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CHILDREN'S ONCOLOGY GROUP

ADVL1823

Larotrectinib (LOXO-101, NSC# 788607, [redacted]) for Previously Untreated TRK Fusion Pediatric Solid Tumors and TRK Fusion Relapsed Pediatric Acute Leukemias

A COG Groupwide Phase 2 Study

IND Sponsor for Larotrectinib: COG

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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 https://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.	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 location on the CTSU members' website (https://www.ctsu.org). 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 Roster Maintenance application and in most cases viewable and manageable via the Roster Update Management System (RUMS) on the CTSU members' website.		
For clinical questions (i.e., patient eligibility or treatment-related) Contact the Study PI of the Lead Protocol Organization.		
For non-clinical questions (i.e., unrelated to patient eligibility, treatment, or clinical data submission) Contact the CTSU Help Desk by phone or e-mail: CTSU General Information Line – 1-888-823-5923, or ctsucontact@westat.com. All calls and correspondence will be triaged to the appropriate CTSU representative.		
The CTSU Website is located at https://www.ctsu.org.		
For IROC Questions regarding imaging, dose calculations or documentation: Contact IROC Rhode Island QA Center at (401) 753-7600 or IROCRI@QARC.org		

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STUDY COMMITTEE

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

AGENT	NSC#	IND#
Agent Supplied by Bayer AG:		
Larotrectinib	788607	[redacted]
Commercial Agents:		
Cytarabine	63878	Exempt
Hydrocortisone	10483	Exempt
Methotrexate	740	Exempt

For Group Operations (GOC) and Statistics and Data Center (SDC) contacts see:
http://members.childrensoncologygroup.org
Telephone: (626) 447-0064

IND Sponsor: COG

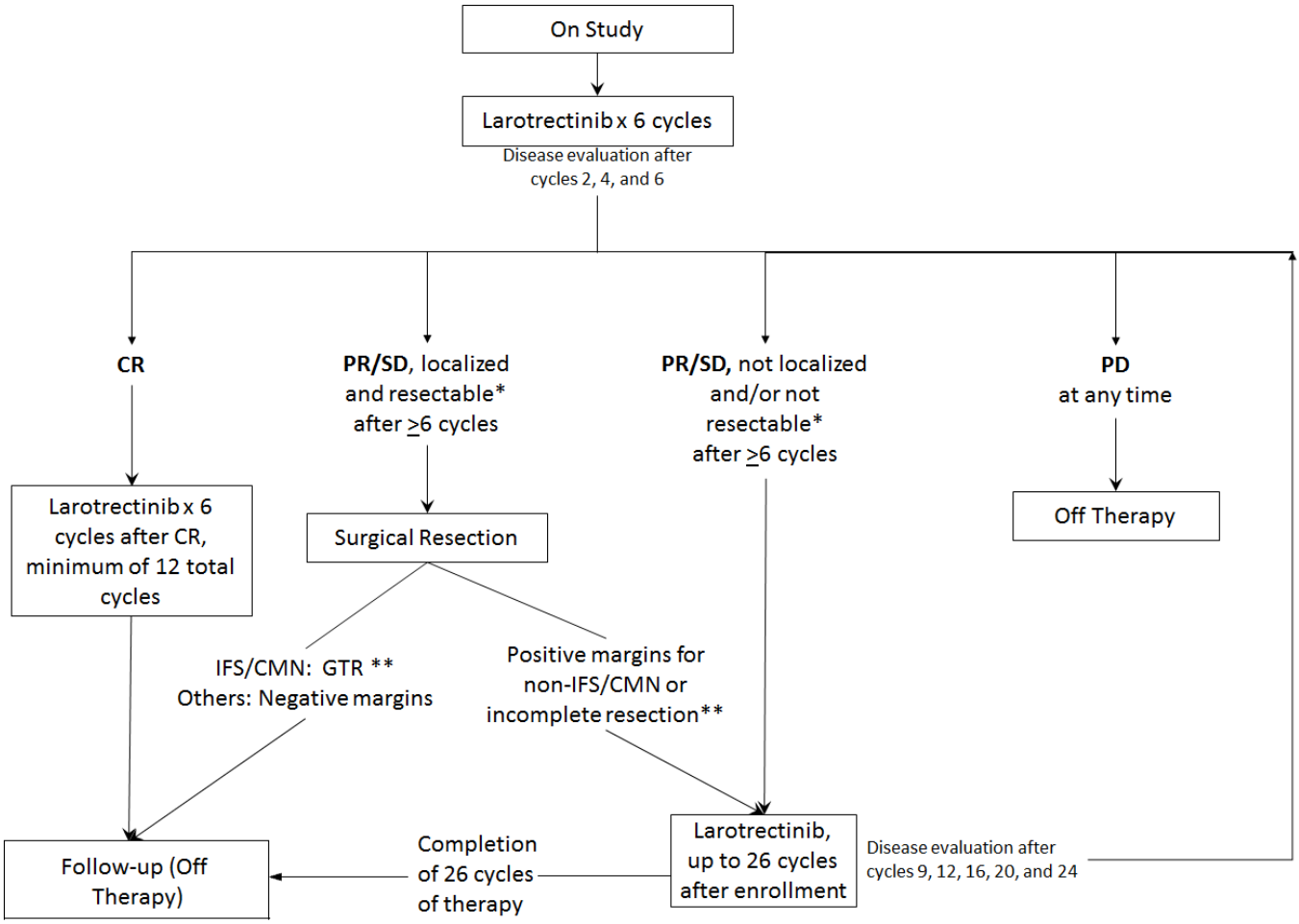
SEE SECTION 7.3 FOR SPECIMEN SHIPPING ADDRESSES

ABSTRACT

Larotrectinib is a highly selective oral small molecule inhibitor of the TRK family of tyrosine kinases (TRKA, TRKB, and TRKC) which are encoded by the NTRK genes (*NTRK1*, *NTRK2*, and *NTRK3*). Fusions of these genes (TRK fusions) occur across a wide range of pediatric and adult malignancies, and are nearly pathognomonic for infantile fibrosarcoma. Preclinical studies have shown that larotrectinib is active in cancer cell lines harboring TRK fusions, while having no activity in cell lines without these fusions. Ongoing clinical trials of larotrectinib in children and adults have shown a 75% centrally confirmed objective response rate in patients with relapsed or refractory TRK fusion cancers across a wide range of tumor types, including a 93% objective response rate in children with TRK fusion cancers on a Phase 1 trial. This study also established a pediatric recommended phase 2 dose. Given the remarkable activity seen in the relapsed/refractory setting, this open label two-stage phase 2 trial will enroll newly diagnosed patients with any TRK fusion solid tumor. The primary cohort will be patients with infantile fibrosarcoma, and patients with other TRK fusion solid tumors will be analyzed in a separate cohort. This study will also include an exploratory cohort for patients with relapsed or refractory TRK fusion acute leukemias, and the results of this cohort will be reported descriptively. Larotrectinib will be administered orally twice daily on a continuous dosing schedule of 28-day cycles at a dose of 100 mg/m^2/dose with a maximum of 100 mg/dose. Patients with localized tumors who achieve sufficient tumor shrinkage to allow complete resection and those who achieve a complete response will discontinue larotrectinib at protocol specified timepoints and continue to be followed for recurrence. Patients who do not meet these criteria will receive 26 cycles (approximately 2 years) of therapy and then be followed for recurrence. The primary endpoint will be the objective response rate in patients with infantile fibrosarcoma. We will also evaluate event-free survival (EFS), duration of response (DOR), and overall survival (OS). These endpoints will be separately evaluated in patients with all other TRK fusion solid tumors combined. A Simon two-stage design that incorporates the best overall response within 6 months will be utilized.

EXPERIMENTAL DESIGN SCHEMA

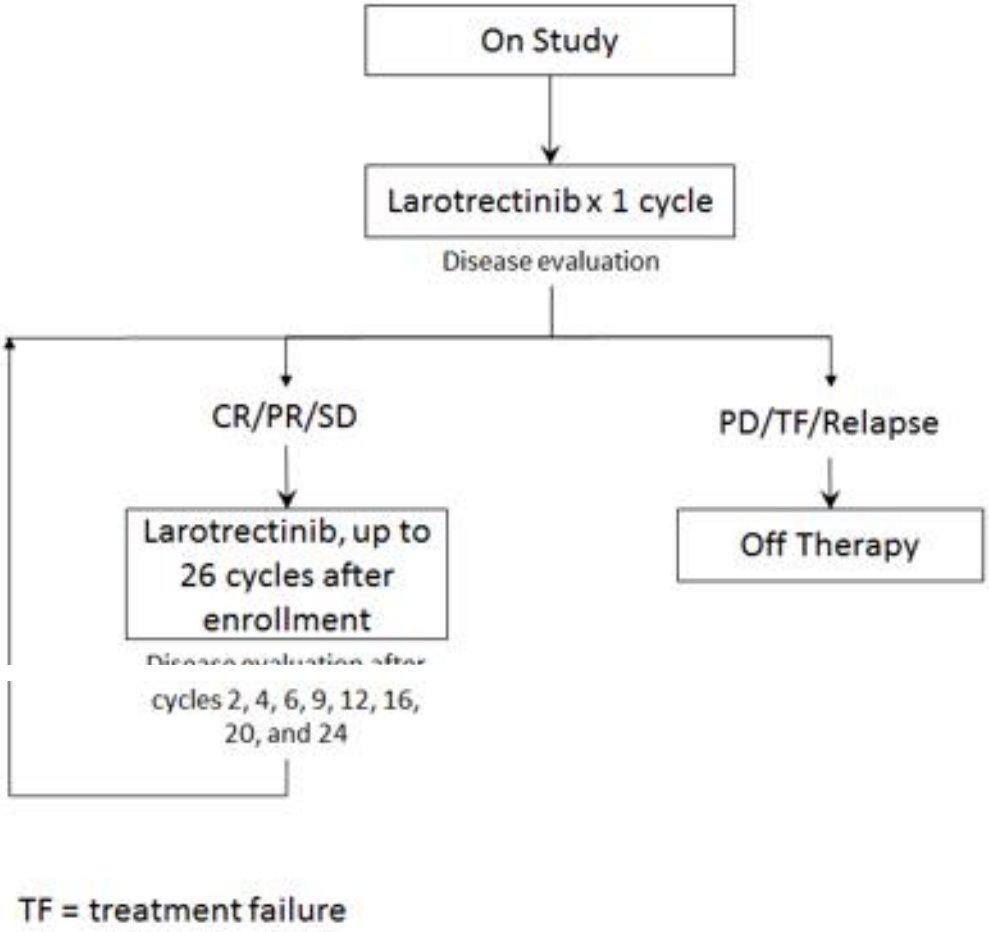
Patients with solid tumors (Cohorts A and B):



Cohort A: Infantile Fibrosarcoma
Cohort B: Other TRK Fusion Solid Tumors

* Resectable is defined as resectable with no anticipated functional, neurologic, or significant cosmetic deficit
** Patients with infantile fibrosarcoma (IFS) or congenital mesoblastic nephroma (CMN) who achieve a gross total resection (GTR) will be observed regardless of margin status, all other patients will receive post-operative larotrectinib if resection margins are positive

Patients with leukemia (Cohort C):



TF = treatment failure

GOALS AND OBJECTIVES (SCIENTIFIC AIMS)

1.1 Primary Aim

1.1.1 To determine the objective response rate (ORR) of children with infantile fibrosarcoma (IFS) treated with neoadjuvant larotrectinib prior to local control.

1.2 Secondary Aims

1.2.1 To determine event-free survival (EFS), overall survival (OS), and duration of response (DoR) of children with IFS treated with neoadjuvant larotrectinib prior to local control.

1.2.2 To determine the ORR, EFS, OS, and DoR of children with newly diagnosed TRK fusion solid tumors other than IFS treated with neoadjuvant larotrectinib prior to local control.

1.2.3 To describe the toxicity of larotrectinib in children with solid tumors and acute leukemia.

1.2.4 To determine the percentage of patients with TRK fusion solid tumors with detectable circulating tumor DNA at baseline and after 2 weeks, 4 weeks, 24 weeks of treatment, at the time of discontinuation of larotrectinib therapy, and at progression.

1.3 Exploratory Aims

1.3.1 To determine the EFS, OS, and DoR of children with TRK fusion solid tumors other than IFS treated with adjuvant larotrectinib following upfront surgery with positive margins after neoadjuvant larotrectinib.

1.3.2 To determine the EFS, OS, and DoR of children with TRK fusion solid tumors who experience a complete response to larotrectinib and subsequently discontinue larotrectinib therapy

1.3.3 To determine the remission induction rate for patients with recurrent/refractory TRK fusion leukemia when treated with larotrectinib.

1.3.4 To evaluate the surgical morbidity and extent of resection of initially unresectable tumors in patients with TRK fusion solid tumors who undergo surgical resection following neoadjuvant larotrectinib.

1.3.5 To evaluate mechanisms of response and resistance to larotrectinib in children with TRK fusion cancers.

1.3.6 To evaluate the morphologic features of TRK fusion solid tumors at time of initial

biopsy to further define criteria for pathologic diagnosis of these tumors.

1.3.7 To evaluate immunohistochemistry for pan-TRK as a screening method for TRK fusion tumors and in resection specimens following neoadjuvant treatment with larotrectinib.

1.3.8 To evaluate the histologic response to larotrectinib in resection specimens following neoadjuvant treatment.

1.3.9 To evaluate circulating tumor DNA for the detection of the emergence of resistance mutations and recurrence in patients with TRK fusion solid tumors treated with larotrectinib.

1.3.10 To evaluate the ratio of CSF to concurrent plasma concentrations of larotrectinib in patients with leukemia.

1.3.11 To evaluate the change in neurocognitive/behavioral functioning over time between baseline and 5 years post-diagnosis of patients treated on this protocol using parent-reported adaptive functioning (ABAS-III General Adaptive Composite), executive function (BRIEF-P or BRIEF-2 Global Executive Composite Score), psychosocial functioning (BASC-3 Internalizing, Externalizing and Behavioral Symptoms Indices) and quality of life (PedsQL Total score).

2.0 BACKGROUND

2.1 Rationale for Development

2.1.1 Tropomyosin Receptor Kinase (TRK) Fusions

The TRKA, TRKB, and TRKC family of neurotrophin tyrosine kinase receptors, encoded respectively by the Neurotrophic Receptor Tyrosine Kinase genes (NTRK1, NTRK2, and NTRK3), are involved in the growth, differentiation, and survival of neurons.[2, 3] Chromosomal rearrangements involving NTRK1, NTRK2, and NTRK3 have been identified in a broad range of malignancies.[4-14] These rearrangements generate fusions in which the 3' region of the NTRK gene is joined with the 5' region of an unrelated gene. The resultant fusion proteins include the TRK kinase domain, joined in-frame with the N terminus of the fusion partner. Thus, the novel fusion oncoprotein is both aberrantly expressed and may have ligand independent kinase activity. TRK fusions have been identified in a range of pediatric cancers, including infantile fibrosarcoma (IFS),[5, 12] cellular congenital mesoblastic nephroma (CMN),[7, 8] other undifferentiated/spindle cell sarcomas,[10] high-grade gliomas,[14] and papillary thyroid cancer.[11] Recently, as discussed below, the highly selective TRK inhibitor larotrectinib has shown a high level of activity in children and adults with relapsed and refractory TRK fusion cancers, regardless of histology, in phase 1 and 2 clinical trials. Thus, we will perform a non-randomized study of larotrectinib in pediatric patients with newly diagnosed IFS and other TRK fusion solid tumors and relapsed/refractory TRK fusion leukemias.

2.1.2 Infantile Fibrosarcoma (IFS):

IFS is a soft tissue sarcoma occurring in young children.[15, 16] While rare, IFS is the most common soft tissue sarcoma in children less than 1 year of age.[17, 18] Despite histologic similarities, infantile fibrosarcoma is distinct from adult fibrosarcoma, with the infantile type harboring a highly recurrent ETV6-NTRK3 fusion in ~85% of cases.[19] Further, case reports of other fusions involving NTRK1 or NTRK3 have been described in ETV6-NTRK3 negative tumors, suggesting that TRK fusions are nearly universal drivers in this disease.[10, 20] Clinically, IFS almost always presents as a localized tumor, although rare cases with metastases have been described.[21, 22] Children with IFS generally have a good prognosis, with overall survival rates reported between 80-100%.[23, 24]

The largest datasets on the therapy and outcome of children with IFS come from the European experience. A retrospective analysis of 56 infants with IFS from the years 1979-2005 has been reported, and the European pediatric Soft tissue sarcoma Study Group (EpSSG) conducted a prospective study of a standardized treatment regimen for such children from 2005-2012.[23, 24] These studies demonstrated that most children with completely resected tumors, with or without positive margins, remain disease free without further therapy. Across both studies, only 1 of 21 Intergroup Rhabdomyosarcoma Studies (IRS) Group 1 patients, and 3 of 19 of IRS Group 2 patients who did not receive adjuvant chemotherapy suffered a relapse.[23, 24]

Despite the good outcome with limited therapy in infants with Group 1 and 2 disease, most infants had IRS Group 3 (incompletely resected) disease (57 of 105 patients across the two series). [23, 24] There is a significant burden of therapy in these children. The majority of children with Group 3 disease are treated with chemotherapy.[24] The prospective EpSSG study was conceived to attempt to reduce alkylator exposure and assess the ability to prevent morbid surgery in these patients. On this protocol, IRS Stage 3 patients were treated with vincristine and actinomycin, and alkylators and/or doxorubicin were only added if there was disease progression or insufficient tumor response to allow subsequent surgical resection. Despite this strategy, 5 of 27 IRS Group 3 patients had progressive disease, 1 suffered a metastatic relapse, 1 died of toxicity, 6 received alkylator based therapy, 3 developed venocclusive disease (VOD), 2 underwent limb amputation, and 1 underwent extenteration.[23] The objective response rate (defined as a >33% reduction in tumor volume) to chemotherapy for these patients was 62.9% (17/27 patients). Of these 27 patients, 7 had an event (death, progressive disease, or relapse), for an estimated 74% event free survival. Thus, there is the opportunity to improve outcome and there remains a significant burden of therapy for the IRS Group 3 patients.

2.1.3 Congenital Mesoblastic Nephroma (CMN):

CMN is a rare pediatric renal tumor, which represents the most common kidney tumor in the first month of life.[25, 26] A recent meta-analysis of the published CMN literature found a 96% overall survival rate among 276 described patients.[27] The majority of patients were cured with nephrectomy alone, but 50 of the 263 patients for whom treatment details were described received post-operative chemotherapy. This meta-analysis identified a high risk of relapse in patients with Stage 3 disease, ranging from 29-58%. The majority of patients with relapsed disease had the cellular subtype (8/11 cases) which commonly harbors the ETV6-NTRK3 fusion

(t(12;15)(p13;q22)).[7, 8] Of the 18 patients with a documented t(12;15)(p13;q22) fusion on cytogenetics, 4 relapsed and 1 died of disease, for an estimated 78% event free survival. The ETV6-NTRK3 fusion appears to define a higher risk subset of patients, particularly in those with unresectable (Stage 3) disease.

2.1.4 Other TRK Fusion Solid Tumors:

In addition to IFS and CMN, TRK fusions have been identified in other undifferentiated/spindle cell sarcomas,[10] low and high-grade gliomas,[14] papillary thyroid cancer,[11] secretory breast cancer,[28] mammary analogue secretory carcinoma (MASC),[29] and spitzoid melanoma.[30] For the these diseases, the outcome of patients with TRK fusions is unknown, as prior therapeutic trials have not evaluated for such fusions, and patients have been treated based on histology. Patients with undifferentiated/spindle cell sarcoma are often treated with risk based chemoradiotherapy in which patients with intermediate or high risk disease receive ifosfamide and doxorubicin per a recently completed Children's Oncology Group protocol (ARST0332). Among intermediate and high risk patients, this study demonstrated 4-year event free survival rates of 64% and 49% for patients treated with adjuvant and neoadjuvant chemoradiotherapy, respectively.

2.1.5 TRK Fusion Acute Leukemias:

Acute lymphoblastic leukemia (ALL) is the most common pediatric cancer, accounting for about 25% of all cancers diagnosed in children.[31] Recently, a subtype of ALL called Ph-like ALL has been identified which has a gene expression profile similar to Philadelphia-chromosome positive ALL, but lacks the BCR-ABL fusion. The outcomes for patients with Ph-like ALL, which accounts for about 15% of pediatric ALL, are poor with a median 5-year event free survival of 58% in children and 42% in adolescents in newly diagnosed patients.[32] For patients who relapse, the outcomes are even worse with most children succumbing to their disease.[33] Multiple recurrent fusions involving kinases have been described in Ph-like ALL, including TRK fusions in a small subset of cases.[32, 34] The precise frequency of TRK fusions in Ph-like ALL is unknown, but such fusions are rare, with a total of 4 children identified in the sequencing effort at St. Jude as of June 2017 (personal communication C. Mulligan). In addition, three adults with acute myeloid leukemia (AML) harboring TRK fusions (NTRK3 and NTRK2) have been described.[34, 35]

2.2 Preclinical Studies

2.2.1 Antitumor Activity

Larotrectinib is a highly selective inhibitor of TRKA, TRKB, and TRKC with low-nanomolar inhibition of these enzymes. Larotrectinib does not inhibit any other tested kinase at concentrations up to 1 uM. Reflecting this specificity, larotrectinib demonstrates in vitro IC50s of less than 100 nM for colorectal, lung, AML, and engineered cell lines harboring fusions of NTRK1, NTRK2, and NTRK3, with essentially no growth inhibitory effects on a range of cancer cell lines not harboring NTRK alterations at concentrations up to 1 uM. In vivo, larotrectinib induces regressions of human colorectal, lung cancer, and AML xenografts harboring NTRK1 and NTRK3 fusions.

2.2.2 Animal Toxicology

In toxicology studies of larotrectinib conducted in the rat and monkey, the most sensitive organ in both species was the liver. Changes that were seen in included increased liver weights concomitant with hepatocellular hypertrophy and minor reversible increases in aminotransferases (AST and ALT). The rat was the more sensitive species and also developed dose-limiting chronic inflammation of the epidermis and dermis.

Safety pharmacology studies have assessed effects on the cardiovascular (CV), central nervous system (CNS), respiratory, and gastrointestinal (GI) systems in vitro and in vivo in rats, dogs, and monkeys. There were no larotrectinib-related neurobehavioral or respiratory function effects in safety pharmacology studies. Larotrectinib accelerated the intestinal transit and significantly increased gastric secretion and acidity in rats.

Cardiac safety was evaluated in an in vitro assay for human ether-à-go-go related gene (hERG) activity, in conscious telemetry-instrumented rats and monkeys. Larotrectinib had a 50% inhibitory concentration (IC50) value of 147 μM in the hERG assay, which is >200-fold higher than the maximum unbound concentration at the human recommended phase 2 dose. No adverse CV effects were noted in rats or monkeys in which telemetry-instrumented animals were dosed up to 300 mg/kg and 100 mg/kg, respectively.

Larotrectinib was not genotoxic in any of the assays conducted. Larotrectinib did not demonstrate any phototoxic potential.

2.2.3 Preclinical Pharmacology

Pharmacokinetic studies of larotrectinib have been conducted in mice, rats, dogs, and monkeys. Oral larotrectinib bioavailability was approximately 30% to 100% across these models. The PK following multiple doses of larotrectinib in mice, rats, and monkeys were generally consistent with single-dose PK, with no unexpected accumulation. In dogs, the AUC of larotrectinib was similar in fed and fasted animals.

The solubility, permeability, and animal PK data suggest that larotrectinib is well absorbed from the GI tract. The compound distributes into tissues, with volumes of distribution ranging from 1–2 L/kg. A brain microdialysis study of larotrectinib in the rat showed that the unbound (free) brain concentration was approximately 4% of the unbound plasma concentration. However, higher CSF levels have been observed in the small number human patients treated with larotrectinib in whom CSF sampling has been obtained.

Larotrectinib is metabolized by microsomal fractions and hepatocytes from mice, rats, rabbits, dogs, monkeys, and humans. The isoform of cytochrome P450 that metabolizes larotrectinib in human liver microsomes is primarily CYP3A4. Larotrectinib and its metabolites distribute freely between red blood cells and plasma; it binds moderately (70%) to plasma proteins independent of concentration. Larotrectinib and its metabolites are eliminated primarily by the renal and biliary routes.

2.3 Adult Studies

2.3.1 Adult Phase 1 Studies

In a phase 1 trial, there was no biomarker required for eligibility, but 8 of 59 enrolled patients had TRK fusions. This study identified a recommended phase 2 dose in adults of 100 mg BID based on exposure, response, and toxicity, but no MTD was reached in adults treated at doses up to 200 mg BID. Larotrectinib was well tolerated in this study, with the most common adverse events regardless of attribution being fatigue, dizziness, dyspnea, and anemia. Few Grade 3/4 adverse events were observed, with fatigue, anemia, dyspnea, increased AST, decreased appetite, lymphocyte count decreased, and pneumonia being the only recurrent Grade 3 events, each occurring in less than 10% of patients. Among the 8 patients with TRK fusions, 7 were evaluable for response as of the last data cut off (November 10, 2016). Six of the 7 evaluable patients achieved confirmed partial responses and all patients remained in response at a median of >15 months of larotrectinib therapy. The seventh patient with a TRK fusion did not have measurable disease at enrollment but remained on study with stable disease for >12 months. No responses were seen in patients without TRK fusions.

2.3.2 Efficacy (Phase 2 and 3 studies)

A phase 2 study of larotrectinib is ongoing in adolescents (age $\geq$ 12 years) and adults with TRK fusion cancers. Patients on this study are treated at a dose of 100 mg BID. Patients enrolled on this study were analyzed with the adults with TRK fusion cancers enrolled on the phase 1 study above, as well as the children with TRK fusion cancers enrolled on the pediatric phase 1 study described below. Fifty-five patients with TRK fusions (12 children, 43 adults, age range: 4 mo. - 76 yrs) were enrolled to these three studies as of July 2017.[36] Fusions involved *NTRK1* (n=25), *NTRK2* (n=1), and *NTRK3* (n=29), and 14 unique upstream partners. 17 discrete tumor types were included: salivary-gland tumor (n=12); non-rhabdomyosarcoma soft tissue sarcoma (NRSTS) including myopericytoma, malignant peripheral nerve sheath tumor, spindle-cell tumor, infantile myofibromatosis, inflammatory myofibroblastic tumor of the kidney, and soft tissue sarcoma NOS (n=11); infantile fibrosarcoma (n=7); thyroid (n=5); colon (n=4); lung (n=4); melanoma (n=4); GIST (n=4); cholangiocarcinoma (n=2); appendix tumor (n=1); breast cancer (n=1); and pancreatic tumor (n=1). By blinded independent radiology review, the ORR for these 55 patients was 75% (95% CI: 61%–85%) which was concordant with the investigator assessed 80% ORR. Responses appeared independent of which NTRK gene was involved, the 5' fusion partner, or the tumor histology. Responses occurred very rapidly, with a median time to first response of 1.8 months, consistent with the first response evaluation mandated in the protocols. A median duration of response had not been reached with 83% of patients with ongoing responses at 6 months and 71% at 12 months. The longest responder remains on treatment for > 2 years. NTRK solvent front mutations were detected in all 9 patients who have developed acquired resistance and had repeat testing. The most common treatment related adverse events were increased AST/ALT (38%), dizziness (25%), constipation, nausea, and fatigue (16% each). Eight of 55 (15%) patients required dose reductions for toxicity; all maintained their response at the lower dose level.

The high response rate to larotrectinib was consistent across the histologic diagnoses of patients expected to enroll on this clinical trial. Among the 7 patients with infantile fibrosarcoma, the response rate was 100% (best responses were 2 CR, 5 PR). Among the 11 patients with NRSTS, the response rate was 91% (best responses were 1 CR, 9 PR, 1 PD).

In addition to these patients enrolled on prospective clinical trials, an adult with AML harboring an *ETV6-NTRK2* fusion achieved a partial response to compassionate access larotrectinib.[34]

Based on these data, the US Food and Drug Administration (FDA) approved larotrectinib for the treatment of adult and pediatric patients with solid tumors that have a neurotrophin receptor tyrosine kinase (*NTRK*) gene fusion without a known acquired resistance mutation, are metastatic or where surgical resection is likely to result in severe morbidity, and have no satisfactory alternative treatments or that have progressed following treatment.

2.4 Pediatric Studies

2.4.1 Pediatric Phase 1 Studies

A pediatric phase 1/2 study of larotrectinib is ongoing. The phase 1 dose escalation component of this study has now completed enrollment and has been published.[1] This study used a modified rolling 6 design and enrolled children > 1 month to 21 years of age. Patients were treated with larotrectinib oral suspension or capsules. As of July 17, 2017, 24 patients with a median age of 4.5 years (0.1 – 18 years) have enrolled to 3 dose levels.[1] The most common diagnoses were infantile fibrosarcoma (n=8) and other soft tissue sarcoma (n=7). 17 patients had TRK fusions. The most common drug related AEs were generally mild increases in liver enzyme levels (AST and ALT in 10 [42%] of 24 patients each, 8 [33%] Grade 1), hematological toxicity (leukocyte count decreased and neutrophil count decreased in 5 [21%] of patients each) and vomiting in 5 (21%) of patients. Fatigue was observed in 3 (13%) of 24 patients; other neurological toxicities were rarely seen. Grade 3 treatment-related adverse events occurred in 4 (17%) of 24 patients: 1 each of ALT elevation, nausea, neutropenia, and ejection fraction decreased. No other cardiotoxicity was seen in the pediatric phase 1 study or on the adult phase 1 or 2 studies. There were no drug related Grade 4 or 5 adverse events. One DLT (Grade 3 ALT elevation in a patient with neuroblastoma without a TRK fusion) occurred at dose level 3 which led to larotrectinib discontinuation. No other patients discontinued larotrectinib for adverse events and a MTD was not identified. One patient had dose reduction for Grade 3 neutropenia in cycle 2. A recommended phase 2 dose of 100 mg/m^2/dose BID with a maximum of 100 mg/dose was identified based on pharmacokinetics, response, and safety of this dose level. As of July 17, 2017, 22 patients were evaluable for response. Fourteen of the 15 (93%) evaluable patients with TRK fusions had PR (n=10) or CR (n=4). Responses were seen in patients with fusions involving each of the 3 NTRK genes and in patients with both infantile fibrosarcoma and other sarcomas. Responses were seen at all dose levels, but due to intrapatient dose escalation, only 3 patients with TRK fusion tumors were treated with larotrectinib at doses of less than 80% of the recommended phase 2 dose. Two patients with TRK fusion papillary thyroid

cancer enrolled on study. Neither had measurable disease at enrollment. Both experienced a reduction in tumor burden (SD by RECIST) and remain on study. With a median follow-up of 8.2 months, only 3 patients with TRK fusions have discontinued larotrectinib. Two of these patients had responses that enabled complete surgical resections with negative margins and continue to be followed on study but off larotrectinib without recurrence. Only 1 of 15 patients with a TRK fusion has progressed on therapy to date with the development of a pG623R solvent front resistance mutation in *NTRK3*. A second patient who electively stopped larotrectinib after 12 cycles of therapy with a PR and without surgical resection of tumor demonstrated progressive disease off larotrectinib. This patient restarted larotrectinib and responded again. No responses were seen in patients without TRK fusion (n=7).

Responses to larotrectinib in children have been very rapid, with a median time to first RECIST response among patients with measurable disease of 1.7 months, consistent with the first protocol mandated response assessment. In patients whose tumors could be evaluated by physical exam, reductions in tumor size were apparent in some patients within days of starting larotrectinib. Of the 15 patients with TRK fusions and measurable disease, 12 (80%) had a RECIST response by imaging within 4 months of starting larotrectinib. Therefore, we believe that evaluating the best response within the first six 28-day cycles of therapy will provide a good assessment of the activity of larotrectinib in the upfront setting.

Five children with locally advanced sarcoma (IFS, n=3; other soft tissue sarcoma, n=2) achieved partial responses to therapy with larotrectinib by imaging and underwent on-study resection on the pediatric phase 1 study. Patients received a median of 6 cycles of larotrectinib (range: 4-9 cycles) before surgery. Per protocol, larotrectinib was held for 24 hours prior to surgery. Two of these patients had pathological clear margins and discontinued larotrectinib. One of these patients had no viable tumor on microscopic examination and was reclassified as a pathological complete response. Both patients with negative margin resections continue to be followed on-study without recurrence; now more than 6 months off larotrectinib. A third patient had an R1 resection with no viable tumor seen and also remains in active follow-up more than 6 months off larotrectinib. The other two patients had marginal or gross residual disease after surgery and remain on therapy with larotrectinib. There were no post-operative or wound healing complications observed in these patients.

In addition to the ongoing clinical trials in children and adults, larotrectinib has been provided to some patients on a compassionate access basis. A 14-year old girl from Bangladesh with secretory carcinoma of the breast harboring an *ETV6-NTRK3* fusion received compassionate access larotrectinib and had a near complete response to therapy.[37] A 3 year old child with an *ETV6-NTRK3* fusion high grade glioma also had a near complete response to compassionate access larotrectinib.[38]

Based on these data, the US Food and Drug Administration (FDA) approved larotrectinib for the treatment of adult and pediatric patients with solid tumors that have a neurotrophin receptor tyrosine kinase (*NTRK*) gene fusion without a known acquired resistance mutation, are metastatic or where surgical resection is likely to

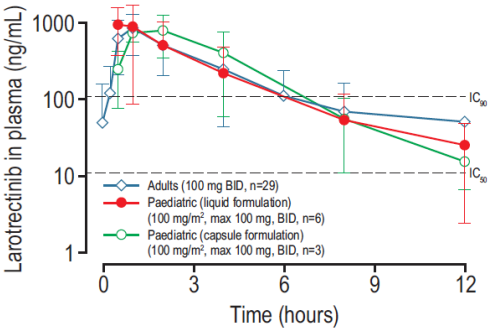
result in severe morbidity, and have no satisfactory alternative treatments or that have progressed following treatment.

Larotrectinib is included in the Pediatric MATCH study (APEC1621A) for children with recurrent disease and a documented TRK fusion. The Phase 2 portion of the Loxo Oncology sponsored phase 1/2 trial is ongoing. Both of these studies will provide additional pediatric data with this agent.

No clinical trials have evaluated larotrectinib in patients with leukemia.

2.4.2 Pharmacology/Pharmacokinetics/Correlative Biological Studies

The pharmacokinetics of larotrectinib have been evaluated in pediatric and adult patients enrolled on the clinical trials described in Section 2.3.1 and Section 2.4.1 (see Figure 1). These studies have demonstrated rapid absorption of larotrectinib after an oral dose, dose proportional increase in Cmax and AUC, and a half-life of approximately 2 hours with no accumulation with continued BID dosing.



Population	N	C_{max} (ng/mL)	T_{max} (h)	AUC_{0-24} (ng*h/mL)	$T_{1/2}$ (h)
Paeds liquid	6	1010 ± 740	0·75 (0·5–1)	5570 ± 5400	1·9 ± 0·3
Paeds capsule	3	882 ± 295	2 (1–2)	6689 ± 3860	1·5 ± 0·2
Adult capsule	29	908 ± 419	1	5340 ± 3520	2·0 ± 0·7

C_{max}, AUC_{0-24}, and $T_{1/2}$ are mean ± standard deviation; T_{max} is median (range)

Figure 1[1]**:** Larotrectinib pharmacokinetics in children (peds) and adults.

The pediatric recommended phase 2 dose was chosen because pharmacokinetic studies demonstrated similar Cmax and AUC between children treated at a dose of 100 mg/m^2 and adults treated at the recommended phase 2 dose of 100 mg. Given the very high response rate in patients with TRK fusion tumors, it has not been possible to define a dose-efficacy relationship for larotrectinib.

Exposure at a dose of 100 mg/m^2 is consistent across the pediatric age range. Patients enrolled to the pediatric phase 1 study were age 31 days to 18 years. When patients were separated by age: <2 years (n=6), 2-11 years (n=9), and 12-18 years (n=5), a dose of 100 mg/m^2 provided an AUC comparable to adults treated at the recommended phase 2 dose of 100 mg in each cohort. The ongoing Loxo Oncology sponsored phase 1/2 pediatric trial has been amended to allow newborns to enroll, providing additional information to span the entire age range proposed for this trial.

CSF larotrectinib concentrations were determined in two patients who had standard of care CSF sampling while on the pediatric phase 1 study. In both patients larotrectinib was detectable in the CSF with CSF:plasma concentrations of 8% (28% after correcting for protein binding) and 123%.

2.5 Overview of Proposed Pediatric Phase 2 Trial

This is a non-randomized study evaluating the objective response rate (ORR) of larotrectinib in patients with IFS and other TRK fusion solid tumors, including CNS tumors other than high grade gliomas (HGG). Patients will be treated with larotrectinib at the established pediatric phase 2 dose of 100 mg/m^2/dose BID with a cap of 100 mg/dose in 28-day cycles.

The primary analytic cohort will be newly diagnosed or previously untreated patients with unresectable infantile fibrosarcoma (IFS). Secondary cohorts, which will not be included in the analysis of the primary objective, will enroll patients with any other newly diagnosed TRK fusion solid tumor except HGG, and patients with relapsed/refractory TRK fusion acute leukemia. Patients with HGG are excluded as they have potentially curative therapy options available with resection and chemotherapy, and there is less data available on the activity of larotrectinib in such patients.

A key objective of this study is to avoid morbidity from aggressive attempts at surgical resection. However, given the <25% chance of recurrence for patients with completely resected IFS and CMN in prior studies, patients who are able to undergo complete resection without predicted functional, neurologic, or significant cosmetic impairment will not be eligible.[23, 24, 27] Patients who relapse after surgery alone, without prior systemic therapy, will be eligible at that time.

Given the high response rate seen in the relapsed setting in children with solid tumors, we anticipate a high ORR to larotrectinib that will enable surgical resection without predicted functional, neurologic, or significant cosmetic impairment in many of these patients. Surgical resection of patients with localized, resectable tumors will be performed after at least 6 cycles of therapy. Patients who achieve a complete resection (with negative margins for patients with diagnoses other than IFS and CMN) will be observed on protocol without further therapy unless they experience recurrence.

Patients with metastatic disease, those whose tumors don't become amenable to resection, and those with residual disease following an attempted surgical resection will continue larotrectinib for up to 26 cycles (approximately 2 years) on this protocol. Such patients will subsequently complete planned therapy and enter Follow-up. Patients who are continuing to experience benefit from larotrectinib at the completion of 26 cycles of therapy and for whom their treating physician determines it is not in their best interest to discontinue therapy and be observed may be able to continue treatment utilizing commercial supply (if approved by the local health authority), an expanded access protocol, or single patient protocol as appropriate and available at that time.

Patients with localized disease who achieve a complete response to therapy will continue receiving larotrectinib for a minimum of 12 cycles (approximately 1 year) or 6 cycles after achieving the complete response (whichever is later). Subsequently, such patients will be observed on study off of therapy unless they experience recurrence.

Patients with TRK fusion leukemias have not been included on any clinical trials of larotrectinib. However, we hypothesize there will be a high level of activity in such patients based on the responses seen in patients with TRK fusion solid tumors, the partial response reported in an adult with an *NTRK2* fusion AML, and the responses to kinase inhibition seen in children and adults with leukemias harboring *BCR-ABL* fusions. Children with relapsed/refractory leukemias with TRK fusions will be treated with larotrectinib at the established pediatric phase 2 dose of 100 mg/m^2/dose BID with a cap of 100 mg/dose. Following 1 cycle (28 days) of this therapy, patients will undergo a disease evaluation to assess response. Patients without progressive disease may continue to receive larotrectinib at their treating physician's discretion for a maximum of 26 cycles.

This is a non-randomized study given the high response rate seen in the relapsed setting and rarity of the patient population. With an expected enrollment of ~6-8 patients with IFS per year, a randomized study with sufficient power to show equivalence or superiority of larotrectinib to standard of care chemotherapy is not feasible within a reasonable accrual timeframe.

The FDA approved larotrectinib during the course of the study, but the study will proceed as written.

2.6 Rationale for Correlative Biology Studies

2.6.1 Central Next Generation Sequencing

Primary and secondary resistance to larotrectinib in the context of documented TRK fusion appears to be a rare occurrence.[1, 36, 39] In order to understand mechanisms of resistance, archival tumor material will be obtained for next generation sequencing to evaluate for the presence of TRK fusions in a central laboratory, clonal or subclonal resistance mutations at initial diagnosis and, for patients who have follow-up tissue obtained, following treatment with larotrectinib.

2.6.2 Central Pathology Review and TRK Immunohistochemistry

Given the high response rate of larotrectinib in the context of TRK fusions, identifying patients with tumors harboring these fusions is a high priority. To improve early recognition of these tumors, we will include a retrospective pathology review of diagnostic material to better define the pathologic features of this group of tumors. While FISH and sequencing approaches are the current standard approach, turnaround times may pose clinical challenges. Therefore, archival tumor material will be used to perform immunohistochemistry for TRK proteins to understand the performance characteristics of this assay in the context of TRK fusions. Similarly, little is known about histologic tumor response post-neoadjuvant larotrectinib. Retrospective pathology review to describe patterns of response (i.e., necrosis, fibrosis, maturation) and correlation with radiographic response is critical. Pan-TRK immunohistochemistry may be informative as to whether single tumor cells remain in a largely necrotic post-treatment specimen and to inform patterns of response with consideration to margin status and disease recurrence.

2.6.3 Circulating Tumor DNA

Novel approaches to detect circulating tumor DNA (ctDNA) may enable a method of minimally invasive detection of TRK fusions at diagnosis, quantification of disease burden over time, and a tool to interrogate the somatic cancer genome serially in response to selective pressure of targeted therapies. Resistance mutations in NTRK genes have been detected in ctDNA in patients in TRK fusion solid tumors treated with larotrectinib who progressed after initial response.[36] Similarly, detection of circulating tumor DNA has been reported in children with other newly diagnosed fusion driven cancers, with a rapid fall in response to treatment and increase at the time of relapse,[1, 40, 41] and patients with Ewing sarcoma and detectable ctDNA have worse outcomes.

In the current study, ctDNA samples will be collected at baseline to quantify and characterize the ability to detect TRK fusions in this population. Serial samples will be collected after 2 weeks , 4 weeks, and 24 weeks of treatment (prior to local control) to quantify and characterize the kinetics of the change in ctDNA in response to larotrectinib therapy. Finally, samples will be obtained at the time of discontinuation of larotrectinib therapy and at progression to evaluate mechanisms of resistance to treatment. Each ctDNA collection time point occurring after the start of therapy can be collected within 72 hours, for any minor and unavoidable issues that prevent ctDNA being collected at the specified time points as listed in Section 7.3.2 and Appendix IV.

2.7 Rationale for Neurocognitive Studies

Studies inducing genetic knock-out of each of the NTRK genes in mice embryos have shown CNS developmental abnormalities consistent with the role of neurotrophin growth factors and their receptors in embryonic development of the brain and nervous system.[42-44] Similarly, humans with germline genetic loss of NTRK1 or NTRK2 demonstrate developmental delay.[45, 46] The severe effects of NTRK gene loss appear to be primarily limited to the developing nervous system in utero. To date, central nervous system side effects reported on clinical trials of larotrectinib have been generally mild and primarily consisted of fatigue and dizziness.[36] No larotrectinib-related neurodevelopmental concerns have been reported, despite treating infants as young as 1 month of age and treating some children for > 2 years. However, prior studies of larotrectinib have not included formal neuropsychiatric testing. Given the presence of TRK fusion cancers in young infants and the high response rate and durable responses observed with larotrectinib to date, there is a strong potential for young children to be treated with larotrectinib for months to years on this protocol. Therefore, formal neurocognitive assessments will be performed from baseline to 5 years after enrollment on this study to better evaluate developmental outcomes.

2.7.1 Rationale for Extending Neurocognitive Assessments until 5 Years after Enrollment

ADVL1823 has now completed accrual and demonstrated that larotrectinib was highly active in patients with newly diagnosed infantile fibrosarcoma and other NTRK-fusion positive sarcomas.[47]ADVL1823 incorporated neurocognitive assessments for the first 2 years after enrollment. Compliance with these assessments has been high, but given the young age of patients enrolled to this study (median age at enrollment was 8 months), there are limitations in the ability to fully detect any potential neurocognitive late effects within 2 years of

enrollment, as the median age of patients at this timepoint is < 3 years. As such, we will add an additional timepoint for assessment of neurocognitive outcomes at 4-5 years after enrollment (prior to the 5th anniversary at which point patients are off study). We have included a relatively broad time window to simplify data collection during a routine visit for these patients, many of whom may not be receiving any therapy.

3.0 ENROLLMENT PROCEDURES AND ELIGIBILITY CRITERIA

3.1 Study Enrollment

3.1.1 Patient Registration

Prior to enrollment on this study, patients must be assigned a COG patient ID number. This number is obtained via the Patient Registry module in OPEN once authorization for the release of protected health information (PHI) has been obtained. The COG patient ID number is used to identify the patient in all future interactions with COG. If you have problems with the registration, please refer to the online help. For additional help or information, please contact the CTSU Help Desk at 1-888-823-5923 or ctsucontact@westat.com.

In order for an institution to maintain COG membership requirements, every patient with a known or suspected neoplasm needs to be offered participation in APEC14B1, *Project:EveryChild A Registry, Eligibility Screening, Biology and Outcome Study*.

A Biopathology Center (BPC) number will be assigned as part of the registration process. Each patient will be assigned only one BPC number per COG Patient ID. For additional information about the labeling of specimens please refer to the Pathology and/or Biology Guidelines in this protocol.

Please see Appendix I for detailed CTEP Registration Procedures for Investigators and Associates, and Cancer Trials Support Unit (CTSU) Registration Procedures including: how to download site registration documents; requirements for site registration, submission of regulatory documents and how to check your site's registration status.

3.1.2 IRB Approval

As of March 1, 2019, all U.S.-based sites must be members of the NCI Central Institutional Review Board (NCI CIRB) in order to participate in Cancer Therapy Evaluation Program (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. 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 through the NCI CIRB must submit the Study Specific Worksheet (SSW) for Local Context 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 (CTSURegPref@ctsu.coccg.org) or by 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 for the site to be able to have an Approved status following processing of the IRB/REB approval record:

- Have an active CTEP status;
- Have an active status at the site(s) on the IRB/REB approval (*applies to US and Canadian sites only*) and on at least one participating organization's roster;
- If using NCI CIRB, be active on the NCI CIRB roster under the applicable CIRB Signatory Institution(s) record;
- Include the IRB number of the IRB providing approval in the Form FDA 1572 in the RCR profile;
- List all sites on the IRB/REB approval as Practice Sites in the Form FDA 1572 in the RCR profile; and
- Have the appropriate CTEP registration type for the protocol.

Additional Requirements
Additional site 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);
- An active roster affiliation with the NCI CIRB roster under at least one CIRB Signatory Institution (US sites only); and
- Compliance with all applicable 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 I.

Institutions with patients waiting that are unable to use the Regulatory Submission Portal should alert the CTSU Regulatory Office immediately by phone or email:

1-866-651-CTSU (2878), or CTSURegHelp@coccg.org 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 in 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.

3.1.3 Reservation Requirements

Prior to obtaining informed consent and enrolling a patient, a reservation must be made following the steps below. Reservations may be obtained 24 hours a day through the Oncology Patient Enrollment Network (OPEN) system. Patients must be enrolled within 5 calendar days of making a reservation.

Patient enrollment for this study will be facilitated using the Slot-Reservation System in conjunction with patient enrollment in OPEN. Prior to discussing protocol entry with the patient, site staff must use the CTSU OPEN Slot Reservation System to ensure that a slot on the protocol is available for the patient. Once a slot-reservation confirmation is obtained, site staff may then proceed to enroll the patient to this study.

If the study is active, a reservation can be made by following the steps below:

1) Log in to https://open.ctsu.org/open/ using your CTEP IAM user name and password.
2) In order to make a reservation, the patient must have an OPEN patient number. Click on the 'Slot Reservation' tab to create an OPEN patient number, under 'Patients'.
3) Using the OPEN patient number '**RESERVE'** a slot for that patient.
4) On the 'Create Slot Reservation' page, select the Protocol Number, enter the COG Patient ID, and choose the required stratum (if applicable) in order to obtain a reservation.

   Refer to the 'Slot Reservation Site User Guide' posted under the 'Help' tab in OPEN for detailed instructions:
   https://www.ctsu.org/open/Site_Resources/Training/Users_Manual/CTSU-OPEN-SlotReservationSiteUserGuide.pdf

3.1.4 Study Enrollment

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 LPOs' registration/randomization systems or the 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:

- Active CTEP registration with the credentials necessary to access secure NCI/CTSU IT systems;
- To perform enrollments or request slot reservations: Must be on an LPO roster, ETCTN corresponding roster, or participating organization roster with the role of Registrar. Registrars must hold a minimum of an Associate Plus (AP) registration type;
- If a Delegation of Tasks Log (DTL) is required for the study, the registrars must hold the OPEN Registrar task on the DTL for the site; and
- Have an approved site registration for the protocol prior to patient enrollment.

To assign an Investigator (IVR) or Non-Physician Investigator (NPIVR) as the treating, crediting, consenting, or receiving investigator for a patient transfer in OPEN, the IVR or NPIVR must list the Institutional Review Board (IRB) number used on the site's IRB approval on their Form Food and Drug Administration (FDA) 1572 in the Registration and Credential Repository (RCR). If a DTL is required for the study, the IVR or NPIVR must be assigned the appropriate OPEN-related tasks on the DTL.

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 Health Insurance Portability and Accountability Act (HIPAA) authorization form (if applicable).

Note: The OPEN system will provide the site with a printable confirmation of registration and treatment information. You may 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.

3.1.5 Timing

Patients must be enrolled before treatment begins. The date protocol therapy is projected to start must be no later than **five (5)** calendar days after the date of study enrollment. **Patients who are started on protocol therapy prior to study enrollment will be considered ineligible and will not be able to receive further protocol therapy.** The only exception to this is for intrathecal methotrexate, intrathecal cytarabine, or intrathecal triples, which can be given within 1 week prior to the patient's first dose of larotrectinib for patients on Part C **ONLY**. If intrathecal methotrexate, intrathecal cytarabine, or intrathecal triples are given prior to enrollment, a separate institutional consent must be obtained.

See Section 3.2 for timing requirements for eligibility studies. **Note: Repeat laboratory and imaging studies may be required if obtained prior to the protocol mandated window.**

3.1.6 Pathology and Molecular Diagnostic Report

Immediately following enrollment, the pathology report for the diagnosis under which the patient is being enrolled and molecular diagnostic (FISH, PCR, or NGS) report confirming the presence of a TRK fusion must be uploaded into Rave. In addition, pathology reports (including reports of surgical margins) from any surgical procedures including tumor resections or tumor/metastatic/recurrent site biopsies done while the patient is on study must be uploaded into RAVE. The reports must include the associated study number and COG patient registration and accession numbers. Personal identifiers, including the patient's name and initials must be removed from the reports prior to submission.

3.1.7 Neurocognitive, Behavioral, and QoL Assessments

Parent-report measures of neurocognitive, behavioral, and QoL functioning are required to be completed at 4 separate time points: (1) within 4 weeks after enrollment; (2) 6 months (± 4 weeks) after enrollment; (3) 12 months (± 4 weeks) after enrollment; (4) 24 months (± 4 weeks), and (5) 4-5 years after enrollment. The appropriate packet of measures will be mailed to the site CRA prior to each assessment window, once a patient has been enrolled on study. Please see Appendix XI for further details.

At least one parent or guardian must have receptive and expressive language skills in English to complete the parent-reported neurocognitive, behavioral, and QoL assessments (See Appendix XI). Patients who do not meet these criteria are still eligible to enroll on study, but will not complete the neurocognitive, behavioral and QoL assessments.

3.2 Eligibility: Inclusion Criteria

Important note: The inclusion 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/research record. These source documents must be available for verification at the time of audit.

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 > 7 days old, 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 and bone marrow biopsy and/or aspirate, if applicable, must be obtained within 28 days prior to start of protocol therapy (repeat the tumor imaging if necessary).

3.2.1 Age: Patients must be ≤ 30 years of age at the time of study entry.

3.2.2 Diagnosis:

i. Cohort A: Patients must have a histologic diagnosis of infantile fibrosarcoma with an *NTRK1*, *NTRK2*, or *NTRK3* fusion identified in a CLIA/CAP certified laboratory. Fusions may be identified by FISH or molecular techniques (RT-PCR using primers flanking the fusion junction or next generation sequencing). For fusions identified by FISH, an *ETV6* rearrangement is sufficient for eligibility in Cohort A. Identification of the upstream TRK fusion partner is not required.

ii. Cohort B: Patients must have a histologic diagnosis of any solid tumor other than infantile fibrosarcoma, including CNS tumors but excluding high grade gliomas. An *NTRK1*, *NTRK2*, or *NTRK3* fusion must be identified in a CLIA/CAP certified laboratory. Fusions may be identified by FISH or molecular techniques (RT-PCR using primers flanking the fusion junction or next generation sequencing). For fusions identified by FISH, there must be an identified rearrangement in *NTRK1*, *NTRK2*, or *NTRK3* (e.g., an *ETV6* rearrangement is **not** sufficient for eligibility) unless the patient has a diagnosis of congenital mesoblastic nephroma in which case an *ETV6* rearrangement is sufficient for eligibility. Identification of the upstream TRK fusion partner is not required.

iii. Cohort C: Patients must have a histologic diagnosis of relapsed or refractory acute leukemia with an *NTRK1*, *NTRK2*, or *NTRK3* fusion identified in a CLIA/CAP certified laboratory. Fusions may be identified by FISH or molecular techniques (RT-PCR using primers flanking the fusion junction or next generation sequencing). For fusions identified by FISH, there must be an identified rearrangement in *NTRK1*, *NTRK2*, or *NTRK3* (e.g., an *ETV6* rearrangement is **not** sufficient for eligibility). Identification of the upstream TRK fusion partner is not required.

3.2.3 Disease Status

i. Solid Tumors (Cohorts A & B): Patients must have measurable disease (see Section 10.3.1 for definition). Patients must have disease that cannot be completely resected without a predicted functional, neurologic, or significant cosmetic deficit in the opinion of the investigator.

ii. Leukemia (Cohort C): Patients must have ≥ 5% blasts in the bone marrow. Extramedullary disease is permitted.

3.2.4 Performance Level

Patients must have a Lansky or Karnofsky performance status score of ≥ 50, corresponding to ECOG categories 0, 1 or 2. Use Karnofsky for patients > 16 years of age and Lansky for patients ≤ 16 years of age. **NOTE:** Neurologic deficits in patients with CNS tumors must have been 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.
(See Appendix IX)

3.2.5 Prior Therapy

- Cohorts A & B: No prior anti-cancer therapy, including radiotherapy, other than surgical resection is permitted.
    - Patients who experience recurrence after surgery alone and no other anti-cancer therapy will be eligible.
    - If not eligible due to prior anticancer therapy, patients may be eligible for the larotrectinib arm of Pediatric MATCH (APEC1621A) or treatment with commercial larotrectinib off study.

- Cohort C: The following apply to patients with relapsed/refractory leukemia:

3.2.5.1 Patients with relapsed leukemia (Cohort C) 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 DVL homepage for the Myelosuppressive, Non-Myelosuppressive, and Antibody Anti-Cancer Agents table (https://cogmembers.org/Site/Disc/DevTherapeutics/Default.aspx). 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.
    - A waiting period prior to enrollment is not required for patients receiving standard cytotoxic maintenance chemotherapy (i.e., corticosteroid, vincristine, 6MP, and/or methotrexate).
    - A waiting period is not required for patients receiving a single dose of intrathecal methotrexate, hydrocortisone, and/or cytarabine within 7 days prior to enrollment
    - ≥ 14 days must have elapsed after the completion of other cytotoxic therapy, with the exception of hydroxyurea, for patients not receiving standard maintenance therapy. Additionally, patients must have fully recovered from all acute toxic effects of prior therapy.

    Note: Cytoreduction with hydroxyurea must be discontinued ≥ 24 hours prior to the start of protocol therapy.

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 DVL homepage for the Myelosuppresive, Non-Myelosuppressive, and Antibody Anti-Cancer Agents table (https://cogmembers.org/Site/Disc/DevTherapeutics/Default.aspx). 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. Anti-cancer agents that are 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. There is an exception for blinatumomab infusions, for which patients must have been off for at least 3 days and all drug related toxicity must have resolved to Grade 2 or lower as outlined in the inclusion/exclusion criteria. See DVL Homepage for the Myelosuppressive, Non-Myelosuppressive, and Antibody Anti-Cancer Agents table (https://cogmembers.org/Site/Disc/DevTherapeutics/Default.aspx).

d. Corticosteroids: See Section 3.3.2.1. If used to modify **immune adverse events** related to prior therapy, ≥ 14 days must have elapsed since last dose of corticosteroid. A waiting period prior to enrollment is not required for patients receiving corticosteroid for leukemia therapy/cytoreduction.

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 agents 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.

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

k. Patients must not have received prior exposure to TRK inhibitors (including larotrectinib, LOXO-195, entrectinib, lorlatinib, crizotinib,

or lestaurtinib).

3.2.6 Organ Function Requirements

3.2.6.1 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)
   - Hemoglobin ≥ 8.0 g/dL at baseline (may receive RBC transfusions)

b. Patients with solid tumors with known bone marrow metastatic disease will be eligible for study provided they meet the blood counts in Section 3.2.6.1.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.

c. For patients with leukemia:
   - Platelet count ≥ 20,000/mm^3 (may receive platelet transfusions).
   - Hemoglobin ≥ 8.0 g/dL at baseline (may receive RBC transfusions)
   - These patients must not be known to be refractory to red cell or platelet transfusion.

3.2.6.2 Adequate Renal Function Defined As:

a. Creatinine clearance or radioisotope GFR ≥ 70 mL/min/1.73 m^2 **or** a serum creatinine based on age/sex as follows:

Age	Maximum Serum Creatinine (mg/dL)	
	Male	Female
1 month to < 6 months	0.4	0.4
6 months to < 1 year	0.5	0.5
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.[48]

- For patients <1 month of age, serum creatinine levels must be <1.5x the treating institution's creatinine ULN for patients <1 month of age or the creatinine clearance or radioisotope GFR must be ≥ 70 mL/min/1.73 m^2.

3.2.6.3 Adequate Liver Function Defined As:

i. Patients with solid tumors:

- Bilirubin (sum of conjugated + unconjugated) ≤ 1.5 x upper limit of normal (ULN) for age. After approval of the study chair or designee, infants with a higher total bilirubin due to physiologic or breast milk jaundice are eligible if the conjugated (direct) bilirubin is ≤ 2 mg/dL.
- SGPT (ALT) ≤ 135 U/L. For the purpose of this study, the ULN for SGPT is 45 U/L.
- Serum albumin ≥ 2 g/dL.

ii. Patients with leukemias:

- Conjugated (direct) bilirubin ≤ 1.5 x upper limit of normal (ULN) for age.
- SGPT (ALT) ≤ 225 U/L. For the purpose of this study, the ULN for SGPT is 45 U/L.
- Serum albumin ≥ 2 g/dL.

3.2.6.4 Central Nervous System Function Defined As:

- Patients with seizure disorder may be enrolled if on a stable antiepileptic regimen for ≥ 14 days and well controlled.
- Nervous system disorders (CTCAE v5) except tendon reflex decreased resulting from prior therapy must be ≤ Grade 2.

3.3 Eligibility: Exclusion Criteria

Important note: The exclusion 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/research record. These source documents must be available for verification at the time of audit.

3.3.1 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, *OR* because there is yet no available information regarding human fetal or teratogenic toxicities. Pregnancy tests must be obtained in girls who are post-menarchal. Female patients of reproductive potential may not participate unless they have agreed to use a highly effective contraceptive method for the duration of study therapy and for at least one month after the final dose of larotrectinib. Males of reproductive potential with a non-pregnant female partner of child-bearing potential must use a highly effective contraception for the duration of the study and for at least one month after the final dose of larotrectinib.

Because of the unknown risk of larotrectinib in nursing infants, nursing women should discontinue breastfeeding during treatment with larotrectinib and for 3 days following the final dose.

3.3.2 Concomitant Medications:

3.3.2.1 Corticosteroids: Patients with solid tumors, including CNS tumors, requiring corticosteroids who have not been on a stable or decreasing dose of corticosteroid for at least 7 days prior to enrollment are not eligible. Patients with leukemia may receive systemic corticosteroids for cytoreduction up to 24 hours prior to the start of protocol therapy. If used to modify **immune adverse events** related to prior therapy, ≥ 14 days must have elapsed since last dose of corticosteroid.

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

3.3.2.3 Anti-cancer Agents: Patients who are currently receiving other anti-cancer agents are not eligible [except leukemia patients receiving corticosteroids or hydroxyurea, which may be continued until 24 hours prior to start of protocol therapy]. Patients with leukemia should receive a single dose of intrathecal cytarabine, hydrocortisone, and/or methotrexate within 7 days prior to Day 1 of Cycle 1 at the time of the baseline lumbar puncture.

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

3.3.2.5 CYP3A4 Inducers/Inhibitors: Patients currently receiving a strong CYP3A4 inducer or inhibitor are not eligible (see Appendix VI). Strong inducers or inhibitors of CYP3A4 should be avoided from 14 days prior to enrollment to the end of the study. **Note:** CYP3A4 inducing anti-epileptic drugs and dexamethasone for CNS tumors or metastases, on a stable dose, are allowed.

3.3.3 Malabsorption:

Patients with malabsorption syndrome or other conditions that significantly limit enteral absorption are not eligible.

3.3.4 Swallow or Gastric Access:

Patients who are unable to swallow capsules or liquid and do not have gastric access via a nasogastric or gastrostomy tube are not eligible.

3.3.5 Infection:

Patients who have an uncontrolled infection are not eligible.

3.3.6 Solid Organ Transplant:

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

3.3.7 Safety Monitoring:

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.

3.3.8 Diagnosis:
Patients with High Grade Gliomas (HGG) are not eligible.

3.4 Regulatory

3.4.1 All patients and/or their parents or legal guardians must sign a written informed consent.

3.4.2 All institutional, FDA, and NCI requirements for human studies must be met.

4.0 TREATMENT PROGRAM

Timing of protocol therapy administration, response assessment studies, and surgical interventions are based on schedules derived from the experimental design or on established standards of care. Minor unavoidable departures (up to 72 hours) from protocol directed therapy and/or disease evaluations for valid clinical, patient and family logistical, or facility, procedure and/or anesthesia scheduling issues are acceptable (except where explicitly prohibited within the protocol).

4.1 Overview of Treatment Plan

Treatment Schedule	
Days 1 – 28	Larotrectinib 100 mg/m^2/dose orally/NG/G-tube twice daily (maximum 100 mg/dose BID)
Day 28	End of Cycle

This is an open label study of larotrectinib administered at 100 mg/m^2/dose PO BID (maximum of 100 mg/dose BID) on a continuous dosing schedule (one cycle = 28 days). Dosing will be performed based on body surface area (BSA) for patients of all ages and may be administered as a capsule or liquid formulation. Patients with infantile fibrosarcoma will be enrolled in Cohort A, the primary analytic cohort. Patients with all other TRK fusion solid tumors will be enrolled in Cohort B. Patients with relapsed/refractory TRK fusion leukemia will be enrolled in Cohort C.

Patients with solid tumors who meet the criteria described in Section 4.3.3 may stop larotrectinib while continuing on study in the Follow-up Period. All other patients will continue therapy until tumor progression or unacceptable toxicity for a maximum of 26 cycles, after which they will also enter the Follow-up Period.

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 X-A for capsule and Appendix X-B for liquid formulations). **Only use larotrectinib provided for investigational use specifically for ADVL1823.**

4.1.1 Dose Reduction

Up to three dose reductions of larotrectinib will be allowed for dose limiting toxicities as outlined in Section 5.0 for patients who recover and meet starting criteria as outlined in Section 3.2.6 within 21 days following drug discontinuation:

- 1st dose reduction: 75 mg/m^2/dose BID (maximum of 75 mg/dose BID)
- 2nd dose reduction: 50 mg/m^2/dose BID (maximum of 50 mg/dose BID)
- 3rd dose reduction: 25 mg/m^2/dose BID (maximum of 25 mg/dose BID)

Patients who do not recover to meet starting criteria within 21 days will be removed from protocol therapy. Patients who experience DLT as outlined in Section 5.0 after three dose reductions will be removed from protocol therapy.

4.1.2 Dose Escalation

There will be no drug dose escalation except for those based on growth of the patient to maintain the same dose on a mg/m^2 basis. The dose of larotrectinib should be recalculated at the start of each cycle based on a recent (within 7 days) height and weight.

4.1.3 Criteria for Starting Subsequent Cycles

A cycle may be repeated every 28 days, up to a maximum of 26 cycles. Larotrectinib will be administered continuously without breaks unless the patient meets criteria for holding or discontinuing larotrectinib as defined in Section 5.1. Patients who experience progressive disease at any time on protocol therapy will be taken off therapy. Patients with solid tumors (Cohorts A & B) who do not have progressive disease will follow the guidelines outlined in Section 4.1.3.1, Section 4.1.3.2 and Section 4.1.3.3.

4.1.3.1 Patients with Localized Disease who Achieve Stable Disease or a Partial Response that Renders Disease Resectable:

Patients with localized disease who achieve sufficient tumor shrinkage to have disease resection (for whom a complete resection is anticipated to be likely without functional, neurologic, or significant cosmetic deficit) will undergo surgical resection of their residual tumor after a minimum of 6 cycles of therapy (see Section 13.1 for surgical guidelines). Such patients may receive up to 1 additional cycle of therapy after their tumor is deemed resectable during surgical planning. Larotrectinib will be held for 24 hours prior to surgery. Following surgery, patients with IFS or CMN who achieve a gross total resection and all other patients with solid tumors who achieve a resection with negative margins (Section 13.2) will have completed planned therapy and enter Follow-up (Section 7.2). Patients who have an incomplete resection or positive margins for diagnoses other than IFS/CMN will resume protocol therapy following surgery. Therapy may be resumed as soon as 24 hours post-operatively once it has been determined that the patient meets protocol criteria to resume therapy and the patient is tolerating enteral fluids.

4.1.3.2 Patients who Achieve Stable Disease or a Partial Response and Do Not Have Localized, Resectable Disease:

Patients who have stable disease or a partial response and do not have localized, resectable disease will continue on larotrectinib therapy for up to 26 cycles. This group includes all patients who enroll with metastatic disease and do not achieve a complete response. After 26 cycles, such patients will have completed planned therapy and enter Follow-up (Section 7.2). Patients who are continuing to experience benefit from larotrectinib at the completion of 26 cycles of therapy and for whom their treating physician determines it is not in their best interest to discontinue therapy and be observed may be able to continue treatment utilizing commercial supply (if approved by the local health authority), an expanded access protocol, or single patient protocol as appropriate and available at that time.

4.1.3.3 Patients who Achieve a Complete Response:
Patients who achieve a complete response from only larotrectinib therapy (without surgery) will receive 6 additional cycles of therapy after achieving CR or a minimum of 12 cycles of therapy (whichever occurs later). Such patients will subsequently have completed planned therapy and enter Follow-up (Section 7.2).

4.1.3.4 Patients with Progressive Disease:
Patients who have progressive disease at any time will be taken off therapy.

4.1.4 Concomitant Therapy

4.1.4.1 No other cancer chemotherapy, radiotherapy, immunomodulating agents, or biologic therapy will be used. If these treatments are administered the patient will be removed from protocol therapy.

4.1.4.2 CYP3A4 inhibitors or inducers: Strong CYP3A4 inhibitors or inducers are prohibited from 14 days prior to enrollment to the end of the study (See Appendix VI for list of agents). **Note:** CYP3A4 inducing anti-epileptic drugs and dexamethasone for CNS tumors or metastases, on a stable dose, are allowed. Avoid grapefruit or grapefruit juice as these may also increase plasma concentrations of larotrectinib.

4.1.4.3 Use caution in patients who are taking concomitant medications that are strong inducers or inhibitors of P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP).

4.1.4.4 Use with caution in patients who are taking concomitant medications that are sensitive or narrow therapeutic range substrates of CYP3A4 (see Appendix VI). **Note:** Patient handout on possible drug interactions with larotrectinib can be found in Appendix V.

4.1.4.5 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 or designee should be notified before growth factors are initiated.

4.1.4.6 Appropriate antibiotics, blood products, antiemetics, fluids, electrolytes and general supportive care are to be used as necessary. Refer to COG Supportive Care Guidelines at https://childrensoncologygroup.org/index.php/cog-supportive-care-guidelines or treat per institutional standards.

4.2 Cycle 1, Cohorts A & B

4.2.1 Therapy Delivery Map – Cycle 1, Cohorts A & B This Therapy Delivery Map (TDM) relates to Cycle 1 for Cohorts A & B. Each cycle lasts 28 days.	_____ Patient COG ID number _____ DOB

Criteria to start each cycle are listed in Section 4.1.3. Extensive treatment details are in Section 4.2.3.
This TDM is 5 pages in length.

DRUG	ROUTE	DOSAGE	DAYS	IMPORTANT NOTES
Larotrectinib IND# 141824	Oral/Nasogastric/Gastrostomy Tube	100 mg/m^2/dose BID	1 – 28	Maximum dose = 100 mg/dose BID. See Appendix X-A and Appendix X-B for dosing nomograms.

Ht _____cm **Wt _____kg** **BSA _____m^2**

Date Due	Date Given	Day	**Larotrectinib** AM dose: ____ mg PM dose: ____ mg		Studies	
			Enter calculated dose above and actual dose administered below			
		Pre-	**AM Dose**	**PM Dose**	a – l, n	
		1	_____ mg	_____ mg		
		2	_____ mg	_____ mg		
		3	_____ mg	_____ mg		
		4	_____ mg	_____ mg		d
		5	_____ mg	_____ mg		
		6	_____ mg	_____ mg		
		7	_____ mg	_____ mg		
		8	_____ mg	_____ mg		
		9	_____ mg	_____ mg		
		10	_____ mg	_____ mg		
		11	_____ mg	_____ mg		d
		12	_____ mg	_____ mg		
		13	_____ mg	_____ mg		
		14	_____ mg	_____ mg		
		15	_____ mg	_____ mg	k	d
		16	_____ mg	_____ mg		

		17	_____ mg	_____ mg		
		18	_____ mg	_____ mg		
		19	_____ mg	_____ mg		
		20	_____ mg	_____ mg		
		21	_____ mg	_____ mg		
		22	_____ mg	_____ mg		
		23	_____ mg	_____ mg		
		24	_____ mg	_____ mg		
		25	_____ mg	_____ mg		d
		26	_____ mg	_____ mg		
		27	_____ mg	_____ mg		
		28	_____ mg	_____ mg	m	

See Section 5.0 for Dose Modifications for Toxicities and the COG Member website for Supportive Care Guidelines.

4.2.2 Required Observations in Cycle 1, Cohorts A & B

All baseline studies must be performed prior to starting protocol therapy unless otherwise indicated below.

a. Hx/Wt /Ht/BSA. Within 7 days prior to Cycle 1.
b. Performance status. Prior to Cycle 1.
c. Physical exam (including VS and neurologic examination). Prior to Cycle 1.
d. CBC/diff/platelets: Prior to Cycle 1 and every week during Cycle 1. If patients have Grade 4 neutropenia then CBCs should be checked every 3 to 4 days until recovery to Grade 3 or until meeting the criteria for dose limiting toxicity.
e. Electrolytes including Ca^{++}. Prior to Cycle 1.
f. Creatinine, ALT, bilirubin. Prior to Cycle 1.
g. Albumin. Prior to Cycle 1.
h. Disease evaluation. Prior to Cycle 1.
i. Pregnancy test. Prior to Cycle 1. Female patients of childbearing potential require a negative pregnancy test prior to starting treatment; sexually active patients must use an acceptable method of birth control.
j. Bone marrow evaluation. Prior to Cycle 1. Bone marrow aspirate and/or biopsy should only be performed on patients with solid tumors with known bone marrow metastasis on the basis of history, symptoms, laboratory evaluation or other clinical data.
k. Circulating tumor DNA. Prior to Cycle 1 and on Day 15 of Cycle 1. See Section 7.3.2 for details.
l. Tumor tissue submission. Prior to Cycle 1. If tissue blocks or slides are unavailable, the study chair must be notified prior to study enrollment. See Section 7.3.1 for details.
m. Patient diary. Uploaded into RAVE at the end of Cycle 1. See Appendix VII-A and Appendix VII-B for details.
n. Neurocognitive assessments. Within 4 weeks after enrollment. See Section 3.1.7 and Appendix XI for details.

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)

4.2.3 Treatment Details: Cycle 1, Cohorts A & B

Larotrectinib: Oral/Nasogastric/Gastrostomy
Days: 1 - 28
Dose: 100 mg/m^2/dose BID (maximum of 100 mg/dose BID).

Only use larotrectinib provided for investigational use specifically for ADVL1823.

Note that this study will enroll very young children, but the dose will be based on body surface area for all patients regardless of age.

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.

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 X-A). Doses of larotrectinib capsules should be rounded to the nearest 25 mg (Appendix X-A). Calculated dosing volumes of larotrectinib liquid formulation should be rounded to the nearest 0.1 mL (2 mg) for doses ≤ 45 mg (in oral syringes ≤ 3 mL) and 0.2 mL (4 mg) for doses > 45 mg (in 5-10 mL oral syringes) for the actual deliverable dose (Appendix X-B).

All patients taking larotrectinib must complete a patient diary (Appendix VII-A and Appendix VII-B).

See Section 5.0 for Dose Modifications based on Toxicities.

Following completion of this cycle, the next cycle starts on Day 29 or when the criteria in Section 4.1.3 are met (whichever occurs later). Larotrectinib will be administered continuously without breaks between cycles unless the patient meets criteria for holding or discontinuing larotrectinib (Section 5.1).

4.3 Therapy Subsequent to Cycle 1 (Cycles 2+), Cohorts A & B

4.3.1 Therapy Delivery Map – Cycles 2+, Cohorts A & B This Therapy Delivery Map (TDM) relates to Cycles 2+ for Cohorts A & B. Each cycle lasts 28 days. Patients may continue on larotrectinib therapy per the guidelines in Section 4.3.3 up to a maximum of 26 cycles.	_____ Patient COG ID number _____ DOB

Criteria to start each cycle are listed in Section 4.1.3. Extensive treatment details are in Section 4.3.3.
This TDM is 6 pages in length.

DRUG	ROUTE	DOSAGE	DAYS	IMPORTANT NOTES
Larotrectinib IND# 141824	Oral/Nasogastric/Gastrostomy Tube	100 mg/m^2/dose BID	1 – 28	Maximum dose = 100 mg/dose BID. See Appendix X-A and Appendix X-B for dosing nomograms.

Ht _____cm **Wt _____kg** **BSA _____m^2**

CYCLE # _____

Date Due	Date Given	Day	**Larotrectinib** AM dose: ____ mg PM dose: ____ mg		Studies
			Enter calculated dose above and actual dose administered below		
		Pre-	**AM Dose**	**PM Dose**	a – h, i, j, l, m
		1	_____ mg	_____ mg	i
		2	_____ mg	_____ mg	
		3	_____ mg	_____ mg	
		4	_____ mg	_____ mg	
		5	_____ mg	_____ mg	
		6	_____ mg	_____ mg	
		7	_____ mg	_____ mg	
		8	_____ mg	_____ mg	
		9	_____ mg	_____ mg	
		10	_____ mg	_____ mg	
		11	_____ mg	_____ mg	

		12	_____ mg	_____ mg	
		13	_____ mg	_____ mg	
		14	_____ mg	_____ mg	
		15	_____ mg	_____ mg	
		16	_____ mg	_____ mg	
		17	_____ mg	_____ mg	
		18	_____ mg	_____ mg	
		19	_____ mg	_____ mg	
		20	_____ mg	_____ mg	
		21	_____ mg	_____ mg	
		22	_____ mg	_____ mg	
		23	_____ mg	_____ mg	
		24	_____ mg	_____ mg	
		25	_____ mg	_____ mg	
		26	_____ mg	_____ mg	
		27	_____ mg	_____ mg	
		28	_____ mg	_____ mg	i, k

See Section 5.0 for Dose Modifications for Toxicities and the COG Member website for Supportive Care Guidelines.

4.3.2 Required Observations for Cycles 2+, Cohorts A & B

a. Hx/Wt /Ht/BSA. Within 7 days prior to subsequent cycles and at the end of study treatment.

b. Performance status. Prior to subsequent cycles.

c. Physical exam (including VS and neurologic examination). Prior to subsequent cycles and at the end of study treatment.

d. CBC/diff/platelets: Prior to subsequent cycles. If patients have Grade 4 neutropenia then CBCs should be checked every 3 to 4 days until recovery to Grade 3 or until meeting the criteria for dose limiting toxicity.

e. Electrolytes including Ca^{++}. Prior to subsequent cycles.

f. Creatinine, ALT, bilirubin. Prior to subsequent cycles.

g. Disease evaluation. After cycles 2, 4, 6, 9, 12, 16, 20, and 24. 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. Please refer to Section 10.4 for Confirmation of objective response by RECIST 1.1.

h. Bone marrow evaluation. With Disease evaluation. Bone marrow aspirate and/or biopsy should only be performed on patients with solid tumors with bone marrow involvement at baseline. If the institutional investigator has determined the patient has progressed based on clinical or laboratory evidence, he/she may opt not to confirm this finding on marrow pathology.

i. Circulating tumor DNA. On Day 1 of Cycle 2, at the end of cycle 6 (Day 1 of Cycle 7 or prior to local control), and at the time of progression. See Section 7.3.2 for details.

j. Tumor tissue submission. Submission of tumor tissue from any surgical resection or bone marrow evaluation for patients with involvement by tumor while on study is required. For patients who undergo resection of their tumor while on study, operative reports and hospital discharge summaries must be uploaded into RAVE following surgical resection. Submission of tumor tissue from any biopsy after progression is optional. See Section 7.3.1 for details.

k. Patient diary. Uploaded into RAVE at the end of each cycle. See Appendix VII-A and Appendix VII-B for details.

l. Pregnancy test. Prior to subsequent cycles. Sexually active patients must use an acceptable method of birth control.

m. Neurocognitive assessments. 6 months (± 4 weeks) after enrollment, 12 months (± 4 weeks) after enrollment, 24 months (± 4 weeks), and 4-5 years after enrollment. See Section 3.1.7 and Appendix XI for details.

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)

4.3.3 Treatment Details: Cycles 2+, Cohorts A & B

Larotrectinib: Oral/Nasogastric/Gastrostomy
Days: 1 - 28
Dose: 100 mg/m^2/dose BID (maximum of 100 mg/dose BID).

Only use larotrectinib provided for investigational use specifically for ADVL1823.

Note that this study will enroll very young children, but the dose will be based on body surface area for all patients regardless of age.

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.

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 X-A). Doses of larotrectinib capsules should be rounded to the nearest 25 mg (Appendix X-A). Calculated dosing volumes of larotrectinib liquid formulation should be rounded to the nearest 0.1 mL (2 mg) for doses ≤ 45 mg (in oral syringes ≤ 3 mL) and 0.2 mL (4 mg) for doses > 45 mg (in 5-10 mL oral syringes) for the actual deliverable dose (Appendix X-B).

All patients taking larotrectinib must complete a patient diary (Appendix VII-A and Appendix VII-B).

See Section 5.0 for Dose Modifications based on Toxicities.

Patients will have disease evaluation at the end of cycles 2, 4, 6, 9, 12, 16, 20, and 24. Patients with progressive disease at any time will discontinue protocol therapy.

Patients who achieve a complete response will receive 6 additional cycles of therapy after achieving CR or a minimum of 12 cycles of therapy (whichever occurs later). Such patients will subsequently enter Follow-up (Section 7.2).

Patients who achieve sufficient tumor shrinkage to have localized, resectable disease (for whom a complete resection is anticipated to be likely without predicted functional, neurologic, or significant cosmetic deficit) will undergo surgical resection of their residual tumor after a minimum of 6 cycles of therapy. See Section 13.1 for surgical guidelines. Such

patients may receive up to 1 additional cycle of therapy after their tumor is deemed resectable during surgical planning. Larotrectinib will be held for 24 hours prior to surgery. For patients who undergo resection of their tumor while on study, operative reports and hospital discharge summaries must be uploaded into RAVE following surgical resection. Following surgery, patients with IFS or CMN who achieve a gross total resection and all other patients with solid tumors who achieve a resection with negative margins (Section 13.2) will enter Follow-up (Section 7.2). Patients who have an incomplete resection or positive margins for diagnoses other than IFS/CMN (Section 13.2) will resume protocol therapy following surgery. Therapy may be resumed as soon as 24 hours post-operatively once it has been determined that the patient meets protocol criteria to resume therapy and the patient is tolerating enteral fluids.

For all other patients, following completion of this cycle, the next cycle starts on Day 29 or when the criteria in Section 4.1.3 are met (whichever occurs later). Larotrectinib will be administered continuously without breaks between cycles unless the patient has progressive disease or meets criteria for holding or discontinuing larotrectinib (Section 5.1).

4.4 Cycle 1, Cohort C

4.4.1 Therapy Delivery Map – Cycle 1, Cohort C This Therapy Delivery Map (TDM) relates to Cycle 1 for Cohort C. Each cycle lasts 28 days.	_____ Patient COG ID number _____ DOB

Criteria to start each cycle are listed in Section 4.1.3. Extensive treatment details are in Section 4.4.3.
This TDM is 7 pages in length.

DRUG		ROUTE	DOSAGE	DAYS	IMPORTANT NOTES
Methotrexate OR Cytarabine OR Triples (methotrexate/ hydrocortisone/ cytarabine)	Methotrexate	Intrathecal	Age (yrs) / Dose < 1 — 7.5 mg 1-1.99 — 8 mg 2-2.99 — 10 mg 3-8.99 — 12 mg ≥ 9 — 15 mg	-7 to -1 8,	Patients should receive one dose of intrathecal therapy between Days -7 to -1 at their physician's discretion. Day 8 for all patients. Continue weekly thereafter ONLY for patients with ALL who are CNS 2 (see Section 10.8) at enrollment until two consecutive clear CSF samples are obtained
	Cytarabine	Intrathecal	Age (yrs) / Dose < 1 — 20 mg 1-1.99 — 30 mg 2-2.99 — 50 mg ≥ 3 — 70 mg	-7 to -1 8, 15, 22	Patients should receive one dose of intrathecal therapy between Days -7 to -1 at their physician's discretion. Days 8 and weekly thereafter only for patients with AML who have positive CSF (see Section 10.9) at enrollment until two consecutive clear CSF samples are obtained.
	Triples (methotrexate/ hydrocortisone/ cytarabine)	Intrathecal	Age (yrs) / Dose < 1 — MTX: 7.5 mg, HC: 7.5 mg, ARAC: 15 mg 1-1.99 — MTX: 8 mg, HC: 8 mg, ARAC: 16 mg 2-2.99 — MTX: 10 mg, HC: 10 mg, ARAC: 20 mg 3-8.99 — MTX: 12 mg, HC: 12 mg, ARAC: 24 mg ≥ 9 — MTX: 15 mg, HC: 15 mg, ARAC: 30 mg	-7 to -1 8, 15, 22	Patients should receive one dose of intrathecal therapy between Days -7 to -1 at their physician's discretion. Days 8, 15, and 22 only for patients with ALL who are CNS 3 (see Section 10.8) at enrollment and regardless of whether or not the patient clears. Patients who do not clear by the end of cycle 1 will be removed from protocol therapy.

Larotrectinib IND# 141824	Oral/Nasogastric/ Gastrostomy Tube	100 mg/m^2/dose BID	1 – 28	Maximum dose = 100 mg/dose BID. See Appendix X-A and Appendix X-B for dosing nomograms.

Ht _____cm **Wt _____kg** **BSA _____m^2**

Date Due	Date Given	Day	**Larotrectinib** AM dose: ____ mg PM dose: ____ mg		**Methotrexate** ____mg	**Cytarabine** ____mg	**Hydrocortisone** ____mg	**Studies**	
			Enter calculated dose above and actual dose administered below						
		Pre-	**AM Dose**	**PM Dose**	_____ mg	_____ mg	_____ mg	a – j, l, m, o	
		1	_____ mg	_____ mg					d
		2	_____ mg	_____ mg					
		3	_____ mg	_____ mg					
		4	_____ mg	_____ mg					
		5	_____ mg	_____ mg					
		6	_____ mg	_____ mg					
		7	_____ mg	_____ mg					
		8	_____ mg	_____ mg	_____ mg	_____ mg	_____ mg	j, k	d
		9	_____ mg	_____ mg					
		10	_____ mg	_____ mg					
		11	_____ mg	_____ mg					
		12	_____ mg	_____ mg					
		13	_____ mg	_____ mg					
		14	_____ mg	_____ mg					
		15	_____ mg	_____ mg	_____ mg	_____ mg	_____ mg	j – l	d
		16	_____ mg	_____ mg					
		17	_____ mg	_____ mg					
		18	_____ mg	_____ mg					
		19	_____ mg	_____ mg					
		20	_____ mg	_____ mg					
		21	_____ mg	_____ mg					

		22	_____ mg	_____ mg	_____ mg	_____ mg	_____ mg	j, k	
		23	_____ mg	_____ mg					
		24	_____ mg	_____ mg					
		25	_____ mg	_____ mg					d
		26	_____ mg	_____ mg					
		27	_____ mg	_____ mg					
		28	_____ mg	_____ mg				h, j, k, n	

See Section 5.0 for Dose Modifications for Toxicities and the COG Member website for Supportive Care Guidelines.

4.4.2 Required Observations in Cycle 1, Cohort C

All baseline studies must be performed prior to starting protocol therapy unless otherwise indicated below.

a. Hx/Wt /Ht/BSA. Within 7 days prior to Cycle 1.
b. Performance status. Prior to Cycle 1.
c. Physical exam (including VS and neurologic examination). Prior to Cycle 1.
d. CBC/diff/platelets: Prior to Cycle 1 and every week during Cycle 1. If patients have Grade 4 neutropenia then CBCs should be checked every 3 to 4 days until recovery to Grade 3 or until meeting the criteria for dose limiting toxicity.
e. Electrolytes including Ca^{++}. Prior to Cycle 1.
f. Creatinine, ALT, bilirubin. Prior to Cycle 1.
g. Albumin. Prior to Cycle 1.
h. Bone marrow evaluation, lumbar puncture, and evaluation of any sites of extramedullary disease. Prior to Cycle 1 and at the end of Cycle 1.
i. Pregnancy test. Prior to Cycle 1. Female patients of childbearing potential require a negative pregnancy test prior to starting treatment; sexually active patients must use an acceptable method of birth control.
j. Cerebral spinal fluid (CSF) cell count and differential. Within 7 days prior to Cycle 1 and at the end of Cycle 1. CSF will be obtained on Days 8, 15, and 22 only for patients who are receiving intrathecal therapy on that date.
k. Cerebral spinal fluid (CSF) and peripheral blood pharmacokinetics. At the end of Cycle 1 at the time of the first disease evaluation for all patients with leukemia, and on Days 8, 15, and 22 for patients who are receiving intrathecal therapy. See Section 7.3.3 for details.

l. Circulating tumor DNA. Prior to Cycle 1 and on Day 15 of Cycle 1.See Section 7.3.2 for details. m. Tumor tissue submission. Prior to Cycle 1. If tissue blocks or slides are unavailable, the study chair must be notified prior to study enrollment. See Section 7.3.1 for details. n. Patient diary. Uploaded into RAVE at the end of Cycle 1. See Appendix VII-A and Appendix VII-B for details. o. Neurocognitive assessments. Within 4 weeks after enrollment. See Section 3.1.7 and Appendix XI for details.

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)

4.4.3 Treatment Details: Cycle 1, Cohort C

Baseline Methotrexate, Cytarabine, OR Triples (Methotrexate/Hydrocortisone/Cytarabine): Intrathecal
Day: -7 to -1

Cycle 1, Cohort C

Dose: A single dose of intrathecal methotrexate or triples should be administered at the treating physician's discretion within 7 days of Day 1 of Cycle 1 of therapy for patients in Cohort C with ALL. A single dose of intrathecal cytarabine should be administered at the treating physician's discretion within 7 days of Day 1 of Cycle 1 of therapy for patients in Cohort C with AML.

See age-based dosing recommendations below. Note: Intrathecal therapy received prior to enrollment within 7 days prior to Day 1 of Cycle 1 will replace the pre-Cycle 1 intrathecal, even if administered at different doses.

Methotrexate: Intrathecal
Days: 8 for all patients. Continue weekly thereafter ONLY for patients with ALL who are CNS 2 (see Section 10.8) at enrollment until two consecutive clear CSF samples are obtained.

Age (yrs)	Dose
<1	7.5 mg
1-1.99	8 mg
2-2.99	10 mg
3-8.99	12 mg
≥ 9	15 mg

Cytarabine: Intrathecal
Days: 8 and weekly thereafter ONLY for patients with AML who have positive CSF (see Section 10.9) at enrollment until two consecutive clear CSF samples are obtained.

Age (yrs)	Dose
< 1	20 mg
1-1.99	30 mg
2-2.99	50 mg
≥ 3	70 mg

Methotrexate (MTX)/Hydrocortisone (HC)/Cytarabine (ARAC): Intrathecal
Days: 1, 8, 15, and 22 ONLY for patients with ALL who are CNS 3 (see Section 10.8) at enrollment. Thereafter, weekly intrathecals should continue until 2 clear CSF samples are obtained, and regardless of whether or not the

patient clears. Thereafter, weekly intrathecals should continue until 2 clear CSF samples are obtained. Patients who do not clear by the end of cycle 1 will be removed from protocol therapy.

Age (yrs)	Dose
<1	MTX: 7.5 mg, HC: 7.5 mg, ARAC: 15 mg
1-1.99	MTX: 8 mg, HC: 8 mg, ARAC: 16 mg
2-2.99	MTX: 10 mg, HC: 10 mg, ARAC: 20 mg
3-8.99	MTX: 12 mg, HC: 12 mg, ARAC: 24 mg
≥ 9	MTX: 15 mg, HC: 15 mg, ARAC: 30 mg

Larotrectinib: Oral/Nasogastric/Gastrostomy
Days: 1 - 28
Dose: 100 mg/m^2/dose BID (maximum of 100 mg/dose BID).

Only use larotrectinib provided for investigational use specifically for ADVL1823.

Note that this study will enroll very young children, but the dose will be based on body surface area for all patients regardless of age.

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.

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 X-A). Doses of larotrectinib capsules should be rounded to the nearest 25 mg (Appendix X-A). Calculated dosing volumes of larotrectinib liquid formulation should be rounded to the nearest 0.1 mL (2 mg) for doses ≤ 45 mg (in oral syringes ≤ 3 mL) and 0.2 mL (4 mg) for doses > 45 mg (in 5-10 mL oral syringes) for the actual deliverable dose (Appendix X-B).

All patients taking larotrectinib must complete a patient diary (Appendix VII-A and Appendix VII-B).

See Section 5.0 for Dose Modifications based on Toxicities.

Following completion of Cycle 1, patients with leukemia will have a disease evaluation. Patients with progressive disease or treatment failure will discontinue protocol therapy.

For all other patients, the next cycle (Section 4.6) starts on Day 29 or when the criteria in Section 4.1.3 are met (whichever occurs later). Patients achieving a response may discontinue protocol therapy at their physician's discretion to receive consolidative therapy (e.g. transplant).

Larotrectinib will be administered continuously without breaks between cycles unless the patient meets criteria for holding or discontinuing larotrectinib (Section 5.1).

Cycle 1, Cohort C

4.5 Therapy Subsequent to Cycle 1 (Cycles 2+), Cohort C

4.5.1 Therapy Delivery Map – Cycles 2+, Cohort C

This Therapy Delivery Map (TDM) relates to Cycles 2+ for Cohort C. Each cycle lasts 28 days.

_____
Patient COG ID number

_____
DOB

Criteria to start each cycle are listed in Section 4.1.3. Extensive treatment details are in Section 4.5.3.
This TDM is on 7 pages.

DRUG		ROUTE	DOSAGE	DAYS	IMPORTANT NOTES
Methotrexate OR Cytarabine OR Triples (methotrexate/ hydrocortisone/ cytarabine)	Methotrexate	Intrathecal	Age (yrs) / Dose < 1 — 7.5 mg 1-1.99 — 8 mg 2-2.99 — 10 mg 3-8.99 — 12 mg ≥ 9 — 15 mg	-3 to 1	Patients with ALL ONLY. Patients should receive one dose of intrathecal therapy between Days -3 to 1 of each cycle.
	Cytarabine	Intrathecal	Age (yrs) / Dose < 1 — 20 mg 1-1.99 — 30 mg 2-2.99 — 50 mg ≥ 3 — 70 mg	-3 to 1	Patients with AML ONLY. Patients should receive one dose of intrathecal therapy between Days -3 to 1 of each cycle.
	Triples (methotrexate/ hydrocortisone/ cytarabine)	Intrathecal	Age (yrs) / Dose < 1 — MTX: 7.5 mg, HC: 7.5 mg, ARAC: 15 mg 1-1.99 — MTX: 8 mg, HC: 8 mg, ARAC: 16 mg 2-2.99 — MTX: 10 mg, HC: 10 mg, ARAC: 20 mg 3-8.99 — MTX: 12 mg, HC: 12 mg, ARAC: 24 mg ≥ 9 — MTX: 15 mg, HC: 15 mg, ARAC: 30 mg	-3 to 1	Patients with ALL who are CNS 3 (see Section 10.8) at enrollment may receive either methotrexate or triples at their physician's discretion. Patients should receive one dose of intrathecal therapy between Days -3 to 1 of each cycle.
Larotrectinib IND# 141824		Oral/Nasogastric/ Gastrostomy Tube	100 mg/m^2/dose BID	1 – 28	Maximum dose = 100 mg/dose BID. See Appendix X-A and Appendix X-B for dosing nomograms.

Cycles 2 +, Cohort C

Ht _____cm **Wt _____kg** **BSA _____m^2**

CYCLE # _____

Date Due	Date Given	Day	**Larotrectinib** AM dose: ____ mg PM dose: ____ mg		**Methotrexate** ____mg	**Cytarabine** ____mg	**Hydrocortisone** ____mg	Studies
			Enter calculated dose above and actual dose administered below					
		Pre-	**AM Dose**	**PM Dose**				a – j, l – n
		1	_____ mg	_____ mg	_____ mg	_____ mg	_____ mg	i
		2	_____ mg	_____ mg				
		3	_____ mg	_____ mg				
		4	_____ mg	_____ mg				
		5	_____ mg	_____ mg				
		6	_____ mg	_____ mg				
		7	_____ mg	_____ mg				
		8	_____ mg	_____ mg				
		9	_____ mg	_____ mg				
		10	_____ mg	_____ mg				
		11	_____ mg	_____ mg				
		12	_____ mg	_____ mg				
		13	_____ mg	_____ mg				
		14	_____ mg	_____ mg				
		15	_____ mg	_____ mg				
		16	_____ mg	_____ mg				
		17	_____ mg	_____ mg				
		18	_____ mg	_____ mg				
		19	_____ mg	_____ mg				
		20	_____ mg	_____ mg				
		21	_____ mg	_____ mg				
		22	_____ mg	_____ mg				

Cycles 2 +, Cohort C

		23	_____ mg	_____ mg				
		24	_____ mg	_____ mg				
		25	_____ mg	_____ mg				
		26	_____ mg	_____ mg				
		27	_____ mg	_____ mg				
		28	_____ mg	_____ mg				k

See Section 5.0 for Dose Modifications for Toxicities and the COG Member website for Supportive Care Guidelines.

4.5.2 Required Observations for Cycles 2+, Cohort C

a. Hx/Wt/Ht/BSA. Within 7 days prior to subsequent cycles and at the end of study treatment.

b. Performance status. Prior to subsequent cycles and at the end of study treatment.

c. Physical exam (including VS). Prior to subsequent cycles and at the end of study treatment.

d. CBC/diff/platelets: Prior to subsequent cycles. If patients have Grade 4 neutropenia then CBCs should be checked every 3 to 4 days until recovery to Grade 3 or until meeting the criteria for dose limiting toxicity.

e. Electrolytes including Ca^{++}. Prior to subsequent cycles.

f. Creatinine, ALT, bilirubin. Prior to subsequent cycles.

g. Disease evaluation, lumbar puncture, and evaluation of any sites of extramedullary disease. After Cycles 2, 4, 6, 9, 12, 16, 20, and 24. Please refer to Section 10.4 for Confirmation of objective response by RECIST 1.1.

h. Bone marrow evaluation. With Disease evaluation. If the institutional investigator has determined the patient has progressed based on clinical or laboratory evidence, he/she may opt not to confirm this finding on marrow pathology.

i. Circulating tumor DNA. On Day 1 of Cycle 2, before Cycle 7, and at the time of progression. See Section 7.3.2 for details.

j. Tumor tissue submission. Submission of tumor tissue from any bone marrow evaluation while on study is required. Submission of tumor tissue from any biopsy after progression is optional. See Section 7.3.1 for details.

Cycles 2 +, Cohort C

k. Patient diary. Uploaded into RAVE at the end of each cycle. See Appendix VII-A and Appendix VII-B for details.

l. Pregnancy test. Prior to subsequent cycles. Sexually active patients must use an acceptable method of birth control.

m. Cerebral spinal fluid (CSF) cell count and differential. With disease evaluation.

n. Neurocognitive assessments. 6 months (± 4 weeks) after enrollment, 12 months (± 4 weeks) after enrollment, 24 months (± 4 weeks), and 4-5 years after enrollment. See Section 3.1.7 and Appendix XI for details.

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)

Cycles 2 +, Cohort C

4.5.3 Treatment Details: Cycles 2+, Cohort C

Methotrexate OR Cytarabine OR Triples (Methotrexate/Hydrocortisone/Cytarabine): Intrathecal
Days: -3 to 1
Dose: A single dose of IT therapy will be administered with each cycle 2+.
Note that patients who do not clear their CSF by the end of Cycle 1 will be removed from protocol therapy.

Methotrexate
Patients with ALL ONLY.

Age (yrs)	Dose
<1	7.5 mg
1-1.99	8 mg
2-2.99	10 mg
3-8.99	12 mg
≥ 9	15 mg

Cytarabine
Patients with AML ONLY.

Age (yrs)	Dose
< 1	20 mg
1 – 1.99	30 mg
2 – 2.99	50 mg
≥ 3	70 mg

Methotrexate (MTX)/Hydrocortisone (HC)/Cytarabine (ARAC)
Patients with ALL who were CNS 3 (see Section 10.8) at enrollment may receive either methotrexate or triples at their physician's discretion.

Age (yrs)	Dose
<1	MTX: 7.5 mg, HC: 7.5 mg, ARAC: 15 mg
1-1.99	MTX: 8 mg, HC: 8 mg, ARAC: 16 mg
2-2.99	MTX: 10 mg, HC: 10 mg, ARAC: 20 mg

Cycles 2 +, Cohort C

3-8.99	MTX: 12 mg, HC: 12 mg, ARAC: 24 mg
≥ 9	MTX: 15 mg, HC: 15 mg, ARAC: 30 mg

Larotrectinib: Oral/Nasogastric/Gastrostomy
Days: 1 - 28
Dose: 100 mg/m^2/dose BID (maximum of 100 mg/dose BID).

Only use larotrectinib provided for investigational use specifically for ADVL1823.

Note that this study will enroll very young children, but the dose will be based on body surface area for all patients regardless of age.

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.

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 X-A). Doses of larotrectinib capsules should be rounded to the nearest 25 mg (Appendix X-A). Calculated dosing volumes of larotrectinib liquid formulation should be rounded to the nearest 0.1 mL (2 mg) for doses ≤ 45 mg (in oral syringes ≤ 3 mL) and 0.2 mL (4 mg) for doses > 45 mg (in 5-10 mL oral syringes) for the actual deliverable dose (Appendix X-B).

All patients taking larotrectinib must complete a patient diary (Appendix VII-A and Appendix VII-B).

See Section 5.0 for Dose Modifications based on Toxicities.

Patients will have disease evaluation at the end of Cycles 2, 4, 6, 9, 12, 16, 20, and 24. Patients with progressive disease, treatment failure, or relapse at any time will discontinue protocol therapy.

For all other patients, the next cycle starts on Day 29 or when the criteria in Section 4.1.3 are met (whichever occurs later). Patients achieving a response may discontinue protocol therapy at their physician's discretion to receive consolidative therapy (e.g., transplant).

Cycles 2 +, Cohort C

5.0 DEFINITIONS AND DOSE MODIFICATION FOR TOXICITY

All dose modifications should be based on the worst preceding toxicity. The severity of adverse events will be graded utilizing the NCI CTCAE, Version 5.

5.1 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.

5.1.1 Non-Hematological Dose-Limiting Toxicity

5.1.1.1 Any Grade 3 or greater non-hematological toxicity with the specific exception of:

- Grade 3 fatigue, nausea, or vomiting of < 3 days duration
- Grade 3 ALT/AST/GGT that return to levels that meet initial eligibility criteria within 7 days of study drug interruption and that do not recur upon re-challenge with study drug. Note: For the purposes of this trial the ULN for ALT is defined as 45 U/L and the ULN for AST as 50 U/L. See Appendix XII for values that represent thresholds between CTCAE grades.
- Grade 3 or 4 total bilirubin elevation in infants who enrolled with physiologic jaundice and in patients with leukemia. For such patients, only the conjugated (direct) bilirubin will be considered a dose limiting toxicity.
- Grade 3 or 4 fever
- Grade 3 infection < 5 days duration
- Grade 3 weight gain
- Grade 3 hypophosphatemia, hypokalemia, hypocalcemia and/or hypomagnesemia responsive to oral supplementation

5.1.1.2 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 will be considered a dose limiting toxicity.

- Grade 2 allergic reactions that necessitate discontinuation of study drug will not be considered a dose-limiting toxicity.

5.1.2 Hematological dose limiting toxicity

5.1.2.1 Hematological dose limiting toxicity is defined as:

a) In patients with solid tumors evaluable for hematological toxicity (see Section 3.2.6.1a),

- Grade 4 thrombocytopenia (platelet count < 25,000/μL) or Grade 4 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

b) In patients with leukemia, DLT will be defined as failure to recover a peripheral ANC > 500/µL and platelets > 20,000/µL without transfusion by 42 days after the first treatment day, not due to malignant infiltration.

Note: Grade 3 or 4 febrile neutropenia will not be considered a dose-limiting toxicity.

5.2 Dose Modifications for Hematological Toxicity

5.2.1 If a patient experiences hematological dose limiting toxicity as defined in Section 5.1.2, the treatment will be held. Counts should be checked every 3-4 days during this time. If the toxicity resolves to meet eligibility parameters within 21 days of drug discontinuation, the patient may resume treatment with a dose reduction. The first dose reduction will be to 75 mg/m^2/dose BID (cap of 75 mg/dose BID), the second dose reduction will be to 50 mg/m^2/dose BID (cap of 50 mg/dose BID), and a third dose reduction of 25 mg/m^2/dose BID (cap of 25 mg/dose BID). Doses reduced for toxicity will not be re-escalated, even if there is minimal or no toxicity with the reduced dose, except as required due to patient growth to maintain the same BSA-based dose.

5.2.2 If toxicity does not resolve to meet eligibility parameters within 21 days of drug discontinuation, the patient must be removed from protocol therapy.

5.2.3 Up to 3 dose reductions are permitted per patient. If hematological dose-limiting toxicity recurs in a patient who has resumed treatment following three dose reductions, the patient must be removed from protocol therapy.

5.3 Dose Modifications for Non-Hematological Toxicity

5.3.1 If a patient experiences non-hematological dose-limiting toxicity as defined in Section 5.1.1, the treatment will be held. When the toxicity resolves to meet eligibility parameters or baseline within 21 days of drug discontinuation, the patient may resume treatment with a dose reduction. The first dose reduction will be to 75 mg/m^2/dose BID (cap of 75 mg/dose BID), the second dose reduction will be to 50 mg/m^2/dose BID (cap of 50 mg/dose BID), and a third dose reduction of 25 mg/m^2/dose BID (cap of 25 mg/dose BID). Doses reduced for toxicity will not be re-escalated, even if there is minimal or no toxicity with the reduced dose, except as required due to patient growth to maintain the same BSA-based dose.

5.3.2 If toxicity does not resolve to meet eligibility or baseline parameters within 21 days of drug discontinuation, the patient must be removed from protocol therapy.

5.3.3 Up to 3 dose reductions are permitted per patient. If a dose-limiting toxicity recurs in a patient who has resumed treatment following three dose reductions, the patient

must be removed from protocol therapy.

6.0 DRUG INFORMATION

6.1 [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

- [redacted]

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6.2 Cytarabine (07/13/15)

(Cytosine arabinoside, Ara-C, Cytosar®) NSC# 63878

6.2.1 Source and Pharmacology

Cytarabine appears to act through the inhibition of DNA polymerase. A limited, but significant, incorporation of cytarabine into both DNA and RNA has also been reported. It exhibits cell phase specificity, primarily killing cells undergoing DNA synthesis (S-phase) and under certain conditions blocking the progression of cells from the G1 phase to the S-phase. Cytarabine is metabolized by deoxycytidine kinase and other nucleotide kinases to the nucleotide triphosphate (Ara-CTP), an effective inhibitor of DNA polymerase. Ara-CTP is inactivated by a pyrimidine nucleoside deaminase, which converts it to the nontoxic uracil derivative (Ara-U). It appears that the balance of kinase and deaminase levels may be an important factor in determining sensitivity or resistance of the cell to cytarabine. It has an initial distributive phase $t_{½}$ of about 10 minutes, with a secondary elimination phase $t_{½}$ of about 1 to 3 hours. Peak levels after intramuscular or subcutaneous administration of cytarabine occur about 20 to 60 minutes after injection and are lower than IV administration. Intrathecally administered doses are metabolized and eliminated more slowly with a $t_{½}$ of about 2 hours.

6.2.2 Toxicity: (Intrathecal)

	Common Happens to 21-100 children out of every 100	**Occasional** Happens to 5-20 children out of every 100	**Rare** Happens to < 5 children out of every 100
Immediate: Within 1-2 days of receiving drug	Nausea, vomiting, fever, headache	Arachnoiditis	Rash, somnolence, meningismus, convulsions, paresis
Prompt: Within 2-3 weeks, prior to the next course			Myelosuppression, ataxia
Delayed: Any time later during therapy, excluding the above condition			Necrotizing leukoencephalopathy, paraplegia, blindness (in combination with XRT & systemic therapy)

6.2.3 Formulation

Cytarabine for Injection is available as a preservative free solution 20 mg/mL (5 mL, 50 mL per vial) or 100 mg/mL (20 mL vial). Hydrochloric acid and/or sodium hydroxide may be added to adjust the pH. Store intact vials of solution at 15°-30°C (59°-86°F). Cytarabine solutions should be protected from light.

6.2.4 Guidelines for Administration

See Treatment and Dose Modification sections of the protocol.

Intrathecal:

For intrathecal administration, dilute with 5-10 mL (or volume per institutional practice) preservative free 0.9% sodium chloride injection, lactated Ringer's

injection, Elliot's B solution. The volume of CSF removed should be equal to at least ½ the volume delivered.

Patient Age (years)	Recommended volume	10% CSF volume	CSF Volume *
1 – 1.99	5 – 10 mL	5 mL	50 ± 10 mL (babies)
2 – 2.99	5 – 10 mL	8 mL	80 ± 20 mL (younger children)
3 – 8.99	5 – 10 mL	10 mL	100 ± 20 mL (older children)
9 or greater	5 – 10 mL	13 mL	130 ± 30 mL (adults)

**Rieselbach, R.E. et.al. Subarachnoid distribution of drugs after lumbar injection; N Engl J Med. 1962 Dec 20; 267:1273-8*

Of Note: Larger volumes approximating at least 10% of the CSF volume, isovolumetric delivery, with the patient remaining prone after the procedure may facilitate drug distribution. These procedures have not been validated in clinical trials. They are allowed but not mandated for patients on COG studies.

Intrathecal cytarabine mixed in NS, lactated Ringer's injection, or Elliot's B solution is stable for 24 hours at 25ºC but contains no preservative and should be administered as soon as possible after preparation.

6.2.5 Supplier

Commercially available from various manufacturers. See package insert for further information.

6.3 Triples (05/08/12)

(Methotrexate/Hydrocortisone/Cytarabine, IT-3)

6.3.1 Source and Pharmacology

The intrathecal route of administration of a drug produces more consistent CSF drug concentrations at relatively smaller doses because of the volume difference between the CSF and blood compartments (140 mL vs. 3500 mL in an adult). (The CSF volume of children after the first 3 years is equivalent to that of an adult). Drug half-lives are longer as well because clearance is related to flow rather than metabolism or protein binding. Intrathecal methotrexate has a biphasic elimination curve from the CSF with a $t_{½}$ of 4.5 and 14 hours respectively. Following IT injection of cytarabine the elimination of the drug from the CSF is biphasic with a $t_{½}$ of 1 and 3.4 hours respectively which is 8-fold longer than the clearance from plasma. The elimination of hydrocortisone is similarly prolonged.

6.3.2 Toxicity

Intrathecal Triple Therapy (Methotrexate/Hydrocortisone/Cytarabine) Toxicity:

	Common Happens to 21-100 children out of every 100	**Occasional** Happens to 5-20 children out of every 100	**Rare** Happens to < 5 children out of every 100
Immediate: Within 1-2 days of receiving drug	Nausea, vomiting, fever, headache	Arachnoditis: (headache, fever,	Rash, anaphylaxis (L), paresis, bleeding into subarachnoid or subdural space (risk > with

		vomiting, meningismus and pleocytosis)	platelet counts <20,000), confusion, fatigue, disorientation, seizures
Prompt: Within 2-3 weeks, prior to the next course			Myelosuppression, somnolence, ataxia, cranial nerve palsy, transient and rarely permanent paraplegia (L), speech disorders
Delayed: Any time later during therapy, excluding the above condition		Cognitive disturbances (L), learning disabilities (L)	Demyelating leukoencephalopathy[1] (L), blindness[1]
Late: Any time after the completion of treatment			Progressive CNS deterioration[1]

[1] *May be enhanced by systemic therapy such as high dose methotrexate or cytarabine and/or cranial irradiation. (L) Toxicity may also occur later.*

6.3.3 Formulation and Stability

Methotrexate 25 mg/mL preservative free 2 mL vial or methotrexate 20 mg preservative free sterile powder for injection vial. Cytarabine 100 mg preservative free sterile powder for injection. Hydrocortisone sodium succinate 100 mg vial sterile powder for injection.

6.3.4 Guidelines for Administration

See Treatment and Dose Modification sections of the protocol.

For intrathecal administration, dilute each agent with 5-10 mL preservative free NS, lactated ringers or Elliot's B solution or as per institutional standard of practice. The volume of CSF removed should be equal to at least half the volume delivered.

Patient Age (years)	Doses (MTX/Hydrocortisone/Ara-C)	Recommended volume	10% CSF volume	CSF Volume *
0 – 0.99	7.5 mg / 7.5 mg / 15 mg	5-10 mL	5 mL	50 ± 10 mL (babies)
1 – 1.99	8 mg / 8 mg / 16 mg	5-10 mL	5 mL	50 ± 10 mL (babies)
2 – 2.99	10 mg / 10 mg / 20 mg	5-10 mL	8 mL	80 ± 20 mL (younger children)
3 – 8.99	12 mg / 12 mg / 24 mg	5-10 mL	10 mL	100 ± 20 mL (older children)
9 or greater	15 mg / 15 mg / 30 mg	5-10 mL	13 mL	130 ± 30 mL (adults)

**Rieselbach, R.E. et.al. Subarachnoid distribution of drugs after lumbar injection. N Engl J Med 1962 Dec 20; 267:1273-8*

Of note: Larger volumes approximating at least 10% of the CSF volume, isovolumetric delivery, with the patient remaining prone after the procedure may facilitate drug distribution. These procedures have not been validated in clinical trials. They are allowed but not mandated for patients on COG studies.

Intrathecal triples are stable in NS for 24 hours at 25ºC but contain no preservative and should be administered as soon as possible after preparation.

6.3.5 Supplier

Commercially available from various manufacturers. See package insert for further information.

6.4 Methotrexate (11/27/17)

(MTX, amethopterin, Trexall®) NSC# 000740

6.4.1 Source and Pharmacology

A folate analogue which reversibly inhibits dihydrofolate reductase, the enzyme that reduces folic acid to tetrahydrofolic acid. Inhibition of tetrahydrofolate formation limits the availability of one carbon fragments necessary for the synthesis of purines and the conversion of deoxyuridylate to thymidylate in the synthesis of DNA and cell reproduction. The polyglutamated metabolites of MTX also contribute to the cytotoxic effect of MTX on DNA repair and/or strand breaks. MTX cytotoxicity is highly dependent on the absolute drug concentration and the duration of drug exposure. MTX is actively transported across cell membranes. At serum methotrexate concentrations exceeding 0.1 µmol/mL, passive diffusion becomes a major means of intracellular transport of MTX. The drug is widely distributed throughout the body with the highest concentration in the kidney, liver, spleen, gallbladder and skin. Plasma concentrations following high dose IV MTX decline in a biphasic manner with an initial half-life of 1.5-3.5 hours, and a terminal half life of 8-15 hours. About 50% is bound to protein. After oral administration, approximately 60% of a 30 mg/m^2 dose is rapidly absorbed from the GI tract, with peak blood levels at 1 hour. At doses > 30 mg/m² absorption decreases significantly. Even at low doses absorption may be very erratic, varying between 23% and 95%. The elimination of MTX from the CSF after an intrathecal dose is characterized by a biphasic curve with half-lives of 4.5 and 14 hours. After intrathecal administration of 12 mg/m², the lumbar concentration of MTX is ~100 times higher than in plasma. (Ventricular concentration is ~ 10% of lumbar concentration). MTX is excreted primarily by the kidneys via glomerular filtration and active secretion into the proximal tubules. Renal clearance usually equals or exceeds creatinine clearance. Small amounts are excreted in the feces. There is significant entero-hepatic circulation of MTX. The distribution of MTX into third-space fluid collections, such as pleural effusions and ascitic fluid, can substantially alter MTX pharmacokinetics. The slow release of accumulated MTX from these third spaces over time prolongs the terminal half-life of the drug, leading to potentially increased clinical toxicity.

6.4.2 Toxicity

Intrathecal Therapy (Methotrexate Single Agent)
Toxicity:

	Common Happens to 21-100 children out of every 100	**Occasional** Happens to 5-20 children out of every 100	**Rare** Happens to < 5 children out of every 100

Immediate: Within 1-2 days of receiving drug	Nausea, headache	Arachnoditis: (headache, fever, vomiting, meningismus, nuchal rigidity, and pleocytosis)	Anaphylaxis, vomiting, seizures(L), malaise, confusion, back pain, rash, bleeding into subarachnoid or subdural space (risk > with platelet counts < 20,000),
Prompt: Within 2-3 weeks, prior to the next course			Myelosuppression, ataxia, somnolence, cranial nerve palsy, subacute myelopathy (paraparesis/paraplegia), speech disorders, pain in the legs, bladder dysfunction
Delayed: Any time later during therapy, excluding the above condition		Cognitive disturbances (L)[1], learning disability (L)[1]	Leukoencephalopathy[1] (L)
Late: Any time after the completion of treatment			Progressive CNS deterioration[1]

[1] *May be enhanced by HDMTX and/or cranial irradiation.*
(L) Toxicity may also occur later.

6.4.3 Formulation and Stability

Methotrexate for Injection is available as a 25 mg/mL solution in 2, 10, and 40 mL preservative free vials. The 2, 10, and 40 mL solutions contain approximately 0.43, 2.15, and 8.6 mEq sodium per vial, respectively.

Sterile methotrexate solution is stable at 20º-25ºC (68º-77ºF); excursions permitted to 15º-30ºC (59º-86Fº). Protect from light.

6.4.4 Guidelines for Administration

See Treatment and Dose Modifications sections of protocol.

For Intrathecal Use: Use **preservative free** 25 mg/mL solution.

For intrathecal administration, dilute with 5-10 mL preservative free NS, lactated Ringer's, or Elliot's B solution as per institutional standard of practice. The volume of CSF removed should be equal to at least half the volume delivered.

Patient Age (years)	Methotrexate dose	Recommended volume	10% CSF volume	CSF Volume *
1–1.99	8 mg	5–10 mL	5 mL	50 ± 10 mL (babies)
2–2.99	10 mg	5-10 mL	8 mL	80 ± 20 mL (younger children)
3–8.99	12 mg	5-10 mL	10 mL	100 ± 20 mL (older children)
9 or greater	15 mg	5-10 mL	13 mL	130 ± 30 mL (adults)

*Rieselbach, R.E. et.al. Subarachnoid distribution of drugs after lumbar injection; N Engl J Med. 1962 Dec 20; 267:1273-8

Of Note: Larger volumes approximating at least 10% of the CSF volume, isovolumetric delivery, with the patient remaining prone after the procedure may facilitate drug distribution. These procedures have not been validated in clinical trials. They are allowed but not mandated for patients on COG studies.

Diluted methotrexate for intrathecal administration is stable for 24 hours at 25ºC but contains no preservative and should be administered as soon as possible after preparation.

6.4.5 Supplier

Commercially available from various manufacturers. See package insert for further information.

7.0 EVALUATIONS/MATERIAL AND DATA TO BE ACCESSIONED

Timing of protocol therapy administration, response assessment studies, and surgical interventions are based on schedules derived from the experimental design or on established standards of care. Minor unavoidable departures (up to 72 hours) from protocol directed therapy and/or disease evaluations (and up to 1 week for surgery) for valid clinical, patient and family logistical, or facility, procedure and/or anesthesia scheduling issues are acceptable (except where explicitly prohibited within the protocol).

7.1 Required and Optional Clinical, Laboratory and Disease Evaluations

See Section 3.2 for eligibility requirements and for requirements to initiate protocol therapy. Laboratory tests used to determine eligibility may be counted as the Week 1 studies if the tests were drawn within 7 days of treatment start and there have been no significant changes in the patient's clinical status.

STUDIES TO BE OBTAINED	Pre-Study	Cycle 1	Prior to Subsequent Cycles^	End of Study Treatment
History	X		X	X
Physical exam with vital signs, including neurologic examination	X		X	X
Height, weight, BSA	X		X	X
Performance status	X		X	X
CBC, differential, platelets[1]	X	Weekly	X	X
Electrolytes including Ca^{++}	X		X	X
Creatinine, ALT, bilirubin	X		X	X
Albumin	X			
Pregnancy test[2]	X		X	X
Disease evaluation[3]	X		X[3]	X
Bone marrow evaluation[7,8]	X		With Disease Evaluation	
Cerebral spinal fluid cell count and differential[11]	X	X	With Disease Evaluation	
Circulating tumor DNA[4]	X	X	X	X
Tumor tissue submission[5]	X		X[9]	X[10]
Patient diary[6]		X	X	
CSF and plasma pharmacokinetics[12]		X		
Neurocognitive assessments[13]		X	X	X

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

1 If patients develop Grade 4 neutropenia then CBCs should be checked every 3 to 4 days until recovery to Grade 3 or until meeting the criteria for dose limiting toxicity.

2 Women of childbearing potential require a negative pregnancy test prior to starting protocol therapy; sexually active patients may not participate unless they have agreed to use an effective double barrier contraceptive method. Abstinence is an acceptable method of birth control.

[3] Disease evaluation includes CT or MRI of all known sites of disease. For patients with solid tumors, disease evaluation will be performed after Cycles 2, 4, 6, 9, 12, 16, 20 and 24. For patients with leukemia, disease evaluation will occur after Cycles 1, 2, 4, 6, 9, 12, 16, 20, and 24. Please note that for solid tumor patients, 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. . Please refer to Section 10.4 for Confirmation of objective response by RECIST 1.1. Patients who enter follow-up after completion of planned therapy per Section 4.1 should follow the disease evaluation schedule defined in Section 7.2 and do not require disease evaluation at the time of discontinuation of larotrectinib.

[4] See Section 7.3.2 for timing of circulating tumor DNA (ctDNA) studies. ctDNA will be obtained at enrollment, Day 15 of Cycle 1 of larotrectinib therapy, Day 1 of Cycle 2 of larotrectinib therapy, at the end of Cycle 6 of larotrectinib therapy (prior to Cycle 7 or local control), at the end of study treatment, and at the time of progression.

[5] See Section 7.3.1 for details regarding tumor tissue submission. If tissue blocks or slides are unavailable, the study chair must be notified prior to study enrollment.

[6] Patient diary (see Appendix VII-A and Appendix VII-B) should be reviewed and uploaded into RAVE at the end of each cycle.

[7] Bone marrow aspirate and/or biopsy only required in patients with leukemia or solid tumors with known bone marrow metastasis on the basis of history, symptoms, laboratory evaluation or other clinical data.

[8] Bone marrow aspirate and/or biopsy should only be performed on patients with leukemia or solid tumors with bone marrow involvement at baseline. If the institutional investigator has determined the patient has progressed based on clinical or laboratory evidence, he/she may opt not to confirm this finding on marrow pathology.

[9] Submission of tumor tissue from any surgical resection or bone marrow evaluation for patients with bone marrow involvement by tumor, including patients with leukemia, while on study is required. For patients who undergo resection of their tumor while on study, operative reports and hospital discharge summaries must be uploaded into RAVE following surgical resection.

[10] Submission of tumor tissue from any biopsy after progression is optional.

[11] CSF sampling for cell count and differential will be performed only for patients with leukemia. To be performed within 7 days prior to Cycle 1 and at the time of each disease evaluation. CSF will also be obtained on Days 8, 15, and 22 of Cycle 1 for those patients who are receiving intrathecal therapy.

[12] See Section 7.3.3. CSF and plasma pharmacokinetics will be obtained at the end of Cycle 1 at the time of disease evaluation for all patients with leukemia. Additionally, CSF and plasma pharmacokinetics will also be obtained on Days 8, 15, and 22 of cycle 1 for patients who are receiving intrathecal therapy.

[13] See Appendix XI. Within 4 weeks after enrollment; 6 months (± 4 weeks) after enrollment, 12 months (± 4 weeks) after enrollment; 24 months (± 4 weeks) after enrollment, and 4-5 years after enrollment. Timing should be based on enrollment, regardless of whether the patient is receiving larotrectinib or is in Follow-up.

7.2 Follow-up

STUDIES TO BE OBTAINED	While in Follow-up after Completion of Planned Therapy per Section 4.1[1]	While in Follow-up for Other Reasons[6]
History, including any anti-cancer therapy received	X[2]	X
Physical exam with VS, including neurologic examination	X[2]	X
Ht, Wt, BSA	X[2]	X
Disease evaluation	X[2]	X
Circulating tumor DNA	X[3]	
Tumor tissue submission	X[4]	X[4]
Neurocognitive assessments	X[5]	

[1] Patients who have progressive disease while in Follow-up after completion of planned therapy will be subsequently monitored per the table for patients in Follow-up for other reasons.

[2] At 3, 6, 12, 18, 24, 30, 36, and 48 months after discontinuation of larotrectinib, and annually thereafter for up to 5 years from the date of study entry. Studies may be obtained ± 14 days of the indicated timepoint.

[3] See Section 7.3.2 for timing of circulating tumor DNA (ctDNA) studies. For patients in Follow-up, ctDNA will be obtained at the time of progression.
[4] Submission of tumor tissue from any biopsy after progression is optional.
[5] See Appendix XI. For patients in Follow-up, neurocognitive tests will be obtained 6 months (± 4 weeks) after enrollment, 12 months (± 4 weeks) after enrollment, 24 months (± 4 weeks) after enrollment, and 4-5 years after enrollment. Timing should be based on enrollment, regardless of whether the patient is receiving larotrectinib or is in Follow-up.
[6] Follow-up for patients who discontinue therapy on this study for reasons other than completion of planned therapy (Section 8.0) is required at 30 days, 6 months, and 12 months from the last date of protocol therapy, and annually thereafter for up to five years from the date of study entry.

See COG Late Effects Guidelines for recommended post treatment Follow-up: http://www.survivorshipguidelines.org/

Note: Follow-up data are expected to be submitted per the Case Report Forms (CRFs) schedule.

7.3 Correlative Biology Studies

7.3.1 Tumor Assessment (Archival: Required and Biopsy: Optional)

7.3.1.1 Description of Studies

Histological review, next generation sequencing, and immunohistochemistry will be performed on tumor tissue from the time of diagnosis to evaluate the morphology of TRK fusion cancers and retrospectively confirm the presence of TRK fusions. Tumor tissue from post-therapy resection specimens will be reviewed to determine histologic response to therapy. Tissue from diagnosis and (if obtained) time of disease progression/recurrence will be used to evaluate resistance mechanisms to TRK inhibition.

7.3.1.2 Sample Collection and Handling Instructions (Appendix III)

a. Submission of archival tumor tissue from the initial diagnostic procedure is required and will be requested to be sent following patient enrollment. Patients without diagnostic tumor available may enroll with prior approval of the principal investigator or designee.
b. Tumor tissue submission is required following resection at time of local control and from bone marrow evaluations for patients with bone marrow involvement by tumor, including patients with leukemia.
c. In the event that a patient experiences disease progression and undergoes clinically-indicated biopsy or surgery, tumor tissue will be requested for analysis of TRK fusions and resistance mechanisms.

7.3.1.3 Sample Requirements

a. All samples must be labeled with two unique identifiers and all data should be recorded on the Tissue Studies Form (Appendix III) including a copy of the pathology report, which must accompany the sample.
b. For patients with solid tumors:

i. In total, 1 H&E stained slide from all available formalin-fixed paraffin embedded (FFPE) tissue blocks and 15 unstained slides from the most representative block (10 unstained slides will be accepted in cases with limited tissue) or the block itself should be submitted from each surgical procedure (initial diagnosis, post-therapy resection and tumor progression/recurrence [if applicable]). The unstained slides must be from FFPE block(s) for which H&E slides are submitted. From post-therapy resections, unstained slides should include viable tumor if present. Further, if viable tumor is present near margin, these slides should be prioritized to allow for immunohistochemical assessment of isolated tumor cells. These slides will used for the following analyses:

- Histology review and TRK immunohistochemistry: 1 H&E stained slide from all available formalin-fixed paraffin embedded (FFPE) tissue blocks and 2 unstained slides.
- Fusion sequencing assay: 10 unstained slides derived from formalin-fixed paraffin embedded (FFPE) tissue (5 unstained slides will be accepted in cases with limited tissue).
- Sequencing to identify the fusion breakpoint for ctDNA analysis and to evaluate mechanisms of resistance to TRK inhibition: 3 unstained slides derived from formalin-fixed paraffin embedded (FFPE) tissue

c. For patients with leukemia or solid tumors with bone marrow involvement without suitable FFPE tumor tissue available:

i. In total, 1 Wright Giemsa stained bone marrow aspirate smear, 1 Wright Giemsa stained peripheral blood smear (if available), 1 H&E stained slide from the bone marrow biopsy (if available), 1 H&E stained slide from clot section (if available), 2 unstained slides from the clot section or core biopsy (if available), and 5-8 unstained bone marrow aspirate smears should be submitted from the baseline bone marrow evaluation and from each bone marrow evaluation while on study. These slides will used for the following analyses:

- Histology review and TRK immunohistochemistry: 1 Wright Giemsa stained bone marrow aspirate smear, 1 Wright Giemsa stained peripheral blood smear (if available), 1 H&E stained slide from the bone marrow biopsy, 1 H&E stained slide from clot section (if available), and 2 unstained slides from the clot section or core biopsy.
- Fusion sequencing assay: 2-5 unstained bone marrow aspirate smears.

- Sequencing to identify the fusion breakpoint for ctDNA analysis and to evaluate mechanisms of resistance to TRK inhibition: 3 unstained bone marrow aspirate smears.

7.3.1.4 Sample Shipping Instructions

a. For FFPE slides (stained and unstained) and bone marrow aspirate smears, ship to the following address:

Boston Children's Hospital, Dept. of Pathology BCH3027
Laboratory for Molecular Pediatric Pathology (LaMPP)
300 Longwood Ave.
Boston, MA
02115

7.3.2 Circulating tumor DNA (Optional)

7.3.2.1 Description of Studies

Blood will be collected to evaluate the ability to detect TRK fusions at enrollment, the clearance of detectable circulating tumor DNA (ctDNA) during therapy, and resistance mutations at progression.

7.3.2.2 Sampling Schedule (see Appendix IV)

Plasma samples will be collected in consenting patients at the following time points:

- Post-enrollment, prior to start of protocol therapy
- Cycle 1, Day 15: Prior to AM Larotrectinib dose
- Cycle 2, Day 1: Prior to AM Larotrectinib dose
- Cycle 6, Day 29 (Cycle 7, Day 1 or prior to local control): prior to AM larotrectinib dose
- End of study treatment
- At the time of progression

7.3.2.3 Streck Tube Acquisition

Site personnel should email ADVL1823@dfci.harvard.edu and copy the study-assigned ADVL1823 Protocol Coordinator as soon as possible following patient consent to the ctDNA correlative to request Streck tubes. Sites will be sent enough Streck tubes to cover every ctDNA collection time point. Sites should specify their preferred shipping address in their initial email request.

7.3.2.4 Sample Collection and Handling Procedures

For patients who choose to participate in both the ctDNA studies and PK studies, the ctDNA sample should be collected prior to the PK sample on Cycle 1, Day 15 to avoid heparin contamination of the ctDNA sample.

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

- For patients $\geq$ 10 kg, collect 20 mL (10 ml per tube x 2 tubes)
- For patients $\geq$ 5 kg but < 10kg, collect 10 mL (1 tube)
- For patients < 5 kg, collect 5 mL (1 tube)

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 5 mL increments (i.e., 0, 5, 10, or 20 mL should be collected such that each Streck Cell-Free DNA blood collection tube [BCT] has a minimum of 5 mL).

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.

7.3.2.5 Sample Shipping Instructions

Streck tubes must be labeled with the patient's study registration number, the study I.D., the specimen type (blood) and the date and time the sample was drawn.

Streck tubes should be shipped by FedEx Priority Overnight at **room temperature** to the Crompton laboratory for immediate separation, extraction, and storage of plasma and cellular DNA. Samples should be shipped from Monday through Thursday for Tuesday through Friday delivery. If blood is collected in the Streck tube on Friday, over the weekend or on the day before a holiday, the sample can be stored at **room temperature** until shipped on the next business day.

Data should be recorded on the ctDNA Correlative Study Form (Appendix IV), which must accompany the sample(s).

Ship specimens to the following address:

[redacted]

[redacted]

7.3.3 CSF and Plasma Pharmacokinetics (Required for Patients in Cohort C, N/A for Patients in Cohorts A & B)

7.3.3.1 Description of Studies

Plasma and CSF concentrations of larotrectinib will be determined to evaluate the penetration of larotrectinib across the blood brain barrier in patients having lumbar punctures for intrathecal chemotherapy administration.

7.3.3.2 Sampling Schedule (See Appendix VIII)

CSF samples (0.5 ml) will be collected at the following time points for patients with leukemia:

- First disease evaluation after starting therapy

In addition, CSF samples (0.5 ml) will be collected at the following time points ONLY for leukemia patients receiving intrathecal therapy:

- Cycle 1, Day 8
- Cycle 1, Day 15
- Cycle 1, Day 22

CSF samples will be collected at the time of lumbar puncture. A plasma sample (3 ml) will be obtained as close as possible to the same time as the CSF sample. There is no required time window from the most recent larotrectinib dose, but the dose and time of administration will be recorded. When possible, it is preferred that the lumbar puncture occur >1 hour after the most recent larotrectinib dose.

7.3.3.3 Sample Collection and Handling Instructions

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

7.3.3.3.1 CSF Samples

Supplies

- 1 Medium biohazard bag
- 2 Cryovials (2 mL each)
- 1 Plastic transfer pipette
- 2 Cryolabels
- 2 Absorbent Pads

- 1 Federal Express Return Shipping Label (Alturas)
- 1 Dry Ice label
- CSF collection kit
- Alcohol swab for cleansing site
- Dry sterile gauze
- Needle disposal container

Collection Procedure

1. Collect 0.5 mL of CSF using your institution's recommended procedure for standard CSF collection technique. Record the exact time that the sample is drawn along with the exact time that the drug is administered.

2. Complete the cryovial labels with subject ID and visit. Adhere the cryovial labels to each of the cryovials.

3. Divide CSF equally between two cryovials. Screw on the lid.
    a. Place the labeled cryovials with CSF into an 81-well cryovial box.

4. Immediately transfer the cryovials filled with CSF to a -80°C freezer.
    a. Only 1 cryovial should be shipped within 1 week to Alturas after each collection. The other should be stored on site in case there is an issue with the first vial.

7.3.3.3.2 Plasma Samples

Collection Procedure

Blood samples (3 ml) will be collected in K_2 EDTA lavender top tubes for PK evaluation. This sample should be collected as close as possible to the same time as the corresponding CSF sample. Record the exact time that the sample is drawn along with the exact time that the drug is administered.

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. The cryovial should be shipped within 1 week to Alturas after each collection.

7.3.3.4 Documentation

1. Ensure the cryovials are properly labeled.

2. Complete the Specimen Submittal Form (Appendix VIII)

3. Complete the dry ice sticker.

   a. On the day of shipment, fill out the dry ice sticker with the shipper's name, address, and weight of dry ice. Ensure at least 15 pounds (~ 7 kg.) of dry ice for shipment.

7.3.3.5 Sample Shipping Instructions

1. Specimens may be shipped to Alturas, Monday through Wednesday only:

   Alturas Analytics, Inc.
   1324 Alturas Dr.
   Moscow, ID 83843
   Phone: (208) 883-3400
   Fax: (208) 974-4475

2. Obtain a large Styrofoam shipping box of adequate size to hold 15-20 pounds (~7-9 kg.) of dryice along with the 81-well box containing the frozen cryovials.

3. Fill the Styrofoam shipping box half full (~10 pounds) of dry ice.

4. Transfer samples from the freezer to the dry ice. Ensure the container is sufficiently surrounded by dry ice. Do not allow the samples to thaw.

5. Fill the rest of the container with dry ice. Ensure that the container is sufficiently filled with dry ice (at least 15 pounds) and the samples are completely covered.

6. Place the completed Specimen Submittal Form (Appendix VIII) inside the cardboard shipping box (but outside the Styrofoam to avoid getting the paper wet). Close and seal shipping box lid with packing tape.

7. Attach the FedEx Return shipping label to the shipper kit box.

   a. Ensure the **return shipping label for Alturas** is selected for shipping.

8. Attach the dry ice sticker to the shipper kit box.

9. Contact Federal Express for shipment (1-800-GOFEDEX or 1-800-466-6669; toll free in the US).

10. Email a copy of the Specimen Submittal Form (Appendix VIII) to the following email addresses:

    [redacted]
    samplecustodian@alturasanalytics.com

11. Include the Protocol ID, Patient ID, and FedEx Tracking Number in the email. Please write the tracking number without spaces (i.e. Correct = 000100020003; Incorrect = 0001 0002 0003).

7.4 Imaging Central Review

Central imaging review will be conducted for all imaging through Cycle 6. Additional central review of imaging evaluations performed for study participants during therapy or follow up on individual basis will occur as determined by the study committee and study radiologist. COG Operations Center will notify the Imaging Research Center of any patient requiring central review. The Imaging Research Center will then request that the treating institution forward the pertinent images for central review. The central image evaluation results will be entered into Rave for review for data analysis. Central imaging review will be performed retrospectively and will not be used to guide individual patient management.

The images are to be forwarded electronically to the Imaging Research Center at Children's Hospital Los Angeles via the ImageInBox.

COG institutions that are not connected via the ImageInBox can send the images on hard copy film, CD ROM, DVD, USB flash drive or by FTP. Submitted imaging studies should be clearly marked with the COG patient ID, study number (ADVL1823) and date, and shipped to Syed Aamer at the address below:

Syed Aamer, MBBS, CCRP
Administrator, Imaging Research Center
Children's Hospital Los Angeles
4650 Sunset Boulevard, MS # 81
Los Angeles, CA 90027
Phone: (323) 361-3898
Fax: (323) 361-3054
Email: saamer@chla.usc.edu

8.0 CRITERIA FOR REMOVAL FROM PROTOCOL THERAPY AND OFF STUDY CRITERIA

8.1 Criteria for Removal from Protocol Therapy

a) Clinical (including physical examination or serum tumor markers) or radiographic evidence of progressive disease or treatment failure while on study (See Section 10.3.3, Section 10.5.2, Section 10.5.3, Section 10.6.6, and Section 10.7.5).
b) Adverse Events requiring removal from protocol therapy, as stated in Section 5.0.
c) Patients who receive concurrent investigational therapy or anticancer therapy, as stated in Section 3.3.2.3 and Section 3.3.2.4.
d) Refusal of further protocol therapy by patient/parent/guardian.
e) Physician determines it is in patient's best interest.
f) Repeat eligibility studies (if required) are outside the parameters required for eligibility prior to the start of larotrectinib (Section 3.2.6).
g) Non-compliance that in the opinion of the investigator does not allow for ongoing participation.
h) Patients who develop a second malignant neoplasm.
i) Study is terminated by sponsor.
j) Pregnancy
k) Completion of planned therapy per Section 4.1.
l) Patients with leukemia who have persistent CNS disease that does not clear by the end of Cycle 1.

Patients who are removed from protocol therapy are to be followed until they meet the criteria for Off Study (Section 8.2). Follow-up data will be required unless consent was withdrawn.

8.2 Off Study Criteria

a) Death.
b) Lost to follow-up.
c) Patient enrollment onto another COG anti-cancer therapeutic study (e.g., at recurrence).
d) Withdrawal of consent for any further data submission.
e) The fifth anniversary of the date the patient was enrolled on this study.
f) The patient does not receive protocol treatment after study enrollment.

9.0 STATISTICAL CONSIDERATIONS

9.1 Sample Size and Study Duration

One disease stratum (infantile fibrosarcoma, Cohort A) has been identified as the primary cohort for reporting upon completion of evaluation. The evaluation rule is described in Section 9.2 below. In addition to the main stratum, enrollment into each of the following tumor

groups ("secondary strata"): (B) Other newly-diagnosed TRK fusion solid tumors, and (C) Relapsed/refractory acute leukemias; will be open to accrual. If nine response-evaluable patients of a particular histology are enrolled in either of the secondary strata, the two-stage design described in Section 9.2 below will be applied to that particular histology. (That is, up to twelve additional response-evaluable patients with that tumor type may be studied.) Upon completion of enrollment to Cohort A, the study committee will make a decision on whether to continue enrollment to the secondary strata or to close the study. This will be based on the enrollment and response rates observed in the strata up until that date.

Review of SEER data indicates the following entry rate can be expected, assuming that 33% of patients with infantile fibrosarcoma have resectable disease at diagnosis, and 33% of the remaining patients don't enroll on this study for other reasons:

Disease Group/Strata	Patients/Year
Infantile fibrosarcoma	8

Assuming an annual enrollment rate of 8 patients/year in Cohort A, the probability of accruing 9 patients to complete the initial stage of evaluation within 17 months is 80% and within 26 months is 90%. The corresponding probability for enrolling 21 patients in 37 months is 80% and within 47 months is 90%. Allowing for a 10% inevaluability rate, a minimum of 9 and a maximum of 70 patients will be enrolled. The study will likely require 3 to 4 years for sufficient patient enrollments to evaluate larotrectinib in IFS.

Assuming all three cohorts fill completely, a maximum of 63 evaluable patients will enroll. Accounting for up to an estimated 10% of patients in Cohort A who do not meet the definition of evaluable for response and therefore require replacement, a maximum of 70 total patients will enroll.

9.2 Study Design

The primary endpoint will be objective response according to the disease specific criteria in Section 10. The best response of disease to larotrectinib will be examined separately in the primary disease stratum and the secondary strata if sufficient enrollment occurs. The following Simon's minimax two-stage design will be used in each stratum.

	Cumulative Number of Responses	Decision
Stage 1: Enter 9 patients	5 or fewer	Terminate the trial: agent ineffective
	6 or more	Inconclusive result, continue trial (proceed to Stage 2)
Stage 2: Enter 12 additional patients	15 or fewer	Terminate the trial: agent ineffective
	16 or more	Terminate the trial: agent effective

We will consider larotrectinib not of sufficient interest for further evaluation in a disease category if the true response rate is 60% and of sufficient activity if the true response rate is 85%. If larotrectinib has a true response rate of 60%, the rule described above will

identify it of sufficient activity for further study with probability 9.05% (type I error), and the trial will have an expected sample size of 14.8 with 51.74% probability of early termination. If larotrectinib has a true response rate of 85%, the rule described above will identify it of sufficient activity for further study with probability 90.40% (power against the alternative hypothesis $p = 0.85$).

If there are 9 confirmed objective responses before observing any nonresponders in Cohort A, consideration of closing Cohort A to enrollment will be discussed by all approved parties (i.e., DSMC, Bayer, and CTEP) following release of the response data by the DSMC. Nine responses among the first 9 response evaluable patients will exclude a true response rate of 60% with $p = 0.014$. If at any time there are 16 confirmed responses in a cohort, then enrollment to that cohort will be closed as the efficacy endpoint for that cohort has been met.

9.3 Methods of Analysis

Response criteria are described in Section 10.2. A responder is defined as a patient who achieves a best response (as defined in Section 10.3.4) 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 accounting for the two-stage design.

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 attribution(s) to the study regimen.

Time-to-event analyses (time to progression, progression-free survival, overall survival, and duration of response) will be computed one year after the last enrollment in a stratum. Duration of response will be defined among patients with a confirmed best response of either PR and CR, and will be defined as the time from the first observation of either PR or CR until either the first observation of PD (event) or last known observation of the patient (censored observation).

9.3.1 Adverse Event Monitoring Rule

We will use a Bayesian rule to monitor for protocol-specific toxicities (list given below). We will assume a beta prior distribution with $\alpha = 0.52$ and $\beta = 2.08$. At least once per month, we will calculate the posterior probability (given the data) that the probability of protocol-specific toxicity exceeds the 20% threshold:

$$\mathrm{P}(p_{\text{protocol-specified toxicities}} > 20\% \mid \text{Data}) = \int_{0.2}^{1} \frac{\binom{n}{x} p^{x}(1-p)^{n-x} \dfrac{\Gamma(2.6)}{\Gamma(0.52)\Gamma(2.08)} p^{-0.48}(1-p)^{1.08}}{\int_{0}^{1} \binom{n}{x} q^{x}(1-q)^{n-x} \dfrac{\Gamma(2.6)}{\Gamma(0.52)\Gamma(2.08)} q^{-0.48}(1-q)^{1.08}\, dq}\, dp$$

Here n is the number of protocol-specific toxicity-evaluable cycles and x is the number of such cycles on which a protocol-specific toxicity event is observed. If there is strong evidence (posterior probability of at least 70% with at least 2 observed toxicities) that there is a per course protocol-specific toxicity probability

of more than 20%, such information will be presented to the DSMC. Examples of situations in which this rule will indicate protocol-specific toxicities have been noted and are presented below:

Number of failures	Number of patient-cycles
2	6
3	10
4	14
5	19
6	23
7	28
8	32
9	37
10	41
11	46
12	51
13	55
14	60

Protocol-specific toxicities of interest include CTCAE v5 Grade 3 or higher fatigue, ataxia, dizziness, ALT increase, AST increase, neutropenia, thrombocytopenia, nausea, and vomiting. For the purpose of this toxicity monitoring rule, patients with leukemia or solid tumors with bone marrow metastases are not evaluable for hematologic toxicities (neutropenia or thrombocytopenia) unless these persist for greater than 14 days after a bone marrow is negative for malignancy and the patient does not have evidence of recurrent disease.

9.4 Evaluability for Response

Any patient who is enrolled and receives at least one dose of larotrectinib will be considered evaluable for response provided: (1) the patient demonstrates progressive disease or death while on protocol therapy; or (2) the patient is observed on protocol therapy for at least one cycle and the tumor is not removed surgically prior to the time complete response or partial response is confirmed, or (3) the patient demonstrates a complete or partial response as confirmed according to protocol criteria. Patients who demonstrate a complete or partial response confirmed by central review will be considered to have experienced a response for the application of the rule given in Section 9.2. All other patients will be considered non-responders. The evaluation period for determination of the best response will be 6 treatment cycles. 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. See Section 7.4 regarding shipping instructions. 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.

9.5 Evaluability for Toxicity

All patients who either (1) receive at least 85% of the required dose of larotrectinib according to protocol guidelines in any cycle of treatment or (2) experience a toxicity at least possibly related to the study regimen will be considered in the evaluation of toxicity.

9.6 Sex and Minority Accrual Estimates

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

DOMESTIC PLANNED ENROLLMENT REPORT					
Racial Categories	**Ethnic Categories**				**Total**
	Not Hispanic or Latino		**Hispanic or Latino**		
	Female	**Male**	**Female**	**Male**	
American Indian/ Alaska Native					
Asian					
Native Hawaiian or Other Pacific Islander					
Black or African American	8	6			14
White	13	19	9	10	51
More Than One Race					
Total	21	25	9	10	65

INTERNATIONAL (including Canadian participants) PLANNED ENROLLMENT REPORT					
Racial Categories	**Ethnic Categories**				**Total**
	Not Hispanic or Latino		**Hispanic or Latino**		
	Female	**Male**	**Female**	**Male**	
American Indian/ Alaska Native					
Asian					
Native Hawaiian or Other Pacific Islander					
Black or African American					
White	2	3			5
More Than One Race					
Total	2	3			5

This distribution was derived from all patients enrolled on prior COG DVL Phase 2 trials.

9.7 Analysis of CSF to Plasma Larotrectinib Concentrations

Larotrectinib concentration in plasma and CSF will be quantified by a validated LC-MS assay for patients with leukemia who have sampling while on study. The ratio of non-protein bound larotrectinib concentration in the plasma and CSF will be calculated. These ratios will be summarized with simple summary statistics, including means, medians, ranges, and standard deviations (if numbers and distribution permit).

9.8 Analysis of Biological and Correlative Endpoints

9.8.1 Histology and Immunohistochemistry

A descriptive review of tumor histology will be performed. This will include central review of all cases at the time of diagnosis. The pattern of immunohistochemical staining with a pan-TRK antibody will be correlated with fusion type, to evaluate use as a surrogate marker of fusion status and better define the patterns of expression as they relate to individual fusion partners and amongst various tumor types. Post-therapy specimens will be reviewed to document patterns of tumor response to therapy and provide centralized review of margin status where applicable. When possible pan-TRK immunohistochemistry will be performed to aid in evaluation of the infiltrative border of the tumor and to confirm the persistence of pan-TRK protein expression in the setting of neoadjuvant larotrectinib.

9.8.2 Central Confirmation of TRK Fusions by Next Generation Sequencing

Anchored multiplex PCR (AMP) is a method for detecting gene rearrangements without prior knowledge of fusion partners (2). Double-stranded cDNA is end-repaired, adenylated, and ligated to universal half functional adapters. Two rounds of nested low-cycle PCR then enriches targets and renders the adapters on the enriched targets functional for sequencing. The assay assesses nucleic acid sequences with a target-specific nested primer on one side, and a universal adapter on the other, such that a priori knowledge of one fusion partner is needed. The assay used in this study includes target-specific primers for all three NTRK genes and thus can detect TRK fusions with both known and novel 5' fusion partners. The method is effective with low nucleic acid input from formalin fixed paraffin-embedded specimens.

VALIDATION: Validation will be completed by December 2018. Thus far we have run over 100 cases, including 60 unique fusion-positive samples. 100% of samples successfully completed library preparation with acceptable QC metrics, including samples derived from both FFPE (5 unstained slides per case) and fresh/frozen tissue as well as samples across a range of nucleic acid input (down to 10 ng of total nucleic acid). So far, fusions have been correctly identified in over 95% of cases. A detailed report will be available when validation is complete.

SPECIFIC QUALITY CONTROL AND QUALITY ASSURANCE PARAMETERS TO DETERMINE SATISFACTORY PERFORMANCE OF THE BIOINFORMATICS PIPELINE:

1. Percentage of nucleated cells that are tumor cells
2. Nucleic acid concentration
3. Library nucleic acid quantification
4. Cluster density
5. Percentage of bases higher than the minimum Phred score (Q30) of all bases called
6. Demultiplexing success
7. Percentage of reads passing a minimum Phred score (Q30)

8. Mean on-target coverage of reads
9. AT/GC mapping bias
10. Depth of coverage
11. Observed sex matches reported sex
12. Specific version of bioinformatics pipeline
13. Integrity of data files during transfer between systems (sequencer to pipeline; pipeline to knowledge database) using a hash/checksum method

9.8.3 Circulating tumor DNA

A combination of hybrid-capture next-generation sequencing (NGS) and digital droplet PCR (ddPCR) will be used to detect and quantify circulating tumor DNA (ctDNA) in blood samples obtained from patients enrolled on this study. NGS will be performed using capture probes targeting the genomic introns involved in NTRK gene fusions and the coding regions of the three NTRK genes. Our assay was designed using the SureSelect Advanced Design Wizard (Agilent Technologies). Normalized and pooled barcoded sequencing libraries are enriched using the SureSelectXT Fast Target Enrichment System (Agilent Technologies) with this bait set. Post-enrichment captures are sequenced with an intended coverage at target regions of 500X. Identification of targeted translocations are detected using BreaKmer.[49] To quantify the number of translocations and wild-type reads detected in each sample, a custom algorithm designed to realign all sequencing reads to either the reference human genome or the patient-specific translocation positive reference sequence (obtained from tumor sequencing) will be used (https://github.com/vanallenlab/peds_ctDNA).[40] The algorithm will report the number of reads aligned at the patient-specific translocation breakpoint and the number of wild-type reads at the equivalent genomic base-pair location within the human reference genome. Because each cancer genome contains one translocated and one wild-type allele, whereas germline genomes contain two wild-type alleles, we used the following formula to calculate the percentage of ctDNA, where T equals the number of translocation reads and W equals the number of wild-type reads:

$$\%\ \text{ctDNA} = \frac{T}{\frac{W-T}{2}+T}$$

ddPCR will be performed using PCR primers designed with Primer3Plus (http://www.bioinformatics.nl/cgi-bin/primer3plus/primer3plus.cgi) to amplify patient-specific translocations identified from tumor DNA sequencing. Sample specific primer pairs will be validated with tumor DNA or synthetic DNA as a positive control (Integrated DNA Technologies) and an unrelated human cell line DNA as a negative control. Primers for the housekeeping gene RPP30 designed by Bio-Rad will be used as a reference gene. ddPCR will be performed with 5 ng of pre-capture sequencing libraries for all samples using QX200 EvaGreen SuperMix and the QX200 Droplet Digital PCR system (Bio-Rad). Analysis will be performed using the QuantaSoft program (Bio-Rad). Samples will be performed in duplicate. For each replicate, translocation-positive droplets will be divided by half of the average number of RPP30-positive droplets for that sample and then averaged.

The percentage of ctDNA and frequency with which patients have detectable ctDNA prior to the start of therapy and at times during therapy when subsequent serial samples are obtained will be summarized with simple summary statistics, including means, medians, ranges, and standard deviations (if numbers and distribution permit). In cases of treatment resistance, we will also perform exploratory deep sequencing of ctDNA to determine whether this method can detect the emergence of resistance mutations.

VALIDATION: The above hybrid capture technique has been used to successfully detect NTRK-rearrangements in tumor biopsy samples validating that the assay is a technical success. A similar strategy has also been successfully used to detect translocations in the blood of patients Ewing sarcoma. The hybrid-capture approach is able to detect these translocations when the circulating tumor DNA makes up as little as 1% of the total cell-free DNA extracted from a plasma sample.[40] Similarly, ddPCR has been used to detect Ewing translocations in the plasma of patients and is sensitive when circulating tumor DNA makes up as little as 0.01% of the cell-free DNA extracted from plasmas.[50] Furthermore, detection of larotrectinib resistance mutations in ctDNA has been shown in the first two patients to develop acquired resistance on the industry sponsored clinical trials of larotrectinib, demonstrating feasibility of this strategy.[39, 40]

9.8.4 Neurocognitive Outcomes

Neurocognitive functions will be analyzed using linear mixed-effects models with exponential covariance measures between observations within each patient. Measures to be analyzed will be the ABAS-III (General Adaptive Composite), BRIEF-P or BRIEF-2 (Global Executive Composite Score), the BASC-3 (Internalizing, Externalizing and Behavioral Symptoms Indices) and Peds QL Total Score (see Appendix XI).

10.0 EVALUATION CRITERIA

10.1 Common Terminology Criteria for Adverse Events (CTCAE)

This study will utilize the CTCAE of the National Cancer Institute (NCI) for toxicity and performance reporting. The descriptions and grading scales found in the revised CTCAE version 5.0 will be utilized for reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 5.0, which can be downloaded from the CTEP web site (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm). Additionally, toxicities are to be reported on the appropriate case report forms.

Please note: 'CTCAE v5.0' is understood to represent the most current version of CTCAE v5.0 as referenced on the CTEP website (i.e., v5.02 and all subsequent iterations prior to version 6.0).

10.2 Response Criteria

As outlined, patients will be assigned to one of the following categories for assessment of response: a) solid tumor and measurable disease (Section 10.3, Section 10.4, and Section 10.5); b) AML (Section 10.6); c) ALL (Section 10.7). Note: Neuroblastoma patients who do not have MIBG positive lesions or bone marrow involvement should be assessed for response as solid tumor patients with measurable or evaluable disease.

10.3 Response Criteria for Patients with Solid Tumors (non-CNS)

Response and progression will be evaluated in this study using the revised Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1).[51] Key points are that 5 target lesions are identified and that changes in the *largest* diameter (unidimensional measurement) of the tumor lesions are used in the RECIST v 1.1 criteria.

10.3.1 Measurable Disease

The presence of at least one lesion that can be accurately measured in at least one dimension with the longest diameter at least 10 mm (CT scan slice thickness no greater than 5 mm). The investigator will identify up to 5 measurable lesions to be followed for response. Patients with previously irradiated lesions are not eligible for Cohorts A and B of this protocol.

Serial measurements of lesions are to be done with appropriate imaging modalities, e.g., CT or MRI. Bone scans cannot be used to measure lesions. The same method of assessment is to be used to characterize each identified and reported lesion at baseline and during follow-up. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

10.3.2 Quantification of Disease Burden

The sum of the longest diameter (LD) for all target lesions will be calculated and reported as the disease measurement.

10.3.3 End-of-Cycle Response

Note: Please also see Table 1 in Section 10.4.

a) Complete Response (CR)
Disappearance of all target and non-target lesions. Normalization of urinary catecholamines (for patients with neuroblastoma), immunocytologic findings, or other tumor markers if abnormal or elevated at study enrollment.

b) Partial Response (PR)
At least a 30% decrease in the disease measurement, taking as reference the disease measurement done to confirm measurable disease at study enrollment. No new lesions or progression of any non-target measurable lesion.

c) Stable Disease (SD)
Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD taking as reference the smallest disease measurement since the treatment started.

d) Progressive Disease (PD)
At least a 20% increase in the sum of the disease measurements for measurable lesions, taking as reference the smallest disease measurement recorded since the start of treatment, or the appearance of one or more new lesions.

10.3.4 Overall Best Response Assessment

Each patient will be classified according to their "best response" for the purposes of analysis of treatment effect. For this analysis, the best response refers to the

response to larotrectinib only and not surgical resection. Best response is determined from the sequence of the objective statuses described in Section 10.4.

10.4 Best Response (Solid Tumors)

Two objective status determinations of disease status, by CT or MRI, 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.

Table 1: Sequences of objective statuses with corresponding best response.

1st Status	2nd Status	3rd Status	Best Response
Progression			Progressive disease
Stable, PR, CR	Progression		Progressive disease
Unknown	Progression		Progressive disease
Stable	Stable	Progression	Stable
Stable, Unknown	PR, CR	Progression	Stable
Stable, Unknown	Unknown	Progression	Unknown
PR	PR	Progression	PR
PR	CR	Progression	PR
PR, CR	Unknown	Progression	Unknown
CR	CR	Progression	CR
Unknown	Stable	Progression	Stable

10.5 Response Criteria for Patients with CNS Tumors

10.5.1 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.

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

10.5.3 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.

10.5.4 Response criteria for tumor markers (if available):

Tumor markers will be classified simply as being at normal levels or at abnormally high levels.

10.5.5 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 10.4 from a sequence of overall response assessments.

10.6 Response Criteria for Patients with AML

The AML response criteria are derived from the revised AML International Working Group (IWG) Criteria.[52]

10.6.1. Complete Remission (CR)

Attainment of an M1 bone marrow (< 5% blasts) with no evidence of circulating blasts or extramedullary disease and with recovery of peripheral blood counts (ANC $\geq 1000/mm^3$ and platelet count $\geq$ 100,000/mm^3). Occasionally, a rare peripheral blood blast may be identified during marrow regeneration; however, the marrow must be M1 status and with no Auer rods. Flow cytometry may also be useful to distinguish between leukemia and a regenerating bone marrow. There is no requirement for bone marrow cellularity.

10.6.2 CR With Partial Recovery of Platelet Count (CRp)

Attainment of an M1 bone marrow (< 5% blasts) with no Auer rods, no evidence of circulating blasts or extramedullary disease and with recovery of ANC $\geq 1000/mm^3$ and platelet transfusion independence (defined as: no platelet transfusions x 1 week).

10.6.3 CR with incomplete blood count recovery (CRi)

Attainment of an M1 bone marrow (< 5% blasts) with no Auer rods, no evidence of circulating blasts or extramedullary disease and with ANC < $1000/mm^3$ or platelet count < 100,000/mm^3 without platelet transfusion independence (defined as: no platelet transfusions x 1 week).

10.6.4 Cytogenetic Complete Remission (CRc)

The patient must also have attained and be assigned to response of morphologic CR or CRp or CRi as defined above. In addition, reversion to a normal karyotype with a minimum analysis of 20 metaphases.

10.6.5 Partial Response (PR)

A decrease of at least 50% in the percentage of blasts to 5% to 25% in the bone marrow aspirate. Bone marrow must have adequate cellularity (e.g., > 15%) to determine response. PR status will not be included in calculation of response to the regimen. A repeat bone marrow aspiration after several weeks may be required to distinguish between a PR and increased blasts caused by bone marrow regeneration. A value of < 5% blasts may also be considered a PR if Auer rods are present.

10.6.6 Treatment Failure (TF)

Any M3 marrow and any M2 marrow that does not qualify for PR status. A M1 marrow with evidence of circulating blasts or extramedullary disease also indicates treatment failure.

10.6.7 Relapse

Morphologic relapse after CR/CRp/CRi is defined as a reappearance of leukemic blasts in the peripheral blood or ≥ 5% blasts in the bone marrow not attributable to any other cause (e.g., bone marrow regeneration after consolidation therapy). In the setting of recent treatment, if there are no circulating blasts and the bone marrow contains 5% to 20% blasts, a repeat bone marrow performed at least a week later is necessary to distinguish relapse from bone marrow regeneration. Should flow cytometric analyses suggest relapse (by the reappearance of a similar immunophenotype to the original leukemia) in the presence of < 5% blasts, or ≥ 5% blasts in a regenerating marrow, a repeat bone marrow(s) performed at least a week later is necessary to confirm relapse by morphologic methods. In such instances the date of recurrence is defined as the first date that more than 5% blasts were observed in the marrow. The reappearance or development of cytologically proven extramedullary disease also indicates relapse. Molecular and/or genetic relapse is characterized by reappearance of a cytogenetics or molecular abnormality.

10.6.8 Unevaluable

Aplastic or severely hypocellular marrow with any blast percentage. In this instance, marrow evaluation should be repeated weekly until response determination can be made through at least Day 49.

10.6.9 Bone Marrow Classification:

M1 is < 5% blasts
M2 is 5 to 25% blasts
M3 is > 25% blasts

10.7 Response Criteria for Patients with ALL

10.7.1 Complete Response (CR)

Complete response (CR) is defined as an M1 marrow (< 5% blasts) with no evidence of circulating blasts or extramedullary disease and with peripheral count recovery, defined as absolute neutrophil count (ANC) ≥ 500/μL and platelet count ≥ to 50,000/μL without transfusion for 7 days.

10.7.2 Complete Response with Incomplete Count Recovery (CRi)

Complete response with incomplete recovery of peripheral blood counts (CRi) is defined as an M1 marrow (< 5% blasts) with no evidence of circulating blasts or extramedullary disease and with an ANC < 500/μL and/or platelet count < 50,000/μL.

10.7.3 Partial Response (PR)

Complete disappearance of circulating blasts and achievement of M2 marrow status if M3 originally, without new sites of extramedullary disease, and with

recovery of absolute neutrophil count (ANC ≥ 500/µL). Complete response in the marrow without resolution of extramedullary sites is a PR.

10.7.4 Stable Disease (SD)
Patient does not satisfy the criteria for PD, or has recovery of ANC ≥ 500/µL and fails to qualify for CR, CRi, or PR.

10.7.5 Progressive Disease (PD)
An increase of at least 25% in the absolute number of bone marrow leukemic cells, development of new sites of extramedullary disease, or other laboratory or clinical evidence of PD, with or without recovery of ANC or platelets.

10.7.6 MRD Negative
Patients will be considered MRD negative if their bone marrow has less than 0.01% blasts by flow cytometric evaluation. MRD should be performed by a COG approved laboratory.

10.8 CNS Leukemia at Diagnosis for Patients with ALL

CNS 1:	In cerebral spinal fluid (CSF), absence of blasts on cytospin preparation, regardless of the number of WBCs.
CNS 2:	In CSF, presence < 5/µL WBCs and cytospin positive for blasts, or ≥ 5/µL WBCs but negative by Steinherz/Bleyer algorithm:
CNS 2a:	< 10/µL RBCs; < 5/µL WBCs and cytospin positive for blasts;
CNS 2b:	≥ 10/µL RBCs; < 5/µL WBCs and cytospin positive for blasts;
CNS 2c:	≥ 10/µL RBCs; ≥ 5/µL WBCs and cytospin positive for blasts but negative by Steinherz/Bleyer algorithm (see below).
CNS 3:	In CSF, presence of ≥ 5/µL WBCs and cytospin positive for blasts and/or clinical signs of CNS leukemia:
CNS 3a:	< 10/µL RBCs; ≥ 5/µL WBCs and cytospin positive for blasts;
CNS 3b:	≥ 10/µL RBCs, ≥ 5/µL WBCs and positive by Steinherz/Bleyer algorithm (see below);
CNS 3c:	Clinical signs of CNS leukemia (such as facial nerve palsy, brain/eye involvement or hypothalamic syndrome).

Method of Evaluating Initial Traumatic Lumbar Punctures:
If the patient has leukemic cells in the peripheral blood and the lumbar puncture is traumatic and contains ≥ 5 WBC/µL and blasts, the following algorithm should be used to distinguish between CNS 2 and CNS 3 disease:

$$\frac{\text{CSF WBC}}{\text{CSF RBC}} > 2X \frac{\text{Blood WBC}}{\text{Blood RBC}}$$

A patient with CSF WBC ≥ 5/µL blasts, whose CSF WBC/RBC is 2X greater than the blood WBC/RBC ratio, has CNS disease at diagnosis.

Example: CSF WBC = 60/µL; CSF RBC = 1500/µL; blood WBC = 46000/µL; blood RBC = 3.0 X 10^6/µL:

$$\frac{60}{1{,}500} = 0.04 > 2X \frac{46{,}000}{3.0 \times 10^6} = 0.015$$

10.9 CNS Leukemia at Diagnosis for Patients with AML

Negative	In cerebral spinal fluid (CSF), absence of blasts on cytospin preparation, regardless of the number of WBCs.
Positive	In CSF, presence blasts on cytospin, regardless of the number of WBCs.

11.0 ADVERSE EVENT REPORTING REQUIREMENTS

11.1 Purpose

Adverse event (AE) 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. Certain adverse events must be reported in an expedited manner to allow for timelier monitoring of patient safety and care. The following sections provide information about expedited reporting.

11.2 Expedited Reporting Requirements – Serious Adverse Events (SAEs)

To ensure compliance with these regulations/this guidance, AEs must be submitted according to the timeframes in the AE reporting table assigned to the protocol, using the CTEP Adverse Event Reporting System (CTEP-AERS).

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.

11.3 Specific Examples for Expedited Reporting

11.3.1 SAEs Occurring More than 30 Days After Last Dose of Study Drug

Any Serious Adverse Event that occurs more than 30 days after the last administration of the investigational agent/intervention **and** has an attribution of a

possible, probable, or definite relationship to the study therapy must be reported according to the CTEP-AERS reporting table in this protocol.

11.3.2 Persistent or Significant Disabilities/Incapacities

Any AE that results in persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions (formerly referred to as disabilities), congenital anomalies or birth defects, must be reported via CTEP-AERS if it occurs at any time following treatment since these are considered serious AEs.

11.3.3 Death

Reportable Categories of Death

- Death attributable to a CTCAE term.
- Death Neonatal: Newborn death 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 term associated with Grade 5.
- Death NOS: A cessation of life that cannot be attributed to a CTCAE 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 disorder 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 process) 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 occurring ***greater than 30 days*** after the last dose of the investigational agent/intervention requires expedited reporting within 24 hours **only if** it is possibly, probably, or definitely related to the investigational agent/intervention.

11.3.4 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 metastasis of the initial neoplasm is not considered a secondary malignancy.

All secondary malignancies that occur following treatment with an agent must be reported via CTEP-AERS. Three options are available to describe the event:

- Leukemia secondary to oncology chemotherapy
- Myelodysplastic syndrome
- Treatment related secondary malignancy

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

11.3.5 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.

11.3.6 Pregnancy, Pregnancy Loss, and Death Neonatal

NOTE: 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 (310) 640-9193. The potential risk of exposure of the fetus to the investigational agent(s) or chemotherapy agent(s) should be documented in the "Description of Event" section of the CTEP-AERS report.

11.3.6.1 **Pregnancy**

Patients who become pregnant on study risk intrauterine exposure of the fetus to agents that may be teratogenic. For this reason, pregnancy occurring on study or within 6 months following the last dose of study therapy should be reported in an expedited manner via CTEP-AERS as **Grade 3 "*Pregnancy, puerperium and perinatal conditions - Other (pregnancy)*"** under the ***Pregnancy, puerperium and perinatal conditions*** SOC.

Pregnancy needs to be followed **until the outcome is known**. If the baby is born with a birth defect or anomaly, then a second CTEP-AERS report is required.

11.3.6.2 **Pregnancy Loss (Fetal Death)**

Pregnancy loss is defined in CTCAE as "*Death in utero*". Any Pregnancy loss should 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.

11.3.6.3 **Death Neonatal**

Neonatal death, defined in CTCAE 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.

A neonatal death should be reported expeditiously as Grade 4 "Death neonatal" under the **"*General disorders and administration*" SOC 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.

11.4 Reporting Requirements for Specialized AEs

11.4.1 Baseline AEs

Although a pertinent positive finding identified on baseline assessment is not an AE, when possible it is to be documented as "Course Zero" using CTCAE terminology and grade. An expedited AE report is not required if a patient is entered on a protocol with a pre-existing condition (e.g., elevated laboratory value, diarrhea). The baseline AE must be re-assessed throughout the study and reported if it fulfills expedited AE reporting guidelines.

a. If the pre-existing condition worsens in severity, the investigator must reassess the event to determine if an expedited report is required.
b. If the AE resolves and then recurs, the investigator must re-assess the event to determine if an expedited report is required.
c. No modification in grading is to be made to account for abnormalities existing at baseline.

11.4.2 Persistent AEs

A persistent AE is one that extends continuously, without resolution between treatment cycles/courses.

ROUTINE reporting: The AE must be reported only once unless the grade becomes more severe in a subsequent course. If the grade becomes more severe the AE must be reported again with the new grade.

EXPEDITED reporting: The AE must be reported only once unless the grade becomes more severe in the same or a subsequent course.

11.4.3 Recurrent AEs

A recurrent AE is one that occurs and resolves during a cycle/course of therapy and then reoccurs in a later cycle/course.

ROUTINE reporting: An AE that resolves and then recurs during a subsequent cycle/course must be reported by the routine procedures.

EXPEDITED reporting: An AE that resolves and then recurs during a subsequent cycle/course does not require CTEP-AERS reporting unless:

1) The grade increases OR
2) Hospitalization is associated with the recurring AE.

11.5 Exceptions to Expedited Reporting

11.5.1 Special Situations as Exceptions to Expedited Reporting

An expedited report may not be required for a specific protocol where an AE is listed as expected. The exception or acceptable reporting procedures will be specified in the protocol. The protocol specific guidelines supersede the NCI Adverse Event Reporting Guidelines. These special situations are listed under the CTEP-AERS reporting table for this protocol.

11.6 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.

Note: All expedited AEs (reported via CTEP-AERS) must also be reported via routine reporting. Routine reporting is accomplished via the Adverse Event (AE) Case Report Form (CRF) within the study database.

11.7 General Instructions for Expedited Reporting via CTEP-AERS

The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for AE reporting and are located on the CTEP website at:
http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.
All appropriate treatment areas should have access to a copy of the CTCAE.

An expedited AE report must be submitted electronically to the NCI via CTEP-AERS at:
https://eapps-ctep.nci.nih.gov/ctepaers.

- 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 event, 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 the investigator learning of the event.

- Any event that results in a persistent or significant incapacity/substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect, or is an IME, which based upon the medical judgment of the investigator may jeopardize the patient and require intervention to prevent a serious AE, must be reported via CTEP-AERS **if the event occurs following investigational agent administration.**

- Any death occurring within 30 days of the last dose, regardless of attribution to an agent/intervention under an NCI IND/IDE requires expedited reporting **within 24 hours**.

- Any death occurring greater than 30 days of the last dose with an attribution of possible, probable, or definite to an agent/intervention under an NCI IND/IDE requires expedited reporting **within 24 hours**.

CTEP-AERS Medical Reporting includes the following requirements as part of the report: 1) whether the patient has received at least one dose of an investigational agent on this study; 2) the characteristics of the adverse event including the *grade* (severity), the *relationship to the study therapy* (attribution), and the *prior experience* (expectedness) of the adverse event; 3) the phase (1, 2, or 3) of the trial; and 4) whether or not hospitalization or prolongation of hospitalization was associated with the event.

Any medical documentation supporting an expedited report (e.g., 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 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.**

11.8 Reporting Table for Late Phase 2 and Phase 3 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]

FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)
NOTE: Investigators MUST immediately report to sponsor (NCI) ANY SAEs, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64).
An AE is considered serious if it results in ANY of the following outcomes:
1) Death
2) A life-threatening AE
3) An AE 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 SAEs that meet the above criteria MUST be immediately reported to the Sponsor via CTEP-AERS within the timeframes detailed in the table below.

Grade 1-3 Timeframes	Grade 4-5 Timeframes
24-Hour notification, 7 calendar days	24-Hour notification, 5 calendar days

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

Expedited AE reporting timelines are defined as:

- "24-Hour notification; 5 Calendar Days" - The SAE must initially be reported via CTEP-AERS within 24 hours of learning of the SAE, followed by a complete expedited report within 5 calendar days of the initial 24-hour report.
- "24-Hour notification, 7 Calendar Days" - The SAE must initially be reported via CTEP-AERS

within 24 hours of learning of the SAE, followed by a complete expedited report within 7 calendar days of the initial 24-hour report.
[1]SAEs 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 notifications are required for all SAEs followed by a complete report** • Within 5 calendar days for Grade 4-5 SAEs • Within 7 calendar days for Grade 1-3 SAEs [2]For studies using nuclear medicine or molecular imaging IND agents (NM, SPECT, or PET), the SAE 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: August 30, 2024

11.9 **Protocol Specific Additional Instructions and Reporting Exceptions**

- **Grades 1 – 4 myelosuppression (anemia, neutropenia, thrombocytopenia, leukopenia, lymphopenia) do not require expedited reporting unless it is associated with hospitalization.**

11.10 **Reporting of Adverse Events for commercial agents – CTEP-AERS abbreviated pathway**

The following are expedited reporting requirements for adverse events experienced by patients on study who have not received any doses of an investigational agent on this study. Commercial reporting requirements are provided in Table B.

COG requires the CTEP-AERS report to be submitted **within 7 calendar days** of learning of the event.

Table B
Reporting requirements for adverse events experienced by patients on study who have NOT received any doses of an investigational agent on this study.

CTEP-AERS Reporting Requirements for Adverse Events That Occur During Therapy with a Commercial Agent or Within 30 Days[1]

Attribution	**Grade 4**		**Grade 5**
	Unexpected	Expected	
Unrelated or Unlikely			CTEP-AERS
Possible, Probable, Definite	CTEP-AERS		CTEP-AERS
[1]This includes all deaths within 30 days of the last dose of treatment with a commercial agent, regardless of attribution. Any death that occurs more than 30 days after the last dose of treatment with a commercial agent that can be attributed (possibly, probably, or definitely) to the agent and is not due to cancer recurrence must be reported via CTEP-AERS.			

11.11 **Routine Reporting of Adverse Events**

Note: The guidelines below are for routine reporting of study specific adverse events on the COG case report forms and do not affect the requirements for CTEP-AERS reporting.

Routine reporting is accomplished via the Adverse Event (AE) Case Report Form (CRF) within the study database. For this study, routine reporting will include all CTEP-AERS reportable events and Grade 3 and higher Adverse Events.

12.0 STUDY REPORTING AND MONITORING

The Case Report Forms and the submission schedule are posted on the COG website with each protocol under "Data Collection/Specimens". A submission schedule is included.

12.1 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 quarterly to CTEP by electronic means. Reports are due January 31, April 30, July 31 and October 31. CDUS reporting is not a responsibility of institutions participating in this trial.

12.2 Data and Safety Monitoring Committee

To protect the interests of patients and the scientific integrity for all clinical trial research by the Children's Oncology Group, the COG Data and Safety Monitoring Committee (DSMC) reviews reports of interim analyses of study toxicity and outcomes prepared by the study statistician, in conjunction with the study chair's report. The DSMC may recommend the study be modified or terminated based on these analyses.

Toxicity monitoring is also the responsibility of the study committee and any unexpected frequency of serious events on the trial are to be brought to the attention of the DSMC. The study statistician is responsible for the monitoring of the interim results and is expected to request DSMC review of any protocol issues s/he feels require special review. Any COG member may bring specific study concerns to the attention of the DSMC.

The DSMC approves major study modifications proposed by the study committee prior to implementation (e.g., termination, dropping an arm based on toxicity results or other trials reported, increasing target sample size, etc.). The DSMC determines whether and to whom outcome results may be released prior to the release of study results at the time specified in the protocol document.

13.0 SURGICAL GUIDELINES

13.1 Guidelines

a. Biopsies may be by needle or as an open procedure.

b. During the resection of the tumor, biopsy tract must be included and kept in continuity with the tumor at all times.

c. For the purpose of this study, a tumor is considered to be resectable if it is anticipated that a complete resection (for tumors other than IFS or CMN; see Section 13.2.1) or marginal resection (for IFS and CMN; see Section 13.2.2) can be achieved without functional loss, neurologic compromise, or significant cosmetic impairment that is not acceptable to the patient/family or surgeon. In particular, tumors that would require amputation of an arm or leg, resection of a major nerve, or for which resection is anticipated to result in major neurologic deficits are NOT considered resectable for the purpose of this protocol. Patients

who do not meet this definition should continue larotrectinib per protocol until their tumor becomes resectable or for a maximum of 26 cycles of therapy (see Section 4.1.3).

13.2 Definition of Margins

13.2.1 Incomplete Resection (Incisional Resection; R2): Tumor resection that leaves gross (macroscopic) residual tumor behind.

13.2.2 Marginal Resection (Gross Total Resection with Positive Microscopic Margins; R1):

a. Tumor resection that leaves no residual macroscopic tumor behind, but there is microscopic tumor present at the margins of the specimen **OR**

b. Biopsies of grossly uninvolved areas of the tumor bed that contain tumor cells microscopically.

13.2.3 Complete Resection (Gross Total Resection with Negative Margins; R0): removal of tumor entirely with microscopic absence of tumor on the inked margins.

13.2.4 If rupture of the tumor occurs during the resection and tumor is spilled, the resection should be considered to be marginal (if gross tumor removal is accomplished) or incomplete (if gross tumor is left behind).

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APPENDIX I: CTEP AND CTSU REGISTRATION PROCEDURES

INVESTIGATOR AND RESEARCH ASSOCIATE REGISTRATION WITH CTEP

Food and Drug Administration (FDA) regulations require sponsors to select qualified investigators. National Cancer Institute (NCI) policy requires all individuals contributing to any NCI-sponsored trials to register with their qualifications and credentials to renew their registration annually. To register, all individuals must obtain Cancer Therapy Evaluation Program (CTEP) credentials necessary to access secure NCI Clinical Oncology Research Enterprise (CORE) systems. Investigators and clinical site staff who are significant contributors to research must register in the Registration and Credential Repository (RCR). The RCR is a self-service online person registration application with electronic signature and document submission capability.

RCR utilizes four person registration types that are applicable to this study.

- Investigator (IVR) — MD, DO, or international equivalent;
- Non-Physician Investigator (NPIVR) — advanced practice providers (e.g., NP or PA) or graduate level researchers (e.g., PhD);
- Associate Plus (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; and
- Associate (A) — other clinical site staff involved in the conduct of NCI-sponsored trials.

RCR requires the following registration documents:

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

IVRs and NPIVRs must list all clinical practice sites and Institutional Review Boards (IRBs) covering their practice sites in RCR to allow the following:

- Addition to a site roster;
- Selection as the treating, credit, or consenting person in OPEN;
- Ability to be named as the site-protocol Principal Investigator (PI) on the IRB approval; and
- Assignment of the Clinical Investigator (CI) task on the Delegation of Tasks Log (DTL).

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

Refer to the NCI RCR page on the CTEP website for additional information. For questions, please contact the **RCR Help Desk** by email at RCRHelpDesk@nih.gov.

CTSU Registration Procedures

Permission to view and download this protocol and its supporting documents is restricted and is based on the person and site roster assignment housed in the Roster Maintenance application and in most cases viewable and manageable via the Roster Update Management System (RUMS) on the Cancer Trials Support Unit (CTSU) members' website.

This study is supported by the NCI 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 to institutions and their associated investigators and staff on a participating roster. To view/download site registration forms:

- Log in to the CTSU members' website (https://www.ctsu.org);
- 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*, *Protocol Related Documents,* and use the *Document Type* filter and select *Site Registration* to download and complete the forms provided. (Note: For sites under the CIRB, IRB data will load automatically to the CTSU.)

Protocol-Specific Requirements For ADVL1823 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)
- This is a study with a radiation and/or imaging (RTI) component and the enrolling site must be aligned to an RTI provider. To manage provider associations, access the Provider Association page from the Regulatory section on the CTSU members' website at https://www.ctsu.org/RSS/RTFProviderAssociation.aspx. Sites must be linked to at least one Imaging and Radiation Oncology Core (IROC) provider to participate on trials with an RTI component. Enrolling sites are responsible for ensuring that the appropriate agreements and IRB approvals are in place with their RTI provider. Only an individual with a primary role on a treating site roster can update the provider associations, though all individuals at a site may view provider associations. To find who holds primary roles at your site, view the Person Roster Browser under the RUMS section on the CTSU members' website.

Submitting Regulatory Documents:
Submit required forms and documents to the CTSU Regulatory Office using the Regulatory Submission Portal on the CTSU members' 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 by phone or email: 1-866-651-CTSU (2878), or CTSURegHelp@coccg.org 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 the 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:

- Active CTEP registration with the credentials necessary to access secure NCI/CTSU IT systems; 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 a Non-Physician Investigator (NPIVR) or Investigator (IVR); and
- Rave Read Only or Rave SLA role must have at a minimum an Associates (A) registration type.

Upon initial site registration approval for the study in the Regulatory application, all persons with Rave roles assigned on the appropriate roster will be sent a study invitation email from iMedidata. No action will be required; each study invitation will be automatically accepted and study access to the study in Rave will be automatically granted. 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 eLearning link in the *Tasks* pane located in the upper right corner of the iMedidata screen. If an eLearning is required for a study and has not yet been taken, the link to the eLearning will appear under the study name in the *Studies* pane located in the center of the iMedidata screen; 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 replace the eLearning link under the study name.

APPENDIX II: YOUTH INFORMATION SHEETS

INFORMATION SHEET REGARDING RESEARCH STUDY ADVL1823
(for children from 7 through 12 years of age)

A study of larotrectinib in patients with a cancer that has a TRK fusion

1. We are asking you to take part in a research study because you have 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. We will do this by trying a new medicine to treat your cancer.

2. People who are part of this study will be treated with a cancer-fighting medicine called larotrectinib. You will also have regular tests and exams done more often while you are in this study. The doctors want to see if larotrectinib will make people with your type of cancer get better. We don't know if larotrectinib will work well to get rid of your cancer. That is why we are doing this study.

3. 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 larotrectinib may cause your cancer to shrink or go away but we don't know for sure if there is any benefit of being part of this study.

4. 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 larotrectinib. Other things may happen to you that we don't yet know about.

5. Your family can choose to be part of this study or not. Your family can also decide to stop being in this study at any time once you start. There may be other treatments for your illness that your doctor can tell you about. Make sure to ask your doctors any questions that you have.

6. 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. These samples would be taken when other standard blood tests are being performed, so there would be no extra procedures. You can still take part in this study even if you don't allow us to collect the extra blood samples for research. If you have leukemia, we will also collect a watery fluid that flows through your brain and spinal cord called cerebrospinal fluid. These samples will be taken when other standard procedures are being performed, so there will be no extra procedures for us to collect the cerebrospinal fluid.

INFORMATION SHEET REGARDING RESEARCH STUDY ADVL1823
(for teens from 13 through 17 years of age)

A study of larotrectinib in patients with a cancer that has a TRK fusion

1. We have been talking with you about your cancer. After doing tests, we have found that you have a type of cancer that has a mutation called a TRK fusion.

2. We are asking you to take part in a research study because you have cancer with a TRK fusion. 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 cancers with TRK fusions.

3. People who are part of this study will be given a cancer-fighting medicine called larotrectinib. Larotrectinib works to fight against TRK fusions. You will be given larotrectinib by mouth twice daily for a 28-day period. This entire 28-day period is called a cycle. You may continue to receive larotrectinib for up to about 2 years (26 cycles) as long as you do not have bad effects from it and your cancer does not get any worse. If your cancer gets better, you may undergo surgery to remove your tumor and/or be told to stop taking larotrectinib but you will continue to be monitored.

4. You will also have regular tests and exams done more often while you are in this study. The doctors want to see if larotrectinib will make people with your type of cancer get better. We don't know if larotrectinib will work well to get rid of your cancer. That is why we are doing this study.

5. 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 larotrectinib may cause your cancer to shrink or go away but we don't know for sure if there is any benefit of being part of this study.

6. 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 larotrectinib. Other things may happen to you that we don't yet know about.

7. Your family can choose to be part of this study or not. Your family can also decide to stop being in this study at any time once you start. There may be other treatments for your illness that your doctor can tell you about. Make sure to ask your doctors any questions that you have.

8. 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. These samples would be taken when other standard blood tests are being performed, so there would be no extra procedures. You can still be treated on this study even if you don't allow us to collect the extra blood samples for research. If you have leukemia, we will also collect a watery fluid that flows through your brain and spinal cord called cerebrospinal fluid. These samples will be taken when other standard procedures are being performed, so there will be no extra procedures for us to collect the cerebrospinal fluid.

APPENDIX III: TISSUE STUDIES FORM

COG Pt ID # _____ ACC # _____ Date:_____
(Please do not write patient names on this form or on samples)

Sample Labeling:
Samples should be labeled with the following information:

Protocol number: **ADVL1823**
Institution: _____
Patient ID #: _____
Accession #: _____
Cycle #: _____ (Write "N/A" for archival tissue)
Sample Date: _____
Site of Acquired Tissue: _____

Tissue obtained at (check one option below):
☐Archived ☐Relapse ☐Time of local control ☐Time of bone marrow evaluation

Tissue sample is from a:
☐ Resection or ☐ Biopsy

Shipment of Tumor Tissue:
Archival tumor tissue submission is required and must be sent following patient enrollment. Additionally, tumor tissue must be sent following resection at time of local control, following bone marrow evaluation for patients with bone marrow involvement, and/or following optional biopsy post disease progression. Archived tissue samples should be in the form of 1 H&E stained slide from all available formalin-fixed paraffin embedded (FFPE) tissue blocks and 15 unstained slides from the most representative block or the block itself. Samples should be accompanied by a copy of the pathology report. Fine needle aspirate samples or other cytology samples are not acceptable and tumor samples obtained from bone metastases are generally not considered acceptable.

All blocks or slides must be labeled with the patient's study registration number (COG Patient ID #), the study I.D. (ADVL1823), and the sample collection date. Data should be recorded on this Tissue Studies Form, which must accompany the sample(s) to the address provided in Section 7.3.1.4.

1. **If sending paraffin block (PREFERRED):**
   a. Place appropriate sample ID label on back of cassette
   b. Place labeled cassette in a Zipper lock bag
   c. Paraffin blocks are shipped to the lab at **ambient temperature**. It is acceptable to send blocks refrigerated if sending blocks and slides together.

2. **If sending slides:**
   If slides will be cut from tissue block, recommended thickness of tissue sections for slides is 4 microns. Positively charged slides are required (Superfrost Plus is recommended). After cutting, the slides should be kept in refrigerator (2-5°C).
   a. Place slides in the plastic slide holder and place sample ID label provided on the slide holder
   b. Place the slide holder in the Zipper lock bag and eliminate as much air (and therefore moisture) as possible prior to sealing the Zip-lock bag
   c. Slides are shipped to the lab **at refrigerated temperature on a cold gel pack**. It is acceptable to send blocks refrigerated if sending blocks and slides together.

One copy of this form should be uploaded into RAVE.

If this form will be used as a source document, the site personnel who collected the samples must sign and date this form below:
Signature: _____ Date:_____
(site personnel responsible for collection of samples)

APPENDIX IV: CIRCULATING TUMOR DNA

COG Pt ID # _____ Date: _____
Please do not write patient names on this form or on samples.

Patient Weight: _____kg Body Surface Area: _____m^2

Larotrectinib Dose Level: _____ mg/m^2 BID Larotrectinib Daily Dose: _____ mg BID

Blood samples will be collected in consenting patients in Streck Cell-Free DNA BCT tubes at the following time points: prior to Cycle 1, Day 15 of Cycle 1 of larotrectinib therapy, Day 1 of Cycle 2 of larotrectinib therapy, at the end of Cycle 6 of larotrectinib therapy (prior to Cycle 7 or local control), at the end of study treatment, and at the time of progression.

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

- For patients ≥ 10 kg, collect 20 mL (10 mL per tube x 2 tubes)
- For patients ≥ 5 kg but < 10kg, collect 10 mL (1 tube)
- For patients < 5 kg, collect 5 mL in 1 tube

Record the exact date and time the sample is drawn.

Blood Sample No.	Time Point	Scheduled Collection Time	Actual Date Sample Collected	Actual Time Sample Collected
1	Pre-Cycle 1, Day 1			|__|__| : |__|__|
2	Cycle 1, Day 15	Prior to AM dose		|__|__| : |__|__|
Larotrectinib AM Dose on Cycle 1, Day 15 Date:___/___/___			**Time Dose Given: |__|__| : |__|__|**	
3	Cycle 2, Day 1	Prior to AM dose		|__|__| : |__|__|
Larotrectinib AM Dose on Cycle 2, Day 1 Date:___/___/___			**Time Dose Given: |__|__| : |__|__|**	
4	End of Cycle 6	Prior to Cycle 7, Day 1 AM dose OR prior to local control		|__|__| : |__|__|
Larotrectinib AM Dose on Cycle 7, Day 1 Date:___/___/___			**Time Dose Given: |__|__| : |__|__|**	
5	End of study treatment			|__|__| : |__|__|
6	At the time of progression[1]			|__|__| : |__|__|

[1] If applicable

One copy of this ctDNA Form should be uploaded into RAVE. A second copy should be sent with the samples to the address listed in Section 7.3.2.4. See Section 7.3.2.3 for detailed guidelines for packaging and shipping PK samples.

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

Signature: _____ Date:_____
(site personnel responsible for collection of samples)

APPENDIX V: LAROTRECTINIB DRUG INTERACTIONS

Some drugs, food, and supplements may interact with larotrectinib. Examples include:

Drugs that may interact with larotrectinib*

• Antibiotics
  • Clarithromycin, erythromycin, nafcillin, rifabutin, rifapentin, rifampin, telithromycin
• Antifungals
  • Fluconazole, itraconazole, isavuconazole, ketoconazole, posaconazole, voriconazole
• Anti-rejection medications
  • Cyclosporine, tacrolimus, sirolimus
• Antiretrovirals and antivirals
  • Atazanavir, darunavir, delaviridine, efavirenz, etravirine, fosamprenavir, indinavir, lapatinib, lopinavir, nelfinavir, nevirapine, ritonavir, saquinavir, Stribild®, telaprevir, tenofovir, tipranavir
• Anti-seizure medications
  • Carbamazepine, fosphenytoin, phenobarbital, phenytoin, primidone
• Heart medications
  • Amiodarone, carvedilol, diltiazem, dronedarone, propafenone, quinidine, ranolazine, verapamil
• Some chemotherapy (be sure to talk to your doctor about this)
• Many other drugs, including the following:
  • Aprepitant, bosentan, cobicistat, conivapatan, deferasirox, eltrombopag, fosnetupitant, ivacaftor, mifepristone, modafinil, nefazodone, netupitant

Food and supplements that may interact with larotrectinib**
• Echinacea • St. John's Wort • Grapefruit, grapefruit juice, Seville oranges, star fruit

**Sometimes these drugs are used with larotrectinib on purpose. Discuss all drugs with your doctor.*

***Supplements may come in many forms, such as teas, drinks, juices, liquids, drops, capsules, pills, or dried herbs. All forms should be avoided.*

The list above does not include everything that may interact with your chemotherapy. Talk to your doctor before starting any new medications, over-the-counter medicines or herbal supplements and before making a significant change in your diet.

APPENDIX VI: CYP3A4 SUBSTRATES, INDUCERS, AND INHIBITORS

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

CYP3A4 substrates	Strong Inhibitors[1]	Moderate Inhibitors	Strong Inducers	Moderate Inducers
abemaciclib	adagrasib	aprepitant	apalutamide	bexarotene
acalabrutinib[5]	atazanavir	avacopan	barbiturates	bosentan
alectinib	ceritinib	berotralstat	carbamazepine	cenobamate
alfentanil[4,5]	clarithromycin	crizotinib	encorafenib	dabrafenib
amiodarone[4]	cobicistat	diltiazem	enzalutamide	efavirenz
apixaban	darunavir	dronedarone	fosphenytoin	eslicarbazepine
aprepitant/fosaprepitant	grapefruit[3]	duvelisib	lumacaftor/	etravirine
aripiprazole	grapefruit juice[3]	erythromycin	ivacaftor	lorlatinib
axitinib	idelalisib	fedratinib	mitotane	mitapivat
benzodiazepines[5]	itraconazole	fluconazole	phenobarbital	modafinil
bortezomib	ketoconazole	fosamprenavir	phenytoin	nafcillin
bosutinib[5]	levoketoconazole	fosnetupitant	primidone	pexidartinib
brexpiprazole	lonafarnib	grapefruit[3]	rifampin	repotrectinib
brigatinib	lopinavir/ritonavir	grapefruit juice[3]	St. John's wort	rifabutin
budesonide[5]	nefazodone	imatinib		rifapentin
buspirone[5]	nelfinavir	isavuconazole		sotorasib
cabozantinib	nirmatrelvir/ritonavir	lenacapavir		
calcium channel blockers	paritaprevir/ritonavir/	letermovir		
carbamazepine	ombitasvir +/- dasabuvir	mifepristone		
ceritinib	posaconazole	netupitant		
citalopram	ritonavir	nilotinib		
clobazam	tipranavir/ritonavir	nirogacestat		
cobimetinib[5]	tucatinib	ribociclib		
cobicistat	voriconazole	verapamil		
codeine				
colchicine[5]				
crizotinib				
cyclosporine[4]				
dabrafenib				
dapsone				
darifenacin[5]				
darunavir[5]				
dasatinib[5]				
daflazacort[2]				
dexamethasone[2]				
dihydroergotamine				
docetaxel				
domperidone				
doxorubicin				
dronedarone[5]				
elagolix				
elbasvir/grazoprevir				

eletriptan[5] eliglustat[5] eplerenone[5] ergotamine[4] erlotinib estrogens etoposide everolimus[5] fentanyl[4] gefitinib haloperidol ibrutinib[5] idelalisib imatinib irinotecan isavuconazole[5] itraconazole ivabradine ivacaftor ketoconazole lapatinib lidocaine linagliptin lorlatinib lurasidone[5] macrolide antibiotics maraviroc[5] medroxyprogesterone methadone midostaurin[5] naldemedine naloxegol[5] nelfinavir neratinib netupitant nevirapine nilotinib nirogacestat olaparib osimertinib oxycodone paclitaxel palbociclib panobinostat pazopanib pimozide[5] ponatinib quetiapine[5] quinidine[4] regorafenib ribociclib				

rilpivirine[5] risperidone rivaroxaban[5] rolapitant romidepsin ruxolitinib selumetinib sildenafil[5] simeprevir sirolimus[4,5] sonidegib sorafenib sotorasib statins sunitinib suvorexant tacrolimus[4,5] tamoxifen tasimelteon temsirolimus teniposide ticagrelor[5] tipranavir[5] tofacitinib tolvaptan[5] tramadol trazodone vandetanib vardenafil[5] vemurafenib venetoclax[5] vilazodone vinca alkaloids vorapaxar voriconazole zaleplon ziprasidone 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 _____ 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 VII-A: MEDICATION DIARY (LAROTRECTINIB CAPSULE FORMULATION)

COG Patient ID:_____ ACC # : _____ Institution :_____ BSA:_____ m^2
Please do not write patient names on this form.

Instructions: 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 larotrectinib. If a dose is accidentally skipped, leave that section blank. ***Make note of other drugs and supplements taken under the Comments section below.*** Larotrectinib capsules should not be opened and must be swallowed whole. You should take each dose of larotrectinib approximately 12 hours apart, at about the same time each day. If you vomit after taking a dose, DO NOT retake the 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. If a dose is accidentally skipped leave that section blank. Add the dates to the calendar below and return the completed diary and the empty bottle or any leftover capsules to the study clinic at each visit (weekly during Cycle 1, and then after each treatment cycle).

EXAMPLE

Day	*Date*	*Time*		*# of larotrectinib capsules prescribed to take*		*Comments (Describe any missed or extra doses, vomiting and/or bothersome effects.)*
				25 mg	*100 mg*	
				AM#_3__ PM#_3__	*AM#___ PM#___*	
				# of larotrectinib tablets taken		
				25 mg	*100 mg*	
Day 1	*09/20/18*	*8:30*	*AM*	*3*		*He felt nauseated an hour after taking the drug but did not vomit.*
		8:30	*PM*	*3*		

Cycle #: _____ Start Date: |__/__|__/__|__/__|
End Date: |__/__|__/__|__/__| **Dose Level: _____mg/m^2/dose**

Day	**Date**	**Time**		**# of 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 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			
Day 8			**AM**			
			PM			
Day 9			**AM**			
			PM			
Day 10			**AM**			
			PM			
Day 11			**AM**			
			PM			
Day 12			**AM**			
			PM			
Day 13			**AM**			
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Day 14			**AM**			
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Day 24			**AM**			
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Day 25			**AM**			
			PM			
Day 26			**AM**			
			PM			
Day 27			**AM**			
			PM			

Day 28			**AM**			
			PM			

APPENDIX VII-B: MEDICATION DIARY (LAROTRECTINIB LIQUID FORMULATION)

COG Patient ID:_____ ACC # : _____ Institution :_____ BSA:_____ m^2
Please do not write patient names on this form.

Instructions: Store the larotrectinib liquid formulation in the refrigerator.

Complete each day with the time and dose given for larotrectinib. If a dose is accidentally skipped, leave that section blank. ***Make note of other drugs and supplements taken in the Comments section below.*** You should take each dose of larotrectinib approximately 12 hours apart, at about the same time each day. If you vomit after taking a dose, DO NOT retake the 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. If a dose is accidentally skipped leave that section blank. 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 the study clinic at each visit (weekly during Cycle 1, and then after each treatment cycle).

EXAMPLE

Day	*Date*	*Time*		*AM Dose: Take ___2__ mL PM Dose: Take ___2__ mL Amount of larotrectinib liquid formulation taken (mL)*	*Comments (Describe any missed or extra doses, vomiting and/or bothersome effects.)*
Day 1	*09/20/18*	*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**

Day	**Date**	**Time**		**AM Dose: Take _____ mL PM Dose: Take _____ mL Amount of 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		
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		
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		
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		

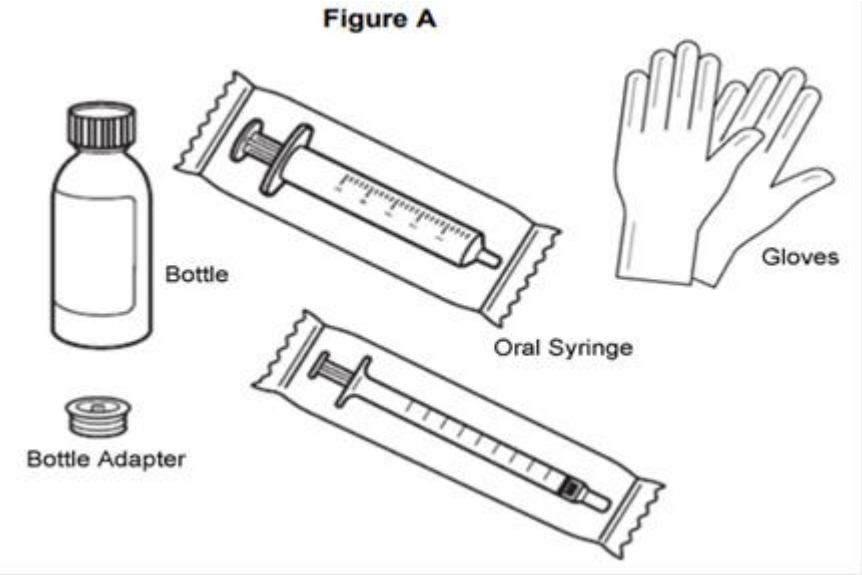
Instructions for drawing up larotrectinib oral solution into a syringe:
Information and images adapted from VITRAKVI® (larotrectinib) package insert.[53]

Important information about measuring larotrectinib oral solution:
• Always use the oral syringes provided with larotrectinib to make sure that you correctly measure the prescribed dose.
• When you receive larotrectinib oral solution, you will get 1 or more glass bottles of larotrectinib oral solution and a bottle adapter.
• You will receive oral syringes that are marked to help you correctly measure the prescribed dose of larotrectinib oral solution. Each oral syringe may be used for up to a 7-day period and then must be discarded. Do not use a household teaspoon to measure the dose.

Supplies needed for administering larotrectinib (See Figure A):

- Bottle of larotrectinib
- Oral syringe
- Bottle adapter
- Gloves

Figure A

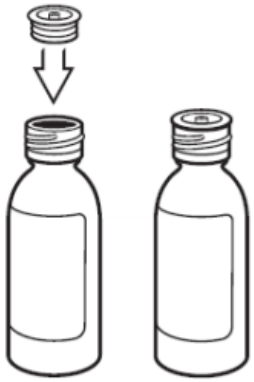


Step 1: Put on gloves. Place the larotrectinib bottle on a flat work surface. Open the bottle by pushing down firmly on the child-resistant cap and turning it in the direction of the arrow (counter-clockwise). See Figure B. Do not throw away the child-resistant cap.

Figure B

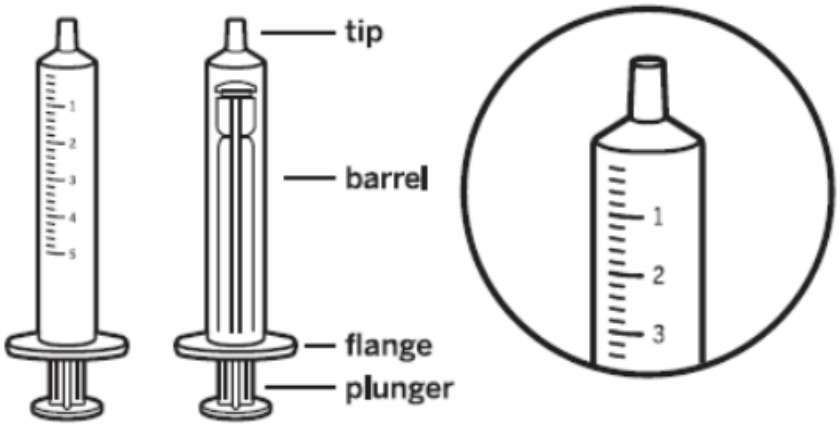
Step 2: Insert the bottle adapter by pressing it into the bottle neck and make sure it is secure. See Figure C. Do not remove the bottle adapter. If the bottle adapter is missing, talk to your healthcare provider.

Figure C



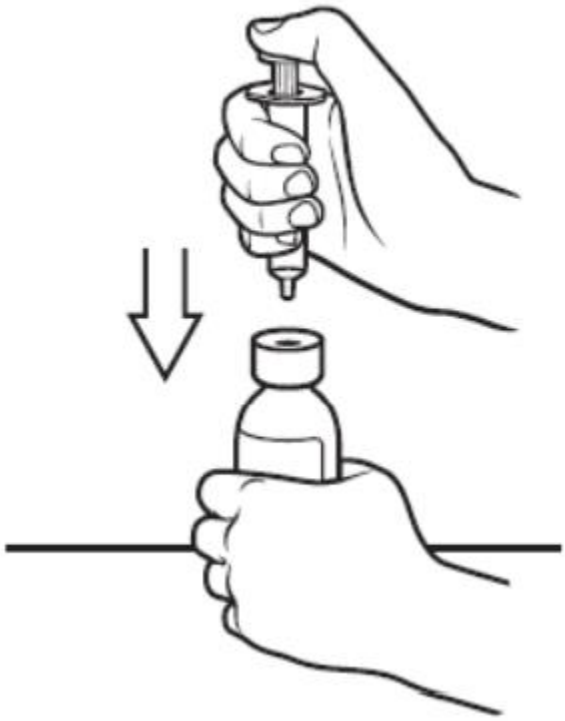
Step 3: Remove the oral syringe from the wrapper. Throw the wrapper away in your household trash. The barrel of the oral syringe has markings in milliliters (mL). Look at the markings on the barrel of the oral syringe and find the mL marking that matches the larotrectinib oral solution dose in mL prescribed by your healthcare provider. See Figure D.

Figure D



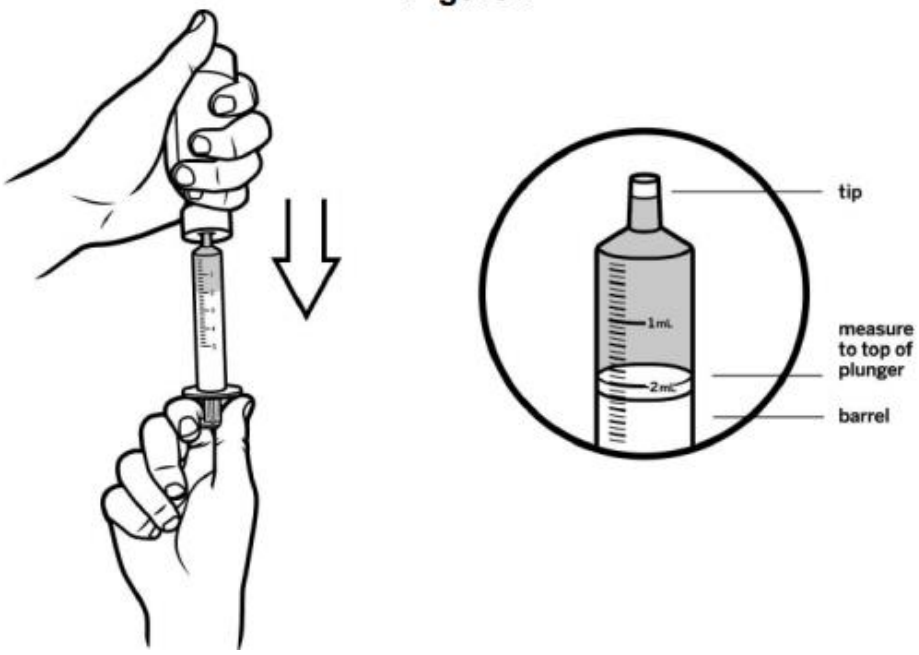
Step 4: With the bottle on your flat work surface, use 1 hand to hold the bottle upright. Using your other hand, push the air out of the oral syringe by pushing the plunger down. Then, insert the tip of the oral syringe into the bottle adapter at the top of the bottle. See Figure E. The tip of the oral syringe should fit snugly into the hole of the bottle adapter.

Figure E



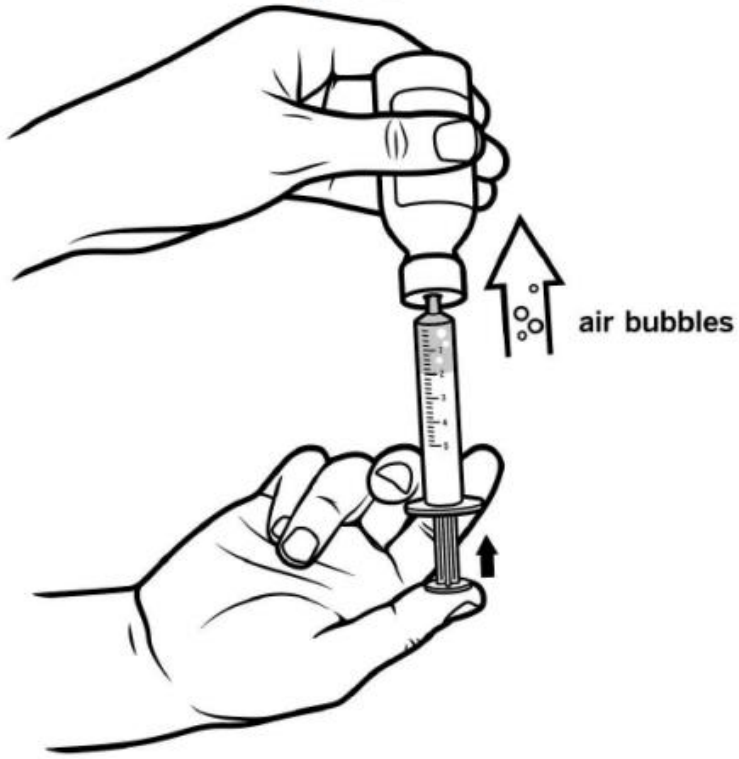
Step 5: Use 1 hand to hold the oral syringe in place. With the other hand, turn the bottle upside down. Pull back on the plunger until the top of the plunger lines up with the marking on the barrel of the oral syringe that matches the dose of larotrectinib oral solution prescribed by your healthcare provider. See Figure F. Your dose may be different than the dose shown in Figure F.

Figure F



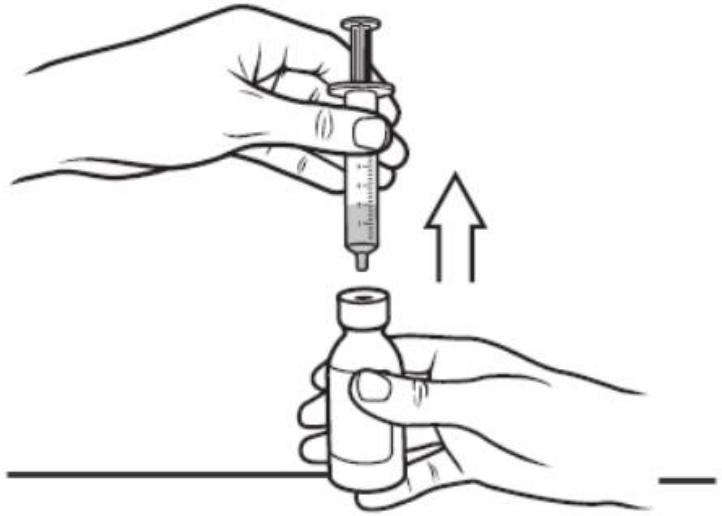
Step 6: Check for air bubbles in the oral syringe. If you see air bubbles, push up gently on the plunger to push any large air bubbles back into the bottle. Then, pull back on the plunger to the prescribed dose. See Figure G.

Figure G



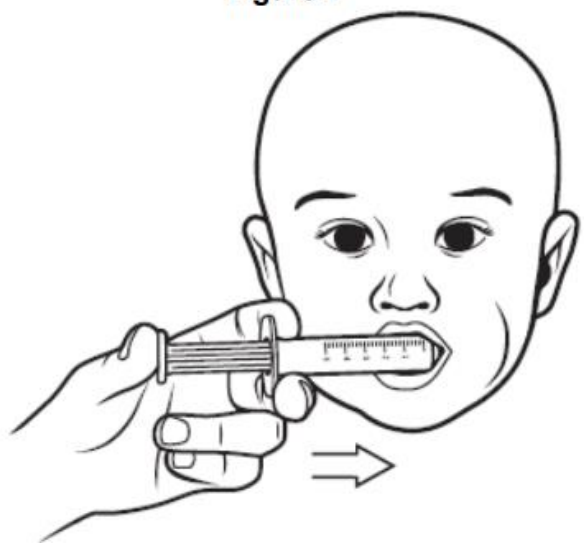
Step 7: Turn the bottle upright again and place it on your work surface. Remove the oral syringe from the bottle adapter by gently pulling up on the syringe barrel. See Figure H. Do not push on the plunger during this step. The bottle adapter should stay attached to the bottle.

Figure H



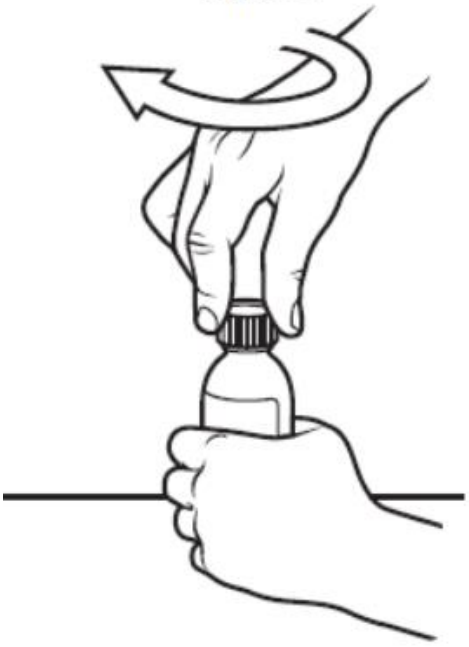
Step 8: Place the tip of the oral syringe into the child's mouth against the inside of the cheek. Slowly squirt larotrectinib oral solution into the mouth by pressing down on the plunger and allow the child to swallow. See Figure I. If the child has an NG or G-tube you may administer larotrectinib via the tube instead of into the mouth if instructed by your healthcare provider. The child should be kept in an upright position for a few minutes right after giving a dose of larotrectinib.

Figure I



Step 9: Replace the child-resistant cap on the bottle of larotrectinib oral solution. Do not remove the bottle adapter. Close the bottle by turning the bottle cap in the direction of the arrow (clockwise). See Figure J.

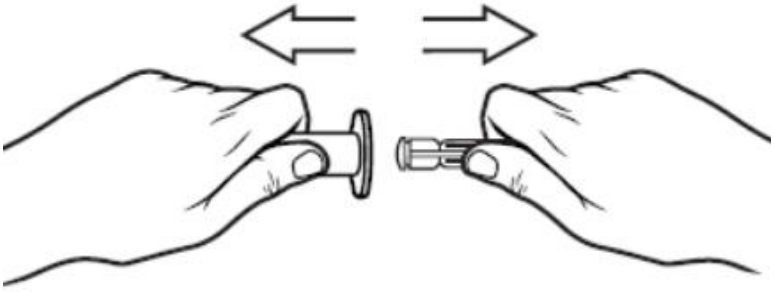
Figure J



Cleaning instructions for oral syringe:
Follow the instructions below for cleaning the oral syringe (Step 10 through Step 16). After 7 days of use, throw away the oral syringe in your household trash. Use a new one for the next 7 days.

Step 10: Remove plunger from the barrel of the oral syringe. See Figure K.

Figure K

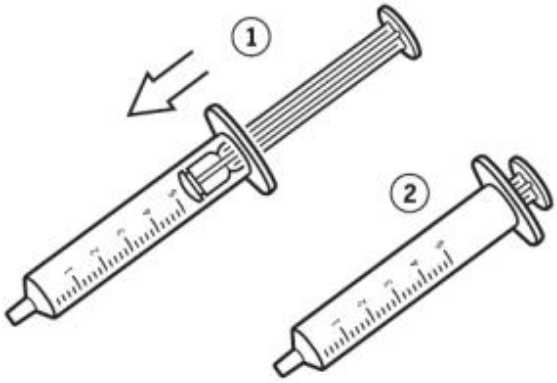


Step 11: Rinse the barrel and plunger in warm running water to help ensure that all of the medicine has been removed from the oral syringe. See Figure L. Do not boil the oral syringe.

Figure L

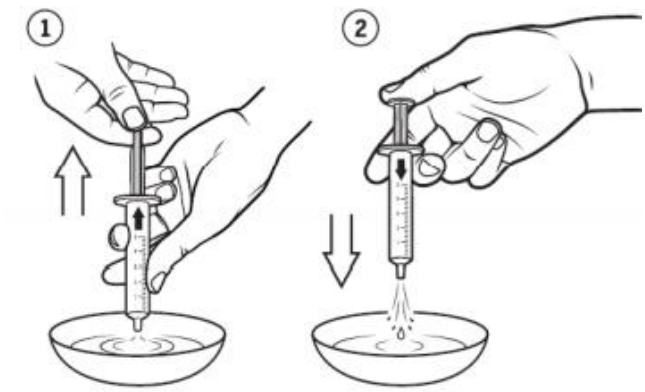
Step 12: Re-insert the plunger into the barrel of the oral syringe. See Figure M.

Figure M



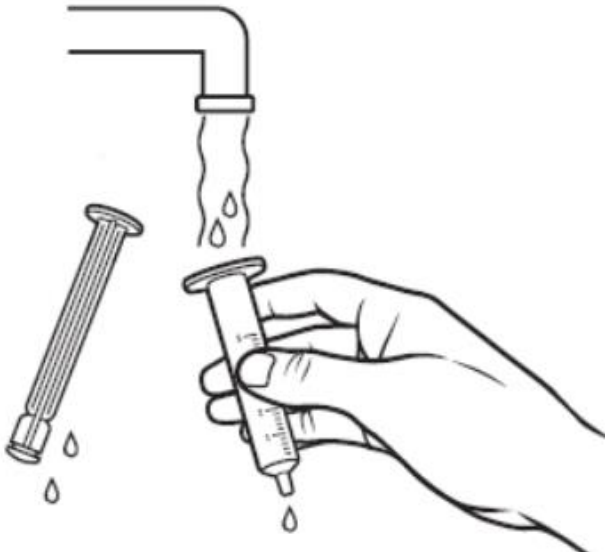
Step 13: Draw warm water several times into the oral syringe and squirt out again until all of the medicine has been removed from the oral syringe. See Figure N.

Figure N



Step 14: Disassemble the oral syringe, and rinse the barrel and plunger again with warm water. See Figure O.

Figure O



Step 15: Shake off excess water or wipe off the outside, and the place the barrel and plunger on a clean, dry paper towel to dry. See Figure P. Remove gloves and place in regular household trash.

Figure P

Step 16: Assemble the oral syringe and store in a clean place until the next use.
Replace the oral syringe after 7 days of use, or if:

- there is any damage to the barrel, plunger, or tip
- the dosage marking is no longer clearly recognizable
- it becomes difficult to move the plunger

APPENDIX VIII: CSF AND PLASMA PHARMACOKINETIC STUDY FORM

COG Pt ID # _____ Date: _____
Please do not write patient names on this form or on samples.

Patient Weight: _____kg Body Surface Area: _____m^2

Larotrectinib Dose Level: _____ mg/m^2 BID Larotrectinib Daily Dose: _____ mg BID

For all patients with leukemia, a CSF and plasma sample will be collected after Cycle 1, during the first disease evaluation after starting protocol therapy. The plasma sample will be obtained as close as possible to the same time as the CSF sample. In patients who are undergoing lumbar puncture (LP) for intrathecal chemotherapy administration, a CSF and plasma sample will also be collected at the time of lumbar puncture. The plasma sample will be obtained as close as possible to the same time as the CSF sample. Samples will be collected during Cycle 1 on the following days: Day 8, Day 15, and Day 22. There is no required time window from the most recent larotrectinib dose, but the dose and time of administration must be recorded.

Record the exact time both samples are drawn along with the exact time and dose of the most recent dose of larotrectinib that was given prior to the lumbar puncture.

Sample No.	Time Point	Scheduled Collection Time	Actual Date Sample Collected	Actual Time CSF Collected (24-hr clock)	Actual Time Plasma Collected (24-hr clock)
Most recent larotrectinib dose prior to LP Date:___/___/___ Time Dose Given: |__|__| : |__|__| Actual larotrectinib dose administered _____ mg = _____ mg/m^2					
1*	Cycle 1, Day 8	At time of lumbar puncture		|__|__| : |__|__|	|__|__| : |__|__|
Most recent larotrectinib dose prior to LP Date:___/___/___ Time Dose Given: |__|__| : |__|__| Actual larotrectinib dose administered _____ mg = _____ mg/m^2					
2*	Cycle 1, Day 15	At time of lumbar puncture		|__|__| : |__|__|	|__|__| : |__|__|
Most recent larotrectinib dose prior to LP Date:___/___/___ Time Dose Given: |__|__| : |__|__| Actual larotrectinib dose administered _____ mg = _____ mg/m^2					
3*	Cycle 1, Day 22	At time of lumbar puncture		|__|__| : |__|__|	|__|__| : |__|__|
Most recent larotrectinib dose prior to LP Date:___/___/___ Time Dose Given: |__|__| : |__|__| Actual larotrectinib dose administered _____ mg = _____ mg/m^2					
4	End of Cycle 1	At time of lumbar puncture		|__|__| : |__|__|	|__|__| : |__|__|

* Only for leukemia patients receiving intrathecal therapy.

One copy of this CSF and Plasma Pharmacokinetic Study Form should be uploaded into RAVE. A second copy should be sent with the samples to the address listed in Section 7.3.3.4. See Section 7.3.3.3 for detailed guidelines for packaging and shipping CSF and plasma PK samples.

Notes_____
_____
_____
_____

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

Signature: _____ Date:_____
(site personnel responsible for collection of samples)

APPENDIX IX: 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 X-A: 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 X-B for dosing preparation of the larotrectinib liquid formulation.

Larotrectinib Dosing Table

BSA (m2)	Starting Dose 100 mg/m2/ dose PO BID	Dose Reduction 1	Dose Reduction 2	Dose Reduction 3
0.66-0.87	75 mg BID	50 mg BID	34 mg/dose BID Use liquid formulation	18 mg/dose BID Use liquid formulation
≥ 0.88	100 mg BID	75 mg BID	50 mg BID	25 mg BID

Patients with BSA ≥ 0.66 m^2 may be switched to the liquid formulation at the same dose level if their ability to swallow capsules changes during the treatment.

APPENDIX X-B: 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 X-A for dosing nomogram for larotrectinib capsule formulation).

Up to three dose reductions of larotrectinib will be allowed for dose limiting toxicities as outlined in Section 5.0:

- 1st dose reduction: 75 mg/m^2/dose BID (maximum of 75 mg/dose BID)
- 2nd dose reduction: 50 mg/m^2/dose BID (maximum of 50 mg/dose BID)
- 3rd dose reduction: 25 mg/m^2/dose BID (maximum of 25 mg/dose BID)

The concentration of 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 (100 mL per bottle).

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

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 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 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 XI: QOL AND NEUROCOGNITIVE ASSESSMENTS

A standardized battery of parent-report measures has been developed to provide a brief assessment of the child's executive, adaptive, and social/emotional/behavioral functioning as well as overall quality of life. The battery was designed to strike a balance between achieving research goals while also minimizing the burden on children with cancer and their families. The battery of measures will take approximately 45 minutes to complete, and all measures will be administered at four distinct time points: within 4 weeks after enrollment, 6 months (± 4 weeks) after enrollment, 12 months (± 4 weeks) after enrollment, 24 months (± 4 weeks) after enrollment, and 4-5 years after enrollment. The measures that are administered at each time point depend on the child's age at the time of the assessment (see Table 1). General information about each of the measures in the battery is provided below. Please refer to Attachment 1 for information about administration order of these measures. Please see Attachment 2 for information about how to respond to critical items for the measures included in the assessment battery.

At least one parent or guardian must have receptive and expressive language skills in English to complete the parent-reported neurocognitive, behavioral, and QoL assessments. Patients who do not meet this criteria will not complete the neurocognitive, behavioral and QoL assessments.

Table 1. COG Standardized Neuropsychological and Behavioral Battery (parent reports)

	Child's Age (Years : Months)		
	< 2:0	2:0 ↓ 5:11	6:0 ↓ older
Attention and Behavioral/Social Function			
BASC-3 *(20 min)*		X	X
Executive Function			
BRIEF-P *(5 min)*		X	
BRIEF-2 *(5min)*			X
Adaptive Function			
ABAS-III *(15 min)*	X	X	X
Quality of Life			
PedsQL 4.0 (Generic Module only)		X	X

Index of Test Abbreviations	
ABAS-III	Adaptive Behavior Assessment System – 3rd Edition
BASC-3	Behavior Assessment System for Children – 3rd Edition
BRIEF-2	Behavior Rating Inventory of Executive Function Scales, Second Edition
BRIEF-P	Behavior Rating Inventory of Executive Function – Preschool Version
PedsQL 4.0	Pediatric Quality of Life Inventory Version 4.0 (Generic Module)

Parent-Report Measures

Adaptive Behavior Assessment System – 3rd Edition (ABAS-III)
The parent-report form of the ABAS-III will be used for the assessment of adaptive skills in individuals from birth to 18 years of age (patients ≥18 years of age will complete a self-report form). Separate scale scores are available for 11 skills areas, as well as for 3 adaptive domains (Conceptual, Social and Practical) and a General Adaptive Composite (GAC). The internal consistency ranges from .91 to .99 for the adaptive domains and the GAC.

Behavior Assessment System for Children – 3rd Edition (BASC-3)
The BASC-3 describes the behaviors, thoughts, and emotions of children and adolescents. The parent rating scale will be utilized for individuals who are at least 2 years and less than 18 years of age. Patients who are ≥ 18 years of age will complete a self-report form and no parent-report form will be used. This measure yields composite and scale scores in the domains of externalizing, internalizing, school, and other problems as well as adaptive skills and behavioral symptoms. **PLEASE NOTE:** General Combined sex norms (i.e., not Clinical or sex-specific norms) should be used when scoring the BASC-3.

Behavior Rating Inventory of Executive Functioning (BRIEF-2; BRIEF-P) is a parent-completed measure of executive function behaviors in the home environment. There are two versions available: one for preschoolers (BRIEF-P) and one for older children and adolescents (BRIEF-2, Second Edition). Executive functions are defined as "a collection of processes that are responsible for guiding, directing, and managing cognitive, emotional and behavioral functions, particularly during active, novel problem solving".[54] The Parent Form of the BRIEF-2 contains 63 items within nine domains that measure different aspects of executive functioning. These nine Scales form three broader indexes of executive function, Behavior Regulation and Emotion Regulation, and Cognitive Regulation, as well as an overall score, The Global Executive Composite. Internal consistency of the Parent Form Scales ranges from .80 to .98. The BRIEF also has well-established content and construct validity.

Pediatric Quality of Life Inventory Version 4 (PedsQL 4.0)
The PedsQL 4.0 is a modular approach to measuring health-related quality of life in healthy children and adolescents as well as in those with acute and chronic health conditions. The Generic Version consists of 23 items, and yields domain scores for Physical, Emotional, Social, and School Functioning as well as summary scores for Total Quality of Life, Physical Health, and Psychosocial Health. Parents will complete the age-appropriate parent-report form for all patients under age 18.

Data Handling
The assessment measures will be provided to all sites who have a patient enrolled. The appropriate packet of measures will be mailed to the site CRA prior to each assessment window. After completion, the questionnaire measures (labeled with the patient's COG ID) should be sent to Krystal Robinson, PsyD (see Study Committee) for scoring. Hard copies of the raw data (completed questionnaire) will be retained at each institution and must be secured according to research standards.

ATTACHMENT 1: ADMINISTRATION ORDER FOR NEUROPSYCHOLOGICAL AND BEHAVIOR BATTERY

The measures vary by age group and should be completed in the order presented below.

Age at Testing	Parent Report
Birth through 1 year, 11 months	1. ABAS-III: *Parent/Primary Caregiver Form (Ages 0-5)*
2 years, 0 months through 5 years, 11 months	1. PedsQL 4.0 Generic Version 2. BASC-3: *Parent Rating Scales-Preschool (Ages 2-5)* 3. BRIEF-Preschool Version 4. ABAS-III: *Parent/Primary Caregiver Form (Ages 0-5)*
6 years, 0 months and older	1. PedsQL 4.0 Generic Version 2. BASC-3: *Parent Rating Scales-Child (Ages 6-11)* or *Parent Rating Scales-Adolescent (Age 12-21)* 3. BRIEF-2 (Second Edition) 4. ABAS-III: *Parent Form (Ages 5-21)*

ATTACHMENT 2: CRITICAL ITEMS

The Behavior Assessment System for Children – 3rd edition (BASC-3) includes questions related to suicidal ideation, known as "critical items." The purpose of highlighting these items is to be sure that the individual administering the battery checks specific items at the end of a testing session. If a critical item is endorsed, it is **IMPERATIVE** that the physician/social worker/psychologist/neuropsychologist is informed immediately and that he/she determines whether the child's parents and/or physician will be contacted. If any indication of a potential problem is detected, parents will receive individual consultation with the physician/social worker/psychologist/neuropsychologist on site who will explain the meaning of the scores and refer to a qualified professional for a more thorough Follow-up evaluation.

Summary of critical items on the BASC-3

- Ages 6 to 11 years: Parent-report
    - Item #92: Says "I want to die" or "I wish I were dead"
    - Item #138: Says "I want to kill myself"

- Ages 12 to 21 years: Parent-report
    - Item #60: Says "I want to kill myself"
    - Item #90: Says "I want to die" or "I wish I were dead"

APPENDIX XII: TOXICITY-SPECIFIC GRADING

Bilirubin

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

ALT: For the purpose of this study, the ULN for SGPT 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 SGOT 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