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Tazemetostat– A Drug review

Anju K Paul[1], Hridya Jayamohanan[2], Keechilat Pavithran*[3]

[1]Department of Pharmacology, Amrita School of Pharmacy, Amrita Vishwa Vidyapeetham, Kochi – 682041, Kerala, India

[2]Department of Pharmacy Practice, Amrita School of Pharmacy, Amrita Vishwa Vidyapeetham, Kochi - 682041, Kerala, India

[3]Department of Medical Oncology, Amrita Institute of Medical Sciences, Amrita Vishwa Vidyapeetham, Kochi - 682041, Kerala, India

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Abstract

Epithelioid sarcoma affects three in 10 million people, usually teenagers and young adults. Tumours grow under the skin of the extremities or they can affect the trunk, head, or neck. It grows slowly, but can infiltrate surrounding tissues, later on, it frequently metastasis to lymph nodes. For advanced case, doxorubicin-based chemotherapy regimen is recommended. In January 2020, FDA approved the first-in-class, small molecule enhancer of zeste homolog 2 (EZH2) inhibitor, tazemetostat (Tazverik) to treat adults and paediatric patients aged 16 years and older with locally advanced or metastatic epithelioid sarcoma not suitable for complete resection. The recommended dosage is 800 mg twice daily until disease progression or unacceptable toxicity. The first-in-human study of tazemetostat was a phase 1 open-label multi-centered dose-escalation study. Tazemetostat is having an oral bioavailability of approximately 33%. Apparent volume of distribution at steady-state (Vss/F) is 1230 L (46%) with 88% bound to human plasma proteins. Metabolism takes place via CYP3A. 15% and 79% of radioactivity is excreted through urine and feces respectively. ≥20% of the adverse reactions and above was fatigue, pain, constipation, nausea, anorexia and vomiting. This article summarizes the history, chemistry, physical properties, mechanism of action, indications, and drug–drug interactions of tazemetostat and we also discuss briefly the results of various clinical trials.

*Corresponding Author

Name: Keechilat Pavithran
Phone: +91-9895367090
Email: drkpavithran@hotmail.com

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INTRODUCTION

Epithelioid sarcoma affects three in 10 million people, usually teenagers and young adults (Leslie, 2020). Epithelioid sarcoma is a soft-tissue malignant tumour characteristically composed of epithelioid cells nodular aggregates and was characterized first by F.M. Enzinger in 1970 (Enzinger, 1970; Thway *et al.*, 2016). Tumours grow under the skin on the limbs, hands, or feet and in the other, they can affect the trunk, head, or neck. Epithelioid sarcoma typically grows slowly, but they can infiltrate surrounding tissues, later on, it frequently metastasis to lymph nodes (Leslie, 2020). The treatment for localized tumors is surgery combined with radiation. For

advanced case, doxorubicin-based chemotherapy regimen is recommended (Czarnecka *et al.*, 2020; Leslie, 2020). In January 2020, US FDA approved the first-in-class, small molecule Enhancer of Zeste 2 (EZH2) inhibitor tazemetostat (Tazverik), developed by Epizyme, to treat adults and paediatric patients aged 16 years and above with locally advanced or metastatic epithelioid sarcoma not eligible for complete resection (Hoy, 2020).

OVERVIEW OF CLINICAL TRIALS

The first-in-human study of tazemetostat was a phase 1open-label multi-centered dose-escalation study. In this study, a 3+3 design was used with expansion cohorts at the 2 highest doses under the maximum tolerated dose. Those who were eligible for this trial were the patients who were over 18 years and with B-cell non-Hodgkin lymphoma, either relapsed or refractory, or with an advanced solid tumour. The primary aim of this trial was to find out the maximum tolerated dose of tazemetostat. 1600 mg from 100 mg twice daily, in 28 days course was the desired dose of the drug. The safety and toxicity profile was monitored throughout the study. In this study, 64 patients were analyzed as part of the study. The adverse effects of the treatment observed were anorexia (6%), vomiting (9%), nausea (20%), muscle spasms (14%), anaemia (14%) and asthenia (33%), which were usually graded 1 or 2 in severity. At the maximum dose of 1600 mg, grade 4 thrombocytopenia was detected. The dose decided for the phase 2 study was 800 mg twice daily. In patients with advanced solid tumours and refractory B-cell non-Hodgkin lymphoma, tazemetostat showed an acceptable safety and antitumour activity (Italiano *et al.*, 2018).

A phase 2 single arm study of tazemetostat 1600 mg once daily and 800 mg twice daily in adults who have relapsed or refractory synovial sarcoma or INII-negative tumors is ongoing [NCT02601950(EZH-202)]. It is a multicentre open-label, 2-stage study. Patients are enrolled into one amongst many cohorts. Response assessment with the drug would be carried out every 8 weeks. The treatment would continue till there is progression of the disease, withdrawal of consent or unacceptable toxicity, or on cessation of the study (Hoy, 2020).

The antitumour activity with tazemetostat 800mg twice daily was demonstrated in a futility analysis of data, from 32 patients (non-mesenchymal solid tumour (16), sarcoma (13), and solid tumor with a mutated EZH2 gain-in-function (3)) takes part in EZH-202 clinical trial. When the initial 15 patients finished the 168 days dosing or on ending study visit or when the consent was withdrawn prematurely, futility analysis in stage 1 was performed. For the stage success, required $\geq$1 patient in stage 1 and $\geq$5 patients in stage 2 with confirmed complete or partial response. Futility analysis showed success in first stage but not in second stage because, - in total only 3 patients (1 patient with sinonasal carcinoma (24 weeks) and 2 patients with spindle cell sarcoma (48 and 16 weeks)) showed response. 13 patients (41%) had stable disease. Even though they did not pass stage 2 futility, the treatment resulted in long-term clinical activity in 2/13 and 1/16 of patients with INI1-negative sarcomas and INI1-negative solid tumor respectively with generally mild to moderate adverse events (Stacchiotti *et al.*, 2018).

A cohort of 62 patients from EZH-202 clinical trial, with INI1-negative epithelioid sarcoma treated with 800mg tazemetostat, was used to determine safety and efficacy of tazemetostat. The primary endpoint was objective response rate (ORR) and the key secondary endpoints were, progression-free survival (PFS), disease control rate (DCR), overall survival (OS)and duration of response (DOR). 15 % of the patients (9/62) had partial responses (PRs) with 15% ORR and 26% DCR. All the patients had an OS of 82.4 weeks (median). The DOR ranged from 7.1+ weeks to 103.0+ weeks. Tazemetostat demonstrated durable clinical activity and favourable safety profile with few patients having treatment-related grade $\geq$3 AEs (Stacchiotti *et al.*, 2019).

A Cohort of 31 patients, who had malignant rhabdoid tumors (MRT) including thoracic sarcoma (TS) and small cell carcinoma of the ovary hypercalcemic type (SCCOHT) from EZH-202 clinical trial, was studied. When the initial 15 patients finished the 168 days dosing or on ending study visit or when the consent was withdrawn prematurely, futility analysis in stage 1 was performed. For the stage success, required $\geq$1 patient in stage 1 and $\geq$5 patients in stage 2 with confirmed complete or partial response. Futility analysis showed success in first stage but not in second stage because, in total only 2 patients (patient with SCCOHT (32 weeks) and patient with TS (8 weeks)) showed response. 7 patients had stable disease. Tazemetostat shows its potential in treating tumors TS and SCCOHT with mild to moderate AEs. Even though it did not pass stage 2 futility, more understanding of the heterogeneity of these highly aggressive tumors may help, to determine the partial response seen in two patients (Stacchiotti *et al.*, 2018).

Tazemetostat as combination therapy using prednisolone or monotherapy was studied in patients with mutated (mt) or wild type (wt) EZH2 refractory or relapsed Diffuse Large B-Cell Lymphoma(DLBCL). 800mg tazemetostat twice daily, 40mg prednisolone, on days one to five and days fifteen to nineteen in a twenty eight day cycle for sixteen weeks. The assessment was done every eight weeks. It was found that tazemetostat was well tolerated at 800mg BID, both as monotherapy or in combination therapy with prednisolone, but the combination therapy with prednisolone did not show any additional improved activity than monotherapy (Ribrag *et al.*, 2018).

The multicentre, open-label, single-arm, phase 2 study (NCT01897571) evaluated 800 mg tazemetostat in 99 patients categorized as wild or mutated EZH2 Relapsed or Refractory (RR) follicular lymphoma (FL). There are 45 and 54 patients in EZH2 mutated cohort and EZH2 wild cohort, respectively. Objective response rate was the primary endpoint. 69% and 35% was the objective response rate found in mutated EZH2 cohort and wild EZH2 cohort. Tazemetostat was tolerated generally well with a low occurrence of AEs (anaemia (2%), neutropenia (3%) and thrombocytopenia (3%) related to treatment. Tazemetostat demonstrated durable clinically meaningful single-agent activity among the patients (Morschhauser *et al.*, 2020). In an open-label, international, basket study of tazemetostat in advanced epithelioid sarcoma with loss of INI1/SMARCB1, exhibited clinical activity and also well tolerated. The result demonstrated its potential to improve results in patients with advanced epithelioid sarcoma (Gounder *et al.*, 2020).

History

Tazemetostat developed by Epizyme, Inc. was approved on 23 January 2020 by the US FDA for its use in epithelioid sarcoma which is locally advanced or metastatic when complete resection is not possible. The important developments over the years are given below (Hoy, 2020).

2011- Preclinical trials

2017- Granted the Orphan Drug Status for soft-tissue sarcoma, mesothelioma, follicular lymphoma in the USA

2018- Granted the Orphan Drug Status for diffuse large B-cell lymphoma, mesothelioma and follicular lymphoma in the EU

2019- New Drug Application for epithelioid sarcoma was accepted in the USA.Preregistration for follicular lymphoma in the USA.

2020- Approved for epithelioid sarcoma.

Chemistry

1. Chemical Name - [1,1'-Biphenyl]-3-carboxamide, N-[(1,2-dihydro-4,6-dimethyl-2-oxo-3-pyridinyl)methyl]-5[ethyl(tetrahydro-2H-pyran-4-yl)amino]-4-methyl-4'-(4 morpholinylmethyl)-, hydrobromide
2. Molecular Formula - C34H44N4O4 HBr
3. Molecular Weight - 653.66 g/mol
4. Structural Formula (Figure 1)

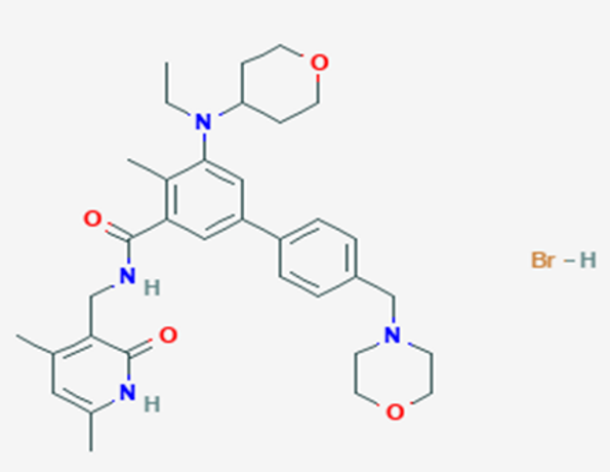

Figure 1: Chemical structure of Tazemetostat

Physical Properties

1. Solid in appearance. With a white to off-white colour.
2. Solubility - slightly water-soluble.
3. PKa values of 5.26, 6.88, and 12.62.

Dosage and Administration

800 mg twice daily orally with or without food till there is any unacceptable toxicity or progression of the disease. The whole tablet needs to be swallowed without crushing. No additional dose is recommended in case of missing a dose or vomiting after the administration of the drug (Epizyme Inc, 2020).

Mechanism of Action

The EZH2 enzymatic activity is selectively and strongly inhibited by Tazemetostat. The EZH2 gene provides instructions for making a type of enzyme called a histone methyltransferase and it modify proteins called histones. Inhibition of EZH2 specifically prevents the methylation of histone H3 lysine 27 (H3K27). This decrease in histone methylation

Table 1: Clinical pharmacology of Tazemetostat

Mechanism of action	EZH2 inhibitor
Dosing and administration	Twice daily 800 mg till there is any unacceptable toxicity or progression of the disease. The whole tablet needs to be swallowed without crushing. No additional dose is recommended in case of missing a dose or vomiting after the administration of the drug.
Dosage form and strength	Tazemetostat is available as round film-coated 200 mg red tablet, which is, biconvex shape and one side debossed with "EZM 200" and other side is plain.
Absorption and distribution	1. Bioavailability: ~33%. 2. Distribution: Vss/F: 1,230 L (46%). 3. Protein binding: 88%.
Metabolism and Excretion	1. Via CYP3A 2. 15% and 79% of radio activity is excreted through urine and feces respectively.

alters gene expression patterns associated with cancer pathways and results in decreased tumor cell proliferation in EZH2 mutated cancer cells. The pharmacology of the drug is enumerated in Table 1.

SPECIFIC POPULATIONS

Pregnancy and breastfeeding females

From the in-vitro studies it was found, tazemetostat can cause fetal harm, hence contraindicated in pregnancy. No studies enumerating the presence of tazemetostat in breast milk. Even though it is not found, the use in lactating women is also not indicated due to the potential for the occurrence of severe adverse reactions.

Females of reproductive potential

The pregnancy status must be evaluated in those females. If they are likely being of reproductive, they must use non-hormonal contraception therapy with and since six months afterward the last dose of tazemetostat. Male patients with female partners also should use effective contraception while on therapy and for three months after the last dose of tazemetostat.

Paediatrics

Tazemetostat 800 mg twice daily is given orally to adolescents who are 16 and above until the progression of the disease or toxicity that cannot be accepted.

Renal and hepatic impairment

There is no dosage adjustment for renal impairment and hepatic impairment according to the manufacturer label.

Adverse Drug Reactions

1. $\geq$20% of the adverse reactions and above was fatigue, pain, constipation, nausea, anorexia and vomiting.
2. Serious adverse reactions ($\geq$3%) included were pleural effusion, haemorrhage, respiratory distress, skin infection and dyspnea.
3. From the clinical trial evidence, 2% of patients permanently discontinued the treatment due to neurological changes like an altered mood. 34% of patients had dosage interruption due to adverse reaction.

Warning

From the clinical trial data of 668 adult patients who received 800 mg of tazemetostat twice daily, 0.6% of them developed secondary malignancies like acute myeloid leukaemia and myelodysplastic syndrome (MDS). In one paediatric patient, there was an occurrence of T-cell lymphoblastic lymphoma (T-LBL).

Drug Interactions

1. Co-administration with strong and moderate CYP3A inhibitors increases tazemetostat plasma concentration. Co-administration with strong and moderate CYP3A inducers may decrease tazemetostat plasma concentration.
2. CYP3A substrates, co-administration may result in decreased concentrations of these substrates, and thus their effects may be limited (Epizyme Inc, 2020).

CONCLUSIONS

Adults and paediatric patients aged 16 years and older with locally advanced or metastatic epithelioid sarcoma not suitable for complete resection can be treated with the first-in-class, small molecule enhancer of zeste homolog 2 inhibitor, tazemetostat (Tazverik).

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Conflict of Interest

The authors declare that they have no conflict of interest for this study.

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