TPS4207 Poster Session

An open-label, randomized, multicenter, phase 3 study of trastuzumab deruxtecan (T-DXd) + chemotherapy (chemo) ± pembrolizumab (pembro) versus chemo + trastuzumab ± pembro in first-line metastatic HER2+ gastric or gastroesophageal junction (GEJ) cancer: DESTINY-Gastric05.

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Background: An unmet medical need remains in patients (pts) with HER2+ gastric or GEJ cancer. HER2 is a validated target in up to 20% of pts with gastric or GEJ cancer. The KEYNOTE-811 trial demonstrated that adding pembro to trastuzumab and chemo improved progression-free survival (PFS) and overall survival (OS) versus placebo for first-line treatment of pts with HER2+ gastric or GEJ cancer with a PD-L1 combined positive score (CPS) ≥1 (Janjigian Y et al. *N Engl J Med.* 391;1360:2024). In the DESTINY-Gastric03 trial, first-line combinations involving T-DXd, a HER2-directed antibody-drug conjugate, and fluoropyrimidine (5-FU or capecitabine [CAPE]) ± pembro showed acceptable safety and encouraging efficacy in pts with HER2+ gastric or GEJ cancer, including pts with CPS < 1 (Janjigian Y et al. *Ann Oncol.* 35;S878:2024). Building on this evidence, the phase 3 DESTINY-Gastric05 trial aims to bring a potentially improved platinum-free treatment approach for all pts with HER2+ gastric or GEJ cancer. **Methods:** DESTINY-Gastric05 (NCT06731478) is an open-label, randomized, multicenter, phase 3 global trial designed to evaluate the efficacy and safety of T-DXd in combination with 5-FU (or CAPE) + pembro versus standard-of-care chemo with trastuzumab + pembro as first-line treatment in pts with unresectable, locally advanced or metastatic centrally confirmed HER2+ (immunohistochemistry [IHC] 3+ or IHC 2+/in situ hybridization+) gastric or GEJ cancer with a CPS ≥1. Pts must have ≥1 RECIST v1.1 measurable lesion, a left ventricular ejection fraction ≥50%, and an Eastern Cooperative Oncology Group performance status of 0 or 1. Approximately 576 pts will be randomly assigned in a 1:1 ratio to receive: T-DXd 5.4 mg/kg + either 5-FU or CAPE + pembro (arm M1); or trastuzumab + platinum-based chemo (either cisplatin + 5-FU or oxaliplatin + CAPE) + pembro (arm M2). The primary efficacy endpoint is PFS based on blinded independent central review (BICR), and the key secondary endpoint is OS. Other secondary endpoints include overall response rate, duration of response, and time to response per RECIST v1.1 assessed by BICR and investigator. Safety and tolerability will also be assessed. An exploratory cohort (approximately 150 pts) will evaluate the efficacy and safety of T-DXd in combination with 5-FU or CAPE versus trastuzumab plus standard-of-care chemo in pts with PD-L1 CPS < 1. Clinical trial information: NCT06731478. Research Sponsor: Daiichi Sankyo, Inc.