Thoracic Cancer

WILEY

ORIGINAL ARTICLE OPEN ACCESS

Treatment-Related Adverse Events of Antibody-Drug Conjugate Monotherapy in Non-Small Cell Lung Cancer: A Systematic Review and Meta-Analysis

Yuwei Li[1,2] | Linjing Zhou[2,3] | Sini Li[2] | Shichao Zhou[2] | Yunfei Chen[1,2] | Yunfeng Tong[1,2] | Jing Sun[1,2] | Le Wang[4] | Yun Fan[1,2]

[1]Postgraduate Training Base Alliance of Wenzhou Medical University, Hangzhou, Zhejiang, China | [2]Department of Thoracic Medical Oncology, Zhejiang Cancer Hospital, Hangzhou, Zhejiang, China | [3]Department of Oncology, the Second Clinical Medical College, Zhejiang Chinese Medical University, Hangzhou, China | [4]Department of Cancer Prevention, Zhejiang Cancer Hospital, Hangzhou, Zhejiang, China

Correspondence: Le Wang (wangle021@hotmail.com) | Yun Fan (fanyun@zjcc.org.cn)

Received: 6 July 2025 | **Revised:** 26 September 2025 | **Accepted:** 17 October 2025

Funding: The authors received no specific funding for this work.

Keywords: antibody-drug conjugate | meta-analysis | non-small cell lung cancer | treatment-related adverse events

ABSTRACT

Background: Antibody-drug conjugates (ADCs) have demonstrated promising efficacy in several prospective clinical studies, offering new possibilities for the treatment of non-small cell lung cancer (NSCLC). Consequently, understanding the toxicity profile associated with ADCs is of critical importance.

Methods: A comprehensive search was performed across PubMed, Embase, Cochrane Library, and ClinicalTrials.gov for studies on ADC monotherapy in NSCLC. Data extraction prioritized treatment-related adverse events (TRAEs), drug-related adverse events (AEs), or treatment-emergent adverse events (TEAEs). Incidences were pooled using a random-effects model.

Results: Thirteen studies including 1566 NSCLC patients were analyzed. The pooled incidence of all-grade TRAEs was 93.67%. Grade ≥ 3 TRAEs occurred in 38.74%, and serious TRAEs in 15.89%. Discontinuation and mortality rates were 9.52% and 0.63%. Hematologic toxicity was common among grade ≥ 3 TRAEs. Additionally, 20 fatal TRAEs were mainly associated with respiratory toxicity. Subgroup analysis for adverse events of special interest (AESIs) showed that Trastuzumab deruxtecan was more likely to cause grade ≥ 3 pneumonitis or interstitial lung disease (ILD), while TROP2-targeted ADCs were prone to high-grade stomatitis and ocular toxicity.

Conclusion: The overall incidence of TRAEs with ADC monotherapy in NSCLC is high, but most are Grade 1 or 2 and overall safety is manageable. Importantly, fatal TRAEs were mainly respiratory in this study, requiring clinical vigilance. Grade ≥ 3 AESIs should also be closely monitored.

Registration: This study was registered at INPLASY (ID: INPLASY2023120046).

1 | Introduction

Lung cancer poses a major health challenge worldwide, as it is the most commonly diagnosed type of cancer and the top cause of cancer-related mortality [1]. Non-small cell lung cancer (NSCLC) makes up about 80%–85% of all instances of lung cancer. Most NSCLC patients are diagnosed at an advanced stage with poor prognosis due to inadequate screening, and late onset

Yuwei Li and Linjing Zhou Contributed equally.

of clinical symptoms [2, 3]. Recently, antibody-drug conjugates (ADCs) [4–7] have emerged as a significant breakthrough in the treatment of NSCLC, demonstrating efficacy alongside a controlled safety profile. These therapeutics combine monoclonal antibodies with the cytotoxic effects of chemotherapy. The monoclonal antibody component precisely recognizes and binds to specific targets at the tumor site, enabling targeted delivery and payload release via endocytosis. This mechanism facilitates both precision-targeted therapy and cytotoxic chemotherapy [4, 8]. On August 11, 2022, the FDA granted accelerated marketing approval for Enhertu (trastuzumab deruxtecan, T-DXD), marking the first ADC approved for previously treated metastatic HER2-mutated NSCLC [9, 10]. Additionally, two ADCs (telisotuzumab vedotin and patritumab deruxtecan) have been awarded FDA Breakthrough Therapy Designation. Numerous promising ADCs are currently in clinical development, solidifying their position as potential therapeutic options for lung cancer patients.

Despite the efficacy of ADCs, their associated toxicities remain a challenge, as they are fundamentally chemotherapy-based agents [6]. Adverse events of special interest (AESIs) such as pneumonitis or interstitial lung disease (ILD), ophthalmic toxicity (including keratitis), and stomatitis have been reported. Additionally, non-special interest adverse events, including myelosuppression, nausea, decreased appetite, diarrhea, and fatigue, are common [10–12]. These toxicities often result from limited drug delivery to tumor cells, as a substantial proportion of the injected dose circulates systemically and undergoes catabolism in non-target tissues, increasing the risk of both on- and off-target toxicities [13, 14]. Thus, evaluating the safety profiles of ADCs is crucial for better risk assessment and more effective toxicity management.

To date, few studies have conducted meta-analyses focusing on the clinical toxicity of ADC monotherapy for lung cancer. With the rapid advancement of ADCs and the continual reporting of associated AEs, the spectrum and incidence of these events are evolving dynamically. To stay informed about AEs associated with ADCs, effective management strategies must be developed. In this context, we employed a random-effects model [15] to quantitatively aggregate data from published clinical trials, aiming to analyze the characteristics and incidence of treatment-related adverse events (TRAEs) linked to ADC monotherapy in NSCLC.

2 | Methods

2.1 | Search Strategy and Selection Criteria

This study adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [16] (Supporting Information 1). The study protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on December 11, 2023, updated for the last time on the same date (registration number INPLASY2023120046). A systematic literature search was conducted using PubMed, Embase, the Cochrane Library, and ClinicalTrials.gov to identify clinical trials reporting TRAEs associated with ADC monotherapy. The search covered articles published from the inception of ADC until September 20, 2024 (see Table S1 for detailed search strategy). A manual snowballing strategy was also employed to identify additional relevant literature. Key search terms included "non-small cell lung cancer (NSCLC)", "antibody-drug conjugates (ADCs)", "trastuzumab deruxtecan," "trastuzumab emtansine," "clinical trials," and "adverse events," among others. The criteria for inclusion were listed as follows: (1) Reported prospective clinical trials. (2) Available count data for TRAEs in patients with NSCLC treated with ADC monotherapy. (3) More current and comprehensive publications from the same research population. Exclusion criteria included: (1) Retrospective studies, meta-analyses, or reviews. (2) Results of phase I clinical trial. (3) Studies with unclear clinical outcomes, incomplete adverse event data, or fewer than 10 patients in the ADC monotherapy group. (4) ADCs or clinical trials with announced terminations. Studies reporting Phase II data from Phase I/II trials were included. For a study with multiple dose groups, the recommended dose group specified in the report was selected for analysis. Two authors (Y.W. Li and L.J. Zhou) independently screened and reviewed eligible trials based on abstracts and full-text articles. Discrepancies were resolved through discussions with two senior authors (L Wang and Y Jin) to reach consensus. Since this study was a retrospective analysis based solely on published data, with no direct involvement of human or animal subjects, it was exempt from ethics review.

2.2 | Data Extraction

The quality of the selected single-arm trials was evaluated using the MINORS criteria [17]. The risk of bias in randomized controlled trials was assessed with the Cochrane Risk of Bias 2 Tool (RoB-2), [18] in accordance with the Cochrane Handbook for Systematic Reviews of Interventions. Among the two RCTs [19, 20] included in the analysis, only the treatment arms with ADC drugs were considered. Because of discrepancies between ClinicalTrials.gov registry data and the published literature in terms of outcome definitions and types of adverse events (AEs) reported (TRAEs versus treatment-emergent AEs [TEAEs]), we used a standardized selection procedure (see Figure S1) to minimize potential bias or inaccuracies. Our protocol prioritized (1) TRAEs, drug-related AEs, or drug-related TEAEs from peer-reviewed publications; (2) matching data types from alternative sources (e.g., ClinicalTrials.gov, conference abstracts) when available; (3) other AE data (e.g., TEAEs or general AEs) from publications if the above were unavailable; and (4) general AE data from additional sources as needed. Peer-reviewed data superseded registry-publication discrepancies. Moreover, for studies reporting multiple AE categories, the most comprehensive dataset was selected to maximize coverage. Data types and sources are detailed in Table S2. Baseline data extracted included the first author's name, ADC monograph name, trial name, NCT number, trial stage, trial design type, publication year, targeted type, linker type, payload type, total number of patients, number of patients with TRAEs (all grades and high grades), number of patients experiencing serious TRAEs, TRAEs leading to drug discontinuation, and treatment-related deaths in the safety population. Notably, many of the NSCLC patient cohorts included in this analysis had received multiple prior lines of therapy. TRAEs reported across the trials were categorized using the National Cancer Institute Common Terminology Criteria for Adverse

Events (CTCAE) [21]. High-grade adverse events were defined as Grade 3 or higher (grade ≥ 3). Serious adverse events were classified as those that resulted in death, required or prolonged hospitalization, were life-threatening, or caused persistent or significant disability or incapacity.

2.3 | Data Analysis

The incidence of TRAEs was calculated by dividing the number of patients experiencing each adverse event by the total number of patients. This meta-analysis was primarily based on single-arm trials, with high clinical and methodological heterogeneity observed across studies due to variations in patient baseline characteristics, intervention protocols, and data reporting standards. To account for within-study and between-study variability, the DerSimonian-Laird random-effects model [15] was employed to ensure robust pooled estimates. Statistical heterogeneity was evaluated using the I^2 statistic [22] ($I^2 > 50\%$ indicating substantial heterogeneity), derived from the random-effects model. Additionally, the significance of heterogeneity was assessed using Cochrane's Q test (df = number of studies −1), with a p value < 0.10 deemed statistically significant rather than the traditional < 0.05. This adjustment was due to the low incidence of certain toxicities, such as death-related adverse events. In the analysis of rare events, a relaxed threshold improves the statistical efficacy of detecting potential heterogeneity, as recommended by the Cochrane Handbook [23]. To address the instability of variance in incidence proportions, particularly at extreme values (0% or 100%), the Freeman-Tukey double arcsine transformation [24, 25] was applied. Finally, pooled effect estimates were reported with 95% confidence intervals (CIs), with the significance of the combined effect sizes defined as a two-tailed p value < 0.05.

Adverse events identified in the selected studies were classified into Adverse Events of Special Interest (AESIs) and non-AESIs, with five overall incidences and high-grade incidences of both AESIs and non-AESIs summarized. Furthermore, the causes of fatal TRAEs were identified. Subgroup analyses were performed for high-grade overall TRAEs and high-grade AESIs to examine the influence of various factors, including prior treatment backgrounds, ADC types, target antigens, and payloads. We further examined the incidence of grade ≥ 3 myelosuppression in relation to different payloads. In addition, the incidence of high-grade TRAEs was analyzed based on different targets within the same technology platform and across different platforms for the same target. Finally, we added a concise practice table to guide clinicians (see Table 4). Nevertheless, given the limited number of studies and small sample sizes ($n \leq 50$) in certain subgroups, these findings may have insufficient statistical power and should be interpreted cautiously. Therefore, subgroup analyses with $n \leq 50$ were regarded as exploratory and were summarized in Table S6.

Sensitivity analyses were performed by sequentially excluding randomized controlled trials (RCTs), as well as studies utilizing CTCAE version 4.x or with unspecified CTCAE versions, to evaluate the robustness of the primary analyses. Publication bias was evaluated through a funnel plot and the Egger test [26–28]. The modified funnel plot, which was created using the trim-and-fill technique, served as a secondary assessment tool; visual asymmetry within this plot indicates the presence of bias [29]. Statistical analyses were performed solely with R (v4.3.1) and GraphPad Prism (v9.5).

3 | Results

3.1 | Study Selection and Characteristics

Our systematic search across PubMed, Embase, the Cochrane Library, and ClinicalTrials.gov initially identified 478 records. After removing 25 duplicates, 453 articles were evaluated by title and abstract, and 397 of them were excluded because of non-conforming study types or phase I trial designs. The remaining 56 publications were evaluated in full text, leading to the exclusion of 46 irrelevant records, including articles on non-ADC monotherapy studies ($n = 32$), lack of available NSCLC AE data ($n = 11$), and clinical trials announced as terminated ($n = 3$). A total of 10 studies were ultimately selected, and 3 additional records were retrieved from conference websites. Therefore, 13 eligible clinical studies involving 1566 patients were selected for quantitative evaluation (Figure 1). Of these 13 trials, 2 were randomized controlled trials (RCTs) [19, 20], and 11 were single-arm clinical trials [10, 30–39]. The ADCs analyzed included Trastuzumab emtansine ($n = 4$), Datopotamab deruxtecan ($n = 3$), Trastuzumab deruxtecan ($n = 2$), and Telisotuzumab vedotin ($n = 1$). Each ADC was associated with specific targets and payload classes. The targets comprised human epidermal growth factor receptor 2 (HER2; $n = 6$), human trophoblast cell surface antigen 2 (Trop-2; $n = 5$), and c-mesenchymal-epithelial transition factor (c-Met; $n = 1$). The categories of payloads comprised deruxtecan (DXd; $n = 6$), emtansine (DM1; $n = 4$), and vedotin (MMAE; $n = 1$). Some with smaller sample sizes were not listed (see Table 1). Quality assessment using the MINORS criteria revealed scores ranging from 13 to 15 out of a maximum of 16, indicating that the included clinical trials were of high quality. The risk of bias was assessed via the RoB-2 tool for RCTs, demonstrating a low risk of bias across included studies. Detailed findings of the risk of bias evaluation are listed in Table S3 and Figure S2.

3.2 | The Overall Incidence of TRAEs

The comprehensive analysis indicated that the overall rate of all-grade TRAEs was 93.67% (95% CI: 89.57%–96.91%, $I^2 = 77\%$). The pooled incidences for specific categories were as follows: high-grade TRAEs, 38.74% (95% CI: 29.06%–48.87%, $I^2 = 93\%$); serious TRAEs, 15.89% (95% CI: 11.84%–20.37%, $I^2 = 58\%$); TRAEs leading to treatment discontinuation, 9.52% (95% CI: 4.98%–15.18%, $I^2 = 84\%$); and death-related adverse events, 0.63% (95% CI: 0.19%–1.24%, $I^2 = 0\%$) (Table 2). Adverse events reported in the 13 studies were categorized into adverse events of special interest (AESIs) and non-AESIs. AESIs included pneumonitis or ILD, stomatitis (oral mucositis), and ophthalmic toxicity (including keratitis/keratopathy), which warrant increased clinical attention. The most frequent all-grade AESIs were ophthalmic toxicity (17.44%; 95% CI: 11.97%–23.68%, $I^2 = 66\%$, including keratitis/keratopathy [4.64%; 95% CI: 2.88%–6.77%, $I^2 = 0\%$]), stomatitis (17.21%; 95% CI: 4.32%–35.95%, $I^2 = 98\%$), and pneumonitis

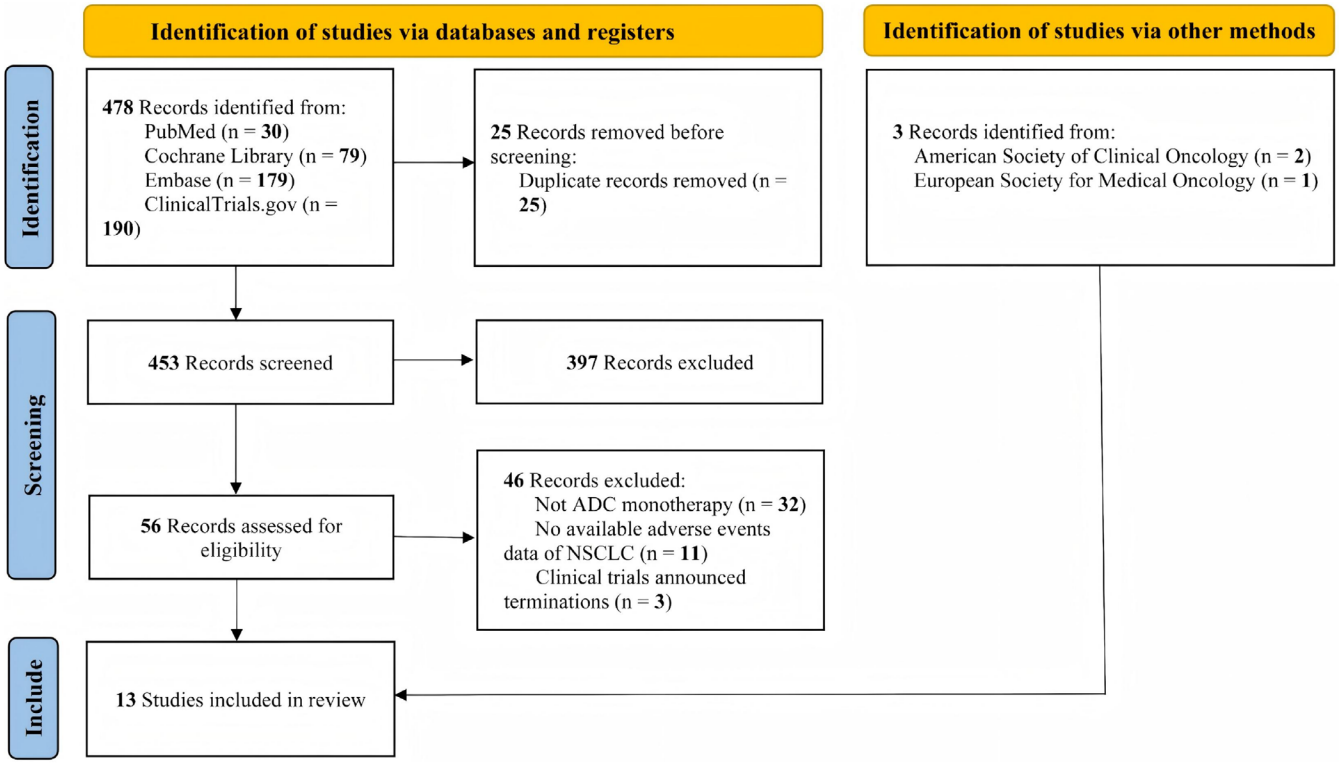


FIGURE 1 | Screening workflow diagram for the study. ADC, antibody-drug conjugate; NSCLC, non-small cell lung cancer.

or ILD (7.35%; 95% CI: 3.10%–13.03%, $I^2 = 85\%$). Among high-grade AESIs, the most common were stomatitis (4.98%; 95% CI: 1.52%–10.06%, $I^2 = 89\%$), pneumonitis or ILD (2.01%; 95% CI: 0.71%–3.83%, $I^2 = 63\%$), and ophthalmic toxicity (1.67%; 95% CI: 0.70%–2.97%, $I^2 = 0\%$, including keratitis/keratopathy [0.50%; 95% CI: 0.00%–2.55%, $I^2 = 68\%$]). For non-AESIs, the most prevalent all-grade events were nausea (37.90%; 95% CI: 25.26%–51.40%, $I^2 = 95\%$), fatigue (34.30%; 95% CI: 21.72%–48.08%, $I^2 = 96\%$), and neutropenia (25.10%; 95% CI: 11.19%–42.24%, $I^2 = 97\%$). The most frequent high-grade non-AESIs were neutropenia (14.76%; 95% CI: 5.74%–26.88%, $I^2 = 96\%$), thrombocytopenia (9.38%; 95% CI: 0.34%–25.72%, $I^2 = 77\%$), and anemia (7.05%; 95% CI: 3.27%–11.98%, $I^2 = 82\%$) (Figure 2).

3.3 | Incidence of Fatal TRAEs

To provide clarity on the causes of fatal TRAEs, we detailed the causes of the 20 deaths observed (Table 3). Respiratory toxicity was the leading cause, accounting for 60% of fatalities ($n = 12$), with pneumonitis or interstitial lung disease (ILD; $n = 10$) being the most frequent contributor, representing 50% of all deaths. Other causes included digestive toxicity, neurotoxicity, febrile neutropenia, septic shock, and sepsis, among others. Among the targets, TROP2 was most commonly associated with fatal TRAEs, responsible for 50% of the deaths, followed by HER2 and HER3, each contributing 20% (Table S4).

3.4 | Grade ≥ 3 TRAEs Subgroup Analysis

A total of 7 different ADCs from 13 clinical trials were pooled for analysis. As the results about telisotuzumab vedotin for c-Met and patritumab deruxtecan for HER3 were derived from a single clinical trial, they are presented descriptively. The ADCs most frequently associated with grade ≥ 3 TRAEs were SKB264 (67.44%; 95% CI: 51.46%–80.92%), patritumab deruxtecan (64.89%), and sacituzumab govitecan (52.70%; 95% CI: 46.84%–58.51%; Figure S3. A. a). Additionally, we examined the high-grade toxicity profiles for ADCs targeting different biomarkers. The most common targets associated with grade ≥ 3 TRAEs were HER3 (64.89%), TROP2 (42.49%; 95% CI: 26.94%–58.83%; $I^2 = 95\%$, $p < 0.01$), and HER2 (32.27%; 95% CI: 19.71%–46.18%; $I^2 = 75\%$, $p < 0.01$; Figure 3). We also analyzed 5 different payloads from the 13 trials. The payloads most frequently causing grade ≥ 3 TRAEs were KL610023 (67.44%; 95% CI: 51.45%–80.84%), govitecan (SN-38; 52.70%; 95% CI: 46.82%–58.56%), and deruxtecan (DXd; 40.86%; 95% CI: 28.56%–53.76%; Figure S3. A. c).

In addition, we conducted subgroup analyses for grade ≥ 3 AESIs based on different ADCs, targets, and payloads. Among the ADCs, SKB264 (9.30%; 95% CI: 2.59%–22.14%) and Datopotamab deruxtecan (8.30%; 95% CI: 5.73%–11.28%) were the most frequent causes of grade ≥ 3 stomatitis (Table S5). The ADCs most commonly associated with grade ≥ 3 pneumonitis or ILD were Trastuzumab deruxtecan (3.94%; 95% CI: 0.58%–9.58%), Telisotuzumab vedotin (5.23%), and Patritumab deruxtecan (1.33%). For grade ≥ 3 ophthalmic toxicity, Datopotamab deruxtecan (1.91%; 95% CI: 0.70%–3.59%) was the most frequently implicated ADC. In terms of target types, TROP2 was the most frequent cause of grade ≥ 3 stomatitis (6.44%; 95% CI: 2.59%–11.72%). The targets most commonly associated with grade ≥ 3 pneumonitis or ILD were c-Met (5.23%) and HER2 (3.94%; 95% CI: 0.58%–9.58%). TROP2 was also the most frequent target associated with grade ≥ 3 ophthalmic toxicity, including

TABLE 1 | Characteristics of included studies.

Authors, year	ADC monotherapy, target types	Research, NCT no.	Study types, phase	No. of patients	No. of All-grade AEs	No. of Grade ≥ 3 AEs	No. of Serious AEs*	No. of Discontinuation due to AEs	No. of Death related to AEs
Ahn (2024) [19]	Datopotamab deruxtecan (TROP2)	TROPION-Lung01 (NCT04656652)	RCT (III)	297	260	76	33	24	3
Paz-Ares (2023) [37]	Datopotamab deruxtecan (TROP2)	TROPION-Lung05 (NCT04484142)	Single-Arm (II)	137	NA	65	34	13	2
Planchard (2024) [38]	Datopotamab deruxtecan (TROP2)	ICARUS-LUNG01 (NCT04940325)	Single-Arm (II)	100	88	24	NA	18	3
Paz-Ares (2024) [20]	Sacituzumab govitecan (TROP2)	EVOKE-01 (NCT05089734)	RCT (III)	296	279	156	NA	20	4
Fang (2023) [34]	SKB264 (TROP2)	KL264-01 (NCT04152499)	Single-Arm (I/II)	43	NA	29	NA	0	0
Li (2022) [10]	Trastuzumab deruxtecan (HER2)	DESTINY-Lung01 (NCT03505710)	Single-Arm (II)	91	88	42	18	23	2
Goto (2023) [35]	Trastuzumab deruxtecan (HER2)	DESTINY-Lung02 (NCT04644237)	Single-Arm (II)	101	97	39	14	14	1
Peters (2019) [32]	Trastuzumab emtansine (HER2)	BO29389 (NCT02289833)	Single-Arm (II)	49	45	11	10	NA	0
Li (2018) [31]	Trastuzumab emtansine (HER2)	15–335 (NCT02675829)	Single-Arm (II)	18	18	1	NA	0	0
Hotta (2018) [30]	Trastuzumab emtansine (HER2)	NA	Single-Arm (II)	15	15	8	3	4	0
Iwama (2022) [33]	Trastuzumab emtansine (HER2)	NA	Single-Arm (II)	22	22	7	3	0	1
Yu (2023) [39]	Patritumab deruxtecan (HER3)	HERTHENA-Lung01 (NCT04619004)	Single-Arm (II)	225	NA	146	NA	16	4

(Continues)

TABLE 1 | (Continued)

Authors, year	ADC monotherapy, target types	Research, NCT no.	Study types, phase	No. of patients	No. of All-grade AEs	No. of Grade ≥ 3 AEs	No. of Serious AEs*	No. of Discontinuation due to AEs	No. of Death related to AEs
Camidge (2024) [36]	Telisotuzumab vedotin (c-Met)	LUMINOSITY (NCT03539536)	Single-Arm (II)	172	140	48	21	37	2

*Serious AEs: Events resulting in death, requiring or prolonging hospitalization, being life-threatening, or causing persistent or significant disability or incapacity.

keratitis/keratoconus (1.91%; 95% CI: 0.70%–3.59%; 1.35%; 95% CI: 0.37%–3.41%).

In terms of payload type, the payloads that most frequently caused grade ≥ 3 stomatitis were KL610023 (9.30%; 95% CI: 3.38%–22.64%) and deruxtecan (DXd; 5.81%; 95% CI: 1.43%–12.61%; Table S5). The most common payloads linked to grade ≥ 3 pneumonitis or ILD were vedotin (MMAE; 5.23%) and deruxtecan (DXd; 1.88%; 95% CI: 0.55%–3.84%). For grade ≥ 3 ophthalmic toxicity, deruxtecan (DXd; 1.91%; 95% CI: 0.70%–3.59%). Because the occurrence of myelosuppression strongly correlates with the payload of ADCs, a subgroup analysis was conducted for high-grade myelosuppression, including neutropenia, thrombocytopenia, and anemia. The payloads most frequently causing grade ≥ 3 neutropenia were KL610023 (32.56%; 95% CI: 19.63%–48.57%), govitecan (SN-38; 24.66%; 95% CI: 19.66%–29.85%), and deruxtecan (DXd; 9.58%; 95% CI: 1.92%–21.82%; Figure S3. C). Grade ≥ 3 thrombocytopenia was most commonly associated with emtansine (DM1; 13.23%; 95% CI: 0.00%–68.58%) and deruxtecan (DXd; 8.18%; 95% CI: 5.39%–11.46%). For grade ≥ 3 anemia, KL610023 (30.23%; 95% CI: 16.21%–46.01%), deruxtecan (DXd; 6.60%; 95% CI: 4.31%–9.30%), and govitecan (SN-38; 6.42%; 95% CI: 3.62%–9.59%).

When analyzing TRAEs within the same technology platform, Daiichi Sankyo's ADC technology revealed TROP2 as the target most frequently associated with high-grade stomatitis (8.30%; 95% CI: 5.73%–11.28%). HER2 was the target most commonly linked to high-grade pneumonitis or ILD (3.94%; 95% CI: 0.58%–9.58%), with a higher incidence compared to TROP2 (1.21%; 95% CI: 0.00%–4.09%; Figure S3. D). The incidence of high-grade TRAEs for the same target varied across different technology platforms. For TROP2, the Klus Pharma Inc. platform was most frequently associated with high-grade stomatitis (9.30%; 95% CI: 2.59%–22.14%), whereas the Daiichi Sankyo platform most frequently caused high-grade pneumonitis or ILD (1.21%; 95% CI: 0.00%–4.09%; Figure S3. E).

Due to the significant heterogeneity of TRAEs in the included studies ($I^2 > 50\%$), we conducted exploratory subgroup analyses on grade ≥ 3 TRAEs. The analyses examined different targeted drug types (results presented above) and prior treatment backgrounds (Figure S3. F). Results showed lower incidence in the first–/second-line (1 L/2 L) treated group (26.38% [22.50%–30.45%], $I^2 = 0\%$, $p = 0.71$) than in the broad prior therapy exposure group (42.08% [30.02%–54.61%], $I^2 = 91\%$, $p < 0.01$), where patients received > 1 prior line of systemic therapy or were enrolled without strict line restriction (potentially including treatment-naïve cases).

3.5 | Robustness of the Study Results

For the primary safety endpoints, publication bias was systematically assessed using funnel plots and the Egger regression test. The trim-and-fill method was further applied to adjust for the potential impact of unpublished studies. The results showed that the funnel plot for high-grade (≥ 3) TRAEs was symmetrical (Egger's test: $p = 0.614$; Figure S4. B), indicating no significant publication bias. The trim-and-fill method supplemented only one potential missing study ($k_0 = 1$), and the incidence

TABLE 2 | Summary of overall incidence of adverse events to ADCs.

AEs type	No. of studies	No. of total patients	Heterogeneity (I^2)	Incidence (95% CI)
All-grade AEs	10	1161	77%	93.67 (89.57; 96.91)
TROP2	3	693	78%	90.40 (85.11; 94.65)
HER2	6	296	0%	97.34 (94.78; 99.19)
c-Met	1	172	/	81.40 (74.76; 86.91)
AEs grade 3 or higher	13	1566	93%	38.74 (29.06; 48.87)
TROP2	5	873	95%	42.49 (26.94; 58.83)
HER2	6	296	75%	32.27 (19.71; 46.18)
HER3	1	225	/	64.89 (58.27; 71.11)
c-Met	1	172	/	27.91 (21.35; 35.24)
Serious AEs	8	884	58%	15.89 (11.84; 20.37)
TROP2	2	434	92%	17.21 (5.99; 32.54)
HER2	5	278	0%	16.75 (12.39; 21.57)
c-Met	1	172	/	12.21 (7.72; 18.06)
AEs associated with discontinuation	12	1517	84%	9.52 (4.98; 15.18)
TROP2	5	873	78%	7.60 (3.02; 13.88)
HER2	5	247	81%	10.19 (1.20; 24.67)
HER3	1	225	/	7.11 (4.12; 11.29)
c-Met	1	172	/	21.51 (15.62; 28.41)
AEs associated with death	13	1566	0%	0.63 (0.19; 1.24)
TROP2	5	873	24%	0.79 (0.13; 1.80)
HER2	6	296	0%	0.55 (0.00; 2.24)
HER3	1	225	/	1.78 (0.49; 4.49)
c-Met	1	172	/	1.16 (0.14; 4.14)

increased slightly from 38.74% to 41.32%, suggesting limited impact. Three additional studies ($k_0 = 3$) were separately included for all-grade and serious TRAEs, with the adjusted pooled incidence both minimally decreased (see Table S7), suggesting limited impact of publication bias. No missing studies ($k_0 = 0$) were detected for AEs leading to discontinuation and death, and estimates remained consistent before and after adjustment. Overall, publication bias had little impact on each primary endpoint, and the incidence rates in this study demonstrated high robustness and reliability.

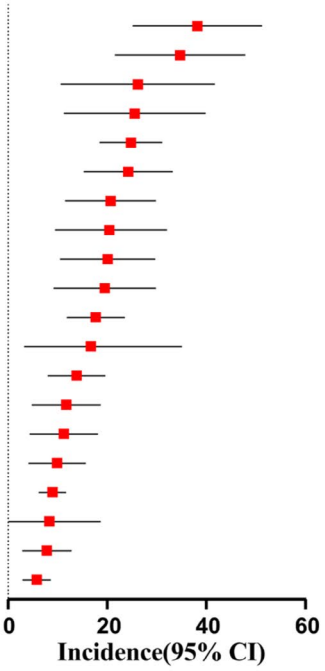
To evaluate result robustness, sensitivity analyses were performed with a two-step stratified validation. After excluding RCTs ($n = 2$), the incidence of serious TRAEs changed only minimally, while the heterogeneity (I^2) decreased from 58% to 40%. This likely reflects differences in study design, patient characteristics, or adverse event reporting practices among study types. Additionally, after removal of studies ($n = 6$) using CTCAE versions prior to 5.0 or with unspecified versions, the incidence of grade ≥3 TRAEs increased from 38.74% to 45.05%, accompanied by a slight rise in heterogeneity. For most other outcomes, neither the incidence estimates nor heterogeneity changed substantially following these two sensitivity analyses. Moreover, there was considerable overlap in the 95% confidence intervals across all sensitivity analyses. These findings indicate that our estimated event rates are relatively robust (Detailed in Table S8).

4 | Discussion

In this meta-analysis, we prioritized the more current and comprehensive publications from overlapping cohorts. To ensure accuracy, the number of patients experiencing TRAEs was utilized to derive precise statistical conclusions. Specifically, a random-effects model was employed to analyze data from 13 studies investigating the incidence of TRAEs associated with ADC monotherapy in NSCLC. Given the evolving toxicity profile and incidence rates of ADCs, it is crucial for clinicians to thoroughly understand these adverse events to ensure timely and effective management strategies. Key adverse events requiring attention during treatment were identified in our study,

A. all-grade adverse events

Event	No. of studies	No. of total patients	Heterogeneity(I^2)	Incidence(95% CI)
Nausea	10	1371	95%	37.90 (25.26; 51.40)
Fatigue	8	1052	96%	34.30 (21.72; 48.08)
Neutropenia	5	1010	97%	25.10 (11.19; 42.24)
Thrombocytopenia	6	506	84%	24.67 (11.73; 40.30)
Decreased appetite	8	1253	81%	24.60 (18.54; 31.19)
Constipation	6	862	84%	21.63 (14.72; 29.43)
Vomiting	6	862	88%	20.17 (11.78; 30.08)
Diarrhea	7	1159	97%	19.98 (9.88; 32.47)
Anemia	8	1249	95%	19.51 (10.79; 29.96)
AST/ALT increased	7	678	85%	18.82 (9.54; 30.17)
Ophthalmic toxicity	3	569	66%	17.44 (11.97; 23.68)
Stomatitis	6	1058	98%	17.21 (4.32; 35.95)
Cough	4	661	76%	13.47 (8.17; 19.79)
Pyrexia	4	592	79%	11.14 (5.07; 18.98)
Epistaxis	3	89	0%	10.67 (4.63; 18.42)
Oedema Peripheral	4	608	83%	9.36 (4.34; 15.91)
Rash	4	454	0%	8.84 (6.24; 11.78)
Peripheral neuropathy	5	651	95%	7.77 (0.97; 19.37)
Pneumonitis/ILD	9	1188	85%	7.35 (3.10; 13.03)
Headache	2	274	0%	5.56 (3.03; 8.72)



B. grade≥3 adverse events

Event	No. of studies	No. of total patients	Heterogeneity(I^2)	Incidence(95% CI)
Neutropenia	6	1053	96%	14.76 (5.74; 26.88)
Thrombocytopenia	4	359	77%	9.38 (0.34; 25.72)
Anemia	9	1380	82%	7.05 (3.27; 11.98)
Stomatitis	6	1098	89%	4.98 (1.52; 10.06)
Fatigue	7	1003	81%	4.54 (1.91; 8.05)
Pneumonitis/ILD	8	1166	63%	2.01 (0.71; 3.83)
Vomiting	5	813	30%	1.82 (0.73; 3.29)
Diarrhea	6	1110	91%	1.70 (0.04; 4.97)
Ophthalmic toxicity	3	569	0%	1.67 (0.70; 2.97)
Nausea	9	1315	68%	1.40 (0.15; 3.44)
Peripheral neuropathy	3	511	92%	1.15 (0.00; 7.29)
Rash	3	357	80%	0.73 (0.00; 7.55)
Decreased appetite	7	1197	38%	0.69 (0.11; 1.61)
Oedema Peripheral	2	468	82%	0.48 (0.00;3.51)
AST/ALT increased	5	531	53%	0.27 (0.00; 2.31)
Pyrexia	2	521	42%	0.25 (0.00; 1.28)
Constipation	5	813	14%	0.06 (0.00; 0.56)

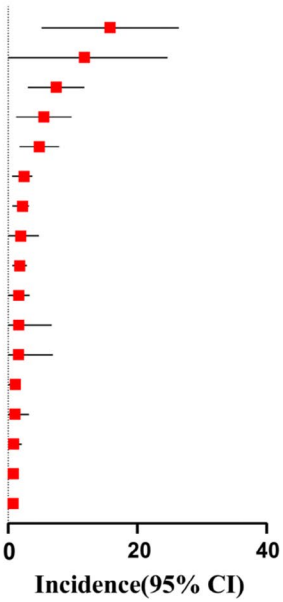


FIGURE 2 | Incidences of common adverse events to antibody-drug conjugates (ADCs). (Common adverse events are categorized as adverse events of special interests (AESIs) and those not of special interest, with events of special interest marked in gray.)

providing valuable guidance for optimizing the use of ADCs in lung cancer management.

The findings revealed that 93.67% of NSCLC patients receiving ADC monotherapy experienced any-grade TRAEs, with 38.74% and 15.89% reporting at least one high-grade and serious TRAEs, respectively. TRAEs leading to treatment discontinuation and death occurred in 9.52% and 0.63% of cases, respectively. Although a relatively high incidence of TRAEs was observed with ADC monotherapy, the majority are Grade 1 or 2, the overall safety profile was manageable. Furthermore, the unique mechanism of action of ADCs has demonstrated considerable therapeutic potential in clinical studies [35, 40]. Currently, ADCs have obtained approval for the treatment of advanced human epidermal growth factor receptor 2 (HER2)-positive and epidermal growth factor receptor (EGFR)-mutated NSCLC populations after failure of first-line standard therapy.

However, fatalities associated with ADC monotherapy have been reported in some studies. In our analysis of 13 studies, we identified a total of 20 fatal TRAEs. Respiratory toxicity, particularly pneumonitis or ILD, was the main contributor to fatal TRAEs, representing 50% of these incidents. This observation was derived from studies on four ADCs: Trastuzumab deruxtecan, Patritumab deruxtecan, Telisotuzumab vedotin, and Datopotamab deruxtecan. Although the exact mechanism of ADC-related pneumonitis has long remained unclear, a recent study has revealed that the intrinsic immune cells of the patients themselves, especially paravascular macrophages, are involved in the development of ILD [41]. From a clinical perspective, one study showed that the fatal ILD observed with Telisotuzumab vedotin may be attributable to the prior use of immune checkpoint inhibitors in NSCLC patients. This treatment history may increase their susceptibility to ILD during subsequent therapies [36, 42]. Furthermore, a systematic review of Trastuzumab deruxtecan-induced pneumonitis or ILD revealed that patients with NSCLC exhibited a higher incidence compared to those with gastric cancer, breast cancer, or other solid tumors. This discrepancy may stem from pre-existing lung damage in patients with NSCLC, such as that caused by smoking, previous radiation therapy, or prior lung surgery. Such elements may increase the likelihood of pulmonary toxicity associated with T-DXd and hinder the recovery from pneumonitis or ILD [35, 43–45]. Thus, in clinical applications of ADC drugs, vigilant monitoring of respiratory symptoms and prompt intervention—such as discontinuation of the ADC or the use of supportive therapies like glucocorticoids—is essential to prevent fatalities in NSCLC patients treated with ADCs [46, 47].

TABLE 3 | Detailed causes of ADC-associated mortality in NSCLC.

	Death due to TRAEs
Deaths, no. (%)	20
Fatal adverse events, no. (%)	
Respiratory	12 (60)
Pneumonitis/ILD	10 (50)
Respiratory failure	2 (10)
Digestive	3 (15)
Hepatobiliary disorder	1 (5)
Neutropenic colitis	1 (5)
GI perforation	1 (5)
Neural	1 (5)
Brain hemorrhage	1 (5)
Others	4 (20)
Febrile neutropenia	1 (5)
Septic shock	1 (5)
Sepsis	2 (10)

Owing to the unique structural characteristics and mechanisms of action of ADCs, their toxicity profile exhibits significant complexity. This complexity is primarily determined by the payload properties, the stability of the linker, the selectivity of the

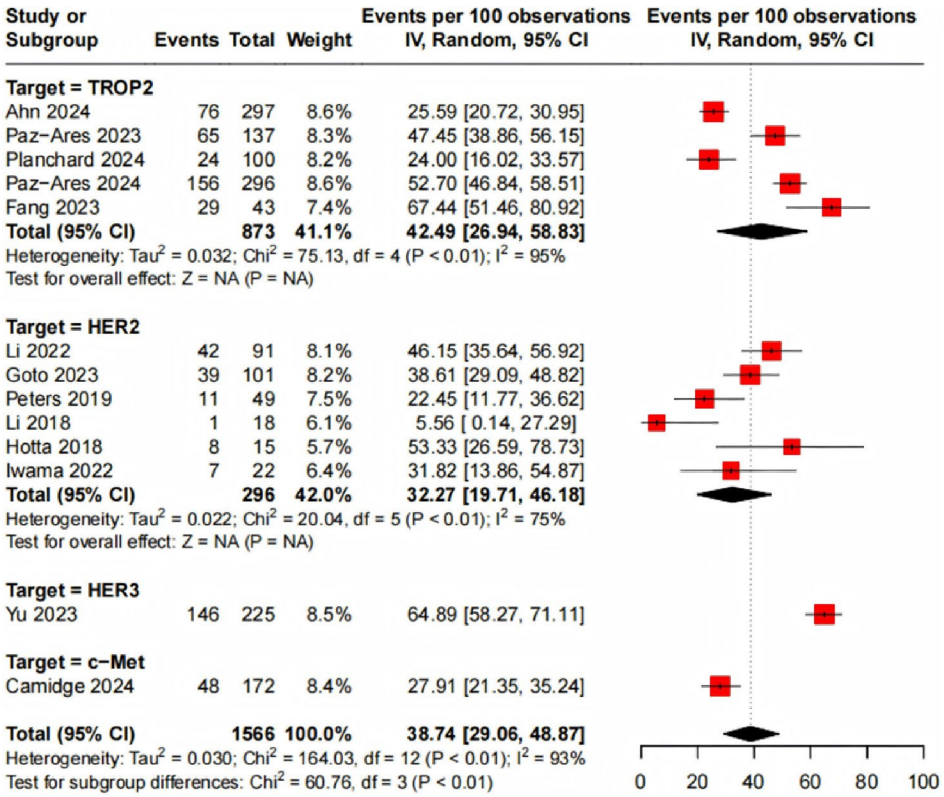


FIGURE 3 | Profile of high-grade toxicities for ADCs with different targets.

TABLE 4 | Prescreening, key monitoring, and hold/discontinuation recommendations for ADC monotherapy in NSCLC.

ADC and target	Indications and/or prescreening criteria	Key monitoring measures	Hold/discontinuation criteria
Datopotamab deruxtecan (TROP2)	Indicated for adult patients with locally advanced or metastatic EGFR-mutant NSCLC who have received prior EGFR TKI and platinum chemotherapy; NCCN v7.2025 lists patients with EGFR exon 19 deletion or L858R mutation as preferred candidates[a]	Gastrointestinal: monitor for oral mucositis signs/symptoms. Ocular: ophthalmic exams including visual acuity, fluorescein staining, slit-lamp, intraocular pressure, and fundus at baseline, annually, at treatment completion, and as clinically indicated; monitor ocular adverse events. Respiratory: monitor for new or worsening respiratory symptoms suggestive of ILD/pneumonitis during treatment[b]	Hold for Grade 1 ILD/pneumonitis until resolution to Grade 0; if recovery ≤ 28 days, resume at same dose; if > 28 days, resume at reduced dose. Permanently discontinue for grade ≥ 2 ILD. Hold for keratitis or vision loss until improvement; discontinue for corneal perforation. Oral mucositis: hold Grade 2 until ≤ 1 and resume; hold Grade 3 until ≤ 1 then resume at reduced dose; discontinue Grade 4. Infusion reactions: hold Grade 2 until ≤ 1 and resume at slower rate; discontinue for grade ≥ 3[b]
Sacituzumab govitecan (TROP2)	In clinical trials for metastatic NSCLC progressing after platinum chemotherapy, PD-(L)1 inhibitor, and targetable genomic alteration (AGA) therapy	Monitor blood counts regularly (especially neutrophils) and consider G-CSF for secondary prophylaxis; monitor diarrhea and provide fluids/electrolytes as needed[b]	Hold if ANC < 1.5 × 10^9/L or febrile neutropenia; hold for severe diarrhea until ≤ Grade 1 then resume at reduced dose[b]
Sacituzumab tirumotecan/SKB264 (TROP2)	In clinical trials for relapsed or refractory locally advanced/metastatic NSCLC.	No formal guidance available; by analogy to other TROP2-ADCs, monitor for hematologic toxicity, mucositis, and ocular events	No official hold/discontinuation criteria; pending label guidance
Trastuzumab deruxtecan (HER2)	Indicated for adult patients with unresectable or metastatic HER2 (ERBB2)-mutant NSCLC who have received prior systemic therapy; NCCN v7.2025 lists HER2 IHC3+ or HER2-mutant patients as recommended subsequent options[a]	Monitor and promptly investigate cough, dyspnea, fever, or other new/worsening respiratory symptoms to detect ILD; monitor CBC and platelets to avoid severe myelosuppression; periodically assess cardiac function to prevent left ventricular dysfunction[a]	Hold Grade 1 ILD/pneumonitis until resolution to Grade 0; if recovery ≤ 28 days, resume at same dose; if > 28 days, resume at reduced dose. Permanently discontinue for grade ≥ 2 ILD. Hold for Grade 3–4 thrombocytopenia until ≤ 1; hold for grade 3–4 neutropenia until ≤ 2; hold for febrile neutropenia (ANC < 1 × 10^9/L with fever > 38.3°C or ≥ 38°C for ≥ 1 h) until recovery, then resume at reduced dose. Discontinue if LVEF < 40% or decreases > 20% from baseline, or if symptomatic CHF occurs[a]
Trastuzumab emtansine (TDM1, HER2)	In clinical trials for metastatic or relapsed HER2-mutant NSCLC	Closely monitor infusion site for extravasation; check AST/ALT and bilirubin before each dose; periodically assess cardiac function; monitor platelets; observe for respiratory symptoms to detect ILD/pneumonitis early[b]	Hold for AST/ALT Grade 3 until ≤ 2, then resume at reduced dose; discontinue for Grade 4. Hold for hyperbilirubinemia Grade 2–3 until ≤ 1; discontinue for grade 4. Hold for thrombocytopenia < 50 000/mm^3 (grade 3–4) until recovery to ≥ 75 000/mm^3. Discontinue if LVEF < 40% or if symptomatic CHF occurs. Hold for peripheral neuropathy Grade 3–4 until ≤ 2. Discontinue permanently for ILD/pneumonitis[b]

(Continues)

TABLE 4 | (Continued)

ADC and target	Indications and/or prescreening criteria	Key monitoring measures	Hold/discontinuation criteria
Patritumab deruxtecan (HER3)	In clinical trials for EGFR-mutant NSCLC after failure of EGFR TKI and platinum chemotherapy	No formal guidance available; monitor CBC and chest CT periodically	No official hold/discontinuation criteria; pending label guidance
Telisotuzumab vedotin (cMET)	Indicated for adult patients with locally advanced or metastatic nonsquamous NSCLC with c-MET overexpression (≥ 50% IHC3+) and EGFR wild-type, who have received ≥ 1 prior systemic therapy[a]	Neurologic: monitor for new or worsening peripheral neuropathy (hypoesthesia, hyperesthesia, paresthesia, burning, neuropathic pain, muscle weakness). Ocular: monitor for ocular surface disease during treatment. Respiratory: monitor for ILD/pneumonitis symptoms during treatment[a]	Hold for peripheral neuropathy Grade 2–3 until ≤ 1 then resume at reduced dose; permanently discontinue for Grade 4. Hold for ILD/pneumonitis grade 1, consider steroids, and resume after radiographic resolution; permanently discontinue for grade ≥ 2. Hold for keratitis grade 2 and refer to ophthalmology; permanently discontinue for grade ≥ 3. Hold for infusion reactions grade 1–3, then resume at half the infusion rate; discontinue for grade 4. Hold for peripheral edema grade ≥ 2 until ≤ 1[a]

Abbreviations: ANC: absolute neutrophil count; AST/ALT: aspartate/alanine aminotransferase; c-MET: mesenchymal-epithelial transition factor; EGFR: epidermal growth factor receptor; G-CSF: granulocyte-colony stimulating factor; HER2: human epidermal growth factor receptor 2; ILD: interstitial lung disease; LVEF: left ventricular ejection fraction; NSCLC: non-small cell lung cancer.
[a]Guidelines: NCCN Guidelines Insights: Non-Small Cell Lung Cancer, Version 7.2025.
[b]For some ADCs, NSCLC-specific recommendations are not available in the current prescribing information; monitoring measures and discontinuation criteria are referenced from breast cancer or other tumor indications and should be considered for guidance only.

antibody, and the expression level of the target protein. Certain adverse events of special interest (AESIs) have been identified through clinical observations, including toxicity affecting ocular, pulmonary, and oral organs. Our analysis revealed that the incidence of ophthalmic toxicity (including keratitis/keratoconus), stomatitis, and pneumonitis or ILD across all grades was 17.44% (4.64%), 17.21%, and 7.35%, respectively. For high-grade events, the incidence was 4.98% for stomatitis, 2.01% for pneumonitis or ILD, and 1.67% (0.50%) for ophthalmic toxicity (including keratitis/keratoconus). Subgroup analyses of high-grade AESIs indicated that SKB264 most frequently caused grade ≥ 3 stomatitis. However, it is important to note that this association is based on an exploratory subgroup analysis ($n = 43$) and should be interpreted with caution due to the limited sample size. The observed trend may arise from the inhibition of topoisomerase I [48] by KL610023, which induces DNA single-strand breaks and disrupts replication processes in oral mucosal cells. High-grade stomatitis warrants particular attention due to its potential to significantly increase the treatment burden on patients. Trastuzumab deruxtecan was the most frequent cause of grade ≥ 3 pneumonitis or ILD, potentially due to the acute or chronic lung damage caused by the medication, leading to inflammatory responses that ultimately result in overt ILD [46, 49, 50]. As Trastuzumab deruxtecan becomes more widely available and increasingly used for NSCLC patients, robust toxicity management strategies must be implemented. Corticosteroid dosages in clinical settings should be titrated according to ILD severity. For symptomatic ILD, discontinuation of ADC therapy is recommended, with reintroduction considered only in asymptomatic complete responders after remission [46, 51]. In addition, Datopotamab deruxtecan was found to most commonly cause grade ≥ 3 ophthalmic toxicity (including keratitis/keratoconus). Although the mechanism remains unclear, it has been hypothesized that TROP2 expression in the cornea facilitates on-target off-tumor absorption into corneal epithelial cells [52, 53]. As the first TROP2-directed ADC for lung cancer patients, Datopotamab deruxtecan (Dato-DXd) is anticipated to become widely available for clinical use. Therefore, refining its adverse event management strategies and implementing regular ophthalmic assessments according to treatment management guidelines for any ocular events are critically important.

In target-specific analyses, monotherapy with HER3-expressing ADCs was linked to a greater occurrence of grade ≥ 3 TRAEs than other targets, although the underlying mechanism remains unclear. As this finding was based on a single trial, the comparative result should be interpreted with caution. Notably, the first ADC targeting HER3 (Patritumab deruxtecan) received FDA breakthrough therapy designation in 2021 and is anticipated to receive approval soon. Consequently, effective management of adverse events associated with Patritumab deruxtecan will be a significant clinical challenge in the future. Further analysis of high-grade AESIs indicated that TROP2-targeting ADCs were most frequently linked to high-grade stomatitis and high-grade ophthalmic toxicity (including keratitis/keratoconus). This may result from the presence of TROP2 on the mucosal layers of healthy human organs, including the epithelium found in the esophagus, the crypts of the tonsils, and the glands that produce saliva, implying a potential on-target, off-tumor mechanism of toxicity [52–54]. Additionally, the average incidence of grade ≥ 3 ILD or pneumonitis was higher for ADCs targeting c-Met compared to other targets. However, as this observation was based

on a single trial, the comparative result should be interpreted with caution. In fact, this incidence was not significantly different from the second-ranked HER2.

Moreover, from the perspective of payloads, grade ≥3 TRAEs occurred at comparable mean incidence across payload types. This may be related to dose-limiting toxicities (DLTs) induced by the released payloads, which necessitate restricting ADC dosages to levels below the optimal anti-cancer thresholds in order to effectively control the risk of adverse events [13]. Notably, myelosuppression was identified as the most frequent high-grade non-AESI, requiring sustained clinical vigilance. Subgroup analysis revealed that the mean incidence of grade ≥3 neutropenia was higher for ADC monotherapy using KL610023, a belotecan-derived topoisomerase I inhibitor, [48] compared to other payloads. This heightened risk may stem from KL610023's ability to arrest the cell cycle at the G2/S phase following internalization, ultimately resulting in cell death [48, 55]. Consequently, infections associated with myelosuppression-induced neutropenia warrant close monitoring [56]. Emtansine (DM1) was identified as the payload most frequently associated with grade ≥3 thrombocytopenia. This likely occurs because, following the internalization of ADCs in megakaryocytes, the payload is released intracellularly, inhibiting their differentiation [56–58]. Thrombocytopenia may present as increased bruising and bleeding, such as gum or nose bleeds, and in severe cases, may lead to mucosal hemorrhage [56]. These symptoms require careful observation and management. Additionally, KL610023 was also the payload most commonly associated with Grade ≥3 anemia. This may be due to its potential to impair hematopoietic function, resulting in anemia. In summary, patients receiving ADCs containing these payloads require increased clinical attention. Determining the most appropriate therapeutic dosage during ADC development is critical to balancing efficacy with safety.

We identified additional findings by examining the influence of the company's technology platform and target. For instance, HER2-targeting ADCs developed using Daiichi Sankyo's platform showed a higher incidence of high-grade pneumonitis or ILD compared to TROP2-targeting ADCs. However, the reason for this phenomenon is unclear. Additionally, when targeting TROP2, the technology platform of Klus Pharma Inc. was associated with a higher incidence of high-grade stomatitis. Although the difference compared to the second-ranked platform was not statistically significant, this suggests further optimization of this technology platform is warranted.

The exploratory subgroup analysis was performed with Grade ≥3 TRAEs to explore the reason for the high between-study heterogeneity. When stratified by targeted drug types, although the pooled incidence of grade ≥3 TRAEs varied across subgroups, substantial heterogeneity persisted within the TROP2-targeted ADC ($I^2=95\%$) and HER2-targeted ADC ($I^2=75\%$) subgroups, while the HER3 and c-Met subgroups were single-study only, precluding assessment of within-group heterogeneity. Therefore, target type may only partially explain the observed heterogeneity rather than representing the primary driver of the overall variability. However, the results indicate that differences in treatment backgrounds may affect the incidence of TRAEs in pooled analyses and the cross-study heterogeneity. Specifically, multiline-treated patients may be exposed to further increased risk due to cumulative organ toxicity, which elevated the pooled incidence rate. In addition, studies with broad prior treatment may have included patients with different therapy backgrounds, increasing cross-study heterogeneity.

To better guide clinical practice, we conducted a literature search and compiled key measures for monitoring AEs, prescreening criteria, and suspension/discontinuation triggers for each ADC used to treat NSCLC (Table 4).

There are several limitations in this study. First, some of the reports included in this meta-analysis are abstracts or conference reports with preliminary or not fully matured results. Second, the majority of the studies included were single-arm trials, which lacked comparators and therefore could not provide control-based analyses. Moreover, many patients in the included cohorts had received extensive prior treatments, which may limit the extrapolation of these findings to earlier treatment stages. Finally, several subgroup analyses were limited by small sample sizes ($n\leq50$). These findings may exhibit reduced stability and reliability, and thus should be considered exploratory. Larger prospective studies with standardized protocols are needed to validate these preliminary results.

5 | Conclusion

ADC monotherapy is correlated with a higher overall incidence of TRAEs, but the majority are Grade 1 or 2, and overall safety is manageable. Importantly, 20 fatal TRAEs were still identified in this study, primarily related to respiratory toxicity, warranting clinical vigilance. Additionally, grade ≥3 AESIs such as stomatitis, pneumonitis or ILD, and ophthalmic toxicity should be closely monitored to optimize safety management.

Author Contributions

Yuwei Li was responsible for extracting data, assessing quality, synthesizing and analyzing data, and writing the manuscript. Linjing Zhou and Le Wang participated in data extraction, quality appraisal, and data synthesis and analysis. Sini Li and Shichao Zhou contributed to methodology, analysis of the results, and editing of the manuscript. Yunfei Chen, Yunfeng Tong, and Jing Sun contributed to the analysis of the results and the editing of the manuscript. Yun Fan determined the scope of the review and contributed to protocol design writing, and editing the manuscript.

Acknowledgments

The authors have nothing to report.

Ethics Statement

The authors have nothing to report.

Consent

The authors have nothing to report.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that supports the findings of this study is available in the Supporting Information of this article.

References

1. F. Bray, M. Laversanne, H. Sung, et al., "Global Cancer Statistics 2022: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries," *CA: A Cancer Journal for Clinicians* 74, no. 3 (2024): 229–263.

2. C. Gridelli, A. Rossi, D. P. Carbone, et al., "Non-Small-Cell Lung Cancer," *Nature Reviews. Disease Primers* 1 (2015): 15009.

3. H. Sung, J. Ferlay, R. L. Siegel, et al., "Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries," *CA: A Cancer Journal for Clinicians* 71, no. 3 (2021): 209–249.

4. C. H. Chau, P. S. Steeg, and W. D. Figg, "Antibody-Drug Conjugates for Cancer," *Lancet* 394, no. 10200 (2019): 793–804.

5. U. Hafeez, S. Parakh, H. K. Gan, and A. M. Scott, "Antibody-Drug Conjugates for Cancer Therapy," *Molecules* 25, no. 20 (2020): 4764.

6. P. Tarantino, R. Carmagnani Pestana, C. Corti, et al., "Antibody-Drug Conjugates: Smart Chemotherapy Delivery Across Tumor Histologies," *CA: A Cancer Journal for Clinicians* 72, no. 2 (2022): 165–182.

7. A. Thomas, B. A. Teicher, and R. Hassan, "Antibody-Drug Conjugates for Cancer Therapy," *Lancet Oncology* 17, no. 6 (2016): e254–e262.

8. D. Sigorski, P. Różanowski, E. Iżycka-Świeszewska, and K. Wiktorska, "Antibody-Drug Conjugates in Uro-Oncology," *Targeted Oncology* 17, no. 3 (2022): 203–221.

9. "FDA Gives Nod to T-DXd for HER2-Mutant NSCLC," *Cancer Discovery* 12, no. 10 (2022): 2224.

10. B. T. Li, E. F. Smit, Y. Goto, et al., "Trastuzumab Deruxtecan in HER2-Mutant Non-Small-Cell Lung Cancer," *New England Journal of Medicine* 386, no. 3 (2022): 241–251.

11. Z. Fu, S. Li, S. Han, C. Shi, and Y. Zhang, "Antibody Drug Conjugate: The 'Biological Missile' for Targeted Cancer Therapy," *Signal Transduction and Targeted Therapy* 7, no. 1 (2022): 93.

12. M. A. Levy, C. M. Lovly, and W. Pao, "Translating Genomic Information Into Clinical Medicine: Lung Cancer as a Paradigm," *Genome Research* 22, no. 11 (2012): 2101–2108.

13. T. D. Nguyen, B. M. Bordeau, and J. P. Balthasar, "Mechanisms of ADC Toxicity and Strategies to Increase ADC Tolerability," *Cancers (Basel)* 15, no. 3 (2023): 713.

14. G. Casi and D. Neri, "Antibody-Drug Conjugates and Small Molecule-Drug Conjugates: Opportunities and Challenges for the Development of Selective Anticancer Cytotoxic Agents," *Journal of Medicinal Chemistry* 58, no. 22 (2015): 8751–8761.

15. M. W. Cheung and S. F. Cheung, "Random-Effects Models for Meta-Analytic Structural Equation Modeling: Review, Issues, and Illustrations," *Research Synthesis Methods* 7, no. 2 (2016): 140–155.

16. M. J. Page, J. E. McKenzie, P. M. Bossuyt, et al., "The PRISMA 2020 Statement: An Updated Guideline for Reporting Systematic Reviews," *BMJ (Clinical Research Ed.)* 372 (2021): n71.

17. K. Slim, E. Nini, D. Forestier, F. Kwiatkowski, Y. Panis, and J. Chipponi, "Methodological Index for Non-Randomized Studies (Minors): Development and Validation of a New Instrument," *ANZ Journal of Surgery* 73, no. 9 (2003): 712–716.

18. J. A. C. Sterne, J. Savović, M. J. Page, et al., "RoB 2: A Revised Tool for Assessing Risk of Bias in Randomised Trials," *BMJ (Clinical Research Ed.)* 366 (2019): l4898.

19. M. J. Ahn, K. Tanaka, L. Paz-Ares, et al., "Datopotamab Deruxtecan Versus Docetaxel for Previously Treated Advanced or Metastatic Non-Small Cell Lung Cancer: The Randomized, Open-Label Phase III TROPION-Lung01 Study," *Journal of Clinical Oncology* 43, no. 3 (2024): Jco2401544, https://doi.org/10.1200/JCO-24-01544.

20. L. G. Paz-Ares, O. Juan-Vidal, G. S. Mountzios, et al., "Sacituzumab Govitecan Versus Docetaxel for Previously Treated Advanced or Metastatic Non-Small Cell Lung Cancer: The Randomized, Open-Label Phase III EVOKE-01 Study," *Journal of Clinical Oncology* 42, no. 24 (2024): 2860–2872.

21. A. Freites-Martinez, N. Santana, S. Arias-Santiago, and A. Viera, "Using the Common Terminology Criteria for Adverse Events (CTCAE - Version 5.0) to Evaluate the Severity of Adverse Events of Anticancer Therapies," *Actas Dermo-Sifiliográficas (English Edition)* 112, no. 1 (2021): 90–92.

22. J. P. Higgins, S. G. Thompson, J. J. Deeks, and D. G. Altman, "Measuring Inconsistency in Meta-Analyses," *BMJ* 327, no. 7414 (2003): 557–560.

23. M. Cumpston, T. Li, M. J. Page, et al., "Updated Guidance for Trusted Systematic Reviews: A New Edition of the Cochrane Handbook for Systematic Reviews of Interventions," *Cochrane Database of Systematic Reviews* 10, no. 10 (2019): Ed000142.

24. L. K. Siegel, M. Silva, L. Lin, Y. Chen, Y. L. Liu, and H. Chu, "Choice of Link Functions for Generalized Linear Mixed Models in Meta-Analyses of Proportions," *Research Methods in Medicine & Health Sciences* 6, no. 1 (2025): 13–23.

25. Y. Chen, D. Chen, Y. Wang, and Y. Han, "Using Freeman-Tukey Double Arcsine Transformation in Meta-Analysis of Single Proportions," *Aesthetic Plastic Surgery* 47, no. 1 (2023): 83–84.

26. M. Egger, G. Davey Smith, M. Schneider, and C. Minder, "Bias in Meta-Analysis Detected by a Simple, Graphical Test," *BMJ (Clinical Research Ed.)* 315, no. 7109 (1997): 629–634.

27. J. L. Peters, A. J. Sutton, D. R. Jones, K. R. Abrams, and L. Rushton, "Comparison of Two Methods to Detect Publication Bias in Meta-Analysis," *JAMA* 295, no. 6 (2006): 676–680.

28. P. Macaskill, S. D. Walter, and L. Irwig, "A Comparison of Methods to Detect Publication Bias in Meta-Analysis," *Statistics in Medicine* 20, no. 4 (2001): 641–654.

29. S. Duval and R. Tweedie, "Trim and Fill: A Simple Funnel-Plot-Based Method of Testing and Adjusting for Publication Bias in Meta-Analysis," *Biometrics* 56, no. 2 (2000): 455–463.

30. K. Hotta, K. Aoe, T. Kozuki, et al., "A Phase II Study of Trastuzumab Emtansine in HER2-Positive Non-Small Cell Lung Cancer," *Journal of Thoracic Oncology* 13, no. 2 (2018): 273–279.

31. B. T. Li, R. Shen, D. Buonocore, et al., "Ado-Trastuzumab Emtansine for Patients With HER2-Mutant Lung Cancers: Results From a Phase II Basket Trial," *Journal of Clinical Oncology* 36, no. 24 (2018): 2532–2537.

32. S. Peters, R. Stahel, L. Bubendorf, et al., "Trastuzumab Emtansine (T-DM1) in Patients With Previously Treated HER2-Overexpressing Metastatic Non-Small Cell Lung Cancer: Efficacy, Safety, and Biomarkers," *Clinical Cancer Research* 25, no. 1 (2019): 64–72.

33. E. Iwama, Y. Zenke, S. Sugawara, et al., "Trastuzumab Emtansine for Patients With Non-Small Cell Lung Cancer Positive for Human Epidermal Growth Factor Receptor 2 Exon-20 Insertion Mutations," *European Journal of Cancer* 162 (2022): 99–106.

34. W. Fang, Y. Cheng, Z. Chen, et al., "SKB264 (TROP2-ADC) for the Treatment of Patients With Advanced NSCLC: Efficacy and Safety Data From a Phase 2 Study," *Journal of Clinical Oncology* 41, no. 16_suppl (2023): 9114.

35. K. Goto, Y. Goto, T. Kubo, et al., "Trastuzumab Deruxtecan in Patients With HER2-Mutant Metastatic Non-Small-Cell Lung Cancer:

Primary Results From the Randomized, Phase II DESTINY-Lung02 Trial," *Journal of Clinical Oncology* 41, no. 31 (2023): 4852–4863.

36. D. R. Camidge, J. Bar, H. Horinouchi, et al., "Telisotuzumab Vedotin Monotherapy in Patients With Previously Treated c-Met Protein-Overexpressing Advanced Nonsquamous EGFR-Wildtype Non-Small Cell Lung Cancer in the Phase II LUMINOSITY Trial," *Journal of Clinical Oncology* 42, no. 25 (2024): 3000–3011.

37. L. Paz-Ares, M. J. Ahn, A. E. Lisberg, et al., "1314MO TROPION-Lung05: Datopotamab Deruxtecan (Dato-DXd) in Previously Treated Non-Small Cell Lung Cancer (NSCLC) With Actionable Genomic Alterations (AGAs)," *Annals of Oncology* 34 (2023): S755–S756.

38. D. Planchard, N. Cozic, M. Wislez, et al., "ICARUS-LUNG01: A Phase 2 Study of Datopotomab Deruxtecan (Dato-DXd) in Patients With Previously Treated Advanced Non-Small Cell Lung Cancer (NSCLC), With Sequential Tissue Biopsies and Biomarkers Analysis to Predict Treatment Outcome," *Journal of Clinical Oncology* 42, no. 16_suppl (2024): 8501.

39. H. A. Yu, Y. Goto, H. Hayashi, et al., "HERTHENA-Lung01, a Phase II Trial of Patritumab Deruxtecan (HER3-DXd) in Epidermal Growth Factor Receptor-Mutated Non-Small-Cell Lung Cancer After Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitor Therapy and Platinum-Based Chemotherapy," *Journal of Clinical Oncology* 41, no. 35 (2023): 5363–5375.

40. H. Hayashi, Y. Goto, H. A. Yu, et al., "11P Patritumab Deruxtecan (HER3-DXd) in Previously Treated Patients (Pts) With Advanced EGFR-Mutated (EGFRm) NSCLC: Updated Safety Results From HERTHENA-Lung01," *ESMO Open* 9 (2024): 102590.

41. Q. Wei, T. Yang, Z. Zhang, et al., "Perivascular Niche-Resident Alveolar Macrophages Promote Interstitial Pneumonitis Related to Trastuzumab Deruxtecan Treatment," *Cancer Research* 85, no. 11 (2025): 2081–2099.

42. Y. Kitahara, Y. Inoue, H. Yasui, et al., "Pan-Cancer Assessment of Antineoplastic Therapy-Induced Interstitial Lung Disease in Patients Receiving Subsequent Therapy Immediately Following Immune Checkpoint Blockade Therapy," *Respiratory Research* 25, no. 1 (2024): 25.

43. Z. Abuhelwa, A. Alloghbi, A. Alqahtani, and M. Nagasaka, "Trastuzumab Deruxtecan-Induced Interstitial Lung Disease/Pneumonitis in ERBB2-Positive Advanced Solid Malignancies: A Systematic Review," *Drugs* 82, no. 9 (2022): 979–987.

44. K. S. Saini, K. Punie, C. Twelves, et al., "Antibody-Drug Conjugates, Immune-Checkpoint Inhibitors, and Their Combination in Breast Cancer Therapeutics," *Expert Opinion on Biological Therapy* 21, no. 7 (2021): 945–962.

45. K. Long and K. Suresh, "Pulmonary Toxicity of Systemic Lung Cancer Therapy," *Respirology* 25, no. Suppl 2 (2020): 72–79.

46. P. Tarantino, S. Modi, S. M. Tolaney, et al., "Interstitial Lung Disease Induced by Anti-ERBB2 Antibody-Drug Conjugates: A Review," *JAMA Oncology* 7, no. 12 (2021): 1873–1881.

47. J. W. Y. Chiu, S. C. Lee, J. C. Ho, et al., "Clinical Guidance on the Monitoring and Management of Trastuzumab Deruxtecan (T-DXd)-Related Adverse Events: Insights From an Asia-Pacific Multidisciplinary Panel," *Drug Safety* 46, no. 10 (2023): 927–949.

48. Y. Cheng, X. Yuan, Q. Tian, et al., "Preclinical Profiles of SKB264, a Novel Anti-TROP2 Antibody Conjugated to Topoisomerase Inhibitor, Demonstrated Promising Antitumor Efficacy Compared to IMMU-132," *Frontiers in Oncology* 12 (2022): 951589.

49. R. G. Crystal, J. E. Gadek, V. J. Ferrans, J. D. Fulmer, B. R. Line, and G. W. Hunninghake, "Interstitial Lung Disease: Current Concepts of Pathogenesis, Staging and Therapy," *American Journal of Medicine* 70, no. 3 (1981): 542–568.

50. C. Xu, Z. Chen, Y. Xia, et al., "Clinical Best Practices in Interdisciplinary Management of Human Epidermal Growth Factor Receptor 2 Antibody-Drug Conjugates-Induced Interstitial Lung Disease/Pneumonitis: An Expert Consensus in China," *Cancer* 130, no. S17 (2024): 3054–3066.

51. D. Wekking, M. Porcu, B. Pellegrino, et al., "Multidisciplinary Clinical Guidelines in Proactive Monitoring, Early Diagnosis, and Effective Management of Trastuzumab Deruxtecan (T-DXd)-Induced Interstitial Lung Disease (ILD) in Breast Cancer Patients," *ESMO Open* 8, no. 6 (2023): 102043.

52. P. Tarantino, B. Ricciuti, S. M. Pradhan, and S. M. Tolaney, "Optimizing the Safety of Antibody-Drug Conjugates for Patients With Solid Tumours," *Nature Reviews. Clinical Oncology* 20, no. 8 (2023): 558–576.

53. L. P. Stepan, E. S. Trueblood, K. Hale, J. Babcook, L. Borges, and C. L. Sutherland, "Expression of Trop2 Cell Surface Glycoprotein in Normal and Tumor Tissues: Potential Implications as a Cancer Therapeutic Target," *Journal of Histochemistry and Cytochemistry* 59, no. 7 (2011): 701–710.

54. R. S. Heist, J. Sands, A. Bardia, et al., "Clinical Management, Monitoring, and Prophylaxis of Adverse Events of Special Interest Associated With Datopotamab Deruxtecan," *Cancer Treatment Reviews* 125 (2024): 102720.

55. J. H. Lee, J. M. Lee, J. K. Kim, et al., "Antitumor Activity of 7-[2-(N-Isopropylamino)ethyl]-(20S)-Camptothecin, CKD602, as a Potent DNA Topoisomerase I Inhibitor," *Archives of Pharmacal Research* 21, no. 5 (1998): 581–590.

56. H. Donaghy, "Effects of Antibody, Drug and Linker on the Preclinical and Clinical Toxicities of Antibody-Drug Conjugates," *MAbs* 8, no. 4 (2016): 659–671.

57. H. Uppal, E. Doudement, K. Mahapatra, et al., "Potential Mechanisms for Thrombocytopenia Development With Trastuzumab Emtansine (T-DM1)," *Clinical Cancer Research* 21, no. 1 (2015): 123–133.

58. J. N. Thon, M. T. Devine, A. Jurak Begonja, J. Tibbitts, and J. E. Italiano, Jr., "High-Content Live-Cell Imaging Assay Used to Establish Mechanism of Trastuzumab Emtansine (T-DM1)—Mediated Inhibition of Platelet Production," *Blood* 120, no. 10 (2012): 1975–1984.

Supporting Information

Additional supporting information can be found online in the Supporting Information section. **Data S1:** tca70178-sup-0001-Supinfo1.docx. **Data S2:** tca70178-sup-0002-Supinfo2.docx.