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NCCN Guidelines Panel: Soft Tissue Sarcoma

On behalf of Epizyme, I respectfully request the NCCN Guidelines Panel for Soft Tissue Sarcoma to review the enclosed data for the inclusion of tazemetostat as a treatment option for adults and pediatric patients aged 16 years and older with metastatic or locally advanced epithelioid sarcoma not eligible for complete resection. Epithelioid sarcoma is a rare form of soft tissue sarcoma (STS) that accounts for <1% of all STS. The prognosis of ES is poor, and prior to the availability of tazemetostat there were no approved drug treatments specifically for ES.

Specific Changes: We suggest adding tazemetostat as a recommended treatment for metastatic or locally advanced ES in the NCCN Guidelines for Soft Tissue Sarcoma.

FDA Approval: Tazemetostat has been approved by the FDA for the treatment of adults and pediatric patients aged 16 years and older with metastatic or locally advanced epithelioid sarcoma not eligible for complete resection on January 23, 2020. This indication is approved under accelerated approval based on overall response rate (ORR) and duration of response (DOR). Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial(s). The FDA Oncologic Drugs Advisory Committee reviewed tazemetostat on December 18, 2019 and voted unanimously in favor of the benefit-risk profile of tazemetostat for this indication.

Mechanism of Action: Tazemetostat is an orally bioavailable, small molecule selective inhibitor of EZH2, a histone methyltransferase. EZH2 is the catalytic subunit of the polycomb repressive complex 2, catalyzing mono-, di-, and trimethylation of lysine 27 of histone H3. Trimethylation leads to transcriptional regulation of important gene sets such as tumor suppressors, differentiation markers, cell cycle regulators, and apoptotic machinery.[1]

Rationale: The efficacy and safety of tazemetostat was demonstrated in the single-arm, multicenter, open-label Phase 2 EZH-202 trial. The trial evaluated tazemetostat 800 mg twice-daily in 7 cohorts of patients, one of which of which (Cohort 5) enrolled 62 patients with *INI1*-negative epithelioid sarcoma as of the September 17, 2018 data cutoff.[2,3]

Key data points from the EZH-202 trial include:

- The overall response rate (ORR; primary endpoint) among patients with epithelioid sarcoma who received twice-daily 800 mg tazemetostat was 15% (95% CI: 6.9, 25.8). All objective responses were confirmed partial responses.[2]
- Key secondary efficacy endpoints:[2,3]
    - Median duration of response was not reached and ranged from 34.1 weeks to 103.0+ weeks.
    - Disease control rate at 32 weeks was 26% (95% CI: 15.5, 38.5).

    - Median PFS was 23.7 weeks (95% CI: 14.7, 25.7) in the overall epithelioid sarcoma cohort, 42.1 weeks (95% CI: 23.7, not estimable [NE]) in the subgroup that has not received prior systemic therapy and 14.7 weeks (95% CI: 8.3, 23.7) in the subgroup that has received prior systemic therapy.
    - Median overall survival was 82.4 weeks (95% CI: 47.4, NE) in the overall epithelioid sarcoma cohort, not reached in the subgroup that had not received prior systemic therapy, and 47.4 weeks (95% CI: 29.0, 68.1) in a subgroup that had received prior systemic therapy.[2]
- Tazemetostat was generally well-tolerated and most were mild-to-moderate in severity.[2,3]
    - Serious adverse reactions occurred in 37% of patients receiving tazemetostat. Serious adverse reactions occurring in ≥3% were hemorrhage, pleural effusion, skin infection, dyspnea, pain, and respiratory distress.
    - The most common (≥20%) adverse events reactions were pain (52%), fatigue (47%), nausea (36%), decreased appetite (26%), vomiting (24%) and constipation (21%).
    - The most commonly (≥15%) reported treatment-related adverse reactions were fatigue (27%), nausea (27%), decreased appetite (16%), and vomiting (16%). Grade ≥3 reported in 2 or more patients included anemia (6%), decreased weight (3%), decreased appetite (2%), and fatigue (2%).[2]
    - One patient discontinued treatment due to an adverse event. No treatment-related deaths were reported.[2]

The following prescribing information and the abstract and presentation of the data at the 2019 American Society of Clinical Oncology Annual Meeting are submitted in support of this proposed inclusion.

Should you have any questions regarding the content of this letter, please do not hesitate to contact us. Thank you for your review and consideration.

Sincerely,

Khalid Mamlouk, PharmD
VP, Head of Medical Affairs
Epizyme Pharmaceuticals, Inc.

1. Epizyme Inc. TAZVERIK [Prescribing Information]. Epizyme; 2020.
2. Stacchiotti S, Schöffski P, Jones R, et al. Safety and efficacy of tazemetostat, a first-in-class EZH2 inhibitor, in patients (pts) with epithelioid sarcoma (ES) (NCT02601950). J Clin Oncol. 2019;37.
3. Stacchiotti S, Schöffski P, Jones R, et al. Safety and efficacy of tazemetostat, a first-in-class EZH2 inhibitor, in patients (pts) with epithelioid sarcoma (ES) (NCT02601950). A phase 2 study of an investigational drug. Presented at the 2019 ASCO Annual Meeting; May 29–June 2, 2019; Chicago, IL.

Enc: TAZVERIK™ (tazemetostat) Prescribing Information
Stacchiotti et al. (2)