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Tazemetostat: EZH2 Inhibitor

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Abstract

Epigenetic regulation is a novel approach to cancer treatment. Inhibition of enhancer of zeste homolog 2 (*EZH2*) is a method to provide targeted epigenetic regulation. Tazemetostat is a first-in-class targeted epigenetic regulator that specifically inhibits EZH2. This new FDA-approved oral treatment received accelerated approval for patients with hematologic and solid malignancies. Tazemetostat was first approved for patients 16 years and older with metastatic or locally advanced epithelioid sarcoma not eligible for complete resection based on the results of an international open-label phase II basket trial. Another open-label multicenter phase II trial led to the approval for patients with relapsed or refractory follicular lymphoma with *EZH2* mutation who have received at least two prior systemic therapies or patients who have no satisfactory alternative treatment options. Tazemetostat as an oral EZH2 inhibitor provides a new effective and tolerable treatment option for these patients.

A growing area of interest within cancer treatment are the targeted epigenetic regulators. Epigenetic regulation is a genomic process that reversibly modifies gene expression without altering DNA sequencing (Zhao et al., 2018). This process involves transcription regulation, which is vital for normal organism development, but any dysregulation in this process can lead to tumorigenesis. Due to this, regulation of this process is a desirable treatment target. One way to regulate gene expression is through inhibition of enhancer of zeste homolog 2 (*EZH2*; Nepali & Liou, 2021; Zhao et al., 2018).

EZH2 is the catalytic subunit of the polycomb repressive complex 2 (PRC2) that functions as a histone methyltransferase. PRC2 is part of a multiprotein complex that regulates cell development through chromatin compaction and gene repression (Nepali & Liou, 2021). As an enzyme within this complex, EZH2 works through PRC2-dependent trimethylation of histone 3 lysine 27 (H3K27). Methylation of H3K27 leads to gene repression and is a major epigenetic phenomenon during tissue development and stem cell determination. EZH2 works as a master regulator of cell cycle progression, autophagy, apoptosis, and promotes DNA damage repair and inhibits cellular senescence (Duan et al., 2020; Gan et al., 2018; Nepali & Liou, 2021; Yin et al., 2019).

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With being a master regulator, any dysregulation of EZH2 may promote cancer development. Overexpression of EZH2 has been found in many solid malignancies. This overexpression can promote significantly greater gene repression leading to cancer growth, metastasis, and immunity (Duan et al., 2020; Qiu et al., 2020). Both solid and hematologic malignancies can develop mutations that affect EZH2 activity. Dysfunction within the switch/sucrose non-fermentable (SWI/SNF) chromatin remodeling complex occurs within 20% of cancers (Gounder et al., 2020). SWI/SNF has the ability to antagonize the regulation of PRC2 so loss of function within the SWI/SNF complex members, such as integrase interactor 1 [*INI1/SNF5/SMARCB1/BAF47*], *SMARCA4*, and *SMARCA2*, can lead to aberrant EZH2 activation (Kang et al., 2020; Epizyme, Inc., 2020). Along with this, hematologic malignancies can express increased EZH2 activity. This increased activity can develop through gain-of-function somatic *EZH2* mutations that results in greater gene repression. These mutations are mostly seen in germinal center-derived diffuse large B-cell lymphoma (DLBCL) and follicular lymphoma (FL; Eich et al., 2020; Gounder et al., 2020). This is because EZH2 plays a major role in the germinal center development and is greatly expressed within pro-B cells (Eich et al., 2020). In addition to mutated *EZH2* in FL, wild-type (WT) *EZH2* can also led to increased EZH2 activity promote cancer development. Follicular lymphoma is characterized by oncogenic alternations, and these oncogenes can interact with WT *EZH2* leading to increased EZH2 activity (Epizyme, Inc., 2021; Huet et al., 2018). The function and expression of EZH2 as stated makes it a desirable epigenetic target for drug therapy (Duan et al., 2020; Li & Chng, 2019).

In contrast to EZH2, EZH1 is a homolog of EZH2 within the PRC2 complex, but it has much lower methyltransferase activity compared EZH2. EZH1 is expressed in differentiated cells and less expressed in actively dividing cells, whereas EZH2 is only expressed in actively dividing cells. EZH1 by itself is a treatment target. However, since EZH1 can replace EZH2 within the PRC2 complex, it is thought that EZH1 can compensate for the loss of EZH2. This leads to dual EZH1/EZH2 inhibition as a potential epigenetic target for drug therapy (Li & Chng, 2019; Lue & Amengual, 2018).

PHARMACOLOGY AND MECHANISM OF ACTION

Tazemetostat (Tazverik) is a first-in-class U.S. Food and Drug Administration (FDA)-approved oral EZH2 inhibitor for FL and epithelioid sarcoma (ES). Within FL, EZH2 activity is elevated due to mutant *EZH2* and the interaction of WT *EZH2* with oncogenes. Tazemetostat inhibits both mutant and WT *EZH2* in FL (Epizyme, Inc., 2020). In addition, tazemetostat inhibits some EZH2 gain-of-function mutations including Y646X and A687V (Epizyme, Inc., 2021). This inhibition suppresses proliferation in B-cell lymphomas with greater activity seen with mutant *EZH2* (Epizyme, Inc., 2020, 2021). On the other hand, ES can develop oncogenic dependence on EZH2 through dysfunction of SWI/SNF complex members, particularly with loss of *INI1*, *SMARCB1*, or both (Epizyme, Inc., 2021; Gounder et al., 2020). In addition to EZH2 inhibition, tazemetostat can inhibit EZH1 activity (Epizyme, Inc., 2020, 2021).

As an oral medication, tazemetostat has a 33% bioavailability (Epizyme, Inc., 2020). Tazemetostat is hepatically metabolized by CYP3A to form its two major inactive metabolites M5 (EPZ-6930) and M3 (EPZ006931), whereas M5 is further metabolized by CYP3A. This accounts for the drug-drug interactions seen with tazmetostat. The mean terminal half-life of tazemetostat is 3.1 hours and is excreted mainly though feces (79%) and urine (15%; Epizyme, Inc., 2020, 2021).

CLINICAL TRIALS

Phase I Data

A phase I clinical trial conducted by Italiano and colleagues (2018) was the first trial to establish the safety and dosing of tazemetostat. This trial included 21 patients with relapsed/refractory (R/R) B-cell non-Hodgkin lymphoma and 43 locally advanced/metastatic solid tumors who were not eligible for or had progressed on approved therapy. Within the lymphoma cohort, the diagnoses included DLBCL (62%) and FL (33%). For the solid cohort, 23% were *INI1*-negative and 7% were *SMARCA4*-negative. A traditional 3+3 dose-escalation design was utilized to determine the maxi-

mally tolerated dose, based upon investigator-reported dose-limiting toxicities. Dosing in this trial ranged from 100 mg orally twice daily to 1,600 mg orally twice daily. The 800-mg twice daily and 1,600-mg twice daily doses were ultimately selected for the dose expansion cohort. The 800-mg twice daily dose was chosen to proceed to phase II trials based upon the study authors' evaluation of adverse effects, clinical efficacy, and pharmacokinetics (Italiano et al., 2018).

Within this study, 36% of patients had grade 3 or worse treatment-emergent adverse events (TEAE), which led to drug interruption in 19% of patients. The most common adverse event (AE) leading to dose interruption was thrombocytopenia (9%). The most common TEAEs of any grade were asthenia (55%), anemia (22%), anorexia (22%), muscle spasms (22%), nausea (20%), and vomiting (19%). Only one patient experienced a dose-limiting toxicity of grade 4 thrombocytopenia; therefore, per the 3+3 protocol, the maximum tolerated dose was not reached (Italiano et al., 2018).

Clinical outcomes found that 38% of lymphoma patients had an objective response rate (ORR), with median time to first response being 3.5 months. The median duration of response, from first response until progression of disease or death, was 12.4 months. Conversely, in the solid tumor cohort, the ORR was 5% of patients, and this only occurred in patients who had either *INI1*- or *SMARCA4*-negative disease. When looking at *INI1*- or *SMARCA4*-negative patients, 38% of this subpopulation had a clinical benefit, defined as stable disease or better (Italiano et al., 2018).

Phase II Data

Following the success of demonstrating safety and tolerability, the dose of 800 mg twice daily proceeded to a phase II basket trial with seven cohorts based on tumor type. The currently published results of two of the cohorts from that basket trial demonstrated the safety and efficacy of tazemetostat, which led to accelerated approval by the FDA (Gounder et al., 2020; Morschhauser et al., 2020).

EPITHELIOID SARCOMA

Tazemetostat was first approved for ES with loss of function of *INI1/SMARCB1* based upon the results of a phase II trial performed in 62 patients with histologically confirmed, locally advanced, or metastatic ES (Gounder et al., 2020). Based on the clinical results of the phase I trial, patients with this tumor were required to have documented loss of *INI1* expression, biallelic *SMARCB1* alterations, or both (Gounder et al., 2020). A dose of 800 mg twice daily was given until disease progression or unacceptable toxicity.

Baseline characteristics showed a patient population that had predominantly good performance status ECOG 0 or 1 (92%), but most had stage IV disease at diagnosis (60%). 61% of patients had prior systemic therapy but could also have prior surgery (77%) or radiotherapy (56%). Median lines of prior systemic therapy was one (Gounder et al., 2020).

Fifteen percent of patients achieved the primary endpoint of objective response, all of which were partial response by investigator assessment. Similarly to the phase I trial, median time to response was 3.9 months; however, median duration of response was not reached. At 12 months, 21% of patients had progression-free survival, with a median of 5.5 months. At the time of data cutoff, 50% of patients had died, with a median overall survival of 19.0 months (Gounder et al., 2020).

While most of the AEs in the trial were grade 1 or 2, the most common grade 3 or more AEs were anemia (13%), weight loss (6%), pleural effusion (5%), decreased appetite (5%), and cancer pain (5%; Gounder et al., 2020).

FOLLICULAR LYMPHOMA

The second approval of tazemetostat was for R/R FL and FL *EZH2* mutant based upon the results of another phase II trial. There were 99 patients enrolled who received a dose of 800 mg twice daily, of which 45 had an *EZH2* mutation and 54 were *EZH2* WT (Morschhauser et al., 2020). The medication was given until disease progression, unacceptable toxicity, or for up to 2 years of treatment. Beyond 2 years, the patients could continue treatment in a rollover study. Trial participants were required to have histologically confirmed FL that had relapsed or was refractory to two or more standard-of-care systemic therapies (Morschhauser et al., 2020).

In this trial, patients primarily were of good performance status (ECOG 0–1), and 100% and

91% *EZH2* mutant and WT, respectively. The patients in the *EZH2*-mutant arm had a median of two lines of prior anticancer therapy, while the WT arm had a median of three lines, which included at least an alkylator, anthracycline, and anti-CD20 agent. 39% of patients also received either a PI3K inhibitor or immunomodulatory agent (Morschhauser et al., 2020).

The ORR was 69% in *EZH2* mutant patients, compared with a response rate of 35% in the *EZH2* WT cohort. Reduction in tumor volume was seen with 98% of the mutant cohort and 65% of the WT cohort. The median duration of response was numerically shorter in the mutant cohort compared with the WT cohort (10.9 vs. 13.0 months), although this was not statistically significant. Again, median time to duration was similar to that of the phase I trial: 3.7 months in both cohorts (Morschhauser et al., 2020). 6.7% of the *EZH2* mutant and 14.8% of the WT patients remained on treatment for the full 2 years and were enrolled in the rollover study. Median progression-free survival was 13.8 and 11.1 months for *EZH2* mutant and WT cohorts, respectively (Morschhauser et al., 2020).

Serious AEs occurred in 27% of patients with the most common grade 3 or more events being anemia (5%), thrombocytopenia (5%), neutropenia (4%), dyspnea (3%), and asthenia (3%; Morschhauser et al., 2020).

IMPLICATIONS FOR THE ADVANCED PRACTITIONER

As a first-in-class EZH2 inhibitor, tazemetostat provides a new oral treatment option for patients with hematologic and solid malignancies. In hematologic malignancies, it is approved for patients with R/R FL with *EZH2* mutation who have received at least two prior systemic therapies and for R/R FL with no satisfactory alternative treatment options. For solid malignancies, tazemetostat is FDA approved for adults and pediatric patients aged 16 years and older with metastatic or locally advanced ES not eligible for complete resection. These indications are approved based on accelerated approval and are contingent on clinical benefit in confirmatory trials.

The dose for all indications is tazemetostat 800 mg taken by mouth twice daily until disease progression or unacceptable toxicity (Epizyme, Inc., 2020). The tablets are supplied as 200-mg tablets and must be swallowed whole with or without food. Administration with high-fat, high-calorie (approximately 800 to 1000 calories) meals was shown not to have significant effect on drug exposure. If a dose is missed or vomited, the patient should continue with the next scheduled dose and not take an additional dose. With 200 mg tablets, tazemetostat is associated with a high pill burden at eight tablets per day for the recommended dose of 800 mg twice daily. Given the duration of therapy and substantial cost associated with the medication, patient assistance programs are available (Epizyme, Inc., 2020, 2021).

Adverse events occurring in 20% or more in patients include fatigue, nausea, and pain, in addition to decreased appetite, vomiting, and constipation for ES, and upper respiratory tract infection and abdominal pain for FL (Epizyme, Inc., 2020). Based on nausea occurring in 36% (all grades) of ES patients and 24% (all grades) of FL patients, clinicians should consider providing the patient with an as-needed antiemetic when starting treatment (Epizyme, Inc., 2020). Since this agent may cause constipation, they should consider initiating a prophylactic bowel regimen at the start of treatment.

Treatment can lead to a risk of developing secondary malignancies; out of the 729 adults included in clinical trials, 0.7% of patients developed myelodysplastic syndrome (MDS) or acute myeloid leukemia (AML), and one pediatric patient developed T-cell lymphoblastic lymphoma (T-LBL; Epizyme, Inc., 2020). The timeframe for development of MDS or AML was about 15 to 26 months relative the first dose of tazemetostat (Morschhauser et al, 2020). Patients should be monitored long term for development of secondary malignancies (Epizyme, Inc., 2020).

Animal studies showed that tazemetostat can cause fetal harm in pregnancy (Epizyme, Inc., 2020). Both females of reproductive potential and males with female partners of reproductive potential should use effective contraception during treatment (Epizyme, Inc., 2020, 2021). Additionally, it is advised that an effective contraceptive be continued for 6 months for females and 3 months for males after the final dose. Females of reproductive potential should have a pregnancy test

prior to starting treatment (Epizyme, Inc., 2020, 2021). Patients at this risk should be counseled on effective forms of contraception.

No dose adjustments are made for renal or hepatic insufficiency (Epizyme, Inc., 2020, 2021). However, tazemetostat has not been studied in moderate or severe hepatic impairment. Dose adjustments are recommended for AEs. A first dose reduction of tazemetostat 600 mg orally twice daily is recommended for AEs. A further second dose reduction of tazemetostat 400 mg orally twice daily can be recommended for AEs. If the 400 mg orally twice daily is not tolerated due to AEs listed in the following paragraph, then tazemetostat should be permanently discontinued (Epizyme, Inc., 2020).

Per the package insert, the medication is recommended to be held for neutropenia defined as neutrophils less than 1×10^9/L, thrombocytopenia defined as platelets less than 50×10^9/L or baseline, anemia defined as hemoglobin less than 8 g/dL, and other grade 3/4 AEs (Epizyme, Inc., 2020). Tazemetostat can resume at either the same dose or reduced dose based on the number of occurrence of AEs when neutrophils are at least 1×10^9/L or baseline, platelets are at least 75×10^9/L or baseline, and anemia and other AEs are grade 1 or baseline (Epizyme, Inc., 2020).

There are no specific laboratory monitoring recommendations in the package insert (Epizyme, Inc., 2020). In the phase II FL trial, laboratory tests including hematology, electrolyte chemistry, liver function, renal function, and urine monitored days 1 and 15 of each 28-day cycle (Morschhauser et al., 2020). In the phase II ES trial, laboratory tests including hematology and blood chemistry were monitoring days 1 and 15 of cycles 1 and 2, and on day 1 of every 28-day cycle thereafter (Gounder et al., 2020). Based on the monitoring parameters in the phase II trials, providers can consider monitoring hematology and blood chemistries at least every 28 days or as clinically indicated.

Since tazemetostat is metabolized by CYP3A, drug-drug interactions occur with CYP3A4 inhibitors and inducers. Concurrent use of tazemetostat and a strong or moderate CYP3A4 inhibitor can increase the plasma concentrations of tazemetostat and should be avoided (Epizyme, Inc., 2020). If coadministration with moderate CYP3A4 inhibitors cannot be avoided, then dose reduction for tazemetostat is recommended. The dose of tazemetostat 800 mg orally twice daily should be reduced to 400 mg orally twice daily. A dose of 600 mg orally twice daily should be reduced to 400 mg for first dose and 200 mg for the second dose. If the patient is on a dose of 400 mg orally twice daily, then it should be reduced to 200 mg orally twice daily. Dose adjustments are not required for coadministration of tazemetostat with strong or moderate CYP3A inducers but should be avoided since this may decrease tazemetostat plasma concentrations (Epizyme, Inc., 2020). The patient's current medication list should be reviewed prior to starting tazemetostat to identify any drug-drug interactions. In addition, while on therapy, any new medications should be reviewed to see if dose modification is warranted.

CONCLUSION

In summary, tazemetostat is a novel EZH2 inhibitor that has shown to be effective and safe with tolerable side effects in clinical trials (Gounder et al., 2020; Morschhauser et al., 2020). However, tazemetostat is just the beginning of the targeted epigenetic regulators. EZH2 has been shown to be involved in oncologic processes in many other solid tumors and lymphomas (Lue & Amengual, 2018). Tazemetostat, along with other EZH2 inhibitors currently in clinical trial, are being studied in DLBCL, mantle cell lymphoma, prostate cancer, mesothelioma, urothelial carcinoma, and rhabdoid tumors to name a few (Duan et al., 2020). Other EZH2 inhibitors are likely to be approved in the near future. Aside from individual EZH2 inhibitor therapy, clinical trials of combination therapy with EZH2 inhibitors and other therapies including immunotherapy, conventional chemotherapy, and targeted therapies are currently underway (Duan et al., 2020; Kang et al., 2020). EZH2 inhibitors combined with immunotherapy or conventional chemotherapy has even potentially shown synergistic effects (Duan et al., 2020). Given the efficacy of EZH2 inhibition and tolerable side effect profile, tazemetostat is the first of likely many more EZH2 inhibitors to be FDA approved.

Disclosure

The authors have no conflicts of interest to disclose.

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