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NCCN Panel: Colon Cancer and Rectal Cancer

On behalf of Daiichi Sankyo, Inc. and AstraZeneca Pharmaceuticals LP, I respectfully request the NCCN Guideline Panel for Colon and Rectal Cancers to review data from the clinical study[1] in support of fam-trastuzumab deruxtecan-nxki, also known as T-DXd, as a monotherapy option for the treatment of patients with HER2-positive unresectable and/or metastatic colorectal cancer.

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

- **COL-D1 through COL-D6 and REC-F1 through REC-F6, "Continuum of Care - Systemic Therapy for Advanced or Metastatic Disease"**
  - Add "Fam-trastuzumab deruxtecan-nxki (HER2-positive and *RAS* and *BRAF* WT)" to the following:
    - COL-D1 and REC-F1: "Patient not appropriate for intensive therapy"
    - COL-D2 and REC-F2: "Previous oxaliplatin-based therapy without irinotecan"
    - COL-D3 and REC-F3: "Previous irinotecan-based therapy without oxaliplatin"
    - COL-D4 and REC-F4: "Previous treatment with oxaliplatin and irinotecan"
    - COL-D5 and REC-F5: "Previous therapy without irinotecan or oxaliplatin"
    - COL-D6 and REC-F6: "FOLFOX or CAPEOX or (FOLFOX or CAPEOX) + bevacizumab"
- **COL-D11 and REC-F11, "Systemic Therapy for Advanced or Metastatic Disease – Chemotherapy 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.[2]

ENHERTU is not FDA-approved for the treatment of HER2-positive unresectable and/or metastatic colorectal cancer.

Rationale: T-DXd has demonstrated clinically meaningful activity (confirmed ORR 45.3%, median PFS 6.9 months, median OS not reached) in the DESTINY-CRC01 trial in patients with HER2-positive unresectable and/or metastatic colorectal cancer.[1]

Key Supporting Literature:

DESTINY-CRC01 (A Phase 2, Multicenter, Open-Label Study of T-DXd in Patients With HER2-Expressing Metastatic Colorectal Cancer)[1]

DESTINY-CRC01 is a phase 2, multicenter, open-label, 3-cohort study assessing the safety and efficacy of T-DXd 6.4 mg/kg every 3 weeks in patients with HER2-expressing, RAS/BRAF wild type unresectable and/or metastatic colorectal cancer that progressed on ≥2 prior regimens. Seventy-eight patients were

enrolled into 3 cohorts: Cohort A (n=53; HER2-positive, immunohistochemistry [IHC] 3+ or IHC 2+/in situ hybridization [ISH]+), Cohort B (n=7; HER2 IHC 2+/ISH-), and Cohort C (n=18; HER2 IHC 1+). The median number of prior lines of cancer treatment in the adjuvant and metastatic setting was 4 (range, 2-11) and included irinotecan (100%), fluorouracil (98.7%)/capecitabine (53.8%), oxaliplatin (100%), cetuximab or panitumumab (98.7%), bevacizumab (79.5%), or prior anti-HER2 agents (20.5%; 30.2% in Cohort A).

In Cohort A, the primary endpoint of confirmed objective response rate (ORR) by independent central review (ICR) was 45.3% (95% CI, 31.6%-59.6%) with a disease control rate of 83.0% (95% CI, 70.2%-91.9%). Median duration of response was not reached (95% CI, 4.2 months-not estimable). Median progression-free survival (PFS) was 6.9 months (95% CI, 4.1-not estimable) and median overall survival was not reached (95% CI, 0.74 months-not estimable). Consistent response rates were generally observed across subgroups, including in patients with (43.8%) or without (45.9%) prior HER2 treatment.

In all patients, the most common (≥5%) grade ≥3 treatment emergent adverse events were neutrophil count decreased (25.6%), anemia (14.1%), platelet count decreased (10.3%), white blood cell count decreased (9.0%), nausea (6.4%), and hypokalemia (6.4%). There were 5 cases of drug-related interstitial lung disease as determined by an independent adjudication committee (grade 2, n=2; grade 3, n=1; grade 5, n=2).

Based on the clinical benefit of T-DXd combined with the safety profile in DESTINY-CRC01, we request your consideration of T-DXd as a treatment option for HER2-positive unresectable and/or metastatic colorectal cancer.

Sincerely,

Dan Liang, PharmD

References (enclosed):

1. Siena S, et al. A phase 2, multicenter, open-label study of trastuzumab deruxtecan (T-DXd; DS-8201) in patients with HER2-expressing metastatic colorectal cancer: DESTINY-CRC01 [presentation]. Presented at: 2020 American Society of Clinical Oncology Virtual Scientific Program; May 29-May 31.
2. ENHERTU (fam-trastuzumab deruxtecan-nxki) prescribing information. 2019. Daiichi Sankyo, Inc. and AstraZeneca Pharmaceuticals, LP.