# EA5163/S1709/INSIGNA

## For Patients with Advanced NSCLC

**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**

### Patient Population

See Section 3.0 for Complete Eligibility Details

- **Histologically/cytologically confirmed stage IV non-squamous NSCLC (includes M1a/M1b/M1c stage disease, AJCC 8th ed.); Stage IIIB/C is eligible if the patient is not a candidate for combined chemo and RT**
- **PD-L1 expression TPS ≥ 1% in tumor cells, per protocol**
- **Must have measurable/non-measurable disease defined per protocol; malignant pleural fluid alone is permitted**
- **Age ≥ 18 years, ECOG PS 0-1, and adequate lab values**
- **No prior systemic chemotherapy/immunotherapy for advanced metastatic NSCLC; no patients treated with prior checkpoint inhibitors for metastatic lung cancer**
  - Immunotherapy for locally advanced Stage III is allowed if at least 6 months have elapsed between the last dose of prior therapy; Local therapy is allowed as long as 14 days has passed between completion and registration (see protocol for details)
- **MTX given in low doses for non-malignant conditions (last dose at least 14 days prior to registration) is permitted**
- **Patients with known EGFR mutations (except exon 20 insertion)/BRAF mutations (V600)/ALK/ROS1 translocations that can be treated with oral TKIs are excluded**
- **Patients with brain metastases are eligible per protocol**
- **No known pre-existing and clinically active interstitial lung disease, or a known history of (non-infectious) pneumonitis that required steroids, or current pneumonitis**
- **No significant GI disorders with diarrhea as a major symptom**
- **No history of auto-immune condition requiring ongoing/intermittent systemic treatment in the past 2 years**
- **Patients with known history/current symptoms of cardiac disease/history of treatment with cardiotoxic agents should have a clinical risk assessment of cardiac function using NYHA; patients should be class 2B or better**
- **No live vaccine within 30 days prior to randomization**
- **HIV+ patients are eligible per protocol**

### Treatment Plan

See Section 5.0 for Complete Treatment Details

**Cycle = 21 days, with +/- 3 days in between cycles**

**Arm A:**

**1st line:** Pembrolizumab 200 mg IV over 30 mins day 1 of each cycle; repeat cycles for a max of 2 yrs or until disease progression (RECIST 1.1). If there is no progression after 2 yrs, pembrolizumab can stop and patients will be followed on observation until progression, at which time proceed to 2nd line therapy within 6wks.

**2nd line:** Pemetrexed 500 mg/m² IV over 10 mins followed by carboplatin AUC 5 IV over 30 mins day 1 of each cycle; repeat for a max of 4 cycles or until disease progression. After cycle 4, pemetrexed can be given alone as maintenance every 3 wks until disease progression per standard of care

**Arm B:**

**1st line:** Pembrolizumab 200 mg IV over 30 mins day 1 of each cycle; repeat cycles for a max of 2 yrs or until disease progression. If there is no progression after 2 yrs, pembrolizumab can stop and patients will be followed on observation until progression, at which time proceed to 2nd line therapy within 6wks.

**2nd line:** Pembrolizumab 200 mg IV over 30 mins followed by Pemetrexed 500 mg/m² IV over 10 mins followed by carboplatin AUC 5 IV over 30 mins day 1 of each cycle; repeat for a max of 4 cycles or until disease progression. After cycle 4, pemetrexed and pembrolizumab can be given as maintenance every 3 wks until disease progression/2 yrs of pembrolizumab; then pemetrexed alone may continue until progression per standard of care

**Arm C:**

**Induction:** same as the 2nd line of Arm B above. **Maintenance:** Pembrolizumab 200 mg IV over 30 mins followed by Pemetrexed 500 mg/m² IV over 10 mins on day 1 of each cycle; repeat for a max of 2 yrs or until disease progression, then pemetrexed alone may continue until progression per standard of care

**Note:** Doses are based on actual body weight; vitamin and steroid premedication for pemetrexed per protocol

### Patient Enrollment

All Sites: Oncology Patient Enrollment Network (OPEN) [https://open.ctsu.org](https://open.ctsu.org)

### Protocol Information

ECOG-ACRIN Operations-Boston: 857-504-2900, [http://ecog-acrin.org](http://ecog-acrin.org) (Member Login)

Please Enroll Your Eligible Patients!