CHILDREN'S ONCOLOGY GROUP

The world's childhood cancer experts

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October 28, 2022

Martha Kruhm, M.S., RAC
Protocol and Information Office (PIO) Head
National Cancer Institute
Executive Plaza North Room 730
Bethesda, MD 20892

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

Dear Ms. Kruhm,

The study committee thanks CTEP for forwarding the Amendment Request dated October 17, 2022. In response to the request, please see attached Amendment #7 to APEC1621A. The complete list of changes can be found below.

Please contact us if you have any further questions.

Sincerely,

Emma Archuleta, B.S., Protocol Coordinator (for)
Katherine Janeway, M.D., **APEC1621A** Study Chair, and
Douglas S. Hawkins, M.D., Group Chair, 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	-	Updated protocol version date in the footer.
2.	Cover Page	1	Updated version date and amendment number.
3.	Table of Contents	3-5	Updated for re-pagination.
4.	Contact Information	2	Cancer Trials Support Unit (CTSU)information updated with email address **CTSURegHelp@coccg.org**
5.	9.1.5	37	Deleted ~~discard unused portion 30 days after first opening~~ Added **after opening, store capsules below 30°C (86°F) and oral solution refrigerated at 2°C to 8°C (36°F to 46°F) for up to 30 days**

Activated: July 24th, 2017
Closed:
Version Date: 10/28/2022
Amendment # 7

CHILDREN'S ONCOLOGY GROUP

APEC1621A

NCI-COG PEDIATRIC MATCH (MOLECULAR ANALYSIS FOR THERAPY CHOICE)- PHASE 2 SUBPROTOCOL OF LOXO-101 (LAROTRECTINIB) IN PATIENTS WITH TUMORS HARBORING ACTIONABLE NTRK FUSIONS

Open to COG Member Institutions 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- CTSU (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 Data Submission Schedule in the CRF packet for further instructions.
The most current version of the **study protocol and all supporting documents** 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 protocol and 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.		

TABLE OF CONTENTS

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AGENT NSC# AND IND#'s
NCI-Supplied Agents
LOXO-101(larotrectinib)
(NSC #788607,IND# [redacted])

IND Sponsor: DCTD, NCI

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.

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ABSTRACT

This subprotocol is a component of the NCI-COG 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. Here we will conduct a phase 2 trial of LOXO-101 (larotrectinib) in children with recurrent or refractory solid tumors (including non-Hodgkin lymphomas, histiocytoses and CNS tumors) harboring NTRK gene fusion proteins.

LOXO-101 (larotrectinib) has shown tumor regression in non-clinical cancer models and in patients with tumors harboring *NTRK* gene fusion proteins. This is a Phase 2 study of LOXO-101 (larotrectinib) an orally bioavailable, potent, ATP-competitive, selective inhibitor of TRKA, TRKB, and TRKC in patients enrolled in APEC1621 who are determined to have *NTRK* 1, 2 or 3 translocations. LOXO-101 (larotrectinib) will be given orally or through NG- or G- tube at a dose of 100 mg/m^2/dose BID (capped at 100 mg per dose). The primary endpoint will be objective response rate as determined by RECIST. Progression free survival (PFS) will be assessed as a secondary endpoint. In addition, toxicity will be assessed, the pharmacokinetics of LOXO-101 (larotrectinib) in children will be evaluated and the ability to detect *NTRK* fusions in circulating cell-free tumor DNA in plasma will be evaluated.

EXPERIMENTAL DESIGN SCHEMA

Treatment Schedule Table	
Days 1-28	LOXO-101 (larotrectinib) orally or via NG- or G-tube twice daily
Day 28	Evaluation

Drug will be administered orally or via NG- or G- tube twice daily with no break; a cycle will be 28 days. Evaluations will occur at the end of every other cycle x 3, then every 3 cycles.

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 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 LOXO-101 (larotrectinib) with advanced solid tumors (including CNS tumors), non-Hodgkin lymphomas or histiocytic disorders harboring NTRK 1/2/3 fusions.

1.2 Secondary Aims

1.2.1 To estimate the progression free survival in pediatric patients treated with LOXO-101 (larotrectinib) with advanced solid tumors (including CNS tumors), non-Hodgkin lymphomas or histiocytic disorders with NTRK 1/2/3 fusions.

1.2.2 To obtain additional information about the tolerability of LOXO-101 (larotrectinib) in children with relapsed or refractory cancer.

1.2.3 To provide preliminary estimates of the pharmacokinetics of LOXO-101 (larotrectinib) in children 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

The TRK family are receptor tyrosine kinases involved in nervous system development. *NTRK1*, *NTRK2* and *NTRK3* encode TRKA, TRKB and TRKC respectively. TRK receptors are expressed in the nervous system and diseases resulting from loss of function mutations in NTRK genes reveal important roles for TRK in pain sensation, appetite control, memory and balance. Gene fusions involving each of the NTRK genes have been identified in a wide range of malignancies including the following seen in pediatric patients: gliomas, mesoblastic nephroma, and infantile fibrosarcoma.[1]

The reported TRK fusions occurring in cancer have the 3' region of TRK including the kinase domain fused to the 5' sequence from another gene. For example, the *ETV6-NTRK3* fusion identified in mesoblastic nephroma, infantile fibrosarcoma and other malignancies has a varying breakpoints but always contains the kinase domain of TRKC and the SAM dimerization domain of ETV6. It has been thought that the *ETV6-NTRK3* fusion was pathognomonic for infantile fibrosarcoma.[2] However, a recent case in which a novel *EML4-NTRK3* fusion was identified in a case with histology and clinical presentation consistent with a more aggressive manifestation of infantile fibrosarcoma raises the possibility that other *TRK* fusions may be identified in this disease.[3] Infantile fibrosarcoma is rare, often treatable with surgery or chemotherapy and infrequently metastatic or recurrent. However, locally aggressive cases do occur and medical management is considered in these cases. Likewise, mesoblastic nephroma has an excellent prognosis with surgery alone. Thus, these pediatric diseases in which *NTRK* fusions are common are less likely to need therapy on a phase 2 trial such as the pediatric MATCH study. In diffuse intrinsic pontine glioma (DIPG) and other pediatric high grade gliomas *NTRK* fusions were identified in 8 of 112 cases sequenced.[4] These pediatric malignancies, particularly DIPG have a poor prognosis.

It is not possible to precisely determine the frequency of NTRK 1/2/3 fusions in childhood malignancies eligible for this arm of the pediatric MATCH protocol using available databases. Detection of fusion events requires whole genome sequencing, RNA sequencing or specific fusion detection, methods that have not been utilized on a sufficient number of samples from recurrent childhood solid tumors and lymphomas with data in these databases for an accurate prediction of frequency of fusions. In the iCat study in which 100 patients with high risk, recurrent or refractory solid tumors had aCGH performed and targeted sequencing with only *NTRK1* assayed for fusions, one patient with an undifferentiated sarcoma was found to have a novel *EML4-NTRK3* fusion event based on a distinct aCGH pattern.[5] In an unpublished institutional tumor sequencing study utilizing a targeted next generation sequencing assay capturing intronic sequences of only NTRK1 for translocation detection, 1 of approximately 100 solid tumors sequenced (a sarcoma secondary to radiation) was found to have an *NTRK1* translocation (Janeway, personal communication).

LOXO-101 is an orally bioavailable, potent, ATP-competitive, selective inhibitor of TRKA, TRKB, and TRKC. LOXO-101 has shown tumor regression in non-clinical cancer models and in adult patients with tumors harboring *NTRK* gene fusion proteins. A phase 1 of LOXO-101 in adult patients with advanced solid tumors is ongoing (discussed further below). LOXO-101 dosing in this trial is flat dose. The maximum tolerated dose (MTD) has not been reached. At all doses administered in the Phase 1 trial, the peak concentrations are sufficient for 98% inhibition of TRKA/B/C and partial responses to LOXO-101 all 3

treated patients with *NTRK* fusions have been seen. [6] A pediatric liquid formulation has been developed and tested in animals.

2.2 Preclinical Studies

2.2.1 Antitumor Activity

LOXO-101 has potent inhibition of cell growth and proliferation driven by alteration in the TRK family of proteins versus control (non-TRK driven) cell lines with IC50 ranging from 1 to 59 nM (Table 1).

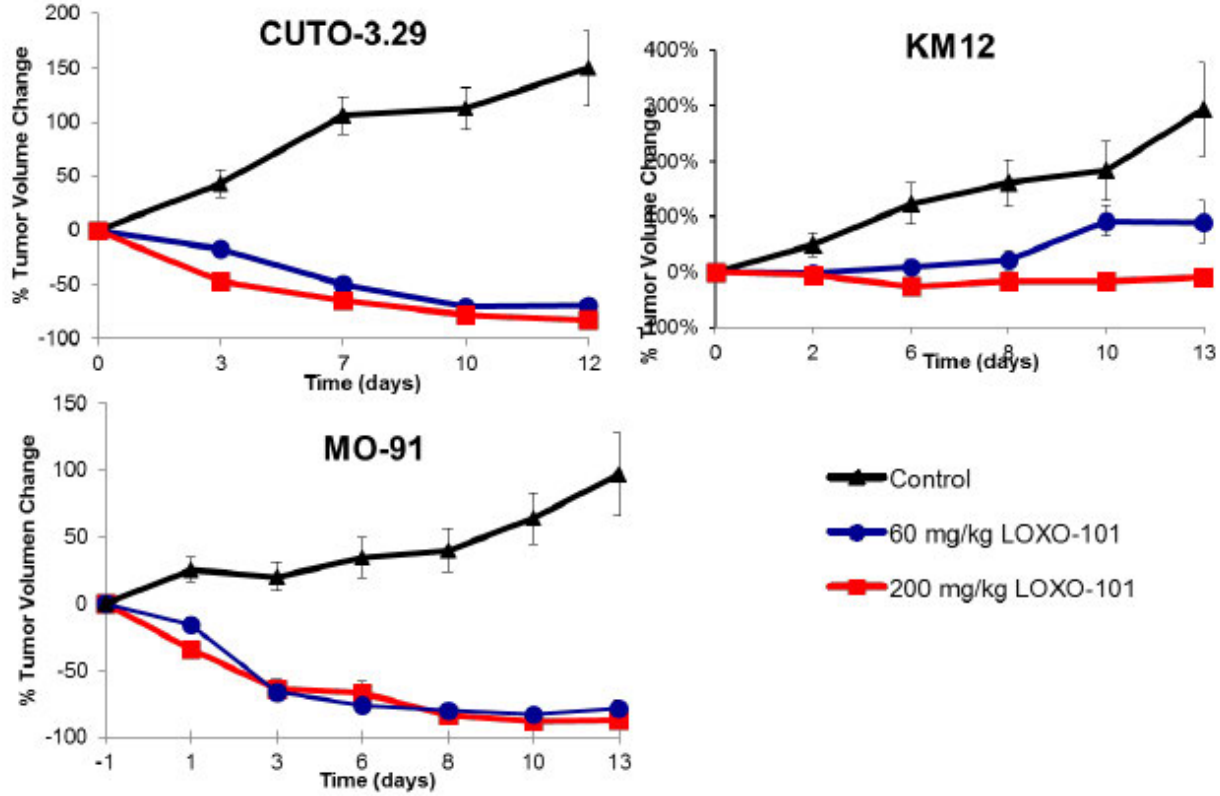
Table 1. Potency of LOXO-101 in TRK driven and non-TRK driven cell lines

Kinase Enzyme	TRK Family Alteration	IC_{50} (nM)
CUTO-3.29	*MPRIP-NTRK1*	59
KM12	*TPM3-NTRK1*	3.5
MO-91	*ETV6-NTRK3*	1.0
H1299, A549, HCC78, H3122, H1650, HCT15, HCT116, HT29, and SW837	None	> 1000

Abbreviations: IC_{50} = 50% inhibitory concentration; TRK = tropomyosin-related kinase (referring to family).

LOXO-101 displays tumor growth inhibition in xenografts of TRK fusion models (Figure 1)

Figure 1. Effect of LOXO-101 on TRK fusion xenografts



2.2.2 Animal Toxicology

LOXO-101 has been evaluated in 2 *in vitro* studies that explored possible cardiac electrophysiological effects using the human ether-à-go-go (hERG) assay, and in 12 *in vivo* safety pharmacology studies of the cardiovascular, gastrointestinal, CNS, and respiratory system in rats, dogs, and monkeys. LOXO-101 displayed a concentration-dependent inhibition of the hERG channel at concentrations from 10–300 μM, with an IC_{50} of 147 μM. No changes were detected in electrocardiogram (ECG) parameters, including the QT interval corrected for heart rate (QTc), in any of the cardiovascular studies. In the monkey, decreases in arterial blood pressure (diastolic and systolic) and heart rate changes (both decreases and increases) were noted at LOXO-101 doses of 100 and 200 mg/kg. Dose-dependent increases in gastric motility were observed in rats given single doses, as well as increases in gastric secretion at a dose of 100 mg/kg. No gastric irritation was detected at any dose. No neurobehavioral effects were seen in rats given single doses of LOXO-101 or multiple doses of 30 mg/kg BID; however, a worsening of Rotorod performance (measuring coordination and neuromuscular coordination) was observed in rats at multiple doses of 100 mg/kg BID.

The toxicological evaluation of LOXO-101 has included a single-dose oral study in rats, 3 repeat-dose BID studies in rats, and 3 repeat-dose once daily (QD) studies in cynomolgus monkeys. Exposures have extended out to 42 days and daily doses have ranged from 100 to 600 mg/kg in the single-dose study and from 20 to 300 mg/kg/day in the repeat-dose studies. The liver appeared to be the body system most consistently affected by LOXO-101. Dose-related increases in liver weights were observed; microscopically this appeared to be due to hepatocellular hypertrophy. Additional findings included increases in alanine aminotransferase (ALT) (both species) and aspartate aminotransferase (AST) (monkey). Decreases in serum albumin and increases in blood urea nitrogen (BUN) occurred in both species. The liver effects in both species were fully reversible. In both rats and monkeys, changes in multiple hematologic parameters were seen with no corresponding microscopic changes in bone marrow. Decreases in red blood cell (RBC) mass indices (RBC count, hematocrit, and hemoglobin) were sometimes accompanied by compensatory increases in reticulocytes and/or splenic extramedullary hematopoiesis with or without increase in spleen weight. Increases in monocytes were seen. Prolonged prothrombin time (PT) (rat, monkey), increased fibrinogen (rat) and shortened partial thromboplastin time (PTT) (rat) were observed but with no apparent coagulation disorders.

Overall, the rat was considered to be the most sensitive species. Body weight gains and increases in food consumption (rats only) were sometimes associated with increases in serum cholesterol. Heart weights were increased in the rat but with no associated histologic findings. Skin lesions were observed consistently and hypersalivation occasionally in rats. Decreases in uterine weights were attributed to uterine atrophy. Increased thyroid weights in female rats correlated with hypertrophy of thyroid follicular epithelia.

Little or no effects on neuromuscular function or cardiac electrophysiology were seen. LOXO-101 was not genotoxic in any of the tests conducted. Based on studies in which the no-observable-adverse-effect-level (NOAEL) was calculable, LOXO-101 had a single-dose NOAEL of 600 mg/kg (rats) and repeat-dose values of 10 mg/kg/day (monkeys) and 20 mg/kg/day (rats).

2.2.3 Preclinical Pharmacokinetic Studies

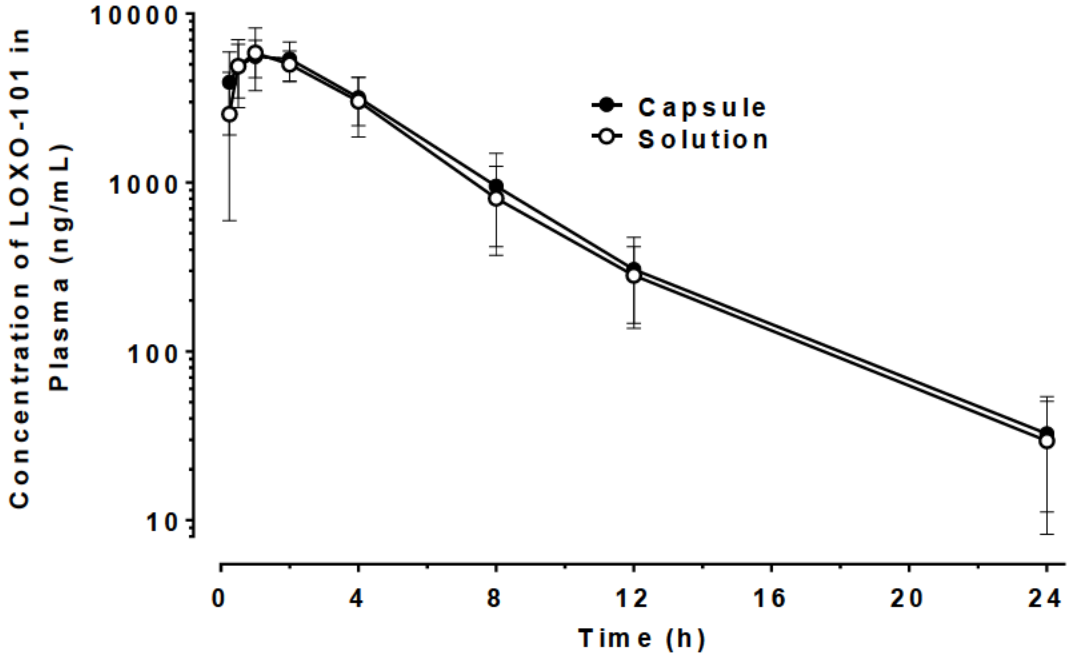
LOXO-101 has low nanomolar potency against all three TRK family members in enzyme and cellular assays, with 100 to 1,000-fold selectivity relative to other kinases. LOXO-101 binds to the human TRKA receptor *in vitro* with an IC_{50} of 11.5 nM. In cellular assays, it inhibits TRKA and constitutively-active TRKA with IC_{50} values of 9.8 and 6.4 nM, respectively. LOXO-101 reduces TRKA phosphorylation in clinically-relevant *NTRK1* gene fusion proteins and in cell lines derived from subjects. As LOXO-101 is a specific inhibitor of the TRK family of kinases, it had no anti-proliferative effect in tumor cell lines that do not express constitutively-active TRKA. LOXO-101 inhibits TRKB and TRKC with potencies approximately equal to its potency against TRKA (IC_{50} = 5.3 nM and 6.4 nM, respectively). It inhibits no other kinase significantly at concentrations up to 1000 nM.

In NIH-3T3 immunocompromised mice implanted with cells that express a constitutively active TRKA that was created by deletion of its second immunoglobulin domain (termed ΔTRKA), single, oral doses of LOXO-101 at 30 and 100 mg/kg suppressed TRKA phosphorylation in tumors for up to 12 hours, while twice-daily oral doses of 100 mg/kg caused significant inhibition of tumor growth.

Pharmacokinetic (PK) investigations of LOXO-101 have been conducted in mice, rats, dogs, and monkeys. Studies demonstrated oral bioavailability of approximately 30% to 100% across all species tested.

In a 2-way cross-over study in dogs that compared the PK of a single 100-mg adult PIC formulation to 5 mL of a 20-mg/kg pediatric solution formulation, maximum drug concentration (C_{max}) and area under the concentration versus time curve (AUC) of LOXO-101 were equal and the plasma concentration-versus-time profiles were superimposable (Figure 2). These data suggest, coupled with the animal PK data and interim clinical PK data, suggest that the PK of the hydroxypropyl-β-cyclodextrin (HP-β-CD) solution formulation will be similar to those of the current capsule formulation in humans.

Figure 2. PK of HP-β-CD Solution Versus Clinical Capsule in Dogs: PK Identical Between the Two Formulations



LOXO-101 distributes into tissues with volumes of distribution ranging from 0.7 to 2.8 L/kg but does not distribute significantly into the brain. LOXO-101 and its metabolites distribute freely between red blood cells and plasma; it binds moderately to plasma proteins independent of concentration over the range of 0.1 to 10 μM. LOXO-101 is metabolized by microsomal fractions and hepatocytes. The isoform of cytochrome P450 (CYP) that metabolizes LOXO-101 in human liver microsomes is primarily CYP3A4. LOXO-101 showed no significant inhibition of the various isoforms of CYP and was not a strong inducer of drug-metabolizing enzymes. LOXO-101 was demonstrated to be a substrate, but not an inhibitor, of P-glycoprotein. LOXO-101 and its metabolites are eliminated by the renal and biliary routes. Ongoing interim analysis of PK parameters of LOXO-101 at steady-state in this study indicates the anticipated exposure (based on C_{max} and AUC) in human patients will not exceed the exposure tested in the 28-day toxicology studies in rats and monkeys.

2.3 Adult Studies

2.3.1 Phase 1 Studies

Loxo Oncology has been conducting a Phase 1, first-in-human clinical study for LOXO-101 (Study LOXO-TRK-14001) that was initiated in May 2014. This Phase 1 study is a multicenter, open-label, dose-escalation study in adult patients with advanced solid tumors. To date, 24 patients have been treated with LOXO-101 at doses up to 150 mg BID. As of September 3, 2015, 24 pts have been treated at each of the first five dose levels (50 mg QD, 100 mg QD, 200 mg QD, 100 mg BID, and 150 mg BID). LOXO-101 has been well tolerated; the MTD has not been reached and the most common adverse events (AEs) are Grade 1 and 2

fatigue (42%), dizziness (29%) and anemia (21%). Two patients have had grade 3 AEs leading to dose cohort expansions: elevated AST, grade 3 (Dose Level 150 mg BID) and delirium, grade 3 (Dose Level 100 mg BID). Each case was subsequently deemed unrelated to study drug by the treating investigator, and the pts remained on study at reduced doses without recurrence. All three pts with NTRK-fusions enrolled have achieved a PR: an undifferentiated sarcoma with an LMNA-NTRK1 fusion (59% decrease; 7 cycles+), a c-kit-negative GI Stromal Tumor (GIST) with an ETV6-NTRK3 fusion (30% decrease; 2 cycles+), and a mammary analogue secretory carcinoma of the salivary glands with an ETV6-NTRK3 fusion (64% decrease; 2 cycles+). These patients were treated at either 100 or 150 mg BID. [7] The adult recommended phase II dose (RP2D) is 100 mg BID.

2.3.2 Phase 2 Studies

A Phase 2 study titled 'A Phase II Basket Study of the Oral TRK Inhibitor LOXO-101 in Subjects with NTRK Fusion-Positive Tumors' (Study LOXO-TRK-15002) has been initiated. This Phase 2 study is a multi-center, open-label study of subjects with advanced cancer harboring a fusion of *NTRK1, NTRK2*, or *NTRK3*. The study will include 8 cohorts of subjects with tumors bearing *NTRK* fusions, including non-small cell lung cancer, thyroid cancer, sarcoma, colorectal cancer, salivary gland cancer, biliary cancer, and primary CNS tumors, as well as a cohort that will enroll subjects not included in the histologies listed above.

2.3.3 Pharmacology/Pharmacokinetics/Correlative and Biological Studies

In the Phase 1, first-in-human clinical study for LOXO-101 (Study LOXO-TRK-14001) PK analysis showed maximum plasma concentrations of LOXO-101 were reached 30-60 minutes following dosing. The unbound drug concentrations of LOXO-101 appear sufficient for approximately 98% inhibition of TRKA/B/C at peak concentrations at all dose levels (50 mg QD, 100 mg QD, 200 mg QD, 100 mg BID, and 150 mg BID).

2.4 Larotrectinib Activity in NTRK Fusion Positive Malignancies

2.4.1 As of a November 10, 2016 data cutoff, 59 patients with refractory solid tumors had been enrolled and treated with single agent LOXO-101, including eight patients with cancers harboring NTRK fusions. Seven patients with NTRK fusion cancers were on study sufficiently long for an efficacy assessment, while an eighth NTRK fusion patient had been recently enrolled and was not yet evaluated for response. Six of the seven efficacy evaluable patients achieved a confirmed partial response, as defined by standard RECIST criteria. The seventh patient, as previously reported, demonstrated clear radiographic tumor regressions, including in the central nervous system, and remains on study, but had not met the threshold required for a RECIST response. All responders remained in response, with one patient in cycle 22, one patient in cycle 19, one patient in cycle 18, two patients in cycle 15 and one patient in cycle 11. Each cycle is 28 days, or approximately one month.

2.5 Pediatric Studies

2.5.1 Prior Experience in Children

A pediatric phase 1 study of LOXO-101 (NCT02637687) enrolled its first patient in December 2015. On this study LOXO-101 is administered PO BID. A physiologically-based PK approach (SimCyp®) was used to determine the starting dose (in mg/m^2) for pediatric patients that is needed to match the exposure (AUC) to a dose (currently 100 mg PO BID) that has been previously tested in adults, has not met dose limiting toxicity (DLT) criteria, and results in sufficient unbound drug concentrations to produce 98% inhibition of TRKA/B/C. A total of 25 patients have been treated as of 4/13/17 (ages ranging from 1 month to 18 years): 4 patients on Cohort 1, 11 patients on Cohort 2, and 10 patients on Cohort 3. The most recent patient was enrolled on 4/12/17 and 24 patients are evaluable for DLT. 10 patients have been treated at 100 mg/m^2/dose (max 100 mg) BID dosing (7 patients from Cohort 3; 3 patients from Cohorts 1 or 2 and dose escalated). Thus far no DLTs have been seen to date at any dose. At 100 mg/m^2/dose BID (n=10), the following grade 3/4 adverse events have been reported: neutropenia (n=2), nausea (n=1), increased ALT (n=1), weight increase (n=1). The pediatric RP2D has been called as 100 mg/m2 (capped at 100 mg) BID.

For this trial, LOXO-101 will be administered at the starting dose of the pediatric phase 1 trial, 100 mg/m^2/dose BID with a maximum of 100 mg BID. In the pediatric phase 1 trial, radiographic responses have been seen in patients with *NTRK* fusions treated at the 100 mg/m^2 dose.

2.5.2 Pharmacology/Pharmacokinetics/Correlative Biological Studies

Pediatric-specific pharmacology and PK are not yet available.

2.6 Overview of Proposed Pediatric Study

This Phase 2 study will assess the clinical effects of LOXO-101 (larotrectinib) administered orally twice daily of a 28-day cycle to pediatric and adolescent patients. LOXO-101 (larotrectinib) will be given at a dose of 100 mg/m^2/dose BID (capped at 100 mg per dose) which corresponds to the RP2D from the pediatric phase I trial.

Disease status will be evaluated by CT or MRI after every other cycle x 3 then every 3 cycles. Radiographic response will be assessed using RECIST criteria. Toxicity will be graded using the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.

In addition to optional pharmacokinetic studies, we propose to collect plasma samples from patients to evaluate the detection of NTRK fusions in ctDNA in solid 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 X 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 APEC1621A study patients (such as whether a specific mutation would be considered actionable for the study) should be directed to the APEC1621SC and APEC1621A study chairs.

The treatment assignment to a MATCH to a subprotocol (if a relevant aMOI is detected) will be communicated to the enrolling institution via the COG treatment assignment mechanism, upon which a reservation to APEC1621A 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 APEC1621A.

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. The date protocol therapy is projected to start must be no later than seven (7) calendar days after the date of study enrollment. Patients enrolling onto APEC1621A will have a COG ID obtained through their prior enrollment onto the master 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 LOXO-101 (larotrectinib) should be placed with CTEP after enrollment and treatment assignment to APEC1621A with consideration for timing of processing and shipping to ensure receipt of drug supply prior to start of protocol therapy.

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 APEC1621SC screening protocol.

3.7 Dose Assignment

The dose level 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 APEC1621A based on the presence of an actionable mutation as defined in APEC1621SC. Examples of actionable mutations for APEC1621A 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 hematopoietic growth factors): ≥ 21 days after the completion of interleukins, interferon or cytokines (other than hematopoietic 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 other NTRK inhibitors including but not limited to LOXO-101 (larotrectinib), entrectinib (RXDX-101), DS6051, PLX7486.

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 utilizing child length and stature data published by the CDC.[8]

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 Neurologic Function Defined as:

- Patients with seizure disorder may be enrolled if on anticonvulsants and well controlled.
- Nervous system disorders (CTCAE v5.0) resulting from prior therapy must be ≤ Grade 2, with the exception of decreased tendon reflex (DTR). Any grade of DTR is eligible.

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 an effective contraceptive method for the duration of study treatment.

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 (GVHD) post bone marrow transplant are not eligible for this trial.

4.2.2.5 CYP3A4 Agents: Patients who are currently receiving drugs that are 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.

4.2.3 Patients who have received prior therapy with a specific inhibitor of TRK (including but not limited to entrectinib (RXDX-101), DS-6051b, and PLX7486) are not eligible.

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

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

4.2.6 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

Treatment Schedule Table	
Days 1-28	LOXO-101 (larotrectinib) 100 mg/m^2/dose orally or via NG- or G- tube twice daily (maximum 100 mg per dose)
Day 28	Evaluation

LOXO-101 (larotrectinib) will be given at 100 mg/m^2/dose PO or via NG- or G- tube BID with a maximum of 100 mg per dose. LOXO-101 (larotrectinib) capsules should not be opened and must be swallowed whole. If vomiting occurs following dosing, doses should NOT be repeated and the next dose should be administered at the regularly scheduled time. If a dose is missed, it may be administered if there is at least 8 hours remaining until the next scheduled dose. Liquid formulation is also available and may be administered orally or via NG- or G- tube.

A cycle of therapy is considered to be 28 days. A cycle may be repeated up to a total duration of therapy of approximately 2 years (max 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, and according to the dosing nomogram (see Appendix IV). Doses of LOXO-101 (larotrectinib) capsules should be rounded to the nearest 25 mg (Appendix IV-A). Calculated dosing volumes of LOXO-101 (larotrectinib) liquid formulation should be rounded to the nearest 0.1 mL (2 mg) for doses ≤ 45 mg (in oral syringes ≤ 3.0 mL) and 0.2 mL (4 mg) for doses > 45 mg (in oral syringes ≥ 5.0 mL) for the actual deliverable dose (Appendix IV-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). Patients who require dose reduction for toxicity will be administered 75% of the starting dose (see Appendix IV-A & IV-B for dosing details). Therapy may otherwise continue for up to 2 years 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).

Larotrectinib is supplied by Bayer and distributed by the Pharmaceutical Management Branch, CTEP, DCTD, NCI. **Do not use commercial supply.**

5.1.1 Therapy Delivery Map

See Appendix VI for APEC1621A Therapy Delivery Map

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 CTCAE v5.0. A copy of the CTCAE v5.0 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 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 XI 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 regardless of baseline.
- 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 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 dose-limiting 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 IV-A for capsule formulation dosing nomogram and Appendix IV-B for preparation of liquid 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 IV-A for capsule formulation dosing nomogram and Appendix IV-B for preparation of liquid 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 a dose-limiting toxicity recurs in a patient who has resumed treatment at the reduced dose, the patient must be removed from protocol therapy.

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. Please see COG Supportive Care guidelines at https://childrensoncologygroup.org/index.php/cog-supportive-care-guidelines. See Section 7.5 for drugs that should not be used concomitantly due to potential interactions with LOXO-101 (larotrectinib).

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 CYP3A4/5 inhibitors or inducers: Strong CYP3A4/5 inhibitors or inducers are prohibited from 14 days prior to enrollment to the end of the study (See Appendix II for list of agents). Avoid grapefruit or grapefruit juice as these may also increase plasma concentrations of larotrectinib.

Note: CYP3A4 inducing anti-epileptic drugs and dexamethasone for CNS tumors or metastases, on a stable dose, are allowed. Use caution in patients who are taking concomitant medications that are substrates of CYP3A4.

7.5.2 If feasible, avoid concomitant treatment with strong p-glycoprotein (P-gp) or breast cancer resistance protein (BCRP) inhibitors and strong P-gp inducers.

7.5.3 Use with caution in patients who are taking concomitant medications that are sensitive or narrow therapeutic range substrates of CYP3A4 (see Appendix II).

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	X	Weekly	X
Neurologic Exam	X		
Height, weight, BSA	X		X
Performance Status	X		
Pregnancy Test[1]	X		
CBC, differential, platelets	X	Twice Weekly (every 3 to 4 days)[2,3]	Weekly[2,3]
Urinalysis	X		
Electrolytes including Ca^{++}, PO_4, Mg^{++}	X	Weekly	X
Creatinine, ALT, bilirubin	X	Weekly	X
Albumin	X		X
Tumor Disease Evaluation[4-A, 4-B, 4-C]	X		Every other cycle x 3 then q 3 cycles [4]
Bone Marrow Aspirate and/or biopsy[5,6]	X[6]		
Medication Diary[7]		Weekly	X
Pharmacokinetics (optional)[8]	X	X	
Circulating Tumor DNA (ctDNA-optional)[9]			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 4 thrombocytopenia then CBCs should be checked every 3 to 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 enrollment if the patient was enrolled with or has a history of having MIBG avid tumor. Otherwise the patient must have both CT/MRI and bone scan 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 bone scan. For patients with neuroblastoma and evaluable disease by MIBG scintigraphy or bone scan, use the same modality (MIBG scintigraphy or bone scan) 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. Should only be performed on patients with known bone marrow involvement at baseline.

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 Medication diary (see Appendix III) should be reviewed weekly during cycle 1, after completion of each treatment cycle, and uploaded into RAVE.

8 See Section 8.3 for details of PK studies.

9 With consent, two samples will be collected on this protocol (Cycle 5 Day 1; and for patients receiving $\geq$ 5 cycles at progression or end of protocol therapy), see Section 8.4 for details of the ctDNA studies. Note that a ctDNA sample is scheduled to be obtained on the APEC1621SC screening protocol prior to the initiation of treatment on this subprotocol.

8.2 Radiology Studies

8.2.1 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 (pre-study) evaluations as well as all end of cycle tumor disease evaluations which occurred while the patient was on the subprotocol therapy study.

8.2.2 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.
Submission of the digital files and reports via TRIAD is preferred. Instructions for TRIAD set up are below.

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 via TRIAD or 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.

Digital RT Data Submission Using TRIAD (if TRIAD is available at your site):
TRIAD is the American College of Radiology's (ACR) image exchange application. TRIAD provides sites participating in clinical trials a secure method to transmit DICOM and DICOM RT files and other digital objects, such as reports. TRIAD de-identifies and validates the images as they are transferred.

TRIAD Access Requirements:
Site physics staff who will submit images through TRIAD will need to be registered with the Cancer Therapy Evaluation Program (CTEP) and have a valid and active CTEP Identity and Access Management (IAM) account. Please refer to CTEP Registration Procedures of the protocol for instructions on how to request a CTEP-IAM account.

To submit images, the site TRIAD user must be on the site roster and be assigned the 'TRIAD site user' role on the CTSU roster. Users should contact the site's CTSU Administrator or Data Administrator to request assignment of the TRIAD site user role.

TRIAD Installations:

When a user applies for a CTEP-IAM account with the proper user role, he/she will need to have the TRIAD application installed on his/her workstation to be able to submit images. TRIAD installation documentation can be found by following this link https://triadinstall.acr.org/triadclient/

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

If you have any questions regarding this information, please send an e-mail to the TRIAD Support mailbox at TRIAD-Support@acr.org.

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

8.3 Pharmacology (optional)

8.3.1 Description of Studies and Assay

Pharmacokinetics (PK) will be performed to determine the PK of LOXO-101 (larotrectinib) in children. Pharmacokinetic analysis will be conducted at a centralized laboratory using validated assays.

8.3.2 Sampling Schedule

Blood samples will be obtained at the following time points:

Blood Sample No.	Time Point	Scheduled Collection Time
1	Cycle 1, Day 1	Pre-dose
2	Cycle 1, Day 1	1 hr after AM dose
3	Cycle 1, Day 1	2 hrs after AM dose
4	Cycle 1, Day 1	4 hrs after AM dose
5	Cycle 1, Day 1	6-8 hrs after AM dose
6	Cycle 2, Day 1	Pre-dose

8.3.3 Sample Collection and Handling Instructions

Blood samples (3 ml) will be collected in K_2 EDTA lavender top for pharmacokinetic evaluation. Record the exact time that the sample is drawn along with the exact time that the drug is administered.

Sites are expected to use their own standard materials for PK sample collection as kits will not be provided for the PK studies for this study.

8.3.4 Sample Processing

Following collection, the sample will be immediately gently mixed by inversion 8-10 times. The sample will be stored on wet ice until centrifugation. The sample will be centrifuged at 1500 x g for 15 minutes at 4° C within 60 minutes after the sample is drawn. The plasma will be transferred to a cryovial, ensuring no RBC contamination, and frozen as soon as possible at -80° C. If a -80° C freezer is not immediately available, the cryovial may be stored on dry ice for short term storage, but must be placed in the appropriate freezer within 24 hours of the draw-time.

8.3.5 Sample Labeling

Each sample must be labeled with the patient's study registration number, the study I.D (#APEC1621A), 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).

8.3.6 Sample Processing and Shipping Instructions

Samples collected for each subject should be shipped to Alturas Inc, on sufficient dry ice in an insulated container. Samples should be shipped between Monday and Wednesday for overnight delivery to ensure delivery to Alturas Analytics, Inc, before Friday.

Samples should be shipped to the following address:
Dr. Jennifer Zimmer
Alturas Analytics, Inc.
1324 Alturas Dr.
Moscow, ID 83843
Phone: (208) 883-3400

Fax: (208) 882-9246
Email: jzimmer@alturasanalytics.com

A notification email should be sent to Jennifer Zimmer with courier name, airway bill number, expected delivery date/time and shipment contact.

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.
- Store blood in Streck tube at **room temperature** until shipment

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 (APEC1621A), 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 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 APEC1621A– Peds MATCH*
700 Children's Drive, WA1340
Columbus, OH 43205
Phone: (614) 722-2865
Fax: (614) 722-2897
Email:BPCBank@nationwidechildrens.org

*Labeling is extremely important for this project. Packages **must** be labeled "Peds MATCH" in order to expedite processing at the BPC. Be sure to include the room number. Packages received without the room number may be returned to the sender.

9.0 AGENT INFORMATION

9.1 Larotrectinib 09/28/22

(larotrectinib sulfate, Vitrakvi®, LOXO-101, BAY 2757556) NSC# 788607, IND# [redacted]

9.1.1 Structure and molecular weight

Larotrectinib sulfate is a small molecule with an empirical formula of $C_{21}H_{24}F_2N_6O_6S$ and a molecular weight of 526.52 (hydrogen sulfate salt), 428.4 (free base). The chemical name is (S)-N-(5-((R)-2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxypyrrolidine-1-carboxamide hydrogen sulfate.

Larotrectinib is an ATP-competitive, selective inhibitor of the tropomyosin-related kinase (TRK) family of neurotrophin receptors, demonstrating inhibition of all three known TRK receptors (TRKA, TRKB and TRKC). In normal tissue, activated TRK receptor signaling may stimulate cellular growth, survival and differentiation. TRK receptors are encoded by NTRK genes; NTRK1, NTRK2, and NTRK3. NTRK gene fusions appear to be oncogenic and inhibition of TRK receptors may provide benefit to patients with malignancies due to oncogenic alterations in the NTRK genes.

9.1.2 Supplied by:

Bayer AG and distributed by the Pharmaceutical Management Branch, CTEP, DCTD, NCI. **Do not use commercial supply**

9.1.3 Formulation

- 25 mg capsules are opaque white, size 2, hard gelatin capsules containing 25 mg of Larotrectinib sulfate. The capsules contain no excipients. Capsules are supplied in 60-count, 72-count or 100-count HDPE bottles with induction seals and child-resistant plastic caps.
- 100 mg capsules are opaque white, size 0, hard gelatin capsules containing 100 mg of Larotrectinib sulfate. The capsules contain no excipients. Capsules are supplied in 60-count, 72-count or 100-count HDPE bottles with induction seals and child-resistant plastic caps.
- 50 mL or 100 mL liquid oral solution containing 20 mg/mL of larotrectinib sulfate filled into 60 mL (ORA-SWEET free) or 100 mL. Kylix, amber type III glass bottles, PP28 neck, with a 28 mm child resistant cap and tamper evident closure with Triseal liner.
    - The 50 mL bottle of oral solution is a colorless to yellow or orange or brownish liquid containing the following inactive ingredients: purified water, USP; Kleptose HPB Parenteral Grade, USP; Citric Acid, anhydrous, USP; Flavor strawberry, specification; Sodium benzoate, NF; Sodium citrate, USP; Sucralose, USP/NF
    - The 100 mL bottle of oral solution is a colorless to clear yellow to orange liquid containing the following inactive ingredients: purified water, USP; Kleptose HPB Parenteral Grade, USP; ORA-SWEET®; Sodium Citrate, Dihydrate, Granular, USP; 231a12 Natural Masking Type Flavor (Abelei); 231a39 Natural Bitterness Masking Type Flavor (Abelei); Bitterness Masking Flavor, Nat (FONA - Liquid); FONATECH® Taste Modifier Flavor, Nat

- **A site-supplied 28 mm LDPE (e.g., Comar® product number 22-0198; B Braun Exadoral®) or polypropylene press-in bottle adapter is required for use with an oral syringe for dosing purposes.**

9.1.4 Storage

Store capsules at room temperature below 30° (86°F). Store liquid oral solution refrigerated at 2°C to 8°C (36°F to 46°F). Do not freeze

If a storage temperature excursion is identified, promptly return larotrectinib capsules to controlled room temperature and larotrectinib liquid oral solution 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.

9.1.5 Stability

Bottle labels contain an expiration date. Larotrectinib sulfate capsules for a cycle may be counted out and repackaged from the manufacturer-supplied HDPE bottle into a pharmacy-supplied HDPE bottle for dispensing purposes. Instruct patients to store the prescription container away from areas of high heat and humidity.

Larotrectinib sulfate liquid oral solution is to be dispensed in the manufacturer's container as a whole bottle. After opening, store capsules below 30°C (86°F) and oral solution refrigerated at 2°C to 8°C (36°F to 46°F) for up to 30 days.

9.1.6 Administration

See Section 6.0 for dose modifications and Section 5.0 Treatment section of the protocol for dosing and administration details. Larotrectinib is administered orally or via NG- or G-tube and may be taken without regard to food. Larotrectinib sulfate may be taken without regard to food. Capsules are to be swallowed whole. Do not chew, crush or open capsules. **Please note the maximum dose of 100 mg per dose BID.**

9.1.7 Potential Drug Interactions

Larotrectinib is a substrate of cytochrome P450 (CYP) 3A, P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP). Co-administration of larotrectinib with strong CYP3A inhibitors, P-gp and BCRP inhibitors increases larotrectinib plasma concentrations. Co-administration of larotrectinib with strong CYP3A and P-gp inducers decreases larotrectinib plasma concentrations. Avoid concomitant use of strong CYP3A inhibitors or inducers for 14 days prior to enrollment through the end of protocol therapy Appendix II). Avoid grapefruit or grapefruit juice as these may also increase plasma concentrations of larotrectinib.

If feasible, avoid concomitant administration with strong P-gp or BCRP inhibitors and strong P-gp inducers.

Larotrectinib inhibits CYP3A weakly both in vitro and in vivo. Exercise caution with concomitant use of CYP3A substrates with narrow therapeutic range (e.g. alfentanil, cyclosporine, dihydroergotamine, ergotamine, fentanyl, pimozide, quinidine, sirolimus, or tacrolimus; Appendix II) in patients taking larotrectinib. If concomitant use of these CYP3A substrates with narrow therapeutic range is

required in patients taking larotrectinib, additional toxicity monitoring and/or dose modification of the CYP3A substrates may be required due to adverse reactions.

Antacid use does not significantly alter the pharmacokinetics of larotrectinib.

9.1.8 Patient Care Considerations

Based on the mechanism of action, fetal harm cannot be excluded when administering larotrectinib to a pregnant woman.
Advise female and male patients of reproductive potential to use highly effective contraception during treatment with larotrectinib and for at least one month after the final dose.

Because of the unknown risk of larotrectinib in nursing infants, advise a nursing woman to discontinue breastfeeding during treatment with larotrectinib and for 3 days (6 plasma half-lives of larotrectinib and its metabolites) following the final dose.

9.1.9 Larotrectinib Toxicities

Comprehensive Adverse Events and Potential Risks list (CAEPR)
for
Larotrectinib sulfate (BAY 2757556, LOXO-101, NSC 788607)

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 388 patients.* Below is the CAEPR for Larotrectinib sulfate (BAY 2757556, LOXO-101).

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, May 12, 2022[1]

Adverse Events with Possible Relationship to Larotrectinib sulfate (BAY 2757556, LOXO-101) (CTCAE 5.0 Term) [n= 388]			**Specific Protocol Exceptions to Expedited Reporting (SPEER)**
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
	Anemia		***Anemia (Gr 2)***
GASTROINTESTINAL DISORDERS			
	Abdominal pain		***Abdominal pain (Gr 2)***
	Constipation		***Constipation (Gr 2)***
	Diarrhea		***Diarrhea (Gr 2)***
	Nausea		***Nausea (Gr 2)***
	Vomiting		***Vomiting (Gr 2)***

GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
	Edema limbs		***Edema limbs (Gr 2)***
	Fatigue		***Fatigue (Gr 2)***
	Fever		***Fever (Gr 2)***
		Gait disturbance	
INVESTIGATIONS			
	Alanine aminotransferase increased		***Alanine aminotransferase increased (Gr 2)***
	Aspartate aminotransferase increased		***Aspartate aminotransferase increased (Gr 2)***
	Neutrophil count decreased		***Neutrophil count decreased (Gr 2)***
	Weight gain		***Weight gain (Gr 2)***
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			
	Myalgia		***Myalgia (Gr 2)***
NERVOUS SYSTEM DISORDERS			
	Dizziness		***Dizziness (Gr 2)***
		Paresthesia	
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
	Cough		***Cough (Gr 2)***
	Dyspnea		***Dyspnea (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.

Adverse events reported on Larotrectinib sulfate (BAY 2757556, LOXO-101) trials, but for which there is insufficient evidence to suggest that there was a reasonable possibility that Larotrectinib sulfate (BAY 2757556, LOXO-101) caused the adverse event:

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Leukocytosis
CARDIAC DISORDERS - Atrial fibrillation; Atrioventricular block first degree; Cardiac disorders - Other (left ventricular dysfunction); Pericardial effusion
ENDOCRINE DISORDERS - Hypothyroidism
EYE DISORDERS - Eye pain; Periorbital edema; Watering eyes
GASTROINTESTINAL DISORDERS - Abdominal distension; Ascites; Dry mouth; Dyspepsia; Dysphagia; Gastrointestinal disorders - Other (enterocutaneous fistula); Gastrointestinal disorders - Other (gastrointestinal obstruction); Gastrointestinal disorders - Other (teething); Oral pain; Small intestinal obstruction; Small intestinal perforation
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Chills; Facial pain; Flu like symptoms; Multi-organ failure; Pain
HEPATOBILIARY DISORDERS - Hepatobiliary disorders - Other (bile duct obstruction); Hepatobiliary disorders - Other (hepatic function abnormal); Hepatobiliary disorders - Other (jaundice cholestatic)
IMMUNE SYSTEM DISORDERS - Allergic reaction
INFECTIONS AND INFESTATIONS - Hepatitis viral; Laryngitis; Lung infection; Sepsis; Skin infection; Upper respiratory infection; Urinary tract infection; Vaginal infection; Viremia; Wound infection
INJURY, POISONING AND PROCEDURAL COMPLICATIONS - Fall
INVESTIGATIONS - Alkaline phosphatase increased; Blood bilirubin increased; Ejection fraction decreased; Electrocardiogram QT corrected interval prolonged; Investigations - Other (hepatic cytolysis); Lipase increased; Lymphocyte count decreased; Serum amylase increased; Weight loss; White blood cell decreased
METABOLISM AND NUTRITION DISORDERS - Anorexia; Dehydration; Hypercalcemia; Hyperglycemia; Hypernatremia; Hypertriglyceridemia; Hyperuricemia; Hypoalbuminemia; Hypokalemia; Hypomagnesemia; Hyponatremia; Hypophosphatemia
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Arthralgia; Back pain; Flank pain;

Generalized muscle weakness; Joint range of motion decreased; Musculoskeletal and connective tissue disorder - Other (muscle twitching); Musculoskeletal and connective tissue disorder - Other (musculoskeletal stiffness); Musculoskeletal and connective tissue disorder - Other (pain in jaw); Pain in extremity
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS) - Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other (acute myeloid leukemia); Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other (bile duct adenocarcinoma); Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other (glioma, glioblastoma multiforme); Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other (malignant neoplasm progression, neoplasm progression); Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other (metastases to central nervous system)
NERVOUS SYSTEM DISORDERS - Ataxia; Depressed level of consciousness; Dysarthria; Dysesthesia; Dysgeusia; Edema cerebral; Extrapyramidal disorder; Headache; Memory impairment; Nervous system disorders - Other (motor dysfunction); Peripheral sensory neuropathy; Somnolence; Spinal cord compression; Syncope
PSYCHIATRIC DISORDERS - Agitation; Confusion; Delirium; Personality change; Restlessness
RENAL AND URINARY DISORDERS - Hematuria; Proteinuria
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Hypoxia; Nasal congestion; Oropharyngeal pain; Pleural effusion; Productive cough; Respiratory failure; Respiratory, thoracic and mediastinal disorders - Other (hypoventilation); Sneezing; Voice alteration; Wheezing
SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Hyperhidrosis; Pruritus; Rash maculo-papular
VASCULAR DISORDERS - Hot flashes; Hypertension; Hypotension; Thromboembolic event

Note: Larotrectinib sulfate (BAY 2757556, LOXO-101) 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.

9.1.10 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 responsible investigator 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 larotrectinib should be placed with CTEP after enrollment and treatment assignment to APEC1621A 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.

9.1.11 Clinical Drug 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, "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.

9.1.12 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.

9.1.12 Investigator Brochure Availability

The current versions of the IB(s) for the agents will also 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.

9.1.13 Useful Links and Contacts

- CTEP Forms, Templates, Documents: http://ctep.cancer.gov/forms/
- NCI CTEP 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/
- CTEP IAM account help: ctepreghelp@ctep.nci.nih.gov
- PMB email:
- PMBAfterHours@mail.nih.gov
- IB Coordinator:
- IBcoordinator@mail.nih.gov
- PMB phone and hours of service: (240) 276-6575
  Monday through Friday between 8:30 am and 4:30 pm (ET)

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 13.4.4, 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 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

APEC1621A will require a minimum of 20 evaluable patients, and a maximum of 49 patients, allowing for 15% inevaluability. Assuming an enrollment rate of 4-9 biomarker positive patients per year, the primary cohort of this subprotocol is expected to be completed within 2.7-6 years.

11.2 Dosing Considerations

Please see Section 5.1 for a specific discussion of the dosing of LOXO-101 (larotrectinib) to be used in this study. Please note that limited pharmacokinetic sampling may be done for patients enrolled on this arm.

11.3 Study Design

The primary cohort will employ a single stage A'Hern design 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	≥ 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:

APEC1621A 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 LOXO-101 (larotrectinib). Using an A'Hern design[9] 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 at any time ≥ 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 VIII 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.[10] 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. When opening expansion cohorts, the evaluation period for determination of best response will be 6 treatment cycles. 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 Pharmacokinetic and Correlative Studies

A descriptive analysis of pharmacokinetic (PK) parameters of LOXO-101 (larotrectinib) will be performed to define systemic exposure, drug clearance, and other pharmacokinetic parameters. The PK parameters will be summarized with simple summary statistics, including means, medians, ranges, and standard deviations (if numbers and distribution permit).

All these analyses will be descriptive and exploratory and hypotheses generating in nature.

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 v5.0 (CTCAE) will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the current CTCAE v5.0. A copy of the CTCAE v5.0 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. Eligible patients must have measurable disease present at baseline and have had their disease re-evaluated after at least one dose of protocol therapy. 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) non-Hodgkin lymphoma/hystiocytosis (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).[11] 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. 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.

12.3.3.4PET-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 or International Pediatric non-Hodgkin Lymphoma Response Criteria 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.

12.3.3.5Tumor 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.

12.3.3.6Cytology, 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.

12.3.3.7FDG-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.[12]

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 urinary catecholamines or other 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 evaluated	No	PR	
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 Scan	Bone Marrow	Catechol	Overall
PD	Any	Any	Any	Any	PD
Any	PD	Any	Any	Any	PD
Any	Any	PD	Any	Any	PD
Any	Any	Any	PD	Any	PD
SD	CR/PR/SD	Non-PD	Non-PD	Any	SD
PR	CR/PR	Non-PD	Non-PD	Any	PR
CR/PR	PR	Non-PD	Non-PD	Any	PR
CR	CR	Non-PD	Non-PD	Elevated	PR
CR	CR	CR	CR	Normal	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 with MIBG Positive Lesions

12.5.1 MIBG Positive Lesions

Patients who have a positive MIBG scan at the start of therapy will be evaluable for MIBG response. The use of ^{123}I for MIBG imaging is recommended for all scans. If the patient has only one MIBG positive lesion and that lesion was radiated, a biopsy must be done at least 28 days after radiation was completed and must show viable neuroblastoma.

12.5.2 The following criteria will be used to report MIBG response by the treating institution:

Complete response: Complete resolution of all MIBG positive lesions
Partial Response: Resolution of at least one MIBG positive lesion, with persistence of other MIBG positive lesions
Stable disease: No change in MIBG scan in number of positive lesions
Progressive disease: Development of new MIBG positive lesions

12.5.3 The response of MIBG lesions will be assessed on central review using the Curie scale14 as outlined below. Central review responses will be used to assess efficacy for study endpoint. See Section 8.2 for details on transferring images to the Imaging Research Center.

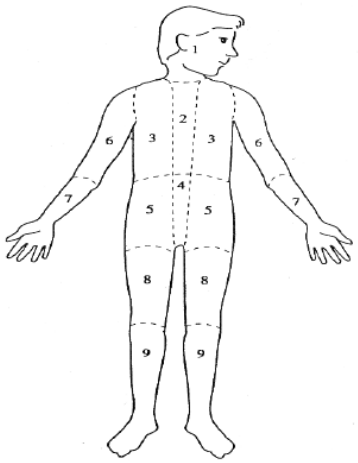
NOTE: This scoring should also be done by the treating institution for end of course response assessments.

The body is divided into 9 anatomic sectors for osteomedullary lesions, with a 10th general sector allocated for any extra-osseous lesion visible on MIBG scan**.** In each region, the lesions are scored as follows. The **absolute extension score** is graded as:

0 = no site per segment,

1 = 1 site per segment,
2 = more than one site per segment,
3 = massive involvement (>50% of the segment).

The **absolute score** is obtained by adding the score of all the segments. See diagram of sectors below:



The **relative score** is calculated by dividing the absolute score at each time point by the corresponding pre-treatment absolute score. The relative score of each patient is calculated at each response assessment compared to baseline and classified as below:

1. **Complete response:** all areas of uptake on MIBG scan completely resolved. If morphological evidence of tumor cells in bone marrow biopsy or aspiration is present at enrollment, no tumor cells can be detected by routine morphology on two subsequent bilateral bone marrow aspirates and biopsies done at least 21 days apart to be considered a **Complete Response**.
2. **Partial response**: Relative score ≤ 0.2 (lesions almost disappeared) to ≤ 0.5 (lesions strongly reduced).
3. **Stable disease**: Relative score > 0.5 (lesions weakly but significantly reduced) to 1.0 (lesions not reduced).
4. **Progressive disease**: New lesions on MIBG scan.

12.5.4 Overall Response Assessment

Table 4: Overall Response Evaluation for Neuroblastoma Patients and MIBG Positive Disease Only

If patients are enrolled without disease measurable by CT/MRI, any new or newly identified lesion by CT/MRI that occurs during therapy would be considered progressive disease.

MIBG	CT/MRI	Bone Scan	Bone Marrow	Catechol	Overall
PD	Any	Any	Any	Any	PD
Any	New Lesion	Any	Any	Any	PD
Any	Any	PD	Any	Any	PD
Any	Any	Any	PD	Any	PD
SD	No New Lesion	Non-PD	Non-PD	Any	SD
PR	No New Lesion	Non-PD	Non-PD	Any	PR
CR	No New Lesion	Non-PD	Non-PD	Elevated	PR
CR	No New Lesion	CR	CR	Normal	CR

12.5.5 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 from the sequence of the overall response assessments as described in Section 12.9.

12.6 Response Criteria for Neuroblastoma Patients with Bone Marrow Involvement

12.6.1 Bone Marrow Involvement

Note: patients with bone marrow as the ONLY site of disease are not eligible for this study. Response criteria in this section are intended to be used when assessing marrow involvement as a component of overall response.

Histologic analysis at the local institution of marrow tumor cell involvement is **required** for patients with a history of marrow involvement. Marrow aspirate and biopsy should be evaluated at baseline and every 2 cycles thereafter. Note: If progressive disease is documented by RECIST criteria using tumor measurements or by MIBG scan, then a repeat BM is not needed to confirm PD.

Complete Response: No tumor cells detectable by routine morphology on 2 consecutive bilateral bone marrow aspirates and biopsies performed at least 21 days apart. Normalization of urinary catecholamines or other tumor markers if elevated at study enrollment.

Progressive Disease: In patients who enroll with neuroblastoma in bone marrow by morphology have progressive disease if there is a doubling in the amount of tumor in the marrow AND a minimum of 25% tumor in bone marrow by morphology. (For example, a patient entering with 5% tumor in marrow by morphology must increase to ≥ 25% tumor to have progressive disease; a patient entering with 30% tumor must increase to > 60%).

In patients who enroll without evidence of neuroblastoma in bone marrow will be defined as progressive disease if tumor is detected in 2 consecutive bone marrow biopsies or aspirations done at least 21 days apart.

Stable Disease: Persistence of tumor in bone marrow that does not meet the criteria for either complete response or progressive disease.

12.6.2 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 from the sequence of the overall response assessments as described in Section 12.9.

12.7 Response Criteria for Patients with CNS Tumors

12.7.1 Measurable Disease

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

12.7.2 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.

12.7.3 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.

12.7.4 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.

12.7.5 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.

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

12.7.7 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 12.9 from a sequence of overall response assessments.

12.8 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, with modification from the Lugano classification.[13,14]

12.8.1 Disease Parameters

12.8.1.1 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).

12.8.1.2 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).

12.8.1.3 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.

12.8.2 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

12.8.3 Evaluation of Non-measured Lesions (CT-based response, PET/CT based response not applicable)[14]

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.

12.8.4 Evaluation of organ enlargement[14]

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

12.9 **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.

12.9.1 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

12.9.2 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; 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: (301) 897-7404).

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://ctepcore.nci.nih.gov/ctepaers/pages/task

Send supporting documentation to the NCI by fax (fax# 301-640-9193) and by email to the APEC1621A 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 NCI CTCAE v5.0. The descriptions and grading scales found in the revised CTCAE v5.0 will be used for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE v5.0. A copy of the CTCAE v5.0 can be downloaded from the CTEP website (http://ctep.cancer.gov).

Step 2: Grade the adverse event using the NCI CTCAE v5.0.

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 CTCAE 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

- 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.

13.4.1 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.

13.4.2 If an adverse event progresses through several grades during one course of therapy, only the most severe grade should be reported.

13.4.3 The duration of the AE is defined as the duration of the highest (most severe) grade of the Adverse Effects.

13.4.4 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."

13.4.5 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 "Neonatal loss", 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.

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.

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.

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.

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: This 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:

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.

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 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] amlodapine 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 elivitegravir/ritonavir grapefruit[3] grapefruit juice[3] idelalisib indinavir/ritonavir itraconazole ketoconazole lopinavir/ritonavir ombitasvi +/- dasabuvir nefazodone nelfinavir paritaprevir/ritonavir 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 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 7.5 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 LOXO-101 (LAROTRECTINIB) (CAPSULE FORMULATION)

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

Store your capsules at room temperature and away from areas of high heat and humidity.

Complete each day with the time and dose given for LOXO-101 (larotrectinib). If a dose is accidentally skipped leave that section blank. ***Make note of other drugs and supplements taken under the Comments section below***. LOXO-101 (larotrectinib) capsules should not opened and must be swallowed whole. You should take LOXO-101 (larotrectinib), approximately 12 hours apart, at about the same time each day. If you vomit after taking the dose, DO NOT retake your dose. This should be noted in the comments section. If you forget a dose and remember it within 4 hours of the time the dose was due, you should take the dose at that time. Otherwise, you should skip the forgotten dose. Either way, the next dose should be taken at the usual time. Add the dates to the calendar below and return the completed diary and the empty bottle or any leftover capsules the study clinic at each visit (weekly during Cycle 1, and then after each treatment cycle).

EXAMPLE			***Number of LOXO-101 (larotrectinib) capsules***		***Comments***
	Date	***Time***	**25 mg**	**100 mg**	
Day 1	*1/15/14*	*8:30 AM*	0	1	*He felt nauseated an hour after taking the drug but did not vomit.*

Cycle #: _____ **Start Date**: |__/__|__/__|__/__|
End Date: |__/__|__/__|__/__| **Dose Level: _____mg/m²/dose**

WEEK 1	**Date**	**Time**		**# of LOXO-101 (larotrectinib) capsules prescribed to take**		**Comments (Describe any missed or extra doses, vomiting and/or bothersome effects.)**
				25 mg	**100 mg**	
				AM#___ PM#___	**AM#___ PM#___**	
				# of LOXO-101 (larotrectinib) capsules taken		
				25 mg	**100 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.

	Cycle #: _____ Start Date: |__/__|__/__|__/__| End Date: | / | / | / | Dose Level: _____mg/m^2/dose					
WEEK 2	**Date**	**Time**		**# of LOXO-101 (larotrectinib) capsules prescribed to take** **25 mg**: AM#___ PM#___ **100 mg**: AM#___ PM#___ **# of LOXO-101 (larotrectinib) capsules taken** **25 mg** / **100 mg**		**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**		**# of LOXO-101 (larotrectinib) capsules prescribed to take** **25 mg**: AM#___ PM#___ **100 mg**: AM#___ PM#___ **# of LOXO-101 (larotrectinib) capsules taken** **25 mg** / **100 mg**		**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			
	Cycle #: _____ Start Date: |__/__|__/__|__/__| End Date: |__/__|__/__|__/__| Dose Level: _____mg/m^2/dose					

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

WEEK 4	Date	Time		# of LOXO-101 (larotrectinib) capsules prescribed to take		Comments (Describe any missed or extra doses, vomiting and/or bothersome effects.)
				25 mg	100 mg	
				AM#___ PM#___	AM#___ PM#___	
				# of LOXO-101 (larotrectinib) capsules taken		
				25 mg	100 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 drug must sign and date this form below:

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

APPENDIX III-B: MEDICATION DIARY FOR LOXO-101 (LAROTRECTINIB) (LIQUID FORMULATION)

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

Please do not write patient names on this form.

Complete each day of the diary below with the time and dose of LOXO-101 (larotrectinib) is given. Store the LOXO-101 (Larotrectinib) liquid formulation in the refrigerator. You should take LOXO-101(larotrectinib) doses, approximately 12 hours apart, at about the same time each day. 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 vomit after taking a dose, DO NOT retake your dose. This should be noted in the comments section. If you forget a dose and remember it within 4 hours of the time the dose was due, you should take the dose at that time. Otherwise, you should skip the forgotten dose. Either way, the next dose should be taken at the usual time. 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 LOXO-101 (larotrectinib) liquid formulation taken (mL)***	
Day 1	*1/15/12*	*8:30*	*AM*	2	*He felt nauseated an hour after taking the drug 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 LOXO-101 (larotrectinib) 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 LOXO-101 (larotrectinib) 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		

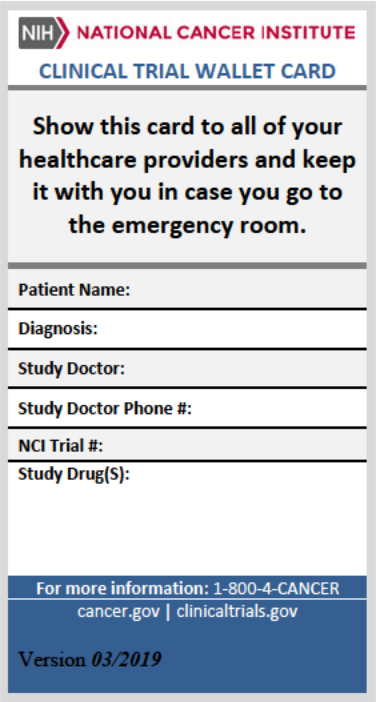
WEEK 3	Date	Time		AM Dose: Take _____mL PM Dose: Take _____mL Amount of LOXO-101 (larotrectinib) liquid formulation taken (mL)	Comments (Describe any missed or extra doses, vomiting and/or bothersome effects.)
Day 15			AM		
			PM		
Day 16			AM		
			PM		
Day 17			AM		
			PM		
Day 18			AM		
			PM		
Day 19			AM		
			PM		
Day 20			AM		
			PM		
Day 21			AM		
			PM		

WEEK 4	Date	Time		AM Dose: Take mL PM Dose: Take ____mL Amount of LOXO-101 (larotrectinib) 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 III-C: LOXO-101 (LAROTRECTINIB) PATIENT CLINICAL TRIAL WALLET CARD



NIH NATIONAL CANCER INSTITUTE

CLINICAL TRIAL WALLET CARD

Show this card to all of your healthcare providers and 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):

For more information: 1-800-4-CANCER

cancer.gov | clinicaltrials.gov

Version *03/2019*

APPENDIX IV-A: LOXO-101 (LAROTRECTINIB) DOSING NOMOGRAM (CAPSULE FORMULATION)

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 a BSA ≥ 0.66 m^2 may take either the capsule or liquid formulation. Patients < 0.66 m^2 must receive the liquid formulation (See Appendix IV-B for dosing preparation of the LOXO-101 (larotrectinib) liquid formulation.)

BSA (m^2)	LOXO-101 (larotrectinib) Dose (mg/dose) PO BID	LOXO-101 (larotrectinib) Dose Reduction for Toxicity (mg/dose) PO BID
0.66-0.87	75	50
≥ 0.88	100	75

Patients with BSA ≥ 0.66 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.

APPENDIX IV-B: LOXO-101 (LAROTRECTINIB) DOSING PREPARATION (LIQUID FORMULATION)

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 < 0.66 m^2 must receive the liquid formulation.

Patients with BSA ≥ 0.66 m^2 may take either the capsule or liquid formulation. (See Appendix IV-A for dosing nomogram for LOXO-101 (larotrectinib) 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.

The concentration of LOXO-101 (larotrectinib) liquid formulation is 20 mg/mL. The clear yellow to orange liquid is supplied in amber glass bottles with a 28 mm child resistant cap and tamper evident closure (60 mL or 100 mL per bottle).

A site-supplied press-in bottle adapter is required for use with an oral syringe for dosing purposes.

LOXO-101 (larotrectinib) will be given at 100 mg/m^2 BID with a maximum of 100 mg per dose. Calculated doses ≤ 45 mg should be prepared in oral syringes ≤ 3 mL with dosing volumes of LOXO-101 (larotrectinib) liquid 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 LOXO-101 (larotrectinib) liquid 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 0.43 m^2, Dose Level 1 (100 mg/m^2) → Calculated Dose = 43 mg BID*
  Calculated Volume (mL) = (100 mg/m^2 x 0.43 m^2) / (20 mg/mL) = 2.15 mL
  Final Dosing Volume (mL) = 2.2 mL (rounded to nearest 0.1 mL for doses ≤ 45 mg)
  Final Dose to be administered = 2.2 mL x 20 mg/mL = 44 mg
- *Patient BSA 0.85 m^2, Dose Level 1 (100 mg/m^2) → Calculated Dose = 85 mg BID*
  Calculated Volume (mL) = (100 mg/m^2 x 0.85 m^2) / (20 mg/mL) =4.25 mL
  Final Dosing Volume (mL) = 4.2 mL (rounded to the nearest 0.2 mL for dose > 45 mg)
  Final Dose to be administered = 4.2 mL x 20 mg/mL = 84 mg

APPENDIX V CORRELATIVE STUDIES

Correlative Study	Section	Blood Volume		Tube Type
		Volume per Sample	Total Cycle 1	
Pharmacokinetics	8.3	3 mL	18 mL	K_2 EDTA lavender top
Total Blood Volume in Cycle 1			**18 mL**	

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	10-20 mL	Streck Cell-Free DNA BCT tubes
Total Blood Volume in Cycle 5 Day 1			**10-20 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	10-20 mL*	Streck Cell-Free DNA BCT tubes
Total Blood Volume in 'Time of progression or End of protocol therapy'			**10-20 10mL**	

* Only collected from patients from whom the sample at Cycle 5 Day 1 is collected.

APPENDIX VI: APEC1621A 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
LOXO-101 (Larotrectinib) IND # [redacted] **Do not use commercial supply**	PO or via NG- or G-tube	100 mg/m^2/dose BID (maximum 100 mg/dose) Refer to the dosing nomogram.	1-28	Patients with a BSA ≥ 0.66 m^2 may take either the capsule or liquid formulation. Patients < 0.66 m^2 must receive the liquid formulation. See Appendix IV-A for dosing nomogram for LOXO-101 (larotrectinib) capsule formulation See Appendix IV-B for dosing preparation of the LOXO-101 (larotrectinib) liquid formulation.)

Ht _____cm Wt _____kg BSA _____m^2

Date Due	Date Given	Day	**LOXO-101 (Larotrectinib)** _____mg AM _____mg PM	Studies
			Enter calculated dose above as per dosing nomogram and actual dose administered below	
		1	_____mg AM _____mg PM	f
		2	_____mg AM _____mg PM	
		3	_____mg AM _____mg PM	
		4	_____mg AM _____mg PM	b
		5	_____mg AM _____mg PM	
		6	_____mg AM _____mg PM	
		7	_____mg AM _____mg PM	
		8	_____mg AM _____mg PM	a, b, c, d, h
		9	_____mg AM _____mg PM	
		10	_____mg AM _____mg PM	
		11	_____mg AM _____mg PM	
		12	_____mg AM _____mg PM	b
		13	_____mg AM _____mg PM	
		14	_____mg AM _____mg PM	
		15	_____mg AM _____mg PM	a, b, c, d, h
		16	_____mg AM _____mg PM	
		17	_____mg AM _____mg PM	
		18	_____mg AM _____mg PM	b
		19	_____mg AM _____mg PM	
		20	_____mg AM _____mg PM	
		21	_____mg AM _____mg PM	
		22	_____mg AM _____mg PM	a, b, c, d, h
		23	_____mg AM _____mg PM	
		24	_____mg AM _____mg PM	
		25	_____mg AM _____mg PM	b
		26	_____mg AM _____mg PM	
		27	_____mg AM _____mg PM	
		28/1	_____mg AM _____mg PM	a, b, c, d, e, g, h

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

Required Observations in Cycle 1

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. 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).
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.
c.	Electrolytes including Ca++, PO4, Mg++
d.	Creatinine, ALT, bilirubin
e.	Albumin
f.	Pharmacokinetics (optional)-see Section 8.3 for details of PK studies.
g.	Ht/Wt/BSA
h.	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.

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).

Cycle 1

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
LOXO-101 (Larotrectinib) IND #[redacted] **Do not use commercial supply**	PO or via NG- or G-tube	100 mg/m^2/dose BID (maximum 100 mg/dose) Refer to the dosing nomogram.	1-28	Patients with a BSA ≥ 0.66 m^2 may take either the capsule or liquid formulation. Patients < 0.66 m^2 must receive the liquid formulation. See Appendix IV-A for dosing nomogram for LOXO-101 (larotrectinib) capsule formulation See Appendix IV-B for dosing preparation of the LOXO-101 (larotrectinib) liquid formulation.)

Enter Cycle #: _____ Ht _____cm Wt _____kg BSA _____m^2

Date Due	Date Given	Day	**LOXO-101 (Larotrectinib)** _____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, k*
		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	c
		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	c
		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	c
		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*

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.

Subsequent Cycles

Required Observations in All Subsequent Cycles

a.	History/Physical Exam (including VS)
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
d.	Electrolytes including Ca++, PO4, Mg++
e.	Creatinine, ALT, bilirubin
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
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. The medication diary should be collected weekly.
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.	Pharmacokinetics (optional)-see Section 8.3 for details of PK studies.

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 APEC1621A 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 SUB-PROTOCOL APEC1621A

INCLUSION VARIANTS				
Fusions				
Gene Name	**Variant ID**	**Variant Type**	**LOE**	**Variant Description**
NTRK1	NTRK1-DYNC2H1.N17D85	Fusion	3	NTRK1 Gene Fusion
NTRK1	TPM3-NTRK1.T7N13	Fusion	3	NTRK1 Gene Fusion
NTRK1	LMNA-NTRK1.L3N11	Fusion	3	NTRK1 Gene Fusion
NTRK1	TPM3-NTRK1.T8N10	Fusion	3	NTRK1 Gene Fusion
NTRK1	TPM3-NTRK1.T7N10.COSF1329	Fusion	3	NTRK1 Gene Fusion
NTRK1	TPR-NTRK1.T21N10.COSF1326	Fusion	2	NTRK1 Gene Fusion
NTRK1	TPR-NTRK1.T6N12.COSF1324	Fusion	2	NTRK1 Gene Fusion
NTRK1	MPRIP-NTRK1.M14N12	Fusion	3	NTRK1 Gene Fusion
NTRK1	MPRIP-NTRK1.M18N12	Fusion	3	NTRK1 Gene Fusion
NTRK1	MPRIP-NTRK1.M21N12	Fusion	3	NTRK1 Gene Fusion
NTRK1	SQSTM1-NTRK1.S5N10	Fusion	3	NTRK1 Gene Fusion
NTRK1	SSBP2-NTRK1.S12N12	Fusion	3	NTRK1 Gene Fusion
NTRK1	TFG-NTRK1.T6N10	Fusion	3	NTRK1 Gene Fusion
NTRK1	BCAN-NTRK1.B13N11	Fusion	3	NTRK1 Gene Fusion
NTRK1	LMNA-NTRK1.L2N11	Fusion	3	NTRK1 Gene Fusion
NTRK1	NFASC-NTRK1.N20N10	Fusion	3	NTRK1 Gene Fusion
NTRK1	RNF213-NTRK1.R15N12	Fusion	3	NTRK1 Gene Fusion
NTRK1	IRF2BP2-NTRK1.I1N10.1	Fusion	3	NTRK1 Gene Fusion
NTRK1	TPR-NTRK1.T6N12.1	Fusion	3	NTRK1 Gene Fusion
NTRK1	CD74-NTRK1.C7N10	Fusion	3	NTRK1 Gene Fusion
NTRK1	SQSTM1-NTRK1.S2N10	Fusion	3	NTRK1 Gene Fusion
NTRK1	TP53-NTRK1.T10N9	Fusion	3	NTRK1 Gene Fusion
NTRK1	LMNA-NTRK1.L10N12	Fusion	3	NTRK1 Gene Fusion
NTRK1	RABGAP1L-NTRK1.R14N16	Fusion	3	NTRK1 Gene Fusion
NTRK1	CHTOP-NTRK1.C5N11	Fusion	3	NTRK1 Gene Fusion
NTRK1	TP53-NTRK1.T8N9	Fusion	3	NTRK1 Gene Fusion
NTRK1	TP53-NTRK1.T9N9	Fusion	3	NTRK1 Gene Fusion
NTRK1	PPL-NTRK1.P12N13	Fusion	3	NTRK1 Gene Fusion
NTRK1	TFG-NTRK1.T6N14	Fusion	3	NTRK1 Gene Fusion
NTRK1	TP53-NTRK1.T11N9	Fusion	3	NTRK1 Gene Fusion
NTRK1	ARHGEF2-NTRK1.A21N10	Fusion	3	NTRK1 Gene Fusion
NTRK1	EPHB2-NTRK1.E3N9	Fusion	3	NTRK1 Gene Fusion
NTRK1	CHTOP-NTRK1.C5N10	Fusion	3	NTRK1 Gene Fusion

NTRK1	LMNA-NTRK1.L10N11	Fusion	3	NTRK1 Gene Fusion
NTRK1	TPR-NTRK1.T21N9	Fusion	3	NTRK1 Gene Fusion
NTRK1	EPS15-NTRK1.E21N9	Fusion	3	NTRK1 Gene Fusion
NTRK1	PPL-NTRK1.P22N11	Fusion	3	NTRK1 Gene Fusion
NTRK1	PPL-NTRK1.P22N10	Fusion	3	NTRK1 Gene Fusion
NTRK1	EPS15-NTRK1.E21N9.1	Fusion	3	NTRK1 Gene Fusion
NTRK1	LMNA-NTRK1.L11N11	Fusion	3	NTRK1 Gene Fusion
NTRK1	TPM3-NTRK1.T7N12	Fusion	3	NTRK1 Gene Fusion
NTRK1	LMNA-NTRK1.L5N10	Fusion	3	NTRK1 Gene Fusion
NTRK1	LMNA-NTRK1.L6N12	Fusion	3	NTRK1 Gene Fusion
NTRK1	MRPL24-NTRK1.M1N9.1	Fusion	3	NTRK1 Gene Fusion
NTRK1	NTRK1-NTRK1.N6N8	Fusion	3	NTRK1 Gene Fusion
NTRK1	MRPL24-NTRK1.M1N9	Fusion	3	NTRK1 Gene Fusion
NTRK1	TPM3-NTRK1.T7N7.ins	Fusion	3	NTRK1 Gene Fusion
NTRK1	CEL-NTRK1.C7N7.2	Fusion	3	NTRK1 Gene Fusion
NTRK1	TPR-NTRK1.T16int9N10	Fusion	3	NTRK1 Gene Fusion
NTRK2	NACC2-NTRK2.N4N13.COSF1448	Fusion	3	NTRK2 Gene Fusion
NTRK2	QKI-NTRK2.Q6N16.COSF1446	Fusion	3	NTRK2 Gene Fusion
NTRK2	AFAP1-NTRK2.A14N12	Fusion	3	NTRK2 Gene Fusion
NTRK2	AGBL4-NTRK2.A6N16	Fusion	3	NTRK2 Gene Fusion
NTRK2	SQSTM1-NTRK2.S5N17	Fusion	3	NTRK2 Gene Fusion
NTRK2	TRIM24-NTRK2.T12N15	Fusion	3	NTRK2 Gene Fusion
NTRK2	VCL-NTRK2.V16N12	Fusion	3	NTRK2 Gene Fusion
NTRK2	DAB2IP-NTRK2.D1N17	Fusion	3	NTRK2 Gene Fusion
NTRK2	TRIM24-NTRK2.T12N16	Fusion	3	NTRK2 Gene Fusion
NTRK2	NAV1-NTRK2.N15N11	Fusion	3	NTRK2 Gene Fusion
NTRK2	SLMAP-NTRK2.S14N16	Fusion	3	NTRK2 Gene Fusion
NTRK3	NTRK3-HOMER1.N17H2	Fusion	3	NTRK3 Gene Fusions
NTRK3	ETV6-NTRK3.E4N15.COSF823.2	Fusion	2	NTRK3 Gene Fusions
NTRK3	ETV6-NTRK3.E5N15.COSF571.1	Fusion	2	NTRK3 Gene Fusions
NTRK3	BTBD1-NTRK3.B4N14	Fusion	3	NTRK3 Gene Fusions
NTRK3	COX5A-NTRK3.C1N15	Fusion	3	NTRK3 Gene Fusions
NTRK3	ETV6-NTRK3.E4N14.1	Fusion	2	NTRK3 Gene Fusions
NTRK3	ETV6-NTRK3.E5N14	Fusion	2	NTRK3 Gene Fusions
NTRK3	FAT1-NTRK3.F2N7	Fusion	3	NTRK3 Gene Fusions
NTRK3	EML4-NTRK3.E2N14	Fusion	3	NTRK3 Gene Fusions
NTRK3	AKAP13-NTRK3.A14N14	Fusion	3	NTRK3 Gene Fusions
NTRK3	LYN-NTRK3.L8N14	Fusion	3	NTRK3 Gene Fusions

NTRK3	RBPMS-NTRK3.R5N14	Fusion	3	NTRK3 Gene Fusions

APPENDIX IX: YOUTH INFORMATION SHEETS
INFORMATION SHEET REGARDING RESEARCH STUDY APEC1621A
(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 that you have.

1. What will happen to me in the study? Children who are part of this study will be given LOXI-101 (Larotrectinib) that could "match" your tumor. The doctors want to see if LOXO-101 (Larotrectinib) will help children with your type of cancer get better. We don't know if LOXO-101 (Larotrectinib) will work well to get rid of your cancer. That is why we are doing the 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 that LOXO-101 (Larotrectinib) 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 risks to you from this study are that you may have problems, or side effects from LOXO-101 (Larotrectinib). There may be risks that we don't know about.

4. 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. The doctors and nurses will still take care of you. 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.

5. We are asking your permission to collect additional blood. We want to see if there are ways to tell how the cancer will respond to treatment. You can still take part in this study even if you don't allow us to collect the extra blood samples for research.

INFORMATION SHEET REGARDING RESEARCH STUDY APEC1621A
(For Teens from 14 through 17 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 that you have.

4. What will happen to me in the study? Children who are part of this study will be given LOXI-101 (Larotrectinib) that could "match" your tumor. The doctors want to see if LOXO-101 (Larotrectinib) will help children with your type of cancer get better. We don't know if LOXO-101 (Larotrectinib) will work well to get rid of your cancer. That is why we are doing the study. We will collect information about 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 that LOXO-101 (Larotrectinib) 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 risks to you from this study are that you may have problems, or side effects from LOXO-101 (Larotrectinib). There may be risks that we don't know about.

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. The doctors and nurses will still take care of you. 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.

7. We are asking your permission to collect additional blood. We want to see if there are ways to tell how the cancer will respond to treatment. You can still take part in this study even if you don't allow us to collect the extra blood samples for research.

APPENDIX X: CTEP AND CTSU REGISTRATION PROCEDURES

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) 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 such as the Roster Update Management System (RUMS), OPEN, Rave, acting as a primary site contact, or with consenting privileges;
- 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; and
- Assign the Clinical Investigator (CI) role on the Delegation of Tasks Log (DTL).

In addition, all investigators acting as the Site-Protocol PI (investigator listed on the IRB approval), consenting/treating/drug shipment investigator in OPEN, or as the CI on the DTL must be rostered at the enrolling site with a participating organization.

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.

CTSU REGISTRATION PROCEDURES

This study is supported by the NCI Cancer Trials Support Unit (CTSU).

Downloading Site Registration Documents:
Download the site registration forms from the protocol-specific page located on the CTSU members' website. Permission to view and download this protocol and its supporting documents is restricted based on person and site roster assignment. To participate, the institution and its associated investigators and staff must be associated with the LPO or a Protocol Organization (PO) on the protocol. One way to search for a protocol is listed below.

- Log in to the CTSU members' website (https://www.ctsu.org) using your CTEP-IAM username and password;
- Click on *Protocols* in the upper left of the screen
  - Enter the protocol number in the search field at the top of the protocol tree; or
  - Click on the By Lead Organization folder to expand, then select *COG*, and protocol number (*insert study number*).
- Click on *Documents*, select *Site Registration*, and download and complete the forms provided. (Note: For sites under the CIRB, IRB data will load automatically to the 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 XI: TOXICITY-SPECIFIC GRADING

Bilirubin

Grade 1:	> ULN- ≤ 1.5 x ULN
Grade 2:	> 1.5 x ULN - 3 x ULN
Grade 3:	> 3 x ULN - 10 x ULN
Grade 4:	> 10 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 x ULN
Grade 3:	> 5 x ULN- 20 x ULN
Grade 4:	> 20 x ULN