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
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NCCN Panel: Head and Neck Cancers Panel

On behalf of Daiichi Sankyo, Inc. and AstraZeneca Pharmaceuticals LP, I respectfully request the NCCN Guidelines Panel for Head and Neck Cancers to review the clinical data[1] in support of fam-trastuzumab deruxtecan-nxki, also referred to as T-DXd, as a monotherapy option for the treatment of patients with HER2-positive advanced/unresectable or metastatic salivary gland tumors.

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

- **SALI-B, "Systemic Therapy for Salivary Gland Tumors"**
  - Add "fam-trastuzumab deruxtecan-nxki" under "HER2 targeted therapy for HER2+ tumors"

FDA Clearance: ENHERTU is not FDA-approved for the treatment of HER2-expressing salivary gland tumors.

Please refer to the enclosed full Prescribing Information for the FDA-approved indications and safety information.[2]

Rationale:

This request is based on a pooled subgroup analysis of patients with advanced/unresectable or metastatic salivary duct carcinoma from the Phase 1 DS8201-A-J101 and DS8201-A-A104 trials.[1]

- DS8201-A-J101 is an ongoing, 2-part, open-label, multicenter, Phase 1, first-in-human, dose escalation and dose expansion study in Japan and the United States evaluating T-DXd in patients with advanced/unresectable or metastatic solid tumors expressing HER2 that are refractory or intolerant to standard treatment, or for whom no standard treatment is available.[3] In the pooled analysis, the data cutoff for this study was August 1, 2019 and 8 patients who received T-DXd 6.4 mg/kg intravenously every 3 weeks were included.[1]
- DS8201-A-A104 is an ongoing, Phase 1, open-label, single-sequence, crossover study in Japan, Korea, and Taiwan evaluating the drug-drug interaction potential between T-DXd and ritonavir or itraconazole in patients with unresectable or metastatic HER2-expressing solid tumors that are refractory to or intolerant of at least 1 prior systemic chemotherapy, or for whom no standard treatment is available. There were no clinically meaningful pharmacokinetic interactions observed.[4] In the pooled analysis, the data cutoff for this study was September 26, 2018 and 9 patients who received T-DXd 5.4 mg/kg intravenously every 3 weeks were included.[1]

HER2 expression at enrollment was determined by local testing according to immunohistochemistry (IHC) and/or amplification by in situ hybridization (ISH) or next generation sequencing. A retrospective analysis of IHC and ISH by a central laboratory was performed after enrollment according to the American Society of Clinical Oncology/College of American Pathologists guidelines for gastric cancer. Tumor response was evaluated per investigator assessment according to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1.[1]

Of 329 patients enrolled in the 2 studies, 17 patients with salivary duct carcinoma were included in the pooled analysis. The median age was 57 years and most patients were male (n=15) and Asian (n=16). The sites of primary disease were the parotid gland, submandibular gland, sublingual gland, and unknown for 6, 4, 1, and 6 patients, respectively. Eleven patients were IHC 3+ and 1 patient was IHC 2+/ISH- according to central laboratory assessment; 5 patients had no available samples. The median number of prior lines of systemic therapy, including adjuvant and locally advanced/metastatic

disease, was 1 (range 0-6). Prior cancer therapies included platinum therapy (n=3), taxane therapy (n=13), trastuzumab (n=13), and trastuzumab emtansine (n=1). At data cutoff, 7 patients were still receiving treatment and the median duration of follow up was 5.6 months.[1]

The confirmed objective response rate was 47.1% with the best overall response being partial response in 8 patients and stable disease in 9 patients. The median duration of response was 12.9 months and the median progression-free survival was 14.1 months.[1]

The safety profile was generally consistent with previously reported results for T-DXd in other solid tumors. Grade ≥3 treatment-emergent adverse events (TEAEs) occurred in 64.7% of patients with the most common being neutrophil count decrease (47.1%), white blood cell count decrease (35.3%), anemia (11.8%), platelet count decrease (11.8%), aspartate aminotransferase increased (11.8%), and alanine aminotransferase increased (11.8%). There were 3 cases of drug-related interstitial lung disease (grade 1, n=2; grade 3, n=1) as determined by an independent adjudication committee. There were 7 (41.2%), 3 (17.6%), and 4 (23.5%) patients with TEAEs associated with dose interruption, dose reduction, and treatment discontinuation, respectively.[1]

Thank you for your consideration.

Sincerely,

Dan Liang, PharmD

References (Enclosed):

1. Bando H, Kinoshita I, Modi S, et al. Trastuzumab deruxtecan (T-DXd) in patients with human epidermal growth factor receptor 2 (HER2)-expressing salivary duct carcinoma: Subgroup analysis of two phase 1 studies [poster]. Presented at: 2021 American Society of Clinical Oncology Annual Meeting; June 4-8, 2021. Abstract 6079.
2. ENHERTU (fam-trastuzumab deruxtecan-nxki) Prescribing Information. 2021. Daiichi Sankyo, Inc. and AstraZeneca Pharmaceuticals LP.
3. Tsurutani J, Iwata H, Krop I, et al. Targeting HER2 with trastuzumab deruxtecan: a dose-expansion, phase I study in multiple advanced solid tumors. *Cancer Discov*. 2020;10(5):688-701.
4. Bang YJ, Karayama M, Takahashi M, et al. Pharmacokinetics (PK), safety, and efficacy of [fam-] trastuzumab deruxtecan with OATP1B/CYP3A inhibitors in patients with HER2-expressing solid tumors [poster]. Presented at: 2019 European Society for Medical Oncology Annual Meeting; September 27-October 1, 2019; Barcelona, Spain. Abstract 330P.