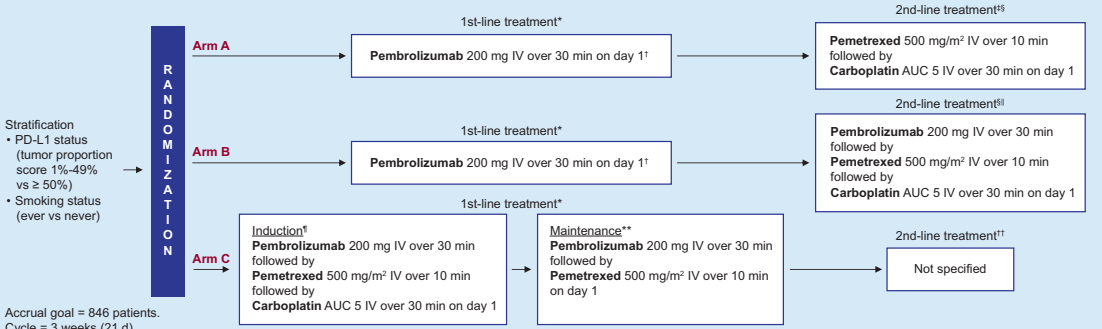
EA5163/S1709/INSIGNA

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



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. Pemetrexed can then be given as maintenance until disease progression per standard of care.

§Following completion of 2nd-line treatment, patient will proceed to long-term follow-up.

‖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. Pemetrexed 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, pemetrexed 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.

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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 (RECIST 1.1)
- Evaluate best objective response rates (RECIST 1.1)
- 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%

Refer to protocol Section 2.3 for the Biomarker Objective, and Section 2.4 for Exploratory Imaging Objectives.

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 stage IIIB and IIIC disease are eligible if they are 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, the patients are not eligible. 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
- Patients with treated brain metastases are eligible if follow-up brain imaging after CNS-directed therapy shows no evidence of progression. Patients with asymptomatic new (at screening) or progressive brain metastases (active at screening) or leptomeningeal disease are eligible if the treating physician determines that immediate CNS-specific treatment is not required and is unlikely to be required during the first therapy cycle. Patients are eligible if off steroids for at least 14 days prior to protocol treatment. Anticonvulsants are allowed. Palliative radiation to non-target lesions is allowed if the patient develops symptoms
- 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, patient 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 or on suppressive therapy; patients with history of hepatitis C virus infection must have been treated and cured or if they are currently being treated, they must have undetectable viral load
- Use of effective contraception or abstinence

Continued

*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 metastatic 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 1 year
- 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.

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