Impact of Prior T-DM1 Exposure on the Efficacy of Trastuzumab Deruxtecan in HER2-Positive Metastatic Breast Cancer

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BACKGROUND

· Trastuzumab deruxtecan (T-DXd) is an effective ADC for HER2-positive mBC after progression on HER2-directed therapy.

· Whether prior exposure to another ADC, trastuzumab emtansine (T-DM1), diminishes subsequent T-DXd benefit remains uncertain.

· Clarifying this sequencing effect can guide individualized treatment strategies in advanced disease.

METHODS

Design & Setting: Multicenter, retrospective cohort across 21 oncology centers in Türkiye.

Population: Patients with HER2-positive mBC treated with T-DXd; clinical, pathological, and treatment data abstracted from institutional records.

Primary Endpoint: Progression-free survival (PFS) from T-DXd start to radiologic/clinical progression or last follow-up.

Exposure: Prior T-DM1 (yes vs no).

Statistics: Kaplan–Meier with log-rank; Cox proportional hazards to estimate HRs.

RESULTS

Among 199 patients, most were <65 years (91.5%), premenopausal (57.3%), and had ECOG 0–1 (99%); visceral metastases were frequent (79.9%), HER2 was IHC 3+ in 75.9%, and 47.7% had ≥2 metastatic sites

Demographic and baseline characteristics of the participants are summarized in Table 1.

Table 1. Baseline demographic and clinical characteristics of patients treated with trastuzumab deruxtecan (N=199).

Variable	Category	n (%)
Age Group	<65 / ≥65	182 (91.5) / 17 (8.5)
Menopausal Status	Premenopausal / Postmenopausal	114 (57.3) / 85 (42.7)
ECOG Performance Status	0 / 1 / ≥2	136 (68.3) / 61 (30.7) / 2 (1)
Histological Subtype	IDC / ILC / Other	177 (88.9) / 9 (4.5) / 10 (5)
Comorbidities	Yes / No	62 (31.2) / 137 (68.8)
ER Status	Positive / Negative	130 (65.3) / 69 (34.7)
PR Status	Positive / Negative	95(47.7) / 104 (52.3)
HER2 IHC Score	IHC 3+ / IHC 2+ ISH+	151 (75.9) / 48 (24.1)
Number of Metastatic Sites	1 / ≥2	104 (52.3) / 95 (47.7)
Visceral Metastasis	Yes / No	159 (79.9) / 40 (20.1)
Prior T-DM1 exposure	Yes / No	134 (67.3) / 65 (32.7)
Line of T-DXd therapy	1st–2nd / 3rd–4th / 5th or later	51 (26.2) / 107 (54.8) / 37 (19.0)

The median follow-up was 8.3 months (mean 10.5 months, ~95% CI 9.5–11.5).
T-DXd was most commonly administered in the third–fourth line (54.8%), with a median treatment line of 3 (range 1st–9th).

Kaplan–Meier estimates of PFS from T-DXd initiation are shown by prior T-DM1 exposure (Yes vs No). Survival distributions differed significantly (log-rank p=0.001). The prior T-DM1 cohort had a median PFS of 12.1 months (95% CI 7.7–16.5), while the T-DM1-naïve cohort did not reach median PFS within the observation window. Progression events occurred in 63 of 134 (47.0%) pretreated patients versus 9 of 65 (13.8%) naïve patients, and the direction and magnitude of effect aligned with the univariate Cox model (HR 3.03; 95% CI 1.51–6.10). Tick marks indicate censored observations; numbers at risk are provided beneath the time axis. PFS was defined as time from T-DXd start to radiologic/clinical progression or last follow-up.

As shown in Figure 1, prior T-DM1 exposure is associated with shorter PFS.

In univariate Cox analysis, prior T-DM1 exposure was associated with a three-fold higher risk of progression on T-DXd (HR = 3.03, 95% CI 1.51–6.10; p = 0.002). Other variables—including age group, menopausal status, ER/PR status, HER2 IHC score, number of metastatic sites, visceral disease, ECOG performance status, and T-DXd line—were not significant (all p > 0.05).

Univariate Cox regression results are shown in Table 2.

Figure 1. PFS on T-DXd by prior T-DM1 exposure.

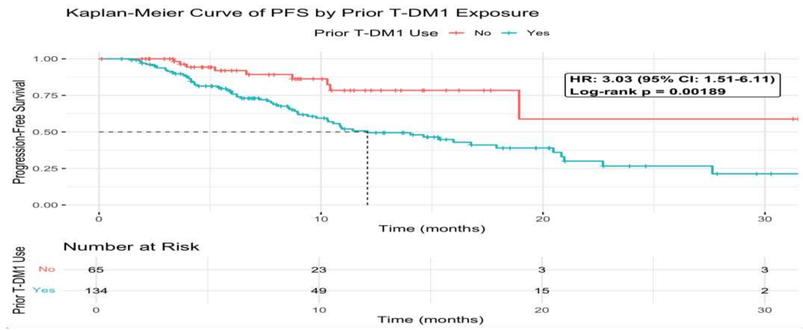


Table 2. Univariate Cox regression for progression-free survival on T-DXd.

Variables	Univariate HR (95% CI)	Univariate p-value
Age (<65 vs. ≥65)	1.03 (0.41–2.56)	0.957
ER status (Negative/Positive)	0.98 (0.60–1.60)	0.930
PR status (Negative/Positive)	1.14 (0.71–1.81)	0.590
HER2 status (low vs. 0)	1.00 (0.58–1.72)	0.999
Histologic Grade (2 vs. 3)	1.12 (0.45–2.81)	0.810
Komorbidity (yes vs. no)	0.91 (0.55–1.49)	0.702
Prios T-DM1 exposure	3.03 (1.51–6.10)	0.002
Menapausal Status	0.92 (0.57–1.47)	0.718
Timing of metastasis (de novo vs recurrent)	1.39 (0.85–2.27)	0.187
Number of metastatic sites	1.00 (0.63–1.59)	0.992
Visceral metastasis	1.22 (0.69–2.17)	0.489

CONCLUSION

- Prior T-DM1 exposure was associated with significantly shorter PFS and a higher risk of progression on subsequent T-DXd.
- Findings suggest treatment sequencing can influence T-DXd effectiveness and support personalized sequencing strategies in HER2-positive mBC.
- Prospective studies should validate these real-world observations and explore underlying resistance biology.

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