FAST FACTS

S1800A, A PHASE II RANDOMIZED STUDY OF RAMUCIRUMAB PLUS MK3475 (PEMBROLIZUMAB) VERSUS STANDARD OF CARE FOR PATIENTS PREVIOUSLY TREATED WITH IMMUNOTHERAPY FOR STAGE IV OR RECURRENT NON-SMALL CELL LUNG CANCER (LUNG-MAP NON-MATCHED SUB-STUDY)

ELIGIBILITY CRITERIA

1. Disease Related Criteria

a. Patients must have been assigned to **S1800A** by the SWOG Statistics and Data Management Center (SDMC). Patients who were screened under **S1400** (legacy screening/pre-screening study) must have had prior PD-L1 testing by the Dako 22C3 PharmDx IHC assay, and must have results available for stratification purposes.

b. Patients must not have EGFR sensitizing mutations, EGFR T790M mutation, ALK gene fusion, ROS 1 gene rearrangement, and BRAF V600E mutation unless they have progressed following all standard of care targeted therapy.

c. Patients must not have an active autoimmune disease that has required systemic treatment in past two 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) is not considered a form of systemic treatment and is allowed.

d. Patients must not have any history of primary immunodeficiency.

e. Patients 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.

f. Patients must not have any history of organ transplant that requires use of immunosuppressives.

g. Patients must not have clinical signs or symptoms of active tuberculosis infection.

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

i. Patients must not have had a serious or nonhealing wound, ulcer, or bone fracture within 28 days prior to sub-study randomization.

j. Patients must not have a history of gastrointestinal perforation or fistula within six months prior to sub-study randomization.

k. Patients must not have Grade 3-4 gastrointestinal bleeding (defined by NCI CTCAE v5) within three months prior to sub-study randomization.

l. Patients 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, patients must be able to safely receive at least one of the standard of care options.

m. Patients must not have any Grade III/IV cardiac disease as defined by the New York Heart Association Criteria (i.e., patients 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 six months prior to sub-study randomization, or serious uncontrolled cardiac arrhythmia (see S1800A Section 18.1).
Patients must not have experienced any arterial thromboembolic events, including but not limited to myocardial infarction, transient ischemic attack, cerebrovascular accident, or unstable angina, within six months prior to sub-study randomization.

n. Patients must not have documented evidence of acute hepatitis or have an active or uncontrolled infection.
o. Patients with known human immunodeficiency virus (HIV) infection are eligible, provided they are on effective anti-retroviral therapy and have undetectable viral load at their most recent viral load test and within 6 months prior to randomization.
p. Patients with evidence of chronic hepatitis B virus (HBV) infection are eligible provided viral load is undetectable on suppressive therapy, if indicated.
q. 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.
r. Patients must not have undergone major surgery within 28 days prior to sub-study randomization, or subcutaneous venous access device placement within 7 days prior to randomization. Any patient with postoperative bleeding complications or wound complications from a surgical procedure performed in the last two months should be excluded. The patient must not have elective or planned major surgery to be performed during the course of the clinical trial.
s. Patients must not have gross hemoptysis within two months of sub-study randomization (defined as bright red blood or ≥1/2 teaspoon) or with radiographic evidence of intratumor cavitation or has radiologically documented evidence of major blood vessel invasion or encasement by cancer.
t. No other prior malignancy is allowed except for the following: adequately treated basal cell or squamous cell skin cancer, in situ cervical cancer, adequately treated Stage I or II cancer from which the patient is currently in complete remission, or any other cancer from which the patient has been disease free for five years.
u. Patients must not have been diagnosed with venous thrombosis less than 3 months prior to randomization. Patients with venous thrombosis diagnosed more than 3 months prior to randomization must be on stable doses of anticoagulants.
v. Patients must not have any of following:
   • cirrhosis at a level of Child-Pugh B (or worse) (See Appendix 18.3);
   • cirrhosis (any degree) and a history of hepatic encephalopathy; or
   • clinically meaningful ascites resulting from cirrhosis. Clinically meaningful ascites is defined as ascites from cirrhosis requiring diuretics or paracentesis.

2. Prior/Concurrent Therapy Criteria

a. Patients must have received at least one line of anti-PD-1 or anti-PD-L1 therapy for Stage III, IV or recurrent disease and at most one line of anti-PD-1 or anti-PD-L1 therapy for Stage IV or recurrent disease, given alone or in combination with platinum-based chemotherapy, an anti-CTLA4 therapy, or other immune-modulatory therapy. Patients must have experienced disease progression during or after this regimen. Disease progression during or after anti-PD-1 or anti-PD-L1 therapy must have occurred more than (>) 84 days following initiation (Cycle 1 Day 1) of anti-PD-1 or PD-L1 therapy (combination or monotherapy).
   Patients 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, are eligible if they experienced disease progression more than (>) 84 days but less than (<) 365 days from their first date of anti-PD-1 or anti-PD-L1 therapy.
   Patients must have been exposed to platinum-based chemotherapy. for stage IV or recurrent disease and experienced disease progression during or after this regimen
   With the following exception: patients that received adjuvant platinum-based chemotherapy post-surgical resection for Stage I-III disease meet this criterion if disease progression occurred within one year from the last dose that the patient received that therapy.
   Prior tyrosine kinase inhibitor therapy for patients with targetable alterations is allowed if criteria 5.2a above is also met.
b. Patients must have progressed (in the opinion of the treating investigator) following the most recent line of therapy.
c. Patients must not have received any prior systemic therapy (systemic chemotherapy, immunotherapy or investigational drug) within 21 days prior to sub-study randomization.

Patients must have recovered (≤ Grade 1) from any side effects of prior therapy, except for alopecia. Patients must not have received any radiation therapy within 14 days prior to sub-study randomization. (See Section 5.3 for criteria regarding therapy for CNS metastases).

d. Patients must not have received nitrosoureas or mitomycin-c within 42 days prior to sub-study randomization.
e. Patients must not have received systemic treatment with corticosteroids (> 10 mg daily prednisone or equivalent) or other immunosuppressive medications within seven 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.
f. Patients must not have received a live attenuated vaccination within 28 days prior to sub-study randomization. (See Appendix 18.4)
g. Patients must not be planning to receive any concurrent chemotherapy, immunotherapy, biologic or hormonal therapy for cancer treatment while receiving treatment on this study. Concurrent use of hormones for non-cancer-related conditions (e.g., insulin for diabetes and hormone replacement therapy) is acceptable.
h. Patients must not be receiving chronic antiplatelet therapy, including aspirin, nonsteroidal anti-inflammatory drugs (NSAIDs, including ibuprofen, naproxen, and others), dipyridamole or clopidogrel, or similar agents within 7 days prior to randomization. Once-daily aspirin use (maximum dose 325 mg/day) is permitted.
i. Patient must not have received radiotherapy within 14 days before the first dose of study treatment or received lung radiation therapy of >30 Gy within 6 months before the first dose of study treatment.
   Note: Participants must have recovered from all radiation-related toxicities to Grade 1 or less, not require corticosteroids, and not have had radiation pneumonitis.

3. Clinical/Laboratory Criteria

a. Patients must have measurable disease (see **S1800A** Section 10.1) documented by CT or MRI. The CT from a combined PET/CT may be used to document only non-measurable disease unless it is of diagnostic quality as defined in **S1800A** Section 10.1c. Measurable disease must be assessed within 28 days prior to sub-study randomization. Pleural effusions, ascites and laboratory parameters are not acceptable as the only evidence of disease. Non-measurable disease must be assessed within 42 days prior to sub-study randomization. All disease must be assessed and documented on the Baseline Tumor Assessment Form. Patients whose only measurable disease is within a previous radiation therapy port must demonstrate clearly progressive disease (in the opinion of the treating investigator) prior to sub-study randomization. See **S1800A** Section 15.0 and **LUNGMAP** Section 15.6 for guidelines and submission instructions for required central radiology review. CT and MRI scans must be submitted for central review via TRIAD.
b. Patients must have a CT or MRI scan of the brain to evaluate for CNS disease within 42 days prior to sub-study randomization. Patient must not have leptomeningeal disease, spinal cord compression or brain metastases unless: (1) metastases have been locally treated and have remained clinically controlled and asymptomatic for at least 14 days following treatment, and prior to sub-study randomization, AND (2) patient has no residual neurological dysfunction and has been off corticosteroids for at least seven days prior to sub-study randomization.
c. Patients must be able to safely receive at least one of the investigator's choice of standard of care regimens described in Section7.3a, per the current FDA-approved package insert(s).
d. Patients must have an ANC ≥ 1,500/mcl, platelet count ≥ 100,000 mcl, and hemoglobin ≥ 9 g/dL obtained within 28 days prior to sub-study randomization.
e. Patients must have adequate hepatic function as defined by serum bilirubin ≤ Institutional Upper Limit of Normal (IULN) and either ALT or AST ≤ 2 x IULN within 28 days prior to sub-study randomization (if both ALT and AST are done, both must be < 2 IULN). For patients with liver metastases, bilirubin and either ALT or AST must be ≤ 5 x IULN (if both ALT and AST are done, both must be ≤ 5 x IULN).

f. Patients must have a serum creatinine ≤ the IULN or calculated creatinine clearance ≥ 50 mL/min using the following Cockroft-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 patient is a female.
   † The kilogram weight is the patient weight with an upper limit of 140% of the IBW.
   * Actual lab serum creatinine value with a minimum of 0.8 mg/ dL.
   Creatinine Calculator:
   https://crawb.crab.org/TXWB/CreatinineClearanceCalculator.aspx

g. Patients' urinary protein must be ≤1+ on dipstick or routine urinalysis (UA). Random analysis of urine protein with a normal value is sufficient. If urine dipstick or routine analysis indicated proteinuria ≥2+, then a 24-hour urine is to be collected and demonstrate <1000 mg of protein in 24 hours to allow participation in the study.

h. Patients must not have a history of uncontrolled or poorly-controlled hypertension defined as SBP > 150 mmHg or DBP > 90 mmHg within 28 days prior to sub-study randomization. Patients are permitted to be receiving multiple anti-hypertensive medications (unless otherwise indicated in the study). All blood pressure measurements within the 14 days prior to registration must be SBP < 150 and DBP < 90. An exception can be made by a healthcare provider for a patient with a single blood pressure elevation who upon rechecking has a normal blood pressure.

i. For patients where an International Normalized Ratio (INR) is clinically indicated, INR must be ≤ 1.5 seconds above the institutional upper limit of normal (IULN) (unless receiving anticoagulation therapy) documented within 28 calendar days prior to sub-study randomization. For patients where a partial thromboplastin time (PTT) is clinically indicated, PTT must be ≤ 5 seconds above the institutional upper limit of normal (IULN) (unless receiving anticoagulation therapy) documented within 28 calendar days prior to sub-study randomization.

j. If receiving warfarin, the patient must have an INR ≤3.0. For warfarin, heparin and low molecular weight heparin (LMWH) there should be no active bleeding (that is, no bleeding within 14 days prior to first dose of protocol therapy) or pathological condition present that carries a high risk of bleeding (for example, tumor involving major vessels or known varices).

k. Patients must have Zubrod performance status 0-1 (see **S1800A** Section 10.4) documented within 28 days prior to sub-study randomization.

l. Pre-study history and physical exam must be obtained within 28 days prior to sub-study randomization.

m. Patients 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 patient 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.

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SCHEMA