Version 10/25/21 (Add. #4)

NCI National Clinical Trials Network

EA5163/S1709/INSIGNA

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 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 6 wks.
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

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Patient Enrollment

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

Protocol Information

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

Please Enroll Your Eligible Patients!

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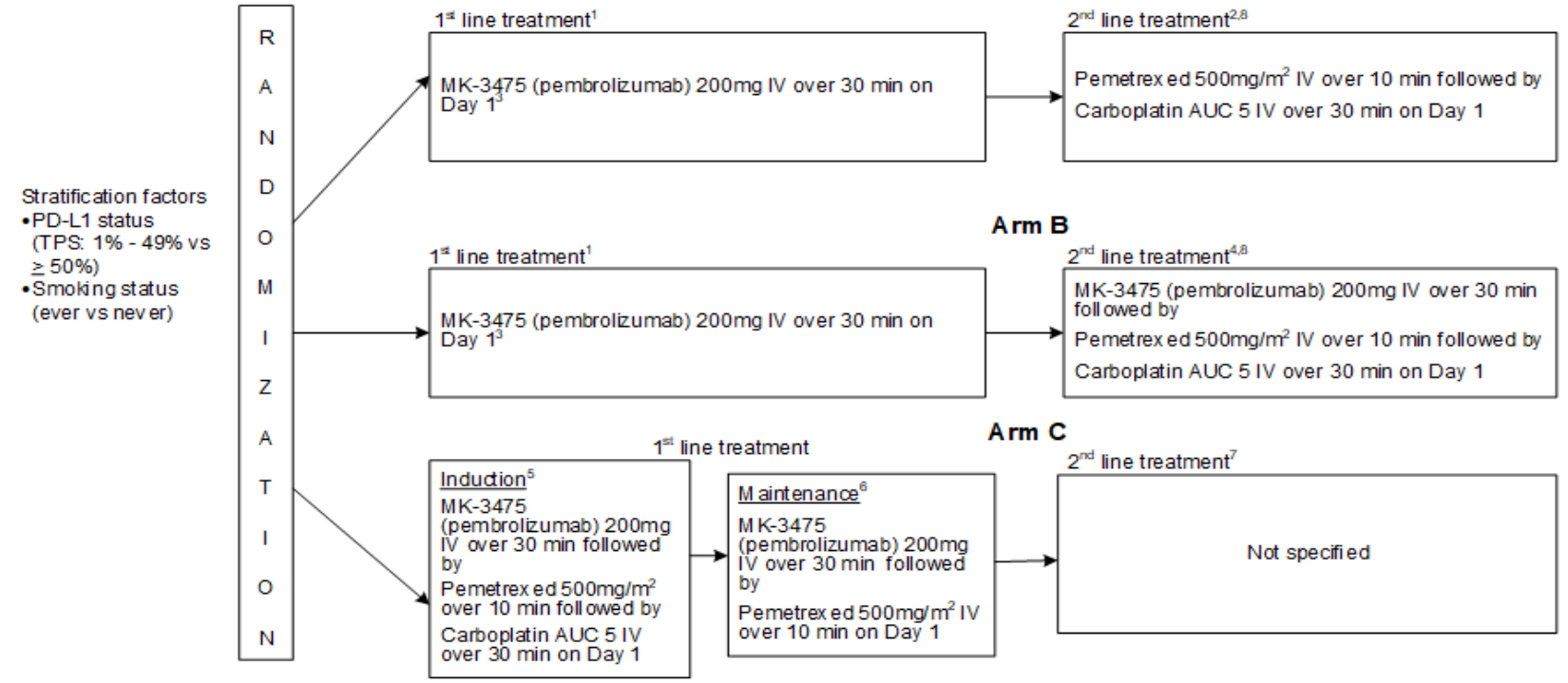
ECOG-ACRIN cancer research group

EA5163

Schema



Accrual Goal: 846 patients
Cycle = 3 weeks (21 days)

1. Repeat until progression or maximum of 2 years. If maximum treatment duration is reached prior to PD, or treatment is discontinued for any other reason, patient will remain in observation until progressionIf patient doesn't progress onto 2nd line treatment, they will proceed to long-term follow-up.
2. Repeat for 4 cycles or until disease progression. Pemetrexed can then be given as maintenance until disease progression per standard of care.
3. If no progression by 2 years of MK-3475 (pembrolizumab), patient continues on observation until progression at which time proceed to 2nd line therapy at which time proceed to 2nd line therapy within 6 weeks of PD.
4. Repeat for 4 cycles or until disease progression. MK-3475 (pembrolizumab) and pemetrexed can then be given as maintenance until disease progression or 2 years of treatment for MK-3475 (pembrolizumab) in total. If after 2 years there is no progression, Pemetrexed alone may be continued until disease progression per standard of care.
5. 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 their 2nd line treatment off-study, per standard of care.
6. 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 be continued until disease progression per standard of care.
7. Patient enters long-term follow-up and receives 2nd line treatment off-study, per standard of care.
8. Following completion of 2nd line treatment, patient will proceed to long-term follow-up.