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ORIGINAL ARTICLE

Outcomes with trastuzumab deruxtecan by biomarker status, line of treatment and prior receipt of sacituzumab govitecan in a large real-world database of patients with metastatic breast cancer

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Background: Most of the published data with trastuzumab deruxtecan (T-DXd) derive from clinical trials with selected populations and little representation of US patients. Limited real-world data are available.

Patients and methods: Using a nationwide electronic health record-derived database, we identified patients with metastatic breast cancer (MBC) who initiated T-DXd between December 2019 and September 2023. Tumors were categorized as human epidermal growth factor receptor 2 (HER2)-positive if positive at any time before starting T-DXd and HER2-negative if never HER2-positive before T-DXd. Hormone receptor (HR) status was derived from the last biopsy before T-DXd initiation. Real-world progression-free survival (rwPFS) and overall survival (OS) were estimated using the Kaplan—Meier method.

Results: Overall, 1490 patients were included: 884 with HER2-positive, 487 with HR-positive/HER2-negative, and 119 with HR-negative/HER2-negative (triple-negative) MBC. Median age was 59 years (range 23-84 years), and median prior lines of systemic treatments were 3 and 4 for HER2-positive and HER2-negative MBC, respectively. rwPFS and OS were 12.3 and 24.6 months for HER2-positive disease; 7.6 and 15.5 months for HR-positive/HER2-negative disease; and 4.3 and 10.4 months for triple-negative disease. T-DXd use in earlier lines of treatment was associated with significantly longer rwPFS in HER2-positive ($P = 0.02$), but not in HR-positive/HER2-negative MBC ($P = 0.07$). Among patients with triple-negative disease pretreated with sacituzumab govitecan (SG, $n = 58$), after adjusting for prior lines of treatment, shorter rwPFS (3.4 versus 5.7 months, $P = 0.009$) and OS (9.0 versus 14.5 months, $P = 0.002$) were observed compared with patients without prior SG ($n = 61$). rwPFS with T-DXd was also significantly shorter in patients with *BRCA* mutations (7.8 versus 9.2 months, $P = 0.02$) and numerically shorter in patients with programmed death-ligand 1-negative disease (6.9 versus 12.6 months, $P = 0.31$).

Conclusions: In a large dataset, T-DXd showed favorable activity for treating MBC, although outcomes for HER2-positive disease appeared worse than those observed in clinical trials. Prior SG treatment was associated with inferior outcomes with T-DXd, suggesting cross-resistance between these antibody—drug conjugates.

Key words: trastuzumab deruxtecan, T-DXd, antibody—drug conjugate, metastatic breast cancer, real—world data

INTRODUCTION

Breast cancer represents the most common cancer diagnosis in women, with an incidence of metastatic disease that is increasing over time.[1,2] Treatment of metastatic breast cancer (MBC) commonly involves sequential lines of systemic treatment, with most patients eventually developing resistance to chemotherapy.[3] In this setting, multiple antibody—drug conjugates (ADCs) have demonstrated improved survival among patients with chemotherapy-refractory MBC and are now being tested in earlier lines of treatment.[4] Among these, trastuzumab deruxtecan (T-DXd) has shown durable activity for the treatment of patients with every subtype of MBC in clinical trials.

T-DXd was first approved in 2019 for the third-line treatment and beyond in patients with human epidermal growth factor receptor 2 (HER2)-positive MBC, based on an

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objective response rate of 62% and median progression-free survival (PFS) of nearly 20 months in the phase II DESTINY-Breast01 trial.[5,6] Randomized phase III trials have subsequently expanded the use of T-DXd to earlier lines and to a larger population of patients with HER2-low expressing [immunohistochemistry (IHC) 1+ and 2+/not amplified] MBC. More recently, the DESTINY-Breast06 trial evaluated the use of T-DXd as first-line chemotherapy among patients with hormone receptor (HR)-positive, HER2-low or HER2-ultralow MBC, leading to improved PFS versus physician's choice chemotherapy (13.2 versus 8.1 months, $P < 0.001$).[7]

Of note, most of the published data with T-DXd derive from clinical trials that enrolled a selected population of patients, which may not represent the patients commonly treated in clinical practice. Indeed, patients in clinical trials are often selected to exclude those with poor performance status, those with progressing brain metastases, uncontrolled comorbidities or those not able to access academic medical centers, categories of patients which are commonly encountered in clinical practice and reflected in real-world data.[8] Additionally, most DESTINY trials were run globally and had limited representation of patients from the USA, which may not fully inform about outcomes in this geographical context, due to the differential availability of innovative anticancer drugs by geographical context.[9] Limited data are also available with T-DXd in certain understudied groups of patients, such as for those with triple-negative disease, those with HER2-0 MBC, with *BRCA* mutations or with high programmed death-ligand 1 (PD-L1) expression. Lastly, no prospective data are available on the activity of T-DXd among patients who have received prior sacituzumab govitecan (SG), an ADC that is commonly utilized for treating MBC and which delivers a payload with a similar mechanism of action to that of T-DXd.

In this study, we aimed to evaluate the real-world activity of T-DXd among patients with MBC, including in specific subgroups of interest and in key understudied populations.

PATIENTS AND METHODS

We conducted a large retrospective observational study on the use of T-DXd and carried out sub-analyses according to HR status, HER2-status (positive, low, 0), *BRCA* mutational status, PD-L1 status, line of treatment (LOT) of T-DXd administration, and prior exposure to SG. The study used the nationwide, longitudinal Flatiron Health electronic health record-derived, deidentified database, comprising patient-level data originated from ~280 US cancer clinics (~800 sites of care) and curated via technology-enabled abstraction.[10,11] Lines of therapy were oncologist-defined and rule-based, included any type of treatment, and were restricted to those administered in the advanced setting. These data were deidentified and subject to obligations to prevent reidentification and protect patient confidentiality.

We included patients with MBC who initiated T-DXd between December 2019 and September 2023. Tumor profile data included HER2 status and HR status. HER2 status was determined by IHC or FISH results. HR status was determined by the most recent estrogen and/or progesterone receptor status before T-DXd initiation. HER2-positive was defined as FISH positive/amplified and any IHC status (0, 1+, 2+, 3+), IHC 3+ regardless of FISH results, or HER2-positive not otherwise specified (NOS). HER2-negative was defined as IHC 0, IHC 1+, negative NOS, IHC-negative NOS, FISH-negative/not amplified, or FISH equivocal.[12] Patients with one or more HER2-positive biopsy results before T-DXd initiation were considered HER2-positive (i.e. 'ever-positive' by Flatiron definition). Conversely, patients without an HER2-positive result and one of the listed biopsy results for HER2-negative were selected accordingly. Then, HER2-negative cases were further divided into HER2-low (IHC 1+ or 2+ not amplified) and HER 2-0 (IHC 0) based on the most recent biopsy before T-DXd initiation.

PD-L1-positive disease was defined as a combined positive score (CPS) ≥10% with the 22C3 assay on the most recent tissue sample collected before T-DXd, while *BRCA*-positive was defined as any *BRCA1* or *2* mutation (germline or somatic) detected at any timepoint.

The primary outcome was real-world PFS (rwPFS) and a secondary outcome was overall survival (OS). rwPFS was defined as the date of T-DXd initiation to either the date of the first eligible real-world progression event or death. A 14-day exclusion window after the T-DXd initiation date was implemented for rwPFS events immediately following T-DXd initiation. Also, because any given patient could have had more than one progression, the earliest progression date for each patient was used. OS was defined as the date of T-DXd initiation to the date of death.

rwPFS and OS were estimated using the Kaplan—Meier method. The log-rank test was carried out to compare rwPFS and OS among tumor profile subgroups. As a secondary analysis, an adjusted Cox proportional hazards model was carried out to assess the effect of prior use of SG on rwPFS and OS for patients with triple-negative MBC, controlling for prior lines of therapy to account for the potential confounding effect of this variable. A P value <0.05 was considered statistically significant. All statistical analyses were carried out using SAS version 9.4, R version 4.3.1, and STATA/MP 18.0.

The study was reviewed by the Yale Human Investigations Committee and determined not to constitute human subjects research.

RESULTS

A total of 1490 patients were included in this study (sample construction flow diagram available in Supplementary Figure S1, available at https://doi.org/10.1016/j.esmoop.2025.105330). The median follow-up for the overall cohort was 6.4 months (range 0-46.7 months). The median age at diagnosis was 59 years (range 23-84 years). Most patients were White (61.6%), followed by 11.5% Black/African American, 9.7% Hispanic/Latino, 2.9% Asian, and 14.3% other or missing.

Clinicopathologic and demographic characteristics for the study population by clinical subtype are provided in Table 1. In total, 884 patients (59.3%) had HER2-positive MBC, 487

Table 1. Demographic and treatment characteristics across the HER2-positive, HR-positive/HER2-negative, and HR-negative/HER2-negative metastatic breast cancer (MBC) cohorts

	HER2+ (*N* = 884)	HR+/HER2− (*N* = 487)	HR−/HER2− (*N* = 119)	*P* value[a]
	N (%)			
Age at diagnosis (years)[b]				0.06
<65	628 (71.0)	317 (65.1)	85 (71.4)	
≥65	256 (29.0)	170 (34.9)	34 (28.6)	
Race/ethnicity				0.20
Asian	28 (3.2)	11 (2.3)	≤5 (≤4.2)	
Black/African American	115 (13.0)	44 (9.0)	13 (10.9)	
Hispanic/Latino	84 (9.5)	48 (9.9)	12 (10.1)	
White	520 (58.8)	325 (66.7)	73 (61.3)	
Other/missing	137 (15.5)	59 (12.1)	≥16 (≥13.4)	
ECOG performance status				0.48
0-1	385 (43.6)	208 (42.7)	57 (47.9)	
2-4	37 (4.2)	23 (4.7)	≤5 (≤4.2)	
Missing	462 (52.3)	256 (52.6)	≥57 (≥47.9)	
Practice type[c]				0.07
Academic	196 (22.2)	130 (26.7)	35 (29.4)	
Community	688 (77.8)	357 (73.3)	84 (70.6)	
Location				0.76
Midwest	87 (9.8)	49 (10.1)	15 (12.6)	
Northeast	113 (12.8)	63 (12.9)	13 (10.9)	
South	301 (34.0)	155 (31.8)	37 (31.1)	
West	144 (16.3)	61 (12.5)	18 (15.1)	
Missing	239 (27.0)	159 (32.6)	36 (30.3)	
Insurance type				0.09
Commercial	291 (32.9)	160 (32.9)	43 (36.1)	
Medicare	280 (31.7)	186 (38.2)	37 (31.1)	
Other, including Medicaid	76 (8.6)	34 (7.0)	14 (11.8)	
Uninsured/unknown	237 (26.8)	107 (22.0)	25 (21.0)	
Year of diagnosis				<0.001
2011-2016	185 (20.9)	85 (17.5)	6 (5.0)	
2017-2018	208 (23.5)	111 (22.8)	7 (5.9)	
2019-2020	250 (28.3)	157 (32.2)	39 (32.8)	
2021-2022	228 (25.8)	126 (25.9)	60 (50.4)	
Missing	13 (1.5)	8 (1.6)	7 (5.9)	
Disease-free interval				<0.001
0 Months (*de novo*)	374 (42.3)	116 (23.8)	31 (26.1)	
<24 Months	114 (12.9)	58 (11.9)	28 (23.5)	
≥24 Months	396 (44.8)	313 (64.3)	60 (50.4)	
Prior sacituzumab govitecan (SG)[d]	12 (1.4)	13 (2.7)	58 (48.7)	<0.001
Prior trastuzumab emtansine (T-DM1)[d]	409 (46.3)	6 (1.2)	0 (0)	<0.001
Prior pertuzumab[d]	594 (67.2)	≤5 (≤1.0)	0 (0)	<0.001
Prior lines of therapy				
Mean (SD)	3.2 (2.3)	3.9 (2.4)	3.0 (2.1)	<0.001
Median (IQR)	3.0 (2.0)	3.0 (3.0)	3.0 (3.0)	

ANOVA, analysis of variance; ECOG, Eastern Cooperative Oncology Group; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; IQR, interquartile range; SD, standard deviation; T-DXd, trastuzumab deruxtecan.
[a]One-way ANOVA tests were conducted for continuous variables and chi-square tests for categorical variables across the HER2 subgroups.
[b]Patients with a birth year of [data cut-off year - 85] or earlier may have an adjusted birth year in Flatiron Health datasets due to patient deidentification requirements.
[c]Practice type is categorized as patients who either only received care at academic cancer centers (academic) or received care at either academic cancer centers or community oncology practices (community).
[d]Treatments before T-DXd initiation.

(32.7%) had HR-positive/HER2-negative disease, and 119 (8%) had HR-negative/HER2-negative (i.e. triple-negative) disease. Among patients with HER2-negative disease, 520 patients had HER2-low, 74 patients had HER2-0, and 12 patients had HER2-negative tumors without further classification (Supplementary Table S1, available at https://doi.org/10.1016/j.esmoop.2025.105330).

Approximately half of patients with triple-negative disease received SG before T-DXd, nearly half of the patients with HER2-positive disease received trastuzumab emtansine (T-DM1) before T-DXd, and two-thirds received prior pertuzumab.

Outcomes with T-DXd in HER2-positive breast cancer

Among 884 patients with HER2-positive MBC receiving T-DXd, most received it in the fifth or subsequent LOT (36.7%) (Supplementary Figure S2, available at https://doi.org/10.1016/j.esmoop.2025.105330). Receipt in the first or second line was uncommon before presentation of the results from the DESTINY-Breast03 trial (September 2021), but significantly increased subsequently (8.5% versus 29.6%, $P < 0.001$, Supplementary Table S2, available at https://doi.org/10.1016/j.esmoop.2025.105330).

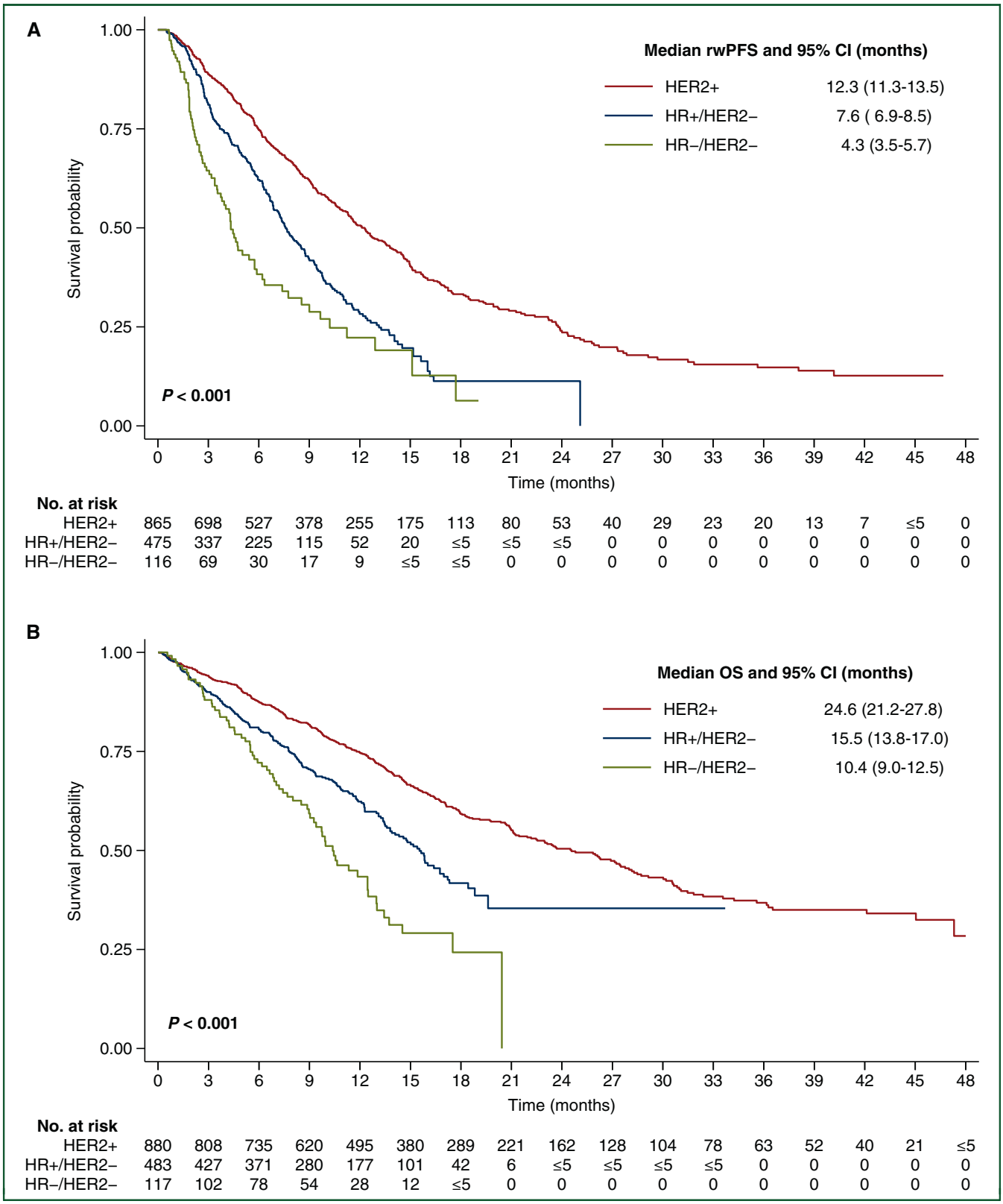

Figure 1. Kaplan–Meier estimates of (A) real-world progression-free survival (rwPFS) and (B) overall survival (OS) stratified by receptor status for patients with metastatic breast cancer (MBC).

CI, confidence interval; HER2, human epidermal growth factor receptor 2; HR, hormone receptor.

In the overall population with HER2-positive disease, median rwPFS and OS were 12.3 months and 24.6 months, respectively (Figure 1, Supplementary Table S3, available at https://doi.org/10.1016/j.esmoop.2025.105330). Patients with HR-positive/HER2-positive MBC experienced a rwPFS of 11.8 months (10.6-13.6 months) and an OS of 23.6

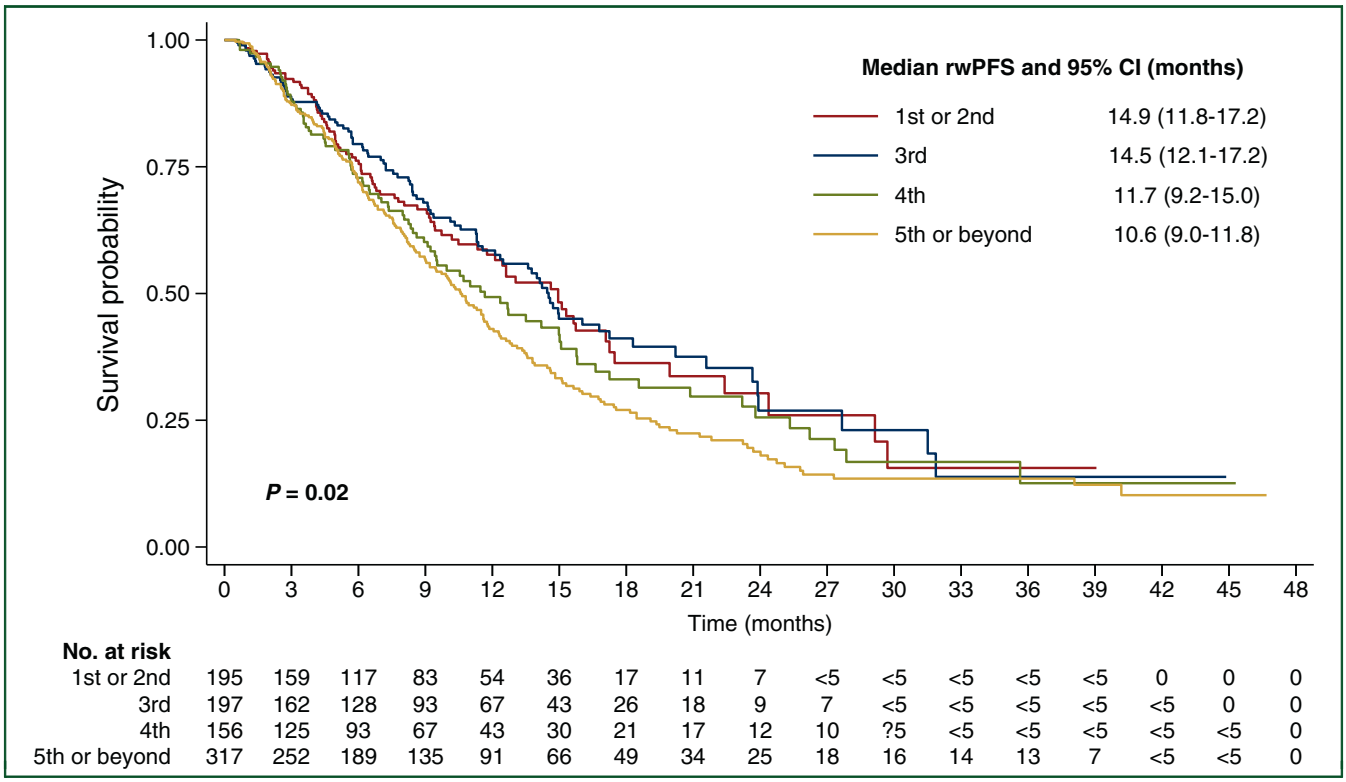

Figure 2. Kaplan–Meier estimates of real-world progression-free survival (rwPFS) by line of therapy (LOT) for patients with HER2-positive metastatic breast cancer (MBC).
HER2, human epidermal growth factor receptor 2; T-DXd, trastuzumab deruxtecan.

months (20.9-27.5 months), whereas patients with HR-negative/HER2-positive disease experienced a rwPFS of 12.6 months (10.8-14.6 months) and an OS of 27.4 months (20.9-31.5 months).

Within the HER2-positive cohort, both rwPFS and OS significantly differed according to the IHC status of the disease ($P < 0.001$). The longest rwPFS and OS were observed among patients with HER2-positive IHC 3+ disease (14.1 months and 28.0 months, respectively), whereas worse outcomes were observed in patients with lower IHC scores (Supplementary Figure S3, available at https://doi.org/10.1016/j.esmoop.2025.105330).

Patients with *de novo* MBC were found to have a numerically longer rwPFS and significantly longer OS (medians 13.6 and 26.2 months, respectively), compared with patients with disease-free interval (DFI) ≥24 months (11.8 and 23.6 months, respectively) or DFI <24 months (11.3 and 20.4 months, respectively) (Supplementary Figure S4, available at https://doi.org/10.1016/j.esmoop.2025.105330).

Significantly longer rwPFS was observed among patients with HER2-positive disease receiving T-DXd in earlier LOT, with the longest median rwPFS of 14.9 months seen in LOT 1 or 2, followed by 14.5 months in LOT 3, 11.7 months in LOT 4, and 10.6 months in LOT ≥5 ($P = 0.021$) (Figure 2). Significant differences in outcomes by LOT were also observed in a sensitivity analysis that excluded patients with the shortest DFI (<24 months) (Supplementary Figure S5, available at https://doi.org/10.1016/j.esmoop.2025.105330). Similar outcomes with T-DXd were observed among patients who had been exposed to prior T-DM1 ($n = 409$) compared with those not exposed to prior T-DM1 ($n = 475$) (Supplementary Figure S6, available at https://doi.org/10.1016/j.esmoop.2025.105330

Real-world outcomes with T-DXd in HR-positive/HER2-negative and triple-negative breast cancer

Among patients with HER2-negative MBC, outcomes significantly differed according to the HR status of the disease (Figure 3A, Supplementary Table S3, available at https://doi.org/10.1016/j.esmoop.2025.105330). Patients with HR-positive/HER2-negative disease had longer median rwPFS (7.6 months) and OS (15.5 months) compared with patients with triple-negative disease, who experienced a median rwPFS of 4.3 months and OS of 10.4 months (Figure 3A, Supplementary Table S3, available at https://doi.org/10.1016/j.esmoop.2025.105330). After excluding prior lines of endocrine treatment, no significant difference in rwPFS was observed depending on LOT of administration of T-DXd in HR-positive/HER2-negative MBC ($P = 0.07$, Figure 3B), including when comparing the rwPFS of T-DXd administered as first cytotoxic treatment versus second cytotoxic treatment and beyond (Supplementary Figure S7, available at https://doi.org/10.1016/j.esmoop.2025.105330).

Outcomes significantly differed according to the HER2-low (versus HER2-0) status for HER2-negative patients. Median rwPFS was 7.8 months in HR-positive/HER2-low

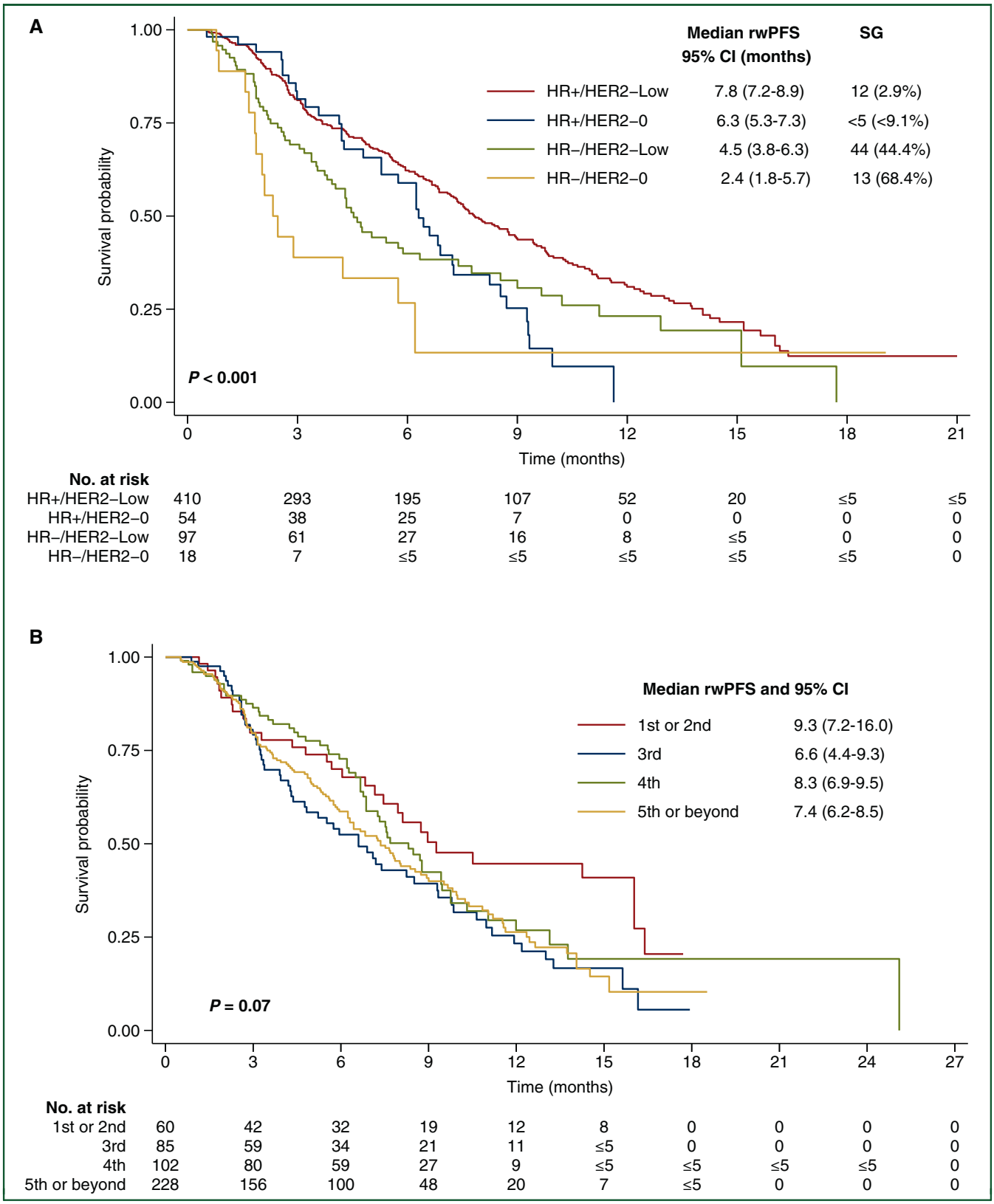

Figure 3. (A) Kaplan–Meier estimates of real-world progression-free survival (rwPFS) by hormone receptor (HR) status for patients with human epidermal growth factor receptor 2 (HER2)-negative metastatic breast cancer (MBC). (B) Kaplan–Meier estimates of rwPFS by line of cytotoxic therapy (LOT) for patients with HR-positive/HER2-negative MBC.
CI, confidence interval; SG, sacituzumab govitecan.

disease, 6.3 months in HR-positive/HER2-0 disease, 4.5 months in HR-negative/HER2-low disease, and 2.4 months in HR-negative/HER2-0 disease ($P < 0.001$) (Figure 3). Notably, within the HER2-low subgroup, no difference in median rwPFS was observed between patients with IHC 1+ and IHC 2+ disease (7.4 versus 7.6 months) (Supplementary

Figure S8, available at https://doi.org/10.1016/j.esmoop.2025.105330).

No differences in rwPFS or OS were observed in patients with HER2-negative MBC according to DFI status ($P = 0.112$ and 0.146, respectively) (Supplementary Figure S9, available at https://doi.org/10.1016/j.esmoop.2025.105330).

Outcomes by prior receipt of sacituzumab govitecan

A total of 83 patients had been exposed to SG before initiating treatment with T-DXd, most of whom had triple-negative disease. Supplementary Table S4, available at https://doi.org/10.1016/j.esmoop.2025.105330 includes the characteristics of the patients with triple-negative MBC by prior exposure to SG.

Among all patients with triple-negative MBC included in our study ($n = 119$), 58 (48.7%) had received prior SG. Patients with prior history of exposure to SG had a median of 3 prior LOT before starting T-DXd (versus 2 lines for patients without history of SG). An adjusted model was conducted to correct for the potential confounding effect of prior LOT on outcomes. Median rwPFS was 3.4 months for patients with prior SG versus 5.7 months for patients without prior SG (hazard ratio = 1.9, $P = 0.009$) (Figure 4A). OS was also significantly shorter among patients with prior receipt of SG versus patients who had not received SG before T-DXd (9.0 months versus 14.5 months, hazard ratio = 2.3, $P = 0.002$) (Figure 4B). Comparable outcomes were observed in the non-adjusted model (Supplementary Figure S10, available at https://doi.org/10.1016/j.esmoop.2025.105330).

Outcomes by BRCA, PD-L1 status, and age

The *BRCA* status was known for 1098 patients in our study; of these, 91 (8.3%) were found to harbor *BRCA1* or *2* mutations, including 40 having germline and 51 having somatic mutations. No significant differences in clinicopathologic characteristics were observed between patients with or without *BRCA* mutations, including a similar rate of HER2-positive, HER2-low, and HER2-0 MBC (Supplementary Table S5, available at https://doi.org/10.1016/j.esmoop.2025.105330). Median rwPFS with T-DXd was 7.8 months for patients with *BRCA* mutations versus 9.2 months for patients without *BRCA* mutations (hazard ratio 1.40, $P = 0.02$) (Supplementary Figure S11A, available at https://doi.org/10.1016/j.esmoop.2025.105330).

Among 149 patients with available PD-L1 CPS status, 18 had PD-L1-positive disease (CPS $\geq$10). No significant differences in clinicopathologic characteristics were observed between patients with PD-L1-positive and -negative disease (Supplementary Table S6, available at https://doi.org/10.1016/j.esmoop.2025.105330). Median rwPFS with T-DXd was 12.6 months for patients with PD-L1-positive versus 6.9 months for patients with PD-L1-negative disease (hazard ratio 0.70, $P = 0.31$) (Supplementary Figure S11B, available at https://doi.org/10.1016/j.esmoop.2025.105330).

Lastly, we looked at outcomes with T-DXd by age ($<$65 versus $\geq$65 years old) (Supplementary Table S7, available at https://doi.org/10.1016/j.esmoop.2025.105330). Outcomes with T-DXd were found to differ by age group, with significantly shorter rwPFS (7.1 versus 9.3 months, $P = 0.002$) in younger patients with HR-positive/HER2-negative MBC, shorter OS in younger patients with triple-negative MBC (9.8 versus 13.4 months, $P = 0.04$), and longer OS in younger patients with HER2-positive MBC (27.2 versus 18.7 months, $P = 0.003$).

DISCUSSION

In this large real-world cohort of US patients with MBC receiving T-DXd, we found favorable activity with the use of T-DXd for treating MBC, with significant differences depending on biomarker status, treatment line, and prior receipt of SG.

The longest rwPFS was observed in HER2-positive breast cancer (12.3 months), followed by HER2-low (7.5 months) and HER2-0 MBC (6.2 months). The HR status of the disease also appeared to be a key determinant of outcomes with T-DXd: median rwPFS was 7.6 months among patients with HR-positive/HER2-negative MBC, compared with 4.3 months for patients with triple-negative disease. Overall, these outcomes compare favorably with the real-world outcomes observed with other treatments for MBC (e.g. chemotherapy, other anti-HER2 drugs, endocrine treatments). For HER2-positive MBC, a rwPFS of 4.7 months has been observed in the Epidemio-Strategie Medico-Economique database with anti-HER2 regimens administered after T-DM1[13]; whereas, for HR-positive/HER2-negative MBC, a rwPFS of 3.7-5.5 months has been reported in pretreated US patients with traditional chemotherapy.[14] Overall, T-DXd is confirmed to be a highly effective treatment option for patients with HER2-positive or HER2-negative MBC.

Importantly, the outcomes observed with T-DXd in our study are extremely similar to those reported in our real-world analysis of patients treated with T-DXd for MBC at Dana-Farber Cancer Institute and Duke Cancer Institute,[15] and in the DAISY phase II trial[16]; whereas they diverge from what was observed in the DESTINY phase III clinical trials. The divergence is particularly meaningful for HER2-positive disease, since the rwPFS observed in our study (approximately 1 year, up to $\sim$15 months in LOT 1 or 2) is approximately half compared with the PFS observed in the DESTINY-Breast03 trial (29 months[17]), which included mostly patients treated in the second line, and also shorter than what seen in the DESTINY-Breast01/02 trials ($\sim$18-20 months),[6,18] which included heavily pretreated patients.

There are several potential reasons for this striking difference in outcomes. First, select populations are enrolled in clinical trials, with patients harboring significantly less comorbidities compared with patients treated in the real world,[19] which may allow for more consistent and prolonged administration of T-DXd. Second, there is limited representation of US patients in the DESTINY trials (e.g. only 6.5% of the patients enrolled in DESTINY-Breast03 and 16% of those in DESTINY-Breast04 were from North America[17,20]), with differences in treatment patterns across countries that may relevantly impact outcomes with T-DXd.

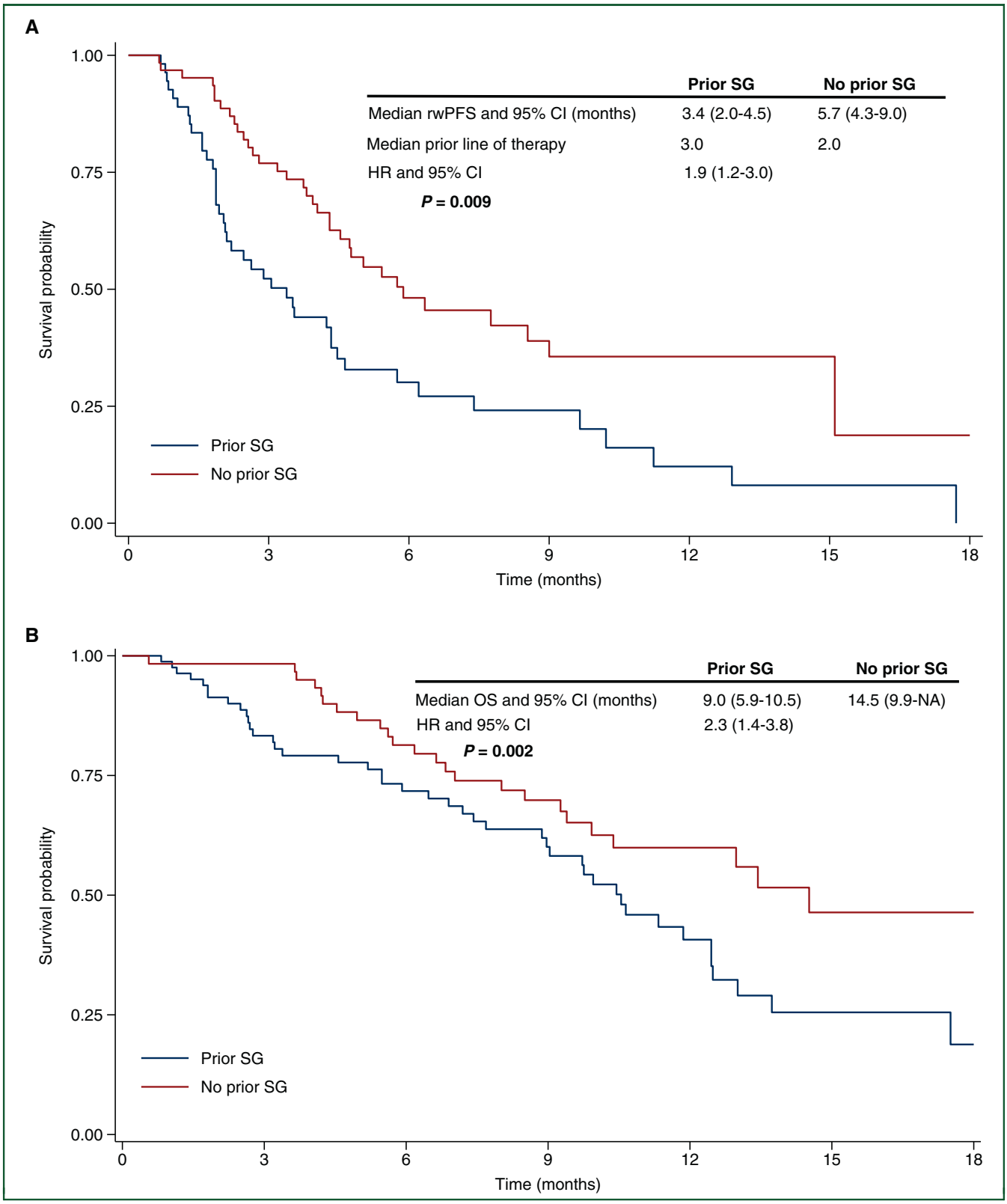

Figure 4. Kaplan–Meier estimates of (A) real-world progression-free survival (rwPFS) and (B) overall survival (OS) stratified by receipt of sacituzumab govitecan (SG) before T-DXd versus no prior SG for patients with triple-negative metastatic breast cancer (MBC).
CI, confidence interval; HR, hazard ratio; T-DXd, trastuzumab deruxtecan.

Third, there are differences in the definition of HER2-positive disease. The DESTINY trials required a centralized confirmation of the HER2 status, whereas no centralized confirmation was conducted in our real-world study, and tumors were considered HER2-positive if ever positive. Finally, there are inherent differences between rwPFS and

PFS as endpoints which can also lead to discrepancies. Overall, based on the results from this study, those of our prior real-world analysis at Dana-Farber Cancer Institute and Duke Cancer Institute,[15] and of several other clinical trials and real-world experiences,[16,21-26] the expected median duration of T-DXd treatment in US patients with treatment-refractory HER2-positive MBC appears to be ∼1 year. This finding may inform discussions in clinical practice and the design of clinical trials enrolling US patients.

Our study also provides effectiveness data with T-DXd in several understudied subgroups of patients. For instance, given its lower incidence (compared with other subtypes), lack of actionable targets, and aggressive pattern of progression, triple-negative MBC poses significant challenges for the development of new drugs. Indeed, T-DXd has been approved by the FDA for metastatic triple-negative MBC based on data from only 40 patients with this subtype in DESTINY-Breast04, warranting integration with real-world data to confirm the efficacy of the drug. Among 119 patients with triple-negative MBC, we observed a rwPFS of 4.3 months and an OS of 10.4 months. Notably, longer rwPFS and OS were observed among patients with triple-negative MBC not previously exposed to SG (rwPFS 5.7 months, OS 14.5 months), approaching the efficacy observed in this population in the DESTINY-Breast04 trial (PFS 6.3 months, OS 17.1 months).[27] Conversely, significantly shorter rwPFS (3.4 months) and OS (9.0 months) with T-DXd were observed in patients with prior exposure to SG. This finding, which is consistent with other real-world experiences,[28-30] suggests some degree of cross-resistance between ADCs that harbor anti-topoisomerase 1 payloads when utilized in sequence, even when the two ADCs target different receptors on the tumor cell (HER2 for T-DXd, Trop2 for SG). This represents a particularly relevant finding given the recent approval of a third topoisomerase 1 ADC for MBC (datopotamab deruxtecan) and given a recent unprecedented expansion in the development of ADCs with anti-topoisomerase 1 payloads, with >200 in clinical development, multiples of which are currently in phase III testing for MBC.[31]

One additional understudied category of patients that was evaluated in our study included those with HER2-0 MBC ($n = 74$). Our study found an encouraging median rwPFS of 6.3 months in patients with HR-positive/HER2-0 MBC, reinforcing the idea that activity with T-DXd can be observed even among patients with absent or extremely low HER2 expression.[32] This is in line with results of the DESTINY-Breast06 phase III trial, which included a subset of 76 patients treated with T-DXd for HER2-ultralow MBC (i.e. HER2-0 with 1%-10% of cells showing faint HER2 staining[33]), who were ultimately found to experience a similar response rate and PFS to those patients with HER2-low MBC.[7] Overall, the findings from the present study support the benefit of T-DXd in patients with HR-positive/HER2-ultralow MBC, an indication for which T-DXd has recently received approval by the FDA. Further testing of T-DXd in patients with HER2-0 MBC is currently ongoing within the DESTINY-Breast15 phase II trial (NCT05950945).

Lastly, our study evaluated the impact of *BRCA1* and *BRCA2* mutations and of tumoral PD-L1 expression on the performance of T-DXd. Patients with *BRCA1/2* mutations were found to have significantly shorter rwPFS with T-DXd (7.8 versus 9.2 months, hazard ratio 1.40, $P = 0.02$), which is consistent with what was observed in the DESTINY-Breast04 trial,[34] and patients with PD-L1 CPS ≥10 appeared to have numerically longer rwPFS with T-DXd (12.6 versus 6.9 months, hazard ratio 0.70, $P = 0.31$), which is also consistent with a positive trend observed in patients with a higher level of tumor infiltrating lymphocytes in DESTINY-Breast04. Further validation of these findings may aid in treatment selection for MBC, providing additional biomarkers for T-DXd besides HER2 expression.

Our study had several limitations. It was an observational, retrospective study, with heterogeneity in patient characteristics and treatment patterns. This limitation, however, is mitigated by the large sample size included in our study and the standardized methods utilized to annotate electronic health record-derived data in the Flatiron Health database.[10] Additionally, there was underrepresentation of certain subgroups of patients, warranting caution in the interpretation of the subgroup analyses carried out within our study. Some clinicopathologic data were not available in our study, including the rate of patients with brain metastases and the percentage of HER2-0 tumors with ultralow (versus HER2-null) expression, preventing the analysis of these specific populations. Lastly, no centralized review of HER2 status was feasible in our study, thus, we relied on local conventional HER2 testing to categorize patients.

In conclusion, in a large real-world database, we found favorable outcomes with T-DXd for the treatment of MBC, although with worse outcomes than those observed in clinical trials for patients with HER2-positive disease. Encouraging rwPFS was observed in understudied groups, such as patients with triple-negative and HR-positive/HER2-0 MBC; whereas shorter rwPFS was seen in patients who had been previously exposed to SG, highlighting potential cross-resistance between topoisomerase 1 ADCs utilized in sequence.

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DATA SHARING

EDM-Derived Data: The data that support the findings of this study were originated by and are the property of Flatiron Health, Inc., which has restrictions prohibiting the authors from making the data set publicly available. Requests for data sharing by license or by permission for the specific purpose of replicating results in this manuscript can be submitted to PublicationsDataAccess@flatiron.com.

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