PRIVILEGED COMMUNICATION
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S1900B: RET Fusion-Positive – Selpercatinib (LOXO-292)

SWOG CANCER RESEARCH NETWORK

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

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

NCT#04268550

This is an FDA Registration Trial; therefore, all participating sites should be FDA "inspection ready". This entails maintaining a Trial Master File that includes essential documents that may be subject to FDA oversight. A list of essential documents is available on the SWOG website under QA/Audits, https://swog.org/Visitors/QA/Index.asp. Additional site requirements include:

- **maintenance of a Trial Master File (https://www.swog.org/sites/default/files/docs/2017-10/Guidance%20on%20FDA%20Inspection.pdf)**
- **completion of a protocol specific Delegation of Task Log (DTL) (see Section 13.2)**
- **additional monitoring (see Appendix 18.8)**

LUNGMAP and its sub-studies are being conducted under SWOG IND 143217 and CIRB. The LUNGMAP study is considered a single study under one IND, consisting of the screening protocol and multiple sub-studies. Each sub-study protocol operates independently and has its own version date. For CIRB Continuing Reviews, LUNGMAP and its sub-studies will be processed separately but have the same expiration date as the LUNGMAP screening protocol.

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Investigational Drug questions: Requests for Investigator's Brochures:	See Protocol Section 3.0
Temperature Excursion Reports:	rlewis@loxooncology.com
Specimen Tracking System (STS) Amendments, Errors, Connectivity Issues and Technical issues with the SWOG CRA Workbench:	technicalquestion@crab.org
Foundation Medicine, Inc. (for ordering ctDNA blood collection kits only):	FMI Client Services E-mail: lung.map@foundationmedicine.com Phone: 1-888/988-3639
Cancer Therapy and Evaluation Program – Identity and Access Management (CTEP-IAM):	To review CTEP-IAM account (new requests, reset passwords): https://ctepcore.nci.nih.gov/iam/index.jsp
Access to iMedidata Rave or Delegation of Task Log (DTL):	See Protocol Section 14.3 or contact CTSU Help Desk: Phone: 1-888-823-5923 or Email: ctsucontact@westat.com
Questions related to Oncology Patient Enrollment Network (OPEN):	See **LUNGMAP** Protocol Section 13.2 or contact CTSU Help Desk: Phone: 1-888-823-5923 or Email: ctsucontact@westat.com
Patient Transfers:	patienttransfer@crab.org
TRIAD installations:	https://triadinstall.acr.org/triadclient/ Questions: TRIAD-Support@acr.org
Adverse Event Reporting questions:	See Protocol Section 8.5 E-mail: adr@swog.org
Source Documentation Portal – Central Monitoring:	centralmonitorquestion@crab.org

CANCER TRIALS SUPPORT UNIT (CTSU) ADDRESS AND CONTACT INFORMATION

CONTACT INFORMATION		
For regulatory requirements:	**For patient enrollments:**	**For data submission:**
Regulatory documentation must be submitted to the CTSU via the Regulatory Submission Portal: (Sign in at www.ctsu.org, and select the Regulatory > Regulatory Submission.) Institutions with patients waiting that are unable to use the Portal should alert the CTSU Regulatory Office immediately at 1-866-651-2878 to receive further instruction and support. Contact the CTSU Regulatory Help Desk at 1-866-651-2878 for regulatory assistance.	Refer to the patient enrollment section of the protocol for instructions on using the Oncology Patient Enrollment Network (OPEN). OPEN is accessed at https://www.ctsu.org/OPEN_SYSTEM/ or https://OPEN.ctsu.org. Contact the CTSU Help Desk with any OPEN-related questions by phone or email : 1-888-823-5923, or ctsucontact@westat.com.	Data collection for this study will be done exclusively through Medidata Rave. Refer to the data submission section of the protocol for further instructions. Other Tools and Reports: Institutions participating through the CTSU continue to have access to other tools and reports available on the SWOG CRA Workbench via the SWOG website (www.swog.org).

The most current version of the **study protocol and all supporting documents** must be downloaded from the protocol-specific Web page of the CTSU Member Web site located at https://www.ctsu.org. Access to the CTSU members' website is managed through the Cancer Therapy and Evaluation Program - Identity and Access Management (CTEP-IAM) registration system and requires user log on with CTEP-IAM username and password.

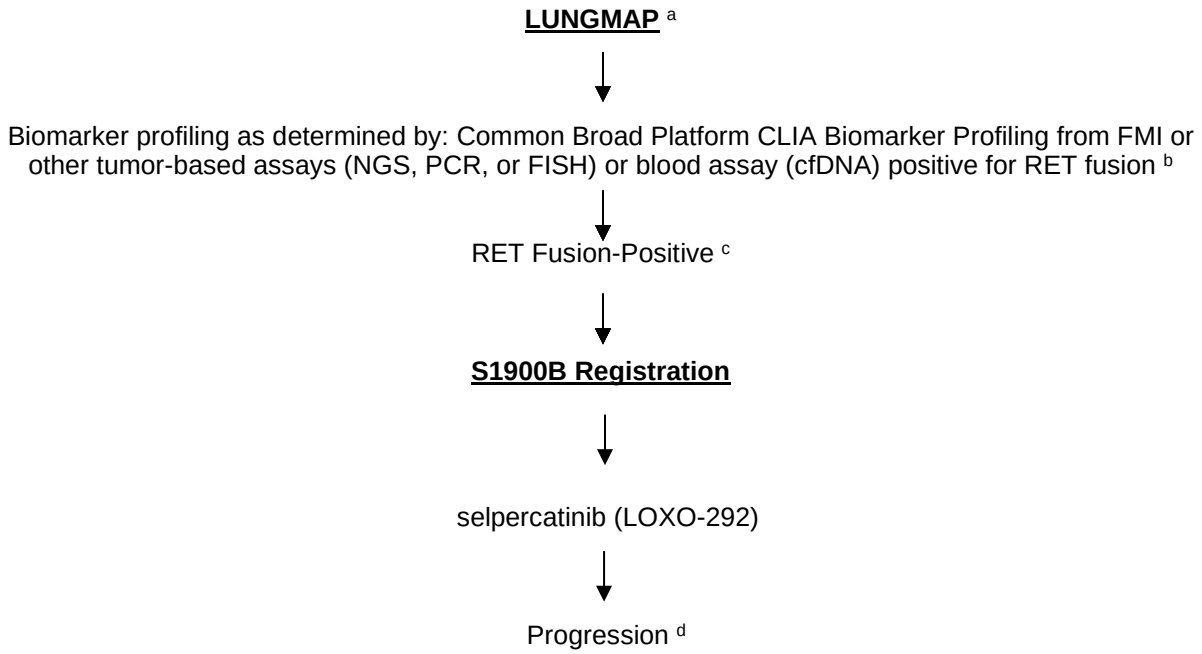
For patient eligibility or data submission questions contact the SWOG Statistics and Data Management Center (SDMC) by phone or email:

206/652-2267
LUNGMAPquestion@crab.org

For treatment or toxicity related questions contact S1900BMedicalQuery@swog.org

For non-clinical questions (i.e. unrelated to patient eligibility, treatment, or clinical data submission)
Contact the CTSU Help Desk by phone or e-mail:
CTSU General Information Line – 1-888-823-5923, or ctsucontact@westat.com. All calls and correspondence will be triaged to the appropriate CTSU representative.

SCHEMA



a See **LUNGMAP** Section 5.1 for registration information.

b See **S1900B** Section 5.1. All patients must submit tissue for **LUNGMAP** screening protocol for the Foundation Medicine testing. Patients with RET fusion-positive results detected outside the Lung-MAP study will be required to submit documentation as outlined in **LUNGMAP** Section 14.4. A committee will review the documentation per **S1900B** Section 15.2.

c See Section 5.0 for the criteria of RET fusion-positive.

d Upon progression (as defined in Section 10.0), patients may be eligible for another sub-study. The new sub-study assignment will be determined by the SWOG Statistics and Data Management Center (see Section 14.4).

1.0 OBJECTIVES

1.1 Primary Objective

To evaluate the objective response rate (ORR) (confirmed complete or partial response) by blinded independent centralized review (BICR) associated with selpercatinib (LOXO-292) in patients with previously-treated Stage IV or recurrent RET fusion-positive non-small cell lung cancer (NSCLC).

1.2 Secondary Objectives

a. A key secondary objective is to evaluate the duration of BICR-assessed response among BICR responders.

Additional secondary objectives are:

b. To evaluate the frequency and severity of toxicities.

c. To evaluate the investigator-assessed objective response rate (confirmed complete or partial response).

d. To evaluate duration of investigator-assessed response among patients with a response as determined by the local investigator.

e. To evaluate investigator-assessed progression-free survival (IA-PFS).

f. To evaluate BICR-assessed PFS.

g. To evaluate overall survival (OS).

h. Among patients with brain metastases at baseline:

i. To evaluate the central nervous system (CNS) response rate (confirmed CR).

ii. To evaluate the duration of intracranial response among patients with a CNS response.

1.3 Translational Medicine Objectives

a. To collect, process, and bank cell-free deoxyribonucleic acid (cfDNA) at baseline, progression, and end of treatment for future development of a proposal to evaluate comprehensive next-generation sequencing of circulating tumor deoxyribonucleic acid (ctDNA).

Note: The translational medicine proposal to use these specimens will be submitted as a revision to CTEP for approval, prior to the SWOG Statistical and Data Management Center (SDMC) review of assay results.

b. To establish a tissue/blood repository from patients with refractory non-small cell lung cancer (NSCLC).

2.0 BACKGROUND

2.1 Overview

RET Fusion-Positive NSCLC:

RET is a receptor tyrosine kinase (RTK) with critical roles in normal organogenesis and in the maintenance of several adult tissue types, including neural, neuroendocrine, hematopoietic, and male germ cell. *(1)* Genetic alterations in the RET gene are implicated in the pathogenesis of several human cancers. RET can be oncogenically activated by two primary mechanisms:

1. chromosomal rearrangements, producing cytoplasmically localized oncogenic hybrid proteins that fuse the RET kinase domain with a partner protein dimerization domain (e.g., CCDC6/PTC1, KIF5B, NCOA4/PTC3), thus endowing the kinase with ligand-independent, constitutive activity; and

2. point mutations that directly or indirectly activate the kinase. The oncogenic potential of RET was first identified as a result of its ability to transform NIH 3T3 cells through deoxyribonucleic acid (DNA) rearrangement. (2)

RET fusions occur in a variety of malignancies, including 1-2% of non-small cell lung cancers (NSCLC). RET alterations possess the hallmarks of cancer drivers: constitutive kinase and signaling activity, transformation of primary cells, and mutually exclusivity from other drivers. (3,4,5,6)

Until recently, only multikinase inhibitors (MKIs) with non-selective RET inhibitory activity have been available for patients with RET-altered cancers. Clinical experience with these nonselective RET inhibitors has shown only modest activity in RET-mutant medullary thyroid carcinomas (MTC) and RET fusion-positive lung cancers. (7,8,9,10,11,12,13) Other MKIs approved for other indications (e.g. sorafenib) possess similar, non-selective anti-RET activity preclinically. (14) In part, this may be due to substantial “off-target” side-effects that limit the degree of RET-specific inhibition and lead to frequent dose reductions. Preliminary data suggests similar, moderate activity for MKIs with anti-RET activity in RET-fusion-positive lung cancer, with response rates of 16-53% (depending on the specific MKI and patient population), but progression free survival (PFS) of only 3.6–7.3 months, in several ongoing Phase 2 studies. (15,16,17,18)

The efficacy of these MKIs is ultimately limited by incomplete inhibition of RET in tumors in patients, significant toxicity from stronger inhibition of other targets (e.g., KDR/VEGFR2, EGFR, MET), and poor pharmacokinetics (PK) (i.e., significant drug accumulation and long half-life contributing to toxicity but not efficacy) in patients. As a result, the majority of patients treated with these agents experience significant toxicities requiring dose interruptions, reductions, and/or treatment cessation. Taken together, patient with RET fusion positive NSCLC represent a population with high unmet clinical need.

Selpercatinib (LOXO-292) is a novel, highly selective, ATP-competitive small molecule RET inhibitor. In contrast to MKIs, selpercatinib (LOXO-292) possesses nanomolar potency against diverse RET alterations (including anticipated acquired resistance mutations), high selectivity for RET, and favorable pharmacokinetic properties, including high bioavailability, predictable exposure, significant central nervous system (CNS) penetration, and a low potential for drug interaction. (19) Initial results from the first-in-human phase 1 clinical trial were presented at the American Society of Clinical Oncology (ASCO) Annual Meeting in 2018, were updated at the World Conference on Lung Cancer (WCLC) Annual Meeting in 2018 and are summarized below. (20) Patients with RET fusion-positive NSCLC represent a population with a high unmet need. Combination chemotherapy has short-term palliative potential in advanced NSCLC, while anti-programmed cell death protein 1 (anti-PD-1) monoclonal antibodies (e.g., nivolumab, pembrolizumab), which have recently been approved for NSCLC patients, may be less effective in tumors marked by single-gene driver oncogenic kinase alterations (including kinase fusions) with otherwise low mutational burdens and low neo-antigen production.

(21,22,23,24) **S1900B** seeks to examine and confirm the activity of selpercatinib (LOXO-292) in RET fusion-positive NSCLC patients.

Prevalence of RET Fusions in Lung Cancer:

The application of next-generation sequencing (NGS) approaches to a large collection of human tumors has led to the identification of RET gene fusions in a small fraction (1–2%) of non-small cell lung cancers (NSCLC, adenocarcinomas). (25)

Study Design:

The proposed sub-study of selpercatinib (LOXO-292) will be a prospective study to evaluate the clinical benefit of this specific RET inhibitor as a single agent in patients with NSCLC. Screening will include the Foundation Medicine panel as part of the screening conducted under the **LUNGMAP** protocol in tumor or molecular assays, as performed for clinical evaluation in the routine course of clinical care. Remaining biopsy tissue from patients who are enrolled based on the Foundation Medicine panel or based on locally available RET fusion results, will be used for central testing (retrospectively, post-enrollment) using the selpercatinib (LOXO-292) Companion Diagnostic (CDx) intended for the market. This is to allow a sensitivity analysis to be performed for the FMI tissue assay and other local tests used to recruit patients to the study by comparing the screening RET testing results with the selpercatinib (LOXO-292) CDx test.

New treatments for advanced RET fusion-positive NSCLC with progressive disease after chemotherapy, immune checkpoint blockade, or appropriate targeted therapies remains an acute area of unmet need. selpercatinib (LOXO-292) has demonstrated early evidence of marked anti-tumor activity in RET fusion-positive NSCLC with a response rate of 77% (95% CI 58-90%) with tolerable toxicity consisting of mostly grade 1-2 adverse events. (26) With additional follow up, a high response rate has been maintained, with most response ongoing for ≥ 6 months, including in the CNS, and irrespective of the number or types of prior therapies. (27) Therefore, it is anticipated that the proposed clinical trial will provide a robust evaluation of selpercatinib (LOXO-292) in patients with RET fusion-positive NSCLC.

A positive study could help to support approval(s) of this potent and selective RET inhibitor for RET fusion-positive NSCLC patients.

2.2 Rationale

The Lung-MAP study is a master protocol for genomic screening and multi-sub-study testing of drug/biomarker combinations in a Phase II/III setting compatible with subsequent Food and Drug Administration (FDA) approval. Genomic screening of a large patient resource provided by sites participating in the NCI National Clinical Trials Network (NCTN) identifies a series of molecular targets/biomarkers which are matched to new drugs, leading to appropriate sub-study assignment and drug treatment. Each molecular target in Lung-MAP is represented by a biomarker for which there is an analytically validated diagnostic assay. This approach provides the basis for this large-scale screening/clinical registration trial with the ability to screen patients, either through genomic analysis or immunohistochemistry-based assays, with homogeneous eligibility criteria and direct them to a sub-study based on the results of screening diagnostic tests.

Based on the results of the tumor analysis, patients will either be assigned to one of the biomarker-driven sub-studies or to a ‘non-match’ sub-study for patients with none of the eligibility biomarkers. The biomarker-driven sub-studies are designed around a genotypically-defined alteration in the tumor and a drug that targets it. The non-match studies are designed around an investigational agent with the potential for efficacy in a broader population. For a full description and justification of the study design, refer to the **LUNGMAP** Screening Protocol.

2.3 Clinical Data

Selpercatinib (LOXO-292) is currently being evaluated in Phase I/II clinical trials addressing RET fusion- positive cancers.

An overview of data from nonclinical and clinical studies of selpercatinib (LOXO-292) are provided below and described in detail in the selpercatinib (LOXO-292) Investigator's Brochure (IB). The global Phase I/II study (NCT0357128) for patients with advanced solid tumors included RET fusion+ NSCLC and papillary thyroid cancer (PTC), RET-mutant medullary thyroid cancer (MTC), and any other cancer with these alterations is enrolling patients at 21 sites in 7 countries. Patients were dosed orally in 28-day cycles. Dose escalation followed a 3+3 design. The primary endpoint of the Phase I part of the study was maximum tolerated dose (MTD) determination. Secondary endpoints included safety, overall response rate (ORR, RECIST 1.1) and duration of response (DoR). As of 02-April-18, 82 patients were treated at 8 doses (20 mg QD→240 mg BID), including 38 RET fusion+ NSCLC. Of the 38 RET fusion+ NSCLC patients, 30 had at least 1 post-baseline assessment or discontinued selpercatinib (LOXO-292) prior to post baseline assessment. 26 of 30 patients (87%) had >20% radiographic tumor reduction. The ORR was 77% (23/30, 3 responses pending confirmation) with a confirmed ORR of 74%. The response rate was similar regardless of prior multikinase inhibitor (MKI) treatment. Responses occurred independent of upstream partner when known (13/16 KIF5B vs 9/11non-KIF5B) and included patients with baseline brain metastases. (28,29) No dose limiting toxicities (DLTs) were observed. The MTD was not reached. Adverse Events (AEs) (≥10% of patients) were fatigue (20%), diarrhea (16%), constipation (15%), dry mouth (12%), nausea (12%) and dyspnea (11%); most were grade 1-2. Most AEs were grade 1 or 2 and not attributed to selpercatinib (LOXO-292). Two grade 3 treatment-related AEs have been described (tumor lysis syndrome and increased ALT). The median DoR was not reached (all responses ongoing, longest > 10 months+, ongoing). Rapid plasma clearance of RET variants was observed, with complete clearance by Day 15 in 10 of 17 (59%) patients with assessable baseline and Day 15 circulating tumor DNA (ctDNA). (30) In addition to these 82 patients, additional patients not eligible for the LOXO-RET-17001 study have been treated with selpercatinib (LOXO-292) monotherapy on FDA-allowed, IRB-approved single patient protocols, two are described in a recent publication. (31) A dose of 160 mg BID was selected for dose expansion.

These data were recently updated at the World Conference on Lung Cancer (WCLC, abstract ID 13922) in 2018. As of July 19, 2018, the ORR and confirmed ORR in the 38 RET fusion-positive NSCLC patient presented at American Society of Clinical Oncology (ASCO) was 68% (26/38 ORR and 25/37 confirmed ORR), including 4/4 confirmed intracranial responses in patients with measurable CNS lesions. With a median follow up of 8.5 months, 9.5 months for responding patients, 96% of responding patients remained on treatment, 92% (24/26) of response were ongoing, and 65% (17/26) of responses were 6 months or longer. The toxicity profile remained consistent with the highly selective drug design.

2.4 Inclusion of Women and Minorities and Planned Enrollment Report

This study was designed to include women and minorities but was not designed to measure differences of intervention effects. The anticipated accrual in the ethnicity/race and sex categories is shown in the table below.

DOMESTIC PLANNED ENROLLMENT REPORT					
Racial Categories	**Ethnic Categories**				**Total**
	Not Hispanic or Latino		**Hispanic or Latino**		
	Female	**Male**	**Female**	**Male**	
American Indian/ Alaska Native	0	0	0	0	0
Asian	1	2	0	0	3
Native Hawaiian or Other Pacific Islander	0	1	0	0	1
Black or African American	4	6	0	0	10
White	47	59	2	2	110
More Than One Race	0	0	0	0	0
Total	52	68	2	2	124

3.0 DRUG INFORMATION

Investigator Brochures

For information regarding Investigator Brochures, please refer to SWOG Policy 15.

For this sub-study, selpercatinib (LOXO-292) is investigational and is being provided under an IND held by SWOG. For INDs filed by SWOG, the protocol serves as the Investigator Brochure for the performance of the protocol. In such instance's submission of the protocol to the IRB should suffice for providing the IRB with information about the drug. However, in cases where the IRB insists on having the official Investigator Brochure from the company, requests may be submitted to the CTSU website by completing the CTSU Request for Clinical Brochure Form under the sub-study's abstract page > Documents > Pharmacy Tab.

3.1 Selpercatinib (LOXO-292) (NSC #812076) (IND 143217)

a. PHARMACOLOGY

Mechanism of Action: Selpercatinib (LOXO-292) is a selective inhibitor of the rearranged during transfection (RET) receptor tyrosine kinase (RTK). RET plays critical roles in normal organogenesis and in the maintenance of several adult tissue types, including neural, neuroendocrine, hematopoietic, and male germ cell. Selpercatinib (LOXO-292) has demonstrated potent in vitro and in vivo activity as a selective inhibitor of both wild-type and oncogenically activated RET, including RET fusions, "founder" mutations, and anticipated acquired resistant mutations.

b. PHARMACOKINETICS

1. Absorption: Tmax after oral administration of selpercatinib (LOXO-292) is approximately 2 hours.

2. Distribution: The mean Cmin (pre-dose, trough concentration) is approximately 600 ng/mL in patients during steady-state treatment with 60 mg BID selpercatinib (LOXO-292) or higher, which corresponds to a mean

plasma free drug concentration approximately equal to the IC90 for inhibition of RET.

3. Metabolism: The plasma half-life of selpercatinib (LOXO-292) is approximately 20 hours.

4. Elimination: Low concentrations of selpercatinib (LOXO-292) were recovered as unchanged drug in urine indicates that kidney contributes minimally to overall clearance.

c. ADVERSE EFFECTS

1. Adverse Effects: The Comprehensive Adverse Events and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements' http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf for further clarification.

Frequency is provided based on 882 patients. Below is the CAEPR for selpercatinib (LOXO-292).

Version 2.3, August 31, 2020[1]

Adverse Events with Possible Relationship to Selpercatinib (LOXO-292) (CTCAE 5.0 Term) [n= 882]		
Likely (> 20%)	**Less Likely (4 ≤ 20%)**	**Rare but Serious (≤ 3%)**
GASTROINTESTINAL DISORDERS		
	Abdominal pain	
	Constipation	
	Diarrhea	
Dry mouth		
	Nausea	
	Vomiting	
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS		
	Edema limbs	
	Fatigue	
IMMUNE SYSTEM DISORDERS		
		Allergic reaction[2]
INVESTIGATIONS		
Alanine aminotransferase increased[2]		
Aspartate aminotransferase increased[2]		
	Creatinine increased[2]	
	Electrocardiogram QT corrected	

Adverse Events with Possible Relationship to Selpercatinib (LOXO-292) (CTCAE 5.0 Term) [n= 882]		
Likely (> 20%)	**Less Likely (4 ≤ 20%)**	**Rare but Serious (≤ 3%)**
	interval prolonged	
	Platelet count decreased[2]	
	White blood cell decreased	
NERVOUS SYSTEM DISORDERS		
	Dysgeusia	
	Headache	
SKIN AND SUBCUTANEOUS TISSUE DISORDERS		
	Rash maculo-papular[2]	
VASCULAR DISORDERS		
Hypertension		

[1]This table will be updated as the toxicity profile of the agent is revised. Updates will be distributed to all Principal Investigators at the time of revision. The current version can be obtained by contacting PIO@CTEP.NCI.NIH.GOV Your name, the name of the investigator, the protocol and the agent should be included in the e-mail.

[2]Patients may experience an allergic reaction (hypersensitivity) to LOXO-292 which may manifest as a maculopapular rash often preceded by fever and associated myalgias/arthralgias typically between 7-21 days post administration. Additionally, platelet count decreased and/or alanine aminotransferase and aspartate aminotransferases decreased are often associated with the allergic reaction; however, less commonly hypotension, tachycardia, and creatinine increased may also be observed.

Adverse events reported on selpercatinib (LOXO-292) trials, but for which there is insufficient evidence to suggest that there was a reasonable possibility that selpercatinib (LOXO-292) caused the adverse event:

BLOOD AND LYMPHATIC SYSTEM DISORDERS – Anemia; Febrile neutropenia
CARDIAC DISORDERS - Cardiac disorders - Other (tachycardia)[2], Heart failure; Pericardial effusion
ENDOCRINE DISORDERS - Hypothyroidism
GASTROINTESTINAL DISORDERS – Abdominal distension; Dysphagia; Gastroesophageal reflux disease; Gastrointestinal disorders - Other (pneumatosis intestinalis); Mucositis oral; Retroperitoneal hemorrhage
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS – Chills; Fever
HEPATOBILIARY DISORDERS - Hepatobiliary disorders - Other (acute hepatitis)
INFECTIONS AND INFESTATIONS - Urinary tract infection

INVESTIGATIONS - Alkaline phosphatase increased; Blood bilirubin increased; Electrocardiogram T wave abnormal; Lymphocyte count decreased; Neutrophil count decreased; Weight gain
METABOLISM AND NUTRITION DISORDERS – Anorexia; Dehydration; Hyperkalemia; Hyperphosphatemia; Hypoalbuminemia; Hypocalcemia; Hypokalemia; Hypomagnesemia; Hyponatremia; Hypophosphatemia; Tumor lysis syndrome
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Arthralgia[2]; Back pain; Myalgia[2]
NERVOUS SYSTEM DISORDERS -Dizziness; Intracranial hemorrhage; Seizure
PSYCHIATRIC DISORDERS - Delirium; Insomnia; Psychiatric disorders - Other (mental status changes)
REPRODUCTIVE SYSTEM AND BREAST DISORDERS - Erectile dysfunction
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Cough; Dyspnea; Hypoxia; Oropharyngeal pain; Pneumonitis; Respiratory, thoracic and mediastinal disorders - Other (lung opacity); Voice alteration
SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Alopecia; Dry skin; Skin and subcutaneous tissue disorders - Other (drug eruption)
VASCULAR DISORDERS - Hypotension[2]

Note: Selpercatinib (LOXO-292) in combination with other agents could cause an exacerbation of any adverse event currently known to be caused by the other agent, or the combination may result in events never previously associated with either agent.

2. Pregnancy and Lactation: Effects on the ovaries, consisting of atrophy of the ovaries characterized by a reduced number or absence of corpora lutea, reduced number and size of follicles, and stromal proliferation were noted in the minipig.

   The effects of selpercatinib (LOXO-292) on sperm are not known. The testes were not a target organ in the rat or minipig. Male study participants should refrain from sperm donation during study treatment and up to 6 months following the last dose of selpercatinib (LOXO-292).

   Women study participants of reproductive potential and fertile men study participants 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).

   There are no clinical studies planned in pregnant women, and it is unknown whether selpercatinib (LOXO-292) or its metabolites are excreted in human milk. Selpercatinib (LOXO-292) must not be administered to pregnant or nursing females.

3. Drug Interactions:

   In-vitro, selpercatinib (LOXO-292) is primarily metabolized by CYP3A4, but not by CYP1A2, CYP2C8, CYP2C9, or CYP 2C19. Use of concomitant medications that are moderate or strong inhibitors or inducers of CYP3A4 are prohibited. Avoid concurrent use with other drugs with potential to lead to prolongation of QTc interval, if possible.

In vitro, selpercatinib (LOXO-292) showed no significant inhibition of CYP1A2, CYP2B6, CYP2C9, CYP2C19, or CYP2D6. Selpercatinib (LOXO-292) is a moderate inhibitor of CYP2C8 and a weak inhibitor of CYP3A4. Avoid use of concomitant medications that are sensitive substrates of CYP2C8 and CYP3A4.

Selpercatinib (LOXO-292) showed weak concentration-dependent induction of CYP1A2, CYP2B6 and CYP3A4 but at clinically relevant doses is not expected to alter pharmacokinetics of medications metabolized by these enzymes.

In vitro, selpercatinib (LOXO-292) is a substrate of transport proteins P-gp and BCRP, but is not a substrate for OAT1, OAT3, OCT1, OCT2, OATP1B1, OATP1B3, MATE1, or MATE2-K.

In vitro, selpercatinib (LOXO-292) inhibited MATE1 and is a weak inhibitor of OCT2, OATP1B1, OATP1B3, and BCRP. Selpercatinib (LOXO-292) did not inhibit OAT1, OAT3, OCT1, or BSEP.

Proton pump inhibitors (PPIs), H2 receptor antagonists and antacids may alter the pharmacokinetics of selpercatinib (LOXO-292) by reducing selpercatinib (LOXO-292) exposure. Concomitant use of PPIs during selpercatinib (LOXO-292) therapy is prohibited. PPIs are to be discontinued at least 1 week prior to the start of selpercatinib (LOXO-292) therapy. If H2 receptor antagonist use is necessary, administer only between 2 and 3 hours after selpercatinib (LOXO-292) administration. If antacid use is necessary, administer 2 or more hours before selpercatinib (LOXO-292) administration or 2 or more hours after selpercatinib (LOXO-292) administration.

Selpercatinib (LOXO-292) is 97% protein-bound in human plasma. Use caution when co-administered with other medications that are highly protein-bound.

d. DOSING & ADMINISTRATION

See Section 7.0 Treatment Plan.

1. Oral Capsules: Capsules are administered orally. Selpercatinib (LOXO-292) is administered twice daily, approximately 12 hours apart. Selpercatinib (LOXO-292) can be taken with or without food. Capsules are to be swallowed whole. Do not chew, crush or open capsules.

2. Late doses (i.e. 4 or more hours after scheduled time) should be noted in the patient diary. Doses that are late by more than 6 hours should be skipped and recorded in the patient diary as missed. Patients are encouraged to record the time of any histamine-2 (H2) blocking agents such as ranitidine (Zantac®), famotidine (Pepcid®), or cimetidine (Tagamet®), or antacids such as aluminum hydroxide/magnesium hydroxide/simethicone (Maalox®) or calcium carbonate (TUMS®), in relationship to each dose of selpercatinib (LOXO-292) in the patient diary (Appendix 18.4). Vomiting after dosing should be noted in the diary and should not be re-dosed or replaced.

e. HOW SUPPLIED

1. Selpercatinib (LOXO-292) is supplied by Loxo Oncology and distributed by the Pharmaceutical Management Branch (PMB).

2. Selpercatinib (LOXO-292) is supplied as two capsule strengths.

- 40 mg capsules are opaque grey, size 2, hard gelatin capsules containing 40 mg of selpercatinib (LOXO-292) (30% by weight) and the following inactive ingredients: microcrystalline cellulose (92 mg) and silicon dioxide (1.3 mg). Capsules are supplied in 60-count HDPE bottles with induction seals and child-resistant plastic caps.

- 80 mg capsules are opaque light blue, size 0, hard gelatin capsules containing 80 mg of selpercatinib (LOXO-292) (30% by weight) and the following inactive ingredients: microcrystalline cellulose (183.4 mg) and silicon dioxide (2.7 mg). Capsules are supplied in 120-count HDPE bottles with inductions seals and child-resistant plastic caps.

f. STORAGE, PREPARATION & STABILITY

1. Selpercatinib (LOXO-292) gelatin capsules are to be stored at controlled room temperature, 20-25°C (68-77°F), with excursions permitted between 15°C and 30°C (59 and 86°F).

2. Stability and Repackaging: Stability studies of the intact bottles are ongoing. It is recommended that selpercatinib (LOXO-292) capsules be dispensed in the original manufacturer's container. If capsules must be repackaged, they are to be repackaged from the manufacturer-supplied white HDPE bottle into a pharmacy-supplied white HDPE bottle for dispensing purposes.

In case of temperature excursion at the site outside of the storage range, complete the Site Storage Temperature Excursion Form (see Appendix 18.6) and email to rlewis@loxooncology.com. Study drug should be quarantined until further instruction is provided by Loxo Oncology.

All product complaints associated with material packaged, label, and release should be reported. The investigator or designee is responsible for reporting a complete description of the product complaint, via email to rlewis@loxooncology.com (see Appendix 18.6).

3.2 NCI-Supplied Agent Ordering and Agent Accountability

NCI-supplied agents may be requested by eligible participating Investigators (or their authorized designee) at each participating institution. The CTEP assigned protocol number (**S1900B**) must be used for ordering all CTEP supplied investigational agents. The eligible participating investigators at each participating institution must be registered with CTEP, DCTD through an annual submission of FDA Form 1572 (Statement of Investigator), NCI Biosketch, Agent Shipment Form, and Financial Disclosure Form (FDF). If there are several participating investigators at one institution, CTEP-supplied investigational agents for the study should be ordered under the name of one lead participating investigator at that institution.

Order Processing (OAOP) application. Access to OAOP requires the establishment of a CTEP Identity and Access Management (IAM) account and the maintenance of an "active"

account status, a "current" password, and active person registration status. For questions about drug orders, transfers, returns, or accountability, call or email PMB any time. Refer to the PMB's website for specific policies and guidelines related to agent management.

No starter supplies may be ordered. Patients must be enrolled and registered to protocol **S1900B** prior to order submission through OAOP.

Useful Links and Contacts

- CTEP Forms, Templates, Documents: http://ctep.cancer.gov/forms/
- NCI CTEP Investigator Registration (RCR) Help Desk: RCRHelpDesk@nih.gov
- PMB policies and guidelines: http://ctep.cancer.gov/branches/pmb/agent_management.htm
- PMB Online Agent Order Processing (OAOP) application:
- https://ctepcore.nci.nih.gov/OAOP/CTEP Identity and Access Management (IAM) account: https://ctepcore.nci.nih.gov/iam/index.jsp
- CTEP IAM account help: ctepreghelp@ctep.nci.nih.gov
- PMB e-mail: PMBAfterHours@mail.nih.gov

a. Drug Return and/or Disposition Instruction

1. Drug Returns: All unused drug supplies must be returned to the PMB. When it is necessary to return study drug (e.g., sealed vials remaining when expired vials are recalled by the PMB), investigators should return the study drug to the PMB using the NCI Return Agent Form available on the NCI home page (http://ctep.cancer.gov).

2. Drug Accountability: The investigator, or a responsible party designated by the investigator, must maintain a careful record of the receipt, disposition, and return of all drugs received from the PMB using the Drug Accountability Record Form available on the NCI home page (http://ctep.cancer.gov).

Questions about drug orders, transfers, returns or accountability should be addressed to the PMB by calling 240/276-6575 Monday through Friday between 8:30 am and 4:30 pm Eastern Time.

4.0 STAGING CRITERIA

Patients must have Stage IV or recurrent disease as outlined below (AJCC Cancer Staging Manual, 8th Edition, 2017):

Stage IVA	Any T	Any N	M1a
	Any T	Any N	M1b
Stage IVB	Any T	Any N	M1c

Primary Tumor (T)

TX	Primary tumor cannot be assessed, or tumor proven by the presence of malignant cells in sputum or bronchial washings but not visualized by imaging or bronchoscopy
T0	No evidence of primary tumor
Tis	Carcinoma in situ Squamous cell carcinoma in situ (SCIS)

Adenocarcinoma in situ (AIS): adenocarcinoma with pure lepidic pattern, ≤ 3 cm in greatest dimension

T1 Tumor ≤ 3 cm in greatest dimension, surrounded by lung or visceral pleura, without bronchoscopic evidence of invasion more proximal than the lobar bronchus (i.e., not in the main bronchus)

T1mi Minimally invasive adenocarcinoma: adenocarcinoma (≤ 3 cm in greatest dimension) with a predominantly lepidic pattern and ≤ 5 mm invasion in greatest dimension

T1a Tumor ≤ 1 cm in greatest dimension. A superficial, spreading tumor of any size whose invasive component is limited to the bronchial wall and may extend proximal to the main bronchus also is classified as T1a, but these tumors are uncommon.

T1b Tumor > 1 cm but ≤ 2 cm in greatest dimension

T1c Tumor > 2 cm but ≤ 3 cm in greatest dimension

T2 Tumor > 3 cm but ≤ 5 cm or having any of the following features:

- Involves the main bronchus regardless of distance to the carina, but without involvement of the carina
- Invades visceral pleura (PL1 or PL2)
- Associated with atelectasis or obstructive pneumonitis that extends to the hilar region, involving part or all of the lung

T2 tumors with these features are classified as T2a if ≤ 4 cm or if the size cannot be determined and T2b if > 4 cm but ≤ 5 cm.

T2a Tumor > 3 cm but ≤ 4 cm in greatest dimension

T2b Tumor >4 cm but ≤ 5 cm in greatest dimension

T3 Tumor > 5 cm but ≤ 7 cm in greatest dimension or directly invading any of the following: parietal pleural (PL3), chest wall (including superior sulcus tumors), phrenic nerve, parietal pericardium, or separate tumor nodule(s) in the same lobe as the primary

T4 Tumor > 7 cm or tumor of any size invading one or more of the following: diaphragm, mediastinum, heart, great vessels, trachea, recurrent laryngeal nerve, esophagus, vertebral body, or carina; separate tumor nodule(s) in an ipsilateral lobe different from that of the primary

Regional Lymph Nodes (N)

NX Regional lymph nodes cannot be assessed

N0 No regional lymph node metastases

N1 Metastasis in ipsilateral peribronchial and/or ipsilateral hilar lymph nodes and intrapulmonary nodes, including involvement by direct extension

N2 Metastasis in ipsilateral mediastinal and/or subcarinal lymph node(s)

N3 Metastasis in contralateral mediastinal, contralateral hilar, ipsilateral or contralateral scalene, or supraclavicular lymph node(s)

Distant Metastasis (M)

M0 No distant metastasis

M1 Distant metastasis

M1a Separate tumor nodule(s) in a contralateral lobe; tumor with pleural or malignant pleural or pericardial effusion. nodules or malignant pleural (or pericardial) effusion. **

M1b Single extrathoracic metastasis in a single organ (including involvement of a single nonregional node)

M1c Multiple extrathoracic metastases in a single organ or in multiple organs

** Most pleural (and pericardial) effusions with lung cancer are due to tumor. In a few patients, however, multiple microscopic examinations of pleural (pericardial) fluid are negative for tumor, and the fluid is non-bloody and is not an exudate. If these elements and clinical judgment dictate that the effusion is not related to the tumor, the effusion should be excluded as a staging descriptor.

5.0 ELIGIBILITY CRITERIA

Each of the criteria in the following section must be met in order for a patient to be considered eligible for registration in OPEN. Section 5 may be printed and used to by the site but is not to be uploaded in RAVE (unless specially stated). 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 SWOG SDMC 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.**

5.1 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 FoundationOne 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.

5.2 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.

5.3 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. Patients 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 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 0.7 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 ≤ 180 and DBP ≤ 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.

5.4 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.

5.5 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 Oncology Patient Enrollment Network (OPEN) registration process (see Section 13.0 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).

6.0 STRATIFICATION FACTORS

Not applicable for this study.

7.0 TREATMENT PLAN

For treatment or dose modification questions, please contact Dr. Yasir Elamin and Dr. Jhanelle Gray at S1900BMedicalQuery@swog.org. For dosing principles or questions, please consult the SWOG Policy #38 "Dosing Principles for Patients on Clinical Trials" at https://www.swog.org/sites/default/files/docs/2017-11/Policy38.pdf.

Initiation of treatment must be planned to start no more than 10 calendar days after sub-study registration.

7.1 Precautions

Concomitant Medications
Selpercatinib (LOXO-292) is a substrate of the CYP3A4 metabolic system; hence, concomitant use of moderate or strong CYP3A4 inhibitors and inducers is prohibited throughout protocol treatment. Selpercatinib (LOXO-292) is a substrate of transport proteins p-glycoprotein (Pgp) and BCRP. Use caution when co-administered with medications that are strong inhibitors or inducers of P-gp and BCRP. These enzymes and transport proteins may interact with over-the-counter, herbal, and prescription medications.

Selpercatinib (LOXO-292) moderately inhibits CYP2C8, weakly inhibits CYP3A4, and inhibits MATE1. Avoid use of concomitant medications that are sensitive substrates of CYP2C8 and CYP3A4. Use caution when co-administered with medications that are substrates of MATE1.

When concurrent use of an H2 blocking agent is necessary, e.g., ranitidine (Zantac®), famotidine (Pepcid®), or cimetidine (Tagamet®), it must be administered only between 2 and 3 hours after the dose of selpercatinib (LOXO-292). If not taken during this time, the dose of H2 blocking agents should not be taken again until 2–3 hours after the next dose of LOXO 292.

When concurrent use of an antacid is necessary, e.g., aluminum hydroxide/magnesium hydroxide/simethicone (Maalox®) or calcium carbonate (TUMS®), it must be administered 2 or more hours before and/or 2 or more hours after the dose of selpercatinib (LOXO-292). See Section 3.0 and Appendix 18.4.

Avoid medications known to prolong QT interval. Examples are available here: https://crediblemeds.org/pdftemp/pdf/CombinedList.pdf.

7.2 Pre-Medication and Supportive Care

Pre-medication associated with standard drug administration and supportive care (including anti-diarrheas, antibiotics, diuretics or other medications) may be given as indicated by the current American Society of Clinical Oncology (ASCO) guidelines.

Small volume, low dose palliative radiotherapy (≤ 20 Gy) for painful bone metastases is permitted, provided that no target lesions are encompassed, and the patient does not have progression as defined in Section 10.0. Delaying the next dose of protocol therapy by up to two weeks is permitted.

7.3 Disease Assessment

See Section 9.0 for disease assessment timepoints and Section 10.2 for more details on disease assessments. Submit scans as outlined in Section 14.0 and Section 15.0. Disease assessment timing is to be based on calendar timing counted as weeks after sub-study registration, not based on cycles or drug administration.

Disease Assessment During Treatment
CT or MRI (the same method used at pre-study to meet the eligibility criteria in Section 5.1) must be repeated every 8 weeks (± 7 day window), for the first year regardless of treatment delays, then every 12 weeks (± 7 day window) until disease progression and discontinuation of protocol treatment. The 8 weeks should start from sub-study registration. If the patient remains on protocol treatment after progression due to clinical benefit in the opinion of the treating investigator (per Section 7.5), scans must continue per protocol schedule until treatment is discontinued. If the patient is removed from protocol treatment prior to progression, scans must continue per protocol schedule until progression.

Pre-study Brain CT/MRI is required per Section 5.1. If patient has brain metastases at baseline, scans must use the same modality as baseline and be repeated every 8 weeks (± 7 days) for the first year regardless of treatment delays, then every 12 weeks (± 7 day window) while on treatment.

Disease Assessment During Off Protocol Treatment, Prior to Progression
After off protocol treatment prior to progression, disease assessments should continue every 12 weeks (± 7 day window) until progression.

If patient has brain metastases at baseline, continue brain CT or MRI scans (same modality as baseline) after off protocol treatment prior to progression, as clinically indicated. For alignment with the protocol and good clinical practice, recommended frequency of brain scans after off protocol treatment (and prior to progression) is at least every 12 weeks, unless more frequent scans are clinically appropriate.

7.4 General Treatment Instructions

Vital Sign Monitoring
Vitals for systolic and diastolic blood pressure, heart rate, respiratory rate, body temperature must be performed per drug safety monitoring at the following timepoints.

- Cycle 1 Days 1 and 8: up to 4 hours pre-dose (as close to dosing as possible)
- Cycle 2-6: up to 4 hours pre-dose (as close to dosing as possible)
- Every 12 weeks while on treatment or as clinically indicated: up to 4 hours pre-dose (as close to dosing as possible)

ECG QTcF Monitoring
A single ECG must be performed for all patients per eligibility (Section 5.3h). If clinically indicated, periodic monitoring of ECG while on treatment must be performed. For example, this includes patients at risk of developing QTc prolongation, including patients with long QT syndromes, clinically significant bradyarrhythmias, and severe or uncontrolled heart failure (NYHA Functional Classification Class III Moderate/IV Severe). See Section 8.3f for management of QTc prolongation.

Note: It has been observed that patients without risk factors can still have QTc prolongation.

7.5 Treatment – **S1900B**

For treatment or dose modification questions, please contact Dr. Elamin and Dr. Gray at S1900BMedicalQuery@swog.org.

a. Selpercatinib (LOXO-292)

Agent	Dose**	Route	Frequency	Schedule
Selpercatinib (LOXO-292)	120 mg (< 50kg) **OR** 160 mg (≥ 50kg)	PO	BID	Daily

* Note: One cycle = 28 calendar days regardless of dose delays.
Total daily dose = 320 mg.
** The dosage of selpercatinib is:

- 120 mg BID for patients with body weight <50 kg (total daily dose = 240 mg)
- 160 mg BID for patients with body weight ≥ 50 kg (total daily dose = 320 mg)

Patients will be instructed to:

- Ingest selpercatinib (LOXO-292) capsules approximately at the same time each day, twice a day, approximately 12 hours apart.
- Swallow capsules whole. Do not chew, crush or open capsules.
- Selpercatinib (LOXO-292) can be taken with or without food.
- Document doses that are 4 or more hours late than scheduled time in patient diary.
- Skip doses that are 6 or more hours late and record in patient diary as missed.
- Encouraged to record the time of any histamine-2 (H2) blocking agents or antacids in relationship to each dose in patient diary.
- If patient vomits, do not retake the dose. Record in patient diary.

7.6 Drug Compliance Documentation

Drug compliance will be recorded by patients in the Patient Diary (see Appendix 18.4). Institutional CRAs will review and ascertain patient adherence with protocol therapy at the end of treatment for each cycle. The Patient Diary should be kept in the patient's research chart. All sites ***must*** use the Patient Diary provided.

7.7 Criteria for Removal from Protocol Treatment

a. Progression of disease or symptomatic deterioration (as defined in Sections 10.2d and 10.2e). However, the patient may continue protocol treatment after progression if the patient is continuing to clinically benefit in the opinion of the treating investigator and the patient is not exposed to unreasonable risk (including absence of symptoms and signs indicating clinically significant progressive disease; no decline in Zubrod performance status; absence of rapid disease progression or threat to vital organs or critical anatomical sites [e.g., CNS metastasis, respiratory failure due to tumor compression, spinal cord compression] requiring urgent alternative medical intervention). Patients should still be removed from protocol treatment for criteria below.

   Patients must sign the **S1900B** Consent Addendum for post-progression treatment. Sites must obtain consent prior the start of the subsequent cycle.

   Upon progression, the Request for New Sub-Study Assignment Form may be submitted under the **LUNGMAP** screening protocol to receive a new sub-study assignment (see Section 14.4i).

b. Unacceptable toxicity.

c. Treatment delay for any reason > 28 days (or as noted in Section 8.0).

d. The patients may withdraw from the study at any time for any reason.

7.8 Discontinuation of Treatment

All reasons for discontinuation of treatment must be documented in the Off-Protocol Treatment Notice.

7.9 Follow-Up Period

All patients will be followed until death or 3 years after sub-study registration, whichever occurs first.

Note: Patients who enroll on a new sub-study following progression must continue follow-up on this sub-study (**S1900B**), in addition to follow-up on the new sub-study.

8.0 TOXICITIES TO BE MONITORED AND DOSE MODIFICATIONS

8.1 NCI Common Terminology Criteria for Adverse Events

This study will utilize the CTCAE (NCI Common Terminology Criteria for Adverse Events) Version 5.0 for toxicity and Serious Adverse Event reporting. A copy of the CTCAE Version 5.0 can be downloaded from the CTEP home page (http://ctep.cancer.gov). All appropriate treatment areas should have access to a copy of the CTCAE Version 5.0.

8.2 General Considerations

a. Missed doses (> 6 hours after the scheduled dose) are to be omitted rather than made up. Skip doses that are > 6 hours late.

b. If multiple toxicities are experienced, dose modifications will be based on the toxicity requiring the largest dose reduction.

c. Once dose is reduced, patients will continue at the new dose. Patients who tolerate selpercatinib (LOXO-292) for at least one cycle without a recurrent toxicity higher

than Grade 1 may be re-escalated after discussion with the Study Chair. Additional guidance is in Section 8.3.

d. A maximum of two dose reductions are allowed.

e. The maximum dose delay for any reason is 28 days.

See Section 7.4 for patient instructions.

8.3 Dose Modifications – Selpercatinib (LOXO-292)

Dose modifications should be made according to the following table.

DRUG	DOSE LEVEL	DOSE**	
Selpercatinib (LOXO-292)		(< 50 kg)	(≥50 kg)
	Full	120 mg BID	160 mg BID
	-1 Level	80 mg BID	120 mg BID
	-2 Level	40 mg BID	80 mg BID
	-3 Level	40 mg OD	40 mg BID
Permanently discontinue in participants unable to tolerate 3 dose reductions*			

* For some AEs (e.g. hypersensitivity and LFT increases), an alternative re-escalation strategy should be followed. Additional information is provided below.
**Dosage is based on body weight (See Section 7.5)

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a. Hypersensitivity Dose Interruptions and Modifications

Recommended actions are shown below.

If selpercatinib (LOXO-292) drug hypersensitivity is suspected, study drug should be withheld and treatment with steroids at 1 mg/kg prednisone (or equivalent) should be initiated. Upon resolution, selpercatinib (LOXO-292) may be resumed at a reduced dose of 40 mg BID while continuing steroids at the same dose. Hypersensitivity has recurred in some patients, typically at 3 to 6 hours following drug administration. Follow the guidelines below if hypersensitivity recurs:

- If recurrence is severe, selpercatinib (LOXO-292) should again be withheld.
- If recurrence is mild (e.g., isolated instances of rash or myalgias or low-grade fever), selpercatinib (LOXO-292) may be continued cautiously, together with treatment with supportive therapy (e.g., topical treatments, ibuprofen).
- After a minimum of 7 days at each dose (while continuing steroids at the same dose) and in the absence of clinically significant recurrent drug hypersensitivity, the dose of selpercatinib (LOXO-292) may be escalated sequentially to 80 mg BID, 120 mg BID, and 160 mg BID for participants with weight ≥ 50 kg and to 80 mg BID, and 120 mg BID for participants with weight < 50 kg. Once the patient has tolerated treatment for a minimum of 7 days at the final dose, steroids may be tapered slowly.

b. Hepatotoxicity Dose Interruptions and Modifications

If a patient experiences ≥Grade 3 elevated liver function test (LFT) increases, study drug should be withheld. Evaluation for potential alternative causes should be conducted (e.g., history of other hepatotoxic medications/substances, viral serologies, liver imaging) and laboratory tests should be conducted (e.g., alanine

aminotransferase, aspartate aminotransferase, alkaline phosphatase, total bilirubin). A repeat value 3 to 5 days after the initial finding of elevation of LFTs should be obtained to confirm the abnormality and to confirm if it is increasing or decreasing. Thereafter, LFTs should be monitored at least weekly until resolution to normal/baseline (depending on the clinical situation, resolution to Grade 1 if baseline is normal may be permitted with prior Study Chair approval). If the LFT abnormalities do not begin to resolve (or worsen) within 5 days of the AE, a hepatology consultation should be considered to evaluate the need for a liver biopsy.

Upon resolution, selpercatinib (LOXO-292) may be resumed at a reduced dose by 2 dose levels and monitor AST and ALT weekly until 4 weeks after reaching dose taken prior to the onset of grade 3 or 4 increased AST or ALT: Increase dose by 1 dose level after a minimum of 2 weeks without recurrence and then increase to dose taken prior to the onset of Grade 3 or 4 increased AST or ALT after a minimum of 4 weeks without recurrence.

c. Thrombocytopenia Dose Interruptions and Modifications

If a patient is discovered to have thrombocytopenia ≥Grade 3, study drug should be withheld and the patient should be evaluated for alternative causes (medications/substances, viral studies). A hematology consultation may be considered, as necessary, to understand the etiology and to consider a role for concomitant steroid therapy. The patient should undergo weekly complete blood count (CBC) testing until the event resolves and CBC level returns to normal/baseline. Upon recovery, the patient should resume selpercatinib (LOXO-292) at a reduced dose (e.g., 120 or 80 mg BID with weekly CBC surveillance for 1 full cycle). The Study Chair should be notified for consideration of concomitant steroid therapy and for further dose re-escalation.

d. Hypertension Dose Interruptions and Modifications

Hypertension is defined as:

- a sustained increase in blood pressure from baseline, as evidenced by ≥2 readings on ≥2 separate occasions, or
- a clinically significant elevation requiring acute treatment.

If hypertension occurs, study drug may be interrupted at the discretion of the investigator while:

- a new antihypertensive medication regimen is initiated, or
- a preexisting regimen is optimized to a reproducible reading of ≤140/90 mmHg.

If study drug is interrupted, it may be resumed at the same or a lower dose at the discretion of the investigator. In all cases, the patient should continue to undergo regular blood pressure monitoring to ensure adequate blood pressure control.

e. Interstitial Lung Disease and Pneumonitis Dose Interruptions and Modifications

If a patient presents with worsening respiratory symptoms that may be indicative of Interstitial Lung Disease (ILD), exclude other causes. For Grade 3 or 4 hold drug and if ILD is confirmed, discontinue. For Grade 1 or 2, consider a dose reduction to the next lower dose level.

f. QTc Prolongation Dose Interruptions, Modifications, and Management

If a patient is at risk of developing QTc prolongation, monitor QT interval. This includes patients with long QT syndromes, clinically significant bradyarrhythmias, and severe or uncontrolled heart failure (NYHA Functional Classification Class III Moderate/IV Severe). If ECG is clinically indicated, patients should be dosed in clinic to ensure accuracy of timing.

- If any ECG demonstrates QTcF 481-500 ms:
  - Obtain repeat ECG 2 hours (+/- 10 minutes) hours after dosing.
- If any ECG demonstrates QTcF >500 ms:
  - Obtain 2 additional ECGs (triplicate in total).
- If 2 of 3 ECGs demonstrate QTcF >500 ms:
  - Hold study drug.
  - Assess for other causes of QTcF prolongation (concomitant medications, electrolyte abnormalities).
  - Maintain serum potassium levels ≥ 4 meq/L (within normal range), magnesium and calcium levels within normal ranges.
  - When QTcF < 470 msec, resume study drug at one level reduced while performing continued ECG monitoring as above.

g. All Other General Dose Interruptions and Modifications

A patient who experiences a clinically significant AE (≥ Grade 3) other than those mentioned above may have selpercatinib (LOXO-292) dosing withheld to evaluate the AE and to allow for recovery (to Grade 1 or baseline level). Upon recovery, the patient may restart therapy if it is considered in his/her best interest to continue therapy and within the 28-day time limit. Upon restarting, the patient may have the dose reduced by at least 1 dose level.

8.4 Dose Modification Contacts

For treatment or dose modification questions, please contact Dr. Yasir Elamin and Dr. Jhanelle Gray at S1900BMedicalQuery@swog.org. For dosing principles or questions, please consult the SWOG Policy #38 "Dosing Principles for Patients on Clinical Trials" at https://www.swog.org/sites/default/files/docs/2017-11/Policy38.pdf.

8.5 Adverse Event Reporting Requirements

Please Note: This protocol utilizes Rave®/CTEP-AERS integration for expedited reporting of serious adverse events. To initiate an expedited report, you must first enter the event information on the appropriate adverse event reporting form in Rave®. If you have questions about this process, please contact the SAE Program Manager 210-614-8808 or email adr@swog.org.

The CTEP-AERS electronic reporting system “Help” feature has detailed instructions in the section "Submitting Reports for RAVE Users".

a. Definition and Purpose

Definition: Adverse event means any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. (FDA, 21 CFR 312.32). See Table 8.5 for definition of a Serious Adverse Event (SAE) and reporting requirements.

Adverse event data collection and reporting, which are required as part of every clinical trial, are done to ensure the safety of patients enrolled in the studies as well as those who will enroll in future studies using similar agents. Adverse events are

reported in a routine manner at scheduled times during a trial. (Directions for routine reporting are provided in Section 14.0.) Additionally, certain adverse events must be reported in an expedited manner to allow for more timely monitoring of patient safety and care. The following guidelines prescribe expedited adverse event reporting for this protocol.

b. Reporting method

This study requires that expedited adverse events be reported to SWOG Operations Office using the Cancer Therapy Evaluation Program Adverse Event Reporting System (CTEP-AERS). CTEP's guidelines for CTEP-AERS can be found at http://ctep.cancer.gov

NOTE: For this study, all adverse events requiring expedited reporting must initially be reported on the Adverse Event Form in the appropriate Treatment Cycle folder in Medidata Rave. The CTEP-AERS report must then be initiated directly from the Adverse Event Form in Medidata Rave. Do not initiate the CTEP-AERS report via the CTEP-AERS website.

c. When to report an event in an expedited manner

Some adverse events require 24-hour notification (refer to Table 8.5) via CTEP-AERS.

In the rare event when internet connectivity is disrupted a 24-hour notification is made to SWOG by telephone at 210-614-8808 or by email adr@swog.org . An electronic report MUST be submitted immediately upon re-establishment of internet connection.

When the adverse event requires expedited reporting, submit the report via CTEP-AERS within the number of calendar days of learning of the event specified in Table 8.5.

d. Other recipients of adverse event reports

The SWOG Operations Office will forward reports and documentation to the appropriate regulatory agencies and drug companies as required.

Adverse events determined to be reportable to the Institutional Review Board responsible for oversight of the patient must be reported according to local policy and procedures.

Copies of all adverse event reports submitted to the FDA should be forwarded electronically to CTEPSupportAE@tech-res.com with the protocol number in the subject line.

e. **Expedited reporting for investigational agents**

Expedited reporting is required if the patient has received at least one dose of the investigational agent(s) as part of the trial. Reporting requirements are provided in Table 8.5. The investigational agent used in this study is selpercatinib (LOXO-292).

If there is any question about the reportability of an adverse event or if on-line CTEP-AERS cannot be used, please telephone or email the SAE Specialist at the Operations Office, 210/614-8808 or adr@swog.org, before preparing the report.

NOTE: For this study, all adverse events requiring expedited reporting must initially be reported on the Adverse Event Form in the appropriated Treatment Cycle folder in Medidata Rave. Once the adverse event is entered into RAVE, the Rules Engine will confirm whether or not the adverse event requires expedited reporting. The CTEP-AERS report must then be initiated directly from the Adverse Event Form in Medidata Rave. Do not initiate the CTEP-AERS report via the CTEP-AERS website. Sites are encouraged to confirm the Expedited Reporting Evaluation Recommendation with the reporting criteria outlined in Table 8.5.

Table 8.5:
Late Phase 2 and Phase 3 Studies: Expedited Reporting Requirements for Adverse Events that Occur on Studies under a Non-CTEP IND within 30 Days of the Last Administration of the Investigational Agent/Intervention selpercatinib (LOXO-292)[1]:

FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)
NOTE: Investigators **MUST** immediately report to the sponsor (NCI) **ANY** Serious Adverse Events, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64)

An adverse event is considered serious if it results in **ANY** of the following outcomes:

1) Death
2) A life-threatening adverse event
3) An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours
4) A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
5) A congenital anomaly/birth defect.
6) Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. (FDA, 21 CFR 312.32; ICH E2A and ICH E6).

ALL SERIOUS adverse events that meet the above criteria **MUST** be immediately reported to the NCI via CTEP-AERS within the timeframes detailed in the table below.

<table>
<tr><th>Hospitalization</th><th>Grade 1 Timeframes</th><th>Grade 2 Timeframes</th><th>Grade 3 Timeframes</th><th>Grade 4 & 5 Timeframes</th></tr>
<tr><td>Resulting in Hospitalization ≥ 24 hrs.</td><td colspan="3">10 Calendar Days</td><td rowspan="2">24-Hour 5 Calendar Days</td></tr>
<tr><td>Not resulting in Hospitalization ≥ 24 hrs.</td><td colspan="2">Not required</td><td>10 Calendar Days</td></tr>
</table>

Expedited AE reporting timelines are defined as:

- "24-Hour; 5 Calendar Days" - The AE must initially be reported via CTEP-AERS within 24 hours of learning of the AE, followed by a complete expedited report within 5 calendar days of the initial 24-hour report.

- "10 Calendar Days" - A complete expedited report on the AE must be submitted within 10 calendar days of learning of the AE.

[1]Serious adverse events that occur more than 30 days after the last administration of investigational agent/intervention and have an attribution of possible, probable, or definite require reporting as follows:

Expedited 24-hour notification followed by complete report within 5 calendar days for:

- All Grade 4, and Grade 5 AEs

Expedited 10 calendar day reports for:

- Grade 2 adverse events resulting in hospitalization or prolongation of hospitalization
- Grade 3 adverse events

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f. **Additional Instructions or Exceptions to CTEP-AERS Expedited Reporting Requirements for Late Phase 2 and Phase 3 Studies Utilizing an Agent under a non-CTEP-IND:**

1. **Group-specific instructions.**

   Supporting Documentation Submission - Within 5 calendar days submit documentation supporting the CTEP-AERS report to the SWOG Operations Office by fax to 210/614-0006. Specific instructions will be sent by email to the reporting site by the SAE Program Manager.

2. The adverse events listed below also require expedited reporting via CTEP-AERS for this trial:

   - Any grade hypersensitivity reactions
   - Grade 3 or higher LFT increases

g. **Reporting Secondary Malignancy, including AML/ALL/MDS**

1. A secondary malignancy is a cancer caused by treatment for a previous malignancy (e.g., treatment with investigational agent/intervention, radiation or chemotherapy). A secondary malignancy is not considered a metastasis of the initial neoplasm.

   SWOG requires all secondary malignancies that occur following treatment with an agent under a Non-NCI IND to be reported via CTEP-AERS. Three options are available to describe the event.

   - Leukemia secondary to oncology chemotherapy (e.g., Acute Myelocytic Leukemia [AML])
   - Myelodysplastic syndrome (MDS)
   - Treatment-related secondary malignancy

   Any malignancy possibly related to cancer treatment (including AML/MDS) should also be reported via the routine reporting mechanisms outlined in each protocol.

2. A second malignancy is one unrelated to the treatment of prior malignancy (and is NOT a metastasis from the initial malignancy). For this protocol, second malignancies also require expedited reporting via CTEP-AERS.

For more information see:
http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf

3. Supporting documentation should be submitted to CTEP in accordance with instructions provided by the CTEP-AERS system. Supporting documentation must also be submitted to SWOG Operations Office by fax to 210-614-0006.

   NOTE: If a patient has been enrolled in more than one NCI-sponsored study, the report must be submitted for the most recent trial.

h. **Reporting Serious Adverse Events to Loxo**

SWOG Operations will forward reports of all serious adverse events and events of overdose (defined as any dose above the protocol-specified dose of selpercatinib (LOXO-292)) associated with an SAE **within 24 hours** of NCI/CTEP receipt of serious adverse event documentation from the study site.

i. **Reporting Pregnancy, Pregnancy Loss, and Death Neonatal**

1. **Pregnancy** Study participants who become pregnant while on study; that pregnancy should be reported in an expedited manner via CTEP-AERS as **Grade 3 "Pregnancy, puerperium and perinatal conditions – Other (pregnancy)"** under the **Pregnancy, puerperium and perinatal conditions** SOC.

   Additionally, the pregnancy outcome for patients on study should be reported via CTEP-AERS at the time the outcome becomes known, accompanied by the same Pregnancy Report Form used for the initial report.

2. **Pregnancy Loss Pregnancy** loss is defined in CTCAE as "Death in utero." Pregnancy loss should be reported expeditiously as **Grade 4 "Pregnancy loss" under the Pregnancy, puerperium and perinatal conditions** SOC.

   A Pregnancy loss should **NOT** be reported as a Grade 5 event under the Pregnancy, puerperium and perinatal conditions SOC, as currently CTEP-AERS recognizes this event as a patient death.

3. **Death Neonatal Death** neonatal is defined in CTCAE as "Newborn death occurring during the first 28 days after birth. A neonatal death should be reported expeditiously as **Grade 4 "Death neonatal"** under the **General disorders and administration** SOC.

   Neonatal death should **NOT** be reported as a Grade 5 event under the General disorders and administration SOC as currently CTEP-AERS recognizes this event as a patient death.

NOTE: When submitting CTEP-AERS reports for "Pregnancy, "Pregnancy loss", or "Neonatal loss", the Pregnancy Information Form should also be completed and faxed with any additional medical information to 210/614-0006. The potential risk of exposure of the fetus to the investigational agent(s) or chemotherapy agent(s) should be documented in the "Description of Event" section of the CTEP-AERS report.

The Pregnancy Information Form is available at:
http://ctep.cancer.gov/protocolDevelopment/adverse_effects.htm.

9.0 STUDY CALENDAR

9.1 Selpercatinib (LOXO-292)

NOTE: The study calendar is a good tool for a general snapshot of study requirements but does not replace details provided in the relevant sections of the protocol. Use the study calendar in conjunction with the detailed procedures and information in the protocol but not as the sole or primary source for managing this trial.

REQUIRED STUDIES	Pre-Reg (w/in 28 days prior to registration, unless otherwise noted)	Cycle Length = 28 days (+/- 3 days)					At Off Tx	Off Tx FU Prior to Prog	Off Tx FU After Prog [2]
		Cycle 1	Cycle 2	Cycle 3	Cycle 4	Subsequent Cycles [1]			
PHYSICAL									
History & Physical Exam	X	X	X	X	X	X	X	X [3]	
Vital Signs [4]		X (days 1 & 8)	X	X	X	X			
12-lead ECG [4]	X	X							
Weight & Performance Status	X	X	X	X	X	X	X	X [3]	
Patient Diary [6]		X	X	X	X	X			
Toxicity Notation		X	X	X	X	X	X	X [7]	X [7]
Smoking Status Assessment	X						X		
LABORATORY									
	If labs obtained w/in 14 days prior to tx, tests need not be repeated on C1D1.	Results up to 48 hours prior to Day 1 tx							
CBC/Diff/Platelets/ Hgb	X	X	X	X	X	X	X	X [7]	X [7]
Chemistry Panel [8]	X	X	X	X	X	X	X	X [7]	X [7]
Urinalysis for protein [9]	X	X							
Hepatitis B/C viral load test [14]	X (within 28 days)								
HIV viral load test [15]	X (within 6 months)								
Serum Pregnancy Test [16]	X								

REQUIRED STUDIES	Pre-Reg (w/in 28 days prior to registration, unless otherwise noted)	Cycle Length = 28 days (+/- 3 days)					At Off Tx	Off Tx FU Prior to Prog	Off Tx FU After Prog [2]
		Cycle 1	Cycle 2	Cycle 3	Cycle 4	Subsequent Cycles [1]			
X-RAYS & SCANS									
CT or MRI for Disease Assessment [5]	X [5]			X [5]		X [5]		X [5]	
Brain CT or MRI	X [10]			X [10]		X [10]		X [10]	
SPECIMEN SUBMISSION									
ctDNA Whole Blood		X [12] (pre-tx)					X [12] (first progression & off treatment)		
Buffy Coat /Plasma for Banking [13]	X		X [13]	X [13]	X [13]		X [13] (first progression)		
TREATMENT (28-day cycle)									
selpercatinib (LOXO-292)		X	X	X	X	X			

NOTE: Forms are found on the protocol abstract page on the SWOG website (www.swog.org) and on the CTSU website (www.ctsu.org). Forms submission guidelines are found in Section 14.0.

NOTE: Unless indicated otherwise in the protocol, scheduled procedures and assessments (treatment administration, toxicity assessment for continuous treatment, disease assessment, specimen collection and follow-up activities) must follow the established SWOG guidelines on the allowed protocol visits/treatment window as outlined in https://www.swog.org/sites/default/files/docs/2017-10/Best%20Practices%20upddate.pdf. SWOG Best Practices allows for a +/- 3-day window for 28-day cycles.

Footnotes for Calendar 9.1 (selpercatinib (LOXO-292):

[1] During continued treatment, items marked under physical and laboratory should be performed prior to every subsequent cycle, unless otherwise noted. Disease assessments and image submission are to take place every 8 weeks (± 7 days) regardless of treatment delays. Treatment and evaluation will continue until any one of the criteria in Section 7.7 is met. If the patient remains on protocol treatment after progression due to clinical benefit (per Section 7.7), treatment schedule must continue per protocol.

[2] After off treatment after progression, follow-up will occur (with lab tests and scans performed at the discretion of the treating physician) every 6 months for 2 years then at end of 3 years from date of sub-study registration. Note: Patients who enroll on a new sub-study following progression must continue follow-up on this sub-study, in addition to follow-up on the new sub-study.

[3] After off treatment prior to progression, patients should be followed by repeating indicated studies every 12 weeks or more often as clinically indicated until progression. Disease assessments should continue every 12 weeks until progression.

[4] An ECG at pre-registration is required for all patients. If clinically indicated, periodic monitoring of ECG while on treatment must be performed. See Section 5.3h, Section 7.4, and Section 8.3f for details and examples.

[5] CT or MRI (the same method used at pre-study to meet the eligibility criteria in Section 5.1) must be repeated every 8 weeks (± 7 day window) for the first year, regardless of treatment delays, then every 12 weeks until disease progression and discontinuation of protocol treatment. The 8 weeks should start from sub-study registration. Submit scans as outlined in Section 14.0 and Section 15.0. If the patient remains on protocol treatment after progression due to clinical benefit (per Section 7.7), scans must continue per protocol schedule until treatment is discontinued. If the patient is removed from protocol treatment prior to progression, scans must continue per protocol schedule until progression.

[6] The CRA will review the Patient Diary at the end of each cycle (see Appendix 18.4).

[7] Assessments should continue if clinically indicated and until resolution of all acute adverse events.

[8] Chemistry panel (non-fasting) must include electrolytes (sodium, potassium, chloride, bicarbonate, calcium), creatinine, BUN, LFTs (ALT, AST), and serum bilirubin. Liver function tests are required on Day 1 and Day 15 of Cycles 1, 2, and 3, then at each subsequent Cycle as clinically indicated. If ALT/AST elevation of ≥ Grade 3, monitor liver function tests weekly until resolution to ≤ Grade 1.

[9] Urinalysis for protein is to be collected only if clinically indicated.

[10] Brain CT or MRI is required per Section 5.1. If patient has brain metastases at baseline, brain scans must use the same modality as baseline and be repeated every 8 weeks (± 7 days) for the first year regardless of treatment delays, then every 12 weeks (± 7 day window) while on treatment. If patient has brain metastases at baseline, continue brain CT or MRI scans (same modality as baseline) after off protocol treatment prior to progression, as clinically indicated. For alignment with the protocol and good clinical practice, recommended frequency of brain scans after off protocol treatment (and prior to progression) is at least every 12 weeks, unless more frequent scans are clinically appropriate.

[11] This footnote has been removed.

[12] See Section 15.4. Note: Kits must be ordered and will take up to 3 days to arrive.

[13] With patient's consent, additional research blood draws will be collected per Section 15.5 .

[14] See Section 5.1 for details.

[15] See Section 5.1 for details.

[16] For persons of child-bearing potential, as defined in Section 5.3n.

10.0 CRITERIA FOR EVALUATION AND ENDPOINT ANALYSIS

10.1 Measurability of Lesions

a. **Measurable disease**: Measurable disease is defined differently for lymph nodes compared with other disease and will be addressed in a separate section below.

1. Lesions that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥ 2.0 cm by chest x-ray, by ≥ 1.0 cm with CT or MRI scans, or ≥ 1.0 cm with calipers by clinical exam. All tumor measurements must be recorded in decimal fractions of centimeters (or millimeters).

   The defined measurability of lesions on CT scan is based on the assumption that CT slice thickness is 0.5 cm or less. It is strongly recommended that CT slice of 0.5 cm be used. If CT scans have slice thickness greater than 0.5 cm, the minimum size for a measurable lesion should be twice the slice thickness.

2. Malignant lymph nodes are to be considered pathologically enlarged and measurable if it measures ≥ 1.5 cm in **SHORT AXIS** (greatest diameter perpendicular to the long axis of the lymph node) when assessed by scan (CT scan slice recommended being no greater than 0.5 cm).

b. **Non-measurable disease**: All other lesions (or sites of disease), including small lesions (longest diameter < 1.0 cm or pathologic lymph nodes with ≥ 1.0 cm to < 1.5 cm short axis), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonitis, inflammatory breast disease, and abdominal masses (not followed by CT or MRI), are considered as non-measurable as are previously radiated lesions that have not progressed.

c. **Notes on measurability**

1. For CT and MRIs, the same type of scanner should be used, and the image acquisition protocol should be followed as closely as possible to prior scans. It is no longer necessary to distinguish between spiral and conventional CT.

2. Body scans should be performed with breath-hold scanning techniques, if possible.

3. PET-CT: At present, the low dose or attenuation correction CT portion of a PET-CT is not always of optimal diagnostic CT quality for use with RECIST measurements. However, if the site can document that the CT performed as part of a PET-CT is of identical diagnostic quality to a diagnostic CT, then the CT portion of the PET-CT can be used for RECIST measurements and can be used interchangeably with stand-alone CT. *The slice thickness of 0.5 cm or less is highly recommended*. If CT scans have slice thickness > 0.5 cm, the minimum size for a measurable lesion should be twice the slice thickness.

4. Ultrasound: Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement.

5. Cystic lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition simple cysts.

6. If a target lesion becomes very small some radiologists indicate that it is too small to measure. If the lesion is actually still present, a default measurement of 0.5 cm should be applied. If the radiologist believes the lesion has gone, a default measurement of 0.0 cm should be recorded.

10.2 Objective Status at Each Disease Evaluation

Objective Status is to be recorded at each evaluation. All measurable lesions up to a maximum of 2 lesions per organ, 5 lesions in total, representative of all involved organs, should be identified as ***target*** lesions at baseline. All other lesions (or sites of disease) including any measurable lesions over and above the 5 target lesions should be identified as ***non-target*** lesions. Measurements must be provided for target measurable lesions, while presence or absence must be noted for non-target measurable and non-measurable disease.

For studies that use disease progression as an endpoint, all potential sites of metastases should be evaluated at each time point rather than following only sites of disease identified at baseline. It is acceptable to image only the areas of the body most likely to be involved with metastatic disease for the tumor type (chest, abdomen, pelvis, and/or bone scan are typical), with the addition of any areas with suspected involvement based upon clinical symptoms. For study-specific imaging requirements, see the Study Calendar in Section 9.0.

a. **Complete Response (CR)**: Complete disappearance of all target and non-target lesions (with the exception of lymph nodes mentioned below). No new lesions. No disease related symptoms. Any lymph nodes (whether target or non-target) must have reduction in short axis to < 1.0 cm. All disease must be assessed using the same technique as baseline.

b. **Partial Response (PR)**: Applies only to patients with at least one measurable lesion. Greater than or equal to 30% decrease under baseline of the sum of appropriate diameters of all target measurable lesions. No unequivocal progression of non-measurable disease. No new lesions. All target measurable lesions must be assessed using the same techniques as baseline.

c. **Stable**: Does not qualify for CR, PR, Progression or Symptomatic Deterioration. All target measurable lesions must be assessed using the same techniques as baseline.

d. **Progression**: One or more of the following must occur: 20% increase in the sum of appropriate diameters of target measurable lesions over smallest sum observed (over baseline if no decrease during therapy) using the same techniques as baseline, as well as an absolute increase of at least 0.5 cm. Unequivocal progression of non-measurable disease in the opinion of the treating physician (an explanation must be provided). Appearance of any new lesion/site. Death due to disease without prior documentation of progression and without symptomatic deterioration (see 10.2e).

Notes on progression and new lesions:

1. For equivocal findings of progression (e.g. very small and uncertain new lesions; cystic changes or necrosis in existing lesions), treatment may continue until the next scheduled assessment. If at the next scheduled

assessment, progression is confirmed, the date of progression should be the earlier date when progression was suspected.

2. FDG-PET imaging can complement regular scans in identifying new lesions according to the following algorithm.
    - Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of progression based on a new lesion.
    - No FDG-PET at baseline and a positive FDG-PET at follow-up corresponding to a potential new site of disease must have a confirmation by anatomical assessment (e.g. CT, MRI, x-ray) as new site of disease to be considered progressive disease. In such a case, the date of progressive disease will be the date of the initial abnormal FDG-PET.

3. A previous abnormal target lymph node that became normal and subsequently enlarged in size meeting the criteria for a pathologic and measurable lymph node (a short axis of ≥ 1.5 cm) should be added to the sum of diameters to determine if criteria for progression are met based on target lesions.

4. A previously abnormal non-target lymph node that became normal and subsequently recurred must meet the criteria for progression based on non-target lesions to be considered progression.

5. A normal lymph node at baseline (<1.0 cm) that subsequently becomes pathologic is considered a new lesion and should be considered progression.

6. If a single pathologic lymph node is driving the progression event, continuation of treatment/follow-up and confirmation by a subsequent exam should be contemplated. If it becomes clear that the new lymph node has not resolved, or has increased in size, the date of progression would be the date the new lymph node was first documented.

e. **Symptomatic deterioration**: Global deterioration of health status requiring discontinuation of treatment without objective evidence of progression. Efforts should be made to obtain objective evidence of progression after discontinuation.

f. **Assessment inadequate, objective status unknown**: Progression or symptomatic deterioration has not been documented, and one or more target measurable lesions have not been assessed or inconsistent assessment methods were used.

Objective status notes:

1. Non-measurable and non-target measurable disease do not affect Objective Status in determination of CR (must be absent--a patient who otherwise has a CR, but who has non-measurable or non-target measurable disease present or not assessed, will be classified as having a PR). However, non-measurable and non-target lesions are included in determination of progression (if new sites of disease develop or if unequivocal progression occurs in the opinion of the treating physician).
2. An objective status of PR or stable cannot follow one of CR. Stable can follow PR only in the rare case that tumor increases too little to qualify as progression, but enough that a previously documented 30% decrease no longer holds.
3. In cases for which initial flare reaction is possible (hypercalcemia, increased bone pain, erythema of skin lesions), objective status is not

progression unless either symptoms persist beyond 4 weeks or there is additional evidence of progression.

4. Lesions that appear to increase in size due to presence of necrotic tissue will not be considered to have progressed.
5. For bone disease documented on bone scan only, increased uptake does not constitute unequivocal progression. However, increase in the soft tissue component of a lesion as measured by CT or MRI would constitute progression.
6. Appearance of new pleural effusions does not constitute unequivocal progression unless cytologically proven of neoplastic origin, since some effusions are a toxicity related to therapy or other medical conditions. Increase in the size of an existing effusion does not constitute unequivocal progression, since the fluid status of the patient could alter the size of the effusion.
7. If CR determination depends on a lesion for which the status is unclear by the required tests, it is recommended the residual lesion be investigated with biopsy or fine needle aspirate.
8. Lymph nodes are considered one organ. Only two lymph nodes should be selected as target lesions. Other involved lymph nodes should be assessed and followed as non-target lesions.
9. "Paired" organs, i.e. lungs, kidneys and ovaries, are considered one organ.
10. Pleural-based lung lesions are considered part of the lung in determining target lesions (a maximum of two lung lesions should be selected), whereas pleural effusions/thickening can be reported as a separate site.

10.3 Best Response

This is calculated from the sequence of objective statuses.

a. **CR**: Two or more objective statuses of CR a minimum of four weeks apart documented before progression or symptomatic deterioration.

b. **PR**: Two or more objective statuses of PR or better a minimum of four weeks apart documented before progression or symptomatic deterioration, but not qualifying as CR.

c. **Unconfirmed CR**: One objective status of CR documented before progression or symptomatic deterioration but not qualifying as CR or PR.

d. **Unconfirmed PR**: One objective status of PR documented before progression or symptomatic deterioration but not qualifying as CR, PR or unconfirmed CR.

e. **Stable/no response**: At least one objective status of stable/no response documented at least 8 weeks after registration and before progression or symptomatic deterioration, but not qualifying as anything else above.

f. **Increasing disease**: Objective status of progression within 12 weeks of registration, not qualifying as anything else above.

g. **Symptomatic deterioration**: Objective status of symptomatic deterioration within 12 weeks of registration, not qualifying as anything else above.

h. **Inadequate assessment, response unknown**: Progression or symptomatic deterioration greater than 12 weeks after registration and no other response category applies.

10.4 Performance Status

Patients will be graded according to the Zubrod Performance Status Scale.

POINT	DESCRIPTION
0	Fully active, able to carry on all pre-disease performance without restriction.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework, office work.
2	Ambulatory and capable of self-care but unable to carry out any work activities; up and about more than 50% of waking hours.
3	Capable of limited self-care, confined to bed or chair more than 50% of waking hours.
4	Completely disabled; cannot carry on any self-care; totally confined to bed or chair.

10.5 Time to Death

From date of sub-study registration to date of death due to any cause. Patients last known to be alive are censored at date of last contact.

10.6 Investigator-Assessed Progression-Free Survival

From date of sub-study registration to date of first documentation of progression assessed by local review or symptomatic deterioration (as defined above), or death due to any cause. Patients last known to be alive without report of progression are censored at date of last disease assessment. For patients with a missing scan (or consecutive missing scans) whose subsequent scan determines progression, the expected date of the first missing scan (as defined by the disease assessment schedule) will be used as the date of progression.

10.7 Progression-Free Survival by Blinded Independent Central Review (BICR)

From date of sub-study registration to date of first documentation of progression assessed by BICR or symptomatic deterioration (as defined above), or death due to any cause. Patients last known to be alive without report of progression are censored at date of last disease assessment. For patients with a missing scan (or consecutive missing scans) whose subsequent scan determines progression, the expected date of the first missing scan (as defined by the disease assessment schedule) will be used as the date of progression.

10.8 Duration of Investigator-Assessed Response (IA-DoR)

From date of first documentation of confirmed response (CR or PR) to date of first documentation of progression assessed by local review or symptomatic deterioration (as defined above), or death due to any cause among patients who achieve a response (CR or PR). Patients last known to be alive without report of progression or symptomatic deterioration are censored at date of last disease assessment. For patients with a missing scan (or consecutive missing scans) whose subsequent scan determines progression, the expected date of the first missing scan (as defined by the disease assessment schedule) will be used as the date of progression.

10.9 Duration of BICR Response (BICR-DoR)

From date of first documentation of confirmed response (CR or PR) to date of first documentation of progression assessed by BICR or symptomatic deterioration (as defined above), or death due to any cause among patients who achieve a response (CR or PR). Patients last known to be alive without report of progression or symptomatic deterioration are censored at date of last disease assessment. For patients with a missing scan (or consecutive missing scans) whose subsequent scan determines progression, the expected date of the first missing scan (as defined by the disease assessment schedule) will be used as the date of progression.

10.10 Central-nervous System Response (CNS-response)

Best response of confirmed CR or PR as defined in 10.2a, 10.2b, and 10.3, taking into consideration target and non-target disease within the central nervous system (CNS) to with no evidence of progressive disease (10.2d) outside of the CNS or symptomatic deterioration (10.2f).

10.11 Duration of CNS Response (CNS-DoR)

From date of first documentation of CNS-response to date of first documentation of progression (CNS or non-CNS) assessed by local review or symptomatic deterioration (as defined above), or death due to any cause among patients who achieve a CNS-response. CNS-DoR for patients last known to be alive without report of progression or symptomatic deterioration is censored at date of last disease assessment. For patients with a missing scan (or consecutive missing scans) whose subsequent scan determines progression, the expected date of the first missing scan (as defined by the disease assessment schedule) will be used as the date of progression.

11.0 STATISTICAL CONSIDERATIONS

11.1 Analysis Populations

The primary analysis population (PAP) will include all eligible patients evaluable for response by blinded independent centralized review (BICR) who receive at least one dose of selpercatinib (LOXO-292).

The safety analysis population (SAP) will include all eligible patients who receive at least one dose of selpercatinib (LOXO-292).

11.2 Sample Size with Power Justification

The primary objective is to evaluate the response rate for selpercatinib (LOXO-292) among patients in the primary analysis population. Patients with a confirmed CR or PR by BICR as defined in Section 10, will be coded as responders. Patients not known to have a response will be coded as non-responders.

As the goal of this study is to be confirmatory of the on-going study being conducted by LOXO, the design of this study is based on ruling out the historical response rate based on 95% 2-sided exact confidence interval boundaries. The accrual goal for this study is 100 patients in the PAP. With 100 patients, the BICR response rate can be estimated to within 10% with 95% confidence. As such, the following table describes the BICR response rate ruled out (based on the lower bound of a 95% CI).

Number of observed responses	Estimated Response Rate	Exact 95% Confidence Bounds	
		Lower	Upper
40	40%	30%	50%
50	50%	40%	60%
60	60%	50%	70%
70	70%	60%	79%

We note that the LIBRETTO-001 study was designed to rule out a 30% response rate, and the observation of at least 40 responses out of 100 patients would be considered evidence to rule out a 30% response rate based on an exact 95% confidence interval.

Assuming approximately 90% of patients will be determined to be eligible, and receive at least one dose of selpercatinib (LOXO-292), and 90% of patients are evaluable for response by BICR, **the total accrual goal to the study is 124 patients to achieve 100 patients in the PAP and 112 in the SAP.**

11.3 Analysis Plan

The primary analysis will take place when 100 patients in the PAP have at least 12 months of follow-up. Proportions and associated confidence intervals will be calculated. Analysis of investigator-assessed response, PFS, and OS will include all eligible patients, which made include a subset of patients not evaluable for the BICR-based outcomes.

The frequency and severity of toxicity will be assessed in the SAP. With 112 patients, binary proportions can be estimated to within 9.4% with 95% confidence. Any toxicity with at least 5% prevalence is likely to be observed (99% probability).

Survival times (BICR-PFS, IA-PFS, OS, _BICR-DoR, IA-DoR, etc.) will be estimated using the method of Kaplan-Meier. The Brookmeyer-Crowley method will be used to estimate confidence intervals for the median using Greenwood's formula and based on a log-log transformation applied on the survival function for landmark times.

With 112 eligible patients accrued over 30 months, and an additional 12 months of follow-up, if PFS follows an exponential distribution and the median PFS is 6 months, the expected number of PFS events is 104. Similarly, if the true median is 9 months, the expected number of PFS events is 95, and if it were 15 months, the expected observed number of events would be 77. The primary analysis of PFS will take place when a minimum of 12 months of follow-up and when at least 77 BICR-PFS events have been reported. The observation of a median PFS of 12.4 months would be considered evidence to rule out a median PFS of 9 months and the observation of a median PFS of 8.3 months would be considered evidence to rule out a median of 6 months, at the 1-sided 2.5% level.

Duration of response (BICR-DoR and IA-DoR, as defined in Section 10), will be evaluated among patients who achieve a confirmed response. The median DoR and percentage with DoR at landmark times at 6 and 12 months after documentation of confirmed response will be estimated. The following table describes the precision that these landmark proportions can be estimated to within based on the number of responses is presented in the following table.

Number of observed responses	Precision of Estimate DOR landmark rates (+/-)
40	15.8%
50	14.1%
60	12.9%
70	12.0%

11.4 Blinded Independent Centralized Review (BICR) of Imaging-Based Endpoints (Response, PFS)

This study will employ complete BICR for all eligible patients to evaluate response by BICR, Duration of Response, and PFS by BICR. DoR and PFS by BICR are defined in Section 10.7. Response (confirmed CR or outcomes by BICR will also follow the definitions as detailed in Section 10.2. However, the outcomes by BICR will not be performed in real time, reported to the sites, or used to determine treatment decisions. BICR outcomes may not be determinable for patients who go off protocol treatment based on the investigator assessment, but the BICR review does not agree with the outcome determination. BICR of a patient's outcomes will commence when the off-treatment notice is submitted (See Appendix 18.8f).

12.0 DISCIPLINE REVIEW

12.1 Radiology Review

a. To ensure the highest standards and consistency between different centers, all scans for disease assessment (baseline, interim and end of treatment scans) must be submitted to the National Cancer Institute's National Clinical Trials Network (NCTN) Imaging and RT Quality Assurance Service Core (IROC) in Ohio for centralized review (see **S1900B** Section 15.0).

b. Centralized review will be performed by 3 radiology experts. The scans will be submitted to IROC. IROC will transmit the scans to the reviewers who will transmit the results to the SWOG Statistics and Data Management Center.

c. Details of submission of scans to IROC for blinded independent centralized review and on the central review process are listed in **S1900B** Section 15.0 and Appendix 18.8f.

13.0 REGISTRATION GUIDELINES

See Section 13.0 of **LUNGMAP** for registration guidelines.

In order to open Lung-MAP studies at the site, a separate Study Specific Worksheet (SSW) is required to be submitted to the CIRB for the **LUNGMAP** screening protocol and each sub-study.

13.1 Registration Timing

Initiation of treatment must be planned to start no more than 10 calendar days after sub-study registration.

13.2 Investigator/Site Registration

For investigator/site registration, please refer to Section 13.2 of the **LUNGMAP** screening protocol. In addition, a Delegation Task Log is required for this sub-study.

Delegation Task Log (DTL):
Each site must complete a protocol-specific Delegation of Tasks Log (DTL) using the DTL application in the Delegation Log section on the CTSU members' website. The Clinical Investigator (CI) is required to review and electronically sign the DTL prior to the site receiving an approved site registration status and enrolling patients to the study. To maintain an approved site registration status the CI must re-sign the DTL at least annually and when a new version of the DTL is released; and activate new task assignments requiring CI sign-off. Any individual at the enrolling site on a participating roster may initiate the site DTL. Once the DTL is submitted for CI approval, only the designated DTL Administrators or the CI may update the DTL. Instructions on completing the DTL are available in the Help Topics button in the DTL application and include a Master Task List, which describes DTL task assignments, CI signature, and CTEP registration requirements.

14.0 DATA SUBMISSION SCHEDULE

14.1 Data Submission Requirements

Data must be submitted according to the protocol requirements for ALL patients registered, whether or not assigned treatment is administered, including patients deemed to be ineligible. Patients for whom documentation is inadequate to determine eligibility will generally be deemed ineligible.

14.2 Master Forms

Master forms can be found on the protocol page on the CTSU website (www.ctsu.org) and (with the exception of the sample consent form and the Registration Worksheet) must be submitted on-line via the Web; see below for details.

14.3 Data Submission Procedures

a. Medidata Rave is a clinical data management system being used for data collection for this trial/study. Access to the trial in Rave is controlled through the CTEP-IAM system and role assignments.

b. Requirements to access Rave via iMedidata:
- A valid CTEP-IAM account; and
- Assigned a Rave role on the LPO or PO roster at the enrolling site of: Rave CRA, Rave Read Only, Rave CRA (LabAdmin), Rave SLA, or Rave Investigator.

Rave role requirements:
- Rave CRA or Rave CRA (Lab Admin) role must have a minimum of an Associate Plus (AP) registration type;
- Rave Investigator role must be registered as an Non-Physician Investigator (NPIVR) or Investigator (IVR); and
- Rave Read Only role must have at a minimum an Associates (A) registration type.

Refer to https://ctep.cancer.gov/investigatorResources/default.htm for registration types and documentation required.

This study has a Delegation of Tasks Log (DTL). Therefore, those requiring write access to Rave must also be assigned the appropriate Rave tasks on the DTL.

Upon initial site registration approval for the study in Regulatory Support System (RSS), all persons with Rave roles assigned on the appropriate roster will be sent a study invitation e-mail from iMedidata. To accept the invitation, site staff must log into the Select Login (https://login.imedidata.com/selectlogin) using their CTEP-IAM username and password and click on the *accept* link in the upper right-corner of the iMedidata page. Site staff will not be able to access the study in Rave until all required Medidata and study specific trainings are completed. Trainings will be in the form of electronic learnings (eLearnings) and can be accessed by clicking on the link in the upper right pane of the iMedidata screen. If an eLearning is required and has not yet been taken, the link to the eLearning will appear under the study name in iMedidata instead of the Rave EDC link; once the successful completion of the eLearning has been recorded, access to the study in Rave will be granted, and a *Rave EDC* link will display under the study name.

Site staff that have not previously activated their iMedidata/Rave account at the time of initial registration approval for the study in RSS will receive a separate invitation from iMedidata to activate their account. Account activation instructions are located on the CTSU website in the Data Management section under the Rave resource materials (Medidata Account Activation and Study Invitation Acceptance). Additional information on iMedidata/Rave is available on the CTSU members' website in the Data Management > Rave section at www.ctsu.org/RAVE/ or by contacting the CTSU Help Desk at 1-888-823-5923 or by e-mail at ctsucontact@westat.com.

a. You may also access Rave® via the SWOG CRA Workbench. Go to the SWOG website (www.swog.org).

   For difficulties with the CRA Workbench, please email technicalquestion@crab.org.

b. Institutions participating through the Cancer Trials Support Unit (CTSU) please refer to the CTSU Participation Table.

c. Data Quality Portal

   The Data Quality Portal (DQP) provides a central location for site staff to manage unanswered queries and form delinquencies, monitor data quality and timeliness, generate reports, and review metrics.

   The DQP is located on the CTSU members' website under Data Management. The Rave Home section displays a table providing summary counts of Total Delinquencies and Total Queries. DQP Queries, DQP Delinquent Forms and the DQP Reports modules are available to access details and reports of unanswered queries, delinquent forms, and timeliness reports. Review the DQP modules on a regular basis to manage specified queries and delinquent forms.

   The DQP is accessible by site staff that are rostered to a site and have access to the CTSU website. Staff that have Rave study access can access the Rave study data using a direct link on the DQP.

To learn more about DQP use and access, click on the Help icon displayed on the Rave Home, DQP Queries, and DQP Delinquent Forms modules.

Note: Some Rave protocols may not have delinquent form details or reports specified on the DQP. A protocol must have the Calendar functionality implemented in Rave by the Lead Protocol Organization (LPO) for delinquent form details and reports to be available on the DQP. Site staff should contact the LPO Data Manager for their protocol regarding questions about Rave Calendar functionality.

14.4 Data Submission Overview and Timepoints

a. WITHIN 15 DAYS OF **S1900B** REGISTRATION, SUBMIT:

Vital Status Form

S1900B Eligibility Criteria Form

S1900B Onstudy Form

If needed, also submit:
Radiation Therapy Form
Brain Metastases Form

S1900B Baseline Concomitant Medication Form

Smoking Status Assessment Form

Baseline Tumor Assessment Form (RECIST 1.1)

Radiology reports from all scans performed to assess disease at baseline

If needed, RT summary and/or planning document*

If needed, radiology report from brain CT/MRI*

*(NOTE: Upload reports via the Source Documentation: Baseline form in Rave®)

Submit to IROC via TRIAD for Central Radiology Review: Images from scans performed to assess disease at baseline as specified in **S1900B** Section 15.6

b. SUBMIT SPECIMENS:

Specimens as specified in Section 15.0 **S1900B**

c. WITHIN 15 DAYS AFTER EACH CYCLE (CYCLE = 28 DAYS) OF TREATMENT, SUBMIT:

Vital Status Form

S1900B Treatment Form

S1900B Adverse Event Form*

S1900B Laboratory Values Form

S1900B Concomitant Medication Form

S1900B Vital Signs Form (see Section 7.4 for details and timepoints)

For Cycle 1 only: Submit the **S1900B** Pre-Treatment Laboratory Values Form.

*For the last cycle of treatment, include all adverse events occurring within 30 days after the last treatment.

d. WITHIN 15 DAYS AFTER EVERY DISEASE ASSESSMENT (INCLUDING BOTH ON TREATMENT AND OFF PROTOCOL TREATMENT PRIOR TO DISEASE PROGRESSION (see **S1900B** Section 7.3 for Disease Assessment Schedule), SUBMIT:

Vital Status Form

Follow-Up Tumor Assessment Form (RECIST 1.1) documenting results of assessment

Radiology reports from all scans performed to assess disease at follow-up (NOTE: Upload reports via the Source Documentation: Follow-up form in Rave®)

Submit to IROC via TRIAD for Central Radiology Review: Images from scans performed to assess disease as specified in **S1900B** Section 15.6.

e. WITHIN 15 DAYS OF DISCONTINUATION OF TREATMENT, SUBMIT:

Vital Status Form

Off Protocol Treatment Notice documenting reasons for off protocol treatment

Smoking Status Assessment Form

Forms specified in Section 14.4c.

f. ONCE OFF PROTOCOL TREATMENT EVERY 6 MONTHS FOR THE FIRST 2 YEARS FROM **S1900B** REGISTRATION, THEN AT THE END OF YEAR 3 FROM SUB-STUDY REGISTRATION SUBMIT WITHIN 30 DAYS:

Vital Status Form

Advanced NSCLC Follow-Up Form

If needed, also submit:
Radiation Therapy Form
Brain Metastases Form

Late Adverse Events (if prior to treatment for progression or relapse or a second primary, and prior to non-protocol treatment, the patient experiences any severe [Grade ≥ 3] adverse event that is possibly, probably, or definitely related to protocol treatment, or a Serious Adverse Event [SAE] of any grade/attribution, that has not been previously reported).

g. WITHIN 15 DAYS OF PROGRESSION/RELAPSE, SUBMIT:

Vital Status Form

Site(s) of Progression or Relapse Form

Follow-Up Tumor Assessment Form (RECIST 1.1)

S1900B Consent Addendum Form*

Radiology reports from all scans performed to assess disease at follow-up (NOTE: Upload reports via the Source Documentation: Follow-up form in Rave®)

Submit to IROC via TRIAD for Central Radiology Review: Images from scans performed to assess disease as specified in **S1900B** Section 15.6.

*If patient will be provided the **S1900B** Consent Addendum to continue protocol treatment after progression, please submit the **S1900B** Consent Addendum Form, available via the "Add Event" dropdown on the main patient page. See Section 7.7.

h. WITHIN 30 DAYS OF KNOWLEDGE OF DEATH:

Vital Status Form

Submit the Notice of Death documenting death information and **S1900B** End of Study form. In addition, if the patient was still on protocol treatment, submit materials specified in **S1900B** Section 14.4e or if patient was no longer on treatment, submit a final Advanced NSCLC Follow-Up Form.

i. DATA SUBMISSION FOR PATIENTS WHO HAVE PROGRESSED AND WISH TO REGISTER TO A NEW SUB-STUDY:

WITHIN 15 DAYS OF PROGRESSION/RELAPSE:

Submit the Request for New Sub-Study Assignment Form under the **LUNGMAP** screening protocol in Rave®. Continue follow-up on **S1900B** per Section 9.0. See Section 14.0 of the screening protocol for additional data submission requirements following request for new sub-study assignment.

j. WITHIN 30 DAYS OF MAXIMUM FOLLOW-UP OF 3 YEARS:

Vital Status Form

S1900B End of Study Form

15.0 SPECIAL INSTRUCTIONS

15.1 Specimen Flow Diagram

Please refer to Section 15 of **LUNGMAP** for the specimen flow diagram for the screening protocol.

15.2 Biomarker Review Panel for RET Fusions Detected Outside of LUNGMAP

This process will occur during LUNGMAP screening prior to sub-study assignment to S1900B:

To determine if the patient meets the biomarker criteria to be assigned to **S1900B**, the biomarker review panel of translational medicine experts must review and confirm the study

biomarker results/reports for those patients who have RET fusion-positive NSCLC detected outside of the Lung-MAP study. Patients must have RET fusion-positive NSCLC as determined by tumor-based assays such as NGS, PCR, or FISH or by cfDNA blood assay. The testing must be done within a laboratory with CLIA, ISO/IEC, CAP, or similar certification. The reviewers will also confirm that the outside reports do not include the presence of oncogenic drivers. The presence of oncogenic drivers will make the patient ineligible per **LUNGMAP** Section 5.1e.

Note: 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.

15.3 SWOG Specimen Tracking System (STS)

See **LUNGMAP** Section 15.1 for SWOG Specimen Tracking System (STS) instructions.

15.4 LUNGMAP ctDNA Assay – Peripheral Whole Blood (***REQUIRED FOR PATIENTS***)

Blood specimens will be collected in order to isolate and investigate circulating tumor DNA (ctDNA) and blood tumor mutational burden (bTMB) – a form of fragmented DNA released into patient peripheral circulation specifically from the tumors. Analysis of ctDNA can reveal the presence of tumor-specific mutations and other abnormalities that can serve as biomarkers. The information collected will be limited to tumor-specific abnormalities known or suspected to play roles in tumor evolution. Patient germ-line genetic information will not be collected.

a. Kit Ordering

Immediately after identifying a patient for trial and prior to treatment initiation, sites must contact Foundation Medicine, Inc. – Blood Samples, Lab #232, to order kits as follows:

- Call FMI Client Services at 1-888/988-3639 or email request to lung.map@foundationmedicine.com
- Site must identify itself as a participant in the SWOG Lung-MAP **S1900B** sub-study and request the "Lung-MAP ctDNA Clinical Trial Kit"
- Reference the FMI Study ID: FoundationOneLiquidDx-AMC-PRO-20-1496
- Provide the following information:
  - Treating physician's name
  - Treating physician's email address
  - Contact name
  - Contact email address
  - Contact phone
  - Address to which kits should be sent
  - Number of kits needed (one per patient per timepoint)

Kits will arrive within 3 days after ordering (excluding weekends and holidays).

Kits will read "Foundation Medicine Clinical Trials Kit," and include two Roche Cell-Free DNA blood collection tubes, collection instructions, FedEx return bags, and pre-printed FedEx airway bills. Blood collection tubes must be used before their expiration date.

b. Timepoints

Collect blood at:

- After sub-study registration and prior to treatment initiation
  - Recommended to collect on Cycle 1 Day 1 (prior to treatment) during other labs to lessen patient visits.

    Note: This is a separate requirement for a ctDNA whole blood specimen for all patients registered to **S1900B**, regardless of whether or not there was a ctDNA blood collection for the **LUNGMAP** screening protocol.

- First progression after study treatment
  - Collection must be within 14 days after site learns of progression and prior to starting non-protocol treatment.

- Off treatment

Note: If the first progression after study treatment and the off treatment timepoints occur at the same time, only a single specimen is to be collected.

c. Specimen Collection and Shipment Instructions

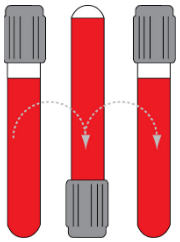
Specimen must be logged via the SWOG Specimen Tracking System.

Step 1: Check special tubes provided in kits to confirm liquid is clear and without cloudiness or crystals.

Step 2: Label tubes with date of collection, patient identifiers as requested on the included labels (patient date of birth can be added as an extra identifier), and sub-study number.

Step 3: Collect two tubes of whole blood (8.5 mL per tube)
- Prevent backflow: tubes contain chemical additives and it is important to avoid backflow into patient
- Collect specimen by venipuncture
- Fill tubes completely (8.5 mL per tube)

Step 4: Remove the tube from adapter and immediately mix by gentle inversion 8 to 10 times. Inadequate or delayed mixing may result in inaccurate test results. One inversion is a complete turn of the wrist, 180° and back, per the figure below.



Step 5: Place specimen into the specimen collection kit.
- Confirm each tube is labeled with the supplied labels indicating the date of collection and two unique patient identifiers (label included in kit).

Step 6: Select “Ship this Shipment and Generate Packing List” in the SWOG Specimen Tracking System to generate the Packing List. A copy of the

SWOG Specimen Tracking Packing List must be included in the shipment. Confirm that the tubes are labeled as specified on the Packing List.

Step 7: Preferably on the same day of collection, ship to FMI – Blood Samples, Lab #232 via FedEx overnight delivery at ambient temperature. Do not freeze or refrigerate blood samples. Keep at 43-99° F (6-37° C).

FMI accepts Saturday deliveries. If shipping on a Friday, please overnight shipment and mark for Saturday delivery.

d. Specimen Usage

Cell-free, circulating DNA will be isolated from the plasma component of the whole blood. Using a hybrid-capture, next-generation sequencing technology (developed by Foundation Medicine), alterations in clinically significant cancer genes (oncogenes and tumor suppressor genes) will be identified and quantitated relative to wild-type sequences. Tumor-specific alterations will include point mutations, small insertions and deletions, chromosomal rearrangements and copy number/amplification events in (**LUNGMAP** ctDNA Assay) including an assessment of tumor mutation burden (TMB) will be conducted using ctDNA. A full proposal will be developed, reviewed, and approved by SWOG and CTEP once funding has been obtained.

The ctDNA results are for research purposes and will not be shared with the investigator or patient.

Note: The translational medicine proposal to use these specimens will be submitted as a revision to CTEP for approval, prior to the SWOG Statistical and Data Management Center review of assay results.

15.5 Translational Medicine and Banking (***OPTIONAL FOR PATIENT***)

Specimens for translational medicine and banking (submitted to the SWOG Biospecimen Bank – Solid Tissue, Myeloma and Lymphoma Division, Lab #201) are considered optional for the patient:

a. With patient's consent, specimens must be collected and submitted as follows:

1. Buffy Coat and Plasma:

Specimens must be collected at the following times.

- Pre-study (after consenting and prior to treatment initiation on sub-study; see Section 15.4 of **LUNGMAP**)
  Note: If a patient provided buffy coat and plasma at pre-screening or screening (see Section 15.0 of **LUNGMAP**) and the blood collection was within 42 days prior to the sub-study registration, then no additional pre-study blood specimen is required.
- Cycles 2, 3, and 4 (at the same time as lab collection, prior to the start of cycle treatment) - Patients that go off protocol treatment are not required to continue to submit specimens.
- First progression.

Collect approximately 8-10 mL of blood in EDTA tubes. Blood should be processed within one hour after venipuncture. If immediate processing within this time frame is not possible, then refrigerate (4°C) blood in EDTA

tubes. The approximate time from collection to processing should be recorded as part of the patient's source documentation. EDTA tubes must be centrifuged at 800 x g for 10 minutes at 4˚C for the collection of plasma. [Note: Sites that do not have a refrigerated centrifuge should spin at room temperature and ensure specimens are placed on ice (regular, not dry) immediately after being drawn and process rapidly.] Using a pipette, transfer the plasma to a 15-mL centrifuge tube. Remove the buffy coat layer (thin white or gray layer of cells between the plasma and red blood cells) and split between two appropriately labeled 2-mL cryovials.

Spin the plasma in the 15-mL centrifuge tube at 800 x g for an additional 10 minutes. Avoiding any pelleted material, pipette the plasma into labeled cryovials at 0.5 ml aliquots. Plasma must be clear before freezing; no cells or debris should be present.

Plasma and buffy coat vials must be placed upright in a -80˚C freezer immediately after processing to ensure long-term viability.

Frozen plasma and buffy coat specimens must be shipped to the SWOG Biospecimen Bank on dry ice. Frozen specimens may be shipped in batches – refer to Section 15.5b.

b. Specimen Submission and Labeling Instructions

Samples for multiple patients may be shipped in batches to the SWOG Biospecimen Bank – Solid Tissue, Myeloma and Lymphoma Division, Lab #201, at least every 3 months (if not more frequently), with a maximum of 5 patients' samples included per batch.

For additional information about labeling and shipping instructions for frozen plasma and buffy coat specimens, refer to the SWOG Specimen Submission webpage (https://www.swog.org/clinical-trials/biospecimen-resources/biospecimen-processing-and-submission-procedures).

1. Liquid specimens must be labeled with the following:
   - SWOG patient number
   - Patient initials
   - Collection date (date the specimen was collected from the patient)
   - Specimen type (e.g. blood, serum, etc.)

c. Specimen collection kits are not being provided for this submission; sites must use institutional supplies.

15.6 Radiology Review (***REQUIRED***)

CT, PET/CT, and/or MRI images must be locally read and interpreted by the local site radiology service. Imaging exams must then be submitted to the Imaging and Radiation Oncology Core (IROC) at Ohio via TRIAD Imaging Submission procedures for central data collection and quality control (QC) check as well as retrospective central review.

a. CT, PET/CT, and/or MRI images must be submitted to IROC Ohio for central review within 15 days after disease assessment scans performed per the schedule in Section 7.3 and 9.0.

The same imaging modality used for the pre-treatment exam must be used for the post-treatment exams (see Section 10.1). Each exam should be performed per Appendix 18.8f. IROC will perform a QC of the imaging exams.

Note: PET-CT: At present, the low dose or attenuation correction CT portion of a PET-CT is not always of optimal diagnostic CT quality for use with RECIST measurements. However, if the site can document that the CT performed as part of a PET-CT is of identical diagnostic quality to a diagnostic CT, then the CT portion of the PET-CT can be used for RECIST measurements and can be used interchangeably with stand-alone CT. *The slice thickness of 0.5 cm or less is highly recommended*. If CT scans have slice thickness > 0.5 cm, the minimum size for a measurable lesion should be twice the slice thickness.

Clinical management and treatment decisions will be made by the treating physician based on local site assessments and other clinically appropriate considerations.

Central review of scans will be triggered once a patient's disease has progressed. A detailed description of the central radiology PFS review, including image acquisition parameters and image submission instructions, can be found in Appendix 18.8f.

b. TRIAD Digital Image Submission

Transfer of Images and Data (TRIAD) is the American College of Radiology's (ACR) image exchange application. TRIAD provides sites participating in clinical trials a secure method to transmit images. TRIAD anonymizes and validates the images as they are transferred.

1. TRIAD Access Requirements:

TRIAD will be the sole means of image transfer to the IROC Ohio. TRIAD should be installed prior to study participant enrollment to ensure prompt secure, electronic submission of imaging.

- A valid CTEP-IAM account (see **LUNGMAP** Section 13.2).
  - Must be registered as an Associate (A), Associate Plus (AP), Non-Physician Investigator (NPIVR), or Investigator (IVR) registration type. Refer to the CTEP Registration Procedures section for instructions on how to request a CTEP-IAM account and complete registration in Registration and Credential Repository (RCR).
- Registration and Credential Repository (RCR) registration type of: Associate (A), Associate Plus (AP), Non-Physician Investigator (NPIVR), or Investigator (IVR) registration type. Refer to the CTEP Registration Procedures section for instructions on how to request a CTEP-IAM account and complete registration in RCR.

All individuals on the Imaging and Radiation Oncology Core provider roster have access to TRIAD and may submit images for credentialing purposes, or for enrollments to which the provider is linked in OPEN.

2. TRIAD Installations:

To submit images, the individual holding the TRIAD Site User role will need to install the TRIAD application on their workstation. TRIAD installation documentation is available at:
https://triadinstall.acr.org/triadclient/.

This process can be done in parallel to obtaining your CTEP-IAM account and RCR registration.

For questions, contact TRIAD Technical Support staff via email TRIAD-Support@acr.org or 1-703-390-9858.

15.7 *RET* Testing Concordance Study

Remaining tissue after the screening *RET* testing will be used for retrospective testing of *RET* fusion status at a central laboratory. This is to allow a sensitivity analysis to be performed for the FMI tissue assay and other local tests used to recruit patients to the study, by comparing the screening *RET* testing results with the selpercatinib (LOXO-292) CDx intended for the market. Details regarding analyses involving selpercatinib (LOXO-292) CDx test results will be described in a Diagnostic SAP. The *RET* Testing concordance study will be submitted in a future amendment (in addition to the Diagnostic SAP).

16.0 ETHICAL AND REGULATORY CONSIDERATIONS

The following must be observed to comply with Food and Drug Administration regulations for the conduct and monitoring of clinical investigations; they also represent sound research practice.

Informed Consent

The principles of informed consent are described by Federal Regulatory Guidelines (Federal Register Vol. 82, No. 12, January 19, 2017) and the Office for Protection from Research Risks Reports: Protection of Human Subjects (Code of Federal Regulations 45 CFR 46). They must be followed to comply with FDA regulations for the conduct and monitoring of clinical investigations.

Institutional Review

This study must be approved by an appropriate institutional review committee as defined by Federal Regulatory Guidelines (Federal Register Vol. 82, No. 12, January 19, 2017) and the Office for Protection from Research Risks Reports: Protection of Human Subjects (Code of Federal Regulations 45 CFR 46).

Drug Accountability

An investigator is required to maintain adequate records of the disposition of investigational drugs according to procedures and requirements governing the use of investigational new drugs as described in the Code of Federal Regulations 21 CFR 312 and the CTEP Investigator's Handbook.

Publication and Industry Contact

The agents supplied by CTEP, DCTD, NCI used in this protocol are provided to the NCI under Collaborative Agreements (CRADA, CTA, CSA) between the Pharmaceutical Companies (hereinafter referred to as "Collaborators") and the NCI Division of Cancer Treatment and Diagnosis. Therefore, the following obligations/guidelines in addition to the provisions in the "Intellectual Property Option to Collaborator" (http://ctep.cancer.gov/industryCollaborations2/intellectual_property.htm) contained within the terms of award apply to the use of the Agents in this study:

a. Agents may not be used for any purpose outside the scope of this protocol, nor can Agents be transferred or licensed to any party not participating in the clinical study. Collaborators data for Agents are confidential and proprietary to Collaborators and shall be maintained as such by the investigators. The protocol documents for studies utilizing Agents contain confidential information and should not be shared or distributed without the permission of the NCI. If a copy of this protocol is requested by a patient or patient's family member participating on the study, the individual should sign a confidentiality agreement. A suitable model agreement can be downloaded from: http://ctep.cancer.gov.

b. For a clinical protocol where there is an investigational Agent used in combination with (an)other investigational Agent(s), each the subject of different Collaborative Agreements, the access to and use of data by each Collaborator shall be as follows (data pertaining to such combination use shall hereinafter be referred to as "Multi-Party Data"):

1. NCI will provide all Collaborators with written notice regarding the existence and nature of any agreements governing their collaboration with NCI, the design of the proposed combination protocol, and the existence of any obligations which would tend to restrict NCI's participation in the proposed combination protocol.

2. Each Collaborator shall agree to permit use of the Multi-Party Data from the clinical trial by any other Collaborator solely to the extent necessary to allow said other Collaborator to develop, obtain regulatory approval or commercialize its own investigational Agent.

3. Any Collaborator having the right to use the Multi-Party Data from these trials must agree in writing prior to the commencement of the trials that it will use the Multi-Party Data solely for development, regulatory approval, and commercialization of its own Agent.

c. Clinical Trial Data and Results and Raw Data developed under a Collaborative Agreement will be made available exclusively to Collaborators, the NCI, and the FDA, as appropriate and unless additional disclosure is required by law or court order as described in the IP Option to Collaborator (http://ctep.cancer.gov/industryCollaborations2/intellectual_property.htm). Additionally, all Clinical Data and Results and Raw Data will be collected, used and disclosed consistent with all applicable federal statutes and regulations for the protection of human subjects, including, if applicable, the *Standards for Privacy of Individually Identifiable Health Information* set forth in 45 C.F.R. Part 164.

d. When a Collaborator wishes to initiate a data request, the request should first be sent to the NCI, who will then notify the appropriate investigators (Group Chair for Cooperative Group studies, or PI for other studies) of Collaborator's wish to contact them.

e. Any data provided to the Collaborators for Phase III studies must be in accordance with the guidelines and policies of the responsible Data Monitoring Committee (DMC), if there is a DMC for this clinical trial.

f. Any manuscripts reporting the results of this clinical trial must be provided to CTEP by the Group office for Cooperative Group studies or by the principal investigator for non-Cooperative Group studies for immediate delivery to Collaborators for advisory review and comment prior to submission for publication. Collaborators will have 30 days from the date of receipt for review. Collaborator shall have the right to request that publication be delayed for up to an additional 30 days in order to ensure that Collaborator's confidential and proprietary data, in addition to the Collaborator's intellectual property rights, are protected. Copies of abstracts must be provided to CTEP for forwarding to Collaborators for courtesy review as soon as possible and preferably at least three (3) days prior to submission, but in any case, prior to presentation at the meeting or publication in the proceedings. Press

releases and other media presentations must also be forwarded to CTEP prior to release. Copies of any manuscript, abstract and/or press release/media presentation should be sent to:

E-mail: ncicteppubs@mail.nih.gov

The Regulatory Affairs Branch will then distribute them to the Collaborators. No publication, manuscript or other form of public disclosure shall contain any of the Collaborator's confidential/proprietary information.

Monitoring

Required submission of patient demographic data for this study will be submitted automatically via OPEN.

Trial Master File

This study is an FDA registration study; therefore, all participating sites should be FDA "inspection ready". This entails maintaining a Trial Master File that includes essential documents that may be subject to FDA oversight. A list of essential documents is available on the SWOG website under QA/Audits, https://swog.org/Visitors/QA/Index.asp.

Confidentiality

Please note that the information contained in this protocol is considered confidential and should not be used or shared beyond the purposes of completing protocol requirements until or unless additional permission is obtained.

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18.0 APPENDIX

18.1 New York Heart Association Classification

18.2 Instructions for the SWOG Biospecimen Bank

18.3 Examples of Cytochrome CYP34A Inhibitors/Inducers

18.4 Patient Diary – Selpercatinib (LOXO-292)

18.5 Patient Drug Information Handout and Wallet Card

18.6 Temperature Excursion Reporting & Product Complaint Form

18.7 Examples of Anti-RET Multi-Kinase and Selective Inhibitors

18.8 Risk Based Monitoring Plan

18.1 New York Heart Association Classification

Class	Cardiac Symptoms	Need for Limitations	Physical Ability Additional Rest*	To Work**
I	None	None	None	Full Time
II	Only moderate	Slight or occasional	Usually only slight	Usually full time
III	Defined, with less than ordinary activity	Marked	Usually moderate	Usually part time
IV	May be present even at rest, & any activity increases discomfort	Extreme	Marked	Unable to work

* To control or relieve symptoms, as determined by the patient, rather than as advised by the physician.
** At accustomed occupation or usual tasks.

18.2 Instructions for the SWOG Biospecimen Bank

Frozen Plasma and Buffy Coat
The SWOG Biospecimen Bank will receive frozen plasma and buffy coat at up to 5 time points per patient. Upon receipt, the Bank will accession, barcode, and Bank specimens in a -80°C freezer.

Formalin-fixed Paraffin-Embedded (FFPE) Tissue
The SWOG Biospecimen Bank will receive FFPE specimens as either blocks or slides/sections at 1 time point per patient. Upon receipt, the Bank will accession, barcode, and Bank specimens at ambient temperature.

At the end of the study, the Bank will receive notification from the SWOG Statistics and Data Management Center to distribute specimens for testing.

18.3 Examples of Cytochrome CYP34A Inhibitors/Inducers

See Section 7.1 for precautions.

Because lists of these agents are constantly changing, it is important to regularly consult a frequently updated list for the most up-to-date listing of agents; medical reference texts such as the Physicians' Desk Reference may also provide this information.

18.4 Patient Diary – Selpercatinib (LOXO-292) **SWOG Study: S1900B**

Site Personnel Instructions

- Bottles should be labeled for patient use in accordance with state and federal regulations for prescription dispensing. The protocol number and patient ID should be referenced on the dispensing label.
- Ensure that patient clearly understand the guidelines for self-medication.
- Patient should be given enough supply to last until their next study visit.
- Unused drug and/or empty bottles should be returned to the site at the next study visit.

Please review the following with the patient:

- Cycle, Start Date and Start Time information with the patient. If possible, have the patient document their first dose in the appropriate calendar box.
- Patient's dose schedule: Selpercatinib (LOXO-292) should be taken twice a day, at the same time of day, and as close to 12 hours apart as possible. Provide patient with the instructions on how to document this schedule appropriately.
- Swallow capsules whole. Do not chew, crush or open capsules.
- Selpercatinib (LOXO-292) can be taken with or without food.
- How to document vomited, missed, late, or skipped doses in the specific areas provided.
- How to document H2 or antacids taken by the patient in the specific areas provided.

SWOG Patient ID _____ Patient Initials (L, F, M) _____ **SWOG Study #** _____
Cycle: _____ Start Date: _____ Start Day (circle one): Sun M Tu W Th F Sat

Instructions for the patient: Record the date and times of the selpercatinib (LOXO-292) capsules you take each day on this calendar. You should:

- Take your medication twice a day, at the same time of day.
- Swallow capsules whole. Do not chew, crush or open capsules.
- Put the date in the box on the calendar and note the time of both doses for each day. The doses should be as close to 12 hours apart as possible.
- Line through the days and times that the medication is not taken.
- You may take the medication if you are less than 6 hours late than the scheduled time.
- Selpercatinib (LOXO-292) can be taken with or without food.
- Document any changes to taking the doses in the comments section below.
  - If you are more than 6 hours late, skip the dose and record this as a "missed" dose with the date and time.
  - Record the date and time of any histamine-2 (H2) blocking agents, such as ranitidine (Zantac®), famotidine (Pepcid®), or cimetidine (Tagamet®), or antacids, such as TUMS. Take histamine-2 (H2) blocking agents only between 2 and 3 hours after your selpercatinib (LOXO-292) dose. Take antacids 2 or more hours before or 2 or more hours after your selpercatinib (LOXO-292) dose.
  - If you vomit a dose, the dose should not be re-taken. Record this as a "missed" dose with the date and time.
  - If you develop any side effects from the capsule, mark the side effect in the comments section with the date and time you developed the side effect.

Storage: selpercatinib (LOXO-292) gelatin capsules are to be stored at controlled room temperature, 66-77°F, with excursion permitted between 59-86°F.

If you have questions, contact: _____ Telephone: _____

Date	Was dose taken?	What time?	Comments
____/____/____	Dose 1 □ Yes □ No	Time 1 ____:____ am/pm	
Day 1	Dose 2 □ Yes □ No	Time 2 ____:____ am/pm	
____/____/____	Dose 1 □ Yes □ No	Time 1 ____:____ am/pm	
Day 2	Dose 2 □ Yes □ No	Time 2 ____:____ am/pm	
____/____/____	Dose 1 □ Yes □ No	Time 1 ____:____ am/pm	
Day 3	Dose 2 □ Yes □ No	Time 2 ____:____ am/pm	
____/____/____	Dose 1 □ Yes □ No	Time 1 ____:____ am/pm	
Day 4	Dose 2 □ Yes □ No	Time 2 ____:____ am/pm	
____/____/____	Dose 1 □ Yes □ No	Time 1 ____:____ am/pm	
Day 5	Dose 2 □ Yes □ No	Time 2 ____:____ am/pm	

____/____/____ **Day 6**	Dose 1 □ Yes □ No Dose 2 □ Yes □ No	Time 1 ____:____ am/pm Time 2 ____:____ am/pm	
____/____/____ **Day 7**	Dose 1 □ Yes □ No Dose 2 □ Yes □ No	Time 1 ____:____ am/pm Time 2 ____:____ am/pm	
____/____/____ **Day 8**	Dose 1 □ Yes □ No Dose 2 □ Yes □ No	Time 1 ____:____ am/pm Time 2 ____:____ am/pm	
____/____/____ **Day 9**	Dose 1 □ Yes □ No Dose 2 □ Yes □ No	Time 1 ____:____ am/pm Time 2 ____:____ am/pm	
____/____/____ **Day 10**	Dose 1 □ Yes □ No Dose 2 □ Yes □ No	Time 1 ____:____ am/pm Time 2 ____:____ am/pm	
____/____/____ **Day 11**	Dose 1 □ Yes □ No Dose 2 □ Yes □ No	Time 1 ____:____ am/pm Time 2 ____:____ am/pm	
____/____/____ **Day 12**	Dose 1 □ Yes □ No Dose 2 □ Yes □ No	Time 1 ____:____ am/pm Time 2 ____:____ am/pm	
____/____/____ **Day 13**	Dose 1 □ Yes □ No Dose 2 □ Yes □ No	Time 1 ____:____ am/pm Time 2 ____:____ am/pm	
____/____/____ **Day 14**	Dose 1 □ Yes □ No Dose 2 □ Yes □ No	Time 1 ____:____ am/pm Time 2 ____:____ am/pm	
____/____/____ **Day 15**	Dose 1 □ Yes □ No Dose 2 □ Yes □ No	Time 1 ____:____ am/pm Time 2 ____:____ am/pm	
____/____/____ **Day 16**	Dose 1 □ Yes □ No Dose 2 □ Yes □ No	Time 1 ____:____ am/pm Time 2 ____:____ am/pm	

____/____/____ **Day 17**	Dose 1 □ Yes □ No Dose 2 □ Yes □ No	Time 1 ____:____ am/pm Time 2 ____:____ am/pm	
____/____/____ **Day 18**	Dose 1 □ Yes □ No Dose 2 □ Yes □ No	Time 1 ____:____ am/pm Time 2 ____:____ am/pm	
____/____/____ **Day 19**	Dose 1 □ Yes □ No Dose 2 □ Yes □ No	Time 1 ____:____ am/pm Time 2 ____:____ am/pm	
____/____/____ **Day 20**	Dose 1 □ Yes □ No Dose 2 □ Yes □ No	Time 1 ____:____ am/pm Time 2 ____:____ am/pm	
____/____/____ **Day 21**	Dose 1 □ Yes □ No Dose 2 □ Yes □ No	Time 1 ____:____ am/pm Time 2 ____:____ am/pm	
____/____/____ **Day 22**	Dose 1 □ Yes □ No Dose 2 □ Yes □ No	Time 1 ____:____ am/pm Time 2 ____:____ am/pm	
____/____/____ **Day 23**	Dose 1 □ Yes □ No Dose 2 □ Yes □ No	Time 1 ____:____ am/pm Time 2 ____:____ am/pm	
____/____/____ **Day 24**	Dose 1 □ Yes □ No Dose 2 □ Yes □ No	Time 1 ____:____ am/pm Time 2 ____:____ am/pm	
____/____/____ **Day 25**	Dose 1 □ Yes □ No Dose 2 □ Yes □ No	Time 1 ____:____ am/pm Time 2 ____:____ am/pm	
____/____/____ **Day 26**	Dose 1 □ Yes □ No Dose 2 □ Yes □ No	Time 1 ____:____ am/pm Time 2 ____:____ am/pm	
____/____/____ **Day 27**	Dose 1 □ Yes □ No Dose 2 □ Yes □ No	Time 1 ____:____ am/pm Time 2 ____:____ am/pm	
____/____/____ **Day 28**	Dose 1 □ Yes □ No Dose 2 □ Yes □ No	Time 1 ____:____ am/pm Time 2 ____:____ am/pm	

18.5 PATIENT DRUG INFORMATION HANDOUT AND WALLET CARD

Information for Patients, Their Caregivers and Non-Study Healthcare Team on Possible Interactions with Other Drugs and Herbal Supplements

Patient Name: **Diagnosis:** **Trial #:**

To the patient: Take this handout with you to your medical appointments and keep the attached information card in your wallet. **These are the things that you need to know:**

The study drug selpercatinib (LOXO-292) may interact with other drugs which can cause side effects. For this reason, it is very important to tell your doctors about all your medicines, including:

a) medicines you are taking before this clinical trial,
b) medicines you start or stop taking during this clinical trial,
c) medicines you buy without a prescription (over-the-counter remedy),
d) herbals or supplements (e.g., St. John's Wort).

Please bring your medication bottles or an updated medication list with you.

Before you enroll onto the clinical trial, your study doctor will work with your regular health care providers to review any medicines and herbal supplements that are considered "moderate or strong" inducers/inhibitors of CYP3A4 and transport proteins P-gp and BCRP; any medicines that are considered substrates of CYP2C8, CYP3A4, and MATE1; certain medicines used to reduce stomach acid; medicines considered highly protein-bound; and medicines that are associated with greater risk for having QTc prolongation.

- Please be very careful! Over-the-counter drugs (including herbal supplements) may contain ingredients that could interact with your study drug. Speak to your doctors or pharmacist to determine if there could be any side effects.
  - Avoid ingesting grapefruit juice, grapefruit and Seville oranges while taking selpercatinib (LOXO-292).
  - Avoid using herbal supplements, such as St. John's Wort while taking LOXO-292.
  - Avoid taking over-the-counter stomach acid reducing medicines called proton pump inhibitors. Examples of proton pump inhibitors include Prilosec, Prevacid and Nexium.
  - Over-the-counter antacids or stomach acid reducing medicines called H2 antagonists may be used if necessary, but your study doctor will inform you how to take these medicines with selpercatinib (LOXO-292). Examples of H2 receptor antagonists include Zantac, Pepcid, and Tagamet.
- Make sure your doctor knows to avoid certain prescription medicines.
  - Do not use any medicines considered "moderate or strong" inducers/inhibitors of CYP3A4 and transport proteins P-gp and BCRP and avoid any medicines considered substrates of CYP2C8, CYP3A4 and MATE1. Avoid medicines that are associated with greater risk for having QTc prolongation.
  - Do not use prescription medicines called proton pump inhibitors.
  - Prescription antacids and H2 receptor antagonists may be used if necessary, but your study doctor will inform you how to take these medications with selpercatinib (LOXO-292).
- Your regular health care provider should check a frequently updated medical reference or call your study doctor before prescribing any new medicine or discontinuing any medicine.

Your study doctor's name is _____ and he or she can be contacted at_____.

Study Doctor:	**Study Doctor Phone #:**	**Study Drug(s):**	**selpercatinib (LOXO-292)**

Please show this paper to all your healthcare providers (doctors, physician assistants, nurse practitioners, pharmacists), and tell them you are taking part in a clinical trial sponsored by National Cancer Institute.
These are the things that your healthcare providers need to know:

Selpercatinib (LOXO-292) interacts with certain specific liver enzymes and certain transport proteins that help move drugs in and out of cells and the heart's electrical activity (QTc prolongation). Selpercatinib (LOXO-292) can also interact with certain stomach acid-reducing medications or medications that are considered highly protein-bound.

	Explanation
CYP Isoenzymes	The enzymes in question are CYP3A4 and CYP2C8. Selpercatinib (LOXO-292) is broken down by CYP3A4 and may be affected by other drugs that strongly inhibit or induce this enzyme. Selpercatinib (LOXO-292) weakly inhibits CYP3A4 and moderately inhibits CYP2C8 and may affect other drugs that are broken by these enzymes.
Protein Transporters	The proteins in question are P-gp, BCRP and MATE1. Selpercatinib (LOXO-292) is moved in and out of cells/organs by P-gp and BCRP and may be affected by other drugs that strongly inhibit or induce these transport proteins. Selpercatinib (LOXO-292) inhibits MATE1 and may affect other drugs that require this transport protein to move in and out of cells/organs.
Acid-reducing medications	Antacids and medications called proton-pump inhibitors and H2 receptor antagonists can change how selpercatinib (LOXO-292) is broken down and distributed throughout your body and may reduce its effectiveness.
Protein-Binding	Selpercatinib (LOXO-292) binds to a high percentage of proteins in your blood and may affect the activity of other drugs that also bind highly to these proteins or the other drugs may affect the activity of selpercatinib (LOXO-292).
Heart's electrical activities	The heart's electrical activity may be affected by selpercatinib (LOXO-292). The study doctor may be concerned about QTc prolongation and any other medicine that is associated with greater risk for having QTc prolongation.

Patient Drug Interaction Wallet Card

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EMERGENCY INFORMATION

Show this card to all of your healthcare providers. Keep it with you in case you go to the emergency room.

Patient Name:

Diagnosis:

Study Doctor:

Study Doctor Phone #:

NCI Trial #:

Study Drug(S): Selpercatinib (LOXO-292)

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Tell your doctors **before** you **start** or **stop** any medicines.

Check with your doctor or pharmacist if you need to use an over-the-counter medicine or herbal supplement!

Use caution and avoid the following drugs if possible:

Avoid ingesting grapefruit juice, grapefruit and Seville oranges while taking s**elpercatinib (LOXO-292)**.

Avoid using herbal supplements, such as St. John's wort while taking s**elpercatinib (LOXO-292)**.

Avoid taking over-the-counter or prescription stomach acid reducing medicines called proton pump inhibitors. Examples of proton pump inhibitors include Prilosec, Prevacid and Nexium. Take over-the-counter or prescription antacids or stomach acid reducing medicines called H2 antagonists only as instructed by your study doctor. Examples of H2 antagonists include Zantac, Pepcid and Tagamet.

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DRUG INTERACTIONS

Carry this card with you at all times

Selpercatinib (LOXO-292) interacts with certain specific liver enzymes and certain transport proteins that help move drugs in and out of cells and the heart's electrical activity (QTc prolongation) and must be used very carefully with other medicines. **Selpercatinib (LOXO-292)** is metabolized by CYP3A4, weakly inhibits CYP3A4, and moderately inhibits CYP2C8**. Selpercatinib (LOXO-292)** is a substrate for transport proteins P-gp and BCRP and inhibits MATE1. Proton pump inhibitors, H2 receptor antagonists and antacids may reduce s**elpercatinib (LOXO-292)** effectiveness. **Selpercatinib (LOXO-292)** is 97% protein bound and may affect or be affected by other drugs that are highly protein-bound. **Selpercatinib (LOXO-292)** may affect the heart's electrical activity (QTc prolongation).

Your healthcare providers should:

- Not prescribe you any medicines that are considered "moderate or strong" inducers/inhibitors of CYP3A4 and transport proteins P-gp and BCRP while taking selpercatinib (LOXO-292)
- Avoid use of any medicines that are considered "sensitive" substrates of CYP2C8 and CYP3A4
- Use caution with any medicines that are considered substrates of MATE1
- Use caution with any medicines considered highly protein-bound
- Avoid use of medicines called proton pump inhibitors
- Use antacids and medicines called H2 antagonists only as instructed by your study doctor
- Avoid medicines that are associated with greater risk for having QTc prolongation.

Before prescribing new medicines, your health care provider should check a **frequently-updated medical reference** for a **list of drugs to avoid** or contact your study doctor.

Version DEC2020

For more information: 1-800-4-CANCER
cancer.gov | clinicaltrials.gov

Folding line

18.6 Temperature Excursion & Product Complaint Form

Loxo Complaint Number: C-_____	
To be completed by the person receiving the notification of complaint or temperature excursion	
☐ Product Complaint ☐ Temperature Excursion ☐ Temp charts/data attached	
Notification Received By:_____ Date Rec'd:_____	
Location or site name	
Complainant Name:	
Address	
Phone Number	
E-mail address	
Product Name or Product ID#:	
Dosage Form: ☐ Capsule ☐ Tablet ☐ Injection ☐ Other (list):	
Lot Number(s)	Study Number:
Date of Occurrence	
If Temperature excursion	
Acceptable Temperature range:	
Min temp and time out of spec:	
Max temp and time out of spec:	
Reason for excursion:	
Location of Occurrence (e.g. Pharmacy, home, warehouse)	
Sample of affected product available ☐ Yes ☐ No	
Photo included (if applicable) ☐ Yes ☐ No	
Nature of complaint and circumstances under which anomaly occurred (attach additional sheets if necessary):	
SEND COMPLETED FORM TO Loxo Oncology QUALITY ASSURANCE at rlewis@loxooncology.com	

18.7 Examples of Anti-RET Multi-Kinase and Selective Inhibitors [a]

Multikinase Inhibitors
alectinib
cabozantinib
vandetanib
lenvatinib
ponatinib
regorafenib
sunitinib
sorafenib
motesanib
RXDX-105
sitravatinib (MGCD516)
Selective Inhibitors
selpercatinib (LOXO-292)
BLU-667
BOS-589 (GSK3352589) [b]
BOS-172738

[a] Questions about other kinase inhibitors should be discussed with Study Chairs
[b] Colon-restricted selective RET kinase inhibitor for Irritable Bowel Syndrome

18.8 Risk-Based Monitoring Plan

a. On Site Auditing

NCI guidelines for Auditing Clinical Trials for the National Clinical Trials Network (NCTN) Program, Community Clinical Oncology Program (CCOP)/NCI Community Oncology Research Program (NCORP) and Research Bases: https://ctep.cancer.gov/branches/ctmb/clinicaltrials/docs/ctmb_audit_guidelines.pdf

The Quality Assurance Program of the Groups participating in the NCTN was developed to enhance the reliability and validity of clinical trials data through the use of routine monitoring procedures which includes auditing as one component. The purpose of an audit is to document the accuracy of data submitted to the SWOG Statistics and Data Management Center (SDMC) and to verify compliance with protocol and regulatory requirements. The program also surveys data management practices at each institution in order to provide educational support to the sites regarding issues related to data quality, data management, and other aspects of quality assurance.

Each institution is audited at least once every three years but remains at annual risk of an audit. Routine monitoring of Institutional Performance Review reports and timeliness of reporting of Serious Adverse Events is conducted to identify institutions that may require more frequent audits.

The audit team consists of qualified individuals capable of providing a medical assessment of the patient cases (Quality Assurance representative from the research base, physician, nurse or experienced clinical research associate [CRA]). A number of patients equal to 10% of the accrual since the last audit with a minimum of three are randomly selected for review at each institution. In addition, a limited review of eligibility and consent only is conducted for at least one unannounced case at each on site audit.

The major objective of the audit process is to verify study data that could affect the interpretation of primary study endpoints. This is done through independent verification of study data against the source documents. Primary source documentation reviewed during an audit includes the following: research records, hospital charts, clinic charts, lab reports, x-rays, scans, radiotherapy reports, operative reports, pathology reports and other special studies required by protocol.

By comparing the data submitted in Rave® against the primary records and the protocol, the audit team reviews the records to determine compliance with protocol requirements for eligibility, treatment administration, response assessment, toxicity reporting and general data quality. NCTN investigators and institutions are expected to follow the protocol and lead Group policy in treating patients registered on Group protocols. Among other requirements, investigators/institutions must follow Group's dosing principles requirements for reporting Serious Adverse Events, and follow-up of all patients.

The audit team verifies that the protocol and its amendments received initial and continuing IRB review and approval and that safety reports and serious adverse events were submitted to the IRB. Investigational drug accountability record forms (DARFs) are reviewed and random patients are cross referenced against the medical record. A tour of the pharmacy is conducted to verify security and storage conditions as well as the physical inventory. Auditors also verify that the current IRB-approved version of the consent form was signed prior to registration and that

subjects were informed of new findings that could affect their willingness to participate in the study.

The audit report is comprised of three components: 1) conformance to IRB and informed consent requirements, 2) the pharmacy and use of NCI DARFs, and 3) patient case review. An acceptable rating requires no deficiencies, few lesser deficiencies, or major deficiencies that were addressed prior to the audit. Institutions found to be "unacceptable" or "acceptable but requires follow-up" on any component are required to submit a written response and/or corrective and preventative (CAPA) action plan. Failure to submit a written response including a corrective and preventative action plan within the required timeframe will result in suspension of registration privileges. A re-audit of any component rated as unacceptable will be conducted within one year after the unacceptable audit. An unacceptable rating for the same audit component on two consecutive audits will result in probation. Accrual will be suspended pending submission of a site improvement plan that addresses key infrastructural issues contributing to poor performance. An unacceptable rating at the second re-audit may result in termination from the group. If systematic misrepresentation of data is identified, an immediate repeat audit is scheduled by the representatives from the Group with the NCI and/or the FDA present.

In some cases, non-compliance for issues such as timeliness of data submission, SAE reporting and submission of specimens is monitored off site rather than scheduling a re-audit. Failure to show improvement may result in scheduling of a re-audit or other disciplinary action.

Results of all Quality Assurance Audits are reported to the NCI, the Principal Investigator of the institution that was audited, and representative of the Group. Protocol specific audit results are also sent to the Lead Group to inform the statisticians, data chairs and study chairs of all discrepancies involving eligibility, treatment, toxicity or response assessment.

The Quality Assurance Program performs their educational role through several mechanisms including presentations during the Group Meetings online Clinical Trials Training Courses, collaboration with others such as Pharmacy Committees and Statistical Centers to develop training tools, and memos and newsletter articles that are distributed to all Group institutions to educate research staff about changes in regulatory and quality assurance issues and audit procedures.

b. On Site Auditing

In addition to the standard auditing process outlined above, the following additional requirements will be implemented for this study:

- First on-site audit visit at each institution within 3 months of first patient registration to a sub-study.
- On site audits for all sites with patients registered to a sub-study twice per year. Additional visits to a site may be scheduled in response to several factors - rate of accrual, previous monitoring visit results, centralized monitoring outcome, change in staff, etc.
- An exception to the onsite audit requirement will be allowed in the following circumstances:
  - Sites that use a centralized pharmacy and data management team may be monitored at this central location.
  - Sites that had an acceptable on site pharmacy audit in the last year may be audited off site at a central location.

- Sites that had an acceptable patient case review outcome at their last audit and have not enrolled patients to any new sub-studies may be put on an annual schedule.

100% effort for two full time auditors is allocated to Lung-MAP for conducting on site audits, but auditing responsibilities are shared by the SWOG audit team members at the Operations Office. Additional site visits may be sub-contracted with other Network Groups, if necessary.

c. Centralized Data Coordinator Monitoring at the SWOG Statistics and Data Management Center

The SWOG Statistics and Data Management Center (SDMC) will support the risk-based monitoring approach for this trial with the following actions:

- Monitor data quality through routine review of submitted data such as on-study, baseline and follow-up tumor assessment, lab, treatment, off protocol treatment, and follow-up case report forms to identify and follow-up on missing data, inconsistent data, data outliers, and potential protocol deviations that may be indicative of systemic or significant errors in data collection and reporting at a site.

- Analyze site characteristics, performance metrics and clinical data to identify trial sites with characteristics correlated with poor performance or noncompliance through the SWOG Institutional Performance Reporting mechanism and other available reports.

- Verify critical source data remotely via the collection and review of pathology, radiology and applicable lab reports. This includes the review and confirmation of appropriate disease classification as determined by the pathology report, and assessment of response to treatment utilizing RECIST 1.1 based on scan reports uploaded to the Electronic Data Capture (EDC) system and submitted follow-up tumor assessment forms.

- To assure data are as consistent, complete and accurate as possible, all subject data must undergo careful review by Data Coordinators (DCs). After verifying that all data forms required to determine eligibility have been received or at a time point designated when all the required forms should have been received, the DC reviews the data and completes an initial evaluation.

The initial review includes the following:

- Determine that all required data fields on each form were completed and are consistent with other data.
- Determine if all pre-study tests and exams were performed within protocol specified time limits.
- Determine if each eligibility criterion was met and properly documented.
- Review and confirm pathology based on the pathology report uploaded to the EDC system.
- Verify that stratification and/or descriptive factors (if applicable) were correctly identified at registration.
- Verify that the subject received the assigned study treatment and correct dose(s).

- Verify that the treatment was started within the time limit indicated in the protocol (if applicable).
- Determine if adverse events reported are consistent with other data and entered as required by study specifications.
- Post internal notes to add additional information which may be useful to the study sponsor, monitors, or statisticians, but which do not require action by site personnel.
- Use the query tool to request additional data classifications and corrections of the CRA.

The DC will perform subsequent review of data when new data become available or queries are answered. Regular review will also occur while patients are still on-study, at the time of progression, once they are removed from study and at the time of death.

Subsequent reviews include the following:

- Determine if all required data fields on each newly submitted form were completed and consistent with other data.
- Evaluate all new treatment documentation for correct treatment and dose.
- Conduct assessment of response to treatment utilizing RECIST 1.1 based on scan reports uploaded to the EDC and submitted follow-up tumor assessment forms.
- Review and code any new concomitant medications as required by study specifications.
- Evaluate if the subject is or should be off protocol treatment per protocol criteria.
- Review and evaluate death if death of subject is reported.
- Use the query tool to request additional data classifications and corrections.
- Post internal query notes to add additional information that may be useful to the study sponsor, monitor, or statisticians but which do not require action by site personnel.
- Review site responses to the queries and the corrected or amended eCRF pages. When corrections and responses are considered satisfactory, queries are closed by the data coordinators. Unsatisfactory responses are re-queried and tracked.
- Perform re-evaluations promptly after responses to queries are received.

d. Safety Specific Centralized Monitoring

Each Serious Adverse Event (SAE) report submitted (via National Cancer Institute systems CTEP-AERS) will be reviewed by the SWOG SAE Coordinator. For each report, supporting documentation will be requested and compiled with the report and sent to the Physician Reviewer. As mentioned below, all sites will undergo mandatory training, and this will include training regarding SAE reporting. SWOG regularly monitors timeliness of SAE reporting and addresses any issues of poor performance with individual sites.

The study will be monitored for underreporting/missed Serious Adverse Events. The SWOG SAE Coordinator receives a weekly report from the database that includes all adverse events that are submitted through routine submission that potentially also meet expedited reporting criteria but for which no CTEP-AERS report is found. The Coordinator is responsible for following up with the responsible site to ensure that SAEs are not missed/underreported.

The study will be monitored for trends in Serious Adverse Events. A "new SAE on study" report is generated each time a new Serious Adverse Event is entered into the SWOG database. It is a cumulative report that lists all SAEs reported for the protocol. This allows those who review the report to identify concerning trends in reported events; events that may be occurring at greater intensity (higher toxicity grade) or frequency than expected. The SAE Coordinator and Physician Reviewer are responsible for regularly monitoring this report as well as the Study Chair and assigned Statisticians.

e. Additional Approaches to be Used

- Mandatory training of key site personnel prior to first patient registration.
- Timely review of all monitoring reports to identify sites that require additional training, monitoring, disciplinary action, etc.
- Routine monthly communication between monitor and site staff to assess potential problem areas, provide feedback, identify staff turnover, etc.
- Additional mandatory centralized training to be provided to all sites if major changes to the protocol occur or common problem areas are identified.

f. Blinded Independent Central Review of Response and Progression-Free Survival Endpoint

For information on the Blinded Independent Centralized Review, please refer to the IROC S1900B Imaging Charter.

All participants will undergo serial CT or MRI imaging: baseline/pre-treatment and every 8 weeks until progression of disease (as determined by local site assessment) and discontinuation of study treatment.

Collection and storage of all images as well as management of the independent review process will be the responsibility of the National Cancer Institute's (NCTN) Imaging and RT Quality Assurance Service Core (IROC).

The same imaging modality MUST be used for an individual patient throughout the course of the trial, with the exception of a PET/Spiral CT used at baseline where the CT is of diagnostic quality, follow-up scans can be done by a spiral CT or if a PET/conventional CT is used at baseline where the CT is of diagnostic quality, follow-up scans can be done by conventional CT. No other methods of assessments are interchangeable. The pre- and post-treatment CT or MRI images must be submitted to IROC for all study participants. CT is the preferred imaging modality unless there is a medical contraindication.

Clinical management and treatment decisions will be made by the treating physician based on local site assessments and other clinically appropriate considerations. The study will collect and archive 100% of scans for randomized patients through the time of confirmed progression. These will be ready for independent review should a sub-study terminate early for a large effect on PFS or ORR.

At the time that central review is indicated, SWOG will provide IROC with the registration date and patient number, along with a blinded code indicating which reviewer will be assigned to each case. This ensures that each reader reviews a balanced number of cases from each study arm. An experienced team of

radiologists will be identified by IROC. A designated radiologist will review each image for assessment of progression of disease per RECIST 1.1 criteria. The same reviewer will read all study images of an individual study participant. Data from local reviews will not be provided to the central reviewers in order to keep the central reviewers blinded to the results of the local investigator-assessed PFS.

The actual progression will be determined at the SWOG Statistics and Data Management Center, using a composite of the IROC assessment, in conjunction with possible data on progression or symptomatic deterioration. Results of the central review will NOT be communicated to the local site. Decisions regarding clinical management of the patient will be made by the treating physician based on local site assessments/reviews and other clinical considerations.

The BICR audit analysis will proceed following the algorithm specified in Dodd et.al 2011. *(1)* Specific details for the inputs of this algorithm are described in Section 11.

Review of pre-treatment CT/MRI exam will be performed as follows: The reader will review all anatomic areas (chest, abdomen) imaged and available. The target lesions to be evaluated will be defined/determined by the review of the pre-treatment exam. A maximum of 5 target lesions will be defined with a maximum of 2 in a single organ. The 5 target lesions will be chosen with representation from all organs involved with the tumor. Additional significant non-target lesions and areas of non-measurable disease will be noted. A screen capture of each target lesion, annotated with a pointer and a lesion reference number assigned to the target lesion, will be generated and archived. This will be used on subsequent reads to ensure concordance of lesions on follow-up/post-treatment exams. Measurements will be made from the axial scan (generally the post contrast scan) that best demonstrates the lesion as distinct from background. All measurements will be made by electronic calipers. A screen capture of the actual measurement axis with calipers will be saved and archived with the exam permanently at IROC.

Review of post-treatment image exam(s) will be performed as follows: The pre-treatment annotated exam and CRF will be reviewed to ensure lesion concordance. Readers will review all images for the current time point prior to making measurements. All measurements will be made by electronic calipers. A screen capture of the actual measurement axis with calipers will be saved and archived with the exam permanently at IROC.

1. Communication of Monitoring Results

The monitoring team will meet monthly to share all aspects of monitoring (on-sites, centralized, safety, alternative). When needed, the SWOG Executive Officer for Quality Assurance will be consulted.

Routine site audits will be reported according to NCI Clinical Trials Monitoring Branch requirements. Additional monitoring visits (those performed at greater frequency than required by the Clinical Trials Monitoring Branch) will be maintained in the CTMB-AIS data base and regularly reviewed by SWOG monitoring staff.

Summarized results of all monitoring visits will be provided annually to the study's Data and Safety Monitoring Committee, the SWOG Board of Governors, the study team and the FDA.

2. Management of Noncompliance

Issues of particular concern related to patient safety and questions of site fraud will be managed according to SWOG standard policies and the policies of the NCI Clinical Trials and Monitoring Branch for auditing of clinical trials under the NCI National Clinical Trials Network (NCTN) Program.

Where important deviations are discovered, additional site training components will be developed and implemented.

As with standard NCTN procedures, sites will be required to develop and implement corrective action plans in response to any deficiencies identified at a monitoring visit.

3. Ensuring Quality Monitoring

All staff involved in monitoring are required to undergo training in the principles of clinical investigations and human subject's protection. They are also required to complete the same protocol specific training required of the site staff.

All monitoring and auditing process for the study will be reviewed by study leadership twice per year to ensure conformance to the monitoring plan.

4. Monitoring Plan Amendments

At each formal review of the monitoring plan and conformance to it, the study leadership will make a recommendation regarding the need for amendments to the monitoring plan. These amendments will be reviewed and approved by NCI and provided in this protocol section and will be submitted to the FDA.

REFERENCES

1 Harrington D, Fleming T, Green S. In Crowley J and Johnson RA Eds. Survival Analysis. Hayward, CA: IMS Lecture Notes Monograph Series, 2:269-286, 1982.