

KEYMAKER-U01F: Umbrella Study of Novel Therapies in Previously Treated Advanced/Metastatic Nonsquamous *KRAS* G12C-Mutant NSCLC

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Background

- KRAS* mutations are common oncogenic drivers of non–small-cell lung cancer (NSCLC) that are associated with poor survival¹
- Preferred first-line treatment for patients with metastatic NSCLC with a *KRAS* G12C mutation is an immune checkpoint inhibitor with or without chemotherapy, depending on PD-L1 tumor proportion score²
- For subsequent lines of therapy, a *KRAS* G12C inhibitor is currently recommended²; however, resistance to *KRAS* G12C inhibitors frequently occurs and new therapeutic approaches are needed³
- Calderasib (MK-1084) is a highly potent and specific next-generation *KRAS* G12C-GDP macrocyclic inhibitor that has demonstrated manageable safety and antitumor activity in previously treated *KRAS* G12C–mutant metastatic NSCLC⁴
- The phase 1b/2 KEYMAKER-U01 substudy F (NCT07286149) will evaluate calderasib in combination with novel therapies, including the HER3-directed antibody–drug conjugate (ADC) patritumab deruxtecan (HER3-DXd; MK-1022) and the trophoblast cell-surface antigen 2 (TROP2)–directed ADC sacituzumab tirumotecan (sac-TMT; MK-2870) in participants with previously treated, advanced or metastatic nonsquamous *KRAS* G12C–mutant NSCLC

Objectives

Primary objectives

- Evaluate safety
 - Dose-limiting toxicities (DLTs) during phase 1b
 - Adverse events (AEs)
 - Treatment discontinuations due to AEs
- Evaluate ORR per RECIST version 1.1 by blinded independent central review (BICR), defined as a confirmed complete response (CR) or confirmed partial response (PR)

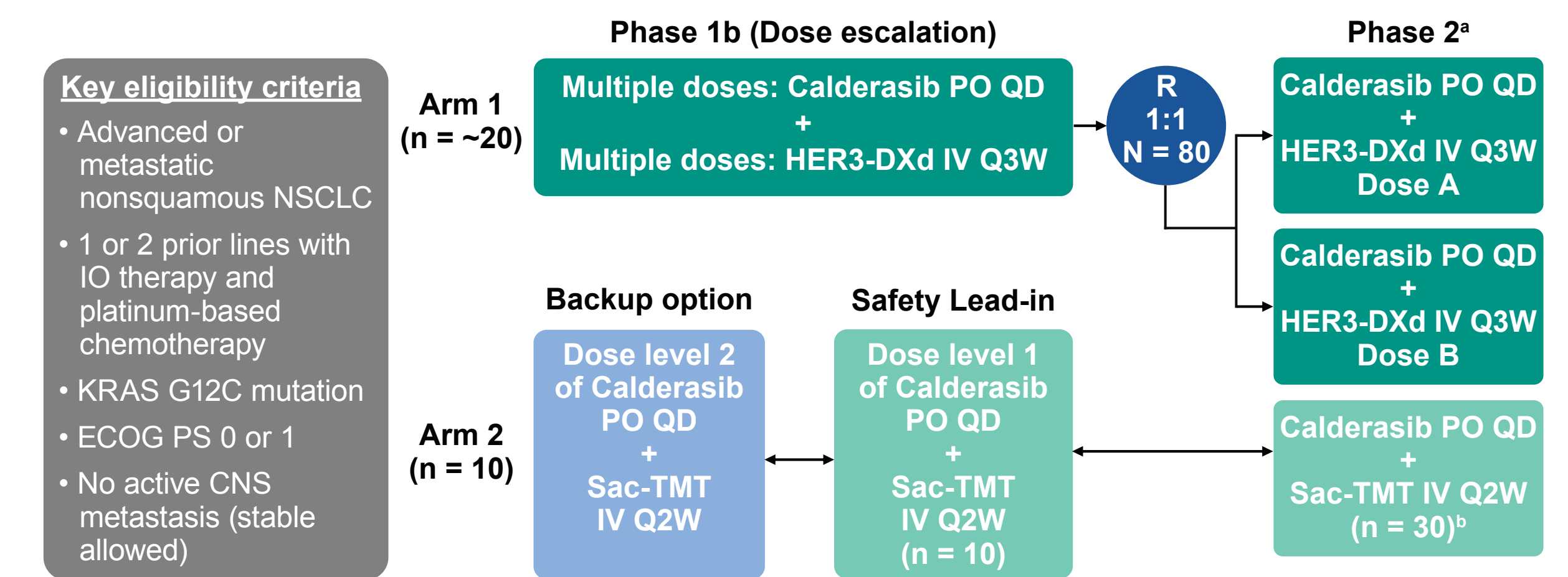
Secondary objectives

- Evaluate duration of response (DOR) per RECIST version 1.1 by BICR, defined as time from first documented CR or PR until first documented disease progression or death due to any cause, whichever occurs first
- Evaluate progression-free survival (PFS) per RECIST version 1.1 by BICR (phase 2 only), defined as time from randomization to first documented disease progression or death due to any cause, whichever occurs first
- Characterize pharmacokinetic (PK) parameters

Methods

Study design, participants, and treatment

Figure. KEYMAKER-U01F study design (NCT07286149)



CNS, central nervous system; ECOG PS, Eastern Cooperative Oncology Group performance status; IO, immuno-oncology; IV, intravenous; PO, oral; Q2W, every 2 weeks; Q3W, every 3 weeks; QD, once daily; R, randomized; RDE, recommended dose for expansion.
^aIn phase 2, dose randomization may be initiated to determine the RDE depending on phase 1b data, and participants will continue at the RDE until a discontinuation criterion is met. At the end of the safety lead-in, if the RDE for arm 2 is tolerable (DLT rate <30%), then phase 2 for arm 2 may continue at the prespecified dose.
^bIf ≤3 DLTs occur, include phase 1b arm 2 participants in efficacy analysis for a total of N = 40.

Table. Key eligibility criteria

Inclusion criteria	Exclusion criteria
- Aged ≥18 y - Histologically or cytologically confirmed advanced or metastatic nonsquamous NSCLC; stage III, not eligible for curative resection or chemoradiation, or stage IV (M1a, M1b, or M1c per AJCC 8th edition)^a - Tumor or ctDNA that demonstrates a <i>KRAS</i> G12C mutation assessed locally - Measurable disease per RECIST version 1.1 by BICR - Documented disease progression per RECIST version 1.1 after receiving anti–PD-(L)1 treatment and platinum-based chemotherapy (administered concurrently or sequentially)^b - ECOG PS of 0 or 1 assessed within 7 d before randomization - Adequate organ function - Provision of archival tumor tissue (before receiving anti–PD-[L]1 therapy) or newly obtained biopsy (after completion of anti–PD-[L]1 therapy and before randomization) of a tumor lesion not previously irradiated - Participants who have AEs due to previous anticancer therapies must have recovered to grade ≤1 or baseline	- Diagnosis of small-cell lung cancer or, for mixed tumors, presence of small-cell elements - Severe pulmonary compromise resulting from intercurrent pulmonary illnesses including underlying pulmonary disorder, or any autoimmune, connective tissue, or inflammatory disorders with pulmonary involvement, or prior complete pneumonectomy - Active CNS metastases and/or carcinomatous meningitis^c - Active inflammatory bowel disease requiring immunosuppressive medication or history of inflammatory bowel disease - Leptomeningeal disease - Uncontrolled or significant cardiovascular or cerebrovascular disease before randomization - Clinically significant corneal disease or history of severe dry eye syndrome, severe Meibomian gland disease and/or blepharitis, or severe corneal disease that prevents/delays corneal healing - HIV infection with history of Kaposi’s sarcoma and/or Multicentric Castleman’s Disease - Receipt of previous agent targeting <i>KRAS</i>; only prior use of sotorasib or adagrasib is allowed and will be capped at 50% of the enrolled population - Prior treatment with a topoisomerase 1 inhibitor or an anti-HER3 antibody and/or ADC that consists of an exatecan derivative that is a topoisomerase 1 inhibitor - Receipt of prior treatment with a TROP2-targeted ADC - Immunodeficiency or receipt of chronic systemic steroid therapy or any immunosuppressive therapy ≤7 d before first dose - Additional malignancy that is progressing or has required active treatment within the past 3 y - History of ILD/pneumonitis irrespective of steroid use, or ILD that is current, suspected, or cannot be ruled out by imaging at screening

AJCC, American Joint Committee on Cancer; ctDNA, circulating tumor DNA; ILD, interstitial lung disease.
^aMixed tumors will be characterized by the predominant cell type (squamous or nonsquamous); however, small-cell elements are not permitted.
^bIf treatments were concurrent, no more than 1 prior line of treatment is allowed. If treatments were sequential, no more than 2 prior lines of treatment are allowed.
^cParticipants with previously treated brain metastases may participate if they are radiologically stable for ≥4 weeks, clinically stable, and have not required steroid treatment for ≥14 days before first dose of study intervention. Participants with known untreated, asymptomatic brain metastases may participate.

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Plain language summary

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Current status

- Enrollment began in April 2026 at 25 global sites

