FDA Briefing Document

Oncologic Drugs Advisory Committee Meeting
December 18, 2019

NDA 211723
Tazemetostat
Applicant: Epizyme

DISCLAIMER STATEMENT

The attached package contains background information prepared by the Food and Drug Administration (FDA) for the panel members of the advisory committee. The FDA background package often contains assessments and/or conclusions and recommendations written by individual FDA reviewers. Such conclusions and recommendations do not necessarily represent the final position of the individual reviewers, nor do they necessarily represent the final position of the Review Division or Office. We have brought the tazemetostat NDA to this Advisory Committee in order to gain the Committee's insights and opinions, and the background package may not include all issues relevant to the final regulatory recommendation and instead is intended to focus on issues identified by the Agency for discussion by the advisory committee. The FDA will not issue a final determination on the issues at hand until input from the advisory committee process has been considered and all reviews have been finalized. The final determination may be affected by issues not discussed at the advisory committee meeting.

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1 PROPOSED INDICATION

In the NDA, the applicant, Epizyme, Inc. (Epizyme) is seeking approval for the following indication:

> Tazemetostat is an EZH2 inhibitor indicated for the treatment of adult patients with metastatic or locally advanced epithelioid sarcoma who are not eligible for curative surgery.

2 EXECUTIVE SUMMARY

Epithelioid sarcoma is a rare subtype of soft tissue sarcoma with approximately 120 cases diagnosed annually in the United States. Surgical resection is the primary method of treatment followed by radiation for patients with local disease; however, rates of locoregional recurrence following surgery and radiation are between 60% and 85%. Patients whose disease is not amenable to surgical resection are typically offered chemotherapy. A common chemotherapeutic agent used in patients with epithelioid sarcoma is doxorubicin, either alone or in combination with another chemotherapy agent. Almost 50% of patients will present with metastatic disease at the time of diagnosis (Thway 2016), which carries a reported 5-year survival rate of 0% (Pink 2014).

On May 23, 2019, Epizyme submitted New Drug Application (NDA) 211723 for tazemetostat. Epizyme requests approval based on the results of a multi-center, global, open-label, multi-cohort, non-randomized trial, EZH-202, conducted in patients with INI1-negative tumors or synovial sarcoma. Cohorts 5 and 6 of study EZH-202 enrolled patients with epithelioid sarcoma.

Cohort 5 was designed to evaluate the efficacy of tazemetostat in patients with epithelioid sarcoma, while Cohort 6 was designed to assess the pharmacodynamic effects of tazemetostat on tumor immune priming in patients with epithelioid sarcoma. Consequently, the eligibility criteria were slightly different for these two cohorts. These differences are discussed in Section 4.1 Trial Design.

Epizyme submitted data from Cohort 5 as the primary evidence of efficacy for the NDA of tazemetostat; however, Cohort 6 enrolled patients using similar eligibility criteria, yielding patients with similar baseline characteristics. Patients in both cohorts received the same dosage regimen of tazemetostat. Therefore, the pooled data from Cohorts 5 and 6 may provide an additional assessment of the efficacy of tazemetostat in this population. For this reason, results

for this pooled population are presented alongside the results from the individual cohorts.

Cohort 5 enrolled 62 patients and Cohort 6 enrolled 44 patients. Across the two cohorts, the study population was 65% male, and 78% White. The median age was 37 years (range: 16 to 79) and 58% had received at least one prior line of therapy.

Table 1 summarizes the primary efficacy results of trial EZH-202, Cohorts 5 and 6, in the intent-to-treat (ITT) population.

Table 1: **Efficacy Results as Assessed by Independent Review Study EZH-202**

	Cohort 5 N=62	**Cohort 6 N=44**	**Pooled N=106**
ORR	15%	11%	13%
(95% CI)	(7, 26)	(4, 25)	(7, 21)
CR (n, %)	1 (1.6)	1 (2)	2 (2)
PR (n, %)	8 (13)	4 (9)	12 (11)
DOR in months (range)	4, 24+	3.5, 18.2+	3.5, 24+
Median follow-up in months (range)	13.8 (0.2, 32)	11.8 (0.2, 21)	12.8 (0.2, 32)

Source: Reviewer's analysis.
Abbreviations: CI: confidence interval; CR: complete response; PR: partial response; DOR: duration of response

2.1 Major Issue for Discussion at ODAC

The key issue for discussion at ODAC is whether the observed ORR of 15% (95% CI: [7, 26]) in Cohort 5 of EZH-202 and observed ORR of 11% (95% CI: [4, 25]) in Cohort 6, with pooled ORR of 13% (95% CI: [7, 21]) observed across cohorts, and duration of response ranging from 3.5 months to 24+ months, represent sufficient benefit to outweigh the risks of tazemetostat in patients with epithelioid sarcoma.

Benefit

Although there are no therapies specifically approved for patients with epithelioid sarcoma, doxorubicin and pazopanib are both approved for the broader population of patients with soft tissue sarcoma (STS) and are administered to patients with epithelioid sarcoma. Doxorubicin was approved for STS in 1974 based on an ORR of 24% (95% CI: [19, 30]) in 234 patients. This response rate was based on summary data submitted to the FDA from nine different cancer treatment centers. Factors that limit the comparability of this data to data generated on EZH-202 include the use of different response criteria, lack of complete information regarding whether patients had received prior therapies, and exclusion of some patients who were unable to receive at least 2 doses of doxorubicin from the efficacy evaluable population, which may

have inflated the response rate. For further discussion, see Section 5.2.3 Comparison of Efficacy of Tazemetostat to Available Therapies. Pazopanib was approved in 2012 for the treatment of patients with STS after prior chemotherapy based on the results of a randomized, placebo-controlled trial that showed that pazopanib resulted in an improvement in PFS when compared to placebo with an estimated hazard ratio of 0.35 (95% CI: [0.26, 0.48]). Median PFS was 4.6 months in the treatment arm versus 1.6 months in the placebo arm. On this trial, the ORR in the pazopanib arm was 4% (95% CI: [2.3, 7.9]) with duration of response ranging from 3.9 to 9.2 months; there were no responders on the placebo arm. Although epithelioid sarcoma represents only a small portion of the overall STS population, the response rate of epithelioid sarcoma to these approved therapies, and to other therapies commonly used but not approved for patients with epithelioid sarcoma, appears similar to the broader STS patient population based on limited published data (See Section 5.2.1 Literature Review).

Targeted therapies, aimed at cancer-specific genes, proteins, or tumor environment, are a focus of cancer drug development. Effective targeted therapies generally produce high response rates, demonstrating that the drug hits the target and that the target is relevant for cancer cell survival. For example, 48% of patients with melanoma harboring a $BRAF^{V600E}$ mutation experienced a confirmed overall response to the BRAF inhibitor vemurafenib, a drug that conferred an overall survival benefit to this population in a randomized, controlled trial (Chapman, 2011).

Tazemetostat inhibits the histone methyltransferase EZH2. Epizyme postulates that tumors that have lost INI1, including most epithelioid sarcomas, are dependent on EZH2 methyltransferase activity and may be sensitive to its inhibition. In patients with epithelioid sarcoma treated with tazemetostat, the modest response rate suggests that the target may not be particularly relevant for cancer cell survival in this population. While the possibility exists that tazemetostat may still confer clinical benefit (e.g., through a delay in tumor growth), this type of benefit typically requires measurement using time-to-event endpoints (e.g., progression-free survival) which cannot reliably be assessed and interpreted in a single-arm trial.

With limited clinical experience and lack of comparative data, FDA is concerned that the ORR of 13% (95% CI: [7, 21]) observed in Cohorts 5 and 6 of EZH-202 does not provide sufficient evidence of benefit to outweigh the risks of tazemetostat in patients with epithelioid sarcoma.

Risks

Overall, FDA agrees with Epizyme that tazemetostat appears to be relatively well-tolerated. The most common (occurred in ≥20 %) adverse events (AEs) experienced by patients enrolled in Cohort 5 were pain, fatigue, nausea, decreased appetite, vomiting, and constipation. A total of 48% of patients experienced a Grade 3 or 4 adverse reaction: the most common were anemia

(13%), pain and decreased weight (7%), and three (4.8%) patients each with hemorrhage, decreased appetite, dyspnea, and pleural effusion. A total of 23 (37%) patients had a serious AE (SAE). SAEs that occurred in ≥ 2 patients were hemorrhage and pleural effusion (6.5%), dyspnea (5%), and cellulitis and pain (3.2%). There were no fatal adverse events attributable to tazemetostat. Although 34% of patients required a dose interruption for toxicity, dose reductions and discontinuations of tazemetostat for toxicity were rare.

An important risk of tazemetostat is the risk of secondary malignancies associated with its use. In the pooled safety population of 725 adults and pediatric patients with solid tumors or hematologic malignancies, 6 (0.8%) patients developed secondary myelodysplastic syndrome (MDS), acute myeloid leukemia (AML), or T-cell lymphoblastic lymphoma (T-LBL). Dedicated carcinogenicity studies were not conducted with tazemetostat, but T-LBL occurred in juvenile and adult rats after ~9 or more weeks of tazemetostat administration during 13-week toxicity studies. Based on nonclinical studies in rats, the risk of T-LBL appears to be greater with longer duration dosing. EZH2 loss-of-function mutations have been identified in patients with spontaneous MDS, T-cell acute lymphoblastic leukemia (T-ALL), and myeloproliferative neoplasms (MPNs) (Kim 2016), suggesting that the development of secondary malignancies may be an on-target effect of tazemetostat.

3 BACKGROUND

3.1 Epithelioid Sarcoma

Epithelioid sarcoma is a rare, slow-growing, malignant STS that accounts for less than 1% of all STSs (Asano 2015). The National Cancer Institute (NCI) estimates that there are 12,000 new cases of STS diagnosed annually in the United States, or approximately 120 new cases of epithelioid sarcoma per year. Epithelioid sarcoma predominately affects the subcutaneous tissue, fascia, or tendon sheaths, most commonly in the distal upper extremities (Asano 2015) and presents as a painful and tender enlarging soft tissue mass (Chase 1985) that can go undiagnosed or misdiagnosed for years. Patients are typically diagnosed between 20 to 40 years of age and there is a 2:1 male predominance (Jones 2012). There is a high propensity for locoregional spread and approximately 50% of patients are diagnosed with metastatic disease at diagnosis (Thway 2016). Patients with metastatic disease have a reported 5-year survival of 0% (Pink 2014).

There are two distinct types of epithelioid sarcoma. Classic (distal-type) epithelioid sarcoma commonly affects the distal upper extremity of adolescents and young adults. The proximal variant of epithelioid sarcoma is diagnosed less frequently, affects young to middle-aged adults and has been associated with a more aggressive clinical course. Proximal variant epithelioid

sarcomas tend to be deep, infiltrating soft-tissue masses, commonly with hemorrhage and necrosis, affecting axial proximal regions (Thway 2016).

Epithelioid sarcoma is diagnosed using histological and immunohistochemical (IHC) staining for both mesenchymal and epithelial markers. It has a distinct immunoprofile with characteristic expression of cytokeratins and epithelial membrane antigen (EMA), and approximately 50% are positive for CD34. Approximately 90% of cases of both classic and proximal types show IHC nuclear loss of INI1 (Thway 2016).

3.2 Epithelioid Sarcoma Treatment

Wide surgical excision remains the mainstay of treatment for localized disease. Neoadjuvant or adjuvant radiation therapy is often administered to reduce local relapse, but the role of adjuvant chemotherapy in this setting is unclear. Systemic chemotherapy is typically reserved for advanced stage disease.

Although there are no therapies approved specifically for patients with epithelioid sarcoma, doxorubicin and pazopanib are both approved for the broader population of patients with STS and are administered to patients with epithelioid sarcoma. In addition, doxorubicin is often given in combination with other agents, most commonly ifosfamide. Gemcitabine and docetaxel are other commonly used agents. Doxorubicin was approved for STS in 1974 based on a response rate of 24% (95% CI: [19, 30]) in 234 patients. (See 5.2.3 Comparison of Efficacy of Tazemetostat to Available Therapies for a discussion of the limitations of interpreting this data).

Pazopanib was approved in 2012 for the treatment of patients with STS after prior chemotherapy based on the results of a randomized, placebo-controlled trial that showed that pazopanib resulted in an improvement in PFS when compared to placebo with an estimated hazard ratio of 0.35 (95% CI: [0.26, 0.48]). Median PFS was 4.6 months in the treatment arm versus 1.6 months in the placebo arm.

Although epithelioid sarcoma represents only a small portion of the overall STS population, the response rate to these approved therapies, and to other therapies commonly used but not approved for patients with epithelioid sarcoma, appears similar to that observed in the broader STS patient population based on limited published data (see Section 5.2.1 Literature Review).

3.3 Tazemetostat

Tazemetostat is a first-in-class, oral, small molecule inhibitor of the methyltransferase, enhancer of zeste homolog 2 (EZH-2). The most well-characterized function of EZH2 is as the catalytic component of polycomb repressive complex 2 (PRC2), catalyzing mono-, di-, and trimethylation of lysine 27 of histone H3. Trimethylation of histone H3 H3K27 generally downregulates transcription. SWItch/Sucrose Non-Fermentable (SWI/SNF) complexes can antagonize PRC2 function in the regulation of the expression of certain genes. Preclinical in vitro and in vivo models with loss or dysfunction of certain SWI/SNF complex members (including INI1) lead to aberrant EZH2 activity or expression and a resulting oncogenic dependence on EZH2. Tazemetostat is postulated to work by reestablishing the balance between the SWI/SNF complex and PRC2 by blocking EZH2 catalytic activity; however, how this impacts cell tumor biology in epithelioid sarcoma is not fully elucidated.

The proposed dosage of tazemetostat in patients with epithelioid sarcoma is 800 mg orally twice daily with or without food, until disease progression or unacceptable toxicity.

3.3.1 Key Regulatory History for the Tazemetostat Development Program

Key pre-submission and post-submission interactions between FDA and Epizyme and issues related to the clinical development of tazemetostat are summarized in Table 2.

Table 2. Key Regulatory Activities Related to the Clinical Development of Tazemetostat

Date	Discussion
6/12/2015	**Pre-IND meeting (written response only).** The purpose of the meeting was to align on the nonclinical and clinical data to support the initiation of clinical studies in adult patients with tumors characterized by INI1-deficiency.
11/23/2015	**IND submitted.**
3/24/2015	**Sponsorship transferred to Epizyme.**
5/12/2017	**End-of-Phase 2 meeting.** Epizyme sought FDA feedback on the overall clinical development program for tazemetostat to support an NDA for the proposed indication of the treatment of epithelioid sarcoma. Key FDA comments included: • FDA did not agree with the proposed primary endpoint of disease control rate. FDA agreed that ORR may be an acceptable primary endpoint for accelerated approval if supported by an adequate characterization of durability of response. • FDA stated that ORR should be determined by blinded independent review and that an application based on this endpoint should have a minimum follow up time of 6 months from the onset of response for responding patients. • FDA agreed that a randomized, active-controlled trial to evaluate the efficacy and safety of tazemetostat for the first-line treatment of patients with epithelioid sarcoma is an appropriate design. If claims will be sought in a treatment-refractory population, a randomized, placebo-controlled trial or a trial employing

	physician's choice of best alternative therapy also could be acceptable. In either scenario, the trial should be designed to demonstrate an improvement in overall survival or a treatment effect on PFS that is large in magnitude such that it can be considered direct evidence of clinical benefit. • FDA agreed that evaluation of databases among cooperative groups and centers of excellence may provide greater insight on the natural history and response to therapy of epithelioid sarcoma. However, FDA cautioned that comparisons of time-to-event endpoints against an historical population are challenging because of difficulties in ensuring matching for known and unknown prognostic factors, which may confound the assessment of observed differences.
6/15/2017	**Orphan Designation granted** for soft tissue sarcoma.
11/21/2017	**Fast Track Designation granted** for the treatment of patients with metastatic or locally advanced epithelioid sarcoma who have progressed on or following an anthracycline-based regimen.
4/19/2018	**Partial Clinical Hold.** New patient enrollment was halted for all clinical trials of tazemetostat due to a reported serious adverse event of second primary malignancy (T-cell lymphoblastic lymphoma).
9/21/2018	**Removal of Partial Clinical Hold.** The partial hold was removed by the FDA after Epizyme modified the informed consent document to describe the risk of secondary malignancies and modified the clinical trial protocols to incorporate additional risk mitigation processes.
1/14/2019	**Administrative pre-NDA meeting.** Gained alignment on the format and content for the proposed NDA submission. FDA stated that the ORR of 13% (95% CI: 6%, 24%) observed to date may be insufficient to serve as evidence of a treatment effect that is reasonably likely to predict clinical benefit in patients with locally advanced or metastatic epithelioid sarcoma. FDA recommend that Epizyme include information regarding the natural history of patients with epithelioid sarcoma, and an analysis of the effectiveness of available therapies in a comparable patient population.
4/29/2019	**Pre-NDA meeting.** FDA stated that the observed ORR of 15% (95% CI: [7, 26]) in Cohort 5 does not appear better than available therapy for patients who are eligible for doxorubicin or pazopanib. FDA did not agree with Epizyme's proposal to use their natural history study in patients with epithelioid sarcoma as a comparator arm to support regular approval.
5/23/2019	**NDA 211723 Submission.** Epizyme requested approval under 21 CFR 314, subpart H for tazemetostat 800 mg BID based on the results of EZH-202 Cohort 5 showing an ORR of 15% (95% CI: [7, 26]) in patients with epithelioid sarcoma.
7/18/2019	**NDA 211723 Review Designation.** FDA designated the review of the application a priority review.

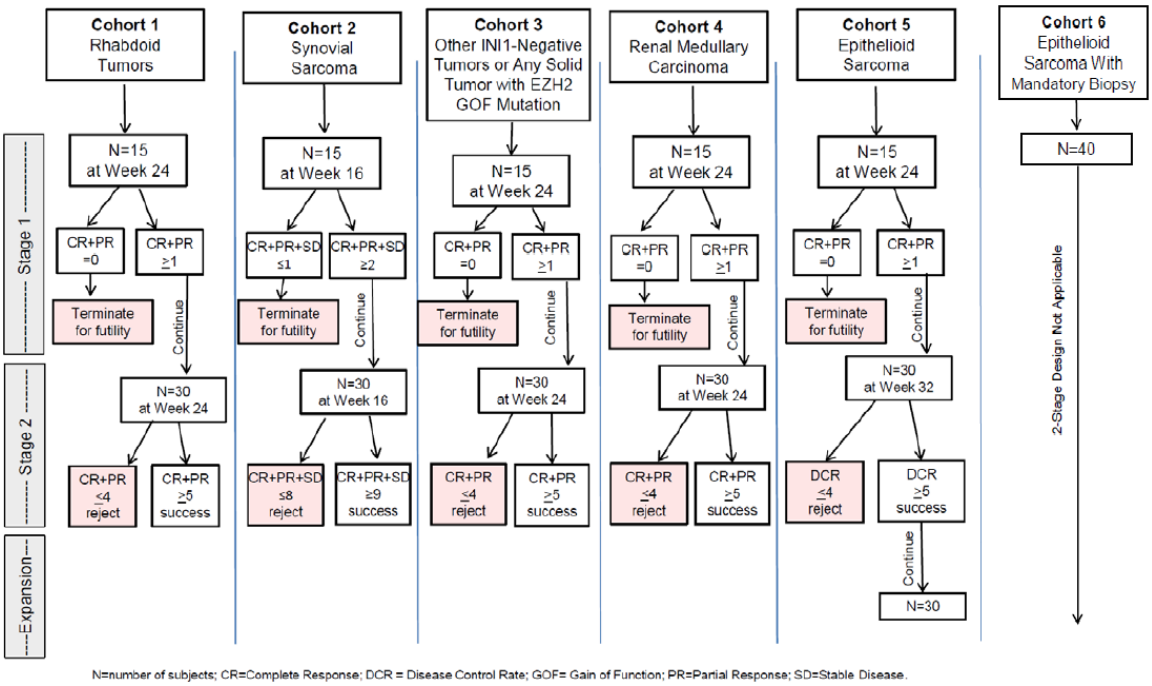
4 CLINICAL STUDIES TO SUPPORT EFFICACY AND SAFETY

4.1 Trial Design

4.1.1 Overview

The assessment of clinical efficacy of tazemetostat in patients with epithelioid sarcoma is based on Cohort 5 with supportive data from Cohort 6 of the EZH-202 trial. Study EZH-202 is an ongoing, multi-center, global, open-label, multi-cohort, non-randomized trial in patients with INI1-negative tumors or relapsed/refractory synovial sarcoma. Figure 1 presents the study schema from EZH-202 Cohorts 5 and 6.

Figure 1: Study Schema of Study EZH-202



Source: Adapted from Figure 2 of Protocol EZH-202 version 4, pg. 38 and Figure 2 of Protocol EZH-202 version 5, pg. 41.

The primary efficacy outcome measure in Cohort 5 was confirmed ORR as assessed by independent review committee (IRC) according to the Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 (Eisenhauer et. al, 2009). As the primary objective of Cohort 6 was to assess the effects of tumor immune priming following administration of tazemetostat, the primary endpoint was not ORR. However, evaluation of confirmed ORR in Cohort 6 was specified in the protocol as a secondary objective in EZH-202. Duration of response was specified as a secondary endpoint for both Cohorts 5 and 6.

Patients received tazemetostat 800 mg orally BID in continuous 28-days cycles for 2 years or until disease progression or unacceptable toxicity.

4.1.2 Study Population

Both Cohorts 5 and 6 enrolled patients with epithelioid sarcoma. Inclusion criteria common to both cohorts included age (at the time of consent) ≥ 18 years (this was amended from age ≥16), Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2, and a life expectancy of >3 months. Table 1 outlines all differences in inclusion criteria between Cohorts 5 and 6.

Table 1: Differences in Inclusion Criteria between Cohorts 5 and 6 Study EZH-202

Cohort 5	Cohort 6
Morphology and immunophenotypic panel consistent with INI1-negative tumors, and • Loss of INI1 confirmed by IHC, or • Molecular confirmation of tumor bi-allelic INI1 loss or mutation when INI1 IHC is equivocal or unavailable, or • Molecular evidence of EZH2 gain of function mutation	Morphology and immunophenotypic panel consistent with epithelioid sarcoma (e.g., CD34, EMA, Keratin, and INI1)
Mandatory biopsy not required	Willingness to provide informed consent to undergo pre- and post-dose biopsy
Progressed within 6 months prior to study enrollment (only for Cohort 5 Expansion, n=30)	Progressed within 6 months prior to study enrollment

Source: Adapted from pg. 43 of Protocol EZH-202, amendment 6.

4.1.3 Efficacy and Safety Assessments

Tumor response assessments were conducted at screening and then every other cycle beginning at Cycle 3 by CT or MRI according to RECIST v1.1. The severity of all AEs and SAEs, including appropriate laboratory values, were graded utilizing the CTCAE v4.03.

4.1.4 Statistical Analysis Plan

Cohort 5 was designed using a Green-Dahlberg two-stage design (referred to hereafter as the "original phase") plus an expansion phase. In the original phase, 30 patients with epithelioid sarcoma were needed to have 80% power to detect an ORR of 20% versus 5%. The trial was planned to stop for futility if 0 of the first 15 patients had a response. In the expansion phase, an additional 30 patients would be added if 5 or more patients in the original phase experienced disease control. In this trial, a patient was said to experience disease control if they achieved SD for 32 weeks or longer, or a partial response (PR) or complete response (CR).

As ORR was not a primary endpoint for Cohort 6, the Statistical Analysis Plan did not provide a hypothesis or power calculations for this cohort.

4.1.5 Major Protocol Amendments

Protocol Amendment 3, dated March 2, 2016, added Cohort 5. Patients with epithelioid sarcoma that had originally been enrolled in Cohort 3 (n=6) were moved to Cohort 5. The original planned enrollment for Cohort 5 was 30 patients (original phase).

Protocol Amendment 4, dated October 25, 2016, added the potential for a Cohort 5 expansion. An additional 30 patients with epithelioid sarcoma were allowed to enroll (expansion phase) if the expansion criteria were met. In addition, the primary endpoint was changed from ORR to disease control rate (DCR), defined as the number of patients with a confirmed response (CR or PR) or who had SD lasting at least 32 weeks. ORR was changed to a secondary endpoint.

Protocol Amendment 5, dated August 7, 2017, added Cohort 6 which would enroll up to 40 patients with epithelioid sarcoma willing and able to undergo a mandatory tumor biopsy. Cohort 6 was added to assess the effects of tazemetostat on pharmacodynamic markers. Patients in Cohort 6 were enrolled regardless of INI1 status. Additionally, the primary endpoint for Cohort 5 was changed back to ORR with duration of response (DOR) in responding subjects being the key secondary endpoint.

Protocol Amendment 6, dated September 28, 2018, added the additional risk mitigation and monitoring regarding the risk of occurrence of secondary malignancies in patients taking tazemetostat.

4.2 Results

4.2.1 Study Population

In the pre-NDA meeting dated April 29, 2019, FDA agreed with Epizyme's proposal that Cohort 5 of EZH-202 could serve as the primary population for an evaluation of efficacy. However, FDA also requested that Epizyme submit supplemental efficacy data from Cohort 6 to aid in the review and to serve as a replication of results. Efficacy and safety data were initially submitted to the NDA for Cohorts 5 and 6 on May 23, 2019, with a data cut-off date of September 17, 2018. Upon receipt of the data from Cohort 6, FDA noted that the ORR for cohort 6 was 5% (95% CI: [0, 16]). FDA acknowledged that the duration of follow-up for patients in Cohort 6 was shorter than that of Cohort 5, and thus requested that Epizyme submit updated efficacy data from Cohort

6 with the 90-day safety update. The new data cut-off date for Cohort 6 was July 31, 2019, which provided an additional 10 months of follow-up. This updated data cut-off date resulted in a similar time of follow-up for patients in Cohort 5 (original submission) and Cohort 6 (updated submission). In the analyses that follows, a cut-off date of September 17, 2018 is used for Cohort 5 and a cut-off date of July 31, 2019 is used for Cohort 6.

4.2.1.1 Patient Disposition

Table 2 displays the patient disposition in the analysis population of EZH-202 at the time of data cut-off for the respective cohorts.

Table 2: Patient Disposition in the Analysis Population Study EZH-202

	Cohort 5 N=62 n (%)	**Cohort 6 N=44 n (%)**	**Pooled Data N=106 n (%)**
End of treatment status			
Ongoing	8 (13)	8 (18)	16 (15)
Discontinued	54 (87)	36 (82)	90 (85)
End of study status			
Ongoing	11 (18)	10 (23)	21 (20)
Alive	15 (24)	11 (25)	26 (25)
Discontinued	36 (58)	23 (52)	59 (56)
Reason for treatment discontinuation			
Ongoing	8 (13)	8 (18)	16 (15)
Death	4 (6)	1 (2.3)	5 (5)
Non-Compliance	0 (0)	1 (2.3)	1 (0.9)
Other	1 (1.6)	0 (0)	1 (0.9)
Physician Decision	1 (1.6)	0 (0)	1 (0.9)
Progressive Disease - Clinical	6 (10)	6 (14)	12 (11)
Progressive Disease - Radiologic	39 (63)	27 (61)	66 (62)
Subject Refused Further Treatment of Study Drug	2 (3.2)	1 (2)	3 (2.8)
Unacceptable Toxicity	1 (1.6)	0 (0)	1 (0.9)
Reason for study discontinuation			
Ongoing	26 (42)	21 (48)	47 (44)

	Cohort 5 N=62 n (%)	Cohort 6 N=44 n (%)	Pooled Data N=106 n (%)
Completion of 2 Years of Treatment or Post-Treatment Follow-Up	1 (1.6)	0 (0)	1 (0.9)
Death	31 (50)	20 (45)	51 (48)
Lost to Follow-Up	4 (6)	1 (2.3)	5 (5)
Withdrawal by Subject	0 (0)	2 (5)	2 (1.9)

Source: Reviewer's analysis.

4.2.1.2 Demographic and Baseline Characteristics

Overall, the demographics and baseline characteristics for Cohorts 5 and 6 were similar. Most patients were male, White, not Hispanic, and had an ECOG performance status of 0. In Cohort 5, 65% of patients were from the U.S., and 39% were from the U.S. in Cohort 6; 42% of patients across cohorts were treatment-naïve. Tables 3 and 4 present the demographics and baseline characteristics for both cohorts and the pooled data.

Table 3: Demographics of Patients in the Analysis Populations of Cohorts 5 and 6 Study EZH-202

	Cohort 5 N=62 n (%)	Cohort 6 N=44 n (%)	Pooled Data N=106 n (%)
Gender			
Female	23 (37)	18 (41)	41 (39)
Male	39 (63)	26 (59)	65 (61)
Age			
Mean years (SD)	37 (15)	38 (13)	37 (14)
ECOG performance status			
0	36 (58)	28 (64)	64 (60)
1	21 (34)	14 (32)	35 (33)
2	5 (8)	2 (4.5)	7 (7)
Race			
Black or African American	4 (6)	1 (2.3)	5 (4.7)
Asian	7 (11)	4 (9)	11 (10)
White	47 (76)	36 (82)	83 (78)

	Cohort 5 N=62 n (%)	Cohort 6 N=44 n (%)	Pooled Data N=106 n (%)
Other/Unknown	4 (6)	3 (7)	7 (7)
Ethnicity			
Not Hispanic or Latino	53 (85)	39 (89)	92 (87)
Hispanic or Latino	7 (11)	4 (9)	11 (10)
Not reported	2 (3.2)	1 (2.3)	3 (2.8)
Country			
France	4 (6)	2 (4.5)	6 (6)
Canada	2 (3.2)	2 (4.5)	4 (3.8)
United States	40 (65)	17 (39)	57 (54)
Taiwan	3 (4.8)	3 (7)	6 (6)
Italy	6 (10)	3 (7)	9 (8)
Great Britain	2 (3.2)	9 (20)	11 (10)
Belgium	5 (8)	3 (7)	8 (8)
Australia	0	2 (4.5)	2 (1.9)
Germany	0	3 (7)	3 (2.8)

Source: Reviewer's analysis

Table 4: Baseline Characteristics of the Analysis Population Study EZH-202

	Cohort 5 N=62	Cohort 6 N=44	Pooled Data N=106
Epithelioid sarcoma subtype (%)			
Not collected	0 (0)	44 (100)	44 (42)
Conventional	31 (50)	0 (0)	31 (29)
Missing	4 (6)	0 (0)	4 (3.8)
Proximal	27 (44)	0 (0)	27 (25)
Stage of disease at diagnosis (%)			
I/II	9 (15)	11 (25)	20 (19)
III/IV	44 (71)	31 (70)	75 (71)
Unknown	9 (15)	2 (4.5)	11 (10)
Number of lines of prior therapy (%)			
0	24 (39)	20 (45)	44 (42)
1+	38 (61)	24 (55)	62 (58)

	Cohort 5 N=62	Cohort 6 N=44	Pooled Data N=106
Most common prior therapies received[1] (%)			
Doxorubicin	28 (45)	19 (43)	47 (44)
Ifosfamide	26 (42)	18 (41)	44 (42)
Gemcitabine	15 (24)	7 (16)	22 (21)
Pazopanib	12 (19)	8 (18)	20 (19)
Docetaxel	13 (21)	6 (14)	19 (18)
Time to last progressive disease (mean (sd)) (months)	2.2 (2.6)	1.7 (1.2)	2.0 (2.2)
Tumor location (%)			
Soft Tissue	21 (34)	17 (39)	38 (36)
Other	41 (66)	27 (61)	68 (64)

Source: Reviewer's analysis.
[1] Patients may have received more than one prior therapy. This list is not exhaustive.

4.2.2 Efficacy Results

The primary population Epizyme submitted for efficacy was from Cohort 5 and consists of 62 patients with epithelioid sarcoma. Supportive efficacy data is presented from Cohort 6 which consisted of an additional 44 patients with epithelioid sarcoma. Efficacy analysis is presented for each cohort separately and pooled. ORR as assessed by RECIST v1.1 was the primary endpoint for Cohort 5 and was used by the FDA as the primary efficacy endpoint for Cohort 6.

In Cohorts 5 and 6, the ORR was similar at 15% and 11%, respectively. Pooled analysis demonstrated an ORR of 13% (95% CI: [7, 21]). The median follow-up time was similar across cohorts. Table 5 presents the analysis of confirmed ORR and DOR as assessed by IRC in the analysis population.

Table 5: Analysis of Confirmed ORR and DOR as Assessed by IRC in the Analysis Population Study EZH-202

	Cohort 5 N=62	Cohort 6 N=44	Pooled Data N=106
ORR	15%	11%	13%
(95% CI)	(7, 26)	(4, 25)	(7, 21)
CR (n, %)	1 (1.6)	1 (2)	2 (2)
PR (n, %)	8 (13)	4 (9)	12 (11)
DOR in months (range)	4, 24+	3.5, 18.2+	3.5, 24+

	Cohort 5 N=62	Cohort 6 N=44	Pooled Data N=106
Median follow-up in months (range)	13.8 (0.2, 32)	11.8 (0.2, 21)	12.8 (0.2, 32)

Source: Reviewer's analysis.
Abbreviations: ORR: overall response rate; CI: confidence interval; CR: complete response; PR: partial response; DOR: duration of response

The pooled DOR ranged from 3.5 months to more than 24 months; DOR was similar across cohorts. A total of seven patients had ongoing responses at the time of the data cut-offs for Cohorts 5 and 6 and were censored, including the patient with a response lasting 24 months. Nine of 14 (64%) responding patients had responses that lasted for 6 months or longer, with 4 patients responding for 12 months or longer. Table 6 shows DOR by landmark time for Cohorts 5 and 6.

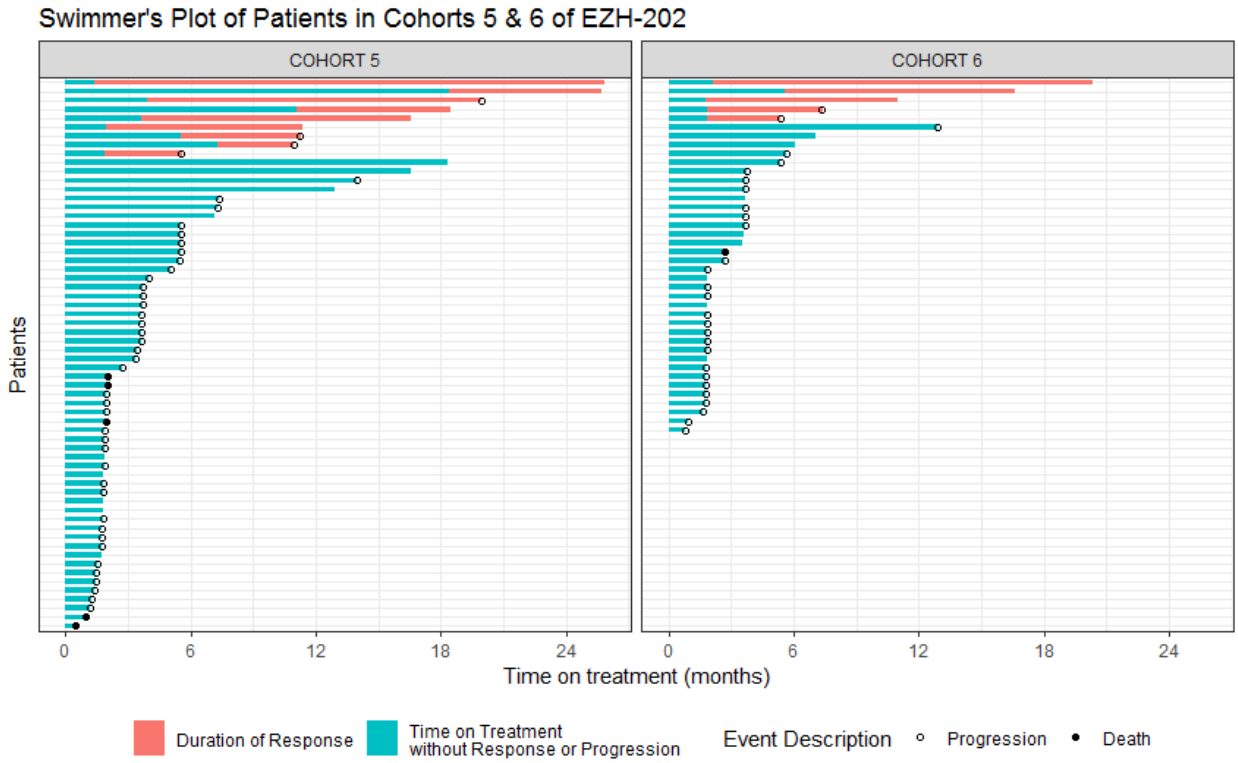
Table 6: Duration of Response by Landmark Time in the Analysis Population Study EZH-202

Responders	Cohort 5 N=9	Cohort 6 N=5	Pooled Data N=14
n with DOR			
≥ 3 months	9	5	14
≥ 6 months	6	3	9
≥ 9 months	4	3	7
≥ 12 months	3	1	4

Source: Reviewer's analysis.

Figure 2 shows a swimmer's plot of patients in the analysis population of EZH-202.

Figure 2: Swimmer's Plot of Patients in the Analysis Population Study EZH-202



Source: Reviewer's analysis.

4.2.2.1 Disease Burden at Baseline

The criteria for response as specified by RECIST v1.1 (Eisenhauer et. al, 2009) require a decrease in tumor size, as measured by the percentage change from baseline of a sum of diameters (longest for non-nodal lesions, short axis for nodal lesions) of all target lesions. Up to 5 lesions are selected as target lesions. Patients enrolled in Cohorts 5 and 6 were required to have measurable disease at baseline. All patients underwent radiographic assessments to document disease burden at baseline and every eight weeks throughout treatment. One measure of disease burden is this sum of diameters of the target lesions. Whether a tumor response alone, in the absence of other supportive data such as patient-reported outcomes, can be considered benefit may depend, in part, on the magnitude of the disease burden prior to receiving therapy and the clinical impact of any reduction in tumor size.

FDA conducted an exploratory analysis of baseline measured disease burden and reduction in measured disease burden to provide a more detailed picture of the responses observed on EZH-202. Tables 7 and 8 summarize the length of all target lesions as assessed by IRC across Cohorts 5 and 6 which included a maximum of two lesions per organ and five lesions total.

Table 7 summarizes the length of the shortest diameter for target lesions at baseline which were lymph nodes, and Table 8 summarizes the length of the longest diameter for target lesions at baseline which were not lymph nodes. Across the two cohorts, all nodal lesions were ≤5 cm, and 81% of non-nodal lesions had a longest diameter of ≤5 cm.

Table 7: Shortest Diameter per IRC of Lymph Node Target Lesions at Baseline for Patients in Cohorts 5 and 6 Study EZH-202

	Cohort 5 N=40	Cohort 6 N=24	Pooled Data N=64
Median shortest diameter in cm (range)	2.0 (1.5, 5.0)	2.1 (1.5, 3.6)	2.0 (1.5, 5.0)

Source: Reviewer's analysis.

Table 8: Longest Diameter per IRC of Non-Lymph Node Target Lesions at Baseline for Patients in Cohorts 5 and 6 Study EZH-202

	Cohort 5 N=90	Cohort 6 N=78	Pooled Data N=168
Median longest diameter in cm (range)	2.5 (1.0, 11.6)	2.4 (1.0, 9.5)	2.4 (1.0, 11.6)
Longest diameter in cm (%)			
1-5 cm	75 (83)	66 (85)	141 (84)
5-10 cm	12 (13)	12 (15)	24 (14)
>10+ cm	3 (3.3)	0 (0.0)	3 (1.8)

Source: Reviewer's analysis.

Most patients had 2 target lesions at baseline (31%), followed by 1 lesion (17%) or 4 lesions (17%); 10% of patients were deemed to not have measurable target lesions at baseline or were not assessed by the IRC at the time of the data cut-off. A patient's total disease burden; however, includes additional non-target lesions. Most patients had either 1 non-target lesion (28%) or 2 non-target lesions (34%). In addition, most patients had a total of 5 or fewer lesions total at baseline (74%), with the maximum being 10 lesions in total.

4.2.2.2 Reduction in Disease Burden in Responders

Table 9 presents the reduction in sum of diameters as defined by RECIST v1.1 for the responders in Cohorts 5 and 6 of Study EZH-202. In the table below, "nadir" refers to the smallest sum of diameters observed at or after the initial response and prior to progression or censoring.

Table 9: Reduction in Sum of Diameters for Responders in Cohorts 5 and 6 Study EZH-202

Subject[1]	Cohort	Sum of Diameters at Baseline (cm)	Sum of Diameters at Nadir (cm)	Change from Baseline (cm)	% Change from Baseline
1	Cohort 6	1.53	0.5	-1.03	-67.3
2	Cohort 6	2.11	1.18	-0.93	-44
3	Cohort 6	2.25	0	-2.25	-100
4	Cohort 5	2.9	2.01	-0.89	-30.7
5	Cohort 5	4.42	2	-2.42	-54.6
6	Cohort 5	4.56	1.66	-2.9	-63.7
7	Cohort 5	4.78	3.16	-1.62	-33.9
8	Cohort 5	5.2	0.5	-4.7	-90.4
9	Cohort 6	6.64	1.44	-5.2	-78.4
10	Cohort 5	7.62	1.89	-5.73	-75.1
11	Cohort 5	10.6	3.01	-7.59	-71.6
12	Cohort 5	10.64	3.26	-7.38	-69.3
13	Cohort 6	17.17	10.2	-6.97	-40.6
14	Cohort 5	19.45	1.73	-17.72	-91.1

Source: Reviewer's analysis.
[1] Subjects are presented in order of sum of diameters at baseline, from smallest to largest.

An important limitation of this analysis is that not all of each patient's burden of disease was measured at baseline or followed for response. Further, the clinical impact of a tumor's size is likely to vary by its precise anatomical site. It is thus difficult to interpret the clinical impact of tumor shrinkage for many of the responding patients, most of whom had individual tumors ≤ 5 cm in the longest diameter at baseline and modest absolute reductions in the sum of diameters.

4.2.3 Safety Results

FDA based the primary evaluation of safety on data from Cohort 5 using a data cut-off date of September 17, 2018. A total of 62 patients with epithelioid sarcoma received at least one dose of tazemetostat at the target dose and were evaluated for safety. The evaluation of safety focused on review of adverse events, laboratory assessments, patient narratives, case report forms, and nonclinical toxicology findings. Below is a brief overview of the safety data from Cohort 5. Safety data from Cohort 6 were also analyzed and showed similar findings; for brevity, these results are not shown in this briefing package.

Overall Safety

Table 10 provides an overall summary of safety of tazemetostat in Cohort 5. Demographic and baseline characteristics were the same as for the efficacy population. All patients experienced at least one treatment-emergent AE (TEAE). There were no deaths attributed to an AE, and there were few AEs that led to dose modifications or discontinuations.

Table 10: **Summary of Safety Cohort 5 Study EZH-202**

	Cohort 5 N = 62 n (%)
All-Grade TEAEs	62 (100)
Grade 3-4 TEAEs	30 (48)
Grade 5 (Deaths due to TEAEs)	0
Serious TEAEs	23 (37)
Treatment Discontinuation due to TEAEs	1 (1.6)
Dose interruption due to TEAEs	21 (34)
Dose reduction due to TEAEs	1 (1.6)

Source: Reviewer generated table from ADSL and ADAE datasets submitted by the Applicant
Abbreviations: TEAE: treatment-emergent adverse event

4.2.3.1 Duration of Exposure

The median duration of exposure to tazemetostat was 5.5 months (range 0.5 to 28). Among patients receiving tazemetostat, 44% were exposed for 6 months or longer and 24% were exposed for greater than 1 year (some patients continued to receive tazemetostat after progression).

4.2.3.2 Most Common Adverse Events

Table 11 displays the most common adverse reactions observed in Cohort 5. The most common (occurred in ≥ 20 %) were pain, fatigue, nausea, decreased appetite, vomiting, and constipation.

Table 11. Most Common Adverse Reaction Occurring in ≥10% Patients Study EZH-202

	Cohort 5 N = 62 n (%)		
	All Grades	**Grade 3**	**Grade 4**
Patients with TEAEs	62 (100)	29 (47)	2 (3.2)
Pain[a]	32 (52)	4 (6.5)	0
Fatigue[b]	29 (47)	1 (1.6)	0
Nausea	22 (35)	0	0
Decreased appetite	16 (26)	3 (5)	0
Vomiting	15 (24)	0	0
Constipation	13 (21)	0	0
Hemorrhage[c]	11 (18)	1 (1.6)	2 (3.2)
Dyspnea[d]	10 (16)	3 (5)	0
Cough	11 (18)	0	0
Headache	11 (18)	0	0
Anemia	10 (16)	8 (13)	0
Decreased weight	10 (16)	4 (6)	0
Diarrhea	10 (16)	0	0
Abdominal pain[e]	8 (13)	1 (1.6)	0
Pleural effusion	6 (10)	3 (5)	0
Peripheral edema	6 (10)	0	0
Dysgeusia	6 (10)	0	0
Hypertension	6 (10)	2 (3.2)	0

Source: Reviewer generated table from ADSL and ADAE datasets provided by the Applicant

[a]Group pain includes PT terms tumor pain, pain in extremity, non-cardiac chest pain, flank pain, back pain, arthalgia, bone pain, cancer pain, musculoskeletal pain, myalgia, and neck pain

[b]Group fatigue includes PT terms fatigue, and asthenia

[c]Group hemorrhage includes PT terms pulmonary hemorrhage, wound hemorrhage, rectal hemorrhage ,hemorrhage intracranial, cerebral hemorrhage, and hemoptysis

[d]Group dyspnea includes PT terms dyspnea, and dyspnea exertional

[e]Group abdominal pain includes PT terms abdominal pain, abdominal pain lower, and gastrointestinal paiz

4.2.3.3 Significant Adverse Events

There were 30 patients who experienced a Grade 3 or 4 adverse reaction. The most common were anemia (13%), pain and decreased weight (7%), and three (4.8%) patients each with hemorrhage, decreased appetite, dyspnea, and pleural effusion. A total of 23 (37%) patients had a serious adverse event (SAE). The majority of SAEs occurred in only one patient. SAEs

that occurred in ≥2 patients were hemoptysis (6.5%), pleural effusion (4.8%), and skin infection, respiratory distress, dyspnea, and pain (3.2%).

4.2.3.4 Deaths

There were seven deaths within 30 days of the last dose of tazemetostat. All deaths were attributed to disease progression.

4.2.3.5 Dose Modifications

Overall, there were few dose modifications due to adverse reactions. One patient each experienced study drug discontinuation and dose reduction due to the adverse reactions of mood alteration and decreased appetite, respectively. A total of 21 patients had a dose interruption. The most common AEs that led to dose interruption were hemoptysis (2.3%), increased ALT (3.2%) and increased AST (3.2%).

4.2.3.6 Analysis of Secondary Malignancies

The Applicant states that T-cell lymphoblastic lymphoma (T-LBL)/T-ALL, MDS, MPN, and acute myeloid leukemia (AML) are considered adverse events of special intertest (AESI) for tazemetostat based on non-clinical and clinical data.

Non-toxicology Data

Good Laboratory Practice (GLP) toxicology studies were conducted in repeat-dose rat and monkey studies. In the 13-week rat study, T-LBL was observed in the thymus of adolescent rats at 300 and 600 mg/kg/day. There were multiple premature deaths at the mid-dose of 300 mg/kg/day due to the occurrence of T-LBL. T-LBL was observed in 11 of 40 rats dosed at 300 mg/kg/day and in 1 of 40 rats dosed at 600 mg/kg/day.

In the 13-week juvenile rat study, T-LBL was observed in the thymus of rats treated with 50 (females only), 100, 150/300, and 150/600 mg/kg/day. The first instance of T-LBL was observed after approximately 11 weeks of dosing, a timeframe similar to that observed in the previous 13-week study in 8-week-old rats. Lymphoma was observed in premature deaths, at the primary necropsy after 13-weeks daily dosing, and at the recovery necropsy following a 4-week off-dosing period.

In 4- and 13-week monkey toxicology studies, at 300 mg/kg/day and above, lymphoid depletion that was dose dependent in incidence and severity was observed, with only minimal effects at 300 mg/kg/day. In the 13-week study, key findings at 300 and 600 mg/kg/day included dose-dependent lymphoid depletion in the spleen, lymph nodes, and thymus. T-LBL was not observed in monkeys in the 4- or 13-week studies.

To understand the relationship of the T-LBL observations to EZH2 inhibition, two additional 13-week rat repeat-dose toxicity studies were conducted with two structurally similar, but chemically distinct EZH2 inhibitors. As with tazemetostat, both EZH2 inhibitors caused T-LBL in 13-week rat studies.

The exact mechanism by which tazemetostat can lead to secondary malignancies is unclear but appears to be linked to EZH2. EZH2 is expressed in a wide range of T-cell neoplasms. Both gain-of-function and loss-of-function mutations in EZH2 have been found in several tumor types.

Clinical Data

Across the overall development program, 6 (0.8%) of 725 patients developed a secondary malignancy as of May 24, 2019. Table 12 displays the secondary malignancies that occurred throughout the development program for tazemetostat. Four patients had a prior history of lymphoma and two had a solid tumor. Of the six patients who experienced a secondary malignancy, five received prior treatment with chemotherapy. Prior to the onset of the secondary malignancy, patients had received tazemetostat from 14 months to more than 4 years. There were no cases of secondary malignancies in the epithelioid sarcoma population.

Table 12. Secondary Malignancies in Patients Receiving Tazemetostat

Age (y) /Sex	Initial Diagnosis	Prior Radiation	Prior Systemic Therapy	Secondary malignancy	Dose of Tazemetostat
61, male	Follicular lymphoma	Yes	6 chemotherapy regimens including doxorubicin, cyclophosphamide, and etoposide. Also underwent stem cell transplant	MDS*	800 mg BID
69, male	DLBCL	No	2 chemotherapy regimens including doxorubicin and cyclophosphamide	MDS	800 mg BID
9, female	Chordoma	Yes	doxorubicin, ifosfamide, pazopanib	T-LBL	900 mg/m^2 BID
57, male	Rhabdoid sarcoma	Yes	No	AML	800 mg BID
68, male	Follicular lymphoma	No	2 prior regimens included chlorambucil, cyclophosphamide, doxorubicin, rituximab, vincristine	AML	800 mg BID (dose reduced to 600 mg BID)
76, male	DLBCL	No	Rituximab,	AML	800 mg BID

Age (y) /Sex	Initial Diagnosis	Prior Radiation	Prior Systemic Therapy	Secondary malignancy	Dose of Tazemetostat
			cyclophosphamide, doxorubicin, prednisone, VCR, carboplatin, cytarabine, dexamethasone		

Source: Reviewer generated based on based on data provided by Applicant in Clinical Summary of Safety
*This patients progressed to AML
Abbreviations: MDS: myelodysplastic syndrome; BID: twice daily; T-LBL: T-cell lymphoblastic lymphoma; AML: acute myeloid leukemia; DLBCL: diffuse large B-cell lymphoma; VCR: vincristine.

Although confounded by the fact that most of the patients who developed secondary malignancies had also received prior therapy with agents known to cause secondary malignancies, the overall clinical and nonclinical data appear to demonstrate an association between tazemetostat and development of secondary malignancies.

4.2.3.7 Safety Summary

Tazemetostat was generally well tolerated with the most common adverse drug reactions being gastrointestinal disturbances, fatigue, and pain. There were no deaths attributed to an AE. While 34% of patients required a dose interruption for toxicity, dose modifications and discontinuations were minimal. An important identified risk of tazemetostat is the risk of secondary malignancies.

On September 19, 2019, Epizyme submitted a 120-day safety update with a cut-off date of May 24, 2019. Review of the safety update did not reveal notable changes in the incidence or severity of adverse events in Cohort 5 or across the development program. However, there was one new case of myelodysplastic syndrome (MDS) reported. Review of safety data from Cohort 6 revealed similar findings to that of Cohort 5 and across the development program for tazemetostat.

5 FDA INTERPRETATION OF EFFICACY DATA

5.1 Epithelioid Sarcoma is a Rare Disease

STS represents only 1% of all cancers and encompasses over 50 different histological subtypes, which may be biologically unique. Epithelioid sarcoma is a rare subtype of STS with approximately 150 cases diagnosed annually in the United States.

5.2 Analysis of Standard Therapy for Epithelioid Sarcoma

Particularly in rare diseases, there is frequently limited information in the literature, lack of in-depth epidemiological or historical data, and little or no experience with other drugs to inform the interpretation of intermediate clinical endpoints such as ORR. FDA thus used a multi-pronged approach to its analysis of available therapies for epithelioid sarcoma. First, FDA conducted a literature review to determine whether patients with epithelioid sarcoma respond to standardly administered therapies in a manner similar to patients with other, non-epithelioid sarcoma forms of STS. Second, FDA reviewed Epizyme's natural history study to determine whether it could be used to (a) inform that same question, or (b) serve as a 'real world control arm' for EZH-202. Finally, FDA compared the data obtained from EZH-202 in patients with epithelioid sarcoma to public summaries of data used to support the approvals of doxorubicin and pazopanib in STS. Due to limitations in the 1974 doxorubicin approval package that preclude a reliable comparison with the tazemetostat data, FDA augmented this analysis by summarizing literature reports of the activity of doxorubicin in patients with STS.

5.2.1 Literature Review of Response to Standard Therapies in Epithelioid Sarcoma

FDA and the Applicant conducted separate reviews of the literature to identify studies that evaluated the effectiveness of standard of care therapies for the treatment of epithelioid sarcoma. The available data retrieved was limited and consisted of small, retrospective case studies in patients with epithelioid sarcoma. The majority of studies were in patients with advanced disease receiving systemic chemotherapy as first-line therapy. Pink, et al (2014) conducted a retrospective analysis of data from three clinical sites. A total of 13 patients with advanced epithelioid sarcoma were treated with an anthracycline with or without ifosfamide between 1989 and 2012. There were no objective responses. In another retrospective analysis conducted by Jones, et al (2012) a total of 19 patients with advanced or metastatic epithelioid sarcoma were treated between 1990 and 2009. The ORR was 20% in patients who received an anthracycline and 11% in patients who received anthracycline in combination with ifosfamide. Touati, et al (2018) reported on 24 patients with inoperable or metastatic epithelioid sarcoma. The ORR with doxorubicin alone was 0%, doxorubicin in combination with ifosfamide 13%, pazopanib 27%. Lastly, Frezza, et al (2018) conducted a retrospective case series of 85 patients with locally advanced or metastatic epithelioid sarcoma treated between 1990 and 2016 who received anthracycline-based chemotherapy, pazopanib or gemcitabine. The ORR to these agents were 22%, 0%, and 27%, respectively. Data regarding duration of response was limited or not reported in any of these analyses. Table 13 provides a summary of the treatment and response rates for patients with epithelioid sarcoma treated with standard therapies.

Table 13 Results from the Literature of Response Rate in Patients with Epithelioid Sarcoma Treated with Available Therapies

Reference/Agent	Number of Patients With Epithelioid Sarcoma	Response Rate % (95% CI)
Tazemetostat	106	13 (7, 21)
Pink, et al (2014)[1]		
Anthracycline +/-Ifosfamide	13	0 (0, 25)
Jones, et al (2012)[2]		
Anthracycline + Ifosfamide	9	11 (0, 48)
Anthracycline	10	20 (3, 56)
Touati, et al (2018)[3]		
Doxorubicin[4]	5	0 (0, 52)
Doxorubicin[4] + Ifosfamide	8	13 (0, 53)
Pazopanib[5]	11	27 (6, 61)
Frezza, et al (2018)[3]		
Pazopanib	18	0 (0, 19)
Anthracycline-based	85	22 (14, 33)
Gemcitabine	41	27 (14, 43)

Source: FDA review of the literature
[1] Response assessed by WHO criteria and RECIST criteria
[2] Response assessed by RECIST criteria
[3] Response assessed by RECIST 1.1
[4] Received as first-line treatment
[5] Two patients received as first-line; nine as second-line

From the data presented in Table 13, some patients with epithelioid sarcoma appear to respond to standardly administered therapies, with reported response rates ranging from 0 to 27%. Overall, the data reported in the literature is limited and retrospective in nature, as there have been no prospective trials conducted in this patient population until now. Based on this data, the FDA cannot conclude that patients with epithelioid sarcoma have substantially different expected response rates to available therapies than patients with non-epithelioid STS.

5.2.2 Natural History Study

EZH-1001 was a multi-center, non-interventional retrospective chart review study conducted by Epizyme in patients 10 years of age or older with histologically confirmed locally advanced unresectable or metastatic ES, who initiated systemic therapy between January 1, 2000, and December 31, 2017. Patient medical charts from five academic cancer centers (i.e., study sites) in the U.S. were screened, reviewed, and abstracted by site research personnel.

The following inclusion criteria were used for selecting patients for the study:

- Diagnosed with histologically confirmed, locally advanced unresectable or metastatic ES requiring systemic therapy between January 1, 2000, and December 31, 2017.
- Initiated treatment with any systemic anti-cancer therapy for the treatment of locally advanced or metastatic, unresectable epithelioid sarcoma between January 1, 2000, and December 31, 2017.
- At least 10 years of age at date of diagnosis (referred to hereafter as the "index date").

Patients were not required to have confirmed INI1 loss to be included in this study.

The primary endpoint was real world ORR (rwORR) as recorded in clinician notes and radiology reports. Verbatim responses were categorized into clinician-assessed complete response, clinician-assessed less-than-complete response (i.e., significant tumor shrinkage), clinician-assessed stable disease (i.e., minimal increases or decreases in size of tumor or permitting ongoing systemic therapy), progressive disease with decision to discontinue therapy, progressive disease with decision to continue therapy for clinical benefit, not evaluable, or not available. Real-world overall response rate was defined as the proportion of patients who have a documented radiological scan showing clinician-assessed complete response or less-than-complete response, of any duration, defined for each regimen and by line. No formal power calculations were performed. Secondary endpoints included real world duration of response (rwDOR) and overall survival.

On 02/11/2019, Epizyme submitted the results of EZH-1001 to the FDA; the FDA communicated its concerns regarding the interpretability of the study in meeting minutes dated May 13, 2019. The FDA has numerous concerns about the design of EZH-1001; and has concluded that the results cannot be used to determine whether patients with epithelioid sarcoma have better outcomes with tazemetostat than they do with available therapies (i.e., serve as a 'real world control arm' for EZH-202) for reasons that include the following:

- FDA considers rwORR not comparable to ORR as assessed on a clinical trial due to differences in imaging frequency, consistency of disease burden assessment, and differences in how the endpoint is measured.
    - In particular, frequency of assessment in retrospective data may depend on multiple factors including clinical status and local-regional practice patterns. This is contrast to EZH-202, in which visits were planned to be at the same time frequency for all patients, and prospective rules were specified for how missed visits would affect the evaluation of response.

  - In addition, no evidence was provided for how concordant assessments of real-world response are with responses assessed according to RECIST v1.1. While the assessment of response per RECIST v1.1 depends primarily on the shrinkage of target lesions, the assessment of non-target and new lesions are also used in its evaluation. Assessments of such lesions were not reported for rwORR. Furthermore, the assessment of a real-world response may vary by tumor size, assessor, location, and other factors which are controlled under RECIST v1.1.

- FDA considers non-randomized comparisons of time-to-event endpoints such as overall survival to be difficult to interpret. This is because there may be important differences in baseline characteristics (both known and unknown) as well as difficulty in determining the correct index (start) date for patients on the historically controlled arm.
- An observational study whose intent is to serve as an historical control for single arm data should be designed such that the patient populations to be compared in the analyses are as similar as possible. The following differences further call into question the validity of the reported historical study for this purpose:
  - Difference in requirement for INI1 loss. All patients are screened for INI1 status for entry into EHZ-202. INI1 status was not captured for many of the patients enrolled in the natural history study.
  - The protocol for the historical study did not clarify whether prior cancer therapies should be discontinued before entry into the study and if so, the minimum length of time between discontinuation of prior cancer therapies and the index date.
  - Difference in age used for inclusion criteria. Study EHZ-202 enrolled patients 18 years of age or older, while the historical study selected patients 10 years of age and older.
  - Difference in years during which patients received treatment. Study EHZ-202 was initiated in 2015, but the historical study included patients from 2000-2017.
- The historical study did not specify any methods to evaluate potential confounding variables in the resulting data set. Because patient characteristics are likely to be different in the historical study compared to those in EHZ-202, comparisons between the two data sets may not accurately reflect the treatment effect of tazemetostat in reference to standard of care. In general, such analyses should be specified before looking at the data to reduce biases resulting from post-hoc inferences.

FDA further concluded that the results also cannot be used to determine whether patients with epithelioid sarcoma can be expected to have different outcomes to standardly administered therapies compared to patients with other forms of soft-tissue sarcoma for similar reasons, as well as because EZH-1001 did not enroll patients with non-epithelioid sarcoma STS to serve as an internal control.

5.2.3 Comparison of Efficacy of Tazemetostat with Standard Therapies

The observed ORR to tazemetostat was 15% (95% CI: [7, 26]) in the 62 patients that comprised Cohort 5 of EZH-202 and 11% (95% CI: [4, 25]) in the 44 patients that comprised Cohort 6, with a pooled ORR of 13% (95% CI: [7, 21]) observed across both cohorts. The true response rate to tazemetostat may thus be as low as 4-7%. Numerically, this is lower than the response rate of 24% (95% CI: [19, 30]) in the 234 patients that comprised the summary data submitted to the FDA from nine different cancer treatment centers and was used to support the approval of doxorubicin for STS in 1974. However, response criteria in this era generally defined a response as greater than 50% measurable decrease in tumor size in lesions that could be measured either uni- or bi-directionally (Blum 1974 and Hayward 1977), in contrast to modern response criteria (e.g. RECIST v1.1) that define a response as at least a 30% decrease in the sum of diameters of target lesions. Thus, the response rate used to support the approval of doxorubicin cannot be directly compared to that of tazemetostat. Several additional factors limit the comparability of this data to data generated on EZH-202. One is that the data submitted to support the approval of doxorubicin lacks complete information regarding whether patients had received prior therapies (among other details regarding baseline characteristics). It is therefore not possible to determine whether the patient populations are comparable. Additionally, several of the historical doxorubicin studies excluded patients who were unable to receive at least 2 doses of doxorubicin from the efficacy evaluable population, which may have inflated the response rate by excluding early progressors from the analysis.

Due to the limitations of the dataset from 1974, FDA performed an exploratory comparison of the activity of tazemetostat in patients with epithelioid sarcoma from Cohorts 5 and 6 of EZH-202 who had not received prior therapies to that of doxorubicin in patients with advanced soft tissue sarcoma as reported in the literature. In this subset of patients (n=44), tazemetostat had an ORR of 16% (95% CI: [8, 29]), which is not numerically higher than the ORR of 8 to 19% observed in patients with STS who received doxorubicin as first-line therapy described in literature reports. There is insufficient data regarding durability of response for both tazemetostat and doxorubicin to enable comparison of this endpoint.

Next, FDA compared the activity of tazemetostat in patients with epithelioid sarcoma from Cohorts 5 and 6 of EZH-202 who had received prior therapies (i.e., second line or greater) to that of pazopanib in patients with STS who had received prior chemotherapy (i.e., second line or greater). In this subset of patients (n=62), tazemetostat had an ORR of 11% (95% CI: [6, 22]). While the point estimate is numerically higher than the ORR of 4% (95% CI: [2, 8]) observed on the registrational study of pazopanib, the confidence intervals overlap.

All these analyses are limited by measured and unmeasured differences in patient populations as well as differences in the frequency, timing, and method of response assessment. The FDA considers their primary utility to be in demonstrating that all therapies used to treat epithelioid sarcoma have low (≤ 20%) response rates, and that tazemetostat does not appear to confer superior benefit compared to these agents based on available data.

6 SUMMARY AND CONCLUSIONS

Epithelioid sarcoma is rare subset of the broader STS population. Most of the agents used to treat epithelioid sarcoma are chemotherapeutic agents, associated with low response rates and substantial toxicities; there is a need for new therapies with a favorable risk-benefit profile. While the FDA commends Epizyme for exploring tazemetostat as a potential therapy for epithelioid sarcoma in a biologically rational way and agrees that the data generated in patients with epithelioid sarcoma may warrant further investigation, the FDA is concerned that there may be insufficient evidence at this time to conclude that tazemetostat confers benefit in patients with epithelioid sarcoma.

The observed ORR for tazemetostat in patients with epithelioid sarcoma from Cohort 5, Cohort 6, and both Cohorts pooled was 15%, 11%, and 13%, respectively, with a lower bound of the 95% confidence interval showing that the "true" estimated response rate could be as low as 4-7%. Although a few patients may have been exceptional responders (e.g., patients with large decrease in tumor volume and long durability of response), the number of such patients would be limited as they would constitute a fraction of the total number of responding patients.

The approval of doxorubicin in STS was based on a response rate of 24% (95% CI: [19, 30]). Although we have pointed out the limitations of this comparison, and literature analysis suggests that the "true" response rate to doxorubicin may be < 20%, there is no evidence to suggest that the response rate of patients with epithelioid sarcoma to tazemetostat is better than that of doxorubicin, nor is there evidence that patients with epithelioid sarcoma derive less benefit from chemotherapeutic agents than patients with non-epithelioid sarcoma STS. In the 2L+ setting, tazemetostat appears to confer a numerically higher response rate than pazopanib, but the patient numbers are small and the confidence intervals overlap. Therefore, it cannot be concluded that tazemetostat has a better ORR than standard therapies.

When assessing benefit, not only is the frequency of response taken into consideration, but also the magnitude and duration of the responses, the safety profile of the drug, available therapies for

the specific tumor type, clinical impact of tumor burden, and the mechanism of action of a drug as it relates to the biology of the tumor. Tazemetostat has a route of administration that many patients may find more convenient and may have improved toxicity profile over standard therapies; however, there is a clear risk of secondary malignancies associated with its administration which has yet to be fully characterized due to the relatively short follow-up of patients who have received tazemetostat on clinical trials.

Reduction in tumor burden can be a direct measure of benefit if it represents an improvement in function and quality of life for patients. Across cohorts 5 and 6, the majority of target lesions were ≤5 cm. Given the absence of other clinically meaningful endpoints assessed on the study, it is uncertain whether the results of EZH-202 that demonstrate a modest ORR and variability in the duration of responses represent an overall benefit in the proposed population.

FDA brought this application to the Oncology Drugs Advisory Committee to enable public discussion of the results of EZH-202 and whether the evidence is sufficient to demonstrate the benefit of tazemetostat in patients with epithelioid sarcoma. A key uncertainty regarding the application is whether the low response rate observed on EZH-202 will translate into a positive impact on survival or other clinical benefit. Epizyme is planning a randomized confirmatory trial of tazemetostat with doxorubicin compared to doxorubicin alone in patients with epithelioid sarcoma which may address this uncertainty; however, enrollment into this trial has not yet begun.

7 ISSUES FOR ODAC

Discuss whether the evidence from Cohorts 5 and 6 of EZH-202 is sufficient to establish the benefit of tazemetostat in patients with epithelioid sarcoma.

Does the demonstrated benefit of tazemetostat outweigh the risks of the drug in the proposed indication?

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