Cancer Research Consortium of West Michigan
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FAST FACTS

LUNGMAP - A MASTER PROTOCOL TO EVALUATE BIOMARKER-DRIVEN THERAPIES AND IMMUNOTHERAPIES IN PREVIOUSLY-TREATED NON-SMALL CELL LUNG CANCER (LUNG-MAP SCREENING STUDY)

S1800D - A Phase II/III Study of N-803 (ALT-803) plus Pembrolizumab versus Standard of Care in Participants with Stage IV or Recurrent Non-Small Cell Lung Cancer Previously Treated with Anti-PD-1 or Anti-PD-L1 Therapy (Lung-MAP Non-Match Sub-Study)

ELIGIBILITY CRITERIA

1. Disease Related Criteria

a. Participants must have been assigned to **S1800D** by the SWOG Statistics and Data Management Center (SDMC). Assignment to **S1800D** is determined by the **LUNGMAP** or **S1400** protocol.

b. Participants must have measurable or non-measurable disease (see Section 10.1) documented by CT or MRI. Measurable disease must be assessed within **28 days** prior to randomization. Non-measurable disease must be assessed within **42 days** prior to randomization. The CT from a combined PET/CT may be used only if it is of diagnostic quality as defined in Section 10.1a. All known sites of disease must be assessed and documented on the Baseline Tumor Assessment Form (RECIST 1.1).

c. Participants must have a CT or MRI scan of the brain to evaluate for CNS disease within **42 days** prior to sub-study randomization.

d. Participants with spinal cord compression or brain metastases must have received local treatment to these metastases and remained clinically controlled and asymptomatic for at least **7 days following stereotactic radiation and/or 14 days following whole brain radiation,** and prior to sub-study randomization.

e. Participants with spinal cord compression or brain metastases must not have residual neurological dysfunction, unless no further recovery is expected, and the participant has been stable on weaning doses of corticosteroids (≤ 10 mg daily prednisone or equivalent) prior to sub-study randomization.

f. Participants must not have leptomeningeal disease that requires CNS-specific treatment prior to registration and must not be planning to receive the CNS-specific treatment through the first cycle of the protocol therapy.

g. Participants must not have experienced the following:
• Any Grade 3 or worse immune-related adverse event (irAE). Exception: asymptomatic nonbullous/nonexfoliative rash.
• Any unresolved Grade 2 irAE.
• Any toxicity that led to permanent discontinuation of prior anti-PD-1/PD-L1 immunotherapy.
Exception to the above: Toxicities of any grade that requires replacement therapy and has stabilized on therapy (e.g., thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency) are allowed.

h. Participants must not have any history of organ transplant that requires use of immunosuppressives.

i. Participants must not have history of (non-infectious) pneumonitis that required steroids or current pneumonitis/interstitial lung disease.

j. Participants must not have any known allergy or reaction to any component of the investigational formulations. If there is a known allergy or reaction to standard of care formulations, participants must be able to safely receive at least one of the standard of care options.

k. Participants must not have any Grade III/IV cardiac disease as defined by the New York Heart Association Criteria (i.e., participants with cardiac disease resulting in marked limitation of physical activity or resulting in inability to carry on any physical activity without discomfort), unstable angina pectoris, and myocardial infarction within **6 months** prior to sub-study randomization, or serious uncontrolled cardiac arrhythmia (see Appendix 18.1).
l. Participants must not have experienced any arterial thromboembolic events, including but not limited to myocardial infarction, transient ischemic attack, cerebrovascular accident, or unstable angina, within **6 months** prior to sub-study randomization.
m. Participants must not have an active or uncontrolled infection in the opinion of the treating investigator.
n. Participants must not have a prior or concurrent malignancy whose natural history or treatment has the potential to interfere with the safety or efficacy assessment of the investigational regimen.
o. Participants must not have any of following:
    i. cirrhosis at a level of Child-Pugh B (or worse) (See Appendix 18.4);
    ii. cirrhosis (any degree) and a history of hepatic encephalopathy;
    iii. or clinically meaningful ascites resulting from cirrhosis. Clinically meaningful ascites is defined as ascites from cirrhosis requiring diuretics or paracentesis.
p. Participants must not have any family or personal history of long or short QT syndrome, Brugada syndrome or known history of QTc prolongation, or Torsade de Pointes or risk factors for Torsade de Pointes including heart failure of hypokalemia.

2. Prior/Concurrent Therapy Criteria

a. Participants must have progressed (in the opinion of the treating investigator) following the most recent line of therapy for NSCLC.
b. Participants with a known sensitizing mutation for which an FDA-approved targeted therapy for NSCLC exists (e.g. EGFR, ALK gene fusions, ROS1, BRAF, RET, NTRK, and MET sensitizing mutations), must have previously received at least one of the approved therapy(s).
c. Participants must have received exactly one line of anti-PD-1 or anti-PD-L1 therapy for advanced disease (Stage IV or recurrent, or Stage III in certain circumstances outlined below) given alone or in combination with platinum-based chemotherapy. Participants must have experienced disease progression during or after this regimen.
    i. Continuing the same agent(s) after progression counts as a single line of therapy. However, a change or addition in agent(s) after progression (e.g. the addition of chemotherapy to anti-PD-1 monotherapy after progression) counts as a subsequent line of therapy and would exclude the participant.
    ii. For participants who received consolidation anti-PD-1 or anti-PD-L1 therapy following concurrent chemoradiation for Stage III disease as their only line of anti-PD-1 or anti-PD-L1 therapy:
        1. If they experienced disease progression less than (<) 365 days from the first date of anti-PD-1 or anti-PD-L1 therapy, this counts as the single line of anti-PD-1 or anti-PD-L1 therapy for advanced disease.
        2. If they experienced disease progression more than or equal to (≥) 365 days from the first date of anti-PD-1 or anti-PD-L1 therapy, this is not considered a line of anti-PD-1 or anti-PD-L1 therapy for advanced disease.
d. Participants must have recovered (≤ Grade 1) from any side effects of prior therapy, except for alopecia.
e. Participants must not have received anti-CTLA4 therapy (e.g. ipilimumab, tremelimumab), or other immune-modulatory therapy (e.g. anti-TIM-3, anti-LAG-3, anti-GITR, IL-2, IL-15).
f. Participants must not have received any prior systemic therapy (systemic chemotherapy, immunotherapy or investigational drug) within **21 days** prior to sub-study randomization.
g. Participants must not have received any radiation therapy within **14 days** prior to sub-study randomization.

h. Participants must not have received nitrosoureas or mitomycin-c within **42 days** prior to sub-study randomization.
i. Participants must not have received systemic treatment with corticosteroids (> 10 mg daily prednisone or equivalent) or other immunosuppressive medications within **7 days** prior to sub-study randomization. Inhaled or topical steroids, and adrenal replacement doses ≤ 10 mg daily prednisone or equivalent are permitted in the absence of active autoimmune disease.
j. Participants must not have received a live attenuated vaccination within **28 days** prior to sub-study randomization (See Appendix 18.6). All COVID-19 vaccines that have received FDA approval or FDA emergency use authorization are acceptable.
k. Participants must not be planning to receive any concurrent chemotherapy, immunotherapy, biologic or hormonal therapy for cancer treatment while receiving treatment on this study.
l. Participants must not have had a major surgery within **14 days** prior to sub-study randomization. Participant must have fully recovered from the effects of prior surgery in the opinion of the treating investigator.

3. Clinical/Laboratory Criteria

a. Participants must be able to safely receive at least one of the investigator's choice of standard of care regimens specified in protocol Section 7.5, per the current FDA-approved package insert. Note: Pemetrexed is not FDA-approved for squamous cell NSCLC and must not be used to treat participants with squamous cell NSCLC.
b. Participants must have an ANC ≥ 1.5 x 10^3/uL, platelet count ≥ 100 x 10^3/uL, and hemoglobin ≥ 9 g/dL obtained within **28 days** prior to sub-study randomization.
c. Participants must have adequate hepatic function as defined by serum bilirubin ≤ Institutional Upper Limit of Normal (IULN) and ALT and AST ≤ 2 x IULN within **28 days** prior to sub-study randomization. For participants with liver metastases, bilirubin and ALT and AST must be ≤ 5 x IULN.
d. Participants must have a serum creatinine ≤ the IULN or calculated creatinine clearance ≥ 50 mL/min using the following Cockcroft-Gault Formula. This specimen must have been drawn and processed within 28 days prior to sub-study randomization:
Calculated Creatinine Clearance = (140 - age) X (weight in kg†)
72 x serum creatinine*
Multiply this number by 0.85 if the participant is a female.
† The kilogram weight is the participant weight with an upper limit of 140% of the IBW.
* Actual lab serum creatinine value with a minimum of 0.7 mg/ dL.
Creatinine Calculator:
https://crawb.crab.org/TXWB/CreatinineClearanceCalculator.aspx
e. Participants' most recent Zubrod performance status must be 0-1 (Section 10.4) and be documented within **28 days** prior to sub-study randomization.
f. Participants must have history and physical exam must be obtained within 28 days prior to sub-study randomization.
g. Participants with known human immunodeficiency virus (HIV) infection must be receiving anti-retroviral therapy and have an undetectable viral load at their most recent viral load test within **6 months** prior to sub-study randomization.
h. Participants must have an ECG performed, with a QTcF ≤ 470 msec, within 28 days prior to sub-study randomization.
i. Participants must not have an active autoimmune disease that has required systemic treatment within **two years** prior to sub-study randomization (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) is not considered a form of systemic treatment and is allowed.
j. Participants must not have any history of primary immunodeficiency.
k. Participants must not be pregnant or nursing. Women/men of reproductive potential must have agreed to use an effective contraceptive method during the study and **4 months** after completion of study treatment. A woman is considered to be of "reproductive potential" if she

has had menses at any time in the preceding 12 consecutive months. In addition to routine contraceptive methods, "effective contraception" also includes heterosexual celibacy and surgery intended to prevent pregnancy (or with a side-effect of pregnancy prevention) defined as a hysterectomy, bilateral oophorectomy or bilateral tubal ligation. However, if at any point a previously celibate participant chooses to become heterosexually active during the time period for use of contraceptive measures outlined in the protocol, he/she is responsible for beginning contraceptive measures during the study and **4 months** after study completion.

SCHEMA