What Clinicians Want to Know About the Management of Relapsed/Refractory Mantle Cell Lymphoma

A CME/MOC-Accredited Virtual Event

Tuesday, September 26, 2023
5:00 PM – 6:00 PM ET

Faculty

Toby A Eyre, MBChB, DipMedEd, MRCP, MD
Brad S Kahl, MD

Moderator

Neil Love, MD

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Faculty

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Haematology Consultant
Honorary Senior Clinical Lecturer in Haematology
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Professor of Medicine
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Director, Lymphoma Program
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St Louis, Missouri

Moderator
Neil Love, MD
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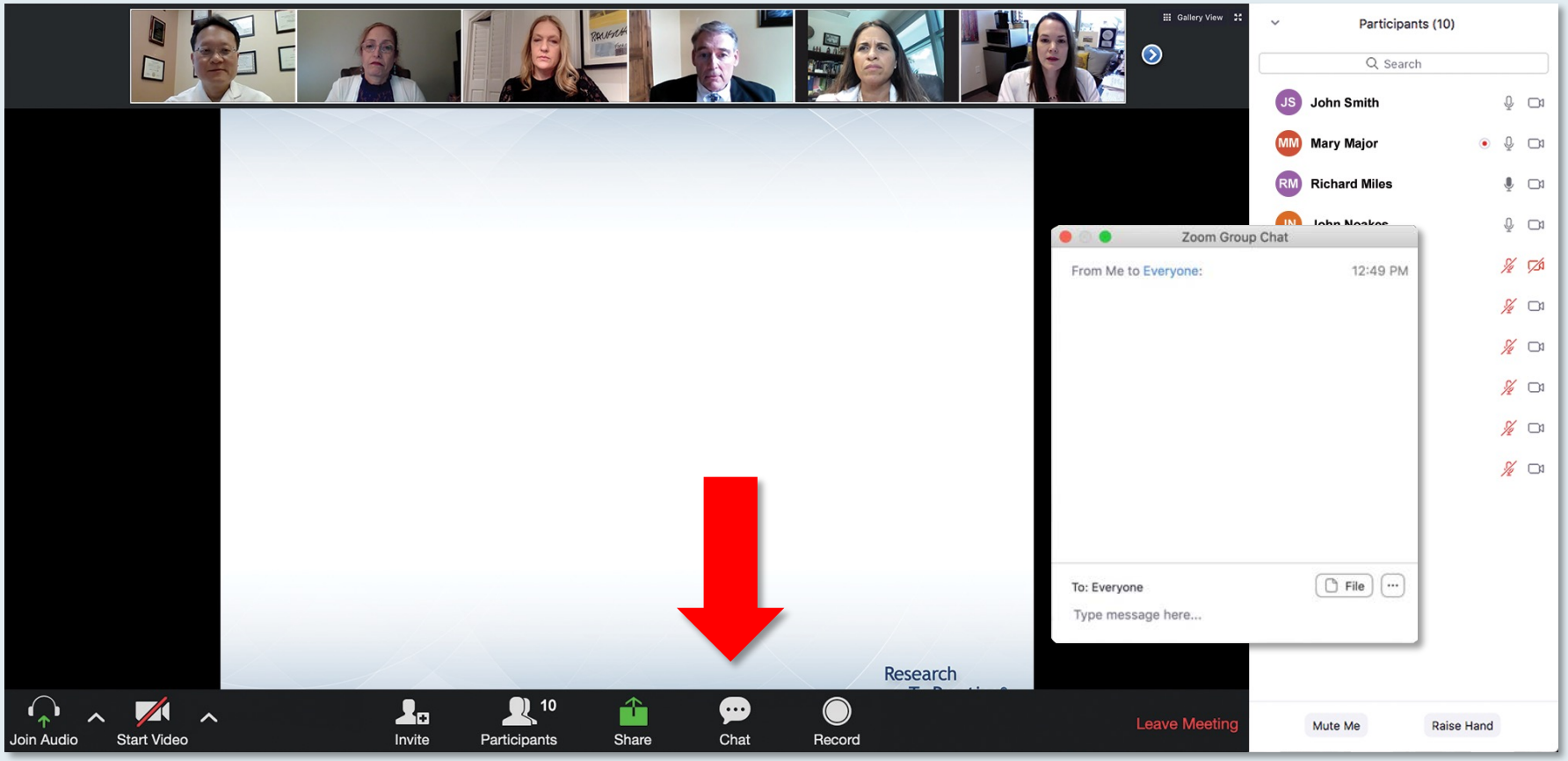

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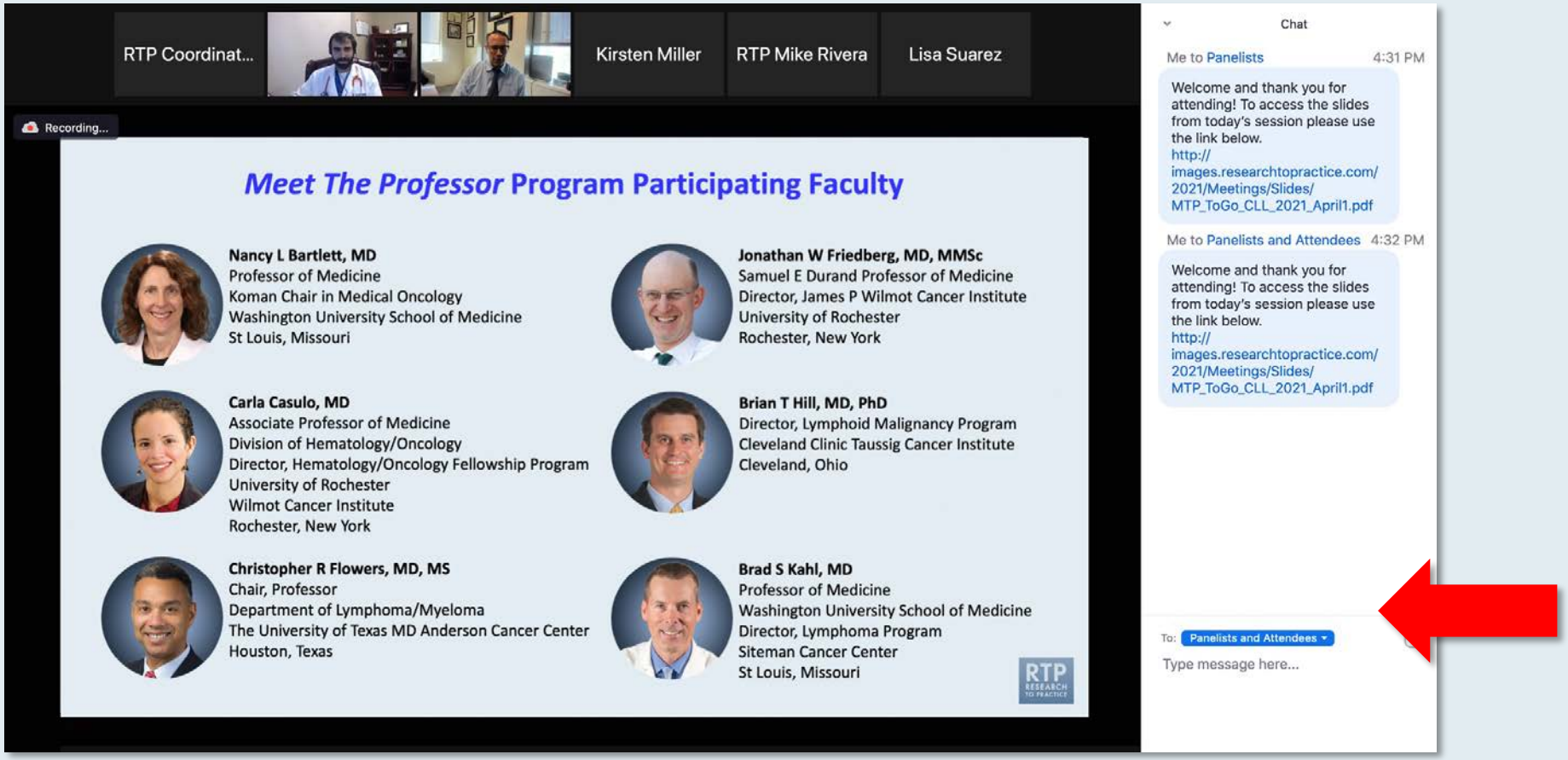

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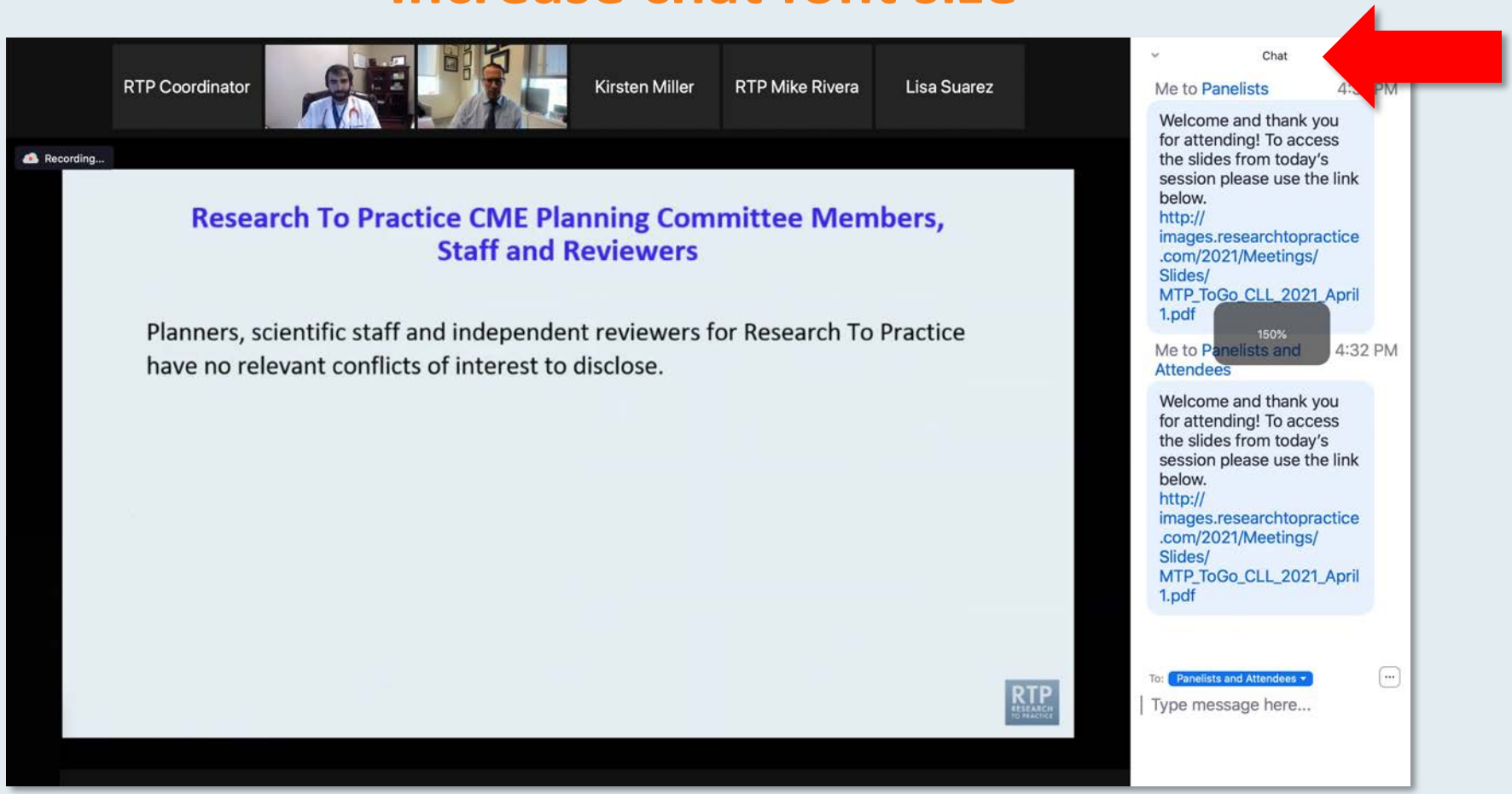

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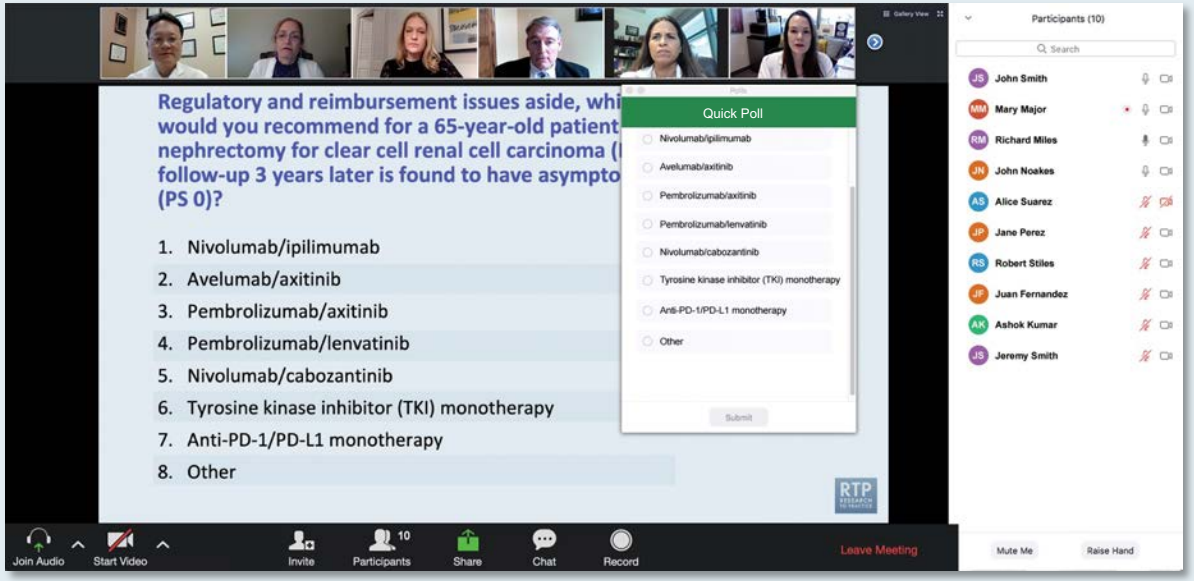

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What Clinicians Want to Know About Toxicity Considerations Associated with BTK Inhibitors

DR NICOLE LAMANNA

COLUMBIA UNIVERSITY HERBERT IRVING COMPREHENSIVE CANCER CENTER

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THE UNIVERSITY OF TEXAS MD ANDERSON CANCER CENTER

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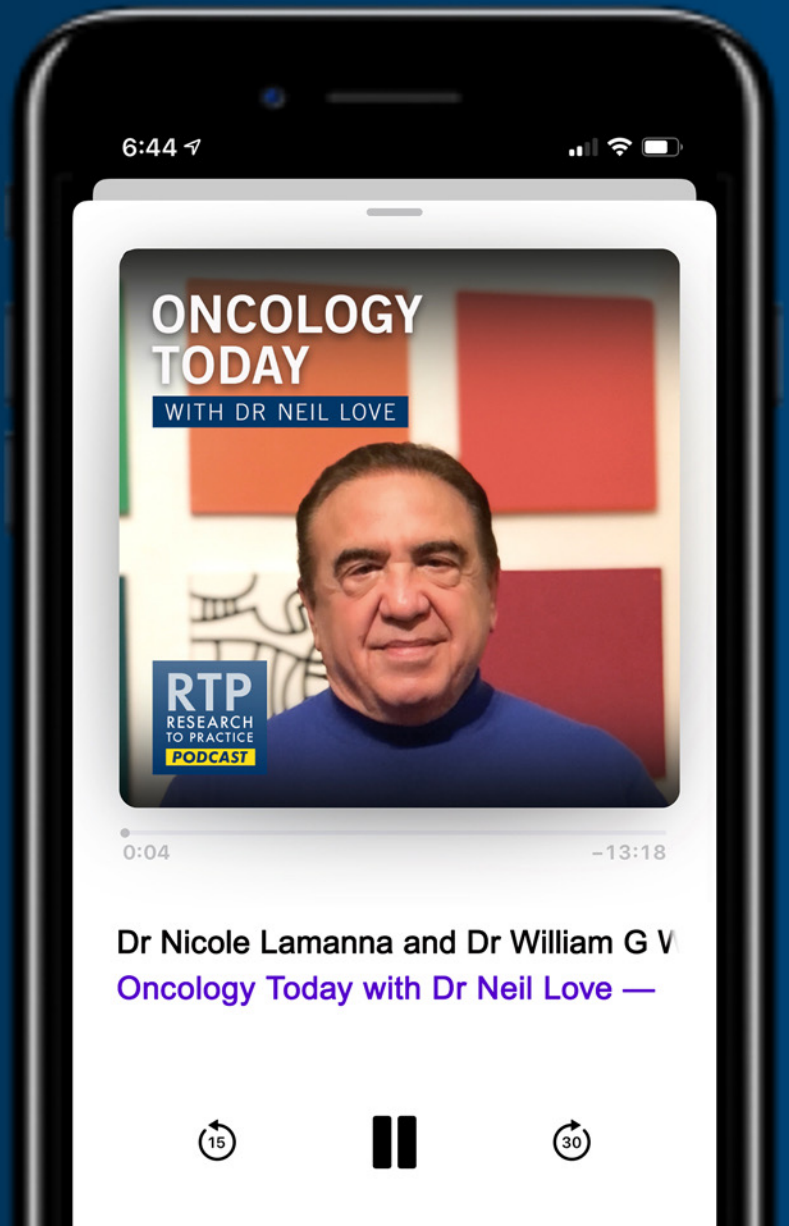

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Optimizing the Management of Gastroesophageal Cancers

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Moderator

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Inside the Issue: Optimizing the Management of Nonmelanoma Skin Cancer

A CME/MOC-Accredited Live Webinar

Tuesday, October 3, 2023
5:00 PM – 6:00 PM ET

Faculty

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Anna C Pavlick, DO, MBA

Moderator

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A Multitumor Educational Symposium in Partnership with Florida Cancer Specialists & Research Institute

Saturday, October 7, 2023

ER-Positive Breast Cancer

7:15 AM – 8:15 AM ET

Faculty

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Komal Jhaveri, MD

Prostate Cancer

8:15 AM – 9:15 AM ET

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A Daylong Multitumor Educational Symposium in Partnership with the American Oncology Network

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Lymphoma

9:30 AM – 10:30 AM PT
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Ann S LaCasce, MD, MMSc

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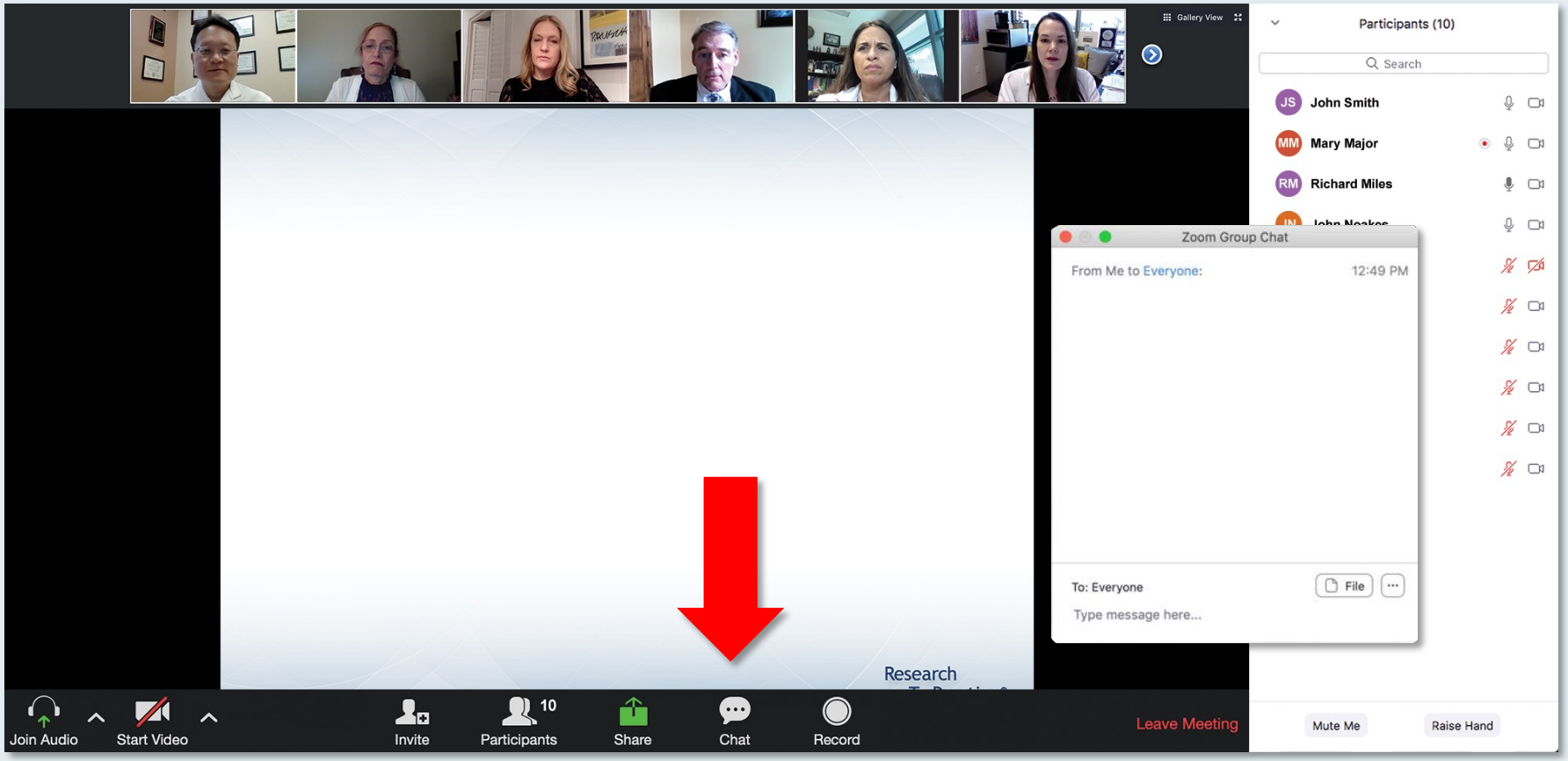

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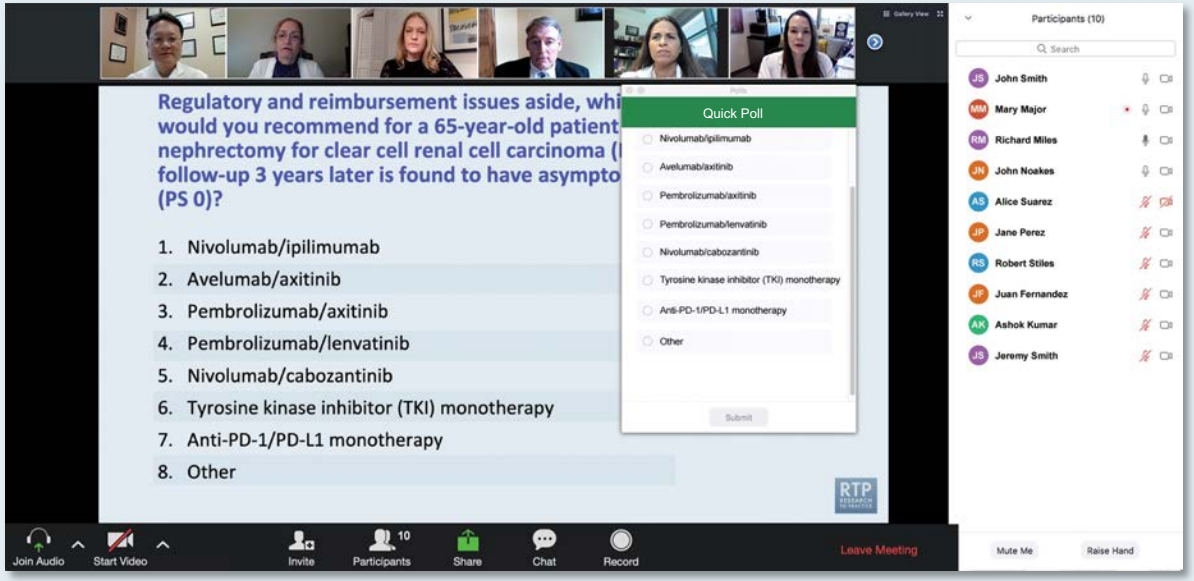

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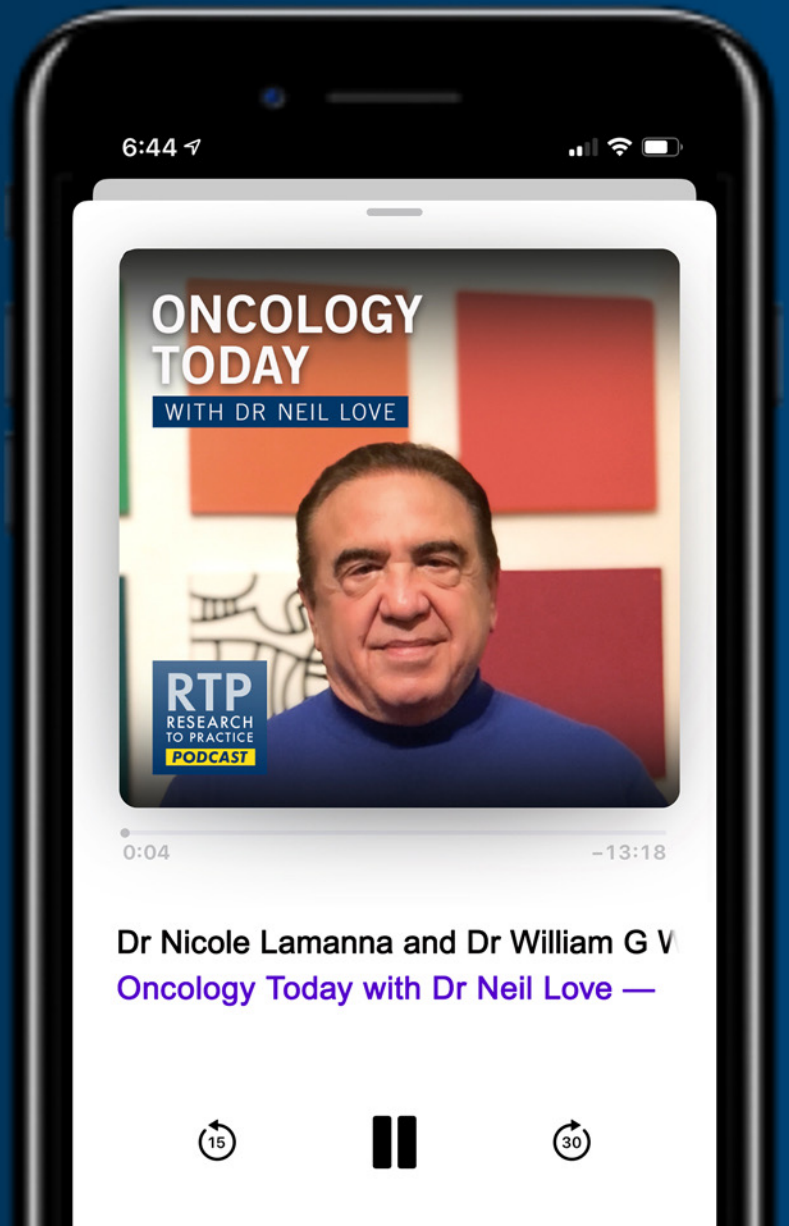

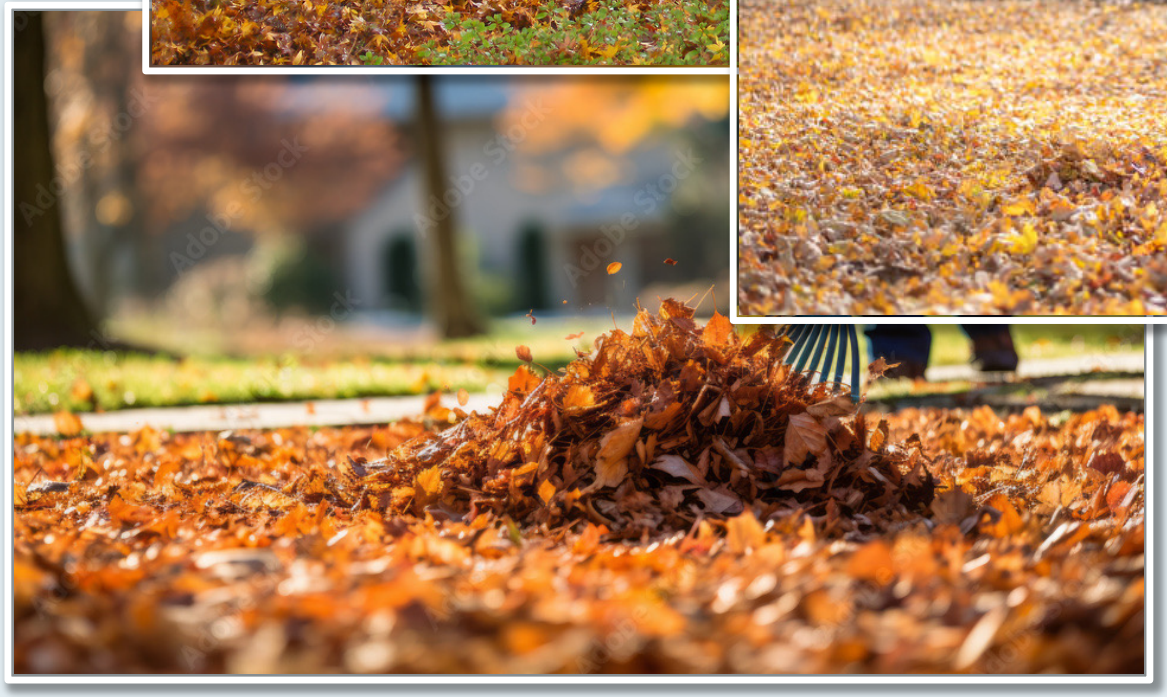

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Summit, New Jersey

Zanetta S Lamar, MD
Florida Cancer
Specialists and Research Institute
Naples, Florida

Henna Malik, MD
Texas Oncology
Houston, Texas

Eric H Lee, MD, PhD
Compassionate Cancer Care
Medical Group
Fountain Valley, California

Michael Wang, MD
MD Anderson Cancer Center
Houston, Texas

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Agenda

INTRODUCTION: Mantle Cell Lymphoma (MCL) and the General Medical Oncologist

MODULE 1: Sequencing of Therapy for MCL: 2009 – 2025

MODULE 2: Cases and Questions from the Community

APPENDIX

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APPENDIX

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Questions and Comments: Frequency of MCL in general medical oncology practice, common questions from general medical oncologists (GMOs)

Dr Eric Lee (Fountain Valley, California)

Dr Zanetta Lamar (Naples, Florida)

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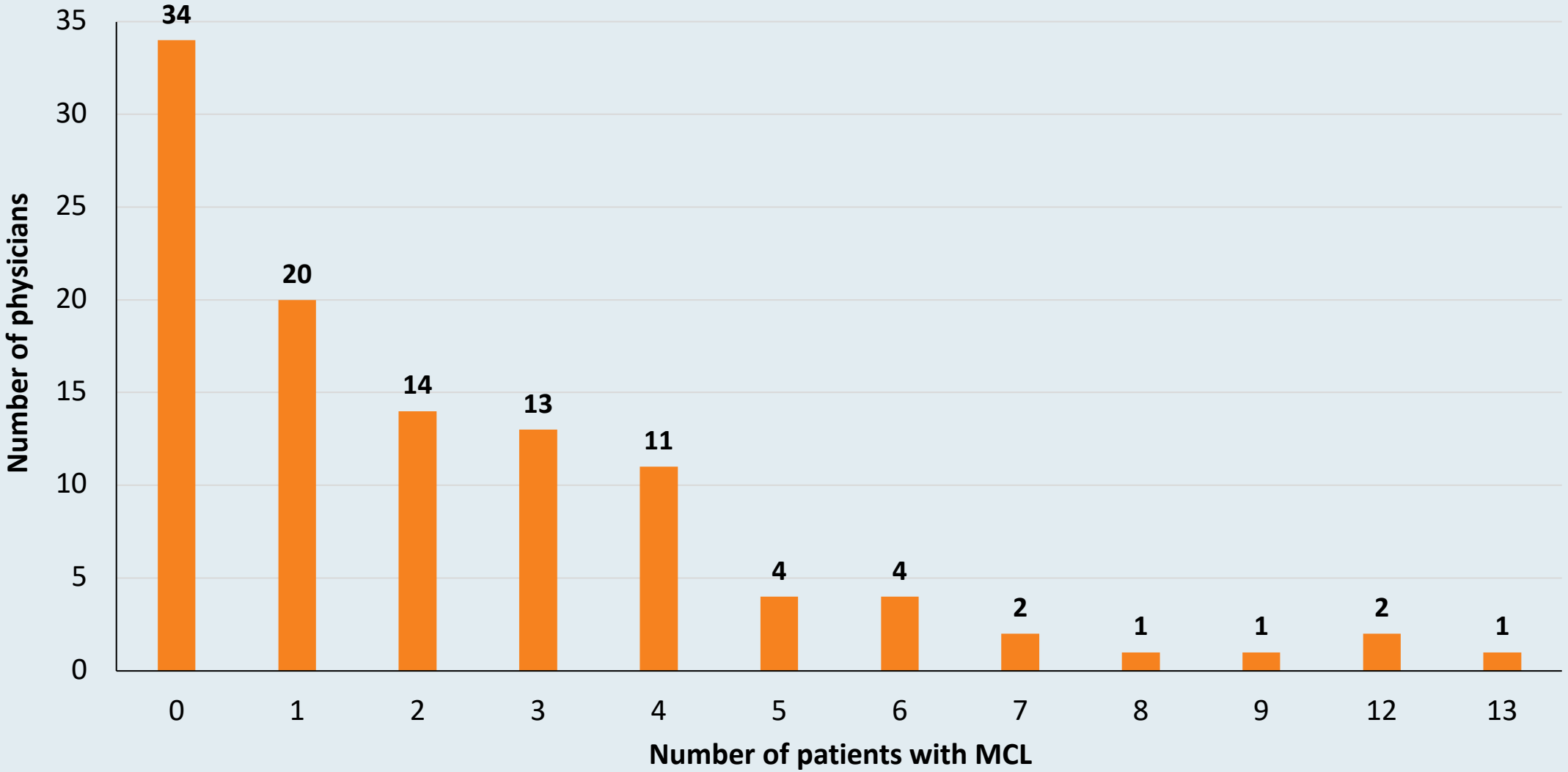
Patients with MCL Seen During the Past Year in the American Oncology Network

243 patients; 107 physicians



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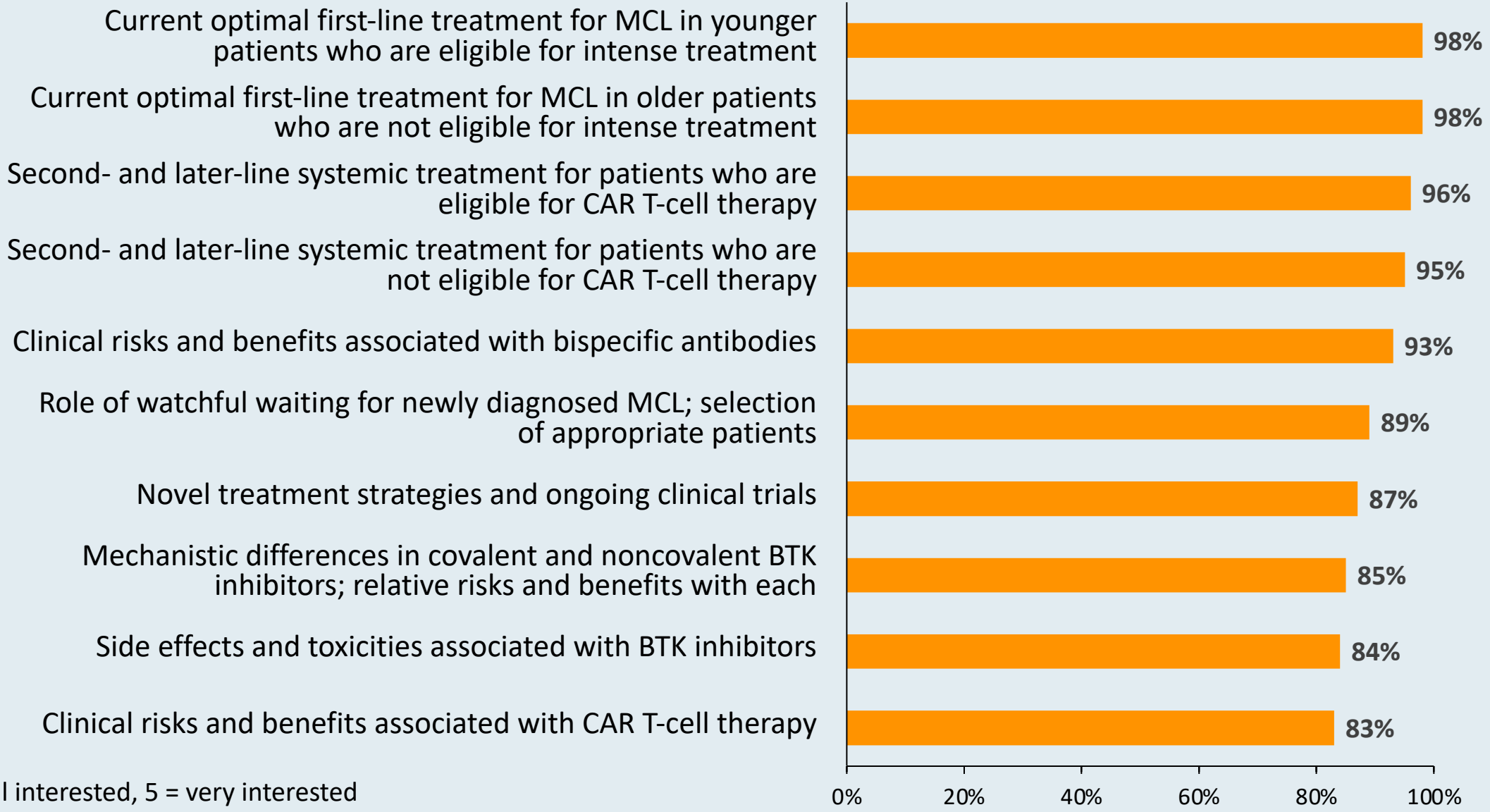
Level of Interest in Listening to Clinical Investigators Discuss the Following Topics: Proportion of Participants Who Responded 4 or 5*



*1 = not at all interested, 5 = very interested

Survey of US-based general medical oncologists, August 2023. N = 55

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Management of Relapsed/Refractory MCL

2009 – 2013

- **First line:** Chemoimmunotherapy (bendamustine/rituximab)
- **Second line:** Targeted treatment (lenalidomide, bortezomib)

2023

- **First line:** Chemoimmunotherapy (bendamustine/rituximab)
- **Second line:**
  - Noncovalent BTK inhibitor (ibrutinib, acalabrutinib, zanubrutinib)
  - Targeted treatment (venetoclax +/- rituximab)
- **Third line and beyond:**
  - Covalent BTK inhibitor (pirtobrutinib)
  - CAR T-cell therapy (brexucabtagene autoleucel)

2025?

- **First line:** BTK inhibitor/anti-CD20 antibody/venetoclax with or without chemotherapy
- **Second line:**
  - Covalent BTK inhibitor (pirtobrutinib)
  - CAR T-cell therapy (brexucabtagene autoleucel)
  - ? Bispecific antibodies (glofitamab)

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Questions and Comments: Front-line treatment without chemotherapy

Dr Michael Wang (Houston, Texas)

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Three generations of BTK inhibitors

FIRST GENERATION

Ibrutinib

covalently binds to Cys481 residue in BTK resulting in blocking of enzymatic activity

SECOND GENERATION

Acalabrutinib | **Zanubrutinib** | **Orelabrutinib**

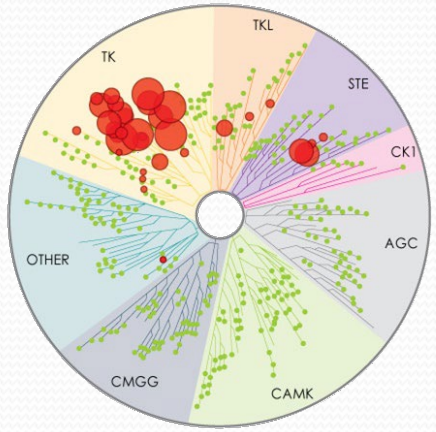
THIRD GENERATION

Nemtabrutinib | **Pirtobrutinib** | **Vecabrutinib**

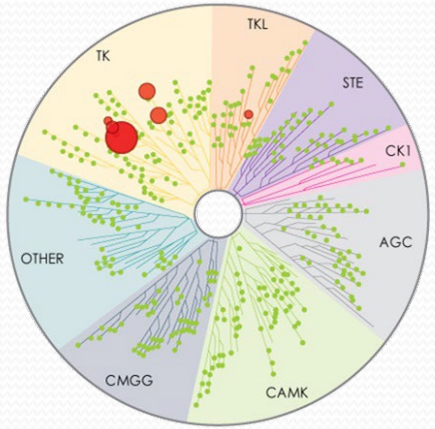
Courtesy of Michael Wang, MD

Covalent BTKi: different kinase selectivity

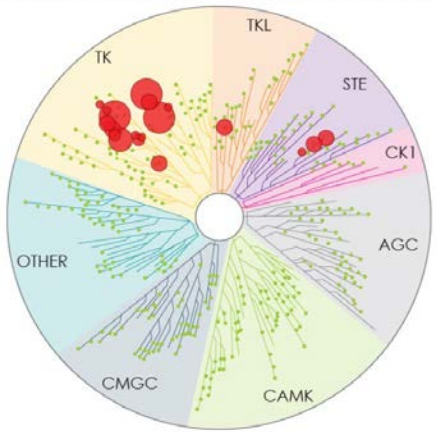
Ibrutinib



Acalabrutinib



Zanubrutinib



IC_{50}/EC_{50} (nM)

Kinase	Ibrutinib	Acalabrutinib	Zanubrutinib
BTK	1.5	5.1	0.5
TEC	10	126	44
ITK	4.9	> 1000	50
BMX	0.8	46	1.4
EGFR	5.3	> 1000	21
ERBB4	3.4	16	6.9
JAK3	32	> 1000	1377
BLK	0.1	> 1000	2.5

Courtesy of Michael Wang, MD

Acalabrutinib with Rituximab as First-Line Therapy for Older Patients (≥65) with Mantle Cell Lymphoma – A Phase II Clinical Trial

Jain P et al.

ICML 2023;Abstract 099.

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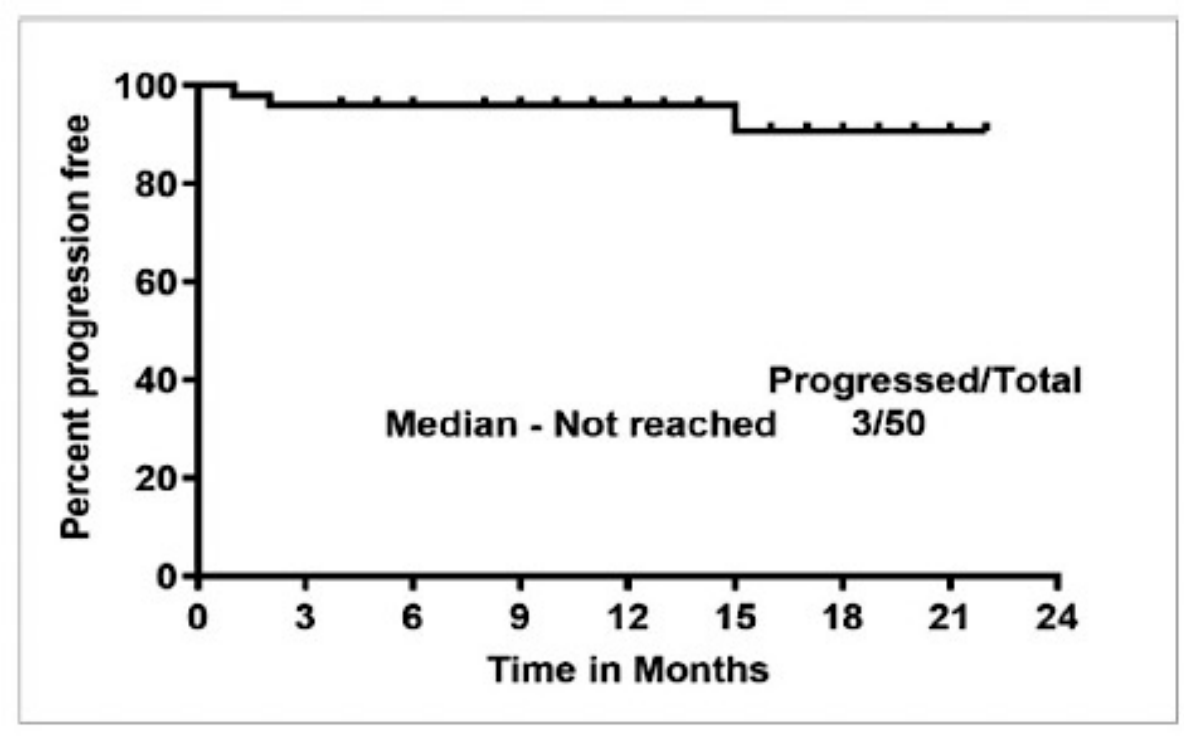
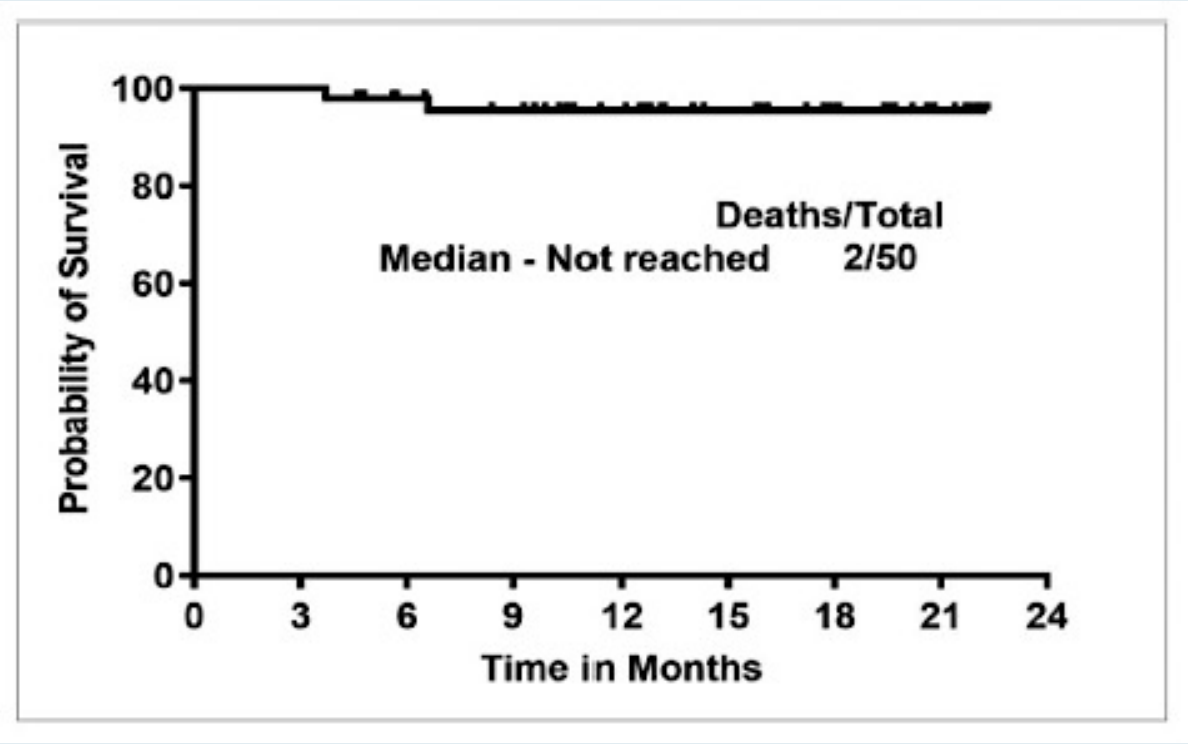
Progression-Free Survival (PFS) and Overall Survival (OS) with Acalabrutinib/Rituximab as First-Line Therapy for Older Patients with MCL

PFS



OS



Response: ORR = 94% (CR = 90%, PR = 4%), nonevaluable = 6%

Jain P et al. ICML 2023;Abstract 099.

RTP RESEARCH TO PRACTICE

Acalabrutinib plus Venetoclax and Rituximab in Patients with Treatment-Naïve Mantle Cell Lymphoma: 2-Year Safety and Efficacy Analysis

Wang M et al.
Blood 2022;140(Supplement 1):6477-9.

RTP
RESEARCH
TO PRACTICE

Study Design

Enrollment target: 20-32 patients

Key inclusion criteria

- **Adults with treatment-naïve MCL**
- **ECOG PS ≤2**

Key exclusion criteria

- **Any history of CNS lymphoma or leptomeningeal disease**
- **Significant CV disease**

→

Acalabrutinib
Starting cycle 1, day 1 with 100 mg BID until disease progression or discontinuation for other reasons

+

Venetoclax
Starting on cycle 2, day 1 with initial 5-week ramp-up (20, 50, 100, and 200 mg/d) to 400 mg daily, through cycle 25

+

Rituximab
375 mg/m² on day 1 of each 28-day cycle for 6 cycles, followed by maintenance every other cycle for patients achieving CR or PR through cycle 24

Primary endpoint
- Safety profile of AVR

Secondary endpoints per Lugano criteria*
- Overall response rate
- Duration of response
- Progression-free survival

Exploratory endpoint
- Minimal residual disease

DLT was assessed from cycle 2, day 1 to cycles 3, day 28†

* Efficacy endpoints evaluated per the Lugano classification for non-Hodgkin lymphoma, which requires PET/CT and bone marrow biopsy confirmation of a CR.

† DLTs were evaluated in the first 6 patients enrolled.

AVR = acalabrutinib + venetoclax + rituximab; BID = twice daily; CNS = central nervous system; CR = complete response; CT = computed tomography; CV = cardiovascular; DLT = dose-limiting toxicity; ECOG PD = Eastern Cooperative Oncology Group performance status; MCL = mantle cell lymphoma; PET = positron-emission tomography; PR = partial response.

Wang M et al. *Blood* 2022;140(Supplement 1):6477-9.

RTP RESEARCH TO PRACTICE

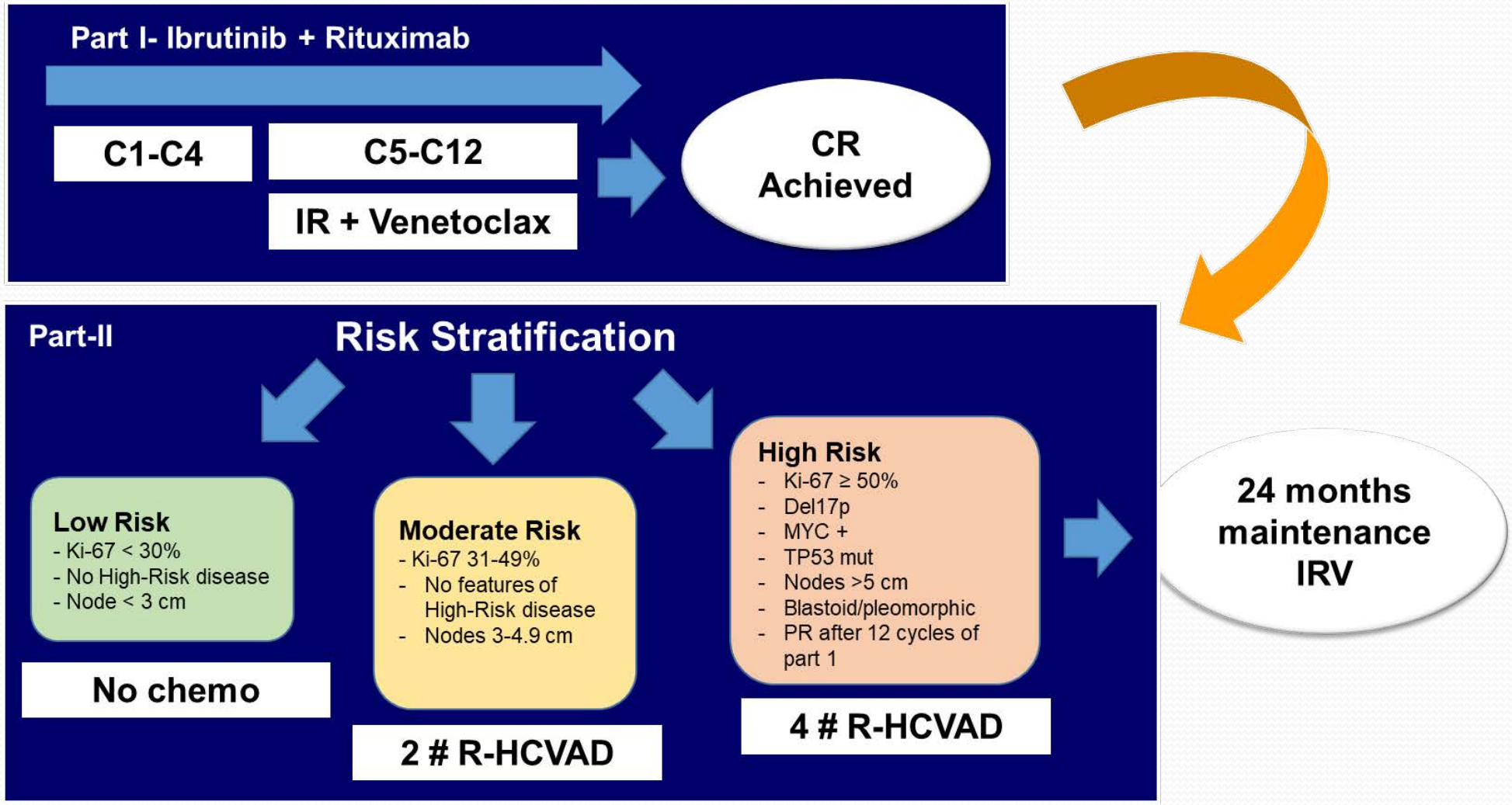
WINDOW-2 Trial
Objectives

- **Primary Objective**
  - **Efficacy- CR PART A:** Complete response rate of the ibrutinib plus rituximab combination followed by venetoclax in newly diagnosed young MCL patients.

- **Secondary Objectives**
  - **PFS, OS, and safety**

Courtesy of Michael Wang, MD

Treatment Schema



Courtesy of Michael Wang, MD

Responses

Response (ITT)	All patients
Part A – IR Best response	N (%)
Evaluable patients	46
ORR	44 (88)
CR	23 (46)
Part A – IRV Best response	
Evaluable patients	46
ORR	46 (96)
CR	46 (92)

- **Two pts had isolated GI/BM disease with CR on part A**
- **Best response to IRV was 100% and CR of 100% (no ITT)**
- **The median number of cycles of triplet IRV to reach best response was 8 cycles (range 2-12)**

Median number of cycles of chemo R-HCVAD was 2 (range 0-4); 3 pts got only one cycle of chemo and discontinued due to AEs; ORR and CR with part B (no ITT) 100%

Courtesy of Michael Wang, MD

TRIANGLE:

autologous **T**ransplantation after a **R**ituximab/**I**brutinib/**A**ra-c containing i**N**duction in **G**eneralized mantle cell **L**ymphoma – a randomized **E**uropean mcl network trial

M Dreyling, J Doorduijn, E Giné, M Jerkeman, J Walewski, M Hutchings, U Mey, J Riise, M Trneny, V Vergote, M Celli, O Shpilberg, M Gomes da Silva, S Leppa, L Jiang, C Pott, W Klapper, D Gözel, C Schmidt, M Unterhalt, M Ladetto*, E Hoster

LMU University Hospital Munich, Germany; Erasmus MC Cancer Institute, University Medical Center Rotterdam, Netherlands; Hospital Clinic of Barcelona, Spain; Skane University Hospital and Lund University, Lund, Sweden; Maria Sklodowska-Curie National Research Institute of Oncology, Warsaw, Poland; Rigshospitalet, Copenhagen University Hospital, Denmark; Kantonsspital Graubuenden, Chur, Switzerland; Oslo University Hospital, Oslo, Norway; Charles University and General University Hospital, Prague, Czech Republic; University Hospitals Leuven, Belgium; Ospedale degli Infermi di Rimini, Italy; Assuta Ramat Hahayal Medical Center, Tel Aviv, Israel; Instituto Português de Oncologia, Lisboa, Portugal; Helsinki University Hospital Comprehensive Cancer Center, Finland;
IBE, LMU University Munich, Germany; University of Schleswig-Holstein, Kiel, Germany; Az Ospedaliera Santi Antonio e Biagio e Cesare Arrigo, Alessandria, Italy

Courtesy of Michael Wang, MD

ORIGINAL ARTICLE

Ibrutinib plus Bendamustine and Rituximab in Untreated Mantle-Cell Lymphoma

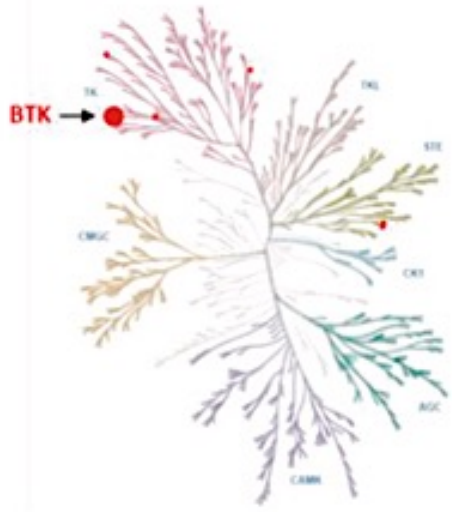
Michael L. Wang, M.D., Wojciech Jurczak, M.D., Ph.D., Mats Jerkeman, M.D., Ph.D., Judith Trotman, F.R.A.C.P., Pier L. Zinzani, M.D., Ph.D., David Belada, M.D., Ph.D., Carola Boccomini, M.D., Ian W. Flinn, M.D., Ph.D., Pratyush Giri, F.R.A.C.P., Andre Goy, M.D., Paul A. Hamlin, M.D., Olivier Hermine, M.D., Ph.D., José-Ángel Hernández-Rivas, M.D., Ph.D., Xiaonan Hong, M.D., Seok Jin Kim, M.D., Ph.D., David Lewis, F.R.C.Path., Ph.D., Yuko Mishima, M.D., Ph.D., Muhit Özcan, M.D., Guilherme F. Perini, M.D., Christopher Pocock, M.D., Ph.D., Yuqin Song, M.D., Ph.D., Stephen E. Spurgeon, M.D., John M. Storring, M.D., Jan Walewski, M.D., Jun Zhu, M.D., Ph.D., Rui Qin, Ph.D., Todd Henninger, Ph.D., Sanjay Deshpande, M.D., Angela Howes, Ph.D., Steven Le Gouill, M.D., Ph.D., and Martin Dreyling, M.D., for the SHINE Investigators*

N Engl J Med 2022;386(26):2482-94

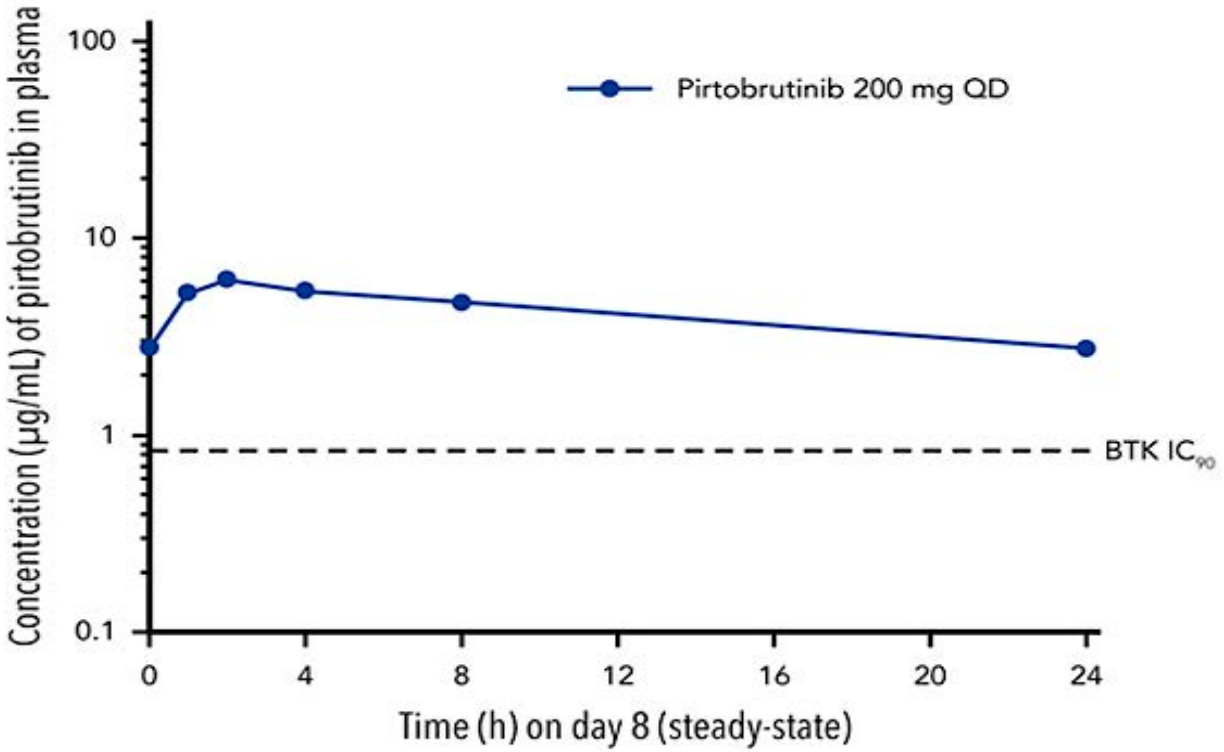
RTP RESEARCH TO PRACTICE

Noncovalent BTK Inhibitor Pirtobrutinib

Mechanism of action: Highly selective for BTK.



Pharmacology: Long half-life with concentration exceeding IC90 throughout the dosing interval.



Thompson PA, Tam CS. *Blood* 2023;141(26):3137-42.

RTP RESEARCH TO PRACTICE

FDA Grants Accelerated Approval to Pirtobrutinib for Relapsed or Refractory Mantle Cell Lymphoma

Press Release: January 27, 2023

"On January 27, 2023, the Food and Drug Administration (FDA) granted accelerated approval to pirtobrutinib for relapsed or refractory mantle cell lymphoma (MCL) after at least two lines of systemic therapy, including a BTK inhibitor.

Efficacy was evaluated in BRUIN (NCT03740529), an open-label, multicenter, single-arm trial of pirtobrutinib monotherapy that included 120 patients with MCL previously treated with a BTK inhibitor. Patients had a median of 3 prior lines of therapy, with 93% having 2 or more prior lines. The most common prior BTK inhibitors received were ibrutinib (67%), acalabrutinib (30%), and zanubrutinib (8%); 83% had discontinued their last BTK inhibitor due to refractory or progressive disease. Pirtobrutinib was administered orally at 200 mg once daily and was continued until disease progression or unacceptable toxicity."

https://www.fda.gov/drugs/resources-information-approved-drugs/fda-grants-accelerated-approval-pirtobrutinib-relapsed-or-refractory-mantle-cell-lymphoma

RTP RESEARCH TO PRACTICE

J Clin Oncol 2023 May 16;[Online ahead of print].

Rapid Communications

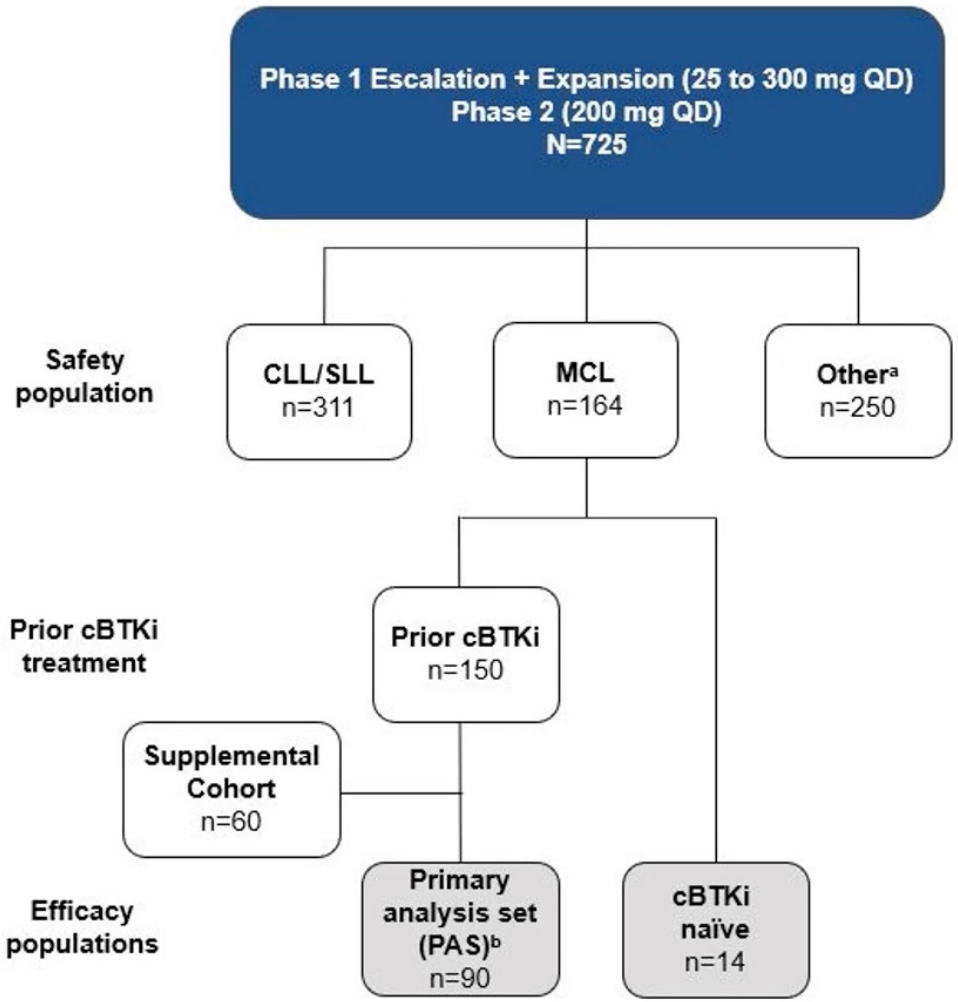
Pirtobrutinib in Covalent Bruton Tyrosine Kinase Inhibitor Pretreated Mantle-Cell Lymphoma

Michael L. Wang, MD[1]; Wojciech Jurczak, MD, PhD[2]; Pier Luigi Zinzani, MD, PhD[3,4]; Toby A. Eyre, MD, MBChB, DipMedEd, MRCP, FRCPath[5]; Chan Y. Cheah, MD[6,7]; Chaitra S. Ujjani, MD[8]; Youngil Koh, MD[9]; Koji Izutsu, MD, PhD[10]; James N. Gerson, MD[11]; Ian Flinn, MD, PhD[12]; Benoit Tessoulin, MD[13]; Alvaro J. Alencar, MD[14]; Shuo Ma, MD, PhD[15]; David Lewis, PhD, MBChB[16]; Ewa Lech-Maranda, MD, PhD[17]; Joanna Rhodes, MD[18,19]; Krish Patel, MD[20]; Kami Maddocks, MD[21]; Nicole Lamanna, MD[22]; Yucai Wang, MD, PhD[23]; Constantine S. Tam, MD[24]; Talha Munir, MBBS[25]; Hirokazu Nagai, MD, PhD[26]; Francisco Hernandez-Ilizaliturri, MD[27]; Anita Kumar, MD[28]; Timothy S. Fenske, MD, MS[29]; John F. Seymour, PhD, MBBS, FRACP[24]; Andrew D. Zelenetz, MD, PhD[28]; Binoj Nair, PhD[30]; Donald E. Tsai, MD, PhD[30]; Minna Balbas, PhD[30]; Richard A. Walgren, MD, PhD[30]; Paolo Abada, MD, PhD[30]; Chunxiao Wang, PhD[31]; Junjie Zhao, PhD[30]; Anthony R. Mato, MD, MSCE[28]; and Nirav N. Shah, MD[29]

DOI https://doi.org/10.1200/JCO.23.00562

RTP RESEARCH TO PRACTICE

Phase 1/2 BRUIN Study Design



Phase 1 3+3 design

- 28-day cycles
- Intra-patient dose escalation allowed
- Cohort expansion permitted at doses deemed safe

Eligibility

- Age ≥18
- ECOG 0-2
- Active disease and in need of treatment
- Previously treated

Key endpoints

- Safety/tolerability
- Determine MTD and recommended phase 2 dose
- Pharmacokinetics
- Efficacy according to ORR and DOR (Lugano) as assessed by IRC

Primary analysis set (PAS)

The PAS comprised the first 90 patients who met the following criteria:

- Enrolled to either phase 1 or 2
- Had measurable disease
- Had received a prior cBTKi containing regimen
- Had no known central nervous system involvement

Data cutoff date of 31 January 2022. [a]Other includes DLBCL, WM, FL, MZL, Richter's transformation, B-PLL, Hairy Cell Leukemia, PCNSL, and other transformation. [b]To ensure adequate follow-up, a cut-off of 31 January 2022 was utilized which allowed the vast majority (>90%) of responders in the PAS to be followed for at least 9 months from onset of initial response to the data cut-off date.

Wang ML et al. ASH 2022;Abstract 4218.

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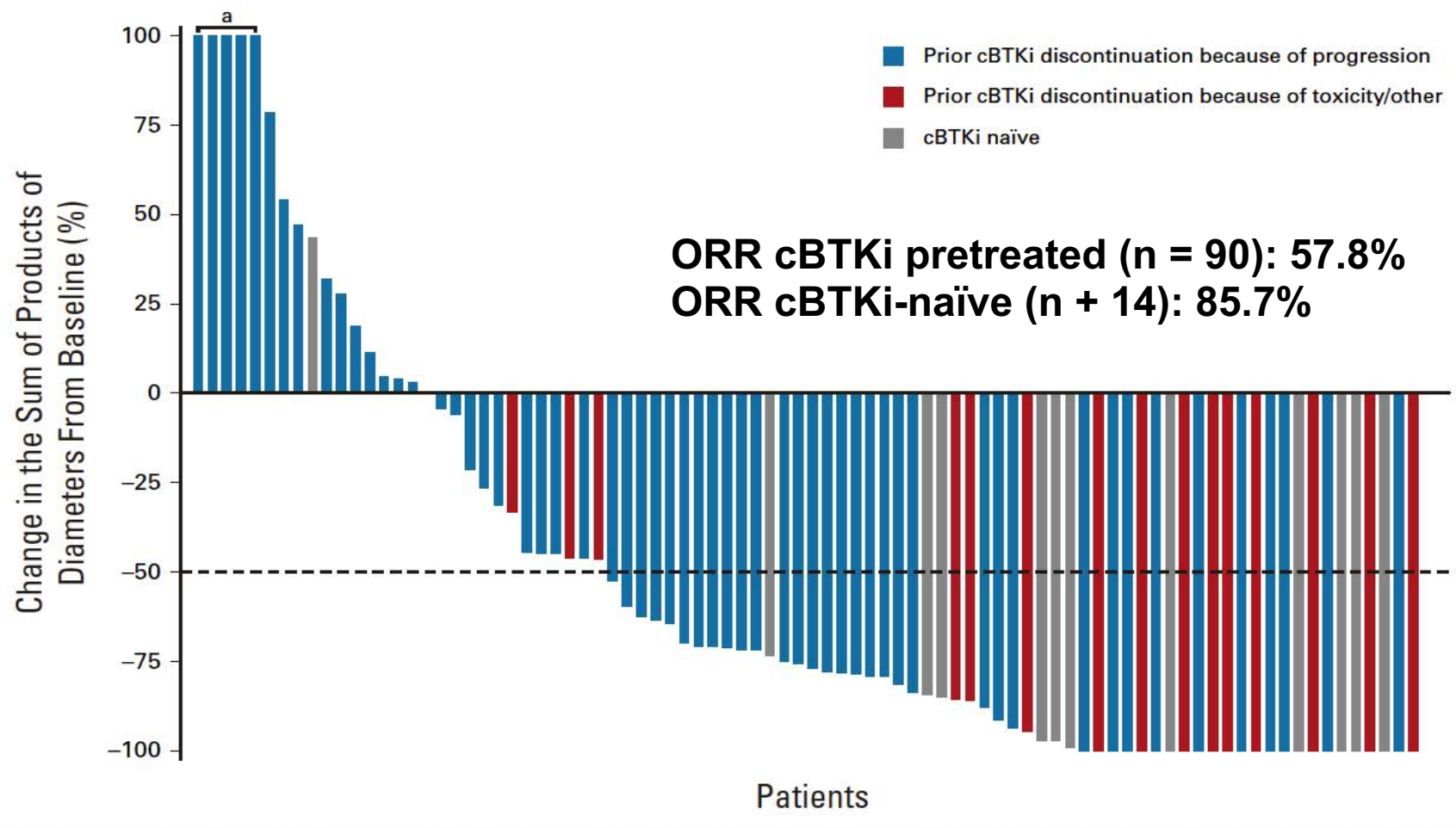
BRUIN: Efficacy of Pirtobrutinib in Patients with cBTKi Pretreated and cBTKi-Naïve MCL



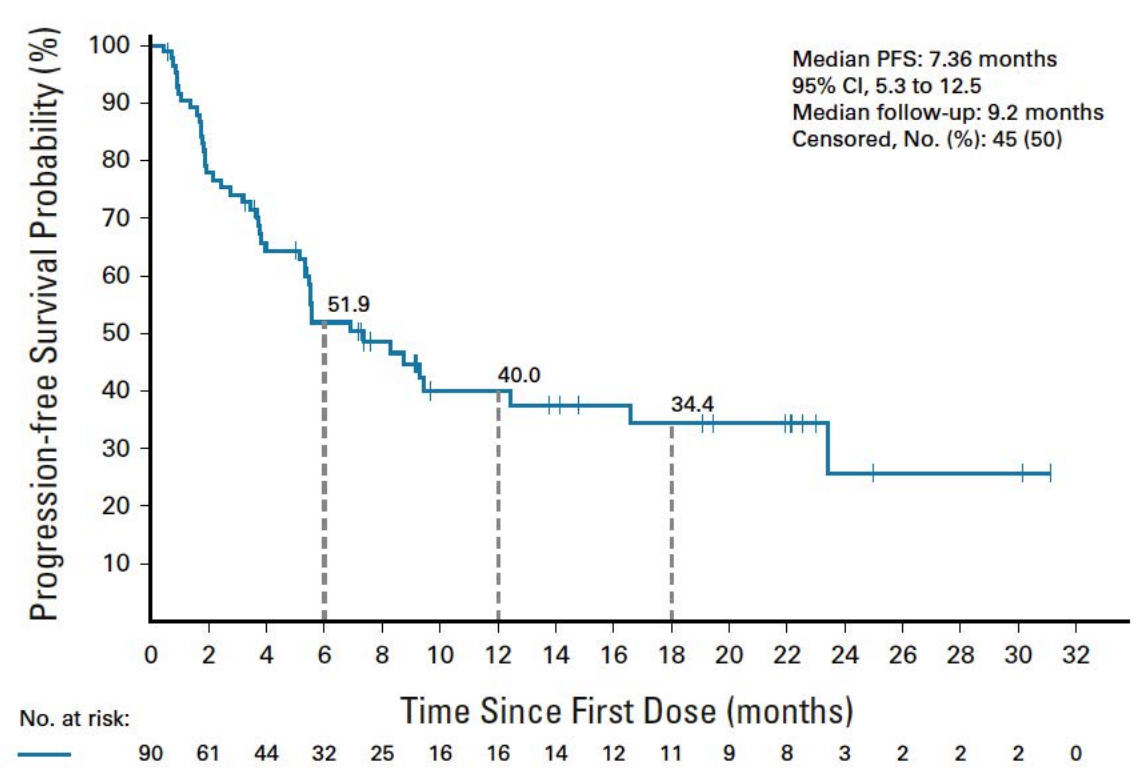
Wang ML et al. *J Clin Oncol* 2023; May 16 [Online ahead of print].

cBTKi = covalent Bruton tyrosine kinase inhibitor

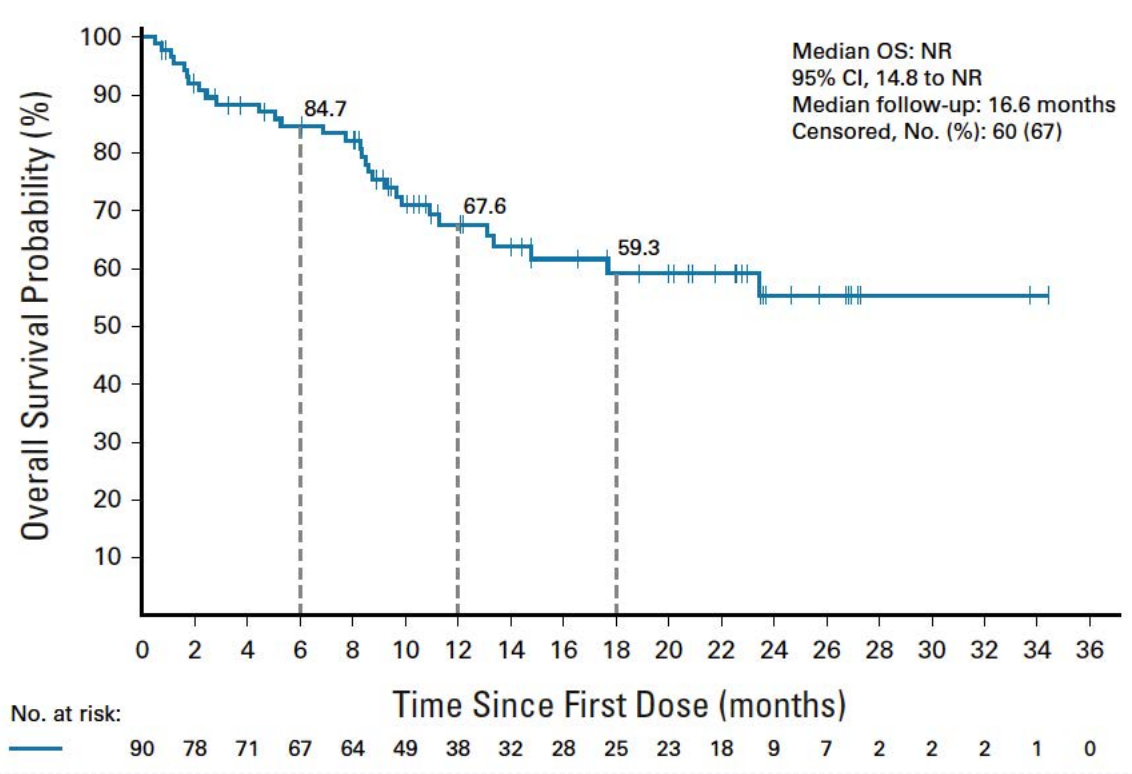
Courtesy of Michael Wang, MD

BRUIN: PFS and OS with Pirtobrutinib in Patients with cBTKi Pretreated MCL

PFS



OS



Wang ML et al. *J Clin Oncol* 2023; May 16 [Online ahead of print].

Courtesy of Michael Wang, MD

Adverse Events of Special Interest with Pirtobrutinib in Patients with MCL

	MCL Safety Population (n = 164)			
	TEAE, (≥10%), No. (%)		TRAE, No. (%)	
Adverse Event	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Infections	59 (36.0)	28 (17.1)	24 (14.0)	5 (3.0)
Bleeding	45 (27.4)	6 (3.7)	26 (15.9)	1 (0.6)
Thrombocytopenia	24 (14.6)	11 (6.7)	2 (1.2)	0
Neutropenia[b]	23 (14.0)	22 (13.4)	15 (9.1)	14 (8.5)
Bruising[c]	27 (16.5)	0	19 (11.6)	0 (0.0)
Hemorrhage	25 (15.2)	6 (3.7)	11 (6.7)	1 (0.6)
Atrial fibrillation/atrial flutter[d]	6 (3.7)	2 (1.2)	1 (0.6)	0 (0.0)

Wang ML et al. *J Clin Oncol* 2023 May 16;[Online ahead of print].

RTP RESEARCH TO PRACTICE

BRUIN MCL-321 Phase III Study Design

BRUIN MCL-321 is a randomized, open-label, global, phase 3 study (NCT04662255)

Key Inclusion Criteria

- Confirmed diagnosis of MCL
- ≥1 prior (non-BTKi) line of systemic therapy for MCL
- Measurable disease per Lugano criteria
- Radiographically/histologically confirmed PD on the most recent line of therapy or relapse
- ≥18 years of age and ECOG 0–2

N=500

1:1 Randomization

Arm A

Pirtobrutinib 200 mg orally once daily

Arm B

Investigator's choice of ibrutinib, acalabrutinib, or zanubrutinib per labeled doses

Stratification factors

- sMIPI risk group (low/intermediate vs high)
- Intended comparator BTK inhibitor (ibrutinib vs acalabrutinib/zanubrutinib)
- Number of prior lines of therapy (1 vs ≥2)

Wang ML et al. ASCO 2023;Abstract TPS7587.

RTP RESEARCH TO PRACTICE

Ongoing Phase II Study of Pirtobrutinib with Venetoclax for Relapsed/Refractory MCL

Clinical trial identifier: NCT05529069

- **Confirmed MCL with or without t(11;14), (q13;q32) and/or cyclin D overexpression**
- **Relapsed MCL including prior BTK inhibitor or CAR-T cell therapy**
- **ECOG PS ≤ 2**

→ **Pirtobrutinib + venetoclax**

Primary endpoint: Overall response rate

Escudier B et al. ESMO 2017;Abstract LBA5; Albiges L et al. *ESMO Open* 2020;5(6):e001079.

RTP RESEARCH TO PRACTICE

Single-Agent Venetoclax for Relapsed or Refractory MCL

Study	N	Median # prior therapies	ORR (CR)	Median PFS	Median DoR	Median OS
Eyre *Haematologica* 2019	20	3	53% (18%)	3.2 mo	8.1 mo	9.4 mo
Zhao *Amer J Hematol* 2020	24	5	50% (21%)	8 mo	4 mo	13.5 mo
Davids *Clin Cancer Res* 2021	28	3	67% (21%)	11.3 mo	15.7 mo	Not reported

Eyre TA et al. *Haematologica* 2019;104(2):e68-71. Zhao S et al. *Am J Hematol* 2020;95(6):623-9. Davids MS et al. *Clin Cancer Res* 2021;27(17):4690-5.

RTP RESEARCH TO PRACTICE

original reports

Three-Year Follow-Up of KTE-X19 in Patients With Relapsed/Refractory Mantle Cell Lymphoma, Including High-Risk Subgroups, in the ZUMA-2 Study

Michael Wang, MD[1]; Javier Munoz, MD, MS, MBA[2]; Andre Goy, MD, MS[3]; Frederick L. Locke, MD[4]; Caron A. Jacobson, MD, MMSc[5]; Brian T. Hill, MD, PhD[6]; John M. Timmerman, MD[7]; Houston Holmes, MD, MBA[8]; Samantha Jaglowski, MD[9]; Ian W. Flinn, MD, PhD[10]; Peter A. McSweeney, MB, ChB[11]; David B. Miklos, MD, PhD[12]; John M. Pagel, MD, PhD, DSc[13]; Marie José Kersten, MD, PhD[14]; Krimo Bouabdallah, MD[15]; Rashmi Khanal, MD[16]; Max S. Topp, MD[17]; Roch Houot, MD, PhD[18]; Amer Beitinjaneh, MD[19]; Weimin Peng, PhD[20]; Xiang Fang, PhD[20]; Rhine R. Shen, PhD[20]; Rubina Siddiqi, PhD[20]; Ioana Kloos, MD[20]; and Patrick M. Reagan, MD[21]

J Clin Oncol 2023;41(3):555-67

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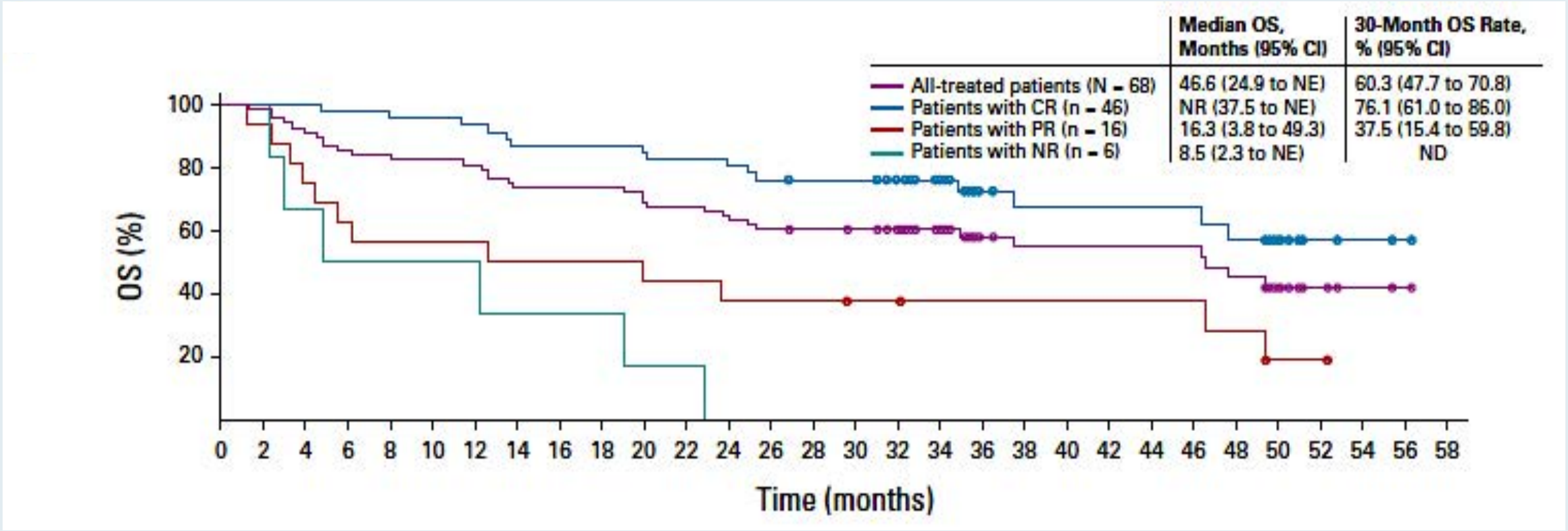
ZUMA-2 Three-Year Follow-Up: Overall Survival with Brexucabtagene Autoleucel in All Treated Patients (N = 68)



Wang M et al. *J Clin Oncol* 2023;41(3):555-67.

ASH 2022;Abstract 74

Glofitamab Monotherapy Induces High Complete Response Rates in Patients with Heavily Pretreated Relapsed or Refractory Mantle Cell Lymphoma

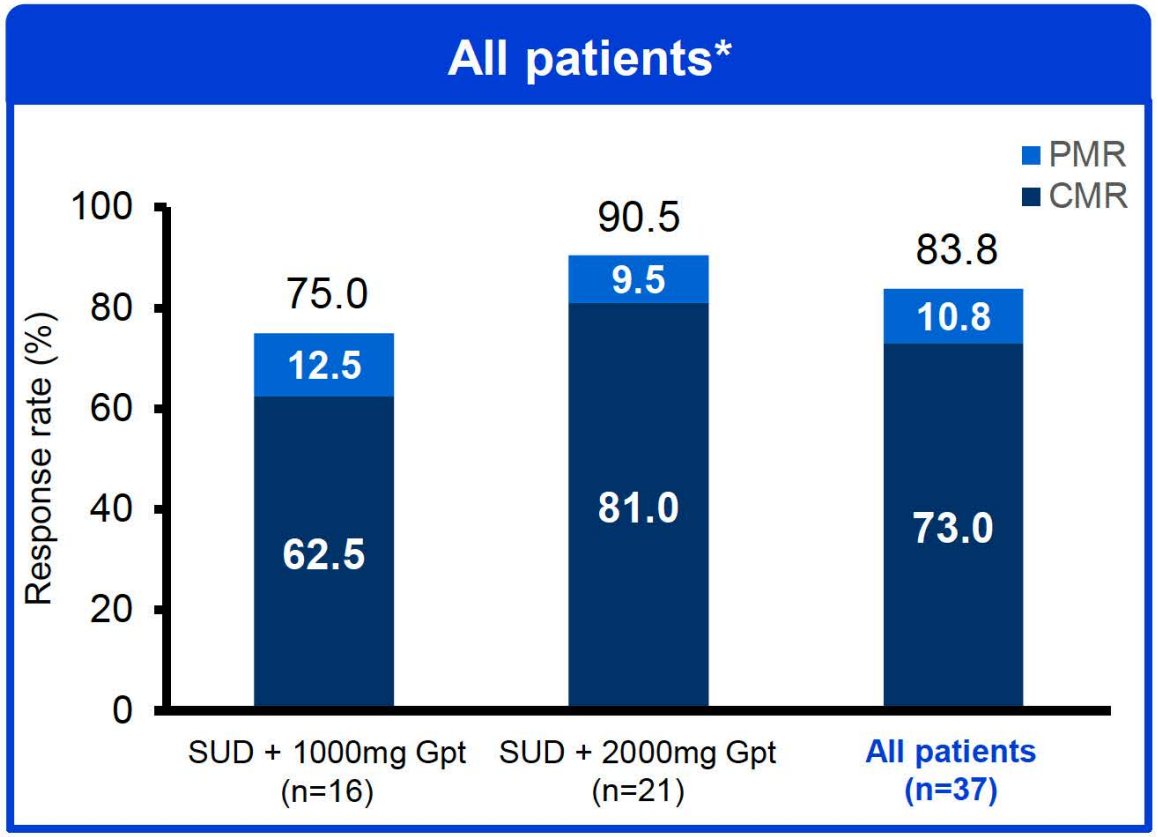
Tycel Phillips,[1] Michael Dickinson,[2] Franck Morschhauser,[3] Emmanuel Bachy,[4] Michael Crump,[5] Marek Trněný,[6] Nancy L. Bartlett,[7] Jan Zaucha,[8] Tomasz Wrobel,[9] Fritz Offner,[10] Kathryn Humphrey,[11] Linda Lundberg,[12] James Relf,[11] Audrey Filezac de L'Etang,[12] David Carlile,[11] Ben Byrne,[11] Naseer Qayum,[11] Carmelo Carlo-Stella[13]

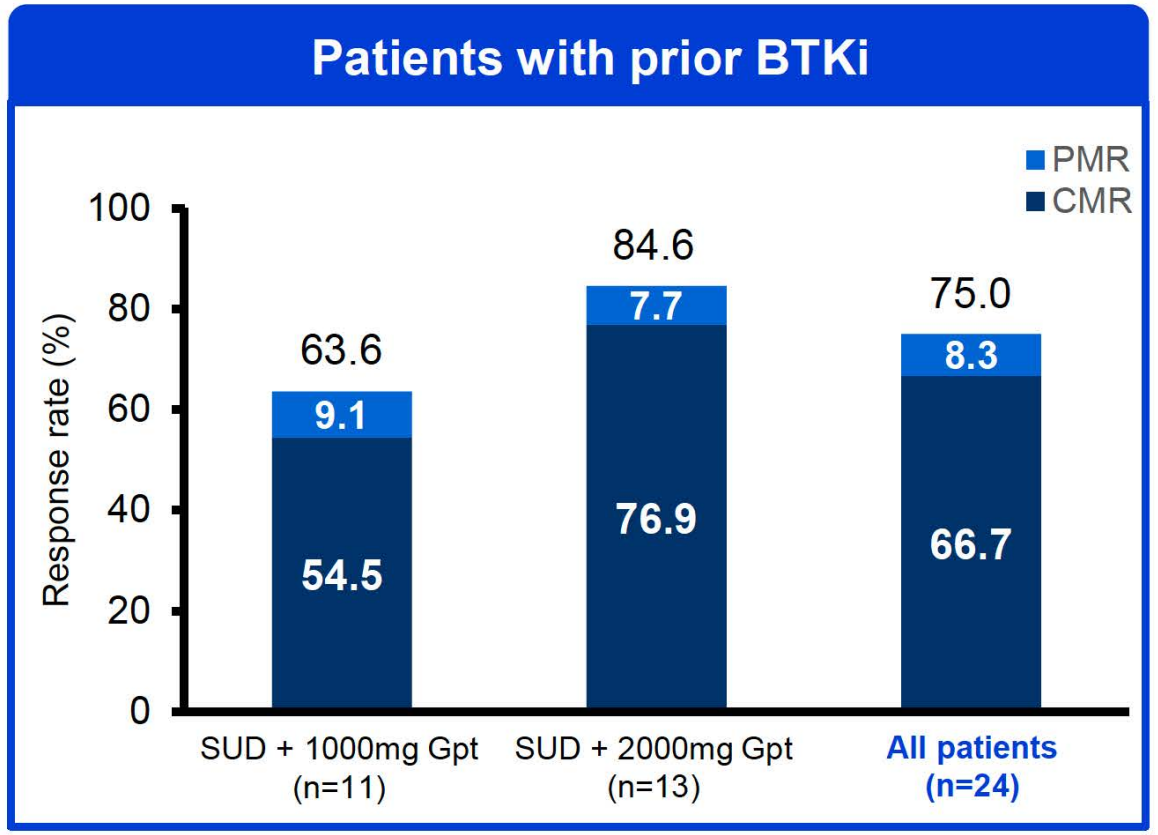
[1]University of Michigan Medical School, Ann Arbor, MI, USA; [2]Peter MacCallum Cancer Centre, Royal Melbourne Hospital and The University of Melbourne, Melbourne, Australia; [3]CHU Lille, Service des Maladies du Sang, Lille, France; [4]Hospices Civils de Lyon and Université Claude Bernard, Pierre-Bénite, France; [5]Princess Margaret Hospital, Toronto, ON, Canada; [6]1st Faculty of Medicine, Charles University, General Hospital, Prague, Czech Republic; [7]Siteman Cancer Center, Washington University, St. Louis, MO, USA; [8]Medical University of Gdańsk, Gdańsk, Poland; [9]Wroclaw Medical University, Wroclaw, Poland; [10]Dept Hematology Universitair Ziekenhuis, Gent, Belgium; [11]Roche Products Ltd, Welwyn Garden City, United Kingdom; [12]F. Hoffmann-La Roche Ltd, Basel, Switzerland; [13]Humanitas University and IRCCS Humanitas Research Hospital, Milan, Italy.

Presented at the 64th ASH Annual Meeting | December 10–13, 2022

RTP RESEARCH TO PRACTICE

Response Rates by Glofitamab Regimen





High response rates with glofitamab monotherapy in patients with R/R MCL

Phillips T et al. ASH 2022;Abstract 74.

RTP RESEARCH TO PRACTICE

Agenda

INTRODUCTION: Mantle Cell Lymphoma (MCL) and the General Medical Oncologist

MODULE 1: Sequencing of Therapy for MCL: 2009 – 2025

MODULE 2: Cases and Questions from the Community

APPENDIX

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Questions and Comments: Ibrutinib and ventricular arrhythmias/sudden cardiac death

Dr Neil Morganstein (Summit, New Jersey)

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Questions and Comments: Acalabrutinib-associated headache; side effect profile of pirtobrutinib

Dr Henna Malik (Houston, Texas)

RTP RESEARCH TO PRACTICE

Case Presentation: 81-year-old man with R/R MCL with “brain fog” on zanubrutinib

Dr Spencer Bachow (Boca Raton, Florida)

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Case Presentation: An uninsured 58-year-old man with symptomatic MCL

Dr Zanetta Lamar (Naples, Florida)

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GMO Survey: Questions and Cases Overview

- **55-yo male in remission after R-Benda in 2021. Now enlarging nodes and B symptoms. Optimal therapy?**
- **41 yo mantle cell in the eyelids only. Rest of the PET negative. Marrow negative...any need for systemic therapy?**
- **Is bendamustine + rituximab a better option than lenalidomide + rituximab as induction Rx in older patients?**
- **72 yo on rituximab maintenance for 17 months post transplant, MRD-negative, would like to discontinue due to risks and inconvenience or switch to a BTKi now or observe?**
- **Does Ki-67 influence your choice of induction therapy, and if so, how?**

Survey of US-based general medical oncologists, August 2023. N = 55

RTP RESEARCH TO PRACTICE

GMO Survey: Questions and Cases
First-Line Management

- **Which MCL can be observed?**
- **How do you approach TP53 indolent MCL?**
- **Would you treat an asymptomatic MCL patient who harbored a very high risk feature such as a p53 mutation?**

Survey of US-based general medical oncologists, August 2023. N = 55

RTP RESEARCH TO PRACTICE

GMO Survey: Questions and Cases
First-Line Management (con't)

- **What is the present role of autotransplant? What is the role of MRD testing? Can MRD testing be used in decision-making to determine who may benefit from intensification or de-escalation of therapy?**
- **Are you still performing auto-SCT in your fit and eligible patients with MCL? Are you using the TRIANGLE trial regimen at all?**
- **Acalabrutinib + venetoclax + rituximab — good chemo-free option? Has good/high response rates. Role of those agents and rituximab in the maintenance therapy.**
- **Is there still a role for R-Hyper-CVAD? Can you discuss the current treatment paradigm for first-line therapy in older and younger MCL?**
- **Role of transplant in 2023?**

Survey of US-based general medical oncologists, August 2023. N = 55

RTP RESEARCH TO PRACTICE

GMO Survey: Questions and Cases
Older Patients; Poor Performance Status

- **85-yo male with R/R mantle CL — would you use BTK inhibitor or lenalidomide?**
- **Mantle cell in a 90 yo man with GI bleeding from disease.**
- **I have an 80-yo F, lives alone, poor support and borderline performance status, presented with anemia and splenomegaly. Flow cytometry revealed low-grade MCL.**
- **In elderly patients, would investigators use first-line BTK inhibitor, and if so, which one? Toxicity management?**

Survey of US-based general medical oncologists, August 2023. N = 55

RTP RESEARCH TO PRACTICE

GMO Survey: Questions and Cases
Noncovalent and Covalent BTKi

- **Can pirtobrutinib be active in patients who have had a prior BTK inhibitor?**
- **I have a 68-year-old male with a prolonged course of MCL. He has had visceral metastasis as well as lymph node disease. I have tried empiric BTK inhibition as he has little exposure (discontinued acalabrutinib due to headache and refused to restart even though this is typically self-limited), and I can't keep him on zanubrutinib empirically due to intolerance (fatigue, dizziness, rise in creatinine). What is the tolerability of pirtobrutinib in patients who do not tolerate other BTK inhibitors?**
- **I have a 79-yo gentleman post BR now on zanubrutinib with worsening neutropenia. Would you recommend G-CSF support if neutropenia is a problem in spite of dose reduction?**

Survey of US-based general medical oncologists, August 2023. N = 55

RTP RESEARCH TO PRACTICE

GMO Survey: Questions and Cases
Noncovalent and Covalent BTKi (con't)

- **I have a 61-yo patient with HTN now on zanubrutinib, but HTN is not controlled. What would you recommend?**
- **I have a 74-yo MCL patient with rate-controlled AF on rivaroxaban. What would you recommend in terms of BTKi use?**
- **A patient with MCL on a BTK inhibitor: how do you differentiate lymphocytosis as a side effect of the BTK inhibitor from development of leukemic-variant MCL?**
- **How do you hold BTKs for surgeries, and do they need to be held for minor surgeries (I think they have an aspirin-like effect)?**

Survey of US-based general medical oncologists, August 2023. N = 55

RTP RESEARCH TO PRACTICE

GMO Survey: Questions and Cases
CAR T-Cell Therapy

- **A 69-yo patient with relapsed MCL, after induction/ASCT then BTKi, who is a candidate for CAR T. Which regimen would you choose to bridge to CAR T?**
- **When should one refer for CAR T-cell therapy for MCL?**
- **What is the age cut-off for CAR T-cell therapy for a patient with R/R MCL?**
- **When will we be doing CAR T-cell therapy for front-line MCL, especially in blastoid variant?**

Survey of US-based general medical oncologists, August 2023. N = 55

RTP RESEARCH TO PRACTICE

GMO Survey: Questions and Cases
Other Novel Approaches; Bispecific Antibodies

- **Sequencing of therapy in post-CART failures?**
- **BiTE therapy and bispecifics in MCL.**
- **If a patient with MCL has aggressive relapse and is not a candidate for CAR T, is there a role for combining a BTKi with venetoclax?**
- **Can intrathecal chemotherapy ever be an adjunct to systemic chemo?**
- **I have an uninsured patient whose disease has progressed through BR and BTKi. What is the best next line of therapy?**

Survey of US-based general medical oncologists, August 2023. N = 55

RTP RESEARCH TO PRACTICE

GMO Survey: Questions and Cases
Other Novel Approaches; Bispecific Antibodies (con't)

- **Have a young MCL patient who is relapsing after brexu-cel. What is your recommendation for next-line treatment?**
- **Does bortezomib have a role anymore?**
- **What is your preferred BTKi in MCL patients with CNS disease?**
- **Is there any role for antibody-drug conjugates against MCL?**

Survey of US-based general medical oncologists, August 2023. N = 55

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Questions and Comments: BTK inhibitor-based front-line treatment for MCL

Dr Michael Wang (Houston, Texas)

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Agenda

INTRODUCTION: Mantle Cell Lymphoma (MCL) and the General Medical Oncologist

MODULE 1: Sequencing of Therapy for MCL: 2009 – 2025

MODULE 2: Cases and Questions from the Community

APPENDIX

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Voluntary Withdrawal of Accelerated Approvals for Ibrutinib for MCL and MZL

Press Release: April 6, 2023

Today the intent to voluntarily withdraw, in the US, accelerated ibrutinib approvals for patients with mantle cell lymphoma (MCL) who have received at least one prior therapy and with marginal zone lymphoma (MZL) who require systemic therapy and have received at least one prior anti-CD20-based therapy was announced.

“Other approved indications for ibrutinib in the US are not affected. This voluntary action is due to requirements related to the accelerated approval status granted by the US FDA for MCL and MZL. These indications were approved via this pathway based on overall response rates in Phase 2 clinical studies. To confirm clinical benefit following accelerated approvals, additional studies are required by the FDA.

The Phase 3 SHINE (NCT01776840) study in previously untreated MCL and the Phase 3 SELENE study (NCT01974440) in relapsed or refractory MZL served as confirmatory studies. The SHINE study met its primary endpoint of progression-free survival. The addition of Iibrutinib to chemoimmunotherapy was associated with increased adverse reactions compared to the placebo-controlled arm.”

https://news.abbvie.com/news/press-releases/update-on-imbruvica-ibrutinib-us-accelerated-approvals-for-mantle-cell-lymphoma-and-marginal-zone-lymphoma-indications.htm

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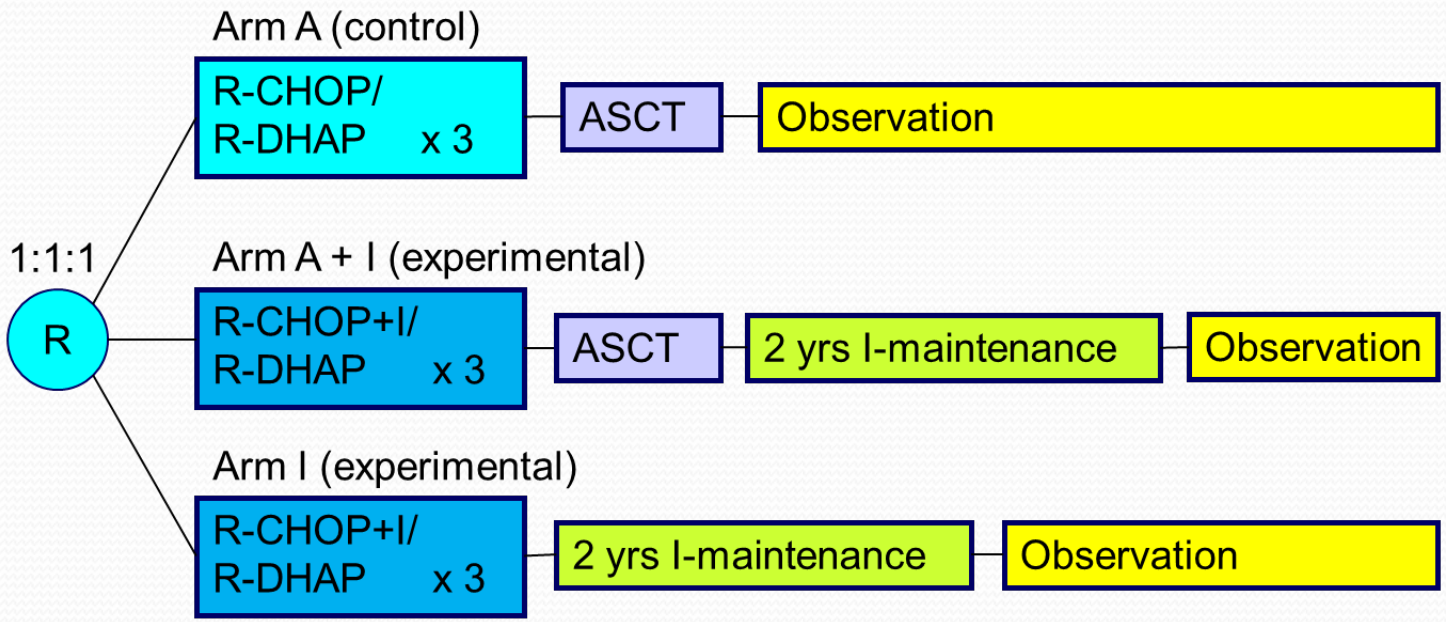
TRIANGLE: Trial Design

- MCL patients
- previously untreated
- stage II-IV
- younger than 66 years
- suitable for HA and ASCT
- ECOG 0-2

- Primary outcome: FFS

- Secondary outcomes:
  - Response rates
  - PFS, RD
  - OS
  - Safety

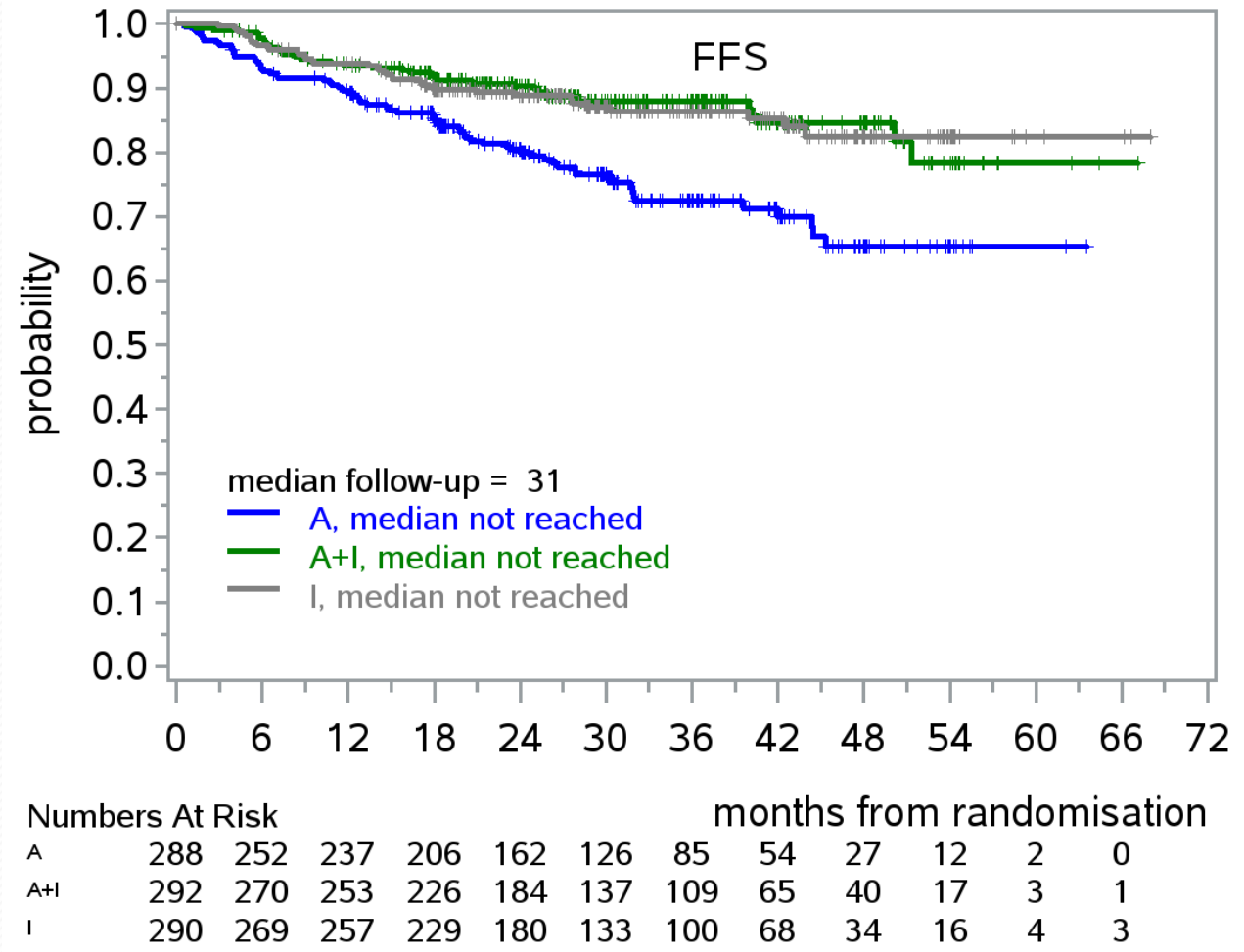


- R maintenance was added following national guidelines in all 3 trial arms
- Rituximab maintenance (without or with Ibrutinib) was started in 168 (58 %)/165 (57 %)/158 (54 %) of A/A+I/I randomized patients.

Dreyling M et al. ASH 2022;Abstract 1.

Courtesy of Michael Wang, MD

TRIANGLE: FFS Superiority of A+I vs. I ?



- Test A+I vs. I ongoing, no decision yet

Next lymphoma treatment (among patients with first treatment failure)	A (n=68)		A+I (n=35)		I (n=37)	
Treatment with Ibrutinib	34	79%	4	24%	3	11%
Treatment without Ibrutinib	9	21%	13	76%	24	89%
No treatment	25		18		10	

A+I arm: IR-CHOP/R-DHAP+ASCT+I; I arm: IR-CHOP/R-DHAP+I. I: ibrutinib

Dreyling M et al. ASH 2022;Abstract 1.

Courtesy of Michael Wang, MD

Key Differences Between Available Covalent BTK Inhibitors and Pirtobrutinib

	Ibrutinib	Acalabrutinib	Zanubrutinib	Pirtobrutinib
BTK binding	Covalent C481	Covalent C481	Covalent C481	Reversible ATP pocket Distant from C481
Half-life	6 hours	1 hour	4 hours	20 hours >90% BTK inhibition
BTK Y223 autophosphorylation	Inhibited	Inhibited	Inhibited	Inhibited
BTK Y551 phosphorylation	No effect	No effect	No effect	Inhibited (maintenance of closed conformation)
BTK C481S mutation	Common	Reported	Reported	Not described Effective against C481S
Kinase-dead mutations	Uncommon and restricted to C481* (active against HCK)	Not reported to date	Reported: L528W > C481Y	Reported: L528W > V416L, A428D, C481R, M477I, and M437R
T474I/T474L gatekeeper mutation	Uncommon*; active against T474I and T474L	Reported	Not reported to date	Reported

Thompson PA, Tam CS. *Blood* 2023;141(26):3137-42.

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ZUMA-2 Three-Year Follow-Up: Overall AEs and AEs Occurring Since the Primary Analysis Report with Brexucabtagene Autoleucel

	All-Treated Patients (N=68)				
	Overall AEs Occurring Since Infusion	AEs Occurring Since the Primary Analysis Report			
		Any Grade	Grade 3	Grade 4	Grade 5
AEs, n (%)					
Any	68 (100)	18 (26)	4 (6)	7 (10)	3 (4)
Any KTE-X19–related	66 (97)	9 (13)	2 (3)	6 (9)	0
Serious AEs, n (%)					
Any	48 (71)	8 (12)	4 (6)	0	3 (4)
Serious KTE-X19–related	37 (54)	2 (3)	2 (3)	0	0
CRS or neurologic events, n (%)	63 (93)	2 (3)	1 (1)	0	0
CRS[a]	62 (91)	0	0	0	0
Neurologic events	43 (63)	2 (3)	1 (1)[b]	0	0
Serious neurologic event	22 (32)	1 (1)	1 (1)[b]	0	0
Cytopenias, n (%)					
Thrombocytopenia	50 (74)	2 (3)	0	2 (3)	0
Neutropenia	59 (87)	8 (12)	1 (1)	7 (10)	0
Anemia	47 (69)	3 (4)	2 (3)	0	0
Infection, n (%)					
Any	36 (53)	7 (10)	3 (4)	0	1 (1)
Serious	21 (31)	4 (6)	3 (4)	0	1 (1)
COVID-19 associated viral	0	0	0	0	0
Non–COVID-19 associated viral	11 (16)	3 (4)	1 (1)	0	0
Hypogammaglobulinemia, n (%)	14 (21)	1 (1)	0	0	0
Tumor lysis syndrome, n (%)	1 (1)	0	0	0	0

Data cutoff for the primary analysis was July 19, 2019[1]; data cutoff for the present analysis was July 24, 2021. Numbers (percentage) of patients with worst grade of AE are shown; AEs occurring after retreatment are not included. [a]CRS events were graded per revised Lee et al. 2014 grading system[17]; all other AEs were graded per Common Terminology Criteria for Adverse Events version 4.03. [b]This serious neurologic event of encephalopathy began on day 397; the event resolved on day 408 and was considered unrelated to KTE-X19. AE, adverse event; CRS, cytokine release syndrome; KTE-X19, brexucabtagene autoleucel. 1. Wang M, et al. N Engl J Med. 2020;382:1331-1342.

Wang M et al. ASCO 2022;Abstract 7518; Wang M et al. *J Clin Oncol* 2023;41(3):555-67.

RTP RESEARCH TO PRACTICE

TRANSCEND FL and TRANSCEND NHL 001 Studies of Lisocabtagene Maraleucel in Relapsed/Refractory Follicular Lymphoma and Mantle Cell Lymphoma Meet Primary Endpoints

Press Release: May 1, 2023

Positive topline results were announced from two studies, TRANSCEND FL, an open-label, global, multicenter, Phase 2, single-arm study evaluating lisocabtagene maraleucel in patients with relapsed or refractory follicular lymphoma (FL), and TRANSCEND NHL 001, an open-label, multicenter, pivotal Phase 1, single-arm study evaluating lisocabtagene maraleucel in patients with relapsed or refractory B-cell non-Hodgkin lymphoma, including mantle cell lymphoma (MCL).

"Results showed both studies met the primary endpoint of overall response rate, with lisocabtagene maraleucel demonstrating statistically significant and clinically meaningful responses in relapsed or refractory FL and MCL. The studies also met the key secondary endpoint of complete response rate, demonstrating high rates of complete responses in both relapsed or refractory FL and MCL. No new safety signals were reported for lisocabtagene maraleucel in either disease in these studies."

https://news.bms.com/news/details/2023/Bristol-Myers-Squibbs-TRANSCEND-FL-and-TRANSCEND-NHL-001-Studies-of-Breyanzi-lisocabtagene-maraleucelin-Relapsed-or-Refractory-Follicular-Lymphoma-and-Mantle-Cell-Lymphoma-Meet-Primary-Endpoint-of-Overall-Response-Rate/default.aspx

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Safety and Preliminary Efficacy in Patients with Relapsed/Refractory Mantle Cell Lymphoma Receiving Lisocabtagene Maraleucel in Transcend NHL 001

Palomba ML et al.

ASH 2020;Abstract 118.

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TRANSCEND NHL 001: Preliminary Efficacy and Safety of Lisocabtagene Maraleucel for R/R MCL at 2 Dose Levels

No. of Patients		Median # prior therapies (range)	ORR		CR		CRS		NE	
DL1	DL2		DL1	DL2	DL1	DL2	DL1	DL2	DL1	DL2
6	26	3 (1-7)	67%	88%	33%	65%	33%	54%	0	28%

DL1, 50 x 10^6 CAR T cells, DL2, 100 x 10^6 CAR T cells
ORR = objective response rate; CR = complete response; CRS = cytokine release syndrome; NE = neurologic event

Palomba ML et al. ASH 2020;Abstract 118.

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Meet The Professor
Optimizing the Management of Gastroesophageal Cancers

Thursday, September 28, 2023
5:00 PM – 6:00 PM ET

Faculty

Peter C Enzinger, MD

Moderator

Neil Love, MD

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Thank you for joining us!

Please take a moment to complete the survey currently up on Zoom. Your feedback is very important to us. The survey will remain open for 5 minutes after the meeting ends.

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

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