Consensus or Controversy? Chronic Lymphocytic Leukemia and Follicular Lymphoma

Tuesday, June 29, 2021
5:00 PM – 6:00 PM ET

Faculty

Nathan H Fowler, MD
Prof John G Gribben, MD, DSc, FMedSci
Brad S Kahl, MD

Moderator

Neil Love, MD

RTP RESEARCH TO PRACTICE

Faculty

Nathan H Fowler, MD
Professor, Department of Lymphoma/Myeloma
The University of Texas
MD Anderson Cancer Center
Houston, Texas

Brad S Kahl, MD
Professor of Medicine
Washington University School of Medicine
Director, Lymphoma Program
Siteman Cancer Center
St Louis, Missouri

Prof John G Gribben, MD, DSc, FMedSci
Chair of Medical Oncology
Barts Cancer Institute
Queen Mary University of London
Charterhouse Square
London, United Kingdom

Commercial Support

This activity is supported by educational grants from AbbVie Inc, Adaptive Biotechnologies Corporation, AstraZeneca Pharmaceuticals LP, Bayer HealthCare Pharmaceuticals, Bristol-Myers Squibb Company, Genentech, a member of the Roche Group, GlaxoSmithKline, Incyte Corporation, Oncopeptides, Pharmacyclics LLC, an AbbVie Company and Janssen Biotech Inc, administered by Janssen Scientific Affairs LLC, Sanofi Genzyme, Seagen Inc, and Takeda Oncology.

Dr Love — Disclosures

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Dr Fowler — Disclosures

No relevant conflicts of interest to disclose.

Prof Gribben — Disclosures

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Dr Kahl — Disclosures

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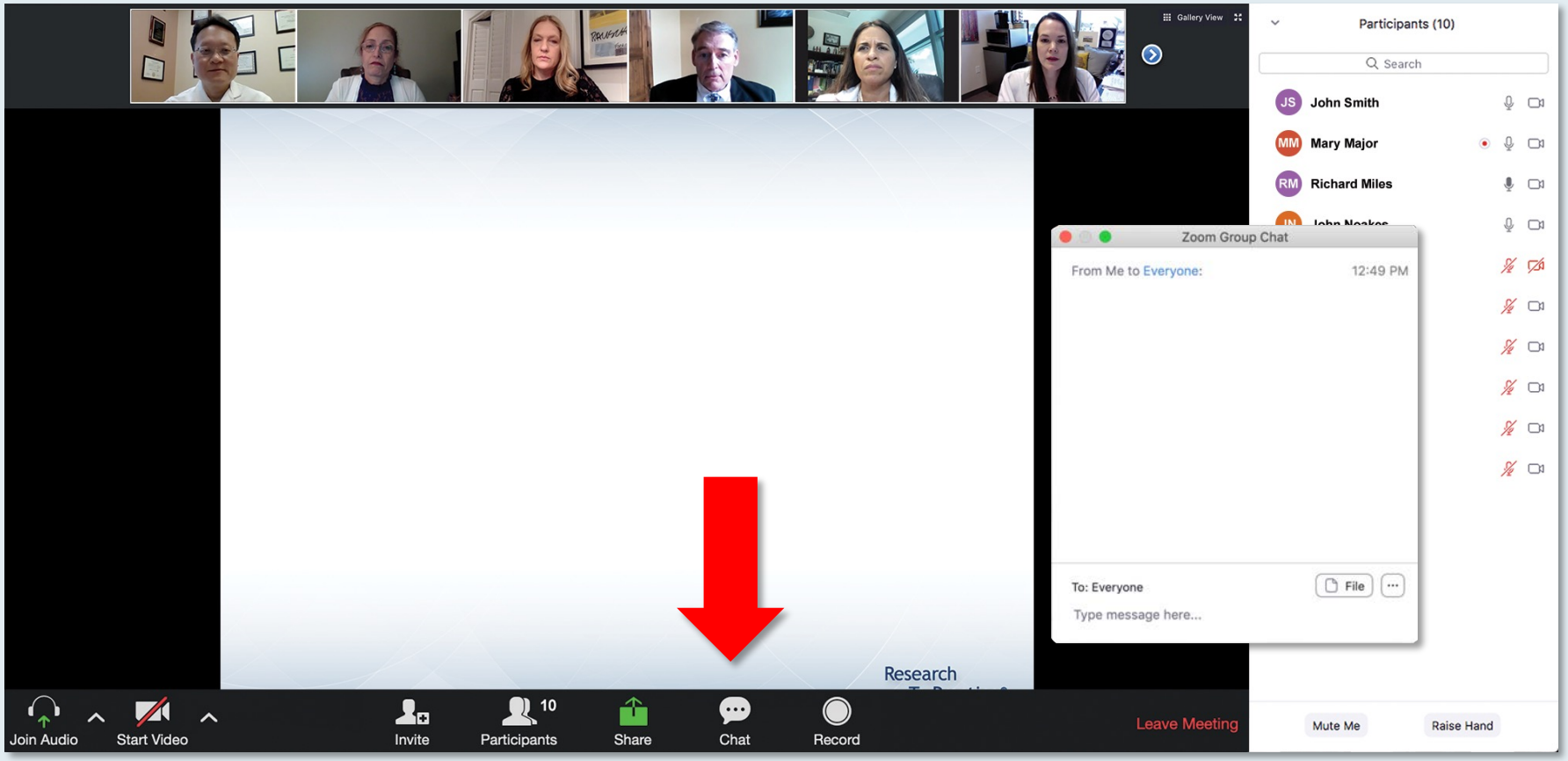
We Encourage Clinicians in Practice to Submit Questions



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

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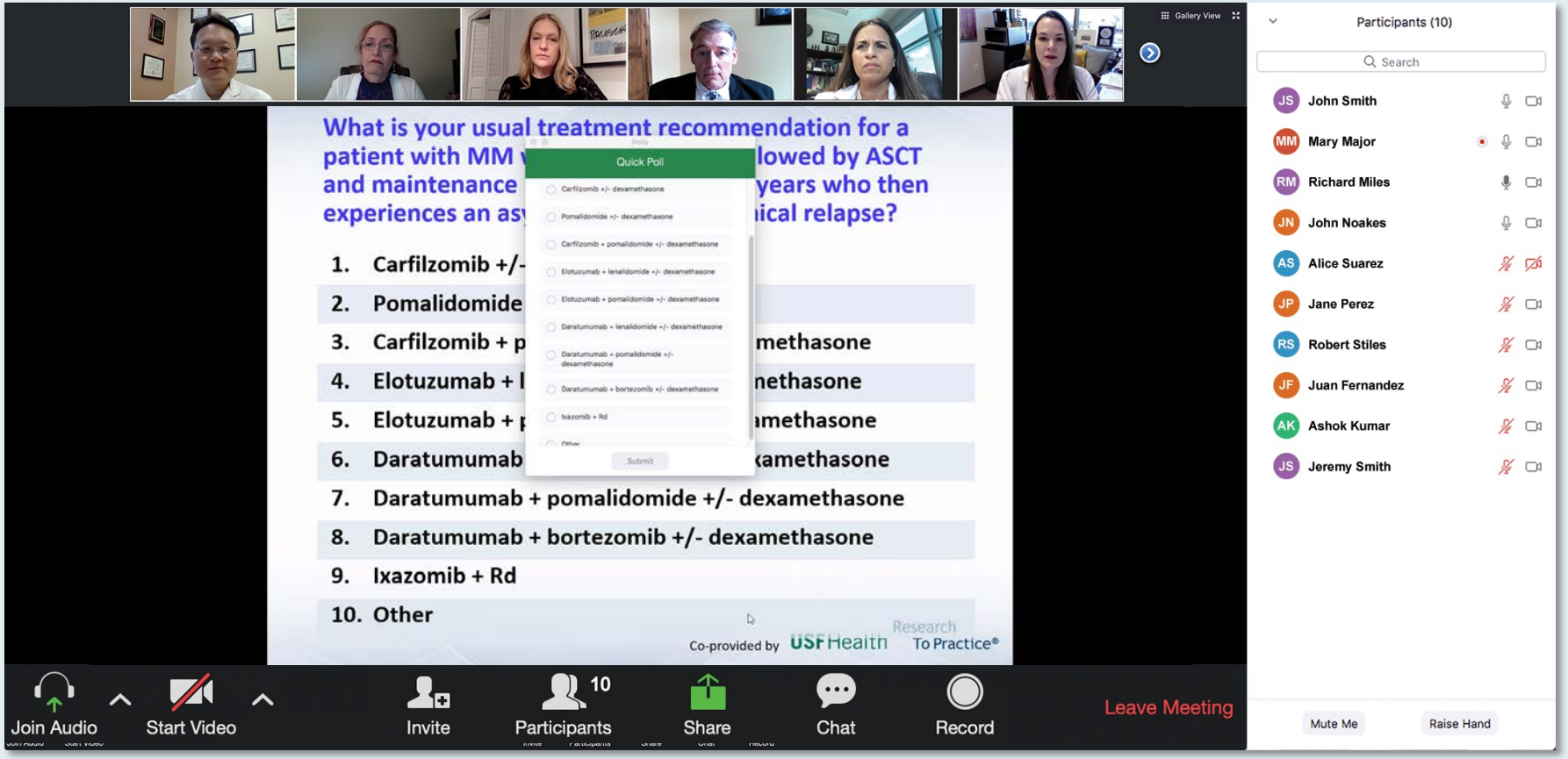
Familiarizing Yourself with the Zoom Interface

How to answer poll questions



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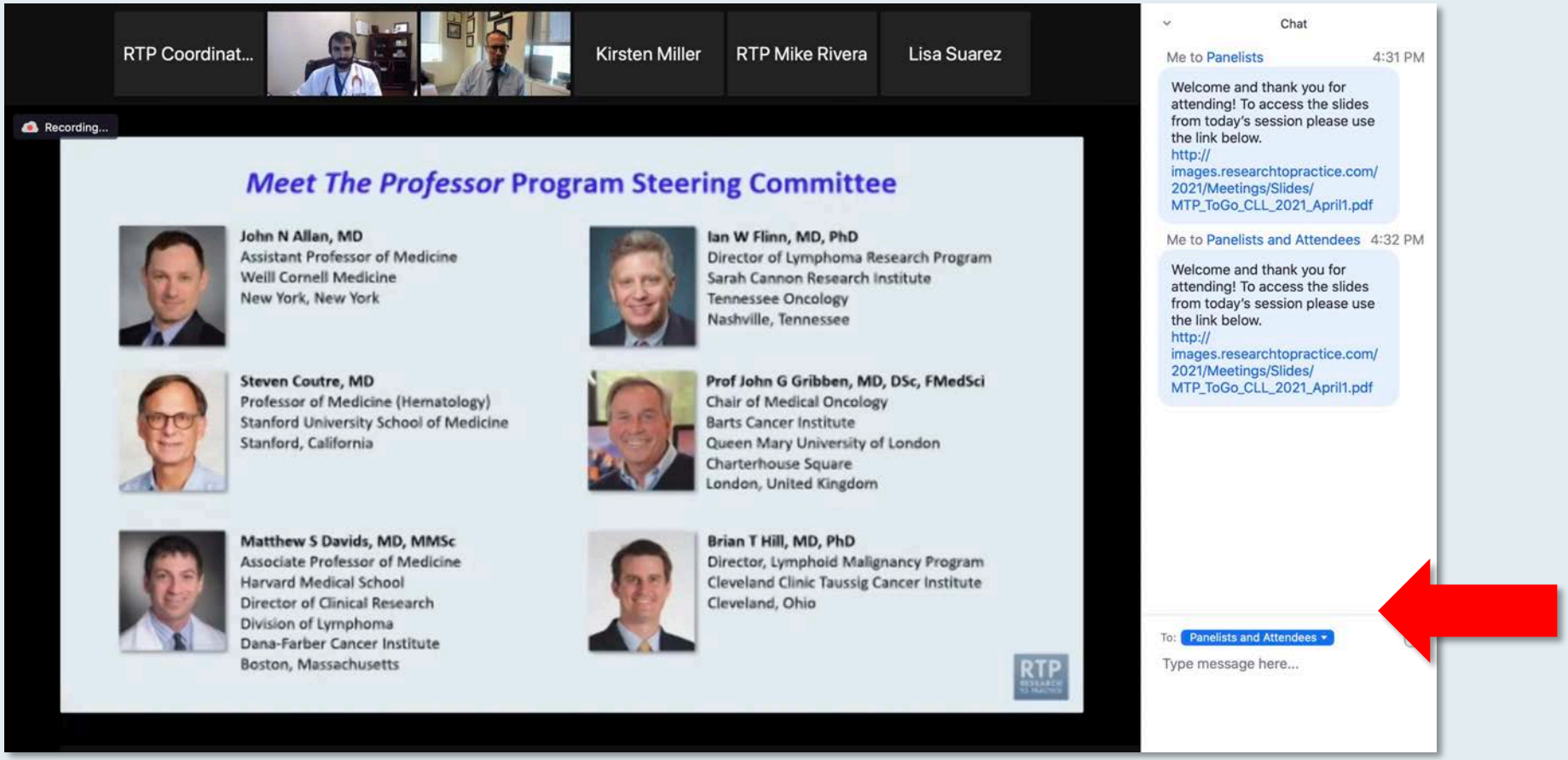
Familiarizing Yourself with the Zoom Interface

Expand chat submission box



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

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Familiarizing Yourself with the Zoom Interface

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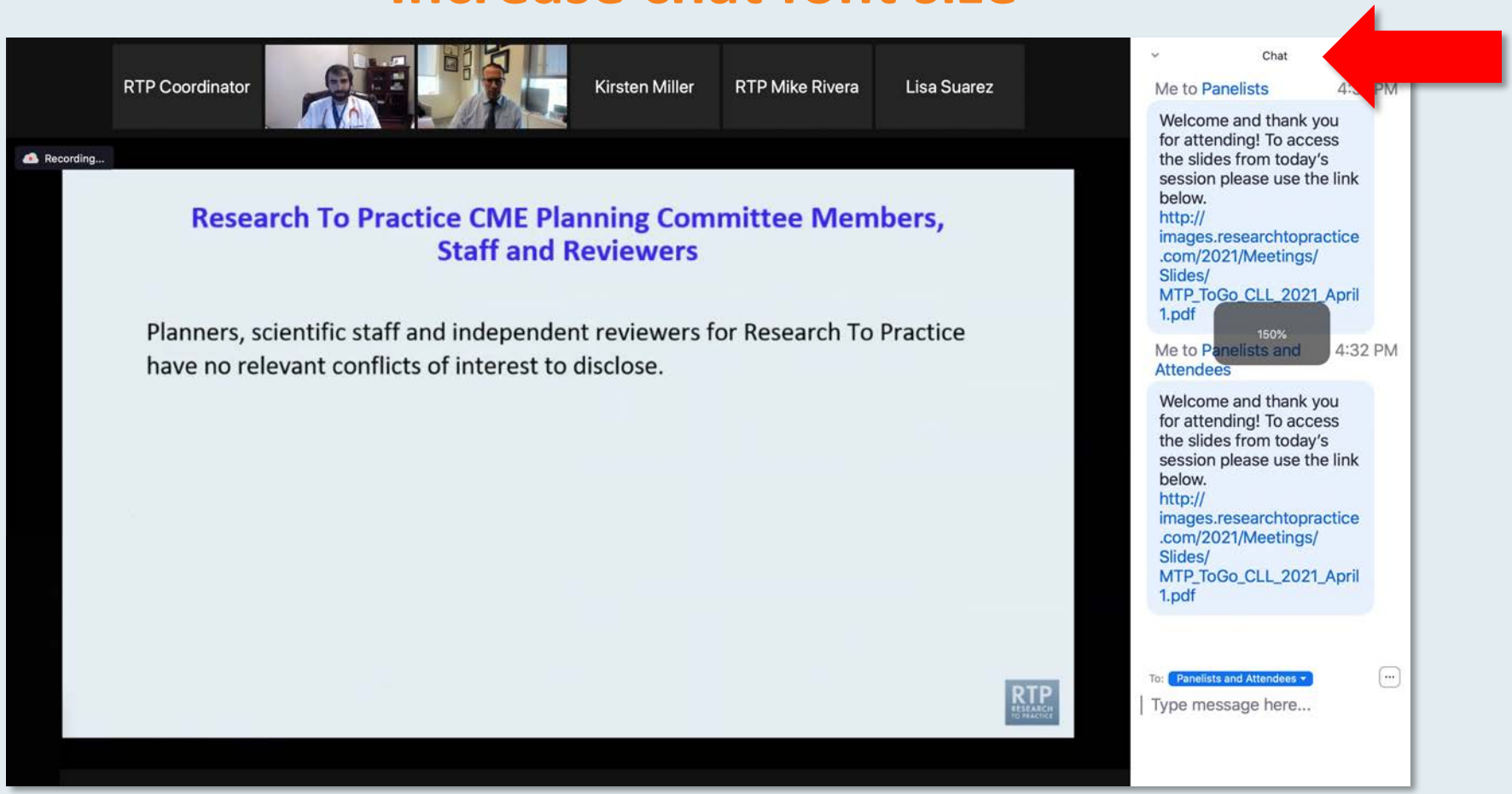

Press Command (for Mac) or Control (for PC) and the + symbol.
You may do this as many times as you need for readability.

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WITH DR NEIL LOVE

Key Presentations on Chronic Lymphocytic Leukemia and Follicular Lymphoma from the 2020 ASH Annual Meeting

DR ANN LACASCE

DANA-FARBER CANCER INSTITUTE

BOSTON, MASSACHUSETTS

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Wednesday, June 30
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Ovarian Cancer
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Hormonal Therapy for Prostate Cancer
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Bladder Cancer
Wednesday, July 21
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Mantle Cell, Diffuse Large B-Cell and Hodgkin Lymphoma
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Head and Neck Cancer
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Consensus or Controversy? Multiple Myeloma

Wednesday, June 30, 2021
5:00 PM – 6:00 PM ET

Faculty

Natalie S Callander, MD
Shaji K Kumar, MD
Sagar Lonial, MD

Moderator

Neil Love, MD

RTP RESEARCH TO PRACTICE

Ask the Expert: Clinical Investigators Provide Perspectives on the Management of Renal Cell Carcinoma

In Partnership with Project Echo® and Florida Cancer Specialists

Tuesday, July 6, 2021
5:00 PM – 6:00 PM ET

Faculty

David I Quinn, MBBS, PhD

Moderator

Neil Love, MD

A Conversation with the Investigators: Ovarian Cancer

Wednesday, July 7, 2021
5:00 PM – 6:00 PM ET

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Michael J Birrer, MD, PhD
Kathleen Moore, MD
Richard T Penson, MD, MRCP

Moderator

Neil Love, MD

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A Conversation with the Investigators: Hormonal Therapy for Prostate Cancer

Monday, July 12, 2021
5:00 PM – 6:00 PM ET

Faculty

Simon Chowdhury, MD, PhD
Tanya B Dorff, MD
Matthew R Smith, MD, PhD

Moderator

Neil Love, MD

RTP RESEARCH TO PRACTICE

A Conversation with the Investigators: Chimeric Antigen Receptor T-Cell Therapy in Hematologic Cancers

Tuesday, July 13, 2021
5:00 PM – 6:00 PM ET

Faculty

Caron Jacobson, MD
David G Maloney, MD, PhD
Nikhil C Munshi, MD

Moderator

Neil Love, MD

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TO PRACTICE

A Conversation with the Investigators: Acute Myeloid Leukemia and Myelodysplastic Syndromes

Wednesday, July 14, 2021
5:00 PM – 6:00 PM ET

Faculty

Courtney D DiNardo, MD, MSCE
Gail J Roboz, MD
Eytan M Stein, MD

Moderator

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RTP RESEARCH TO PRACTICE

Consensus or Controversy? Clinical Investigator Perspectives on the Current and Future Management of Mantle Cell, Diffuse Large B-Cell and Hodgkin Lymphoma

Monday, August 2, 2021
5:00 PM – 6:00 PM ET

Faculty

Stephen M Ansell, MD, PhD
Craig Moskowitz, MD
Laurie H Sehn MD, MPH

Moderator

Neil Love, MD

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Thank you for joining us!

CME and MOC credit information will be emailed to each participant within 24 hours.

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Barts Cancer Institute
Queen Mary University of London
Charterhouse Square
London, United Kingdom

Consensus or Controversy Consulting Investigators

Dr Jeff Sharman

Dr Ian Flinn

Dr Christopher Flowers

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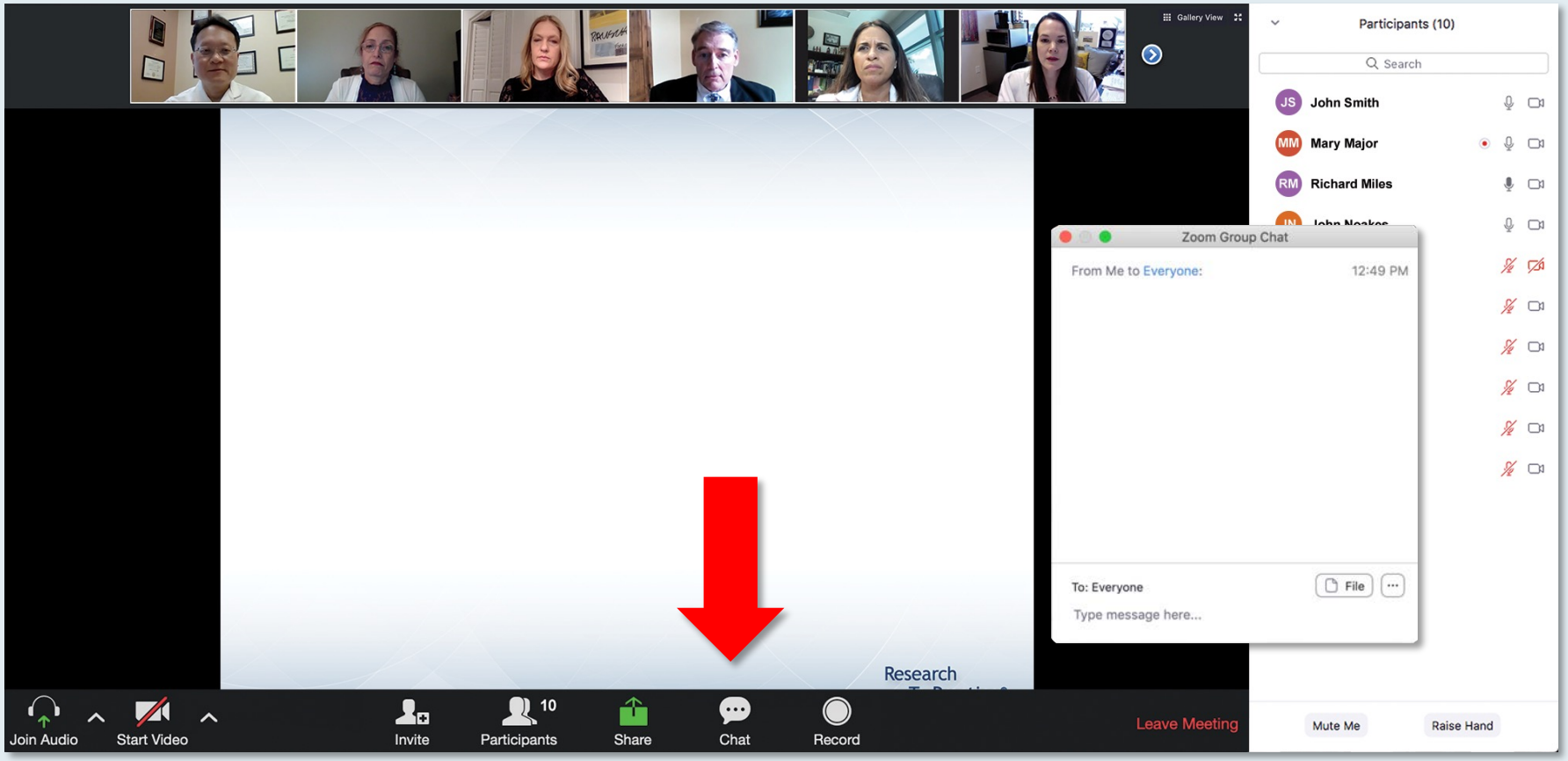

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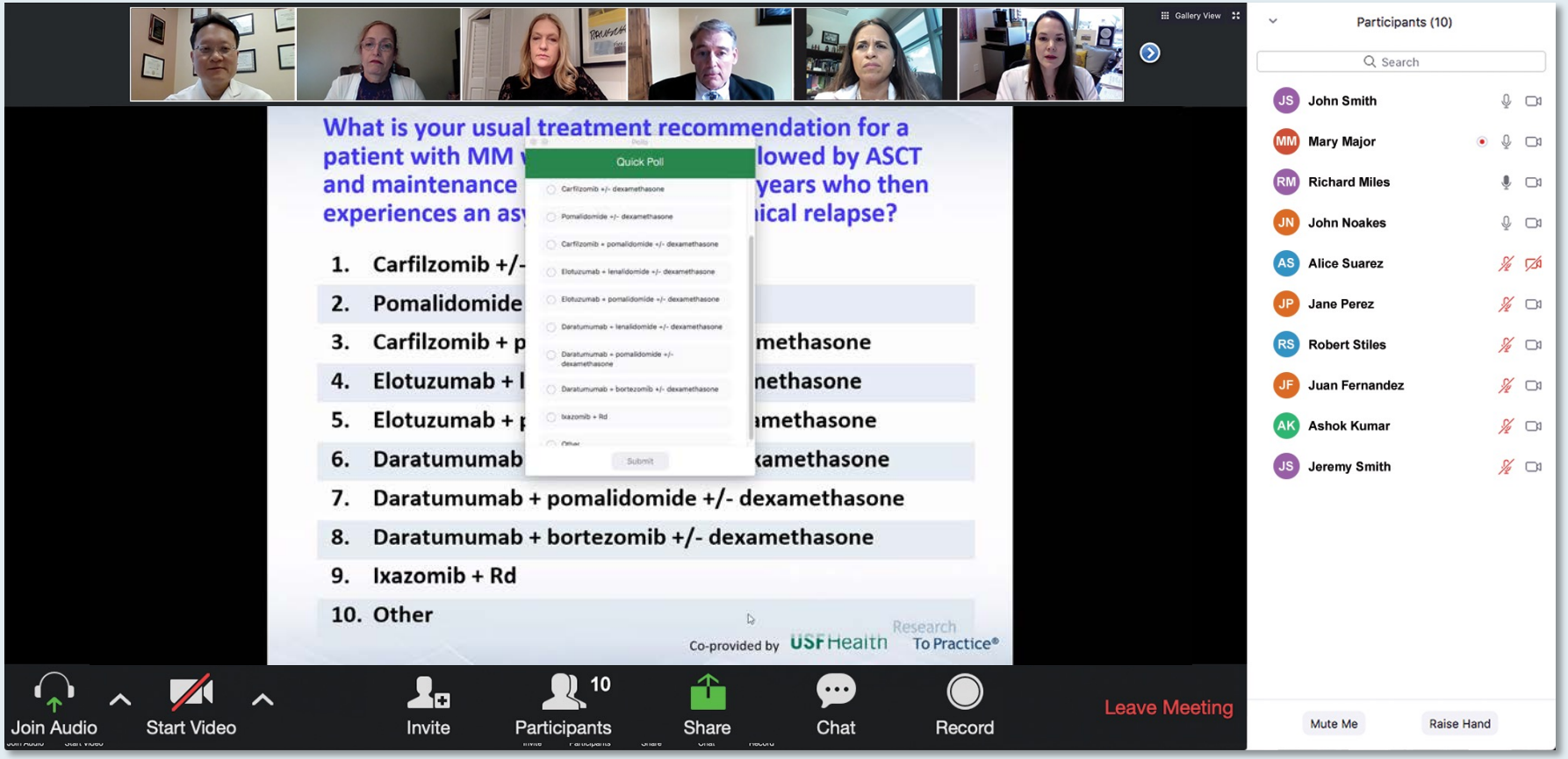

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Agenda

MODULE 1: Chronic Lymphocytic Leukemia

- Choice of front-line therapy
- Selection of a BTK inhibitor
- Second-line therapy
- Third-line therapy
- Ongoing research: Combination strategies, noncovalent BTK inhibitors, CAR T-cell therapy

MODULE 2: Follicular Lymphoma

- Selection of first- and second-line treatment
- Third-line therapy: Tazemetostat, PI3K inhibitors, CAR T-cell therapy

Agenda

MODULE 1: Chronic Lymphocytic Leukemia

- Choice of front-line therapy
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MODULE 2: Follicular Lymphoma

- Selection of first- and second-line treatment
- Third-line therapy: Tazemetostat, PI3K inhibitors, CAR T-cell therapy

Regulatory and reimbursement issues aside, what is your preferred initial regimen for a 60-year-old patient with IGHV-mutated chronic lymphocytic leukemia without del(17p) or TP53 mutation who requires treatment?

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

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

 Dr Fowler	Ibrutinib	 Dr Flowers	FCR
 Prof Gribben	FCR	 Dr Leonard	Acalabrutinib
 Dr Kahl	Venetoclax + obinutuzumab	 Dr Moskowitz	Ibrutinib + rituximab
 Dr Ansell	Ibrutinib + obinutuzumab	 Dr Sehn	FCR or acalabrutinib
 Dr Flinn	Venetoclax + obinutuzumab	 Dr Sharman	FCR or venetoclax + obinutuzumab

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Young patients with IGHV-mutated disease

Dr Jeff Sharman

Dr Ian Flinn

Dr Christopher Flowers

Dr John Leonard

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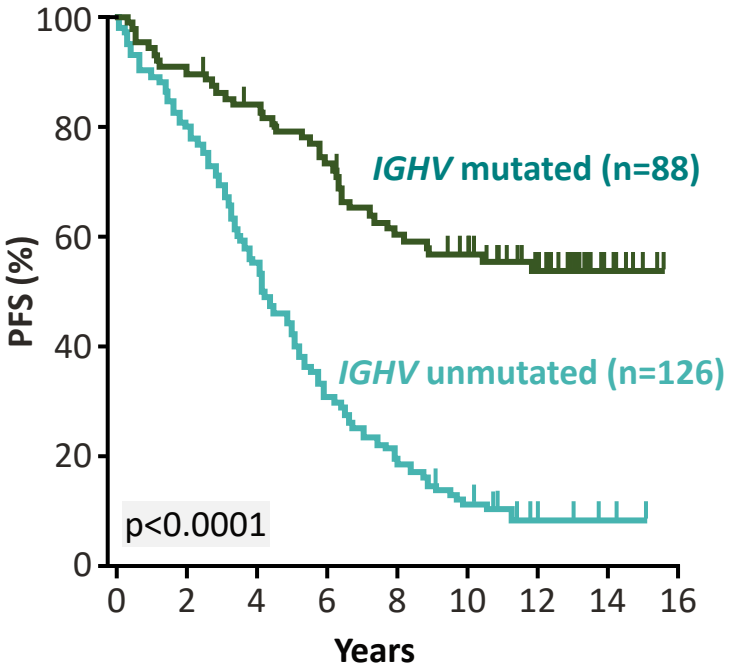
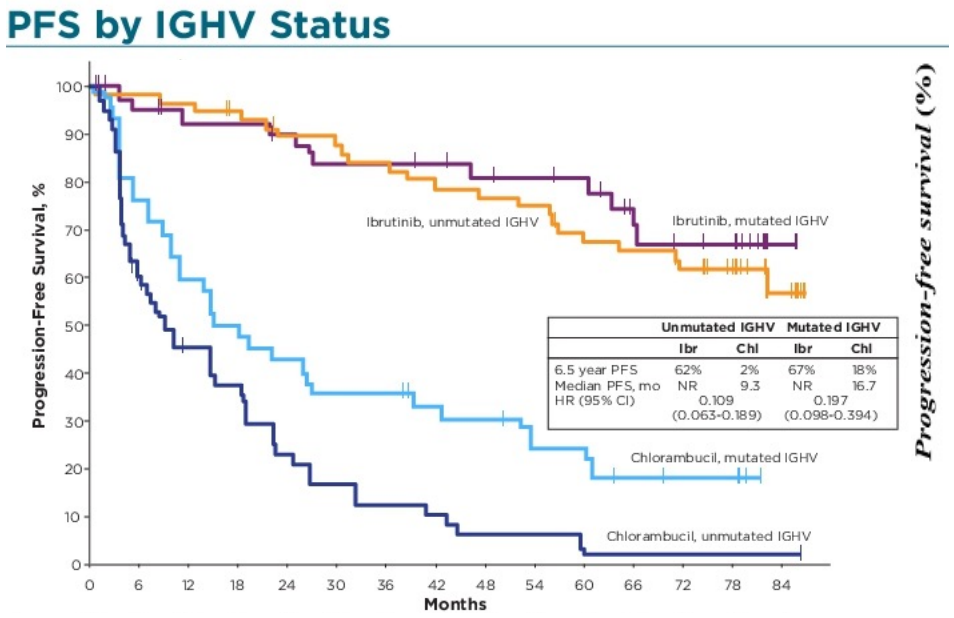
Chalk talk – Prof Gribben

Younger (fit) patient with newly diagnosed *IGHV*-mutated CLL – optimal treatment

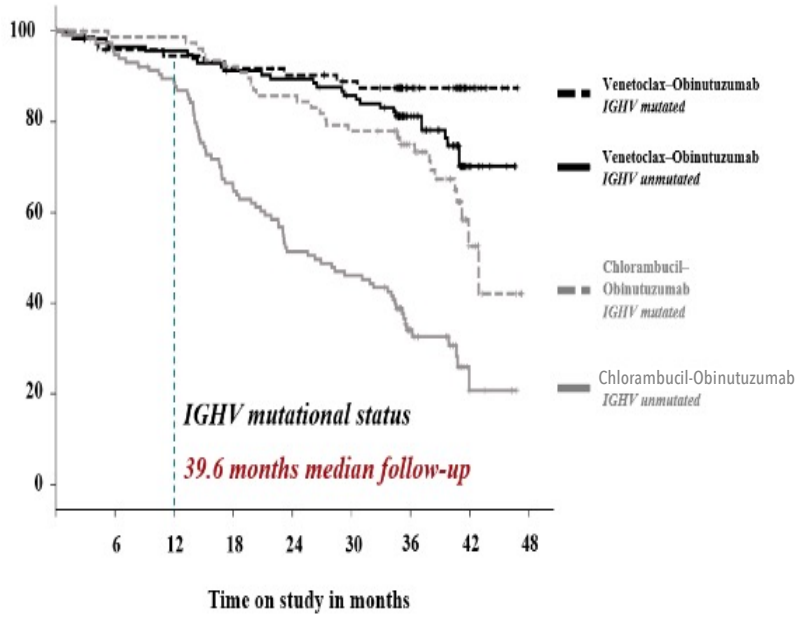
FCR



Ibrutinib



Venetoclax Obinutuzumab



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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?

 Dr Fowler	Ibrutinib	 Dr Flowers	Acalabrutinib OR venetoclax + obinutuzumab
 Prof Gribben	Ibrutinib	 Dr Leonard	Acalabrutinib
 Dr Kahl	Venetoclax + obinutuzumab	 Dr Moskowitz	Venetoclax + obinutuzumab
 Dr Ansell	Ibrutinib + obinutuzumab	 Dr Sehn	Venetoclax + obinutuzumab
 Dr Flinn	Venetoclax + obinutuzumab	 Dr Sharman	Venetoclax + obinutuzumab

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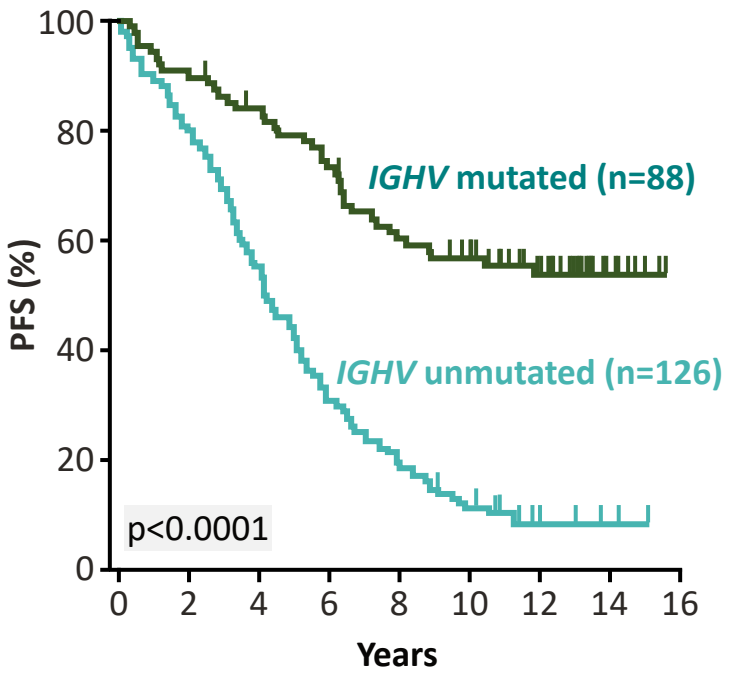
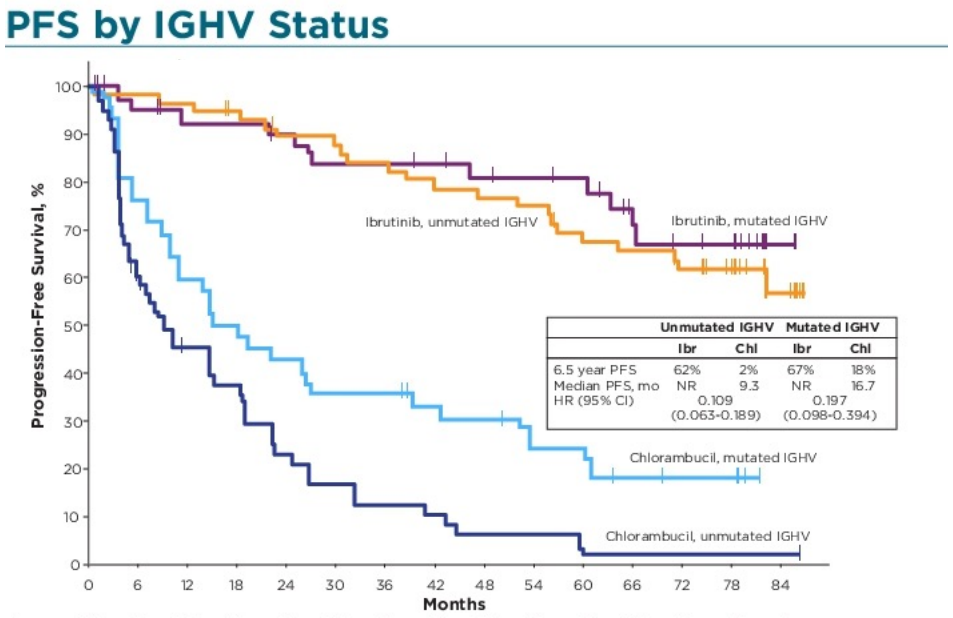
Chalk talk – Prof Gribben

Younger (fit) patient with newly diagnosed *IGHV*-unmutated CLL – optimal treatment

FCR



Ibrutinib



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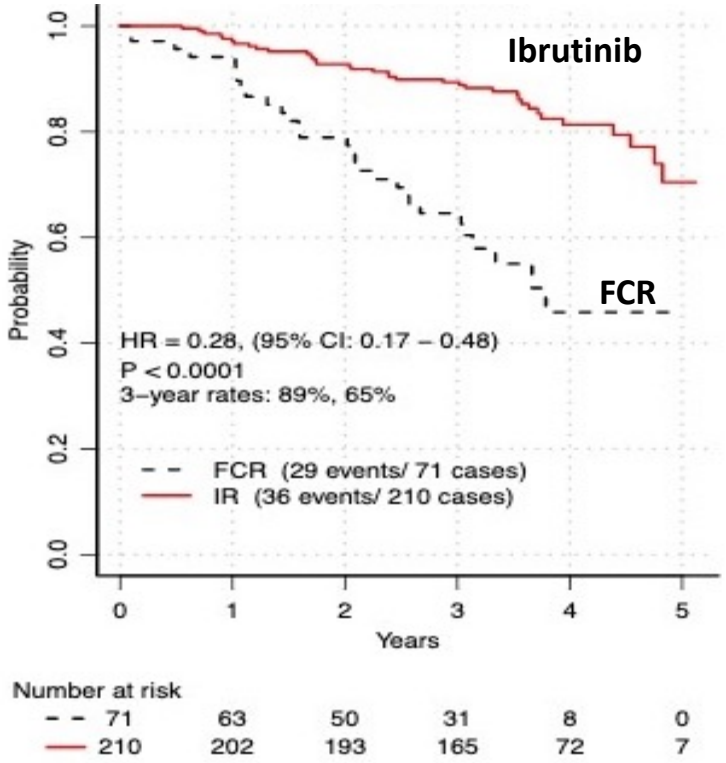

OS survival advantage for Ibrutinib

HR: 0.34 (95% CI: 0.15–0.79); p=0.009

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?

 Dr Fowler	Acalabrutinib	 Dr Flowers	Acalabrutinib
 Prof Gribben	Venetoclax + obinutuzumab	 Dr Leonard	Venetoclax + obinutuzumab
 Dr Kahl	Venetoclax + obinutuzumab	 Dr Moskowitz	Acalabrutinib
 Dr Ansell	Ibrutinib	 Dr Sehn	Venetoclax + obinutuzumab
 Dr Flinn	Venetoclax + obinutuzumab	 Dr Sharman	Venetoclax + obinutuzumab

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 Prof Gribben	Acalabrutinib	 Dr Leonard	Venetoclax + obinutuzumab
 Dr Kahl	Venetoclax + obinutuzumab	 Dr Moskowitz	Acalabrutinib
 Dr Ansell	Ibrutinib + obinutuzumab	 Dr Sehn	Venetoclax + obinutuzumab
 Dr Flinn	Venetoclax + obinutuzumab	 Dr Sharman	Venetoclax + obinutuzumab

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Older patients; choice of BTK inhibitor

Dr Jeff Sharman

Dr Ian Flinn

Dr Christopher Flowers

Dr John Leonard

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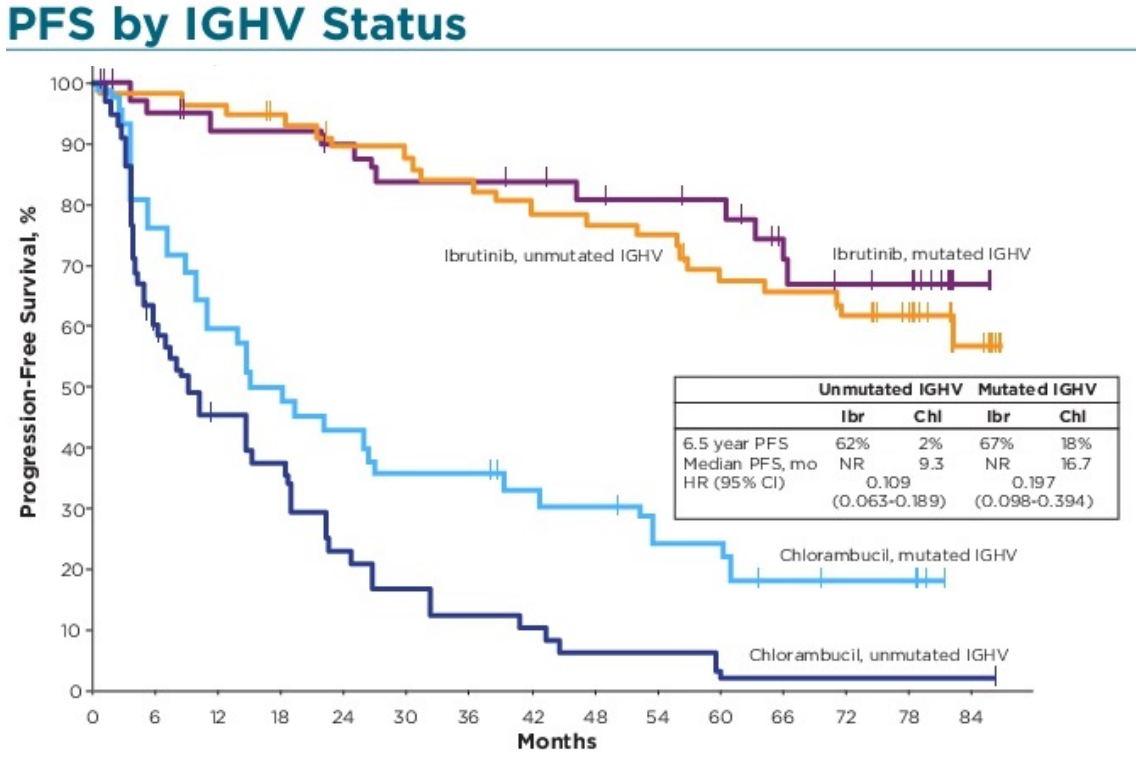
RESEARCH
TO PRACTICE

Chalk talk – Prof Gribben

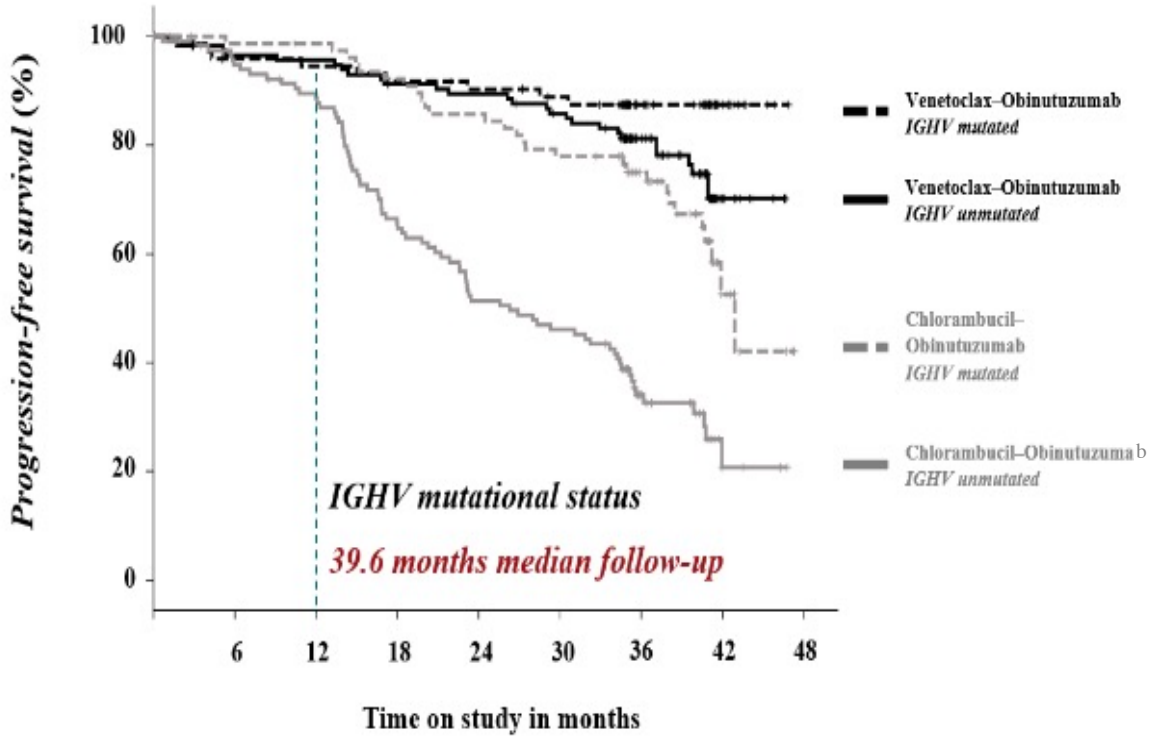
Older (unfit) patient with newly diagnosed CLL – optimal treatment with novel agents is <u>independent</u> of *IGHV*-mutational status

Ibrutinib



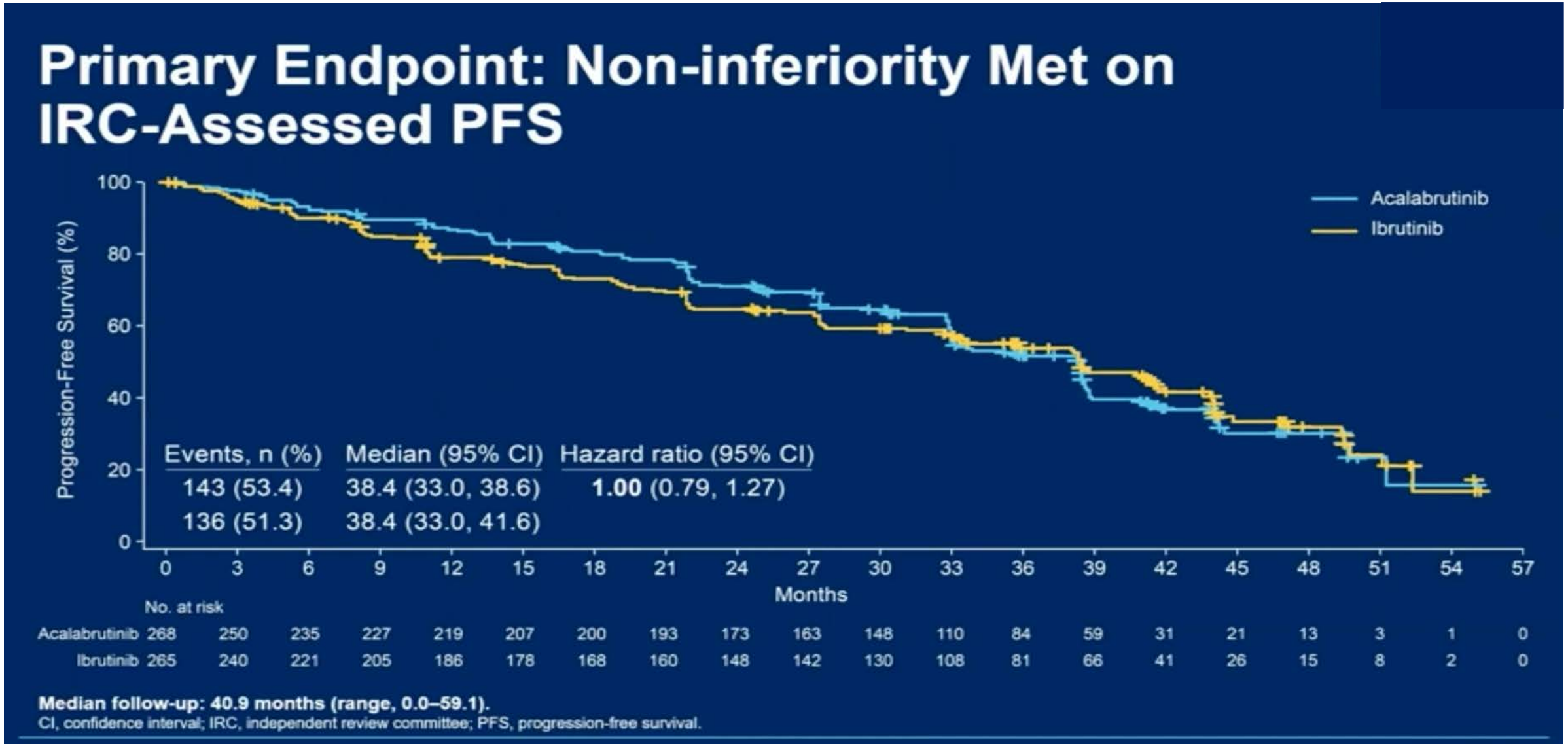
Continuous therapy

Venetoclax Obinutuzumab



One year fixed duration therapy

ELEVATE RR Trial Acalabrutinib vs Ibrutinib in R/R CLL



J Byrd et al ASCO 2021

Courtesy of Prof John G Gribben, MD, DSc, FMedSci

ELEVATE RR – Adverse events of special interest

Events, n (%)	Any grade		Grade ≥3	
	Acalabrutinib (n=266)	Ibrutinib (n=263)	Acalabrutinib (n=266)	Ibrutinib (n=263)
Cardiac events	64 (24.1)	79 (30.0)	23 (8.6)	25 (9.5)
Atrial fibrillation[a]*	25 (9.4)	**42 (16.0)**	13 (4.9)	10 (3.8)
Ventricular arrhythmias[b]	0	3 (1.1)	0	1 (0.4)
Bleeding events*	101 (38.0)	**135 (51.3)**	10 (3.8)	12 (4.6)
Major bleeding events[c]	12 (4.5)	14 (5.3)	10 (3.8)	12 (4.6)
Hypertension[d]*	25 (9.4)	**61 (23.2)**	11 (4.1)	**24 (9.1)**
Infections[e]	208 (78.2)	214 (81.4)	82 (30.8)	79 (30.0)
ILD/pneumonitis*	7 (2.6)	**17 (6.5)**	1 (0.4)	2 (0.8)
SPMs excluding NMSC	24 (9.0)	20 (7.6)	16 (6.0)	14 (5.3)

Higher incidence indicated in **bold yellow** for terms with statistical differences.
*Two-sided P-value for event comparisons <0.05 without multiplicity adjustment.
[a]Includes events with preferred terms atrial fibrillation and atrial flutter.
[b]Includes events with preferred terms torsade de pointes, ventricular arrhythmia, ventricular extrasystoles, ventricular fibrillation, ventricular flutter, ventricular tachyarrhythmia, and ventricular tachycardia.
[c]Defined as any hemorrhagic event that was serious, grade ≥3 in severity, or a central nervous system hemorrhage (any severity grade).
[d]Included events with the preferred terms of hypertension, blood pressure increased, and blood pressure systolic increased.
[e]Most common grade ≥3 infections were pneumonia (acalabrutinib, 10.5%; ibrutinib, 8.7%), sepsis (1.5% vs 2.7%, respectively), and UTI (1.1% vs 2.3%).
ILD, interstitial lung disease; NMSC, nonmelanoma skin cancer; SPMs, second primary malignancies; UTI, urinary tract infection.

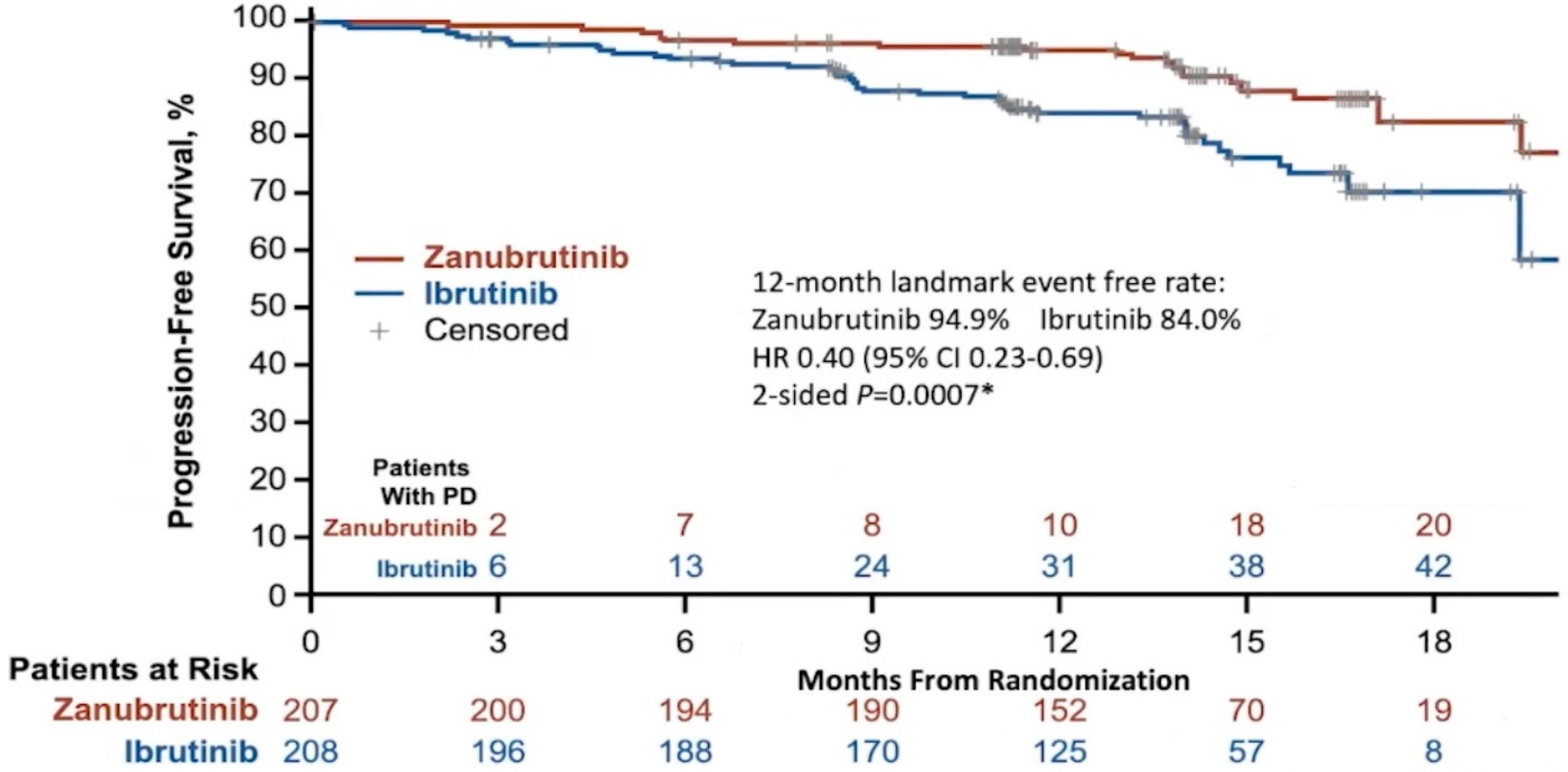
Byrd et al SCO 20221

Courtesy of Prof John G Gribben, MD, DSc, FMedSci

ALPINE STUDY – Zanubrutinib vs Ibrutinib in RR CLL

ORR (INV assessment): Zanubrutinib 78.3%, ibrutinib 62.5% (2-sided *p* = 0.0006)

PFS by Investigator Assessment



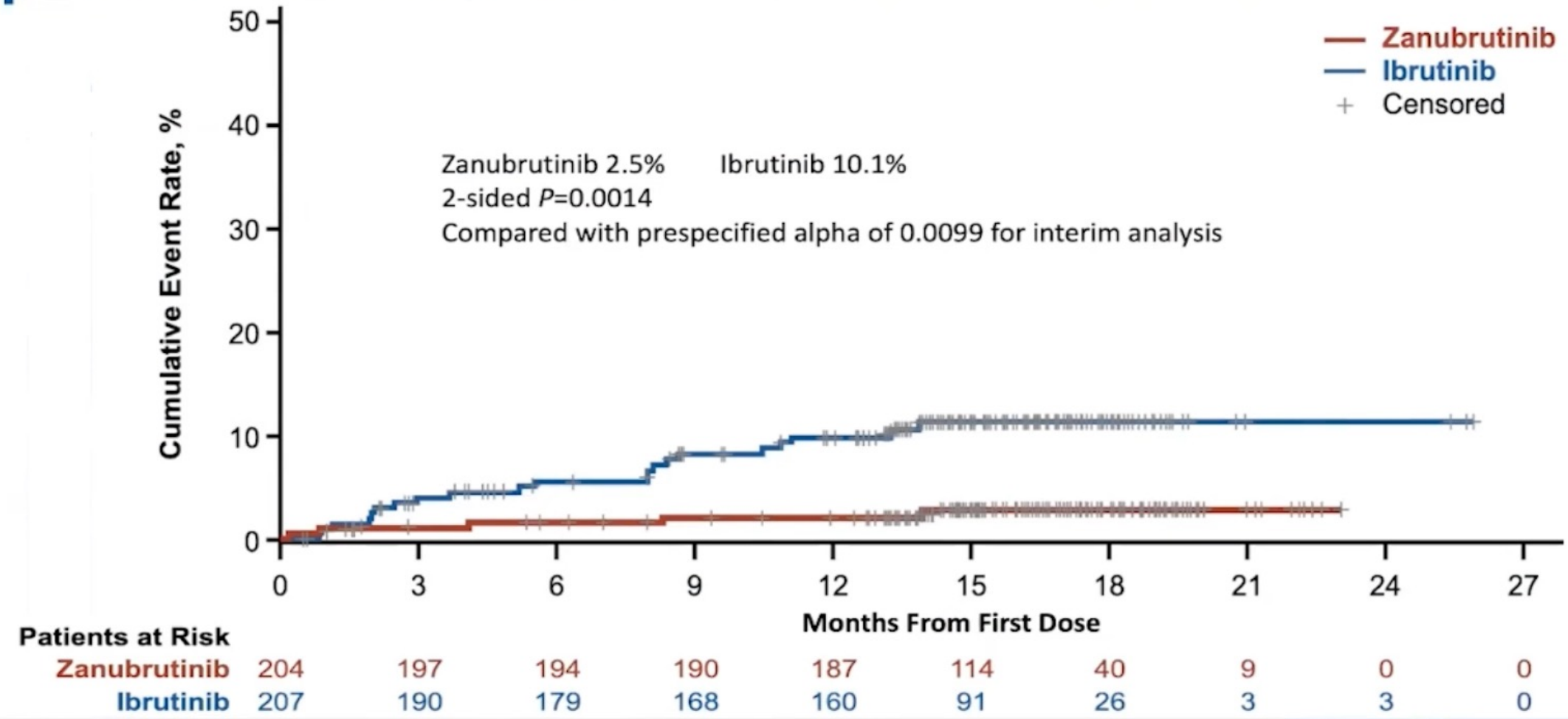
*Not a prespecified analysis; formal analysis of PFS will be based on all patients when the target number of events is reached.
Median PFS follow-up was 14.0 months for both zanubrutinib and ibrutinib arms by reverse KM method.
PFS, progression-free survival

ALPINE study. Hillmen et al. LB1900 EHA 2021. EHA2021 VIRTUAL

Courtesy of Prof John G Gribben, MD, DSc, FMedSci

ALPINE

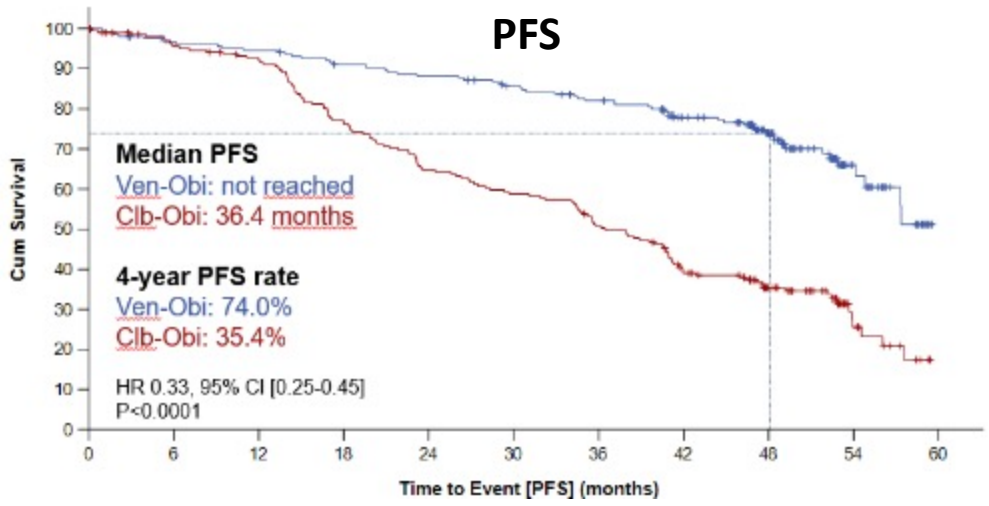
Atrial Fibrillation/Flutter



Courtesy of Prof John G Gribben, MD, DSc, FMedSci

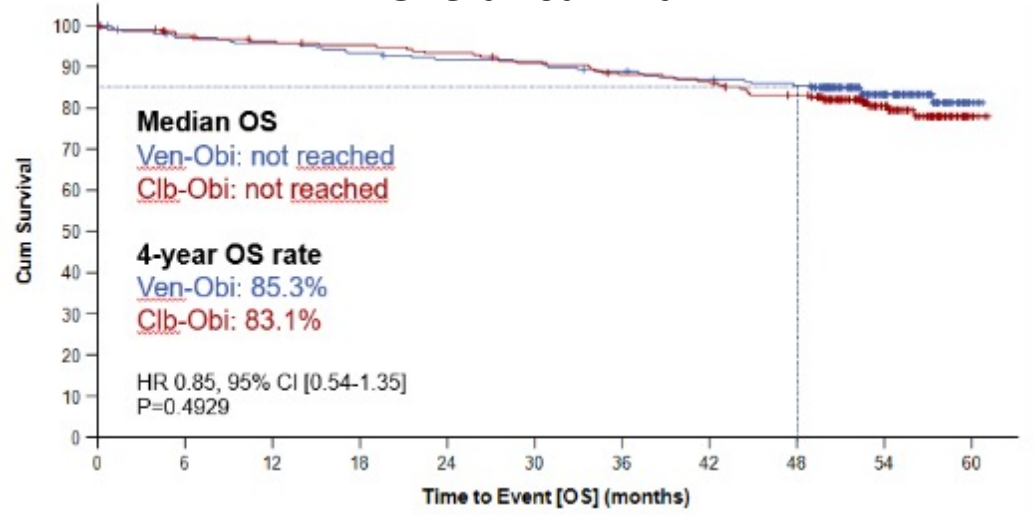
Venetoclax plus obinutuzumab (CLL14): 4-year progression-free survival and overall survival

PFS



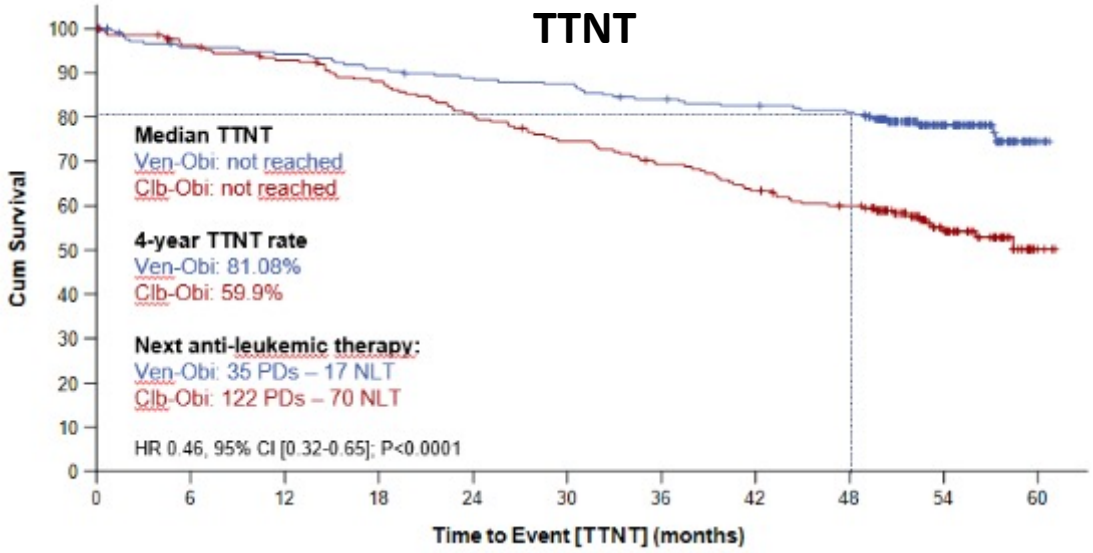
Median observation: 52.4 mos

Overall survival



Courtesy of Prof John G Gribben, MD, DSc, FMedSci

TTNT



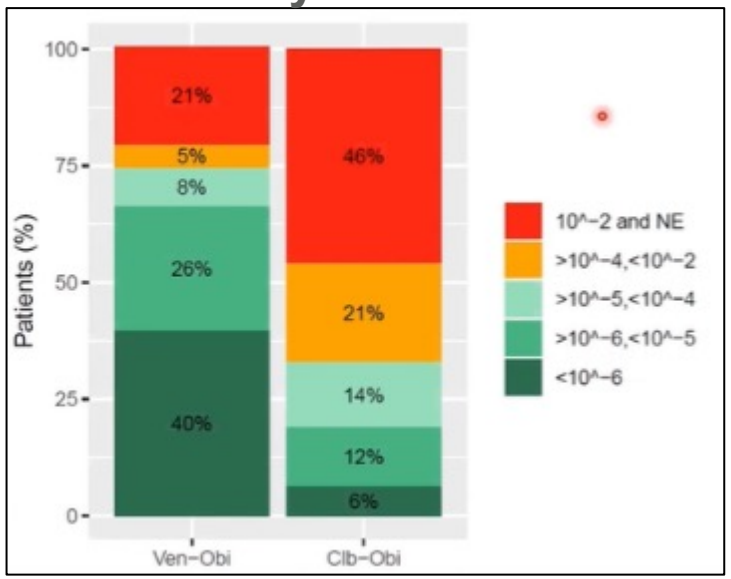
Author conclusions

- Individual clonal growth rates can be used to **estimate growth dynamics** after a fixed-duration treatment.
- **Clonal growth was lower after Ven-Obi** than after Clb-Obi, indicating more **effective MRD eradication** and **clonal growth modulation** with Ven-Obi.
- In a considerable subgroup (approx. 20%) of Ven-Obi treated patients, **no clonal growth** was measurable during observation, **indicating deepest remissions**.
- This **translates into a sustained PFS** benefit for several years after treatment completion, with a **4-year-PFS rate of 74% for Ven-Obi** treated patients.

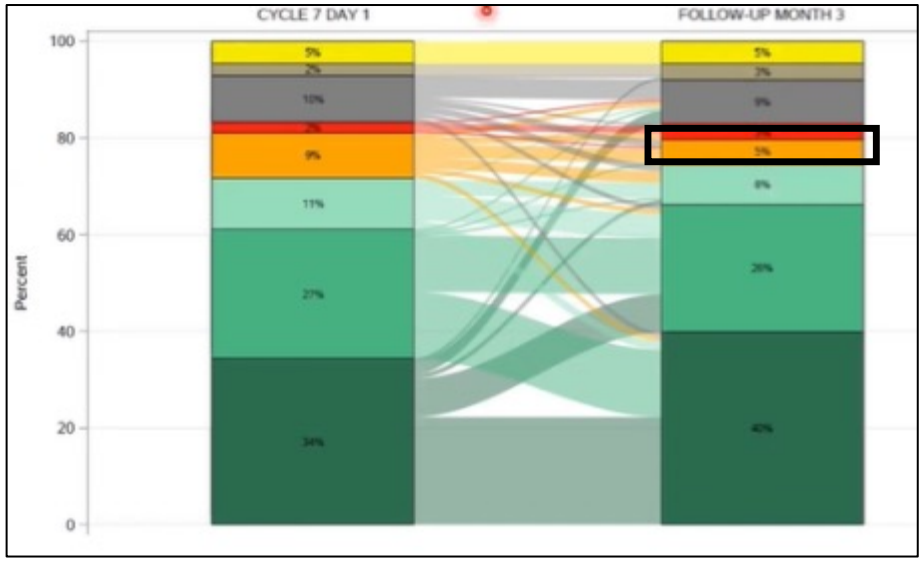
Al-Sawaf O, et al., Presented at ASH 2020. Abstract 127

CLL14: Clonal dynamics after venetoclax-obinutuzumab therapy

MRD by NGS at EOT

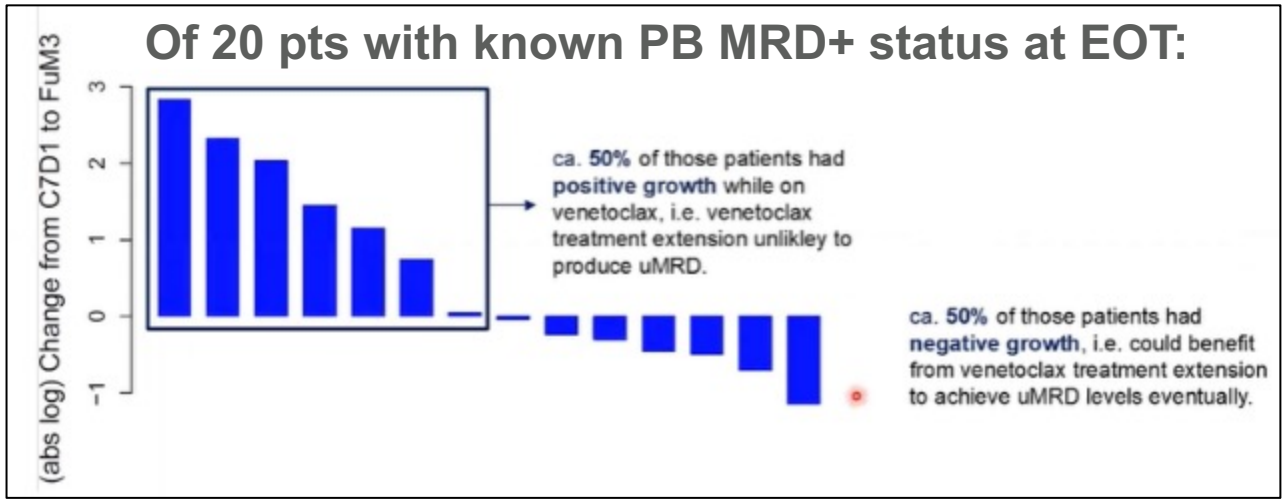


MRD During and After Ven-Obi



- About 1/3 of patients had a continued reduction in MRD from C7 onward
- Some patients have deep responses that deepen even further
- At EOT some were MRD+ (black box) – would more treatment help?

Of 20 pts with known PB MRD+ status at EOT:



Al-Sawaf O, et al., Presented at ASH 2020. Abstract 127

Courtesy of Prof John G Gribben, MD, DSc, FMedSci

Regulatory and reimbursement issues aside, what is your preferred initial regimen for a 60-year-old patient with del(17p) CLL who requires treatment?

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

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

 Dr Fowler	Ibrutinib	 Dr Flowers	Acalabrutinib
 Prof Gribben	Ibrutinib	 Dr Leonard	Acalabrutinib
 Dr Kahl	Acalabrutinib + obinutuzumab	 Dr Moskowitz	Venetoclax + obinutuzumab
 Dr Ansell	Ibrutinib + obinutuzumab	 Dr Sehn	Acalabrutinib
 Dr Flinn	Acalabrutinib	 Dr Sharman	Acalabrutinib + obinutuzumab

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What is your usual preferred initial regimen for a 75-year-old patient with del(17p) CLL who requires treatment?

 Dr Fowler	Acalabrutinib	 Dr Flowers	Acalabrutinib
 Prof Gribben	Ibrutinib	 Dr Leonard	Venetoclax + obinutuzumab
 Dr Kahl	Acalabrutinib	 Dr Moskowitz	Venetoclax + obinutuzumab
 Dr Ansell	Ibrutinib + obinutuzumab	 Dr Sehn	Acalabrutinib
 Dr Flinn	Acalabrutinib	 Dr Sharman	Acalabrutinib + obinutuzumab

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High-risk disease (eg, del[17p])

Dr Jeff Sharman

Dr Ian Flinn

Dr Christopher Flowers

Dr John Leonard

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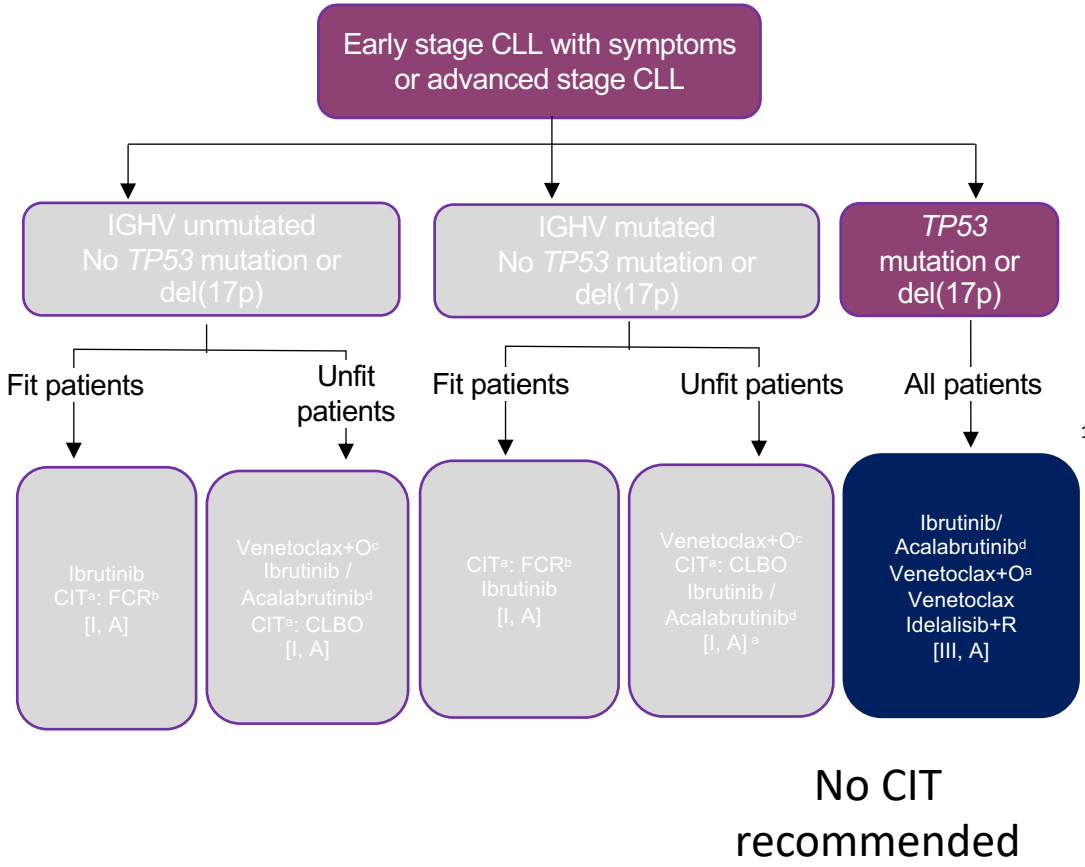
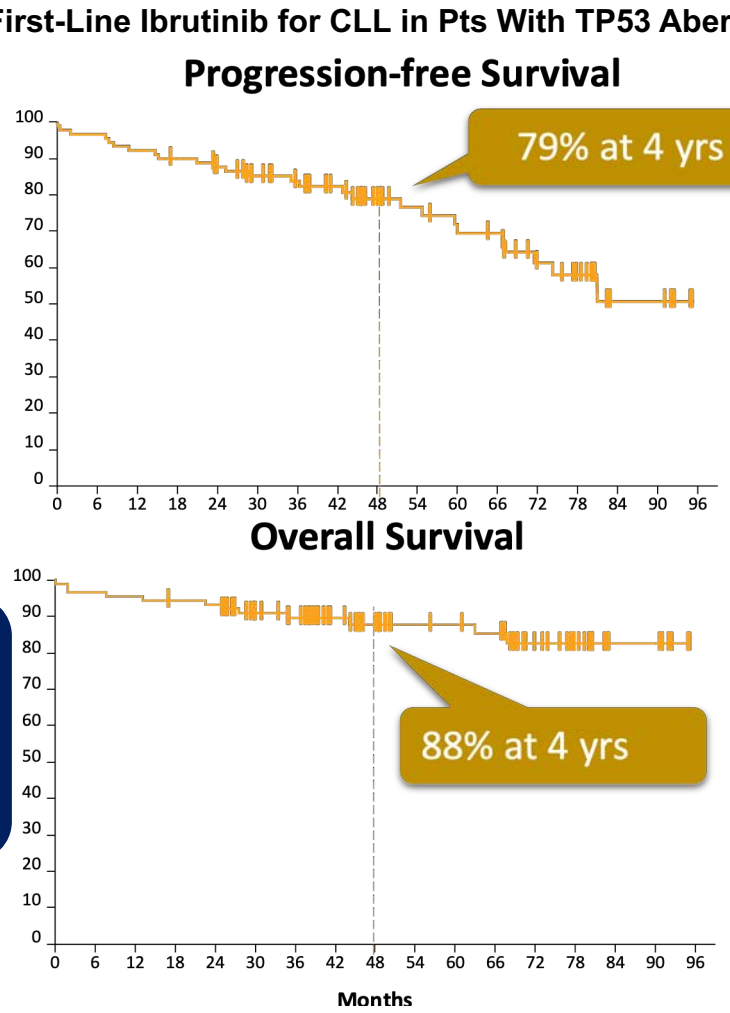
Chalk talk – Prof Gribben

What is the optimal first-line therapy for a patient with CLL and del(17p) or a TP53 mutation?

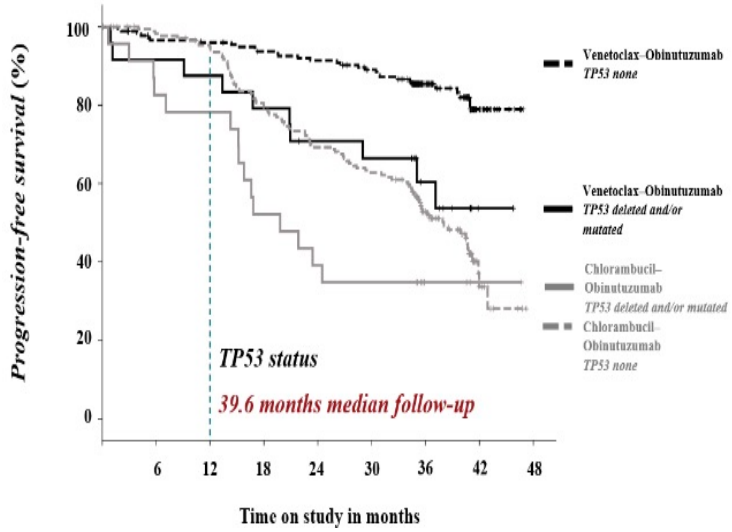
Ibrutinib



No CIT recommended



Venetoclax
Obinutuzumab



CIT: chemoimmunotherapy; Obin: obinutuzumab; CLBO: Chlorambucil plus Obinutuzumab; R: rituximab; [a] if approved and available;
[b]Chemoimmunotherapy as alternative treatment only if no TP53 dysfunction and reasons against continuous treatment with ibrutinib or non-availability;
[c] CLBO might be considered as well, but no data in fit patients are available.

Allan J, et al., ASH 2020. Abstract #2219

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. Acalabrutinib
3. Acalabrutinib + obinutuzumab
4. Venetoclax
5. Venetoclax + rituximab
6. Venetoclax + obinutuzumab
7. A PI3K inhibitor
8. Other

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 responded to ibrutinib and then experienced disease progression 3 years later?

 Dr Fowler	Acalabrutinib	 Dr Flowers	Venetoclax + rituximab
 Prof Gribben	Venetoclax + rituximab	 Dr Leonard	Venetoclax + obinutuzumab
 Dr Kahl	Venetoclax + rituximab	 Dr Moskowitz	Venetoclax + obinutuzumab
 Dr Ansell	Venetoclax + rituximab	 Dr Sehn	Venetoclax + rituximab
 Dr Flinn	Venetoclax + obinutuzumab	 Dr Sharman	Venetoclax + rituximab

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Choice of anti-CD20 antibody

Dr Jeff Sharman

Dr Ian Flinn

Dr Christopher Flowers

Dr John Leonard

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

1. Continue treatment
2. Discontinue treatment

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

 Dr Fowler	Discontinue treatment	 Dr Flowers	Continue treatment
 Prof Gribben	Discontinue treatment	 Dr Leonard	Discontinue treatment
 Dr Kahl	Discontinue treatment	 Dr Moskowitz	Continue treatment
 Dr Ansell	Continue treatment	 Dr Sehn	Discontinue treatment
 Dr Flinn	Discontinue treatment	 Dr Sharman	Discontinue treatment

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Off-protocol role, if any, of MRD testing

Dr Jeff Sharman

Dr Ian Flinn

Dr Christopher Flowers

Dr John Leonard

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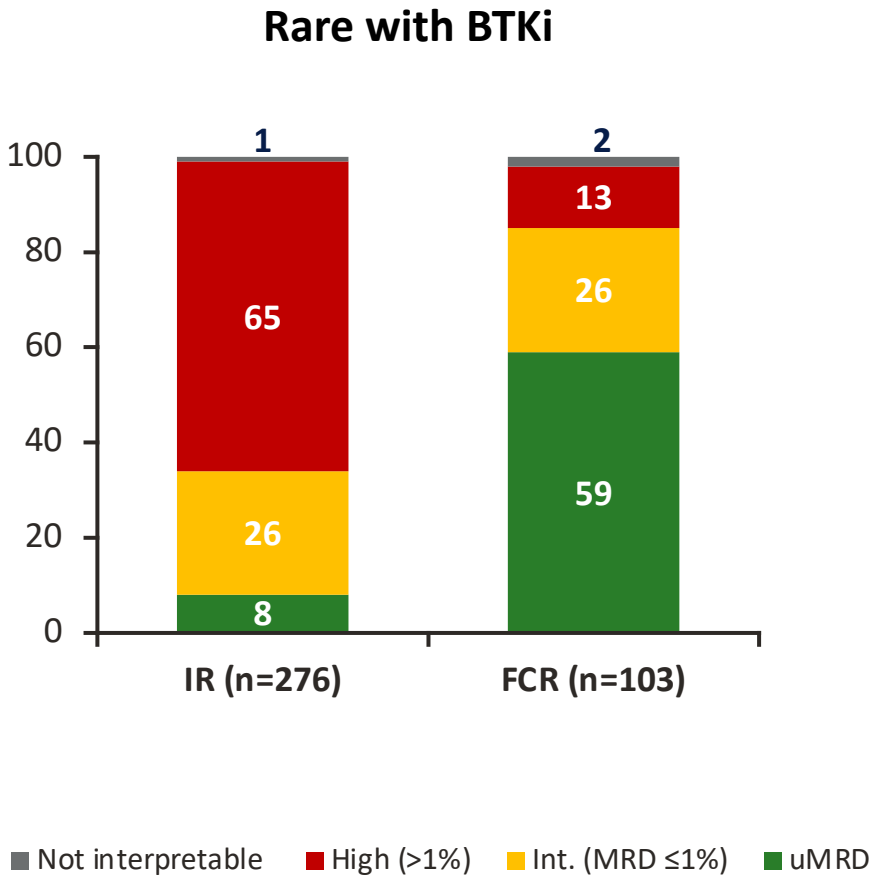
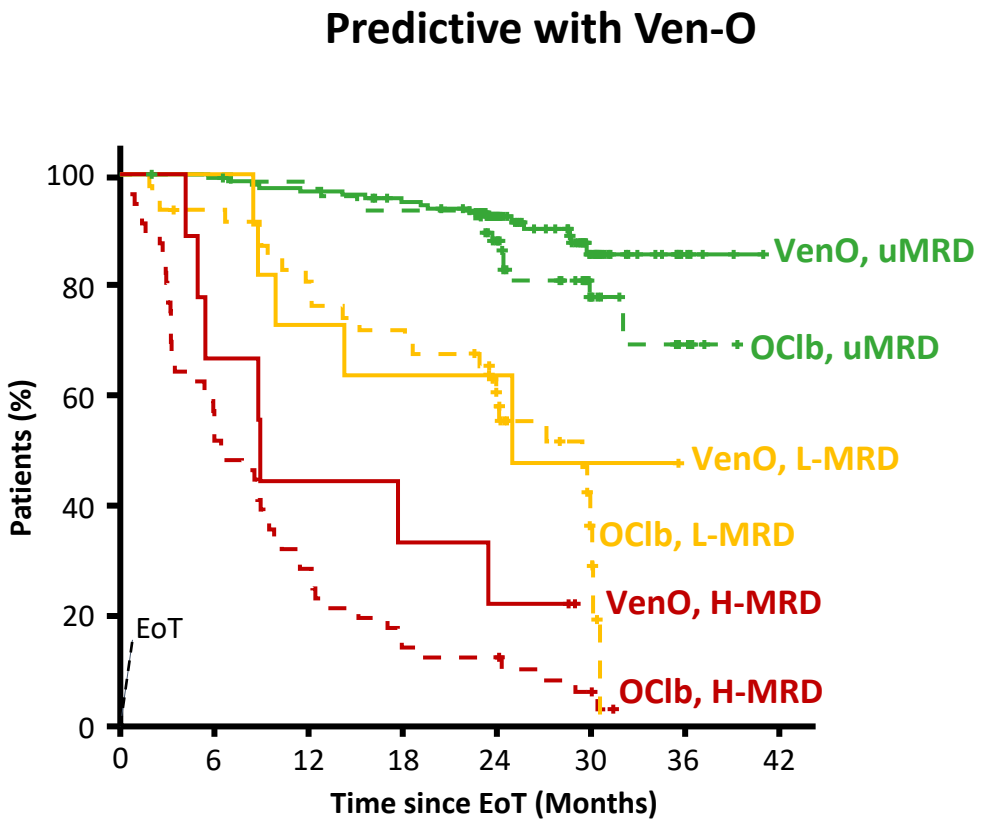
Chalk talk – Prof Gribben

Should you monitor MRD in CLL?

Not for Prime Time Yet!





But … we give 1 year fixed duration therapy and not yet any evidence that longer treatment matters

Have you or would you administer ibrutinib or acalabrutinib in combination with venetoclax to a patient with CLL outside of a clinical trial setting?

1. I haven’t and would not
2. I haven’t but would for the right patient
3. I have

Have you administered or would you administer ibrutinib or acalabrutinib in combination with venetoclax to a patient with CLL outside of a clinical trial setting?

 Dr Fowler	I haven't and would not	 Dr Flowers	I haven't but would for the right patient
 Prof Gribben	I haven't and would not	 Dr Leonard	I haven't and would not
 Dr Kahl	I haven't and would not	 Dr Moskowitz	I haven't and would not
 Dr Ansell	I haven't and would not	 Dr Sehn	I haven't and would not
 Dr Flinn	I have: Ven resistant and PI3Ki resistant	 Dr Sharman	I haven't and would not

RTP RESEARCH TO PRACTICE

Combining BTK inhibitors and venetoclax

Dr Jeff Sharman

Dr Ian Flinn

Dr Christopher Flowers

Dr John Leonard

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Chalk Talk – Dr Kahl

Do you believe there is a benefit to administering BTK inhibitors and venetoclax in combination as opposed to sequentially in patients with CLL? Are there any situations in which you would do so outside of a clinical trial today?

- The appeal comes if it facilitates time limited therapy
- More side effects encountered during dual therapy (personal experience in CLL and MCL)
- Theoretically possible dual therapy advantageous in scenarios of unfavorable biology (17p del, p53 mutated)
- No situation where I would do it outside a trial in CLL at present

Primary analysis of the Phase III GLOW Study: Fixed duration Ibrutinib and Venetoclax (I+V) versus Chlorambucil plus Obinutuzumab (Clb+O) for first-line CLL

- Patients aged ≥65 years or 18-64 years with cumulative illness rating scale (CIRS) score >6 or creatinine clearance <70 mL/min randomized to I+V or Clb+O
- All-oral, fixed duration I+V demonstrated superior PFS versus Clb+O as first-line treatment (HR 0.216, $p < 0.0001$)
- At 3 mo after end of treatment, rate of uMRD was significantly higher for I+V vs Clb+O in BM (51.9% vs 17.1%; $p < 0.0001$) and peripheral blood (PB; 54.7% vs 39.0%; $p = 0.0259$)

Kater A et al. EHA 2021;Abstract LB1902

Courtesy of Prof John G Gribben, MD, DSc, FMedSci

Primary analysis of the fixed duration cohort from the Phase II CAPTIVATE study of first-line ibrutinib + venetoclax for CLL

- First-line ibrutinib plus venetoclax, an all-oral, once-daily, chemotherapy-free fixed-duration regimen provides deep, durable responses in patients with CLL/SLL
- Benefit was observed regardless of genomic high-risk features.
- No new safety signals were identified

Allan J et al. EHA 2021;Abstract S147

Courtesy of Brad S Kahl, MD

If you could access one of the novel noncovalent BTK inhibitors (eg, pirtobrutinib) for your patients with relapsed CLL today, would you want to use it in clinical practice?

 Dr Fowler	Yes: In second line, ibrutinib failure	 Dr Flowers	Yes: Covalent BTK refractory
 Prof Gribben	No	 Dr Leonard	Yes: For BTKi-resistant patients
 Dr Kahl	Yes: Would prefer it over idelalisib	 Dr Moskowitz	Yes: Far better BTK inhibitor, will be drug of choice when approved
 Dr Ansell	No	 Dr Sehn	Yes: Covalent BTK refractory
 Dr Flinn	Yes: BTK failure c481 mutated	 Dr Sharman	Yes: Generally post covalent inhibitor with progression

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Future role of noncovalent BTKi (pirtobrutinib)

Dr Jeff Sharman

Dr Ian Flinn

Dr Christopher Flowers

Dr John Leonard

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Chalk Talk – Dr Kahl

If you could access one of the novel noncovalent BTK inhibitors, would you want to use it in clinical practice? For which type of patient would you be inclined to use these agents?

- Attractive when encountering resistance to 1st and 2nd generation BTKi
- Attractive when encountering intolerance to 1st and 2nd generation BTKi
- True for CLL and MCL and WM and MZL
- RCTs will determine whether 3rd generation will supplant 1st and 2nd generation

Pirtobrutinib (LOXO-305): Response

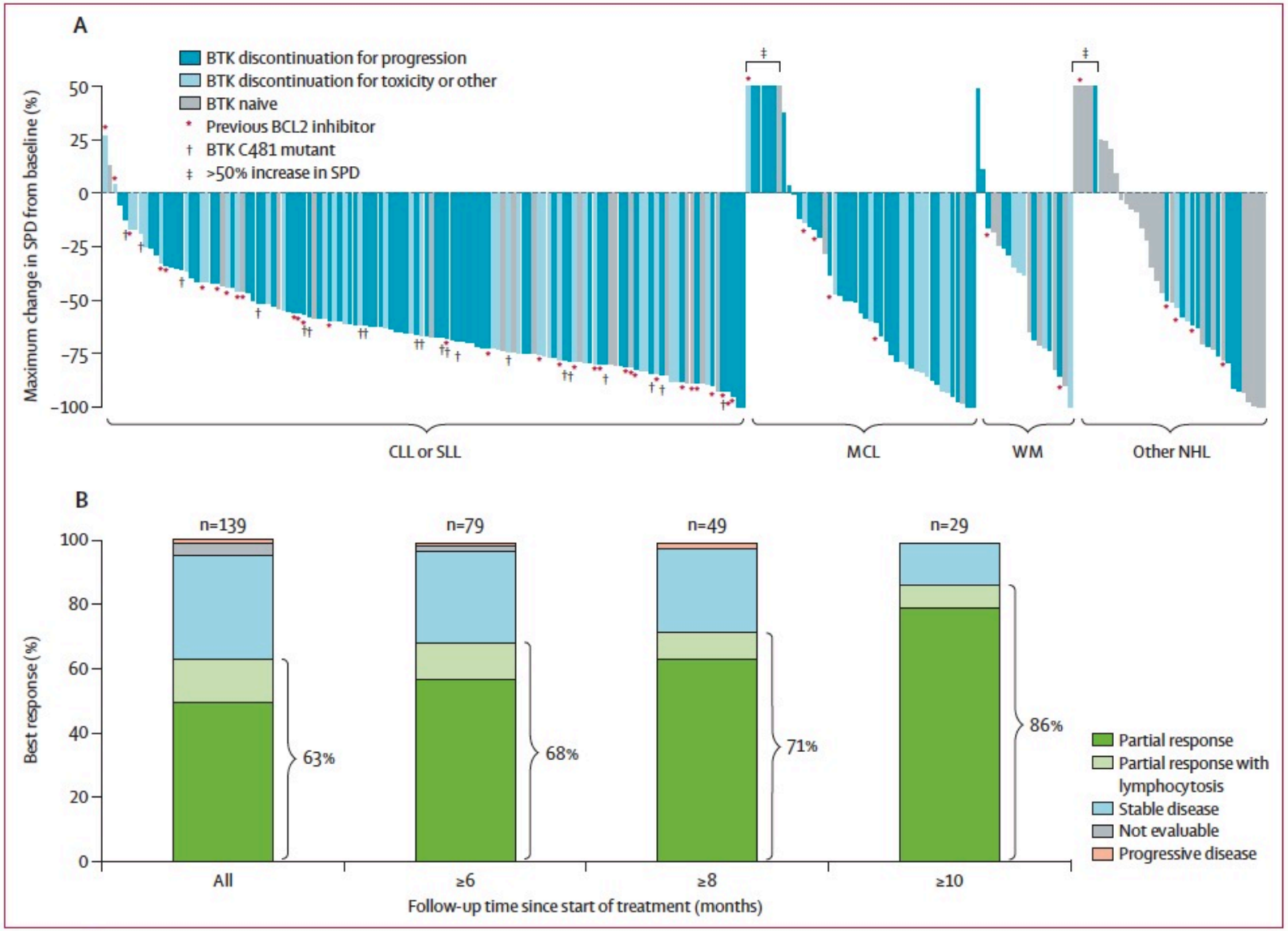

Figure 2: Efficacy

Courtesy of Brad S Kahl, MD

LOXO-305 Safety Profile

All doses and patients (n=323)							
	Treatment-emergent AEs, (≥10%), n (%)[a]					Treatment-related AEs, n (%)	
Adverse Event	Grade 1	Grade 2	Grade 3	Grade 4	Any Grade	Grades 3/4	Any Grade
Fatigue	40 (12%)	22 (7%)	3 (1%)	-	65 (20%)	2 (<1%)	27 (8%)
Diarrhea	45 (14%)	10 (3%)	-	-	55 (17%)	-	28 (9%)
Contusion	37 (12%)	5 (2%)	-	-	42 (13%)	-	29 (9%)
AEs of special interest[b,c]							
Bruising	48 (15%)	5 (2%)	-	-	53 (16%)	-	37 (12%)
Rash	30 (9%)	5 (2%)	-	-	35 (11%)	-	18 (6%)
Arthralgia	13 (4%)	3 (1%)	-	-	16 (5%)	-	5 (2%)
Hemorrhage	10 (3%)	4 (1%)	1 (<1%)[d]	-	15 (5%)	-	5 (2%)
Hypertension	2 (<1%)	9 (3%)	4 (1%)	-	15 (5%)	-	4 (1%)
Atrial fibrillation/flutter	-	2 (<1%)[e]	-	-	2 (<1%)	-	-

No DLTs reported and MTD not reached
5 of 323 patients (1.5%) discontinued due to treatment-related AEs
200mg QD selected as recommended Phase 2 dose

Courtesy of Brad S Kahl, MD

Which third-line therapy would you generally recommend for a 75-year-old patient with IGHV-unmutated CLL without del(17p) or TP53 mutation who responded to ibrutinib for 3 years, experienced disease relapse, then received venetoclax for 18 months followed by disease progression?

 Dr Fowler	Obinutuzumab	 Dr Flowers	Umbralisib
 Prof Gribben	Idelalisib	 Dr Leonard	Idelalisib
 Dr Kahl	Idelalisib	 Dr Moskowitz	Idelalisib
 Dr Ansell	Duvelisib	 Dr Sehn	Duvelisib
 Dr Flinn	Duvelisib	 Dr Sharman	Idelalisib + rituximab

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Double-refractory CLL (BTKi, venetoclax)

Dr Jeff Sharman

Dr Ian Flinn

Dr Christopher Flowers

Dr John Leonard

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Agenda

MODULE 1: Chronic Lymphocytic Leukemia

- Choice of front-line therapy
- Selection of a BTK inhibitor
- Second-line therapy
- Third-line therapy
- Ongoing research: Combination strategies, noncovalent BTK inhibitors, CAR T-cell therapy

MODULE 2: Follicular Lymphoma

- Selection of first- and second-line treatment
- Third-line therapy: Tazemetostat, PI3K inhibitors, CAR T-cell therapy

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

 Dr Fowler	Rituximab/ lenalidomide	 Dr Flowers	BR
 Prof Gribben	BR	 Dr Leonard	BR
 Dr Kahl	BR	 Dr Moskowitz	BR
 Dr Ansell	BR	 Dr Sehn	BR
 Dr Flinn	BR	 Dr Sharman	BR

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First-line therapy for FL

Dr Jeff Sharman

Dr Ian Flinn

Dr Christopher Flowers

Dr John Leonard

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Chalk talk – Dr Fowler

Do you believe community-based oncologists/hematologists should be presenting the R^2 regimen of lenalidomide/rituximab as a front-line option to patients with newly diagnosed FL?

- Patients with bulky/symptomatic low-grade lymphoma should be treated with combination regimens.
- RELEVANCE study compared R-Chemo to R^2 in untreated FL.
- Overall response rate and progression-free survival was excellent (and similar) in both arms.
- Lenalidomide combination has more rash, chemotherapy had more neutropenia and severe infections.
- No increased risk of secondary cancers was seen in either arm.
- Treatment should be individualized for each patient.

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 6 cycles of BR but then experiences disease relapse 4 years later?

1. Re-treatment with BR
2. Obinutuzumab/bendamustine
3. R-CHOP
4. Rituximab/lenalidomide
5. A PI3K inhibitor
6. Tazemetostat
7. 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 6 cycles of BR but then experiences disease relapse 4 years later?

 Dr Fowler	Rituximab/ lenalidomide	 Dr Flowers	Rituximab/ lenalidomide
 Prof Gribben	Chemotherapy → autologous transplant	 Dr Leonard	Rituximab/ lenalidomide
 Dr Kahl	Rituximab/ lenalidomide	 Dr Moskowitz	Rituximab/ lenalidomide
 Dr Ansell	Rituximab/ lenalidomide	 Dr Sehn	Rituximab/ lenalidomide
 Dr Flinn	Rituximab/ lenalidomide	 Dr Sharman	Rituximab/ lenalidomide

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What is your usual third-line treatment for a patient with FL with an EZH2 mutation who received first-line BR, second-line lenalidomide/rituximab and then develops disease progression?

1. Idelalisib
2. Copanlisib
3. Duvelisib
4. Umbralisib
5. Tazemetostat
6. R-CHOP
7. Obinutuzumab +/- chemotherapy
8. Other

What is your usual third-line treatment for a patient with FL with an EZH2 mutation who receives first-line BR, second-line lenalidomide/rituximab and then develops disease progression?

 Dr Fowler	Tazemetostat	 Dr Flowers	Tazemetostat
 Prof Gribben	Tazemetostat	 Dr Leonard	Tazemetostat
 Dr Kahl	Tazemetostat	 Dr Moskowitz	Tazemetostat
 Dr Ansell	Tazemetostat	 Dr Sehn	Tazemetostat
 Dr Flinn	Tazemetostat	 Dr Sharman	Tazemetostat or consider CAR-T therapy

RTP RESEARCH TO PRACTICE

If you were going to administer a PI3 kinase inhibitor to a patient with relapsed/refractory FL, which do you generally prefer?

1. Idelalisib
2. Copanlisib
3. Duvelisib
4. Umbralisib

What is your usual third-line treatment for a patient with FL (EZH2 wild type) who receives first-line BR, second-line lenalidomide/rituximab and then develops disease progression?

 Dr Fowler	Tazemetostat	 Dr Flowers	Tazemetostat
 Prof Gribben	Rituximab/ lenalidomide	 Dr Leonard	Idelalisib
 Dr Kahl	Tazemetostat	 Dr Moskowitz	Umbralisib
 Dr Ansell	Tazemetostat	 Dr Sehn	Obinutuzumab +/- chemotherapy
 Dr Flinn	Rituximab/ lenalidomide or umbralisib	 Dr Sharman	Umbralisib or consider CAR-T therapy

RTP RESEARCH TO PRACTICE

Third-line therapy for FL

Dr Jeff Sharman

Dr Ian Flinn

Dr Christopher Flowers

Dr John Leonard

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Chalk talk – Dr Fowler

What is the optimal therapeutic approach for a patient with FL with and without an EZH2 mutation who has experienced disease progression on bendamustine/rituximab and then R^2?

- Several effective options exist for patients with relapsed FL.
  - Single agent anti-CD20 agents
  - EZH2 inhibitors (also effective in EZH2 wild type disease)
  - CAR-T
  - Auto SCT
  - PI3K
  - Clinical trials (anti-CD19, BiTE, anti-CD47, anti-Syk, BTKi)
- <u>Always</u> repeat a biopsy to confirm the dx and exclude transformed disease.
- The selection of next-line therapy should be informed by patient's prior disease course and length of prior remissions.
  - Helps understand patient's short- and long-term risk from FL.
  - There is no "right answer."

Chalk talk – Dr Fowler

Do you believe that there are discernible differences in terms of efficacy or tolerability that make one of the four FDA-approved PI3K inhibitors for relapsed/refractory FL a better therapeutic option?

- Currently approved PI3K inhibitors are associated with remarkable and similar efficacy.
  - PFS ranging from 10-11 mo.
  - ORR of around 50%.
- Different isoforms and drug structures have resulted in very different toxicity profiles.
  - ↑↓ colitis, infection, hyperglycemia, hypertension and rash.
- Patients should be counseled on the potential risks as well as *how to manage* side effects.
  - Especially infection risk and GI side effects.
- Dose interruption and/or reduction is effective and often allows for re-starting the drug.
- Choice of drug should be individualized.
- Ongoing studies looking at different schedules to reduce toxicity look promising.

Approved PI3K inhibitors in R/R Follicular Lymphoma

	Idelalisib	Copanlisib	Duvelisib	Umbralisib
FDA approval	Jul 29, 2014	Sep 14, 2017	Sep 24, 2018	Feb 5, 2021
Isoforms	PI3K delta	Pan-PI3K	PI3K delta/gamma	PI3K-delta and CK1-epsilon
Formulation	150 mg **PO** BID	60 mg **IV** Q weekly 3 wks on, 1 wk off	25 mg **PO** BID	800 mg **PO** QD
Indication in FL	Relapsed after at least two prior systemic therapies	Relapsed after at least two prior systemic therapies	Relapsed after at least two prior systemic therapies	Relapsed after at least three prior systemic therapies
Pivotal trial	Study 101-09	CHRONOS-1	NCT02204982	UTX-TGR-205
Results	iNHL, n=125 **ORR 57%, CR 6%**	FL, n=104 **ORR 59%, CR 14%**	FL, n=83 **ORR 42%, 1 CR**	FL, n = 117 **ORR 43%, CR 3%**
	mDOR 12.5 mo	**mDOR 12.2 mo**	**43% maintained responses for ≥6mo, 17% maintained responses for ≥12mo**	**mDOR 11.1 mo**
Side effects	**Pneumonitis, transaminitis, colitis**	**Hyperglycemia, hypertension**, infections, neutropenia	**Infection, diarrhea or colitis, pneumonia**	**Infection, neutropenia, diarrhea or noninfectious colitis**

S deVos Sep 2019 (Gopal A, et al. NEJM 2014; 370:1008-18)

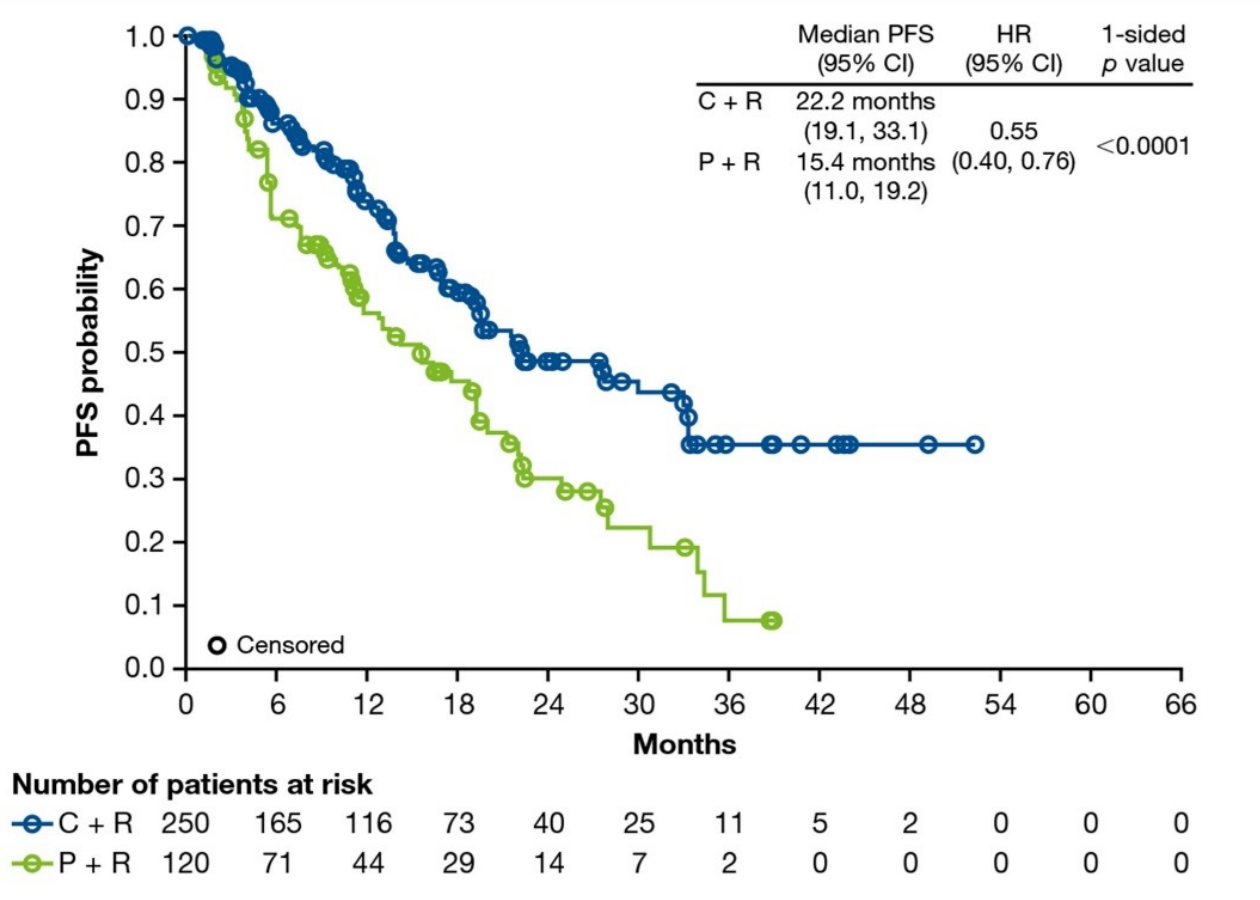
(https://www.fda.gov/Drugs/Information)

CHRONOS-3 Trial: Copanlisib plus rituximab vs Rituximab plus placebo for Patients with R/R iNHL

	Copanlisib + rituximab (*n*=250)	Placebo + rituximab (*n*=120)	Total (*N*=370)
Male, *n* (%)	115 (46.0)	62 (51.7)	177 (47.8)
Median age, years (range)	62 (28-91)	60 (34-82)	62 (28-91)
ECOG performance status, *n* (%) 0 1 2	 156 (62.4) 85 (34.0) 9 (3.6)	 84 (70.0) 36 (30.0) 0	 240 (64.9) 121 (32.7) 9 (2.4)
Medical history of diabetes, *n* (%)	37 (14.8)	16 (13.3)	53 (14.3)
Medical history of hypertension, *n* (%)	95 (38.0)	41 (34.2)	136 (36.8)
Histology of lymphoma, *n* (%) FL Grade 1 Grade 2 Grade 3a MZL Extranodal Nodal Splenic	 184 (73.6) 56 (22.4) 88 (35.2) 40 (16.0) 66 (26.4) 24 (9.6) 25 (10.0) 17 (6.8)	 91 (75.8) 31 (25.8) 40 (33.3) 20 (16.7) 29 (24.2) 11 (9.2) 12 (10.0) 6 (5.0)	 275 (74.3) 87 (23.5) 128 (34.6) 60 (16.2) 95 (25.7) 35 (9.5) 37 (10.0) 23 (6.2)
Median time since last systemic therapy, months (range)	25.2 (1.0-192.5)	25.4 (1.2-161.2)	25.3 (1.0-192.5)
Median time since initial diagnosis, months (range)	68.1 (10.3-349.2)	72.6 (13.3-245.7)	68.9 (10.3-349.2)
Progression- and treatment-free for ⩾12 months since last rituximab-containing regimen, *n* (%)	194 (77.6)	94 (78.3)	288 (77.8)
Unwilling or unfit to receive chemotherapy, *n* (%)	56 (22.4)	26 (21.7)	82 (22.2)
Previous lines of anti-cancer therapy, *n* (%) 1 2 ⩾3	 118 (47.2) 65 (26.0) 67 (26.8)	 56 (46.7) 33 (27.5) 31 (25.8)	 174 (47.0) 98 (26.5) 98 (26.5)

Matasar M, et al ASCO 2021

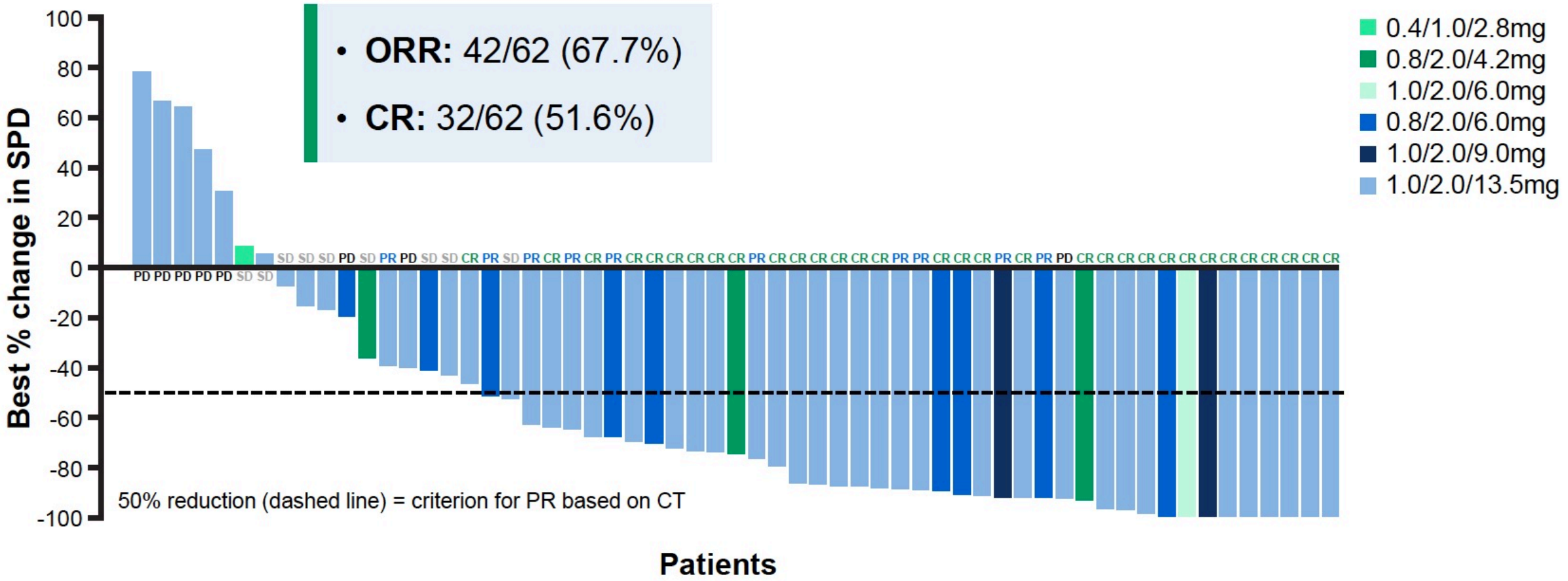
CHRONOS-3 Trial: Copanlisib plus rituximab vs Rituximab plus placebo



n (%) [95% CI]	Copanlisib + rituximab (*n*=250)	Placebo + rituximab (*n*=120)
Best response		
Complete response	94 (37.6)	22 (18.3)
Partial response	112 (44.8)	39 (32.5)
Stable disease	24 (9.6)[a]	42 (35.0)
Progressive disease	6 (2.4)	9 (7.5)
Not evaluable/not available	14 (5.6)	8 (6.7)
Objective response rate	206 (82.4) [77.1, 86.9]	61 (50.8) [41.6, 60.1]

Matasar M, et al ASCO 2021

Mosunetuzumab antitumor activity in patients with R/R FL across dose levels

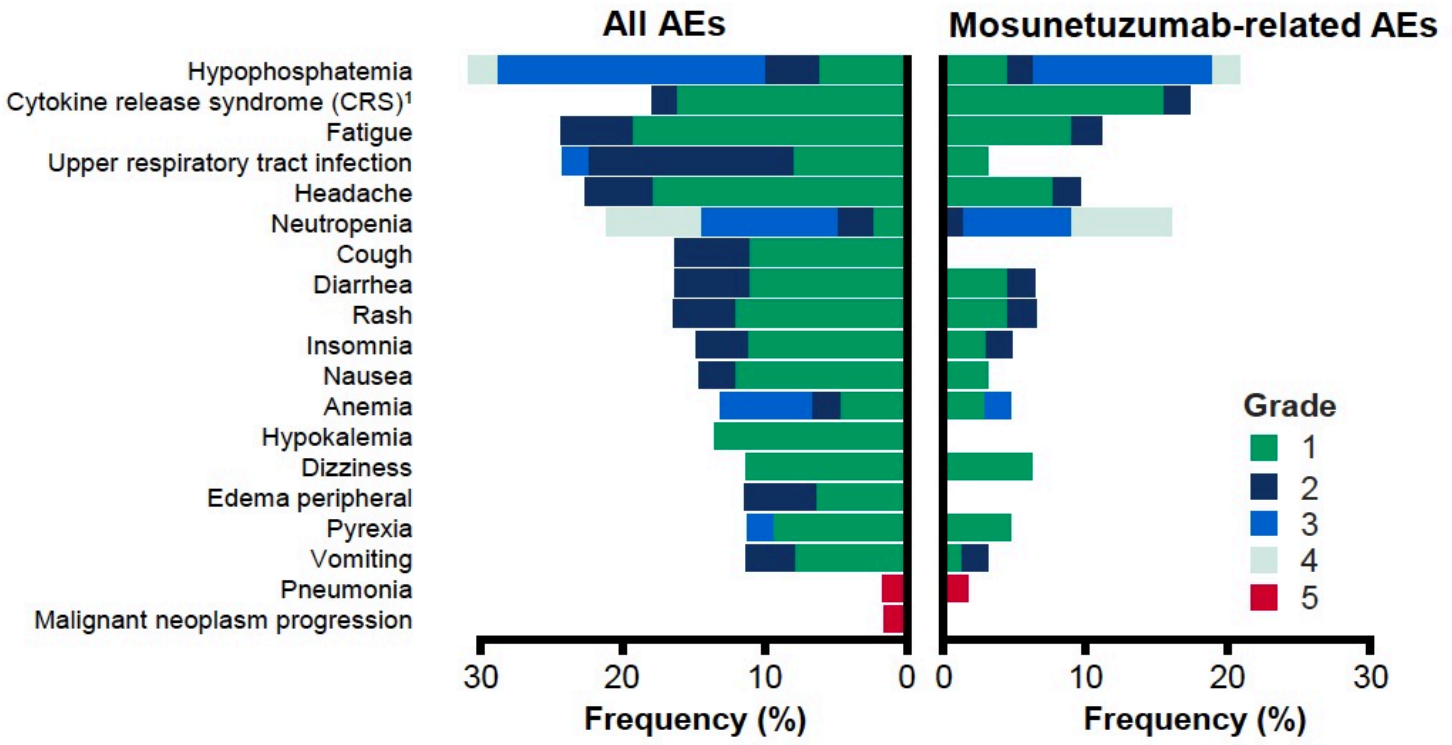


Courtesy of Brad S Kahl, MD

Mosunetuzumab: Adverse events

Summary of AEs*, n (%)	Safety evaluable patients (N=62)
Any AE	60 (96.8)
Treatment related	45 (72.6)
Serious AE	22 (35.5)
Treatment related	9 (14.5)
Grade ≥3 AE	42 (67.7)
Treatment related	22 (35.5)
Grade 5 AE (excluding disease progression)	1* (1.6)
AE leading to treatment discontinuation	5** (8.1)
Treatment related	4 (6.5)

Grade 1–4 AEs with an incidence of ≥10% or an NCI-CTCAE Grade of 5



*Grade 5 AE: pneumonia (n=1; onset Day 73)
**AEs leading to treatment discontinuation: pneumonia, atrial flutter (unrelated to treatment), neutropenia, arthritis, alanine aminotransferase increased (n=1 each)

1. Lee DW, et al. Biol Blood Marrow Transplant 2019;25(4):625–38.

Courtesy of Brad S Kahl, MD

Glofitamab step-up dosing: Complete response rates in updated efficacy data in heavily pretreated relapsed/refractory (R/R) non-Hodgkin lymphoma (NHL) patients

- High and durable response rates were observed in patients with aggressive (n=28) and indolent R/R NHL (n=24) who had failed multiple lines of therapy and who were treated with the bispecific antibody glofitamab
- CRS, the most common adverse event, was mostly manageable

Carlo-Stella C et al ASCO 2021 Abstract 7519

Courtesy of Brad S Kahl, MD

Subcutaneous epcoritamab in patients with relapsed/refractory B-cell non-Hodgkin lymphoma: Safety profile and antitumor activity

- Phase I/II Study: patients with R/R CD20+ B-NHL (FL n=12, DLBCL n=46, MCL n=4, others n=6) were treated with subcutanoues epcoritamab, a bispecific CD20xCD3 antibody

- Epcoritamab demonstrated substantial single-agent activity, inducing deep and durable clinically meaningful responses, with a consistent safety profile.

Clausen MR et al ASCO 2021 Abstract 7518

Courtesy of Brad S Kahl, MD

Consensus or Controversy Consulting Investigators

Dr Jeff Sharman

Dr Ian Flinn

Dr Christopher Flowers

Dr John Leonard

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Consensus or Controversy? Multiple Myeloma

Wednesday, June 30, 2021
5:00 PM – 6:00 PM ET

Faculty

Natalie S Callander, MD
Shaji K Kumar, MD
Sagar Lonial, MD

Moderator

Neil Love, MD

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