# A Closer Look at Tazemetostat

Connie Lee Batlevi, MD, PhD
Medical Oncologist
Memorial Sloan Kettering Cancer Center
New York, New York

Tazemetostat (Tazverik, Epizyme) is an oral EZH2 inhibitor. In June 2020, the US Food and Drug Administration (FDA) granted accelerated approval to tazemetostat for the treatment of adult patients with relapsed/refractory follicular lymphoma. The approval encompasses 2 subgroups: patients whose tumors are positive for an *EZH2* mutation as detected by an FDA-approved test and who have received at least 2 prior systemic therapies, and patients who have no satisfactory alternative treatment options. This approval was based on results from a phase 2 trial of tazemetostat that reported an overall response rate of 69% in patients with *EZH2*-mutated disease and 34% in patients with *EZH2*–wild-type disease. The median duration of response was 10.9 months vs 13.0 months, respectively. Tazemetostat has a well-tolerated safety profile and is suitable for appropriate patients with relapsed or refractory follicular lymphoma, regardless of their *EZH2* mutational status.

**H&O** How does tazemetostat work?

**CB** Tazemetostat is a new type of therapy that inhibits EZH2, which is a histone methyltransferase and a component of the polycomb repressive complex 2 (PRC2). This complex deposits epigenetic methylation markers leading to trimethylation of lysine 27 on histone H3. The methylation markers suppress genes that control cell differentiation and pause transition of B cells from terminal differentiation.

**H&O** What are the indications of tazemetostat in follicular lymphoma?

**CB** Tazemetostat is approved by the US Food and Drug Administration (FDA) for the treatment of patients with relapsed/refractory follicular lymphoma with an *EZH2* mutation who have received at least 2 prior systemic therapies. This approval is accompanied by a companion diagnostic test for the *EZH2* mutation. In addition, tazemetostat is approved for patients with relapsed/refractory follicular lymphoma who have no other satisfactory treatment options. This approval offers physician discretion when selecting appropriate patients for this therapy.

**H&O** What trial data led to the approvals of tazemetostat in follicular lymphoma?

**CB** Tazemetostat was approved based on data from an open-label, single-arm, multicenter phase 2 trial that enrolled patients with diffuse large B-cell lymphoma (DLBCL) or follicular lymphoma. Results for the follicular lymphoma cohort were published in October 2020. Within this cohort, 45 patients were *EZH2*-mutated and 54 patients were *EZH2*–wild-type. The objective response rate was 69% in those with the *EZH2* mutation and 35% in those with wild-type *EZH2*. The median duration of response was 10.9 months (95% CI, 7.2 to not estimable) vs 13.0 months (95% CI, 5.6 to not estimable), respectively. The median progression-free survival was 13.8 months (95% CI, 10.7-22.0) vs 11.1 months (95% CI, 3.7-14.6).

Tazemetostat was generally well tolerated. The most common side effects included lowered energy, anemia, anorexia, muscle spasms, nausea, vomiting, constipation, thrombocytopenia, dry skin, neutropenia, and diarrhea. The majority of these toxicities were grade 1 or 2, and transient. Grade 3 or higher adverse events were relatively uncommon. They included thrombocytopenia, neutropenia, hypertension, elevated bilirubin, and elevated transaminases. Two cases of myelodysplastic syndromes/acute myeloid leukemia were reported; both patients had received extensive prior treatments, including multiple chemotherapy agents.

**H&O** Were there any other notable findings from the trial?

**CB** Tumor reduction was observed in 98% of patients with mutated *EZH2*. The time to response was 3.7 months, and responses tended to occur slowly. Responses

can improve over time, and therefore prolonged therapy is advised if patients are tolerating the treatment and experiencing clinical benefit. Additionally, 65% of patients in the *EZH2*–wild-type group showed evidence of a reduction in tumor volume. The rates of complete response were 13% in the *EZH2*-mutated group and 4% in the *EZH2*–wild-type group. Patients with a partial or complete response were able to continue treatment for a long period and did very well.

Subgroup analysis of high-risk populations—including patients who progressed within 24 months of first-line therapy and patients who were double refractory to rituximab and an alkylating agent——demonstrated similar response rates in the mutated and wild-type subgroups.

**H&O** How does testing for the *EZH2* mutation fit into treatment with tazemetostat?

**CB** Molecular testing was previously considered an investigational component of lymphoma management. Tazemetostat is the first treatment in lymphoma that permits selection of patients who may have a heightened response. With the advent of this treatment option, patients with follicular lymphoma should be offered molecular profiling that includes the *EZH2* mutation at diagnosis or first relapse. For oncologists, testing for the *EZH2* mutation represents a new paradigm. It is necessary to test patients early in the course of their disease. For most of the sequencing tests, results can take 2 to 4 weeks. It is easier to plan the treatment course when the patient's mutation status is known early. However, it is possible to begin treatment with tazemetostat before the patient's *EZH2* mutation status is known.

**H&O** Where do you see tazemetostat fitting into your practice?

**CB** Tazemetostat is an epigenetic modulator that is now FDA-approved to treat relapsed or refractory follicular lymphoma in patients with the *EZH2* mutation or patients with no satisfactory alternative therapy, regardless of *EZH2* mutation status. The latter may include patients for whom phosphatidylinositol 3-kinase (PI3K) inhibitors are not suitable and those for whom re-challenge with rituximab as a single agent or in a combination regimen is not the preferred option. Tazemetostat is an appropriate treatment in the third-line setting for patients who have been previously treated with rituximab and chemotherapy. Based on the mild toxicity profile, this agent is suitable for a variety of patients, including those who are frail, those with a low performance status, or those who are unable to tolerate additional treatment with rituximab-based regimens or PI3K inhibitors.

**H&O** How do you describe tazemetostat to your patients?

**CB** I tell them that tazemetostat is a molecularly targeted agent that works by controlling the expression of genes that regulate growth and differentiation of the lymphoma. It is an orally administered medication given twice a day.

> Tazemetostat is the first treatment in lymphoma that permits selection of patients who may have a heightened response.

**H&O** What is the procedure for monitoring patients during treatment with tazemetostat?

**CB** In my practice, patients are typically monitored every 2 weeks for the first month of treatment, and then every month thereafter with laboratory work. We first assess for a response approximately 3 months after treatment begins. In patients who have stable disease or better, we recommend that treatment is continued as long as it is well tolerated. Patients can develop responses in later cycles of treatment.

**H&O** Do the adverse events reported in trials match your clinical experience?

**CB** The toxicity profile is very manageable. The most common adverse events include transient episodes of low energy, decreased appetite, and mild gastrointestinal upset. Less than 10% of patients experience side effects that require drug interruption or discontinuation.

Infections including pulmonary, urinary, and upper respiratory infections were observed during treatment with tazemetostat. Most events were considered unrelated to tazemetostat. However, surveillance of quantitative immunoglobulins (Ig) or IgG subclasses is helpful to determine whether patients require intravenous IgG supplementation.

In my experience, tazemetostat is well tolerated. The need for dose reductions is rare. There are not many cases of significant cytopenias or neutropenias. However, patients should still undergo monitoring with blood work. Unlike other treatments in this setting, tazemetostat is administered orally. Therefore, patients can be

managed via telehealth. Patients can undergo blood work elsewhere to monitor their side effect profile.

**H&O** Do you anticipate that the role of tazemetostat will evolve?

**CB** Tazemetostat is a promising agent for combination therapy because of its mild toxicity profile. There are interesting studies utilizing combinations of tazemetostat with rituximab and lenalidomide (Revlimid, Bristol Myers Squibb) in second-line follicular lymphoma. In a recent trial, tazemetostat in combination with rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) was tolerated. Larger trials are needed to test the efficacy of this regimen.

***Disclosure***

*Dr Batlevi has received research funding from Janssen, Novartis, Epizyme, Xynomic, Bayer, Autolus, and Roche. She is a consultant/advisory board member of LifeSci, GLG, Juno/Celgene, Seattle Genetics, Kite, and Karyopharm. She has received honoraria from Dava Oncology and Skipta.*

## Suggested Readings


Brach D, Johnston-Blackwell D, Drew A, et al. EZH2 inhibition by tazemetostat results in altered dependency on B-cell activation signaling in DLBCL. *Mol Cancer Ther*. 2017;16(11):2586-2597.

ClinicalTrials.gov. Oral tazemetostat in combination with rituximab in R/R FL. https://www.clinicaltrials.gov/ct2/show/NCT04590820. Identifier: NCT04590820. Accessed November 9, 2020.

ClinicalTrials.gov. Study in subjects with relapsed/refractory follicular lymphoma. https://clinicaltrials.gov/ct2/show/NCT04224493. Identifier: NCT04224493. Accessed November 9, 2020.

ClinicalTrials.gov. Tazemetostat rollover study (TRuST): an open-label rollover study (TRuST). https://www.clinicaltrials.gov/ct2/show/NCT02875548. Identifier: NCT02875548. Accessed November 9, 2020.

Italiano A, Soria JC, Toulmonde M, et al. Tazemetostat, an EZH2 inhibitor, in relapsed or refractory B-cell non-Hodgkin lymphoma and advanced solid tumours: a first-in-human, open-label, phase 1 study. *Lancet Oncol*. 2018;19(5):649-659.

Morschhauser F, Tilly H, Chaidos A, et al. Tazemetostat for patients with relapsed or refractory follicular lymphoma: an open-label, single-arm, multicentre, phase 2 trial. *Lancet Oncol*. 2020;21(11):1433-1442.

Sarkozy C, Morschhauser F, Dubois S, et al. A LYSA phase Ib study of tazemetostat (EPZ-6438) plus R-CHOP in patients with newly diagnosed diffuse large B-cell lymphoma (DLBCL) with poor prognosis features. *Clin Cancer Res*. 2020;26(13):3145-3153.