Phase 3 study of trastuzumab deruxtecan (T-DXd) with or without pertuzumab vs a taxane, trastuzumab and pertuzumab in first-line, human epidermal growth factor receptor 2–positive metastatic breast cancer: DESTINY-Breast09

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Background

The current standard-of-care (SOC) treatment for patients with human epidermal growth factor receptor 2 (HER2)–positive metastatic breast cancer (mBC) is a first-line (1L) regimen of a taxane, trastuzumab, and pertuzumab (TTHP)1

● Many patients ultimately develop treatment resistance

● More treatment options are needed in the 1L setting to address treatment resistance and improve clinical outcomes in patients with HER2-positive mBC

● Trastuzumab deruxtecan (T-DXd) is an antibody-drug conjugate (ADC) composed of an anti-HER2 antibody, a tetrapeptide-cleavable linker, and a topoisomerase I inhibitor payload2

Structure of T-DXd

- HER2
- Deruxtecan2
- Topoisomerase I Inhibitor Payload

T-DXd in HER2-Positive mBC

In the primary analysis of the DESTINY-Breast01 phase 2 trial, T-DXd demonstrated antitumor activity in patients with HER2-positive mBC, with a response to treatment seen in 112 of 184 patients (60.9%)3

Data from the DESTINY-Breast01 trial supported global approvals of T-DXd for the treatment of unresectable or metastatic HER2-positive breast cancer that has progressed on ≥2 prior therapies2,3

In the recent DESTINY-Breast03 trial, T-DXd showed improved efficacy compared with the ADC trastuzumab emtansine (T-DM1) in HER2-positive mBC, with a confirmed objective response rate (ORR) of 79.7% with T-DXd vs 34.2% for T-DM14

Combining T-DXd with pertuzumab may further enhance the efficacy seen with T-DXd monotherapy and may be a more efficacious option for 1L treatment of HER2-positive mBC

Previously, a study combining pertuzumab with T-DXd showed that pertuzumab facilitated internalization of the ADC2

Here we describe DESTINY-Breast09, an open-label, phase 3 trial evaluating the efficacy and safety of T-DXd alone or in combination with pertuzumab compared with the SOC for 1L treatment of patients with HER2-positive mBC

For more information, please visit ClinicalTrials.gov (NCT04784715)

References

Disclosures

Dr Tolaney reports grants and personal fees from AstraZeneca during the conduct of the study and the following outside the conduct of the study: grants and personal fees from AstraZeneca; El Lilly, Merck, Novartis, Pfizer, GSK/Sanofi, EMBL, Bristol Myers Squibb, Eisai, Servier, Otsuka, and NovenPharmaceuticals: personal fees from Puma, Cellectis, Seattle Genetics, Genentech, Astrazeneca; C1 Therapeutics, Actasan, OncoPhar, Daiichi-Sankyo, Amgen, Amgen; Gilead; and grants from CytoDyn.

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DESTINY-Breast09: A Phase 3, Open-Label Trial of T-DXd Alone or in Combination With Pertuzumab for First-Line Treatment of Human Epidermal Growth Factor Receptor 2–Positive Metastatic Breast Cancer

Patient population

N=1136

Advanced and/or metastatic breast cancer

HER2 positive (IHC 3+ or ISH+)

No previous chemotherapy or HER2-targeted therapy for advanced or metastatic breast cancer

Patients will be stratified by prior treatment status (detected vs not detected), PIK3CA mutation status (positive vs negative), and PDK4 mutation status (detected vs not detected)

Study Design and Population

Enrollment Start: 26 April 2021 | Currently Recruiting Patients

Recruitment: 26 April 2021 to 28 January 2022

Objective

To evaluate the efficacy and safety of T-DXd alone or in combination with pertuzumab in comparison to T-DXd alone in 1L treatment of patients with HER2-positive mBC

Key Inclusion Criteria

Age ≥ 18 years

Pathologically documented advanced or metastatic breast cancer that is locally advanced or clinically confirmed as HER2 positive (IHC 3+ or ISH+) in the metastatic setting. HR status must be documented by local testing

No prior chemotherapy or HER2-targeted therapy for advanced or metastatic breast cancer except for 1 previous line of endocrine therapy in the metastatic setting. Patients who have received chemotherapy or HER2-targeted therapy in the neoadjuvant or adjuvant setting are eligible if time from treatment to metastatic diagnosis is >6 months

Adequate tumor tissue sample from the metastatic setting available for assessment of HER2 and PDK4 status by central laboratory

Protocol-defined adequate organ and bone marrow function

LVEF ≥50% within 28 days before randomization

Key Exclusion Criteria

Inability to give or for any of the agents used in the study

Surgical or endoscopic intervention or clinically active CNS metastases. Patients with clinically inactive CNS metastases that cannot be ruled out by imaging at screening

Active or prior documented ILD/diuretics or suspected ILD/diuretics that may interfere with the patient’s participation or study results

Prior randomization or treatment in a previous T-DXd study regardless of treatment arm assignment

Key Study Endpoints

1. PFS by BICR2

2. PFS by investigator3

3. OS

4. ORR by BICR and investigatora

5. PFS by investigatora

6. HRQOL using the EORTC QLQ-C30

HRQOL using the EORTC QLQ-C30 and QLQ-BR45

Time to deterioration in EORTC QLQ-C30 scores

HRQOL using the EORTC QLQ-BR45

Immunogenicity assessed by serum concentrations of T-DXd and pertuzumab

Safety and tolerability

Abbreviations

ADRs, adverse drug reactions; AUC, area under the curve; BICR, blinded independent central review; BM, bone metastasis; CNS, central nervous system; DOC, duration of response; EORTC, European Organisation for Research and Treatment of Cancer; HR, hormone receptor; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; ISH, in situ hybridisation; LVEF, left ventricular ejection fraction; mBC, metastatic breast cancer; mCR, metastatic recurrence; mPFS, median progression-free survival; mPD, metastatic disease; mPFS, median progression-free survival; mPFS, median progression-free survival; mOS, median overall survival; PFS, progression-free survival; PFS2, second progression of death; QLQ-BR45, Quality of Life Questionnaire Breast Cancer module; QLQ-C30, Quality of Life Questionnaire Core 30; R, randomization; RECIST, Response Evaluation Criteria in Solid Tumors.

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For more details on DESTINY-Breast09, please visit https://clinicaltrials.gov/ct2/show/NCT04784715

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