Rationale for combination therapy

- NSCLC accounts for approximately 85% of lung cancers and a high proportion of patients with NSCLC have advanced or metastatic disease at diagnosis.1
- Pembrolizumab (pembro), a PD-1 inhibitor, has demonstrated antitumour activity in various solid tumours.2
- There remains an unmet need for treatments that extend survival and maintain quality of life in patients with NSCLC.3
- Platinum-based chemotherapy induces DNA double-strand breaks, leading to cytotoxicity, which may be further increased by impairment of DNA damage repair via PARP inhibition.4
- Nira, a PARP inhibitor, promotes PARP trapping, activating the STING pathway, recruits T cells, and upregulates PD-L1, making it a promising partner for PD-1 inhibition.5
- Nira crosses the blood-brain barrier in animal models with 34-fold higher brain-tissue exposure than other PARP inhibitors, suggesting it may reduce reactivation of BM.6
- Nira + pembro has shown antitumour activity and acceptable safety in triple-negative breast cancer and platinum-resistant ovarian cancer (TOPAC1012KEYNOTE-162), and is now being explored in advanced/metastatic NSCLC (JAPSK6161).7

Objective

- ZEAL-1L (NCT04473936) is a Phase 3, randomised, double-blind trial in patients with advanced or metastatic NSCLC without known driver mutations that will compare efficacy and safety of nira + pembro versus placebo + pembro.

Study design

- **Patients**
  - **Recruitment began in November 2020.**
  - **Randomisation (1:1)**
  - **Approximately 650 patients**
  - **Recruitment criteria**
    - **Eligibility:** 18–70 years; stage IIIB/IV NSCLC; ECOG 0–1; chemotherapy naïve; no prior immunotherapy or targeted therapy
    - **Exclusion:** Previous radiotherapy, brain metastases, leptomeningeal disease, active inflammatory disorder, coagulopathy, life expectancy <3 months
  - **Placebo + pembro arm:** 200 or 300 mg, orally, each 21-day cycle
  - **Nira + pembro arm:** 100 mg daily

- **Study population**
  - **Dual primary endpoints**
    - PFS* and OS† of patients treated with nira + pembro versus placebo + pembro
  - **Secondary endpoints**
    - TTP in the CNS assessed by BICR per RANO-BM criteria
  - **Investigation assessment:** PFS and OS by RECIST v1.1 criteria

Study endpoints

- **Key inclusion criteria**
  - Histologically/ cytologically confirmed diagnosis of NSCLC without known driver mutations (non-squamous, squamous or mixed)
  - Advanced (stage IBB not amenable to definitive chemotherapy or stage IC or metastatic (stage IV) NSCLC
  - Completed ≥4 cycles of standard-of-care platinum-based 1L induction chemotherapy or prior pembro

- **Key exclusion criteria**
  - Mixed SCLC or sarcomatoid histology
  - BM permitted if patient is off corticosteroids and anticoagulants for ≥45 days

- **Assessed by BICR per RECIST v1.1 criteria. †Defined as time from randomisation to date of death due to any cause. ‡Time from randomisation to meaningful deterioration on a composite endpoint of death and meaningful deterioration on a composite endpoint of death and progression on MRI of any site.**

References