

BTK Inhibitors for B-Cell Lymphomas: A Summary Resource



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Bruton tyrosine kinase (BTK) inhibitors are a class of agents that inhibit BTK in the B-cell signaling cascade, stopping cell proliferation and inducing apoptosis. Oral BTK-targeted agents have been proven safe and effective for various B-cell malignancies, including chronic lymphocytic leukemia (CLL)/small lymphocytic leukemia (SLL), mantle cell lymphoma (MCL), marginal zone lymphoma (MZL), and Waldenström macroglobulinemia (WM). Ibrutinib is a first-generation BTK inhibitor; acalabrutinib and zanubrutinib are more selective second-generation BTK inhibitors. All are potent and irreversible.

Current Indications and Recommendations for Use

FDA-Approved BTK Inhibitors for B-Cell Lymphomas	Indications and Recommendations
Acalabrutinib ¹	FDA-approved indications: - Adults with MCL who have received ≥ 1 prior therapy (accelerated approval) - Adults with CLL or SLL <i>For B-cell lymphomas, National Comprehensive Cancer Network (NCCN®) guideline recommends acalabrutinib as a preferred therapy in adults with MCL as second-line or subsequent therapy (category 2A).²</i> <i>The NCCN® guideline also recommends acalabrutinib with or without obinutuzumab in first-line therapy for adult patients with CLL/SLL without del(17p) or the TP53 mutation (category 1) and acalabrutinib monotherapy in second-line or subsequent therapy for adult patients with CLL/SLL without del(17p) or the TP53 mutation (category 1). In patients with del(17p) or the TP53 mutation, acalabrutinib with or without obinutuzumab is a preferred first-line therapy (category 2A), and acalabrutinib monotherapy is recommended in second-line or subsequent therapy (category 1).³</i>
Ibrutinib ⁴	FDA-approved indications: - Adults with MCL with ≥ 1 prior therapy (accelerated approval) - Adults with MZL who require systemic therapy and who have received ≥ 1 prior anti-CD20–based therapy (accelerated approval) - Adults with WM - Adults with CLL or SLL with or without del(17p) - Adults with chronic graft-vs-host disease (GVHD) after failure of ≥ 1 lines of systemic therapy <i>For B-cell lymphomas, NCCN guideline recommends ibrutinib as a preferred therapy in adults with MCL as second-line or subsequent therapy (category 2A) and in certain circumstances in combination with lenalidomide and rituximab (category 2B) or venetoclax (category 2B); in adults with MZL as second-line or subsequent therapy (category 2A), including older or infirm patients; and ibrutinib with or without rituximab is a preferred regimen for adult patients with primary or previously treated WM (category 1).²</i> <i>The NCCN guideline for CLL/SLL also recommends ibrutinib monotherapy in first-line and second-line or subsequent therapy for adult patients with CLL/SLL without del(17p) or the TP53 mutation (category 1). In patients with del(17p) or the TP53 mutation, ibrutinib monotherapy is a preferred first-line therapy (category 2A) and second-line or subsequent therapy (category 1).³</i> <i>Ibrutinib is also a recommended regimen for adult patients with chronic GVHD after failure of ≥ 1 lines of systemic therapy (category 2A).</i>
Zanubrutinib ⁵	FDA-approved indications: - Adults with MCL with ≥ 1 prior therapy (accelerated approval) - Adults with MZL who require systemic therapy and who have received ≥ 1 prior anti-CD20–based therapy (accelerated approval) - Adults with WM <i>For B-cell lymphomas, NCCN guideline recommends zanubrutinib as preferred second-line or subsequent therapy for adults with MCL (category 2A); as preferred therapy as second-line or subsequent therapy (category 2A), including older or infirm patients, in adults with relapsed/refractory MZL after ≥ 1 prior anti-CD20–based regimen; and as a preferred regimen for adult patients with primary or previously treated WM (category 1).²</i>

Zanubrutinib ⁵	<i>The NCCN guideline for CLL/SLL also recommends zanubrutinib as an option in first-line and second-line or subsequent therapy for adult patients with CLL/SLL with or without del(17p) or the TP53 mutation (category 2A).</i>
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Dosing and Administration Considerations

BTK Therapy	Dosage and Administration	Dosage Form and Strength
Acalabrutinib ¹	Twice-daily dosing • 100 mg PO every 12 hours for CLL/SLL and MCL	100-mg capsules
Ibrutinib ⁴	Once-daily dosing • 420 mg PO daily for CLL/SLL and WM • 560 mg PO daily for MCL and MZL	70-mg and 140-mg capsules 140-mg, 280-mg, 420-mg, and 560-mg tablets
Zanubrutinib ⁵	Once-daily dosing • 320 mg PO daily for MCL, MZL, and WM Twice-daily dosing • 160 mg PO every 12 hours for MCL, MZL, and WM	80-mg capsules

Additional Considerations^{1,4,5}

- Acalabrutinib: Drug–drug interactions can occur with CYP3A inhibitors or inducers and gastric acid–reducing agents
 - Avoid concomitant use of acalabrutinib with moderate and strong CYP3A inhibitors or CYP3A inducers
 - If coadministration with moderate CYP3A inhibitors cannot be avoided, reduce dose of acalabrutinib to 100 mg once daily
 - If strong CYP3A inhibitor is needed short term (eg, 7-day anti-infective course of therapy), hold acalabrutinib therapy until end of CYP3A inhibitor therapy
 - If strong CYP3A inducer cannot be avoided, increase acalabrutinib dose to 200 mg every 12 hours
 - Avoid coadministration of acalabrutinib with proton pump inhibitors; stagger dosing with H2-receptor antagonists or antacids
- Ibrutinib: Drug–drug interactions can occur with CYP3A inhibitors or inducers
 - Avoid concomitant use of ibrutinib with moderate and strong CYP3A inhibitors or CYP3A inducers
 - If coadministration with moderate CYP3A inhibitors cannot be avoided, reduce dose of ibrutinib
 - If strong CYP3A inhibitor is needed short term (eg, 7-day anti-infective course of therapy), hold ibrutinib inhibitor therapy until end of CYP3A inhibitor therapy as recommended in package insert instructions
- Zanubrutinib: Drug–drug interactions can occur with CYP3A inhibitors or inducers
 - Avoid concomitant use of zanubrutinib with moderate and strong CYP3A inhibitors or CYP3A inducers
 - If coadministration with moderate or strong CYP3A inhibitors cannot be avoided, reduce dose of zanubrutinib as recommended in package insert instructions

Key Adverse Event Management Considerations

The most common adverse events (AEs) associated with BTK inhibitors are diarrhea, cytopenias, myalgias/arthralgias, upper respiratory tract infection, bleeding, rash, fatigue, and cardiac events. These AEs are most often mild (grade 1/2) and self-limiting; dose interruption or reduction is typically not required. However, serious AEs requiring dose reduction or interruption may occur in 3% to 10% of patients and can include neutropenia, anemia, thrombocytopenia, atrial fibrillation, hypertension, and bleeding/hemorrhage.

Although BTK inhibitor therapy is generally well tolerated and there are no specific mandatory contraindications to therapy, there are a few patient populations with special considerations for BTK inhibitor therapy. In particular, patients who are already at risk for cardiovascular disease with an infection or with prior heart rhythm problems are more likely to develop atrial fibrillation. Of note, patients who are receiving an anticoagulant or an antiplatelet agent are at the highest risk from BTK inhibitor–associated bleeding and bruising.

BTK Inhibitor	AE	Toxicity Occurrence	Dose Modification	
Acalabrutinib ¹	- Grade ≥ 3 nonhematologic toxicities - Grade 3 thrombocytopenia with bleeding	First and second	Interrupt acalabrutinib; once toxicity is reduced to grade ≤ 1 , resume at 100 mg every 12 hours	
		Third	Interrupt acalabrutinib; once toxicity is reduced to grade ≤ 1 , resume at reduced dose of 100 mg daily	
	- Grade 4 thrombocytopenia - Grade 4 neutropenia lasting longer than 7 days	Fourth	Discontinue acalabrutinib	
Ibrutinib ⁴	- Grade ≥ 3 nonhematologic toxicities - Grade ≥ 3 neutropenia with infection or fever - Grade 4 hematologic toxicities		Interrupt ibrutinib; once toxicity is reduced to grade ≤ 1 , resume ibrutinib per below	
			Dose modification after recovery: MCL and MZL (560 mg daily)	Dose modification after recovery: CLL/SLL, WM, chronic GVHD (420 mg daily)
		First	560 mg daily	420 mg daily
		Second	420 mg daily	280 mg daily
		Third	280 mg daily	140 mg daily
		Fourth	Discontinue ibrutinib	Discontinue ibrutinib
Zanubrutinib ⁵	- Grade ≥ 3 nonhematologic toxicities (evaluate risk vs benefit before resuming after grade 4 AEs) - Grade 3 febrile neutropenia - Grade 3 thrombocytopenia with significant bleeding - Grade 4 thrombocytopenia lasting >10 consecutive days - Grade 4 neutropenia lasting >10 consecutive days	First	Interrupt zanubrutinib; once toxicity is reduced to grade ≤ 1 , resume at starting dose of 160 mg twice daily or 320 mg once daily	
		Second	Interrupt zanubrutinib; once toxicity is reduced to grade ≤ 1 , resume at reduced dose of 80 mg twice daily or 160 mg once daily	
		Third	Interrupt zanubrutinib; once toxicity is reduced to grade ≤ 1 , resume at reduced dose of 80 mg once daily	
		Fourth	Discontinue zanubrutinib	

- For an interactive resource on how to manage BTK inhibitor–related AEs, please visit the CCO website (clinicaloptions.com/BTKitool)

Select Ongoing Trials With BTK Inhibitors Recruiting Patients With B-Cell Lymphomas

Agent	Study
Acalabrutinib	• A Combination of Acalabrutinib With R-CHOP in Subjects With Previously Untreated Non-GCB DLBCL (ACE-LY-312) (NCT04529772) • Acalabrutinib and Anti-CD19 CAR T-cell Therapy for the Treatment of B-cell Lymphoma (NCT04257578) • A Study of BR Alone Versus in Combination With Acalabrutinib in Subjects With Previously Untreated MCL (NCT02972840) • Study of Acalabrutinib and Tafasitamab in MZL Patients (NCT04646395)
Ibrutinib	• Ibrutinib and Standard Immuno-Chemotherapy in Younger, High-Risk Patients With Diffuse Large B-Cell Lymphoma (NCT03399513) • Ibrutinib Before and After Stem Cell Transplant in Treating Patients With Relapsed or Refractory Diffuse Large B-cell Lymphoma (NCT02443077) • Abexinostat and Ibrutinib in Diffuse Large B-cell Lymphoma and Mantle Cell Lymphoma (NCT03939182) • Safety and Efficacy Study of Loncastuximab Tesirine + Ibrutinib in Diffuse Large B-Cell or Mantle Cell Lymphoma (NCT03684694) • Venetoclax, Ibrutinib, Prednisone, Obinutuzumab, and Lenalidomide (ViPOR) in Relapsed/Refractory B-cell Lymphoma (NCT03223610) • A Study of Ibrutinib With Rituximab in People With Untreated Marginal Zone Lymphoma (NCT04212013, NCT03697512) • Phase II Palbociclib +Ibrutinib in Mantle Cell Lymphoma (NCT03478514)
Zanubrutinib	• Study of Zanubrutinib, Rituximab and Combination Chemotherapy in Newly Diagnosed Aggressive B-cell Non-Hodgkin Lymphoma (NCT05164770) • A Study of Zanubrutinib Versus Lenalidomide in Participants With Relapsed/Refractory Marginal Zone Lymphoma (NCT05100862) • Zanubrutinib Combined With Standard Chemotherapy in the Treatment for Patients With Diffuse Large B Cell Lymphoma (NCT04668365) • Zanubrutinib (BGB-3111) in Participants With Previously Treated B-Cell Lymphoma Intolerant of Prior Bruton Tyrosine Kinase (BTK) Inhibitor Treatment (NCT04116437)
Pirtobrutinib (LOXO-305)	• Study of BTK Inhibitor LOXO-305 Versus Approved BTK Inhibitor Drugs in Patients With Mantle Cell Lymphoma (MCL) (BRUIN-MCL-321) (NCT04662255) • A Study of Oral LOXO-305 in Patients With Previously Treated CLL/SLL or NHL (NCT03740529)

References

1. Acalabrutinib PI. 2. National Comprehensive Cancer Network. Clinical practice guidelines in oncology: B-cell lymphomas. v.5.2021. nccn.org.
3. National Comprehensive Cancer Network. Clinical practice guidelines in oncology: Chronic lymphocytic leukemia/small lymphocytic leukemia. v.1.2022. nccn.org.
4. Ibrutinib PI. 5. Zanubrutinib PI.