# Consensus or Controversy? Investigators Discuss Clinical Practice Patterns and Available Research Data Guiding the Management of Hematologic Cancers

# Chronic Lymphocytic Leukemia

**Friday, December 4, 2020**
**12:00 PM – 1:30 PM Pacific Time**

## Faculty


**Paul M Barr, MD**
**Matthew S Davids, MD, MMSc**
**Kerry Rogers, MD**
**Tanya Siddiqi, MD**
**Stephan Stilgenbauer, MD**


## Moderator


**Neil Love, MD**


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# Commercial Support

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

# Dr Love — Disclosures

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

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# Dr Rogers — Disclosures

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# Dr Siddiqi — Disclosures

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| **Speakers Bureau** | AstraZeneca Pharmaceuticals LP, Janssen Biotech Inc, Pharmacyclics LLC, an AbbVie Company |

# Dr Stilgenbauer — Disclosures

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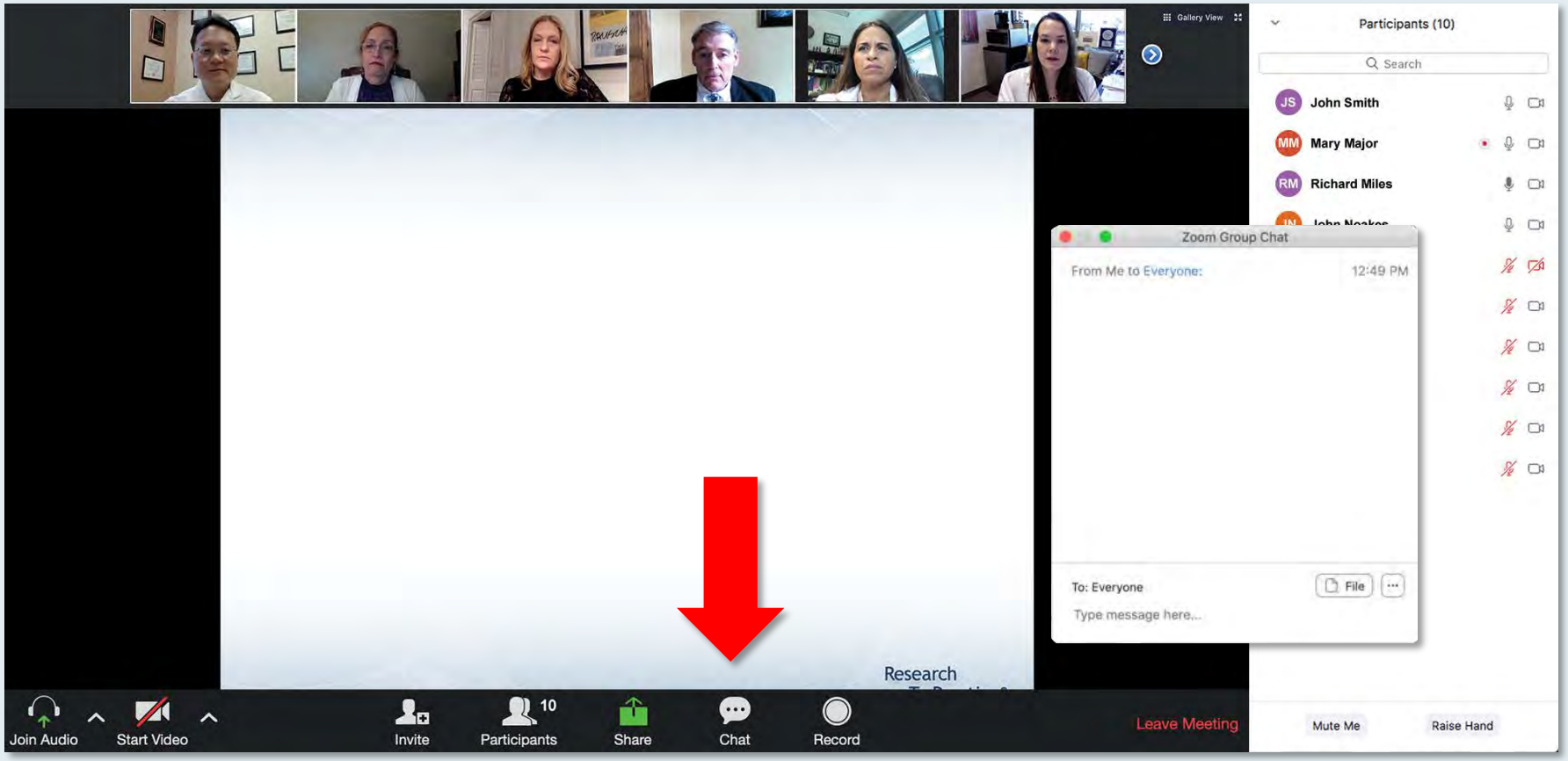


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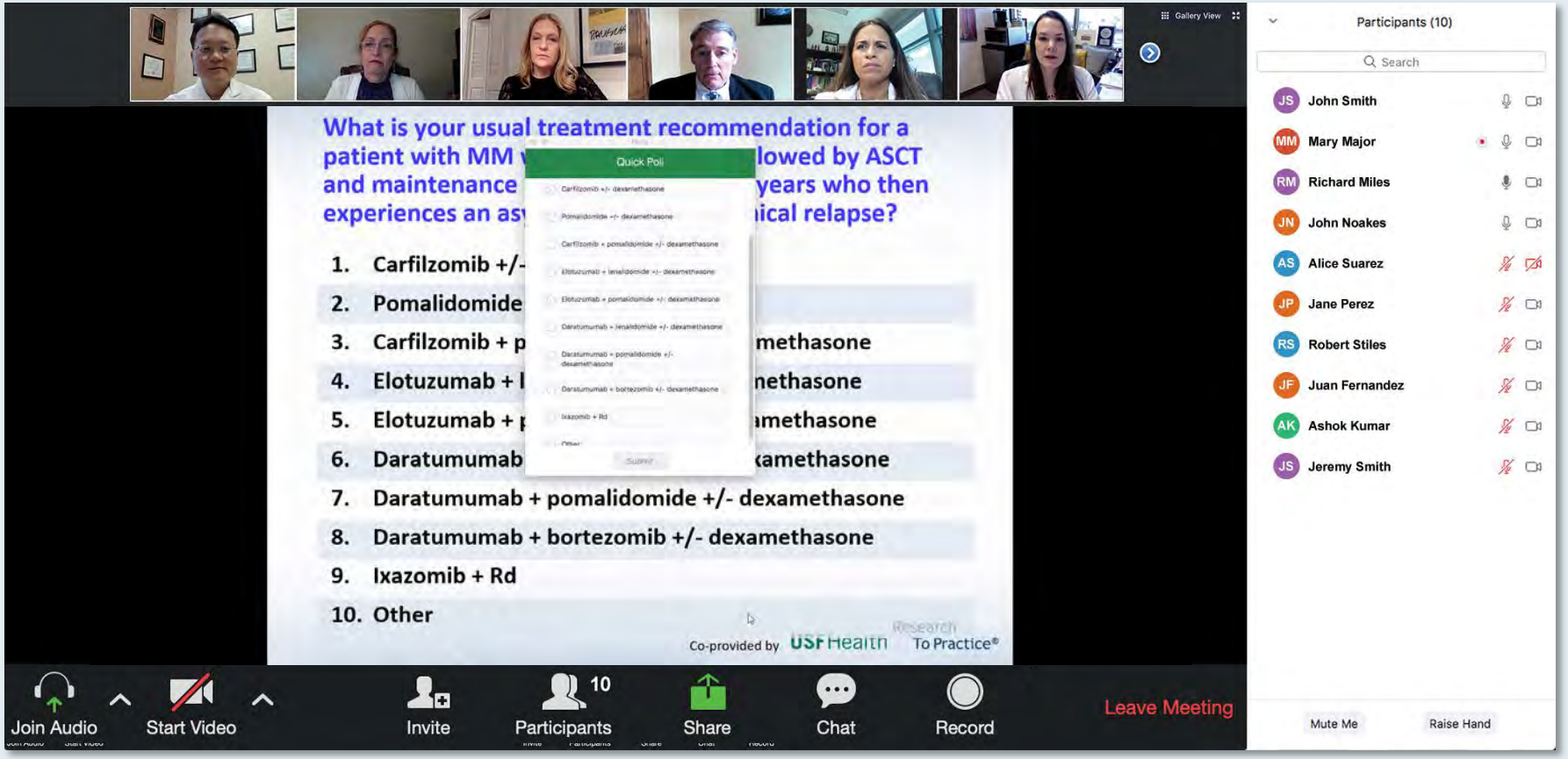
# Familiarizing Yourself with the Zoom Interface

## How to answer poll questions

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# Upcoming Webinars

## Tuesday, December 8, 2020
## 5:00 PM – 6:00 PM ET

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

**Faculty**
Peter C Enzinger, MD
Zev Wainberg, MD, MSc

**Moderator**
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**Meet The Professor: Immunotherapy and Novel Agents in Gynecologic Cancers**

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Hope S Rugo, MD
Professor Peter Schmid, MD, PhD

**Moderator**

Neil Love, MD

***Thank you for joining us!***

***CME credit information will be emailed to each participant within 3 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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**Alexander Perl, MD**
**Daniel A Pollyea, MD, MS**
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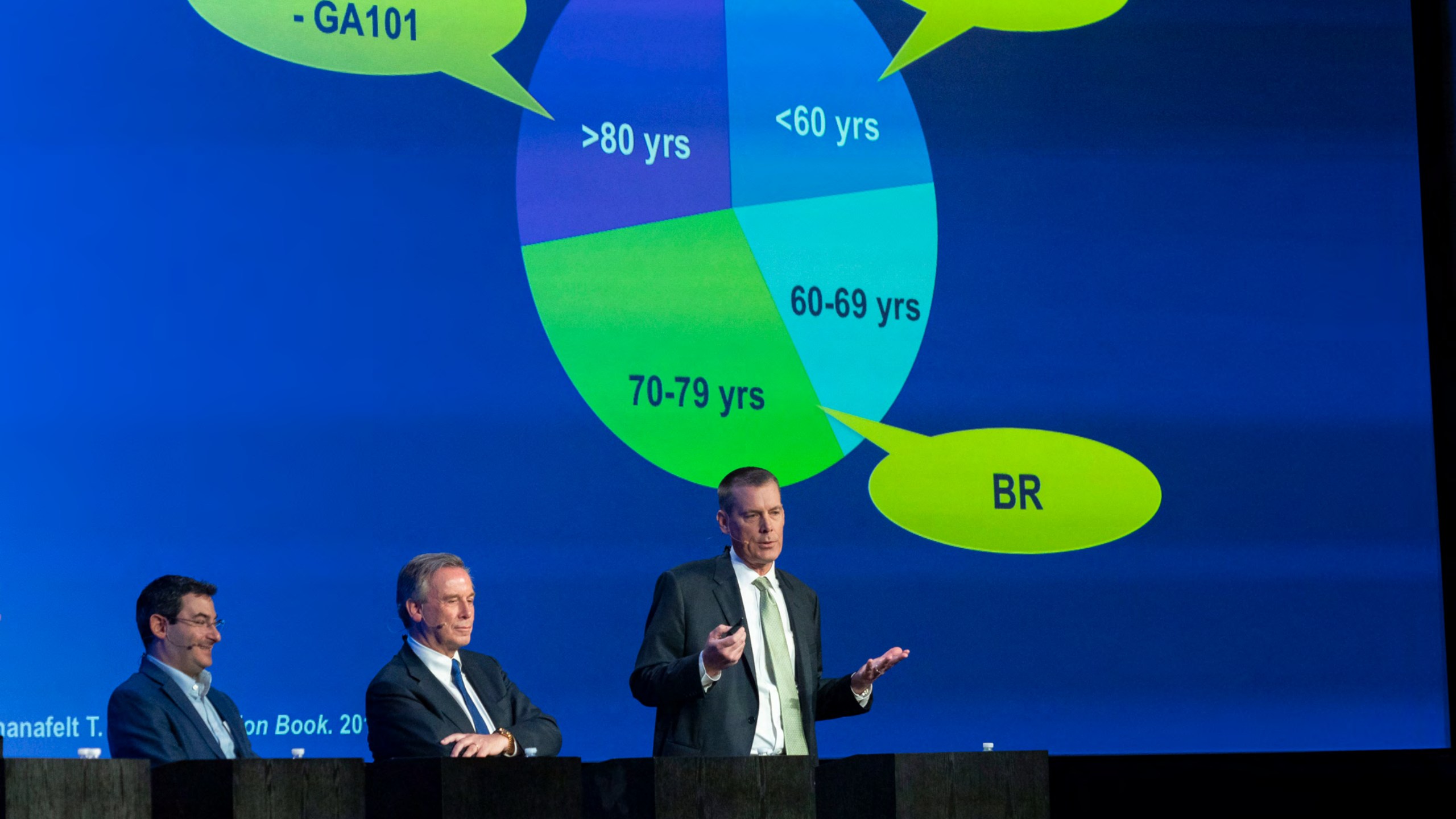
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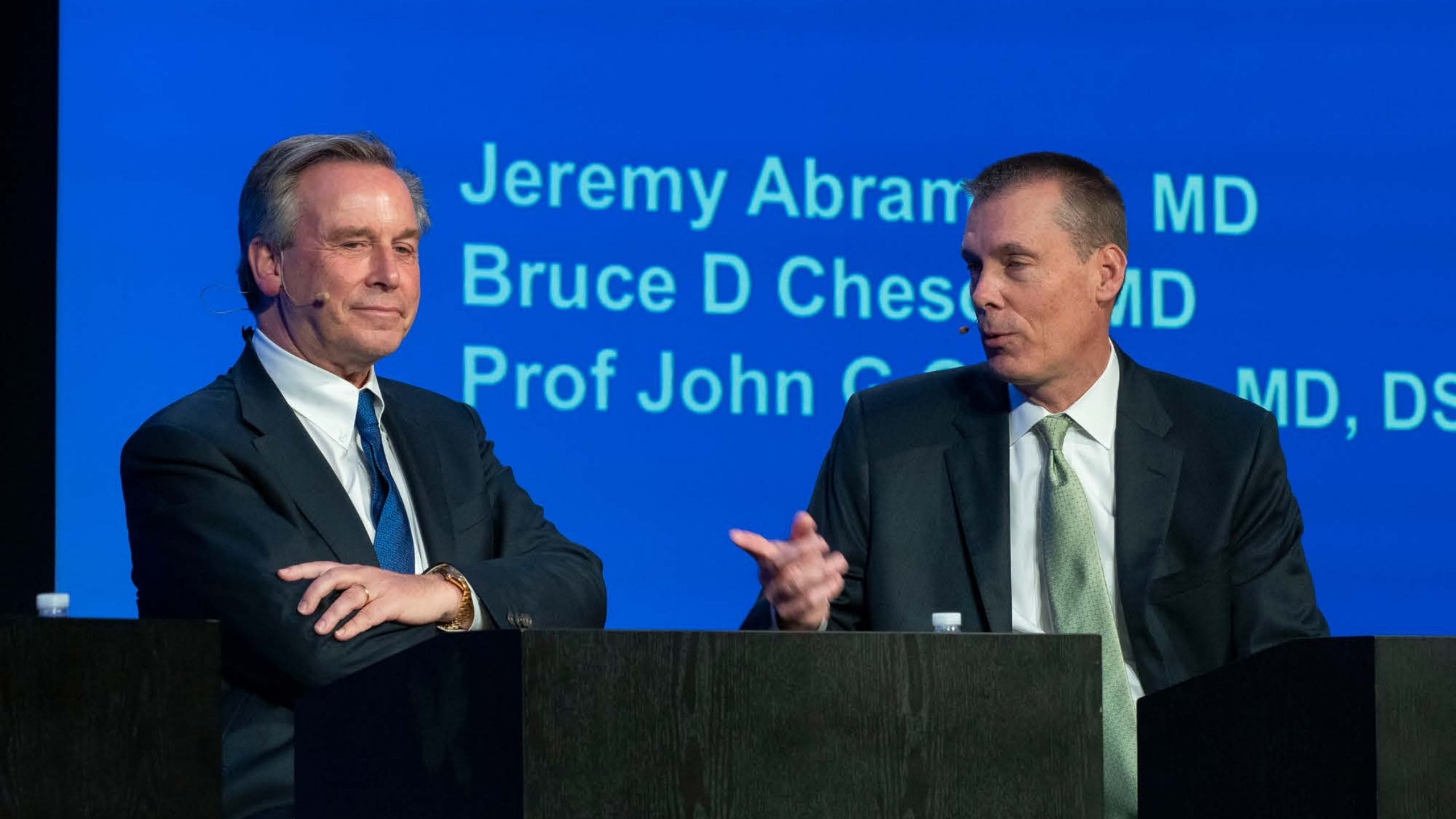
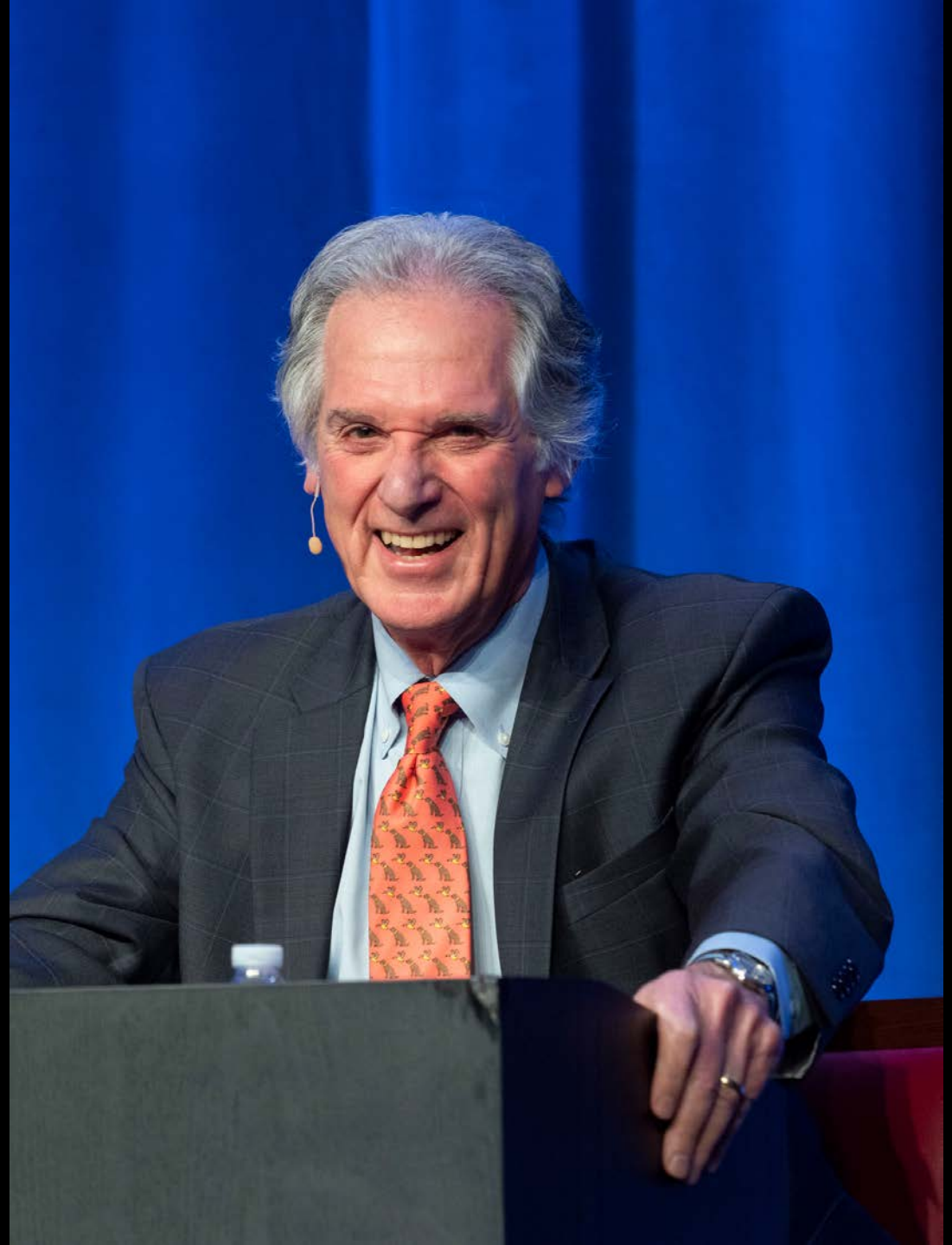
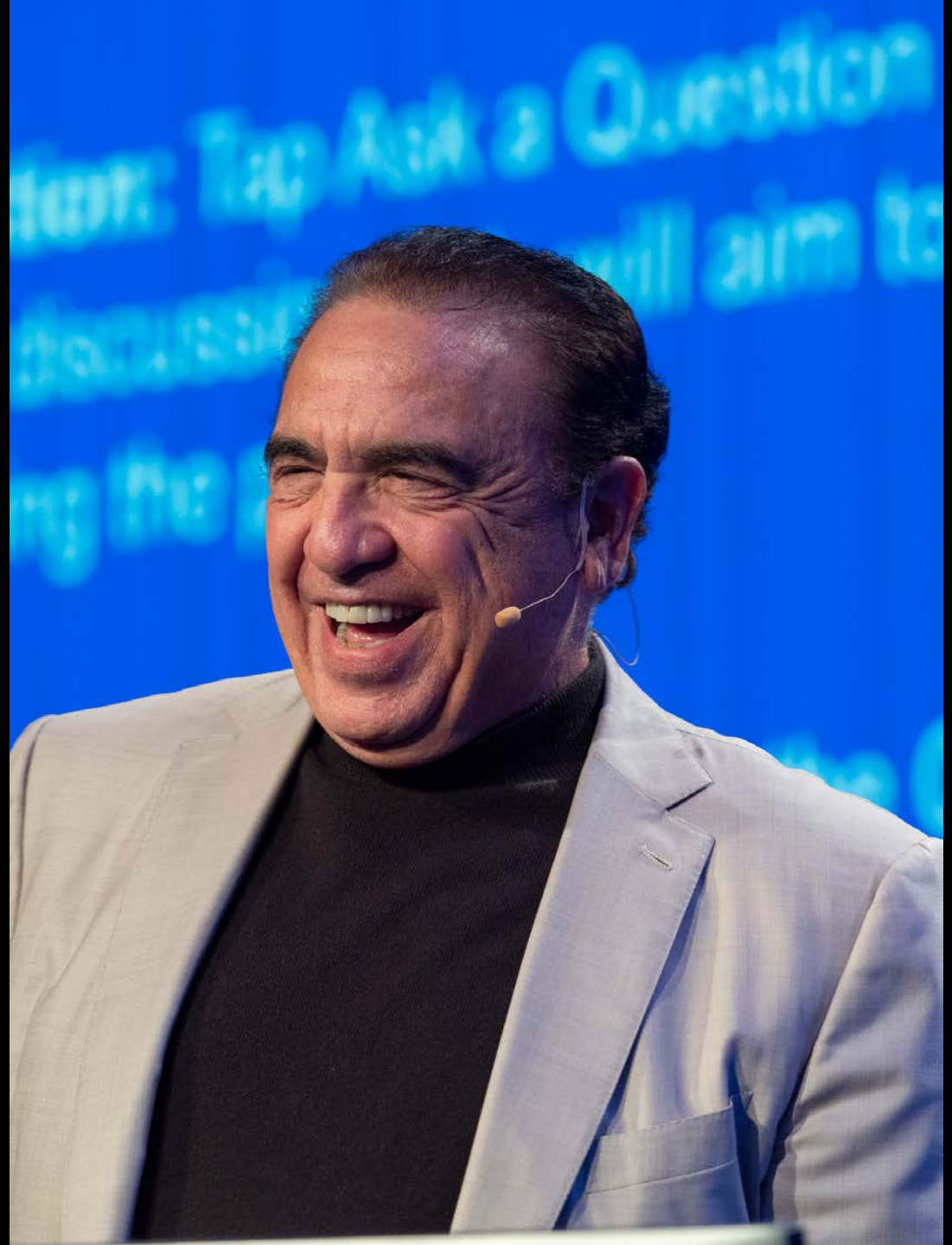

Jeremy Abram MD
Bruce D Ches MD
Prof John C MD, DS





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# Faculty

**Paul M Barr, MD**
Medical Director, Clinical Trials Office
Professor of Medicine
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Rochester, New York

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

**Matthew S Davids, MD, MMSc**
Associate Professor of Medicine
Harvard Medical School
Director, DFCI Lymphoma BioBank
Associate Director, CLL Center
Dana-Farber Cancer Institute
Boston, Massachusetts

**Tanya Siddiqi, MD**
Associate Professor
Director, Chronic Lymphocytic Leukemia Program
Department of Hematology and Hematopoietic Cell Transplantation
City of Hope National Medical Center
Duarte, California

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# Faculty

**Stephan Stilgenbauer, MD**
Department of Internal Medicine I
Saarland University
Department of Internal Medicine III
Ulm University
Homburg, Germany

***Moderator***
**Neil Love, MD**
Research To Practice
Miami, Florida

# Consensus or Controversy Survey Participants (in Addition to Our Faculty)

**Brad S Kahl, MD**
Siteman Cancer Center
St Louis, Missouri

**Jeff Sharman, MD**
Willamette Valley Cancer Institute and Research Center
Eugene, Oregon

**John M Pagel, MD, PhD**
Swedish Cancer Institute
Seattle, Washington

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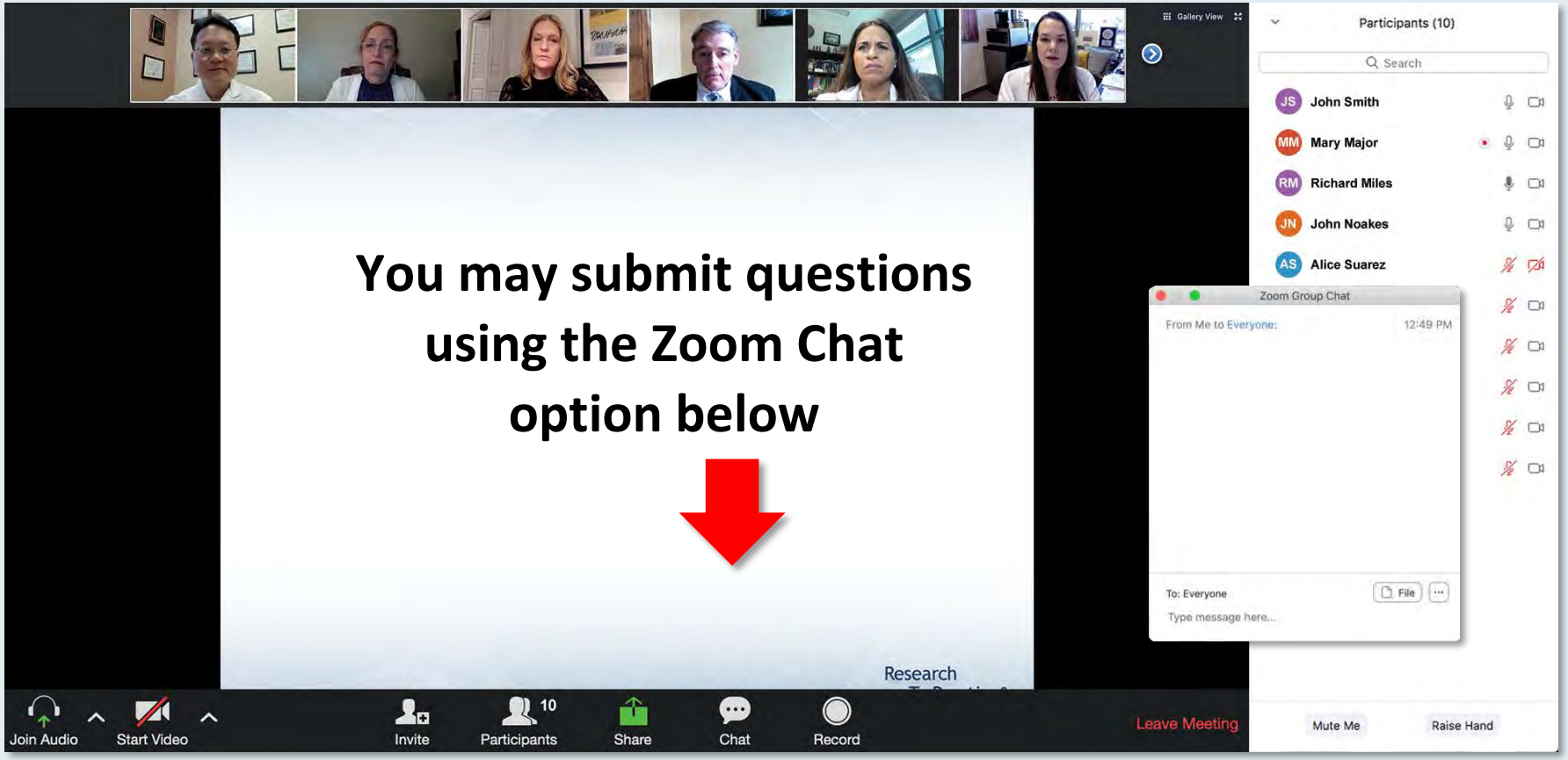


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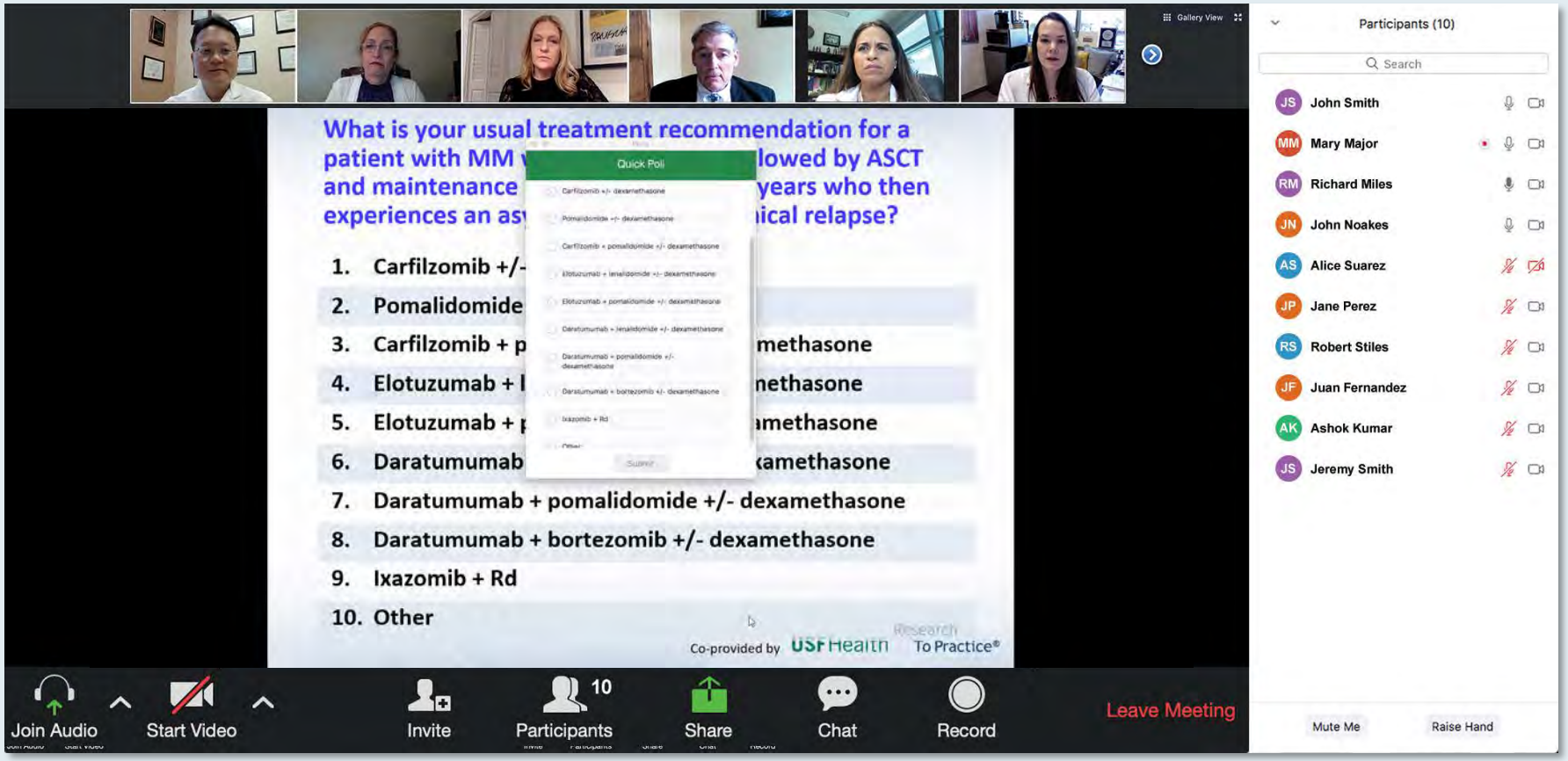


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# Recent Advances in Hematologic Oncology: A 4-Part Live Webinar Series Reviewing Key Data and Presentations from the 62nd ASH Annual Meeting

## Acute Myeloid Leukemia

**Wednesday, January 20, 2021**
5:00 – 6:00 PM ET

**Faculty**
Daniel A Pollyea, MD, MS
Professor Andrew H Wei, MBBS, PhD
*Additional faculty to be announced*

## Multiple Myeloma

**Wednesday, February 10, 2021**
5:00 – 6:00 PM ET

**Faculty**
Robert Z Orlowski, MD, PhD
Edward A Stadtmauer, MD
*Additional faculty to be announced*

## Hodgkin and Non-Hodgkin Lymphoma

**Wednesday, February 3, 2021**
5:00 – 6:00 PM ET

**Faculty**
John Kuruvilla, MD
John P Leonard, MD
Michael E Williams, MD, ScM

## Chronic Lymphocytic Leukemia

**Wednesday, February 24, 2021**
5:00 – 6:00 PM ET

**Faculty**
Matthew S Davids, MD, MMSc
*Additional faculty to be announced*

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# ASH CLL 2020 Presentation Library

**First-line treatment options for younger, fit patients**
Paul M Barr, MD

Download Slides

**Up-front management of chronic lymphocytic leukemia in older patients or those with comorbidities**
Stephan Stilgenbauer, MD

Download Slides

**Optimal management of adverse events with BTK and Bcl-2 inhibitors**
Matthew S Davids, MD, MMSc

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**Selection and sequencing of therapies for relapsed/refractory disease**
Kerry Rogers, MD

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**Novel strategies under investigation**
Tanya Siddiqi, MD

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# Agenda

**Module 1: First-line treatment options for younger, fit patients — Dr Barr**

**Module 2: Up-front management of chronic lymphocytic leukemia in older patients or those with comorbidities — Dr Stilgenbauer**

**Module 3: Optimal management of adverse events with BTK and Bcl-2 inhibitors — Dr Davids**

**Module 4: Selection and sequencing of therapies for relapsed/refractory disease — Dr Rogers**

**Module 5: Novel strategies under investigation — Dr Siddiqi**

# Treatment Indications

- Anemia and/or thrombocytopenia (hemoglobin <10 g/dL or platelets <100 x$10^9$/L)
- Symptomatic splenomegaly (≥6 cm below the left costal margin)
- Symptomatic lymphadenopathy (≥10 cm in longest diameter)
- Lymphocytosis increase of more than 50% over a 2-month period or lymphocyte doubling time (LDT) of less than 6 months
- Autoimmune anemia and/or thrombocytopenia that is poorly responsive to corticosteroids or other standard therapy
- Symptomatic or functional extranodal involvement (e.g. skin, kidney, lung, spine)
- Constitutional symptoms:
  - Unintentional weight loss of ≥10% within the previous 6 months;
  - Significant fatigue (i.e. inability to work or perform usual activities);
  - Fevers higher than 100.5°F or 38.0°C for 2 or more weeks; or
  - Night sweats for ≥1 month without evidence of infection

Hallek M et al. *Blood.* 2018;131:2745-2760.

Courtesy of Paul M Barr, MD

# iwCLL Recommended Testing Before Treatment

| Diagnostic Test | Practice Recommendation |
|---|---|
| History, physical, infection status | Always |
| CBC, chemistry, Igs, DAT | Always |
| Serum β2 microglobulin | Desirable |
| Marrow aspirate and biopsy | When needed (unclear cytopenia) |
| CT scan of chest, abdomen, pelvis | If possible |
| IGHV mutational status | Always* |
| FISH for add(12), del(13q), del(11q), del(17p) in peripheral blood | Always |
| TP53 mutation | Always |
| Conventional karyotyping | Not generally indicated** |

*Does not need to be repeated before subsequent therapy

**Conventional karyotyping (with specific stimulation) may be useful before therapy, if established methodology is available

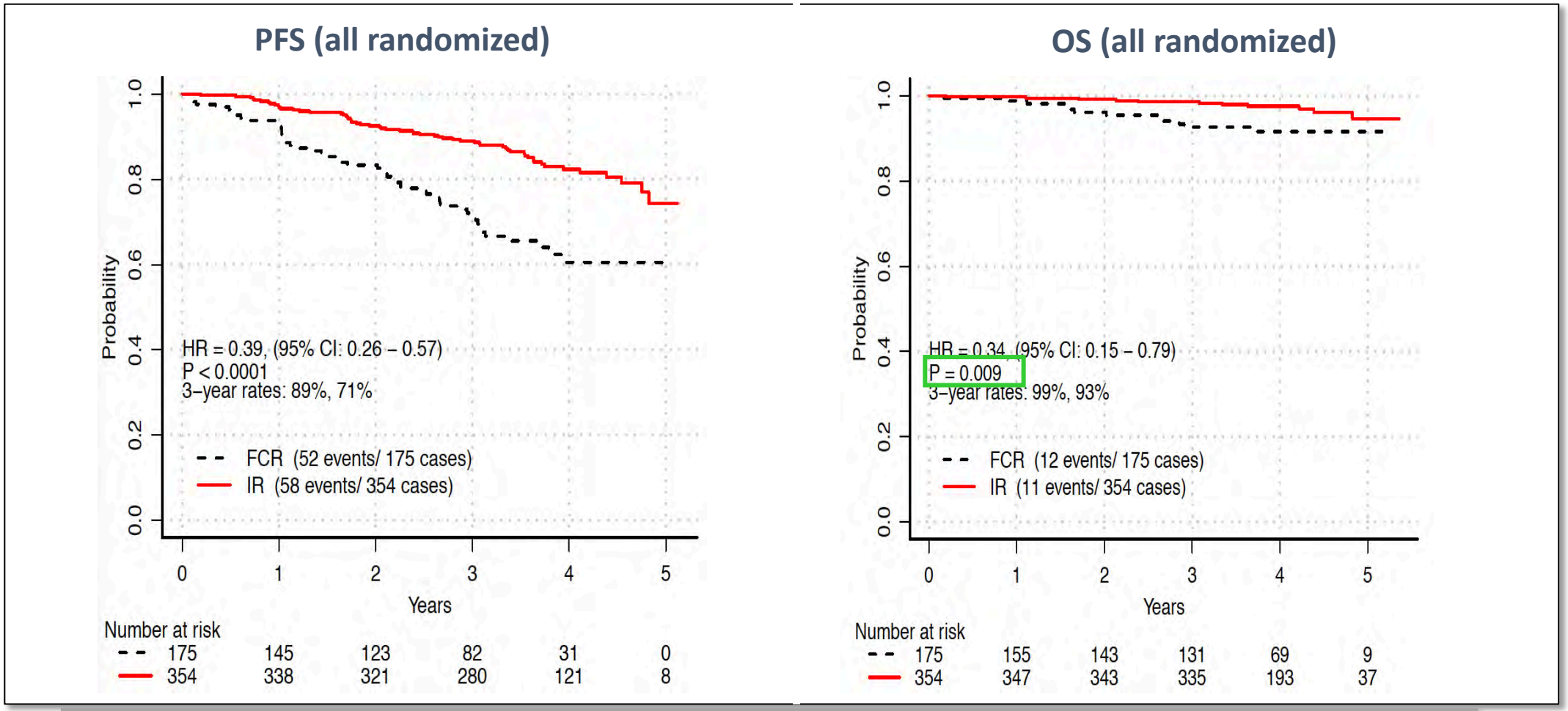
CBC = complete blood count; IGHV = immunoglobin heavy chain variable region; iwCLL = International Workshop on Chronic Lymphocytic Leukemia.

Hallek M et al. *Blood*. 2018;131:2745-2760.

Courtesy of Paul M Barr, MD

# Ibrutinib vs FCR

## *In Untreated Younger Patients with CLL (E1912)*

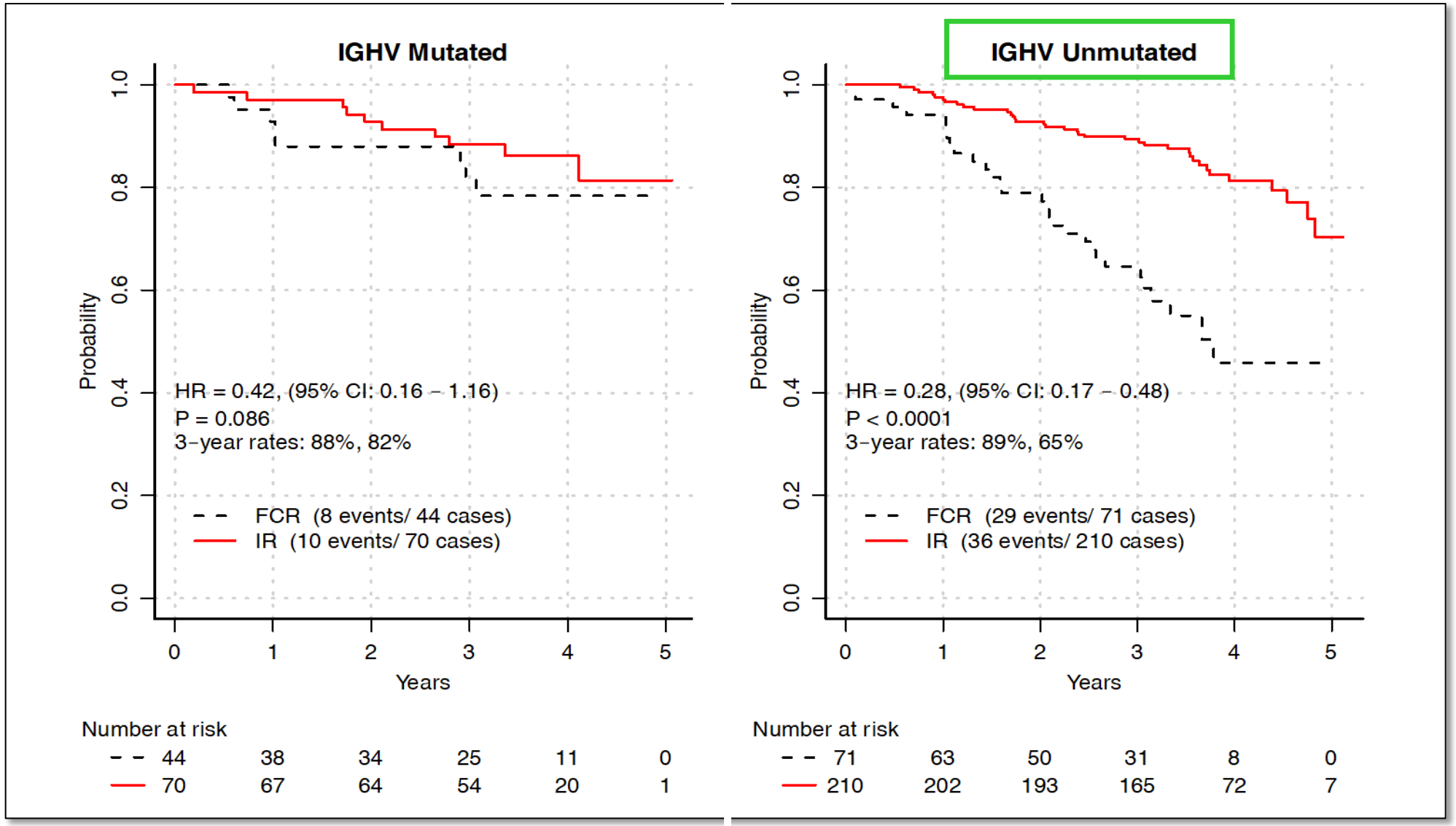



***With a median follow-up of 48 months, 73% of IR patients remain on treatment; Only 7% of ibrutinib treated patients progressed while on therapy***

Shanafelt TD et al. *Blood.* 2019;(suppl 1):Abstract 33.

Courtesy of Paul M Barr, MD

# Progression Free Survival: IGHV Status




Shanafelt TD et al. *Blood.* 2019;(suppl 1):Abstract 33.

Courtesy of Paul M Barr, MD

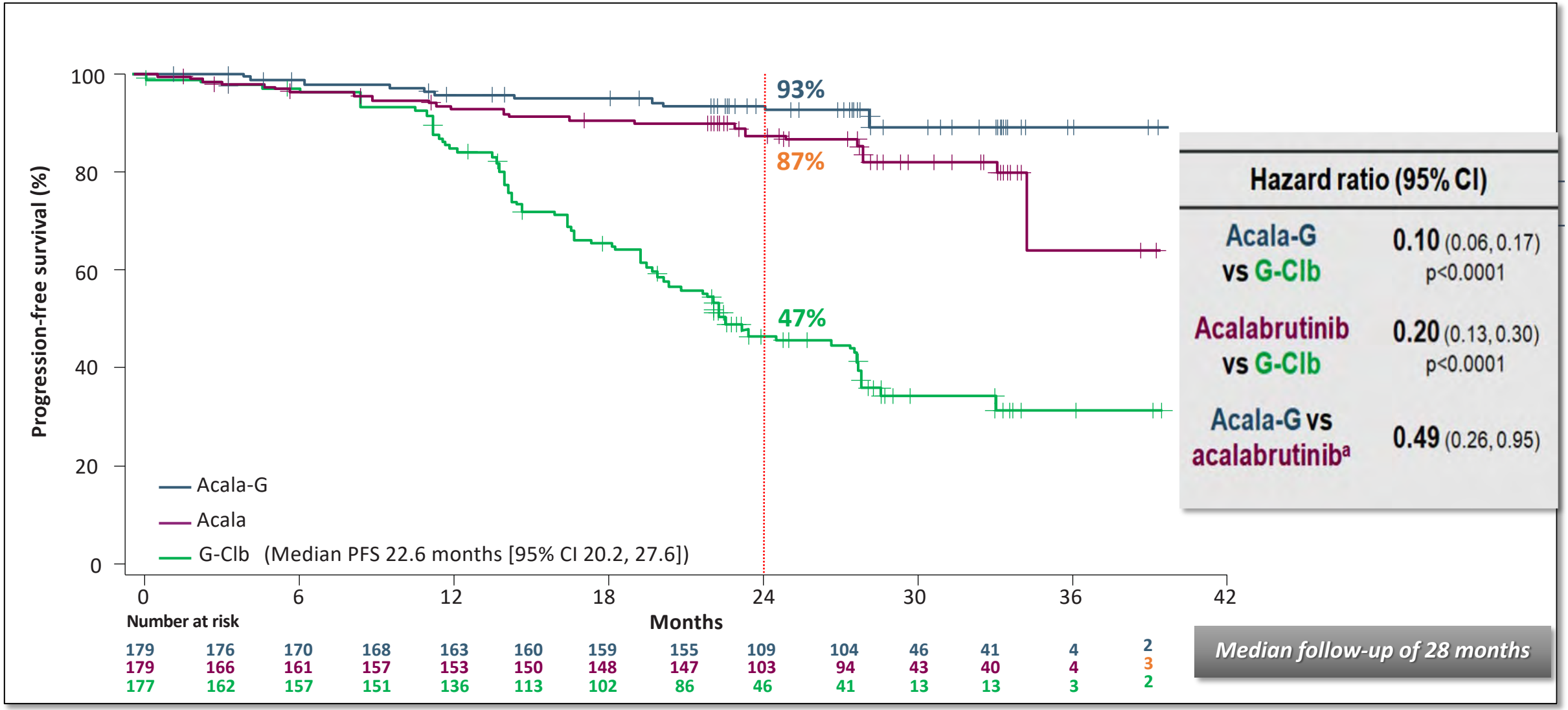
# E1912: Grade 3-5 Treatment-related Adverse Events

| Adverse Event | IR (n=352, %) | FCR (n=158, %) | *P*-value |
|---|---|---|---|
| Anemia | 4.3 | **15.8** | <0.001 |
| Arthralgia | **5.1** | 0.6 | 0.011 |
| Diarrhea | **2.6** | 0.6 | 0.185 |
| Hemolysis | 0 | 2.5 | 0.009 |
| Hypertension | **8.5** | 1.9 | 0.003 |
| Neutrophil count decreased | 27 | **43** | <0.001 |
| Platelet count decreased | 3.1 | **15.8** | <0.001 |
| Febrile neutropenia | 2.3 | **15.8** | <0.001 |
| Infection | 7.1 | 8.9 | 0.477 |
| Sepsis | 0.6 | **3.2** | 0.032 |
| Other infections | 7.1 | 6.3 | 0.851 |
| Cardiac | **5.4** | 0 | 0.001 |
| Atrial fibrillation | **2.8** | 0 | 0.036 |
| Other cardiac | **3.4** | 0 | 0.022 |
| **Any Grade 3 or higher AE** | **69.6** | **80.4** | **0.013** |

Shanafelt TD et al. *Blood.* 2019;(suppl 1):Abstract 33.

Courtesy of Paul M Barr, MD

# ELEVATE-TN: PFS Benefit of Acalabrutinib




Sharman JP et al. *Blood.* 2019;(suppl 1):Abstract 31.

Courtesy of Paul M Barr, MD

# ELEVATE-TN

## *Events of Clinical Interest for Acalabrutinib*

| AEs, n (%) | Acala-G N=178 | | Acalabrutinib N=179 | | G-Clb N=169 | |
|---|---|---|---|---|---|---|
| | Any | Grade ≥3 | Any | Grade ≥3 | Any | Grade ≥3 |
| Atrial fibrillation | 6 (3.4) | 1 (0.6) | 7 (3.9) | 0 | 1 (0.6) | 0 |
| Hypertension | 13 (7.3) | 5 (2.8) | 8 (4.5) | 4 (2.2) | 6 (3.6) | 5 (3.0) |
| Bleeding | 76 (42.7) | 3 (1.7) | 70 (39.1) | 3 (1.7) | 20 (11.8) | 0 |
| Major bleeding[a] | 5 (2.8) | 3 (1.7) | 3 (1.7) | 3 (1.7) | 2 (1.2) | 0 |
| Infections | 123 (69.1) | 37 (20.8) | 117 (65.4) | 25 (14.0) | 74 (43.8) | 14 (8.3) |
| Second primary malignancies, excluding NMSC | 10 (5.6) | 6 (3.4) | 5 (2.8) | 2 (1.1) | 3 (1.8) | 2 (1.2) |

On November 21, 2019, the FDA approved acalabrutinib for adults with CLL or small lymphocytic lymphoma.

Sharman JP et al. *Blood.* 2019;134(Suppl 1):31.
[a]Defined as any serious or grade ≥3 hemorrhagic event, or any grade hemorrhagic event in the central nervous system

Courtesy of Paul M Barr, MD

# Grade 3-5 Treatment-related Adverse Events

*BTKi + anti-CD20 arms*

## Comparing BTKi + anti-CD20 Treated Patients

| Adverse Event | IR Arm[3] E1912 n=352 | IR Arm[4] Alliance n=181 | AG Arm[1] ELEVATE-TN n=179 |
|---|---|---|---|
| Median Age | 57 yrs | 71 yrs | 70 yrs |
| Age range | 31-70 | 65-86 | 41-88 |
| Median follow up (months) | 33 | 38 | 28 |
| Infection | 5% | 19% | 21% |
| Atrial fibrillation (all grades) | 3% (7%) | 6% (14%) | 1% (6%) |
| Bleeding | 1% | 4% | 2% |
| Hypertension | 18% | 34% | 3% |
| % of pts remaining on ibrutinib | 79% | 64% | 79% |

1. Sharman et al. Lancet 2020;395:1278-91. 2. Moreno et al. Lancet Onc 2019;20-43-56. 3. Shanafelt TD et al. *Blood.* 2019;(suppl 1):Abstract 33; 4. Woyach JA et al. *N Engl J Med*. 2018;379:2517-2528.

Courtesy of Paul M Barr, MD

# Young Fit Patients: Factors to Consider

## Indefinite therapy

- Favors acalabrutinib
  - Convenience (avoids early monitoring with venetoclax)
  - PFS benefit with anti-CD20 addition
  - Less side effects (arrhythmias, hypertension, arthralgias, rash)
- Favors ibrutinib
  - Longer follow-up and more phase III data
  - More data supporting efficacy of venetoclax after ibrutinib vs little data on the reverse
  - Convenience (once daily)
  - Compatible with PPI/H2 inhibitors

## Time limited therapy

- Favors venetoclax + anti-CD20
  - High CR and undetectable MRD
  - Avoid selection pressure for resistance
  - Fewer long-term side effects
- Favors FCR
  - 60% of mutated IGHV patients plateau on PFS curve
  - Less cost

Courtesy of Paul M Barr, MD

# Randomized Front Line Studies for Fit Patients

*Future upfront therapy for CLL*

- EA9161: Ibrutinib/Venetoclax/Obinu vs. Ibrutinib/Obinu (<70 yrs)
- CLL13 (GAIA): FCR/BR vs. Venetoclax/Obinu vs. Venetoclax/Ritux vs. Ibrutinib/Venetoclax/Obinu (Fit pts)
- CLL17: Venetoclax/Obinu vs. Ibrutinib/Venetoclax vs. Ibrutinib (Fit pts)
- ACE-CL-311: FCR/BR vs. Acalabrutinib/Venetoclax vs. Acalabrutinib/Venetoclax/Obinu vs. FCR (Fit pts)

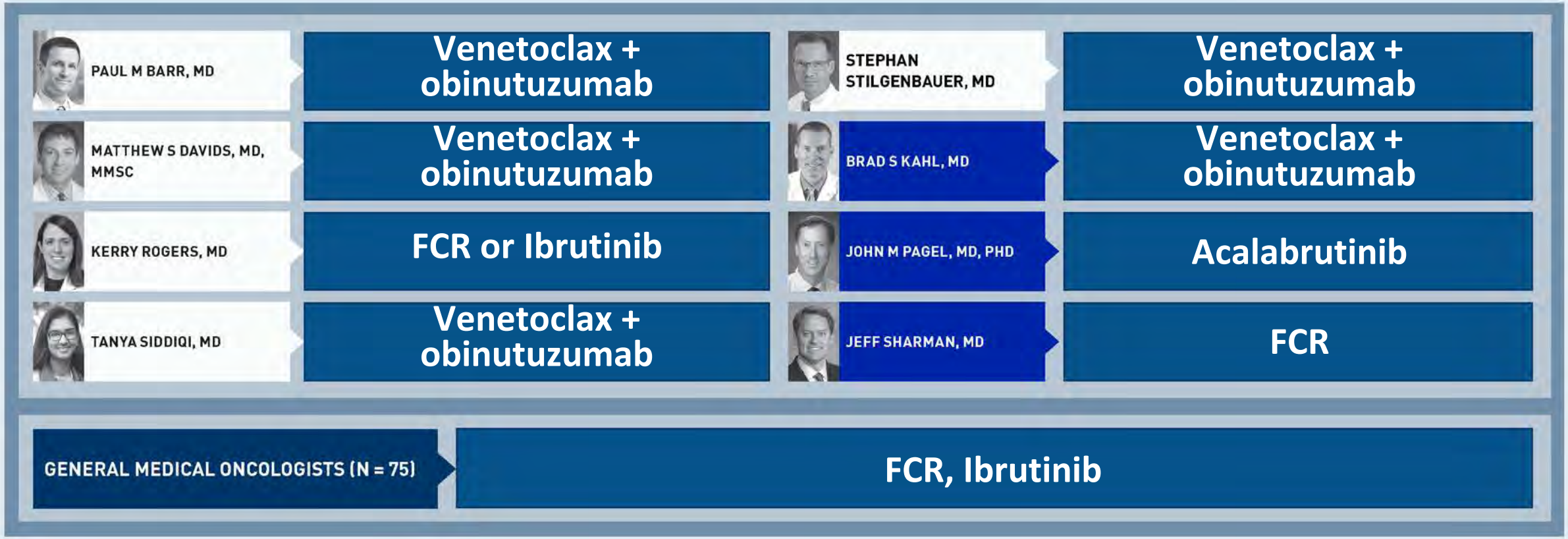
Jain et al. ASCO 2017 #7522, Davids et al. Lancet Haem 2019;6:E419-E428, Tam et al. *Blood* (2019) 134 (Supplement_1): 35, ClinicalTrials.gov: NCT03701282, ClinicalTrials.gov: NCT04608318, ClinicalTrials.gov: NCT03836261

Courtesy of Paul M Barr, MD

# What is your usual preferred initial regimen for a 60-year-old patient with IGHV-mutated CLL without del(17p) or TP53 mutation who requires treatment?

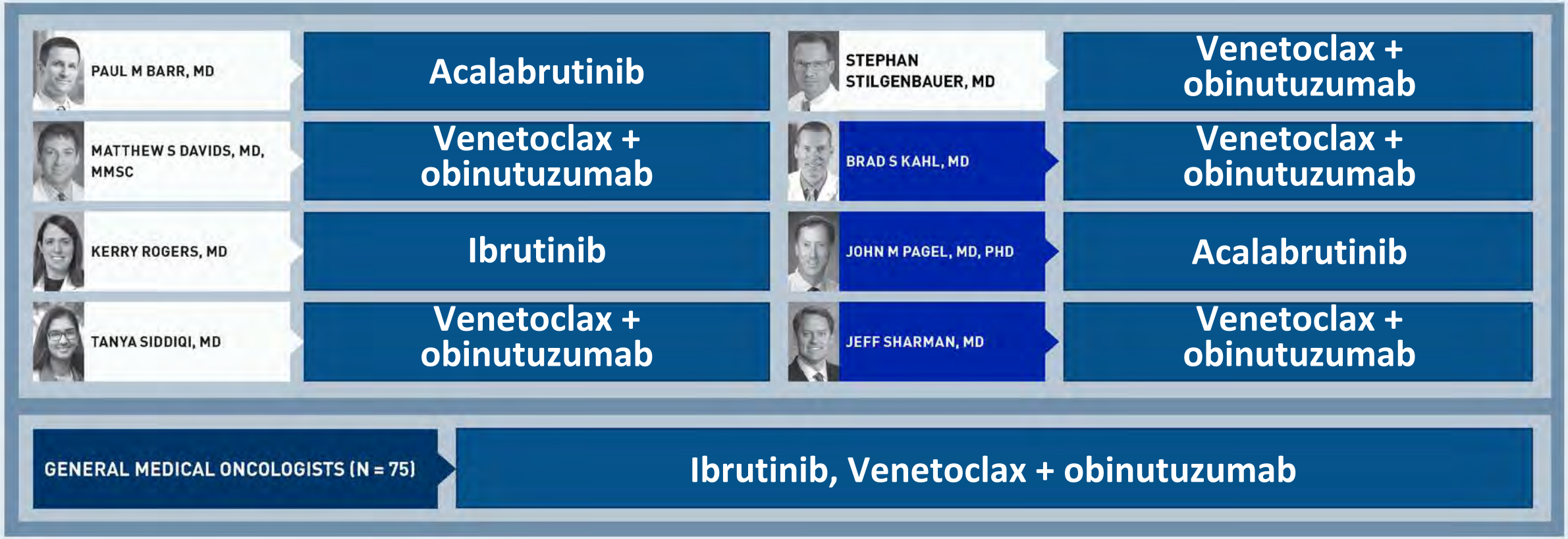
1. FCR
2. BR
3. Ibrutinib
4. Ibrutinib + rituximab
5. Acalabrutinib
6. Acalabrutinib + obinutuzumab
7. Venetoclax + obinutuzumab
8. Other

# What is your usual preferred initial regimen for a 60-year-old patient with IGHV-mutated CLL without del(17p) or TP53 mutation who requires treatment?




FCR = fludarabine/cyclophosphamide/rituximab

# What is your usual preferred initial regimen for a 60-year-old patient with IGHV-unmutated CLL without del(17p) or TP53 mutation who requires treatment?

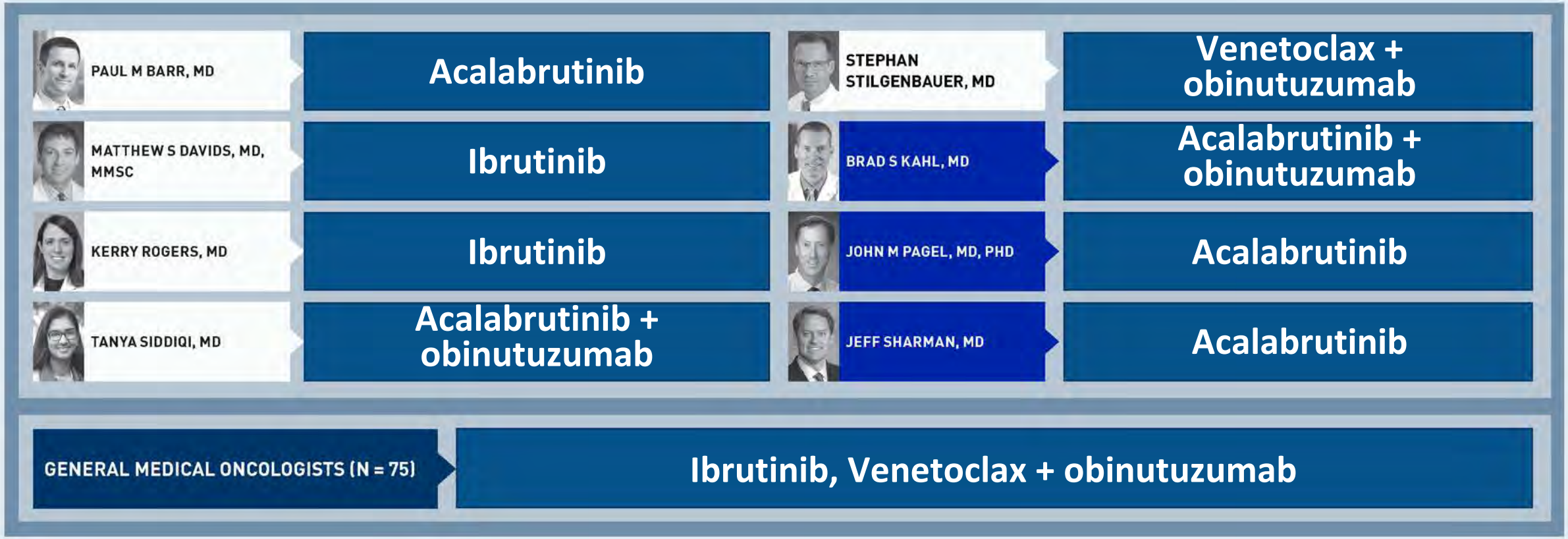


# What is your usual preferred initial regimen for a 60-year-old patient with del(17p) CLL who requires treatment?

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

RTP
RESEARCH
TO PRACTICE

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



# Based on current clinical trial data and your personal experience, how would you compare the global efficacy of a single-agent Bruton tyrosine kinase (BTK) inhibitor to that of venetoclax/obinutuzumab in CLL?

| | | | |
|---|---|---|---|
|  PAUL M BARR, MD | About the same |  STEPHAN STILGENBAUER, MD | About the same |
|  MATTHEW S DAVIDS, MD, MMSC | About the same |  BRAD S KAHL, MD | About the same |
|  KERRY ROGERS, MD | There are not enough available data |  JOHN M PAGEL, MD, PHD | About the same |
|  TANYA SIDDIQI, MD | About the same |  JEFF SHARMAN, MD | There are not enough available data |

| | |
|---|---|
| GENERAL MEDICAL ONCOLOGISTS (N = 75) | About the same |

# Case Presentation – Dr Barr: A 65-year-old man with CLL - IGHV mutation, del(13q)

- 55-year-old male c/o fatigue for 1.5 years
  - Police officer, exercises daily
- Low testosterone identified in 2016, referred to urology for replacement. CBC performed.
- CBC
  - ALC 74,000/uL, confirmed CLL
  - Hgb 16 g/dL
  - Platelets 164,000/uL
- Risk factor testing at diagnosis demonstrated mutated IGHV genes and del(13q).
- Diffuse lymphadenopathy on exam

| | WBC | ALC | Hgb | PLT |
|---|---|---|---|---|
| 2/2016 | 79K | 74K | 16.2 | 164K |
| 4/2016 | 72K | 68K | 15.6 | 128K |
| 7/2016 | 84K | 77K | 14.3 | 147K |

- Enrolled on ECOG-E1912
  - CTs with diffuse ~2-3cm lymphadenopathy
  - Bone marrow 60% involvement by CLL
  - Randomized to Ibrutinib/Rituximab
- Oral sensitivity, diarrhea, GI upset/reflux, muscle cramping, HTN
  - Probiotics, tonic water, dose hold
  - Loperamide daily, PPI, antihypertensive
- 11/2017
  - CTs: near resolution of lymphadenopathy
  - Marrow: 2% involvement by CLL
- Ibrutinib dose reduction 280mg 2/2019, 140mg 6/2020
  - Improved muscle cramping and diarrhea

| | WBC | ALC | Hgb | PLT |
|---|---|---|---|---|
| 11/2016 | 9K | 4K | 15.1 | 123K |
| 11/2017 | 7K | 2K | 15.7 | 134K |
| 9/2020 | 5K | 2K | 16.4 | 163K |

Courtesy of Paul M Barr, MD

# Agenda

Module 1: First-line treatment options for younger, fit patients — Dr Barr

**Module 2: Up-front management of chronic lymphocytic leukemia in older patients or those with comorbidities — Dr Stilgenbauer**

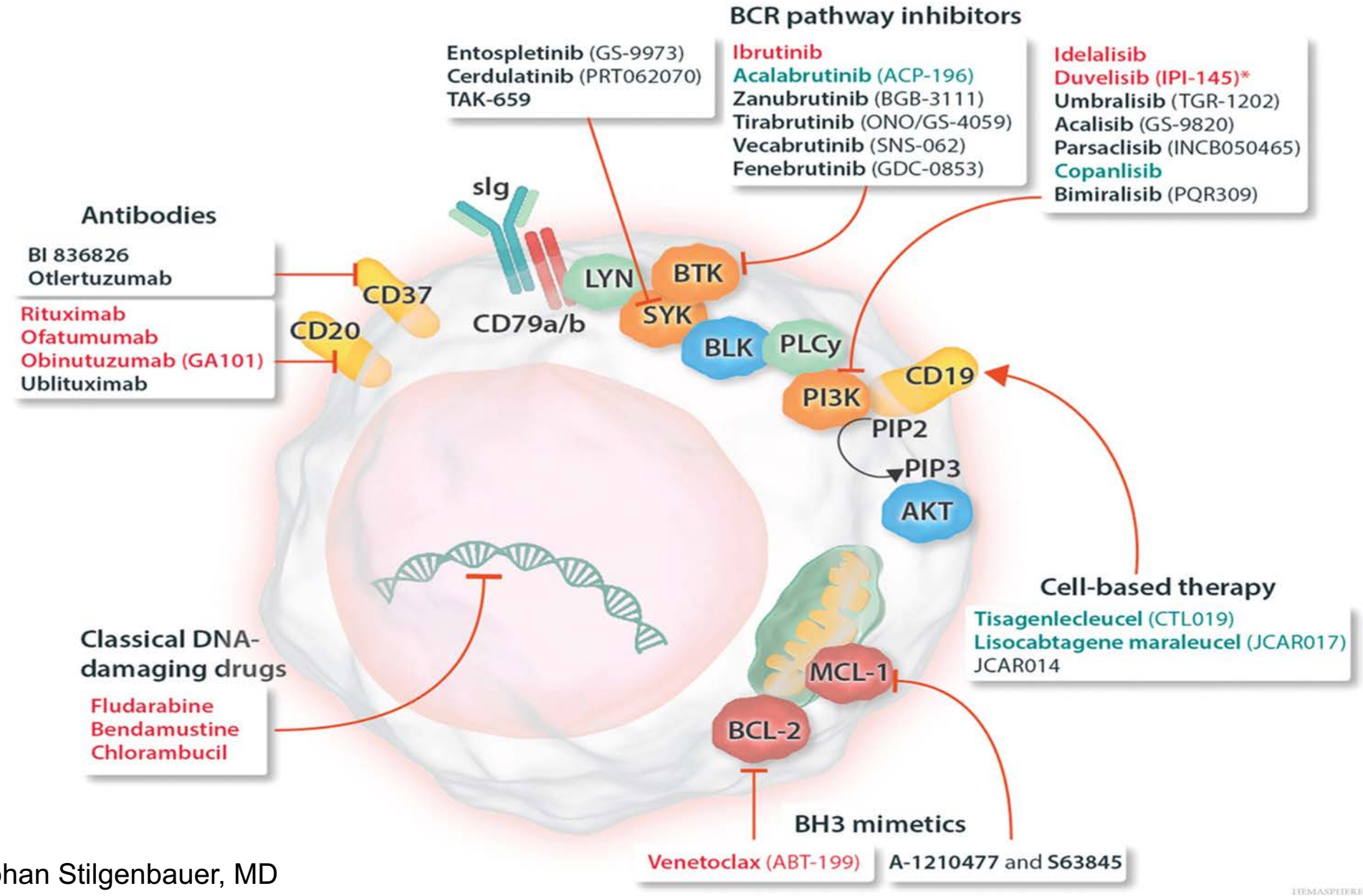
Module 3: Optimal management of adverse events with BTK and Bcl-2 inhibitors — Dr Davids

Module 4: Selection and sequencing of therapies for relapsed/refractory disease — Dr Rogers

Module 5: Novel strategies under investigation — Dr Siddiqi

# From Biology to Therapy: New Treatment Options in CLL

***Yosifov, Wolf, Stilgenbauer, Mertens. Hemashere (review) 2019***

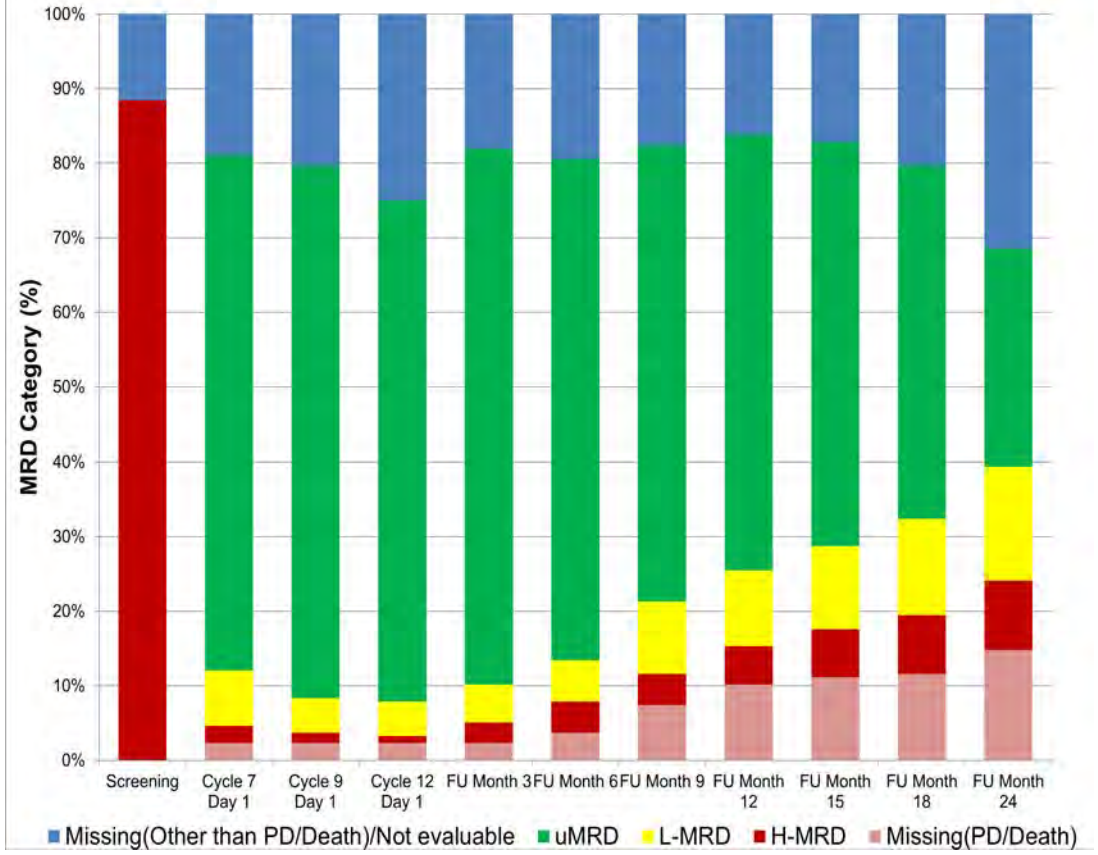



Courtesy of Stephan Stilgenbauer, MD

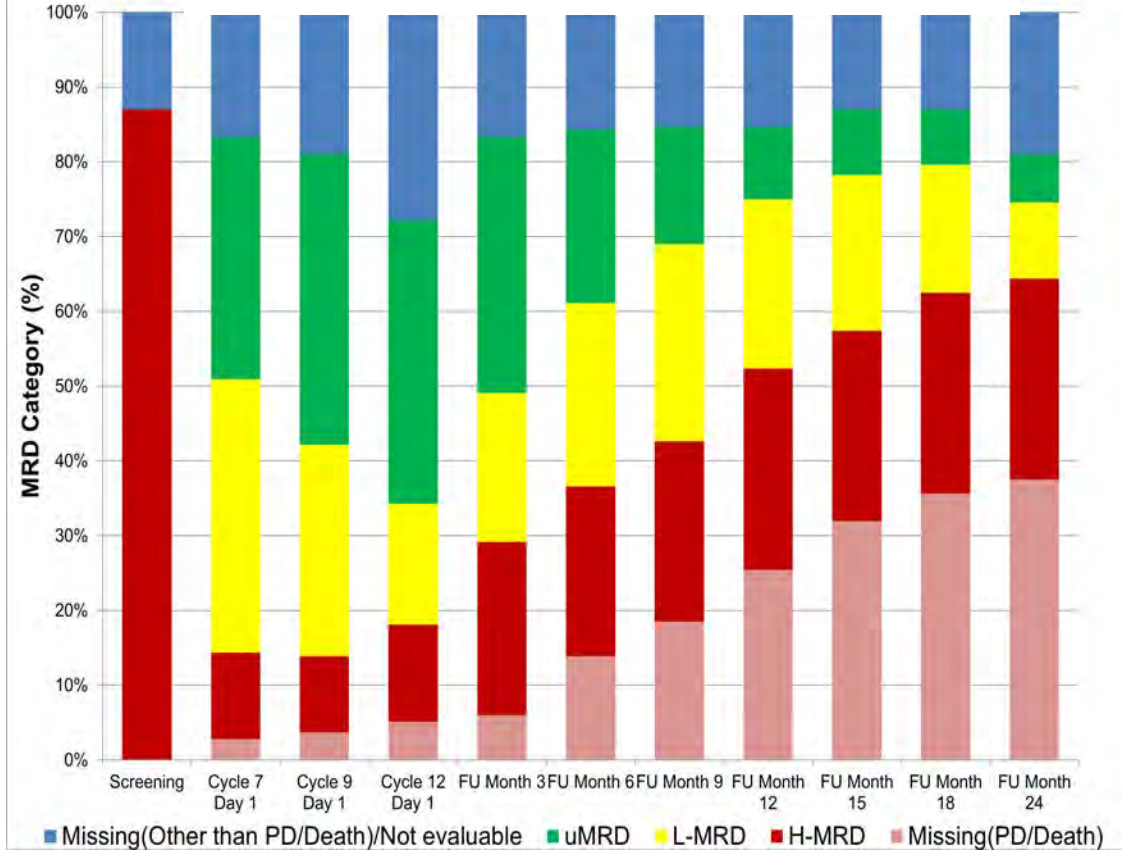
# CLL14: untreated elderly/unfit CLL: MRD Response and Time Course

*Fischer et al. NEJM 2019; Al-Sawaf et al. Lancet Onc 2020*

## Venetoclax + Obinutuzumab




## Chlorambucil + Obinutuzumab




**uMRD rate at 18month FU**
Ven-Obi: 47.2%
Clb-Obi: 7.4%

uMRD $<10^{-4}$
L-MRD $10^{-4} < 10^{-2}$
H-MRD $\geq 10^{-2}$

Courtesy of Stephan Stilgenbauer, MD

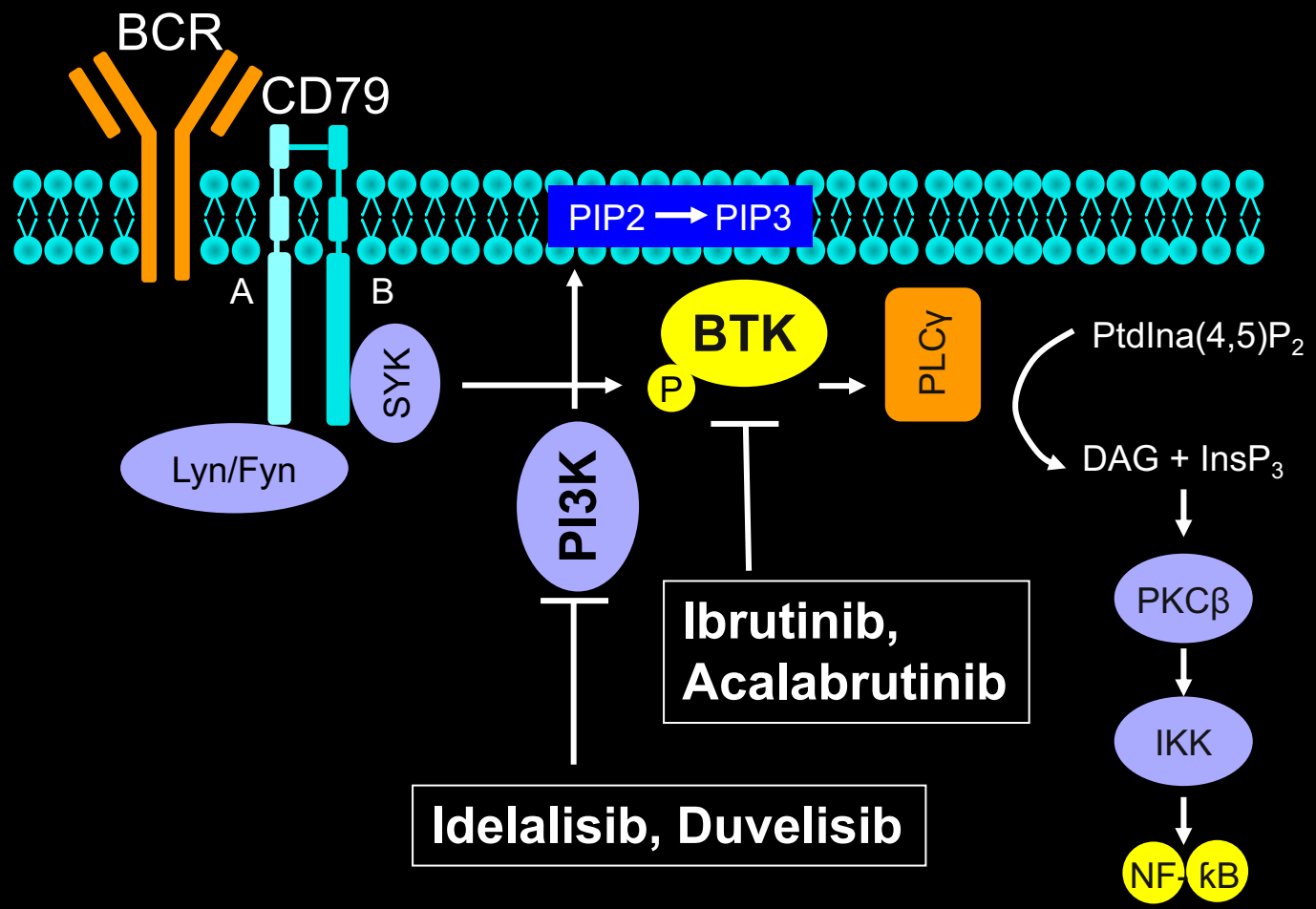
# CLL14: untreated elderly/unfit CLL
# Adverse Events

***Fischer et al. NEJM 2019; Al-Sawaf et al. Lancet Onc 2020***

| | Venetoclax-obinutuzumab (N=212) | | Chlorambucil-obinutuzumab (N=214) | |
|---|---|---|---|---|
| | **During Treatment** | **After Treatment** | **During Treatment** | **After Treatment** |
| Neutropenia | 51.9% | 4.0% | 47.2% | 1.9% |
| Thrombocytopenia | 13.7% | 0.5% | 15.0% | 0.0% |
| Anemia | 7.5% | 1.5% | 6.1% | 0.5% |
| Febrile neutropenia | 4.2% | 1.0% | 3.3% | 0.5% |
| Infusion-related reaction | 9.0% | 0.0% | 9.8% | 0.5% |
| Tumour lysis syndrome | 1.4% | 0.0% | 3.3% | 0.0% |
| Neoplasms | 1.4% | 6.4% | 1.4% | 1.9% |

Courtesy of Stephan Stilgenbauer, MD

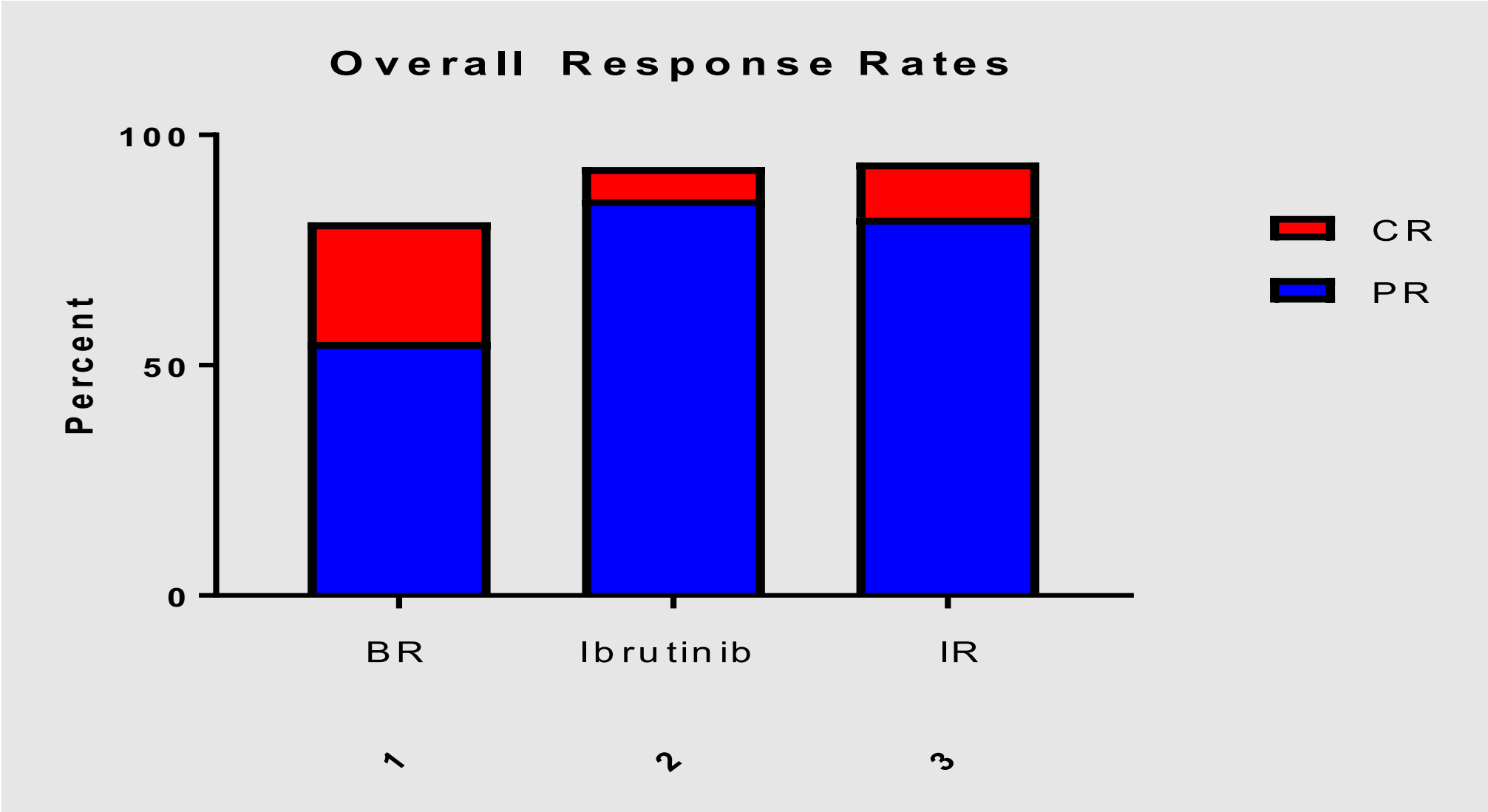
# B-Cell Receptor Signaling Inhibition as Therapeutic Principle




Courtesy of Stephan Stilgenbauer, MD

# ALLIANCE A041202: untreated older CLL Patients Response

*Woyach et al. N Engl J Med 2018*




Courtesy of Stephan Stilgenbauer, MD

# ALLIANCE A041202: untreated older CLL Patients Adverse Events

*Woyach et al. N Engl J Med 2018*

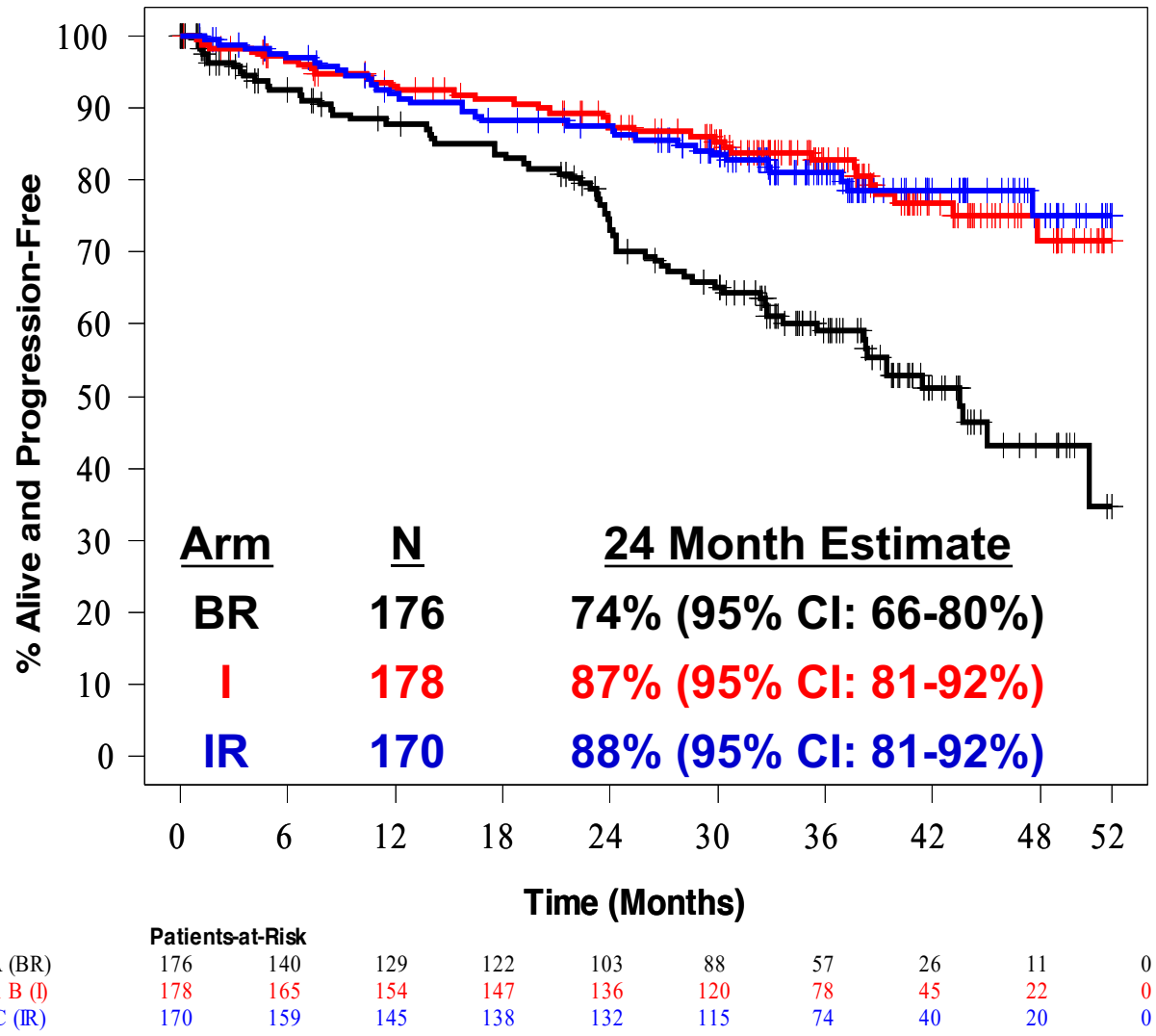
**Grade 3- 5 adverse events during treatment + 30 days, excl. crossover (Median time on treatment: BR 6 months, I and IR: 32 months)**

| Adverse event | BR (n=176) | Ibrutinib (n=180) | IR (n=181) | P-value |
|---|---|---|---|---|
| **Hematologic, no (%)** | **107 (61)** | **74 (41)** | **70 (38)** | **<0.001** |
| Anemia | 22 (13) | 21 (12) | 11 (6) | 0.09 |
| Neutropenia | 71 (40) | 27 (15) | 39 (22) | <0.001 |
| Thrombocytopenia | 26 (15) | 12 (7) | 9 (5) | 0.08 |
| **Non-hematol., no (%)** | **111 (63)** | **133 (74)** | **134 (74)** | **0.04** |
| Bleeding | 0 | 3 (2) | 5 (3) | 0.46 |
| Infections | 26 (15) | 37 (21) | 37 (20) | 0.62 |
| Febrile neutropenia | 13 (7) | 3 (2) | 1 (1) | <0.001 |
| Atrial fibrillation | 5 (3) | 17 (9) | 10 (6) | 0.05 |
| Hypertension | 25 (14) | 53 (29) | 61 (34) | <0.001 |

Courtesy of Stephan Stilgenbauer, MD

# ALLIANCE A041202: untreated older CLL Patients
# Primary Endpoint: PFS

***Woyach et al. N Engl J Med 2018***




**Pairwise comparisons**

**I vs BR**
HR: 0.39 (95% CI: 0.26-0.58)
(1-sided p value <0.001)

**IR vs BR**
HR: 0.38 (95% CI: 0.25-0.59)
(1-sided p value <0.001)

**IR vs I**
HR: 1.00 (95% CI: 0.62-1.62)
(1-sided p value 0.49)

Courtesy of Stephan Stilgenbauer, MD

# ELEVATE-TN: untreated older CLL Patients Acalabrutinib +/- Obinutuzumab compared with Obinutuzumab+Chlorambucil

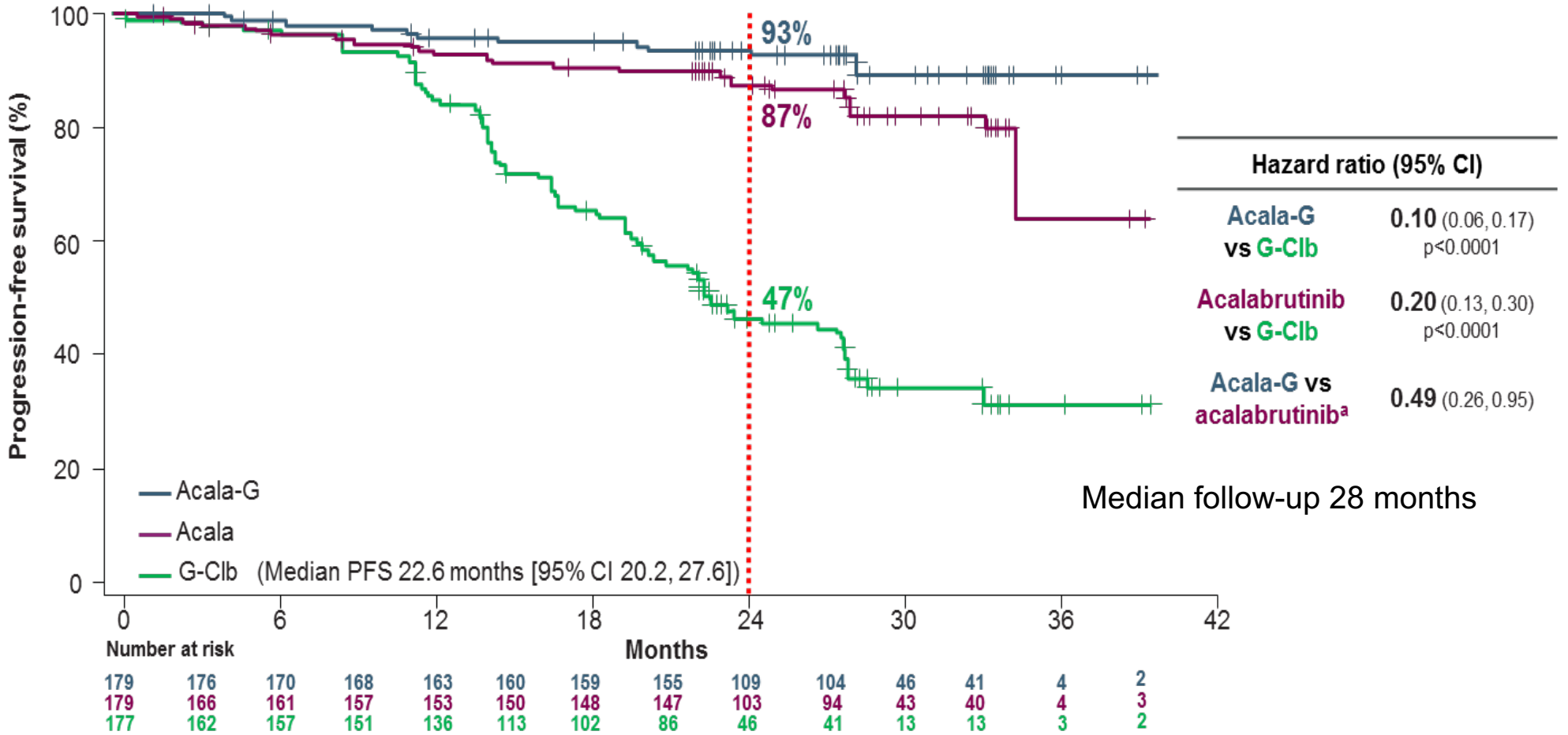
***Sharman et al. Lancet 2020***

| AEs, n (%) | Acala-G N=178 | | Acalabrutinb N=179 | | G-Clb N=169 | |
|---|---|---|---|---|---|---|
| | Any | Grade ≥3 | Any | Grade ≥3 | Any | Grade ≥3 |
| Headache | 71 (39.9) | 2 (1.1) | 66 (36.9) | 2 (1.1) | 20 (11.8) | 0 |
| Diarrhea | 69 (38.8) | 8 (4.5) | 62 (34.6) | 1 (0.6) | 36 (21.3) | 3 (1.8) |
| Neutropenia | 56 (31.5) | 53 (29.8) | 19 (10.6) | 17 (9.5) | 76 (45.0) | 70 (41.4) |
| Fatigue | 50 (28.1) | 3 (1.7) | 33 (18.4) | 2 (1.1) | 29 (17.2) | 1 (0.6) |
| Contusion | 42 (23.6) | 0 | 27 (15.1) | 0 | 7 (4.1) | 7 (4.1) |
| Arthralgia | 39 (21.9) | 2 (1.1) | 28 (15.6) | 1 (0.6) | 8 (4.7) | 2 (1.2) |
| Cough | 39 (21.9) | 0 | 33 (18.4) | 1 (0.6) | 15 (8.9) | 0 |
| URTI | 38 (21.3) | 4 (2.2) | 33 (18.4) | 0 | 14 (8.3) | 1 (0.6) |
| Nausea | 36 (20.2) | 0 | 40 (22.3) | 0 | 53 (31.4) | 0 |
| Dizziness | 32 (18.0) | 0 | 21 (11.7) | 0 | 10 (5.9) | 0 |
| IRR | 24 (13.5) | 4 (2.2) | 0 | 0 | 67 (39.6) | 9 (5.3) |
| Pyrexia | 23 (12.9) | 0 | 12 (6.7) | 1 (0.6) | 35 (20.7) | 1 (0.6) |

Courtesy of Stephan Stilgenbauer, MD

# ELEVATE-TN: untreated older CLL Patients Acalabrutinib +/- Obinutuzumab compared with Obinutuzumab+Chlorambucil

***Sharman et al. Lancet 2020***



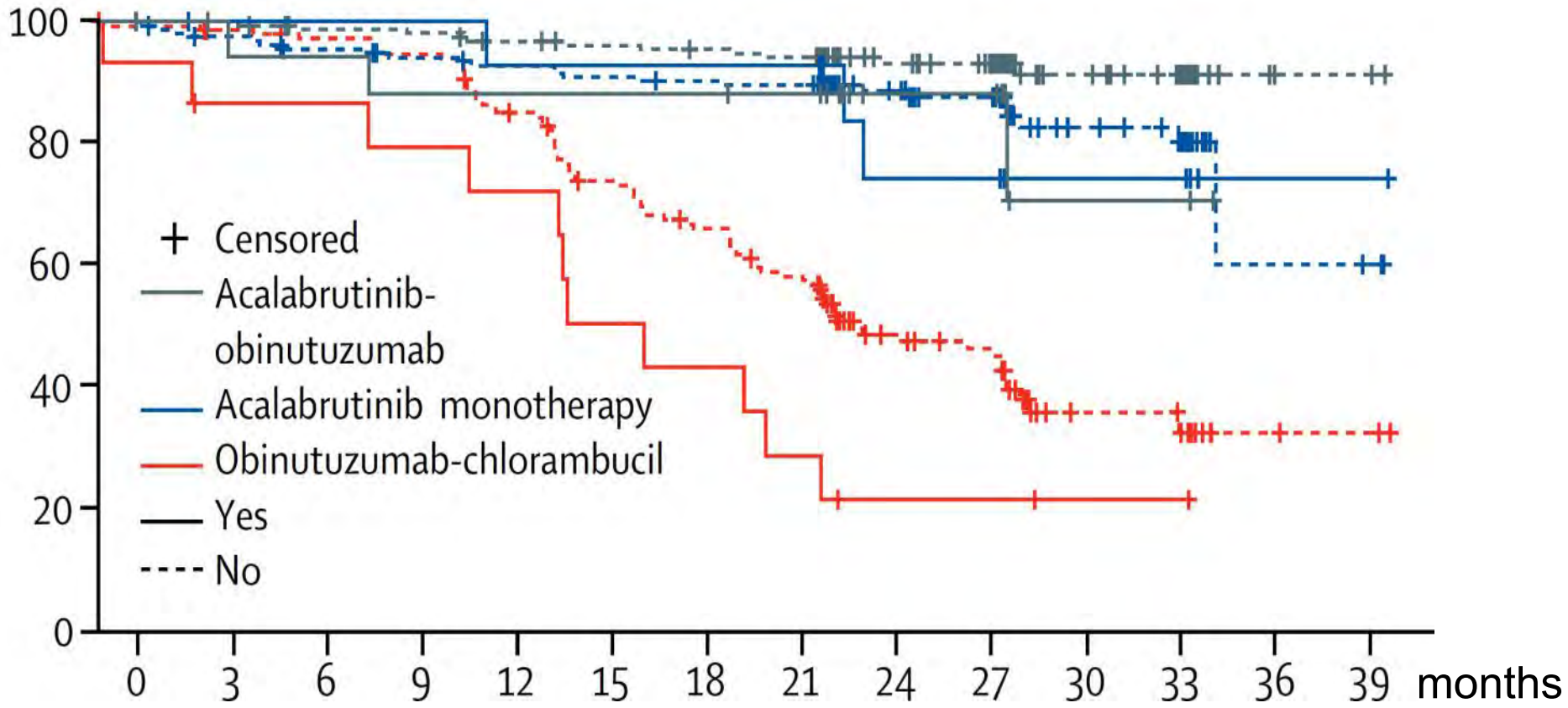

Median follow-up 28 months

Courtesy of Stephan Stilgenbauer, MD

# ELEVATE-TN: untreated older CLL Patients Acalabrutinib +/- Obinutuzumab compared with Obinutuzumab+Chlorambucil

*Sharman et al. Lancet 2020*

## PFS: 17p- Subgroup




Courtesy of Stephan Stilgenbauer, MD

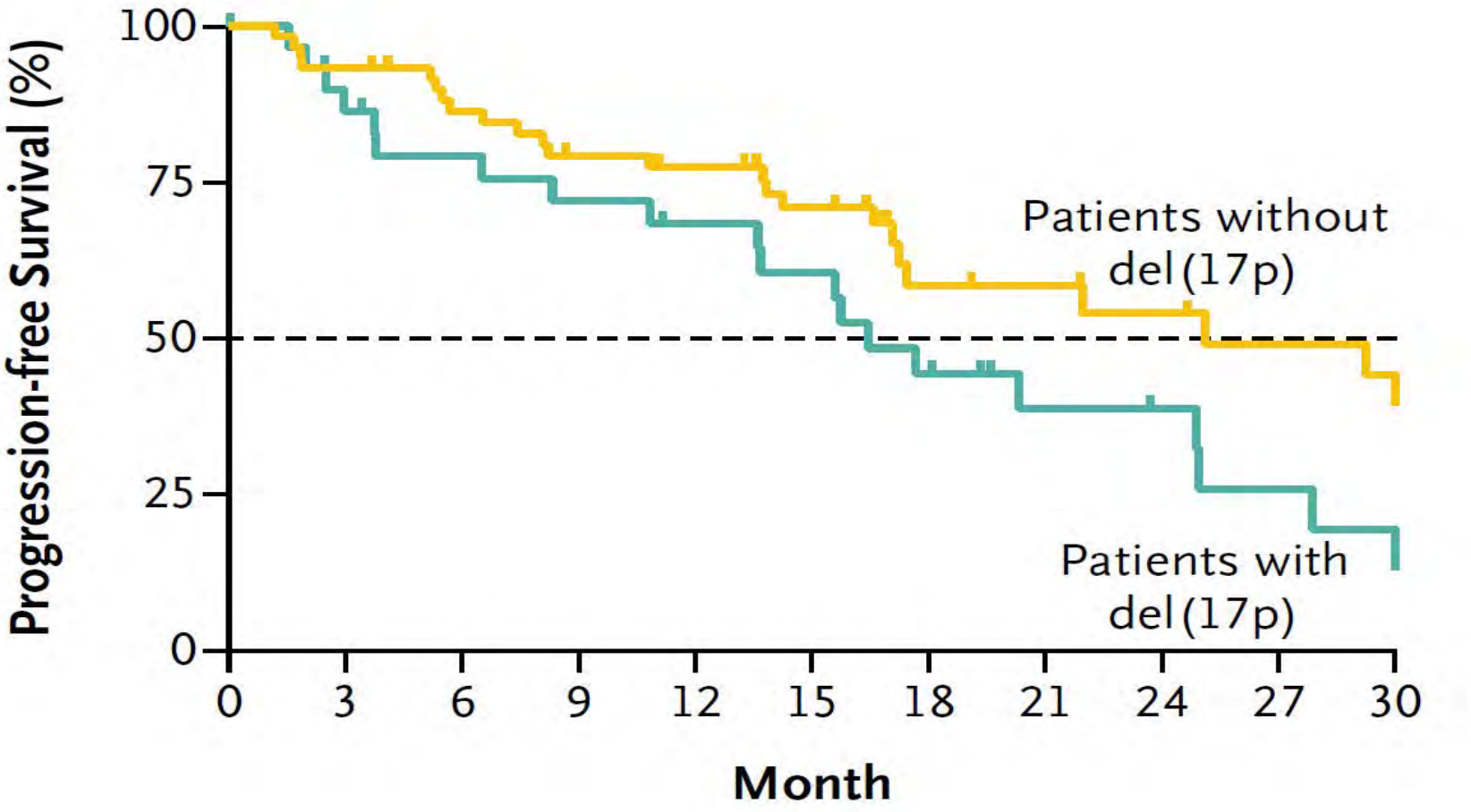
# Upfront Management of CLL in Patients Who Are Older or Have Comorbidities

- PFS improvement with targeted therapy, i.e. venetoclax + obinutuzumab, ibrutinib and acalabrutinib (+/- CD20 antibody) over chemoimmunotherapy
- PFS appears similar for all targeted approaches in cross trial comparison
- Benefit most pronounced in CLL with unmutated IGHV
- Outcome of 17p-/*TP53*$^{mut}$ CLL still inferior with all targeted therapy approaches but much improved over chemoimmunotherapy
- Choice of BCL2 or BTK targeting agent largely based on tolerability:
  - Patient preference (treatment duration and monitoring)
  - Coexisting conditions (hypertension, cardiovascular and renal disease)
  - Concomitant medication (anticoagulants, antiplatelets, CYP3A interaction)

Courtesy of Stephan Stilgenbauer, MD

# Venetoclax (ABT-199) First in Human Trial

***Roberts et al., NEJM 2016; Anderson et al., Blood 2017***




**Factors associated with failure (n=67): F-refract., complex karyotype**

Courtesy of Stephan Stilgenbauer, MD

# CLL14: untreated elderly/unfit CLL: MRD Response

***Fischer et al. NEJM 2019***

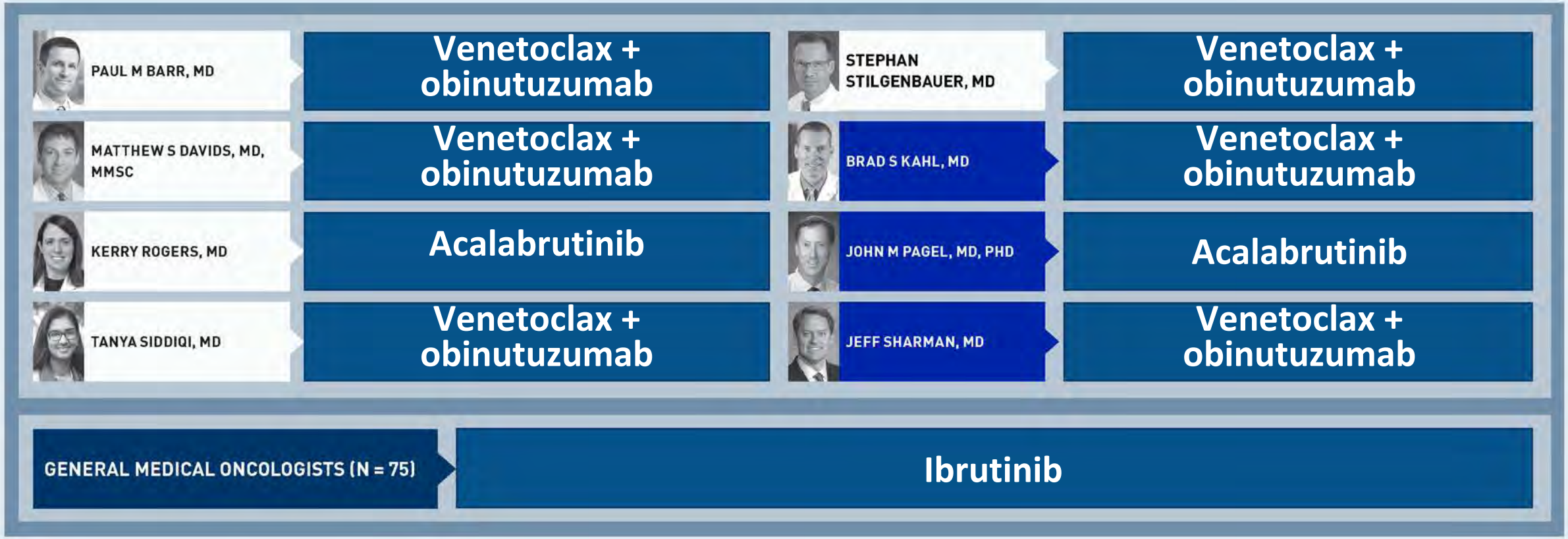
| | Obi-Ven | Obi-Clb | *P* value |
|---|---|---|---|
| Number of patients, N | 216 | 216 | |
| **Peripheral blood** | | | |
| Negative ($<10^{-4}$) | 76 % | 35 % | < 0.001 |
| Negative ($<10^{-4}$) in CR | 42 % | 14 % | < 0.001 |
| **Bone marrow** | | | |
| Negative ($<10^{-4}$) | 57 % | 17 % | < 0.001 |
| Negative ($<10^{-4}$) in CR | 34 % | 11 % | < 0.001 |

Courtesy of Stephan Stilgenbauer, MD

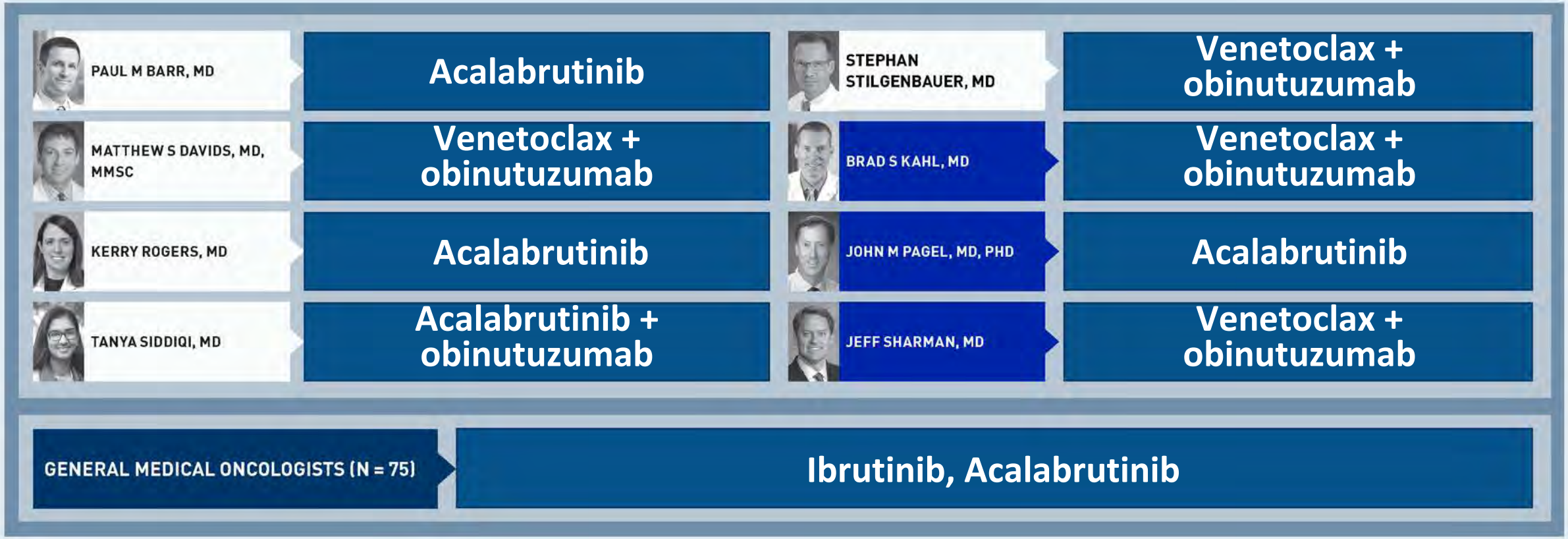
# What is your usual preferred initial regimen for a 75-year-old patient with IGHV-mutated CLL without del(17p) or TP53 mutation who requires treatment?

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

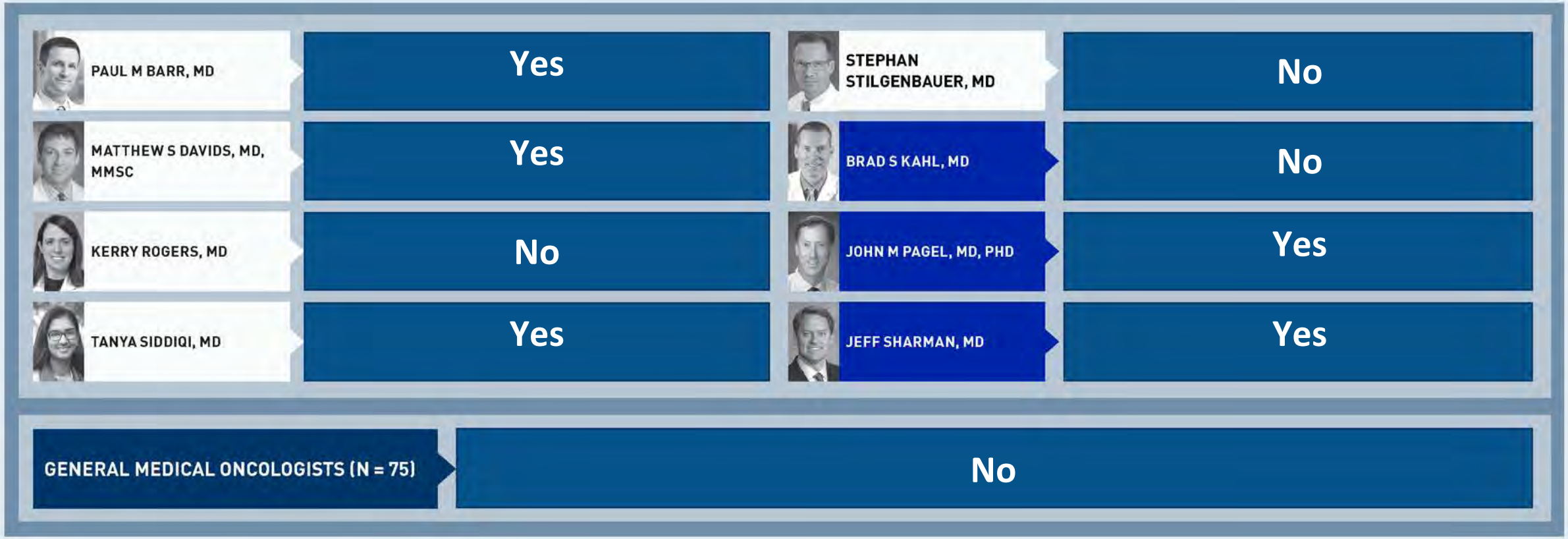
# What is your usual preferred initial regimen for a 75-year-old patient with IGHV-mutated CLL without del(17p) or TP53 mutation who requires treatment?



# What is your usual preferred initial regimen for a 75-year-old patient with IGHV-unmutated CLL without del(17p) or TP53 mutation who requires treatment?



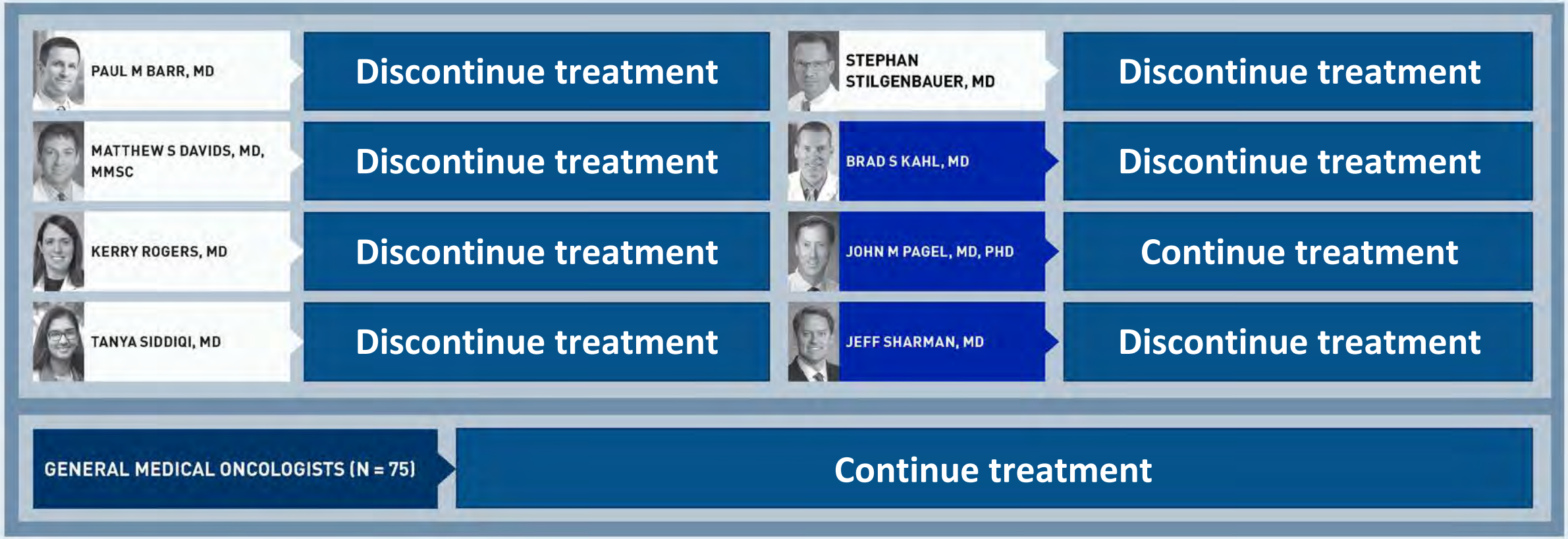
# Have you ordered a minimal residual disease (MRD) assay for a patient with CLL to guide treatment decisions outside of a clinical trial setting?



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

1. Continue treatment
2. Discontinue treatment

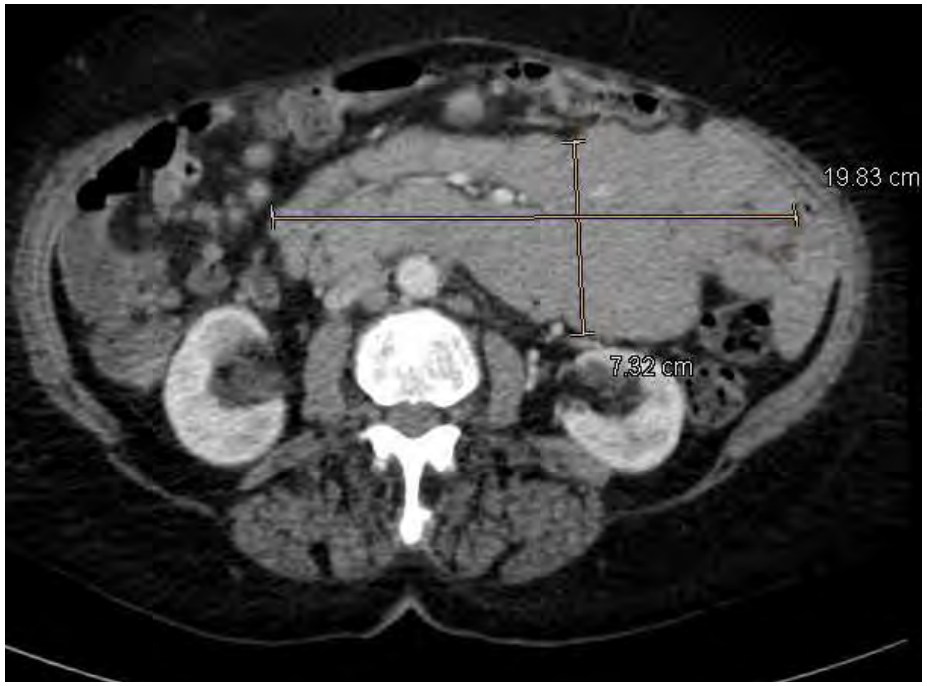
# What would be your most likely approach for a patient with newly diagnosed CLL to whom you decide to administer up-front venetoclax/obinutuzumab who has detectable MRD after completing 1 year of treatment?



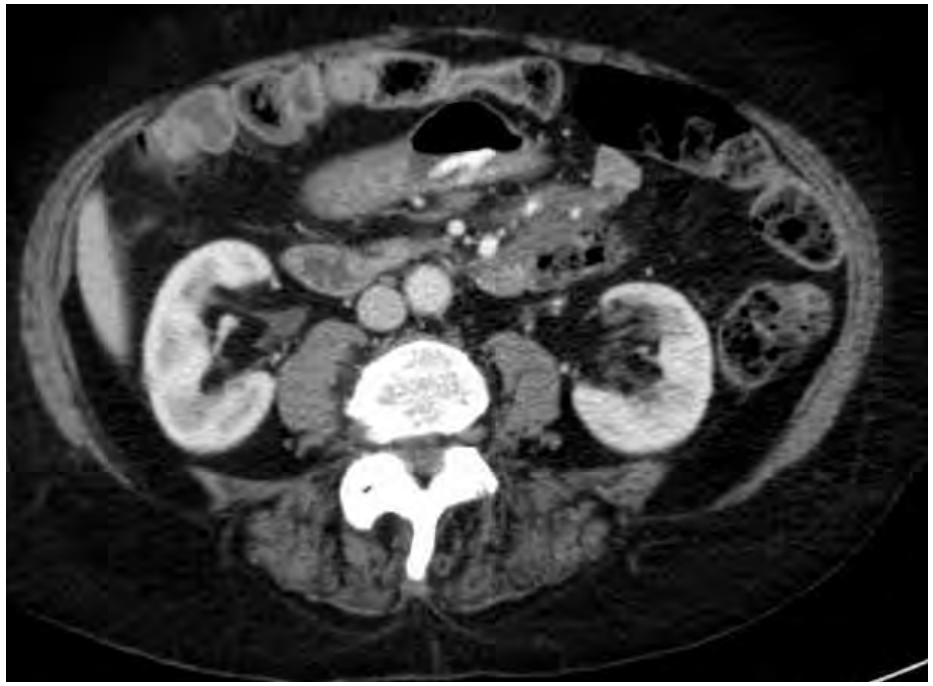
# Case Presentation – Dr Stilgenbauer: A 76 year-old woman with relapsed/refractory CLL - 17p

## Novel Therapy: Selective BCL2 Targeting
## Small Molecule Inhibitor Venetoclax (ABT-199)

**Baseline CT staging:**




**Month 3 on therapy:**



Courtesy of Stephan Stilgenbauer, MD

# Agenda

Module 1: First-line treatment options for younger, fit patients — Dr Barr

Module 2: Up-front management of chronic lymphocytic leukemia in older patients or those with comorbidities — Dr Stilgenbauer

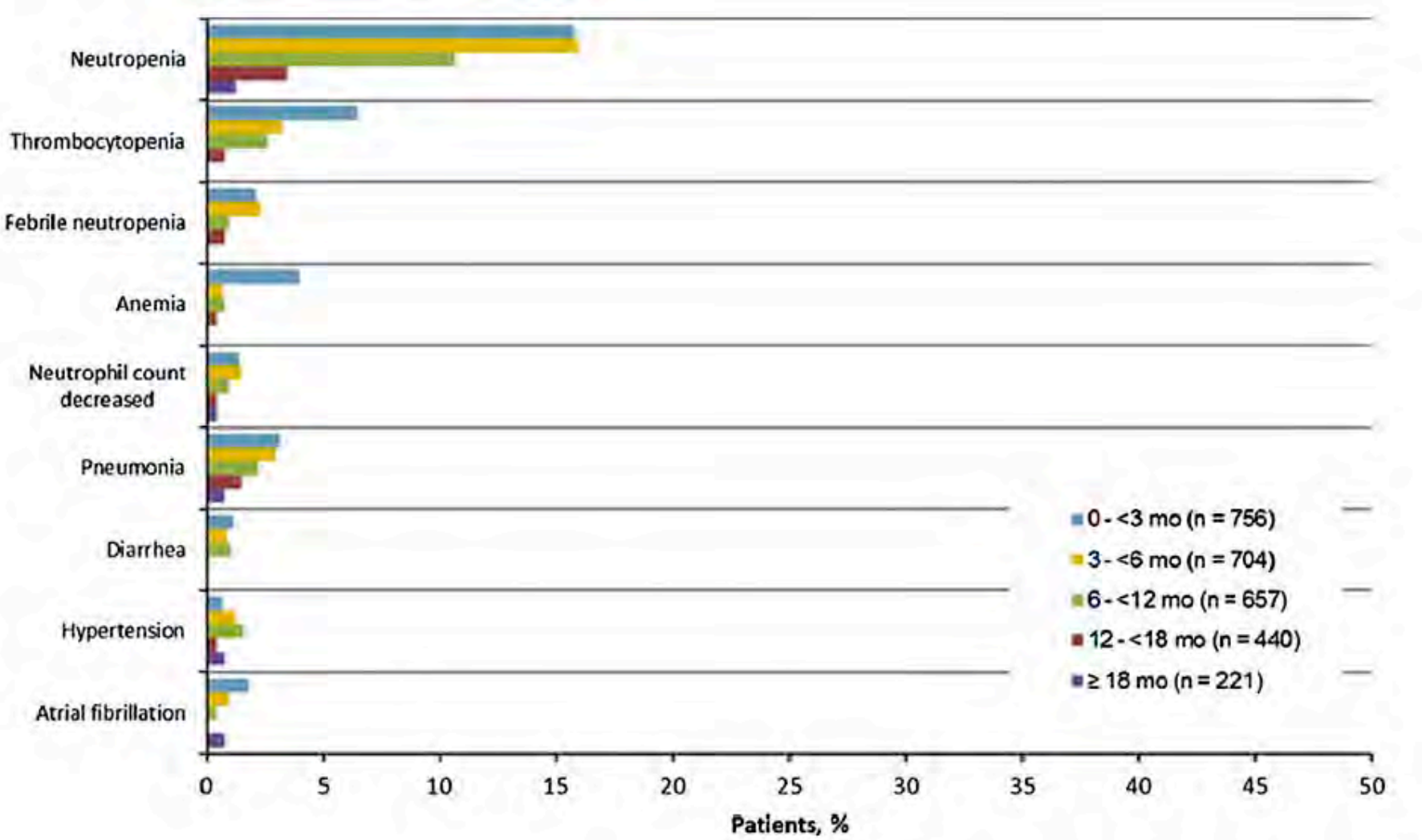
**Module 3: Optimal management of adverse events with BTK and Bcl-2 inhibitors — Dr Davids**

Module 4: Selection and sequencing of therapies for relapsed/refractory disease — Dr Rogers

Module 5: Novel strategies under investigation — Dr Siddiqi

# Prevalence of Most Common Grade 3/4 Adverse Events With Ibrutinib Over Time

BTK inhibitors




Courtesy of Matthew S Davids, MD, MMSc

O'Brien et al., *Clin Lymphoma Myeloma Leuk*. 2018 Oct;18(10):648-657.e15

BTK inhibitors

# Bleeding Events: Cumulative and Exposure-adjusted Incidence Rates

| Event | Ibr (n = 756) | | Comp (n = 749) | | Δ, %[a] | Δ, EAIR[a] |
|---|---|---|---|---|---|---|
| | % | EAIR | % | EAIR | | |
| Any bleeding event[b] | 38 | 0.486 | 17 | 0.2628 | 21.3 | 0.2232 |
| Grade 3/4 bleeding event | 3 | 0.0252 | 2 | 0.0276 | 0.8 | −0.0024 |
| Major hemorrhage | 4 | 0.0348 | 3 | 0.0348 | 1.3 | 0 |
| Grade 3/4 major hemorrhage | 3 | 0.0252 | 2 | 0.0276 | 0.8 | −0.0024 |

Abbreviations: Comp = comparator; EAIR = exposure-adjusted incidence rate per patient-years; Ibr = ibrutinib.
[a]Negative numbers indicate higher rates with comparator.
[b]Based on the number of patients with any bleeding event by preferred term.

Courtesy of Matthew S Davids, MD, MMSc

O'Brien et al., *Clin Lymphoma Myeloma Leuk*. 2018 Oct;18(10):648-657.e15

# We recently reported that pneumocystis jiroveci pneumonia (PJP) incidence on BTKi was low, even in patients not on prophylaxis

- Overall prevalence of PJP in patients NOT on prophylaxis: **3.4%** (3/87)
- Prevalence of PJP in patients ON prophylaxis: 0% (0/125)
- Incidence rate in patients not on prophylaxis: 1.9 per 100 person-years
- Number needed to treat to prevent 1 case of PJP: 42 patients

Courtesy of Matthew S Davids, MD, MMSc

Ryan, *et al*, *iwCLL*, 2019

# Acalabrutinib: a safer BTKi?

**Compared to ibrutinib:**

- ***Overlapping toxicities*: mild diarrhea, mild bleeding, infections**
- ***New toxicities*: headache, weight gain**
- ***Less commonly seen with acalabrutinib*: afib, major hemorrhage, significant skin toxicity, pneumonitis**
- **No ventricular arrhythmias reported**

| Adverse Event | All Grades | Grades 1–2 | Grades 3–4 |
|---|---|---|---|
| Number of patients (%) | | | |
| Headache | 26 (43) | 26 (43) | 0 |
| Diarrhea | 24 (39) | 23 (38) | 1 (2) |
| Increased weight | 16 (26) | 15 (25) | 1 (2) |
| Pyrexia | 14 (23) | 12 (20) | 2 (3) |
| Upper respiratory tract infection | 14 (23) | 14 (23) | 0 |
| Fatigue | 13 (21) | 11 (18) | 2 (3) |
| Peripheral edema | 13 (21) | 13 (21) | 0 |
| Hypertension | 12 (20) | 8 (13) | 4 (7) |
| Nausea | 12 (20) | 12 (20) | 0 |
| Contusion | 11 (18) | 11 (18) | 0 |
| Arthralgia | 10 (16) | 9 (15) | 1 (2) |
| Petechiae | 10 (16) | 10 (16) | 0 |
| Decreased weight | 10 (16) | 10 (16) | 0 |

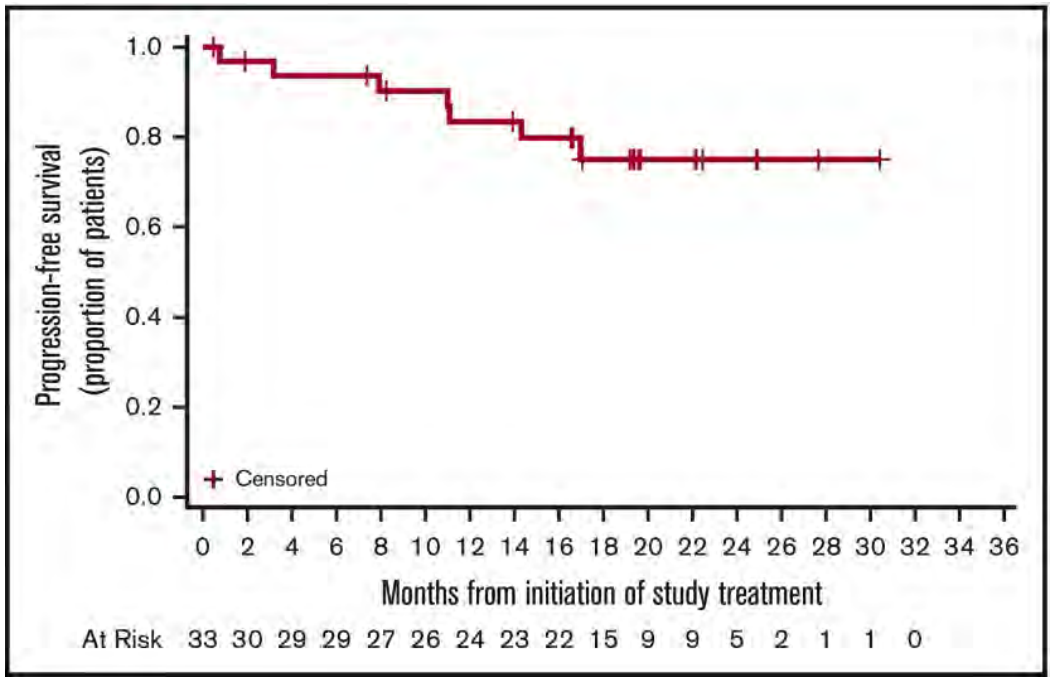
Courtesy of Matthew S Davids, MD, MMSc

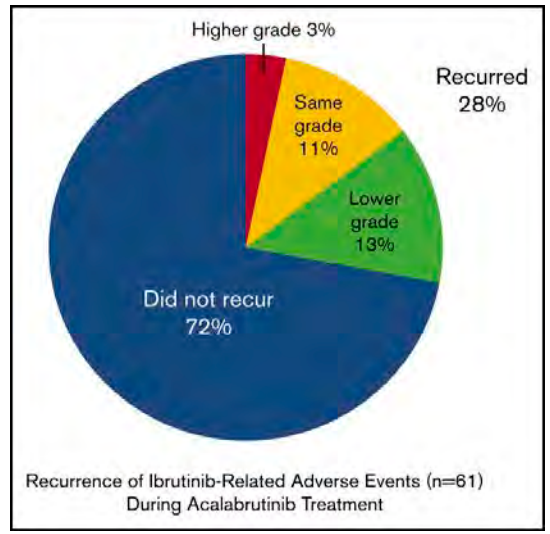
Byrd JC, et al. *N Engl J Med*. 2016; Wang M, et al. *Lancet*. 2017; FDA Prescribing Information.

# Acalabrutinib in Ibrutinib-Intolerant Patients

**Subset analysis of patients with ibrutinib intolerance enrolled in phase 1/2 ACE-CL-001 (n = 33)**

- Median duration of prior ibrutinib, 11.6 months
- ~70% of patients remained on acalabrutinib after a median of 19 months
  - 3 patients had discontinued acalabrutinib due to AEs; 4 patients discontinued due to progressive disease




- Median duration of response was not reached
- Median PFS was not reached
- 1-year PFS was 83.4% (95% CI, 64.5%-92.7%)

Courtesy of Matthew S Davids, MD, MMSc

Awan FT, et al. *Blood.* 2019

# ASPEN Trial (Waldenström Macroglobulinemia): BTKi Class Adverse Events of Interest

| AE Categories, % | All Grades | | Grade ≥ 3 | |
|---|---|---|---|---|
| | Zanubrutinib (n = 101) | Ibrutinib (n = 98) | Zanubrutinib (n = 101) | Ibrutinib (n = 98) |
| Atrial fibrillation/flutter* | 3.0 | 18.4 | 0.0 | 7.1 |
| Diarrhea (PT) | 21.8 | 32.7 | 3.0 | 2.0 |
| Hemorrhage | 50.5 | 60.2 | 5.9 | 9.2 |
| ▪ Major hemorrhage‡ | 5.9 | 10.2 | 5.9 | 9.2 |
| Hypertension | 12.9 | 20.4 | 7.9 | 15.3 |
| Neutropenia*† | 31.7 | 15.3 | 22.8 | 8.2 |
| Infection | 69.3 | 71.4 | 18.8 | 23.5 |
| Second malignancy | 12.9 | 12.2 | 3.0 | 1.0 |
| Discontinuation rate | 4.0 | 9.0 | | |

*Descriptive 2-sided $P < .05$.

†PT terms of neutropenia, neutrophil count decreased, febrile neutropenia, agranulocytosis, neutropenic infection and neutropenic sepsis.

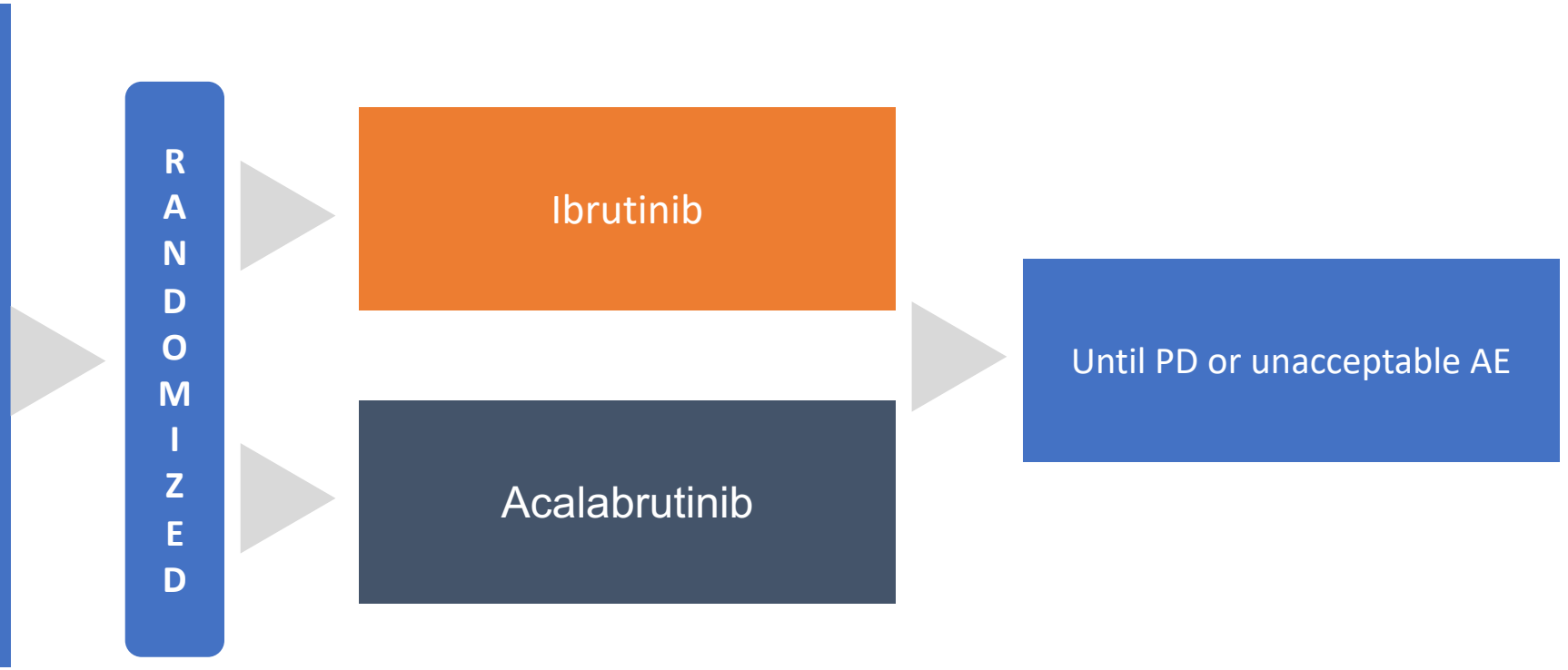
‡Major hemorrhage defined as grade ≥ 3 hemorrhage or any grade CNS hemorrhage.

Courtesy of Matthew S Davids, MD, MMSc

Tam et al., *Blood*, 2020

# ELEVATE-R/R Trial: Ibrutinib vs Acalabrutinib in Patients With High-Risk R/R CLL

- Ongoing phase 3, randomized, multicenter, open-label, noninferiority trial
- Patients with del(17p) or del(11q) CLL with active disease (N=533)
- ≥1 previous line of treatment
- ECOG 0-2




Status:
Active, fully accrued

**Primary endpoint:** PFS

**Secondary endpoints:** OS, incidence of treatment-emergent AEs, atrial fibrillation, Richter's transformation

Courtesy of Matthew S Davids, MD, MMSc

# MAIC: Acalabrutinib ± G Demonstrated Lower Rates of Several Clinically Important AEs vs Ibrutinib ± G in TN CLL

## AEs With Statistically Significant Differences After Matching

### Acalabrutinib vs Ibrutinib

| AE rate, % | Acala ESS=79 | Ibr n=136 | Rate difference % (95% CI) | *P*-value |
|---|---|---|---|---|
| **Grade 3/4 AEs** | | | | |
| Infections | 12.4 | 24.0 | −11.6 (−21.9,−1.0) | <0.05 |
| Atrial fibrillation | 0 | 4.0 | −4.0 (−7.3 ,0.0) | <0.05 |
| **Grade 1-4 AEs** | | | | |
| Peripheral edema | 7.5 | 21.0 | −13.5 (−21.7,−5.0) | <0.001 |
| Pyrexia | 6.2 | 20.0 | −13.8 (−21.6,−6.0) | <0.001 |
| Hypertension | 6.4 | 18.0 | −11.6 (−19.9,−3.0) | <0.01 |
| Major hemorrhage | 1.8 | 7.0 | −5.2 (−10.2,0.0) | <0.05 |

### Acalabrutinib + G vs Ibrutinib + G

| AE rate, % | Acala + G ESS=97 | Ibr + G n=113 | Rate difference % (95% CI) | *P*−value |
|---|---|---|---|---|
| **Grade 3/4 AEs** | | | | |
| Peripheral edema | 0.6 | 12.0 | −11.4 (−17.5,−5.3) | <0.001 |
| Febrile neutropenia | 0.5 | 5.0 | −4.5 (−8.6,−0.4) | <0.05 |
| **Grade 1-4 AEs** | | | | |
| Headache | 32.1 | 8.0 | +24.1 (+14.6,+33.6) | <0.001 |
| Thrombocytopenia | 20.7 | 36.0 | −15.3 (−26.8,−3.9) | <0.01 |
| Atrial fibrillation | 3.4 | 12.0 | −8.6 (−15.6,−1.7) | <0.05 |

G = Obinutuzumab

Courtesy of Matthew S Davids, MD, MMSc

Davids et al., EHA, 2020 (Abstract EP724)

# Phase I FIH: venetoclax was generally well tolerated, although specific toxicities were noted



**Adverse events, serious adverse events and toxicity in the 116 study patients**

| Adverse event* | Any Grade [n (%)] | Grade 3 or 4 [n (%)] |
|---|---|---|
| Any | **115** (99) | **96** (83) |
| Diarrhea | **60** (52) | **2** (2) |
| Upper respiratory tract infection | **56** (48) | **1** (1) |
| Nausea | **55** (47) | **2** (2) |
| Neutropenia | **52** (45) | **48** (41) |
| Fatigue | **46** (40) | **4** (3) |
| Cough | **35** (30) | **0** |
| Pyrexia | **30** (26) | **1** (1) |
| Anaemia | **29** (25) | **14** (12) |
| Headache | **28** (24) | **1** (1) |
| Constipation | **24** (21) | **1** (1) |
| Thrombocytopenia | **21** (18) | **14** (12) |
| Arthralgia | **21** (18) | **1** (1) |
| Vomiting | **21** (18) | **2** (2) |
| Peripheral edema | **18** (16) | **0** |
| Pyrexia | **17** (15) | **10** (9) |

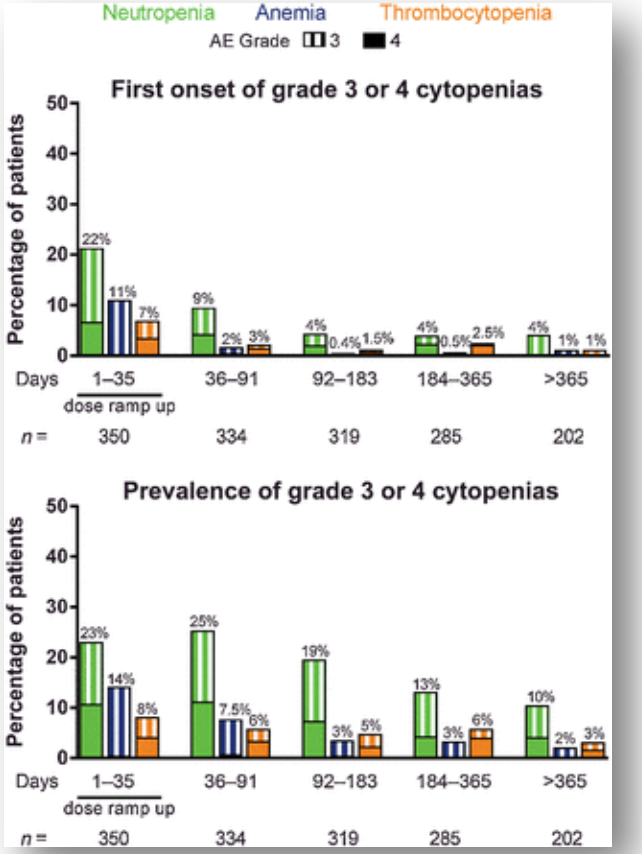
| Serious adverse event† | Any Grade [n (%)] | Grade 3 or 4 [n (%)] |
|---|---|---|
| Any | **52** (45) | |
| Febrile neutropenia | **7** (6) | |
| Pneumonia | **5** (4) | |
| Upper respiratory tract infection | **4** (3) | |
| Immune thrombocytopenia | **3** (3) | |
| Tumor lysis syndrome | **3** (3) | |
| Diarrhoea | **2** (2) | |
| Fluid overload | **2** (2) | |
| Hyperglycemia | **2** (2) | |
| Prostate cancer | **2** (2) | |
| Pyrexia | **2** (2) | |

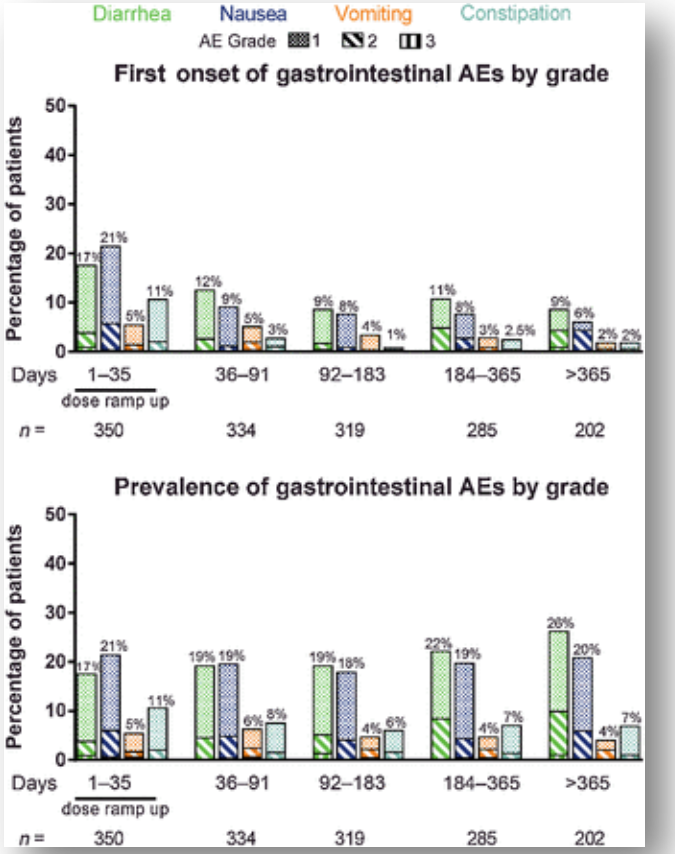
| Toxicity | Any Grade (%) | Grade 3 or 4 (%) |
|---|---|---|
| Neutropenia | **45** | **41** |
| GI | **52** | **2** |
| TLS | **3** | **3** |

*Listed are adverse events that were reported in at least 15% patients. Preexisting grade 1/2 abnormalities not reported, unless grade increased during the study.
†Listed are serious adverse events that were reported in at least two patients. Excluded are serious adverse events that were related to disease progression in two patients.
**GI,** gastrointestinal; **TLS**, tumor lysis syndrome
Roberts AW, et al. *N Engl J Med* 2016;374:311–322.

Courtesy of Matthew S Davids, MD, MMSc

# Venetoclax risks include neutropenia, GI toxicities, and TLS



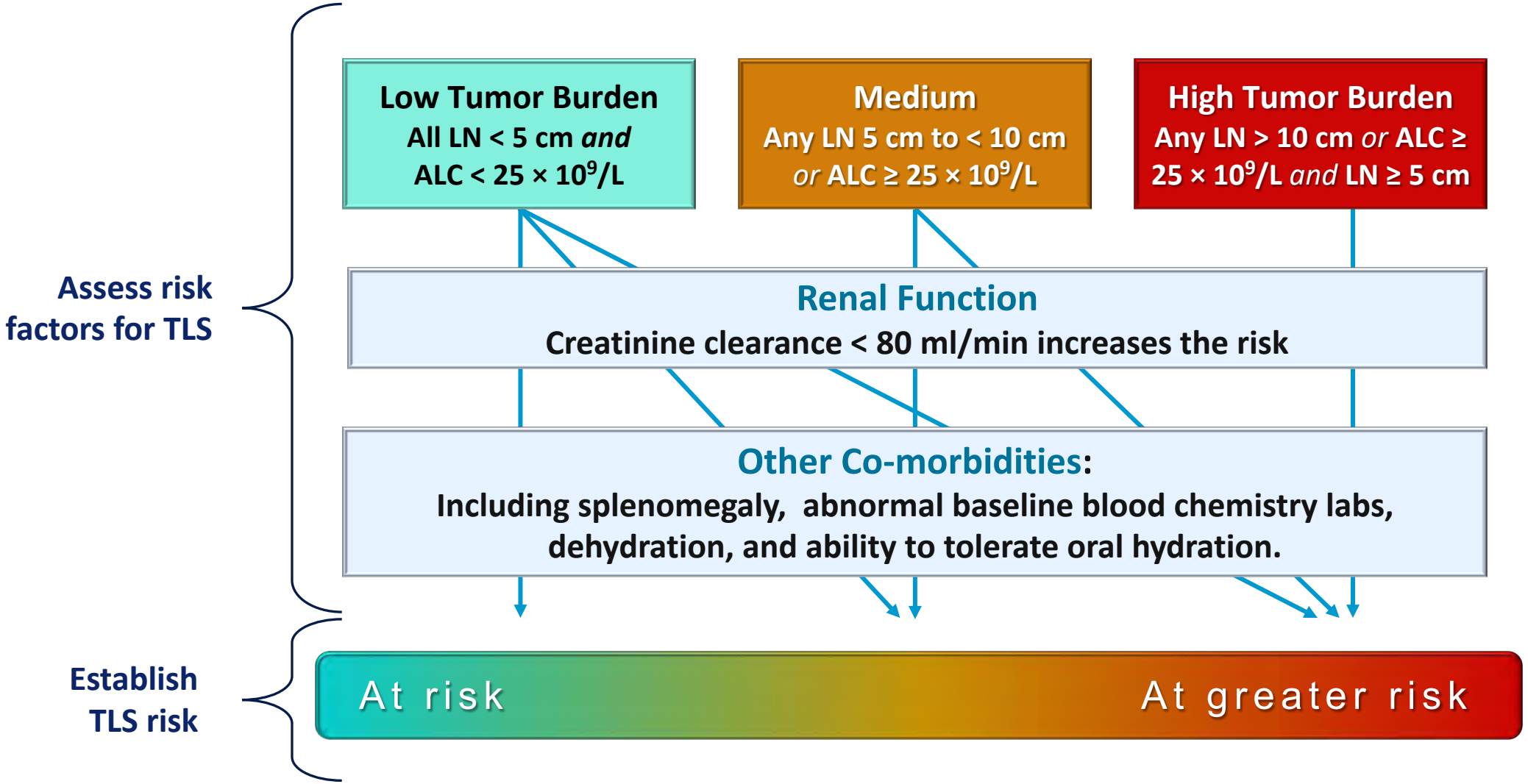




- **2/166 (1.4%) treated with current dosing had lab TLS, but none had clinical TLS**
- **TLS in phase 3 trials:**
  - **MURANO (ven + rituximab) 3.1% (1 clinical, 5 lab)**
  - **CLL14 (ven + obinutuzumab) 3 patients all before starting venetoclax**

Courtesy of Matthew S Davids, MD, MMSc

Davids MS et al., *Clin Cancer Res*, 2018

# TLS risk with venetoclax is a continuum based on multiple factors

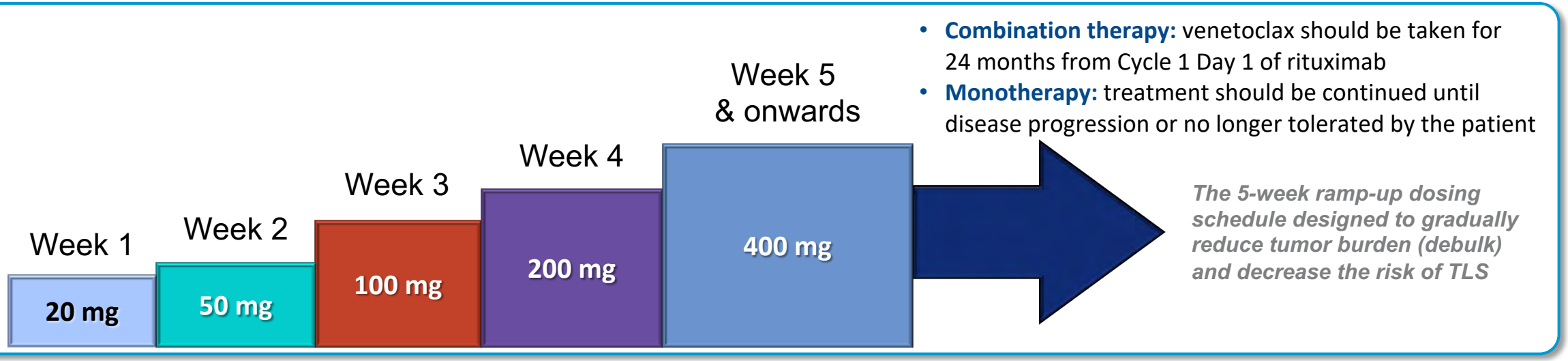



**ALC**, absolute lymphocyte count; **CrCl**, creatinine clearance; **LN**, lymph node; **TLS**, tumor lysis syndrome

1. Venetoclax SmPC: https://www.medicines.org.uk/emc/product/2267/smpc (accessed October 2019); 2. Stilgenbauer S, et al. *Lancet Oncol* 2016;17:768–778.

Courtesy of Matthew S Davids, MD, MMSc

# Venetoclax dose initiation




- **Combination therapy:** venetoclax should be taken for 24 months from Cycle 1 Day 1 of rituximab
- **Monotherapy:** treatment should be continued until disease progression or no longer tolerated by the patient

*The 5-week ramp-up dosing schedule designed to gradually reduce tumor burden (debulk) and decrease the risk of TLS*

The 5-week dose-titration schedule is designed to gradually reduce tumour burden and decrease the risk of TLS

**Combination therapy:** recommended dose of venetoclax in combination with rituximab is 400 mg once daily; rituximab should be administered after the patient has completed the dose-titration schedule and has received the recommended daily dose of 400 mg venetoclax for 7 days.

**Monotherapy:** the recommended dose of venetoclax is 400 mg once daily.

Venetoclax SmPC: https://www.medicines.org.uk/emc/product/2267/smpc (accessed October 2019).

Courtesy of Matthew S Davids, MD, MMSc

# Venetoclax: TLS prophylaxis and monitoring

| | |
|---|---|
| [a] **HYDRATION** | **Oral** (1.5 – 2 L); start 2 days prior to treatment start. **IV** if needed due to higher TLS risk |
| **ANTI-HYPER-URICAEMIC AGENTS** | Patients with high uric acid or TLS risk should be administered with anti-hyperuricaemic agents **2 to 3 days prior** to treatment start |
| [b,c] **LABORATORY MONITORING** | • **Pre-dose, 6–8, 24 hours** (at 1st dose of 20 mg and 50 mg, and for patients who continue to be at risk<br>• Pre-dose at subsequent ramp-up doses<br>Evaluate blood chemistries and review in real time |
| **HOSPITALIZATION** | Based on physician assessment, some patients consider hospitalisation on first dose of venetoclax for more intensive prophylaxis and monitoring during the first 24 hours. |

[a]Administer intravenous hydration for any patient who cannot tolerate oral hydration; [b]Evaluate blood chemistries (potassium, uric acid, phosphorus, calcium, and creatinine); review in real time; [c]For patients at risk of TLS, monitor blood chemistries at 6–8 hours and at 24 hours at each subsequent ramp-up dose. Changes in blood chemistries consistent with TLS that require prompt management can occur as early as 6-8 hours following the first dose of venetoclax, and at each dose increase. **LN,** lymph node; **ALC**, absolute lymphocyte count; **TLS**, tumour lysis syndrome; **VEN**, venetoclax

1. Venetoclax SPC https://www.medicines.org.uk/emc/product/2267/smpc (accessed October 2019); 2. Stilgenbauer S, et al. *Lancet Oncol.* 2016; 17:768–778

Courtesy of Matthew S Davids, MD, MMSc

# General considerations for toxicity management with novel agents

- **In the setting of active infection it is generally best to hold drug at least until seeing signs of clinical improvement**
- **For most toxicities requiring drug hold, it is preferable to either rechallenge with full dose or to start back at dose reduction but then get back to full dose**
- **In general I am more hesitant to hold drug soon after starting a novel agent or in a patient who is progressing on a novel agent**
- **I am less concerned about stopping drug in patients who have been on novel agents for at least a few months and are in a good clinical response**

Courtesy of Matthew S Davids, MD, MMSc

# General considerations (continued)

- **Novel agents are infrequently the main cause of cytopenias (exception: venetoclax and neutropenia)**
- **It is generally safe to give growth factor support concomitantly with novel agents**
- **Patients who have to permanently discontinue a novel agent due to toxicity do not necessarily need to immediately start on a new therapy**

Courtesy of Matthew S Davids, MD, MMSc

# A 75-year-old patient with IGHV-mutated CLL without del(17p) or TP53 mutation is responding to ibrutinib but develops significant problems with bruising. What would you recommend?

1. Continue ibrutinib at the same dose
2. Continue ibrutinib at a reduced dose
3. FCR
4. BR
5. Acalabrutinib
6. Acalabrutinib + obinutuzumab
7. Venetoclax + obinutuzumab
8. Other

# A 75-year-old patient with IGHV-mutated CLL without del(17p) or TP53 mutation is responding to ibrutinib but develops significant problems with bruising. What would you recommend?

| | | | |
|---|---|---|---|
|  PAUL M BARR, MD | Stop ibrutinib and observe patient |  STEPHAN STILGENBAUER, MD | Acalabrutinib |
|  MATTHEW S DAVIDS, MD, MMSC | Stop ibrutinib and observe patient |  BRAD S KAHL, MD | Venetoclax + obinutuzumab |
|  KERRY ROGERS, MD | Acalabrutinib |  JOHN M PAGEL, MD, PHD | Acalabrutinib |
|  TANYA SIDDIQI, MD | Acalabrutinib |  JEFF SHARMAN, MD | Acalabrutinib |
| GENERAL MEDICAL ONCOLOGISTS (N = 75) | Continue ibrutinib at reduced dose, Acalabrutinib | | |

# A 75-year-old patient with IGHV-mutated CLL without del(17p) or TP53 mutation is responding to ibrutinib but develops atrial fibrillation requiring anticoagulation. What would you recommend?

| | | | |
|---|---|---|---|
|  PAUL M BARR, MD | Acalabrutinib |  STEPHAN STILGENBAUER, MD | Acalabrutinib |
|  MATTHEW S DAVIDS, MD, MMSC | Acalabrutinib |  BRAD S KAHL, MD | Venetoclax + obinutuzumab |
|  KERRY ROGERS, MD | Continue ibrutinib at the same dose |  JOHN M PAGEL, MD, PHD | Acalabrutinib |
|  TANYA SIDDIQI, MD | Acalabrutinib |  JEFF SHARMAN, MD | Acalabrutinib |

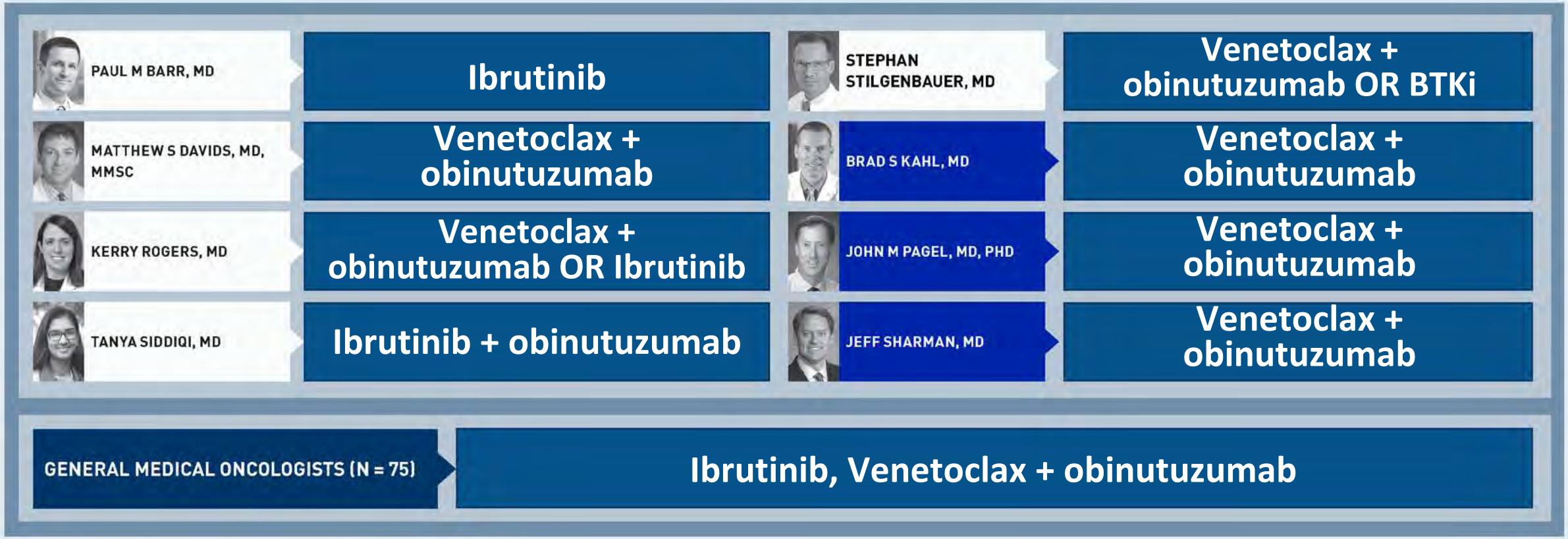
| | |
|---|---|
| GENERAL MEDICAL ONCOLOGISTS (N = 75) | Acalabrutinib, Continue ibrutinib at the same dose |

# What is your usual preferred initial regimen for a 75-year-old patient with IGHV-unmutated CLL without del(17p) or TP53 mutation who requires treatment and is receiving anticoagulation for atrial fibrillation?

| | | | |
|---|---|---|---|
|  PAUL M BARR, MD | Venetoclax + obinutuzumab |  STEPHAN STILGENBAUER, MD | Venetoclax + obinutuzumab |
|  MATTHEW S DAVIDS, MD, MMSC | Venetoclax + obinutuzumab |  BRAD S KAHL, MD | Venetoclax + obinutuzumab |
|  KERRY ROGERS, MD | Venetoclax + obinutuzumab |  JOHN M PAGEL, MD, PHD | Venetoclax + obinutuzumab |
|  TANYA SIDDIQI, MD | Acalabrutinib + obinutuzumab |  JEFF SHARMAN, MD | Venetoclax + obinutuzumab |

| | |
|---|---|
| GENERAL MEDICAL ONCOLOGISTS (N = 75) | Venetoclax + obinutuzumab, Acalabrutinib |

# What is your usual preferred initial regimen for a 75-year-old patient with IGHV-unmutated CLL without del(17p) or TP53 mutation who requires treatment and is receiving a proton pump inhibitor for GERD?



# Case Presentation – Dr Davids: A 73-year-old man with CLL – del(11q), no IGHV mutation

A 73 y/o man with HTN and diet-controlled DM has del(11q), unmutated IGHV, TP53 wildtype, Rai stage 4 CLL and needs initial treatment. He starts on ibrutinib, and about 10 weeks into his course he has marked reduction in lymphadenopathy and improvement in cytopenias, but on routine check is found to be in afib with a rate in the low 100s. Ibrutinib is held, and anticoagulation is started.

How do you proceed at this point?

Courtesy of Matthew S Davids, MD, MMSc

# Case Presentation – Dr Davids: A 67-year-old woman with relapsed/refractory CLL – del(17p)

A fit 67 y/o woman with del(17p) CLL relapsed 2 years after FCR now develops recurrent bulky internal lymphadenopathy and splenomegaly of 22 cm. She is started on venetoclax + rituximab, and on week 2 of rituximab her ANC has trended down from a baseline of 1,600 to 950. She is afebrile and tolerating therapy well.

How do you proceed?

Courtesy of Matthew S Davids, MD, MMSc

# Agenda

Module 1: First-line treatment options for younger, fit patients — Dr Barr

Module 2: Up-front management of chronic lymphocytic leukemia in older patients or those with comorbidities — Dr Stilgenbauer

Module 3: Optimal management of adverse events with BTK and Bcl-2 inhibitors — Dr Davids

**Module 4: Selection and sequencing of therapies for relapsed/refractory disease — Dr Rogers**

Module 5: Novel strategies under investigation — Dr Siddiqi

# Treatment Selection in R/R CLL

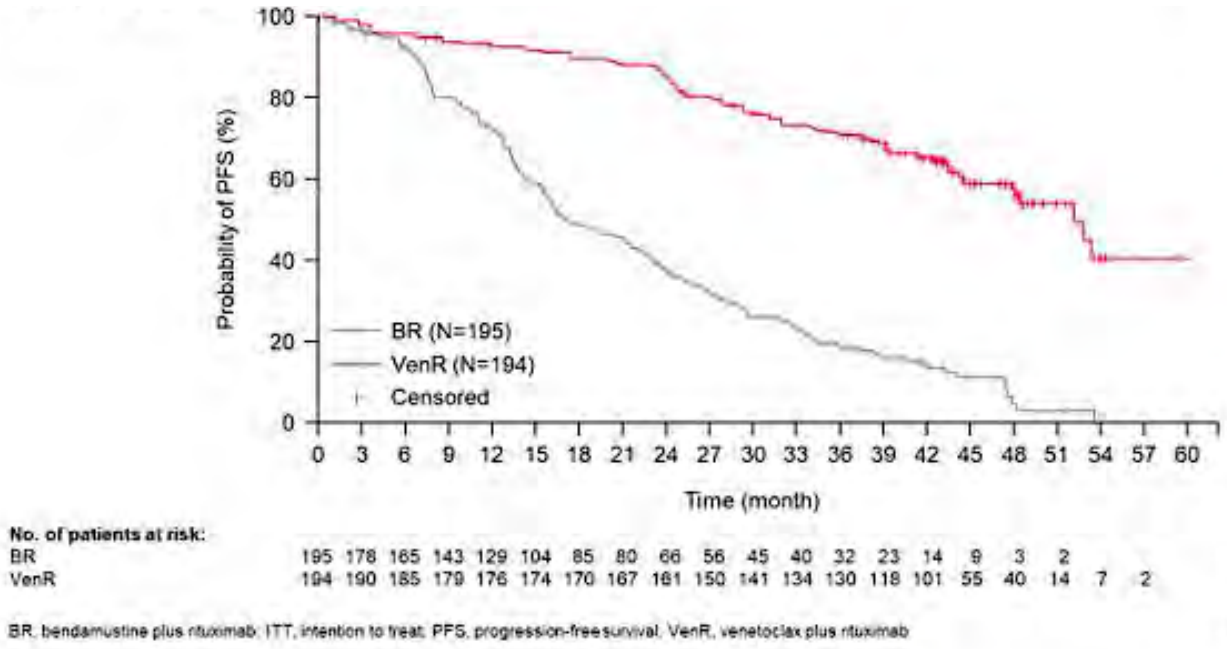
- Targeted agents now preferred over chemoimmunotherapy
- Several classes of approved agents
  - BCL2 inhibitors: venetoclax +/- rituximab
  - BTK inhibitors: ibrutinib, acalabrutinib
  - PI3K inhibitors: idelalisib + rituximab, duvelisib
- Major questions
  - Which is most effective?
  - What side effect profile might be best for my patient?
  - Does the order these drugs are given in matter?



Courtesy of Kerry Rogers, MD

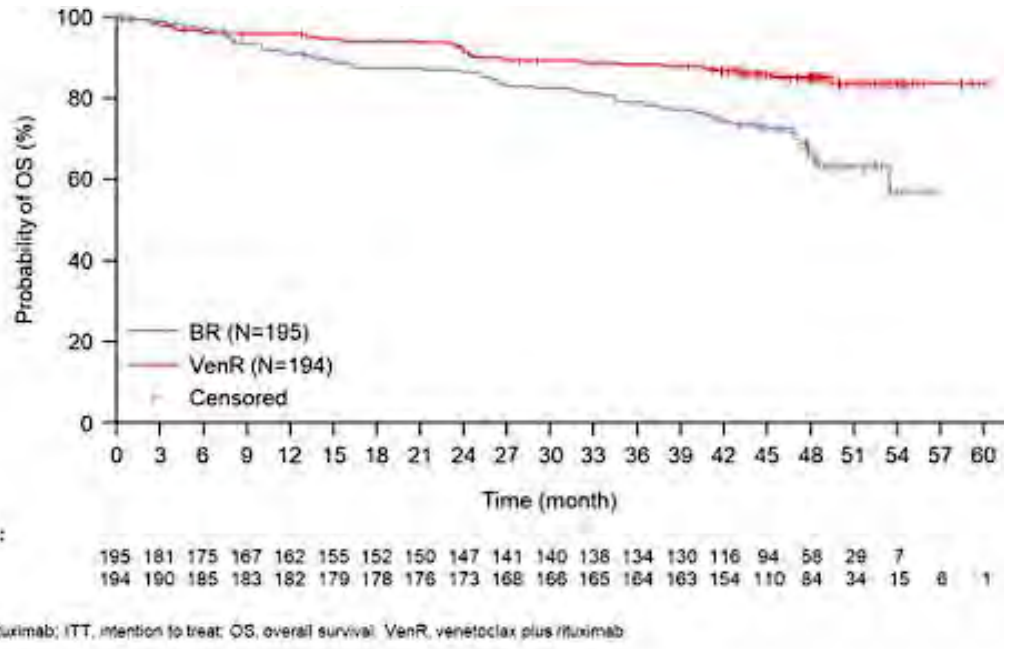
# MURANO Study 4-year follow-up

Progression-Free Survival




BR, bendamustine plus rituximab; ITT, intention to treat; PFS, progression-free survival; VenR, venetoclax plus rituximab

Overall Survival



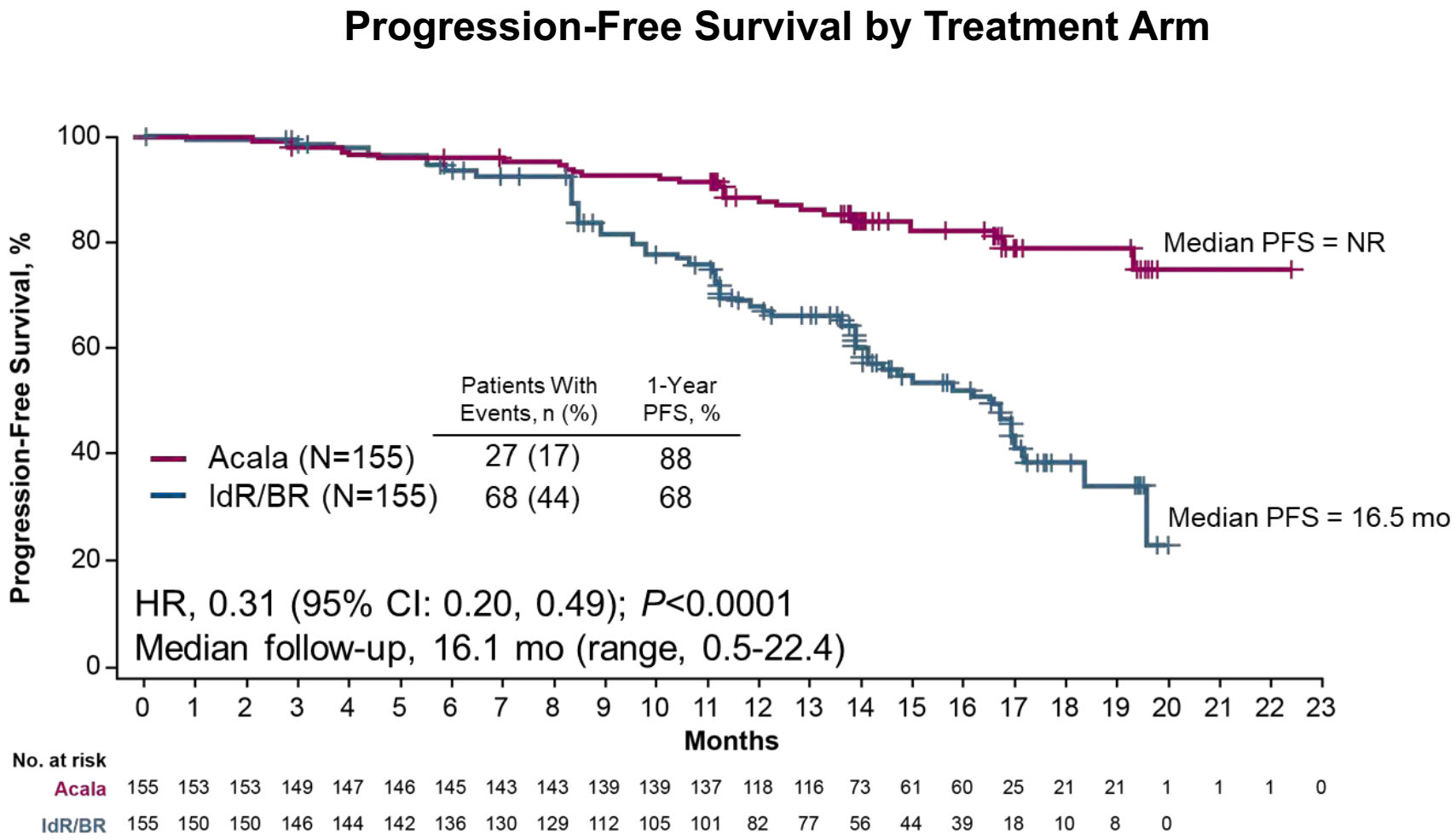

BR, bendamustine plus rituximab; ITT, intention to treat; OS, overall survival; VenR, venetoclax plus rituximab

| | VenR (n = 194) | BR (n = 195) | HR (95% CI) | P Value |
|---|---|---|---|---|
| 4-yr PFS, % | 57.3 | 4.6 | 0.19 (0.14-0.25) | < .0001 |
| 4-yr OS, % | 85.3 | 66.8 | 0.41 (0.26-0.65) | < .0001 |

Seymour JF et al. ASH 2019. Abstract 134.

Courtesy of Kerry Rogers, MD

# ASCEND Primary Endpoint




Ghia et al., EHA 2019

Courtesy of Kerry Rogers, MD

The James

The Ohio State University
Comprehensive Cancer Center

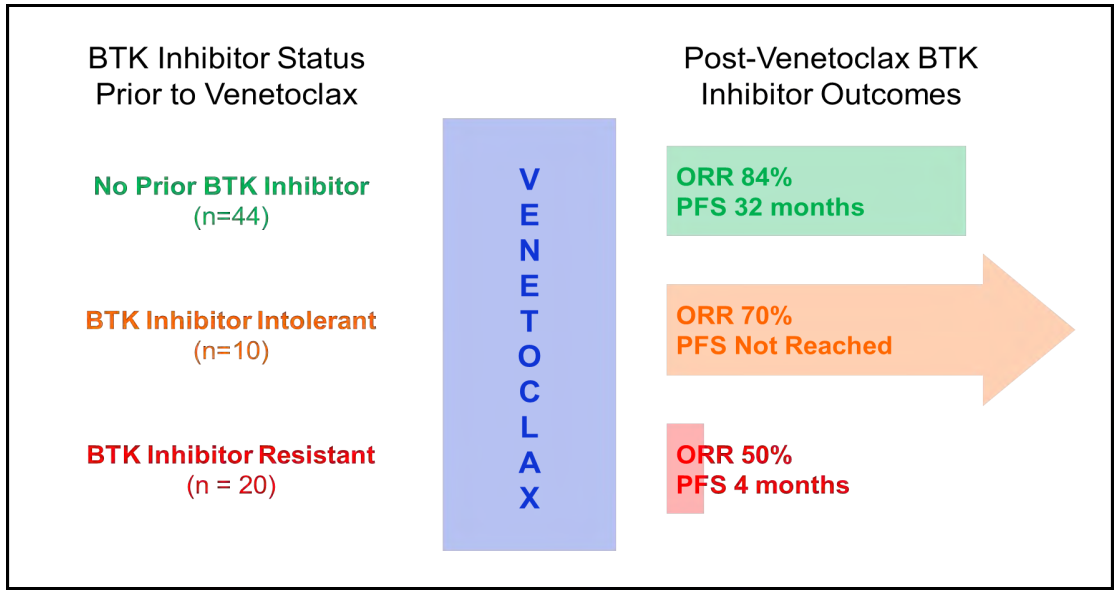
# The PI3K Inhibitors

| | Idelalisib | Duvelisib | *Umbralisib* |
|---|---|---|---|
| **Isoform Specificity** | **δ** | **δ/γ** | **δ** |
| **Approval** | ▪ R/R CLL in combination with rituximab<br>▪ R/R SLL CLL after ≥2 prior treatments | ▪ R/R CLL after ≥2 prior treatments | *Currently being investigated in combination trials* |
| **Phase 3 Trial** | ▪ **Median PFS not Reached**<br>▪ R-Placebo 5.5 mo<br>▪ HR 0.15, P<0.001 | ▪ **Median PFS 13.3 months**<br>▪ Ofatumumab 9.9 mo<br>▪ HR 5 0.52, P<.0001 | |
| **Major Toxicities** | ▪ Colitis<br>▪ Pneumonitis<br>▪ Hepatitis<br>▪ Infections | ▪ Infection<br>▪ Colitis<br>▪ Rash<br>▪ Pneumonitis | |

Furman et al., NEJM 2014; Flinn et al., Blood 2018

Courtesy of Kerry Rogers, MD

# Ibrutinib After Venetoclax?




- Multi-institution cohort study of venetoclax discontinuation (n=326; BTKi n=74)
  - BTKi were effective if not previously resistant
- (MURANO Study Subsequent BTKi Treatment (n=12)
  - BTKi 10/10 (100%) evaluable responded
  - Venetoclax re-treatment 6/11 (55%) evaluable

Mato et al., Clinical Cancer Research 2020; Seymour JF et al. ASH 2019. Abstract 134.

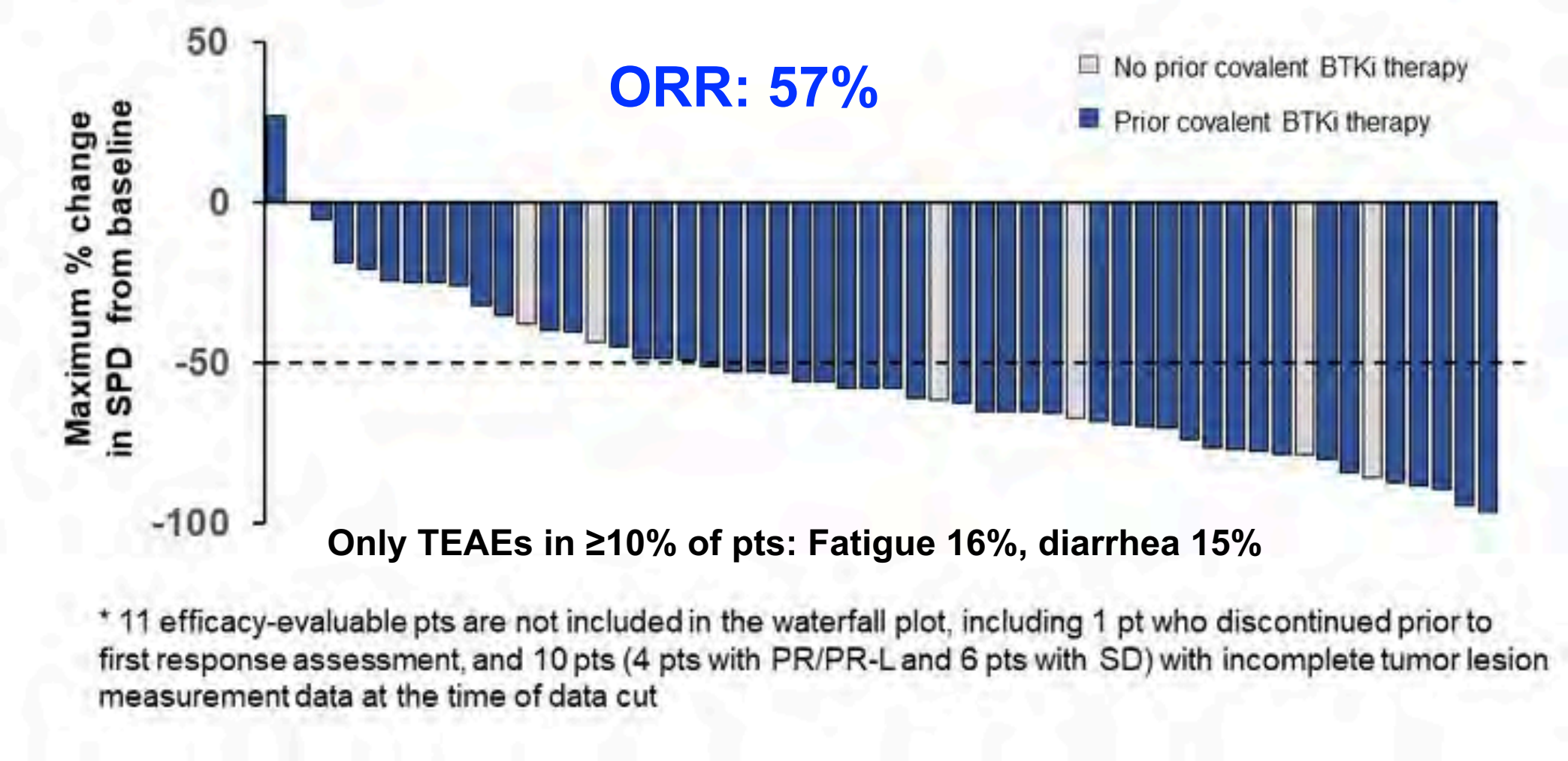
Courtesy of Kerry Rogers, MD

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

Mato AR et al.

ASH 2020;Abstract 542.

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



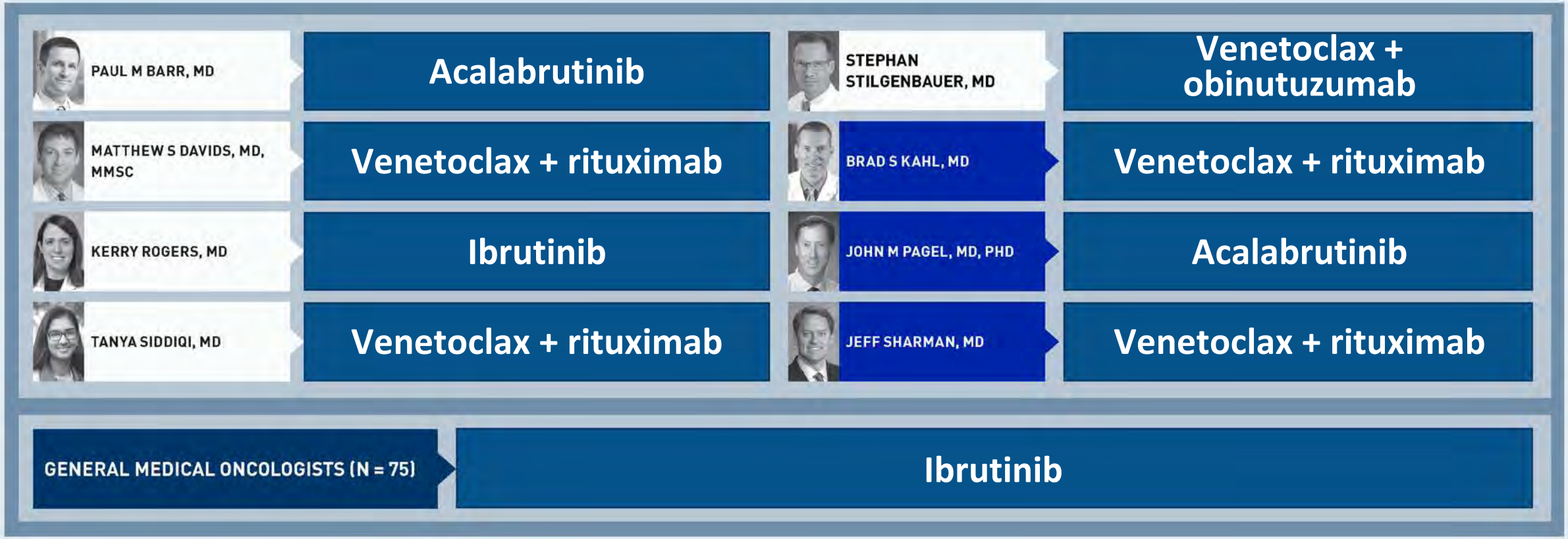

Mato AR et al. ASH 2020;Abstract 542.

## Which second-line systemic therapy would you recommend for a 60-year-old patient with IGHV-mutated CLL without del(17p) or TP53 mutation who responds to FCR and then experiences disease progression 3 years later?

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

RTP
RESEARCH
TO PRACTICE

# Which second-line systemic therapy would you recommend for a 60-year-old patient with IGHV-mutated CLL without del(17p) or TP53 mutation who responds to FCR and then experiences disease progression 3 years later?

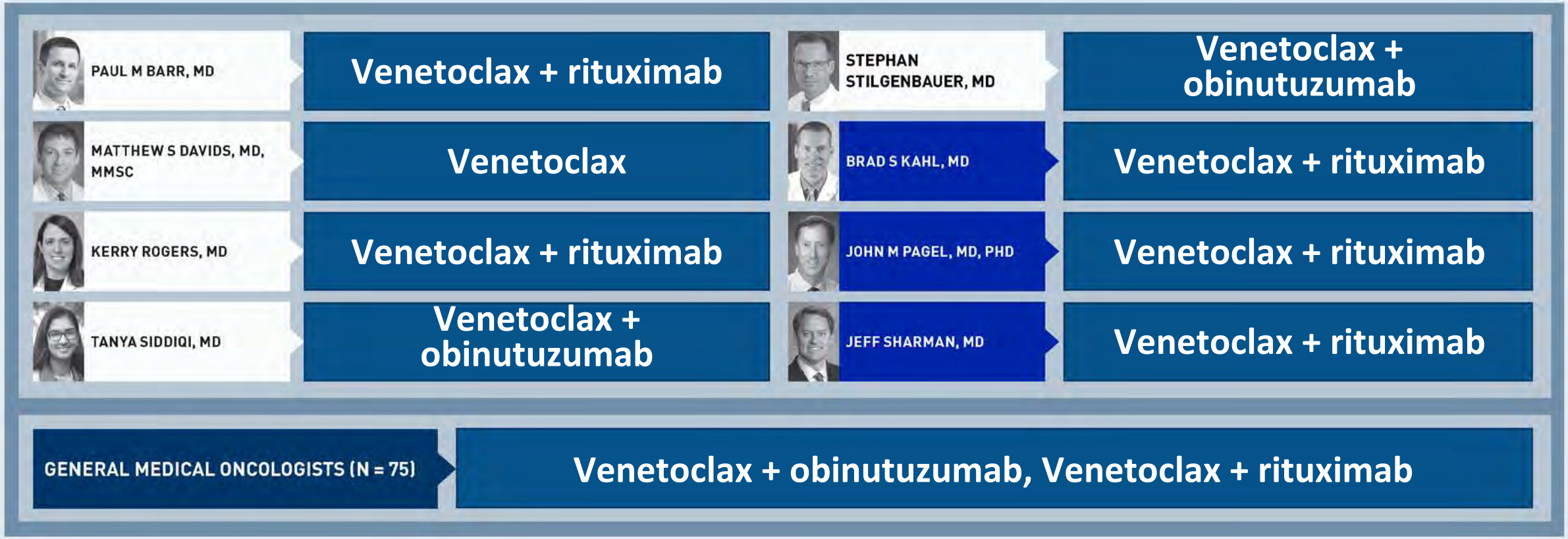


**Which second-line systemic therapy would you recommend for a 60-year-old patient with IGHV-unmutated CLL without del(17p) or TP53 mutation who responds to ibrutinib and then experiences disease progression 3 years later?**

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

RTP RESEARCH TO PRACTICE

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



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

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

RTP RESEARCH TO PRACTICE

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

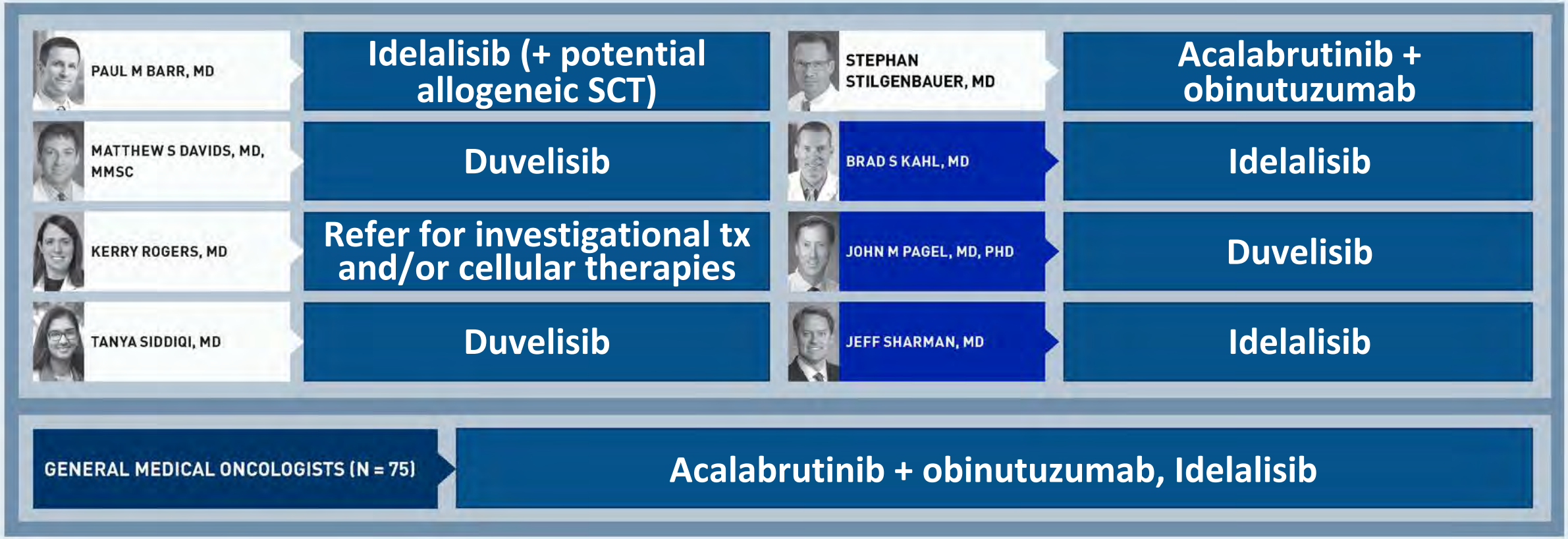
| | | | |
|---|---|---|---|
|  PAUL M BARR, MD | Acalabrutinib |  STEPHAN STILGENBAUER, MD | Venetoclax + obinutuzumab |
|  MATTHEW S DAVIDS, MD, MMSC | Venetoclax + obinutuzumab |  BRAD S KAHL, MD | Acalabrutinib |
|  KERRY ROGERS, MD | Ibrutinib |  JOHN M PAGEL, MD, PHD | Acalabrutinib |
|  TANYA SIDDIQI, MD | Acalabrutinib + obinutuzumab |  JEFF SHARMAN, MD | Acalabrutinib |

| | |
|---|---|
| GENERAL MEDICAL ONCOLOGISTS (N = 75) | Acalabrutinib, Acalabrutinib + obinutuzumab |

**Which third-line therapy would you generally recommend for a 60-year-old patient with IGHV-unmutated CLL without del(17p) or TP53 mutation who responds to ibrutinib for 3 years, experiences disease relapse, then receives venetoclax for 18 months followed by disease progression?**

1. BR
2. Acalabrutinib
3. Acalabrutinib + obinutuzumab
4. Idelalisib
5. Duvelisib
6. Other

# Which third-line therapy would you generally recommend for a 60-year-old patient with IGHV-unmutated CLL without del(17p) or TP53 mutation who responds to ibrutinib for 3 years, experiences disease relapse, then receives venetoclax for 18 months followed by disease progression?




CAR = chimeric antigen receptor

# Case Presentation – Dr Rogers: A 53-year-old woman with relapsed/refractory CLL

- 2007 – Lymphocytosis noted on routine CBC
  - Diagnosed by peripheral blood flow
  - Observed
- June 2011 – FCR x5
  - Treatment started due to LAD
  - IGHV indeterminate, FISH panel negative
  - Stopped after 5 cycles due to prolonged neutropenia
  - Observed after treatment
- January 2015
  - Again noted enlarging lymph nodes
  - Repeat FISH panel +del17p
  - Discussed treatment options

PHM/PSH:
- *Depression*
- *Hypertension*
- *Insomnia*
- *Endometriosis*
- *s/p tubal ligation*
- *s/p cholecystectomy*
- *s/pORIF R ankle*

Meds:
- *Lisinopril*
- *Sertraline*
- *Valacyclovir*

Allergies:
- *Trimethoprim-sulfamethoxazole*

Social:
- *Never smoker*
- *No alcohol use*
- *Married*
- *Social worker*

Family:
- *Hypertension*

Courtesy of Kerry Rogers, MD

# Case Presentation – Dr Rogers: A 53-year-old woman with relapsed/refractory CLL (continued)

- March 2015 – Started ibrutinib 420mg
  - Lymph nodes improved
  - Some diarrhea and arthritis
- May 2015 – Developed painful skin nodules
  - Biopsy proven panniculitis
  - Recurred after several courses of prednisone 20mg
  - Did not improve with dose reduction to 280mg
  - Ibrutinib discontinued
- December 2015
  - Developed debilitating fatigue, night sweats, and enlarging lymph nodes
  - Discussed treatment options

PHM/PSH:
*Depression*
*Hypertension*
*Insomnia*
*Endometriosis*
*s/p tubal ligation*
*s/p cholecystectomy*
*s/pORIF R ankle*

Meds:
*Lisinopril*
*Sertraline*
*Valacyclovir*

Allergies:
*Trimethoprim-sulfamethoxazole*

Social:
*Never smoker*
*No alcohol use*
*Married*
*Social worker*

Family:
*Hypertension*

Courtesy of Kerry Rogers, MD

# Case Presentation – Dr Rogers: A 53-year-old woman with relapsed/refractory CLL (continued)

- January 2016 – Started acalabrutinib
  - All symptoms improved
  - Developed a few non-painful skin nodules
  - Good disease response
- October 2018 – Progressive disease
  - Developed enlarged lymph nodes and night sweats
  - ALC increased
  - Discussed treatment options
- October 2018 – Started venetoclax
  - Good response of the CLL
  - Chronic diarrhea impairing her lifestyle
- October 2020 – Progressive disease

PHM/PSH:
*Depression*
*Hypertension*
*Insomnia*
*Endometriosis*
*s/p tubal ligation*
*s/p cholecystectomy*
*s/pORIF R ankle*

Meds:
*Lisinopril*
*Sertraline*
*Valacyclovir*

Allergies:
*Trimethoprim-sulfamethoxazole*

Social:
*Never smoker*
*No alcohol use*
*Married*
*Social worker*

Family:
*Hypertension*

Courtesy of Kerry Rogers, MD

# Agenda

Module 1: First-line treatment options for younger, fit patients — Dr Barr

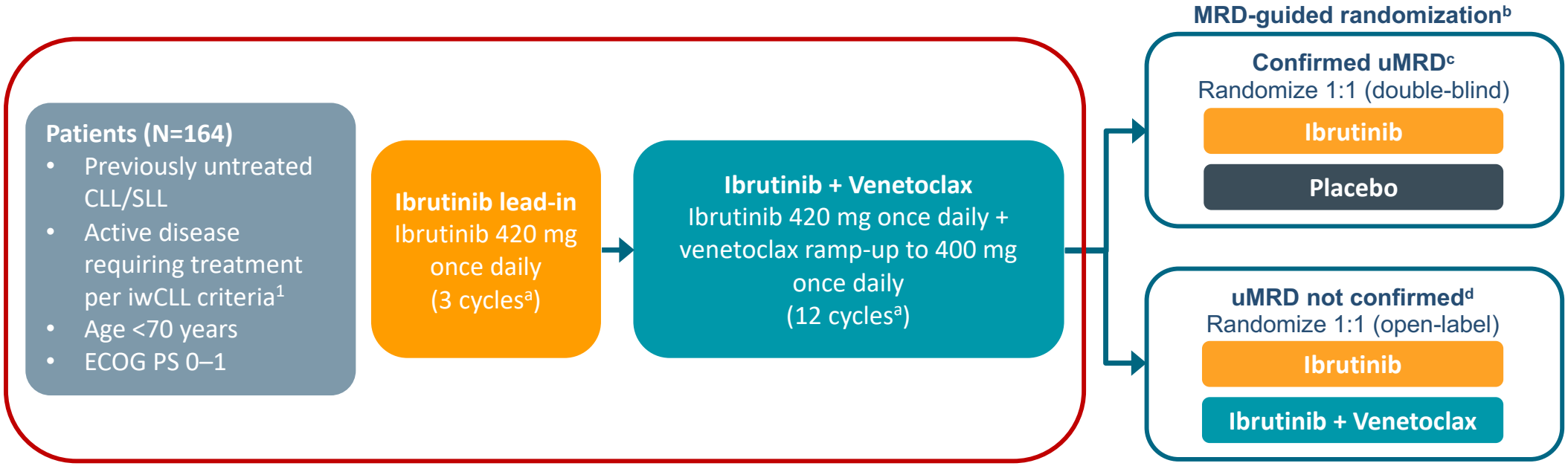
Module 2: Up-front management of chronic lymphocytic leukemia in older patients or those with comorbidities — Dr Stilgenbauer

Module 3: Optimal management of adverse events with BTK and Bcl-2 inhibitors — Dr Davids

Module 4: Selection and sequencing of therapies for relapsed/refractory disease — Dr Rogers

**Module 5: Novel strategies under investigation — Dr Siddiqi**

# CAPTIVATE MRD Cohort: Study Design




- Results are presented for pre-randomization phase of the CAPTIVATE MRD cohort (N=164) with 12 cycles of ibrutinib + venetoclax prior to MRD-guided randomization
- Time-limited therapy with 12 cycles of ibrutinib + venetoclax to be evaluated in a separate fixed-duration cohort (N=159)

[a]1 cycle = 28 days; patients may have received 1 additional cycle while awaiting confirmation of undetectable MRD for randomization. [b]Stratified by IGHV mutation status. [c]Confirmed as having undetectable MRD ($<10^{-4}$ by 8-color flow cytometry) serially over at least 3 cycles in PB, and undetectable MRD in both PB and BM. [d]Defined as having detectable MRD or undetectable MRD not confirmed serially or not confirmed in both PB and BM.

1. Hallek M et al. *Blood*. 2008;111:5446-5456.

# High Rates of Undetectable MRD Achieved in PB and BM With Up to 12 Cycles of I + V Combination

| | Peripheral Blood n=163 | Bone Marrow[a] n=155 |
|---|---|---|
| **Best response of undetectable MRD in evaluable patients[b]** (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
- Proportion of patients with undetectable MRD in peripheral blood increased over the 12 cycles of combination therapy
- At 15 months, 98% of patients were progression free with no deaths

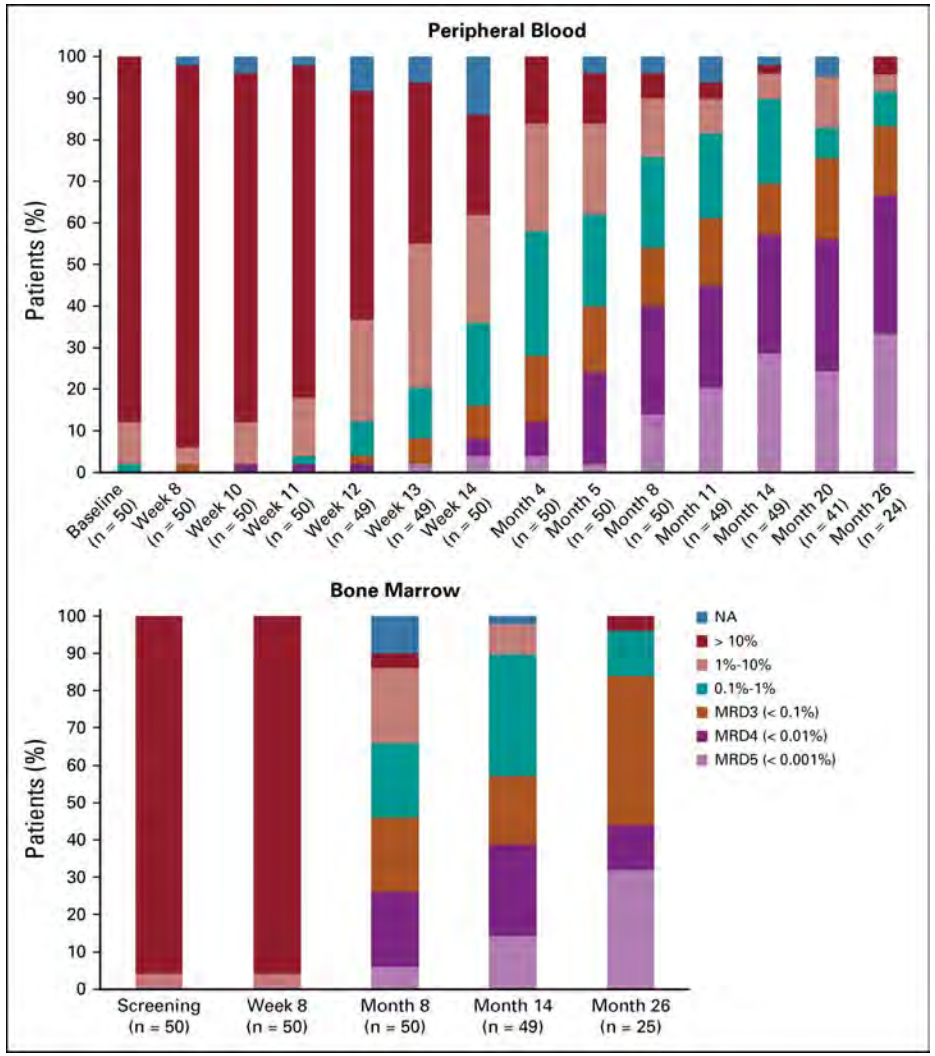
[a]BM MRD assessment was scheduled after completion of 12 cycles of combination treatment.
[b]Patients with undetectable MRD at any postbaseline assessment; evaluable patients are those who had at least 1 MRD sample taken postbaseline.



EHA 2020, CAPTIVATE-MRD; Siddiqi et al.

Courtesy of Tanya Siddiqi, MD

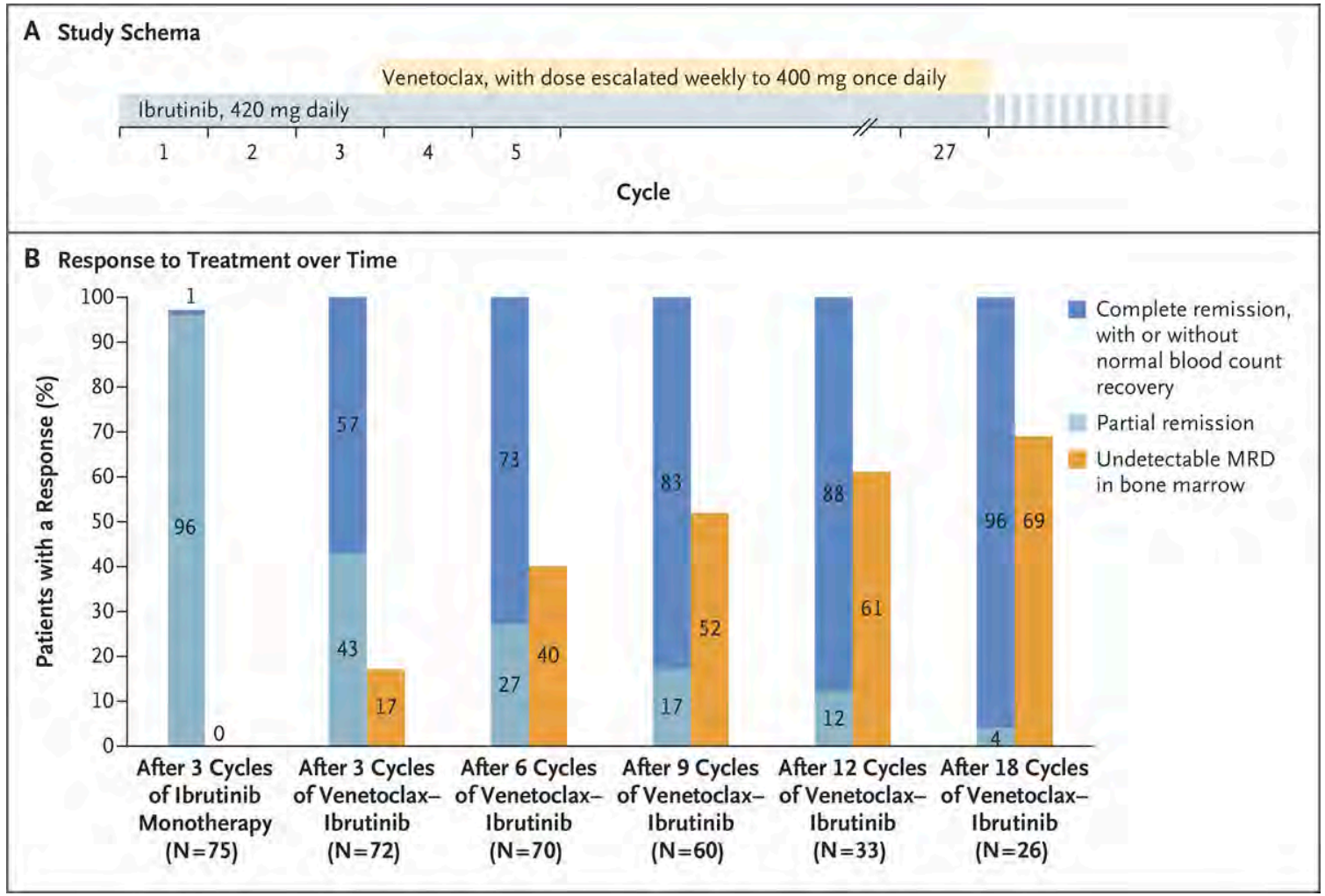
# CLARITY Ph2 trial (up to 2 yrs of treatment)




Hillmen P, et al. J Clin Oncol 2019; 37:2722-2729

Courtesy of Tanya Siddiqi, MD

# MDACC: IIT, Ph2, frontline high risk and older CLL pts, I+V for 24 cycles

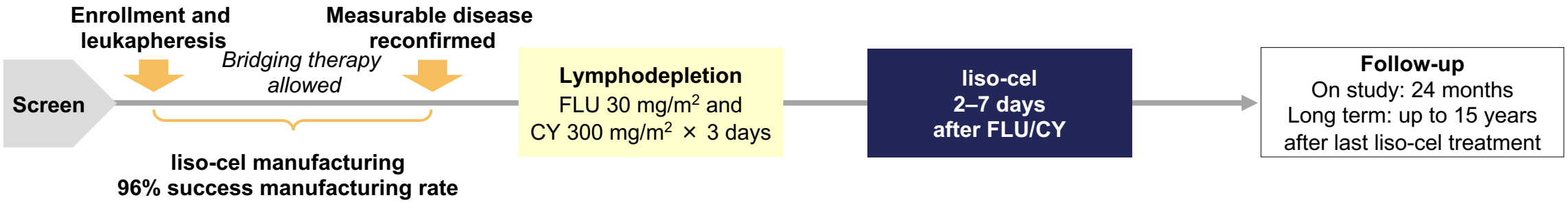



N Jain et al. N Engl J Med 2019;380:2095-2103.

Courtesy of Tanya Siddiqi, MD

# CAR T cell therapy in CLL

## TRANSCEND CLL 004 Study Design




**Key Eligibility**

- Relapsed/refractory CLL/SLL
- Failed or ineligible for BTKi
- High-risk disease: failed ≥2 prior therapies
- Standard-risk disease: failed ≥3 prior therapies
- ECOG PS of 0–1

**Dose Escalation: mTPI-2 Design**

**28-day DLT period**

***Primary Objectives***

- Safety
- Determine recommended dose

***Exploratory Objectives***

- Antitumor activity
- Pharmacokinetic profile

| Dose Level | Dose | Evaluable (N=23) |
|---|---|---|
| 1 | 50 × $10^6$ CAR+ T cells | 9 |
| 2 | 100 × $10^6$ CAR+ T cells | 14 |



Siddiqi T, et al. ASH annual mtg 2019

Courtesy of Tanya Siddiqi, MD

# Incidence and Management of CRS and NEs

| | All Patients (N=23) |
|---|---|
| **CRS—any grade, n (%)** | 17 (74) |
| Median time to first onset, days (range) | 4 (1–10) |
| Median duration of first event, days (range) | 12 (2–50) |
| Grade 3, n (%) | 2 (9) |
| **NE[a]—any grade, n (%)** | 9 (39) |
| Median time to first onset, days (range) | 4 (2–21) |
| Median duration of first event, days (range) | 21 (6–56) |
| Grade ≥3,[b] n (%) | 5 (22) |
| **Any CRS or NE, n (%)** | 18 (78) |
| **CRS only, n (%)** | 9 (39) |
| **NE only, n (%)** | 1 (4) |
| **Tocilizumab and/or steroid use** | |
| Tocilizumab only | 5 (22) |
| Steroids only | 3 (13) |
| Both tocilizumab and steroids | 9 (39) |
| Tocilizumab and/or steroid use | 17 (74) |

- No grade 5 CRS or NE occurred

[a]NEs are liso-cel related neurologic adverse events defined by the investigator; [b]NEs are not mutually exclusive; encephalopathy (n=3); aphasia (n=1); confusional state (n=1); muscular weakness (n=1); somnolence (n=1). BTKi, Bruton tyrosine kinase inhibitor; CRS, cytokine release syndrome; NE, neurological events; TEAEs, treatment-emergent adverse events.



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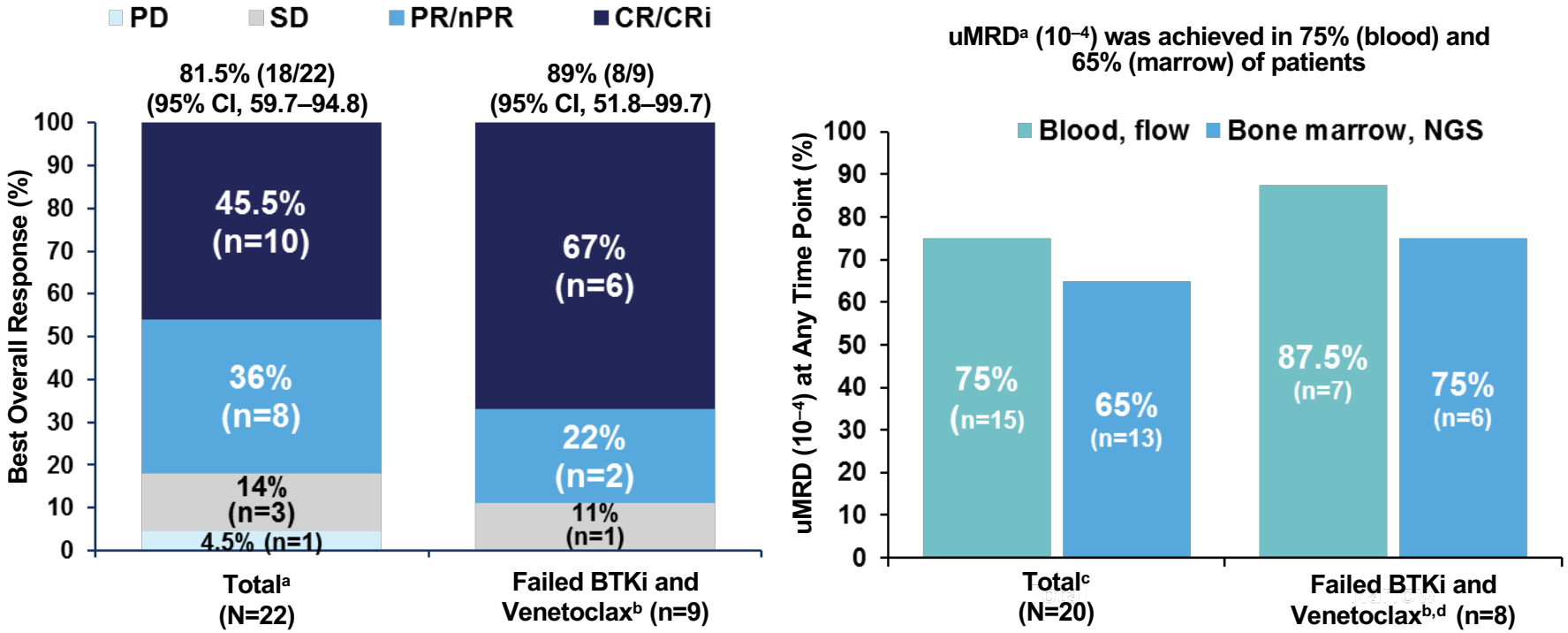
Courtesy of Tanya Siddiqi, MD

# Best Overall Response and Undetectable MRD




**Median study follow-up: 11 months**

All percentages are rounded to whole numbers except those ending in .5. [a]Evaluable for response defined as having a pretreatment assessment and ≥1 postbaseline assessment. One patient was not evaluable for response. [b]Failed venetoclax defined as discontinuation due to PD or <PR after ≥3 months of therapy. [c]Evaluable for MRD was defined as patients with detectable MRD at baseline. Two patients were not evaluable for MRD. [d]One patient in this subset was not evaluable for MRD. BTKi, Bruton tyrosine kinase inhibitor; CI, confidence interval; CR, complete response; CRi, complete response with incomplete blood count recovery; MRD, minimal residual disease; NGS, next-generation sequencing; nPR, nodular partial response; PD, progressive disease; PR, partial response; SD, stable disease; uMRD, undetectable minimal residual disease.



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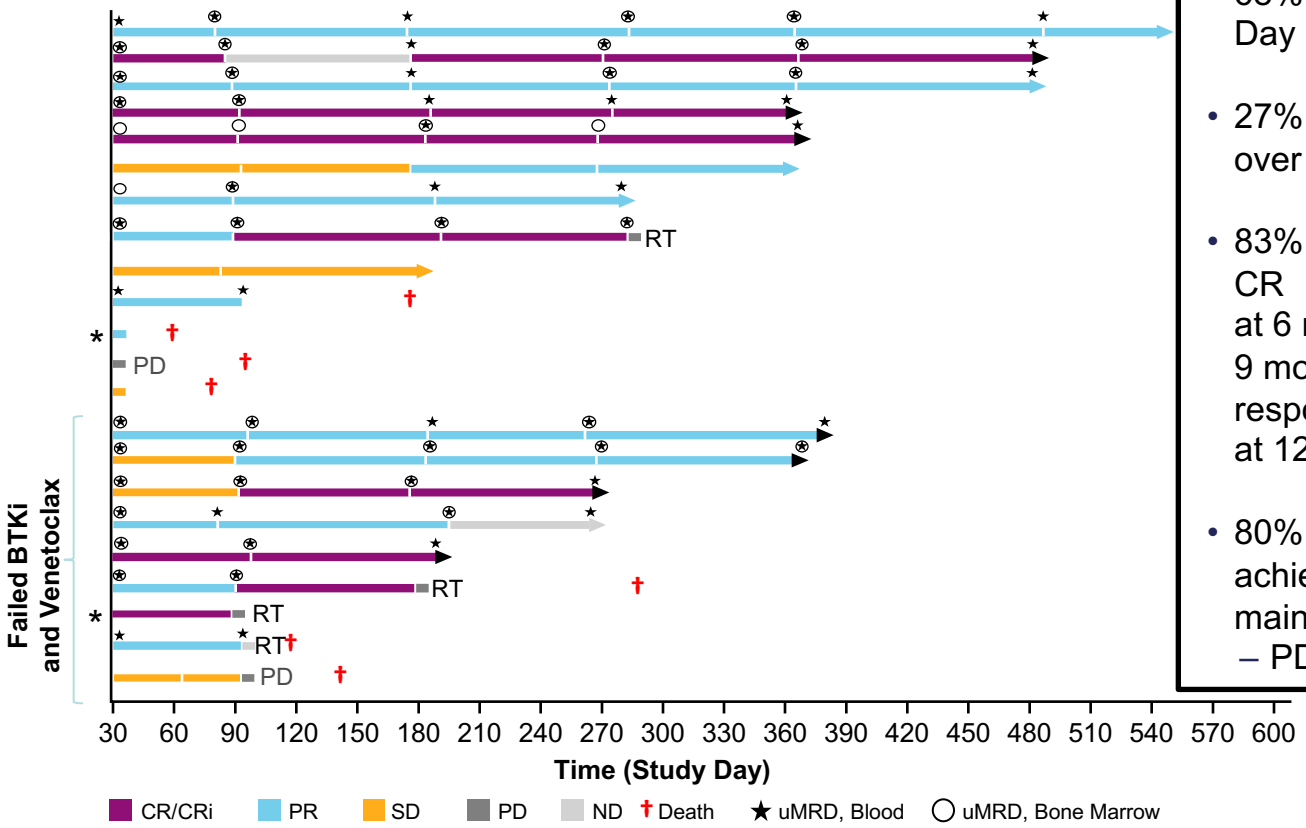
Courtesy of Tanya Siddiqi, MD

# Individual Patient Response Assessments




- 68% (15/22) had a response by Day 30
- 27% (6/22) of responses deepened over time
- 83% (10/12) of patients with PR or CR
  at 6 months remain in response at 9 months, with 8 patients in response
  at 12 months or longer
- 80% (12/15) of patients who achieved uMRD in blood maintained their responses
  – PDs were all with RT

*MRD non-evaluable. There were 7 on-study deaths: 5 patients died from disease progression; 1 patient had grade 5 respiratory failure (DL1) unrelated to liso-cel treatment; 1 patient had septic shock, acute kidney injury, and pneumonia (DL2), unrelated to liso-cel treatment. No deaths occurred within the first 30 days. BTKi, Bruton tyrosine kinase inhibitor; CR, complete response; CRi, complete response with incomplete blood count recovery; DL, dose level; MRD, minimal residual disease; ND, not done; PD, progressive disease; PR, partial response; RT, Richter transformation; SD, stable disease; uMRD, undetectable MRD.



Siddiqi T, et al. ASH annual mtg 2019

Courtesy of Tanya Siddiqi, MD

# Other ongoing CAR T-cell trials in CLL

- ZUMA-8 (axi-cel)
- JCAR014 + ibrutinib
- CTL019 + ibrutinib
- Novel CAR T targets like ROR1 and CD22
- Off-the-shelf CAR T-cell trials



Courtesy of Tanya Siddiqi, MD

# At what point in the treatment course are you referring patients with multiple regimen-relapsed CLL for consultation regarding CAR T-cell therapy?

1. At first relapse
2. At second relapse
3. At third relapse
4. Other
5. I am not referring patients for CAR T-cell therapy

# At what point in the treatment course are you referring patients with multiple regimen-relapsed CLL for consultation regarding CAR T-cell therapy?

| | |
|---|---|
|  PAUL M BARR, MD | At third relapse |
|  MATTHEW S DAVIDS, MD, MMSC | At third relapse |
|  KERRY ROGERS, MD | At second relapse |
|  TANYA SIDDIQI, MD | At second relapse |
|  STEPHAN STILGENBAUER, MD | After third relapse |
|  BRAD S KAHL, MD | At third relapse |
|  JOHN M PAGEL, MD, PHD | At third relapse |
|  JEFF SHARMAN, MD | At second relapse |
| GENERAL MEDICAL ONCOLOGISTS (N = 75) | At third relapse |

# Case Presentation - Dr Siddiqi: A 67-year-old man with relapsed/refractory CLL – del(13q), del(11q), no IGHV mutation

- 67 yo Caucasian man seen in consultation on 9/18/17
- CLL/SLL diagnosed in 10/2006: high WBCs, ZAP70 pos, del13q, del11q, unmutated IGHV
- Rituximab+lenalidomide x7 (through 10/2008)
- At PD, high dose methylpred + ofatumumab x3
- Nodular PR then PD
- Ibrutinib (with rituximab initially) through 10/2015 when he developed blistering rash and stopped this drug
- Venetoclax started 3/2016 – PR initially but then PD (drug stopped 8/2017)
- High dose methylpred + obinutuzumab



Courtesy of Tanya Siddiqi, MD

# Case Presentation - Dr Siddiqi: A 67-year-old man with relapsed/refractory CLL – del(13q), del(11q), no IGHV mutation (continued)

- Enrolled on liso-cel CAR T-cell trial
- Idelalisib controlled disease during cell manufacturing
- Received liso-cel cells on 1/31/18 after Flu/Cy lymphodepletion
- Complications included TLS, CRS, encephalopathy requiring ICU stay, CMV reactivation
- MRD positive remission at Day 30 that deepened to uMRD
- Remains in remission almost 3 years later



Courtesy of Tanya Siddiqi, MD

# Case Presentation – Dr Siddiqi: A 40-year-old man with previously untreated CLL – del(13q)

- 36 yo M with previously untreated CLL/SLL and del13q had rapid lymphocyte doubling time and progressing lymphadenopathy soon after diagnosis in 2016
- He consented to participate in the CAPTIVATE Ph2 trial and enrolled on the MRD cohort
- After 16 cycles of combination I+V therapy. He achieved MRD undetectable CR and was randomized to ibrutinib maintenance vs. placebo on 1/25/2018
- He remains on study on maintenance and has no toxicity



Courtesy of Tanya Siddiqi, MD

# Consensus or Controversy? Investigators Discuss Clinical Practice Patterns and Available Research Data Guiding the Management of Hematologic Cancers

# Acute Myeloid Leukemia

**Friday, December 4, 2020**
**3:00 PM – 4:30 PM Pacific Time**

## Faculty


**Mark Levis, MD, PhD**
**Alexander Perl, MD**
**Daniel A Pollyea, MD, MS**
**Eytan M Stein, MD**
**Professor Andrew H Wei, MBBS, PhD**


## Moderator


**Neil Love, MD**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*Thank you for joining us!*

*CME credit information will be emailed to each participant within 3 business days.*

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