EA5163/S1709/INSIGNA

A Randomized, Phase III Study of Firstline Immunotherapy Alone or in Combination With Chemotherapy in Induction/Maintenance or Postprogression in Advanced Nonsquamous Non-Small Cell Lung Cancer (NSCLC) With Immunobiomarker SIGNature-driven Analysis

Study Schema

Stratification
- PD-L1 status (tumor proportion score 1%-49% vs ≥ 50%)
- Smoking status (ever vs never)

Arm A
- 1st-line treatment
  - Pembrolizumab 200 mg IV over 30 min on day 1

Arm B
- 1st-line treatment
  - Pembrolizumab 200 mg IV over 30 min on day 1

Arm C
- Induction
  - Pembrolizumab 200 mg IV over 30 min followed by
    - Pemetrexed 500 mg/m² IV over 10 min
  - Maintenance
    - Pembrolizumab 200 mg IV over 30 min followed by
      - Pemetrexed 500 mg/m² IV over 10 min on day 1

2nd-line treatment
- Pembrolizumab 200 mg IV over 30 min followed by
  - Pemetrexed 500 mg/m² IV over 10 min
  - Carboplatin AUC 6 IV over 30 min on day 1

Accrual goal = 846 patients.
Cycle = 3 weeks (21 d).
*Repeat until progression or maximum of 2 years. If patient does not progress onto 2nd-line treatment, proceed to long-term follow-up. If maximum treatment duration is reached prior to progression, or treatment is discontinued for any reason, patient remains in observation until progression.
†If no progression by 2 years of pembrolizumab (MK-3475), patient continues on observation until progression, at which time proceed to 2nd-line therapy within 6 weeks of progression.
‡Repeat for 4 cycles or until disease progression. Pembrolizumab and pemetrexed can then be given as maintenance until disease progression or 2 years of pembrolizumab treatment in total. Pembrolizumab alone may continue per standard of care.
¶Repeat for 4 cycles, then proceed to maintenance. If disease progression occurs prior to the completion of 4 cycles, patient should instead enter long-term follow-up and continue to the 2nd-line treatment off study, per standard of care.
**Repeat for 2 years of total treatment across induction and maintenance, or until disease progression. If after 2 years there is no progression, pembrolizumab alone may continue per standard of care.
††Patient enters long-term follow-up and receives 2nd-line treatment off study, per standard of care.

PD-L1 = programmed death-ligand 1.
Overall EA5163/S1709/INSIGNA Study Objective
To determine whether first-line treatment with pembrolizumab alone followed by second-line treatment with pemetrexed and carboplatin, with or without pembrolizumab, after disease progression versus an induction/maintenance regimen of pembrolizumab, pemetrexed, and carboplatin can provide a survival benefit to patients with advanced, stage IV NSCLC.

Study Objectives

Primary Objective
- Evaluate overall survival in each of the experimental arms (arms A and B) versus control (arm C)

Secondary Objectives
- Evaluate progression-free survival per RECIST 1.1 for arm C versus each of arms A and B
- Evaluate best objective response rates per RECIST 1.1 for arm C versus each of arms A and B
- Estimate toxicity within each of the treatment arms via CTCAE criteria
- Compare outcomes between arms A and B
- Compare outcomes by treatment arm within subgroups defined by a cutpoint of PD-L1 expression at ≥ 50%

Biomarker Objective
- Collect and bank tissue and blood for future research studies, including potential development of a prognostic and predictive signature for pembrolizumab in combination with chemotherapy versus pembrolizumab alone

Eligibility Criteria*

Main Inclusion Criteria
- ≥ 18 years of age with histologically or cytologically confirmed stage IV nonsquamous NSCLC (includes M1a, M1b, and M1c stage disease, AJCC 8th edition); patients with T4NX disease (stage IIIB and IIIC) with nodule in ipsilateral lung lobe are eligible if not candidates for combined chemotherapy and radiation
• PD-L1 expression tumor proportion score (TPS) ≥ 1% in tumor cells; if PD-L1 expression TPS is unevaluable or testing could not be completed, then ineligible. Assay must be performed by CLIA (or equivalent) certified laboratory.

• Measurable or nonmeasurable disease; presence of malignant pleural fluid alone is sufficient to satisfy this eligibility criterion. Baseline imaging assessments and measurements must be done within 4 weeks prior to study registration.

• ECOG performance status 0-1.

• Treated brain metastases eligible if follow-up brain imaging after CNS-directed therapy shows no evidence of progression. Active brain metastases or leptomeningeal disease eligible if treating physician has determined that immediate CNS-specific treatment is not required and is unlikely to be required during first therapy cycle. Eligible if off steroids for 14 days prior to protocol treatment; anticonvulsants allowed.

• Prior or concurrent malignancy whose natural history or treatment has no potential to interfere with safety or efficacy assessment.

• If known history or current symptoms of cardiac disease, or history of treatment with cardiotoxic agents, should have a clinical risk assessment of cardiac function using NYHA functional classification; must be class 2B or better.

• Adequate laboratory values and hepatic and renal function within 14 days of randomization.

• If HIV-infected, on effective antiretroviral therapy with undetectable viral load within 6 months.

• For chronic hepatitis B virus infection, viral load must be undetectable on suppressive therapy; patients with history of hepatitis C virus infection that has been treated and cured or currently being treated must have undetectable viral load.

• Use of effective contraception or abstinence.

*When evaluating patients for this study, please refer to the full protocol for the complete list of eligibility criteria.
Eligibility Criteria* (cont)

Main Exclusion Criteria

- Received prior systemic chemotherapy or immunotherapy for advanced metastatic NSCLC or checkpoint inhibitors for lung cancer
- Known EGFR mutations (except exon 20 insertion), BRAF mutations (V600), or ALK or ROS1 translocations that can be treated with oral tyrosine kinase inhibitors
- Known preexisting and clinically active interstitial lung disease, history of (noninfectious) pneumonitis that required steroids, or current pneumonitis
- Significant gastrointestinal disorders with diarrhea as a major symptom
- History of autoimmune condition requiring ongoing or intermittent systemic treatment in the past 2 years

- Concomitant serious illness or organ system dysfunction that in the investigator’s opinion would either compromise safety or interfere with evaluation of the study drug’s safety
- Receiving any other investigational agents during the course of therapy
- History of active tuberculosis
- Diagnosis of immunodeficiency or receiving systemic steroid therapy or any other form of immunosuppressive therapy within 7 days prior to the first dose of protocol treatment
- Receiving a live vaccine within 30 days prior to randomization; seasonal flu vaccines that do not contain live virus are permitted
- Pregnancy or breastfeeding

*When evaluating patients for this study, please refer to the full protocol for the complete list of eligibility criteria.