For Patients with Advanced NSCLC

EA5163/ S1709 Available Through ECOG-ACRIN Cancer Research Group

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 nonsquamous NSCLC (includes M1a/M1b/M1c stage disease, AJCC 8th ed.); patients with T4NX disease (Stage IIIB/C) with nodule in ipsilateral lung lobe are eligible if they are not candidates for combined chemo and radiation
- 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
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- No prior systemic chemotherapy/immunotherapy for advanced metastatic NSCLC; no patients treated with prior checkpoint inhibitors for metastatic lung cancer; chemotherapy for non-metastatic disease/immunotherapy for locally advanced Stage III disease/local therapy are permitted per protocol
- 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 cardioactive 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
- No history of active TB; HCB/HCV permitted per protocol

Treatment Plan
See Section 5.0 for Complete Treatment Details

Cycle = 21 days

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 6 wks.
2nd line: Pemetrexed 500 mg/m² IV over 10 mins followed by carboplatin AUC 6 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:
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 6 wks.
Pembrolizumab 200 mg IV over 30 mins followed by Pemetrexed 500 mg/m² IV over 10 mins followed by carboplatin AUC 6 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!