

Dan Liang, PharmD
Associate Director, Medical Information & Education
Daiichi Sankyo, Inc.
211 Mount Airy Road
Basking Ridge, NJ 07920
Phone: 908-992-7054
Email: daliang@dsi.com
Date of request: January 2, 2020

NCCN Breast Cancer Panel
Request review of newly FDA-approved ENHERTU (fam-trastuzumab deruxtecan-nxki) for HER2-Positive Metastatic Breast Cancer

On behalf of Daiichi Sankyo, Inc. and AstraZeneca Pharmaceuticals LP, I respectfully request the NCCN Breast Cancer panel to review the enclosed FDA label¹ and clinical studies^{2,3} in support of fam-trastuzumab deruxtecan-nxki (T-DXd) for HER2-positive metastatic breast cancer.

Specific Changes: Please consider the following:

- **BINV-Q1, “Chemotherapy Regimens for Recurrent or Stage IV (M1) Disease”:**
 - **Under “HER2-Positive”:** Add fam-trastuzumab deruxtecan-nxki (T-DXd)
- **BINV-24 and BINV-25,** addition of fam-trastuzumab deruxtecan-nxki (T-DXd) to the treatment algorithm schema for systemic treatment of recurrent or stage IV (M1) disease as a monotherapy option

FDA Clearance: ENHERTU (fam-trastuzumab deruxtecan-nxki) is a HER2-directed antibody and topoisomerase inhibitor conjugate 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.¹

Rationale: T-DXd is a HER2-directed antibody-drug conjugate with a potent topoisomerase I inhibitor payload. Efficacy of this agent (ORR 60.9%, DOR 14.8 mo, PFS 16.4 mo) in HER2-positive metastatic breast cancer has been shown in a broad range of settings in two studies that included patients who had received a combination of standard therapies including trastuzumab, T-DM1, pertuzumab, or lapatinib.^{2,3} These studies demonstrate the value of T-DXd as a new effective option for patients with HER2-positive metastatic breast cancer.

Key Supporting Literature:

DESTINY-Breast01 (T-DXd in Previously Treated HER2-positive Breast Cancer) Study²

DESTINY-Breast01 is the pivotal phase 2 global study that enrolled 184 adult patients with HER2-positive unresectable and/or metastatic breast cancer who received T-DXd at the recommended phase 2 dose (5.4 mg/kg every 3 weeks). Patients had previously received a combination of trastuzumab, T-DM1, pertuzumab, and other anti-cancer therapies (median 6 prior cancer regimens in the metastatic setting). The primary endpoint is objective response rate (ORR) as determined by independent central review. Secondary endpoints include duration of response (DOR), disease control rate (DCR), clinical benefit rate (CBR), progression-free survival (PFS) and overall survival (OS).

At a median follow-up of 11.1 months, the ORR was 60.9%. The DCR was 97.3% and CBR was 76.1%. The median time to response was 1.6 months, which corresponds with the first post baseline scan. The median DOR and PFS was 14.8 and 16.4 months, respectively. The median OS was not reached and estimated OS at 12 months was 86.2%. Pre-specified subgroup analyses including prior pertuzumab use, hormone receptor status, and presence of inactive brain metastases showed consistent responses.

Phase 1 Dose Escalation and Expansion (DS8201-A-J101) Study³

DESTINY-Breast01 confirmed the efficacy of T-DXd in a previous phase 1 dose escalation and expansion study (DS8201-A-J101). DS8201-A-J101 enrolled patients with advanced, unresectable, or metastatic HER2-expressing solid tumors including patients with previously treated HER2-positive breast cancer. Tumor response was evaluated according to investigator assessment. In patients evaluable for confirmed response, the ORR was 59.5% and DCR was 93.7%. The median DOR was 20.7 months and median PFS was 22.1 months. In a subgroup analysis of patients who received prior pertuzumab in addition to trastuzumab and T-DM1, 62.5% achieved objective response and 93.8% achieved disease control; median PFS in this subgroup was 16.4 months.

Safety

In DESTINY-Breast01, 57.1% of patients experienced at least 1 grade ≥ 3 treatment-emergent adverse event (TEAE). TEAEs leading to drug interruption, dose reduction, and drug discontinuation occurred in 35.3%, 23.4%, and 15.2% of patients, respectively. Twenty-five deaths occurred, 7 of which occurred while on treatment as a result of disease progression (n=3) or TEAE (n=4). Of the 18 deaths that occurred during survival follow up, 2 were due to interstitial lung disease (ILD) events that started during treatment and 16 were considered not related to T-DXd by investigators. The most common ($\geq 5\%$) grade ≥ 3 TEAEs were decreased neutrophil count (20.7%), anemia (8.7%), nausea (7.6%), decreased white blood cell count (6.5%), decreased lymphocyte count (6.5%), and fatigue (6.0%). Three patients (1.6%) experienced febrile neutropenia.

No clinically significant cardiotoxicity was observed with T-DXd. Three patients experienced decreased left ventricular ejection fraction (LVEF; 2 grade 2 and 1 grade 3); all cases were asymptomatic and resolved or improved with drug interruption. There were no events of cardiac failure with LVEF decline and no patients had an LVEF of $<40\%$ at any time or a decrease of $\geq 20\%$. No patients discontinued treatment due to a LVEF change.

There were 25 (13.6%) cases of ILD attributed to T-DXd as determined by an independent adjudication committee. Of the 20 patients reported to have grade ≥ 2 ILD, 13 received glucocorticoids and 7 were hospitalized. As of August 1, 2019, 7 patients had recovered, 2 were recovering, 10 had ongoing ILD, 4 had a fatal outcome; the status was unknown for 2 patients.

The safety profile of T-DXd in DESTINY-Breast01 was consistent with DS8201-A-J101.³

Sincerely,

Dan Liang, PharmD

References (enclosed):

1. ENHERTU (fam-trastuzumab deruxtecan-nxki) prescribing information. 2019. Daiichi Sankyo, Inc. and AstraZeneca Pharmaceuticals, LP.
2. Modi S, et al. Trastuzumab deruxtecan in previously treated HER2-positive breast cancer [published online ahead of print December 11, 2019]. *N Engl J Med*. 2019.
3. Tamura K, et al. Trastuzumab deruxtecan (DS-8201a) in patients with advanced HER2-positive breast cancer previously treated with trastuzumab emtansine: a dose-expansion, phase 1 study. *Lancet Oncol*. 2019;20(6):816-826.