

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.
2. Patients must have PD-L1 expression Tumor Proportion Score (TPS) $\geq 1\%$ 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-measurable 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 is allowed if at least 6 months have elapsed between the last dose 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 local therapy and study registration. Registration prior to treatment during the 14 days is allowed. Palliative radiation must be to non-target lesions.
 - 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.
7. Patients with known EGFR mutations (except exon 20 insertion), BRAF mutations (V600) or ALK or ROS1 translocations that can be treated with oral tyrosine kinase inhibitors are excluded.

8. Patients with treated brain metastases are eligible if follow-up brain imaging 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) 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 cycle of therapy.
 - a. Patients are eligible if off steroids for at least 14 days prior to protocol treatment.
 - b. Palliative radiation to non-target lesions (bone metastasis) is allowed if patient develops symptoms
 - c. Anticonvulsants are allowed
 - d. 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 requiring ongoing or intermittent systemic treatment in the past 2 years (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. Women must not be pregnant or breast-feeding due to potential harm to the fetus or infant from cytotoxic chemotherapy and the unknown risk of MK-3475 (pembrolizumab). Patients must also not expect to conceive or father children from the time of registration, while on study treatment, and until at least 120 days after the last dose of study treatment.

All females of childbearing potential must have a blood test or urine study within 72 hours prior to registration to rule out pregnancy. A female of childbearing potential is any woman, 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).

Female of childbearing potential? _____ (Yes or No)

Date of blood test or urine study: _____

17. Women of childbearing potential and sexually active males must use an accepted and effective method of contraception or abstain 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 within 14 days of randomization:

ANC \geq 1500/mm³

ANC: _____ Date of test: _____

Platelets \geq 100,000/mm³

Platelet count: _____ Date of test: _____

PT/INR \leq 1.5

Or if patient on therapeutic anticoagulation, PT/INR \leq 3.0

PT/INR: _____ Date of test: _____

Is patient on therapeutic anticoagulation and PTT is clinically indicated (i.e., warfarin therapy)? _____ (YES or NO)

If YES, patient is on anticoagulants:

____ PTT \leq institutional upper limit of normal (ULN) OR, if patient is on therapeutic anticoagulation, PTT must be \leq 1.5 x ULN.

PTT: _____ Date of test: _____

ULN: _____

19. Patients must have adequate liver function as determined by the following tests obtained within 14 days of randomization:

Total Bilirubin \leq 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 \geq 45ml/min to be eligible to receive pemetrexed

Creatinine clearance: _____ Date of test: _____

Serum creatinine \leq 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. Seasonal flu vaccines that do not contain live virus are permitted.
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.

