Data + Perspectives: Clinical Investigators Discuss the Current and Future Management of Chronic Lymphocytic Leukemia

A Virtual CME Satellite Symposium Series in Conjunction with the Society of Hematologic Oncology 2021 Annual Meeting

Monday, August 30, 2021
5:00 PM – 6:00 PM ET

Faculty

Jeff Sharman, MD
Mitchell R Smith, MD, PhD
Philip A Thompson, MB, BS

Moderator

Neil Love, MD

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Faculty

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

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Division of Cancer Medicine
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Clinical Professor of Medicine
George Washington University
Washington, DC

Moderator
Neil Love, MD
Research To Practice
Miami, Florida

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Commercial Support

This activity is supported by educational grants from AbbVie Inc, BeiGene Ltd and Bristol-Myers Squibb Company.

Dr Love — Disclosures

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Dr Sharman — Disclosures

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Dr Smith — Disclosures

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Dr Thompson — Disclosures

Advisory Committee	Adaptive Biotechnologies Corporation, Janssen Biotech Inc
Consulting Agreement	Janssen Biotech Inc
Contracted Research	AbbVie Inc, Adaptive Biotechnologies Corporation, Amgen Inc, Genentech, a member of the Roche Group, Pharmacyclics LLC, an AbbVie Company
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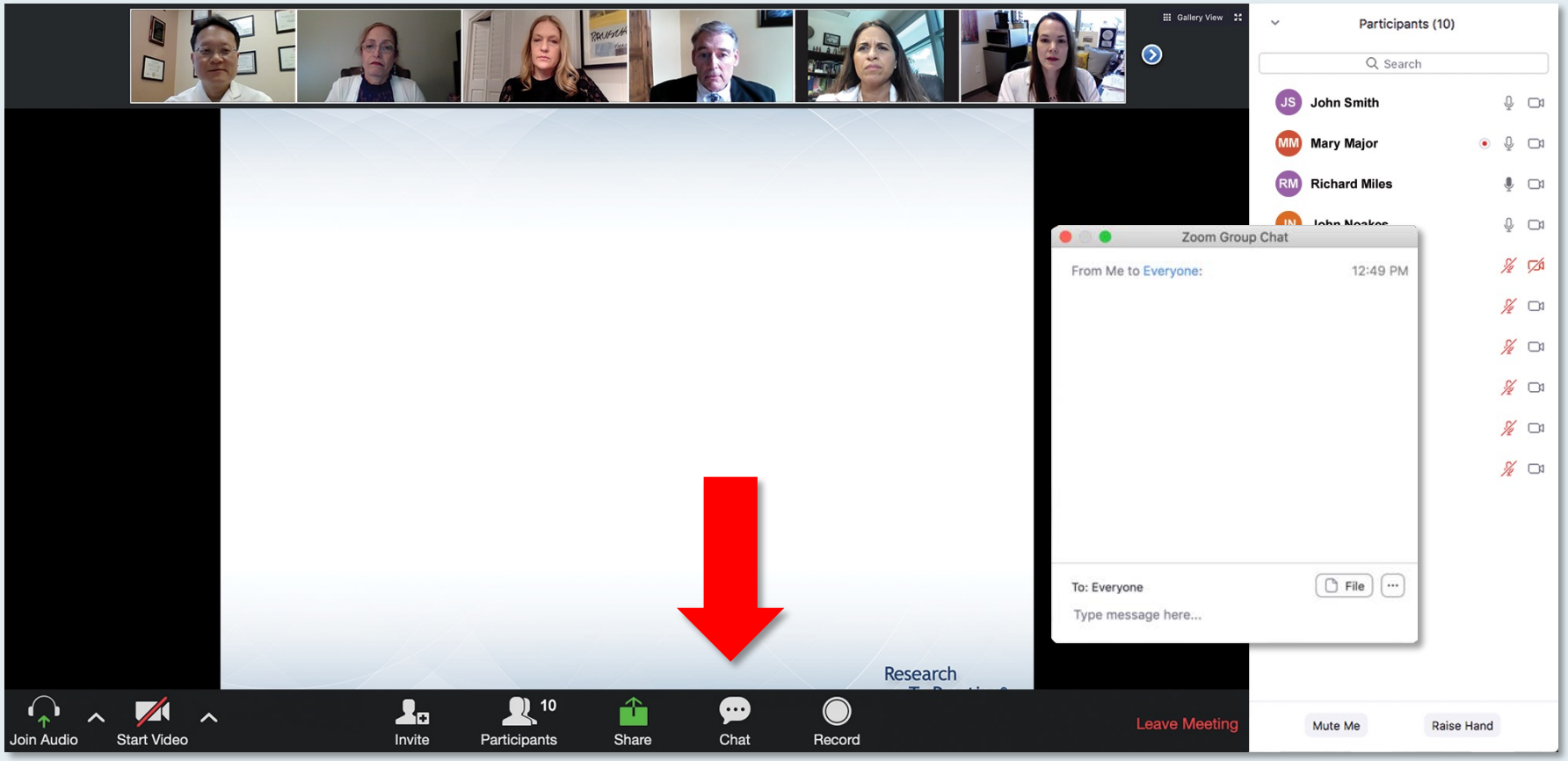
We Encourage Clinicians in Practice to Submit Questions



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

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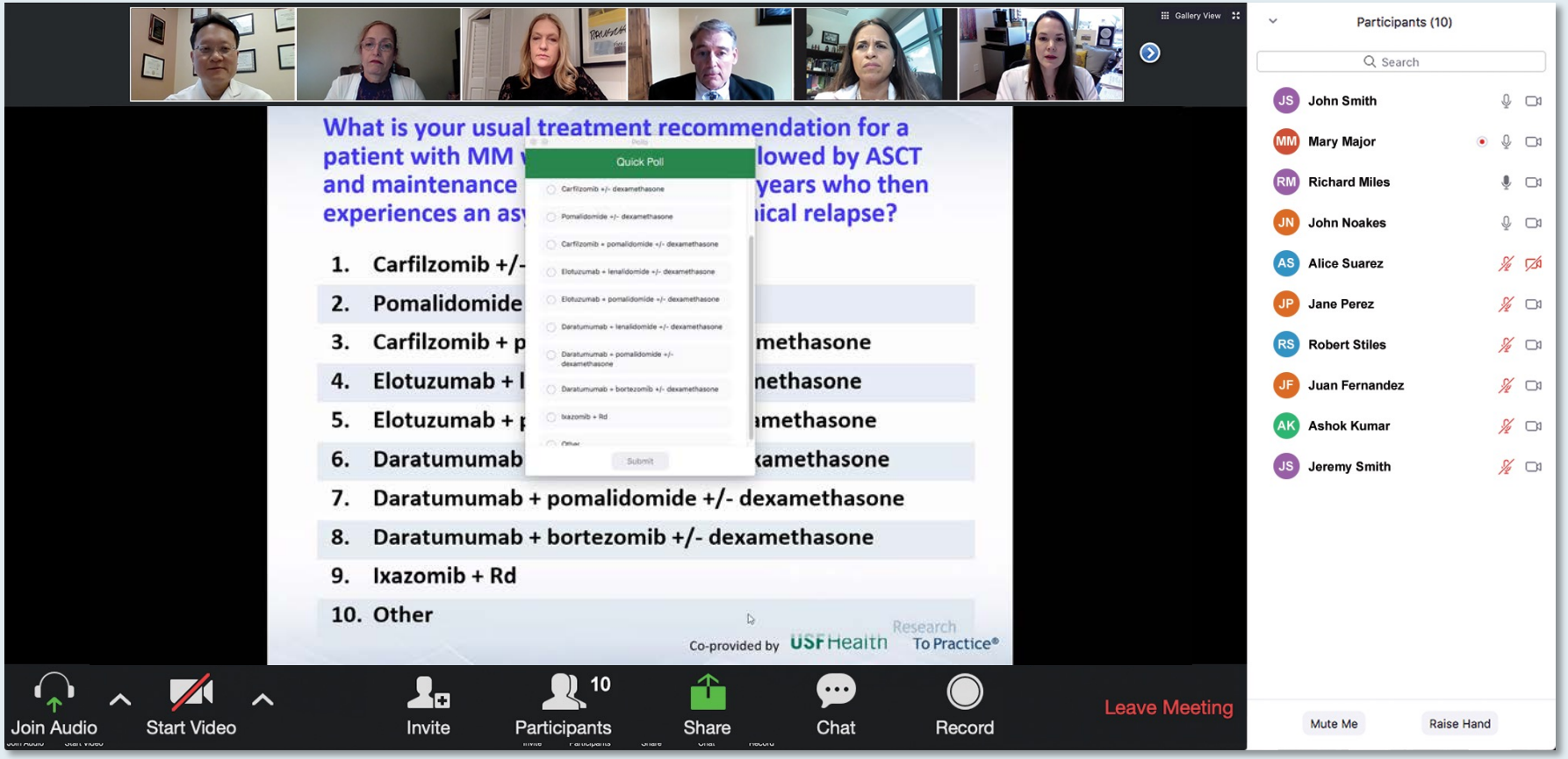

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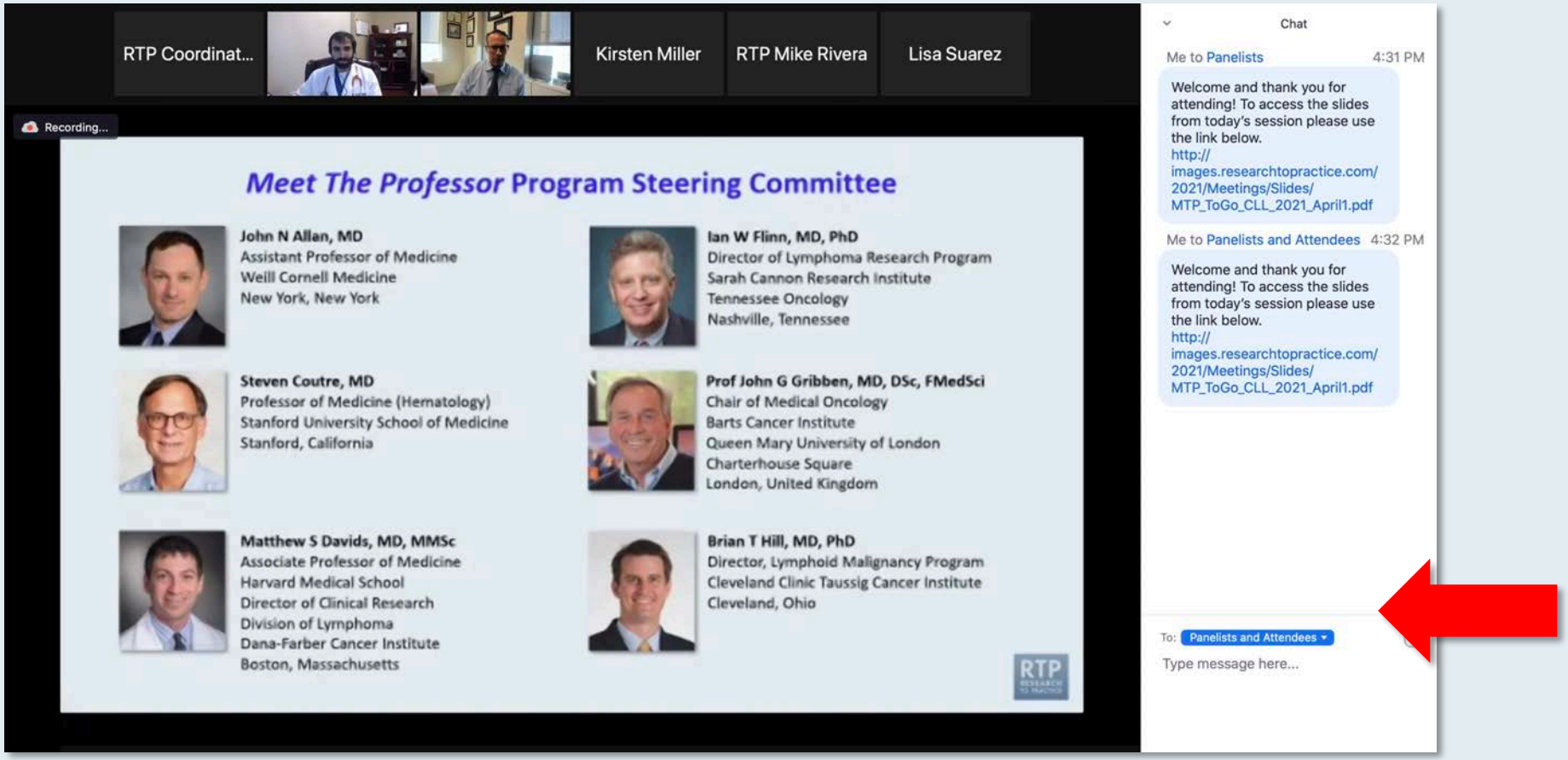

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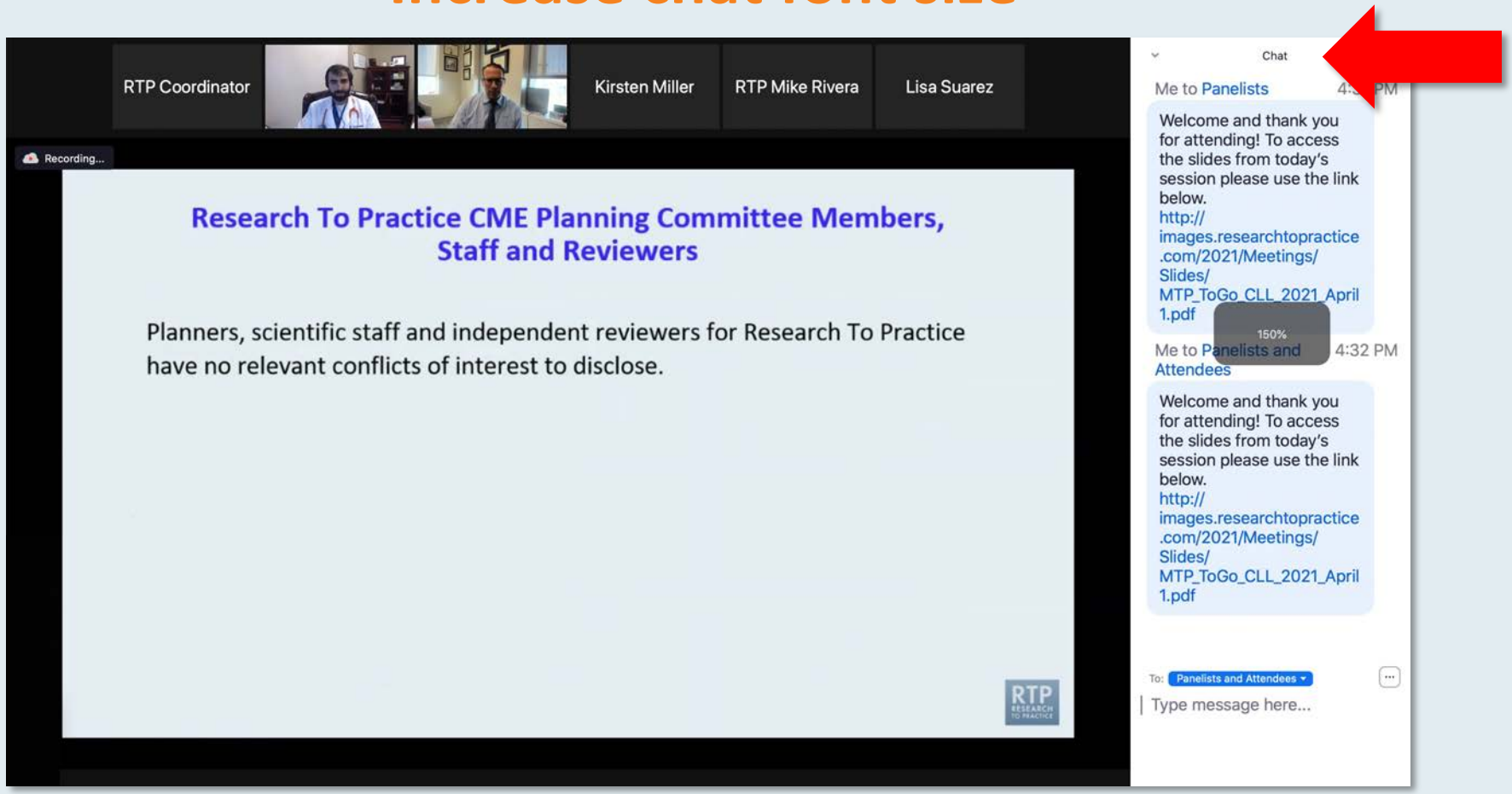

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WITH DR NEIL LOVE

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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Data + Perspectives: Clinical Investigators Discuss the Current and Future Management of Non-Hodgkin Lymphoma

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Tuesday, August 31, 2021
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Faculty

Andrew M Evens, DO, MSc
Ian W Flinn, MD, PhD
Gilles Salles, MD, PhD

Moderator

Neil Love, MD

RTP RESEARCH TO PRACTICE

Meet The Professor

Immunotherapy and Novel Agents in Gynecologic Cancers

Wednesday, September 1, 2021
5:00 PM – 6:00 PM ET

Faculty

Joyce F Liu, MD, MPH

Moderator

Neil Love, MD

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RESEARCH TO PRACTICE

Data + Perspectives: Clinical Investigators Discuss the Current and Future Management of Acute Myeloid Leukemia and Myelodysplastic Syndromes

A Virtual CME Satellite Symposium During the Society of Hematologic Oncology 2021 Annual Meeting

Wednesday, September 8, 2021
7:30 PM – 9:00 PM Central Time

Faculty

Courtney D DiNardo, MD, MSCE
Daniel A Pollyea, MD, MS
David Sallman, MD
Eunice S Wang, MD

Moderator

Neil Love, MD

RTP RESEARCH TO PRACTICE

Exploring Key Issues Affecting the Care of Patients with Metastatic Colorectal Cancer with BRAF Mutations

A CME/MOC-Accredited Virtual Event

Thursday, September 9, 2021
5:00 PM – 6:00 PM ET

Faculty
Scott Kopetz, MD, PhD

Consulting Clinical Investigator
Wells A Messersmith, MD

Moderator
Neil Love, MD

RTP RESEARCH TO PRACTICE

Expert Second Opinion: Investigators Discuss Available Clinical Research in the Care of Patients with Early-Stage Non-Small Cell Lung Cancer

A Live Webinar Held as a Satellite CME/MOC Symposium During the IASLC 2021 World Conference on Lung Cancer Worldwide Virtual Event

Sunday, September 12, 2021
9:15 PM – 10:15 PM MDT / 11:15 PM – 12:15 AM ET

Faculty

Edward B Garon, MD, MS
Harvey I Pass, MD
Heather Wakelee, MD

Moderator

Neil Love, MD

RTP RESEARCH TO PRACTICE

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Optimizing the Clinical Management of Hodgkin and Non-Hodgkin Lymphomas

Thursday, September 16, 2021
5:00 PM – 6:00 PM ET

Faculty

Loretta Nastoupil, MD

Moderator

Neil Love, MD

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Thank you for joining us!

CME credit information will be emailed to each participant shortly.

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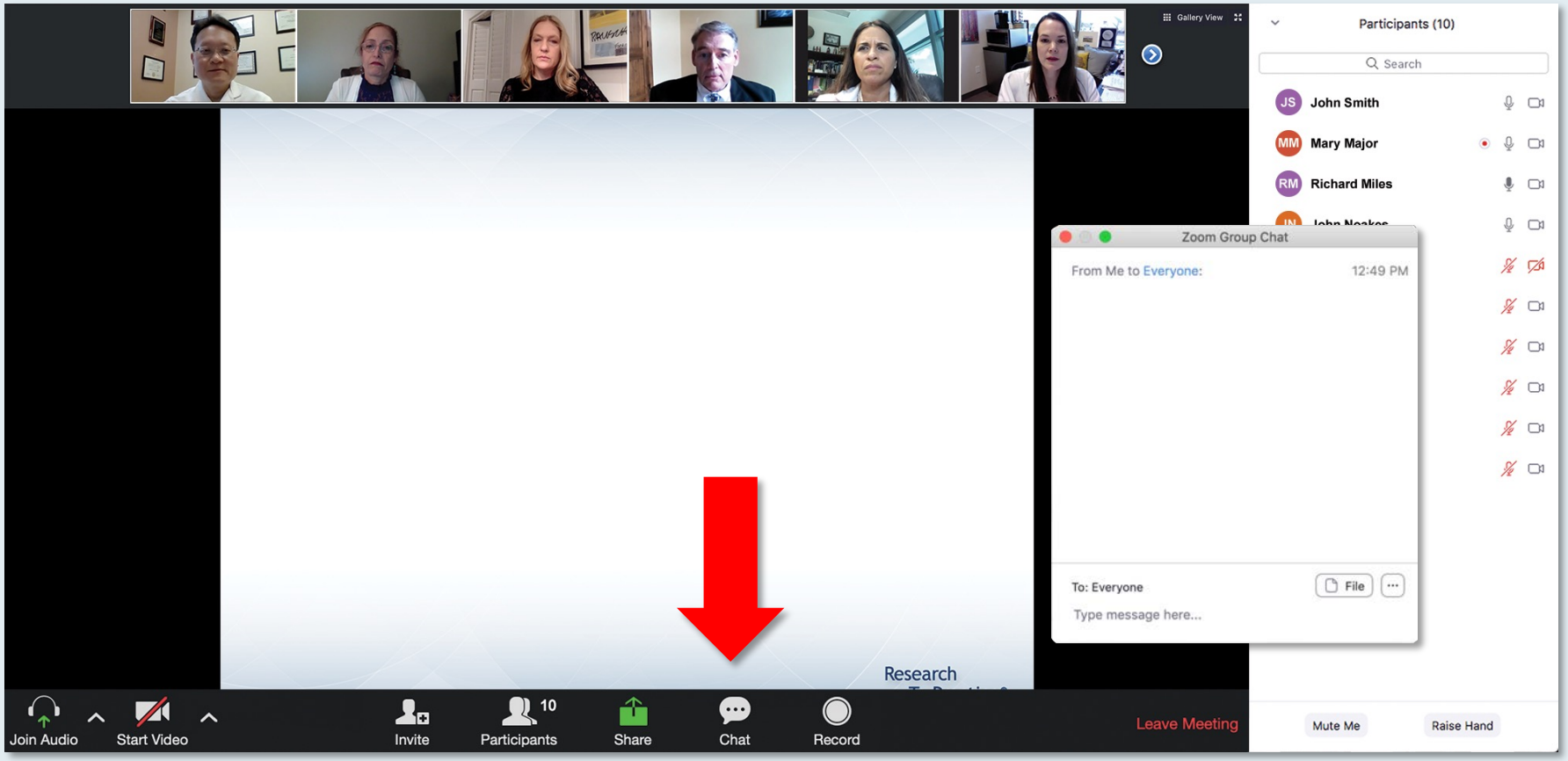

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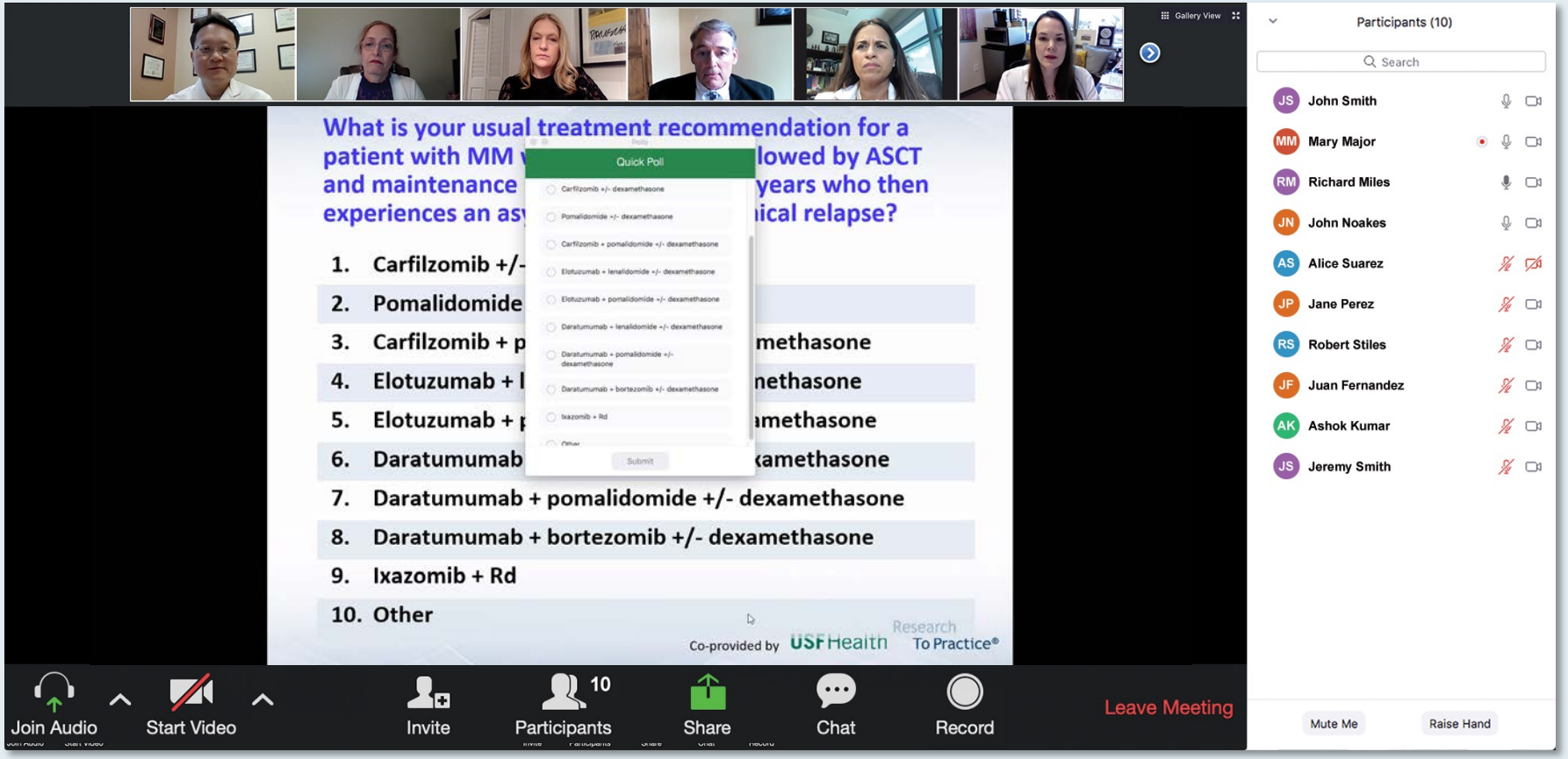

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Agenda

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- How do you think through first-line therapy for a patient with CLL who is younger and fit?
- How do you think through first-line therapy for a patient with CLL who is older and frail?
- How do you think through first-line therapy for a patient with high-risk CLL (eg, deletion 17p)?
- What is the most effective strategy to mitigate the risk of tumor lysis syndrome with venetoclax and/or obinutuzumab?
- How do you choose among the available BTK inhibitors for the treatment of CLL?
- What is the role of MRD assessment in the management of CLL?
- How do you approach COVID-19 prevention for patients with CLL?

Module 2: Future Treatment of CLL

- What is the future role of BTK inhibitors combined with venetoclax in the management of CLL?
- What is the future role of pirtobrutinib (LOXO 305) in the management of CLL?
- What is the current and future role of CAR T-cell therapy?

Beyond the Guidelines Survey Respondents

Jeremy Abramson, MD
John N Allan, MD
Bruce Cheson, MD
Steven Coutre, MD
Alexey V Danilov, MD, PhD
Matthew S Davids, MD, MMSc
Andrew M Evens, DO, MSc
Christopher R Flowers, MD, MS
Nathan H Fowler, MD
Jonathan W Friedberg, MD, MMSc
Brian T Hill, MD, PhD
Nitin Jain, MD
Brad S Kahl, MD
Ann S LaCasce, MD, MMSc
Anthony R Mato, MD, MSCE
Susan O'Brien, MD
John M Pagel, MD, PhD
Kerry Rogers, MD
Laurie H Sehn, MD, MPH
Jeff Sharman, MD
Mitchell R Smith, MD, PhD
Sonali M Smith, MD
Philip A Thompson, MB, BS
Julie M Vose, MD, MBA
William G Wierda, MD, PhD

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- What is the current and future role of CAR T-cell therapy?

How do you think through first-line therapy for a patient with CLL who is younger and fit? (Do you continue to use the "pre-novel therapy era" criteria when initiating treatment for CLL?)

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

1. FCR
2. Ibrutinib +/- CD20 antibody
3. Acalabrutinib +/- CD20 antibody
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7. Other

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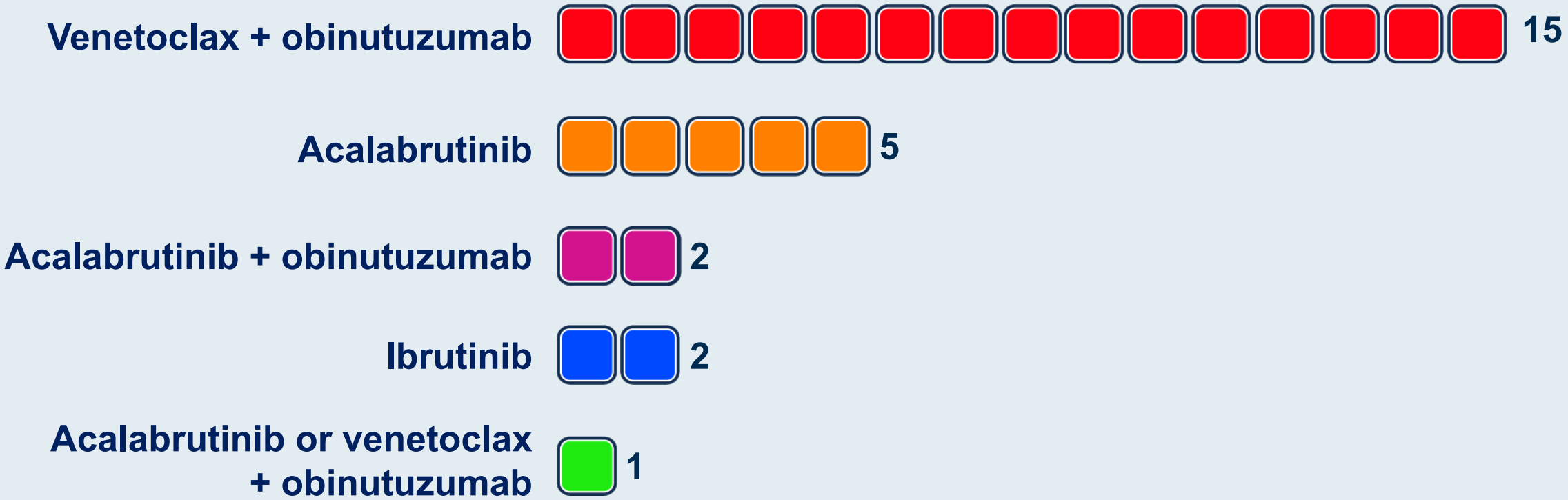

Survey of 25 US-based clinical investigators

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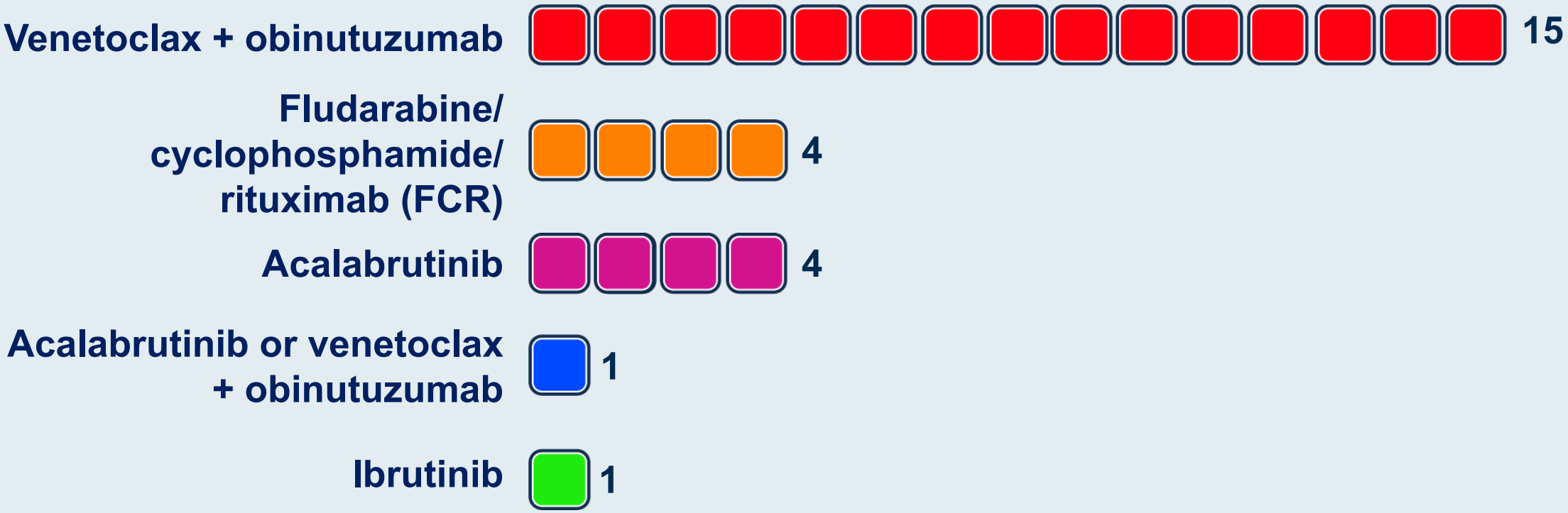

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Case Presentation: Dr Smith – 64-year-old man with IGHV-unmutated CLL

- 64-year-old man, evaluated for increasing fatigue, found to have on exam bilateral neck and axillary adenopathy 2-3 cm, palpable spleen tip.
- Labs showed WBC 32.9, 90% small lymphocytes. Hgb 11.5, platelets 175. Chemistry panel normal, LDH normal. Immunoglobulins normal. Thyroid function normal.
- Flow cytometry consistent with CLL.
- FISH trisomy 12, no del17p.
- IGHV unmutated.
- Two months later, worsening fatigue though still working (senior partner in a law firm), so ECOG PS 1, nodes on exam significantly increased in number and size, bilateral neck/supraclavicular.
- WBC 40.2, ALC 36, Hgb 11.3 platelets 179.
- CT with multiple bilateral 3-4 cm cervical and supraclavicular, 5 cm axillary nodes, 2-3 cm retroperitoneal nodes.
- Discussed whether to start treatment and, if so, options.
- Elected venetoclax-obinutuzumab per CLL14 regimen.
- Has had good response, minimal toxicity.
- Managed the initial 8 weeks in terms of TLS risk and tried to minimize visits to the clinic.

Case Presentation: Dr Thompson – 36-year-old man with IGHV-unmutated CLL

- 36M, diagnosed in 2011, aged 27. Asymptomatic, WBC 52.
- Came to MDA for discussion of treatment options in early 2020 just at the dawn of the COVID-19 pandemic.
- WBC 366.9, Hgb 10.4, Plt 129.
- Asymptomatic. Keen outdoorsman. Minimal lymphadenopathy, but spleen palpable 8-10cm below costal margin in mid-clavicular line.
- Unmutated *IGHV* (VH3-21, 0%). Negative FISH, no mutations on NGS panel.

Case Presentation: Dr Thompson – 36-year-old man with IGHV-unmutated CLL (continued)

- Chemotherapy not considered due to unmutated *IGHV.*
- Discussed:
  1. Time-limited venetoclax + obinutuzumab.
  2. Ibrutinib +/- rituximab or obinutuzumab.
  3. Acalabrutinib +/- obinutuzumab.
- Patient desired a “low-touch” therapy with minimal immunosuppression due to COVID-19 pandemic.
- Proceeded with acalabrutinib monotherapy.
- Currently doing very well, with mild residual lymphocytosis, normalization of hemoglobin and platelet count, resolution of splenomegaly.
- Advised to avoid double black diamond runs when snowboarding (!)

Case Presentation: Dr Sharman – 67-year-old woman with IGHV-mutated, trisomy 12, TP53 wild-type CLL

Unusual presentation of symptomatic CLL treated with obinutuzumab/venetoclax:

- 67-year-old woman followed for several years with asymptomatic CLL.
- IGHV mutated, trisomy 12, TP53 wt.
- Stable blood counts with WBC 50K, Hgb 12, Plt 240k.
- Interestingly, developed myositis with elevated CPK and proximal weakness.
- Difficulty rising from chair or lifting arms above head. Seen by neurology – unclear relationship to CLL.
- Elected to treat in case there was relationship – symptoms improved with treatment.

How do you think through first-line therapy for a patient with CLL who is older and frail?

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

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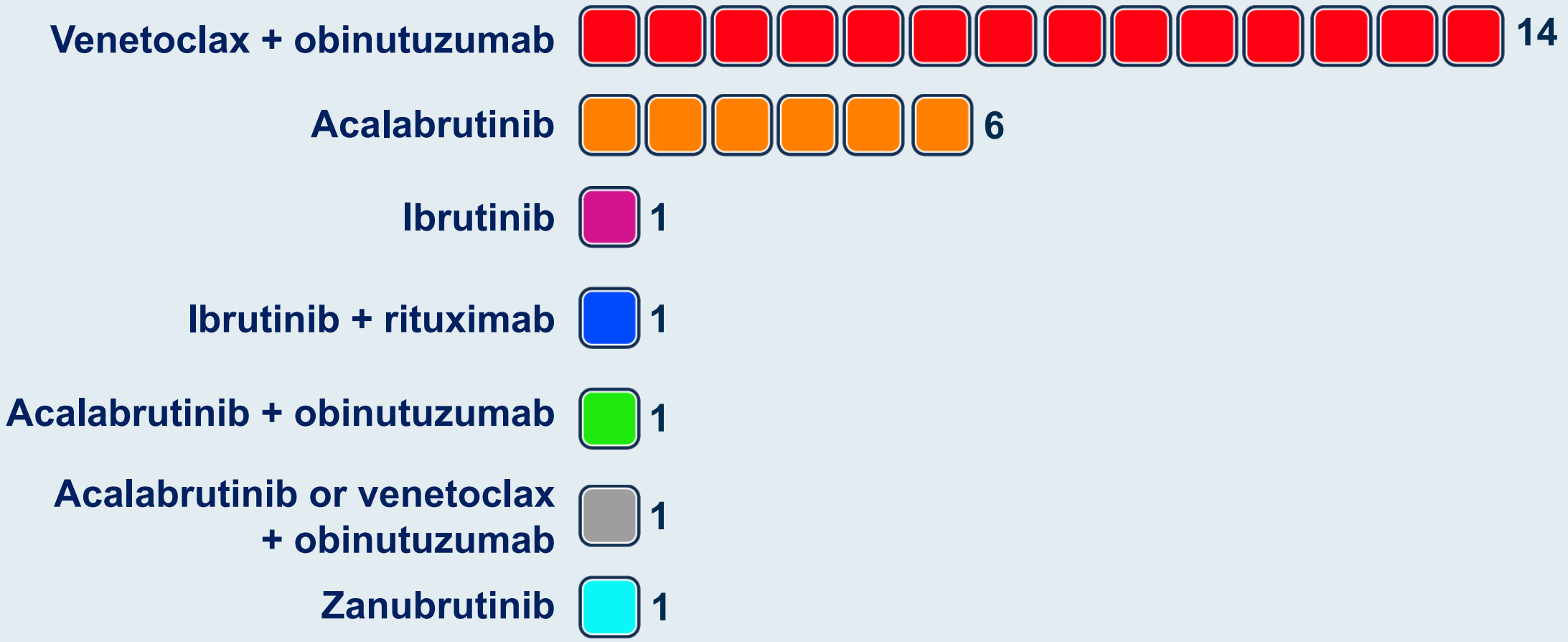

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7. Other

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?

Survey of 25 US-based clinical investigators

Case Presentation: Dr Thompson – 70-year-old man with IGHV-unmutated CLL

- 70M
- Diagnosed CLL 1998. Unmutated *IGHV*, del(13q).
- FCR x6 2005. Achieved CR.
- Asymptomatic relapse 8/2012. Observed until 3/2015. Started ibrutinib on a clinical trial (aged 64), in combination with rituximab.
- Rapid clinical response with resolution of lymphadenopathy and normalization of hematologic parameters.
- 5/2015, developed paroxysmal AF, with rapid ventricular rate, but no other symptoms. Continued to have episodes with ventricular rate in the 130—140s. Treated with escalating doses of metoprolol succinate (up to 150mg/d), then stopped ibrutinib 6/2015 due to persistent AF with uncontrolled ventricular rate.
- Structurally normal heart on echo. No significant symptoms other than palpitations. Normal TFTs, electrolytes.
- CHA2-DS2-Vasc score of 1 (hypertension) – no anticoagulation.

Case Presentation: Dr Thompson – 70-year-old man with IGHV-unmutated CLL (continued)

- 7/2015. After >1 month with no recurrence, resumed at 140mg/d. Continued metoprolol succinate 150mg/d.
- Continued to have PAF, ~1/month, mostly at night. No symptoms other than palpitations. Rate well controlled (80-90).
- 12/2015. Escalated dose back to 280mg/d.
- 2/2016. Escalated dose to 420mg/d. 2 days later, had an episode of AF with rate 130, associated with atypical chest pain.
- Serial troponin negative. Coronary arteries normal.
- Patient unwilling to resume ibrutinib at low dose given resolution of problematic migratory arthralgias since stopping drug.
- Current status (2021) – gradual, asymptomatic disease progression (LDT ~18m, low-volume lymphadenopathy). Continues in observation with no disease-related symptoms 5y after ibrutinib cessation.

How do you think through first-line therapy for a patient with high-risk CLL (eg, deletion 17p)?

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

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

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What is the most effective strategy to mitigate the risk of tumor lysis syndrome (TLS) with venetoclax and/or obinutuzumab?

Case Presentation: Dr Smith – 68-year-old woman with IGHV-unmutated CLL

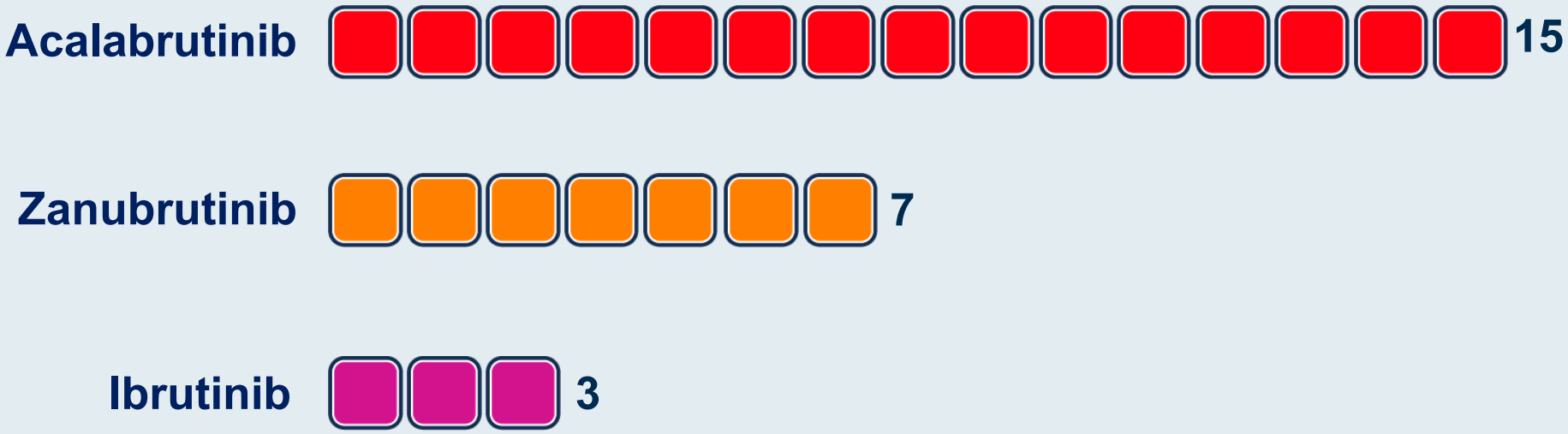
- 68-year-old woman with CLL, WBC 140,000, ANC 1.9, Hgb 10.9, platelets 101,000, del11q on FISH, unmutated IGHV, diffuse small adenopathy. Counts had been falling over 12 months.
- Started on venetoclax-obinutuzumab. During initial obinutuzumab, ALC fell to 16,000 but ANC to 0.9, Hgb and platelets stable.
- We delayed start of venetoclax 1 week, still had persistent borderline ANC during ramp-up that prolonged that process and required G-CSF.
- Was able to get to full dose.
- Month 3, ALC normal, Hgb 12.0 and platelets 155,000, but ANC 1.4 and hospitalized with pneumococcal pneumonia.
- Responded to antibiotic therapy and a dose of IVIG for hypogammaglobulinemia.
- Now continues on CLL therapy, ANC 2-3, no additional infections.

Case Presentation: Dr Sharman – 71-year-old man with IGHV-unmutated, trisomy 12, NOTCH1-mutated, TP53 wild-type CLL

- 71-year-old attorney with disabling fatigue.
- Had to cut back on work hours due to his CLL.
- Diagnosed in 2017 with CLL, IGHV unmutated, trisomy 12, TP53 wild type, NOTCH1 mutated.
- Developed progressive adenopathy, bulky retroperitoneal disease >10cm. WBC only 24K, Hgb 11, Plt 100K.
- Started on “debulking protocol” with obinutuzumab for 2 months and re-staging prior to initiating venetoclax.
- Required 4 months of obi prior to starting ven.
- After venetoclax ramp up, which was done as outpatient, developed neutropenia. Responded well to WBC growth factors. No dose reduction needed.

How do you choose among the available BTK inhibitors for the treatment of CLL?

Regulatory and reimbursement issues aside, when you are going to administer a BTK inhibitor as initial treatment for a patient with CLL, which would you generally prefer?

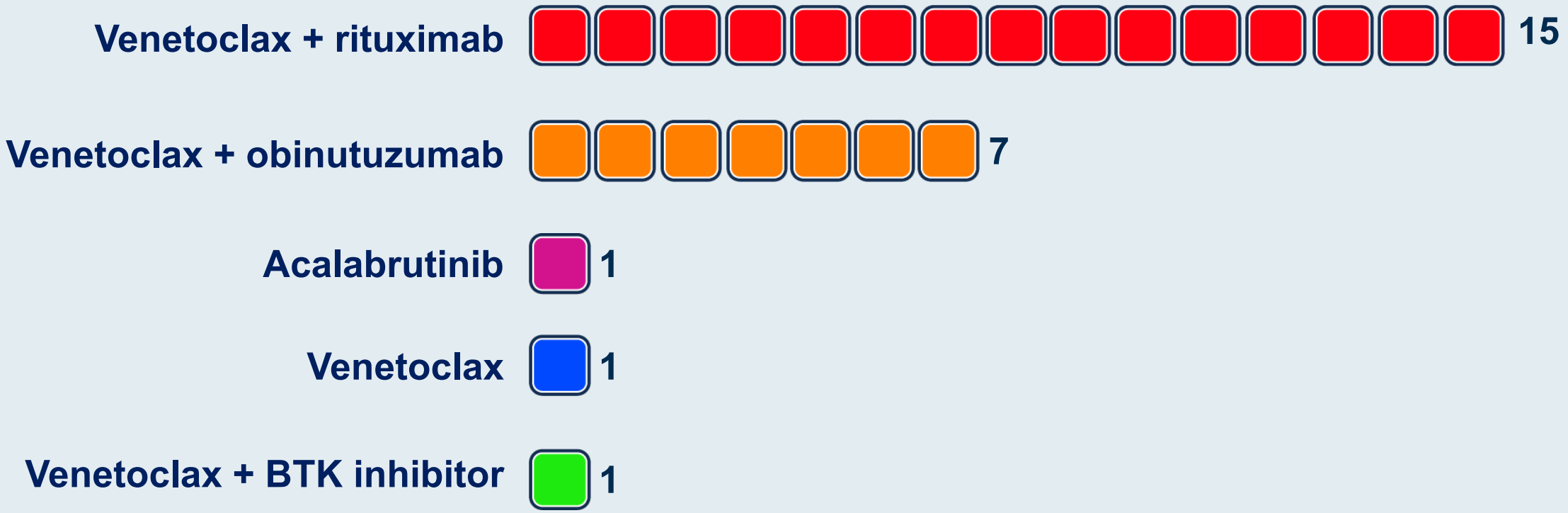


Survey of 25 US-based clinical investigators

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 responds to ibrutinib and then experiences disease progression 3 years later?



Survey of 25 US-based clinical investigators

What is the role of MRD assessment in the management of CLL?

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

What would be your most likely approach for a patient with newly diagnosed CLL who receives up-front venetoclax/obinutuzumab and 1 year after completing treatment has...

Detectable MRD

Undetectable MRD

Survey of 25 US-based clinical investigators

How do you approach COVID-19 prevention for patients with CLL? How do you manage patients with CLL who develop COVID-19?

Key Recent Data Sets

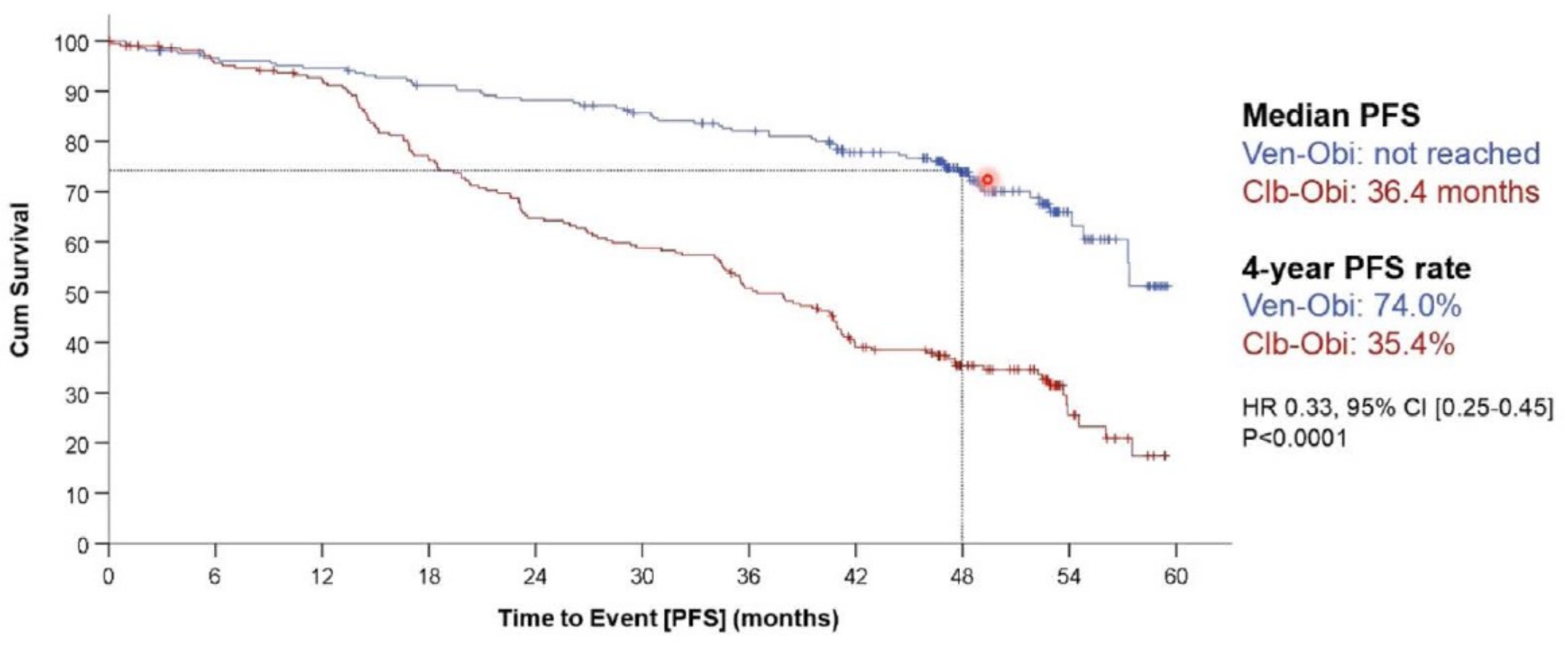
Articles

Venetoclax plus obinutuzumab versus chlorambucil plus obinutuzumab for previously untreated chronic lymphocytic leukaemia (CLL14): follow-up results from a multicentre, open-label, randomised, phase 3 trial

Othman Al-Sawaf, Can Zhang, Maneesh Tandon, Arijit Sinha, Anna-Maria Fink, Sandra Robrecht, Olga Samoylova, Anna M Liberati, Javier Pinilla-Ibarz, Stephen Opat, Liliya Sivcheva, Katell Le Dû, Laura M Fogliatto, Carsten U Niemann, Robert Weinkove, Sue Robinson, Thomas J Kipps, Eugen Tausch, William Schary, Matthias Ritgen, Clemens-Martin Wendtner, Karl-Anton Kreuzer, Barbara Eichhorst, Stephan Stilgenbauer, Michael Hallek, Kirsten Fischer**

Lancet Oncol 2020;21(9):1188-200.

CLL14: Updated 4-Year PFS



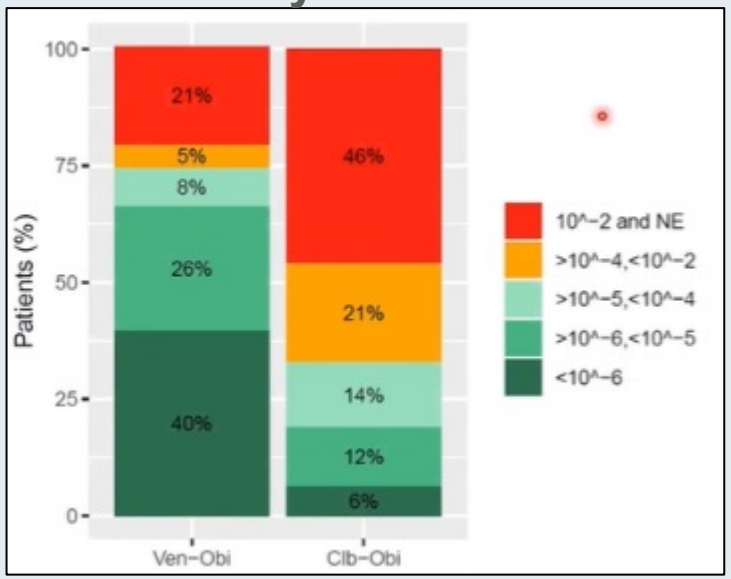
Median observation time: 52.4 months

Al-Sawaf O et al. ASH 2020;Abstract 127 .

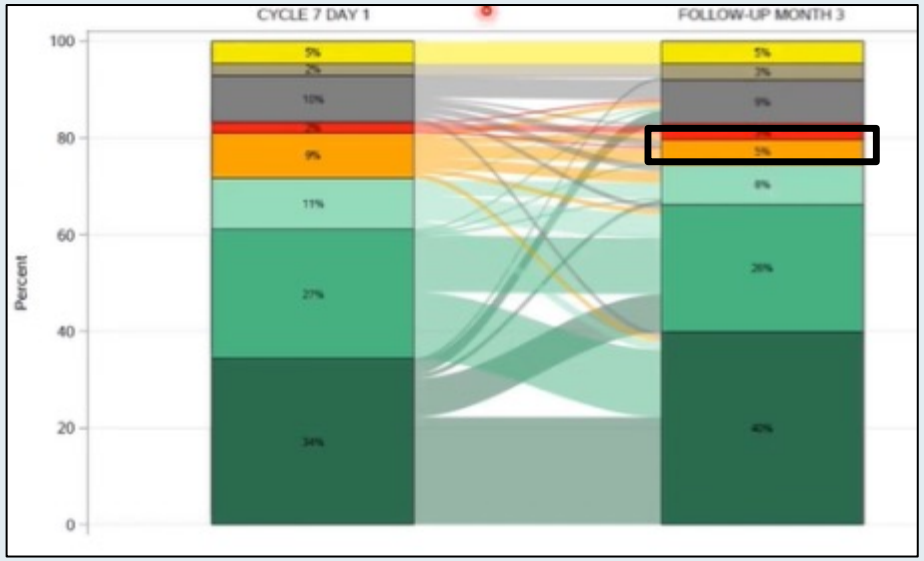
RTP RESEARCH TO PRACTICE

CLL14: Clonal Dynamics After Venetoclax-Obinutuzumab Therapy

MRD by NGS at EOT

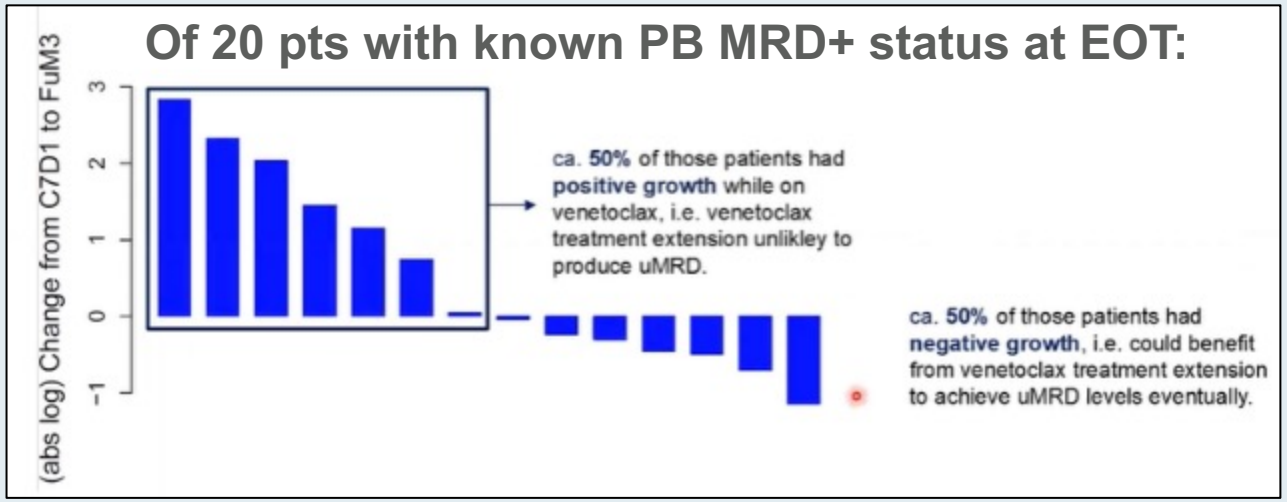


MRD During and After Ven-Obi



- 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:

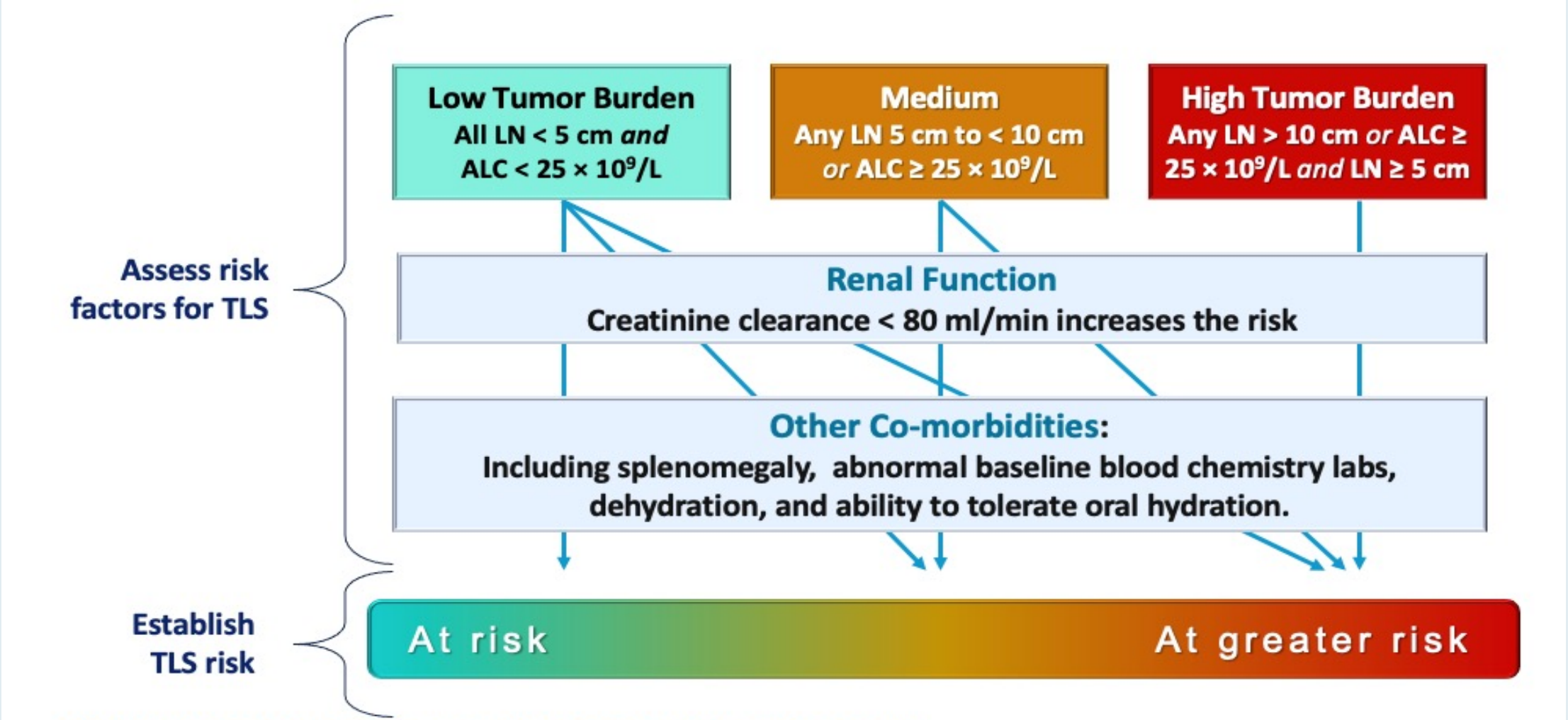


Al-Sawaf O et al. ASH 2020. Abstract 127

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

RTP RESEARCH TO PRACTICE

TLS Risk with Venetoclax Is a Continuum Based on Multiple Factors

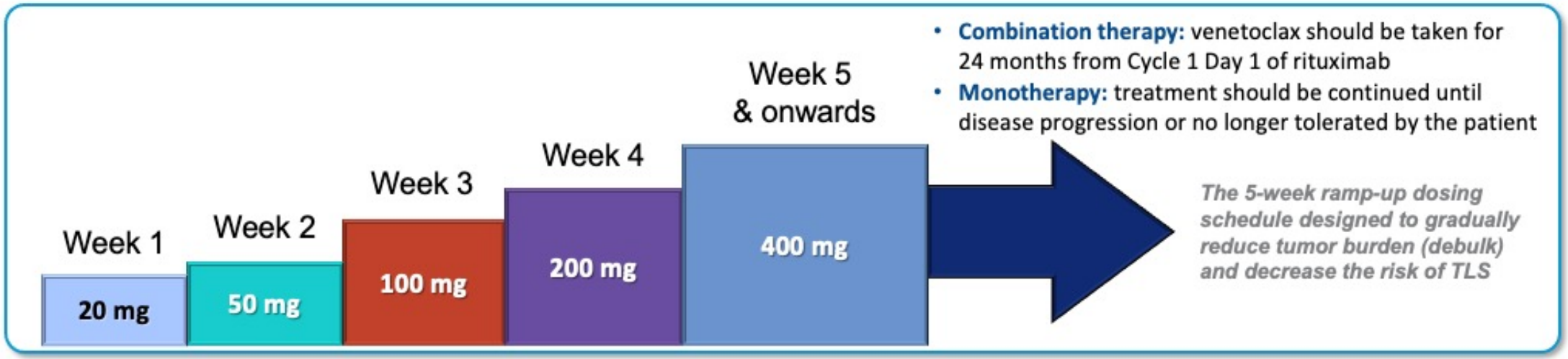


ALC, absolute lymphocyte count; **CrCl**, creatinine clearance; **LN**, lymph node; **TLS**, tumor lysis syndrome

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

Courtesy of Matthew S Davids, MD, MMSc

Venetoclax Dose Initiation



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

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

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

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

Courtesy of Matthew S Davids, MD, MMSc

Venetoclax: TLS Prophylaxis and Monitoring

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

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

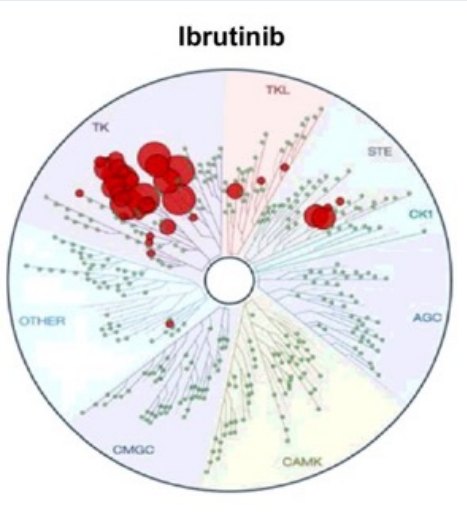
1. Venetoclax SPC https://www.medicines.org.uk/emc/product/2267/smpc (accessed October 2019); 2. Stilgenbauer S, et al. *Lancet Oncol*. 2016; 17:768–778

Courtesy of Matthew S Davids, MD, MMSc

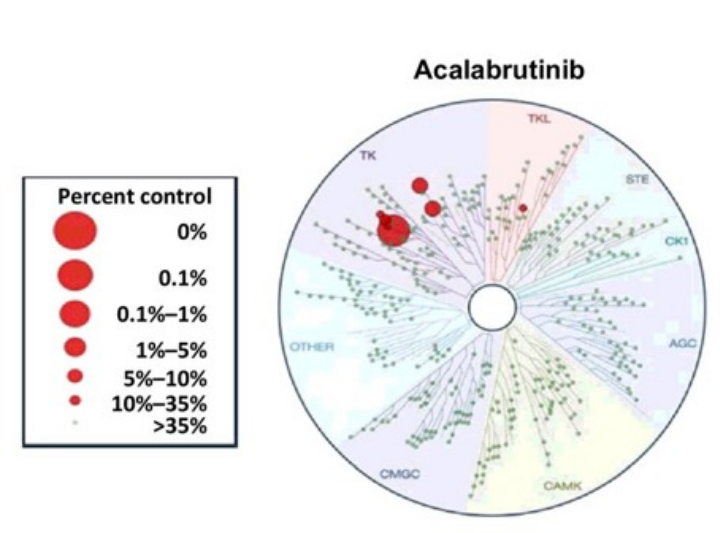
Overview of BTK Inhibitors in CLL

Irreversible

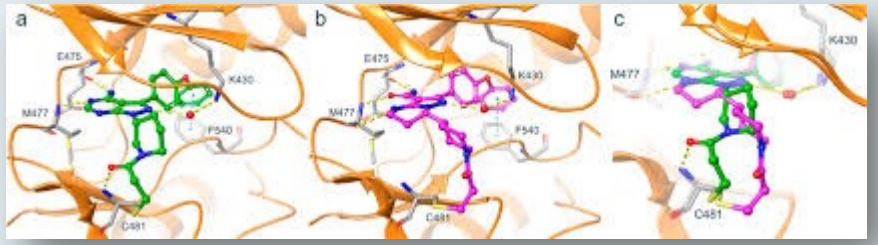
Ibrutinib



Acalabrutinib

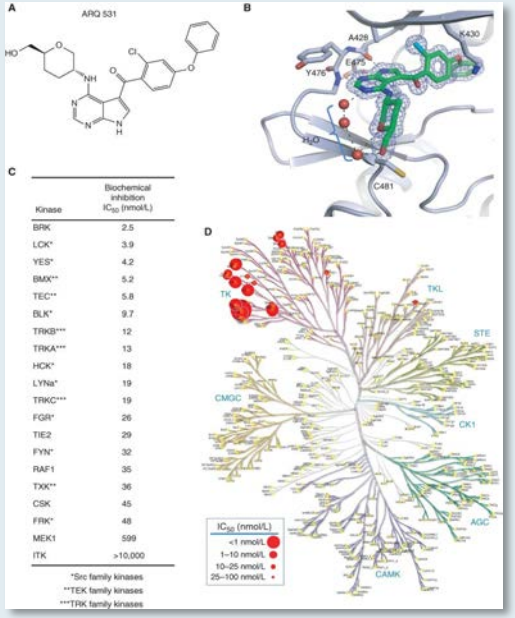


Zanubrutinib

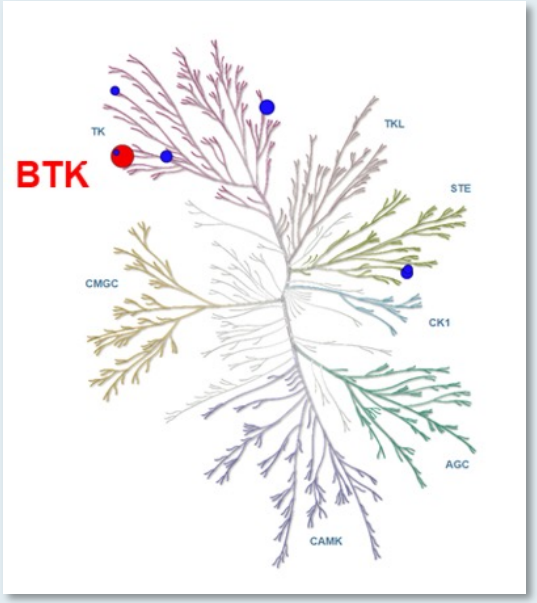


Reversible

ARQ-531 (MK-1026)



Pirtobrutinib (LOXO-305)



Courtesy of Matthew S Davids, MD, MMSc

RTP RESEARCH TO PRACTICE

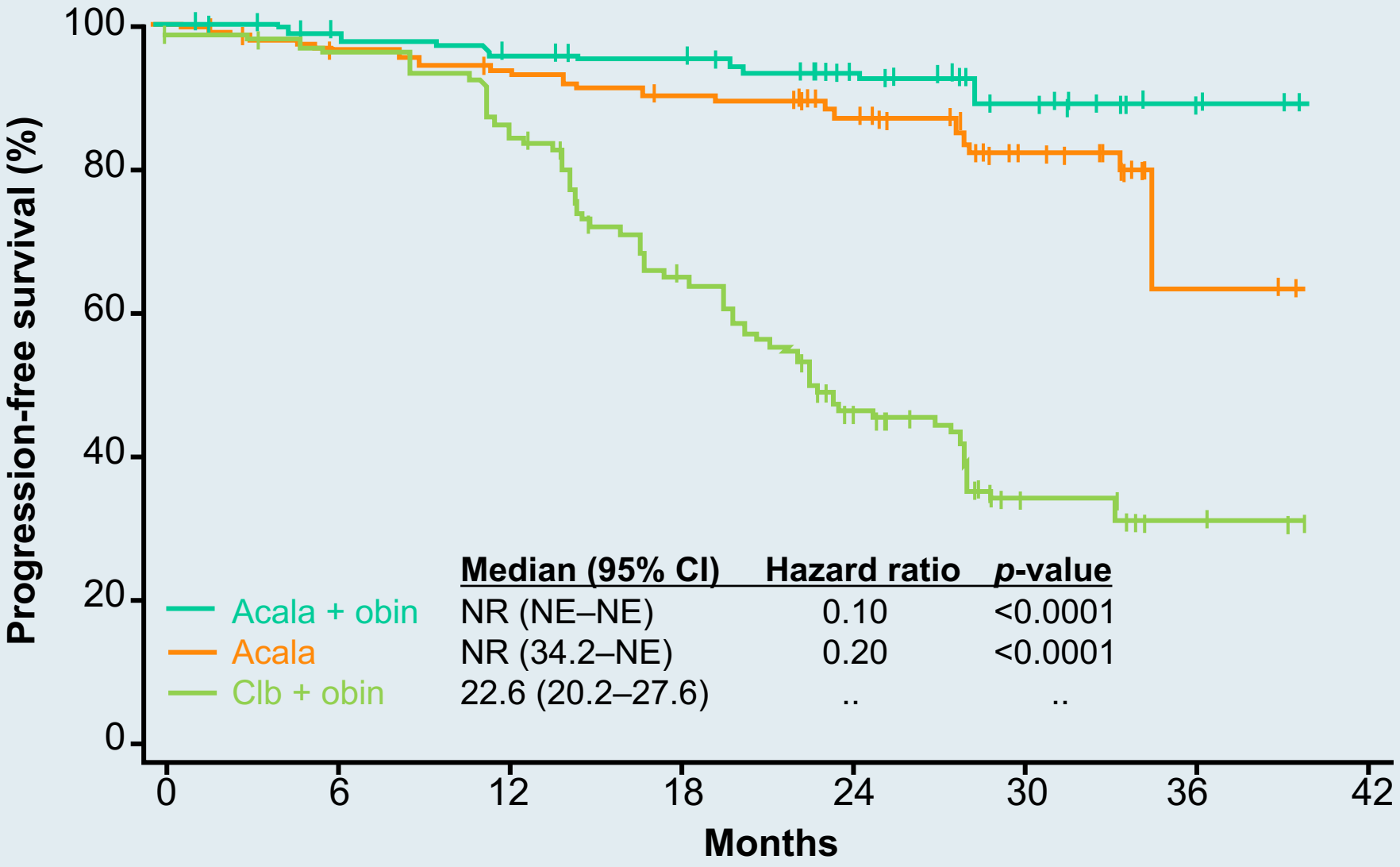
Articles

Acalabrutinib with or without obinutuzumab versus chlorambucil and obinutuzumab for treatment-naive chronic lymphocytic leukaemia (ELEVATE-TN): a randomised, controlled, phase 3 trial

Jeff P Sharman, Miklos Egyed, Wojciech Jurczak, Alan Skarbnik, John M Pagel, Ian W Flinn, Manali Kamdar, Talha Munir, Renata Walewska, Gillian Corbett, Laura Maria Fogliatto, Yair Herishanu, Versha Banerji, Steven Coutre, George Follows, Patricia Walker, Karin Karlsson, Paolo Ghia, Ann Janssens, Florence Cymbalista, Jennifer A Woyach, Gilles Salles, William G Wierda, Raquel Izumi, Veerendra Munugalavadla, Priti Patel, Min Hui Wang, Sofia Wong, John C Byrd

Lancet 2020;395(10232):1278-91.

ELEVATE-TN: PFS (IRC)



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

original reports

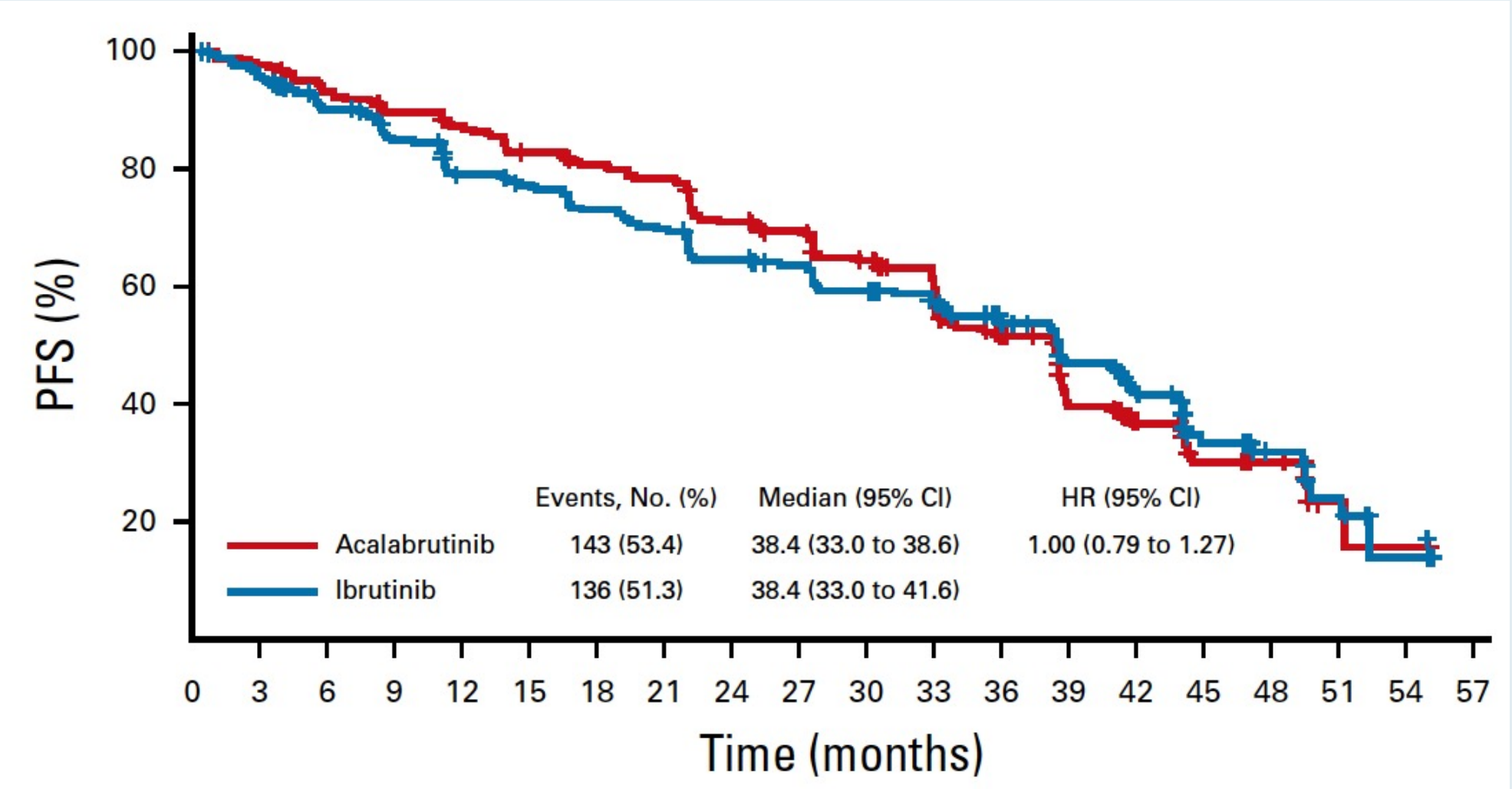
Acalabrutinib Versus Ibrutinib in Previously Treated Chronic Lymphocytic Leukemia: Results of the First Randomized Phase III Trial

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

J Clin Oncol 2021;[Online ahead of print].

RTP RESEARCH TO PRACTICE

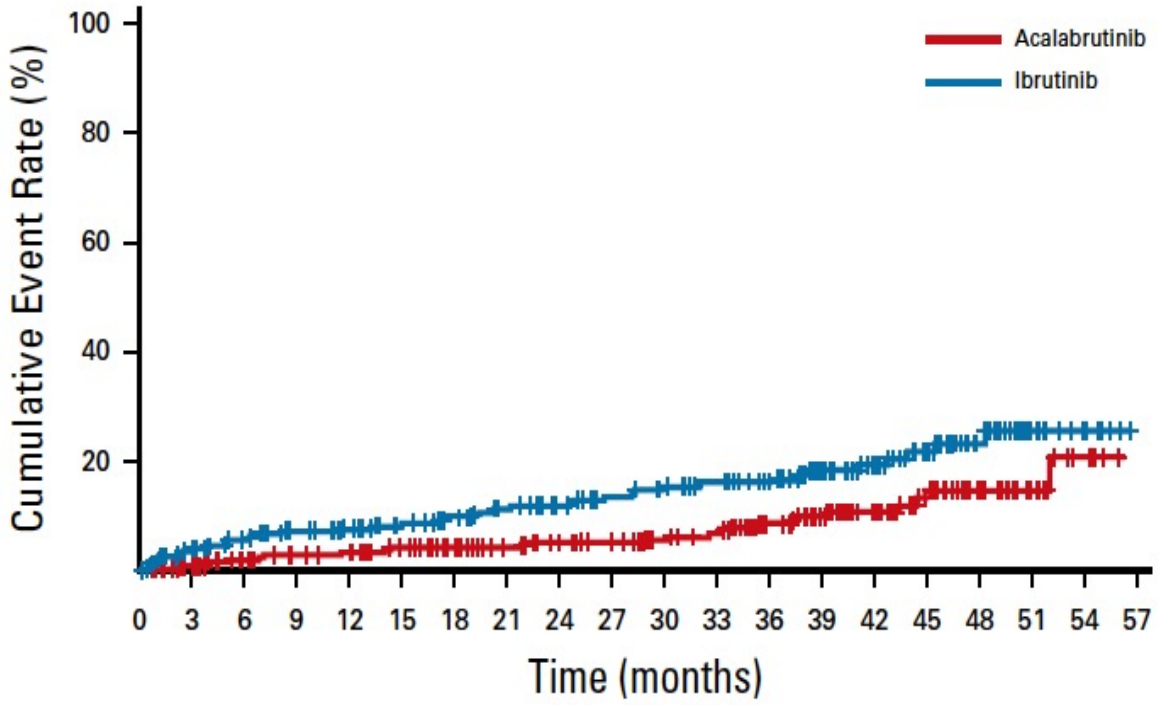
ELEVATE-RR: Primary Endpoint – Noninferiority Met on IRC-Assessed PFS



Byrd JC et al. *J Clin Oncol* 2021;[Online ahead of print]; ASCO 2021;Abstract 7500.

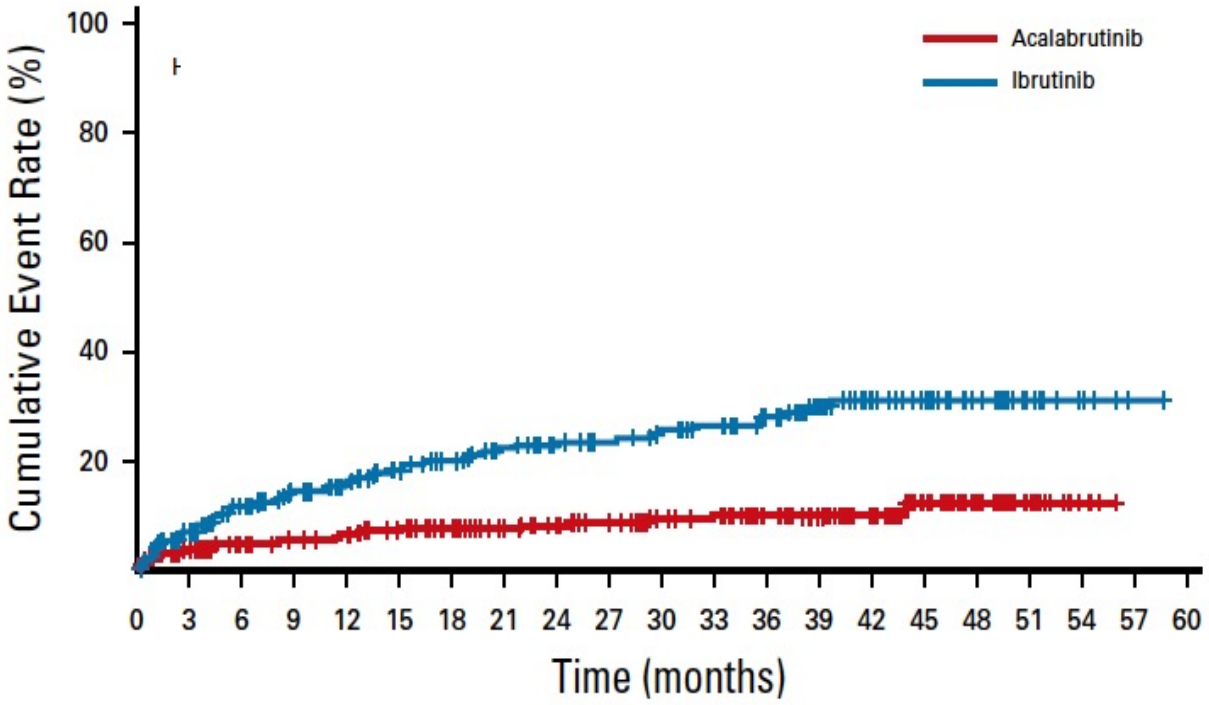
ELEVATE-RR: Cumulative Incidences of Atrial Fibrillation and Hypertension with Acalabrutinib versus Ibrutinib

Atrial Fibrillation



Acalabrutinib:Ibrutinib
HR (95% CI): 0.52 (0.32 to 0.86)

Hypertension



Acalabrutinib:Ibrutinib
HR (95% CI): 0.34 (0.21 to 0.54)

Byrd JC et al. *J Clin Oncol* 2021;[Online ahead of print]; ASCO 2021;Abstract 7500.

RTP RESEARCH TO PRACTICE

ELEVATE-RR: Adverse Events of Special Interest

Adverse events (AEs)	Acalabrutinib (n = 266)		Ibrutinib (n = 263)	
	Any grade	Grade ≥3	Any grade	Grade ≥3
Cardiac events	24.1%	8.6%	30.0%	9.5%
Atrial fibrillation	9.4%	4.9%	**16.0%**	3.8%
Ventricular tachyarrhythmias	0	0	0.4%	0.4%
Hypertension	9.4%	4.1%	**23.2%**	9.1%
Bleeding events	38.0%	3.8%	51.3%	4.6%
Major bleeding events	4.5%	3.8%	5.3%	4.6%
Infections	78.2%	30.8%	81.4%	30.0%
SPMs	9.0%	6.0%	7.6%	5.3%
Headache	34.6%		20.2%	
AEs leading to treatment discontinuation	14.7%		21.3%	

SPMs = Second primary malignancies, excluding nonmelanoma skin cancers

Byrd JC et al. ASCO 2021;Abstract 7500.

Positive Topline Results Announced from the Phase III SEQUOIA Trial: Zanubrutinib versus BR for Treatment-Naïve CLL

Press Release: July 29, 2021

"The SEQUOIA trial met the primary endpoint at interim analysis, with zanubrutinib significantly prolonging progression-free survival compared to chemoimmunotherapy, and safety and tolerability consistent with its known profile. SEQUOIA is the second positive global Phase 3 trial of zanubrutinib in chronic lymphocytic leukemia, following ALPINE in the relapsed or refractory setting.

With a median follow-up of 25.8 months, the SEQUOIA trial met the primary endpoint of progression-free survival (PFS) as assessed by independent review committee (IRC), as zanubrutinib achieved a highly statistically significant improvement in PFS compared to B + R.

In addition, the trial demonstrated a statistically significant improvement in PFS per investigator assessment, a secondary endpoint. Zanubrutinib was also generally well-tolerated, consistent with its known safety profile."

https://www.businesswire.com/news/home/20210729006225/en/BeiGene-Announces-Positive-Topline-Results-from-Phase-3-SEQUOIA-Trial-Comparing-BRUKINSA%C2%AE-Zanubrutinib-to-Bendamustine-Plus-Rituximab-in-Patients-with-Treatment-Na%C3%AFve-Chronic-Lymphocytic-Leukemia

FIRST INTERIM ANALYSIS OF ALPINE STUDY: RESULTS OF A PHASE 3 RANDOMIZED STUDY OF ZANUBRUTINIB VS IBRUTINIB IN PATIENTS WITH RELAPSED/REFRACTORY CHRONIC LYMPHOCYTIC LEUKEMIA/ SMALL LYMPHOCYTIC LYMPHOMA

Peter Hillmen, MBChB, PhD[1]; Barbara Eichhorst, MD[2]; Jennifer R. Brown, MD, PhD[3]; Nicole Lamanna MD[4]; Susan O'Brien, MD[5]; Constantine S. Tam, MBBS, MD[6,7,8,9]; Lugui Qiu, MD, PhD[10]; Maciej Kazmierczak, MD, PhD[11]; Keshu Zhou, MD, PhD[12]; Martin Šimkovič, MD, PhD[13,14]; Jiri Mayer, MD[15]; Amanda Gillespie-Twardy, MD[16], Mazyar Shadman, MD, MPH[17,18]; Alessandra Ferrajoli, MD[19]; Peter S. Ganly, BMBCh, PhD[20,21]; Robert Weinkove, MBBS, PhD[22,23]; Tommi Salmi, MD[24]; Meng Ji, MD[24]; Jessica Yecies, PhD[24]; Kenneth Wu, PhD[24]; William Novotny, MD[24]; Jane Huang, MD[24]; Wojciech Jurczak, MD, PhD[25]

[1]St James's University Hospital, Leeds, United Kingdom; [2]Department of Internal Medicine, University of Cologne, Cologne, Germany; [3]Department of Medical Oncology, Dana-Farber Cancer Institute, Boston, MA, USA; [4]Herbert Irving Comprehensive Cancer Center, Columbia University, New York, NY, USA; [5]Chao Family Comprehensive Cancer Center, University of California, Irvine, CA, USA; [6]Peter MacCallum Cancer Centre, Melbourne, Victoria, Australia; [7]University of Melbourne, Parkville, Victoria, Australia; [8]St Vincent's Hospital, Fitzroy, Victoria, Australia; [9]Royal Melbourne Hospital, Parkville, Victoria, Australia; [10]Chinese Academy of Medical Sciences, Peking Union Medical College, Tianjin, China; [11]Department of Hematology and Bone Marrow Transplantation, Poznan University of Medical Sciences, Poznan, Poland; [12]Affiliated Cancer Hospital of Zhengzhou University, Henan Cancer Hospital, Zhengzhou, China; [13]4th Department of Internal Medicine - Hematology, University Hospital, Hradec Kralove, Czech Republic; [14]Faculty of Medicine, Charles University, Prague, Czech Republic; [15]Department of Internal Medicine-Hematology and Oncology, Masaryk University and University Hospital, Brno, Czech Republic; [16]Blue Ridge Cancer Care, Roanoke, VA, USA; [17]Fred Hutchinson Cancer Research Center, Seattle, WA, USA; [18]Department of Medicine, University of Washington, Seattle, WA, USA; [19]Department of Leukemia, The University of Texas MD Anderson Cancer Center, Houston, TX, USA; [20]Department of Haematology, Christchurch Hospital, Christchurch, New Zealand; [21]Department of Pathology and Biomedical Science, University of Otago, Christchurch, New Zealand; [22]Wellington Blood and Cancer Centre, Capital and Coast District Health Board, Wellington, New Zealand; [23]Malaghan Institute of Medical Research, Wellington, New Zealand; [24]BeiGene (Beijing) Co, Ltd., Beijing, China and BeiGene USA, Inc, San Mateo, CA, USA; and [25]Maria Sklodowska-Curie National Institute of Oncology, Krakow, Poland

June 11, 2021
Presidential Symposium (Abstract LB1900)

EHA

EHA2021 VIRTUAL

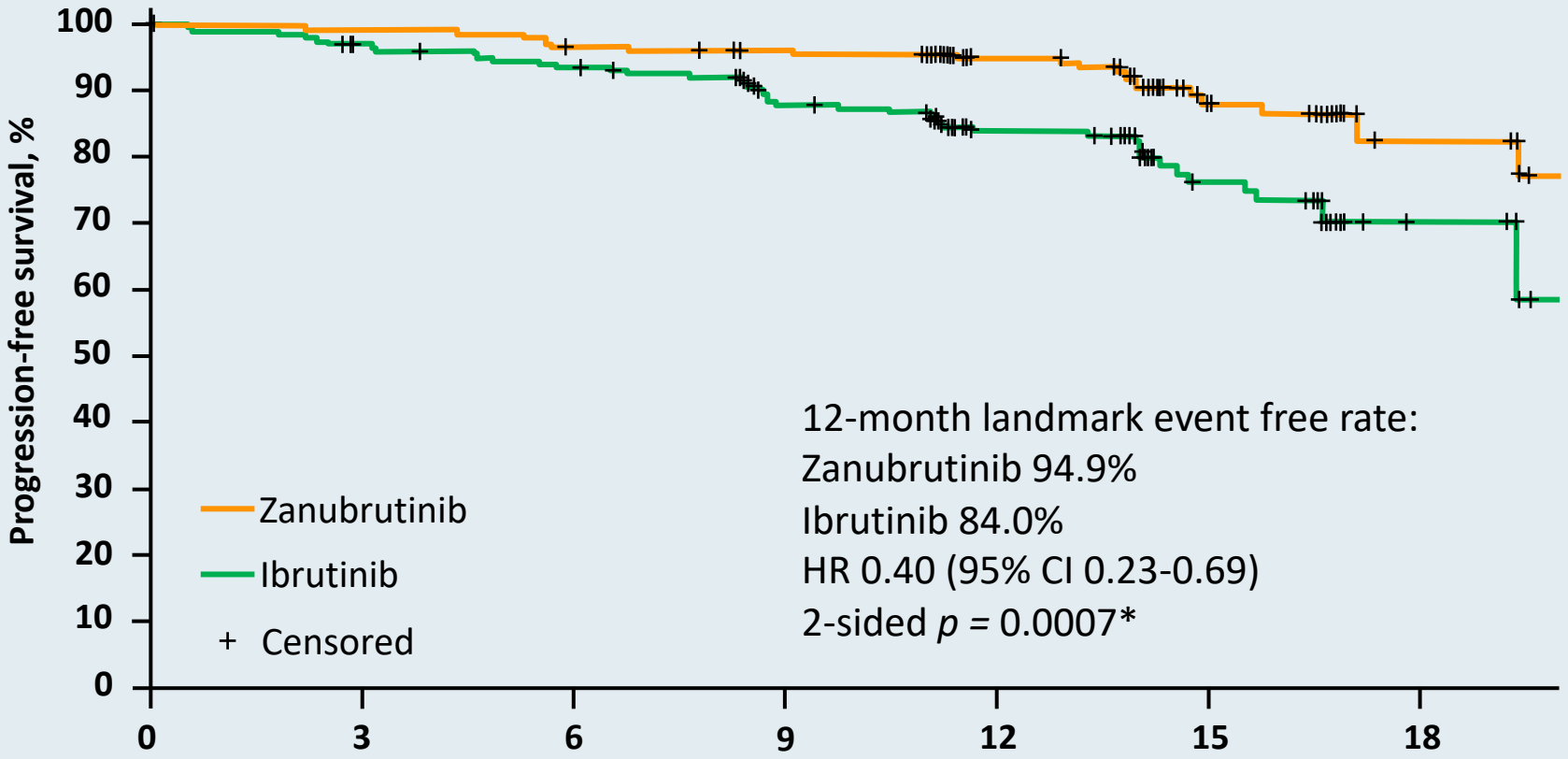
RTP RESEARCH TO PRACTICE

ALPINE: Primary Endpoint – ORR by Investigator Assessment

	Zanubrutinib (n = 207), n (%)	Ibrutinib (n = 208), n (%)
Primary endpoint: ORR (PR + CR)	162 **(78.3)** 95% CI: 72.0, 83.7	130 **(62.5)** 95% CI: 55.5, 69.1
	Superiority 2-sided *p* = 0.0006 compared with prespecified alpha of 0.0099	
CR/CRi	4 (1.9)	3 (1.4)
nPR	1 (0.5)	0
PR	157 (75.8)	127 (61.1)
ORR (PR-L + PR + CR)	*183 (88.4)*	*169 (81.3)*
PR-L	21 (10.1)	39 (18.8)
SD	17 (8.2)	28 (13.5)
PD	1 (0.5)	2 (1.0)
Discontinued or new therapy prior to first assessment	6 (2.9)	9 (4.3)
	Del(17p) (n = 24), n (%)	**Del(17p) (n = 26), n (%)**
ORR (PC + CR)	20 (83.3)	14 (53.8)

Hillmen P et al. EHA 2021;Abstract LB1900.

ALPINE: PFS by Investigator Assessment



Patients at Risk							
Zanubrutinib	207	200	194	190	152	70	19
Ibrutinib	208	196	188	170	125	57	8

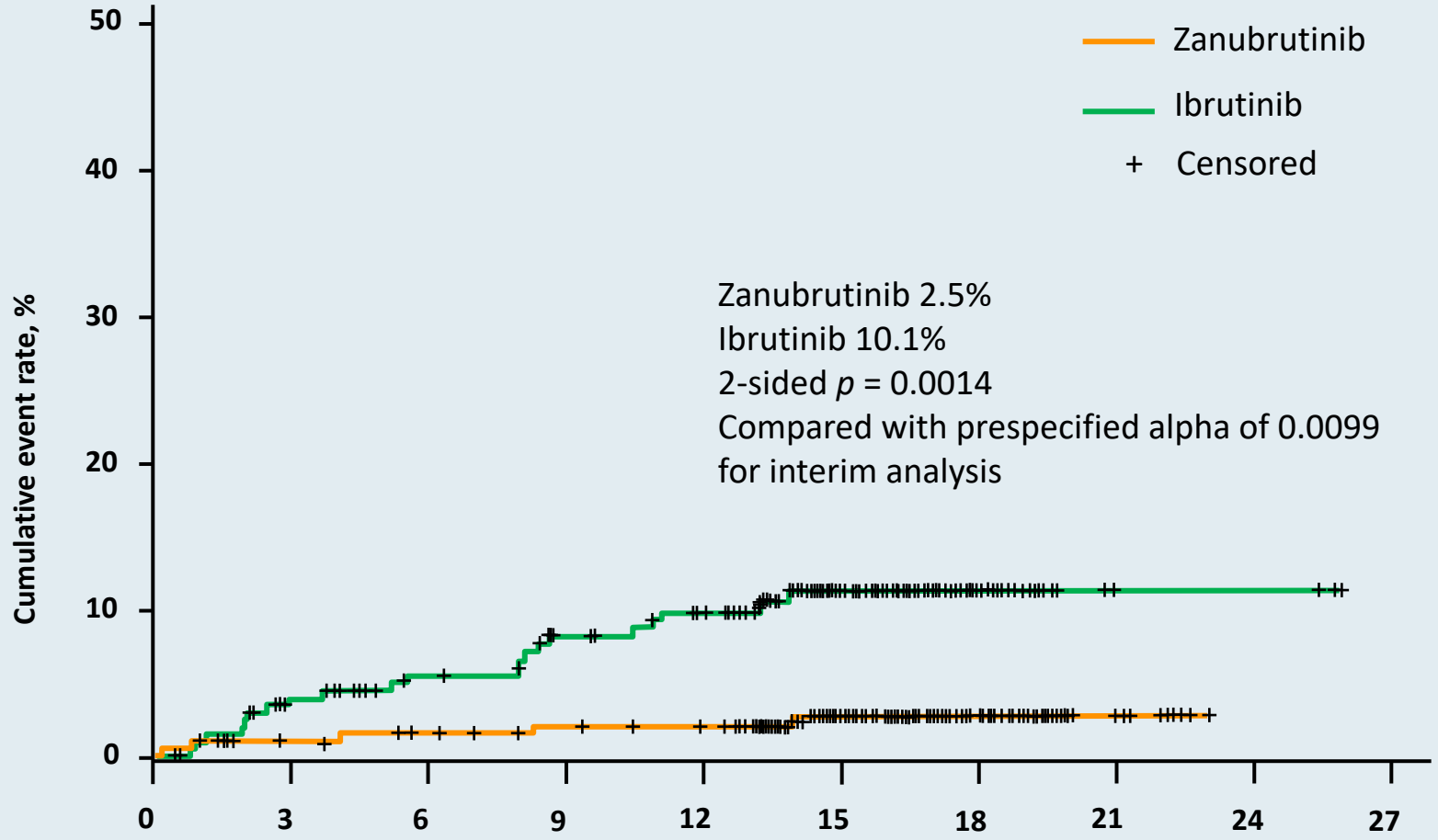
- Although not a pre-specified analysis, the overall 12-month PFS was higher with zanubrutinib vs ibrutinib (94.9% vs 84.0%)

*Not a prespecified analysis; formal analysis of PFS will be based on all patients when the target number of events are reached.

Hillmen P et al. EHA 2021;Abstract LB1900.

RTP RESEARCH TO PRACTICE

ALPINE: Incidence of Atrial Fibrillation with Zanubrutinib versus Ibrutinib



Patients at Risk										
Zanubrutinib	204	197	194	190	187	114	40	9	0	0
Ibrutinib	207	190	179	168	160	91	26	3	3	0

Hillmen P et al. EHA 2021;Abstract LB1900.

RTP RESEARCH TO PRACTICE

ALPINE: Adverse Events of Special Interest

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

[a]Cardiac disorders leading to treatment discontinuation: zanubrutinib 0 patients and ibrutinib 7 (3.4%) patients.
[b]Includes serious or Grade ≥3 hemorrhage or any Grade CNS hemorrhage
[c]Pooled terms including neutropenia, neutrophil count decreased, and febrile neutropenia; thrombocytopenia and platelet count decreased.

Hillmen P et al. EHA 2021;Abstract LB1900.

Five-year Analysis of MURANO Study Demonstrates Enduring Undetectable Minimal Residual Disease (uMRD) in a Subset of Relapsed/Refractory Chronic Lymphocytic Leukemia (R/R CLL) Patients Following Fixed-Duration Venetoclax-Rituximab (VenR) Therapy

Arnon P. Kater*[1], Thomas J. Kipps[2], Barbara F. Eichhorst[3], Peter Hillmen[4], James D'Rozario[5], Carolyn Owen[6], Sarit Assouline[7], Nicole Lamanna[8], Tadeusz Robak[9], Javier de la Serna[10], Ulrich Jaeger[11], Guillaume Cartron[12], Marco Montillo[13], Clemens Mellink[1], Brenda Chyla[14], Cameron Wilson[15], Jenny Wu[16], Yanwen Jiang[16], Marcus Lefebure[15], Michelle Boyer[15], John F. Seymour[17]

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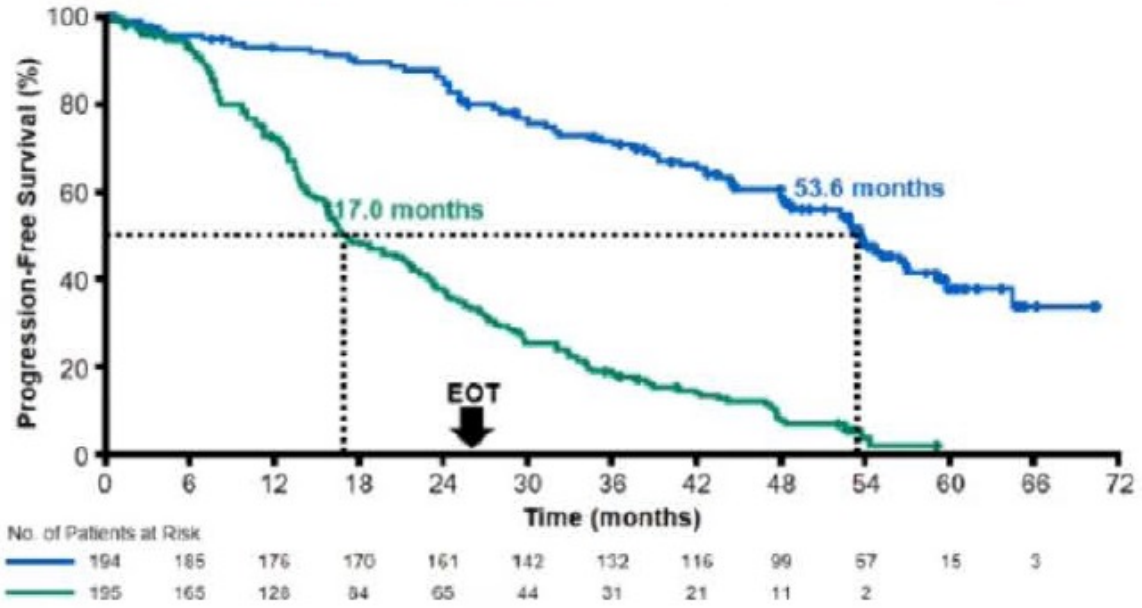
Accepted as an Oral Presentation at the 62nd ASH Annual Meeting and Exposition

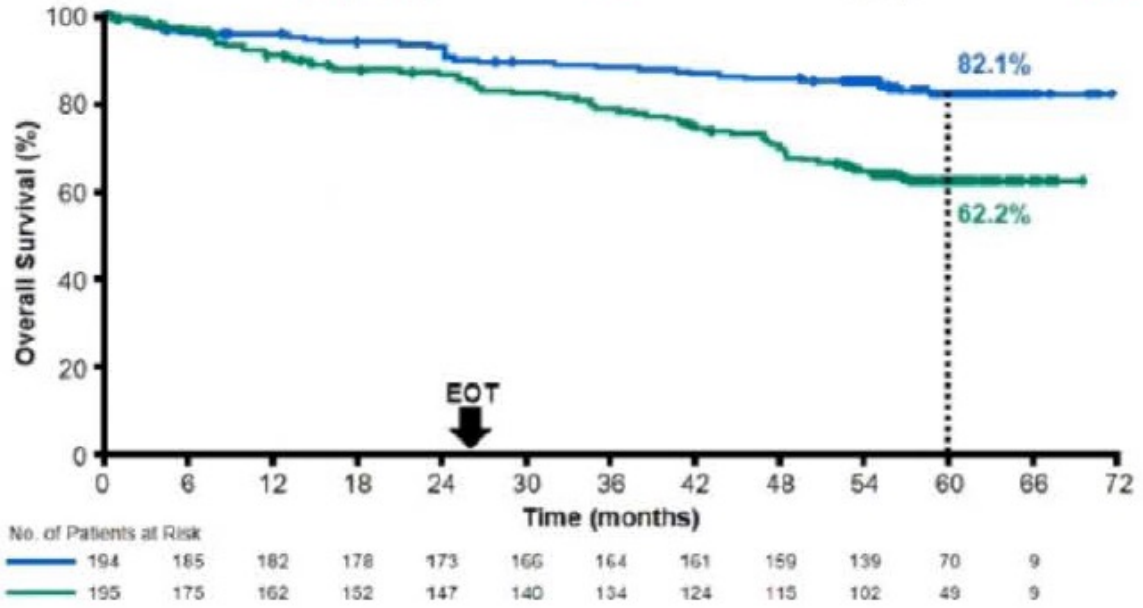
Abstract 125

MURANO: Survival

	Median PFS (95% CI), months	HR* (95% CI)	5-yr PFS (%)
VenR (N=194)	53.6 (48.4, 57.0)	0.19 (0.15, 0.26) Stratified P-value <0.0001†	37.8
BR (N=195)	17.0 (15.5, 21.7)		NE



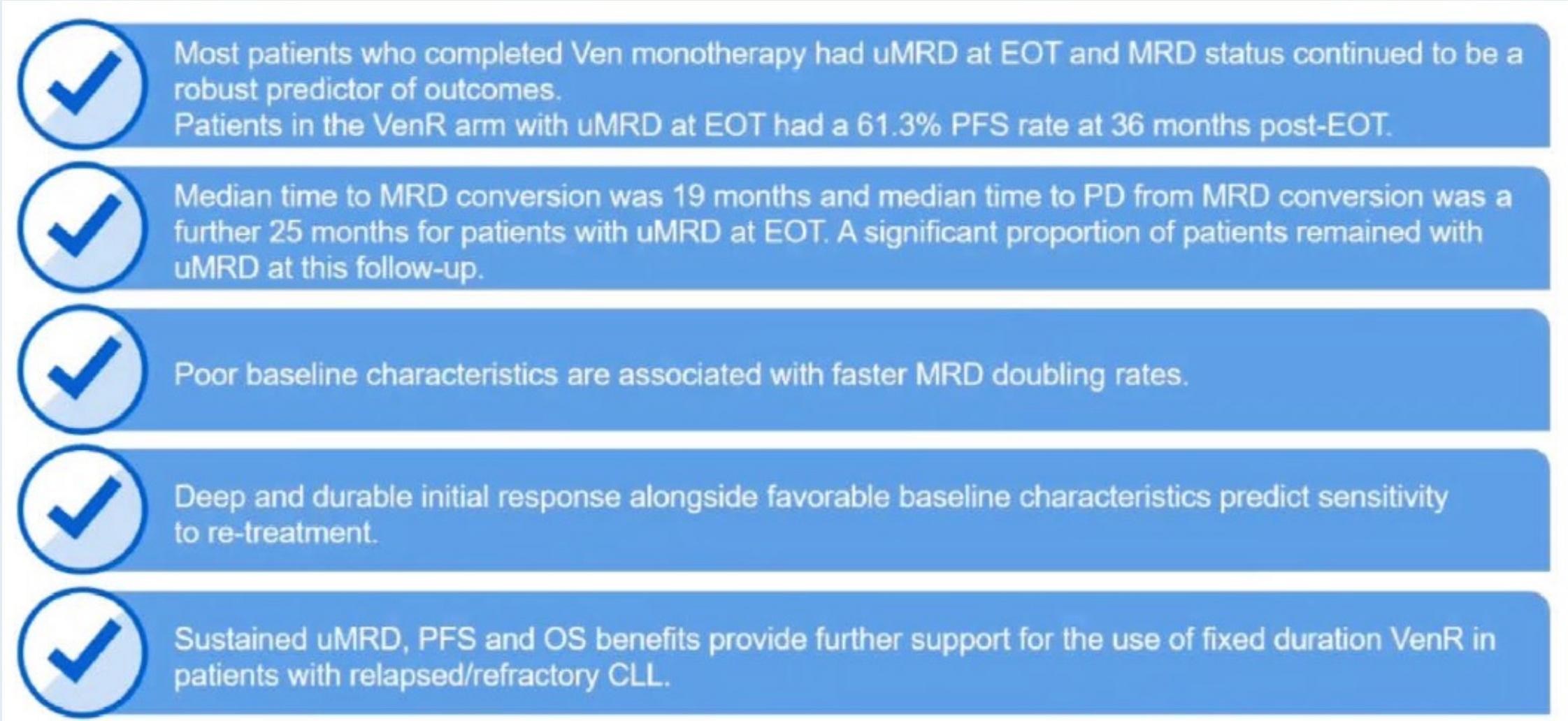
	Median OS (95% CI), months	HR‡ (95% CI)	5-yr OS (%)
VenR (N=194)	NE	0.40 (0.26, 0.62) Stratified P-value <0.0001†	82.1
BR (N=195)	NE		62.2



- With this 5-year update we can now accurately define the median PFS of VenR-treated patients
- No new safety signals were identified 3 years after EOT with longer follow up and patients are outside of the adverse event reporting window

Kater AP et al. ASH 2020;Abstract 125.

MURANO: Conclusions

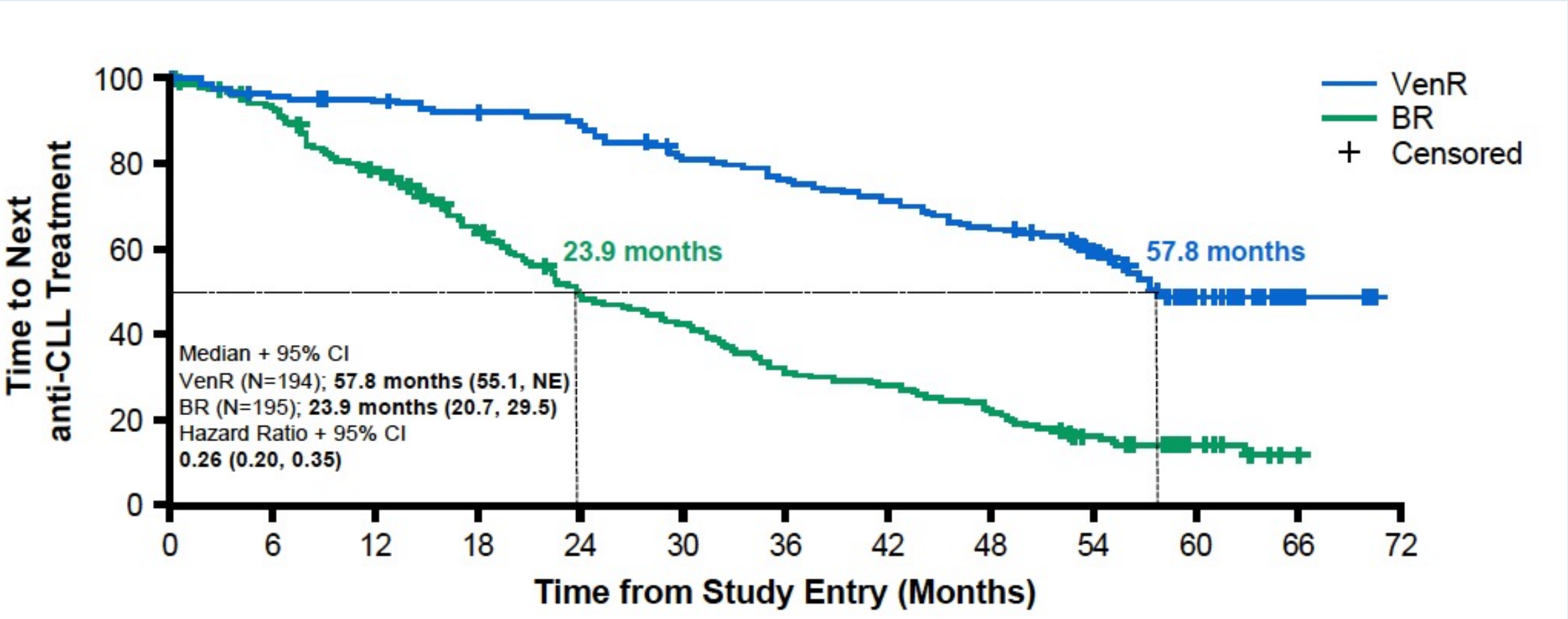


Kater AP et al. ASH 2020;Abstract 125.

Efficacy of Subsequent Novel Targeted Therapies, Including Repeated Venetoclax-Rituximab (VenR), in Patients with Relapsed/Refractory Chronic Lymphocytic Leukemia (R/R CLL) Previously Treated with Fixed-Duration VenR in the MURANO Study

Harrup R et al.
ASH 2020;Abstract 3139.

MURANO: TTNT with VenR versus BR



Harrup R et al. ASH 2020;Abstract 3139.

RTP RESEARCH TO PRACTICE

ASH Annual Meeting 2020 **Abstract Publication Number 3136**

Venetoclax Re-Treatment of Chronic Lymphocytic Leukemia Patients after a Previous Venetoclax-based Regimen

Meghan C. Thompson, MD[1], John N. Allan, MD[2], Kavita Sail, PhD[3], Beenish S. Manzoor, PhD, MPH[4], Jeffrey J. Pu, MD, PhD[5], Paul M. Barr, MD[6], Callie C. Coombs, MD[7], Stephen J. Schuster, MD[8], Alan Skarbnik, MD[9], Joanna M Rhodes, MD[10], Jacqueline C. Barrientos, MD[10], Lindsey E Roeker, MD[1], Lori A. Leslie, MD[11], Manali Kamdar, MD[12], Michael Y. Choi, MD[13], Martin Simkovic, MD, PhD[14], Frederick Lansigan, MD[15], Brittany Jane Hale, MD[15], Andrew D Zelenetz, MD, PhD[16], Alison J. Moskowitz, MD[1], Kurt S. Bantilan, MPH[1], Celina J. Komari, BS[1], Andre H. Goy, MD[1], Tatyana A. Feldman, MD[11], Richard R. Furman, MD[2] and Anthony R. Mato, MD[1]

Study Design and Endpoints

- Multicenter, retrospective study
- 13 centers and the CLL Collaborative Study of Real-World Evidence (CORE) database
- Eligibility:
  - CLL patients treated with Ven-based regimen (any line of therapy, Ven1)
  - Then re-treated with second Ven-based regimen (Ven2) in a later line of therapy
- Data collected by investigators at individual sites
  - Demographics, prognostic disease characteristics, tumor lysis syndrome risk and incidence, clinical response and reasons for treatment discontinuation

- Primary endpoint:
  - Investigator-assessed ORR
  - CR: complete response, PR: partial response, SD: stable disease, PD: progression of disease, iwCLL 2018
- PFS estimated by Kaplan-Maier method
- All other analyses descriptive

Memorial Sloan Kettering Cancer Center
Weill Cornell Medicine
UPSTATE CANCER CENTER
UC San Diego Health
University of Colorado
UR MEDICINE
UNC
Penn
Hackensack Meridian John Theurer Cancer Center
NOVANT HEALTH
Northwell Health
Dartmouth-Hitchcock NORRIS COTTON CANCER CENTER
FAKULTNÍ NEMOCNICE HRADEC KRÁLOVÉ

Thompson MC et al. ASH 2020;Abstract 3136.

RTP RESEARCH TO PRACTICE

Conclusions

- **ORR:** High ORR of 72.2% for Ven re-treatment
- **Heavily pretreated population:** Cohort studied had median 2 prior therapies, majority R/R (88%), BTKi exposed (60%)
- **Safety:** TLS rare event and majority were able to tolerate 400 mg daily
- **Improved outcomes with time:** Patients with CR to Ven re-treatment had a longer median follow-up than PR or SD patients
  - Potential for better responses with longer time on therapy?
- **Next steps:** Longer follow-up and prospective validation of Ven re-treatment → potential role of Ven re-treatment in sequencing algorithms

Thompson MC et al. ASH 2020;Abstract 3136.

Agenda

Module 1: Treatment of CLL in 2021

- How do you think through first-line therapy for a patient with CLL who is younger and fit?
- How do you think through first-line therapy for a patient with CLL who is older and frail?
- How do you think through first-line therapy for a patient with high-risk CLL (eg, deletion 17p)?
- What is the most effective strategy to mitigate the risk of tumor lysis syndrome with venetoclax and/or obinutuzumab?
- How do you choose among the available BTK inhibitors for the treatment of CLL?
- What is the role of MRD assessment in the management of CLL?
- How do you approach COVID-19 prevention for patients with CLL?

Module 2: Future Treatment of CLL

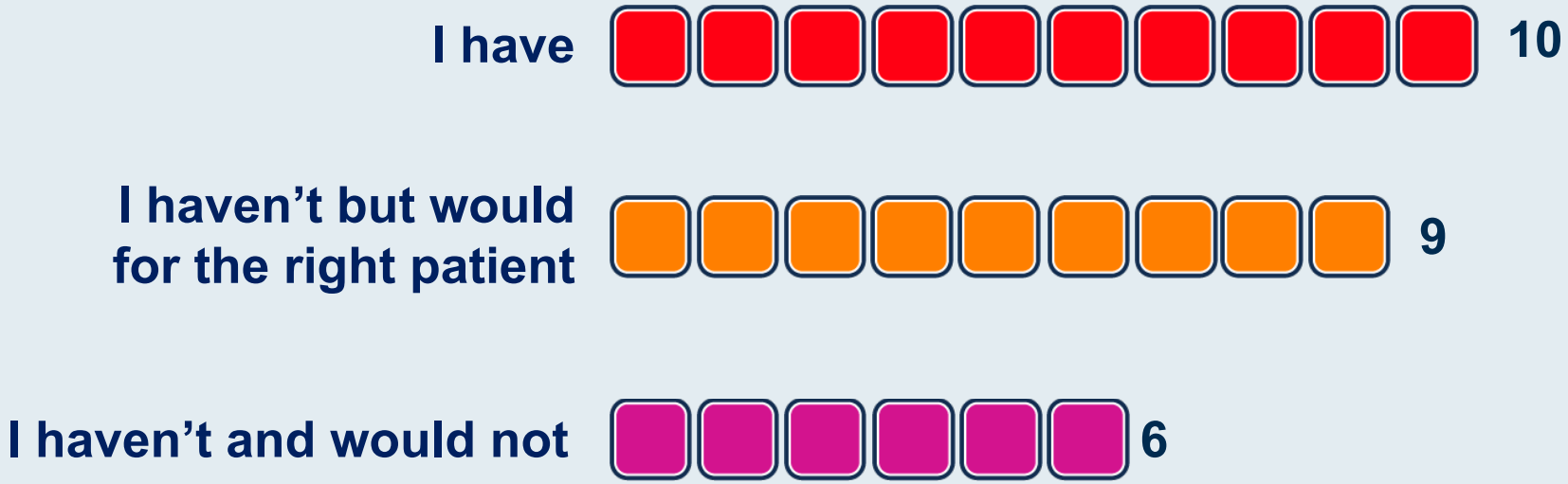
- What is the future role of BTK inhibitors combined with venetoclax in the management of CLL?
- What is the future role of pirtobrutinib (LOXO 305) in the management of CLL?
- What is the current and future role of CAR T-cell therapy?

What is the future role of BTK inhibitors combined with venetoclax in the management of CLL?

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?

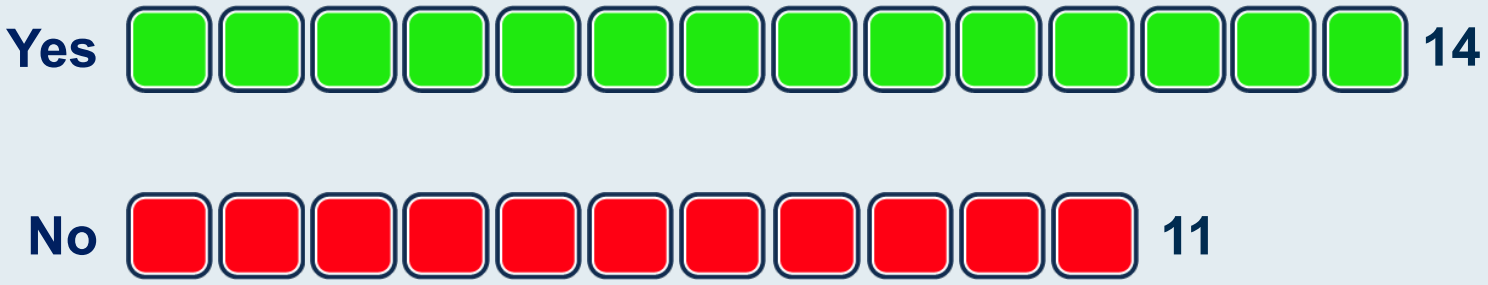
1. I haven’t and would not
2. I haven’t but would for the right patient
3. I have

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?



Survey of 25 US-based clinical investigators

Do you believe there is a benefit to administering a BTK inhibitor in combination with venetoclax as opposed to sequentially for patients with CLL?



Survey of 25 US-based clinical investigators

What is the future role of pirtobrutinib (LOXO 305) in the management of CLL?

What is the current and future role of CAR T-cell therapy?

Case Presentation: Dr Thompson – 54-year-old woman with multiregimen-relapsed CLL

- 54F (born 1967).
- Dx 2004 age 37. Unknown *IGHV* mutation status (non-productive PCR), del(13q) by FISH.
- Treatment:
  1. 2009 – FCR x3. PR, MRD 0.5%. Stopped due to fatigue/abdominal pain (intermittent intussusception of small bowel without clear etiology).
  2. 1/2012 – rituximab + lenalidomide. Stopped due to neutropenia.
  3. 12/2012 – ofatumumab x8 – transient response.
  4. 12/2013 – ibrutinib. Dose reduced 7/2014 due to arthralgia, rash, then developed PD 2/2015 (sequencing not available for BTK mutations).
  5. 4/2015 – venetoclax on clinical trial. CR with U-MRD. Continued venetoclax 400mg/d until 2019, when she required recurrent dose reduction for neutropenia (G-CSF very poorly tolerated) and she then developed PD. BCL2 mutation analysis not yet available.
  6. 10/2019 – ibrutinib + JCAR017 on TRANSCEND CLL 004 study. CR with U-MRD.
  7. 7/2021. Remains in CR, doing well.

Case Presentation: Dr Sharman – 69-year-old woman with multiregimen-relapsed CLL

- 69-year-old woman initially treated in 2004, 2008 with FCR by another provider.
- Transferred to my clinic when that provider left practice.
- Relapsed with del11q, IGHV unmutated disease. Treated on protocol with AVL-292 (early second generation BTK inhibitor) prior to commercial availability of ibrutinib. Stayed on therapy for about a year.
- Enrolled on study with obinutuzumab/venetoclax. Interestingly – got one dose of venetoclax when study abruptly closed due to TLS in other early studies of venetoclax. One pill provided several months of disease control.
- In 2013 proceeded to bendamustine/rituximab with PR. Subsequently enrolled on study of ibrutinib/ublituximab and had several years of benefit.
- Progressed with massive retroperitoneal adenopathy and del17P. Received idelalisib/rituximab with PR followed by progression.
- Started venetoclax/rituximab in 2017.
- After several years, developed recurrent lymphocytosis and was treated with lisocabtagene maraleucel CAR-T cell therapy to which she maintains a CR today. On replacement IVIG.

Case Presentation: Dr Smith – 58-year-old man with multiregimen-relapsed CLL

- 58-year-old man, CLL x 8 years. IGHV unmutated. Initial FiSH normal.
- Treated with initial FCR, tolerated well and achieved remission.
- Relapse 3 years later, now del17p positive.
- Started ibrutinib, did well for 18 months. ALC started to rise. Otherwise well with normal counts.
- Received tisagenlecleucel CAR T-cell therapy on research study at UPenn.
- Remains in remission, clinically well, continues on ibrutinib and requires replacement IVIg.

Key Recent Data Sets

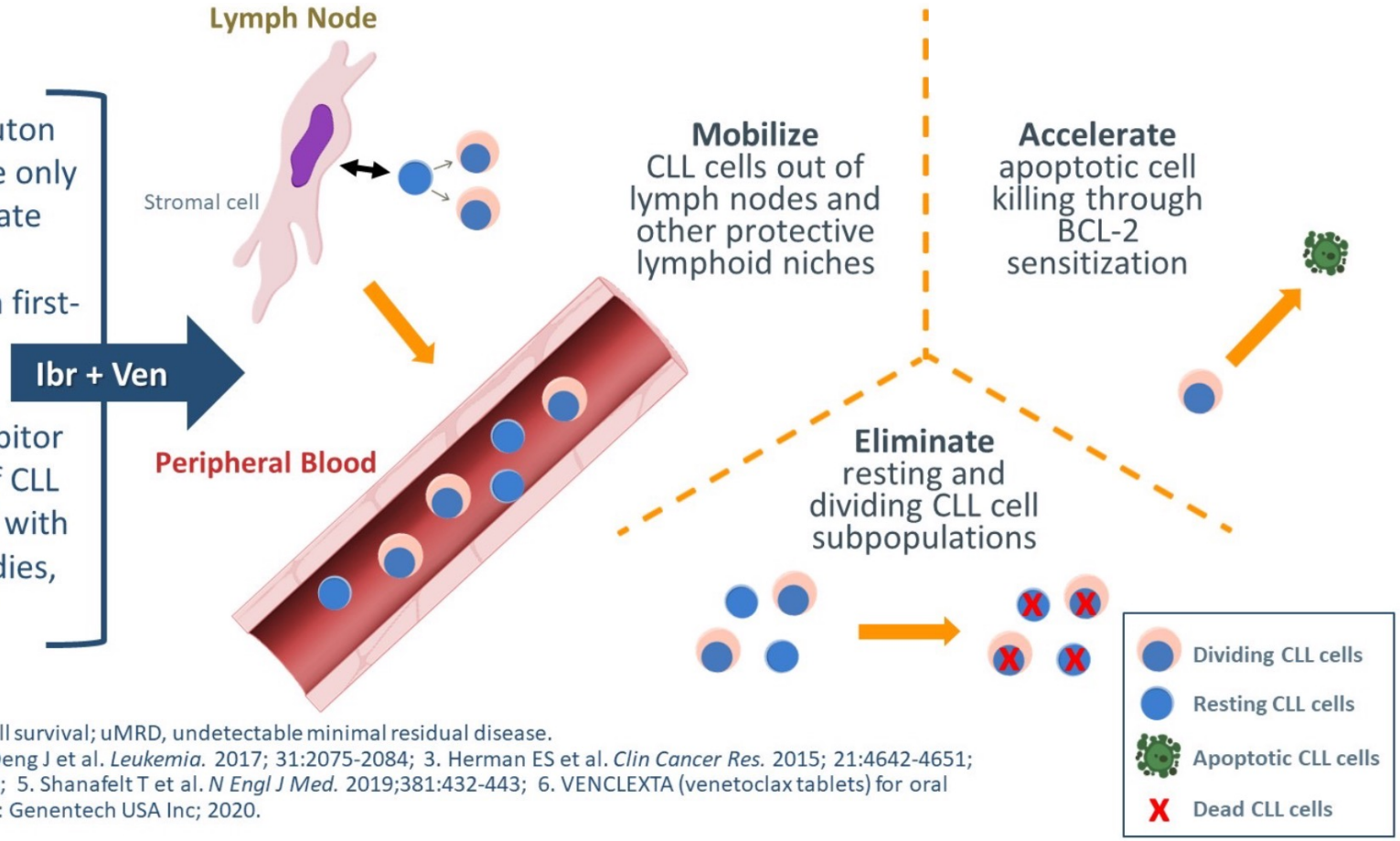
Fixed-Duration (FD) First-Line Treatment With Ibrutinib Plus Venetoclax for Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma: Primary Analysis of the FD Cohort of the Phase 2 CAPTIVATE Study

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

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

Rationale: Ibrutinib and Venetoclax Have Distinct and Complementary Modes of Action That Work Synergistically[1-3]

- Ibrutinib, a once-daily oral Bruton tyrosine kinase inhibitor, is the only targeted therapy to demonstrate significant OS benefit in randomized phase 3 studies in first-line CLL[4,5]
- Venetoclax, an oral BCL-2 inhibitor approved for the treatment of CLL as a single agent or combined with anti-CD20 monoclonal antibodies, achieves high rates of uMRD[6]

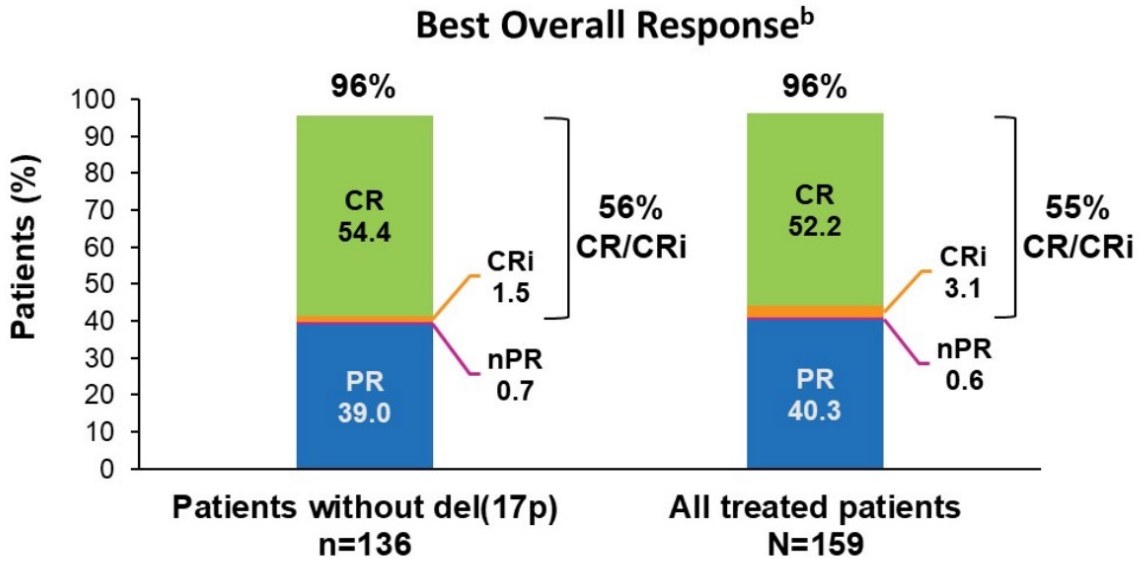


CLL, chronic lymphocytic leukemia; OS, overall survival; uMRD, undetectable minimal residual disease.

1. Lu P et al. *Blood Cancer J.* 2021; 11:39; 2. Deng J et al. *Leukemia.* 2017; 31:2075-2084; 3. Herman ES et al. *Clin Cancer Res.* 2015; 21:4642-4651; 4. Burger JA et al. *Leukemia.* 2020;34:787-798; 5. Shanafelt T et al. *N Engl J Med.* 2019;381:432-443; 6. VENCLEXTA (venetoclax tablets) for oral use [package insert]. South San Francisco, CA: Genentech USA Inc; 2020.

Ghia P et al. ASCO 2021;Abstract 7501.

Primary Endpoint of CR Rate[a]: Fixed-Duration Treatment with Ibrutinib + Venetoclax Provides Deep, Durable Responses



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

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

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

nPR, nodular partial response; PR, partial response; DOCR, duration of complete response.
[a]Proportion of patients with CR or CRi. [b]Overall response was assessed at the end of Cycle 3, on Day 1 of Cycles 7, 10, 13, 19, 25, 28, and 31, and every 6 months thereafter.

1. Eichhorst B et al. *Lancet Oncol.* 2016;17:928-942.

ASCO 2021, CAPTIVATE-FD; Ghia et al.

Ghia P et al. ASCO 2021;Abstract 7501.

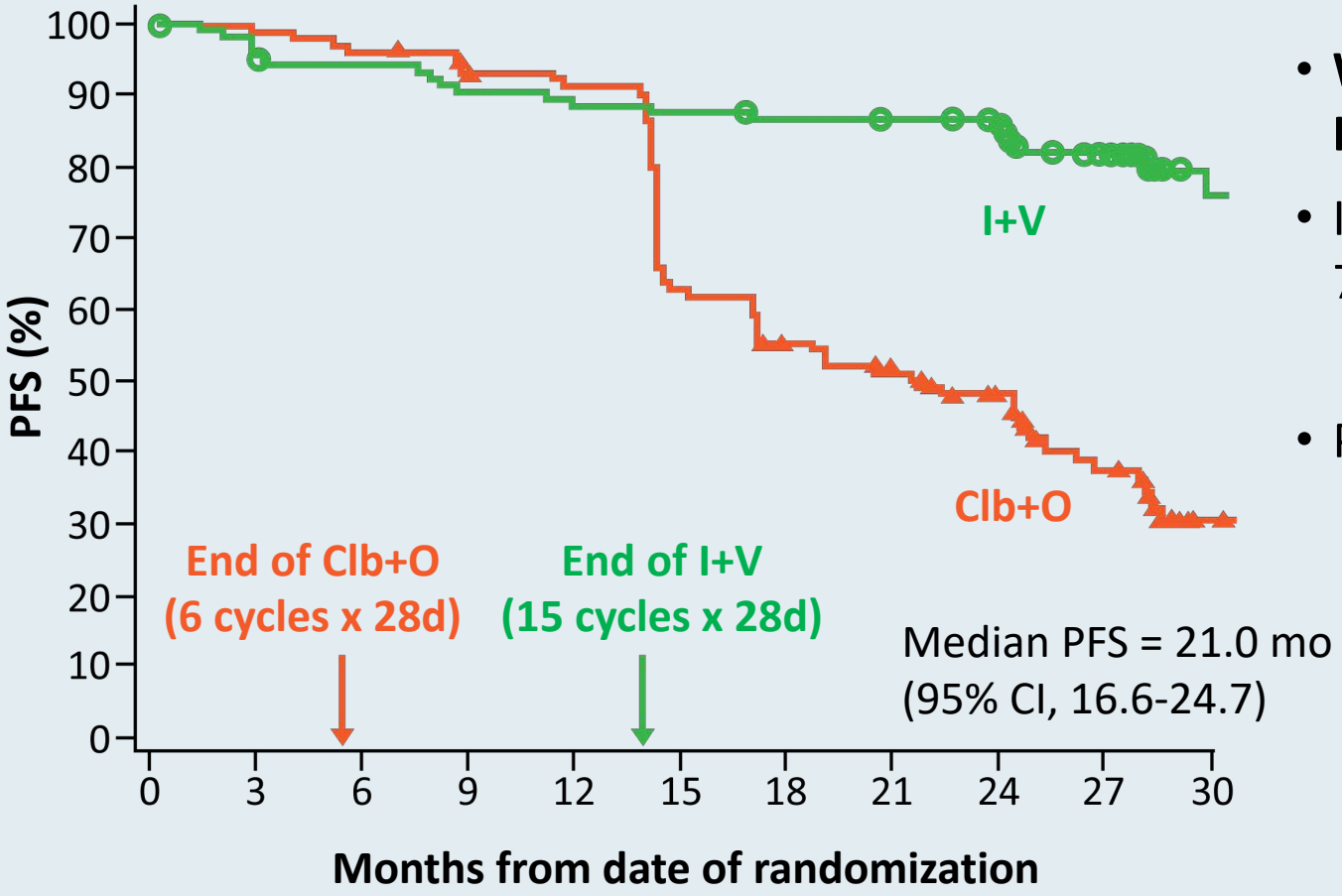
FIXED-DURATION IBRUTINIB PLUS VENETOCLAX (I+V) VERSUS CHLORAMBUCIL PLUS OBINUTUZUMAB (CLB+O) FOR FIRST-LINE TREATMENT OF CHRONIC LYMPHOCYTIC LEUKEMIA (CLL): PRIMARY ANALYSIS OF THE PHASE 3 GLOW STUDY

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

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

Kater AP et al. EHA 2021;Abstract LB1902.

GLOW: Progression-Free Survival by IRC

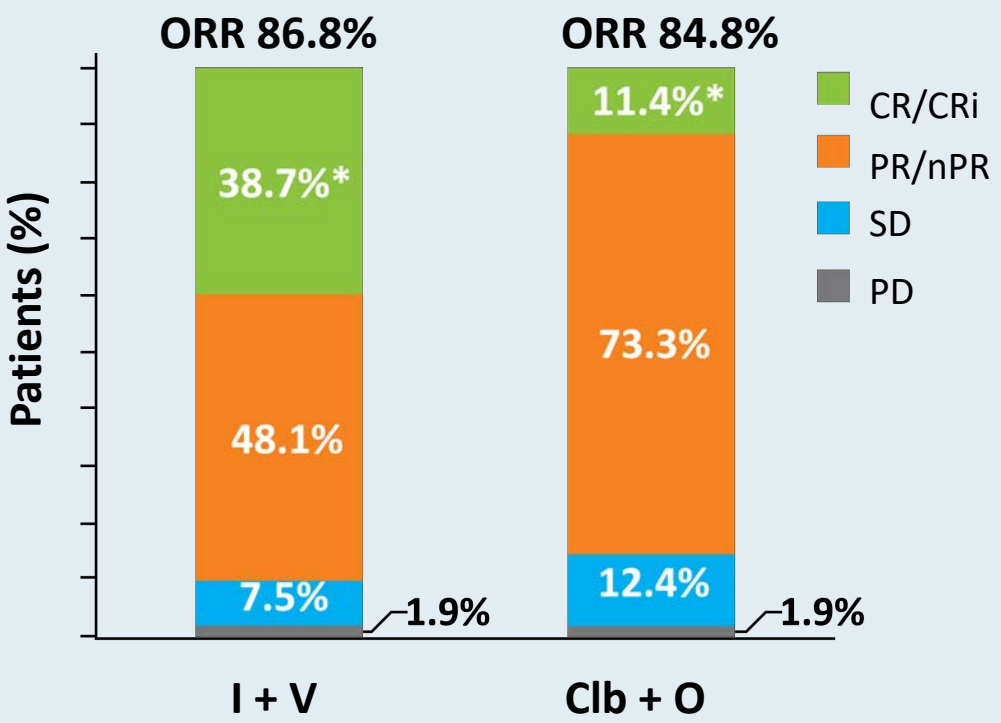


- **With a median follow up of 27.7 months, IRC-assessed PFS for I + V was superior to Clb + O**
- I + V reduced the risk of progression or death by 78% vs Clb + O
  - **HR 0.216** (95% CI, 0.131-0.357; $p < 0.0001$)
- PFS by INV assessment was consistent with IRC
  - **HR 0.207** (95% CI, 0.120-0.357;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

Kater AP et al. EHA 2021;Abstract LB1902.

GLOW: Overall Response Rates

Response by IRC



* $p < 0.0001$

- CR/CRi rates were significantly higher for I + V vs Clb + O by both IRC and INV assessments:
  - 38.7% vs 11.4% by IRC ($p < 0.0001$)
  - 45.3% vs 13.3% by IRC ($p < 0.0001$)
- Responses to I + V were more durable:
  - 90% of responders in the I + V arm sustained IRC response 24 months after initial response vs 41% in Clb + O arm

Kater AP et al. EHA 2021;Abstract LB1902.

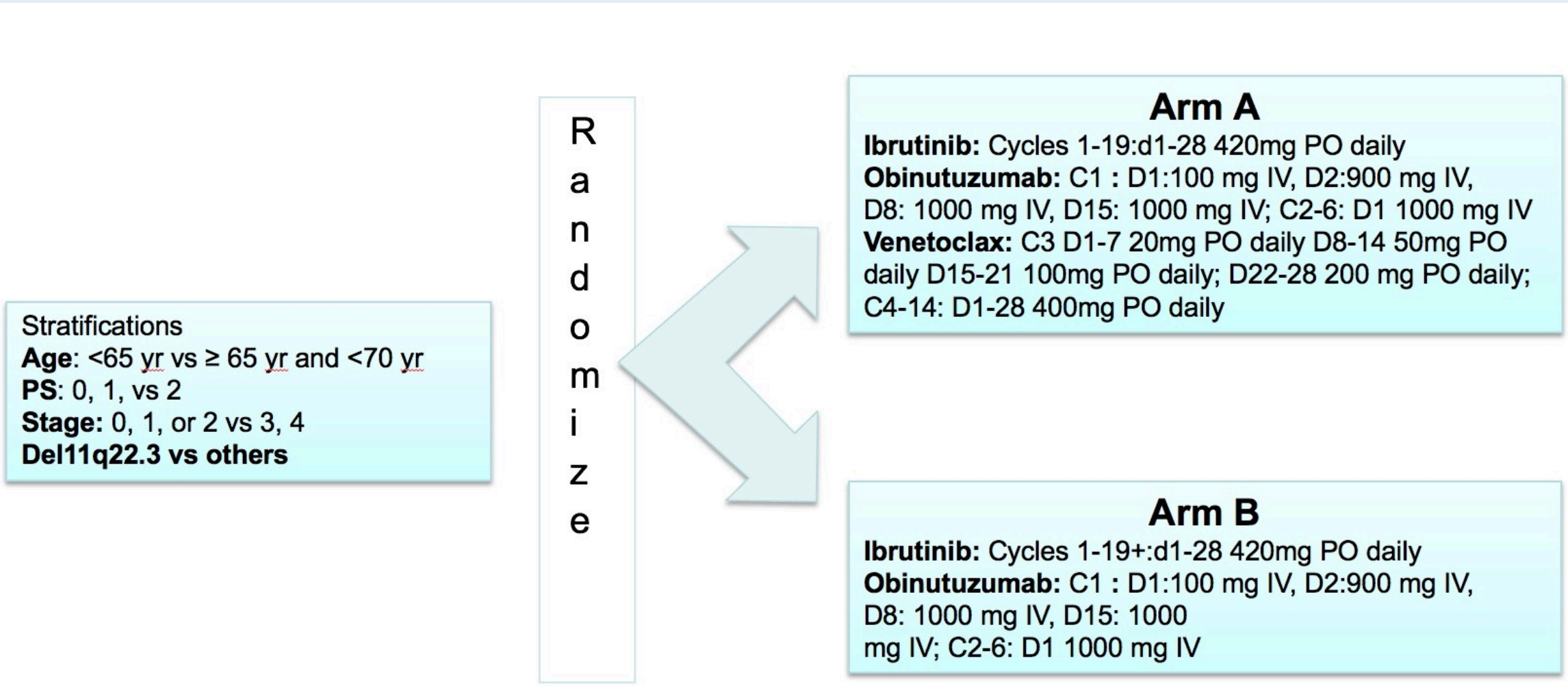
GLOW: Summary of Adverse Events and TLS Risk

	I + V (N = 106)	Clb + O (N = 105)
Median exposure, mo (range)	13.8 (0.7-19.5)	5.1 (1.8-7.9)
Any, %	75.5	69.5
Neutropenia	34.9	49.5
Infections	17.0	11.4
Thrombocytopenia	5.7	20.0
Diarrhea	10.4	1.0
Hypertension	5.7	0
TLS	0	5.7

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

Kater AP et al. EHA 2021;Abstract LB1902.

Phase III EA9161 Schema



Clinicaltrials.gov/ct2/show/NCT03701282?term=EA9161&draw=2&rank=1, Accessed March 1, 2021

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

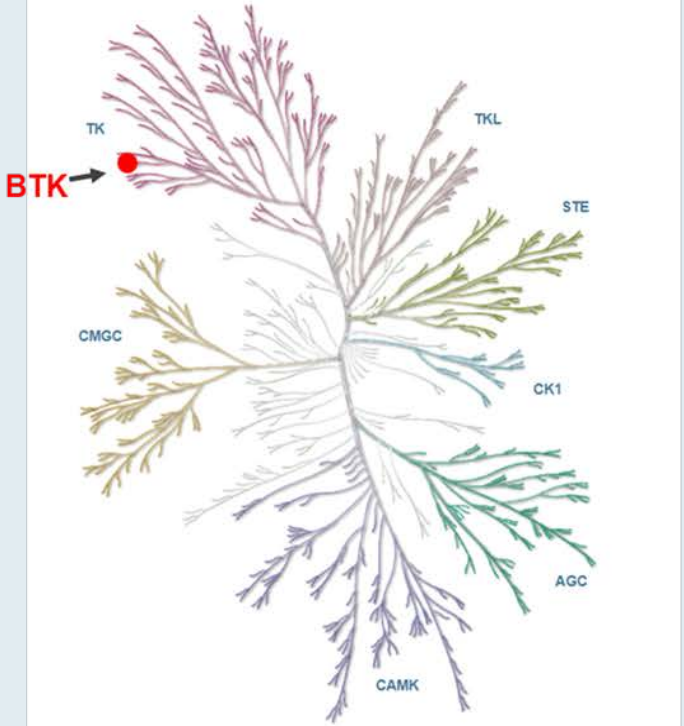
Mato AR et al.

ASH 2020;Abstract 542.

LOXO-305 is a Highly Potent and Selective Non-Covalent BTK Inhibitor

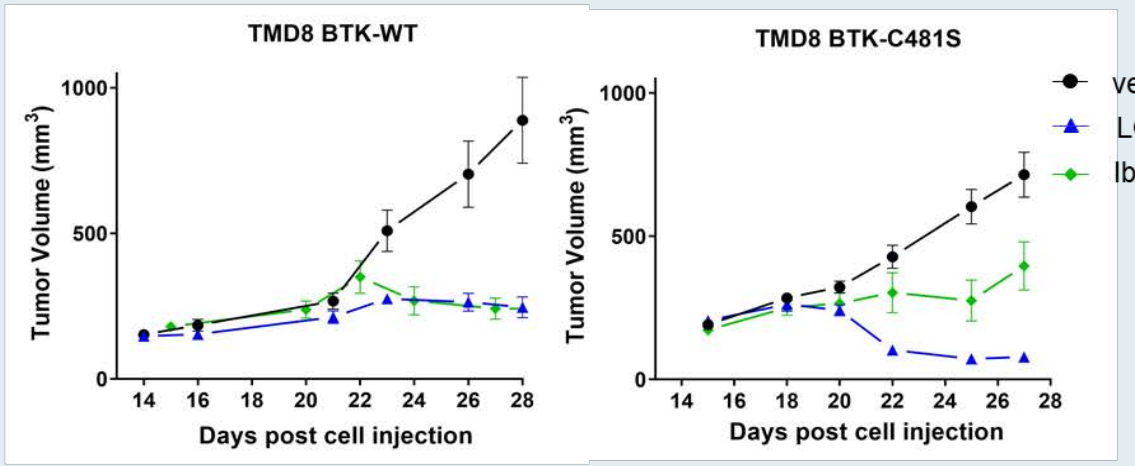
Kinome selectivity

Highly selective for BTK



Xenograft models

In vivo activity similarly efficacious as ibrutinib in WT; superior in C481S

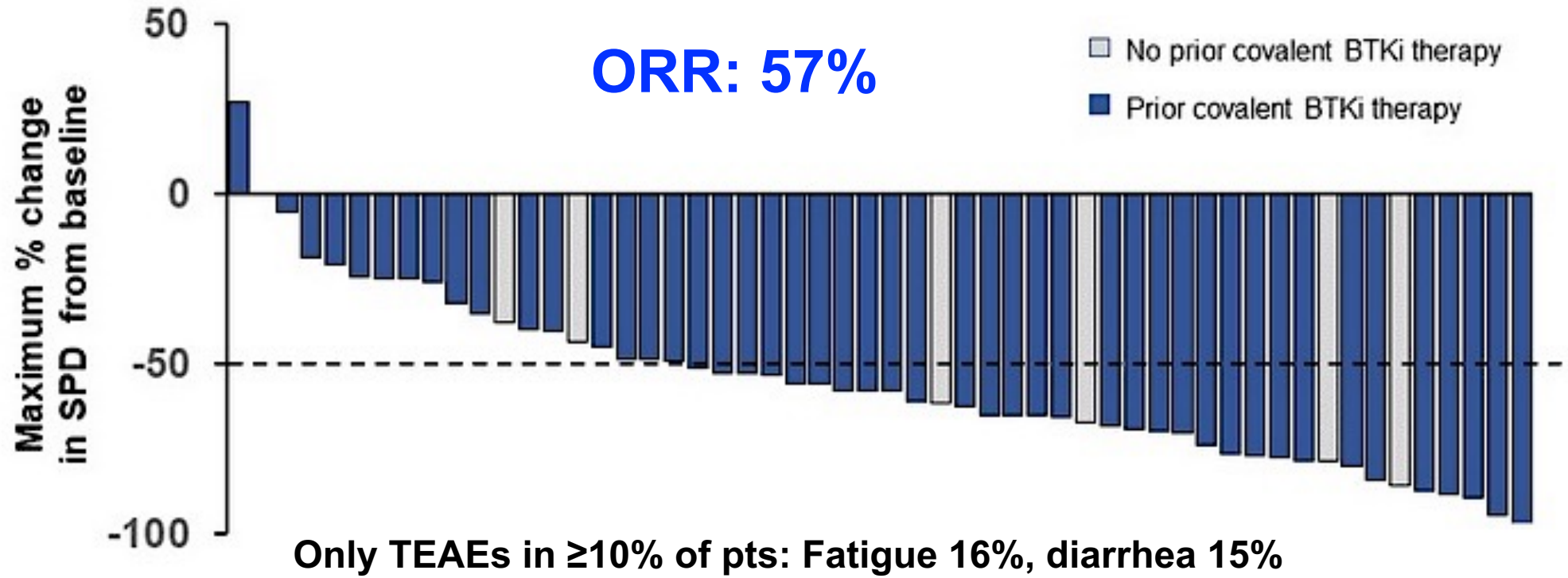


- Nanomolar potency against WT & C481-mutant BTK in cell and enzyme assays[1,2]
- >300-fold selectivity for BTK vs 370 other kinases[1]
- Due to reversible binding mode, BTK inhibition not impacted by intrinsic rate of BTK turnover[1]
- Favorable pharmacologic properties allow sustained BTK inhibition throughout dosing interval[1]

BID, twice-daily; BTK, Bruton tyrosine kinase. Illustration reproduced courtesy of Cell Signaling Technology, Inc. (www.cellsignal.com). [1]Brandhuber et al. *Clin. Lymphoma Myeloma Leuk.* 2018;18:S216. [2]Mato et al. *Blood.* 2019:134 (Suppl 1):501.

Mato AR et al. ASH 2020;Abstract 542.

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



Only TEAEs in ≥10% of pts: Fatigue 16%, diarrhea 15%

* 11 efficacy-evaluable pts are not included in the waterfall plot, including 1 pt who discontinued prior to first response assessment, and 10 pts (4 pts with PR/PR-L and 6 pts with SD) with incomplete tumor lesion measurement data at the time of data cut

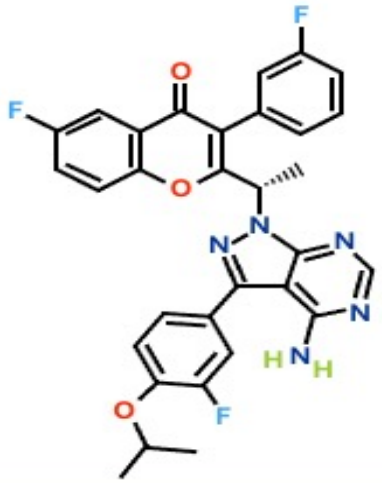
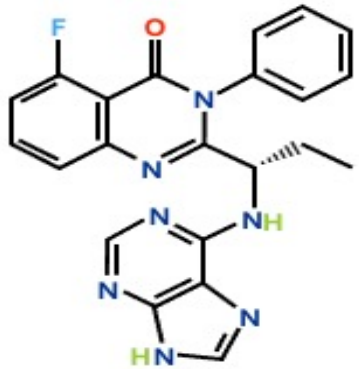
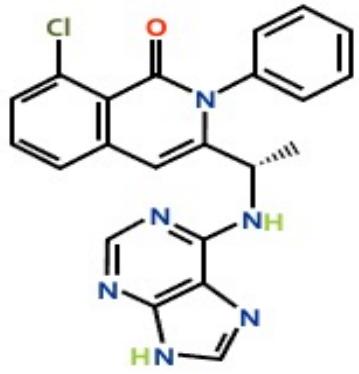
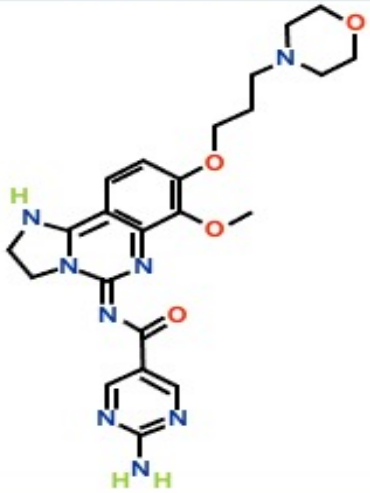
Mato AR et al. ASH 2020;Abstract 542.

Umbralisib plus Ublituximab (U2) Is Superior to Obinutuzumab plus Chlorambucil (O + Chl) in Patients with Treatment Naïve (TN) and Relapsed/Refractory (R/R) Chronic Lymphocytic Leukemia (CLL): Results from the Phase 3 Unity-CLL Study

Gribben JG et al.

ASH 2020;Abstract 543.

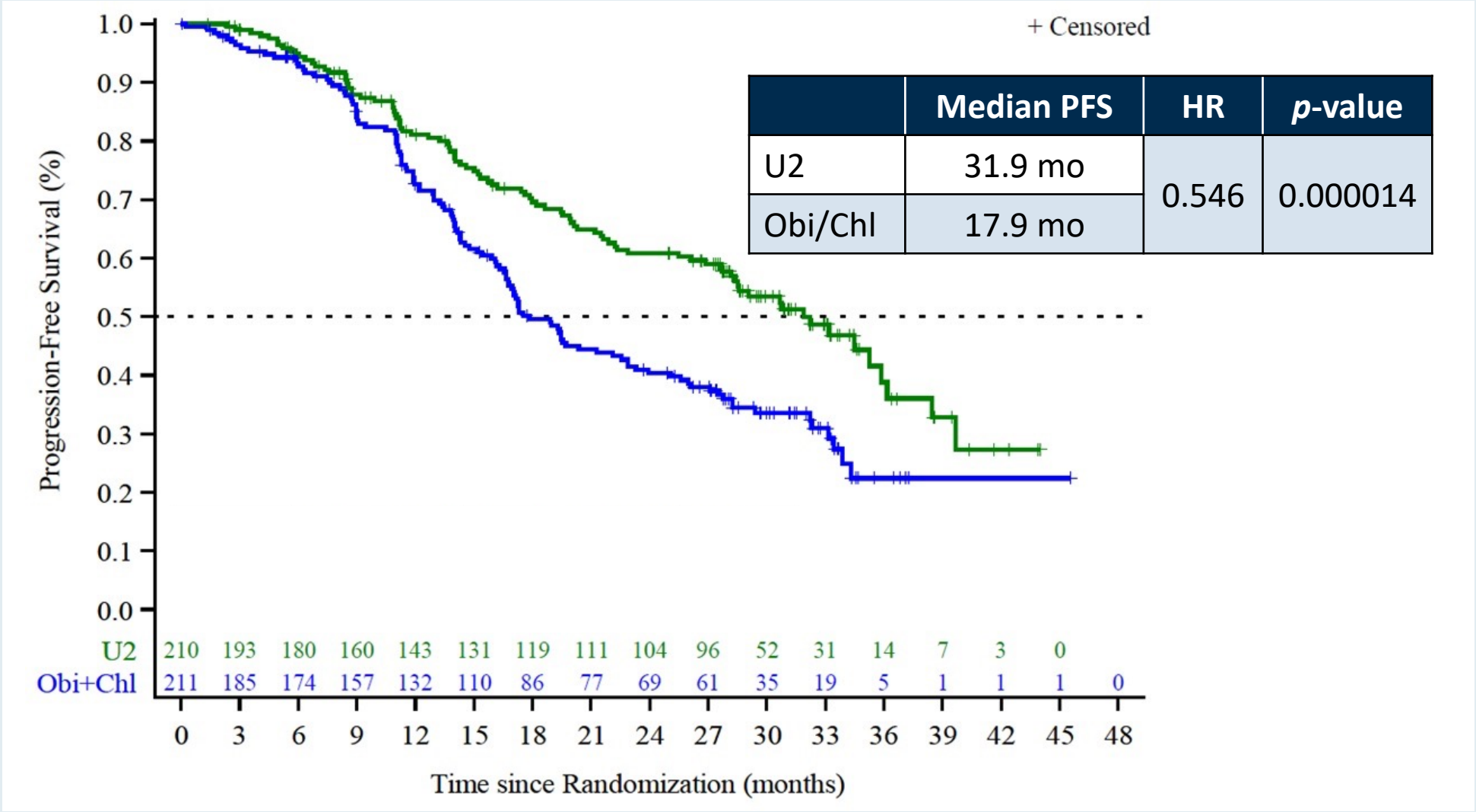
Umbralisib – Dual Inhibitor of PI3Kδ and CK1ε

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

- Umbralisib is an oral, once daily, dual inhibitor of PI3Kδ and CK1ε
- Umbralisib has >1000-fold greater selectivity for PI3Kδ compared to α and β isoforms[3]
- Umbralisib is also **>200-fold** more selective for PI3Kδ relative to **PI3Kγ**

Gribben JG et al. ASH 2020;Abstract 543.

UNITY-CLL: PFS with Umbralisib/Ublituximab (U2) versus Obinutuzumab/Chlorambucil



	Median PFS	HR	*p*-value
U2	31.9 mo	0.546	0.000014
Obi/Chl	17.9 mo		

Gribben JG et al. ASH 2020;Abstract 543.

TRANSCEND CLL 004: Phase 1 Cohort of Lisocabtagene Maraleucel (liso-cel) in Combination with Ibrutinib for Patients with Relapsed/Refractory (R/R) Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma (CLL/SLL)

William G. Wierda,[1] Kathleen A. Dorritie,[2] Javier Munoz,[3] Deborah M. Stephens,[4] Scott Solomon,[5] Heidi H. Gillenwater,[6] Lucy Gong,[6] Lin Yang,[6] Ken Ogasawara,[7] Jerill Thorpe,[6] Tanya Siddiqi[8]

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Presentation 544

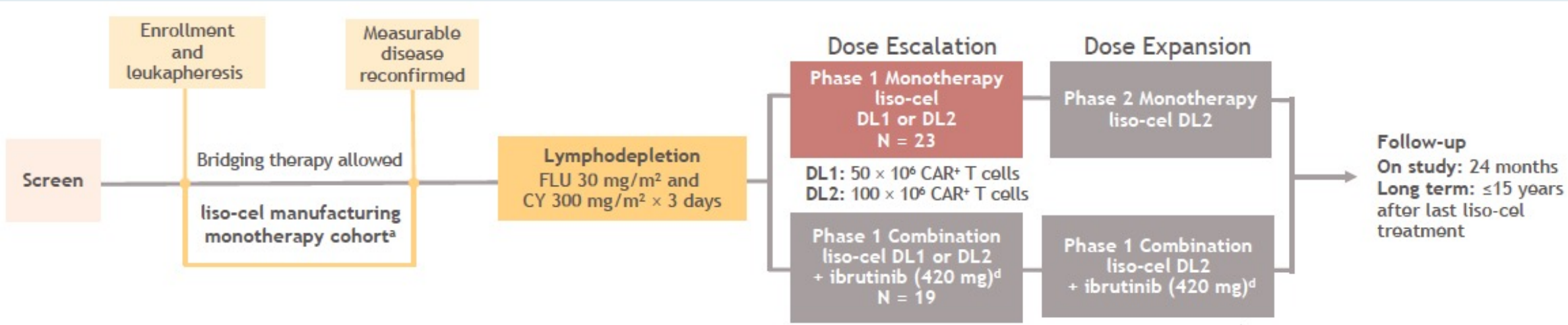
Updated Follow-Up of Patients with Relapsed/Refractory Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma Treated with Lisocabtagene Maraleucel in the Phase 1 Monotherapy Cohort of TRANSCEND CLL 004, Including High-Risk and Ibrutinib-Treated Patients

Tanya Siddiqi,[1] Jacob D. Soumerai,[2] Kathleen A. Dorritie,[3] Deborah M. Stephens,[4] Peter A. Riedell,[5] Jon Arnason,[6] Thomas J. Kipps,[7] Heidi H. Gillenwater,[8] Lucy Gong,[8] Lin Yang,[8] Ken Ogasawara,[9] William G. Wierda[10]

[1]City of Hope National Medical Center, Duarte, CA, USA; [2]Center for Lymphoma, Massachusetts General Hospital Cancer Center, Boston, MA, USA; [3]UPMC Hillman Cancer Center, University of Pittsburgh, Pittsburgh, PA, USA; [4]Huntsman Cancer Institute, University of Utah, Salt Lake City, UT, USA; [5]University of Chicago Medical Center, Chicago, IL, USA; [6]Beth Israel Deaconess Medical Center, Boston, MA, USA; [7]Moores Cancer Center, University of California San Diego Health, San Diego, CA, USA; [8]Bristol Myers Squibb, Seattle, WA, USA; [9]Bristol Myers Squibb, Princeton, NJ, USA; [10]The University of Texas MD Anderson Cancer Center, Houston, TX, USA

Presentation 546

TRANSCEND CLL 004: Study Design



Key Eligibility for Monotherapy Cohort

- R/R CLL/SLL
- Ineligible for BTKi or prior BTKi failure[b]
- High-risk disease[c]: ≥2 prior therapies failed
- Standard-risk disease: ≥3 prior therapies failed
- ECOG PS of 0–1

Dose Escalation: mTPI-2 Design[2]

28-day dose-limiting toxicity period

Primary objectives

- Safety
- Determine recommended dose

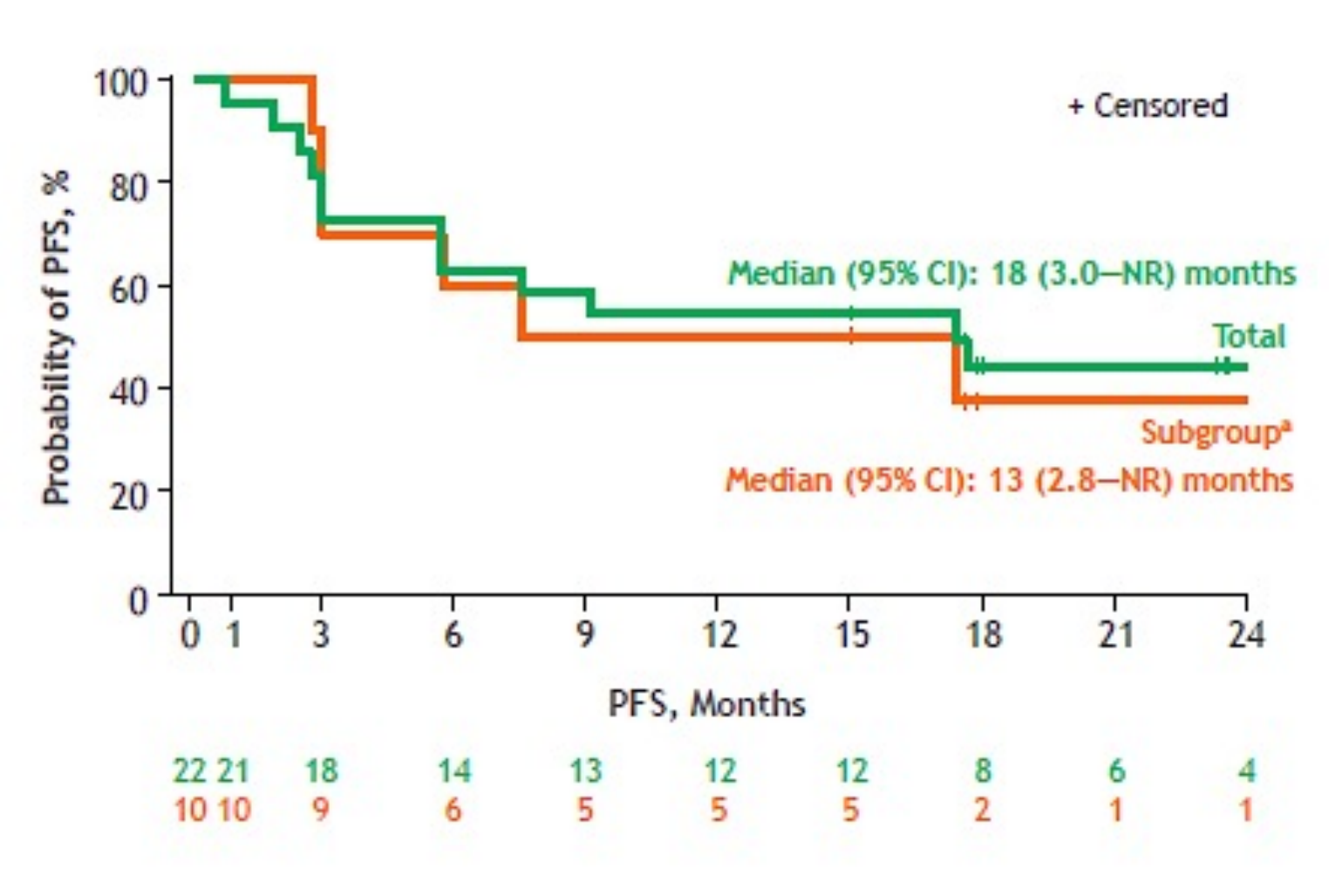
Exploratory objectives

- Antitumor activity (iwCLL 2018)[3]
  - Testing for MRD[e]
- Cellular kinetic profile (qPCR)

Wierda WG et al. ASH 2020;Abstract 544; Siddiqi T et al. ASH 2020;Abstract 546.

RTP RESEARCH TO PRACTICE

TRANSCEND CLL 04: Liso-cel Monotherapy Cohort



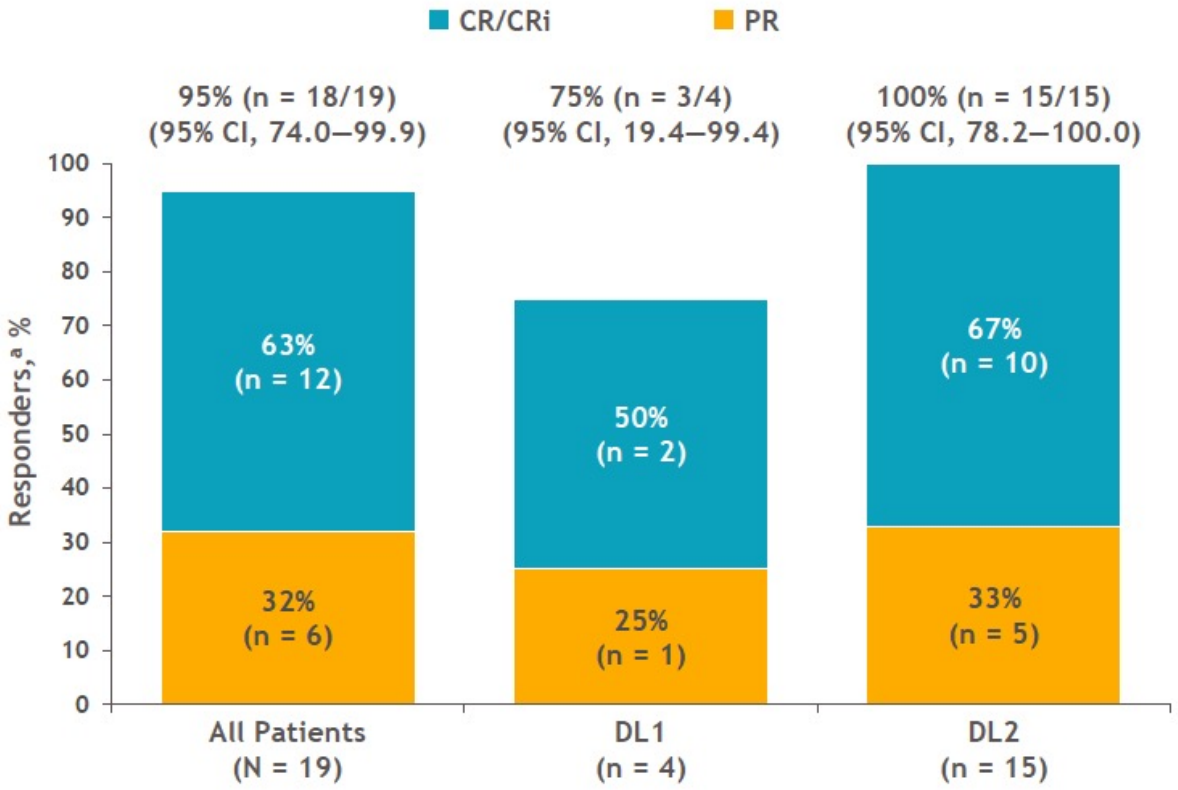
- ORR/CR = 82%/68%
- Median PFS 13 mo and DOR 50% at 12 mo
- Gr 3 CRS= 9% and NE 22% (No Grade 4/5)
- 4 of 6 progressions due to RT

Siddiqi T et al. ASH 2020;Abstract 546.

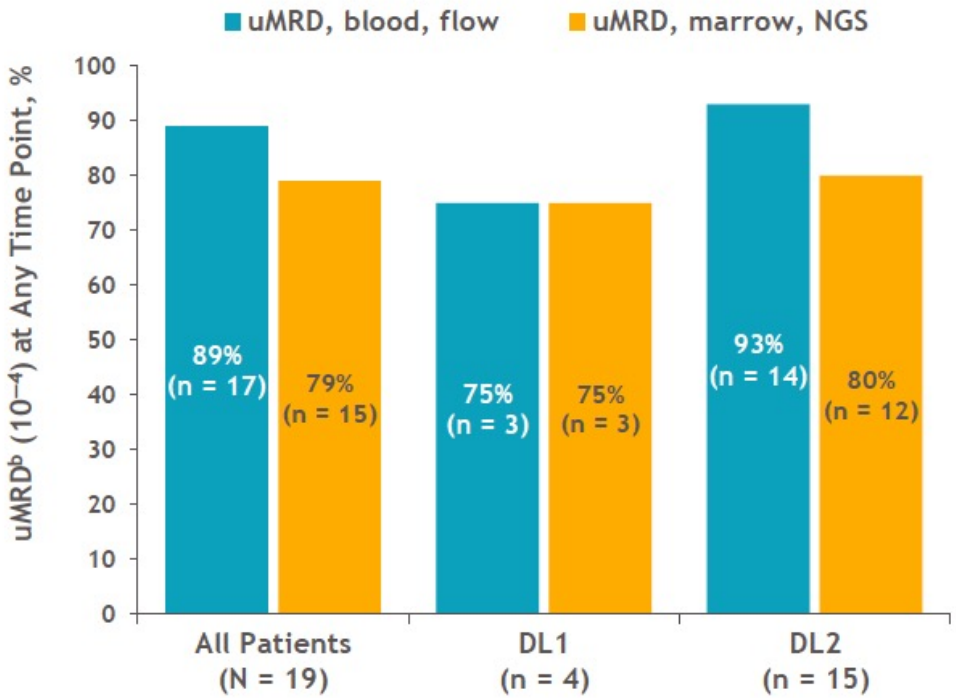
RTP RESEARCH TO PRACTICE

TRANSCEND CLL 04: Liso-cel and Ibrutinib Cohort

Best Overall Response



Undetectable Minimal Residual Disease



- No patients had PD during the first month after liso-cel
- One patient at DL1 had SD for 6 months but later progressed

Weirda WG et al. ASH 2020;Abstract 544.

RTP RESEARCH TO PRACTICE

Data + Perspectives: Clinical Investigators Discuss the Current and Future Management of Non-Hodgkin Lymphoma

A Virtual CME Satellite Symposium Series in Conjunction with the Society of Hematologic Oncology 2021 Annual Meeting

Tuesday, August 31, 2021
7:00 PM – 8:00 PM ET

Faculty

Andrew M Evens, DO, MSc
Ian W Flinn, MD, PhD
Gilles Salles, MD, PhD

Moderator

Neil Love, MD

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Thank you for joining us!

CME credit information will be emailed to each participant shortly.

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