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NCCN Guidelines Panel: B-Cell Lymphomas

On behalf of Epizyme, I respectfully request the NCCN Guideline Panel for B-Cell Lymphomas to review the new FDA approval¹ and clinical study results² of tazemetostat for the treatment of patients with relapsed or refractory follicular lymphoma.

Specific Changes: We respectfully ask the NCCN Panel to consider the following:

FOLL-B 2 of 4, “Second-line and Subsequent Therapy”:

- Under “Preferred regimens”, add “Tazemetostat (preferred for EZH2 mutant) ^{Footnote}”
- Under “Other recommended regimens”. Add “Tazemetostat (if EZH2 status unknown or EZH2 wild type) ^{Footnote}”
- Add Footnote: “Tazemetostat can also be used for patients with no satisfactory treatment options.”

FDA Approval: TAZVERIKTM (tazemetostat) is indicated for the treatment of:

- Adult patients with relapsed or refractory follicular lymphoma whose tumors are positive for an EZH2 mutation as detected by an FDA-approved test and who have received at least 2 prior systemic therapies.
- Adult patients with relapsed or refractory follicular lymphoma who have no satisfactory alternative treatment options.
- Adults and pediatric patients aged 16 years and older with metastatic or locally advanced epithelioid sarcoma not eligible for complete resection.

These indications are approved under accelerated approval based on overall response rate and duration of response. Continued approval for these indications may be contingent upon verification and description of clinical benefit in a confirmatory trial(s).¹

Rationale: Tazemetostat received FDA approval for relapsed or refractory follicular lymphoma based on two open-label, single-arm cohorts of a multi-center study (Study E7438-G000-101, NCT01897571) after at least 2 prior systemic therapies (range: 1–11).¹ Overall response rate (ORR) was 69% in patients with EZH2-mutant (MT EZH2 FL and 35% in patients with wild type EZH2 (WT EZH2) FL, including patients who had been heavily pretreated (16% MT EZH2 and 30% WT EZH2 of patients received ≥5 prior therapies, respectively). Duration of response (DOR), progression-free survival (PFS), and overall survival (OS) were similar in the two cohorts. With significant activity combined with a favorable safety profile, tazemetostat provides an effective option that is well tolerated by pretreated patients.

The phase 2 study was an open-label, single-arm multicenter study in 2 cohorts of patients with histologically confirmed follicular lymphoma after at least 2 prior systemic therapies. Study results were presented at the American society of Hematology in 2019 as an oral presentation. The study enrolled 99 patients aged 36 to 87 years with relapsed or refractory follicular lymphoma following two or more prior systemic regimens. As a whole, 55% were refractory to rituximab-containing regimen, and 52% had disease progression within 24 months of diagnosis (POD24). All patients were treated

with 800 mg tazemetostat twice daily.² **The study has entered the fast-track publication process at a top-tier journal.**

Key Results:²

	MT EZH2 (n = 45)	WT EZH2 (n = 54)
Median prior therapies, n (range)	2 (1-11)	3 (1-8)
ORR, %	69	35
Median DOR, months (range)	10.9 (0.0+, 22.1+)	13.0 (0.5, 22.5+)
Median PFS, months	13.8	11.1
Median OS	Not reached	Not reached
Median follow-up, months	22	35.9

Tazemetostat was generally well-tolerated:

- Serious adverse reactions occurred in 30% of patients who received tazemetostat. Serious adverse reactions occurring in $\geq 2\%$ were general physical health deterioration, abdominal pain, pneumonia, sepsis, and anemia. The most common ($\geq 20\%$) adverse reactions were fatigue (36%), upper respiratory tract infection (30%), musculoskeletal pain (22%), nausea (24%), and abdominal pain (20%).¹
- Treatment-related grade ≥ 3 adverse events were thrombocytopenia (3%), anemia (2%), fatigue (1%), and asthenia (1%).²
- Eight percent (8%) of patients discontinued treatment due to adverse reactions, 9% had a dose reduction due to adverse reactions, and 27% of patients had a dose interruption due to adverse reactions.
- There were no treatment-related deaths.

Mechanism of Action: Tazemetostat is an inhibitor of the methyltransferase, EZH2, and some EZH2 gain-of-function mutations including Y646X, A682G and A692V. Tazemetostat also inhibited EZH1 with a half-maximal inhibitory concentration (IC_{50}) of 392 nM, approximately 36 times higher than the IC_{50} for inhibition of EZH2. The most well-characterized function of EZH2 is as the catalytic subunit of the polycomb repressive complex 2 (PRC2), catalyzing mono-, di-, and trimethylation of lysine 27 of histone H3. Trimethylation of histone H3 leads to transcriptional repression.¹

Tazemetostat suppressed proliferation of B-cell lymphoma cell lines in vitro and demonstrated antitumor activity in a mouse xenograft model of B-cell lymphoma with or without EZH2 gain-of-function mutations. Tazemetostat demonstrated greater effects on the inhibition of proliferation of lymphoma cell lines with mutant EZH2.¹

Thank you for your consideration.

Sincerely,

Khalid Mamlouk, PharmD
VP, Head of Medical Affairs
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References (enclosed):

1. TAZVERIK. [prescribing information]. Cambridge, MA: Epizyme, Inc; 2020.
2. Morschhauser F, Tilly H, Chaidos A, et al. Phase 2 Multicenter Study of Tazemetostat, an EZH2 Inhibitor, in Patients with Relapsed or Refractory Follicular Lymphoma. *Blood*. 2019;134(S1):123.