NDA 211723: Tazemetostat

FDA Opening Remarks

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Proposed Indication

Tazemetostat is indicated for the treatment of patients with metastatic or locally advanced epithelioid sarcoma who are not eligible for curative surgery

Epithelioid Sarcoma

- Rare soft tissue sarcoma
- Approximately 125 cases per year in the U.S.
- Patients typically diagnosed between 20-40 years of age
- Approximately 50% have metastatic disease at diagnosis
- 5-year survival of patients with metastatic disease: 0%
- Approximately 90% show nuclear loss of integrase interactor 1 (INI-1)

Therapeutic Approaches

- Wide surgical excision, with or without radiation
- Systemic chemotherapy reserved for metastatic disease
- FDA-approved therapies for soft-tissue sarcoma:
  - Doxorubicin (1974)
  - Pazopanib (2012)

Tazemetostat

- First-in-class, oral, small molecule inhibitor of the methyltransferase enhancer of zeste homolog 2 (EZH2)
- Postulated to restore balance to a set of proteins involved in chromatin remodeling and gene expression in tumors that have lost the tumor suppressor gene integrase interactor 1 (INI-1)
- Impact of this on cancer cell biology not well understood

Study EZH-202: Design

	Cohort 1 Rhabdoid Tumors	Cohort 2 Synovial Sarcoma	Cohort 3 INI-1 Loss or EZH2 mutation	Cohort 4 Renal Medullary Carcinoma	Cohort 5 Epithelioid Sarcoma	Cohort 6 Epithelioid Sarcoma	Cohort 7 Chordoma
Stage 1	N=15	N=15	N=15	N=15	N=15	N=40	N=15
Stage 2	N=30	N=30	N=30	N=30	N=30		N=30
Expansion					N=30		

All patients received tazemetostat 800 mg by mouth twice daily

Study EZH-202: Efficacy Results

	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)
Range of DOR	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)

[1] By independent review according to RECIST v1.1

Key: ORR, Overall Response Rate; CI, Confidence Interval; CR, Complete Response; PR, Partial Response; DOR, Duration of Response

Study EZH-202: Safety Results

	Cohort 5 N=62
All grade adverse events	62 (100%)
Grade 3-4 adverse events	30 (48%)
Serious adverse events	23 (37%)
Treatment discontinuations due to adverse events	1 (1.6%)
Dose interruptions due to adverse events	21 (34%)
Dose reductions due to adverse events	1 (1.6%)

Warning: Risk of Secondary Malignancies

Issues

- 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.
  - Observed ORR 11-15% (lower bound of 95% CI: 4-7%)
- Does the demonstrated benefit of tazemetostat outweigh the risks of the drug in the proposed indication?
  - Uncertainty around risk profile due to single arm study design; 48% with Grade 3-4 adverse event, 37% with serious adverse event
  - Identified risk: secondary malignancies


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NDA 211723: TAZEMETOSTAT

Oncologic Drugs Advisory Committee Meeting
Efficacy and Safety Analyses and Issues
December 18, 2019

Leslie Doros, MD
Clinical Reviewer
Division of Oncology 3
Office of Oncologic Diseases

Proposed Indication

Proposed Indication for Accelerated Approval:

Tazemetostat is indicated for the treatment of patients with metastatic or locally advanced epithelioid sarcoma who are not eligible for curative surgery

Proposed Dosing Regimen:

800 mg orally twice daily with or without food

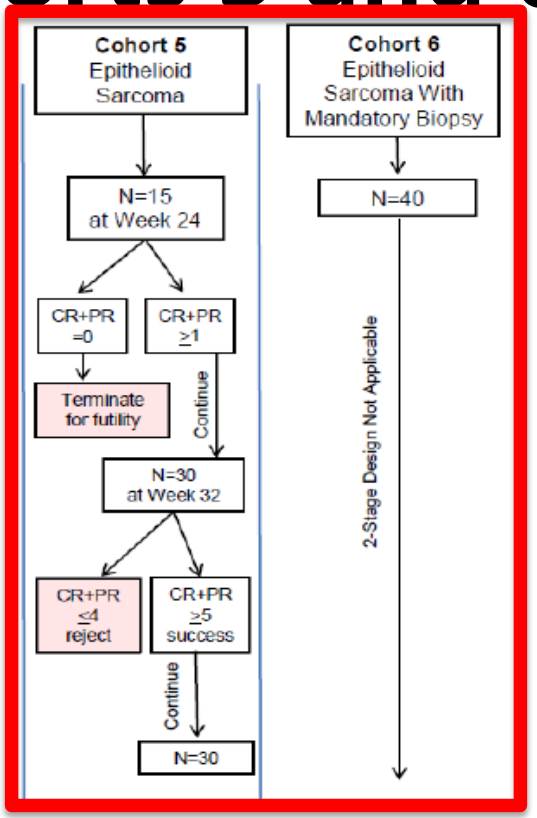
Key Issue for Consideration

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

Study Scheme for EZH-202 Cohorts 5 and 6

Original Cohort

Expansion Cohort



Source: Copied from Protocol EZH-202 Amendment 5 page 41

Rationale for Pooling Cohorts 5 and 6

- Eligibility criteria differences not expected to have large efficacy impact
  - Integrase interactor 1 (INI1) loss required for Cohort 5
  - Tumor biopsy required for Cohort 6
  - Must have progressed within 6 months of study entry for Cohort 6
    - This criterion only applied to expansion stage of Cohort 5

- Similarities between Cohorts 5 and 6
  - Demographic and baseline characteristics were similar
    - 34/44 patients in Cohort 6 had INI1 loss; 4 retained INI1 and 6 had missing INI1 status
  - Same dose and regimen of tazemetostat
  - Similar follow-up (using updated cut-off for Cohort 6)
  - Overall response rate (ORR) and duration of response (DOR) collected on both cohorts in same manner

Study EZH-202: Overall Response Rate

	EZH-202 Cohort 5 N=62	EZH-202 Cohort 6 N=44	EZH-202 Pooled N=106
ORR[1]	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)

[1]As assessed by Response Evaluation Criteria for Solid Tumors (RECIST) v1.1 by independent review committee (IRC)

Key: ORR, Overall Response Rate; CI, Confidence Interval; CR, Complete Response; PR, Partial Response

Study EZH-202: Duration of Response

	Cohort 5 N=62	Cohort 6 N=44	Pooled N=106
Number of Responders	9	5	14[1]
≥ 6 months	6	3	9
≥ 12 months	3	1	4
Range of DOR	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)

[1]Seven patients had an ongoing response at the time of the data cutoff.

Key: DOR, Duration of Response

ORR per IRC by Subgroup

Subgroup	# Responses	N	ORR[1] (95% CI)
Prior lines of therapy			
0	7	44	16% (7%, 30%)
1+	7	62	11% (5%, 22%)
INI1 status at baseline			
Missing	0	6	0% (0%, 46%)
Deficient	14	96	15% (8%, 23%)
Present	0	4	0% (0%, 60%)
Cohort			
Cohort 5	9	62	15% (7%, 26%)
Cohort 5: Original cohort	6	31	19% (7%, 37%)
Cohort 5: Expansion cohort	3	31	10% (2%, 26%)
Cohort 6	5	44	11% (4%, 25%)

[1]ORR based on pooled data from Cohorts 5 and 6 except as indicated.

Key: ORR, Overall Response Rate

Factors FDA Considers When Interpreting ORR

- Magnitude and durability of effect
- Benefits and risks of other therapies used to treat the disease
- Location, size, and clinical impact of tumor
- Mechanism of drug action and underlying disease biology
- Body of knowledge regarding the drug's effects in other settings
- Safety of the drug

FDA-Approved Drugs for Soft Tissue Sarcoma

Doxorubicin

- Approved in 1974 for treatment in soft tissue sarcoma (STS)
  - Approval based on response rate[1] of 24% (95% CI: [19, 30])
  - Range of response rate in published studies is 8-19%

Pazopanib

- Approved in 2012 for the treatment of STS after chemotherapy
  - Based on progression-free survival (PFS)[2]:
    - Hazard ratio: 0.35 (95% CI: [0.26, 0.48])
    - Median PFS 4.6 months vs. 1.6 months in placebo arm
  - ORR: 4% (vs. 0%)
  - OS: 12.6 months (vs. 10.7 months)

[1]Response defined as a decrease of 50% in tumor mass.

[2] https://www.accessdata.fda.gov/drugsatfda_docs/label/2012/022465s-010S-012lbl.pdf

Activity in Patients with Epithelioid Sarcoma

	Number of ES Patients	Response Rate (95% CI)
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 (1st line)	5	0 (0, 52)
Doxorubicin + Ifosfamide (1st line)	8	13 (0, 53)
Pazopanib (1st and 2nd line)	11	27 (6, 61)
Frezza, et al (2018)[3]		
Pazopanib	18	0 (0, 19)
Anthracycline-based	85	22 (14, 33)

[1] Response assessed by World health Organization (WHO) criteria and RECIST crit

[2] Response assessed by RECIST criteria

[3] Response assessed by RECIST 1.1

Tumor Burden

Study EZH-202 did not collect data regarding clinical impact (e.g., cosmetic, functional) of baseline tumor burden

- Most patients (74%) had 5 or fewer measurable tumors at baseline; maximum was 10
- 84% of non-nodal target lesions were 5 centimeter (cm) or smaller in longest diameter; only 3 non-nodal target lesions were >10 cm

Mechanism of Action and Tumor Response

- The methyltransferase enhancer of zeste homolog 2 (EZH2) catalyzes the activity of histone H3, generally downregulating transcription
- INI1 loss can lead to abnormal activity/expression of EZH2 and an oncogenic dependence on EZH2
- Tazemetostat inhibits EZH2, restoring transcriptional homeostasis
- Low response rate to tazemetostat in patients with INI1 deficient epithelioid sarcoma could be due to:
  - Lack of relevance of the target in this disease, or
  - Effects that inhibit tumor cell growth rather than cause tumor cell death
- Activity of tazemetostat in follicular lymphoma:
  - ORR of 69% for patients with EZH2 mutation; 35% for patients with wild-type EZH2

Safety Summary for Cohort 5

- Most common treatment-emergent adverse events (TEAEs):
  - Pain, fatigue, nausea, decreased appetite, vomiting, and constipation
- Grade 3 to 4 TEAEs: 30 (48%) patients
  - Anemia, pain, decreased weight, decreased appetite, hemorrhage, dyspnea, and pleural effusion
- Serious AEs: 23 (37%) patients
  - Hemorrhage, pleural effusion, dyspnea, pain, and skin infection
- Dose Interruptions: 21 (34%) patients
  - Hemorrhage, increased alanine aminotransferase (ALT), and increased aspartate aminotransferase (AST)

Secondary Malignancies

- At the target dose (n=668) in adults
  - 3 patients developed acute myeloid leukemia (AML)
  - 2 patients developed myelodysplastic syndrome (MDS) (1 subsequently evolved to AML)
- Across the development program (n=822), including pediatric patients
  - 6 (0.7%) developed secondary malignancies
- Of the 6 patients who developed secondary malignancies:
  - Time from start of tazemetostat to development of malignancy ranged from 14 months to 4 years (median 27 months)
  - 5 patients received prior chemotherapy

Toxicology Studies

Adult rats

- T cell lymphoma with concurrent leukemia led to early death in multiple animals starting 9 weeks into dosing and was present in surviving animals at terminal and recovery necropsy
  - 28% at the mid dose
  - 2.5% at the high dose

Juvenile rats

- T cell lymphoma led to early deaths in multiple animals starting 11 weeks into dosing and was present in surviving animals at terminal and recovery necropsy

Summary of the Major Review Issue

With limited clinical experience and lack of comparative data, FDA is concerned that activity observed in Cohorts 5 and 6 of EZH-202 may not be sufficient to establish the benefit of tazemetostat in patients with epithelioid sarcoma.

Confirmatory study of tazemetostat with doxorubicin compared to doxorubicin alone in patients with epithelioid sarcoma is planned; enrollment has not yet begun.

Summary of Data

Factor	Conclusion
Commonly used therapies	Existing therapies for soft tissue sarcoma yield response rates generally <20% with considerable toxicity. Response rate similar for epithelioid sarcoma.
Magnitude and duration of effect	Point estimate of ORR with tazemetostat is 11-15%. Limited number of responders precludes accurate assessment of DOR.
Tumor burden	84% of non-nodal target lesions were 5cm or smaller in longest diameter at baseline. However, this does not completely characterize baseline tumor burden.
Mechanism of action	Target of tazemetostat (EZH2) may not be particularly relevant for cancer cell survival in epithelioid sarcoma.
Safety	48% of patients with Grade 3-4 adverse event, 37% with serious adverse event. 34% required dose interruption for adverse event; dose reduction or discontinuation was uncommon. Secondary malignancies are an identified risk.
Prior experience	Tazemetostat not approved for any indication; activity of the drug observed in follicular lymphoma.

Discussion and Voting Questions

Discussion Question:

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.

Voting Question:

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

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BACK UP SLIDES SHOWN

Interpretation of Stable Disease

- FDA does not consider stable disease in efficacy assessments.
  - While a response may be attributed directly the activity of a treatment, stable disease may occur with or without treatment.

- In addition, the percentage of patients who experience stable disease by a given time point depends heavily on the natural history of the disease and timing of assessments.

Interpretation of Stable Disease

Consider the number of patients who experienced stable disease in the placebo arm of PALETTE[1]:

	Pazopanib N = 246	Placebo N = 123
Partial Response[2]	14 (6%)	0 (0%)
Stable disease	164 (67%)	47 (38%)
Progression	57 (23%)	70 (57%)
Early death	3 (1%)	6 (5%)

[1] As reported in Van Der Graaf et. al (2012). Response rate may differ from labeled response rate due to updated data at the time of publishing.

[2] Assessed by RECIST v1.0.