INPLASY PROTOCOL

To cite: Zhao et al. Treatment-related adverse events of EZH2 inhibitor therapies in clinical trials: a systematic review and meta-analysis. Inplasy protocol 202330028. doi: 10.37766/inplasy2023.3.0028

Received: 07 March 2023

Published: 07 March 2023

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Support: **None.**

Review Stage at time of this submission: **The review has not yet started.**

Conflicts of interest:
None declared.

Treatment-related adverse events of EZH2 inhibitor therapies in clinical trials: a systematic review and meta-analysis

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Review question / Objective: **What is the treatment-related adverse events spectrums of EZH2 inhibitor therapies? Patient: Inclusion criteria: Participants were treated with EZH2 inhibitor monotherapy or combination therapy. Exclusion criteria: (1) Participants were treated with combination therapies comprising three or more classes of agents (eg. triple combination therapies, quadruple combination therapies); (2) Participants were treated with sequentially combination therapies; (3) Duplicate cohort. Intervention: EZH2 inhibitor monotherapy or combination therapy (eg. other immunotherapy, chemotherapy, targeted therapy). Comparison: Placebo therapy, chemotherapy, targeted therapy, immunotherapy, or radiation therapy Outcomes: (1) The overall incidence of treatment-related adverse event (trAE); (2) The profile of trAE incidence. (3) The incidence of treatment-related deaths.**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 07 March 2023 and was last updated on 07 March 2023 (registration number INPLASY202330028).

INTRODUCTION

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Rationale: EZH2 inhibitors have recently been approved by the FDA for the treatment of relapsed or refractory lymphoma. In addition, a number of ongoing trials are testing EZH2 inhibitors as monotherapy or in combination in other tumors. Understanding the toxicity profile of treatment-related adverse events is critical. The purpose of this study was to comprehensively investigate the incidence and profile of treatment-related adverse events in EZH2 inhibitor therapy.

Condition being studied: Cancers, including solid tumors and hematologic malignancies that were suitable for EZH2 inhibitor therapies.

METHODS

Search strategy: The PubMed, Embase, and Cochrane databases were searched for papers of clinical trials published from Jan 1, 2000, to March 1, 2023, with the search terms "EZH2 inhibitor", "tazemetostat", "TAZVERIK" and"clinical trials". Manually screen of bibliography of included studies and relevant reviews will also be conducted to avoid omission. The language of publication will be restricted to English.

Participant or population: Participants were treated with EZH2 inhibitor monotherapy or combination therapy.

Intervention: EZH2 inhibitor monotherapy or combination therapy (eg. other immunotherapy, chemotherapy, targeted therapy).

Comparator: Placebo therapy, chemotherapy, targeted therapy, immunotherapy, or radiation therapy.

Study designs to be included: Prospective clinical trials.

Eligibility criteria: Inclusion criteria: (1) Published articles reporting prospective clinical trials; (2) Participants were treated with EZH2 inhibitor therapy; (3) Clinical trials reported overall treatment-related adverse event (trAE) incidence, incidence of treatment-related deaths, tabulated data of trAE profile; (4) Studies published in English.Exclusion criteria: (1) Participants were treated with combination therapies comprising three or more classes of agents (eg. triple combination therapies, quadruple combination therapies); (2) Participants were treated with sequentially combination therapies; (3) Duplicate cohort; (4) Patient number in combination therapy arm was less than 10; (5) Meeting abstracts without published full-text original articles.

Information sources: Information sources were obtained through publications in electronic databases (PubMed, Embase, and Cochrane databases). If the data in the article is incomplete, it will be included in the analysis if it is obtained from the contact with the author, and it will not be included in the analysis if the contact cannot be obtained. Unpublished literature will not be included in the study.

Main outcome(s): (1) The overall incidence of treatment-related adverse event (trAE); (2) The profile of trAE incidence.

Additional outcome(s): The causes and incidence of treatment-related deaths.

Data management: Two authors will independently review the included studies and extract the following data. Any discrepancy will be resolved by the third author.

1. Basic information: author, publication year, NCT number, trial name.
2. Study methods: trial phase, randomization of trial, blinding method, trial arm, CTCAE version.
3. Participants: cancer type, cancer stage, drug name EZH2 inhibitor, dose of EZH2 inhibitor, type of combination therapy, sample size.
4. Exposures: Adverse event type, criteria for adverse event reporting.
5. Outcomes:

Total number of cancer patients with EZH2 inhibitor therapy; number and proportion of patients with at least one treatment-related adverse event (trAE); number and proportion of patients with at least one grade≥3 trAE; number and proportion of all adverse events (all-grade and grade≥3); number, causes, and reasons of treatment-related deaths.

Quality assessment / Risk of bias analysis: The JBI evaluation tool is used to evaluate the bias risk assessment of single-arm clinical studies. The Cochrane Collaboration's tool is used to evaluate the bias risk assessment of randomized controlled studies. Two reviewers assessed the risk of bias of included studies, and resolved disagreements by discussion.

Strategy of data synthesis: All the statistical analysis will be performed by STATA software. Incidence of adverse events were pooled with a random-effect model. Summary measures with a logit transformation (logit(x) = log(x)-log(1-x)) were adopted for pooling of arms. A classic continuity correction of 0.5 was applied for zero cells and the corresponding sample sizes. Heterogeneity among studies was evaluated utilizing the Cochran Q statistic and I^2 test with a random-effect model.

Subgroup analysis: The overall incidence and profile of treatment-related adverse event (all-grade and grade≥3) will be pooled separately in each class of EZH2 inhibitor combination therapies (eg. other immunotherapy, chemotherapy, targeted therapy). Furthermore, subgroup analyses for the target of combination agent will be performed in each class of EZH2 inhibitor combination therapies (eg. other immunotherapy, chemotherapy, targeted therapy).

Sensitivity analysis: NA.

Language restriction: English.

Country(ies) involved: China.

Keywords: EZH2 inhibtor, Tazemetostat, TAZVERIK, clinical trials, adverse events.

Contributions of each author:

Author 1 - Zhou Zhao - Author 1 drafted the manuscript, contributed to the development of the selection criteria, and contributed to the risk of bias assessment strategy.
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Author 5 - Bo Zhang - The author read, provided feedback and approved the final manuscript.
Author 6 - Xiufeng Chen - The author read, provided feedback and approved the final manuscript.