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NCCN Panel: Non-Small Cell Lung Cancer

On behalf of Daiichi Sankyo, Inc. and AstraZeneca Pharmaceuticals LP, I respectfully request the NCCN Guideline Panel for Non-Small Cell Lung Cancer to review data from 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*-mutated unresectable and/or metastatic non-squamous non-small cell lung cancer (NSCLC).

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

- **NSCL-18, "Advanced or Metastatic Disease"**
  - Add "*HER2* testing" and corresponding new HER2 algorithm page with fam-trastuzumab deruxtecan-nxki (preferred for *HER2*-mutated NSCLC)
  - The dose of fam-trastuzumab deruxtecan-nxki is 6.4 mg/kg IV on Day 1, cycled every 21 days. 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.
- **NSCL-18A, "Footnotes for Advanced or Metastatic Disease: Histological Subtypes and Testing"**
  - Add *HER2* to footnote ii
- **NSCL-G, "Principles of Molecular and Biomarker Analysis"**
  - Under "Molecular Targets for Analysis", add *HER2* Gene Mutations
- **NSCL-H, "Emerging Biomarkers to Identify Novel Therapies for Patients with Metastatic NSCLC"**
  - Add "fam-trastuzumab deruxtecan-nxki"
- **NSCL-I1, "Targeted Therapy or Immunotherapy for Advanced or Metastatic Disease"**
  - Add "*HER2*-Mutation Positive" with "fam-trastuzumab deruxtecan-nxki" as "Subsequent therapy"

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*-mutated unresectable and/or metastatic NSCLC.

Rationale: T-DXd has demonstrated significant activity (61.9% to 72.7%% confirmed ORR) in 2 independent international studies of patients with advanced *HER2*-mutated NSCLC.[1,2] To our knowledge, this represents the highest activity reported for heavily pretreated patients with *HER2*-mutated NSCLC.[4] On May 18, 2020, fam-trastuzumab deruxtecan-nxki was granted Breakthrough Designation in the US for the treatment of patients with metastatic NSCLC whose tumors have a *HER2* mutation and with disease progression on or after platinum-based therapy based on the phase 2 DESTINY-Lung01 and phase 1 dose expansion studies.

Key Supporting Literature:

DESTINY-Lung01 (T-DXd in Patients with HER2-mutated Metastatic Non-Small Cell Lung Cancer) Study[1]

DESTINY-Lung01 is a phase 2 trial of T-DXd in patients with HER2-expressing or *HER2*-mutated unresectable and/or metastatic NSCLC. Interim results are shown for Cohort 2 which included 42 patients with *HER2*-mutated NSCLC who received T-DXd 6.4 mg/kg every 3 weeks. Patients received a median of 2 prior lines of therapy (range, 1-6) including platinum-based therapy (90.5%), anti-PD-1 or -PD-L1 therapy (54.8%), and docetaxel (19.0%).

The primary endpoint of confirmed objective response rate (ORR) by independent central review (ICR) was 61.9% (95% confidence interval [CI], 45.6%-76.4%) and the disease control rate (DCR) was 90.5% (95% CI, 77.4%-97.3%). Median overall survival (OS) was not reached (95% CI, 11.8 months-not estimable) nor was the median duration of response (95% CI, 5.3 months-not estimable). Median progression-free survival (PFS) was 14.0 months (95% CI, 6.4-14.0).

The most common any-grade TEAEs (≥25%) were gastrointestinal (nausea [76.2%], decreased appetite [42.9%], vomiting [40.5%], diarrhea [35.7%], and constipation [26.2%]), hematologic (decreased neutrophil count [42.9%], anemia [42.9%], and decreased white blood cell count [26.2%]), alopecia (47.6%), decreased weight (31.0%), and fatigue (26.2%). Overall, 5 deaths occurred during the study as a result of a TEAE. There were 5 cases (11.9%) of drug-related ILD as adjudicated by an independent committee (all grade 2). There were no grade 5 ILD events. One case of grade 1 ILD is pending adjudication.

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

A phase 1, dose-expansion study evaluated T-DXd 6.4 mg/kg every 3 weeks in HER2-expressing or *HER2*-mutated advanced solid tumors that were refractory to standard treatment or for which no standard treatment was available. In a subset of 11 patients with *HER2*-mutated NSCLC, the confirmed ORR was 72.7% with a confirmed DCR of 90.9%. The median DOR was 9.9 months. Median PFS was 11.3 months and median OS was 17.3 months. Consistent with the DESTINY-Lung01 clinical trial, the most common adverse events were gastrointestinal or hematologic in nature.

Based on the clinical benefit of T-DXd combined with the consistent safety profile reported in the phase 2 DESTINY-Lung01 and phase 1 dose escalation studies, we request your consideration of T-DXd as a treatment option for patients with previously treated *HER2*-mutated unresectable and/or metastatic non-squamous NSCLC.

Sincerely,

Dan Liang, PharmD

Enclosed References:

1. Smit EF, et al. Trastuzumab deruxtecan (T-DXd; DS-8201) in patients with HER2-mutated metastatic non-small cell lung cancer: interim results of DESTINY-Lung01 [presentation]. Presented at: 2020 American Society of Clinical Oncology Virtual Scientific Program; May 29-31, 2020.
2. Tsurutani J, et al. Targeting HER2 with trastuzumab deruxtecan: a dose-expansion, phase 1 study in multiple advanced solid tumors. *Cancer Discov*. 2020;10(5):688-701.
3. ENHERTU (fam-trastuzumab deruxtecan-nxki). Prescribing information. Daiichi Sankyo, Inc. and AstraZeneca Pharmaceuticals, LP; 2019.

Additional References:

4. Li BT, et al. Ado-trastuzumab emtansine for patients with HER2-mutant lung cancers: results from a phase II basket trial. *J Clin Oncol*. 2018;36(24):2532-2537.