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Efficacy and safety of antibody-drug conjugates in pretreated HER2-low metastatic breast cancer: A systematic review and network meta-analysis

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ABSTRACT

Introduction: Antibody-drug conjugates (ADCs) trastuzumab-deruxtecan (T-DXd) and sacituzumab-govitecan (SG) provided significant progression-free survival (PFS) and overall survival (OS) improvements over chemotherapy (CT) in pretreated hormone receptor-positive (HR+) and triple-negative (TN)/HER2-low metastatic breast cancer

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HER2-low
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(MBC). However, no direct comparison between the two exists, nor with the more recent datopotamab-deruxtecan (Dato-DXd).

Methods: We conducted a network meta-analysis (NMA) to compare efficacy and safety of T-DXd and SG in CT-pretreated HR+ and TN/HER2-low MBC and assess their benefit over standard CT, exploring also a comparison with Dato-DXd. Hazard ratios (HRs) with 95 % confidence intervals (CI) were calculated for PFS/OS. P-score was used for treatment ranking.

Results: Three RCTs (956 patients) were included in the primary analysis and 5 (1,445) in the exploratory NMA with Dato-DXd. In HR+/HER2-low, T-DXd showed no significant difference in PFS and OS when compared to SG. Similarly, in TN/HER2-low, PFS and OS did not differ significantly between the two ADCs. The P-score analysis favored T-DXd over SG in HR+/HER2-low in PFS (0.90 vs. 0.60) and OS (0.89 vs. 0.60). SG was favored over T-DXd in OS in TN/HER2-low (0.80 vs. 0.69). Similar results were obtained for HR+ MBC when including Dato-Dxd, which showed the worst performance, while T-DXd was the only ADC significantly outperforming CT in OS. The ADCs showed significantly better PFS and OS than CT in HR+/HER2-low and TN/HER2-low (all $p < 0.001$). SG had higher rates of neutropenia, diarrhea and alopecia vs. T-DXd, which showed more thrombocytopenia, fatigue and nausea. Pneumonitis and cardiotoxicity were typically T-DXd-related, and T-DXd showed more toxicity-related discontinuations.

Conclusions: Similar efficacy with T-DXd and SG in HER2-low MBC was observed, regardless of HR status. Safety profile, local drug-approval criteria and guidelines, patients' preferences and overall quality of evidence should ultimately guide therapeutic decision-making. Dato-DXd role remains uncertain.

Introduction

HER2-low breast cancer (BC) represents 32 %–65 % of all human epidermal growth factor receptor 2 (HER2)-negative breast tumors[1,2]. It is currently defined as all HER2-negative BC with a HER2 score by immunohistochemistry (IHC) of 1+, or 2 + according to ASCO/CAP guidelines, without *ERBB2* gene amplification by *in situ* hybridization (ISH)[3]. While accumulating evidence support that this BC subgroup should not be considered as an independent nosological entity[1,4–9], its clinical relevance is currently based on its targetability by novel antibody-drug conjugates (ADCs) directed against HER2, such as trastuzumab deruxtecan (T-DXd). This potent anti-HER2 ADC unexpectedly showed impressive efficacy in this group of patients without HER2-overexpressing tumors[10]. After showing notable improvements in progression-free survival (PFS) and overall survival (OS) over standard chemotherapy (CT) in chemo-pretreated metastatic HER2-low BC in the DESTINY-Breast04 phase III randomized controlled trial (RCT), regardless of hormone receptor status, T-DXd was approved by all major regulatory agencies. At the same time, a novel ADC targeted against surface antigen TROP2, namely sacituzumab govitecan (SG), demonstrated significant improvements in PFS and OS in both chemo-pretreated metastatic triple negative breast cancer (mTNBC) in the ASCENT phase III RCT and in metastatic hormone receptor-positive (HR+)/HER2-negative BC pretreated with endocrine therapy (ET) and CT in the TROPiCS-02 phase III RCT[11–13]. Hence, SG was approved for pretreated HER2-negative metastatic breast cancer (MBC). This has led to the possibility of potentially using both T-DXd and SG in the context of HER2-low MBC. However, the two drugs have not been compared in RCT, nor will likely be in the next few years. Moreover, uncertainties exists regarding their correct therapeutic sequencing in HR+ and triple negative (TN) MBC, as both drugs feature an anti-topoisomerase I cytotoxic payload[14,15]. Separate efficacy data for HR+/HER2-low and TN/HER2-low MBC were provided in the DESTINY-Breast04, and recent subgroup analyses of efficacy of SG in HER2-low disease were presented for both the ASCENT and TROPiCS-02 trials. Considering this background, here we present a systematic review and network meta-analysis (NMA) to compare the efficacy and safety of the two ADCs and confirm their superiority over single-agent CT in HR+/HER2-low and TN/HER2-low MBC, already pretreated with CT in the metastatic setting[16]. We also performed an exploratory analysis including patients treated with T-DXd as upfront CT-based treatment in the context of the novel DESTINY-Breast06 RCT and patients treated with another anti-TROP2 ADC with the potential to be approved in the near future for HR+/HER2-negative MBC, namely datopotamab-deruxtecan (Dato-DXd)[17,18].

Methods

Literature search and data extraction

We included in the primary study analyses only the most up-to-date results from the pivotal phase III RCTs of T-DXd and SG administered in HR+ and TN HER2-low MBC treated with at least 1 line of CT in the metastatic setting. PubMed database was used for the systematic literature search. The search query was the following: (trastuzumab deruxtecan OR sacituzumab govitecan) AND breast AND (advanced OR metastatic) and was launched on January 18th, 2024. Additionally, online archives of main international oncology congresses, including the San Antonio Breast Cancer Symposium (SABCS), the European Society for Medical Oncology (ESMO) annual congress, the ESMO Breast annual congress and the American Society of Clinical Oncology (ASCO) annual meeting were screened in January 2024. The literature search was performed by SN and FS. In addition, an exploratory expanded analysis was performed on November 2024, including results from the DESTINY-Breast06 and TROPION-Breast01 phase III RCTs[17,18]. These studies were not included in the primary analysis because the former was conducted in CT-naïve patients for the metastatic setting, and the latter included the anti-TROP2 ADC Dato-DXd that is currently not available in the clinical practice scenario. Moreover, results restricted to the HER2-low population have not been disclosed so far for Dato-DXd. In all published trials, T-DXd, SG and Dato-DXd were compared to a treatment of physician's choice (TPC) based on single-agent CT (Table 1) [11,13,17–19]. For the selected studies the following variables were extracted: NCT code, study population, year of publication, study sample size, sample size for experimental and control arm, published hazard ratios (HR) for PFS and OS, and the proportion of the most clinically-relevant toxicities of any grade (G) and of $G \geq 3$ according to Common Terminology Criteria for Adverse Events (CTCAE) [11,13,18–21]. Kaplan-Meier curves of PFS and OS in the HER2-low population were digitalized to extract individual patient data (IPD). The reconstruction quality was assessed through a comprehensive examination of estimated hazard ratios (HRs), the shape of Kaplan-Meier curves, the median PFS and OS, the survival rates at specific timepoints and numbers at risk tables.

The project was registered in the Open Science Framework online database with DOI https://doi.org/10.17605/OSF.IO/JG63N.

Study endpoints

The primary endpoint for this study was PFS of T-DXd vs. SG in CT-pretreated HR+/HER2-low and TN/HER2-low. Secondary endpoints

were OS of T-DXd vs. SG in CT-pretreated HR+/HER2-low and TN/HER2-low, PFS and OS of T-DXd and SG vs. standard CT, a comparison of safety for main treatment-related adverse events (TRAEs) between T-DXd and SG in late lines. Exploratory endpoints included PFS and OS comparisons of T-DXd, SG and Dato-DXd in HR+/HER2-low without restriction for treatment line and a description of the most common TRAEs associated to Dato-DXd. PFS was defined as the time from randomization to disease progression or death from any cause, whichever occurred first. OS was defined as the time from randomization to death from any cause.

Statistical analysis

A NMA with a frequentist framework was performed to simultaneously compare all study treatments. To summarize the overall effect, HRs with 95 % CI were calculated for the PFS and OS analysis. Random-effects models were fitted for all the analysis regardless the amount of heterogeneity of the model (estimated by means of I^2), assuming that there is not one true intervention effect but a distribution of true intervention effect. To evaluate the inconsistency of the network, the transitivity assumption could not be evaluated as no direct comparisons from published RCTs could be included in this NMA. The ranking of treatments for each outcome was performed using the P-score, which measures the extent of certainty that a treatment is better than another, averaged over all competing treatments[22]. Possible values of the P-score range between 0 and 1; higher values correspond to a higher ranking (i.e., better results when referred to efficacy). A specific cut-off to declare that a difference between different scores is meaningful has not been established, therefore P-score differences should be critically evaluated in combination with other evidence, clinical expertise and patients preferences. For the extracted IPD meta-analysis, a stratified Cox model was used to estimate HRs with the study as a stratification factor to compare the overall ADC effect on PFS and OS against standard CT in HR+/HER2-low and TN/HER2-low, separately. The rates of each TRAE occurring in $\geq$ 20 % of patients for at least one of the two ADCs and other TRAEs of interest (i.e. cardiotoxicity and interstitial lung disease [ILD]) were compared with χ^2 test. Statistical significance was considered for $p < 0.05$. For SG, the jointed cohorts of the ASCENT and TROPiCS-02 trials were considered. A risk of bias analysis (RoB) was performed according to Cochrane RoB assessment tool included in RevMan vers. 5.4 (The Cochrane Collaboration, London, UK) for MacOS X. No data imputation was performed. All analyses were undertaken using R statistical software version 4.3.1 (R packages *metafor* and *meta*).

Results

A total of 3 RCTs (956 patients) met the eligibility criteria for the primary analyses of efficacy and safety [11,13,19,20] and 5 (1,445 patients) for the exploratory analyses of PFS and OS [11,13,17–20]. Study selection is reported in Fig. 1. All studies were phase III RCTs. The TROPiCS-02 and TROPION-Breast01 were specifically designed for HR+/HER2-negative MBC, the ASCENT was designed for mTNBC, the DESTINY-Breast04 was specifically designed for HER2-low BC and primarily of HR+ histology, as TNBC represented a small exploratory subcohort, whilst the DESTINY-Breas06 only included HR+/HER2-low MBC and a small subset of HR+/HER2-ultralow tumors (HER2 IHC 0 with incomplete or faint staining in $>$ 0 and $\leq$ 10 % of invasive tumor cells), excluded from this NMA[17]. With the exception of the DESTINY-Breast06, these trials included pretreated patients with MBC that had received at least 1 line of CT in the advanced setting and, in the case of

Table 1
Main characteristics of the studies included in the principal and expanded network *meta*-analysis.

Clinical trial	Year*	Sample size	Study design	Key inclusion criteria	Proportion of HER2-low and HER2-0	Study treatments	Allowed drugs as TPC	Primary endpoint
DESTINY-Breast04 (NCT03734029)	2022	557	Phase III, randomized, open label (R 2:1)	HR+/TNBC HER2-low (IHC 1 + or IHC 2+/ISH-) 1-2 previous CT lines 1 previous ET line	88.6 % HR+ 11.3 % TNBC	E: T-DXdC: TPC	Eribulin, capecitabine, nab-paclitaxel, gemcitabine or paclitaxel	PFS by BICR in HR+
ASCENT (NCT02574455)	2022/ 2024	529#	Phase III, randomized, open label (R 1:1)	TNBC ≥2 previous CT lines (prior exposure to a taxane)§	65.7 % HER2-low 34.2 % HER2-0	E: SGC: TPC	Eribulin, vinorelbine, capecitabine or gemcitabine	PFS by BICR in patients without baseline BM
TROPiCS-02 (NCT03901339)	2023	543#	Phase III, randomized, open label (R 1:1)	HR+/HER2- 2-4 previous CT lines (prior exposure to taxanes in any setting) 1 previous ET line and a CDK4/6i-based regimen	57.0 % HER2-low 43.0 % HER2-0	E: SGC: TPC	Eribulin, vinorelbine, capecitabine or gemcitabine	PFS by BICR
DESTINY-Breast06 (NCT04494425)	2024	866°	Phase III, randomized, open label (R 1:1)	HR+/HER2-low (IHC 1 + or IHC 2+/ISH-) and ultralow (IHC 0 +) ≥ 2 previous ET lines or PD ≤ 6 months from the start of a CDK4/6i-based regimen, no CT for MBC	100 % HR+	E: T-DXdC: TPC	Capecitabine, nab-paclitaxel or paclitaxel	PFS by BICR in HER2-low
TROPION-Breast01 (NCT05104866)	2024	732	Phase III, randomized, open label (R 1:1)	HR+/HER2- 1-2 previous CT lines ≥1 ET line or no ET if unsuitable	100 % HR+/ HER2-	E: Dato-DXdC: TPC	Eribulin, vinorelbine, capecitabine or gemcitabine	PFS and OS by BICR (dual primary endpoint)

Legend. BICR: blinded independent central review; BM: brain metastasis; C: control arm; CDK4/6i: cyclin-dependent kinase 4/6 inhibitor; CT: chemotherapy; E: experimental arm; ET: endocrine therapy; HER2: human epidermal growth factor receptor 2; HR: hormone receptor; IHC: immunohistochemistry; ISH: *in situ* hybridization; MBC: metastatic breast cancer; OS: overall survival; PD: disease progression; PFS: progression-free survival; R: randomization; SG: sacituzumab govitecan; T-DXd: trastuzumab deruxtecan; TNBC: triple negative breast cancer; TPC: treatment of physician's choice; +: positive: −: negative. *: year of publication of the results of the analysis in the HER2-low population; #: including HER2-0; §: in the ASCENT trial enrollment was also allowed after 1 CT in advanced setting in case of progression during or within 12 months from the completion of (neo)adjuvant CT; °: the HER2-ultralow population also included in the DESTINY-Breast06 was excluded from this analysis but the total number of patients is referred to the entire intention-to-treat population.

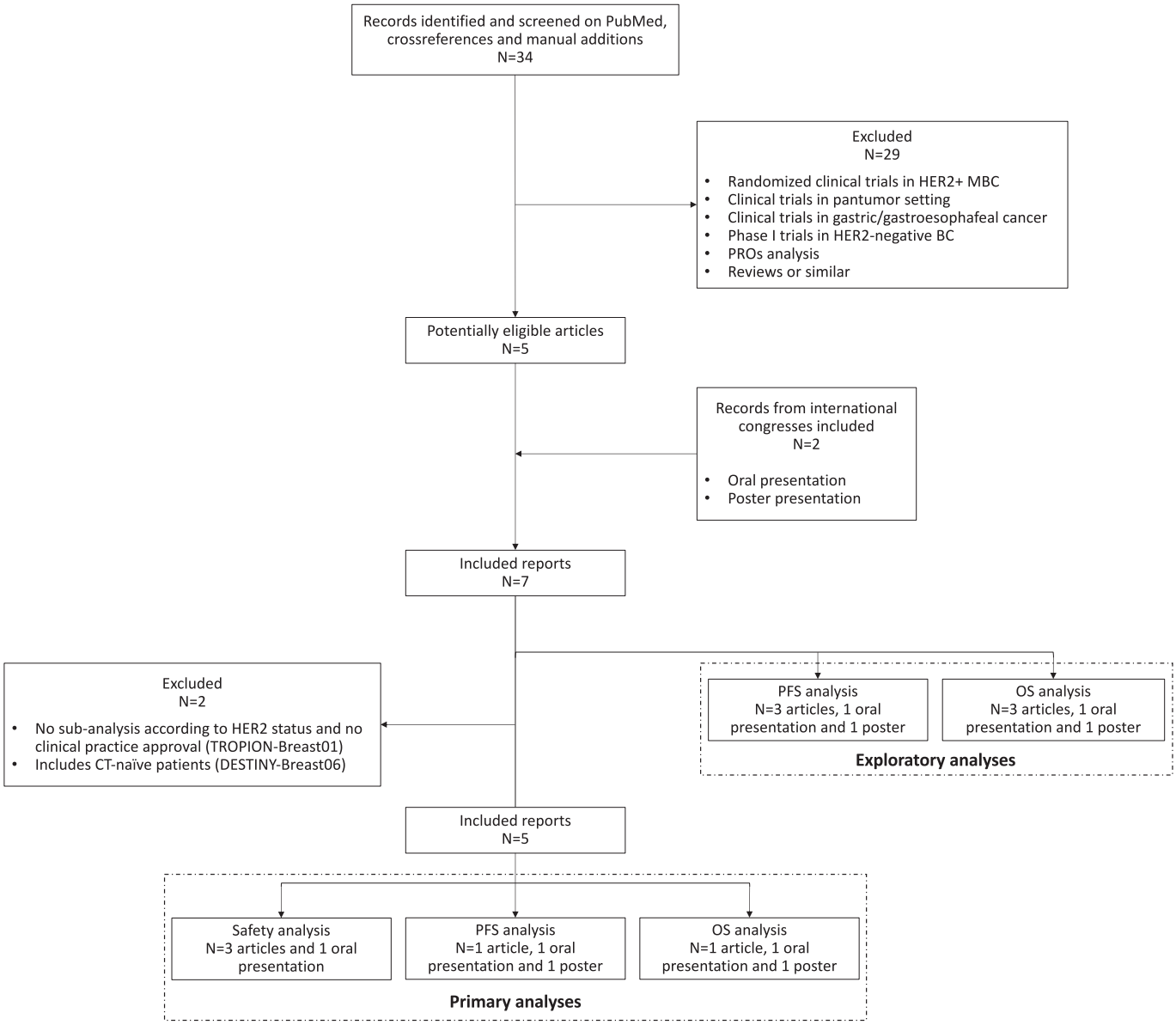

Fig. 1. PRISMA flow chart**. Legend**. BC: breast cancer; MBC: metastatic breast cancer; CT: chemotherapy; HER2: human epidermal growth factor receptor 2; OS: overall survival; PFS: progression-free survival; PROs: patient-reported outcomes; +: positive.

DESTINY-Breast04, DESTINY-Breast06, TROPION-Breast01 and TROPiCS-02, at least 1 or 2 lines of ET. The median number of prior CT lines in the metastatic setting was 3 (range: 0–8) in the TROPiCS-02 and 3 (range: 1–16) in the ASCENT. Regarding DESTINY-Breast04, 28.3 % patients in the HR+/HER2-low and 55.2 % patients in the TN/HER2-low cohort had received 2 prior lines of CT in the metastatic setting. In the TROPION-Breast01 38.1 % of patients had received at least 2 lines of CT. All patients had received CDK4/6-inhibitors + ET in the TROPiCS-02, 70.4 % in the HR+ DESTINY-Breast04 cohort, 88.9 % in the HER2-low cohort of the DESTINY-Breast06 and 82.5 % in the TROPICS-Breast01. There is an important difference in the number of highly pretreated patients among the 5 studies, with 62.1 % of patients in the DESTINY-Breast04, 86.1 % in the ASCENT, 98.9 % in the TROPiCS-02, 15.6 % in the DESTINY-Breast06 and 37.7 % in the TROPION-Breast01 receiving at least 3 metastatic lines (considering both CT and ET, if HR+) before study treatment administration ($p < 0.001$). In the TROPiCS-02, if not considering previous CDK4/6-inhibitor-based regimens and other possible ET, 57.6 % had received at least 3 previous CT lines.

A total of 69.8 % of patients presented with liver metastases in the DESTINY-Breast04, 66.6 % in the DESTINY-Breast06, 86.6 % in the TROPiCS-02, 71.9 % in the TROPION-Breast01 and 42.6 % in the ASCENT trial, respectively. All studies could include patients with stable brain metastases (BM), but the proportion *per* trial was low, being 5.7 % for the DESTINY-Breast04, 8.1 % for the DESTINY-Breast06, 12.0 % for the ASCENT and 7.9 % for the TROPION-Breast01 trial, respectively [23]. The proportion was not reported for the TROPiCS-02. Other main trial features are reported in Table 1.

Efficacy

In terms of PFS and OS, both T-DXd and SG presented statistically significant better outcomes than TPC. Specifically, T-DXd showed better results than TPC in PFS (HR: 0.51, 95 %CI: 0.40–0.65) and OS (HR: 0.64, 95 %CI: 0.48–0.86) in HR+/HER2-low, as well as in TN/HER2-low, (PFS HR: 0.46, 95 %CI: 0.24–0.89 and OS HR: 0.48, 95 %CI: 0.24–0.95). SG also showed statistically significant improvements compared to TPC in HR+/HER2-low (PFS HR: 0.60, 95 %CI: 0.44–0.82 and OS HR: 0.75, 95

%CI: 0.57–0.98), and in TN/HER2-low (PFS HR: 0.44, 95 %CI: 0.27–0.72 and OS HR: 0.43, 95 %CI: 0.28–0.67) (Fig. 2A and B). Similar results were observed in HR+ disease with regard to PFS when also including Dato-DXd in the NMA. However, only T-DXd was significantly superior to TPC in terms of OS (HR: 0.74, 95 %CI: 0.57–0.95) in this case (Fig. 2C). When comparing T-DXd with SG, neither significant differences were observed between the two ADCs in HR+/HER2-low MBC (PFS HR: 0.85, 95 %CI: 0.58–1.26; OS HR: 0.85, 95 %CI: 0.58–1.27), nor in TN/HER2-low MBC (PFS HR: 1.05, 95 %CI: 0.46–2.37; OS HR: 1.12, 95 %CI: 0.49–2.52) (Fig. 2A and B). Nevertheless, the treatment ranking based on P-scores favored T-DXd over SG in HR+/HER2-low both in PFS (P-score 0.90 vs. 0.60, respectively) and OS (0.89 vs. 0.60, respectively), whilst for TN/HER2-low SG was favored over T-DXd in OS (P-score 0.80 vs. 0.69, respectively), with no meaningful difference in PFS (P-score 0.77 vs. 0.72, respectively) (Fig. 3A). Similar results were observed in HR+ disease when adding Dato-DXd to the networks. No ADC showed any superior PFS or OS when compared to the others (Fig. 2C), but P-scores still favored T-DXd in HR+/HER2-low, followed by SG, then Dato-DXd (Fig. 3B). TPC was clearly unfavored in all therapeutic scenarios in comparison to both T-DXd and SG at the trial-level (Figs. 2 and 3).

At the individual patient-level, when combining T-DXd and SG, they outperformed standard CT (jointed TPC arms) in terms of PFS (median PFS [mPFS] 9.2 months, 95 %CI: 8.3–10.0 vs. mPFS 4.5 months, 95 %CI: 4.3–5.6; HR: 0.49, 95 %CI: 0.41–0.58) and OS (mOS 20.8 months, 95 % CI: 18.8–23.6 vs. mOS 14.4 months, 95 %CI: 12.8–16.2; HR: 0.64, 95 % CI: 0.53–0.78) in HR+/HER2-low. The same was observed in TN/HER2-low, both in terms of PFS (mPFS 6.9 months, 95 %CI: 5.5–8.4 vs. mPFS 2.9 months, 95 %CI: 2.0–4.2; HR: 0.43, 95 %CI: 0.29–0.64) and OS (mOS 16.5 months, 95 %CI: 13.6–20.1 vs. mOS 8.7 months, 95 %CI: 7.8–10.7; HR: 0.44, 95 %CI: 0.30–0.64) (Fig. 4).

Safety

The most frequent toxicities for T-DXd and SG were hematologic and gastrointestinal (GI) accompanied by alopecia and fatigue. In terms of hematologic toxicities, the most notable differences were observed in neutropenia, significantly higher with SG than T-DXd (66.7 % vs. 33.2

A) HR+/HER2-low

Overall survival (OS)	Progression-free survival (PFS)		
	Treatment of Physician's Choice	0.60 (0.44 - 0.82)	0.51 (0.40 - 0.65)
	0.75 (0.57 - 0.98)	Sacituzumab Govitecan	0.85 (0.58 - 1.26)
	0.64 (0.48 - 0.86)	0.85 (0.58 - 1.27)	Trastuzumab Deruxtecan

Direction of the PFS comparison

Direction of the OS comparison

B) TN/HER2-low

Overall survival (OS)	Progression-free survival (PFS)		
	Treatment of Physician's Choice	0.44 (0.27 - 0.72)	0.46 (0.24 - 0.89)
	0.43 (0.28 - 0.67)	Sacituzumab Govitecan	1.05 (0.46 - 2.37)
	0.48 (0.24 - 0.95)	1.12 (0.49 - 2.52)	Trastuzumab Deruxtecan

Direction of the PFS comparison

Direction of the OS comparison

C) HR+/HER2-low*

Overall survival (OS)	Progression-free survival (PFS)			
	Treatment of Physician's Choice	0.63 (0.49 - 0.81)	0.60 (0.42 - 0.85)	0.57 (0.47 - 0.69)
	0.84 (0.57 - 1.24)	Datopotamab Deruxtecan	0.95 (0.62 - 1.47)	0.90 (0.66 - 1.24)
	0.75 (0.52 - 1.08)	0.89 (0.52 - 1.52)	Sacituzumab Govitecan	0.95 (0.64 - 1.42)
	0.74 (0.57 - 0.95)	0.88 (0.55 - 1.40)	0.99 (0.63 - 1.53)	Trastuzumab Deruxtecan

Direction of the PFS comparison

Direction of the OS comparison

Fig. 2. Trial-level PFS and OS comparisons among ADCs and TPC. **Legend**. HER2: human epidermal growth factor receptor 2; HR+: hormone receptor-positive; SG: sacituzumab govitecan; T-DXd: trastuzumab deruxtecan; TN: triple negative; TPC: treatment of physician's choice. Orange boxes represent statistical significance. *Efficacy data for the TROPION-Breast01 trial including datopotamab deruxtecan were only provided for the entire HR+/HER2-negative population.

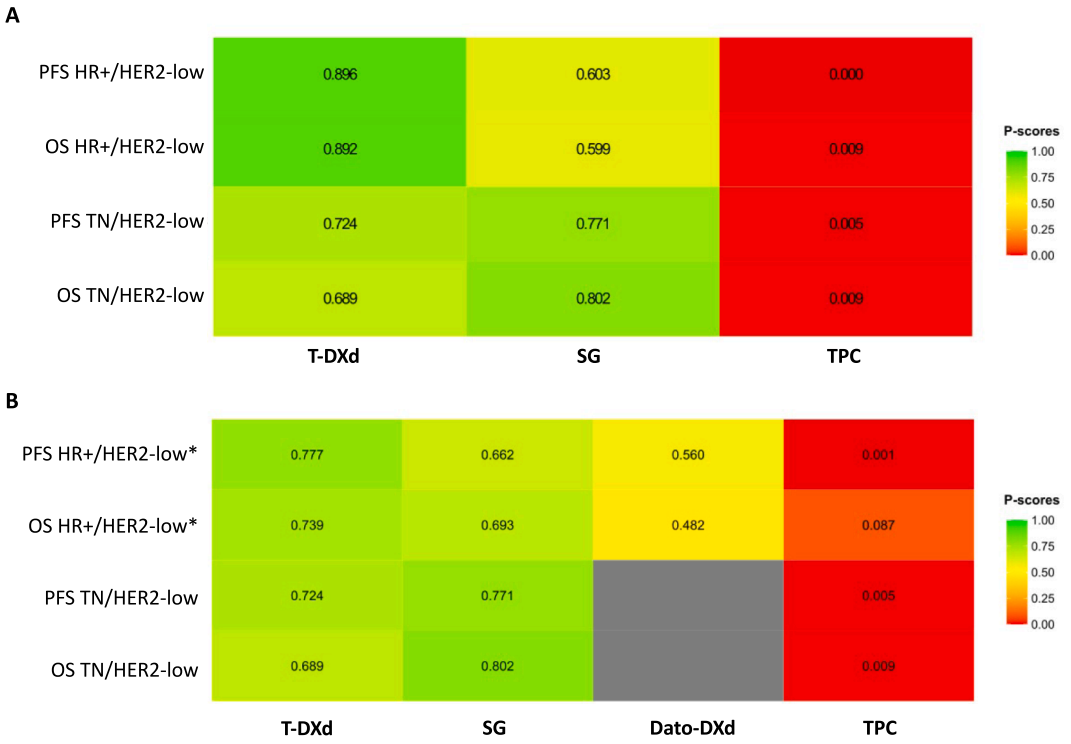

Fig. 3. Treatments' performance based on P-scores**. Legend**. (A) P-scores for the trial-level NMA including DB04, TROPiCS-02 and ASCENT trials; (B) P-scores for the trial-level NMA including all 5 RCTs. Dato-DXd: datopotamab deruxtecan; HR+: hormone receptor-positive; HER2: human epidermal growth factor receptor 2; OS: overall survival; PFS: progression-free survival; SG: sacituzumab govitecan; T-DXd: trastuzumab deruxtecan; TN: triple negative; TPC: treatment of physician's choice. *Efficacy data for datopotamab deruxtecan were only provided for the entire HR+/HER2-negative population.

%, $p < 0.001$), and thrombocytopenia, more frequent with T-DXd (23.7 % vs. 5.9 %, $p < 0.001$). The most notable differences in GI toxicities were observed with nausea, vomiting and diarrhea, the first two significantly more frequent with T-DXd (73.0 % vs. 56.1 %, $p < 0.001$ and 34.0 % vs. 23.8 %, $p < 0.001$) and the latter significantly more frequent with SG (22.4 % vs. 58.0 %, $p < 0.001$). Pneumonitis/ILD was almost only induced by T-DXd (12.1 % vs. 2.1 %, $p < 0.001$), though ≥ G3 only occurred in 2 cases (0.5 %). Alopecia was slightly more frequent with SG (37.7 % vs. 40.9 %, $p = 0.014$), while fatigue was more frequent with T-DXd (47.7 % vs. 40.9 %, $p = 0.042$). With the exception of neutropenia with SG, the proportion of ≥ G3 TRAEs always remained below 10 % (Fig. 5). Additionally, T-DXd was associated with a cardiac left ventricular dysfunction in a small proportion of patients, i.e. 17 patients (4.6 %), with a G3 decreased ejection fraction (>20 % decrease from baseline) in 5 cases (1.5 %). A dose reduction due to TRAEs was required in a similar proportion of patients between T-DXd and SG (22.6 % vs. 28.1 %, $p = 0.064$), while a significantly higher proportion of treatment discontinuations was observed with T-DXd in comparison to SG due to TRAEs (16.2 % vs. 5.5 %, $p < 0.001$) (Supplementary Table 1).

Although not formally compared, Dato-DXd showed the lowest hematologic toxicity rates (all G neutropenia 10.8 %, anemia 11.0 % and thrombocytopenia 1.9 %) and GI events rates in terms of diarrhea or constipation (all G 7.5 % and 18.1 %, respectively), similar alopecia to T-DXd (all G 36.0 %) and similar nausea/vomiting (all G 51.7 %/19.1 %) to SG. Pneumonitis/ILD was infrequent (3.3 % all G, 0.9 % G3-5), but a high rate of oral mucositis/stomatitis (all G 55.6 %, G3-5 6.9 %) and ocular surface events (all G 40.0 %, G3-5 0.8 %), like keratitis, dry eye, blepharitis and increased lacrimation typically occurred with Dato-DXd, representing AEs of special interest for this novel ADC[18].

Risk of bias analysis

The risk of bias analysis revealed no specific concerns, except for a potential selection bias for allocation concealment, due to the absence of detailed information on this aspect in all of the 5 RCTs (Supplementary Figure 1).

Discussion

We conducted a NMA to determine the best therapeutic option between T-DXd and SG for CT-pretreated HR+/HER2-low and TN/HER2-low MBC. Our direct comparison of the two ADCs at the trial-level did not reveal significant differences in terms of PFS and OS in either scenario. However, some notable differences emerged in their safety profile, with T-DXd being also associated with a slightly higher discontinuation rate due to TRAEs. Besides, we performed an exploratory analysis including also Dato-DXd to provide a more comprehensive assessment of the efficacy of different ADCs in HR+ disease, which substantially confirmed the primary analysis results.

As observed in pivotal trials, a significant and clinically relevant benefit was obtained with both ADCs over standard CT. At the combined *in silico* individual patient-level analysis, the ADCs significantly outperformed standard CT (including nab-paclitaxel, paclitaxel, capecitabine, eribulin etc.) in HR+/HER2-low by providing a significant 51 % reduction in the instantaneous risk of progression or death and a 36 % reduction in the instantaneous risk of death, with an absolute benefit in mPFS of 4.7 months and in mOS of 6.4 months. Similarly, the ADCs combined showed a significant 57 % reduction in the instantaneous risk of progression or death and an impressive 56 % reduction in the instantaneous risk of death, as compared to late-line CT in TN/HER2-low. This translated in an absolute benefit of 4.0 months in mPFS and 7.8 months in mOS in favor of ADCs, thus confirming the large therapeutic benefit provided by these novel anticancer agents, in comparison to standard 2nd/further-line CT options. Consistently, at the P-score analysis, T-DXd and SG, taken separately, clearly outperformed standard CT on all endpoints in both HR+/HER2-low and TN/HER2-low. Conversely, when directly comparing the two ADCs at the trial-level, no significant differences in PFS and OS were observed in both HR+/

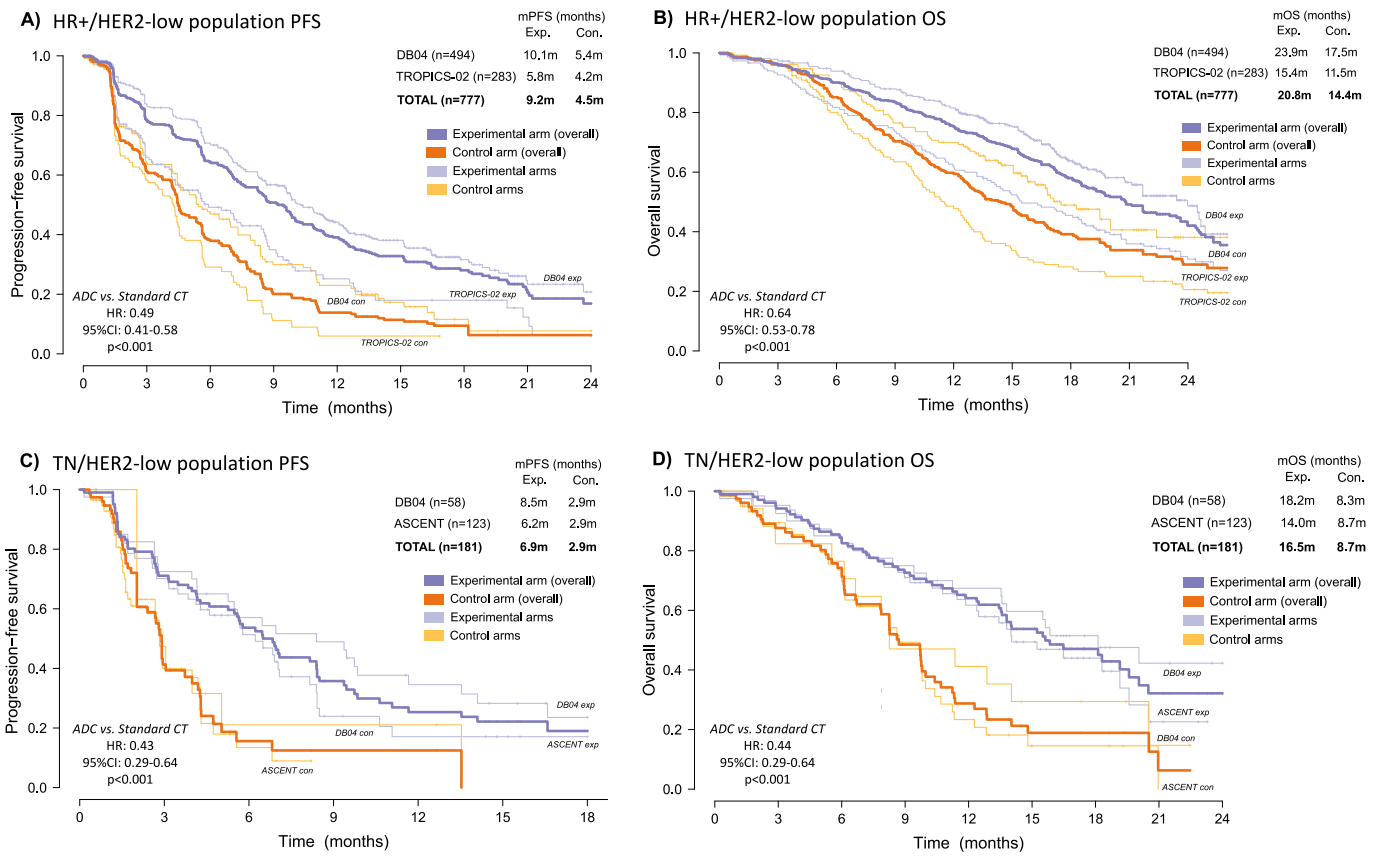

Fig. 4. Kaplan-Meier curves of PFS and OS resulting from the individual patient-level meta-analysis. **Legend.** ADC: antibody-drug conjugates; CI: confidence interval; Con.: controls treated with standard CT; CT: chemotherapy; DB04: DESTINY-Breast04; Exp.: patients exposed to ADC; HER2: human epidermal growth factor receptor 2; HR: hazard ratio; HR+: hormone receptor-positive; m: months; mOS: median overall survival; mPFS: median progression-free survival; OS: overall survival; PFS: progression-free survival; TN: triple negative. HRs are stratified for the clinical trials.

HER2-low and TN/HER2-low. Nevertheless, the P-score analysis suggested that T-DXd had some higher mean probability of providing better PFS and OS than SG for pretreated HR+/HER2-low MBC. When adding to the equation the results from the DESTINY-Breast06 in earlier treatment lines and results from the TROPION-Breast01, a more clear advantage of T-DXd over SG emerged in the trial-level meta-analysis, as well as over the other anti-TROP2 ADC Dato-DXd. T-DXd was the only ADC to show a statistically significant superior OS than standard CT in HR+/HER2-low MBC and P-score analysis confirmed the higher likelihood of benefit with the anti-HER2 ADC, in comparison to the other two and standard CT. The analysis in the TN subset was not affected by the addition of DESTINY-Breast06 and TROPION-Breast01, as those studies only included HR+ disease. For TN/HER2-low, P-score analysis suggested a higher mean probability of SG being better than T-DXd in terms of OS, but not PFS.

Overall, these results seem to support the use of T-DXd in HR+/HER2-low, especially in earlier treatment lines, while suggesting a higher likelihood of benefit with SG in TN/HER2-low, leaving Dato-DXd in the rear guard.

When dissecting results by taking a closer look at the evidence that generated them, it should be noted that patients included in the TROPiCS-02 and ASCENT were more pretreated than those in DESTINY-Breast04/06, potentially justifying a numerically poorer performance of SG in comparison to T-DXd in the absolute benefit obtained over standard CT both in HR+ and TN HER2-low (although a relatively weaker comparator might have also favored within-trial performance of SG). Regarding Dato-DXd in HR+ disease, the population included in the TROPION-Breast01 was similar to that of DESTINY-Breast04 but still more pretreated than in DESTINY-Breast06, where T-DXd was administered as 1st line CT. At the same time, the TPC arm of the TROPiCS-02 and TROPION-Breast01 included eribulin, vinorelbine, gemcitabine and capecitabine, while the control arm of the DESTINY-Breast04/06 included capecitabine, nab-paclitaxel and paclitaxel (all standard 1st line CT options), did not include vinorelbine, and only the DESTINY-Breast04 included eribulin and gemcitabine[11,17–19]. Consequently, T-DXd in its pivotal trials showed a solid PFS and OS benefit with a stronger comparator arm than both SG and Dato-DXd [16,24], somewhat compensating the presence of less pretreated populations in the DESTINY-Breast04/06 than TROPiCS-02 and TROPION-Breast01. In HR+/HER2-low, while the addition of the TROPION-Breast01 and DESTINY-Breast06 to the original efficacy networks still resulted in no significant differences among ADCs when artificially compared head-to-head, T-DXd was the only ADC to retain a significant superiority in OS when compared to a stronger TPC arm including more taxanes, capecitabine and more patients treated in earlier lines. In TN/HER2-low, the imbalances involving the DESTINY-Breast04 and ASCENT do not allow to draw definitive conclusions based on efficacy. Still, the evidence for SG in this context is stronger (an entire phase III RCT only dedicated to pretreated TN MBC). To note, the statistical power to demonstrate superiority between experimental treatments in NMA is usually low. In this context, the P-score, which measures the certainty that one treatment is better than another, can help quantify differences between treatments. For TN/HER2-low, P-score analysis supported a higher likelihood of benefit with SG, especially in terms of OS.

Unfortunately, a direct comparison of the median PFS and OS of T-DXd, SG and Dato-DXd to quantify absolute benefit differences could not be carried out, as only the DESTINY-Breast04 included T-DXd for TN

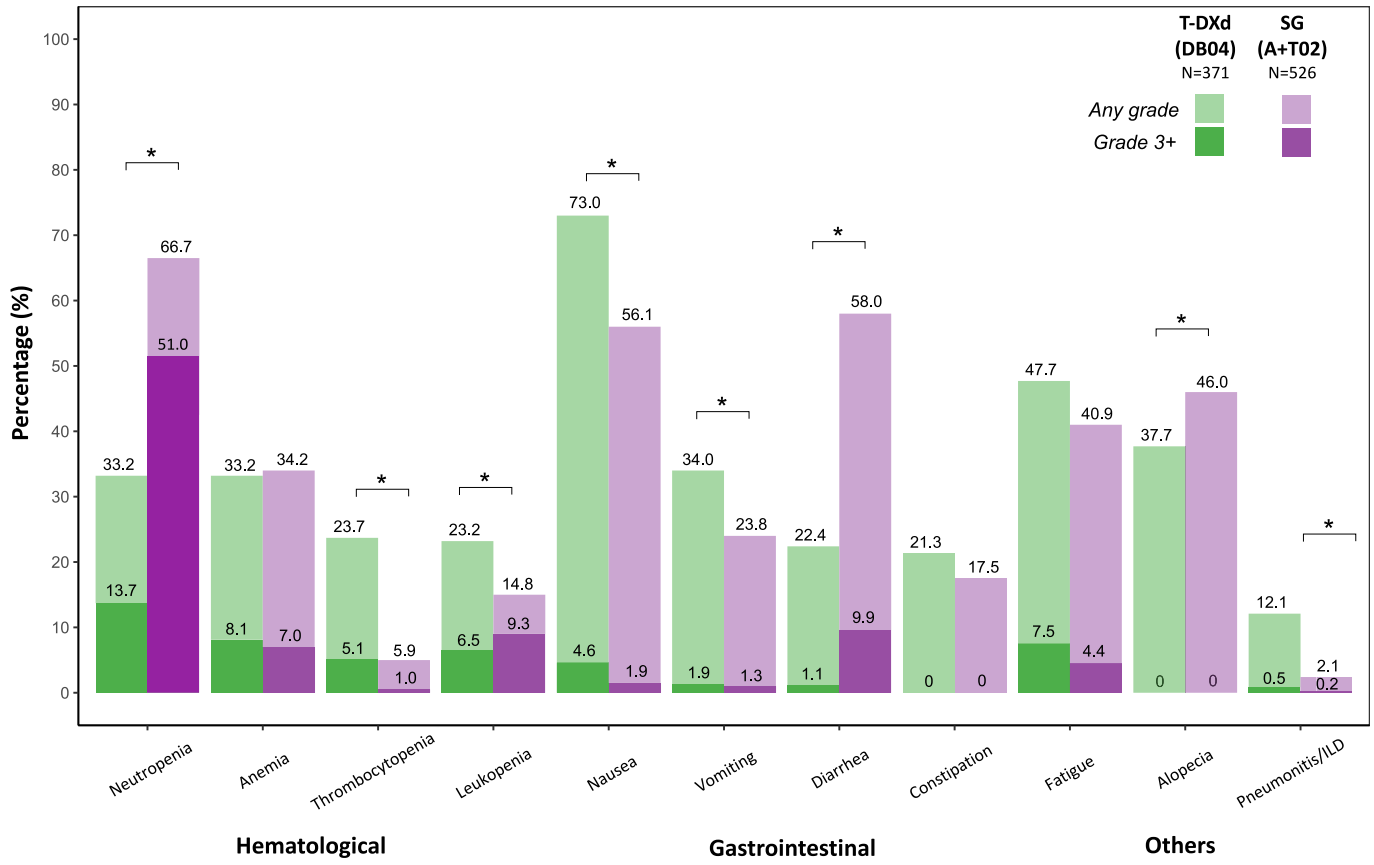

Fig. 5. Most relevant drug-related adverse events of T-DXd and SG in CT-treated patients with HER2-low MBC. **Legend and footnotes**. A: ASCENT; DB04: DESTINY-Breast04; G: grade; G3+: grade 3 or more; ILD: interstitial lung disease; SG: sacituzumab govitecan; T-DXd: trastuzumab deruxtecan; T02: TROPiCS-02. Adverse events were reported for the entire study populations, regardless of HER2 status, thus including also HER2-0 cases for the ASCENT and TROPICS-02. For alopecia, only grade 1 and 2 CTCAE exist. To compare treatment safety between T-DXd and SG, all TRAEs occurring in ≥ 20 % of patients for at least one of the two ADCs were considered, with the exception of pneumonitis, that was also reported in the original publication despite lower incidence. For SG, the jointed cohorts of the ASCENT and TROPiCS-02 trials were considered. *Significantly different for $p < 0.05$.

disease, only the TROPiCS-02 and ASCENT included SG, respectively in HR+ and TN MBC and only TROPION-Breast01 included Dato-DXd for HR+ disease.

When looking at the safety profile of approved ADCs, despite being reasonably safe with most adverse events of G1-2, SG showed significantly higher rates of alopecia, neutropenia and diarrhea in comparison to T-DXd, including of ≥ G3, while the latter showed higher rates of fatigue, thrombocytopenia, nausea and vomiting as the most significantly different and frequent TRAEs. Furthermore, T-DXd seemed to be more frequently discontinued than SG due to TRAEs. In any case, these toxicities are usually well managed in clinical practice and no new safety concerns have been observed in the real-world scenario[25]. Moreover, nausea and vomiting with T-DXs are often efficiently prevented or managed if the same prophylactic strategies recommended for high hematogenic CT regimens are adopted[25–27], while optimal prevention of SG-related ≥ G3 neutropenia and diarrhea can be achieved with short-course prophylactic G-CSF and loperamide, respectively[28]. However, strict monitoring of ILD with focus on early symptoms onset and CT scan at the minimum suspect is required when administering T-DXd, in order to provide the most adequate and timely management, as this can be a potentially lethal side effect[29]. Moreover, being based on the anti-HER2 agent trastuzumab, T-DXd requires the same cardiac monitoring strategy, though serious cardiotoxicities seem to be infrequent, in line with other anti-HER2 agents[30]. In this scenario, the development of an ADC with comparable efficacy but improved tolerability could represent a valuable addition to the therapeutic armamentarium. Unfortunately, this does not appear to be the case with Dato-DXd. While it demonstrated low rates of hematologic and GI toxicities and scarce pneumonitis/ILD events, it was associated with a notable incidence of ocular toxicity and stomatitis (~50 % of patients). Although these TRAEs are not life-threatening, they pose a significant challenge to patients' quality of life. This concern is further amplified given that, to date, Dato-DXd has not demonstrated a survival benefit over standard CT, with TROPION-Breast01 recently failing to meet its OS co-primary endpoint[31].

Overall, taking into account our results, along with the current body of evidence on T-DXd and SG in HR+/HER2-low, an earlier use of T-DXd appear to be reasonable, aligning with current recommendation of the European and American guidelines for advanced HER2-negative MBC and strengthening the evidence in support of the current European Society for Medical Oncology (ESMO) expert consensus for the management of HER2-low BC[3,32–34]. Regarding the potential use of T-DXd as 1st line after ET in the HR+/HER2-low metastatic scenario, several considerations should be taken into account. At present, T-DXd in 1st line is only recommended and approved by main regulatory agencies when recurrence occur within 6 months from or during (neo)adjuvant CT administration[32,33]. However, the indication will likely change after positive results of DESTINY-Breast06[17]. In our study, the addition of this trial in the HR+/HER2-low network added more evidence to strengthen the efficacy of T-DXd over standard CT in earlier lines. However, the relatively high incidence of ILD (up to 15 %) observed in all trials with T-DXd and its potential life-threatening consequences [35,36], along with potential trastuzumab-related cardiotoxicity issues in a therapeutic scenario where safer and effective options are still

available (fuvestrant+ capivasertib, elacestrant, taxane or capecitabine monotherapy etc.) impose the need to carefully identify which patients might benefit most from a 1st line CT regimen based on T-DXd [24,32–34]. For example, very symptomatic disease, including the presence of active brain metastases, a short interval from (neo)adjuvant CT, the presence/absence of biomarkers to guide effective ET-based regimens (*ESR1* mutations, *PIK3CA/PTEN* alterations, germline *BRCA1/2* pathogenic variants etc.)[37–40], patient's preferences and comorbilities should be all critical criteria at the time of selecting the best systemic approach after failure of standard 1st/2nd line ET in HR+/HER2-low MBC.

In the mTNBC scenario, we observed a higher likelihood of SG to provide a superior benefit in OS in comparison to T-DXd. However, provided the small difference in the therapeutic benefit obtained with T-DXd or SG, the higher quality of evidence in this population with the latter and the lower discontinuation rates due to TRAEs along with the substantial absence of ILD, it might be reasonable to suggest the prior use of SG, followed by T-DXd, in line with the ESMO expert consensus for the management of HER2-low BC(3). Patients' preferences regarding experiencing side effects like alopecia, differences in administration schedule (every 21 days [q21] for T-DXd vs. day1,8 q21 for SG), or the need of achieving an objective response (50–53 % with T-DXd vs. 21–31 % with SG)[11,13,19] for symptomatic palliation might be other elements to consider. However, choosing to administer a specific ADC vs. another implies that a specific therapeutic sequence will be ultimately provided to a patient during the disease course, whenever allowed by regulatory agencies. Despite being directed against different targets, T-DXd and SG have a similar drug:antibody ratio (DAR) and a similar cytotoxic payload, consisting in an anti-topoisomerase I agent[41–43]. While mechanisms of resistance based on the target might not affect the therapeutic sequencing, other forms of resistance involving the payload drug class likely could. At present, only few real-world experiences of ADC sequencing involving these two drugs have been presented, including a small whole-exome sequencing analysis to identify potential mechanisms of resistance on tumor tissue, and a biomarker analysis from the small DAISY phase II trial with T-DXd, but data are mostly inconclusive[44–48]. The key message from published evidence is that the second ADC is usually less effective, regardless of whether others therapeutic lines are intercalated, but there is a small proportion of patients where the sequencing is effective or an even smaller proportion where the second ADC is more effective than the first. No clear conclusions can be drawn but it appears more than reasonable that huge efforts towards a more refined identification of patients benefiting from a specific ADC should be done. For example, the sequencing-based randomized TRADE-DXd (TBCRC064) trial of T-DXd and Dato-DXd in the 1st/2nd-line of HR+/HER2-negative and TN MBC will provide interesting insights in the next future[49]. However, it will not answer the specific question of the sequencing of SG and T-DXd. Although Dato-DXd is another anti-TROP2 ADC with the same payload as T-DXd, thus partially resembling SG, the DAR is lower on average (4:1 vs 7.6:1) and the linker is different, suggesting that efficacy and safety might not be easily comparable[14,42,50]. Moreover, our exploratory analyses relegated Dato-DXd in the third position behind SG and T-DXd, when ranking the PFS and OS benefit in HR+ MBC. Furthermore, studies like TRADE-DXd may not address optimal sequencing for a significant proportion of patients, likely requiring an individualized approach. In this regard, the translational research effort represented by the SOLTI HER2-PREDICT (NCT04257162) study might shed light on predictors of response and resistance to ADCs. Identifying biomarkers of response to T-DXd (and, in general, to other ADC) may lead in the future to a more precise biomarker-based approach to optimize therapeutic sequencing according to predictive biomarkers of response/resistance. To note, in the same TRADE-DXd trial, a translational research program to identify the potential causes of resistance to T-DXd and Dato-DXd will be also carried out[49].

In any case, in HER2-low MBC pretreated with at least 1-2 lines of standard CT in the metastatic setting, currently approved ADCs are undoubtedly more effective than further CT options and should thus be prioritized in the absence of specific contraindications or prescribing constraints.

Our study is not exempt from limitations. As extensively discussed in the previous sections, the RCTs included in the primary and exploratory analyses partially differed in terms of treatment line and CT regimens included in the comparator arms. Moreover, only in the TROPiCS-02 all patients had to be previously treated with a CDK4/6-inhibitor-based regimen. To note, the proportion of patients with baseline BM was higher in the ASCENT (as expectable for mTNBC in comparison to HR+/HER2-negative MBC) than in the other trials, although several studies have shown intracranial activity of the 3 ADCs in this scenario [23,51–55]. Another limitation is based on the very small cohort of mTNBC included in the DESTINY-Breast04, since the study was primarily designed for the HR+ population. Regarding P-scores, when differences are small, as observed in some comparisons presented in this work, the evidence for determining which treatment is superior is limited. In such cases, treatment decisions need to be guided by additional clinical considerations. Finally, the transitivity assumption in the NMA could not be evaluated as no direct comparisons between the 3 ADCs in RCTs exist.

Our study has several strengths. First, this is the first and only study providing a formal comparison between SG and T-DXd in the HER2-low MBC scenario so far, which is the only therapeutic setting where both ADC are currently approved, and the correct therapeutic sequencing is matter of a fervent debate. In addition, it is unlikely that the two treatments will be compared head-to-head in randomized fashion in the next few years. Furthermore, we provided separate analyses for HR+ and TN disease and adopted a solid methodological approach. No significant risk of bias was substantially observed, highlighting the high quality of the evidence produced by the studies included in this NMA. Importantly, in order to provide a more comprehensive assessment of ADCs efficacy in the HER2-low scenario, we also decided to include the DESTINY-Breast06 and the TROPION-Breast01 trials. However, to mitigate the introduction of more methodological biases and the need for further methodological assumptions associated to the peculiarities of these two studies (e.g. CT-naïve patients in DESTINY-Breast06, partially different control arms, no results specific to the HER2-low for the TROPION-Breast01 etc.), we generated separate exploratory networks of PFS/OS. Reassuringly results from the primary analysis restricted to T-DXd and SG were substantially confirmed.

In conclusion, T-DXd showed a higher mean probability of being better than SG in the context of CT- and ET-pretreated HR+/HER2-low in terms of PFS and OS, while SG showed a higher mean probability of being better than T-DXd in CT-pretreated TN/HER2-low in terms of OS, despite different, though overall manageable toxicity profiles. Dato-DXd was the worst performing ADC in the HR+ scenario and its role remains currently uncertain. However, the direct comparison among all ADCs failed to show statistically significant differences. At present only T-DXd and SG are approved by regulatory agencies and whether administering the former or the latter, should be mostly based on country-specific availability, drug approval constraints and guidelines reflecting trials' eligibility criteria, ADCs' safety profile, patients' preferences and comorbilities. Of note, the DESTINY-Breast06 will likely lead to an earlier use of T-DXd in the HR+/HER2-negative MBC. Hence, high-quality real-world evidence studies and prospective trials on ADC therapeutic sequencing will be crucial to support a more informed and effective therapeutic decision-making. Furthermore, translational studies to identify biomarkers of sensitivity and resistance to different ADCs will help shaping more personalized therapeutic sequences.

Author contribution

F. Schettini, S. Nucera and G. Villacampa conceived the study. S. Nucera and F. Schettini performed the literature review and extracted

data from published studies. G. Villacampa performed the statistical analyses. All authors participated in the interpretation of study results. A first manuscript draft was written by F. Schettini, S. Nucera and G. Villacampa. All authors revised and approved the final version of the manuscript.

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Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: **F. Schettini** reports honoraria from Novartis, Gilead and Daiichy-Sankyo for educational events/materials and travel expenses from Novartis, Gilead and Daiichy-Sankyo. **T. Pascual** has received honoraria for speaker activities from Pfizer, AstraZeneca, Novartis, Veracyte and Argenetics and has held an advisory role with Novartis. **O. Martínez-Sáez** reports advisory/consulting fees from Reveal Genomics, Roche and Astrazeneca and lecture fees from Daiichi Sankyo, Pfizer, Novartis and Eisai and travel expenses from Gilead and Novartis. **R. 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Appendix A. Supplementary data

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