CHILDREN'S ONCOLOGY GROUP

The world's childhood cancer experts

PPD

PPD

October 28, 2022

PPD

RE: Request for Amendments with FDA requested language for Pediatric MATCH consents

Dear PPD,

The study committee thanks CTEP for forwarding the Amendment Request dated October 17, 2022. In response to the request, please see attached Amendment #3 to APEC1621N. The complete list of changes can be found below.

Please contact us if you have any further questions.

Sincerely,

PPD

CHILDREN'S ONCOLOGY GROUP

SUMMARY OF CHANGES: PROTOCOL

In accordance with the above discussion, the following specific revisions have been made to the protocol.
Additions are in boldfaced font and deletions in ~~strikethrough~~ font.

#	Section	Page(s)	Change
1.	General	All	Updated protocol version date in the footer.
2.	Cover Page	1	Updated version date and amendment number.
3.	Contact Information	2	Cancer Trials Support Unit (CTSU)information updated with email address **CTSURegHelp@coccg.org**
4.	Table of Contents	3-5	Updated for re-pagination.
5.	Study Committee	7	Added PPD as Research Coordinator Removed PPD and added PPD as Protocol Coordinator

Activated: 09/14/2020
Closed:

Version Date: 10/28/2022
Amendment: # 3

CHILDREN'S ONCOLOGY GROUP

APEC1621N

NCI-COG PEDIATRIC MATCH (MOLECULAR ANALYSIS FOR THERAPY CHOICE)- PHASE 2 SUBPROTOCOL OF LOXO-292 IN PATIENTS WITH TUMORS HARBORING RET GENE ALTERATIONS

Open to COG Member Institutions in Australia, New Zealand, Canada, and in the USA

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Contact Information

For Regulatory Requirements	**For patient enrollments:**	**For Data Submission**
Regulatory documentation must be submitted to the Cancer Trials Support Unit (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 by phone or email: 1-866-651- CTSU (2878), or CTSURegHelp@coccg.org to receive further instruction and support. Contact the CTSU Regulatory Help Desk at 1-866-651-2878 for regulatory assistance..	Please 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. Please see the Submission Schedule in the CRF packet for further instructions.

The most current version of the study protocol must be downloaded from the protocol-specific page located on the CTSU members' website (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 log in with a CTEP-IAM username and password. Permission to view and download this protocoland its supporting documents is restricted and is based on person and site roster assignment housed in the CTSU Regulatory Support System (RSS).

For clinical questions (ie, patient eligibility or treatment-related)
Contact the Study PI of the Lead Protocol Organization.

For non-clinical questions (ie, 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.

The CTSU Website is located at https://www.ctsu.org.

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STUDY COMMITTEE, CONT.

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SEE SECTION 8.4.4 FOR SPECIMEN SHIPPING ADDRESSES

The Children's Oncology Group has received a Certificate of Confidentiality from the federal government, which will help us protect the privacy of our research subjects. The Certificate protects against the involuntary release of information about subjects collected during the course of our covered studies. The researchers involved in the studies cannot be forced to disclose the identity or any information collected in the study in any legal proceedings at the federal, state, or local level, regardless of whether they are criminal, administrative, or legislative proceedings. However, the subject or the researcher may choose to voluntarily disclose the protected information under certain circumstances. For example, if the subject or his/her guardian requests the release of information in writing, the Certificate does not protect against that voluntary disclosure. Furthermore, federal agencies may review our records under limited circumstances, such as a DHHS request for information for an audit or program evaluation or an FDA request under the Food, Drug and Cosmetics Act.

The Certificate of Confidentiality will not protect against mandatory disclosure by the researchers of information on suspected child abuse, reportable communicable diseases, and/or possible threat of harm to self or others.

ABSTRACT

This subprotocol is a component of the Pediatric MATCH trial APEC1621. The APEC1621SC screening protocol details the process used to identify actionable mutations in patient tumor samples which will determine eligibility for this subprotocol. This is a phase 2 trial of selpercatinib (LOXO-292) in children with relapsed or refractory solid tumors (including lymphomas, histiocytoses and CNS) harboring RET genomic alterations. Selpercatinib (LOXO-292) is a novel, highly selective, ATP-competitive small molecule inhibitor of the RET receptor tyrosine kinase that has shown promise in adults with *RET*-altered cancers. The selectivity and highly potent activity of selpercatinib (LOXO-292) against RET in combination with favorable pharmacokinetic properties (high bioavailability, predictable exposure, significant CNS penetration, and low potential for drug interactions) suggest it may be a promising agent in pediatric patients with *RET*-altered tumors. Selpercatinib (LOXO-292) will be given at the recommended phase 2 dose (RP2D) of 90 mg/m^2/dose twice daily (BID) continuously for 28-day cycles. The primary endpoint will be objective response rate as determined by RECIST. Progression free survival (PFS) will be assessed as a secondary endpoint.

EXPERIMENTAL DESIGN SCHEMA

Treatment Schedule Table	
Days 1-28	selpercatinib (LOXO-292)
Day 28	Evaluation

Selpercatinib (LOXO-292) will be administered at a dose of 90 mg/m^2/dose twice daily (max dose 160 mg BID); a cycle will be 28 days. Evaluations will occur every other cycle x 3, then every third cycle.

Therapy will be discontinued if there is evidence of progressive disease or drug related dose-limiting toxicity that requires removal from therapy. Therapy may otherwise continue for up to 2 years (maximum of 26 cycles) provided the patient meets the criteria for starting subsequent cycles (Section 5.2) and does not meet any of the criteria for removal from protocol therapy criteria (Section 10.0).

1.0 GOALS AND OBJECTIVES (SCIENTIFIC AIMS)

1.1 Primary Aims

1.1.1 To determine the objective response rate (ORR; complete response + partial response) in pediatric patients treated with selpercatinib (LOXO-292) with advanced solid tumors (including CNS tumors), lymphomas or histiocytic disorders that harbor activating genetic alterations in the RET pathway.

1.2 Secondary Aims

1.2.1 To estimate the progression free survival in pediatric patients treated with selpercatinib (LOXO-292) with advanced solid tumors (including CNS tumors), lymphomas or histiocytic disorders that harbor activating genetic alterations in the RET pathway.

1.2.2 To obtain information about the tolerability of selpercatinib (LOXO-292) in children and adolescents with relapsed or refractory cancer.

1.3 Exploratory Aims

1.3.1 To explore approaches to profiling changes in tumor genomics over time through evaluation of circulating tumor DNA.

2.0 BACKGROUND

2.1 Introduction/Rationale for Development

Constitutive activation of receptors within the family of receptor tyrosine kinases (RTKs) is one of the most common molecular defects found in cancers. The "rearranged during transfection" (*RET*) protooncogene is one such receptor in the RTK family that is found to be dysregulated in many cancers. The RET receptors are transmembrane glycoproteins and have critical roles in the normal development of kidney and enteric nervous system development and in the maintenance of several tissues, including neural, neuroendocrine, hematopoietic and male germ cell tissues.[1] Normal RET activation is initiated by a ligand from the glial cell line-derived neurotropic factor (GDNF) family ligands (GFLs), where this ligand does not bind to RET directly but instead binds to the GNDF family receptor-alpha (GFRα) RET co-receptors. Ligand binding to GFRα leads to RET dimerization and subsequently to RET kinase-mediated auto-phosphorylation of the tyrosine residues in the RET intracellular domain. Constitutive activation of RET can lead to the activation of several signal transduction pathways involved in cellular proliferation, motility, differentiation, and survival. Such downstream pathways include Mitogen-Activated Protein Kinase (MAPK), Phophatidylinositol-3-Kinase (PI3k), Janus Kinase-Signal Transducer and Activator of Transcription (JAK-STAT), Protein Kinase A (PKA) and Protein Kinase C (PKC).

RET is oncogenically activated through one of two mechanisms: chromosomal rearrangement leading to a constitutively-activated fusion protein or through a point mutation leading to kinase activation.

Oncogenic *RET* fusions have been identified in 6% of papillary thyroid cancer (PTC) and

2% of lung adenocarcinoma in adults.[2,3] In addition, activating *RET* mutations occur at high frequency in medullary thyroid cancer (MTC), with *RET* mutations present in >90% of MTCs in patients with multiple endocrine neoplasia type 2 (MEN2) and ~50-60% of sporadic MTCs.[4-10] Recent sequencing of tumors from 4,871 adult patients with diverse tumor types demonstrated that *RET* aberrations occurred in 1.8% of all solid tumors, most commonly as *RET* mutations (38.6%), followed by fusions (30.7%) and amplifications (25.0%).[11] Though generally infrequent, pathogenic *RET* mutations have been described in a variety of adult cancers, including renal papillary cell carcinoma, low grade glioma, testicular germ cell tumor, and pheochromocytoma.[12]

The incidence of *RET* fusions in PTC estimated to be between 24-37%, with *RET* fusions more frequently seen in pediatric PTC than PTC in adults.[13-15] The presence of a *RET* fusion in pediatric PTC is associated with a more aggressive phenotype than PTCs without a *RET* fusion.[16] Activating *RET* mutations are seen in MTC in the adolescent and young adult population at a similarly high frequency (93%) when compared to MTC in older adults.[15] Lastly, *RET* mutations have been detected in circulating tumor DNA obtained from children with malignant peripheral nerve sheath tumors.[17] Given the recent adult sequencing data demonstrating *RET* aberrations in 1.8% of a large variety of solid tumors, including sarcomas, it is likely that similar *RET* aberrations will be described in other pediatric solid tumors as well.

Several multi-kinase inhibitors (MKIs) with some degree of anti-RET activity are commercially-available or are currently being studied in clinical trials, such as the Federal Drug Administration (FDA)-approved MKIs sorafenib, sunitinib, cabozantinib, and vandetanib. However, in *RET*-altered tumors, the efficacy of these MKIs is limited due to dose limitations related to off-target toxicities and/or undesirable pharmacokinetic (PK) properties and only modest inhibition of RET signaling. Two MKIs, cabozantinib and vandetanib, have received regulatory approval for advanced MTC, regardless of *RET* mutation status, with response rates of 28% and 45%, respectively, and progression-free survival benefit of 7.2 and 11.2 months, respectively.[18,19] In both studies, subset analyses revealed that patients whose tumors harbored *RET*-activating mutations had greater benefit than patients whose tumors were not *RET*-altered.[19,20]

Patients with *RET*-altered cancers represent a population with an unmet need. Cytotoxic chemotherapy is often ineffective in patients with relapsed or refractory cancers, and targeted therapy may provide an alternative approach. Highly selective RET TKIs have not been developed to date. Selpercatinib (LOXO-292) is a novel, small molecule inhibitor of the RET receptor tyrosine kinase that has shown clinical promise in adults with *RET*-altered cancers.

2.2 Preclinical Studies

Selpercatinib (LOXO-292) is a novel, highly selective, ATP-competitive small molecule inhibitor of the RET receptor tyrosine kinase. Several pre-clinical studies[21] of selpercatinib (LOXO-292) have demonstrated potent RET inhibition in both *RET* fusion and *RET* mutant models.[21] In *vitro,* selpercatinib (LOXO-292) has been shown to potently inhibit the KIF5B-RET fusion protein and the full-length RET receptor harboring activating mutations (IC_{50} 1-10 nM), with much less cytotoxicity against human cancer cell lines without RET alterations (IC_{50} 100-10,000 nM). Minimal loss of inhibitory activity of selpercatinib (LOXO-292) was seen in the setting of potential acquired resistant mutations (i.e. V804L/M "gatekeeper" substitutions), which causes resistance to multi-kinase

inhibitors (MKIs). In xenograft models of human cancer cell lines harboring endogenous *RET* alterations, (non-small cell lung cancer CCDC6-RET and medullary thyroid cancer RET-C643W), and two patient-derived xenografts (PDXs) with CCDC6-RET fusions, selpercatinib (LOXO-292) inhibited tumor growth in a dose-dependent manner.[21]

Additionally, selpercatinib (LOXO-292) was more than 250-fold selective for RET than for 98% of 329 non-RET kinases tested in a large in vitro screen. This high degree of selectivity was maintained against both kinase and non-kinase off-targets when validated in additional enzyme, cell-based, radio-ligand binding and in vivo assays.[21]

2.2.1 Animal Toxicology

In toxicology studies of selpercatinib (LOXO-292) that were conducted in the rat and minipig, the primary pathologic findings for both species were noted in the tongue, pancreas, bone marrow and lymphoid tissues.[21] Other target tissues identified in the minipig included the gastrointestinal (GI) tract and ovaries. In the rat, other target tissues identified included multi-tissue mineralization, physeal cartilage, incisor teeth, lung, and possibly liver. Assessment of doses associated with moribundity/death revealed a steep dose-response curve for both species.

Selpercatinib (LOXO-292) was not mutagenic in the GLP bacterial mutation assay. When evaluated in two *in vitro* assays, selpercatinib (LOXO-292) was not genotoxic. Selpercatinib (LOXO-292) was not found to be phototoxic when evaluated in an *in vitro* neutral red uptake phototoxicity assay.[21]

2.3 Adult Studies

2.3.1 Phase 1/2 Studies

Results from a Phase 1/2 study of selpercatinib (LOXO-292) in patients ≥ 12 years of age (LIBRETTO-001, NCT03157128) were initially presented at the American Society of Clinical Oncology (ASCO) annual meeting in 2018.[22] As of June 2019, safety data were available from 531 patients who had received selpercatinib (LOXO-292) from active ongoing Phase 1/2. In the phase 1 portion of the study, dose range from 20 mg QD to 240 mg BID. The median age of patients was 59 years and ranged from 15 to 90 years.

Selpercatinib (LOXO-292) was well-tolerated, with most treatment-emergent AEs (TEAEs) categorized as Grade 1 in severity. A total of 271/531 (51.0%) across all dose levels experienced Grade 3-4 TEAEs, and considered to be related to study drug in 132 patients (24.9%). The most common Grade 3-4 TEAEs included hypertension (13.9%; 8.1% related), ALT increased (8.5%; 7.0% related), AST increased (6.4%; 4.5% related), hyponatremia (5.1%; 0.4% related), ECG QT prolonged (3.6%; 2.4% related), lymphopenia (3.4%; 1.1% related), thrombocytopenia and neutropenia (each 2.3%; 1.9% and 1.5% related, respectively), and diarrhea (2.1%; 0.8% related). Grade 4 TEAES of AST and ALT elevation, thrombocytopenia, and hypertension were noted in a total of 6 patients (6/531, 1.1%), none of which were life-threatening.

Patient plasma exposures were dose-dependent and linear in the dose range used (20 mg daily to 240 mg BID). The RP2D was determined to be a fixed dose of 160 mg BID (90 mg/m^2/dose). A total of 3 patients (0.6%) experienced AEs that met criteria for TLDs, and two of these occurred at a dose of 240 mg BID. The only DLT observed at 160 mg BID was in one patient Grade 2 hypersensitivity. A total of 24 patients were started at this dose during phase one dose escalation, and therefore the single DLT did not affect the selection of 160 mg BID as the RP2D. The Phase 2 dose expansion portion of this study is ongoing.

Efficacy in *RET* Fusion-positive Non-Small Cell Lung Cancer

As of June 2019, clinical data were presented at the IASLC World Conference on Lung Cancer, with a primary analysis set of 105 patients with *RET* fusion-positive non-small cell lung cancer (NSCLC). Within this patient subset, the objective response rate (ORR) by investigator response assessment was 67.6% (71/105; 95% confidence interval (CI): 58-75). The median duration of response (DOR) was 20.3 months (95% CI: 13.8-24.0), and the progression-free survival (PFS) was 18.4 months (95% CI: 12.9-24.9). ORR, DOR, and PFS were similar prior to prior therapy the patients had received (e.g. anti-PD-1/PD-L1, MKIs, etc). Of note, 11 patients in the primary analysis set had measurable CNS metastasis at baseline (based on investigator assessment), and the intracranial ORR in these patients was 90.9% (10/22; 95% CI: 59-100). Lastly, in a subset of efficacy-evaluable patients who were treatment naïve with *RET* fusion-positive NSCLS, the ORR was 85.3% (29/34; 95% CI: 69-95), including 7 partial response (PRs) pending confirmation as of December 2019.

Efficacy in *RET*-mutant and *RET* Fusion-positive Thyroid Cancer

As presented at the 2019 European Society of Medical Oncology Congress, 226 patients with *RET*-mutant medullary thyroid cancer (MTC) and 27 patients with *RET* fusion-positive thyroid cancer. The primary analysis set consisted of the first 55 *RET*-mutant MTC patients who had received prior cabozantinib and/or vandetanib. The ORR was 56.4% (31/55; 95% CI: 42-70). The median DOR was not reached, with 6/29 events observed and a median follow up of 10.6 months.

In a total of 88 patients with cabozantinib/vandetanib-naïve *RET*-mutant MTC treated with selpercatinib (LOXO-292), 76 were evaluable for efficacy, with an ORR of 59.2% (45/76; 95% CI: 47-70). The median PFS was not reached, with 1/76 (1.3%) events observed at a median follow-up of 5.7 months.

A total of 27 patients with *RET* fusion-positive thyroid cancer were treated with selpercatinib (LOXO-292), and represented 4 thyroid cancer histologies (papillary, poorly-differentiated, anaplastic, and Hurthle cell). Of these, 26 patients were eligible for efficacy evaluation. The ORR was found to be 61.5% (16/26; 95% CI: 41-80). The median follow-up was 9.9 months with a median PFS not reached, with 5/26 (19.2%) events observed.

Selpercatinib (LOXO-292) was granted Breakthrough Therapy Designation in September 2018 based on the results from LIBRETTO-001 and achieved FDA approval in May 2020.

***RET* Fusion/Mutation as biomarker**

Data from this phase 1/2 study of selpercatinib (LOXO-292) suggest that neither the specific *RET* fusion partner nor the specific *RET* point mutation altered the efficacy seen across the spectrum of tumor types. These data suggest that similar efficacy may be seen in pediatric patients with *RET* fusions or mutations, regardless of tumor type.

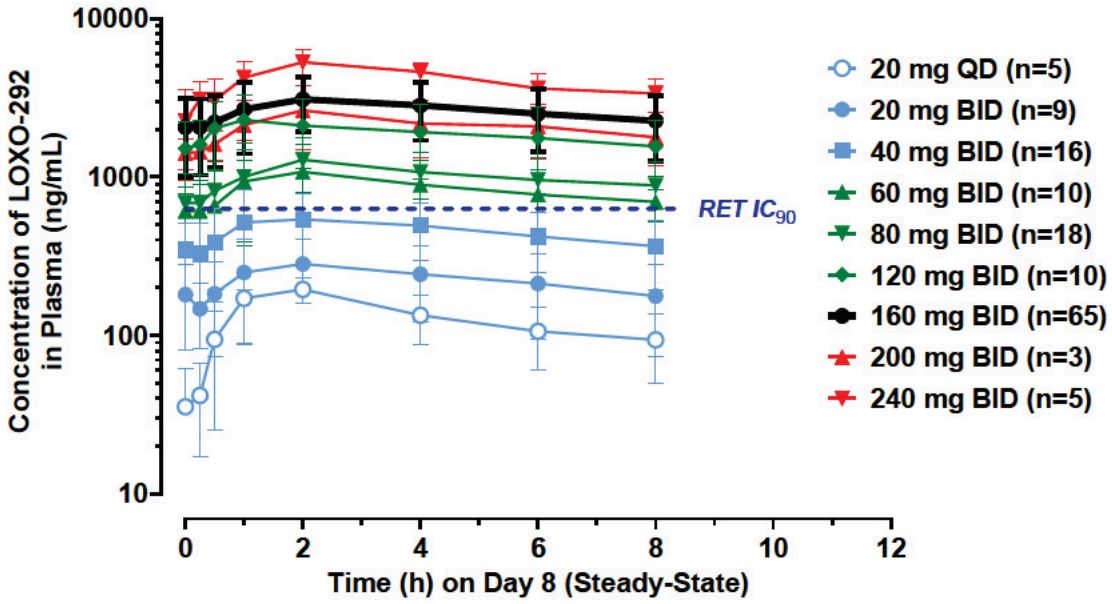
Pediatric Single Patient Protocols
As of 17 June 2019, Loxo Oncology has initiated 5 pediatric single patient protocols (SPPs), Special Access Scheme, or Temporary Authorization Use (ATU) cases to provide access to selpercatinib (LOXO-292) for patients with clinical need not meeting eligibility criteria for the ongoing clinical study. To date, no SAEs or TEAEs greater than Grade 3 have been attributed to study drug for these patients.

2.3.2 Pharmacology/Pharmacokinetics/Correlative and Biological Studies

Absorption:
Solubility and PK studies suggest that the PK exposure of selpercatinib (LOXO-292) may be reduced by proton pump inhibitors and other antacids. Modeling data suggest that human exposure will be higher under fed conditions (vs. fasted) at higher doses of selpercatinib (LOXO-292) (≥ 100 mg BID). Data from the study LOXO-RET-17001 analyzed as of August 2018 at steady-state (Cycle 1 Day 8) show that selpercatinib (LOXO-292) is absorbed after oral administration with a median time to maximum concentration (T_{max}) of approximately 2 hours. Plasma half-life was calculated to be approximately 20 hours (though was limited by a small sampling interval of 0 to 8 hours).

The mean C_{min} (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 IC_{90} for inhibition of RET.

Preliminary Pharmacokinetics of selpercatinib (LOXO-292) on Day 8 (Steady-State) in Cancer Patients



Metabolism:
Selpercatinib (LOXO-292) was stable during incubation with human whole blood, but was metabolized by microsomal fractions and hepatocytes from mice, rats, dogs, minipigs, and humans. The rates of metabolism suggest that selpercatinib (LOXO-292) will have moderate clearance in humans.[21]

Selpercatinib (LOXO-292) was not metabolized by cloned, expressed human cytochrome P-450 (CYP450) enzymes CYP1A2, CYP2C8, CYP2C9, CYP2C19, and CYP2D6. However, CYP3A4 was able to metabolize selpercatinib (LOXO-292). These data indicate that CYP3A4 is responsible for the metabolism of selpercatinib (LOXO-292).[21]

Elimination:
Renal excretion appears to be a minor pathway of elimination of selpercatinib (LOXO-292). In minipigs given an IV dose of selpercatinib (LOXO-292), urine collected through 48 hours after dosing contained 2.63% of the administered dose.[21]

In preliminary analysis of the adult PK study, low concentrations of selpercatinib (LOXO-292) were recovered as unchanged drug in urine. This finding indicates that the kidney contributes to overall clearance.[21]

Clinical Pharmacology:
Based on preclinical pharmacology studies with human cancer cells *in vitro* and in murine xenograft models, meaningful inhibition of RET in tumors is expected to be achievable with oral dose regimens at total daily doses $\geq$ 40 mg/day. 160 mg BID was selected as the recommended phase 2 dose (RP2D) based on

safety data (N=82) and preliminary efficacy data in 64 evaluable patients treated at doses from 20 mg QD through 240 mg BID.[23]

2.4 Pediatric Studies

2.4.1 Prior Experience in Children

An industry-sponsored phase 1/2 study of selpercatinib (LOXO-292) in pediatric patients is open for enrollment as of March 2019 (NCT03899792). A small number of patients have been treated with selpercatinib (LOXO-292).

2.4.2 Pharmacology/Pharmacokinetics/Correlative Biological Studies

There have been no pediatric Pharmacology/Pharmacokinetic/Correlative Biological Studies of selpercatinib (LOXO-292).

2.5 Overview of Proposed Pediatric Study

This is a phase 2 trial of selpercatinib (LOXO-292) monotherapy in children with recurrent or refractory solid tumors, CNS tumors, non-Hodgkin lymphomas and histiocytic disorders harboring specific activating mutations in the RET receptor tyrosine kinase.

No MTD was reached in the adult phase 1 study and the RP2D was determined to be 160 mg BID (90 mg/m^2/dose). The dose of 90 mg/m^2/dose administered BID will be used in this study.

The primary aim of this trial will be to establish the objective response rate to selpercatinib (LOXO-292). While there will not be multiple pre-determined mutation-based cohorts, responses will be analyzed retrospectively with respect to *RET* fusions versus *RET*-activating mutations.

Key secondary objectives include evaluation of the tolerability of selpercatinib (LOXO-292) in pediatric patients. Toxicity will be assessed using the CTCAE V5.0. Imaging for disease evaluation will occur every other cycle x3, then every three cycles. Disease response will be assessed according to RECIST v1.1 for solid tumors and 2-dimensional measurement for CNS tumors.

3.0 SCREENING AND STUDY ENROLLMENT PROCEDURES

3.1 Study Enrollment

Patient enrollment for this study will be facilitated using the Oncology Patient Enrollment Network (OPEN), a web-based registration system available on a 24/7 basis. It is integrated with the NCI Cancer Trials Support Unit (CTSU) Enterprise System for regulatory and roster data and, upon enrollment, initializes the patient position in the RAVE database.

3.1.1 **Access requirements for OPEN**:

Patient enrollment will be facilitated using the Oncology Patient Enrollment Network (OPEN). The Oncology Patient Enrollment Network (OPEN) is a web-based registration system available on a 24/7 basis. OPEN is integrated with CTSU regulatory and roster data and with the Lead Protocol Organization (LPOs) registration/randomization systems or Theradex Interactive Web Response System

(IWRS) for retrieval of patient registration/randomization assignment. OPEN will populate the patient enrollment data in NCI's clinical data management system, Medidata Rave.

Requirements for OPEN access:

- A valid CTEP-IAM account;
- To perform enrollments: Be on a LPO roster, ETCTN Corresponding roster, or PO roster with the role of Registrar. Registrars must hold a minimum of an AP registration type;
- Have an approved site registration for a protocol prior to patient enrollment.

To assign an Investigator (IVR) or Non-Physician Investigator (NPIVR) as the treating, crediting, consenting, drug shipment (IVR only), or receiving investigator for a patient transfer in OPEN, the IVR or NPIVR must list the IRB number used on the site's IRB approval on their Form FDA 1572 in RCR.

Prior to accessing OPEN, site staff should verify the following:

- Patient has met all eligibility criteria within the protocol stated timeframes; and
- All patients have signed an appropriate consent form and HIPAA authorization form (if applicable).

Note: The OPEN system will provide the site with a printable confirmation of registration and treatment information. Please print this confirmation for your records.

Access OPEN at https://open.ctsu.org or from the OPEN link on the CTSU members' website. Further instructional information is in the OPEN section of the CTSU website at https://www.ctsu.org or https://open.ctsu.org. For any additional questions, contact the CTSU Help Desk at 1-888-823-5923 or ctsucontact@westat.com.

Please see Appendix IX for detailed CTEP and CTSU Registration Procedures including registration in Registration and Credential Repository (RCR), requirements for site registration, submission of regulatory documents and how to check your site's registration status.

3.1.2 IRB Approval

Each investigator or group of investigators at a clinical site must obtain IRB approval for this protocol and submit IRB approval and supporting documentation to the CTSU Regulatory Office before they can be approved to enroll patients. For CTEP and Division of Cancer Prevention (DCP) studies open to the National Clinical Trials Network (NCTN) and NCI Community Oncology Research Program (NCORP) Research Bases after March 1, 2019, all U.S.-based sites must be members of the NCI Central Institutional Review Board (NCI CIRB). In addition, U.S.-based sites must accept the NCI CIRB review to activate new studies at the site after March 1, 2019. Local IRB review will continue to be

accepted for studies that are not reviewed by the CIRB, or if the study was previously open at the site under the local IRB. International sites should continue to submit Research Ethics Board (REB) approval to the CTSU Regulatory Office following country-specific regulations.

Sites participating with the NCI CIRB must submit the Study Specific Worksheet for Local Context (SSW) to the CIRB using IRBManager to indicate their intent to open the study locally. The NCI CIRB's approval of the SSW is automatically communicated to the CTSU Regulatory Office, but sites are required to contact the CTSU Regulatory Office at CTSURegPref@ctsu.coccg.org to establish site preferences for applying NCI CIRB approvals across their Signatory Network. Site preferences can be set at the network or protocol level. Questions about establishing site preferences can be addressed to the CTSU Regulatory Office by email or calling 1-888-651-CTSU (2878).

Sites using their local IRB or REB, must submit their approval to the CTSU Regulatory Office using the Regulatory Submission Portal located in the Regulatory section of the CTSU website. Acceptable documentation of local IRB/REB approval includes:

- Local IRB documentation;
- IRB-signed CTSU IRB Certification Form; and/or
- Protocol of Human Subjects Assurance Identification/IRB Certification/Declaration of Exemption Form.

In addition, the Site-Protocol Principal Investigator (PI) (i.e. the investigator on the IRB/REB approval) must meet the following criteria in order for the processing of the IRB/REB approval record to be completed:

- Holds an active CTEP status;
- Rostered at the site on the IRB/REB approval (*applies to US and Canadian sites only*) and on at least one participating roster;
- If using NCI CIRB, rostered on the NCI CIRB Signatory record;
- Includes the IRB number of the IRB providing approval in the Form FDA 1572 in the RCR profile; and
- Holds the appropriate CTEP registration type for the protocol.

Additional Requirements

Additional requirements to obtain an approved site registration status include:

- An active Federal Wide Assurance (FWA) number;
- An active roster affiliation with the Lead Protocol Organization (LPO) or a Participating Organization (PO); and
- Compliance with all protocol-specific requirements (PSRs).

For information about the submission of IRB/REB approval documents and other regulatory documents as well as checking the status of study center registration packets, please see Appendix X.

Institutions with patients waiting that are unable to use the Portal should alert the CTSU Regulatory Office immediately at 1-866-651-2878 in order to receive further instruction and support. For general (non-regulatory) questions call the

CTSU General Helpdesk at: 1-888-823-5923.

Note: Sites participating on the NCI CIRB initiative and accepting CIRB approval for the study are not required to submit separate IRB approval documentation to the CTSU Regulatory Office for initial, continuing or amendment review.

Investigators and site staff will need to be registered with CTEP and have a valid and active Cancer Therapy Evaluation Program-Identity and Access Management (CTEP-IAM) account (check at < https://ctepcore.nci.nih.gov/iam/ >). This is the same account (user id and password) used for credentialing in the CTSU members' web site. To perform registrations in OPEN, the site user must have been assigned the 'Registrar' role on the relevant Group or CTSU roster. OPEN can be accessed at https://open.ctsu.org or from the OPEN tab on the CTSU members' side of the website at https://www.ctsu.org. Registrars must hold a minimum of an AP registration type.

3.1.3 Genetic Screening Procedures for Eligibility

Patient enrollment onto the APEC1621SC screening protocol is required. In Stage 2 of Pediatric MATCH (effective with Amendment #4 of APEC1621SC for patients enrolling on screening protocol) tumor genomic testing results from a CAP/CLIA-certified laboratory will be reviewed by the APEC1621SC Molecular Review Committee after APEC1621SC screening protocol enrollment to confirm the identification of an actionable Mutation of Interest (aMOI) for which a MATCH treatment subprotocol is available. Questions regarding interpretation of tumor testing results for potential APEC1621N study patients (such as whether a specific mutation would be considered actionable for the study) should be directed to the APEC1621SC and APEC1621N study chairs.

The treatment assignment to MATCH to a subprotocol (if a relevant aMOI is detected) will be communicated to the enrolling institution via the COG or MATCHBox treatment assignment mechanism at the time the results of MATCH are returned, upon which a reservation to APEC1621N will be secured by COG. Reservations should be withdrawn by the institution if at any point the patient indicates they do NOT intend to consent to participation or the site investigator indicates the patient will never be eligible for APEC1621N.

3.2 Informed Consent/Assent

The investigational nature and objectives of the trial, the procedures and treatments involved and their attendant risks and discomforts, and potential alternative therapies will be carefully explained to the patient or the patient's parents or guardian if the patient is a child, and a signed informed consent and assent will be obtained according to institutional guidelines.

3.3 Screening Procedures

Diagnostic or laboratory studies performed exclusively to determine eligibility for this trial must only be done after obtaining written informed consent. This can be accomplished through the study-specific protocol. Documentation of the informed consent for screening will be maintained in the patient's research chart. Studies or procedures that were

performed for clinical indications (not exclusively to determine eligibility) may be used for baseline values even if the studies were done before informed consent was obtained.

3.4 Eligibility Checklist

Before the patient can be enrolled, the responsible institutional investigator must sign and date the completed eligibility checklist. A signed copy of the checklist will be uploaded into RAVE immediately following enrollment.

3.5 Study Enrollment

Following a MATCH treatment assignment to a protocol, patients may be enrolled on the study once all eligibility requirements for the study have been met. Before enrolling a patient on study, the Study Chair or Vice Chair should be notified. Patients who give informed consent for the protocol in order to undergo screening for eligibility are not considered enrolled and should not be enrolled until the screening is completed and they are determined to meet all eligibility criteria. Study enrollment in Stage 2 of Pediatric MATCH (effective with Amendment #4 of APEC1621SC for patients enrolling on screening protocol) is outlined in Section 3.1.3.

Patients must be enrolled within 2 weeks (14 days) of treatment assignment. Protocol therapy must start no later than 7 calendar days after the date of enrollment. Patients enrolling onto APEC1621N will have a COG ID obtained through their prior enrollment onto the screening protocol or from a prior COG study. Patients who are started on protocol therapy prior to study enrollment will be considered ineligible.

All clinical and laboratory studies to determine eligibility must be performed within 7 days prior to enrollment unless otherwise indicated in the eligibility section below.

Note: No starter supplies will be provided. Drug orders of selpercatinib **(LOXO-292) should be placed with CTEP after enrollment and treatment assignment to APEC1621N with consideration for timing of processing and shipping to ensure receipt of drug supply prior to start of protocol therapy**

3.5.1 Reassignment Request through APEC1621SC (if unable to enroll within 8 week timeframe)

The treating team may email PedsMATCHOps@childrensoncologygroup.org and the APEC1621SC study co-chairs (dwparson@txch.org seibelnl@mail.nih.gov) with a request for a single treatment re-assignment for any patient who was previously matched to a therapeutic subprotocol arm, but were unable to enroll during the original specified reservations window. The request can be made within a year of the 'Pediatric MATCH-Reservation expiration date' stipulated in the original treatment assignment email when the patient was assigned. The treatment re-assignment request is subject to slot availability on the therapeutic subprotocol at the time of the request.

3.6 Institutional Pathology Report

The institutional pathology report from the tumor specimen submitted for sequencing will have been uploaded into RAVE immediately following enrollment on the APEC1621 master screening protocol.

3.7 Dose Assignment

The dose will be assigned via OPEN at the time of study enrollment.

4.0 PATIENT ELIGIBILITY

All clinical and laboratory studies to determine eligibility must be performed within 7 days prior to enrollment unless otherwise indicated. Laboratory values used to assess eligibility must be no older than seven (7) days at the start of therapy. Laboratory tests need **not** be repeated if therapy starts **within** seven (7) days of obtaining labs to assess eligibility. If a post-enrollment lab value is outside the limits of eligibility, or laboratory values are older than 7 days, then the following laboratory evaluations must be re-checked within 48 hours prior to initiating therapy: CBC with differential, bilirubin, ALT (SGPT) and serum creatinine. If the recheck is outside the limits of eligibility, the patient may not receive protocol therapy and will be considered off protocol therapy. Imaging studies, bone marrow biopsy and/or aspirate (when applicable) must be obtained within 14 days prior to start of protocol therapy (repeat the tumor imaging if necessary).

Clarification in timing when counting days: As an example, please note that if the patient's last day of prior therapy is September 1st, and the protocol requires waiting at least 7 days for that type of prior therapy, then that patient cannot be enrolled until September 8th.

Important note: The eligibility criteria listed below are interpreted literally and cannot be waived. All clinical and laboratory data required for determining eligibility of a patient enrolled on this trial must be available in the patient's medical or research record which will serve as the source document for verification at the time of audit.

4.1 Inclusion Criteria

4.1.1 APEC1621SC: Patient must have enrolled onto APEC1621SC and must have been given a treatment assignment to MATCH to APEC1621N based on the presence of an actionable mutation as defined in APEC1621SC. Examples of actionable mutations for APEC1621N are listed in Appendix VIII.

4.1.2 Age: Patients must be ≥ than 12 months and ≤ 21 years of age at the time of study enrollment.

4.1.3 Disease Status: Patients must have radiographically **measurable** disease (See Section 12) at the time of study enrollment. Patients with neuroblastoma who do not have measurable disease but have MIBG+ evaluable disease are eligible. Measurable disease in patients with CNS involvement is defined as any lesion that is at minimum 10 mm in one dimension on standard MRI or CT.

Note: The following do not qualify as measurable disease:
- malignant fluid collections (e.g., ascites, pleural effusions)
- bone marrow infiltration except that detected by MIBG scan for neuroblastoma
- lesions only detected by nuclear medicine studies (e.g., bone, gallium or PET scans) except as noted for neuroblastoma
- elevated tumor markers in plasma or CSF

- previously radiated lesions that have not demonstrated clear progression post radiation
- leptomeningeal lesions that do not meet the measurement requirements for RECIST 1.1.

4.1.4 Performance Level: Karnofsky ≥ 50% for patients > 16 years of age and Lansky ≥ 50 for patients ≤ 16 years of age (See Appendix I). Note: Neurologic deficits in patients with CNS tumors must have been relatively stable for at least 7 days prior to study enrollment. Patients who are unable to walk because of paralysis, but who are up in a wheelchair, will be considered ambulatory for the purpose of assessing the performance score.

4.1.5 Prior Therapy

4.1.5.1 Patients must have fully recovered from the acute toxic effects of all prior anti-cancer therapy and must meet the following minimum duration from prior anti-cancer directed therapy prior to enrollment. If after the required timeframe, the numerical eligibility criteria are met, e.g. blood count criteria, the patient is considered to have recovered adequately.

a. Cytotoxic chemotherapy or other anti-cancer agents known to be myelosuppressive. See https://www.cogmembers.org/site/disc/devtherapeutics/default.aspx for commercial and Phase 1 investigational agent classifications. For agents not listed, the duration of this interval must be discussed with the study chair and the study-assigned Research Coordinator prior to enrollment.
   i. ≥ 21 days after the last dose of cytotoxic or myelosuppressive chemotherapy (42 days if prior nitrosourea).

b. Anti-cancer agents not known to be myelosuppressive (e.g. not associated with reduced platelet or ANC counts): ≥ 7 days after the last dose of agent. See https://www.cogmembers.org/site/disc/devtherapeutics/default.aspx for commercial and Phase 1 investigational agent classifications. For agents not listed, the duration of this interval must be discussed with the study chair and the study-assigned Research Coordinator prior to enrollment.

c. Antibodies: ≥ 21 days must have elapsed from infusion of last dose of antibody, and toxicity related to prior antibody therapy must be recovered to Grade ≤ 1.

d. Corticosteroids: See Section 4.2.2.1. If used to modify **immune adverse events** related to prior therapy, ≥ 14 days must have elapsed since last dose of corticosteroid.

e. Hematopoietic growth factors: ≥ 14 days after the last dose of a long-acting growth factor (e.g. pegfilgrastim) or 7 days for short-acting growth factor. For growth factors that have known adverse events occurring beyond 7 days after administration, this period must be extended beyond the time during which adverse events are known to occur. The duration of this interval must be discussed with the study

chair and the study-assigned Research Coordinator.

f. Interleukins, Interferons and Cytokines (other than hematopoetic growth factors): ≥ 21 days after the completion of interleukins, interferon or cytokines (other than hematopoetic growth factors)

g. Stem cell Infusions (with or without TBI):
- Allogeneic (non-autologous) bone marrow or stem cell transplant, or any stem cell infusion including DLI or boost infusion: ≥ 84 days after infusion and no evidence of GVHD.
- Autologous stem cell infusion including boost infusion: ≥ 42 days.

h. Cellular Therapy: ≥ 42 days after the completion of any type of cellular therapy (e.g. modified T cells, NK cells, dendritic cells, etc.)

i. XRT/External Beam Irradiation including Protons: ≥ 14 days after local XRT; ≥ 150 days after TBI, craniospinal XRT or if radiation to ≥ 50% of the pelvis; ≥ 42 days if other substantial BM radiation.

Note: Radiation may not be delivered to "measurable disease" tumor site(s) being used to follow response to subprotocol treatment.

j. Radiopharmaceutical therapy (e.g., radiolabeled antibody, 131I-MIBG): ≥ 42 days after systemically administered radiopharmaceutical therapy.

k. Patients must not have received prior exposure to selpercatinib (LOXO-292) or other specific RET inhibitors.

4.1.6 Organ Function Requirements

4.1.6.1 Adequate Bone Marrow Function Defined as:

a. For patients with solid tumors without known bone marrow involvement:
- Peripheral absolute neutrophil count (ANC) ≥ 1000/mm^3
- Platelet count ≥ 100,000/mm^3 (transfusion independent, defined as not receiving platelet transfusions for at least 7 days prior to enrollment)

b. Patients with known bone marrow metastatic disease will be eligible for study provided they meet the blood counts in 4.1.6.1.a (may receive transfusions provided they are not known to be refractory to red cell or platelet transfusions). These patients will not be evaluable for hematologic toxicity.

4.1.6.2 Adequate Renal Function Defined as:
- Creatinine clearance or radioisotope GFR ≥ 70ml/min/1.73 m^2 or
- A serum creatinine based on age/gender as follows:

Age	Maximum Serum Creatinine (mg/dL)	
	Male	Female
1 to < 2 years	0.6	0.6
2 to < 6 years	0.8	0.8
6 to < 10 years	1	1
10 to < 13 years	1.2	1.2
13 to < 16 years	1.5	1.4
≥ 16 years	1.7	1.4

The threshold creatinine values in this Table were derived from the Schwartz formula for estimating GFR (Schwartz et al. J. Peds, 106:522, 1985) utilizing child length and stature data published by the CDC.

4.1.6.3 Adequate Liver Function Defined as:

- Bilirubin (sum of conjugated + unconjugated) ≤ 1.5 x upper limit of normal (ULN) for age
- SGPT (ALT) ≤ 135 U/L. (For the purpose of this study, the ULN for SGPT is 45 U/L.)
- Serum albumin ≥ 2 g/dL.

4.1.6.4 Adequate Cardiac Function Defined As:

- QTc interval ≤ 480 milliseconds

4.1.7 Informed Consent: All patients and/or their parents or legally authorized representatives must sign a written informed consent. Assent, when appropriate, will be obtained according to institutional guidelines.

4.2 Exclusion Criteria

4.2.1 Pregnancy or Breast-Feeding

Pregnant or breast-feeding women will not be entered on this study due to risks of fetal and teratogenic adverse events as seen in animal/human studies. Pregnancy tests must be obtained in girls who are post-menarchal. Males or females of reproductive potential may not participate unless they have agreed to use two (2) highly effective contraceptive method for the duration of study treatment and for at least 2 weeks after the last dose of selpercatinib (LOXO-292). Male study participants are to refrain from sperm donation during treatment and for 2 weeks after the last dose of selpercatinib (LOXO-292).

4.2.2 Concomitant Medications

4.2.2.1 Corticosteroids: Patients receiving corticosteroids who have not been on a stable or decreasing dose of corticosteroid for at least 7 days prior to enrollment are not eligible. If used to modify **immune adverse events** related to prior therapy, ≥ 14 days must have elapsed since last dose of corticosteroid (See Section 4.1.5.1.d).

4.2.2.2 Investigational Drugs: Patients who are currently receiving another investigational drug are not eligible.

4.2.2.3 Anti-cancer Agents: Patients who are currently receiving other anti-cancer

agents are not eligible.

4.2.2.4 Anti-GVHD agents post-transplant:
Patients who are receiving cyclosporine, tacrolimus or other agents to prevent graft-versus-host disease post bone marrow transplant are not eligible for this trial.

4.2.2.5 CYP3A4 Agents: Patients who are currently receiving drugs that are moderate or strong inducers or inhibitors of CYP3A4 are not eligible. Strong inducers or inhibitors of CYP3A4 should be avoided from 14 days prior to enrollment to the end of the study. See Appendix II for a list of agents. Note: CYP3A4 inducing anti-epileptic drugs and dexamethasone for CNS tumors or metastases, on a stable dose, are allowed.

4.2.2.6 Proton Pump Inhibitors (PPIs), H2 receptor antagonists and antacids: Concomitant use of PPIs during selpercatinib (LOXO-292) therapy should be avoided if feasible. If co-administration of selpercatinib and PPI is necessary, administer selpercatinib with a meal. If H2 receptor antagonist is necessary, administer selpercatinib 2 hours before or 10 hours after H2 receptor antagonist administration. If antacid use is necessary, administer selpercatinib 2 or more hours before or 2 or more hours after antacid administration.

4.2.3 Surgery: Patients who have major surgery within 14 days prior to C1D1 are not eligible. (Central line placement or subcutaneous port placement is not considered major surgery)

4.2.4 Patients with known clinically significant active malabsorption syndrome or other condition likely to affect gastrointestinal absorption of selpercatinib (LOXO-292) are excluded.

4.2.5 Patients with known hypersensitivity to any of the components of the investigational agent, LOXO 292 are excluded.

4.2.6 Patients with uncontrolled hypertension are excluded

4.2.7 Patients with uncontrolled symptomatic hyperthyroidism and hypothyroidism (i.e. the patient required a modification to current thyroid medication in 7 days prior to enrollment) are excluded.

4.2.8 Patients with uncontrolled symptomatic hypercalcemia and hypocalcemia are excluded.

4.2.9 Infection: Patients who have an uncontrolled infection are not eligible.

4.2.10 Patients who have received a prior solid organ transplantation are not eligible.

4.2.11 Patients who in the opinion of the investigator may not be able to comply with the safety monitoring requirements of the study are not eligible.

5.0 TREATMENT PROGRAM

5.1 Overview of Treatment Plan

Selpercatinib (LOXO-292) Treatment Schedule Table	
Days 1-28	90 mg/m^2/dose orally twice daily (max dose 160 mg BID)
Day 28	Evaluation

Patients will receive selpercatinib orally twice daily, continuously for 28-day cycles (please see capsule dosing nomogram in Appendix V-A). Evaluations will occur at the end of every other cycle x 3, then every 3 cycles. A cycle may be repeated up to a total duration of therapy of 2 years (maximum of 26 cycles).

Drug doses should be adjusted based on the BSA calculated from height and weight measured within 7 days prior to the beginning of each cycle. Selpercatinib is administered orally twice daily, approximately 12 hours apart. Doses may be taken without regard to food. Capsules are to be swallowed whole. Do not chew, crush or open capsules. Oral suspension may be administered orally or by naso- or gastric-feeding tube. If study subject vomits immediately after taking a capsule dose and the capsules are still intact, the dose may be repeated. If study subject vomits after taking an oral suspension dose, the dose should not be repeated. If a dose is missed, it may be administered if there are at least 6 hours remaining until the next scheduled dose.

Doses of selpercatinib capsules should be rounded to the nearest 40 mg (Appendix V-A). Calculated dosing volumes of selpercatinib suspension formulation should be rounded to the nearest 0.1 mL (2 mg) for doses ≤ 45 mg (in oral syringes ≤ 3 mL) and 0.2 mL (4 mg) for doses > 45 mg (in oral syringes ≥ 5 mL) for the actual deliverable dose (Appendix V-B).

Therapy will be discontinued if there is evidence of progressive disease or drug related dose-limiting toxicity that requires removal from therapy (Section 6.0). Therapy may otherwise continue for up to 2 years (maximum of 26 cycles) provided the patient meets the criteria for starting subsequent cycles (Section 5.2) and does not meet any of the criteria for removal from protocol therapy criteria (Section 10.0).

Selpercatinib is provided by the NCI PMB. **Do not use commercial supply**.

5.1.1 Therapy Delivery Map

See Appendix VI for therapy delivery map for Cycle 1 and subsequent cycles.

5.1.2 Intra-Patient Escalation

Intrapatient dose escalation is not allowed.

5.2 Criteria for Starting Subsequent Cycles

A cycle may be repeated every 28 days if the patient has at least stable disease and has again met laboratory parameters as defined in the eligibility section, Section 4.0 and eligible to continue agent administration per the requirements in Section 6.0

5.3 Grading of Adverse Events

Adverse events (toxicities) will be graded according to the current version of the NCI Common Terminology Criteria for Adverse Events (CTCAE). All appropriate treatment areas should have access to a copy of the current version of the CTCAEv5.0. A copy of the CTCAEv5.0 can be downloaded from the CTEP website (http://ctep.cancer.gov). Any suspected or confirmed dose-limiting toxicity should be reported immediately (within 24 hours) to the Study Chair.

5.4 Definition of Dose-Limiting Toxicity (DLT)

DLT will be defined as any of the following events that are possibly, probably or definitely attributable to protocol therapy. Dose limiting hematological and non-hematological toxicities are defined differently.

5.4.1 Non-Hematological Dose-Limiting Toxicity

5.4.1.1 Grade 2 Electrocardiogram QT corrected interval prolonged (QTC > 480ms) will be considered a non-hematological toxicity.

5.4.1.2 Any Grade 3 or greater non-hematological toxicity attributable to the investigational drug with the specific exclusion of:

- Grade 3 nausea and vomiting of less < 3 days duration
- Grade 3 liver enzyme elevation, including ALT/AST/GGT that returns to levels that meet initial eligibility criteria or baseline within 7 days. See Appendix X for values that represent thresholds between CTCAE grades. Note: For the purposes of this study the ULN for ALT is defined as 45 U/L.
- Grade 3 or 4 fever < 5 days duration.
- Grade 3 infection < 5 days duration.
- Grade 3 hypophosphatemia, hypokalemia, hypocalcemia or hypomagnesemia responsive to supplementation

- Any Grade 2 non-hematological toxicity that persists for ≥ 7 days and is considered sufficiently medically significant or sufficiently intolerable by patients that it requires treatment interruption.
- Note: Allergic reactions that necessitate discontinuation of study drug will not be considered a dose-limiting toxicity.

5.4.2 Hematological dose limiting toxicity

5.4.2.1 Hematological dose limiting toxicity is defined as:

a) In patients evaluable for hematological toxicity (see Section 4.1.6.1),

- Grade 4 thrombocytopenia or neutropenia, not due to malignant infiltration
- Grade 3 thrombocytopenia that persists for ≥ 7 days
- Grade 3 thrombocytopenia requiring a platelet transfusion on two separate days within a 7-day period
- Grade 3 thrombocytopenia with clinically significant bleeding
- Neutropenia or thrombocytopenia that causes a delay of > 14 days between treatment cycles (e.g. platelets <100K or ANC<1000).

5.4.2.2 Note: Grade 3 or 4 febrile neutropenia will not be considered a dose-

limiting toxicity.

6.0 DOSE MODIFICATIONS FOR ADVERSE EVENTS

The Study Chair must be notified of any dosage modification or use of myeloid growth factor.

6.1 Dose Modifications for Hematological Toxicity

6.1.1 If a patient experiences hematological toxicity as defined in Section 5.4.2.1, the treatment will be held. Counts should be checked every 3-4 days for thrombocytopenia and every other day for neutropenia during this time. If the toxicity resolves to meet eligibility parameters within 14 days of drug discontinuation, the patient may resume treatment at a reduced dose (see Appendix V-A for capsule formulation dosing nomogram and Appendix V-B for preparation of oral solution formulation). Doses reduced for toxicity will not be re-escalated, even if there is minimal or no toxicity with the reduced dose.

6.1.2 If toxicity does not resolve to meet eligibility parameters within 14 days of drug discontinuation, the patient must be removed from protocol therapy.

6.1.3 If hematological dose-limiting toxicity recurs in a patient who has resumed treatment at the reduced dose, the patient must be removed from protocol therapy.

6.2 Dose Modifications for Non-Hematological Toxicity

6.2.1 If a patient experiences non-hematological dose-limiting toxicity as defined in Section 5.4.1, the treatment will be held. When the toxicity resolves to meet eligibility parameters or baseline within 14 days of drug discontinuation, the patient may resume treatment at a reduced dose (see Appendix V-A for capsule formulation dosing nomogram and Appendix V-B for oral suspension formulation). Doses reduced for toxicity will not be re-escalated, even if there is minimal or no toxicity with the reduced dose.

6.2.2 If toxicity does not resolve to meet eligibility or baseline parameters within 14 days of drug discontinuation, the patient must be removed from protocol therapy.

6.2.3 If dose-limiting toxicity recurs in a patient who has resumed treatment at the reduced dose, the patient must be removed from protocol therapy.

6.3 Growth Plate Toxicity

6.3.1 Patients who are found to have radiographic evidence of an open tibial growth plate should follow the radiographic monitoring as outlined in Section 8.2.1.

6.4 Dose Modification for QTc Prolongation

Adverse Reactions	Recommended Action
QTc interval ≥ 480-499	• Monitor and supplement electrolyte levels as clinically indicated, evaluation by a cardiologist and other necessary interventions may be considered, perform an additional EKG. • Selpercatinib may be resumed at the dose reduction outlined in Appendix V-A and Appendix V-B when QTc has returned to baseline value, and with continued ECG monitoring as clinically indicated.
QTc interval > 500 msec.	• Monitor and supplement electrolyte levels as clinically indicated, evaluation by a cardiologist and other necessary interventions may be considered, If any EKG demonstrates QTc > 500 msec, repeat the EKG twice (triplicate in total) and manually review to confirm accuracy. If QTc > 500 msec is confirmed on 2/3 ECGs, hold selpercatinib (LOXO-292) and assess for alternative causes (concomitant medications, electrolyte abnormalities). • Selpercatinib may be resumed at one reduced dose level when QTc has returned to baseline value, and with continued ECG monitoring as clinically indicated.
QTc interval prolongation with signs/symptoms of life-threatening arrhythmia	Discontinue selpercatinib permanently.

6.5 Dose Modification for Hypersensitivity

6.5.1 Signs and symptoms of hypersensitivity included fever, rash and arthralgias or myalgias with concurrent decreased platelets or transaminitis. If hypersensitivity occurs, withhold selpercatinib and begin corticosteroids at a dose of 1 mg/kg. Upon resolution of the event, resume selpercatinib at a reduced dose and increase the dose of selpercatinib by 1 dose level each week as tolerated until reaching the dose taken prior to onset of hypersensitivity. Continue steroids until patient reaches target dose and then taper. Permanently discontinue selpercatinib for recurrent hypersensitivity.

7.0 SUPPORTIVE CARE AND OTHER CONCOMITANT THERAPY

7.1 Concurrent Anticancer Therapy

Concurrent cancer therapy, including chemotherapy, radiation therapy, immunotherapy, or biologic therapy may NOT be administered to patients receiving study drug. If these treatments are administered the patient will be removed from protocol therapy.

7.2 Investigational Agents

No other investigational agents may be given while the patient is on study.

7.3 Supportive Care

Appropriate antibiotics, blood products, antiemetics, fluids, electrolytes and general supportive care are to be used as necessary. See Section 7.5 for drugs that should not be used concomitantly due to potential interactions with selpercatinib.

7.4 Growth Factors

Growth factors that support platelet or white cell number or function can only be administered for culture proven bacteremia or invasive fungal infection. The Study Chair should be notified before growth factors are initiated.

7.5 Concomitant Medications

7.5.1 CYP3A4 inhibitors or inducers: Strong or moderate CYP3A4 inhibitors or inducers are prohibited from 14 days prior to enrollment to the end of the study (see Appendix II for list of agents). Note: CYP3A4 inducing anti-epileptic drugs and dexamethasone for CNS tumors or metastases, on a stable dose, are allowed.

7.5.2 Selpercatinib is a moderate inhibitor of CYP2C8 and a weak inhibitor of CYP3A4. Avoid use of concomitant medications that are sensitive substrates of CYP2C8 or CYP3A4.

7.5.3 *In vitro*, selpercatinib is a substrate of transport proteins P-gp and BCRP. Use caution when selpercatinib is co-administered with medications that are strong inhibitors or inducers of P-gp and BCRP. In addition, selpercatinib inhibits MATE1, P-gp and BCRP. Use caution when co-administered with medications that are sensitive substrates of MATE1, P-gp and BCRP.

7.5.4 Selpercatinib is highly protein bound. Use caution when co-administered with other medications that are highly protein-bound.

7.5.5 PPIs, H2 Receptor Antagonists and Antacids:
Proton pump inhibitors (PPIs), H2 receptor antagonists and antacids may alter the pharmacokinetics of selpercatinib by reducing selpercatinib exposure. Avoid concomitant use of PPIs if possible. If co-administration of selpercatinib and PPI is necessary, administer selpercatinib with a meal. If H2 receptor antagonist is necessary, administer selpercatinib 2 hours before or 10 hours after H2 receptor antagonist administration. If antacid use is necessary, administer selpercatinib 2 or more hours before or 2 or more hours after antacid administration.

7.5.6 Avoid combination with other drugs with potential to lead to prolongation of QTc interval, if possible (see Appendix XIII). Monitor the QT interval with ECGs more frequently in patients who require treatment with concomitant medications known to prolong the QT interval

8.0 EVALUATIONS/MATERIAL AND DATA TO BE ACCESSIONED

8.1 Required Clinical, Laboratory and Disease Evaluation

All clinical and laboratory studies to determine eligibility must be performed within 7 days prior to enrollment unless otherwise indicated. Laboratory values used to assess eligibility (see Section 4.0) must be no older than seven (7) days at the start of therapy. Laboratory tests need **not** be repeated if therapy starts **within** seven (7) days of obtaining labs to assess eligibility. If a post-enrollment lab value is outside the limits of eligibility, or laboratory

values are older than 7 days, then the following laboratory evaluations must be re-checked within 48 hours prior to initiating therapy: CBC with differential, bilirubin, ALT (SGPT) and serum creatinine. If the recheck is outside the limits of eligibility, the patient may not receive protocol therapy and will be considered off protocol therapy. Imaging studies, bone marrow aspirate and/or biopsy, must be obtained within 14 days prior to start of protocol therapy (repeat the tumor imaging if necessary).

STUDIES TO BE OBTAINED	Pre-Study	During Cycle 1	Prior to Subsequent Cycles^
History	X	Weekly	X
Physical Exam with vital signs, Tanner Staging, and dentition exam	X	Weekly	X
Height, weight, BSA	X		X
Performance Status	X		
Pregnancy Test[1]	X		
CBC, differential, platelets	X	Weekly [2,3]	X[2,3]
Urinalysis	X		
Electrolytes including Ca^{++}, PO_4, Mg^{++}	X	Weekly	X
Creatinine, ALT, AST, bilirubin	X	Weekly	X[11]
Albumin	X	Weekly	X
Tumor Disease Evaluation[4-A, 4-B, 4-C]	X		Every other cycle x 3 then q 3 cycles [4]
Plain radiograph tibial growth plate (bone x-ray tests)[9]	X		Cycles 2 and 4, (concurrent with tumor disease evaluation), then every 6 months
EKG[10]	X	Day 1 and Day 8[10]	X[10]
Bone Marrow Aspirate and/or biopsy[5,6]	X		
Medication Diary[7]		Weekly	X
Circulating Tumor DNA (ctDNA-optional)[8]			Cycle 5, Day 1 and (for patients receiving ≥ 5 cycles only) at end of Protocol Therapy OR disease progression

^ Studies may be obtained within 72 hours prior to the start of the subsequent cycle.

1 Women of childbearing potential require a negative pregnancy test prior to starting treatment; sexually active patients must use an acceptable method of birth control. Abstinence is an acceptable method of birth control.

2 If patients have Grade 4 neutropenia then CBCs should be checked at least every other day until recovery to Grade 3 or until meeting the criteria for dose limiting toxicity.

3 If patients develop Grade 3 or higher thrombocytopenia then CBCs should be checked every 3-4 days until recovery per section 6.1

4 Tumor Disease Evaluation should be obtained on the next consecutive cycle after initial documentation of either a PR or CR. Subsequent scans may restart 2 cycles after the confirmatory scan. If the institutional investigator determines that the patient has progressed based on clinical or laboratory evidence, he/she may opt not to confirm this finding radiographically.

4-A Neurological exam also required for CNS patients.

4-B Non- Hodgkin Lymphoma/ Histiocytosis patients are required to have PET scans within 2 weeks prior to start of therapy and should also be followed with PET scans if positive at diagnosis. Refer to Section 12.8

[4-C] Patients with neuroblastoma must have both CT/MRI and MIBG scintigraphy prior to the start of protocol therapy if the patient was enrolled with or has a history of having MIBG avid tumor. Otherwise the patient must have either FDG-PET/CT or PET/MR prior to enrollment. For patients with neuroblastoma and measurable disease by CT or MRI, lesions should be measured and followed using the same modality (CT or MRI) in addition to MIBG or FDG-PET/CT. For patients with neuroblastoma and evaluable disease by MIBG scintigraphy, use the same modality (MIBG scintigraphy) to image and follow patients; CT/MRI are not required but may be performed as clinically indicated. Refer to Section 12.5.4 and Section 12.9.

[5] Bone marrow aspirate and/or biopsy only required in patients suspected of having bone marrow metastasis on the basis of history, symptoms, laboratory evaluation or other clinical data.

[6] Bone marrow aspirate and/or biopsy should be performed only when complete response or partial response is identified in target disease or when progression in bone marrow is suspected.

[7.] Patient diary (see Appendix III) should be reviewed after completion of each treatment cycle and uploaded into RAVE.

[8.] With consent two samples will be collected on this protocol (Cycle 5 Day 1; and for patients receiving ≥ 5 cycles, at progression or end of protocol therapy) see Section 8.4 and Appendix IV for details of the ctDNA studies. Note that a ctDNA sample is scheduled to be obtained on the APEC162SC screening protocol prior to the initiation of treatment on this subprotocol

[9.] Plain radiographs of at least one tibial growth plate should be obtained in all patients prior to first dose of protocol therapy. In patients with open growth plates, follow-up plain radiographs of the same growth plate(s) should be obtained according to Section 8.2.1.

[10] On Cycle 1 Day 1, Cycle 1 Day 8, and prior to subsequent cycles the morning dose of selpercatinib (LOXO-292 should be held until the pre-dose EKG assessment can be obtained.

[11] To be performed prior to the start of every subsequent cycle, and Day 15 of Cycle 2 and Cycle 3

8.2 Monitoring for Specific Toxicities

8.2.1 Growth Plate Toxicity

Patients will have a plain AP radiograph of a single proximal tibial growth plate obtained prior to the first dose of protocol therapy.

a. If patients are found to have a closed tibial growth plate, no further radiographs will be required.

b. If patients are found to have an open tibial growth plate, then repeat plain AP radiographs of the same tibial growth plate will be obtained prior to Cycles 2, 5 and every 6 months.

- Patients with evidence of growth plate thickening or other changes should have a knee MRI performed to further assess the degree of physeal pathology and undergo more frequent x-ray follow up at least every 3 cycles or as clinically indicated. MRI should be performed without contrast.
- Patients with knee MRI changes should be managed in an individualized manner. Decisions regarding continuation of selpercatinib (LOXO-292) should be made after discussion with the Study Chair or Study Vice-Chair and MATCH Leadership, taking into account the presence of any symptoms referable to the knee as well as the patient's response to selpercatinib (LOXO-292). Consultation with an orthopedic surgeon may also be indicated. Plans for follow-up imaging will also be made on an individualized basis, taking into account the presence of symptoms at the knee or other joints as well as the decision to continue selpercatinib (LOXO-292) or not.

8.3 Radiology Studies

8.3.1 Central Radiology Review for Response: Patients who respond (CR, PR) to therapy or have long term stable disease (SD) (≥ 6 cycles) on protocol therapy will be centrally reviewed. The Operations center will notify the site when a patient has met the criteria for review. The tumor disease evaluations to be submitted for review include baseline (prestudy) evaluations as well as all end of cycle tumor disease evaluations which occurred while the patient was on the subprotocol therapy study.

8.3.2 Technical Details of Submission:

To ensure an adequate interpretation of FDG-PET and CT with contrast scans, scans transferred between the treating institutions and the Imaging and Radiation Oncology Core Group IROC RI (QARC) must be submitted in Digital Imaging and Communications in Medicine (DICOM) format. BMP files, JPG files, or hard copies (films) are unacceptable for adequate interpretation of PET and CT with contrast scans. Imaging studies must be submitted electronically as outlined in the following paragraph. The images will be made available to study radiologists and nuclear medicine physicians for central review. Submission of Diagnostic Imaging data in DICOM format is required.

Alternatively, the images and reports may be submitted via sFTP to IROC Rhode Island. Digital data submission instructions including instructions for obtaining a sFTP account, can be found at http://irocri.qarc.org. Follow the link labeled digital data. Sites using the Dicommunicator software to submit imaging may continue to use that application.

Corresponding Radiology reports may be submitted along with the electronic submission sFTP or may be emailed to DataSubmission@QARC.org. The COG operations center and IROC are available to assist with any queries regarding the corresponding radiology reports which should be included when the scans are submitted

Questions may be directed to DataSubmission@QARC.org or 401.753.7600.

IROC Rhode Island (formerly QARC) will facilitate the central reviews.

For FDG-PET imaging, the transferred imaging data should include uncorrected and attenuation-corrected PET projection data, as well as the reconstructed PET or PET/CT images used by the institution to achieve a response assessment. If low-dose CT was used for attenuation correction, the acquired CT images should also be submitted. The imaging data submitted for central review must allow the study to be reconstructed and displayed in transaxial, sagittal and coronal formats using standard reconstruction techniques. Reconstructed MPEG clips and similar types of reconstructions will not be accepted. CT and MRI images similarly should be submitted in a format that either includes properly reconstructed multi-planar viewing formats in soft tissue and bone windows, or includes the thin-section axial acquisition data from which multi-planar reconstructions can be re-created.

Sites not able to submit imaging electronically may submit imaging via CD. CD's may be sent by courier to:

Address for submission: IROC RI (QARC)
Building B, Suite 201
640 George Washington Highway
Lincoln, RI 02865-4207
Phone: (401) 753-7600
Fax: (401) 753-7601
Web: http://irocri.qarc.org

8.4 Circulating Tumor DNA Study (optional)

8.4.1 Sampling Schedule

An initial sample was previously requested at time of enrollment onto the APEC1621SC screening protocol. Two additional samples (optional) will be collected into Streck Cell-Free DNA BCT tubes at the timepoints:

(1) Cycle 5 Day 1
(2) At disease progression or end of protocol therapy (for patients receiving ≥ 5 cycles of therapy only)

Peripheral blood samples for circulating tumor DNA should be obtained as follows:

- For patients ≥ 10 kg collect 20 mLs (10 mL per tube x 2 tubes)
- For patients ≥ 5 kg but < 10 kg collect 10 mL (one tube)
- For patients < 5 kg research samples will not be collected

In all cases, blood draw volumes should strictly adhere to institutional limitations, taking other blood draws into consideration. However, if a reduction in volume is required, samples should be collected in 10 mL increments (ie. 0, 10, or 20 mL should be collected such that each Streck Cell-Free DNA BCT is completely filled).

Established institutional guidelines should be followed for blood collection via vascular access devices. Heparin should be avoided in pre-collection flush procedures. If therapeutic heparin dosing contamination is a possibility, venipuncture is recommended as a first choice collection method. If a Streck Cell-Free DNA BCT tube immediately follows a heparin tube in the draw order, we recommend collecting an EDTA tube as a waste tube prior to collection in the Streck Cell-Free DNA BCT.

For patients who do not have indwelling catheters, blood should be collected via venipuncture. To guard against backflow, observe the following precautions:

- Keep patient's arm in the downward position during the collection procedure.
- Hold the tube with the stopper in the uppermost position so that the tube contents do not touch the stopper or the end of the needle during sample collection.
- Release tourniquet once blood starts to flow in the tube, or within 2 minutes of application.
- Fill tube completely.

- Remove tube from adapter and immediately mix by gentle inversion 8 to 10 times. Inadequate or delayed mixing may result in inaccurate test results.

8.4.2 Sample Processing

Samples do not need to be processed at the collection site.

8.4.3 Sample Labeling

Each tube must be labeled with the patient's study registration number, the study I.D (APEC1621N), and the date and time the sample was drawn. Data should be recorded on the appropriate transmittal form found in RAVE, which must accompany the sample(s).

8.4.4 Sample Shipping Instructions

Specimen should be shipped at room temperature to the BPC (address below). Upon arrival separation, extraction, and storage of plasma and cellular DNA will be performed. Samples should be shipped from Monday through Friday for Tuesday through Saturday delivery. If blood is collected in the Streck tube on Friday, over the weekend or on the day before a holiday, the sample should be stored in a refrigerator until shipped on the next business day. Ship by FedEx Priority Overnight using the COG FedEx account. Blood samples should be shipped the same day as collection, ship blood for Saturday delivery if shipped on Friday.

Ship specimens to the following address:

Biopathology Center
Nationwide Children's Hospital
Protocol APEC1621N-Peds MATCH*
700 Children's Drive, WA1340*
Columbus, OH 43205
Phone: (614) 722-2865
Fax: (614) 722-2897
Email: BPCBank@nationwidechildrens.org

*Be sure to include the room number. Packages received without the room number may be returned to the sender. Packages must be labeled "Peds MATCH" in order to expedite processing at the BPC.

9.0 AGENT INFORMATION

9.1 Selpercatinib (12/30/2021)

(LOXO-292, LY3527723, RETEVMO®) NSC# 812076, IND# [redacted]

9.1.1 Source and Pharmacology:

Selpercatinib (LOXO-292) is a potent selective, small molecule inhibitor of human RET receptor tyrosine kinase (RTK), designed to competitively block the adenosine triphosphate binding sites of RET RTK in tumors with oncogenic RET gene fusions, RET gene alterations or increased RET activity.

9.1.2 Pharmacokinetics (PK)/Pharmacodynamics (PD):

Selpercatinib is absorbed after oral administration with a median Tmax of approximately 2 hours. The mean absolute bioavailability of selpercatinib capsules is 73% (60% to 82%) in healthy subjects. The apparent volume of distribution (Vss/F) of selpercatinib is 191L. Protein binding of selpercatinib is 97% in vitro and is independent of concentration. The apparent half-life is 32 hours and steady state is reached in approximately 7 days. Following oral administration 69% of the administered dose was recovered in feces (14% unchanged) and 24% in urine (12% unchanged). The mean Cmin (pre-dose, trough concentration) is approximately 600 ng/mL in patients during steady-state treatment with 60 mg BID selpercatinib or higher, which corresponds to a mean plasma free drug concentration approximately equal to the IC90 for inhibition of RET. Selpercatinib exhibits linear PK with dose-proportionate increases in area under the curve (AUC_{0-24}) and maximum concentrations (Cmax) at 20 mg to 160 mg BID dosing range. Mean steady-state selpercatinib CV% Cmax was 2,980 (53%) ng/ml and AUC0-24 was 51,600 (58%) ng*h/ml.The mean plasma clearance range is 6.2-8.73 L/h within the above dosing range. Based on preclinical pharmacology experiments with human cancer cells in vitro and in murine xenograft models, meaningful inhibition of RET in tumors is expected to be achievable with oral dose regimens at total daily doses ≥ 40 mg/day. The dosage of 160 mg BID was selected as the adult recommended phase 2 dose (RP2D) based on safety data (N=82) and preliminary efficacy data in 64 evaluable patients treated at doses from 20 mg QD through 240 mg BID.

Studies in pediatric patients are ongoing. The dose of 92mg/m^2 BID up to a maximum of 160 mg BID in pediatric patients resulted in a similar range of exposrure as seen in adult cancer patietns treated with 160 mg BID (AUC_{0-24} of 51,600 ng*h/ml). No clinically significant differences in the PK of selpercatinib were observed based on mild or moderate renal impairment (creatinine clearance [CLcr] > 30 mL/min as estimated by Cockcroft-Gault). The effect of severe renal impairment (CLcr < 30mL/min) on selpercatinib PK has not been adequately studies. The selpercatinib AUC_{0-inf} increased 7%, 32%, and 77% in subjects with mild, moderate and severe hepatic impairment, respectively.

Selpercatinib has pH-dependent solubility and its PK can be affected by agents that modify gastric pH such as PPIs (e.g., omeprazole). Coadministration with multiple daily doses of omeprazole (PPI) decreased selpercatinib AUC_{0-inf} and C_{max} by 69% and 88%, respectively when selpercatinib was administered fasting. Coadministration with multiple daily doses of omeprazole did not significantly

change the selpercatinib $AUC_{0\text{-}inf}$ and C_{max} when selpercatinib was administered with food.

9.1.3 Potential Drug Interactions

In-vitro, selpercatinib is primarily metabolized by CYP3A4, but not by CYP1A2, CYP2C8, CYP2C9, or CYP2C19. Avoid use of concomitant medications that are moderate and strong inhibitors or inducers of CYP3A4.

In vitro, selpercatinib showed no significant inhibition or induction of CYP1A2, CYP2B6, CYP2C9, CYP2C19, or CYP2D6. Selpercatinib 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.

In vitro, selpercatinib 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. Use caution when co-administered with medications that are strong inhibitors or inducers of P-gp and BCRP.

In vitro, selpercatinib inhibits MATE1, P-gp and BCRP. Selpercatinib did not inhibit OAT1, OAT3, OCT1, OCT2, OATP1B1, OATP1B3, MATE2-K or BSEP. Use caution when co-administered with medications that are sensitive substrates of MATE1, P-gp and BCRP.

Proton pump inhibitors (PPIs), H2 receptor antagonists and antacids may alter the pharmacokinetics of selpercatinib by reducing selpercatinib exposure. Avoid concomitant use of PPIs if possible. If co-administration of selpercatinib and PPI is necessary, administer selpercatinib with a meal. If H2 receptor antagonist is necessary, administer selpercatinib 2 hours before or 10 hours after H2 receptor antagonist administration. If antacid use is necessary, administer selpercatinib 2 or more hours before or 2 or more hours after antacid administration.

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

Selpercatinib can cause concentration-dependent QT prolongation. Monitor the QT interval more frequently when concomitantly administered with strong and moderate CYP3A4 inhibitors and drugs known to prolong QT interval and in patients at significant risk of developing QT prolongation.

9.1.4 Patient Care Implications:

Selpercatinib must not be administered to pregnant or nursing females. 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 2 weeks after the last dose of selpercatinib. Discontinue breastfeeding during treatment and for at least 2 weeks after the last dose of selpercatinib. Male study participants are to refrain from sperm donation during treatment and for 2 weeks after the last dose of selpercatinib.

Impaired wound healing can occur in patients taking selpercatinib. Withhold selpercatinib for at least 7 days prior to elective surgery. Do not administer for at

least 2 weeks following major surgery and until adequate wound healing.

9.1.5 **Toxicity:**

Comprehensive Adverse Events and Potential Risks list (CAEPR)
for
Selpercatinib (LOXO-292, NSC 812076)

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. In addition to the comprehensive list, a subset, the Specific Protocol Exceptions to Expedited Reporting (SPEER), appears in a separate column and is identified with bold and italicized text. This subset of AEs (SPEER) is a list of events that are protocol specific exceptions to expedited reporting to NCI (except as noted below). 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.

NOTE: Report AEs on the SPEER **ONLY IF** they exceed the grade noted in parentheses next to the AE in the SPEER. If this CAEPR is part of a combination protocol using multiple investigational agents and has an AE listed on different SPEERs, use the lower of the grades to determine if expedited reporting is required.

Version 2.3, August 31, 2020[1]

Adverse Events with Possible Relationship to Selpercatinib (CTCAE 5.0 Term) [n= 882]			**Specific Protocol Exceptions to Expedited Reporting (SPEER)**
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
GASTROINTESTINAL DISORDERS			
	Abdominal pain		
	Constipation		***Constipation (Gr 2)***
	Diarrhea		***Diarrhea (Gr 2)***
Dry mouth			***Dry mouth (Gr 2)***
	Nausea		
	Vomiting		
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
	Edema limbs		***Edema limbs (Gr 2)***
	Fatigue		***Fatigue (Gr 2)***
IMMUNE SYSTEM DISORDERS			
		Allergic reaction[2]	
INVESTIGATIONS			
Alanine aminotransferase increased[2]			***Alanine aminotransferase increased[2] (Gr 2)***
Aspartate aminotransferase increased[2]			***Aspartate aminotransferase increased[2] (Gr 2)***
	Creatinine increased[2]		***Creatinine increased[2] (Gr 2)***
	Electrocardiogram QT corrected interval prolonged		***Electrocardiogram QT corrected interval prolonged (Gr 2)***
	Platelet count decreased[2]		***Platelet count decreased[2] (Gr 2)***
	White blood cell decreased		
NERVOUS SYSTEM DISORDERS			
	Dysgeusia		

Adverse Events with Possible Relationship to Selpercatinib (CTCAE 5.0 Term) [n= 882]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
	Headache		
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
	Rash maculo-papular[2]		*Rash maculo-papular[2] (Gr 2)*
VASCULAR DISORDERS			
Hypertension			*Hypertension (Gr 2)*

[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 selpercatinib (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 LOXO-292 (selpercatinib) 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.

9.1.6 Formulation and Stability:

Selpercatinib will be provided as 40 mg and 80 mg capsules formulation, as well as 1.4 gram powder for oral suspension

- 40 mg capsules are opaque grey, size 2, hard gelatin capsules. The capsule shell is composed of gelatin, titanium dioxide, ferric oxide black and is imprinted with "Lilly", "3977" and "40 mg" in black ink. Each capsule contains 40 mg of selpercatinib (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. The capsule shell is composed of gelatin, titanium dioxide, FD&C blue #1 and is imprinted with "Lilly", "2980", and "80 mg" in black ink. Each capsule contains 80 mg of selpercatinib (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 induction seals and child-resistant plastic caps.

- 1.4 gram powder for oral suspension is supplied in amber glass bottles, PP28 neck, with a 28 mm child resistant cap. The white to off-white powder for oral suspension bottles contains no excipients.
  - Site-supplied Ora-Sweet® SF and Ora-Plus® are required for oral suspension preparation and site-supplied 28 mm LDPE (e.g., Comar® product number 22-0198) press-in bottle adapters are required for use with an oral syringe for dosing purposes.

9.1.6.1 Oral Suspension Preparation:

1.4 gm Powder for oral suspension: Add 35 mL of Ora-Plus® and 35 mL of Ora-Sweet® SF (70 mL total volume) to each 1.4 gm bottle to yield a suspension of 20 mg/mL. Shake well.

1. Remove the cap from the amber glass bottle containing 1.4 g of selpercatinib.
2. To the amber glass bottle containing powder add 35 mL of Ora-Plus®, cap the bottle and shake by hand. Then add 35 mL of Ora-Sweet® SF to make a total volume of 70 mL (final suspension concentration = 20 mg/mL).
3. Cap the bottle tightly and then shake by hand until no solids are observed on the bottom of the bottle. A vortex can be used if available.
4. Insert adapter into bottle via the ribbed end. This will require some minimum force to insert all the way.
5. Replace the cap
6. Prior to measuring out each dose, shake the bottle by hand to ensure a smooth suspension of the liquid. Try to avoid the formation of bubbles.
7. The dosing syringe should be filled with an equal volume of water after each dose administration to be sure all residue of the suspension is ingested. A new syringe should be used for each dose.

9.1.6.2 Storage

Store capsules at controlled room temperature between 20°C to 25°C (66°F to 77°F). Excursions permitted between 15°C to 30°C (59°F to 86°F). Store intact powder for oral suspension bottles at controlled room temperature between 20°C to 25°C (66°F to 77°F). Excursions permitted between 15°C to 30°C (59°F to 86°F). Store prepared oral suspension bottles refrigerated at 2°C to 8°C. Do not freeze the suspension.

If a storage temperature excursion is identified, promptly return selpercatinib capsules and intact powder for oral suspension bottles to controlled room temperature, or prepared oral suspension bottles to refrigerated temperature and quarantine the supplies. Provide a detailed report of the excursion (including documentation of temperature monitoring and duration of the excursion) to PMBAfterHours@mail.nih.gov for determination of suitability.

9.1.6.3 Stability

Stability studies of the intact bottles (capsules and powder for oral suspension) are ongoing. It is recommended that selpercatinib 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. When repackaged into the pharmacy HDPE bottles there is no difference in expiration from the source material.

Selpercatinib powder for oral suspension is to be dispensed in the manufacturer's container. Oral suspension must be used within 42 days following preparation under refrigerated storage conditions.

9.1.7 **Guidelines for Administration:**

Refer to treatment (Section 5.0) and dose modification (Section 6.0) sections of

the protocol. Capsules are administered orally. Oral suspension may be administered orally or by naso- or gastric-feeding tube. In the case of enteral administration, the tube must be flushed appropriate amount of water (up to 30 mL) post administration of each dose.

Selpercatinib is administered twice daily, approximately 12 hours apart. Doses may be taken without regard to food. Capsules are to be swallowed whole. Do not chew, crush or open capsules. If study subject vomits immediately after taking a capsule dose and the capsules are intact, dose may be repeated. If study subject vomits after taking an oral suspension dose, the dose **should not** be repeated. If a dose is missed, it may be administered if there are at least 6 hours remaining until the next scheduled dose. Instruct patients to shake oral suspension bottles well prior to dosing.

9.1.8 **Supplier:**
Selpercatinib is supplied by Eli Lilly and distributed by the Pharmaceutical Management Branch, CTEP, DCTD, NCI. **Do not use commercial supply.**

9.2 Obtaining the Agent

9.2.1 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 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.

Note: No starter supplies will be provided. Drug orders of selpercatinib should be placed with CTEP after enrollment and treatment assignment to APEC1621N with consideration for timing of processing and shipping to ensure receipt of drug supply prior to start of protocol therapy. If expedited shipment is required, sites should provide an express courier account through the Online Agent Order Processing (OAOP) application. Provide the patient ID number in the comment box when submitting an order request.

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

9.3 Agent Accountability

9.3.1 Agent Inventory Records
The investigator, or a responsible party designated by the investigator, must maintain a careful record of the receipt, dispensing and final disposition of all

agents received from the PMB using the appropriate NCI Investigational Agent (Drug) Accountability Record (DARF) available on the CTEP forms page. Store and maintain separate NCI Investigational Agent Accountability Records for each agent, strength, formulation and ordering investigator on this protocol.

9.3.2 Investigator Brochure Availability

The current version(s) of the IB(s) for the agent will be accessible to site investigators and research staff through the PMB Online Agent Order Processing (OAOP) application. Access to OAOP requires the establishment of a CTEP IAM account and the maintenance of an "active" account status, a "current" password, and active person registration status. Questions about IB access may be directed to the PMB IB coordinator via email.

9.4 Useful Links and Contacts

- CTEP Forms, Templates, Documents: http://ctep.cancer.gov/forms/
- NCI CTEP Investigator Registration: 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/

- PPD
- PPD
- PPD

Monday through Friday between 8:30 am and 4:30 pm (ET)

- PPD
- Registration and Credential Repository (RCR): https://ctepcore.nci.nih.gov/rcr/

10.0 CRITERIA FOR REMOVAL FROM PROTOCOL THERAPY AND OFF STUDY CRITERIA

10.1 Criteria for Removal from Protocol Therapy

a) Clinical (including physical examination or serum tumor markers) or radiographic evidence of progressive disease (See Section 12).
b) Adverse Events requiring removal from protocol therapy (See Section 6).
c) Refusal of protocol therapy by patient/parent/guardian
d) Non-compliance that in the opinion of the investigator does not allow for ongoing participation.
e) Completion of 26 cycles of therapy.
f) Physician determines it is not in the patient's best interest.
g) Repeated eligibility laboratory studies (CBC with differential, bilirubin, ALT (SGPT) or serum creatinine) are outside the parameters required for eligibility prior to the start of protocol therapy (See Section 8.1).
h) Study is terminated by Sponsor.
i) Pregnancy
j) Patient did not receive protocol treatment after study enrollment

Patients who are removed from protocol therapy during cycle 1 should continue to have the required observations in Section 8.1 until the originally planned end of the cycle or until all adverse events have resolved per Section 13.4, whichever happens LATER. The only exception is with documentation of the patient's withdrawal of consent from the APEC1621SC screening protocol. Patients who are removed from protocol therapy in subsequent cycles should have the necessary observations to ensure adequate clinical care.

10.2 Follow-Up Data Submission and APEC1621SC Off Study Criteria

Patients who are off subprotocol therapy will initially be followed on the therapeutic subprotocol for a 30-day period. During follow-up on the therapeutic subprotocol ongoing adverse events, or adverse events that emerge after the patient is removed from protocol therapy, but within 30 days of the last dose of investigational agent, must be followed and reported via RAVE and CTEP-AERS (if applicable). Upon completion of subprotocol follow-up period, the patient will continue to be followed on the APEC1621SC screening protocol. Follow-up data submission will occur until one of the APEC1621SC Off Study Criteria is met (See Section 10 of APEC1621SC for details); consent is withdrawn or the patient dies or is lost to follow-up.

11.0 STATISTICAL AND ETHICAL CONSIDERATIONS

11.1 Sample Size and Study Duration

APEC1621N will require a minimum of 20 evaluable patients and a maximum of 49 patients, allowing for 15% inevaluability. Assuming an enrollment rate of 2-6 biomarker positive patients per year, the primary cohort of this subprotocol is expected to be completed within 4-12 years.

11.2 Dosing Considerations

11.2.1 Pediatric MATCH Sub-arm Dosing in the Absence of Pediatric Phase 1 Data

Please see Section 5.1 for a specific discussion of the dosing of selpercatinib (LOXO-292) to be used in this study. If there is no prior pediatric phase 1 data, study investigators will review relevant data with the pharmaceutical partner to identify a drug specific dosing plan for testing in children with relapsed or refractory cancer, and trial participants will be closely monitored to ensure tolerability of the selected dose. In general, the dosing for the Pediatric MATCH subprotocols will follow the guidelines below:

- For agents for which the adult RP2D is below the adult MTD, the adult RP2D (normalized to body surface area or body weight) will be used for evaluation in the Pediatric MATCH, understanding that further dose optimization may be required in a future pediatric study.

11.3 Study Design

The primary cohort will employ a single stage A'Hern designs of N=20. The agent will be deemed worthy of further study in the relevant subset of patients (i.e. biomarker positive in any histology, biomarker positive in a particular histology, etc) if the decision rule is met. Operating characteristics are shown below.

Cohort	N	Decision Rule	Alpha	Power
Primary biomarker positive	20	$\geq$ 3 responses	10%	90%

Histology-specific biomarker positive expansion cohorts will, by definition, be deemed worthy of further study, since they will have at least 3 responses. The table below shows 90% confidence intervals (Wilson method) for a range of observable response rates.

Cohort Size	Observed Response Rate	90% Confidence Interval
10	30%	13% - 56%
10	40%	19% - 65%
10	50%	27% - 73%

11.3.1 Primary Cohort:

APEC1621N will evaluate a primary cohort of 20 mutation-matched ("biomarker positive") evaluable patients of any histology for the primary study aim of determining the objective response rate (CR/PR according to the response criteria in Section 12.3) to the agent. Using an A'Hern design[24] with alpha=10%, a sample of N=20 will provide 90% power to detect an improvement in response rate from

5%, if the treatment is ineffective, to 25% if the targeted therapy is sufficiently effective to warrant further study. If there are at least 3 responses out of 20 in the primary cohort, the biomarker/therapy match will be deemed a success.

11.3.2 Histology-Specific Biomarker Positive Expansion Cohorts:

If ≥ 3 patients in the primary cohort with the same histology show signs of objective response (CR/PR according to the response criteria in Section 12.3), a histology-specific biomarker positive expansion cohort will open after the primary cohort is completed to up to 7 evaluable patients for a total sample size of 10 evaluable biomarker positive patients with that histology. This will allow us to estimate more precisely the activity in biomarker positive patients of that histology. See Appendix VII for a list of target tumor histologies.

We will open up to 3 such expansion cohorts for biomarker positive patients (i.e., if 3 histologies have ≥ 3 responses, we will open a total of 3 expansion cohorts as described above). Note that this can only happen if the response rate in the primary cohort is at least 45% (9/20) and there cannot be more than 21 additional evaluable patients in total for these expansion cohorts.

11.4 Methods of Analysis

Response criteria are described in Section 12. A responder is defined as a patient who achieves a best response of PR or CR on the study. Response rates will be calculated as the percent of evaluable patients who are responders, and confidence intervals will be constructed using the Wilson score interval method.[25] Decision making for A'Hern design cohorts will follow rules described above.

Toxicity tables will be constructed to summarize the observed incidence by type of toxicity and grade. A patient will be counted only once for a given toxicity for the worst grade of that toxicity reported for that patient. Toxicity information recorded will include the type, severity, time of onset, time of resolution, and the probable association with the study regimen.

11.5 Evaluability for Response

Any eligible patient who is enrolled and receives at least one dose of protocol therapy will be considered evaluable for response. Any patient who receives non-protocol anti-cancer therapy during the response evaluation period will be considered a non-responder for the purposes of the statistical rule, unless they show an objective response prior to receiving the non-protocol anti-cancer therapy (in which case they will be considered a responder). Patients who demonstrate a complete or partial response confirmed by central review will be considered to have experienced a response. All other patients will be considered non-responders. Patients who are not evaluable for response evaluation may be replaced for the purposes of the statistical rule. All patients considered to have a response (CR or PR) must have imaging studies reviewed centrally at the COG. Centers will be notified by the COG about requests for scans of patients with stable disease. Preliminary assessment of activity using institutionally provided tumor measurements will be entered into CDUS quarterly. The central review by COG will be provided as the final reviewed assessment of response when such becomes available.

11.6 Evaluability for Toxicity

All eligible patients who receive at least one dose of protocol therapy will be considered in the evaluation of toxicity

11.7 Progression free survival (PFS)

Progression free survival will be defined as time from the initiation of protocol treatment to the occurrence of any of the following events: disease progression or disease recurrence or death from any cause. All patients surviving at the time of analyses without events will be censored at their last follow-up date.

PFS along with the confidence intervals will be estimated using the Kaplan-Meier method. Patients with local calls of disease progression (i.e. calls made by the treating institution), will be counted as having had an event, even if the central review does not declare progression. We will also report PFS based on central radiology review as a secondary analysis, if adequate number of disagreements in progressions exist between the treating institutions and the central radiology review to make such an analysis meaningful.

11.8 Correlative Studies

A descriptive analysis of the exploratory aims described in Section 1.3 will be performed and will be summarized with simple summary statistics. All of these analyses will be descriptive in nature.

11.9 Gender and Minority Accrual Estimates

The gender and minority distribution of the study population is expected to be:

Racial category	Ethnicity				
	Not Hispanic or Latino		Hispanic or Latino		
	Female	Male	Female	Male	Total
American Indian/Alaska Native	0	0	0	0	0
Asian	1	1	0	0	2
Native Hawaiian or Other Pacific Islander	0	0	0	0	0
Black or African American	3	5	0	0	8
White	12	20	4	2	38
More than one race	1	0	0	0	1
Total	17	26	4	2	49

This distribution was derived from the demographic data for patients enrolled on recent COG Phase 2 trials.

12.0 EVALUATION CRITERIA

12.1 Common Terminology Criteria for Adverse Events (CTCAE)

The descriptions and grading scales found in the current version of the NCI Common Terminology Criteria for Adverse Events (CTCAE) will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the current CTCAEv5.0. A copy of the CTCAEv5.0 can be downloaded from the CTEP website (http://ctep.cancer.gov).

12.2 Progression-Free Survival

Progression-free survival (PFS) is defined as the duration of time from start of subprotocol treatment to time of progression or death, whichever occurs first.

Development of new disease or progression in any established lesions is considered progressive disease, regardless of response in other lesions – e.g., when multiple lesions show opposite responses, the progressive disease takes precedence.

12.3 Response Criteria for Patients with Solid Tumors

See the table in Section 8.0 for the schedule of tumor evaluations. In addition to the scheduled scans, a confirmatory scan should be obtained on the next consecutive cycle following initial documentation of objective response.

As outlined, patients will be assigned to one of the following categories for assessment of response: a) solid tumor (non-CNS) and measurable disease (Section 12.4); b) neuroblastoma with MIBG positive lesions (Section 12.5); c) CNS tumor (Section 12.7); and d) lymphoma/histiocytosis (Section 12.8). Note: Neuroblastoma patients who do not have MIBG positive lesions should be assessed for response as solid tumor patients with measurable disease.

Response and progression will be evaluated in this study using the revised Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1) [*Eur J Ca* 45:228-247, 2009]. Key points are that 5 target lesions are identified and that changes in the *largest* diameter (unidimensional measurement) of the tumor lesions but the *shortest* diameter of malignant lymph nodes are used in the RECIST v 1.1 criteria.

12.3.1 Definitions

12.3.1.1 Evaluable for objective response:

Eligible patients who receive at least one dose of protocol therapy will be considered evaluable for response. Evaluable patients who demonstrate a complete or partial response confirmed by central review before receiving non-protocol anti-cancer therapy will be considered a responder. All other evaluable patients will be considered non-responders

12.3.1.2 Evaluable Non-Target Disease Response:

Eligible patients who have lesions present at baseline that are evaluable but do not meet the definitions of measurable disease and have received at least one dose of protocol therapy will be considered evaluable for non-target disease response. The response assessment is based on the presence, absence, or unequivocal progression of the lesions.

12.3.2 Disease Parameters

12.3.2.1 Measurable disease:

Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥ 20 mm by chest x-ray, as ≥ 10 mm with CT scan, or ≥ 10 mm with calipers by clinical exam. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

Note: Tumor lesions that are situated in a previously irradiated area might or might not be considered measurable. If the investigator thinks it appropriate to include them, the conditions under which such lesions should be considered must be defined in the protocol.

12.3.2.2 Malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be ≥ 15 mm in short axis when assessed by CT scan (CT scan slice thickness no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

12.3.2.3 Non-measurable disease: All other lesions (or sites of disease), including small lesions (longest diameter < 10 mm or pathological lymph nodes with ≥ 10 to < 15 mm 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.

Note: 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. 'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.

12.3.2.4 Target lesions: All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as target lesions and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion that can be measured reproducibly should be selected. A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

12.3.2.5 Non-target lesions: 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 and should also be recorded at baseline. Measurements of these lesions are not required, but the presence, absence, or in rare cases unequivocal progression of each should be

noted throughout follow-up.

12.3.3 Methods for Evaluation of Measurable Disease
All measurements should be taken and recorded in metric notation using a ruler or calipers.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

12.3.3.1 Clinical lesions: Clinical lesions will only be considered measurable when they are superficial (e.g., skin nodules and palpable lymph nodes) and ≥ 10 mm diameter as assessed using calipers (e.g., skin nodules). In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

12.3.3.2 Chest x-ray: Lesions on chest x-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT is preferable.

12.3.3.3 Conventional CT and MRI: This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. If CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (e.g. for body scans). Ideally, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans.

12.3.3.4 PET-CT: At present, the low dose or attenuation correction CT portion of a combined 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 (with IV and oral contrast), then the CT portion of the PET-CT can be used for RECIST measurements and can be used interchangeably with conventional CT in accurately measuring cancer lesions over time. Note, however, that the PET portion of the CT introduces additional data which may bias an investigator if it is not routinely or serially performed.

12.3.3.5 Tumor markers: Tumor markers alone cannot be used to assess response. If markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response.

12.3.3.6 Cytology, Histology: These techniques can be used to differentiate between partial responses (PR) and complete responses (CR) in rare cases (e.g., residual lesions in tumor types, such as germ cell tumors, where known residual benign tumors can remain).

Cytology should be obtained if an effusion appears or worsens during treatment when the measurable tumor has met criteria for response or stable disease.

12.3.3.7 FDG-PET: While FDG-PET response assessments need additional study, it is sometimes reasonable to incorporate the use of FDG-PET scanning to complement CT scanning in assessment of progression (particularly possible 'new' disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:

a. Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.
b. No FDG-PET at baseline and a positive FDG-PET at follow-up: If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD. If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan). If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.

Note: A 'positive' FDG-PET scan lesion means one that is FDG avid with an uptake greater than twice that of the surrounding tissue on the attenuation corrected image.

For patients with a positive PET scan at diagnosis, PET can be used to follow response in addition to a CT scan using the International Pediatric non-Hodgkin Lymphoma Response Criteria.[26]

12.4 Response Criteria for Patients with Solid Tumor and Measurable Disease

12.4.1 Evaluation of Target Lesions

Complete Response (CR): Disappearance of all target and non-target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm. If immunocytology is available, no disease must be detected by that methodology. Normalization of tumor markers if elevated at study enrollment (for patients with neuroblastoma).

Partial Response (PR): At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters.

Progressive Disease (PD): At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute

increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progressions). Note: in presence of SD or PR in target disease but unequivocal progression in non-target or non-measurable disease, the patient has PD if there is an overall level of substantial worsening in non-target disease such that the overall tumor burden has increased sufficiently to merit discontinuation of therapy.

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

12.4.2 Evaluation of Non-Target Lesions

Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10 mm short axis).

Note: If tumor markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response.

Non-CR/Non-PD: Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.

Progressive Disease (PD): Appearance of one or more new lesions and/or *unequivocal progression* of existing non-target lesions. *Unequivocal progression* should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase.

12.4.3 Overall Response Assessment

Table 1: For Patients with Measurable Disease (i.e., Target Disease)

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Overall Response when Confirmation is Required*
CR	CR	No	CR	≥ 28 days Confirmation
CR	Non-CR/Non-PD	No	PR	≥ 28 days Confirmation
CR	Not evaluated	No	PR	
PR	Non-CR/Non-PD/not	No	PR	

	evaluated			
SD	Non-CR/Non-PD/not evaluated	No	SD	documented at least once ≥ 28 days from baseline
PD	Any	Yes or No	PD	no prior SD, PR or CR
Any	PD**	Yes or No	PD	
Any	Any	Yes	PD	

* See RECIST 1.1 manuscript for further details on what is evidence of a new lesion.

** In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.

Note: Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "*symptomatic deterioration.*" Every effort should be made to document the objective progression even after discontinuation of treatment.

Table 2: For Patients with Non-Measurable Disease (i.e., Non-Target Disease)

Non-Target Lesions	**New Lesions**	**Overall Response**
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD*
Not all evaluated	No	not evaluated
Unequivocal PD	Yes or No	PD
Any	Yes	PD

* 'Non-CR/non-PD' is preferred over 'stable disease' for non-target disease since SD is increasingly used as an endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised

Table 3: Overall Response for Patients with Neuroblastoma and Measurable Disease

CT/MRI	**MIBG**	**Bone Marrow**	**Overall**
PD	Any	Any	PD
Any	PD	Any	PD
Any	Any	Any	PD
Any	Any	PD	PD
SD	CR/PR/SD	Non-PD	SD
PR	CR/PR	Non-PD	PR
CR/PR	PR	Non-PD	PR
CR	CR	Non-PD	PR
CR	CR	CR	CR

12.4.4 Overall Best Response Assessment

Each patient will be classified according to his "best response" for the purposes of analysis of treatment effect. Best response is determined as outlined in Section 12.9 from a sequence of overall response assessments.

12.5 Response Criteria for Neuroblastoma Patients

This study will use the revised International Neuroblastoma Response Criteria for disease assessment. [27]The updated response criteria incorporate current approaches to imaging of neuroblastoma, including functional imaging. Furthermore, a standardized approach to assessment of bone marrow involvement is included. The current INRC do **not** include methods of disease assessment that are less sensitive and/or specific for neuroblastoma (^{99}Tc bone scan and catecholamine levels).

Key sites and terms

Primary site: The primary site will be identified as a measurable lesion ≥ 10 mm in diameter as assessed by cross sectional imaging (CT or MRI scan). Primary site measurements must be recorded in millimeters (or decimal fractions of centimeters). The longest diameter of the primary tumor will be recorded at baseline. Serial measurements of the primary tumor will include assessment of tumor size in the same orthogonal plane at the time of each evaluation.[28] In patients with bilateral adrenal lesions, response will be based on the sum of the longest dimensions of both adrenal lesions unless biopsy proves one to be ganglioneuroma rather than neuroblastoma/ganglioneuroblastoma. In patients with multi-focal non-adrenal disease, the largest tumor will be considered the primary tumor. Response in additional lesions will be assessed as described below for metastatic lesions.

Tracer avidity (^{123}I-MIBG or FDG-PET) in the primary site will be recorded at baseline. The scan appropriate for serial disease assessments should be used at each disease re-evaluation timepoint (e.g. ^{123}I-MIBG avid primary lesions should be followed using ^{123}I-MIBG scans during therapy).

Malignant lymph nodes: To be considered pathologically enlarged and measurable, a metastatic lymph node must be ≥ 15 mm in short axis when assessed by CT or MRI scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis of a discreet lymph node will be measured and followed as per RECIST criteria. Patients with neuroblastoma may have conglomerate masses of non-discrete lymph nodes (i.e. multiple contiguous retroperitoneal nodes). When a short axis of a discreet node cannot be identified, a lymph node conglomerate can be measured using the longest diameter of the composite lesion. Tracer avidity of metastatic nodes will be recorded at baseline and during disease evaluations.

For the purposes of response assessment, target lesions are disease sites that are measurable (non-nodal soft tissue mass ≥ 10 mm in longest dimension or lymph node ≥ 15 mm in short axis) and tracer avid OR are biopsy positive for neuroblastoma or ganglioneuroblastoma. The sum of diameters of target lesions is defined as the sum of the short axis of discrete lymph nodes (i.e., cervical, axillary nodes) added to the sum of the longest diameters of non-lymph node soft tissue metastases.

Non-measurable disease: All other lesions (or sites of disease), including small lesions (longest diameter < 10 mm or pathological lymph nodes with ≥ 10 to < 15 mm short axis), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions are considered non-measurable.

Bone lesions: Osteomedullary disease will be assessed using ^{123}I-MIBG scans or FDG-PET scans. Technetium bone scans are no longer used as part of the revised INRC and are not included as part of disease reassessments during this trial. The extent of tracer avid disease will be evaluated using the Curie scoring system (see Curie Scoring System). SPECT may be used to confirm the presence or absence of lesions in a given segment of the body. The absolute Curie score should be reported at baseline. A relative score (Curie score at the time of disease assessment divided by baseline Curie score) should be recorded at the time of each disease evaluation.

Bone marrow disease: Bilateral bone marrow aspirates and trephine biopsies are required at disease assessment timepoints. The extent of marrow involvement in all four samples should be recorded. Use of immunohistochemical staining for evaluation of trephine biopsies is strongly encouraged. The percentage of tumor infiltration of bone marrow space assessed by histologic evaluation of trephine/biopsies or counting the number of tumor cells in aspirates by cytology or

immunocytology (recommended if available) divided by the number of hematopoietic/mononuclear cells evaluated to obtain a percentage involvement (methodology described by Burchill et al.).[29] The bone marrow sample with the highest percentage of tumor infiltration is used for response assessment. If > 0% to ≤ 5% tumor infiltration is the highest percentage seen among samples obtained, the result should be recorded as minimal marrow disease.

Response Criteria

PRIMARY (SOFT TISSUE) TUMOR RESPONSE[1]

RESPONSE	ANATOMICAL IMAGING + MIBG (FDG-PET[2]) IMAGING
Complete Response (CR)	• < 10 mm residual soft tissue at primary site, AND • complete resolution of MIBG or FDG-PET uptake (for MIBG non-avid tumors) at primary site
Partial Response (PR)	• ≥ 30% decrease in longest diameter (LD) of primary site • MIBG or FDG-PET uptake at primary site stable, improved or resolved
Progressive Disease (PD)	• > 20% increase in longest diameter taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study), AND • a minimum absolute increase of 5 mm in longest dimension[3]
Stable Disease (SD)	Neither sufficient shrinkage for PR nor sufficient increase for PD at the primary site

[1]Not for use in assessment of metastatic sites
[2] For ^{123}I-MIBG non-avid tumors
[3] A mass that has not met PD measurement criteria but has fluctuating ^{123}I-MIBG avidity will not be considered progressive disease.

RESPONSE AT METASTATIC SOFT TISSUE AND BONE SITES

RESPONSE	ANATOMICAL IMAGING + MIBG (FDG-PET[1]) IMAGING
Complete Response (CR)	• Resolution of all sites of disease defined as:

	• Non-primary target and non-target lesions measure < 10 mm AND • Lymph nodes identified as target lesions decrease to a short axis < 15 mm, AND • MIBG uptake or FDG-PET uptake (for MIBG non-avid tumors) of non-primary lesions resolves completely
Partial Response (PR)	• ≥ 30% decrease in sum of diameters[2] of non-primary target lesions compared to baseline, AND all of the following: • Non-target lesions may be stable or smaller in size AND • No new lesions AND • ≥ 50% reduction in MIBG absolute bone score (Relative MIBG bone score ≥ 0.1 to ≤ 0.5) or ≥ 50% reduction in number of FDG-PET avid bone lesions[3,4]
Progressive Disease (PD)	Any of the following[5]: • Any new soft tissue lesion detected by CT or MRI that is also MIBG avid or FDG-PET avid; • Any new soft tissue lesion seen on anatomic imaging that is biopsied and confirmed to be a neuroblastoma or ganglioneuroblastoma; • Any new bone site that is MIBG avid; • A new bone site that is FDG-PET avid (for MIBG non-avid tumors) AND has CT or MRI findings consistent with tumor OR has been confirmed histologically to be neuroblastoma or ganglioneuroblastoma; • > 20% increase in longest diameter taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study), AND a minimum absolute increase of 5 mm in sum of diameters of target soft tissue lesions; • Relative MIBG score ≥ 1.2[4]
Stable Disease (SD)	Neither sufficient shrinkage for PR nor sufficient increase for PD of non-primary lesions

[1] Used for MIBG non-avid tumors

[2]Sum of diameters is defined as the sum of the short axis of discrete lymph nodes (i.e., cervical, axillary nodes) added to the sum of the longest diameters of non-lymph node soft tissue metastases. Masses of conglomerate non-discrete lymph nodes will be measured using longest diameter.

[3] For patients with soft tissue metastatic disease, resolution of MIBG and/or FDG-PET uptake at the soft tissue sites is not required; all size reduction criteria must be fulfilled.

[4]Relative Curie score is the absolute score for bone lesions at time of response assessment divided by the absolute score for bone lesions at entry onto a clinical trial. MIBG-SPECT or MIBG-SPECT/CT may be used for scoring purposes but the same imaging methodology should be used for all evaluations.

[5]The post-infusion MIBG scan is not considered a diagnostic study for the purposes of response assessment. Progressive disease should NOT be designated on the basis of this scan.

BONE MARROW RESPONSE

RESPONSE	BONE MARROW STATUS[1]

Complete response (CR)	Bone marrow with no tumor infiltration upon reassessment, independent of baseline tumor involvement
Progressive disease (PD)	Any of the following: • Bone marrow without tumor infiltration that becomes > 5% tumor infiltration upon reassessment; or • Bone marrow with tumor infiltration that increases by > 2 fold and has > 20% tumor infiltration upon reassessment.
Minimal disease (MD)	Any of the following: • Bone marrow with ≤ 5% tumor infiltration and remains > 0-≤ 5% tumor infiltration upon reassessment; or • Bone marrow with no tumor infiltration that becomes ≤ 5% tumor infiltration upon reassessment; or • Bone marrow with >20% tumor infiltration that has > 0-≤ 5% tumor infiltration upon reassessment.
Stable disease (SD)	Bone marrow with tumor infiltration that remains positive with > 5% tumor infiltration upon reassessment but does not meet CR, MD or PD criteria

[1]Immunohistochemistry strongly encouraged

DETERMINATION OF OVERALL RESPONSE

RESPONSE	**CRITERIA**
Complete Response (CR)	All components meet criteria for CR
Partial Response (PR)	PR in at least one component and all other components are either CR, MD (Bone marrow), PR (Soft tissue or Bone) or Not involved (NI); no component with PD.
Minor Response (MR)	PR or CR in at least one component but at least one other component with SD; no component with PD.
Stable Disease (SD)	SD in one component with no better than SD or NI in any other component; no component with PD.
Progressive Disease (PD)	Any component with PD

NI = Not involved, site not involved at study entry and remains not involved; MD = Minimal Disease, for bone marrow assessment only.

Overall Best Response Assessment

Each patient will be classified according to his "best response" for the purposes of analysis of treatment effect. Best response is determined as outlined in Section 12.8 from a sequence of overall response assessments.

Primary Tumor	Soft Tissue and Bone Metastatic Disease (MIBG or FDG-PET or PET/MR)	Bone Marrow Metastatic Disease	Overall
CR	CR	CR	CR
CR for one response component with either CR or NI for other components			CR
CR	CR	MD	PR
CR	PR	CR	PR
CR	PR	MD	PR
CR	PR	NI	PR
CR	NI	MD	PR
PR	CR	CR	PR
PR	CR	NI	PR
PR	CR	MD	PR
PR	PR	CR	PR
PR	PR	NI	PR
PR	PR	MD	PR
PR	NI	CR	PR
PR	NI	NI	PR
PR	NI	MD	PR
NI	CR	MD	PR
NI	PR	CR	PR
NI	PR	MD	PR
CR	CR	SD	MR
CR	PR	SD	MR
CR	SD	CR	MR
CR	SD	MD	MR
CR	SD	SD	MR
CR	SD	NI	MR
CR	NI	SD	MR
PR	CR	SD	MR
PR	PR	SD	MR
PR	SD	CR	MR
PR	SD	MD	MR
PR	SD	SD	MR
PR	SD	NI	MR
PR	NI	SD	MR
SD	CR	CR	MR
SD	CR	MD	MR
SD	CR	SD	MR
SD	CR	NI	MR
SD	PR	CR	MR
SD	PR	MD	MR
SD	PR	SD	MR
SD	PR	NI	MR
SD	SD	CR	MR
SD	NI	CR	MR
NI	CR	SD	MR
NI	PR	SD	MR
NI	SD	CR	MR
SD	SD	MD	SD
NI	SD	MD	SD
SD	NI	MD	SD
NI	NI	MD	SD
SD	SD	SD	SD
SD	NI	SD	SD
NI	SD	SD	SD
NI	SD	NI	SD
NI	NI	SD	SD

PD in any one component	PD
Response of Not Evaluable for any one of the 3 components that had measurable/evaluable tumor at study enrollment and no PD for any component	Not Evaluable
No response evaluation performed for any of the 3 components	Not Done

CR: Complete Response; MD: Minimal Disease; PR: Partial Response; MR: Minor Response; SD: Stable Disease; PD: Progressive disease; NI: not involved; site not involved at study entry and remains not involved

Curie Scoring Summary

Table 1a. Scoring skeletal disease

Regions 1 – 9	
Scoring	MIBG uptake
0	No MIBG uptake
1	1 focal site
2	> 1 focal site
3	≥ 50% of a region

Table 1b. Scoring soft tissue disease

Region 10 (Primary soft tissue site)	
Scoring	MIBG uptake
0	No soft tissue uptake
1	1 focal soft tissue site
2	> 1 focal soft tissue site
3	≥ 50% of a region (chest, abdomen)

Region	Site	Curie score
1	Head / Neck	
2	Cervico-Thoracic spine	
3	Ribs / Sternum / Clavicles/ Chest	
4	Lumbar / Sacral spine	
5	Abdomen/Pelvis	
6	Upper Extremity (Proximal)	
7	Upper Extremity (Distal)	
8	Lower Extremity (Proximal)	
9	Lower Extremity (Distal)	
10	Soft Tissue	
TOTAL	Total scores from Regions 1 - 10	

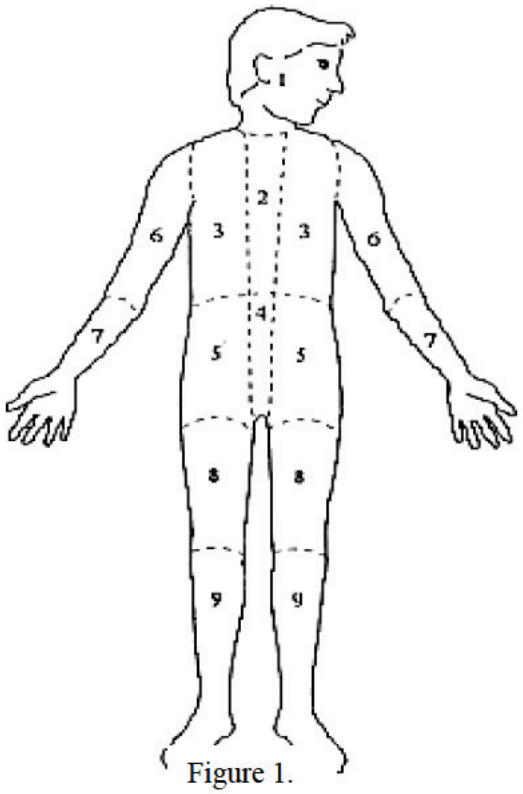


Figure 1.

12.6 Response Criteria for Patients with CNS Tumors

12.6.1 Measurable Disease

Any lesion that is at minimum 10 mm in one dimension on standard MRI or CT, for CNS tumors.

12.6.2 Evaluable Disease

Evaluable disease is defined as at least one lesion, with no lesion that can be accurately measured in at least one dimension. Such lesions may be evaluable by

nuclear medicine techniques, immunocytochemistry techniques, tumor markers, CSF cytology, or other reliable measures.

12.6.3 Selection of Target and Non-Target Lesions

For most CNS tumors, only one lesion/mass is present and therefore is considered a "target" for measurement/follow up to assess for tumor progression/response. If multiple measurable lesions are present, up to 5 should be selected as "target" lesions. Target lesions should be selected on the basis of size and suitability for accurate repeated measurements. All other lesions will be followed as non-target lesions. The lower size limit of the target lesion(s) should be at least twice the thickness of the slices showing the tumor to decrease the partial volume effect (e.g., 8 mm lesion for a 4 mm slice).

Any change in size of non-target lesions should be noted, though does not need to be measured.

12.6.4 Response Criteria for Target Lesions

Response criteria are assessed based on the product of the longest diameter and its longest perpendicular diameter. Development of new disease or progression in any established lesions is considered progressive disease, regardless of response in other lesions – e.g., when multiple lesions show opposite responses, the progressive disease takes precedence. Response Criteria for target lesions:

- **Complete Response (CR):** Disappearance of all target lesions. Off all steroids with stable or improving neurologic examination.

- **Partial response (PR):** ≥ 50% decrease in the sum of the products of the two perpendicular diameters of all target lesions (up to 5), taking as reference the initial baseline measurements; on a stable or decreasing dose of steroids with a stable or improving neurologic examination.

- **Stable Disease (SD):** Neither sufficient decrease in the sum of the products of the two perpendicular diameters of all target lesions to qualify for PR, nor sufficient increase in a single target lesion to qualify for PD; on a stable or decreasing dose of steroids with a stable or improving neurologic examination.

- **Progressive Disease (PD):** 25% or more increase in the sum of the products of the perpendicular diameters of the target lesions, taking as reference the smallest sum of the products observed since the start of treatment, or the appearance of one or more new lesions.

Increasing doses of corticosteroids required to maintain stable neurological status should be strongly considered as a sign of clinical progression unless in the context of recent wean or transient neurologic change due e.g. to radiation effects.

12.6.5 Response Criteria for Non-Target Lesions:

- **Complete Response (CR):** Disappearance of all non-target lesions.

- **Incomplete Response/Stable Disease (IR/SD):** The persistence of one or more non-target lesions.

- **Progressive Disease (PD):** The appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions.

12.6.6 Response criteria for tumor markers (if available):
Tumor markers will be classified simply as being at normal levels or at abnormally high levels.

12.6.7 Overall Response Assessment
The overall response assessment takes into account response in both target and non-target lesions, the appearance of new lesions and normalization of markers (where applicable), according to the criteria described in the table below. The overall response assessment is shown in the last column, and depends on the assessments of target, non-target, marker and new lesions in the preceding columns.

Target Lesions	**Non-target Lesions**	**Markers**	**New Lesions**	**Overall Response**
CR	CR	Normal	No	**CR**
CR	IR/SD	Normal	No	**PR**
CR	CR, IR/SD	Abnormal	No	**PR**
PR	CR, IR/SD	Any	No	**PR**
SD	CR, IR/SD	Any	No	**SD**
PD	Any	Any	Yes or No	**PD**
Any	PD	Any	Yes or No	**PD**
Any	Any	Any	Yes	**PD**

Each patient will be classified according to his "best response" for the purposes of analysis of treatment effect. Best response is determined as outlined in Section 12.8 from a sequence of overall response assessments.

12.7 Response Criteria for Patients with Non- Hodgkin Lymphoma/Histiocytosis

Response and progression will be evaluated in this study using the new international criteria proposed by the revised Response Evaluation Criteria in Pediatric non-Hodgkin Lymphoma Criteria[26], with modification from the Lugano classification.[30]

12.7.1 Disease Parameters

12.7.1.1 Measurable disease: A measurable node must have an LDi (longest diameter) greater than 1.5 cm. A measurable extranodal lesion should have an LDi greater than 1.0 cm. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

12.7.1.2 Non-measured disease: All other lesions (including nodal, extranodal, and assessable disease) should be followed as nonmeasured disease (e.g., cutaneous, GI, bone, spleen, liver, kidneys, pleural or pericardial effusions, ascites).

12.7.1.3 Target lesions: For patients staged with CT, up to six of the largest target nodes, nodal masses, or other lymphomatous lesions that are measurable

in two diameters (longest diameter [LDi] and shortest diameter) should be identified from different body regions representative of the patient's overall disease burden and include mediastinal and retroperitoneal disease, if involved.

12.7.2 Evaluation of Measurable Disease

Complete Response (CR)
Disappearance of all disease. CT or MRI should be free of residual mass or evidence of new disease. FDG-PET should be negative.

Complete Response Unconfirmed (CRu)
Residual mass is negative by FDG-PET; no new lesions by imaging examination; no new and/or progressive disease elsewhere

Partial Response (PR)
50% decrease in SPD (the sum of the products of the largest diameter and the perpendicular diameter for a tumor mass) on CT or MRI; FDG-PET may be positive (Deauville score or 4 or 5 with reduced lesional uptake compared with baseline); no new and/or PD; morphologic evidence of disease may be present in BM if present at diagnosis; however, there should be 50% reduction in percentage of lymphoma cells.

No Response (Stable Disease)
Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

Progressive disease
For those with > 25% increase in SPD on CT or MRI, Deauville score 4 or 5 on FDG-PET with increase in lesional uptake from baseline, or development of new morphologic evidence of disease in BM

12.7.3 Evaluation of Non-measured Lesions (CT-based response, PET/CT based response not applicable)[30]

Complete Response (CR): Absent non-measured lesions.

Partial response (PR): Absent/normal, regressed, lesions, but no increase.

Stable Disease (SD): No increase consistent with progression

Progressive Disease (PD): New or clear progression of preexisting non-measured lesions.

12.7.4 Evaluation of organ enlargement[30]

Complete Response (CR): Regress to normal

Partial response (PR): Spleen must have regressed by >50% in length beyond normal

Stable Disease (SD): No increase consistent with progression

Progressive Disease (PD): In the setting of splenomegaly, the splenic length must increase by 50% of the extent of its prior increase beyond baseline. If no prior splenomegaly, must increase by at least 2 cm from baseline.

New or recurrent splenomegaly

12.8 Best Response

Two objective status determinations of disease status, obtained on two consecutive determinations, separated by at least a 3 week time period, are required to determine the patient's overall best response. Two objective status determinations of CR before progression are required for best response of CR. Two determinations of PR or better before progression, but not qualifying for a CR, are required for a best response of PR. Two determinations of stable/no response or better before progression, but not qualifying as CR or PR, are required for a best response of stable/no response; if the first objective status is unknown, only one such determination is required. Patients with an objective status of progression on or before the second evaluations (the first evaluation is the first radiographic evaluation after treatment has been administered) will have a best response of progressive disease. Best response is unknown if the patient does not qualify for a best response of progressive disease and if all objective statuses after the first determination and before progression are unknown.

12.8.1 Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started). The patient's best response assignment will depend on the achievement of both measurement and confirmation criteria.

Table 5. Sequences of overall response assessments with corresponding best response.

1st Assessment	2nd Assessment	Best Response
Progression		Progressive disease
Stable, PR, CR	Progression	Progressive disease
Stable	Stable	Stable
Stable	PR, CR	Stable
Stable	Not done	Not RECIST classifiable
PR	PR	PR
PR	CR	PR
PR, CR	Not done	Not RECIST classifiable
CR	CR	CR

12.8.2 Duration of Response

Duration of overall response: The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started).

The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that progressive disease is objectively documented.

Duration of stable disease: Stable disease is measured from the start of the treatment until the criteria for progression are met, taking as reference the smallest measurements recorded since the treatment started, including the baseline measurements.

13.0 ADVERSE EVENT 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. (Please follow directions for routine reporting provided in the Case Report Forms for this protocol). Additionally, certain adverse events must be reported in an expedited manner to allow for optimal monitoring of patient safety and care. The following sections provide information about expedited reporting.

Reporting requirements may include the following considerations: 1) whether the patient has received an investigational or commercial agent; 2) whether the adverse event is considered serious; 3) the grade (severity); and 4) whether or not hospitalization or prolongation of hospitalization was associated with the event.

An investigational agent is a protocol drug administered under an Investigational New Drug Application (IND). In some instances, the investigational agent may be available commercially, but is actually being tested for indications not included in the approved package label.

13.1 Expedited Reporting Requirements – Serious Adverse Events (SAEs)

Any AE that is serious qualifies for expedited reporting. An AE is defined as any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. A Serious Adverse Event (SAE) is any adverse drug event (experience) occurring at any dose that results in ANY of the following outcomes:

1) Death.
2) A life-threatening adverse drug experience.
3) An adverse event resulting in inpatient hospitalization or prolongation of existing hospitalization (for ≥ 24 hours). This does not include hospitalizations that are part of routine medical practice.
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 a serious adverse drug experience 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.

13.1.1 Reporting Requirements - Investigator Responsibility

Clinical investigators in the treating institutions and ultimately the Study Chair have the primary responsibility for AE identification, documentation, grading, and assignment of attribution to the investigational agent/intervention. It is the responsibility of the treating physician to supply the medical documentation needed to support the expedited AE reports in a timely manner.

Any medical documentation supporting an expedited report (eg, H & P, admission and/or notes, consultations, ECG results, etc.) MUST be faxed within 48-72 hours to the NCI. NOTE: English is required for supporting documentation submitted to the numbers listed below in order for the NCI to meet the regulatory reporting timelines.

Fax supporting documentation **for AEs related to investigational agents supplied under a CTEP IND** to: PPD

Also: Fax or email supporting documentation to COG for **all** IND studies (Fax# (310) 640-9193; email: COGAERS@childrensoncologygroup.org; Attention: COG AERS Coordinator).

- **ALWAYS include the ticket number on all faxed documents.**
- **Use the NCI protocol number and the protocol-specific patient ID provided during trial registration on all reports.**

13.1.2 CTEP-AERS Expedited Reporting Methods

Expedited AE reporting for this study must only use CTEP-AERS (Adverse Event Expedited Reporting System), accessed via the CTEP home page https://eapps-ctep.nci.nih.gov/ctepaers.

Send supporting documentation to the NCI by fax (fax# 301-640-9193) and by email to both COGCAdEERS@childrensoncologygroup.org , the APEC1621N COG Study Assigned Research Coordinator, and COGAERS@childrensoncologygroup.org; Attention: COG AERS Coordinator. **ALWAYS include the ticket number on all faxed and emailed documents**.

13.2 Steps to Determine If an Adverse Event Is To Be Reported In an Expedited Manner

Step 1: Identify the type of adverse event using the current version of the NCI CTCAEv5.0. The descriptions and grading scales found in the current version of the CTCAEv5.0 will be used for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAEv5.0. A copy of the CTCAEv5.0 can be downloaded from the CTEP website (http://ctep.cancer.gov).

Step 2: Grade the adverse event using the NCI CTCAEv5.0.

Step 3: Review Table A in this section to determine if:

- the adverse event is considered serious;
- there are any protocol-specific requirements for expedited reporting of specific adverse events that require special monitoring; and/or
- there are any protocol-specific exceptions to the reporting requirements.

- Any medical event equivalent to CTCAEv5.0 grade 3, 4, or 5 that precipitates hospitalization (or prolongation of existing hospitalization) must be reported regardless of attribution and designation as expected or unexpected with the exception of any events identified as protocol-specific expedited adverse event reporting exclusions.
- Any event that results in persistent or significant disabilities/incapacities, congenital anomalies, or birth defects must be reported via CTEP-AERS if the event occurs following treatment with an agent under a CTEP IND.
- Use the NCI protocol number and the protocol-specific patient ID provided during trial registration on all reports.
- As referenced in the CTEP Adverse Events Reporting Requirements, an AE that resolves and then recurs during a subsequent cycle does not require CTEP-AERS reporting unless (1) the Grade increases; or (2) hospitalization is associated with the recurring AE.
- Some adverse events require notification **within 24 hours** (refer to Table A) to NCI via the web at http://ctep.cancer.gov (telephone CTEP at: **301-897-7497** within 24 hours of becoming aware of the event if the CTEP-AERS 24-Hour Notification web-based application is unavailable). Once internet connectivity is restored, a 24-hour notification phoned in must be entered electronically into CTEP-AERS by the original submitter at the site.
- When the adverse event requires expedited reporting, submit the report **within 5 or 7 calendar days** of learning of the event (refer to Table A).

Table A: Phase 1 and Early Phase 2 Studies: Expedited Reporting Requirements for Adverse Events that Occur on Studies under an IND/IDE within 30 Days of the Last Administration of the Investigational Agent/Intervention [1, 2]

FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)
NOTE: Investigators **MUST** immediately report to the sponsor **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 via CTEP-AERS within the timeframes detailed in the table below.

Hospitalization	Grade 1 and Grade 2 Timeframes	Grade 3-5 Timeframes
Resulting in Hospitalization ≥ 24 hrs	7 Calendar Days	24-Hour 5 Calendar Days
Not resulting in Hospitalization ≥ 24 hrs	Not required	

NOTE: Protocol specific exceptions to expedited reporting of serious adverse events are found in the Specific Protocol Exceptions to Expedited Reporting (SPEER) portion of the CAEPR.

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.
- "7 Calendar Days" - A complete expedited report on the AE must be submitted within 7 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 3, 4, and Grade 5 AEs

Expedited 7 calendar day reports for:

- Grade 2 AEs resulting in hospitalization or prolongation of hospitalization

[2] For studies using PET or SPECT IND agents, the AE reporting period is limited to 10 radioactive half-lives, rounded UP to the nearest whole day, after the agent/intervention was last administered. Footnote "1" above applies after this reporting period.

Effective Date: May 5, 2011

13.3 Additional Instructions or Exceptions to CTEP-AERS Expedited Reporting Requirements:

- Myelosuppression, (Grade 1 through Grade 4 adverse events as defined in the table below), does not require expedited reporting, unless it is associated with hospitalization.

Category	Adverse Events
INVESTIGATIONS	Platelet count decreased
INVESTIGATIONS	White blood cell decreased
INVESTIGATIONS	Neutrophil count decreased
INVESTIGATIONS	Lymphocyte count decreased
BLOOD/LYMPHATICS DISORDERS	Anemia

- Grade 1 and 2 adverse events listed in the table below do not require expedited reporting via CTEP-AERS, unless it is associated with hospitalization.

Category	Adverse Events
GASTROINTESTINAL DISORDERS	Diarrhea
INVESTIGATIONS	Alanine aminotransferase increased
INVESTIGATIONS	Aspartate aminotransferase increased
NERVOUS SYSTEM DISORDERS	Headache

- See also the Specific Protocol Exceptions to Expedited Reporting (SPEER) in Section 9.1.8 of the protocol.

13.4 Definition of Onset and Resolution of Adverse Events

Note: These guidelines below are for reporting adverse events on the COG case report forms and do not alter the guidelines for CTEP-AERS reporting.

- If an adverse event occurs more than once in a course (cycle) of therapy only the most severe grade of the event should be reported.
- If an adverse event progresses through several grades during one course of therapy, only the most severe grade should be reported.
- The duration of the AE is defined as the duration of the highest (most severe) grade of the Adverse Effects.
- The resolution date of the AE is defined as the date at which the AE returns to baseline or less than or equal to Grade 1, whichever level is higher (note that the resolution date may therefore be different from the date at which the grade of the AE decreased from its highest grade). If the AE does not return to baseline the resolution date should be recorded as "ongoing."
- An adverse event that persists from one course to another should only be reported once unless the grade becomes more severe in a subsequent course. An adverse event which resolves and then recurs during a different course, must be reported each course it recurs.

13.5 Other Recipients of Adverse Event Reports

13.5.1 Events that do not meet the criteria for CTEP-AERS reporting (Section 13.2) should be reported at the end of each cycle using the forms provided in the CRF packet (See Section 14.1).

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

13.6 Specific Examples for Expedited Reporting

13.6.1 Reportable Categories of Death

- Death attributable to a CTCAE v5.0 term.
- Death Neonatal: A disorder characterized by "Newborn deaths occurring during the first 28 days after birth."
- Sudden Death NOS: A sudden (defined as instant or within one hour of the onset of symptoms) or an unobserved cessation of life that cannot be attributed to a CTCAE v5.0 term associated with Grade 5.
- Death NOS: A cessation of life that cannot be attributed to a CTCAE v5.0 term associated with Grade 5.
- Death due to progressive disease should be reported as ***Grade 5 "Disease progression"*** under the system organ class (SOC) of General disorders and administration site conditions." Evidence that the death was a manifestation of underlying disease (*e.g.*, radiological changes suggesting tumor growth or progression: clinical deterioration associated with a disease) should be submitted.

- Any death occurring within 30 days of the last dose, regardless of attribution to the investigational agent/intervention requires expedited reporting within 24 hours.
- Any death that occurs more than 30 days after the last dose of treatment with an investigational agent which can be attributed (possibly, probably, or definitely) to the agent and is not clearly due to progressive disease must be reported via CTEP-AERS per the timelines outlined in the table above.

13.6.2 Reporting Secondary Malignancy

Secondary Malignancy:
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.

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

1) Leukemia secondary to oncology chemotherapy (e.g., acute myelocytic leukemia [AML])
2) Myelodysplastic syndrome (MDS)
3) 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.

Second Malignancy:
A *second malignancy* is one unrelated to the treatment of a prior malignancy (and is **NOT** a metastasis from the initial malignancy). Second malignancies require **ONLY** routine reporting via CDUS unless otherwise specified.

13.6.3 Reporting Pregnancy, Pregnancy Loss, and Death Neonatal

When submitting CTEP-AERS reports for "Pregnancy", "Pregnancy loss", or "Death Neonatal", the Pregnancy Information Form, available at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/PregnancyReportForm.pdf, needs to be completed and faxed along with any additional medical information to 301-897-7404. The potential risk of exposure of the fetus to the investigational agent should be documented in the "Description of Event" section of the CTEP-AERS report.

13.6.4 Pregnancy

Patients who become pregnant on study risk intrauterine exposure of the fetus to agents that may be teratogenic. For this reason, pregnancy needs to 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.

Pregnancy needs to be followed **until the outcome of the pregnancy is known** at intervals deemed appropriate by her physicians. The "Pregnancy Information Form" should be used for all necessary follow ups. This form is available at https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/PregnancyReportForm.pdf. If the baby is born with a birth defect or anomaly, then a second CTEP-AERS report is required.

13.6.5 Pregnancy Loss (Fetal Death)

Pregnancy loss is defined in CTCAE v5.0 as "Death in utero."

Any pregnancy loss needs to be reported expeditiously, as **Grade 4 "*Pregnancy loss*"** *under the "**Pregnancy, puerperium and perinatal conditions" SOC***. Do NOT report a pregnancy loss as a Grade 5 event since CTEP-AERS recognizes any Grade 5 event as a patient death.

13.6.6 Death Neonatal

Neonatal death, defined in CTCAE v5.0 as "***Newborn deaths occurring during the first 28 days after birth***" that is felt by the investigator to be at least possibly due to the investigational agent/intervention, should be reported expeditiously, as **Grade 4 "*Death Neonatal*"** under the system organ class (SOC) of "General disorders and administration site conditions." **When the death is the result of a patient pregnancy or pregnancy in partners of men on study**.

Do NOT report a neonatal death resulting from a patient pregnancy or pregnancy in partners of men on study as a Grade 5 event since CTEP-AERS recognizes any Grade 5 event as a patient death.

13.7 Reporting of Study Drug Overdose

Study drug overdose refers to the uses of the study drug outside of that specified by the protocol.

- Overdose: Accidental or intentional use of the study drug in an amount higher than the protocol defined dose.

Any study drug overdose should be reported on the Reporting Period-Dosing CRF. All AEs associated with an overdose should be entered both on the Reporting Period CRF and reported expeditiously using the CTEP-AERS.

14.0 RECORDS, REPORTING, AND DATA AND SAFETY MONITORING PLAN

14.1 Categories of Research Records

Research records for this study can be divided into three categories

1. Non-computerized Information: Roadmaps, Pathology Reports, Surgical Reports. These forms are uploaded into RAVE.

2. Reference Labs, Biopathology Reviews, and Imaging Center data: These data accompany submissions to these centers, which forward their data electronically to the COG Statistics & Data Center.

3. Computerized Information Electronically Submitted: All other data will be entered in RAVE with the aid of schedules and worksheets (essentially paper copies of the OPEN and RAVE screens) provided in the case report form (CRF) packet.

See separate CRF Packet, which includes submission schedule.

14.2 CDUS

This study will be monitored by the Clinical Data Update System (CDUS) version 3.0. Cumulative protocol- and patient-specific CDUS data will be submitted electronically to CTEP on a quarterly basis. Reports are due January 31, April 30, July 31 and October 31. This is not a responsibility of institutions participating in this trial

Note: If your study has been assigned to CDUS-Complete reporting, all adverse events (both routine and expedited) that have occurred on the study and meet the mandatory CDUS reporting guidelines must be reported via the monitoring method identified above.

14.3 CRADA/CTA/CSA

Standard Language to Be Incorporated into All Protocols Involving Agent(s) Covered by a Clinical Trials Agreement (CTA) or a Cooperative Research and Development Agreement.

The agent(s) supplied by CTEP, DCTD, NCI used in this protocol is/are provided to the NCI under a Collaborative Agreement (CRADA, CTA, CSA) between the Pharmaceutical Company(ies) (hereinafter referred to as "Collaborator(s)") 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 Agent(s) in this study:

14.3.1.1 Agent(s) may not be used for any purpose outside the scope of this protocol, nor can Agent(s) be transferred or licensed to any party not participating in the clinical study. Collaborator(s) data for Agent(s) are confidential and proprietary to Collaborator(s) and shall be maintained as such by the investigators. The protocol documents for studies utilizing investigational 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.

14.3.1.2 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"):

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

proposed combination protocol.

b. 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.

c. 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 investigational Agent.

3. Clinical Trial Data and Results and Raw Data developed under a Collaborative Agreement will be made available exclusively to Collaborator(s), 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.

4. 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.

5. Any data provided to Collaborator(s) for Phase 3 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.

6. Any manuscripts reporting the results of this clinical trial must be provided to CTEP for immediate delivery to Collaborator(s) for advisory review and comment prior to submission for publication. Collaborator(s) 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 Collaborator(s)'s intellectual property rights, are protected. Copies of abstracts must be provided to CTEP for forwarding to Collaborator(s) 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:

   Email: ncicteppubs@mail.nih.gov

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

14.4 Data and Safety Monitoring Plan

Data and safety is ensured by several integrated components including the COG Data and Safety Monitoring Committee.

14.4.1 Data and Safety Monitoring Committee

This study will be monitored in accordance with the Children's Oncology Group policy for data and safety monitoring of Phase 1 and 2 studies. In brief, the role of the COG Data and Safety Monitoring Committee is to protect the interests of patients and the scientific integrity for all Phase 1 and 2 studies. The DSMC consists of a chair; a statistician external to COG; one external member; one consumer representative; the lead statistician of the developmental therapy scientific committee; and a member from the NCI. The DSMC meets at least every 6 months to review current study results, as well as data available to the DSMC from other related studies. Approximately 6 weeks before each meeting of the Phase 1 and 2 DSMC, study chairs will be responsible for working with the study statistician to prepare study reports for review by the DSMC. The DSMC will provide recommendations to the COG Developmental Therapeutics Chair and the Group Chair for each study reviewed to change the study or to continue the study unchanged. Data and Safety Committee reports for institutional review boards can be prepared using the public data monitoring report as posted on the COG Web site.

14.4.2 Monitoring by the Study Chair and MATCH Leadership

The study chair will monitor the study regularly and enter evaluations of patients' eligibility, evaluability, and dose limiting toxicities into the study database. In addition, study data and the study chair's evaluations will be reviewed by the MATCH Chair, Vice Chair and Statistician on a weekly conference call.

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APPENDIX I: PERFORMANCE STATUS SCALES/SCORES

Karnofsky		**Lansky**	
Score	Description	Score	Description
100	Normal, no complaints, no evidence of disease	100	Fully active, normal.
90	Able to carry on normal activity, minor signs or symptoms of disease.	90	Minor restrictions in physically strenuous activity.
80	Normal activity with effort; some signs or symptoms of disease.	80	Active, but tires more quickly
70	Cares for self, unable to carry on normal activity or do active work.	70	Both greater restriction of and less time spent in play activity.
60	Required occasional assistance, but is able to care for most of his/her needs.	60	Up and around, but minimal active play; keeps busy with quieter activities.
50	Requires considerable assistance and frequent medical care.	50	Gets dressed, but lies around much of the day; no active play, able to participate in all quiet play and activities.
40	Disabled, requires special care and assistance.	40	Mostly in bed; participates in quiet activities.
30	Severely disabled, hospitalization indicated. Death not imminent.	30	In bed; needs assistance even for quiet play.
20	Very sick, hospitalization indicated. Death not imminent.	20	Often sleeping; play entirely limited to very passive activities.
10	Moribund, fatal processes progressing rapidly.	10	No play; does not get out of bed.

APPENDIX II: CYP3A4 SUBSTRATES INDUCERS AND INHIBITORS

This is NOT an all-inclusive list. Because the lists of these agents are constantly changing, it is important to regularly consult frequently updated medical references.

CYP3A4 substrates	Strong Inhibitors[1]	Moderate Inhibitors	Strong Inducers	Moderate Inducers
abemaciclib acalabrutinib[5] alfentanil[4,5] alprazolam[5] amiodarone[4] amlodipine aprepitant/fosaprepitant atorvastatin avanafil[5] axitinib bortezomib bosutinib[5] brexpiprazole brigatinib budesonide[5] buspirone[5] cabozantinib calcium channel blockers cisapride citalopram/escitalopram cobimetinib[5] colchicine[5] conivaptan[5] copanlisib crizotinib cyclosporine[4] dabrafenib dapsone darifenacin[5] darunavir[5] dasatinib[5] dexamethasone[2] diazepam dihydroergotamine docetaxel doxorubicin dronedarone[5] ebastine[5] eletriptan[5] eliglustat[5] eplerenone[5] ergotamine[4] erlotinib estrogens etoposide everolimus[5] felodipine[5] fentanyl[4]	atazanavir boceprevir clarithromycin ceritinib cobicistat danoprevir/ritonavir darunavir delavirdine elvitegravir/ritonavir grapefruit[3] grapefruit juice[3] idelalisib indinavir/ritonavir itraconazole ketoconazole lopinavir/ritonavir nefazodone nelfinavir paritaprevir/ritonavir/ ombitasvir +/- dasabuvir posaconazole ritonavir saquinavir telaprevir telithromycin tipranavir/ritonavir tucatinib voriconazole	aprepitant conivaptan crizotinib diltiazem dronedarone duvelisib erythromycin fedratinib fluconazole fosamprenavir fosnetupitant grapefruit[3] grapefruit juice[3] imatinib isavuconazole lefamulin letermovir mifepristone netupitant nilotinib ribociclib verapamil	apalutamide barbiturates carbamazepine enzalutamide fosphenytoin lumacaftor/ ivacaftor mitotane phenobarbital phenytoin primidone rifampin St. John's wort	bosentan cenobamate dabrafenib efavirenz eslicarbazepine etravirine lorlatinib modafinil nafcillin pexidartinib rifabutin rifapentin

gefitinib haloperidol ibrutinib[5] idelalisib imatinib indinavir[5] irinotecan isavuconazole[5] itraconazole ivacaftor ketoconazole lansoprazole lapatinib lomitapide[5] lorlatinib losartan lovastatin[5] lurasidone[5] macrolide antibiotics maraviroc[5] medroxyprogesterone methadone midazolam[5] midostaurin[5] modafinil naloxegol[5] nefazodone nilotinib nisoldipine[5] olaparib ondansetron osimertinib paclitaxel palbociclib pazopanib pimozide[5] quetiapine[5] quinidine[4] regorafenib rilpivirine[5] rivaroxaban[5] romidepsin saquinavir[5] sildenafil[5] simvastatin[5] sirolimus[4,5] sonidegib sunitinib tacrolimus[4,5] tamoxifen tadalafil[5] telaprevir temsirolimus				

teniposide tetracycline ticagrelor[5] tipranavir[5] tolvaptan[5] triazolam[5] trimethoprim vardenafil[5] vemurafenib venetoclax[5] vinca alkaloids zolpidem				

[1] Certain fruits, fruit juices and herbal supplements (star fruit, Seville oranges, pomegranate, gingko, goldenseal) may inhibit CYP 3A4 isozyme, however, the degree of that inhibition is unknown.
[2]Refer to Section 4.2.2.1 regarding use of corticosteroids.
[3]The effect of grapefruit juice (strong vs moderate CYP3A4 inhibition) varies widely among brands and is concentration-, dose-, and preparation-dependent.
[4]Narrow therapeutic range substrates
[5]Sensitive substrates (drugs that demonstrate an increase in AUC of ≥5-fold with strong inhibitors)

APPENDIX III-A: MEDICATION DIARY FOR SELPERCATINIB (LOXO-292) (CAPSULE FORMULATION)

COG Patient ID:_____ **Acc#**_____ **Institution :**_____
Please do not write patient names on this form.

Complete each day of the diary below with the dose and time selpercatinib (LOXO-292) is given. Store the selpercatinib capsules at room temperature. You should take selpercatinib doses, approximately 12 hours apart, at about the same time each day. Selpercatinib capsules should not be opened or crushed and must be swallowed whole. Gloves should be worn when handling selpercatinib capsules. If capsule is broken and the powder of the capsules gets on skin, wash the exposed area with as much water as necessary. Selpercatinib can be taken with or without food. If you forget to take a dose, you may take the dose if there are at least 6 hours remaining until the next scheduled dose. Otherwise, you should skip the forgotten dose. Either way, the next dose should be taken at the usual time. If a dose is accidentally skipped leave that section blank. ***Make note of other drugs and supplements taken under the Comments section below.*** If you take any proton pump inhibitors, such as Prilosec (Omeprazole), Prevacid (Lansoprazole), or Nexium (Esomeprazole), take selpercatinib with a meal. If you take any histamine-2 (H2) blocking agents, such as ranitidine (Zantac®), famotidine (Pepcid®), or cimetidine (Tagamet®), or antacids, such as TUMS, record the date and time in the Comments section below. Take selpercatinib 2 hours before or 10 hours after any histamine-2 (H2) blocking agents. Take selpercatinib 2 or more hours before or 2 or more hours after antacid administration. If vomiting occurs immediately after taking a capsule dose and the capsules are intact, the dose may be repeated. Inform your study doctor or nurse if that occurs. Add the dates to the calendar below and return the completed diary and any empty bottles or remaining capsules to your institution after each treatment cycle.

EXAMPLE			***Number of Selpercatinib capsules***		***Comments***
	Date	***Time***	**40mg**	**80 mg**	
Day 1	*5/15/19*	*8:30 AM*	1	1	*He felt nauseated an hour after taking the drug but did not vomit.*
Day 1	*5/15/19*	*8:30 PM*	1	1	

Cycle #: ____ **Start Date:** |__/__|__/__|__/__|
End Date: |__/__|__/__|__/__| **Dose Level:** _____**mg/m²/dose** **Part of Study:**_____

WEEK 1	**Date**	**Time**		**# of Selpercatinib capsules prescribed to take**		**Comments (Describe any missed or extra doses, vomiting and/or bothersome effects.)**
				40 mg AM#____ PM#____	**80 mg** AM#____ PM#____	
				# of Selpercatinib capsules taken		
				40 mg	**80 mg**	
Day 1			**AM**			
			PM			
Day 2			**AM**			
			PM			
Day 3			**AM**			
			PM			
Day 4			**AM**			
			PM			
Day 5			**AM**			
			PM			
Day 6			**AM**			

			PM			
Day 7			AM			
			PM			

COG Patient ID: _____ **ACC# :** _____ **Institution :**_____
Please do not write patient names on this form.

WEEK 2	Date	Time		# of Selpercatinib capsules prescribed to take		Comments (Describe any missed or extra doses, vomiting and/or bothersome effects.)
				40 mg	80 mg	
				AM#____ PM#____	AM# ____ PM#_____	
				# of Selpercatinib capsules taken		
				40 mg	80 mg	
Day 8			AM			
			PM			
Day 9			AM			
			PM			
Day 10			AM			
			PM			
Day 11			AM			
			PM			
Day 12			AM			
			PM			
Day 13			AM			
			PM			
Day 14			AM			
			PM			
WEEK 3	Date	Time		# of Selpercatinib capsules prescribed to take		Comments (Describe any missed or extra doses, vomiting and/or bothersome effects.)
				40 mg	80 mg	
				AM#____ PM#____	AM# ____ PM#_____	
				# of Selpercatinib-292 capsules taken		
				40 mg	80 mg	
Day 15			AM			
			PM			
Day 16			AM			
			PM			
Day 17			AM			
			PM			
Day 18			AM			
			PM			
Day 19			AM			

			PM			
Day 20			AM			
			PM			
Day 21			AM			
			PM			

COG Patient ID: _____ **ACC# :** _____ **Institution :**_____

Please do not write patient names on this form.

WEEK 4	Date	Time		# of Selpercatinib capsules prescribed to take		Comments (Describe any missed or extra doses, vomiting and/or bothersome effects.)
				40 mg	80 mg	
				AM#____ PM#____	AM# ____ PM#_____	
				# of Selpercatinib capsules taken		
				40 mg	80 mg	
Day 22			AM			
			PM			
Day 23			AM			
			PM			
Day 24			AM			
			PM			
Day 25			AM			
			PM			
Day 26			AM			
			PM			
Day 27			AM			
			PM			
Day 28			AM			
			PM			

If this form will be used as a source document, the site personnel who administered the study drug must sign and date this form below:

Signature: _____ Date: _____

(site personnel who administered study drug)

APPENDIX III-B MEDICATION DIARY FOR SELPERCATINIB (LOXO-292) (ORAL SUSPENSION)

COG Patient ID: _____ **Acc #**_____ **Institution:** _____
Please do not write patient names on this form.

Complete each day of the diary below with the dose and time selpercatinib (LOXO-292) is given. Store the selpercatinib (LOXO-292) liquid formulation in the refrigerator. Gloves should be worn when preparing selpercatinib suspension for administration. Prior to measuring out each dose, shake the bottle by hand to ensure a smooth suspension of the liquid. Try to avoid the formation of bubbles. The dosing syringe should be filled with an equal volume of water after each dose administration to be sure all residue of the suspension is ingested. A new syringe should be used for each dose. You should take selpercatinib doses, approximately 12 hours apart, at about the same time each day. Selpercatinib can be taken with or without food. If you forget to take a dose, you may take the dose if there are at least 6 hours remaining until the next scheduled dose. Otherwise, you should skip the forgotten dose. Either way, the next dose should be taken at the usual time. If a dose is accidentally skipped leave that section blank. Make note of other drugs and supplements taken in the Comments section below. If you take any proton pump inhibitors, such as Prilosec (Omeprazole), Prevacid (Lansoprazole), or Nexium (Esomeprazole), take selpercatinib with a meal. If you take any histamine-2 (H2) blocking agents, such as ranitidine (Zantac®), famotidine (Pepcid®), or cimetidine (Tagamet®), or antacids, such as TUMS, record the date and time in the Comments section below. Take selpercatinib 2 hours before or 10 hours after any histamine-2 (H2) blocking agents. Take selpercatinib 2 or more hours before or 2 or more hours after antacid administration. If you vomit after taking a dose, DO NOT retake your dose. This should be noted in the comments section. Add the dates to the calendar below and return the completed diary and the empty liquid formulation bottle(s) or any leftover liquid formulation to your institution after each treatment cycle.

EXAMPLE				***AM Dose: Take 2 mL PM Dose: Take 2 mL***	***Comments (Describe any missed or extra doses, vomiting and/or bothersome effects.)***
WEEK 1	***Date***	***Time***		***Amount of Selpercatinib liquid formulation taken(mL)***	
Day 1	*5/15/19*	*8:30*	*AM*	2	*He felt nauseated but did not vomit.*
		8:30	*PM*	2	

Cycle #: **Start Date:** | / | / | / | **End Date:** | / | / | / |

Dose Level: _____ mg/m^2/dose

WEEK 1	**Date**	**Time**		**AM Dose: Take _____mL PM Dose: Take _____mL Amount of Selpercatinib liquid formulation taken (mL)**	**Comments (Describe any missed or extra doses, vomiting and/or bothersome effects.)**
Day 1			**AM**		
			PM		
Day 2			**AM**		
			PM		
Day 3			**AM**		
			PM		
Day 4			**AM**		
			PM		
Day 5			**AM**		

			PM		
Day 6			AM		
			PM		
Day 7			AM		
			PM		

COG Patient ID: _____ **ACC# :** _____ **Institution :**_____

Please do not write patient names on this form.

Cycle #: _____ **Start Date:** |__/__|__/__|__/__| **End Date:** |__/__|__/__|__/__|

Dose Level: _____mg/m^2/dose

WEEK 2	Date	Time		AM Dose: Take _____mL PM Dose: Take _____mL Amount of Selpercatinib liquid formulation taken (mL)	Comments (Describe any missed or extra doses, vomiting and/or bothersome effects.)
Day 8			AM		
			PM		
Day 9			AM		
			PM		
Day 10			AM		
			PM		
Day 11			AM		
			PM		
Day 12			AM		
			PM		
Day 13			AM		
			PM		
Day 14			AM		
			PM		

WEEK 3	Date	Time		AM Dose: Take _____mL PM Dose: Take _____mL Amount of Selpercatinib liquid formulation taken(mL)	Comments (Describe any missed or extra doses, vomiting and/or bothersome effects.)
Day 15			AM		
			PM		
Day 16			AM		
			PM		
Day 17			AM		
			PM		
Day 18			AM		
			PM		
Day 19			AM		
			PM		
Day 20			AM		

			PM		
Day 21			AM		
			PM		

COG Patient ID: _____ ACC# : _____ Institution :_____
Please do not write patient names on this form.

WEEK 4	Date	Time		AM Dose: Take _____mL PM Dose: Take _____mL Amount of Selpercatinib liquid formulation taken(mL)	Comments (Describe any missed or extra doses, vomiting and/or bothersome effects.)
Day 22			AM		
			PM		
Day 23			AM		
			PM		
Day 24			AM		
			PM		
Day 25			AM		
			PM		
Day 26			AM		
			PM		
Day 27			AM		
			PM		
Day 28			AM		
			PM		

If this form will be used as a source document, the site personnel who administered the drug must sign and date this form below:

Signature: _____ Date: _____
(site personnel who administered study drug)

APPENDIX IV CORRELATIVE STUDIES

Correlative Study	Section	Blood Volume		Tube Type
		Volume per Sample	Total Cycle 5 Day 1	
Circulating tumor DNA (optional)	8.4	• For patients ≥ 10 kg collect 20 mLs (10 mL per tube x 2 tubes) • For patients > 5 kg but < 10 kg collect 10 mL (one tube) • For patients < 5 kg research samples will not be collected	10mL	Streck Cell-Free DNA BCT tubes
Total Blood Volume in Cycle 5 Day 1		**10 mL**		

Correlative Study	Section	Blood Volume		Tube Type
		Volume per Sample	Total 'Time of progression' or 'End of protocol therapy'	
Circulating tumor DNA (optional)	8.4	• For patients ≥ 10 kg collect 20 mLs (10 mL per tube x 2 tubes) • For patients > 5 kg but < 10 kg collect 10 mL (one tube) • For patients < 5 kg research samples will not be collected	10mL*	Streck Cell-Free DNA BCT tubes
Total Blood Volume in 'Time of progression or End of protocol therapy'		**10mL**		

*Only for patients receiving ≥ 5 cycles of therapy only

APPENDIX V-A: SELPERCATINIB (LOXO-292) CAPSULE DOSING NOMOGRAM

Drug doses should be adjusted based on the BSA calculated from height and weight measured within 7 days prior to the beginning of each cycle. Patients receiving the capsule formulation who experience dose-limiting toxicity should have their dose reduced by ~ 25% as shown in the table below.

Patients with a BSA ≥ 0.84 m^2 may take either the capsule or liquid formulation. Patients with a BSA < 0.84 m^2 must receive the liquid formulation (See Appendix V-B for dosing preparation of the selpercatinib liquid formulation).

Patients with BSA ≥ 0.84 m^2 may be switched to the liquid formulation at the same dose as the capsules if their ability to swallow capsules changes during the treatment

Selpercatinib Dose Assignment: 90 mg/m^2/dose BID (max dose 160 mg BID)

BSA (m2)	Selpercatinib Dosing	Total Daily Dose (mg/day)	Dose Reduction
0.84-1	80 mg PO BID	160	80 mg PO AM 40 mg PO PM
1.01-1.22	120 mg PO AM 80 mg PO PM	200	80 mg PO BID
1.23-1.44	120 mg PO BID	240	80 mg PO BID
1.45-1.66	160 mg PO AM 120 mg PO PM	280	120 mg PO AM 80 mg PO PM
≥1.67	160 mg PO BID	320	120 mg PO BID

APPENDIX V-B: SELPERCATINIB (LOXO-292) ORAL SUSPENSION DOSING

Drug doses should be adjusted based on the BSA calculated from height and weight measured within 7 days prior to the beginning of each cycle.

Patients with BSA < 0.84 m^2 must receive the oral suspension formulation.

Patients with BSA ≥ 0.84 m^2 may take either the capsule or suspension formulation (See Appendix V-A for dosing nomogram for selpercatinib capsule formulation).

Patients receiving the liquid formulation who experience dose-limiting toxicity should have their dose reduced by 25% so that patients receive 75% of the original prescribed dose.

Selpercatinib white to off-white powder for oral suspension is provided to the pharmacy in 1.4 gm amber glass bottles where it is compounded into a 20 mg/mL suspension with the addition of 1:1 Ora-Plus® and Ora-Sweet® SF. **A site-supplied 28 mm press-in bottle adapter is required for use with an oral syringe for dosing purpose.**

Selpercatinib will be given at 90 mg/m^2/dose BID (maximum of 160 mg BID). Calculated doses ≤ 45 mg should be prepared in oral syringes ≤ 3 mL with dosing volumes of selpercatinib suspension formulation rounded to the nearest 0.1 mL (2 mg). Calculated doses > 45 mg should be prepared in oral syringes ≥ 5 mL with dosing volumes of selpercatinib suspension formulation rounded to the nearest 0.2 mL (4 mg). It is recommended that oral dosing syringes should be only filled up to 75% of the maximum volume.

To calculate dosing volumes for each patient based on BSA, the following formula should be used:

$$\textit{Dosing Volume (mL)} = \frac{\textit{Prescribed Dose (mg/m}^2\textit{) x BSA (m}^2\textit{)}}{\textit{20 (mg/mL)}}$$

Round dosing volumes according to the above rules.
***Examples**:*

- *Patient BSA 0.44 m^2, Dose Level 1 (90 mg/m^2/dose) → Calculated Dose = 39.6 mg BID*
  Calculated Volume (mL) = (90 mg/m^2/dose x 0.44 m^2) / (20 mg/mL) = 1.98 mL
  Final Dosing Volume (mL) = 2 mL (rounded to nearest 0.1 mL for doses ≤ 45 mg)
  Final Dose to be administered = 2 mL x 20 mg/mL = 40 mg BID
- *Patient BSA 0.87 m^2, Dose Level 1 (90 mg/m^2/dose) → Calculated Dose = 78.3 mg BID*
  Calculated Volume (mL) = (90 mg/m^2/dose x 0.87 m^2) / (20 mg/mL) =3.915 mL
  Final Dosing Volume (mL) = 4 mL (rounded to the nearest 0.2 mL for dose > 45 mg)
  Final Dose to be administered = 4 mL x 20 mg/mL = 80 mg BID

APPENDIX VI: APEC1621N THERAPY DELIVERY MAP

Therapy Delivery Map – Cycle 1 This Therapy Delivery Map (TDM) relates to Cycle 1. Each cycle lasts 28 days.	_____ Patient COG ID number _____ Accession number

Criteria to start each cycle are listed in Section 5.2. Extensive treatment details are in Section 5.1.

DRUG	ROUTE	DOSAGE	DAYS	IMPORTANT NOTES
Selpercatinib (LOXO-292) IND # [redacted] **Do not use commercial supply**	PO	90 mg/m^2/dose orally twice daily (max dose 160 mg BID) Refer to the dosing nomogram.	1-28	See Appendix V-A for selpercatinib capsule dosing nomogram. See Appendix V-B for oral suspension dosing. Selpercatinib is administered twice daily, approximately 12 hours apart. Doses may be taken without regard to food. Capsules are to be swallowed whole. Do not chew, crush or open capsules. If study subject vomits immediately after taking a capsule dose and the capsule is still intact, the dose may be repeated. If study subject vomits after taking an oral suspension dose, the dose should not be repeated. If a dose is missed, it may be administered if there are at least 6 hours remaining until the next scheduled dose.

Ht _____cm Wt _____kg BSA _____m^2

Date Due	Date Given	Day	selpercatinib **(LOXO-292)** _____mg AM _____mg PM	Studies
			Enter calculated dose above as per dosing nomogram and actual dose administered below	
		1	_____mg AM _____mg PM	i
		2	_____mg AM _____mg PM	
		3	_____mg AM _____mg PM	
		4	_____mg AM _____mg PM	
		5	_____mg AM _____mg PM	
		6	_____mg AM _____mg PM	
		7	_____mg AM _____mg PM	
		8	_____mg AM _____mg PM	a, b, c, d, e, g, i
		9	_____mg AM _____mg PM	
		10	_____mg AM _____mg PM	
		11	_____mg AM _____mg PM	
		12	_____mg AM _____mg PM	
		13	_____mg AM _____mg PM	
		14	_____mg AM _____mg PM	
		15	_____mg AM _____mg PM	a, b, c, d, e, g,
		16	_____mg AM _____mg PM	
		17	_____mg AM _____mg PM	
		18	_____mg AM _____mg PM	
		19	_____mg AM _____mg PM	
		20	_____mg AM _____mg PM	
		21	_____mg AM _____mg PM	
		22	_____mg AM _____mg PM	a, b, c, d, e, g,
		23	_____mg AM _____mg PM	
		24	_____mg AM _____mg PM	
		25	_____mg AM _____mg PM	
		26	_____mg AM _____mg PM	
		27	_____mg AM _____mg PM	
		28/1	_____mg AM _____mg PM	a, b, c, d, e, f, g, h,

See Section 6.0 for Dose Modifications for Toxicities and the COG Member website for Supportive Care Guidelines.

Cycle 1

Cycle 1

Required Observations in Cycle 1

All baseline studies must be performed prior to starting protocol therapy unless otherwise indicated below. For information related to prestudy observations please refer to Section 8.1

***Please refer to section 8.1 for the specific timing of these observations. For information related to prestudy observations please refer to Section 8.1 Studies on Day 28/1 may be obtained within 72 hours prior to the start of the subsequent cycle.**

a.	**History/Physical Exam** (including VS, Tanner Staging, and routine dentition examination per local SOC).
b.	**CBC/differential/platelets**- If patients have Grade 4 neutropenia then CBCs should be checked at least every other day until recovery to Grade 3 or until meeting the criteria for dose limiting toxicity. If patients develop Grade 3 or higher thrombocytopenia then CBCs should be checked every 3-4 days until recovery
c.	**Electrolytes including Ca++, PO4, Mg++**
d.	**Creatinine, ALT,AST, bilirubin**
e.	**Albumin**
f.	**Ht/Wt/BSA**
g.	**Medication Diary** (see Appendix III-A and Appendix III-B) should be reviewed after completion of each treatment cycle and uploaded into RAVE. The medication diary should be collected weekly.
h.	**Plain radiograph tibial growth plate (bone x-ray tests)** prior to cycles 2 and 5, then every 6 months.
i.	**EKG-** Collected on Cycle 1 Day 1 and Cycle Day 8. On Cycle 1 Day 1 and Cycle 1 Day 8 the morning dose of selpercatinib (LOXO-292) should be held until the Pre-dose EKG assessment can be obtained. Please refer to Section 8.1 for more information.

This listing only includes evaluations necessary to answer the primary and secondary aims. OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD CLINICAL CARE.

Comments
(Include any held doses, or dose modifications)

Treatment Details: Cycle 1

Following completion of this cycle, the next cycle starts on Day 29 or when the criteria in Section 5.2 are met (whichever occurs later).

Subsequent Cycles

All Subsequent Cycles

Therapy Delivery Map – All Subsequent Cycles This Therapy Delivery Map (TDM) relates to all subsequent cycles. Each cycle lasts 28 days. Treatment may continue in the absence of disease progression or unacceptable toxicity. Use a copy of this page once for each cycle (please note cycle number below).	Patient COG ID number Accession number

Criteria to start each cycle are listed in Section 5.2. Extensive treatment details are in Section 5.1.

DRUG	ROUTE	DOSAGE	DAYS	IMPORTANT NOTES
Selpercatinib (LOXO-292) IND #[redacted] **Do not use commercial supply**	PO	90 mg/m^2/dose orally twice daily (max dose 160 mg BID) Refer to the dosing nomogram.	1-28	See Appendix V-A for selpercatinib capsule dosing nomogram. See Appendix V-B for oral suspension dosing. Selpercatinib is administered twice daily, approximately 12 hours apart. Doses may be taken without regard to food. Capsules are to be swallowed whole. Do not chew, crush or open capsules. If study subject vomits within immediately after taking a capsule dose and the capsules are intact, the dose may be repeated once. If study subject vomits after taking an oral suspension dose, the dose should not be repeated. If a dose is missed, it may be administered if there are at least 6 hours remaining until the next scheduled dose.

Enter Cycle #: _____ Ht _____cmWt _____kgBSA _____m^2

Date Due	Date Given	Day	selpercatinib (LOXO-292) _____mg AM _____mg PM	Studies
			Enter calculated dose above as per dosing nomogram and actual dose administered below	
		1	_____mg AM _____mg PM	a-f, i
		2	_____mg AM _____mg PM	
		3	_____mg AM _____mg PM	
		4	_____mg AM _____mg PM	
		5	_____mg AM _____mg PM	
		6	_____mg AM _____mg PM	
		7	_____mg AM _____mg PM	
		8	_____mg AM _____mg PM	
		9	_____mg AM _____mg PM	
		10	_____mg AM _____mg PM	
		11	_____mg AM _____mg PM	
		12	_____mg AM _____mg PM	
		13	_____mg AM _____mg PM	
		14	_____mg AM _____mg PM	
		15	_____mg AM _____mg PM	e (for Cycles 2 and 3 only)
		16	_____mg AM _____mg PM	
		17	_____mg AM _____mg PM	
		18	_____mg AM _____mg PM	
		19	_____mg AM _____mg PM	
		20	_____mg AM _____mg PM	
		21	_____mg AM _____mg PM	
		22	_____mg AM _____mg PM	
		23	_____mg AM _____mg PM	
		24	_____mg AM _____mg PM	
		25	_____mg AM _____mg PM	
		26	_____mg AM _____mg PM	
		27	_____mg AM _____mg PM	
		28/1	_____mg AM _____mg PM	a,-f, g*, h*, i, j*, k*, l*

See Section 6.0 for Dose Modifications for Toxicities and the COG Member website for Supportive Care Guidelines

*** Please refer to section 8.1 for the specific timing of these observations. Studies on Day 28/1 may be obtained within 72 hours prior to the start of the subsequent cycle.**

Required Observations in All Subsequent Cycles

a.	**History/Physical Exam** (including VS, Tanner Staging, and routine dentition examination per local SOC)
b.	**Ht/Wt/BSA**
c.	**CBC/differential/platelets** If patients develop Grade 4 neutropenia then CBCs should be checked every 3 to 4 days until recovery to Grade 3 or until meeting the criteria for dose limiting toxicity. If patients develop Grade 3 or higher thrombocytopenia then CBCs should be checked every 3-4 days until recovery
d.	**Electrolytes including Ca++, PO4, Mg++**
e.	**Creatinine, ALT, AST, bilirubin** (required prior to the start of the next cycle, and on Day 15 of Cycles 2 and 3)
f.	**Albumin**
g.	**Tumor Disease Evaluation** – Every other cycle x 3 then q 3 cycles. Tumor Disease Evaluation should be obtained on the next consecutive cycle after initial documentation of either a PR or CR. Subsequent scans may restart 2 cycles after the confirmatory scan. If the institutional investigator determines that the patient has progressed based on clinical or laboratory evidence, he/she may opt not to confirm this finding radiographically. Neurological exam also required for CNS patients. Non-Hodgkin Lymphoma/ Histiocytosis patients are required to have PET scans within 2 weeks prior to start of therapy and should also be followed with PET scans if positive at diagnosis.
h.	**Bone Marrow Aspirate and/or biopsy**- Every other cycle x 3 then q 3 cycles. Only required in patients suspected of having bone marrow metastasis on the basis of history, symptoms, laboratory evaluation or other clinical data. Should only be performed on patients with known bone marrow involvement at baseline. Bone marrow aspirate and/or biopsy should be performed only when complete response or partial response is identified in target disease or when progression in bone marrow is suspected.
i.	**Medication Diary**- (see Appendix III-A and Appendix III-B) should be reviewed after completion of each treatment cycle and uploaded into RAVE.
j.	**Circulating Tumor DNA (ctDNA-optional)**- With consent, two samples will be collected on this protocol (Cycle 5 Day 1; and for patients receiving ≥ 5 cycles, at progression or end of protocol therapy) see Section 8.4 for details of the ctDNA studies.
k.	**Plain radiograph tibial growth plate (bone x-ray tests)** prior to cycles 2 and 5, then every 6 months.
l.	**EKG-** Prior the start of subsequent cycles, the morning dose of selpercatinib (LOXO-292) should be held until the Pre-dose EKG assessment can be obtained. Please refer to Section 8.1 for more information.

This listing only includes evaluations necessary to answer the primary and secondary aims. OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD CLINICAL CARE.

Comments
(Include any held doses, or dose modifications)

Treatment Details: Subsequent Cycles

Following completion of this cycle, the next cycle starts on Day 29 or when the criteria in Section 5.2 are met (whichever occurs later)

APPENDIX VII: TARGET HISTOLOGIES FOR APEC1621N EXPANSION COHORTS

Target tumor types considered for biomarker-positive expansion cohorts in the event of agent activity in a specific tumor type.

Tumor type
1. Ependymoma
2. Ewing Sarcoma/Peripheral PNET
3. Hepatoblastoma
4. Glioma, high grade
5. Glioma, low grade
6. Langerhans Cell Histiocytosis
7. Malignant Germ Cell Tumor
8. Medulloblastoma
9. Neuroblastoma
10. Non-Hodgkin Lymphoma
11. Non-RMS Soft Tissue Sarcoma
12. Osteosarcoma
13. Rhabdoid Malignancy
14. Rhabdomyosarcoma
15. Wilms Tumor
16. Other Histology (based on COG/NCI-CTEP approval)

APPENDIX VIII: EXAMPLES OF ACTIONABLE MUTATIONS FOR SUBPROTOCOL APEC1621N

INCLUSION	VARIANTS			
Hotspots				
Gene Name	Variant ID	Variant Type	aMOI	LOE
RET	COSM29803	SNV	p.C618R	3
RET	COSM980	SNV	p.C618Y	3
RET	COSM29804	SVN	p.C620R	3
RET	COSM29805	SNV	p.C620S	3
RET	COSM968	DEL	p.E632_L633del	2
RET	COSM1048	INDEL	p.E632_T636delinsSS	2
RET	COSM982	DEL	p.E632_L633del	2
RET	COSM973	DEL	p.E632_C634del	2
RET	COSM1049	INDEL	p.E632_A640delinsVRP	2
RET	COSM1237919	SNV	p.C634F	3
RET	COSM1738369	SNV	p.C634G	3
RET	COSM966	SNV	p.C634R	3
RET	COSM1237918	SNV	p.C634S	3
RET	COSM975	SNV	p.C634W	3
RET	COSM974	SNV	p.C634Y	3
RET	COSM1716312	SNV	p.E768Q	3
RET	COSM1347811	SNV	p.E768G	3
RET	COSM21338	SNV	p.E768D	3
RET	rs79658334	SNV	p.V804M	2
RET	COSM977	MNV	p.A883F	2
RET	COSM981	MNV	p.A883F	2
RET	COSM133167	SNV	p.A883S	3
RET	COSM3415038	SNV	p.R912W	3
RET	COSM188545	SNV	p.R912L	3
RET	COSM3437793	SNV	p.R912Q	3
RET	COSM965	SNV	p.M918T	2
RET	COSM1347818	SNV	p.M918V	3

Fusions				
Gene Name	Variant ID	Variant Type	aMOI	LOE
RET	ACBD5-RET.A11R12	Fusion	RET Fusion	2
RET	AFAP1-RET.A3R12	Fusion	RET Fusion	2
RET	AKAP13-RET.A35R12	Fusion	RET Fusion	2
RET	AKAP13-RET.A36R12	Fusion	RET Fusion	2

RET	CCDC6-RET.C1R11	Fusion	RET Fusion	2
RET	CCDC6-RET.C1R11.1	Fusion	RET Fusion	2
RET	CCDC6-RET.C1R12	Fusion	RET Fusion	2
RET	CCDC6-RET.C1R12.COSF1271	Fusion	RET Fusion	2
RET	CCDC6-RET.C1R13	Fusion	RET Fusion	2
RET	CCDC6-RET.C1R9	Fusion	RET Fusion	2
RET	CCDC6-RET.C2R11	Fusion	RET Fusion	2
RET	CCDC6-RET.C2R12.1	Fusion	RET Fusion	2
RET	CCDC6-RET.C5ins16R11	Fusion	RET Fusion	2
RET	CCDC6-RET.C8R11	Fusion	RET Fusion	2
RET	CCDC6-RET.C8R11.COSF1518	Fusion	RET Fusion	2
RET	CCDC6-RET.C8R12	Fusion	RET Fusion	2
RET	CUX1-RET.C10R12	Fusion	RET Fusion	2
RET	ERC1-RET.E11R12.COSF1507	Fusion	RET Fusion	2
RET	ERC1-RET.E12R12	Fusion	RET Fusion	2
RET	ERC1-RET.E17R12	Fusion	RET Fusion	2
RET	ERC1-RET.E7R12	Fusion	RET Fusion	2
RET	FKBP15-RET.F25R12	Fusion	RET Fusion	2
RET	GOLGA5-RET.G7R12.COSF1503	Fusion	RET Fusion	2
RET	HOOK3-RET.H11R12.COSF1509	Fusion	RET Fusion	2
RET	KIAA1468-RET.K10R12	Fusion	RET Fusion	2
RET	KIF5B-RET.K15R11.COSF1255.1	Fusion	RET Fusion	2
RET	KIF5B-RET.K15R12.COSF1232	Fusion	RET Fusion	2
RET	KIF5B-RET.K16R12.COSF1230	Fusion	RET Fusion	2
RET	KIF5B-RET.K18R12	Fusion	RET Fusion	2
RET	KIF5B-RET.K22R12.COSF1253	Fusion	RET Fusion	2
RET	KIF5B-RET.K23R12.COSF1234	Fusion	RET Fusion	2
RET	KIF5B-RET.K24R11.COSF1262	Fusion	RET Fusion	2
RET	KIF5B-RET.K24R8.COSF1236	Fusion	RET Fusion	2
RET	KTN1-RET.K29R12.COSF1513	Fusion	RET Fusion	2
RET	MYH13-RET.M35R12	Fusion	RET Fusion	2
RET	NCOA4-RET.N6R12.COSF1340	Fusion	RET Fusion	2

RET	NCOA4-RET.N7R12.COSF1491	Fusion	RET Fusion	2
RET	PCM1-RET.P29R12.COSF1481	Fusion	RET Fusion	2
RET	PRKAR1A-RET.P7R12.COSF1511	Fusion	RET Fusion	2
RET	RUFY2-RET.R9R12	Fusion	RET Fusion	2
RET	SPECC1L-RET.S10R11.NGS.1	Fusion	RET Fusion	2
RET	SPECC1L-RET.S10R12	Fusion	RET Fusion	2
RET	TBL1XR1-RET.T9R11.NGS.1	Fusion	RET Fusion	2
RET	TBL1XR1-RET.T9R12	Fusion	RET Fusion	2
RET	TRIM24-RET.T9R12.COSF1521	Fusion	RET Fusion	2
RET	TRIM27-RET.T3R12.COSF1519	Fusion	RET Fusion	2
RET	TRIM33-RET.T11R12	Fusion	RET Fusion	2
RET	TRIM33-RET.T15R12	Fusion	RET Fusion	2
RET	TRIM33-RET.T16R12.COSF1525	Fusion	RET Fusion	2

APPENDIX IX: CTEP AND CTSU REGISTRATION PROCEDURES

Requirements For APEC1621N Site Registration:

Food and Drug Administration (FDA) regulations and National Cancer Institute (NCI) policy require all individuals contributing to NCI-sponsored trials to register and to renew their registration annually. To register, all individuals must obtain a Cancer Therapy Evaluation Program (CTEP) Identity and Access Management (IAM) account at https://ctepcore.nci.nih.gov/iam. In addition, persons with a registration type of Investigator (IVR), Non-Physician Investigator (NPIVR), or Associate Plus (AP) (i.e., clinical site staff requiring write access to OPEN, Rave, or acting as a primary site contact) must complete their annual registration using CTEP's web-based Registration and Credential Repository (RCR) at https://ctepcore.nci.nih.gov/rcr.

RCR utilizes five-person registration types.

- IVR — MD, DO, or international equivalent;
- NPIVR — advanced practice providers (e.g., NP or PA) or graduate level researchers (e.g., PhD);
- AP — clinical site staff (e.g., RN or CRA) with data entry access to CTSU applications (e.g., Roster Update Management System (RUMS), OPEN, Rave,);
- Associate (A) — other clinical site staff involved in the conduct of NCI-sponsored trials; and
- Associate Basic (AB) — individuals (e.g., pharmaceutical company employees) with limited access to NCI-supported systems.

RCR requires the following registration documents:

Documentation Required	IVR	NPIVR	AP	A	AB
FDA Form 1572	✓	✓			
Financial Disclosure Form	✓	✓	✓		
NCI Biosketch (education, training, employment, license, and certification)	✓	✓	✓		
GCP training	✓	✓	✓		
Agent Shipment Form (if applicable)	✓				
CV (optional)	✓	✓	✓		

An active CTEP-IAM user account and appropriate RCR registration is required to access all CTEP and Cancer Trials Support Unit (CTSU) websites and applications. In addition, IVRs and NPIVRs must list all clinical practice sites and Institutional Review Boards (IRBs) covering their practice sites on the FDA Form 1572 in RCR to allow the following:

- Addition to a site roster;
- Assign the treating, credit, consenting, or drug shipment (IVR only) tasks in OPEN;
- Act as the site-protocol Principal Investigator (PI) on the IRB approval
- Assigned the Clinical Investigator (CI) role on the Delegation of Tasks Log (DTL).

In addition, all investigators act as the Site-Protocol PI, consenting/treating/drug shipment, or as the CI on the DTL must be rostered at the enrolling site with a participating organization (i.e., Alliance).

Additional information is located on the CTEP website at https://ctep.cancer.gov/investigatorResources/default.htm. For questions, please contact the **RCR Help Desk** by email at RCRHelpDesk@nih.gov.

Cancer Trials Support Unit (CTSU) Registration Procedures

This study is supported by the NCI CTSU.

Protocol-Specific Requirements For Site Registration:

- IRB approval (For sites not participating via the NCI CIRB; local IRB documentation, an IRB-signed CTSU IRB Certification Form, Protocol of Human Subjects Assurance Identification/IRB Certification/Declaration of Exemption Form, or combination is accepted)

Submitting Regulatory Documents:

Submit required forms and documents to the CTSU Regulatory Office using the Regulatory Submission Portal on the CTSU website.

To access the Regulatory Submission Portal log in to the CTSU members' website, go to the Regulatory section and select Regulatory Submission.

Institutions with patients waiting that are unable to use the Regulatory Submission Portal should alert the CTSU Regulatory Office immediately at 1-866-651-2878 in order to receive further instruction and support.

Checking Your Site's Registration Status

Site registration status may be verified on the CTSU members' website.

- Click on *Regulatory* at the top of the screen;
- Click on *Site Registration; and*
- Enter the site's 5-character CTEP Institution Code and click on Go.
  - Additional filters are available to sort by Protocol, Registration Status, Protocol Status, and/or IRB Type.

Note: The status shown only reflects institutional compliance with site registration requirements as outlined within the protocol. It does not reflect compliance with protocol requirements for individuals participating on the protocol or the enrolling investigator's status with NCI or their affiliated networks.

Data Submission / Data Reporting

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.

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.

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 in to 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 site 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.

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 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 Calendaring functionality.

APPENDIX X: TOXICITY-SPECIFIC GRADING

Bilirubin

Grade 1:	> ULN- ≤ 1.5 x ULN
Grade 2:	> 1.5 x ULN - 3.0 x ULN
Grade 3:	> 3.0 x ULN -10.0 x ULN
Grade 4:	> 10.0 x ULN

ALT: For the purpose of this study, the ULN for ALT is 45 U/L regardless of baseline.

Grade 1:	> 45 U/L - ≤ 135 U/L
Grade 2:	136 U/L - 225 U/L
Grade 3:	226 U/L - 900 U/L
Grade 4:	> 900 U/L

AST: For the purpose of this study, the ULN for AST is 50 U/L regardless of baseline.

Grade 1:	> 50 U/L - ≤ 150 U/L
Grade 2:	151 U/L -250 U/L
Grade 3:	251 U/L -1000 U/L
Grade 4:	> 1000 U/L

GGT:

Grade 1:	> ULN- 2.5 x ULN
Grade 2:	> 2.5 x ULN - 5.0 x ULN
Grade 3:	> 5.0 x ULN -20.0 x ULN
Grade 4:	> 20.0 x ULN

APPENDIX XI: PATIENT DRUG INTERACTIONS 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 #:**	
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 the National Cancer Institute.

These are the things that your healthcare providers need to know:

Selpercatinib interacts with certain specific liver enzymes and certain transport proteins that help move drugs in and out of cells. Selpercatinib can also interact with certain stomach acid-reducing medications, medications that are considered highly protein-bound or medications that can affect your heart's electrical activity.

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

These are the things that you need to know:

The study drug selpercatinib, 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). It is helpful to 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 "strong" inducers/inhibitors of transport proteins P-gp and BCRP; any medicines that are considered substrates of CYP2C8, CYP3A4, P-gp, BCRP and MATE1; certain medicines that can affect your heart's electrical activity; certain medicines used to reduce stomach acid; and, medicines considered highly protein-bound.

- 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.
    - Avoid using herbal supplements, such as St. John's wort while taking selpercatinib.
    - Over-the-counter antacids or stomach acid reducing medicines called proton pump inhibitors or H2 antagonists may be used if necessary, but your study doctor will inform you how to take these medicines with selpercatinib. Examples of proton pump inhibitors include Prilosec (omeprazole), Prevacid (lansoprazole) and Nexium (esomeprazole). Examples of H2 receptor antagonists include Zantac (ranitidine), Pepcid (famotidine), and Tagamet (cimetidine).
- Make sure your doctor knows to avoid certain prescription medicines.
    - Avoid any medicines considered "moderate" or "strong" inducers/inhibitors of CYP3A4 and "strong" inducers/inhibitors of transport proteins P-gp and BCRP.
    - Avoid any medicines considered sensitive substrates of CYP2C8 and CYP3A4.
    - Use caution with any medicines considered substrates of MATE1, P-gp or BCRP.
    - Prescription and over-the-counter antacids and stomach acid reducing medicines such as proton pump inhibitors and H2 receptor antagonists may be used if necessary, but your study doctor will inform you how to take these medications with selpercatinib.
- 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.

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(Next page: Patient Drug Interaction Wallet Card)

Patient Drug Interaction Wallet Card

NIH NATIONAL CANCER INSTITUTE

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

NIH NATIONAL CANCER INSTITUTE

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 **Selpercatinib.**

Avoid using herbal supplements, such as St. John's wort while taking **Selpercatinib.**

Take over-the-counter or prescription antacids or stomach acid reducing medicines called proton pump inhibitors or H2 antagonists only as instructed by your study doctor. Examples of proton pump inhibitors include Prilosec (omeprazole), Prevacid (lansoprazole) and Nexium (esomeprazole). Examples of H2 antagonists include Zantac (ranitidine), Pepcid (famotidine) and Tagamet (cimetidine).

NIH NATIONAL CANCER INSTITUTE

DRUG INTERACTIONS

Carry this card with you at all times

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

Your healthcare providers should:

- Avoid use of any medicines that are considered "moderate: or "strong" inducers/inhibitors of CYP3A4 and "strong" inducers/inhibitors of transport proteins P-gp and BCRP
- Avoid use of any medicines that are considered sensitive substrates of CYP2C8 and CYP3A4
- Use caution with any medicines considered substrates of MATE1, P-gp and BCRP.
- Use caution with any medicines that can cause QTc interval prolongation
- Use caution with any medicines considered highly protein-bound
- Use antacids and medicines called proton pump inhibitors and/or H2 antagonists only as instructed by your study doctor

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 OCT2021

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

APPENDIX XII: YOUTH INFORMATION SHEETS
INFORMATION SHEET REGARDING RESEARCH STUDY APEC1621N
(For Children from 7 through 13 Years of Age)

We want to tell you all about this study. You and your family can decide if you want to be in it. Ask questions if you don't understand.

1. What is the name of the study? **A study of Molecular Analysis for Therapy Choice (MATCH) in children with a cancer that has come back after treatment or is difficult to treat**

2. Who is in charge of the study? The study is being done by Children's Oncology Group and is being done at other hospitals.

3. What is the study about? We are asking you to take part in a research study because other treatments did not get rid of the cancer. A research study is when doctors work together to try out new ways to help people who are sick. In this study, we are trying to learn more about how to treat the kind of cancer you have.

4. What will happen to me in the study? Children who are part of this study have been "matched" to a medicine. We think that this medicine will help you and other kids that have the same kind of cancer as you have. If you decide to be treated with this medicine, you will have some tests and check-ups done more often than if you weren't part of this study. We will follow your health after you finish the study treatment.

   Sometimes good things can happen to people when they are in a research study. These good things are called "benefits." We hope that a benefit to you of being part of this study is for your cancer to stop growing, or even shrink, but we don't know for sure if there is any benefit of being part of this study.

   Sometimes bad things can happen to people when they are in a research study. These bad things are called "risks." The risks to you from this study are that you may have more problems, or side effects, from a medicine used in this study. There may be risks that we don't know about yet.

5. Do I have to be in the study? You and your family can choose to be part of this study or not. You and your family can also decide to stop being in this study at any time once you start. There may be other treatments for your illness that your doctor can tell you about. If you have any questions or don't like what is happening, please tell your parent, the doctor or nurse.

6. We are asking your permission to collect additional tumor tissue. We want to see if there are ways to tell how the cancer will respond to treatment. These samples would be taken on tumor samples that we already have, so there would be no extra procedures. This would not change what medicines we would use to treat your tumor and would not provide any "benefits" to you. We hope that it might help us learn how to better treat other children's cancers in the future. You do not have to participate if you do not want to.

INFORMATION SHEET REGARDING RESEARCH STUDY APEC1621N
(For Teens from 14 through 17 Years of Age)

1. What is the name of the study? **A study of Molecular Analysis for Therapy Choice (MATCH) in children with a cancer that has come back after treatment or is difficult to treat**

2. Who is in charge of the study? The study is being done by Children's Oncology Group and is being done at other hospitals.

3. What is the study about? We are asking you to take part in a research study because other treatments did not get rid of the cancer. A research study is when doctors work together to try out new ways to help people who are sick. In this study, we are trying to learn more about how to treat the kind of cancer that you have.

4. What will happen to me on the study? Your tumor has a mutation that matches selpercatinib (LOXO-292), and so you have been assigned to selpercatinib (LOXO-292). The doctors want to see if selpercatinib (LOXO-292) will make children with your type of cancer get better. We don't know if selpercatinib (LOXO-292) will work well to get rid of your cancer. That is why we are doing the study.

   Sometimes good things can happen to people when they are in a research study. These good things are called "benefits." We hope that a benefit to you of being part of this study is that selpercatinib may cause your cancer to stop growing or to shrink for a period of time but we don't know for sure if there is any benefit of being part of this study.

   Sometimes bad things can happen to people when they are in a research study. These bad things are called "risks." The primary risk to you from this study is that you may have side effects, from selpercatinib. Your doctor will talk to you about the risks we know about from selpercatinib. There may be other risks from selpercatinib that we don't know about yet.

5. Will I be paid to be in this study? You will not be paid for being in this study.

6. Do I have to be in the study? You and your family can choose to be part of this study or not. You and your family can also decide to stop being in this study at any time once you start. There may be other treatments for your illness that your doctor can tell you about. If you have any questions or don't like what is happening, please tell your parent, the doctor or nurse.

8. We are asking your permission to collect additional tumor tissue. We want to see if there are ways to tell how the cancer will respond to treatment. These samples would be taken on blood samples that we already have, so there would be no extra procedures. This would not change what medicines we would use to treat your tumor and would not provide any "benefits" to you. We hope that it might help us learn how to better treat other children's cancers in the future. You do not have to participate if you do not want to.

APPENDIX XIII MEDICATIONS ASSOCIATED WITH PROLONGED QTC

The use of the following medications should be avoided during protocol therapy if reasonable alternatives exist. **This is not an inclusive list.** Because the lists of these agents are constantly changing, it is important to regularly consult frequently updated medical references. For the most current list of medications, please refer to the following reference: Woosley, RL and Romero, KA, www.Crediblemeds.org, QTdrugs List, Accession Date December 19th, 2019, AZCERT, Inc. 1822 Innovation Park Dr., Oro Valley, AZ 85755

Medications with known risk of Torsades de Pointes (TdP)	
Amiodarone	Fluconazole
Anagrelide	Haloperidol
Arsenic trioxide	Hydroxychloroquine
Azithromycin	Ibutilide
Chloroquine	Levofloxacin
Chlorpromazine	Methadone
Cilostazol	Moxifloxacin
Ciprofloxacin	Ondansetron
Citalopram	Oxaliplatin
Clarithromycin	Papaverine HCL (intra-coronary)
Disopyramide	Pentamidine
Dofetilide	Pimozide
Domperidone	Procainamide
Donepezil	Propofol
Droperidol	Quinidine
Dronedarone	Sevoflurane
Erythromycin	Sotalol
Escitalopram	Thioridazine
Flecainide	Vandetanib

Medications with possible risk of Torsades de Pointes (TdP)	
Alfuzosin	Lofexidine
Apalutamide	Lopinavir/Ritonavir
Apomorphine	Maprotilin
Aripiprazole	Memantine
Artemeter/Lumefantrine	Midostaurin
Asenapine	Mifepristone
Atomoxetine	Mirabegron
Bedaquiline	Mirtazapine
Bendamustine	Moexipril/Hydrochlorothiazide
Betrixaban	Necitumumab
Bortezomib	Nicardipine
Bosutinib	Nilotinib
Buprenorphine	Nortriptyline
Cabozantinib	Nusinersen
Capecitabine	Ofloxacin

Ceritinib	Osimertinib
Clomipramine	Oxytocin
Clozapine	Paliperidone
Cobimetinib	Palonosetron
Crizotinib	Panobinostat
Dabrafenib	Pasireotide
Dasatinib	Pazopanib
Degarelix	Perflutren lipid microspheres
Desipramine	Perphenazine
Deutetrabenazine	Pimavanserin
Dexmedetomidine	Pitolisant (Tiprolisant)
Dextromethorphan/Quinidine	Pretomanid
Dolasetron	Primaquine phosphate
Efavirenz	Promethazine
Eliglustat	Ribociclib
Encorafenib	Rilpivirine
Entrectinib	Romidepsin
Epirubicin	Saquinavir
Eribulin mesylate	Siponimod
Ezogabine (Retigabine)	Sorafenib
Felbamate	Sunitinib
Fingolimod	Tacrolimus
Fluorouracil (5-FU)	Tamoxifen
Gemifloxacin	Telavancin
Gilteritinib	Telithromycin
Glasdegib	Tetrabenazine
Granisetron	Tipiracil/Trifluridine
Hydrocodone-ER	Tizanidine
Iloperidone	Tolterodine
Imipramine (Melipramine)	Toremifene
Inotuzumab ozogamicin	Tramadol
Isradipine	Trimipramine
Ivosidenib	Valbenazine
Lapatinib	Vardenafil
Lefamulin	Vemurafenib
Lenvatinib	Venlafaxine
Leuprolide (Leuprorelin)	Vorinostat
Lithium	