

Safety profile of EZH2 inhibitors for cancer: a systematic review and meta-analysis

Zhou Zhao^{1,2,*}, Xiufeng Chen^{3,*}, Huayang Pang³, Yan Shi² and Hao Sun³

¹ Chongqing Key Laboratory of Translational Research for Cancer Metastasis and Individualized Treatment, Chongqing University Cancer Hospital, Chongqing, China

² Department of General Surgery, Center for Minimally Invasive Gastrointestinal Surgery, Southwest Hospital, Third Military Medical University, Chongqing, China

³ Gastrointestinal Cancer Center, Chongqing University Cancer Hospital, Chongqing, China

* These authors contributed equally to this work.

ABSTRACT

Objective: To evaluate the safety profiles of EZH2-targeted inhibitors in cancer treatment, focusing on treatment-related adverse events (TRAEs) across various clinical trials.

Methods: We conducted a systematic review and meta-analysis using data from clinical trials involving EZH2 inhibitors reported up to May 31, 2024. Databases searched included PubMed, Embase, CENTRAL (Cochrane Central Register of Controlled Trials), and [ClinicalTrials.gov](https://clinicaltrials.gov). Studies included were those involving patients treated with EZH2 inhibitors as monotherapy or in combination, specifically detailing the incidence of TRAEs. Data on all-grade TRAEs, grade 3 or higher TRAEs, and severe TRAEs were extracted and analyzed using random-effects models.

Results: Our systematic review and meta-analysis included 22 studies encompassing 1,002 patients who met the inclusion criteria. TRAEs were commonly observed during EZH2 inhibitor therapy, affecting 86% of patients (95% CI [79–94%]; $I^2 = 89.5\%$). The incidence of grade 3 or higher TRAEs was 33% (95% CI [21–44%]; $I^2 = 93.5\%$), while severe TRAEs occurred in 15% of the cases (95% CI [9–22%]; $I^2 = 87.5\%$). The most frequently reported grade 3 or higher TRAEs in the pooled analysis were neutropenia (8%), thrombocytopenia (8%), and anemia (6%). Specifically, for tazemetostat, the most common grade 3 or higher TRAE was neutropenia (5%). For SHR2554, the most prevalent grade 3 or higher TRAEs were thrombocytopenia (17%), neutropenia (8%), and anemia (7%). Notably, treatment-related fatalities were rare, with only 0.9% of patients experiencing potentially fatal outcomes due to therapy.

Conclusion: EZH2 inhibitors demonstrate a manageable safety profile with a low incidence of severe TRAEs, emphasizing their potential as safe therapeutic options in cancer treatment. The low rate of severe TRAEs and the rare occurrences of treatment-related deaths support the continued clinical use and further investigation of EZH2 inhibitors.

Submitted 26 September 2024

Accepted 24 December 2024

Published 27 January 2025

Corresponding authors

Yan Shi, doctor_shiyan@126.com

Hao Sun, sunhao_med@cqu.edu.cn

Academic editor

Hilal Ozdag Sevgili

Additional Information and
Declarations can be found on
page 18

DOI [10.7717/peerj.18871](https://doi.org/10.7717/peerj.18871)

© Copyright

2025 Zhao et al.

Distributed under

Creative Commons CC-BY 4.0

OPEN ACCESS

Subjects Clinical Trials, Drugs and Devices, Evidence Based Medicine, Hematology, Oncology
Keywords EZH2 inhibitors, Safety profile, Meta-analysis, Systematic review, Cancer

INTRODUCTION

The targeting of Enhancer of Zeste Homolog 2 (EZH2) has emerged as a pivotal strategy in cancer treatment, driven by its central role in the epigenetic regulation of gene expression (Liu *et al.*, 2023; Rosenthal, Munoz & Villasboas, 2023). As the catalytic subunit of the Polycomb Repressive Complex 2, EZH2 is instrumental in mediating trimethylation of histone H3 at lysine 27, leading to transcriptional repression of key tumor suppressor genes (Li *et al.*, 2023; Romero *et al.*, 2024). The clinical potential of EZH2 inhibitors has been demonstrated across various malignancies, with ongoing trials continuously exploring broader applications (Kaur, Shankar & Gupta, 2024; Liu & Yang, 2023). This surge in clinical utilization underscores the relevance of EZH2 as a therapeutic target, particularly in malignancies characterized by its overexpression or mutational activation.

The advent of EZH2 inhibitors, such as tazemetostat and valemetostat, has shown promising results in malignancies like lymphomas and solid tumors (Gounder *et al.*, 2020; Sabour-Takanlou, Sabour-Takanlou & Biray-Avci, 2024; Zauderer *et al.*, 2022).

Tazemetostat was approved by FDA (Food and Drug Administration) for the treatment of advanced or metastatic epithelioid sarcoma in 2020 (Hoy, 2020). In the same year, the FDA extended the approval of tazemetostat for adult patients with relapsed or refractory (R/R) follicular lymphoma (Straining & Eighmy, 2022). Valemetostat was approved in Japan in September 2022 for treating patients with R/R adult T-cell leukemia/lymphoma (Dou *et al.*, 2022). In China, SHR2554 is also undergoing multiple clinical trials (An *et al.*, 2023).

Despite their efficacy, the clinical application of EZH2 inhibitors is accompanied by a range of adverse events (Izutsu *et al.*, 2023; Morschhauser *et al.*, 2020; Tachibana *et al.*, 2024). These adverse effects vary widely, from mild and manageable to severe and potentially life-threatening, impacting patient quality of life and clinical outcomes. The complexity of these adverse event profiles necessitates a comprehensive analysis to better understand and manage the potential risks associated with EZH2-targeted therapies.

In response to this need, we conducted a systematic review and meta-analysis of treatment-related adverse events (TRAEs) associated with EZH2 inhibitors used in clinical trials. Our objectives were to collate and synthesize existing data on the safety profiles of these agents, and assess the incidence of specific TRAEs. This analysis would offer valuable insights for clinicians in optimizing treatment strategies and enhancing patient care.

MATERIALS AND METHODS

Search strategy and selection criteria

We conducted a systematic review and meta-analysis to identify published clinical trials that employed EZH2-targeted inhibitors and reported TRAEs. Comprehensive searches were conducted in PubMed, Embase, CENTRAL, and ClinicalTrials.gov before May 31, 2024. The search terms used included “EZH2”, “inhibitor”, and “clinical trial” (see Table S1 for detailed search details). To ensure thorough coverage, references of relevant reviews and articles were manually reviewed.

Selection was based on the following criteria: (1) studies reporting on prospective clinical trials before May 31, 2024, (2) clinical trials of EZH2 inhibitors as monotherapy or in combination in patients with solid or hematological tumors, (3) clinical trials that provided detailed incidence or data on TRAEs, and (4) studies published in English. Exclusion was based on the following criteria: (1) studies with fewer than ten participants in the EZH2 inhibitor group, (2) trials using sequential therapies, (3) studies without clear TRAEs data, (4) publications reporting duplicate populations. For duplicated publications, we only included the most recent study or the study reporting the most complete profile of TRAEs.

Literature searches and data extraction were independently conducted by two reviewers (ZZ and XC), with discrepancies resolved through discussion or consultation with a senior author (HS).

This study adhered to the PRISMA guidelines ([Page et al., 2021](#)), and a prospective protocol was registered with INPLASY (202330028).

Data extraction

Data extracted included trial name (or author details), publication year, trial phase, type of cancer, name of the EZH2 inhibitor, dose of EZH2 inhibitor, number of patients receiving the therapy, and the number of patients experiencing at least one TRAEs. Specific data on all-grade TRAEs (Common Terminology Criteria for Adverse Events (CTCAE) grades 1 to 5) ([Shah, 2022](#)), Grade 3+ TRAEs (CTCAE grades 3 to 5), severe TRAEs, treatment-related deaths, TRAEs leading to dose reduction, TRAEs leading to therapy interruption, TRAEs leading to therapy discontinuation, and TRAEs leading to death were recorded. Adverse event terminology was standardized according to the Medical Dictionary for Regulatory Activities (MedDRA) ([MedDRA, 2018](#)).

Outcomes

According to the prespecified protocol, the primary outcomes were the overall incidences of TRAEs (defined as the number of patients experiencing at least one adverse event divided by the total number of patients), the profiles of all grade TRAEs, severe TRAEs, grades 3 or higher TRAEs, and treatment-related death. Additional analyses included the incidence of TRAEs leading to dose reduction, therapy interruption, and therapy discontinuation.

Statistical analysis

We applied random-effects models with logit transformation for meta-analysis of TRAEs incidences and TRAEs profiles. The effect size of all pooled results was represented by 95% CI with an upper limit and a lower limit. Subgroup analyses were performed using incidence with 95% confidence intervals, calculated through random-effects models.

Heterogeneity among studies was assessed using I^2 statistics. All included studies (single-arm studies) were assessed by methodological index for non-randomized studies (MINORS) ([Slim et al., 2003](#)). The sensitivity analysis was performed by excluding each study one by one for the pooled results with high heterogeneity. Potential publication bias

was evaluated through visual inspection of funnel plots. All statistical analyses were performed using STATA software, employing packages suitable for meta-analysis.

Protocol deviations

In the course of this systematic review and meta-analysis, several deviations from the initially registered protocol were necessary to accommodate new data and expand the scope of the analysis. Firstly, the cut-off time for including published clinical trials was extended to May 31, 2024. This adjustment was made to incorporate the most recent clinical trials involving EZH2 inhibitors, ensuring that our analysis reflects the latest developments and data in this rapidly evolving field. Secondly, we expanded our selection criteria to include combination therapies comprising three or more classes of therapeutic agents. This inclusion was driven by the growing clinical interest in more complex combination regimens that target multiple pathways, which may influence the safety profile and efficacy of EZH2-targeted treatments. These changes were made to enhance the comprehensiveness and relevance of our meta-analysis, allowing for a more detailed and current understanding of the TRAEs profiles associated with EZH2 inhibitors in cancer treatment.

RESULTS

Study selection and characteristics

[Figure 1](#) shows a flowchart of the study selection procedure. The electronic searches yielded 351 potentially relevant records, of which 79 potentially eligible records were assessed ([Table S2](#)). After further screening, we identified 28 studies reporting adverse events data of EZH2 inhibitors in cancer treatment (including treatment-emergent adverse events (TEAEs) and TRAEs) ([Table 1](#)). Finally, 22 eligible studies (20 trials) involving 1,002 patients, were included in the quantitative analysis ([Abida et al., 2021](#); [Chawla et al., 2021](#); [Chi et al., 2022, 2023](#); [Eisai, 2022](#); [Feng et al., 2023](#); [Gounder et al., 2020](#); [Harb et al., 2018](#); [Hussain et al., 2024](#); [Italiano et al., 2018](#); [Izutsu et al., 2023](#); [Morschhauser et al., 2020](#); [Palmieri et al., 2023](#); [Palomba et al., 2022](#); [Puram et al., 2023](#); [Salles et al., 2023](#); [Sarkozy et al., 2020](#); [Schweizer et al., 2022](#); [Song et al., 2024, 2022](#); [Yap et al., 2019](#); [Zauderer et al., 2022](#)).

[Table S3](#) shows the baseline characteristics of the 22 studies (20 trials). Four trials (NCT04407741, NCT04224493, NCT04204941, and NCT04179864) are randomised controlled trials in phase II or phase III. However, the results of these phases have not yet been published. Cancer types tested in these studies included hematologic malignancies ($n = 9$), solid tumors ($n = 7$), and both ($n = 6$). Among the 1,002 patients included in the meta-analysis, 666 patients (15 studies) received tazemetostat, 174 patients (three studies) received SHR2554, 57 patients (one studies) received PF-06821497, 41 (one studies) received GSK2816126, 32 patients (one studies) received CPI-1205, and 25 patients (one studies) received valemetostat. For drug combinations, 744 patients (13 studies) received monotherapy, 33 patients (two studies) received tazemetostat with chemotherapy, 117 patients (four studies) received tazemetostat/SHR2554 with immunotherapy, 44 patients (one study) received tazemetostat with targeted therapy, 43 patients (one study) received

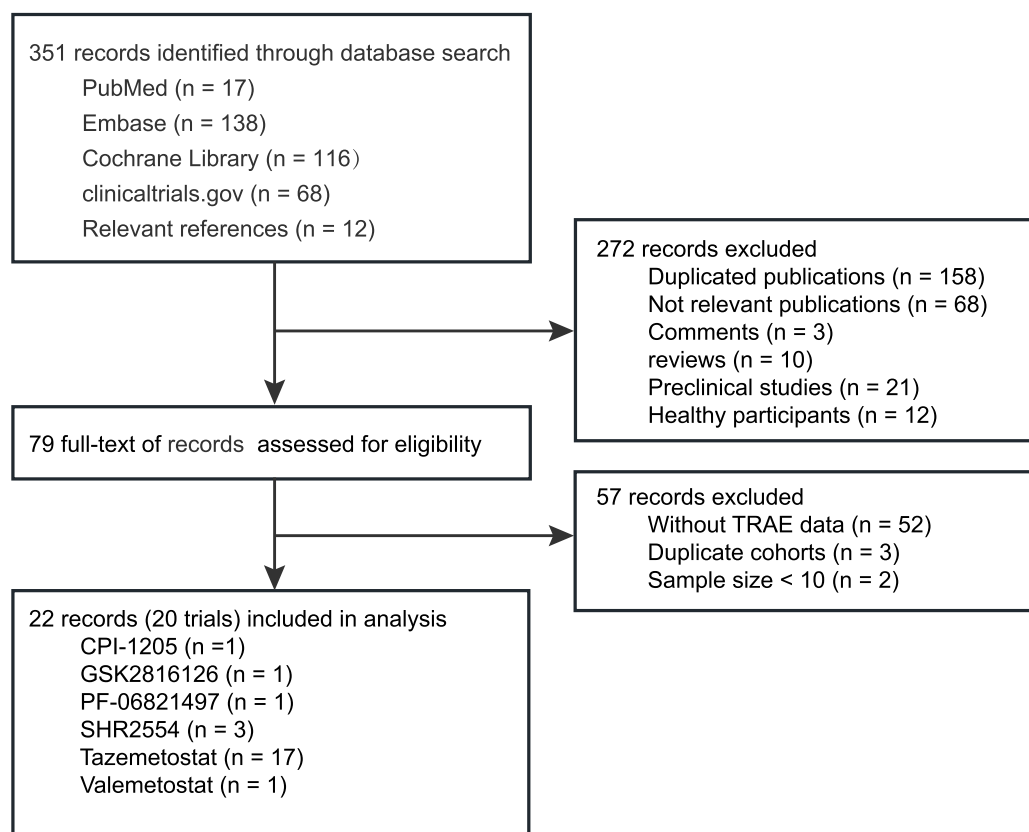


Figure 1 Flow chart of studies selection process.

Full-size DOI: 10.7717/peerj.18871/fig-1

Table 1 Information of clinical studies reporting adverse events.

Phase	Trial ID	Cancer type	Involved EZH2 inhibitors	Dose	Sample size, n
1/2	NCT04104776 ^A	Advanced HM and ST	CPI-0209	200/300/350 mg, qd, po, q28d	117
1	NCT02395601	BCL	CPI-1205	200/400/800/1,600 mg, bid, po, q28d	32
1	NCT02082977	Advanced HM and ST	GSK2816126	50 to 3,000 mg, biw, po, D1-21, q28d	41
1	NCT03460977	R/R CRPC/SCLC/FL	PF-06821497	dose escalation, bid, po	57
1	NCT03603951 ^B	R/R mature lymphomas	SHR2554	50 to 800 mg, bid, po, q28d	113
1	NCT03603951 ^B	R/R PTCL	SHR2554	350 mg, bid, po, q28d	28
1/2	NCT04407741	Advanced ST and BCL	SHR2554	300 to 350 mg, bid, po, q21d	33
1/3	NCT04224493	R/R FL	Tazemetostat	400/600/800 mg, bid, po, q28d	44
2	NCT01897571 ^C	R/R FL	Tazemetostat	800 mg, bid, po, q28d	99
1	NCT01897571 ^C	R/R DLBCL or ST	Tazemetostat	100 to 1,600 mg, bid, po, q28d	64
2	NCT02601950	INI1-Negative tumors or R/R synovial sarcoma	Tazemetostat	800 mg, bid, po, q28d	62
1/3	NCT04204941	Advanced epithelioid sarcoma	Tazemetostat	400/600/800 mg, bid, po	16

(Continued)

Table 1 (continued)

Phase	Trial ID	Cancer type	Involved EZH2 inhibitors	Dose	Sample size, n
2	NCT03213665	Tumors with alterations in EZH2 or SWI/SNF complex	Tazemetostat	1,200 mg/m ² , bid, po, q28d	20
1/2	NCT04179864	Metastatic CRPC	Tazemetostat	Arm 1: escalated to 1,600 mg, bid, po Arm 2: escalated to 800 mg, bid, po	14 7
–	NCT02875548 ^D	Advanced HM and ST	Tazemetostat	800 mg, bid, po, q28d	99
2	NCT02860286	R/R malignant mesothelioma	Tazemetostat	800 mg, bid, po, q21d	74
1/2	NCT02889523	DLBCL or FL	Tazemetostat	400/600/800 mg, bid, po, q21d	17
2	NCT04762160 ^E	R/R FL	Tazemetostat	800 mg, bid, po, q28d	5
2	NCT03456726	R/R BCL with EZH2 gene mutation	Tazemetostat	800 mg, bid, po, q28d	20
1	NCT02601937	R/R INI1-negative tumors or synovial sarcoma	Tazemetostat	800 mg, bid, po, q28d 800 mg, tid, po, q28d	46 63
1/2	NCT03854474	Advanced urothelial carcinoma	Tazemetostat	800 mg, bid, po	25
1	NCT03009344 ^E	R/R B-cell NHL	Tazemetostat	800 mg, bid, po, q28d	7
1	NCT02220842	R/R DLBCL	Tazemetostat	800 mg, bid, po, q21d	43
2	NCT04705818	Advanced MSS CRC	Tazemetostat	800 mg, bid, po, q21d	47
1	NCT04624113	Pembrolizumab- or nivolumab-resistant R/R HNSCC	Tazemetostat	400/600/800 mg, bid, po, q21d	12
1	NCT02732275 ^A	R/R NHL	Valemetostat	150 to 300 mg, qd, po, q28d	78
2	NCT04703192 ^A	R/R PTCL	Valemetostat	200 mg, qd, po, q28d	133
2	NCT04102150	R/R T-cell leukemia/lymphoma	Valemetostat	200 mg, qd, po, q28d	25

Note:

^AThese studies reported only treatment-emergent adverse events, but no data were available on treatment-related adverse events; ^Bthese two records were from different subgroups in the same study, and there is no duplicate reporting of data; ^Cthese two records are phase 1 and phase 2 studies in the same study, and no duplicate patients are reported in their data; ^Dthe patients in this study were those who received treatment for more than 2 years in the NCT01897571 study; ^Esample size less than 10. ^{A/D/E}Not included in subsequent calculations; ^{B/C}included in subsequent calculations. **Abbreviation:** BCL, B-cell lymphoma; CRC, colorectal cancer; CRPC, castration resistant prostate cancer; DLBCL, diffuse large B cell lymphoma; FL, follicular lymphoma; HL, Hodgkin lymphoma; HM, hematologic malignancies; HNSCC, head and neck squamous cell carcinoma; MSS, microsatellite stable; NHL, non-Hodgkin lymphoma; PTCL, peripheral T cell lymphoma; R/R, relapsed/refractory; SCLC, small cell lung cancer; ST, solid tumor.

tazemetostat with immunotherapy and targeted therapy, 14 patients (one study) received tazemetostat with endocrine therapy.

Quality assessment

Two independent authors (Z.Z. and X.C.) assessed the quality of each study included in the meta-analysis using MINORS. Evaluations were compared, and any inconsistencies between the review authors were discussed and resolved. The MINORS scores ranged from 12 to 16 out of a possible score of 16 (Table 2).

Any-grade TRAEs

Any-grade TRAEs were reported in 418/487 patients of 10 studies. The pooled result of any-grade TRAEs was 86% (95% CI [79–94%]; $I^2 = 89.5\%$). Subgroup analyses were performed based on drug, drug combination, tumor type, and drug dose. For Tazemetostat, the pooled rates were 85% (95% CI [77–94%]; $I^2 = 68.5\%$) for all-grade TRAEs. In the case of SHR2554, the pooled rates were 82% (95% CI [64–100%];

Table 2 Methodological index for non-randomized studies (MINORS).

Trial name	Year	MINORS total score	1	2	3	4	5	6	7	8
NCT02395601	2018	15	●	●	●	●	●	●	●	●
NCT02082977	2019	15	●	●	●	●	●	●	●	●
NCT03460977	2023	14	●	●	●	●	●	●	●	●
NCT03603951	2022	13	●	●	●	●	●	●	●	●
NCT03603951	2024	15	●	●	●	●	●	●	●	●
NCT04407741	2023	14	●	●	●	●	●	●	●	●
NCT04224493	2023	14	●	●	●	●	●	●	●	●
NCT01897571	2020	15	●	●	●	●	●	●	●	●
NCT01897571	2017	15	●	●	●	●	●	●	●	●
NCT02601950	2020	16	●	●	●	●	●	●	●	●
NCT04204941	2021	12	●	●	●	●	●	●	●	●
NCT03213665	2023	14	●	●	●	●	●	●	●	●
NCT04179864	2021	12	●	●	●	●	●	●	●	●
NCT02860286	2022	15	●	●	●	●	●	●	●	●
NCT02889523	2020	14	●	●	●	●	●	●	●	●
NCT03456726	2022	15	●	●	●	●	●	●	●	●
NCT02601937	2021	14	●	●	●	●	●	●	●	●
NCT03854474	2024	13	●	●	●	●	●	●	●	●
NCT02220842	2022	15	●	●	●	●	●	●	●	●
NCT04705818	2023	12	●	●	●	●	●	●	●	●
NCT04624113	2023	13	●	●	●	●	●	●	●	●
NCT04102150	2023	15	●	●	●	●	●	●	●	●

Note:

Items 1–12 represent: 1, a clearly stated aim; 2, inclusion of consecutive patients; 3, prospective collection of data; 4, endpoints appropriate to the aim of the study; 5, unbiased assessment of the study endpoint; 6, follow-up period appropriate to the aim of the study; and 7, loss to follow-up less than 5%; 8, prospective calculation of the study size. An item scored 0 means not mentioned, one means reported but inadequate, and two means reported and adequate. The total score was 16 for self-controlled studies. Use red for 0, yellow for 1 and green for 2.

$I^2 = 96.3\%$). The rate of any-grade TRAEs in GSK2816126 and valemestostat each reported in only one study, were 90% and 96%, respectively (Fig. 2A). When restricted to monotherapy studies, the pooled rates for tazemetostat, SHR2554, and valemestostat were 80%, 99%, and 96%, respectively (Fig. S1A). Further limiting the analysis to monotherapy studies using active doses, the pooled rates for tazemetostat, SHR2554, and valemestostat were 82%, 100%, and 96%, respectively (Fig. S2A).

When subgroup analysis was performed based on drug combination, the probability of any-grade TRAEs was 90%, 39%, 86%, and 95% for monotherapy, combination with immunotherapy, combination with endocrine therapy, and combination with targeted and immunotherapy, respectively (Fig. S3A). When analyzed by cancer type, the rates of any-grade TRAEs were 94%, 86%, and 70% in studies that included only hematologic tumors, only solid tumors, and both, respectively (Fig. S3B).

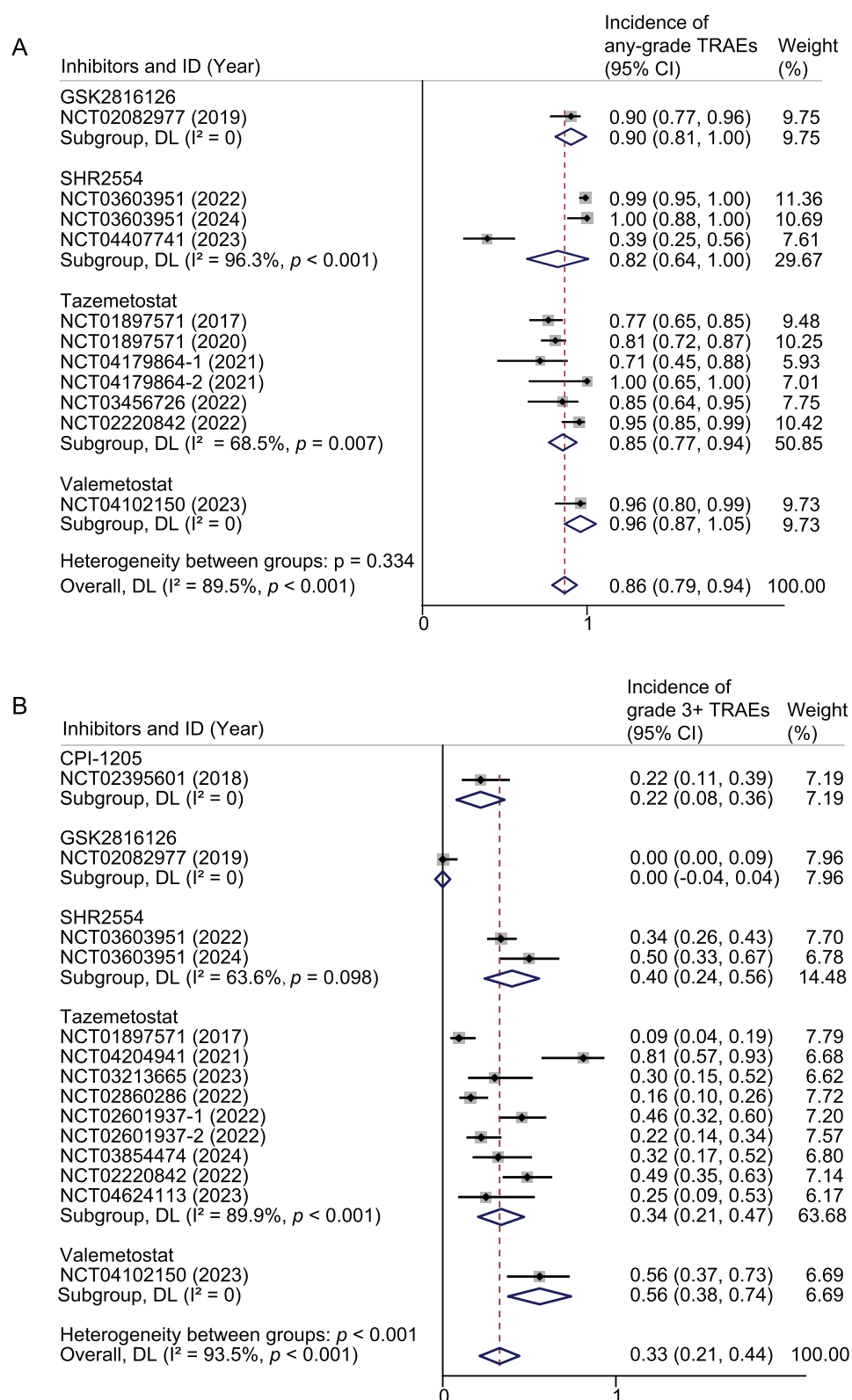


Figure 2 Pooled results of any-grade TRAEs (A) and grade 3 or higher TRAEs (B) by inhibitor subgroup. Weights and between-subgroup heterogeneity test are from random-effects model.

Full-size  DOI: 10.7717/peerj.18871/fig-2

Grade 3 or higher TRAEs

Grade 3 or higher TRAEs were reported in 177/602 patients of 13 studies. The pooled result of grade 3 or higher TRAEs was 33% (95% CI [21–44%]; $I^2 = 93.5\%$). For tazemetostat, the pooled rates were 34% (95% CI [21–47%]; $I^2 = 89.9\%$) for grade 3 or higher TRAEs. In the case of SHR2554, the pooled rates were 40% (95% CI [24–56%]; $I^2 = 63.6\%$). The rate of grade 3 or higher TRAEs in CPI-1205, GSK2816126 and valemestostat each reported in only one study, were 22%, 0, and 56%, respectively (Fig. 2B). When restricted to monotherapy studies, the pooled rates for tazemetostat, SHR2554, and valemestostat were 23%, 40%, and 56%, respectively (Fig. S1B). Further limiting the analysis to monotherapy studies using active doses, the pooled rates for tazemetostat, SHR2554, and valemestostat were 27%, 50%, and 56%, respectively (Fig. S2B).

When subgroup analysis was performed based on drug combination, the pooled rates were 27%, 29%, 81%, and 49% for monotherapy, combination immunotherapy, combination chemotherapy, and combination targeted and immunotherapy, respectively (Fig. S4A). When analyzed by cancer type, the pooled rates were 41%, 35%, and 4% in studies that included only hematologic tumors, only solid tumors, and both, respectively (Fig. S4B).

Severe TRAEs

Severe TRAEs were reported in 87/586 patients of 11 studies. The pooled result of severe TRAEs was 15% (95% CI [9–22%]; $I^2 = 87.5\%$). For tazemetostat, the pooled rates were 15% (95% CI [7–23%]; $I^2 = 87.9\%$) for severe TRAEs. In the case of SHR2554, the pooled rates were 20% (95% CI [8–32%]; $I^2 = 51.4\%$). The rate of severe TRAEs in GSK2816126 and valemestostat each reported in only one study, were 0% and 28%, respectively (Fig. 3A). When restricted to monotherapy studies, the pooled rates for tazemetostat, SHR2554, and valemestostat were 15%, 20%, and 28%, respectively (Fig. S1C). Further limiting the analysis to monotherapy studies using active doses, the pooled rates for tazemetostat, SHR2554, and valemestostat were 19%, 29%, and 28%, respectively (Fig. S2C).

When subgroup analysis was performed based on drug combination, the pooled rates were 15%, 12%, and 21% for monotherapy, combination chemotherapy, and combination targeted and immunotherapy, respectively (Fig. S5A). When analyzed by cancer type, the pooled rates were 20%, 18%, and 1% in studies that included only hematologic tumors, only solid tumors, and both, respectively (Fig. S5B).

Compliance

Compliance was analyzed from three aspects: TRAEs leading to discontinuation, dose reduction, and interruption. TRAEs leading to discontinuation was reported in 28/583 patients of 11 studies. The pooled result of discontinuation was 4% (95% CI [2–5%]; $I^2 = 15.0\%$). For tazemetostat, the pooled rate was 4% (95% CI [1–7%]; $I^2 = 45.5\%$). In the case of SHR2554, the pooled rate was 4% (95% CI [0–7%]; $I^2 = 0$). The rate in GSK2816126 and valemestostat each reported in only one study, were 2% and 8%, respectively (Fig. 3B).

TRAEs leading to dose reduction was reported in 53/587 patients of 11 studies. The pooled result of dose reduction was 8% (95% CI [4–13%]; $I^2 = 80.4\%$). For tazemetostat,

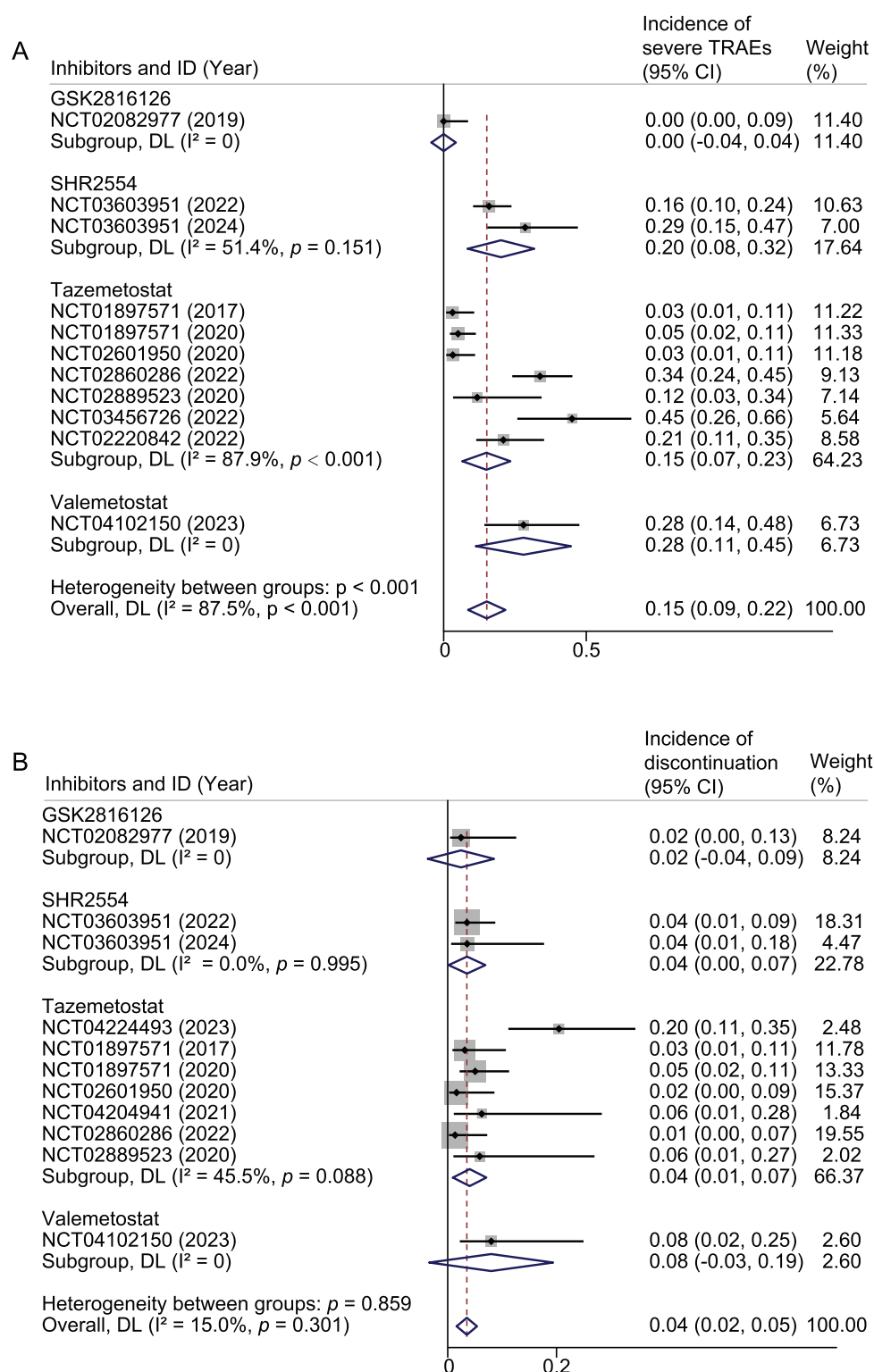


Figure 3 Pooled results of severe TRAEs (A) and TRAEs leading to discontinuations by inhibitor subgroup. Weights and between-subgroup heterogeneity test are from random-effects model.

Full-size DOI: 10.7717/peerj.18871/fig-3

the pooled rates were 10% (95% CI [3–16%]; $I^2 = 87.2\%$) for dose reduction. In the case of SHR2554, the pooled rates were 8% (95% CI [3–12%]; $I^2 = 0$). The rate in GSK2816126 and valemestostat each reported in only one study, were 5% and 8%, respectively (Fig. S6A). TRAEs leading to interruption was reported in 175/505 patients of nine studies. The pooled result of interruption was 34% (95% CI [30–38%]; $I^2 = 88.8\%$). For tazemetostat, the pooled rate was 36% (95% CI [31–41%]; $I^2 = 93.5\%$). In the case of SHR2554, the pooled rate was 36% (95% CI [28–44%]; $I^2 = 0$). The rate in GSK2816126 and valemestostat each reported in only one study, were 24% and 16%, respectively (Fig. S6B).

TRAEs leading to death

TRAEs leading to death was reported in 5/583 (0.9%) patients of 11 studies. Among them, three died due to infection, two died due to cardiopulmonary failure. In the study (NCT03603951) (Song *et al.*, 2022), one patient died due to skin infection and toxic epidermal necrolysis and another one patient died because of respiratory failure. Both patients received SHR2554 350 mg twice daily. In the study (NCT02889523) (Sarkozy *et al.*, 2020), one patient died because of infection-related death. The patient received tazemetostat (800 mg twice daily) with R-CHOP regimen every 21 days. In the study (NCT02220842), one died due to cardiac decompensation secondary to the event of hyponatremia, and one died due to septic shock. Both of them received tazemetostat (800 mg twice daily) every 21 days in combination with atezolizumab (1,200 mg) on day 1 of each cycle.

Specific any-grade TRAE spectrum

The most common laboratory any-grade TRAEs for EZH2 inhibitors were thrombocytopenia (139/466, 30%), anemia (158/597, 26%), neutropenia (98/450, 22%), ALT increased (30/456, 7%), lymphopenia (25/391, 5%), AST increased (21/403, 5%), and hypokalemia (14/277, 5%) (Fig. 4A). The most common non-laboratory any-grade TRAEs for EZH2 inhibitors were nausea (148/597, 25%), fatigue (139/584, 24%), decreased appetite (32/163, 20%), alopecia (27/144, 19%), muscle spasms (17/106, 16%), rash (21/121, 17%), vomiting (67/484, 14%), diarrhea (64/524, 12%), and pyrexia (17/279, 6%) (Fig. 4B).

For tazemetostat, the most common laboratory any-grade TRAEs were anemia (63/347, 18%), neutropenia (35/273, 13%), thrombocytopenia (31/257, 12%), lymphopenia (7/189, 4%), hypokalemia (3/125, 2%), ALT increased (4/251, 2%), and AST increased (4/251, 2%) (Fig. 4C). The most common non-laboratory any-grade TRAEs for tazemetostat were fatigue (83/322, 26%), nausea (80/335, 24%), decreased appetite (24/127, 19%), rash (21/121, 17%), alopecia (17/119, 14%), vomiting (32/247, 13%), diarrhea (34/274, 12%), and pyrexia (9/226, 4%) (Fig. 4D).

For SHR2554, the most common laboratory any-grade TRAEs were thrombocytopenia (88/173, 51%), anemia (71/173, 41%), neutropenia (52/141, 37%), hyperbilirubinemia (18/141, 37%), AST increased (17/141, 12%), ALT increased (16/141, 11%), lymphopenia (12/141, 9%), and hypokalemia (11/141, 8%) (Fig. 4E). The most common non-laboratory

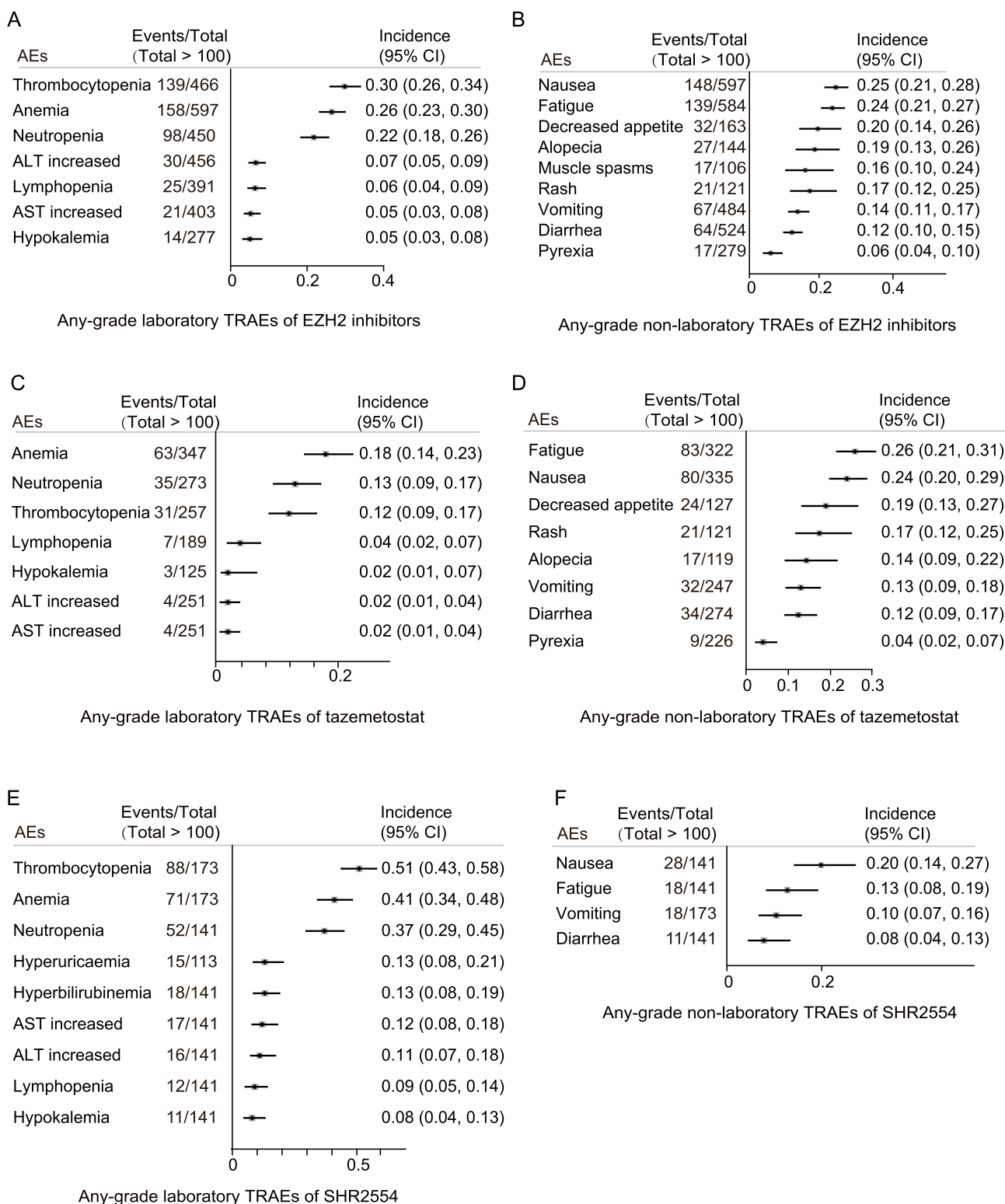


Figure 4 Specific any-grade TRAE spectrum. (A) Any-grade laboratory TRAE spectrum of EZH2 inhibitors; (B) any-grade non-laboratory TRAE spectrum of EZH2 inhibitors; (C) any-grade laboratory TRAE spectrum of tazemetostat; (D) any-grade non-laboratory TRAE spectrum of tazemetostat; (E) any-grade laboratory TRAE spectrum of SHR2554; (F) any-grade non-laboratory TRAE spectrum of SHR2554.

Full-size  DOI: 10.7717/peerj.18871/fig-4

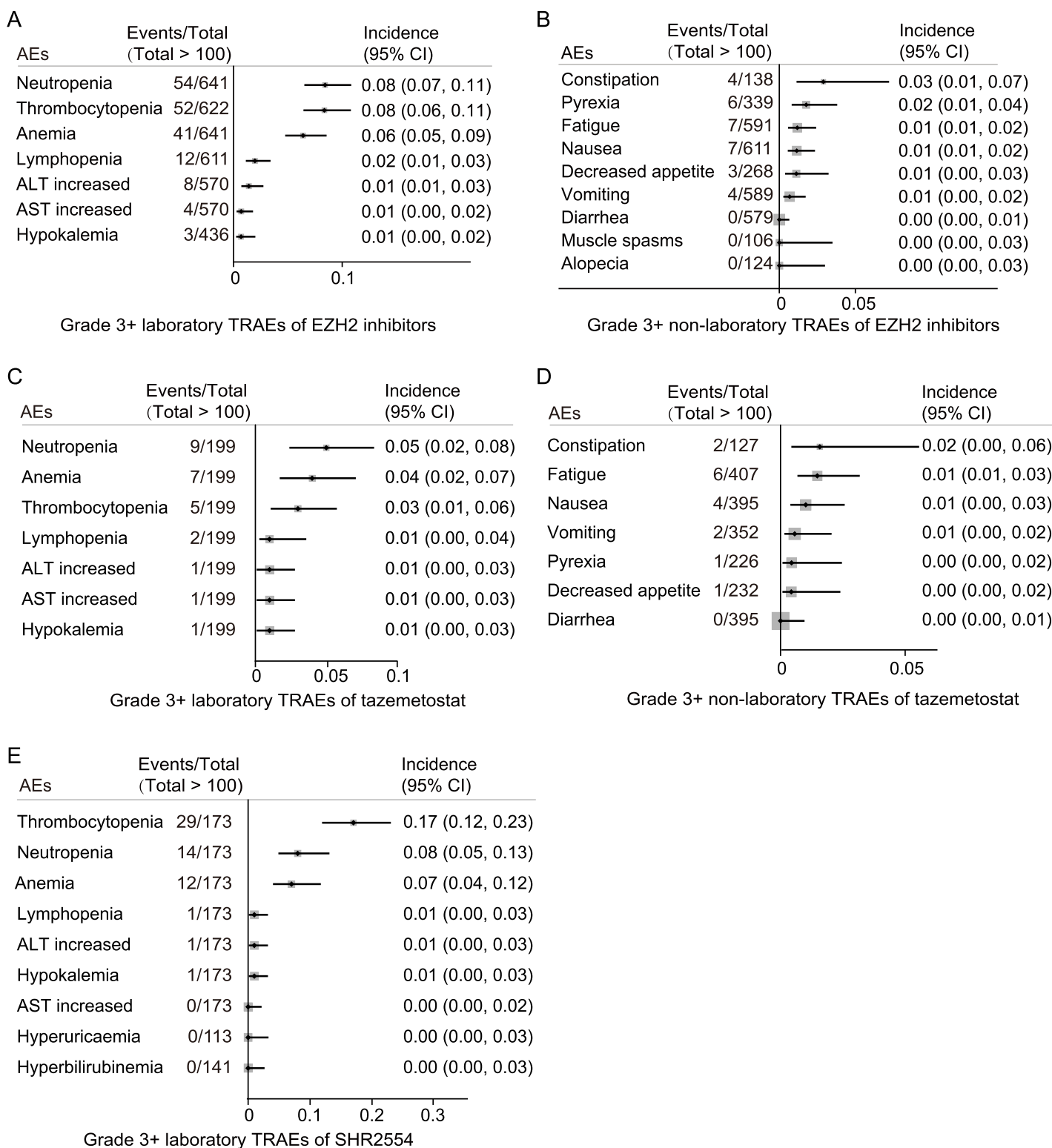


Figure 5 Specific grade 3 or higher TRAE spectrum. (A) Grade 3 or higher laboratory TRAE spectrum of EZH2 inhibitors; (B) grade 3 or higher non-laboratory TRAE spectrum of EZH2 inhibitors; (C) grade 3 or higher laboratory TRAE spectrum of tazemetostat; (D) grade 3 or higher non-laboratory TRAE spectrum of tazemetostat; (E) grade 3 or higher laboratory TRAE spectrum of SHR2554.

Full-size  DOI: 10.7717/peerj.18871/fig-5

any-grade TRAEs for SHR2554 were nausea (28/141, 20%), fatigue (18/141, 13%), vomiting (18/173, 10%), and diarrhea (11/141, 8%) (Fig. 4F).

Specific grade 3 or higher TRAE spectrum

The most common laboratory grade 3 or higher TRAEs for EZH2 inhibitors were neutropenia (54/641, 8%), thrombocytopenia (52/622, 8%), anemia (41/641, 6%), lymphopenia (12/611, 2%), ALT increased (8/570, 1%), AST increased (4/570, 1%), and hypokalemia (3/436, 1%) (Fig. 5A). The most common grade 3 or higher non-laboratory TRAEs for EZH2 inhibitors were constipation (4/138, 3%), pyrexia (6/339, 6%), fatigue (7/591, 1%), nausea (7/611, 1%), decreased appetite (3/268, 1%), and vomiting (4/589, 1%) (Fig. 5B).

The most common laboratory grade 3 or higher TRAEs for tazemetostat were neutropenia (9/199, 5%), anemia (7/199, 4%), thrombocytopenia (5/199, 3%), lymphopenia (2/199, 1%), ALT increased (1/199, 1%), AST increased (1/199, 1%), and hypokalemia (1/199, 1%) (Fig. 5C). The incidence of grade 3 or higher non-laboratory TRAEs with tazemetostat is limited (all < 2%) (Fig. 5D).

For SHR2554, the most common laboratory grade 3 or higher TRAEs were thrombocytopenia (29/173, 17%), neutropenia (14/173, 8%), and anemia (12/173, 7%) (Fig. 5E). The incidence of grade 3 or higher non-laboratory TRAEs with SHR2554 was not reported.

Sensitivity analysis

Sensitivity analyses were conducted to evaluate the robustness of the pooled estimates for any-grade TRAEs (Fig. S7A), grade 3 or higher TRAEs (Fig. S7B), and TRAEs leading to discontinuation (Fig. S7C). The analyses involved sequentially omitting individual studies from the meta-analysis. The overall results remained stable and were not significantly altered by the exclusion of any single study, suggesting that our findings are robust and not unduly influenced by any particular study.

Risk of bias

To assess the presence of risk of bias in our meta-analysis, funnel plots were constructed for any-grade TRAEs (Fig. S8A), grade 3 or higher TRAEs (Fig. S8B), and TRAEs leading to discontinuation (Fig. S8C). The analysis of the funnel plots for any-grade TRAEs suggested potential publication bias in three studies: NCT01897571 (2017), NCT01897571 (2020), and NCT04407741 (2023). Similarly, the evaluation for grade 3 or higher TRAEs revealed potential biases in five studies: NCT01897571 (2017), NCT02601937-2 (2022), NCT02860286 (2022), NCT02395601 (2018), and NCT04204941 (2021). For TRAEs that led to therapy discontinuation, potential publication bias was observed in one study, NCT04224493 (2023). These findings indicate the need for cautious interpretation of the pooled results, particularly in the presence of indicated biases.

DISCUSSION

This meta-analysis evaluated the safety profiles of EZH2-targeted inhibitors in cancer treatment, focusing particularly on TRAEs. Our extensive review included 22 studies with

1,002 patients, uncovering a high prevalence of any-grade TRAEs at 86%. Common any-grade TRAEs included thrombocytopenia, anemia, neutropenia, nausea, fatigue, and decreased appetite, each affecting more than 20% of patients (Figs. 2 and 4). Meanwhile, grade 3 or higher TRAEs occurred in 33% of the cohort, primarily as neutropenia, thrombocytopenia, and anemia (Figs. 2 and 4).

EZH2 plays a critical role in cancer progression through the epigenetic regulation of gene expression (Huang *et al.*, 2023; Liu *et al.*, 2023). Inhibitors targeting EZH2 are increasingly recognized for their therapeutic potential, especially in cancers characterized by overexpression or mutation of EZH2 (Grünewald *et al.*, 2024; Wan *et al.*, 2023). Our findings corroborate broader research that attests to the safety of these inhibitors (Marzochi *et al.*, 2023).

Our subgroup analyses revealed variability in TRAEs across different inhibitor types, drug combinations, and cancer types. To explore which EZH2 inhibitor may be safer, we analyzed pooled data on TRAEs from monotherapy trials involving approved EZH2 inhibitors. The results suggest that, compared to SHR2554 and valemestostat, tazemetostat may have a lower incidence of any-grade TRAEs (80%), grade 3 or higher TRAEs (23%), and severe TRAEs (15%) (Fig. S7). However, due to the limited number of studies reporting adverse events for each inhibitor, definitive conclusions regarding the comparative safety profiles of these inhibitors cannot yet be drawn. Notably, the overall incidence of severe TRAEs at 15% indicates that EZH2 inhibitors are generally manageable and well-tolerated. Furthermore, treatment discontinuation due to adverse events was low, at only 4%.

In terms of drug combinations, most studies involved monotherapy. The rates of any-grade, grade 3 or higher, and severe TRAEs, were 90%, 27%, and 15%, respectively, in monotherapy settings (Figs. S3–S5). For rate of any-grade, one study reported a notably low incidence of any-grade TRAEs (39%) for SHR2254 combined with immunotherapy, though this study had a small sample size and potential risk of bias (NCT04407741) (Fig. S3A). Conversely, a high incidence of grade 3 or higher TRAEs was observed in a study evaluating tazemetostat combined with chemotherapy (NCT04204941) (Fig. S4A). Interestingly, a recent study revealed that the combination of valemestostat and irinotecan was not tolerated in patients with recurrent small-cell lung cancer, highlighting the potential for overlapping toxicity when EZH2 inhibitors are used in combination with chemotherapeutic agents (Choudhury *et al.*, 2024). These findings underscore the importance of carefully selecting combination regimens to minimize treatment-related toxicities.

In terms of cancer types, it is noteworthy that studies involving both hematologic malignancies and solid tumors reported unexpectedly low rates of all-grade TRAEs, grade 3 or higher TRAEs, and severe TRAEs, at 70%, 4%, and 1%, respectively (Figs. S3–S5). For instance, one terminated study reported limited anticancer activity of GSK2816126, which contributed to the low TRAE rates observed (Yap *et al.*, 2019). Another study (NCT01897571 (2017)) (Italiano *et al.*, 2018) served as a first-in-human, open-label, phase 1 trial evaluating tazemetostat in cancer treatment. This trial was designed as a dose-escalation study, with dosages ranging from 100 to 1,600 mg administered twice

daily. This dosing approach could explain the relatively low incidence of grade 3 or higher and severe TRAEs observed in the study. After excluding these two studies, our analysis revealed no significant differences in the rates of all-grade TRAEs, grade 3 or higher TRAEs, or severe TRAEs between hematologic malignancies and solid tumors treated with EZH2 inhibitors (94% vs. 86%, $p = 0.610$; 41% vs. 35%, $p = 0.573$; 20% vs. 18%, $p = 0.904$) (Figs. S9A–S9C).

Our study highlights the critical need for infection prevention, especially considering that EZH2 inhibitors can cause neutropenia and lymphopenia, which may predispose patients to infections. Out of the five patient deaths identified, three were potentially due to infectious diseases, underscoring the importance of vigilant monitoring and preventive measures against infection during treatment with EZH2 inhibitors.

In addition to assessing the safety profiles of EZH2 inhibitors, it is essential to evaluate their efficacy (Gold & Shilatifard, 2024). Research on EZH2 inhibitors has been most extensive in certain types of R/R lymphoma (Izutsu et al., 2023; Song et al., 2024, 2022). These types of lymphoma are common indications for all three approved inhibitors (Hoy, 2020; Keam, 2022; Song et al., 2024). In patients with R/R T-cell lymphoma treated with valemestostat at 200 mg per day, the objective response rate (ORR) was 44% (52/119) (Zinzani et al., 2024). In patients with R/R T-cell lymphoma treated with SHR2554 at 350 mg twice daily, the ORR was 62% (17/28) (Song et al., 2024). In patients with R/R follicular lymphoma treated with tazemetostat at 800 mg daily, the ORR was 55% (50/99) (Morschhauser et al., 2020). The efficacy of EZH2 inhibitors may be influenced by the EZH2 mutation status of the tumor. In trial of tazemetostat for patients with R/R follicular lymphoma, the ORR was 69% (31/45) in the EZH2-mutant cohort (95% CI [53–82]), compared to 35% (19/54) in the EZH2 wild-type cohort (95% CI [23–49]). Due to significant tumor heterogeneity and patient heterogeneity across studies, as well as the lack of direct comparisons between drugs, it is difficult to determine which inhibitor is most effective. However, in our review, tazemetostat appears to have a more favorable safety profile. Among the approved inhibitors (tazemetostat, valemestostat, and SHR2554), tazemetostat has been the most thoroughly studied (Orleni & Beumer, 2024). It has shown substantial efficacy in treating metastatic or relapsed epithelioid sarcoma, follicular lymphoma, and pleural mesothelioma (Grünwald et al., 2024; Morschhauser et al., 2020; Zauderer et al., 2022). For solid tumors, EZH2 inhibitors may be less effective. In one study, only 15% (9/62) of patients with advanced epithelioid sarcoma and loss of INI1/SMARCB1 responded to treatment (Gounder et al., 2020). However, these results are limited, and further studies are needed to confirm these findings.

While our results are robust, as confirmed by sensitivity analyses, the potential publication bias detected necessitates cautious interpretation of the data. This bias could arise from the preferential publication of studies with favorable safety outcomes or discrepancies in reporting adverse events.

Several limitations in this study warrant consideration. First, the inherent biases of included studies, particularly those related to the non-randomized design of many trials, may affect the generalizability of the findings. Non-randomized designs also limit the

ability to identify the unique adverse events specifically attributable to EZH2 inhibitors and the potential overlapping toxicities in combination regimens. Second, the diversity in trial designs and populations, as well as variations in inhibitor type, dosage, and combination therapies, introduces heterogeneity that complicates direct comparisons across studies. Third, the disproportionate representation of tazemetostat in our dataset reflects its more advanced clinical development and greater number of published trials compared to other EZH2 inhibitors, such as SHR2554 and valemetostat. As a result, the meta-analysis findings may be more reflective of tazemetostat's safety profile, potentially limiting the generalizability of the results to other inhibitors. These findings underscore the need for additional studies focusing on newer EZH2 inhibitors to provide a more balanced comparison in future meta-analyses. Moreover, we acknowledge that the inclusion of valemetostat, an EZH1/2 dual inhibitor, introduces complexity given its distinct mechanism of action compared to other EZH2-specific inhibitors. With only one study on valemetostat included in this analysis, its unique on-target and off-target toxicities could not be adequately evaluated. Future research should focus on further elucidating these differences. Finally, the presence of publication bias, as suggested by funnel plot asymmetry, indicates that the actual incidence of adverse events may be underreported, which could skew the perceived safety profile of these therapies.

CONCLUSIONS

Our meta-analysis provides the first pooled assessment of TRAE rates for approved and investigational EZH2 inhibitors, offering critical insights for clinicians and researchers. The identified differences in adverse event profiles between monotherapy and combination regimens, as well as between individual inhibitors, provide a foundation for optimizing future clinical trial designs and therapeutic strategies. EZH2 inhibitors maintain an acceptable safety profile. Their potential for serious adverse events is manageable, making them viable for cancer treatment. Future research should focus on refining dosing strategies, reducing adverse effects, and enhancing long-term safety and efficacy profiles of these potent epigenetic modifiers. As of May 31, 2024, our search identified 79 studies on EZH2 inhibitors in cancer treatment, with 51 still ongoing. These ongoing studies are expected to significantly enrich our understanding of the efficacy and safety of EZH2 inhibitors.

ABBREVIATIONS

EZH2	Enhancer of Zeste Homolog 2
MedDRA	Medical Dictionary for Regulatory Activities
MINORS	A methodological index for non-randomized studies
ORR	objective response rate
R/R	relapsed or refractory
TEAE	treatment-emergent adverse event
TRAE	Treatment-related adverse event

ADDITIONAL INFORMATION AND DECLARATIONS

Funding

This work was funded by the Natural Science Foundation of Chongqing (CSTB2024NSCQ-MSX0514), and the Research Institutions Performance Incentive Guidance Special Fund of Chongqing (cstc2022jxjl0234). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Grant Disclosures

The following grant information was disclosed by the authors:
Natural Science Foundation of Chongqing: CSTB2024NSCQ-MSX0514.
Research Institutions Performance Incentive Guidance Special Fund of Chongqing: cstc2022jxjl0234.

Competing Interests

The authors declare that they have no competing interests.

Author Contributions

- Zhou Zhao conceived and designed the experiments, performed the experiments, analyzed the data, prepared figures and/or tables, authored or reviewed drafts of the article, and approved the final draft.
- Xiufeng Chen performed the experiments, analyzed the data, prepared figures and/or tables, and approved the final draft.
- Huayang Pang performed the experiments, prepared figures and/or tables, and approved the final draft.
- Yan Shi conceived and designed the experiments, authored or reviewed drafts of the article, and approved the final draft.
- Hao Sun conceived and designed the experiments, authored or reviewed drafts of the article, and approved the final draft.

Data Availability

The following information was supplied regarding data availability:

The raw data are available in the [Supplemental File](#).

Supplemental Information

Supplemental information for this article can be found online at <http://dx.doi.org/10.7717/peerj.18871#supplemental-information>.

REFERENCES

- Abida W, Iannotti N, Argon EK, Appleman L, Michaud N, Rajarethinam A, Adib D, Saltzstein D. 2021. 586P Safety of tazemetostat (TAZ) in combination with abiraterone/ prednisone (A/P) or enzalutamide (E) in patients (Pts) with metastatic castration-resistant prostate cancer (mCRPC). *Annals of Oncology* 32:S636 DOI 10.1016/j.annonc.2021.08.1099.

- An R, Li Y-Q, Lin Y-L, Xu F, Li M-M, Liu Z. 2023. EZH1/2 as targets for cancer therapy. *Cancer Gene Therapy* 30(2):221–235 DOI 10.1038/s41417-022-00555-1.
- Chawla SP, Falchook GS, Burgess MA, Chen JL, Jones RL, Chua VS, Tapia C, Ainscough J, Hamlett A, Merchant MS. 2021. Results of the phase 1b soft-tissue sarcoma (STS) portion of the global randomized, double-blind, placebo-controlled study of tazemetostat (TAZ) plus doxorubicin (DOX) as frontline therapy for advanced epithelioid sarcoma (ES). Philadelphia, Pennsylvania: Wolters Kluwer Health.
- Chi SN, Bourdeaut F, Casanova M, Kilburn LB, Hargrave DR, McCowage GB, Pinto NR, Yang J, Chadha R, Kahali B. 2022. Update on phase 1 study of tazemetostat, an enhancer of zeste homolog 2 inhibitor, in pediatric patients with relapsed or refractory integrase interactor 1-negative tumors. Alexandria, Virginia: American Society of Clinical Oncology.
- Chi SN, Yi JS, Williams PM, Roy-Chowdhuri S, Patton DR, Coffey BD, Reid JM, Piao J, Saguilig L, Alonzo TA, Berg SL, Ramirez NC, Jaju A, Mhlanga JC, Fox E, Hawkins DS, Mooney MM, Takebe N, Tricoli JV, Janeway KA, Seibel NL, Parsons DW. 2023. Tazemetostat for tumors harboring SMARCB1/SMARCA4 or EZH2 alterations: results from NCI-COG pediatric MATCH APEC1621C. *JNCI: Journal of the National Cancer Institute* 115(11):1355–1363 DOI 10.1093/jnci/djad085.
- Choudhury NJ, Lai WV, Makhnin A, Heller G, Eng J, Li B, Preeshagul I, Santini FC, Offin M, Ng K, Paik P, Larsen C, Ginsberg MS, Lau Y, Zhang X, Baine MK, Rekhman N, Rudin CM. 2024. A phase I/II study of valemestostat (DS-3201b), an EZH1/2 inhibitor, in combination with irinotecan in patients with recurrent small-cell lung cancer. *Clinical Cancer Research* 30:3697–3703 DOI 10.1158/1078-0432.Ccr-23-3383.
- Dou F, Tian Z, Yang X, Li J, Wang R, Gao J. 2022. Valemestostat: first approval as a dual inhibitor of EZH1/2 to treat adult T-cell leukemia/lymphoma. *Drug Discoveries & Therapeutics* 16(6):297–299 DOI 10.5582/ddt.2022.01085.
- Eisai. 2022. Study of tazemetostat in participants with relapsed or refractory B-cell non-hodgkin's lymphoma With EZH2 gene mutation. Available at <https://clinicaltrials.gov/study/NCT03456726?term=NCT03456726&rank=1&tab=results>.
- Feng K, Liu Y, Wang C, Nie J, Xia Y, Jiang J, Han W. 2023. Phase I study of the bifunctional anti-PD-L1/TGF-βRII agent SHR-1701 combined with SHR2554, an EZH2 inhibitor, in patients with previously treated advanced lymphoma and solid tumors. Alexandria, Virginia: American Society of Clinical Oncology.
- Gold S, Shilatfard A. 2024. Epigenetic therapies targeting histone lysine methylation: complex mechanisms and clinical challenges. *Journal of Clinical Investigation* 134(20):e183391 DOI 10.1172/JCI183391.
- Gounder M, Schöffski P, Jones RL, Agulnik M, Cote GM, Villalobos VM, Attia S, Chugh R, Chen TW, Jahan T, Loggers ET, Gupta A, Italiano A, Demetri GD, Ratan R, Davis LE, Mir O, Dileo P, Van Tine BA, Pressey JG, Lingaraj T, Rajarethinam A, Sierra L, Agarwal S, Stacchiotti S. 2020. Tazemetostat in advanced epithelioid sarcoma with loss of INI1/SMARCB1: an international, open-label, phase 2 basket study. *The Lancet Oncology* 21(11):1423–1432 DOI 10.1016/S1470-2045(20)30451-4.
- Grünewald TGP, Postel-Vinay S, Nakayama RT, Berlow NE, Bolzicco A, Cerullo V, Dermawan JK, Frezza AM, Italiano A, Jin JX, Le Loarer F, Martin-Broto J, Pecora A, Perez-Martinez A, Tam YB, Tirode F, Trama A, Pasquali S, Vescia M, Wortmann L, Wortmann M, Yoshida A, Webb K, Huang PH, Keller C, Antonescu CR. 2024. Translational aspects of Epithelioid Sarcoma: current consensus. *Clinical Cancer Research* 30(6):1079–1092 DOI 10.1158/1078-0432.CCR-23-2174.

- Harb W, Abramson J, Lunning M, Goy A, Maddocks K, Lebedinsky C, Senderowicz A, Trojer P, Bradley W, Flinn I. 2018. A phase 1 study of CPI-1205, a small molecule inhibitor of EZH2, preliminary safety in patients with B-cell lymphomas. *Annals of Oncology* 29:iii7 DOI 10.1093/annonc/mdy048.001.
- Hoy SM. 2020. Tazemetostat: first approval. *Drugs* 80(5):513–521 DOI 10.1007/s40265-020-01288-x.
- Huang N, Liao P, Zuo Y, Zhang L, Jiang R. 2023. Design, synthesis, and biological evaluation of a potent dual EZH2-BRD4 inhibitor for the treatment of some solid tumors. *Journal of Medicinal Chemistry* 66(4):2646–2662 DOI 10.1021/acs.jmedchem.2c01607.
- Hussain MH, Kocherginsky M, Singh P, Tan W, Myint Z, Jiang D, Wulff-Burchfield EM, Ma Y, Sharon E, Piekarz R. 2024. A pilot study of tazemetostat and pembrolizumab in advanced urothelial carcinoma (ETCTN 10183). Alexandria, Virginia: American Society of Clinical Oncology.
- Italiano A, Soria JC, Toulmonde M, Michot JM, Lucchesi C, Varga A, Coindre JM, Blakemore SJ, Clawson A, Suttle B, McDonald AA, Woodruff M, Ribich S, Hedrick E, Keilhack H, Thomson B, Owa T, Copeland RA, Ho PTC, Ribrag V. 2018. Tazemetostat, an EZH2 inhibitor, in relapsed or refractory B-cell non-Hodgkin lymphoma and advanced solid tumours: a first-in-human, open-label, phase 1 study. *The Lancet Oncology* 19(5):649–659 DOI 10.1016/S1470-2045(18)30145-1.
- Izutsu K, Makita S, Nosaka K, Yoshimitsu M, Utsunomiya A, Kusumoto S, Morishima S, Tsukasaki K, Kawamata T, Ono T, Rai S, Katsuya H, Ishikawa J, Yamada H, Kato K, Tachibana M, Kakurai Y, Adachi N, Tobinai K, Yonekura K, Ishitsuka K. 2023. An open-label, single-arm phase 2 trial of valemestostat for relapsed or refractory adult T-cell leukemia/lymphoma. *Blood* 141(10):1159–1168 DOI 10.1182/blood.2022016862.
- Kaur P, Shankar E, Gupta S. 2024. EZH2-mediated development of therapeutic resistance in cancer. *Cancer Letters* 586:216706 DOI 10.1016/j.canlet.2024.216706.
- Keam SJ. 2022. Valemestostat tosilate: first approval. *Drugs* 82(16):1621–1627 DOI 10.1007/s40265-022-01800-5.
- Li B, Xia Y, Mei S, Ye Z, Song B, Yan X, Lin F, Rao T, Yu W, Mei C, Lv J, Wu M, Mao Z, Zhou X, Cheng F. 2023. Histone H3K27 methyltransferase EZH2 regulates apoptotic and inflammatory responses in sepsis-induced AKI. *Theranostics* 13(6):1860–1875 DOI 10.7150/thno.83353.
- Liu L, Xiao B, Hirukawa A, Smith HW, Zuo D, Sanguin-Gendreau V, McCaffrey L, Nam AJ, Muller WJ. 2023. Ezh2 promotes mammary tumor initiation through epigenetic regulation of the Wnt and mTORC1 signaling pathways. *Proceedings of the National Academy of Sciences of the United States of America* 120(33):e2303010120 DOI 10.1073/pnas.2303010120.
- Liu Y, Yang Q. 2023. The roles of EZH2 in cancer and its inhibitors. *Medical Oncology* 40(6):167 DOI 10.1007/s12032-023-02025-6.
- Marzochi LL, Cuzziol CI, Nascimento Filho C, Dos Santos JA, Castanhole-Nunes MMU, Pavarino EC, Guerra ENS, Goloni-Bertollo EM. 2023. Use of histone methyltransferase inhibitors in cancer treatment: a systematic review. *European Journal of Pharmacology* 944(14):175590 DOI 10.1016/j.ejphar.2023.175590.
- MedDRA M. 2018. *Introductory guide for standardised MedDra queries (SMQs) Version 21.0*. Geneva, Switzerland: International Federation of Pharmaceutical Manufacturers and Associations.
- Morschhauser F, Tilly H, Chaidos A, McKay P, Phillips T, Assouline S, Batlevi CL, Campbell P, Ribrag V, Damaj GL, Dickinson M, Jurczak W, Kazmierczak M, Opat S, Radford J, Schmitt A, Yang J, Whalen J, Agarwal S, Adib D, Salles G. 2020. Tazemetostat for patients

- with relapsed or refractory follicular lymphoma: an open-label, single-arm, multicentre, phase 2 trial. *The Lancet Oncology* **21**(11):1433–1442 DOI [10.1016/S1470-2045\(20\)30441-1](https://doi.org/10.1016/S1470-2045(20)30441-1).
- Orleni M, Beumer JH. 2024.** Pharmacology and pharmacokinetics of tazemetostat. *Cancer Chemotherapy and Pharmacology* **93**(5):509–517 DOI [10.1007/s00280-024-04658-4](https://doi.org/10.1007/s00280-024-04658-4).
- Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, Shamseer L, Tetzlaff JM, Akl EA, Brennan SE, Chou R, Glanville J, Grimshaw JM, Hróbjartsson A, Lalu MM, Li T, Loder EW, Mayo-Wilson E, McDonald S, McGuinness LA, Stewart LA, Thomas J, Tricco AC, Welch VA, Whiting P, Moher D. 2021.** The PRISMA, 2020 statement: an updated guideline for reporting systematic reviews. *Systematic Reviews* **10**(1):89 DOI [10.1186/s13643-021-01626-4](https://doi.org/10.1186/s13643-021-01626-4).
- Palmieri LJ, Cousin S, Spalato M, Guégan JP, Bessede A, Pernot S, Italiano A. 2023.** Targeting EZH2 to overcome the resistance to immunotherapy in microsatellite stable colorectal cancer: results from the CAIRE study. Alexandria, Virginia: American Society of Clinical Oncology.
- Palomba ML, Cartron G, Popplewell L, Ribrag V, Westin J, Huw L-Y, Agarwal S, Shivhare M, Hong W-J, Raval A. 2022.** Combination of atezolizumab and tazemetostat in patients with relapsed/refractory diffuse large B-cell lymphoma: results from a phase Ib study. *Clinical Lymphoma Myeloma and Leukemia* **22**(7):504–512 DOI [10.1016/j.clml.2021.12.014](https://doi.org/10.1016/j.clml.2021.12.014).
- Puram S, Oppelt PJ, Ley JC, Cohen J, Alberti J, Shannon E, Liu J, Adkins D. 2023.** Tazemetostat, a selective EZH2 inhibitor, with pembrolizumab as treatment of anti-PD-1 resistant head and neck squamous-cell carcinoma (HNSCC): a phase 1-2 trial. Alexandria, Virginia: American Society of Clinical Oncology.
- Romero P, Richart L, Aflaki S, Petitalot A, Burton M, Michaud A, Masliah-Planchon J, Kuhnowski F, Le Cam S, Baliñas-Gavira C, Méaudre C, Luscan A, Hamza A, Legoix P, Vincent-Salomon A, Wassef M, Holoch D, Margueron R. 2024.** EZH2 mutations in follicular lymphoma distort H3K27me3 profiles and alter transcriptional responses to PRC2 inhibition. *Nature Communications* **15**:3452 DOI [10.1038/s41467-024-47701-x](https://doi.org/10.1038/s41467-024-47701-x).
- Rosenthal AC, Munoz JL, Villasboas JC. 2023.** Clinical advances in epigenetic therapies for lymphoma. *Clinical Epigenetics* **15**(1):39 DOI [10.1186/s13148-023-01452-6](https://doi.org/10.1186/s13148-023-01452-6).
- Sabour-Takanlou M, Sabour-Takanlou L, Biray-Avci C. 2024.** EZH2-associated tumor malignancy: a prominent target for cancer treatment. *Clinical Genetics* **106**(4):377–385 DOI [10.1111/cge.14576](https://doi.org/10.1111/cge.14576).
- Salles G, Park SI, Phillips TJ, Amengual JE, Andorsky DJ, Campbell P, McKay P, Leonard JP, Chen Y, Chen J. 2023.** Tazemetostat in combination with lenalidomide and rituximab in patients with relapsed/refractory follicular lymphoma: updated phase 1b results of symphony-1 with 22.5 months follow-up. *Blood* **142**:3035 DOI [10.1182/blood-2023-179910](https://doi.org/10.1182/blood-2023-179910).
- Sarkozy C, Morschhauser F, Dubois S, Molina T, Michot JM, Cullières-Dartigues P, Suttle B, Karlin L, Le Gouill S, Picquenot JM, Dubois R, Tilly H, Herbaux C, Jardin F, Salles G, Ribrag V. 2020.** A LYSA phase Ib study of tazemetostat (EPZ-6438) plus R-CHOP in patients with newly diagnosed diffuse large B-cell lymphoma (DLBCL) with poor prognosis features. *Clinical Cancer Research* **26**(13):3145–3153 DOI [10.1158/1078-0432.CCR-19-3741](https://doi.org/10.1158/1078-0432.CCR-19-3741).
- Schweizer M, Penkov K, Tolcher A, Choudhury A, Doronin V, Aljumaily R, Calvo E, Frank R, Hamm J, Garcia VM. 2022.** 488P Phase I trial of PF-06821497, a potent and selective inhibitor of enhancer of zeste homolog 2 (EZH2), in follicular lymphoma (FL), small cell lung cancer (SCLC) and castration-resistant prostate cancer (CRPC). *Annals of Oncology* **33**:S763–S764 DOI [10.1016/j.annonc.2022.07.616](https://doi.org/10.1016/j.annonc.2022.07.616).
- Shah S. 2022.** Common terminology criteria for adverse events. Bethesda: National Cancer Institute.

- Slim K, Nini E, Forestier D, Kwiatkowski F, Panis Y, Chipponi J. 2003. Methodological index for non-randomized studies (minors): development and validation of a new instrument. *ANZ Journal of Surgery* 73(9):712–716 DOI 10.1046/j.1445-2197.2003.02748.x.
- Song Y, Jin Z, Li ZM, Liu Y, Li L, He C, Su H, Zhou H, Li K, Hao S, Zuo X, Wu J, Li D, Wu M, Sun X, Qi J, Cai Z, Li Z, Li Y, Huang Y, Shen J, Xiao Z, Zhu J. 2024. Enhancer of zeste homolog 2 inhibitor SHR2554 in relapsed or refractory peripheral T-cell lymphoma: data from the first-in-human phase I study. *Clinical Cancer Research* 30(7):1248–1255 DOI 10.1158/1078-0432.CCR-23-2582.
- Song Y, Liu Y, Li ZM, Li L, Su H, Jin Z, Zuo X, Wu J, Zhou H, Li K, He C, Zhou J, Qi J, Hao S, Cai Z, Li Y, Wang W, Zhang X, Zou J, Zhu J. 2022. SHR2554, an EZH2 inhibitor, in relapsed or refractory mature lymphoid neoplasms: a first-in-human, dose-escalation, dose-expansion, and clinical expansion phase 1 trial. *The Lancet Haematology* 9(7):e493–e503 DOI 10.1016/S2352-3026(22)00134-X.
- Straining R, Eighmy W. 2022. Tazemetostat: EZH2 inhibitor. *Journal of the Advanced Practitioner in Oncology* 13(2):158–163 DOI 10.6004/jadpro.2022.13.2.7.
- Tachibana M, Matsuki S, Toyama K, Maekawa Y, Fukae M, Shimizu T, Tsutsumi J, Shinohara S, Ishizuka H. 2024. Safety, tolerability, and pharmacokinetics of valemetostat tablets and the effect of food on valemetostat pharmacokinetics in healthy subjects: two phase 1 studies. *Clinical Pharmacology in Drug Development* 13(1):77–86 DOI 10.1002/cpdd.1315.
- Wan G, Feng H, Su C, Zhu Y, Zhang L, Zhang Q, Yu L. 2023. A patent review of EZH2 inhibitors from 2017 and beyond. *Expert Opinion on Therapeutic Patents* 33(4):293–308 DOI 10.1080/13543776.2023.2206018.
- Yap TA, Winter JN, Giulino-Roth L, Longley J, Lopez J, Michot JM, Leonard JP, Ribrag V, McCabe MT, Creasy CL, Stern M, Pene Dumitrescu T, Wang X, Frey S, Carver J, Horner T, Oh C, Khaled A, Dhar A, Johnson PWM. 2019. Phase I study of the novel enhancer of Zeste homolog 2 (EZH2) inhibitor GSK2816126 in patients with advanced hematologic and solid tumors. *Clinical Cancer Research* 25(24):7331–7339 DOI 10.1158/1078-0432.CCR-18-4121.
- Zauderer MG, Szlosarek PW, Le Moulec S, Popat S, Taylor P, Planchard D, Scherpereel A, Koczywas M, Forster M, Cameron RB, Peikert T, Argon EK, Michaud NR, Szanto A, Yang J, Chen Y, Kansra V, Agarwal S, Fennell DA. 2022. EZH2 inhibitor tazemetostat in patients with relapsed or refractory, BAP1-inactivated malignant pleural mesothelioma: a multicentre, open-label, phase 2 study. *The Lancet Oncology* 23(6):758–767 DOI 10.1016/S1470-2045(22)00277-7.
- Zinzani PL, Izutsu K, Mehta-Shah N, Barta SK, Ishitsuka K, Córdoba R, Kusumoto S, Bachy E, Cwynarski K, Gritti G, Prica A, Jacobsen E, Feldman T, Guillermin Y, Ennishi D, Yoon DH, Domenech ED, Zain J, Wang J, Kim JS, Poel MV, Jin J, Wu S, Chen Y, Moriyama T, Inoue A, Nakajima K, Horwitz SM. 2024. Valemetostat for patients with relapsed or refractory peripheral T-cell lymphoma (VALENTINE-PTCL01): a multicentre, open-label, single-arm, phase 2 study. *The Lancet Oncology* 25(12):1602–1613 DOI 10.1016/S1470-2045(24)00503-5.