

Epigenetic Therapy in Indolent B-Cell Lymphomas: A Summary Resource



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Mechanism of Action

Tazemetostat is a methyltransferase inhibitor that inhibits *EZH2*, some *EZH2* gain-of-function mutations (including Y646X, A682G, and A692V), and *EZH1*, at a half-maximal inhibitory concentration (IC_{50}) 36 times greater than the IC_{50} for *EZH2* inhibition.¹ In vitro, tazemetostat suppressed growth of B-cell lymphoma cell lines and showed antitumor activity in a mouse xenograft model of B-cell lymphoma with or without *EZH2* gain-of-function mutations. Tazemetostat demonstrated greater effects on the inhibition of proliferation of lymphoma cell lines with mutant *EZH2*.

Panobinostat and vorinostat are histone deacetylase inhibitors, which allow acetyl groups to accumulate on lysines and results in an open chromatin structure and transcriptional activation of tumor suppressor genes.^{2,3} In vitro, vorinostat induces cell cycle arrest and/or apoptosis of certain transformed cells.³

Current Indications and Recommendations for Use

FDA-Approved Epigenetic Therapy	Indications and Recommendations
Tazemetostat ¹	Currently FDA-approved (accelerated approval) for adult patients with: • R/R FL whose tumors are positive for an <i>EZH2</i> mutation as detected by an FDA-approved test and who have received ≥ 2 prior systemic therapies • R/R FL who have no satisfactory alternative treatment options • Also approved for adult and pediatric patients aged 16 years or older with metastatic or locally advanced epithelioid sarcoma not eligible for complete resection <i>The National Comprehensive Cancer Network (NCCN®) guideline recommends tazemetostat in FL:</i> • <i>Second-line therapy in older or infirm patients if other options are not satisfactory</i>⁴ • <i>Third-line or subsequent therapy for patients with R/R FL with an <i>EZH2</i> mutation who have no satisfactory alternative treatment options after ≥ 2 prior systemic therapies</i>⁴

FL, follicular lymphoma; R/R, relapsed/refractory

Panobinostat and vorinostat are not approved by the FDA for the treatment of any B-cell lymphomas.^{2,3}

Dosing and Administration Considerations for Tazemetostat

Epigenetic Therapy	Dosage and Administration	Dosage Form and Strength
Tazemetostat ¹	800 mg PO BID For dose reductions: 600 mg PO BID then 400 mg PO BID	200-mg tablets

Additional Considerations

- Capsules should be swallowed whole, with or without food
- If dose is missed or vomited, do not take an additional dose and continue with the next scheduled dose
- Avoid concomitant use with moderate and strong CYP3A inhibitors or inducers
 - If coadministration with CYP3A inhibitors cannot be avoided, reduce tazemetostat dose
 - Avoid drinking grapefruit juice and taking St John's wort
- Coadministration with CYP3A substrates (eg, hormonal contraceptives) will decrease the concentration and efficacy of the CYP3A substrate

Key Adverse Event Management Considerations for Epigenetic Therapies Approved for B-Cell Lymphomas

The most common adverse events ($\geq 20\%$) in patients with FL receiving tazemetostat included fatigue, upper respiratory tract infection, musculoskeletal pain, nausea, and abdominal pain.

Tazemetostat also increased the risk of developing secondary malignancies, including myelodysplastic syndromes and acute myeloid leukemia (in 0.7% of patients). Monitor patients for the development of secondary malignancies.

Dose Modifications for Tazemetostat¹

Adverse Event	Severity	Dose Modification
Neutropenia	Neutrophil count: <1 x 10 ⁹ /L	- Hold tazemetostat until neutrophil count improves to $\geq 1 \times 10^9$/L or baseline - Resume tazemetostat at same dose for first occurrence or resume at reduced dose for second and third occurrence - Permanently discontinue tazemetostat after fourth occurrence
Thrombocytopenia	Platelet count: <50 x 10 ⁹ /L	- Hold the tazemetostat until the platelet count improves to $\geq 75 \times 10^9$/L - Resume the drug at a reduced dose for first and second occurrence - Permanently discontinue tazemetostat after second occurrence
Anemia	Hemoglobin: <8 g/dL	Hold tazemetostat until resolution to baseline or grade 1, then resume at same or a reduced dose
Other adverse events	Grade 3	- Hold tazemetostat until resolution baseline or grade 1, then resume tazemetostat at a reduced dose at first and second occurrence - Permanently discontinue tazemetostat after third occurrence
	Grade 4	- Hold tazemetostat until baseline or grade 1 - Resume tazemetostat at a reduced dose at first occurrence - Permanently discontinue tazemetostat after second occurrence

Select Ongoing Clinical Trials of Epigenetic Therapies in B-Cell Lymphomas

Agent	Study
Tazemetostat	- Phase Ib/III study of tazemetostat or placebo in combination with lenalidomide + rituximab in patients with R/R FL (NCT04224493) - Phase II SYMPHONY-2 study of tazemetostat + rituximab in patients with R/R FL with ≥ 2 prior lines of systemic therapy for FL (NCT04762160) - Phase IB/II study of tazemetostat in patients with newly diagnosed DLBCL or high-risk FL with R-CHOP treatment (NCT02889523) - Phase I study to assess the safety, pharmacokinetics, and preliminary efficacy of an orally available small molecule, CC-99282, alone and in combination with antilymphoma agents in patients with R/R NHL (NCT03930953)
Vorinostat	Phase I study of pembrolizumab + vorinostat for relapsed or refractory DLBCL, FL, and Hodgkin lymphoma (NCT03150329)

DLBCL, diffuse large B-cell lymphoma; NHL, non-Hodgkin lymphoma; R-CHOP, rituximab/cyclophosphamide/doxorubicin/vincristine/prednisone.

References

1. Tazemetostat PI. 2. Panobinostat PI. 3. Vorinostat PI. 4. National Comprehensive Cancer Network. Clinical practice guidelines in oncology: B-cell lymphomas. V2.2022. nccn.org.