Identifying, Managing and Mitigating Therapy-Related Adverse Events in Patients with Chronic Lymphocytic Leukemia and Mantle Cell Lymphoma

A CME/MOC-Accredited Virtual Event

Monday, October 4, 2021
5:00 PM – 6:00 PM ET

Faculty

Richard R Furman, MD
Lindsey Roeker, MD

Consulting Cardiologist

Daniel J Lenihan, MD

Moderator

Neil Love, MD

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Faculty

Richard R Furman, MD
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Lindsey Roeker, MD
Assistant Attending Physician
Memorial Sloan Kettering Cancer Center
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Consulting Cardiologist

Daniel J Lenihan, MD
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St Louis, Missouri

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 and AstraZeneca Pharmaceuticals LP.

Dr Love — Disclosures

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Speaking Engagements	AbbVie Inc, AstraZeneca Pharmaceuticals LP, BeiGene Ltd

Dr Lenihan — Disclosures

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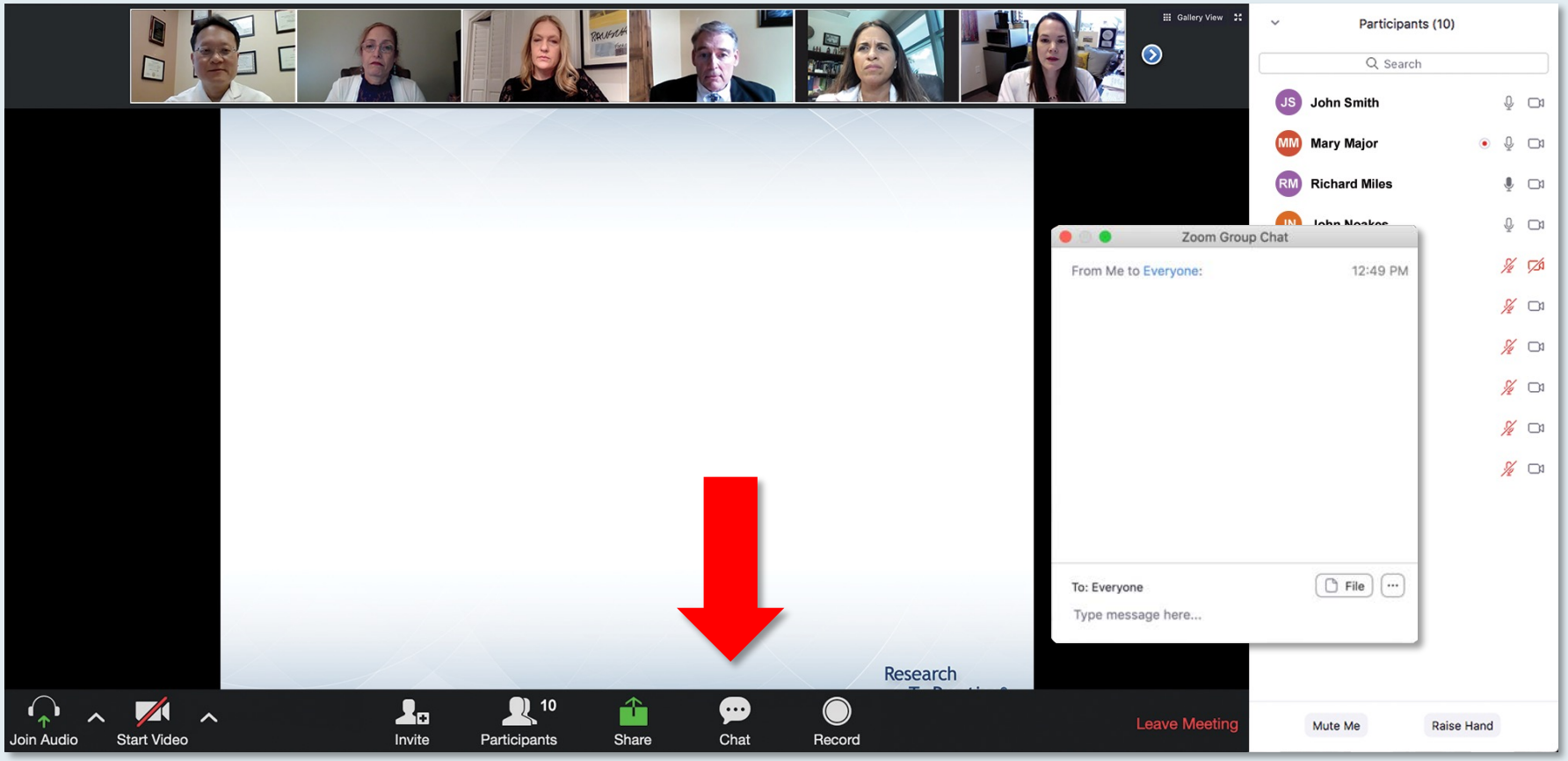
We Encourage Clinicians in Practice to Submit Questions



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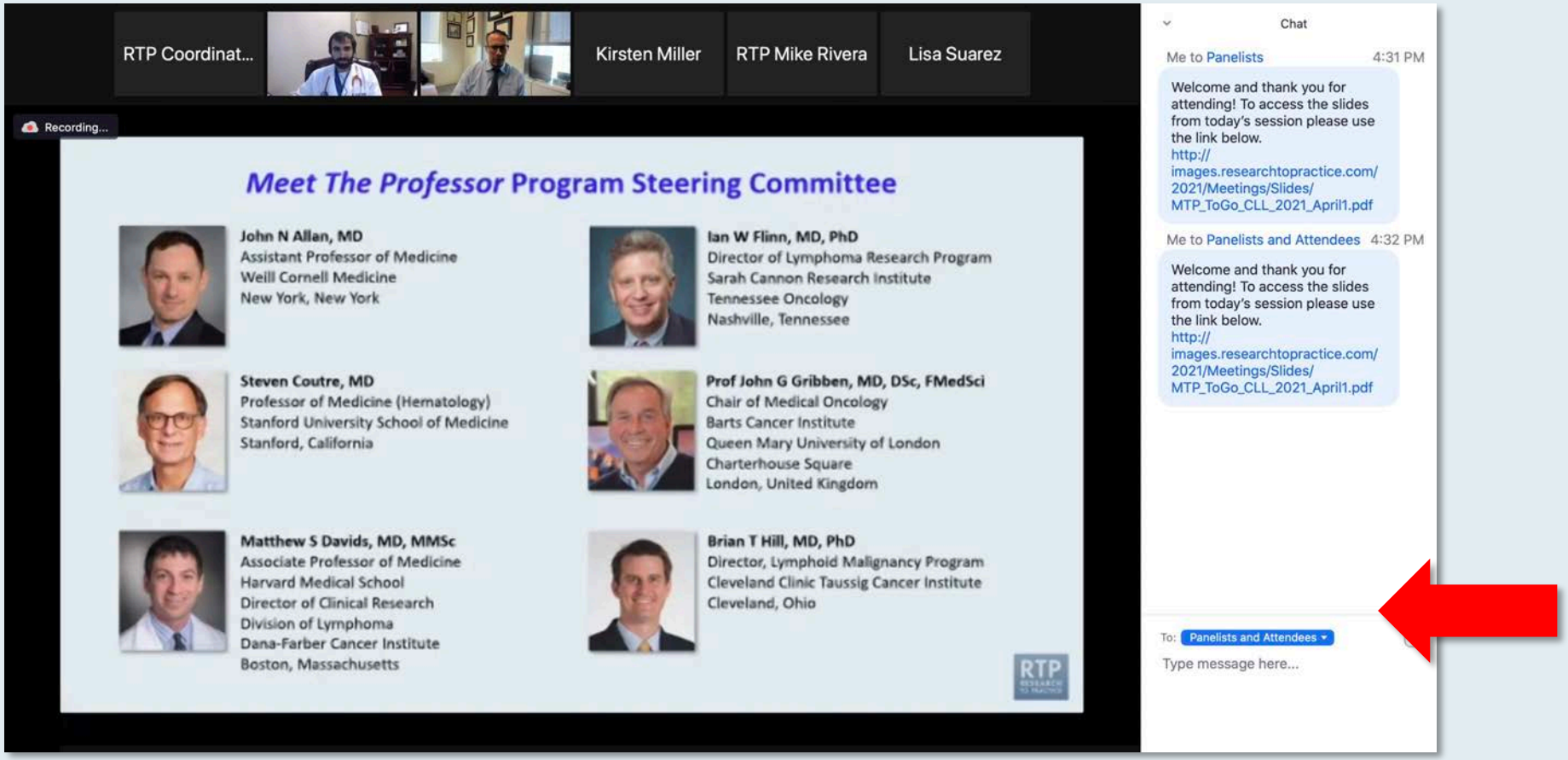

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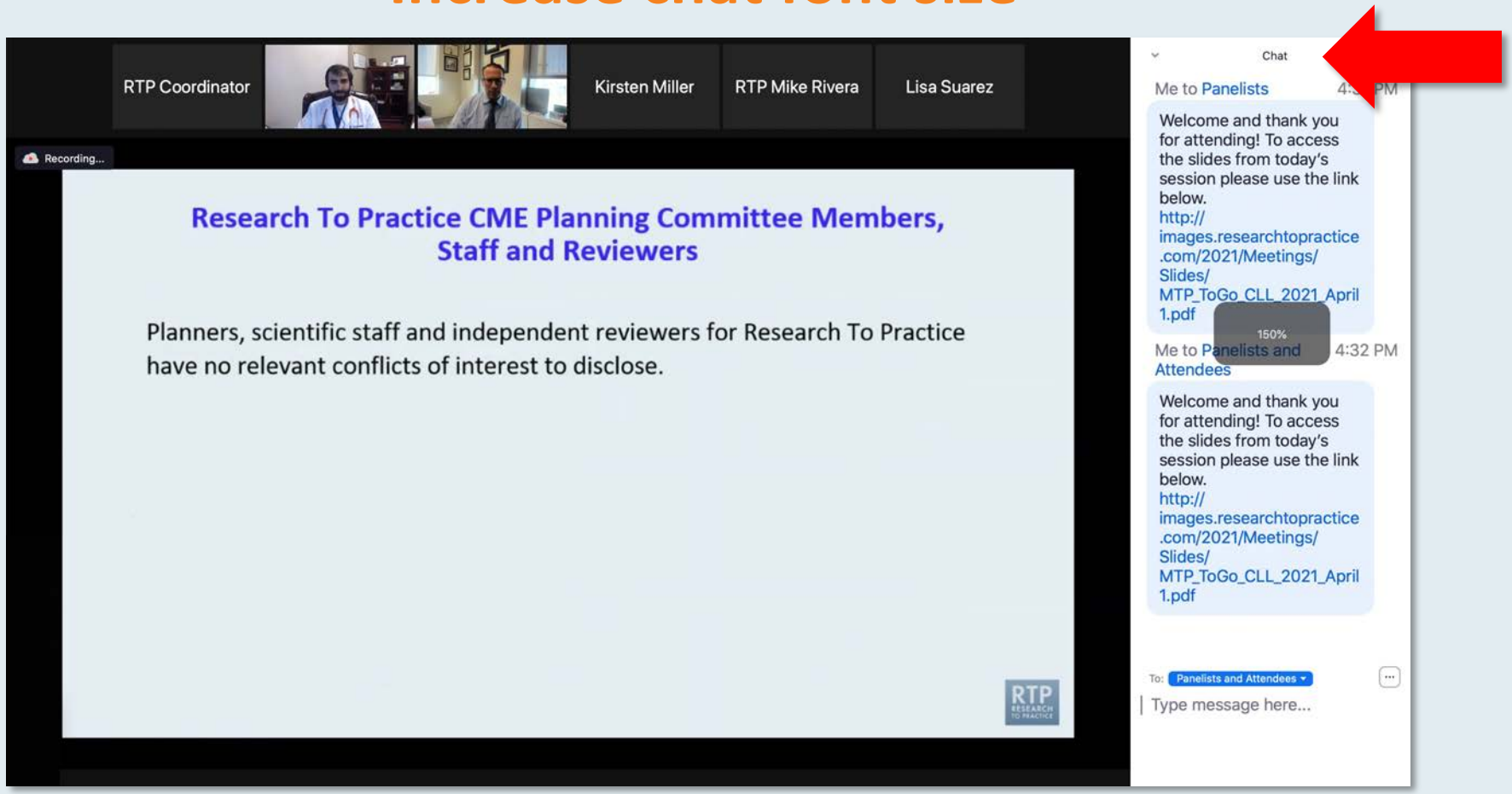

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ONCOLOGY TODAY

WITH DR NEIL LOVE

Key Presentations on Non-Hodgkin and Hodgkin Lymphomas from the 2020 ASH Annual Meeting

DR LAURIE SEHN

BC CANCER CENTRE FOR LYMPHOID CANCER

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Meet The Professor

Optimizing the Selection and Sequencing of Therapy for Patients with ER-Positive Breast Cancer

Wednesday, October 6, 2021
5:00 PM – 6:00 PM ET

Faculty

Virginia Kaklamani, MD, DSc

Moderator

Neil Love, MD

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Meet The Professor

Optimizing the Selection and Sequencing of Therapy for Patients with Advanced Gastrointestinal Cancers

Friday, October 8, 2021
12:00 PM – 1:00 PM ET

Faculty

Eileen M O'Reilly, MD

Moderator

Neil Love, MD

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Meet The Professor

Optimizing the Selection and Sequencing of Therapy for Patients with Renal Cell Carcinoma

Monday, October 11, 2021
5:00 PM – 6:00 PM ET

Faculty

Elizabeth R Plimack, MD, MS

Moderator

Neil Love, MD

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Meet The Professor

Immunotherapy and Novel Agents in Gynecologic Cancers

Tuesday, October 12, 2021
5:00 PM – 6:00 PM ET

Faculty

Shannon N Westin, MD, MPH

Moderator

Neil Love, MD

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Meet The Professor

Optimizing the Selection and Sequencing of Therapy for Patients with HER2-Positive Breast Cancer

Wednesday, October 13, 2021
5:00 PM – 6:00 PM ET

Faculty

Erika Hamilton, MD

Moderator

Neil Love, MD

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Recent Advances and Future Directions in Oncology: A Daylong Multitumor Educational Webinar in Partnership with Florida Cancer Specialists

A CME-MOC/NCPD Accredited Virtual Event

Saturday, October 23, 2021
9:30 AM – 4:30 PM ET

Faculty

Tanios Bekaii-Saab, MD
Kristen K Ciombor, MD, MSCI
Brad S Kahl, MD
Mark Levis, MD, PhD
Mark D Pegram, MD
Daniel P Petrylak, MD
Noopur Raje, MD
David Sallman, MD
Lecia V Sequist, MD, MPH
David R Spigel, MD

Additional faculty to be announced.

Moderator

Neil Love, MD

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Thank you for joining us!

CME credit information will be emailed to each participant within 3 business days.

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St Louis, Missouri

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Neil Love, MD
Research To Practice
Miami, Florida

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Contributing Oncologist

Warren S Brenner, MD
Lynn Cancer Institute
Boca Raton, Florida

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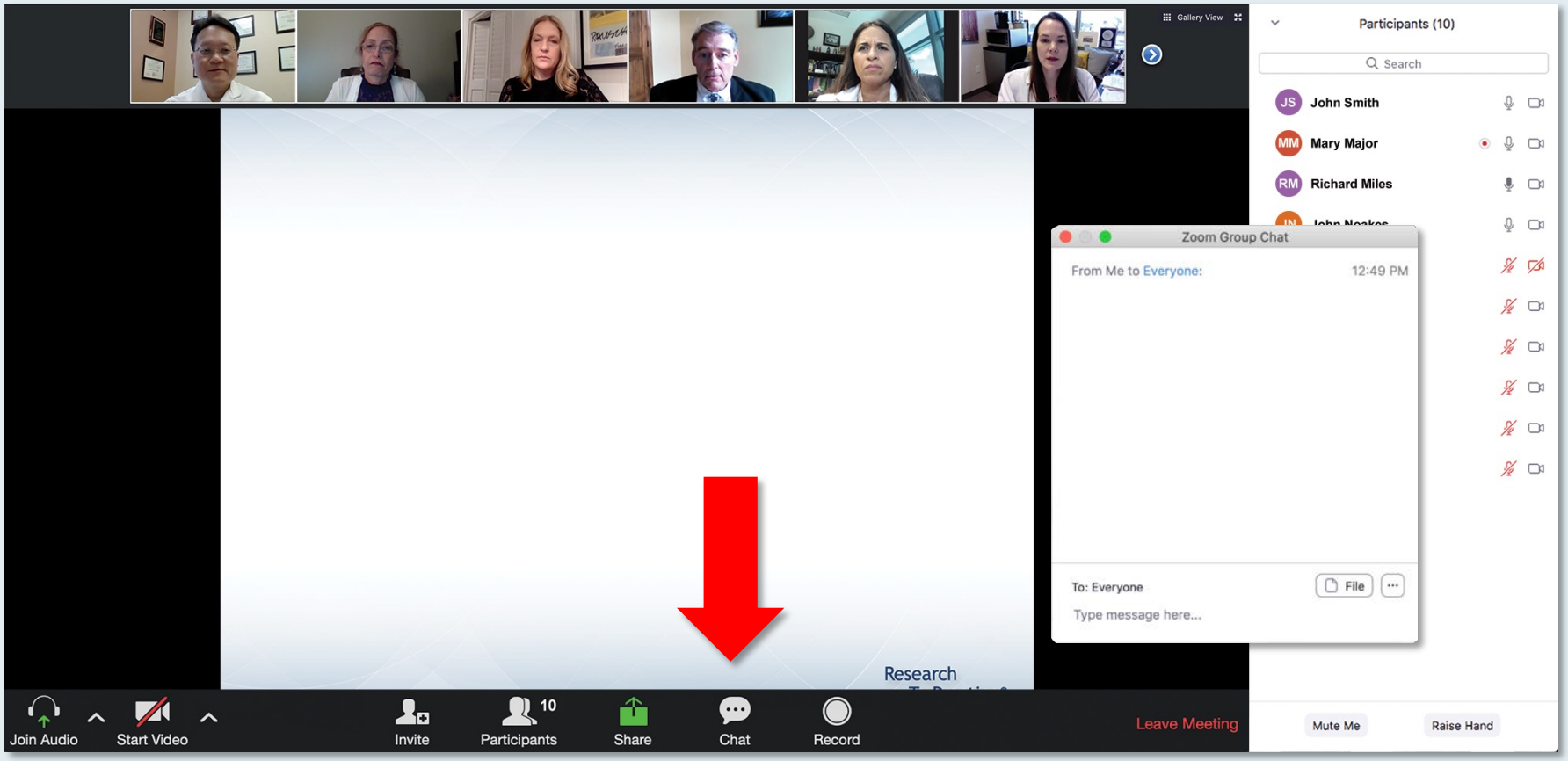

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Module 1: Breast Cancer – 9:30 AM – 10:20 AM

Module 2: Lung Cancer – 10:30 AM – 11:20 AM

Module 3: Gastrointestinal Cancers – 11:30 AM – 12:20 PM

Module 4: Genitourinary Cancers – 12:30 PM – 1:20 PM

Module 5: CLL and Lymphomas – 1:30 PM – 2:20 PM

Module 6: Multiple Myeloma – 2:30 PM – 3:20 PM

Module 7: AML and MDS – 3:30 PM – 4:20 PM

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Agenda

Module 1: Chronic Lymphocytic Leukemia (CLL)

- Prevention and management of cardiovascular issues associated with Bruton tyrosine kinase (BTK) inhibitors
- Amelioration of tumor lysis syndrome (TLS) and other adverse events with venetoclax and anti-CD antibody combinations

Module 2: Mantle Cell Lymphoma (MCL)

- Prevention and management of cardiovascular issues associated with BTK inhibitors
- Amelioration of TLS and other adverse events with venetoclax-based regimens

Module 3: Novel Agents and Strategies in CLL and MCL

Agenda

Module 1: Chronic Lymphocytic Leukemia (CLL)

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Module 3: Novel Agents and Strategies in CLL and MCL

Case Presentation – Dr Brenner: A 73-year-old woman with recurrent CLL and ibrutinib-associated atrial fibrillation

Dr Warren Brenner

- 2005: S/p fludarabine/rituximab x 4 for CLL
- 2009: PD → Bendamustine/rituximab (BR) x 4, with good response
- 2014: Progressive leukocytosis, LAD, splenomegaly → Ibrutinib
  - 8/2015: Atrial fibrillation, s/p cardioversion and dronedarone and apixaban
  - 10/2015: Ibrutinib re-challenge then discontinued due to recurrent atrial fibrillation
- 2/2017: Progressive elevation in white count → Dose-reduced BR
- 11/2017 Genetic profiling: New 17p deletion, biallelic deletion of 13q, 3 missense mutations in p53 gene
- 2/2018: Early disease progression → 1/2019: Venetoclax
  - 6/2019: Venetoclax discontinued due to progressive diarrhea and numerous other side effects
- 4/2021: PD, with increasing splenomegaly and abdominal discomfort; increasing WBC count
- Acalabrutinib 100 mg BID

Questions

- ***How often do you see clinically significant reactions other than tumor lysis syndrome with venetoclax? How frequently do you see side effects such as diarrhea and myalgias?***

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CV concerns in CLL and MCL common treatments

General Concerns

- Atrial fibrillation
- QT prolongation
- Ventricular tachycardia (+sudden cardiac death)
- Bleeding

Courtesy of Daniel J Lenihan, MD

Drugs associated with Atrial Fibrillation

- Anthracyclines
- BTK inhibitors (esp ibrutinib)
- Certain VEGF inhibiting TKIs (sorafenib, ponatinib)
- IMiDs (esp thalidomide, ? lenalidomide)
- Checkpoint inhibitors
- SCT with melphalan

Courtesy of Daniel J Lenihan, MD

Drugs to avoid if there is concern about QT

TABLE 4 Drugs to Avoid (if Possible) in Patients Taking Oral Antineoplastic Agents With QT-Prolonging Potential

Anti-Infective Agents	Antiemetics	Antidepressants	Antipsychotic Agents	Antiarrhythmic Agents	Other
Fluoroquinolones	Domperidone	SSRIs	Clozapine	Amiodarone	Fosphenytoin
Ciprofloxacin	Droperidol	Citalopram	Thioridazine	Disopyramide	Methadone
Levofloxacin	Ondansetron	Escitalopram	Haloperidol	Dofetilide	Methylphenidate
Moxifloxacin		Fluoxetine	Quetiapine	Dronedarone	Phenytoin
Macrolide antibiotics		Paroxetine	Risperidone	Ibutilide	
Azithromycin		Sertraline	Ziprasidone	Procainamide	
Clarithromycin		Trazodone		Quinidine	
Erythromycin		SNRIs		Sotalol	
Azole antifungals		Venlafaxine			
Fluconazole		TCAs			
Itraconazole		Amitriptyline			
Ketoconazole		Clomipramine			
Voriconazole		Desipramine			
Antimalarials		Doxepin			
Chloroquine		Imipramine			
Hydroxychloroquine		Nortriptyline			
Mefloquine					

SNRI = serotonin norepinephrine reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor; TCA = tricyclic antidepressant.

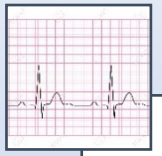
Courtesy of Daniel J Lenihan, MD

Drugs associated with VT
(including sudden death)

- Arsenic
- Certain TKIs (nilotinib, sunitinib, vandetanib)
- Ibrutinib
- Checkpoint inhibitors (esp with myocarditis)
- CDK 4/6 inhibitors (ribociclib)
- CAR-T therapy?

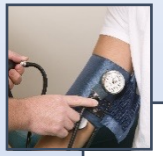
Courtesy of Daniel J Lenihan, MD

Cardiac Impact of Oral Targeted Therapy



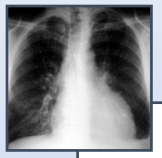
QT Prolongation

- Bosutinib
- Ceritinib
- Crizotinib
- Dabrafenib
- Dasatinib
- Encorafenib
- Entrectinib
- Gilteritinib
- Glasdegib
- Ivosidenib
- Lapatinib
- Lenvatinib
- Midostaurin
- Nilotinib
- Osimertinib
- Panobinostat
- Pazopanib
- Ribociclib
- Sorafenib
- Sunitinib
- Vandetanib
- Vemurafenib
- Vorinostat



Hypertension

- Abiraterone
- Axitinib
- Brigatinib
- Cabozantinib
- Everolimus
- Ibrutinib
- Lenvatinib
- Niraparib
- Pazopanib
- Regorafenib
- Sorafenib
- Sunitinib



Heart Failure

- Binimetinib
- Cobimetinib
- Dabrafenib
- Entrectinib
- Fedratinib
- Lapatinib
- Lenalidomide
- Lenvatinib
- Osimertinib
- Pazopanib
- Pomalidomide
- Ponatinib
- Sunitinib
- Thalidomide
- Trametinib

Courtesy of Daniel J Lenihan, MD

Pathophysiology of Atrial Fibrillation and Potential Mechanisms Whereby a BTK Inhibitor Could Increase Risk

Dr Daniel Lenihan

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Evaluation and Care of Patients Who Develop Atrial Fibrillation

Dr Daniel Lenihan

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Initiating a BTK Inhibitor for Patients on Oral Anticoagulation for Atrial Fibrillation; Variability in Cardiac Arrhythmias Among BTK Inhibitors

Dr Warren Brenner

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Interdisciplinary Care of Patients Who Experience Atrial Fibrillation on Ibrutinib; Risk of Ibrutinib-Associated Bleeding

Dr Daniel Lenihan

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Reinitiating BTK Inhibitor Therapy After a Cardiac Event; Management of BTK Inhibitor-Induced Hypertension

Dr Warren Brenner

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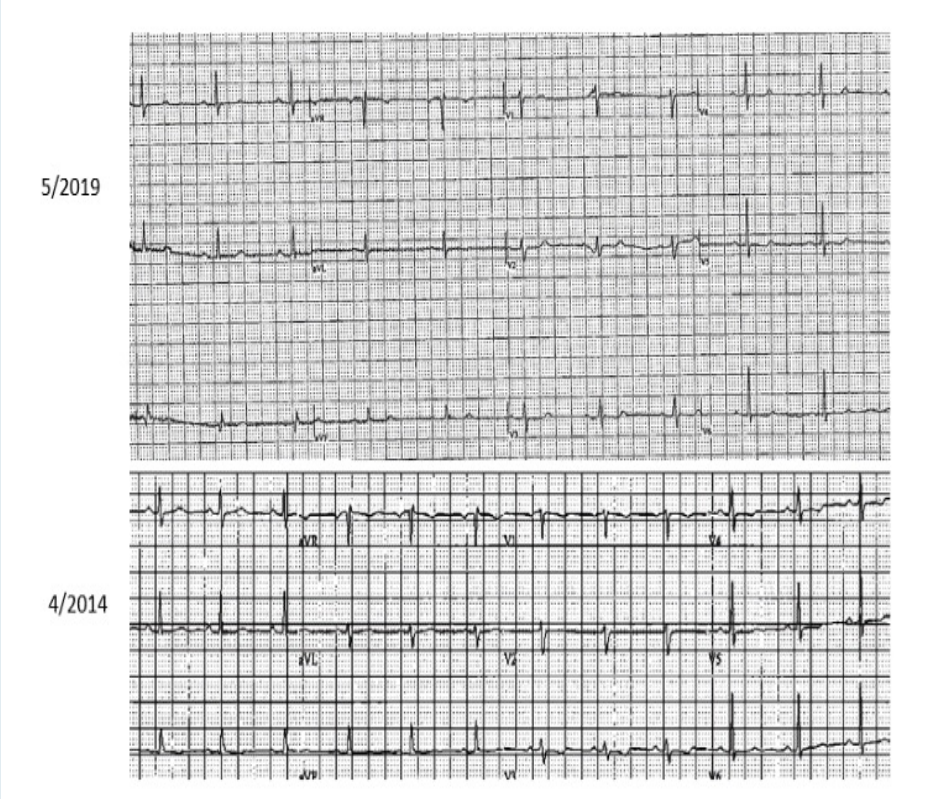
Case Presentation – Dr Lenihan: A 46-year-old woman with CLL in remission on ibrutinib who experiences ventricular fibrillation

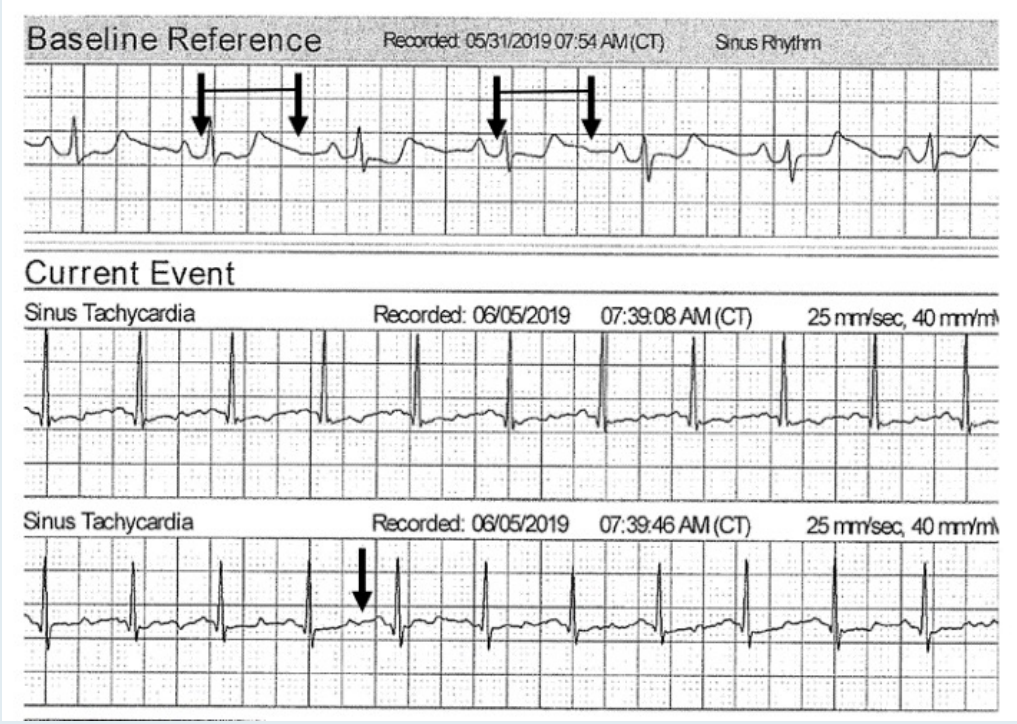
Dr Daniel Lenihan

- Chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma since 2011
- Presented urgently to a local hospital after being found unresponsive in her bedroom by family
- Cardiopulmonary resuscitation initiated
- Patient defibrillated, intubated, and stabilized throughout the next 48 hours
  - Presenting rhythm identified by EMS was ventricular fibrillation
- Subcutaneous implantable cardioverter defibrillator (ICD) implanted without difficulty
- Of note, patient's other medications included dextroamphetamine-amphetamine, levothyroxine, and desvenlafaxine ER
- Additionally, she reported drinking alcohol heavily for three days prior to her cardiac arrest

Case Presentation – Dr Lenihan: A 46-year-old woman with CLL in remission on ibrutinib who experiences ventricular fibrillation (continued)

Dr Daniel Lenihan





After the event, it appeared as though the patient did have intermittent prolongation of the QT interval that is only detected with prolonged monitoring

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Case Presentation – Dr Brenner: A 77-year-old man with CLL who receives obinutuzumab/venetoclax

Dr Warren Brenner

- 9/2000: SLL diagnosed during pelvic lymph node dissection at the time of prostate cancer surgery
- Rising WBC count, with flow cytometry confirming CLL with widespread, non-bulky LAD (del13q, IGHV rearrangement) → Observation
- 6/2020: Obinutuzumab (WBC 2,000 after 2 doses) with venetoclax ramp up

Questions

- In patients who have significantly elevated white count do you have any pearls about the initiation of obinutuzumab?
- How can you potentially decrease the incidence of first-dose reactions when their white count is very high? Are you concerned about tumor lysis syndrome from obinutuzumab, even if it's just biochemical rather than clinical?
- In patients who have a significant drop in their white count do you feel comfortable initiating venetoclax as an outpatient?
- In patients with CLL who have elevated white counts and significant LAD do we have any data regarding how effective obinutuzumab is in decreasing the bulk of their LAD?
- Is there a specific GFR that you use as a cutoff for initiating venetoclax as an inpatient versus on an outpatient basis?

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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].

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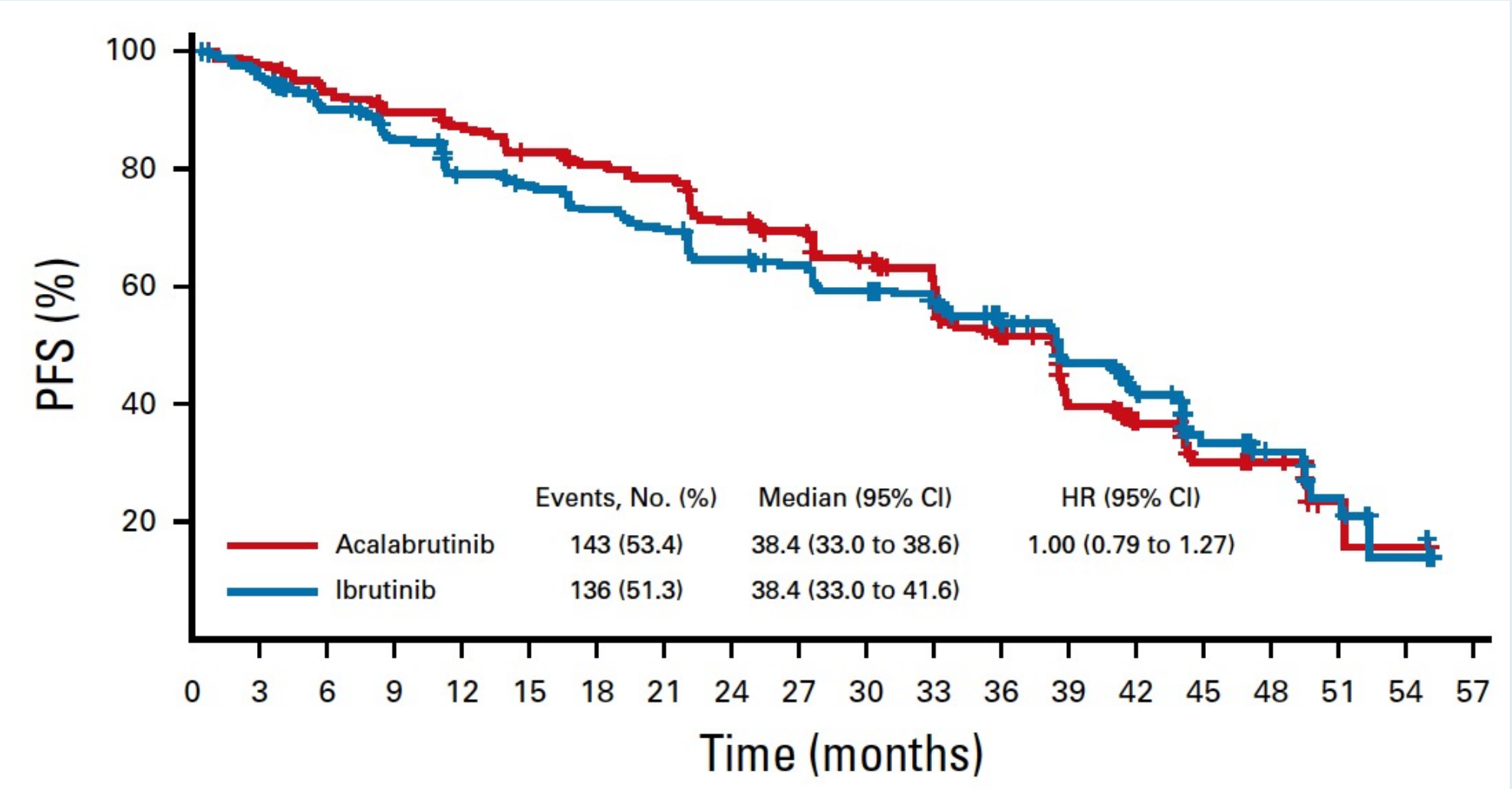
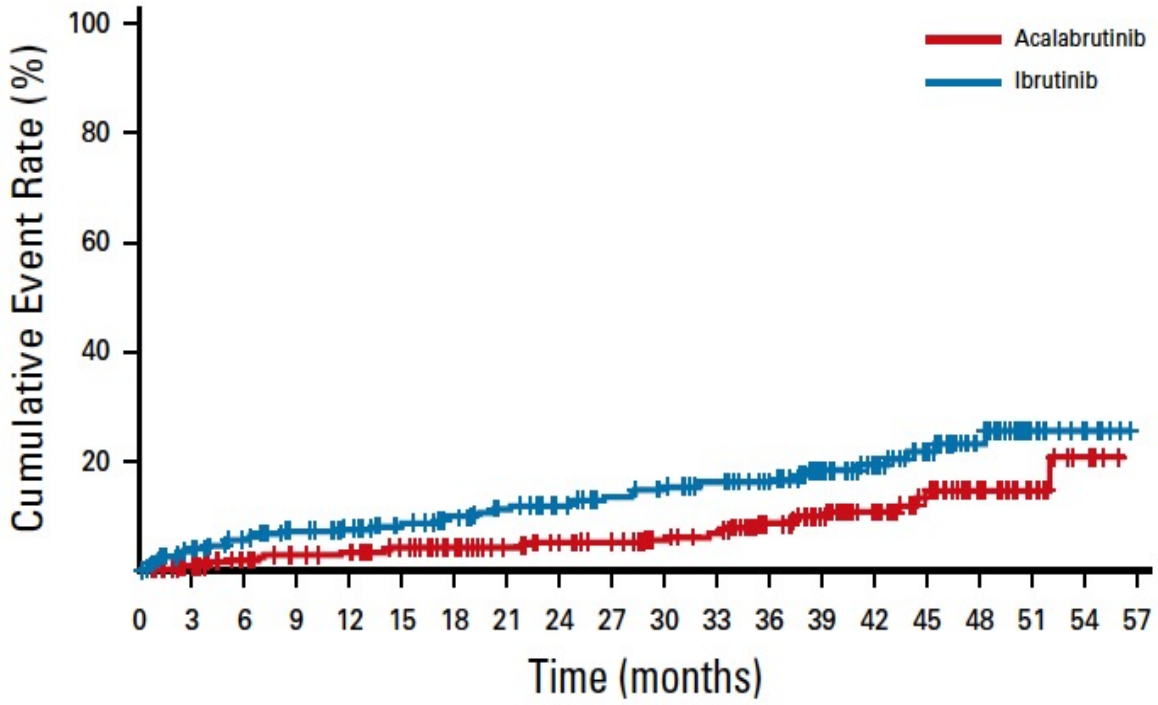
ELEVATE-RR: Primary Endpoint – Noninferiority Met on IRC-Assessed PFS



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

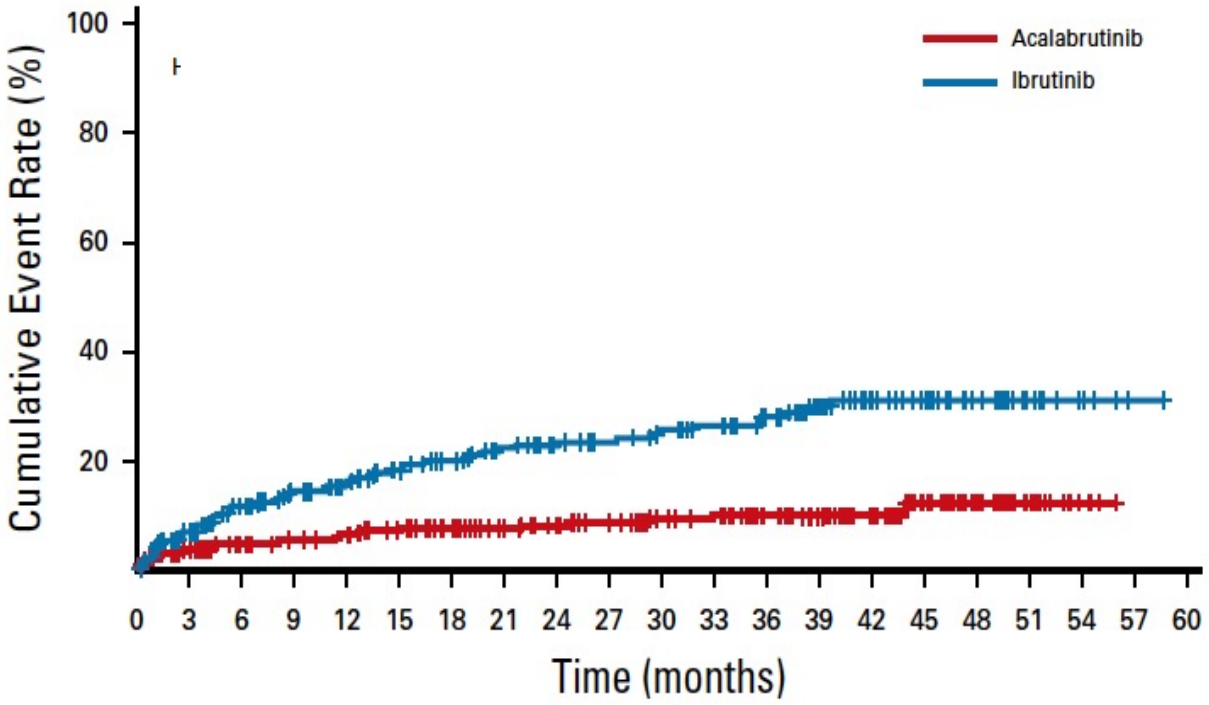
ELEVATE-RR: Cumulative Incidences of Atrial Fibrillation and Hypertension with Acalabrutinib versus Ibrutinib

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.

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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.

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

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June 11, 2021
Presidential Symposium (Abstract LB1900)

EHA

EHA2021 VIRTUAL

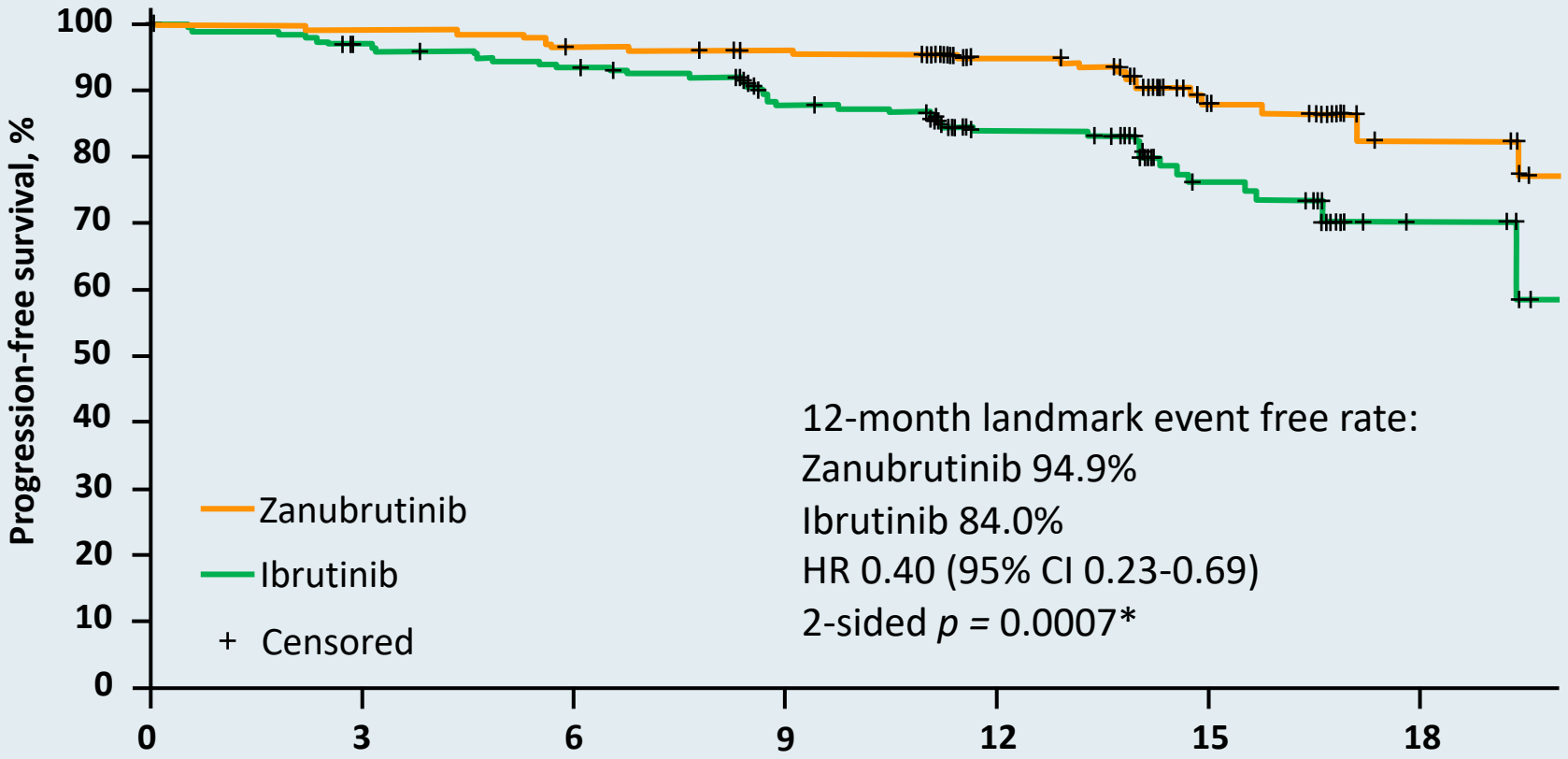
RTP RESEARCH TO PRACTICE

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

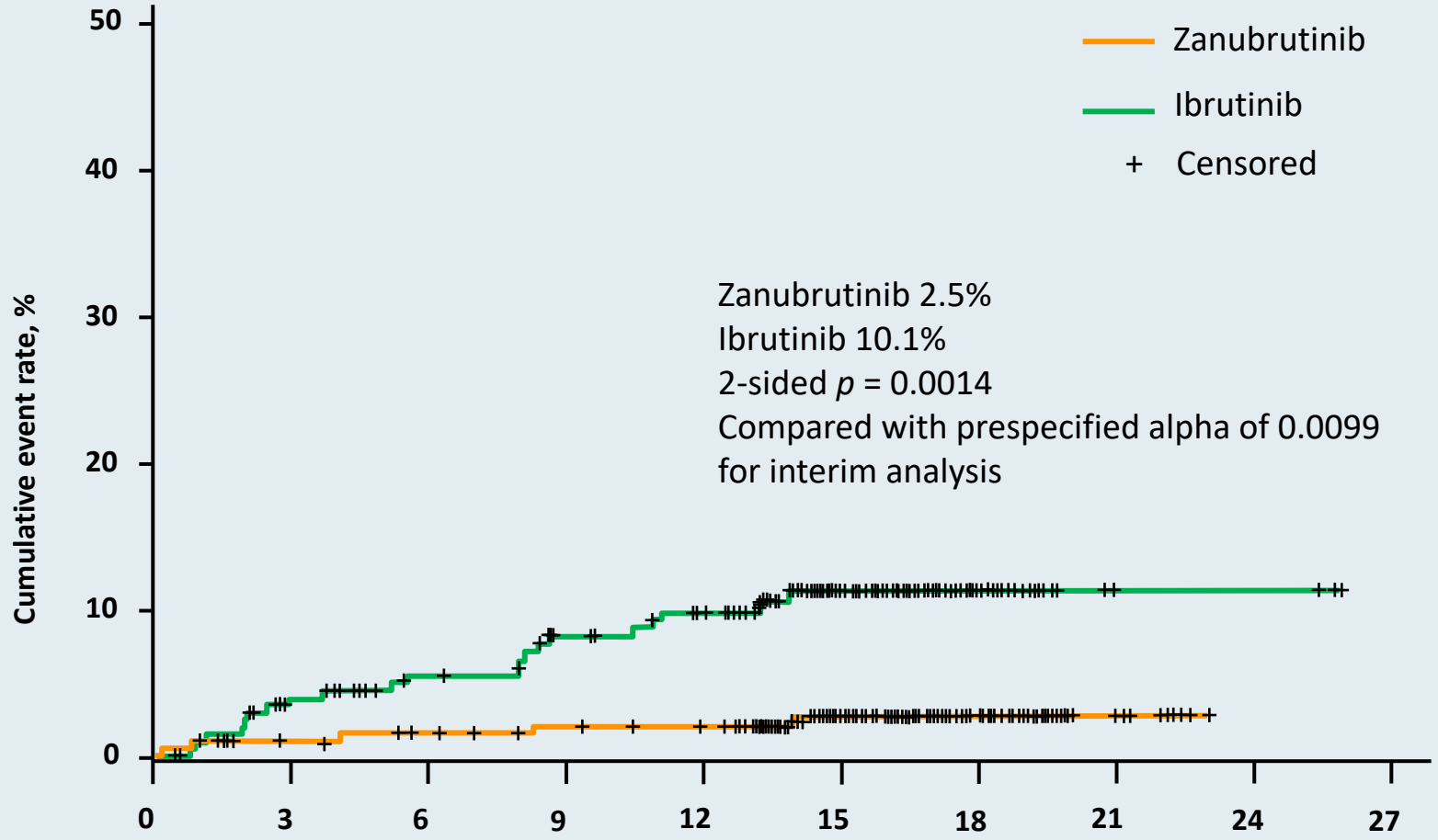
- Although not a pre-specified analysis, the overall 12-month PFS was higher with zanubrutinib vs ibrutinib (94.9% vs 84.0%)

*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.

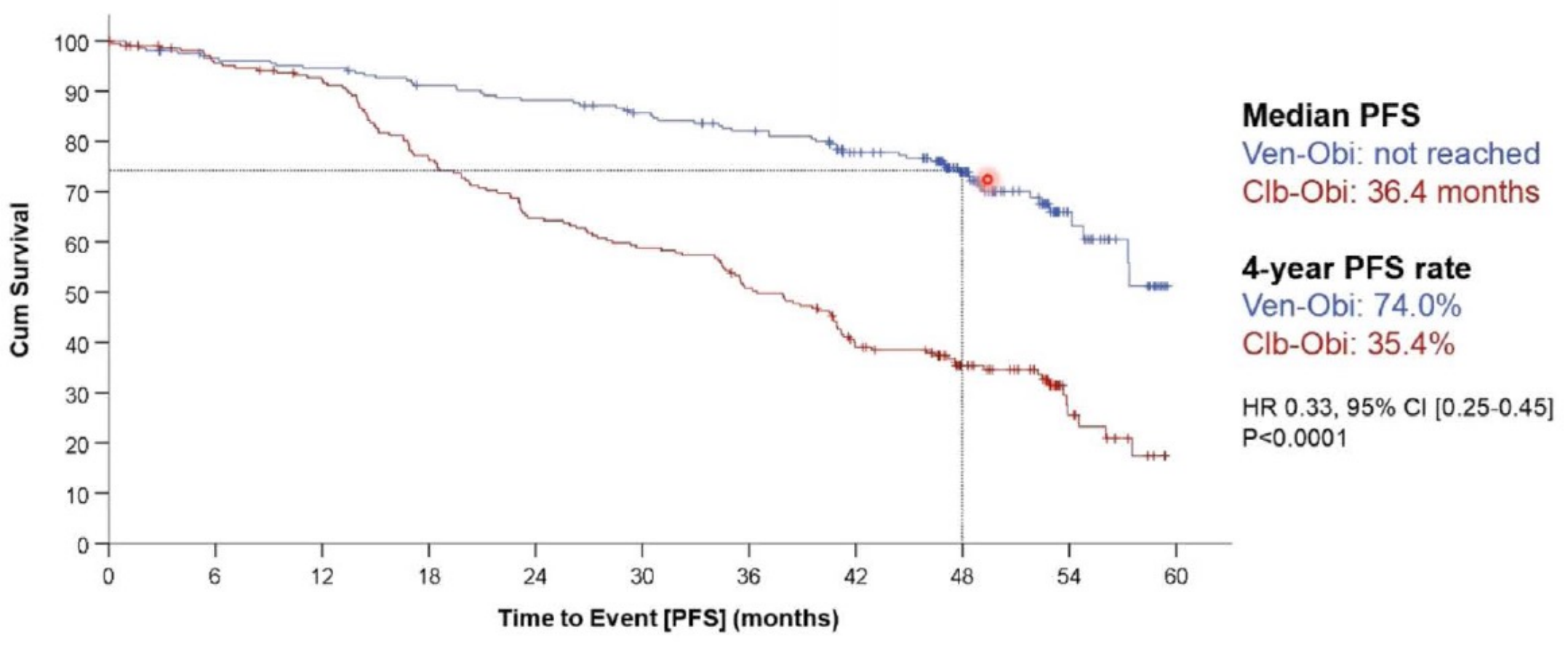
Articles

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



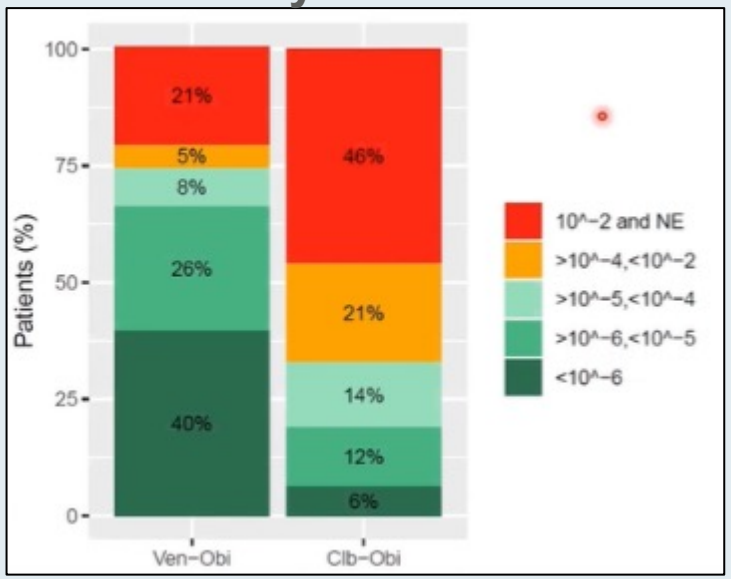
Median observation time: 52.4 months

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

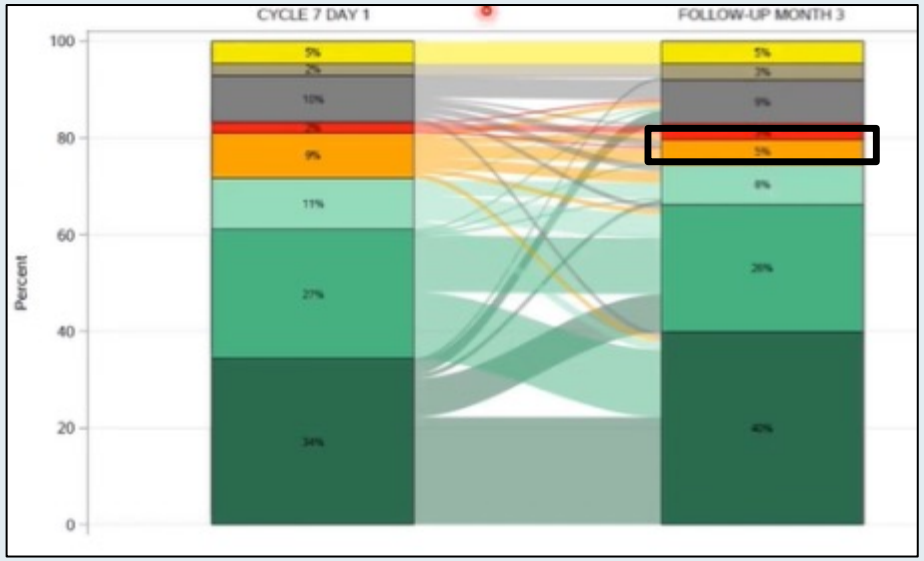
RTP RESEARCH TO PRACTICE

CLL14: Clonal Dynamics After Venetoclax-Obinutuzumab Therapy

MRD by NGS at EOT

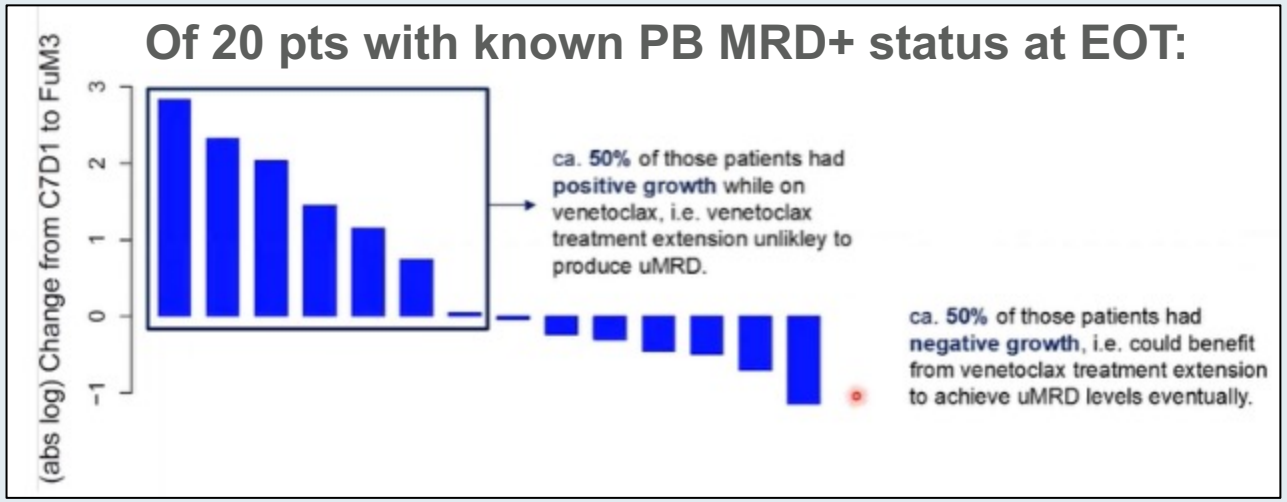


MRD During and After Ven-Obi



- 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?

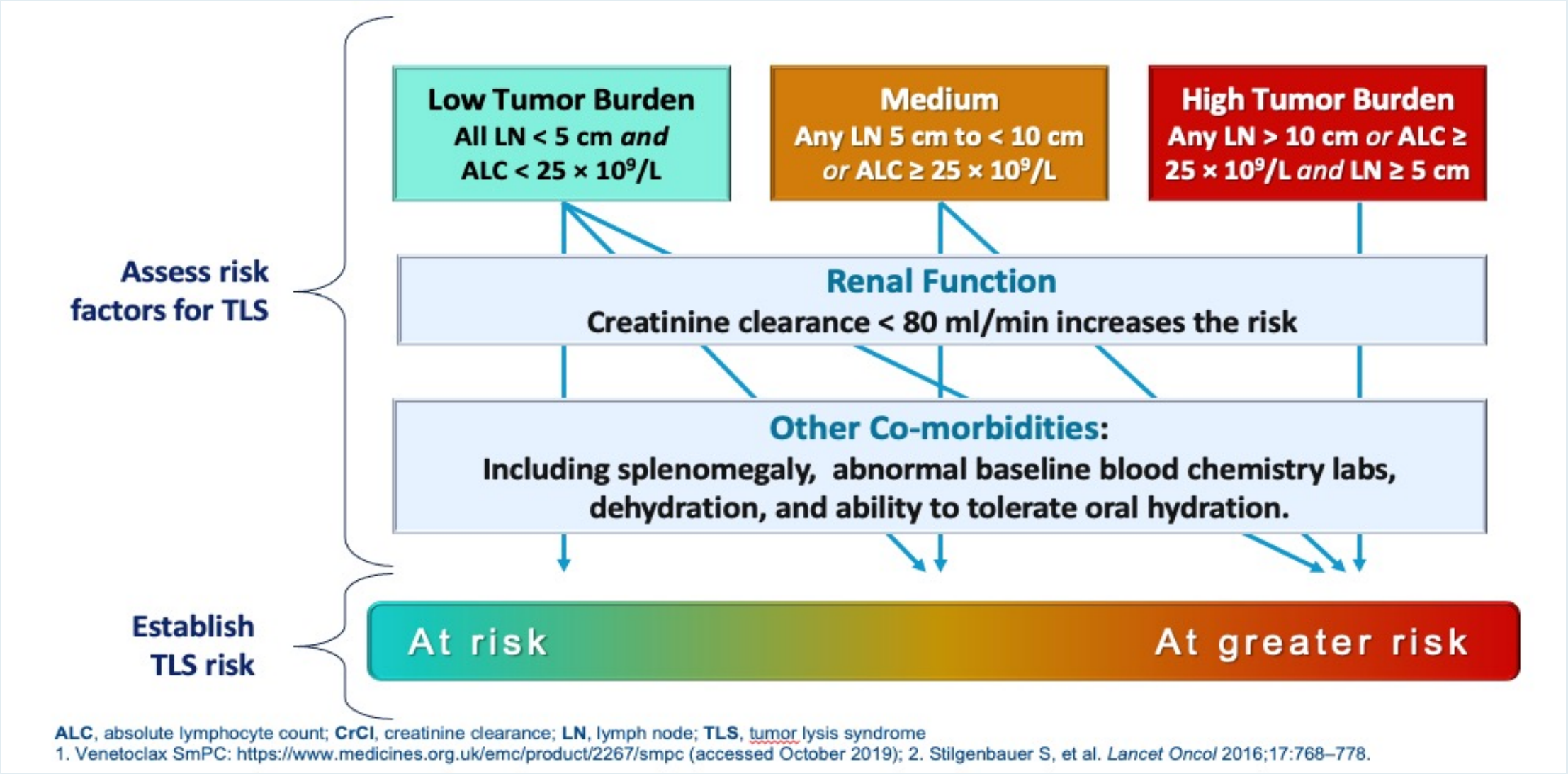
Of 20 pts with known PB MRD+ status at EOT:



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

RTP RESEARCH TO PRACTICE

TLS Risk with Venetoclax Is a Continuum Based on Multiple Factors



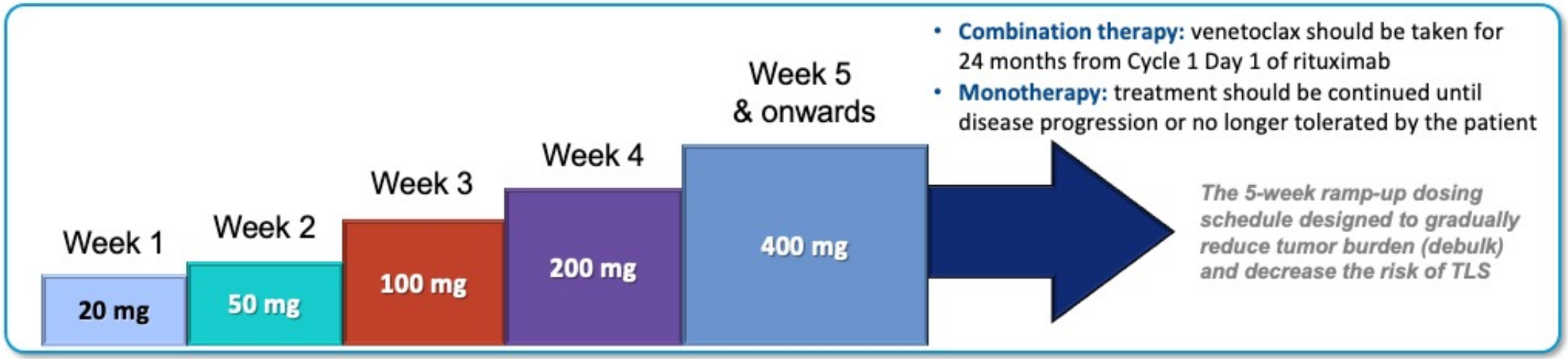
ALC, absolute lymphocyte count; **CrCl**, creatinine clearance; **LN**, lymph node; **TLS**, tumor lysis syndrome

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

RTP RESEARCH TO PRACTICE

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

RTP RESEARCH TO PRACTICE

Agenda

Module 1: Chronic Lymphocytic Leukemia (CLL)

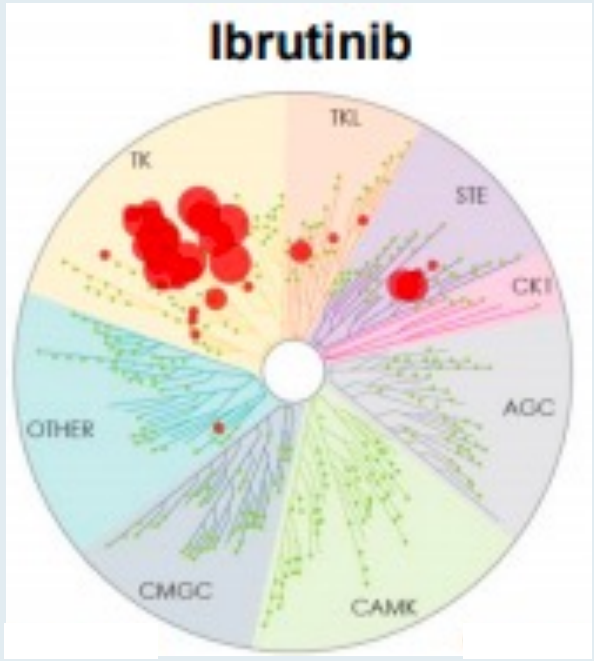
- Prevention and management of cardiovascular issues associated with Bruton tyrosine kinase (BTK) inhibitors
- Amelioration of tumor lysis syndrome (TLS) and other adverse events with venetoclax and anti-CD antibody combinations

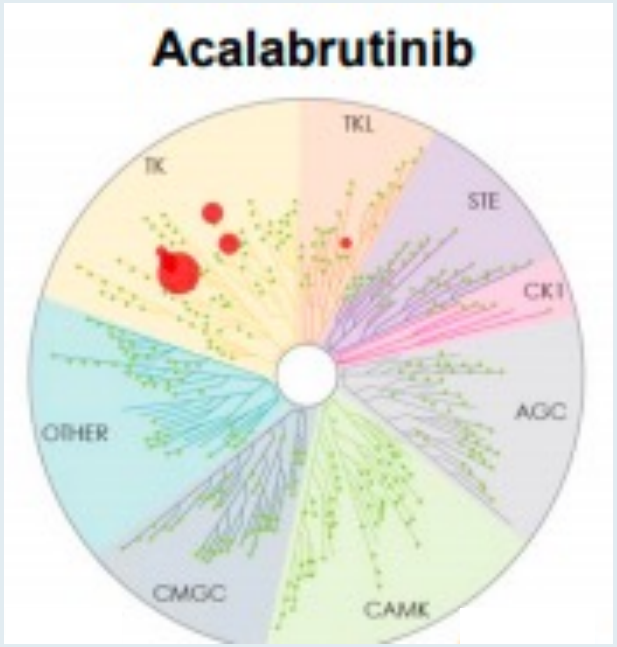
Module 2: Mantle Cell Lymphoma (MCL)

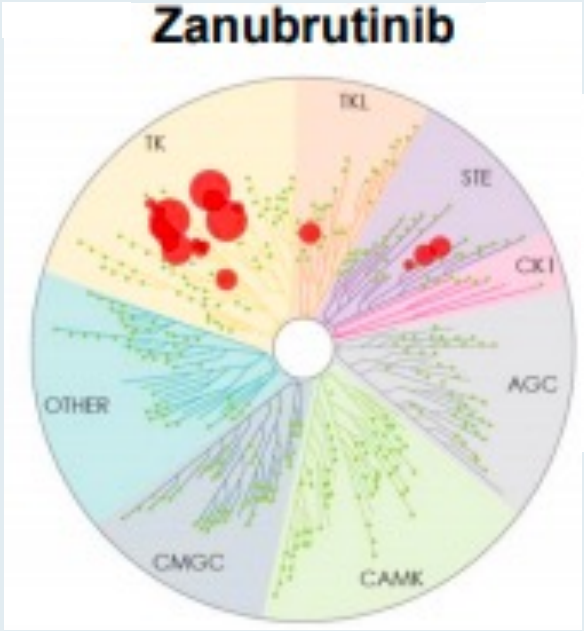
- Prevention and management of cardiovascular issues associated with BTK inhibitors
- Amelioration of TLS and other adverse events with venetoclax-based regimens

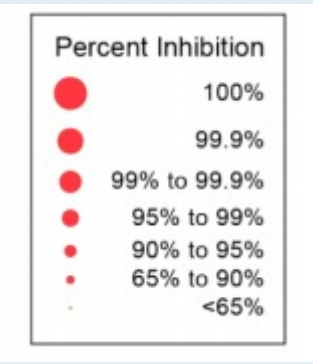
Module 3: Novel Agents and Strategies in CLL and MCL

FDA-Approved BTK Inhibitors for Relapsed MCL









Second-generation BTKi were designed to maximize BTK occupancy and minimize off-target inhibition of TEC- and EGFR-family kinases

RTP RESEARCH TO PRACTICE

Pooled Analysis of Ibrutinib for R/R MCL: Median 41 Months Follow-Up

(Phase II PCYC-1104 and SPARK and Phase III RAY Studies)

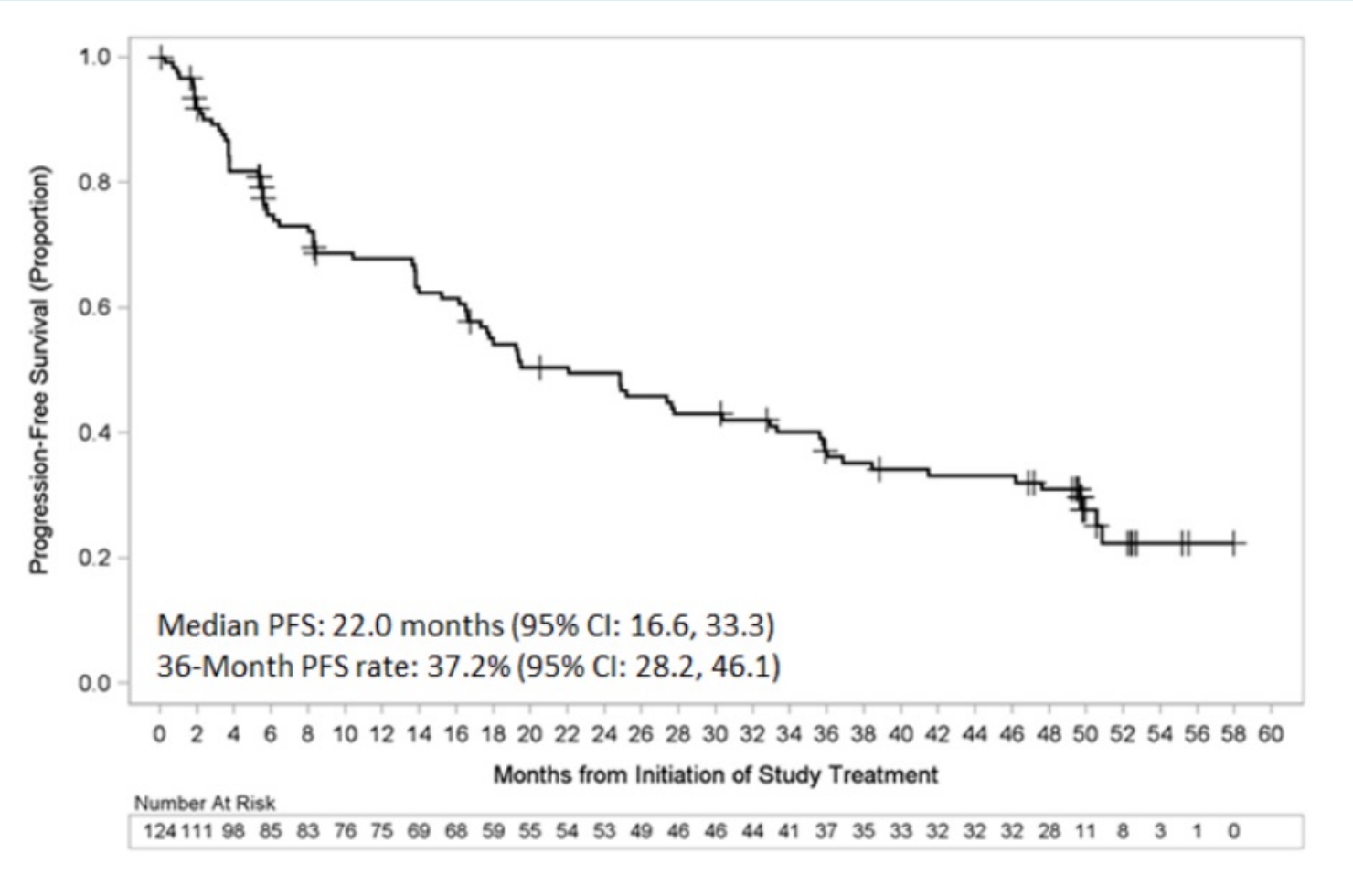
Endpoint	Overall (N = 370)	Prior lines of therapy	
		1 (n = 99)	>1 (n = 271)
Median PFS	**12.5 mo**	**25.4 mo**	**10.3 mo**
Median PFS by best response CR (n = 102) PR (n = 156)	 67.7 mo 12.6 mo	 68.5 mo 24.2 mo	 67.7 mo 10.5 mo
Median OS	**26.7 mo**	**61.6 mo**	**22.5 mo**
Median OS by best response CR (n = 102) PR (n = 156)	 Not reached 23.6 mo	 Not reached 36.0 mo	 Not reached 22.6 mo
ORR, CR	**70%, 28%**	**78%, 37%**	**67%, 24%**

Rule S et al. ASH 2019;Abstract 1538.

Acalabrutinib Monotherapy in Patients with Relapsed/Refractory Mantle Cell Lymphoma: Long-Term Efficacy and Safety Results from a Phase 2 Study

Wang M et al.
ASH 2020;Abstract 2040.

ACE-LY-004 Long-Term Follow-Up: Progression-Free Survival



The adverse event profile was largely unchanged with an additional year of follow-up.

Wang M et al. ASH 2020;Abstract 2040.

RTP RESEARCH TO PRACTICE

Efficacy of Zanubrutinib for MCL

Study	Evaluable patients	ORR, CR	Median DoR	Median PFS
Phase I/II (NCT02343120)	N = 48 R/R = 37 TN = 11	87%, 31% 87%, 30% 88%, 38%	16.2 mo (all) 14.7 mo 14.7 mo	15.4 mo
Phase II (NCT03206970)	N = 86 R/R	84%, 69%	19.5 mo	22.1 mo

Song Y et al. ICML 2019;Abstract 015; Tam CS et al. ICML 2019;Abstract 191;
Tam CS. *Clin Advances in Hem Oncol* 2019;17(1):32-34; Song Y et al. *Clin Cancer Res* 2020;26(16):4216-24.

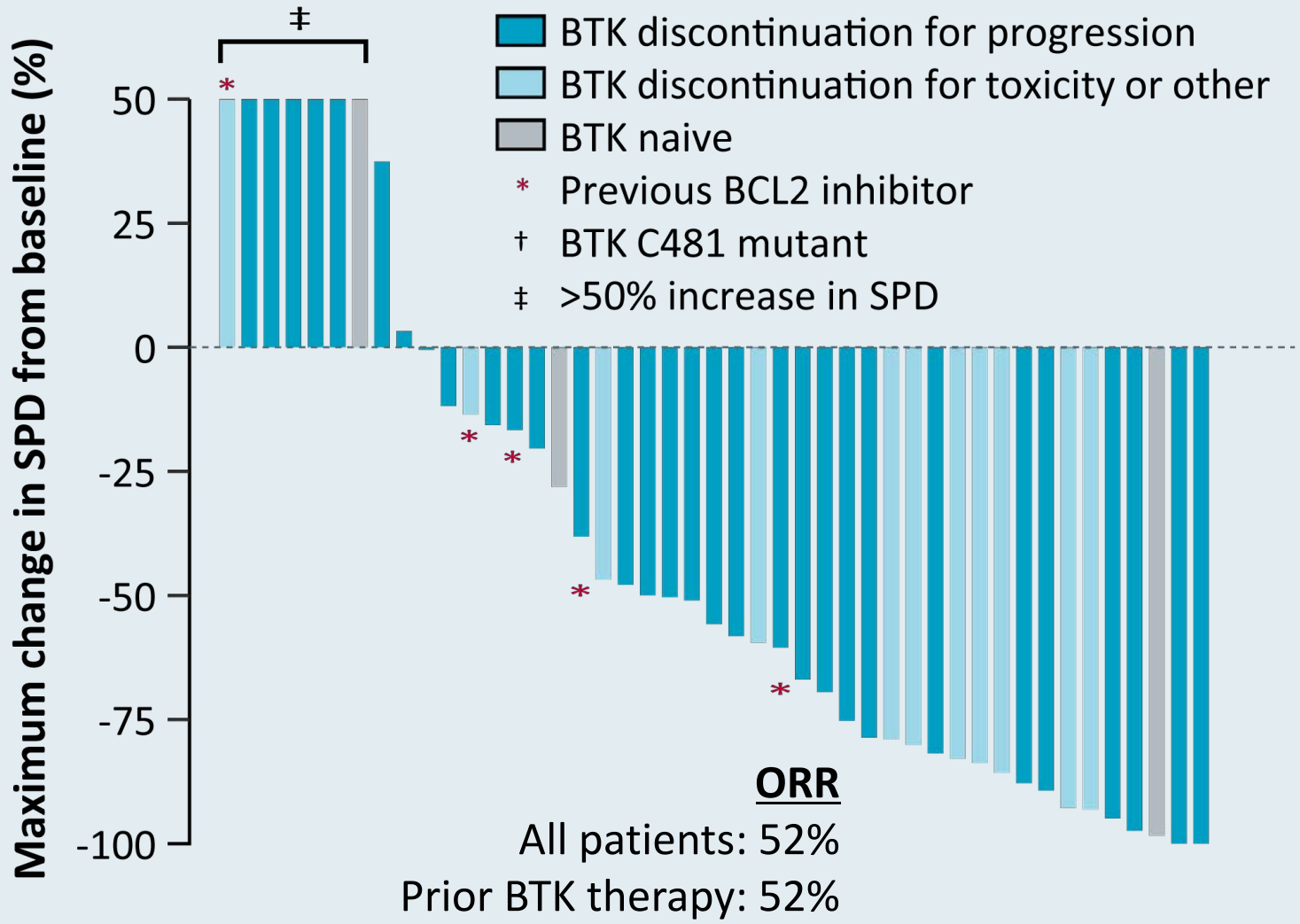
Articles

Pirtobrutinib in relapsed or refractory B-cell malignancies (BRUIN): a phase 1/2 study

Anthony R Mato, Nirav N Shah, Wojciech Jurczak, Chan Y Cheah, John M Pagel, Jennifer A Woyach, Bita Fakhri, Toby A Eyre, Nicole Lamanna, Manish R Patel, Alvaro Alencar, Ewa Lech-Maranda, William G Wierda, Catherine C Coombs, James N Gerson, Paolo Ghia, Steven Le Gouill, David John Lewis, Suchitra Sundaram, Jonathon B Cohen, Ian W Flinn, Constantine S Tam, Minal A Barve, Bryone Kuss, Justin Taylor, Omar Abdel-Wahab, Stephen J Schuster, M Lia Palomba, Katharine L Lewis, Lindsey E Roeker, Matthew S Davids, Xuan Ni Tan, Timothy S Fenske, Johan Wallin, Donald E Tsai, Nora C Ku, Edward Zhu, Jessica Chen, Ming Yin, Binoj Nair, Kevin Ebata, Narasimha Marella, Jennifer R Brown, Michael Wang

Lancet 2021;397(10277):892-901.

BRUIN: Change in Tumor Burden from Baseline with Pirtobrutinib (LOXO-305) in Evaluable Patients with MCL



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

RTP RESEARCH TO PRACTICE

Venetoclax Monotherapy for BTK Inhibitor-Resistant MCL: Results Summary

Clinical endpoint	Venetoclax (N = 20)
Overall response rate (ORR) Complete response rate	60% 20%
ORR (prior response to BTKi) ORR (primary resistance to BTKi)	72.7% 44.4%
Median PFS	2.6 mo
Median OS	4.3 mo

No cases of clinical TLS were observed.

Eyre T et al. EHA 2018;Abstract S855.

Agenda

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Module 3: Novel Agents and Strategies in CLL and MCL

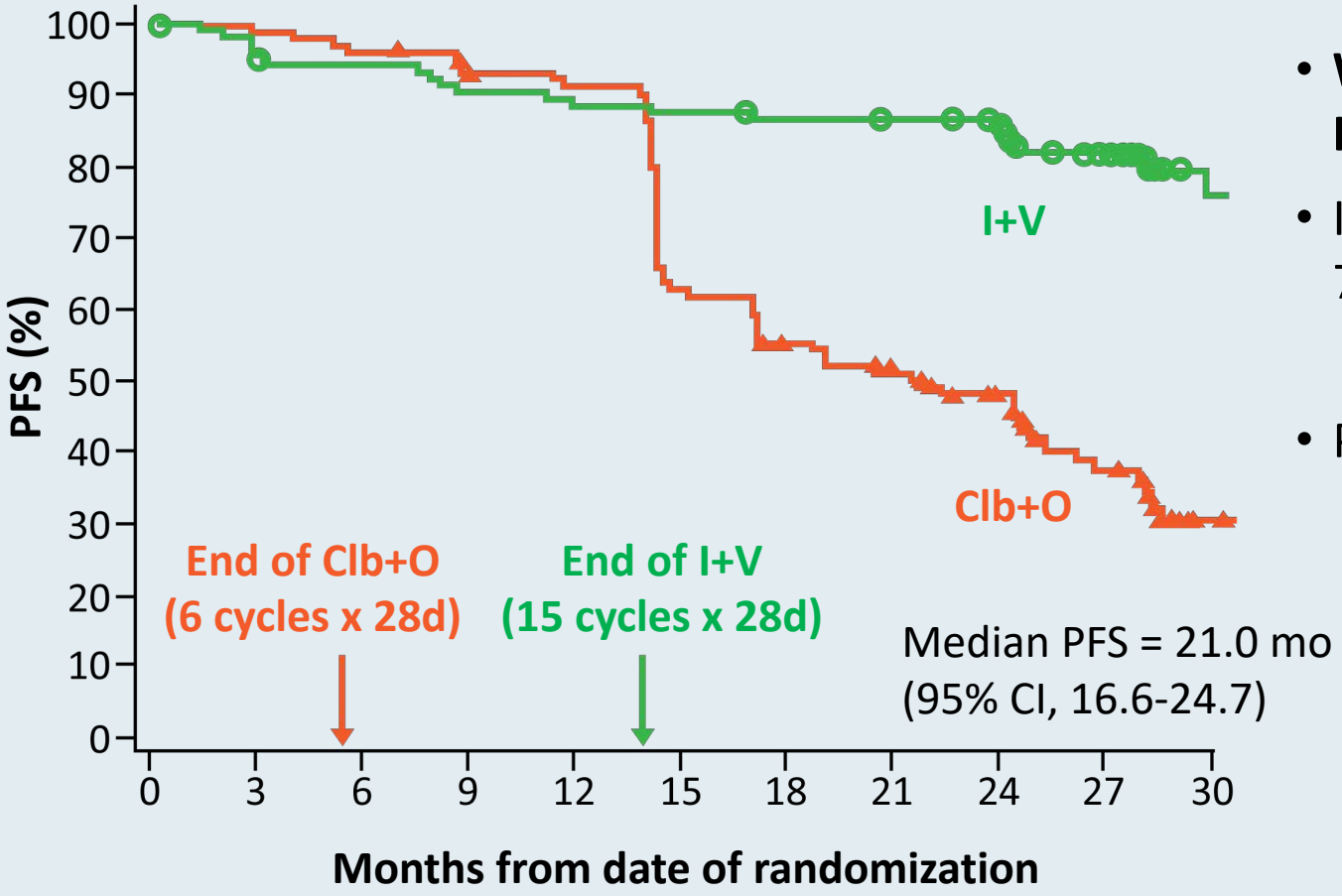
FIXED-DURATION IBRUTINIB PLUS VENETOCLAX (I+V) VERSUS CHLORAMBUCIL PLUS OBINUTUZUMAB (CLB+O) FOR FIRST-LINE TREATMENT OF CHRONIC LYMPHOCYTIC LEUKEMIA (CLL): PRIMARY ANALYSIS OF THE PHASE 3 GLOW STUDY

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

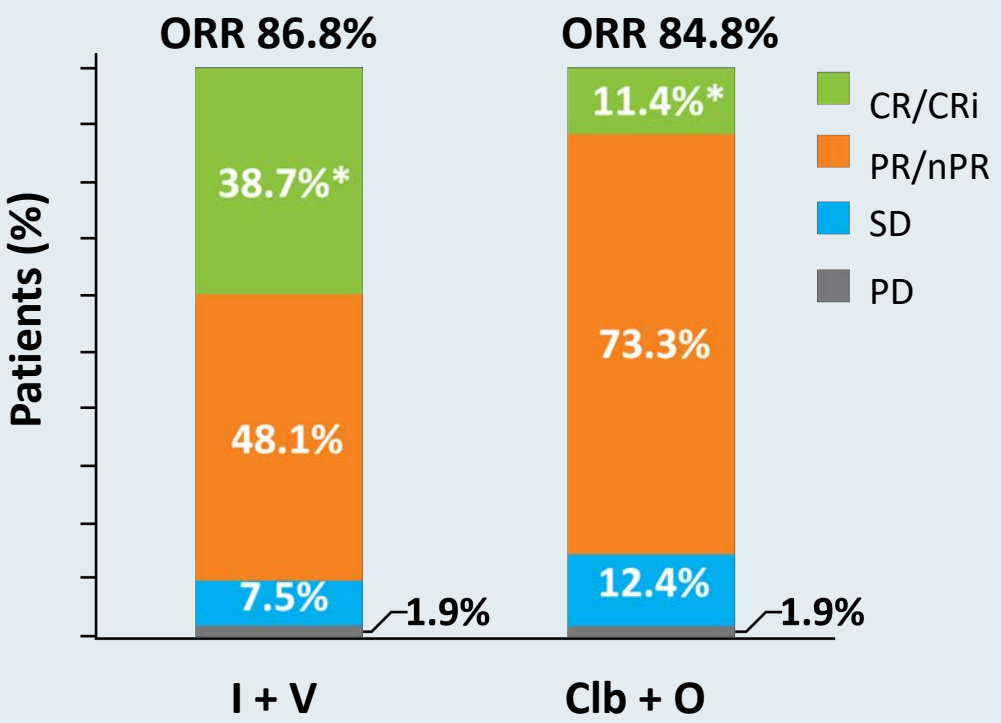


- **With a median follow up of 27.7 months, IRC-assessed PFS for I + V was superior to Clb + O**
- I + V reduced the risk of progression or death by 78% vs Clb + O
  - **HR 0.216** (95% CI, 0.131-0.357; $p < 0.0001$)
- PFS by INV assessment was consistent with IRC
  - **HR 0.207** (95% CI, 0.120-0.357;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

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%

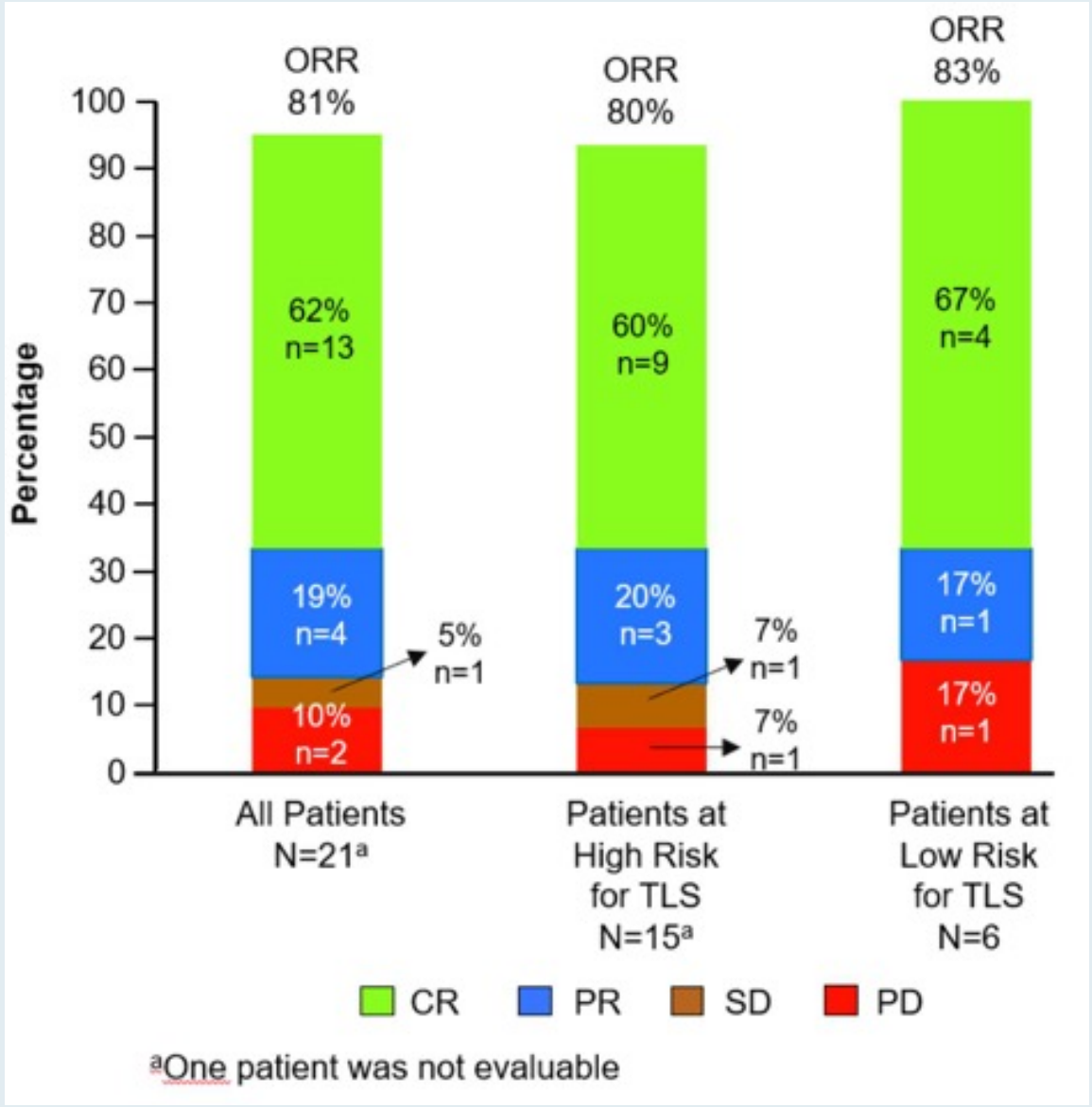
Kater AP et al. EHA 2021;Abstract LB1902.

Ibrutinib plus Venetoclax in Patients with Relapsed/Refractory Mantle Cell Lymphoma: Results from the Safety Run-In Period of the Phase 3 SYMPATICO Study

Tam CS et al.

ASH 2020;Abstract 2938.

SYMPATICO: Response in Patients at High and Low Risk for TLS



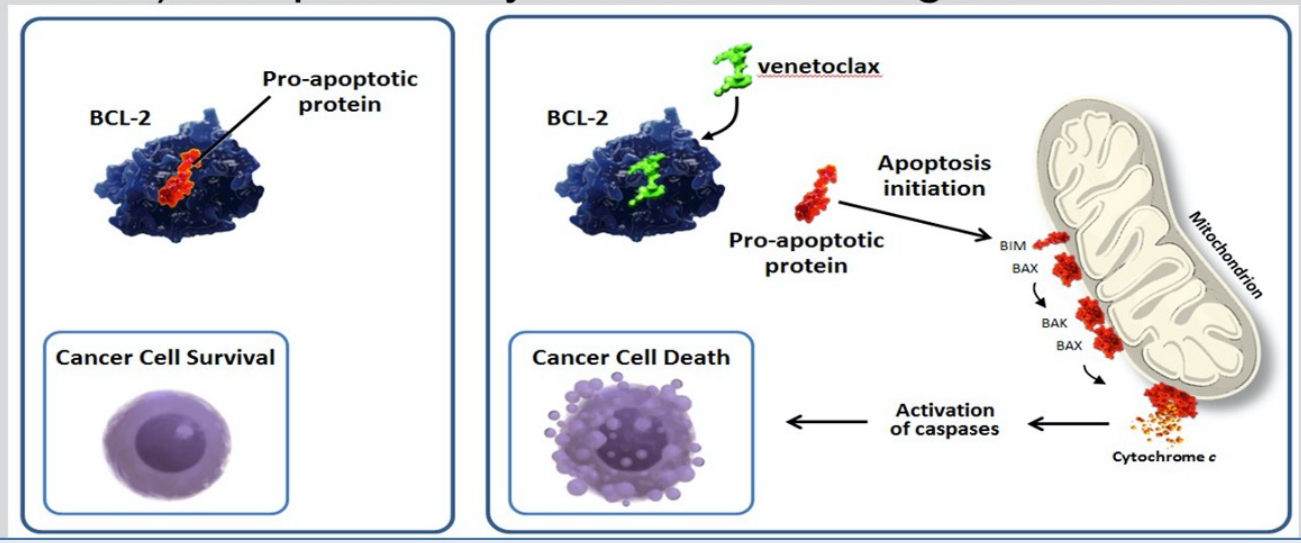
Tam CS et al. ASH 2020;Abstract 2938.

The Combination of Venetoclax, Lenalidomide, and Rituximab in Patients with Newly Diagnosed Mantle Cell Lymphoma Induces High Response Rates and MRD Undetectability

Phillips TJ et al.
ASCO 2021;Abstract 7505.

Biologic Rationale for Combining Venetoclax with R^2

- Venetoclax is oral BCL-2 inhibitor with a current FDA approval in CLL and R/R AML.
- Study by Davids et al. demonstrated efficacy in R/R MCL[1].
- Pre-clinical data suggested synergy with lenalidomide[2].
- We hypothesized that the combination of venetoclax, lenalidomide and rituximab would be safe with the potential to improve ORR, time to best response (as compared to what was reported for R2) and potentially induce MRD negative disease.



Phillips TJ et al. ASCO 2021;Abstract 7505.

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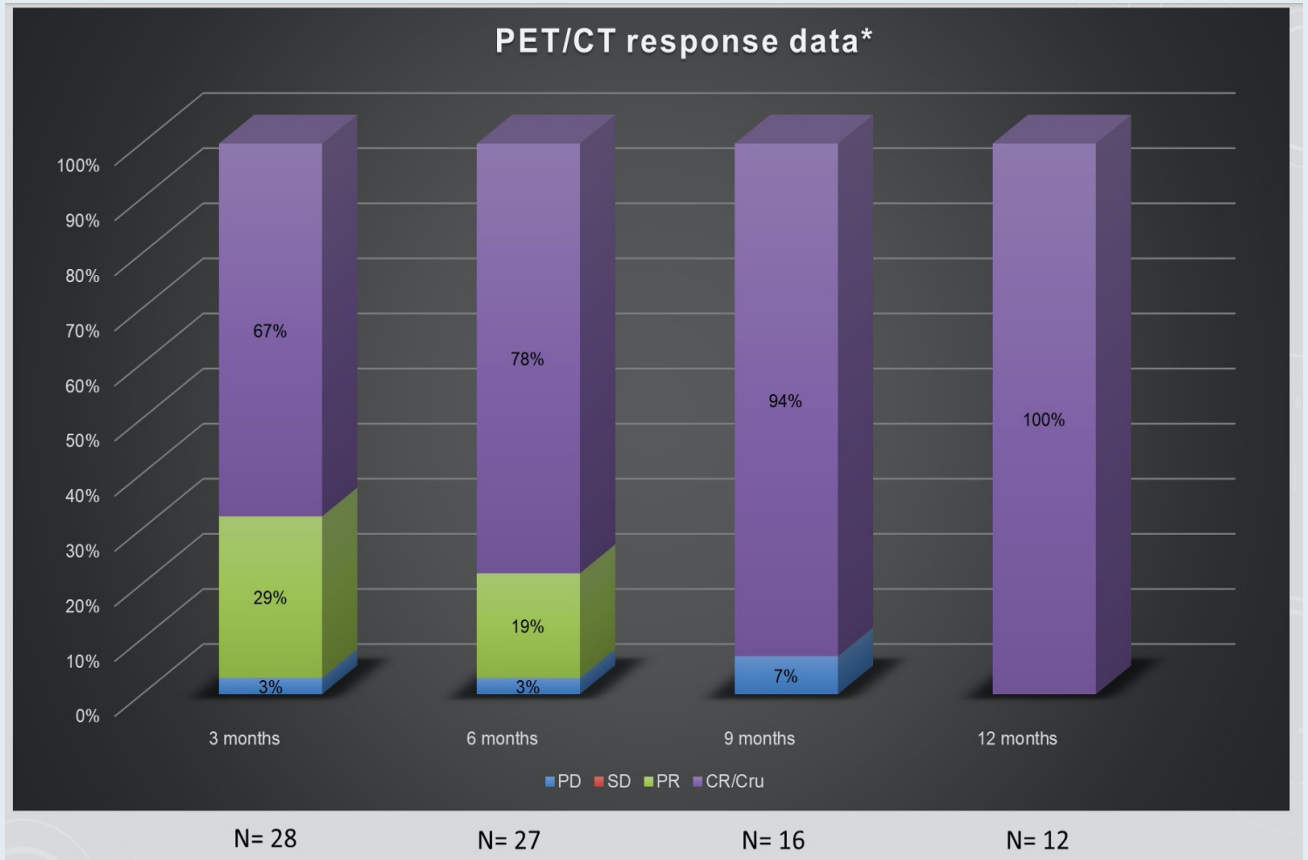
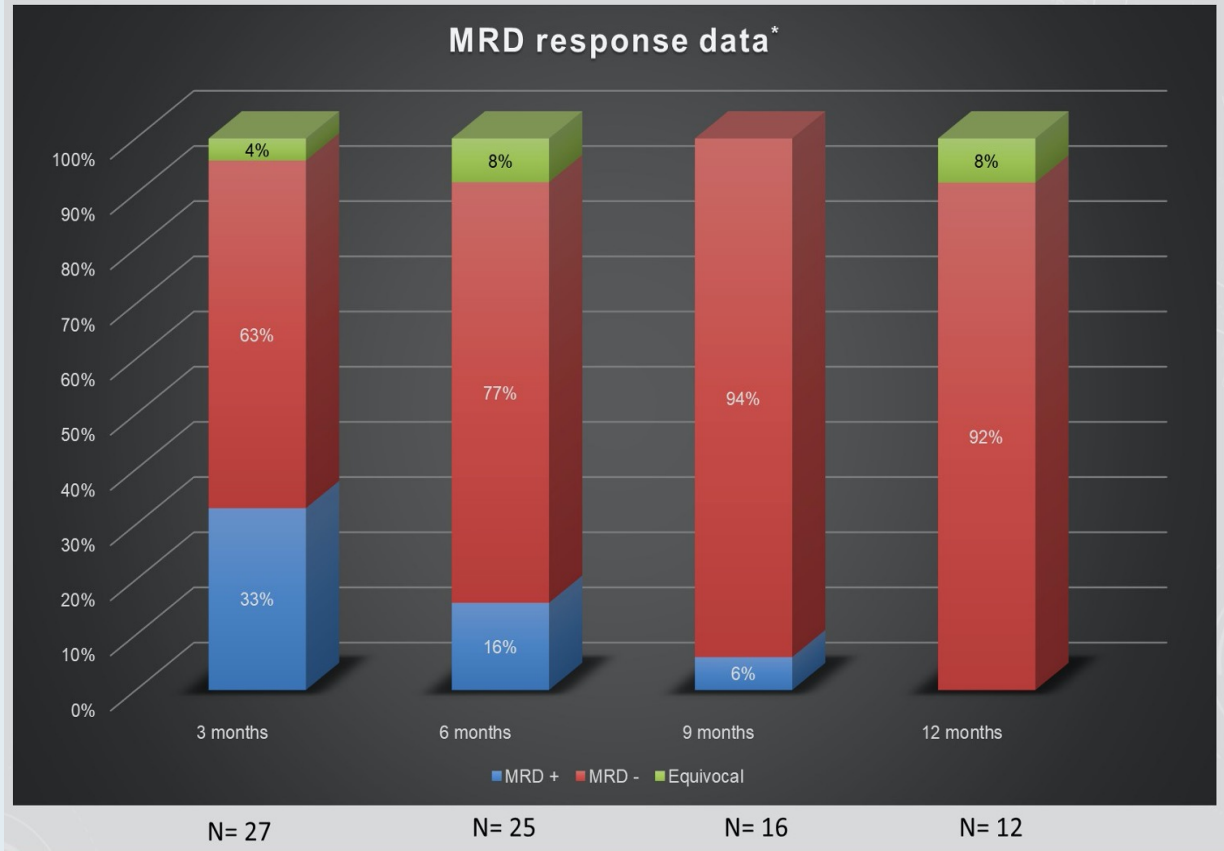
Response and MRD Rates with Venetoclax and R^2

Radiographic Response



MRD Results (negative if <10^{-6})



Phillips TJ et al. ASCO 2021;Abstract 7505.

RTP RESEARCH TO PRACTICE

Meet The Professor

Optimizing the Selection and Sequencing of Therapy for Patients with ER-Positive Breast Cancer

Wednesday, October 6, 2021
5:00 PM – 6:00 PM ET

Faculty

Virginia Kaklamani, MD, DSc

Moderator

Neil Love, MD

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Thank you for joining us!

CME credit information will be emailed to each participant within 3 business days.