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: June 4, 2020
NCCN Panel: Gastric Cancer and Esophageal/Esophagogastric Junction Cancers

On behalf of Daiichi Sankyo, Inc. and AstraZeneca Pharmaceuticals LP, I respectfully request the NCCN Guideline Panel for Gastric and Esophageal/Esophagogastric Junction Cancers to review the clinical studies[1,2] in support of fam-trastuzumab deruxtecan-nxki, also known as T-DXd, as a monotherapy option for the treatment of patients with previously treated HER2-positive advanced gastric and gastroesophageal junction (GEJ) adenocarcinoma.

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

- **GAST-B3 and ESOPH-B3, "Principles of Pathologic Review and Biomarker Testing"**
  - Under "Assessment of Overexpression or Amplification of HER2 in Gastric/Esophageal and Esophagogastric Junction Cancers," consider changing to "For patients with inoperable locally advanced, recurrent or metastatic adenocarcinoma of the stomach/esophagus or EGJ, assessment for tumor HER2 overexpression using immunohistochemistry (IHC) and fluorescence in situ hybridization (FISH) or other in situ hybridization (ISH) methods is recommended."
- **GAST-F1 and ESOPH-F1, "Principles of Systemic Therapy"**
  - Add "Fam-trastuzumab deruxtecan-nxki monotherapy as subsequent therapy for HER2-positive advanced adenocarcinoma"
- **GAST-F4 and ESOPH-F4, "Systemic Therapy for Unresectable Locally Advanced, Recurrent, or Metastatic Disease: Second-Line or Subsequent Therapy, Preferred Regimens"**
  - Add bullet above table "Fam-trastuzumab deruxtecan-nxki is recommended for previously treated HER2-positive adenocarcinoma"
  - Under "Preferred Regimens" add "Fam-trastuzumab deruxtecan-nxki for HER2-positive adenocarcinomas"
- **GAST-F11 and ESOPH-F11, "Principles of Systemic Therapy, Regimens and Dosing Schedules: Second-Line and Subsequent Therapy"**
  - Under "Preferred Regimens" add "Fam-trastuzumab deruxtecan-nxki 6.4 mg/kg IV on Day 1, cycled every 21 days" with a footnote: "fam-trastuzumab deruxtecan-nxki is approved for metastatic HER2-positive breast cancer at a different dose of 5.4 mg/kg IV on Day 1, cycled every 21 days"

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.[3]

ENHERTU is not FDA-approved for the treatment of HER2-expressing advanced gastric and GEJ adenocarcinoma.

Rationale: T-DXd has demonstrated significant activity (43% confirmed ORR) in 2 independent studies of patients from the US, Japan, or South Korea with pretreated advanced gastric or GEJ cancers.[1,2] To our knowledge, this represents the highest activity reported for heavily pretreated patients with HER2-positive gastric cancers.[4,5] Compared with chemotherapy, T-DXd was associated with significantly improved ORR, PFS, and OS.[1]

Key Supporting Literature:

DESTINY-Gastric01 (T-DXd in Previously Treated HER2-positive Gastric Cancer) Study[1]

DESTINY-Gastric01 is a randomized, phase 2 trial in patients from Japan and South Korea with HER2-expressing, locally advanced or metastatic gastric or GEJ cancer that had progressed on two or more prior regimens, which included a fluoropyrimidine and a platinum agent.[1] Data shown are for the primary cohort, which included patients who are HER2-positive defined as immunohistochemistry [IHC] 3+ and IHC 2+/in situ hybridization [ISH]+ and progressed on trastuzumab. Patients were randomized 2:1 to T-DXd 6.4 mg/kg every 3 weeks (n=125) or physician's choice (PC) of irinotecan or paclitaxel (n=62). The median number of prior systemic therapies for advanced/metastatic disease was 2 (range, 2-9) and 17% received ≥4 prior therapies; all patients previously received trastuzumab, 86% previously received taxanes, and 72% previously received ramucirumab.

The primary endpoint of the study was met with a significant improvement in objective response rate (ORR) by independent central review (ICR) with T-DXd versus PC (51% vs 14%, respectively; *P* <0.001) and was supported by a confirmed ORR of 43% for T-DXd vs 12% for PC. The median duration of confirmed response was 11.3 months (95% confidence interval [CI], 5.6-not estimable) for T-DXd versus 3.9 months (95% CI, 3.0-4.9) for PC.

There was a statistically significant improvement in overall survival (OS) in the T-DXd arm versus the PC arm (median, 12.5 vs 8.4 months, respectively; hazard ratio [HR], 0.59 [95% CI, 0.39-0.88]; *P* = 0.01). The estimated 6- and 12-month OS rates for T-DXd versus PC were 80% vs 66% and 52% vs 29%, respectively. Median progression-free survival (PFS) was 5.6 months with T-DXd vs 3.5 months with PC (HR, 0.47 [95% CI, 0.31-0.71]). Estimated 6- and 12-month PFS for T-DXd vs PC was 43% vs 21% and 30% vs 0%, respectively.

The most common grade ≥3 treatment emergent adverse events (T-DXd vs PC) were neutrophil count decreased (51% vs 24%), anemia (38% vs 23%), white blood cell count decreased (21% vs 11%), and decreased appetite (17% vs 13%). There was one drug-related death due to pneumonia which occurred in the T-DXd arm. Left ventricular ejection fraction decrease and heart failure were not observed in either arm. There were 12 cases of T-DXd related interstitial lung disease (ILD)/pneumonitis as determined by an independent adjudication committee (grade 1, n=3; grade 2, n=6; grade 3, n=2; grade 4, n=1). No grade 5 events occurred and there were no events in the PC group.

Phase 1 Dose Escalation and Expansion (DS8201-A-J101) Study[2]

T-DXd also demonstrated activity in a phase 1 dose-escalation and dose-expansion trial in the US and Japan including 44 patients with heavily pretreated (median prior lines, 3; range, 2-5) advanced HER2-positive gastric or GEJ cancer. The confirmed ORR by investigator assessment was 43.2% with a median duration of response of 7.0 months. Median progression-free survival was 5.6 months. Tumor shrinkage was observed in 35 (80%) of the patients by the first 6-week postbaseline tumor assessment. Consistent with the DESTINY-Gastric01 clinical trial, the most common adverse events were gastrointestinal or hematologic in nature.

Based on the clinical benefit of T-DXd versus chemotherapy and consistent safety profile reported across clinical trials, we request your consideration of T-DXd as a treatment option for patients with previously treated HER2-positive advanced gastric and GEJ adenocarcinoma.

Sincerely,

Dan Liang, PharmD

Enclosed References:

1. Shitara K, et al. Trastuzumab deruxtecan in previously treated HER2-positive gastric cancer [published online ahead of print May 29, 2020]. N Engl J Med. 2020.
2. Shitara K, et al. Trastuzumab deruxtecan (DS-8201a) in patients with advanced HER2-positive gastric cancer: a dose-expansion, phase 1 study. Lancet Oncol. 2019;20(6):827-836.
3. ENHERTU (fam-trastuzumab deruxtecan-nxki) prescribing information. 2019. Daiichi Sankyo, Inc. and AstraZeneca Pharmaceuticals, LP.

Additional References:

4. Thuss-Patience PC, et al. Trastuzumab emtansine versus taxane use for previously treated HER2-positive locally advanced or metastatic gastric or gastro-oesophageal junction adenocarcinoma (GATSBY): an international randomised, open-label, adaptive, phase 2/3 study. Lancet Oncol. 2017;18(5):640-653.
5. Satoh T, et al. Lapatinib plus paclitaxel versus paclitaxel alone in the second-line treatment of HER2-amplified advanced gastric cancer in Asian populations: TyTAN—a randomized, phase III study. J Clin Oncol. 2014;32(19):2039-2049.