Meet The Professor
Management of Chronic Lymphocytic Leukemia

Mitchell R Smith, MD, PhD
Professor of Medicine
Associate Center Director for Clinical Investigations
Director, Division of Hematology and Oncology
GW Cancer Center
Washington, DC

Commercial Support

These activities are supported by educational grants from AbbVie Inc and AstraZeneca Pharmaceuticals LP.

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Dr Love — Disclosures

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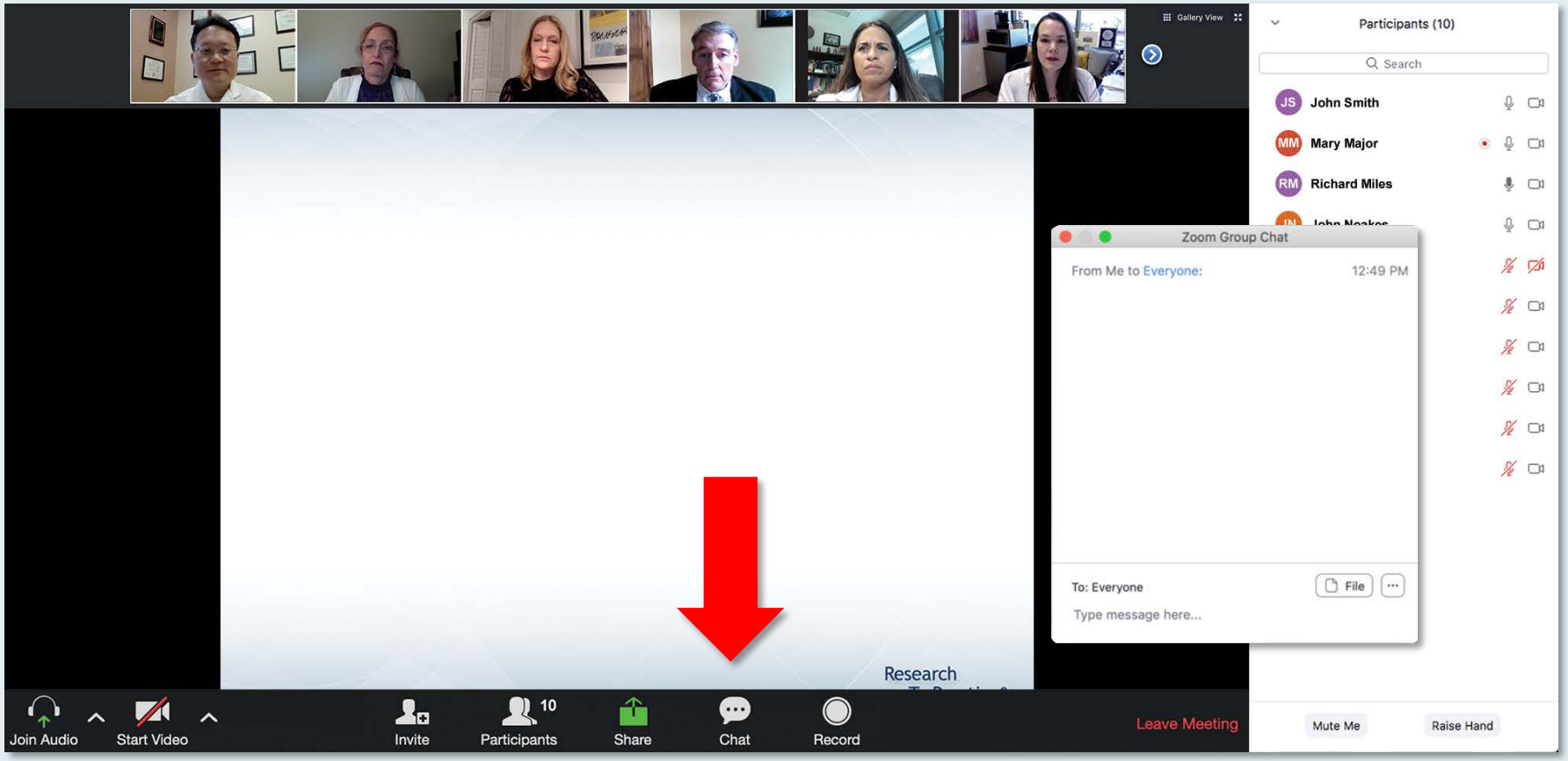
We Encourage Clinicians in Practice to Submit Questions



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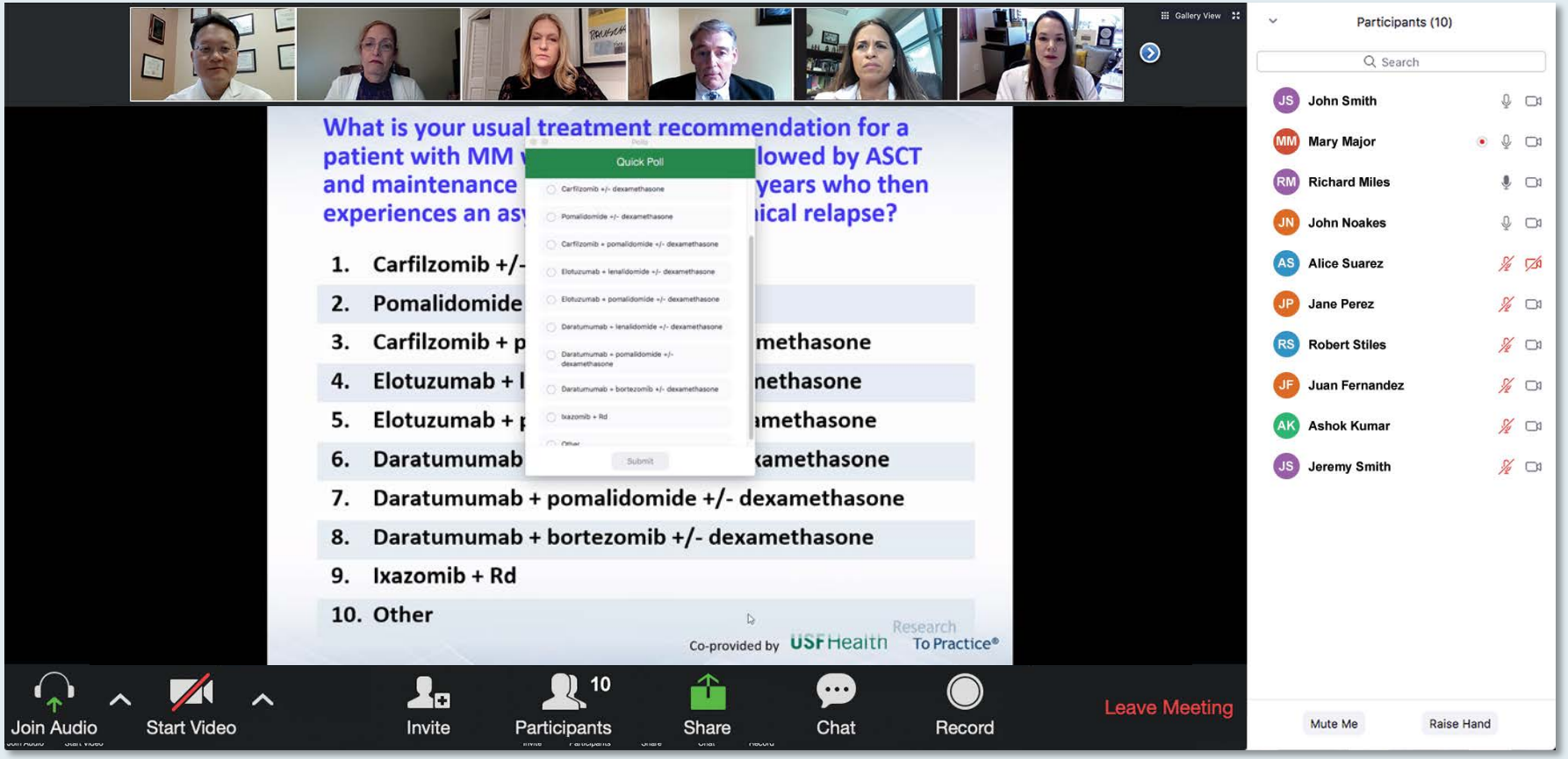

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Upcoming Live Webinars

Thursday, October 8, 2020
12:00 PM – 1:00 PM ET

Meet The Professor: Immunotherapy and Novel Agents in Gynecologic Cancers

Faculty
Brian M Slomovitz, MD

Moderator
Neil Love, MD

Tuesday, October 13, 2020
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Meet The Professor: Management of Lung Cancer

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Paul K Paik, MD

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Meet The Professor: Management of Ovarian Cancer

Faculty
Kathleen Moore, MD

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Upcoming Live Webinars

Friday, October 16, 2020
11:00 AM – 12:00 PM ET

Addressing Current Questions and Controversies in the Management of Non-Small Cell Lung Cancer with EGFR Mutation

Faculty
Roy S Herbst, MD, PhD
Suresh S Ramalingam, MD
Helena Yu, MD

Moderator
Neil Love, MD

Thank you for joining us!

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

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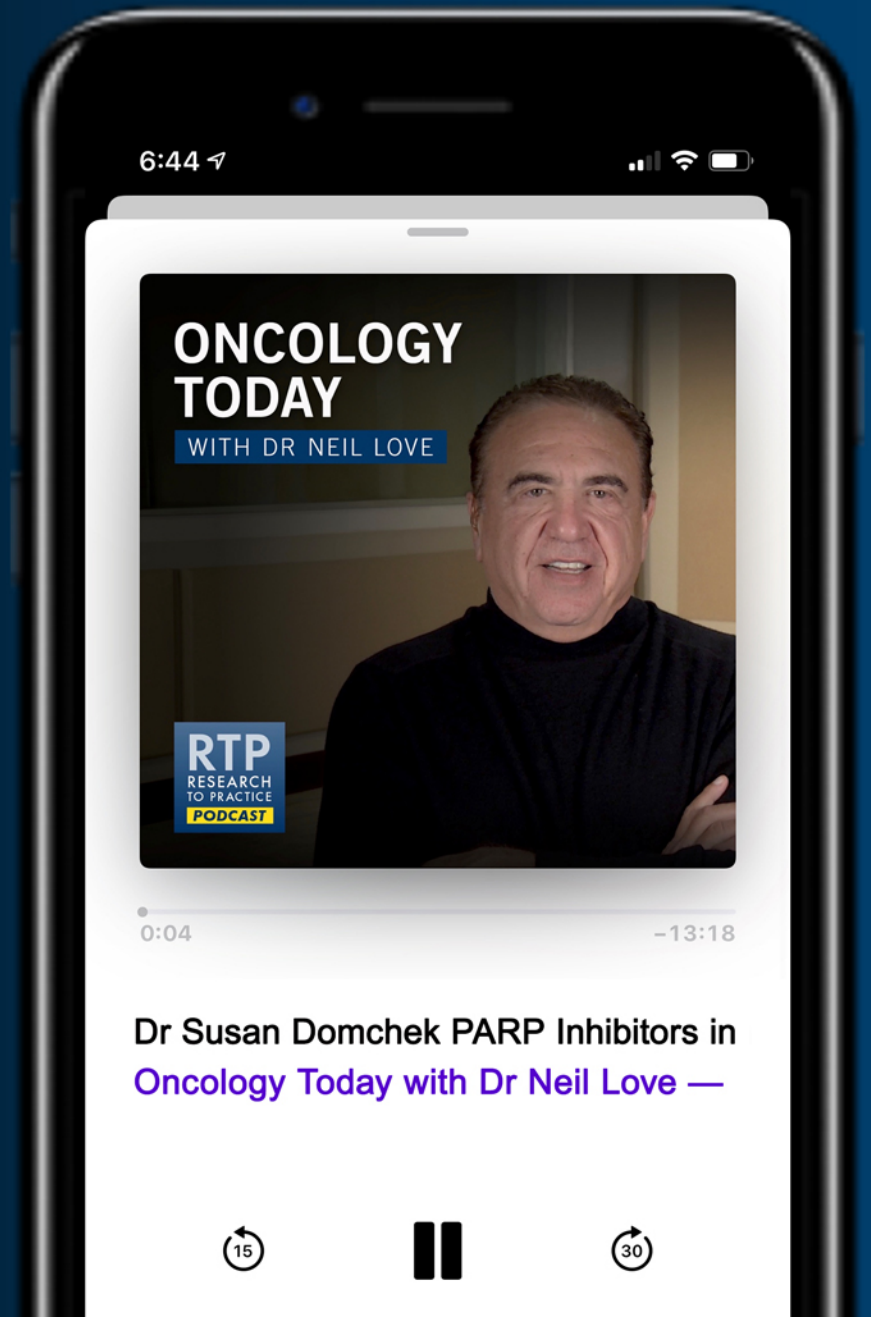

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Division of Lymphoma
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Brian T Hill, MD, PhD
Director, Lymphoid Malignancy Program
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Cleveland, Ohio

Ian W Flinn, MD, PhD
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Meet The Professor Program Participating Faculty

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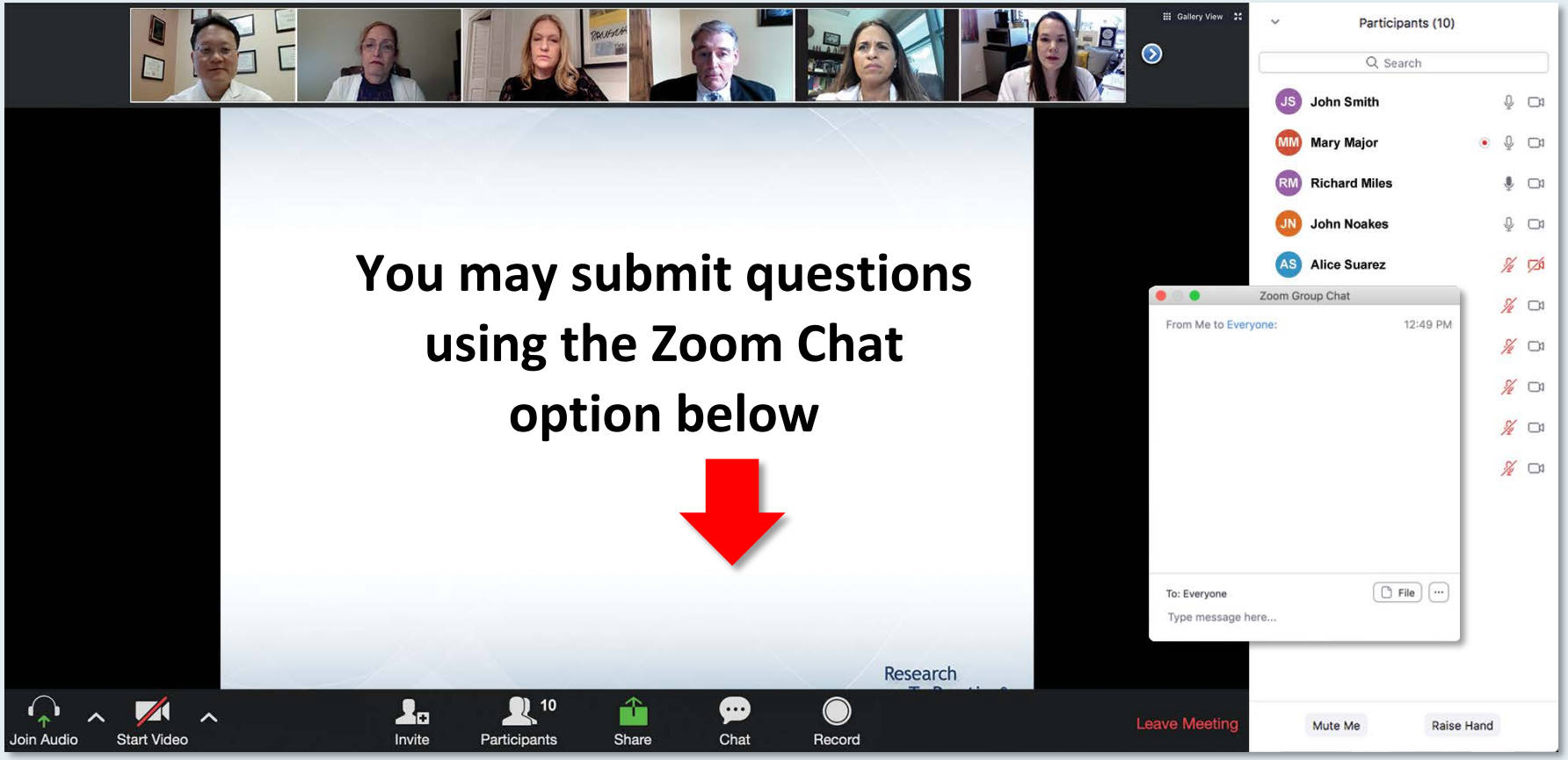

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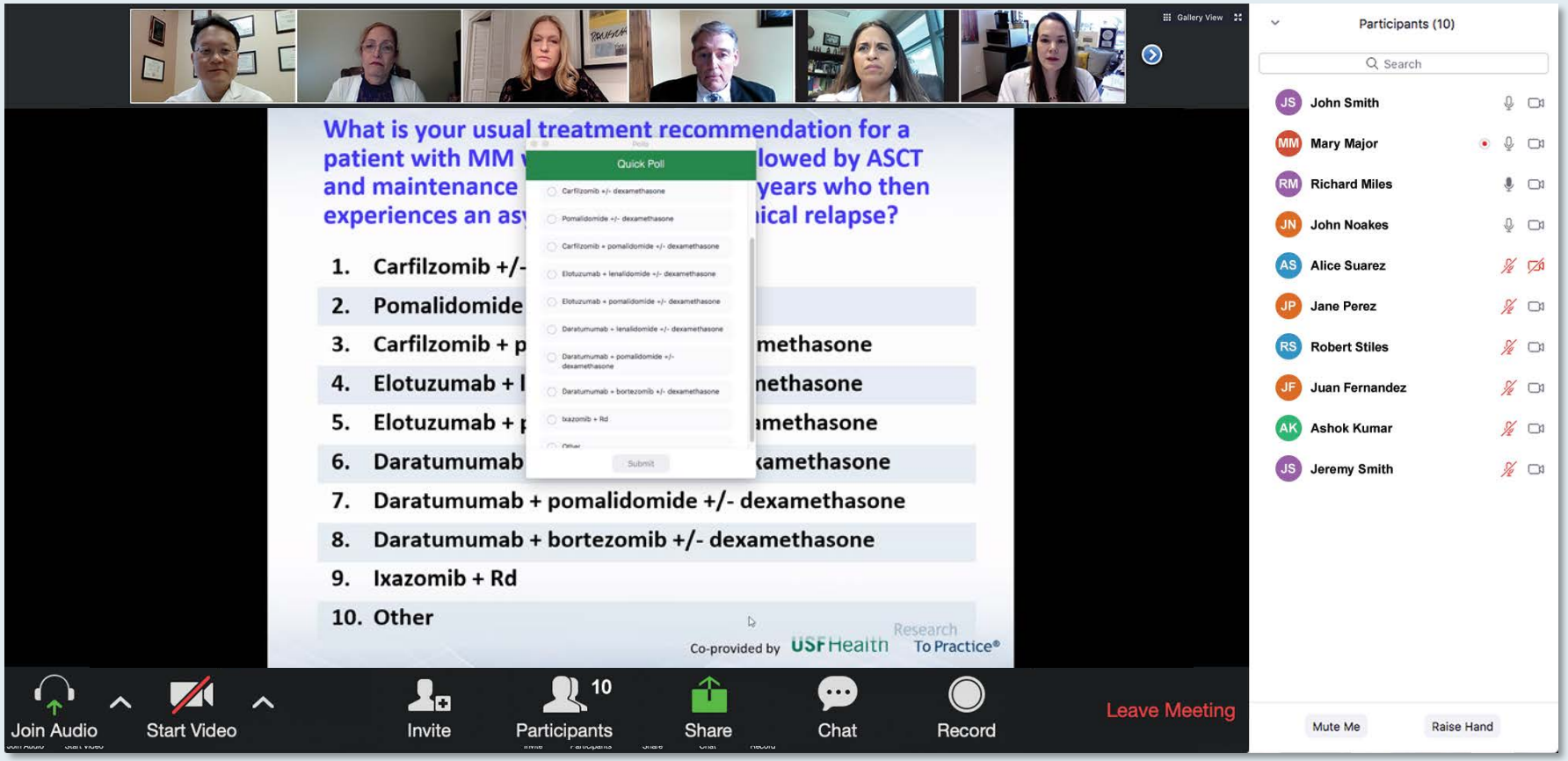

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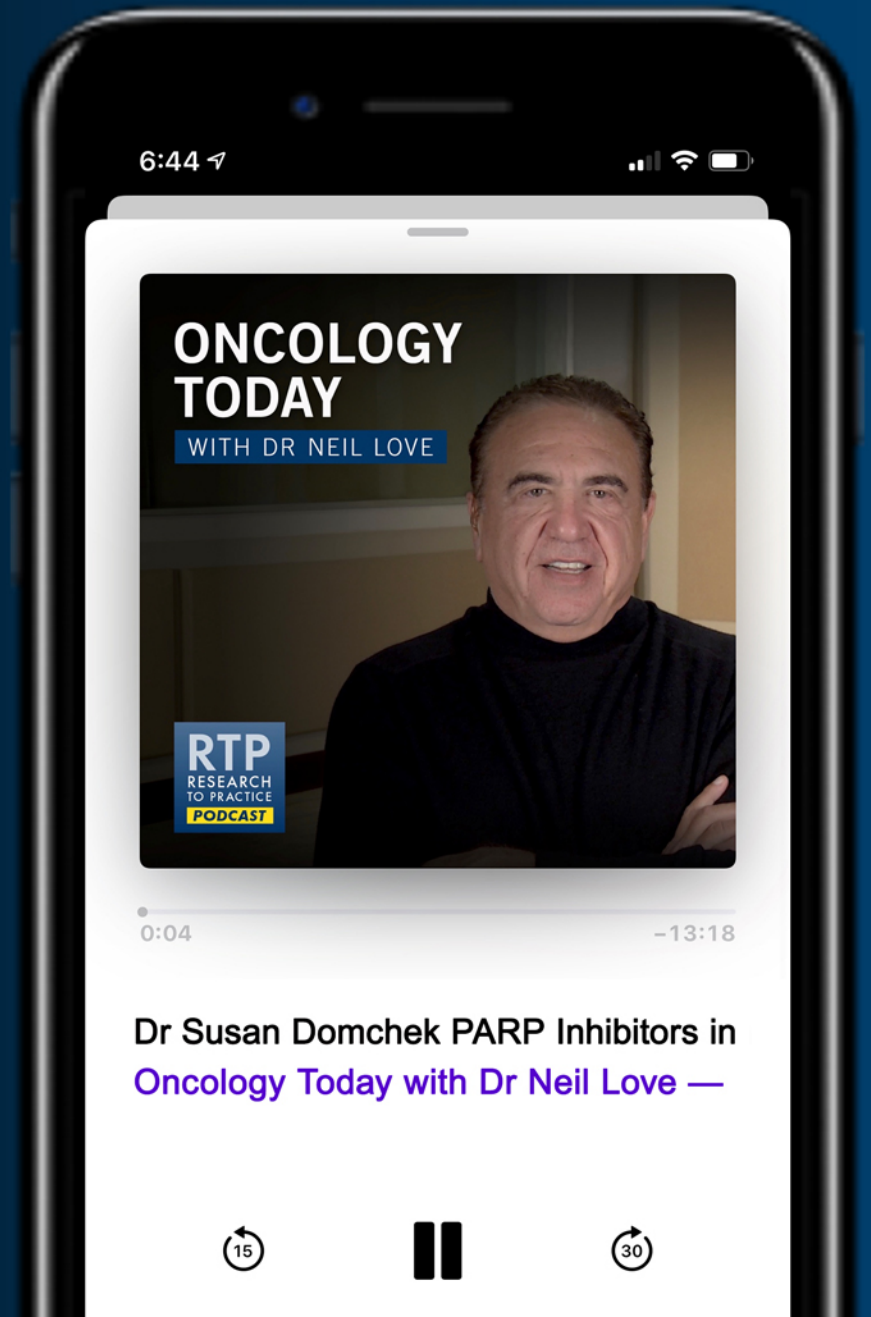

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- Optimizing the use of new targeted drugs
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MODULE 4: Key Recent Data Sets

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The NEW ENGLAND JOURNAL of MEDICINE

N Engl J Med 2020;383:460-73

REVIEW ARTICLE

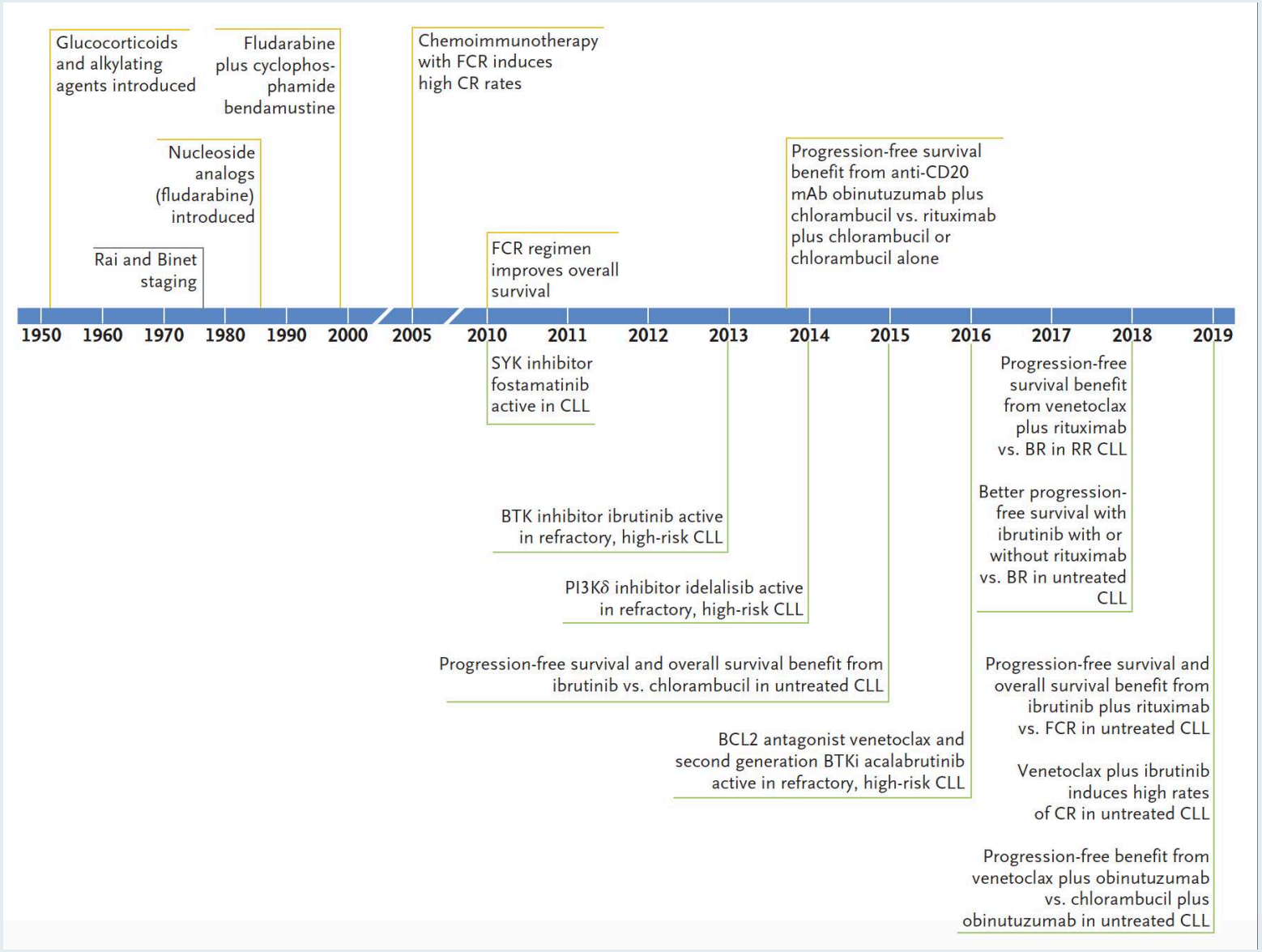
Dan L. Longo, M.D., *Editor*

Treatment of Chronic Lymphocytic Leukemia

Jan A. Burger, M.D., Ph.D.

Clinical Research in CLL

Traditional chemotherapy-based treatments are denoted with yellow



Targeted therapies are denoted with green

Burger JA. *N Engl J Med* 2020;383:460-73.

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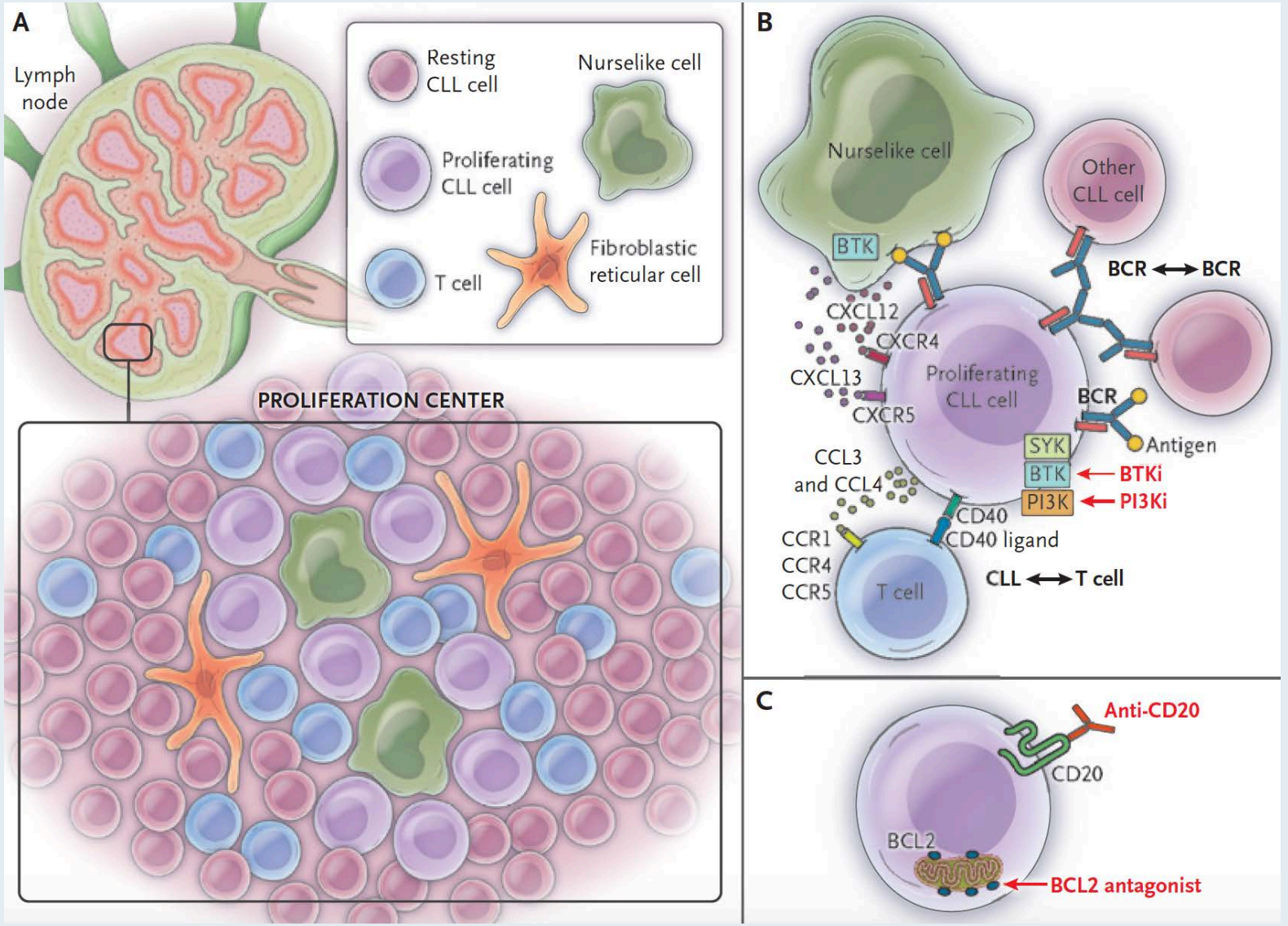
CLL Cell Proliferation and B-Cell Receptor (BCR) Signaling

Activation of BCR signaling in CLL cells in secondary lymphatic organs by antigens



Homotypic BCR interactions result in autonomous signaling

Therapeutic targets on CLL cell

Burger JA. *N Engl J Med* 2020;383:460-73.

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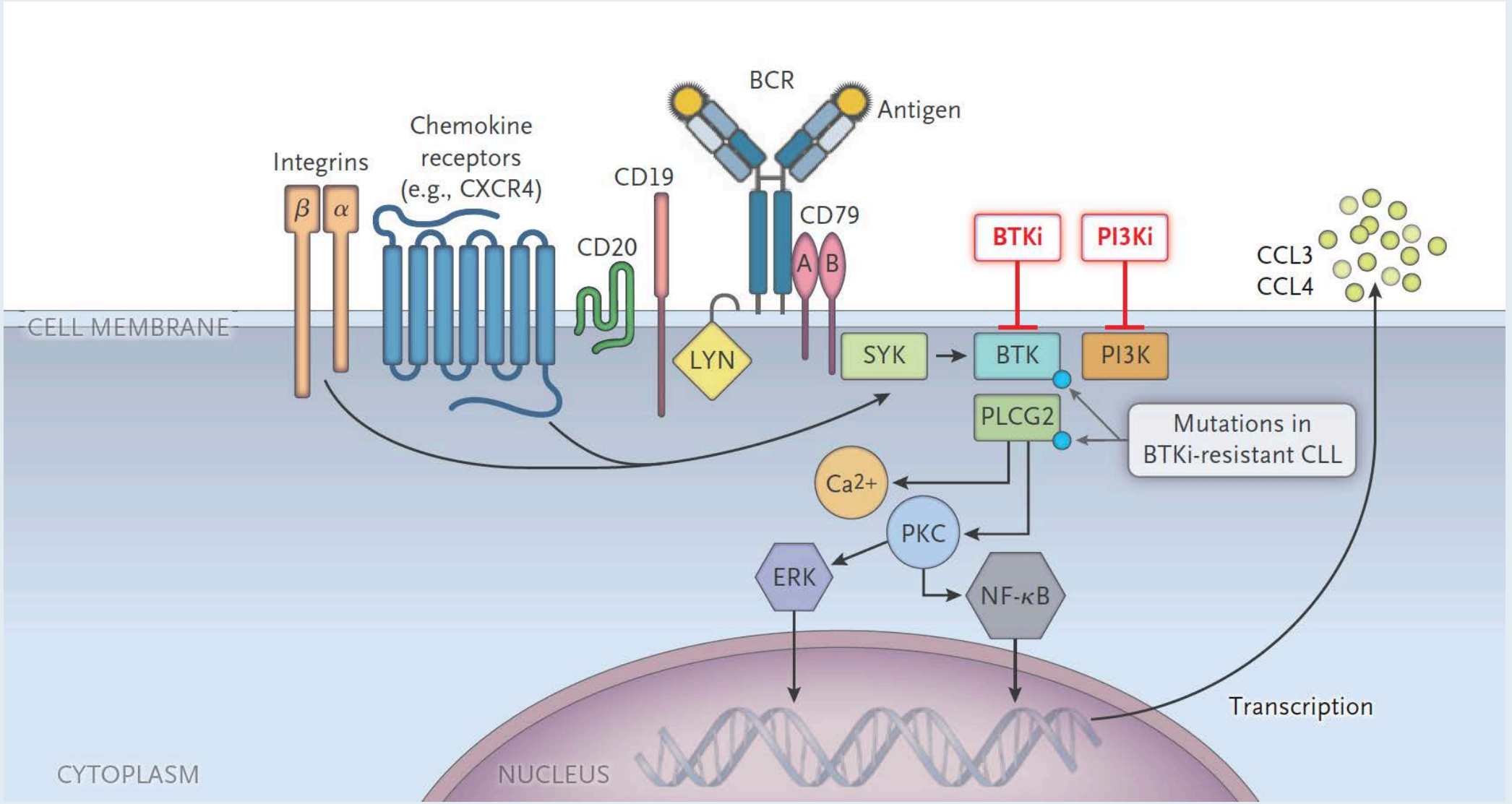
BCR Signaling Pathways



Burger JA. *N Engl J Med* 2020;383:460-73.

Questions and Comments: EVOLVE trial

Dr Brian Hill

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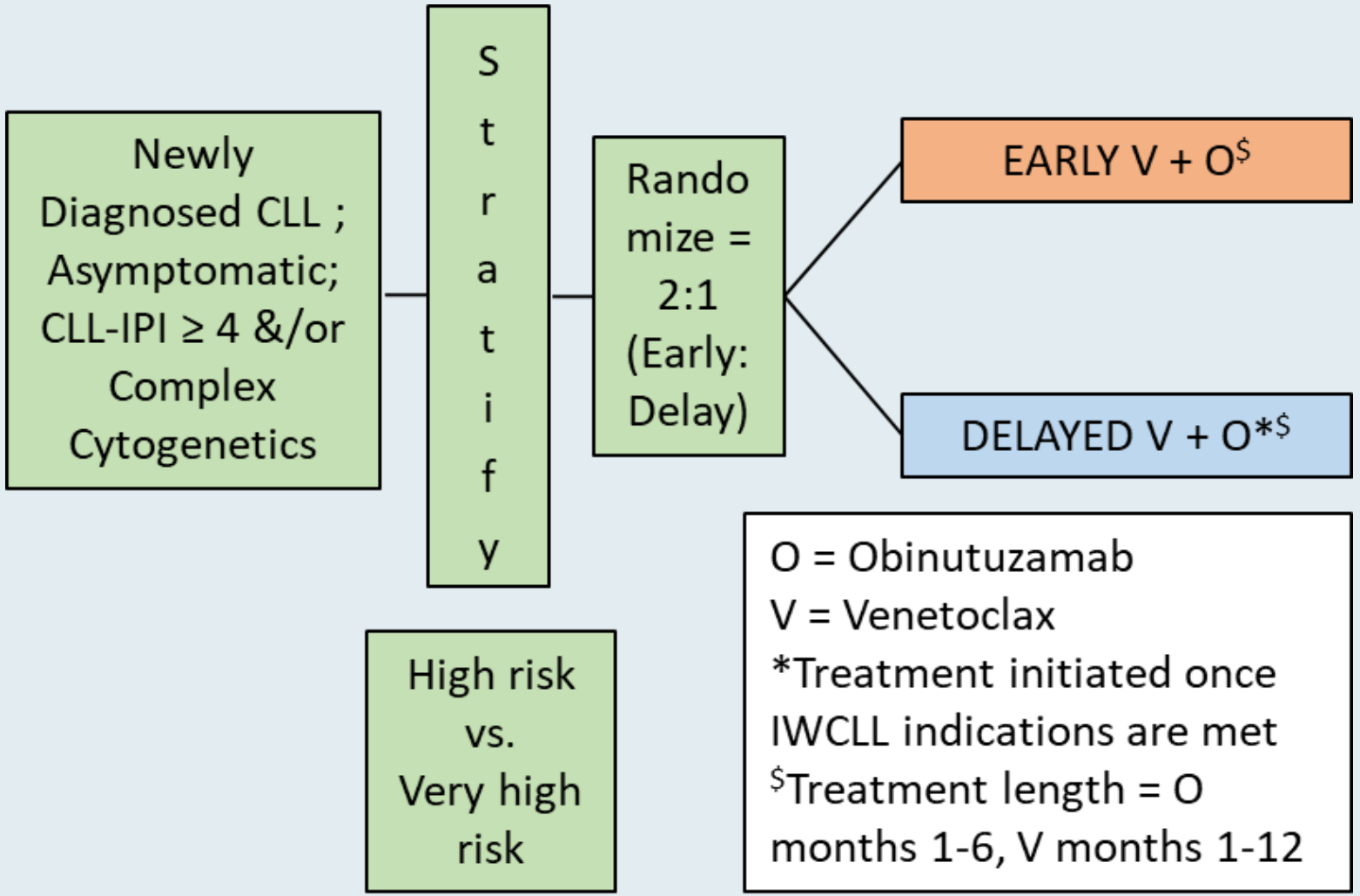
S1925: EVOLVE Study



Primary Endpoint:
Overall Survival

Accrual goal: 247 patients

Secondary Endpoints:
Safety, ORR, DOR, PFS, PFS2, TTNT, MRD, QOL

Translational Endpoints:
MRD, resistance

Courtesy of Brian T Hill, MD, PhD.

Questions and Comments: Venetoclax versus a BTK inhibitor for del(17p) CLL

Dr Brian Hill

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Questions and Comments: Double-refractory CLL

Dr Brian Hill

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Case Presentation – Dr Hill: A 58-year-old man with CLL and severe ibrutinib-associated arthralgias

Dr Brian Hill

- 2010: Avid golfer, diagnosed with IGHV mutated, del11p mutation-positive CLL
- 2013: BR initiated (age 61)
  - Treated with BR x 5 yrs; achieved remission
- 2018: Developed progressive anemia
- 2019: Ibrutinib initiated (420 mg)
  - Severe arthralgias, mouth sores, cracking of his fingertips/nails, and hypertension

Questions

- What would you do next for this patient experiencing these side effects from ibrutinib? What is your tolerance level of these toxicities before switching to another therapy?

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blood®

How I Treat

How I manage ibrutinib intolerance and complications in patients with chronic lymphocytic leukemia

Deborah M. Stephens[1] and John C. Byrd[2-4]

blood® 21 MARCH 2019 | VOLUME 133, NUMBER 12

Highlighted Adverse Events on Selected Landmark Ibrutinib Studies

Adverse event	Phase 2, follow-up 21 mo[6] (n = 85)	Phase 3 RESONATE		Phase 3 RESONATE2	
		Follow-up 9 mo[4] (n = 195)	Follow-up 19 mo[16,17] (n = 195)	Follow-up 18 mo[5] (n = 135)	Follow-up 21 mo[18] (n = 135)
Atrial fibrillation					
All grades	3 (4)	10 (5)	13 (7)	8 (6)	14 (10)
Grade ≥3	0	6 (3)	7 (4)	2 (1)	6 (4)
Bleeding					
All grades	14 (16)	86 (44)	NR	NR	9 (7)
Grade ≥3	4 (5)	2 (1)	4 (2)	6 (4)	8 (6)
Infection					
All grades	NR	137 (70)	NR	NR	NR
Grade ≥3	NR	47 (24)	59 (30)	NR	31 (23)
Arthralgia					
All grades	23 (27)	34 (17)	44 (23)	22(16)	27 (20)
Grade ≥3	0	2 (1)	NR	2 (1)	3 (2)
Myalgia					
All grades	16 (19)	19 (10)	NR	NR	NR
Grade ≥3	1 (1)	1 (1)	NR	NR	NR

Values represent number (percentage) of patients.

NR, not reported.

Stephens DM, Byrd JC. *Blood* 2019;133 (12):1298–307.

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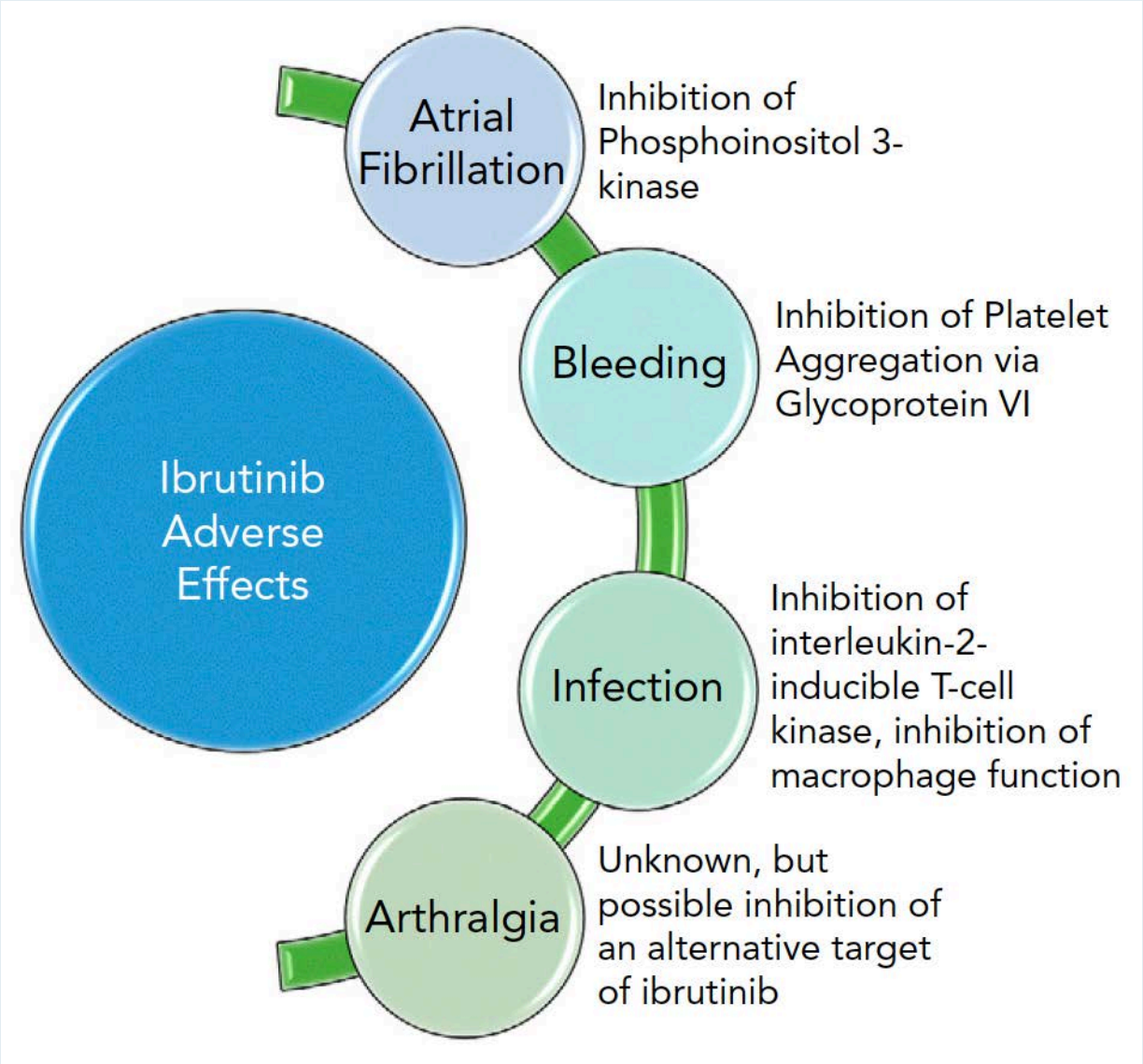
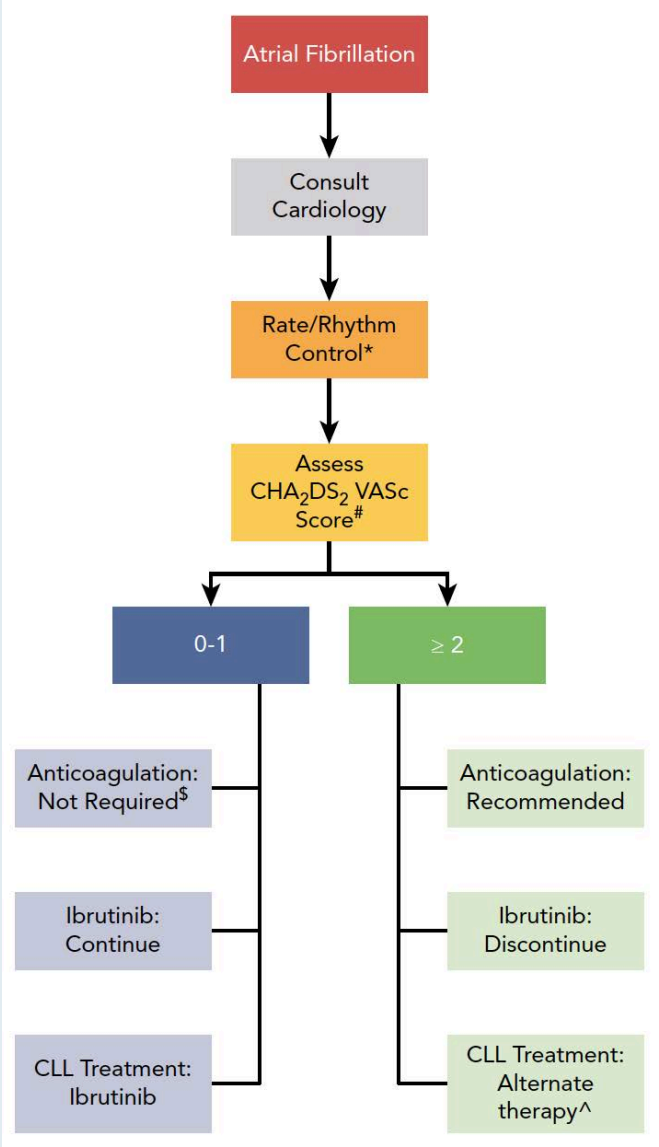
Proposed Mechanisms for Adverse Events Associated with Ibrutinib



Stephens DM, Byrd JC. *Blood* 2019;133 (12):1298–307.

Management of Atrial Fibrillation Associated with Ibrutinib Therapy



Stephens DM, Byrd JC. *Blood* 2019;133 (12):1298–307.

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Questions and Comments: BR as first-line therapy for older patients with low-risk CLL

Dr Brian Hill

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Case Presentation – Dr Hill: An 87-year-old woman with relapsed CLL and a del(17p) mutation receives venetoclax

Dr Brian Hill

- 2013: Initial diagnosis of unmutated IGHV CLL with trisomy 12 and del17p mutation at age 82
- 2014: Ibrutinib initiated → excellent response, transfusion independent
  - Initially had diarrhea, mild abdominal cramping, and easy bruisability
- 2018: Rapidly progressive lymphocytosis (age 87)
- Molecular features: BTK C481S mutation testing → positive
- Patient hesitantly agrees to receive venetoclax → in complete remission after 24 months of therapy
  - Completed 5-week venetoclax ramp-up without tumor lysis, no tolerance issues

Questions

- Would you have any qualms starting this patient, with normal renal function, on venetoclax?

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Questions and Comments: Stopping venetoclax therapy per the MURANO protocol

Dr Brian Hill

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Case Presentation – Dr Hill: A 50-year-old man with relapsed CLL and symptomatic lymphadenopathy receives venetoclax

Dr Brian Hill

- 2008: Initial diagnosis of mutated IGHV CLL with trisomy 12
- 2015: BR initiated → remission
- 2020: Progressive symptomatic lymphadenopathy
- Patient is a utility company linesman and is still working; he wants to received time-limited therapy
- Venetoclax therapy initiated

Questions

- How do you approach the third, fourth and fifth weeks of venetoclax ramp-up?

Questions and Comments: Debulking strategies in the second-line setting

Dr Brian Hill

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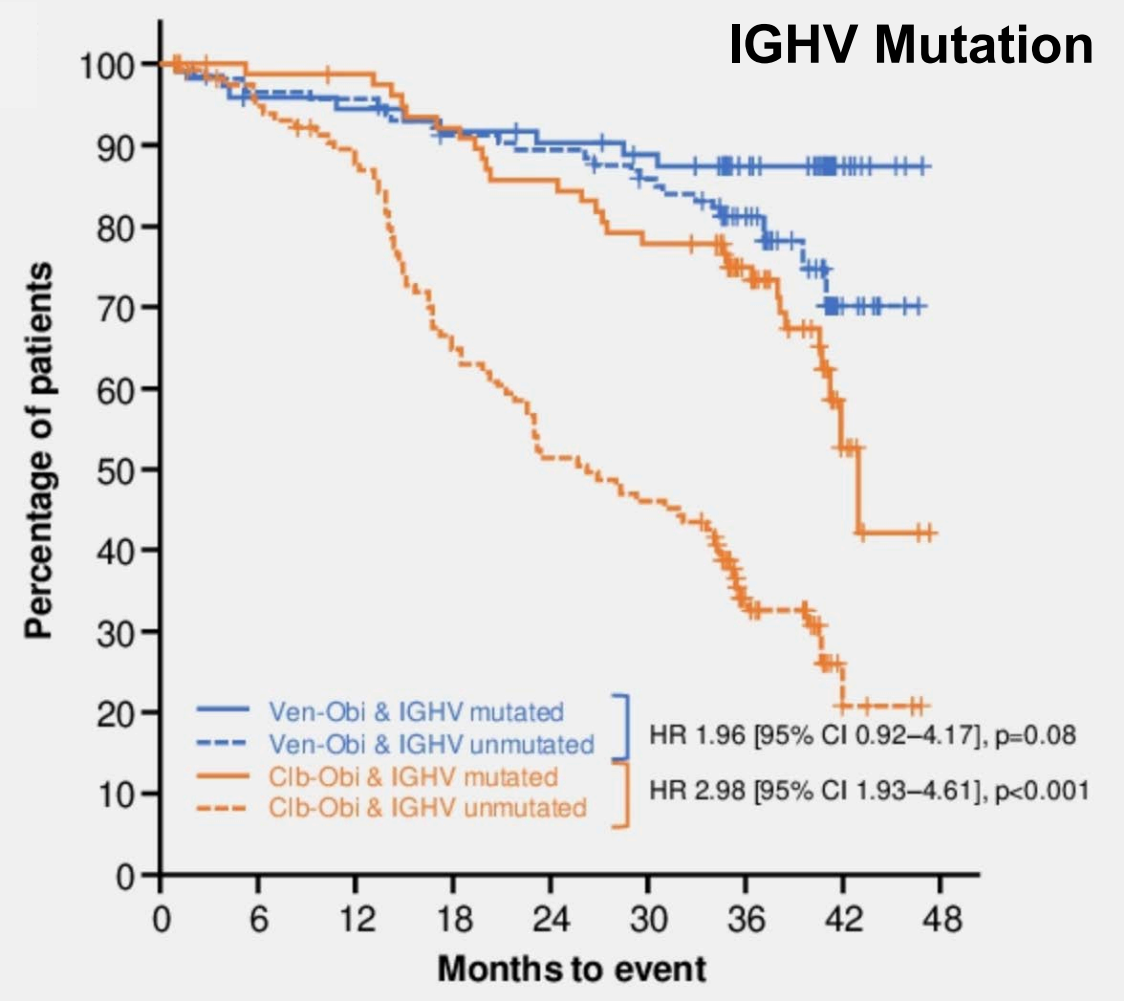
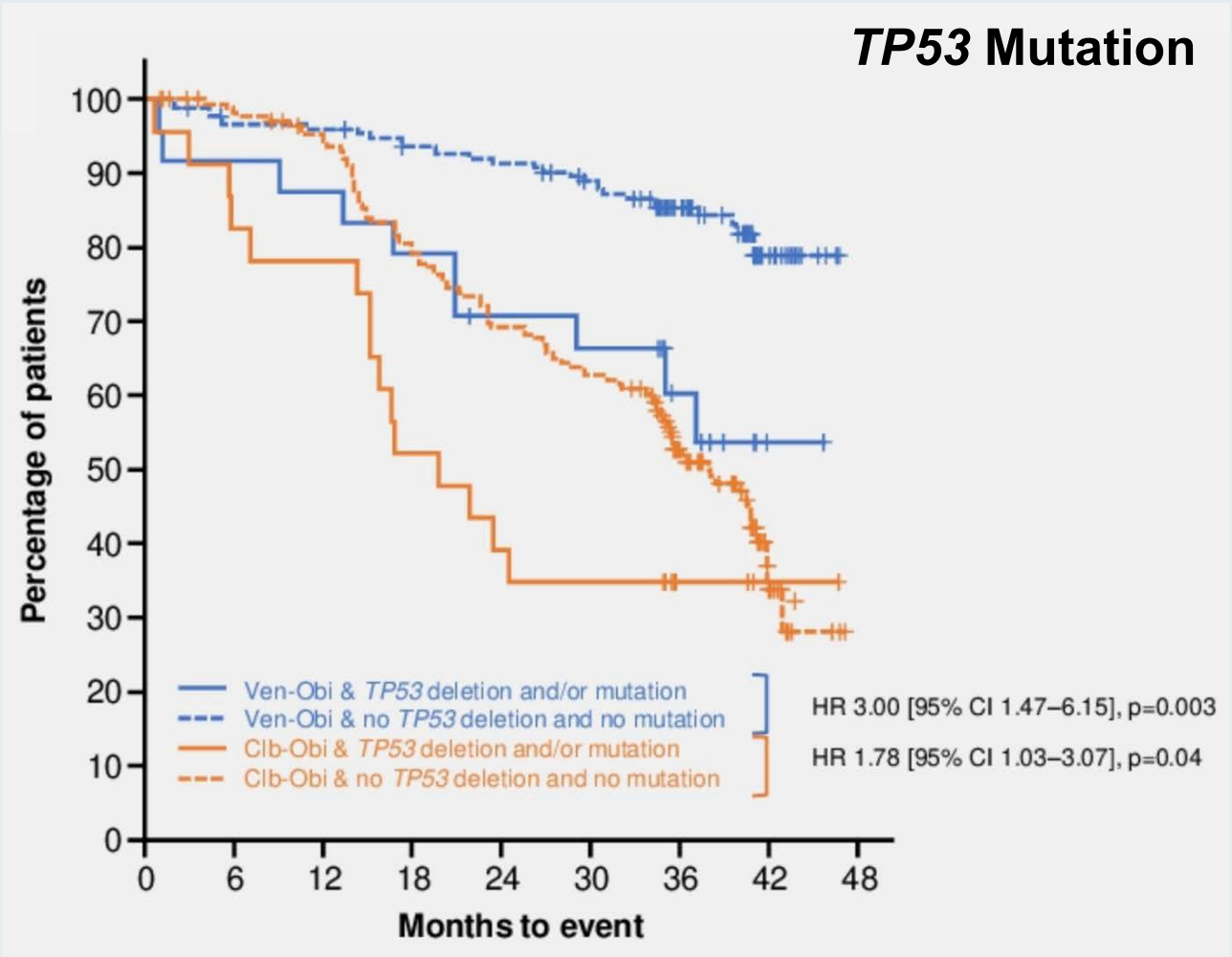
Fixed-Duration Venetoclax-Obinutuzumab for Previously Untreated Patients with Chronic Lymphocytic Leukemia: Follow-up of Efficacy and Safety Results from the Multicenter, Open-Label, Randomized, Phase III CLL14 Trial

Al-Sawaf O et al.

ASCO 2020;Abstract 8027.

CLL14: PFS by IGHV and TP53 Mutation Status





Al-Sawaf O et al. ASCO 2020;Abstract 8027.

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

Byrd JC et al.

ASCO 2020;Abstract 8024.

ACE-CL-001 Phase II Study Expansion: Key Conclusions

- This phase 2 trial of acalabrutinib monotherapy in patients with TN CLL demonstrates favorable safety and response after a median follow-up of 53 months
  - Acalabrutinib treatment produced a high ORR regardless of genomic characteristics; the estimated 48-month DOR rate among responders overall was 97% (95% CI: 90%, 99%)
  - The estimated 48-month EFS rate was 90% (95% CI, 82%, 94%)
  - AEs were generally mild, with only a small subset of patients (6%) discontinuing treatment due to drug toxicity
- The long-term data from ACE-CL-001 support the positive phase 3 results of acalabrutinib in patients with TN CLL and demonstrate durable responses with no new long-term safety issues

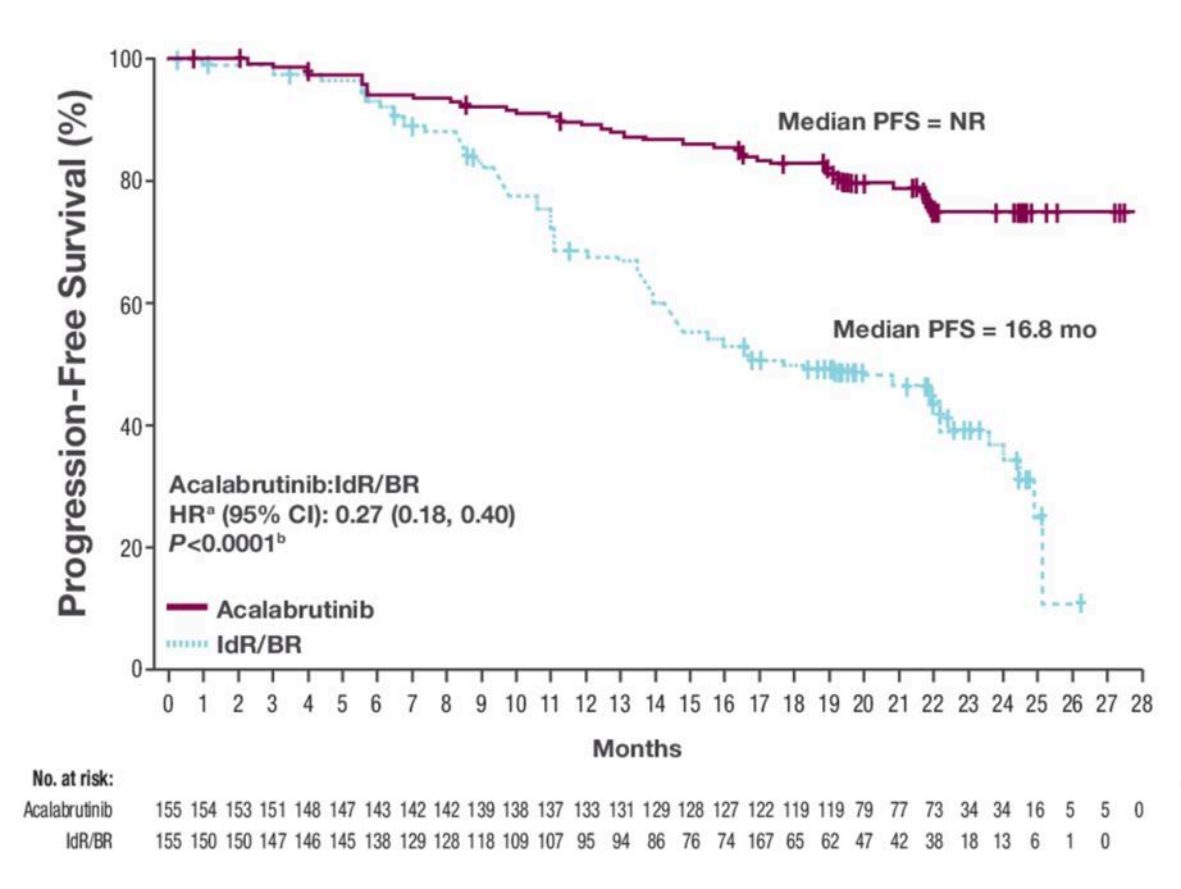
Byrd JC et al. ASCO 2020;Abstract 8024.

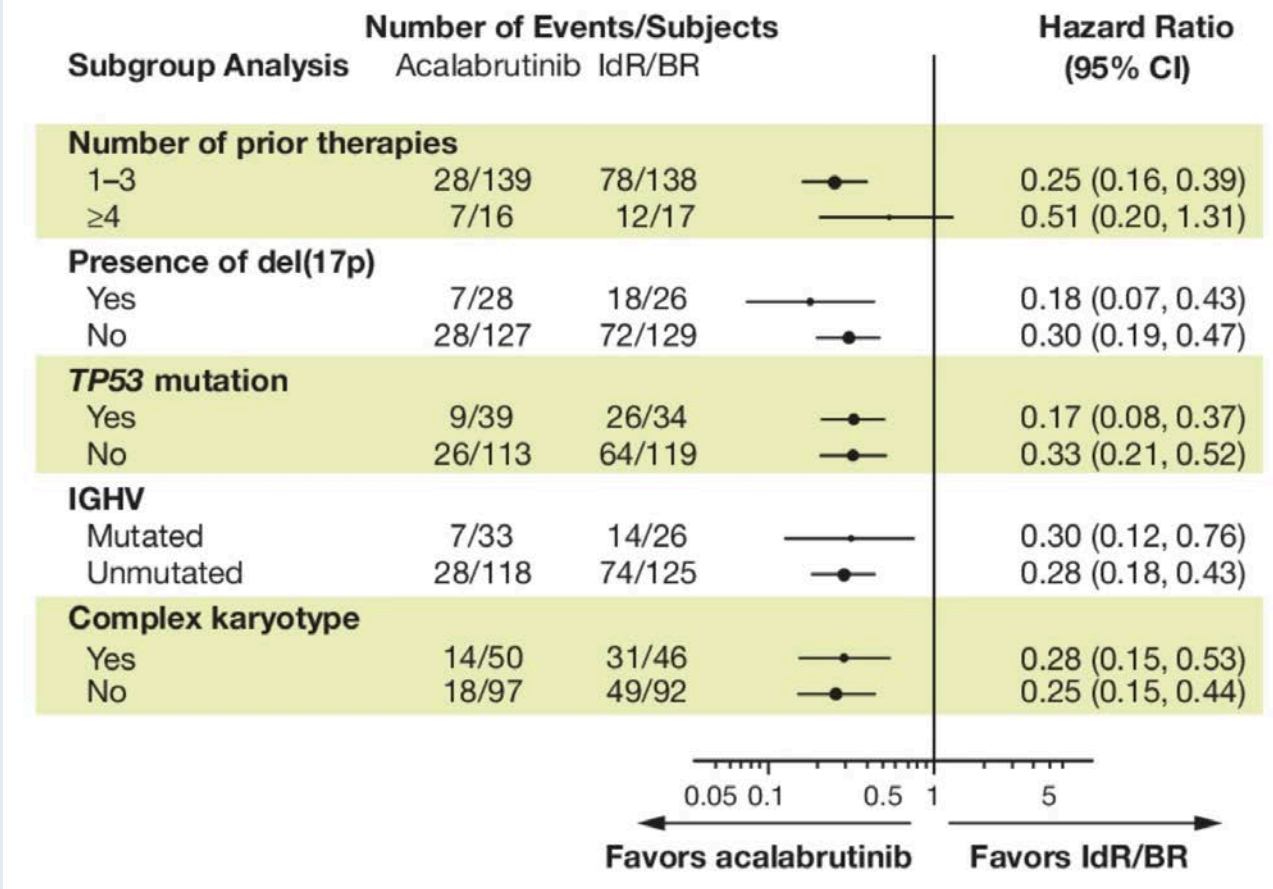
Acalabrutinib (Acala) versus Idelalisib plus Rituximab (IdR) or Bendamustine plus Rituximab (BR) in Relapsed/Refractory (R/R) Chronic Lymphocytic Leukemia (CLL): ASCEND Final Results

Ghia P et al.

ASCO 2020;Abstract 8015.

ASCEND Final Results: Investigator-Assessed PFS for Acalabrutinib vs IdR/BR and Key Subgroups Analysis





Ghia P et al. ASCO 2020;Abstract 8015.

A Multicenter Phase II Study of Venetoclax plus Dose-Adjusted R-EPOCH (VR-EPOCH) for Richter's Syndrome

Davids MS et al.

ASCO 2020;Abstract 8004.

VR-EPOCH in Richter's Syndrome: Key Efficacy Data

20 pts started combination therapy and are evaluable for response by protocol:

- CR at end of combination therapy (primary endpoint): 11/20 (55%)
- Best response in evaluable patients: ORR: 16/20 (80%), CR: 13/20 (65%)
- ITT analysis: CR: 13/26 (50%), ORR: 16/26 (62%)
- All 11 patients who achieved CR and had BM-MRD assessment for CLL were undetectable
- Both patients with prior ven who received combination therapy achieved CR
- 8/17 (47%) alloHCT candidates underwent transplant in remission
- Longest patient post alloHCT now >2.5 years in CR
- Longest patient on ven maintenance is now 2 years post chemo
- Median PFS: 16.3 mos
- Median OS: 16.3 mos

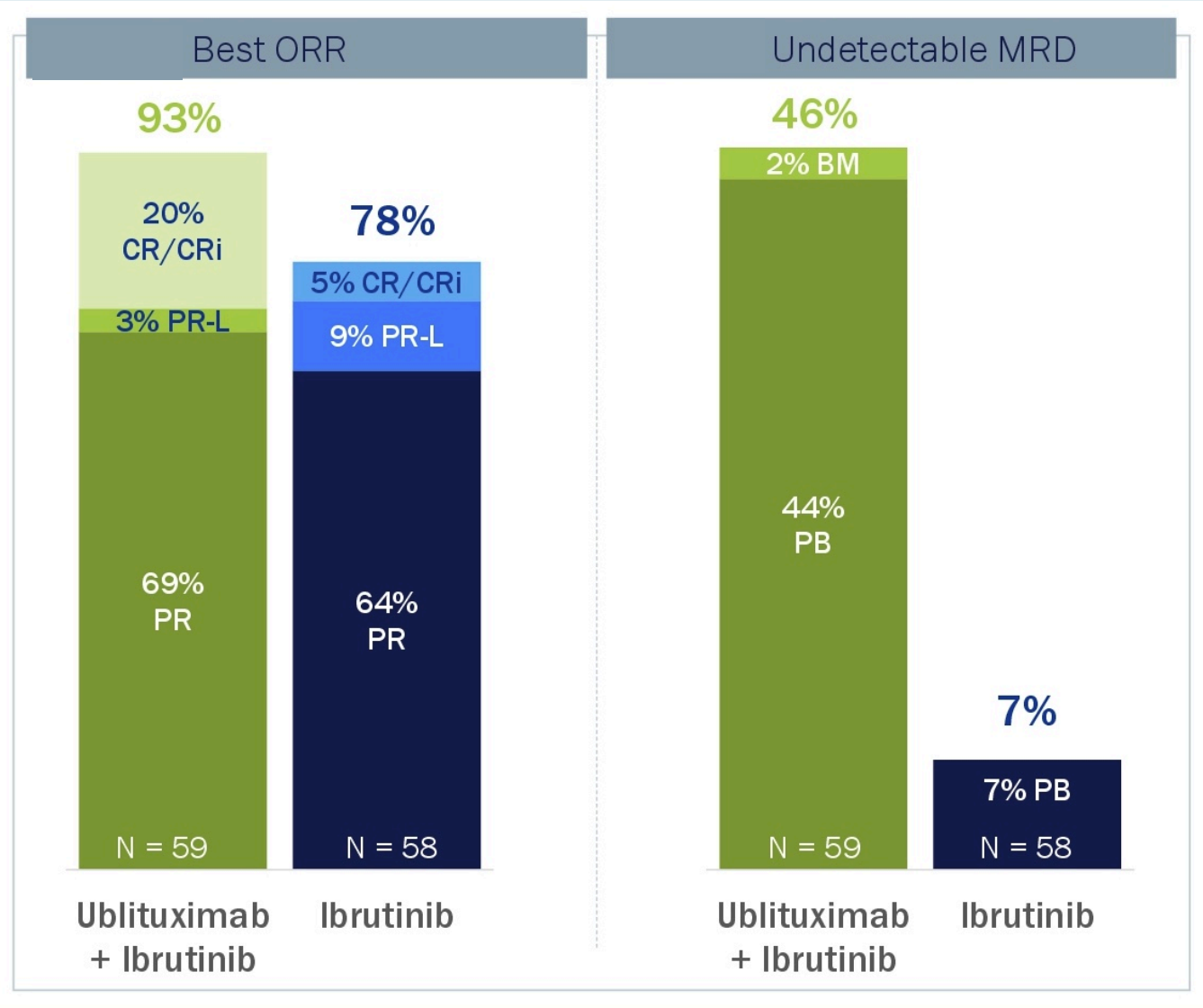
Davids MS et al. ASCO 2020;Abstract 8004.

Effect of Adding Ublituximab to Ibrutinib on PFS, ORR, and MRD Negativity in Previously Treated High-Risk Chronic Lymphocytic Leukemia: Final Results of the GENUINE Phase III Study

Sharman JP et al.

ASCO 2020;Abstract 8022.

Phase III GENUINE Study Primary Endpoint: ORR



Sharman JP et al. ASCO 2020;Abstract 8022.

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MODULE 4: Key Recent Data Sets

RTP RESEARCH TO PRACTICE

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

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

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

 MATTHEW S DAVIDS, MD, MMSC	Venetoclax + obinutuzumab
 IAN W FLINN, MD, PHD	Venetoclax + obinutuzumab
 BRIAN T HILL, MD, PHD	Venetoclax + obinutuzumab or BR
 BRAD S KAHL, MD	Venetoclax + obinutuzumab
 ANTHONY R MATO, MD, MSCE	FCR
 JOHN M PAGEL, MD, PHD	Acalabrutinib
 KERRY A ROGERS, MD	Ibrutinib or FCR
 JEFF SHARMAN, MD	FCR
 MITCHELL R SMITH, MD, PHD	FCR
 WILLIAM G WIERDA, MD, PHD	FCR
 JENNIFER WOYACH, MD	Venetoclax + obinutuzumab

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

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

 MATTHEW S DAVIDS, MD, MMSC	Venetoclax + obinutuzumab
 IAN W FLINN, MD, PHD	Acalabrutinib
 BRIAN T HILL, MD, PHD	Obinutuzumab
 BRAD S KAHL, MD	Venetoclax + obinutuzumab
 ANTHONY R MATO, MD, MSCE	Acalabrutinib
 JOHN M PAGEL, MD, PHD	Acalabrutinib
 KERRY A ROGERS, MD	Acalabrutinib or venetoclax + obinutuzumab
 JEFF SHARMAN, MD	Venetoclax + obinutuzumab
 MITCHELL R SMITH, MD, PHD	Ibrutinib
 WILLIAM G WIERDA, MD, PHD	Venetoclax + obinutuzumab
 JENNIFER WOYACH, MD	Ibrutinib

RTP RESEARCH TO PRACTICE

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

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

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

 MATTHEW S DAVIDS, MD, MMSC	Venetoclax + obinutuzumab
 IAN W FLINN, MD, PHD	Venetoclax + obinutuzumab
 BRIAN T HILL, MD, PHD	Venetoclax + obinutuzumab
 BRAD S KAHL, MD	Venetoclax + obinutuzumab
 ANTHONY R MATO, MD, MSCE	Venetoclax + obinutuzumab
 JOHN M PAGEL, MD, PHD	Acalabrutinib
 KERRY A ROGERS, MD	Acalabrutinib or venetoclax + obinutuzumab
 JEFF SHARMAN, MD	Acalabrutinib
 MITCHELL R SMITH, MD, PHD	Venetoclax + obinutuzumab
 WILLIAM G WIERDA, MD, PHD	Venetoclax + obinutuzumab
 JENNIFER WOYACH, MD	Ibrutinib

RTP RESEARCH TO PRACTICE

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

 MATTHEW S DAVIDS, MD, MMSC	Venetoclax + obinutuzumab
 IAN W FLINN, MD, PHD	Acalabrutinib
 BRIAN T HILL, MD, PHD	Venetoclax + obinutuzumab
 BRAD S KAHL, MD	Venetoclax + obinutuzumab
 ANTHONY R MATO, MD, MSCE	Acalabrutinib
 JOHN M PAGEL, MD, PHD	Acalabrutinib
 KERRY A ROGERS, MD	Acalabrutinib or venetoclax + obinutuzumab
 JEFF SHARMAN, MD	Acalabrutinib
 MITCHELL R SMITH, MD, PHD	Ibrutinib
 WILLIAM G WIERDA, MD, PHD	Acalabrutinib
 JENNIFER WOYACH, MD	Ibrutinib

RTP RESEARCH TO PRACTICE

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

 MATTHEW S DAVIDS, MD, MMSC	Venetoclax + obinutuzumab
 IAN W FLINN, MD, PHD	Acalabrutinib
 BRIAN T HILL, MD, PHD	Venetoclax + obinutuzumab
 BRAD S KAHL, MD	Venetoclax + obinutuzumab
 ANTHONY R MATO, MD, MSCE	Acalabrutinib + obinutuzumab
 JOHN M PAGEL, MD, PHD	Acalabrutinib
 KERRY A ROGERS, MD	Acalabrutinib
 JEFF SHARMAN, MD	Acalabrutinib
 MITCHELL R SMITH, MD, PHD	Venetoclax + obinutuzumab
 WILLIAM G WIERDA, MD, PHD	Acalabrutinib
 JENNIFER WOYACH, MD	Ibrutinib

RTP RESEARCH TO PRACTICE

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

 MATTHEW S DAVIDS, MD, MMSC	Ibrutinib
 IAN W FLINN, MD, PHD	Acalabrutinib
 BRIAN T HILL, MD, PHD	Acalabrutinib
 BRAD S KAHL, MD	Acalabrutinib + obinutuzumab
 ANTHONY R MATO, MD, MSCE	Acalabrutinib
 JOHN M PAGEL, MD, PHD	Acalabrutinib
 KERRY A ROGERS, MD	Ibrutnib
 JEFF SHARMAN, MD	Acalabrutinib
 MITCHELL R SMITH, MD, PHD	Venetoclax + obinutuzumab
 WILLIAM G WIERDA, MD, PHD	Acalabrutinib
 JENNIFER WOYACH, MD	Ibrutinib

RTP RESEARCH TO PRACTICE

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

1. Continue treatment
2. Discontinue treatment

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

 MATTHEW S DAVIDS, MD, MMSC	Discontinue treatment
 IAN W FLINN, MD, PHD	Discontinue treatment
 BRIAN T HILL, MD, PHD	Discontinue treatment
 BRAD S KAHL, MD	Discontinue treatment
 ANTHONY R MATO, MD, MSCE	Continue treatment
 JOHN M PAGEL, MD, PHD	Continue treatment
 KERRY A ROGERS, MD	Discontinue treatment
 JEFF SHARMAN, MD	Discontinue treatment
 MITCHELL R SMITH, MD, PHD	Discontinue treatment
 WILLIAM G WIERDA, MD, PHD	Continue treatment
 JENNIFER WOYACH, MD	Discontinue treatment

RTP RESEARCH TO PRACTICE

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

 MATTHEW S DAVIDS, MD, MMSC	Discontinue treatment
 IAN W FLINN, MD, PHD	Discontinue treatment
 BRIAN T HILL, MD, PHD	Discontinue treatment
 BRAD S KAHL, MD	Discontinue treatment
 ANTHONY R MATO, MD, MSCE	Discontinue treatment
 JOHN M PAGEL, MD, PHD	Discontinue treatment
 KERRY A ROGERS, MD	Discontinue treatment
 JEFF SHARMAN, MD	Discontinue treatment
 MITCHELL R SMITH, MD, PHD	Discontinue treatment
 WILLIAM G WIERDA, MD, PHD	Discontinue treatment
 JENNIFER WOYACH, MD	Discontinue treatment

RTP RESEARCH TO PRACTICE

Which second-line systemic therapy would you recommend for a 60-year-old patient with CLL with no IGHV mutation and no del(17p) or TP53 mutation who responds to ibrutinib and then experiences disease progression 3 years later?

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

Which second-line systemic therapy would you recommend for a 60-year-old patient with CLL with unmutated IGHV and no del(17p) or TP53 mutation who responds to ibrutinib and then experiences disease progression 3 years later?

 MATTHEW S DAVIDS, MD, MMSC	Venetoclax + rituximab
 IAN W FLINN, MD, PHD	Venetoclax + obinutuzumab
 BRIAN T HILL, MD, PHD	Venetoclax + rituximab
 BRAD S KAHL, MD	Venetoclax + rituximab
 ANTHONY R MATO, MD, MSCE	Venetoclax + rituximab
 JOHN M PAGEL, MD, PHD	Venetoclax
 KERRY A ROGERS, MD	Venetoclax + rituximab
 JEFF SHARMAN, MD	Venetoclax + rituximab
 MITCHELL R SMITH, MD, PHD	Venetoclax + obinutuzumab
 WILLIAM G WIERDA, MD, PHD	Venetoclax + rituximab
 JENNIFER WOYACH, MD	Venetoclax + rituximab

RTP RESEARCH TO PRACTICE

Which second-line systemic therapy would you recommend for a 60-year-old patient with CLL with no IGHV mutation and no del(17p) or TP53 mutation who responds to venetoclax/obinutuzumab and then experiences disease progression 3 years later?

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

Which second-line systemic therapy would you recommend for a 60-year-old patient with CLL with unmutated IGHV and no del(17p) or TP53 mutation who responds to venetoclax/obinutuzumab and then experiences disease progression 3 years later?

 MATTHEW S DAVIDS, MD, MMSC	Venetoclax + obinutuzumab
 IAN W FLINN, MD, PHD	Acalabrutinib
 BRIAN T HILL, MD, PHD	Acalabrutinib
 BRAD S KAHL, MD	Acalabrutinib
 ANTHONY R MATO, MD, MSCE	Venetoclax + rituximab
 JOHN M PAGEL, MD, PHD	Acalabrutinib
 KERRY A ROGERS, MD	Ibrutinib
 JEFF SHARMAN, MD	Acalabrutinib
 MITCHELL R SMITH, MD, PHD	Ibrutinib
 WILLIAM G WIERDA, MD, PHD	Venetoclax + rituximab
 JENNIFER WOYACH, MD	Ibrutinib

RTP RESEARCH TO PRACTICE

A 60-year-old patient with CLL, an absolute lymphocyte count of 20,000 and several involved lymph nodes that are smaller than 2 centimeters is about to receive venetoclax. What preemptive measures, if any, would you take to address tumor lysis syndrome prior to the initiation of therapy?

 MATTHEW S DAVIDS, MD, MMSC	Encourage oral hydration and allopurinol
 IAN W FLINN, MD, PHD	IV hydration and allopurinol
 BRIAN T HILL, MD, PHD	Encourage oral hydration and allopurinol
 BRAD S KAHL, MD	Encourage oral hydration and allopurinol
 ANTHONY R MATO, MD, MSCE	IV hydration and allopurinol
 JOHN M PAGEL, MD, PHD	Encourage oral hydration and allopurinol
 KERRY A ROGERS, MD	Encourage oral hydration and allopurinol
 JEFF SHARMAN, MD	Give the obinutuzumab first to debulk, then after 1 month can start as outpatient with hydration and allopurinol
 MITCHELL R SMITH, MD, PHD	Encourage oral hydration and allopurinol
 WILLIAM G WIERDA, MD, PHD	Encourage oral hydration and allopurinol
 JENNIFER WOYACH, MD	Encourage oral hydration and allopurinol

RTP RESEARCH TO PRACTICE

A 60-year-old patient with CLL, an absolute lymphocyte count of 80,000 and several involved lymph nodes that are larger than 5 centimeters is about to receive venetoclax. What preemptive measures, if any, would you take to address tumor lysis syndrome prior to the initiation of therapy?

 MATTHEW S DAVIDS, MD, MMSC	Admit to hospital
 IAN W FLINN, MD, PHD	Debulk with obinutuzumab
 BRIAN T HILL, MD, PHD	Admit to hospital
 BRAD S KAHL, MD	Admit to hospital
 ANTHONY R MATO, MD, MSCE	Admit to hospital
 JOHN M PAGEL, MD, PHD	Admit to hospital
 KERRY A ROGERS, MD	Admit to hospital
 JEFF SHARMAN, MD	Obinutuzumab for 1 month to lower patient risk, then outpatient hydration and allopurinol
 MITCHELL R SMITH, MD, PHD	Admit to hospital
 WILLIAM G WIERDA, MD, PHD	Admit to hospital
 JENNIFER WOYACH, MD	IV hydration and allopurinol

RTP RESEARCH TO PRACTICE

For your patients with CLL whom you admit to the hospital to receive venetoclax, for how long do you typically admit them?

 MATTHEW S DAVIDS, MD, MMSC	8 days
 IAN W FLINN, MD, PHD	2 days
 BRIAN T HILL, MD, PHD	2 days (<48 hours)
 BRAD S KAHL, MD	2 days
 ANTHONY R MATO, MD, MSCE	2-3 days
 JOHN M PAGEL, MD, PHD	1 day

 KERRY A ROGERS, MD	2 nights for each dose escalation
 JEFF SHARMAN, MD	2 days
 MITCHELL R SMITH, MD, PHD	1- 2 days
 WILLIAM G WIERDA, MD, PHD	2 days
 JENNIFER WOYACH, MD	2 days or rapid escalation to full dose over 5 days

RTP RESEARCH TO PRACTICE

Meet The Professor with Dr Smith

MODULE 1: Cases from Dr Hill

- Questions and Comments: EVOLVE trial
- Questions and Comments: Venetoclax versus a BTK inhibitor for del(17p) CLL
- Questions and Comments: Double-refractory CLL
- A 58-year-old man with CLL and severe ibrutinib-associated arthralgias
- Questions and Comments: Bendamustine/rituximab (BR) as first-line therapy for older patients with low-risk CLL
- An 87-year-old woman with relapsed CLL and a del(17p) mutation receives venetoclax
- Questions and Comments: Stopping venetoclax therapy per the MURANO protocol
- A 50-year-old man with relapsed CLL and symptomatic lymphadenopathy receives venetoclax
- Questions and Comments: Debulking strategies in the second-line setting

MODULE 2: CLL Journal Club with Dr Smith

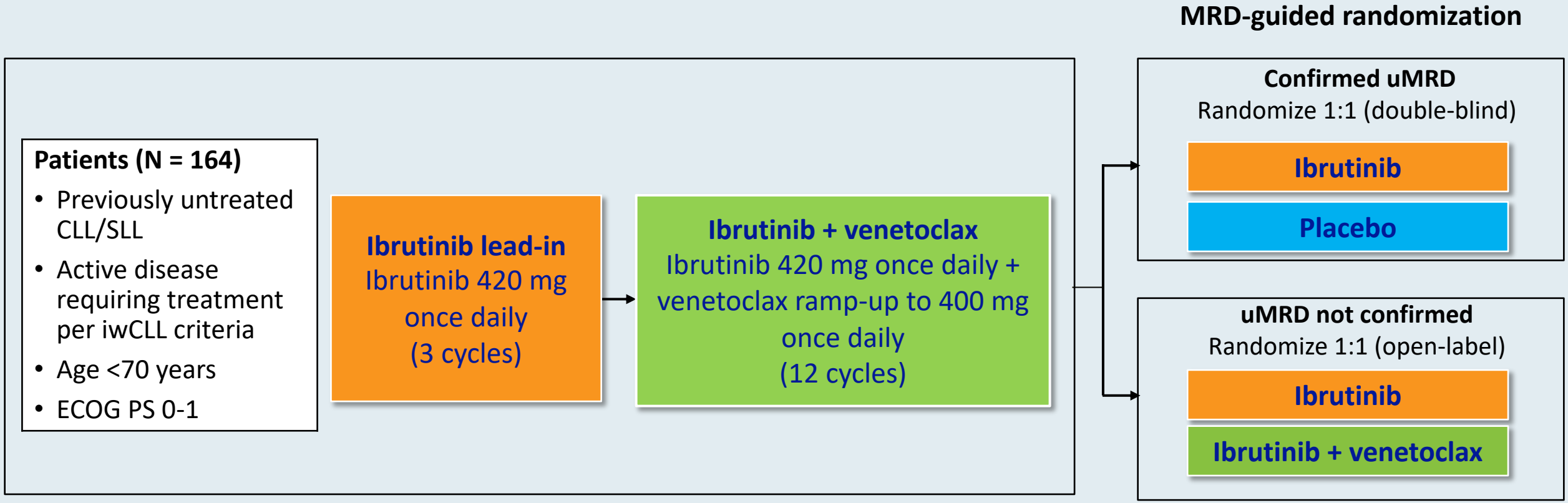
- Optimizing the use of new targeted drugs
- ASCO 2020 highlights
- Management of ibrutinib intolerance and complications

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

MODULE 4: Key Recent Data Sets

RTP RESEARCH TO PRACTICE

CAPTIVATE MRD Cohort: Study Design

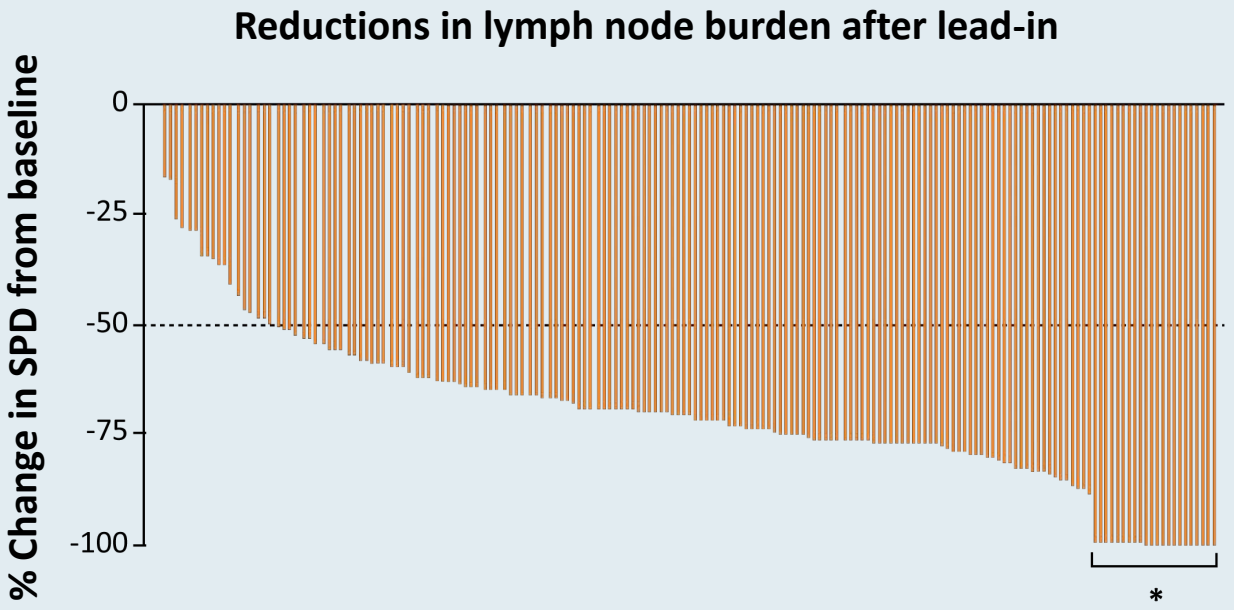


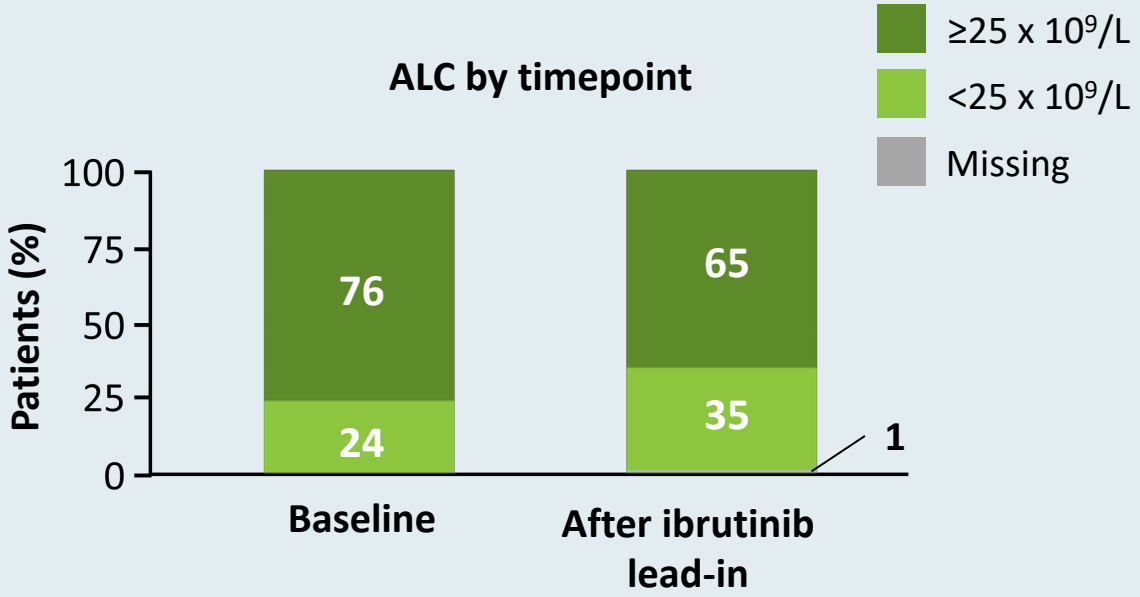
uMRD = undetectable minimal residual disease

Results presented for prerandomization phase of the MRD cohort (n = 164) with 12 cycles of ibrutinib + venetoclax prior to MRD-guided randomization

Siddiqi S et al. EHA 2020;Abstract S158.

CAPTIVATE MRD Cohort: 3 Cycles of Ibrutinib Lead-In





Three cycles of ibrutinib lead-in reduces TLS risk and indication for hospitalization

Siddiqi S et al. EHA 2020;Abstract S158.

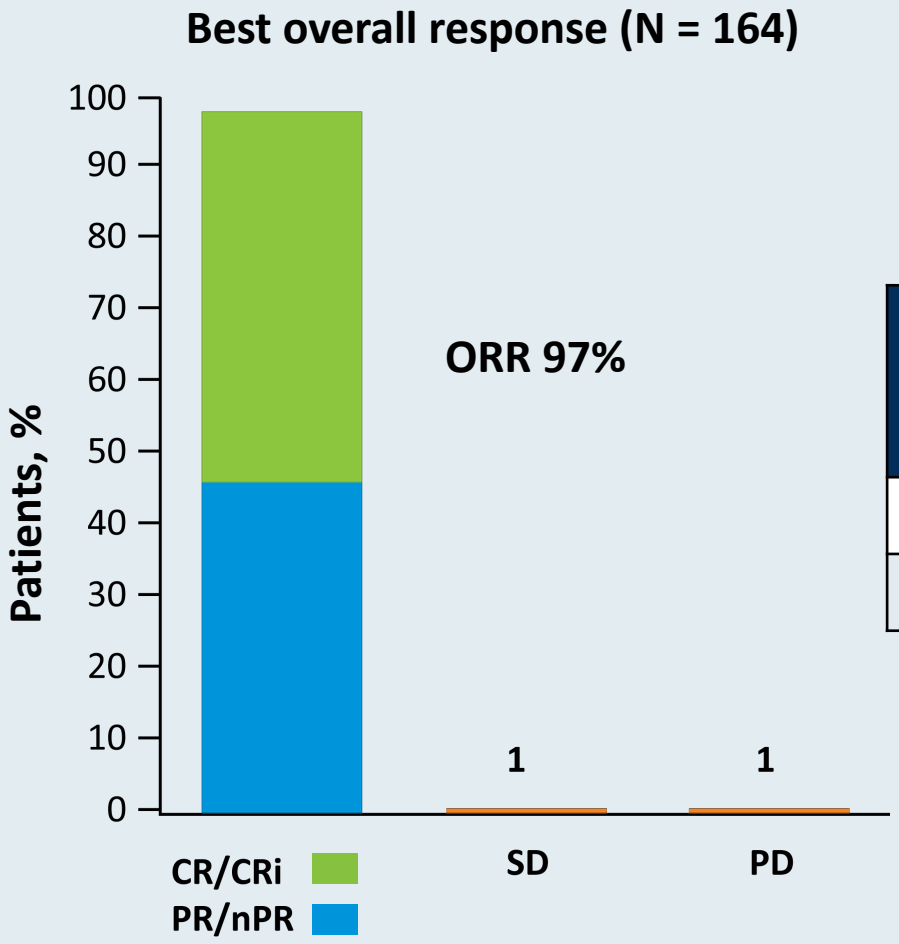
CAPTIVATE MRD Cohort: Undetectable MRD Rate

	Peripheral blood n = 163	Bone marrow n = 155
Best response of undetectable MRD in evaluable patients (95% CI)	**75%** (68-82)	**72%** (64-79)

- Rates of undetectable MRD in peripheral blood and bone marrow were highly concordant at Cycle 16 (91%)
- In the all-treated population (N = 164), undetectable MRD was achieved in 75% of patients in peripheral blood and in 68% of patients in bone marrow with up to 12 cycles of combination ibrutinib/venetoclax

Siddiqi S et al. EHA 2020;Abstract S158.

CAPTIVATE MRD Cohort: Undetectable MRD in Patients with CR/PR



Best overall response (up to Cycle 16)	CR n = 84	PR n = 75	ORR (CR + PR) n = 159
Undetectable MRD in PB, n (%)	71 (85)	52 (69)	123 (77)
Undetectable MRD in BM, n (%)	67 (80)	44 (59)	111 (70)

At 15 months, 98% of patients were progression free with no deaths

Siddiqi S et al. EHA 2020;Abstract S158.

CAPTIVATE MRD Cohort: Summary of Grade 3 and 4 AEs of Interest

AEs, n (%)	Ibrutinib lead-in (3 cycles) N = 164		Ibrutinib + venetoclax combination (12 cycles) N = 159		Overall (15 cycles) N = 164
	Grade 3	Grade 4	Grade 3	Grade 4	Grade 3-4
Atrial fibrillation	2 (1)	0	1 (1)	0	3 (2)
Major hemorrhage	0	0	1 (1)	0	1 (1)
Infections	4 (2)	0	10 (6)	0	14 (9)
Neutropenia	4 (2)	7 (4)	27 (17)	26 (16)	58 (35)
Febrile neutropenia	1 (1)	0	2 (1)	0	3 (2)
Laboratory TLS	0	0	2 (1)	0	2 (1)

- Low rates of Grade 3 atrial fibrillation, major hemorrhage, infections, febrile neutropenia and laboratory TLS (no Grade 4 event)
- No patients developed clinical TLS
  - Laboratory TLS reported as AE in 3 patients (only 1 met Howard criteria)
- No fatal AEs

Siddiqi S et al. EHA 2020;Abstract S158.

Ongoing Phase III EA9161 Trial Schema

Stratifications
Age: <65 yr vs ≥ 65 yr and <70 yr
PS: 0, 1, vs 2
Stage: 0, 1, or 2 vs 3, 4
Del11q22.3 vs others

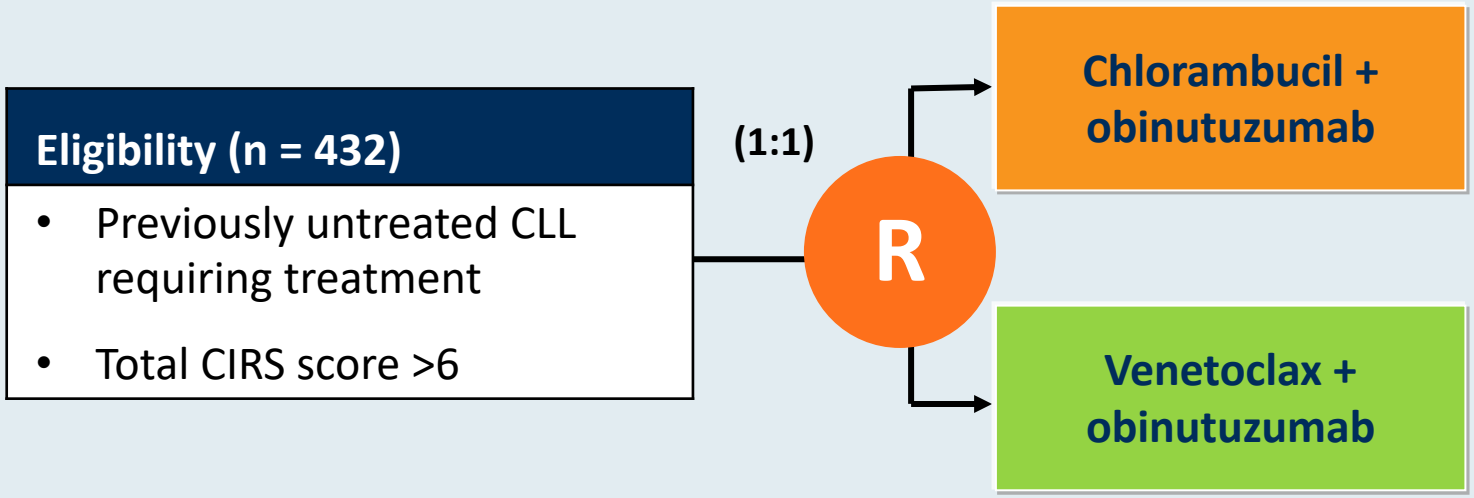
Randomize

Arm A
Ibrutinib: Cycles 1-19:d1-28 420mg PO daily
Obinutuzumab: C1 **:** D1:100 mg IV, D2:900 mg IV, D8: 1000 mg IV, D15: 1000 mg IV; C2-6: D1 1000 mg IV
Venetoclax: C3 D1-7 20mg PO daily D8-14 50mg PO daily D15-21 100mg PO daily; D22-28 200 mg PO daily; C4-14: D1-28 400mg PO daily

Arm B
Ibrutinib: Cycles 1-19+:d1-28 420mg PO daily
Obinutuzumab: C1 **:** D1:100 mg IV, D2:900 mg IV, D8: 1000 mg IV, D15: 1000 mg IV; C2-6: D1 1000 mg IV

Courtesy of Brad Kahl, MD

CLL14 Phase III Study Schema

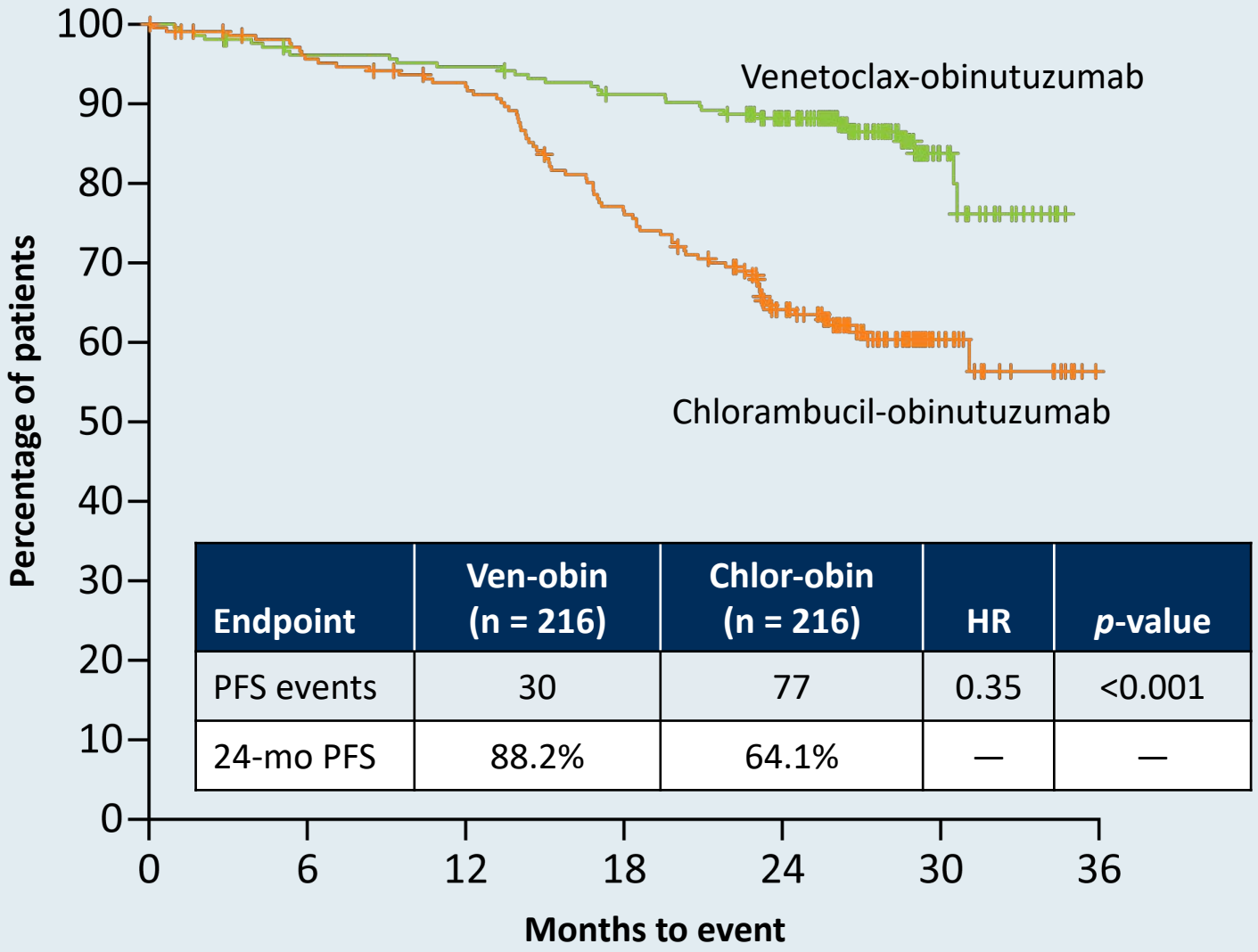


Primary endpoint: Progression-free survival

- Treatment duration in both groups: 12 cycles, 28 days each
- No crossover was allowed
- Daily oral venetoclax regimen:
  - Initiated on day 22 of cycle 1, starting with a 5-week dose ramp-up (1 week each of 20, 50, 100 and 200 mg, then 400 mg daily for 1 week)
  - Thereafter continuing at 400 mg daily until completion of cycle 12

www.clinicaltrials.gov (NCT02242942). Accessed August 2020.
Fischer K et al. *N Engl J Med* 2019;380(23):2225-36.

CLL14: Investigator-Assessed Progression-Free Survival



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

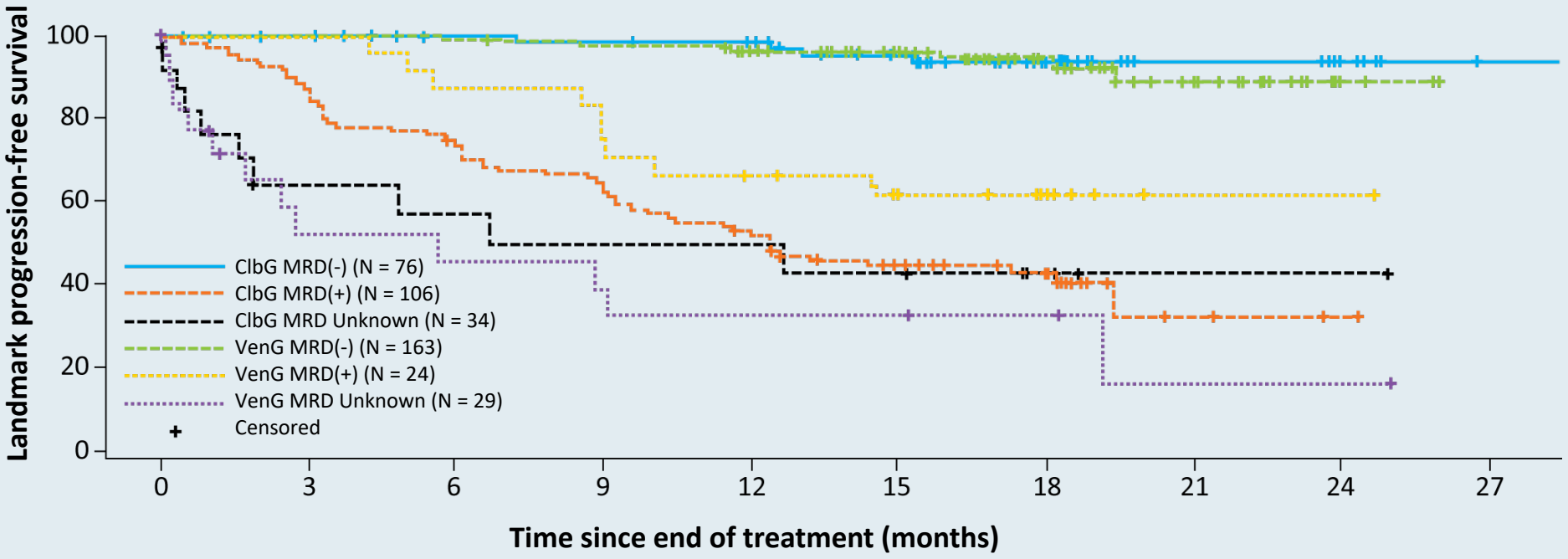
Fischer K et al. *N Engl J Med* 2019;380(23):2225-36.

CLL14: Minimal Residual Disease 3 Months After Treatment

MRD 3 months after treatment	MRD-negative		MRD responders	
	Veneto/obin (N = 216)	Chloram/obin (N = 216)	Veneto/obin (N = 216)	Chloram/obin (N = 216)
MRD in bone marrow	56.9%	17.1%	33.8%	10.6%
Odds ratio, *p*-value	OR 6.4, $p < 0.0001$		OR 4.3, $p < 0.0001$	
MRD in peripheral blood	75.7%	35.2%	42.1%	14.4%
Odds ratio, *p*-value	OR 5.7, $p < 0.0001$		OR 4.3, $p < 0.0001$	

Fischer K et al. *N Engl J Med* 2019;380(23):2225-36.

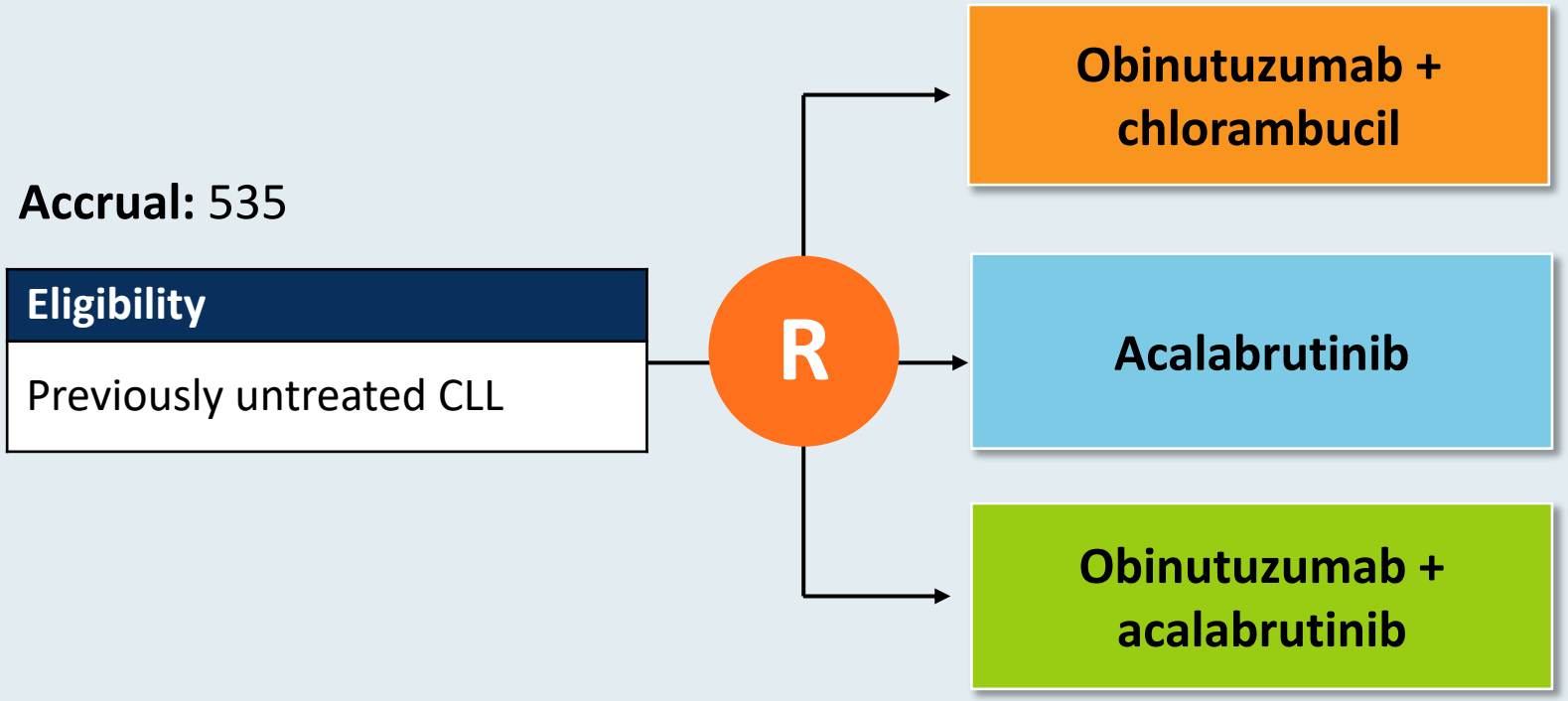
CLL14: Landmark Analysis from End of Therapy PFS by MRD Group



Further landmark analysis of PFS by MRD status showed that undetectable MRD translated into improved PFS regardless of the clinical response status at end of therapy.

Fischer K et al. ASH 2019;Abstract 36.

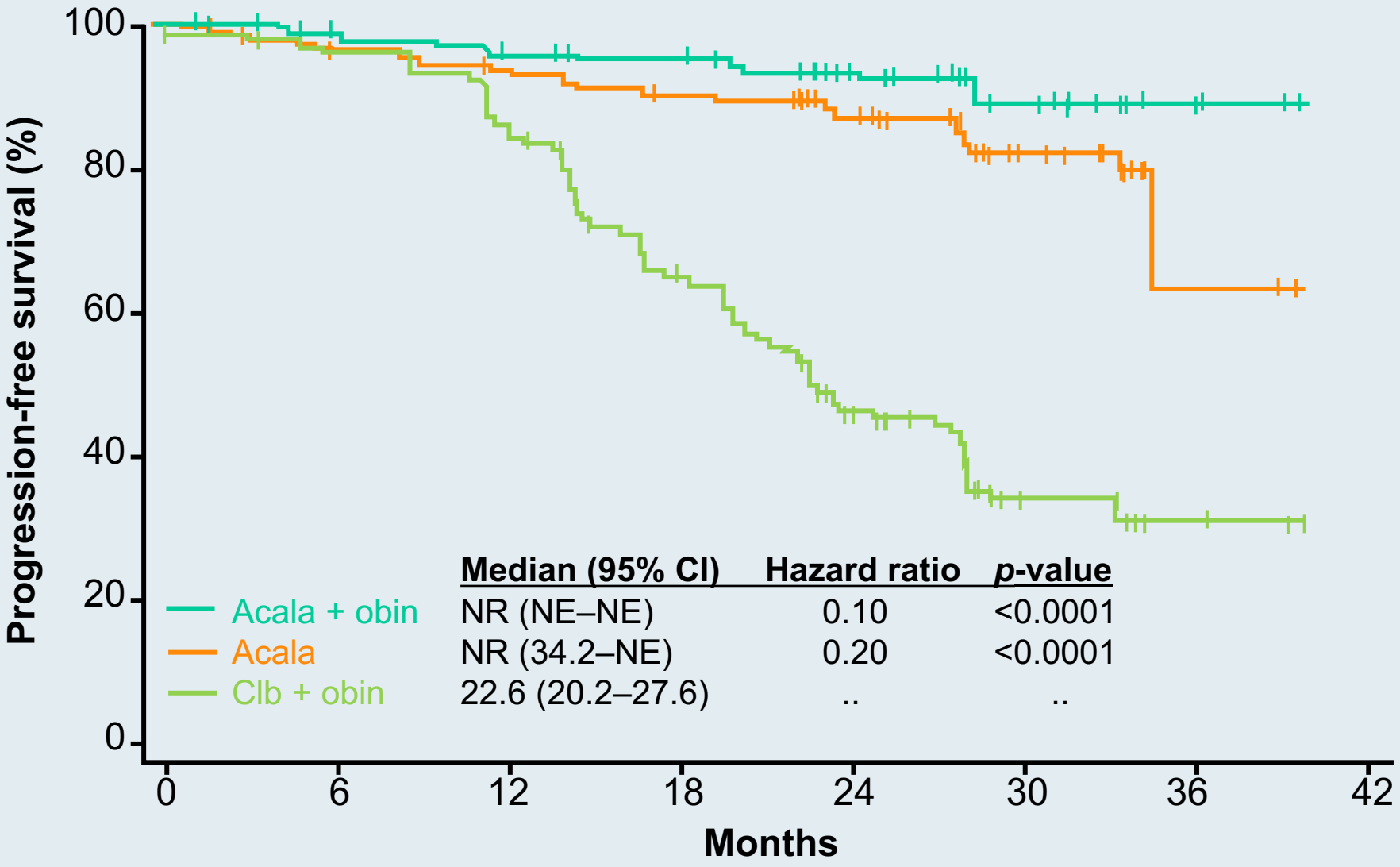
ELEVATE-TN Phase III Trial Schema



Primary endpoint: Progression-free survival

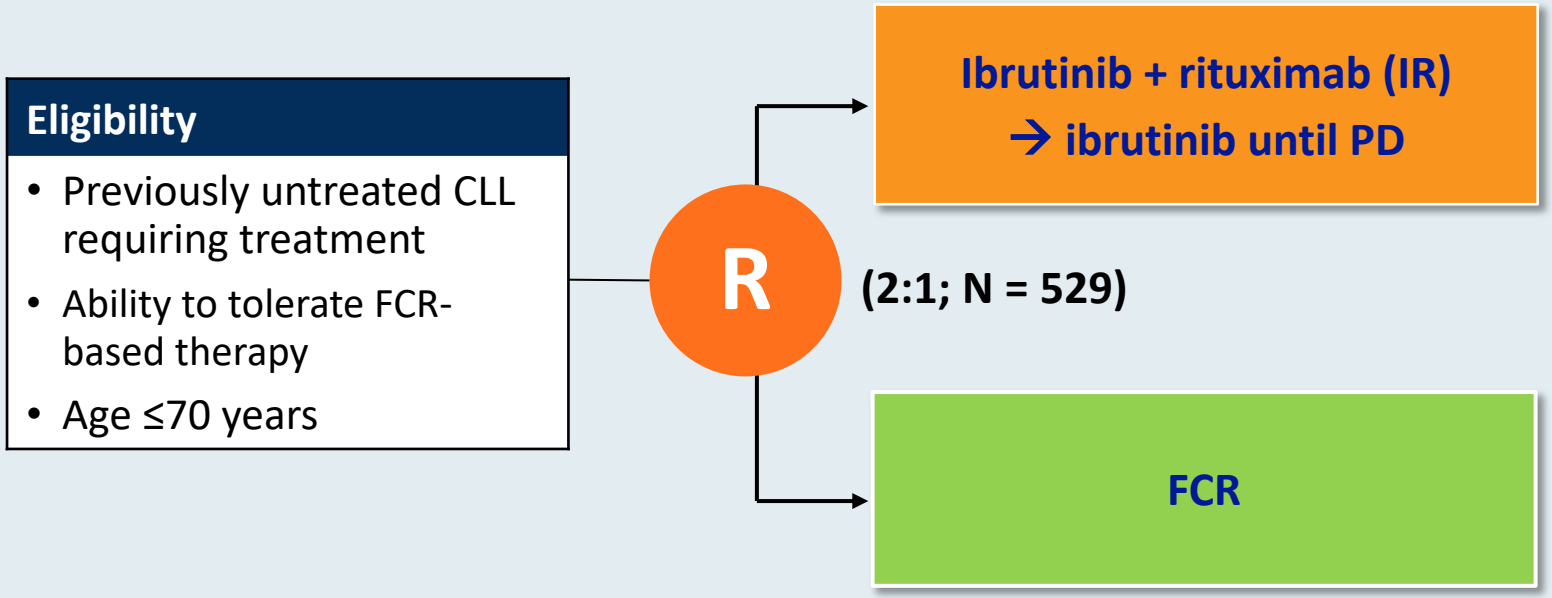
www.clinicaltrials.gov (NCT02475681). Accessed August 2020.

ELEVATE-TN: PFS (IRC)



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

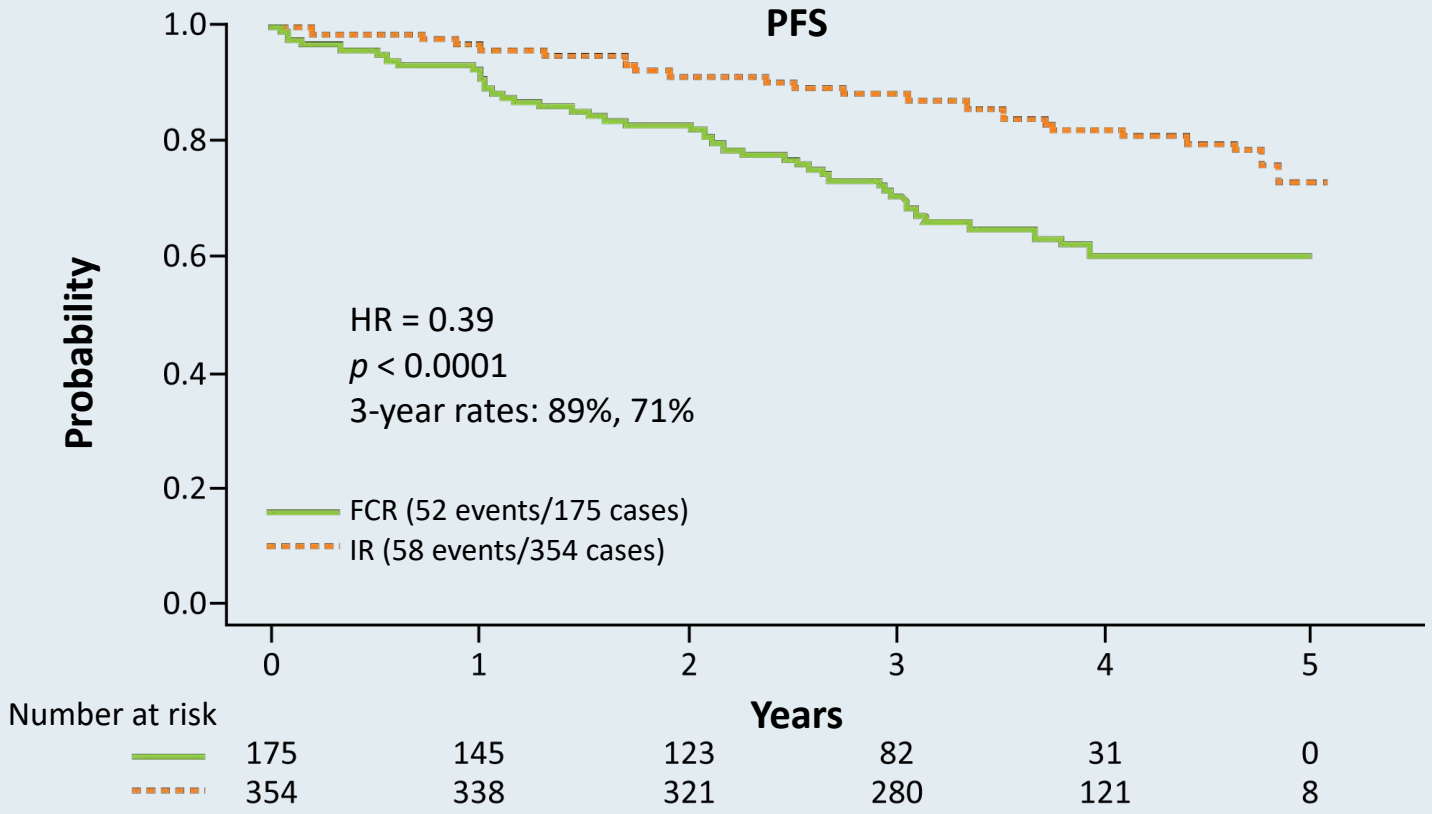
Phase III ECOG-ACRIN E1912 Study Design



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

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

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

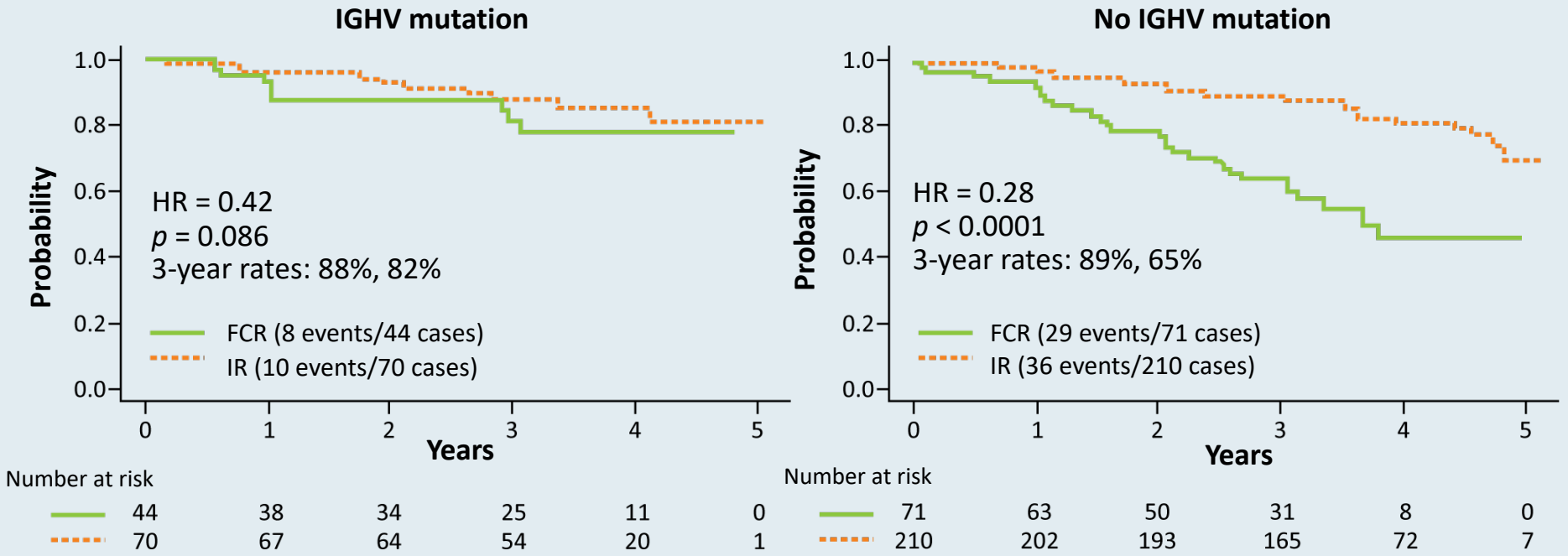


- Grade ≥3 treatment-related AEs were reported in 70% of patients receiving IR and 80% of patients receiving FCR (odds ratio = 0.56; $p = 0.013$).
- Among the 95 patients who discontinued ibrutinib, the most common cause was AE or complication.

Shanafelt TD et al. ASH 2019;Abstract 33.

RTP RESEARCH TO PRACTICE

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



- On subgroup analysis by IGHV mutation status, IR was superior to FCR for CLL with no IGHV mutation (HR = 0.28; $p < 0.0001$).
- With current follow-up the difference between IR and FCR is not significant for CLL with IGHV mutation (HR = 0.42; $p = 0.086$).

Shanafelt TD et al. ASH 2019;Abstract 33.

Meet The Professor
Immunotherapy and Novel Agents in Gynecologic Cancers

Thursday, October 8, 2020
12:00 PM – 1:00 PM ET

Faculty

Brian M Slomovitz, MD

Moderator

Neil Love, MD

RTP
RESEARCH
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Thank you for joining us!

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

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