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

TPS4209

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OBJECTIVES

- To evaluate the safety and efficacy of first-line I-DXd plus pembrolizumab with or without chemotherapy for advanced ESCC

Primary

- Safety and tolerability (dose-limiting toxicities [DLTs], adverse events [AEs])
- Objective response rate (ORR) per RECIST v1.1 by blinded independent central review (BICR) for the selected dose

Secondary

- Duration of response (DOR) per RECIST v1.1 by BICR
- Disease control rate (DCR) per RECIST v1.1 by BICR
- Progression-free survival (PFS) per RECIST v1.1 by BICR
- Overall survival (OS)
- Pharmacokinetics of I-DXd in combination with other agents
- Immunogenicity (antidrug antibody assay)

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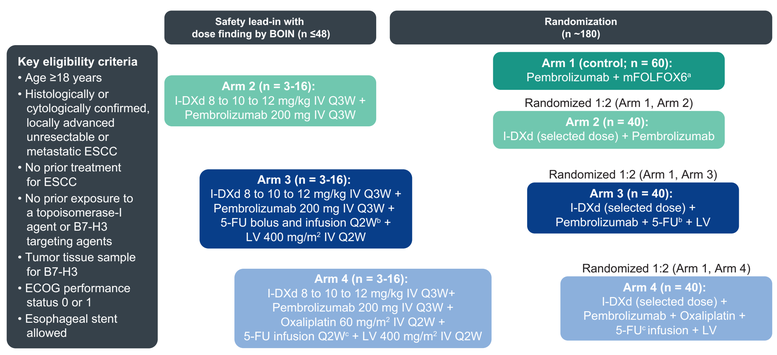
BACKGROUND

- Esophageal squamous cell carcinoma (ESCC) is an aggressive malignancy with 5-year survival rates of 15-25%[1]; 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[2]
- Ifinatamab deruxtecan (I-DXd; formerly DS-7300a/MK-2400) is a B7-H3–directed antibody-drug conjugate (ADC) 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[3]
  - In the phase 1/2 DS7300-A-J101 study, I-DXd monotherapy showed promising antitumor activity in participants with advanced ESCC[3,4]
- 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 evaluate I-DXd plus pembrolizumab with or without chemotherapy as first-line therapy for advanced ESCC

METHODS

Study design and participants

Figure 1. Study design of KEYMAKER-U06 substudy E



[a]mFOLFOX6: 5-FU 400 mg/m² bolus plus 2400 mg/m² continuous IV Q2W + oxaliplatin 85 mg/m² IV Q2W + leucovorin 400 mg/m² IV Q2W.
[b]5-FU: 400 mg/m² bolus plus 2400 mg/m2 continuous IV Q2W.
[c]5-FU: 2400 mg/m² continuous IV Q2W.

Number of participants

- New treatment arms will be open for enrollment on a rolling basis to evaluate new investigational treatment combinations
  - Efficacy enrollment for each arm will start once the dose finding phase is complete
  - The safety lead-in phase for Arm 3 will be initiated once the DLT period is complete for 1 dose level in Arm 2
  - The highest dose escalation in Arms 3 and 4 will be based on the selected dose in Arms 2 and 3

Participant eligibility

Key inclusion criteria

- Aged ≥18 years
- Histologically or cytologically confirmed, locally advanced unresectable or metastatic ESCC
- Measurable disease per RECIST v1.1 by investigator and verified by BICR
- Archival tumor tissue sample provided or newly obtained core, incisional, or excisional biospy of a tumor lesion not previously irradiated
- Any AEs from prior anticancer therapies must have improved to grade ≤1 or baseline
- Participants with HIV infection must have well controlled HIV on antiretroviral therapy
- ECOG performance status 0 or 1

Key exclusion criteria

- Prior systemic anticancer therapy for locally advanced or metastatic esophageal cancer
- Received prior therapy with
  - Anti–PD-1, anti–PD-L1, or anti–PD-L2 agent
  - An agent directed to another stimulatory or coinhibitory T cell receptor (eg, CTLA-4, OX-40, CD137)
  - Orlotamab, enoblituzumab, or other B7–H3-targeted agent
  - Topoisomerase-I inhibitor, including ADC
- Tumor invasion into organs adjacent to the esophageal disease site at an increased risk of fistula as assessed by investigator
- Known additional malignancy that is progressing or required active treatment in the past 3 years
- Known active CNS metastasis and/or carcinomatous meningitis
- History of (noninfectious) pneumonitis or interstitial lung disease that required steroids or current pneumonitis or interstitial lung disease
- Clinically significant corneal disease
- History of Kaposi sarcoma and/or Multicentric Castleman's Disease for participants with HIV infection

Assessment and follow-up

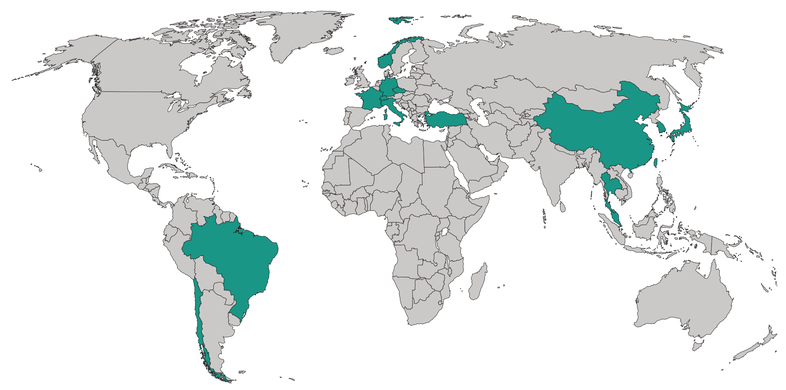
	Detail
Tumor response	• Response assessments (CT or MRI) will be performed 6 weeks from the date of randomization, then Q6W or more frequently if clinically indicated • After year 1, assessments will be performed Q9W until discontinuation criteria are met
AEs	• AEs will be monitored and assessed by investigators throughout the study and for 40 days after cessation of study treatment • Serious AEs will be monitored and assessed by investigators throughout the study and for 90 days after cessation of study treatment (40 days if new anticancer therapy is initiated) • Severity will be graded per National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0

Analyses

	Detail
Efficacy	• Efficacy analyses will be conducted for all participants with a baseline scan that showed measurable disease by BICR and who received ≥1 dose of study treatment • ORR (95% CI) will be calculated for each treatment arm using the Clopper-Pearson method – The difference in ORR between treatment arms will be calculated using the Miettinen and Nurminen method • PFS, OS, and DOR will be estimated using the Kaplan-Meier method
Safety	• Safety analyses will be conducted in all participants who received ≥1 dose of study treatment • Safety will be summarized descriptively

CURRENT STATUS

Sites of enrollment for KEYMAKER-U06 (green)



ABBREVIATIONS

5-FU, 5-fluorouracil; BOIN, Bayesian optimal interval; CD137, tumor necrosis factor receptor superfamily member 9; CNS, central nervous system; CT, computed tomography; CTLA-4, cytotoxic T-lymphocyte associated protein 4; MRI, magnetic resonance imaging; IV, intravenous; LV, leucovorin; OX-40, tumor necrosis factor superfamily member 4; PD-1, programmed cell death protein 1; PD-L1, programmed cell death ligand 1; PD-L2, programmed cell death ligand 2; QXW, every X weeks.

REFERENCES

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