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PHASE 2 PERI-OPERATIVE STUDY OF FIANLIMAB + CEMIPLIMAB + CHEMOTHERAPY VS CEMIPLIMAB + CHEMOTHERAPY IN RESECTABLE EARLY-STAGE NON-SMALL CELL LUNG CANCER (NSCLC)

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Introduction Co-blockade of lymphocyte-activation gene 3 (LAG-3) may enhance the efficacy of anti–programmed cell death-1 (anti–PD-1) therapies. Fianlimab (anti–LAG-3) and cemiplimab (anti–PD-1) are high-affinity, fully human, IgG4 monoclonal antibodies. In a Phase 1 study (NCT03005782), fianlimab + cemiplimab showed promising clinical activity with durable responses and an acceptable risk-benefit profile in patients with anti–PD-1/L1-naïve, advanced NSCLC. Immuno-Oncology + chemotherapy is a new standard of care in the peri-operative setting, but potential improvements to outcomes in early-stage disease remain under investigation.

Materials and methods This is a randomized, multicenter, double-blind, Phase 2 peri-operative study (NCT06161441) in patients with early-stage resectable stage II to stage IIIB (N2), squamous or non-squamous histology, operable, treatment-naïve NSCLC. The aim of this study is to investigate the efficacy and safety of fianlimab + cemiplimab + chemotherapy versus cemiplimab + chemotherapy as peri-operative treatment.

The study will be conducted globally at ~130 sites. Key inclusion criteria: age ≥18 years; newly diagnosed, histologically confirmed, fully resectable stage II to IIIB (N2) NSCLC; no distant metastases; evaluable PD-L1 immunohistochemistry results; no cancer treatment within the prior 3 years, except adjuvant hormone therapy for hormone-sensitive cancers in long-term remission; Eastern Cooperative Oncology Group

performance status ≤1; no known *EGFR* mutations or *ALK* aberrations; and adequate organ and bone marrow function. Mediastinal lymph node sampling is required for patients with mediastinal adenopathy. Enrolled patients (n=∼180) will be stratified by clinical TNM stage (II vs III), histology (non-squamous vs squamous), and PD-L1 expression (<1%, 1–49%, ≥50%), and randomized (1:1:1) to the following study arms for the neoadjuvant period (up to four cycles; each cycle is every 3 weeks): arm A: placebo + cemiplimab 350 mg + platinum doublet chemotherapy; arm B: fianlimab dose 1 + cemiplimab 350 mg + platinum doublet chemotherapy; arm C: fianlimab dose 2 + cemiplimab 350 mg + platinum doublet chemotherapy.

After surgery, in the adjuvant period (≤14 cycles), patients in all arms will continue the same regimen without platinum doublet chemotherapy. Treatment will last ∼12 months (12 weeks neoadjuvant therapy + 42 weeks adjuvant therapy), or until disease recurrence, unacceptable toxicity, patient's decision, or investigator's decision.

Primary endpoint: pathological complete response by blinded independent pathological review (BIPR). Key secondary endpoints: event-free survival by investigator assessment, major pathological response by BIPR, tumor response by investigator assessment, safety, pharmacokinetics, immunogenicity, and patient-reported outcomes.

Trial Registration NCT06161441

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