Cancer Research Consortium of West Michigan
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FAST FACTS

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

Eligibility Criteria

1. Patients must have histologically or cytologically confirmed stage IV non-squamous 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. Prior chemo-RT for stage III with recurrence is allowed.
2. Patients must have PD-L1 expression Tumor Proportion Score (TPS) ≥ 1% in tumor cells. If PD-L1 expression TPS is unevaluable or the testing could not be completed, the patients are not eligible. The assay must have been performed by a CLIA (or equivalent) certified laboratory.
   TPS score _____

3. Patients must have measurable or non-measureable disease as defined in Section 6.1.2. The presence of malignant pleural fluid alone is sufficient to satisfy this eligibility criterion. Baseline imaging assessments and measurements used to evaluate all measurable or non-measurable sites of disease must be done within 4 weeks prior to study registration.
   NOTE: If patient receives pemetrexed, follow institutional guidelines to drain fluids.

4. Patients must be ≥ 18 years of age.

5. Patients must have an ECOG Performance Status of 0 to 1

6. Patients must NOT have received the following:

    a. Prior systemic chemotherapy or immunotherapy for advanced metastatic NSCLC. Patients treated with any prior checkpoint inhibitors for metastatic lung cancer are ineligible. Chemotherapy for non-metastatic disease (e.g. adjuvant therapy) or immunotherapy for locally advanced Stage III disease, or treated with neoadjuvant IO, is allowed if at least 6 months have elapsed between the lastdose of the prior therapy and study registration. Local therapy, e.g., palliative radiation, is allowed as long as a period of 14 days has passed between completion of localtherapy and the start of protocol treatment. Registration during the 14 days is allowed. Palliative radiation must be to non-target lesions. Palliative radiation to pre-existing lesions while on protocol treatment is allowed as long as these areas have not grown to RECIST defined progression. Development of any new metastasis is considered progression. Concurrent radiation and protocoltreatment is not allowed; protocol treatment may resume after completion of radiation as long as patient does not have greater than grade 2 side effects from radiation per physician discretion.

   b. Methotrexate (MTX) given in low doses for non-malignant conditions with last dose at least 14 days prior to date of registration will be allowed. Other low dose chemotherapeutics for non-malignant conditions will be considered, but review by the study chair is required.
   c. Palliative radiation to non-target lesions (bone metastasis)is allowed if patient develops symptoms.

7. Patients with known EGFR mutations (except exon 20 insertion), BRAF mutations (V600) or ALK or ROS1 translocations or other driver mutations that can be treated with oral tyrosine kinase inhibitors are excluded.

8. Patients with treated brain metastases are eligible if follow-up brain imaging obtained at least 14 days after central nervous system (CNS)-directed therapy shows no evidence of progression. CNS progression counts as progression and patients must move on to the next phase after CNS treatment. Patients with asymptomatic new (at screening) or progressive brain metastases (active brain metastases at screening) are eligible if the treating physician determines that immediate CNS specific treatment is not required and is unlikely to be required during the first cycle of therapy.
   a. Patients are eligible if off steroids for at least 14 days prior to protocol treatment.
   b. Anticonvulsants are allowed
   c. Patients with asymptomatic, sub-centimeter brain metastasis who at the discretion of investigators do not need immediate CNS directed therapies are eligible
9. Patients with prior or concurrent malignancy whose natural history or treatment does not have the potential to interfere with the safety or efficacy assessment of the investigational regimen are eligible for this trial.

10. Patients must not have known pre-existing and clinically active interstitial lung disease, or a known history of (non-infectious) pneumonitis that required steroids, or current pneumonitis.

11. Patients must not have significant gastrointestinal disorders with diarrhea as a major symptom (e.g. Crohn's disease, malabsorption, etc.)

12. Patients must not have history of auto-immune condition (includingGuillain-Barre Syndrome or Multiple Sclerosis) requiring ongoing or intermittent systemic treatment in the past 2 years prior to registration (i.e. with use of disease modifying agents, corticosteroids or immunosuppressive drugs). Replacement therapy (e.g., thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc.) is not considered a form of systemic treatment.

13. Patients with 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 the New York Heart Association Functional Classification. To be eligible for this trial, patients should be class 2B or better.

14. Patients must not have any other concomitant serious illness or organ system dysfunction that in the opinion of the investigator would either compromise patient safety or interfere with the evaluation of the safety of the study drug.

15. Patients must not receive any other investigational agents during the course of therapy.

16. Patients must not be pregnant or breast-feeding due to potential harm to the fetus or infant from cytotoxic chemotherapy and the unknown risk of pembrolizumab (MK-3475).

    All patients of childbearing potential must have a blood test or urine study within 72 hours prior to registration to rule out pregnancy.

    A patient of childbearing potential is anyone, regardless of sexual orientation or whether they have undergone tubal ligation, who meets the following criteria: 1) has achieved menarche at some point; 2) has not undergone a hysterectomy or bilateral oophorectomy; or 3) has not been naturally postmenopausal (amenorrhea following cancer therapy does not rule out childbearing potential) for at least 24 consecutive months (i.e., has had menses at any time in the preceding 24 consecutive months).
    Patient of childbearing potential? _____ (Yes or No)
    Date of blood test or urine study: _____

17. Patients must use accepted and effective method(s) of contraception or by abstaining from sexual intercourse from time of registration, while on study treatment, and continue for 120 days after the last dose of study treatment.

18. Patients must meet the following laboratory values obtained within 14 days prior to randomization:
    ANC ≥ 1500/mm3
    ANC: _____ Date of test: _____

    Platelets ≥ 100,000/mm3
    Platelet count: _____Date of test: _____

    PT/INR ≤ 1.5(only if on active anticoagulation with warfarin or any formulations of heparin) ≤ 3.0
    PT/INR: _____ Date of test: _____

19. Patients must have adequate liver function as determined by the following tests obtained within 14 days prior to randomization:
    Total Bilirubin ≤ 1.5 mg/dL
    Total Bilirubin: _____ Date of test: _____

    SGOT (AST) < 5X upper limit of normal (ULN)
    SGOT (AST):_____Date of test: _____
    ULN: _____

    SGPT (ALT) < 5X upper limit of normal ULN)
    SGPT (ALT):_____Date of test: _____
    UNL: _____

20. Patients must have adequate renal function as determined by the following tests obtained within 14 days prior to randomization:
    Calculated creatinine clearance ≥ 45ml/min to be eligible to receive pemetrexed
    Creatinine clearance: _____ Date of test: _____

Serum creatinine ≤ 1.5X institutional upper limit of normal (ULN)
Serum creatinine_____ Date of test: _____
ULN:_____

21. Patients must not have a known history of active tuberculosis (TB).

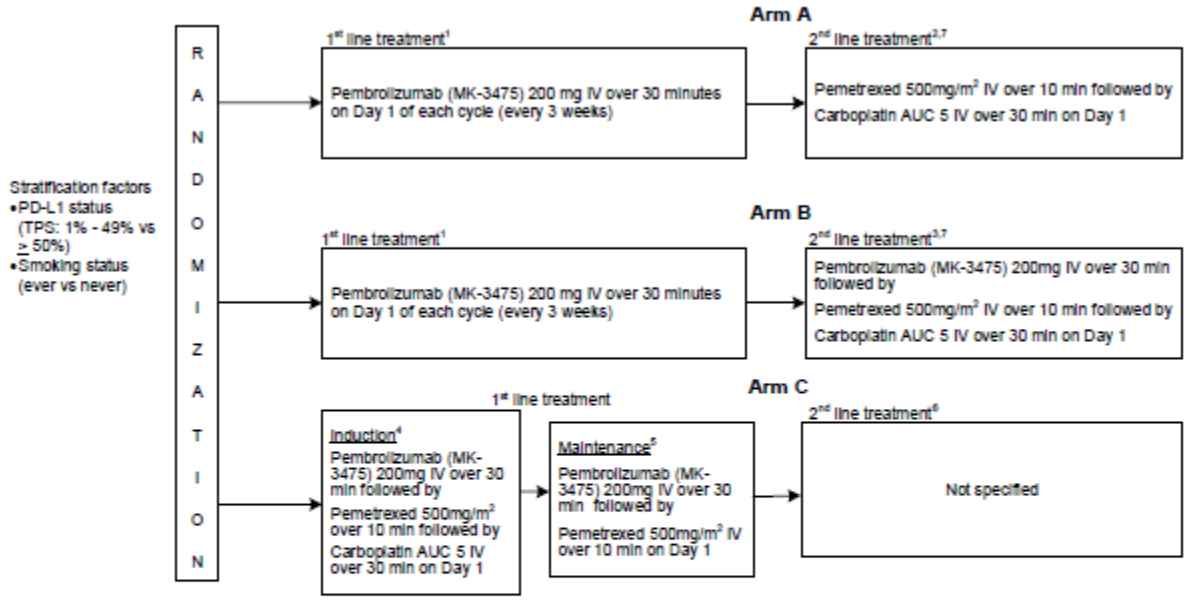
22. Patients must not have a diagnosis of immunodeficiency or receive systemic steroid therapy or any other form of immunosuppressive therapy within 7 days prior to the first dose of protocol treatment.

23. Patients must not have received a live vaccine within 30 days prior to randomization. Patients are permitted to receive inactivated vaccinesand any non-live vaccines including those for the seasonal influenza and COVID-19 (Note: intranasal influenza vaccines, such as Flu- Mist® are live attenuated vaccines and are not allowed). If possible, itis recommended to separate study drug administration from vaccine administration by about a week (primarily, in order to minimize an overlap of adverse events).

24. Human immunodeficiency virus (HIV)-infected patients on effective anti-retroviral therapy with undetectable viral load within 6 months are eligible for this trial.

25. For patients with evidence of chronic hepatitis B virus (HBV) infection, the HBV viral load must be undetectable or on suppressive therapy, if indicated. Patients with a history of hepatitis C virus (HCV) infection must have been treated and cured. For patients with HCV infection who are currently on treatment, they are eligible if they have an undetectable HCV viral load.

Schema



Accrual Goal: 600 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 progression. If patient doesn't continue onto 2nd line treatment, they will proceed to long-term follow-up.
2. Repeat for a maximum of 4 cycles or until disease progression. After cycle 4, pemetrexed can be given alone as maintenance until disease progression or unacceptable toxicity per standard of care.
3. Repeat for a maximum of 4 cycles or until disease progression. After cycle 4, pembrolizumab (MK-3475) and pemetrexed should be given as maintenance until disease progression or two years of treatment for pembrolizumab (MK-3475) in total across 1st and 2nd line treatment. Thereafter, if disease progression is not seen after 2 years, pemetrexed alone may continue until progression per standard of care.
4. Repeat for a maximum of 4 cycles then proceed to maintenance regimen. 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.
5. Repeat for 2 years of total treatment across induction and maintenance, or until disease progression. If after 2 years there is no progression, Pemetrexed will continue to be given as maintenance until disease progression per standard of care.
6. Patient enters long-term follow-up and receives 2nd line treatment off-study, per standard of care.
7. Following completion of 2nd line treatment, patient will proceed to long-term follow-up.