# Key Questions and Emerging Research in the Management of Chronic Lymphocytic Leukemia and Follicular Lymphoma

**Wednesday, June 24, 2020**
**5:00 PM – 6:00 PM ET**


## Faculty

**Jeff Sharman, MD**
**Julie M Vose, MD, MBA**

## Moderator

**Neil Love, MD**

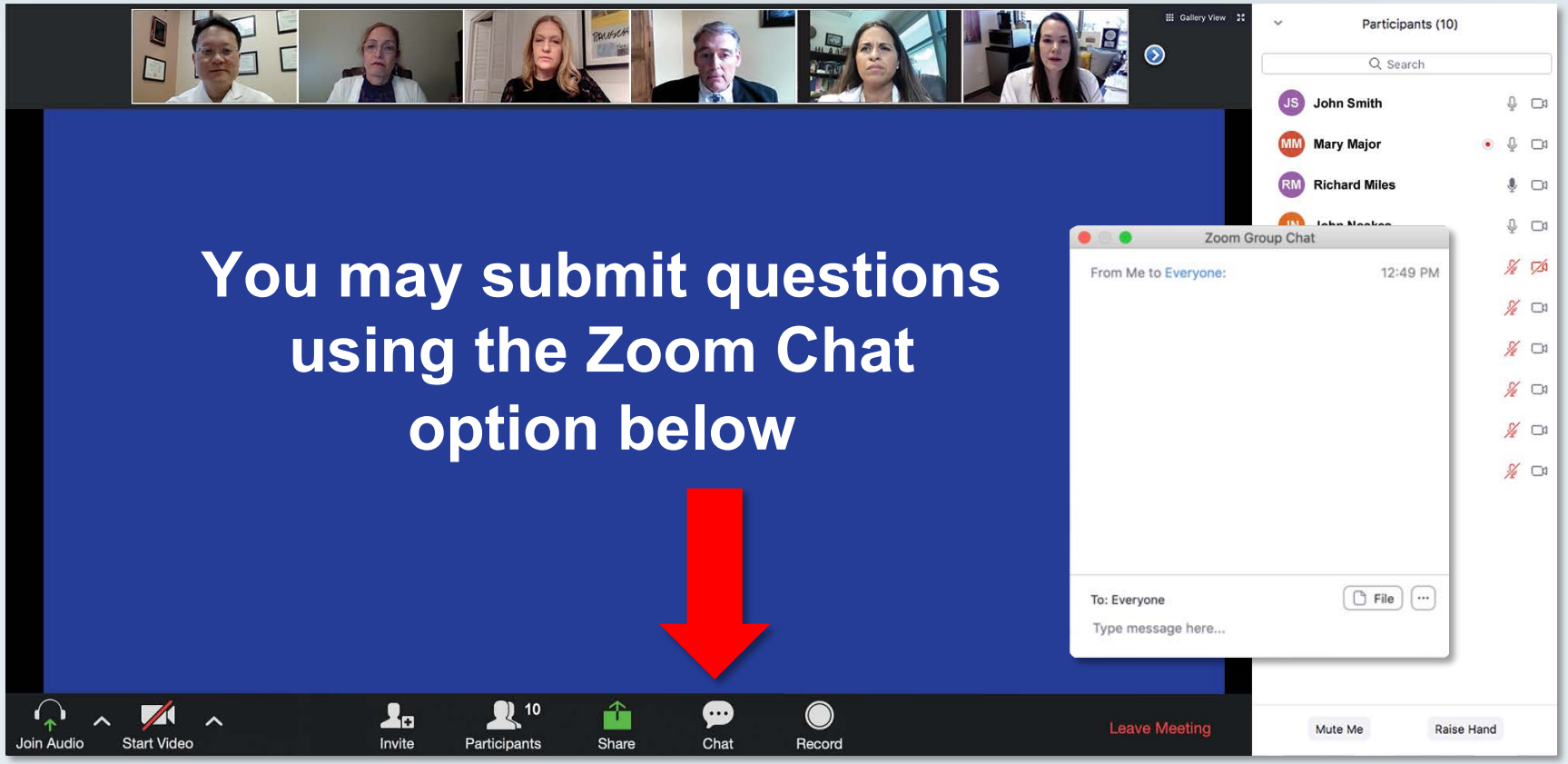

RTP RESEARCH TO PRACTICE

# Faculty

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

**Julie M Vose, MD, MBA**
Neumann M and Mildred E Harris Professor
Chief, Division of Hematology/Oncology
Nebraska Medical Center
Omaha, Nebraska

# Dr Love and Faculty Encourage You to Ask Questions




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

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# Acute Myeloid Leukemia and the General Medical Oncologist: New Agents and Treatment Strategies, Particularly for Older Patients

*A Meet The Professor Series*

**Thursday, June 25, 2020**
**12:00 PM – 1:00 PM ET**

**Richard M Stone, MD**
Chief of Staff
Director, Translational Research Leukemia Division
Dana-Farber Cancer Institute
Professor of Medicine
Harvard Medical School
Boston, Massachusetts

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# Oncology Grand Rounds

## New Agents and Strategies in PARP Inhibition in the Management of Common Cancers

**Thursday, June 25, 2020**

**5:00 PM – 6:30 PM ET**

### Faculty


**Emmanuel S Antonarakis, MD**
**Gretchen Santos Fulgencio, MSN, FNP-BC**
**Erika Meneely, APRN, BC**
**Kathleen Moore, MD**
**Joyce O'Shaughnessy, MD**
**Michael J Pishvaian, MD, PhD**
**Deborah Wright, MSN, APRN, CNS**


### Moderator


**Neil Love, MD**


Research To Practice®

# Clinical Investigator Perspectives on the Current and Future Management of Multiple Myeloma

## *A Meet The Professor Series*

**Friday, June 26, 2020**
**12:00 PM – 1:00 PM ET**

**Nikhil C Munshi, MD**
Professor of Medicine, Harvard Medical School
Director of Basic and Correlative Science
Associate Director, Jerome Lipper Multiple Myeloma Center
Department of Medical Oncology
Dana-Farber Cancer Institute
Boston, Massachusetts

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# Conversations with the Investigators: Prostate Cancer

**Wednesday, July 1, 2020**
**5:00 PM – 6:00 PM ET**

## Faculty

**Robert Dreicer, MD, MS, MACP, FASCO**
**Daniel P Petrylak, MD**
**Christopher Sweeney, MBBS**
***Additional faculty to be announced***

## Moderator

**Neil Love, MD**

RTP RESEARCH TO PRACTICE

# COVID-19 AND LUNG CANCER

## What We Know, What We Don't Know and What It All Means for Current Patient Care – *A Live CME Webinar*

**Thursday, July 2, 2020**
**12:00 PM – 1:00 PM ET**

**Moderator**
**Neil Love, MD**

**Faculty**
**Leora Horn, MD, MSc**
**Naiyer A Rizvi, MD**
**Lecia V Sequist, MD, MPH**

# Key Questions and Emerging Research in the Management of Chronic Lymphocytic Leukemia and Follicular Lymphoma

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RTP RESEARCH TO PRACTICE

# About the Enduring Program

- This webinar is being video and audio recorded.
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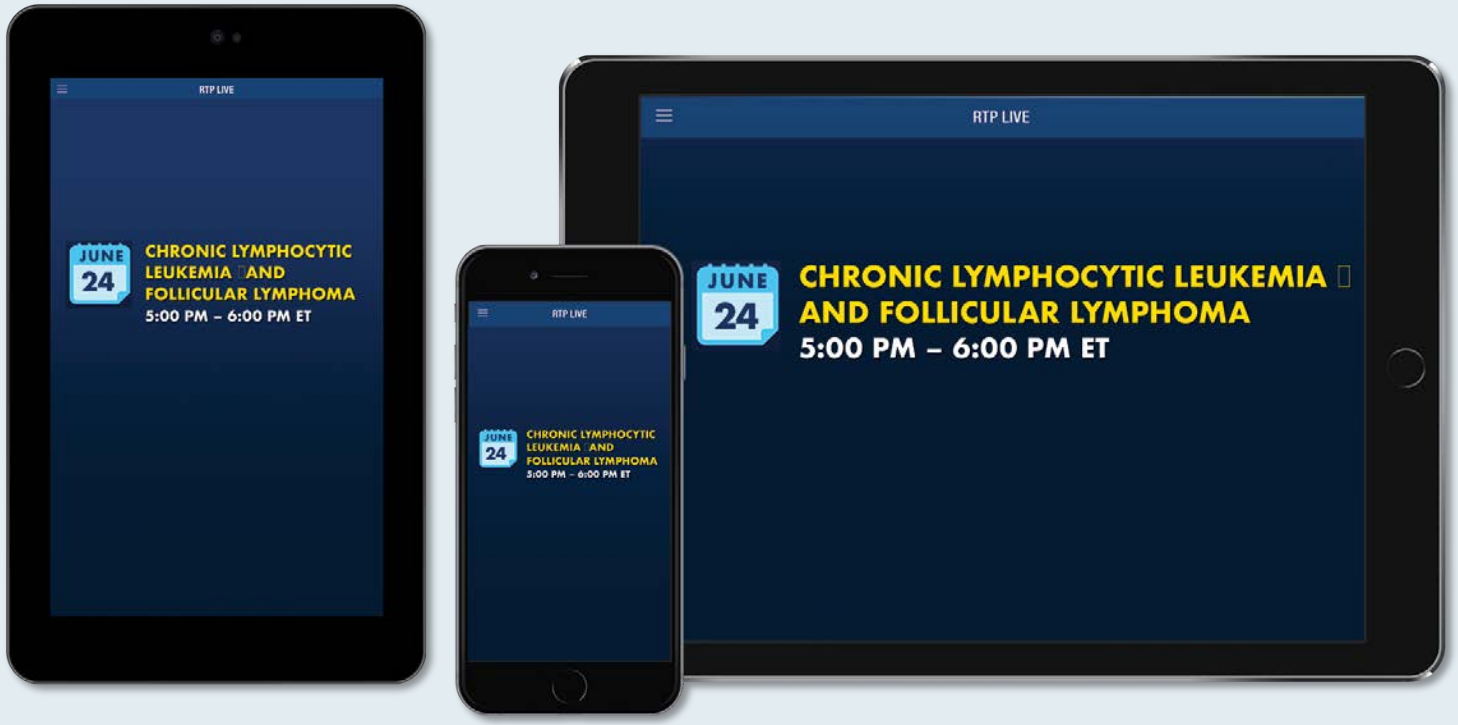


# Agenda

## Module 1: Chronic Lymphocytic Leukemia (CLL) – Dr Sharman

- Phase III trials of ibrutinib-based therapy in younger (ECOG-E1912) and older (A041202, RESONATE-2) patients
- Acalabrutinib for treatment-naïve (ELEVATE-TN) and relapsed/refractory CLL (ASCEND)
- Long-term follow-up of venetoclax-based therapy for newly diagnosed (CLL14) and relapsed CLL (MURANO)
- PI3 kinase inhibitors idelalisib and duvelisib in relapsed CLL
- Ongoing trials

## Module 2: Follicular Lymphoma – Dr Vose

- Role of obinutuzumab-based chemoimmunotherapy for treatment-naïve FL (GALLIUM)
- Lenalidomide/rituximab (R-squared) in the up-front (RELEVANCE) and relapsed/refractory settings (AUGMENT)
- Comparison of FDA-approved PI3 kinase inhibitors in FL: idelalisib, duvelisib and copanlisib

# Module 1: Chronic Lymphocytic Leukemia (CLL) – Dr Sharman

- Selection of first-line treatment
- BTK inhibitor tolerability profiles
- Adding an anti-CD20 antibody to a BTK inhibitor
- Management of MRD positivity after venetoclax/obinutuzumab
- Sequencing of venetoclax and anti-CD20 antibodies
- Recent relevant publications

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

a. FCR (fludarabine/cyclophosphamide/rituximab)

b. BR (bendamustine/rituximab)

c. Ibrutinib

d. Ibrutinib + rituximab

e. Ibrutinib + obinutuzumab

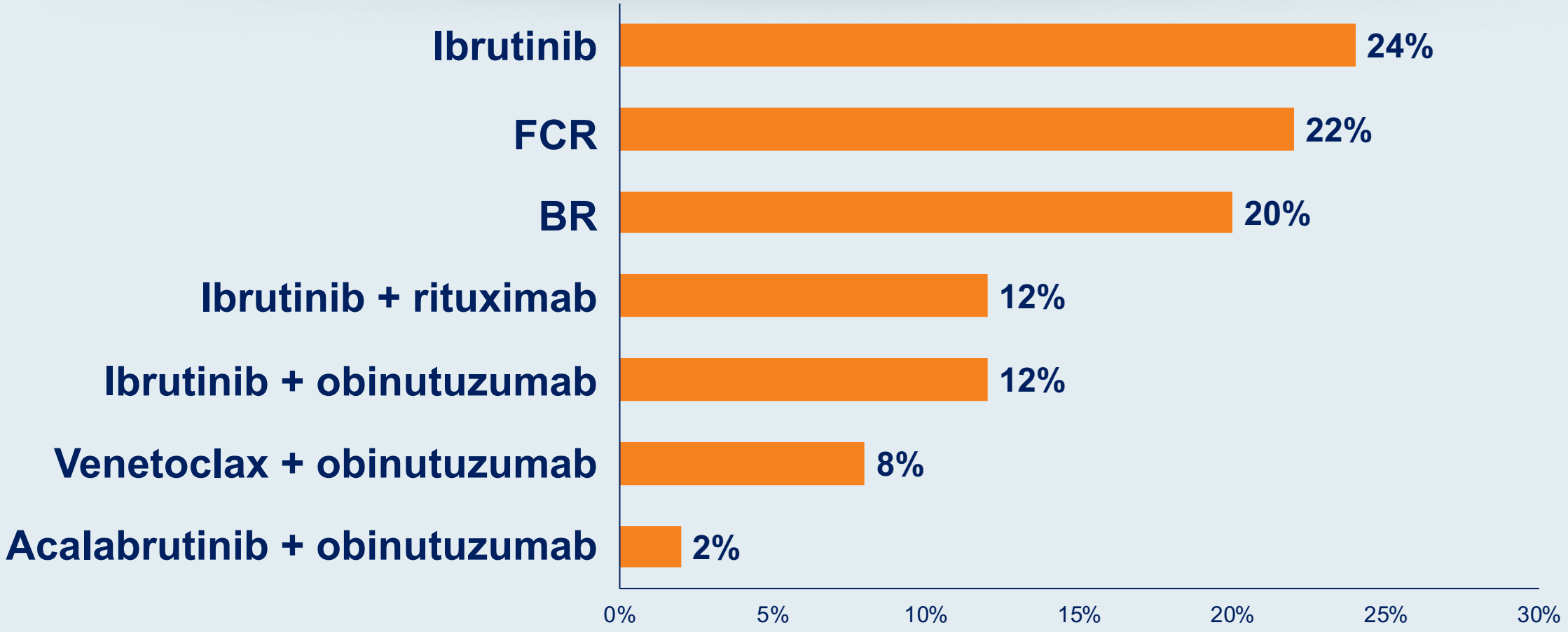
f. Acalabrutinib

g. Acalabrutinib + obinutuzumab

h. Venetoclax + obinutuzumab

i. Other

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




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

Survey of 50 US-based medical oncologists, June 2020

**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?**

a. FCR

b. BR

c. Ibrutinib

d. Ibrutinib + rituximab

e. Ibrutinib + obinutuzumab

f. Acalabrutinib

g. Acalabrutinib + obinutuzumab

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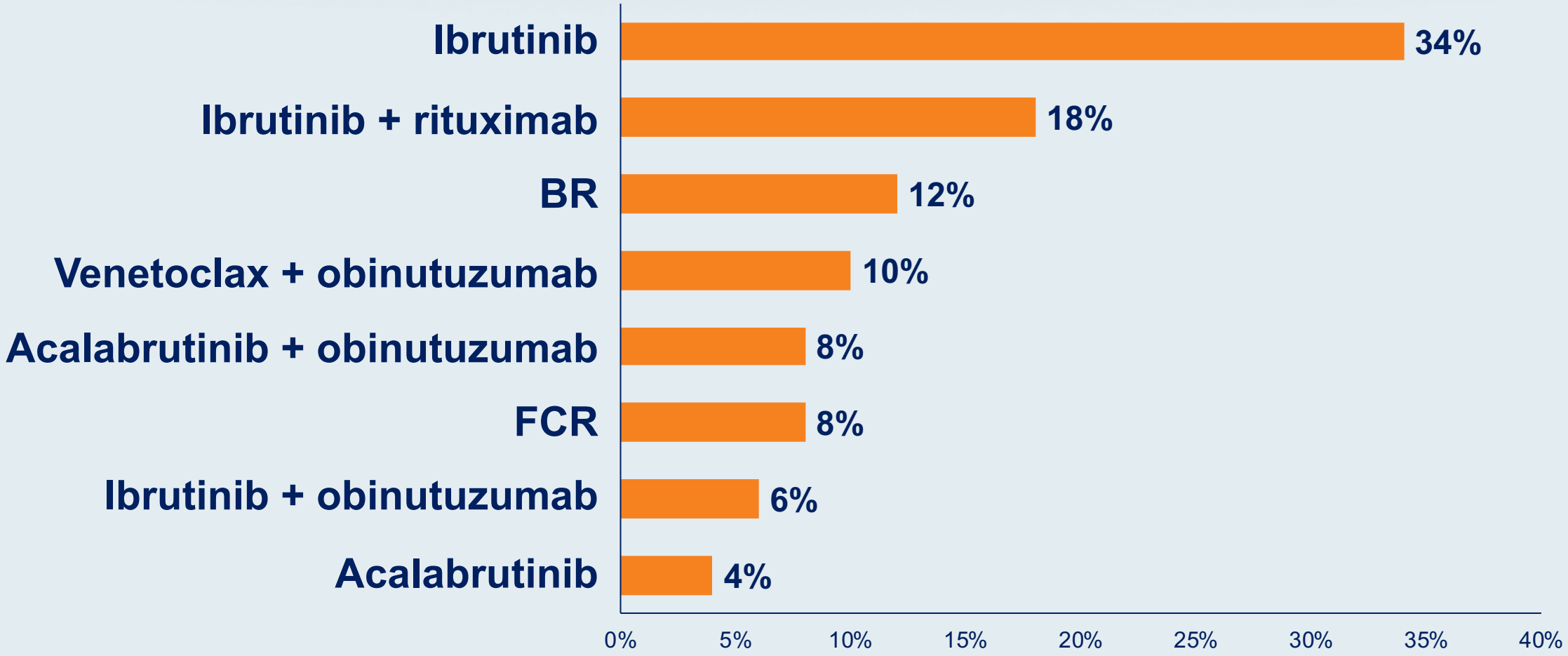


Survey of 50 US-based medical oncologists, June 2020

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

a. FCR

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f. Acalabrutinib

g. Acalabrutinib + obinutuzumab

h. Venetoclax + obinutuzumab

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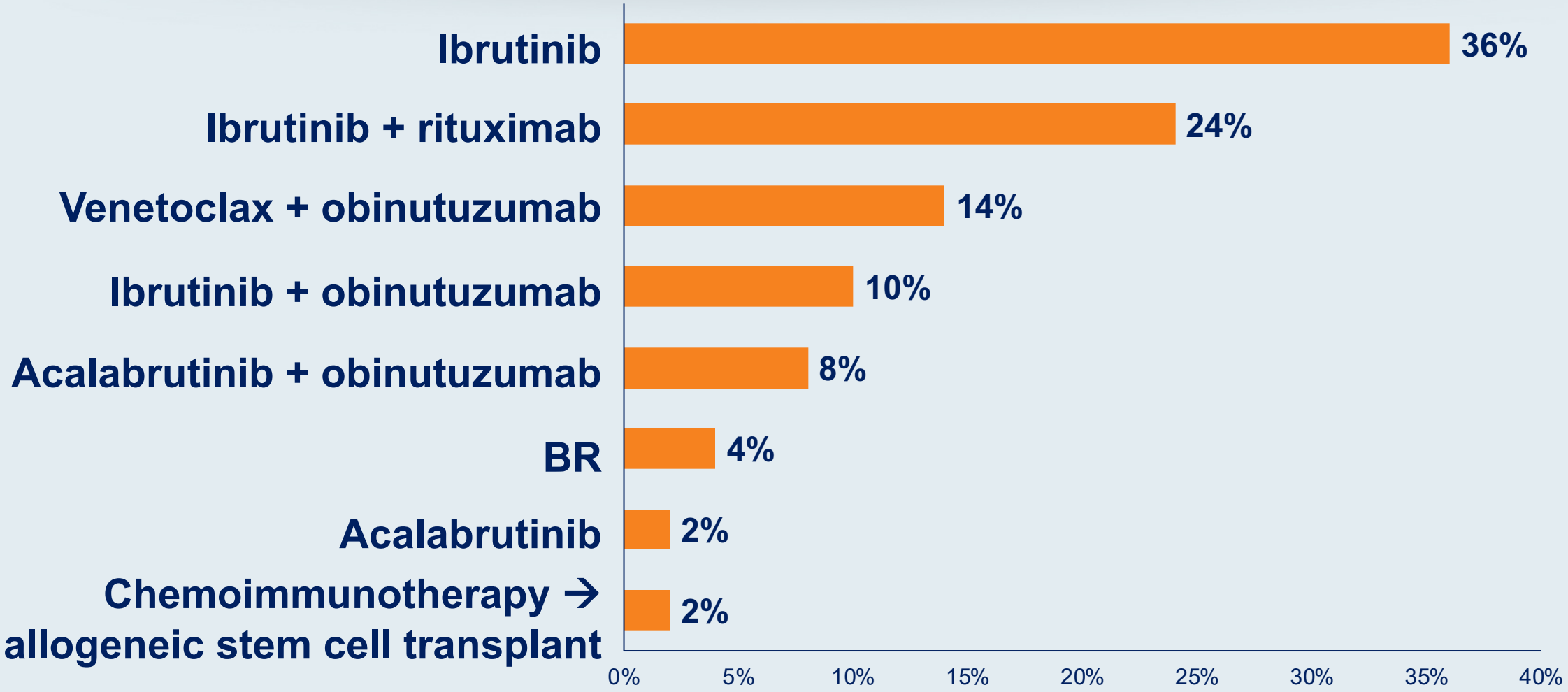



Survey of 50 US-based medical oncologists, June 2020

**What is your usual preferred initial regimen for a 60-year-old patient with del(17p) CLL who requires treatment, has a history of atrial fibrillation and is receiving anticoagulation therapy?**

a. FCR

b. BR

c. Ibrutinib

d. Ibrutinib + rituximab

e. Ibrutinib + obinutuzumab

f. Acalabrutinib

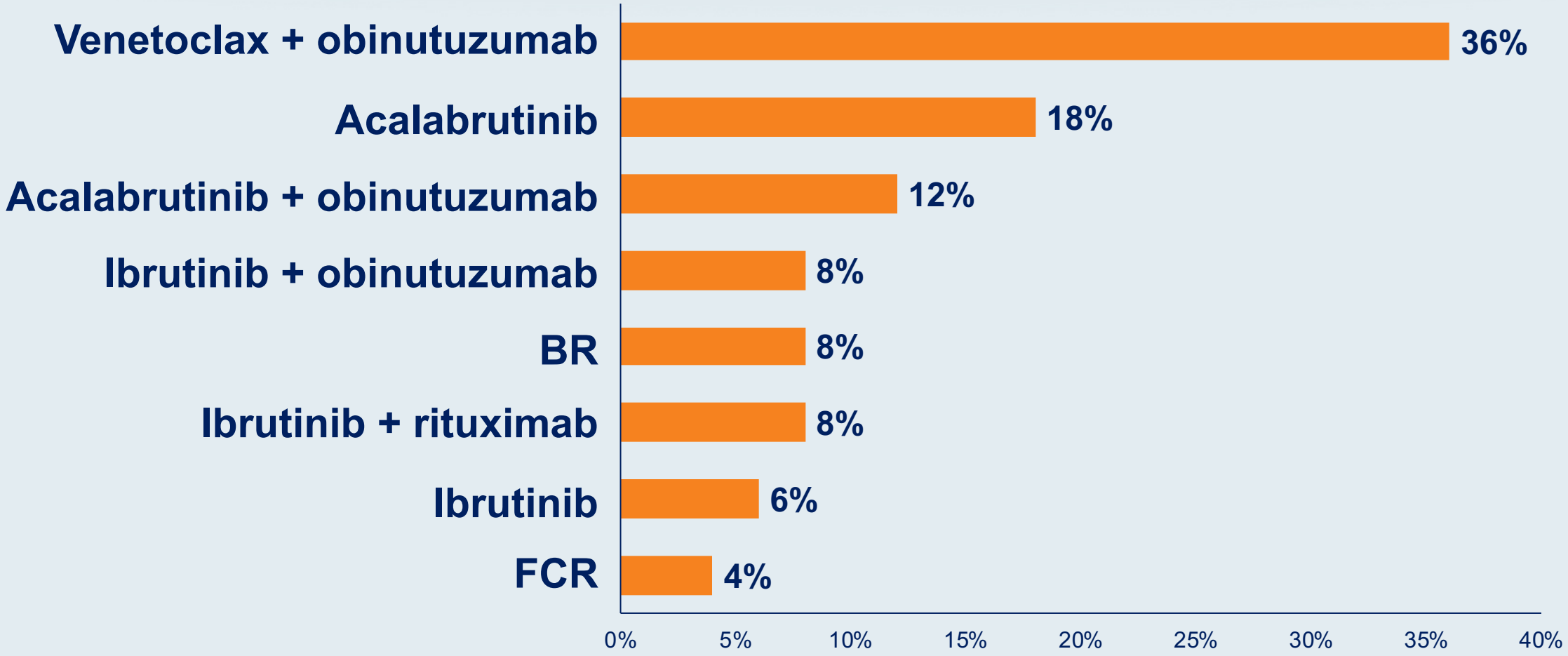
g. Acalabrutinib + obinutuzumab

h. Obinutuzumab + chlorambucil

i. Venetoclax + obinutuzumab

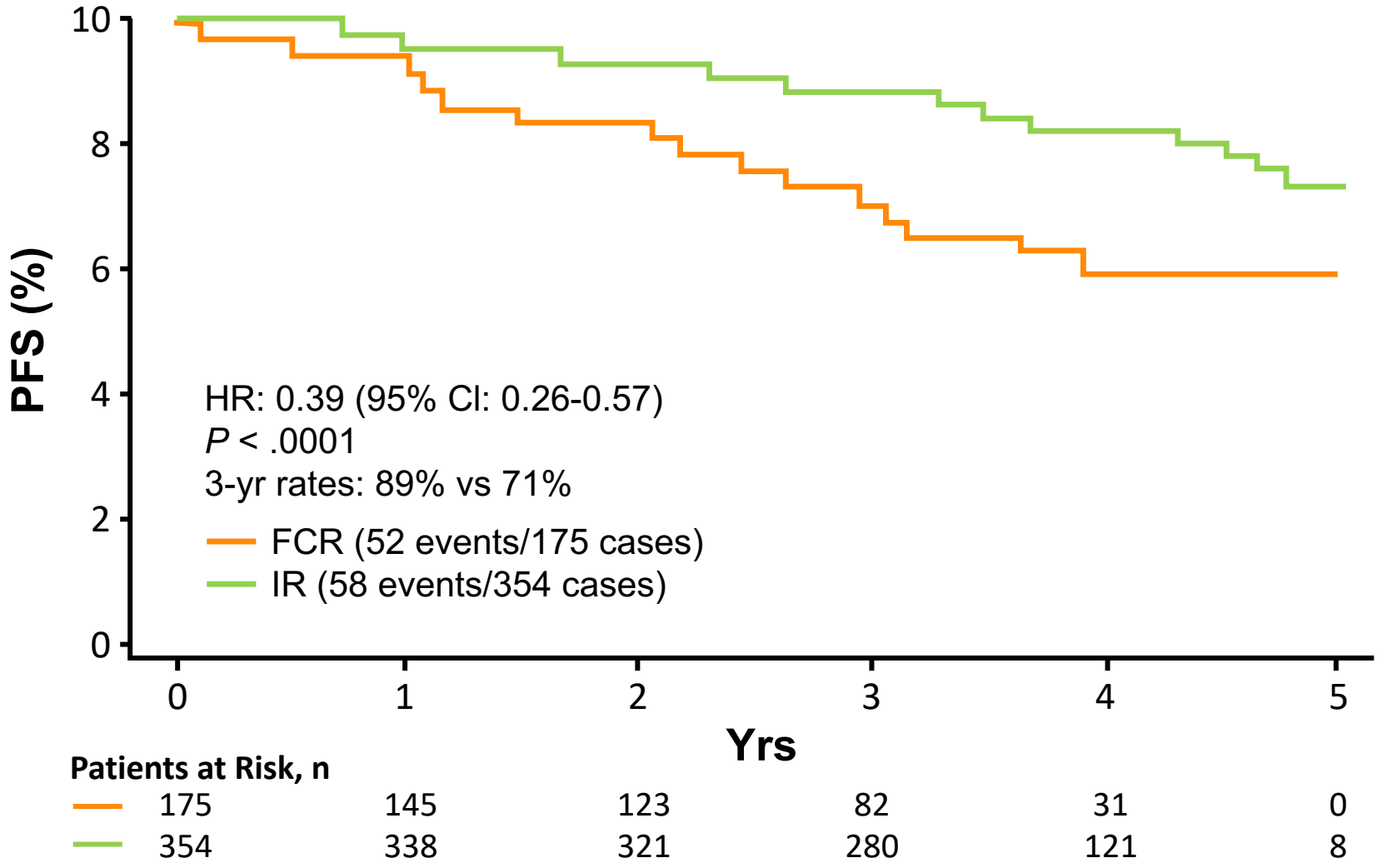
j. Other

# What is your usual preferred initial regimen for a 60-year-old patient with del(17p) CLL who requires treatment, has a history of atrial fibrillation and is receiving anticoagulation therapy?



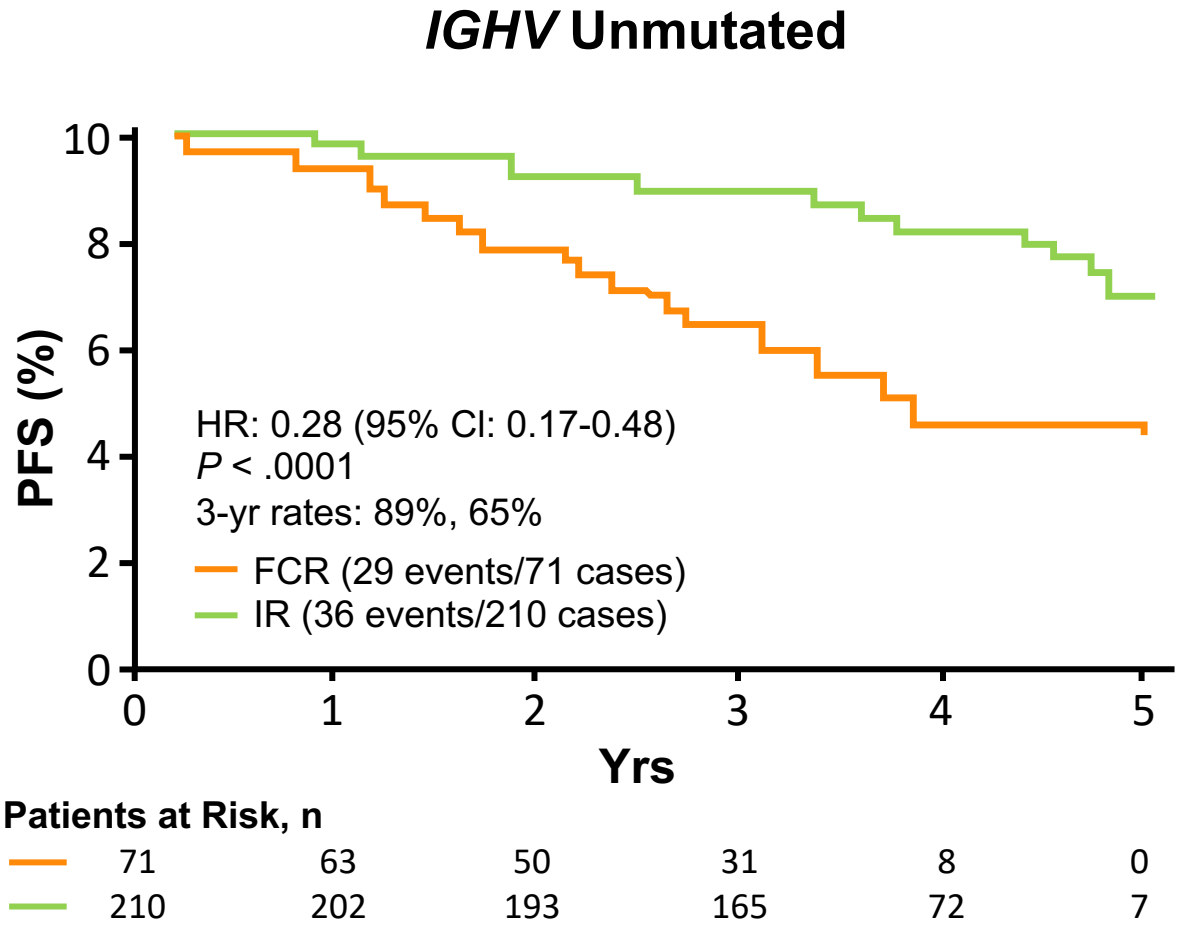

Survey of 50 US-based medical oncologists, June 2020

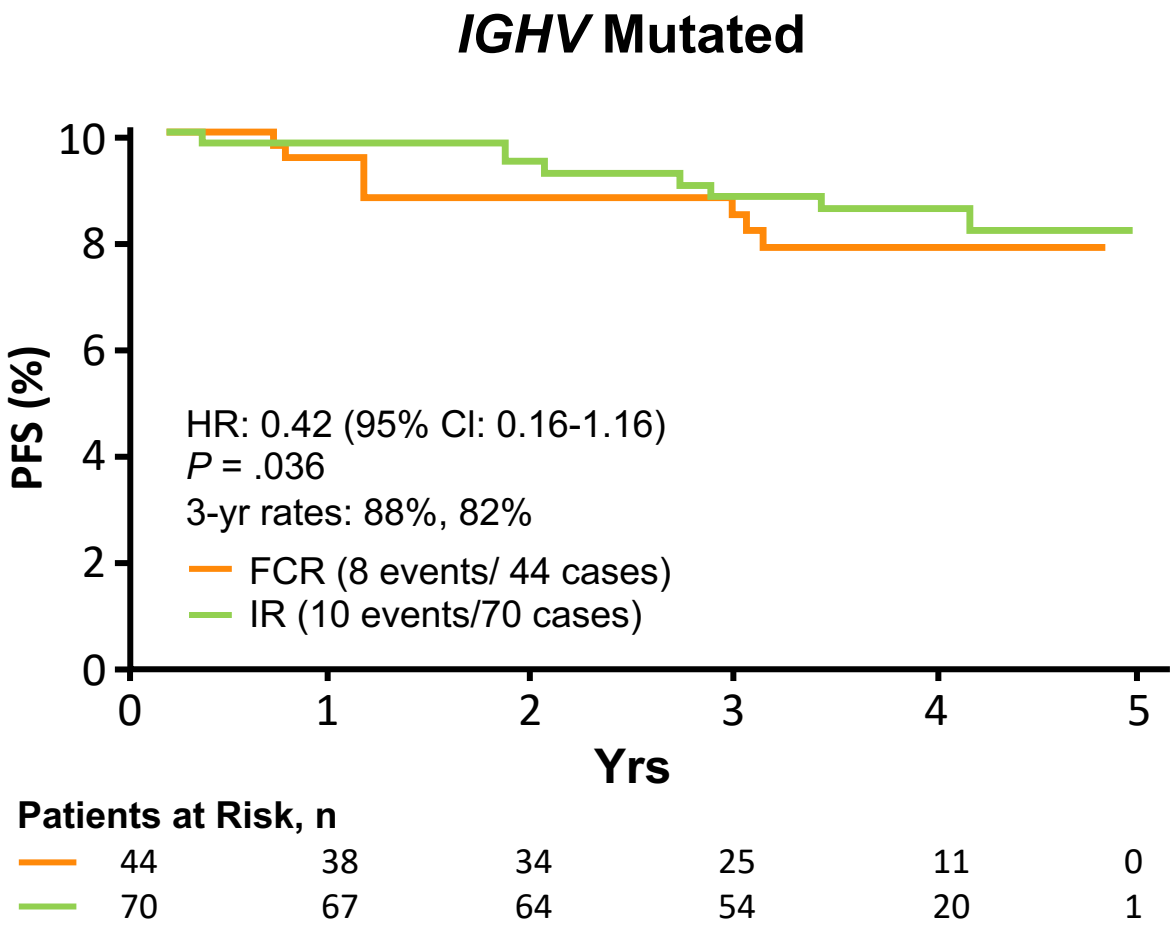
# E1912: Updated PFS With Longer Follow-up of First-line Ibrutinib + Rituximab in Untreated CLL




Shanafelt. ASH 2019. Abstr 33.

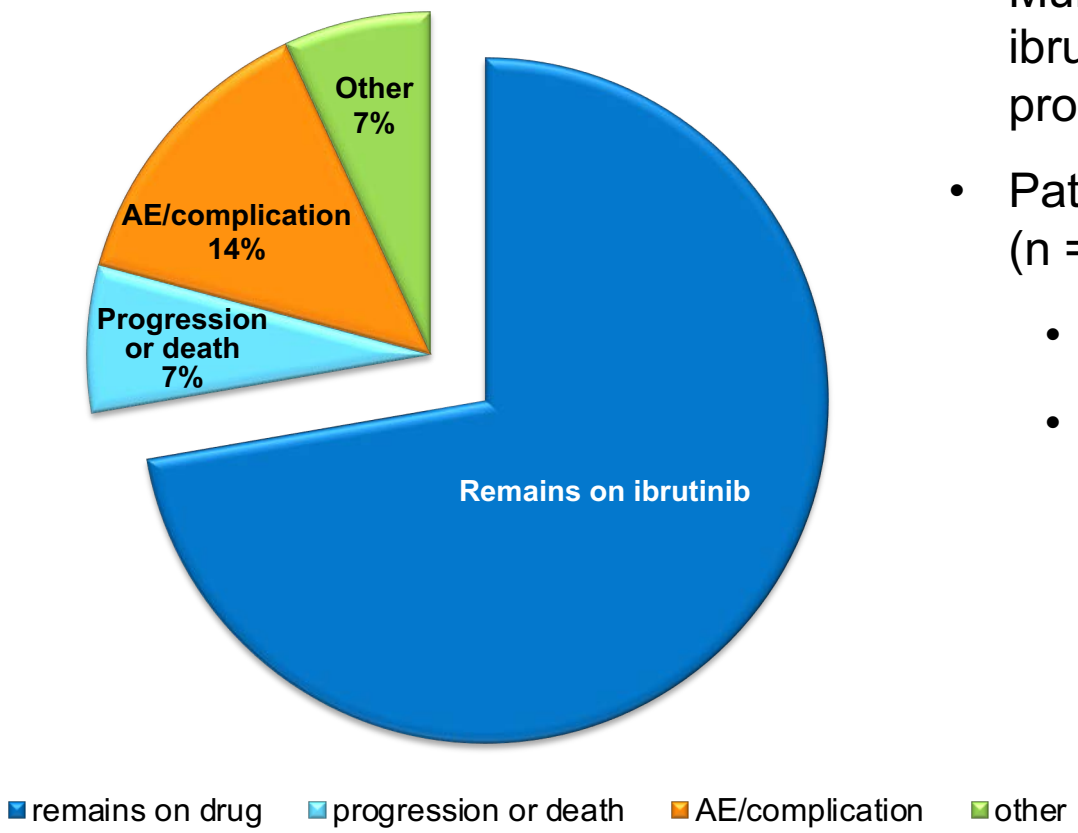
# E1912: Updated PFS by *IGHV* Status




Shanafelt. ASH 2019. Abstr 33.

# ECOG-E1912: Adverse Events in Younger CLL Patients




- Multivariate Cox regression analysis: CIRS predicted ibrutinib discontinuation for reasons other than progression or death
- Patient discontinuing ibrutinib due to AEs or other reason (n = 72)
  - Time on ibrutinib: 15.1 mo (range: 0.2-58.2)
  - Median PFS: 23 mo

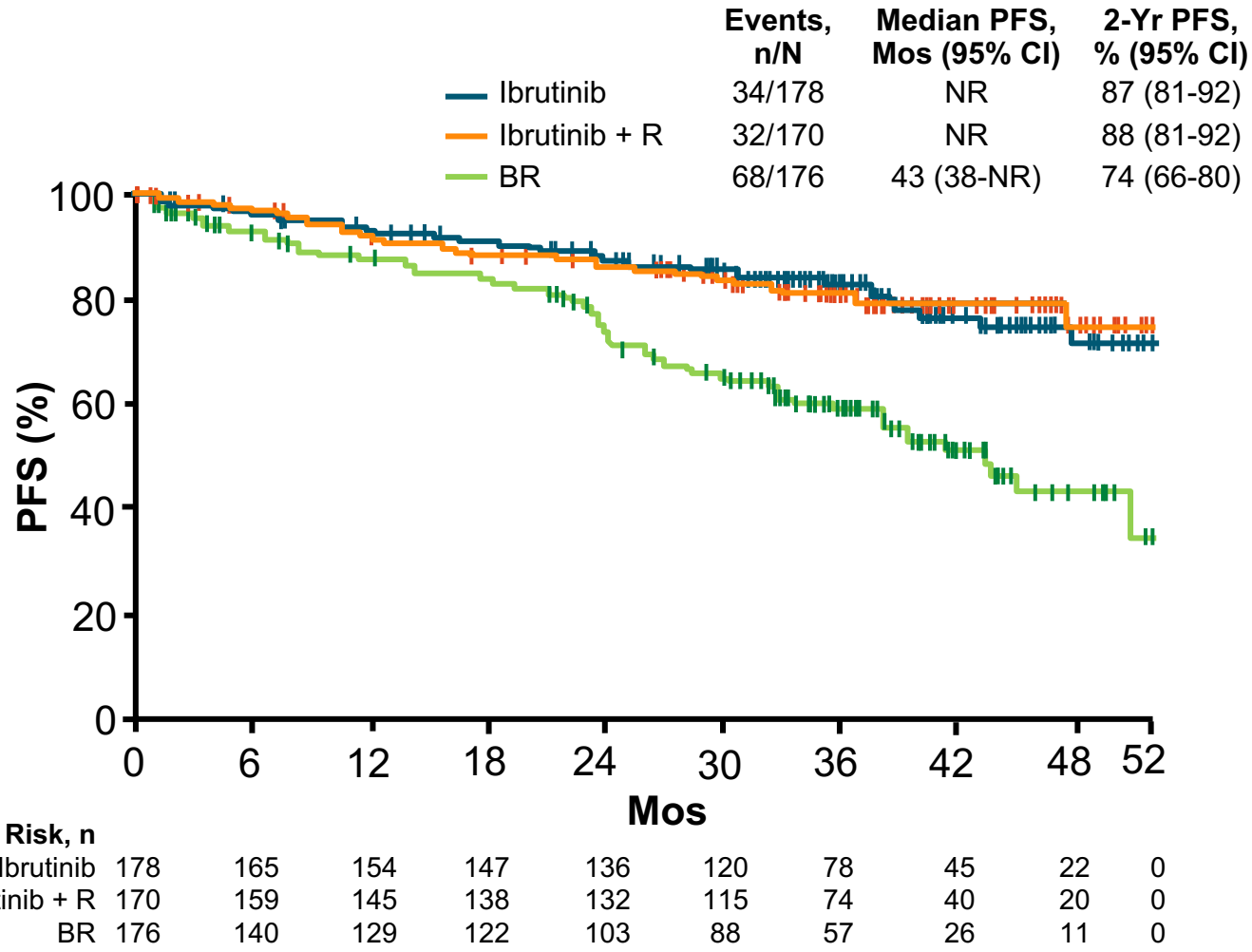
**Select Grade 3/5 TRAE throughout observation**

| | IR (n = 352) | FCR (n = 158) | *p*-value |
|---|---|---|---|
| Any Grade ≥3 AE | 69.6 | 80.4 | .013 |
| Neutropenia | 27.0 | 43.0 | <.001 |
| Anemia | 4.3 | 15.8 | <.001 |
| Thrombocytopenia | 3.1 | 15.8 | <.001 |
| Atrial fibrillation | 2.8 | 0 | .036 |
| Hypertension | 8.5 | 1.9 | .003 |

Shanafelt. ASH 2019. Abstr 33.

# A041202: PFS of Eligible Patients* (Primary Endpoint)

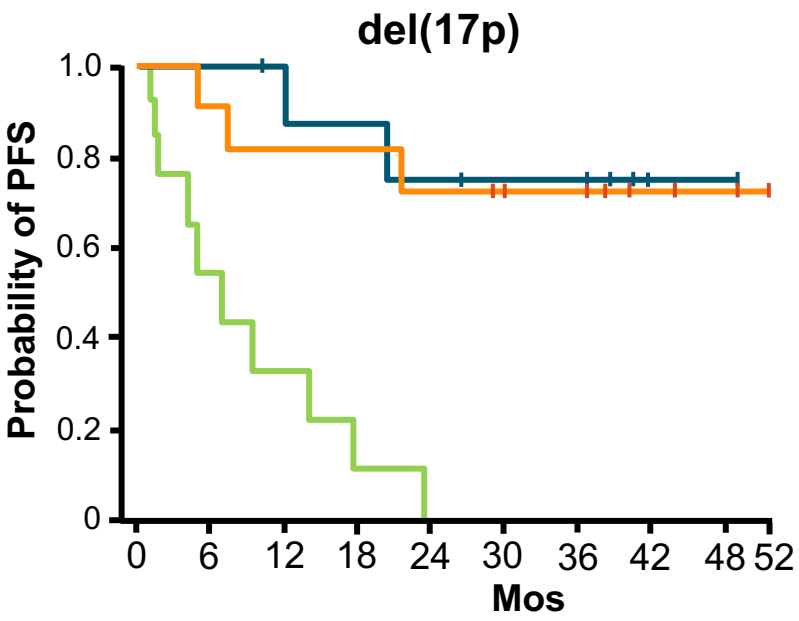
- PFS significantly improved with ibrutinib vs BR and ibrutinib + R vs BR (both 1-sided $P < .001$)
  - HR for ibrutinib vs BR: 0.39 (95% CI: 0.26-0.58)
  - HR for ibrutinib + R vs BR: 0.38 (95% CI: 0.25-0.59)
- No significant difference for ibrutinib + R vs ibrutinib only (1-sided $P = .49$)
  - HR: 1.00 (95% CI: 0.62-1.62)



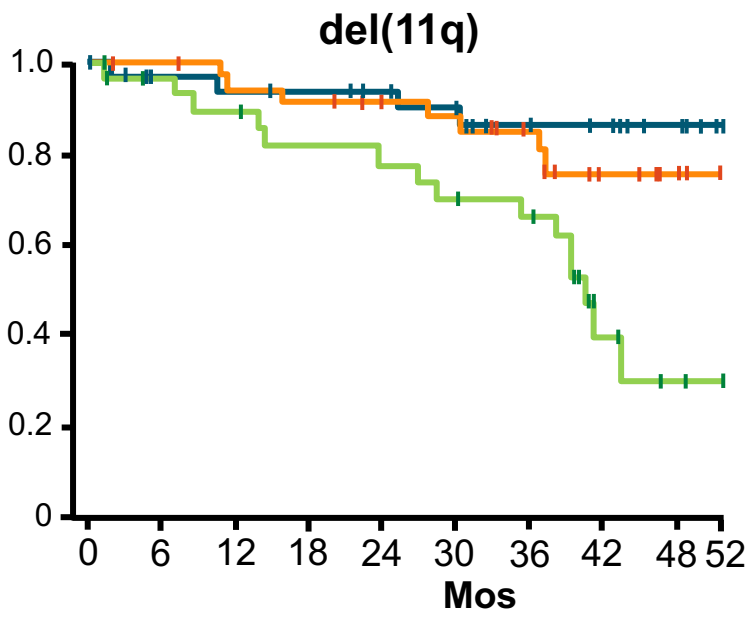

*524 of 547 randomized patients.

Woyach. NEJM. 2018;379:2517.

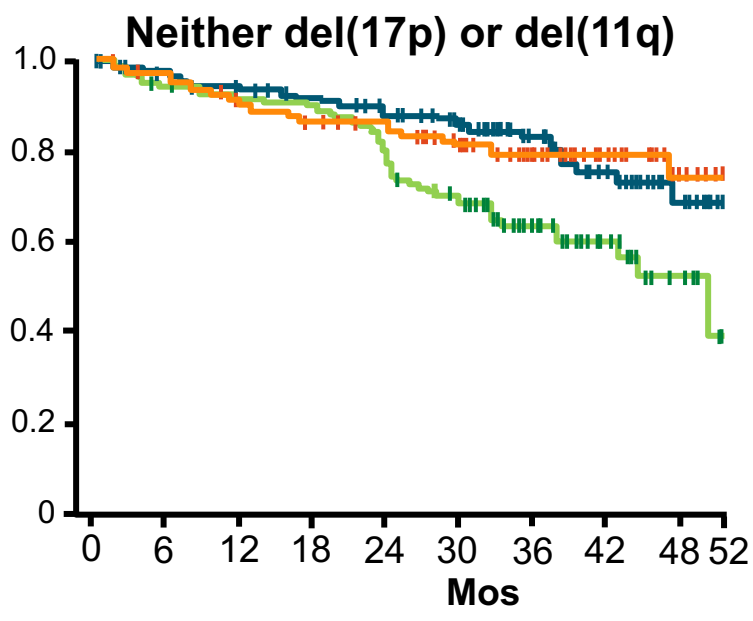
# A041202: PFS by FISH and Complex Karyotype (CK), and *IGHV*




| | Events, n/N | Median PFS, Mos (95% CI) |
|---|---|---|
| Ibrutinib | 2/9 | NE |
| Ibrutinib + R | 3/11 | NE |
| BR | 10/14 | 7 (4-23) |




| | Events, n/N | Median PFS, Mos (95% CI) |
|---|---|---|
| Ibrutinib | 4/35 | NE |
| Ibrutinib + R | 7/37 | NE |
| BR | 15/33 | 41 (36-NE) |



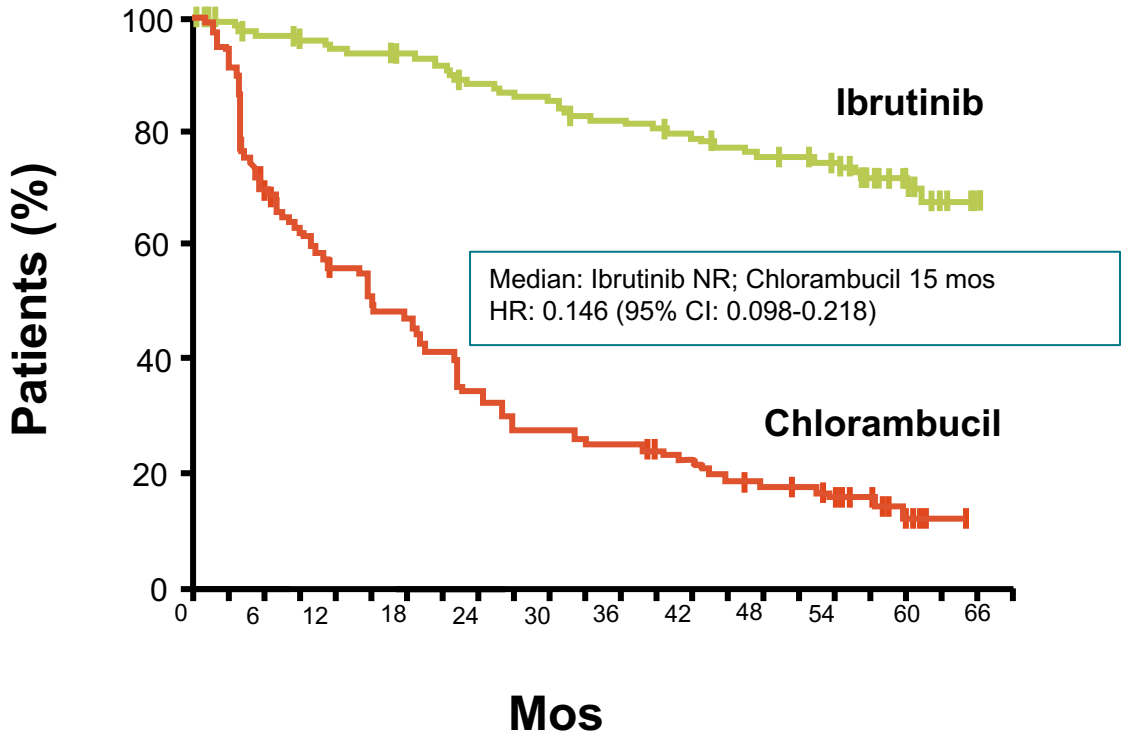

| | Events, n/N | Median PFS, Mos (95% CI) |
|---|---|---|
| Ibrutinib | 27/137 | NE |
| Ibrutinib + R | 25/132 | NE |
| BR | 45/134 | 51 (43-NE) |

- PFS benefit with ibrutinib vs BR observed in all cytogenetic factor–related subgroups, with del(17p13.1) being most pronounced
- In CK, 24-month PFS: BR (59%; 42% to 73%) vs I (91%, 75% to 97%) vs IR (87%, 75% to 94%); no influence on ibrutinib-associated PFS
- No significant interaction between *IGHV* mutation status and PFS benefit by regimen
  - Increased PFS among patients with mutated vs unmutated *IGHV* disease (HR: 0.51; 95% CI: 0.32-0.81)

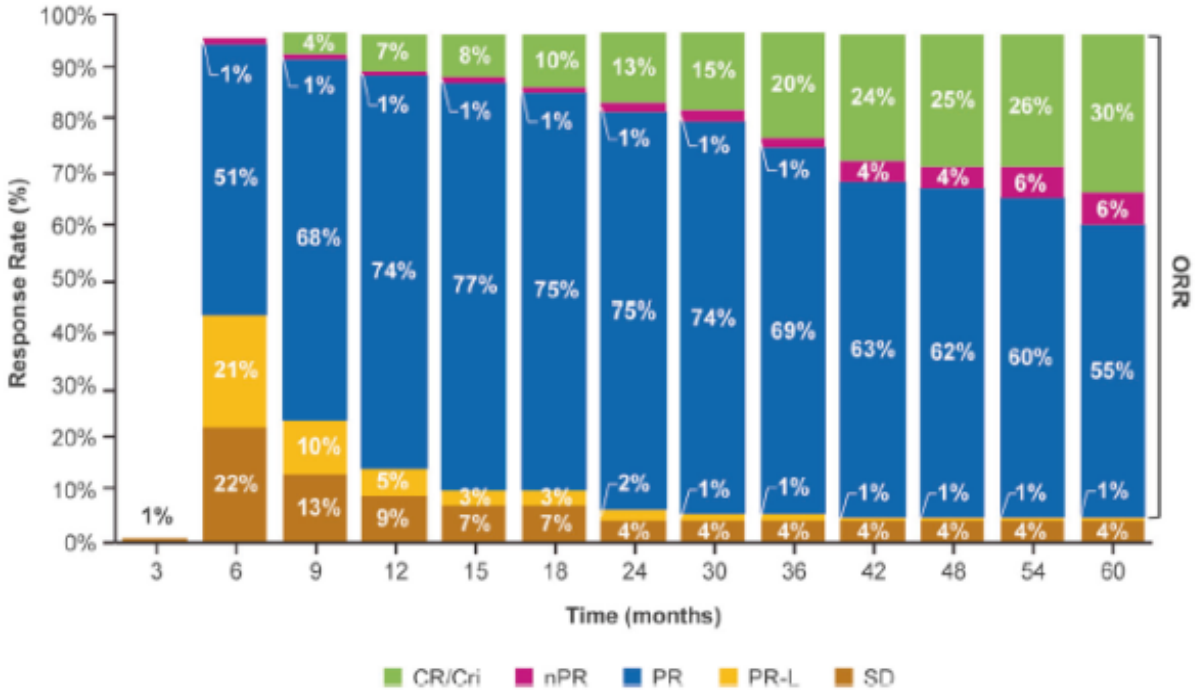
Woyach. NEJM. 2018;379:2517.

# RESONATE-2: 5-Year Follow-up of Ibrutinib vs Chlorambucil in Treatment-Naïve Older Patients with CLL

**PFS**

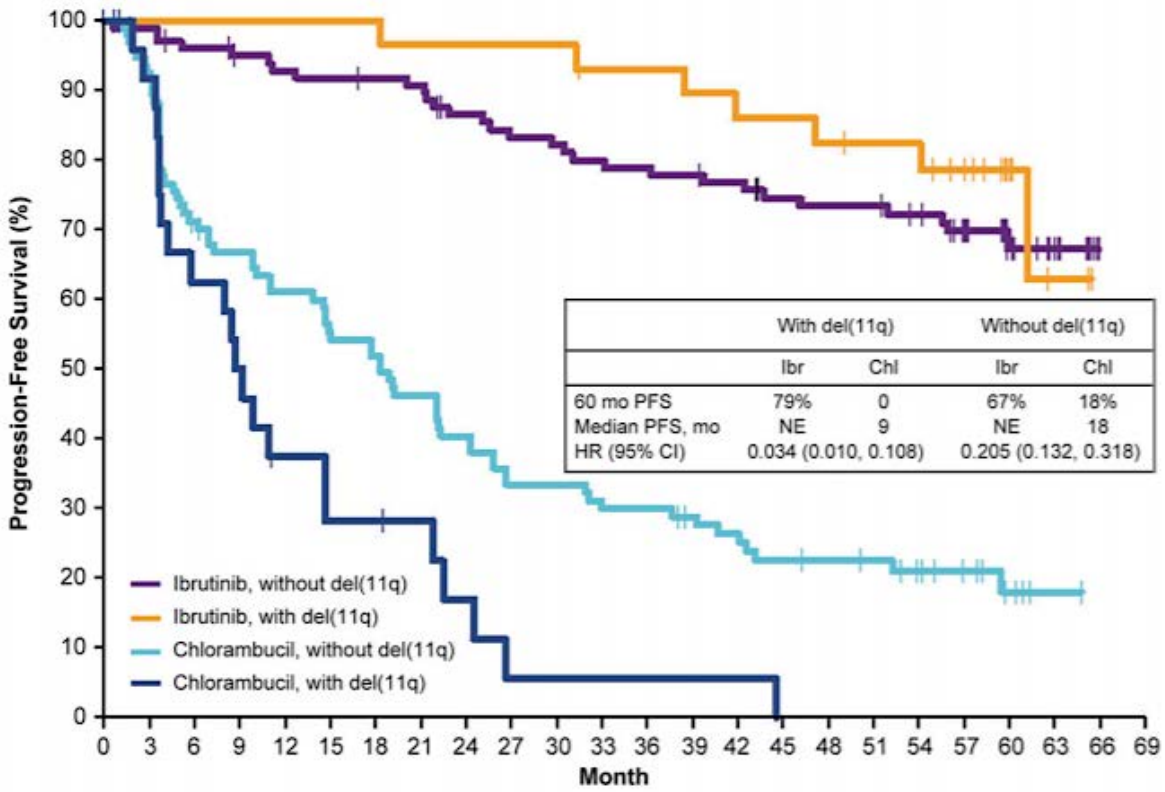



**ORR**

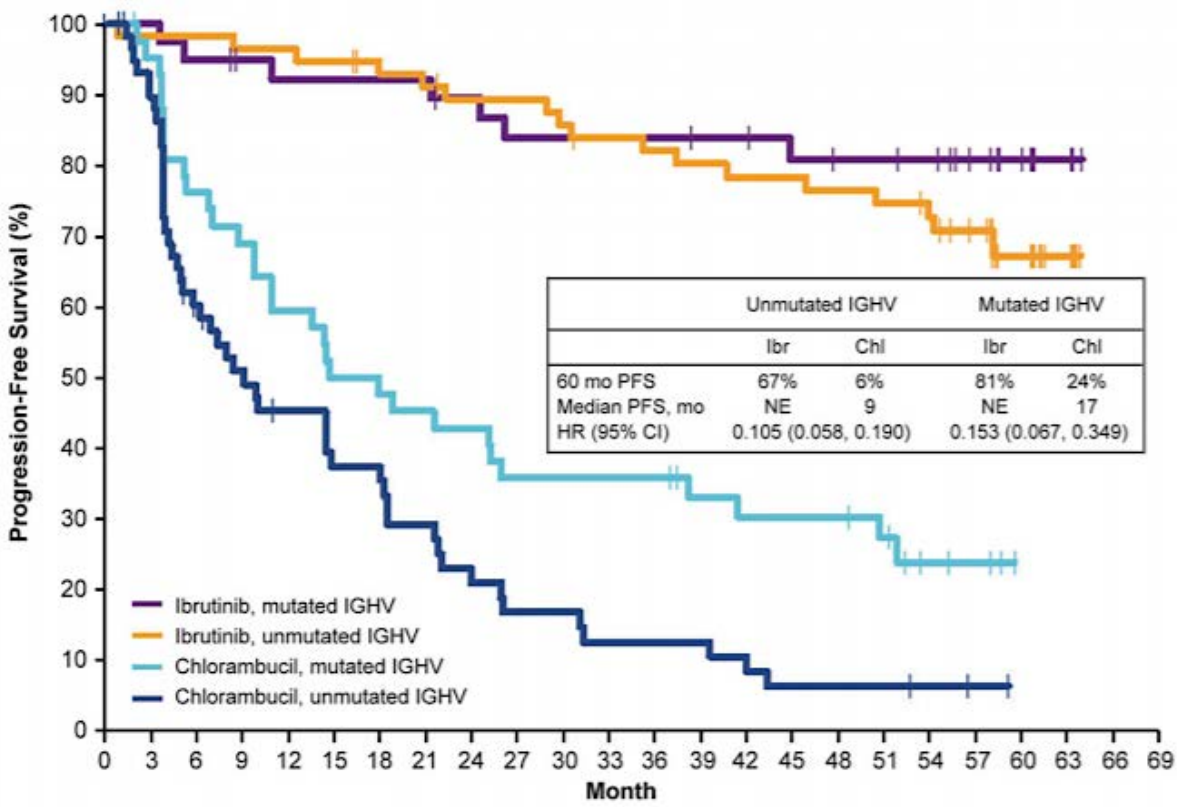



Burger JA, et al. *Leukemia*. 2020;34:787-798.

# Long Term RESONATE-2 by 11Q & IgHV




| | With del(11q) | | Without del(11q) | |
|---|---|---|---|---|
| | Ibr | Chl | Ibr | Chl |
| 60 mo PFS | 79% | 0 | 67% | 18% |
| Median PFS, mo | NE | 9 | NE | 18 |
| HR (95% CI) | 0.034 (0.010, 0.108) | | 0.205 (0.132, 0.318) | |




| | Unmutated IGHV | | Mutated IGHV | |
|---|---|---|---|---|
| | Ibr | Chl | Ibr | Chl |
| 60 mo PFS | 67% | 6% | 81% | 24% |
| Median PFS, mo | NE | 9 | NE | 17 |
| HR (95% CI) | 0.105 (0.058, 0.190) | | 0.153 (0.067, 0.349) | |

## What management strategy would you generally recommend for a patient who is experiencing acalabrutinib-associated headache?

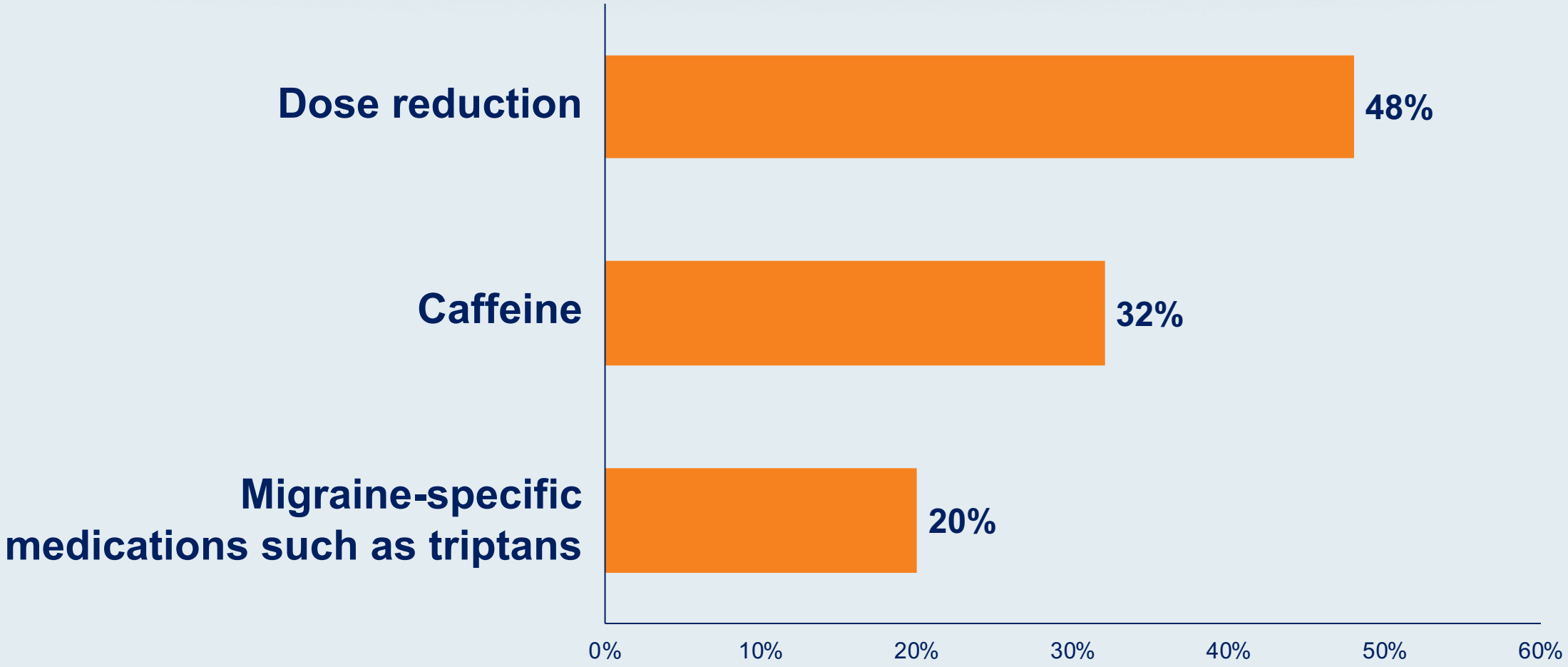
a. Dose reduction

b. Caffeine

c. Migraine-specific medications such as triptans

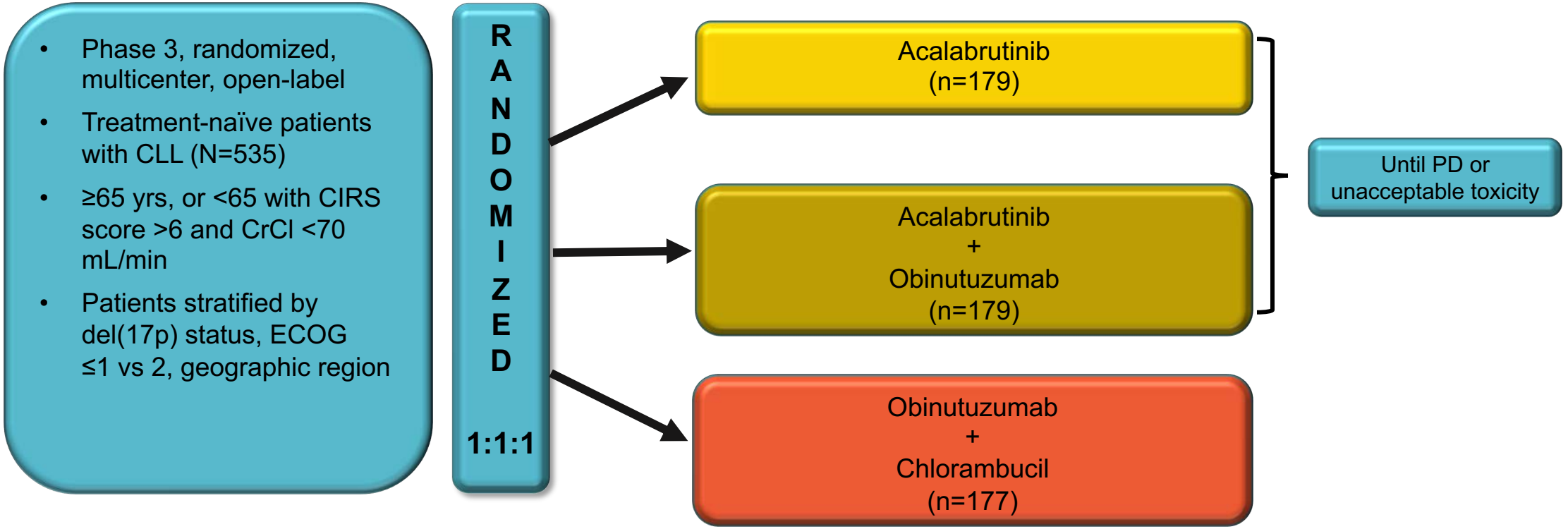
d. Other

# What management strategy would you generally recommend for a patient who is experiencing acalabrutinib-associated headache?




Survey of 50 US-based medical oncologists, June 2020

# ELEVATE-TN Trial: Acalabrutinib ± Obinutuzumab vs Obinutuzumab + Chlorambucil in Treatment-naïve CLL



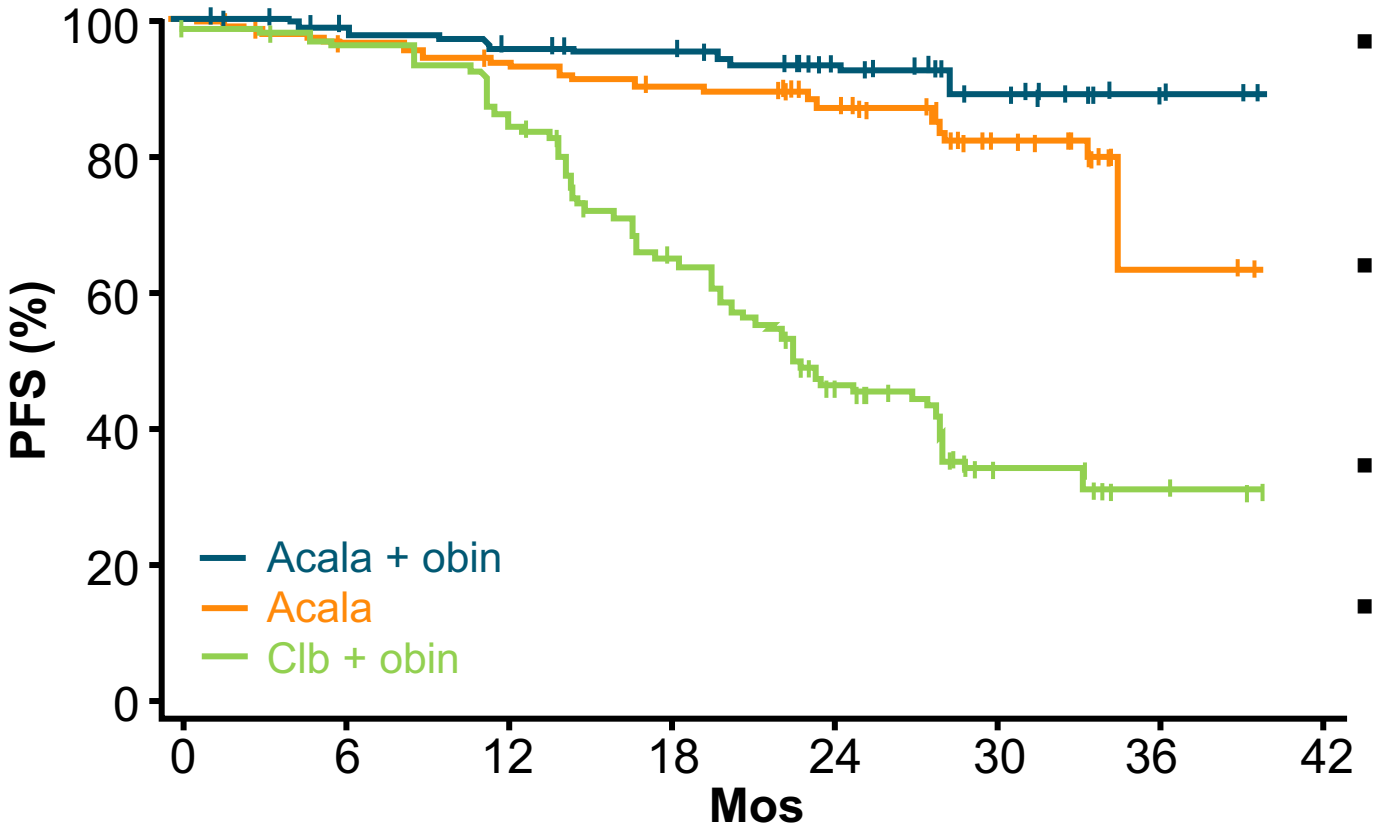

**Primary endpoint:** PFS per IRC (acalabrutinib/obinutuzumab vs chlorambucil/obinutuzumab)

**Secondary endpoints:** PFS of acalabrutinib monotherapy vs obinutuzumab/chlorambucil, ORR, TTNT, OS, safety

BID, twice daily; CIRS, Cumulative Illness Rating Scale for Geriatrics; CrCl, creatinine clearance; ECOG, Eastern Cooperative Oncology Group; IRC, independent review committee; ORR, overall response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; TTNT, time to next treatment

Sharman JP, et al. *Lancet.* Published online April 18, 2020

# ELEVATE-TN: IRC-Assessed PFS




- 30-month PFS estimates
  - Acala + obin: 90%, acala: 82%, Clb + obin: 34%
- ORR of acala + obin (93.9%) vs acala (85.5%) did not achieve significance at current follow-up
- CR rates higher with acala + obin (13%) vs acala (1%)
- 30-month OS estimates
  - Acala + obin: 95%, acala: 94%, Clb + obin: 90%

| Outcome | Acalabrutinib + Obinutuzumab | Acalabrutinib | Obinutuzumab + Chlorambucil |
|---|---|---|---|
| Median PFS, mo | Not reached | Not reached | 22.6 |
| ▪ HR vs acala (95% CI) | 0.49 (0.26-0.95) | -- | -- |
| ▪ HR vs obin/clb (95% CI) | 0.10 (0.6-0.17); $p < .001$ | 0.20 (0.13-0.30); $p < .001$ | -- |

Sharman. Lancet. 2020;395:1278.

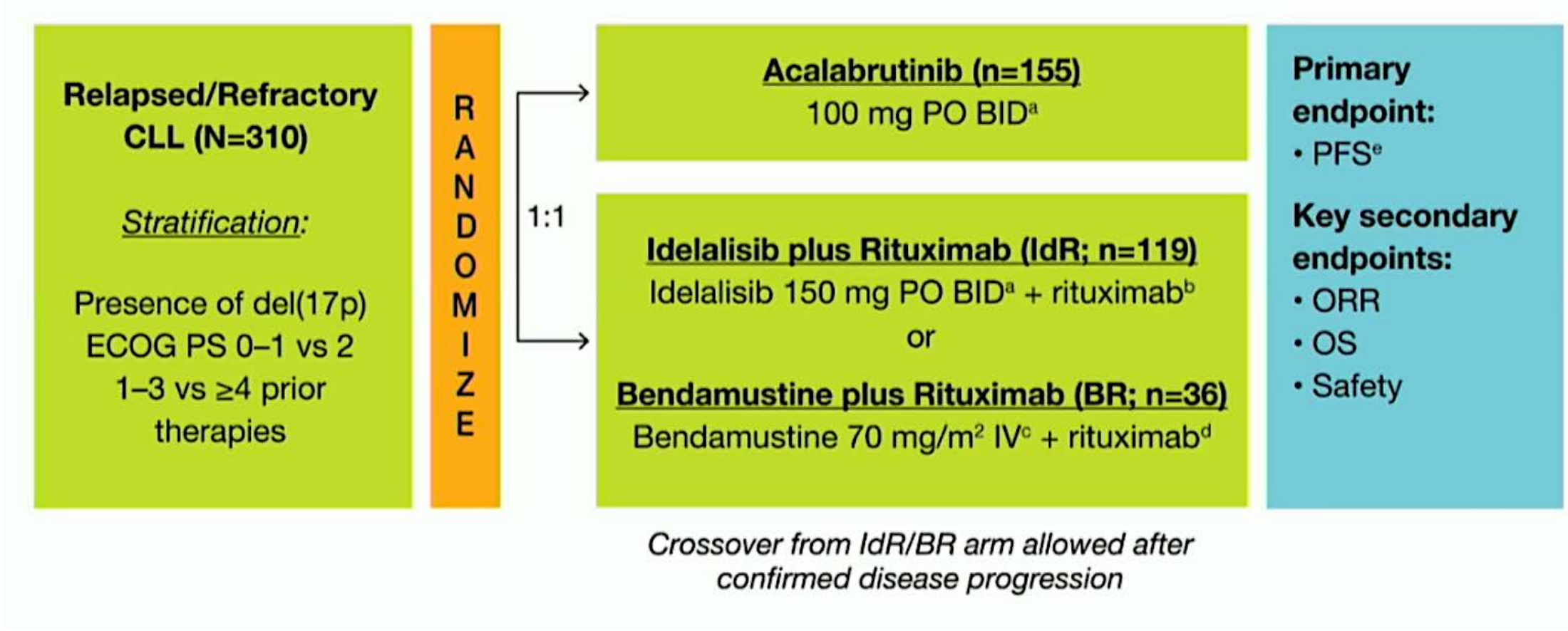
# ELEVATE-TN: Safety

| Adverse Events, n (%) | Acala + Obin* (n = 178) | | Acala* (n = 179) | | Obin + Clb (n = 169) | |
|---|---|---|---|---|---|---|
| | Any grade | Grade ≥3 | Any grade | Grade ≥3 | Any grade | Grade ≥3 |
| Any | 171 (96) | 125 (70) | 170 (95) | 89 (50) | 167 (99) | 118 (70) |
| Serious | 69 (39) | | 57 (32) | | 37 (22) | |
| Headache | 71 (40) | 2 (1) | 66 (37) | 2 (1) | 20 (12) | 0 |
| Diarrhea | 69 (39) | 8 (4) | 62 (35) | 1 (1) | 36 (21) | 3 (2) |
| Neutropenia | 56 (31) | 53 (30) | 19 (11) | 17 (9) | 76 (45) | 70 (41) |
| Nausea | 36 (20) | 0 | 40 (22) | 0 | 53 (31) | 0 |
| Infusion-related reaction | 24 (13) | 4 (2) | 0 | 0 | 67 (40) | 9 (5) |
| Atrial fibrillation | 6 (3) | 1 (<1) | 7 (4) | 0 | 1 (<1) | 0) |
| Hypertension | 13 (7) | 5 (3) | 8 (5) | 4 (2) | 6 (4) | 5 (3) |
| Bleeding | 76 (43) | 3 (2) | 70 (39) | 3 (2) | 20 (12) | 0 |
| Infections | 123 (69) | 37 (21) | 117 (65) | 25 (14) | 74 (44) | 14 (8) |
| Fatigue | 50 (28) | 3 (2) | 33 (18) | 2 (1) | 29 (17) | 1 (<1) |
| Grade 5 | 5 (3) | | 7 (4) | | 12 (7) | |

*Treatment duration 27.7 mo in both arms

Sharman. Lancet. 2020;395:1278.

# ASCEND: Phase III Trial of Acalabrutinib vs Rituximab with Either Idelalisib or Bendamustine

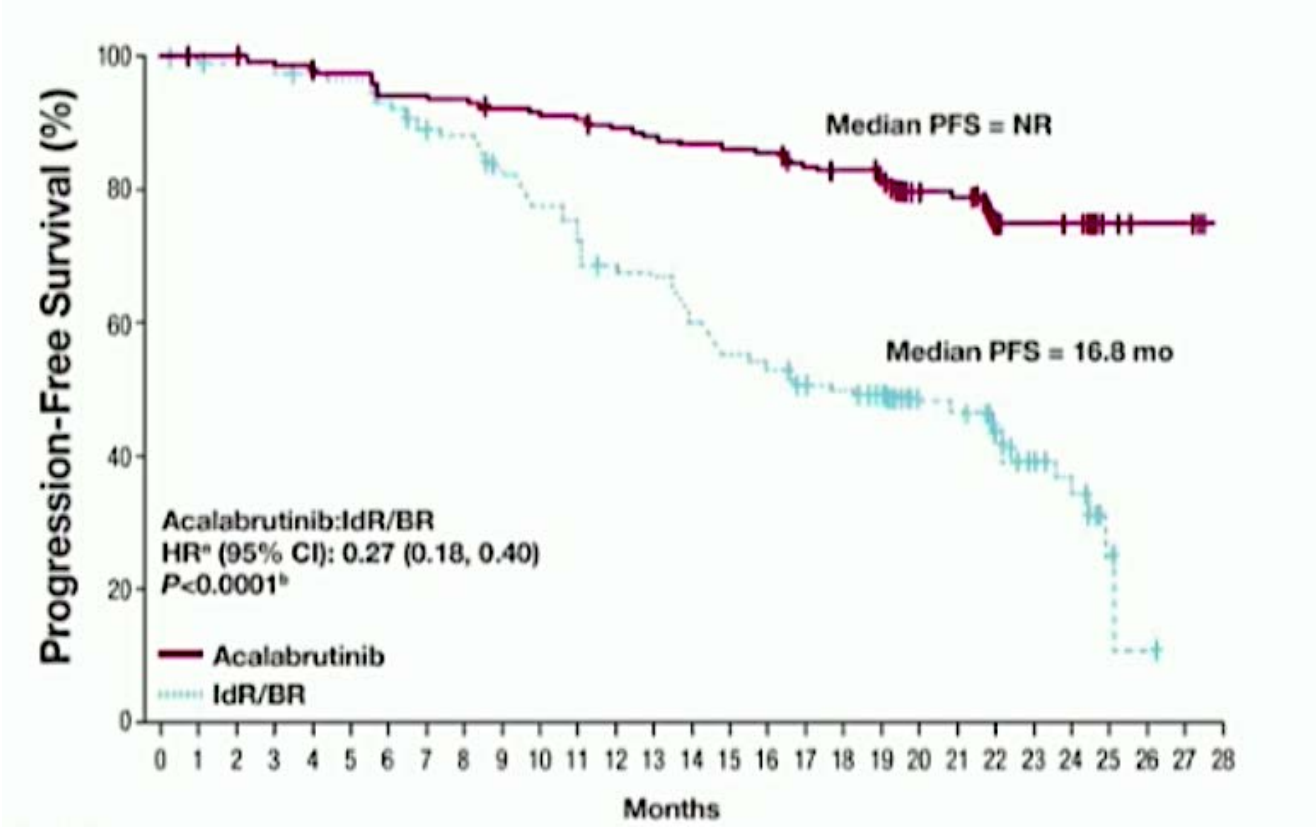



The data cut-off date for this analysis was August 1, 2019

Ghia P et al. *Proc EHA* 2020; Abstract S159.

# ASCEND: Final Analysis of Investigator-Assessed PFS

## PFS for Acalabrutinib vs IdR/BR




After a median of 22 months, acalabrutinib prolonged PFS vs investigator's choice of therapy (estimated 18-mo PFS: 82% and 48%, respectively)

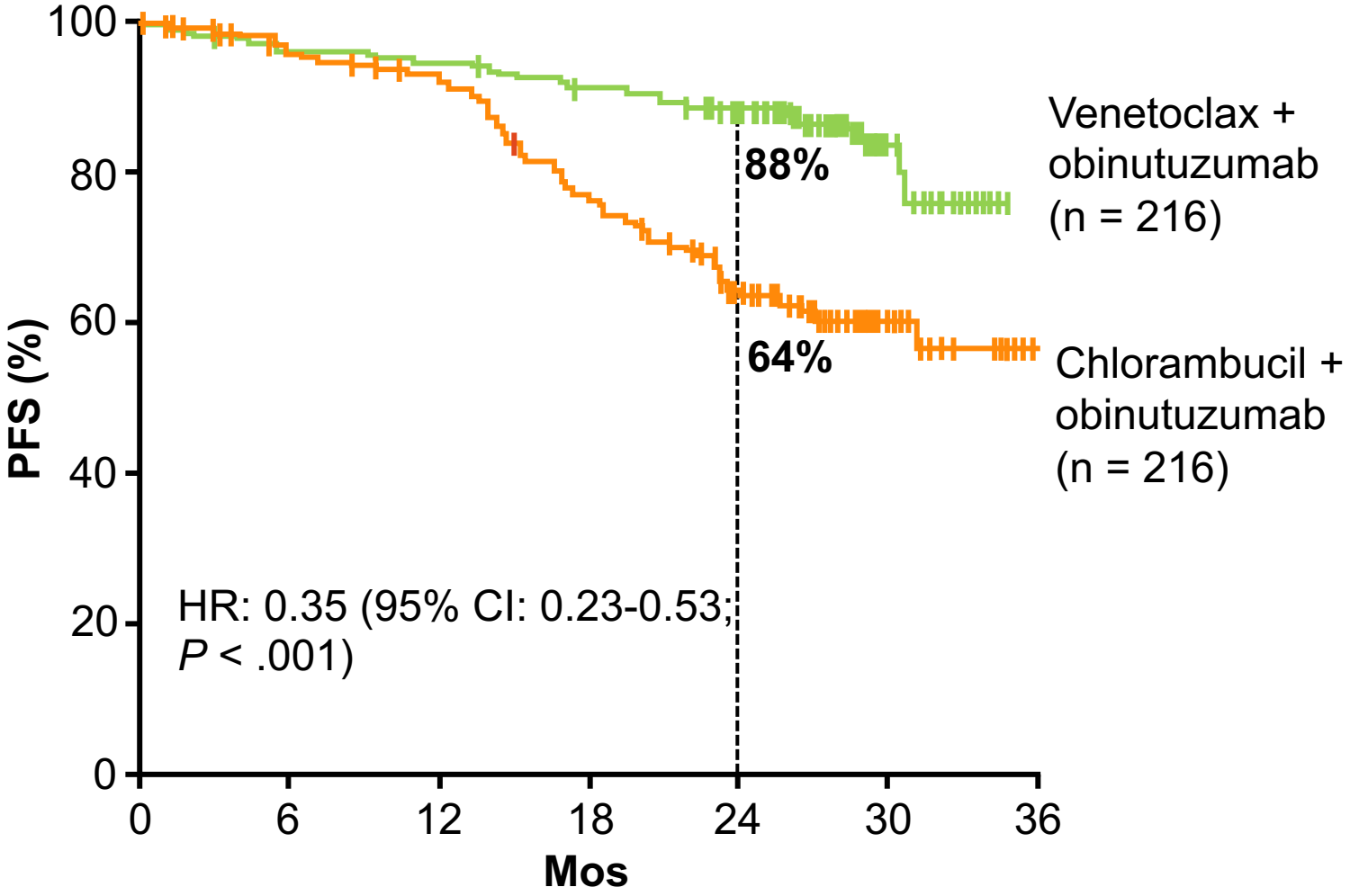
Ghia P et al. *Proc EHA* 2020; Abstract S159.

# ASCEND: Adverse Events of Clinical Interest

| AE, n (%) | Acalabrutinib (n=154) | | IdR (n=118) | |
|---|---|---|---|---|
| | Any | Grade ≥3 | Any | Grade ≥3 |
| Atrial fibrillation | 9 (6) | 2 (1) | 5 (3) | 2 (1) |
| Hemorrhage | 44 (29) | 4 (3) | 12 (8) | 4 (3) |
| Major hemorrhage[a] | 5 (3) | 4 (3)[b] | 4 (3) | 4 (3)[c] |
| Hypertension | 7 (5) | 4 (3) | 6 (4) | 1 (1) |
| Infections | 97 (63) | 30 (20) | 99 (65) | 38 (25) |
| Second primary malignancies excluding non-melanoma skin carcinomas | 8 (5) | 6 (4) | 3 (2) | 2 (1) |
| Tumor lysis syndrome | 1 (1) | 1 (1) | 1 (1) | 1 (1) |

Ghia P et al. EHA 2020; Abstract S159.

# CLL14 Primary Endpoint: Investigator-Assessed PFS with Venetoclax/obinutuzumab in Previously Untreated CLL



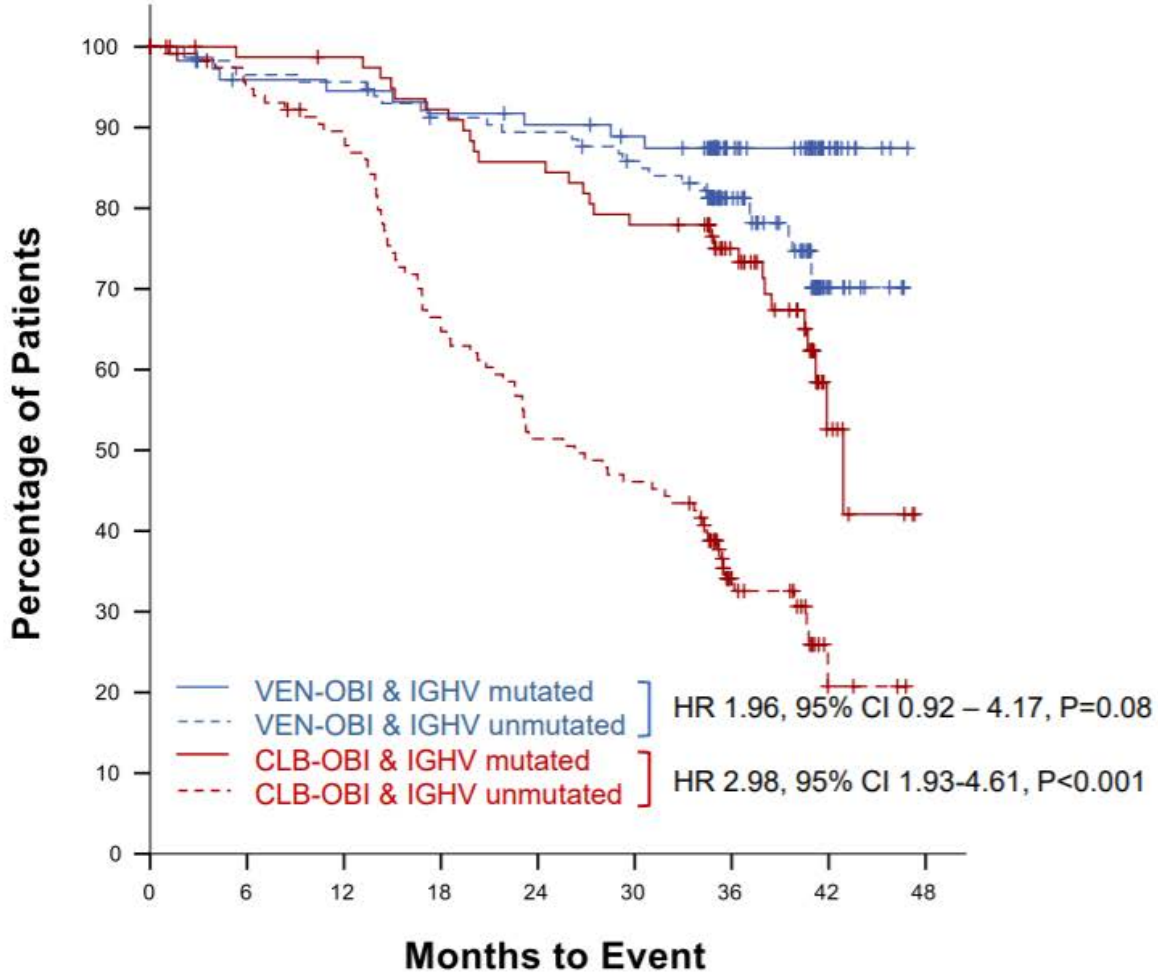

- PFS benefit remains at median follow-up of 39.6 mos
- mPFS
  - Clb + Obin: 36 mos
  - Ven + Obin: NR
  - HR 0.31 (95% CI: 0.22-0.44)
  - *P* < .0001
- 36-mo estimated PFS
  - Clb + Obin: 50%
  - Ven + Obin: 82%

Fischer. ASCO 2019. Abstr 7502. Fischer. NEJM. 2019;380:2225. Fischer. ASH 2019. Abstract 36.

# CLL14: PFS by *IGHV* Mutation and *TP53* Status

## PROGRESSION-FREE SURVIVAL

According to *IGHV* status




**Median PFS**

Ven-Obi IGHV*mut*: not reached

Ven-Obi IGHV*unmut*: not reached

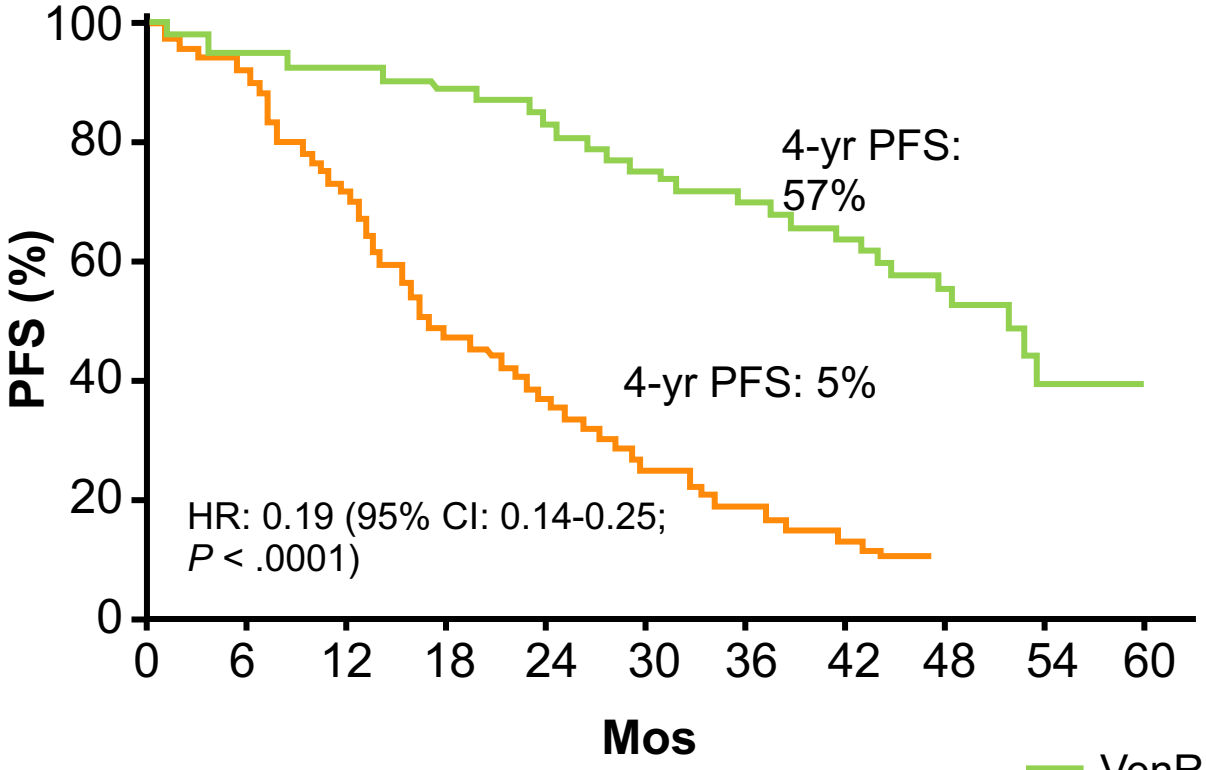
Clb-Obi IGHV*mut*: 42.9 months

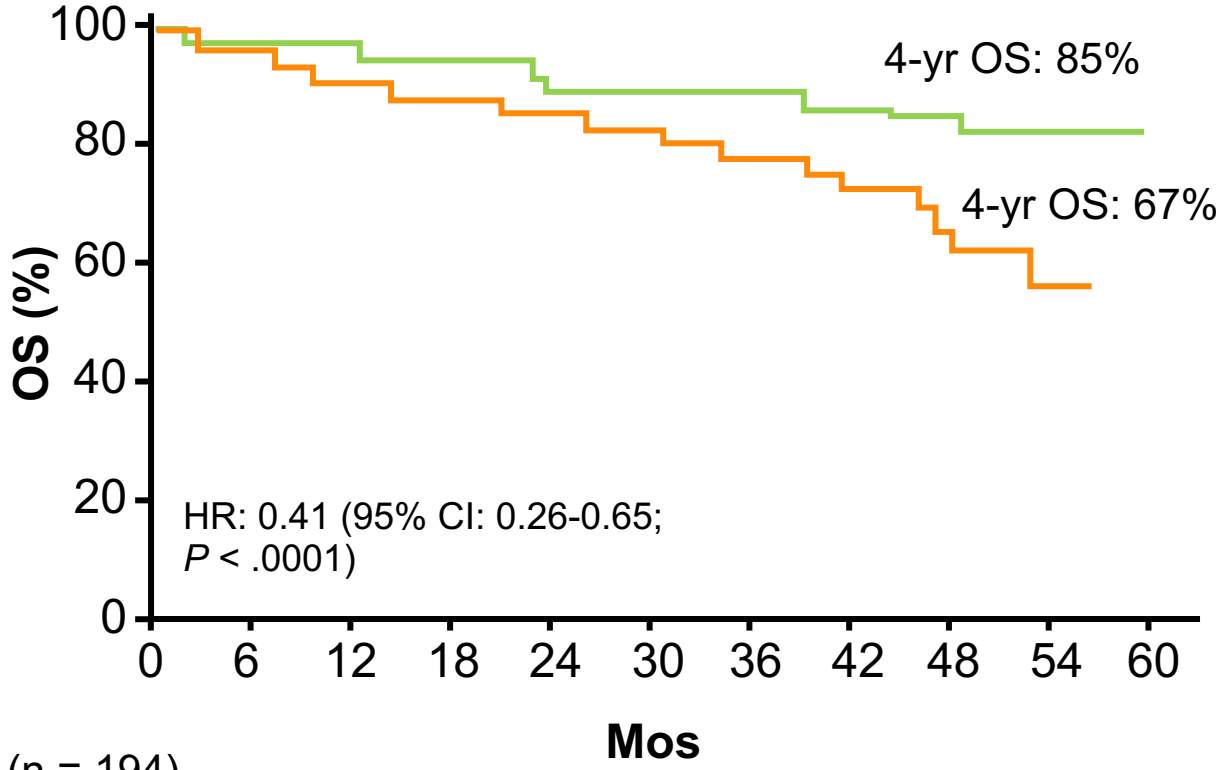
Clb-Obi IGHV*unmut*: 26.3 months

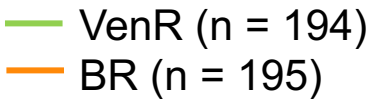
Al-Sawaf EHA 2020

# MURANO: Updated PFS and OS with Venetoclax/Rituximab in Previously Treated CLL

- Phase III trial in patients with R/R CLL after 1-3 previous lines of tx
  - **Venetoclax** 5-wk dose ramp-up then 400 mg PO QD for C1-6 + **rituximab** (n = 194) vs **bendamustine** + **rituximab** (n = 195) for 6 cycles
  - ORR: 93.3% with venetoclax + R vs 67.7% with bendamustine + R



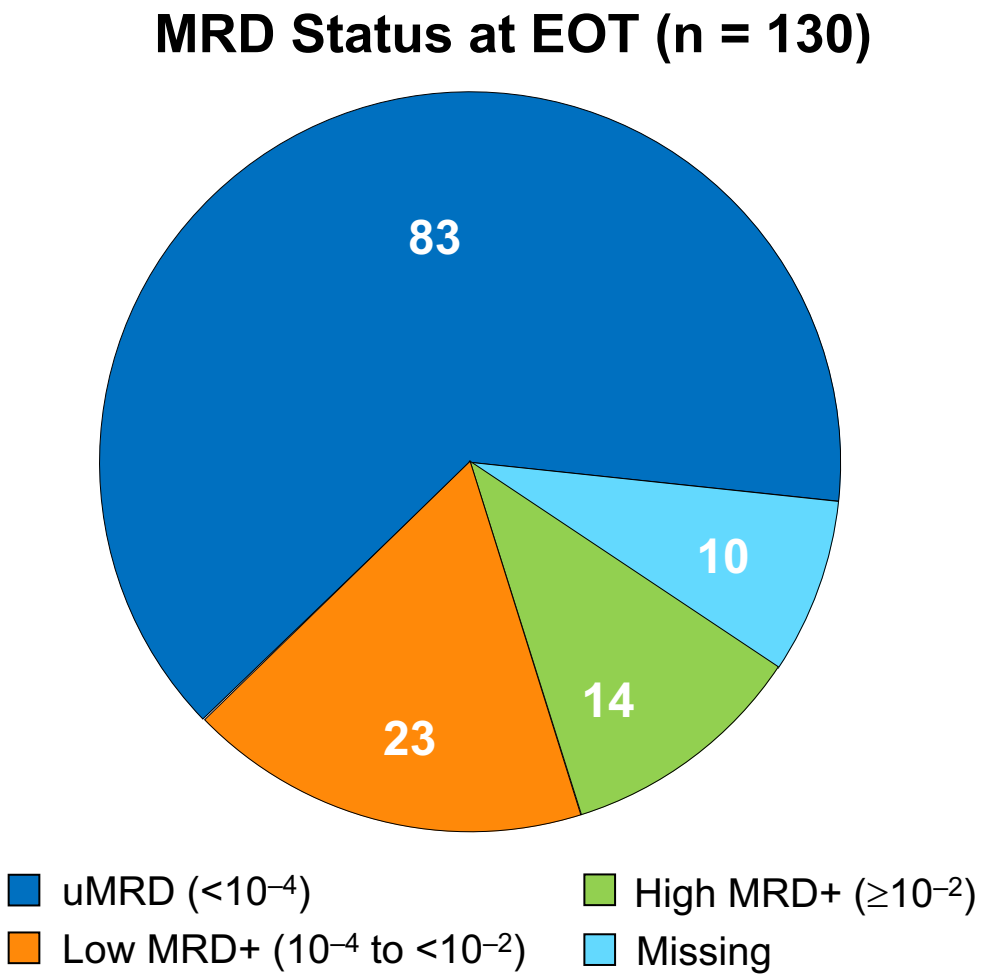




- Median follow-up: 48.0 mos

Seymour. ASH 2019. Abstr 355.

# MURANO: MRD and Progression Status at EOT

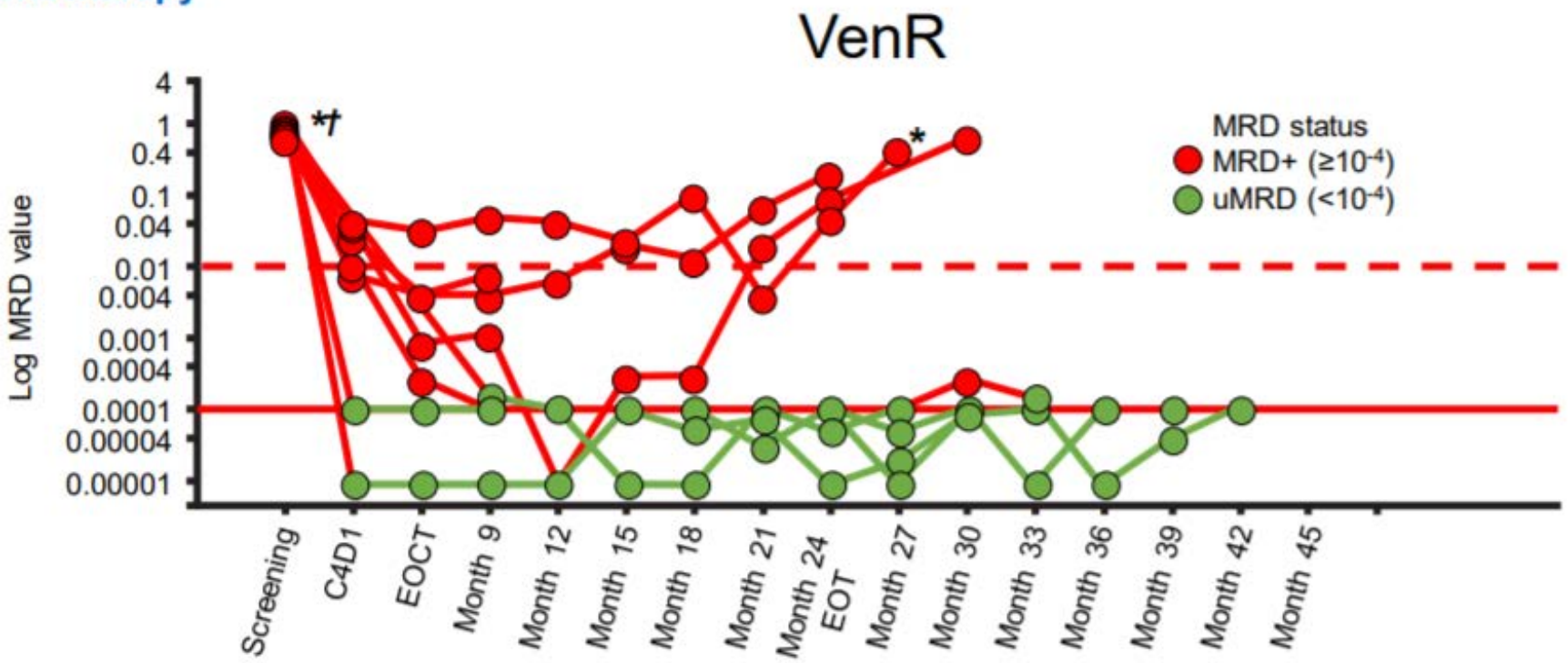



| Status Off Therapy, n (%) | uMRD (n = 83) | Low MRD+ (n = 23) | High MRD+ (n = 14) | Missing (n = 10) |
|---|---|---|---|---|
| Progression free | 72 (87) | 14 (61) | 1 (7) | 8 (80) |
| Progressive disease | 11 (13) | 9 (39) | 13 (93) | 2 (20) |

Seymour. ASH 2019. Abstr 355.

# MRD over time with venetoclax (MURANO)

**Figure 2. MRD kinetics during treatment and follow-up: VenR combination therapy→Ven monotherapy**




* *TP53* mutated
† 17p del- present

Kater et al EHA 2020

# Approach to first line therapy: Disease Characteristics

| Characteristic | Favor | Over |
|---|---|---|
| IgHV Unmutated | Targeted Agent | CIT |
| IgHV Mutated | Consider Secondary Characteristics | |
| 17P | BTK | Ven-G |
| Bulky Disease | BTK | Ven-G |

# Approach to first line therapy: Patient Characteristics

| Characteristic | Favor | Over |
|---|---|---|
| Hypertension | Acalabrutinib | Ibrutinib |
| Chronic Kidney Disease | BTK | Ven-G |
| Compliance Concerns | Acala/Obin | Acala mono |
| GERD/PPI | Ibrutinib | Acalabrutinib |
| Ibrutinib Intolerance | Acalabrutinib | Class Change |
| Anti-Coagulation / DOAC | Ven-G | BTK |

**Reimbursement and regulatory issues aside, which second-line systemic therapy would you recommend for a 75-year-old patient with IGHV-mutated CLL without del(17p) or TP53 mutation who responds to ibrutinib and then experiences disease progression 3 years later?**

a. FCR

b. BR

c. Acalabrutinib

d. Acalabrutinib + obinutuzumab

e. Venetoclax

f. Venetoclax + rituximab

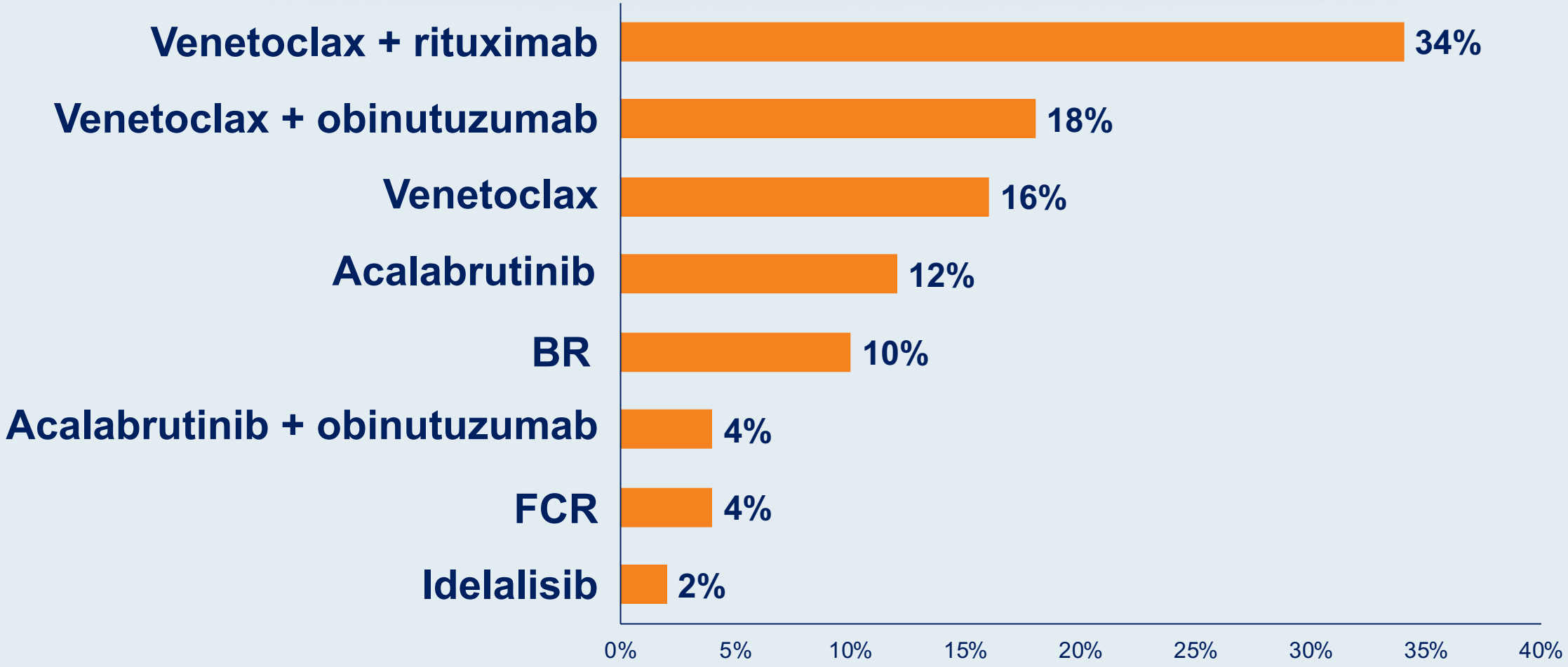
g. Venetoclax + obinutuzumab

h. Idelalisib

i. Duvelisib

j. Other

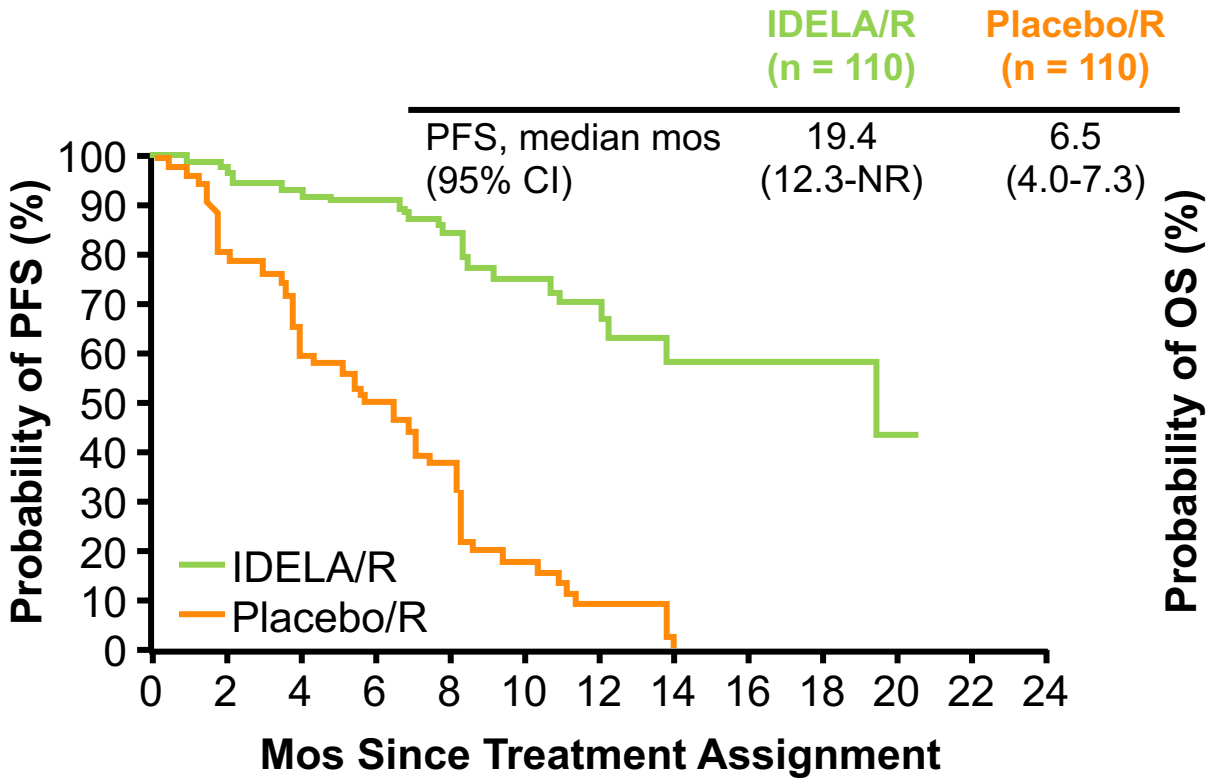
## Reimbursement and regulatory issues aside, which second-line systemic therapy would you recommend for a 75-year-old patient with IGHV-mutated CLL without del(17p) or TP53 mutation who responds to ibrutinib and then experiences disease progression 3 years later?

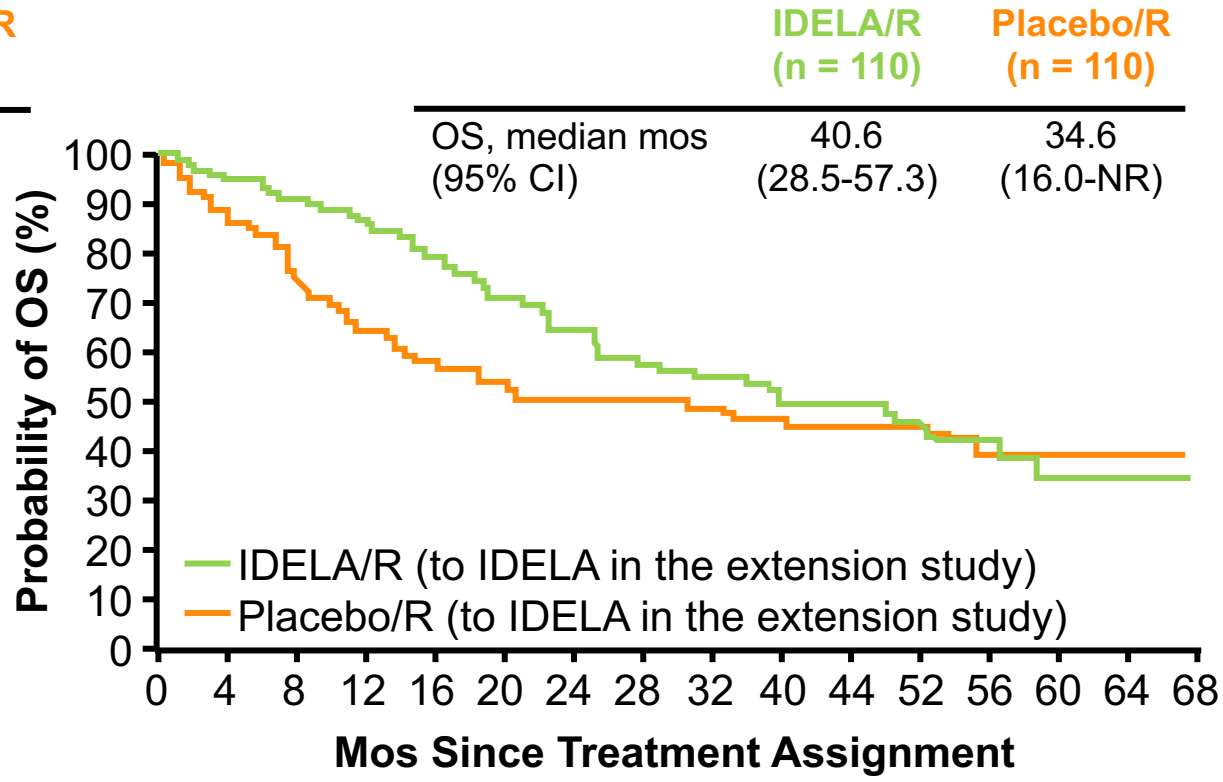



Survey of 50 US-based medical oncologists, June 2020

# Phase III Trial of Idelalisib + Rituximab in Relapsed CLL: Final Results of PFS (Primary Endpoint) and OS

- Phase III trial in patients with relapsed CLL after at least 1 prior line of tx
  - Primary study 116 with idelalisib/rituximab followed by extension study 117 with single agent idelalisib

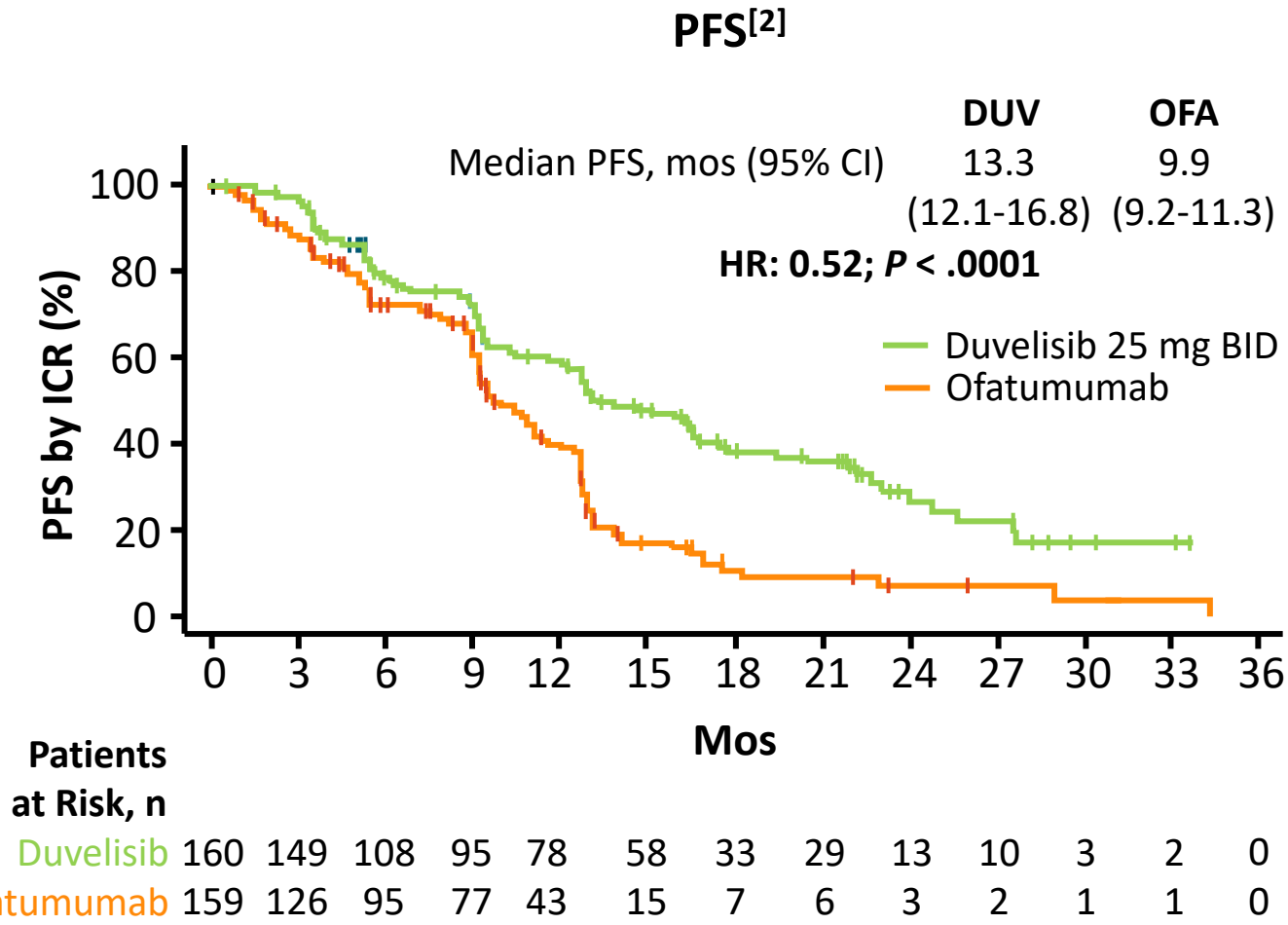



Sharman. JCO. 2019;37:1391.

# Phase III DUO Trial of Duvelisib vs Ofatumumab in R/R CLL

- Duvelisib is a dual inhibitor of PI3K delta and PI3K gamma[1]
- Administered orally twice daily[1]
- Prolonged PFS compared with ofatumumab in the DUO study[2]
- FDA approved for patients with R/R CLL/SLL and ≥2 previous therapies in September 2018




1. Flinn. Blood. 2018;131:877. 2. Flinn. Blood. 2018;132:2446.

# Major Pending Trials

- GLOW: Ibr/Ven vs Clb/Obin – registration study of novel/novel all oral combo
- CLL13: FCR/BR vs Ven with Obi or Rtx – can Ven based regimen beat aggressive CIT and which CD20 is better
- ACE-CL-311: FCR/BR vs Acala/Ven +/- Obi – Acala doublet or triplet vs CIT
- UNITY-CLL: Umbralisib/Ublituximab vs Clb/Obi – can PI3 be salvaged as a drug class
- ELEVATE-RR: Ibrutinib vs Acalabrutinib – clash of the BTK giants

Science Immunology

RESEARCH ARTICLES

Cite as: M. Roschewski *et al.*, *Sci. Immunol.* 10.1126/sciimmunol.abd0110 (2020).

CORONAVIRUS

# Inhibition of Bruton tyrosine kinase in patients with severe COVID-19

**Mark Roschewski[1*], Michail S. Lionakis[2*], Jeff P. Sharman[3*], Joseph Roswarski[4*], Andre Goy[5], M. Andrew Monticelli[6], Michael Roshon[7], Stephen H. Wrzesinski[8], Jigar V. Desai[2], Marissa A. Zarakas[2], Jacob Collen[9], Keith Rose[5], Ahmed Hamdy[10], Raquel Izumi[10], George W. Wright[11], Kevin K. Chung[9], Jose Baselga[12], Louis M. Staudt[1#], Wyndham H. Wilson[1#†]**

[1]Lymphoid Malignancies Branch, National Cancer Institute, Bethesda, MD; [2]Fungal Pathogenesis Section, Laboratory of Clinical Immunology and Microbiology, National Institute of Allergy and Infectious Diseases, Bethesda, MD; [3]Willamette Valley Cancer Institute and Research Center, US Oncology, Eugene, OR; [4]Hematology-Oncology Department, Walter Reed National Military Medical Center, Bethesda, MD; [5]John Theurer Cancer Center, Hackensack Meridian and School of Medicine at Seton Hall, NJ; [6]Rocky Mountain Cancer Center, US Oncology, Colorado Springs, CO; [7]Department of Emergency Medicine, Penrose-St. Francis Health Services, Colorado Springs, CO; US Acute Care Solutions, Canton, OH; [8]Department of Medicine, St. Peter's Hospital and US Oncology, Albany, NY; [9]Department of Medicine, Uniformed Services University of the Health Sciences, Bethesda, MD; [10]Acerta Pharma, South San Francisco, CA; [11]Biometric Research Branch, Division of Cancer Diagnosis and Treatment, National Cancer Institute, Bethesda, MD, USA [12]AstraZeneca, One MedImmune Way, Gaithersburg, MD

# Dr Sharman Case Presentation: 66-Year-Old Man with CLL

- 66 y/o male
- ALC 7400 in 2016, CLL diagnosis  in 2/2018  WBC 37K
- No organomegaly or LN, normal Hb, PLT
- HbcoreAb+, Hypertension, Gout, BPH, Vertigo
- 7/2019 STEMI PTCA + stent x2, 11/2019 PTCA x1
  - Paroxismal atrial fibrillation
  - Renal failure Cr 1.6 mg/dl
  - Mild LV dysfunction, normal relaxation, mildly dilated LA, mild-mod MR, EF 45%
- Medications: apixaban, clopidogrel, diltiazem, omeprazole, allopurinol, FISH neg, US – spleen 16.5 cm
- Progressive lymphocytosis and anemia – non bulky nodes

| | WBC | ALC | Hb | PLT | Cr |
|---|---|---|---|---|---|
| 6/2018 | 47K | 40K | 15 | 128 | 1.3 |
| 5/2019 | 125K | 97K | 14.5 | 102K | 1.58 |
| 5/2020 | 258K | 236K | 11.5 | 109K | 1.78 |

# Dr Sharman Case Presentation: 69-Year-Old Woman with CLL

- 69 year old female in good health. Initially presented with only lymph node but workup revealed ALC 500K, Hgb 12, Plt 120
- IgHV unmutated, trisomy 12
- Initially treated (2014) with FCR x6 complicated by prolonged cytopenias but ultimately recovered
- 2017 had rapid progression – started on ibrutinib c/b drug related severe mucositis and neutropenia
- 2018 started on Ven/Rtx – MRD pos at end of two years, therapy continued, but sequential MRD showed rising levels
- 2020 started on acalabrutinib monotherapy – thus far (4 months) well tolerated

# Agenda

## Module 1: Chronic Lymphocytic Leukemia (CLL) – Dr Sharman

- Phase III trials of ibrutinib-based therapy in younger (ECOG-E1912) and older (A041202, RESONATE-2) patients
- Acalabrutinib for treatment-naïve (ELEVATE-TN) and relapsed/refractory CLL (ASCEND)
- Long-term follow-up of venetoclax-based therapy for newly diagnosed (CLL14) and relapsed CLL (MURANO)
- PI3 kinase inhibitors idelalisib and duvelisib in relapsed CLL
- Ongoing trials

## Module 2: Follicular Lymphoma – Dr Vose

- Role of obinutuzumab-based chemoimmunotherapy for treatment-naïve FL (GALLIUM)
- Lenalidomide/rituximab (R-squared) in the up-front (RELEVANCE) and relapsed/refractory settings (AUGMENT)
- Comparison of FDA-approved PI3 kinase inhibitors in FL: idelalisib, duvelisib and copanlisib

# Module 2: Follicular Lymphoma – Dr Vose

- Selection of first-line treatment (rituximab monotherapy)
- Selection of second-line treatment (rituximab/lenalidomide)
- Selection of third-line treatment (choice of PI3K inhibitor)
- Recent relevant publications

**Regulatory and reimbursement issues aside, what would be your most likely initial treatment choice for a 78-year-old patient with Stage III, Grade 1/2 follicular lymphoma (FL) with fatigue and symptomatic bulky adenopathy who requires treatment?**

a. Rituximab (R) alone

b. R-bendamustine

c. R-CHOP or R-CVP

d. Obinutuzumab (O) alone

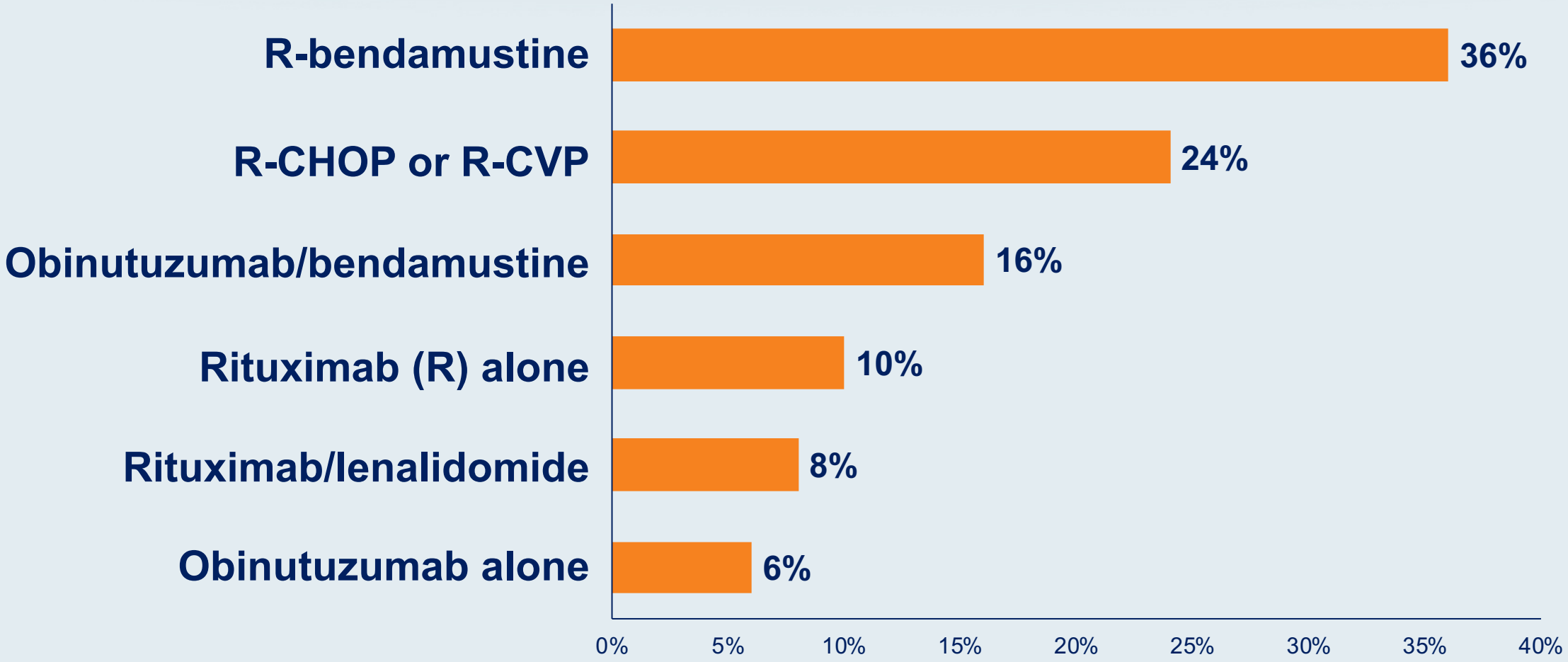
e. O-bendamustine

f. O-CHOP or O-CVP

g. Rituximab/lenalidomide

h. Other

## Regulatory and reimbursement issues aside, what would be your most likely initial treatment choice for a 78-year-old patient with Stage III, Grade 1/2 follicular lymphoma (FL) with fatigue and symptomatic bulky adenopathy who requires treatment?




Survey of 50 US-based medical oncologists, June 2020

**Regulatory and reimbursement issues aside, what would be your most likely initial treatment choice for a 60-year-old patient with Stage IV, Grade 3A FL with fatigue and symptomatic bulky adenopathy who requires treatment?**

a. Rituximab (R) alone

b. R-bendamustine

c. R-CHOP or R-CVP

d. Obinutuzumab (O) alone

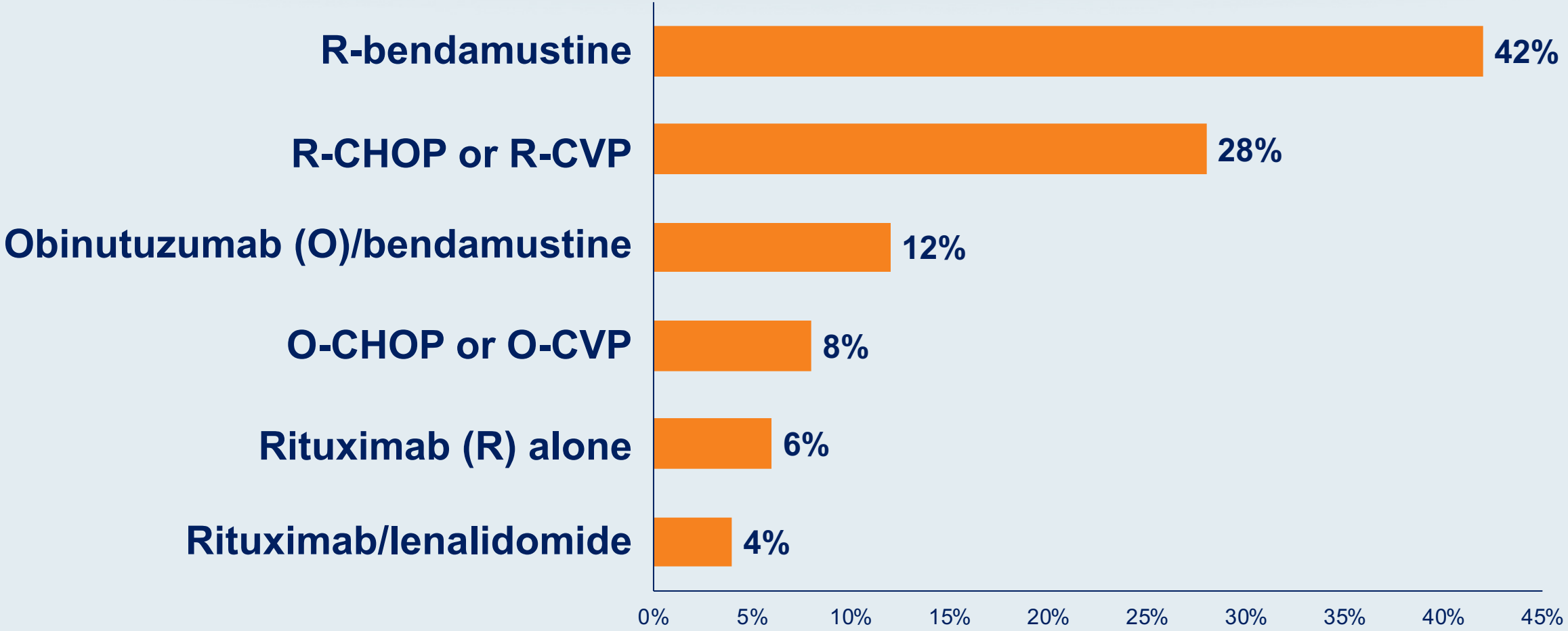
e. O-bendamustine

f. O-CHOP or O-CVP

g. Rituximab/lenalidomide

h. Other

# Regulatory and reimbursement issues aside, what would be your most likely initial treatment choice for a 60-year-old patient with Stage IV, Grade 3A FL with fatigue and symptomatic bulky adenopathy who requires treatment?

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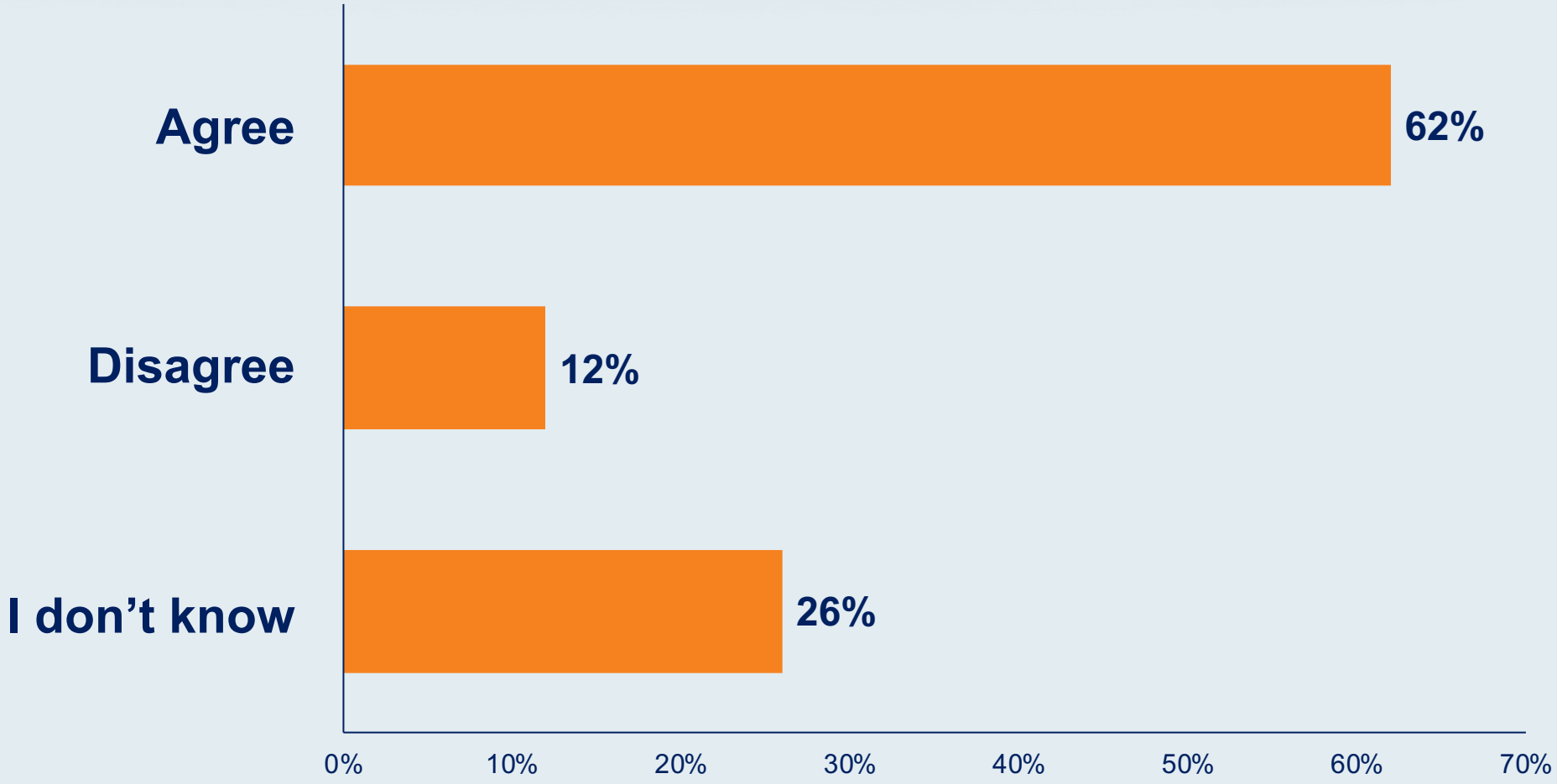
## Obinutuzumab/chemotherapy results in fewer relapses prior to 24 months than rituximab/chemotherapy when used as initial treatment for FL.

a. Agree

b. Disagree

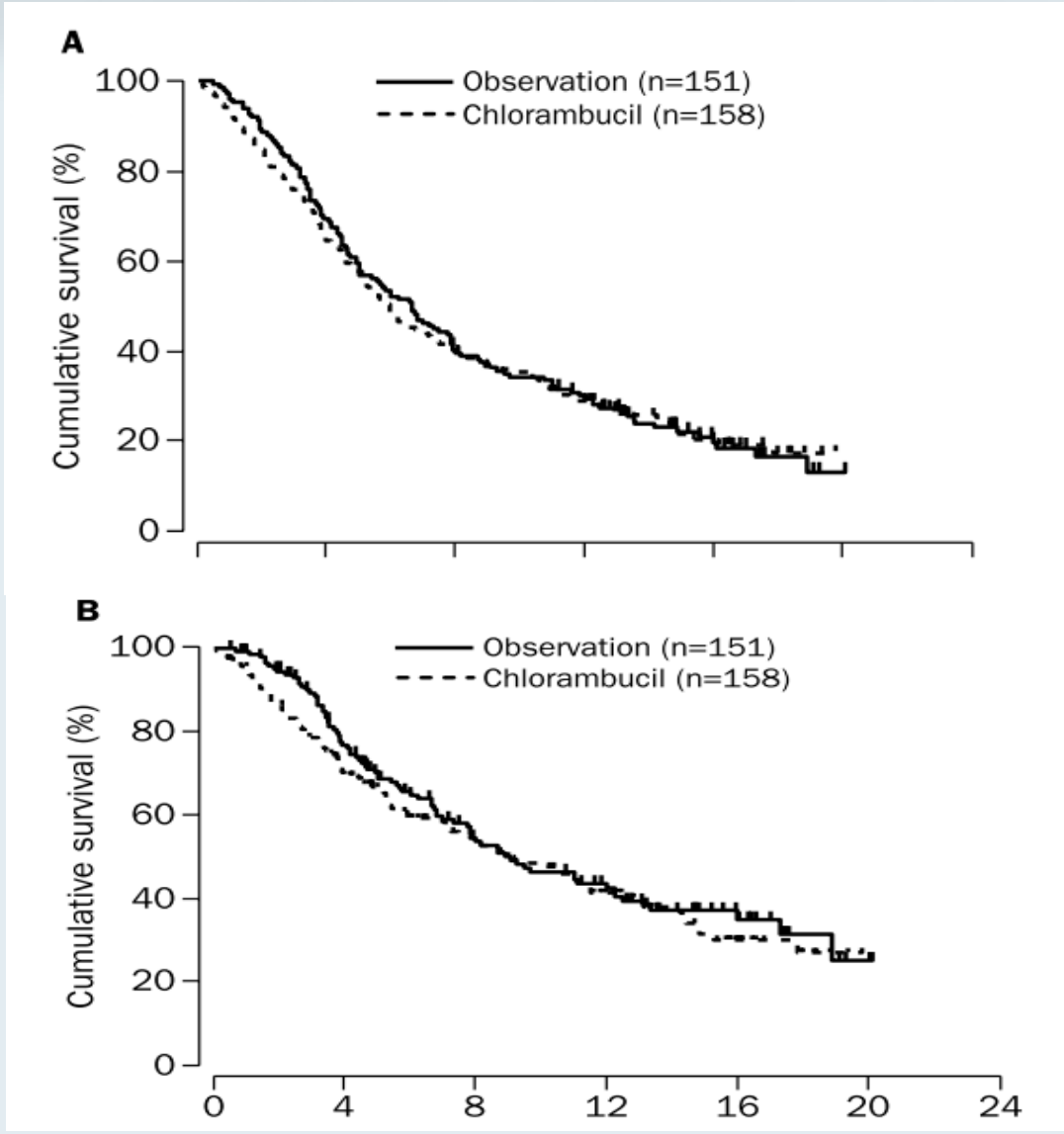
c. I don’t know

# Obinutuzumab/chemotherapy results in fewer relapses prior to 24 months than rituximab/chemotherapy when used as initial treatment for FL.



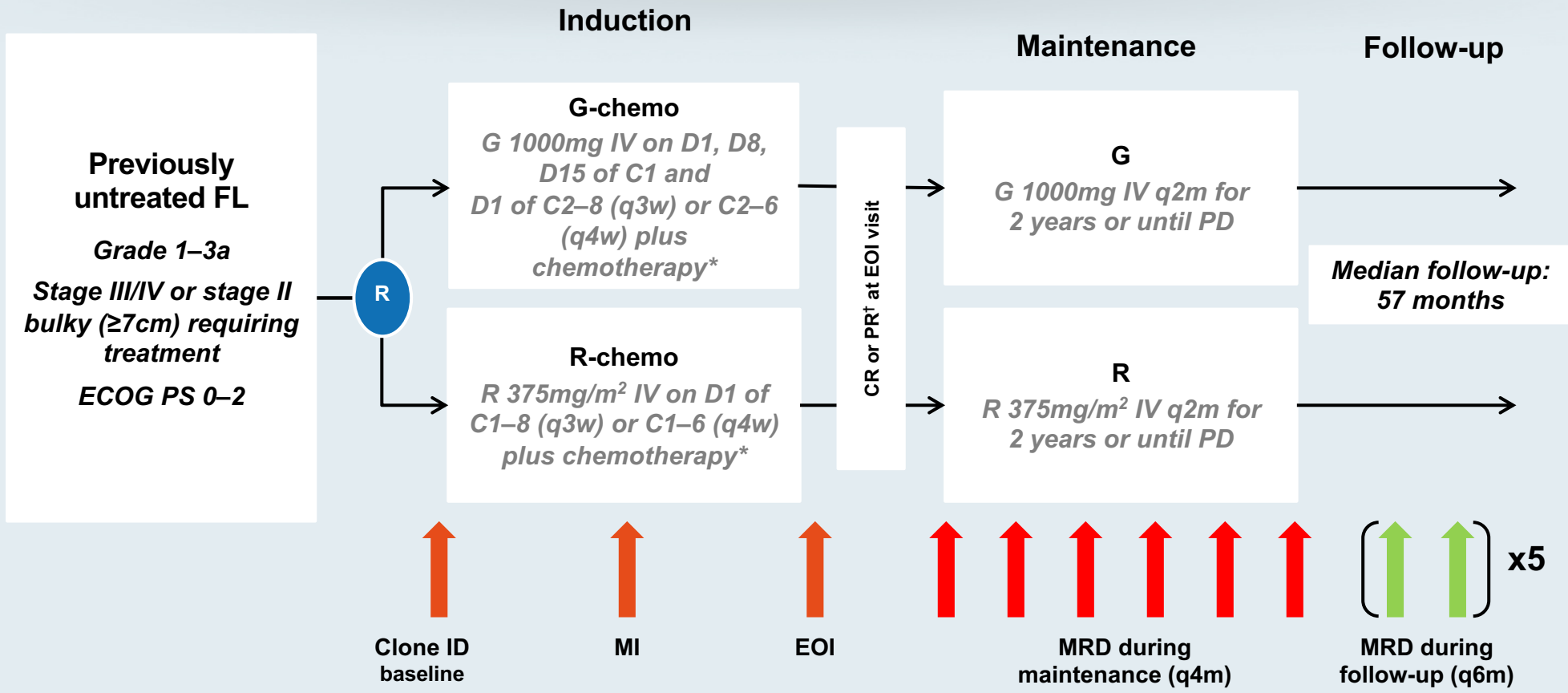

Survey of 50 US-based medical oncologists, June 2020

# Watch and Wait in FL: BNLI (n = 309)



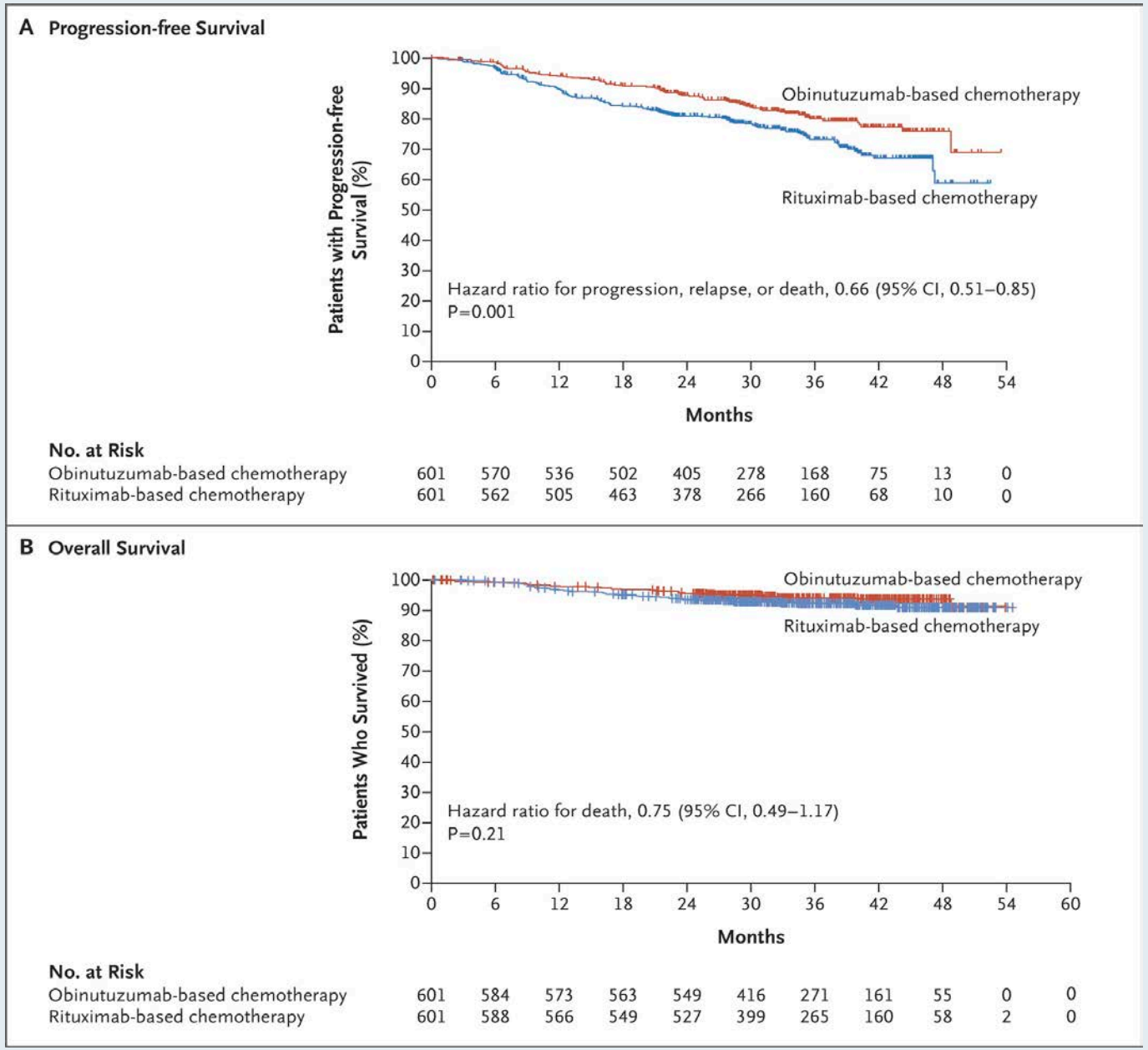

Ardeshna et al, Lancet 362:516, 2003

# GALLIUM Study with MRD assessment



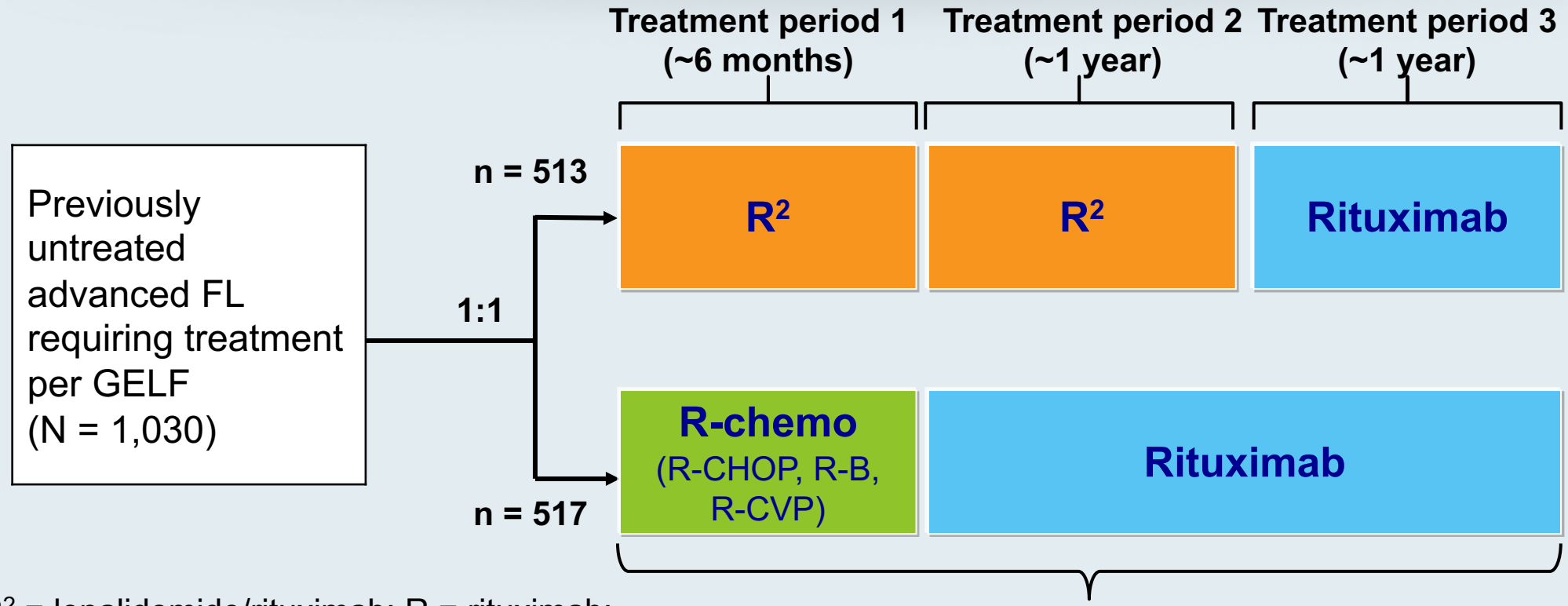

Marcus, et al NEJM 2017; 377(14): 1331-1344

# GALLIUM: Kaplan–Meier Estimates of Investigator-Assessed Progression-free Survival and Overall Survival among Patients with Follicular Lymphoma




Marcus, et al NEJM 2017; 377(14):1331-1344

# RELEVANCE: Phase III Trial Design

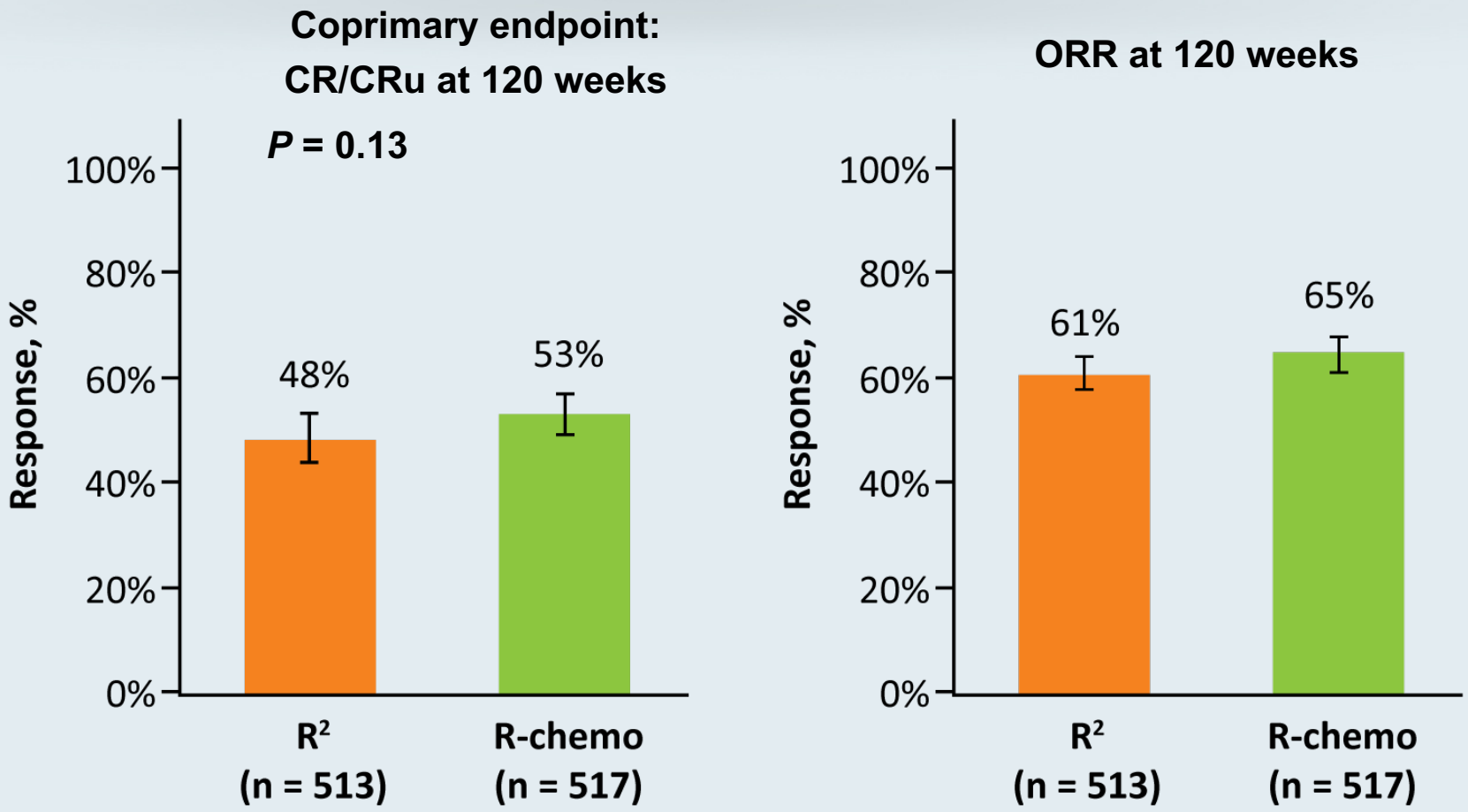



$R^2$ = lenalidomide/rituximab; R = rituximab; B = bendamustine; CVP = cyclophosphamide/vincristine/prednisone

**Primary endpoints: CR/CRu at 120 weeks and PFS**

Fowler NH et al. *Proc ASCO* 2018;Abstract 7500.

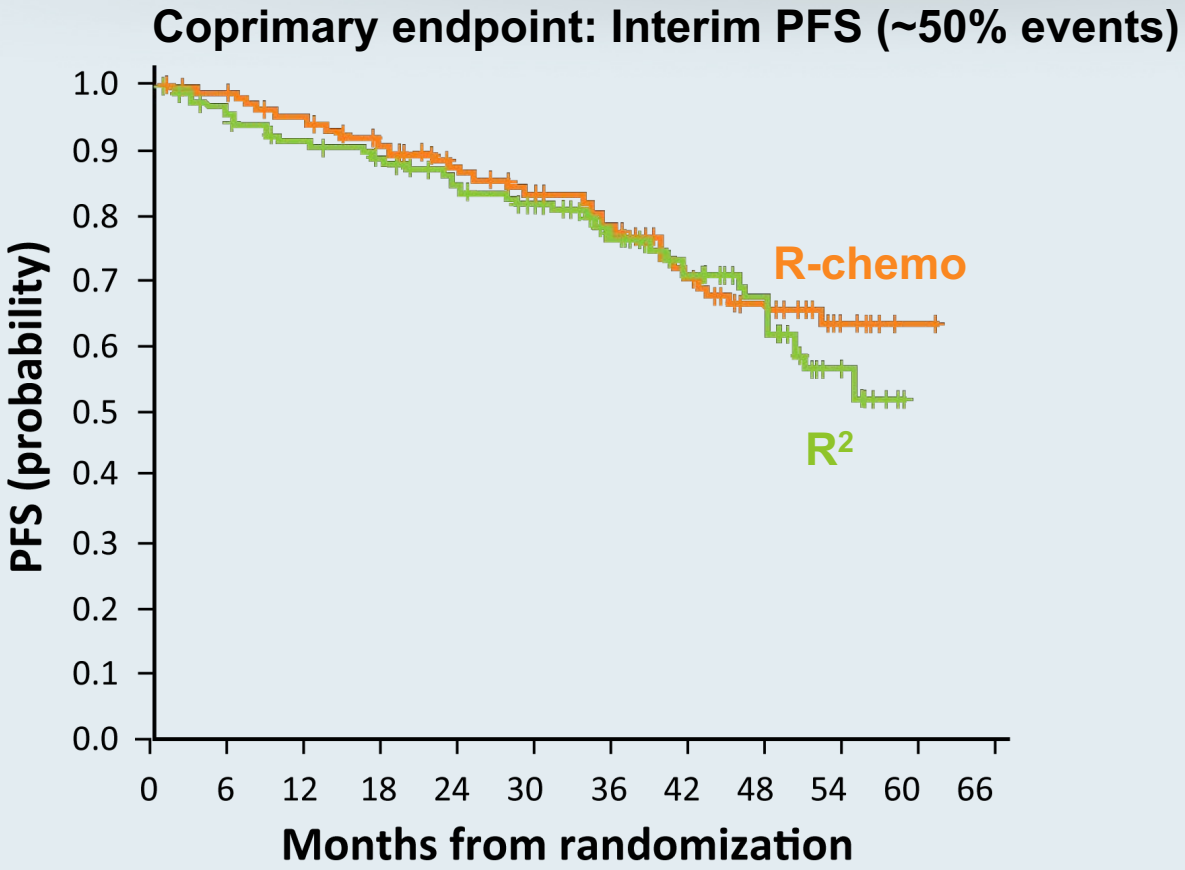
# RELEVANCE: Response




- 3-year duration of response = 77% ($R^2$) versus 74% (R-chemo)

Fowler NH et al. *Proc ASCO* 2018;Abstract 7500;
Morschhauser F et al. *N Engl J Med* 2018;379(10):934-47.

# RELEVANCE: Interim PFS by Independent Review Committee

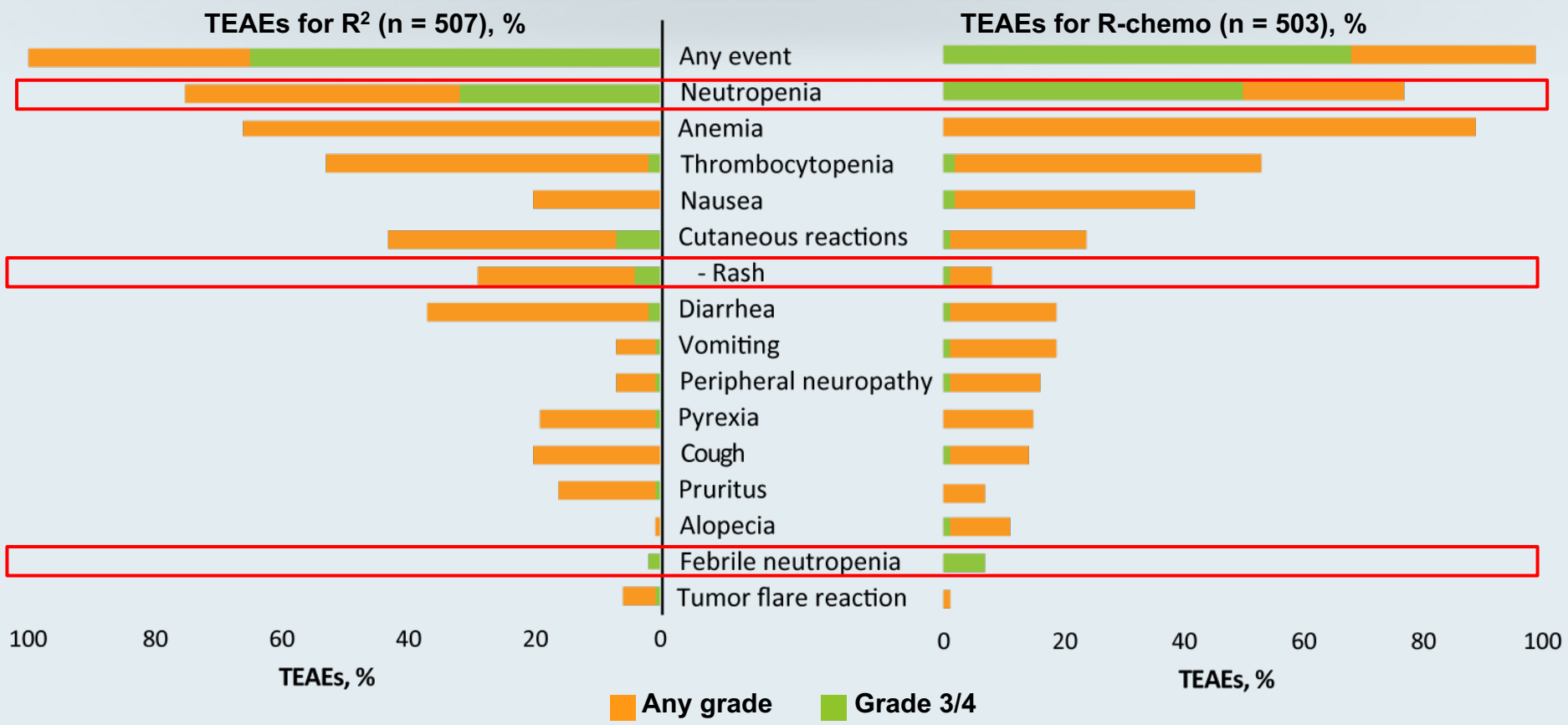



| | R² (n = 513) | R-chemo (n = 517) |
|---|---|---|
| 3-year PFS | 77% | 78% |
| HR | 1.10 | |
| *p*-value | 0.48 | |

- At median follow-up of 37.9 mo, interim PFS was similar in both arms
- 3-y OS (immature in ITT) = 94% ($R^2$) vs 94% (R-chemo); HR = 1.16

Fowler NH et al. *Proc ASCO* 2018;Abstract 7500.

# RELEVANCE: Select Treatment-Emergent AEs (TEAEs)




- Early discontinuation of trial treatment: 11% with $R^2$ versus 3% with R-chemo
- Second primary cancers: 7% with $R^2$ versus 10% with R-chemo


Fowler NH et al. *Proc ASCO* 2018;Abstract 7500;
Morschhauser F et al. *N Engl J Med* 2018;379(10):934-47.

National Comprehensive Cancer Network®

# NCCN Guidelines Version 1.2020
# Follicular Lymphoma (grade 1–2)

NCCN Guidelines Index
Table of Contents
Discussion

## SUGGESTED TREATMENT REGIMENS[a,b,c]

An FDA-approved biosimilar is an appropriate substitute for rituximab.

**First-line Therapy**

- Preferred regimens (in alphabetical order)
  - Bendamustine[d] + obinutuzumab[e] or rituximab
  - CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) + obinutuzumab[e] or rituximab
  - CVP (cyclophosphamide, vincristine, prednisone) + obinutuzumab[e] or rituximab
  - Lenalidomide + rituximab
- Other recommended regimens
  - Lenalidomide + obinutuzumab (category 2B)
  - Rituximab (375 mg/m$^2$ weekly for 4 doses) (consider for low tumor burden)[f]

**First-line Therapy for Elderly or Infirm** (if none of the above are expected to be tolerable in the opinion of treating physician)

- Preferred regimen
  - Rituximab (375 mg/m$^2$ weekly for 4 doses)
- Other recommended regimens
  - Chlorambucil ± rituximab
  - Cyclophosphamide ± rituximab
  - Ibritumomab tiuxetan[g] (category 2B)

**First-line Consolidation or Extended Dosing** (optional)

- Preferred regimens following chemoimmunotherapy
  - Rituximab maintenance 375 mg/m$^2$ one dose every 8–12 weeks for 12 doses for patients initially presenting with high tumor burden (category 1)[h]
  - Obinutuzumab maintenance (1000 mg every 8 weeks for 12 doses)
- Other recommended regimens
  - If initially treated with single-agent rituximab, consolidation with rituximab 375 mg/m$^2$ one dose every 8 weeks for 4 doses
  - Ibritumomab tiuxetan[g,i] (category 2B)

See Second-line and Subsequent Therapy on FOLL-B 2 of 4

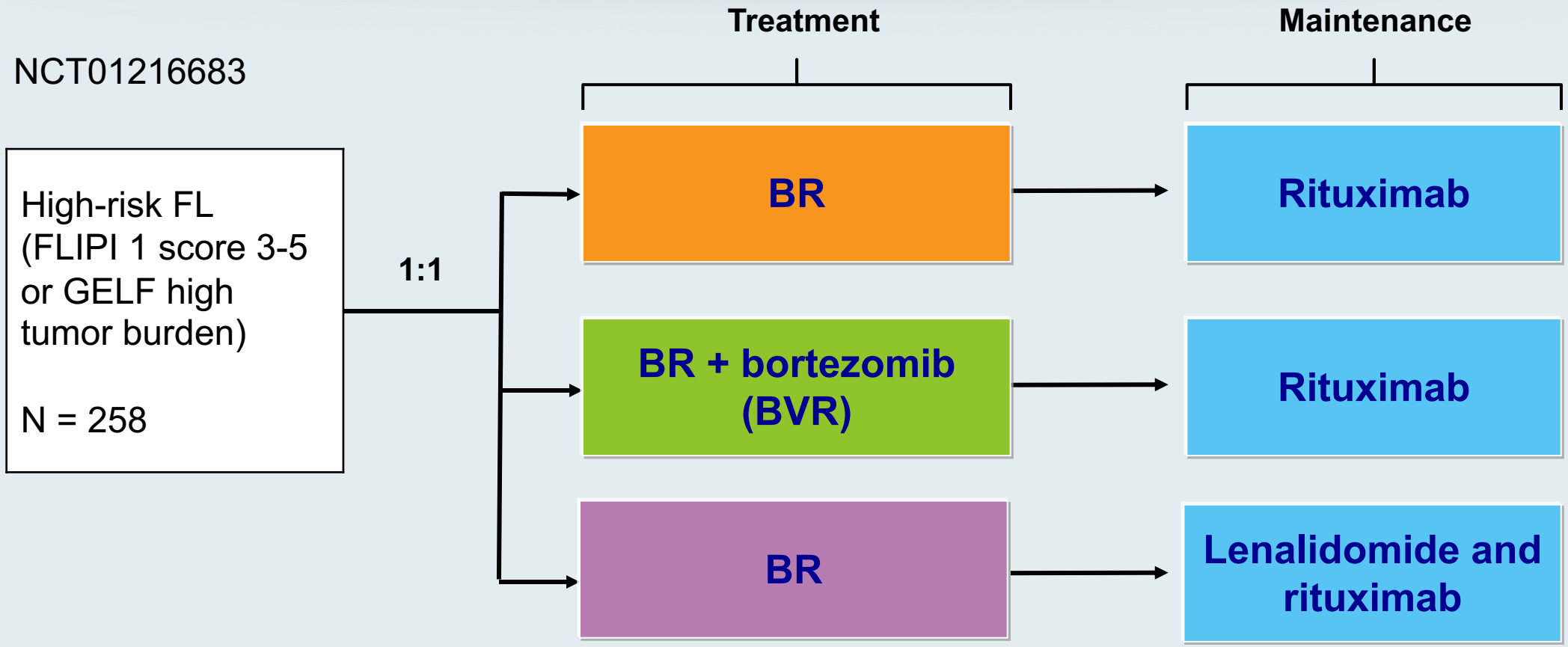
Consider prophylaxis for tumor lysis syndrome (See NHODG-B)
See monoclonal antibody and viral reactivation (NHODG-B)

# A 3-Arm Randomized Phase II Study of Bendamustine/Rituximab with Bortezomib Induction or Lenalidomide Continuation in Untreated Follicular Lymphoma: ECOG-ACRIN E2408

Andrew M. Evens[1], Fangxin Hong[2], Thomas M. Habermann[3], Ranjana H. Advani[4], Randy D. Gascoyne[5], Thomas E. Witzig[3], Andrew Quon[6], Erik Ranheim[7], Stephen M. Ansell[3], Puneet Singh Cheema[8], Philip A. Dy[9], Timothy E. O'Brien[10], Jane N. Winter[11], Terrence P. Cescon[12], Julie E. Chang[7], Brad S. Kahl[13]

*Clin Cancer Res* 2020;[Online ahead of print].

# ECOG-ACRIN E2408: Phase II Trial Design



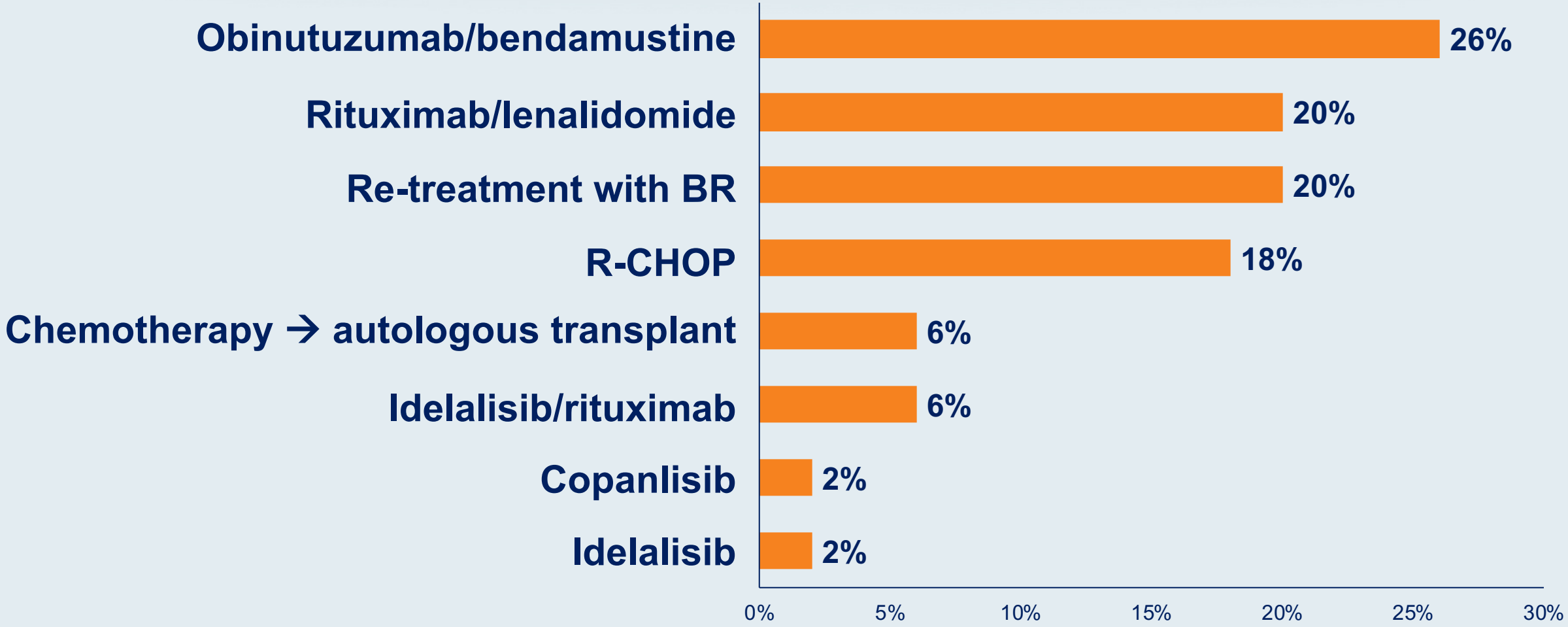

**Primary endpoints: Complete remission rate of BR vs BVR induction**
**1-year DFS with maintenance rituximab vs rituximab and lenalidomide**

Sharman J et al. *Clin Cancer Res* 2020;[Online ahead of print].

**Regulatory and reimbursement issues aside, what is your usual second-line therapy for a 65-year-old patient with FL who achieves a complete response to BR followed by 2 years of rituximab maintenance but then experiences disease relapse 4 years later?**

a. Re-treatment with BR
b. Obinutuzumab/bendamustine
c. R-CHOP
d. Rituximab/lenalidomide
e. Idelalisib
f. Idelalisib/rituximab
g. Copanlisib
h. Duvelisib
i. Chemotherapy → autologous transplant
j. Other

## Regulatory and reimbursement issues aside, what is your usual second-line therapy for a 65-year-old patient with FL who achieves a complete response to BR followed by 2 years of rituximab maintenance but then experiences disease relapse 4 years later?

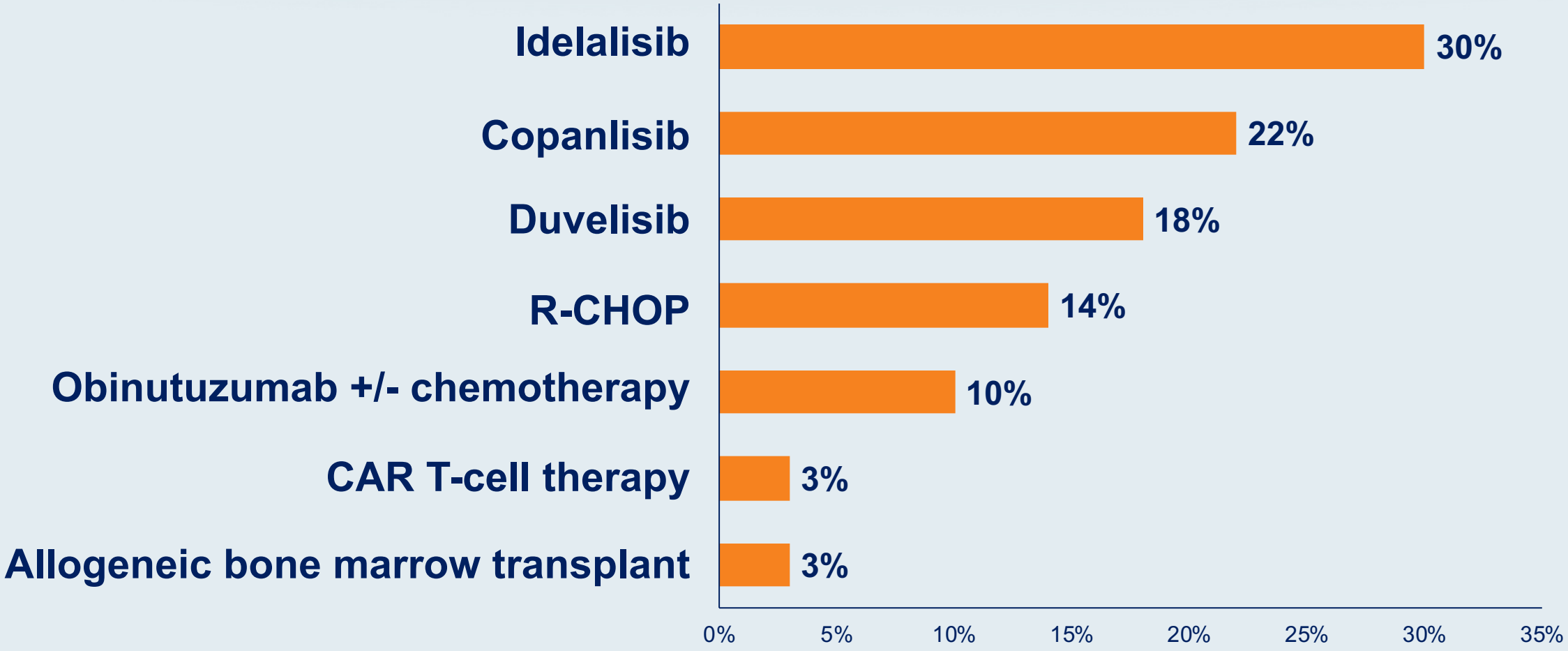



Survey of 50 US-based medical oncologists, June 2020

**What is your usual third-line treatment for a patient with FL who received first-line BR, second-line lenalidomide/rituximab and then develops disease progression?**

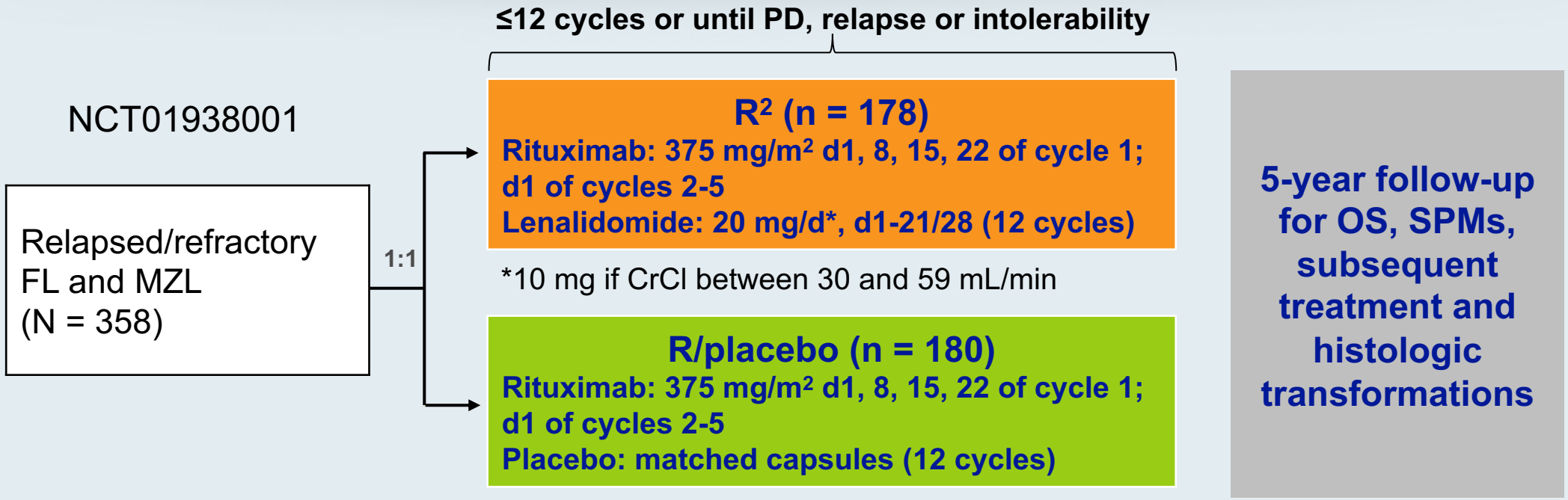
a. Idelalisib
b. Copanlisib
c. Duvelisib
d. R-CHOP
e. Radioimmunotherapy
f. Obinutuzumab +/- chemotherapy
g. Other

# What is your usual third-line treatment for a patient with FL who receives first-line BR, second-line lenalidomide/rituximab and then develops disease progression?




Survey of 50 US-based medical oncologists, June 2020

# AUGMENT: A Randomized, Double-Blind Phase III Trial




- Prophylactic anticoagulation/antiplatelet Rx recommended for patients at risk
- Growth factor use was allowed per ASCO/ESMO guidelines[1,2]

**Primary endpoint: PFS by IRC (2007 IWG criteria w/o PET)**

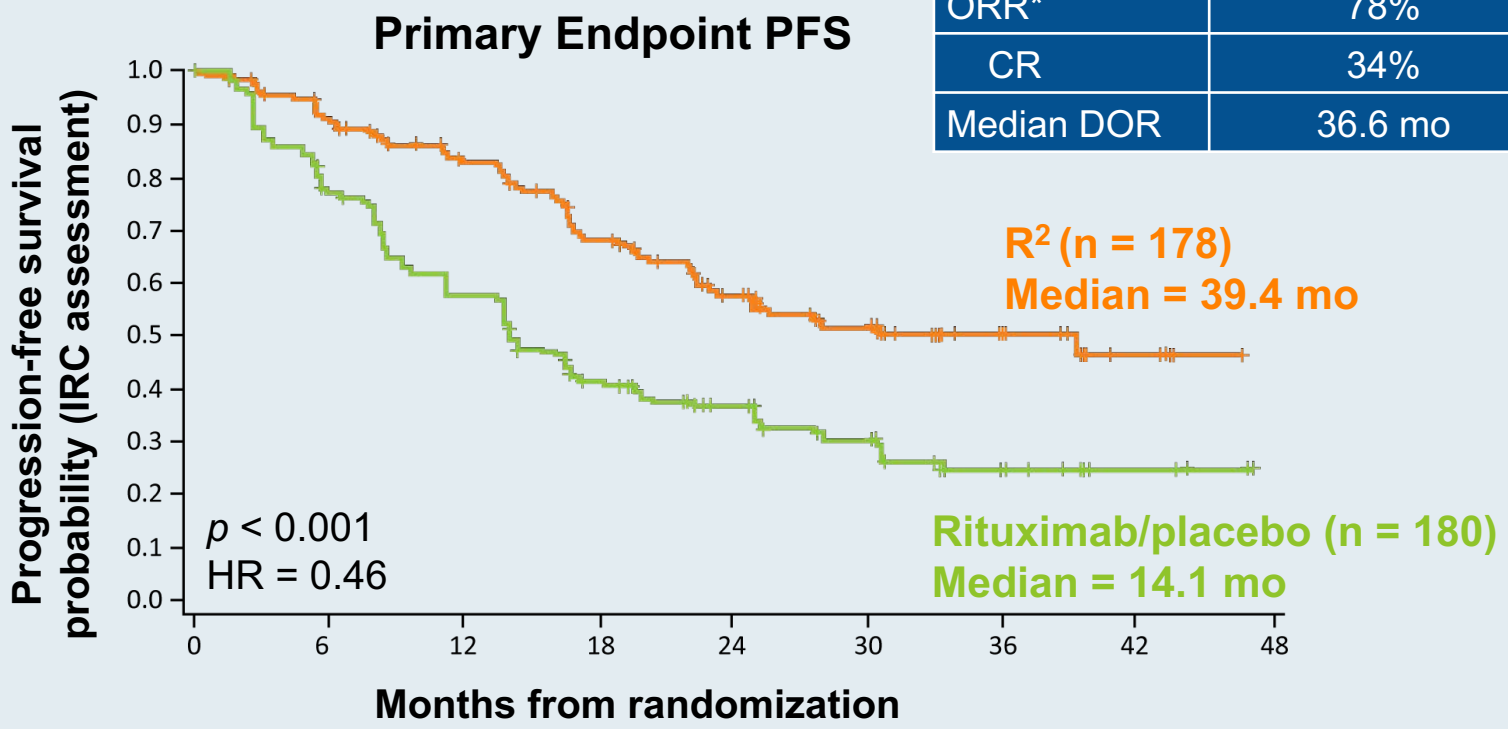
[1] Crawford J et al. *Ann Oncol* 2010;21(Suppl 5):248-51. [2] Smith TJ et al. *J Clin Oncol* 2015;33:3199-212.

Leonard JP et al. *J Clin Oncol* 2019; 1188-1199; *Proc ASH* 2018;Abstract 445.

# AUGMENT: R² versus Rituximab/Placebo for R/R FL or Marginal Zone Lymphoma

| By IRC | R² (n = 178) | R/placebo (n = 180) |
|---|---|---|
| ORR* | 78% | 53% |
| CR | 34% | 18% |
| Median DOR | 36.6 mo | 21.7 mo |

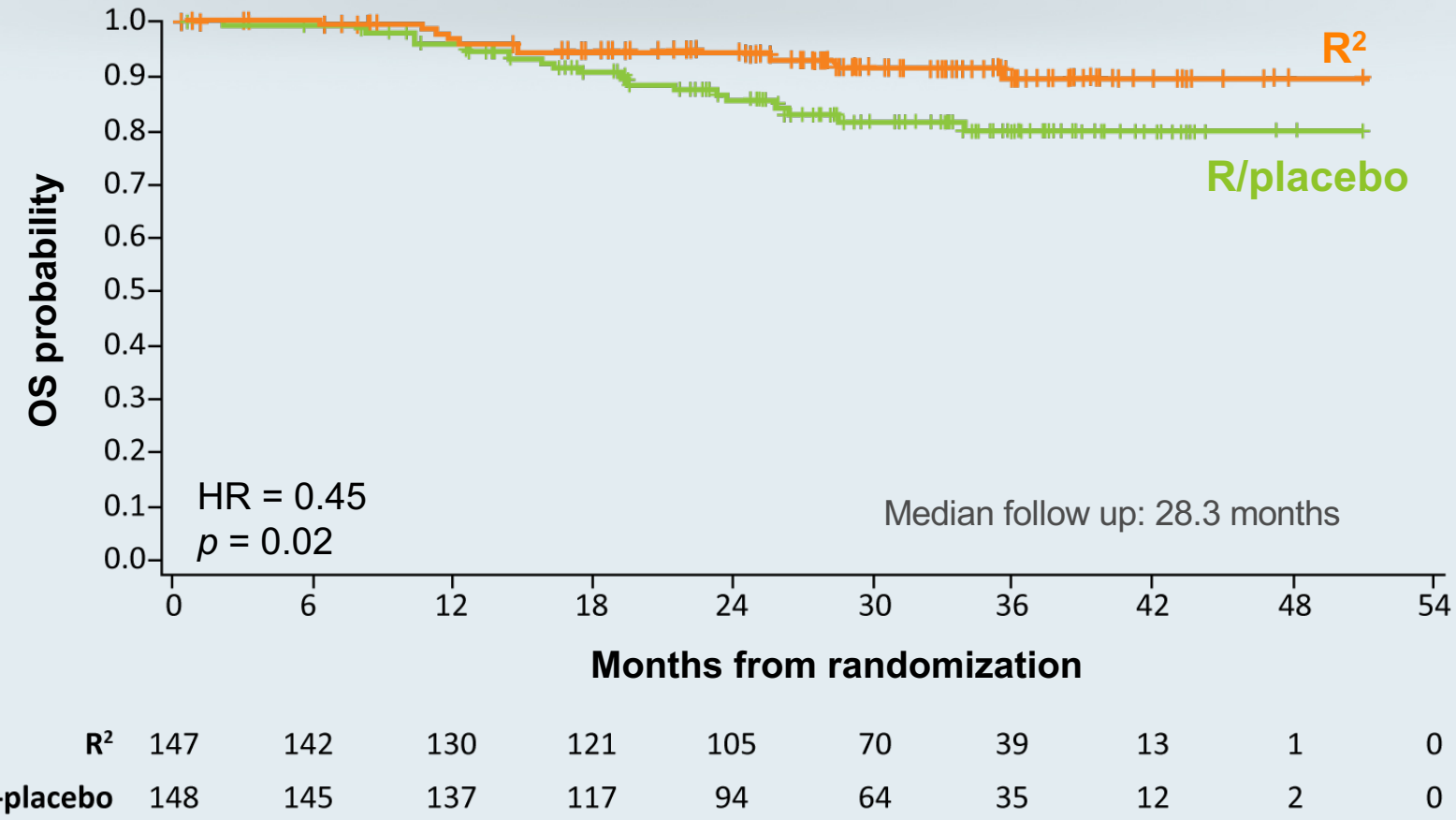
* $p < 0.001$




- Grade 3 or 4 treatment-emergent adverse events: 69% with R² versus 32% with R/placebo
  - Neutropenia: 50% with R² versus 13% with R/placebo
  - Leukopenia: 7% with R² versus 2% with R/placebo

Leonard JP et al. *J Clin Oncol* 2019; 1188-1199

# AUGMENT: Overall Survival for Patients with FL (Prespecified Subgroup Analysis)




- 35 total deaths (11 $R^2$, 24 R/placebo)
- 2-year OS was 95% for $R^2$ and 86% for R/placebo

Leonard JP et al. *J Clin Oncol* 2019; 1188-1199

# Comparison of FDA-Approved PI3 Kinase Inhibitors

| Agent | Idelalisib | Copanlisib | Duvelisib |
|---|---|---|---|
| Route | Oral- BID | IV | Oral- BID |
| Indication | Relapsed CLL/SLL, FL | Relapsed FL | Relapsed CLL/SLL, FL |
| Toxicities | Diarrhea – 14%<br>Pneumonitis – 4%<br>Cytopenias – 28%<br>Hepatotoxicity – 18%<br>Infections – 21% | Hyperglycemia – 41%<br>Hypertension – 26%<br>Cytopenias – 24%<br>Rash – 3%<br>Diarrhea<br>Hepatotoxicity | Diarrhea – 18%<br>Cytopenias – 24-42%<br>Rash – 5%<br>Pneumonitis – 5%<br>Hepatotoxicity – 5% |
| Efficacy | FL: ORR – 54%<br>CR – 8%<br>CLL: ORR – 58% | ORR – 59%<br>CR – 20% | ORR 78% (CLL/SL),<br>42% (FL) |
| Prophylaxis | PJP prophylaxis<br>CMV monitoring or prophylaxis | PJP prophylaxis<br>CMV monitoring or prophylaxis | PJP prophylaxis<br>CMV monitoring or prophylaxis |

National Comprehensive Cancer Network®

# NCCN Guidelines Version 1.2020
# Follicular Lymphoma (grade 1–2)

NCCN Guidelines Index
Table of Contents
Discussion

## SUGGESTED TREATMENT REGIMENS[a,b,c]

**An FDA-approved biosimilar is an appropriate substitute for rituximab.**

### Second-line and Subsequent Therapy

- Preferred regimens[j] (alphabetical order)
  - Bendamustine[k] + obinutuzumab[l] or rituximab
  - CHOP + obinutuzumab[l] or rituximab
  - CVP + obinutuzumab[l] or rituximab
  - Lenalidomide + rituximab
- Other recommended regimens (alphabetical order)
  - Ibritumomab tiuxetan[g]
  - Lenalidomide (if not a candidate for anti-CD20 monoclonal antibody therapy)
  - Lenalidomide + obinutuzumab
  - Obinutuzumab
  - PI3K inhibitors (relapsed/refractory after 2 prior therapies)
    - ◊ Copanlisib[m]
    - ◊ Duvelisib[m]
    - ◊ Idelalisib[m]
  - Rituximab
  - See Second-line Therapy for DLBCL (BCEL-C 2 of 4) without regard to transplantability

Consider prophylaxis for tumor lysis syndrome (See NHODG-B)
See monoclonal antibody and viral reactivation (NHODG-B)

### Second-line and Subsequent Therapy for Elderly or Infirm

(if none of the therapies are expected to be tolerable in the opinion of treating physician)

- Preferred regimen
  - Rituximab (375 mg/m$^2$ weekly for 4 doses)
- Other recommended regimens
  - Chlorambucil ± rituximab
  - Cyclophosphamide ± rituximab
  - Ibritumomab tiuxetan[g] (category 2B)

### Second-line Consolidation or Extended Dosing (optional)

- Preferred regimen
  - Rituximab maintenance 375 mg/m$^2$ one dose every 12 weeks for 2 years (category 1)
  - Obinutuzumab maintenance for rituximab-refractory disease (1 g every 8 weeks for total of 12 doses)
- Other recommended regimens
  - High-dose therapy with autologous stem cell rescue
  - Allogeneic hematopoietic cell transplant for highly selected patients

### Histologic Transformation to DLBCL

- Anti-CD19 CAR T-cell therapy (only after ≥2 prior chemoimmunotherapy regimens)[n,o]
  - Axicabtagene ciloleucel
  - Tisagenlecleucel

# FDA Granted Acclerated Approval to Tazemetostat for R/R FL

## Press Release – June 18, 2020

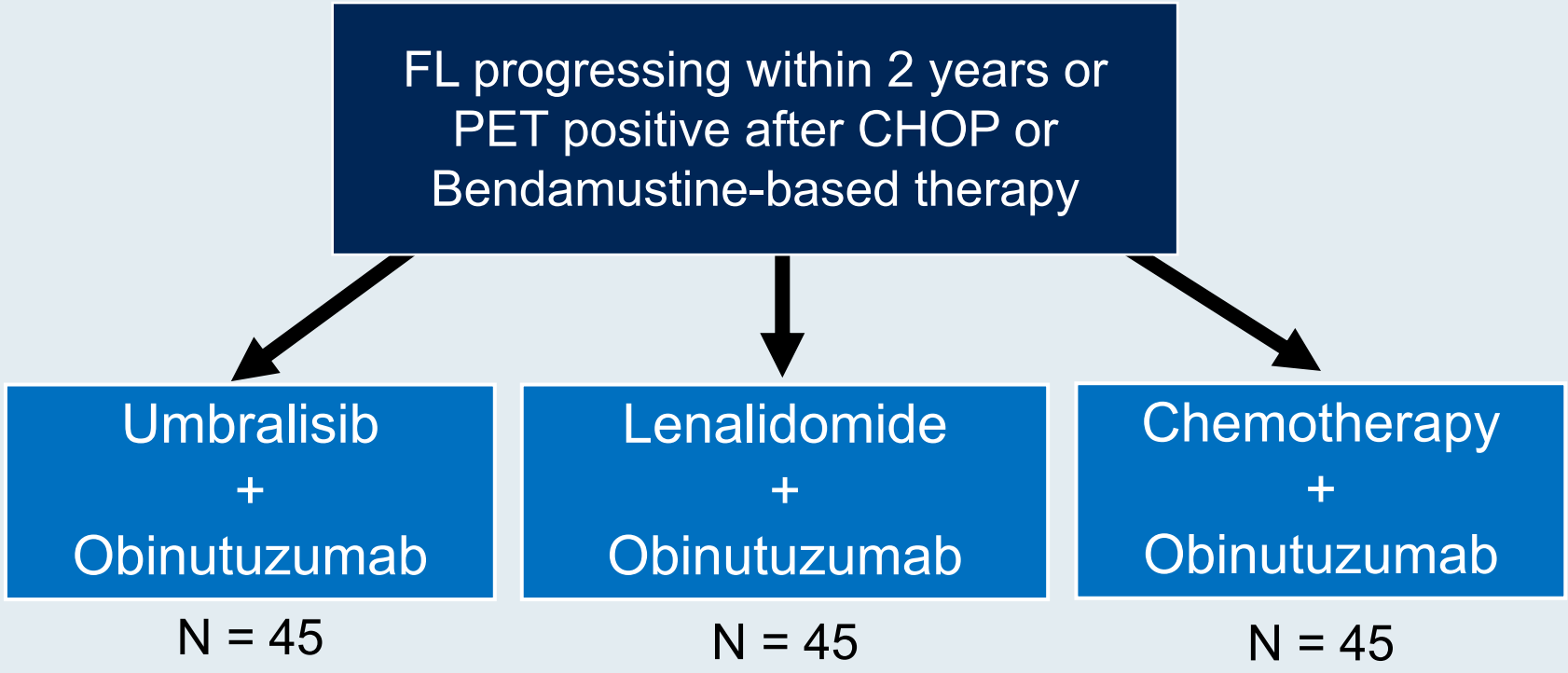
"On June 18, 2020, the Food and Drug Administration granted accelerated approval to tazemetostat, an EZH2 inhibitor, for adult patients with relapsed or refractory (R/R) follicular lymphoma (FL) whose tumors are positive for an EZH2 mutation as detected by an FDA-approved test and who have received at least 2 prior systemic therapies, and for adult patients with R/R FL who have no satisfactory alternative treatment options. Today, the FDA also approved the cobas EZH2 Mutation Test (Roche Molecular Systems, Inc.) as a companion diagnostic for tazemetostat.

Approval was based on two open-label, single-arm cohorts (Cohort 4 - EZH2 mutated FL and Cohort 5 - EZH2 wild-type FL) of a multi-center trial (Study E7438-G000-101, NCT01897571) in patients with histologically confirmed FL after at least 2 prior systemic therapies. The prescribing information includes a warning and precaution for secondary malignancies.The recommended tazemetostat dose is 800 mg taken orally twice daily with or without food."

https://www.fda.gov/drugs/fda-granted-accelerated-approval-tazemetostat-follicular-lymphoma

# SWOG-S1608: Randomized trial in early progressing/refractory FL

Primary clinical objective: CR by PET/CT
Primary translational objective: Validation of m7-FLIPI




www.clinicaltrials.gov (Accessed June 2020).

# Dr Vose Case Presentation: 60-Year-Old Man with FL

- 60 y/o Male who presented with Stage IVA FL – extensive lymphadenopathy and pancytopenia
- Bendamustine/Obinutuzumab X 6 cycles – CR
- Followed by Obinutuzumab maintenance 2 years
- Acyclovir and trimethoprim-sulfamethoxazole prophylaxis
- Remains in CR 1 year after stopping Obinutuzumab

# Dr Vose Case Presentation: 72-Year-Old Woman with FL

- 72 y/o female patient who had stage IIIA FL diagnosed 7 years ago
- She received Bendamustine/Rituximab X 6 at diagnosis, then Rituximab maintenance X 2 yrs
- She relapsed 5 years after finishing maintenance
- She was started on Rituximab/Lenalidomide ($R^2$) – in CR at 9 months after starting

**Thank you for joining us!**

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