Received: 31 August 2022 | Accepted: 4 September 2022

DOI: 10.1111/jcpt.13777

ORIGINAL ARTICLE

Journal of Clinical Pharmacy and Therapeutics WILEY

Safety of trastuzumab deruxtecan: A meta-analysis and pharmacovigilance study

Zihan Guo MS[1,2] | Yunlan Ding MS[1,2] | Mengmeng Wang MS[1,2] | Jiyong Liu MD[1,2] | Qing Zhai MD[1,2] | Qiong Du MS[1,2]

[1]Department of Pharmacy, Fudan University Shanghai Cancer Center, Shanghai, China

[2]Department of Oncology, Shanghai Medical College, Fudan University, Shanghai, China

Correspondence
Qiong Du, Department of Pharmacy, Fudan University Shanghai Cancer Center; Department of Oncology, Shanghai Medical College, Fudan University, Shanghai 200032, China.
Email: dujoan-88@163.com

Funding information
Shanghai "Rising Stars of Medical Talent" Youth Development Program Youth Medical Talents Clinical Pharmacist Program, Grant/Award Number: SHWRS (2020)087; Clinical Research Plan of SHDC, Grant/Award Number: SHDC2020CR3085B

Abstract

What Is Known and Objective: This study aimed to explore the safety profile of trastuzumab deruxtecan (T-DXd, formerly DS-8201a) using multi-source medical data.

Methods: We explored trastuzumab deruxtecan related adverse events (AEs) in clinical trials available in ClinicalTrials.gov and electronic databases (MEDLINE, EMBASE and PubMed) up to July 16, 2022. Meta-analysis was performed by using incidence rate with 95%CIs. In the pharmacovigilance study of FDA Adverse Event Reporting System (FAERS), the reporting odds ratio (ROR) and the medicines and healthcare products regulatory agency (MHRA) methods were used to analyse the real-world AEs (up to June 28, 2022).

Results and Discussion: A 8 clinical trials enrolled 1457 patients were included. The most common AEs of any grade were gastrointestinal disorders and blood and lymphatic system disorders. The most common AE of grade 3 or higher was neutropenia (21.4%, 95%CI: 14.7%–28.1%, $I^2 = 91\%$). The incidence of interstitial lung disease (ILD) and decreased left ventricular ejection fraction were 10.9% (95%CI: 7.2%–14.5%, $I^2 = 82\%$) and 1.2% (95%CI: 0.7%–2.2%, $I^2 = 98\%$), respectively. A total of 1244 AE reports were identified in the pharmacovigilance study. Gastrointestinal toxicity (ROR = 21.65), myelosuppression (ROR = 36.88), interstitial lung disease (ROR = 50.30), pneumonitis (ROR = 36.59), decreased ejection fraction (ROR = 16.08), and taste disorder (ROR = 14.06) mentioned in the instructions showed strong signals. Also, ascites (ROR = 14.90), lung opacity (ROR = 78.80), pulmonary fibrosis (ROR = 5.59), and increased KL-6 (ROR = 1761.97), which were not mentioned in the instructions, showed strong signals.

What Is New and Conclusion: Trastuzumab deruxtecan was well tolerated, and more attention should be paid on ILD as well as decreased ejection fraction.

KEYWORDS
adverse event, meta-analysis, pharmacovigilance, real-world, trastuzumab deruxtecan

1 | INTRODUCTION

Human epidermal growth factor receptor-2 (HER2) is a tyrosine kinase receptor growth-promoting protein expressed on the surface of various types of cancer cells, including breast, gastric, lung and colorectal cancer. It is associated with aggressive disease and poor prognosis. Although the advent of targeted drugs such as trastuzumab and pertuzumab has brought hope and more choices to HER2-positive patients in recent years, the effect is still limited, and patients are prone to drug resistance after treatment.

Trastuzumab deruxtecan (T-DXd, formerly DS-8201a) is an antibody–drug conjugate (ADC) targeting HER2. It comprises humanized anti-HER2 antibody, cleavable tetrapeptide-based linker and membrane-permeable topoisomerase I inhibitor payload, targeting cancer cells and delivering drugs inside the cells. It has shown excellent efficacy in multiple cancer types.[1,2] On December 21, 2019, the US Food and Drug Administration (FDA) officially approved using trastuzumab deruxtecan for the late-line treatment of HER2-positive breast cancer. On January 15, 2021, the US FDA officially approved using trastuzumab deruxtecan for treating patients with locally advanced or metastatic HER2-positive gastric cancer or gastroesophageal junction adenocarcinoma who received trastuzumab therapy. On May 4, 2022, the US FDA officially approved trastuzumab deruxtecan for the second-line treatment of HER2-positive breast cancer. In addition, on April 19, 2022, trastuzumab deruxtecan was granted the priority review status by the FDA for the treatment of patients with HER2-positive unresectable or metastatic non-small cell lung cancer.

The adverse events (AEs) of trastuzumab deruxtecan in patients were generally manageable. The most common AEs were gastrointestinal or haematological, which were mostly mild. Trastuzumab deruxtecan is also associated with a risk of interstitial lung disease (ILD), without early identification and proper management; ILD may develop to be fatal in some instances, which poses a considerable challenge in daily clinical treatment.[3]

Isolated clinical trials and their systematic review present the highest quality of evidence and are the basis for guidelines issued by healthcare organizations. However, the evaluation of entire profiles of rare AEs derived from clinical trials is difficult owing to their stringent diagnostic standards and selection criteria, relatively small sample sizes, and limited follow-up time. The FDA Adverse Event Reporting System (FAERS), one of the largest pharmacovigilance databases with a large number of reported AEs and patient information, could provide data to verify and supplement the findings of clinical trials. Therefore, we evaluate the overall spectrum of the safety profile of trastuzumab deruxtecan by combining these two approaches.

1.1 | Methods

Firstly, we did a meta-analysis to investigate the AEs of trastuzumab deruxtecan. Furthermore, a retrospective data mining analysis was conducted using the FAERS database to further examine the safety of trastuzumab deruxtecan in clinical practice.

1.2 | Meta-analysis

1.2.1 | Search strategy and selection criteria

On July 16, 2022, we systematically searched MEDLINE, EMBASE, PubMed and ClinicalTrials.gov from inception as well as abstracts from the ASCO, ESMO and JSCO congresses in the last 3 years. The keywords used were "trastuzumab deruxtecan", "fam-trastuzumab deruxtecan-nxki", "Enhertu", "DS-8201" and "T-Dxd". The study type was limited to clinical trial. Two review authors (ZG, YD) independently screened titles and abstracts against eligibility criteria and disagreements were resolved by a third investigator (MW).

1.2.2 | Study outcomes, data extraction, and quality assessment

The primary outcomes were overall safety outcomes, viz. drug-related AEs, as defined in each study, including grade 1–5 and grade 3–5, respectively. The secondary outcomes were AEs (grade 1–5 and grade 3–5) of special interest (interstitial lung disease, decreased left ventricular ejection fraction, prolonged QT interval). AEs were graded according to the Common Terminology Criteria for Adverse Events (CTCAE Version 5.0),[4] as reported in each study. Two review authors (ZG, YD) applied a predesigned format to extract data independently, containing study characteristics, demographics and data of reported safety outcomes. All information was extracted from the main text and supplementary files, and only extractable data were analysed. The methodological quality of the involved trials was evaluated using the Joanna Briggs Institute (JBI) checklist.[5]

1.2.3 | Statistical analysis

We conducted a meta-analysis to compute the incidence rate and its 95%CI of each class and subclass of AE using a logit transformation and the inverse variance weighting. Summary of prevalence estimates were obtained using fixed-effects or random-effects meta-analysis which determined by I^2. Statistical heterogeneity was assessed through I^2 statistic and its values of 25%, 50%, and 75% correspond to low, moderate and high heterogeneity. The date which was low heterogeneity was chose the fixed-effects meta-analysis and others were chose random-effects meta-analysis. All the statistical analysis were performed with RevMan (Version 5.4).

2 | PHARMACOVIGILANCE STUDY

2.1 | Study design and data source

The data for this study were retrieved from the public release of the FAERS database, which adheres to the international safety reporting guidance issued by the International Conference on Harmonization

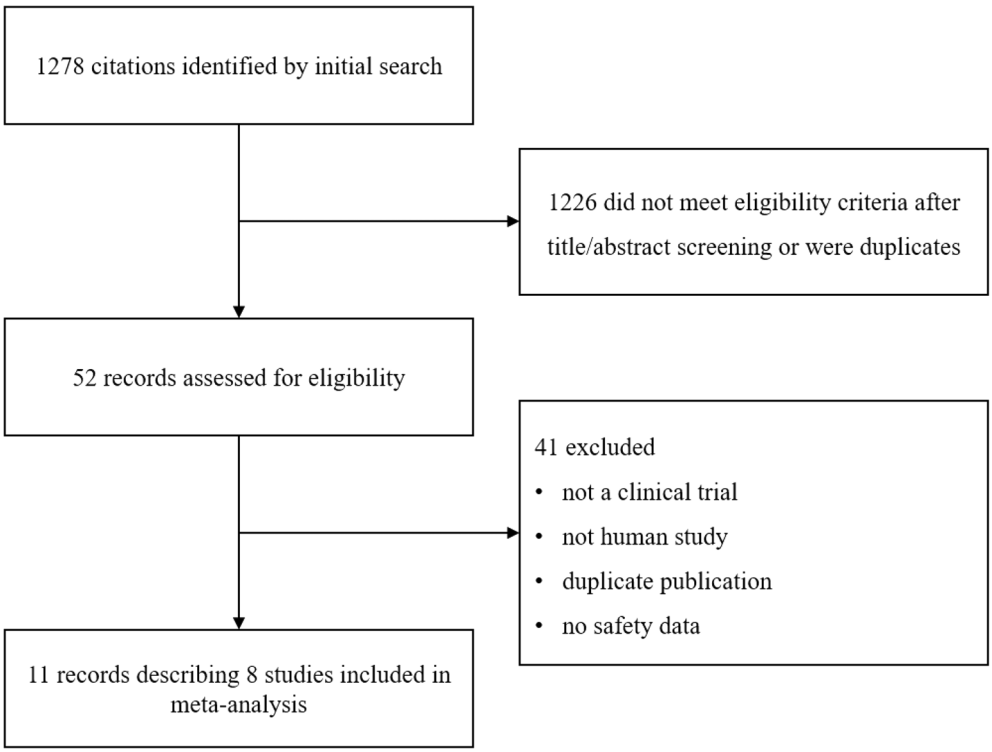

FIGURE 1 Flow diagram for the selection of eligible studies

(ICH E2B). OpenVigil FDA, a pharmacovigilance tool, was adapted to extract FAERS data.

The retrieval time range was "December 21, 2019 (marketing time of trastuzumab deruxtecan)," to "June 28, 2022," and "trastuzumab deruxtecan" was used as the target drug. The generic name "trastuzumab deruxtecan" and the brand name "Enhertu" were used as the keywords.

2.2 | Statistical analysis

In this study, the preferred system organ class (SOC) and preferred term (PT) of adverse drug reaction terminology set in the Medical Dictionary for Regulatory Activities (MedDRA) Version 25.0 were used to evaluate AEs. The measure of disproportionality is the main method for research on AE signals, based on the two-by-two contingency table (Table S1). Its principle is to compare the difference between the frequency of the target drug event and the background frequency. When the frequency of the target drug event is significantly higher than the background frequency and exceeds the set threshold, it is called disproportionality, indicating that some connection may exist between the suspicious drugs and suspected AEs, not due to chance factors or the "noisy background" of the database.[6–8]

AE was detected using the reporting odds ratio (ROR) method and the medicines and healthcare products regulatory agency (MHRA) method, which had high reliability and sensitivity in the proportional imbalance method. The study used ROR and its confidence interval and portional reporting ratio (PRR) and its χ^2 value to detect the adverse event signal of trastuzumab deruxtecan. For avoiding the appearance of false-positive signals, the data should meet the number of AE reports ≥3, the 95% CI lower limit of ROR >1, PRR >2, and χ^2 >4,[9] further excluding reports that did not meet the requirements. The signal intensities were arranged in the descending order of the ROR value. The larger the ROR value, the stronger the signal, indicating a stronger correlation between the drug and the adverse event. All data processing and statistical analysis were performed using SPSS software (version 26.0).

3 | RESULTS

3.1 | Characteristics and quality of studies included in the meta-analysis

Of 1278 articles obtained from the initial search of the databases, 8 studies enrolled a total of 1457 patients included in the final analysis (Figure 1). Detailed baseline characteristics of the included trials were summarized in Table S2. Of these 8 studies,[2,10–19] 1 was phase trial, 5 were phase II trials and 2 were phase III trials. Regarding the indication, 3 trials were conducted in patients with breast cancer, 2 in patients with gastric cancer, 1 in patients with lung cancer, 1 in patients with colorectal cancer, 1 in patients with multiple advanced solid tumours. Details of the quality assessment are presented in Table S3.

3.2 | Incidence of AEs in meta-analysis of clinical trials

The incidence of drug-related serious adverse events was 16.6% (95%CI: 11.8%–21.3%, $I^2 = 84\%$) in the trastuzumab deruxtecan

TABLE 1 Meta-analysis of the incidence of drug-related adverse events

Adverse events	All-grade adverse events			Grade ≥3 adverse events		
	No. of studies	Incidence rate% [95%CI]	I^2	No. of studies	Incidence rate% [95%CI]	I^2
Most common drug-related adverse events						
Gastrointestinal disorders						
Nausea	8	71.0 [66.7, 75.2]	68	8	5.0 [3.8, 6.1]	9
Vomiting	8	38.4 [32.8, 43.9]	79	8	1.8 [1.1, 2.9]	98
Diarrhoea	8	29.4 [25.0, 33.7]	69	8	2.0 [0.8, 4.6]	99
Constipation	8	26.7 [20.9, 32.6]	83	8	0.4 [0.2, 0.7]	98
Blood and lymphatic system disorders						
Neutropenia[a]	8	37.0 [28.3, 44.8]	91	8	21.4 [14.7, 28.1]	91
Anaemia[b]	8	35.2 [28.7, 41.6]	85	8	13.7 [8.3, 18.6]	90
Thrombocytopenia[c]	7	26.6 [21.8, 37.1]	74	7	6.4 [4.0, 10.3]	97
Leukopenia[d]	7	25.2 [20.9, 29.6]	70	7	9.4 [6.3, 14.0]	96
General disorders						
Fatigue[e]	8	41.3 [33.8, 48.8]	88	8	4.7 [3.3, 6.9]	99
Metabolism and nutrition disorders						
Decreased appetite	7	38.7 [28.1, 49.4]	94	7	2.1 [1.0, 4.5]	99
Skin and subcutaneous tissue disorders						
Alopecia	8	34.0 [27.1, 40.8]	87	8	0.4 [0.2, 0.6]	97
Adverse events of special interest						
Interstitial lung disease	8	10.9 [7.2, 14.5]	82	8	1.8 [1.1, 3.1]	98
Prolonged QT interval	8	0.7 [0.2, 2.1]	100	8	0.4 [0.2, 0.7]	98
Decreased left ventricular ejection fraction	8	1.2 [0.7, 2.2]	98	8	0.4 [0.3, 0.5]	96

[a]This category includes the preferred terms neutrophil count decreased and neutropenia.
[b]This category includes the preferred terms haemoglobin decreased, red-cell count decreased, anaemia, and haematocrit decreased.
[c]This category includes the preferred terms platelet count decreased and thrombocytopenia.
[d]This category includes the preferred terms white-cell count decreased and leukopenia.
[e]This category includes the preferred terms fatigue, asthenia, and malaise.

group, and the incidence of drug-related adverse events of grade 3 or higher was 50.0% (95%CI: 41.8%–58.2%, $I^2 = 90\%$). The incidence of adverse events associated with discontinuation of treatment was 12.2% (95%CI: 8.2%–16.2%, $I^2 = 83\%$), and the incidence of adverse events associated with dose reductions was 22.1% (95%CI: 18.9%–25.3%, $I^2 = 51\%$). 0.8% (95%CI: 0.4%–1.8%, $I^2 = 99\%$) of patients had adverse events that were associated with drug-related death. The main causes of death were interstitial lung disease and pneumonitis (Table S4).

The most common drug-related adverse events of any grade included nausea (71.0%, 95%CI: 66.7%–75.2%, $I^2 = 68\%$), vomiting (38.4%, 95%CI: 32.8%–43.9%, $I^2 = 79\%$), diarrhoea (29.4%, 95%CI: 25.0%–33.7%, $I^2 = 69\%$), constipation (26.7%, 95%CI: 20.9%–32.6%, $I^2 = 83\%$), fatigue (41.3%, 95%CI: 33.8%–48.8%, $I^2 = 88\%$), decreased appetite (38.7%, 95%CI: 28.1%–49.4%, $I^2 = 94\%$), neutropenia (37.0%, 95%CI: 28.3%–44.8%, $I^2 = 91\%$), anaemia (35.2%, 95%CI: 28.7%–41.6%, $I^2 = 85\%$), thrombocytopenia (26.6%, 95% CI: 21.8%–37.1%, $I^2 = 74\%$), leukopenia (25.2%, 95%CI: 20.9%–29.6%, $I^2 = 70\%$), and alopecia (34.0%, 95%CI: 27.1%–40.8%, $I^2 = 87\%$). The most common adverse events of grade 3 or higher were neutropenia (21.4%, 95%CI: 14.7%–28.1%, $I^2 = 91\%$), anaemia (13.7%, 95%CI: 8.3%–18.6%, $I^2 = 90\%$), leukopenia (9.4%, 95%CI: 6.3%–14.0%, $I^2 = 96\%$) and thrombocytopenia (6.4%, 95% CI: 4.0%–10.3%, $I^2 = 97\%$). Details on incidence rate per AE classes and subclasses were shown in Table 1.

Drug-related ILD occurred in 10.9% (95%CI: 7.2%–14.5%, $I^2 = 82\%$) patients, and the grade 3 or higher ILD was 1.8% (95%CI: 1.1%–3.1%, $I^2 = 98\%$). The time to the onset of ILD ranged from 129–193 days in breast cancer or lung cancer patients. ILD occurs relatively early in gastric cancer or colorectal cancer (range 77–84.5 days).

The incidence of cardiotoxicity was low in patients treated with trastuzumab deruxtecan, the incidence of decreased left ventricular ejection fraction and prolonged QT interval were 1.2% (95%CI: 0.7%–2.2%, $I^2 = 98\%$) and 0.7% (95%CI: 0.2%–2.1%, $I^2 = 100\%$), respectively.

TABLE 2 Signal strength of AEs of trastuzumab deruxtecan at the Preferred Terms (PTs) level in Food and Drug Administration Adverse Event Reporting System (FAERS) database

SOC	PT	Number of reports	ROR (95%CI)	PRR (χ2)
Gastrointestinal disorders	Gastrointestinal toxicity	5	21.65 (8.99–52.14)	78.44 (21.56)
	Ascites[a]	27	14.9 (10.18–21.83)	328.73 (14.60)
	Nausea	227	5.53 (4.79–6.39)	685.31 (4.71)
	Colitis[a]	7	3.44 (1.64–7.23)	9.73 (3.43)
	Vomiting	88	3.24 (2.61–4.03)	124.81 (3.09)
	Constipation	33	2.71 (1.91–3.82)	32.89 (2.66)
Blood and lymphatic system disorders	Myelosuppression	19	36.88 (23.43–58.06)	616.42 (36.34)
	Cytopenia	6	12.30 (5.51–27.44)	51.19 (12.25)
	Neutropenia[b]	72	7.83 (6.17–9.94)	397.75 (7.44)
	Febrile neutropenia	27	7.36 (5.02–10.77)	138.81 (7.22)
	Thrombocytopenia[d]	68	5.45 (4.27–6.96)	5.21 (229.30)
	Leukopenia[e]	21	3.31 (2.15–5.1)	31.11 (3.28)
	Anaemia[c]	34	2.86 (2.04–4.03)	38.27 (2.81)
Respiratory, thoracic and mediastinal disorders	Lung opacity[a]	6	78.8 (35.24–176.2)	381.97 (78.42)
	Interstitial lung disease	127	50.30 (41.85–60.45)	5445.72 (45.27)
	Pneumonitis	52	36.59 (27.71–48.32)	1686.11 (35.11)
	Pulmonary fibrosis[a]	6	5.59 (2.50–12.46)	18.14 (5.57)
	Pleural effusion[a]	21	5.44 (3.54–8.38)	70.54 (5.37)
	Lung disorder	10	3.48 (1.87–6.48)	15.14 (3.46)
General disorders and administration site conditions	Fatigue[f]	116	2.70 (2.23-3.27)	110.90 (2.54)
Metabolism and Nutrition Disorders	Decreased appetite	71	5.54 (4.36–7.04)	244.60 (5.28)
	Dehydration	24	2.85 (1.90–4.26)	26.38 (2.81)
Investigations	KL-6 increased[a]	5	1761.97 (687.98–4512.54)	6188.21 (1754.90)
	Ejection fraction decreased	15	16.08 (9.66–26.77)	194.73 (15.90)
	Blood bilirubin increased	13	7.28 (4.22–12.58)	63.61 (7.22)
	Blood sodium decreased[a]	5	2.76 (1.6–4.77)	12.73 (2.74)
	Weight decreased	45	2.72 (2.02–3.66)	45.34 (2.65)
Skin and Subcutaneous Tissue Disorders	Alopecia	64	5.35 (4.16–6.88)	210.45 (5.13)
Infections and infestations	Pneumonia bacterial	11	24.43 (13.49–44.26)	221.91 (24.23)
	Septic shock[a]	11	4.36 (2.41–7.90)	25.03 (4.33)
	Pneumonia aspiration	5	3.30 (1.37–7.93)	5.84 (3.29)
	Pneumocystis jirovecii pneumonia	7	13.70 (6.52–28.82)	69.74 (13.63)
Nervous system disorders	Taste disorder	9	14.06 (7.3–27.1)	95.7 (13.97)
	Cerebral haemorrhage[a]	6	2.59 (1.16–5.78)	4.36 (2.59)
Hepatobiliary disorders	Hepatic function abnormal	8	3.74 (1.87–7.5)	13.35 (3.72)
Eye Disorders	Dry eye	7	3.12 (1.48–6.55)	8.00 (3.10)

[a]Adverse drug events are not included in the label of trastuzumab deruxtecan.
[b]This category includes the preferred terms neutrophil count decreased and neutropenia.
[c]This category includes the preferred terms haemoglobin decreased, red-cell count decreased, anaemia, and haematocrit decreased.
[d]This category includes the preferred terms platelet count decreased and thrombocytopenia.
[e]This category includes the preferred terms white-cell count decreased and leukopenia.
[f]This category includes the preferred terms fatigue, asthenia, and malaise.

TABLE 3 Clinical characteristics of patients with selected adverse events

		Nausea	Vomiting	Neutropenia	Thrombocytopenia	Interstitial lung disease	pneumonitis
Drug dosing	5.4 mg/kg	16.7%	6.9%	16.7%	20.0%	22.7%	20.0%
	6.4 mg/kg	4.8%	6.9%	25.0%	10.0%	11.4%	NA
	Other	4.8%	17.2%	20.8%	20.0%	2.3%	13.3%
	Unreported	73.8%	69.0%	37.5%	50.0%	63.6%	66.7%
Time to AE onset, days		4 (1–580)	131 (3–580)	18 (1–281)	11 (11–365)	43 (1–350)	55 (35–133)
Outcome	Death	9.5%	3.5%	50.0%	10.0%	18.2%	NA
	Hospitalization	19.1%	17.2%	20.8%	20.0%	20.5%	26.7%
	Life-threatening	2.4%	NA	NA	NA	4.6%	13.3%
	Other	16.7%	10.3%	29.2%	30.0%	56.8%	60.0%
	Unreported	52.4%	69.0%	NA	40.0%	NA	NA

3.3 | Characteristics of AEs recorded in FAERS

A total of 14,869,812 AE reports were extracted, among which 1244 were AE reports with trastuzumab deruxtecan as the suspected drug, accounting for 0.0084% of all AE reports. Among 1244 reports, 677 (54.4%) were female and 187 (15.0%) were male. They were mainly aged from 18 to 64 years (19.1%). The reporting population comprised mainly doctors (59.4%). The United States was the most reported country (69.8%). Breast cancer was the main indication (61.3%), as shown in Table S5.

3.4 | Disproportionality analysis of data from FAERS

The ROR and MHRA methods were used to detect the signals of the top 100 AEs in the number of reported cases. The results showed that a total of 46 suspicious signals were generated. After screening, AEs unrelated to drugs, such as disease progression, product administration error, metastases to liver, and hospice care, were excluded. Finally, 36 warning signals remained, of which 9 were suspicious signals that were not included in the instructions. AE involved 11 types of SOCs, ranked according to the number of AE signals. The top 3 SOCs were 387 cases of gastrointestinal disorders (31.1%), 247 cases of blood and lymphatic system disorders (19.9%), and 222 cases of respiratory, thoracic, and mediastinal disorders (17.8%), as shown in Table S6.

Gastrointestinal toxicity (ROR = 21.65), myelosuppression (ROR = 36.88), interstitial lung disease (ROR = 50.30), pneumonitis (ROR = 36.59), decreased ejection fraction (ROR = 16.08), and taste disorder (ROR = 14.06) mentioned in the instructions showed the strong signals. In addition, ascites (ROR = 14.90), lung opacity (ROR = 78.80), pulmonary fibrosis (ROR = 5.59), and increased KL-6 (ROR = 1761.97), which were not mentioned in the instructions, also showed strong signals (Table 2).

We described the clinical characteristics of cases with AEs occurring in patients treated with trastuzumab deruxtecan (Table 3). Differences were found in the time to the onset of different AEs. Gastrointestinal toxicity occurred relatively early. The median time to the onset of nausea from the start of treatment was 4 days (range 1–580 days). The median time to the onset of neutropenia and thrombocytopenia was 18 days (range 1–281 days) and 11 days (range 11–365 days), respectively. Pulmonary toxicity appeared later. The median time to the onset of interstitial lung disease and pneumonitis was 43 days (range 1–350 days) and 55 days (range 35–133 days), respectively. ILD was associated with a higher risk of death compared with other AEs.

4 | DISCUSSION

Our study highlights the toxicity profile of trastuzumab deruxtecan based on the meta-analysis of 8 clinical trials involving 1457 patients, as well as the disproportionality analysis of the pharmacovigilance database containing 1244 reports. The results suggested that the most common adverse events were gastrointestinal toxicity and hematologic toxicity.

In this study, nausea was the most common gastrointestinal adverse reaction, with an incidence of 71.0% and 5.0% of grade 3–4 nausea.[13,14,16] Currently, no management guideline exists for nausea and vomiting caused by ADCs. A potential strategy is to use antiemetics prophylactically. However, the frequency of use is unknown, and no data are available to verify their effectiveness. The treatment can refer to the National Comprehensive Cancer Network (NCCN) guidelines for antiemesis.[3] Ascites is a new AE of trastuzumab deruxtecan with a strong signal, but no relevant report exists in the existing literature, which may be related to the disease itself. No evidence suggests that the AE is caused by the drug itself, and hence further observation is suggested.

Hematologic toxicity was also common in patients receiving trastuzumab deruxtecan.[13,14,18,19] The most common grade ≥3

hematologic toxicity was neutropenia, with an incidence of 21.4%, which also showed strong signal intensity in disproportionality analysis (ROR = 36.88). Granulocyte colony-stimulating factor (G-CSF) is widely used in treating neutropenia because it can promote the activation, proliferation and differentiation of myeloid precursor cells.[20] The NCCN guidelines recommend G-CSF for preventing febrile neutropenia based on patient risk factors.[21] Weekly blood routine monitoring is recommended during treatment, and G-CSF, antibiotics, or blood transfusion should be considered if necessary.[3]

ILD was considered an important established risk and is given a black-box warning by the FDA. In our study, ILD showed strong signal intensity (ROR = 50.3). Increased KL-6 (ROR = 1761.97), lung consolidation (ROR = 78.8), and pneumonitis (ROR = 36.59) also showed a strong signal strength. KL-6, also known as Krebs von den Lungen-6, is Mucin-1 usually expressed on the surface of human type II alveolar epithelial cells. When the alveolar basement membrane is damaged, type II alveolar cells secrete a large amount of KL-6 into the alveoli and blood to repair the damage, causing an increase in the serum KL-6 level. Therefore, the KL-6 level is closely related to the occurrence and development of lung diseases. Several recent studies reported that high expression of KL-6 might be associated with ILD.[22–24] ILD is a group of more than 200 lung diseases with varying degrees of involvement in the pulmonary interstitium and alveolar space, manifested as pneumonitis and/or pulmonary fibrosis. In the context of drug-induced lung injury in patients with cancer, ILD is often used interchangeably with pneumonitis. Lung opacity is more common in chest imaging and cannot be ruled out as a result of ILD. Counting these parts of the population, the ILD signal strength further increased. In our pooled analysis, the incidence of ILD was 10.9%, and mostly mild (9.1%). The time to the onset of ILD was associated with tumour type. ILD occurs relatively early in gastric cancer or colorectal cancer. The risk factors included high doses of drugs, Japanese population, low baseline blood oxygen saturation, moderate-to-severe baseline renal impairment and underlying lung diseases.[25,26] The specific mechanism of lung injury caused by anti-HER-2 ADC is still unclear; some studies have shown that ADC target-independent absorption may be the main cause of lung injury.[27,28] Close monitoring for symptoms of cough, dyspnea, and fever is recommended during the administration of trastuzumab deruxtecan. Once ILD is suspected, the drug should be discontinued and adrenal corticosteroid therapy should be initiated as soon as possible.[29]

Cardiotoxicity is a serious side effect in patients with breast cancer receiving HER-2-targeted therapy, including trastuzumab deruxtecan,[30–32] primarily as a decrease in ejection fraction. However, the incidence of cardiotoxicity was low in patients treated with trastuzumab deruxtecan, but our real-world research showed a strong signal intensity (ROR = 16.08). It is recommended that a comprehensive assessment of cardiovascular risk factors be performed before treatment and that cardiac function be reviewed periodically during and after treatment.

The main superiority of this study was the scientific and systematic quantification of the potential risks associated with trastuzumab deruxtecan, with the steady support of pooled analysis of clinical trials and real-world pharmacovigilance. However, our study had several limitations: (1) Among the 8 clinical trials included for the pooled analysis, 3 were significantly more extensive and had more weightage, potentially affecting the analysis. (2) FEARS database used in this study was in the form of spontaneous reporting, with a certain bias in the quality and integrity of the reported data. (3) All signal detection results could only indicate the existence of statistical correlation. Whether a real causal relationship exists needs further evaluation and research. Nonetheless, our real-world data analysis contributed to the cumulative knowledge about the safety of trastuzumab deruxtecan in an unselected population using a global database. There are no evidences to support the existence of major distortions to the data. We implemented a priori major strategies to increase the accuracy of the disproportionality analysis, thus supporting pharmacovigilance as a potential indicator of risk in the real world.

5 | CONCLUSION

Based on the clinic trials and FAERS database, this study analysed adverse event data of trastuzumab deruxtecan comprehensively. The incidence of gastrointestinal toxicity disorders and hematologic toxicity was higher. At the same time, this study also unearthed some new adverse event signals, such as ascites, increased KL-6, lung opacity and pulmonary fibrosis. To a certain extent, this study made up for the lack of pre-marketing clinical samples and short observation time of trastuzumab deruxtecan, providing a reference for clinical rational drug use and ensuring the safety of patients' medication.

FUNDING INFORMATION

Qiong Du was supported by Shanghai "Rising Stars of Medical Talent" Youth Development Program Youth Medical Talents Clinical Pharmacist Program (SHWRS [2020]087). Qing Zhai was supported by "Clinical Research Plan of SHDC" [SHDC2020CR3085B].

CONFLICT OF INTEREST

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

DATA AVAILABILITY STATEMENT

All data generated or analysed during this study are included in this published article [and its supplementary information files].

ORCID

Qiong Du https://orcid.org/0000-0003-4830-9704

REFERENCES

1. Ogitani Y, Aida T, Hagihara K, et al. DS-8201a, a novel HER2-targeting ADC with a novel DNA topoisomerase I inhibitor, demonstrates a promising antitumor efficacy with differentiation from T-DM1. *Clin Cancer Res*. 2016;22(20):5097-5108.

2. Shitara K, Iwata H, Takahashi S, et al. Trastuzumab deruxtecan (DS-8201a) in patients with advanced HER2-positive gastric cancer: a dose-expansion, phase 1 study. *Lancet Oncol*. 2019;20(6):827-836.
3. Shitara K, Baba E, Fujitani K, Oki E, Fujii S, Yamaguchi K. Discovery and development of trastuzumab deruxtecan and safety management for patients with HER2-positive gastric cancer. *Gastric Cancer*. 2021;24(4):780-789.
4. Freites-Martinez A, Santana N, Arias-Santiago S, Viera A. Using the common terminology criteria for adverse events (CTCAE - version 5.0) to evaluate the severity of adverse events of anticancer therapies. *Actas Dermosifiliogr (Engl Ed)*. 2021;112(1):90-92.
5. Munn Z, Moola S, Lisy K, Riitano D, Tufanaru C. Methodological guidance for systematic reviews of observational epidemiological studies reporting prevalence and cumulative incidence data. *Int J Evid Based Healthc*. 2015;13(3):147-153.
6. Bate A, Lindquist M, Edwards IR, et al. A Bayesian neural network method for adverse drug reaction signal generation. *Eur J Clin Pharmacol*. 1998;54(4):315-321.
7. van Puijenbroek E, Diemont W, van Grootheest K. Application of quantitative signal detection in the Dutch spontaneous reporting system for adverse drug reactions. *Drug Saf*. 2003;26(5):293-301.
8. Evans SJ, Waller PC, Davis S. Use of proportional reporting ratios (PRRs) for signal generation from spontaneous adverse drug reaction reports. *Pharmacoepidemiol Drug Saf*. 2001;10(6):483-486.
9. van Puijenbroek EP, Bate A, Leufkens HG, Lindquist M, Orre R, Egberts AC. A comparison of measures of disproportionality for signal detection in spontaneous reporting systems for adverse drug reactions. *Pharmacoepidemiol Drug Saf*. 2002;11(1):3-10.
10. Tamura K, Tsurutani J, Takahashi S, et al. Trastuzumab deruxtecan (DS-8201a) in patients with advanced HER2-positive breast cancer previously treated with trastuzumab emtansine: a dose-expansion, phase 1 study. *Lancet Oncol*. 2019;20(6):816-826.
11. Modi S, Park H, Murthy RK, et al. Antitumor activity and safety of Trastuzumab Deruxtecan in patients with HER2-low-expressing advanced breast cancer: results from a phase Ib study. *J Clin Oncol*. 2020;38(17):1887-1896.
12. Tsurutani J, Iwata H, Krop I, et al. Targeting HER2 with Trastuzumab Deruxtecan: a dose-expansion, phase I study in multiple advanced solid tumors. *Cancer Discov*. 2020;10(5):688-701.
13. Modi S, Saura C, Yamashita T, et al. Trastuzumab Deruxtecan in previously treated HER2-positive breast cancer. *N Engl J Med*. 2020;382(7):610-621.
14. Cortés J, Kim SB, Chung WP, et al. Trastuzumab Deruxtecan versus Trastuzumab Emtansine for Breast Cancer. *N Engl J Med*. 2022;386(12):1143-1154.
15. Modi S, Jacot W, Yamashita T, et al. Trastuzumab Deruxtecan in previously treated HER2-low advanced breast cancer. *N Engl J Med*. 2022;387(1):9-20.
16. Shitara K, Bang YJ, Iwasa S, et al. Trastuzumab Deruxtecan in previously treated HER2-positive gastric cancer. *N Engl J Med*. 2020;382(25):2419-2430.
17. Van Cutsem E, di Bartolomeo M, Smyth E, et al. Primary analysis of a phase 2 single-arm trial of trastuzumab deruxtecan (T-DXd) in western patients with HER2-positive (HER2+) unresectable or metastatic gastric or gastroesophageal junction (GEJ) cancer who progressed on or after a trastuzumab containing regimen. Presented at: ESMO Congress; September 16–21, 2021.
18. Li BT, Smit EF, Goto Y, et al. Trastuzumab Deruxtecan in HER2-mutant non-small-cell lung cancer. *N Engl J Med*. 2022;386(3):241-251.
19. Siena S, Di Bartolomeo M, Raghav K, et al. Trastuzumab deruxtecan (DS-8201) in patients with HER2-expressing metastatic colorectal cancer (DESTINY-CRC01): a multicentre, open-label, phase 2 trial. *Lancet Oncol*. 2021;22(6):779-789.
20. Mehta HM, Malandra M, Corey SJ. G-CSF and GM-CSF in neutropenia. *J Immunol*. 2015;195(4):1341-1349.
21. Griffiths EA, Roy V, Alwan L, et al. NCCN clinical practice guidelines in oncology (NCCN guidelines): *Hematopoietic Growth Factors Version* 1. 2022: MGFA-MGFB.
22. Yokoyama A, Kondo K, Nakajima M, et al. Prognostic value of circulating KL-6 in idiopathic pulmonary fibrosis. *Respirology*. 2006;11(2):164-168.
23. Kohno N, Kyoizumi S, Awaya Y, Fukuhara H, Yamakido M, Akiyama M. New serum indicator of interstitial pneumonitis activity. Sialylated carbohydrate antigen KL-6. *Chest*. 1989;96(1):68-73.
24. Nakajima H, Harigai M, Hara M, et al. KL-6 as a novel serum marker for interstitial pneumonia associated with collagen diseases. *J Rheumatol*. 2000;27(5):1164-1170.
25. Powell CA MS, Iwata H, Takahashi S, Smit EF, Siena S. Pooled analysis of drug-related interstitial lung disease in 8 single-arm trastuzumab deruxtecan studies. Presented at: AACR Annual Meeting 2021; April 10–15, 2021; Virtual. [abstract CT167]. 2021.
26. Yin O, Iwata H, Lin CC, et al. Exposure-response relationships in patients with HER2-positive metastatic breast cancer and other solid tumors treated with Trastuzumab Deruxtecan. *Clin Pharmacol Ther*. 2021;110(4):986-996.
27. Servier Medical Art templates. Creative Commons Attribution 3.0 Unported License. Accessed March 1, 2021. https://smart.servier.com.
28. Kumagai K, Aida T, Tsuchiya Y, Kishino Y, Kai K, Mori K. Interstitial pneumonitis related to trastuzumab deruxtecan, a human epidermal growth factor receptor 2-targeting ab-drug conjugate, in monkeys. *Cancer Sci*. 2020;111(12):4636-4645.
29. Swain SM, Nishino M, Lancaster LH, et al. Multidisciplinary clinical guidance on trastuzumab deruxtecan (T-DXd)-related interstitial lung disease/pneumonitis-focus on proactive monitoring, diagnosis, and management. *Cancer Treat Rev*. 2022;106:102378.
30. Krop IE, Suter TM, Dang CT, et al. Feasibility and cardiac safety of trastuzumab emtansine after anthracycline-based chemotherapy as (neo)adjuvant therapy for human epidermal growth factor receptor 2-positive early-stage breast cancer. *J Clin Oncol*. 2015;33(10):1136-1142.
31. Procter M, Suter TM, de Azambuja E, et al. Longer-term assessment of trastuzumab-related cardiac adverse events in the Herceptin adjuvant (HERA) trial. *J Clin Oncol*. 2010;28(21):3422-3428.
32. Lenihan D, Suter T, Brammer M, Neate C, Ross G, Baselga J. Pooled analysis of cardiac safety in patients with cancer treated with pertuzumab. *Ann Oncol*. 2019;30(6):1021.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Guo Z, Ding Y, Wang M, Liu J, Zhai Q, Du Q. Safety of trastuzumab deruxtecan: A meta-analysis and pharmacovigilance study. *J Clin Pharm Ther*. 2022;47(11):1837-1844. doi:10.1111/jcpt.13777