tazemetostat (Tazverik™)

EOCCO POLICY

Policy Type: PA/SP Pharmacy Coverage Policy: EOCCO184

Description

Tazemetostat (Tazverik) is an orally administered inhibitor of methyltransferase, EZH2.

Length of Authorization

- N/A

Quantity Limits

Product Name	Dosage Form	Indication	Quantity Limit
tazemetostat (Tazverik)	200 mg tablets	Epithelioid sarcoma, advanced or metastatic, not eligible for resection; Follicular lymphoma, relapsed or refractory, EZH2 mutation-positive, in that that have received at least two therapies; Follicular lymphoma, relapsed or refractory, in those with no satisfactory alternative therapy	240 tablets/30 days

Initial Evaluation

I. Tazemetostat (Tazverik) is considered investigational when used for all conditions, including but not limited to:
   A. Epithelioid sarcoma
   B. Non-Hodgkin lymphoma, including follicular lymphoma

Renewal Evaluation

I. N/A

Supporting Evidence

I. Background: Epithelioid sarcoma is a very rare cancer of the soft tissue, generally seen in younger populations (average age of 27). This aggressive condition is known for recurrence, spread to locoregional lymph nodes, and eventually distant metastases. Common sites of origin include fingers, hands, forearms, feet, and other limbs. First-line management is typically surgery, with local recurrence necessitating amputation in many cases. Although, not specifically FDA-approved for epithelioid sarcoma, there are several systemic therapies used in the metastatic setting. Often, anthracycline based regimens (e.g., doxorubicin with or without ifosfamide), gemcitabine, pazopanib (Votrient), doxetaxel, sunitinib (Sutent), dacarbazine, epirubicin, and temozolomide.

II. Efficacy: Tazemetostat (Tazverik) was approved on data from a Phase 2 trial. Pooled data from two cohorts, five and six (n=62, n=44), were used to support the approval. Seventy-seven percent of patients had prior surgery and 61% had prior chemotherapy. Primary outcomes included objective response rate (ORR) assessed every eight weeks and progression-free survival (PFS). Secondary endpoints were duration of response (DOR), disease control rate (DCR) and overall survival (OS). The pooled data showed an objective response rate of 13% (CR 1.6%, PR 11%). Duration of response was 12.8 months (3.5-24 months). Pooled data for progression-free survival (PFS), disease control rate (DCR) and overall survival (OS) were not reported for the pooled data; however, for Cohort 5 PFS was 23.7 weeks, DCR was 21%, and OS was 82 weeks.

III. Safety: There are no contraindications for tazemetostat (Tazverik); however, there is a warning for development of secondary malignancies, such as T-cell lymphoblastic lymphoma, myelodysplastic syndrome, and acute myeloid leukemia. Six out of 668 treated patients had developed secondary malignancy as of quarter May 2019. Common (≥ 20%) adverse reactions noted from the trial included: fatigue, nausea, decreased appetite, vomiting and constipation. One patient in the clinical trial discontinued therapy due to adverse events, 34% required a dose interruption, and there were not deaths from treatment. Tazemetostat (Tazverik) has significant drug interactions with CYPP450 inhibitors and inducers, and there is a warming for embryo fetal toxicity and lactation. Due to the limited number of subjects treated and short duration of use, the safety profile of tazemetostat (Tazverik) is largely unknown at this time.

IV. The quality of the evidence is low given the Phase 2, open-label, single-arm trial. The primary endpoints have not been correlated with clinically meaningful outcomes such as improvement in morbidity, mortality or symptom relief, and results have not been confirmed in other studies. Additionally, due to the limited number of subjects treated, the safety profile is highly unknown. Coupled with the low rates of response, there is uncertain usefulness of tazemetostat (Tazverik) at this time.

V. Tazemetostat (Tazverik) was approved under the accelerated approval pathway and orphan drug designation. Continued approval may be contingent upon verification and description of clinical benefit in confirmatory trials.

VI. Follicular lymphoma (FL), is an indolent form of NHL that arises from B-lymphocytes. Treatment is dependent on stage, or histologic grade of condition, and may include the following: radiation therapy, immunotherapy, and chemotherapy. In the space of relapsed or refractory to two prior therapies, the PI3K inhibitors are recommended per NCCN (e.g., copanlisib, duvelisib, idelalisib), as well as selinexor.

VII. Tazemetostat (Tazverik) for FL was evaluated for safety and efficacy in one open-label, single-arm, Phase 2 trial at 800 mg twice daily. There were 99 patients included in the trial , 45 of which were EZH2 mutated, and 54 were EZH2 wild type. Patients were adults with confirmed FL (grade 1-3b), relapsed or refractory to two or more standard systemic therapies, with life expectancy of three months or more, and adequate organ function. Some patients had up to five or more previous therapies, and up to 59% were rituximab refractory, up to 28% were double refractory, and up to 29% had hematopoietic stem cell transplant.

VIII. Tazemetostat (Tazverik) was approved under the accelerated approval pathway for FL based on objective response rate, duration or response, and progression free survival. Continued approval may be contingent upon verification and description of clinical benefit in confirmatory trials. Treatment emergent adverse events (TEAE) occurred in 99% of patients, and serious AE occurred in 27%. The most common serious AE being sepsis, physical health deterioration, and anemia. Other notable serious AE were neutropenia, pancytopenia, global amnesia, arrhythmia, and myelodysplastic syndrome. Dose reductions due to adverse events as well as dose interruptions occurred at rates of 27%, and 8% of patients permanently discontinued due to AE. One case of AML was reported, and four patients died within 30 days of the last dose of study drug. The study investigators deemed these not related to treatment.

IX. Given the observational nature of the data, true medication safety and efficacy is unknown. Open-label, single-arm trials are insufficient for determining cause and effect of treatment. Additionally, ORR, DoR, and PFS have not been correlated with clinically meaningful outcomes such as improvement in quality of life, symptom control, or overall survival.

Investigational or Not Medically Necessary Uses

I. There is a lack of high-quality data from randomized controlled trials to indicate the safety and efficacy of tazemetostat (Tazverik) in the following indications:
   A. Soft tissue sarcoma, including epithelioid sarcoma
   B. Non-Hodgkin lymphoma, including follicular lymphoma
   C. Other types of lymphoma, including but not limited to mediastinal, B-Cell, Mantle-Cell, Marginal Zone,
   D. Rhabdoid tumors
   E. Mesothelioma
   F. Kidney, bladder, urothelial cancers
   G. Hepatocellular carcinoma

References

1. Tazverik [Prescribing Information]. Epizyme, Inc. Cambridge, MA. July 2020.
2. Morschhauser F., Tilly H., Chaidos A., et al. Tazemetostat for patients with relapsed or refractory follicular lymphoma: an open-label, single-arm, multicenter, phase 2 trial. *Lancet Oncol.* 2020 Nov;21(11): 1433-1442. PMID 33035457.
3. National Comprehensive Cancer Network. NCCN Guidelines: Treamtn of B-Cell Lymphomas. Version 4.2020, updated August 2020.
4. ClinicalTrials.gov, Available at https://clinicaltrials.gov/ct2/results?cond=&term=tazemetostat&cntry=&state=&city=&dist=. Accessed February 2020. Tazverik [Prescribing Information]. Epizyme, Inc. Cambridge, MA. January 2020.
5. National Comprehensive cancer Network. NCCN Guidelines: Soft Tissue Sarcoma. Version 6.2019. Available at https://www.nccn.org/store/login/login.aspx?ReturnURL=https://www.nccn.org/professionals/physician_gls/PDF/sarcoma.pdf. February 2020.
6. U.S. National Library of Medicine. A phase II, multicenter study of the EZH2 inhibitor tazemetostat in adult subjects with INI1-negative tumors or relapsed/refractory synovial sarcoma. Available at https://clinicaltrials.gov/ct2/show/NCT02601950?term=NCT02601950&draw=2&rank=1. Accessed February 2020.
7. U.S. Food & Drug Administration. FDA approved tazemetostat for advanced epithelioid sarcoma. Available at https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-tazemetostat-advanced-epithelioid-sarcoma. January 24, 2020.
8. Sobanko JF, Meijer L, Nigra TP. Epithelioid sarcoma: a review and update. *J Clin Aesthet Dermatol*. 2009;2(5):49-54.
9. Frezza AM, Jones RL, Lo vullo S, et al. Anthracycline, gemcitabine, and pazopanib in epithelioid sarcoma: A multi-institutional case series. *JAMA Oncol*. 2018;4(9):e180219.
10. Jones RL, Constantinidou A, Olmos D, et al. Role of palliative chemotherapy in advanced epithelioid sarcoma. *Am J Clin Oncol*. 2012;35(4):351-7.

Policy Implementation/Update:

Action and Summary of Changes	Date
Indication of Follicular Lymphoma reviewed and supporting evidence added to policy	01/2021
Policy created	05/2020