TPS8652 **Poster Session**

KEYMAKER-U01 substudy 01A: Phase 1/2 study of pembrolizumab plus ifinatamab deruxtecan (I-DXd) or patritumab deruxtecan (HER3-DXd) with or without chemotherapy in untreated stage IV non–small-cell lung cancer.

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Background: A standard-of-care option for metastatic non–small-cell lung cancer (NSCLC) with no targetable genetic alterations includes pembrolizumab plus chemotherapy. However, there remains an unmet need for patients who do not respond to standard treatment. Ifinatamab deruxtecan (I-DXd) and patritumab deruxtecan (HER3-DXd) are investigational antibody-drug conjugates (ADCs) against B7 homologue 3 and human epidermal growth factor receptor 3, respectively, two proteins that are highly expressed in NSCLC tumors. Both I-DXd and HER3-DXd are conjugated with a topoisomerase 1 inhibitor payload, resulting in apoptosis of target cells. Preclinical and preliminary clinical data suggest that combining an immune checkpoint inhibitor with an ADC may provide robust antitumor activity. KEYMAKER-U01 substudy 01A (NCT04165070) is a phase 1/2, two-part, rolling arm, open-label study assessing the efficacy and safety of pembrolizumab plus an investigational agent (part A: vibostolimab, boserolimab, MK-4830, and MK-0482; part B: I-DXd and HER3-DXd), with or without chemotherapy in untreated stage IV NSCLC. We present the study design for KEYMAKER-U01 substudy 01A part B. **Methods:** Eligible participants for KEYMAKER-U01 substudy 01A part B are aged ≥18 years with previously untreated histologically or cytologically confirmed stage IV (per American Joint Committee on Cancer v8) squamous or nonsquamous NSCLC and measurable disease per RECIST v1.1 as assessed by investigator and verified by blinded independent central review (BICR). Additional eligibility criteria include ECOG PS of 0 or 1, provision of an archival tumor sample or newly obtained biopsy of a nonirradiated tumor for biomarker analysis, and no *EGFR, ALK, or ROS1* mutations for which first-line targeted therapy is indicated. In part B, 10–30 participants will be allocated to treatment arms 5–7. In Arms 5 and 6, participants will receive I-DXd plus pembrolizumab 200 mg Q3W (Arm 5) or I-DXd plus pembrolizumab with 4 cycles of carboplatin area under the curve 5 or 6 mg/ml/min (Arm 6); I-DXd dose will be at 8mg/kg. In Arm 7, participants will receive HER3-DXd 3.2, 4.8, or 5.6 mg/kg plus pembrolizumab and carboplatin. Participants can receive I-DXd and HER3-DXd until disease progression or unacceptable toxicity and pembrolizumab up to 35 cycles. The primary endpoint is incidence of dose-limiting toxicities until the start of cycle 2, and AEs and treatment discontinuations due to AEs until 40 days after last treatment (90 days for serious AEs); secondary endpoints include ORR and DOR, both per RECIST v1.1 by BICR, and pharmacokinetic parameters, including maximum concentration (C_{max}) and maximum trough concentration (C_{trough}) of I-DXd and HER3-DXd. Enrollment will be ongoing globally. Clinical trial information: NCT04165070. Research Sponsor: Daiichi Sankyo Company, Limited and Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA.