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Trastuzumab deruxtecan (T-DXd) in combination with capecitabine or capivasertib in patients with HER2-low metastatic breast cancer: a Phase 1b, multicenter, open-label study (DESTINY-Breast08)

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Objectives

- The primary objective of the dose-expansion phase of the DESTINY-Breast08 clinical trial was to assess the safety and tolerability of T-DXd in combination with other anticancer therapies, including capecitabine and capivasertib, in patients with human epidermal growth factor receptor 2 (HER2)–low advanced/metastatic breast cancer (mBC)
- The key secondary objective was to assess the antitumor activity of these T-DXd–based combinations

Conclusions

- The safety profiles for T-DXd plus capecitabine and T-DXd plus capivasertib were generally consistent with the known safety profile of each agent
- T-DXd in combination with capecitabine or capivasertib demonstrated preliminary antitumor activity in patients with HER2-low mBC
- Due to small datasets and heterogeneous populations, interpretation of the efficacy results is limited; further research is warranted

Plain language summary

Why did we perform this research?

Breast cancer cells can have different levels of a protein called human epidermal growth factor receptor 2 (HER2), which helps cancer cells to grow.[1] Trastuzumab deruxtecan (T-DXd) is used to treat HER2-expressing breast cancer cells, including those with a low level of the HER2 protein (HER2-low), when they cannot be completely removed with surgery (unresectable) or when they have spread from the original site to other parts of the body (metastatic).[2,3] Currently, doctors may only prescribe T-DXd to these patients if other anticancer drugs do not work or after they have stopped working.[2,3]

This study was designed to find out which side effects are experienced when T-DXd is given together with capecitabine (a chemotherapy) or capivasertib (a drug that blocks the activity of a protein called AKT, reducing the growth of cancer cells), and how well these combinations work as a treatment for advanced/metastatic breast cancer (mBC).

How did we perform this research?

This analysis of T-DXd in combination with capecitabine or capivasertib was carried out in participants who had a maximum of one previous treatment for mBC. Participants treated with T-DXd and capecitabine had breast cancer with hormone receptors for estrogen and/or progesterone (hormone receptor [HR]–positive) or HR-negative disease status. All participants treated with T-DXd and capivasertib had HR-negative disease status.

What were the findings of this research?

The side effects experienced by participants given T-DXd in combination with capecitabine or capivasertib were generally as expected for these drugs. In both groups, there was evidence that tumors shrank following treatment (antitumor activity). The percentage of participants who had a decrease in tumor size after treatment (known as the objective response rate) was 60% for both T-DXd plus capecitabine and T-DXd plus capivasertib.

What are the implications of this research?

T-DXd in combination with capecitabine or capivasertib demonstrated preliminary antitumor activity, with no unexpected side effects, in participants who received a maximum of one previous treatment for mBC. As only a small number of participants were included in this study, further research is needed to fully evaluate the effects of these combinations.

Where can I access more information?

ClinicalTrials.gov. A Phase 1b study of T-DXd combinations in HER2-low advanced or metastatic breast cancer (DB-08). https://www.clinicaltrials.gov/study/NCT04556773.

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Poster

Please scan this quick response (QR) code with your smartphone camera or app to obtain a copy of the virtual poster. Alternatively, please visit the link: https://bit.ly/3M2qezn

This study was sponsored by AstraZeneca and Daiichi Sankyo. In March 2019, AstraZeneca entered into a global development and commercialization collaboration agreement with Daiichi Sankyo for trastuzumab deruxtecan (T-DXd; DS-8201).
Capivasertib was discovered by AstraZeneca subsequent to a collaboration with Astex Therapeutics Limited (and its collaboration with the Institute of Cancer Research and Cancer Research Technology Limited).
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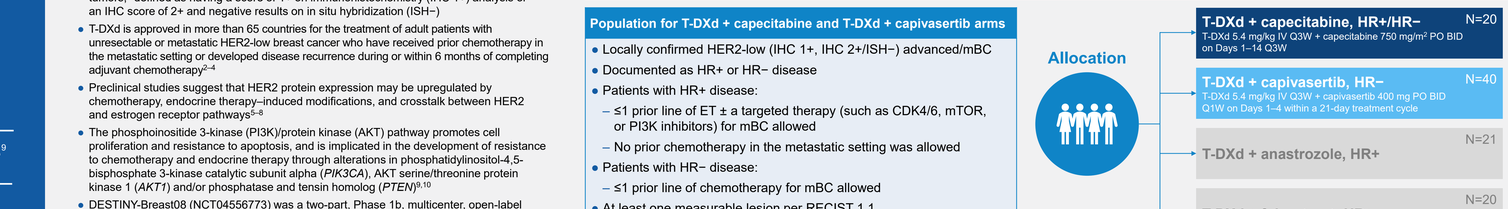
Introduction

- Across studies, approximately 50% of patients with primary or mBC have HER2-low tumors,[1] defined as having a score of 1+ on immunohistochemistry (IHC 1+) analysis or an IHC score of 2+ and negative results on in situ hybridization (ISH−)
- T-DXd is approved in more than 65 countries for the treatment of adult patients with unresectable or metastatic HER2-low breast cancer who have received prior chemotherapy in the metastatic setting or developed disease recurrence during or within 6 months of completing adjuvant chemotherapy[2–4]
- Preclinical studies suggest that HER2 protein expression may be upregulated by chemotherapy, endocrine therapy–induced modifications, and crosstalk between HER2 and estrogen receptor pathways[5–8]
- The phosphoinositide 3-kinase (PI3K)/protein kinase (AKT) pathway promotes cell proliferation and resistance to apoptosis, and is implicated in the development of resistance to chemotherapy and endocrine therapy through alterations in phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha (*PIK3CA*), AKT serine/threonine protein kinase 1 (*AKT1*) and/or phosphatase and tensin homolog (*PTEN*)[9,10]
- DESTINY-Breast08 (NCT04556773) was a two-part, Phase 1b, multicenter, open-label study designed to establish the safety, tolerability, and preliminary activity of T-DXd in combination with widely used standard-of-care therapies in HER2-low advanced/mBC
- Results for T-DXd + anastrozole and T-DXd + fulvestrant arms were reported previously;[11] results reported here are from the dose-expansion phase for T-DXd + capecitabine and T-DXd + capivasertib

Methods

Figure 1. Study design (dose-expansion phase)*



*Patients were treated with the recommended Phase 2 dose determined in the dose-finding phase (Part 1) of the study; †investigator-reported ILD/pneumonitis events were reviewed by an independent adjudication committee
AE, adverse event; BID, twice daily; CDK4/6, cyclin-dependent kinase 4 and 6; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; ET, endocrine therapy; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; IHC, immunohistochemistry; ILD, interstitial lung disease; ISH, in situ hybridization; IV, intravenous; mBC, metastatic breast cancer; mTOR, mammalian target of rapamycin; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PI3K, phosphoinositide 3-kinase; PO, orally; Q1W, every week; Q3W, every 3 weeks; RECIST, Response Evaluation Criteria in Solid Tumours; SAE, serious adverse event; T-DXd, trastuzumab deruxtecan

Results

T-DXd + capecitabine

Patient demographics and disposition

- At the final data cutoff (DCO; August 16, 2023), 20 patients had received T-DXd + capecitabine
- All patients were female, median age was 57.5 years (range: 36.0–74.0), half of patients were Asian (n=10), and the other half were White; all patients had an Eastern Cooperative Oncology Group performance status (ECOG PS) of 0 (n=10) or 1 (n=10)
- HER2 status was IHC 1+ in 11 patients (55.0%) and IHC 2+/ISH− in nine patients (45.0%)
- Nine patients (64.3%) with hormone receptor (HR)–positive disease had received a prior line of therapy for mBC; of the remaining five patients, four (28.6%) had received adjuvant treatment only and one (7.1%) had de-novo disease
- Five patients (83.3%) with HR-negative disease had received a prior line of therapy for mBC; one patient (16.7%) had received adjuvant treatment only
- Median actual treatment duration* was 11.1 months (range: 0.7–16.6) for T-DXd and 7.0 months (range: 0–16.1) for capecitabine
- Median duration of follow up† was 15.2 months (range: 0.5–17.5)
- At DCO, patient disposition was as follows:
  - Treatment ongoing: n=7 (35.0%)
  - T-DXd + capecitabine discontinued: n=13 (65.0%)
  - T-DXd discontinued: n=13 (65.0%)
    - Objective disease progression, n=10 (50.0%); patient decision, n=2 (10.0%); adverse event, n=1 (5.0%)
  - Capecitabine discontinued: n=15 (75.0%)
    - Objective disease progression, n=10 (50.0%); adverse event, n=3 (15.0%); patient decision, n=2 (10.0%)

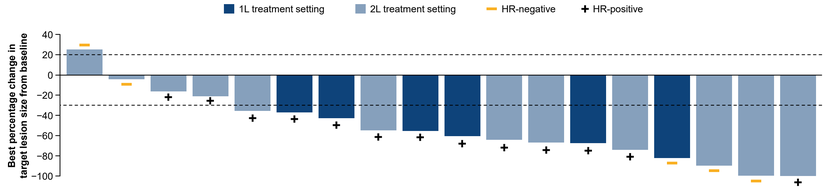
*Total treatment duration, excluding duration of dose interruptions and delays; †time from first dose to the date of death or date of censoring (for those who are not known to have died) in all patients

Table 1. Safety results

	Patients, n (%)
Any-grade AEs	20 (100)
Any-grade AEs occurring in ≥30% of patients	
Nausea	16 (80.0)
Fatigue	12 (60.0)
Vomiting	11 (55.0)
Stomatitis	7 (35.0)
Any AEs ≥Grade 3	11 (55.0)
Any AEs ≥Grade 3 possibly related to either drug	9 (45.0)
AEs leading to dose interruptions of T-DXd	11 (55.0)
AEs leading to dose reduction of T-DXd	7 (35.0)*
AEs leading to discontinuation of T-DXd	1 (5.0)
Any SAEs	2 (10.0)
AEs leading to death	1 (5.0)†
AESIs	
Pneumonitis (adjudicated as ILD related to T-DXd)	3 (15.0)
≤Grade 2	2 (10.0)‡
Grade 5	1 (5.0)†

*Seven patients experienced eight AEs that led to T-DXd dose reduction (asthenia, coronavirus disease 2019, fatigue, neutrophil count decrease, stomatitis, vomiting [all n=1], blood bilirubin increase [n=2]); †reported as drug-induced ILD/pneumonitis by investigator (Grade 2 at onset) and confirmed by adjudication committee (Grade 3 at onset). Patient presented without any symptoms on Day 44 of study treatment; however, radiologic findings indicated a hypersensitivity pneumonitis pattern. T-DXd and capecitabine were discontinued. The patient was hospitalized and received prednisolone (1–4 mg/kg daily), along with treatment for other non-serious AEs. Pneumonitis was reported as fatal 18 days after discontinuing T-DXd and capecitabine; ‡at DCO, one case had resolved, one was ongoing
AE, adverse event; AESI, adverse event of special interest; DCO, data cutoff; ILD, interstitial lung disease; SAE, serious adverse event; T-DXd, trastuzumab deruxtecan

Figure 2. Best percentage change in target lesion size from baseline for T-DXd + capecitabine (N=20)*



*Two patients (10.0%) did not have any post-baseline RECIST 1.1 data and thus no data were available for percentage change in target lesion size from baseline
1L, first line; 2L, second line; HR, hormone receptor; RECIST, Response Evaluation Criteria in Solid Tumours; T-DXd, trastuzumab deruxtecan

Antitumor activity

- Confirmed objective response rate (**cORR**) was **60.0%** (n=12/20; 95% confidence interval [CI] 36.1, 80.9)
- **Median** duration of response (**DOR**) was not estimable (**NE**) months (95% CI 4.4, NE) (n=12)
- By DCO, there were a total of **five deaths** (25.0%)
- **Median** overall survival (**OS**) was **NE** months (95% CI 14.8, NE); **OS** at **12 months** was **78.0%** (95% CI 51.5, 91.1)
- By DCO, there were a total of **ten** progression-free survival (**PFS**) **events** (50.0%)
- **Median PFS** was **13.4 months** (95% CI 5.5, NE); **PFS** at **6** and **12 months** was **66.7%** (95% CI 40.4, 83.4) and **55.6%** (95% CI 30.5, 74.8), respectively

T-DXd + capivasertib

Patient demographics and disposition

- At the final DCO, 40 patients had received T-DXd + capivasertib
- All patients were female, median age was 56.0 years (range: 33.0–78.0), the majority of patients were Asian (n=18) or White (n=18), three patients were Black or African American, and one patient was reported as 'Other'; all patients had an ECOG PS of 0 (n=30) or 1 (n=10)
- HER2 status was IHC 1+ in 29 patients (72.5%), IHC 2+/ISH− in ten patients (25.0%), and IHC 2+/ISH missing in one patient (2.5%)
- All patients had HR-negative disease;* 18 patients (45.0%) received a prior line of therapy for mBC; of the remaining 22 patients, 19 (47.5%) had received adjuvant treatment only and three (7.5%) had de-novo disease
- Centrally confirmed *PIK3CA/AKT1/PTEN*-altered tumors were detected† in 13 patients (32.5%); 21 patients (52.5%) had non-altered tumors; and six patients (15.0%) had an unknown alteration status / circulating tumor DNA (ctDNA) low‡
- Median actual treatment duration§ was 6.2 months (range: 0.7–12.4) for T-DXd and 5.5 months (range: 0.2–13.7) for capivasertib
- Median duration of follow up¶ was 8.6 months (range: 1.2–14.9)
- At DCO, patient disposition was as follows:
  - Treatment ongoing: n=17 (42.5%)
  - T-DXd + capivasertib discontinued: n=23 (57.5%)
  - T-DXd discontinued: n=26 (65.0%)
    - Objective disease progression, n=17 (42.5%); adverse event, n=7 (17.5%); patient decision, n=2 (5.0%)
  - Capivasertib discontinued: n=28 (70.0%)
    - Objective disease progression, n=16 (40.0%); adverse event, n=9 (22.5%); patient decision, n=1 (2.5%); start of alternative anticancer therapy, n=1 (2.5%); subjective disease progression, n=1 (2.5%)

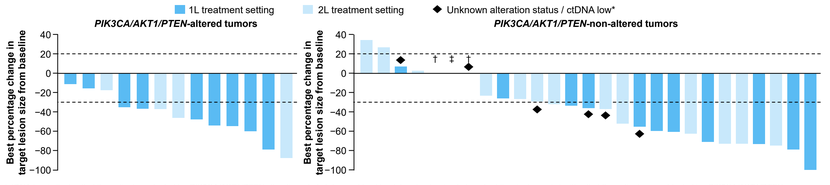
*One patient was confirmed as HR-negative after first dose; †by ctDNA assays using the Guardant Health OMNI platform at baseline; ‡ctDNA low indicates that the alteration status could not be determined owing to low shedding; 'unknown' signifies that the patient was not tested for alterations; §total treatment duration, excluding duration of dose interruptions and delays; ¶time from first dose to the date of death or date of censoring (for those who are not known to have died) in all patients

Table 2. Safety results for T-DXd + capivasertib

	Patients, n (%)
Any-grade AEs	40 (100)
Any-grade AEs occurring in ≥30% of patients	
Nausea	37 (92.5)
Diarrhea	34 (85.0)
Vomiting	23 (57.5)
Fatigue	18 (45.0)
Alopecia	15 (37.5)
Anemia	14 (35.0)
Decreased appetite	12 (30.0)
Hypokalemia	12 (30.0)
Any AEs ≥Grade 3	27 (67.5)
Any AEs ≥Grade 3 possibly related to either drug	27 (67.5)
AEs leading to dose interruptions of T-DXd	17 (42.5)
AEs leading to dose reduction of T-DXd	5 (12.5)*
AEs leading to discontinuation of T-DXd	7 (17.5)
Any SAEs	13 (32.5)
AEs leading to death	0
AESIs	
Pneumonitis (adjudicated as ILD related to T-DXd), Grade	8 (20.0), all ≤Grade 2†
Hyperglycemia (reported by investigator as possibly related to capivasertib)	8 (20.0)‡
Rash (reported by investigator as possibly related to capivasertib)	7 (17.5)§

*Five patients experienced ten AEs that led to T-DXd dose reduction (vomiting, platelet count decrease, neutropenia, anemia, thrombocytopenia, and *Pneumocystis jirovecii* pneumonia [all n=1], fatigue and nausea [both n=2]); †Grade 1, n=1; Grade 2, n=7; at DCO, three cases had resolved, and five were ongoing; ‡Grade 1, n=3; Grade 2, n=2; Grade 3, n=3; §Grade 1, n=2; Grade 2, n=2; Grade 3, n=3
AE, adverse event; AESI, adverse event of special interest; ILD, interstitial lung disease; SAE, serious adverse event; T-DXd, trastuzumab deruxtecan

Figure 3. Best percentage change in target lesion size from baseline for T-DXd + capivasertib (N=40)



*ctDNA low indicates that the patient was tested for *PIK3CA/AKT1/PTEN* alterations, but status could not be determined owing to low shedding; 'unknown' signifies that the patient was not tested for *PIK3CA/AKT1/PTEN* alterations; †1L treatment setting; ‡2L treatment setting
1L, first line; 2L, second line; *AKT1*, *AKT* serine/threonine kinase 1; ctDNA, circulating tumor DNA; *PIK3CA*, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; *PTEN*, phosphatase and tensin homolog; T-DXd, trastuzumab deruxtecan

Antitumor activity

- **cORR** was **60.0%** (n=24/40; 95% CI 43.3, 75.1)
  - **cORR** in patients with ***PIK3CA/AKT1/PTEN*-altered tumors** was **76.9%** (n=10/13; 95% CI 46.2, 95.0)
  - **cORR** in patients with ***PIK3CA/AKT1/PTEN*-non-altered tumors** was **52.4%** (n=11/21; 95% CI 29.8, 74.3)
  - **cORR** in patients with an **unknown** and **ctDNA low** status was **50.0%** (n=1/2) and **50.0%** (n=2/4), respectively
- Median **DOR** was **7.1 months** (95% CI 5.0, NE) (n=24)
- By DCO, there were a total of **four deaths** (10.0%); **median OS** was **NE** months (95% CI 13.5, NE) and **OS** at **12 months** was **92.0%** (95% CI 77.2, 97.4)
- By DCO, there were a total of **18 PFS events** (45.0%); **median PFS** was **9.0 months** (95% CI 5.6, NE) and **PFS at 6** and **12 months** was **65.5%** (95% CI 48.0, 78.4) and **33.9%** (95% CI 12.7, 56.6), respectively

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DESTINY Breast08