

Phase 3 Study of Adjuvant Subcutaneous MK-3475A Plus Calderasib or Placebo in Resected Stage IIA–IIIB (N2), *KRAS* G12C–Mutated NSCLC

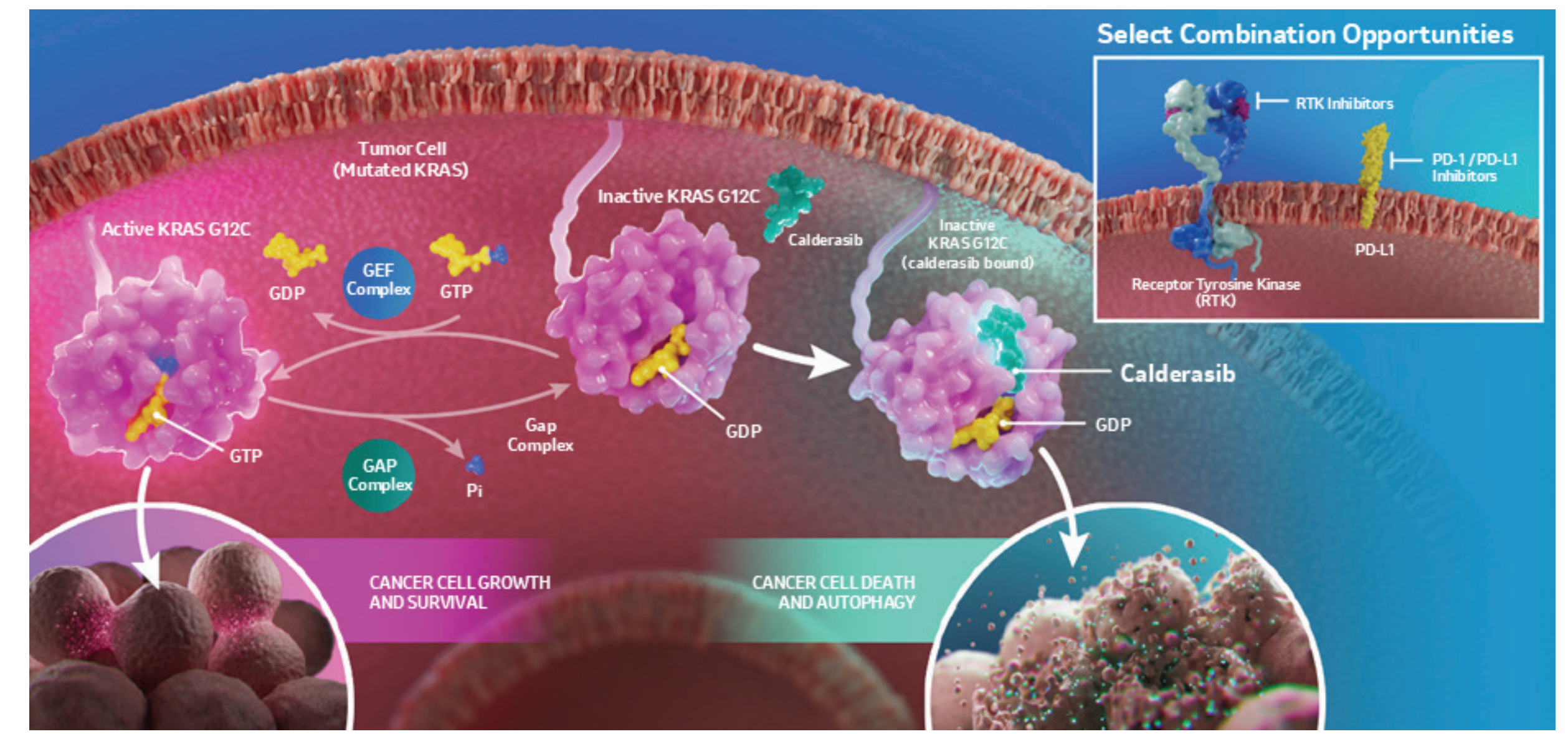
R. Hui¹; I. Attili²; C.I. Rojas³; R. Mingarini Terra⁴; M. Liberman⁵; J. Cornell⁶; J.C. Thompson⁶; A. Samkari⁶; E. Giroux Leprieur⁷

¹Centre of Cancer Medicine, School of Clinical Medicine, LKS Faculty of Medicine, University of Hong Kong, Pokfulam, Hong Kong; ²European Institute of Oncology, IRCCS, Milan, Italy; ³Bradford Hill Centro de Investigación Clínica, Universidad Finis Terrae, Santiago, Chile; ⁴Hospital Israelita Albert Einstein, São Paulo, SP, Brazil; ⁵Centre Hospitalier de l'Université de Montréal (CHUM), Montréal, QC, Canada; ⁶Merck & Co., Inc., Rahway, NJ, USA; ⁷Cancer Institute AHP, Paris-Saclay University, UVSQ, Ambroise Paré Hospital, Boulogne-Billancourt, France

Background

- KRAS* mutations are common oncogenic drivers associated with poor survival in patients with non–small-cell lung cancer (NSCLC)¹
 - KRAS* G12C is the most frequently observed *KRAS* mutation in NSCLC¹
- Preclinical data showed that inhibition of *KRAS* G12C promoted a proinflammatory tumor microenvironment responsive to immune checkpoint inhibition²
- Calderasib (MK-1084) is a highly potent and specific *KRAS* G12C-GDP inhibitor (**Figure 1**)^{3,4}

Figure 1. Calderasib inhibition of the *KRAS* signaling pathway^a



^a*KRAS* GTPase cycle based on Liu P, et al. 2019.⁵

- The phase 1 KANDLELIT-001 study of participants with *KRAS* G12C–mutated metastatic NSCLC demonstrated antitumor activity and manageable safety with calderasib monotherapy in previously treated disease and with calderasib plus pembrolizumab (a PD-1 inhibitor) with or without chemotherapy in previously untreated disease³
 - Hepatic toxicity with calderasib plus pembrolizumab was low, with grade ≥3 treatment-related adverse events (AEs) of elevated liver enzymes occurring in ≤10% of participants³
- Standard of care for resectable stage II–IIIB (N2) NSCLC includes pembrolizumab either as perioperative therapy with neoadjuvant chemotherapy and surgery, or as adjuvant monotherapy after surgery and adjuvant chemotherapy, based on benefits observed in the KEYNOTE-671 and KEYNOTE-091 studies^{6–9}
- MK-3475A (pembrolizumab SC) is pembrolizumab with berahyaluronidase alfa (MK-5180)¹⁰
 - Berahyaluronidase alfa, a variant of human hyaluronidase developed and manufactured by Alteogen Inc. (Daejeon, South Korea), enables subcutaneous (SC) administration of pembrolizumab¹⁰
- The phase 3 KANDLELIT-013 study is evaluating adjuvant calderasib in combination with pembrolizumab SC in participants with completely resected, stage IIA–IIIB (N2), *KRAS* G12C–mutated NSCLC following receipt of either neoadjuvant pembrolizumab plus chemotherapy or adjuvant chemotherapy

Objectives

Primary

- Evaluate disease-free survival (DFS), defined as the time from randomization to any recurrence, occurrence of new primary NSCLC, or death due to any cause, as assessed by the investigator

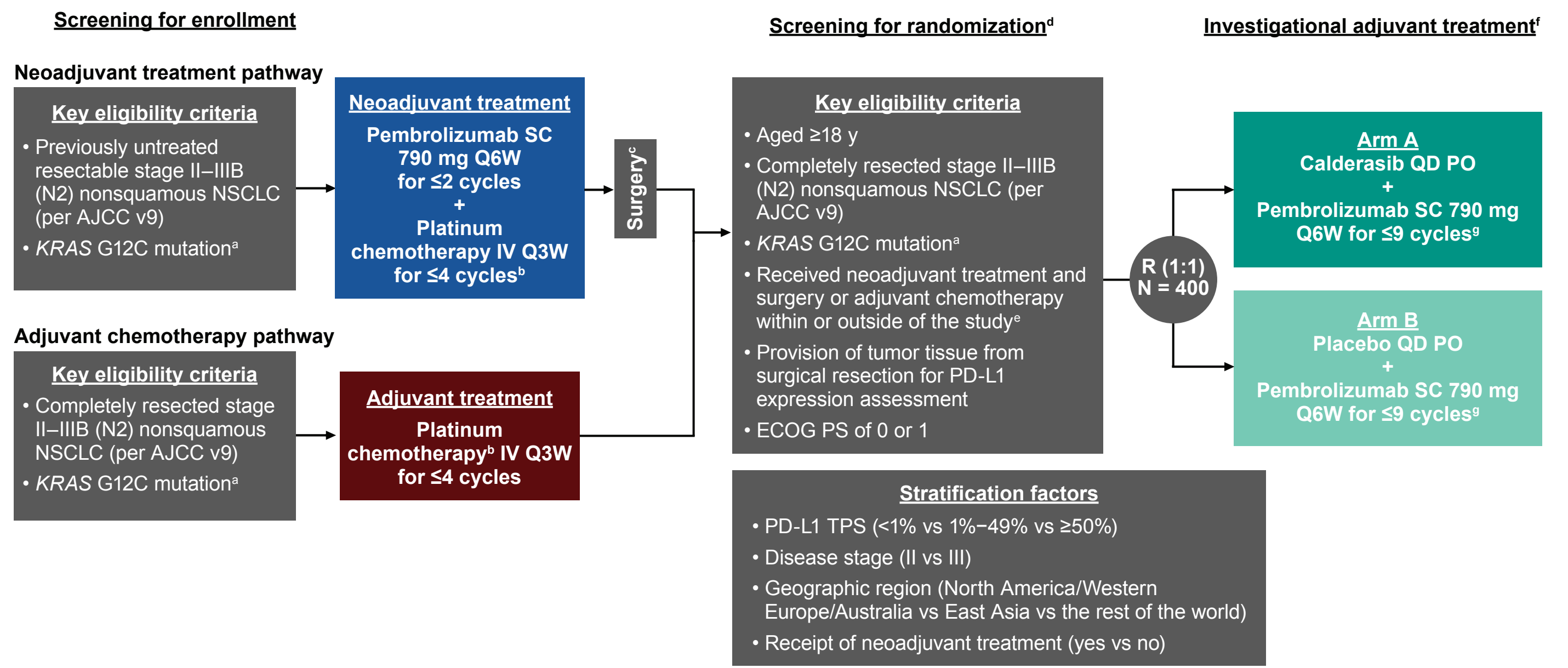
Secondary

- Evaluate overall survival (OS), defined as the time from randomization to death due to any cause
- Evaluate
 - Distant metastasis–free survival (DMFS), defined as the time from randomization to the first documented distant metastasis or death due to any cause, as assessed by the investigator
 - Lung cancer–specific survival (LCSS), defined as the time from randomization to death due to lung cancer
 - The mean change from baseline in global health status/quality of life, physical functioning, role functioning, dyspnea, cough, and chest pain scores using the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire–Core 30 (QLQ-C30) and supplemental lung cancer–specific module (QLQ-LC24)
 - AEs and AEs resulting in treatment discontinuations

Methods

Study design, participants, and treatment

Figure 2. KANDLELIT-013 study design (NCT07431827)



AJCC, American Joint Committee on Cancer; ECOG PS, Eastern Cooperative Oncology Group performance status; IV, intravenous; PO, orally; Q3W, every 3 weeks; Q6W, every 6 weeks; QD, once daily.
^aAs assessed locally or by central laboratory.
^bInvestigator's choice of cisplatin and pemetrexed or carboplatin and pemetrexed.
^cSurgery must occur ≤20 weeks from the first neoadjuvant dose or ≤8 weeks from the last neoadjuvant dose.
^dScreening for randomization must occur ≤12 weeks after surgery (following neoadjuvant treatment) or ≤12 weeks after the last dose of adjuvant platinum chemotherapy.
^eParticipants are permitted for screening if they received off-study neoadjuvant treatment with ≤3 cycles of platinum chemotherapy Q3W plus 2–4 cycles of pembrolizumab or pembrolizumab SC Q3W or 1–2 cycles of pembrolizumab or pembrolizumab SC Q6W per local label or surgery and off-study adjuvant treatment with ≤3 cycles of platinum chemotherapy.
^fThe first dose of investigational adjuvant treatment will be administered ≤12 weeks after surgery or ≤12 weeks after the last dose of adjuvant platinum chemotherapy.
^gParticipants who received in-study or off-study neoadjuvant treatment will receive ≤7 cycles of pembrolizumab SC.

Table. Key eligibility criteria

Inclusion criteria	Exclusion criteria
- Aged ≥18 y For the neoadjuvant treatment pathway - Previously untreated resectable stage II, IIIA, or IIIB (N2) nonsquamous NSCLC (per AJCC v9) - Presence of <i>KRAS</i> G12C mutation as assessed locally or by central laboratory - Able to undergo protocol therapy, including necessary surgery, as determined by the investigator For the adjuvant chemotherapy pathway - Completely resected stage II, IIIA, or IIIB (N2) nonsquamous NSCLC (per AJCC v9) - Presence of <i>KRAS</i> G12C mutation as assessed locally or by central laboratory - Able to begin adjuvant platinum-based chemotherapy ≤12 wk of surgical resection For the investigational adjuvant treatment - Completely resected stage II, IIIA, or IIIB (N2) nonsquamous NSCLC (per AJCC v9) - Provision of tumor tissue from surgical resection for assessment of PD-L1 expression - Provision of tumor tissue demonstrating the presence of a <i>KRAS</i> G12C mutation assessed by central laboratory - Received on-study or off-study neoadjuvant treatment and surgery or adjuvant platinum chemotherapy ≤12 wk between the surgery after neoadjuvant treatment or the last dose of adjuvant chemotherapy and the first dose of investigational adjuvant treatment - ECOG PS of 0 or 1 - Adequate organ function	- Small-cell lung cancer or, for mixed tumors, presence of small-cell elements, and a neuroendocrine tumor with large-cell components, or sarcomatoid carcinoma - Received prior anti–PD-(L)1 or anti–PD-L2 therapy or any agent directed to another stimulatory or coinhibitory T-cell receptor - Received or is a candidate to receive radiotherapy for NSCLC - Received prior treatment with an agent targeting <i>KRAS</i> - Active inflammatory bowel disease requiring immunosuppressive medication or a history of inflammatory bowel disease - Active autoimmune disease that required systemic treatment ≤2 y before randomization - Diagnosis of immunodeficiency or receiving chronic systemic steroids ≤7 d before first dose of study treatment - History of noninfectious pneumonitis or interstitial lung disease that required steroids or active pneumonitis or interstitial lung disease - Additional malignancy that is progressing or that required treatment ≤3 y before randomization

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Disclosures

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Contact information

Contact Dr Rina Hui at rinhui@hku.hk for questions or comments

Assessments

- KRAS* G12C mutation status will be assessed locally by a sponsor-approved assay or, if unavailable, tumor tissue can be submitted for central testing for the neoadjuvant treatment and adjuvant chemotherapy pathways; for randomization to investigational adjuvant treatment, central laboratory testing using the Therascreen *KRAS* RGQ PCR kit will be performed
- PD-L1 status will be assessed using PD-L1 IHC 22C3 pharmDx (Agilent Technologies, Carpinteria, CA, USA)
- Tumor imaging will be performed within 42 days before allocation to the neoadjuvant treatment pathway or within 3 months before allocation to the adjuvant chemotherapy pathway
- During the investigational adjuvant treatment period, tumor imaging will be performed at baseline (within 28 days before randomization), every 12 weeks through week 48, then every 24 weeks through week 144, and every 48 weeks thereafter
- Patient-reported outcome (PRO) questionnaires will be administered before any other procedures on days 1 and 22 of each cycle through cycle 15, then on day 1 of every second cycle thereafter, first with EORTC QLQ-C30 and then with EORTC QLQ-LC24
- AEs will be monitored throughout study treatment until 30 days after last study dose (90 days for serious AEs) and graded in severity according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0

Statistical analysis

- Efficacy will be analyzed in all randomized participants (intention-to-treat population)
- Safety will be analyzed in all randomized participants who received ≥1 dose of study treatment (as-treated population)
- PROs will be analyzed in all randomized participants who have ≥1 PRO assessment available for the specific endpoint and who received ≥1 dose of study treatment (PRO full analysis set)
- DFS, OS, and DMFS will be estimated using the non-parametric Kaplan–Meier method, with treatment differences assessed using the stratified log-rank test; hazard ratios with 95% CIs will be estimated using a stratified Cox proportional hazard model with the Efron method of tie handling
- LCSS will be estimated using the cumulative incidence function; hazard ratios with 95% CIs will be estimated using a stratified cause-specific Cox proportional hazard model with Efron method of tie handling
- Change from baseline in PRO scores will be assessed with a stratified mixed-effect model repeated measures
 - Between-treatment differences in least-squares (LS) mean change from baseline and 95% CIs will be estimated from this model
- Between-treatment differences in the PRO overall improvement rate (proportion of participants who have achieved an overall improvement) will be estimated using the stratified Miettinen and Nurminen method, with strata weighting by sample size
 - The overall improvement rate point estimate and its 95% CI will be provided using the exact binomial method by Clopper and Pearson
- Safety will be analyzed with descriptive statistics
 - For specific AEs that meet prespecified threshold rules, point estimates and 95% CIs for between-treatment differences in the percentages of participants with events will be provided using the Miettinen and Nurminen method

Current status

- Enrollment began in March 2026 and is planned across 210 sites globally

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