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T-DXd Yields Superior Outcomes Over Chemotherapy-based Regimens in Patients Previously Treated with T-DM1

SAN ANTONIO – Compared with capecitabine-based regimens, trastuzumab deruxtecan (T-DXd) led to higher response rates and longer survival in the third-line setting for patients with HER2-positive metastatic breast cancer previously treated with trastuzumab emtansine (T-DM1), according to results from the phase III DESTINY-Breast02 trial presented at the San Antonio Breast Cancer Symposium, held December 6-10, 2022.

T-DXd is an antibody-drug conjugate that uses the HER2-targeted antibody trastuzumab to deliver a cytotoxic payload selectively to HER2-expressing cells. In the single-arm DESTINY-Breast01 phase II clinical trial, T-DXd showed clinical activity in the third-line setting for patients with HER2-positive metastatic breast cancer who were previously treated with T-DM1, another HER2-targeted antibody-drug conjugate. These results led to the accelerated approval of T-DXd in 2019 as a third-line therapy for patients with metastatic or unresectable breast cancer who have received two or more prior HER2-targeted therapies.

“While DESTINY-Breast01 established T-DXd as a new treatment for this population, it was a modestly sized, single-arm phase II trial,” said Ian Krop, MD, PhD, associate cancer center director for Clinical Research and the chief clinical research officer at the Yale Cancer Center. The DESTINY-Breast02 trial was designed as a confirmatory study for DESTINY-Breast01 to evaluate T-DXd versus treatment of physician’s choice (TPC) in patients previously treated with T-DM1, he explained.

“In addition to confirming the favorable benefit-to-risk profile of T-DXd in this population, this research was also important to evaluate the efficacy of one antibody-drug conjugate, T-DXd, in patients whose cancer has already progressed on another antibody-drug conjugate, T-DM1,” Krop noted. “This is the first randomized trial to ask this important question.”

The DESTINY-Breast02 trial enrolled 608 patients whose metastatic breast cancers had progressed on or after T-DM1 treatment. Patients were randomly assigned 2:1 to receive either T-DXd or TPC (a combination of capecitabine with either trastuzumab or lapatinib).

Among the patients treated with T-DXd, 69.7 percent experienced an objective response, as compared with 29.2 percent of patients treated with TPC. Those treated with T-DXd were also 64 percent less likely to experience disease progression than patients receiving TPC, with a median progression-free survival of 17.8 months and 6.9 months for patients in the T-DXd and TPC arms, respectively. Overall survival was also significantly longer for patients treated with T-DXd (39.2 months with T-DXd vs. 26.5 months with TPC).

Krop noted that adverse events in patients who received T-DXd were consistent with prior studies. T-DXd-related interstitial lung disease was observed in 10.4 percent of patients who received the therapy; most of these cases were grade 1 or 2, but two cases of grade 5 interstitial lung disease were reported.

“The results of DESTINY-Breast02 confirm the findings of DESTINY-Breast01, demonstrating high levels of efficacy of T-DXd in patients with HER2-positive metastatic breast cancer previously treated with T-DM1,” said Krop. “Furthermore, they extend these findings, demonstrating that T-DXd is not only highly active, but also superior to conventional chemotherapy-based regimens in this patient population.”

Follow-up analyses may assess patient-reported outcomes from this trial, and additional studies may examine adverse events, efficacy, and safety of the treatment in patients with metastases to the central nervous system, Krop noted. Ongoing studies are also evaluating T-DXd as a first-line therapy for patients with HER2-positive metastatic breast cancer and for patients with early-stage disease.

A limitation of this study was that the control arm was limited to therapies based on capecitabine, precluding direct comparison of T-DXd to treatment regimens containing other chemotherapeutic agents. An additional limitation is that patients with progressive metastases to the central nervous system were not eligible for the trial.

The DESTINY-Breast02 trial was designed and funded by Daiichi Sankyo in collaboration with AstraZeneca. Krop has received funding to his institution from AstraZeneca, Daiichi Sankyo, Genentech/Roche, Macrogenics, and Pfizer; consulting fees from AstraZeneca, Bristol Myers Squibb, Daiichi Sankyo, Genentech/Roche, MacroGenics, Seattle Genetics, and Taiho Oncology; and honoraria from AstraZeneca. Krop has participated on a data safety monitoring board or advisory board for Merck and Novartis, and his spouse holds a leadership position and stock in PureTech Health.

Abstract

GS2-01

Trastuzumab deruxtecan vs physician’s choice in patients with HER2+ unresectable and/or metastatic breast cancer previously treated with trastuzumab emtansine: primary results of the randomized, phase 3 study DESTINY-Breast02

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In DESTINY-Breast01 (NCT03248492) and DESTINY-Breast03 (NCT03529110), trastuzumab deruxtecan (T-DXd) demonstrated unprecedented activity in patients (pts) with HER2+ (immunohistochemistry 3+; immunohistochemistry 2+/in situ hybridization+) advanced metastatic breast cancer (mBC), leading to regulatory approvals in several countries for HER2+ unresectable/mBC after a prior anti–HER2-based regimen. DESTINY-Breast02 (NCT03523585) is a phase 3 trial of T-DXd vs treatment of physician’s choice (TPC) in patients with centrally confirmed HER2+ mBC previously treated with trastuzumab emtansine (T-DM1). It acts as a confirmatory study for the pivotal phase 2 DESTINY-Breast01 trial. Here we report the primary results of DESTINY-Breast02.

Methods
Pts with HER2+ mBC were randomized 2:1 to receive T-DXd or TPC (trastuzumab + capecitabine or lapatinib + capecitabine) and stratified by hormone receptor (HR) status (HR+/HR-), prior pertuzumab treatment, and history of visceral disease. The primary endpoint of this time-driven primary analysis was progression-free survival (PFS) as determined by blinded independent central review (BICR). The powered secondary endpoint was overall survival (OS). Other secondary endpoints included confirmed objective response rate (ORR) by BICR, duration of response (DoR) by BICR, PFS by investigator assessment, safety, and others.

Results
608 pts were randomized to receive T-DXd (n = 406) or TPC (n = 202). Pts receiving T-DXd and TPC had

a median age of 54.2 years (range, 22.4-88.5 years) and 54.7 years (range, 24.7-86.5 years), respectively, with a median of 2 (range, 0-10 and range,1-8) prior lines of systemic therapy (excluding hormone therapy) in the metastatic setting. Median treatment duration was 11.3 mo in the T-DXd arm and ~4.5 mo in the TPC arm. Efficacy and safety results are shown in the table below. T-DXd significantly improved PFS (HR, 0.36; 95% CI, 0.28-0.45; P <0.000001) and OS (HR, 0.66; 95% CI, 0.50-0.86; P = 0.0021) compared with TPC. Confirmed ORR was 69.7% (14% complete response) with T-DXd and 29.2% (5.0% complete response) with TPC. Grade ≥3 treatment-emergent adverse events (TEAEs) occurred in 52.7% and 44.1% of pts receiving T-DXd and TPC, respectively. Adjudicated drug-related interstitial lung disease (ILD) occurred in 10.4% of pts with T-DXd vs 0.5% of pts with TPC. In pts receiving T-DXd, most ILD cases (88.1%) were grade 1/2 and grade 5 ILD was reported in 2 (0.5%) pts.

Conclusions
Results from DESTINY-Breast02 confirmed the clinical benefit and superiority of T-DXd over conventional chemotherapy-based regimens in pts with HER2+ mBC previously treated with T-DM1, as evidenced by significant and clinically meaningful improvements in PFS and OS. These data, together with earlier reported results from the DESTINY-Breast03 study of T-DXd vs T-DM1 solidify T-DXd as an optimal treatment option in pts with progressive HER2+ mBC across broad settings.

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