Tazemetostat (TAZVERIK)
National Drug Monograph
September 2022

VA Pharmacy Benefits Management Services, Medical Advisory Panel, and VISN Pharmacist Executives

The purpose of VA PBM Services drug monographs is to provide a focused drug review for making formulary decisions. Updates will be made if new clinical data warrant additional formulary discussion. The Product Information or other resources should be consulted for detailed and most current drug information.

FDA Approval Information

Description/Mechanism of Action

- Tazemetostat is a first-in-class oral inhibitor of the methyltransferase, EZH2 (enhancer of zeste homolog 2), and EZH2 gain-of-function mutations such as Y646X, A682G and A692V.

Indication(s) Under Review in This Document

- Metastatic or locally advanced epithelioid sarcoma, not eligible for complete resection
- Relapsed or refractory follicular lymphoma (FL), with an EZH2 mutation
- Relapsed or refractory FL without a mutation, but no alternative treatment options

Dosage Form(s) Under Review

- 200 mg oral tablets

Clinical Evidence Summary

Efficacy Considerations

Metastatic or locally advanced epithelioid sarcoma

Tazemetostat in advanced epithelioid sarcoma with loss of INI1/SMARCB1: an international, open-label phase 2 basket study *Lancet Oncol* 2020; 21: 1423

Design		Intervention (n=62)	Results
Open-label, single-arm cohort of a multicenter basket study		Tazemetostat 800 mg PO twice daily until PD or unacceptable toxicity	Median follow-up@ 14 mos ORR 15%; CR 1.6%; PR 13%
Inclusion	**Exclusion**	mAge 34 yrs; male 63%; white 76%; ECOG 0-1 92%; ECOG 2 8% s/p surgery 77%; chemotherapy 61% Tumor assessments q8 wks	mTTR 3.9 months mDoR not reached Duration $\geq$ 6 months in 67%
Metastatic or locally advanced epithelioid sarcoma; *INI*1 loss; ECOG PS 0-2	Active CNS mets BMS > Grade 3		

Within this cohort of patients with epithelioid sarcoma and *INI*1 loss (a tumor suppressor gene), a modest benefit was noted in terms of ORR 15%, made up primarily of partial responses.

Efficacy Considerations

Relapsed or refractory follicular lymphoma (FL), with an EZH2 mutation
Relapsed or refractory FL without a mutation, but no alternative treatment options

Tazemetostat for patients with relapsed or refractory follicular lymphoma: an open-label, single-arm, multicenter, Phase 2 trial *Lancet Oncol* 2020; 21: 1433

Design	Intervention	Results
Open-label, single-arm, P2 trial; categorized by EZH2 status: mutant or wild-type (WT)	Tazemetostat 800 mg PO twice daily until PD or unacceptable toxicity n=99: 45 mutant, 54 WT Tumor assessments q8 wks	Median follow-up@ 22 mos (mutant) and 36 mos (WT)

Inclusion	Exclusion
FL s/p 2 prior therapies; ECOG 0-2; HBsAg neg; undetectable HCV RNA	CNS mets; Any prior hx myeloid malignancies, including MDS; Hx T-LBL, T-ALL

Mutant (45)	Wild-Type (54)
mAge 62 yrs	mAge 61 yrs
Female 58%	Female 37%
2 prior lines	3 prior lines
All ECOG 0-1	91% ECOG 0-1

Mutant	Wild-Type
ORR 69%	ORR 34%
CR 12%	CR 4%
mDOR 10.9 mos	mDOR 13 mos

Among these patient populations that have relapsed on 2-3 prior lines of therapy, tazemetostat therapy provided clinical response in terms of ORR, CR and duration of response. Patients with EZH2 mutations, overall, had a greater response to tazemetostat therapy, but it is important to note that in the EZH2-wild type group complete responses were noted in 4%.

Safety Considerations

- **Boxed warnings:** none
- **Contraindications:** none
- **Other warnings / precautions**:
    - Secondary malignancies – increases risk of secondary malignancies, including T-cell lymphoblastic lymphoma, MDS and AML. Monitor patients long-term for development of secondary malignancies.
    - Embryo-Fetal Toxicity – Can cause fetal harm; advise patients of potential risk and to use effective non-hormonal contraception
- **Adverse reactions:**
    - **Common in epithelioid sarcoma:** pain, fatigue, nausea, decreased appetite, vomiting, constipation
        - **SAEs in 37%:** hemorrhage, pleural effusion, skin infection, dyspnea, pain and respiratory distress
    - **Common in follicular lymphoma:** fatigue, upper RTI, musculoskeletal pain, nausea, abdominal pain
        - **SAEs in 30%:** physical health deterioration, abdominal pain, pneumonia, sepsis, anemia
- **Drug-drug-food interactions:**
    - Avoid concomitant administration with strong and moderate CYP3A inhibitors; reduce the dose of tazemetostat if the interaction cannot be avoided
    - Avoid coadminstration with strong and moderate CYP3A inducers
    - Tazemetostat can reduce concentration and efficacy of CYP3A substrates, including hormonal contraceptives
    - Avoid grapefruit, grapefruit juice or concomitant St. John's wort

Other Considerations

Risk-Benefit Assessment (for Oncology NMEs only)

- **Outcome in clinically significant area:** ORR, Duration of Response (DoR)
- **Effect Size:** no comparator in either study
- **Potential Harms:** risk of secondary malignancies
- **Net Clinical Benefit:** n/a – await confirmatory trials for verification/description of clinical benefit

Other Therapeutic Options

For the treatment of Epithelioid Sarcoma

- Anthracycline-based chemotherapy ORR ~ 22% with median PFS 6 months.
- Gemcitabine with reported ORR 27% and median PFS 4 months

For the treatment of R/R Follicular Lymphoma

- Lenalidomide + rituximab vs. PBO + rituximab, mPFS 39 vs. 14 months; ORR 78 vs. 53%; CR 34 vs. 18%; Toxicity was higher in the treatment arm: infection 63 vs. 49%; cutaneous reactions 32 vs. 12%; gr 3-4 neutropenia 50 vs. 13%
- Copanlisib + rituximab vs. PBO + rituximab, mPFS 22 vs. 14 months; Significant toxicity was associated with the treatment arm: TEAEs 47 vs. 18%, hyperglycemia 56 vs. 8%, HTN 40 vs. 9%

Projected Place in Therapy

- Epigenetic regulation is the process of altering gene expression without altering DNA sequencing. Gene expression can be modified through inhibition of enhancer of zeste homolog 2 (EZH2), which functions as a histone methyltransferase and a regulator of cell cycle progression, autophagy, apoptosis and promotes DNA damage repair. Dysregulation of EZH2 can promote cancer development. Both solid tumors and hematologic malignancies can possess mutations affecting EZH2 activity.
- Tazemetostat is a novel, first-in-class EZH2 inhibitor that was granted accelerated approval by the FDA for both epithelioid sarcoma and follicular lymphoma indications.
- Epithelioid sarcoma is a rare soft tissue sarcoma accounting for ~1% of all sarcomas. It affects primarily a younger population, with a peak incidence at 35 years of age.
    - Tazemetostat has not been directly compared to chemotherapy but is a reasonable option in this patient population, especially to avoid known cumulative toxicities of chemotherapy. Although consideration may be given to the use of chemotherapy due to slightly improved response rates of anthracycline and non-anthracycline-based regimens.
- Follicular lymphoma is the most common indolent lymphoma, accounting for 20% of all cases. EZH2 gain-of-function mutations are present in ~ 20% of patients. Such activating mutations result in epigenetic silencing, which allows B cells to proliferate, along with malignant clones.
    - Patients with FL may experience multiple relapses during their treatment course. The optimal sequency of therapy to manage relapses has not been established. Immunotherapy with anti-CD20 antibodies with or without chemotherapy is considered standard in patients with relapse, depending upon their initial therapy and time to relapse. Novel therapies in subsequent relapse include lenalidomide, copanlisib and tazemetostat.
    - Tazemetostat has activity in both the EZH2-mutant and EZH2-wild type settings, although a greater response was noted in the mutant population. As such, if an EZH2-mutation is detected after 2 prior therapies, then tazemetostat therapy may be considered. In the relapsed setting where no other reasonable therapeutic alternatives exist, regardless of EZH2-mutation status, tazemetostat may be a consideration.

References

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