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Original Article

Characterization of the safety profile of trastuzumab deruxtecan by dose: a pooled analysis across DESTINY studies

Yeon Hee Park*[,1], Javier Cortes[2,3,4,5,6], Shanu Modi[7], Sara A. Hurvitz[8], Giampaolo Bianchini[9], Hiroji Iwata[10], Kohei Shitara[11], Salvatore Siena[12], Yasushi Goto[11], Geoffrey Y. Ku[7], Charles A. Powell[13], Sandra M. Swain[14], Meena Arunachalam[15], Martin Janek[15], Yingkai Cheng[15], Changan Chu[15], Purnima Verma[15], Nataliya Kuptsova-Clarkson[16], Elton Mathias[15], Erin Goodman[15], Hope S. Rugo[17]

[1]Division of Hematology-Oncology, Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea
[2]Oncology Department, International Breast Cancer Center (IBCC), Pangaea Oncology, Quiron Group, Barcelona, Spain
[3]IOB Madrid, Institute of Oncology, Hospital Beata María Ana, Madrid, Spain
[4]Oncology Department, Hospital Universitario Torrejón, Ribera Group, Madrid, Spain
[5]Department of Medicine, Faculty of Biomedical and Health Sciences, Universidad Europea de Madrid, Madrid, Spain
[6]Medica Scientia Innovation Research (MEDSIR) - Oncoclínicas&Co, Jersey City, NJ, United States
[7]Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, NY, United States
[8]Division of Hematology and Oncology and Clinical Research Division, Department of Medicine, UW Medicine, Fred Hutchinson Cancer Center, Seattle, WA, United States
[9]Department of Medical Oncology, IRCCS Ospedale San Raffaele and Università Vita-Salute San Raffaele, Milan, Italy
[10]Breast Oncology Department, Aichi Cancer Center Hospital, Nagoya, Japan
[11]Department of Gastrointestinal Oncology, National Cancer Center Hospital East, Kashiwa, Japan
[12]Department of Oncology and Hemato-Oncology, Università degli Studi di Milano, Department of Hematology, Oncology, and Molecular Medicine, Niguarda Cancer Center, and Grande Ospedale Metropolitano Niguarda, Milan, Italy
[13]Division of Pulmonary, Critical Care and Sleep Medicine, Tisch Cancer Center, Icahn School of Medicine at Mount Sinai, New York, NY, United States
[14]Georgetown Lombardi Comprehensive Cancer Center, Georgetown University Medical Center and Genetic Medicine, MedStar Health, Washington DC, United States
[15]Daiichi Sankyo, Inc., Basking Ridge, NJ, United States
[16]Patient Safety, Oncology, AstraZeneca, Gaithersburg, MD, United States
[17]Department of Medicine, University of California San Francisco Helen Diller Family Comprehensive Cancer Center, San Francisco, CA, United States

*Corresponding author: Yeon Hee Park, MD, PhD, Division of Hematology-Oncology, Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, 81 Irwon-Ro Gangnam-gu, Seoul 06351, Republic of Korea (yhparkhmo@skku.edu).
Affiliation at the time of the analysis: Department of Medicine, University of California San Francisco Helen Diller Family Comprehensive Cancer Center, San Francisco, CA, United States; Patient Safety, Oncology, AstraZeneca, Gaithersburg, MD, United States

Abstract

Background: Trastuzumab deruxtecan (T-DXd), an approved human epidermal growth factor receptor 2 (HER2)-directed antibody–drug conjugate, may cause treatment-emergent adverse events (TEAEs), most commonly gastrointestinal and hematologic TEAEs. This pooled analysis evaluated TEAEs across 2 doses of T-DXd in patients with different cancers to support safe and effective real-world use.

Patients and Methods: Data were pooled from 9 phase I-III clinical trials (DS8201-A-J101; DESTINY-Breast01/02/03/04; DESTINY-Lung01/02; DESTINY-Gastric01/02) of T-DXd 5.4 or 6.4 mg/kg every 3 weeks in patients ($N = 1678$) with metastatic breast, gastric, or lung cancer with varying HER2 expression or *HER2* mutation status. Nausea, vomiting, neutropenia, fatigue, and interstitial lung disease (ILD) were evaluated for time to onset and dose-related outcomes. Antiemetic analysis was limited before a 2020 protocol change recommending prophylaxis.

Results: Common TEAEs (in ≥20%) were fatigue, nausea, vomiting, neutropenia, anemia, and thrombocytopenia; mostly grade 1 or 2. TEAEs leading to dose reduction, drug interruption, and discontinuation with T-DXd were 22.6%, 42.8%, and 17.7% (5.4 mg/kg), and 29.7%, 47.6%, and 16.6% (6.4 mg/kg), respectively. Neutropenia, nausea, and fatigue occurred in 34.6%, 74.6%, and 56.5% of patients (5.4 mg/kg) and 49.3%, 65.5%, and 52.8% (6.4 mg/kg). Adjudicated drug-related ILD occurred in 12.0% and 10.9%, respectively.

Conclusion: Gastrointestinal and hematologic TEAEs were most common, with nausea, neutropenia, and fatigue most commonly reported. ILD/pneumonitis occurred in ~11%-12% of patients, with severe cases infrequent. Most TEAEs were low grade, though dose modifications highlight the need for proactive TEAE management, particularly in older patients and those with renal impairment.

Key words: breast cancer; gastric cancer; lung cancer; safety; trastuzumab deruxtecan; T-DXd.

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Implications for Practice

This pooled safety analysis of trastuzumab deruxtecan (T-DXd) showed that the most common adverse events were gastrointestinal, hematologic, and fatigue-related but were generally low grade. Interstitial lung disease occurred in ~11%-12% of patients, with severe cases being infrequent. These findings highlight the importance of routine monitoring and early supportive care to minimize dose modifications and maintain treatment benefit. Proactive management is particularly critical in older patients and those with renal impairment, supporting safe, sustained use of T-DXd across diverse oncology populations.

Introduction

Trastuzumab deruxtecan (T-DXd) is a human epidermal growth factor receptor 2 (HER2)-directed antibody–drug conjugate (ADC) comprising a humanized monoclonal immunoglobulin G1 targeting HER2 and shares the same amino acid sequence as trastuzumab.[1,2] It features a cleavable tetrapeptide-based linker for enhanced plasma stability compared with other ADCs and a potent topoisomerase I inhibitor payload. T-DXd is engineered to achieve optimal antitumor effects by efficiently delivering and releasing the cytotoxic payload directly at the tumor site.[1–3]

T-DXd is approved for multiple indications, including HER2-positive (immunohistochemistry [IHC] 3+ or IHC 2+ and in situ hybridization [ISH]-positive), HER2-low (IHC 1+ or IHC 2+/ISH–), and HER2-ultralow (IHC 0 with membrane staining) metastatic breast cancer (mBC); *HER2 (ERBB2)*-mutant (*HER2*m) metastatic non–small cell lung cancer (mNSCLC); HER2-positive (IHC 3+ or IHC 2+/ISH-positive) metastatic gastric cancer (mGC); and HER2-positive (IHC 3+) solid tumors.[4] The recommended dosage for HER2-positive mBC, HER2-low mBC, non-GC HER2-positive (IHC 3+) solid tumors, and *HER2*m mNSCLC is 5.4 mg/kg, administered intravenously once every 3 weeks (Q3W). For HER2-positive mGC, the recommended dosage is 6.4 mg/kg, administered intravenously Q3W.[4] The higher 6.4 mg/kg dose in HER2-positive mGC is supported by pharmacokinetic, efficacy, and safety data showing adequate exposure and manageable adverse events (AEs).[5–7]

T-DXd has been evaluated in the DESTINY clinical trial program. Across the DESTINY trials, the most common treatment-emergent AEs (TEAEs) with T-DXd (5.4 or 6.4 mg/kg) are gastrointestinal (GI) and hematologic events.[7–15] Most TEAEs are low grade,[7–15] though some patients experience potentially severe events including interstitial lung disease (ILD)/pneumonitis and neutropenia (including febrile neutropenia).[4] GI, hematologic, and respiratory events often lead to T-DXd dose modifications or discontinuations, potentially affecting adherence.

To mitigate severe hematologic and respiratory TEAEs, clinical guidelines and postmarketing recommendations recommend delaying T-DXd in patients with suspected ILD/pneumonitis until diagnosis is confirmed.[16] If ILD/pneumonitis is confirmed as grade ≥2, treatment must be discontinued.[4,16] For grade ≥3 thrombocytopenia or neutropenia, treatment should also be delayed until resolution or improvement allows safe reinitiation.[4,16] Because T-DXd is effective and often administered long term, characterizing its safety profile can help manage TEAEs and optimize patient benefit.

We present a pooled analysis of safety data from 9 phase I-III clinical trials (DS8201-A-J101, NCT02564900; DESTINY-Breast01, NCT03248492; DESTINY-Breast02, NCT03523585; DESTINY-Breast03, NCT03529110; DESTINY-Breast04, NCT03734029; DESTINY-Lung01, NCT03505710; DESTINY-Lung02, NCT04644237; DESTINY-Gastric01, NCT03329690; DESTINY-Gastric02, NCT04014075) of T-DXd 5.4 mg/kg or 6.4 mg/kg in patients with HER2-positive or HER2-low mBC, *HER2*m or HER2-overexpressing mNSCLC, or HER2-positive mGC. Expanding on previous pooled studies, this analysis includes additional tumor types and doses to better characterize T-DXd safety. The findings presented here offer a high-level summary of T-DXd safety across approved doses and indications, supporting management in real-world practice.

Patients and methods

Patients and study design

Clinical trials with safety data for T-DXd 5.4 or 6.4 mg/kg were pooled to assess safety outcomes. Trials were selected based on approved dose (5.4 or 6.4 mg/kg) and indications (mBC, mNSCLC, or mGC) at the time of analysis (Figure S1).[4] Twenty patients with mGC from J101 (NCT02564900) who received T-DXd 5.4 mg/kg were included. Trials not included, such as DESTINY-Breast06 (NCT04494425), DESTINY-Breast12 (NCT04739761), and DESTINY-PanTumour02 (NCT04482309), and certain treatment arms were excluded due to ongoing recruitment or incomplete datasets at the time of analysis. Included trials were open label, randomized or nonrandomized, phase I-III studies; details are given in Table S1.

Safety investigations

AEs were coded using the Medical Dictionary for Regulatory Activities (MedDRA), version 25.0, and graded per National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), versions 4.0-5.0 (depending on each study protocol). Safety analyses included any-cause AEs, defined as any untoward medical occurrence temporally associated with T-DXd, regardless of causality. T-DXd–related AEs, particularly TEAEs, grade ≥3 TEAEs, and TEAEs leading to dose modifications or discontinuations were assessed. Serious AEs were defined per International Conference on Harmonisation Harmonized Tripartite Guidelines: Guideline E2A.[17] Adjudicated drug-related ILD was also assessed, with cases reviewed by a single independent committee overseeing adjudication across the DESTINY program. Time to onset and outcome were analyzed for selected TEAEs (nausea, vomiting, neutropenia, fatigue, and adjudicated drug-related ILD), chosen for their high frequency despite being mostly low grade. ILD/pneumonitis was included because it is a known safety concern in patients treated with T-DXd.

Management guidelines

Nausea and vomiting (N/V) were analyzed separately to assess GI toxicity differences between patients with mGC and those with other tumor types. From 2020, T-DXd trial protocols were amended to recommend prophylactic antiemetics per prescribing information and institutional guidelines. As antiemetic use was not prespecified or recommended before 2020, this analysis did not evaluate their effectiveness.

DESTINY protocols allowed dose delays for grade 3 or 4 hematologic events until resolution to grade ≤2, with subsequent treatment resumption at the same dose level (depending on the specific AE and grade). For grade 4 neutropenia and thrombocytopenia, dose reductions by one level were required. Granulocyte colony-stimulating factor (G-CSF) use was allowed for prophylaxis or treatment based on the clinical judgment of the investigator.[7–15]

ILD/pneumonitis management guidelines were implemented in March 2020. All subsequent ILD/pneumonitis cases were managed according to the amended protocol-defined guidelines. The latest ILD/pneumonitis management guidelines are provided in Table S2.[18]

Statistical analysis

Statistical analyses are detailed in the primary publications of each trial.[7–15] This analysis did not statistically compare the 2 dose groups, but instead it provides a descriptive summary of the safety results, acknowledging that the data were not intended for direct comparison.

Ethics

All included clinical trials were conducted per the Declaration of Helsinki and the International Council for Harmonisation Guidelines for Good Clinical Practice. Ethics approval was obtained for each study per local regulations. All patients provided written informed consent before enrollment. No additional informed consent was required for this pooled analysis, as patients had already consented in the original studies. Ethical considerations are detailed in the primary publications of each trial.[7–15]

Results

Baseline characteristics and patient demographics

A total of 1678 patients were included: 1287 with HER2-positive or HER2-low mBC, 249 with HER2-positive mGC, and 142 with *HER2*m or HER2-overexpressing mNSCLC (Figure S1). All patients received ≥1 dose of T-DXd. Patients with mBC and mNSCLC received T-DXd 5.4 mg/kg, while those with mGC received T-DXd 5.4 mg/kg ($n=20$) or T-DXd 6.4 mg/kg ($n=229$) (Figure S1; Table 1). All patients were treated in a second-line setting or later. The median duration of treatment in the 5.4-mg/kg pool was 9.6 months (range, 0.2-45.1 months) and in the 6.4-mg/kg pool was 4.6 months (range, 0.7-29.7 months). Total patient-years of exposure were 1493.9 years and 115.1 years, respectively.

Patients receiving T-DXd 5.4 mg/kg had a median age of 56.2 years (range, 22-96 years), while those receiving T-DXd 6.4 mg/kg had a median age of 65.0 years (range, 20-82 years). Most patients in the 5.4-mg/kg pool were female (94.7%), compared with 24.9% in the 6.4-mg/kg pool. The 5.4-mg/kg pool had 41.9% Asian patients and 39.6% patients living in Asia (in the 6.4-mg/kg pool: 67.2% and 65.5%, respectively). The Eastern Cooperative Oncology Group performance status (ECOG PS) distributions were as follows: T-DXd 5.4 mg/kg: 53.6% with ECOG PS 0, 46.2% with ECOG PS 1, and 0.1% with ECOG PS 2; T-DXd 6.4 mg/kg: 48.0% with ECOG PS 0; and 52.0% with ECOG PS 1.

At baseline, in the 5.4-mg/kg pool, 51.9% (752/1449) of patients had normal renal function (creatinine clearance [CrCl] ≥90 mL/min), 35.5% (514/1449) had mild renal impairment (CrCl ≥60 but <90 mL/min), 12.0% (174/1449) had moderate renal impairment (CrCl ≥30 but <60 mL/min), and 0.1% (2/1449) had severe renal impairment (CrCl ≥15 but <30 mL/min). In the 6.4-mg/kg pool, 29.7% (68/229) of patients had normal renal function, 39.7% (91/229) had mild renal impairment, and 24.5% (56/229) had moderate renal impairment. No patients in the 6.4-mg/kg pool had severe renal impairment. Per study protocols, patients with severe renal impairment were excluded.[7–15]

The median number of prior regimens was 4 (range, 1-27) in the 5.4-mg/kg pool and 2 (range, 1-9) in the 6.4-mg/kg pool. Some trials collected locally advanced and metastatic regimens together, while others collected these separately.

Incidence of the most common TEAEs

The most common TEAEs (≥20% of patients) in the 5.4-mg/kg pool ($n=1449$) were predominantly GI and hematologic (Figure 1A). Nausea was the most frequent TEAE (74.6%), while vomiting occurred in 41.6% of patients. Neutropenia was the most frequent hematologic TEAE (34.6%). Fatigue was reported in 56.5% of patients.

In the 6.4-mg/kg pool ($n=229$), GI and hematologic events were the most common (Figure 1B). Nausea and vomiting were reported in 65.5% and 32.3% of patients, respectively, with decreased appetite reported in 54.1%. Neutropenia and anemia were the most frequent hematologic TEAEs, each affecting 49.3% of patients, while fatigue occurred in 52.8%.

Most drug-related TEAEs were grade 1 or 2 in both dose pools (Figure 2). Grade ≥3 drug-related TEAEs were mainly hematologic for both doses: neutropenia (16.0% and 35.4%) and anemia (7.8% and 19.7%). In the 5.4-mg/kg pool, grade ≥3 TEAEs were reported in 51.0% of patients aged <65 years (560/1099) and 62.0% of patients aged ≥65 years (217/350). In the 6.4-mg/kg pool, grade ≥3 TEAEs were experienced by 78.0% of patients aged <65 years (85/109) and 68.3% of patients aged ≥65 years (82/120) (Table S3).

Dose modifications due to TEAEs

For most TEAEs, T-DXd dose modifications (reductions, interruptions, or discontinuations) occurred in <10% of patients (Table S4). In the 5.4-mg/kg pool, fatigue (4.8%) and nausea (4.8%) were the most common causes of dose reduction. In the 6.4-mg/kg pool, fatigue (5.7%) and nausea (6.6%) were the most prevalent. Prophylactic or rescue antiemetics use was not reflected in these modifications. Dose reductions related to decreased appetite and neutropenia occurred in 1.1% and 3.2% of patients in the 5.4-mg/kg pool, and in 8.3% and 9.2% of patients in the 6.4-mg/kg pool. Hematologic TEAEs led to dose interruptions in 13.0%, 4.6%, 3.7%, and 3.0% of patients for neutropenia, anemia, leukopenia, and thrombocytopenia, respectively, in the 5.4-mg/kg pool, and in 17.9%, 8.3%, 5.2%, and 2.6%, respectively, in the 6.4-mg/kg pool.

Table 1. Patient demographics and baseline characteristics.

	T-DXd 5.4-mg/kg Pool *n* = 1449	T-DXd 6.4-mg/kg Pool *n* = 229
Age, median (range), years	56.2 (22-96)	65.0 (20-82)
≥65 years, *n* (%)	350 (24.2)	120 (52.4)
Female, *n* (%)	1372 (94.7)	57 (24.9)
Region, *n* (%)		
Asia	574 (39.6)	150 (65.5)
Europe	483 (33.3)	34 (14.8)
North America	236 (16.3)	45 (19.7)
Rest of world	156 (10.8)	0
Race, *n* (%)		
White	692 (47.8)	69 (30.1)
Asian	607 (41.9)	154 (67.2)
Black or African American	36 (2.5)	1 (0.4)
American Indian or Alaska Native	5 (0.3)	0
Native Hawaiian or Other Pacific Islander	2 (0.1)	1 (0.4)
Multiple	2 (0.1)	NE
Other	101 (7.0)	3 (1.3)
Missing	4 (0.3)	1 (0.4)
BMI, median, kg/m^2	23.7	22.0
Min, max	14.1, 48.8	13.9, 36.4
ECOG PS, *n* (%)		
0	777 (53.6)	110 (48.0)
1	670 (46.2)	119 (52.0)
2	2 (0.1)	0
Primary tumor type, *n* (%)		
Breast cancer	1287 (88.8)	0
Lung cancer	142 (9.8)	0
Gastric cancer	20 (1.4)	229 (100)
Renal function,[a] *n* (%)		
Normal function	752 (51.9)	68 (29.7)
Mild impairment	514 (35.5)	91 (39.7)
Moderate impairment	174 (12.0)	56 (24.5)
Severe impairment	2 (0.1)	0
Missing[b]	7 (0.5)	14 (6.1)
Number of prior regimens,[c] *n* (%)		
1	105 (7.2)	77 (33.6)
2	250 (17.3)	67 (29.3)
3	291 (20.1)	40 (17.5)
4	272 (18.8)	27 (11.8)
≥5	531 (36.6)	18 (7.9)
Median (range)	4 (1-27)	2.0 (1-9)

Percentages calculated using the number of patients in the safety analysis set as the denominator.
Abbreviations: BMI, body mass index; CrCl, creatinine clearance; ECOG PS, Eastern Cooperative Oncology Group performance status; eCRF, electronic case report form; NE, not evaluable; T-DXd, trastuzumab deruxtecan.
[a]Renal function: normal = CrCl ≥90 mL/min, mild impairment = CrCl ≥60 to <90 mL/min, moderate impairment = CrCl ≥30 to <60 mL/min, severe impairment = CrCl ≥15 to <30 mL/min.
[b]The creatinine values were available in the eCRF for all patients. However, the CrCl values were "missing" in the eCRF. The creatinine value, weight, age, and sex were available to derive CrCl using the Cockcroft-Gault equation. These 14 patients met the renal impairment inclusion criterion at baseline based on the creatinine value using the Cockcroft-Gault equation.
[c]Study J101, DESTINY-Gastric01, DESTINY-Breast01, and DESTINY-Lung01 collected locally advanced and metastatic prior regimen intent as a combined parameter, whereas DESTINY-Gastric02, DESTINY-Lung02, and DESTINY-Breast02/03/04 collected locally advanced and metastatic regimen intent separately.

Fatigue caused dose interruptions in 4.8% and 4.4% of patients in the 5.4-mg/kg and 6.4-mg/kg pools, respectively. Dose discontinuations due to TEAEs were <1% in both pools, except for ILD/pneumonitis, which is discussed below.

Selected TEAEs

Nausea and vomiting

Grade 1 and 2 nausea occurred in 41.2% and 27.6% of patients in the 5.4-mg/kg pool and 38.0% and 21.4% in the 6.4-mg/kg pool (Table S5). Grade 3 and serious cases of nausea were infrequent among patients receiving T-DXd 5.4 mg/kg (5.8% and 1.1%, respectively) and T-DXd 6.4 mg/kg (6.1% and 2.2%, respectively). By the data cutoff, more patients had recovered or were recovering from nausea (74.6% and 60.0%, respectively) than patients who had not recovered or achieved resolution (25.0% and 37.3%, respectively). Median time to and duration of the first onset of nausea were 3 days (range, –30 to 911 days) and 19 days (range, 15-22 days) in the 5.4-mg/kg pool and 4 days (range, 1-177 days) and 11 days (range, 1-194 days) in the 6.4-mg/kg pool.

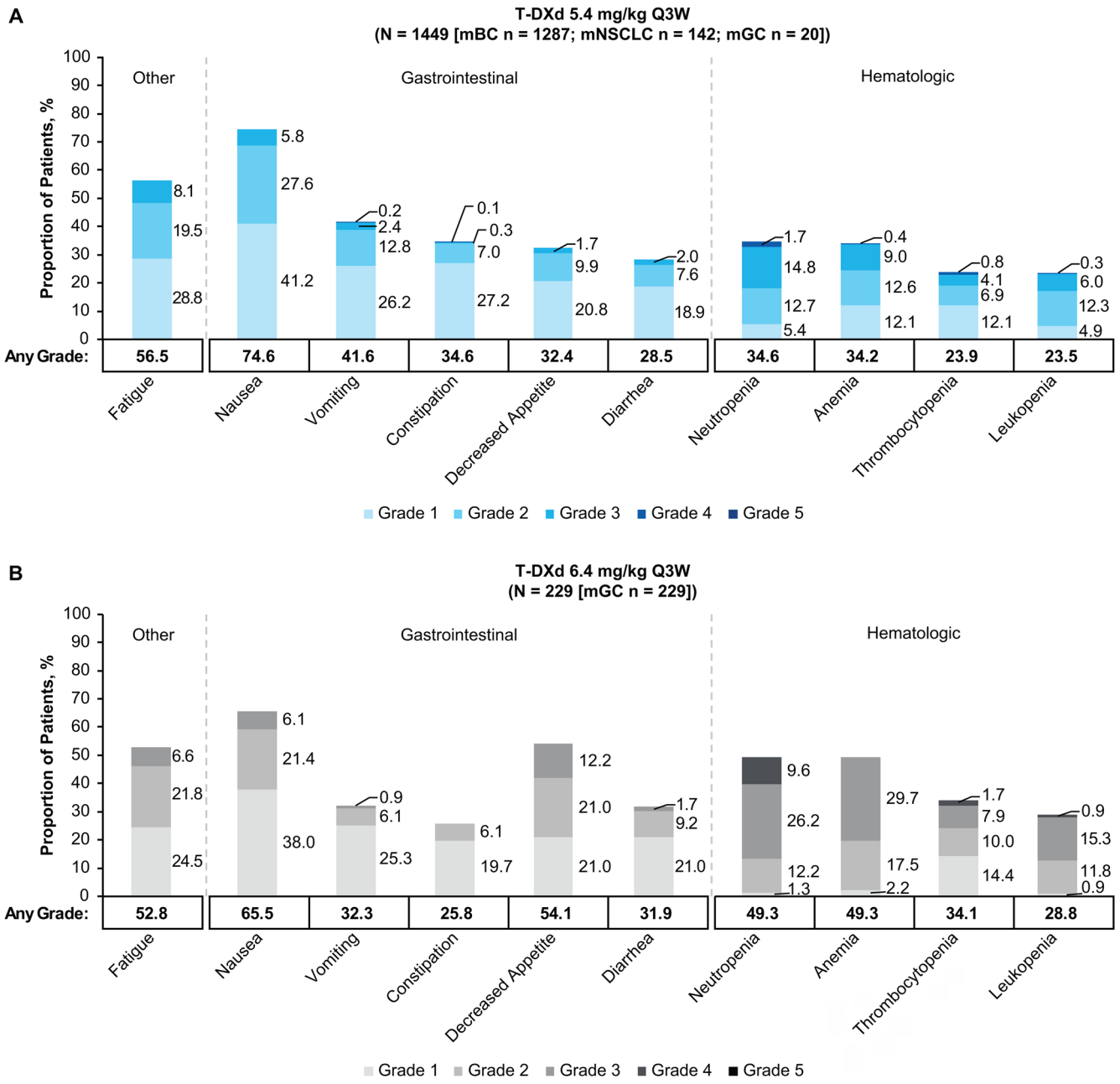

Figure 1. Most common TEAEs (in ≥20% of patients) reported in the pooled analysis with (A) T-DXd 5.4 mg/kg and (B) T-DXd 6.4 mg/kg. Percentages were calculated using the number of patients in the safety analysis set as the denominator. TEAEs are arranged by the type of events (GI, hematologic, and other [non-GI/nonhematologic]). Selected TEAE terms include abdominal pain (included PTs: abdominal discomfort, abdominal pain, abdominal pain lower, abdominal pain upper, and gastrointestinal pain), anemia (included PTs: hemoglobin decreased, red blood cell count decreased, anemia, and hematocrit decreased), constipation, decreased appetite, diarrhea, fatigue (included PTs: fatigue, asthenia, and malaise), febrile neutropenia, headache (included PTs: migraine, headache, and sinus headache), leukopenia (included PTs: white blood cell count decreased and leukopenia), lymphopenia (included PTs: lymphocyte count decreased and lymphopenia), nausea, neutropenia (included PTs: neutrophil count decreased and neutropenia), rash (included PTs: rash, rash pustular, and rash maculo-papular), stomatitis (included PTs: stomatitis, aphthous ulcer, mouth ulceration, oral mucosa erosion, and oral mucosal blistering), thrombocytopenia (included PTs: platelet count decreased and thrombocytopenia), upper respiratory tract infection (included PTs: influenza, influenza-like illness, and upper respiratory tract infection), and vomiting. GI, gastrointestinal; mBC, metastatic breast cancer; mGC, metastatic gastric cancer; mNSCLC, metastatic non-small cell lung cancer; PT, preferred term; Q3W, every 3 weeks; T-DXd, trastuzumab deruxtecan; TEAE, treatment-emergent adverse event.

Vomiting was reported in 41.6% of patients receiving the 5.4-mg/kg dose and 32.3% of those receiving the 6.4-mg/kg dose (Table S6). Most vomiting events were of low severity, with grade 1 and 2 occurring in 26.2% and 12.8% of the 5.4-mg/kg pool and 25.3% and 6.1% of the 6.4-mg/kg pool, respectively. Grade ≥3 and serious cases of vomiting were infrequent among patients in the 5.4-mg/kg pool (2.6%; 1.4%) and the 6.4-mg/kg pool (0.9%; 1.7%). In both the 5.4-mg/kg and 6.4-mg/kg pools, there were more patients who recovered or were recovering from vomiting (90.6% and 83.8%, respectively) than patients who had not recovered or achieved resolution (9.3% and 16.2%, respectively) by data cutoff. The

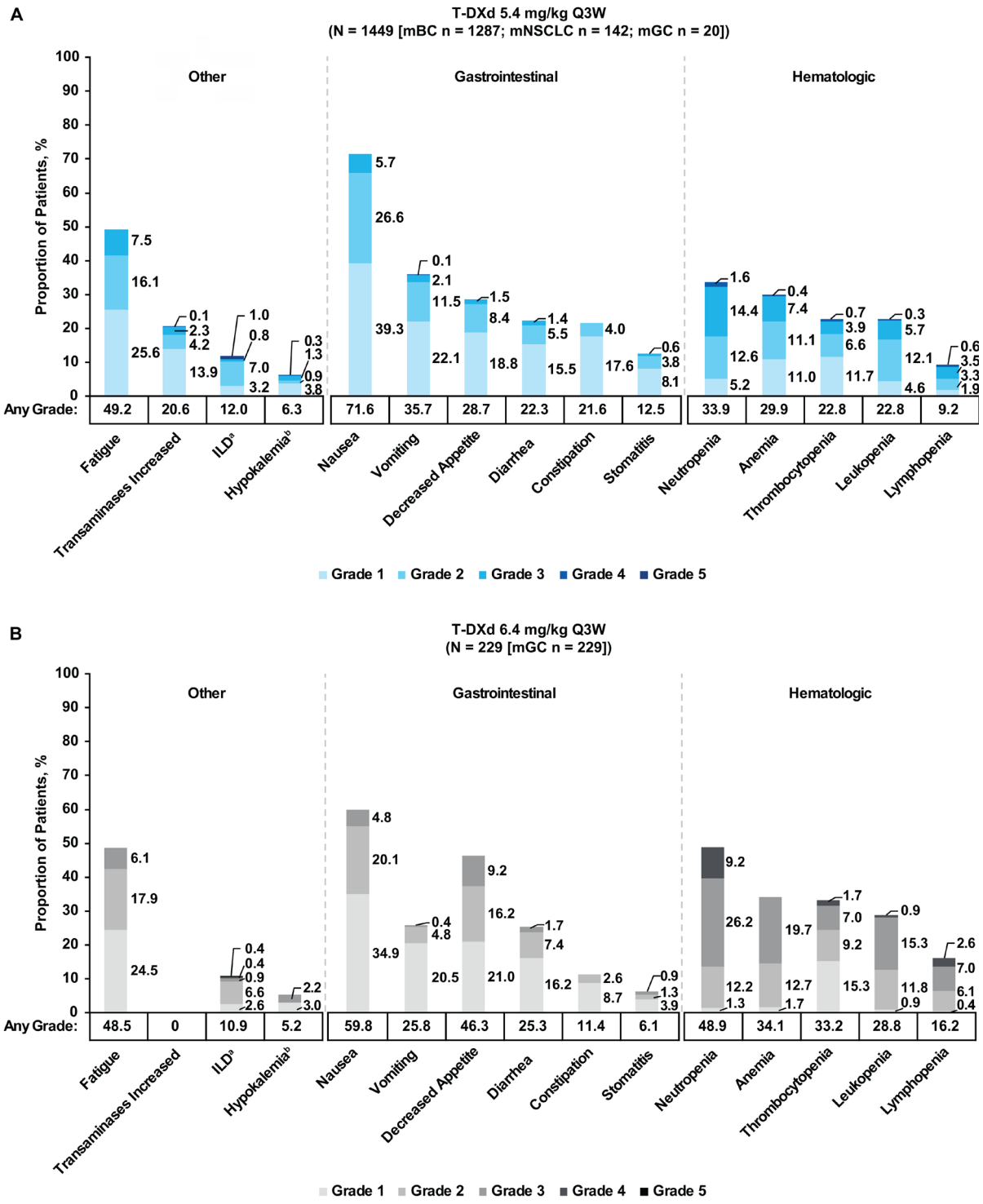

Figure 2. Drug-related TEAEs reported in the pooled analysis with (A) T-DXd 5.4 mg/kg and (B) T-DXd 6.4 mg/kg. Percentages were calculated using the number of patients in the safety analysis set as the denominator. TEAEs are arranged by the type of events (GI, hematologic, and other [non-GI/nonhematologic]). Selected TEAE terms include: abdominal pain (included PTs: abdominal discomfort, abdominal pain, abdominal pain lower, abdominal pain upper, and gastrointestinal pain), anemia (included PTs: hemoglobin decreased, red blood cell count decreased, anemia, and hematocrit decreased), constipation, decreased appetite, diarrhea, fatigue (included PTs: fatigue, asthenia, and malaise), febrile neutropenia, headache (included PTs: migraine, headache, and sinus headache), leukopenia (included PTs: white blood cell count decreased and leukopenia), lymphopenia (included PTs: lymphocyte count decreased and lymphopenia), nausea, neutropenia (included PTs: neutrophil count decreased and neutropenia), rash (included PTs: rash, rash pustular, and rash maculo-papular), stomatitis (included PTs: stomatitis, aphthous ulcer, mouth ulceration, oral mucosa erosion, and oral mucosal blistering), thrombocytopenia (included PTs: platelet count decreased and thrombocytopenia), upper respiratory tract infection (included PTs: influenza, influenza like illness, and upper respiratory tract infection), and vomiting. [a]ILD events are adjudicated drug-related ILD events. [b]Hypokalemia is divided into grade 1 or 2 and grade ≥3. GI, gastrointestinal; ILD, interstitial lung disease; mBC, metastatic breast cancer; mGC, metastatic gastric cancer; mNSCLC, metastatic non–small cell lung cancer; PT, preferred term; Q3W, every 3 weeks; T-DXd, trastuzumab deruxtecan; TEAE, treatment-emergent adverse event.

Table 2. Adjudicated drug-related ILD.

	T-DXd 5.4-mg/kg Pool $n=1449$	T-DXd 6.4-mg/kg Pool $n=229$
Adjudicated as drug-related ILD, *n* (%)	174 (12.0)	25 (10.9)
Grade 1	46 (3.2)	6 (2.6)
Grade 2	102 (7.0)	15 (6.6)
Grade 3	12 (0.8)	2 (0.9)
Grade 4	0	1 (0.4)
Grade 5	14 (1.0)	1 (0.4)
ILD associated with discontinuation of study drug, *n* (%)	127 (8.8)	15 (6.6)
ILD associated with dose reduction, *n* (%)	12 (0.8)	1 (0.4)
ILD associated with study drug interruption, *n* (%)	35 (2.4)	8 (3.5)
ILD associated with outcome of death, *n* (%)	14 (1.0)	1 (0.4)

Abbreviations: ILD, interstitial lung disease; T-DXd, trastuzumab deruxtecan.

median time to and duration of the first onset of vomiting were 9 days (range, 1-820 days) and 3 days (range, 1-863 days) for the 5.4-mg/kg pool and 7 days (range, 1-291 days) and 2 days (range, 1-279 days) for the 6.4-mg/kg pool. Most patients who experienced N/V did so during the initial 21 days, with rates decreasing in subsequent cycles (Figure S2).

Neutropenia

Neutropenia occurred in 34.6% of patients in the 5.4-mg/kg pool and 49.3% of patients in the 6.4-mg/kg pool (Table S7). Rates of grade 3 and 4 neutropenia were 14.8% and 1.7% in the 5.4-mg/kg pool and 26.2% and 9.6% in the 6.4-mg/kg pool, respectively. By data cutoff, 78.4% and 85.8% of patients in the 5.4-mg/kg and 6.4-mg/kg pools recovered, respectively. The median time to first onset of neutropenia was 43 days (range, 1-972 days) in the 5.4-mg/kg pool and 16.0 days (range, 6-756 days) in the 6.4-mg/kg pool. In the 5.4-mg/kg pool, 100 patients (6.9%) were treated with G-CSF within 28 days after onset of neutropenia (including febrile neutropenia). In the 6.4-mg/kg pool, 35 patients (15.3%) were treated with G-CSF.

Fatigue

Fatigue was common, reported in 56.5% and 52.8% of patients in the 5.4-mg/kg and 6.4-mg/kg pools, respectively (Table S8). At data cutoff, unresolved fatigue occurred in 44.9% and 53.7% of patients in the 5.4-mg/kg and 6.4-mg/kg pools, with a median time to first onset of 12.0 days (range, –19 to 1078 days) and 7.0 days (range, 1-294 days) in the 5.4-mg/kg and 6.4-mg/kg pools, respectively. Median duration of the first onset of fatigue was 16 days (range, 1-960 days) and 12 days (range, 3-367 days) in the 5.4-mg/kg and 6.4-mg/kg pools, respectively. Duration of first event is provided in Table S9 for all selected TEAEs.

TEAE of special interest: ILD

Adjudicated drug-related ILD occurred in 12.0% and 10.9% of patients in the 5.4-mg/kg and 6.4-mg/kg pools, respectively (Table 2). Most ILD cases were grade 1 or 2, with grade 2 more common (7.0% and 6.6%, respectively). Grade ≥3 ILD occurred in 1.8% and 1.7% of the 5.4-mg/kg and 6.4-mg/kg pools, respectively. Adjudicated ILD-related mortality occurred in 1.0% ($n=14$) of patients in the 5.4-mg/kg pool and 0.4% ($n=1$) in the 6.4-mg/kg pool. The median time to first onset of adjudicated drug-related ILD was 168.0 days (range, 26-960 days) and 85.0 days (range, 36-638 days) in the respective dose pools. In the 5.4-mg/kg and 6.4-mg/kg pools, respectively, the median time to first onset of investigator-reported ILD was 215.0 days (range, 26-1163 days) and 85.0 days (range, 36-680 days).

Drug discontinuations due to ILD occurred in 8.8% and 6.6% of patients in the 5.4-mg/kg and 6.4-mg/kg pools, respectively, attributed to grade 1 (2.1%; 1.3%), grade 2 (5.6%; 4.4%), and grade ≥3 (1.1%; 0.9%) events. Patients with symptomatic ILD (grade ≥2) were required to discontinue T-DXd permanently. Dose reductions due to ILD occurred in 0.8% and 0.4% of patients, and drug interruptions in 2.4% and 3.5% of patients in the 5.4-mg/kg and 6.4-mg/kg pools, respectively. ILD subgroup analyses are detailed in Table S10.

Discussion

In this pooled analysis, the most common TEAEs with T-DXd included fatigue, GI toxicities (especially N/V), hematologic toxicities (neutropenia, anemia, and thrombocytopenia), and ILD/pneumonitis. Most TEAEs were low grade, with infrequent dose modifications or drug discontinuations, consistent with previous analyses.[19–26] Unlike prior analyses, this analysis represents the largest dataset to date assessing T-DXd safety, with patients across multiple tumor types and key age groups, thereby providing a more comprehensive evaluation of the safety profile of the treatment in a broad population and confirming the consistency of findings across studies. Unlike GI toxicities, hematologic AEs, such as neutropenia, were less frequent in the 5.4-mg/kg pool relative to the 6.4-mg/kg pool, but comparisons between the 2 dose pools in this analysis should be interpreted with caution due to their population size difference, differences in patient characteristics, primary cancer types, and imbalance of sex distribution.

A previous pooled analysis and other studies, such as this one, showed higher risk of ILD/pneumonitis in Japan compared with regions outside Japan.[16,27–30] The cause of this disparity remains unclear, potentially involving biological factors or differences in monitoring and management practices.[16] Other potential factors with a higher risk of ILD/pneumonitis may include renal impairment, comorbid lung conditions, and baseline oxygen saturation <95%.[16]

Patients receiving T-DXd 5.4 mg/kg were younger than those receiving T-DXd 6.4 mg/kg, likely due to the higher proportion of patients with mBC in the 5.4-mg/kg pool, who usually have a lower median age compared with patients with mGC.[31,32] The lack of mBC or mNSCLC in the 6.4-mg/kg pool may further confound toxicity interpretation. Vomiting was more frequent in the 5.4-mg/kg pool, composed mainly of women (94.7%), consistent with reports of higher rates of N/V in women.[25] However, N/V may be less pronounced in patients with mGC, possibly due to underlying disease pathology presenting with symptoms, such as nausea, vomiting, decreased appetite, and abdominal discomfort.[33] This overlap complicates distinguishing mGC symptoms from T-DXd–related TEAEs, challenging direct dose-based toxicity comparisons.

Patients ≥65 years had a higher incidence of grade 3 or 4 AEs compared with patients <65 years with HER2-positive or

HER2-low mBC, though no significant safety differences were observed in patients with *HER2*m NSCLC or mGC.[4] This was reflected in the current analysis, where patients aged ≥65 years had a higher incidence of grade 3 or 4 AEs in the 5.4-mg/kg pool (mainly HER2-positive or HER2-low mBC) compared with those <65 years. In the 6.4-mg/kg pool (primarily patients with mGC), both age groups had a similar incidence of grade ≥3 TEAEs (85/109 [78.0%] and 82/120 [68.3%], respectively). Patients with moderate renal impairment had a higher incidence of low-grade ILD/pneumonitis, warranting closer monitoring per real-world reports.[4] While no dose adjustments are required for mild-to-moderate hepatic impairment, data on safety and pharmacokinetics in severe hepatic impairment are lacking.[4]

Fam-trastuzumab deruxtecan-nxki (T-DXd) was initially classified as moderately emetogenic, but the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Antiemesis V.2.2024 recently reclassified it as highly emetogenic.[4,34] This update reflects evolving clinical recognition of the emetic potential of fam-trastuzumab deruxtecan-nxki, supported by institutional retrospective data that show that many patients needed an NK1 receptor antagonist in addition to standard double therapy (ie, $5HT_3$RA plus dexamethasone) for adequate N/V control.[34–37] The American Society of Clinical Oncology (ASCO) antiemesis guidelines, last updated in 2020, still classify T-DXd as moderately emetogenic,[38] highlighting a discrepancy in guideline recommendations.[37,39]

Premedication with antiemetic agents is recommended to mitigate the emetogenic effects of fam-trastuzumab deruxtecan-nxki.[19,34,37,40] The antiemetic regimen may be tapered or escalated based on individual tolerances and emesis risk.[36] However, the optimal combination of antiemetics for prophylaxis and/or treatment in patients receiving T-DXd is still unclear.[37,40] Results from the EN-hance study (jRCTs031200336) did not meet the primary endpoint, supporting the need for further research to better characterize nausea and vomiting in patients treated with T-DXd to tailor an antiemetic regimen that suits the needs of the patient.[41] While not life-threatening, N/V are distressing toxic conditions that can significantly reduce quality of life.[37,40] Effective management remains critically important for treatment adherence and reducing discontinuations.[37,40] Results from the ERICA study (jRCTs031210410) suggest that triple antiemetic therapy, including first-cycle olanzapine, can reduce nausea duration and severity, particularly in delayed (24-120 hours after T-DXd) and persistent (120-504 hours after T-DXd) phases.[42] Furthermore, an exploratory phase 2 study conducted in Japan also supports that patients treated with T-DXd require triple antiemetic therapy, including NK1RA administration.[39] Other recent findings suggest that guideline-recommended triple antiemetic regimens used in the first cycle of T-DXd may reduce the need for dose reductions and improve persistence by maintaining dose intensity.[43,44] Given the potentially long-term nature of T-DXd therapy, optimizing prophylactic antiemetic strategies can support improved tolerability and treatment outcomes.[37,40] In this analysis, prophylactic antiemetic use was not prespecified or captured.

ILD/pneumonitis is an important risk with T-DXd, although most cases in this pooled analysis were low grade. Early recognition and timely intervention are critical to preventing progression.[19,20,25] However, risk factors for ILD/pneumonitis remain poorly understood, and it is unclear why some patients develop higher- versus lower-grade disease.[16] Close monitoring and patient/physician education are essential, and patients should be instructed to immediately report any new or worsening symptoms, such as cough, dyspnea, or other respiratory issues, which can overlap with other conditions including chronic obstructive pulmonary disease, tuberculosis, pneumonia, asthma, heart failure, and allergies.[19,20,45] Japanese post-marketing surveillance reported an incidence of adjudicated drug-related ILD of 16.06% in patients with HER2-positive BC treated with T-DXd (≤5.4 mg/kg), consistent with trials, indicating no new safety concerns despite higher ECOG PS and greater number of comorbidities.[46] Treatment duration of T-DXd significantly influences the risk of ILD/pneumonitis. Both a pooled analysis and the surveillance study reported that most cases of ILD/pneumonitis cases occurred within the first 12 months, with a median onset of ~5 months.[16,46] Here, patients receiving T-DXd 5.4 mg/kg had a longer median treatment duration (9.6 months) compared with 4.6 months for those receiving T-DXd 6.4 mg/kg, potentially influencing the assessment of ILD/pneumonitis.

A multidisciplinary team involving an oncologist, pulmonologist, radiologist, and infectious disease specialist is recommended for accurate ILD/pneumonitis diagnosis.[19] Guidelines recommend delaying treatment for grade 1 (asymptomatic) and permanently discontinuing T-DXd for grade ≥2 (symptomatic) ILD/pneumonitis.[11,16] The approved T-DXd label includes warnings and detailed management guidelines for ILD/pneumonitis.[4,16]

Patient-reported outcomes and quality-of-life data (QoL) were not consistently collected across all studies included in this pooled analysis. Despite this, results from individual studies indicate that health-related QoL was generally maintained during treatment with T-DXd. In DESTINY-Breast02, -03, and -04, mean baseline European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30) global health status/QoL scores were comparable between treatment arms and remained stable over time, with only transient early-cycle increases in N/V scores.[47–49] Similar findings were observed in other tumor types, with maintained health-related QoL in DESTINY-Gastric02 and DESTINY-Lung02.[50,51] Overall, these data suggest that treatment with T-DXd was generally associated with preserved health-related QoL across studies.

This analysis has several limitations. Variability in clinical trial protocols for AE management, particularly the lack of standardized prophylactic antiemetic protocols for N/V,[7–15] limits the ability to evaluate the impact of preventative strategies on these events and overall patient experience. Data on the indication, regimen, and timing of antiemetic administration were not captured, precluding assessment of their effectiveness. The relatively short median follow-up, especially in the 6.4-mg/kg pool, may have influenced the assessment of TEAEs, including ILD, which develop over longer timelines. Pooling patients by dose rather than by indication limits the ability to assess safety profiles by tumor type or HER2 expression levels.

Clinical trials often report higher TEAEs rates than real-world studies.[52–56] TEAEs are often underestimated in real-world studies due to subjective symptom reporting and/or less comprehensive documentation compared with the rigorous causal assessments conducted in clinical trials.[52] This analysis provides a descriptive summary of safety outcomes for each dose cohort in clinical trial settings, although without statistical

comparisons. Pooling data across multiple indications and doses provides a broader understanding of the safety profile of T-DXd to support patient outcomes.

Conclusion

This pooled analysis of 9 phase I-III trials summarizes the safety profile of T-DXd at 5.4-mg/kg and 6.4-mg/kg doses. GI and hematologic events were the most common TEAEs, with nausea, neutropenia, and fatigue consistently observed. Most TEAEs were low grade, but dose modification rates highlight the need for proactive toxicity management, particularly in older patients (≥65 years) and those with renal impairment. ILD/pneumonitis remains a clinically significant safety concern, occurring in ~11%-12% of patients, though severe ILD and ILD-related mortality were infrequent. Further studies should define optimal antiemetic and supportive care strategies to enhance tolerability, maximize time on treatment, and improve quality of life for patients receiving T-DXd.

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Author contributions

Yeon Hee Park (Formal analysis, Investigation, Resources, Supervision, Validation, Writing—original draft, Writing—review & editing), Javier Cortes (Formal analysis, Investigation, Resources, Supervision, Validation, Writing—original draft, Writing—review & editing), Shanu Modi (Formal analysis, Investigation, Resources, Supervision, Validation, Writing—original draft, Writing—review & editing), Sara A. Hurvitz (Formal analysis, Investigation, Resources, Supervision, Validation, Writing—original draft, Writing—review & editing), Giampaolo Bianchini (Formal analysis, Investigation, Resources, Supervision, Validation, Writing—original draft, Writing—review & editing), Hiroji Iwata (Formal analysis, Investigation, Resources, Supervision, Validation, Writing—original draft, Writing—review & editing), Kohei Shitara (Formal analysis, Investigation, Resources, Supervision, Validation, Writing—original draft, Writing—review & editing), Salvatore Siena (Formal analysis, Investigation, Resources, Supervision, Validation, Writing—original draft, Writing—review & editing), Yasushi Goto (Formal analysis, Investigation, Resources, Supervision, Validation, Writing—original draft, Writing—review & editing), Geoffry Y. Ku (Formal analysis, Investigation, Resources, Supervision, Validation, Writing—original draft, Writing—review & editing), Charles A. Powell (Formal analysis, Investigation, Resources, Supervision, Validation, Writing—original draft, Writing—review & editing), Sandra M. Swain (Formal analysis, Investigation, Resources, Supervision, Validation, Writing—original draft, Writing—review & editing), Meena Arunachalam (Conceptualization, Formal analysis, Methodology, Resources, Supervision, Validation, Writing—original draft, Writing—review & editing), Martin Janek (Conceptualization, Formal analysis, Methodology, Resources, Supervision, Validation, Writing—original draft, Writing—review & editing), Yingkai Cheng (Conceptualization, Data curation, Formal analysis, Methodology, Resources, Supervision, Validation, Writing—original draft, Writing—review & editing), Changan Chu (Conceptualization, Formal analysis, Methodology, Resources, Supervision, Validation, Writing—original draft, Writing—review & editing), Purnima Verma (Conceptualization, Data curation, Formal analysis, Methodology, Resources, Supervision, Validation, Writing—original draft, Writing—review & editing), Nataliya Kuptsova-Clarkson (Conceptualization, Formal analysis, Methodology, Resources, Supervision, Validation, Writing—original draft, Writing—review & editing), Elton Mathias (Conceptualization, Formal analysis, Methodology, Resources, Supervision, Validation, Writing—original draft, Writing—review & editing), Erin Goodman (Data curation, Formal analysis, Methodology, Resources, Validation, Writing—original draft, Writing—review & editing), and Hope S. Rugo (Formal analysis, Investigation, Resources, Supervision, Validation, Writing—original draft, Writing—review & editing)

Supplementary material

Supplementary material is available at *The Oncologist* online.

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Conflicts of interest

YHP has received grants or contracts from MSD, AstraZeneca, Pfizer, Gencurix, Roche, Genome Insight, and Novartis; has received consulting fees from AstraZeneca, MSD, Pfizer, Eisai, Lilly, Roche, Gilead, Daiichi Sankyo, Menarini, Everest, and Novartis; has received payment or honoraria from AstraZeneca, MSD, Pfizer, Roche, Lilly, Daiichi Sankyo, Novartis, and Gilead; has received support for attending meetings and/or travel from Gilead, Pfizer, and AstraZeneca; has participated on a data safety monitoring board or advisory board for AstraZeneca, Menarini, Pfizer, Novartis, Roche, and Daiichi Sankyo; and has received equipment, materials, drugs, medical writing, gifts, or other services from Dong-A ST, Sanofi, Roche, and Pfizer. JC has received consulting fees from Roche, AstraZeneca, Seattle Genetics, Daiichi Sankyo, Lilly, MSD, Leuko, Bioasis, Clovis Oncology, Boehringer Ingelheim, Ellipses, HiberCell, BioInvent, GEMoaB, Gilead, Menarini, Zymeworks, Reveal Genomics, Scorpion Therapeutics, ExpreS2ion Biotechnologies, Jazz Pharmaceuticals, AbbVie, BridgeBio, BioNTech, Biocon, Circle Pharma; has received payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing, or educational events from Roche, Novartis, Eisai, Pfizer, Lilly, MSD, Daiichi Sankyo, AstraZeneca, Gilead,

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Data sharing statement

Anonymized individual participant data on completed studies and applicable supporting clinical study documents may be available upon request at https://vivli.org/. In cases where clinical study data and supporting documents are provided pursuant to our company policies and procedures, Daiichi Sankyo Companies will continue to protect the privacy of company and our clinical study subjects. Details on data sharing criteria and the procedure for requesting access can be found at this web address: https://vivli.org/ourmember/daiichi-sankyo/.

References

1. Nakada T, Sugihara K, Jikoh T, Abe Y, Agatsuma T. The latest research and development into the antibody-drug conjugate, [fam-] trastuzumab deruxtecan (DS-8201a), for HER2 cancer therapy. *Chem Pharm Bull (Tokyo)*. 2019;67:173-185.
2. 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;22:5097-5108.
3. Ogitani Y, Hagihara K, Oitate M, et al. Bystander killing effect of DS-8201a, a novel anti-human epidermal growth factor receptor 2 antibody-drug conjugate, in tumors with human epidermal growth factor receptor 2 heterogeneity. *Cancer Sci*. 2016;107:1039-1046.
4. Daiichi Sankyo, Inc. ENHERTU® (fam-trastuzumab deruxtecan-nxki) for injection, for intravenous use. Published January 2025. Accessed February 2025. https://daiichisankyo.us/prescribing-information-portlet/getPIContent? productName=Enhertu&inline=true
5. Yoshihara K, Kobayashi Y, Endo S, et al. Trastuzumab deruxtecan dosing in human epidermal growth factor receptor 2-positive gastric cancer: population pharmacokinetic modeling and exposure-response analysis. *J Clin Pharmacol*. 2023;63:1232-1243.
6. 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;20:827-836.
7. Shitara K, Bang YJ, Iwasa S, et al. DESTINY-Gastric01 Investigators. Trastuzumab deruxtecan in previously treated HER2-positive gastric cancer. *N Engl J Med*. 2020;382:2419-2430.
8. André F, Hee Park Y, Kim S-B, et al. Trastuzumab deruxtecan versus treatment of physician's choice in patients with HER2-positive metastatic breast cancer (DESTINY-Breast02): a randomised, open-label, multicentre, phase 3 trial. *Lancet*. 2023;401:1773-1785.
9. Cortés J, Kim SB, Chung WP, et al. DESTINY-Breast03 Trial Investigators. Trastuzumab deruxtecan versus trastuzumab emtansine for breast cancer. *N Engl J Med*. 2022;386:1143-1154.
10. Goto K, Goto Y, Kubo T, 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. *J Clin Oncol*. 2023;41:4852-4863.
11. Li BT, Smit EF, Goto Y, et al. DESTINY-Lung01 Trial Investigators. Trastuzumab deruxtecan in HER2-mutant non–small-cell lung cancer. *N Engl J Med*. 2022;386:241-251.
12. Modi S, Jacot W, Yamashita T, et al. DESTINY-Breast04 Trial Investigators. Trastuzumab deruxtecan in previously treated HER2-low advanced breast cancer. *N Engl J Med*. 2022;387:9-20.
13. Modi S, Saura C, Yamashita T, et al. DESTINY-Breast01 Investigators. Trastuzumab deruxtecan in previously treated HER2-positive breast cancer. *N Engl J Med*. 2020;382:610-621.
14. 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;20:816-826.
15. Van Cutsem E, di Bartolomeo M, Smyth E, et al. Trastuzumab deruxtecan in patients in the USA and Europe with HER2-positive advanced gastric or gastroesophageal junction cancer with disease progression on or after a trastuzumab-containing regimen (DESTINY-Gastric02): primary and updated analyses from a single-arm, phase 2 study. *Lancet Oncol*. 2023;24:744-756.
16. Powell CA, Modi S, Iwata H, et al. Pooled analysis of drug-related interstitial lung disease and/or pneumonitis in nine trastuzumab deruxtecan monotherapy studies. *ESMO Open*. 2022;7:100554.
17. International Conference for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use. Clinical Safety Data Management: Definitions and Standards for Expedited Reporting E2A. Published October 1994. Accessed February 2025. https://www.ich.org/page/efficacy-guidelines
18. Rugo HS, Tokunaga E, Iwata H, et al. Pooled analysis of trastuzumab deruxtecan retreatment after recovery from grade 1 interstitial lung disease/pneumonitis. *Ann Oncol*. 2025;36(11):1389–1399
19. Chiu JWY, Lee SC, Ho JC, 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 Saf*. 2023;46:927-949.
20. Ciruelos E, García-Sáenz J, Gavilá J, Martín M, Rodríguez CA, Rodríguez-Lescure Á. Safety profile of trastuzumab deruxtecan in advanced breast cancer: expert opinion on adverse event management. *Clin Transl Oncol*. 2024;26:1539-1548.
21. Dowling GP, Daly GR, Keelan S, et al. Efficacy and safety of trastuzumab deruxtecan in breast cancer: a systematic review and meta-analysis. *Clin Breast Cancer*. 2023;23:847-855.e2. e842.
22. 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;47:1837-1844.
23. Kou L, Chen X, Xie X, Wen Q, Li J, Li Y. The efficacy and safety of trastuzumab deruxtecan (T-DXd) in HER2-expressing solid tumours: a single-arm meta-analysis. *Jpn J Clin Oncol*. 2023;53:722-729.
24. Ma R, Shi Y, Yan R, Yin S, Bu H, Huang J. Efficacy and safety of trastuzumab deruxtecan in treating human epidermal growth factor receptor 2-low/positive advanced breast cancer: a meta-analysis of randomized controlled trials. *Crit Rev Oncol Hematol*. 2024;196:104305.
25. Nonomiya Y, Nakayama I, Kobayashi K, et al. Analysis of adverse events associated with trastuzumab deruxtecan in patients with gastric and breast cancer: a retrospective study. *Biol Pharm Bull*. 2024;47:411-416.
26. Xu H, Zhang H, Guo W, et al. Safety and efficacy profile of trastuzumab deruxtecan in solid cancer: pooled reanalysis based on clinical trials. *BMC Cancer*. 2022;22:923.
27. Conte P, Ascierto PA, Patelli G, et al. Drug-induced interstitial lung disease during cancer therapies: expert opinion on diagnosis and treatment. *ESMO Open*. 2022;7:100404.
28. Iwasa E, Fujiyoshi Y, Kubota Y, et al. Interstitial lung disease as an adverse drug reaction in Japan: exploration of regulatory actions as a basis for high reporting. *Drug Saf*. 2020;43:1121-1131.
29. Kubo K, Azuma A, Kanazawa M, et al. Japanese Respiratory Society Committee for Formulation of Consensus Statement for the Diagnosis and Treatment of Drug-Induced Lung Injuries. Consensus

statement for the diagnosis and treatment of drug-induced lung injuries. *Respir Investig*. 2013;51:260-277.
30. Skeoch S, Weatherley N, Swift AJ, et al. Drug-induced interstitial lung disease: a systematic review. *J Clin Med*. 2018;7:356.
31. SEER Cancer Stat Facts: Female Breast Cancer. National Cancer Institute. Bethesda, MD. Accessed 2024. https://seer.cancer.gov/statfacts/html/breast.html.
32. SEER Cancer Stat Facts: Stomach Cancer. National Cancer Institute. Bethesda, MD. Accessed 2024. https://seer.cancer.gov/statfacts/html/stomach.html.
33. Mithany RH, Shahid MH, Manasseh M, et al. Gastric cancer: a comprehensive literature review. *Cureus*. 2024;16:e55902.
34. Berger MJ, et al. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) Antiemesis. Version 2.2024. © 2024. National Comprehensive Cancer Network, Inc. Available at NCCN.org. Accessed November 26, 2024.
35. Stankowicz M, Mauro L, Harnden K, Pennisi A. Management of chemotherapy-induced nausea and vomiting with trastuzumab deruxtecan: a case series. *Breast Care (Basel)*. 2021;16:408-411.
36. Rugo HS, Bianchini G, Cortes J, Henning JW, Untch M. Optimizing treatment management of trastuzumab deruxtecan in clinical practice of breast cancer. *ESMO Open*. 2022;7:100553.
37. Bianchini G, Arpino G, Biganzoli L, et al. Emetogenicity of antibody-drug conjugates (ADCs) in solid tumors with a focus on trastuzumab deruxtecan: insights from an Italian expert panel. *Cancers (Basel)*. 2022;14:1022.
38. Hesketh PJ, Kris MG, Basch E, et al. Antiemetics: ASCO guideline update. *J Clin Oncol*. 2020;38:2782-2797.
39. Iihara H, Shimokawa M, Bando H, et al. Doublet or triplet antiemetic prophylaxis for nausea and vomiting induced by trastuzumab deruxtecan: an open-label, randomized, and multicenter exploratory phase 2 study. *J Cancer*. 2023;14:2644-2654.
40. Notini G, Naldini MM, Sica L, et al. Management of trastuzumab deruxtecan-related nausea and vomiting in real-world practice. *Front Oncol*. 2024;14:1374547.
41. Aoyama T, Ooki A, Oba K, et al. A multicenter randomized open-label phase 2 study investigating optimal antiemetic therapy for patients with advanced/recurrent gastric cancer treated with trastuzumab deruxtecan: the EN-hance study. *Int J Clin Oncol*. 2025;30:1162-1173.
42. Sakai H, Tsurutani J, Ozaki , YII, et al. A randomized, double-blind, placebo-controlled phase. Study of olanzapine based prophylactic antiemetic therapy for delayed and persistent nausea and vomiting in patients with HER2-positive or HER2-low breast cancer treated with trastuzumab deruxtecan: ERICA study (WJOG14320B). *Ann Oncol*. 2025;36:31-42.
43. Rosenfeld S, Gorantla V, Choksi R, et al. Trends in antiemetic use in patients receiving fam-trastuzumab Deruxtecan-nxki for metastatic breast cancer: a retrospective analysis of data from the IntegraConnect PrecisionQ de-identified database. Presented at San Antonio Breast Cancer Symposium 2024; December 10-13, 2024; San Antonio, TX. Abstract P2-12-15.
44. Shin S, Kim JY, Ahn JS, et al. Impact of antiemetic prophylaxis on maintaining dose intensity of trastuzumab deruxtecan in HER2-positive advanced breast cancer. Presented at San Antonio Breast. Abstract. *Cancer Symposium*. 2025;31:P4-05-08 December 10-13, 2024; San Antonio, TX.
45. Arcana RI, Crișan-Dabija RA, Caba B, et al. Speaking of the "devil": diagnostic errors in interstitial lung diseases. *J Pers Med*. 2023;13:1589.
46. Tsurutani J, Noguchi K, Tanabe A. Real-world analysis of interstitial lung disease/pneumonitis in patients with HER2-positive unresectable or recurrent breast cancer treated with trastuzumab deruxtecan: all-patient post-marketing surveillance study in Japan. Presented at San Antonio Breast Cancer Symposium 2024; December 10-13, 2024; San Antonio, TX. Abstract P1-02-10.
47. Fehm T, Cottone F, Dunton K, et al. Trastuzumab deruxtecan versus treatment of physician's choice in patients with HER2-positive metastatic breast cancer (DESTINY-Breast02): patient-reported outcomes from a randomised, open-label, multicentre, phase 3 trial. *Lancet Oncol*. 2024;25:614-625.
48. Curigliano G, Dunton K, Rosenlund M, et al. Patient-reported outcomes and hospitalization data in patients with HER2-positive metastatic breast cancer receiving trastuzumab deruxtecan or trastuzumab emtansine in the phase III DESTINY-Breast03 study. *Ann Oncol*. 2023;34:569-577.
49. Ueno NT, Cottone F, Dunton K, et al. Patient-reported outcomes from DESTINY-Breast04: trastuzumab deruxtecan versus physician's choice of chemotherapy in patients with HER2-low mBC. *The Oncologist*. 2025;30: oyaf048.
50. Ku GY, Di Bartolomeo M, Smyth E, et al. 1205MO updated analysis of DESTINY-Gastric02: a phase II single-arm trial of trastuzumab deruxtecan (T-DXd) in Western patients (pts) with HER2-positive (HER2+) unresectable/metastatic gastric/gastroesophageal junction (GEJ) cancer who progressed on or after trastuzumab-containing regimen. *Ann Oncol*. 2022; 33: S1100.
51. Jänne PA, Goto Y, Kubo T, et al. Final analysis results and patient-reported outcomes from DESTINY-Lung02-a dose-blinded, randomized, phase 2 study of trastuzumab deruxtecan in patients with HER2-mutant metastatic NSCLC. *J Thorac Oncol*. 2025;20(12):1814–1828.
52. Di Maio M, Perrone F, Conte P. Real-world evidence in oncology: opportunities and limitations. *Oncologist*. 2020;25:e746-e752.
53. Botticelli A, Caputo R, Scagnoli S, et al. Real-world outcomes of trastuzumab deruxtecan in patients with HER2+ metastatic breast cancer: the DE-REAL study. *Oncologist*. 2024;29:303-310.
54. Buono G, Deleuze A, Klocker EV, et al. 237P real-world safety and efficacy of trastuzumab-deruxtecan (T-DXd) in HER2-positive advanced breast cancer (ABC) elderly patients (pts): the TREX-Old retrospective registry. *ESMO Open*. 2023;8:101425.
55. Fountzilas E, Lalla T, Karakatsoulis G, et al. Real-world data on the safety and efficacy of trastuzumab deruxtecan and sacituzumab govitecan in patients with advanced breast cancer: the experience of the Hellenic Cooperative Oncology Group. *Eur J Cancer*. 2024;200:113954.
56. Vosoughi E, Nafissi N, Mahadevan A, et al. Real-life experience of trastuzumab deruxtecan (T-DXd) in patients with heavily pretreated HER2 positive advanced breast cancer: a retrospective single institution study. *J Clin Oncol*. 2023;41:e13035-e13035.