Systematic Review

Efficacy and Safety of Trastuzumab Deruxtecan in Breast Cancer: A Systematic Review and Meta-Analysis

Gavin P. Dowling,^{1,2,3} Gordon R. Daly,² Stephen Keelan,² Fiona Boland,⁴ Sinead Toomey,¹ Arnold D.K. Hill,² Bryan T. Hennessy¹

Abstract

Trastuzumab deruxtecan (T-DXd) is a novel antibody-drug-conjugate (ADC), primarily used in the treatment of HER2positive breast cancer. This study aimed to conduct a systematic review to evaluate the efficacy and safety of T-DXd in treating breast cancer, based on clinical trials. A systematic search of the literature was conducted to identify clinical trials investigating the efficacy and safety of T-DXd in breast cancer. Clinical trials of any phase were included. Outcome measures were any adverse events and survival. Meta-analysis was conducted where possible. Pooled prevalence for each adverse event of any grade and grade 3 or greater were estimated. Progression-free survival (PFS), overall survival (OS) and objective response rates (ORRs) were also reported to evaluate the efficacy of T-DXd in breast cancer. A total of 1593 patients from 6 clinical trials were included. Common adverse events of any grade were nausea, anemia, neutropenia, vomiting, fatigue, constipation and diarrhea, occurring in greater than 30% of cases. In terms of adverse events of grade 3 or more, only anemia and neutropenia occurred at a relatively high rate. Median PFS ranged from 11.1 to 22.1 months. There was evidence of a benefit of T-DXd compared to controls in terms of both PFS (OR: 0.38; 95% CI: 0.32, 0.45) and OS (OR: 0.61; 95% CI: 0.48, 0.78). ORRs ranged from 37% to 79.9%. The present systematic review shows evidence that T-DXd is a safe and effective agent in the treatment of breast cancer based on currently available data. The most common adverse events affected the blood, lymphatic and gastrointestinal systems. Interstitial lung disease (ILD) is a notable and potentially serious adverse event.

Clinical Breast Cancer, Vol. 23, No. 8, 847–855 © 2023 The Author(s). Published by Elsevier Inc. This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/) **Keywords:** Human epidermal growth factor receptor 2, Adverse events, Progression free survival

Introduction

Human epidermal growth factor receptor 2 (HER2) is overexpressed in approximately 20% of all breast cancers. HER2positive breast cancer is associated with an aggressive phenotype and patients historically had poor outcomes. However, the introduction of HER2-targeted therapies has dramatically improved treatment outcomes in these patients.¹⁻³ The current standard of

¹Department of Molecular Medicine, Medical Oncology Lab, Royal College of Surgeons in Ireland (RCSI) University of Medicine and Health Sciences, Dublin, Ireland

³Department of Surgery, Bons Secours Hospital, Dublin, Ireland

⁴Data Science Centre, RCSI University of Medicine and Health Sciences, Dublin, Ireland

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E-mail contact: gavindowling@rcsi.com

1526-8209/\$ - see front matter © 2023 The Author(s). Published by Elsevier Inc. This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/) https://doi.org/10.1016/j.clbc.2023.09.005 care for patients diagnosed with metastatic HER2-positive breast cancer is dual HER2-blockade with trastuzumab and pertuzumab in combination with chemotherapy, based on results from the CLEOPATRA study.⁴ Treatment with the antibody-drug conjugate (ADC), trastuzumab emtansine (T-DM1), was previously the standard second-line therapy, as evidenced by the EMILIA trial.⁵

Trastuzumab deruxtecan (T-DXd) is an ADC which is composed of 3 parts: a monoclonal antibody targeting HER2, a cleavable tetrapeptide-based linker, and a cytotoxic payload.⁶ The antibody is a human monoclonal IgG1, with the same amino acid sequence as trastuzumab.⁷ The linker, which is stable in plasma, is cleaved by lysosomal cathepsins once in the cell, causing the release of the cytotoxic drug. The cytotoxic payload is a topoisomerase I inhibitor, deruxtecan, which works by forming a stable complex with DNA topoisomerase I and induces DNA damage.⁸ The drug-to-antibody ratio of T-DXd is 8, which is significantly higher than other ADCs.⁹

Recent clinical trial results show evidence that T-DXd is an effective therapy in HER2-positive and HER2-low breast cancer. This systematic review focuses on the published clinical trials of T-DXd

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²Department of Surgery, RCSI University of Medicine and Health Sciences, Dublin, Ireland

Address for correspondence: Gavin P. Dowling, MB, BCh, BAO, Department of Molecular Medicine, Medical Oncology Lab, Royal College of Surgeons in Ireland (RCSI) University of Medicine and Health Sciences, 123 St Stephen's Green, D09 YD60 Dublin, Ireland.

Efficacy and Safety of Trastuzumab Deruxtecan in Breast Cancer

Figure 1 PRISMA flow diagram detailing search and trial selection process.



treatment in breast cancer and aims to review the efficacy and safety data currently available.

Methods

This systematic review and meta-analysis was reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. All authors contributed to formulating the study protocol and it was then registered with the International Prospective Register of Systematic Reviews (PROSPERO Registration ID: CRD42022364161).

Search Strategy

An electronic search was performed of the PubMed Medline, EMBASE and Scopus databases on 14 September 2022 for relevant studies that would be suitable for inclusion in this meta-analysis. Search terms included "trastuzumab deruxtecan/ trastuzumabderuxtecan," "T-DXd" or "DS-8201a" and "breast cancer," which were linked with Boolean operators, "AND" and "OR." Included studies were limited to clinical trials published in the English language and were not restricted by year of publication. The search was focused on articles conducting clinical trials on patients with breast cancer.

Inclusion and Exclusion Criteria

Studies meeting the following inclusion criteria were included: (1) any phase clinical trial evaluating the efficacy and safety of T-DXd whether they had control groups or not; (2) patients in the clinical trials were pathologically confirmed to have breast cancer. Studies meeting any of the following exclusion criteria were excluded from this meta-analysis: (1) in the form of laboratory articles, meta-

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First Author	Year of Publication	Phase	Pathology	Study Design	Treatment	Dose (mg/kg)	Number of Patients			
Modi	2019	II	HER2-positive metastatic breast cancer	Single-arm trial	T-DXd	5.4 or 6.4 or 7.4	184			
Tamura	2019	I	HER2-positive advanced/ metastatic breast cancer	Single-arm trial	T-DXd	5.4 or 6.4	259			
Modi	2020	I	Advanced/ metastatic HER2-low-expressing breast cancer	Single-arm trial	T-DXd	5.4 or 6.4	54			
Cortés	2022	111	HER2-positive metastatic breast cancer	Randomized controlled trial	T-DXd	5.4	524 (261, 263)			
					T-DM1					
Modi	2022	111	HER2-low metastatic breast cancer	Randomized controlled trial	T-DXd	5.4	557 (373, 184)			
					Physicians choice of therapy					
Bartsch	2022	II	HER2-positive metastatic breast cancer with brain metastases	Single-arm trial	T-DXd	5.4	15			

Abbreviations: T-DXd = trastuzumab deruxtecan; T-DM1 = trastuzumab emtansine.

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analysis, review articles or letters; (2) using other treatment strategies without using T-DXd alone; (3) not in English.

Selection Process

The literature search was performed by 2 independent reviewers (G.P.D.) and (G.R.D) using the previously discussed predesigned search strategy. All duplicate studies were manually removed, before titles and abstracts were screened, and studies considered appropriate had their full text reviewed. Retrieved studies were reviewed to ensure inclusion criteria was met. In cases of discrepancies of opinion, a third author was asked to arbitrate (S.K).

Data Extraction and Quality Assessment

The following data was extracted from all eligible articles: (1) first author name, (2) year of publication (3) study design, (4) number of participants, (5) treatment received (6) study phase, (7) type and number of adverse events, numbers of all grade and grade ≥ 3 adverse events, (8) survival outcomes for progression-free survival (PFS) and overall survival (OS), (9) odds ratios (ORs) for PFS and OS. An adaptation of the Newcastle-Ottawa Scale was used to assess the risk of bias of the included studies.^{10,11}

Statistical Analysis

The total number of participants and the number of adverse events were extracted for each arm in each included study. Random effects meta-analyses were undertaken to estimate summary estimates of the odds of each adverse event (, constipation, diarrhea, fatigue, interstitial lung disease (ILD) nausea, neutropenia and vomiting) of any grade and grade ≥ 3 in the intervention vs the control group. For single arm trials, where possible, random effect meta-analyses were conducted to estimate the pooled prevalence for each adverse event (anemia, constipation, diarrhea, fatigue, ILD, nausea, neutropenia, and vomiting) of any grade and grade ≥ 3 .

The I^2 value was identified in order to measure the overall variation due to heterogeneity across the different prevalence rates, where 30% to 60% denotes moderate, 50% to 90% substantial, and 75% to 100% considerable heterogeneity.^{12,13} All analyses were performed using Review Manager (*RevMan*) version 5.4 (*Nordic Cochrane Centre, Copenhagen, Denmark*) and Stata version 17 (*Stata-Corp. 2021. Stata Statistical Software: Release 17. College Station, TX: StataCorp LLC.*)

Results

Search Results

A total of 612 potentially relevant articles were searched in PubMed Medline, EMBASE and Scopus in October 2022 (Figure 1). After reviewing the titles and abstracts, 600 articles were excluded. After reading the full texts of the remaining articles, 6 articles were finally included.^{6,14-18}

Included Studies and Participants

A total of 6 trials with 1593 participants were included (Table 1). Studies included 2 phase I trials, 2 single-arm phase II trials and 2 phases III randomized-controlled trials. With regards to the controlled trials, Cortés et al. compared T-DXd with T-DM1, and Modi et al. compared T-DXd with the physician's choice of therapy, both in terms of adverse events and efficacy.

A total of 1593 patients (T-DXd: 1146; control: 447) across 6 articles were included. Two trials (T-DXd: 634; control: 447) compared T-DXd with other agents. The others (n = 512) received single T-DXd for therapy.

All studies were judged to be at low risk of bias (Supplemental Table 1).

Safety Analysis

All included articles reported adverse events. Adverse events were graded according to the National Cancer Institute Common Efficacy and Safety of Trastuzumab Deruxtecan in Breast Cancer

Figure 2 Prevalence of any grade adverse event rates in single-arm trials.

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$\begin{array}{c} \text{Mod. 2019} \\ \text{Mod. 2019} \\ \text{Mod. 2020} \\ \text{Bartsch 2022} \\ \text{Subtolal (P2 = 0.05\%, p = 0.96)} \\ \hline \\ \text{Mod. 2019} \\ \text{Tarwira 2019} \\ \text{Mod. 2020} \\ \text{Bartsch 2022} \\ \text{Subtolal (P2 = 0.05\%, p = 0.96)} \\ \hline \\ \text{Mod. 2019} \\ \text{Tarwira 2019} \\ \text{Mod. 2019} \\ \text{Tarwira 2019} \\ \text{Mod. 2020} \\ \text{Bartsch 2022} \\ \text{Subtolal (P2 = 0.05\%, p = 0.11)} \\ \hline \\ \text{Fatigue} \\ \text{Mod. 2019} \\ \text{Mod. 2019} \\ \text{Tarwira 2019} \\ \text{Mod. 2019} \\ \text{Tarwira 2019} \\ \text{Mod. 2020} \\ \text{Bartsch 2022} \\ \text{Subtolal (P2 = 60.35\%, p = 0.11)} \\ \hline \\ \text{Fatigue} \\ \text{Mod. 2019} \\ \text{Mod. 2020} \\ \text{Bartsch 2022} \\ \text{Subtolal (P2 = 60.37\%, p = 0.02)} \\ \hline \\ \text{Inferstilla lung disease} \\ \text{Mod. 2020} \\ \text{Bartsch 2022} \\ \text{Subtolal (P2 = 66.34\%, p = 0.08)} \\ \hline \\ \text{Mod. 2019} \\ \text{Tarwira 2019} \\ \text{Mod. 2020} \\ \text{Bartsch 2022} \\ \text{Subtolal (P2 = 66.34\%, p = 0.08)} \\ \hline \\ \text{Nauread} \\ \text{Mod. 2019} \\ \text{Tarwira 2019} \\ \text{Mod. 2020} \\ \text{Bartsch 2022} \\ \text{Subtolal (P2 = 66.34\%, p = 0.08)} \\ \hline \\ \text{Nauread} \\ \text{Mod. 2019} \\ \text{Tarwira 2019} \\ \text{Mod. 2019} \\ \text{Tarwira 2019} \\ \text{Mod. 2020} \\ \text{Subtolal (P2 = 56.34\%, p = 0.08)} \\ \hline \\ \text{Nauread} \\ \text{Mod. 2019} \\ \text{Tarwira 2019} \\ \text{Mod. 2020} \\ \text{Subtolal (P2 = 2.25\%, p = 0.38)} \\ \hline \\ \text{Neutropenia} \\ \text{Mod. 2019} \\ \text{Tarwira 2019} \\ \text{Mod. 2020} \\ \text{Subtolal (P2 = 2.25\%, p = 0.38)} \\ \hline \\ \text{Vornling} \\ \text{Mod. 2019} \\ \text{Tarwira 2019} \\ \text{Mod. 2020} \\ \hline \\ \text{Vornling} \\ \hline \\ \text{Mod. 2020} \\ \hline \\ \text{Vornling} \\ \hline \\ \text{Mod. 2020} \\ \hline \\ \text{Vornling} \\ \hline \\ \text{Mod. 2020} \\ \hline \\ \\ \hline \\ \text{Mod. 2020} \\ \hline \\ \\ \hline \\ \\ \text{Mod. 2020} \\ \hline \\ \\ \\ \text{Mod. 2020} \\ \hline \\ \\ \hline \\ \\ \text{Mod. 2020} \\ \hline \\ \\ \hline \\ \\ \\ \\ \text{Mod. 2020} \\ \hline \\ \\ \hline \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ $	Constipation		0.36 (0.20, 0.42)	40.96	66	104
$ \begin{array}{c} \mbox{Mod} 2020 \\ \mbox{Bartsch} 2022 \\ \mbox{Bartsch} 2023 \\ \mbox{Bartsch} 2023 \\ \mbox{Bartsch} 2022 \\ \mbox{Bartsch} 2022 \\ \mbox{Subtolal} (l'2 = 50.35\%, p = 0.1) \\ \mbox{Failgue} \\ \mbox{Mod} 2019 \\ \mbox{Bartsch} 2022 \\ \mbox{Bartsch} 2022 \\ \mbox{Subtolal} (l'2 = 50.35\%, p = 0.1) \\ \mbox{Failgue} \\ \mbox{Mod} 2019 \\ \mbox{Bartsch} 2022 \\ \mbox{Subtolal} (l'2 = 56.75\%, p = 0.02) \\ \mbox{Interstillal lung disease} \\ \mbox{Mod} 2019 \\ \mbox{Tarmura 2019} \\ \mbox{Mod} 2020 \\ \mbox{Bartsch} 2022 \\ \mbox{Subtolal} (l'2 = 56.75\%, p = 0.02) \\ \mbox{Interstillal lung disease} \\ \mbox{Mod} 2019 \\ \mbox{Tarmura 2019} \\ \mbox{Mod} 2020 \\ \mbox{Bartsch} 2022 \\ \mbox{Subtolal} (l'2 = 56.34\%, p = 0.02) \\ \mbox{Interstillal lung disease} \\ \mbox{Mod} 2019 \\ \mbox{Tarmura 2019} \\ \mbox{Mod} 2019 \\ \mbox{Tarmura 2019} \\ \mbox{Mod} 2019 \\ \mbox{Tarmura 2019} \\ \mbox{Mod} 2020 \\ \mbox{Bartsch} 2022 \\ \mbox{Subtolal} (l'2 = 53.93\%, p = 0.09) \\ \mbox{Nutropenia} \\ \mbox{Mod} 2019 \\ \mbox{Tarmura 2019} \\ \mbox{Mod} 2020 \\ \mbox{Bartsch} 2022 \\ \mbox{Subtolal} (l'2 = 53.93\%, p = 0.09) \\ \mbox{Nutropenia} \\ \mbox{Mod} 2019 \\ \mbox{Tarmura 2019} \\ \mbod 2020 \\ \mbox{Bartsch} 2022 \\ \mbox{Subtolal} (l'2 = 53.93\%, p = 0.09) \\ \mbox{Nutropenia} \\ \mbox{Mod} 2019 \\ \mbox{Tarmura 2019} \\ \mbod 2020 \\ \mbox{Bartsch} 2022 \\ \mbox{Subtolal} (l'2 = 52.93\%, p = 0.38) \\ \mbox{Nutropenia} \\ \mbox{Mod} 2019 \\ \mbox{Tarmura 2019} \\ \mbod 2020 \\ \mbox{Bartsch} 2022 \\ \mbox{Subtolal} (l'2 = 52.93\%, p = 0.38) \\ \mbox{Nutropenia} \\ \mbox{Mod} 2019 \\ \mbox{Tarmura 2019} \\ \mbod 2020 \\ \mbox{Subtolal} (l'2 = 2.29\%, p = 0.38) \\ \mbox{Nutropenia} \\ \mbox{Mod} 2019 \\ \mbox{Tarmura 2019} \\ \mbod 2020 \\ \mbox{Mod} 2019 \\ \mbox{Tarmura 2019} \\ \mbod 2020 \\ \mbox{Mod} 2019 \\ \mbox{Tarmura 2019} \\ \mbod 2020 \\ \mbox{Tarmura 2019} \\ \mbod 2020 \\ \mbox{Tarmura 2019} \\ \mbod 2020 \\ Tarmura 2019$	Tamura 2019		0.37 (0.28, 0.43)	49.00	42	104
$ \begin{array}{c} \text{Bartsch 2022} \\ \text{Subtotal } (l^{N} 2 = 0.00\%, \text{p} = 0.96) \\ \hline \\ \text{Diarrhea} \\ \text{Modi 2019} \\ \text{Tarura 2019} \\ \text{Modi 2020} \\ \text{Bartsch 2022} \\ \text{Subtotal } (l^{N} 2 = 60.35\%, \text{p} = 0.11) \\ \hline \\ \text{Falique} \\ \text{Modi 2019} \\ \text{Tarura 2019} \\ \text{Modi 2019} \\ \text{Tarura 2019} \\ \text{Modi 2020} \\ \text{Bartsch 2022} \\ \text{Subtotal } (l^{N} 2 = 66.73\%, \text{p} = 0.02) \\ \hline \\ \text{Interstitial lung disease} \\ \text{Modi 2019} \\ \text{Tarura 2019} \\ \text{Modi 2020} \\ \text{Bartsch 2022} \\ \text{Subtotal } (l^{N} 2 = 66.73\%, \text{p} = 0.02) \\ \hline \\ \text{Interstitial lung disease} \\ \text{Modi 2019} \\ \text{Modi 2020} \\ \text{Bartsch 2022} \\ \text{Subtotal } (l^{N} 2 = 66.73\%, \text{p} = 0.09) \\ \hline \\ \text{Nussaa} \\ \text{Modi 2019} \\ \text{Modi 2020} \\ \text{Bartsch 2022} \\ \text{Subtotal } (l^{N} 2 = 65.34\%, \text{p} = 0.09) \\ \hline \\ \text{Nussaa} \\ \text{Modi 2019} \\ \text{Modi 2020} \\ \text{Bartsch 2022} \\ \text{Subtotal } (l^{N} 2 = 53.93\%, \text{p} = 0.09) \\ \hline \\ \text{Nussaa} \\ \text{Modi 2019} \\ \text{Tarura 2019} \\ \text{Modi 2020} \\ \text{Bartsch 2022} \\ \text{Subtotal } (l^{N} 2 = 53.93\%, \text{p} = 0.09) \\ \hline \\ \text{Nussaa} \\ \text{Modi 2019} \\ \text{Tarura 2019} \\ \text{Modi 2020} \\ \text{Bartsch 2022} \\ \text{Subtotal } (l^{N} 2 = 53.93\%, \text{p} = 0.09) \\ \hline \\ \text{Nussaa} \\ \text{Modi 2019} \\ \text{Tarura 2019} \\ \text{Modi 2020} \\ \text{Bartsch 2022} \\ \text{Subtotal } (l^{N} 2 = 2.29\%, \text{p} = 0.38) \\ \hline \\ \text{Vormiting} \\ \text{Modi 2019} \\ \text{Tarura 2019} \\ \text{Modi 2020} \\ \text{Bartsch 2022} \\ \text{Subtotal } (l^{N} 2 = 2.29\%, \text{p} = 0.38) \\ \hline \\ \text{Vormiting} \\ \text{Modi 2019} \\ \text{Tarura 2019} \\ \text{Modi 2020} \\ \text{Bartsch 2022} \\ \text{Subtotal } (l^{N} 2 = 2.29\%, \text{p} = 0.38) \\ \hline \\ \text{Vormiting} \\ \text{Modi 2019} \\ \text{Tarura 2019} \\ \text{Modi 2020} \\ \text{Bartsch 2022} \\ \text{Subtotal } (l^{N} 2 = 2.29\%, \text{p} = 0.38) \\ \hline \\ \text{Vormiting} \\ \text{Modi 2019} \\ \text{Tarura 2019} \\ \text{Modi 2020} \\ \text{Bartsch 2022} \\ \text{Subtotal } (l^{N} 2 = 2.29\%, \text{p} = 0.38) \\ \hline \\ \text{Modi 2019} \\ \text{Tarura 2019} \\ \text{Modi 2020} \\ \text{Bartsch 2022} \\ \text{Subtotal } (l^{N} 2 = 2.29\%, \text{p} = 0.38) \\ \hline \\ \text{Vormiting} \\ \text{Modi 2019} \\ \text{Tarura 2019} \\ \text{Modi 2020} \\ \text{Modi 2019} \\ \text{Tarura 2019} \\ \text{Modi 2020} \\ \text{Modi 2019} \\ \text{Tarura 2019} \\ \text{Modi 2020} \\ Modi$	Modi 2020		0.39 (0.26, 0.53)	14.73	21	54
Subtolal ($l^{2} = 0.00\%, p = 0.96$) 0.38 (0.32, 0.42) 100.00 Diarhea 0.29 (0.23, 0.36) 37.36 54 1 Modi 2019 0.37 (0.28, 0.47) 31.78 43 1 Modi 2020 0.46 (0.33, 0.60) 21.97 25 5 Subtolal ($l^{2} = 50.35\%, p = 0.11$) 0.46 (0.33, 0.60) 21.97 25 5 Modi 2020 0.40 (0.16, 0.68) 8.89 6 1 0.36 (0.28, 0.44) 100.00 1 Fatigue 0.44 (0.42, 0.57) 33.34 91 1 0.36 (0.28, 0.44) 100.00 1 Modi 2020 Datasch 2022 0.37 (0.24, 0.51) 24.11 20 5 0.80 (0.52, 0.96) 12.12 13	Bartsch 2022		0.40 (0.16, 0.68)	4.19	6	15
Durinhea Modi 2019 Tarrura 2019 Subtotal ($^{12} = 50.35\%$, p = 0.11) Fatigue Modi 2020 Bartsch 2022 Subtotal ($^{12} = 50.35\%$, p = 0.11) Fatigue Modi 2019 Tarrura 2019 Modi 2020 Bartsch 2022 Subtotal ($^{12} = 68.78\%$, p = 0.02) Interstitul lung disease Modi 2019 Tarrura 2019 Modi 2020 Bartsch 2022 Subtotal ($^{12} = 68.78\%$, p = 0.02) Interstitul lung disease Modi 2019 Tarrura 2019 Modi 2020 Bartsch 2022 Subtotal ($^{12} = 68.78\%$, p = 0.02) Interstitul lung disease Modi 2019 Tarrura 2019 Modi 2020 Bartsch 2022 Subtotal ($^{12} = 56.34\%$, p = 0.08) Nuex 2019 Tarrura 2019 Modi 2020 Bartsch 2022 Subtotal ($^{12} = 56.34\%$, p = 0.08) Nuex 2019 Tarrura 2019 Modi 2019 Tarrura 2019 Modi 2019 Tarrura 2019 Modi 2020 Bartsch 2022 Subtotal ($^{12} = 58.34\%$, p = 0.08) Nuex 2019 Tarrura 2019 Modi 2020 Bartsch 2022 Subtotal ($^{12} = 2.93\%$, p = 0.08) Nuex 2019 Tarrura 2019 Modi 2020 Bartsch 2022 Subtotal ($^{12} = 2.29\%$, p = 0.38) Vortifing Modi 2019 Tarrura 2019 Modi 2020 Add ($^{12} = 2.29\%$, p = 0.38) Vortifing Modi 2019 Tarrura 2019 Modi 2020 Add ($^{12} = 2.29\%$, p = 0.38) Vortifing Modi 2019 Tarrura 2019 Modi 2020 Add ($^{12} = 2.29\%$, p = 0.38) Vortifing Modi 2019 Tarrura 2019 Modi 2020 Modi 2019 Tarrura 2019 Modi 2020 Modi 2019 Tarrura 2019 Modi 2020 Modi 2019 Tarrura 2019 Modi 2020 Modi 2020 Modi 2020 Modi 2019 Tarrura 2019 Modi 2020 Modi	Subtotal (I ² = 0.00%, p = 0.96)	\diamond	0.36 (0.32, 0.42)	100.00		
Tamura 2019 Tamura 2019 Modi 2020 Bartsch 2022 Subtotal ($1^{12} = 50.35\%, p = 0.11$) Fatigue Modi 2020 Bartsch 2022 Subtotal ($1^{12} = 68.78\%, p = 0.02$) Interstitial tung disease Modi 2020 Bartsch 2022 Bartsch 202 Bartsch 202 Bartsch 202 Bartsch 202	Diarrhea Modi 2019	_ _	0.29 (0.23, 0.36)	37 36	54	184
$ \begin{array}{c} \mbox{Mod} 2020 \\ \mbox{Bartsch} 2022 \\ \mbox{Bartsch} 2022 \\ \mbox{Subtotal} (l^{n}2 = 60.35\%, p = 0.11) \\ \mbox{Fatgue} \\ \mbox{Mod} 2019 \\ \mbox{Tamura} 2019 \\ \mbox{Mod} 2020 \\ \mbox{Bartsch} 2022 \\ \mbox{Subtotal} (l^{n}2 = 68.78\%, p = 0.02) \\ \mbox{Interstilial lung disease} \\ \mbox{Mod} 2019 \\ \mbox{Tamura} 2019 \\ \mbox{Mod} 2020 \\ \mbox{Bartsch} 2022 \\ \mbox{Subtotal} (l^{n}2 = 68.78\%, p = 0.02) \\ \mbox{Interstilial lung disease} \\ \mbox{Mod} 2019 \\ \mbox{Tamura} 2019 \\ \mbox{Mod} 2020 \\ \mbox{Bartsch} 2022 \\ \mbox{Subtotal} (l^{n}2 = 66.78\%, p = 0.08) \\ \mbox{Nausea} \\ \mbox{Mod} 2019 \\ \mbox{Tamura} 2019 \\ \mbox{Mod} 2020 \\ \mbox{Bartsch} 2022 \\ \mbox{Subtotal} (l^{n}2 = 56.34\%, p = 0.08) \\ \mbox{Nausea} \\ \mbox{Mod} 2020 \\ \mbox{Subtotal} (l^{n}2 = 5.3.93\%, p = 0.09) \\ \mbox{Nausea} \\ \mbox{Mod} 2019 \\ \mbox{Tamura} 2019 \\ \mbox{Mod} 2020 \\ \mbox{Subtotal} (l^{n}2 = 5.3.93\%, p = 0.09) \\ \mbox{Nausea} \\ \mbox{Mod} 2019 \\ \mbox{Tamura} 2019 \\ \mbox{Mod} 2020 \\ \mbox{Subtotal} (l^{n}2 = 2.29\%, p = 0.38) \\ \mbox{Nausea} \\ \mbox{Mod} 2019 \\ \mbox{Tamura} 2019 \\ \mbox{Mod} 2020 \\ \mbox{Subtotal} (l^{n}2 = 2.29\%, p = 0.38) \\ \mbox{Nausea} \\ \mbox{Mod} 2019 \\ \mbox{Tamura} 2019 \\ \mbox{Mod} 2019 \\ \mbox{Tamura} 2019 \\ \mbox{Mod} 2020 \\ \mbox{Subtotal} (l^{n}2 = 2.29\%, p = 0.38) \\ \mbox{Nuting} \\ \mbox{Mod} 2019 \\ \mbox{Tamura} 2019 \\ \mbox{Mod} 20120 \\ \mbox{Mod} 2019 \\ \mbox{Tamura} 2019 \\ \mbox{Mod} 2019 \\ \mbox{Tamura} 2019$	Tamura 2019	·	0.37 (0.29, 0.47)	31.78	43	115
Bartsch 2022 Subtotal ($h^2 = 50.35\%, p = 0.11$) Fatigue Modi 2019 Tamura 2019 Modi 2020 Districh 2022 Subtotal ($h^2 = 68.78\%, p = 0.02$) Interstitial lung disease Modi 2019 Tamura 2019 Modi 2020 Bartsch 2022 Subtotal ($h^2 = 68.78\%, p = 0.02$) Interstitial lung disease Modi 2019 Tamura 2019 Modi 2020 Bartsch 2022 Subtotal ($h^2 = 68.78\%, p = 0.08$) Nausea Modi 2019 Tamura 2019 Modi 2020 Bartsch 2022 Subtotal ($h^2 = 50.34\%, p = 0.08$) Nausea Modi 2019 Tamura 2019 Modi 2020 Bartsch 2022 Subtotal ($h^2 = 50.34\%, p = 0.08$) Nausea Modi 2019 Tamura 2019 Modi 2020 Bartsch 2022 Subtotal ($h^2 = 50.39\%, p = 0.08$) Nausea Modi 2019 Tamura 2019 Modi 2020 Bartsch 2022 Subtotal ($h^2 = 2.29\%, p = 0.38$) Vormiting Modi 2019 Tamura 2019 Modi 2020 Bartsch 2022 Subtotal ($h^2 = 2.29\%, p = 0.38$) Vormiting Modi 2019 Tamura 2019 Modi 2020 Bartsch 2022 Subtotal ($h^2 = 2.29\%, p = 0.38$) Vormiting Modi 2019 Tamura 2019 Modi 2020 Bartsch 2022 Subtotal ($h^2 = 2.29\%, p = 0.38$) Vormiting Modi 2019 Tamura 2019 Modi 2020 Data Addi Data Data Data Data Data Data Data Dat	Modi 2020		0.46 (0.33, 0.60)	21.97	25	54
Subtolal $(h^2 = 50.35\%, p = 0.11)$ Paigue Modi 2019 Tamura 2019 Modi 2020 Nausea Modi 2020 Nausea Modi 2019 Tamura 2019 Modi 2020 Neutropenia Modi 2019 Tamura 2019 Modi 2020 Neutropenia Modi 2020 Neutropenia Modi 2019 Tamura 2019 Modi 2020 Neutropenia Modi 2020 Neutropenia Modi 2019 Tamura 2019 Modi 2019 Tamura 2019 Modi 2019 Tamura 2019 Modi 2020 Neutropenia Modi 2020 Neutropenia Modi 2020 Neutropenia Modi 2020 Neutropenia Modi 2020 Neutropenia Modi 2020 Neutrop	Bartsch 2022		0.40 (0.16, 0.68)	8.89	6	15
Faigue 0.49 (0.42, 0.57) 33.34 91 1 Modi 2019 0.44 (0.35, 0.54) 30.43 51 1 Modi 2020 0.37 (0.24, 0.51) 24.11 20 5 Bartsch 2022 0.49 (0.42, 0.57) 0.33.44 91 1 Subtotal ($h^2 = 66.78\%, p = 0.02$) 0.49 (0.38, 0.59) 100.00 10 Interstitial lung disease 0.44 (0.09, 0.19) 36.06 25 1 Modi 2019 0.56 (0.02, 0.11) 31.44 6 1 Tamura 2019 0.56 (0.02, 0.11) 31.44 6 1 Modi 2020 Bartsch 2022 0.07 (0.00, 0.32) 9.79 1 1 Subtotal ($h^2 = 56.34\%, p = 0.08$) 0.14 (0.09, 0.19) 36.58 143 1 Nausea 0.78 (0.71, 0.84) 36.58 143 1 Modi 2020 Bartsch 2022 0.07 (0.00, 0.32) 9.79 1 1 Subtotal ($h^2 = 53.93\%, p = 0.09$) 0.76 (0.62, 0.87) 31.40 32 1 Modi 2020 Bartsch 2022 0.33 (0.28, 0.42) 49.17 64 1	Subtotal (I ² = 50.35%, p = 0.11)	\sim	0.36 (0.28, 0.44)	100.00		
$\begin{array}{cccccccccccccccccccccccccccccccccccc$	Fatigue		0.40 (0.42, 0.57)	22.24	01	104
$\begin{array}{cccccccccccccccccccccccccccccccccccc$	Tamura 2019		0.44 (0.35, 0.54)	30.43	51	104
Bartsch 2022 0.80 (0.52, 0.96) 12.12 12 12 Subtotal ($h^2 = 68.78\%, p = 0.02$) 0.49 (0.38, 0.59) 100.00 10 Interstitial lung disease 0.14 (0.09, 0.19) 36.06 25 1 Modi 2019 0.55 (0.02, 0.11) 31.44 6 1 Tamura 2019 0.76 (0.07, 0.27) 22.72 8 5 Modi 2019 0.76 (0.07, 0.27) 22.72 8 5 Tamura 2019 0.76 (0.71, 0.84) 36.58 14.3 1 Modi 2019 0.78 (0.71, 0.84) 36.58 14.3 1 Tamura 2019 0.76 (0.62, 0.87) 32.42 41 5 Bartsch 2022 0.55 (0.28, 0.42) 49.17 64 1 Subtotal ($h^2 = 53.93\%, p = 0.09$)	Modi 2020	•	0.37 (0.24, 0.51)	24.11	20	54
Subtotal ($P2 = 68.78\%, p = 0.02$) 0.49 (0.38, 0.59) 100.00 Interstitial lung disease 0.14 (0.09, 0.19) 36.06 25 1 Modi 2019 0.56 (0.20, 0.11) 31.44 6 1 Modi 2020 0.15 (0.07, 0.27) 22.72 8 5 Bartsch 2022 0.07 (0.00, 0.32) 9.79 1 1 Nausea 0.16 (0.05, 0.16) 100.00 101 100.05 100.00 Nausea 0.78 (0.71, 0.84) 36.58 143 1 1 Modi 2019	Bartsch 2022	+	0.80 (0.52, 0.96)	12.12	12	15
$\begin{array}{c} \mbox{Interstillal lung disease} \\ \mbox{Modi 2019} \\ \mbox{Tarmura 2019} \\ \mbox{Modi 2020} \\ \mbox{Bartsch 2022} \\ \mbox{Subtotal (} l^{h_2} = 56.34\%, p = 0.08) \end{array} \qquad $	Subtotal (I ² = 68.78%, p = 0.02)	\sim	0.49 (0.38, 0.59)	100.00		
$\begin{array}{cccccccccccccccccccccccccccccccccccc$	Interstitial lung disease	•	0 14 (0 09 0 19)	36.06	25	184
Modi 2020 $0.15 (0.07, 0.27)$ 22.72 8 50 Bartsch 2022 $0.07 (0.00, 0.32)$ 9.79 1 1 Subtotal (I^2 = 56.34%, p = 0.08) $0.10 (0.05, 0.16)$ 100.00 $0.10 (0.05, 0.16)$ 100.00 Nausea $0.78 (0.71, 0.84)$ 36.58 14.3 1 $0.79 (0.71, 0.84)$ 36.58 14.3 1 Modi 2019 $0.79 (0.71, 0.84)$ 36.58 14.3 1 $0.76 (0.68, 0.87)$ 22.42 41 50 Bartsch 2022 0.09 $0.76 (0.68, 0.83)$ 100.00 $0.76 (0.68, 0.83)$ 100.00 Neutropenia $0.35 (0.28, 0.42)$ 49.17 64 $10.28 (0.20, 0.37)$ 31.40 32 $10.28 (0.20, 0.37)$ 31.40 32 $10.28 (0.20, 0.37)$ 31.40 32 $10.28 (0.20, 0.37)$ 31.40 32 $10.28 (0.20, 0.37)$ 31.40 32 $10.28 (0.20, 0.37)$ 31.40 32 $10.32 (0.27, 0.37)$ 100.00 $0.32 (0.27, 0.37)$ 100.00 $0.32 (0.27, 0.37)$ 100.00 $0.32 (0.27, 0.37)$ 100.00 $0.32 (0.27, 0.37)$ 100.20 $0.$	Tamura 2019	•	0.05 (0.02, 0.11)	31.44	6	115
Bartsch 2022 Subtotal ($h^2 = 56.34\%$, p = 0.08) Nausea Modi 2019 Tamura 2019 Neutropenia Modi 2019 Neutropenia Modi 2019 Subtotal ($h^2 = 53.93\%$, p = 0.09) Neutropenia Modi 2019 Tamura 2019 Neutropenia Modi 2019 Tamura 2019 Neutropenia Modi 2019 Tamura 2019 Neutropenia Modi 2019 Tamura 2019 Neutropenia Modi 2019 Tamura 2019 Modi 2020 Neutropenia Modi 2020 Modi 20	Modi 2020	←	0.15 (0.07, 0.27)	22.72	8	54
Subtotal (I^2 = 56.34%, p = 0.08) 0.10 (0.05, 0.16) 100.00 Nausea 0.78 (0.71, 0.84) 36.58 143 1 Modi 2019 0.79 (0.71, 0.84) 36.58 143 1 Modi 2020 0.79 (0.71, 0.84) 36.58 143 1 Modi 2020 0.78 (0.62, 0.87) 22.42 41 5 Bartsch 2022 0.76 (0.68, 0.83) 100.00 0.76 (0.68, 0.83) 100.00 Neutropenia 0.35 (0.28, 0.42) 49.17 64 1 Modi 2019 0.36 (0.28, 0.42) 49.17 64 1 Tamura 2019 0.35 (0.28, 0.42) 49.17 64 1 Modi 2020 0.30 (0.18, 0.44) 15.09 16 5 Subtotal (I^2 = 2.29%, p = 0.38) 0.32 (0.27, 0.37) 100.00 0.32 (0.27, 0.37) 100.00 Vomiting 0.46 (0.38, 0.53) 37.51 84 1 Modi 2019 0.46 (0.38, 0.53) 37.51 84 1 Tamura 2019 0.46 (0.38, 0.53) 37.51 84 1 Modi 2019 0.46 (0.38, 0.53) 37.51 84	Bartsch 2022		0.07 (0.00, 0.32)	9.79	1	15
Nausea $0.78 (0.71, 0.84)$ 36.58 143 1 Tamura 2019 $0.79 (0.71, 0.84)$ 36.58 143 1 Modi 2020 $0.79 (0.71, 0.84)$ 36.58 143 1 Bartsch 2022 $0.76 (0.62, 0.87)$ 22.42 41 50 Subtotal (I^2 = 53.93%, p = 0.09) $0.76 (0.68, 0.83)$ 100.00 $0.76 (0.68, 0.83)$ 100.00 Neutropenia $0.35 (0.28, 0.42)$ 49.17 64 1 Modi 2019 $0.35 (0.28, 0.42)$ 49.17 64 1 Bartsch 2022 $0.30 (0.18, 0.44)$ 15.09 16 5 Subtotal (I^2 = 2.29%, p = 0.38) $0.32 (0.27, 0.37)$ 4.34 7 1 Vomiting $0.32 (0.27, 0.37)$ 10.00 $0.46 (0.38, 0.53)$ 37.51 84 1 Tamura 2019 $0.46 (0.38, 0.53)$ 37.51 84 1 Modi 2019 $0.46 (0.38, 0.53)$ 37.51 84 1 Tamura 2019 $0.46 (0.38, 0.53)$ 37.51 84 1 Modi 2019 $0.46 (0.38, 0.59)$	Subtotal (I^2 = 56.34%, p = 0.08)	>	0.10 (0.05, 0.16)	100.00		
Tamura 2019 0.79 (0.71, 0.86) 31.59 91 1 Modi 2020 Bartsch 2022 0.76 (0.82, 0.87) 22.42 41 5 Subtotal (I^2 = 53.93%, p = 0.09) 0.76 (0.62, 0.87) 22.42 41 5 Neutropenia 0.76 (0.68, 0.83) 100.00 10.76 (0.68, 0.83) 100.00 Neutropenia 0.35 (0.28, 0.42) 49.17 64 1 Modi 2020 0.35 (0.28, 0.42) 49.17 64 1 Bartsch 2022 0.33 (0.18, 0.44) 15.09 16 5 Bartsch 2022 0.47 (0.21, 0.73) 4.34 7 1 Subtotal (I*2 = 2.29%, p = 0.38) 0.32 (0.27, 0.37) 100.00 0.32 (0.27, 0.73) 4.34 7 1 Vorniting 0.46 (0.38, 0.53) 37.51 84 1 1 Modi 2019 0.52 (0.43, 0.62) 31.82 60 1 Tamura 2019 0.52 (0.43, 0.52) 31.82 60 1 Modi 2019 0.52 (0.43, 0.52) 31.82 60 1 Tamura 2019 0.52 (0.43, 0.52) 1.88 24 56	Nausea Modi 2019		0.78 (0.71, 0.84)	36.58	143	184
Modi 2020 0.76 (0.62, 0.87) 22.42 41 50 Bartsch 2022 0.47 (0.21, 0.73) 9.41 7 1 Subtolal (I^2 = 53.93%, p = 0.09) 0.76 (0.68, 0.83) 100.00 100 Neutropenia 0.35 (0.28, 0.42) 49.17 64 1 Modi 2019 0.35 (0.28, 0.42) 49.17 64 1 Tamura 2019 0.30 (0.18, 0.44) 15.09 16 5 Bartsch 2022 0.30 (0.18, 0.44) 15.09 16 5 Subtotal (I^2 = 2.29%, p = 0.38) 0.32 (0.27, 0.37) 100.00 1 Vomiting 0.46 (0.38, 0.53) 37.51 84 1 Modi 2019 0.52 (0.43, 0.52) 31.82 60 1 Modi 2020 0.52 (0.43, 0.52) 21.88 24 5 <td>Tamura 2019</td> <td></td> <td>0.79 (0.71, 0.86)</td> <td>31.59</td> <td>91</td> <td>115</td>	Tamura 2019		0.79 (0.71, 0.86)	31.59	91	115
Bartsch 2022 0.47 (0.21, 0.73) 9.41 7 1 Subtotal (I^2 = 53.93%, p = 0.09) 0.76 (0.68, 0.83) 100.00 100.00 Neutropenia 0.35 (0.28, 0.42) 49.17 64 1 Modi 2019 0.38 (0.20, 0.37) 31.40 32 1 Tamura 2019 0.30 (0.18, 0.44) 15.09 16 5 Bartsch 2022 0.47 (0.21, 0.73) 4.34 7 1 Subtotal (I^2 = 2.29%, p = 0.38) 0.32 (0.27, 0.37) 100.00 100.00 Vomiting 0.46 (0.38, 0.53) 37.51 84 1 Modi 2019	Modi 2020		0.76 (0.62, 0.87)	22.42	41	54
Subtrata (In:2 = 53.93%, p = 0.09) 0.76 (0.86, 0.83) 100.00 Neutropenia 0.35 (0.28, 0.42) 49.17 64 1 Modi 2019 0.36 (0.28, 0.42) 49.17 64 1 Modi 2020 0.30 (0.18, 0.44) 15.09 16 5 Bartsch 2022 0.32 (0.27, 0.37) 100.00 0.32 (0.27, 0.37) 100.00 Vomiting 0.32 (0.27, 0.37) 100.00 0.32 (0.27, 0.37) 100.00 Vomiting 0.46 (0.38, 0.53) 37.51 84 1 Modi 2020 0.44 (0.31, 0.59) 31.82 60 1	Bartsch 2022		0.47 (0.21, 0.73)	9.41	7	15
Neutropenia 0.35 (0.28, 0.42) 49.17 64 1 Modi 2019 0.28 (0.20, 0.37) 31.40 32 1 Modi 2020 0.30 (0.18, 0.44) 15.09 16 5 Bartsch 2022 0.32 (0.27, 0.37) 100.00 16 5 Vomiting 0.32 (0.27, 0.37) 100.00 100.00 100.00 Vomiting 0.46 (0.38, 0.53) 37.51 84 1 Modi 2019 0.52 (0.43, 0.62) 31.82 60 1 Modi 2020 0.44 (0.31, 0.59) 21.88 24 60 1	Subtotal ($I^2 = 53.93\%$, p = 0.09)		0.76 (0.68, 0.83)	100.00		
Tamura 2019 0.28 (0.20, 0.37) 31.40 32 1 Modi 2020 0.30 (0.18, 0.44) 15.09 16 5 Bartsch 2022 0.30 (0.18, 0.44) 15.09 16 5 Subtotal (l^2 = 2.29%, p = 0.38) 0.32 (0.27, 0.37) 100.00 100.00 Vomiting 0.46 (0.38, 0.53) 37.51 84 1 Tamura 2019 0.52 (0.43, 0.62) 31.82 60 1 Modi 2020 0.44 (0.31, 0.59) 21.88 24 5	Neutropenia Modi 2019		0.35 (0.28, 0.42)	49.17	64	184
Modi 2020 0.30 (0.18, 0.44) 15.09 16 5 Bartsch 2022 0.47 (0.21, 0.73) 4.34 7 1 Subtotal (IV2 = 2.29%, p = 0.38) 0.32 (0.27, 0.37) 100.00 100.00 Vomiting 0.46 (0.38, 0.53) 37.51 84 1 Tamura 2019 0.52 (0.43, 0.62) 31.82 60 1 Modi 2020 0.44 (0.31, 0.59) 21.88 24 50	Tamura 2019		0.28 (0.20, 0.37)	31.40	32	115
barson 2022 0.47 (0.21, 0.73) 4.34 7 1 Subtotal (I^2 = 2.29%, p = 0.38) 0.32 (0.27, 0.37) 100.00 100.00 Vomiting 0.46 (0.38, 0.53) 37.51 84 1 Tamura 2019 0.52 (0.43, 0.62) 31.82 60 1 Modi 2020 0.44 (0.31, 0.59) 21.88 24 5	Modi 2020	<u>,</u>	0.30 (0.18, 0.44)	15.09	16	54
Vomiting 0.46 (0.38, 0.53) 37.51 84 1 Tamura 2019	Bartsch 2022 Subtotal (IA2 = 2.29% n = 0.39)		0.47 (0.21, 0.73)	4.34	7	15
Vomiting 0.46 (0.38, 0.53) 37.51 84 1 Tamura 2019	Subiotal (112 - 2.29%, p = 0.38)	\sim	0.32 (0.27, 0.37)	100.00		
Tamura 2019 ● 0.52 (0.43, 0.62) 31.82 60 1 Modi 2020 ● 0.44 (0.31, 0.59) 21.88 24 5	Vomiting Modi 2019		0.46 (0.38, 0.53)	37.51	84	184
Modi 2020 0.44 (0.31, 0.59) 21.88 24 5	Tamura 2019		0.52 (0.43, 0.62)	31.82	60	115
Bortrob 2022	Modi 2020		0.44 (0.31, 0.59)	21.88	24	54
UL2U (UU4, UA8) 8, Y 3 1 Subtolai (U22 49, 63%, p = 0, 11) 045 (0 37 0 63) 100 00	Subtotal (1/2 = 49.63%, p = 0.11)	\sim	0.45 (0.37 0.53)	0.79 100.00	ى	10
			0.40 (0.07, 0.00)	100.00		

Terminology Criteria for Adverse Events. After evaluating the any grade and grade ≥ 3 adverse events, we found that the most common events were nausea, anemia, neutropenia, vomiting, fatigue, constipation, and diarrhea, occurring in greater than 30% of cases.

Single-arm studies were analyzed to estimate pooled prevalence of adverse event rates of all grade (Figure 2, Supplemental Table 2) and grade \geq 3 (Figure 3, Supplemental Table 3).

For all grade adverse events, the estimated pooled prevalence of nausea was highest at 76% (95% CI: 68, 83). The pooled estimated prevalence of anemia, neutropenia, vomiting, fatigue, constipation, and diarrhea were similar; at 36% (95% CI: 29, 44), 32% (95% CI:

27, 37), 47% (95% CI: 42, 52), 45% (CI 95%: 37, 53), 36% (95% CI: 32, 42), and 36% (95% CI: 28, 44), respectively.

In terms of adverse events of special interest, the event rate of ILD was 10% (95% CI: 5, 16), with the rate of grade ≥ 3 ILD being only 1% (95% CI: 0, 3). The estimated pooled prevalence of grade ≥ 3 adverse events was low overall, with only neutropenia and anemia occurring at a relatively high rate, 15% (CI 95%: 8, 23) and 12% (CI 95%: 7, 17), respectively. The I^2 value was identified in order to measure the overall variation due to heterogeneity across the different prevalence rates and illustrated considerable heterogeneity in some cases.

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Figure 3 Prevalence of grade \geq 3 adverse event rates in single-arm trials.

Study				ES (95% CI)	% Weight	n	N
Anaemia Modi 2019	_			0.09 (0.05, 0.14)	40.37	16	184
Tamura 2019	•			0 17 (0 10 0 25)	32.26	19	115
Modi 2020	4	<u> </u>		0.15 (0.07, 0.27)	20.15	8	54
Bartsch 2022	•			0.07 (0.00, 0.32)	7.23	1	15
Subtotal (I^2 = 36.72%, p = 0.19)	\sim	>		0.12 (0.07, 0.17)	100.00		
Constipation Modi 2019				0.01 (0.00, 0.03)	49.86	1	184
Tamura 2019	—			0.01 (0.00, 0.05)	31.22	1	115
Modi 2020	<u>+</u>			0.00 (0.00, 0.07)	14.73	0	54
Bartsch 2022	•			0.00 (0.00, 0.22)	4.19	0	15
Subtotal (I^2 = 0.00%, p = 0.94)	D			0.00 (0.00, 0.01)	100.00		
Diarrhea Modi 2019				0.03 (0.01.0.06)	49.86	5	184
Tamura 2019				0.02 (0.00, 0.06)	31.22	2	115
Modi 2020	· •	-		0.06 (0.01, 0.15)	14.73	3	54
Bartsch 2022	.			0.07 (0.00, 0.32)	4.19	1	15
Subtotal (I^2 = 0.00%, p = 0.43)	\diamond			0.02 (0.01, 0.04)	100.00		
Fatigue Modi 2019				0.06 (0.03, 0.10)	49.86	11	184
Tamura 2019				0.04 (0.01, 0.10)	31 22	5	115
Modi 2020	`			0.04 (0.00, 0.13)	14.73	2	54
Bartsch 2022				0.13 (0.02, 0.40)	4.19	2	15
Subtotal (I^2 = 0.00%, p = 0.55)	\diamond			0.05 (0.03, 0.07)	100.00		
Interstitial lung disease	-			0.01 (0.00, 0.03)	40.57	1	184
Tamura 2019	—			0.01 (0.00, 0.05)	32.28	1	115
Modi 2020	·	-		0.06 (0.01, 0.15)	20.02	3	54
Bartsch 2022	÷			0.00 (0.00, 0.22)	7.13	ō	15
Subtotal (I^2 = 35.83%, p = 0.20)	\diamond			0.01 (0.00, 0.03)	100.00		
Nausea Modi 2019	_			0.08 (0.04, 0.12)	48.21	14	184
Tamura 2019				0.03 (0.01, 0.09)	31.64	4	115
Modi 2020				0.04 (0.00, 0.13)	15.59	2	54
Bartsch 2022	٠ ــــ			0.00 (0.00, 0.22)	4.56	0	15
Subtotal (I ² = 5.59%, p = 0.37)	\diamond			0.05 (0.02, 0.07)	100.00		
Neutropenia Modi 2019		+		0.21 (0.15. 0.27)	34.31	38	184
Tamura 2019		-		0.14 (0.08, 0.22)	30.83	16	115
Modi 2020		+		0.20 (0.11, 0.34)	23.65	11	54
Bartsch 2022	•			0.00 (0.00, 0.22)	11.21	0	15
Subtotal (I ² = 64.39%, p = 0.04)				0.15 (0.08, 0.23)	100.00		
Vomiting Modi 2019				0.04 (0.02, 0.08)	41.47	8	184
Tamura 2019	—			0.04 (0.01, 0.10)	32.33	5	115
Modi 2020	◆───			0.00 (0.00, 0.07)	19.47	0	54
Bartsch 2022	+			0.00 (0.00, 0.22)	6.73	0	15
Subtotal (I ² = 31.91%, p = 0.22)	\sim			0.02 (0.00, 0.05)	100.00		
					_		_
	0.1	.2	.3	.4			
		Proportion					

For the 2 randomized control-arm trials, adverse events were analyzed for all grade (Figure 4 and Supplemental Table 4) and grade \geq 3 (Figure 5 and Supplemental Table 4) with results reported as odds ratio (OR) and 95% CI). In terms of all grade adverse events, all were statistically significant, except for thrombocytopenia. In particular, the odds of ILD was higher in T-DXd compared to controls with an odds ratio of 9.32 (95% CI: 2.41, 36.03), and higher for nausea (OR: 7.73; 95% CI: 5.82, 10.26). There was no evidence of a significant difference for grade \geq 3 adverse events except for nausea (OR: 17.93; 95% CI: 3.46, 92.81).

Efficacy Analysis

PFS data was presented in all included trials (2 controlled trials and 3 single-arm studies) (Table 2). The median PFS varied from 11.1 to 22.1 months for single-arm studies. In the 2 controlled trials, the pooled OR for progression or death was 0.38 (95% CI: 0.32, 0.45), indicating a longer PFS in the T-DXd group (Figure 6). The OS data from the controlled trials had a pooled OR of 0.61 (95% CI: 0.48, 0.78) (Figure 6). Overall response rates (ORR) of patients with breast cancer treated with T-DXd ranged from 37% to 79.9%.

Figure 4 All grade adverse events ORs and 95% CI of random model control-arm trials.

Study or Subgroup	T-DX Events	d Total	Contro Events	ol Total	Weight	Odds Ratio M-H, Random, 95% CI	Odds Ratio M-H, Random, 95% Cl
L.Z.I Anaemia		255			10.00	2 64 14 20 4 2 3	_
Lortes 2022	/8	257	37	261	48.8%	2.64 [1.70, 4.09]	
viodi 2022	123	371	39	172	51.2%		
Fotol overt-	201	028	70	433	100.0%	2.10 [1.30, 3.25]	
lotal events	201	: ² 2 0	ب عد ا ۱۵	1 /D	0.15).12	F 20/	
Fest for overall effect	= 0.05; Ch : Z = 3.34	P = 2.0 (P = 0.1)	.0008)	1 (P =	0.15); 1- =	- 52%	
1.2.2 Neutropenia							
Cortés 2022	110	257	29	261	49.9%	5.99 [3.79, 9.47]	
Modi 2022	123	371	88	172	50.1%	0.47 [0.33, 0.68]	
subtotal (95% Cl)		628		433	100.0%	1.68 [0.14, 20.30]	
Fotal events	233		117	.		2	
Heterogeneity: Tau ² = Fest for overall effect	= 3.19; Ch : Z = 0.41	$i^2 = 71$ (P = 0.	.85, df = .68)	= 1 (P <	< 0.00001); I ² = 99%	
1.2.5 Nausea							_
Cortés 2022	187	257	72	261	54.1%	7.01 [4.77, 10.32]	
Modi 2022	271	371	41	172	45.9%	8.66 [5.69, 13.17]	
Suptotal (95% CI)		628	1.1.2	433	100.0%	7.73 [5.82, 10.26]	▼
lotal events	458	:2 0 -	113 113	1 /P	0 471-12	00/	
Teterogeneity: Tau ² = Test for overall effect	z = 0.00; Ch z = 14.1	1 (P < 0	0.00001)) 1 (P =	U.47); I ⁻ =	= U%	
1.2.6 Vomiting							_
Cortés 2022	113	257	15	261	49.5%	12.87 [7.23, 22.91]	
4odi 2022	126	371	17	172	50.5%	4.69 [2.72, 8.09]	
Suptotal (95% CI)		628		433	100.0%	7.73 [2.88, 20.80]	
Heterogeneity: Tau ² = Fest for overall effect	= 0.43; Ch : Z = 4.05	$i^2 = 6.2$ (P < 0.	22, df = 1 .0001)	1 (P =	0.01); I ² =	- 84%	
1.2.8 Constipation							
Cortés 2022	58	257	25	261	50.5%	2.75 [1.66, 4.56]	
Modi 2022	79	371	22	172	49.5%	1.84 [1.11, 3.08]	⊢ ∎−
Subtotal (95% CI)		628		433	100.0%	2.26 [1.53, 3.34]	•
Fotal events	137	_	47				
Heterogeneity: Tau ² = Fest for overall effect	= 0.01; Ch : Z = 4.07	$i^2 = 1.1$ (P < 0.	19, df = 1 .0001)	1 (P =	0.28); l ² =	= 16%	
1.2.9 Fatigue							
Cortés 2022	115	257	77	261	50.1%	1.94 [1.35, 2.78]	
1odi 2022	177	371	73	172	49.9%	1.24 [0.86, 1.78]	₩
subtotal (95% CI)		628		433	100.0%	1.55 [1.00, 2.40]	◆
Fotal events	292	.2 -	150		o o o > - ?		
Heterogeneity: Tau ² = Fest for overall effect	= 0.07; Ch : Z = 1.95	$i^2 = 2.9$ (P = 0.	91, df = 1 .05)	1 (P =	0.09); l ² =	- 66%	
1.2.11 Drug-related	interstiti	al lung	disease				
Cortés 2022	27	257	5	261	68.0%	6.01 [2.28, 15.87]	│∎
Modi 2022	45	371	1	172	32.0%	23.60 [3.23, 172.72]	
Subtotal (95% CI)		628		433	100.0%	9.32 [2.41, 36.03]	
Fotal events	72	2	6				
Heterogeneity: Tau ² = Fest for overall effect	= 0.46; Ch : Z = 3.23	$i^2 = 1.7$ (P = 0.	71, df = 1 .001)	1 (P =	0.19); l ² =	= 42%	
							0.01 0.1 1 10 100 Favours T-DXd Favours control

Discussion

Trastuzumab deruxtecan (T-DXd) is a promising novel ADC for treating patients with both HER2-positive and HER2-low breast cancer. Although treatment outcomes have significantly improved for HER2-positive breast cancer patients in recent years, many patients still progress on the currently available therapies. Thus, novel agents such as T-DXd are the subject of great interest. This study explores the pooled efficacy and safety profiles of T-DXd specifically in the treatment of breast cancer patients.

According to our analysis, the most common adverse events associated with T-DXd in all grades were nausea, fatigue, vomiting, anemia, constipation, neutropenia, and diarrhea. In terms of adverse events of grade 3 or more, only anemia and neutropenia

Figure 5 Grade \geq 3 adverse events ORs and 95% Cl of random model control-arm trials.



Efficacy and Safety of Trastuzumab Deruxtecan in Breast Cancer

Table 2 PFS and ORR of Control-Arm and Single-Arm Trials

Control Arm Trials:								
Study		PFS (Median Mo)						
	T-DXd	Control	OR (95% CI)					
Cortés 2022	NR	6.8	NR (18.5, NE)	79.9 (74.3-84.4)				
Modi 2022	9.9	5.1	0.50 (0.40, 0.63)	52.3 (47.1-57.4)				
Single arm trials:								
Study	Median PFS (9	5% CI) (Mo)		ORR (%)				
Modi 2019	16.4 (12.	7, NR)		60.9 (53.4-68.0)				
Tamura 2019	22.1 (NE)		59.5 (49.7-68.7)				
Modi 2020	11.1 (7.	6, NE)		37.0 (24.3-51.3)				
Bartsch 2022	14 (11,	NR)		62.5 (24.5-91.5)				

Abbreviations: CI = confidence interval; NR = not reached; NE = not estimable; OR = odds ratio; ORR = overall response rate; PFS = progression-free survival.

Figure 6 ORs and 95% CI for PFS and OS in Control-Arm Trials



occurred at a relatively high rate. The rate of nausea (72.8% vs. 73%) and anemia (30.4% vs. 33.2%) was similar in both randomized control trials, while neutropenia occurred more frequently in the study by Cortés et al., occurring in 42.8% of patients treated with T-DXd, with 19.1% experiencing neutropenia of grade \geq 3. The adverse events rates were similar among the single-arm trials, with only the study by Bartsch et al. differing in terms of the rate of anemia, fatigue, nausea, and vomiting, most likely due to the small number of participants in this study (n = 15).

Of note, drug-related ILD is a life-threatening adverse event and despite its low incidence, the high OR value (9.32, CI 95%: 2.41, 36.03) shows a definite association between T-DXd treatment and ILD, although the CI was very large. This association is now well recognized and with close monitoring for symptoms, prompt discontinuation of treatment and early intervention with systemic corticosteroids, the severity of this adverse event may be successfully reduced.^{15,19,20} This is evidenced by a reduction in mortality as a result of drug-related ILD or pneumonitis in more recent trials. For example, the rate of death attributable to ILD or pneumonitis in earlier trials such as Tamura et al. 2019 was more than double that of more recent trials such as Cortés et al. 2022 (1.7% and 0.77%, respectively).^{14,16} Patients who experience grade 1 ILD may continue treatment with T-DXd either at a maintained or reduced dose, depending on the severity, following interruption of treatment and complete resolution of ILD. However, patients who experience symptomatic ILD (grade 2 or 3), must permanently discontinue treatment.²¹ Our analysis showed that treatment with T-DXd had an acceptable safety profile. The relative safety of this agent may be attributable to its stability in plasma, with cleavage of its linker by lysosomal enzymes occurring only in tumor cells.²²

This analysis also explored the efficacy of T-DXd in terms of PFS, OS and ORR. As demonstrated in single-arm trials, T-DXd stabilized disease for between 11 and 22 months. In the control-arm trials, T-DXd was more effective both in terms of PFS and OS, compared to the control. Cortés et al. compared T-DXd with T-DM1, and Modi et al. compared T-DXd treatment with the physician's choice of therapy. When compared to previous targeted therapies against HER2, such as T-DM1, T-DXd was more effective in treating patients with metastatic HER2-positive breast cancer. For example, recent studies evaluating the efficacy of T-DM1 for metastatic disease after pertuzumab and trastuzumab in combination with a taxane, such as the KATE2 trial, median PFS ranged from 3.0 to 6.8 months.²³ The durable antitumor activity of T-DXd is also shown by the impressive objective response rates (ORR) in patients with HER2-positive and HER2-low advanced or metastatic breast cancer, with ORRs of up to 79.9% achieved.

This study is subject to a number of limitations. Firstly, the dose of T-DXd evaluated in the included trials varied from 5.4 to 7.4 milligrams per kilogram of body weight. Results from dose escalation and expansion studies have now established 5.4 mg/kg as the recommended dose, based on having clinical activity comparable with higher doses, improved tolerability and an acceptable safety profile. Moreover, differences in breast tumor type existed, with HER2-positive and HER2-low tumors being included in both the advanced and metastatic setting. For example, 1 study investigated the efficacy of T-DXd in patients with HER2-positive breast cancer with newly diagnosed brain metastases only, which markedly influences survival outcomes.¹⁸ Furthermore, various prior treatments were received by patients in the different studies. In addition, studies were limited to those written in English. Overall, there is a small number of studies included in this analysis, and the majority of them were single-arm trials. Therefore, further large, randomized control trials are needed to accurately evaluate the efficacy and safety of T-DXd in breast cancer.

The present systematic review demonstrates the durable antitumor activity of T-DXd in breast cancer. T-DXd is a relatively safe agent, with the most common adverse events being nausea, fatigue, vomiting, constipation, neutropenia, and anemia. Of these, neutropenia and anemia tended to occur most frequently with high grades. ILD is a notable adverse event and requires close monitoring and early intervention to reduce its severity. In conclusion, T-DXd is a safe and effective agent in the treatment of advanced or metastatic breast cancer based on currently available data, and further studies are required to fully elucidate its potential.

Disclosure

The authors have stated that they have no conflicts of interest.

Ethical Approval

Not required.

Author Contributions

All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by Gavin P. Dowling, Gordon R. Daly, Stephen Keelan and Fiona Boland. The first draft of the manuscript was written by Gavin P. Dowling and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Supplementary material

Six domains were adapted to assess bias in the studies:

Supplemental Table 1	Newcas	Newcastle-Ottawa Adapted to Include Single-Arm Trials						
		i. Representativeness of the exposed cohort,						
		ii. Ascertainment of exposure,						
		iii. Demonstration that the outcome of interest was not present at start of study,						
		iv. Assessment of outcome,						
		v. Follow-up long enough for outcomes to occur and,						
		vi. Adequacy of the cohort follow-up.						

The information was presented as domains fulfillment, a study that fulfill all domains ("6 of 6 NOS domains met") from adapted NOS, is considered at low risk of bias. Fulfillment is denoted by "*."

Article	i	ii	iii	iv	v	vi
Modi 2019	*	*	*	*	*	*
Tamura 2019	*	*	*	*	*	*
Modi 2020	*	*	*	*	*	*
Cortés 2022	*	*	*	*	*	*
Modi 2022	*	*	*	*	*	*
Bartsch 2022	*	*	*	*	*	*

Supplemental Table 2	Supplemental Table 2 Any Grade Adverse Event Rates of Single-Arm Trials (Pooled Prevalence, 95% CI)									
Adverse Event	Modi 2019	Tamura 2019	Modi 2020	Bartsch 2022	Overall (Random Effects Model)	²				
Anemia	0.30 (0.24, 0.37)	0.39 (0.31, 0.48)	0.39 (0.27, 0.52)	0.53 (0.29, 0.76)	0.36 (0.29, 0.44)	44.71%				
Constipation	0.36 (0.29, 0.43)	0.37 (0.28, 0.46)	0.39 (0.27, 0.52)	0.40 (0.19, 0.65)	0.36 (0.32, 0.42)	0%				
Diarrhea	0.29 (0.23, 0.36)	0.37 (0.29, 0.47)	0.46 (0.34, 0.60)	0.40 (0.19, 0.65)	0.36 (0.28, 0.44)	49.97%				
Interstitial lung disease	0.14 (0.09, 0.19)	0.05 (0.02, 0.11)	0.15 (0.08, 0.27)	0.07 (0.01, 0.35)	0.10 (0.05, 0.16)	48.99%				
Nausea	0.78 (0.71, 0.83)	0.79 (0.71, 0.86)	0.76 (0.63, 0.86)	0.47 (0.24, 0.71)	0.76 (0.68, 0.83)	57.43%				
Neutropenia	0.35 (0.28, 0.42)	0.28 (0.20, 0.37)	0.30 (0.19, 0.43)	0.47 (0.24, 0.71)	0.32 (0.27, 0.37)	3.59%				
Vomiting	0.46 (0.39, 0.53)	0.52 (0.43, 0.61)	0.44 (0.32, 0.58)	0.20 (0.07, 0.47)	0.47 (0.42, 0.52)	43.87%				
Fatigue	0.50 (0.42, 0.57)	0.44 (0.36, 0.54)	0.37 (0.25, 0.51)	0.80 (0.53, 0.93)	0.45 (0.37, 0.53)	64.02%				

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Supplemental Table 3 Grade \geq 4 Adverse Event Rates of Single-Arm Trials (Pooled Prevalence, 95% CI)							
Adverse Event	Modi 2019	Tamura 2019	Modi 2020	Bartsch 2022	Overall (Random Effects Model)	²	
Anemia	0.09 (0.05, 0.14)	0.17 (0.12, 0.25)	0.15 (0.08, 0.27)	0.07 (0.01, 0.35)	0.12 (0.07, 0.17)	37.49%	
Constipation	0.01 (0.00, 0.04)	0.01 (0.00, 0.06)	0.01 (0.00, 0.13)	0.03 (0.00, 0.35)	0.00 (0.00, 0.01)	0%	
Diarrhea	0.03 (0.01, 0.06)	0.02 (0.00, 0.07)	0.06 (0.02, 0.16)	0.07 (0.01, 0.35)	0.02 (0.01, 0.04)	0%	
Interstitial lung disease	0.01 (0.00, 0.04)	0.01 (0.00, 0.06)	0.06 (0.02, 0.16)	0.03 (0.00, 0.35)	0.01 (0.00, 0.03)	45.49%	
Nausea	0.08 (0.04, 0.12)	0.04 (0.01, 0.09)	0.04 (0.01, 0.14)	0.03 (0.00, 0.35)	0.05 (0.02, 0.07)	0%	
Neutropenia	0.21 (0.15, 0.27)	0.14 (0.09, 0.21)	0.20 (0.12, 0.33)	0.03 (0.00, 0.35)	0.15 (0.08, 0.23)	27.17%	
Vomiting	0.04 (0.02, 0.09)	0.04 (0.02, 0.10)	0.01 (0.00, 0.13)	0.03 (0.00, 0.35)	0.02 (0.00, 0.05)	0%	
Fatigue	0.06 (0.03, 0.11)	0.04 (0.02, 0.10)	0.04 (0.01, 0.14)	0.13 (0.03, 0.41)	0.05 (0.03, 0.07)	0%	

Supplemental Table 4 OR Values and Models of Control-Arm Trials Adverse Events, Random Effects Model

Control-Arm Trials:								
	All	Grade	Grad	e ≥3				
Adverse Events	Odds Ratio (95% CI)	²	Odds Ratio (95% CI)	²				
Neutropenia	1.68 (0.14, 20.30)	99%	1.30 (0.04, 43.14)	98%				
Anemia	2.10 (1.36, 3.25)	52%	1.59 (0.90, 2.80)	0%				
Nausea	7.73 (5.82, 10.26)	0%	17.93 (3.46, 92.81)	0%				
Leukopenia	1.54 (1.14, 2.09)	97%	2.11 (0.02, 203.93)	95%				
Fatigue	1.55 (1.00, 2.40)	66%	2.94 (0.75, 11.60)	63%				
Diarrhea	2.53 (1.75, 3.65)	94%	0.69 (0.18, 2.59)	0%				
Constipation	2.26 (1.53, 3.34)	16%	Not estimable					
Interstitial lung disease	9.32 (2.41, 36.03)	42%	4.16 (0.74, 23.23)	0%				
Vomiting	7.73 (2.88, 20.80)	84%	4.47 (0.78, 25.78)	0%				
Thrombocytopenia	0.70 (0.53, 0.92)	98%	1.29 (0.03, 61.24)	93%				