2081eTiP

KEYMAKER-U01 Phase 2 Substudies 01H/01I: Ifinatamab Deruxtecan (I-DXd), Raludotatug Deruxtecan (R-DXd), or Docetaxel in Stage IV Non–Small-Cell Lung Cancer

E. Nadal[1]; C. Rojas[2]; K.N. Syrigos[3]; N. Peled[4]; G. Lo Russo[5]; D.M. Kowalski[6]; M.A. Nahit Sendur[7]; B. Ricciuti[8]; J. Niu[9]; S. Trivedi[10]; J.Y. Wu[11]; H. Zhou[11]; M. Shamoun[11]; N. Frost[12]

[1]Institu Català d'Oncologia, L'Hospitalet, Barcelona, Spain; [2]Centro de Investigacion Clinica, Bradford Hill, Santiago, Chile; [3]Athens Medical School, National and Kapodistrian University of Athens, Sotiria General Hospital, Athens, Greece; [4]Helmsley Cancer Center, Shaare Zedek Medical Center, The Hebrew University, Jerusalem, Israel; [5]Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy; [6]Maria Sklodowska-Curie National Research Institute of Oncology, Warsaw, Poland; [7]Ankara Yildirim Beyazit University, Ankara Bilkent City Hospital, Ankara, Türkiye; [8]Lowe Center for Thoracic Oncology, Dana-Farber Cancer Institute, Boston, MA, USA; [9]Banner MD Anderson Cancer Center, Gilbert, AZ, USA; [10]Daiichi Sankyo Inc., Basking Ridge, NJ, USA; [11]Merck & Co., Inc., Rahway, NJ, USA; [12]Charité-Universitätsmedizin Berlin, corporate member of Freie Universität Berlin, Humboldt-Universität zu Berlin and Berlin Institute of Health, Berlin, Germany

Background

- Pembrolizumab plus chemotherapy is a standard of care first-line therapy for metastatic non–small-cell lung cancer (NSCLC) with no targetable genetic mutations[1]; however, treatment options are limited for patients who progress on or after anti–PD-(L)1 treatment
- B7 homologue 3 (B7H3) and cadherin-6 (CDH6) are transmembrane proteins that are overexpressed in several cancer types, including NSCLC, and are associated with poor prognosis[2-4]
- I-DXd and R-DXd are investigational antibody–drug conjugates (ADCs) against B7H3 and CDH6, respectively
  - Each ADC contains its respective anti-B7H3 or anti-CDH6 monoclonal antibody plus an enzymatically cleavable peptide linker and a topoisomerase I inhibitor, which lead to apoptosis of the target cells
- Preclinical and clinical evidence suggest that the addition of ADCs to immune checkpoint inhibitors (ICI), or following ICI therapy, with or without chemotherapy, may provide promising antitumor activity in advanced solid tumors, including NSCLC[3,5-8]
- We present the study design for the randomized, phase 2, rolling-arm KEYMAKER-U01 substudies 01H (NCT06780085) and 01I (NCT06780098) evaluating R-DXd, I-DXd, or docetaxel in stage IV NSCLC with progressive disease (PD) following anti–PD-(L)1 treatment and platinum-based chemotherapy

Objectives

Primary

- Objective response (OR) per RECIST version 1.1 by blinded independent central review (BICR)
- Safety and tolerability assessed by adverse events (AEs) and discontinuations due to AEs

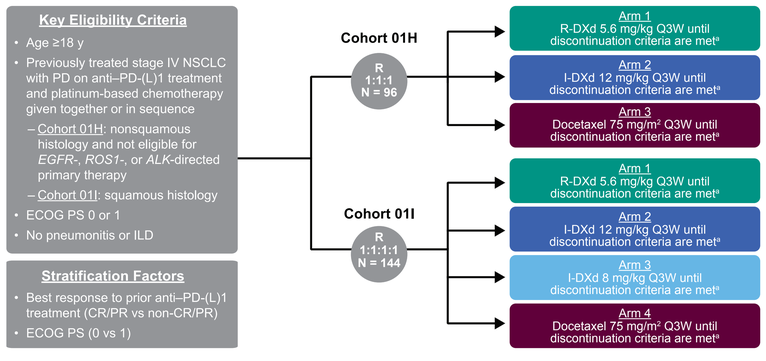
Secondary

- Duration of response (DOR) per RECIST version 1.1 by BICR
- Progression-free survival (PFS) per RECIST version 1.1 by BICR
- Overall survival (OS)

Methods

Study design, participants, and treatment

Figure. Study design of KEYMAKER-U01 substudies 01H and 01I



CR, complete response; ECOG PS, Eastern Cooperative Oncology Group performance status; ILD, interstitial lung disease; PR, partial response, Q3W, every 3 weeks.
[a]Participants can continue treatment until PD (verified by BICR), prolonged interruption of study drug, development of a new primary malignancy, pregnancy, toxicity, or participant withdrawal.

Table. Key eligibility criteria

Inclusion criteria	Exclusion criteria
• Aged ≥18 y • Histologically or cytologically confirmed stage IV (per AJCC 8th edition) NSCLC – Cohort 01H: nonsquamous NSCLC and *EGFR*-, *ALK*-, or *ROS1*-directed therapy is not indicated as primary therapy – Cohort 01I: squamous NSCLC • Documented PD as assessed by investigator per RECIST version 1.1 after ≥2 cycles of each anti–PD-(L)1 treatment and platinum-based chemotherapy for stage IV disease (no more than 1 prior line of therapy if administered concurrently and no more than 2 prior lines of therapy if administered sequentially) • ECOG PS of 0 or 1 • Life expectancy ≥3 mo • Adequate organ function • Provision of an archival tumor sample or newly obtained biopsy of a tumor lesion not previously irradiated	• Diagnosis of small-cell lung cancer or presence of small-cell elements • Received radiotherapy >30 Gy to the lung ≤6 mo before study treatment • Received radiotherapy ≤2 wk before first dose of study treatment or has radiation-related toxicities requiring corticosteroids • Uncontrolled or significant cardiovascular disorder • Clinically severe pulmonary compromise resulting from intercurrent pulmonary illnesses[a] • Received prior treatment with a CDH6-targeted agent and/or orlotamab, enoblituzumab, or another B7H3-targeted agent, or an ADC that is an exatecan derivative of a topoisomerase I inhibitor • Immunodeficiency or receipt of chronic systemic steroid therapy or other immunosuppressive therapy ≤7 d before first dose of study treatment • Additional malignancy that is progressing or required active treatment within the last 3 y • Known untreated CNS metastases and/or carcinomatous meningitis; participants with treated brain metastases may participate if they are radiologically stable for at least 4 wk before randomization and do not require glucocorticoids for at least 14 d before randomization • History of noninfectious pneumonitis/ILD that required steroids, current pneumonitis/ILD, or suspected pneumonitis/ILD that cannot be ruled out by imaging • Active autoimmune disease requiring systemic treatment within the last 2 y

AJCC, American Joint Committee on Cancer; CNS, central nervous system.
[a]Includes any underlying pulmonary disorder, any autoimmune, connective tissue, or inflammatory disorders with pulmonary involvement, or prior pneumonectomy.

Assessments

- Tumor imaging is performed at baseline (within 28 days before randomization), every 6 weeks from randomization until week 24, then every 9 weeks until week 51, and every 12 weeks thereafter until PD (identified by the investigator and verified by BICR), pregnancy, withdrawal of consent, or death
- AEs and serious AEs are monitored from randomization until 40 days after the last dose of study treatment or before initiation of new anticancer therapy
- AEs are graded per National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0

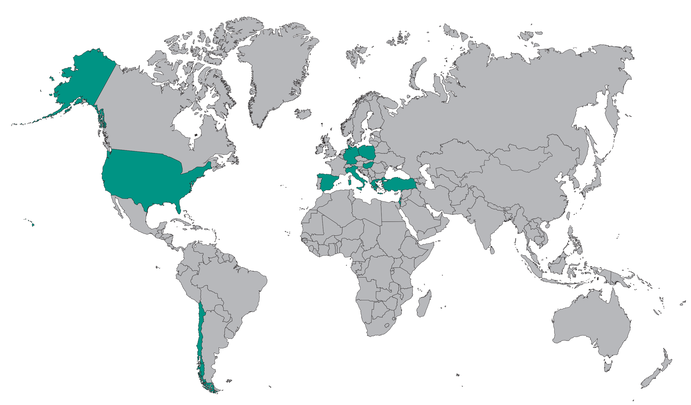
Analyses

- Efficacy will be assessed in all randomized participants
- Safety will be assessed in all randomized participants who receive ≥1 dose of study treatment
- For ORR, defined as the proportion of participants who have OR, point estimates and 95% CIs will be provided using the Clopper-Pearson exact binomial method
  - Because of the sample size, analyses will be pooled across strata
  - Treatment group differences and 95% CIs will be estimated using the unstratified Miettinen and Nurminen method

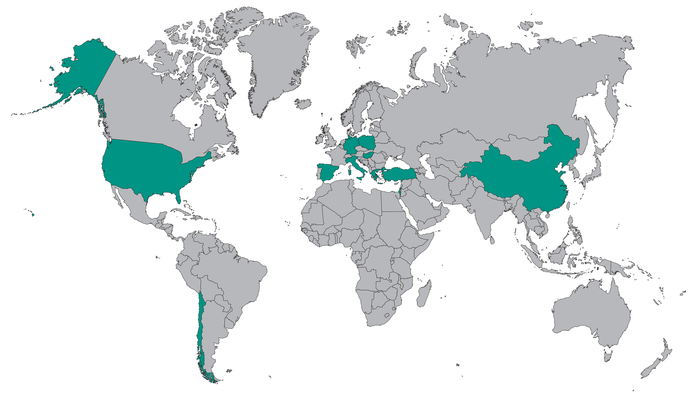
Current status

- Enrollment began on May 12, 2025, for cohort H and May 15, 2025, for cohort I and is ongoing globally

Cohort H



Cohort I



References

1. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines). Non-Small Cell Lung Cancer. Version 7.2025. https://www.nccn.org/.
2. Altan M, et al. *Clin Cancer Res.* 2017;23(17):5202-5209.
3. Suzuki H, et al. *Mol Cancer Ther.* 2024;23(3):257-271.
4. Casal JI and Bartolome RA. *Int J Mol Sci.* 2019;20(13):3373.
5. Levy BP, et al. *J Clin Oncol.* 2025;43(16_Supplement):8501.
6. Rudin CM, et al. *J Thorac Oncol.* 2024;19(10_Supplement): S15-S16.
7. Moore KN, et al. *ESMO Open.* 2025;10(Supplement_5):8.
8. Salifu I, et al. *Cancer Treat Res Commun.* 2023;36:100713.

Acknowledgments

The authors thank the participants and their families and all investigators and site personnel participating in this study. This study was funded by Daiichi Sankyo Company, Limited and Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA (MSD). Medical writing assistance was provided by Young-A Heo, PhD, of ICON plc (Blue Bell, PA, USA). This assistance was funded by MSD.

Disclosures

Dr. Nadal has advisory roles for Amgen, Apollomics, AstraZeneca, BeiGene, Boehringer Ingelheim, Bristol Myers Squibb, Daiichi Sankyo, Genmab, Janssen, Lilly, Merck Serono, MSD, Pfizer, Pierre Fabre, Qiagen, Regeneron, Roche, Sanofi, and Takeda; was an invited speaker for AbbVie, Amgen, AstraZeneca, Bristol Myers Squibb, Daiichi Sankyo, Illumina, Janssen, Lilly, MSD, Pfizer, Qiagen, Roche, Sanofi, and Takeda; receives funding (to institution) from Bristol Myers Squibb, Merck Serono, and Roche; and BMS and Merck Serono funded a clinical trial.

Contact Information

Contact Dr. Ernest Nadal at esnadal@iconcologia.net for questions or comments

Poster presented
https://bit.ly/4ngturv

Poster slides
https://bit.ly/4ny3rML

Plain Language Summary
https://bit.ly/4mVGO4L

Presented at The European Society for Medical Oncology (ESMO) Congress; Berlin, Germany; October 17-21, 2025.