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Real-world outcomes of patients with HER2+ metastatic breast cancer after treatment with trastuzumab deruxtecan (T-DXd) in the United States

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PURPOSE

- This study aimed to characterize real-world treatment patterns and clinical outcomes in patients with HER2+ mBC who were previously treated with T-DXd in the real-world practice setting

DISCUSSION

Clinical Outcomes

- Patients who initiated a subsequent LOT following T-DXd exhibited a short median real-world progression-free survival (rwPFS, 4.3 mo; 95% CI, 3.5-5.0), overall survival (rwOS, 15.7 mo; 95% CI, 12.1-19.9), time to next treatment or death (rwTTNT/D, 6.9 mo; 95% CI, 5.4-8.8), and time to discontinuation or death (rwTTD/D, 6.2 mo; 95% CI, 4.9-8.3)
- The median rwPFS and rwOS align with reported data in the HER2+ population of patients with mBC in a retrospective analysis[6]

Treatment Patterns

- Subsequent to T-DXd, ≈50% of patients received regimens based on trastuzumab + tucatinib + chemo (TTC) (34.2%) or other anti-HER2 agents (18.9%)

Limitations

- Due to limited follow-up time, clinical outcomes should be interpreted with caution

CONCLUSIONS

- Therapies based on trastuzumab + tucatinib + chemotherapies and other anti-HER2 agents are mainly used in the post–T-DXd real-world setting, although potential differences by line exist
- This study demonstrates an ongoing and substantial unmet need for more effective treatments among patients with HER2+ mBC previously treated with T-DXd, as shown by the short rwPFS/OS and short times observed on subsequent therapy following T-DXd
- Future analysis using a real-world sample with longer follow-up, especially for patients treated with T-DXd in the early line setting (1L and 2L) is warranted

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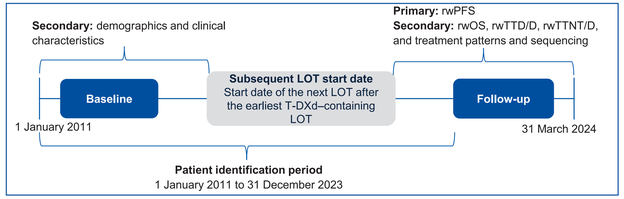
BACKGROUND

- HER2+ BC accounts for 15% to 20% of the ≈300,000 new BC cases diagnosed annually in the US[1]
- T-DXd—a HER2-directed antibody-drug conjugate—was first approved by the US Food and Drug Administration in 2019 for the treatment of HER2+ unresectable or mBC following ≥2 prior anti–HER2-based therapies; it is now the preferred standard of care in the 2L setting, following additional approval in 2022 based on results from DESTINY-Breast03[2-4]
- Treatment selection and associated clinical outcomes in patients with HER2+ mBC after treatment with T-DXd are unclear
- The purpose of this study was to assess real-world outcomes and treatment patterns in patients with HER2+ mBC who initiated a subsequent treatment following T-DXd in the US

METHODS

- This was a noninterventional, retrospective, observational cohort study
- Study time periods and key outcomes are described in **Figure 1**; key inclusion criteria are outlined in **Figure 2**
- EHR-based data were obtained from the US-based Flatiron Health Enhanced Datamart (EDM), a database of de-identified patient information from ≈280 US oncology clinics (≈800 sites of care)[5]
- Kaplan-Meier methods were used to analyze rwPFS, rwOS, rwTTD/D, and rwTTNT/D at prespecified time points (3, 6, 12, and 24 months)

Figure 1. Study Design Schema

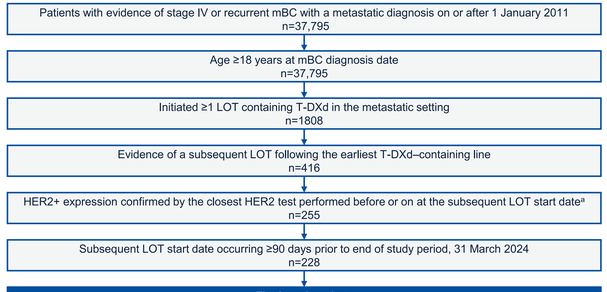


RESULTS

Patient Selection

- Overall, 228 patients met the eligibility criteria and were included in the final study cohort (**Figure 2**)

Figure 2. Patient Attrition



[a]A HER2+ test result was defined as IHC 3+ or ISH+.

RESULTS (CONT.)

Baseline Characteristics

- Almost a third of patients (31.1%) received T-DXd in the 3L and thus initiated a subsequent LOT in the 4L (**Table 1**)
- The majority of patients received either T-DM1 or THP in the line directly before T-DXd (38.5% and 24.3%, respectively)

Table 1. Demographic and Clinical Characteristics (N=228)

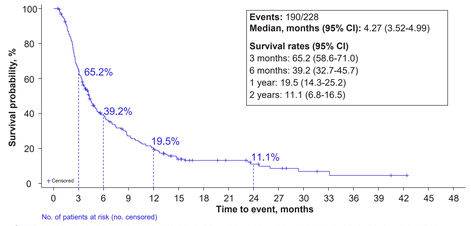
Age at the subsequent LOT start date, mean (SD), years	60.3 (11.9)
Sex, n (%)	
Female	227 (99.6)
Male	1 (0.4)
Race, n (%)	
Asian	4 (1.8)
Black or African American	34 (14.9)
White	152 (66.7)
Other	223 (10.1)
Unknown	15 (6.6)
Practice type, n (%)	
Academic	59 (25.9)
Community	158 (69.3)
Both	11 (4.8)
BMI at the subsequent LOT start date, median (Q1-Q3), kg/m²	25.6 (21.6-30.3)
ECOG PS at the subsequent LOT start date, n (%)	
0	77 (33.8)
1	95 (41.7)
2	22 (9.6)
3	7 (3.1)
4	1 (0.4)
Unknown	26 (11.4)
Regimen received directly prior to T-DXd, n (%)[a]	
THP-based regimen	53 (24.3)
T-DM1–based regimen	84 (38.5)
TTC-based regimen	18 (8.3)
Trastuzumab + chemo	18 (8.3)
Anti-HER2 mAbs/TKIs	25 (11.5)
Anti-HER2 TKI + chemo	15 (6.9)
Other	5 (2.3)
Line in which T-DXd was prescribed, median (Q1-Q3)	3 (2-4)
T-DXd LOT; subsequent treatment LOT, n (%)	
1L T-DXd; 2L subsequent treatment	10 (4.4)
2L T-DXd; 3L subsequent treatment	51 (22.4)
3L T-DXd; 4L subsequent treatment	71 (31.1)
4L T-DXd; 5L subsequent treatment	52 (22.8)
5L T-DXd; 6L subsequent treatment	25 (11.0)
6L+ T-DXd; 7L+ subsequent treatment	19 (8.3)
Follow-up time from the subsequent LOT start date, median (Q1-Q3), mo	10.4 (4.6-17.0)
Number of metastatic sites prior to or in the month of the subsequent LOT start date	
Median [Q1-Q3]	3.0 [2.0-4.0]
1, n (%)	36 (15.8)
2, n (%)	45 (19.7)
≥3, n (%)	147 (64.5)
Sites of metastases prior to or in the month of the subsequent LOT start date, n (%)	
Bone only	16 (7.0)
Visceral only	64 (28.1)
Bone and visceral	148 (64.9)

[a]Treatments were categorized according to the following hierarchical system: **THP-based regimen** if regimen contained trastuzumab in any form (including T-DM1 or T-DXd) ***or*** pertuzumab + taxane, *otherwise*; **T-DM1–based regimen** if regimen contained T-DM1, *otherwise*; **TTC-based regimen** if regimen contained any HER2-targeted TKI + trastuzumab in any form (including T-DM1 or T-DXd) + any chemo, *otherwise*; **Trastuzumab + chemo** if regimen contained trastuzumab + chemo, *otherwise*; **Anti-HER2 mAbs/TKIs** if regimen contained any HER2-targeted drug besides T-DM1 and T-DXd and no chemo, *otherwise*; **Anti-HER2 TKI + chemo** if regimen contained HER2-targeted TKI + chemo, *otherwise*; **Other** for all other regimens.

Real-World Clinical Outcomes in All Patients

- The median rwPFS from the subsequent LOT start date was 4.3 mo (95% CI, 3.5-5.0) (**Figure 3**)

Figure 3. rwPFS Among Patients Who Initiated a Subsequent LOT (N=228)



- The median rwOS, rwTTNT/D, and rwTTD/D were 15.7 mo (95% CI, 12.1-19.9), 6.9 mo (95% CI, 5.4-8.8), and 6.2 mo (95% CI, 4.9-8.3), respectively (**Table 2**)

Table 2. rwOS, rwTTNT/D, and rwTTD/D Among Patients Who Initiated a Subsequent LOT (N=228)

	rwOS	rwTTNT/D	rwTTD/D
Events, N	119	168	172
Median (95% CI) , months	15.67 (12.12-19.94)	6.87 (5.42-8.80)	6.24 (4.93-8.31)
Survival probability (95% CI)			
3 months	90.2 (85.5-93.4)	75.5 (69.3-80.6)	72.8 (66.4-78.1)
6 months	75.5 (69.1-80.7)	54.9 (48.0-61.2)	51.9 (45.0-58.3)
1 year	57.8 (50.6-64.3)	32.6 (26.2-39.2)	30.1 (23.8-36.6)
2 years	35.1 (27.3-43.0)	16.3 (10.7-23.0)	14.1 (8.8-20.5)

Real-World Clinical Outcomes by Line of Subsequent LOT Initiation

- The median rwPFS, rwOS, and rwTTNT/D decreased with advancing line in which the subsequent LOT was received (**Table 3**)

Table 3. Real-World Clinical Outcomes by Line of Subsequent LOT Initiation[a]

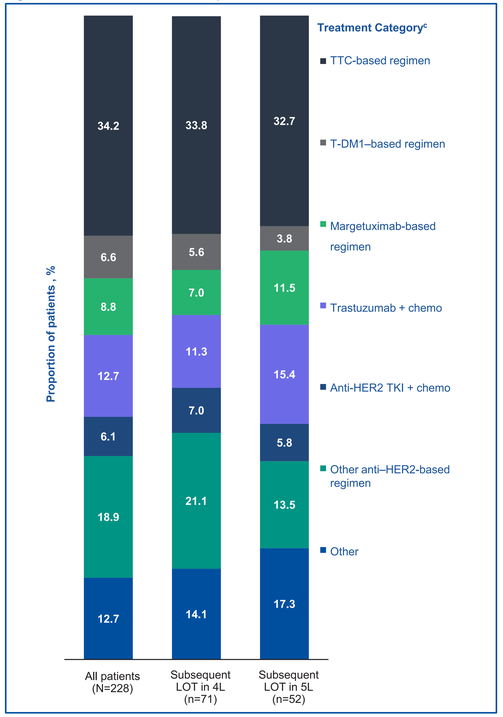
Median (95% CI), months	4L (n=71)	5L (n=52)	6L+ (n=44)
rwPFS	6.01 (4.30-8.05)	4.17 (2.69-6.54)	3.33 (2.46-4.60)
rwOS	20.60 (12.19-27.99)	13.63 (8.77-NE)	10.64 (5.82-17.18)
rwTTNT/D	10.15 (8.41-13.34)	6.28 (3.58-11.60)	5.32 (3.19-8.15)
rwTTD/D	10.15 (6.97-13.24)	4.60 (3.02-8.97)	4.93 (3.19-8.11)
Follow-up time	12.2 (7.0-20.6)	10.3 (5.2-16.7)	9.8 (4.5-16.9)

[a]Results from patients who initiated a subsequent LOT (that which followed their earliest T-DXd-containing line) in the 2L or 3L setting were omitted due to the recency of T-DXd approval in the early-line setting, resulting in limited endpoint maturity.

Treatment Patterns Subsequent to T-DXd

- In the subsequent LOT following T-DXd, TTC-based regimens were most common (34.2%), followed by other anti–HER2-based regimens, including trastuzumab combinations (excluding trastuzumab + chemo) and T-DXd (18.9%), and trastuzumab + chemo (12.7%) (**Figure 4**)

Figure 4. Treatment Patterns Subsequent to T-DXd[a,b]



[a]Results from patients who initiated a subsequent LOT (that which followed their earliest T-DXd-containing line) in the 2L or 3L setting were omitted due to the recency of T-DXd approval in the early-line setting, resulting in limited endpoint maturity. [b]Categories of treatment following earliest line of T-DXd. Data are shown for all patients and for patients who received a subsequent LOT (that which followed their earliest line of T-DXd) in the 4L or 5L setting; [c]Treatments were categorized according to the following hierarchical system: **TTC-based regimen** if regimen contained any HER2-targeted TKI + trastuzumab in any form (including T-DM1 or T-DXd) + any chemo, *otherwise*; **T-DM1-based regimen** if regimen contained T-DM1, *otherwise*; **Margetuximab-based regimen** if regimen contained margetuximab, *otherwise*; **Trastuzumab + chemo** if regimen contained trastuzumab + chemo, *otherwise*; **Other anti-HER2 TKI + chemo** if regimen contained HER2-targeted TKI + chemo, *otherwise*; **Other anti-HER2 regimen** if regimen contained other anti-HER2 drug(s), *otherwise*; **Other** for all other regimens (eg, ET only, other targeted therapies, chemo only, and regimens containing IO).

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ABBREVIATIONS

1L, first line; 2L, second line; 3L, third line; 4L, fourth line; 5L, fifth line; 6L, sixth line; 7L, seventh line; BC, breast cancer; BMI, body mass index; CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; chemo, chemotherapy; ECOG PS, Eastern Cooperative Oncology Group performance status; EDM, Enhanced Datamart; EHR, electronic health record; ET, endocrine therapy; HER, human epidermal growth factor receptor; IHC, immunohistochemistry; IO, immuno-oncology; ISH, in situ hybridization; LOT, line of therapy; mAb, monoclonal antibody; mBC, metastatic breast cancer; Q, quartile; rwOS, real-world overall survival; rwPFS, real-world progression-free survival; rwTTD, real-world time to discontinuation or death; rwTTNT/D, real-world time to next treatment or death; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan; THP, taxane + trastuzumab + pertuzumab; TKI, tyrosine kinase inhibitor; TTC, trastuzumab + tucatinib + chemo.

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