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Tazemetostat

Updated: August 4, 2023.

OVERVIEW

Introduction

Tazemetostat is a methyltransferase inhibitor and antineoplastic agent used in the therapy of advanced epithelioid sarcoma. Tazemetostat is associated with a moderate rate of transient serum enzyme elevations during therapy, but has not been implicated in cases of clinically apparent acute liver injury with jaundice.

Background

Tazemetostat (taz' met o stat) is a small molecule inhibitor of the histone methyltransferase, enhancer of zest homolog 2 (EZH2), an enzyme that can be overexpressed as a result of gene mutations in certain cancers. In early clinical studies tazemetostat was found to have activity in vitro and in vivo against epithelioid sarcoma, a rare malignant soft tissue sarcoma that has a poor prognosis and is often resistant to other antineoplastic agents. In preregistration open-label trials, tazemetostat therapy was associated with an objective response rate of only 13%. Nevertheless, tazemetostat was given accelerated approval in the United States in 2020 as therapy of adults and children (16 years of age or older) with metastatic or advanced unresectable epithelioid sarcoma. Confirmatory trials were required for its continued approval, and subsequently higher rates of response have been reported in treatment of patients with epithelioid sarcoma as well as other tumors with confirmed mutations in EZH2 or in its pathway of activation. Tazemetostat is available in tablets of 200 mg under the brand name Tazverik. The recommended dose is 800 mg (4 tablets) twice daily in 28-day cycles until unacceptable toxicity or disease progression. Adverse events are common and can include pain, fatigue, nausea, vomiting, constipation, diarrhea, decreased appetite, weight loss, anemia, lymphopenia, alopecia, cough, dyspnea, and headache. Rare but potentially severe adverse events include secondary malignancies including lymphoma, leukemia and myelodysplastic syndromes, and embryo-fetal toxicity.

Hepatotoxicity

In clinical trials, serum ALT elevations occurred in 14% and AST elevations in 18% of patients on tazemetostat therapy and rose to more than 5 times ULN in 3.5%. Nevertheless, there were no instances of clinically apparent liver injury with symptoms or jaundice in several multicenter open-label trials of tazemetostat. Despite the frequency of adverse events during tazemetostat therapy, discontinuations due to adverse events are uncommon. Clinical experience with tazemetostat, however, is limited and the frequency of de novo serum enzyme elevations during treatment raises the issue of its potential for causing hepatotoxicity.

Likelihood score: E* (unproven but suspected rare cause of clinically apparent liver injury).

Mechanism of Injury

Tazemetostat is metabolized in the liver, largely via CYP 3A4 and is likely to be susceptible to drug-drug interactions with moderate or strong inducers or inhibitors of CYP 3A4 which should be avoided during therapy. The cause of the serum aminotransferase elevations during tazemetostat therapy is unknown but may relate to the inhibition of EZH2 methyltransferase or to the production of a toxic or immunogenic metabolite.

Outcome and Management

The serum enzyme elevations during tazemetostat therapy are mostly mild-to-moderate in severity but elevations above 5 times the ULN should trigger a search for other causes and, if none are found, to use dose modification or transient discontinuation until they fall into the normal or near normal range. Tazemetostat has not been linked to cases of acute liver failure, chronic hepatitis or vanishing bile duct syndrome. There is no information on cross sensitivity to hepatic injury between tazemetostat and other agents used for soft tissue sarcoma such as doxorubicin or pazopanib.

Drug Class: Antineoplastic Agents

PRODUCT INFORMATION

REPRESENTATIVE TRADE NAMES

Tazemetostat – Tazverik®

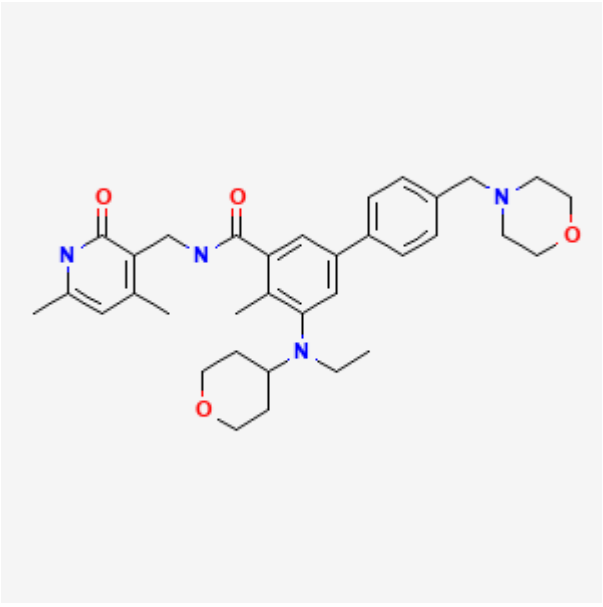
DRUG CLASS

Antineoplastic Agents

COMPLETE LABELING

Product labeling at DailyMed, National Library of Medicine, NIH

CHEMICAL FORMULA AND STRUCTURE

DRUG	CAS REGISTRY NUMBER	MOLECULAR FORMULA	STRUCTURE
Tazemetostat	1403254-99-8	C34-H44-N4-O4	

ANNOTATED BIBLIOGRAPHY

References updated: 04 August 2023

FDA. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2020/211723Orig1s000MultidisciplineR.pdf

(FDA website including product label and multidiscipline review of data submitted by the sponsor in support of the approval of tazemetostat, mentions that in a safety cohort of 62 treated subjects ALT elevations arose 14% and were above 5 times the upper limit of normal (ULN) in 3.5% while AST elevations arose in 18% and were above 5 times ULN in 3.5%. Nevertheless, there were no hepatic serious adverse events or deaths from liver failure, and the FDA reviewer concluded that "the overall safety profile of tazemetostat is acceptable for treatment of a serious and life-threatening condition").

Morschhauser F, Tilly H, Chaidos A, McKay P, Phillips T, Assouline S, Batlevi CL, et al. Tazemetostat for patients with relapsed or refractory follicular lymphoma: an open-label, single-arm, multicentre, phase 2 trial. Lancet Oncol 2020;21:1433-1442. PubMed PMID: 33035457.

(Among 99 adults with relapsed or refractory follicular lymphoma treated with tazemetostat [800 mg twice daily], the overall objective response rate was 69% in patients with the EZH2 mutant and 35% in those with wild type EZH2, and adverse events were frequent [99%] and were scored as serious in 27%, most frequently nausea, diarrhea, alopecia, cough and fatigue; ALT elevations which were above 5 times ULN arose in one patient but were not associated with symptoms or jaundice and resolved despite continuing therapy; there were no treatment related deaths).

Gounder M, Schöffski P, Jones RL, Agulnik M, Cote GM, Villalobos VM, Attia S, et al. Tazemetostat in advanced epithelioid sarcoma with loss of INI1/SMARCB1: an international, open-label, phase 2 basket study. Lancet Oncol. 2020;21:1423-1432. PubMed PMID: 33035459.

(Among 62 patients with advanced epithelioid sarcoma treated with tazemetostat [800 mg twice daily in 28-day cycles until disease progression], 9 [15%] had an objective response with a median follow up of 14 months, and while adverse events were frequent, ALT elevations arose in only 3 patients [5%], treatment related serious adverse events were uncommon [3%], and there were no treatment related deaths).

Izutsu K, Ando K, Nishikori M, Shibayama H, Teshima T, Kuroda J, Kato K, et al. Phase II study of tazemetostat for relapsed or refractory B-cell non-Hodgkin lymphoma with EZH2 mutation in Japan. Cancer Sci. 2021;112:3627-3635. PubMed PMID: 34159682.

(Among 20 Japanese patients with relapsed or refractory B-cell lymphoma harboring EZH2 mutations who were treated with tazemetostat, the objective response rate was 80% and complete response rate 50%, and while all patients had at least one adverse event, there were only 3 treatment related serious adverse events, none of which were liver related, and only 2 subjects had ALT elevations, both of which were transient and less than 5 times ULN).

Zauderer MG, Szlosarek PW, Le Moulec S, Popat S, Taylor P, Planchard D, Scherpereel A, et al. EZH2 inhibitor tazemetostat in patients with relapsed or refractory, BAP1-inactivated malignant pleural mesothelioma: a multicentre, open-label, phase 2 study. Lancet Oncol. 2022;23:758-767. PubMed PMID: 35588752.

(Among 74 adults with refractory or relapsed malignant pleural mesothelioma and a BAP-1 mutation treated with tazemetostat, the disease control rate at 12 weeks was 54% but there were no complete responses and only one ongoing partial response, and while adverse events were common [99%] and serious adverse events arose in 34%, there was no mention of ALT elevations or treatment related hepatic adverse events).