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Review Article

Efficacy and safety of trastuzumab deruxtecan in patients with solid tumors: a systematic review and meta-analysis of 3 randomized controlled trials

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Abstract: Trastuzumab deruxtecan (T-DXd, DS-8201) is a targeted antibody-drug conjugate that specifically targets human epidermal growth factor receptor 2 (HER2). In 2019, it was approved by the US Food and Drug Administration for the treatment of HER2-positive breast cancer. However, ongoing research is exploring its potential efficacy in other solid tumors, such as non-small-cell lung cancer and colorectal cancer, as well as in tumors with low HER2 levels. It is important to examine the safety and effectiveness of trastuzumab deruxtecan in these various types of solid tumors, as some studies have raised concerns about potential serious adverse events associated with its use. In this meta-analysis, we conducted a comprehensive search of PubMed, EMBASE, Cochrane Library, and Web of Science to identify randomized controlled trials (RCTs) that evaluated the efficacy and safety of trastuzumab deruxtecan in solid tumors. We used RevMan 5.4 software to perform a meta-analysis, calculating odds ratios (OR), risk ratios (RR), and weighted mean differences (WMD) with 95% confidence intervals (CIs). After an exhaustive search, we identified three articles that met our inclusion criteria, which included a total of 1268 patients. The results of the meta-analysis showed that the treatment group had significantly higher overall survival (WMD=5.12, 95% CI (2.79, 7.44), P<0.0001), progression-free survival (WMD=3.45, 95% CI (0.8, 6.1), P=0.01), overall response rate (OR=6.49, 95% CI (4.90, 8.58), P<0.00001), and disease control rate (OR=4.68, 95% CI (2.78, 7.89), P<0.00001), TRAEs (RR=6.93, 95% CI (2.06, 23.25), P=0.002). However, there was no significant difference in TRAEs≥3 (RR=1.08, 95% CI (0.75, 1.56), P=0.68) between the trials. Based on the available evidence, trastuzumab deruxtecan appears to be an effective and safe treatment option for HER2-positive solid tumors. Although the number of studies included in this analysis is limited, ongoing trials are being conducted, further evaluating its potential in various solid tumors. The results of these trials will enhance our understanding of trastuzumab deruxtecan and potentially expand its applications, bringing hope to more patients with solid tumors.

Keywords: Trastuzumab deruxtecan, safety, efficacy, solid tumors, meta-analysis

Introduction

For decades, chemotherapies based on cytotoxic agents have been the mainstay of treatment for various types of cancers [1]. However, these chemotherapeutic agents have limitations, such as a low therapeutic index, which means they can cause severe side effects due to nonspecific drug exposure to off-target tissues [2, 3]. In order to address these limitations and improve the efficacy of cancer treatment, scientists have been researching and inventing molecular targeted drugs, such as specific kinase inhibitors and monoclonal antibodies [4].

One significant advancement in recent years has been the development of human epidermal growth factor receptor 2 (HER2) targeted therapy. Targeted drugs like trastuzumab and pertuzumab have shown promising results in improving the quality of life for patients with HER2-positive solid tumors, particularly in the context of adjuvant and neoadjuvant therapy

[5]. These targeted therapies have provided hope and more treatment choices for patients with HER2-positive breast cancer and metastatic gastric cancer.

Several anti-HER2 drugs have already been approved for the treatment of breast cancer, including the combination of trastuzumab and pertuzumab, both of which are humanized monoclonal antibodies against HER2. Additionally, drugs like trastuzumab emtansine (also known as T-DM1) and Lapatinib, an HER2 kinase inhibitor, have been approved for further treatment. Trastuzumab combined with chemotherapy is considered the standard first-line treatment for HER2-positive metastatic gastric cancer.

However, the effectiveness of these HER2-targeted therapies is still limited, especially in a growing number of solid tumor types and drug resistance [6]. Researchers are actively working on further developing and improving HER2-targeted therapies. Trastuzumab deruxtecan is a newer HER2 targeting antibody-drug conjugate that has shown promise, including breast cancer, stomach cancer, colorectal cancer, and non-small cell lung cancer with HER2 expression or mutations.

Trastuzumab deruxtecan, approved by the FDA in 2019, is composed of a humanized monoclonal antibody specifically targeting HER2, a stable linker that is selectively cleaved in tumor cells, and a potent cytotoxic drug [7-11]. This design allows the drug to be released specifically in tumor cells, minimizing exposure to normal cells [12]. Trastuzumab deruxtecan has been widely used in HER2-positive breast cancer and has shown an acceptable safety profile so far [13]. Ongoing clinical studies are also exploring its potential benefits in other solid tumors [14].

However, it is important to note that studies have also shown potentially serious adverse events in some patients treated with trastuzumab deruxtecan [15]. Therefore, a meta-analysis of randomized controlled trials is needed to evaluate the overall safety and efficacy of trastuzumab deruxtecan in the treatment of various solid tumors. This analysis aims to provide evidence-based medical evidence for guidelines and clinical treatment.

Methods

This study has been registered in the International Prospective Register of Systematic Reviews (CRD42023411099). We the meta-analysis under the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guide.

Search strategy

In order to gather comprehensive and up-to-date information, we conducted a systematic search of several databases including PubMed, Web of Science, EMBASE, and Cochrane Library. We did not impose any restrictions on language, ensuring that relevant articles from various languages are included in our study. Given that solid tumors may not always be explicitly mentioned in the article titles or abstracts, we utilized Medical Subject headings (MeSH) and related terms specific to trastuzumab deruxtecan and neoplasms. This helped us identify relevant articles that might not have directly mentioned solid tumors in their titles or abstracts. To optimize our search strategy, we adjusted the search format for each database to suit their unique characteristics. The specific steps for retrieving articles from each database are detailed in Supplementary Methods 1, 2, 3, 4.

In addition to the initial database search, we also conducted a thorough review of systematic reviews and scanned the reference lists of retrieved articles to identify any additional relevant studies. This approach increases the likelihood of capturing all relevant information available in the literature. To ensure the accuracy and consistency of our screening process, two review authors independently assessed the articles according to predefined criteria. In case of any disagreements, a third author was consulted to reach a consensus and resolve any discrepancies. This multi-step screening process helps maintain the rigor and validity of our study.

Inclusion and exclusion criteria

Inclusion criteria: 1) The study design had to be randomized controlled trials (RCTs). 2) Patients had to have a histological diagnosis of advanced metastatic HER2-positive breast cancer that

had progressed after prior treatment with TDM-1. Additionally, patients with HER2-positive gastric cancer or gastroesophageal junction cancer who had previously received trastuzumab were also eligible. Patients with breast cancer characterized by low HER2 expression (IHC 1+ or 2+, negative in situ hybridization), other solid tumors expressing HER2 (defined as IHC 3+, 2+ or 1+ or amplification), or HER2 mutations were also included. 3) The experimental group consisted of patients who were treated with trastuzumab deruxtecan. 4) The control group received chemotherapy based on the physician's choice, following either the local label or the National Comprehensive Cancer Network guidelines. 5) The main outcomes assessed in the study included overall survival (OS), progression-free survival (PFS), objective response rate (ORR), and disease control rate (DCR). Secondary outcomes focused on adverse reactions (TRAEs) and treatment-related adverse events of grade 3 or higher (TRAEs≥3).

Exclusion criteria: 1) The study was not an RCT; 2) The trial object was not a person; 3) Trastuzumab deruxtecan was used in combination with other drugs; 4) The study was deficient in data or had no full-text.

Data extraction

After the study selection process was completed, two reviewers collected various characteristics from the selected studies. These characteristics included the name of the first author, the year of publication, the sample size, the age and sex of the patients, the type of tumor, any previous treatment received by the patients, the status of the organs involved, the Eastern Oncology Collaborative (ECOG) physical status, the intervention methods used, and baseline statistical data such as overall survival (OS), progression-free survival (PFS), objective response rate (ORR), disease control rate (DCR), treatment-related adverse events (TRAEs), and severe treatment-related adverse events (TRAEs≥3). In case any additional information was needed, the corresponding author could be contacted. All the necessary information was extracted from both the main text and supplementary files of the selected studies, and only the data that could be easily extracted were included in the analysis. The primary outcomes of interest for this study were OS, PFS, ORR, and DCR, while the secondary outcomes included TRAEs and TRAEs≥3.

Quality risk assessment tools

The risk of bias tool, as outlined in the Cochrane Handbook for Systematic Reviews of Interventions, was utilized to thoroughly evaluate the methodological quality of each individual study included in the analysis. This tool assessed various factors such as random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome data, incomplete data, selective reporting, and any other potential sources of bias. The assessment of bias was classified into three categories: high risk, unclear risk, and low risk. Each study was carefully examined and assigned a determination based on these classifications, with detailed explanations provided for each type of bias identified. To present the results of the bias assessment, Review Manager 5.4 software was employed to generate both a risk of bias summary and a risk of bias graph. These visual representations allowed for a clear and comprehensive depiction of the overall risk of bias across all included studies.

Statistical processing

We utilized RevMan5.4, a software tool specifically designed for conducting meta-analyses, to perform our analysis. In this analysis, we focused on calculating the odds ratio (OR) or the risk ratio (RR) or weighted mean difference (WMD) along with their respective 95% confidence intervals (CIs). To determine the most appropriate statistical model, we employed both fixed effects and random effects models.

The fixed effects model was employed when there was no significant heterogeneity observed among the studies, indicating that the studies are relatively similar in terms of their characteristics. On the other hand, if a considerable amount of heterogeneity was observed (indicated by an I^2 value greater than 50%), we employed the random effects model. The random effects model takes into account the potential variations between studies due to differences in populations, interventions, or study designs. By using these different models, we

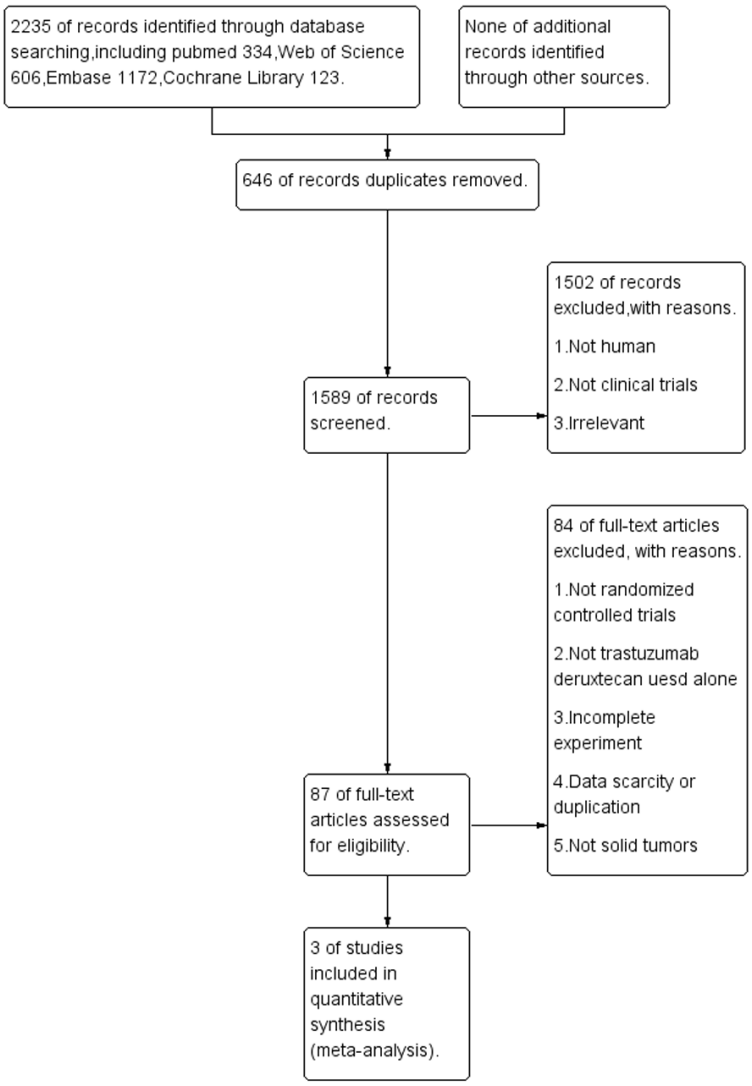

Figure 1. Flow diagram for the selection of eligible studies.

aimed to provide a comprehensive analysis that accurately captures the effect sizes and their associated uncertainties.

Results

Literature screening process

After conducting the initial search, a comprehensive search of various databases resulted in the identification of a total of 2235 articles. These articles underwent a meticulous deletion and the exclusion process to remove any duplicates or irrelevant studies. The remaining articles were then subjected to a thorough screening process, where their content was carefully reviewed and analyzed. This screening process involved a rigorous assessment of the study design, methodology, and relevance to the research question at hand. After this meticulous screening process, three articles [16-18] were deemed suitable for inclusion in this analysis. These articles met all the necessary criteria and provided valuable information pertaining to the topic under investigation. In total, 1268 patients were included in this analysis, as reported in these three selected articles. These patients had been recruited from various research studies and provided valuable data that could be utilized in this analysis. The entire literature screening process, from the initial search to the final selection of articles, is visually represented in **Figure 1**.

Basic features of literature

A total of 3 studies [16-18] were included in this meta-analysis. These studies included a total of 1268 subjects, with 759 subjects in the experimental group and 509 subjects in the control group. **Table 1** presents the basic characteristics of the included literature.

Literature bias risk assessment

The three studies [16-18] included in this study have been carefully selected to mitigate any potential biases that could affect the results. Over all, the three studies have shown low risks of selection bias, reporting bias, and other biases. However, the limited information on performance bias, the presence of detection bias in some studies, and the high risk of attrition bias in one study call. In summary, the assessment of bias in the included literature is presented in **Figure 2**.

Results of meta-analysis

Overall survival (OS): According to the data analysis, all three articles included in the study

Table 1. Characteristics of studies and subjects included in the review

Study author (year)	Study design	Gender (M/F)	Case Experimental vs control	Patients' characteristics	Intervention methods
Cortés 2021 [16]	RCT phase 3	3/522	524 261 vs 263	Unresectable and/or metastatic breast cancer, HER2-positive; previously treated with trastuzumab and taxane in the advanced/metastatic setting or progressed within 6 months after neoadjuvant or adjuvant treatment involving a regimen including trastuzumab and taxane; brain metastases were eligible for enrollment if clinical stable, previously treated brain metastases; adequate renal and hepatic function; ECOG 0-1; ≥18 years old.	Trastuzumab deruxtecan 5.4 mg/kg ivgtt d1/3 weeks vs Trastuzumab emtansine (T-DM1) 3.6 mg/kg ivgtt d1/3 weeks.
Shitara 2020 [17]	RCT phase 3	142/45	187 125 vs 62	Pathologically documented locally advanced or metastatic adenocarcinoma of gastric or gastroesophageal junction; progression on and after at least 2 prior regimens; adequate tumor sample; measurable disease based on Response Evaluation Criteria In Solid Tumors (RECIST) version 1.1v; adequate organ function; ECOG 0-1; ≥20 years old.	Trastuzumab deruxtecan 6.4 mg/kg ivgtt d1/3 weeks vs irinotecan 150 ivgtt mg/m^2 d1/2 weeks or paclitaxel 80ivgtt mg/m^2 d1, 8, 15/4 weeks.
Modi 2022 [18]	RCT phase 3	2/555	557 373 vs 184	Pathologically documented breast cancer that: unresectable or metastatic; low-HER2 expression defined as IHC 2+/ISH- or IHC 1+ (ISH- or untested); HR-positive or HR-negative; progressed on, and would no longer benefit from, endocrine therapy; previously treated with 1 to 2 prior lines of chemotherapy/adjuvant in the metastatic setting; never previously HER2-positive (ICH 3+ or ISH+) on prior pathology testing; adequate archival tumor samples; adequate cardiac, bone marrow, renal, hepatic and blood clotting functions; ECOG 0-1; ≥18 years old.	Trastuzumab deruxtecan 5.4 mg/kg ivgtt d1/3 weeks vs Capecitabine or Eribulin or Gemcitabine or Paclitaxel or Nab-paclitaxel (the physician's choice of chemotherapy was administered in accordance with the local label or the National Comprehensive Cancer Network guidelines).

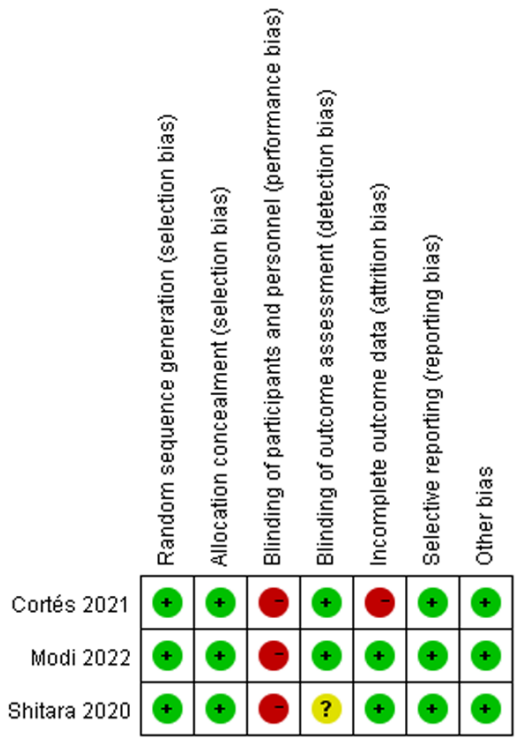

Figure 2. Quality assessment of the included studies.

reported overall survival (OS) as an outcome measure. Two of the articles specifically reported the median OS values and were selected for further analysis [17, 18]. According to the results, there was little heterogeneity (P=0.30, I^2=6%), and the OS of the treatment group was significantly higher than that of the control group, and the difference was statistically significant [WMD=5.12, 95% CI (2.79, 7.44), P<0.0001] (**Figure 3**).

Progression-free survival (PFS): Based on the information provided, three articles were reviewed, and all of them reported the median progression-free survival (PFS) outcome. However, one of the articles did not provide detailed information about the 95% confidence interval (95% CI) for the reported PFS. Therefore, to ensure accuracy and completeness in the review, the other two articles that did report the 95% CI interval in detail were selected for further analysis [17, 18]. According to the results, the heterogeneity was large (P=0.03, I^2=78%>50%), so the random model was selected. Results: The PFS of the treatment group was significantly higher than that of the control group, and the difference was statistically significant [WMD=3.45, 95% CI (0.8, 6.1), P=0.01] (**Figure 4**).

Objective response rate (ORR): ORR included a total of three RCTs [16-18]. The test for heterogeneity I^2=0 and the fixed effects model was applied. The results of Meta-analysis showed that the ORR of the experimental group was significantly better than that of the control group [OR=6.49, 95% CI (4.90, 8.58), P<0.00001] (**Figure 5**).

Disease control rate (DCR): A total of 3 RCTs were included in DCR. Heterogeneity test I^2=54%, random effects model was applied. The results of meta-analysis showed that the DCR of the experimental group was significantly better than that of the control group [OR=4.68, 95% CI (2.78, 7.89), P<0.00001] (**Figure 6**).

Treatment-related adverse events (TRAEs) and treatment-related adverse events ≥ grade 3 (TRAEs≥3): The results of meta-analysis of adverse reactions in the three groups showed that the TRAEs in the experimental group were more than those in the control group, and the difference was statistically significant [RR=6.93, 95% CI (2.06, 23.25), P=0.002]. However, there was no significant difference in TRAEs≥3 among the three groups [RR=1.08, 95% CI (0.75, 1.56), P=0.68], indicating that the serious adverse reactions of the experimental group and the control group were similar (**Figures 7**, **8**).

Discussion

Currently, trastuzumab deruxtecan is widely used in the treatment of breast cancer. However, its effectiveness in treating other solid tumors still needs further investigation. The purpose of this article is to analyze the clinical efficacy and safety of trastuzumab deruxtecan based on RCTs. By conducting a meta-analysis of the results, it becomes evident that patients in the trastuzumab deruxtecan group experienced significantly better OS, PFS, ORR, and DCR compared to those in the control group or the group treated with the doctor's choice of therapy. These differences were statistically significant.

Regarding TRAEs, the experimental group had a slightly higher incidence of adverse reactions compared to the control group, but the difference was not significant. There was also no significant difference in the incidence of TRAEs≥3 between the two groups.

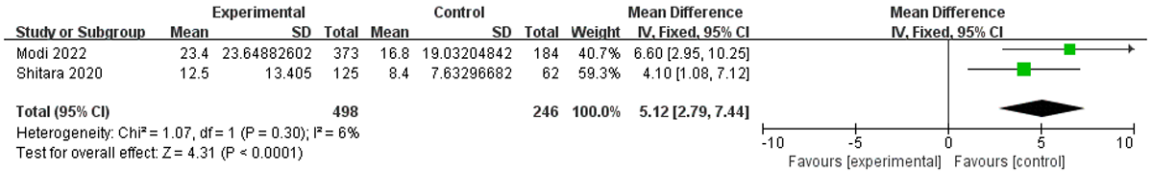

Figure 3. Meta-analysis of the overall survival (OS) of solid tumors treated with trastuzumab deruxtecan.

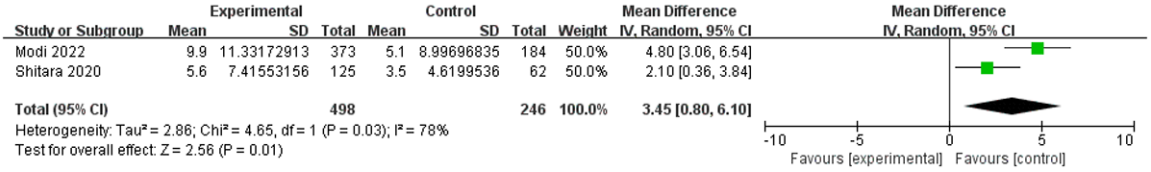

Figure 4. Meta-analysis of the progression-free survival (PFS) of solid tumors treated with trastuzumab deruxtecan.

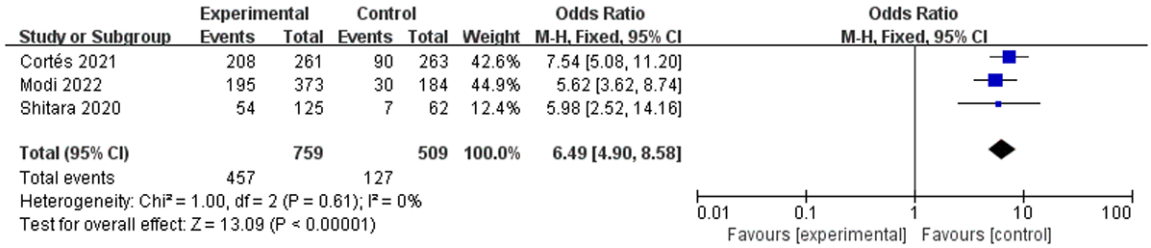

Figure 5. Meta-analysis of the objective response rate (ORR) of solid tumors treated with trastuzumab deruxtecan.

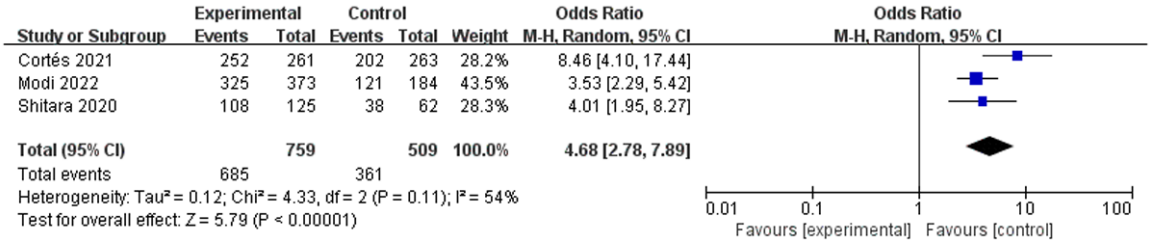

Figure 6. Meta-analysis of the disease control rate (DCR) of solid tumors treated with trastuzumab deruxtecan.

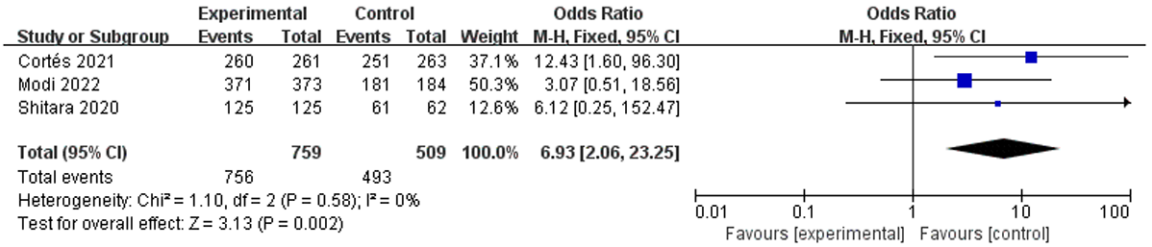

Figure 7. Meta-analysis of the treatment-related adverse events (TRAEs) of solid tumors treated with trastuzumab deruxtecan.

The most common TRAEs reported in trastuzumab deruxtecan treatment for solid tumors were nausea, fatigue, vomiting, neutropenia, anemia, leukopenia, and thrombocytopenia.

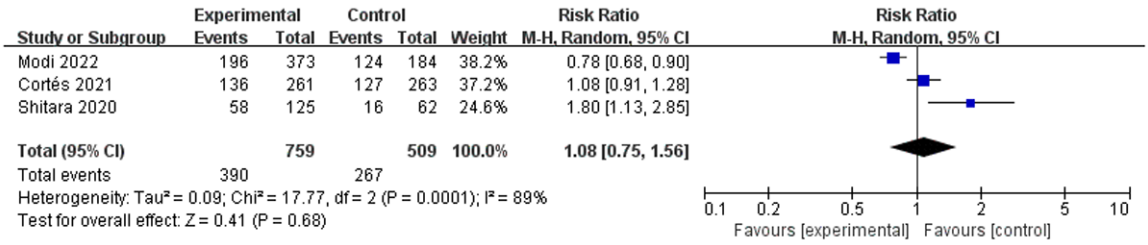

Figure 8. Meta-analysis of the treatment-related adverse events ≥ grade 3 (TRAEs≥3) of solid tumors treated with trastuzumab deruxtecan.

These toxic effects were mostly manageable through dose adjustment or interruption. Particularly, myelosuppression and interstitial lung disease were the most significant adverse events observed in the three included studies, but they could be controlled with appropriate dose reduction or interruption. Gastrointestinal events were mostly low-grade, while hematologic events were more frequent and often of higher grade, but they too could be addressed by dose adjustment. However, it should be noted that trastuzumab deruxtecan has been associated with cardiotoxic effects, although these were rarely reported in the trials.

In conclusion, trastuzumab deruxtecan has shown significant efficacy in the treatment of solid tumors, with manageable adverse reactions through dose adjustment, glucocorticoid therapy, and supportive care. Active monitoring and prompt management of adverse reactions are essential to ensure patient safety. Trastuzumab deruxtecan has the potential to improve outcomes for patients with HER2-positive solid tumors, even in those whose disease progresses during treatment. Additionally, it may become an important therapeutic option for patients with HER2-positive gastric cancer.

However, there are limitations to this meta-analysis. The included studies had a high risk of bias, and their small sample size affected the statistical power and accuracy of the results. Heterogeneity in outcome indicators and different control groups used further contribute to uncertainty in the findings. Moreover, the limited number of RCTs and their focus on specific tumor types limit the generalizability of the results.

Conclusion

According to the available literature, trastuzumab deruxtecan has shown promising efficacy and safety in the treatment of solid tumors characterized by HER2 positivity. However, it is important to note that the number of studies included in this article is limited, and thus further research is required to fully establish its effectiveness. Fortunately, ongoing trials indicate that a substantial number of researchers and clinicians are actively investigating the potential of trastuzumab deruxtecan in various related trials. This presents an exciting prospect, as the results from these trials have the potential to expand the usage of trastuzumab deruxtecan beyond its current indications, allowing it to reach a wider range of solid tumors and provide lifesaving treatment to an even larger number of patients. The anticipation for the outcomes of these trials is palpable, as they hold the key to a future where trastuzumab deruxtecan becomes a widely available and highly effective treatment option for a multitude of solid tumors.

Disclosure of conflict of interest

None.

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Supplementary Method 1 - Search strategy for PubMed

#1 (((trastuzumab deruxtecan) OR (T-DXd)) OR (DS-8201a)) OR (DS-8201)

#2 ((((((((((((((((("Neoplasms"[Mesh]) OR (Tumor)) OR (Neoplasm)) OR (Tumors)) OR (Neoplasia)) OR (Neoplasias)) OR (Cancer)) OR (Cancers)) OR (Malignant Neoplasm)) OR (Malignancy)) OR (Malignancies)) OR (Malignant Neoplasms)) OR (Neoplasm, Malignant)) OR (Neoplasms, Malignant)) OR (Benign Neoplasms)) OR (Benign Neoplasm)) OR (Neoplasms, Benign)) OR (Neoplasm, Benign))

#1 AND #2

Supplementary Method 2 - Search strategy for Cochrane

#1 (trastuzumab deruxtecan):ti,ab,kw OR (T-DXd):ti,ab,kw OR (DS-8201a):ti,ab,kw OR (DS-8201):ti,ab,kw

#2 MeSH descriptor: [Neoplasms] explode all trees OR (Tumor):ti,ab,kw OR (Neoplasm):ti,ab,kw OR (Tumors):ti,ab,kw OR (Neoplasia):ti,ab,kw OR (Neoplasias):ti,ab,kw OR (Cancer):ti,ab,kw OR (Cancers):ti,ab,kw OR (Malignant Neoplasm):ti,ab,kw OR (Malignancy):ti,ab,kw OR (Malignancies):ti,ab,kw OR (Malignant Neoplasms):ti,ab,kw OR (Neoplasm, Malignant):ti,ab,kw OR (Neoplasms, Malignant):ti,ab,kw OR (Benign Neoplasms):ti,ab,kw OR (Benign Neoplasm):ti,ab,kw OR (Neoplasms, Benign):ti,ab,kw OR (Neoplasm, Benign):ti,ab,kw

#1 AND #2

Supplementary Method 3 - Search strategy for EMBASE

#1 'trastuzumab deruxtecan'/exp OR 'trastuzumab deruxtecan' OR (('trastuzumab'/exp OR trastuzumab) AND ('deruxtecan'/exp OR deruxtecan)) OR 't dxd' OR 'ds 8201a' OR 'ds 8201'#2 'neoplasms'/exp OR neoplasms* OR tumor* OR neoplasia* OR cancer* OR (malignant AND neoplasm) OR malignancy OR benign neoplasms

#1 AND #2

Supplementary Method 4 - Search strategy for Web of Science

#1 (((TS=(trastuzumab deruxtecan)) OR TS=(T-DXd)) OR TS=(DS-8201a)) OR TS=(DS-8201)

#2 ((((((((((((((((TS=(Neoplasms)) OR TS=(Tumor)) OR TS=(Neoplasm)) OR TS=(Tumors)) OR TS=(Neoplasia)) OR TS=(Neoplasias)) OR TS=(Cancer)) OR TS=(Cancers)) OR TS=(Malignant Neoplasm)) OR TS=(Malignancy)) OR TS=(Malignancies)) OR TS=(Malignant Neoplasms)) OR TS=(Neoplasm, Malignant)) OR TS=(Neoplasms, Malignant)) OR TS=(Benign Neoplasms)) OR TS=(Benign Neoplasm)) OR TS=(Neoplasms, Benign)) OR TS=(Neoplasm, Benign)

#1 AND #2