Cancer Research Consortium of West Michigan
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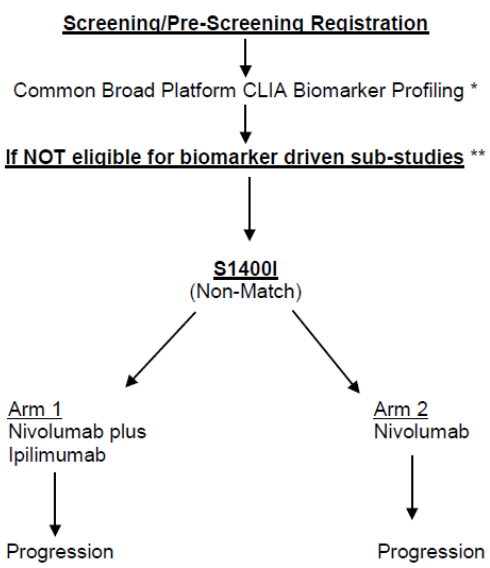
FAST FACTS

S1400I: (Non-Match Sub-Study): Nivolumab plus Ipilimumab versus Nivolumab

A Biomarker-Driven Master Protocol for Previously Treated Squamous Cell Lung Cancer

A Phase III Randomized Study of Nivolumab plus Ipilimumab versus Nivolumab for Previously Treated Patients with Stage IV Squamous Cell Lung Cancer and No Matching Biomarker (LUNG-MAP SUB-STUDY)

SCHEMA



***Drugs Provided**

ELIGIBILITY CRITERIA

Patient must meet the eligibility criteria below to be eligible for **S1** sub-study specific eligibility criteria listed in Section 5.1 and Secti sub-study criteria listed in Section 5.3 of **S1400I**, submit the **S14** Form for sub-study reassignment. Each of the criteria in the follo patient to be considered eligible for registration. For each criterio record this information on the Onstudy Form and submit via Medi potential eligibility issues should be addressed to the SWOG Sta (SDMC) in Seattle at 206/652-2267 or S1400question@crab.org allow for waiver of any eligibility criterion (http://ctep.cancer.gov/protocolDevelopment/policies_deviations. 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.

Sub-Study Specific Disease Related Criteria

a. Patients must have been assigned to S1400I.
b. Patients must not have had prior treatment with an anti-PD-1, anti-PDL1, anti-PD-L2, anti-CTLA-4 antibody, or any other antibody or drug specifically targeting T-cell costimulation or immune checkpoint pathways.
c. Patients must not have an active, known, or suspected autoimmune disease. Patients are permitted to enroll if they have vitiligo, type I diabetes mellitus, hypothyroidism only requiring hormone replacement, psoriasis not requiring systemic treatment, or conditions not expected to recur in the absence of an external trigger.

Sub-Study Specific Clinical/Laboratory Criteria

a. Patients must not have any known allergy or reaction to any component of the nivolumab and ipilimumab formulations.
b. 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.
c. Patients must not have a known positive test for hepatitis B virus surface antigen (HBV sAg) or hepatitis C virus ribonucleic acid (HCV antibody) indicating acute or chronic infection. Patients with a positive hepatitis C antibody with a negative viral load are allowed. [This criterion replaces common eligibility criteria in Section 5.3m.]
d. Patients must not have known history of testing positive for human immunodeficiency virus (HIV) or known acquired immunodeficiency syndrome (AIDS). [This criterion replaces common eligibility criteria in Section 5.3n.]
e. Patients must not have interstitial lung disease that is symptomatic or disease that may interfere with the detection or management of suspected drug-related pulmonary toxicity.
f. Patients must also be offered participation in banking for future use of specimens as described in Section 15.0
g. Patients must have a Lipase, Amylase, TSH with reflex Free T3/T4 performed within 7 days prior to sub-study registration. Additional timepoints are noted in Section 9.0, Study Calendar.
h. Patients who can complete PRO forms in English are required to complete a pre-study **S1400I** Patient Reported Outcomes (PRO) Questionnaire and a pre-study S1400I EQ-5D Questionnaire within 14 days prior to registration (see Section 18.2 of **S1400I**). NOTE: Patients enrolled to **S1400I** prior to **S1400** Revision #5 are not eligible for the PRO study.

Common Eligibility Criteria for all Sub-Studies

The S1400 Common Eligibility Criteria have been incorporated into Section 5.0 of each sub-study for ease of reference.

a. Patients whose biomarker profiling results indicate the presence of an EGFR mutation or EML4/ALK fusion are not eligible. Due to existence of approved therapies the biomarker exclusion rules are as follows:

Gene	Alteration type	Ineligible Alteration
EGFR	Substitution	L858R, T790M, A289V, G719A, S768I, G719C, R108K, G598V, R222C, L62R, L861Q, P596L, V774M
	Indel	non-frame shifting insertions or deletions between amino acids 740 and 780, in exons 19 and 20, transcript NM_005228
	Fusion	None
	Amplification	None
ALK	Substitution	None
	Indel	None
	Fusion	EML4-ALK, CLIP4-ALK, CLTC-ALK, KIF5B-ALK, NPM1-ALK, RANB2-ALK, STRN-ALK, TFG-ALK
	Amplification	None

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 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 5.3e for criteria regarding therapy for CNS metastases).
d. Patients must have measurable disease (see 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 S1400 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 registration. See Sections 15.0 and 18.1c for guidelines and submission instructions for required central radiology review.
e. 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 prior to regisitration, AND (2) patient has no residual neurological dysfunction and has been off corticosteroids for at least 24 hours prior to sub-study registration.
f. Patients must have fully recovered from the effects of major surgery at least 14 days prior to sub-study registration.
g. Patients must not be planning to receive any concurrent chemotherapy, immunotherapy, biologic or hormonal therapy for cancer treatment. Concurrent use of hormones for non-cancer-related conditions (e.g., insulin for diabetes and hormone replacement therapy) is acceptable.
h. 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.
i. 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).
j. Patients must have a serum creatinine ≤ the IULN OR measured or calculated creatinine clearance ≥ 50 mL/min using the following Cockroft- Gault Formula: Calculated Creatinine Clearance = (140 - age) X (actual body weight in kg) † 72 x serum creatinine* Multiply this number by 0.85 if the patient is a female. These tests must have been performed within 28 days prior to sub-study registration. †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.

k. Patients must have Zubrod performance status of 0-1 (see Section 10.4) documented within 28 days prior to sub-study registration.
l. 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 (see Section 18.1b).
m. Prestudy history and physical exam must be obtained within 28 days prior to sub-study registration.
n. 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.
o. 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.
p. As a part of the OPEN registration process (see Section 13.4 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.
q. 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).
r. 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.

Arm 1: Nivolumab plus Ipilimumab

Nivolumab 3 mg/kg IV 30 minutes Q 14 days

Ipilimumab 1 mg/kg IV 60 minutes Q 42 days

Arm 2: Nivolumab

Nivolumab 3 mg/kg IV 30 minutes Q 14 days

Pre-Study Parameters

- History and Physical, Weight, PS
- Smoking Status Assessment

- CBC/Diff/plts
- CMP
- Blood urea nitrogen
- LDH
- Amylase/Lipase
- TSH w. reflex Free T3/T4
- CT or MRI for disease assessment
- Brain CT/MRI
- Image submission / blood for banking