLL
  - WBC 14k, Hgb 15, PLT 212k
- 8/2020: WBC rising to 108.6k; Diagnosed with B12 deficiency anemia, Hgb 13.9, PLT 168
  - B12 injections
- Currently, WBC 188k, Hgb 13, PLT 158 and continues to feel well
- IGHV borderline mutated, Deletion 13q14, Deletion 11q
- Patient feels great (asymptomatic) and is concerned about cost of care and insurance coverage

**Questions**

- Patient questions whether he needs treatment now?
- Is there an absolute WBC that will trigger you to treat? If you did decide to treat, what would you recommend?

# Case Presentation – Dr Feinstein: A 75-year-old man with CLL who experiences ibrutinib-related arthralgias

**Dr Lyle Feinstein**

- Referred by PCP for leukocytosis, anemia, fatigue; No B symptoms
  - WBC: 32.5k; ALC: 29.9k, Hgb: 9.7, PLT: 101k, LDH: 210
  - Peripheral flow cytometry: CLL, IGHV mutated
  - BMB: CLL, 80% cellularity, FISH: 13q-
  - CT/PET: Enlarged lymph nodes (none > 3 m) above and below diaphragm, Spleen: 16.4 cm
- Patient desires oral monotherapy
- Ibrutinib ongoing, tolerating remarkably well
  - Initial rise in lymphocytes, decrease in WBCs, CBC normalized
  - Arthralgias managed with NSAIDs

**Questions**

- How do you manage ibrutinib-associated arthralgias?
- How do you choose between ongoing therapy with either ibrutinib or acalabrutinib versus fixed-duration therapy with venetoclax/obinutuzumab?

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

1. FCR (fludarabine/cyclosphosphamide/rituximab)
2. Ibrutinib
3. Ibrutinib + rituximab
4. Ibrutinib + obinutuzumab
5. Acalabrutinib
6. Acalabrutinib + obinutuzumab
7. Venetoclax + obinutuzumab
8. Other

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

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

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

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

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

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

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

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

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

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

1. Continue treatment
2. Discontinue treatment

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

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

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# 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 |

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# Case Presentation – Dr Gupta: An 80-year-old man who is receiving apixaban for DVT/PE and develops CLL that requires treatment

Dr Ranju Gupta

- PMH: HTN, DVT/PE on apixaban since 2019
- 2018: Diagnosed with CLL, asymptomatic, 13q14 deletion
- Observation → Anemia, fatigue, mild adenopathy

**Questions**

- What is the optimal first-line treatment for an elderly patient with a good performance status on anticoagulation? Would you recommend a BTK inhibitor, and if so, which one – ibrutinib or acalabrutinib?
- Should we be using venetoclax and obinutuzumab in all of these patients?
- Is there any role for rituximab with bendamustine for 4 to 6 cycles in first-line treatment?

# Case Presentation – Dr Peles: A 79-year-old woman with CLL who experiences venetoclax-related cytopenias

**Dr Shachar Peles**

- PMH: Heart disease s/p CABG 2-3 months prior to CLL diagnosis
- 1/2020: Diagnosed with CLL, trisomy 12, IGHV mutated
- Obinutuzumab/venetoclax
  - Dose delays and reductions of venetoclax to 200 mg due to persistent neutropenia and thrombocytopenia
  - Repeat bone marrow due to concerns she may not be responding
  - 7/2020 FLOW: CD5 positive/CD3 23+ B cells <0.1% of cells – Consistent with MRD

**Questions**

- What's your experience with cytopenias with obinutuzumab/venetoclax, and how do you usually manage them? Do you use growth factors? Do you dose reduce? Do you discontinue one or the other agent? Do you feel one or the other agent is a more important part of this regimen?
- How do I incorporate MRD testing into my day-to-day clinical practice in CLL?

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- Dr Peles: A 79-year-old woman with CLL who experiences venetoclax-related cytopenias

## MODULE 4: Beyond the Guidelines – Part 2

## MODULE 5: Cases from Drs Choksi and Bachow

- Dr Choksi: An 87-year-old man with CLL who receives obinutuzumab/venetoclax
- Dr Bachow: A 55-year-old woman with relapsed CLL and a BRAF V600E mutation

## MODULE 6: Key Recent Data Sets

RTP
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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 Coutre

## MODULE 1: Cases from Drs Favaro, Flores and Feinstein

- Dr Favaro: A 69-year-old physician with CLL who received rituximab/venetoclax
- Dr Flores: A very active 75-year-old man with asymptomatic CLL and a WBC count of 188k
- Dr Feinstein: A 75-year-old man with CLL who experiences ibrutinib-related arthralgias

## MODULE 2: Beyond the Guidelines – Part 1

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# Case Presentation – Dr Choksi: An 87-year-old man with CLL who receives obinutuzumab/venetoclax

**Dr Mamta Choksi**

- PMH: HTN, diabetes, CAD, shingles
- 8/2020: Evaluated for lymphocytosis and thrombocytopenia
  - PLT: 90,000, Absolute lymphocytes: 6,000
- Workup: CD38-negative CLL, trisomy 12, IGHV-unmutated; Mild LAD in neck, chest, abdomen and pelvis with more extensive LAD in mediastinum and bilateral axillary region
- 9/2020: Initiates obinutuzumab/venetoclax regimen
  - Allopurinol → Obinutuzumab 100 mg C1D1, 900 mg C1D2
    - Thrombocytopenia with PLT: 14,000 → Platelet transfusion → PLT 40,000
    - Holding treatment for another week to re-evaluate

**Question**

- What are your experiences with obinutuzumab/venetoclax in older patients with CLL?

# Case Presentation – Dr Bachow: A 55-year-old woman with relapsed CLL and a BRAF V600E mutation

**Dr Spencer Bachow**

- 9/2012: Diagnosed with CLL → Surveillance
- 7/2013: Presents to MD Anderson, with CLL Del (13q), IGHV-unmutated → Continues surveillance
- 7/2015: Increasing fatigue, anemia, RBC → patient declines chemotherapy
- 7/2016: FCR x 3, Complete hematologic remission but declined further FCR due to toxicity → Surveillance
  - WBC increased from 6.6k to 27.7k in 4 months
  - Molecular testing: BRAF V600E and KRAS mutations
- 10/2016: Ibrutiinib, with arthralgias and weight gain → Switched to 2 tablets daily
  - 2/2019: Ibrutinib discontinued due to severe arthralgias, fatigue → Surveillance
- 10/2020: WBC increased to 157.0k, with more prominent axlllary, cervical and supraclavicular LAD, fatigue
- Acalabrutinib

**Question**

- Have you ever seen BRAF V600E mutations in CLL? Could she have more of a hairy cell leukemia-like B-cell lymphoproliferative disorder? Have you ever used BRAF-targeted therapy in CLL off protocol?

# Meet The Professor with Dr Coutre

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## MODULE 6: Key Recent Data Sets

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

RTP
RESEARCH
TO PRACTICE

The NEW ENGLAND JOURNAL of MEDICINE

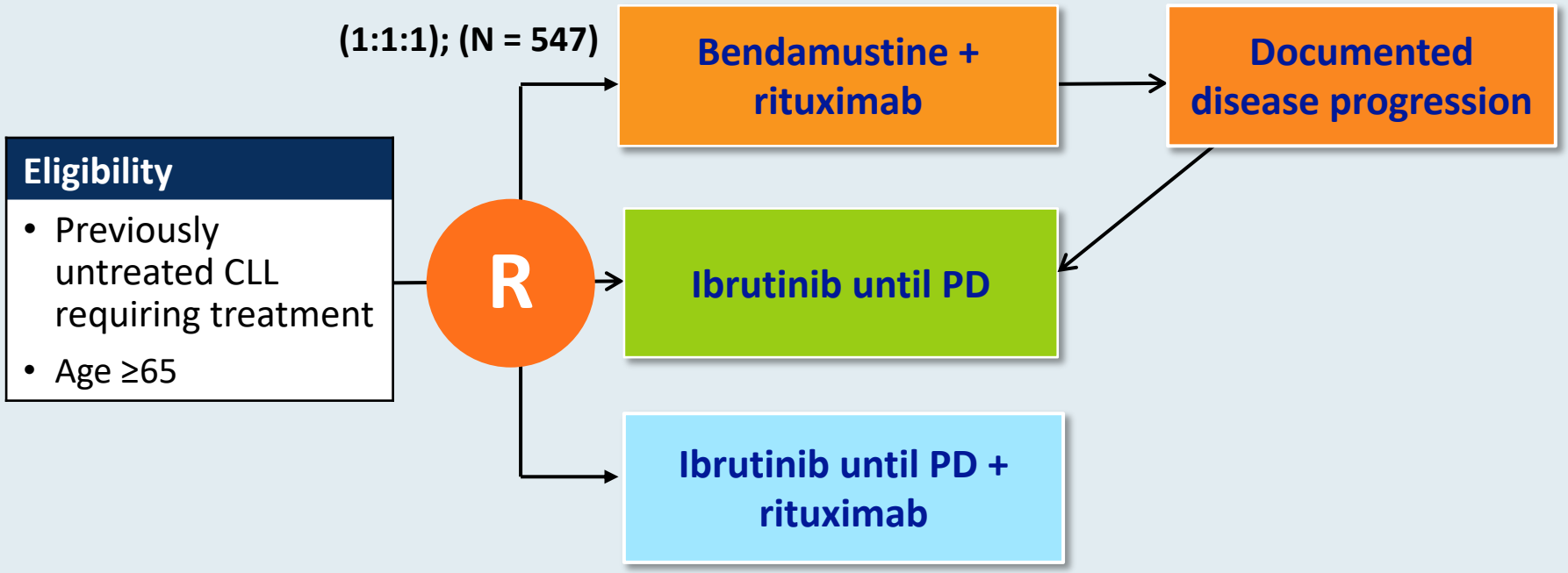
ORIGINAL ARTICLE

# Ibrutinib Regimens versus Chemoimmunotherapy in Older Patients with Untreated CLL

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

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

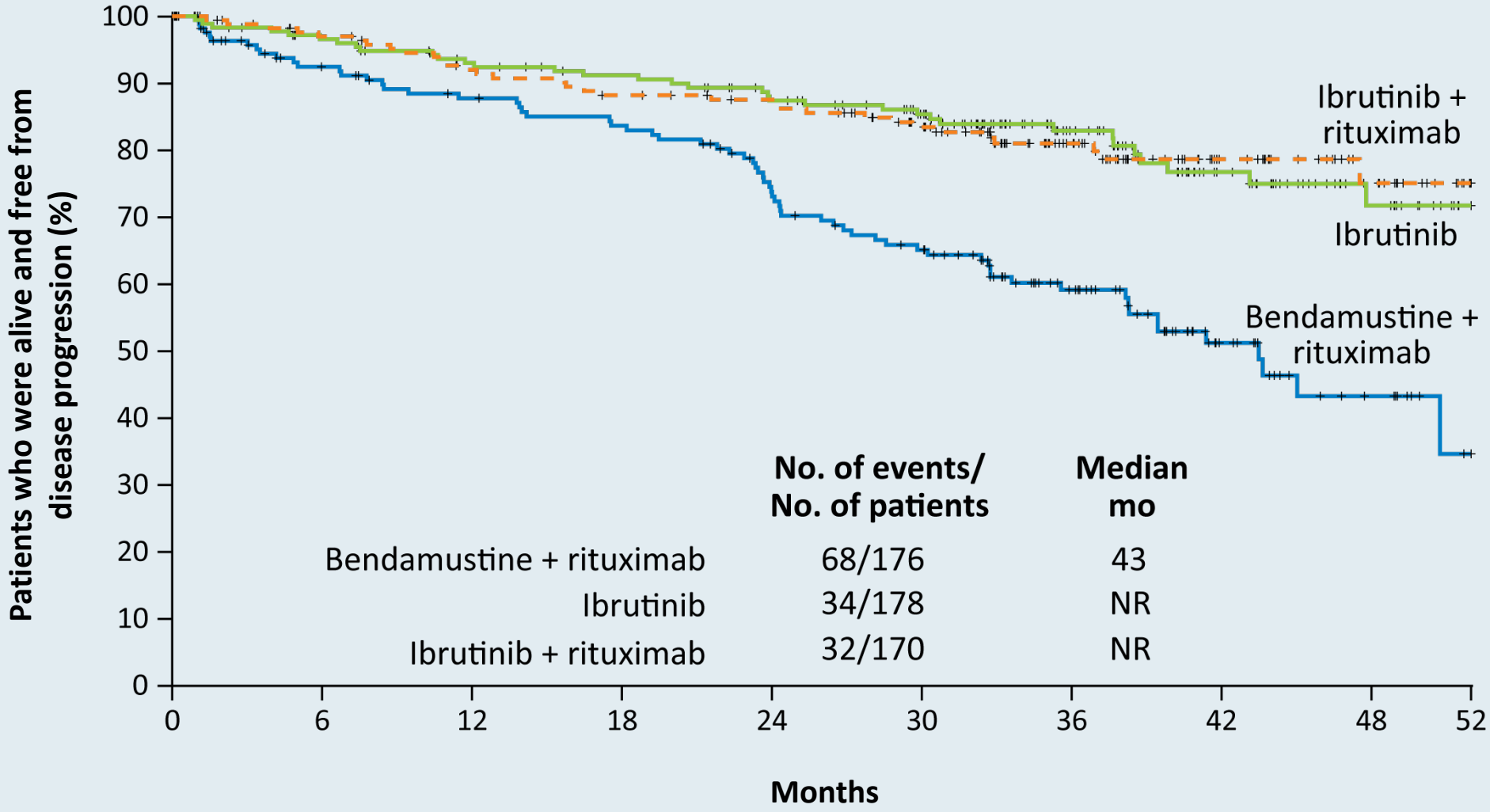
# Phase III Alliance A041202 Study Design




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

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

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




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

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

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

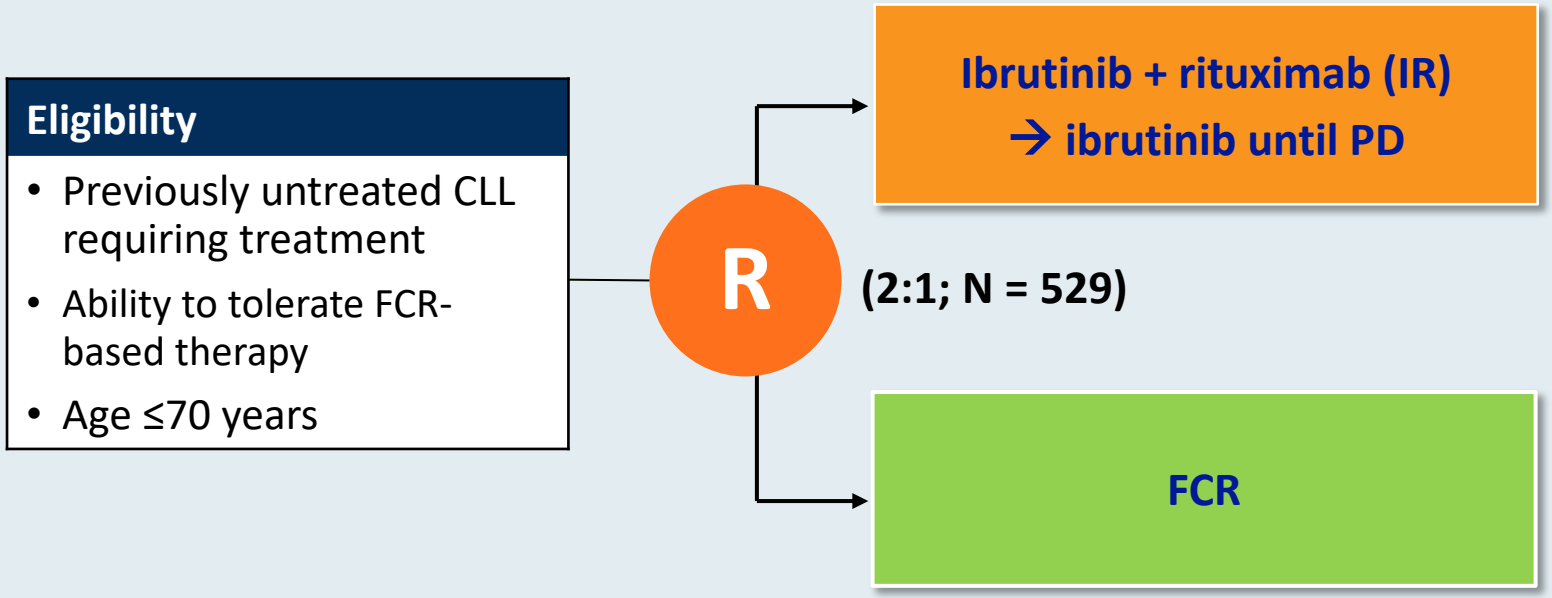
Woyach JA et al. *N Engl J Med* 2018;379(26):2517-28.

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

Shanafelt TD et al.

ASH 2019;Abstract 33.

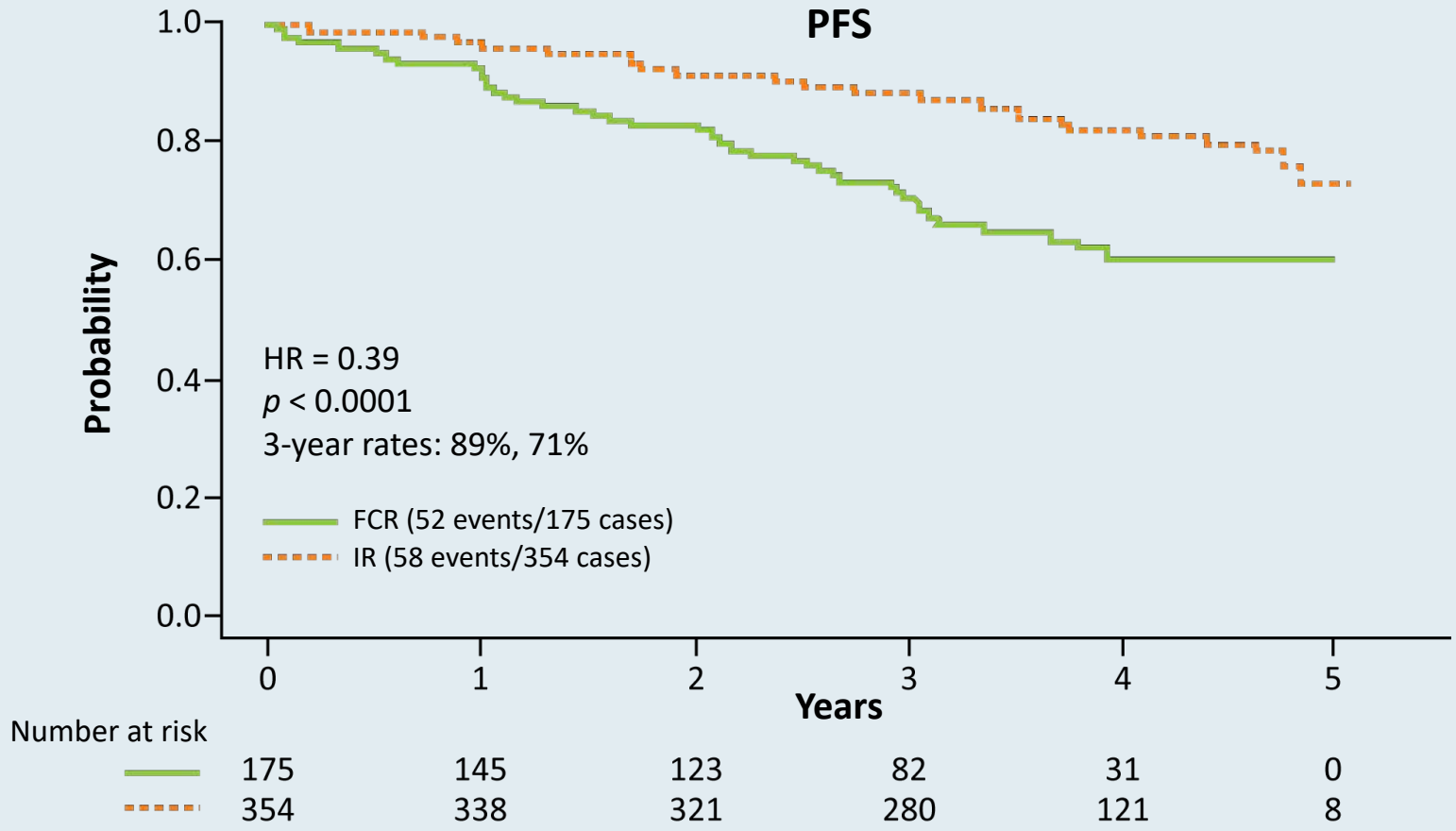
# Phase III ECOG-ACRIN E1912 Study Design




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

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

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




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

Shanafelt TD et al. ASH 2019;Abstract 33.

RTP RESEARCH TO PRACTICE

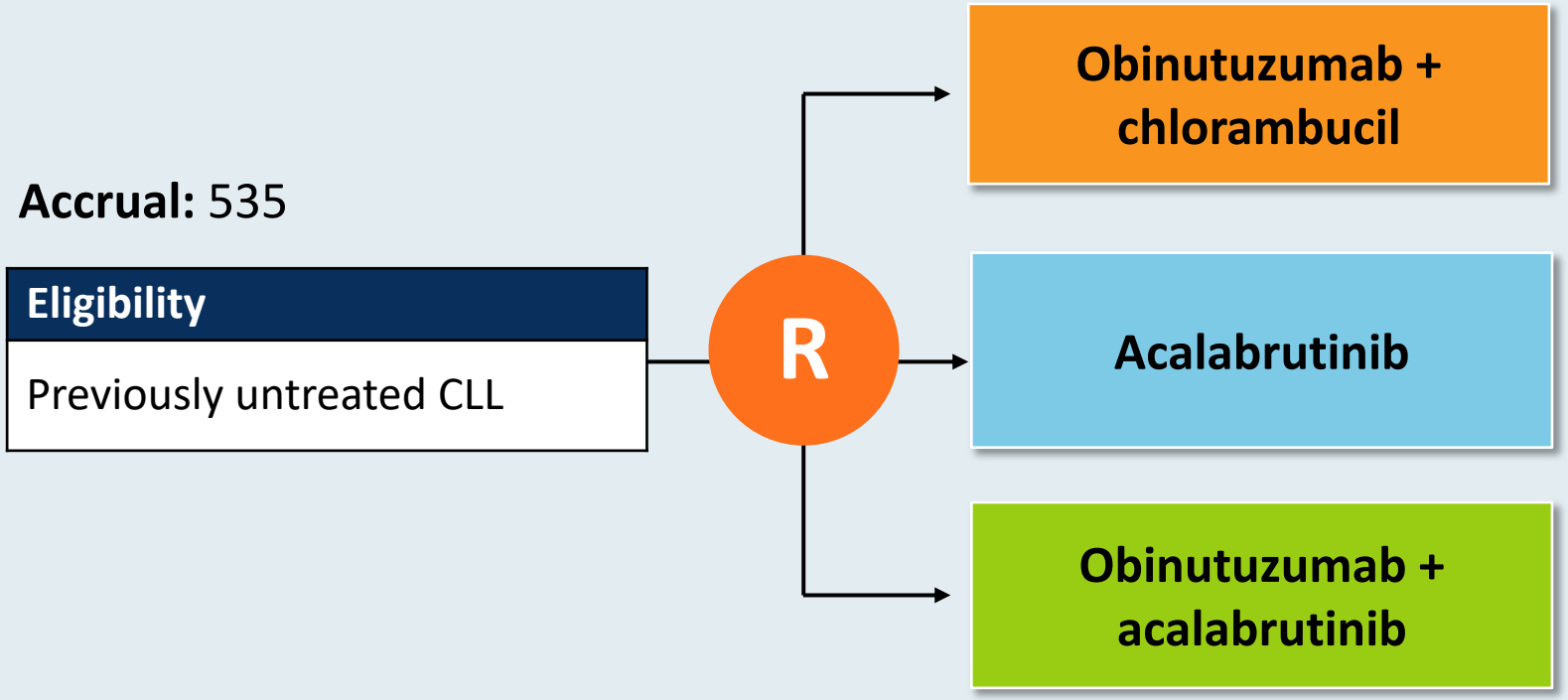
Articles

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

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

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

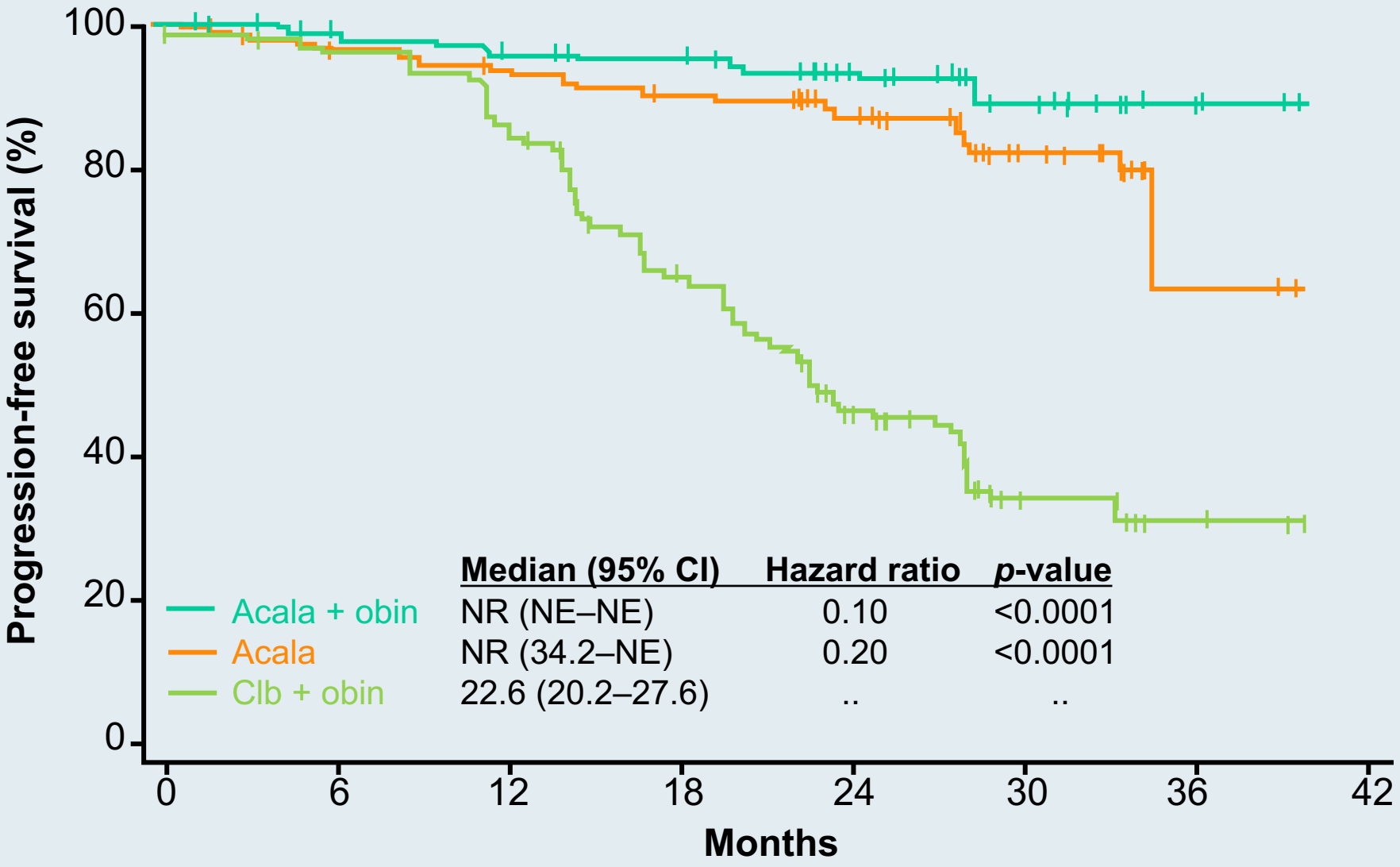
# ELEVATE-TN Phase III Trial Schema




**Primary endpoint:** Progression-free survival

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

# ELEVATE-TN: PFS (IRC)




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

# ELEVATE-TN: Select Safety Parameters

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

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

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

## Press Release — January 25, 2021

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

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

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

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

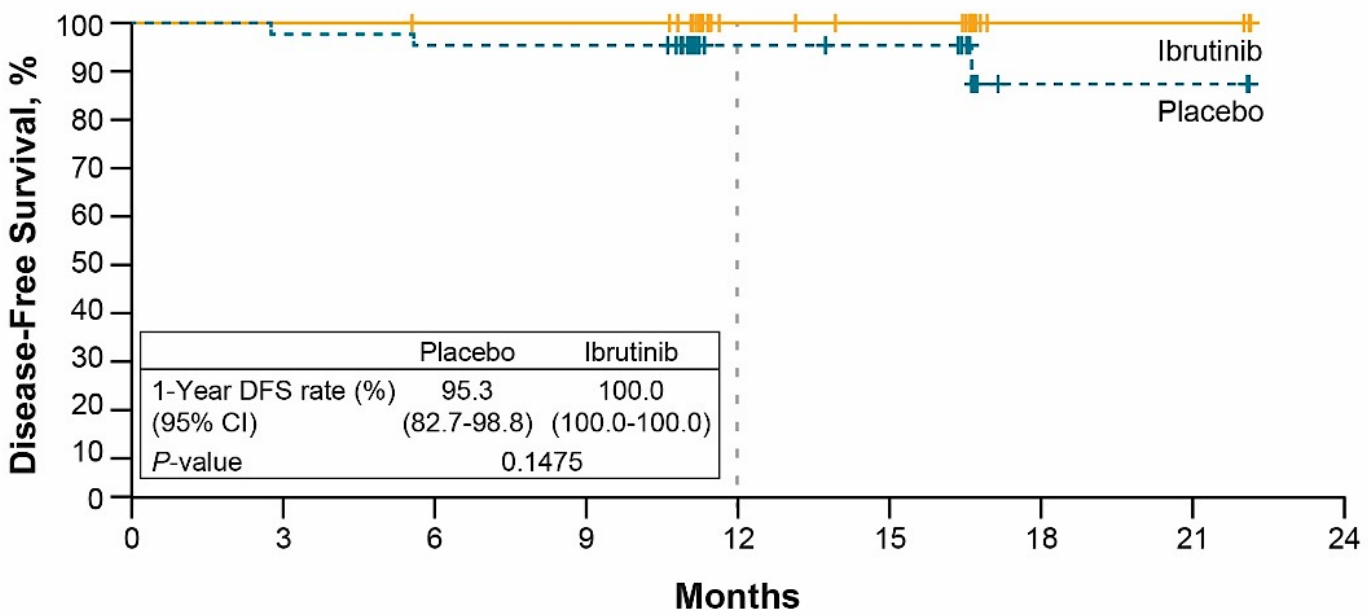
# Ibrutinib (Ibr) plus Venetoclax (Ven) for First-Line Treatment of Chronic Lymphocytic Leukemia (CLL)/Small Lymphocytic Lymphoma (SLL): 1-Year Disease-Free Survival (DFS) Results from the MRD Cohort of the Phase 2 CAPTIVATE Study Trial

Wierda WG et al.

ASH 2020;Abstract 123.

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

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




**Patients at Risk**

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

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

**30 month PFS Rate:**

Confirmed uMRD:

- 95.3% placebo
- 100% ibrutinib

Without confirmed uMRD:

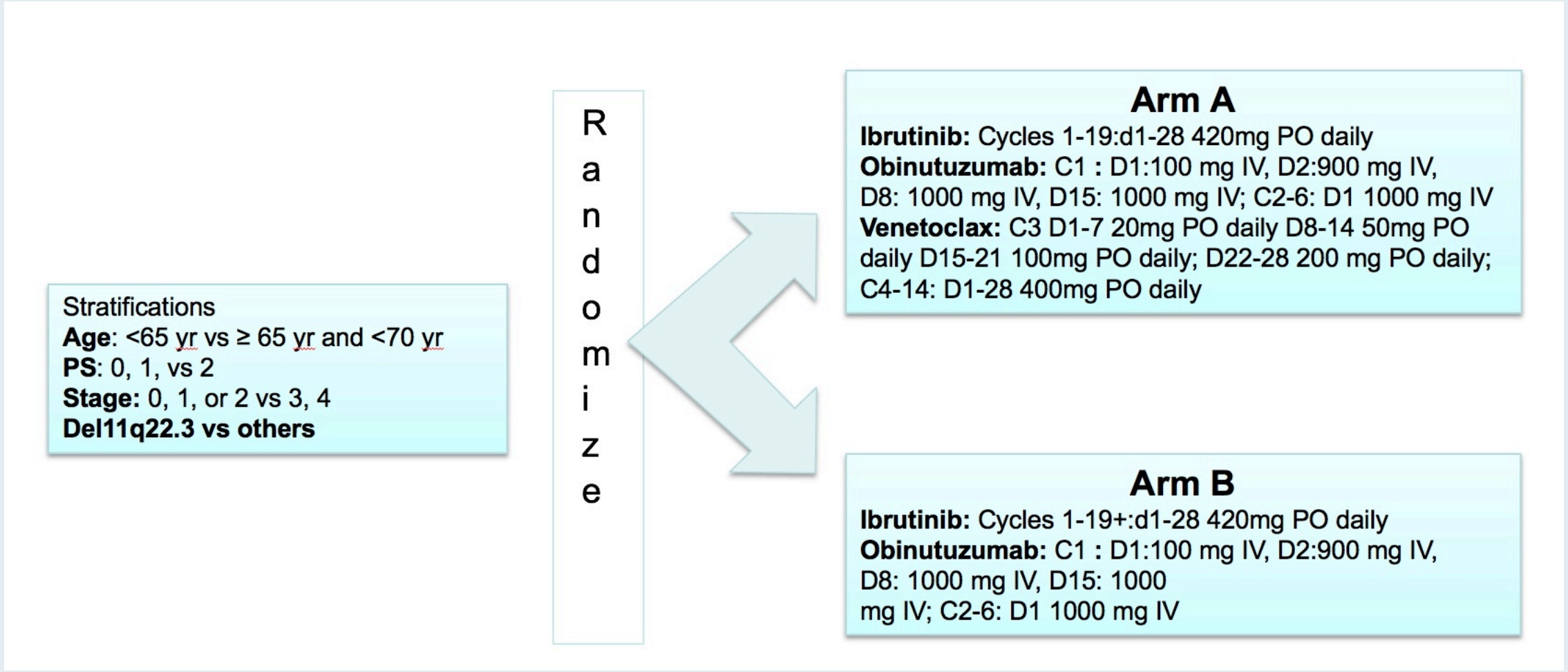
- 95.2% ibrutinib
- 96.7% ibr/ven

**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

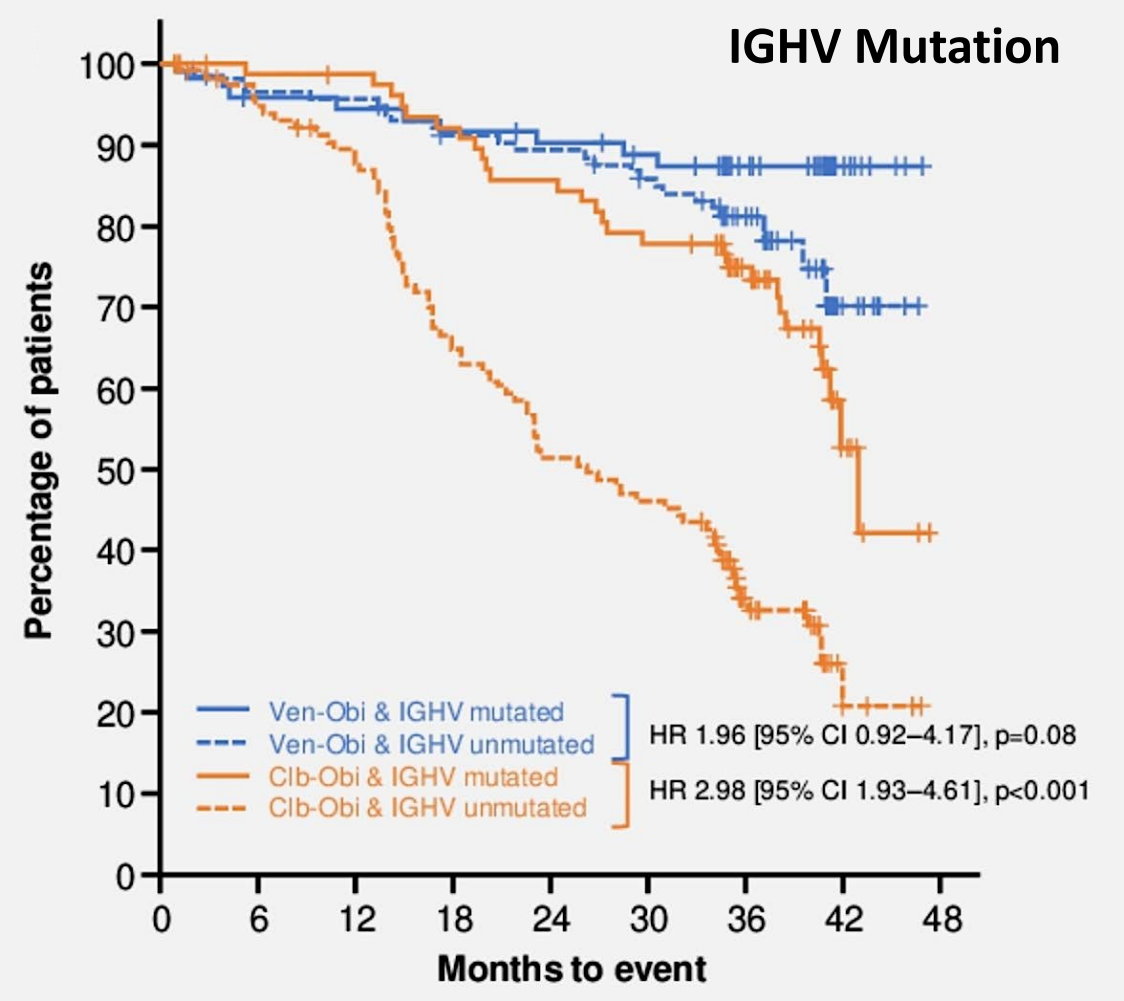
Articles

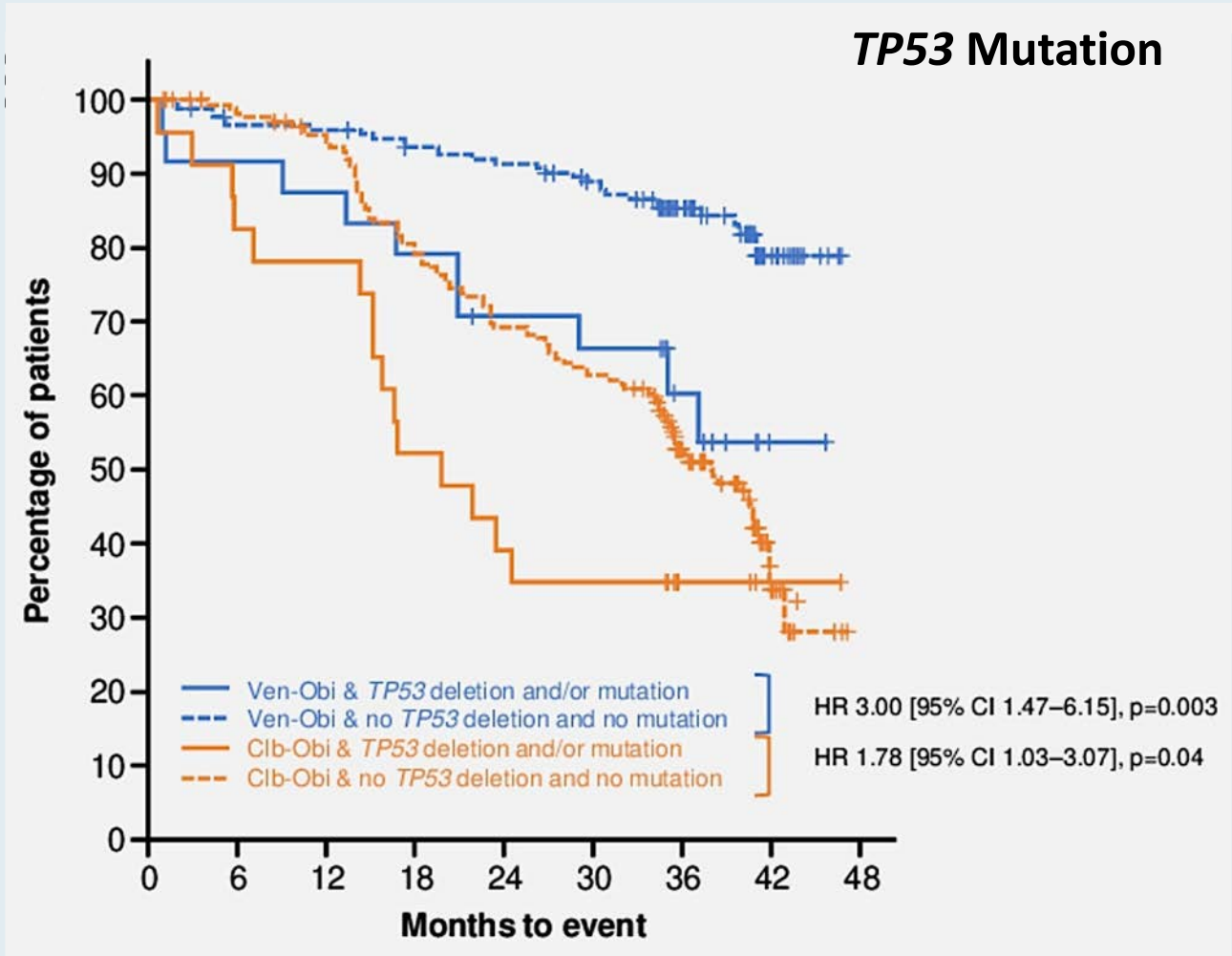
# Venetoclax plus obinutuzumab versus chlorambucil plus obinutuzumab for previously untreated chronic lymphocytic leukaemia (CLL14): follow-up results from a multicentre, open-label, randomised, phase 3 trial

*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

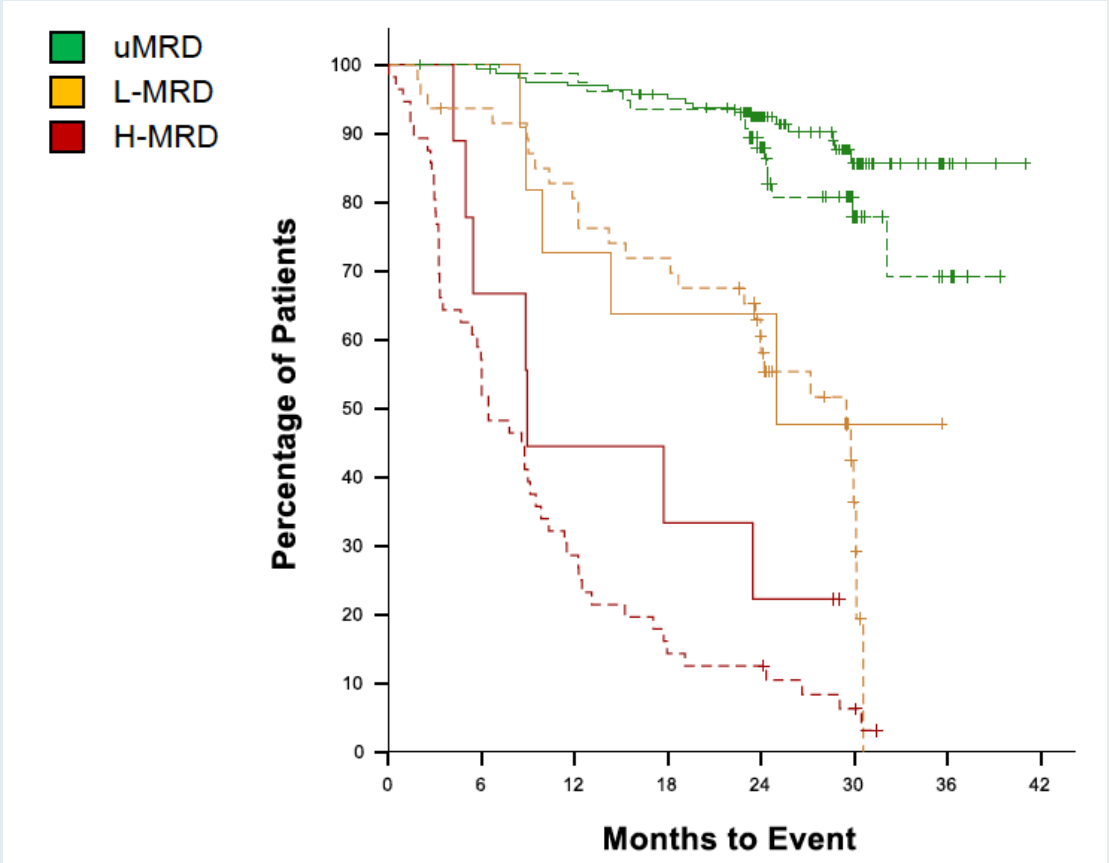



Al-Sawaf O et al. *Lancet Oncol* 2020;21(9):1188-200.

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 |

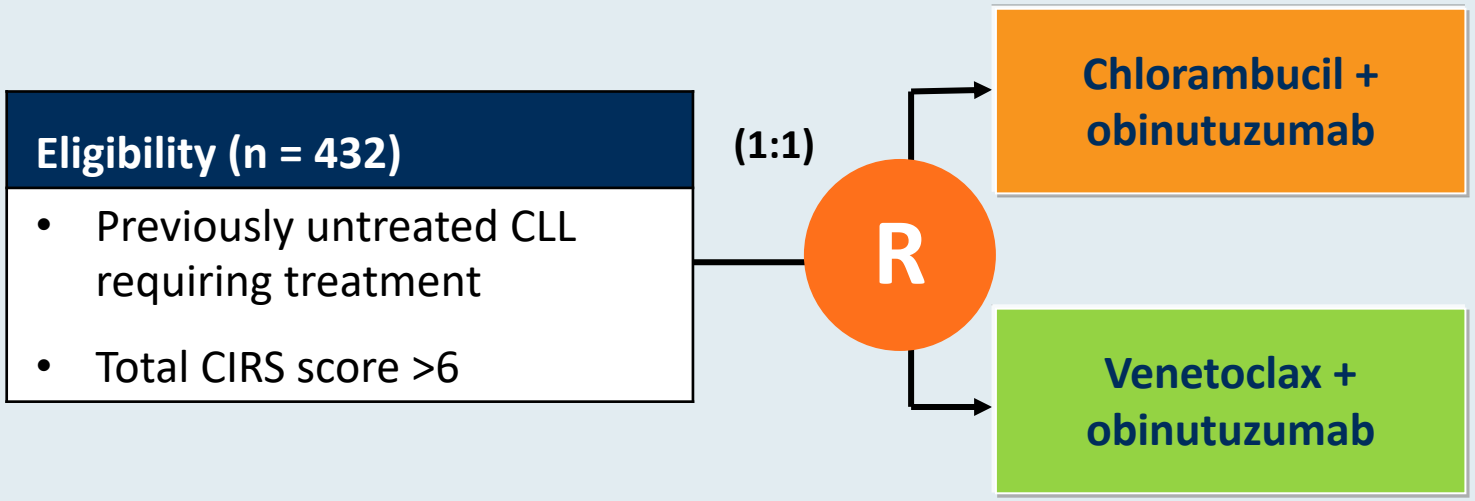
Al-Sawaf O et al. *Lancet Oncol* 2020;21(9):1188-200.

# 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

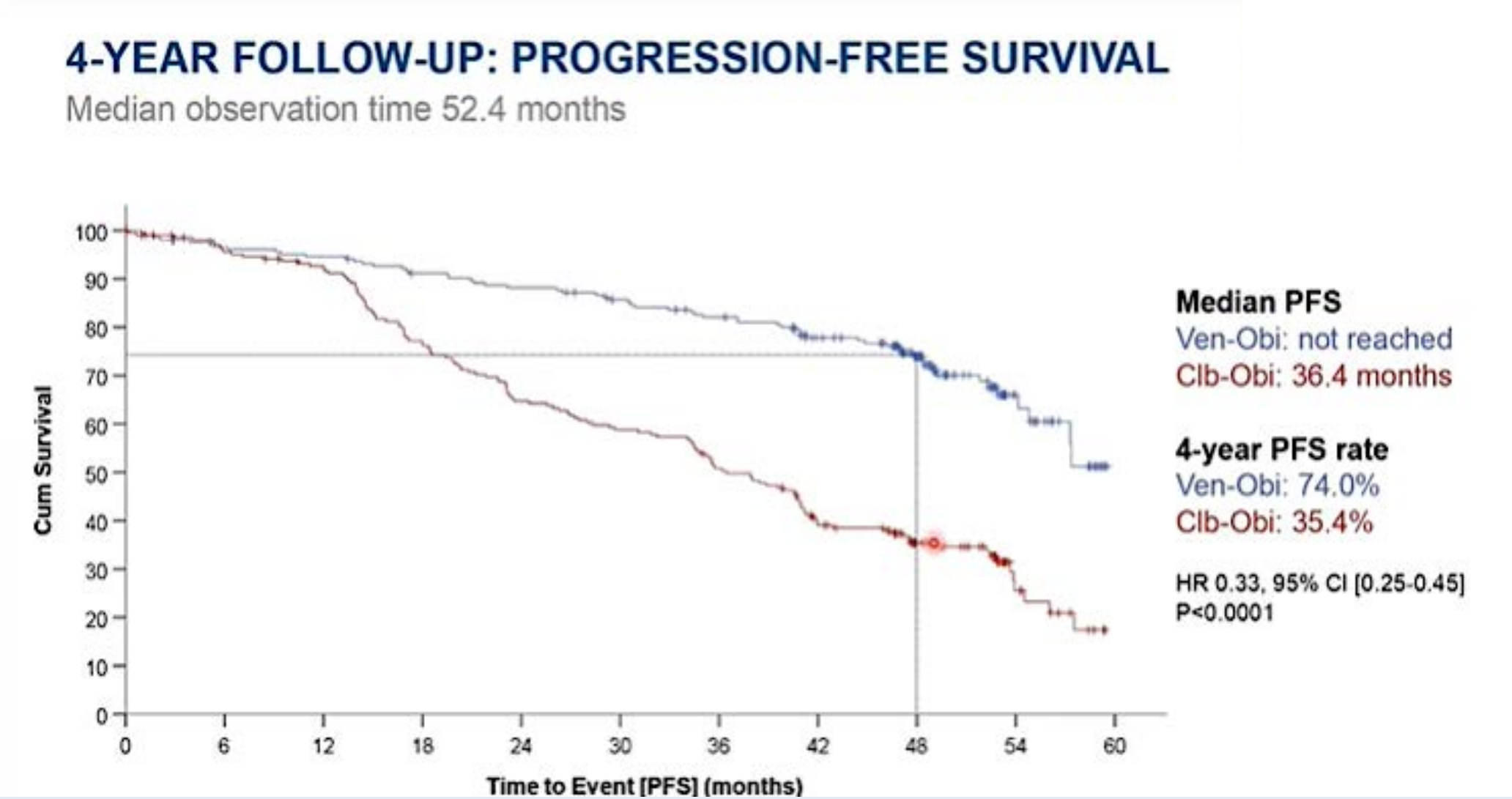



**Primary endpoint:** Progression-free survival

- 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 .

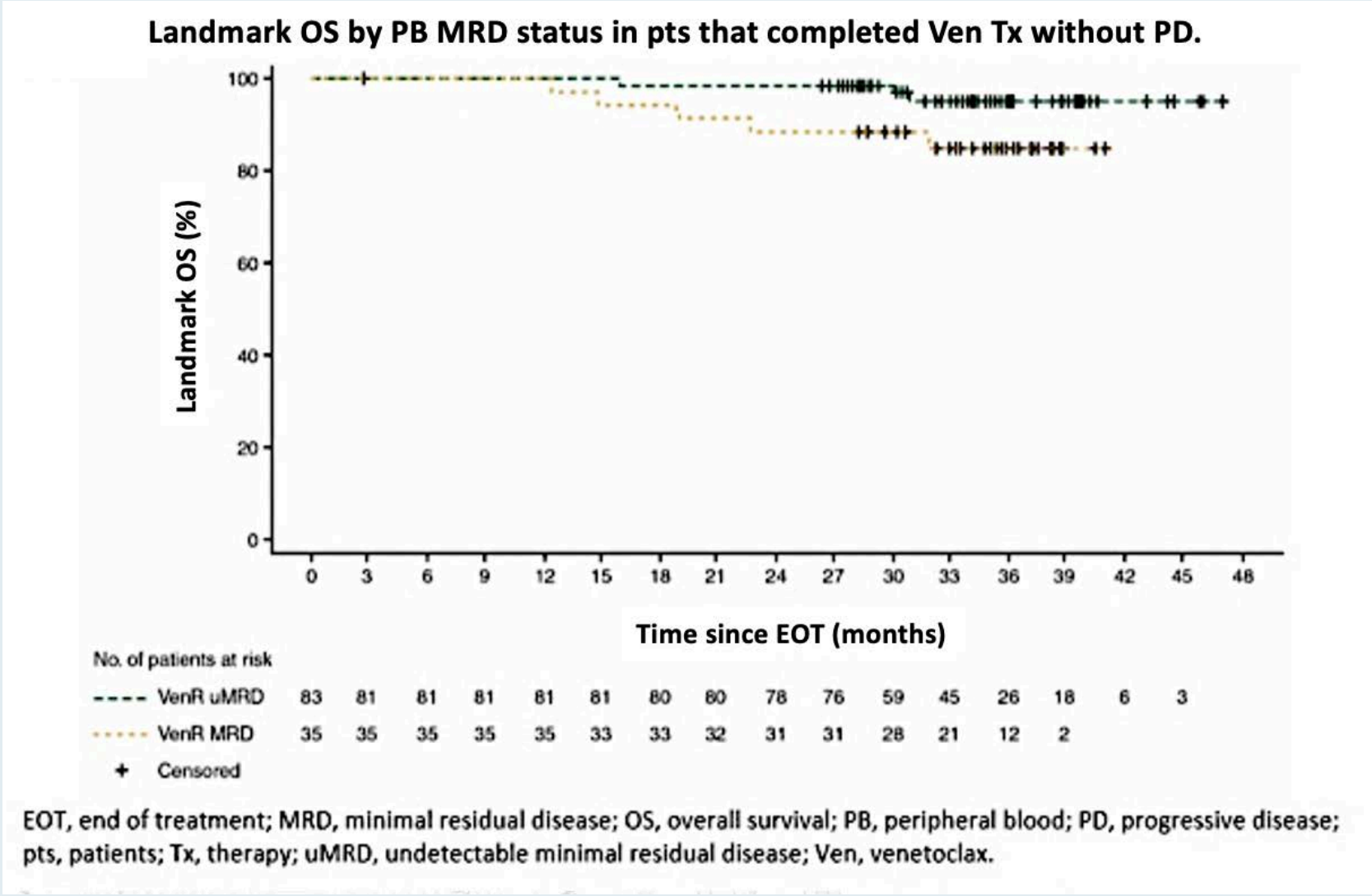
# Management of Relapsed/Refractory CLL

# 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

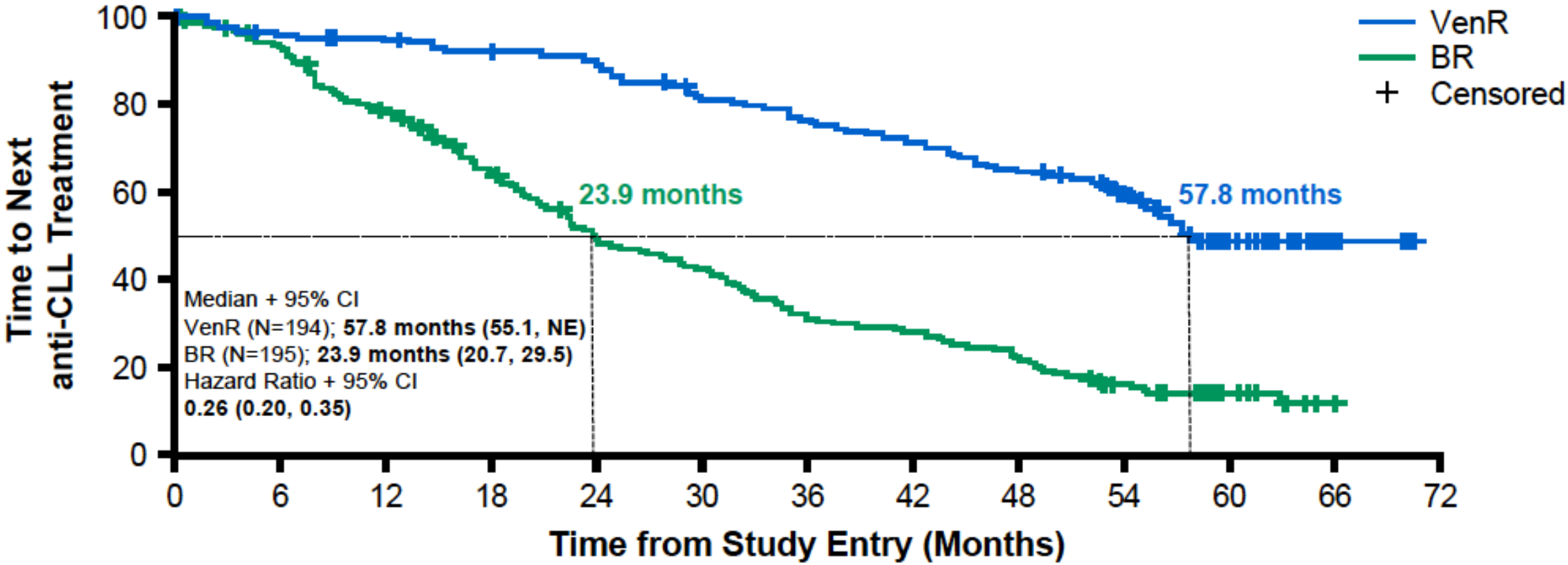
Kater AP et al. ASH 2020;Abstract 125.

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.

# 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

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# 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

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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

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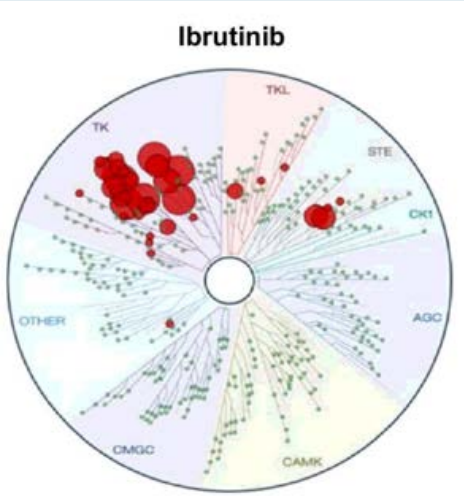
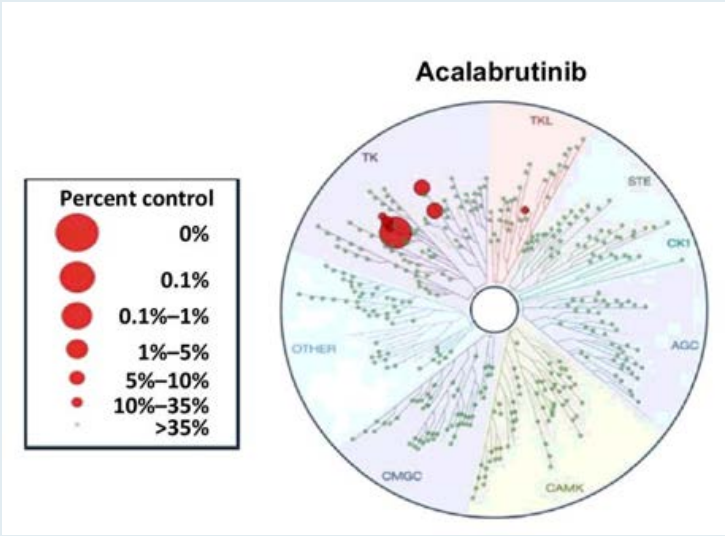
# Overview of BTK Inhibitors in CLL

## Irreversible

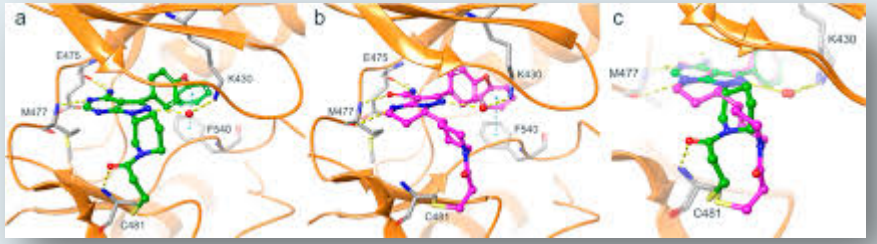
**Ibrutinib**




**Acalabrutinib**

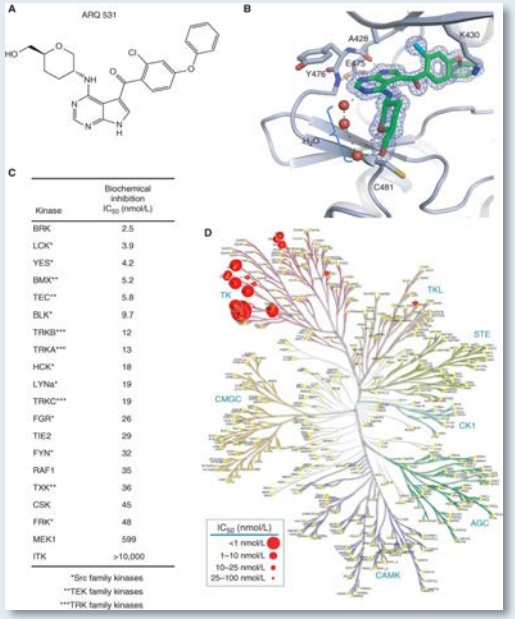



**Zanubrutinib**

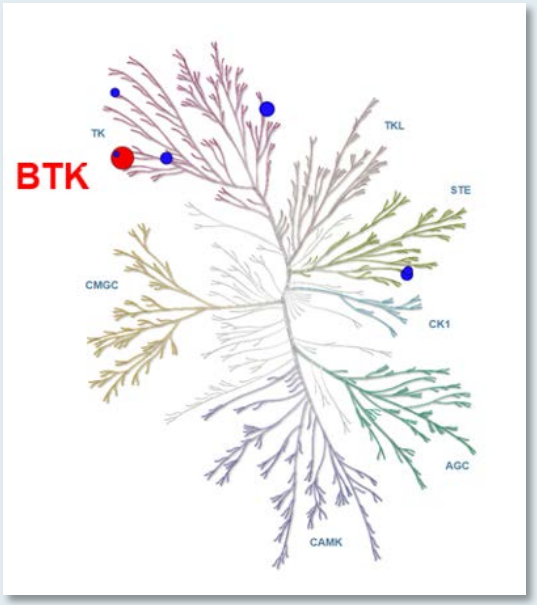



## Reversible

**ARQ-531 (MK-1026)**




**LOXO-305**




Courtesy of Matthew S Davids, MD, MMSc

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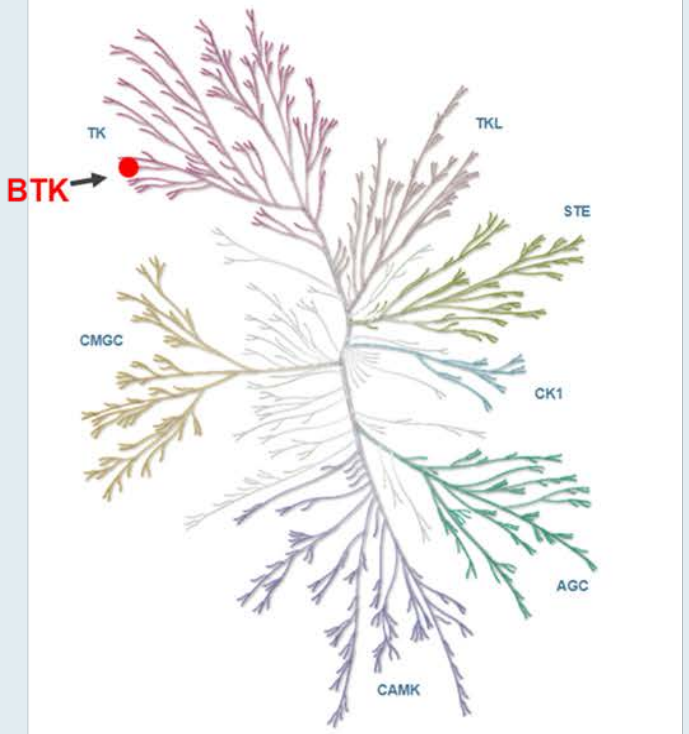
# LOXO-305 is a Highly Potent and Selective Non-Covalent BTK Inhibitor

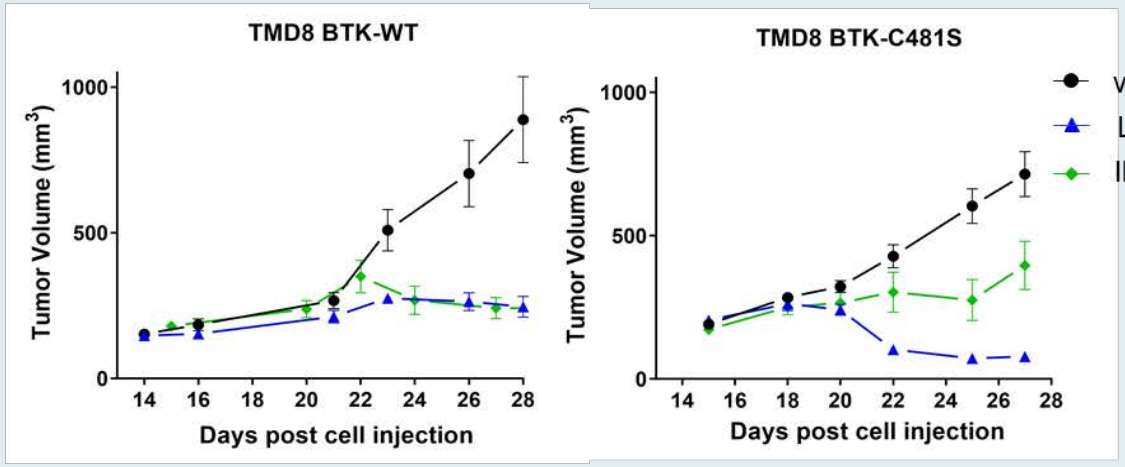
## Kinome selectivity

Highly selective for BTK




## Xenograft models

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




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

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

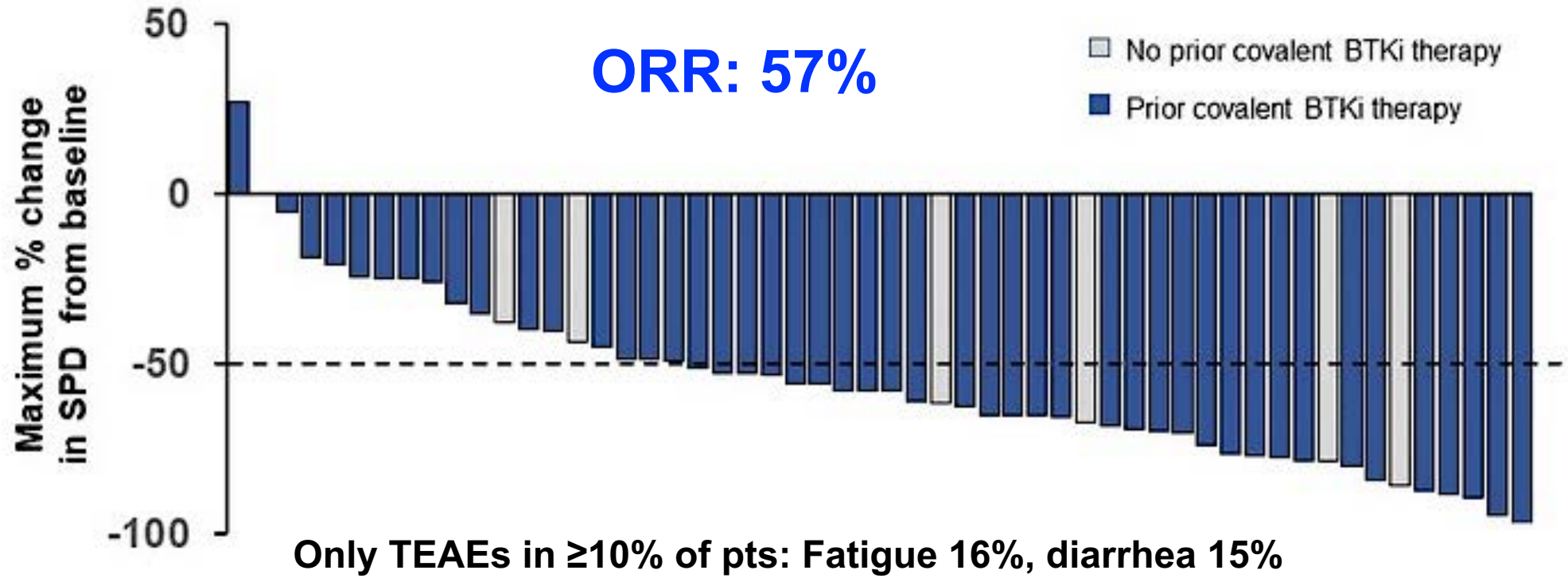
Mato AR et al. ASH 2020;Abstract 542.

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

Mato AR et al.

ASH 2020;Abstract 542.

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




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

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

Mato AR et al. ASH 2020;Abstract 542.

# BRUIN: Safety

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

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

Mato AR et al. ASH 2020. Abstract 542.

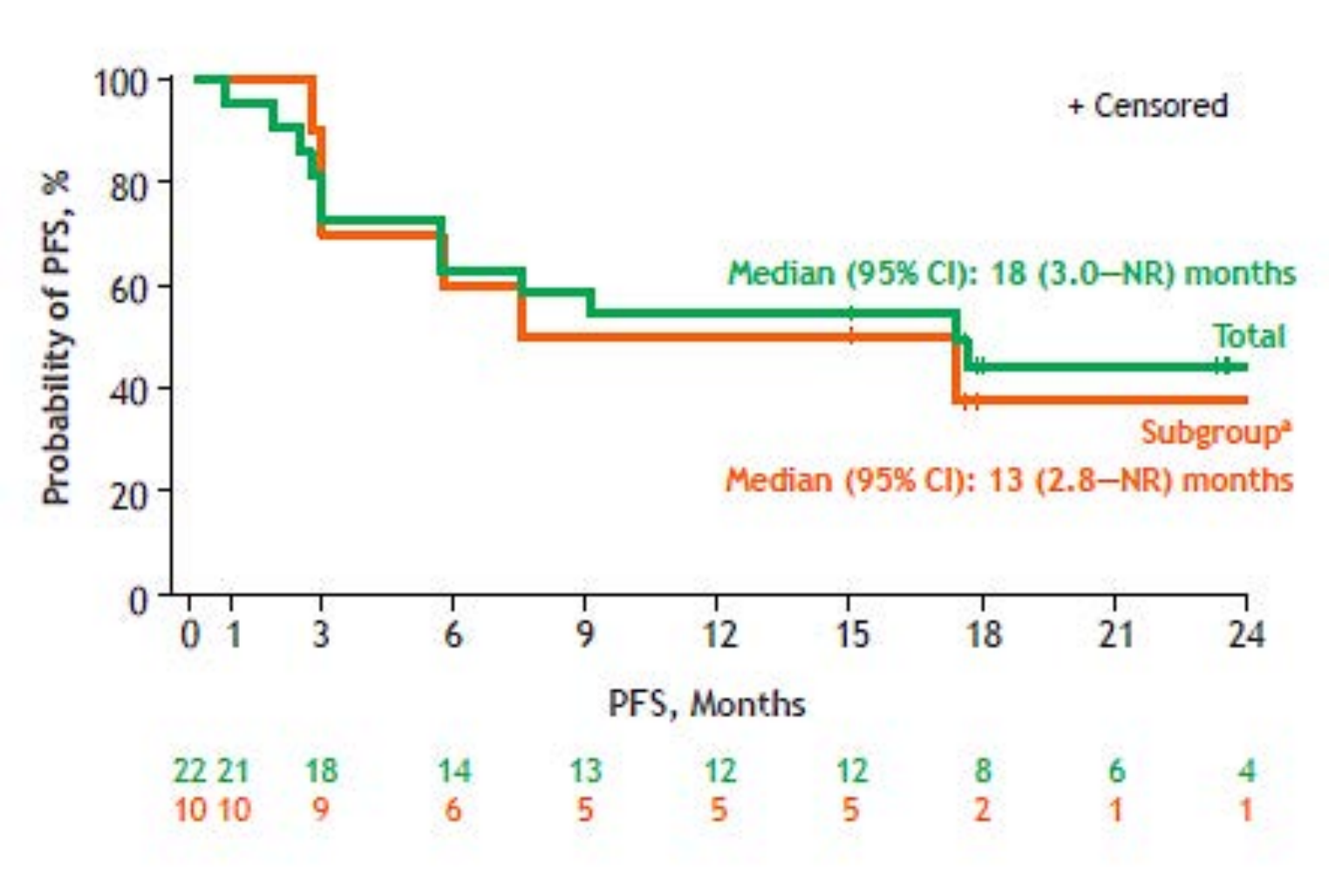
Courtesy of Matthew S Davids, MD, MMSc

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

Siddiqi T et al.

ASH 2020;Abstract 546.

# TRANSCEND CLL 04: Liso-cel Monotherapy Cohort




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

Siddiqi T et al. ASH 2020;Abstract 546.

RTP RESEARCH TO PRACTICE

# Dissecting the Decision: Clinical and Nursing Investigators Provide Practical Perspectives on Key Issues in Cancer Care

# Part 1 — Acute Myeloid Leukemia

**Tuesday, March 16, 2021**
**5:00 PM – 6:00 PM ET**

## Faculty

**Rhonda Hewitt, MSN, ANP, AOCNP**
**Mark Levis, 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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