TPS4209 Poster Session

# KEYMAKER-U06 substudy 06E: A phase 1/2 open-label, umbrella platform study of ifinatamab deruxtecan in combination with pembrolizumab with or without chemotherapy for first-line treatment of advanced esophageal squamous cell carcinoma (ESCC).

Ken Kato, Toshihiko Doi, Antoine Adenis, Manish A. Shah, Peter C. Enzinger, Lin Shen, Tatiane Cristine Ishida, Leah Suttner, Kanu Sharan, Pooja Bhagia, Jong-Mu Sun; National Cancer Center Hospital, Tokyo, Japan; National Cancer Center Hospital East, Chiba, Japan; Institut du Cancer de Montpellier and IRCM, Université de Montpellier, Montpellier, France; NewYork-Presbyterian Hospital, New York, NY; Dana-Farber Cancer Institute, Boston, MA; Beijing Cancer Hospital, Beijing, China; Daiichi Sankyo, Inc., Basking Ridge, NJ; Merck & Co., Inc., Rahway, NJ; Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, South Korea

**Background:** There is a substantial need for more effective and tolerable first-line treatment options for patients with advanced ESCC. B7-H3 is a type 1 transmembrane protein that is highly expressed in several cancers, including ESCC, and is associated with a poor prognosis. Ifinatamab deruxtecan (I-DXd; formerly DS-7300a/MK-2400) is a B7-H3–directed antibody-drug conjugate comprising a humanized anti–B7-H3 IgG1 monoclonal antibody (ifinatamab) covalently linked to a potent topoisomerase I inhibitor payload (DXd; an exatecan derivative) by a cleavable linker. In the phase 1/2 DS7300-A-J101 study, I-DXd monotherapy showed promising antitumor activity in participants (pts) with advanced ESCC. KEYMAKER-U06 is an open-label, phase 1/2, umbrella platform study designed to evaluate investigational agents with or without pembrolizumab and/or chemotherapy for advanced gastroesophageal cancer. Substudy 06E (NCT06780111) will be conducted to evaluate I-DXd plus pembrolizumab with or without chemotherapy as first-line therapy for advanced ESCC. **Methods:** Eligible pts are aged ≥18 years with previously untreated, histologically or cytologically confirmed, locally advanced unresectable or metastatic ESCC, measurable disease per RECIST v1.1 by investigator review and verified by blinded independent central review (BICR), and an Eastern Cooperative Oncology Group performance status of 0 or 1. Pts will be assigned to 1 of 4 treatment arms: arm 1 (reference treatment; pembrolizumab 200 mg IV Q3W for ≤35 cycles plus chemotherapy [mFOLFOX6: oxaliplatin 85 mg/m$^2$ IV Q2W plus 5-FU 400 mg/m$^2$ (bolus) and 2400 mg/m$^2$ (continuous) IV Q2W plus leucovorin 400 mg/m$^2$ IV Q2W]); arm 2 (I-DXd 12 mg/kg IV Q3W plus pembrolizumab); arm 3 (I-DXd 12 mg/kg plus pembrolizumab plus 5-FU 400 mg/m$^2$ [bolus] and 2400 mg/m$^2$ [continuous] IV Q2W plus leucovorin 400 mg/m$^2$ IV Q2W); and arm 4 (I-DXd [8 mg/kg or 12 mg/kg] IV plus pembrolizumab plus 5-FU 2400 mg/m$^2$ IV and oxaliplatin 60 mg/m$^2$). Approximately 209 pts will be enrolled. A safety lead-in phase with ≤29 pts will be conducted in arms 2 (n ≤6), 3 (n ≤10), and 4 (n ≤13) using a Bayesian optimal interval design to confirm the safety and recommended phase 2 dose (RP2D; arm 4 only) of I-DXd in combination with other agents; this phase will be conducted sequentially, starting with arm 2, followed by arms 3 and 4. Thereafter, ≤180 pts will be included in the randomized phase (≤60 in arm 1; ≤40 each in arms 2-4). Pts will be randomly assigned 1:2 to arm 1 and the investigational arms. Primary outcomes are safety and tolerability, RP2D of I-DXd, and objective response rate per RECIST v1.1 by BICR for the selected dose. Secondary outcomes include DOR and PFS per RECIST v1.1 by BICR, OS, and pharmacokinetics of I-DXd in combination with other agents. Enrollment is ongoing. Clinical trial information: NCT06780111. Research Sponsor: Daiichi Sankyo Company, Limited and Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA.