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Impact of HER2 status dynamics on fam-trastuzumab deruxtecan-nxki treatment outcomes in metastatic breast cancer: real-world insights

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Background

- Metastatic breast cancer (MBC) remains a significant clinical challenge.
- Fam-trastuzumab deruxtecan-nxki (T-DXd) has demonstrated notable efficacy in clinical trials such as DESTINY-Breast01 and DESTINY-Breast09.[1-3]
- T-DXd has shown promising results in treating not only HER2-positive but also HER2-low and HER2-ultralow subtypes.[4]
- However, it is still unclear how HER2 status and its changes over time affect treatment outcomes with T-DXd.
- Moreover, there is evidence that HER2 status can change during or after T-DXd treatment.[5]
- This study uses real-world data (RWD) from a large, clinically annotated cohort to evaluate the impact of HER2 status and its dynamics on treatment outcome as well as T-DXd treatment on HER2 status.

Methods

- A retrospective analysis was conducted using RWD from 300 MBC patients treated with T-DXd, sourced from the Tempus database[6].
- Key endpoints included real-world (rw) best overall response (rwBOR; responder as reference), rw-progression free survival (rwPFS), rw-time to next treatment (rwTTNT), and rw-overall survival (rwOS).
- Patient outcomes were curated by Tempus based on the physician assessment. Patients with complete response (CR) or partial response (PR) were classified as responders while those with stable disease (SD) or progressive disease (PD) were classified as non-responders.
- HER2 status was defined using immunohistochemistry (IHC; 0, 1+, 2+, 3+) and in-situ hybridization (ISH; negative, positive). HER2 low was defined as IHC 1+ or IHC 2+ with a negative ISH, HER2 positive was defined as IHC 2+ with a positive ISH or IHC 3+.
- HER2 status change was assessed in patients with both pre- and post-T-DXd HER2 status data, with post-treatment IHC conducted at least six weeks after treatment initiation.
- Patients with multiple pre-T-DXd treatment measurements showing no change in HER2 status over time were considered HER2 IHC Stable.
- Logistic regression was used for rwBOR, and Cox proportional hazards models with log-rank tests were applied for rwPFS, rwTTNT, and rwOS while adjusting for age at T-DXd treatment, ER/PR status, care plan, sampling time, tissue location.

Results

Table 1. Key characteristic tables.

Characteristic	N = 300
Gender, n (%)	
Female	295 (98)
Male	5 (1.7)
Age at T-DXd, mean (SD)	58 (13)
Year between diagnosis and T-DXd, mean (SD)	5.5 (4.9)
Histology at diagnosis, n (%)	
Ductal	226 (77)
Lobular	25 (8.5)
Other	44 (15)
Unknown	5
HER2 status, n (%)	
HER2+	102 (34)
HER2+/Low	17 (5.7)
HER2 Low	140 (47)
HER2-/Low	18 (6.0)
HER2-	21 (7.0)
HER2 IHC stable before T-DXd, n (%)	
Change	155 (70)
Stable	68 (30)
HER2 status change post T-DXd, n (%)	
Unchanged	42 (63)
Decrease/Increase	25 (37)
Tissue location, n (%)	
Breast	75 (25)
Liver	69 (23)
Other	156 (52)
ER status before T-DXd, n (%)	
ER+	201 (69)
ER-	89 (30)
ER+, ER-	3 (1.0)
Unknown	7
PR status before T-DXd, n (%)	
PR+	115 (40)
PR-	173 (59)
PR+, PR-	3 (1.0)
Unknown	9
Hormone receptor status before T-DXd, n (%)	
HR+	207 (72)
HR-	82 (28)
Unknown	11
HER2 IHC change post T-DXd, n (%)	
Unchanged	38 (47)
Decrease	32 (40)
Increase	11 (14)

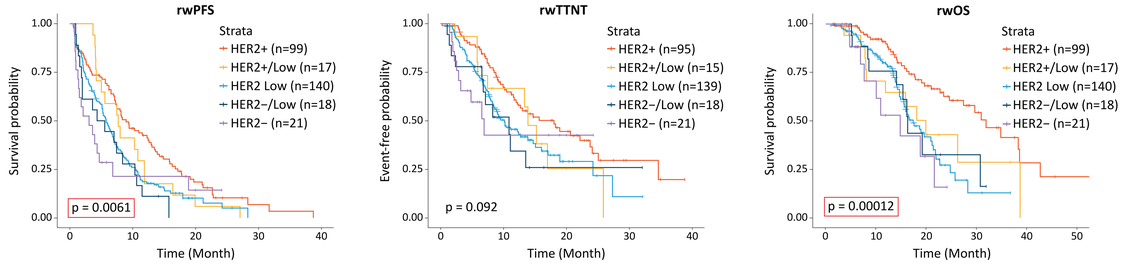
ER+,ER- and PR+,PR- indicating patients with conflicting report of ER+ and ER- or PR+ and PR- during data curation
'Unknown' category was not included in calculations for histology, ER status, PR status, or hormone receptor status characteristics

Table 2. HER2 Status or Changes in Association with T-DXd Clinical Outcome.

Characteristic	rwBOR OR	rwBOR 95% CI	rwBOR P-value	rwPFS HR	rwPFS 95% CI	rwPFS P-value	rwTTNT HR	rwTTNT 95% CI	rwTTNT P-value	rwOS HR	rwOS 95% CI	rwOS P-value
HER2 status before T-DXd												
HER2+	1(ref)			1(ref)			1(ref)			1(ref)		
HER2+/Low	8.86	2.26, 34.65	$1.73X10^{-3}$	1.36	0.79, 2.34	0.270	1.60	0.79, 3.23	0.190	1.94	0.96, 3.91	0.064
HER2 Low	1.87	1.05, 3.33	0.035	1.60	1.18, 2.16	$2.32X10^{-3}$	1.75	1.19, 2.58	$4.30X10^{-3}$	2.35	1.5, 3.69	$2.02X10^{-4}$
HER2-/Low	3.92	1.24, 12.39	0.020	1.92	1.11, 3.31	0.019	1.94	0.98, 3.83	0.056	2.13	1.01, 4.45	0.046
HER2-	3.09	1.05, 9.05	0.040	1.87	1.08, 3.26	0.026	1.75	0.85, 3.59	0.128	3.21	1.47, 6.99	$3.31X10^{-3}$
HER2 IHC stable before T-DXd												
Change	1(ref)			1(ref)			1(ref)			1(ref)		
Stable	0.27	0.14, 0.53	$1.23X10^{-4}$	0.58	0.41, 0.81	$1.41X10^{-3}$	0.61	0.4, 0.94	0.025	0.48	0.29, 0.78	$2.98X10^{-3}$
HER2 IHC change post T-DXd												
Unchanged	1(ref)			1(ref)			1(ref)			1(ref)		
Decrease	1.33	0.39, 4.51	0.650	1.31	0.71, 2.44	0.391	0.72	0.34, 1.51	0.382	1.37	0.45, 4.15	0.582
Increase	4.12	0.64, 26.57	0.136	2.21	1.01, 4.82	0.047	1.86	0.76, 4.53	0.173	1.02	0.23, 4.46	0.980
HER2 status change post T-DXd												
Unchanged	1(ref)			1(ref)			1(ref)			1(ref)		
Increase/Decrease	1.15	0.29, 4.5	0.843	1.89	1.02, 3.5	0.041	1.20	0.58, 2.46	0.623	2.13	0.68, 6.66	0.195

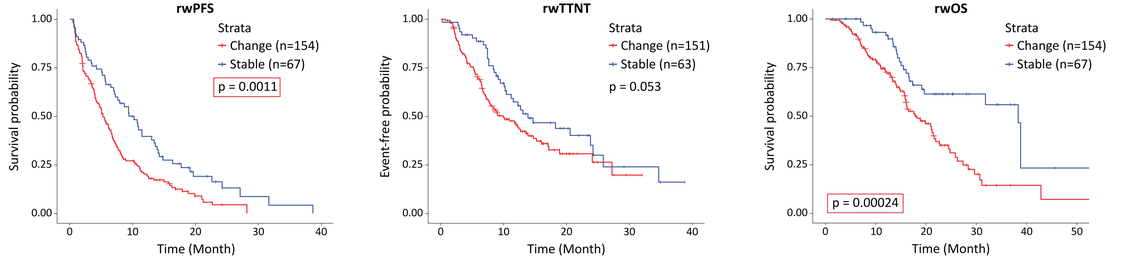
HER2+/Low – HER2 IHC 2+, missing FISH
HER2-/Low – HER2 IHC numerical missing, categorical is Negative

Figure 1. Patients with HER2+ before T-DXd Showed Trend towards More Favorable Outcomes for rwPFS, rwTTNT, and rwOS After T-DXd as Compared with HER2 low and/or HER2-



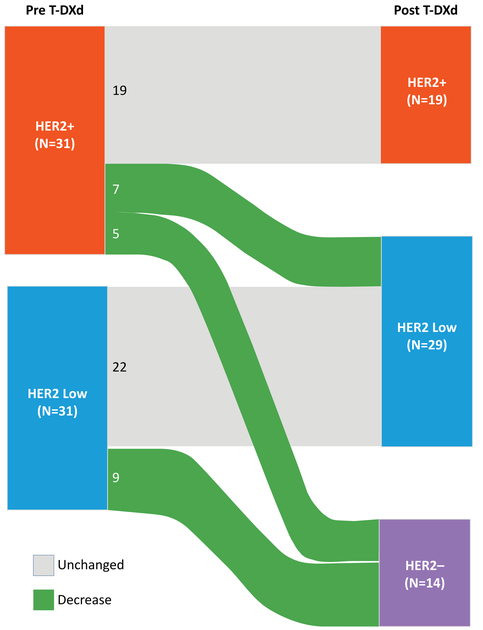
P values if not specified are from log-rank tests

Figure 2: HER2 IHC Changes Pre T-DXd Showed Trend towards Worse rwPFS, rwTTNT, and rwOS. HER2 IHC stable before T-DXd associated with favorable outcomes of all the listed endpoints



P values if not specified are from log-rank tests

Figure 3: Changes in HER2 Status in Patients' Tumors after T-DXd Treatment. Following treatment, 21 (34%) of these 62 patients exhibited a decrease in HER2 status with T-DXd treatment. Among 31 HER2-positive patients, 5 (16%) dropped to HER2-negative and 7 (22%) to HER2-low. Among 31 HER2-low patients, 9 (29%) dropped to HER2-negative.



3 HER2-/Low and 2 HER2- patients not included in the figure

Conclusions

- This study highlights the clinical relevance of monitoring HER2 status and the dynamics of HER2 status and its impact on treatment outcome with a HER2-targeting ADC, T-DXd in MBC.
- Following treatment with T-DXd, 34% had a decrease in HER2 status.
- Changes in HER2 status on- or post-treatment with T-DXd were associated with poorer progression-free survival, underscoring the importance of ongoing HER2 monitoring.
- These real-world insights can inform personalized treatment strategies for MBC.

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References: **1.** Modi et al. *N Engl J Med*. 2020;382:610-621; **2.** Tolaney et al. *J Clin Oncol*. 2025;43(17_suppl); **3.** Hamilton et al. *J Clin Oncol*. 2024;42:1025; **4.** Bardia et al. *N Engl J Med*. 2024;391:2110-2122; **5.** Gouda et al. *Clin Cancer Res*. 2025;31(7):1268-1274; **6.** Tempus. https://www.tempus.com.

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