Cancer Research Consortium of West Michigan
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FAST FACTS

S1900B, A PHASE II STUDY OF LOXO-292 IN PATIENTS WITH RET FUSION-POSITIVE STAGE IV OR RECURRENT NON-SMALL CELL LUNG CANCER (LUNG-MAP SUB-STUDY)

ELIGIBILITY CRITERIA

1. Disease Related Criteria

a. Patients must have been assigned to S1900B based on biomarker analysis of tissue and/or blood and determined to have RET fusion-positive NSCLC as defined here:
Patients must have RET fusion-positive NSCLC as determined by the FMI tissue-assay or other tumor-based assays such as NGS, PCR, or FISH, or by cfDNA blood assay as outlined in Section 7.1 of the LUNGMAP screening protocol. Patients previously tested for and determined to have RET-fusion-positive NSCLC outside of LUNGMAP, must also submit tissue for central FMI testing on the LUNGMAP screening protocol. Patients with RET fusions detected by IHC alone are not eligible. The testing must be done within a laboratory with CLIA, ISO/IEC, CAP, or similar certification. Presence of RET fusions detected on tests performed outside of LUNGMAP must have been confirmed by the study biomarker review panel (see Section 15.2).

b. For patients whose prior therapy was for Stage IV or recurrent disease, the patient must have received at least one line of a platinum-based chemotherapy regimen. For patients whose prior systemic therapy was for Stage I-III disease only (i.e. patient has not received any treatment for Stage IV or recurrent disease), disease progression on platinum-based chemotherapy must have occurred within one year from the last date that the patient received that therapy. Prior anti-PD-1/PD-L1 therapy, alone or in combination (e.g. Nivolumab, Pembrolizumab, or Durvalumab) is allowed.

c. Patients must be negative for all additional validated oncogenic drivers that could cause resistance to selpercatinib (LOXO-292) treatment. This includes EGFR sensitizing mutations, EGFR T790M, ALK gene fusion, ROS1 gene fusion, KRAS activating mutation, BRAF V600E mutation and MET exon 14 skipping mutation or high-level amplification and expression.
Note: EGFR, ALK, ROS, KRAS, and BRAF testing is performed as part of the LUNGMAP screening/pre-screening Foundation One test. If prior data is not available, results from the FMI testing must be obtained prior to sub-study registration.

d. Patients must not have received any prior treatment with selective anti-RET inhibitors (anti-RET multikinase inhibitors are permitted). See Appendix 18.7 for examples.

e. 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 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 Section 15.0 and Appendix 18.8f for guidelines and submission instructions for required central radiology review. CT and MRI scans must be submitted for central review via TRIAD.

f. Patients must have a CT or MRI scan of the brain to evaluate for CNS disease within 42 days prior to sub-study registration.
g. 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 registration, AND (2) patient has no residual neurological dysfunction and has been off corticosteroids for at least 24 hours prior to sub-study registration.
h. Patients with evidence of chronic hepatitis B virus (HBV) infection must have undetectable HBV viral load on suppressive therapy within 28 days prior to registration.
i. 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 registration.
j. 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 registration.
k. Patients must be able to swallow capsules.

2. Prior/Concurrent Therapy Criteria

a. Patients must not have received any prior systemic therapy (systemic chemotherapy, immunotherapy or investigational drug) within 14 days prior to sub-study registration.
b. Patients must have progressed (in the opinion of the treating physician) following the most recent line of therapy.
c. 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 Section 5.1f for criteria regarding therapy for CNS metastases).
d. 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.
e. 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.

3. Clinical/Laboratory Criteria

a. 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.
b. 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).
c. 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 registration:
Calculated Creatinine Clearance = $\frac{(140 - \text{age}) \times (\text{weight in kg})}{72 \times \text{serum creatinine}}$ †
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 0.7 mg/ dL.
Creatinine Calculator:
https://crawb.crab.org/TXWB/CreatinineClearanceCalculator.aspx
d. Patients' most recent Zubrod performance status must be 0-1 (see Section 10.4) documented within 28 days prior to sub-study registration.

e. 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 Appendix 18.1).
f. Pre-study history and physical exam must be obtained within 28 days prior to sub-study registration.
g. 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.
h. Patients must have an ECG performed within 28 days prior to sub-study registration. It is suggested that a local cardiologist review the QTcF intervals.
i. Patients must not have any clinically significant uncontrolled systemic illness, including but not limited to uncontrolled infection, requiring intravenous antibiotics, unstable angina pectoris, myocardial infarction within the past 6 months, uncontrolled cardiac arrhythmias, uncontrolled hypertension, or uncontrolled diabetes mellitus.
Uncontrolled diabetes: Patients who have a diagnosis of diabetes must have an Hb A1C < 7% within 28 days prior to registration. The same criterion will be used in patients with confirmed diagnosis of diabetes mellitus who have been on a stable dietary or therapeutic regimen for this condition in the last three months.
Uncontrolled blood pressure and hypertension: All blood pressure measurements within the 28 days prior to registration must be SBP $\leq$ 180 and DBP $\leq$ 100. An exception can be made by a healthcare provider for a patient with a single blood pressure elevation who upon rechecking has a blood pressure within the parameters above.
j. Patients must not have any impairment of gastrointestinal function or gastrointestinal disease that may significantly alter the absorption of selpercatinib (LOXO-292) (e.g., ulcerative disease, uncontrolled nausea, vomiting, diarrhea, malabsorption syndrome, small bowel resection, or active peptic ulcer disease).
k. Patients must not be planning to receive any moderate or strong inhibitors or inducers of CYP3A4 at least 14 days prior to sub-study registration and throughout protocol treatment. (See Appendix 18.3 for examples)
l. Patients must not be planning to use proton pump inhibitors (PPIs) at least one week prior to sub-study registration and throughout protocol treatment. (See Section 7.1 for examples)
m. Patients must have electrolytes and blood urea nitrogen (BUN) performed within 14 days prior to sub-study registration. Additional timepoints are notes in Section 9.0.
n. Patients must not be pregnant or nursing. Women study patients of reproductive potential and fertile men study patients and their partners must abstain or use effective contraception (including barrier method) while receiving study treatment and for at least 3 months after the last dose of selpercatinib (LOXO-292). Male study patients must agree not to donate sperm for 6 months after the last dose of selpercatinib (LOXO-292). 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.

4. Specimen Submission Criteria

a. Patients must agree to have blood specimens submitted for circulating tumor DNA (ctDNA) as outlined in Section 15.0.
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 15.0.

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