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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

- Pembrolizumab, an anti–PD-1 monoclonal antibody, plus chemotherapy is a standard of care first-line treatment option for patients with stage IV non–small-cell lung cancer (NSCLC) with no targetable genetic alterations regardless of PD-L1 expression[1]; however, there remains an unmet medical need to improve outcomes for these patients
- Antibody-drug conjugates (ADCs) typically target receptors that are overexpressed in tumors, such as B7 homologue 3 (B7H3) and human epidermal growth factor receptor 3 (HER3), both of which are highly expressed in NSCLC tumors[2-4]
  - I-DXd and HER3-DXd are investigational ADCs against B7H3 and HER3, respectively, and are conjugated with a topoisomerase 1 inhibitor, resulting in apoptosis of target cells[5,6]
- Preclinical and preliminary clinical data suggest that combining an ADC with an immune checkpoint inhibitor may provide robust antitumor activity compared with either agent alone[7-9]
- 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, with or without chemotherapy, in participants with previously untreated stage IV NSCLC
  - Part A includes 4 treatment arms and is evaluating the investigational agents vibostolimab, boserolimab, MK-4830, and MK-0482 in combination with pembrolizumab with or without chemotherapy
  - Part B includes 3 treatment arms and is evaluating the investigational agents I-DXd and HER3-DXd in combination with pembrolizumab with or without chemotherapy
- We present the study design for KEYMAKER-U01 substudy 01A part B

Objectives

Primary

- Evaluate safety and tolerability by analyzing the incidence of adverse events (AEs), AEs leading to discontinuation, and dose-limiting toxicities (DLTs)

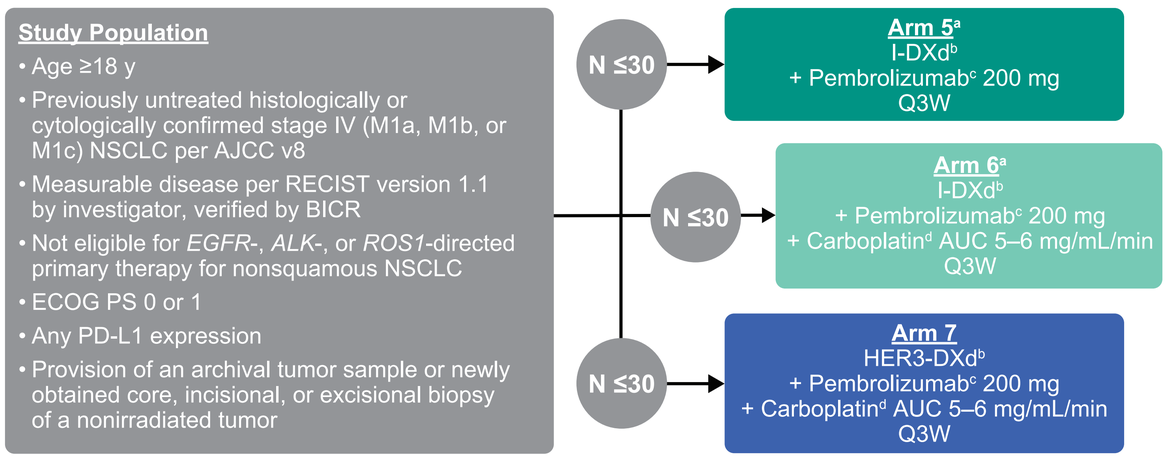
Secondary

- Evaluate ORR per RECIST version 1.1 by blinded independent central review (BICR)
- Evaluate duration of response (DOR) per RECIST version 1.1 by BICR
- Characterize pharmacokinetic parameters including maximum concentration (C_{max}) and maximum trough concentration (C_{trough})

Methods

Study design, participants, and treatment

Figure. KEYMAKER-U01 substudy 01A part B (NCT04165070) study design



AJCC, American Joint Committee on Cancer; *ALK*, anaplastic lymphoma kinase; AUC, area under the curve; ECOG PS, Eastern Cooperative Oncology Group performance status; *EGFR*, epidermal growth factor reaceptor; PD, progressive disease; *ROS1*, c-ros oncogene 1.

[a]Enrollment in arms 5 and 6 is staggered. Enrollment in arm 6 will begin upon confirmation that no DLTs occurred in the first 3 participants treated in arm 5.

[b]Different doses of I-DXd and HER3-DXd will be tested. Treatment with I-DXd or HER3-DXd can continue until PD, unacceptable toxicity, or participant/physician decision.

[c]Treatment with pembrolizumab can continue for up to 35 cycles or until PD, unacceptable toxicity, or participant/physician decision.

[d]Participants receive 4 cycles of carboplatin.

Assessments

- Tumor imaging is performed at baseline, every 6 weeks from the first dose of study treatment through week 24, every 9 weeks through week 51, then every 12 weeks until end of study or until disease progression, start of new anticancer treatment, withdrawal of consent, pregnancy, or death
- AEs are monitored from the first dose of study treatment until 40 days after the last dose (90 days for serious AEs) and graded according to National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0
  - DLTs, based on the occurrence of protocol-specified toxicities and as determined by the investigator to be related to study treatment, will be monitored from the first dose of study treatment until the start of cycle 2

Analyses

- Efficacy will be assessed in the full analysis set population, comprising all participants with measurable disease at baseline who receive ≥1 dose of study treatment
- Safety will be assessed in the all-participants-as-treated (APaT) population, comprising all participants who receive ≥1 dose of study treatment
  - The DLT-evaluable population includes participants in the APaT population who completed treatment up to cycle 2 or who experienced a DLT in the DLT evaluation period

Table. Key eligibility criteria

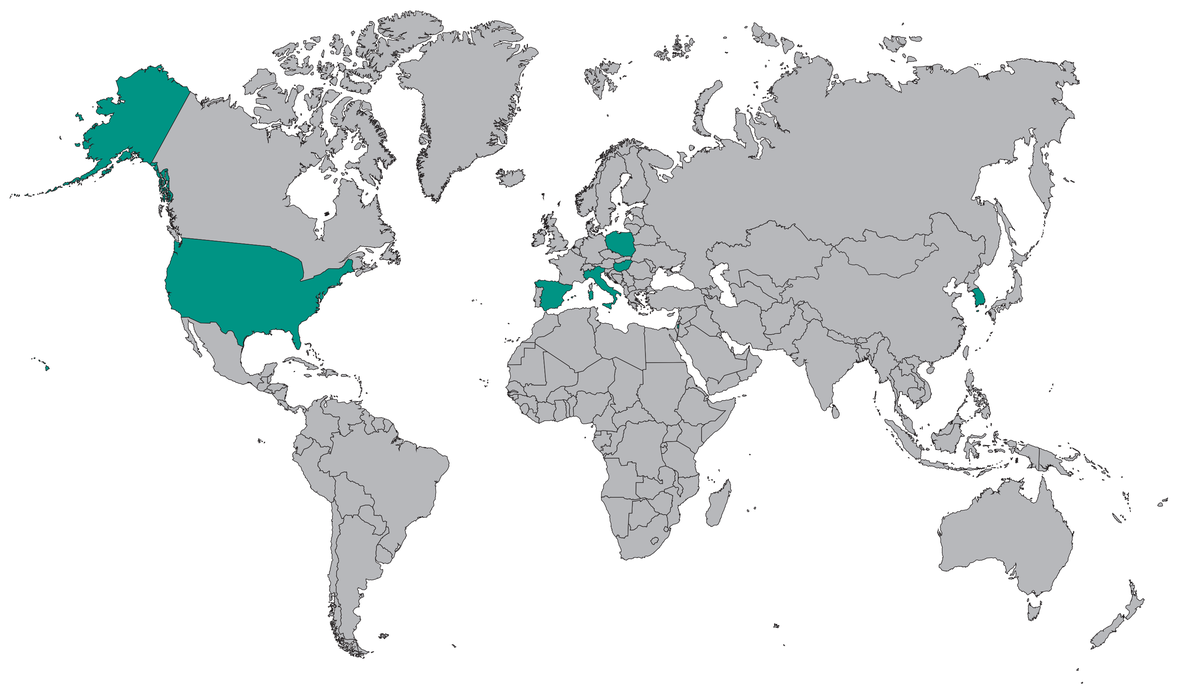
Inclusion criteria	Exclusion criteria
• Age ≥18 y • Histologically or cytologically confirmed stage IV (M1a, M1b, or M1c) NSCLC per AJCC version 8 • Measurable disease per RECIST v1.1 by investigator per BICR • *EGFR*-, *ALK*-, or *ROS1*-directed therapy is not indicated as primary therapy for those with nonsquamous NSCLC • ECOG PS of 0 or 1 • Any PD-L1 expression • Life expectancy ≥3 mo • Adequate organ function • Provision of an archival tumor sample or newly obtained core, incisional, or excisional biopsy of a tumor not previously irradiated	• Prior systemic anticancer therapy for metastatic NSCLC, including anti–PD-(L)1 or any agent directed to another stimulatory or coinhibitory T-cell receptor – Prior chemotherapy or radiation as neoadjuvant or adjuvant therapy for nonmetastatic NSCLC is permitted if completed ≥12 mo before metastatic NSCLC diagnosis • Received prior treatment with a topoisomerase I inhibitor, anti-HER3 antibody, ADC that is an exatecan derivative, or orlotamab, enoblituzumab, or other B7H3-targeted agent • Received radiotherapy ≤2 wk before first dose of study treatment or has radiation-related toxicities requiring corticosteroids • Received radiation therapy to the lung >30 Gray ≤6 mo before study treatment • Clinically severe pulmonary compromise from intercurrent illnesses[a] • Known active CNS metastases and/or carcinomatous meningitis • Additional malignancy that is progressing or required active treatment within ≤3 y • Uncontrolled or significant cardiovascular disorder • Immunodeficiency or receiving chronic systemic steroid therapy or other immunosuppressive therapy ≤7 d before first dose • Active autoimmune disease requiring systemic treatment within ≤2 y • History of (noninfectious) pneumonitis/interstitial lung disease that required steroids or current pneumonitis/interstitial lung disease

CNS, central nervous system.

[a]Including any underlying pulmonary disorder; any autoimmune, connective tissue, or inflammatory diseases with pulmonary involvement; or prior complete pneumonectomy.

Current status

- Enrollment is ongoing globally



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