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

**Nitin Jain, MD**
Associate Professor of Medicine
Department of Leukemia
The University of Texas MD Anderson Cancer Center
Houston, Texas

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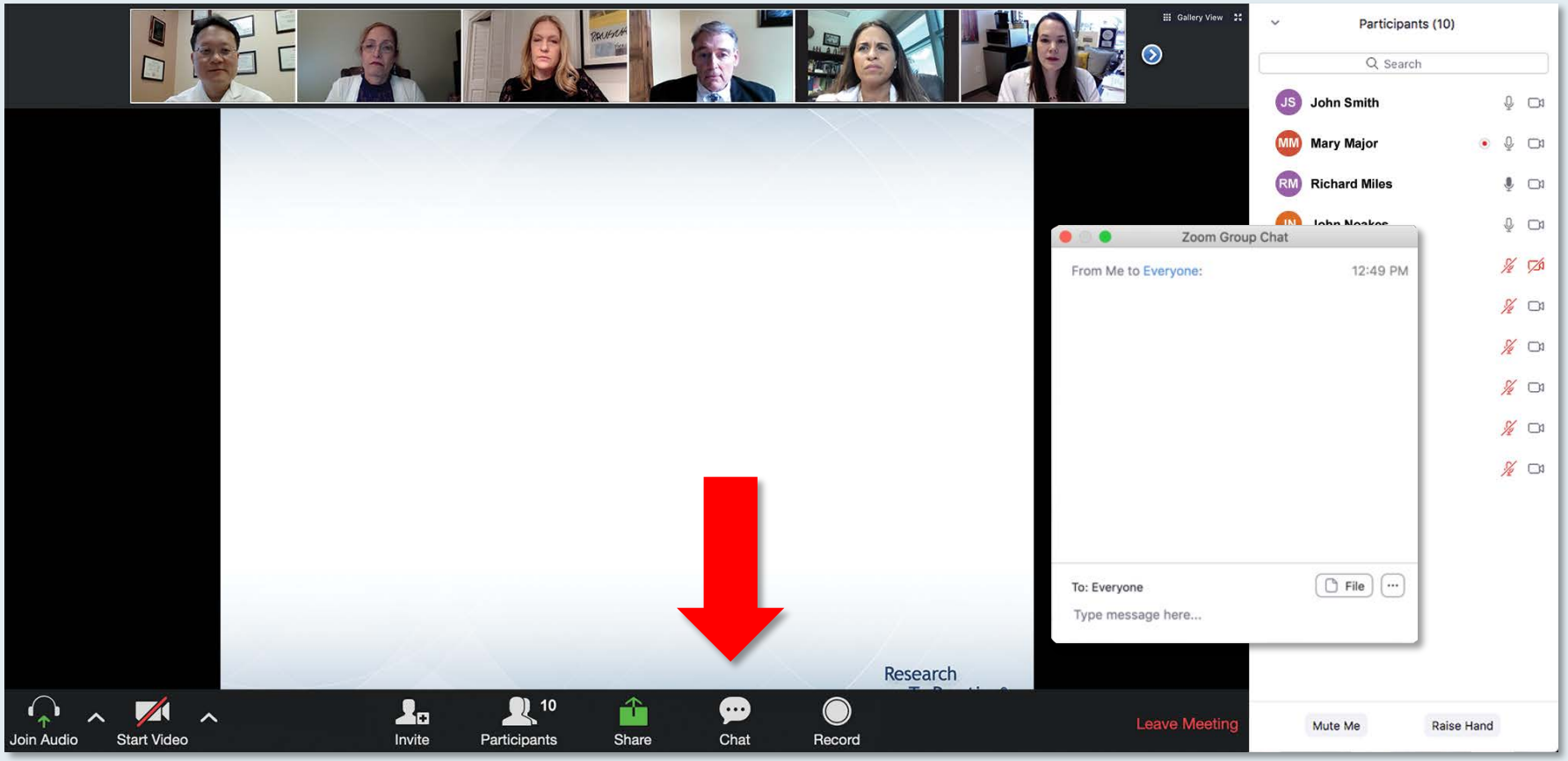


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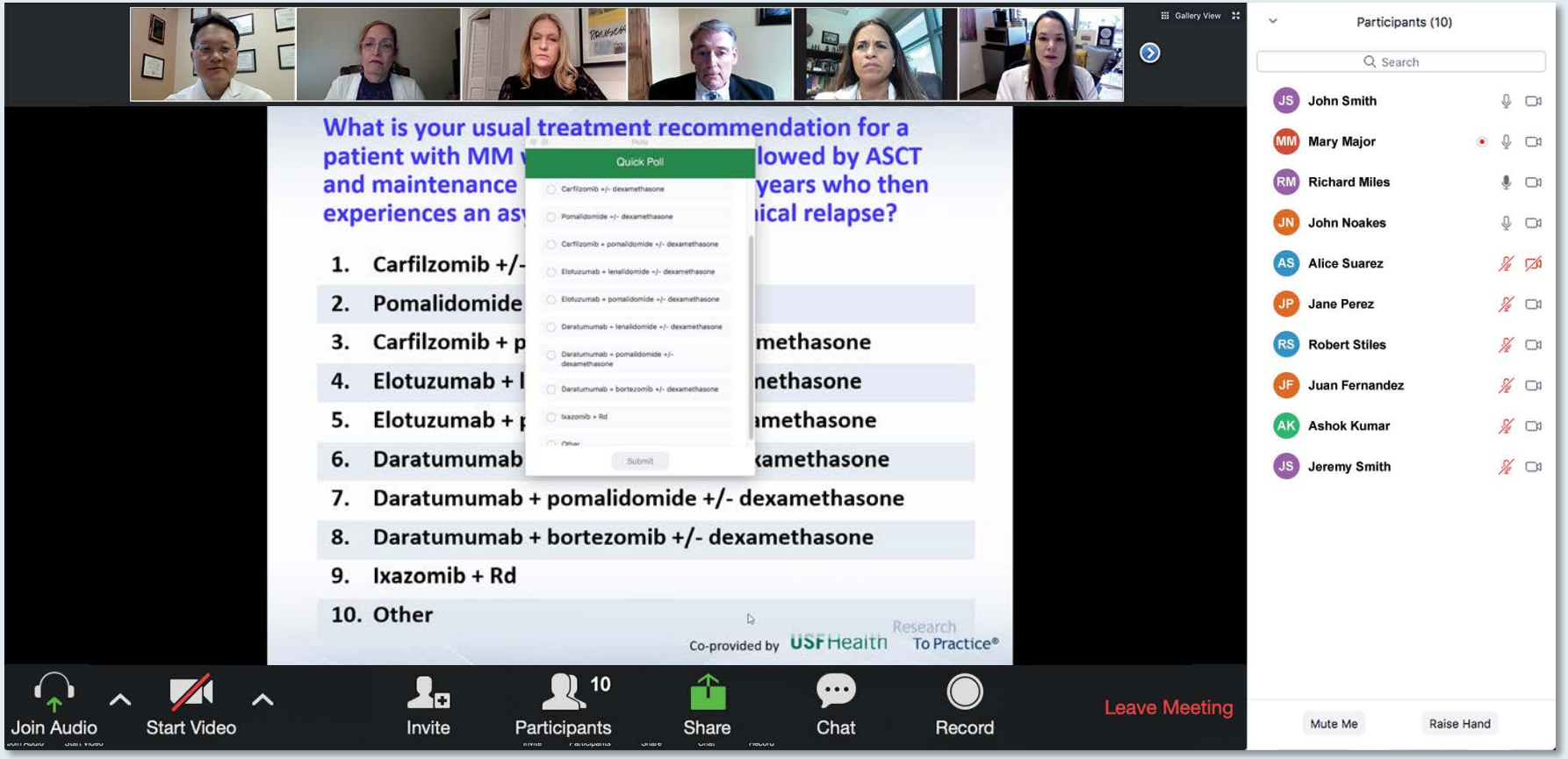


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# Year in Review: Clinical Investigators Provide Perspectives on the Most Relevant New Publications, Data Sets and Advances in Oncology

## Acute Myeloid Leukemia and Myelodysplastic Syndromes

**Tuesday, January 5, 2020**
**5:00 PM – 6:00 PM ET**

### Faculty

**Mikkael A Sekeres, MD, MS**
**Richard M Stone, MD**

### Moderator

**Neil Love, MD**

Year in Review 2020

*Thank you for joining us!*

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

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# ONCOLOGY TODAY

## WITH DR NEIL LOVE

# FRONT-LINE TREATMENT OF CHRONIC LYMPHOCYTIC LEUKEMIA


DR JOHN PAGEL
SWEDISH CANCER INSTITUTE
SEATTLE, WASHINGTON


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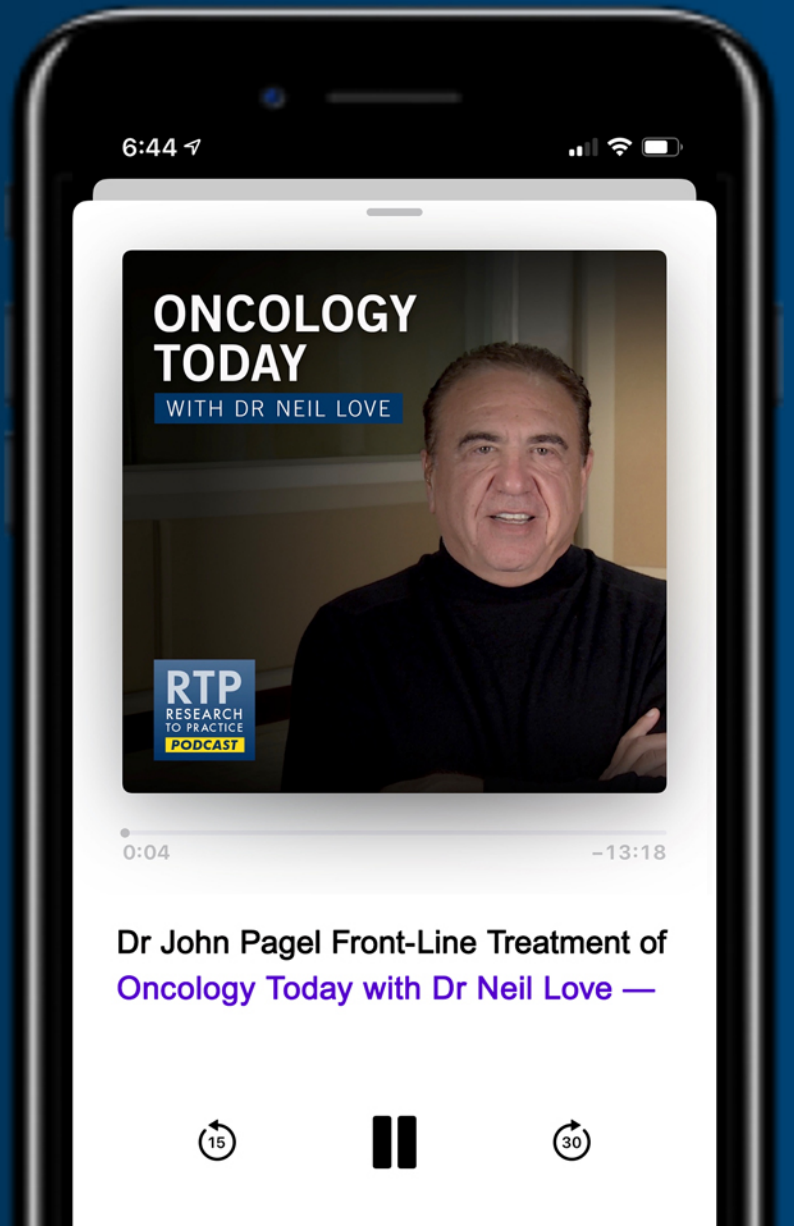
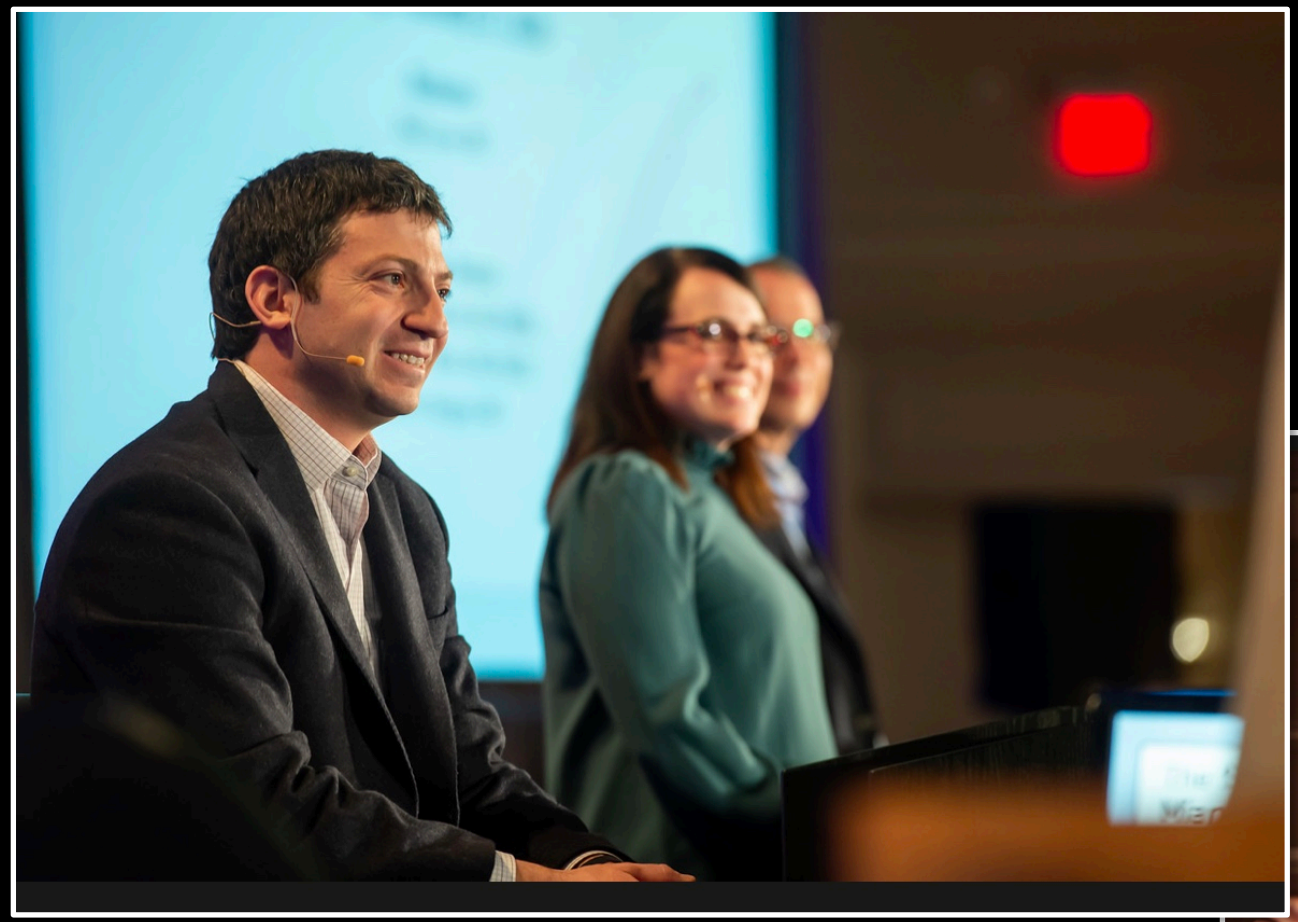



What would be your most likely approach for a patient with newly diagnosed CLL to whom you decide to administer up-front venetoclax/obinutuzumab who has detectable MRD after completing 1 year of treatment?




What are the key studies in selecting front line therapy?

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# *Meet The Professor* Program Participating Faculty

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**Nitin Jain, MD**
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# *Meet The Professor* Program Participating Faculty

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# *Meet The Professor* Program Participating Faculty

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**Neil Love, MD**
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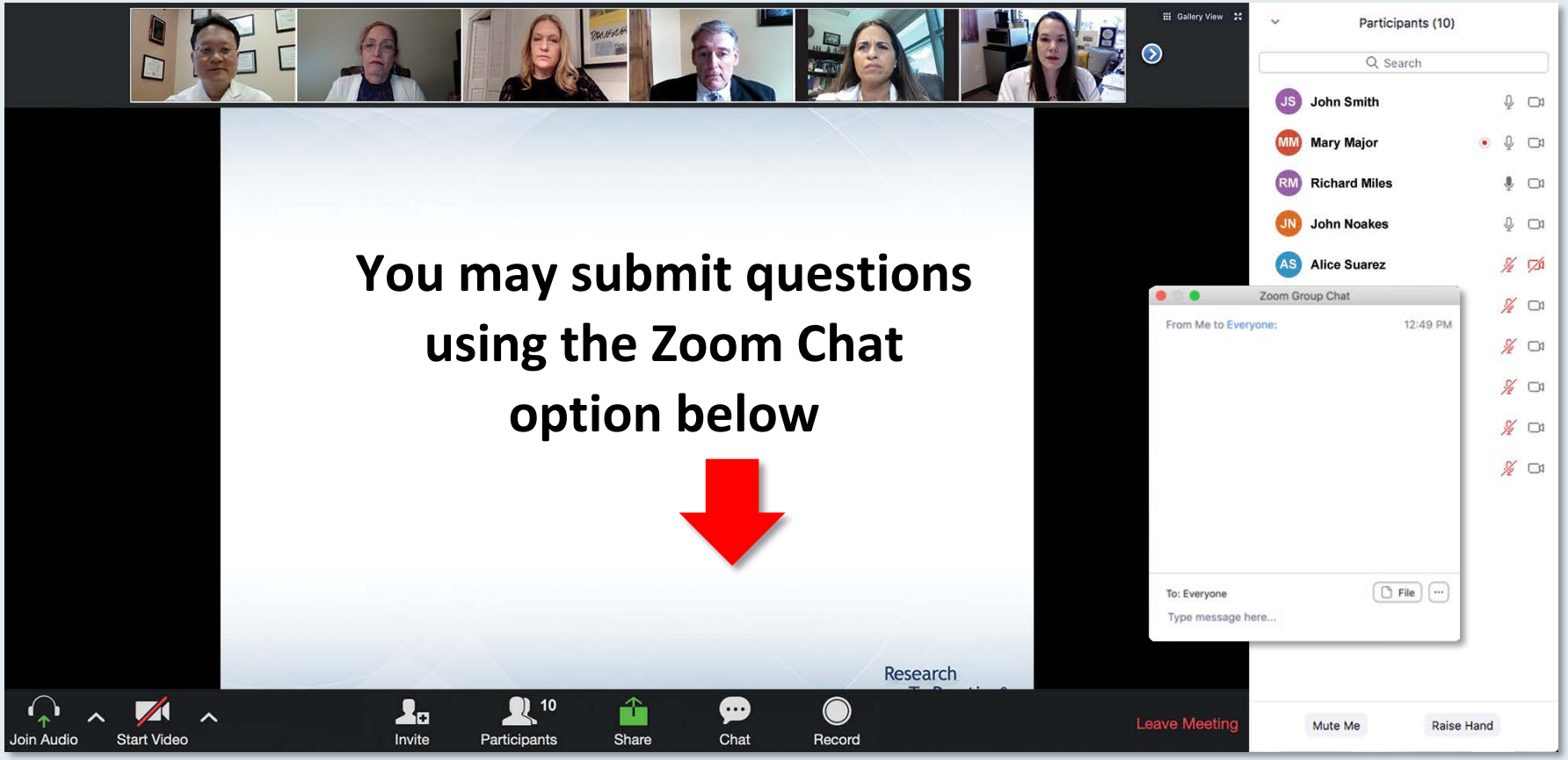


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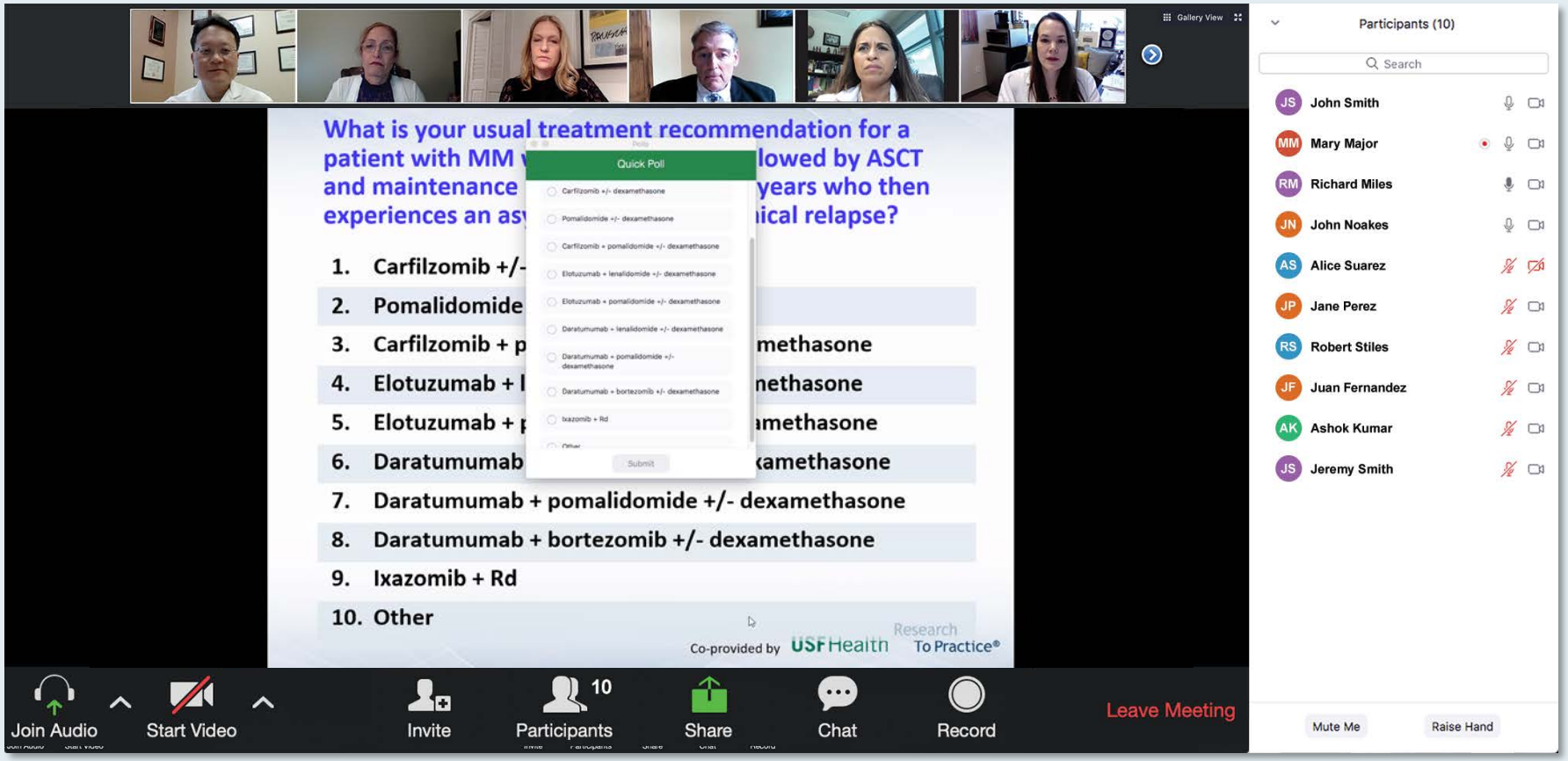


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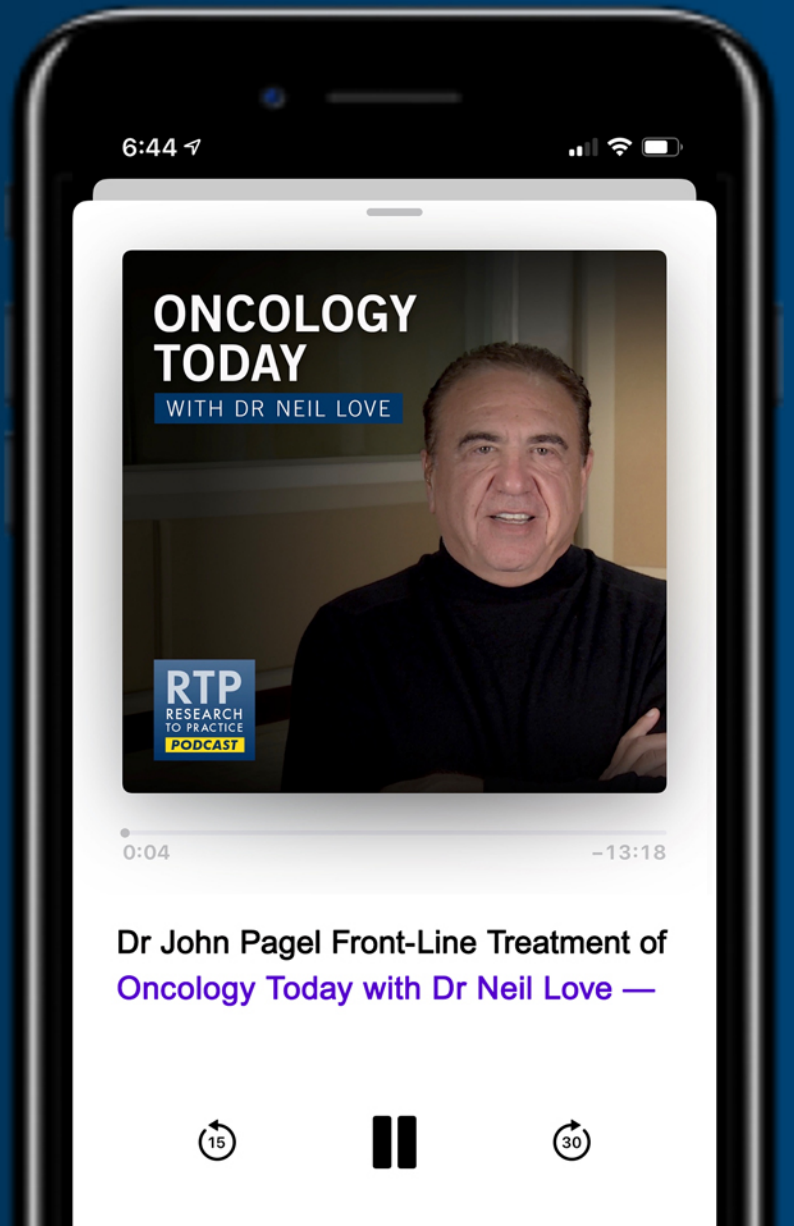

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**Syed Farhan Zafar, MD**
Hematologist and Medical Oncologist
Florida Cancer Specialists and Research Institute
Chief, Division of Hematology and Oncology
Lee Health
Fort Myers, Florida

# Meet The Professor with Dr Jain

## MODULE 1: Cases from Dr Zafar

- A 91-year-old woman with chronic lymphocytic leukemia (CLL) with unmutated IGHV and del(17p)
- Question and Comments: Selection of up-front therapy – Chemotherapy, ibrutinib or acalabrutinib
- A frail 89-year-old woman with slowly progressing CLL

**MODULE 2: CLL Journal Club with Dr Jain**

**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 Zafar: A 91-year-old woman with CLL with unmutated IGHV and del(17p)

Dr Syed Zafar

- 2011: Diagnosis of RAI stage 0 CLL, WBC 15-18k, no anemia/thrombocytopenia
- 2013: Diagnosed with atrial fibrillation, CHF – began apixaban
- 2018: Decrease in platelets detected, no B symptoms
  - FISH: del(6q), no del(17p) detected
- 2019: Episode of cellulitis, *C. diff* colitis X 2, atrial fibrillation with RVR (labs showing WBC 20-30k, Hgb 10-11, platelets 80-110k)
- 2020: Symptomatic with B symptoms, splenomegaly, Ig levels normal (WBC > 50k, Hgb 10, platelets 50-60k)
  - Cytogenetics: unmutated IGHV
  - Repeat FISH: del(17p) and del(6q) detected

**Questions**

- What would you recommend for this 91-year-old woman? Would you consider single-agent acalabrutinib, venetoclax or anti-CD20 antibody?

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# Question and Comments: Selection of up-front therapy – Chemotherapy, ibrutinib or acalabrutinib

**Dr Syed Zafar**

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# Case Presentation – Dr Zafar: A frail 89-year-old woman with slowly progressing CLL

Dr Syed Zafar

- 2016: Diagnosed with RAI Stage I CLL; asymptomatic with no high-risk features; multiple pre-existing conditions, including CHF and chronic kidney disease
  - She is the primary care-taker of her husband who has Alzheimer's disease
- 2016 – 2019: Observation
- 2020: Patient begins to be symptomatic – B symptoms, debilitating fatigue, palpable spleen, rising WBC count
  - Repeat FISH: no high-risk features detected
- Discussed single-agent acalabrutinib – began TLS prophylaxis, optimization of renal function, cardiology consulted
- Acalabrutinib 100 mg daily (no BID dosing) → improvement in systemic symptoms

**Questions**

- Should I increase the dose of acalabrutinib? How important is it to get her to standard dosing levels?

# Meet The Professor with Dr Jain

**MODULE 1: Cases from Dr Zafar**

**MODULE 2: CLL Journal Club with Dr Jain**

- Shifting paradigm in CLL: Is chemotherapy still relevant?
- Durable remissions with up-front ibrutinib in patients with CLL and del(17p)
- Ibrutinib versus ibrutinib with rituximab for CLL
- Cardiovascular and renal effects associated with ibrutinib
- Clinical significance of and predictive factors in achieving complete remission with ibrutinib in patients with CLL
- Phase I trial of eprenetapopt with ibrutinib or venetoclax-based therapy for relapsed/refractory CLL with TP53 mutation
- Mature results of a Phase II trial of acalabrutinib for treatment-naïve CLL
- Ibrutinib combined with venetoclax as initial therapy for CLL; MRD analyses
- Genetic determinants and evolutionary history of Richter's syndrome
- Metastatic lung adenocarcinoma mimicking Richter's transformation in a patient with CLL
- Incidental Richter's transformation in patients with CLL during interruption of ibrutinib
- Fungal infections in patients with CLL receiving ibrutinib
- Occurrence of other cancers in patients with CLL and mutations in the POT1 gene
- Allogeneic stem cell transplant after small molecule inhibitors in patients with CLL and lymphomas
- Treating leukemia in the time of COVID-19

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

**MODULE 4: Key Recent Data Sets**

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REVIEW ARTICLE

# The Shifting Paradigm in Chronic Lymphocytic Leukemia

## *Is Chemotherapy Still Relevant?*

*Nitin Jain, MD,* and Susan O'Brien, MD†*

***Cancer J* 2019;25(6):374-7.**

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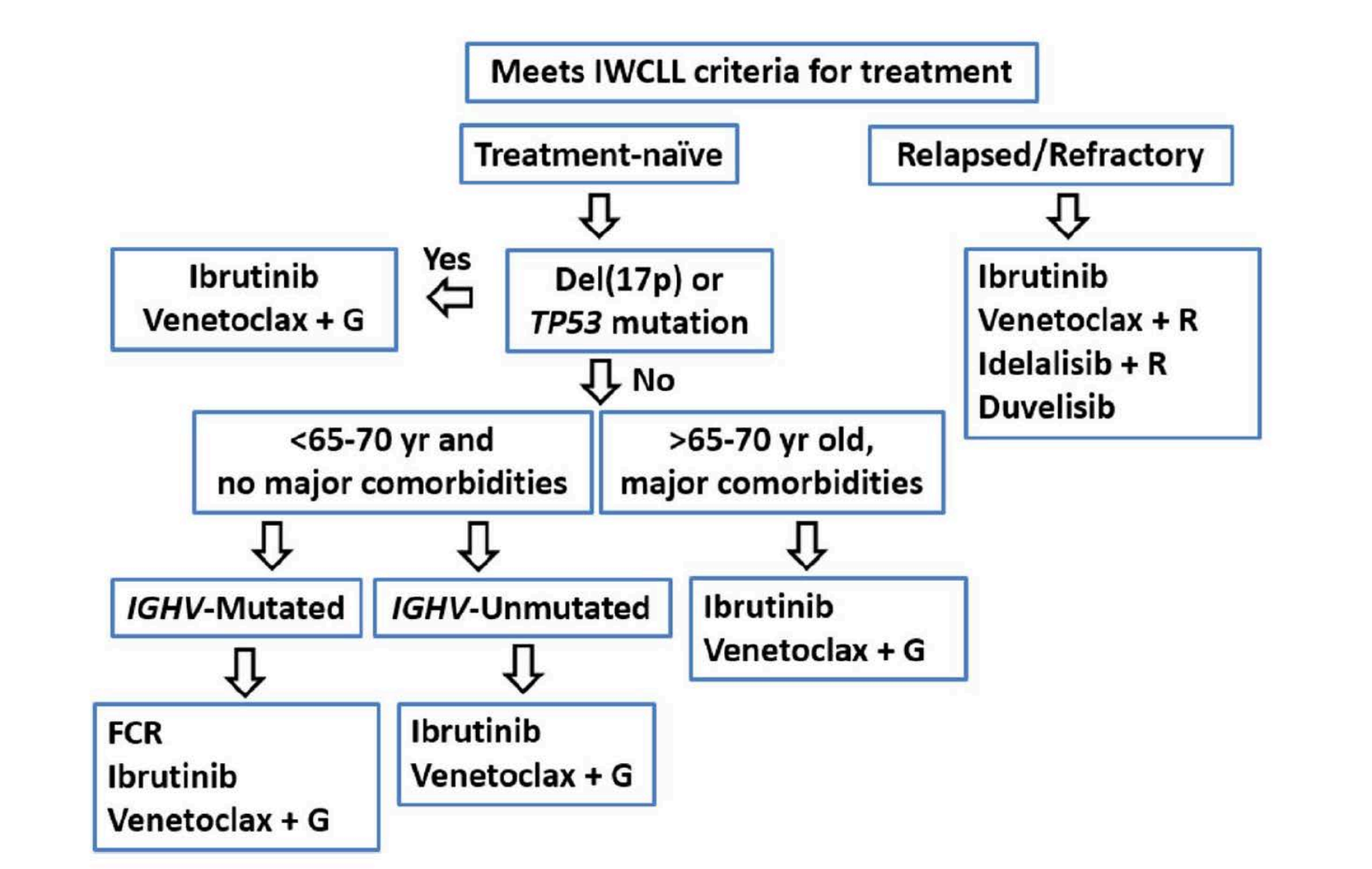
# Recommended Treatment of CLL




Jain N and O'Brien S. *Cancer J* 2020;25(6):374-77.

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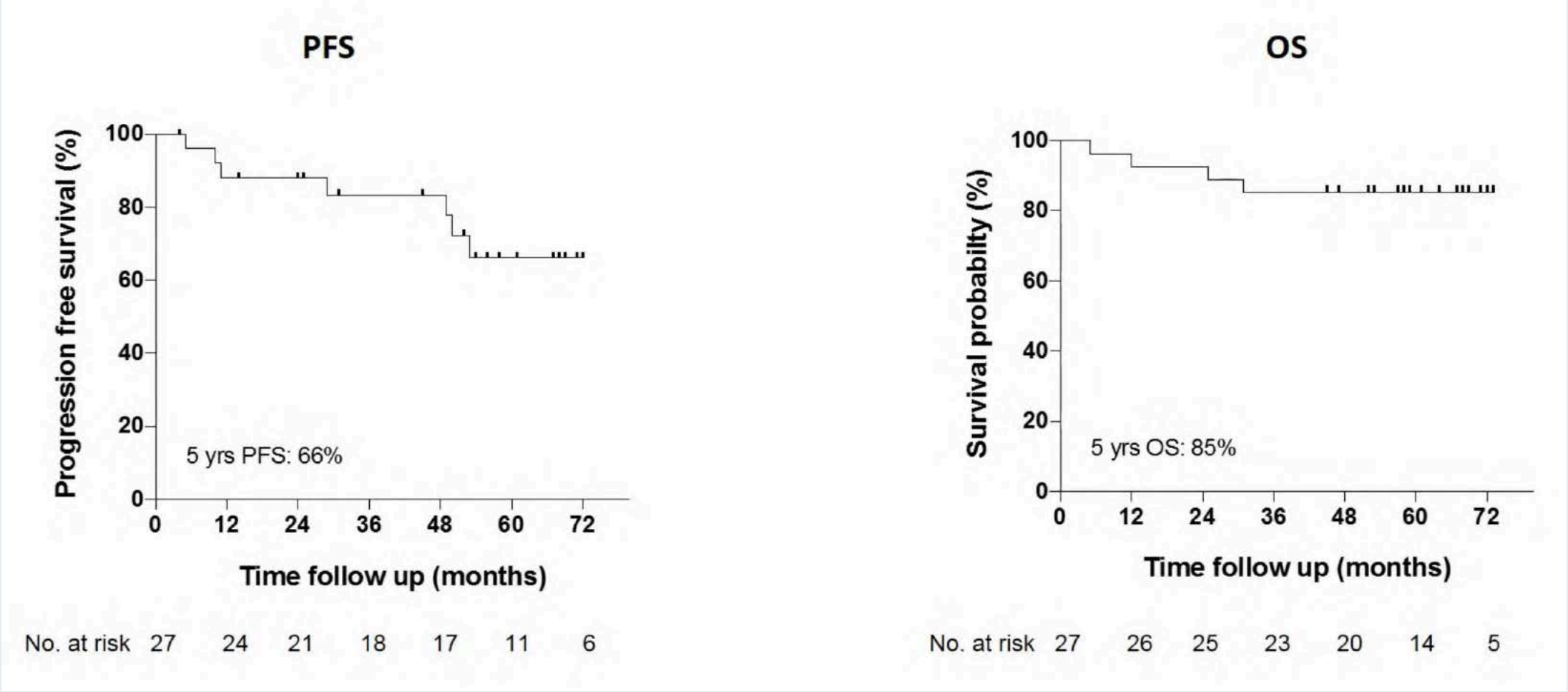
# Ibrutinib Induces Durable Remissions in Treatment-Naïve CLL Patients with 17p Deletion/TP53 Mutations: Five Year Follow-Up from a Phase 2 Study

Burger J et al.

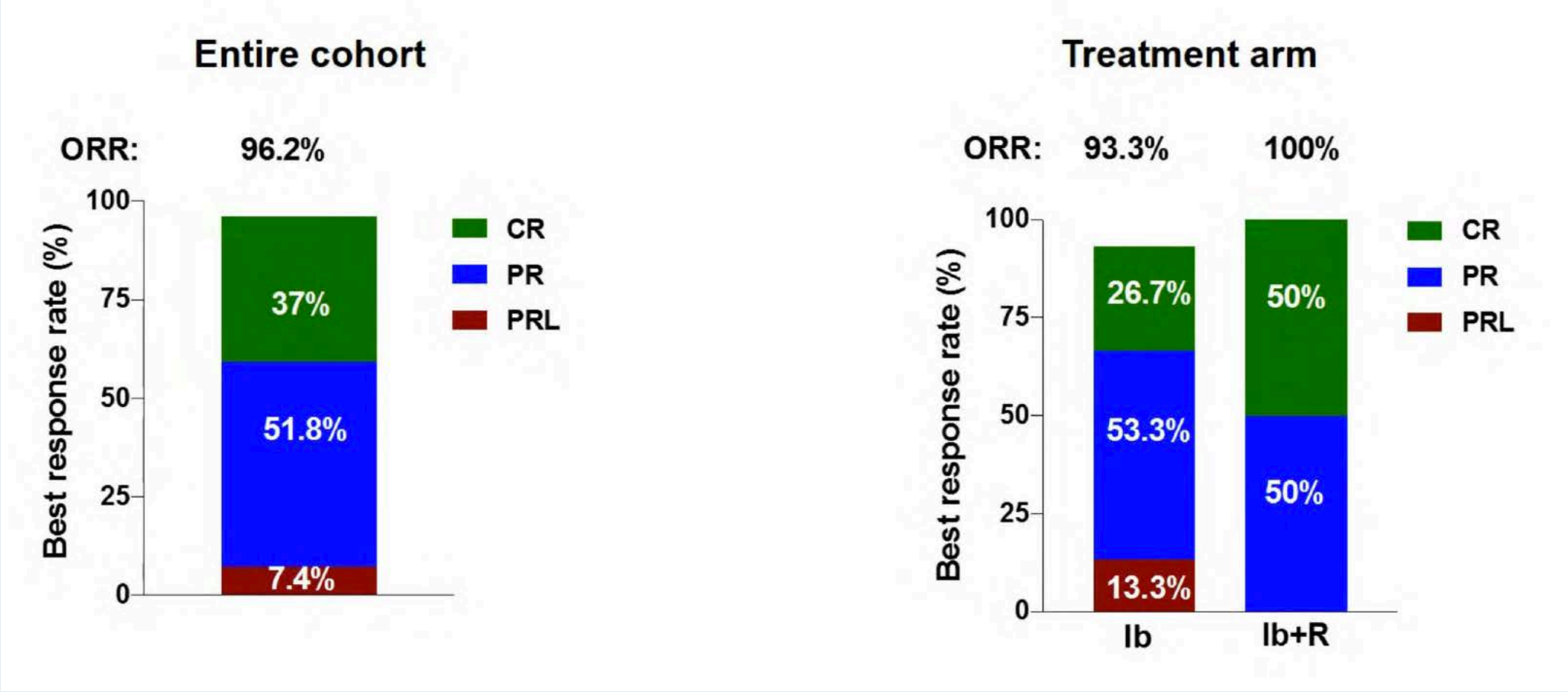
ASH 2020;Abstract 2218.

# Five-Year Follow-Up with Ibrutinib: PFS and OS



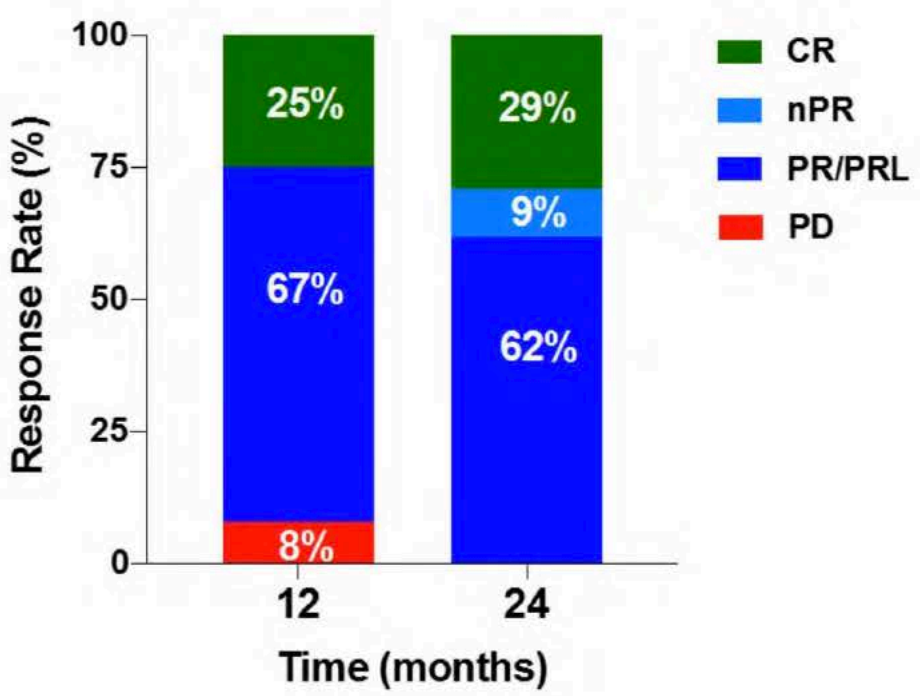

Burger J et al. *ASH* 2020;Abstract 2218.

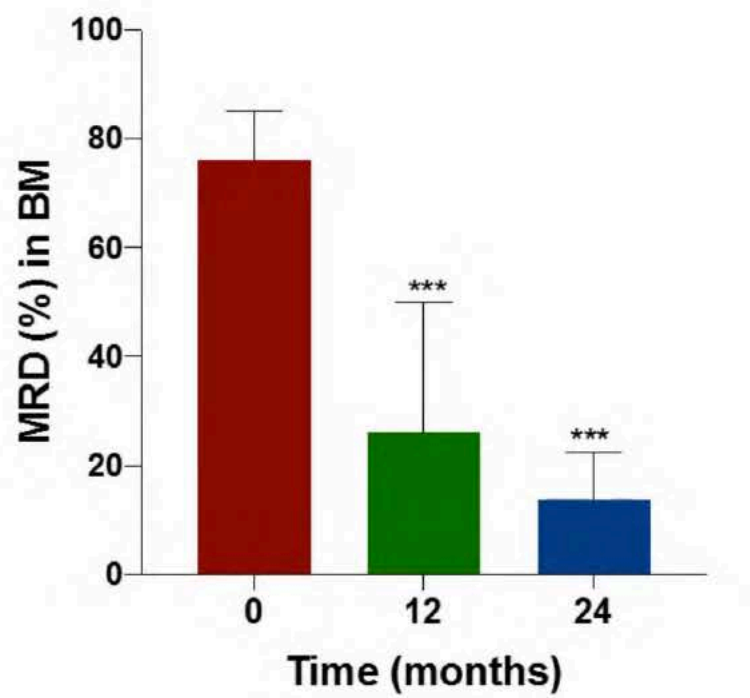
# Five-Year Follow-Up with Ibrutinib: Best Response to Treatment




Burger J et al. *ASH* 2020;Abstract 2218.

# Five-Year Follow-Up with Ibrutinib: Response Rate and MRD in the Bone Marrow

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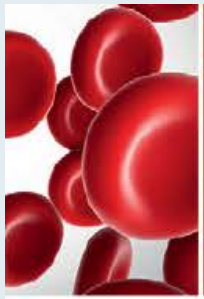

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Plenary Paper

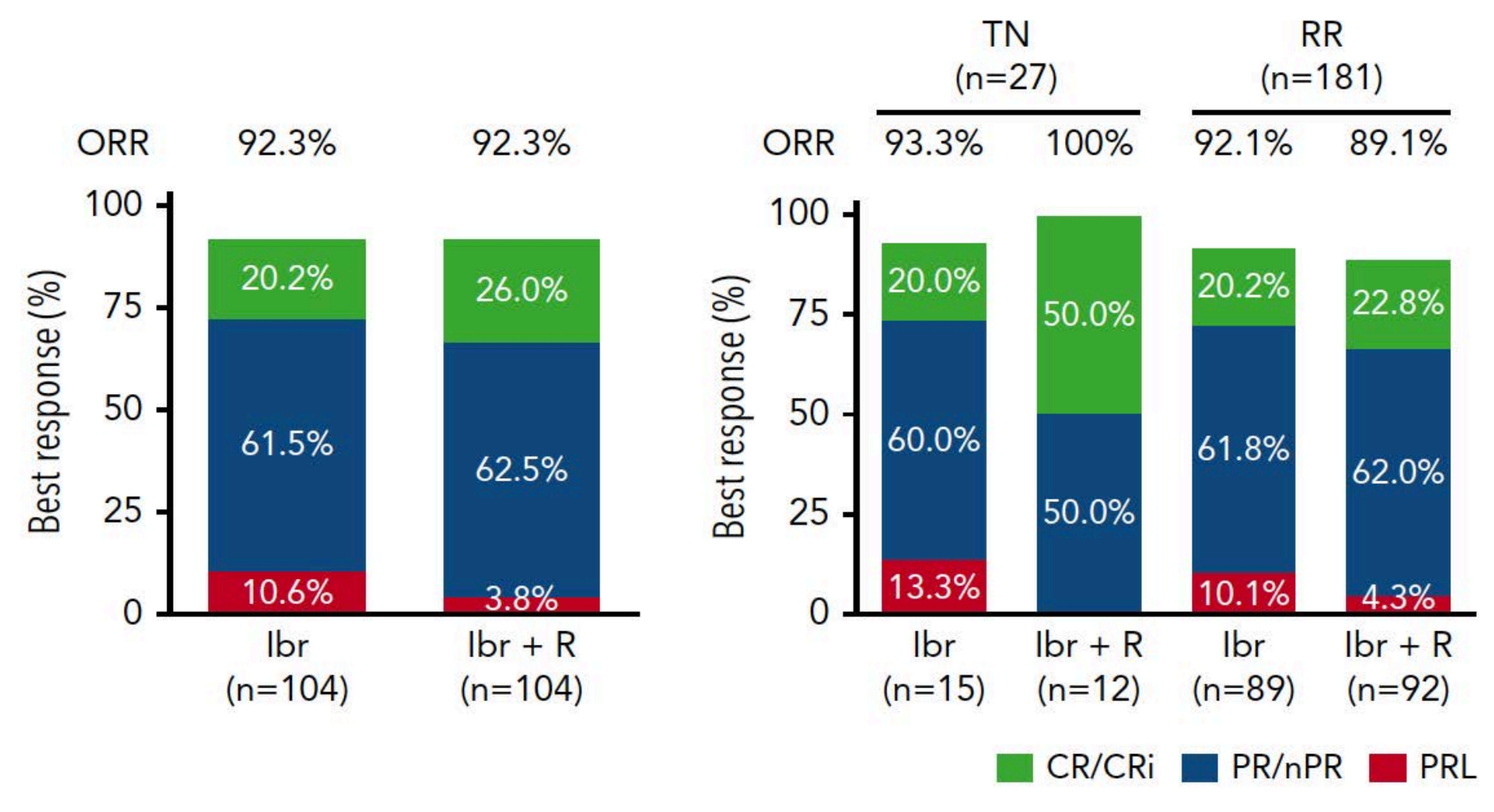
CLINICAL TRIALS AND OBSERVATIONS

# Randomized trial of ibrutinib vs ibrutinib plus rituximab in patients with chronic lymphocytic leukemia

Jan A. Burger,[1] Mariela Sivina,[1] Nitin Jain,[1] Ekaterina Kim,[1] Tapan Kadia,[1] Zeev Estrov,[1] Graciela M. Nogueras-Gonzalez,[2] Xuelin Huang,[2] Jeffrey Jorgensen,[3] Jianling Li,[4] Mei Cheng,[4] Fong Clow,[4] Maro Ohanian,[1] Michael Andreeff,[1] Thomas Mathew,[1] Philip Thompson,[1] Hagop Kantarjian,[1] Susan O'Brien,[5] William G. Wierda,[1,*] Alessandra Ferrajoli,[1,*] and Michael J. Keating[1,*]

*Blood* 2019;133(10):1011-9.

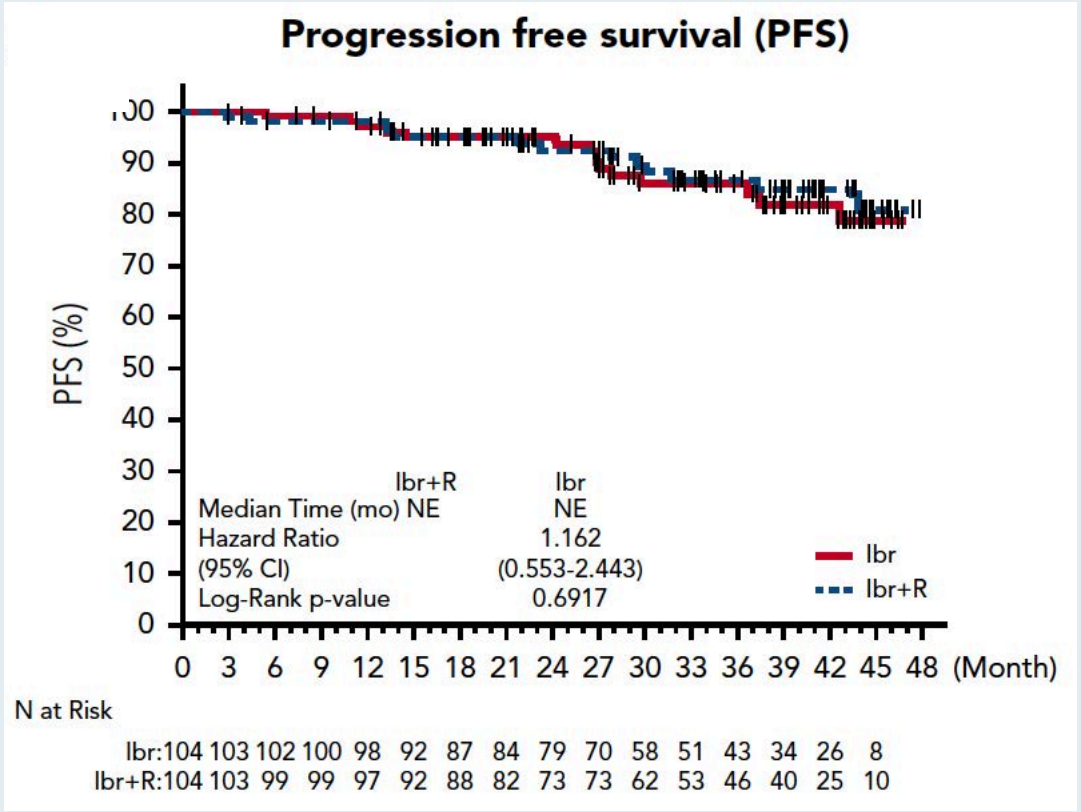
# Best Response to Treatment

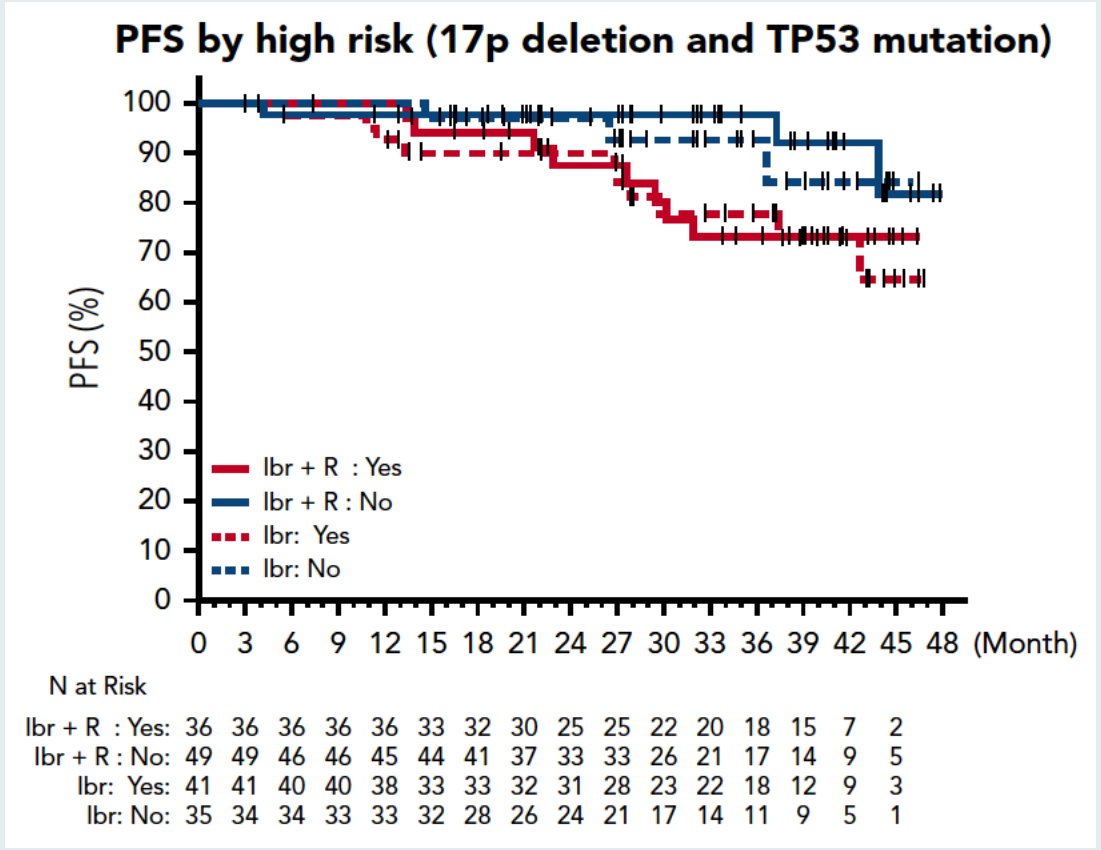



TN, treatment-naïve; RR, relapsed/refractory

Burger J et al. *Blood* 2019;133(10):1011-19.

# PFS in Overall and High-Risk Patient Groups




Burger J et al. *Blood* 2019;133(10):1011-19.

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# Long-Term Effects of Ibrutinib on Blood Pressure in Patients with Chronic Lymphocytic Leukemia (CLL)

Jones J et al.

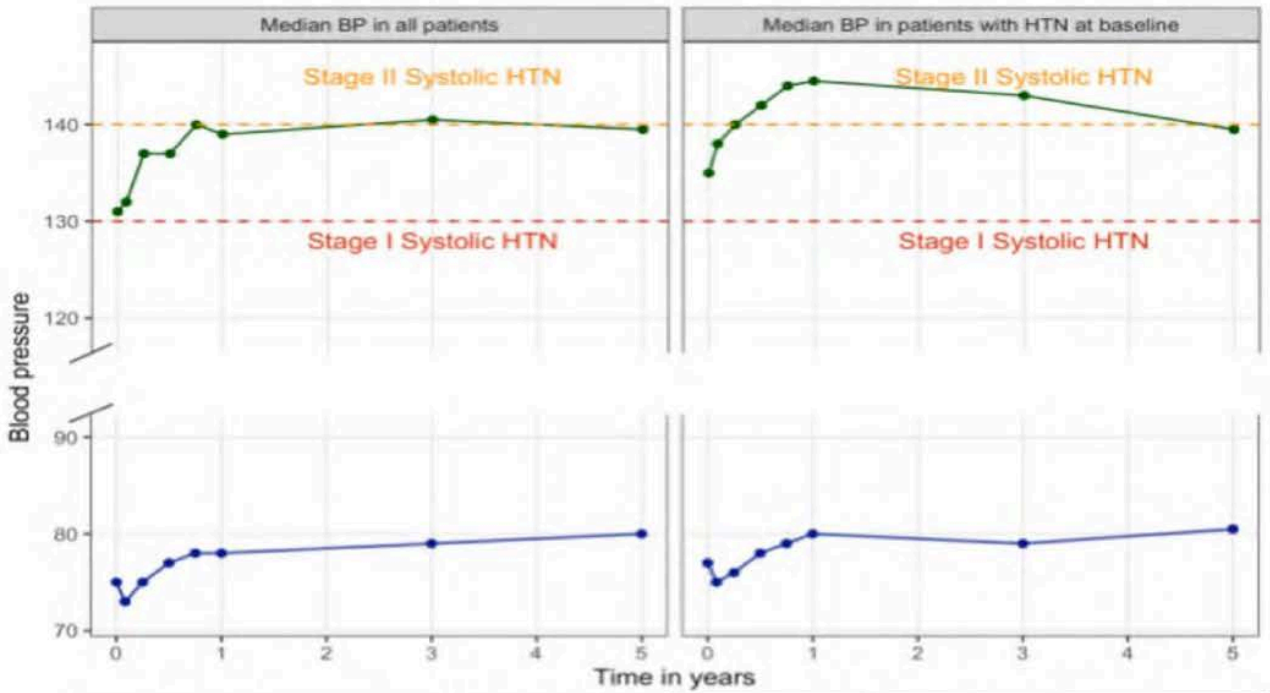
ASCO 2019;Abstract e19009.

# Hypertension, Cardiovascular and Renal Complications Observed in Patients with Chronic Lymphocytic Leukemia Receiving Long-Term Therapy with Ibrutinib

Jones J et al.

ASH 2020;Abstract 1321.

# Changes in Systolic and Diastolic Blood Pressure with Ibrutinib




| Median SBP | Baseline | 5 year |
|---|---|---|
| No HTN at baseline | 118 mmHg | 138 mmHg |
| HTN at baseline | 141 mmHg | 145 mmHg |

| Median DBP | Baseline | 5 year |
|---|---|---|
| No HTN at baseline | 70 mmHg | 78.5 mmHg |
| HTN at baseline | 84 mmHg | 82 mmHg |

- Median follow-up was 3 years.
- New HTN developed in 71% of patients without prior diagnosis of HTN.
- Worsening HTN developed in 56% of patients who had HTN at baseline
- Mean increase in systolic BP: 8.15 (95% CI: 5.9 – 10.4)
- Mean increase in diastolic BP: 3.2 (95% CI: 2.0 – 4.4)
- 37% of patients with new or worsening HTN were started on antihypertensive therapy or received additional antihypertensive therapy.

Jones J et al. *ASH* 2020;Abstract 1321.

# Incidence of Cardiovascular and Renal Complications with Ibrutinib

| | Rate in pts w/ HTN at baseline (n=207) | Rate in pts w/o HTN at baseline (n=94) | P-value |
|---|---|---|---|
| New or worsening CKD | 16.9% | 8.5% | 0.07 |
| New or worsening CHF | 3.9% | 1.1% | 0.28 |
| New or worsening AFIB | 19.4% | 12.8% | 0.19 |
| Brain hemorrhage | 1.0% | 6.4% | 0.01 |
| Stroke/TIA | 4.8% | 0.0% | 0.03 |
| New or worsening CAD | 9.2% | 5.3% | 0.36 |

Jones J et al. *ASH* 2020;Abstract 1321.

# Conclusions

- An increase in BP is common in patients with CLL being treated with ibrutinib.
- HTN occurred early on treatment and independently of most other known common risk factors for HTN.
- Cardiovascular and renal complications of chronic HTN were observed and were more common in patients with HTN at baseline.
- Only 37% of patients in our study received new or additional medications to control HTN, which may account for the persistent elevations.
- Patients with CLL on treatment with ibrutinib need close BP monitoring and optimal HTN management

Jones J et al. *ASH* 2020;Abstract 1321.

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Letter to *Blood*

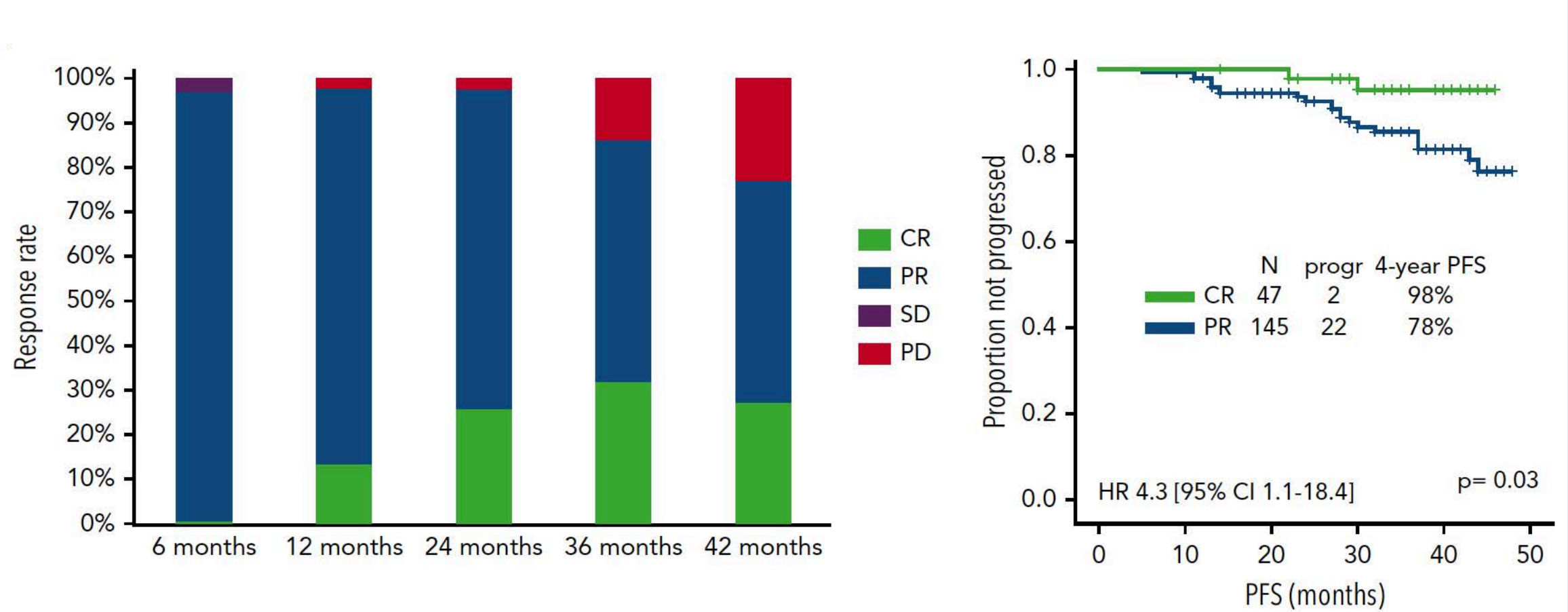
**TO THE EDITOR:**

# Achieving complete remission in CLL patients treated with ibrutinib: clinical significance and predictive factors

Paolo Strati,[1] Ellen J. Schlette,[2] Luisa M. Solis Soto,[3] Daniela E. Duenas,[3] Mariela Sivina,[4] Ekaterina Kim,[4] Michael J. Keating,[4] William G. Wierda,[4] Alessandra Ferrajoli,[4] Hagop Kantarjian,[4] Zeev Estrov,[4] Nitin Jain,[4] Philip A. Thompson,[4] Ignacio I. Wistuba,[3] and Jan A. Burger[4]

***Blood* 2020;135(7):510-13.**

# Response Rate and PFS with Ibrutinib by Quality of Response




Burger J et al. *Blood* 2020;135(7):510-13.

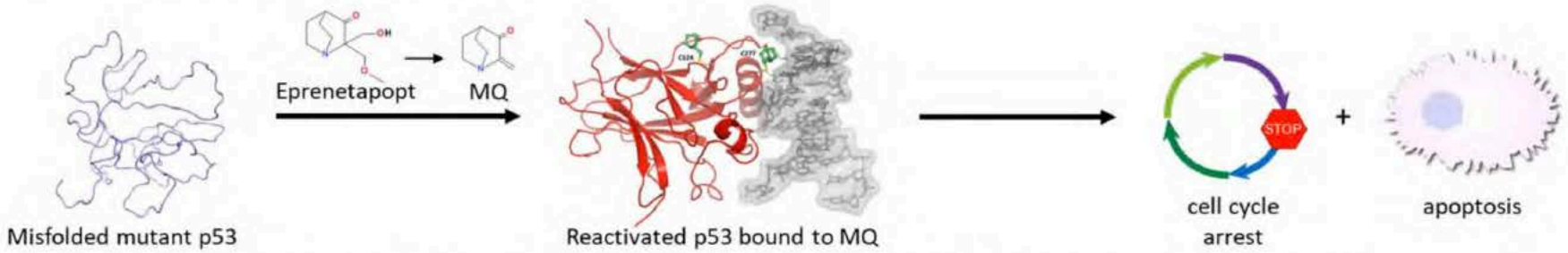
# Phase 1 and Dose Expansion Study of APR-246 in Combination with Ibrutinib or Venetoclax-Based Therapy in Subjects with TP53-Mutant Relapsed and/or Refractory Non-Hodgkin Lymphomas (NHL) Including Chronic Lymphocytic Leukemia (CLL) and Mantle Cell Lymphoma (MCL)

Thompson M et al.

ASH 2020;Abstract 1311.

# Background: Eprenetapopt

- **Eprenetapopt (APR-246)**: first in class small molecule that binds and reactivates mutant p53 to restore wildtype p53 function



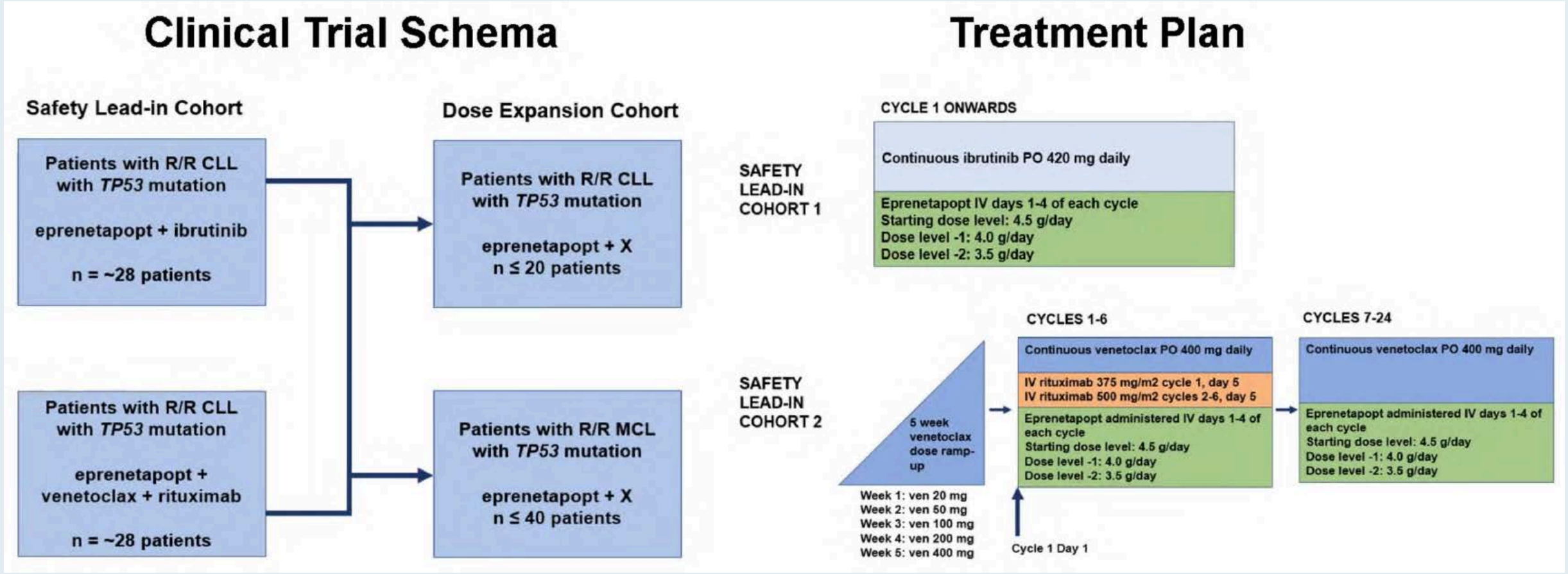

- **Preclinical activity in CLL:** induces apoptosis in *TP53* mutated CLL cells
- **Clinical activity:**
  - Two independent trials evaluating eprenetapopt + azacitidine in myeloid malignancies
    - 75-88% ORR and 57-61% CR in *TP53* mutant MDS
    - 82-88% ORR and 27-50% CR in *TP53* mutant AML
  - Ongoing phase I trial of eprenetapopt in combination with venetoclax and azacitadine in AML (NCT04214860); no DLTs reported in safety cohorts
  - Single agent activity in advanced CLL observed in the eprenetapopt first-in-human clinical trials

Zhang et al *Cell Death Disease* 2018; Liu et al *Nat Commun* 2017; Sallman et al ASH 2019; Cluzeau et al EHA 2020; Lehmann S et al *JCO* 2012; Deneberg S et al *Blood Canc J* 2016; Jaskova et al *Leuk Res* 2020

Thompson M et al. *ASH* 2020;Abstract 1311.

RTP RESEARCH TO PRACTICE

# Study Design and Treatment Plan



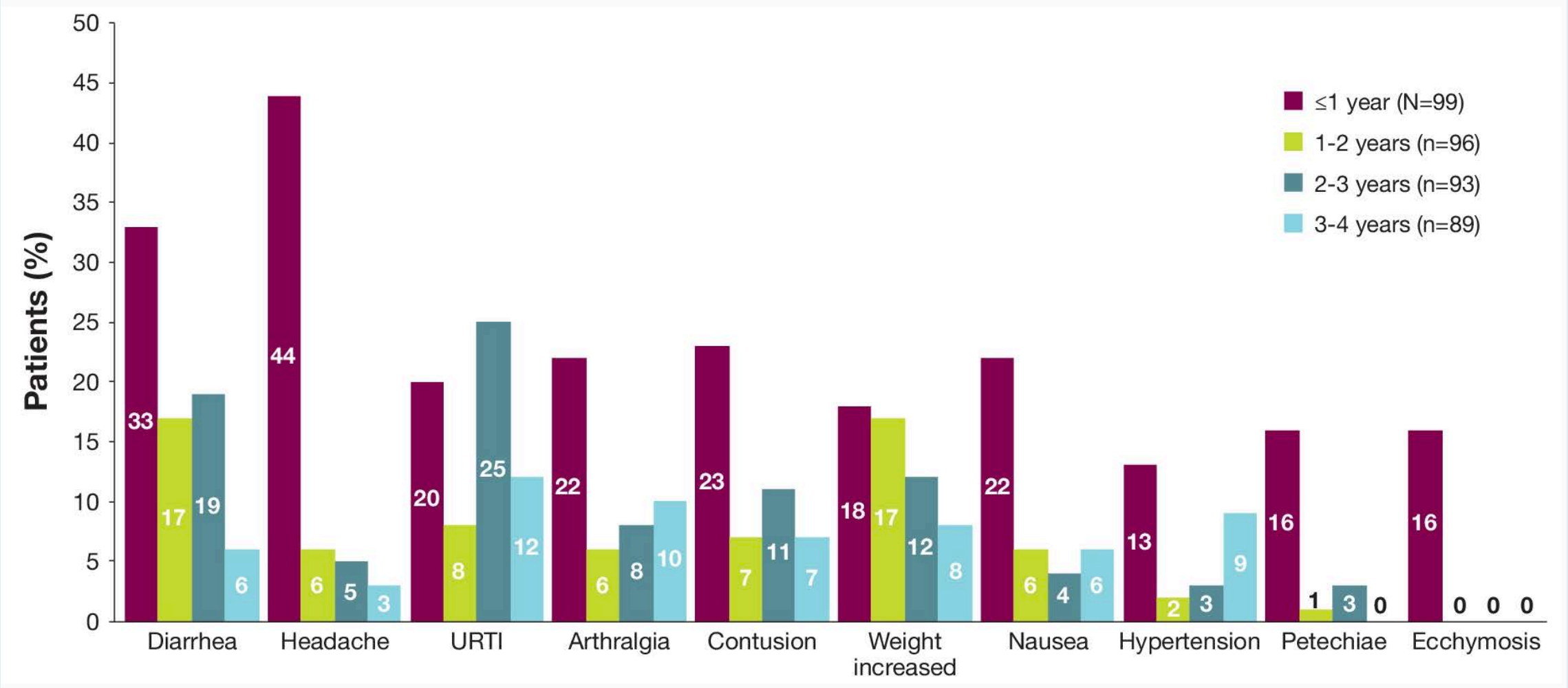

Thompson M et al. *ASH* 2020;Abstract 1311.

# Acalabrutinib in Treatment-Naïve Chronic Lymphocytic Leukemia: Mature Results from Phase II Study Demonstrating Durable Remissions and Long-Term Tolerability

Byrd JC et al.

ASCO 2020;Abstract 8024.

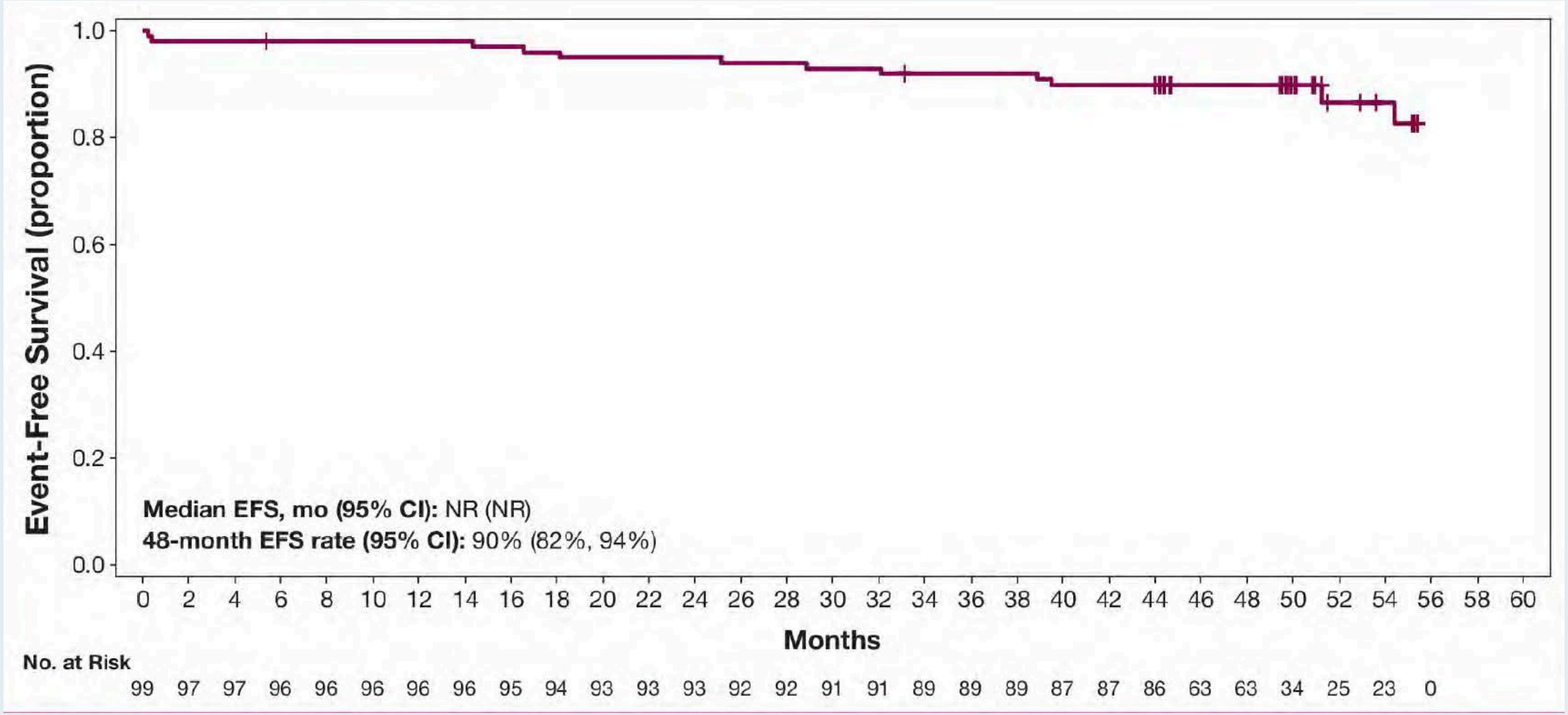
# Incidence of Select TEAEs Associated with Acalabrutinib by Yearly Intervals




Byrd JC et al. *ASCO* 2020;Abstract 8024.

RTP RESEARCH TO PRACTICE

# Event-Free Survival with Acalabrutinib




Byrd JC et al. *ASCO* 2020;Abstract 8024.

RTP RESEARCH TO PRACTICE

# Combined Ibrutinib and Venetoclax for First-Line Treatment for Patients with Chronic Lymphocytic Leukemia (CLL): Focus on MRD Results

Jain N et al.

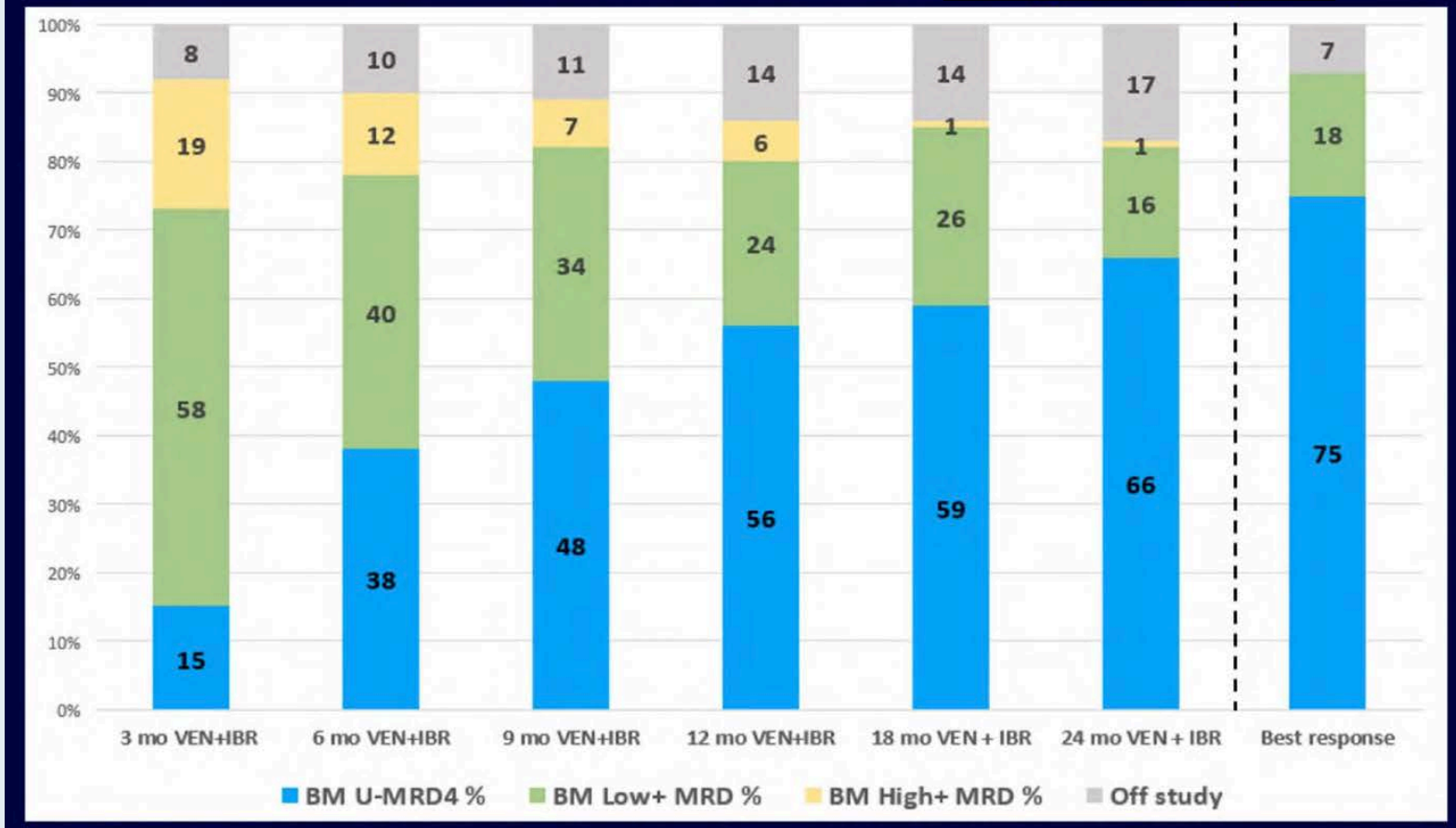
ASH 2020;Abstract 3138.

# Ibrutinib with Venetoclax Trial Description

- **Investigator-initiated phase II trial**
- **Patients with treatment-naïve CLL/SLL with at least one of the following features:**
  - **Del(17p) or mutated TP53**
  - **Del(11q)**
  - **Unmutated IGHV**
  - **Age ≥65 years**

Jain N et al. *ASH* 2020;Abstract 3138.

# Marrow MRD Response at Serial Time Points
# Intent-to-Treat (N = 80)




MRD assessed by flow-cytometry in bone marrow with sensitivity $10^{-4}$

U-MRD4: <0.01%
Low MRD: 0.01% to <1%
High MRD: ≥1%

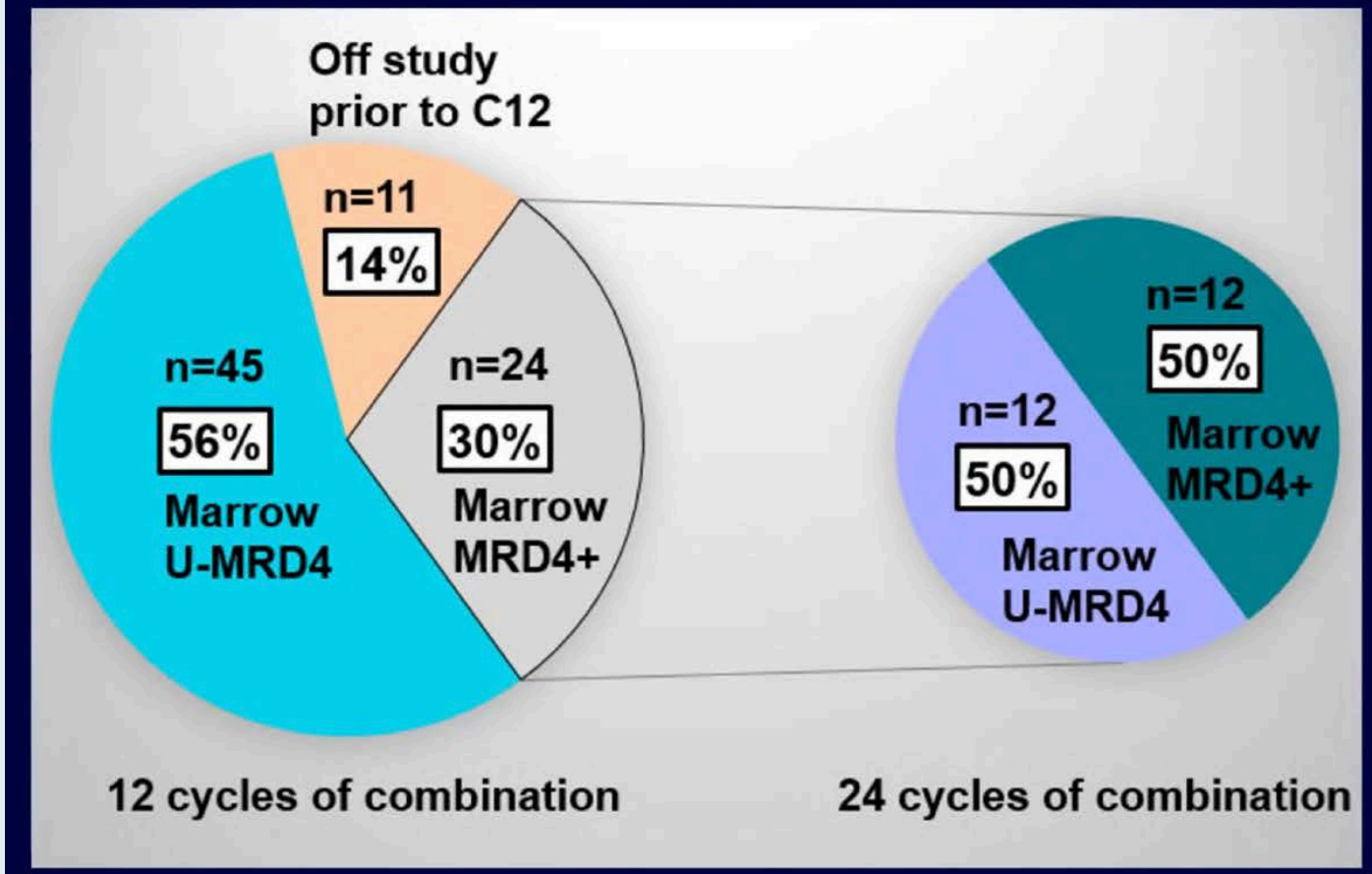
Marrow U-MRD4 % (ITT)
At 12 months = 56%
At 24 months = 66%
Best response = 75%

This figure shows all 80 pts, including 5 pts who came off study during the IBR monotherapy phase (never started VEN)

None of the pretreatment characteristics (age, gender, ALC, HGB, PLT, FISH abnormalities, *IGHV* status, CD38, ZAP-70, *TP53*-m, *NOTCH1*-m, *SF3B1*-m) were statistically associated with achievement of BM U-MRD at C6, C12, C24, or U-MRD at any time

Jain N et al. *ASH* 2020;Abstract 3138.

# 50% of Marrow MRD+ Response at Cycle 12 Achieved Marrow U-MRD at Cycle 24 with Ongoing VEN + IBR




At end of C12, 24 pts were BM MRD+ (19 low MRD+; 5 high MRD+)

12/24 (50%) achieved BM U-MRD at end of cycle 24

- low MRD+ 10/19 (53%)
- high MRD+ 2/5 (40%)

Based on this data, the trial is now amended to allow 12 additional cycles of combo therapy for those marrow MRD+ at C24

Jain N et al. *ASH* 2020;Abstract 3138.

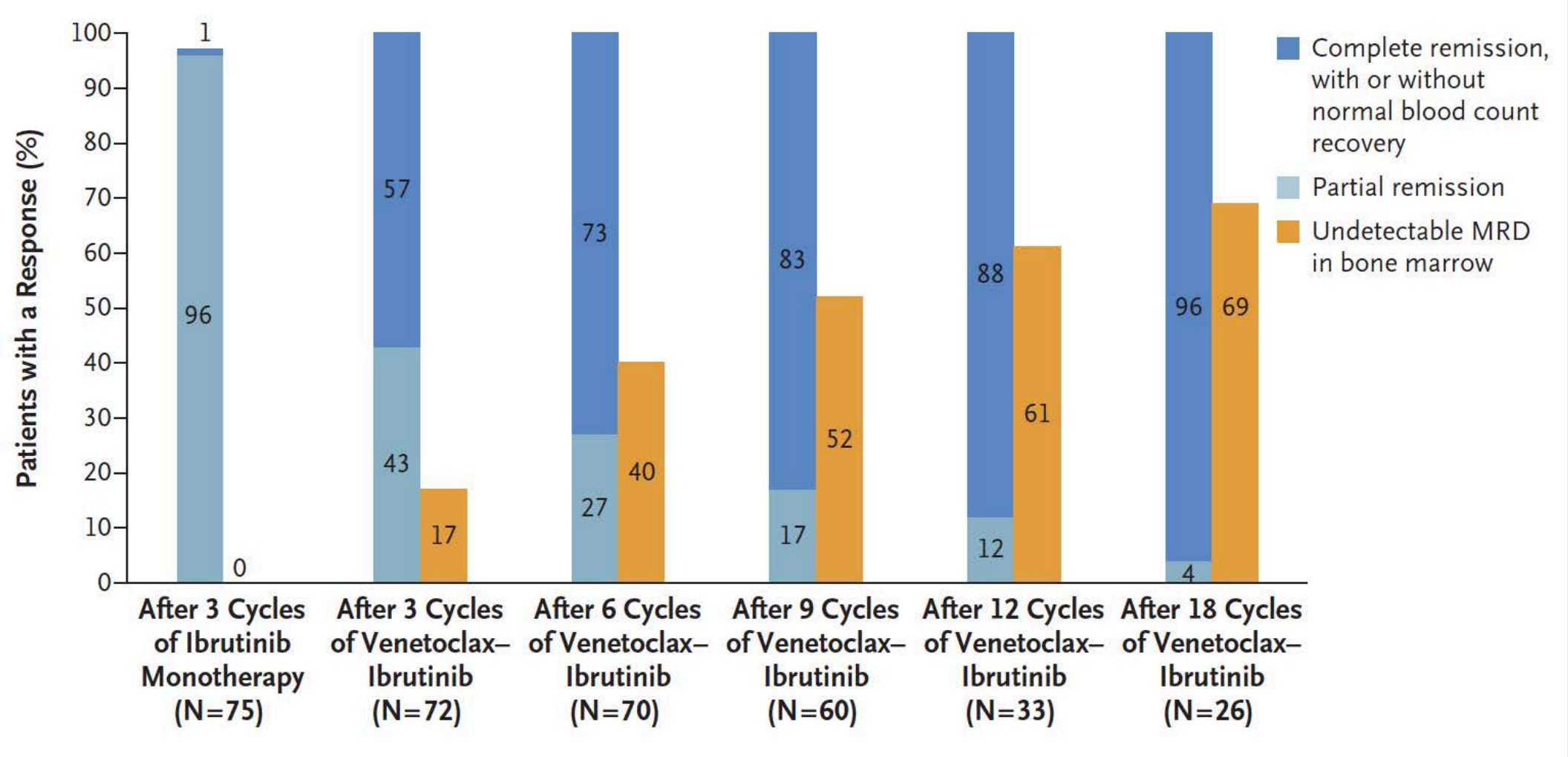
The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MAY 30, 2019 VOL. 380 NO. 22

# Ibrutinib and Venetoclax for First-Line Treatment of CLL

Nitin Jain, M.D., Michael Keating, M.D., Philip Thompson, M.D., Alessandra Ferrajoli, M.D., Jan Burger, M.D., Ph.D., Gautam Borthakur, M.D., Koichi Takahashi, M.D., Zeev Estrov, M.D., Nathan Fowler, M.D., Tapan Kadia, M.D., Marina Konopleva, M.D., Ph.D., Yesid Alvarado, M.D., Musa Yilmaz, M.D., Courtney DiNardo, M.D., Prithviraj Bose, M.D., Maro Ohanian, D.O., Naveen Pemmaraju, M.D., Elias Jabbour, M.D., Koji Sasaki, M.D., Rashmi Kanagal-Shamanna, M.D., Keyur Patel, M.D., Ph.D., Jeffrey Jorgensen, M.D., Ph.D., Naveen Garg, M.D., Xuemei Wang, M.S., Katrina Sondermann, B.A., Nichole Cruz, R.N., Chongjuan Wei, Ph.D., Ana Ayala, R.N., William Plunkett, Ph.D., Hagop Kantarjian, M.D., Varsha Gandhi, Ph.D., and William Wierda, M.D., Ph.D.

# First-Line Ibrutinib with Venetoclax: Response to Treatment




Jain N et al. *N Engl J Med* 2019;380(22):2095-2103.

RTP RESEARCH TO PRACTICE

# First-Line Ibrutinib with Venetoclax: Nonhematologic Adverse Events

| Event | Any Grade | Grade 3 or Higher |
|---|---|---|
| | *no. of patients (%)* | |
| Easy bruising | 48 (60) | 0 |
| Arthralgia | 38 (48) | 1 (1) |
| Diarrhea | 33 (41) | 1 (1) |
| Nausea or vomiting | 29 (36) | 0 |
| Myalgia | 22 (28) | 1 (1) |
| Rash | 19 (24) | 0 |
| Nail changes | 13 (16) | 0 |
| Atrial fibrillation or flutter | 12 (15) | 8 (10) |
| Oral mucositis | 12 (15) | 0 |
| Hypertension | 11 (14) | 8 (10) |
| Fatigue | 11 (14) | 1 (1) |
| Dry skin | 9 (11) | 0 |
| Gastroesophageal reflux disease | 8 (10) | 0 |
| Constipation | 7 (9) | 0 |
| Headache | 6 (8) | 0 |
| Increased creatinine level | 6 (8) | 0 |
| Epistaxis | 5 (6) | 0 |
| Increased aminotransferase level | 5 (6) | 1 (1) |

Jain N et al. *N Engl J Med* 2019;380(22):2095-2103.

# The Addition of Venetoclax to Ibrutinib Achieves a High Rate of Undetectable Minimal Residual Disease in Patients with High-Risk CLL

Thompson P et al.

ASH 2020;Abstract 2222.

# Conclusions

- Venetoclax added to ibrutinib achieves a 64% rate of U-MRD4 in bone marrow after 12 months of combination therapy.
- No case of disease progression seen (although one case of MRD re-emergence during ibrutinib monotherapy was seen).
- The regimen was well-tolerated.
- Important future questions include:

1. Durability of unmaintained remission.
2. Response to re-treatment.
3. Role of MRD-directed maintenance therapy.

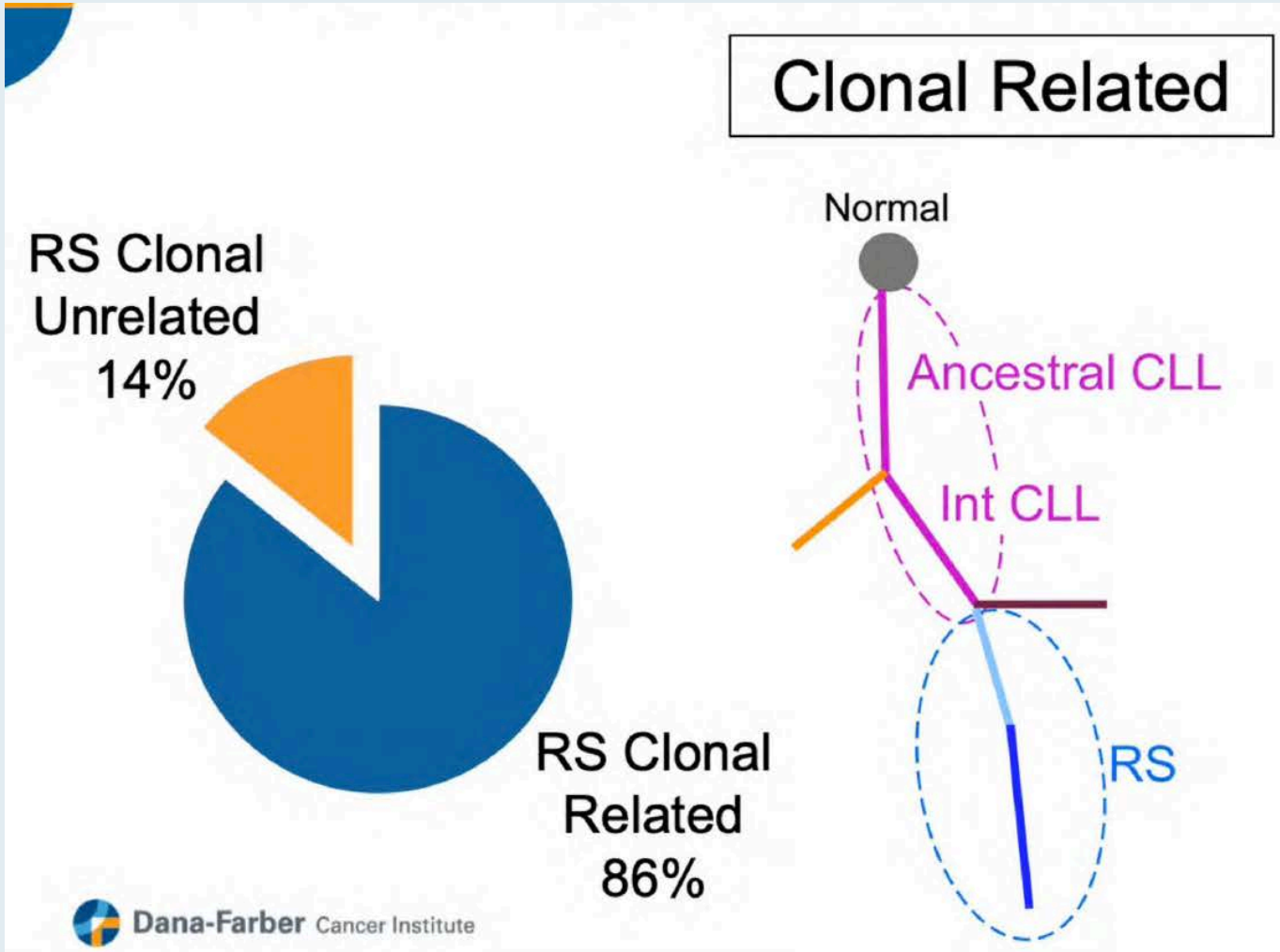
Thompson P et al. *ASH* 2020;Abstract 2222.

# Genetic Determinants and Evolutionary History of Richter's Syndrome

Parry EM et al.

ASH 2020;Abstract 1297.

# The Majority of Richter's Syndrome Cases Are Clonally Related to CLL




- RS clones displayed additional mutations compared to related CLL clones
  - 2.47 v. 0.86 Mut/Mb
- Mutational signatures
  - cAID, ncAID, aging (CpG)

Mukherjee A et al. *ASH* 2020; Abstract 1297.

Leukemia Research 98 (2020) 106445

Contents lists available at ScienceDirect

Leukemia Research

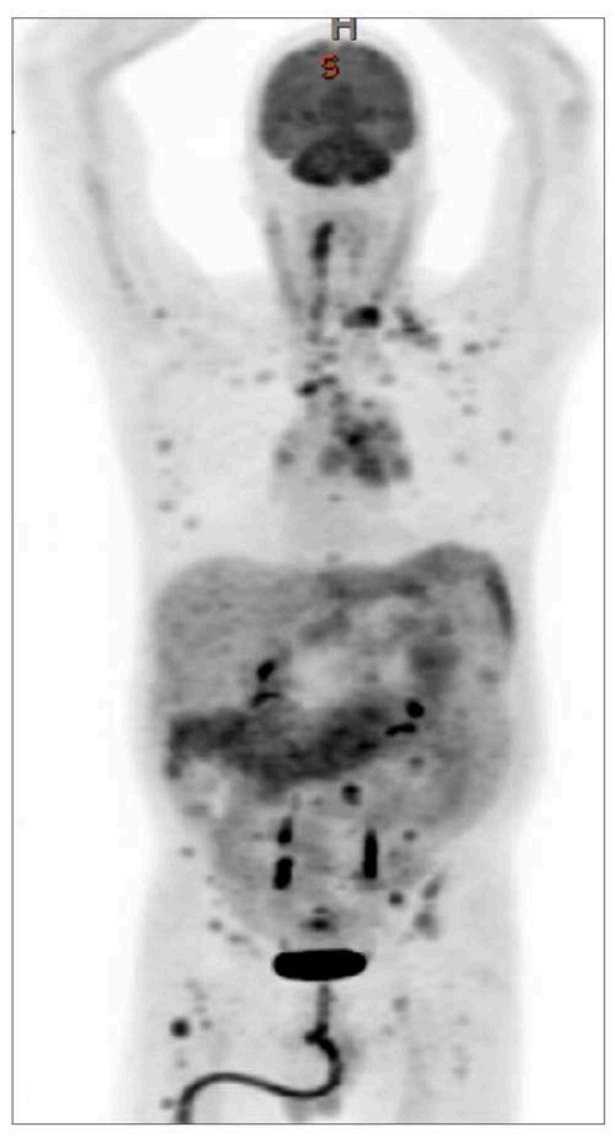
journal homepage: www.elsevier.com/locate/leukres

Correspondence

# Metastatic lung adenocarcinoma mimicking Richter transformation in a patient with chronic lymphocytic leukemia

Cherng H-J et al. *Leuk Res* 2020;98:106445.

# PET Scan: Lymphadenopathy, Splenomegaly, Omental Caking and Osseous Lesions




Cherng H-J et al. *Leuk Res* 2020;98:106445.

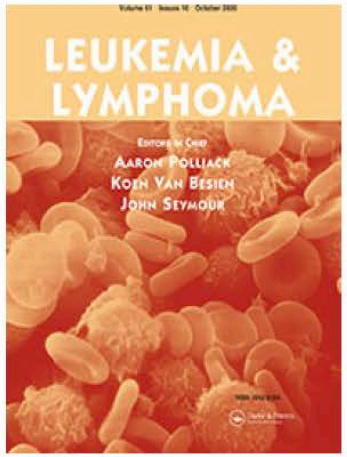
STIMULUS REPORT

blood advances

# Incidental Richter transformation in chronic lymphocytic leukemia patients during temporary interruption of ibrutinib

Paul J. Hampel,[1,*] Hua-Jay J. Cherng,[2,*] Timothy G. Call,[1] Wei Ding,[1] Mahsa Khanlari,[3] Ellen D. McPhail,[4] Roberto N. Miranda,[3] Pei Lin,[3] Hussein A. Tawbi,[5] Alessandra Ferrajoli,[2] William G. Wierda,[2] Nitin Jain,[2] and Sameer A. Parikh[1]

*Blood Adv* 2020;4(18):4508-11.

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Leukemia & Lymphoma

ISSN: 1042-8194 (Print) 1029-2403 (Online) Journal homepage: https://www.tandfonline.com/loi/ilal20

# Incidence and characterization of fungal infections in chronic lymphocytic leukemia patients receiving ibrutinib

Michael Frei, Samuel L. Aitken, Nitin Jain, Philip Thompson, William Wierda, Dimitrios P. Kontoyiannis & Adam J. DiPippo

*Leuk Lymphoma* 2020;61(10):2488-91.

# Occurrence of Other Cancers in Patients with Chronic Lymphocytic Leukemia and Mutations in Protection of Telomeres 1 (POT1) Gene

Molica M et al.

ASCO 2019;Abstract 7529.

# Other Cancers in 52 Patients with CLL and POT1 Mutations

| | Type of Neoplasm | N |
|---|---|---|
| OC before CLL diagnosis (12/23% pts) | Kidney | 3 |
| | Melanoma | 2 |
| | Thyroid | 2 |
| | Prostate | 2 |
| | Head and Neck | 1 |
| | Non-Hodgkin Lymphoma (DLBCL) | 1 |
| | Breast | 1 |
| OC after CLL diagnosis (7/13% pts) | Prostate | 4 |
| | Melanoma | 3 |
| | Head and Neck | 1 |
| | Kidney | 1 |
| | Pancreatic | 1 |
| | Liver | 1 |

Molica M et al. *ASCO* 2019; Abstract 7529.

# Allogeneic Stem Cell Transplantation (AlloSCT) for Patients (Pts) with Lymphoma and Chronic Lymphocytic Leukemia (CLL) Following Targeted Small Molecules Inhibitors (SMIs)

Mukherjee A et al.

ASCO 2019;Abstract 7550.

Review

Acta Haematologica

Acta Haematol
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Accepted: April 26, 2020
Published online: May 11, 2020

# Treating Leukemia in the Time of COVID-19

Shilpa Paul[a] Caitlin R. Rausch[a] Nitin Jain[b] Tapan Kadia[b] Farhad Ravandi[b]
Courtney D. DiNardo[b] Mary Alma Welch[b] Bouthaina S. Dabaja[c] Naval Daver[b]
Guillermo Garcia-Manero[b] William Wierda[b] Naveen Pemmaraju[b]
Guillermo Montalban Bravo[b] Philip Thompson[b] Srdan Verstovsek[b]
Marina Konopleva[b] Hagop Kantarjian[b] Elias Jabbour[b]

*Acta Haematol* 2020;[Online ahead of print].

# Leukemia-Specific Risk Factors for COVID-19

| | Risk Factor |
|---|---|
| CLL | Hypogammaglobulinemia |
| | Impaired B-cell function due to CD20-targeted monoclonal antibodies |
| | Impaired innate immune response as well as B-cell and T-cell function with BTK inhibitors |

Paul S et al. *Acta Haematol* 2020 May:1-13. Epub ahead of print.

# Treatment Alternatives for Patients with Leukemia During COVID-19 High-Risk Periods

| Leukemia Scenario | Treatment Recommendations |
|---|---|
| CLL Initiation<br>Not Meeting IWCLL Criteria | Watch and wait |
| CLL Initiation<br>Meeting IWCLL Criteria | Avoid FCR |
| | Consider ibrutinib or acalabrutinib weighing benefit versus risk |
| | Consider obinutuzumab + venetoclax, but may require additional clinic visits or hospitalization for tumor lysis syndrome monitoring and can cause neutropenia |
| CLL Continuation | If on FCR, consider switching or oral targeted therapy if feasible |
| | If on venetoclax, maintain therapy if tolerating |
| | If on ibrutinib or acalabrutinib, maintain therapy if tolerating; abrupt discontinuation may cause disease flare |

Paul S et al. *Acta Haematol* 2020 May:1-13. Epub ahead of print.

RTP RESEARCH TO PRACTICE

# Meet The Professor with Dr Jain

**MODULE 1: Cases from Dr Zafar**

**MODULE 2: CLL Journal Club with Dr Jain**

- Shifting paradigm in CLL: Is chemotherapy still relevant?
- Durable remissions with up-front ibrutinib in patients with CLL and del(17p)
- Ibrutinib versus ibrutinib with rituximab for CLL
- Cardiovascular and renal effects associated with ibrutinib
- Clinical significance of and predictive factors in achieving complete remission with ibrutinib in patients with CLL
- Phase I trial of eprenetapopt with ibrutinib or venetoclax-based therapy for relapsed/refractory CLL with TP53 mutation
- Mature results of a Phase II trial of acalabrutinib for treatment-naïve CLL
- Ibrutinib combined with venetoclax as initial therapy for CLL; MRD analyses
- Genetic determinants and evolutionary history of Richter's syndrome
- Metastatic lung adenocarcinoma mimicking Richter's transformation in a patient with CLL
- Incidental Richter's transformation in patients with CLL during interruption of ibrutinib
- Fungal infections in patients with CLL receiving ibrutinib
- Occurrence of other cancers in patients with CLL and mutations in the POT1 gene
- Allogeneic stem cell transplant after small molecule inhibitors in patients with CLL and lymphomas
- Treating leukemia in the time of COVID-19

**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 |
|  PROF JOHN G GRIBBEN, MD, DSC, FMEDSCI | FCR |
|  BRIAN T HILL, MD, PHD | Venetoclax + obinutuzumab or BR |
|  NITIN JAIN, MD | Venetoclax + obinutuzumab |
|  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 |
|  PROF JOHN G GRIBBEN, MD, DSC, FMEDSCI | Venetoclax + obinutuzumab |
|  BRIAN T HILL, MD, PHD | Obinutuzumab |
|  NITIN JAIN, MD | 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 | 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 |
|  IAN W FLINN, MD, PHD | Venetoclax + obinutuzumab |
|  PROF JOHN G GRIBBEN, MD, DSC, FMEDSCI | Ibrutinib |
|  BRIAN T HILL, MD, PHD | Venetoclax + obinutuzumab |
|  NITIN JAIN, MD | Venetoclax + obinutuzumab |
|  BRAD S KAHL, MD | Venetoclax + obinutuzumab |
|  ANTHONY R MATO, MD, MSCE | Venetoclax + obinutuzumab |
|  JOHN M PAGEL, MD, PHD | Acalabrutinib |
|  KERRY A ROGERS, MD | Acalabrutinib or venetoclax + obinutuzumab |
|  JEFF SHARMAN, MD | Acalabrutinib |
|  TANYA SIDDIQI, MD | Venetoclax + obinutuzumab |
|  MITCHELL R SMITH, MD, PHD | Venetoclax + obinutuzumab |
|  WILLIAM G WIERDA, MD, PHD | Venetoclax + obinutuzumab |
|  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 |
|  PROF JOHN G GRIBBEN, MD, DSC, FMEDSCI | Ibrutinib |
|  BRIAN T HILL, MD, PHD | Venetoclax + obinutuzumab |
|  NITIN JAIN, MD | 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 |
|  PROF JOHN G GRIBBEN, MD, DSC, FMEDSCI | Ibrutinib |
|  BRIAN T HILL, MD, PHD | Venetoclax + obinutuzumab |
|  NITIN JAIN, MD | Acalabrutinib |
|  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 |
|  PROF JOHN G GRIBBEN, MD, DSC, FMEDSCI | Ibrutinib |
|  BRIAN T HILL, MD, PHD | Acalabrutinib |
|  NITIN JAIN, MD | Acalabrutinib |
|  BRAD S KAHL, MD | Acalabrutinib + obinutuzumab |
|  ANTHONY R MATO, MD, MSCE | Acalabrutinib |
|  JOHN M PAGEL, MD, PHD | Acalabrutinib |
|  KERRY A ROGERS, MD | Ibrutinib |
|  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 |  JOHN M PAGEL, MD, PHD | Continue treatment |
|  IAN W FLINN, MD, PHD | Discontinue treatment |  KERRY A ROGERS, MD | Discontinue treatment |
|  PROF JOHN G GRIBBEN, MD, DSC, FMEDSCI | Discontinue treatment |  JEFF SHARMAN, MD | Discontinue treatment |
|  BRIAN T HILL, MD, PHD | Discontinue treatment |  TANYA SIDDIQI, MD | Continue treatment |
|  NITIN JAIN, MD | Continue treatment |  MITCHELL R SMITH, MD, PHD | Discontinue treatment |
|  BRAD S KAHL, MD | Discontinue treatment |  WILLIAM G WIERDA, MD, PHD | Continue treatment |
|  ANTHONY R MATO, MD, MSCE | 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 |  JOHN M PAGEL, MD, PHD | Discontinue treatment |
|  IAN W FLINN, MD, PHD | Discontinue treatment |  KERRY A ROGERS, MD | Discontinue treatment |
|  PROF JOHN G GRIBBEN, MD, DSC, FMEDSCI | Discontinue treatment |  JEFF SHARMAN, MD | Discontinue treatment |
|  BRIAN T HILL, MD, PHD | Discontinue treatment |  TANYA SIDDIQI, MD | Discontinue treatment |
|  NITIN JAIN, MD | Discontinue treatment |  MITCHELL R SMITH, MD, PHD | Discontinue treatment |
|  BRAD S KAHL, MD | Discontinue treatment |  WILLIAM G WIERDA, MD, PHD | Discontinue treatment |
|  ANTHONY R MATO, MD, MSCE | 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

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?

| | |
|---|---|
|  MATTHEW S DAVIDS, MD, MMSC | Venetoclax + rituximab |
|  IAN W FLINN, MD, PHD | Venetoclax + obinutuzumab |
|  PROF JOHN G GRIBBEN, MD, DSC, FMEDSCI | Venetoclax + rituximab |
|  BRIAN T HILL, MD, PHD | Venetoclax + rituximab |
|  NITIN JAIN, MD | Venetoclax + obinutuzumab |
|  BRAD S KAHL, MD | Venetoclax + rituximab |
|  ANTHONY R MATO, MD, MSCE | Venetoclax + rituximab |
|  JOHN M PAGEL, MD, PHD | Venetoclax |
|  KERRY A ROGERS, MD | Venetoclax + rituximab |
|  JEFF SHARMAN, MD | Venetoclax + rituximab |
|  TANYA SIDDIQI, MD | Ibrutinib + obinutzumab OR venetoclax + obinutuzumab |
|  MITCHELL R SMITH, MD, PHD | Venetoclax + obinutuzumab |
|  WILLIAM G WIERDA, MD, PHD | Venetoclax + rituximab |
|  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 |
|  IAN W FLINN, MD, PHD | Acalabrutinib |
|  PROF JOHN G GRIBBEN, MD, DSC, FMEDSCI | Ibrutinib |
|  BRIAN T HILL, MD, PHD | Acalabrutinib |
|  NITIN JAIN, MD | Acalabrutinib |
|  BRAD S KAHL, MD | Acalabrutinib |
|  ANTHONY R MATO, MD, MSCE | Venetoclax + rituximab |

| | |
|---|---|
|  JOHN M PAGEL, MD, PHD | Acalabrutinib |
|  KERRY A ROGERS, MD | Ibrutinib |
|  JEFF SHARMAN, MD | Acalabrutinib |
|  TANYA SIDDIQI, MD | Acalabrutinib + obinutuzumab |
|  MITCHELL R SMITH, MD, PHD | Ibrutinib |
|  WILLIAM G WIERDA, MD, PHD | Venetoclax + rituximab |
|  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 |
|  IAN W FLINN, MD, PHD | IV hydration and allopurinol |
|  PROF JOHN G GRIBBEN, MD, DSC, FMEDSCI | Encourage oral hydration and allopurinol |
|  BRIAN T HILL, MD, PHD | Encourage oral hydration and allopurinol |
|  NITIN JAIN, MD | Encourage oral hydration and allopurinol |
|  BRAD S KAHL, MD | Encourage oral hydration and allopurinol |
|  ANTHONY R MATO, MD, MSCE | IV hydration and allopurinol |
|  JOHN M PAGEL, MD, PHD | Encourage oral hydration and allopurinol |
|  KERRY A ROGERS, MD | Encourage oral hydration and allopurinol |
|  JEFF SHARMAN, MD | Give the obinutuzumab first to debulk, then after 1 month can start as outpatient with hydration and allopurinol |
|  TANYA SIDDIQI, MD | Encourage oral hydration and allopurinol |
|  MITCHELL R SMITH, MD, PHD | Encourage oral hydration and allopurinol |
|  WILLIAM G WIERDA, 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 |
|  IAN W FLINN, MD, PHD | Debulk with obinutuzumab |
|  PROF JOHN G GRIBBEN, MD, DSC, FMEDSCI | IV hydration and allopurinol |
|  BRIAN T HILL, MD, PHD | Admit to hospital |
|  NITIN JAIN, MD | Admit to hospital |
|  BRAD S KAHL, MD | Admit to hospital |
|  ANTHONY R MATO, MD, MSCE | Admit to hospital |
|  JOHN M PAGEL, MD, PHD | Admit to hospital |
|  KERRY A ROGERS, MD | Admit to hospital |
|  JEFF SHARMAN, MD | Obinutuzumab for 1 month to lower patient risk, then outpatient hydration and allopurinol |
|  TANYA SIDDIQI, MD | Admit to hospital |
|  MITCHELL R SMITH, MD, PHD | Admit to hospital |
|  WILLIAM G WIERDA, 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 |
|  PROF JOHN G GRIBBEN, MD, DSC, FMEDSCI | 1 day |
|  BRIAN T HILL, MD, PHD | 2 days (<48 hours) |
|  NITIN JAIN, MD | 2 days |
|  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 Jain

**MODULE 1: Cases from Dr Zafar**

**MODULE 2: CLL Journal Club with Dr Jain**

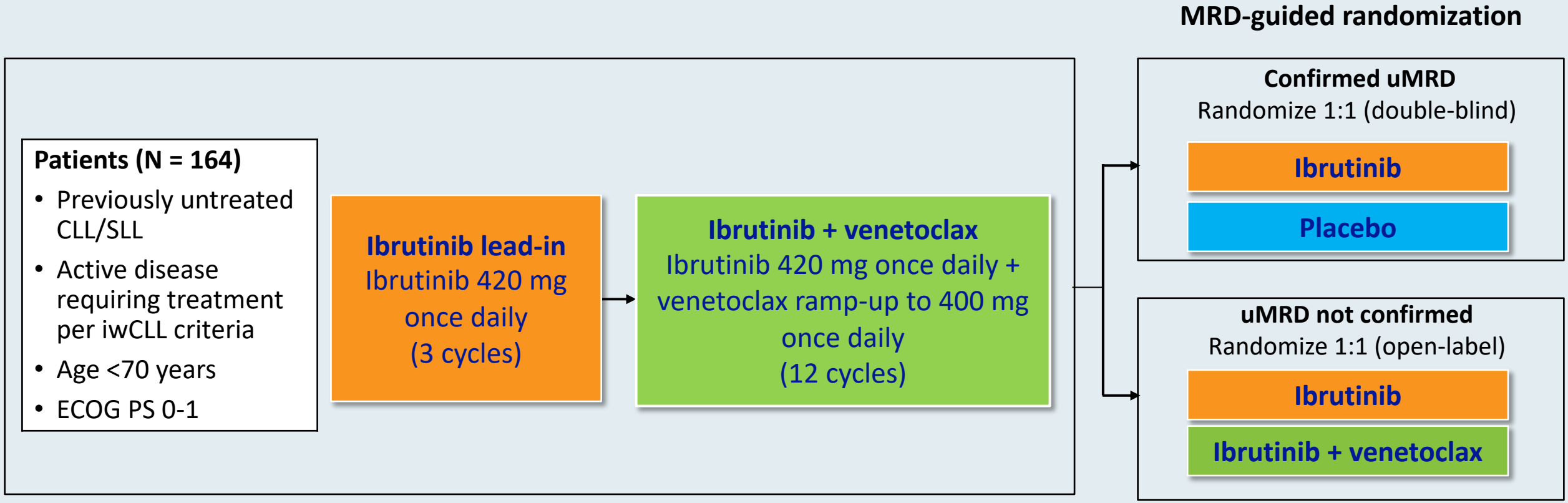
- Shifting paradigm in CLL: Is chemotherapy still relevant?
- Durable remissions with up-front ibrutinib in patients with CLL and del(17p)
- Ibrutinib versus ibrutinib with rituximab for CLL
- Cardiovascular and renal effects associated with ibrutinib
- Clinical significance of and predictive factors in achieving complete remission with ibrutinib in patients with CLL
- Phase I trial of eprenetapopt with ibrutinib or venetoclax-based therapy for relapsed/refractory CLL with TP53 mutation
- Mature results of a Phase II trial of acalabrutinib for treatment-naïve CLL
- Ibrutinib combined with venetoclax as initial therapy for CLL; MRD analyses
- Genetic determinants and evolutionary history of Richter's syndrome
- Metastatic lung adenocarcinoma mimicking Richter's transformation in a patient with CLL
- Incidental Richter's transformation in patients with CLL during interruption of ibrutinib
- Fungal infections in patients with CLL receiving ibrutinib
- Occurrence of other cancers in patients with CLL and mutations in the POT1 gene
- Allogeneic stem cell transplant after small molecule inhibitors in patients with CLL and lymphomas
- Treating leukemia in the time of COVID-19

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

**MODULE 4: Key Recent Data Sets**

RTP RESEARCH TO PRACTICE

# CAPTIVATE MRD Cohort: Study Design

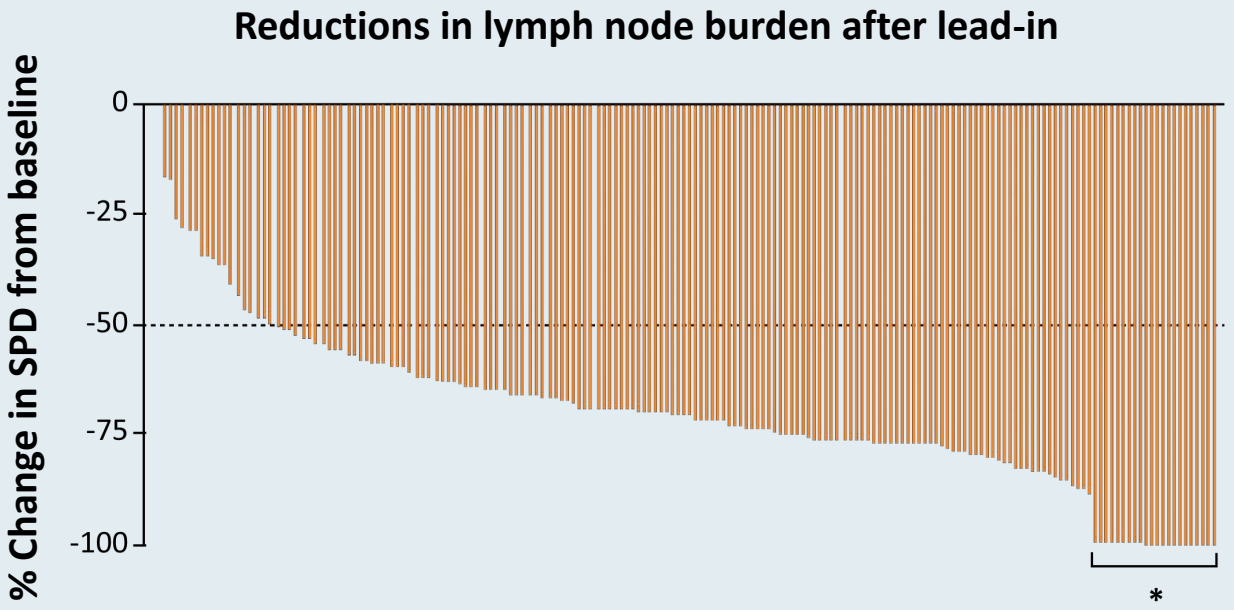


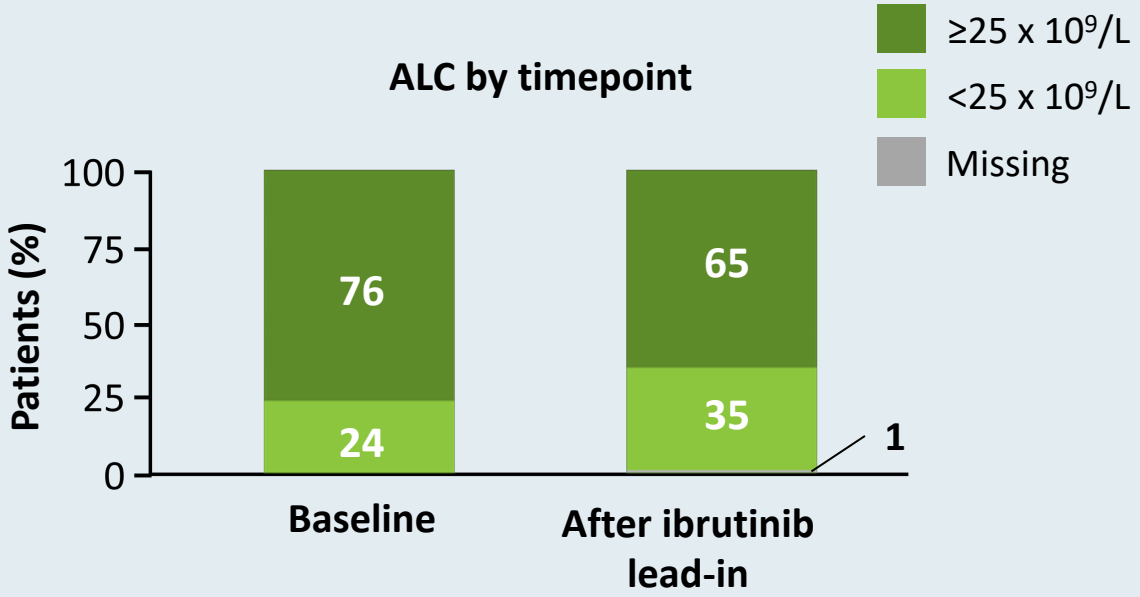

uMRD = undetectable minimal residual disease

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.

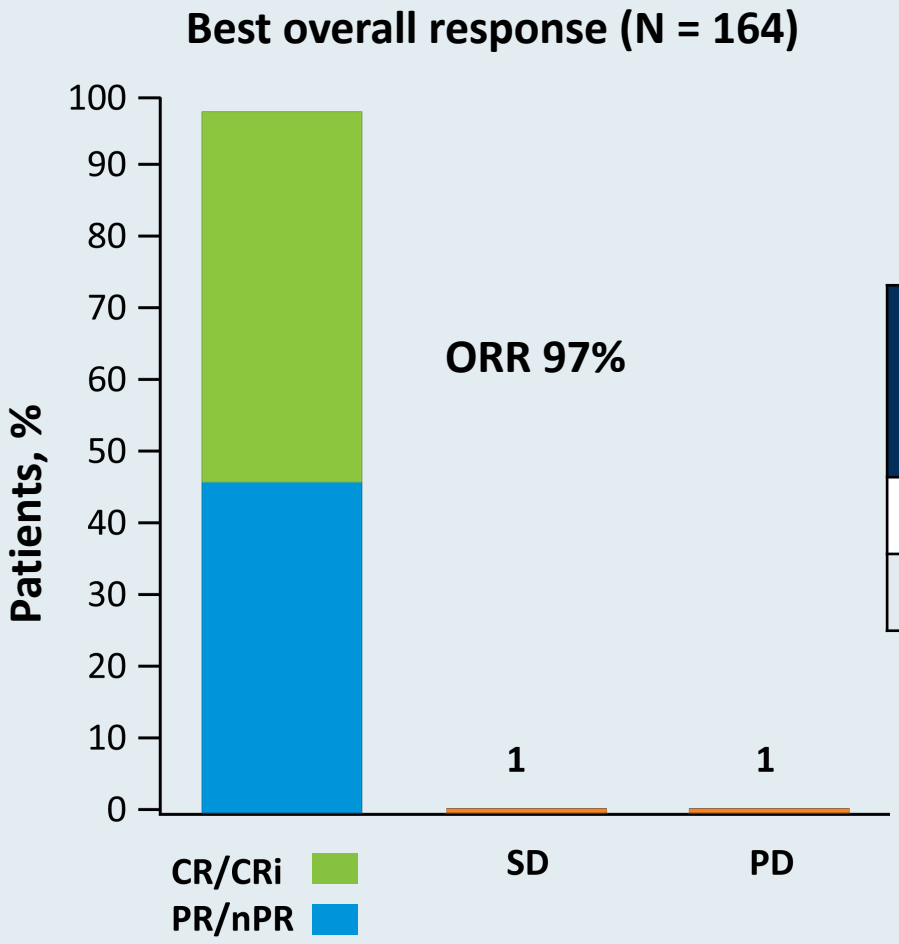
# CAPTIVATE MRD Cohort: Undetectable MRD Rate

| | 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**

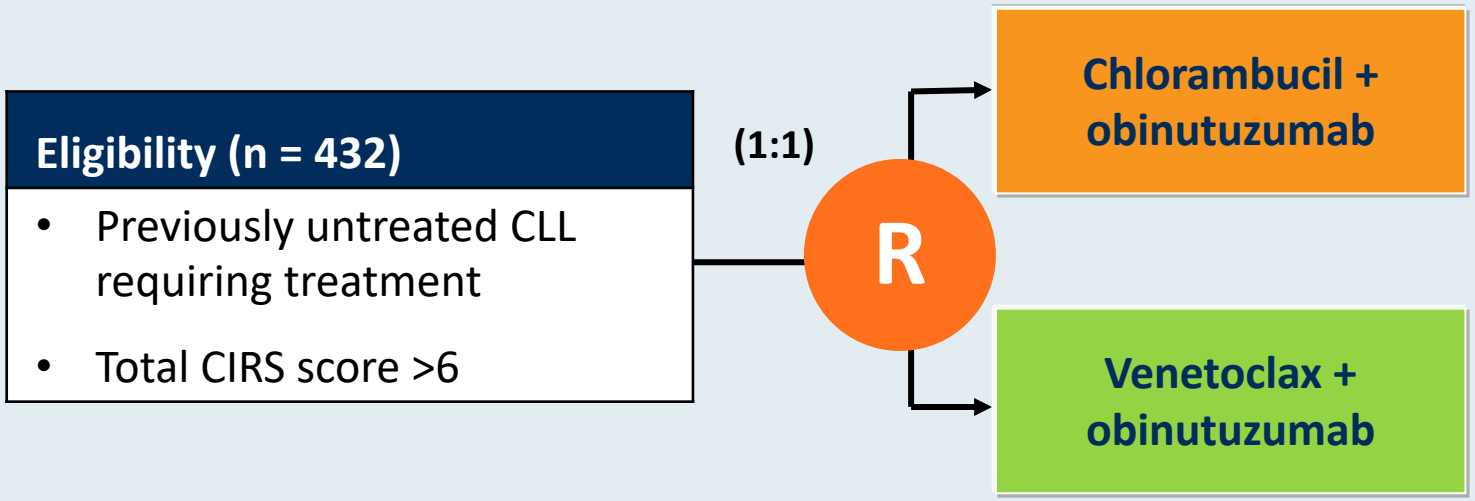
Randomize

**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

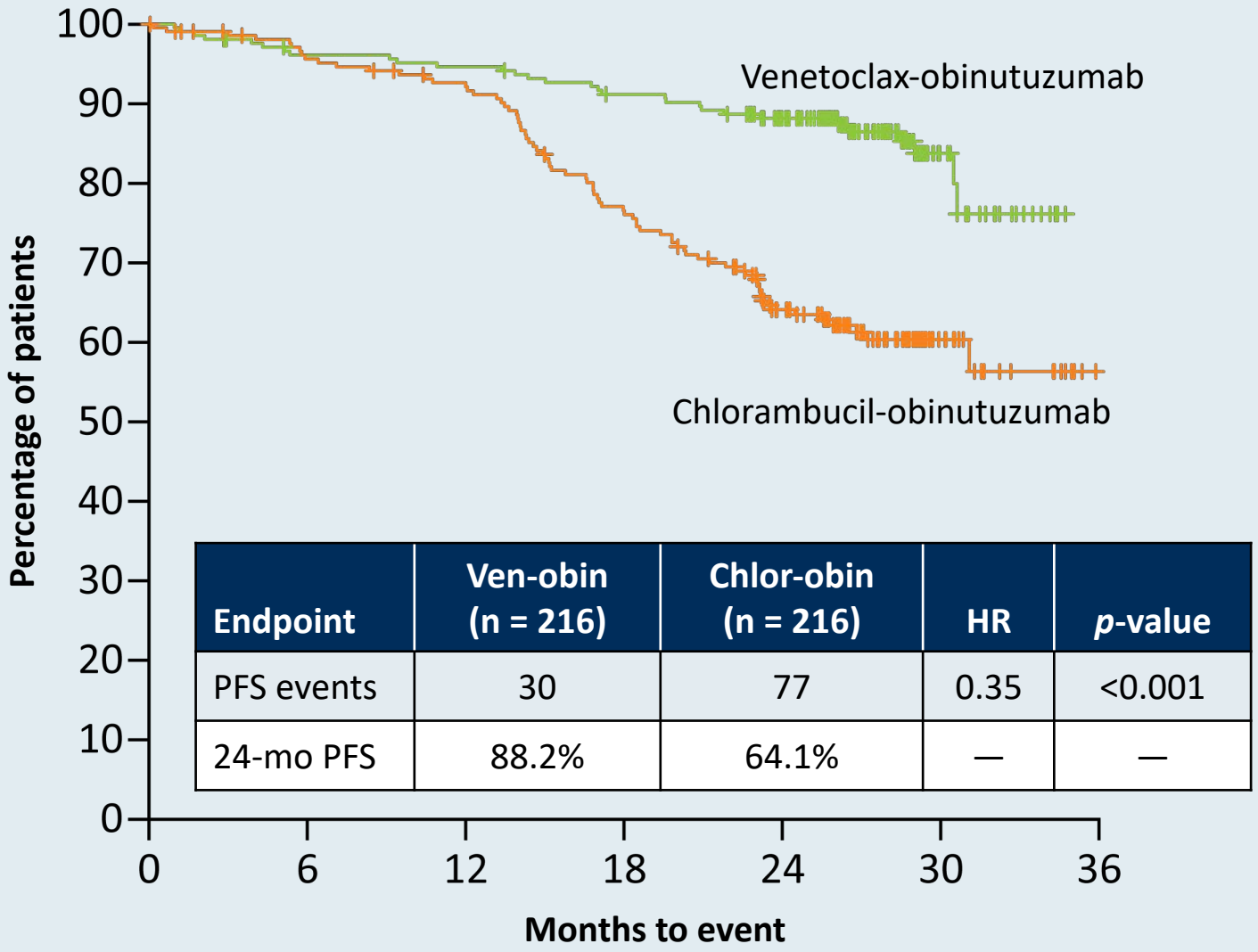



**Primary endpoint:** Progression-free survival

- 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.

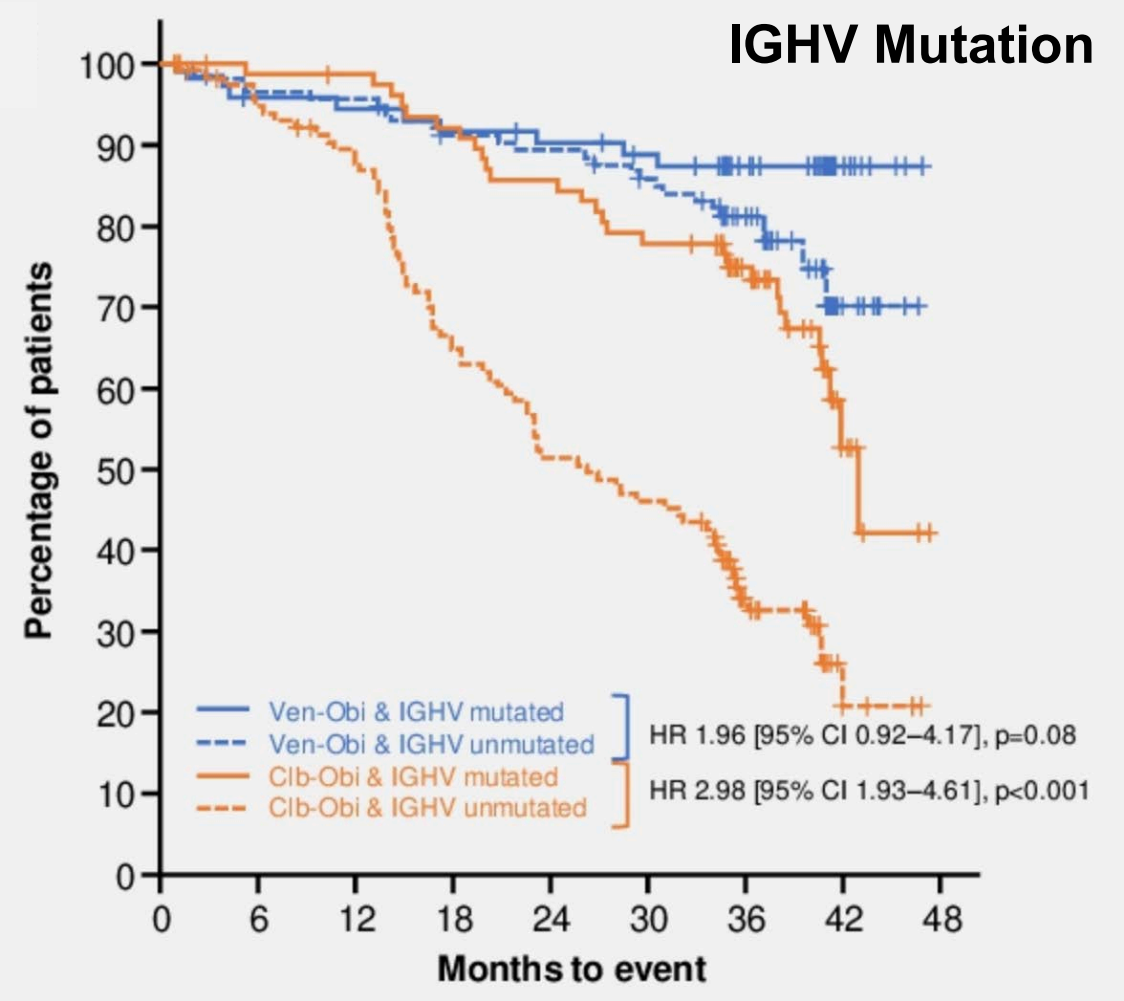
# CLL14: Investigator-Assessed Progression-Free Survival

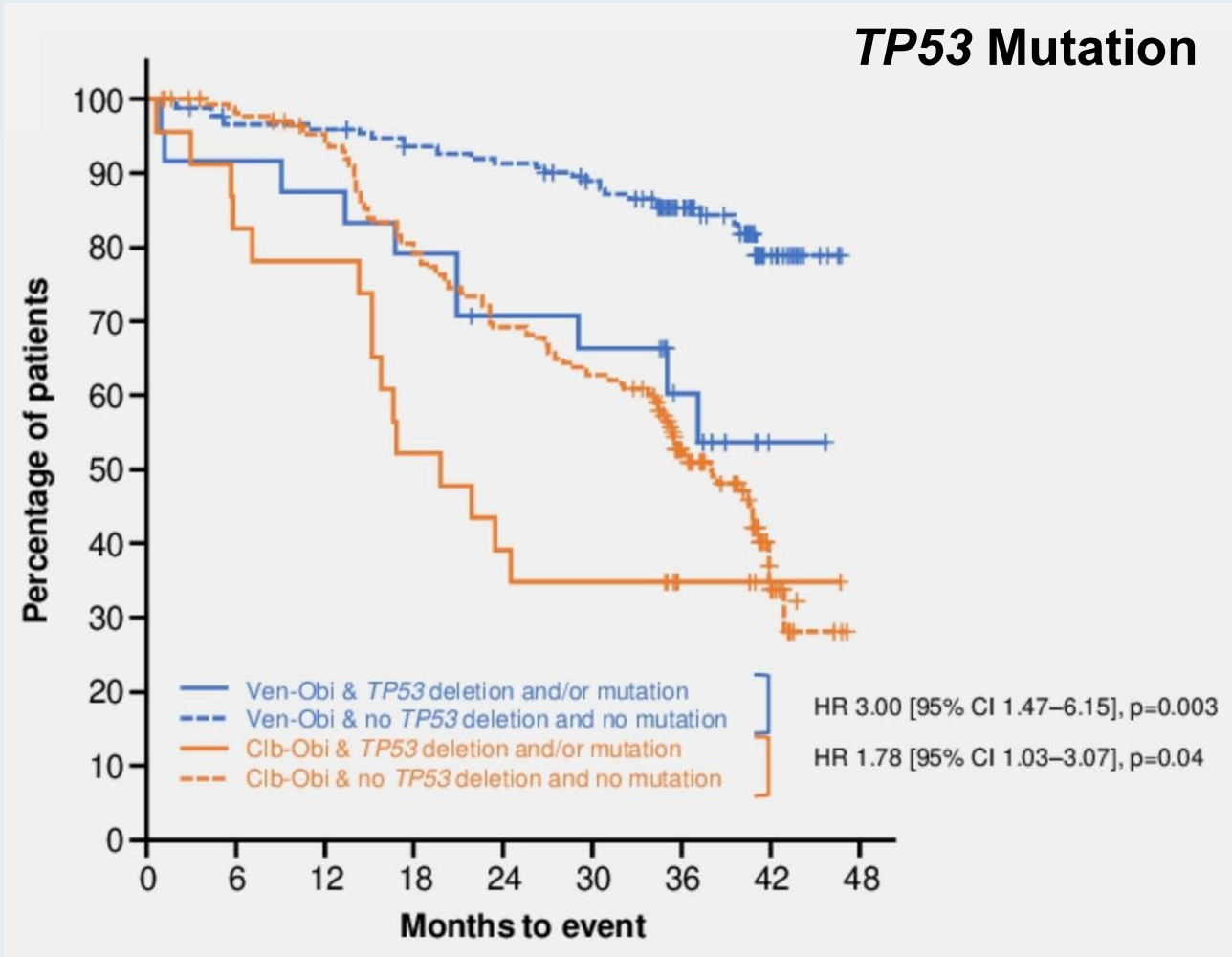



| Endpoint | Ven-obin (n = 216) | Chlor-obin (n = 216) | HR | *p*-value |
|---|---|---|---|---|
| PFS events | 30 | 77 | 0.35 | <0.001 |
| 24-mo PFS | 88.2% | 64.1% | — | — |

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.

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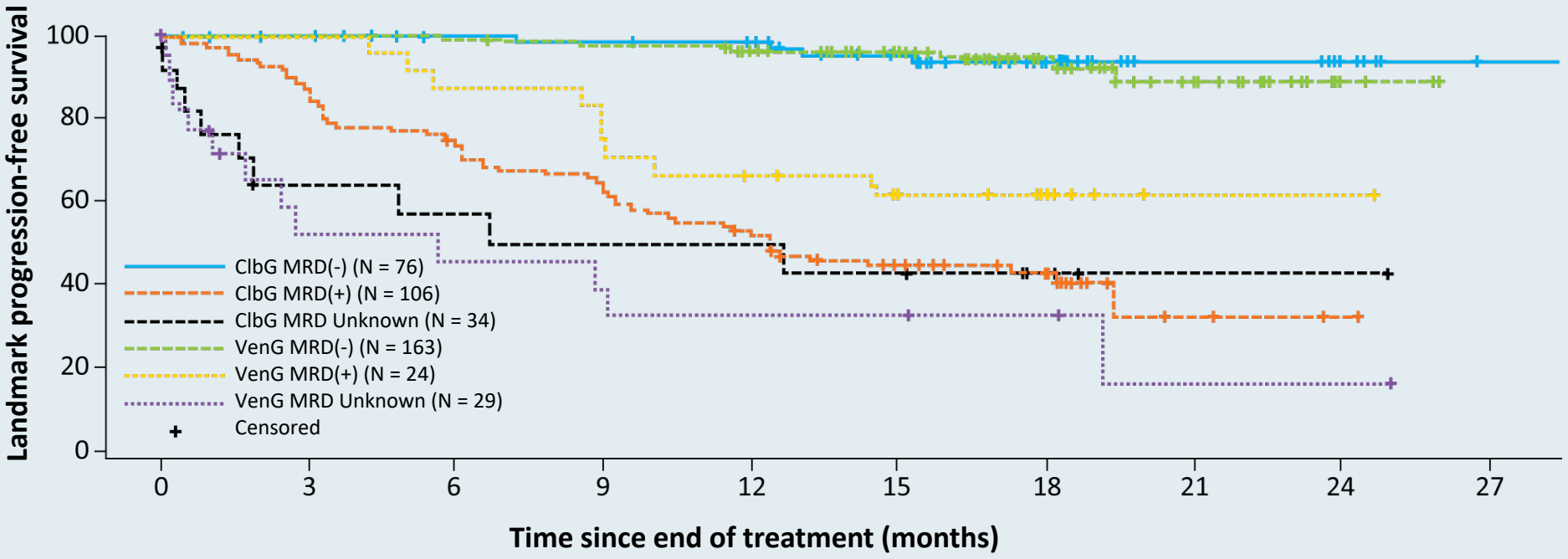
# CLL14: Minimal Residual Disease 3 Months After Treatment

| 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.

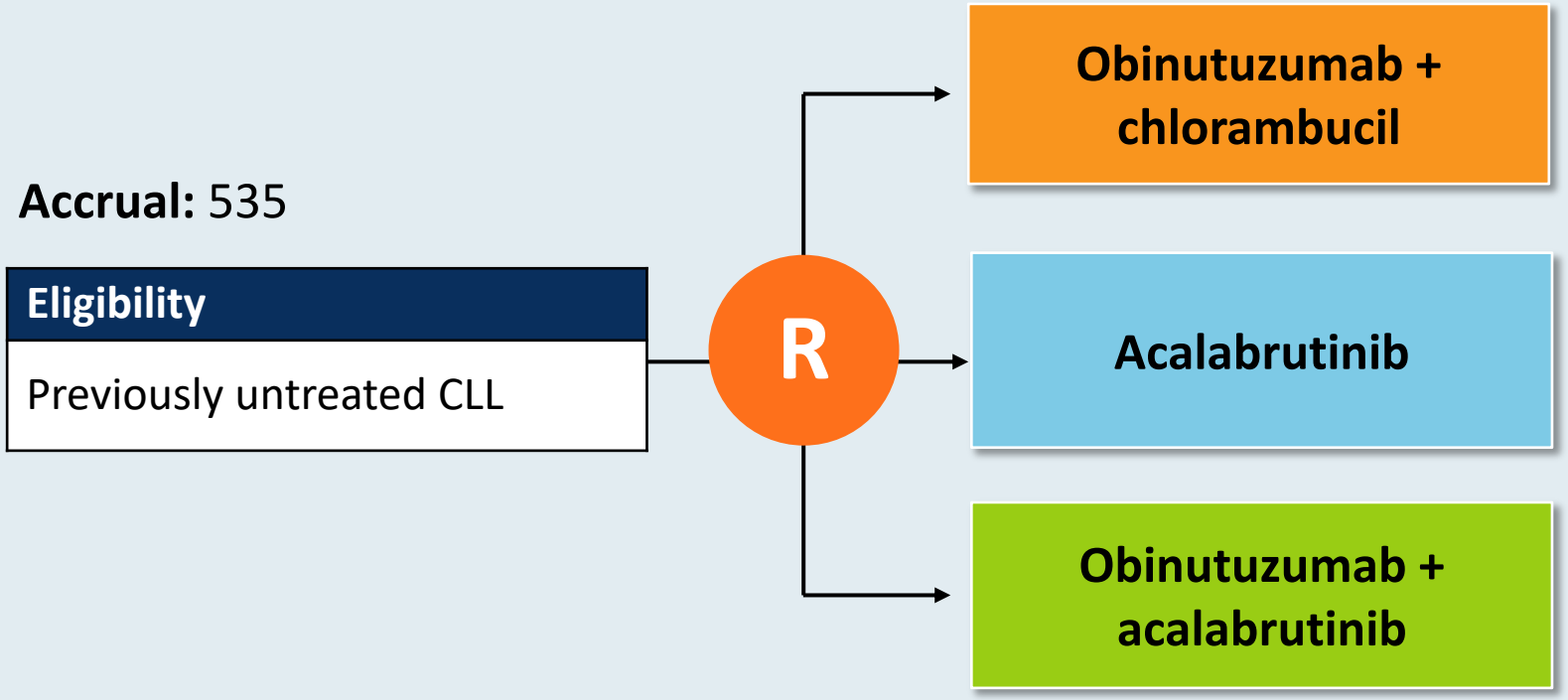
# CLL14: Landmark Analysis from End of Therapy PFS by MRD Group




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.

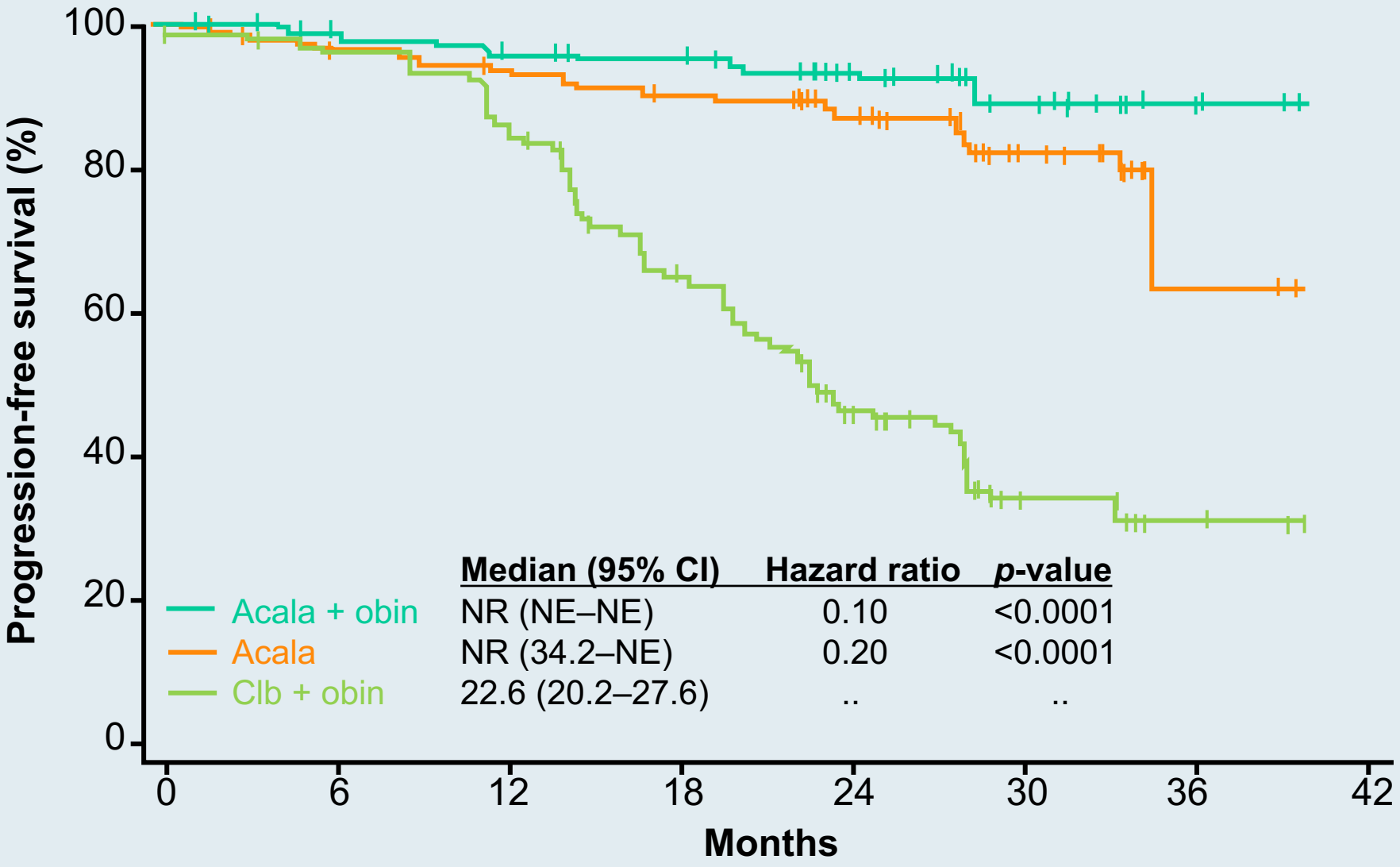
# ELEVATE-TN Phase III Trial Schema




**Primary endpoint:** Progression-free survival

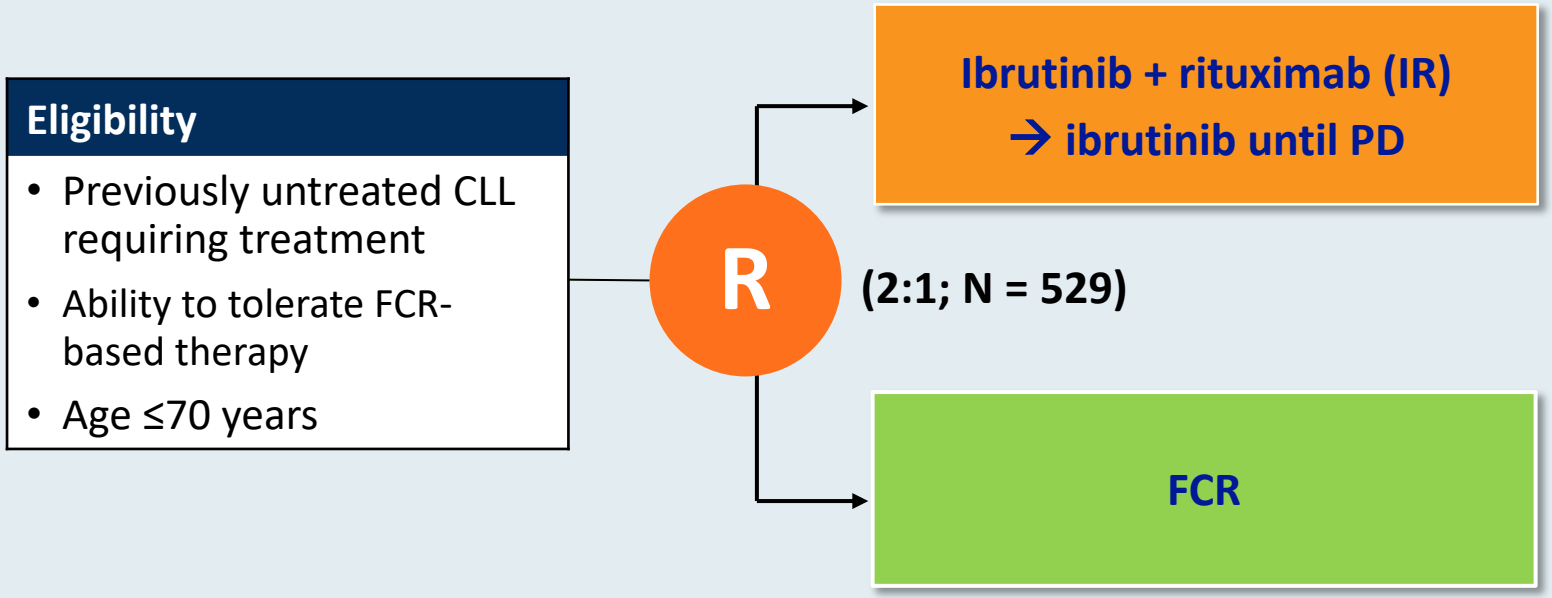
www.clinicaltrials.gov (NCT02475681). Accessed August 2020.

# ELEVATE-TN: PFS (IRC)




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

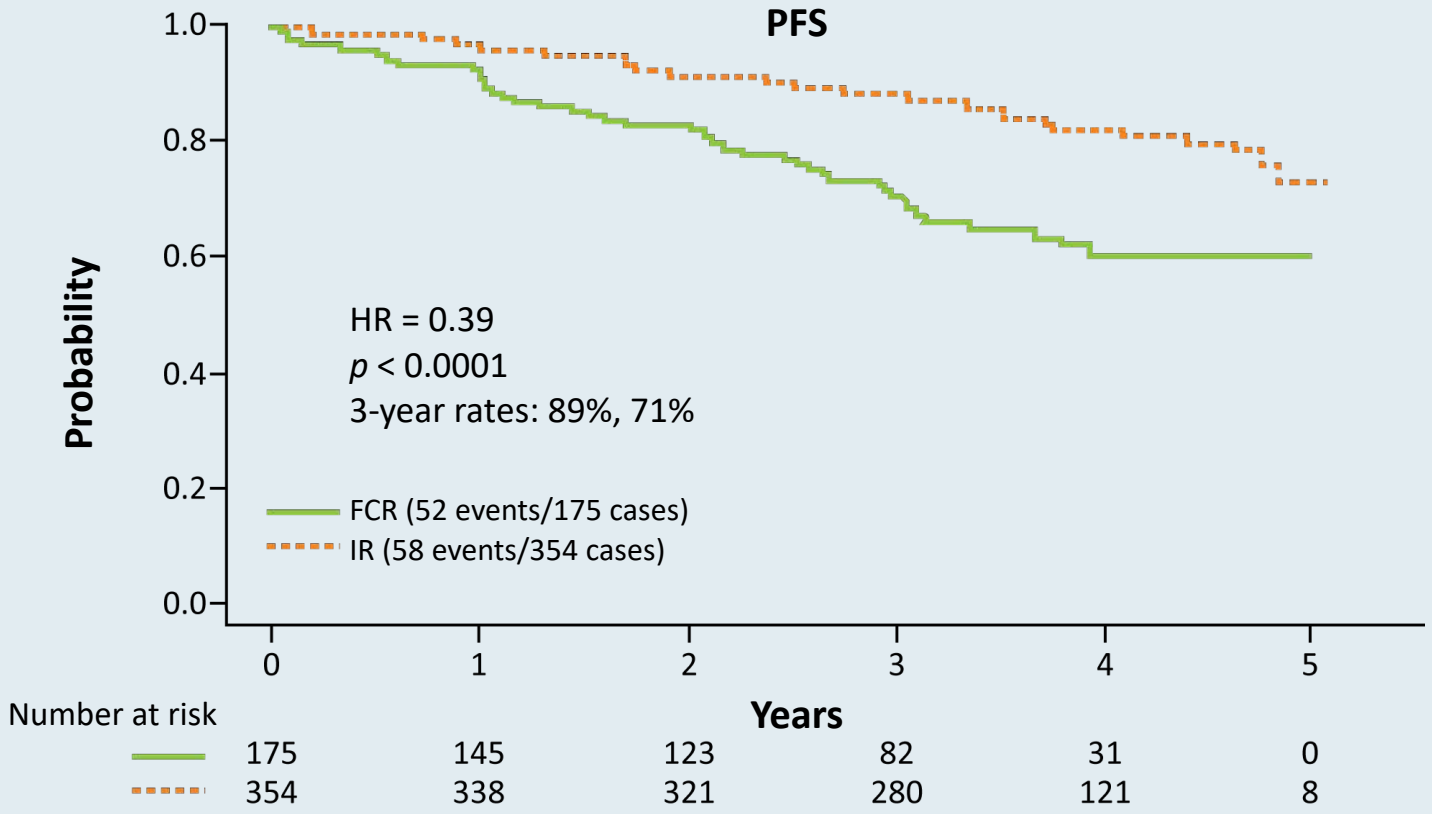
# Phase III ECOG-ACRIN E1912 Study Design




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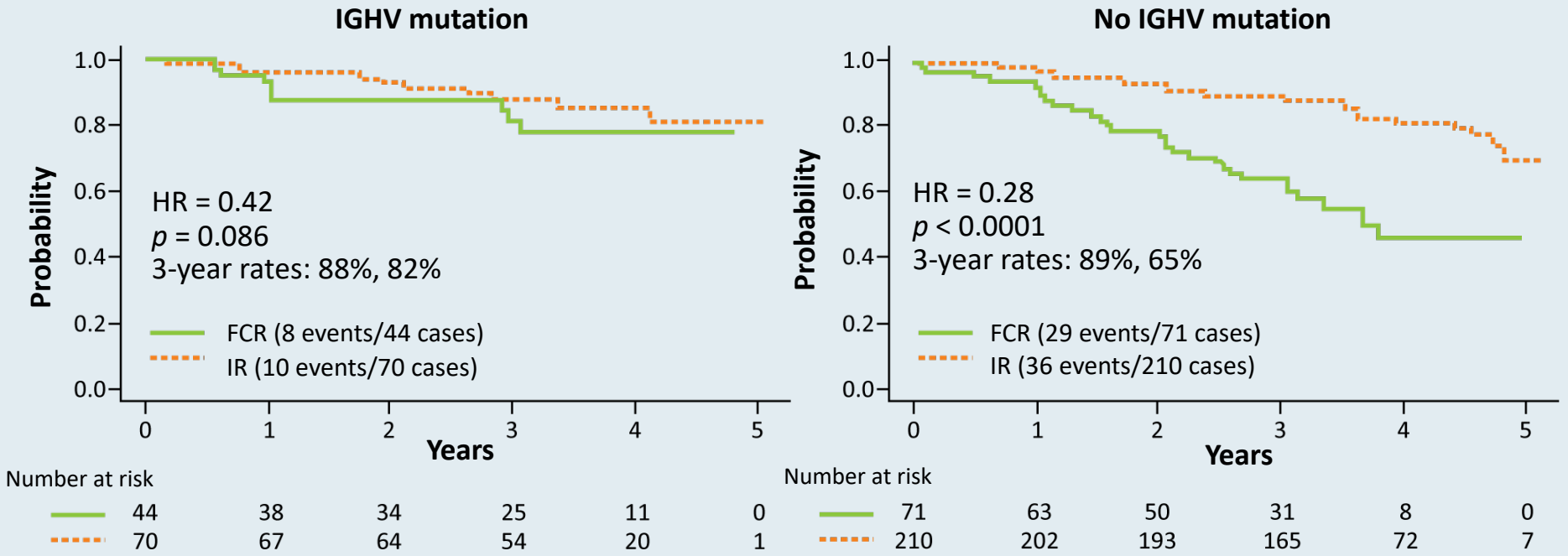
# ECOG-ACRIN E1912 Extended Follow-Up: PFS by IGHV Mutation Status




- 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.

# Year in Review: Clinical Investigators Provide Perspectives on the Most Relevant New Publications, Data Sets and Advances in Oncology

## Acute Myeloid Leukemia and Myelodysplastic Syndromes

**Tuesday, January 5, 2020**
**5:00 PM – 6:00 PM ET**

### Faculty

**Mikkael A Sekeres, MD, MS**
**Richard M Stone, MD**

### Moderator

**Neil Love, MD**

Year in Review 2020

*Thank you for joining us!*

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

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