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NCCN Panel: Breast Cancer

On behalf of Daiichi Sankyo, Inc. and AstraZeneca Pharmaceuticals LP, I respectfully request the NCCN Guideline Panel for Breast Cancer to review the enclosed data[1] for the inclusion of fam-trastuzumab deruxtecan-nxki, also known as T-DXd, in the guidelines as a monotherapy option for the treatment of patients with unresectable or metastatic HER2-positive breast cancer who have received a prior anti-HER2-based regimen. This request is based on the randomized, active-controlled, phase 3 trial DESTINY-Breast03 presented at the 2021 European Society for Medical Oncology Virtual Congress.[1]

Specific Changes: We respectfully ask the NCCN panel to consider the following:

- BINV-Q (2 of 8): Systemic Therapy Regimens for Recurrent Unresectable (Local or Regional) or Stage IV (M1) Disease
    - Move fam-trastuzumab deruxtecan-nxki to the second line setting as a preferred regimen, category 1 recommendation
    - Add footnote: “Fam-trastuzumab deruxtecan-nxki demonstrated significantly improved PFS (HR, 0.28; 95% CI, 0.22-0.37) compared to T-DM1 in the phase 3 head-to-head trial DESTINY-Breast03.”
    - Add footnote “Consider fam-trastuzumab deruxtecan-nxki in the first-line setting for patients with rapid progression within 6 months of neoadjuvant or adjuvant therapy (12 months for pertuzumab-containing regimens) based on the DESTINY-Breast03 trial.”

FDA Clearance

Enhertu is indicated for the treatment of adult patients with unresectable or metastatic HER2-positive breast cancer who have received two or more prior anti-HER2-based regimens in the metastatic setting. This indication is approved under accelerated approval based on tumor response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial.[2]

Rationale

T-DXd demonstrated significantly improved PFS by blinded independent central review compared to T-DM1 (HR, 0.28; 95% CI, 0.22-0.37; $P = 7.8 \times 10^{-22}$) in an interim analysis of the phase 3 DESTINY-Breast03 trial. PFS by investigator assessment demonstrated consistent results (HR, 0.26; 95% CI, 0.20-0.35; $P = 6.5 \times 10^{-24}$). There was a trend towards improved OS with T-DXd compared to T-DM1 (HR, 0.56; 95% CI, 0.36-0.86; $P = .007172$, does not cross pre-specified boundary of $P < .000265$), although OS data are still immature. Additionally, the confirmed ORR for T-DXd was 79.7% (16.1% CR, 63.6% PR) versus 34.2% (8.7% CR, 25.5% PR) for T-DM1.[1]

Key Supporting Literature

DESTINY-Breast03[1]

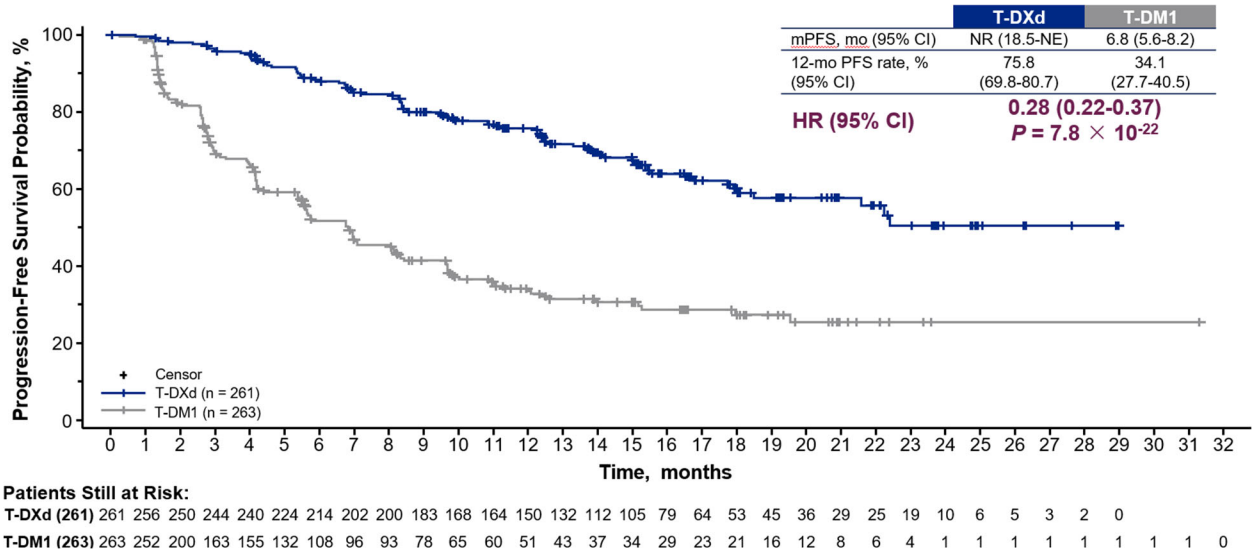
DESTINY-Breast03 is a multicenter, randomized, active-controlled, open-label, phase 3 trial evaluating the efficacy and safety of T-DXd versus ado-trastuzumab emtansine (T-DM1) in patients with unresectable or metastatic HER2-positive breast cancer previously treated with trastuzumab and a taxane. Patients with rapid progression within 6 months of neoadjuvant or adjuvant therapy (12 months for pertuzumab-containing regimens) were included.

The primary endpoint is progression-free survival (PFS) based on blinded independent central review (BICR) and the key secondary endpoint is overall survival (OS). Additional secondary endpoints include objective response rate (ORR), PFS by investigator assessment, and safety. Data below are from a planned interim analysis for PFS (data cutoff May 21, 2021). The efficacy boundary for superiority was $P < 0.000204$ based on 245 events, and the independent data monitoring committee recommended unblinding the study.

Patients were randomized 1:1 to receive T-DXd 5.4 mg/kg (n=261) or T-DM1 3.6 mg/kg (n=263) intravenously every 3 weeks. Approximately half of all patients were hormone receptor positive and 23.8% and 19.8% of patients in the T-DXd and T-DM1 groups had stable, treated brain metastases, respectively. There were 130 (49.8%) patients in the T-DXd arm and 123 (46.8%) patients in the T-DM1 arm who received 1 line of prior therapy in the metastatic setting (includes rapid progressors as 1 line of treatment and excludes endocrine therapy). Twenty-one (8.1%) patients in the T-DXd arm and 29 (11.0%) patients in the T-DM1 arm did not have any prior treatments in the metastatic setting, the majority of which progressed within 6 months of completing neoadjuvant or adjuvant treatment (12 months for pertuzumab-containing regimens). Almost all patients in each arm (99.6%) received prior trastuzumab and approximately 60% of patients in both arms received prior pertuzumab. At data cutoff, 51.4% and 18.0% of patients remained on treatment in the T-DXd and T-DM1 arms, respectively.

T-DXd significantly improved the primary endpoint of PFS by BICR compared to T-DM1 (Figure 1). Subgroup analyses of key subgroups including hormone receptor status, prior pertuzumab treatment, presence or absence of visceral disease, number of prior lines of therapy, and presence or absence of stable, treated brain metastases showed consistent responses.

Figure 1. Kaplan-Meier Curve for Primary Endpoint: PFS by BICR[a]



BICR = blinded independent central review; HR = hazard ratio; mo = month; NE = not estimable; NR = not reached; PFS = progression-free survival; T-DM1 = ado-trastuzumab emtansine; T-DXd = fam-trastuzumab deruxtecan-nxki. [a]Median PFS follow-up for T-DXd was 15.5 months (range, 15.1-16.6) and for T-DM1 was 13.9 months (range, 11.8-15.1).

Median PFS by investigator assessment was 25.1 months in the T-DXd arm compared to 7.2 months in the T-DM1 arm (hazard ratio [HR], 0.26, 95% confidence interval [CI], 0.20-0.35; $P = 6.5 \times 10^{-24}$). The median OS was not reached in either arm and the HR for OS between T-DXd and T-DM1 was 0.56 (95% CI, 0.36-0.86; $P = .007172$) although it did not cross the pre-specified boundary for statistical significance of $P < .000265$ based on 86 events. The OS data are immature and additional analyses are planned. The 12-month OS rate was 94.1% (95% CI, 90.3-96.4) for T-DXd and 85.9% (95% CI,

80.9-89.7) for T-DM1. Confirmed ORR was 79.7% (16.1% complete response [CR], 63.6% partial response [PR]) for T-DXd versus 34.2% (8.7% CR, 25.5% PR) for T-DM1.

The safety of T-DXd was consistent with the safety profile established in previous clinical trials. The median treatment duration was 14.3 months (range 0.7-29.8) for T-DXd and 6.9 months (range 0.7-25.1) for T-DM1. In the T-DXd arm, 98.1% of patients experienced drug-related treatment-emergent adverse events (TEAEs) compared to 86.6% of patients receiving T-DM1. Drug-related TEAEs associated with discontinuation and dose reduction occurred in 12.8% and 24.1% of patients in the T-DXd group and 5.0% and 12.6% of patients in the T-DM1 group, respectively. There were no drug-related TEAEs associated with death.

Drug-related TEAEs occurring in ≥20% of patients (T-DXd vs T-DM1) include neutropenia (42.8% vs 11.1%), anemia (30.4% vs 14.2%), leukopenia (30.0% vs 7.7%), thrombocytopenia (24.9% vs 51.7%), nausea (72.8% vs 27.6%), vomiting (44.0% vs 5.7%), diarrhea (23.7% vs 3.8%), constipation (22.6% vs 9.6%), fatigue (44.7% vs 29.5%), aspartate aminotransferase increased (23.3% vs 37.2%), alanine aminotransferase increased (19.5% vs 27.2%), decreased appetite (26.1% vs 12.6%), and alopecia (36.2% vs 2.3%). There were 27 (10.5%) cases of drug-related ILD/pneumonitis in the T-DXd arm and 5 (1.9%) cases in the T-DM1 arm as determined by an independent adjudication committee. There were no grade 4 or 5 drug-related ILD/pneumonitis events. In the T-DXd arm, 6 patients (2.3%) experienced grade 2 decreased ejection fraction and 1 (0.4%) experienced grade 1 left ventricular dysfunction. One (0.4%) patient in the T-DM1 arm experienced decreased ejection fraction (grade 2).

Thank you for your consideration.

Sincerely,

Dan Liang, Pharm.D.

References (Enclosed)

1. Cortés J, Kim S-B, Chung W-P, et al. Trastuzumab deruxtecan (T-DXd) vs trastuzumab emtansine (T-DM1) in patients with HER2+ metastatic breast cancer: results of the randomized, phase 3 study DESTINY-Breast03. Oral presentation presented at: European Society for Medical Oncology; September 16-21, 2021.
2. ENHERTU (fam-trastuzumab deruxtecan-nxki) prescribing information. 2021. Daiichi Sankyo, Inc. and AstraZeneca Pharmaceuticals, LP.