

PI3K Inhibitor Therapy in Indolent B-Cell Lymphomas: A Summary Resource



powered by CEA

Mechanism of Action and Molecular Targets

The discovery that phosphoinositide 3-kinase (PI3K) is overactive in cancer resulted in the development of therapeutic PI3K inhibitors.¹ Two PI3K inhibitors are currently FDA approved for B-cell lymphomas: copanlisib² and umbralisib.³ Duvelisib and idelalisib are 2 other PI3K inhibitors. Duvelisib is approved for relapsed chronic lymphocytic leukemia/small lymphocytic lymphoma and idelalisib is approved for relapsed chronic lymphocytic leukemia. **In April 2022, umbralisib was voluntarily withdrawn from sale for approved indications.**

PI3K Inhibitor	Mechanism of Action
Copanlisib ²	Inhibits PI3K, primarily PI3Kα and PI3Kδ isoforms Inhibits key cell-signaling pathways involving the BCR, CXCR12-mediated chemotaxis, and NF- κ B Induces tumor cell death by apoptosis and inhibition of proliferation of malignant B-cells
Umbralisib ³	Inhibits multiple kinases, including PI3Kδ (in normal and malignant B-cells), CK1ϵ (implicated in cancer cell pathogenesis), and a mutated form of ABL1 (biochemical assay) Inhibits cell proliferation, CXCL12-mediated cell adhesion, and CCL19-mediated cell migration in lymphoma cell lines

BCR, B-cell receptor.

Current Indications and Recommendations for PI3K Inhibitors in B-Cell Lymphomas

FDA-Approved PI3K Inhibitors	Indications and Recommendations
Copanlisib ²	FDA-approved indications: Adults with relapsed FL after ≥ 2 previous systemic therapies (accelerated approval) <i>The National Comprehensive Cancer Network (NCCN[®]) guidelines recommend copanlisib for MZL after ≥ 2 previous therapies and for R/R FL after ≥ 2 previous therapies and has been shown to be effective for high-risk patients with FL with disease relapse ≤ 2 years after first-line therapy⁴</i>
Umbralisib ⁵	FDA-approved indications: - Adults with R/R MZL after ≥ 1 prior anti-CD20-based regimen (accelerated approval) - Adults with R/R FL after ≥ 3 previous systemic therapies (accelerated approval) <i>The NCCN[®] also recommends duvelisib for MZL after ≥ 2 previous therapies and for R/R FL after ≥ 3 previous therapies (including for patients who are older or infirm)⁸</i>

FL, follicular lymphoma; MZL, marginal zone lymphomas; R/R, relapsed/refractory.

NOTE: FDA accelerated approval for duvelisib and idelalisib in R/R FL has been withdrawn.

Dosage and Administration Considerations in Indolent Lymphomas^{2,3}

PI3K Inhibitor	Dosage	Administration Considerations
Copanlisib ²	60 mg IV infusion over 1 hour on Days 1, 8, and 15 of 28-day cycles (3 weeks on, 1 week off)	- Reduce dose to 45 mg if moderate hepatic impairment - Avoid concomitant use of strong CYP3A inhibitors or inducers and reduce dose to 45 mg if strong CYP3A inhibitor is needed - Consider PJP prophylaxis for patients at risk
Umbralisib ³	800 mg PO once daily	- Concomitant use of strong CYP3A inhibitors or inducers has not been studied - PJP prophylaxis should be provided; consider prophylactic antivirals for CMV infection or reactivation

CMV, cytomegalovirus; PJP, pneumocystis jirovecii pneumonia.

Key Adverse Events Associated With PI3K Inhibitors in Indolent Lymphomas^{2,3}

Key AE	PI3K Inhibitors With PI Warning	Key Considerations
Infection	Copanlisib Umbralisib	Patients should be monitored for signs and symptoms of infection • Treat any infection prior to starting therapy with a PI3K inhibitor and advise patients to report any symptoms of infection to their care team • Monitor for any new or worsening signs and symptoms of infection • Hold PI3K inhibitors for grade ≥ 3 infections • Provide PJP prophylaxis for patients at risk and hold PI3K inhibitor for suspected PJP infection • CMV infection may occur; consider prophylaxis and hold PI3K inhibitor for positive CMV polymerase chain reaction or antigen test until viremia resolves and continue to monitor for CMV reactivation at least monthly • For copanlisib: If PJP infection is confirmed, treat infection until resolution and then resume copanlisib with concomitant PJP prophylaxis • For umbralisib: Hold for suspected PJP infection and permanently discontinue if PJP infection confirmed
Noninfectious pneumonitis	Copanlisib	Noninfectious pneumonitis may occur in some patients receiving PI3K inhibitors (~5%) • Hold copanlisib for patients experiencing symptoms such as cough, dyspnea, and hypoxia or for patients with interstitial infiltrates on radiologic exam • Evaluate for etiology of pneumonitis to confirm noninfectious vs infectious causes • Consider administration of systemic corticosteroids for patients with pneumonitis
Neutropenia	Copanlisib Umbralisib	Grade ≥ 3 neutropenia and/or serious neutropenic events may occur in patients receiving PI3K inhibitors • For copanlisib: Monitor blood counts at least weekly during therapy with copanlisib • For umbralisib: Monitor neutrophil counts at least every 2 weeks for the first 2 months of therapy and at least weekly in patients with neutrophil counts $< 1 \times 10^9/L$
Cutaneous reactions	Copanlisib Umbralisib	Reported AEs include dermatitis exfoliative, exfoliative rash, pruritus, and rash or maculopapular rash • Monitor for new or worsening cutaneous reactions • Consider supportive measures to manage symptoms of rash and follow prescribing information instructions to hold, dose reduce, or discontinue PI3K inhibitors due to these AEs • For umbralisib: Serious cutaneous reactions, including a fatal case of exfoliative dermatitis, have occurred with umbralisib. Review all concomitant medications and discontinue any medications potentially contributing to cutaneous reactions. Permanently discontinue for life-threatening cutaneous reactions or for cases of SJS, TEN, or DRESS
Hyperglycemia	Copanlisib	• Treatment may result in infusion-related hyperglycemia, typically peaking 5-8 hours post infusion and then declining to baseline in most patients • Achieve optimal blood glucose control before starting therapy with copanlisib
Hypertension	Copanlisib	• Treatment may result in infusion-related hypertension, with mean blood pressure remaining elevated for 6-8 hours after start of the infusion • Achieve optimal blood pressure control before starting therapy with copanlisib and monitor blood pressure before and after infusion
Diarrhea or colitis	Umbralisib	• Patients may experience diarrhea/colitis while receiving therapy with PI3K inhibitors • Advise patients to report any new or worsening diarrhea and follow guidelines in prescribing information for managing this AE, including use of antidiarrheal agents for supportive care
Hepatotoxicity	Umbralisib	• Hepatotoxicity may occur in patients receiving umbralisib • Monitor hepatic function during therapy
Allergic reaction to FD&C Yellow No. 5	Umbralisib	• Umbralisib contains FD&C Yellow No. 5 and may cause allergic-type reactions, including bronchial asthma, in susceptible patients (frequently in patients who also have aspirin hypersensitivity)

AE, adverse event; DRESS, drug reaction with eosinophilia and systemic symptoms; SJS, Stevens-Johnson syndrome; TEN, toxic epidermal necrolysis.

Hold, dose reduce, or discontinue PI3K inhibitors depending on severity and persistence of these and any other AEs experienced while receiving PI3K inhibitors^{2,3}

Key Ongoing Clinical Trials of PI3K Inhibitors for the Treatment of B-Cell Lymphomas

PI3K Inhibitor	Study
Copanlisib	- Phase II study of response-adapted therapy with copanlisib + rituximab in untreated FL (N = 65) (NCT03789240) - Phase II study of copanlisib + ketogenic diet in R/R FL or endometrial cancer (N = 42) (NCT04750941) - Phase II COUP-1 study of copanlisib + rituximab in MZL (N = 56) (NCT03474744) - Phase IIb/III Unity non-Hodgkin lymphoma study of umbralisib + ublituximab (± bendamustine) in B-cell lymphomas (N = 900) (NCT02793583) - Phase II study of umbralisib + rituximab in newly diagnosed FL and MZL (N = 41) (NCT03919175) - Phase II study of ublituximab + umbralisib in treatment-naïve FL and small lymphocytic lymphoma (N = 50) (NCT03828448) - Phase I/II study of tazemetostat, umbralisib + ublituximab in R/R FL (N = 48) (NCT05152459)
Umbralisib	- Phase IIb/III Unity non-Hodgkin lymphoma study of umbralisib + ublituximab (± bendamustine) in B-cell lymphomas (N = 900) (NCT02793583) - Phase II study of umbralisib + rituximab in newly diagnosed FL and MZL (N = 41) (NCT03919175) - Phase II study of ublituximab + umbralisib in treatment-naïve FL and SLL (N = 50) (NCT03828448) - Phase I/II study of tazemetostat, umbralisib + ublituximab in R/R FL (N = 48) (NCT05152459)
Zandelisib	- Phase II study of zandelisib in R/R FL and MZL after 2 or more therapies (NCT03768505) - Phase III study of zandelisib + rituximab compared to standard therapy in R/R FL and MZL (NCT04745832)

References

1. Vanhaesebroeck. Nat Rev Drug Disc. 2021;20:741. 2. Copanlisib PI. 3. Umbralisib PI. 4. National Comprehensive Cancer Network. Clinical practice guidelines in oncology: B-cell lymphomas. v.2.2022. nccn.org.