IMPROVING CARDIAC CARE IN PATIENTS WITH CLL RECEIVING BTK INHIBITORS

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BTK, Bruton's tyrosine kinase; CLL, chronic lymphocytic leukemia.

1

Overview of Cardiac Events Associated With BTK Inhibitors in Patients With CLL

Patients With CLL Are Typically Elderly and Present With Comorbidities[1-4]

The median age at CLL diagnosis is 70 years, and the age at first treatment is even higher as many patients do not require treatment right away[1,2]

Elderly patients often present with comorbidities (eg, the prevalence of atrial fibrillation in patients with newly diagnosed CLL is 6.1% at diagnosis)[2-5]

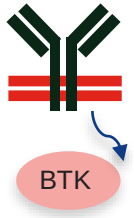
Comorbidities may contribute to inferior outcomes, including reduced treatment tolerance and increased mortality[2-4]

Even in the era of targeted therapies, HCPs must consider how to optimally manage relevant comorbidities as part of the treatment decision-making process[3]

CLL, chronic lymphocytic leukemia; HCP, health care provider.

1. Hallek M, Al-Sawaf O. *Am J Hematol.* 2021;96(12):1679-1705. 2. Stauder R. et al. *Ann Oncol.* 2017;28(2):218-227. 3. Rigolin GM. et al. *Blood.* 2017;139(26):3495-3498. 4. Dzeshka MS, et al. *Am J Hypertens.* 2017;30(8):733-755. 5. Shanafelt TD, et al. *Leuk Lymphoma.* 2017;58(7):1630-1639.

The Role of BTK Inhibitors in Treatment of B-Cell Malignancies, Including CLL



BTK acts downstream of BCR pathway and is essential for B-cell differentiation, proliferation, and survival[1,2]

BTK inhibitors have revolutionized the treatment of B-cell malignancies, including CLL/SLL and MCL[1-6]

Studies with longer follow-up of patients treated with BTK inhibitors revealed an increase in cardiac adverse events[1,2,7]

BCR, B-cell receptor; BTK, Bruton's tyrosine kinase; CLL, chronic lymphocytic leukemia; MCL, mantle cell lymphoma; SLL, small lymphocytic lymphoma.

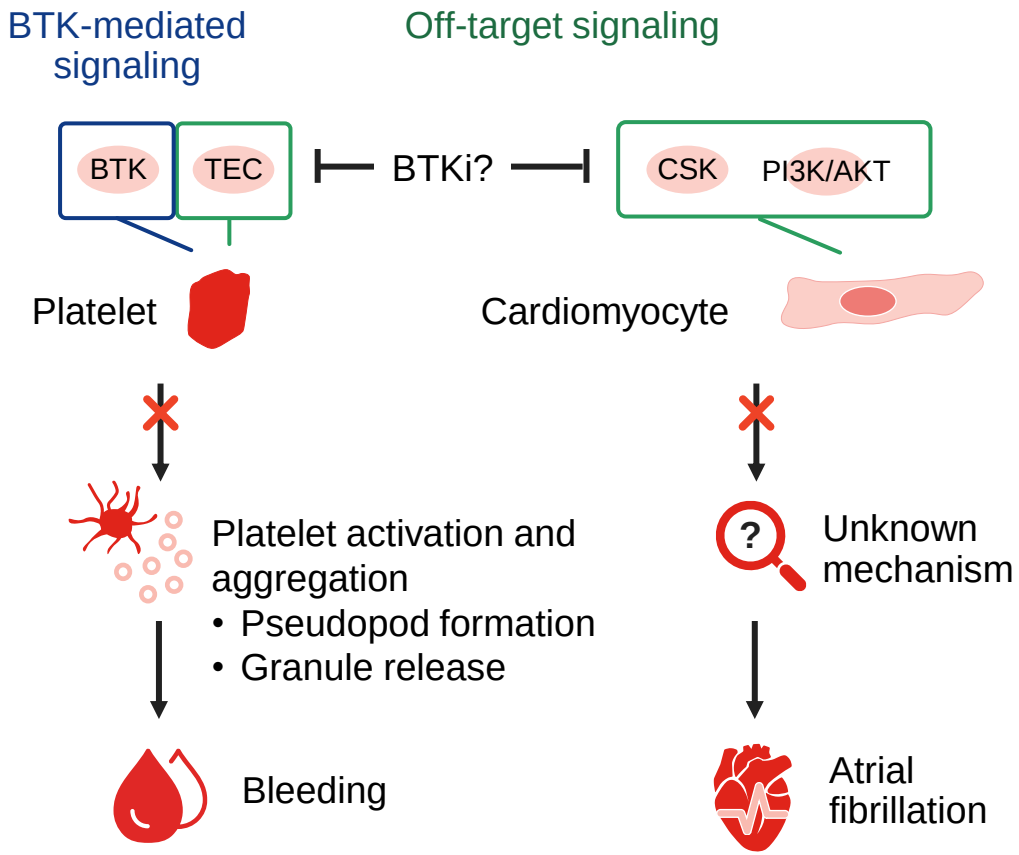
1. Fleming MR, et al. *Circ Res.* 2021;128(12):1973-1987. 2. Quartermaine C, et al. *J Am Coll CardioOnc.* 2023;5(5):570-590. 3. Imbruvica. Package insert. Janssen Biotech, Inc; 2024. https://www.rxabbvie.com/pdf/imbruvica_pi.pdf 4. Brukinsa. Package insert. BeiGene, Ltd; 2024. https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/213217s014lbl.pdf 5. Calquence. Package insert. AstraZeneca, Inc; 2024. https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/210259s010lbl.pdf 6. Jaypirca. Package insert. Eli Lilly and Company, Inc; 2024. https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/216059s002lbl.pdf 7. Chen ST, et al. *J Hematol Oncol.* 2022;15(1):92.

The Mechanisms Underlying BTK Inhibitor–Mediated Atrial Fibrillation and Bleeding

BTK inhibitors may lead to cardiotoxicity through **on-target (BTK-mediated)** and **off-target effects**[1,2]

- On-target blockade of platelet activation and aggregation via inhibition of BTK[1]
- Off-target effects (inhibition of another kinase or non-kinase targets, such as CSK or PI3K/AKT)[1-3]

Off-target effects can potentially be lessened with more specific BTK inhibitors[1,4]



CSK, C-terminal Src kinase; BTK, Bruton tyrosine kinase; BTKi, Bruton tyrosine kinase inhibitor; PI3K, phosphoinositide 3-kinase; TEC, tyrosine protein kinase.

1. Fleming MR, et al. *Circ Res.* 2021;128(12):1973-1987. 2. Chohan KL and Kapoor P. *Hemato.* 2023;4(2):135-157. 3. Dong R, et al. *Drug Des Devel Ther.* 2022;16:3225-3239. 4. Quartermaine C, et al. *J Am Coll CardioOnc.* 2023; 5(5):570-590.

Signs and Symptoms of Cardiotoxicity in Patients Receiving BTK Inhibitor Treatment

Cardiotoxicities in patients treated with BTK inhibitors vary in terms of time of onset and types of signs/symptoms

Cardiotoxicity	Incidence	Usual Onset	Signs and Symptoms
Minor bleeding[1-6]	37%-55%*	Within 49 days	Ecchymoses, petechiae or contusions
Major bleeding/ hemorrhage[5-11]	3%-4.2%	Within 6 months	Major hemorrhage, needing transfusion or hospitalization (≥ grade 3, such as intracranial hemorrhage, GI bleeding, hematuria, and post procedural hemorrhage)
Hypertension[4,6-10,12,13]	3.2%-24.5%	Within 6 months	Elevated blood pressure during BTK inhibitor treatment
Atrial fibrillation[6-10]	3.2%-8.4%	Within 1 year	Palpitations, dyspnea, fatigue
Ventricular arrhythmias[4,6,7,13]	0.4%-1%	Within 1 year	Palpitations, syncope, shortness of breath, HF, chest pressure
Heart failure[6,7,13]	0.3%-1.7%	Within 3 years	Edema, weight gain, exercise intolerance, orthopnea

*Grade ≤2 bleeding.

BTK, Bruton's tyrosine kinase; GI, gastrointestinal; HF, heart failure.

1. Lipsky AH, et al. *Haematologica.* 2015;100(12):1571-1578. 2. Lipsky A, et al. *Hematology Am Soc Hematol Educ Program.* 2020;2020(1):336-345. 3. Sharman JP, et al. [published correction appears in Lancet. 2020 May 30;395(10238):1694]. Lancet. 2020;395(10232):1278-1291. 4. Tam CS, et al. [published correction appears in *Lancet Oncol.* 2023;24(3):e106]. *Lancet Oncol.* 2022;23(8):1031-1043. 5. von Hundelshausen P, et al. *Cancers (Basel).* 2021;13(5):1103. 6. Quartermaine C, et al. *J Am Coll CardioOnc.* 2023; 5(5):570-590. 7. Imbruvica. Package insert. Janssen Biotech, Inc; 2024. https://www.rxabbvie.com/pdf/imbruvica_pi.pdf 8. Brukinsa. Package insert. BeiGene, Ltd; 2024. https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/213217s014lbl.pdf 9. Calquence. Package insert. AstraZeneca, Inc; 2024. https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/210259s010lbl.pdf 10. Jaypirca. Package insert. Eli Lilly and Company, Inc; 2024. https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/216059s002lbl.pdf 11. Stephens DM, et al. *Blood.* 2019;133(12):1298-1307. 12. Dimopoulos MA, et al. *J Clin Oncol.* 2023;41(33):5099-5106. 13. Brown JR, et al. *N Engl J Med.* 2023; 388:319-32.

How are you currently managing cardiac events in patients with CLL?

CLL, chronic lymphocytic leukemia.

2

Best Practices for Managing BTK Inhibitors in Patients With a History of Cardiac Events

Considerations When Using BTK Inhibitors in Patients With CV Comorbidities

Pretreatment workup[1]
- Perform a cardiovascular workup

Click for more details regarding pretreatment workup and CV level risk assessment prior to BTK inhibitor initiation

Patients without baseline CV risk factors[1]
- BTK inhibitors are appropriate

Patients with well-managed CV risk[1]
- BTK inhibitors are appropriate
  - More selective BTK inhibitors are preferred

Patients with high CV risk[1]
- Second-generation covalent and noncovalent BTK inhibitors are often appropriate with multidisciplinary team involved
- First-generation covalent BTK inhibitors should be avoided

- Patients who have been intolerant to prior BTK inhibitor due to cardiac events may experience CV tolerability with more selective BTK inhibitors[2-4]

Monitor patients regularly and manage toxicities with the goal of maintaining BTK inhibitor treatment[1]
- **Patients with established CV disease require more detailed monitoring**

BTK, Bruton's tyrosine kinase; CV, cardiovascular; ECG, electrocardiogram.

1. Awan FT, et al. *Blood Adv.* 2022;6(18):5516-5525. 2. Shah NN, et al. Presented at American Society of Hematology; Dec. 10-13, 2022; New Orleans, LA. Poster #17972. 3. Shadman M, et al. *Lancet Haematol.* 2023;10(1):e35-e45. 4. Rogers KA, et al. *Haematologica*. 2021;106(9):2364-2373.

Recommendations for Treatment Selection and Monitoring

CV Risk	Treatment Selection[1]		Monitoring[1-6]
Hypertension 	• If HTN is well controlled, BTK inhibitor may be used		• Monitor blood pressure at least biweekly for the first 3-6 months of BTK inhibitor therapy • Maintain early threshold for treatment during BTK inhibitor therapy • If grade 3 or 4 toxicity occurs, interrupt BTK inhibitor, reduce the dose or permanently discontinue BTK inhibitor
Atrial fibrillation 	• Low-risk patients may be treated with BTK inhibitors • Second-generation BTK inhibitors are preferred in patients with pre-existing AF • BTK inhibitor treatment may be continued in consultation with MDT for patients with: – Permanent/persistent AF – HTN – History of MI	• BTK inhibitors are NOT recommended for patients with: – History of ventricular arrhythmia – Family history of sudden cardiac death – Severe, uncontrolled HTN – Severe or uncontrolled CHF (LVEF <30%)	• BTK inhibitor therapy is still often possible in patients with ongoing AF • Manage care with MDT, including a cardio-oncologist or cardiologist with expertise in hematologic malignancies • If grade 3 or 4 toxicity occurs, interrupt BTK inhibitor, reduce the dose, or permanently discontinue BTK inhibitor Click for highlights from PI on the management of BTK inhibitor-associated CV events
Ventricular arrhythmias 	• First-generation BTK inhibitors should be avoided • The risk with second-generation BTK inhibitors is not currently known, a BCL-2 antagonist may be preferred in these patients		• If grade 3 or 4 toxicity occurs, interrupt BTK inhibitor, reduce the dose, or permanently discontinue BTK inhibitor
Heart failure 	• Second-generation BTK inhibitors preferred • Patients with well-controlled CHF may receive BTK inhibitor	• BTK inhibitors should be avoided in patients with active CHF	• Manage care with MDT (preferred) or in collaboration with a cardio-oncologist • Examine ECG; monitor blood pressure twice weekly • Restrict to <2 grams daily sodium intake • If grade 2 or greater cardiac failure occurs with older BTK inhibitor, reduce the dose or discontinue BTK inhibitor • If grade 3 or 4 toxicity occurs with second-generation BTK inhibitor, reduce the dose or permanently discontinue BTK inhibitor

AF, atrial fibrillation; BCL-2, B-cell lymphoma 2; BTK, Bruton tyrosine kinase; CHF, congestive heart failure; CV, cardiovascular; ECG, electrocardiogram; HTN, hypertension; LVEF, left ventricular ejection fraction; MDT, multidisciplinary team; MI, myocardial infarction.

1. Awan FT, et al. *Blood Adv.* 2022;6(18):5516-5525. 2. Quartermaine C, et al. *J Am Coll CardioOnc.* 2023; 5(5):570-590. 3. Imbruvica. Package insert. Janssen Biotech, Inc; 2024. https://www.rxabbvie.com/pdf/imbruvica_pi.pdf 4. Brukinsa. Package insert. BeiGene, Ltd; 2024. https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/213217s014lbl.pdf 5. Calquence. Package insert. AstraZeneca, Inc; 2024. https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/210259s010lbl.pdf 6. Jaypirca. Package insert. Eli Lilly and Company, Inc; 2024. https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/216059s002lbl.pdf

Recommendations for Managing Cardiotoxicity

Cardiotoxicities in patients treated with a BTK inhibitor are monitored and managed based on type and severity[1]

CV Risk	Diagnostic and Risk Stratification Tools[1]	Proposed Management[1-3]
Hypertension 	• Ambulatory BP monitoring • ECG • Echo	• Begin regular home blood pressure monitoring • Manage treatment decisions with multidisciplinary team • Treatment of BP should follow published guidelines and avoid CYP3A4 inhibitors where possible • If systolic persists >160 or diastolic >100 mmHg despite medical therapy, consider holding BTK inhibitor and/or reducing dose until BP better controlled
Atrial fibrillation 	• ECG, Holter monitoring • Echo • Calculate CHA_2DS_2-VASc	• Manage care involving multidisciplinary team • If other risk factors are limited (eg CHA_2DS_2-VASc 0 or 1), continue BTK inhibitor • If CHA_2DS_2-VASc >1, anticoagulate with DOAC, hold BTK inhibitor • Once atrial fibrillation is controlled, use more selective BTK inhibitor or reduce dose
Ventricular arrhythmias 	• ECG, Holter monitoring • Echo or cardiac MRI	• Consider holding BTK inhibitor, if appropriate • Consider ischemia or heart failure evaluation • Consider alternative non-BTK inhibitor therapy where appropriate
Heart failure 	• ECG • Echo or cardiac MRI • Brain natriuretic peptide	• For patients with emerging CHF, stop BTK inhibitor and initiate ACEi/ARB/ARNI, beta blocker, and SGLT2i, according to guidelines • For patients with active CHF, monitor cardiac function with periodic ECG or other EF assessment every 6-12 months • Consider holding BTK inhibitor and using alternative therapies
Minor and major bleeding 	-	• Majority of bleeding events are minor. If a patient has a history of major hemorrhage, further risk-benefit analysis may be needed if anticoagulation is considered for patients with atrial fibrillation on BTK inhibitor • BTK inhibitor should be held for 7 days prior to planned major surgery and can be restarted 1 to 3 days postoperatively

Even with appropriate selection and management of BTK inhibitor treatment, cardiotoxicity may lead to dose reductions or dose interruption/discontinuation[1-4]

ACEi, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor neprilysin inhibitor; BP, blood pressure; BTK, Bruton tyrosine kinase; CHA2DS2-VASc, (congestive heart failure, hypertension, age ≥75 [doubled], diabetes, stroke [doubled], vascular disease, age 65 to 74 and sex category [female]) score; CHF congestive heart failure; CLL, chronic lymphocytic leukemia; DOAC, direct oral anticoagulant; ECG, electrocardiogram; EF, ejection fraction; MI, myocardial infarction; SGLT2i, sodium/glucose cotransporter-2 inhibitor.

1. Quartermaine C, et al. *J Am Coll CardioOnc.* 2023; 5(5):570-590. 2. Awan FT, et al. *Blood Adv.* 2022;6(18):5516-5525. 3. Fleming MR, et al. *Circ Res.* 2021;128(12):1973-1987. 4. Shatzel JJ, et al. *J Thromb Haemost.* 2017;15(5):835-847.

Does this information increase your awareness about using BTK inhibitors in patients with CLL and CV comorbidities?

BTK, Bruton tyrosine kinase; CLL, chronic lymphocytic leukemia; CV, cardiovascular.

3

Data Regarding Cardiac Events Reported With BTK Inhibitors in Patients With CLL

Introduction

The following BTK inhibitors are currently approved for treatment of B-cell malignancies, including CLL: ibrutinib, acalabrutinib, zanubrutinib, and pirtobrutinib[1-4]

Differences in the incidence of cardiac events have been reported among approved BTK inhibitors[5-9]

More-selective BTK inhibitors are associated with fewer cardiac events than less-selective BTK inhibitors[5-10]

BTK, Bruton's tyrosine kinase; CLL, chronic lymphocytic leukemia.

1. Imbruvica. Package insert. Janssen Biotech, Inc; 2024. https://www.rxabbvie.com/pdf/imbruvica_pi.pdf 2. Brukinsa. Package insert. BeiGene, Ltd; 2024. https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/213217s014lbl.pdf 3. Calquence. Package insert. AstraZeneca, Inc; 2024. https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/210259s010lbl.pdf 4. Jaypirca. Package insert. Eli Lilly and Company, Inc; 2024. https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/216059s002lbl.pdf . 5. Fleming MR, et al. *Circ Res.* 2021;128(12):1973-1987. 6. Quartermaine C, et al. *J Am Coll CardioOnc.* 2023; 5(5):570-590. 7. Seymour JF, et al. *Blood.* 2023;142(8):687-699. 8. Dimopoulos MA, et al. *J Clin Oncol.* 2023;41(33):5099-5106. 9. Brown JR, et al. *N Engl J Med.* 2023; 388:319-32. 10. Awan FT, et al. *Blood Adv.* 2022;6(18):5516-5525.

Ibrutinib Overview

Mechanism of Action[1,2]

Ibrutinib inhibits the downstream effects of BTK through irreversible, covalent binding of the cysteine-481 (C481) BTK residue

Indications[3]

Treatment of adult patients with

- CLL/SLL
- CLL/SLL with 17p deletion
- WM

Selectivity

TEC Family Kinase IC50[2]

BTK	0.5 nM
ITK	10.7 nM
TEC	78 nM

Key Off-Target Kinases[4,5]

- BMX/ETK
- EGFR
- ERBB2/HER2
- ERBB4/HER4
- ITK
- JAK3
- RLK/TXK
- Src-kinases (BLK, FYN, LYN, SRC, YES)
- TEC

Cardiotoxicity Warnings and Precautions: Prescribing Information[3]

Hemorrhage: Monitor for bleeding and manage

Cardiac Arrhythmias, Cardiac Failure, and Sudden Death: Monitor for symptoms of arrhythmias and cardiac failure and manage

Hypertension: Monitor blood pressure and treat

Incidence of Cardiac Events: Prescribing Information[3]

	All Grade	Grade ≥3
Hemorrhage*	23%	4.2%
Hypertension†	14%-16%	4%-8%
Atrial fibrillation‡,§	8.4%	4.0%
Ventricular arrhythmias‡	1%	0.3%
Heart failure‡	1.7%	1.2%

Click for prescribing information on ibrutinib and CTCAE criteria for relevant cardiac events

*Data from 27 pooled clinical trials of ibrutinib. †Data from CLL/SLL patients treated with single-agent ibrutinib in Study 1102 and RESONATE-2 trials. ‡Data from pooled RCT of ibrutinib. §Data includes the incidence of atrial flutter.

BTK, Bruton tyrosine kinase; CTCAE, common terminology criteria for adverse events; cGVHD, chronic graft versus host disease; CLL, chronic lymphocytic leukemia; RCT, randomized controlled trial; SLL, small lymphocytic lymphoma; T/N, treatment naïve; WM, Waldenström's macroglobulinemia.

1. Shirley M. *Target Oncol.* 2022;17(1):69-84. 2. Lipsky A, et al. *Hematology Am Soc Hematol Educ Program.* 2020;2020(1):336-345. 3. Imbruvica. Package insert. Janssen Biotech, Inc; 2024. https://www.rxabbvie.com/pdf/imbruvica_pi.pdf
4. von Hundelshausen P, et al. *Cancers (Basel).* 2021;13(5):1103. 5. Estupiñán HY, et al. *Front Cell Dev Biol.* 2021;9:630942.

Acalabrutinib Overview

Mechanism of Action[1,2]

Acalabrutinib inhibits the downstream effects of BTK through irreversible, covalent binding of the cysteine-481 (C481) BTK residue

Indications[3,4]

Treatment of adult patients with

- Chronic lymphocytic leukemia/small lymphocytic lymphoma
- Mantle cell lymphoma who have received at least 1 prior therapy

Selectivity

TEC Family Kinase IC50[2]

BTK	5.1 nM
ITK	>1000 nM
TEC	93 nM

Key Off-Target Kinases[5,6]

- BMX/ETK
- ERBB4/HER4
- TEC

Cardiotoxicity Warnings and Precautions: Prescribing Information[3]

Hemorrhage: Monitor for bleeding and manage appropriately

Cardiac Arrhythmias: Monitor for symptoms of arrhythmias and manage

Incidence of Cardiac Events: Prescribing Information[3]

	All Grade	Grade ≥3
Hemorrhage*	16%-20%	1.3%-1.7%
Hypertension*	3.2%-5%	NR
Atrial fibrillation*,†	3.6%-5%	NR
Ventricular arrhythmias	NR	NR
Heart failure	NR	NR

Click for prescribing information on acalabrutinib CTCAE criteria for relevant cardiac events

*Data from CLL/SLL patients treated with single-agent acalabrutinib in ASCEND and ELEVATE-TN trials. †Data includes the incidence of atrial flutter.

BTK, Bruton tyrosine kinase; CTCAE, common terminology criteria for adverse events; NR, not reported.

1. Shirley M. *Target Oncol.* 2022;17(1):69-84. 2. Lipsky A, et al. *Hematology Am Soc Hematol Educ Program.* 2020 Dec 4;2020(1):336-345. 3. Calquence. Package insert. AstraZeneca, Inc; 2024. https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/210259s010lbl.pdf 4. FDA grants accelerated approval to acalabrutinib for mantle cell lymphoma. October 31, 2017. Accessed August 22, 2024. https://www.fda.gov/drugs/resources-information-approved-drugs/fda-grants-accelerated-approval-acalabrutinib-mantle-cell-lymphoma 5. von Hundelshausen P, et al. *Cancers (Basel).* 2021;13(5):1103. 6. Estupiñán HY, et al. *Front Cell Dev Biol*. 2021;9:630942.

Head-to-head Comparison of Cardiac Events in Patients Receiving Acalabrutinib vs Ibrutinib

Study name	ELEVATE-RR (N=533)[1-3]			
Phase	Open-label, randomized, noninferiority, phase 3 trial			
ClinicalTrials.gov #	NCT02477696			
	Cardiotoxicity-related adverse events (%)			
	Any Grade (%)	Grade 3-4 (%)	Any Grade (%)	Grade 3-4 (%)
	Acalabrutinib (n=266)		**Ibrutinib (n=263)**	
Bleeding/hemorrhage	38%	4%	51%	5%
Major hemorrhage	5%	4%	5%	5%
Hypertension	9%	4%	23%	9%
Cardiac events	24%	9%	30%	10%
Atrial fibrillation/flutter	9%	5%	16%	4%
Congestive heart failure	NR	NR	NR	NR
Cardiorespiratory arrest	0.4%	0.4%	0	0
Cardiac arrest	0	0	0.8%	0.8%
Ventricular extrasystoles	0	0	0.4%	0
Ventricular arrhythmia	0	0	0.4%	0
Ventricular fibrillation	0	0	0.4%	0.4%
Discontinuations and deaths (%)				
Disc due to all-cause AE	14.7%		21.3%	
Disc due to TRAE	NR		NR	
Death due to TRAE	NR		NR	

In a direct head-to-head comparison of acalabrutinib versus ibrutinib in patients with CLL, cardiovascular events were less frequent with acalabrutinib compared with ibrutinib[1]

AE, adverse event; BTK, Bruton tyrosine kinase; CLL, chronic lymphocytic leukemia; NR, not reported; TRAE, treatment-related adverse event.

1. Byrd JC, et al. *J Clin Oncol.* 2021;39(31):3441-3452. 2. Seymour JF, et al. *Blood.* 2023;142(8):687-699. 3. ClinicalTrials.gov. Accessed August 22, 2024. https://www.clinicaltrials.gov/study/NCT02477696

Cardiac Events in Acalabrutinib-Treated Patients Intolerant to Prior Ibrutinib

- A phase 2 study (2016-2017) enrolled 60 patients with R/R CLL who were intolerant to ibrutinib

~27% of whom discontinued ibrutinib due to atrial fibrillation or flutter

- 24/41 patients experienced recurrence of AEs that led to ibrutinib intolerance, with 75% of recurrences occurring at a lower grade of severity

Two patients treated with acalabrutinib had recurrence of atrial fibrillation with a lower severity (grade 3/2 and grade 2/1 during ibrutinib/acalabrutinib treatment)

Ibrutinib-intolerance Adverse Events and Recurrence After Acalabrutinib Treatment

Adverse event	Patients with ibrutinib intolerance,* n	Acalabrutinib experience for same patients, n			
		Total	Lower grade	Same grade	Higher grade
Atrial fibrillation	16†	2	2	0	0
Diarrhea	7	5	3	2	0
Rash	7	3	3	0	0
Bleeding‡,§	6	5	3	2	0
Arthralgia	7¶	2	1	1	0
Total	41	24	18	6	1

Acalabrutinib can be an option for patients, even if they experienced cardiac events on prior ibrutinib

*Among 60 patients meeting the study enrollment criteria, 41 patients had a medical history of 1 or more (43 events in total) of the following categories of ibrutinib-intolerance events: atrial fibrillation, diarrhea, rash, bleeding, or arthralgia. †Includes patients with atrial flutter (n=2). ‡Events categorized as bleeding included ecchymosis, hemorrhage, epistaxis, contusion, hematuria, and subdural hematoma. §All but one patient experienced a different type of bleeding event with acalabrutinib compared with ibrutinib treatment. ¶Includes 1 patient with arthritis.

AE, adverse event; BTK, Bruton tyrosine kinase; BTKi, Bruton tyrosine kinase inhibitor; CLL, chronic lymphocytic leukemia; R/R, relapsed/refractory.

1. Rogers KA, et al. *Haematologica.* 2021;106(9):2364-2373.

Zanubrutinib Overview

Mechanism of Action[1,2]

Zanubrutinib inhibits the downstream effects of BTK through irreversible, covalent binding of the cysteine-481 (C481) BTK residue

Indications[3-6]

Treatment of adult patients with

- MCL who have received at least 1 prior therapy
- WM
- R/R MZL who have received at least 1 anti–CD20-based regimen
- CLL/SLL
- R/R FL in combination with obinutuzumab, after 2 or more lines of systemic therapy

Selectivity

TEC Family Kinase IC50[2]

BTK	0.22 nM
ITK	30 nM
TEC	1.9 nM

Key Off-Target Kinases[7,8]

- BLK
- BMX/ETK
- EGFR
- ERBB4/HER4
- ITK
- RLK/TXK
- TEC

Cardiotoxicity Warnings and Precautions: Prescribing Information[3]

Hemorrhage: Monitor for bleeding and manage appropriately

Cardiac Arrhythmias: Monitor for signs and symptoms of arrhythmias and manage appropriately

Incidence of Cardiac Events: Prescribing Information[3]

	All Grade	Grade ≥3
Hemorrhage*	24%-28%	2.5%-4.5%
Hypertension*	11%-19%	5.4%-13%
Atrial fibrillation†	3.3%-4.6%[a]	1.9%[c]
Ventricular arrhythmias‡	NR	0.3%
Heart failure	NR	NR

Click for prescribing information on zanubrutinib CTCAE criteria for relevant cardiac events

*Data from CLL/SLL patients treated with single-agent zanubrutinib in SEQUOIA and ALPINE trials. †Data includes the incidence of atrial flutter. ‡Data from patients treated with zanubrutinib.

BTK, Bruton tyrosine kinase; CLL, chronic lymphocytic leukemia; CTCAE, common terminology criteria for adverse events; FL, follicular lymphoma; MCL, mantle cell lymphoma; MZL, marginal zone lymphoma; NR, not reported; R/R, relapsed/refractory; SLL, small lymphocytic lymphoma; WM, Waldenström's macroglobulinemia.

1. Shirley M. *Target Oncol.* 2022;17(1):69-84. 2. Lipsky A, et al. *Hematology Am Soc Hematol Educ Program.* 2020;2020(1):336-345. 3. Brukinsa. Package insert. BeiGene, Ltd; 2024. https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/213217- s014lbl.pdf 4. FDA. Accessed August 22, 2024. https://www.fda.gov/drugs/resources-information-approved-drugs/fda-grants-accelerated-approval-zanubrutinib-mantle-cell-lymphoma 5. FDA. Accessed August 22, 2024. https://www.fda.gov/drugs/resources-information-approved-drugs/fda-grants-accelerated-approval-zanubrutinib-marginal-zone-lymphoma 6. FDA. Accessed August 22, 2024. https://www.fda.gov/drugs/resources-information-approved-drugs/fda-grants-accelerated-approval-zanubrutinib-relapsed-or-refractory-follicular-lymphoma 7. von Hundelshausen P, et al. *Cancers (Basel).* 2021;13(5):1103. 8. Estupiñán HY, et al. *Front Cell Dev Biol.* 2021;9:630942.

Head-to-head Comparison of Cardiac Events in Patients Receiving Zanubrutinib vs Ibrutinib

Study name	ALPINE (N=652)[1,2]			
Phase	Multicenter, open-label, randomized, phase 3 study			
ClinicalTrials.gov #	NCT03734016			
	Cardiotoxicity-related adverse events (%)			
	Any Grade (%)	Grade 3-4 (%)	Any Grade (%)	Grade 3-4 (%)
	Zanubrutinib (n=324)		**Ibrutinib (n=324)**	
Bleeding/hemorrhage	42.3%	3.4%	41.4%	3.7%
Major hemorrhage	3.7%	3.4%	4.3%	3.7%
Hypertension	23.5%	15.1%	22.8%	13.6%
Cardiac events	21.3%	NR	29.6%	NR
Atrial fibrillation/flutter*	5.2%	2.5%	13.3%	4.0%
Congestive heart failure	0.3%	NR	0.6%	NR
Cardiac failure	1.5%	NR	1.9%	NR
Cardiac arrest	0	NR	0.9%	NR
Ventricular extrasystoles	0.3%	NR	0	NR
Ventricular arrhythmia	0.6%	NR	0.3%	NR
Ventricular fibrillation	0	NR	0.6%	NR
Discontinuations and deaths (%)				
Disc due to all-cause AE	NR		NR	
Disc due to TRAE	15.4%		22.2%	
Death due to TRAE	10.2%		11.1%	

In a direct head-to-head comparison of zanubrutinib versus ibrutinib in patients with CLL, cardiovascular events were less frequent with zanubrutinib compared with ibrutinib[1]

*1-sided p<.025 in any grade and/or G≥3.

AE, adverse event; CLL, chronic lymphocytic leukemia; NR, not reported; TRAE, treatment-related adverse event.

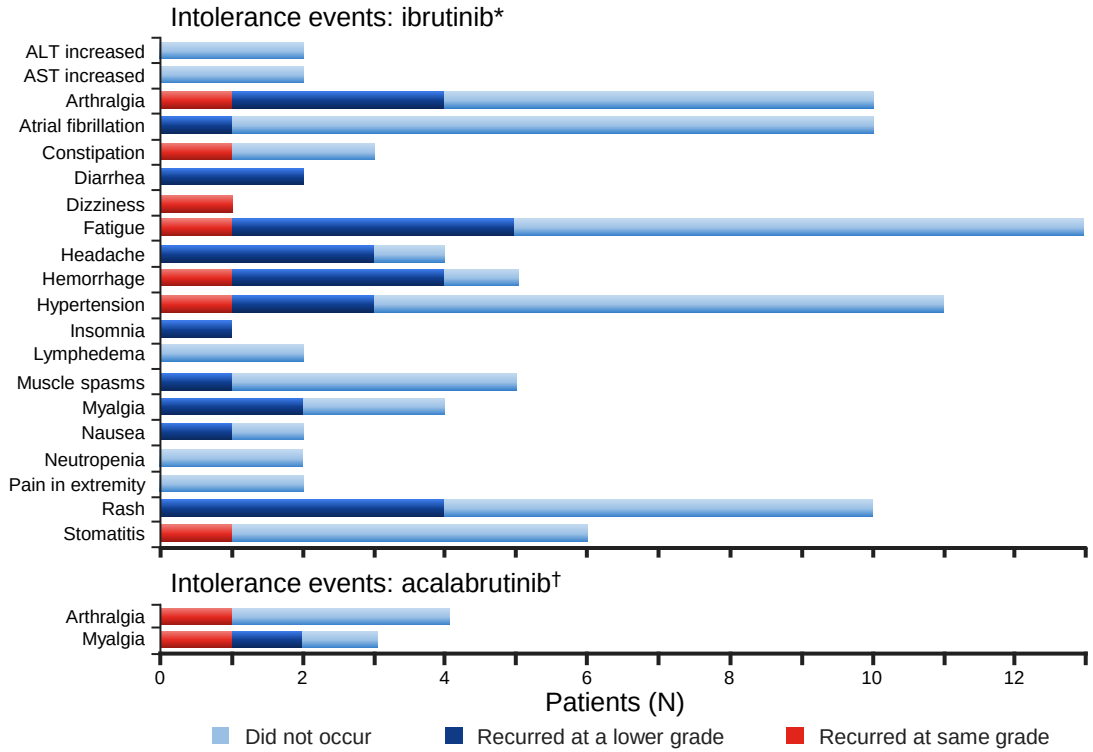
1. Brown JR, et al. *N Engl J Med.* 2023; 388:319-332. 2. ClinicalTrials.gov. Accessed August 22, 2024. https://www.clinicaltrials.gov/study/NCT03734016

Cardiac Events in Zanubrutinib-Treated Patients Intolerant to a Prior Covalent BTK Inhibitor

- A phase 2 study (2019-2021) enrolled 67 patients with B-cell malignancies who were intolerant to prior covalent BTK inhibitor
  - 18% of ibrutinib intolerance events were due to hypertension and 16% due to atrial fibrillation
- Most intolerance events did not recur with zanubrutinib (70% and 83% of prior intolerance events to ibrutinib and acalabrutinib, respectively)
  - Of the recurring events, 79% of ibrutinib intolerance events recurred at lower severity with zanubrutinib
  - Most (67%) of acalabrutinib intolerance events recurred at the same severity with zanubrutinib

Zanubrutinib can be an option for patients, even if they experienced cardiac events on prior ibrutinib

Recurrence and Change in Severity of Ibrutinib and Acalabrutinib Intolerance Events During Treatment With Zanubrutinib



*18 additional ibrutinib-related intolerance events (arthritis, bone pain, bronchitis, embolism, irregular heart rate, malaise, pericardial effusion, pleural effusion, pneumonia, psoriasis, pyrexia, sinusitis, subcutaneous abscess, supraventricular tachycardia, aminotransferases increased, ventricular extrasystoles, vertigo, and vomiting) occurred in 1 patient and did not recur on zanubrutinib (data not shown). †11 additional acalabrutinib-related intolerance events (abdominal pain, asthenia, atrial fibrillation, dyspepsia, fatigue, groin pain, headache, insomnia, malaise, pain in extremity, and rash) occurred in 1 patient and did not recur on zanubrutinib (data not shown).

AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BTK, Bruton tyrosine kinase.

1. Shadman M, et al. *Lancet Haematol.* 2023;10(1):e35-e45.

Pirtobrutinib Overview

Mechanism of Action[1,2]

Pirtobrutinib inhibits the downstream effects of BTK through reversible, non-covalent, C481-independent binding to the BTK ATP pocket

Indications[3-5]

Treatment of adult patients with

- R/R MCL after at least 2 lines of systemic therapy, including a BTK inhibitor
- CLL/SLL who have received at least 2 prior lines of therapy, including a BTK inhibitor and a BCL-2 inhibitor

Selectivity

TEC Family Kinase IC50[2]

BTK	3.15 nM
ITK	>5000 nM
TEC	1,234 nM

Key Off-Target Kinases[6]

- BRK
- ERBB4/HER4
- MEK1
- MEK2
- TXK
- YES/YES1

Cardiotoxicity Warnings and Precautions: Prescribing Information[3]

Hemorrhage: Monitor for bleeding and manage appropriately

Cardiac Arrhythmias: Monitor for signs and symptoms of arrhythmias and manage appropriately

Incidence of Cardiac Events: Prescribing Information[3]

	All Grade	Grade ≥3
Hemorrhage*	22%	2.7%
Hypertension*	12%	5%
Atrial fibrillation†	3.2%	1.5%
Ventricular arrhythmias	NR	NR
Heart failure	NR	NR

Click for prescribing information on pirtobrutinib CTCAE criteria for relevant cardiac events

*Data from CLL/SLL patients treated with single-agent pirtobrutinib in BRUIN trial. †Data from patients with hematologic malignancies treated with pirtobrutinib in the BRUIN study.

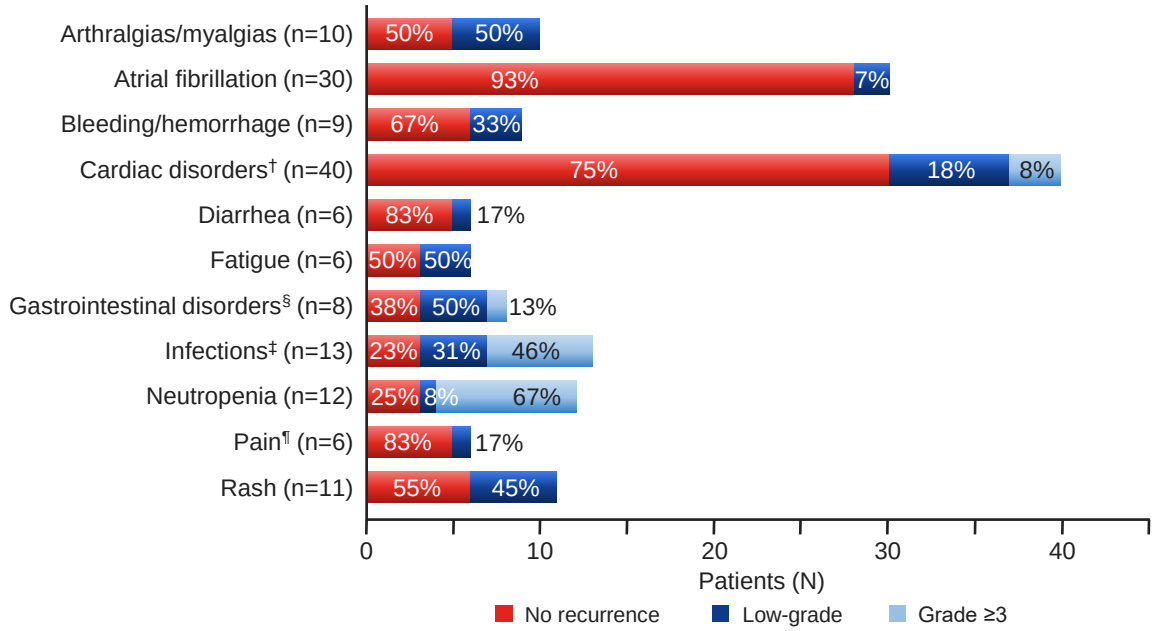
BCL-2, B-cell lymphoma 2; BTK, Bruton tyrosine kinase; CLL, chronic lymphocytic leukemia; CTCAE, common terminology criteria for adverse events; MCL, mantle cell lymphoma; NR, not reported; R/R, relapsed/refractory; SLL, small lymphocytic lymphoma.

1. Shirley M. *Target Oncol.* 2022;17(1):69-84. 2. Lipsky A, et al. *Hematology Am Soc Hematol Educ Program*. 2020;2020(1):336-345. 3. Jaypirca. Package insert. Eli Lilly and Company, Inc; 2024. https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/216059s002lbl.pdf 4. FDA grants accelerated approval to pirtobrutinib for relapsed or refractory mantle cell lymphoma. January 27, 2023. Accessed August 22, 2024. https://www.fda.gov/drugs/resources-information-approved-drugs/fda-grants-accelerated-approval-pirtobrutinib-relapsed-or-refractory-mantle-cell-lymphoma 5. FDA grants accelerated approval to pirtobrutinib for chronic lymphocytic leukemia and small lymphocytic lymphoma. December 7, 2023. Accessed August 22, 2024. https://www.fda.gov/drugs/resources-information-approved-drugs/fda-grants-accelerated-approval-pirtobrutinib-chronic-lymphocytic-leukemia-and-small-lymphocytic 6. Gomez EB, et al. *Blood*. 2023;142(1):62-72.

Cardiac Events in Pirtobrutinib-Treated Patients Who Were Intolerant to a Prior Covalent BTK Inhibitor

- The phase 1/2 BRUIN enrolled >100 patients who were intolerant to prior covalent BTK inhibitor
  - >30% of whom discontinued due to cardiotoxicity
  - This included patients with active cardiac comorbidities/ongoing antithrombotics
- Most patients did not experience high-grade recurrence of AEs that led to discontinuation of prior BTKi
  - Among those who did, none discontinued pirtobrutinib because of this AE

Pirtobrutinib TEAEs Recurring in the Same Patient as Those Leading to Prior BTKi Discontinuations*



Pirtobrutinib can be administered to patients who experienced cardiac events on a prior BTK inhibitor

*Most common TEAE categories that led to discontinuation of prior cBTKi are shown; an individual patient may be counted in more than 1 category. †Cardiac disorders include atrial fibrillation. ‡Prior discontinuation infection types were not specified for most patients, so any infection recurrence was investigated. Eleven grade ≥3 infections in the 6 patients with an infection recurrence included: pneumonia (n=6, including COVID-19 pneumonia, n=2 and fungal pneumonia, n=1), bacteremia, diarrhea, salmonellosis, septic shock, and COVID-19 (n=1 each). §Gastrointestinal disorders include diarrhea. ¶1 had recurrence of pain in the same site, 3 had new/different pain, and 2 had no pain; no patient discontinued pirtobrutinib for pain.

AE, adverse event; BTK, Bruton tyrosine kinase; BTKi, Bruton tyrosine kinase inhibitor; CV, cardiovascular; TRAE, treatment-related adverse event

1. Shah NN, et al. Presented at American Society of Hematology; Dec. 10-13, 2022; New Orleans, LA. Poster #17972.

Do these data increase your confidence about BTK inhibitors to treat patients with CLL?

CLL, chronic lymphocytic leukemia.

Key Takeaways

- The majority of patients with CLL are elderly and present with comorbidities that must be managed to foster a positive patient experience[1-3]
- Appropriate assessment, monitoring, and management of cardiotoxicity-associated complications are necessary for optimal use of BTK inhibitors, particularly in patients with baseline risk factors[4,5]
- More-selective BTK inhibitors are associated with fewer CV events than less-selective BTK inhibitors, thereby enabling—with appropriate monitoring and management—their administration to a broader patient population[5-8]
- Available data suggest acalabrutinib and zanubrutinib can be administered to patients who experienced cardiac events on prior ibrutinib; similarly, pirtobrutinib can be administered to patients who were intolerant to covalent BTK inhibitors (including those with active cardiac comorbidities/ongoing antithrombotics)[9-11]

BTK, Bruton tyrosine kinase; CLL, chronic lymphocytic leukemia; CV, cardiovascular.

1. Hallek M, Al-Sawaf O. *Am J Hematol.* 2021;96(12):1679-1705. 2. Stauder R, et al. *Ann Oncol.* 2017;28(2):218-227. 3. Rigolin GM. et al. *Blood.* 2017;139(26):3495-3498. 4. Quartermaine C, et al. *J Am Coll CardioOnc.* 2023;5(5):570-590. 5. Awan FT, et al. *Blood Adv.* 2022;6(18):5516-5525. 6. Seymour JF, et al. *Blood.* 2023;142(8):687-699. 7. Dimopoulos MA, et al. *J Clin Oncol.* 2023;41(33):5099-5106. 8. Brown JR, et al. *N Engl J Med.* 2023; 388:319-32. 9. Rogers KA, et al. *Haematologica.* 2021;106(9):2364-2373. 10. Shadman M, et al. *Lancet Haematol.* 2023;10(1):e35-e45. 11. Shah NN, et al. Presented at American Society of Hematology; Dec. 10-13, 2022; New Orleans, LA. Poster #17972

Appendix

Pretreatment Workup Pertaining to Use of BTK Inhibitors in Patients With CV Comorbidities

PRETREATMENT WORKUP

Comprehensive patient history[1,2]	CV risk level assessment[1]	More detailed screening in patients with high CV risk/established CV disease[1]
• Assessment of blood pressure, ECG, and concomitant medications	• Presence of diabetes, obesity, hypertension, dyslipidemia, chronic renal disease • History of valvular heart disease • History of arrythmias, heart failure, or left ventricular dysfunction/reduced ejection fraction	• Echocardiogram, baseline cardiac biomarkers • Consider FRS-CVD score for stratification

CV, cardiovascular; ECG, electrocardiogram; FRS-CVD, Framingham risk score-cardiovascular disease.

1. Awan FT, et al. *Blood Adv.* 2022;6(18):5516-5525. 2. Quartermaine C, et al. *J Am Coll CardioOnc.* 2023; 5(5):570-590.

Recommendations for Management of BTK Inhibitor–Associated Cardiovascular Events

Recommendations for the management of BTK inhibitor-associated cardiotoxicities: Prescribing Information

Ibrutinib[1]

- ***Cardiac Arrhythmias, Cardiac Failure, and Sudden Death*** Evaluate cardiac history and function at baseline, and monitor patients for cardiac arrhythmias and cardiac function. Obtain further evaluation (eg ECG, echocardiogram) as indicated for patients who develop symptoms of arrhythmia (eg palpitations, lightheadedness, syncope, chest pain), new onset dyspnea, or other cardiovascular concerns. Manage cardiac arrhythmias and cardiac failure appropriately, follow dose modification guidelines [see Dosage and Administration (2.2)], and consider the risks and benefits of continued ibrutinib treatment
- ***Hemorrhage*** Consider the risks and benefits of anticoagulant or antiplatelet therapy when co-administered with ibrutinib. Consider the benefit-risk of withholding ibrutinib for at least 3 to 7 days pre- and postsurgery depending upon the type of surgery and the risk of bleeding
- ***Hypertension*** Monitor blood pressure in patients treated with ibrutinib, initiate or adjust anti-hypertensive medication throughout treatment with ibrutinib as appropriate, and follow dosage modification guidelines for Grade 3 or higher hypertension

Acalabrutinib[2]

- ***Atrial Fibrillation and Flutter*** Monitor for symptoms of arrhythmia (eg palpitations, dizziness, syncope, dyspnea) and manage as appropriate
- ***Hemorrhage*** Consider the risks and benefits of antithrombotic agents when co-administered with acalabrutinib. Monitor patients for signs of bleeding. Consider the benefit-risk of withholding acalabrutinib for 3 to 7 days pre- and post-surgery depending upon the type of surgery and the risk of bleeding

Zanubrutinib[3]

- ***Cardiac Arrhythmias*** Monitor for signs and symptoms of cardiac arrhythmias (eg palpitations, dizziness, syncope, dyspnea, chest discomfort), manage appropriately [see Dosage and Administration (2.4)], and consider the risks and benefits of continued zanubrutinib treatment
- ***Hemorrhage*** Monitor for signs and symptoms of bleeding. Discontinue zanubrutinib if intracranial hemorrhage of any grade occurs. Consider the benefit-risk of withholding zanubrutinib for 3-7 days before and after surgery depending upon the type of surgery and the risk of bleeding

Pirtobrutinib[4]

- ***Cardiac Arrhythmias*** Monitor for signs and symptoms of arrhythmias (eg palpitations, dizziness, syncope, dyspnea) and manage appropriately. Based on severity, reduce dose, temporarily withhold, or permanently discontinue pirtobrutinib [see Dosage and Administration (2.2)]
- ***Hemorrhage*** Consider the risks and benefits of antithrombotic agents when co-administered with pirtobrutinib. Monitor patients for signs of bleeding. Based on severity of bleeding, reduce dose, temporarily withhold, or permanently discontinue pirtobrutinib [see Dosage and Administration (2.2)]
- Consider the benefit-risk of withholding pirtobrutinib for 3 to 7 days pre-and post-surgery depending upon the type of surgery and risk of bleeding

1. Imbruvica. Package insert. Janssen Biotech, Inc; 2024. https://www.rxabbvie.com/pdf/imbruvica_pi.pdf 2. Calquence. Package insert. AstraZeneca, Inc; 2024. https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/210259s010lbl.pdf
3. Brukinsa. Package insert. BeiGene, Ltd; 2024. https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/213217s014lbl.pdf 4. Jaypirca. Package insert. Eli Lilly and Company, Inc; 2024. https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/216059s002lbl.pdf

CTCAE Criteria for Relevant Cardiac Events

CTCAE Term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Atrial fibrillation Definition: A disorder characterized by a dysrhythmia without discernible P waves and an irregular ventricular response due to multiple reentry circuits. The rhythm disturbance originates above the ventricles.	Asymptomatic, intervention not indicated	Non-urgent medical intervention indicated	Symptomatic, urgent intervention indicated; device (eg pacemaker); ablation; new onset	Life-threatening consequences; embolus requiring urgent intervention	Death
Atrial flutter Definition: A disorder characterized by a dysrhythmia with organized rhythmic atrial contractions with a rate of 200-300 beats per minute. The rhythm disturbance originates in the atria.	Asymptomatic, intervention not indicated	Non-urgent medical intervention indicated	Symptomatic, urgent intervention indicated; device (eg pacemaker); ablation	Life-threatening consequences; embolus requiring urgent intervention	Death
Heart failure Definition: A disorder characterized by the inability of the heart to pump blood at an adequate volume to meet tissue metabolic requirements, or, the ability to do so only at an elevation in the filling pressure.	Asymptomatic with laboratory (e.g., BNP [B-Natriuretic Peptide]) or cardiac imaging abnormalities	Symptoms with moderate activity or exertion	Symptoms at rest or with minimal activity or exertion; hospitalization; new onset of symptoms	Life-threatening consequences; urgent intervention indicated (eg continuous IV therapy or mechanical hemodynamic support)	Death
Ventricular arrhythmia Definition: A disorder characterized by a dysrhythmia that originates in the ventricles.	Asymptomatic, intervention not indicated	Non-urgent medical intervention indicated	Urgent intervention indicated	Life-threatening consequences; hemodynamic compromise	Death
Hypertension Definition: A disorder characterized by a pathological increase in blood pressure.	**Adult:** Systolic BP 120-139 mm Hg or diastolic BP 80-89 mm Hg; **Pediatric:** Systolic/diastolic BP >90th percentile but< 95th percentile; **Adolescent:** BP ≥120/80 even if <95th percentile	**Adult:** Systolic BP 140–159 mm Hg or diastolic BP 90–99 mmHg if previously WNL; change in baseline medical intervention indicated; recurrent or persistent (≥24 h); symptomatic increase by >20 mmHg (diastolic) or to >140/90 mmHg; monotherapy indicated initiated; **Pediatric and adolescent:** Recurrent or persistent (≥24 h) BP >ULN; monotherapy indicated; systolic and /or diastolic BP between the 95th percentile and 5 mmHg above the 99th percentile; **Adolescent:** Systolic between 130-139 or diastolic between 80-89 even if <95th percentile	**Adult:** Systolic BP ≥160 mm Hg or diastolic BP ≥100 mmHg; medical intervention indicated; more than 1 drug or more intensive therapy than previously used indicated; **Pediatric and adolescent:** Systolic and/or diastolic >5 mmHg above the 99th percentile	**Adult and pediatric:** Life threatening consequences (eg malignant hypertension, transient or permanent neurologic deficit, hypertensive crisis); urgent intervention indicated	Death

BP, blood pressure; CTCAE, common terminology criteria for adverse events; ULN, upper limit normal; WNL within normal limits.

1. U.S. Department of Health and Human Services. Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0. November 27, 2017. Accessed May 24, 2024. https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_5x7.pdf