# *Meet The Professor*
# Current and Future Management of Chronic Lymphocytic Leukemia

**Peter Hillmen, MB ChB, PhD**
Professor of Experimental Haematology
University of Leeds
Honorary Consultant Haematologist
Leeds Teaching Hospitals NHS Trust
Leeds, United Kingdom

# Commercial Support

This activity is supported by educational grants from AstraZeneca Pharmaceuticals LP, Genentech, a member of the Roche Group, and Pharmacyclics LLC, an AbbVie Company and Janssen Biotech Inc, administered by Janssen Scientific Affairs LLC.

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# Dr Love — Disclosures

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Planners, scientific staff and independent reviewers for Research To Practice have no relevant conflicts of interest to disclose.

# Prof Hillmen — Disclosures

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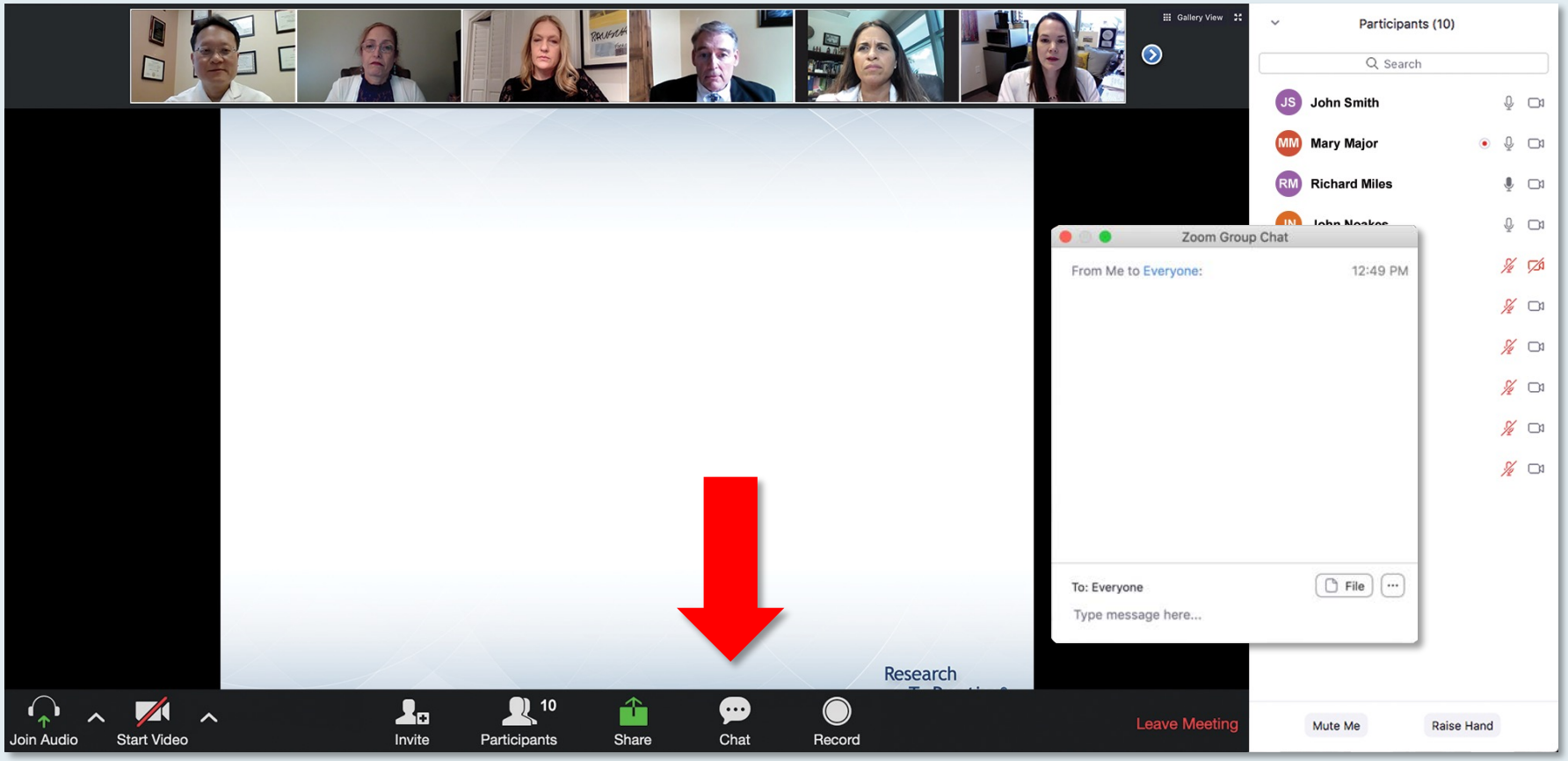
# We Encourage Clinicians in Practice to Submit Questions




**Feel free to submit questions now before the program begins and throughout the program.**

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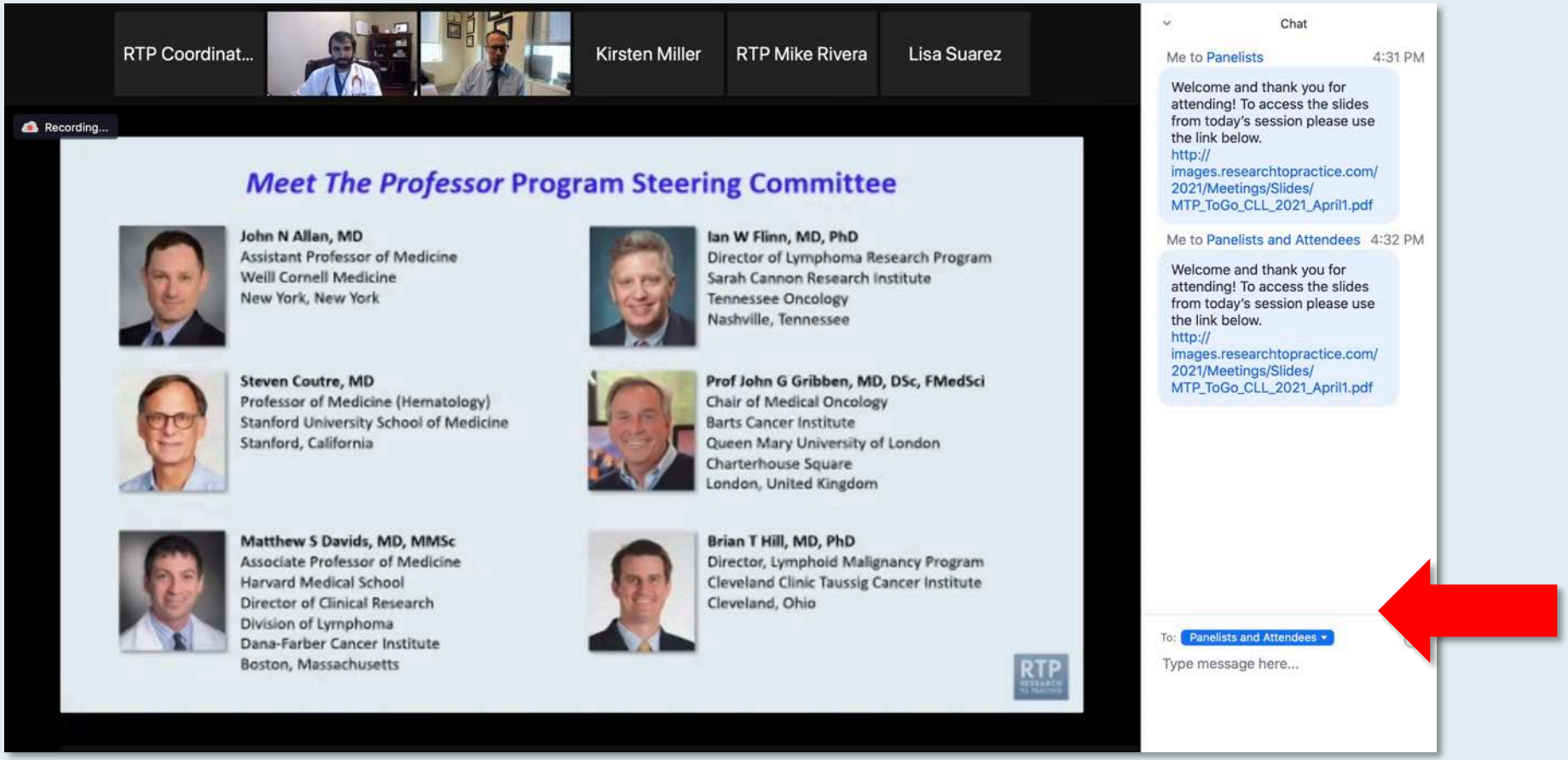
# Familiarizing Yourself with the Zoom Interface

## Expand chat submission box




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

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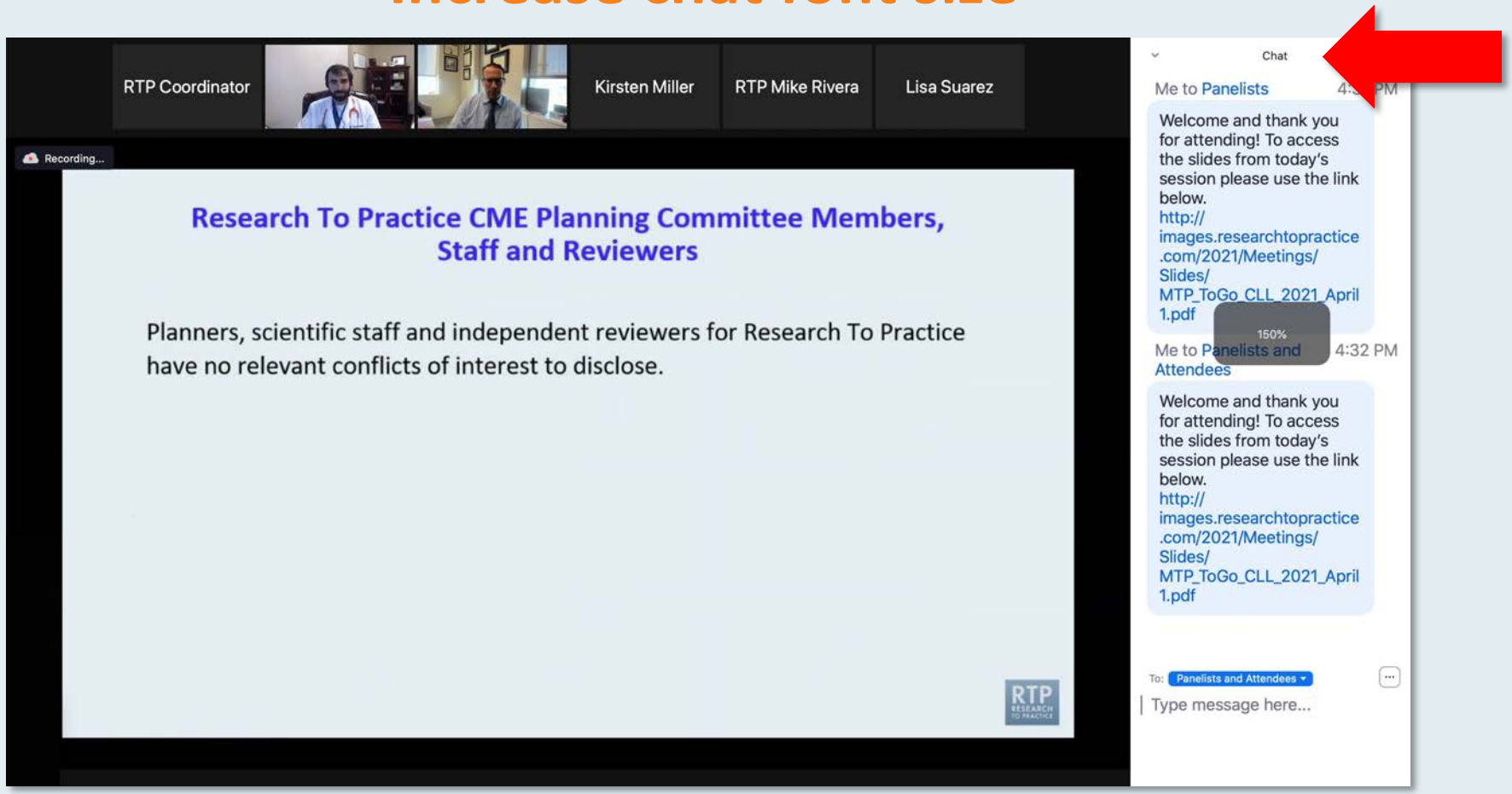
## Increase chat font size




**Press Command (for Mac) or Control (for PC) and the + symbol.**
**You may do this as many times as you need for readability.**

# ONCOLOGY TODAY

WITH DR NEIL LOVE

## Recent Advances in the Treatment of Chronic Lymphocytic Leukemia

DR PETER HILLMEN
UNIVERSITY OF LEEDS

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Spotify

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# Data + Perspectives: Clinical Investigators Discuss the Current and Future Management of Ovarian Cancer

**Saturday, March 19, 2022**

**2:30 PM – 4:00 PM ET**

## Faculty

**Mansoor Raza Mirza, MD**
**Kathleen N Moore, MD, MS**
**David M O'Malley, MD**

## Moderator

**Robert L Coleman, MD**

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# *Meet The Professor*

## Current and Future Role of Immunotherapy in the Management of Lung Cancer

**Wednesday, March 30, 2022**
**5:00 PM – 6:00 PM ET**

### Faculty

**Sarah B Goldberg, MD, MPH**

### Moderator

**Neil Love, MD**

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# *Meet The Professor*

# Current and Future Management of Chronic Lymphocytic Leukemia

**Thursday, March 31, 2022**
**5:00 PM – 6:00 PM ET**

## Faculty

**Kerry Rogers, MD**

## Moderator

**Neil Love, MD**

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# *Meet The Professor*

# Optimizing the Management of Myelodysplastic Syndromes

**Tuesday, April 5, 2022**
**5:00 PM – 6:00 PM ET**

## Faculty

**Rami Komrokji, MD**

## Moderator

**Neil Love, MD**

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# *Meet The Professor*

# Optimizing the Clinical Management of Hodgkin and Non-Hodgkin Lymphomas

**Wednesday, April 6, 2022**
**5:00 PM – 6:00 PM ET**

## Faculty

**Andrew M Evens, DO, MSc**

## Moderator

**Neil Love, MD**

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# "What I Tell My Patients"
# 16th Annual RTP/ONS CE Seminar Series
# ONS Congress, Anaheim, California — April 27 - May 1, 2022

| | | |
|---|---|---|
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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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Professor of Experimental Haematology
University of Leeds
Honorary Consultant Haematologist
Leeds Teaching Hospitals NHS Trust
Leeds, United Kingdom

# *Meet The Professor* Program Participating Faculty

**Jennifer R Brown, MD, PhD**
CLL Center Director and Institute Physician
Dana-Farber Cancer Institute
Worthington and Margaret Collette Professor of Medicine in the Field of Hematologic Oncology
Harvard Medical School
Boston, Massachusetts

**Susan O'Brien, MD**
Professor, Division of Hematology/Oncology
School of Medicine
UCI Chao Family Comprehensive Cancer Center
Orange, California

**Peter Hillmen, MB ChB, PhD**
Professor of Experimental Haematology
University of Leeds
Honorary Consultant Haematologist
Leeds Teaching Hospitals NHS Trust
Leeds, United Kingdom

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

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# *Meet The Professor* Program Participating Faculty

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

## Moderator

**Neil Love, MD**
Research To Practice

**William G Wierda, MD, PhD**
DB Lane Cancer Research Distinguished Professor
Section Chief, Chronic Lymphocytic Leukemia
Center Medical Director
Department of Leukemia, Division of Cancer Medicine
Executive Medical Director, Inpatient Medical Services
The University of Texas MD Anderson Cancer Center
Houston, Texas

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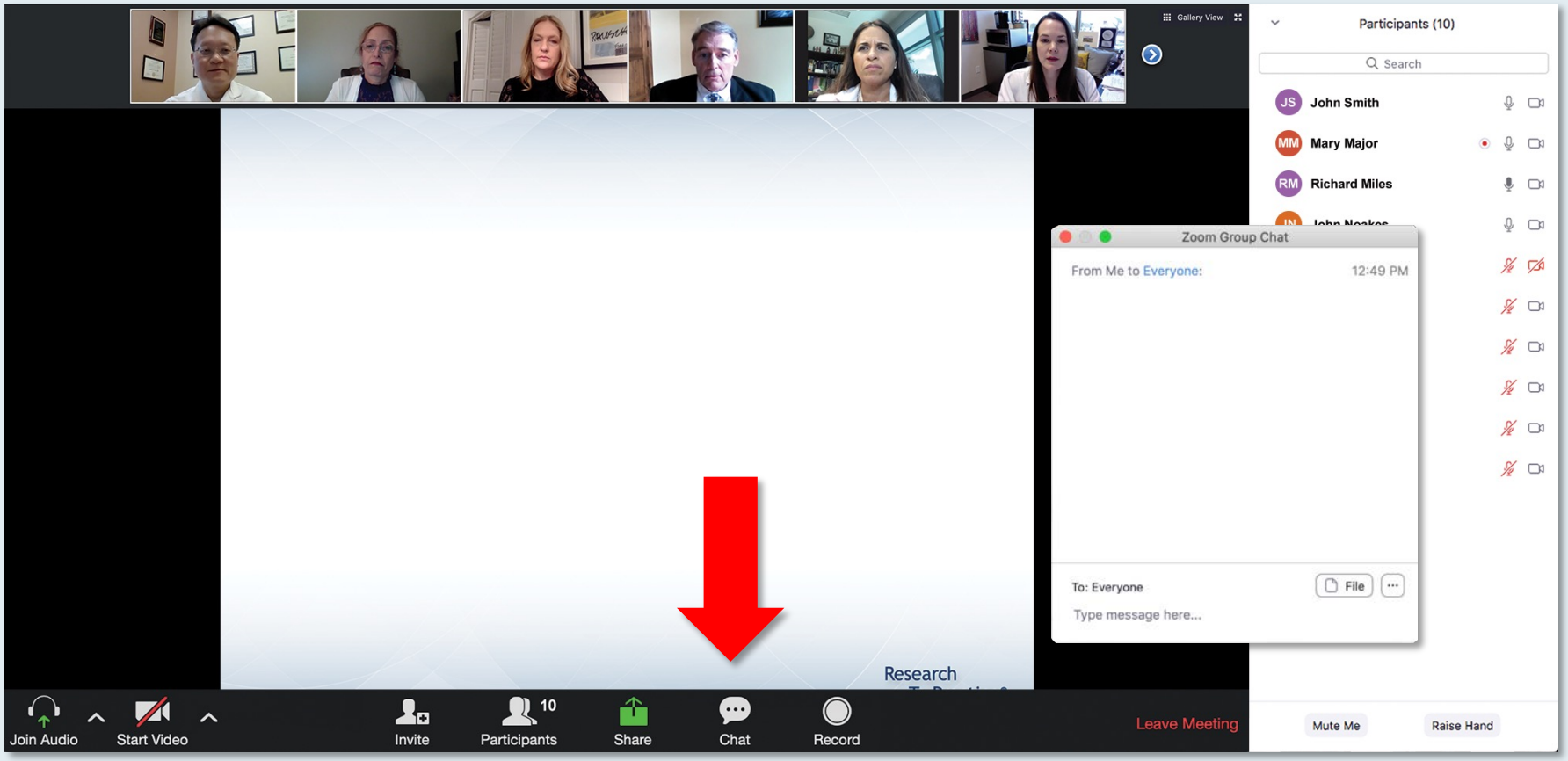


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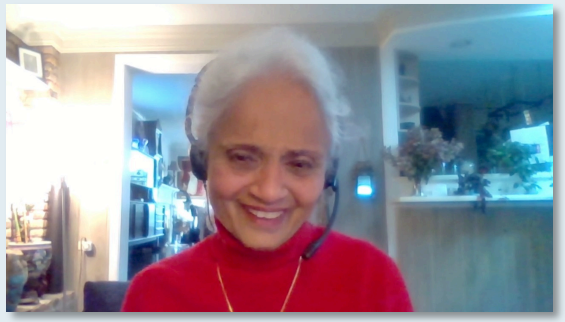
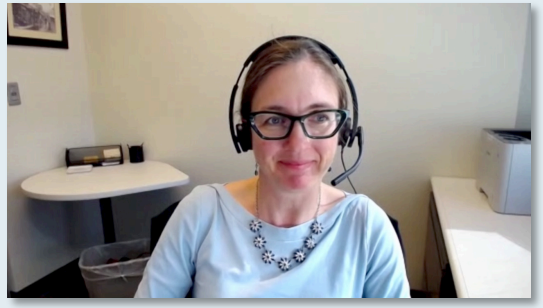
**Amanda Blackmon, DO, MS**
University of California, Irvine
Irvine, California

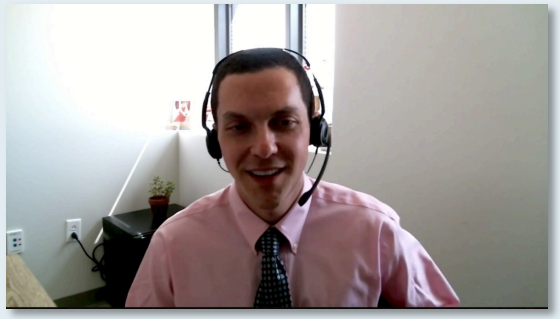


**Rajalaxmi McKenna**
Southwest Medical Consultants SC
Willowbrook, Illinois

**Alexey V Danilov, MD, PhD**
City of Hope National Medical Center
Duarte, California



**Jeanne Palmer, MD**
Mayo Clinic
Phoenix, Arizona



**Jeremy Lorber, MD**
Cedars-Sinai Medical Center
Beverly Hills, California

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# Meet The Professor with Prof Hillmen

## Introduction

## MODULE 1: Case Presentations

- Dr Blackmon: A 60-year-old man with CLL and Richter's transformation to Hodgkin lymphoma
- Dr Palmer: A 76-year-old man with relapsed CLL after 3 years of second-line ibrutinib
- Dr Danilov: A 52-year-old man with newly diagnosed IGHV-unmutated CLL — Del(17p), TP53 mutation
- Dr McKenna: A 53-year-old woman who presents with persistent lymphocytosis
- Dr Blackmon: A 58-year-old man with CLL who receives FCR and remains in complete remission 5 years later
- Dr Danilov: A 71-year-old man with relapsed CLL who is concerned about contracting COVID-19

## MODULE 2: Journal Club with Prof Hillmen

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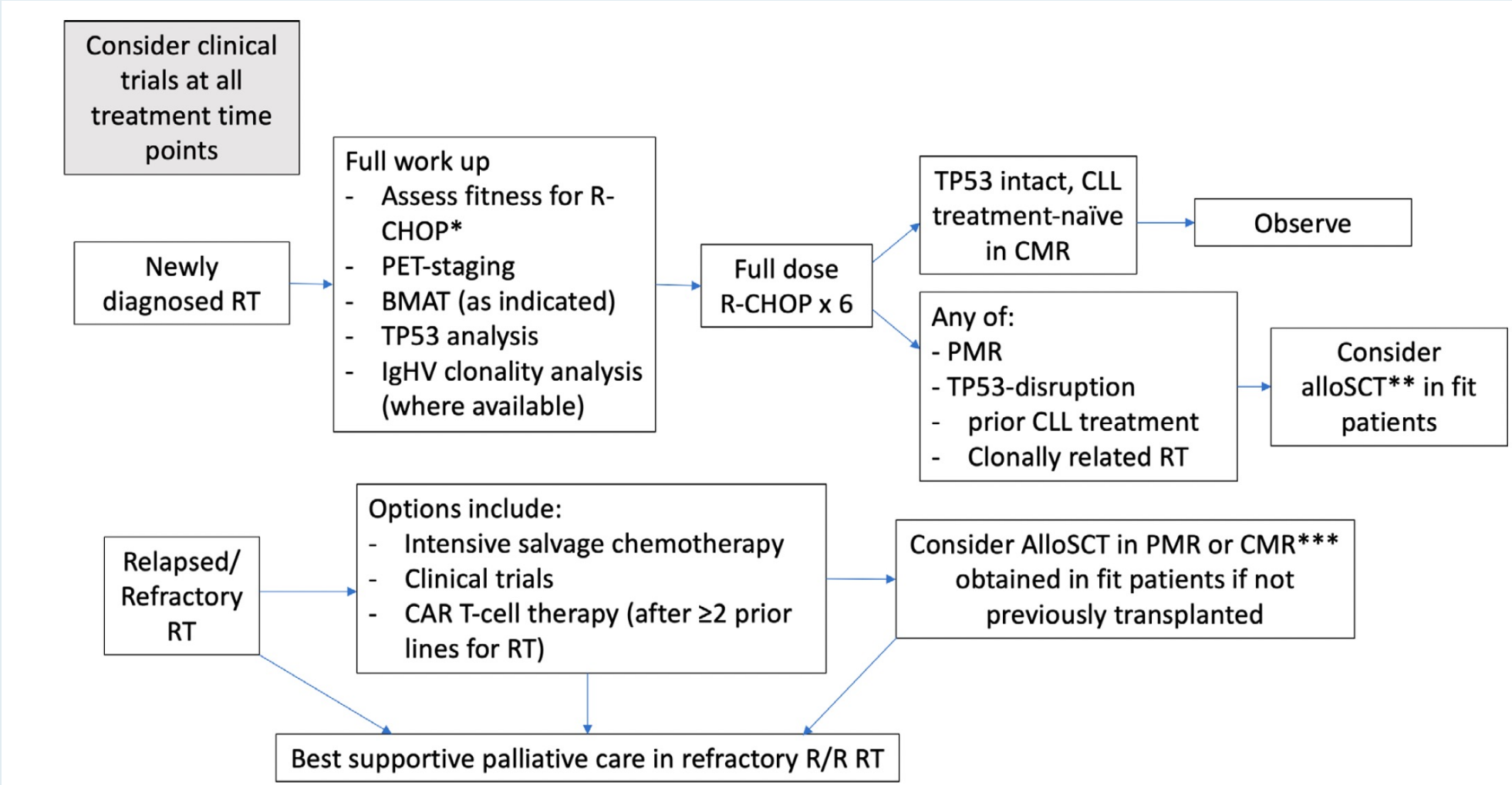
bjh good practice papers

# Richter transformation of chronic lymphocytic leukaemia: a British Society for Haematology Good Practice Paper

Toby A. Eyre,[1] John C. Riches,[2] Piers E. M. Patten,[3,4] Renata Walewska,[5] Helen Marr,[6] George Follows,[7] Peter Hillmen,[8,9] Anna H. Schuh[1,10] On behalf of the Haemato-Oncology Task Force of the British Society for Haematology

# Richter's Transformation of CLL




*in those unfit for full dose R-CHOP consider R-miniCHOP, R-GCVP, R-CEOP in appropriate patients (but no data in RT). **Autologous SCT can be considered and discussed in chemo-sensitive disease. ***CMR post CAR-T can be reasonably observed.
Abbreviations: RT: Richter transformation, CAR: chimeric antigen receptor, BMAT: bone marrow aspirate and trephine, PET: positron emission tomography, CMR: complete metabolic response, PMR: partial metabolic response, R-CHOP: rituximab, cyclophosphamide, vincristine, prednisolone

Eyre et al *British Journal of Haematology* 2022;196:864-70.

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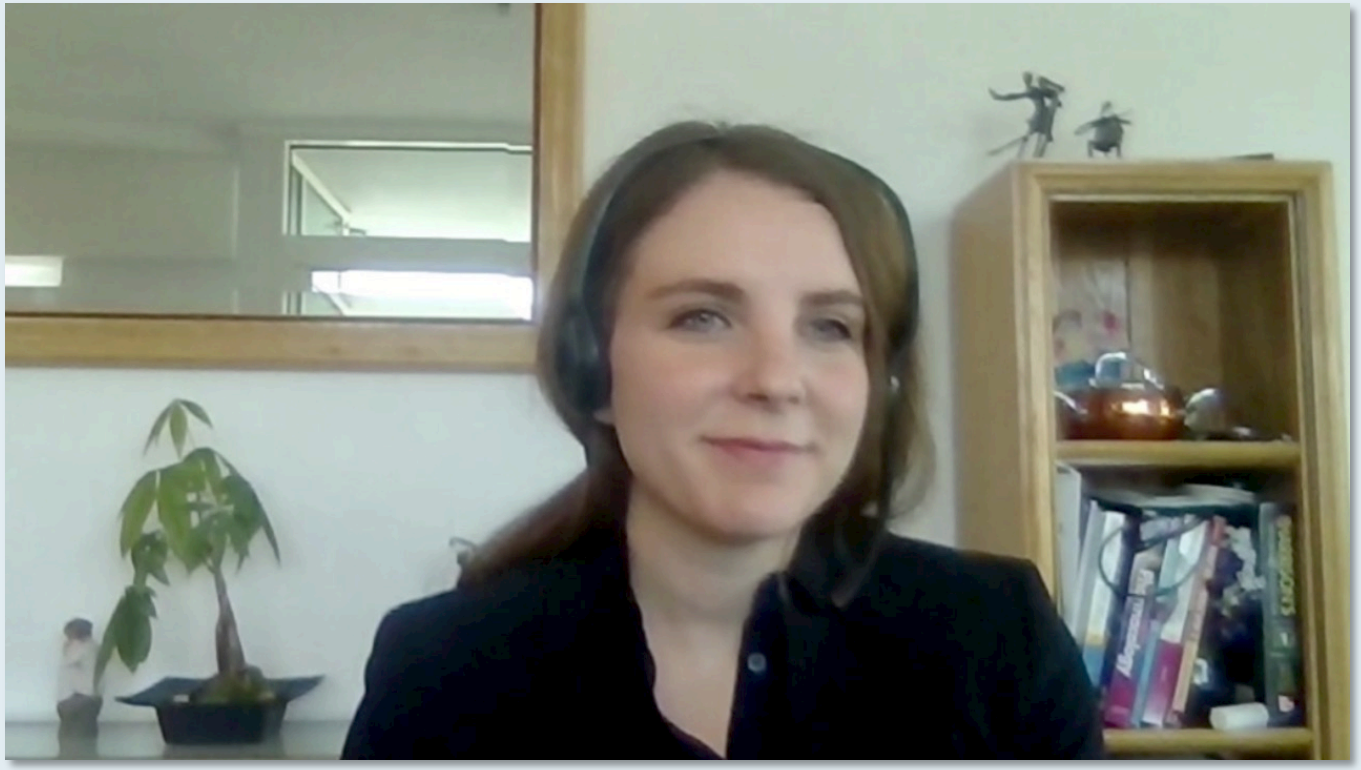

**Dr Amanda Blackmon (Irvine, California)**

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# Case Presentation: A 76-year-old man with relapsed CLL after 3 years of second-line ibrutinib

Dr Jeanne Palmer (Phoenix, Arizona)

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# Venetoclax/obinutuzumab in younger patients

Dr Jeremy Lorber (Beverly Hills, California)

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# Case Presentation: A 52-year-old man with newly diagnosed IGHV-unmutated CLL — Del(17p), TP53 mutation

Dr Alexey Danilov (Duarte, California)

# Case Presentation: A 52-year-old man with newly diagnosed IGHV-unmutated CLL — Del(17p), TP53 mutation (continued)

Dr Alexey Danilov (Duarte, California)

# Case Presentation: A 53-year-old woman who presents with persistent lymphocytosis

**Dr Rajalaxmi McKenna (Willowbrook, Illinois)**

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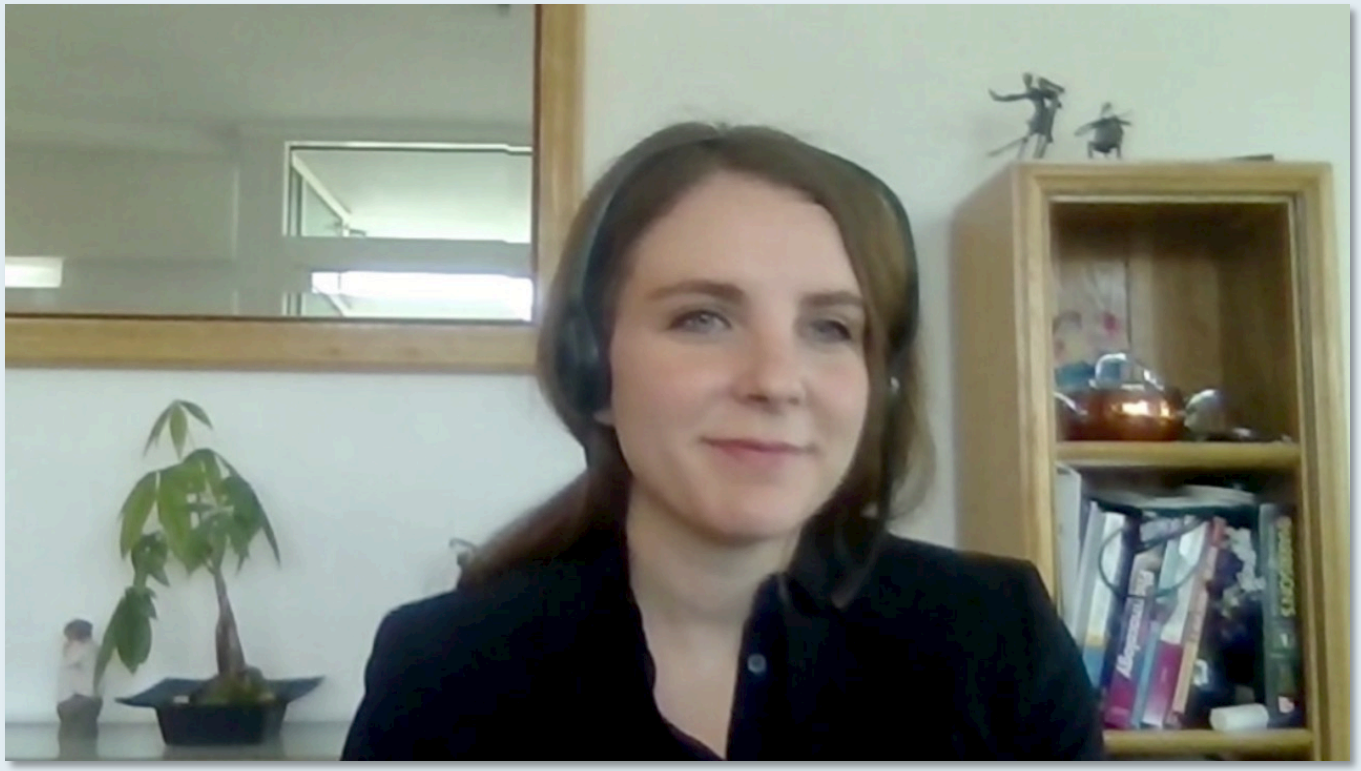
# Case Presentation: A 58-year-old man with CLL who receives FCR and remains in complete remission 5 years later



Dr Amanda Blackmon (Irvine, California)

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# Clinical experience with ibrutinib combined with venetoclax

Dr Alexey Danilov (Duarte, California)

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# Case Presentation: A 71-year-old man with relapsed CLL who is concerned about contracting COVID-19

**Dr Alexey Danilov (Duarte, California)**

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# Case Presentation: A 71-year-old man with relapsed CLL who is concerned about contracting COVID-19 (continued)

Dr Alexey Danilov (Duarte, California)

# Approach to COVID-19 vaccinations for patients with CLL who are on active treatment

Dr Alexey Danilov (Duarte, California)

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Received: 25 November 2021 | Revised: 28 January 2022 | Accepted: 31 January 2022

*Am J Hematol* 2022;1-4.

DOI: 10.1002/ajh.26483

CORRESPONDENCE

# Long-term follow-up of 415 patients with chronic lymphocytic leukemia treated with fludarabine and cyclophosphamide-based chemoimmunotherapy in the frontline ADMIRE and ARCTIC trials: A comprehensive assessment of prognostic factors

Allsup DJ and Zucchetto A

# Ibrutinib Plus Rituximab Is Superior to FCR in Previously Untreated CLL: Results of the Phase III NCRI *Flair* Trial

**Peter Hillmen**, Alexandra Pitchford, Adrian Bloor, Angus Broom, Moya Young, Ben Kennedy, Renata Walewska, Michelle Furtado, Gavin Preston, Jeffrey R. Neilson, Nicholas Pemberton, Gamal Sidra, Nicholas Morley, Kate Cwynarski, Anna Schuh, Francesco Forconi, Nagah Elmusharaf, Shankara Paneesha, Christopher P. Fox, Dena Howard, Anna Hockaday, David Cairns, Sharon Jackson, Natasha Greatorex, Piers EM Patten, David Allsup and Talha Munir

Abstract No: 642, Oral Presentation, ASH Annual Meeting
Monday, December 13th 2021

National Cancer Research Institute

CANCER RESEARCH UK

ctru University of Leeds

LEEDS CLINICAL TRIALS UNIT

# Flair Serious Adverse Events & malignancies

## SAE's by organ class*

| | Number of participants reporting one or more SAE | |
|---|---|---|
| | FCR (n=378) | IR (n=384) |
| Infections and infestations | 127 (33.6%) | 104 (27.1%) |
| Blood and lymphatic system disorders | 75 (19.8%) | 41 (10.7%) |
| Gastrointestinal disorders | 22 (5.8%) | 27 (7%) |
| Cardiac disorders | 4 (1.1%) | 32 (8.3%) |
| General disorders and administration site conditions | 14 (3.7%) | 10 (2.6%) |
| Musculoskeletal and connective tissue disorders | 4 (1.1%) | 18 (4.7%) |
| Neoplasms benign, malignant and unspecified (including cysts and polyps) | 6 (1.6%) | 13 (3.4%) |
| Skin and subcutaneous tissue disorders | 12 (3.2%) | 7 (1.8%) |
| Nervous system disorders | 1 (0.3%) | 14 (3.6%) |
| Renal and urinary disorders | 1 (0.3%) | 13 (3.4%) |
| Respiratory, thoracic and mediastinal disorders | 2 (0.5%) | 9 (2.3%) |

## Secondary malignancies (SM)

| | Number of participants reporting one or more SM | |
|---|---|---|
| | FCR (n=378) | IR (n=384) |
| MDS/AML | 5 | 1 |
| Breast | 2 | 0 |
| Non-melanoma skin | 23 | 7 |
| Melanoma | 1 | 4 |
| Lung | 4 | 1 |
| Richter's transformation | 3 | 2 |
| Prostate | 6 | 4 |
| Urological other | 2 | 3 |
| Lower gastrointestinal | 2 | 1 |
| Other | 9 | 6 |
| TOTAL: | 57 | 29 |

*Occurring in ≥ 10 participants in the safety population.

Data-lock: 24th May 2021

Hillmen *et al.*, Abstract 642, ASH 2021

NCRI National Cancer Research Institute | CANCER RESEARCH UK | ctru University of Leeds | LEEDS CLINICAL TRIALS UNIT

# Relative risk of sudden unexplained death or cardiac death, accounting for pre-existing HTN/cardiac disorder at trial entry*, by Flair arm

*Defined as being on medication for HTN or CV conditions at study entry

| | FCR | | | | IR | | | |
|---|---|---|---|---|---|---|---|---|
| | Sudden unexplained death or cardiac death | | | | Sudden unexplained death or cardiac death | | | |
| Hypertension or prior history of cardiac disorder (on treatment at trial entry) | | No | Yes | Total | | No | Yes | Total |
| | No | 288 | 2 | 290 | No | 276 | 1 | 277 |
| | Yes | 88 | 0 | 88 | Yes | 100 | 7 | 107 |
| | Total | 376 | 2 | 378 | Total | 376 | 8 | 384 |
| | Relative Risk IE* Fisher's Exact P IE* | | | | Relative Risk 18.1, 95%CI (2.3-146) Fisher's Exact P <0.001 | | | |

**Meta-analysis**

FLAIR is not an outlier for sudden unexplained or cardiac deaths in ibrutinib-containing arms and is consistent with other phase III CLL ibrutinib-containing trials including ALLIANCE, iLLUMINATE, RESONATE, GENUINE and HELIOS.

See poster abstract (#2636) for more details: *'Sudden or Cardiac Deaths on Ibrutinib-Based Therapy Were Associated with a Prior History of Hypertension or Cardiac Disease and the Use of ACE-Inhibitors at Study Entry: Analysis from the Phase III NCRI FLAIR Trial''*, Munir, T.

# Flair Conclusions

- Ibrutinib+rituximab has a superior PFS compared to FCR with a Hazard Ratio of 0.44 (p<0.001)
  - Superior PFS for IR observed in patients with CLL with unmutated IgHV, 11q deletion, and normal karyotype
  - IgHV mutated shows a non-significant improvement in PFS for IR with a Hazard Ratio of 0.68 (p=0.197) (95% CI, 0.38-1.22)
- There is no difference in overall survival but almost all patients relapsing after FCR received either ibrutinib or venetoclax+rituximab
- Sudden cardiac deaths are observed with ibrutinib particularly in patients with preceding hypertension or other cardiac conditions requiring therapy
- Deaths due to secondary AML/MDS and infections more common with FCR

haematologica

Journal of The Ferrata-Storti Foundation

# Cardiovascular adverse events in patients with chronic lymphocytic leukemia receiving acalabrutinib monotherapy: pooled analysis of 762 patients

by Jennifer R. Brown, John C. Byrd, Paolo Ghia, Jeff P. Sharman, Peter Hillmen, Deborah M. Stephens, Clare Sun, Wojciech Jurczak, John M. Pagel, Alessandra Ferrajoli, Priti Patel, Lin Tao, Nataliya Kuptsova-Clarkson, Javid Moslehi, and Richard R. Furman

*Received: April 6, 2021.*
*Accepted: September 21, 2021.*

10.3324/haematol.2021;278901.

blood®
Regular Article

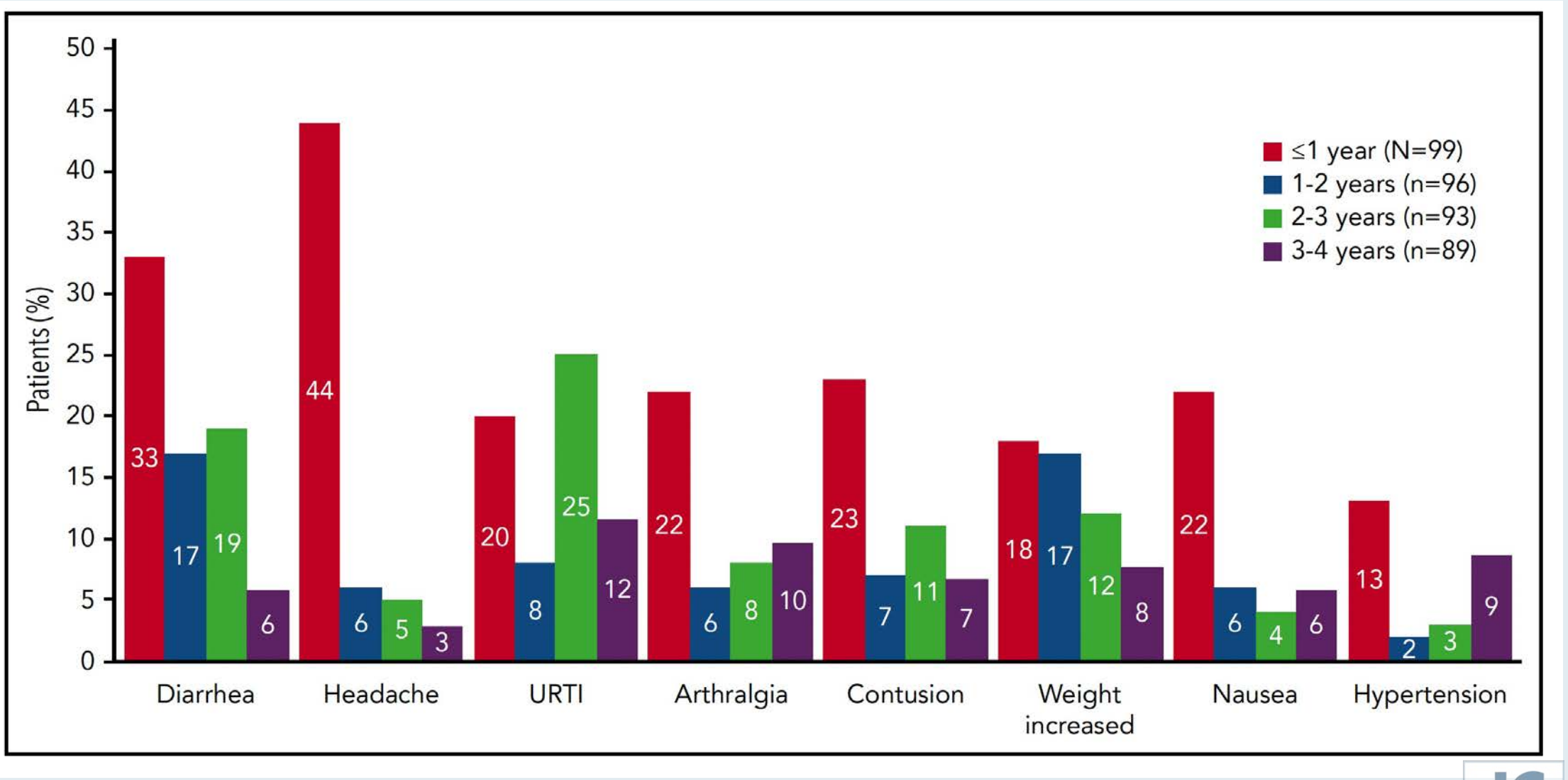
CLINICAL TRIALS AND OBSERVATIONS

# Acalabrutinib in treatment-naive chronic lymphocytic leukemia

John C. Byrd,[1] Jennifer A. Woyach,[1] Richard R. Furman,[2] Peter Martin,[2] Susan O'Brien,[3] Jennifer R. Brown,[4] Deborah M. Stephens,[5] Jacqueline C. Barrientos,[6] Stephen Devereux,[7] Peter Hillmen,[8] John M. Pagel,[9] Ahmed Hamdy,[10] Raquel Izumi,[10] Priti Patel,[10] Min Hui Wang,[10] Nitin Jain,[11] and William G. Wierda[11]

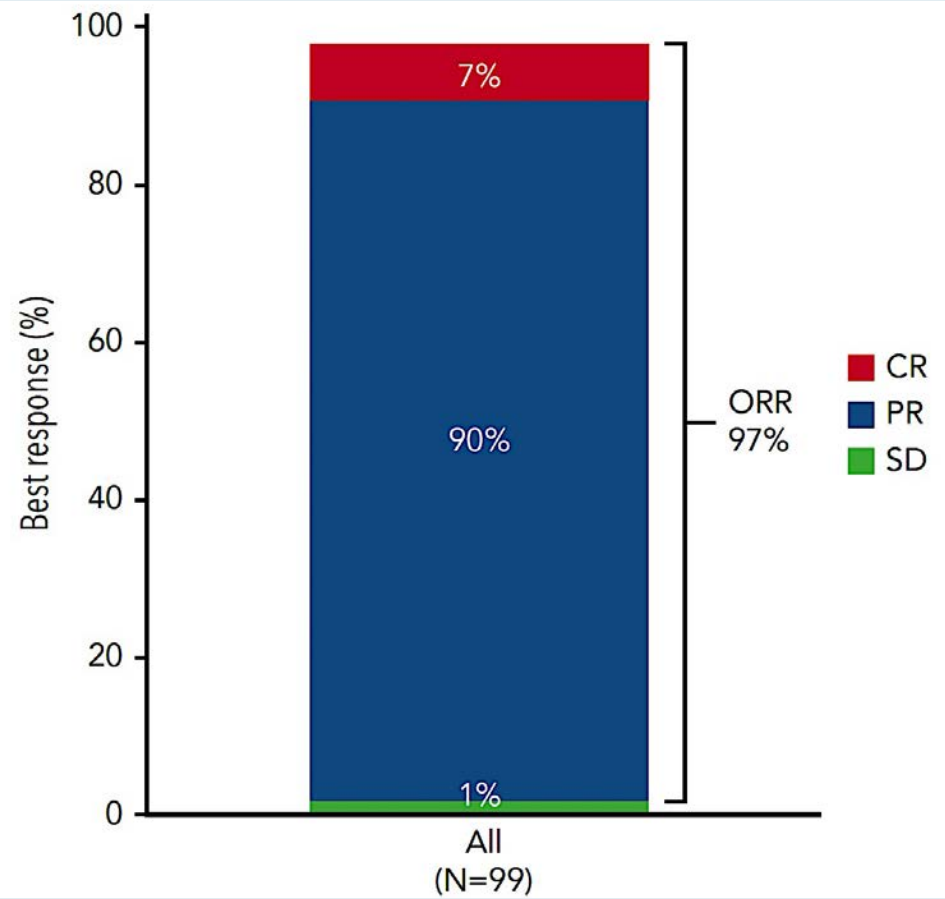
2021;137(24):3327-38.

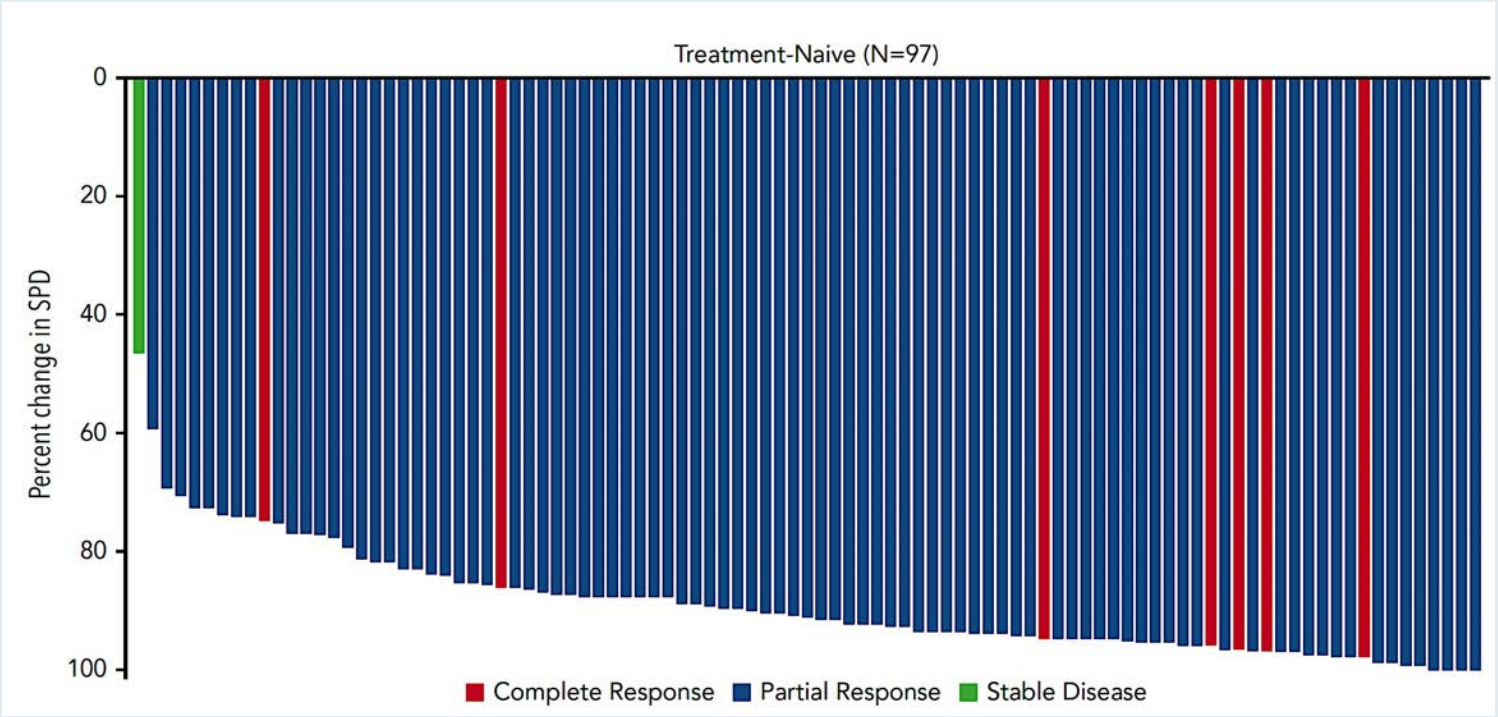
# Incidence of Select Treatment-Emergent Adverse Events by Yearly Intervals




Byrd JC et al. *Blood* 2021;137(24):3327-38.

# Response to Acalabrutinib and Best Change in Tumor Size




Byrd JC et al. *Blood* 2021;137(24):3327-38.

bjh good practice papers

# Management of cardiovascular complications of bruton tyrosine kinase inhibitors

Chloe Pek Sang Tang,[1,*] Gregory Y.H. Lip,[2,3,*] Terry McCormack,[4] Alexander R. Lyon,[5] Peter Hillmen,[6] Sunil Iyengar,[7] Nicolas Martinez-Calle,[8] Nilima Parry-Jones,[9] Piers E.M. Patten,[10] Anna Schuh,[1] and Renata Walewska[11], on behalf of the BSH guidelines committee, UK CLL Forum

*British Journal of Haematology* 2022;196:70-8.

Abstract 3721

# Characterization of Bruton Tyrosine Kinase Inhibitor (BTKi)-Related Adverse Events in a Head-to-Head Trial of Acalabrutinib Versus Ibrutinib in Previously Treated Chronic Lymphocytic Leukemia (CLL)

John F. Seymour[1], John C. Byrd[2], Peter Hillmen[3], Paolo Ghia[4], Arnon P. Kater[5], Asher Chanan-Khan[6], Richard R. Furman[7], Susan O'Brien[8], Jennifer R. Brown[9], Anthony Mato[10], Stephan Stilgenbauer[11], Nataliya Kuptsova-Clarkson[12], Paulo Miranda[12], Dennis Wagner[13], Kara Higgins[14], Sophia Sohoni[14], Wojciech Jurczak[15]

ASH 2021

JC JOURNAL CLUB RTP RESEARCH TO PRACTICE

# Sudden or Cardiac Deaths on Ibrutinib-Based Therapy Were Associated with a Prior History of Hypertension or Cardiac Disease and the Use of ACE-Inhibitors at Study Entry: Analysis from the Phase III NCRI FLAIR Trial

Munir T et al.

ASH 2021;Abstract 2636.

Leukemia (2021) 35:3059–3072
https://doi.org/10.1038/s41375-021-01241-1

REVIEW ARTICLE

Chronic lymphocytic leukemia

# Measurable residual disease in chronic lymphocytic leukemia: expert review and consensus recommendations

William G. Wierda[1] · Andrew Rawstron[2] · Florence Cymbalista[3] · Xavier Badoux[4] · Davide Rossi[5] · Jennifer R. Brown[6] · Alexander Egle[7] · Virginia Abello[8] · Eduardo Cervera Ceballos[9] · Yair Herishanu[10] · Stephen P. Mulligan[11] · Carsten U. Niemann[12] · Colin P. Diong[13] · Teoman Soysal[14] · Ritsuro Suzuki[15] · Hoa T. T. Tran[16] · Shang-Ju Wu[17] · Carolyn Owen[18] · Stephan Stilgenbauer[19] · Paolo Ghia[20] · Peter Hillmen[21]

# SEQUOIA: RESULTS OF A PHASE 3 RANDOMIZED STUDY OF ZANUBRUTINIB VERSUS BENDAMUSTINE + RITUXIMAB IN PATIENTS WITH TREATMENT-NAIVE CHRONIC LYMPHOCYTIC LEUKEMIA/SMALL LYMPHOCYTIC LYMPHOMA

**Constantine S. Tam, MBBS, MD[1,2,3,4]; Krzysztof Giannopoulos, MD, PhD[5,6]; Wojciech Jurczak, MD, PhD[7]; Martin Šimkovič, MD, PhD[8,9]; Mazyar Shadman, MD, MPH[10,11]; Anders Österborg, MD, PhD[12,13]; Luca Laurenti, MD[14]; Patricia Walker, MBBS, BMedSci, FRACP, FRCPA[15]; Stephen Opat, MBBS (Hons), FRACP, FRCPA[16,17]; Henry Chan, MBChB, FRACP, FRCPA[18]; Hanna Ciepluch, MD, PhD[19]; Richard Greil, MD[20,21,22]; Monica Tani, MD[23]; Marek Trněný, MD[24]; Danielle M. Brander, MD[25]; Ian W. Flinn, MD, PhD[26]; Sebastian Grosicki, MD, PhD[27]; Emma Verner, MBBS, BMedSci, FRCPA, FRACP[28,29]; Jennifer R. Brown MD, PhD[30]; Brad S. Kahl, MD[31]; Paolo Ghia, MD, PhD[32]; Jianyong Li, MD, PhD[33]; Tian Tian, PhD[34]; Lei Zhou, MD[34]; Carol Marimpietri[34]; Jason C. Paik, MD, PhD[34]; Aileen Cohen, MD, PhD[34]; Jane Huang, MD[34]; Tadeusz Robak, MD, PhD[35]; and Peter Hillmen, MBChB, PhD[36]**

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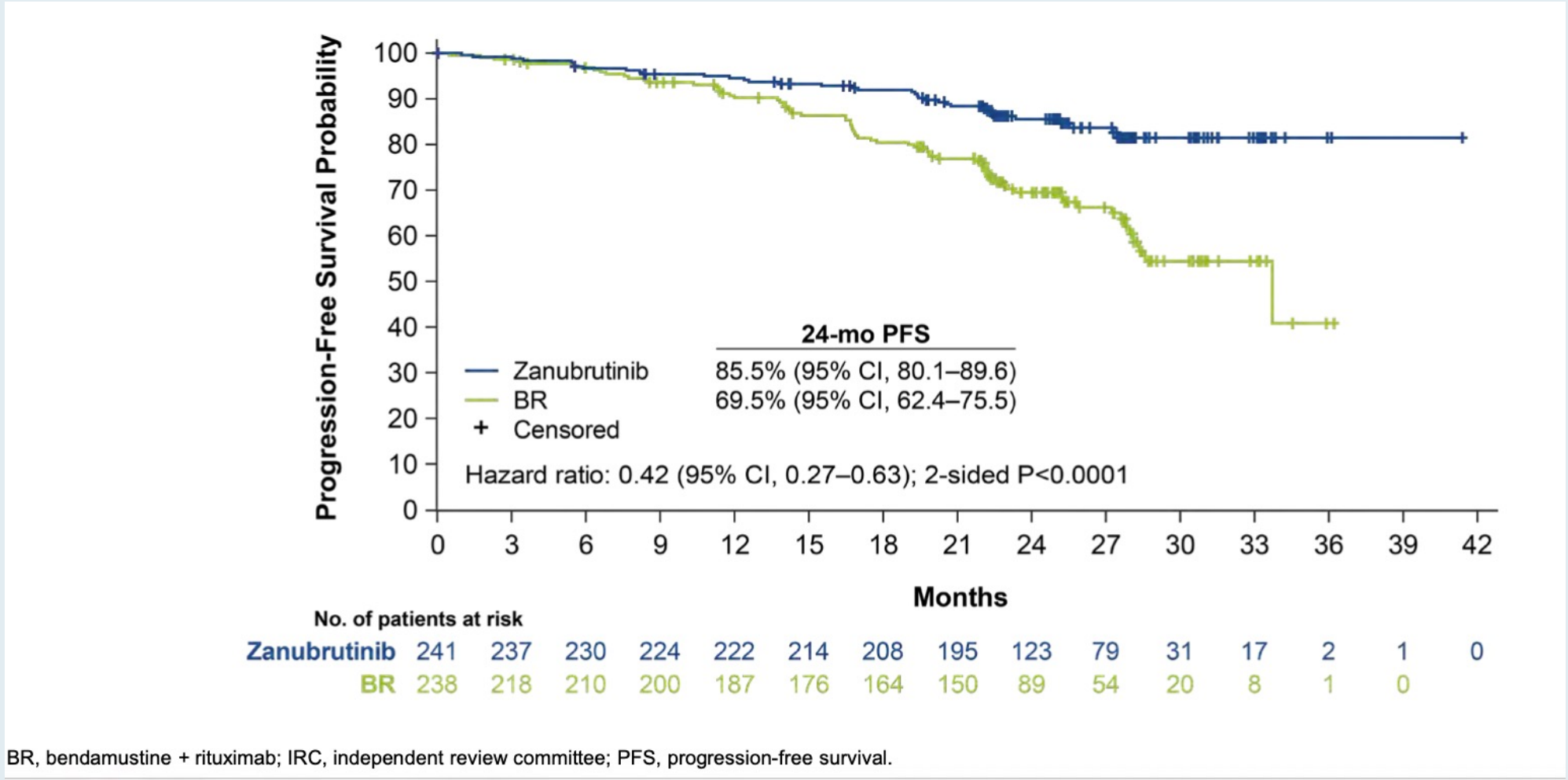
**Sunday, December 12, 2021**
642. Chronic Lymphocytic Leukemia: Clinical and Epidemiological I

American Society of Hematology

63rd ASH Annual Meeting and Exposition, December 11-14, 2021
**Abstract 396**

# SEQUOIA: Progression-Free Survival per IRC Assessment




BR, bendamustine + rituximab; IRC, independent review committee; PFS, progression-free survival.

Tam CS et al. ASH 2021;Abstract 396.

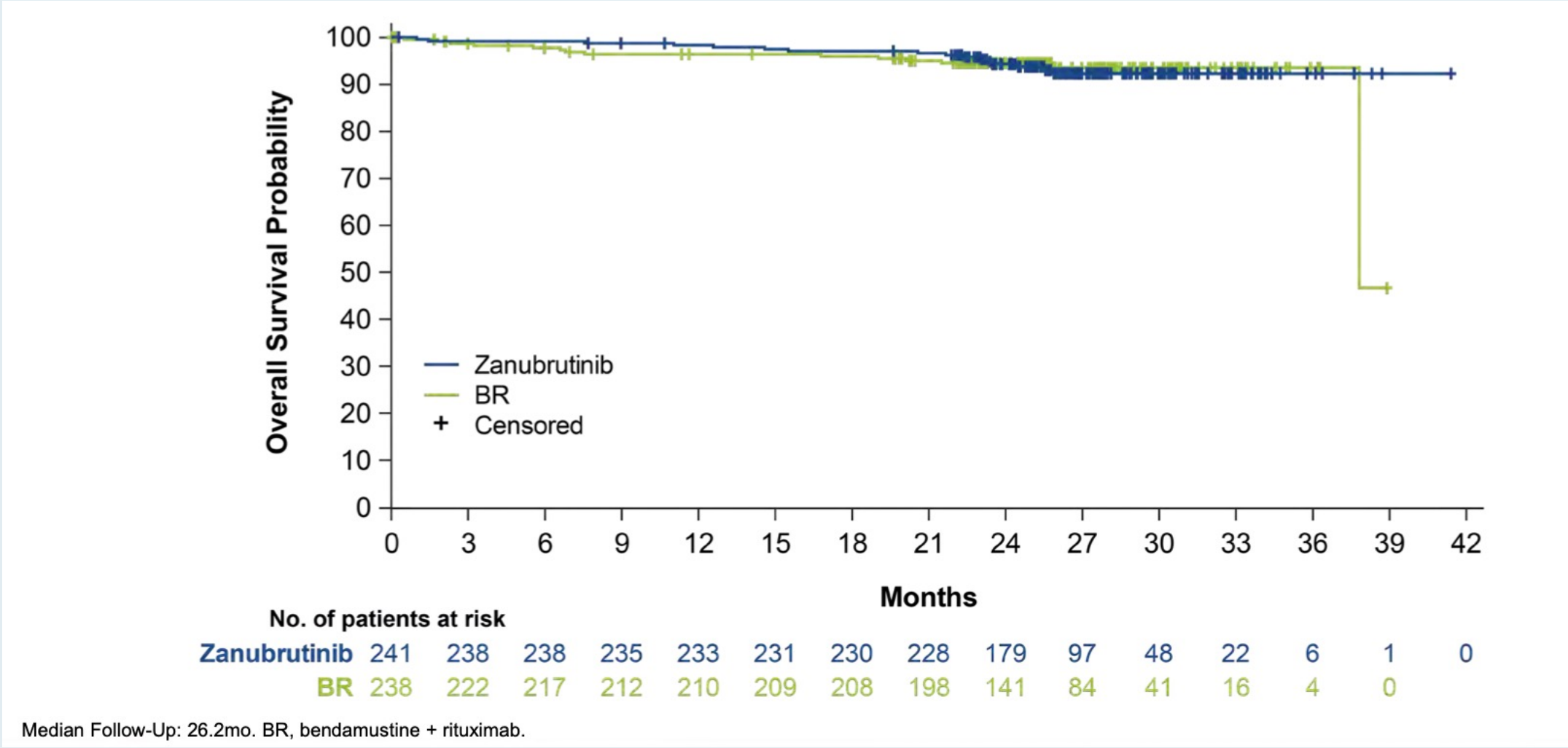
# SEQUOIA: Progression-Free Survival per IRC Assessment by Key Patient Subgroup

| Subgroup | Event/Patient Zanubrutinib | Event/Patient BR | Hazard Ratio (95% CI), %[a] |
|---|---|---|---|
| **All Patients** | 36/241 | 71/238 | 0.42 (0.28–0.63) |
| **Age (years)** | | | |
| <65 | 6/45 | 19/46 | 0.25 (0.10–0.62) |
| ≥65 | 30/196 | 52/192 | 0.47 (0.30–0.74) |
| **Sex** | | | |
| Male | 24/154 | 47/144 | 0.39 (0.24–0.64) |
| Female | 12/87 | 24/94 | 0.45 (0.23–0.91) |
| **Binet stage** | | | |
| A or B | 24/171 | 52/168 | 0.39 (0.24–0.64) |
| C | 12/70 | 19/70 | 0.48 (0.23–1.00) |
| **ECOG** | | | |
| 0 | 12/110 | 24/101 | 0.39 (0.19–0.78) |
| ≥1 | 24/131 | 47/137 | 0.43 (0.26–0.71) |
| **Bulky disease (LDi <5 cm vs ≥5 cm)** | | | |
| <5 cm | 21/172 | 44/165 | 0.37 (0.22–0.63) |
| ≥5 cm | 15/69 | 27/73 | 0.52 (0.27–0.97) |
| **IGHV mutational status** | | | |
| Mutated | 18/109 | 25/110 | 0.67 (0.36–1.22) |
| Unmutated | 15/125 | 45/121 | 0.24 (0.13–0.43) |
| **Cytopenias at baseline[b]** | | | |
| Yes | 21/102 | 34/109 | 0.55 (0.32–0.95) |
| No | 15/139 | 37/129 | 0.31 (0.17–0.57) |
| **Chromosome 11q deletion** | | | |
| Yes | 7/43 | 22/46 | 0.21 (0.09–0.50) |
| No | 29/198 | 49/192 | 0.50 (0.32–0.80) |


[a]Hazard ratios were calculated using a stratified Cox regression model.
[b]Defined as having anemia (hemoglobin ≤110 g/L) or thrombocytopenia (platelets ≤100 × $10^9$/L) or neutropenia (absolute neutrophil count ≤1.5 × $10^9$/L).
BR, bendamustine + rituximab; ECOG, Eastern Cooperative Oncology Group; IGHV, gene encoding the immunoglobulin heavy chain variable region; IRC, independent review committee; LDi, longest diameter.

Tam CS et al. ASH 2021;Abstract 396.

# SEQUOIA: Overall Survival




Median Follow-Up: 26.2mo. BR, bendamustine + rituximab.

Tam CS et al. ASH 2021;Abstract 396.

# SEQUOIA: Adverse Event Summary

| | Arm A Zanubrutinib (n=240[a]) | Arm B Bendamustine + Rituximab (n=227[a]) |
|---|---|---|
| **Any AE, n (%)** | 224 (93.3) | 218 (96.0) |
| **Grade ≥3 AE, n (%)** | 126 (52.5) | 181 (79.7) |
| **Serious AE, n (%)** | 88 (36.7) | 113 (49.8) |
| **Fatal AE, n (%)** | 11 (4.6) | 11 (4.8) |
| **AE leading to dose reduction, n (%)** | 18 (7.5) | 84 (37.4) |
| **AE leading to dose interruption/delay, n (%)** | 111 (46.3) | 154 (67.8) |
| **AE leading to discontinuation, n (%)** | 20 (8.3) | 31 (13.7) |

AEs were recorded until disease progression to support safety evaluation over an equivalent time period

[a]Safety was assessed in patients who received ≥1 dose of treatment; 1 patient in Arm A and 11 patients in Arm B did not receive treatment.
AE, adverse event.

Tam CS et al. ASH 2021;Abstract 396.

# SEQUOIA: Adverse Events of Interest

| AE, n (%) | Arm A Zanubrutinib (n=240[a]) | | Arm B Bendamustine + Rituximab (n=227[a]) | |
|---|---|---|---|---|
| | Any Grade | Grade ≥3 | Any Grade | Grade ≥3 |
| **Anemia** | 11 (4.6) | 1 (0.4) | 44 (19.4) | 4 (1.8) |
| **Neutropenia[b]** | 38 (15.8) | 28 (11.7) | 129 (56.8) | 116 (51.1) |
| **Thrombocytopenia[c]** | 11 (4.6) | 5 (2.1) | 40 (17.6) | 18 (7.9) |
| **Arthralgia** | 32 (13.3) | 2 (0.8) | 20 (8.8) | 1 (0.4) |
| **Atrial fibrillation** | 8 (3.3) | 1 (0.4) | 6 (2.6) | 3 (1.3) |
| **Bleeding[d]** | 108 (45.0) | 9 (3.8) | 25 (11.0) | 4 (1.8) |
| Major bleeding[e] | 12 (5.0) | 9 (3.8) | 4 (1.8) | 4 (1.8) |
| **Diarrhea** | 33 (13.8) | 2 (0.8) | 31 (13.7) | 5 (2.2) |
| **Hypertension[f]** | 34 (14.2) | 15 (6.3) | 24 (10.6) | 11 (4.8) |
| **Infections[g]** | 149 (62.1) | 39 (16.3) | 127 (55.9) | 43 (18.9) |
| **Myalgia** | 9 (3.8) | 0 (0.0) | 3 (1.3) | 0 (0.0) |
| **Other cancers** | 31 (12.9) | 17 (7.1) | 20 (8.8) | 7 (3.1) |
| Dermatologic other cancers | 16 (6.7) | 2 (0.8) | 10 (4.4) | 2 (0.9) |

[a]Safety was assessed in patients who received ≥1 dose of treatment; 1 patient in Arm A and 11 patients in Arm B did not receive treatment. [b]Neutropenia, neutrophil count decreased, or febrile neutropenia. [c]Thrombocytopenia or platelet count decreased. [d]Pooled term of all-cause bleeding including bruising, petechiae, purpura, and contusion. [e]Major bleeding included all grade ≥3, serious, and any-grade central nervous system hemorrhage. [f]Hypertension, blood pressure increased, or hypertensive crisis. [g]All infection terms pooled.
AE, adverse event.

Tam CS et al. ASH 2021;Abstract 396.

# ZANUBRUTINIB IN COMBINATION WITH VENETOCLAX FOR PATIENTS WITH TREATMENT-NAIVE CHRONIC LYMPHOCYTIC LEUKEMIA OR SMALL LYMPHOCYTIC LYMPHOMA WITH DEL(17P): EARLY RESULTS FROM ARM D OF THE SEQUOIA (BGB-3111-304) TRIAL

**Alessandra Tedeschi, MD[1]; Emmanuelle Ferrant, MD[2]; Ian Flinn MD, PhD[3]; Constantine S. Tam MBBS, MD[4,5,6,7]; Paolo Ghia, MD, PhD[8]; Tadeusz Robak, MD, PhD[9]; Jennifer R. Brown, MD, PhD[10]; Vanitha Ramakrishnan, PhD[11]; Tian Tian, PhD[11]; Sowmya B. Kuwahara, PharmD[11]; Fangfang Yin, PhD[11]; Jason C. Paik, MD, PhD[11]; Aileen Cohen, MD, PhD[11]; Jane Huang, MD[11]; and Peter Hillmen, MBChB, PhD[12]**

*[1]ASST Grande Ospedale Metropolitano Niguarda, Milan, Italy; [2]Centre Hospitalier Lyon-Sud, University Claude Bernard Lyon 1, Pierre-Bénite, France; [3]Sarah Cannon Research Institute/Tennessee Oncology, Nashville, TN, USA; [4]Peter MacCallum Cancer Centre, Melbourne, Victoria, Australia; [5]University of Melbourne, Parkville, Victoria, Australia; [6]St Vincent's Hospital, Fitzroy, Victoria, Australia; [7]Royal Melbourne Hospital, Parkville, Victoria, Australia; [8]Università Vita-Salute San Raffaele and IRCCS Ospedale San Raffaele, Milano, Italy; [9]Medical University of Lodz, Lodz, Poland; [10]Dana-Farber Cancer Institute, Boston, MA, USA; [11]BeiGene (Beijing) Co., Ltd., Beijing, China and BeiGene USA, Inc., San Mateo, CA, USA; [12]Saint James's University Hospital, Leeds, UK*

**Saturday, December 11, 2021**

642. Chronic Lymphocytic Leukemia: Clinical and Epidemiological: Combination Small Molecules

American Society *of* Hematology

63rd ASH Annual Meeting and Exposition, December 11-14, 2021

**Abstract 67**

# Meet The Professor with Prof Hillmen

## Introduction

## MODULE 1: Case Presentations

- Dr Blackmon: A 60-year-old man with CLL and Richter's transformation to Hodgkin lymphoma
- Dr Palmer: A 76-year-old man with relapsed CLL after 3 years of second-line ibrutinib
- Dr Danilov: A 52-year-old man with newly diagnosed IGHV-unmutated CLL — Del(17p), TP53 mutation
- Dr McKenna: A 53-year-old woman who presents with persistent lymphocytosis
- Dr Blackmon: A 58-year-old man with CLL who receives FCR and remains in complete remission 5 years later
- Dr Danilov: A 71-year-old man with relapsed CLL who is concerned about contracting COVID-19

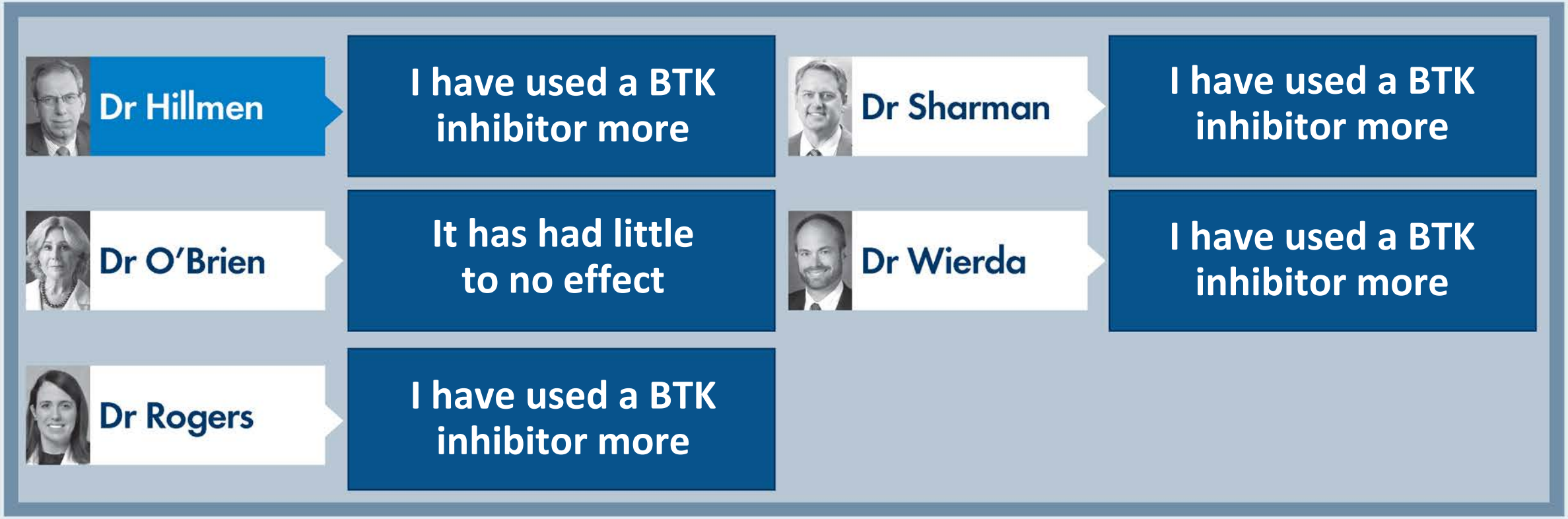
## MODULE 2: Journal Club with Prof Hillmen

## MODULE 3: Faculty Survey

## MODULE 4: Key Recent Data Sets

RTP
RESEARCH
TO PRACTICE

# In general, how if at all has the COVID-19 pandemic affected your selection of first-line therapy for patients with chronic lymphocytic leukemia (CLL) who require treatment?




BTK = Bruton tyrosine kinase

RTP RESEARCH TO PRACTICE

# For which patients with CLL are you using Evusheld™ (tixagevimab copackaged with cilgavimab) as pre-exposure prophylaxis for COVID-19?

| | |
|---|---|
|  Dr Hillmen | Not available in United Kingdom |
|  Dr O'Brien | All patients with CLL |
|  Dr Rogers | Anyone with CLL/SLL |
|  Dr Sharman | Any patient on tx in last 24 mo if neg Ab titer |
|  Dr Wierda | All who are on tx or received tx within past year |

SLL = small lymphocytic lymphoma

RTP RESEARCH TO PRACTICE

# For patients with CLL who are receiving a BTK inhibitor and contract an asymptomatic COVID-19 infection, should the BTK inhibitor generally be continued or held?

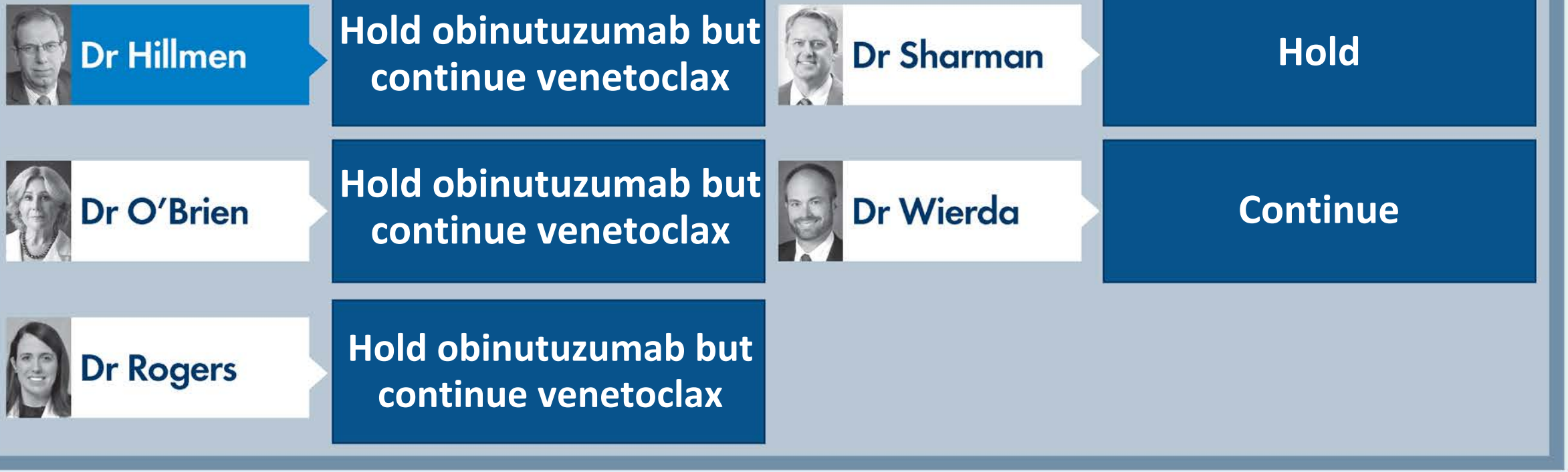
1. BTK inhibitor should be continued
2. BTK inhibitor should be held
3. I’m not sure

RTP
RESEARCH
TO PRACTICE

# For patients with CLL who are receiving a BTK inhibitor and contract an asymptomatic COVID-19 infection, do you generally continue or hold the BTK inhibitor?


RTP RESEARCH TO PRACTICE

# For patients with CLL who are receiving obinutuzumab/venetoclax and contract an asymptomatic COVID-19 infection, do you generally continue or hold the treatment?

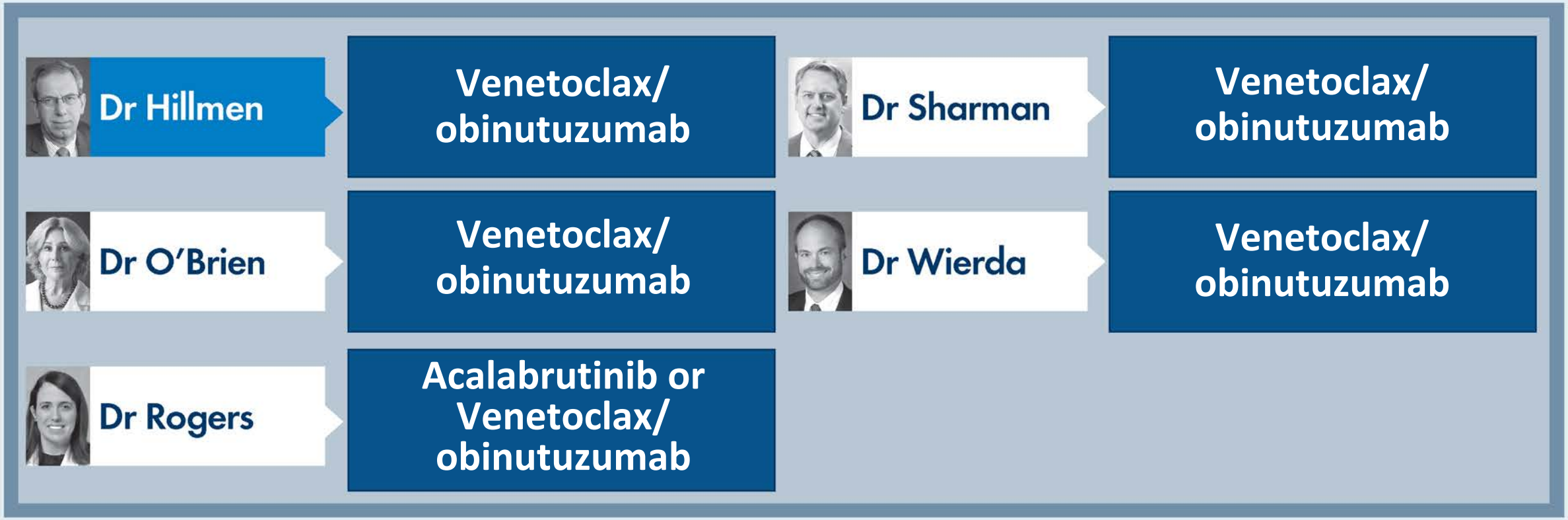



RTP RESEARCH TO PRACTICE

# 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. BR (bendamustine/rituximab)
3. Ibrutinib
4. Ibrutinib + anti-CD20 antibody
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?



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

1. Ibrutinib
2. Ibrutinib + anti-CD20 antibody
3. Acalabrutinib
4. Acalabrutinib + obinutuzumab
5. Zanubrutinib
6. Venetoclax + obinutuzumab
7. Venetoclax + ibrutinib
8. Other

# Regulatory and reimbursement issues aside, what would be your preferred initial regimen for a 60-year-old patient with CLL, unmutated IGHV and no del(17p) or TP53 mutation who required treatment?

| | |
|---|---|
|  Dr Hillmen | Venetoclax/ibrutinib |
|  Dr O'Brien | Venetoclax/ibrutinib |
|  Dr Rogers | Acalabrutinib or Venetoclax/ obinutuzumab |
|  Dr Sharman | Venetoclax/ obinutuzumab |
|  Dr Wierda | Venetoclax/ibrutinib |

RTP RESEARCH TO PRACTICE

# What is your usual preferred initial regimen for a 60-year-old patient with CLL, IGHV mutation and del(17p) or TP53 mutation who requires treatment?

1. FCR
2. BR
3. Ibrutinib
4. Ibrutinib + anti-CD20 antibody
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 and IGHV mutation and del(17p) or TP53 mutation who requires treatment?

| | | | |
|---|---|---|---|
|  Dr Hillmen | Acalabrutinib |  Dr Sharman | Acalabrutinib |
|  Dr O'Brien | Acalabrutinib |  Dr Wierda | Acalabrutinib |
|  Dr Rogers | Acalabrutinib | | |

RTP RESEARCH TO PRACTICE

**Which second-line systemic therapy would you recommend for a 60-year-old patient with CLL and unmutated IGHV without del(17p) or TP53 mutation who responds to venetoclax/obinutuzumab and then experiences disease progression 3 years after completing treatment?**

1. Ibrutinib
2. Ibrutinib + anti-CD20 antibody
3. Acalabrutinib
4. Acalabrutinib + obinutuzumab
5. Idelalisib
6. Duvelisib
7. Venetoclax + rituximab
8. Other

# Which second-line systemic therapy would you recommend for a 60-year-old patient with CLL and unmutated IGHV without del(17p) or TP53 mutation who responds to venetoclax/obinutuzumab and then experiences disease progression 3 years after completing treatment?

| | | | |
|---|---|---|---|
|  Dr Davids | Acalabrutinib |  Dr Rogers | Acalabrutinib |
|  Dr Hillmen | Venetoclax + rituximab |  Dr Sharman | Acalabrutinib |
|  Dr O'Brien | Acalabrutinib + obinutuzumab |  Dr Wierda | Re-treat with venetoclax + obinutuzumab |

RTP RESEARCH TO PRACTICE

# For patients with CLL who are receiving obinutuzumab/venetoclax as initial therapy, do you generally order a minimal residual disease (MRD) assay at the end of 12 months?

1. Yes
2. No

# For patients with CLL who are receiving obinutuzumab/venetoclax as initial therapy, do you generally order a minimal residual disease (MRD) assay at the end of 12 months?


RTP
RESEARCH
TO PRACTICE

# 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?

1. Continue treatment
2. Discontinue treatment

# 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?


RTP RESEARCH TO PRACTICE

# Should community-based medical oncologists/hematologists be ordering MRD assessment in any CLL clinical situations?

1. Yes
2. No

RTP
RESEARCH
TO PRACTICE

# Should community-based medical oncologists/hematologists be ordering MRD assessment for patients with CLL in any clinical situations?


RTP
RESEARCH
TO PRACTICE

# Meet The Professor with Prof Hillmen

## Introduction

## MODULE 1: Case Presentations

- Dr Blackmon: A 60-year-old man with CLL and Richter's transformation to Hodgkin lymphoma
- Dr Palmer: A 76-year-old man with relapsed CLL after 3 years of second-line ibrutinib
- Dr Danilov: A 52-year-old man with newly diagnosed IGHV-unmutated CLL — Del(17p), TP53 mutation
- Dr McKenna: A 53-year-old woman who presents with persistent lymphocytosis
- Dr Blackmon: A 58-year-old man with CLL who receives FCR and remains in complete remission 5 years later
- Dr Danilov: A 71-year-old man with relapsed CLL who is concerned about contracting COVID-19

## MODULE 2: Journal Club with Prof Hillmen

## MODULE 3: Faculty Survey

## MODULE 4: Key Recent Data Sets

RTP RESEARCH TO PRACTICE

# Minimal Residual Disease

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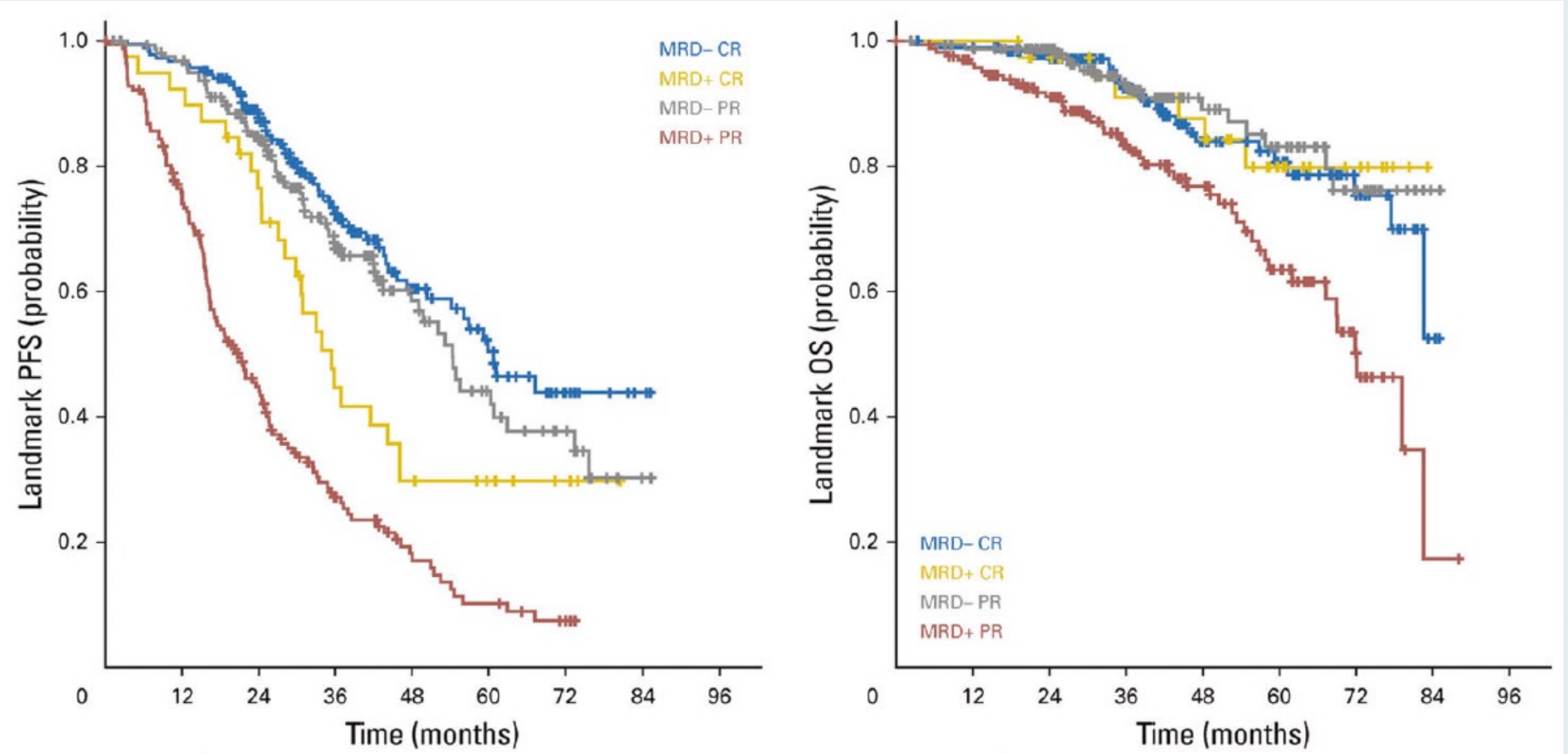
TO PRACTICE

# Currently Applied Methods for MRD Assessment

| Method | Sensitivity | Features | Advantages | Disadvantages |
|---|---|---|---|---|
| **Flow cytometry** | | | | |
| 4-color flow | $10^{-4}$ | Detection of surface markers by established antibody panels | ERIC consensus guidelines available, widely accessible, relatively affordable, quantitative results relatively quick | Fresh (<48 h) PB or BM samples necessary, sufficient number of cells required to achieve sensitivity |
| ≥6-color flow | $10^{-5}$ | | | |
| 8-color flow | $10^{-6}$ | | | |
| 10-color flow | $10^{-5}$ | | | |
| **Polymerase chain reaction (PCR)** | | | | |
| ASO PCR | $10^{-5}$ | Quantification based on allele- and pt-specific primers for hypervariable CDR3 of IgH | Good sensitivity, use of DNA (instead of fresh material), quantitative results | Pt-specific primers required, baseline reference sample necessary, relatively time and labor intensive |
| **Next-generation sequencing** | | | | |
| ClonoSEQ® | $10^{-6}$ | Measurement of CLL-specific IgH sequences based on consensus primers | High sensitivity, use of DNA, tracking of clones possible, quantitative results | Relatively expensive, baseline reference sample necessary, not widely used yet |

Al-Sawaf O et al. *Hematol Oncol Clin N Am* 2021;35(4):775-91. Wierda WG et al. *Leukemia* 2021;35:3059-72.

# Landmark Analysis in the CLL8 and CLL10 Trials of Chemoimmunotherapy for CLL: Survival According to MRD Status




Wierda WG et al. *Leukemia* 2021;35:3059-72.

RTP RESEARCH TO PRACTICE

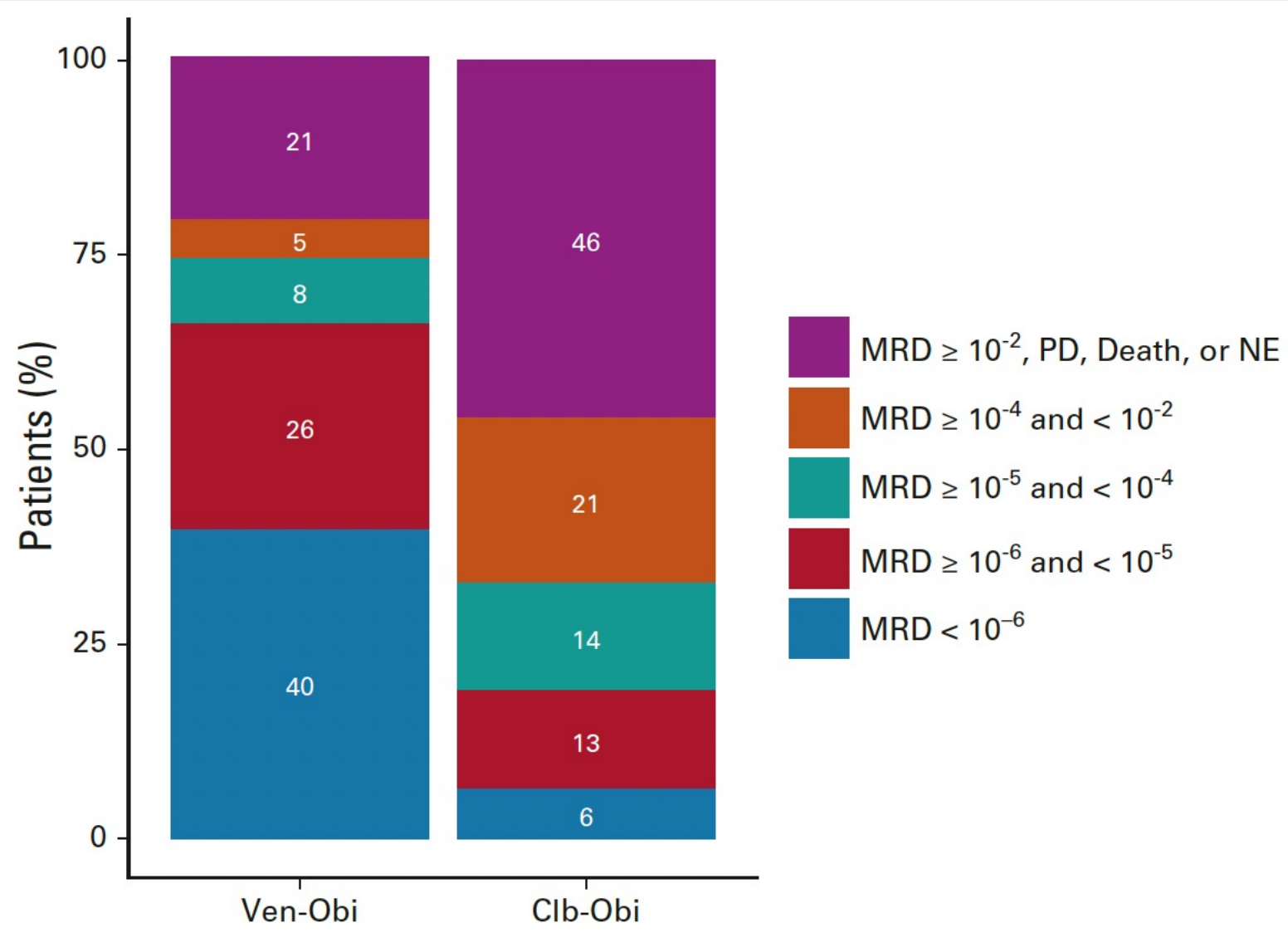
original reports

# Minimal Residual Disease Dynamics after Venetoclax-Obinutuzumab Treatment: Extended Off-Treatment Follow-up From the Randomized CLL14 Study

Othman Al-Sawaf, MD[1,2,3]; Can Zhang, PhD[1]; Tong Lu, PhD[4]; Michael Z. Liao, PhD[4]; Anesh Panchal, MSc[5]; Sandra Robrecht, PhD[1]; Travers Ching, PhD[6]; Maneesh Tandon, MBChB[5]; Anna-Maria Fink, MD[1]; Eugen Tausch, MD[7]; Christof Schneider, MD[7]; Matthias Ritgen, MD[8]; Sebastian Böttcher, MD[9]; Karl-Anton Kreuzer, MD[1]; Brenda Chyla, PhD[10]; Dale Miles, PhD[4]; Clemens-Martin Wendtner, MD[11]; Barbara Eichhorst, MD[1]; Stephan Stilgenbauer, MD[7,12]; Yanwen Jiang, PhD[4]; Michael Hallek, MD[1]; and Kirsten Fischer, MD[1]

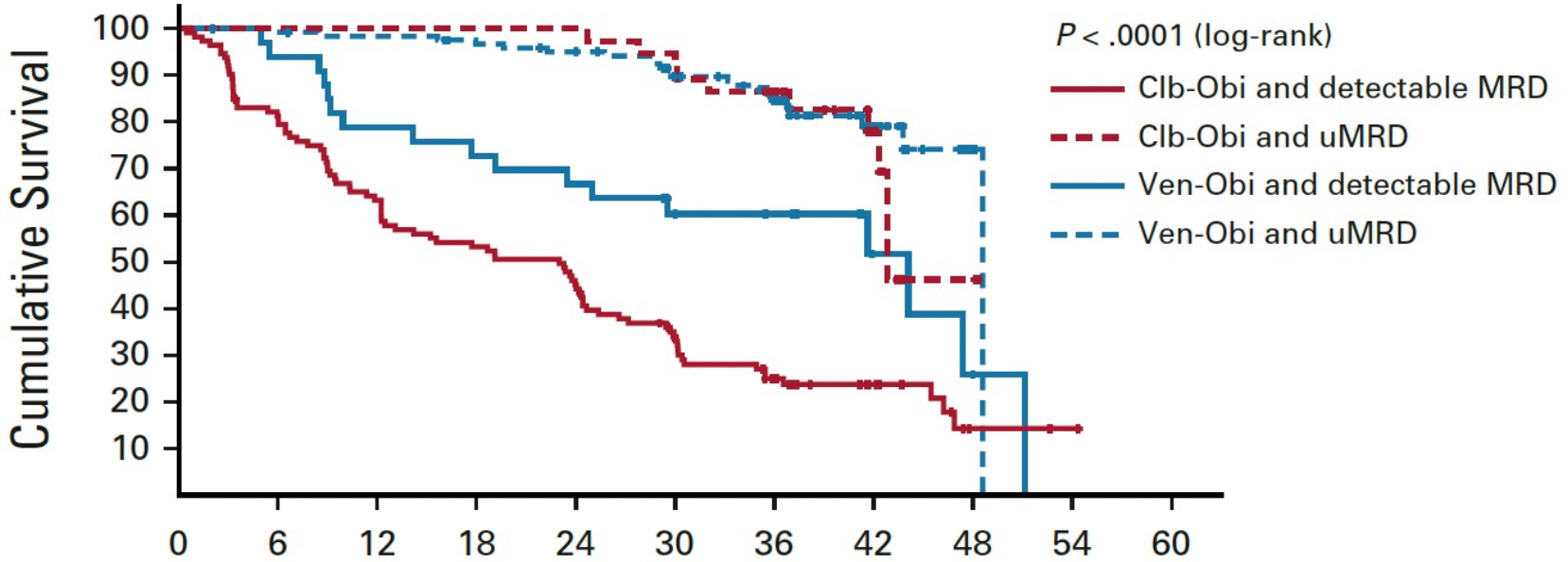
*J Clin Oncol* 2021;39(36):4049-60.

# CLL14 Update: Minimum Residual Disease (MRD) Status by Next-Generation Sequencing 2 Months After Completion of Treatment




Al-Sawaf O et al. *J Clin Oncol* 2021;39(36):4049-60.

# CLL14: PFS According to Bone Marrow MRD Status, from Last Treatment Exposure



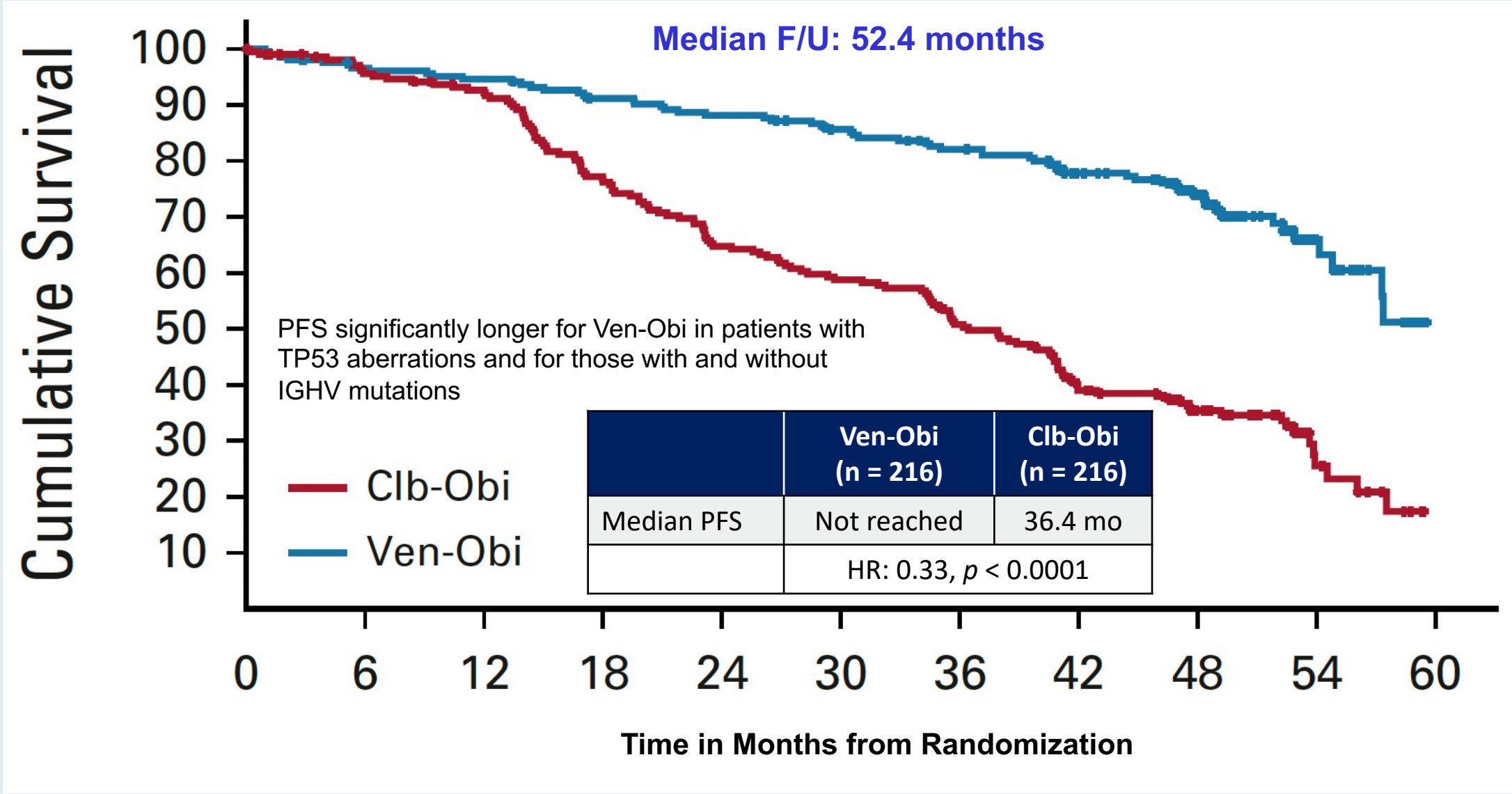

No. at risk:

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Ven-Obi & uMRD | 123 | 121 | 119 | 115 | 111 | 96 | 66 | 25 | 3 | 0 | 0 |
| Ven-Obi & detectable MRD | 33 | 31 | 26 | 24 | 22 | 18 | 12 | 4 | 2 | 0 | 0 |
| Clb-Obi & uMRD | 37 | 37 | 37 | 37 | 37 | 34 | 27 | 12 | 2 | 0 | 0 |
| Clb-Obi & detectable MRD | 112 | 90 | 70 | 59 | 50 | 34 | 22 | 12 | 2 | 1 | 0 |

Al-Sawaf O et al. *J Clin Oncol* 2021;39(36):4049-60.

# Current Approach to First-Line Treatment

# CLL14 Update: Progression-Free Survival




| | Ven-Obi (n = 216) | Clb-Obi (n = 216) |
|---|---|---|
| Median PFS | Not reached | 36.4 mo |
| | HR: 0.33, $p < 0.0001$ | |

Al-Sawaf O et al. *J Clin Oncol* 2021;39(36):4049-60.

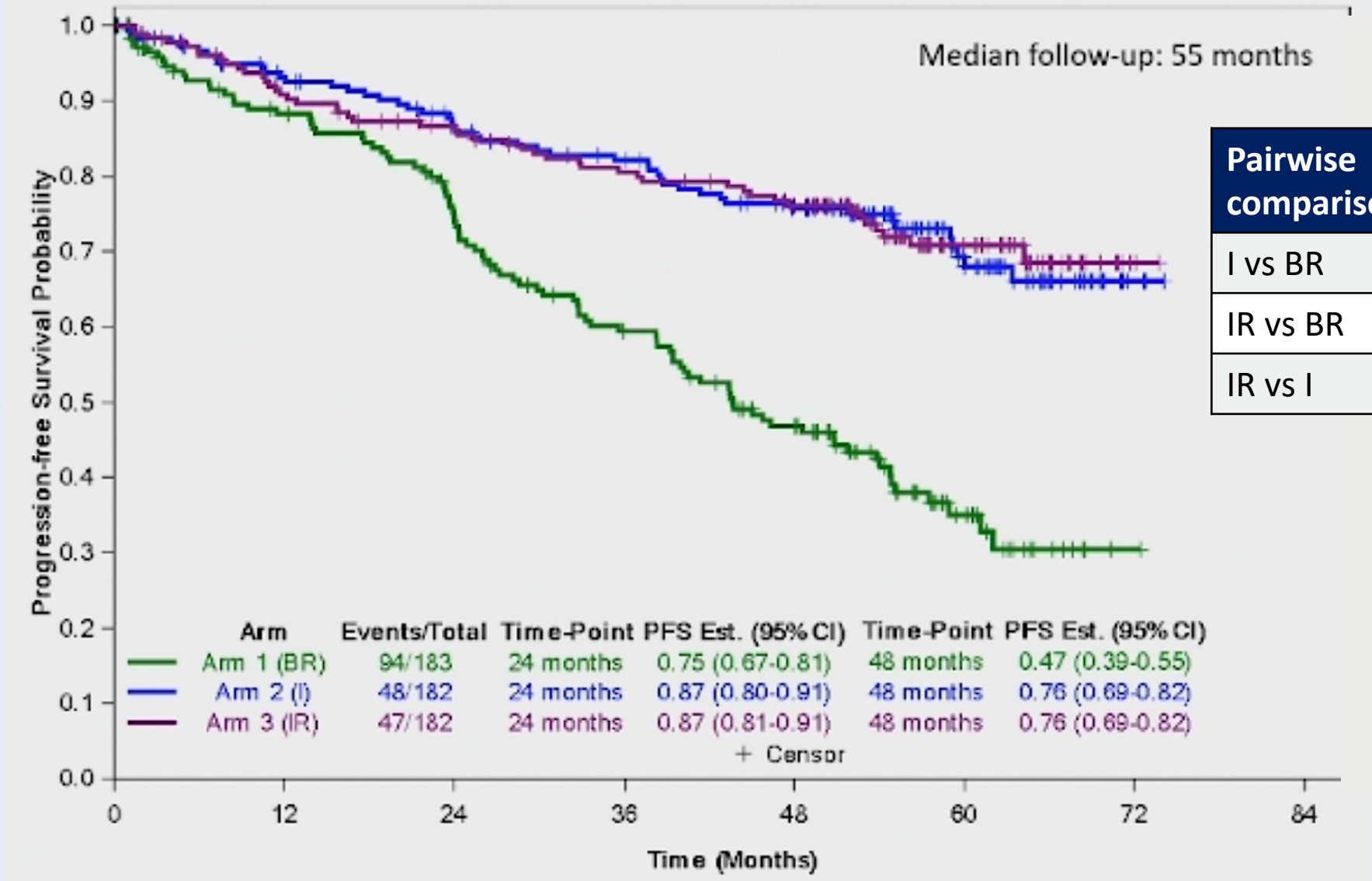
RTP RESEARCH TO PRACTICE

# Long-Term Results of Alliance A041202 Show Continued Advantage of Ibrutinib-Based Regimens Compared with Bendamustine Plus Rituximab (BR) Chemoimmunotherapy

Woyach JA et al.

ASH 2021;Abstract 639.

# Alliance A041202: Progression-Free Survival




| Pairwise comparisons | Hazard ratio | *p*-value |
|---|---|---|
| I vs BR | 0.36 | <0.0001 |
| IR vs BR | 0.36 | <0.001 |
| IR vs I | 0.99 | 0.96 |

Woyach JA et al. ASH 2021;Abstract 639.

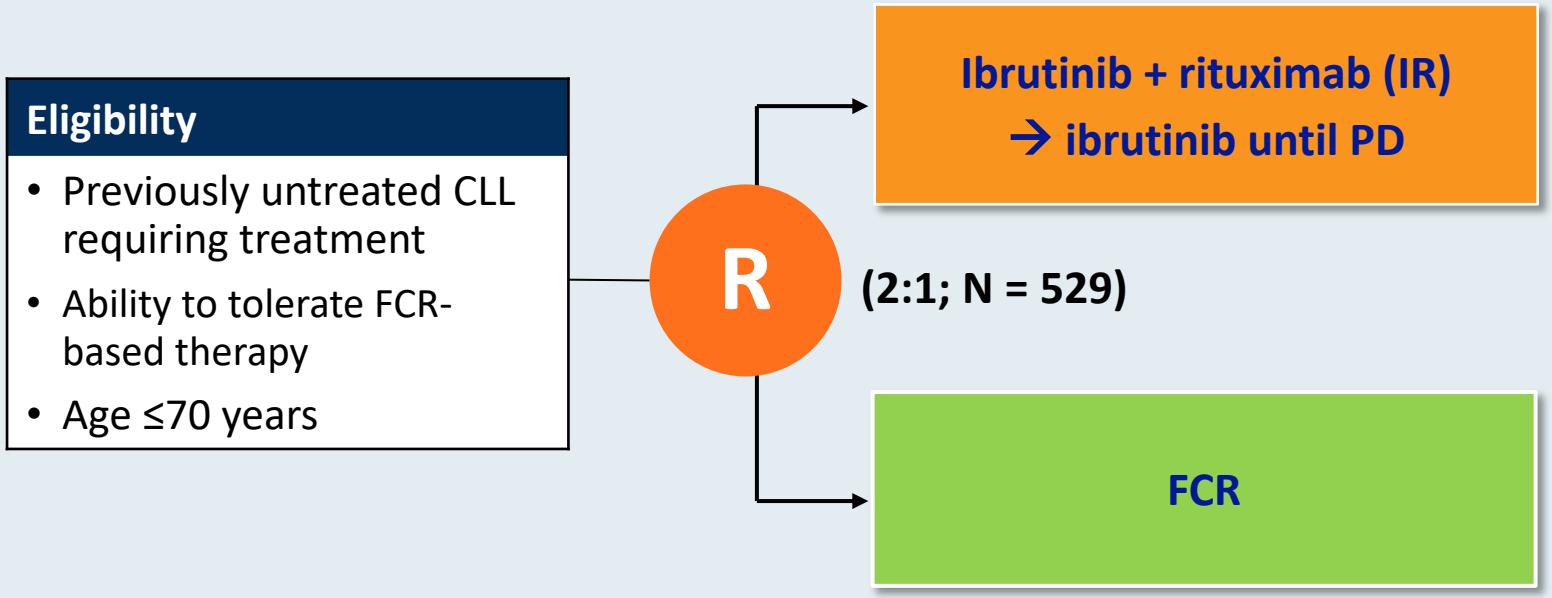
RTP RESEARCH TO PRACTICE

# 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.

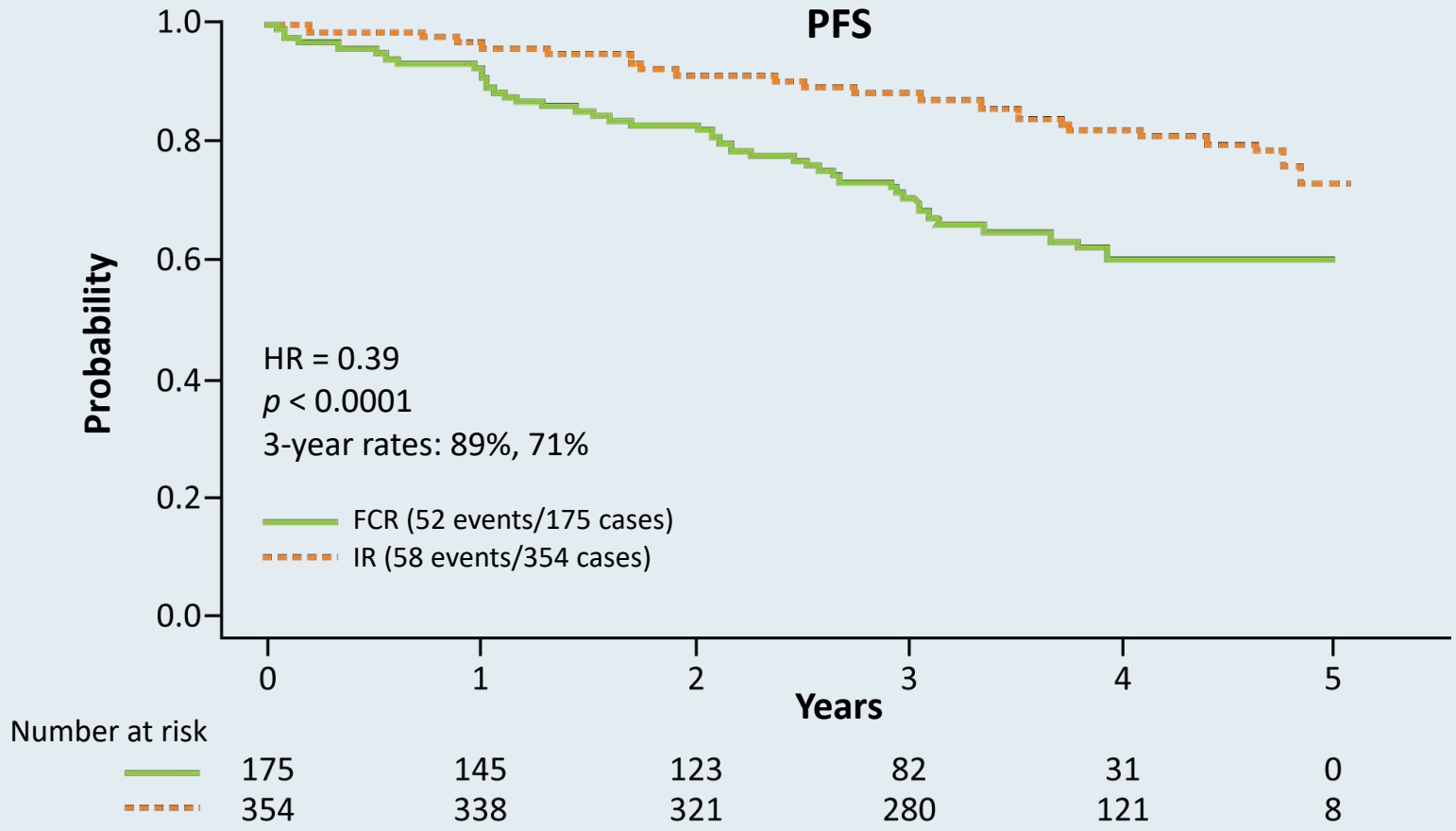
# Phase III ECOG-ACRIN E1912 Study Design




**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.

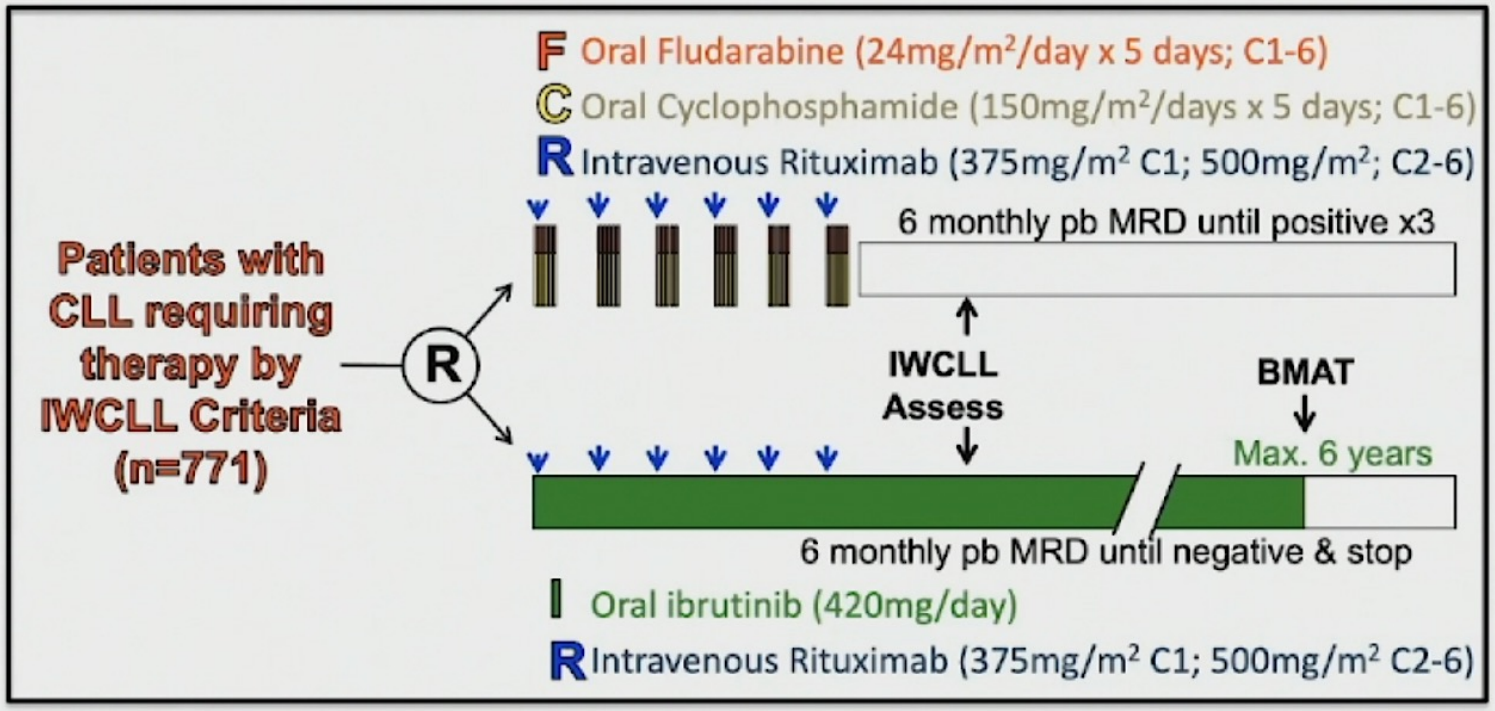
RTP RESEARCH TO PRACTICE

# Ibrutinib plus Rituximab Is Superior to FCR in Previously Untreated CLL: Results of the Phase III NCRI FLAIR Trial

Hillmen P et al.

ASH 2021;Abstract 642.

# NCRI FLAIR Study Design




**Primary end-point:**
To assess whether IR is superior to FCR in terms of PFS

**Key secondary end-points:**
Overall survival
Response including MRD
Safety and toxicity

**Key Inclusion Criteria:**

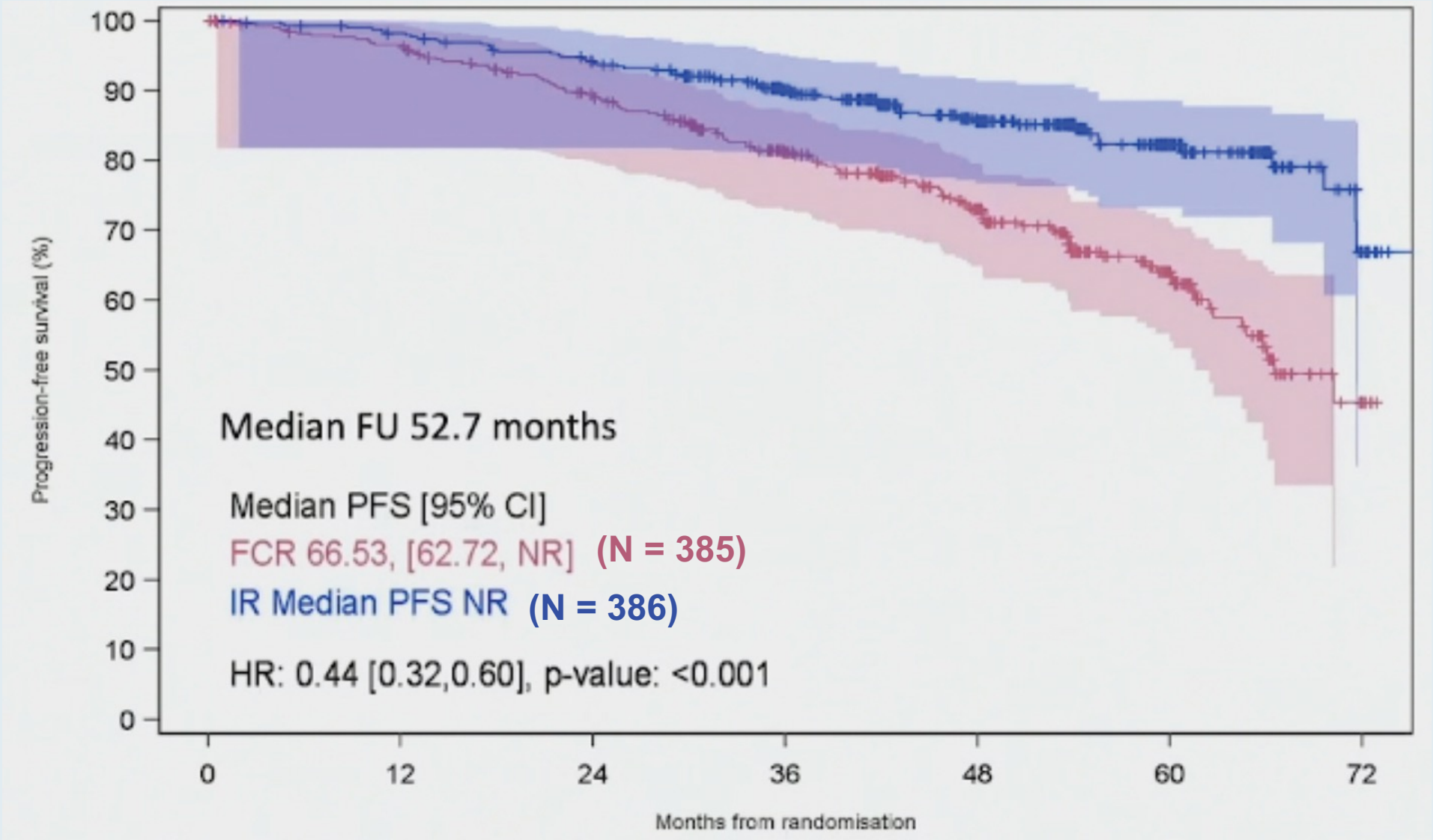
- Previously untreated CLL requiring therapy by IWCLL criteria
- Considered fit for FCR
- ≤75 years old

**Key Exclusion Criteria:**
Prior therapy for CLL; History of Richter's transformation; >20% TP53 deletion by FISH; Concomitant warfarin (or equivalent) Symptomatic cardiac failure or angina

Hillmen *et al.*, Abstract 642, ASH 2021

Hillmen P et al. ASH 2021;Abstract 642.

# NCRI FLAIR: Progression-Free Survival




Hillmen P et al. ASH 2021;Abstract 642.

RTP RESEARCH TO PRACTICE

CHRONIC LYMPHOCYTIC LEUKEMIA

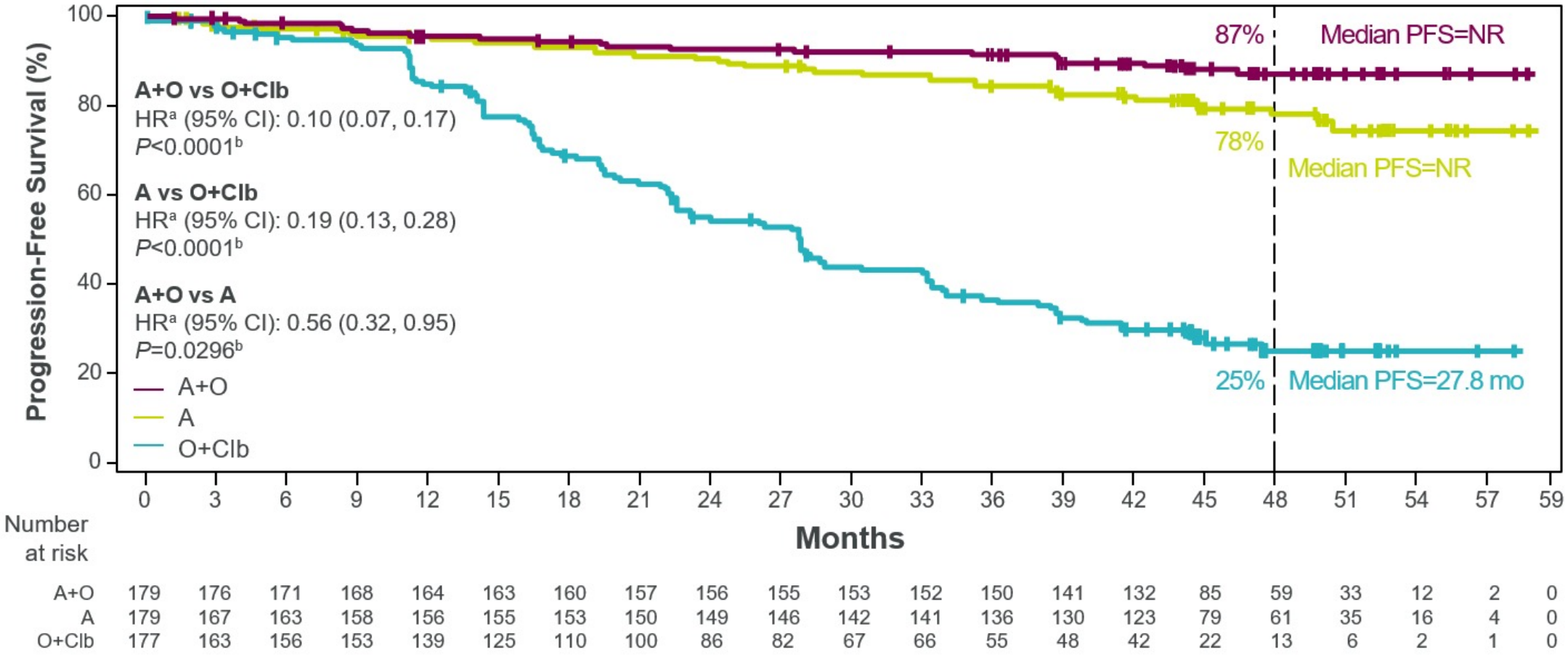
*Leukemia* 2022;[Online ahead of print].

# Efficacy and safety in a 4-year follow-up of the ELEVATE-TN study comparing acalabrutinib with or without obinutuzumab versus obinutuzumab plus chlorambucil in treatment-naïve chronic lymphocytic leukemia

Jeff P. Sharman[1]✉, Miklos Egyed[2], Wojciech Jurczak[3], Alan Skarbnik[4], John M. Pagel[5], Ian W. Flinn[6], Manali Kamdar[7], Talha Munir[8], Renata Walewska[9], Gillian Corbett[10], Laura Maria Fogliatto[11], Yair Herishanu[12], Versha Banerji[13], Steven Coutre[14], George Follows[15], Patricia Walker[16], Karin Karlsson[17], Paolo Ghia[18], Ann Janssens[19], Florence Cymbalista[20], Jennifer A. Woyach[21], Emmanuelle Ferrant[22], William G. Wierda[23], Veerendra Munugalavadla[24], Ting Yu[24], Min Hui Wang[24] and John C. Byrd[21]

# ELEVATE-TN: Investigator-Assessed PFS (Overall)

## *4-Year Follow-Up*




Sharman JP et al. *Leukemia* 2022;[Online ahead of print].

RTP RESEARCH TO PRACTICE

American Society of Hematology
Helping hematologists conquer blood diseases worldwide

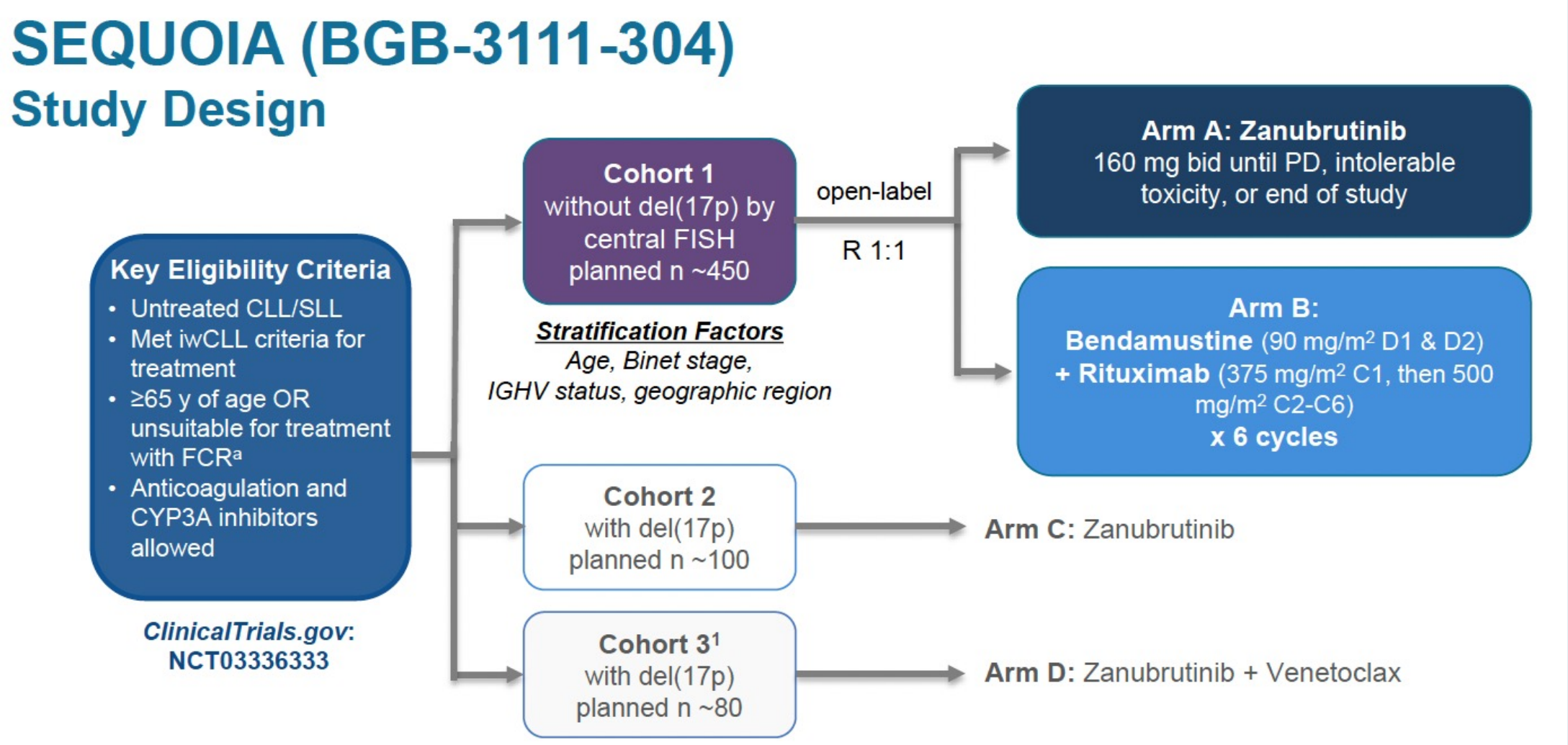
# SEQUOIA: RESULTS OF A PHASE 3 RANDOMIZED STUDY OF ZANUBRUTINIB VERSUS BENDAMUSTINE + RITUXIMAB IN PATIENTS WITH TREATMENT-NAIVE CHRONIC LYMPHOCYTIC LEUKEMIA/SMALL LYMPHOCYTIC LYMPHOMA

**Constantine S. Tam, MBBS, MD[1,2,3,4]; Krzysztof Giannopoulos, MD, PhD[5,6]; Wojciech Jurczak, MD, PhD[7]; Martin Šimkovič, MD, PhD[8,9]; Mazyar Shadman, MD, MPH[10,11]; Anders Österborg, MD, PhD[12,13]; Luca Laurenti, MD[14]; Patricia Walker, MBBS, BMedSci, FRACP, FRCPA[15]; Stephen Opat, MBBS (Hons), FRACP, FRCPA[16,17]; Henry Chan, MBChB, FRACP, FRCPA[18]; Hanna Ciepluch, MD, PhD[19]; Richard Greil, MD[20,21,22]; Monica Tani, MD[23]; Marek Trněný, MD[24]; Danielle M. Brander, MD[25]; Ian W. Flinn, MD, PhD[26]; Sebastian Grosicki, MD, PhD[27]; Emma Verner, MBBS, BMedSci, FRCPA, FRACP[28,29]; Jennifer R. Brown MD, PhD[30]; Brad S. Kahl, MD[31]; Paolo Ghia, MD, PhD[32]; Jianyong Li, MD, PhD[33]; Tian Tian, PhD[34]; Lei Zhou, MD[34]; Carol Marimpietri[34]; Jason C. Paik, MD, PhD[34]; Aileen Cohen, MD, PhD[34]; Jane Huang, MD[34]; Tadeusz Robak, MD, PhD[35]; and Peter Hillmen, MBChB, PhD[36]**

*[1]Peter MacCallum Cancer Centre, Melbourne, Victoria, Australia; [2]University of Melbourne, Parkville, Victoria, Australia; [3]St Vincent's Hospital Melbourne, Fitzroy, Victoria, Australia; [4]Royal Melbourne Hospital, Parkville, Victoria, Australia; [5]Experimental Hematooncology Department, Medical University of Lublin, Lublin, Poland; [6]Hematology Department, St. John's Cancer Centre, Lublin, Poland; [7]Maria Sklodowska-Curie National Research Institute of Oncology, Krakow, Poland; [8]Fourth Department of Internal Medicine - Haematology, University Hospital, Hradec Kralove, Czech Republic; [9]Faculty of Medicine, Charles University, Prague, Czech Republic; [10]Fred Hutchinson Cancer Research Center, Seattle, WA, USA; [11]Department of Medicine, University of Washington, Seattle, WA, USA; [12]Department of Oncology-Pathology, Karolinska Institutet, Stockholm, Sweden; [13]Department of Hematology, Karolinska University Hospital, Stockholm, Sweden; [14]Fondazione Policlinico Universitario A Gemelli UCSC, Rome, Italy; [15]Peninsula Private Hospital, Frankston, Victoria, Australia; [16]Monash Health, Clayton, Victoria, Australia; [17]Monash University, Clayton, Victoria, Australia; [18]North Shore Hospital, Auckland, New Zealand; [19]Copernicus Regional Oncology Center, Gdansk, Poland; [20]Third Medical Department with Hematology, Medical Oncology, Rheumatology and Infectiology, Paracelsus Medical University, Salzburg, Austria; [21]Salzburg Cancer Research Institute (SCRI) Center for Clinical Cancer and Immunology Trials (CCCIT), Salzburg, Austria; [22]Cancer Cluster Salzburg (CCS), Salzburg, Austria; [23]Hematology Unit, Santa Maria delle Croci Hospital, Ravenna, Italy; [24]First Department of Medicine, First Faculty of Medicine, Charles University, General Hospital, Prague, Czech Republic; [25]Hematologic Malignancies and Cellular Therapy, Duke University School of Medicine, Durham, NC, USA; [26]Sarah Cannon Research Institute/Tennessee Oncology, Nashville, TN, USA; [27]Department of Hematology and Cancer Prevention, Health Sciences Faculty, Medical University of Silesia, Katowice, Poland; [28]Concord Repatriation General Hospital, Concord, New South Wales, Australia; [29]University of Sydney, Sydney, New South Wales, Australia; [30]Dana-Farber Cancer Institute, Boston, MA, USA; [31]Washington University School of Medicine, St Louis, MO, USA; [32]Università Vita-Salute San Raffaele and IRCCS Ospedale San Raffaele, Milano, Italy; [33]Department of Hematology, The First Affiliated Hospital of Nanjing Medical University, Jiansu Province Hospital, Nanjing, China; [34]BeiGene (Beijing) Co., Ltd., Beijing, China and BeiGene USA, Inc., San Mateo, CA, USA; [35]Medical University of Lodz, Lodz, Poland; and [36]St James's University Hospital, Leeds, United Kingdom*

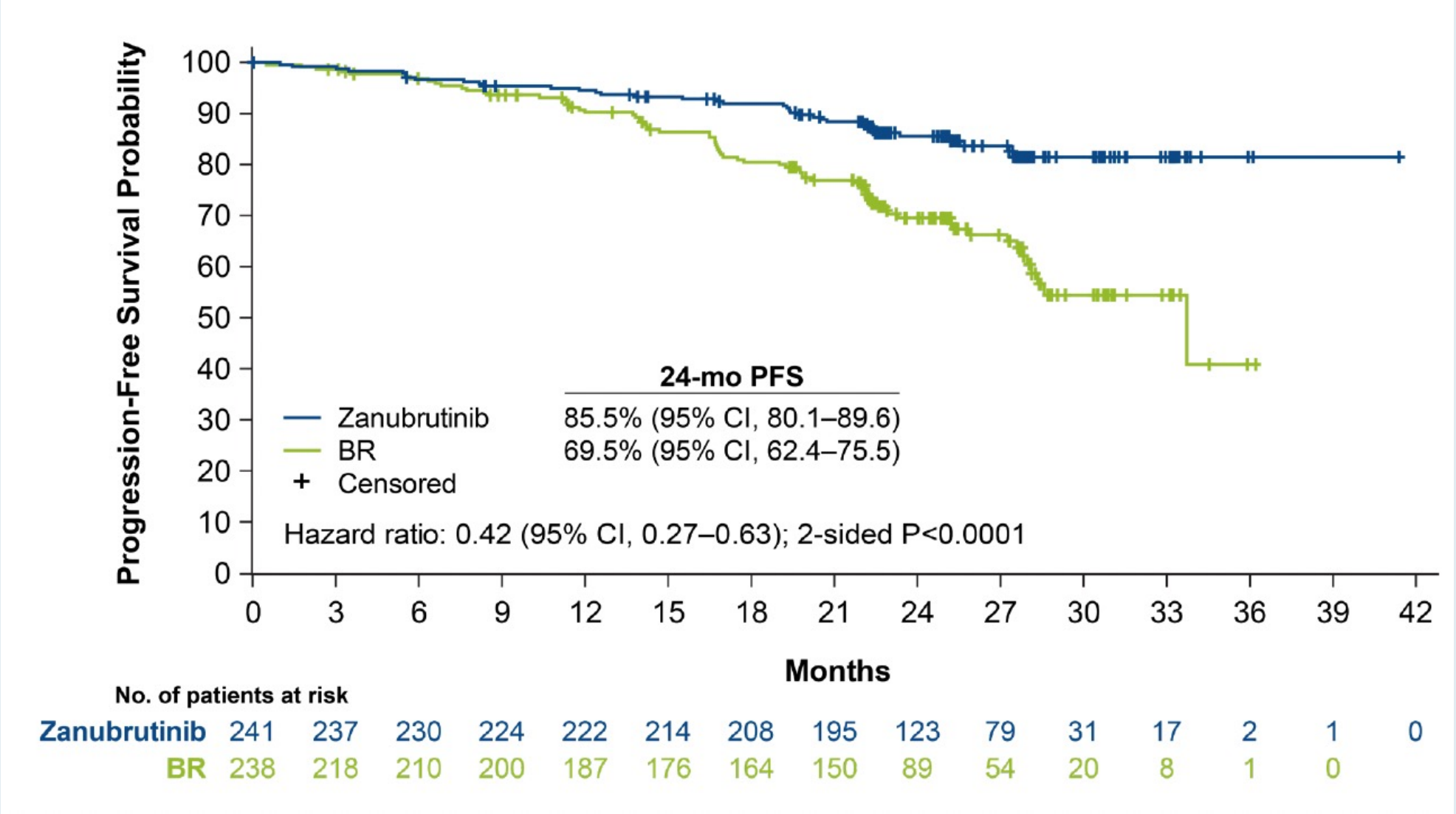
**Sunday, December 12, 2021**
642. Chronic Lymphocytic Leukemia: Clinical and Epidemiological I

# SEQUOIA Phase III Study Design




Tam CS et al. ASH 2021;Abstract 396.

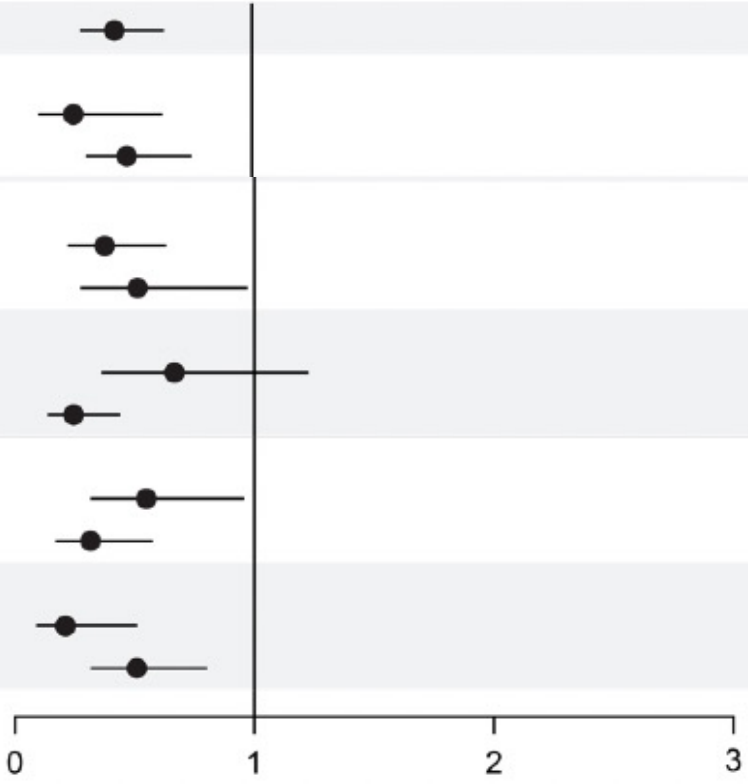
# SEQUOIA: Progression-Free Survival by IRC




Tam CS et al. ASH 2021;Abstract 396.

# SEQUOIA: Progression-Free Survival by Subgroups

| Subgroup | Event/Patient Zanubrutinib | Event/Patient BR | Hazard Ratio (95% CI), %[a] |
|---|---|---|---|
| **All Patients** | 36/241 | 71/238 | 0.42 (0.28–0.63) |
| **Age (years)** | | | |
| <65 | 6/45 | 19/46 | 0.25 (0.10–0.62) |
| ≥65 | 30/196 | 52/192 | 0.47 (0.30–0.74) |
| **Bulky disease (LDi <5 cm vs ≥5 cm)** | | | |
| <5 cm | 21/172 | 44/165 | 0.37 (0.22–0.63) |
| ≥5 cm | 15/69 | 27/73 | 0.52 (0.27–0.97) |
| **IGHV mutational status** | | | |
| Mutated | 18/109 | 25/110 | 0.67 (0.36–1.22) |
| Unmutated | 15/125 | 45/121 | 0.24 (0.13–0.43) |
| **Cytopenias at baseline[b]** | | | |
| Yes | 21/102 | 34/109 | 0.55 (0.32–0.95) |
| No | 15/139 | 37/129 | 0.31 (0.17–0.57) |
| **Chromosome 11q deletion** | | | |
| Yes | 7/43 | 22/46 | 0.21 (0.09–0.50) |
| No | 29/198 | 49/192 | 0.50 (0.32–0.80) |




Tam CS et al. ASH 2021;Abstract 396.

# SEQUOIA: Adverse Events of Interest

| AE, n (%) | Arm A Zanubrutinib (n=240[a]) | | Arm B Bendamustine + Rituximab (n=227[a]) | |
|---|---|---|---|---|
| | Any Grade | Grade ≥3 | Any Grade | Grade ≥3 |
| **Anemia** | 11 (4.6) | 1 (0.4) | 44 (19.4) | 4 (1.8) |
| **Neutropenia[b]** | 38 (15.8) | 28 (11.7) | 129 (56.8) | 116 (51.1) |
| **Thrombocytopenia[c]** | 11 (4.6) | 5 (2.1) | 40 (17.6) | 18 (7.9) |
| **Arthralgia** | 32 (13.3) | 2 (0.8) | 20 (8.8) | 1 (0.4) |
| **Atrial fibrillation** | 8 (3.3) | 1 (0.4) | 6 (2.6) | 3 (1.3) |
| **Bleeding[d]** | 108 (45.0) | 9 (3.8) | 25 (11.0) | 4 (1.8) |
| Major bleeding[e] | 12 (5.0) | 9 (3.8) | 4 (1.8) | 4 (1.8) |
| **Diarrhea** | 33 (13.8) | 2 (0.8) | 31 (13.7) | 5 (2.2) |
| **Hypertension[f]** | 34 (14.2) | 15 (6.3) | 24 (10.6) | 11 (4.8) |
| **Infections[g]** | 149 (62.1) | 39 (16.3) | 127 (55.9) | 43 (18.9) |
| **Myalgia** | 9 (3.8) | 0 (0.0) | 3 (1.3) | 0 (0.0) |
| **Other cancers** | 31 (12.9) | 17 (7.1) | 20 (8.8) | 7 (3.1) |
| Dermatologic other cancers | 16 (6.7) | 2 (0.8) | 10 (4.4) | 2 (0.9) |

Tam CS et al. ASH 2021;Abstract 396.

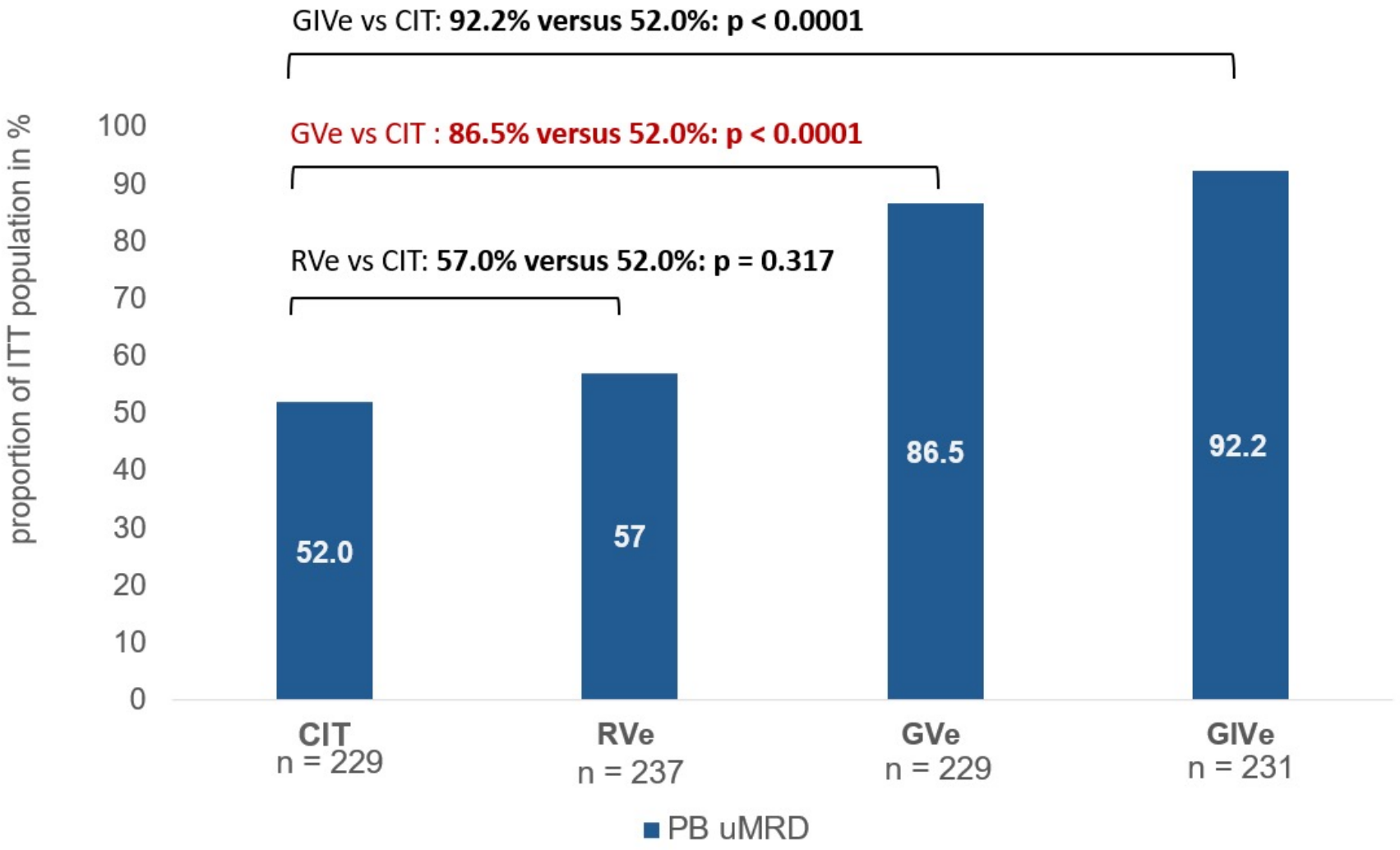
# Venetoclax Combination Regimens

# A Randomized Phase III Study of Venetoclax-Based Time-Limited Combination Treatments (RVe, GVe, GIVe) vs Standard Chemoimmunotherapy (CIT: FCR/BR) in Frontline Chronic Lymphocytic Leukemia (CLL) of Fit Patients: First Co-Primary Endpoint Analysis of the International Intergroup GAIA (CLL13) Trial

Eichhorst B et al.

ASH 2021;Abstract 71.

# GAIA/CLL13 Coprimary Endpoint: Undetectable MRD (uMRD) (<$10^{-4}$) at Month 15 in Peripheral Blood by 4-Color Flow




**CIT**
- BR >65
- ≤FCR 65

**RVe**
Rituximab/venetoclax

**GVe**
Obinutuzumab/venetoclax

**GIVe**
Obinutuzumab/ibrutinib/venetoclax

Eichhorst B et al. ASH 2021;Abstract 71.

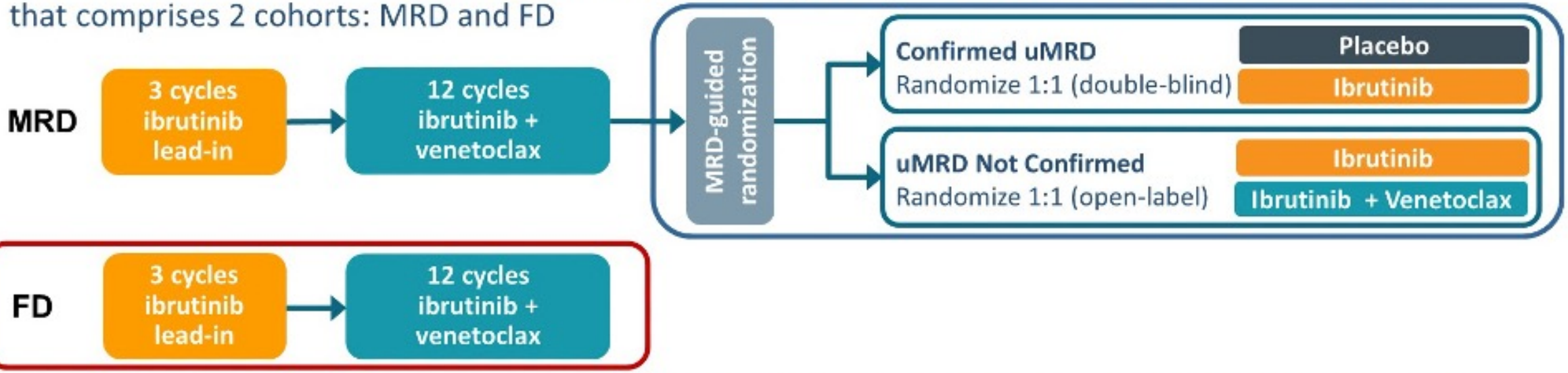
# Fixed-Duration (FD) First-Line Treatment With Ibrutinib Plus Venetoclax for Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma: Primary Analysis of the FD Cohort of the Phase 2 CAPTIVATE Study

**Paolo Ghia, MD, PhD**[1]; John N. Allan, MD[2]; Tanya Siddiqi, MD[3]; Thomas J. Kipps, MD, PhD[4]; Ryan Jacobs, MD[5]; Stephen Opat, FRACP, FRCPA, MBBS[6]; Paul M. Barr, MD[7]; Alessandra Tedeschi, MD[8]; Livio Trentin, MD[9]; Rajat Bannerji, MD, PhD[10]; Sharon Jackson, MD[11]; Bryone Kuss, MBBS, PhD, FRACP, FRCPA[12]; Carol Moreno, MD, PhD[13]; Edith Szafer-Glusman, PhD[14]; Kristin Russell, BS[14]; Cathy Zhou, MS[14]; Joi Ninomoto, PharmD[14]; James P. Dean, MD, PhD[14]; William G. Wierda, MD, PhD[15]; Constantine Tam, MBBS, MD[16]

*[1]Division of Experimental Oncology, Università Vita-Salute San Raffaele and IRCCS Ospedale San Raffaele, Milan, Italy; [2]Weill Cornell Medicine, New York, NY, USA; [3]City of Hope National Medical Center, Duarte, CA, USA; [4]UCSD Moores Cancer Center, San Diego, CA, USA; [5]Levine Cancer Institute, Charlotte, NC, USA; [6]Monash University, Clayton, VIC, Australia; [7]Wilmot Cancer Institute, University of Rochester Medical Center, Rochester, NY, USA; [8]ASST Grande Ospedale Metropolitano Niguarda, Milan, Italy; [9]Hematology and Clinical Immunology Unit, Department of Medicine, University of Padova, Padova, Italy; [10]Rutgers Cancer Institute of New Jersey, New Brunswick, NJ, USA; [11]Middlemore Hospital, Auckland, New Zealand; [12]Flinders University and Medical Centre, Bedford Park, SA, Australia; [13]Hospital de la Santa Creu i Sant Pau, Autonomous University of Barcelona, Barcelona, Spain; [14]Pharmacyclics LLC, an AbbVie Company, Sunnyvale, CA, USA; [15]Department of Leukemia, University of Texas MD Anderson Cancer Center, Houston, TX, USA; [16]Peter MacCallum Cancer Center & St. Vincent's Hospital and the University of Melbourne, Melbourne, VIC, Australia*

# CAPTIVATE Study Design

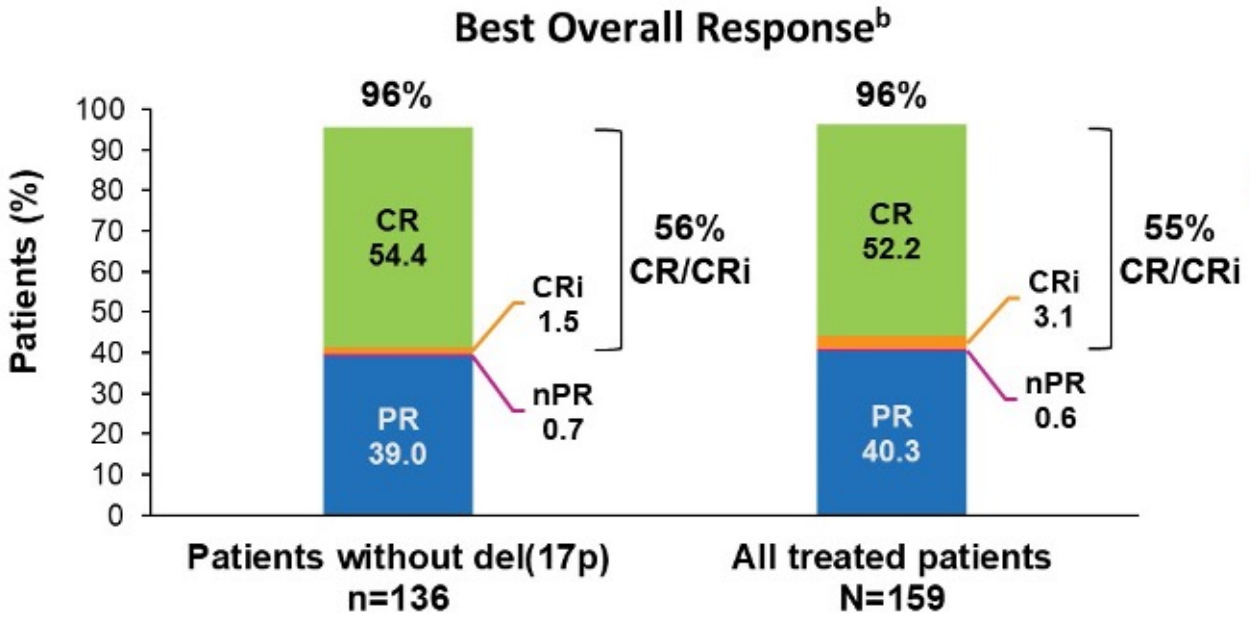
- CAPTIVATE (PCYC-1142) is an international, multicenter phase 2 study evaluating first-line treatment with 3 cycles of ibrutinib followed by 12 cycles of combined ibrutinib + venetoclax that comprises 2 cohorts: MRD and FD




- Results from the MRD cohort demonstrated uMRD in more than two-thirds of patients treated with 12 cycles of ibrutinib + venetoclax (PB, 75%; BM, 68%), and 30-month PFS rates of ≥95% irrespective of subsequent MRD-guided randomized treatment[1]

Ghia P et al. ASCO 2021;Abstract 7051.

# CAPTIVATE: Response



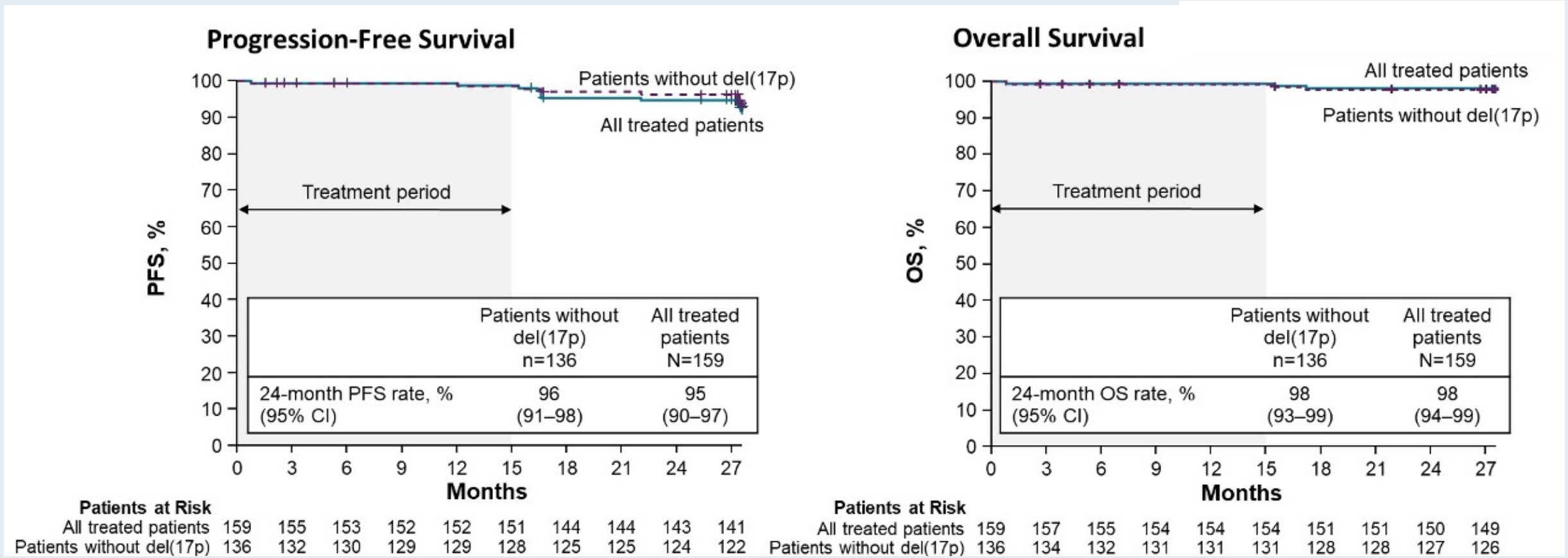

| | | |
|---|---|---|
| **DOCR ≥12 cycles n/N (%)** | 66/76 (87) | 78/88 (89)* |

- Primary endpoint was met: 56% (95% CI, 48–64) CR rate[a] in patients without del(17p)
  - Significantly excludes 37% minimum rate ($P<0.0001$)
  - Meaningful improvement over 40% rate of historical comparator of FCR in CLL10[1]

*After achieving CR[a], 9 patients with <1 year of follow-up were not evaluable; 1 patient died 7 months after CR and completion of therapy.

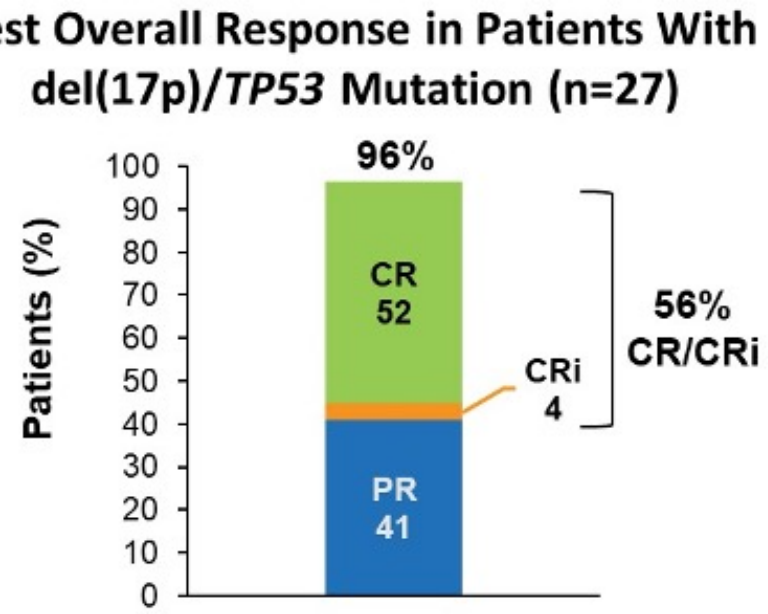
Ghia P et al. ASCO 2021;Abstract 7051.

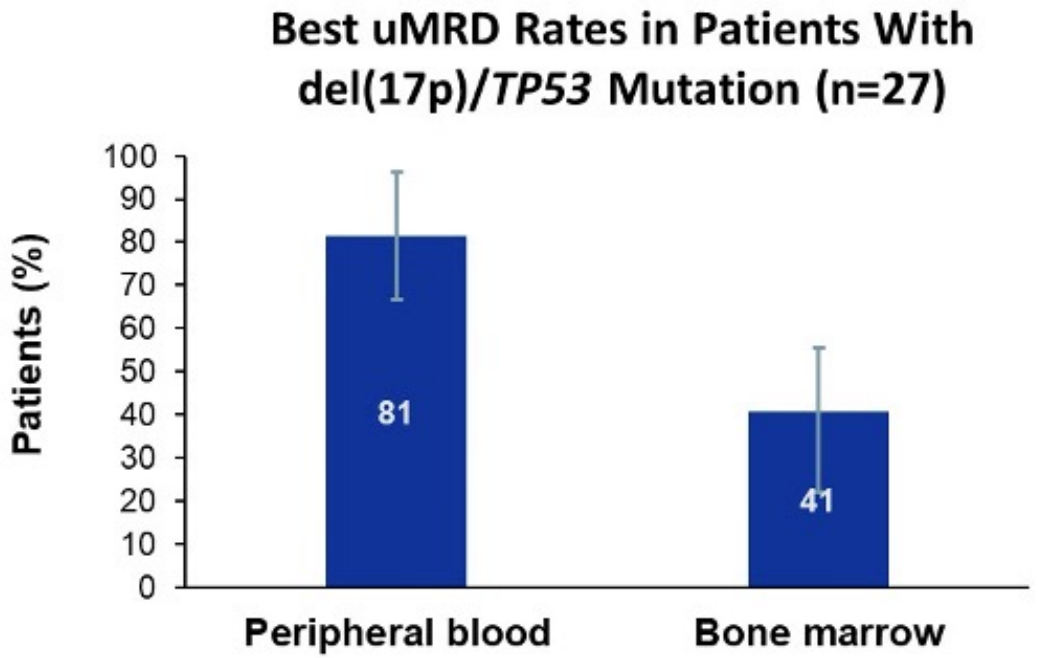
# CAPTIVATE: Progression-Free and Overall Survival




Ghia P et al. ASCO 2021;Abstract 7051.

# CAPTIVATE: Efficacy Outcomes for Patients with Del(17p)/TP53 Mutation




- Patients with DOCR ≥12 cycles was 87% (13/15)
- Estimated 24-month PFS rate was 84% (95% CI, 63–94)
- Estimated 24-month OS rate was 96% (95% CI, 76–99)

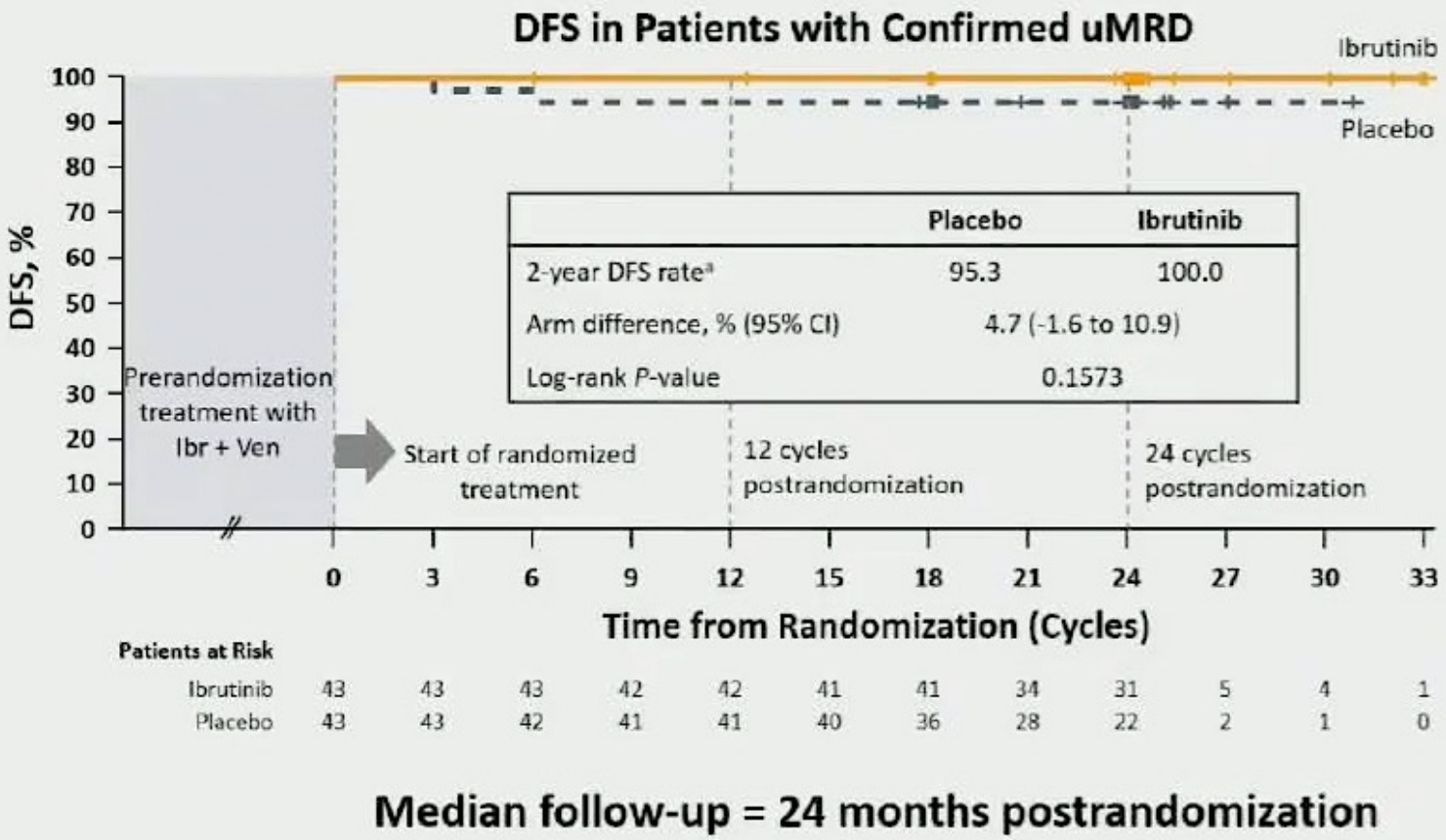
Ghia P et al. ASCO 2021;Abstract 7051.

# First-Line Treatment with Ibrutinib (Ibr) plus Venetoclax (Ven) for Chronic Lymphocytic Leukemia (CLL): 2-Year Post-Randomization Disease-Free Survival (DFS) Results from the Minimal Residual Disease (MRD) Cohort of the Phase 2 Captivate Study

Ghia P et al.

ASH 2021;Abstract 68.

# CAPTIVATE MRD Cohort: DFS Events in Patients with Confirmed uMRD

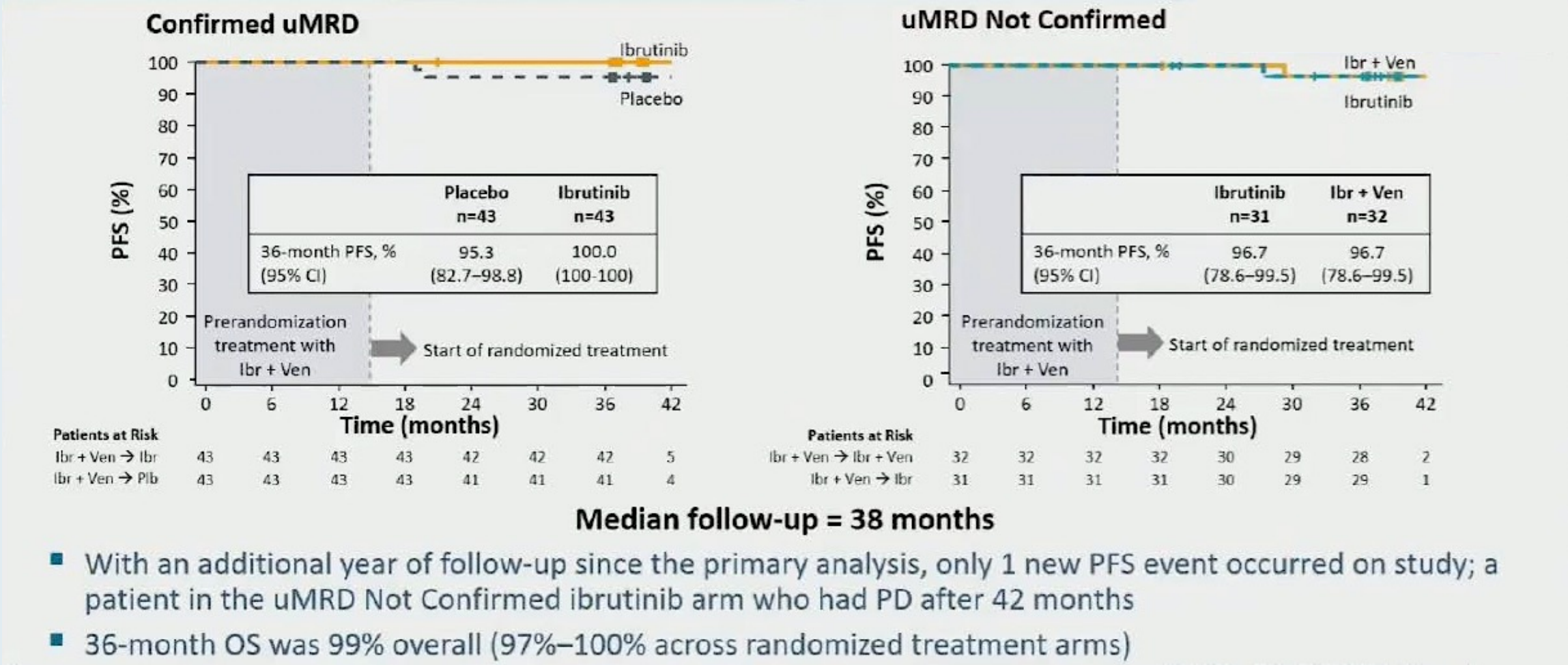



**Median follow-up = 24 months postrandomization**

- DFS was defined as freedom from MRD relapse ($\geq 10^{-2}$ confirmed on 2 separate occasions) and without PD or death starting from randomization after 15 cycles of treatment
- In the additional year of follow-up since the 1-year DFS primary analysis, no new MRD relapses, PD, or deaths occurred in patients with Confirmed uMRD randomized to ibrutinib or placebo

Ghia P et al. ASH 2021;Abstract 68.

# CAPTIVATE MRD Cohort: Three-Year PFS Rates

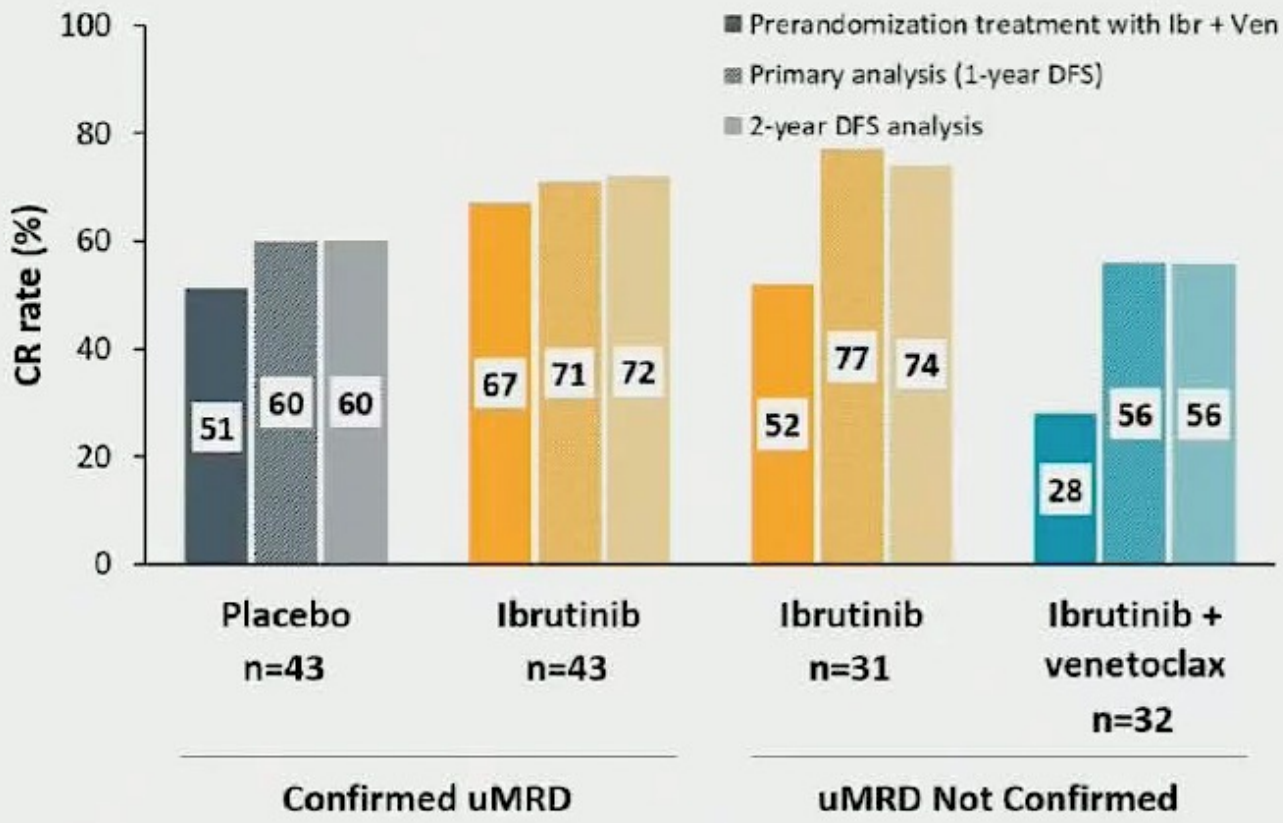



**Median follow-up = 38 months**

- With an additional year of follow-up since the primary analysis, only 1 new PFS event occurred on study; a patient in the uMRD Not Confirmed ibrutinib arm who had PD after 42 months
- 36-month OS was 99% overall (97%–100% across randomized treatment arms)

Ghia P et al. ASH 2021;Abstract 68.

# CAPTIVATE MRD Cohort: CR Rates with 24 Months Postrandomization Follow-Up




- Greatest CR rate[a] improvements occurred during the first year of randomized treatment
  - Modest improvements observed in patients with Confirmed uMRD[b] randomized to placebo or ibrutinib
  - Improvements in CR rates[a] were similar with ibrutinib + venetoclax and ibrutinib in patients with uMRD Not Confirmed[b]

Ghia P et al. ASH 2021;Abstract 68.

# First Prospective Data on Minimal Residual Disease (MRD) Outcomes After Fixed-Duration Ibrutinib Plus Venetoclax (Ibr+Ven) Versus Chlorambucil Plus Obinutuzumab (Clb+O) for First-Line Treatment of CLL in Elderly or Unfit Patients: The GLOW Study

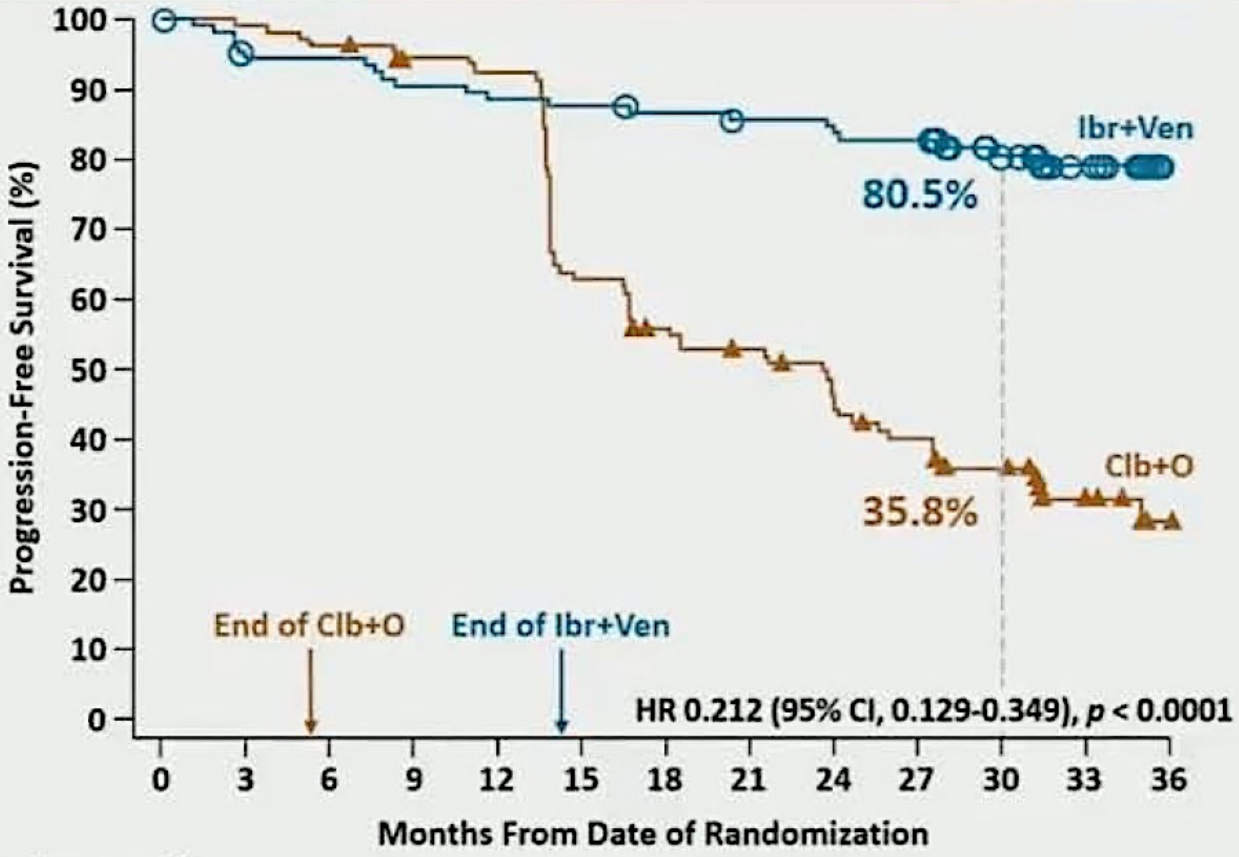
**Talha Munir**,[1] Carol Moreno,[2] Carolyn Owen,[3] George Follows,[4] Ohad Benjamini,[5] Ann Janssens,[6] Mark-David Levin,[7] Anders Osterborg,[8] Tadeusz Robak,[9] Martin Simkovic,[10] Don Stevens,[11] Sergey Voloshin,[12] Vladimir Vorobyev,[13] Munci Yagci,[14] Loic Ysebaert,[15] Qianya Qi,[16] Andrew J. Steele,[17] Natasha Schuier,[18] Kurt Baeten,[19] Donne Bennett Caces,[16] Carsten U. Niemann,[20] Arnon P. Kater[21]

*[1]St James's Hospital, Leeds, UK; [2]Hospital de la Santa Creu i Sant Pau, Autonomous University of Barcelona, Spain; [3]Tom Baker Cancer Centre, Calgary, Canada; [4]Addenbrookes Hospital, Cambridge, UK; [5]Sheba Medical Center, Ramat Gan, Israel; [6]UZ Leuven Gasthuisberg, Leuven, Belgium; [7]Albert Schweitzer Hospital, Dordrecht, Netherlands; [8]Karolinska University Hospital, Stockholm, Sweden; [9]Medical University of Lodz, Copernicus Memorial Hospital, Lodz, Poland; [10]University Hospital Hradec Kralove, Hradec Kralove, Czech Republic; [11]Norton Cancer Institute, Louisville, KY, USA; [12]Russian Scientific and Research Institute of Hematology and Transfusiology, St. Petersburg, Russia; [13]S.P. Botkin Moscow City Clinical Hospital, Moscow, Russia; [14]Gazi Universitesi Tip Fakultesi, Ankara, Turkey; [15]Institut Universitaire du Cancer Toulouse Oncopole, Toulouse, France; [16]Janssen Research & Development, Raritan, NJ, USA; [17]Janssen Research & Development, Spring House, PA, USA; [18]Janssen Research & Development, Düsseldorf, Germany; [19]Janssen Research & Development, Beerse, Belgium; [20]Rigshospitalet Copenhagen University Hospital, Copenhagen, Denmark; [21]Amsterdam University Medical Centers, Cancer Center Amsterdam, University of Amsterdam, Netherlands*



ASH 2021;Abstract 70.

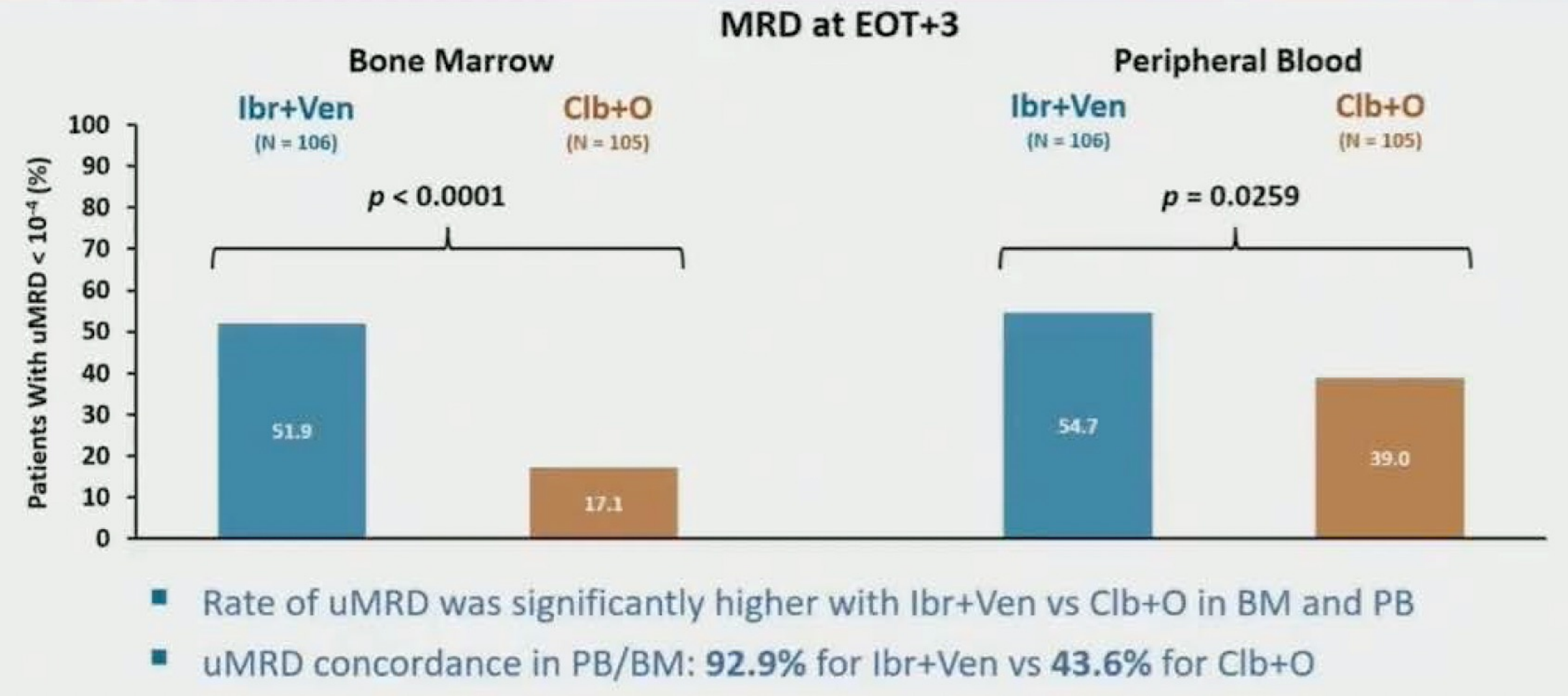
# GLOW: Independent Review Committee (IRC)-Assessed PFS




- IRC-assessed PFS for Ibr+Ven was superior to Clb+O at primary analysis (median 27.7 months of follow-up)
  - HR 0.216 (95% CI, 0.131-0.357; $p < 0.0001$)
- **With median follow-up of 34.1 months:**
  - IRC-assessed PFS remained superior for Ibr+Ven (HR 0.212, 95% CI, 0.129-0.349; $p < 0.0001$)
  - 30-month PFS: 80.5% for Ibr+Ven vs 35.8% for Clb+O
  - Overall survival HR 0.76 (95% CI, 0.35-1.64), with 11 deaths for Ibr+Ven vs 16 for Clb+O

Munir T et al. ASH 2021;Abstract 70.

# GLOW: uMRD <$10^{-4}$ Rate




- Rate of uMRD was significantly higher with Ibr+Ven vs Clb+O in BM and PB
- uMRD concordance in PB/BM: **92.9%** for Ibr+Ven vs **43.6%** for Clb+O

Munir T et al. ASH 2021;Abstract 70.

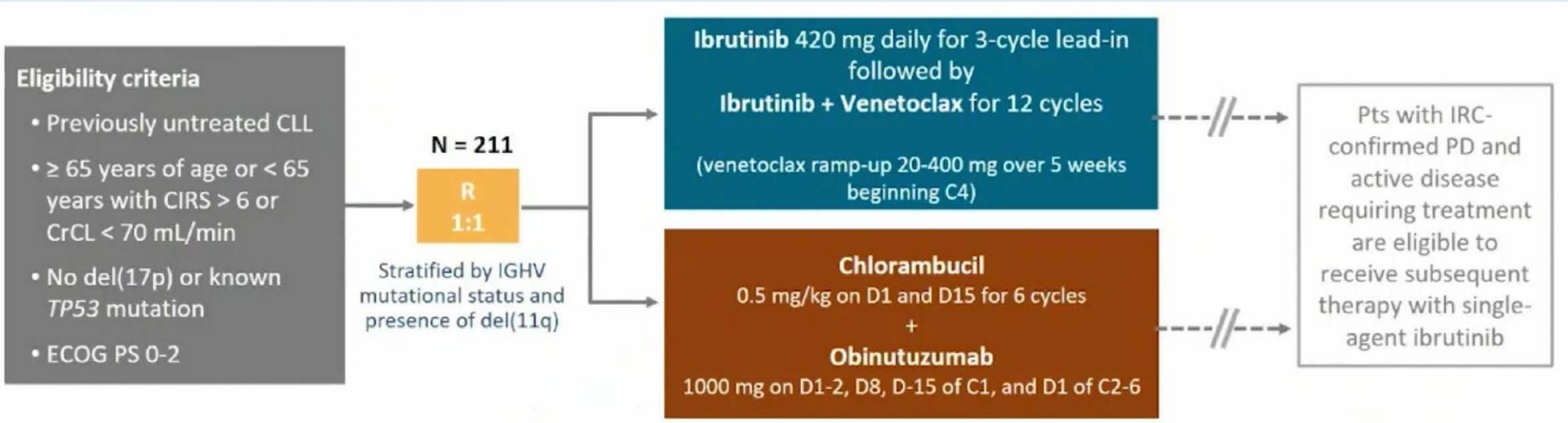
RTP RESEARCH TO PRACTICE

# Fixed-Duration Ibrutinib and Venetoclax (I + V) versus Chlorambucil plus Obinutuzumab (Clb + O) for First-Line (1L) Chronic Lymphocytic Leukemia (CLL): Primary Analysis of the Phase 3 GLOW Study

Kater A et al.

EHA 2021;Abstract LB1902.

# GLOW: Study Design and Endpoints



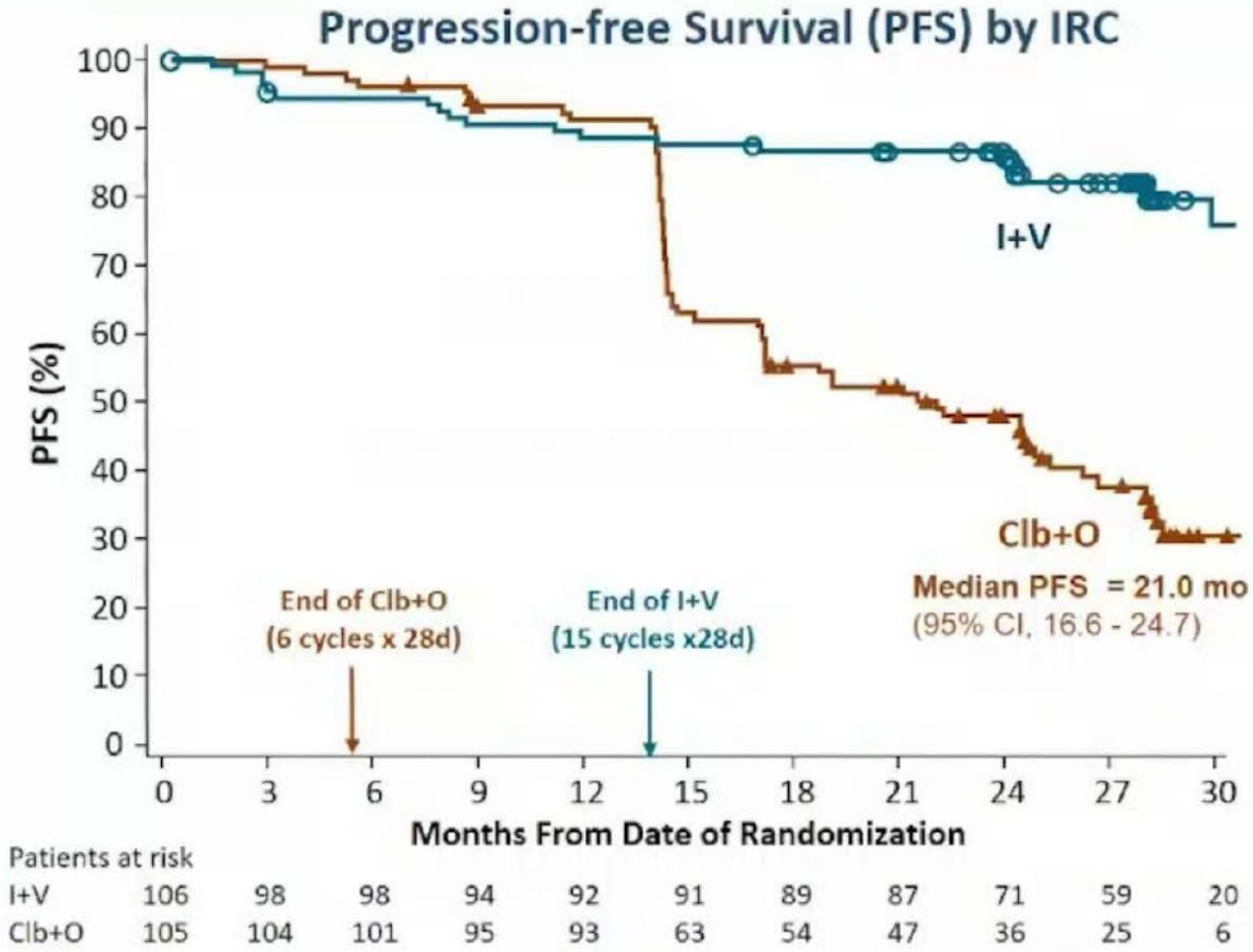

**Primary end point**: Progression-free survival by independent review committee (IRC)

- 71 PFS events to detect an effect size with an HR = 0.5 (80% power at a 2-sided significance level of 0.05)

**Key secondary end points**: Undetectable MRD in BM, CR rate (IRC), ORR (IRC), OS; safety was also evaluated.

Kater A et al. EHA 2021;Abstract LB1902.

# GLOW: Progression-Free Survival

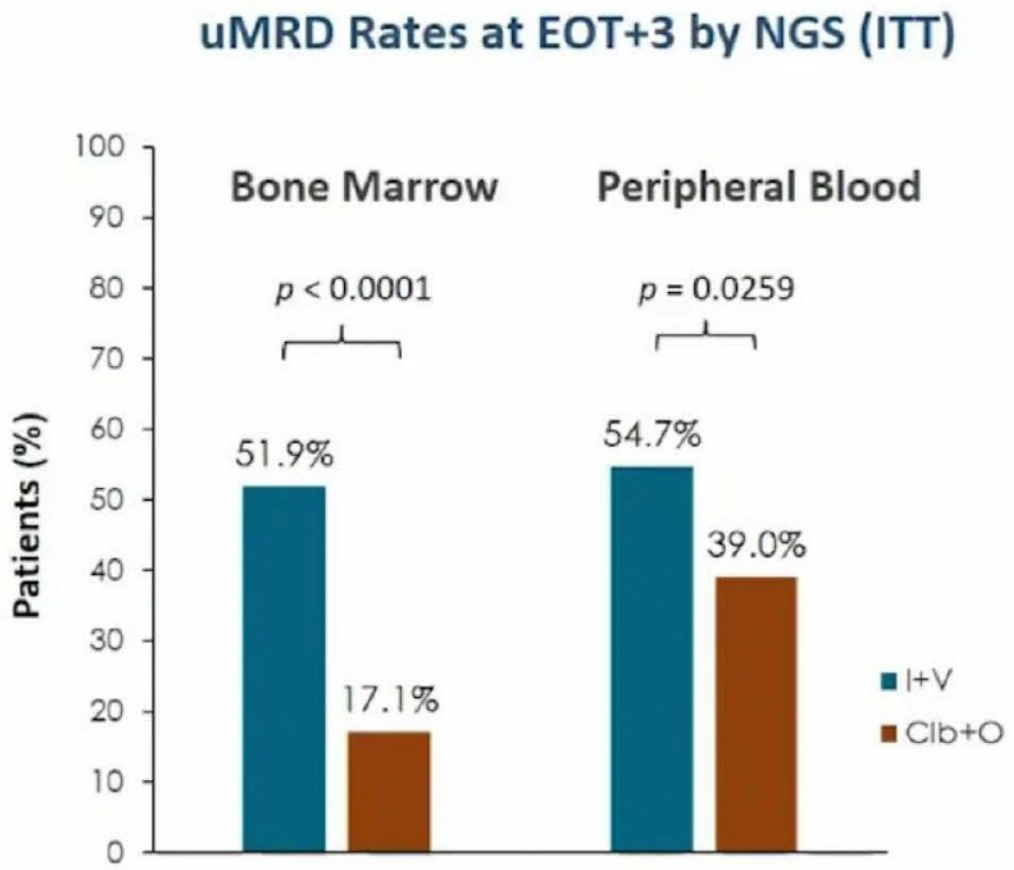



- **With a median follow up of 27.7 months, IRC-assessed PFS for I+V was superior to Clb+O**
- I+V reduced the risk of progression or death by 78% vs Clb+O
  - **HR 0.216** (95% CI, 0.131-0.357; p < 0.0001)
- PFS by INV assessment was consistent with IRC
  - **HR 0.207** (95% CI, 0.120, 0.357; p < 0.0001)

Kater A et al. EHA 2021;Abstract LB1902.

RTP RESEARCH TO PRACTICE

# GLOW: Undetectable MRD Rate




- Rate of uMRD at EOT+3 was significantly higher for I+V vs Clb+O, irrespective of compartment
- With I+V, PB/BM uMRD concordance[b] was 92.9% (52/56)
  - Versus 43.6% (17/39) for Clb+O
- Best uMRD rates were higher for I+V (by flow cytometry)
  - I+V: 67.9% (BM) and 80.2% (PB)
  - Clb+O: 22.9% (BM) and 46.7% (PB)

Kater A et al. EHA 2021;Abstract LB1902.

# GLOW: Safety

| | I+V (N = 106) | Clb+O (N = 105) |
|---|---|---|
| Median exposure, mos (range) | 13.8 (0.7-19.5) | 5.1 (1.8-7.9) |
| Any, % | 75.5 | 69.5 |
| Neutropenia[a] | 34.9 | 49.5 |
| Infections[b] | 17.0 | 11.4 |
| Thrombocytopenia | 5.7 | 20.0 |
| Diarrhea | 10.4 | 1.0 |
| Hypertension | 7.5 | 1.9 |
| Atrial fibrillation | 6.6 | 0 |
| Hyponatremia | 5.7 | 0 |
| TLS | 0 | 5.7 |

[a]Includes 'neutrophil count decreased'; grade ≥3 febrile neutropenia: 1.9% for I+V vs 2.9% for Clb+O

[b]Includes multiple preferred terms

- After 3 cycles of ibrutinib lead-in, <2% of patients remained at risk for TLS based on high tumor burden
- 2 (1.9%) patients in I+V arm discontinued ibrutinib due to atrial fibrillation
- SAEs in ≥5% of patients for I+V vs Clb+O: Infections (12.3% vs 8.6%) and atrial fibrillation (6.6% vs 0%)
- Rate of secondary malignancies at time of analysis: 8.5% for I+V vs 10.5% for Clb+O
  - NMSC: 3.8% vs 1.9%
  - Other: 4.7% vs 8.6%

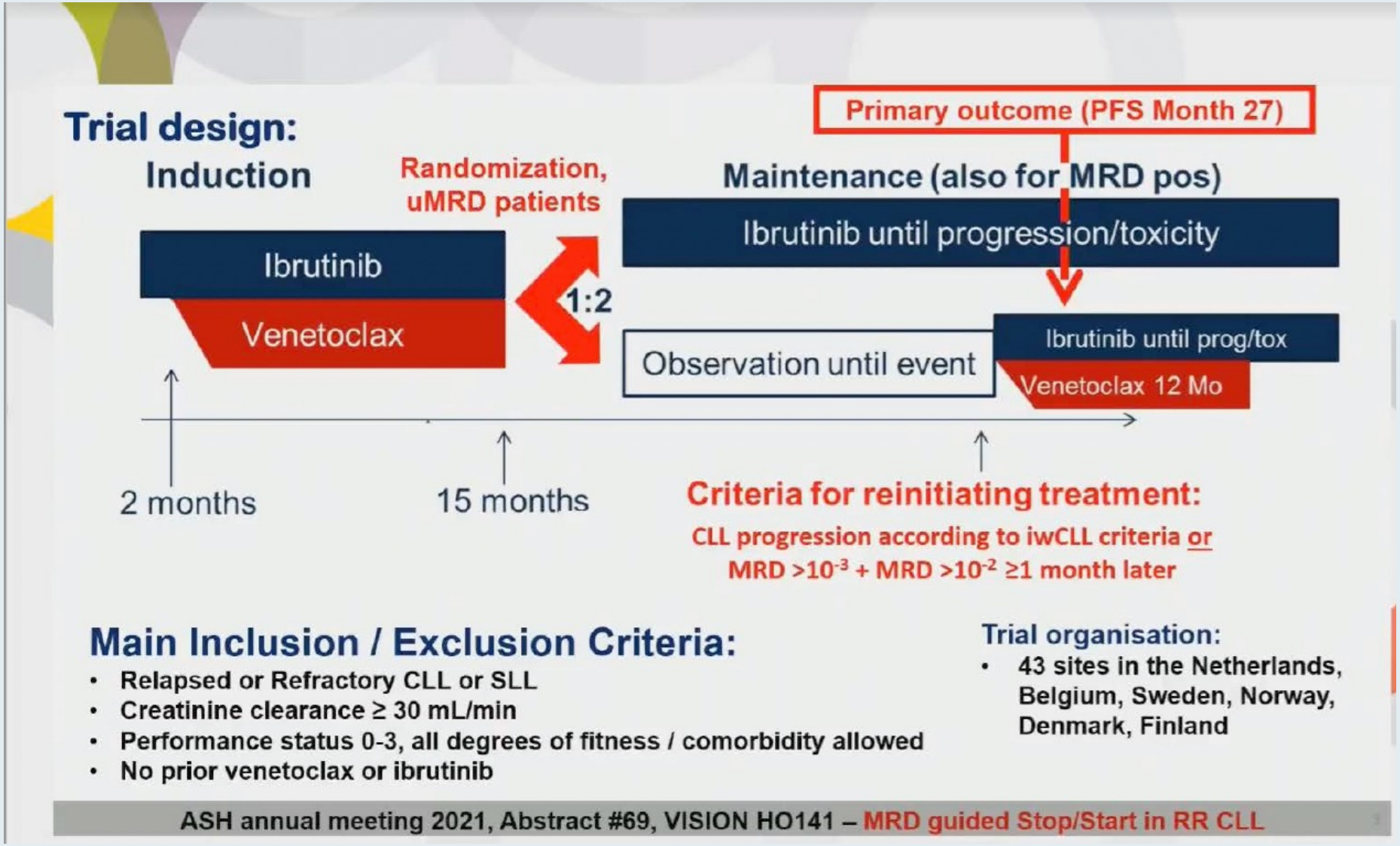
Kater A et al. EHA 2021;Abstract LB1902.

# Time-limited Venetoclax and Ibrutinib for Patients with Relapsed/Refractory Chronic Lymphocytic Leukemia (RR CLL) who have Undetectable Minimal Residual Disease (uMRD) – Primary Analysis from the Randomized Phase 2 VISION HO141 Trial

## MRD guided Stop / Start in RR CLL

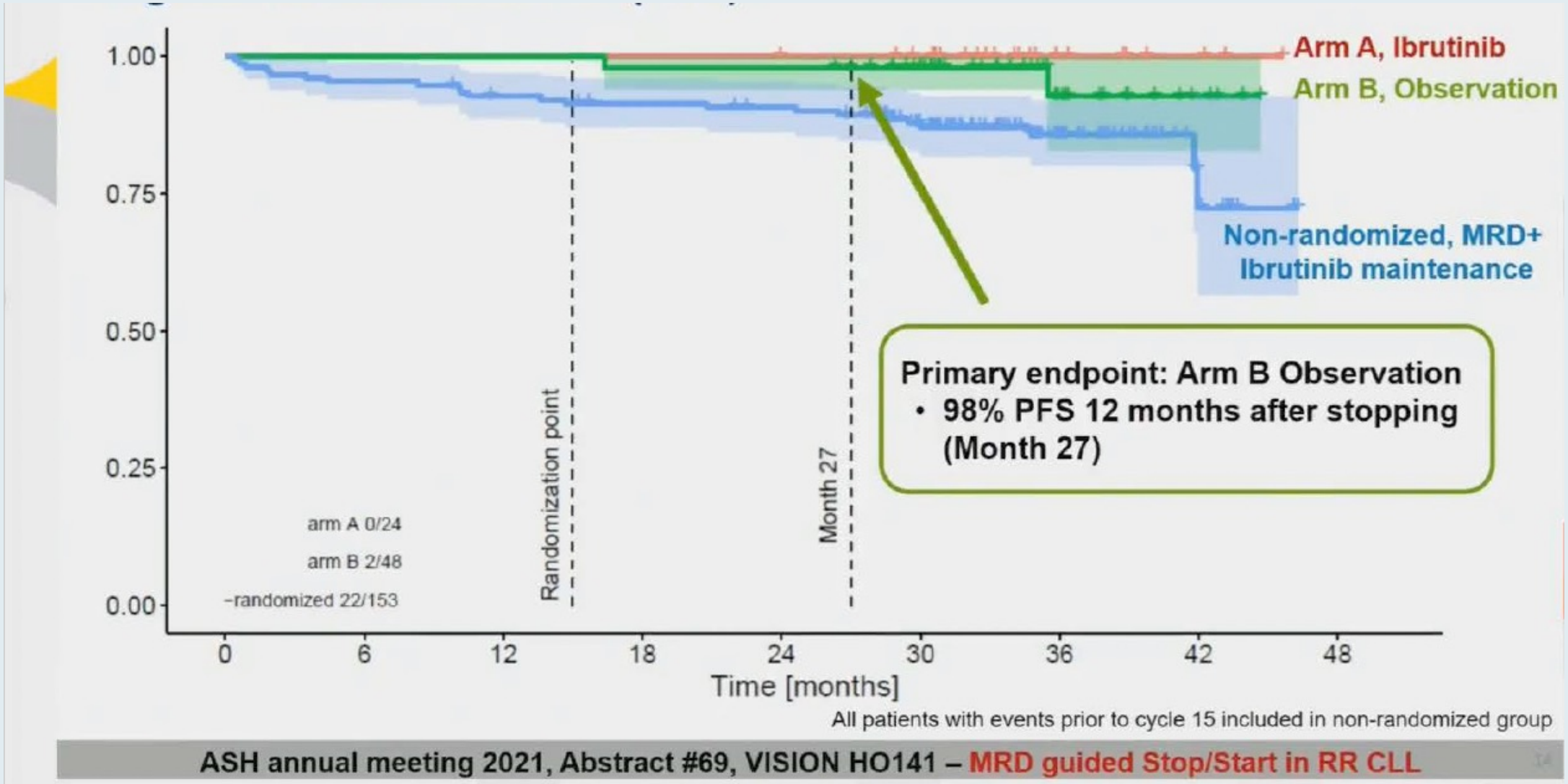
**Carsten U Niemann**, Julie Dubois, Christian Brieghel, Sabina Kersting, Lisbeth Enggaard, Gerrit J. Veldhuis, Rogier Mous, Clemens HM Mellink, Johan A Dobber, Christian B Poulsen, Henrik Frederiksen, Ann Janssens, Ida Schjødt, Ellen C Dompeling, Juha Ranti, Mattias Mattsson, Mar Bellido, Hoa TT Tran, Kazem Nasserinejad, Mark-David Levin, **Arnon P Kater**

# VISION H0141 Study Schema




Niemann CU et al. ASH 2021;Abstract 69.

# VISION H0141: Progression-Free Survival




ASH annual meeting 2021, Abstract #69, VISION HO141 – MRD guided Stop/Start in RR CLL

# Selection of BTK Inhibitor

original reports

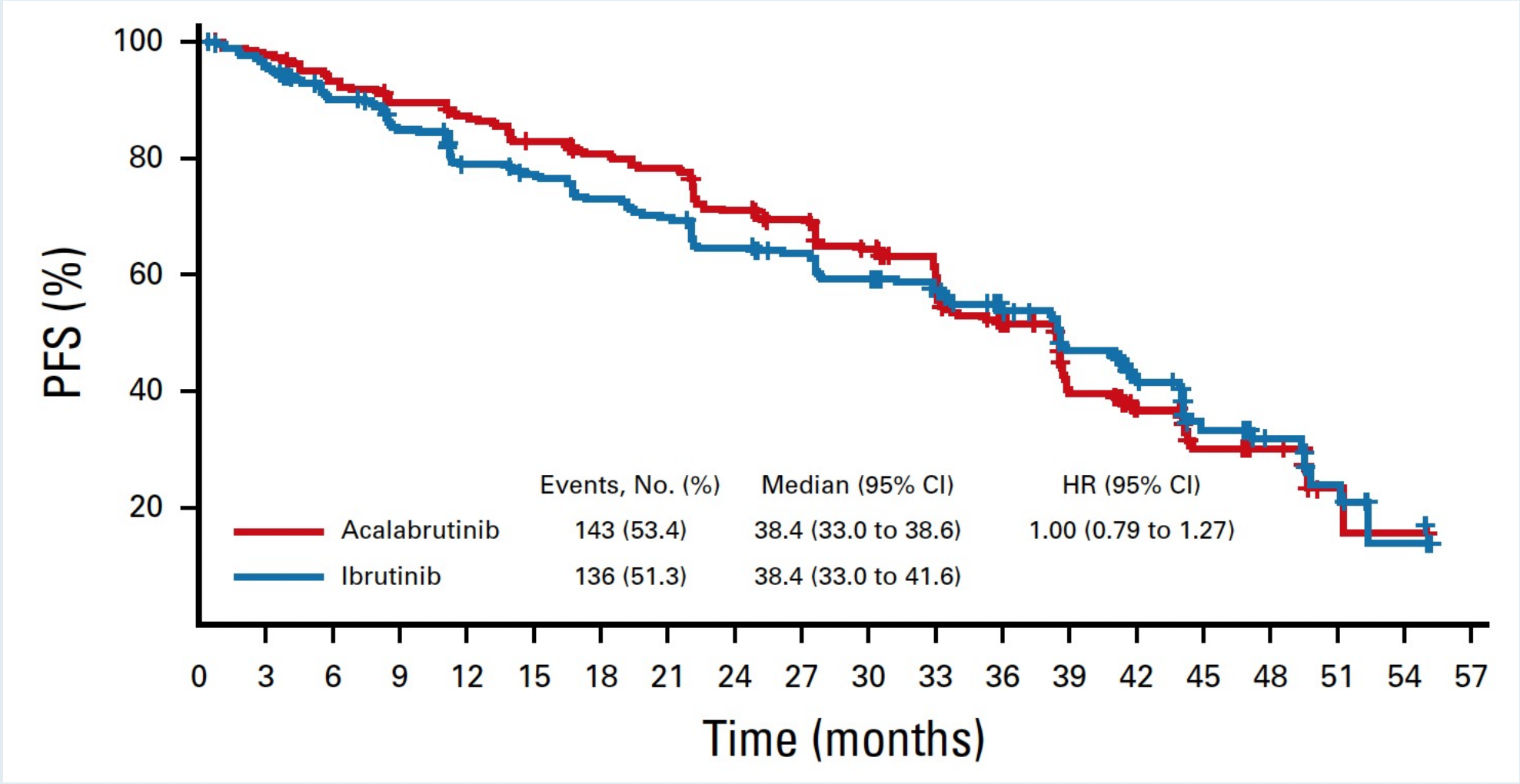
# Acalabrutinib Versus Ibrutinib in Previously Treated Chronic Lymphocytic Leukemia: Results of the First Randomized Phase III Trial

John C. Byrd, MD[1]; Peter Hillmen, MD, MBChB, PhD[2]; Paolo Ghia, MD, PhD[3,4]; Arnon P. Kater, MD, PhD[5]; Asher Chanan-Khan, MD[6]; Richard R. Furman, MD[7]; Susan O'Brien, MD[8]; Mustafa Nuri Yenerel, MD[9]; Arpad Illés, MD[10]; Neil Kay, MD[11]; Jose A. Garcia-Marco, MD, PhD[12]; Anthony Mato, MD[13]; Javier Pinilla-Ibarz, MD, PhD[14]; John F. Seymour, PhD[15]; Stephane Lepretre, MD[16,17]; Stephan Stilgenbauer, MD[18]; Tadeusz Robak, PhD[19]; Wayne Rothbaum, MS[20]; Raquel Izumi, PhD[20]; Ahmed Hamdy, MD[20]; Priti Patel, MD[21]; Kara Higgins, MS[21]; Sophia Sohoni, MD[21]; and Wojciech Jurczak, MD, PhD[22]

*J Clin Oncol* 2021;39(31):3441-52.

RTP RESEARCH TO PRACTICE

# ELEVATE-RR: Independent Review Committee-Assessed PFS




Byrd JC et al. *J Clin Oncol* 2021;39(31):3441-52.

# ELEVATE-RR: Characterization of Adverse Events with Acalabrutinib versus Ibrutinib

| | Incidence, % | | | | Exposure-Adjusted Incidence[b] | | | | Exposure-Adjusted Time With Event[c] | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Any grade | | Grade ≥3 | | Any grade | | Grade ≥3 | | Any grade | | Grade ≥3 | |
| | Acala[d] | Ibru[e] | Acala[d] | Ibru[e] | Acala[d] | Ibru[e] | Acala[d] | Ibru[e] | Acala[d] | Ibru[e] | Acala[d] | Ibru[e] |
| **ECIs** | | | | | | | | | | | | |
| Cardiac events | 24% | 30% | 9% | 10% | 1.2 | 1.9 | 0.4 | 0.5 | 7.1 | 13.0 | 0.4 | 0.2 |
| Afib/flutter | 9% | **16%*** | 5% | 4% | 0.4 | 0.7 | 0.2 | 0.1 | 1.3 | 3.8 | 0.3 | 0.1 |
| HTN[f] | 9% | **23%*** | 4% | **9%*** | 0.4 | 1.2 | 0.1 | 0.4 | 4.1 | 15.0 | 1.6 | 4.0 |
| Bleeding events[g] | 38% | **51%*** | 4% | 5% | 2.4 | 3.8 | 0.1 | 0.2 | 13.7 | 24.6 | 0.1 | 0.1 |
| Major bleeding events[h] | 5%[i] | 5%[j] | 4% | 5% | 0.2 | 0.2 | 0.1 | 0.2 | 0.1 | 0.3 | 0.1 | 0.1 |
| Infections[k] | 78% | 81% | 31% | 30% | 8.9 | 10.4 | 1.6 | 2.0 | 14.6 | 15.6 | 1.5 | 1.1 |
| **Selected Common AEs (preferred term)** | | | | | | | | | | | | |
| Diarrhea | 35% | **46%*** | 1% | **5%*** | 1.9 | 2.8 | <0.1 | 0.2 | 6.7 | 9.6 | <0.1 | 0.1 |
| Headache | **35%*** | 20% | **2%*** | 0 | 1.8 | 1.1 | <0.1 | 0 | 7.8 | 5.4 | <0.1 | 0 |
| Cough | **29%*** | 21% | 1% | <1% | 1.3 | 1.1 | <0.1 | <0.1 | 5.6 | 4.9 | <0.1 | <0.1 |
| Fatigue | 20% | 17% | **3%*** | 0% | 0.9 | 0.9 | 0.1 | 0 | 7.4 | 7.0 | 0.6 | 0 |
| Arthralgia | 16% | **23%*** | 0 | 1% | 0.6 | 1.3 | 0 | <0.1 | 7.5 | 10.4 | 0 | <0.1 |
| Back pain | 8% | **13%*** | 0 | 1% | 0.3 | 0.5 | 0 | <0.1 | 1.9 | 3.2 | 0 | 0.1 |
| Muscle spasms | 6% | **13%*** | 0 | 1% | 0.2 | 0.7 | 0 | <0.1 | 0.8 | 10.0 | 0 | 0.1 |
| Dyspepsia | 4% | **12%*** | 0 | 0 | 0.1 | 0.5 | 0 | 0 | 1.0 | 2.4 | 0 | 0 |

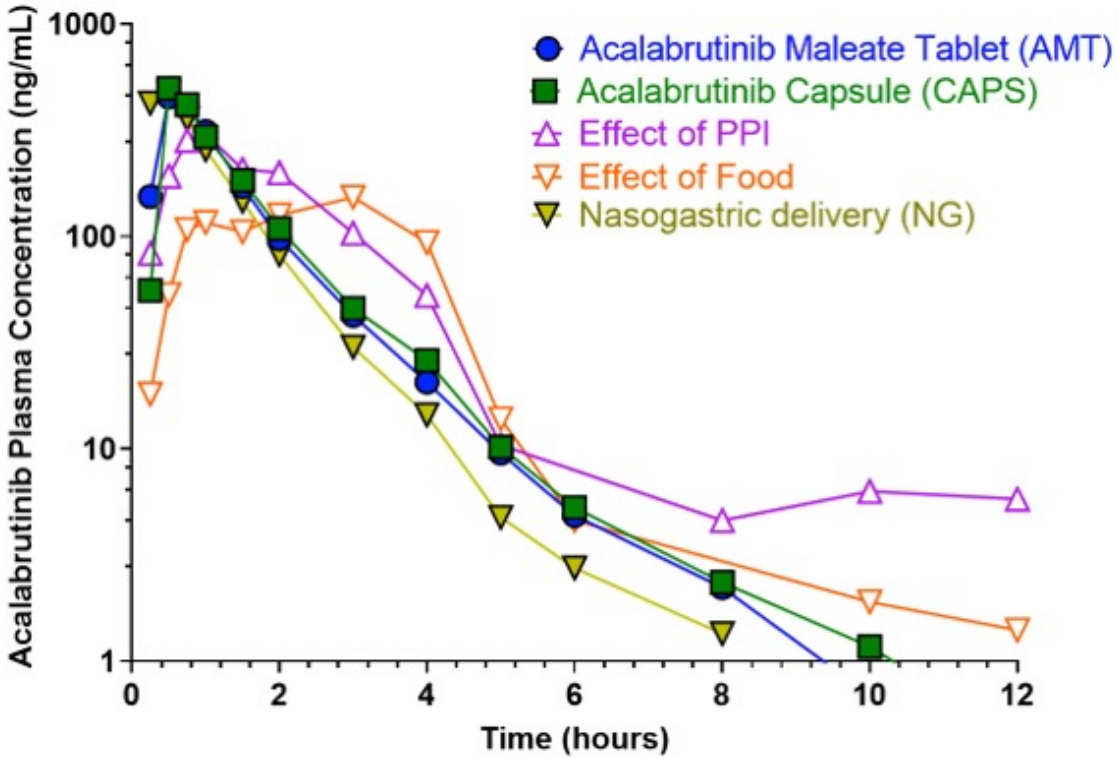
Seymour JF et al. ASH 2021;Abstract 3721.

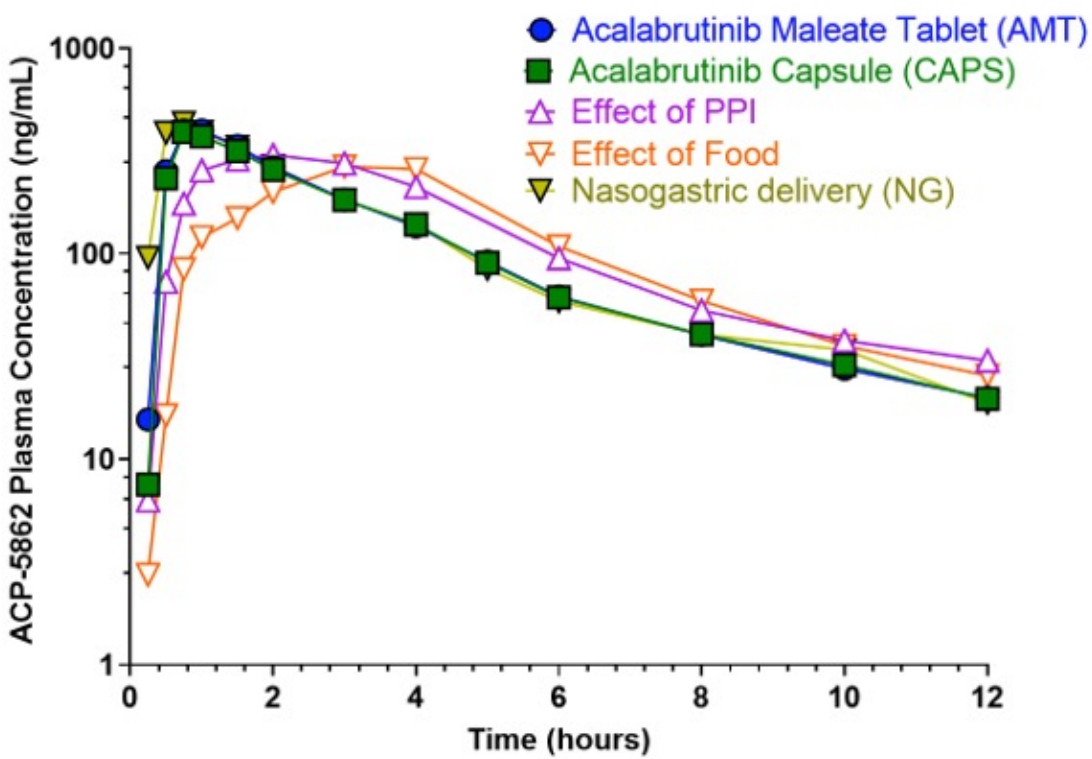
# New Acalabrutinib Formulation Enables Co-Administration with Proton Pump Inhibitors and Dosing in Patients Unable to Swallow Capsules (ELEVATE-PLUS)

Sharma S et al. ASH 2021;Abstract 4365.

***Author Conclusions:*** Acalabrutinib maleate, administered as a tablet or suspension, is safe and well tolerated. Based on the PK (and associated variability), BTK-TO, and established exposure-efficacy/safety relationship, AMT clinical effect is expected to be comparable to acalabrutinib capsules at the approved 100-mg BID dosing, regardless of use of PPIs and ingestion of food. Additionally, AMT improves swallowing ability given the film coating and a 50% reduced volume compared with the capsule, and can be easily suspended in a small amount of water to allow dosing in patients unable to swallow tablets.

# ELEVATE-PLUS: Pharmacokinetic Profiles of Acalabrutinib and Its Major Pharmacologically Active Metabolite Across 3 Clinical Trials




Sharma S et al. ASH 2021;Abstract 4365.

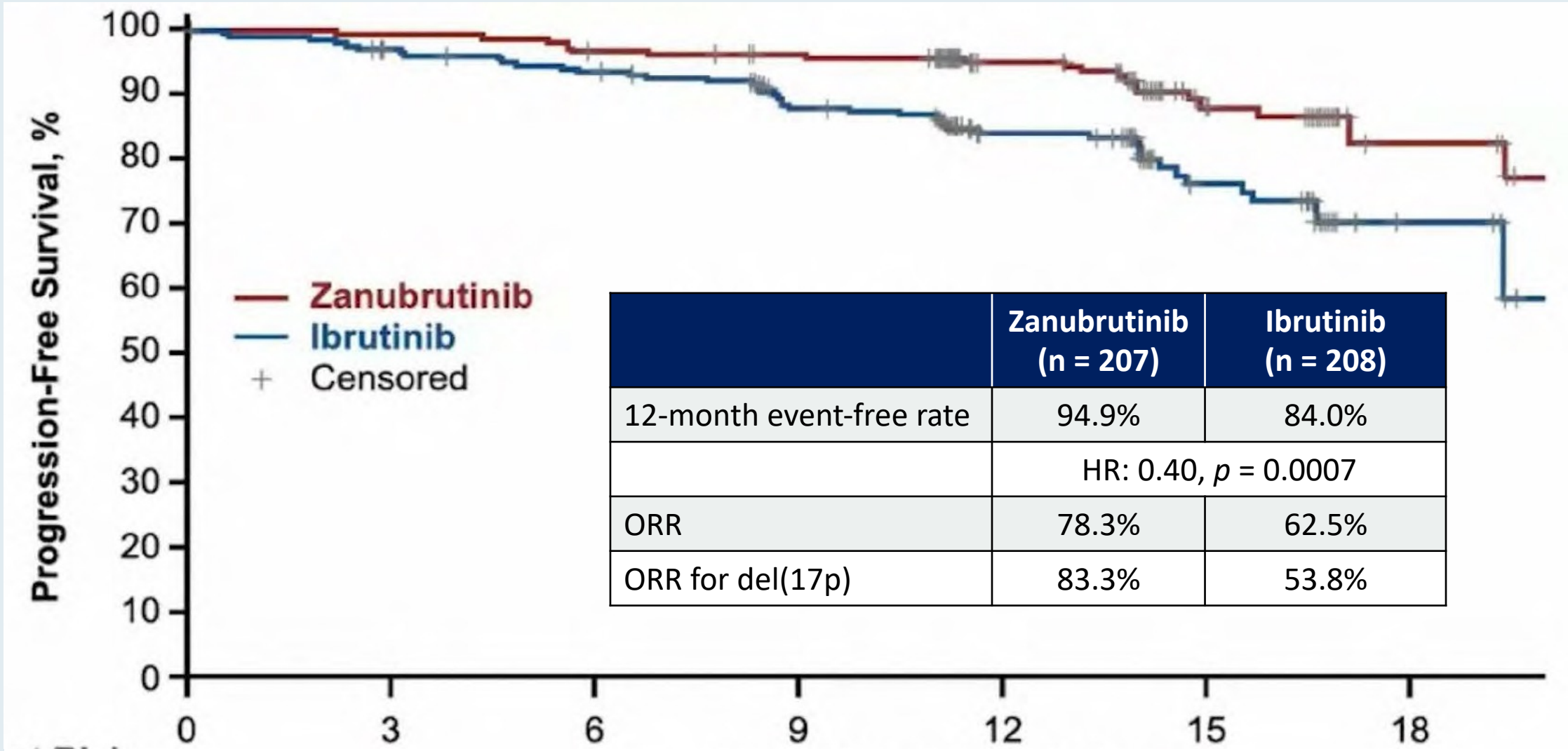
RTP RESEARCH TO PRACTICE

# First Interim Analysis of ALPINE Study: Results of a Phase 3 Randomized Study of Zanubrutinib vs Ibrutinib in Patients with Relapsed/Refractory Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma

Hillmen P et al.

EHA 2021;Abstract LBA1900.

# ALPINE: Response and Investigator-Assessed PFS




| | Zanubrutinib (n = 207) | Ibrutinib (n = 208) |
|---|---|---|
| 12-month event-free rate | 94.9% | 84.0% |
| | HR: 0.40, *p* = 0.0007 | |
| ORR | 78.3% | 62.5% |
| ORR for del(17p) | 83.3% | 53.8% |

Hillmen P et al. EHA 2021;Abstract LBA1900.

# ALPINE: Adverse Events of Special Interest

| Safety Analysis Population | Zanubrutinib (n=204), n (%) | | Ibrutinib (n=207), n (%) | |
|---|---|---|---|---|
| | Any Grade | Grade ≥3 | Any Grade | Grade ≥3 |
| Cardiac disorders[a] | 28 (13.7) | 5 (2.5) | 52 (25.1) | 14 (6.8) |
| **Atrial fibrillation and flutter (key 2º endpoint)** | **5 (2.5)** | **2 (1.0)** | **21 (10.1)** | **4 (1.9)** |
| Hemorrhage | 73 (35.8) | 6 (2.9) | 75 (36.2) | 6 (2.9) |
| Major hemorrhage[b] | 6 (2.9) | 6 (2.9) | 8 (3.9) | 6 (2.9) |
| Hypertension | 34 (16.7) | 22 (10.8) | 34 (16.4) | 22 (10.6) |
| Infections | 122 (59.8) | 26 (12.7) | 131 (63.3) | 37 (17.9) |
| Neutropenia[c] | 58 (28.4) | 38 (18.6) | 45 (21.7) | 31 (15.0) |
| Thrombocytopenia[c] | 19 (9.3) | 7 (3.4) | 26 (12.6) | 7 (3.4) |
| Secondary primary malignancies | 17 (8.3) | 10 (4.9) | 13 (6.3) | 4 (1.9) |
| Skin cancers | 7 (3.4) | 3 (1.5) | 10 (4.8) | 2 (1.0) |

Hillmen P et al. EHA 2021;Abstract LBA1900.

# Relapsed/Refractory CLL

*Blood* 2021;138(10):836-46.

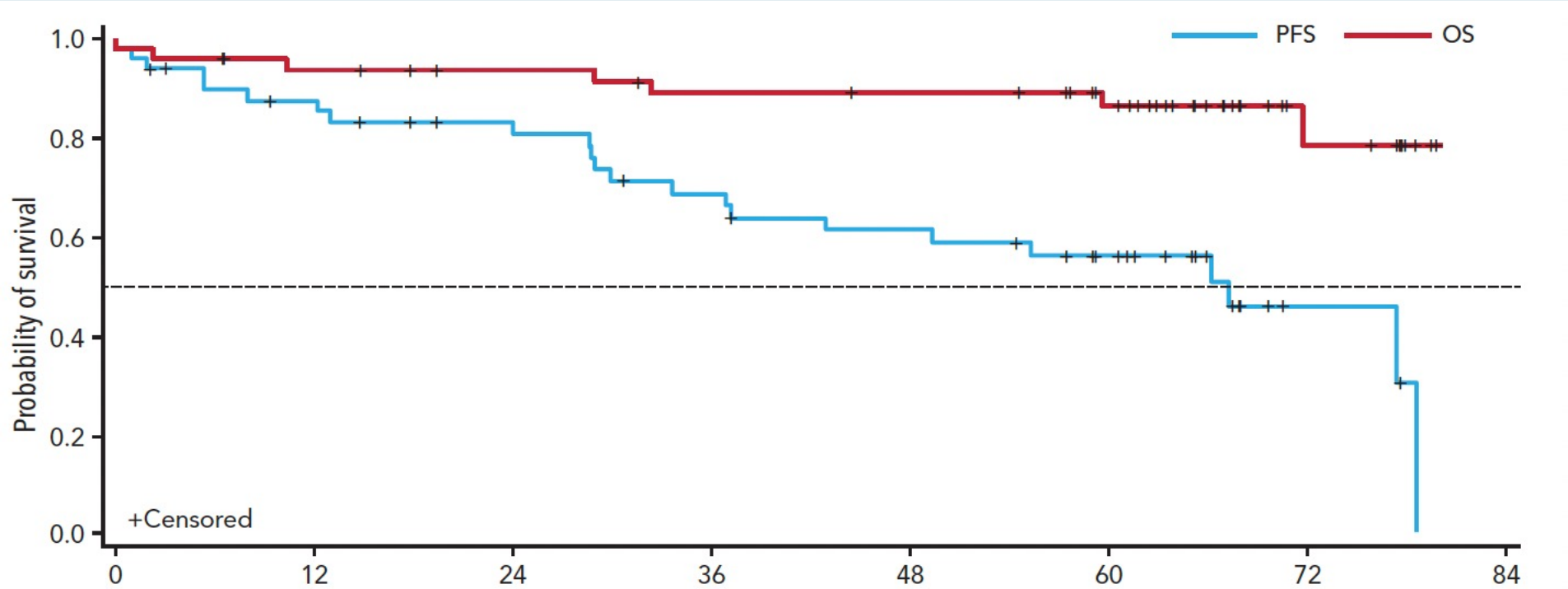
Regular Article

CLINICAL TRIALS AND OBSERVATIONS

# Efficacy of venetoclax plus rituximab for relapsed CLL: 5-year follow-up of continuous or limited-duration therapy

Shuo Ma,[1,*] John F. Seymour,[2,3,*] Danielle M. Brander,[4] Thomas J. Kipps,[5] Michael Y. Choi,[5] Mary Ann Anderson,[2,3,6] Kathryn Humphrey,[7] Abdullah Al Masud,[8] John Pesko,[8] Ruby Nandam,[8] Ahmed Hamed Salem,[8,9] Brenda Chyla,[8] Jennifer Arzt,[8] Amanda Jacobson,[8] Su Young Kim,[8] and Andrew W. Roberts[2,3,6]

# MURANO 5-Year Follow-Up: Overall and Progression-Free Survival (All Patients)




Patients at risk

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| PFS | 49 | 40 | 34 | 28 | 24 | 18 | 3 | 0 |
| OS | 49 | 44 | 41 | 38 | 37 | 31 | 10 | 0 |

Survival estimate (95% CI)

| | Events | Month 24 | Month 36 | Month 60 | Month 72 | Median months (95% CI) |
|---|---|---|---|---|---|---|
| PFS (N = 49) | 23 | 80.7% (66.2–89.5) | 68.8% (52.9–80.3) | 56.1% (39.9–69.5) | 45.9% (27.8–62.2) | 67.3 (37.1–78.6) |
| OS (N = 49) | 7 | 93.8% (82.0–98.0) | 89.2% (75.8–95.3) | 86.4% (71.9–93.7) | 78.5% (54.7–90.8) | NR (NR–NR) |

Ma S et al. *Blood* 2021;138(10):836-46.

RTP RESEARCH TO PRACTICE

# MURANO 5-Year Follow-Up: Durability of Benefit in Deep Responders (CR or uMRD Response)

| | Continuous Ven (n = 14) | Limited-duration Ven* (n = 19) | All deep responders (n = 33) |
|---|---|---|---|
| Median time on Ven, y (range) | 5.6 (2.4-6.6) | 1.4 (0.4-4.2) | 3.1 (0.5-6.6) |
| **PFS†** | | | |
| Median, y (95% CI) | 6.6 (4.6-6.6) | 6.5 (3.6-6.5) | 6.5 (5.5-6.6) |
| 3-y estimate (95% CI) | 92.9% (59.1-99.0) | 87.1% (57.3-96.6) | 89.9% (71.8-96.6) |
| 5-y estimate (95% CI) | 78.6% (47.2-92.5) | 79.8% (49.4-93.0) | 79.1% (59.1-90.0) |
| **Duration of response†** | | | |
| Median, y (95% CI) | 6.3 (4.4-6.3) | 6.2 (3.4-6.2) | 6.2 (5.4-6.3) |
| 3-y estimate (95% CI) | 85.7% (53.9-96.2) | 86.7% (56.4-96.5) | 86.2% (67.2-94.6) |
| 5-y estimate (95% CI) | 70.7% (39.4-87.9) | 79.4% (48.8-92.9) | 73.9% (52.4-86.8) |

CR = complete response; uMRD = undetectable minimal residual disease

Ma S et al. *Blood* 2021;138(10):836-46.

# MURANO: Grade 3 or 4 Treatment-Emergent Adverse Events (AEs) Within and Beyond 2 Years of Treatment

| AE preferred term | Within the first 2 y of treatment; all patients, N = 49* | After 2 y of treatment; all patients n = 21† |
|---|---|---|
| **Grade 3/4 (≥5% of total patients), n (%)** | 40 (82) | 11 (52) |
| Neutropenia | 26 (53) | 4 (19)‡ |
| Thrombocytopenia | 8 (16) | 1 (5) |
| Anemia | 7 (14) | 0 |
| Leukopenia | 7 (14) | 3 (14) |
| Febrile neutropenia | 5 (10) | 0 |
| Decreased neutrophil count | 4 (8) | 0 |
| Lower respiratory tract infection | 3 (6) | 1 (5) |
| Lymphopenia | 3 (6) | 0 |
| Pneumonia | 3 (6) | 1 (5) |
| Pyrexia | 3 (6) | 1 (5) |

Ma S et al. *Blood* 2021;138(10):836-46.

# MURANO: Serious AEs Within and Beyond 2 Years of Treatment

| AE preferred term | Within the first 2 y of treatment; all patients, N = 49* | After 2 y of treatment; all patients n = 21† |
|---|---|---|
| **SAEs (>2% of total patients), n (%)** | 28 (57) | 9 (43) |
| Pyrexia | 5 (10) | 1 (5) |
| Febrile neutropenia | 4 (8) | 0 |
| Pneumonia | 4 (8) | 2 (10) |
| Lower respiratory tract infection | 3 (6) | 1 (5) |
| Diarrhea | 2 (4) | 1 (5) |
| Infusion-related reaction | 2 (4) | 0 |
| Osteoarthritis | 2 (4) | 2 (10) |
| Tumor lysis syndrome | 2 (4) | 0 |

Ma S et al. *Blood* 2021;138(10):836-46.

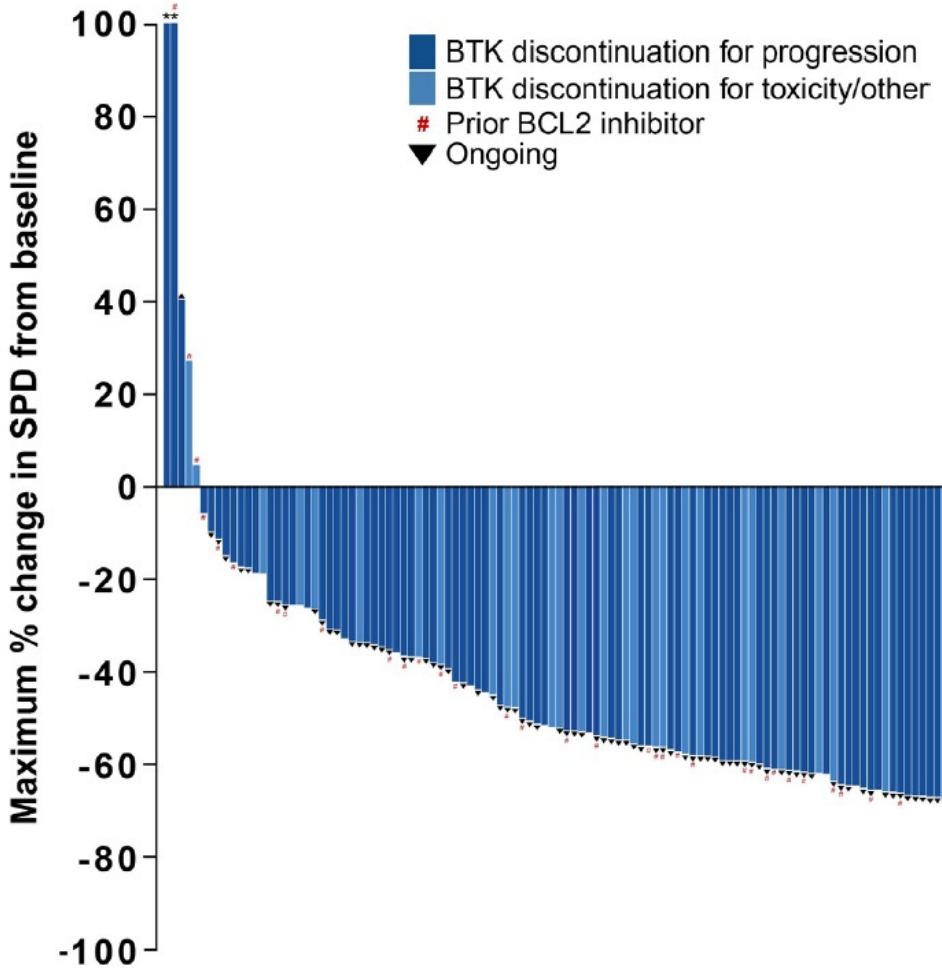
# Novel Strategies Under Investigation

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

Mato AR et al.

ASH 2021;Abstract 391.

# BRUIN: Pirtobrutinib Efficacy in Patients with BTK-Pretreated CLL or Small Lymphocytic Lymphoma (SLL)




| Efficacy evaluable BTK pre-treated CLL/SLL Patients[a] | n = 252 |
|---|---|
| **Overall Response Rate, % (95% CI)[b]** | **68 (62 – 74)** |
| **Best response** | |
| CR, n (%) | 2 (1) |
| PR, n (%) | 137 (54) |
| PR-L, n (%) | 32 (13) |
| SD, n (%) | 62 (25) |

Mato AR et al. ASH 2021;Abstract 391.

RTP RESEARCH TO PRACTICE

# BRUIN: Pirtobrutinib Safety Profile

| | All doses and patients (n=618) | | | | | | |
|---|---|---|---|---|---|---|---|
| | Treatment-emergent AEs, (≥15%), % | | | | | Treatment-related AEs, % | |
| Adverse Event | Grade 1 | Grade 2 | Grade 3 | Grade 4 | Any Grade | Grades 3/4 | Any Grade |
| Fatigue | 13% | 8% | 1% | - | 23% | 1% | 9% |
| Diarrhea | 15% | 4% | <1% | <1% | 19% | <1% | 8% |
| Neutropenia[a] | 1% | 2% | 8% | 6% | 18% | 8% | 10% |
| Contusion | 15% | 2% | - | - | 17% | - | 12% |
| AEs of special interest[b] | | | | | | | |
| Bruising[c] | 20% | 2% | - | - | 22% | - | 15% |
| Rash[d] | 9% | 2% | <1% | - | 11% | <1% | 5% |
| Arthralgia | 8% | 3% | <1% | - | 11% | - | 3% |
| Hemorrhage[e] | 5% | 2% | 1%[g] | - | 8% | <1% | 2% |
| Hypertension | 1% | 4% | 2% | - | 7% | <1% | 2% |
| Atrial fibrillation/flutter[f] | - | 1% | <1% | <1% | 2%[h] | - | <1% |

**No DLTs reported and MTD not reached**
**96% of patients received ≥1 pirtobrutinib dose at or above RP2D of 200 mg daily**
**1% (n=6) of patients permanently discontinued due to treatment-related AEs**

Mato AR et al. ASH 2021;Abstract 391.

# FDA Has Placed a Partial Clinical Hold on Some Combination Candidate Studies for Leukemia and Lymphoma

## Press Release – January 27, 2022

The FDA placed partial holds on studies of the U2 combination umbralisib and ublituximab for chronic lymphocytic leukemia (CLL) and non-Hodgkin lymphoma (NHL).

The updated overall survival (OS) preliminary results from the UNITY-CLL study showed improvement. The OS hazard ratio was 1.23, and, including COVID-19-related deaths, the ratio reached 1.04.

An OS hazard ratio above 1.00 implies a risk that the investigational therapy might be causing harm.

No new patients can be enrolled in some CLL and NHL trials, but those deriving a benefit may continue with consent.

https://www.yahoo.com/now/tg-therapeutics-falls-30-ceo-173034141.html

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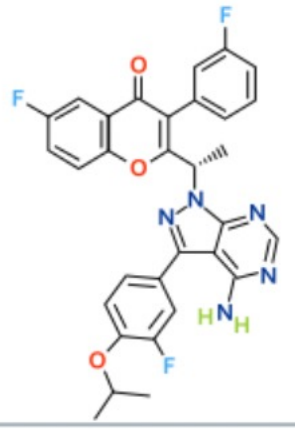
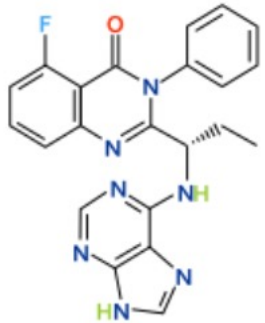
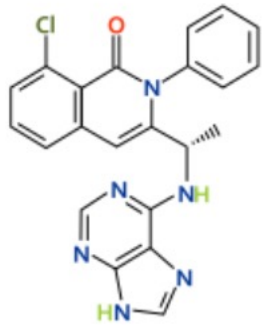
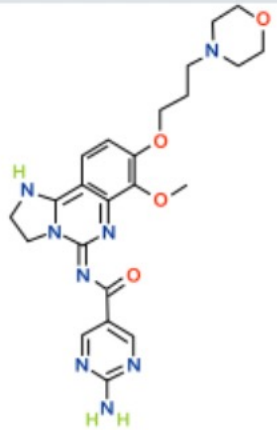
# Efficacy and Safety of Ublituximab in Combination with Umbralisib (U2) in Patients with Chronic Lymphocytic Leukemia (CLL) By Treatment Status: A Sub-Analysis of the Phase 3 Unity-CLL Study

Jacobs R et al.

ASH 2021;Abstract 3726.

# Umbralisib: A Selective Inhibitor of PI3Kδ and CK1ε

| | Umbralisib[1] | Idelalisib[1] | Duvelisib[1] | Copanlisib[2] |
|---|---|---|---|---|
| |  |  |  |  |
| **Isoform** | **$K_d$ (nM)** | | | |
| PI3kα | >10000 | 600 | 40 | 0.04 |
| PI3Kβ | >10000 | 19 | 0.89 | 1.5 |
| PI3Kγ | 1400 | 9.1 | 0.21 | 0.31 |
| PI3Kδ | 6.2 | 1.2 | 0.047 | 0.068 |
| CK1ε | 180 | >30,000 | >30,000 | >6,000 |

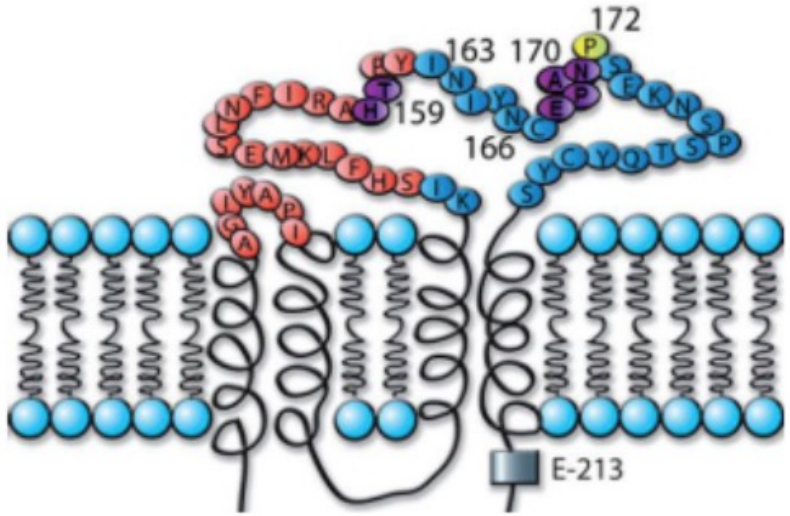
- Umbralisib is an oral, once daily, selective inhibitor of PI3Kδ and CK1ε
- Umbralisib has >1000-fold greater selectivity for PI3Kδ compared to α and β isoforms
- Umbralisib is also **>200-fold** more selective for PI3Kδ relative to **PI3Kγ**

Jacobs R et al. ASH 2021;Abstract 3726.

# Ublituximab: A Novel Glycoengineered Anti-CD20 Monoclonal Antibody

- Ublituximab (TG-1101, UTX) is a novel, glycoengineered, Type I, anti-CD20 monoclonal antibody with several defining features:
  - Targets a unique epitope on the CD20 antigen
  - Type I maintains complement-dependent cytotoxicity (CDC)
  - Glycoengineered to enhance affinity for all variants of FcγRIIIa receptors, thereby demonstrating greater antibody-dependent cellular cytotoxicity (ADCC) activity than rituximab and ofatumumab, including in 17p deleted CLL cells[1]

**Ublituximab**




**Red**: Key ofatumumab epitope amino acids
**Purple**: Core amino acids of ublituximab epitope

*Figure adapted from Ruuls et al, 2008*[2]

Jacobs R et al. ASH 2021;Abstract 3726.

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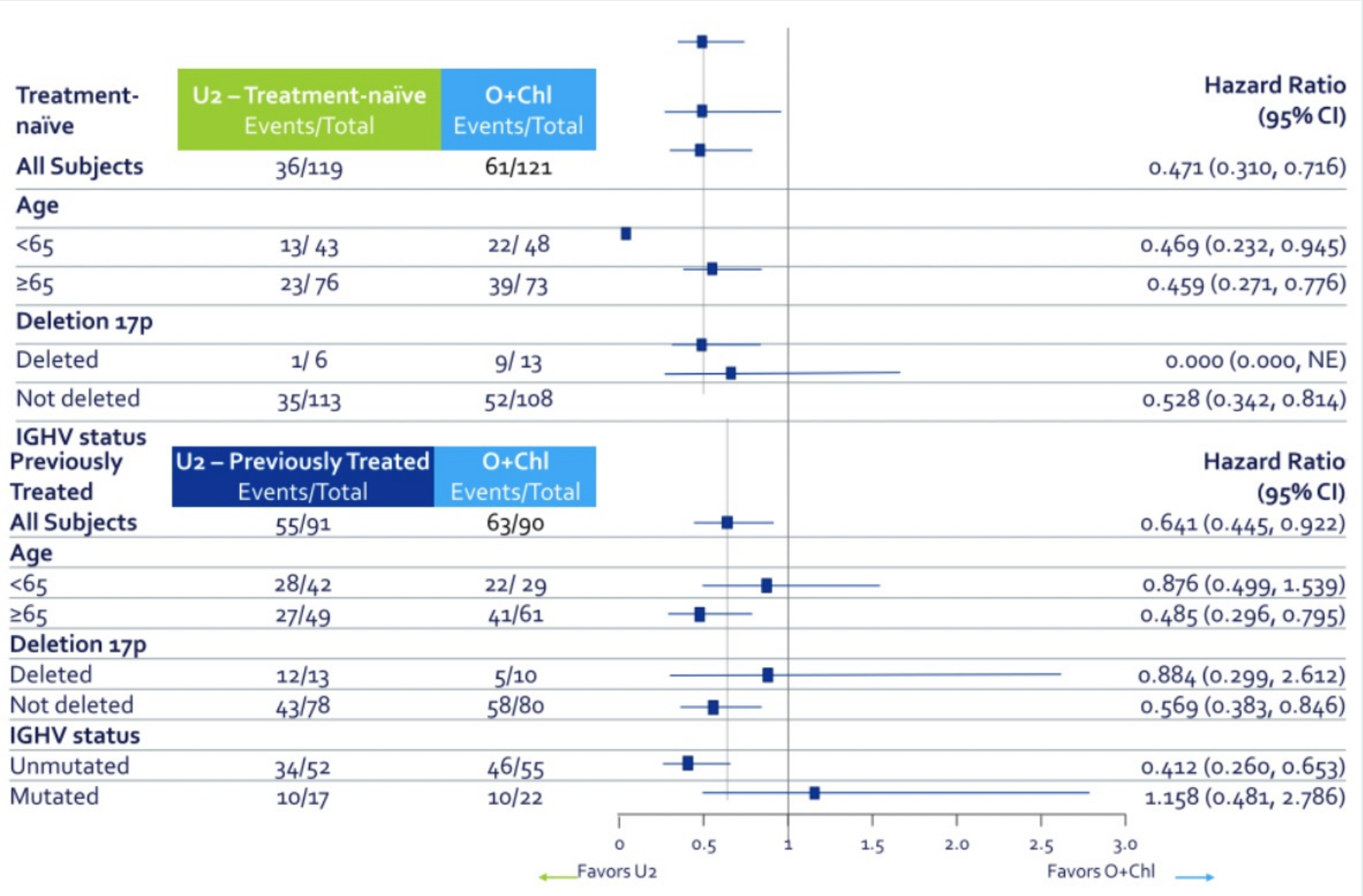
# UNITY-CLL: IRC-Assessed PFS by Treatment Status




Jacobs R et al. ASH 2021;Abstract 3726.

# UNITY-CLL: Adverse Events (AEs) of Clinical Interest

| AEs, n (%) | Treatment-naïve N=116 | | | Previously Treated N=90 | | |
|---|---|---|---|---|---|---|
| | Any | Grade ≥3 | Discontinued U2[b] | Any | Grade ≥3 | Discontinued U2[b] |
| ALT elevation | 27 (23) | 14 (12) | 3 (3) | 8 (9) | 3 (3) | - |
| AST elevation | 21 (18) | 9 (8) | 3 (3) | 7 (8) | 2 (2) | - |
| Rash[a] | 17 (15) | 4 (3) | 1 (1) | 9 (10) | 1 (1) | 1 (1) |
| Pneumonia | 14 (12) | 8 (7) | 1 (1) | 18 (20) | 10 (11) | 1 (1) |
| Colitis (non-infectious)[a] | 8 (7) | 3 (3) | - | 2 (2) | 1 (1) | 1 (1) |
| Pneumonitis | 4 (3) | 1 (1) | 2 (2) | 2 (2) | - | 1 (1) |
| Opportunistic infections[a] | 3 (3) | 1 (1) | 1 (1) | 3 (3) | 1 (1) | - |

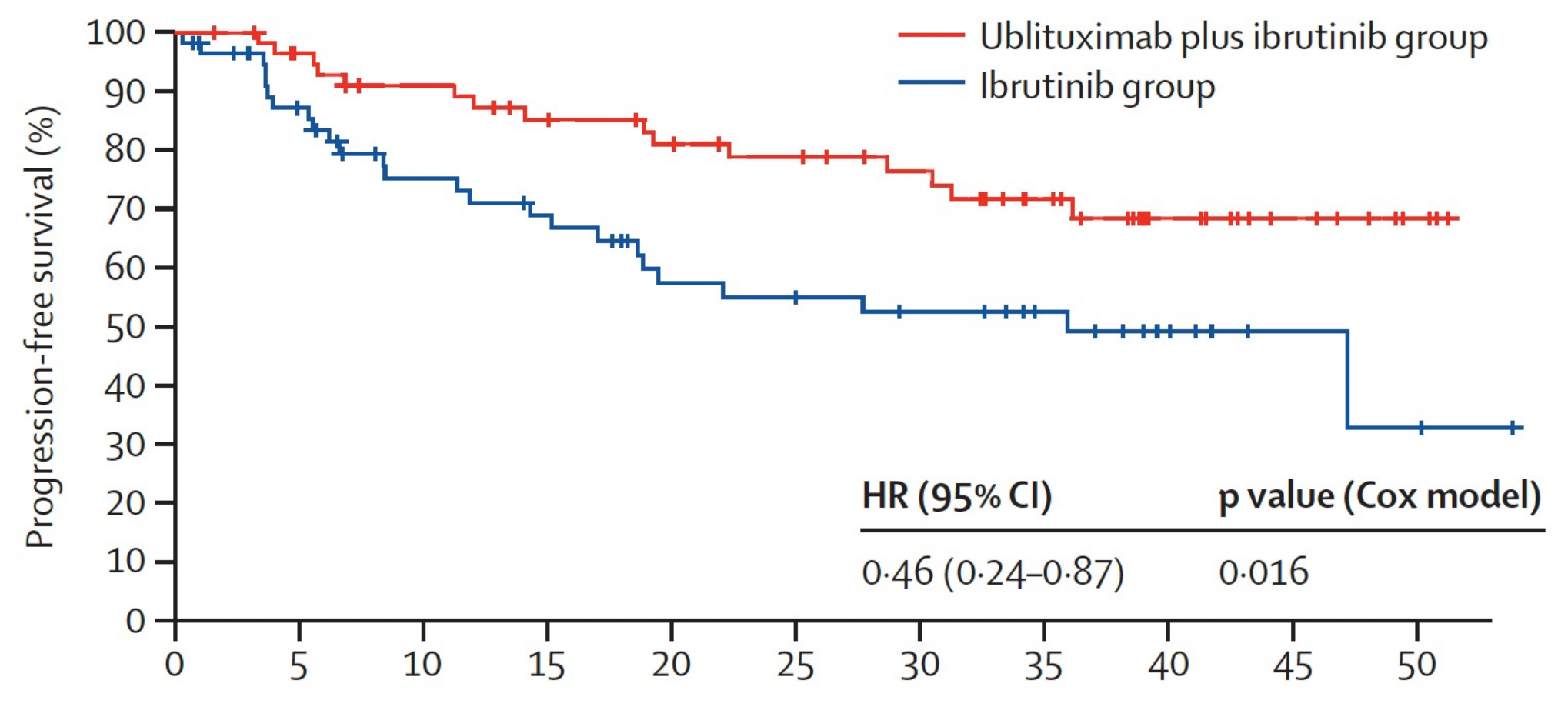
Jacobs R et al. ASH 2021;Abstract 3726.

*Lancet Haematol* 2021;8:e254-66.

# Ublituximab plus ibrutinib versus ibrutinib alone for patients with relapsed or refractory high-risk chronic lymphocytic leukaemia (GENUINE): a phase 3, multicentre, open-label, randomised trial

*Jeff P Sharman, Danielle M Brander, Anthony R Mato, Nilanjan Ghosh, Stephen J Schuster, Suman Kambhampati, John M Burke, Frederick Lansigan, Marshall T Schreeder, Scott D Lunin, Alexander Zweibach, Mikhail Shtivelband, Patrick M Travis, Jason C Chandler, Kathryn S Kolibaba, Peter Sportelli, Hari P Miskin, Michael S Weiss, Ian W Flinn*

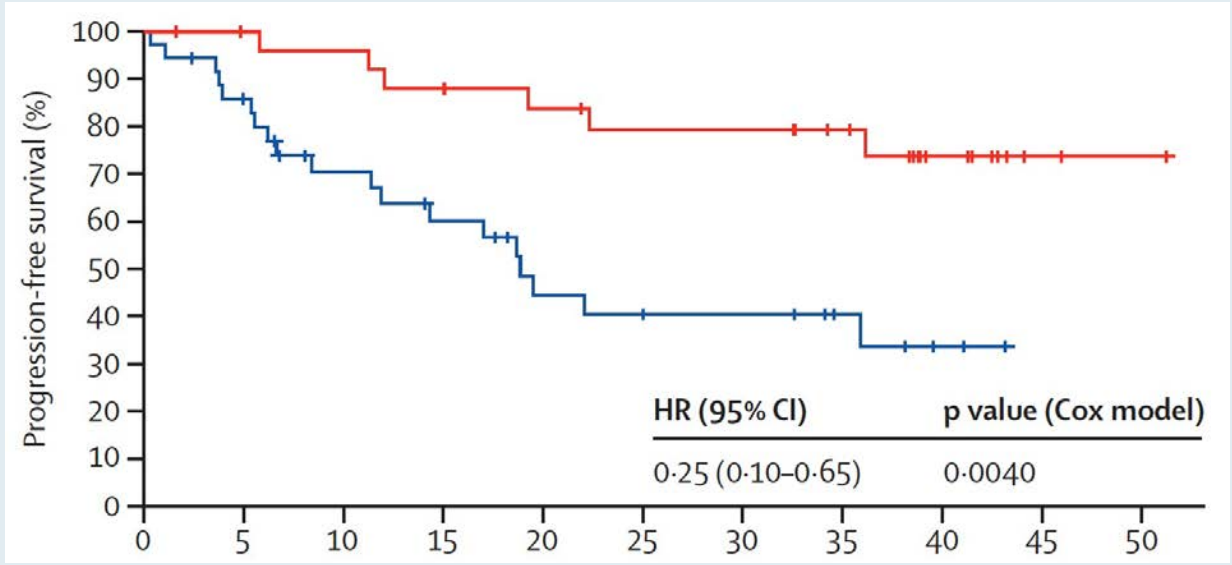
# GENUINE: Progression-Free Survival (All Patients)




Sharman JP et al. *Lancet Haematol* 2021;8:e254-56.

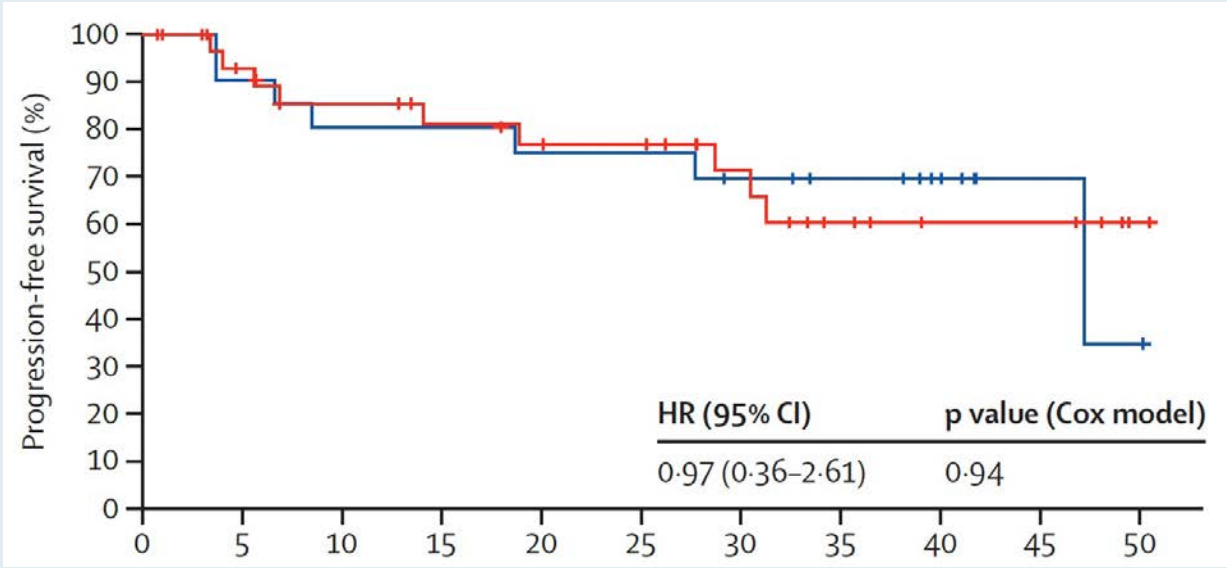
# GENUINE: Progression-Free Survival in Subgroups

**Patients with 17p deletion, *TP* mutation, or both**




Time since randomization (months)

**Patients with 11q deletion**




Time since randomization (months)

Sharman JP et al. *Lancet Haematol* 2021;8:e254-56.

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*Nature* 2022;[Online ahead of print].

Article

# Decade-long leukaemia remissions with persistence of CD4$^+$ CAR T cells

https://doi.org/10.1038/s41586-021-04390-6

Received: 7 May 2021

Accepted: 29 December 2021

Published online: 02 February 2022

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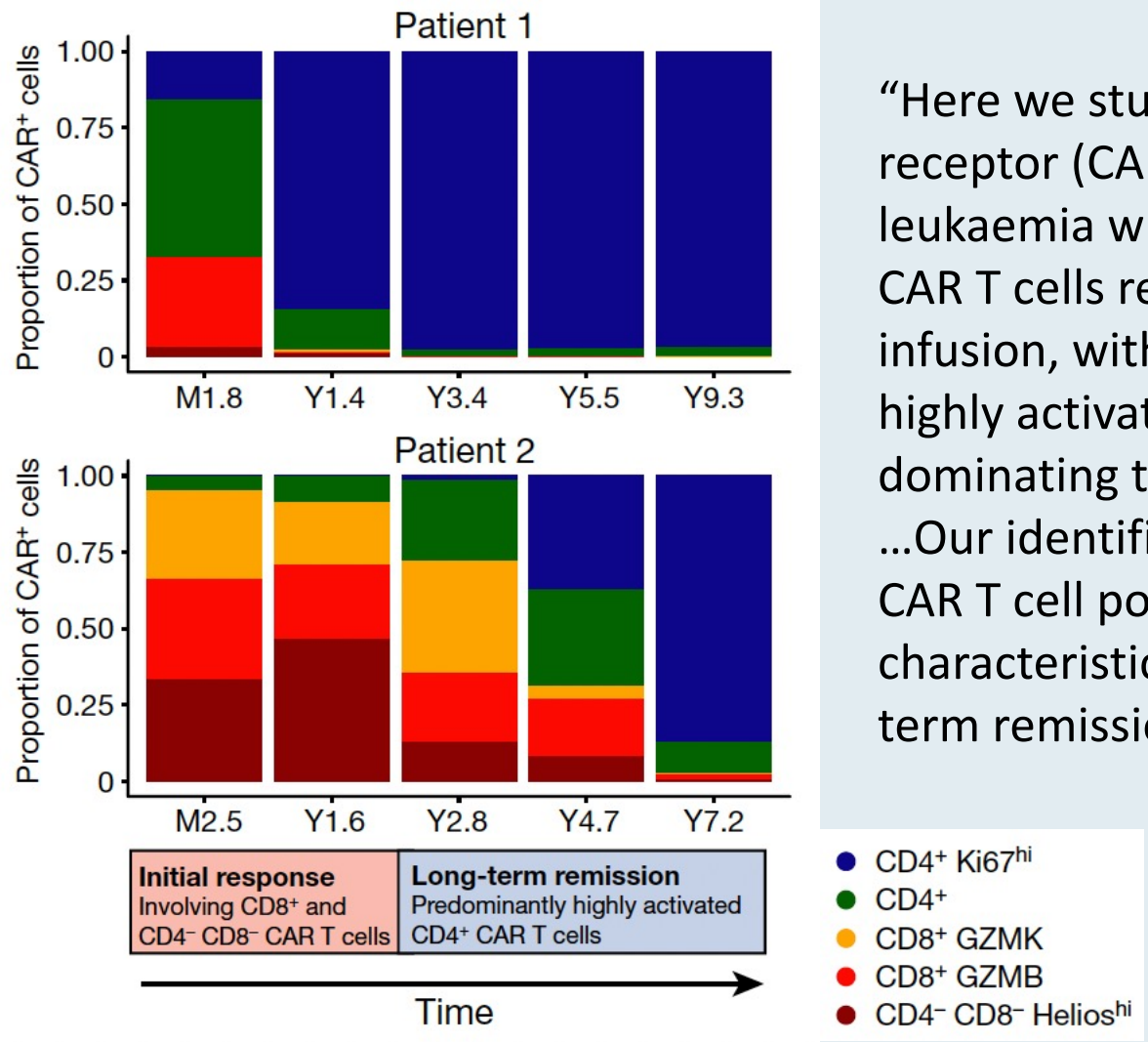
# Analysis of CD3+ CAR+ T Cells Using CyTOF Across Multiple Time Points




"Here we studied long-lasting CD19-redirected chimeric antigen receptor (CAR) T cells in two patients with chronic lymphocytic leukaemia who achieved a complete remission in 2010. CAR T cells remained detectable more than ten years after infusion, with sustained remission in both patients. Notably, a highly activated CD4+ population emerged in both patients, dominating the CAR T cell population at the later time points… …Our identification and characterization of these unexpected CAR T cell populations provide novel insight into the CAR T cell characteristics associated with anti-cancer response and long-term remission in leukaemia."

Melenhorst JJ et al. *Nature* 2022;[Online ahead of print].

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American Society of Hematology
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Washington, DC 20036
Phone: 202-776-0544 | Fax 202-776-0545
editorial@hematology.org

*Blood* 2021;[Online ahead of print].

# Phase 1 TRANSCEND CLL 004 study of lisocabtagene maraleucel in patients with relapsed/refractory CLL or SLL

Tracking no: BLD-2021-011895R2

Tanya Siddiqi (City of Hope Medical Center, United States) Jacob Soumerai (Massachusetts General Hospital Cancer Center, United States) Kathleen Dorritie (UPMC, United States) Deborah Stephens (University of Utah, United States) Peter Riedell (University of Chicago, United States) Jon Arnason (BIDMC, United States) Thomas Kipps (University of California-San Diego School of Medicine, United States) Heidi Gillenwater (Bristol Myers Squibb, United States) Lucy Gong (Bristol Myers Squibb, United States) Lin Yang (Bristol Myers Squibb, United States) Ken Ogasawara (Bristol Myers Squibb, United States) Jerill Thorpe (Bristol Myers Squibb, United States) William Wierda (University of Texas M.D. Anderson Cancer Center, United States)

# TRANSCEND CLL 004: Rates of Cytokine Release Syndrome (CRS), Neurologic Events (NE) and Rehospitalization After Liso-cel Infusion

| | All patients (N = 23) | Dose level 1 $50 \times 10^6$ (n = 9) | Dose level 2 $100 \times 10^6$ (n = 14) |
|---|---|---|---|
| CRS any grade | 17 (74%) | 7 (78%) | 10 (71%) |
| CRS Grade ≥3 | 2 (9%) | 0 | 2 (14%) |
| NE any grade | 9 (39%) | 2 (22%) | 7 (50%) |
| NE Grade ≥3 | 5 (21%) | 2 (22%) | 2 (14%) |
| Reasons for patient rehospitalization | | | |
| Adverse events | 11 (48%) | 3 (33%) | 8 (57%) |
| CRS and/or NE | 5 (22%) | 1 (11%) | 4 (29%) |
| CRS and NE | 2 (9%) | 0 | 2 (14%) |
| NE only | 3 (13%) | 1 (11%) | 2 (14%) |

Siddiqi T et al. *Blood* 2021;[Online ahead of print].

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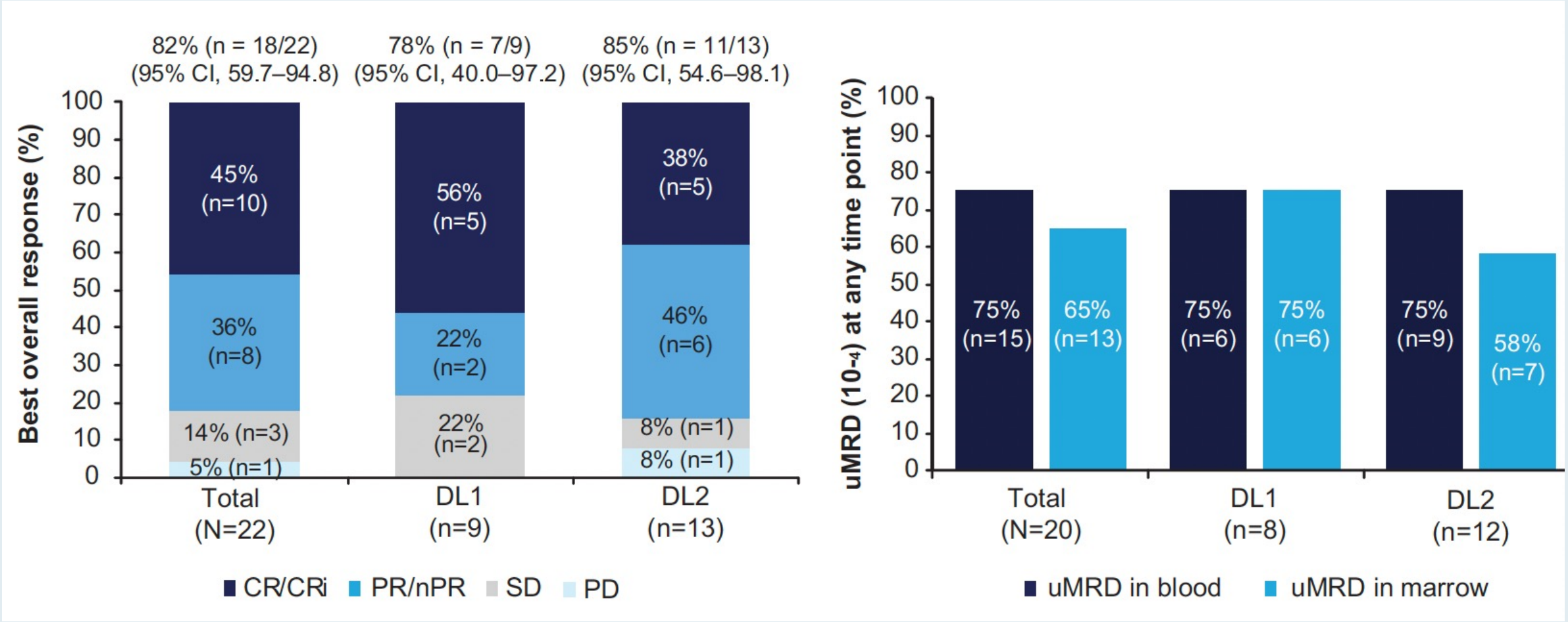
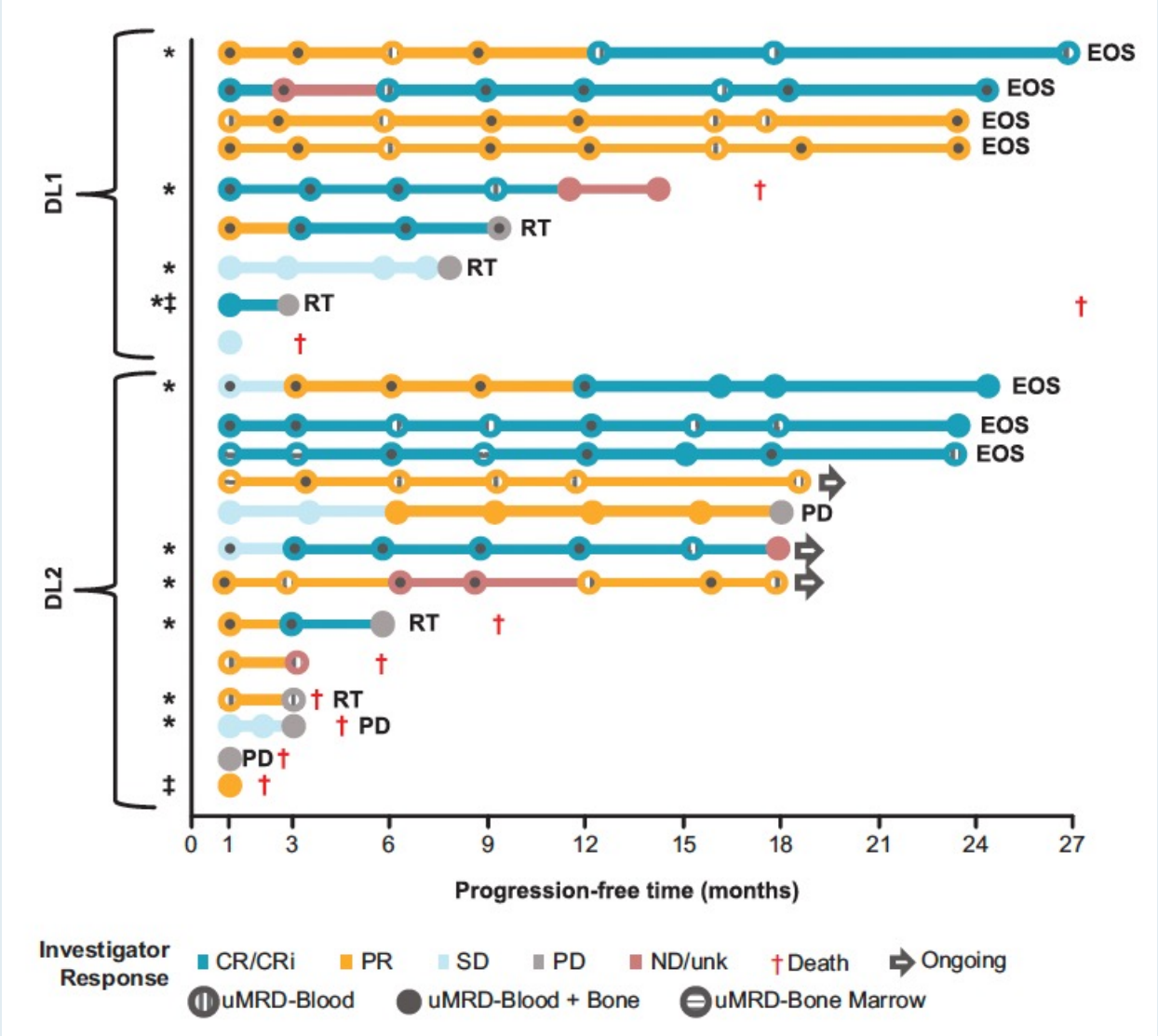
# TRANSCEND CLL 004: Response and uMRD ($10^{-4}$) Rates




Siddiqi T et al. *Blood* 2021;[Online ahead of print].

# TRANSCEND CLL 004: Swim Lane Plot, Duration of Response and PFS




Siddiqi T et al. *Blood* 2021;[Online ahead of print].

# Data + Perspectives: Clinical Investigators Discuss the Current and Future Management of Ovarian Cancer

**Saturday, March 19, 2022**

**2:30 PM – 4:00 PM ET**

## Faculty

**Mansoor Raza Mirza, MD**
**Kathleen N Moore, MD, MS**
**David M O'Malley, MD**

## Moderator

**Robert L Coleman, 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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