Poster P5-07-29

Trastuzumab deruxtecan with pembrolizumab in previously treated HER2-expressing advanced or metastatic breast cancer: Interim analyses of the breast cohorts from the open-label, multicenter, phase 1b study DS8201-A-U106

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Objective

- To evaluate the efficacy and safety of trastuzumab deruxtecan (T-DXd) in combination with pembrolizumab in patients with previously treated human epidermal growth factor receptor 2 (HER2)-positive or HER2-low metastatic breast cancer (mBC)

Conclusions

- Combination therapy with T-DXd plus pembrolizumab showed encouraging efficacy in heavily pretreated patients with HER2-positive and HER2-low mBC
- Durable progression-free survival (PFS) and responses were observed in patients with HER2-low mBC despite lower than expected confirmed objective response rate (ORR) in this cohort
- The safety profile was consistent with the known profiles of the individual drugs and was generally manageable, with no grade 4 or 5 interstitial lung disease (ILD)/pneumonitis events reported
- The value of adding immunotherapy to T-DXd patients with HER2-positive or HER2-low mBC remains to be determined

Plain Language Summary

Why did we perform this research?
Trastuzumab deruxtecan (T-DXd) is an anticancer therapy that targets a protein called human epidermal growth factor receptor 2 (HER2).[1,2] There is evidence to suggest that combining therapies that target HER2 with other agents that help to control immune system responses (immunotherapy) could result in enhanced anticancer activity.[3] Given that T-DXd monotherapy has been shown to be effective in patients with metastatic breast cancer (mBC) with either positive (HER2-positive) or low (HER2-low) levels of HER2 expression in their tumor cells, researchers are interested in assessing potential additive effects when combining T-DXd with immunotherapy in these 2 patient populations.

How did we perform this research?
Patients with previously treated HER2-positive or HER2-low mBC were enrolled in this study. There were 2 parts to the study. Part 1 determined the recommended dose for safety of additional study of T-DXd plus immunotherapy with pembrolizumab. Then, in part 2, patients were assigned according to their HER2 levels to either cohort 1 (HER2-positive mBC that had progressed during treatment with another HER2-targeted drug called trastuzumab emtansine) or cohort 2 (HER2-low mBC that had progressed with standard therapy). At data cutoff (November 18, 2023), 30 patients in cohort 1 and 26 patients in cohort 2 had received T-DXd 5.4 mg/kg plus pembrolizumab 200 mg intravenously every 3 weeks.

What were the findings of this research?
This interim analysis found that T-DXd plus pembrolizumab had a manageable safety profile and demonstrated promising efficacy in heavily pretreated patients with HER2-positive and HER2-low mBC. The confirmed objective response rate (the proportion of patients who had either a partial or complete response to treatment according to assessment of tumor shrinkage/tumor reduction) was 80% in patients with HER2-positive mBC and 23% in patients with HER2-low mBC.

What are the implications of this research?
Combining an immunotherapy agent such as pembrolizumab with T-DXd may have beneficial additive effects in this patient population; however, further research in larger databases is needed to confirm these findings.

Where can I access more information?
To learn more about the DS8201-A-U106 study, you can visit https://clinicaltrials.gov/study/NCT04042701.

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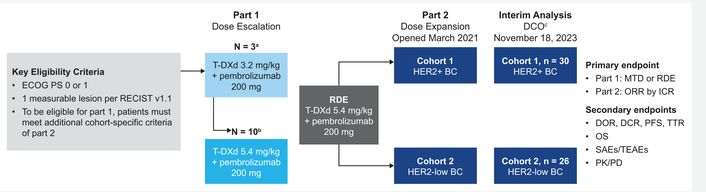
Introduction

- T-DXd, a HER2-directed antibody-drug conjugate,[1,2] has shown strong and durable antitumor activity in patients with previously treated HER2-positive and HER2-low or HER2-ultralow mBC[3-6]
- T-DXd is approved for the treatment of patients with unresectable or metastatic HER2-positive (immunohistochemistry [IHC] 3+ or IHC 2+ and in situ hybridization [ISH]-positive) breast cancer who have received at least 1 prior anti-HER2–based regimen, based on results of DESTINY-Breast03 (NCT03529110)[7,8]
- T-DXd is also approved for patients with unresectable or metastatic HER2-low (IHC 1+ or IHC 2+ and ISH-negative) breast cancer who have received chemotherapy in the metastatic setting or developed disease recurrence during or within 6 months of completing adjuvant chemotherapy[7,8]
- In the ongoing DESTINY-Breast06 study (NCT04494425), patients with hormone receptor–positive, HER2-low or HER2-ultralow (IHC 0 with membrane staining) mBC showed significant improvements in PFS with T-DXd versus treatment of physician's choice[5]
  - This led to breakthrough therapy designation of T-DXd in the United States for the treatment of patients with unresectable or metastatic hormone receptor–positive, HER2-low or HER2-ultralow breast cancer who have received at least 1 prior line of endocrine therapy[9]
- Previous preclinical studies combining HER2-targeted therapy with immune checkpoint inhibitors that target the programmed death 1/ programmed death ligand 1 pathway demonstrated the potential for additive effects of enhancing tumor immunogenicity together with direct tumor cell death in animal models[10,11]
- The efficacy of T-DXd monotherapy in patients with HER2-positive and HER2-low or HER2-ultralow breast cancer and potential additive effects of immune checkpoint inhibition provide a rationale for investigating T-DXd combined with immunotherapy in these patient populations
- We report interim efficacy and safety results for T-DXd plus pembrolizumab in patients with previously treated HER2-positive or HER2-low mBC in the DS8201-A-U106 study (U106; NCT04042701)

Methods

- U106 is an open-label, multicenter, 2-part, phase 1b study (**Figure 1**)
- Part 1 determined the recommended dose for expansion (RDE) of T-DXd plus pembrolizumab
- In part 2, patients with mBC were included by centrally determined HER2 expression status in one of the following cohorts:
  - Cohort 1 (HER2-positive; IHC 3+, IHC 2+/ISH+ that progressed on trastuzumab emtansine [T-DM1])
  - Cohort 2 (HER2-low; IHC 1+ or IHC2+/ISH− that progressed on standard therapy)
- The primary endpoint in part 2 was confirmed ORR by independent central review (ICR), and key secondary efficacy endpoints included ICR- and investigator-assessed disease control rate (DCR), duration of response (DOR), PFS, overall survival (OS), and time to response (TTR)

Figure 1. Study design



[a]Includes 1 patient with NSCLC.
[b]Includes 3 patients with NSCLC.
[c]DCO determined by time that all patients in cohorts 1 and 2 would have at least 12 months of follow-up or discontinued treatment.
Cohorts 3 and 4 (patients with immune-oncology–naive HER2-expressing NSCLC [n = 22] and *HER2*-mutant NSCLC [n = 30]) assigned to the RDE in part 2 of this study are not shown.

Results

- The RDE was T-DXd 5.4 mg/kg (the approved dose in mBC) and pembrolizumab 200 mg intravenously every 3 weeks (Q3W)
- At data cutoff (November 18, 2023), 56 patients with mBC had received the RDE (30 in cohort 1 [HER2-positive mBC]; 26 in cohort 2 [HER2-low mBC, including 7 patients treated with the RDE during part 1])

Patient Characteristics

- The median age of all patients with mBC in the study was 57.5 years. Most patients (90%) with HER2-positive mBC were from Europe, whereas 62% of patients with HER2-low mBC were from the United States. Overall, patients had received a median of 3 prior chemotherapy regimens and a median of 1 prior hormonal therapy in the metastatic/ locally advanced setting (**Table 1**). All patients with HER2-positive mBC had received T-DM1

Table 1. Baseline characteristics

	T-DXd 5.4 mg/kg + Pembrolizumab 200 mg Q3W		
Characteristics	**Cohort 1 (HER2-positive) n = 30**	**Cohort 2 (HER2-low) n = 26**	**All Patients N = 56**
Age, median (range), years	58.6 (37.0-81.8)	56.3 (37.3-73.0)	57.5 (37.0-81.8)
Female sex, n (%)	29 (96.7)	25 (96.2)	54 (96.4)
Region/country of enrollment, n (%)			
United States	3 (10.0)	16 (61.5)	19 (33.9)
European Union	27 (90.0)	10 (38.5)	37 (66.1)
ECOG PS, n (%)			
0	13 (43.3)	7 (26.9)	20 (35.7)
1	17 (56.7)	19 (73.1)	36 (64.3)
Tumor stage at study entry, n (%)			
IIIB	1 (3.3)	0	1 (1.8)
IV	29 (96.7)	26 (100.0)	55 (98.2)
Centrally assessed HER2 status (IHC), n (%)			
1+	0	13 (50.0)	13 (23.2)
2+/ISH-	0	13 (50.0)	13 (23.2)
2+/ISH+	7 (23.3)	0	7 (12.5)
3+	23 (76.7)	0	23 (41.1)
Hormone receptor status, n (%)			
Positive	17 (56.7)	25 (96.2)	42 (75.0)
Negative	12 (40.0)	0	12 (21.4)
Indeterminate/missing	1 (3.3)	1 (3.8)	2 (3.6)
Prior regimens in the metastatic/locally advanced setting, median (range)	3.0 (2-12)	4.5 (1-12)	4.0 (1-12)
Chemotherapy	3 (2-12)	2.5 (0-7)	3.0 (0-12)
Endocrine therapy	0 (0-4)	2.0 (0-6)	1.0 (0-6)
History of brain metastases, n (%)	5 (16.7)	5 (19.2)	10 (17.9)
History of lung metastases, n (%)	9 (30.0)	9 (34.6)	18 (32.1)
History of liver metastases, n (%)	15 (50.0)	20 (76.9)	35 (62.5)

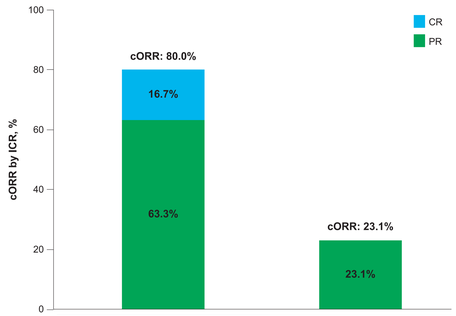
Patient Disposition

- Median duration of T-DXd treatment was 9.9 months (range, 1-24 months) in patients with HER2-positive mBC and 6.2 months (range, 1-30 months) in patients with HER2-low mBC. Median duration of pembrolizumab treatment was 9.7 months (range, 1-22 months) and 6.2 months (range, 1-24 months), respectively
- At data cutoff, T-DXd and pembrolizumab treatment was ongoing in 7 and 4 patients, respectively, in patients with HER2-positive mBC and no patients with HER2-low mBC
- The most common reasons for discontinuation of T-DXd treatment in cohorts 1 (HER2-positive mBC) and 2 (HER2-low mBC), respectively, were progressive disease (12 [40.0%] and 16 [61.5%]), clinical progression (4 [13.3%] and 5 [19.2%]), and adverse events (7 [23.3%] and 2 [7.7%]). The most common reasons for discontinuation of pembrolizumab treatment in cohorts 1 and 2, respectively, were progressive disease (13 [43.3%] and 15 [57.7%]), clinical progression (4 [13.3%] and 5 [19.2%]), and adverse events (8 [26.7%] and 2 [7.7%])

Efficacy

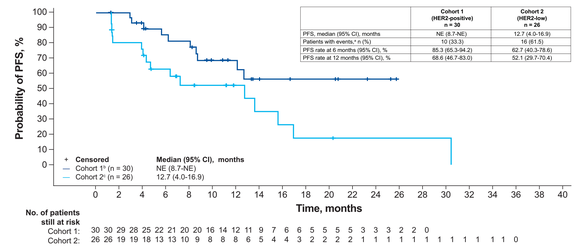
- Median duration of follow-up was 16.1 months (range, 3.0-30.2 months) in patients with HER2-positive mBC and 15.3 months (range, 1.4-34.1 months) in patients with HER2-low mBC
- Key efficacy results are summarized in **Figures 2** and **3**
  - In patients with HER2-positive mBC, cORR by ICR was 80.0% and median PFS was not evaluable
  - In patients with HER2-low mBC, cORR by ICR was 23.1% and median PFS was 12.7 months

Figure 2. Efficacy results by ICR



	Cohort 1 HER2-positive n = 30	Cohort 2 HER2-low n = 26
cORR by ICR, n (% [95% CI])	24 (80.0 [61.4-92.3])	6 (23.1 [9.0-43.6])
CR	5 (16.7)	0
PR	19 (63.3)	6 (23.1)
SD	6 (20.0)	15 (57.7)
PD	0	4 (15.4)
NE	0	1 (3.8)
DCR, n (% [95% CI])	30 (100.0 [88.4-100.0])	21 (80.8 [60.6-93.4])
DOR, median (95% CI), months	NE (6.9-NE)	11.4 (2.8-NE)

Figure 3. Probability of PFS by ICR in cohorts 1 (HER2-positive mBC) and 2 (HER2-low mBC)



	Cohort 1 (HER2-positive) n = 30	Cohort 2 (HER2-low) n = 26
PFS, median (95% CI), months	NE (8.7-NE)	12.7 (4.0-16.9)
Patients with events,[a] n (%)	10 (33.3)	16 (61.5)
PFS rate at 6 months (95% CI), %	85.3 (65.3-94.2)	62.7 (40.3-78.6)
PFS rate at 12 months (95% CI), %	68.6 (46.7-83.0)	52.1 (29.7-70.4)

No. of patients still at risk																														
Cohort 1:	30	30	29	28	25	22	21	20	20	16	14	12	11	9	7	6	6	5	5	5	3	3	3	2	2	0				
Cohort 2:	26	26	19	19	18	13	13	10	9	8	8	8	6	5	4	4	3	2	2	2	2	1	1	1	1	1	1	1	1	0

[a]Progressive disease or death.
[b]Patients with HER2-positive mBC who received T-DXd 5.4 mg/kg in part 1 and part 2.
[c]Patients with HER2-low mBC who received T-DXd 5.4 mg/kg in part 1 and part 2.

Safety

- Drug-related treatment-emergent adverse events (TEAEs) were consistent with the safety profiles of T-DXd and pembrolizumab, and there were no drug-related TEAEs associated with death (**Table 3**)
- The overall incidence of independently adjudicated drug-related cases of ILD/pneumonitis is summarized in **Table 4**; no grade 4 or 5 events were reported

Table 3. Overall safety summary (drug-related TEAEs)[a]

	Cohort 1 (HER2-positive) n = 30	Cohort 2 (HER2-low) n = 26	All Patients N = 56
Treatment duration, median (range), months			
T-DXd	9.9 (1-24)	6.2 (1-30)	8.0 (1-30)
Pembrolizumab	9.7 (1-22)	6.2 (1-24)	8.0 (1-24)
Any drug-related TEAE[a]	30 (100.0)	25 (96.2)	55 (98.2)
Grade ≥3 drug-related TEAE[a]	13 (43.3)	6 (23.1)	19 (33.9)
Serious drug-related TEAE[a]	6 (20.0)	2 (7.7)	8 (14.3)
Drug-related TEAE associated with discontinuation[a]	9 (30.0)	2 (7.7)	11 (19.6)
Drug-related TEAE associated with dose reduction[b]	8 (26.7)	4 (15.4)	12 (21.4)
Drug-related TEAE associated with interruption[a]	14 (46.7)	3 (11.5)	17 (30.4)
Drug-related TEAE associated with an outcome of death[a]	0	0	0

[a]Drug-related TEAEs may be associated with T-DXd and/or pembrolizumab.
[b]All events were related to T-DXd.

Table 4. Independently adjudicated drug-related ILD/pneumonitis

	Cohort 1 (HER2-positive) n = 30	Cohort 2 (HER2-low) n = 26	All Patients N = 56
Independently adjudicated drug-related ILD/pneumonitis			
Any grade	3 (10.0)	4 (15.4)	7 (12.5)
Grade 1	0	0	0
Grade 2	3 (10.0)	3 (11.5)	6 (10.7)
Grade 3	0	1 (3.8)	1 (1.8)
Grade 4	0	0	0
Grade 5	0	0	0

Abbreviations

BC, breast cancer; CR, complete response; CTCAE, Common Terminology Criteria for Adverse Events; DCO, data cutoff; DCR, disease control rate; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; HER2, human epidermal growth factor receptor 2; ICR, independent central review; IHC, immunohistochemistry; ILD, interstitial lung disease; mBC, metastatic breast cancer; MTD, maximum tolerated dose; NE, not estimable; NSCLC, non–small cell lung cancer; ORR, objective response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response; Q3W, every 3 weeks; RDE, recommended dose for expansion; RECIST v1.1, Response Evaluation Criteria in Solid Tumours, version 1.1; SD, stable disease; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan; TEAE, treatment-emergent adverse event.

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