Year in Review – Clinical Investigator Perspectives on the Most Relevant New Data Sets and Advances in Oncology:

Chronic Lymphocytic Leukemia

Tuesday, January 25, 2022
5:00 PM – 6:00 PM ET

Faculty

Lindsey Roeker, MD
Jeff Sharman, MD

Moderator

Neil Love, MD

RTP Year in Review 2022

YiR Chronic Lymphocytic Leukemia Faculty

Lindsey Roeker, MD
Assistant Attending Physician
Memorial Sloan Kettering Cancer Center
New York, New York

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

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Dr Love — Disclosures

Dr Love is president and CEO of Research To Practice. Research To Practice receives funds in the form of educational grants to develop CME activities from the following companies: AbbVie Inc, Adaptive Biotechnologies Corporation, ADC Therapeutics, Agios Pharmaceuticals Inc, Alexion Pharmaceuticals, Amgen Inc, Array BioPharma Inc, a subsidiary of Pfizer Inc, Astellas, AstraZeneca Pharmaceuticals LP, Aveo Pharmaceuticals, Bayer HealthCare Pharmaceuticals, BeiGene Ltd, BeyondSpring Pharmaceuticals Inc, Blueprint Medicines, Boehringer Ingelheim Pharmaceuticals Inc, Bristol-Myers Squibb Company, Celgene Corporation, Clovis Oncology, Coherus BioSciences, CTI BioPharma Corp, Daiichi Sankyo Inc, Eisai Inc, EMD Serono Inc, Epizyme Inc, Exact Sciences Inc, Exelixis Inc, Five Prime Therapeutics Inc, Foundation Medicine, G1 Therapeutics Inc, Genentech, a member of the Roche Group, Genmab, Gilead Sciences Inc, GlaxoSmithKline, Grail Inc, Halozyme Inc, Helsinn Healthcare SA, ImmunoGen Inc, Incyte Corporation, Ipsen Biopharmaceuticals Inc, Janssen Biotech Inc, administered by Janssen Scientific Affairs LLC, Jazz Pharmaceuticals Inc, Karyopharm Therapeutics, Kite, A Gilead Company, Lilly, Loxo Oncology Inc, a wholly owned subsidiary of Eli Lilly & Company, Merck, Mersana Therapeutics Inc, Natera Inc, Novartis, Novocure Inc, Oncopeptides, Pfizer Inc, Pharmacyclics LLC, an AbbVie Company, Puma Biotechnology Inc, Regeneron Pharmaceuticals Inc, Sanofi Genzyme, Seagen Inc, Servier Pharmaceuticals LLC, Sumitomo Dainippon Pharma Oncology Inc, Taiho Oncology Inc, Takeda Pharmaceuticals USA Inc, Tesaro, A GSK Company, TG Therapeutics Inc, Turning Point Therapeutics Inc, Verastem Inc and Zymeworks Inc.

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Contracted Research	Aptose Biosciences, Loxo Oncology Inc, a wholly owned subsidiary of Eli Lilly & Company, Pfizer Inc
Ownership Interest	Abbott Laboratories

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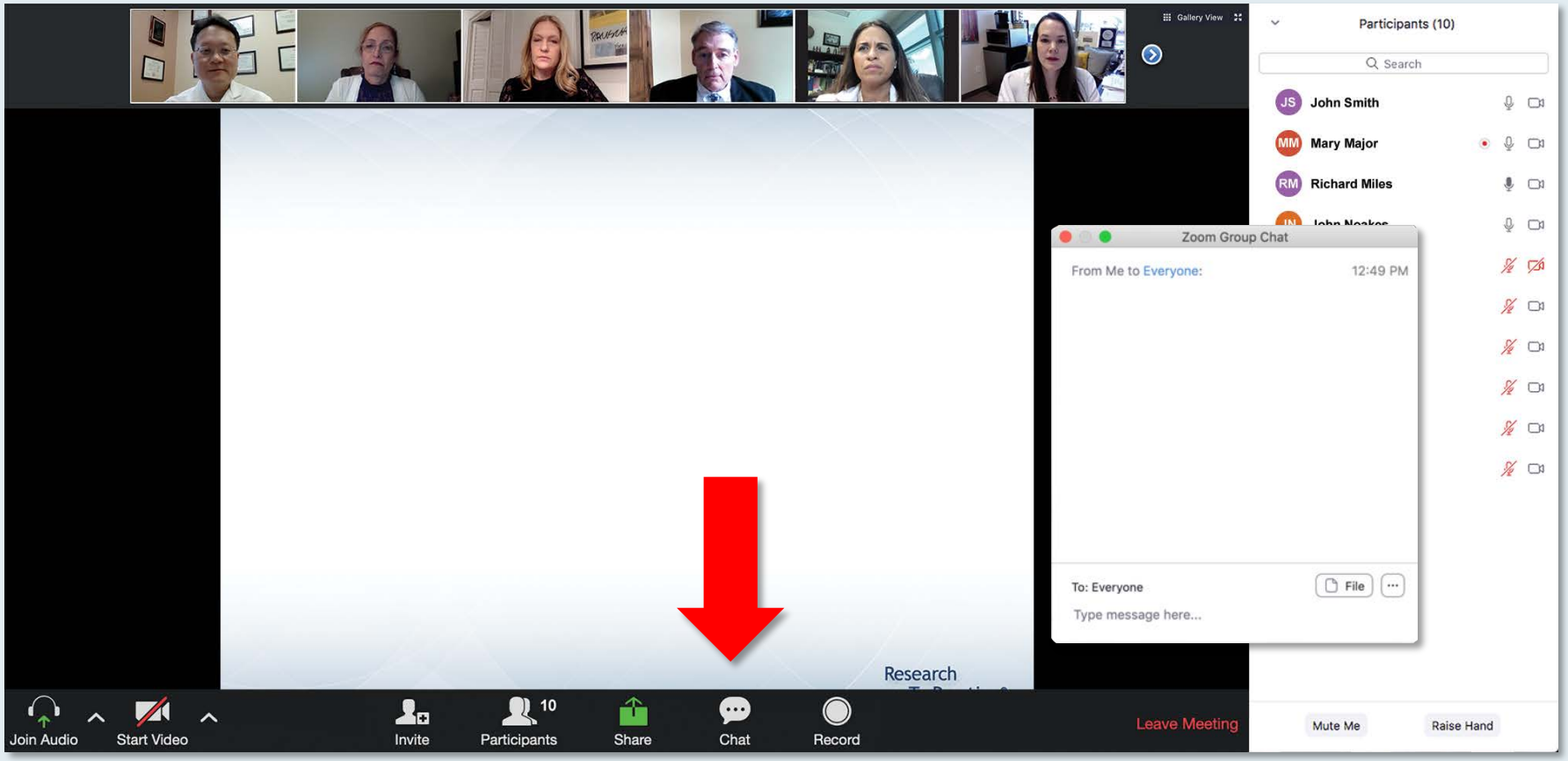
We Encourage Clinicians in Practice to Submit Questions



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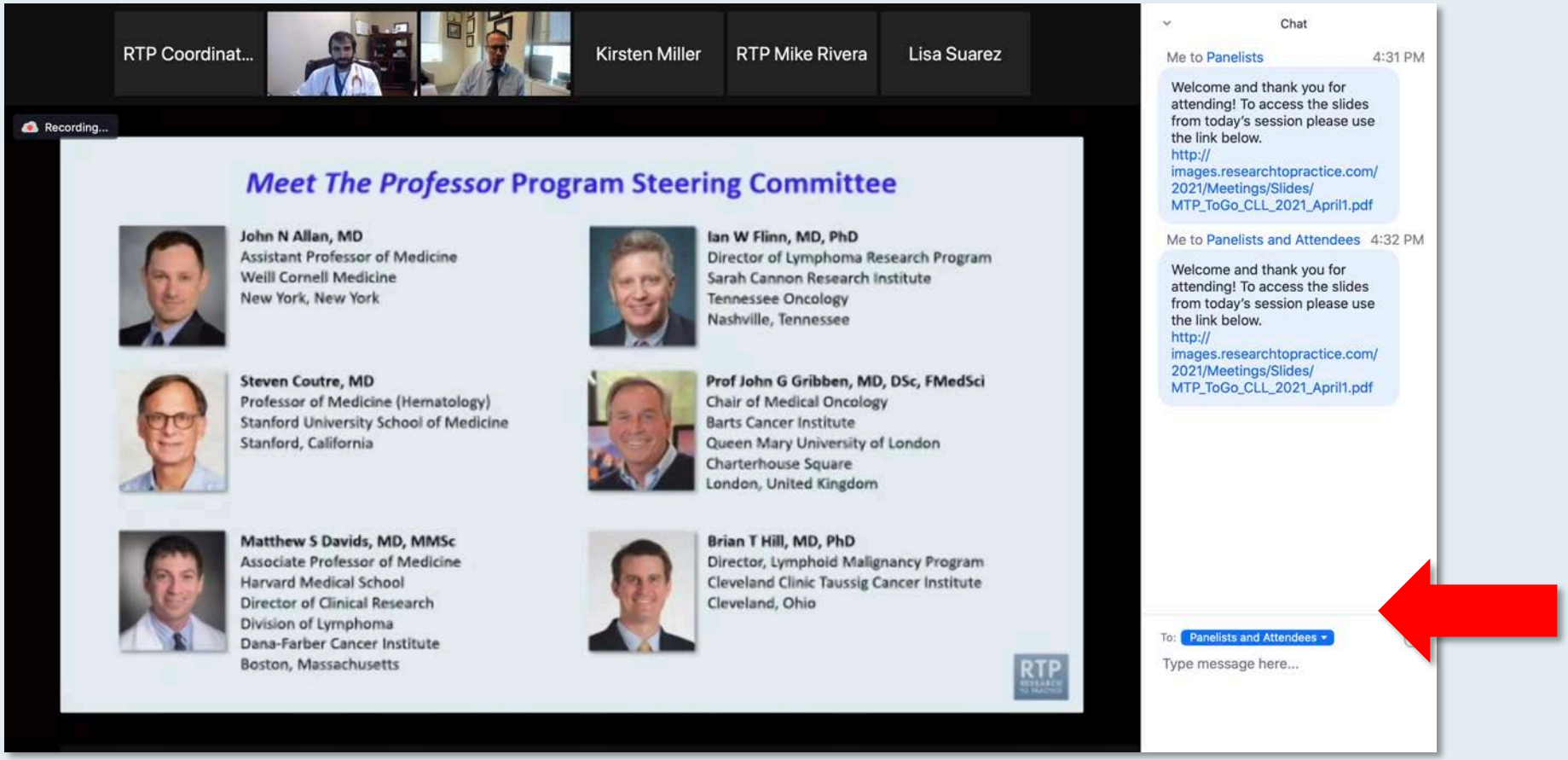
Expand chat submission box



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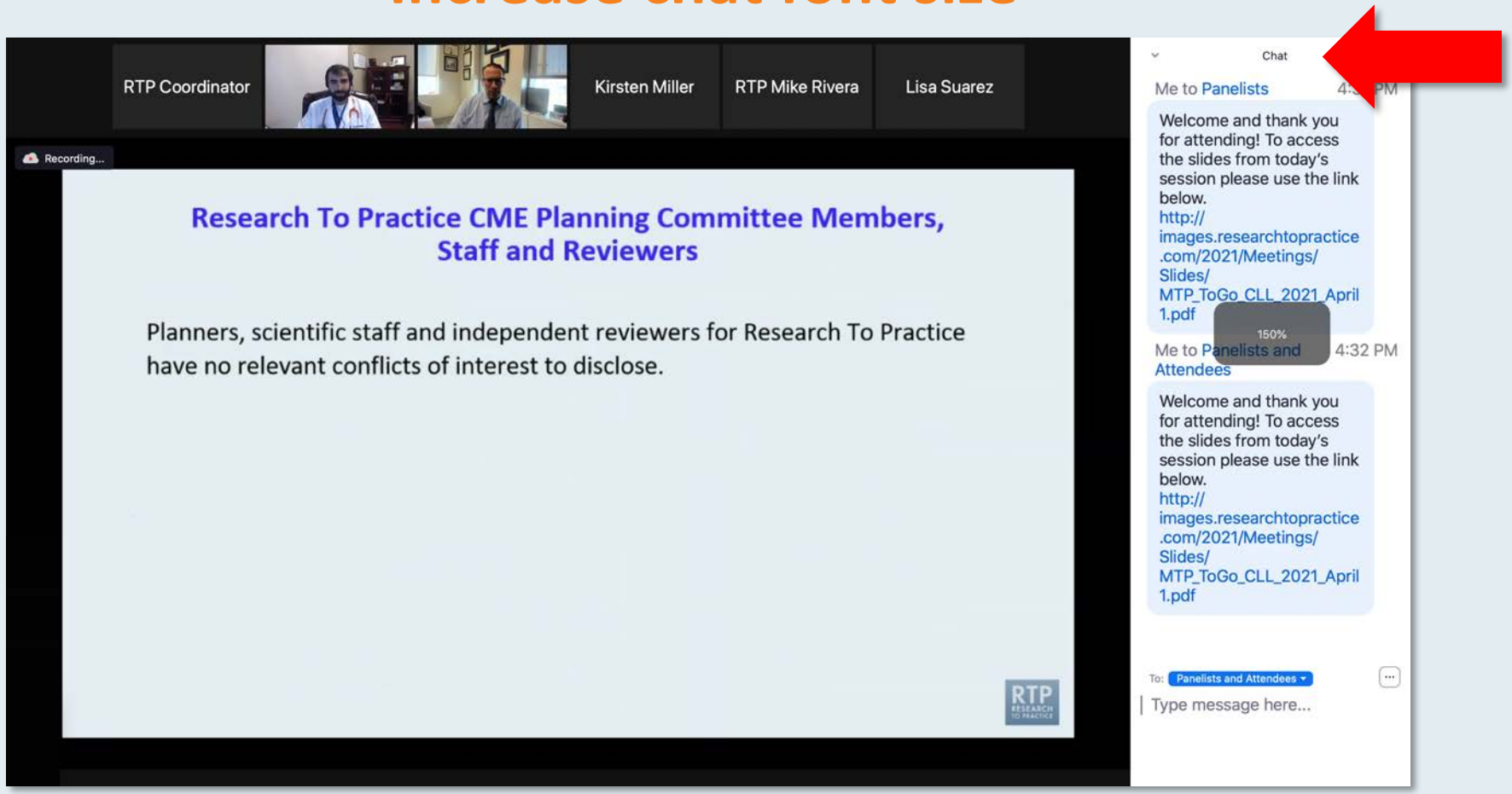

Press Command (for Mac) or Control (for PC) and the + symbol.
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ONCOLOGY TODAY

WITH DR NEIL LOVE

Chronic Lymphocytic Leukemia

DR PETER HILLMEN
UNIVERSITY OF LEEDS

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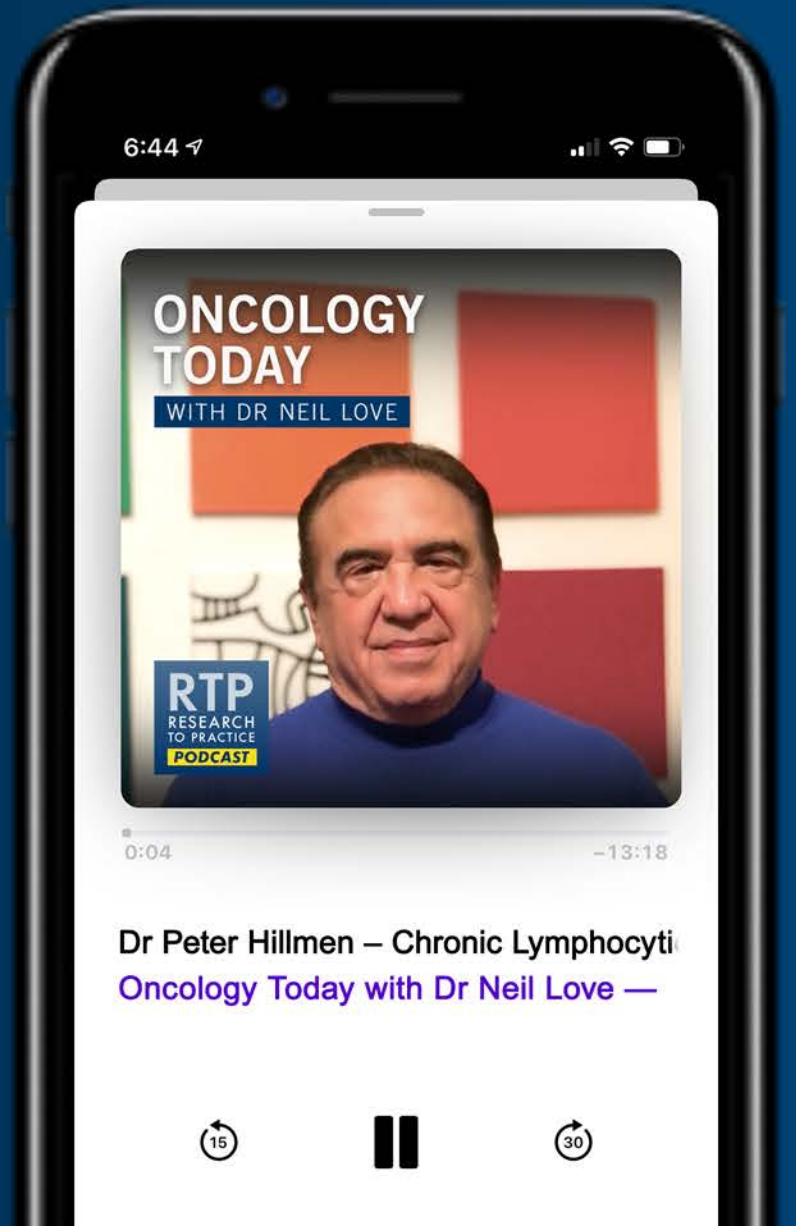

Promising Investigational Agents and Strategies for Patients with Metastatic Non-Small Cell Lung Cancer Who Experience Disease Progression on Immune Checkpoint Inhibitor Therapy

Wednesday, January 26, 2022
5:00 PM – 6:00 PM ET

Faculty

Edward B Garon, MD, MS

Moderator

Neil Love, MD

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Year in Review – Clinical Investigator Perspectives on the Most Relevant New Data Sets and Advances in Oncology:

Acute Myeloid Leukemia and Myelodysplastic Syndromes

Thursday, January 27, 2022
5:00 PM – 6:00 PM ET

Faculty

Daniel A Pollyea, MD, MS
Gail J Roboz, MD

Moderator

Neil Love, MD

RTP Year in Review 2022

Year in Review – Clinical Investigator Perspectives on the Most Relevant New Data Sets and Advances in Oncology: Gastric, Gastroesophageal Junction and Esophageal Cancer

Tuesday, February 1, 2022
5:00 PM – 6:00 PM ET

Faculty

David H Ilson, MD, PhD

Zev Wainberg, MD, MSc

Moderator

Neil Love, MD

RTP Year in Review 2022

Exploring the Current and Changing Paradigm for the Management of Newly Diagnosed Diffuse Large B-Cell Lymphoma

Wednesday, February 2, 2022
5:00 PM – 6:00 PM ET

Faculty

Christopher R Flowers, MD, MS
Neha Mehta-Shah, MD, MSCI
Grzegorz Nowakowski, MD

Moderator

Neil Love, MD

RTP RESEARCH TO PRACTICE

Exploring the Current and Future Role of B-Cell Maturation Antigen-Directed Therapy in the Management of Multiple Myeloma

Monday, February 7, 2022
5:00 PM – 6:00 PM ET

Faculty

Jesús G Berdeja, MD
Noopur Raje, MD

Moderator

Neil Love, MD

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Key Considerations in the Optimal Clinical Care of Patients with Small Cell Lung Cancer

Wednesday, February 9, 2022
5:00 PM – 6:00 PM ET

Faculty

Luis Paz-Ares, MD, PhD
Jared Weiss, MD

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 5 business days.

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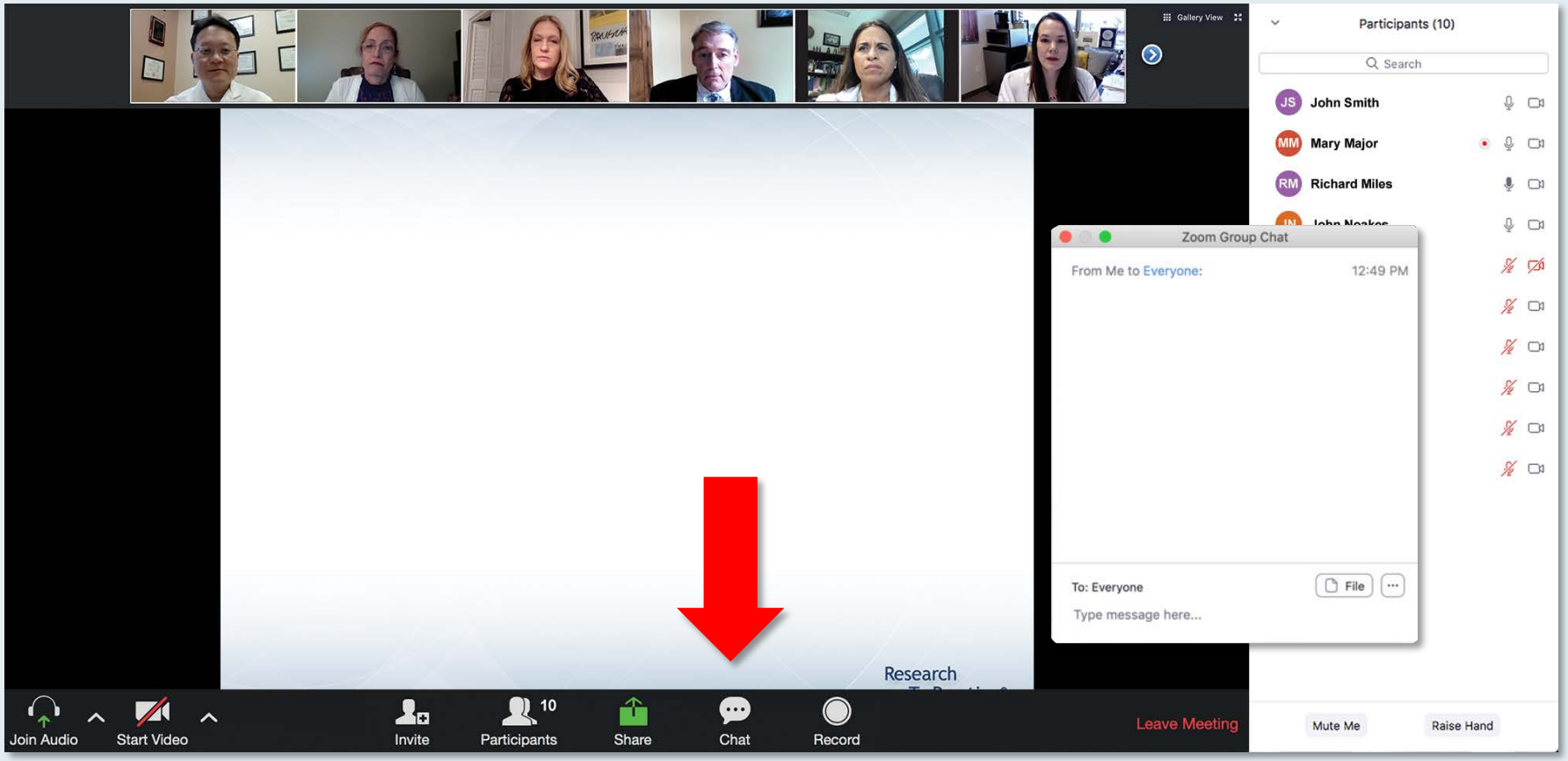

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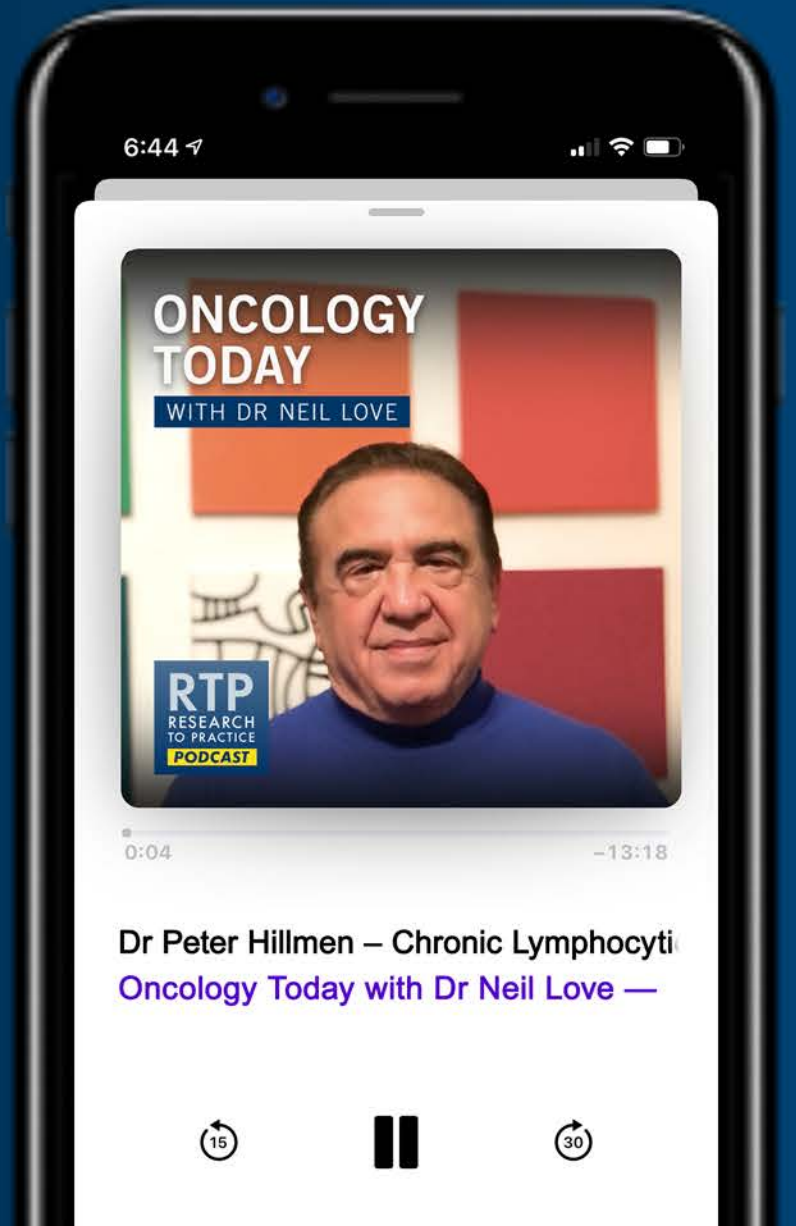

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Agenda

Module 1: Current and Future Selection of First-Line Therapy for Chronic Lymphocytic Leukemia (CLL)

Module 2: Management of Relapsed/Refractory CLL

Module 3: Novel Investigational Strategies


Steven Coutre, MD

To what extent is COVID-19 currently affecting your ability to staff your outpatient clinic?

1. Not at all
2. Minimally
3. Moderately
4. A great deal

LETTER TO BLOOD | NOVEMBER 4, 2021

COVID-19 in patients with CLL: improved survival outcomes and update on management strategies

Clinical Trials & Observations

Lindsey E. Roeker, Toby A. Eyre, Meghan C. Thompson, Nicole Lamanna, Alexander R. Coltoff, Matthew S. Davids, Peter O. Baker, Lori Leslie, Kerry A. Rogers, John N. Allan, Raul Cordoba, Alberto Lopez-Garcia, Darko Antic, John M. Pagel, Nicolas Martinez-Calle, José Antonio García-Marco, Jose-Ángel Hernández-Rivas, Fatima Miras, Catherine C. Coombs, Anders Österborg, Lotta Hansson, Amanda N. Seddon, Javier López Jiménez, Matthew R. Wilson, Dima El-Sharkawi, Daniel Wojenski, Shuo Ma, Talha Munir, Susana Valenciano, Erlene Seymour, Paul M. Barr, Jeffrey Pu, Piers E. M. Patten, Guilherme F. Perini, Scott F. Huntington, Helen Parry, Suchitra Sundaram, Alan Skarbnik, Manali Kamdar, Ryan Jacobs, Harriet Walter, Renata Walewska, Angus Broom, Sonia Lebowitz, Krista M. Isaac, Craig A. Portell, Inhye E. Ahn, Chaitra S. Ujjani, Mazyar Shadman, Sigrid S. Skånland, Elise A. Chong, Anthony R. Mato

Blood (2021) 138 (18): 1768–1773.

- International collaboration – real world series across 45 centers
- 374 patients with CLL diagnosed with COVID-19 between 2/17/2020 and 2/1/2021
- “Early cohort” = diagnosed from 2/17/20 – 4/30/20
- “Later cohort” = diagnosed from 5/1/20 – 2/1/21

Roeker LE et al. Blood 2021;138(18):1768-73.

Courtesy of Lindsey Roeker, MD

Conclusions:

Impact on patient care and treatment algorithms

- COVID-19 related mortality has fallen over time, mirroring population-based studies
- COVID directed therapies may be associated with outcomes that vary from a general population to those with CLL

Implications for future research

- COVID-19 directed therapy may have different outcomes in patients with CLL than other hosts, require study of disease-specific outcomes

Courtesy of Lindsey Roeker, MD

Agenda

Module 1: Current and Future Selection of First-Line Therapy for Chronic Lymphocytic Leukemia (CLL)

Module 2: Management of Relapsed/Refractory CLL

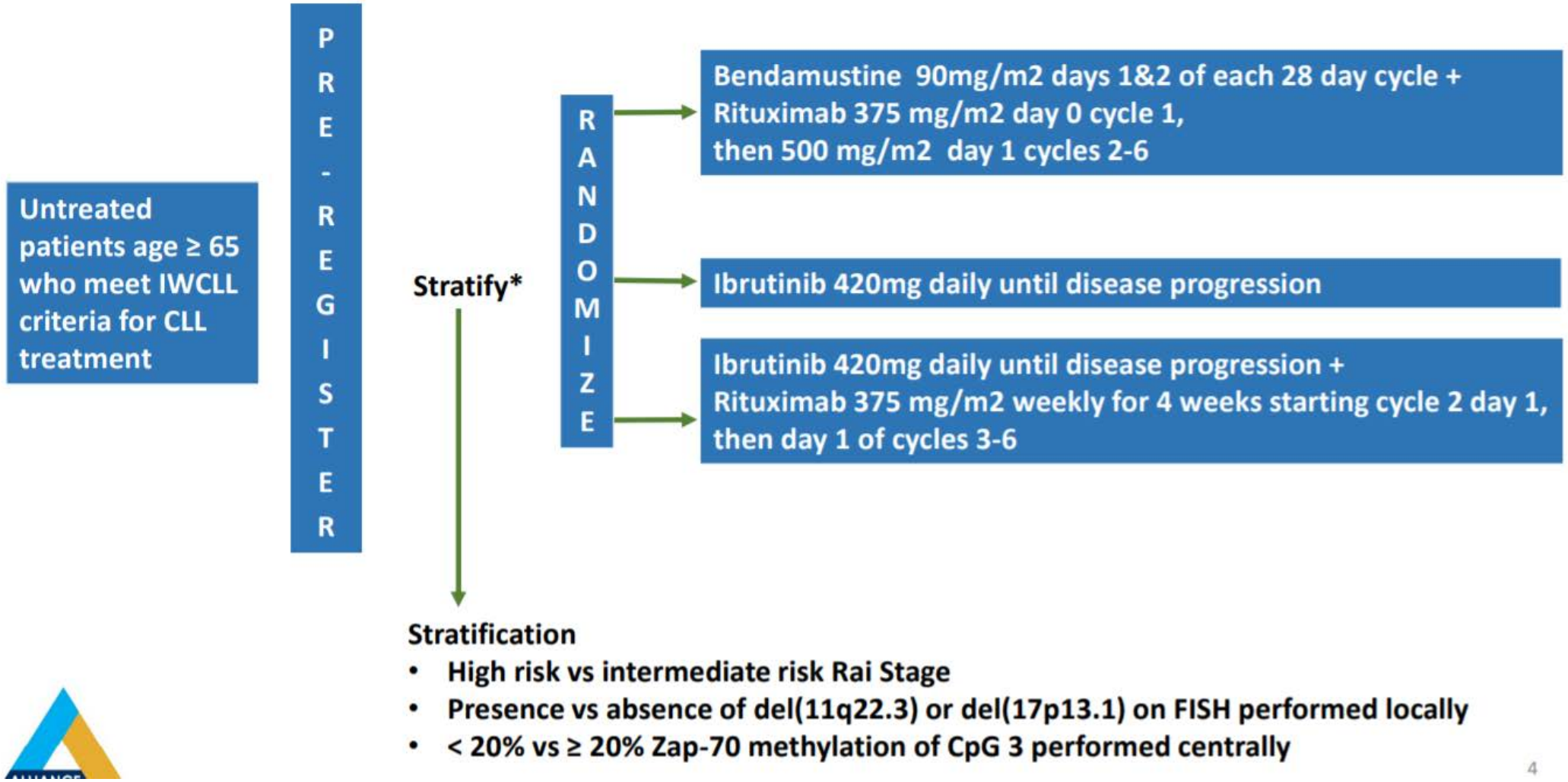
Module 3: Novel Investigational Strategies

Agenda

Module 1: Current and Future Selection of First-Line Therapy for Chronic Lymphocytic Leukemia (CLL)

- ALLIANCE Study: IR versus I versus BR
- FLAIR Study: FCR versus IR
- Novel formulation of acalabrutinib
- ELEVATE-TN: Acalabrutnib plus obinutuzumab
- SEQUOIA: Frontline zanubrutinib
- Zanubrutinib monotherapy in 17P deletion disease
- BTK updates
- Venetoclax updates
- BTK inhibitors plus venetoclax

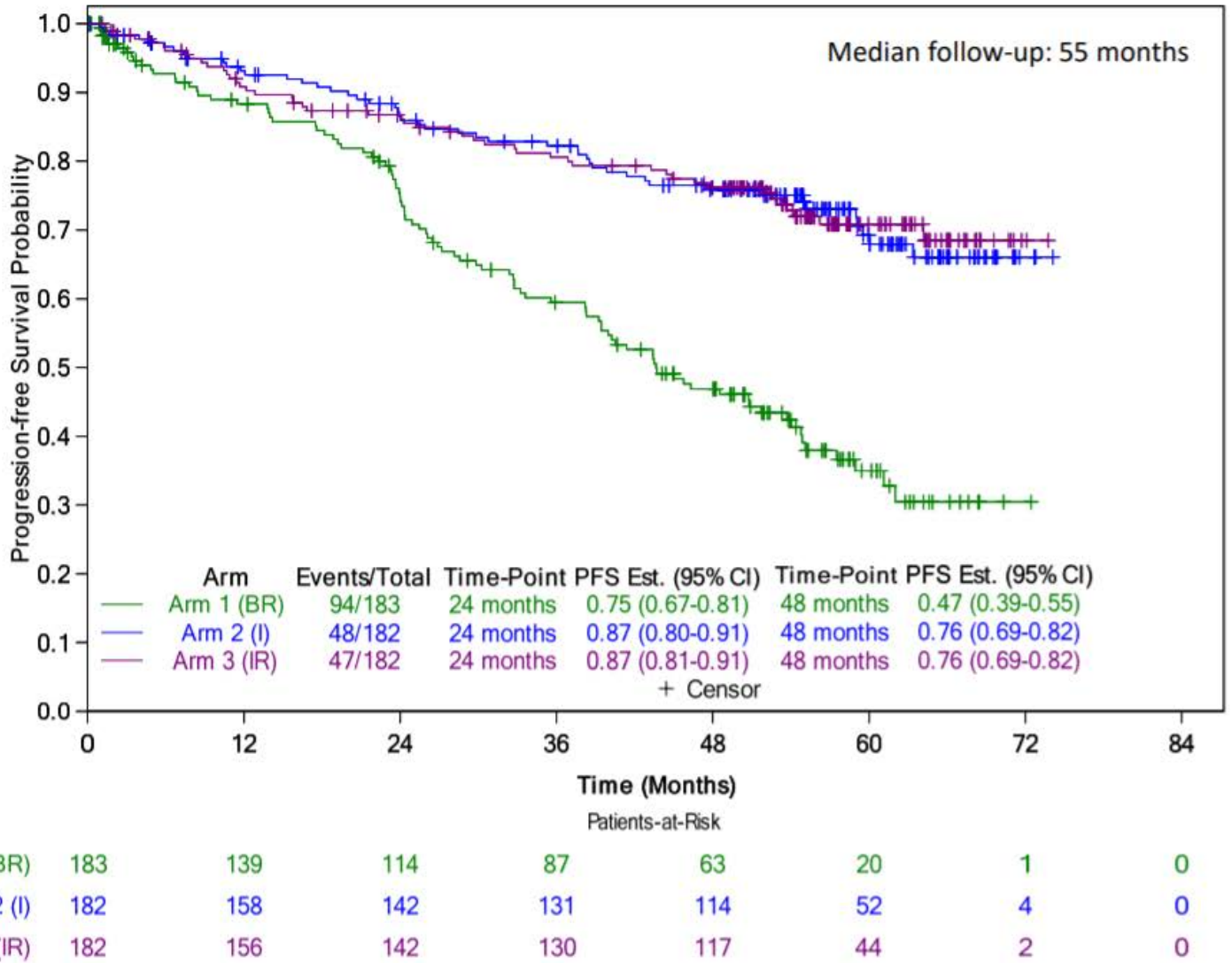
Alliance Study (IR vs I vs BR)



Courtesy of Jeff Sharman, MD

Woyach 2021

Alliance Study



Pairwise Comparisons

I vs BR:
Hazard Ratio 0.36
95% CI: 0.26-0.52
P <0.0001

IR vs BR:
Hazard Ratio 0.36
95% CI: 0.25-0.51
P <0.0001

IR vs I:
Hazard Ratio 0.99
95% CI: 0.66-1.48
P = 0.96

Courtesy of Jeff Sharman, MD

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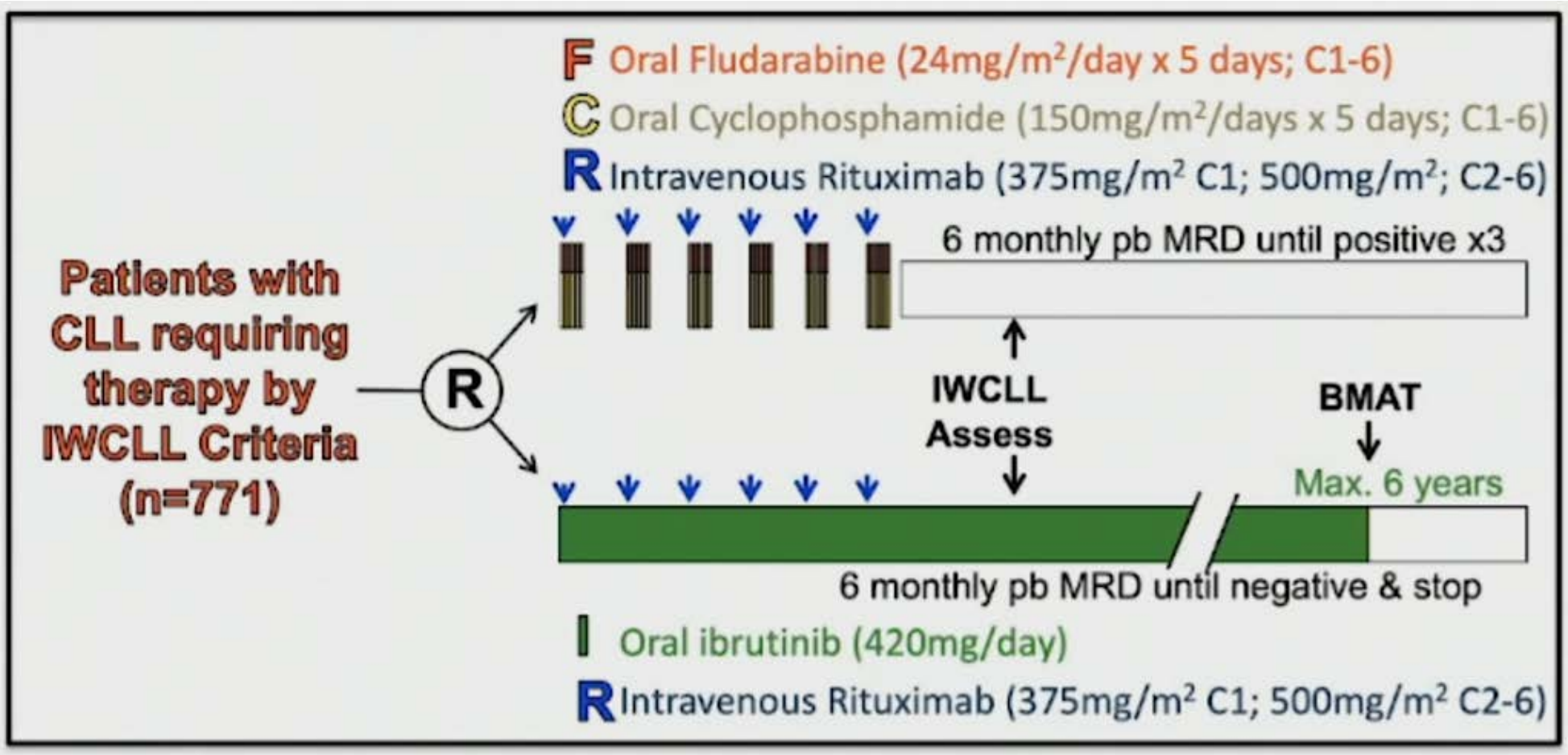
UK Flair Study: IR vs FCR



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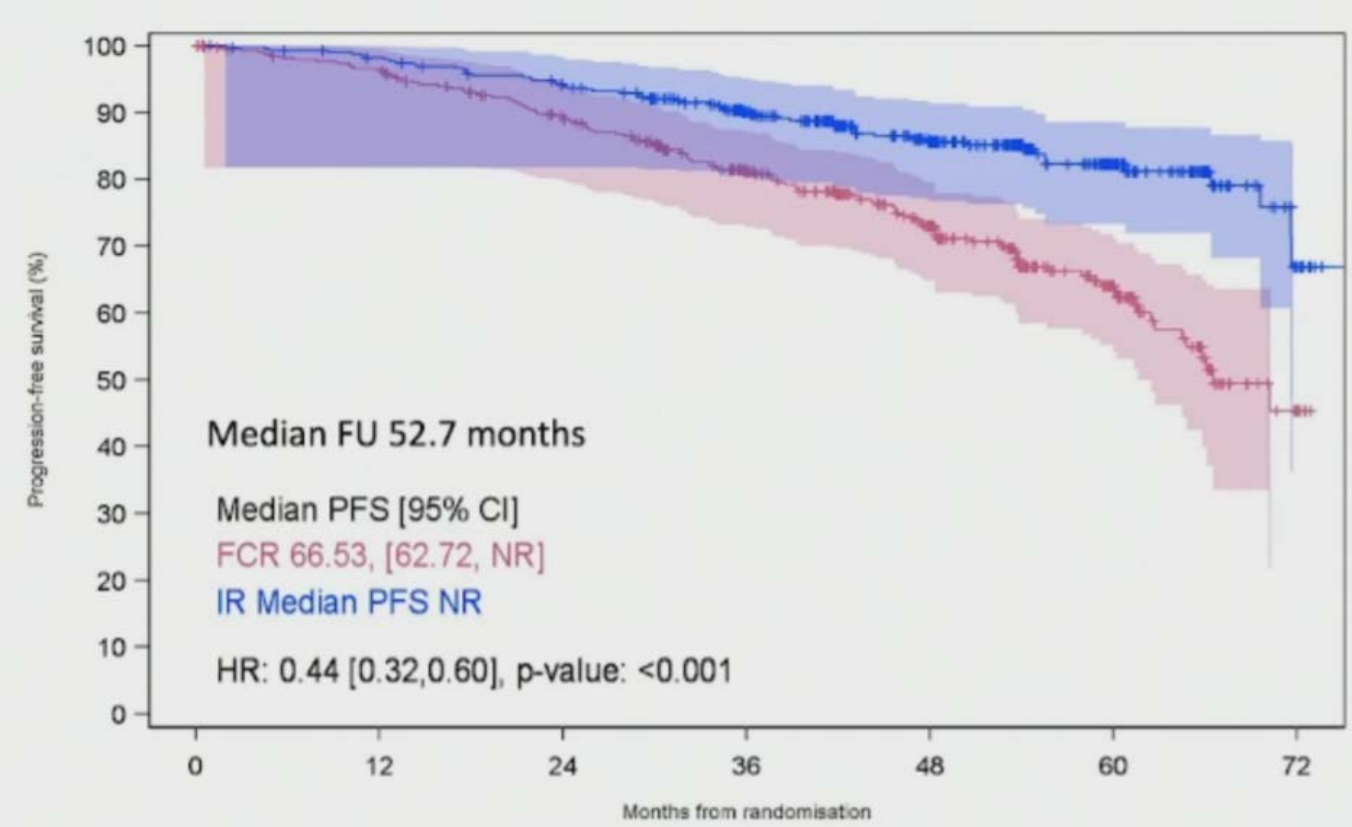
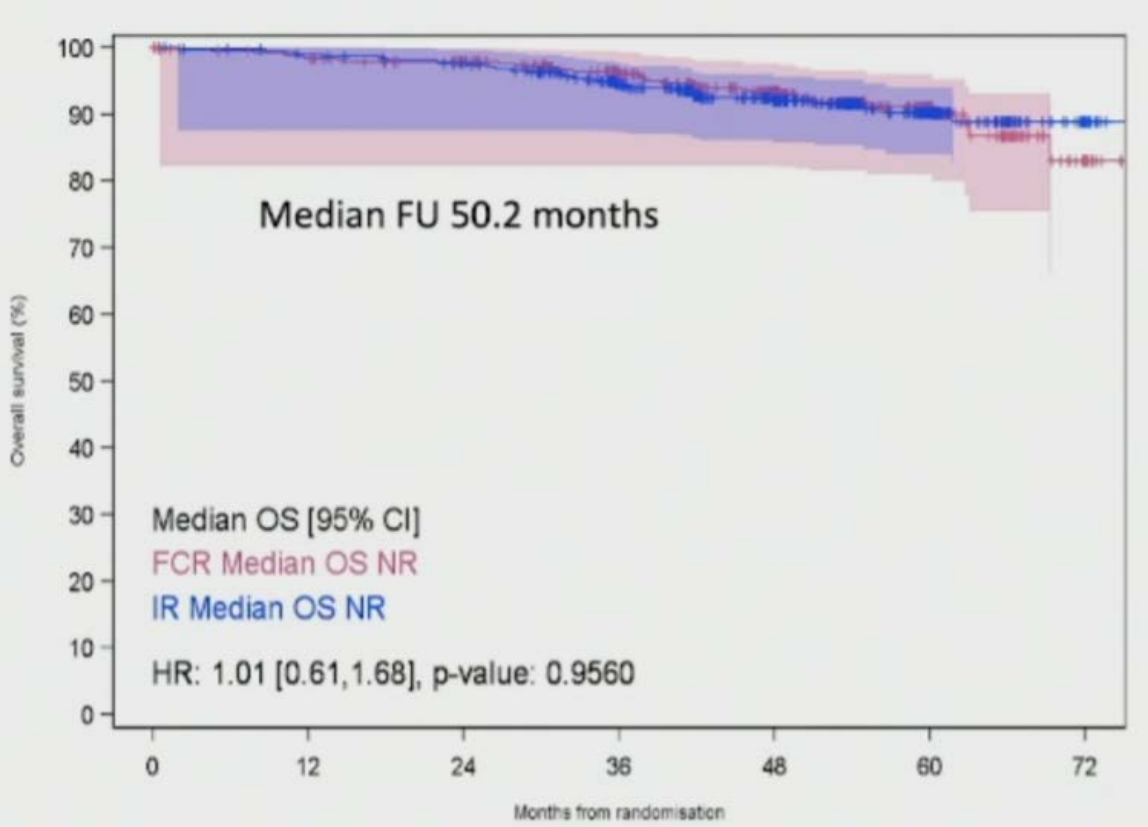
UK Flair Study: IR vs FCR





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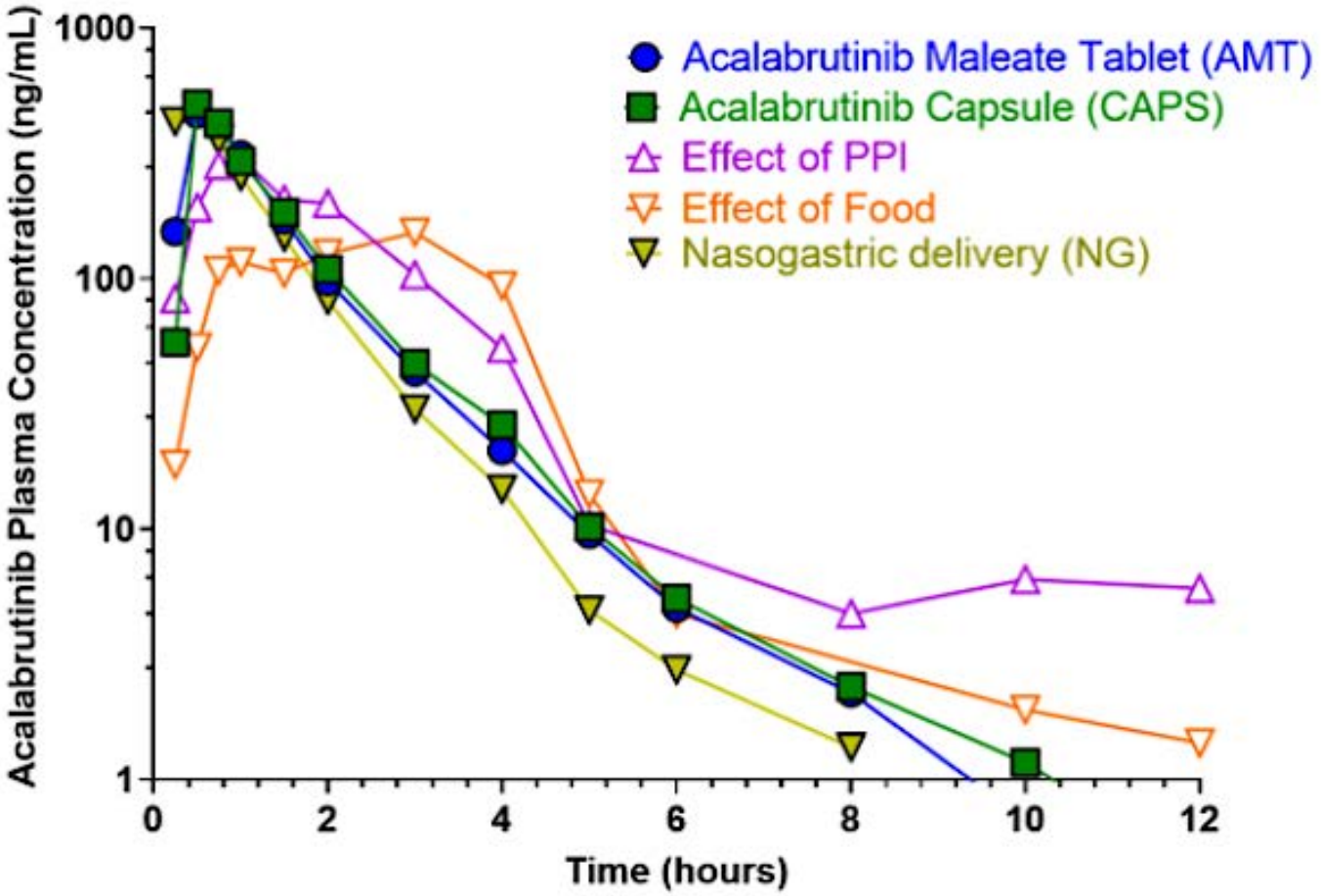
Acalabrutinib: Novel Formulation

Figure 1: PK Profiles of Acalabrutinib and its Major Pharmacologically Active Metabolite, ACP-5862, Across 3 Clinical Trials



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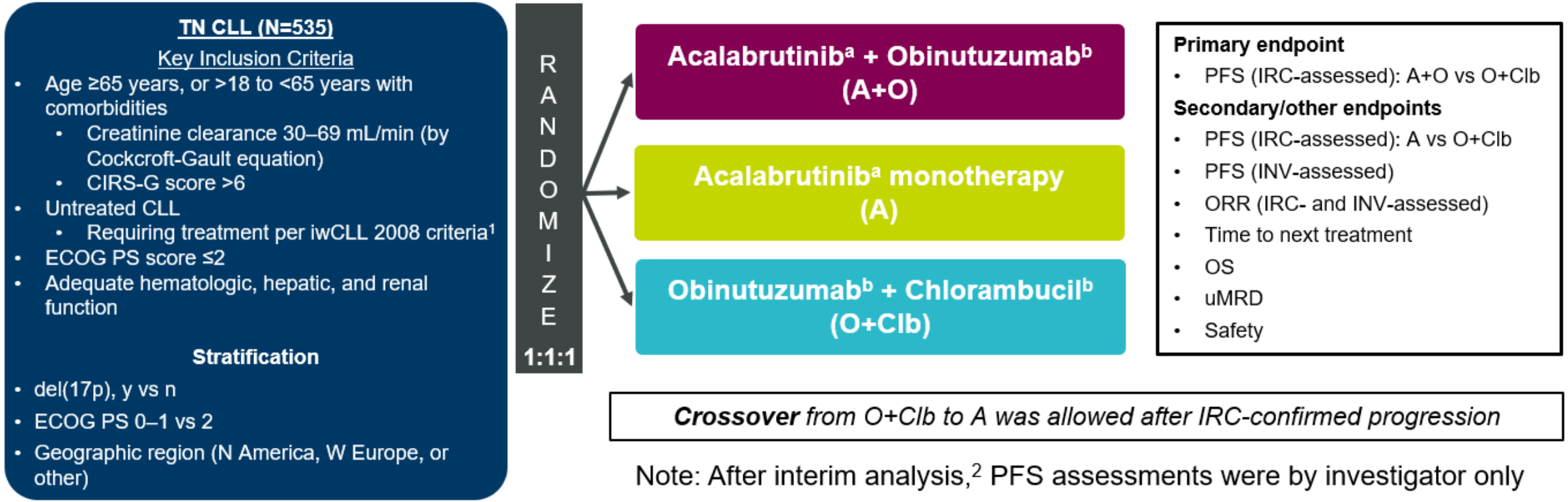
ELEVATE-TN study



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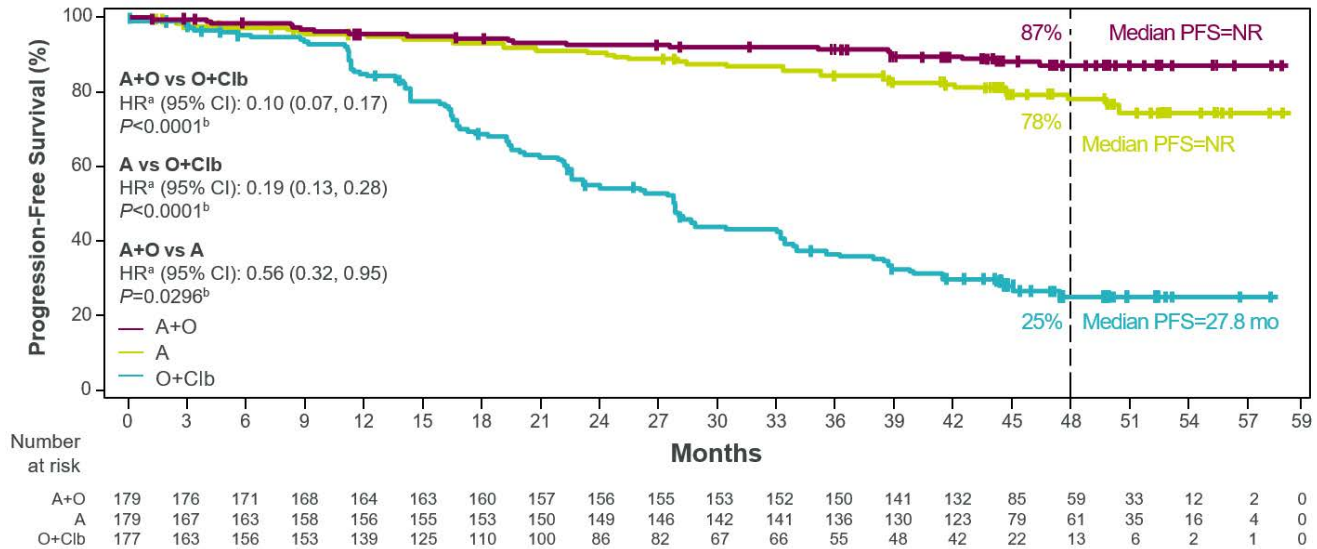
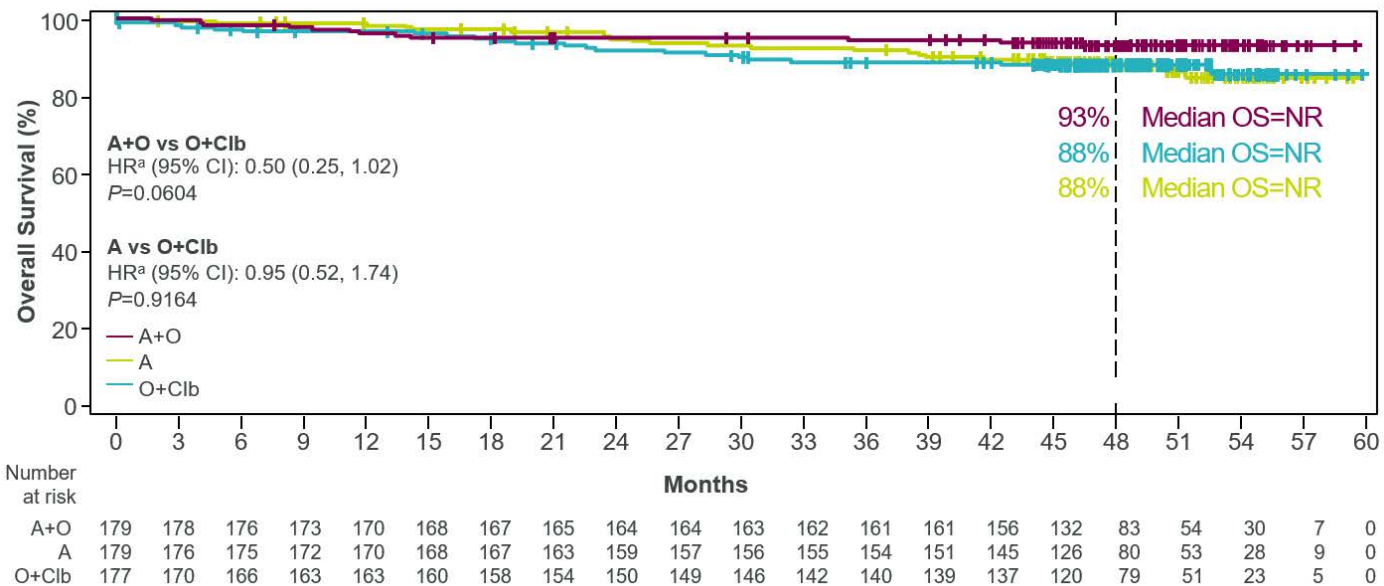
Investigator-assessed PFS Overall



Overall Survival



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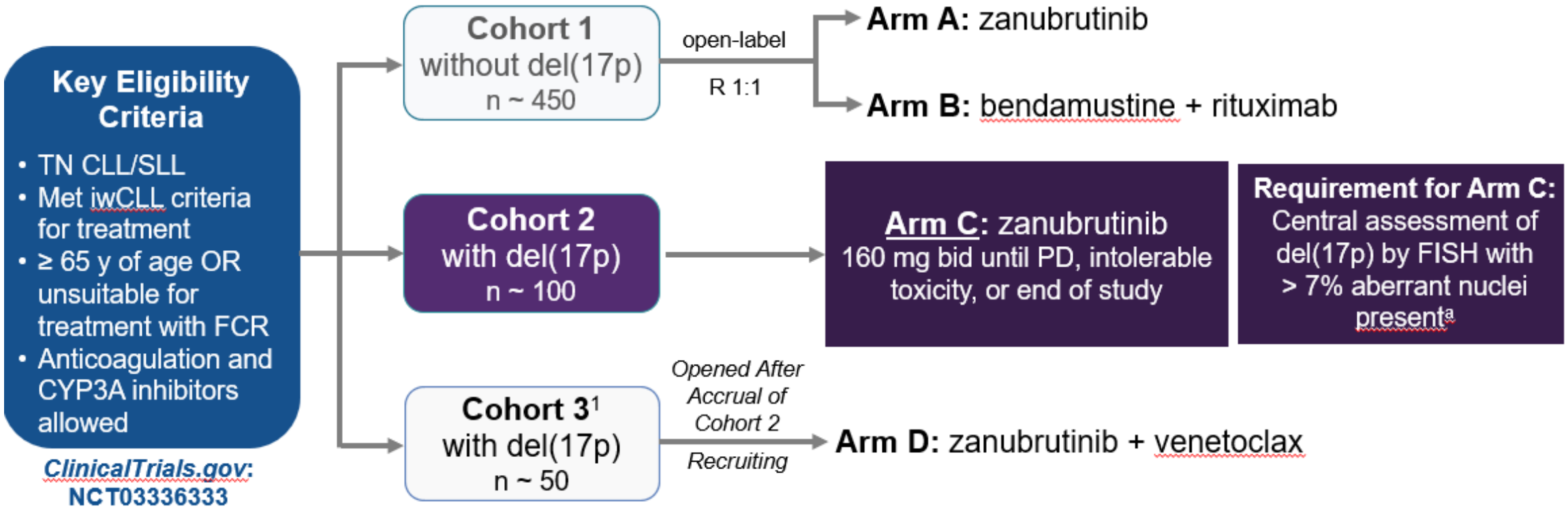
Courtesy of Jeff Sharman, MD

Zanubrutinib Monotherapy in 17P



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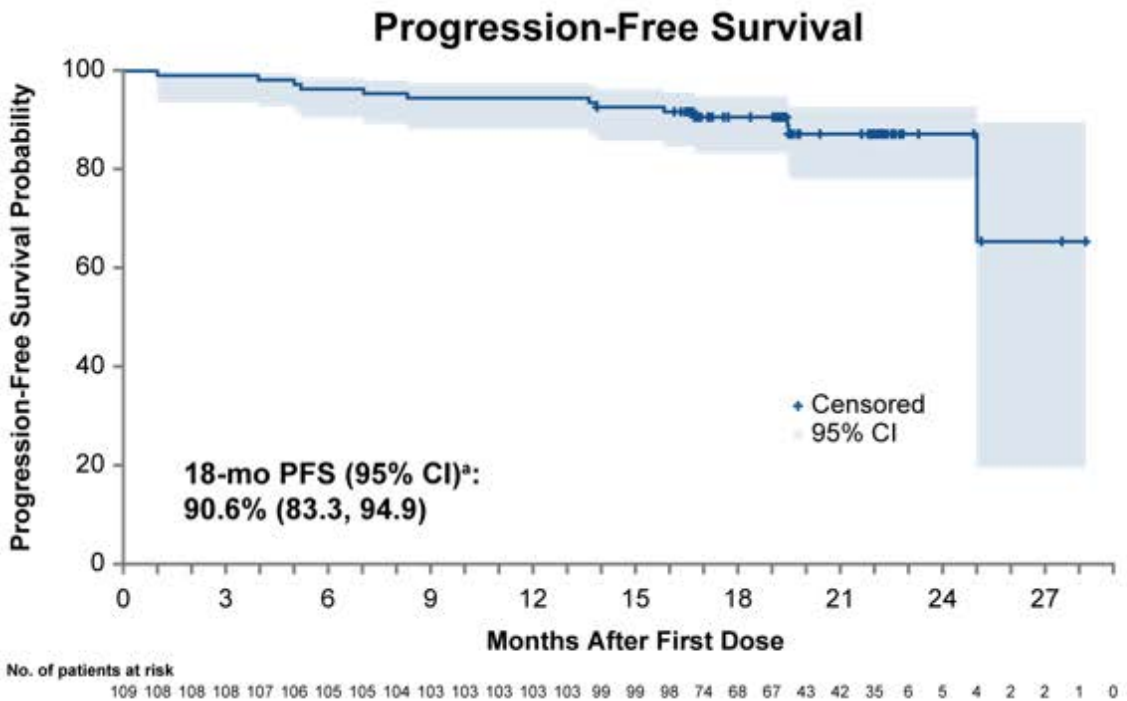
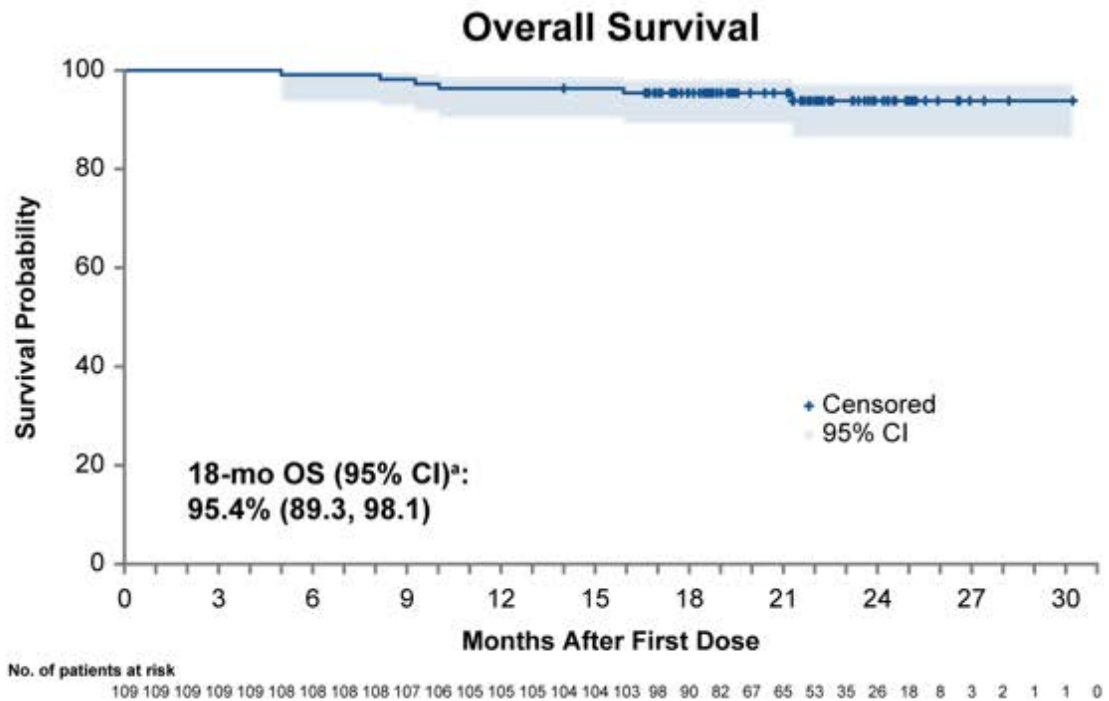
Zanubrutinib Monotherapy in 17P

Progression-Free Survival and Overall Survival
Investigator Assessment





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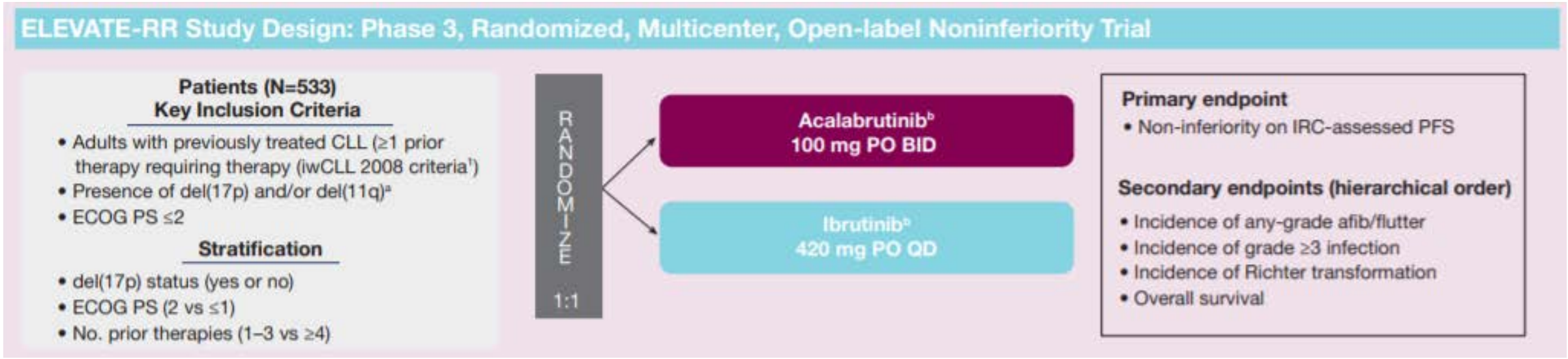
ELEVATE-RR: Acala vs Ibrutinib



Courtesy of Jeff Sharman, MD

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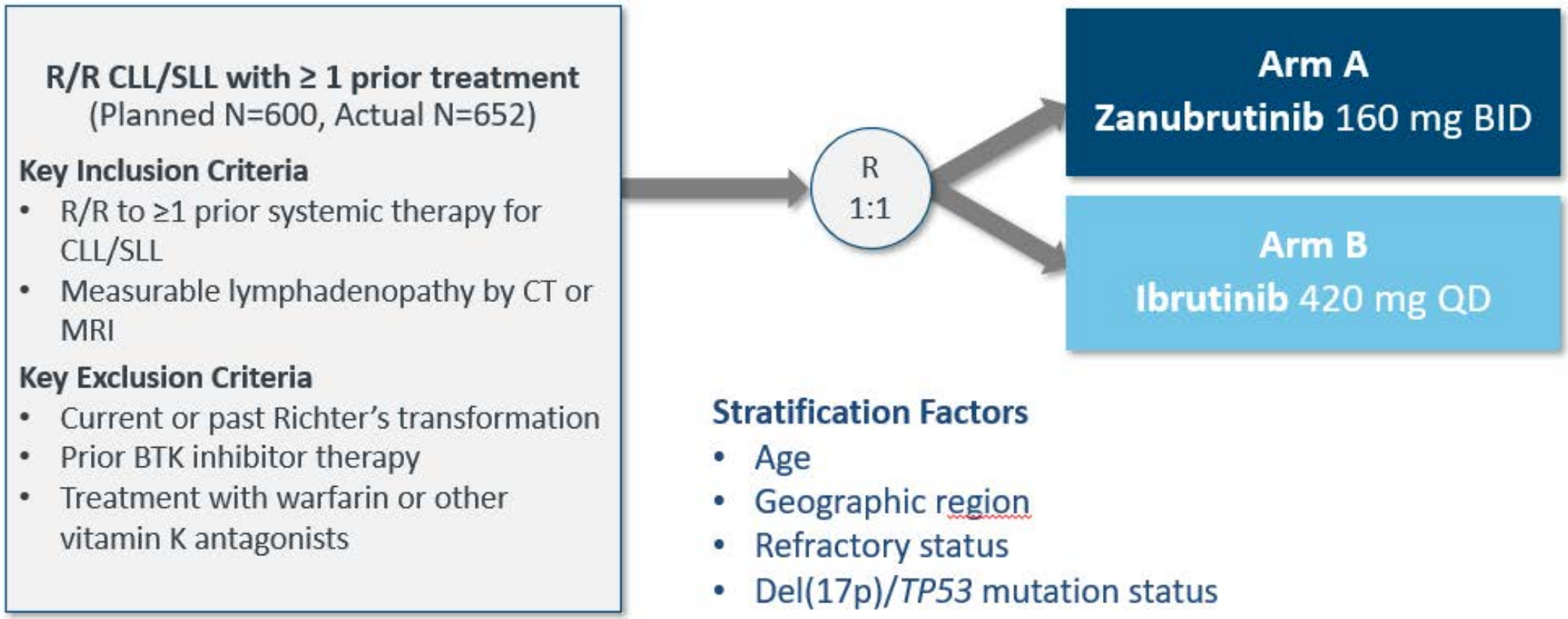
ELEVATE-RR: Acala vs Ibrutinib

	Incidence, %				Exposure-Adjusted Incidence[b]				Exposure-Adjusted Time With Event[c]			
	Any grade		Grade ≥3		Any grade		Grade ≥3		Any grade		Grade ≥3	
	Acala[d]	Ibru[e]	Acala[d]	Ibru[e]	Acala[d]	Ibru[e]	Acala[d]	Ibru[e]	Acala[d]	Ibru[e]	Acala[d]	Ibru[e]
ECIs												
Cardiac events	24%	30%	9%	10%	1.2	1.9	0.4	0.5	7.1	13.0	0.4	0.2
Afib/flutter	9%	**16%***	5%	4%	0.4	0.7	0.2	0.1	1.3	3.8	0.3	0.1
HTN[f]	9%	**23%***	4%	**9%***	0.4	1.2	0.1	0.4	4.1	15.0	1.6	4.0
Bleeding events[g]	38%	**51%***	4%	5%	2.4	3.8	0.1	0.2	13.7	24.6	0.1	0.1
Major bleeding events[h]	5%[i]	5%[j]	4%	5%	0.2	0.2	0.1	0.2	0.1	0.3	0.1	0.1
Infections[k]	78%	81%	31%	30%	8.9	10.4	1.6	2.0	14.6	15.6	1.5	1.1
Selected Common AEs (preferred term)												
Diarrhea	35%	**46%***	1%	**5%***	1.9	2.8	<0.1	0.2	6.7	9.6	<0.1	0.1
Headache	**35%***	20%	**2%***	0	1.8	1.1	<0.1	0	7.8	5.4	<0.1	0
Cough	**29%***	21%	1%	<1%	1.3	1.1	<0.1	<0.1	5.6	4.9	<0.1	<0.1
Fatigue	20%	17%	**3%***	0%	0.9	0.9	0.1	0	7.4	7.0	0.6	0
Arthralgia	16%	**23%***	0	1%	0.6	1.3	0	<0.1	7.5	10.4	0	<0.1
Back pain	8%	**13%***	0	1%	0.3	0.5	0	<0.1	1.9	3.2	0	0.1
Muscle spasms	6%	**13%***	0	1%	0.2	0.7	0	<0.1	0.8	10.0	0	0.1
Dyspepsia	4%	**12%***	0	0	0.1	0.5	0	0	1.0	2.4	0	0

Courtesy of Jeff Sharman, MD

Seymour 2021

Alpine: Ibrutinib vs Zanubrutinib



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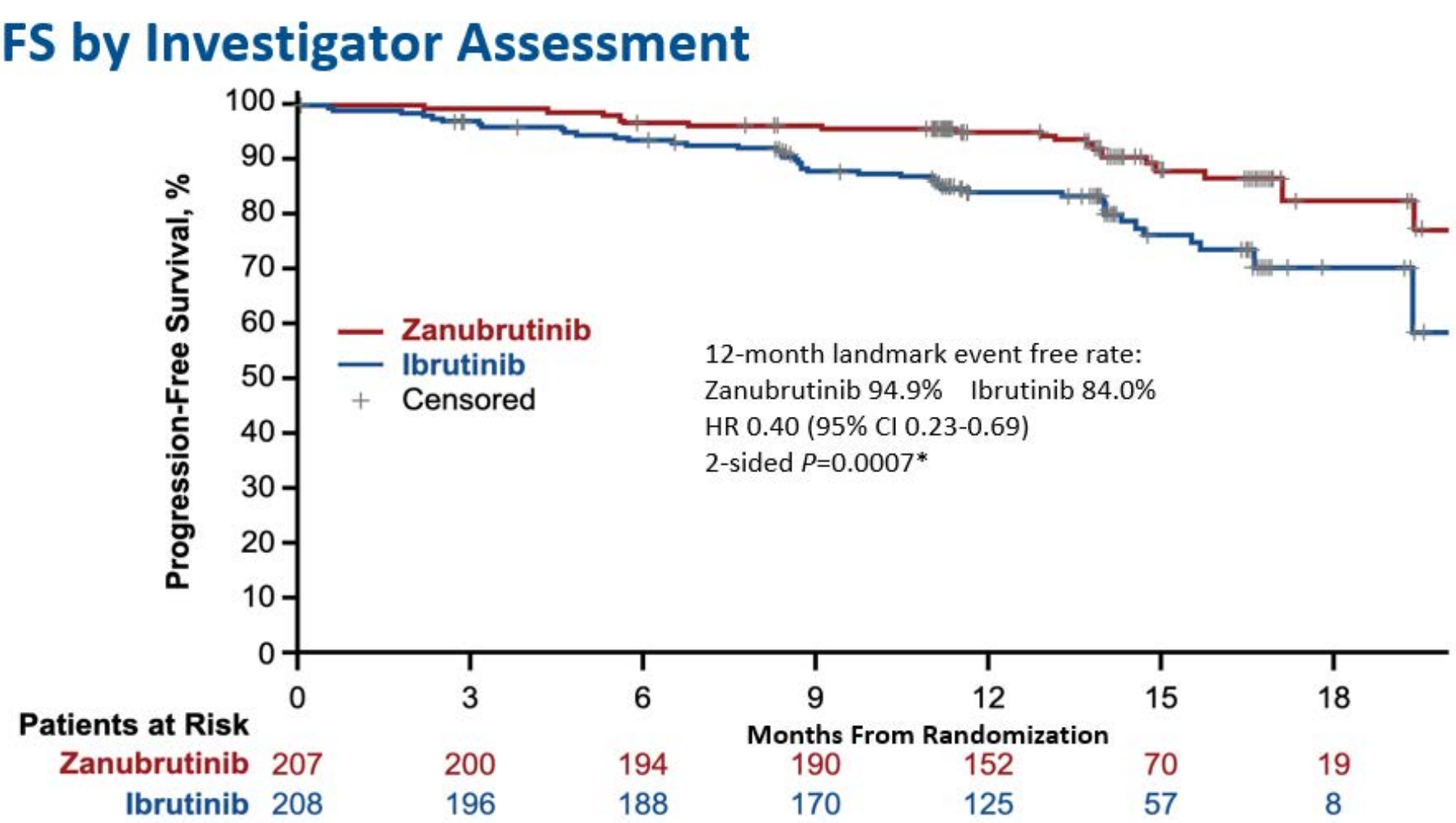
Alpine: Zanubrutinib vs Ibrutinib



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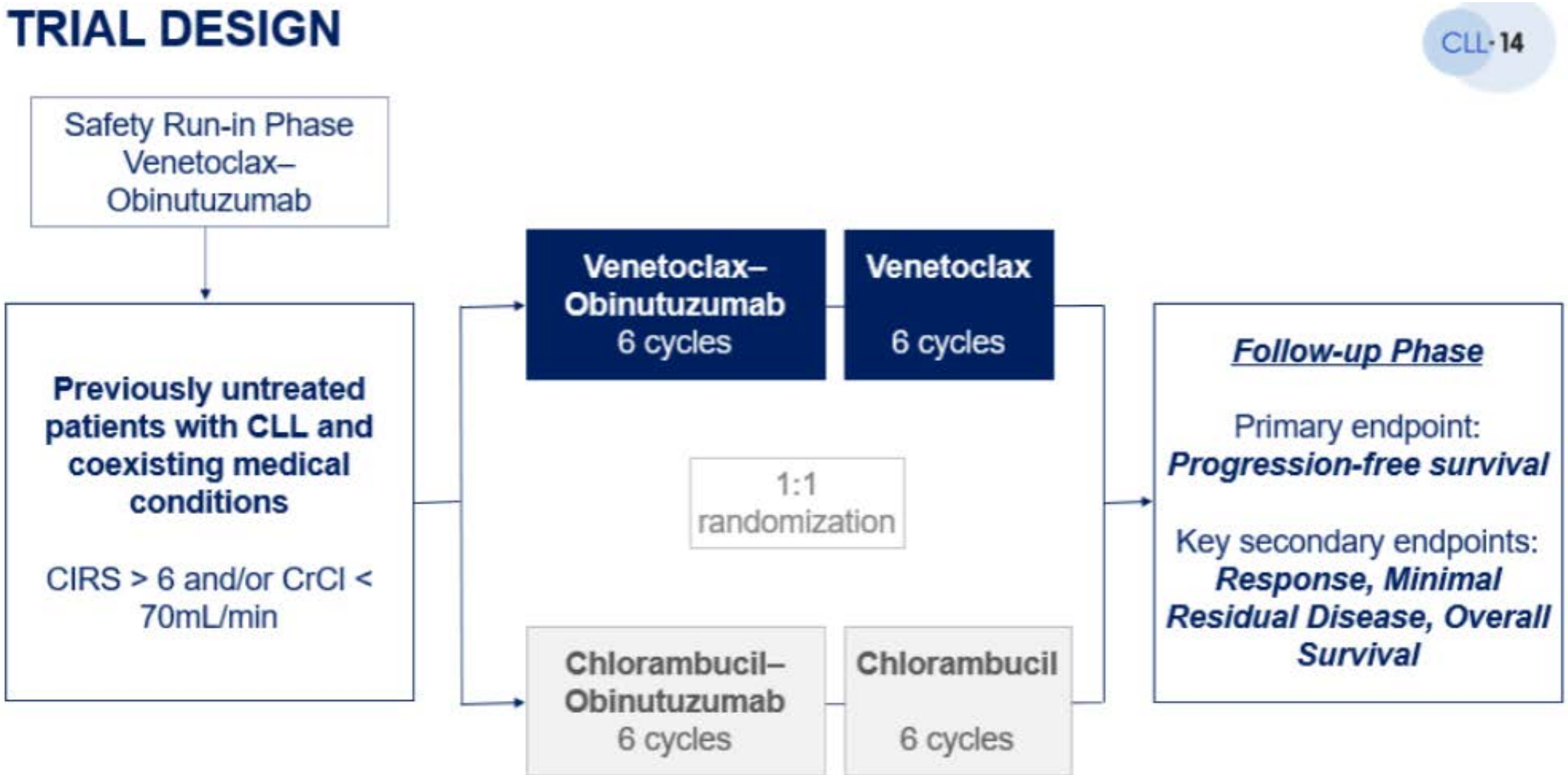
CLL-14 Update



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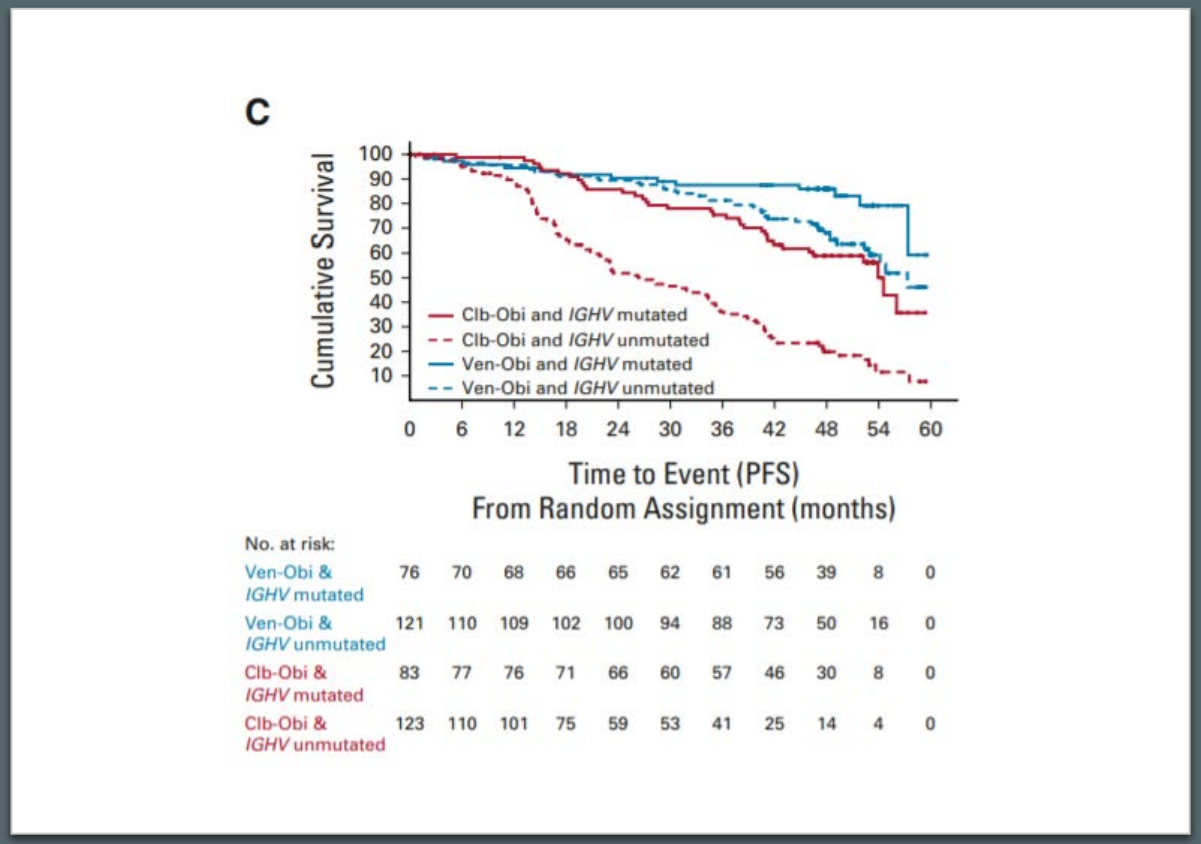
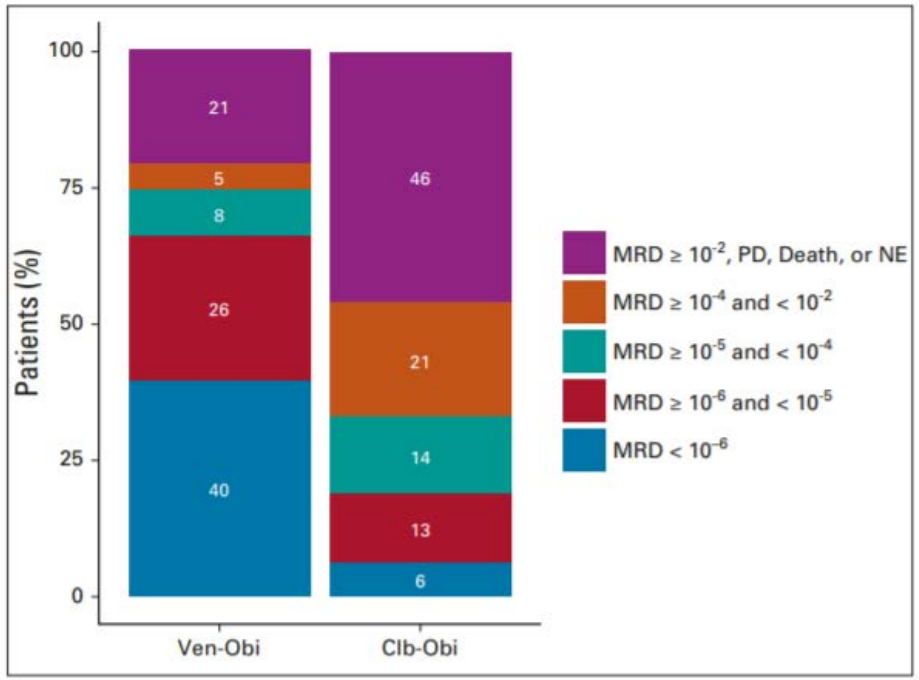
CLL-14 Update

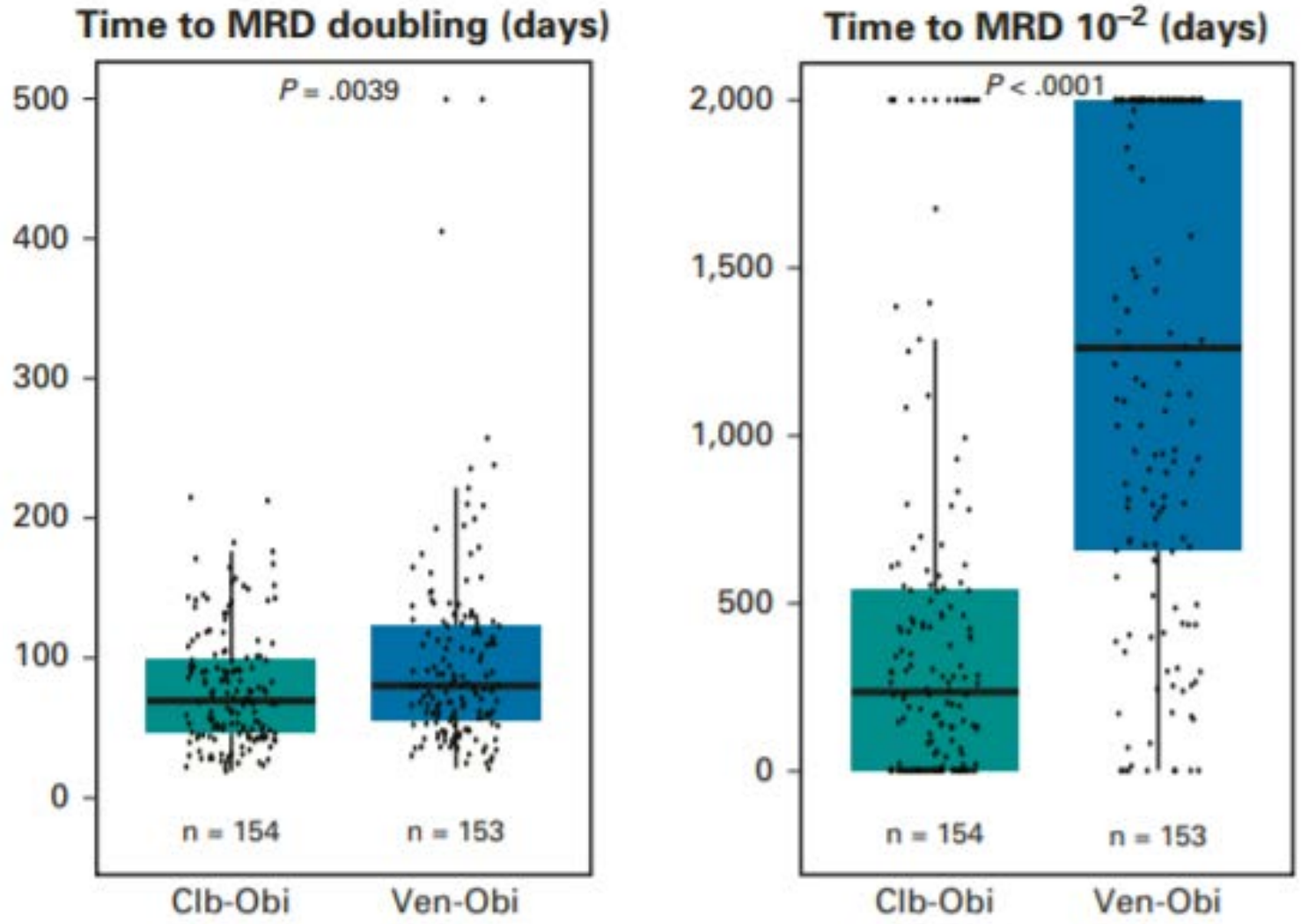




Courtesy of Jeff Sharman, MD

Al-Sawaf JCO 2021

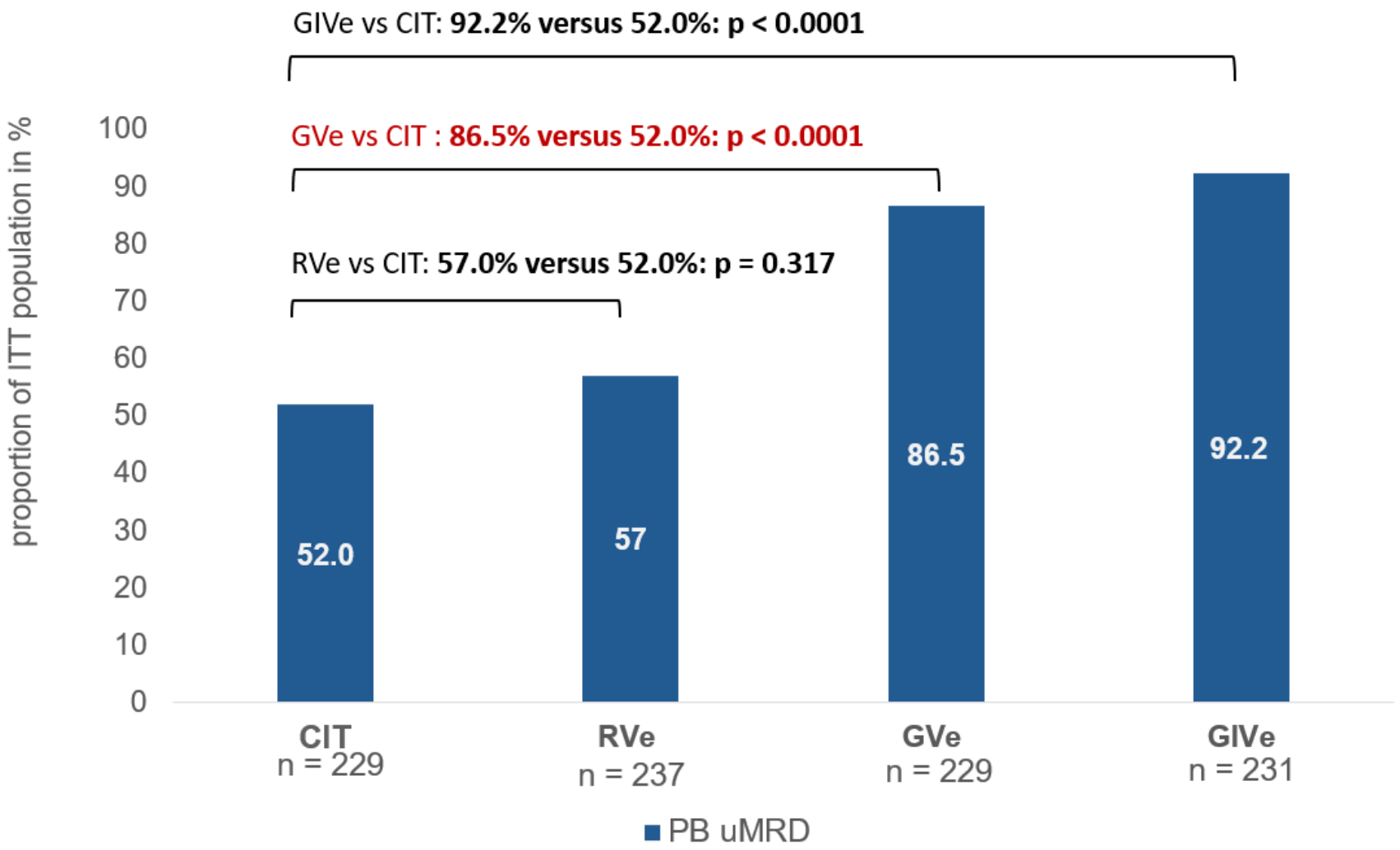
CLL-14 Update



Al-Sawaf JCO 2021

Courtesy of Jeff Sharman, MD

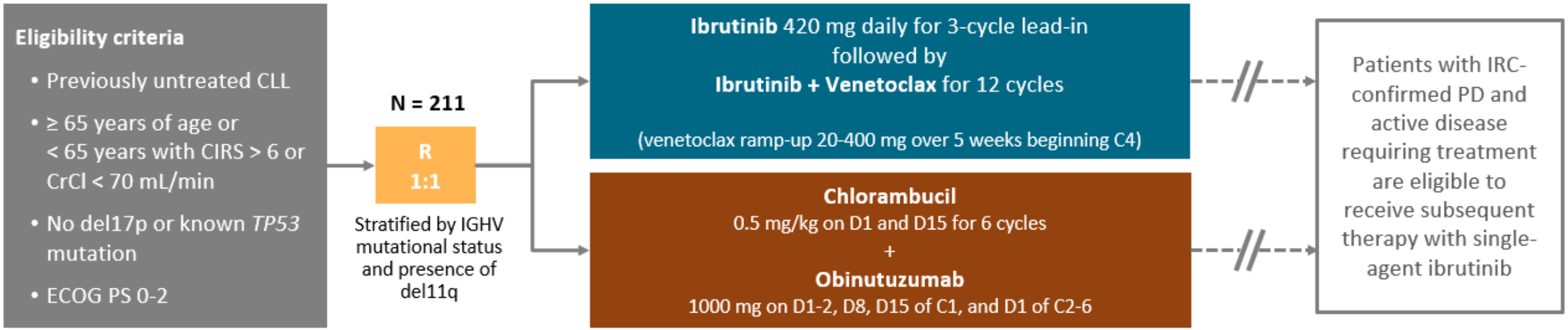
CLL13 Coprimary Endpoint: MRD by Flow



Eichhorst 2021

Courtesy of Jeff Sharman, MD

GLOW: Ibrutinib/Venetoclax Pivotal Study

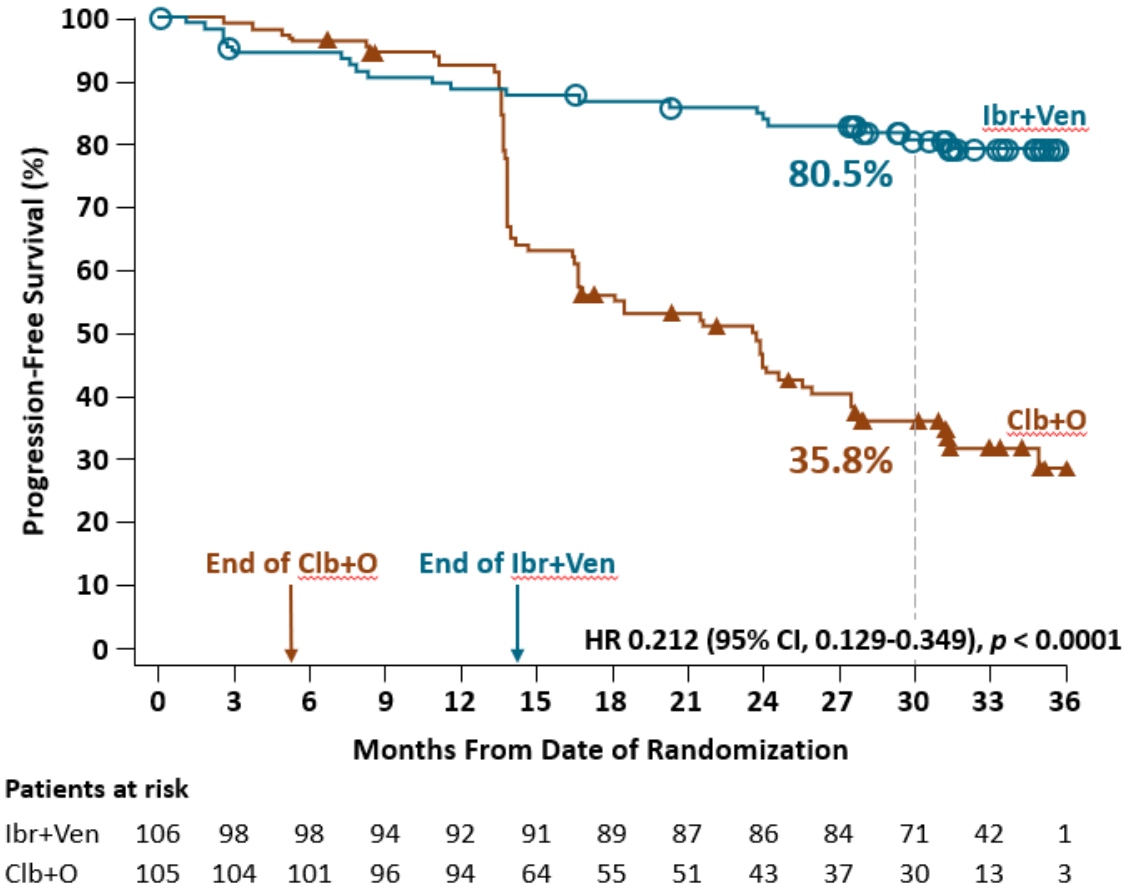


- **Study primary endpoint:** PFS as assessed by IRC

Courtesy of Jeff Sharman, MD

Kater 2021

GLOW: Ibrutinib/Venetoclax Pivotal Study



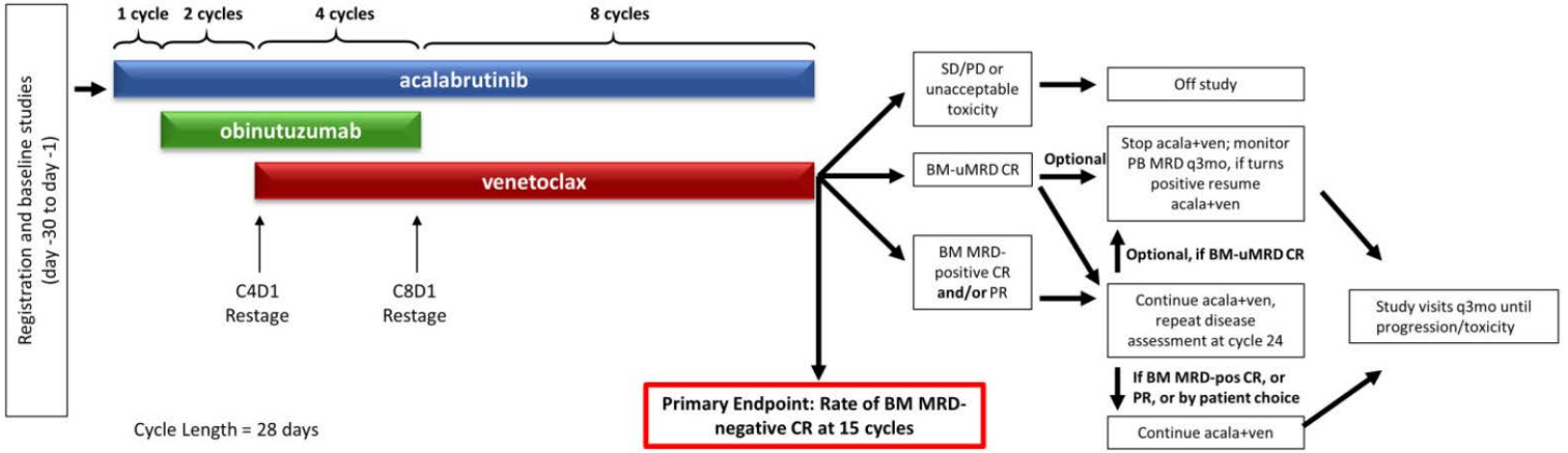
Grade 3 or Higher AEs in ≥5% of Patients

	I+V (N = 106)	Clb+O (N = 105)
Median exposure, mos (range)	13.8 (0.7-19.5)	5.1 (1.8-7.9)
Any, %	75.5	69.5
Neutropenia[a]	34.9	49.5
Infections[b]	17.0	11.4
Thrombocytopenia	5.7	20.0
Diarrhea	10.4	1.0
Hypertension	7.5	1.9
Atrial fibrillation	6.6	0
Hyponatremia	5.7	0
TLS	0	5.7

Courtesy of Jeff Sharman, MD

Kater 2021

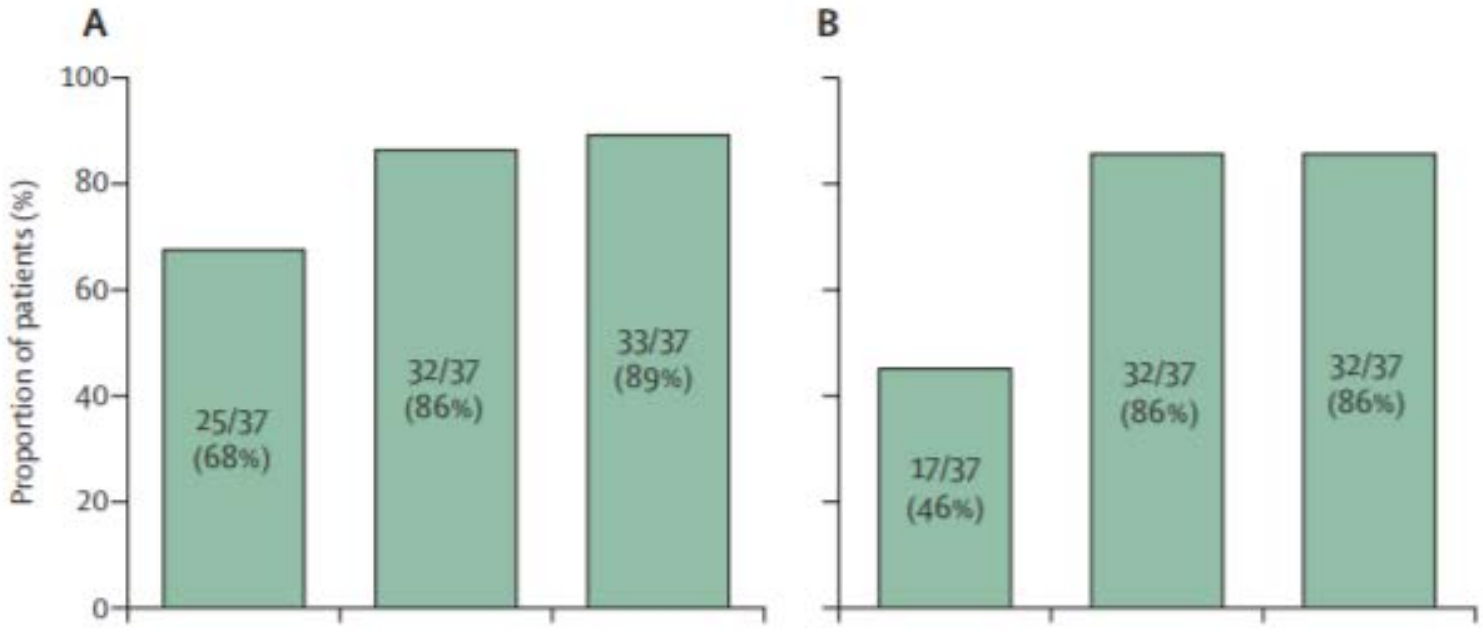
Triplet: Acalabrutinib Obinutuzumab Venetoclax



Davids 2021

Courtesy of Jeff Sharman, MD

Triplet: AVO MRD at 8/16/25 months



Blood

Marrow

Davids 2021

Courtesy of Jeff Sharman, MD

Conclusions

- BTK effective frontline strategy versus CIT
- Second Generation BTK inhibitors offer distinct safety profile
- Zanubrutinib effective in frontline 17P as monotherapy or in combination
- Venetoclax allows fixed duration therapy and partners with obinutuzumab better than rituximab
- Uncertain if BTK or anti-CD20 better partner for Venetoclax (MAJIC study)
- Doublet vs triplet data emerging

Courtesy of Jeff Sharman, MD

Agenda

Module 1: Current and Future Selection of First-Line Therapy for Chronic Lymphocytic Leukemia (CLL)

Module 2: Management of Relapsed/Refractory CLL

Module 3: Novel Investigational Strategies

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. Zanubrutinib
5. Venetoclax
6. Venetoclax + rituximab
7. Venetoclax + obinutuzumab
8. Other

Agenda

Module 2: Management of Relapsed/Refractory CLL

- Acalabrutinib in ibrutinib-intolerant disease
- MURANO trial follow-up: VenR versus BR
- VISION HO141 trial: Time-limited venetoclax plus ibrutinib
- MRD: Expert review and consensus recommendations

Ferrata Storti Foundation

Phase II study of acalabrutinib in ibrutinib-intolerant patients with relapsed/refractory chronic lymphocytic leukemia

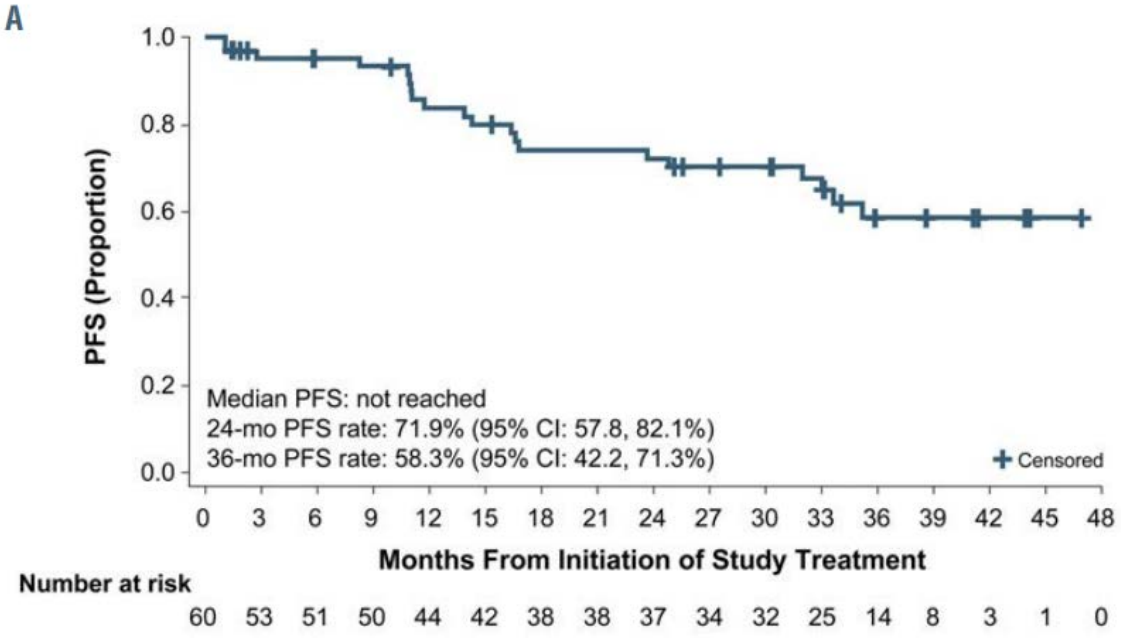
Kerry A. Rogers,[1] Philip A. Thompson,[2] John N. Allan,[3] Morton Coleman,[3] Jeff P. Sharman,[4] Bruce D. Cheson,[5] Daniel Jones,[1] Raquel Izumi,[6] Melanie M. Frigault,[6] Cheng Quah,[6] Rakesh K. Raman,[6] Priti Patel,[6] Min Hui Wang[6] and Thomas J. Kipps[7]

[1]The Ohio State University, Columbus, OH; [2]MD Anderson Cancer Center, Houston, TX; [3]Weill Cornell Medicine, New York, NY; [4]Willamette Valley Cancer Institute, Eugene, OR; [5]Georgetown University Hospital, Washington, DC; [6]AstraZeneca, South San Francisco, CA; and [7]UC San Diego Moores Cancer Center, San Diego, CA, USA

Haematologica 2021
Volume 106(9):2364-2373

Acalabrutinib is active for patients with Ibrutinib intolerance

- 60 ibrutinib intolerant patients with disease activity received acalabrutinib; med 2 prior tx (range 1-10)



Parameter, n (%)	Patients (N=60)
Median follow-up, mo (range)	34.6 (1.1-47.4)
On acalabrutinib	29 (48)
Discontinued acalabrutinib	31 (52)
▪ PD	14 (23)
▪ AE	10 (17)
▪ Patient withdrawal	3 (5)
▪ Physician decision	3 (5)
▪ Death	1 (2)[a]
▪ Other	1 (2)[b]
Death on study	11 (18)

At median follow-up of 34.6 mo,
48% of patients remain on acalabrutinib

Rogers K et al. Hematologica 2021;106(9):2364-2373

Courtesy of Lindsey Roeker, MD

Acalabrutinib is well tolerated in patients with Ibrutinib intolerance

Adverse Event	Patients with Ibrutinib Intolerance	Acalabrutinib Experience for Same Patients			
		Total	Lower Grade	Same Grade	Higher Grade
Atrial fibrillation	16	2	2	0	0
Diarrhea	7	5	3	2	0
Rash	7	3	3	0	0
Bleeding[b,c]	6	5	3	2	0
Arthralgia	7	2	1	1	0
Total	41	24	18	6	1

Among 60 patients meeting study enrollment criteria,

41 patients had a medical history of ≥1 of the listed categories of ibrutinib-intolerance events (43 events total)

Rogers K et al. Hematologica 2021;106(9):2364-2373

Courtesy of Lindsey Roeker, MD

Conclusions:

Impact on patient care and treatment algorithms

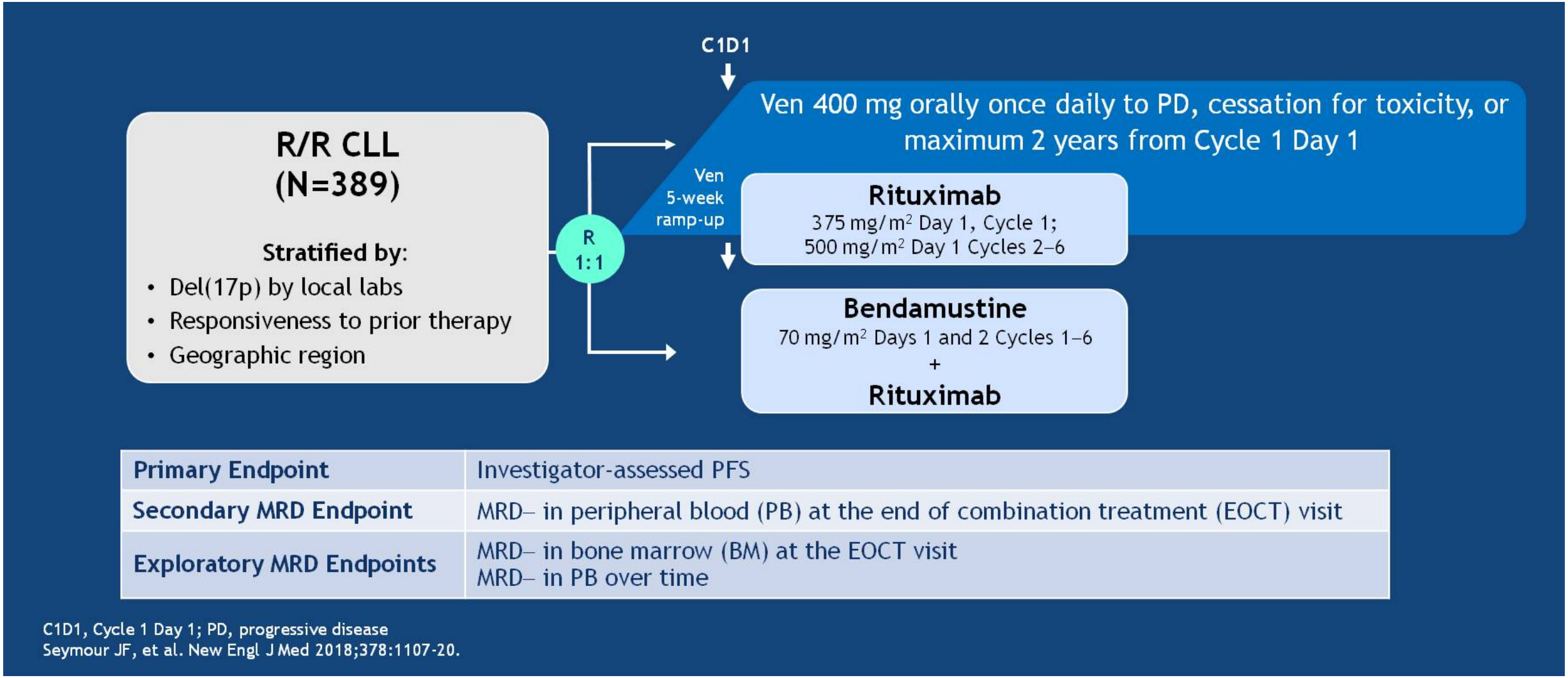
- Acalabrutinib is a data-driven treatment choice for patients with ibrutinib intolerance

Implications for future research

- With extended follow up, do other AEs emerge?

Courtesy of Lindsey Roeker, MD

Phase III MURANO Trial: VenR vs. BR in R/R CLL



Primary Endpoint	Investigator-assessed PFS
Secondary MRD Endpoint	MRD– in peripheral blood (PB) at the end of combination treatment (EOCT) visit
Exploratory MRD Endpoints	MRD– in bone marrow (BM) at the EOCT visit MRD– in PB over time

C1D1, Cycle 1 Day 1; PD, progressive disease
Seymour JF, et al. New Engl J Med 2018;378:1107-20.

Courtesy of Lindsey Roeker, MD

Clinical trial information, NCT02005471

Conclusions:

Impact on patient care and treatment algorithms

- Median PFS following 2-year fixed duration VenR is approximately 54 months
- uMRD at EOT is associated with improved outcomes post-EOT in the VenR treated patients

Implications for future research

- Is fixed duration therapy the appropriate approach? Should we be treating to a biological / MRD endpoint?
- Is rituximab the best partner for venetoclax in the R/R setting?

Courtesy of Lindsey Roeker, MD

Time-limited Venetoclax and Ibrutinib for Patients with Relapsed/Refractory Chronic Lymphocytic Leukemia (RR CLL) who have Undetectable Minimal Residual Disease (uMRD) – Primary Analysis from the Randomized Phase 2 VISION HO141 Trial

MRD guided Stop / Start in RR CLL

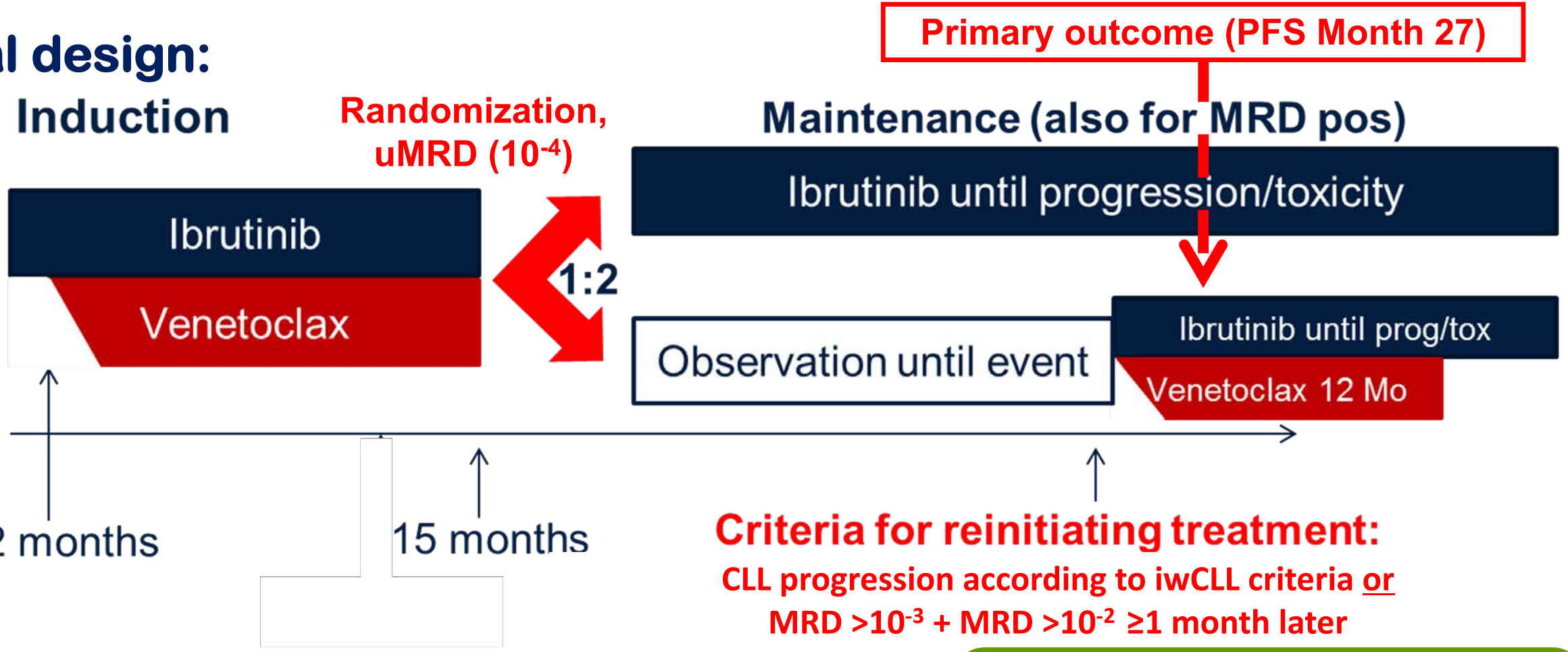
Carsten U Niemann, Julie Dubois, Christian Brieghel, Sabina Kersting, Lisbeth Enggaard, Gerrit J. Veldhuis, Rogier Mous, Clemens HM Mellink, Johan A Dobber, Christian B Poulsen, Henrik Frederiksen, Ann Janssens, Ida Schjødt, Ellen C Dompeling, Juha Ranti, Mattias Mattsson, Mar Bellido, Hoa TT Tran, Kazem Nasserinejad, Mark-David Levin, **Arnon P Kater**

HOVON

Nordic CLL Study Group

Courtesy of Lindsey Roeker, MD

Trial design:



Primary endpoint: Arm B Observation

- **PFS 12 months after stopping**
  - **MRD test every 3 months, with reinitiation upon becoming MRD+ not considered progression**

Main Inclusion / Exclusion Criteria:

- **Relapsed or Refractory CLL or SLL**
- **Creatinine clearance ≥ 30 mL/min**
- **Performance status 0-3, all degrees of fitness / comorbidity allowed**
- **No prior venetoclax or ibrutinib**

Niemann CU et al. ASH 2021;Abstract 69.

Courtesy of Lindsey Roeker, MD

Conclusions:

Impact on patient care and treatment algorithms

- No significant MRD eradication is observed with ibrutinib maintenance in patients who have detectable MRD after the combination of ibrutinib and venetoclax
- Retreatment with consolidation strategy in case of MRD relapse is a feasible experimental approach

Implications for future research

- What is a clinically meaningful progression event – MRD+ or iwCLL criteria for clinical progression?
- What is the appropriate duration of novel-agent combination therapy? Should it be guided by MRD?

Courtesy of Lindsey Roeker, MD

Leukemia (2021) 35:3059–3072
https://doi.org/10.1038/s41375-021-01241-1

REVIEW ARTICLE

Chronic lymphocytic leukemia

Measurable residual disease in chronic lymphocytic leukemia: expert review and consensus recommendations

William G. Wierda[1] · Andrew Rawstron[2] · Florence Cymbalista[3] · Xavier Badoux[4] · Davide Rossi[5] · Jennifer R. Brown[6] · Alexander Egle[7] · Virginia Abello[8] · Eduardo Cervera Ceballos[9] · Yair Herishanu[10] · Stephen P. Mulligan[11] · Carsten U. Niemann[12] · Colin P. Diong[13] · Teoman Soysal[14] · Ritsuro Suzuki[15] · Hoa T. T. Tran[16] · Shang-Ju Wu[17] · Carolyn Owen[18] · Stephan Stilgenbauer[19] · Paolo Ghia[20] · Peter Hillmen[21]

- International steering committee: 174-member multidisciplinary panel
- "Recommendations are presented regarding methodology for measurable residual disease determination, assay requirements and in which tissue to assess measurable residual disease, timing and frequency of assessment, use of measurable residual disease in clinical practice versus clinical trials, and the future usefulness of measurable residual disease assessment"

Wierda WG et al. Leukemia 2021;35(11):3059-72.

Courtesy of Lindsey Roeker, MD

Recommendations

- Nomenclature
  - MRD = measurable residual disease / U-MRD rather than “MRD negative”
- MRD methodology
  - Validated assay needed meeting standards
    - flow (ERIC) or RQ-PCR (EuroMRD-compliant)
- Compartment
  - “In clinical trials aimed at disease eradication, MRD status should be assessed in both PB and BM.”
- Timing of MRD assessment
  - To align with response assessments, at least 2 months after completion of therapy or after achievement of best response for continuous therapy
  - Clinical trials should incorporate MRD kinetics and relationship to time-to-event outcomes

Wierda WG et al. Leukemia 2021;35(11):3059-72.

Courtesy of Lindsey Roeker, MD

Recommendations

- Use in clinical trials
  - U-MRD as a potential surrogate endpoint
    - More data are needed to determine the utility of MRD in treatment-specific contexts, clinical trials should investigate relationship between MRD and outcomes
  - Disease related factors
    - Clinical trials should identify factors associated with achieving U-MRD for each treatment regimen
  - MRD relapse
    - Further study needed to define MRD relapse (threshold, duration) and association with outcomes
- Use in clinical practice
  - Current guidelines do not recommend MRD testing in clinical practice, more data are needed on using MRD to guide treatment decision making

Wierda WG et al. Leukemia 2021;35(11):3059-72.

Courtesy of Lindsey Roeker, MD

Conclusions:

Impact on patient care and treatment algorithms

- Consensus recommendations regarding when, how, and for whom to test MRD
- MRD should be reserved as a clinical decision making tool for clinical trial settings
- MRD does not currently have a role in routine clinical practice

Implications for future research

- Sets standards for use of MRD in clinical trials in order to generalize results

Courtesy of Lindsey Roeker, MD

Agenda

Module 1: Current and Future Selection of First-Line Therapy for Chronic Lymphocytic Leukemia (CLL)

Module 2: Management of Relapsed/Refractory CLL

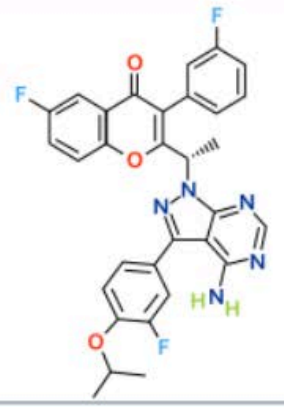
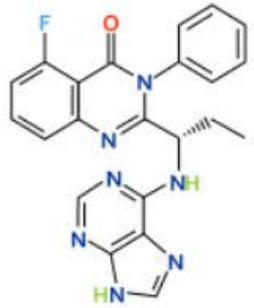
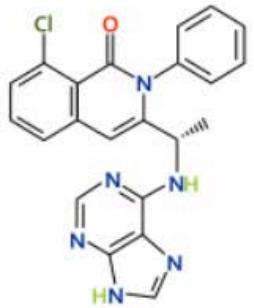
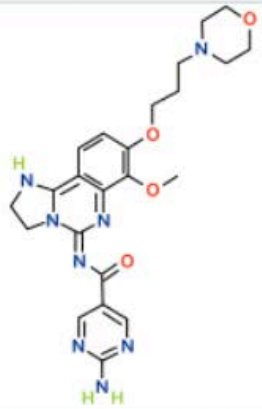
Module 3: Novel Investigational Strategies

Agenda

Module 3: Novel Investigational Strategies

- **BRUIN study: Pirtobrutinib in BTK inhibitor-pretreated CLL**
- **TRANSCEND CLL 004 study: Lisocabtagene maraleucel alone or in combination with ibrutinib**

Umbralisib: Mechanism of Action

	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, selective inhibitor of PI3Kδ and CK1ε
- Umbralisib has >1000-fold greater selectivity for PI3Kδ compared to α and β isoforms
- Umbralisib is also **>200-fold** more selective for PI3Kδ relative to **PI3Kγ**

Jacobs R et al. ASH 2021;Abstract 3726.

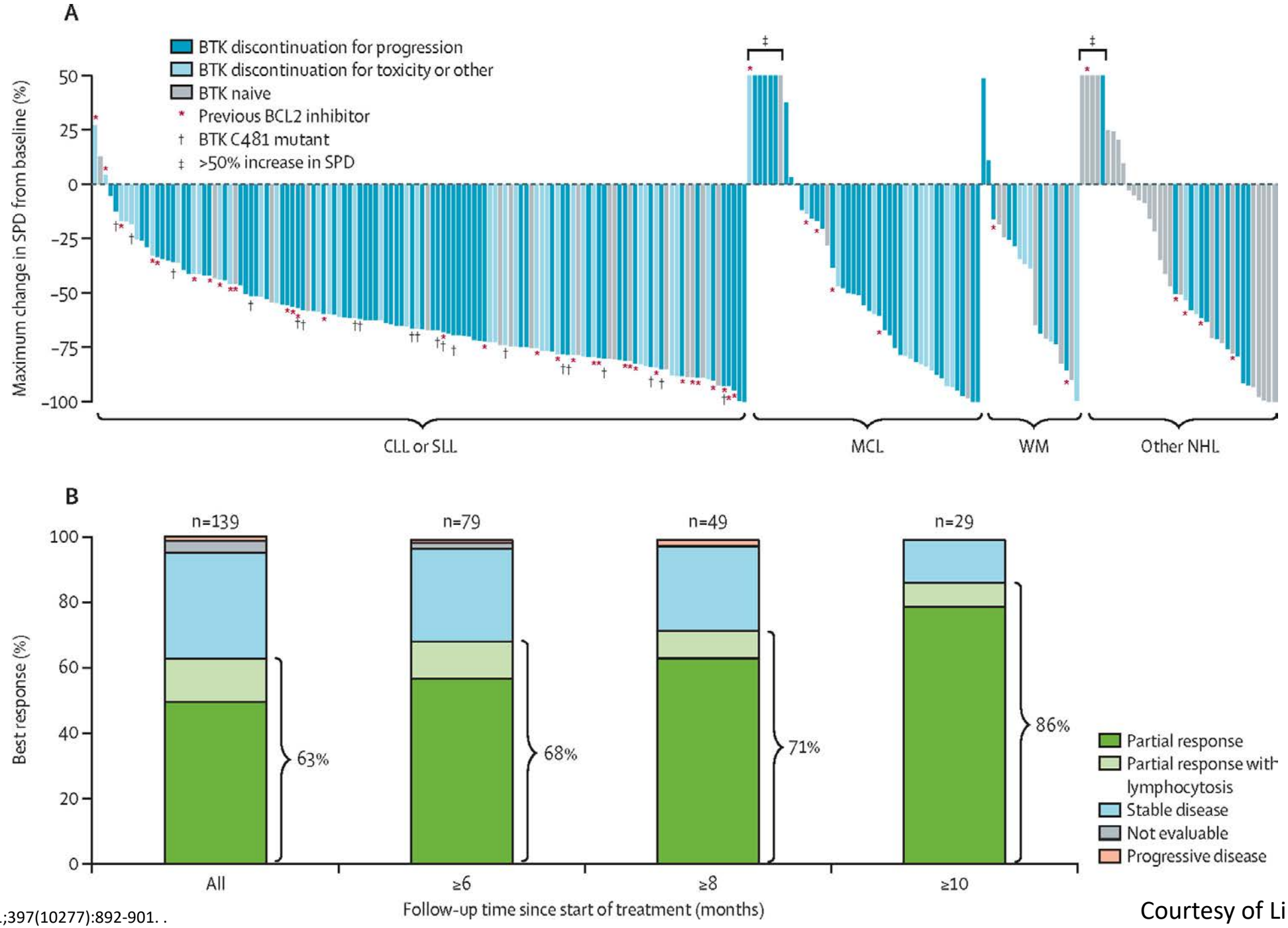
What is the optimal treatment approach for a patient with double-refractory (BTK inhibitor and venetoclax) CLL?

Pirtobrutinib, A Highly Selective, Non-covalent (Reversible) BTK Inhibitor In Previously Treated CLL/SLL: Updated Results From The Phase 1/2 BRUIN Study

Anthony R. Mato[1], John M. Pagel[2], Catherine C. Coombs[3], Nirav N. Shah[4], Nicole Lamanna[5], Talha Munir[6], Ewa Lech-Maranda[7], Toby A. Eyre[8], Jennifer A. Woyach[9], William G. Wierda[10], Chan Y. Cheah[11], Jonathan B. Cohen[12], Lindsey E. Roeker[1], Manish R. Patel[13], Bita Fakhri[14], Minal A. Barve[15], Constantine S. Tam[16], David J. Lewis[17], James N. Gerson[18], Alvaro J. Alencar[19], Chaitra S. Ujjani[20], Ian W. Flinn[21], Suchitra Sundaram[22], Shuo Ma[23], Deepa Jagadeesh[24], Joanna M. Rhodes[25], Justin Taylor[19], Omar Abdel-Wahab[1], Paolo Ghia[26], Stephen J. Schuster[18], Denise Wang[27], Binoj Nair[27], Edward Zhu[27], Donald E. Tsai[27], Matthew S. Davids[28], Jennifer R. Brown[28], Wojciech Jurczak[29]

[1]Memorial Sloan Kettering Cancer Center, New York, USA; [2]Swedish Cancer Institute, Seattle, USA; [3]University of North Carolina at Chapel Hill, Chapel Hill, USA; [4]Medical College of Wisconsin, Milwaukee, USA; [5]Herbert Irving Comprehensive Cancer Center, Columbia University, New York, USA; [6]Department of Haematology, St. James's University Hospital, Leeds, UK; [7]Institute of Hematology and Transfusion Medicine, Warsaw, Poland; [8]Oxford University Hospitals NHS Foundation Trust, Churchill Cancer Center, Oxford, UK; [9]The Ohio State University Comprehensive Cancer Center, Columbus, USA; [10]MD Anderson Cancer Center, Houston, USA; [11]Linear Clinical Research and Sir Charles Gairdner Hospital, Perth, Australia; [12]Winship Cancer Institute, Emory University, Atlanta, GA, USA; [13]Florida Cancer Specialists/Sarah Cannon Research Institute, Sarasota, USA; [14]University of California San Francisco, San Francisco, USA; [15]Mary Crowley Cancer Research, Dallas, USA; [16]Peter MacCallum Cancer Center, Royal Melbourne Hospital, and University of Melbourne, Melbourne, Australia; [17]Plymouth Hospitals NHS Trust - Derriford Hospital, Plymouth, UK; [18]Lymphoma Program, Abramson Cancer Center, University of Pennsylvania, Philadelphia, USA; [19]University of Miami Miller School of Medicine, Miami, USA; [20]Fred Hutchinson Cancer Research Center, [21]Sarah Cannon Research Institute, Nashville, USA; [22]Department of Hematology and Medical Oncology, Tisch Cancer Institute, Icahn School of Medicine at Mount Sinai, New York, NY, [23]Robert H. Lurie Comprehensive Cancer Center of Northwestern University, Chicago, IL, USA; [24]Cleveland Clinic, Cleveland, OH, USA; [25]Northwell Health Cancer Institute, Donald and Barbara Zucker School of Medicine at Hofstra/Northwell Health, New Hyde Park, NY; [26]Università Vita-Salute San Raffaele and IRCCS Ospedale San Raffaele, Milan, Italy; [27]Loxo Oncology at Lilly, Stamford, CT, USA; [28]Dana-Farber Cancer Institute and Harvard Medical School, Boston, USA; [29]Maria Sklodowska-Curie National Research Institute of Oncology, Krakow, Poland

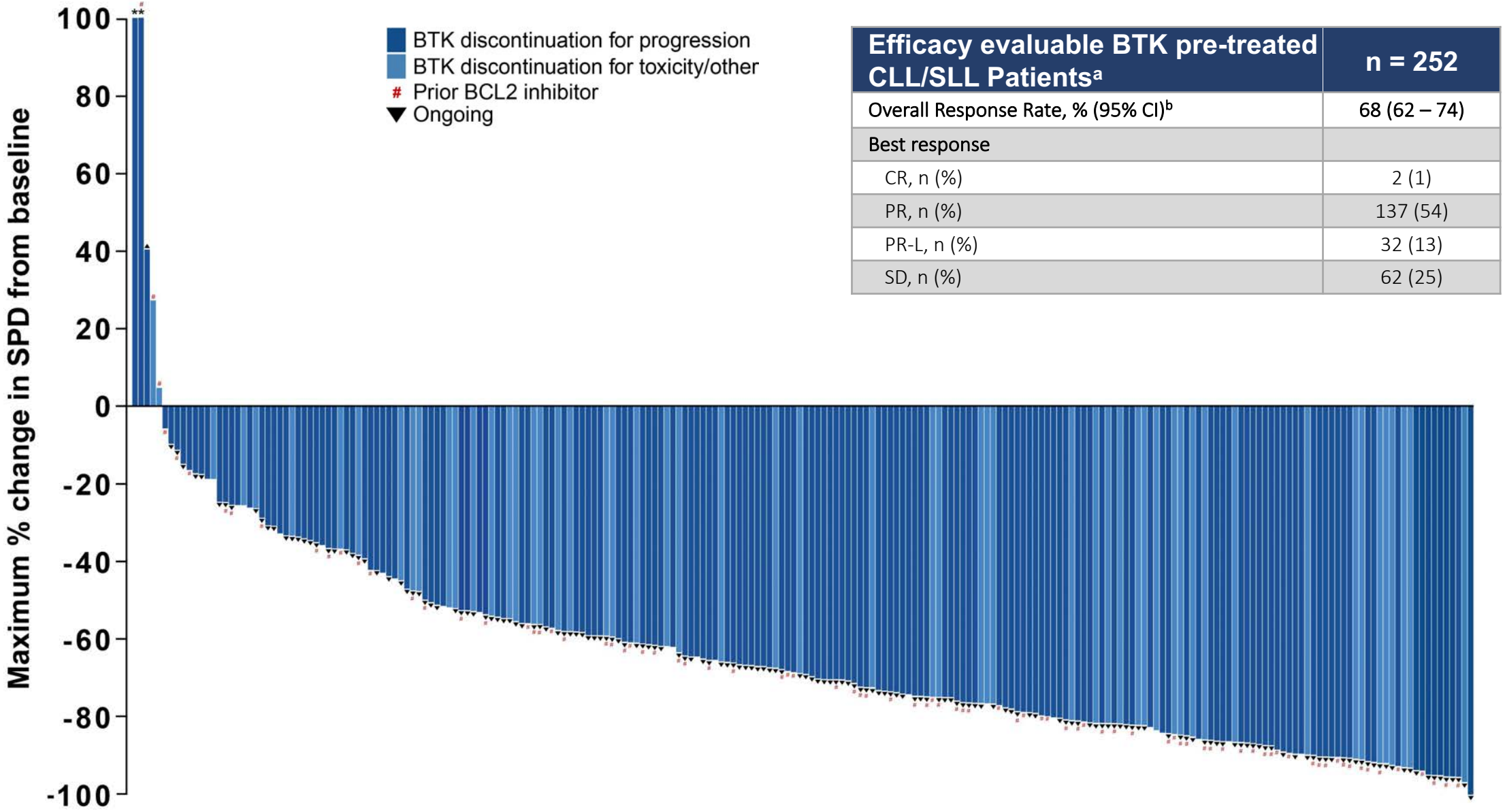
Courtesy of Lindsey Roeker, MD



Mato AR et al. Lancet 2021;397(10277):892-901. .

Courtesy of Lindsey Roeker, MD

Pirtobrutinib Efficacy in BTK Pre-treated CLL/SLL Patients



Efficacy evaluable BTK pre-treated CLL/SLL Patients[a]	n = 252
Overall Response Rate, % (95% CI)[b]	68 (62 – 74)
Best response	
CR, n (%)	2 (1)
PR, n (%)	137 (54)
PR-L, n (%)	32 (13)
SD, n (%)	62 (25)

Mato AR et al. ASH 2021;Abstract 391.

Courtesy of Lindsey Roeker, MD

Pirtobrutinib Safety Profile

	All doses and patients (n=618)						
	Treatment-emergent AEs, (≥15%), %					Treatment-related AEs, %	
Adverse Event	Grade 1	Grade 2	Grade 3	Grade 4	Any Grade	Grades 3/4	Any Grade
Fatigue	13%	8%	1%	-	23%	1%	9%
Diarrhea	15%	4%	<1%	<1%	19%	<1%	8%
Neutropenia[a]	1%	2%	8%	6%	18%	8%	10%
Contusion	15%	2%	-	-	17%	-	12%
AEs of special interest[b]							
Bruising[c]	20%	2%	-	-	22%	-	15%
Rash[d]	9%	2%	<1%	-	11%	<1%	5%
Arthralgia	8%	3%	<1%	-	11%	-	3%
Hemorrhage[e]	5%	2%	1%[g]	-	8%	<1%	2%
Hypertension	1%	4%	2%	-	7%	<1%	2%
Atrial fibrillation/flutter[f]	-	1%	<1%	<1%	2%[h]	-	<1%

No DLTs reported and MTD not reached
96% of patients received ≥1 pirtobrutinib dose at or above RP2D of 200 mg daily
1% (n=6) of patients permanently discontinued due to treatment-related AEs

Mato AR et al. ASH 2021;Abstract 391.

Courtesy of Lindsey Roeker, MD

Conclusions:

Impact on patient care and treatment algorithms

- About half of patients discontinue frontline or salvage ibrutinib, either due to resistance or intolerance
- Venetoclax is the most effective standard option for these patients, but remission duration is limited
- Alternative and less effective treatment options include PI3K inhibitors and chemoimmunotherapy
- Pirtobrutinib is a novel experimental BTKi, safe and effective for patients who relapse after BTKi, including those with C481S mutation

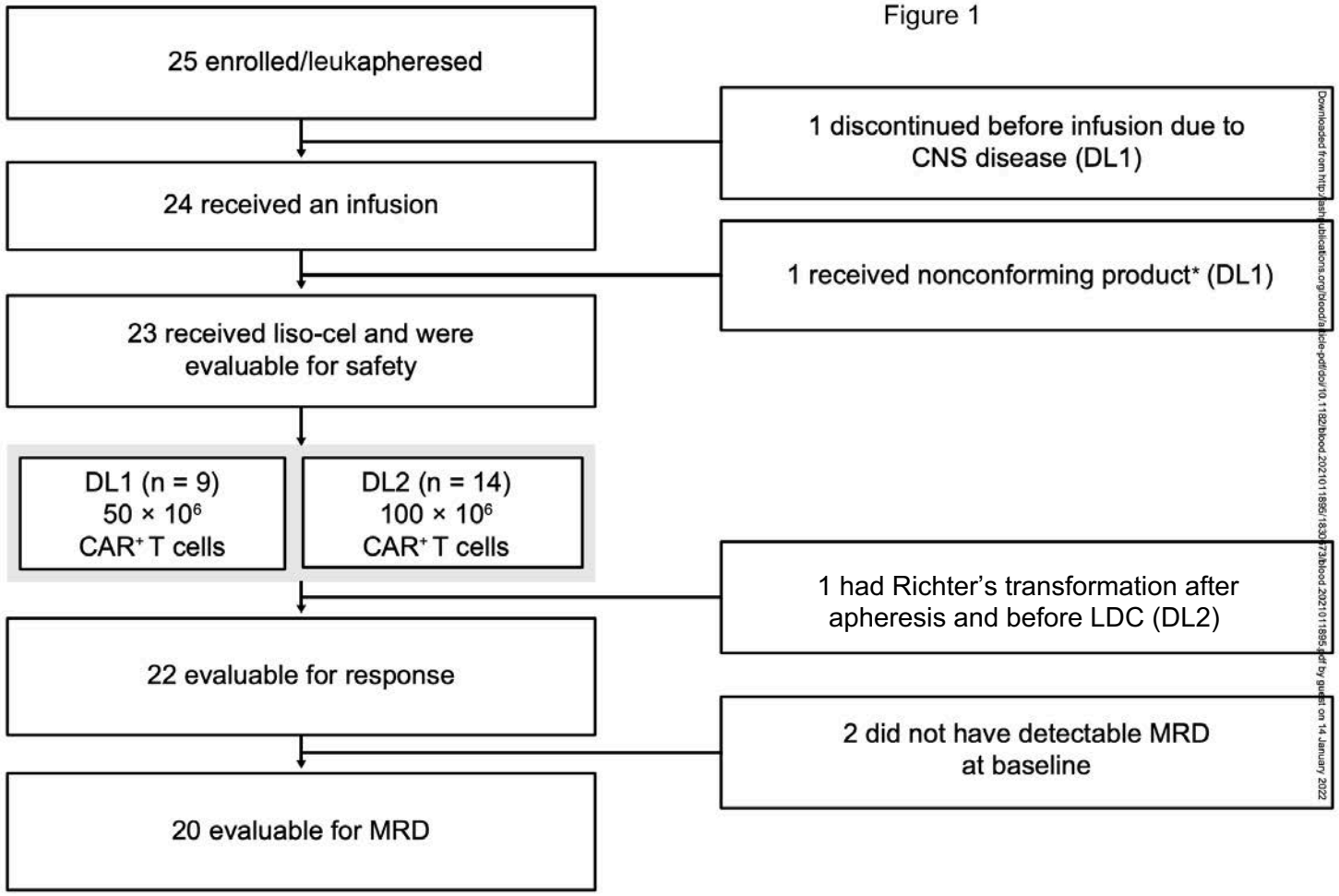
Implications for future research

- Ongoing studies examining BTKi in novel-agent refractory populations and in combination with other novel agents

Courtesy of Lindsey Roeker, MD

Phase 1 TRANSCEND CLL 004 study of lisocabtagene maraleucel in patients with R/R CLL or SLL

Characteristic	All patients (n = 23)
Age, y	66 (50-80)
High-risk features, any	19 (83)
del17p	8 (35)
mutated TP53	14 (61)
unmutated IGHV	8 (35)
complex karyotype	11 (48)
Lines of prior therapy	4 (2 – 11)
prior CIT	20 (87)
prior ibrutinib	23 (100)
prior venetoclax	15 (65)



Siddiqi T et al. Blood 2021; blood.2021011895 [Online ahead of print].

Courtesy of Lindsey Roeker, MD

Conclusions:

Impact on patient care and treatment algorithms

- Efficacy in heavily pre-treated, high-risk group
- 82% overall response rate
- Cytokine release syndrome relatively common, neurologic events in 39%

Implications for future research

- Phase 2 study ongoing, examining 100 x 10^6 CAR T cell dose

Courtesy of Lindsey Roeker, MD

TRANSCEND CLL-004: PHASE 1 COHORT OF LISOCABTAGENE MARALEUCEL (LISO-CEL) COMBINED WITH IBRUTINIB FOR R/R CLL/SLL

Eligibility: ≥1 of the following:

- Progressed on ibrutinib
- High risk features on Ibr for at least 6 months with CR
- BTK or PLCγ2 mutation
- Previous ibrutinib and no contraindication to continuing it

Study Design:

- Started or continued ibrutinib at enrollment, continued through 90 days following Liso-cell infusion
- 2 dose levels: 50 x 10^6 or 100 x 10^6
- Primary objective: Safety, RP2D

Characteristic	All patients (n = 19)
Age	61 (50-77)
High risk (TP53 aberration and/or CK)	18 (95)
Prior LOT	4 (1-10)
R/R to ibr	19 (100)
Refractory to Ibr and Ven	11 (58)

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Parameter	All Evaluable Patients (N = 19)	DL1 (n = 4)	DL2 (n = 15)
Grade ≥3 TEAEs in ≥25% of pts, n (%)	18 (95)	4 (100)	14 (93)
Neutropenia/neutrophil count decrease	17 (89)	3 (75)	14 (93)
Anemia	9 (47)	3 (75)	6 (40)
Febrile neutropenia	5 (26)	1 (25)	4 (27)
Grade 5 TEAEs, n (%)	0	0	0
AEs of special interest			
All-grade CRS, n (%)	14 (74)	4 (100)	10 (67)
Median time to CRS onset, days (range)	6.5 (1–13)	8 (6–13)	5.5 (1–8)
Median duration of CRS, days (range)	6 (3–13)	6.5 (4–7)	5.5 (3–13)
Grade ≥3 CRS, n (%)	1 (5)	1 (25)	0
All-grade NEs, n (%)	6 (32)	2 (50)	4 (27)
Median time to NE onset, days (range)	8 (5–12)	9 (6–12)	8 (5–10)
Median duration of NE, days (range)	6.5 (1–8)	8 (8–8)	5 (1–7)
Grade ≥3 NEs, n (%)	3 (16)	0	3 (20)
Management of CRS and/or NEs, n (%)			
Tocilizumab only	2 (11)	0	2 (13)
Corticosteroids only	3 (16)	2 (50)	1 (7)
Tocilizumab and corticosteroids	3 (16)	1 (25)	2 (13)
Ibr-related TEAEs, n (%)	15 (79)	3 (75)	12 (80)
Grade ≥3 ibr-related TEAEs[a]	7 (37)	2 (50)	5 (33)
Ibr dose reduced due to TEAE, n (%)	2 (11)	0	2 (13)
Ibr discontinued due to TEAE, n (%)	4 (21)	1 (25)	3 (20)
Median duration of ibr therapy after liso-cel infusion (range), days	97 (14–388)	132 (59–197)	97 (14–388)
Best objective response rate,[b] n (%)	18 (95)	3 (75)	15 (100)
CR/CRi	12 (63)	2 (50)	10 (67)
PR	6 (32)	1 (25)	5 (33)
uMRD (≤10^{-4}blood, flow cytometry), n (%)	17 (89)	3 (75)	14 (93)
uMRD (≤10^{-4}marrow, NGS), n (%)	15 (79)	3 (75)	12 (80)

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Conclusions:

Impact on patient care and treatment algorithms

- Liso-cell + ibrutinib is associated with manageable safety profile and promising efficacy in a high risk patient population

Implications for future research

- Do novel agents enhance the activity or improve the safety profile of CAR-T in CLL?
- Which novel agent is the optimal partner for CAR-T therapy?

Courtesy of Lindsey Roeker, MD

Promising Investigational Agents and Strategies for Patients with Metastatic Non-Small Cell Lung Cancer Who Experience Disease Progression on Immune Checkpoint Inhibitor Therapy

Wednesday, January 26, 2022
5:00 PM – 6:00 PM ET

Faculty

Edward B Garon, MD, MS

Moderator

Neil Love, MD

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