FAST FACTS

S1900C, A PHASE II STUDY OF TALAZOPARIB PLUS AVELUMAB IN PATIENTS WITH STAGE IV OR RECURRENT NON-SQUAMOUS NON-SMALL CELL LUNG CANCER BEARING PATHOGENIC *STK11* GENOMIC ALTERATIONS (LUNG-MAP SUB-STUDY)

ELIGIBILITY CRITERIA

Each of the criteria in the following section must be met in order for a patient to be considered eligible for registration. For each criterion requiring test results and dates, please record this information on the Onstudy Form and submit via Medidata Rave® (see Section 14.0). Any potential eligibility issues should be addressed to the Statistics and Data Management Center in Seattle at 206/652-2267 or LUNGMAPQuestion@crab.org prior to registration. **NCI policy does not allow for waiver of any eligibility criterion** (http://ctep.cancer.gov/protocolDevelopment/policies_deviations.htm).

In calculating days of tests and measurements, the day a test or measurement is done is considered Day 0. Therefore, if a test is done on a Monday, the Monday 4 weeks later would be considered Day 28. This allows for efficient patient scheduling without exceeding the guidelines. **If Day 7, 14, 16, 28, or 42 falls on a weekend or holiday, the limit may be extended to the next working day.**

1. Disease Related Criteria
    a. Patients must be assigned to **S1900C**. Assignment to **S1900C** is determined by the **LUNGMAP** protocol genomic profiling using the FoundationOne assay. Biomarker eligibility for **S1900C** is based on the identification of a pathogenic somatic mutation in *STK11* or *STK11* bi-allelic loss on tumor.
    b. Patients must have histologically or cytologically confirmed Stage IV or recurrent non-squamous, mixed squamous/non-squamous (e.g., adeno-squamous carcinoma), or non-small cell lung cancer not otherwise specified (NSCLC NOS). Patients with pure squamous cell carcinoma are not eligible.
    c. Patients with evidence of chronic hepatitis B virus (HBV) infection must have undetectable HBV viral load on suppressive therapy within 28 days prior to sub-study registration.
    d. Patients with a history of hepatitis C virus (HCV) infection must have been treated and cured. Patients with HCV infection who are currently on treatment must have an undetectable HCV viral load within 28 days prior to sub-study registration.
    e. 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 sub-study registration.
    f. 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.
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.
   Any number of additional, non-platinum-based chemotherapy or targeted therapy regimens for recurrent or metastatic disease are allowed.
   1. Patients may not have received more than one line of anti-PD-1 or anti-PD-L1 therapy in the Stage IV or recurrent setting. Anti-PD-1 or anti-PD-L1 therapy may have been given alone or in combination with platinum-based chemotherapy, an anti-CTLA4 therapy, or other immune-modulatory therapy. Patients must have experienced disease progression>42 days following initiation (Cycle 1 Day 1) of the anti-PD-1 or anti-PD-L1 containing regimen.
   2. Patients who did not receive anti-PD-1 or anti-PD-L1 therapy in combination with platinum-based chemotherapy, must have also received prior platinum-based chemotherapy and experienced disease progression >42 days following initiation (Cycle 1 Day 1) of platinum based chemotherapy.
   3. Patients who received 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 less than (<) 365 days from the date of initiation of anti-PD-1 or anti-PD-L1 therapy.

b. Patients who received prior adjuvant platinum-based therapy post-surgical resection for Stage I-III disease (i.e. the patient has not received platinum-based chemotherapy for Stage IV or recurrent disease) must have had disease progression during or after platinum-based chemotherapy that occurred less than (<) 365 days from the last date that the patient received that therapy.

c. Patients must be able to swallow capsules whole.

d. Patients must not have had prior exposure to any agent with a PARP inhibitor (e.g., veliparib, olaparib, rucaparib, niraparib, talazoparib) as its primary pharmacology.

e. Patients must not be taking, nor plan to take while on protocol treatment strong P-gp inhibitors (e.g. droneradone, quinidine, ranolazine, itraconazole, ketononazole), P-gp inducers (rifampin, ritonavir, tipranavir), or strong breast cancer resistance protein (BCRP) inhibitors (e.g. elacridar).

f. Patients must have progressed (in the opinion of the treating physician) following their most recent line of therapy.

g. Patients must not have received prior systemic immunotherapy within 28 days prior to sub-study registration and must not have received any prior systemic therapy (including systemic chemotherapy or investigational drug) within 21 days prior to sub-study registration. Patients must have recovered (≤ Grade 1) from any side effects of prior therapy. Patients must not have received any radiation therapy within 14 days prior to sub-study registration. (See 5.2c.2 for criteria regarding therapy for CNS metastases).

h. 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.

3. Clinical/Laboratory Criteria

a. Patients must have measurable disease (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 Section 10.1c. Measurable disease must be assessed within 28 days prior to sub-study registration. 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 registration. 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 registration. See Sections 15.5 and Appendix 18.2 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 registration. 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 registration, AND (2) patient has no residual neurological dysfunction and has been off corticosteroids for at least 24 hours prior to sub-study registration.

c. Patient must not have had a major surgery within 14 days prior to sub-study registration. Patient must have fully recovered from the effects of prior surgery in the opinion of the treating investigator.

d. 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 registration (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).

e. clearance ≥ 60 mL/min using the following Cockroft-Gault Formula. This specimen must have been drawn and processed within 28 days prior to sub-study registration:

$$\text{Calculated Creatinine Clearance} = \frac{(140 - \text{age}) \times (\text{weight in kg})\ \dagger}{72 \times \text{serum creatinine}^*}$$

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

f. Patients must have Zubrod performance status 0-1 (Section 10.4) documented within 28 days prior to sub-study registration.

g. 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 6 months, or serious uncontrolled cardiac arrhythmia (Appendix 18.1).

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

i. 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.

j. Patients must not be pregnant or nursing. Women/men of reproductive potential must have agreed to use an effective contraceptive method. 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.

k. Patients must not have a history of prior organ transplantation, including allogeneic stem-cell transplantation.

l. Patients must not have received systemic treatment with corticosteroids (> 10 mg daily prednisone or equivalent) or other immunosuppressive medications within 14 days prior to sub-study registration. Inhaled or topical steroids, and adrenal replacement doses ≤ 10 mg daily prednisone or equivalent are permitted in the absence of active autoimmune disease.

m. Patients must not have active autoimmune disease that requires systemic steroids (equivalent of >10 mg of prednisone) or immunosuppressive agents within 14 days prior to sub-study registration (for example disease-modifying anti-rheumatic drugs). Exceptions include: patients with controlled type 1 diabetes mellitus, controlled hypo- or hyperthyroidism, vitiligo, resolved childhood asthma/atopy, or psoriasis not requiring immunosuppressive therapy.

n. Patients must not have any impairment of gastrointestinal function or gastrointestinal disease that may significantly alter the absorption of talazoparib (e.g., ulcerative disease, uncontrolled nausea, vomiting, diarrhea, malabsorption syndrome, small bowel resection, or active peptic ulcer disease). Patients must not have active small or large intestine inflammation such as Crohn's disease or ulcerative colitis within 12 months prior to sub-study registration.

o. Patients must not have known prior or suspected hypersensitivity to monoclonal antibodies (Grade ≥3).

p. Patients must not have any history of anaphylaxis or uncontrolled asthma. Uncontrolled asthma is defined as a patient having any one of the following criteria:

i. Poor symptom control: ACQ consistently >1.5 or ACT <20 (or "not well controlled" by NAEPP or GINA guidelines over the 3 months or evaluation).
ii. Frequent severe exacerbations: 2 or more bursts of systemic CSs (>3 days each) in the previous year.
iii. Serious exacerbations: at least one hospitalization, Intensive Care Unit stay or mechanical ventilation in the previous year.
iv. Airflow limitation: FEV1<80% predicted (in the presence of reduced FEV1/FVC defined as less than the normal lower limit) following a withhold of both short- and long-acting bronchodilators.

q. Patients must not have experienced any immune related adverse event, including pneumonitis that led to permanent discontinuation of prior immunotherapy and/or required prolonged high dose of steroids.
r. Patients must not have evidence of active infection requiring systemic therapy.
s. Patients must not have received any live attenuated vaccinations within 28 days prior to sub-study registration.
t. 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 registration. Patients must be transfusion independent (i.e., no blood product transfusions for a period of at least 14 days prior to sub-study registration).

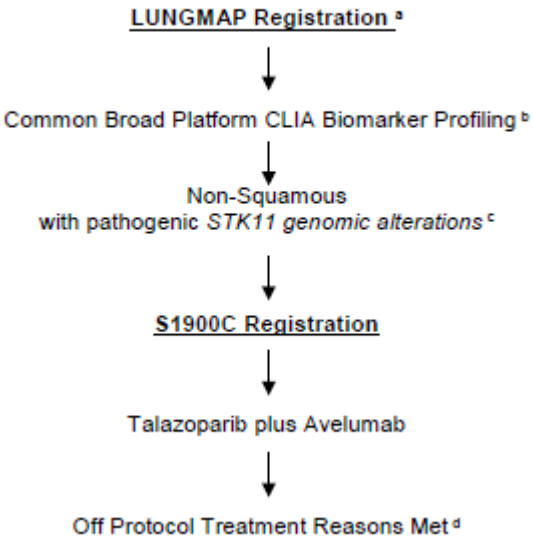
4. Specimen Submission Criteria

a. Patients must agree to have blood specimens submitted for circulating tumor DNA (ctDNA) as outlined in Section 15.3.
b. Patients must also be offered participation in banking and in the correlative studies for collection and future use of specimens as described in Section 15.4.

5. Regulatory Criteria

a. Patients ***must*** be informed of the investigational nature of this study and must sign and give written informed consent in accordance with institutional and federal guidelines.
b. As a part of the OPEN registration process (**LUNGMAP** Section 13.2 for OPEN access instructions) the treating institution's identity is provided in order to ensure that the current (within 365 days) date of institutional review board approval for this study has been entered in the system.
c. Patients with impaired decision-making capacity are eligible as long as their neurological or psychological condition does not preclude their safe participation in the study (e.g., tracking pill consumption and reporting adverse events to the investigator).

SCHEMA


LUNGMAP Registration [a]
Common Broad Platform CLIA Biomarker Profiling [b]
Non-Squamous
with pathogenic *STK11 genomic alterations* [c]
S1900C Registration
Talazoparib plus Avelumab
Off Protocol Treatment Reasons Met [d]