Inside the Issue — Optimizing the Management of Adverse Events Associated with BTK Inhibitors

A CME/MOC-Accredited Virtual Event

Thursday, February 2, 2023
5:00 PM – 6:00 PM ET

Faculty

Farrukh T Awan, MD
Kerry A Rogers, MD

Moderator

Neil Love, MD

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Faculty

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Professor of Internal Medicine
Director of Lymphoid Malignancies Program
Harold C Simmons Comprehensive Cancer Center
The University of Texas Southwestern Medical Center
Dallas, Texas

Kerry A Rogers, MD
Associate Professor in the Division of Hematology
The Ohio State University
Columbus, Ohio

Moderator
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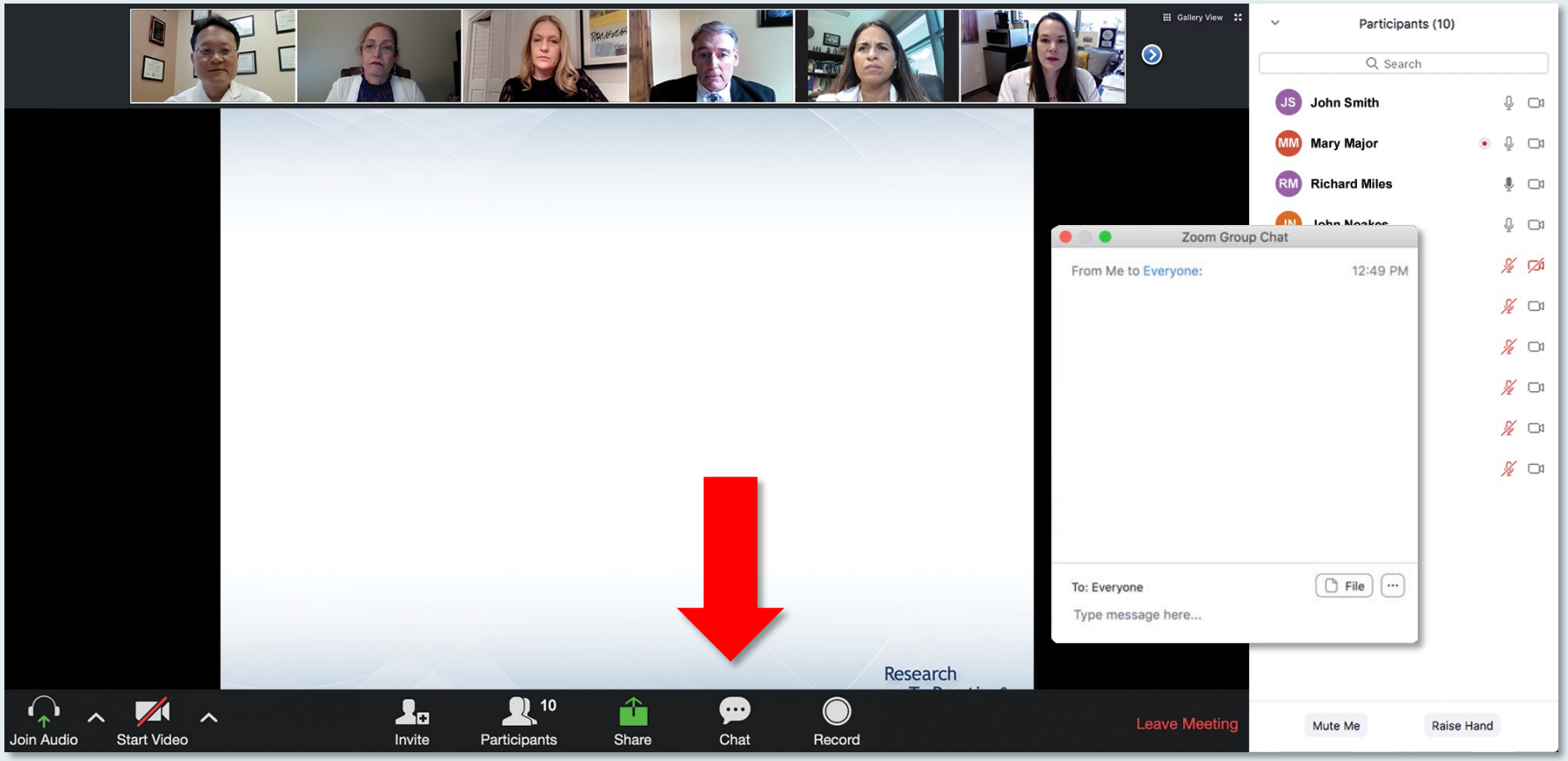
We Encourage Clinicians in Practice to Submit Questions



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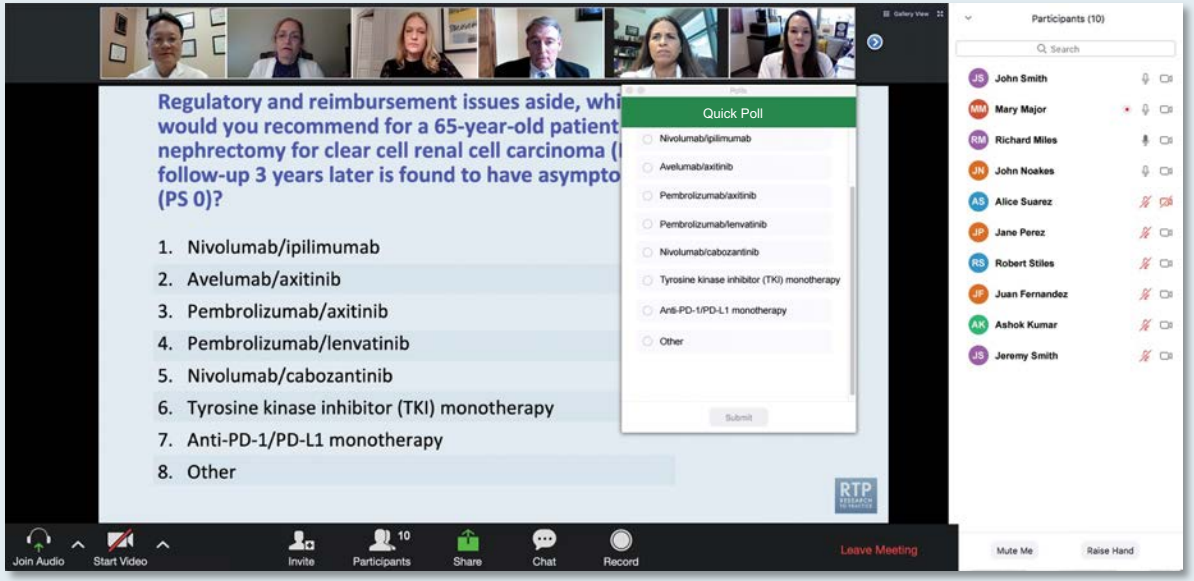

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Prof Karim Fizazi, MD, PhD

Maha Hussain, MD, FACP, FASCO

Matthew R Smith, MD, PhD

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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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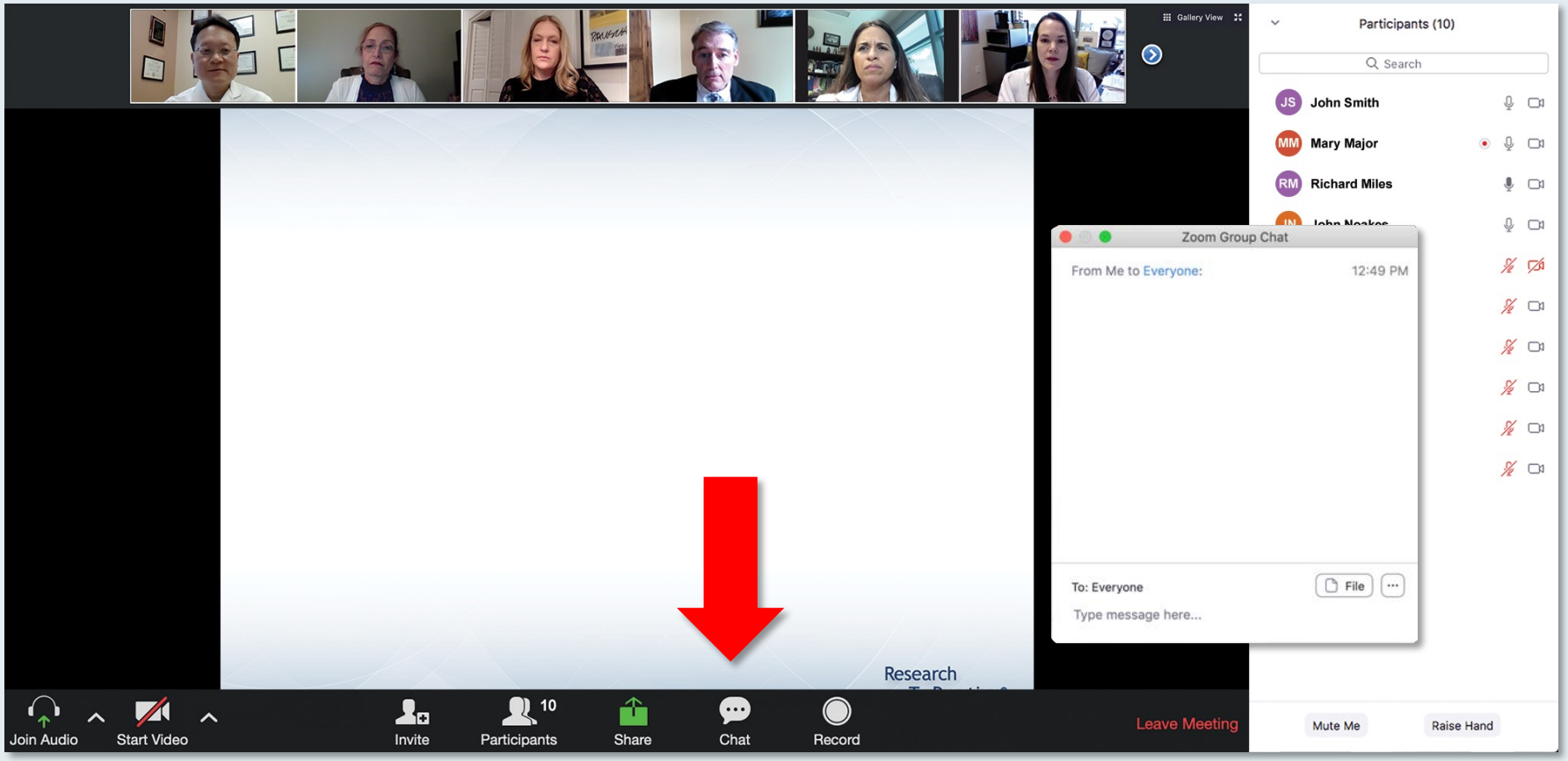

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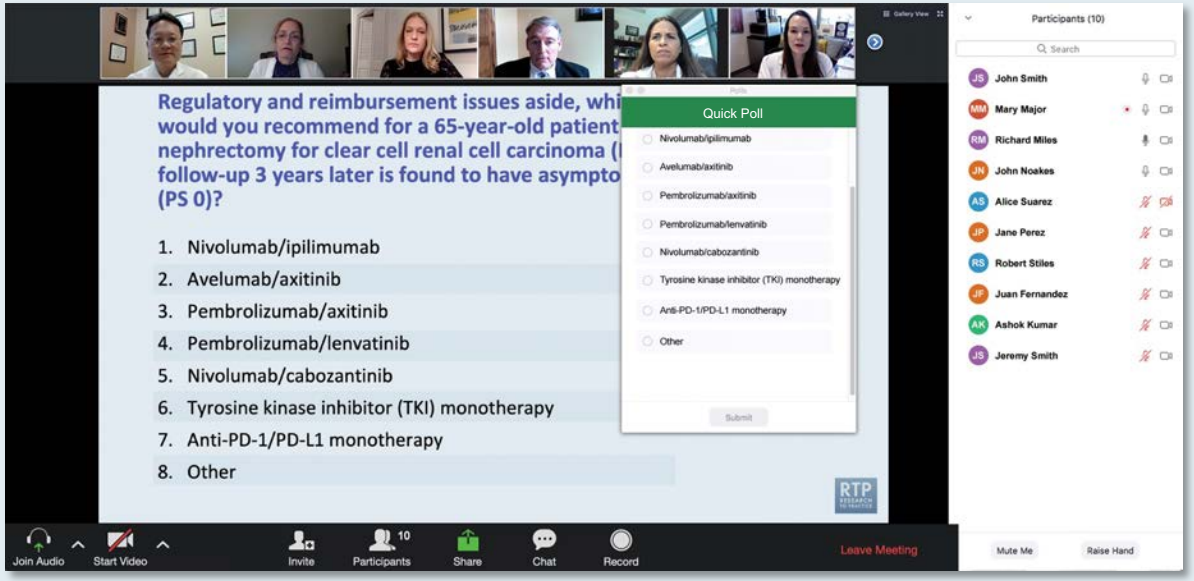

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Warren S Brenner, MD
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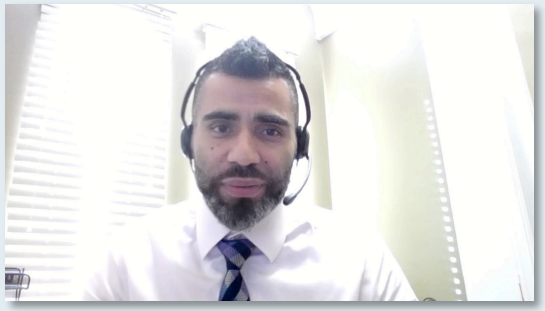
Boca Raton, Florida

Sulfi Ibrahim, MD
Reid Health
Richmond, Indiana

Gigi Chen, MD
John Muir Health
Pleasant Hill, California

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



Rohit Gosain, MD
UPMC Hillman Cancer Center
Jamestown, New York

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

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Yanjun Ma, MD
Tennessee Oncology
Murfreesboro, Tennessee

Neil Morganstein, MD
Atlantic Health System
Summit, New Jersey

Laurie Matt-Amaral, MD, MPH
Cleveland Clinic Akron General
Akron, Ohio

Erik Rupard, MD
The Reading Hospital
West Reading, Pennsylvania

William R Mitchell, MD
Southern Oncology Specialists
Charlotte, North Carolina

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Inside the Issue: BTK Inhibitors

Introduction

Module 1: Very Elderly Patients

Module 2: Cardiac Issues

Module 3: Other BTKi Toxicities

Module 4: BTKis Combined with Chemotherapy for MCL

Inside the Issue: BTK Inhibitors

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 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?utm_medium=email&utm_source=govdelivery

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FDA Approves Zanubrutinib for Chronic Lymphocytic Leukemia or Small Lymphocytic Lymphoma

Press Release: January 19, 2023

“On January 19, 2023, the Food and Drug Administration approved zanubrutinib for chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL).

Efficacy in patients with treatment-naïve CLL/SLL was evaluated in SEQUOIA (NCT03336333). In the randomized cohort including patients without 17p deletion, a total of 479 patients were randomized 1:1 to receive either zanubrutinib until disease progression or unacceptable toxicity or bendamustine plus rituximab (BR) for 6 cycles.

Efficacy in patients with relapsed or refractory CLL/SLL was evaluated in ALPINE (NCT03734016). A total of 652 patients were randomized 1:1 to receive either zanubrutinib or ibrutinib.

The recommended zanubrutinib dosage is 160 mg taken orally twice daily or 320 mg taken orally once daily until disease progression or unacceptable toxicity.”

https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-zanubrutinib-chronic-lymphocytic-leukemia-or-small-lymphocytic-lymphoma

Inside the Issue: BTK Inhibitors

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Module 1: Very Elderly Patients

- Dr Rupard: 90-year-old woman with underlying COPD was observed for 20 years for CLL before initiating treatment with acalabrutinib and quickly develops fatigue, headache and diarrhea
- Dr Morganstein: 87-year-old frail man with CLL requiring treatment develops nonspecific side effects with acalabrutinib

Module 2: Cardiac Issues

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Case Presentation: 90-year-old woman with underlying COPD was observed for 20 years for CLL before initiating treatment with acalabrutinib and quickly develops fatigue, headache and diarrhea

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Case Presentation: 87-year-old frail man with CLL requiring treatment develops nonspecific side effects with acalabrutinib

Dr Neil Morganstein (Summit, New Jersey)

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Wang *et al.*
Experimental Hematology & Oncology (2022) 11:60
https://doi.org/10.1186/s40164-022-00315-9

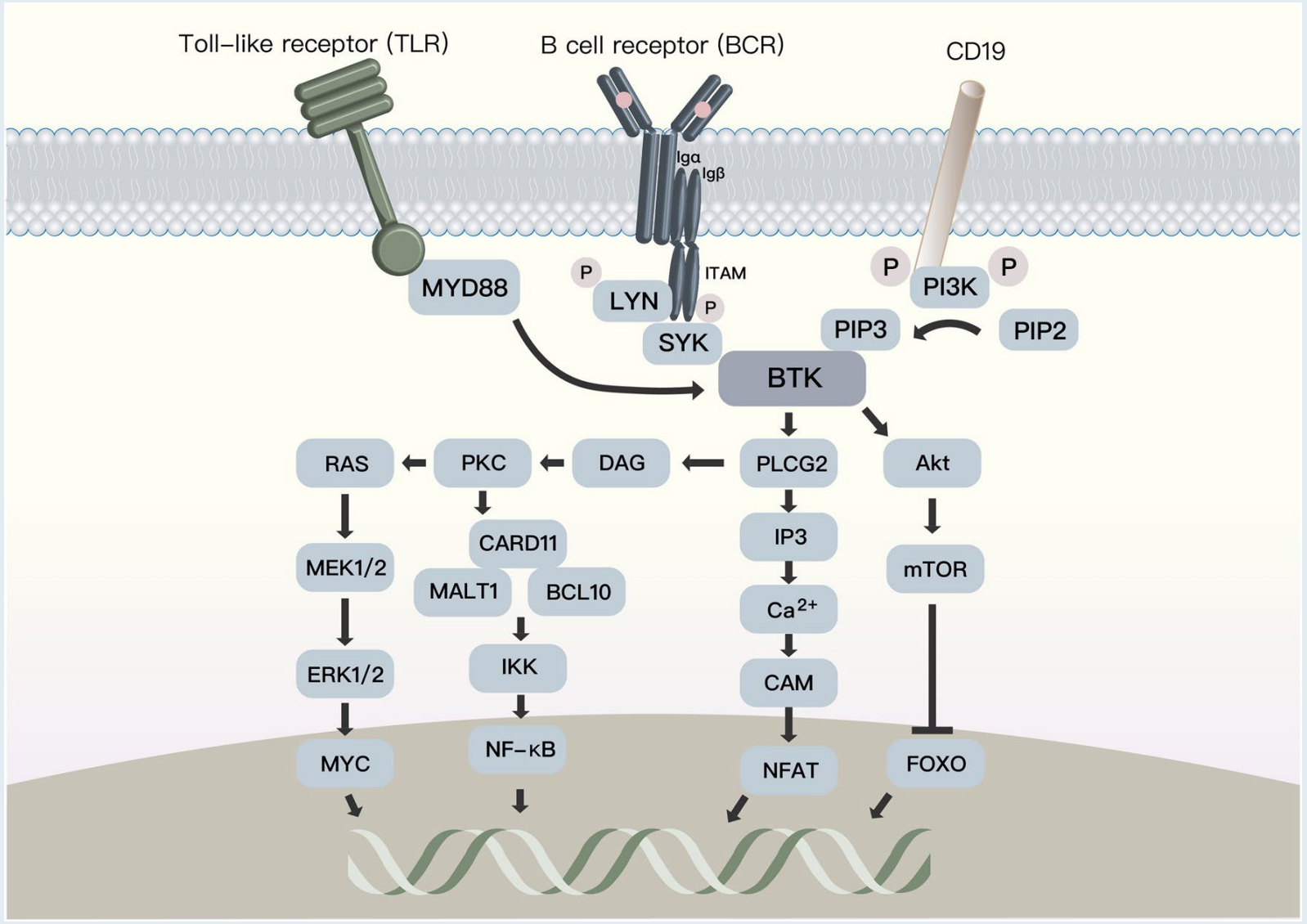
Experimental Hematology & Oncology

REVIEW Open Access

Bruton tyrosine kinase inhibitors in B-cell lymphoma: beyond the antitumour effect

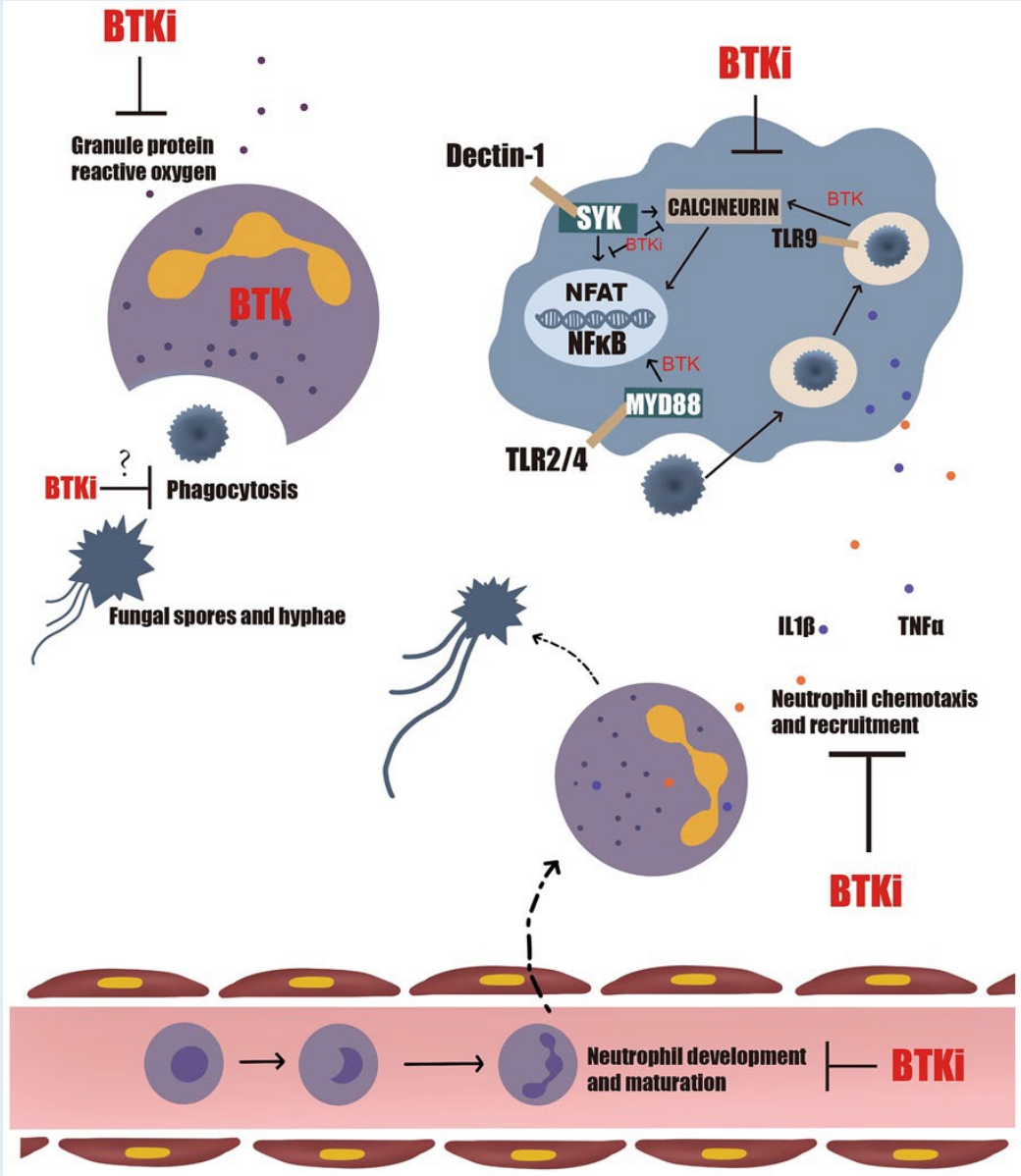
Haoran Wang, Hao Guo, Jingyi Yang, Yanyan Liu, Xingchen Liu, Qing Zhang and Keshu Zhou*

B-Cell Receptor/BTK Signaling in Normal and Malignant B Cells



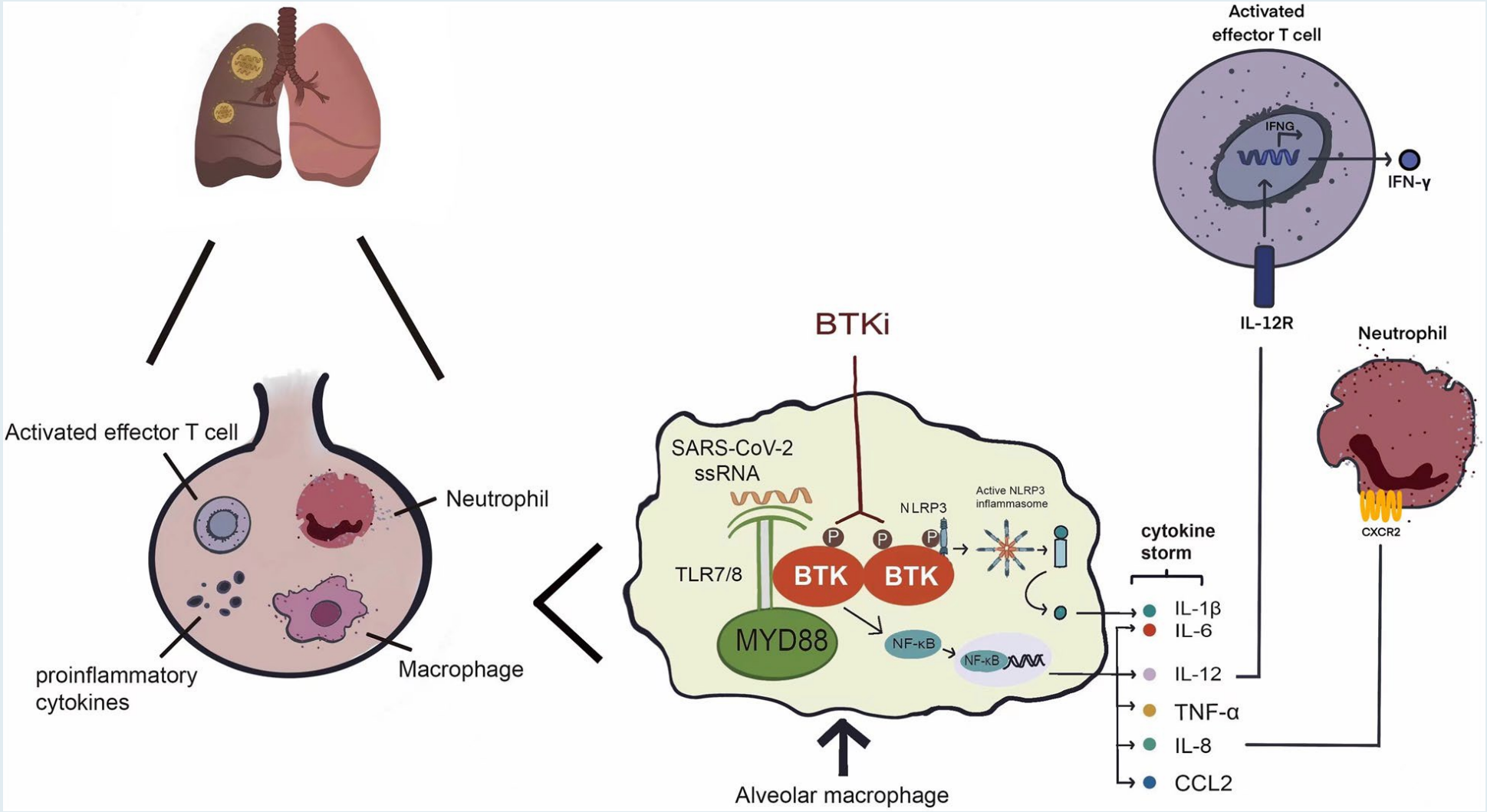
Wang H et al. *Exp Hematol Oncol* 2022;11:60.

Role of a BTK Inhibitor in the Immune Cell Response to Fungal Infection



Wang H et al. *Exp Hematol Oncol* 2022;11:60.

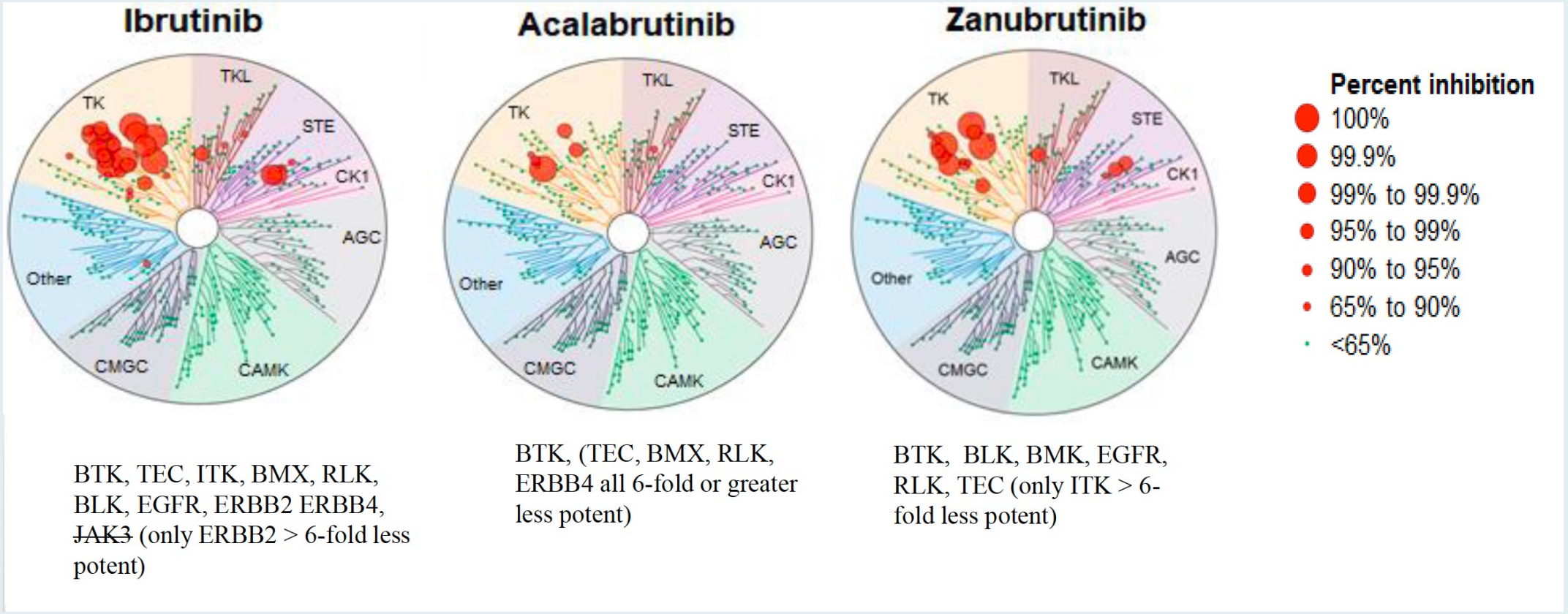
Mechanism by Which BTK Inhibition Mitigates Lung Injury Mediated by a Cytokine Storm



Wang H et al. *Exp Hematol Oncol* 2022;11:60.

Irreversible and Reversible BTK Inhibitors in CLL

BTKi	Binding	T1/2 (hours)	IC50 [nM]	Dosing
Ibrutinib	Covalent irreversible C481	4-8	0.5	420 mg
Acalabrutinib	Covalent irreversible C481	0.9	5.1	100 mg BID
Zanubrutinib	Covalent irreversible C481	2-4	0.5	160 or 320 mg BID



Robak T et al. *Cancers* 2022 Feb 2;14(3):771; Byrd JC. SOHO 2022;Abstract 177-CLL.

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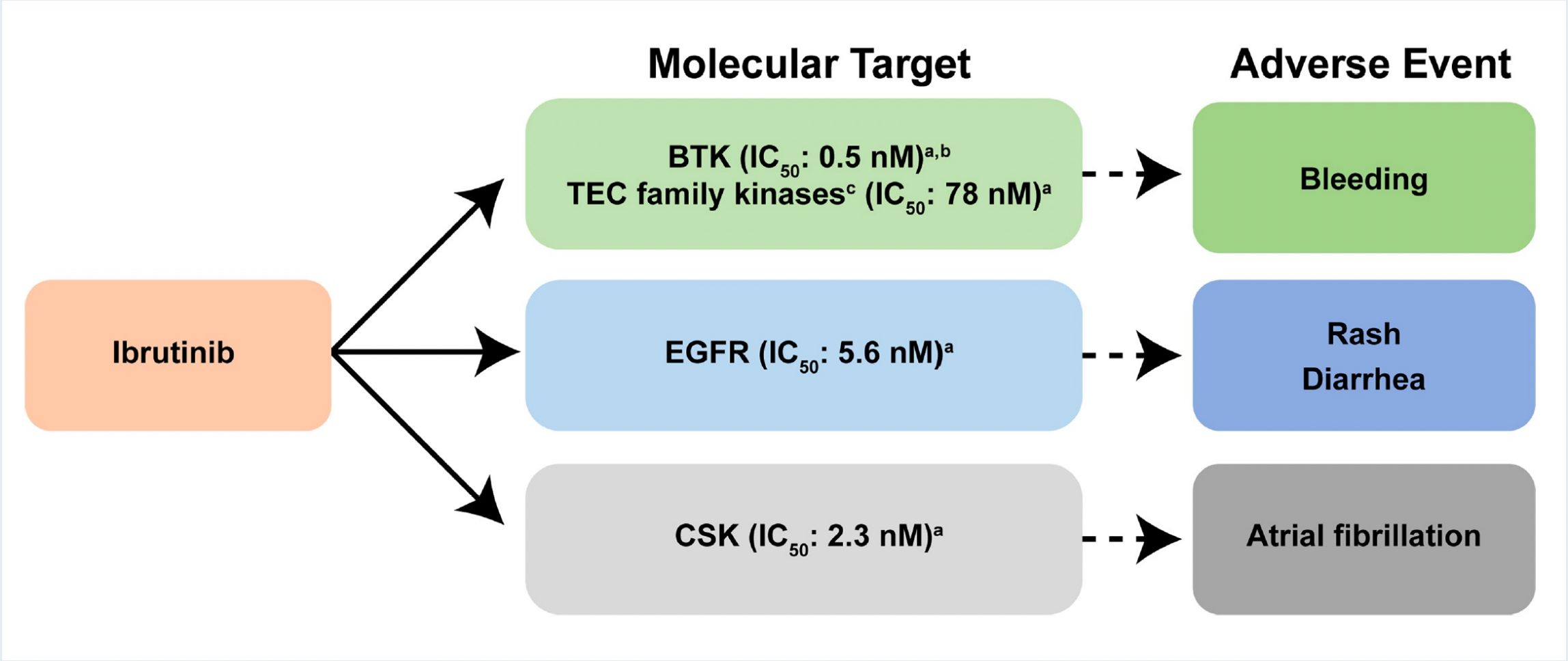
Description and Pharmacological Properties of Approved BTKis

Parameter	Ibrutinib	Acalabrutinib	Zanubrutinib
Mode of binding	Covalent, irreversible	Covalent, irreversible	Covalent, irreversible
BTK binding site	Cys-481	Cys-481	Cys-481
Selectivity	Moderate	High	High
IC_{50}			
BTK	0.5 nM	3.0-5.1 nM	0.3nM
BMX	0.8 nM	46 nM	
EGFR	5.3 nM	>1000 nM	21 nM
HER2	9.4 nM	>1000 nM	661 nM
HER4		16 nM	
ITK	4.9 nM	>1000 nM	50 nM
JAK3	32 nM	>1000 nM	>1000 nM
TEC	10 nM	126 nM	44nM
Absolute bioavailability	<10%	25%	45%-50%
Half-life	4-13 h	1-2 h	2-4 h
Target occupancy in PBMCs	>90%	97%-99%	>95%

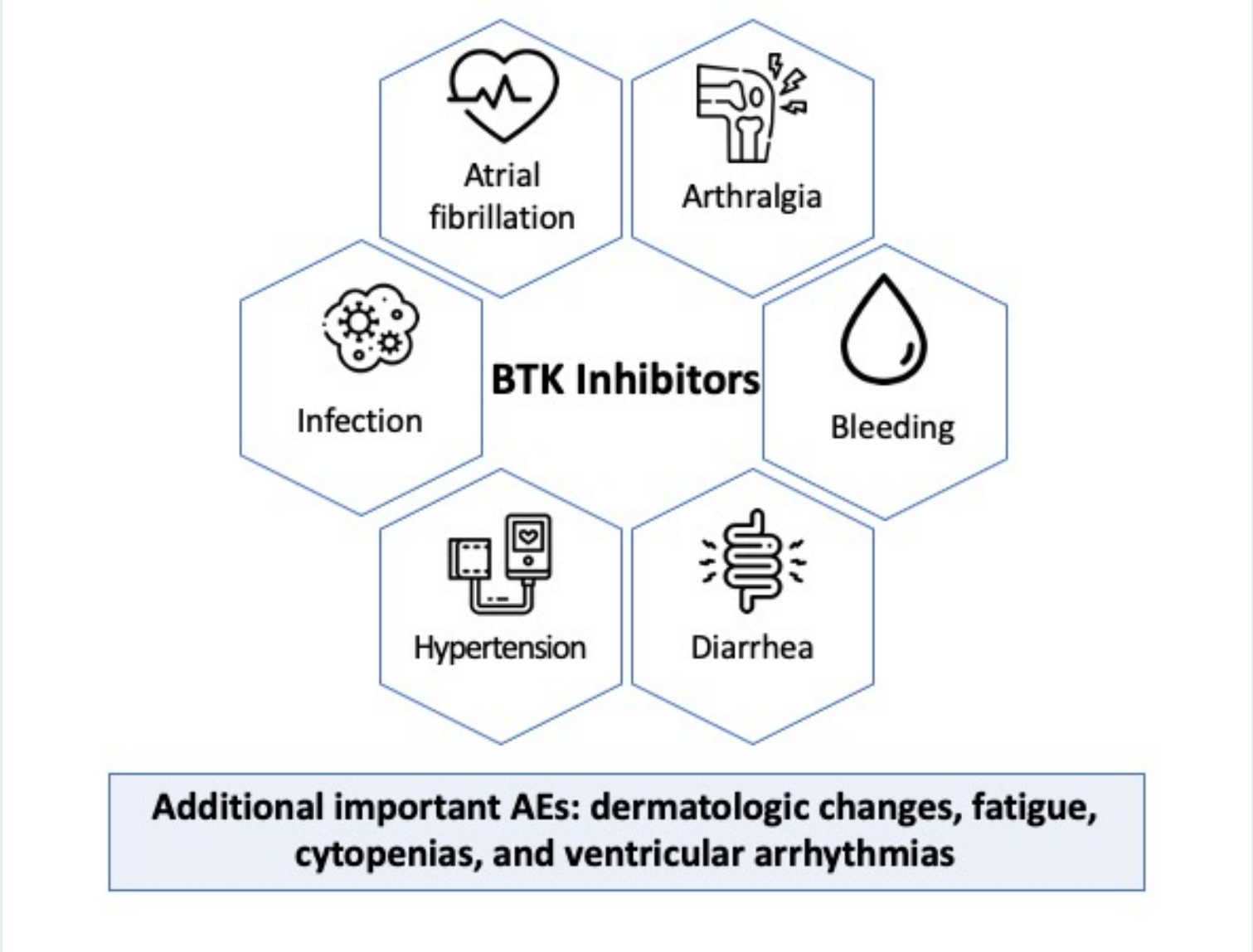
Shirley M et al. *Targeted Oncol* 2022;17:69-84.

Reported Molecular Targets of Ibrutinib and Their Associated Adverse Events

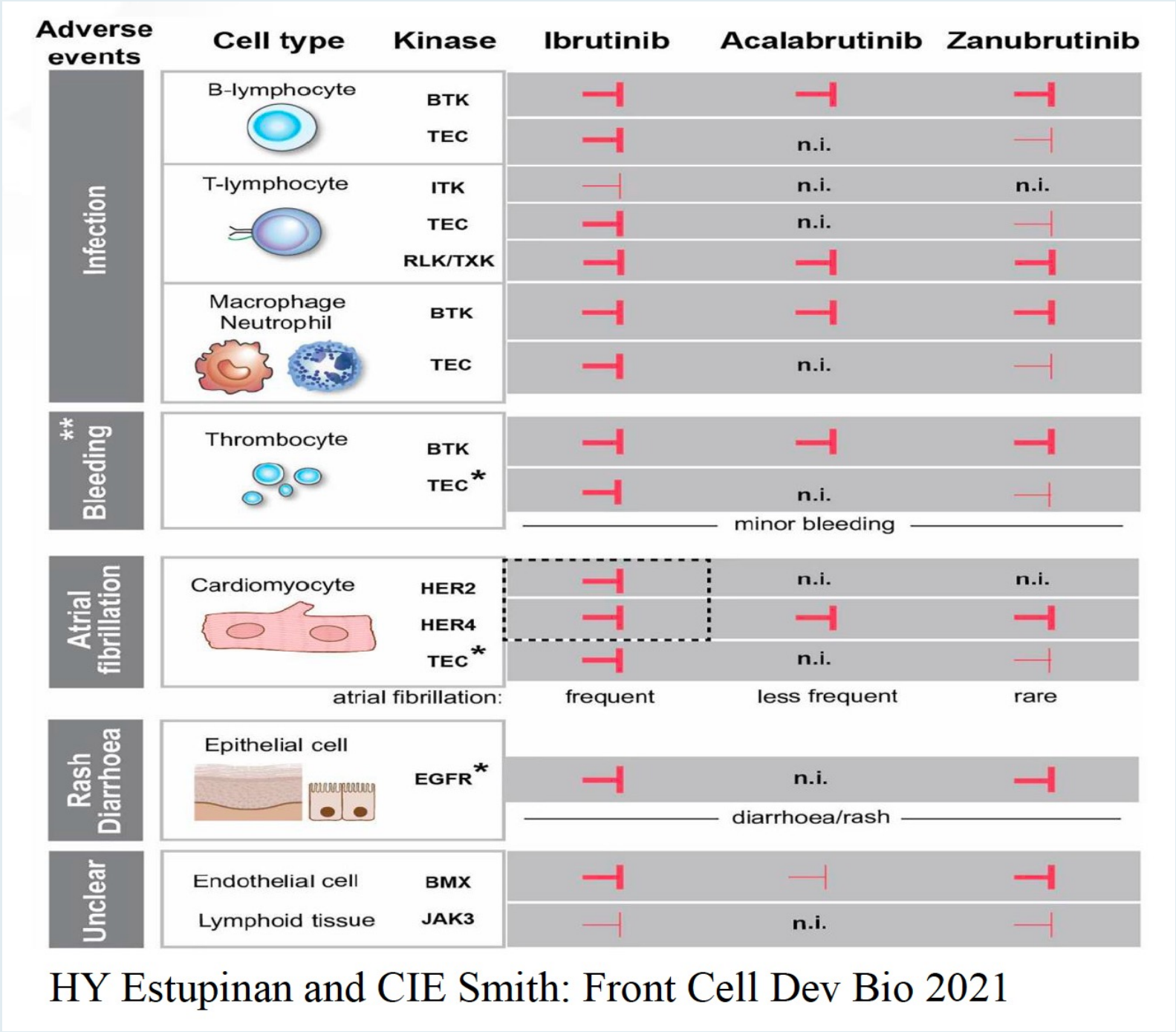


O'Brien SM et al. *Front Oncol* 2021;11:720704.

Summary of Adverse Events with BTK Inhibitors



Courtesy of Matthew S Davids, MD, MMSc

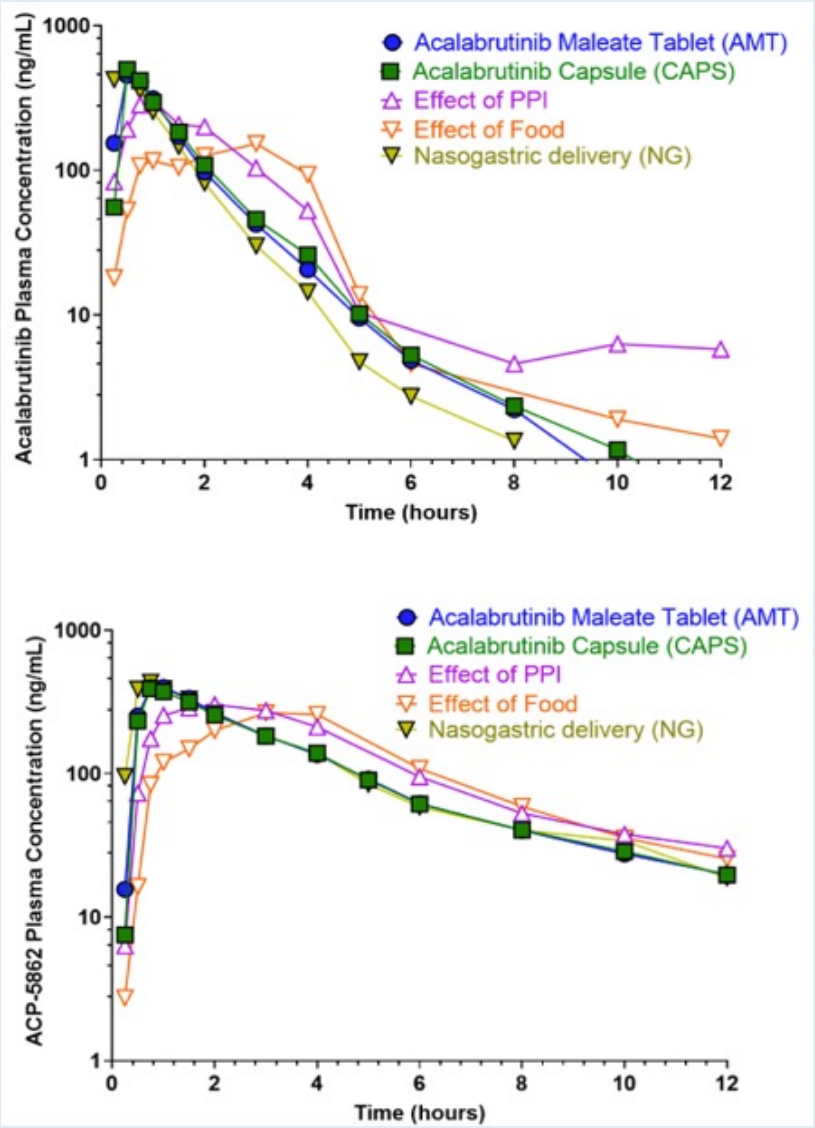


HY Estupinan and CIE Smith: Front Cell Dev Bio 2021

ELEVATE-PLUS: Acalabrutinib Maleate Tablet (AMT) Formulation Allowing Coadministration with PPI and Administration to Patients Unable to Swallow Capsules

- **Three Phase I, open-label, single-dose, crossover studies conducted in healthy subjects demonstrated**
  - **Similar systemic exposure between AMT and acalabrutinib capsules**
  - **No clinically relevant differences in acalabrutinib and ACP-5862 exposures was observed following administration of AMT +/- PPI**
  - **No clinically relevant impact of food on exposures**
  - **Similar BTK target occupancy**
  - **No new safety concerns with the AMT**

PK Profiles of Acalabrutinib/ACP-5862



PPI = proton pump inhibitor

ACP-5862 is a major pharmacologically active metabolite of acalabrutinib.

Sharma S, et al. ASH 2021. Abstract 4365

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Selected Features of Approved BTKis

Parameter	Ibrutinib	Acalabrutinib	Zanubrutinib
Dosage[b]	420 mg QD in CLL; 560 mg QD in MCL/MZL	100 mg bid	160 mg bid or 320 mg QD
Use in patients with renal impairment			
Mild	Yes	Yes	Yes
Moderate	Yes	Yes	Yes
Severe	No data	No data	Yes
ESRD	No data	No data	No data
Use in patients with hepatic impairment			
Mild	Reduce dose	Yes	Yes
Moderate	Reduce dose	Yes	Yes
Severe	No	No	Reduce dose
Food effect	No	No	No

Shirley M et al. *Targeted Oncol* 2022;17:69-84.

Recommended Acalabrutinib Dose Modifications for Adverse Reactions

Event	Adverse reaction occurrence	Dose modifications (Starting dose 100 mg approximately every 12 h)
Grade ≥3 nonhematologic toxicities, Grade 3 thrombocytopenia with bleeding, Grade 4 thrombocytopenia or Grade neutropenia lasting longer than 7 days	First and second	• Interrupt acalabrutinib • Once toxicity has resolved to Grade 1 or baseline level, acalabrutinib may be resumed at 100 mg approximately every 12 h
	Third	• Interrupt acalabrutinib • Once toxicity has resolved to Grade 1 or baseline level, acalabrutinib may be resumed at a reduced frequency of 100 mg once daily
	Fourth	• Discontinue acalabrutinib

Acalabrutinib package insert, revised 8/2022.

Recommended Zanubrutinib Dose Modifications for Adverse Hematologic Reactions

Event	Adverse reaction occurrence	Dose modifications (Starting dose 160 mg BID or 320 mg qd)
Grade ≥3 or Grade 4 febrile neutropenia Platelet count decreased to 25,000-50,000/mm^3 with significant bleeding Neutrophil count decreased to <500/mm^3 (lasting more than 10 consecutive days) Platelet count decreased to <25,000/mm^3 (lasting more than 10 consecutive days)	First	• Interrupt zanubrutinib • Once toxicity has resolved to Grade 1 or lower or baseline, resume at 160 mg twice daily or 320 mg once daily
	Second	• Interrupt zanubrutinib • Once toxicity has resolved to Grade 1 or lower or baseline, resume at 80 mg twice daily or 160 mg once daily
	Third	• Interrupt zanubrutinib • Once toxicity has resolved to Grade 1 or lower or baseline, resume at 80 mg once daily
	Fourth	• Discontinue zanubrutinib

Zanubrutinib package insert, revised 1/2023.

Recommended Zanubrutinib Dose Modifications for Adverse Nonhematologic Reactions

Event	Adverse reaction occurrence	Dose modifications (Starting dose 160 mg BID or 320 mg qd)
Severe or life-threatening nonhematologic toxicities	First	• Interrupt zanubrutinib • Once toxicity has resolved to Grade 1 or lower or baseline, resume at 160 mg twice daily or 320 mg once daily
	Second	• Interrupt zanubrutinib • Once toxicity has resolved to Grade 1 or lower or baseline, resume at 80 mg twice daily or 160 mg once daily
	Third	• Interrupt zanubrutinib • Once toxicity has resolved to Grade 1 or lower or baseline, resume at 80 mg once daily
	Fourth	• Discontinue zanubrutinib

Zanubrutinib package insert, revised 1/2023.

Inside the Issue: BTK Inhibitors

Introduction

Module 1: Very Elderly Patients

Module 2: Cardiac Issues

- Dr Matt-Amaral: 89-year-old man with CLL was observed for 28 years before starting ibrutinib and then develops atrial fibrillation
- Dr Lee: 84-year-old man with CLL develops atrial fibrillation on ibrutinib while traveling overseas
- Dr Brenner: 74-year-old man with relapsed del(11q) SLL develops ibrutinib-associated atrial fibrillation and receives an oral anticoagulant

Module 3: Other BTKi Toxicities

Module 4: BTKis Combined with Chemotherapy for MCL

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Case Presentation: 89-year-old man with CLL was observed for 28 years before starting ibrutinib and then develops atrial fibrillation

Dr Laurie Matt-Amaral (Akron, Ohio)

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Case Presentation: 84-year-old man with CLL develops atrial fibrillation on ibrutinib while traveling overseas

Dr Eric Lee (Fountain Valley, California)

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Case Presentation: 74-year-old man with relapsed del(11q) SLL develops ibrutinib-associated atrial fibrillation and receives an oral anticoagulant

Dr Warren Brenner (Boca Raton, Florida)

Inside the Issue: BTK Inhibitors

Introduction

Module 1: Very Elderly Patients

Module 2: Cardiac Issues

Module 3: Other BTKi Toxicities

- Dr Ma: 65-year-old man with relapsed CLL treated with ibrutinib develops significant epistaxis and ecchymoses
- Dr Chen: 62-year-old man with Waldenström macroglobulinemia receives ibrutinib/rituximab and develops elevated liver enzymes
- Dr Gosain: 68-year-old woman with CLL experiences acalabrutinib-associated headaches
- Dr Mitchell: 54-year-old man with monoclonal B-cell lymphocytosis with a CLL-like phenotype has an excellent response to acalabrutinib for relapsed disease but develops nausea and vomiting
- Dr Ibrahim: 81-year-old man with CLL on a CYP3A4 inhibitor receives acalabrutinib

Module 4: BTKis Combined with Chemotherapy for MCL

Case Presentation: 65-year-old man with relapsed CLL treated with ibrutinib develops significant epistaxis and ecchymoses

Dr Yanjun Ma (Murfreesboro, Tennessee)

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Case Presentation: 62-year-old man with Waldenström macroglobulinemia receives ibrutinib/rituximab and develops elevated liver enzymes

Dr Gigi Chen (Pleasant Hill, California)

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Case Presentation: 68-year-old woman with CLL experiences acalabrutinib-associated headaches

Dr Rohit Gosain (Jamestown, New York)

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Case Presentation: 54-year-old man with monoclonal B-cell lymphocytosis with a CLL-like phenotype has an excellent response to acalabrutinib for relapsed disease but develops nausea and vomiting

Dr William Mitchell (Charlotte, North Carolina)

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Case Presentation: 81-year-old man with CLL on a CYP3A4 inhibitor receives acalabrutinib

Dr Sulfi Ibrahim (Richmond, Indiana)

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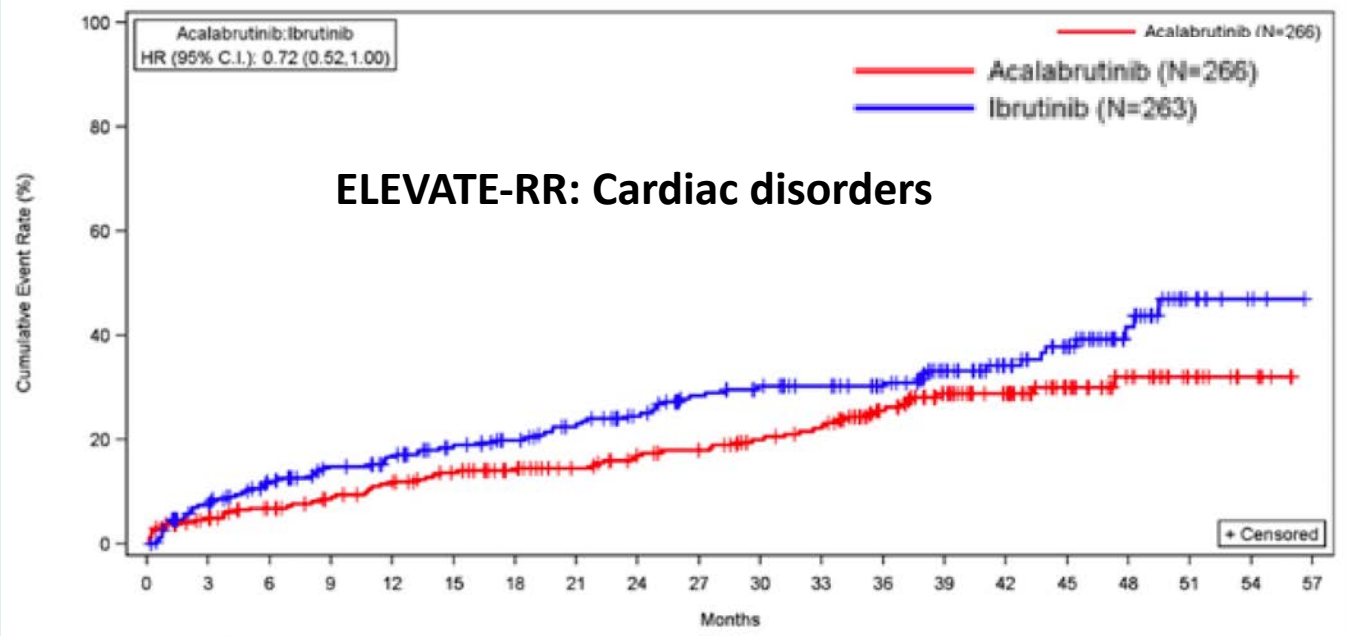
ELEVATE-RR and ALPINE: Cardiac, Hypertension and Bleeding Events

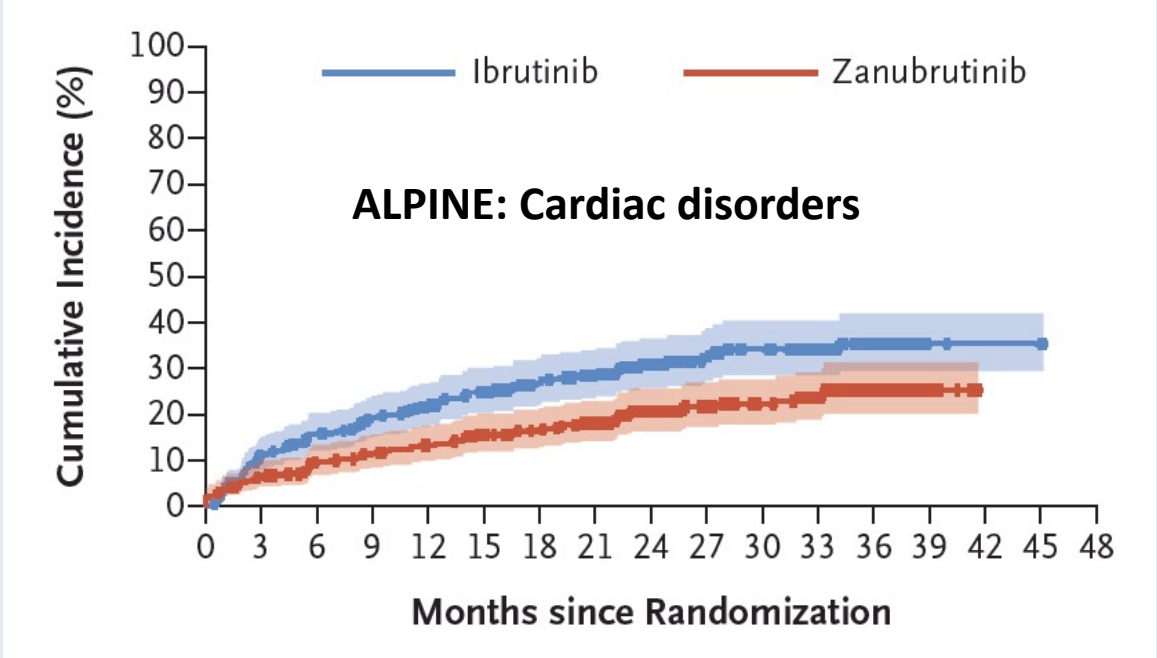
	ELEVATE-RR[1]				ALPINE[2]			
	Acalabrutinib (n = 266)		Ibrutinib (n = 263)		Zanubrutinib (n = 324)		Ibrutinib (n = 324)	
	Any grade	Grade ≥3	Any grade	Grade ≥3	Any grade	Grade ≥3	Any grade	Grade ≥3
Any cardiac event	24.1%	8.6%	30.0%	9.5%	21.3%	NR	29.6%	NR
Atrial fibrillation/flutter	9.4%	4.9%	16.4%	3.8%	5.2%	2.5%	13.3%	4.0$
Hypertension	8.6%	4.1%	23.2%	9.1%	23.5%	15.1%	22.8%	13.6%
Hemorrhage	38.0%	3.8%	51.3%	4.6%	42.3%	3.4%	41.4%	3.7%

NR = not reported

[1] Byrd JC et al. *J Clin Oncol* 2021;39:3441-52; [2] Brown JR et al. *N Engl J Med* 2022 Dec 13;[Online ahead of print].

ELEVATE-RR and ALPINE: Any-Grade Cardiac Event





Byrd JC et al. *J Clin Oncol* 2021;39:3441-52; Brown JR et al. *N Engl J Med* 2022 Dec 13;[Online ahead of print].

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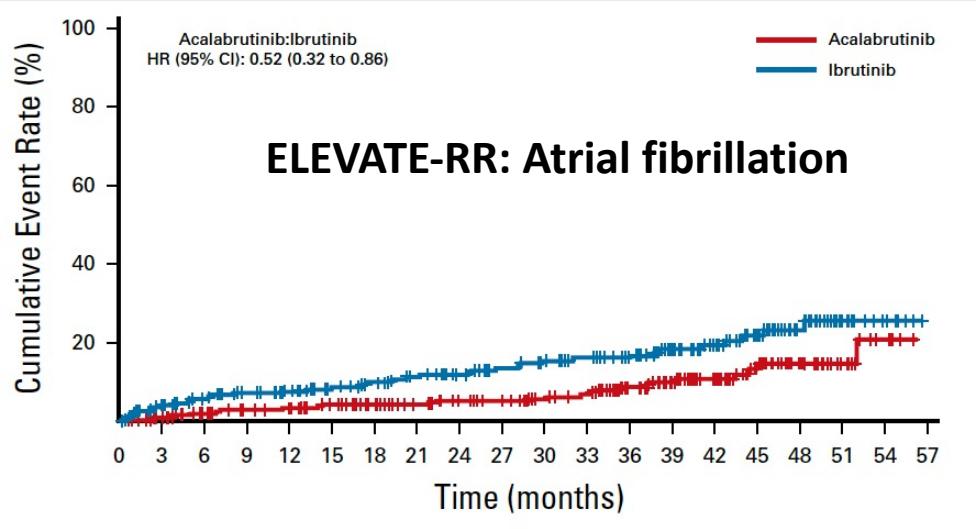
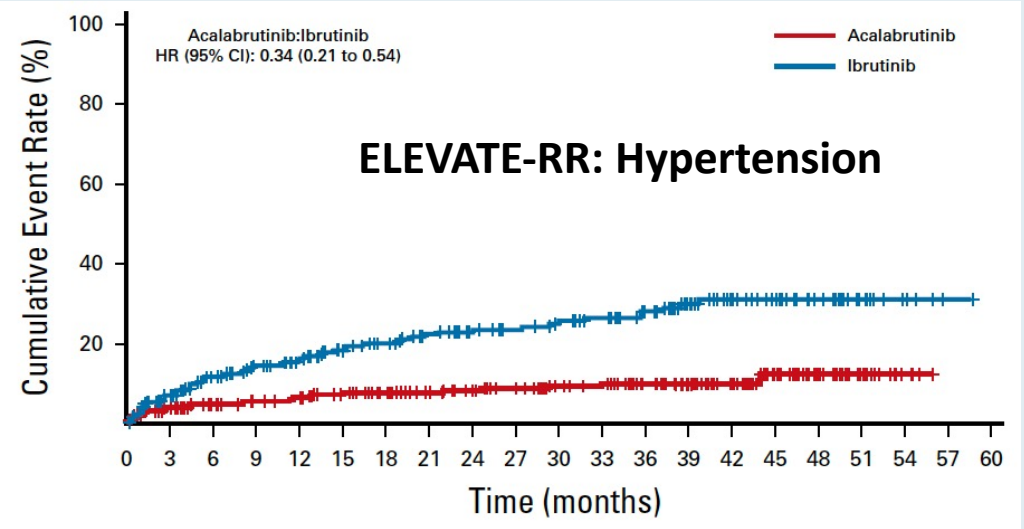
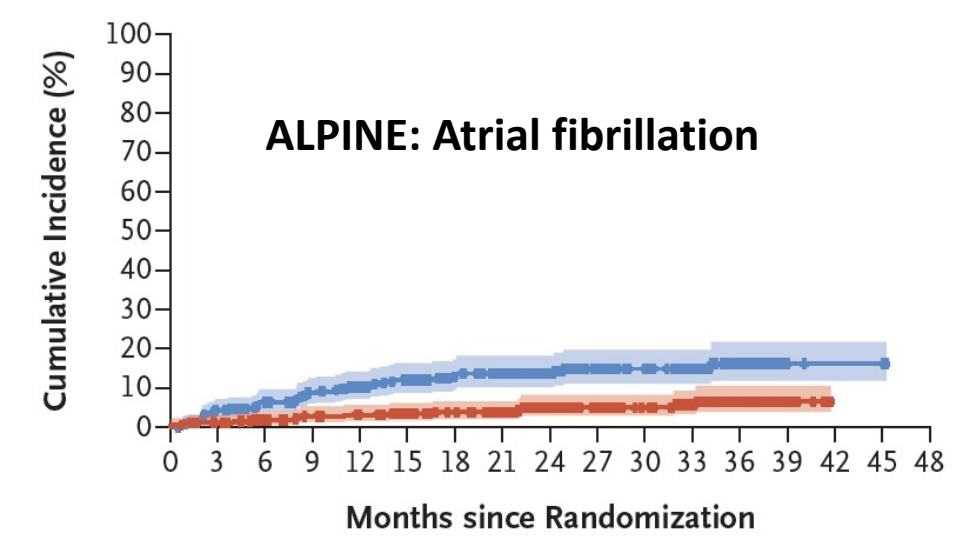
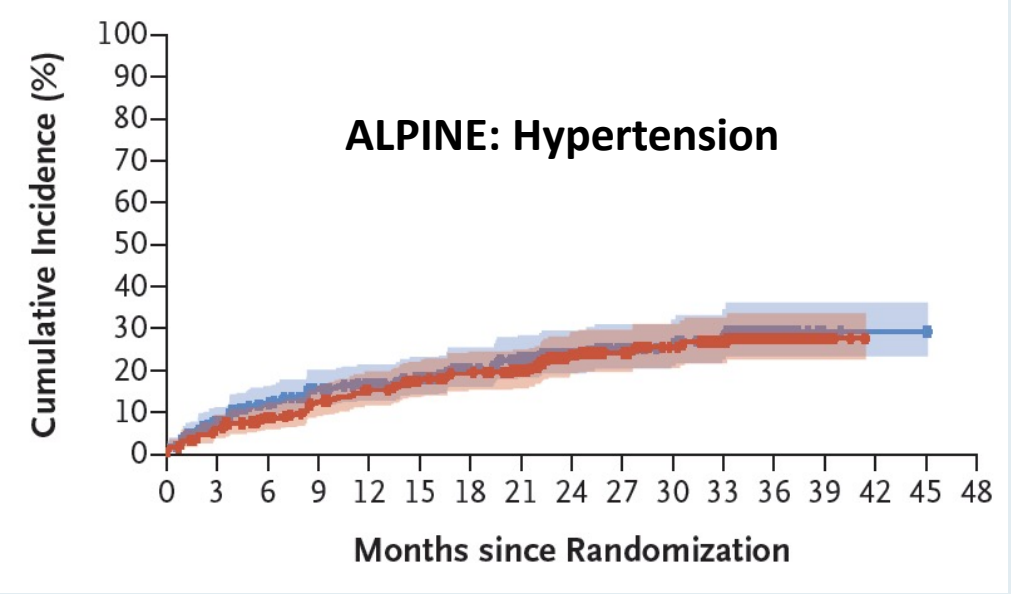
ELEVATE-RR and ALPINE: Atrial Fibrillation and Hypertension









[1] Byrd JC et al. *J Clin Oncol* 2021;39:3441-52; [2] Brown JR et al. *N Eng J Med* 2022 Dec 13;[Online ahead of print].

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ELEVATE-RR and ALPINE: Cytopenias and Infections

	ELEVATE-RR[1]				ALPINE[2]			
	Acalabrutinib (n = 266)		Ibrutinib (n = 263)		Zanubrutinib (n = 324)		Ibrutinib (n = 324)	
	Any grade	Grade ≥3	Any grade	Grade ≥3	Any grade	Grade ≥3	Any grade	Grade ≥3
Anemia	21.8%	11.7%	18.6%	12.9%	15.4%	2.2%	16.4%	2.5%
Thrombocytopenia	15.8%	10.2%	13.7%	6.8%	13.0%	3.4%	15.4%	5.2%
Neutropenia	23.3%	21.8%	25.9%	24.0%	29.3%	21.0%	24.4%	18.2%
Infections	78.2%	30.8%	81.4%	30.0%	71.3%	26.5%	73.1%	28.1%
ILD/pneumonitis*	2.6%	0.4%	6.5%	0.8%	5.9%	NR	8.0%	NR

NR = not reported
* Pneumonia only

[1] Byrd JC et al. *J Clin Oncol* 2021;39:3441-52; [2] Brown JR et al. *N Eng J Med* 2022 Dec 13;[Online ahead of print].

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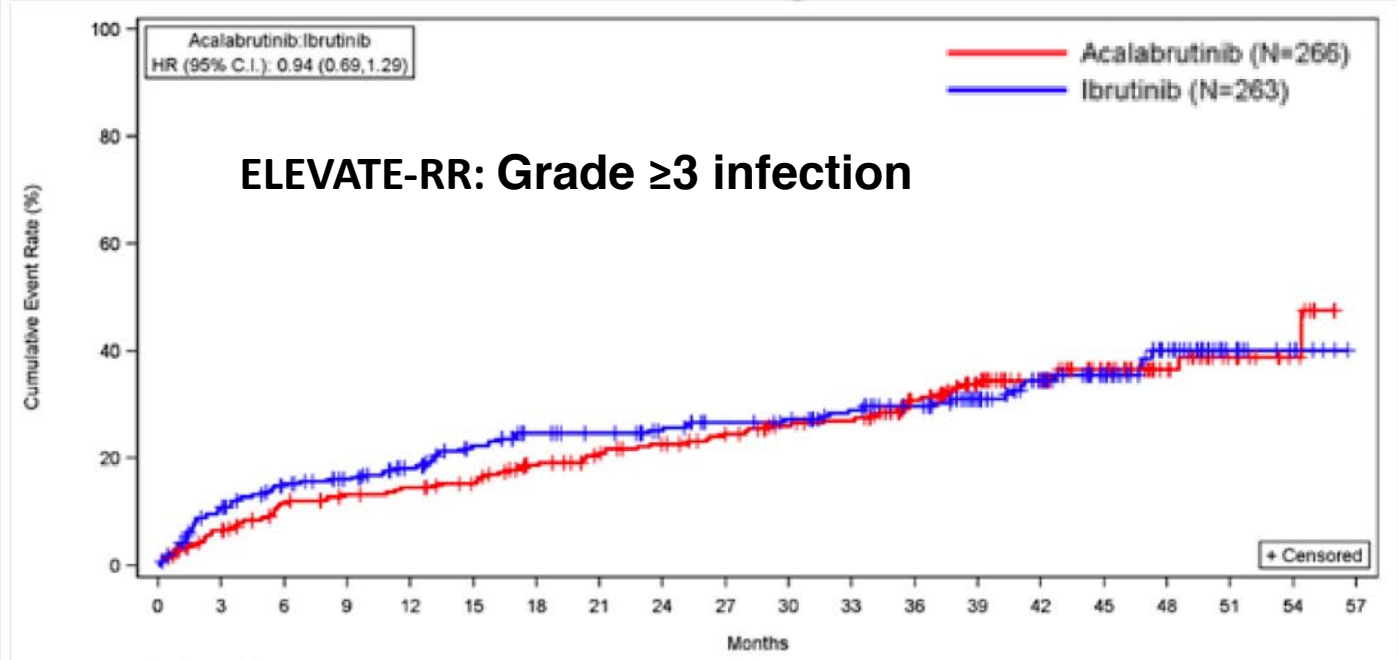
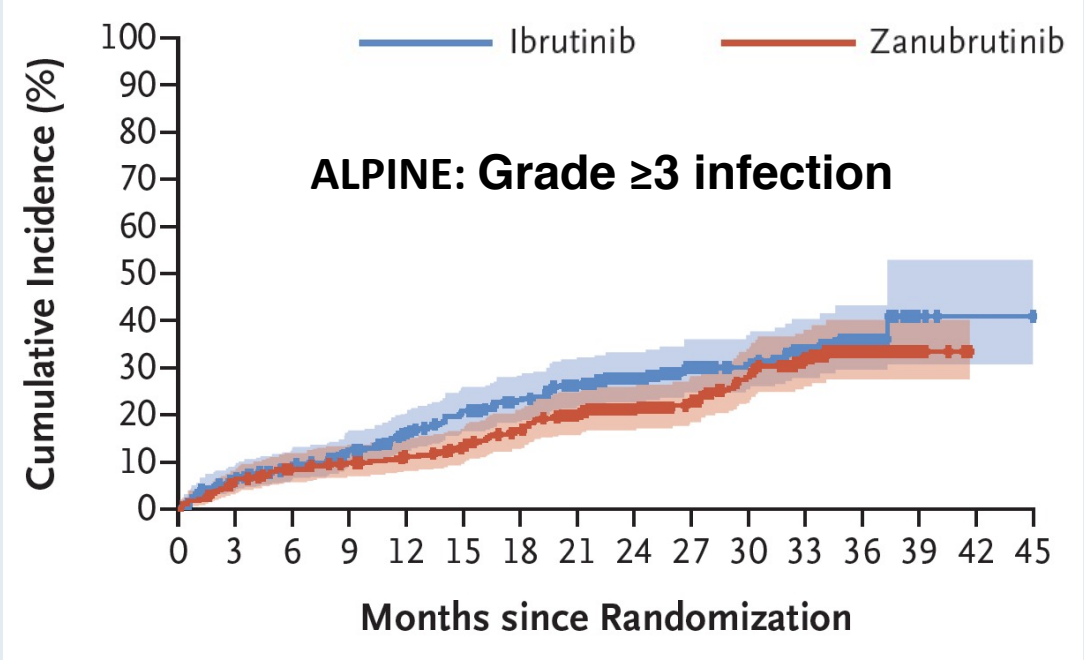
ELEVATE-RR and ALPINE: Grade ≥3 Infection





[1] Byrd JC et al. *J Clin Oncol* 2021;39:3441-2452; [2] Brown JR et al. *N Eng J Med* 2022 Dec 13;[Online ahead of print].

ELEVATE-RR and ALPINE: Common Nonhematologic Adverse Events

	ELEVATE-RR[1]				ALPINE[2,3]			
	Acalabrutinib (n = 266)		Ibrutinib (n = 263)		Zanubrutinib (n = 324)		Ibrutinib (n = 324)	
	Any grade	Grade ≥3	Any grade	Grade ≥3	Any grade	Grade ≥3	Any grade	Grade ≥3
Diarrhea	34.6%	1.1%	**46.0%**	**4.9%**	16.0%	1.5%*	24.1%	0.9%*
Headache	**34.6%**	1.5%	20.2%	0	NR	NR	NR	NR
Fatigue	20.3%	**3.4%**	16.7%	0	9.6%	0.9%*	13.3%	0.9%
Arthralgia	15.8%	0	22.8%	0.8%	14.5%	NR	16.4%	NR
Rash	9.8%	0.8%	12.5%	0	10.2%	1.2%*	12.3%	0.9%*
Secondary primary malignancies	18.8%	8.6%	13.7%	5.7%	12.3%	13.3%	13.3%	5.2%

NR = not reported

[1] Byrd JC et al. *J Clin Oncol* 2021;39:3441-52; [2] Brown JR et al. *N Engl J Med* 2022 Dec 13;[Online ahead of print];
[3] Hillmen P et al. EHA 2021;Abstract S145; * Zanubrutinib prescribing information, revised 1/2023.

Frequency of Adverse Events in Landmark Studies of Currently Approved BTK Inhibitors for Treatment-Naïve CLL

Adverse event	Ibrutinib RESONATE-2 TN (n = 135)		Acalabrutinib ELEVATE-TN TN (n = 179)		Zanubrutinib* SEQUOIA TN (n = 240)	
	All grades	Grade ≥3	All grades	Grade ≥3	All grades	Grade ≥3
Atrial fibrillation	10%	4%	3.6%	NR	3.3%	0.4%
Bleeding	7%	6%	39%	2%	41%	3%
Hypertension	14%	4%	5%	2%	6%	6%
Arthralgia	20%	2%	16%	0.6%	13%	1%
Infection	NR	23%	65%	14%	62.2%	16.3%
Diarrhea	42%	4%	35%	0.6%	13%	1%

* In patients without del(1)(p13.1)

Lipsky A, Lamanna N. *Hematology Am Soc Hematol Educ Program* 2020 Dec 4;2020(1):336-45. Tam CS et al. *Lancet Oncol* 2022;23:1031-43.

Inside the Issue: BTK Inhibitors

Introduction

Module 1: Very Elderly Patients

Module 2: Cardiac Issues

Module 3: Other BTKi Toxicities

Module 4: BTKis Combined with Chemotherapy for MCL

- Dr Lamar: 73-year-old man presents with relapsed MCL s/p BR on a clinical trial followed by acalabrutinib on progression

Case Presentation: 73-year-old man presents with relapsed MCL s/p BR on a clinical trial followed by acalabrutinib on progression

Dr Zanetta Lamar (Naples, Florida)

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NEJM Evidence 1(7)

Published May 13, 2022

ORIGINAL ARTICLE

Fixed-Duration Ibrutinib-Venetoclax in Patients with Chronic Lymphocytic Leukemia and Comorbidities (27.7 months follow up)

Arnon P. Kater, M.D., Ph.D.,[1] Carolyn Owen, M.D.,[2] Carol Moreno, M.D.,[3] George Follows, B.M.Bch., Ph.D.,[4] Talha Munir, M.B.B.S.,[5] Mark-David Levin, M.D.,[6] Ohad Benjamini, M.D.,[7] Ann Janssens, M.D., Ph.D.,[8] Anders Osterborg, M.D., Ph.D.,[9] Tadeusz Robak, M.D., Ph.D.,[10] Martin Simkovic, M.D., Ph.D.,[11] Don Stevens, M.D.,[12] Sergey Voloshin, M.D., Ph.D.,[13] Vladimir Vorobyev, Ph.D.,[14] Loic Ysebaert, M.D., Ph.D.,[15] Rui Qin, Ph.D.,[16] Andrew J. Steele, Ph.D.,[17] Natasha Schuier, M.D.,[18] Kurt Baeten, Ph.D.,[19] Donne Bennett Caces, M.D., Ph.D.,[16] and Carsten U. Niemann, M.D., Ph.D.,[20] for the GLOW Investigators*

GLOW: Ibrutinib + Venetoclax — Select Grade ≥3 Adverse Events

	Ibrutinib-Venetoclax (n=106)		Chlorambucil-Obinutuzumab (n=105)	
Treatment exposure — mo, median (range)	13.8 (0.7–19.5)		5.1 (1.8–7.9)	
Adverse events — n (%)	**Grade 3/4**	**Grade 5**	**Grade 3/4**	**Grade 5**
Patients with ≥1 adverse events	73 (68.9)	7 (6.6)	71 (67.6)	2 (1.9)
Neutropenia†	37 (34.9)	0	52 (49.5)	0
Infections and infestations‡	16 (15.1)	2 (1.9)§	11 (10.5)	1 (1.0)
Diarrhea¶	11 (10.4)	0	1 (1.0)	0
Hypertension	8 (7.5)	0	2 (1.9)	0
Atrial fibrillation	7 (6.6)	0	0	0
Thrombocytopenia	6 (5.7)	0	21 (20.0)	0
Hyponatremia	6 (5.7)	0	0	0
Cardiac failure	3 (2.8)	1 (0.9)§	0	0
Sinus node dysfunction	1 (0.9)	1 (0.9)§	0	0
Cholestasis	1 (0.9)	0	0	1 (1.0)
Sudden death	0	2 (1.9)	0	0
Ischemic stroke	0	1 (0.9)	0	0
Malignant neoplasm	0	1 (0.9)	0	0
Cardiac arrest	0	1 (0.9)	0	0
Tumor lysis syndrome	0	0	6 (5.7)	0

Kater AP et al. *N Engl J Med Evidence* 2022 May 13;1(7).

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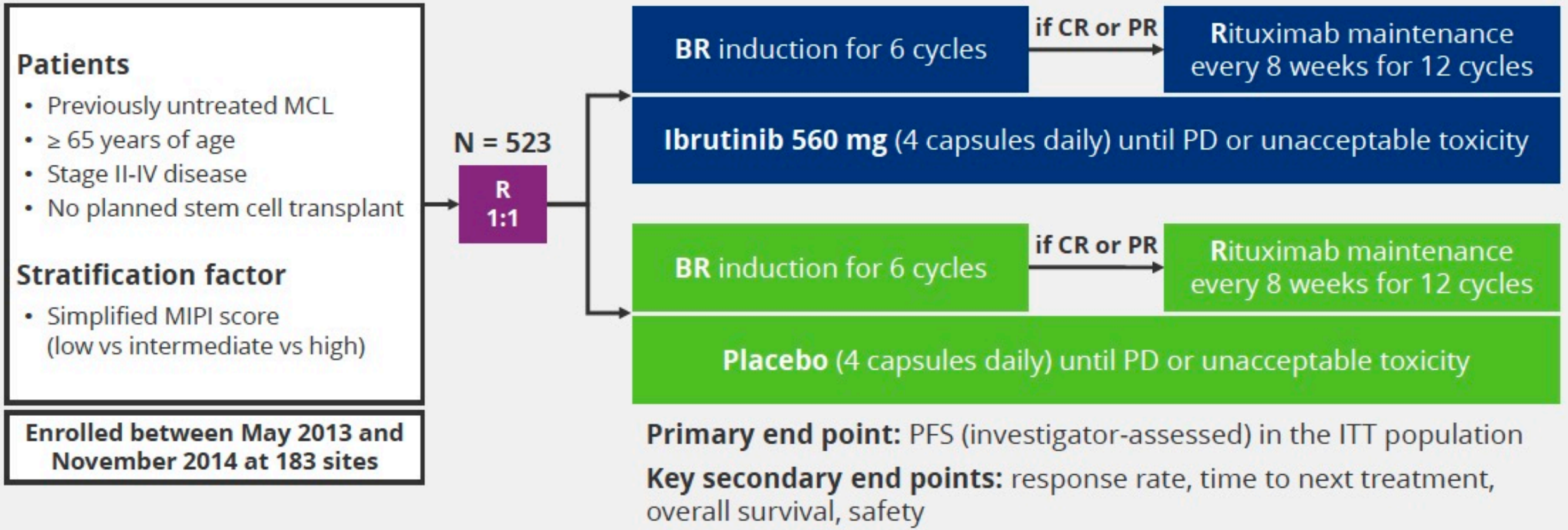
SHINE: A Randomized, Double-Blind, Phase III Study



Wang et al, NEJM 2022

Induction: Bendamustine 90 mg/m2 Days 1 and 2, Rituximab 375 mg/m2 Day 1, Q4W. A cycle is defined as 28 days.

CR, complete response; ITT, intent-to-treat; MIPI, Mantle Cell Lymphoma International Prognostic Index; PD, progressive disease; PFS, progression-free survival; PR, partial response.

Courtesy of Laurie H Sehn, MD, MPH

SHINE: Adverse Events with Ibrutinib and Bendamustine/Rituximab for MCL

Select most common grade 3 or 4 adverse events (%)	Ibrutinib group (n = 259)		Placebo group (n = 260)	
	Any grade	Grade 3 or 4	Any grade	Grade 3 or 4
Neutropenia	51.4	47.1	52.3	48.1
Pneumonia	33.6	20.1	23.5	14.2
Lymphopenia	18.1	16.2	13.5	11.9
Anemia	33.6	15.4	24.6	8.8
Thrombocytopenia	35.9	12.7	26.5	13.1
Rash	37.8	12.0	21.9	1.9
Adverse events of clinical interest (%)				
Atrial fibrillation	13.9	3.9	6.5	0.8
Hypertension	13.5	8.5	11.2	5.8
Diarrhea	46.3	6.9	36.9	3.8
Major hemorrhage	5.8	Not reported	4.2	Not reported
Arthralgia	17.4	1.2	16.9	0

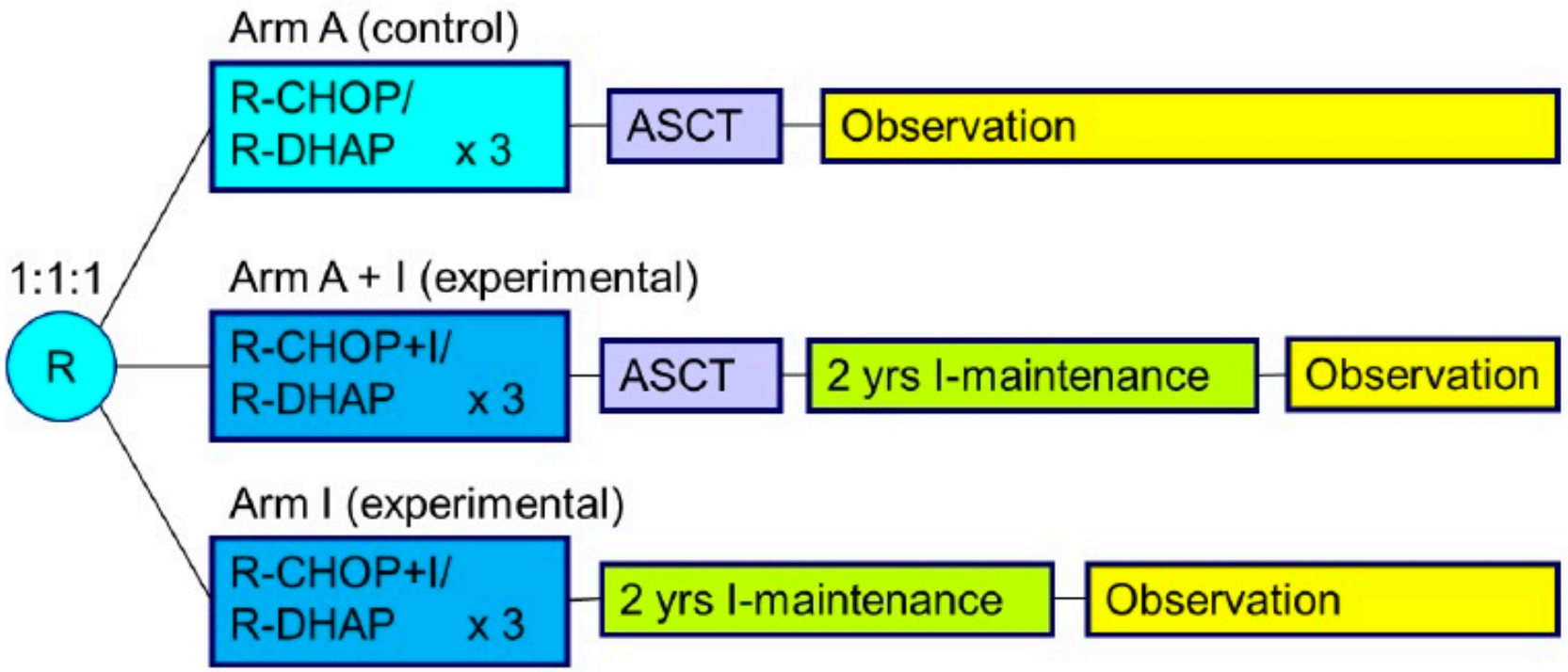
Wang ML et al. *N Engl J Med* 2022;386(26):2482-94.

TRIANGLE Study: Ibrutinib combined with first-line treatment or as a substitute for ASCT in untreated MCL

- 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

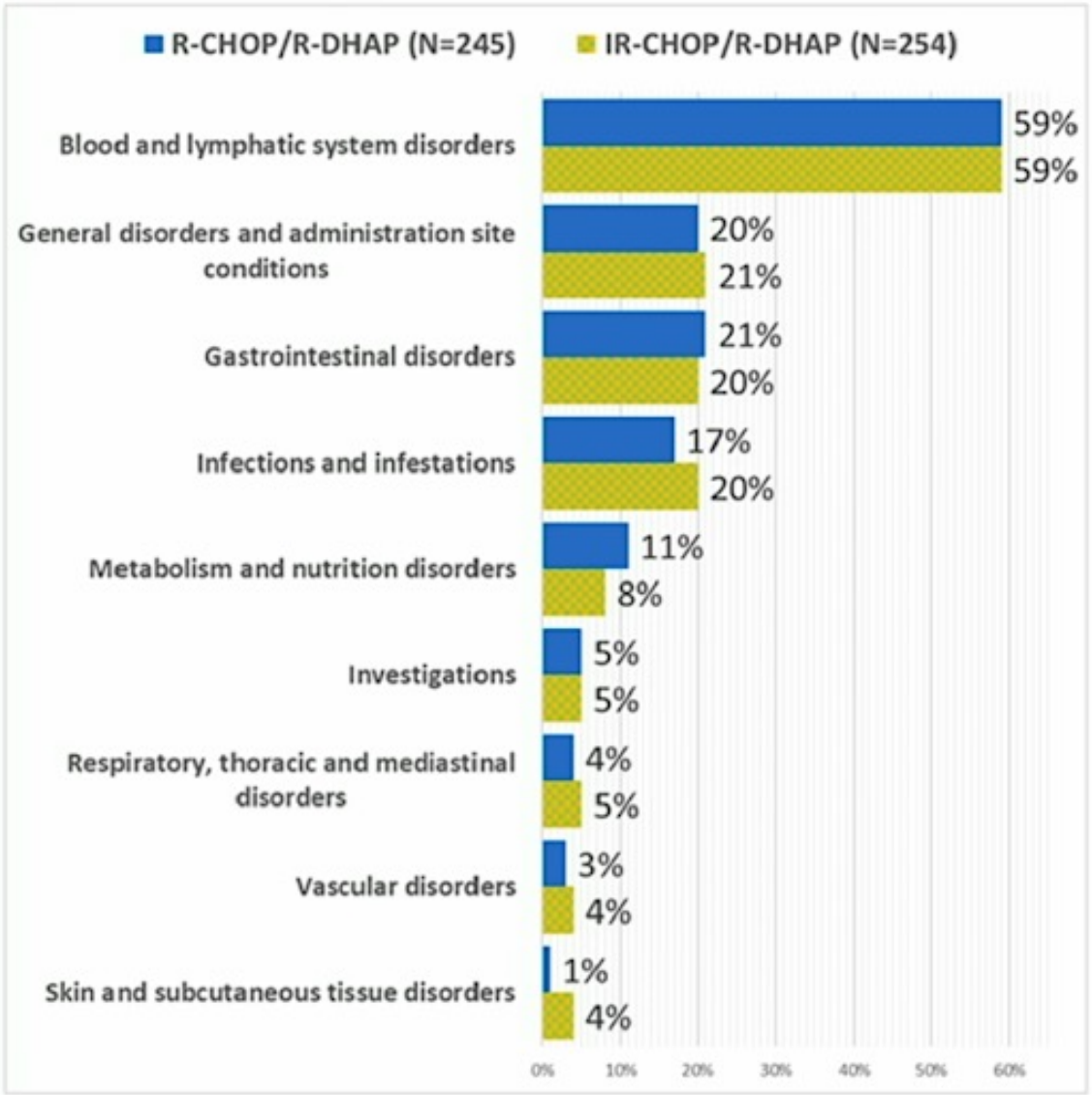


- R maintenance was added following national guidelines in all 3 trial arms
- Rituximab maintenance (without or with Ibrutinib) was started in 168 (58 %)/165 (57 %)/158 (54 %) of A/A+I/I randomized patients.

Dreyling et al, ASH 2022; Abstract 1

Courtesy of Laurie H Sehn, MD, MPH

TRIANGLE: Grade 3-5 AEs (ASCT; >2% frequency)



Grade 3-5

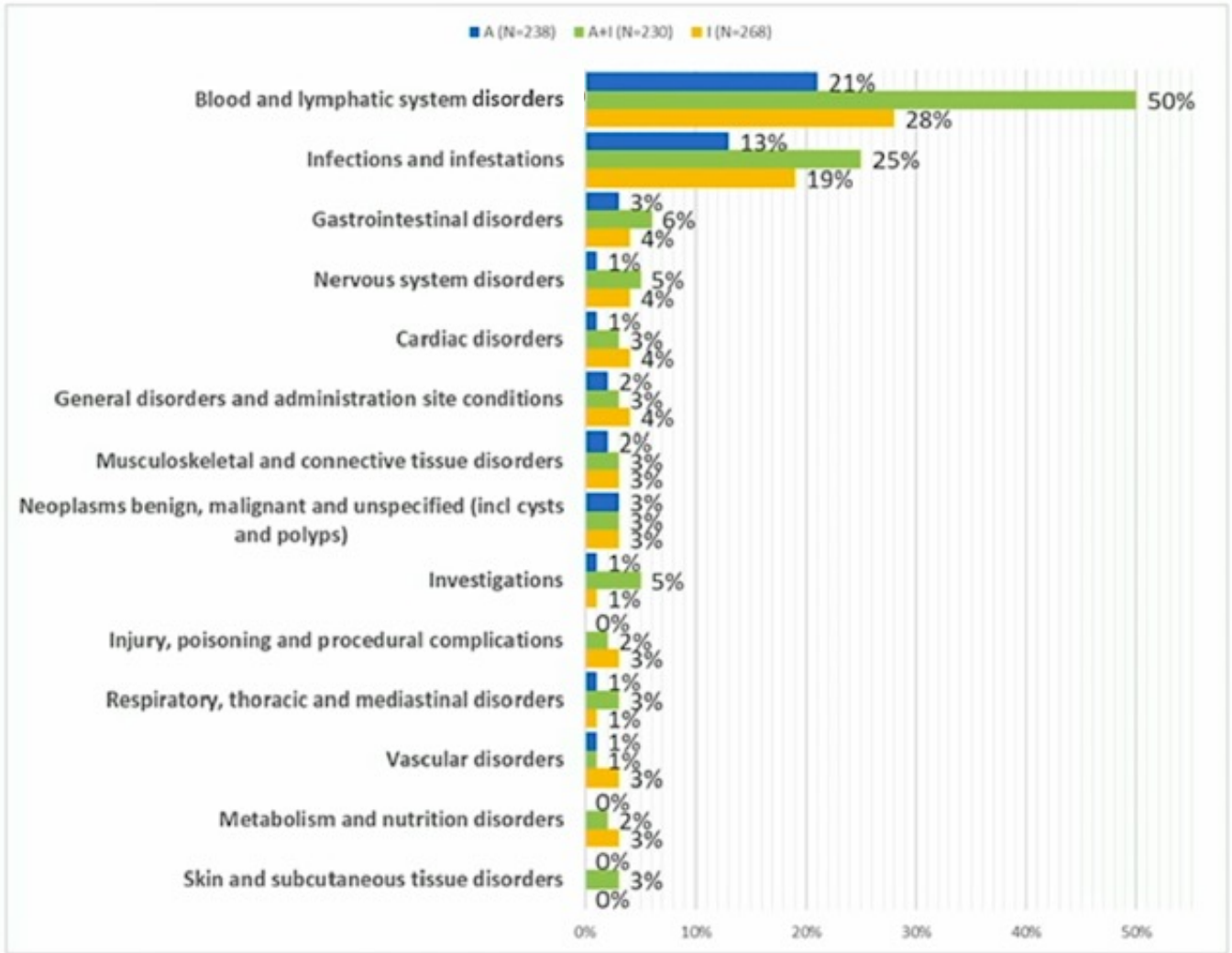
Adverse Events by Preferred Term	R-CHOP/R-DHAP (N=245)		IR-CHOP/R-DHAP (N=254)	
Thrombocytopenia	119	49%	111	44%
Neutropenia	88	36%	83	33%
Anaemia	50	20%	56	22%
Febrile neutropenia	49	20%	56	22%
Leukopenia	42	17%	42	17%
Lymphopenia	9	4%	7	3%

Grade 5

Adverse Events by System Organ Class	R-CHOP/R-DHAP (N=245)		IR-CHOP/R-DHAP (N=254)	
Infections and infestations	4	2%	5	2%
Gastrointestinal disorders	1	0%	1	0%
Respiratory, thoracic and mediastinal disorders	1	0%	1	0%
Blood and lymphatic system disorders	0	0%	1	0%
Congenital, familial and genetic disorders	1	0%	0	0%
General disorders and administration site conditions	1	0%	0	0%
Nervous system disorders	1	0%	0	0%

Dreyling et al, ASH 2022; Abstract 1

TRIANGLE: Grade 3-5 AEs (maintenance/follow-up, >2%)



Grade 3-5

Adverse Events by Preferred Term	A (N=238)		A+I (N=230)		I (N=268)	
Neutropenia	40	17%	101	44%	62	23%
Febrile neutropenia	6	3%	14	6%	7	3%
Thrombocytopenia	5	2%	13	6%	8	3%
Leukopenia	4	2%	10	4%	6	2%
Anaemia	4	2%	6	3%	4	1%
Lymphopenia	3	1%	1	0%	5	2%

Grade 5

Patients with at least one grade 5 AE by SOC

Adverse Events by System Organ Class	A (N=238)		A+I (N=230)		I (N=268)	
Infections and infestations	3	1%	2	1%	2	1%
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1	0%	1	0%	0	0%
Cardiac disorders	0	0%	0	0%	1	0%
Respiratory, thoracic and mediastinal disorders	0	0%	1	0%	0	0%
Vascular disorders	1	0%	0	0%	0	0%

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

Dreyling et al, ASH 2022; Abstract 1

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Gigi Chen, MD
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Zanetta S Lamar, MD
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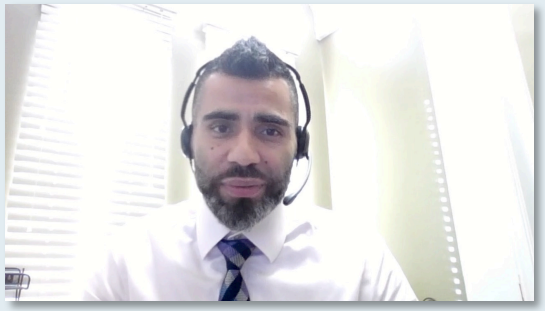

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Inside the Issue — Exploring the Current Role of Ovarian Suppression in the Management of Breast Cancer

A CME/MOC-Accredited Virtual Event

Wednesday, February 8, 2023
5:00 PM – 6:00 PM ET

Faculty

Kathy D Miller, MD
Ann Partridge, MD, MPH

Moderator

Neil Love, MD

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Thank you for joining us!

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

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