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June 11, 2024

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Dear Ms. Kruhm,

Enclosed please find Amendment #8 to protocol APEC1621F, *NCI-COG Pediatric MATCH (Molecular Analysis for Therapy Choice)- Phase 2 subprotocol of Ensartinib in patients with tumors harboring ALK or ROS1 genomic alterations*, for CTEP review.

Amendment #8 is in response to a Request for Rapid Amendment (RRA) from Dr. Steven Gore (steven.gore@nih.gov) dated May 21, 2024. The purpose of this requested amendment is to provide new and/or modified risk information for ensartinib. The revised CAEPR for ensartinib (Version 2.4, April 18, 2024) has been inserted in the protocol, and the associated risk information in the informed consent document has been revised. The requested revisions are detailed in the summary of changes below. Please find attached the revised APEC1621F protocol and consent documents.

Sincerely,

Lee Baker, MPH, Protocol Coordinator (for)
Meredith Irwin, MD, APEC1621F Study Chair and
Douglas S. Hawkins, MD, COG Group Chair

CHILDREN'S ONCOLOGY GROUP

SUMMARY OF CHANGES: PROTOCOL DOCUMENT

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

#	Section	Comments
1.	Throughout	The version date has been updated throughout.
2.	Title Page	Page numbers were added to the title page.
3.	9.1	The version date of Section 9.1 (Ensartinib) has been updated to May 22nd, 2024.
4.	9.1.3	The Comprehensive Adverse Events and Potential Risks list (CAEPR) for Ensartinib ((X-396 hydrochloride) NSC# 784729)) has been updated to Version 2.4, dated April 18, 2024.
5.	9.2.1; 9.3.1.3; 9.3.2	The Agent Ordering Information has been updated with PMB's centralized inventory management system (AURORA).
6.	9.3.1.1	The statement was revised as follows: • The investigator, or a responsible party designated by the investigator, must maintain a ~~careful record~~**complete accountability** of the receipt, dispensing and final disposition of all agents received from the PMB using the appropriate NCI Investigational Agent (Drug) Accountability Record (DARF) available on the CTEP forms page.
7.	9.3.1.2	A new subsection, Product Quality Complaint (PQC), has been added.

Activated: July 24th, 2017
Closed:

Version Date: 06/11/2024
Amendment # 8
Page Number(s): 105

CHILDREN'S ONCOLOGY GROUP

APEC1621F

NCI-COG PEDIATRIC MATCH (MOLECULAR ANALYSIS FOR THERAPY CHOICE)- PHASE 2 SUBPROTOCOL OF ENSARTINIB IN PATIENTS WITH TUMORS HARBORING ALK OR ROS1 GENOMIC ALTERATIONS

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

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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, or CTSURegHelp@coccg.org to receive further instruction and support. Contact the CTSU Regulatory Help Desk at 1-866-651-CTSU (2878) for regulatory assistance.	Please refer to the patient enrollment section of the protocol for instructions on using the Oncology Patient Enrollment Network (OPEN). OPEN is accessed at https://www.ctsu.org/OPEN_SYSTEM/ or https://open.ctsu.org. Contact the CTSU Help Desk with any OPEN-related questions by phone or email: 1-888-823-5923, or ctsucontact@westat.com.	Data collection for this study will be done exclusively through Medidata Rave. Please see the Data Submission Schedule in the CRF packet for further instructions.

The most current version of the study protocol must be downloaded from the protocol-specific page located on the CTSU members' website (https://www.ctsu.org). Access to the CTSU members' website is managed through the Cancer Therapy and Evaluation Program - Identity and Access Management (CTEP-IAM) registration system and requires log in with a CTEP-IAM username and password. Permission to view and download this protocol and its supporting documents is restricted and is based on person and site roster assignment housed in the CTSU Regulatory Support System (RSS).

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

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

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

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SEE Section 8.3.6, AND Section 8.4.4 FOR SPECIMEN SHIPPING ADDRESSES

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AGENT NSC# AND IND#'s
NCI-Supplied Agents:
Ensartinib
(NSC#784729 , IND#[redacted]
IND Sponsor: DCTD, NCI

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ABSTRACT

This subprotocol is a component of the NCI-COG Pediatric MATCH trial APEC1621. The APEC1621SC screening protocol details the process used to identify actionable mutations in patient tumor samples which will determine eligibility for this subprotocol. Here we will conduct a phase 2 trial of ensartinib in children with recurrent or refractory solid tumors (including non-Hodgkin lymphomas, histiocytoses and CNS involvement) harboring specified activating genetic alterations in ALK or ROS1 pathway genes. Ensartinib is a second-generation oral ALK inhibitor that also has activity against a panel of kinases including ROS1, c-met, trkA, and axl. Pre-clinical studies demonstrate ensartinib activity in cells with *ALK* and *ROS1* fusions as well as *ALK* missense mutations, including the subset of crizotinib-resistant *ALK* mutations commonly detected in neuroblastoma. Ensartinib inhibits ALK downstream signaling pathways. In comparison to crizotinib, ensartinib has also shown greater potency *in vitro* and *in vivo*. Ensartinib also has demonstrated activity in an ongoing Phase 1/2 trial for adults with NSCLC with ALK alterations. In the dose escalation portion of the trial both ALK inhibitor resistant and ALK inhibitor naive patients had measurable responses, including a subset with CNS metastases. Ensartinib has been well tolerated by adults and the most significant toxicity has been skin rash, which has been easily managed. Ensartinib will be given daily to patients with *ALK* and *ROS1* genetic aberrations in 28-day cycles.

EXPERIMENTAL DESIGN SCHEMA

Treatment Schedule Table	
Days 1-28	130 mg/m^2 once daily Ensartinib
Day 28	Evaluation

Ensartinib will be administered orally in capsules given daily in 28-day cycles. Evaluations will occur at the end of every other cycle x 3, then every 3 cycles.

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

1.0 GOALS AND OBJECTIVES (SCIENTIFIC AIMS)

1.1 Primary Aims

1.1.1 To determine the objective response rate (ORR; complete response + partial response) in pediatric patients treated with ensartinib with advanced solid tumors (including CNS tumors), non-Hodgkin lymphomas or histiocytic disorders that harbor *ALK* or *ROS1* fusions or that harbor *ALK* missense mutations.

1.2 Secondary Aims

1.2.1 To estimate the progression free survival in pediatric patients treated with ensartinib with advanced solid tumors (including CNS tumors), non-Hodgkin lymphomas or histiocytic disorders that harbor *ALK* or *ROS1* fusions or that harbor *ALK* missense mutations.

1.2.2 To obtain information about the tolerability of ensartinib in children with relapsed or refractory cancer.

1.2.3 To provide preliminary estimates of the pharmacokinetics of ensartinib in children with relapsed or refractory cancer.

1.3 Exploratory Aims

1.3.1 To evaluate other biomarkers as predictors of response to ensartinib and specifically, whether tumors that harbor different missense mutations or fusions (including the crizotinib resistant F1174L *ALK* variant) will demonstrate differential response to ensartinib treatment.

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

2.0 BACKGROUND

2.1 Introduction/Rationale for Development

ALK alterations in pediatric cancer:
The *ALK* gene encodes the anaplastic lymphoma kinase (ALK), which is a receptor tyrosine kinase that is activated in a variety of histologically distinct tumors as a result of genomic alterations, including rearrangements, missense mutations and amplifications. *ALK*, which is localized on the short arm of chromosome 2p23, encodes a 220kd protein that is a member of the insulin receptor superfamily with extracellular, transmembrane and intracellular kinase domains. ALK alterations in tumors include translocations, missense mutations, and overexpression, due in part to amplification. In ALK rearrangements the N-terminal (5') fusion partners provide dimerization domains to the ALK kinase domain leading to ligand independent activation of the ALK kinase. Signaling pathways downstream of ALK activation that mediate growth and cell cycle progression include PI3-Kinase-Akt, Jak/STAT3, Ras/MAPK (reviewed in [1]). Many tyrosine kinase inhibitors (TKIs) have been developed to target ALK and ROS1 alterations and current challenges include resistance to 1st generation ALK TKIs, difficulty targeting subsets of missense mutations, and inability to cross the blood brain barrier and demonstrate efficacy against

CNS metastatic lesions.

ALK Point mutations: Neuroblastoma: Missense mutations result in single amino acid substitutions and are localized to the tyrosine kinase domain (exons 22-28), promoting constitutive activation of the ALK kinase and are detected in approximately 10% of neuroblastoma tumors at the time of diagnosis. [2-4] In addition, germline *ALK* mutations have been identified in a rare subset of patients with familial neuroblastoma predisposition syndrome [8]. The most comprehensive analysis of the prevalence of somatic alterations involved 1,596 newly diagnosed neuroblastoma tumors. *ALK* amplification was detected in 4% and *ALK* point mutations were identified in 10% of tumors [5]. Although more than 85% of tumors harboured one of the three hotspot alterations R1275 (43%), F1174 (30%), and F1245 (12%) 24 different point mutations were identified many of which were shown to have oncogenic properties in vitro, and a subset were also tested for sensitivity to ALK inhibition by crizotinib or PF-06463922 (lorlatinib). [2,6] The expression of at least 11 of the 24 different patient derived *ALK* mutations identified by Bressler et al were shown to promote transformation of NIH 3T3 cells and to be associated with constitutive activation of ALK and downstream signaling. The most well characterized activating mutations in neuroblastoma in addition to mutations at the three hotspot codons (1174, 1245, 1275) include I1170N, I1170S, I1171N, Y1278S, R1192P, M1166R, L1196M AND G1128A. In the recent COG pilot study ANBL12P1 *ALK* status was assessed on diagnostic tumor samples by performing Sanger sequencing and fluorescence in situ hybridization (FISH) to detect tyrosine kinase domain (TKD) missense mutations and *ALK* amplification, respectively. The incidence of ALK aberrations in the subset of tumors from patients with newly diagnosed high-risk neruoblastoma was 14% (10% missense mutations and 4% amplification) (Personal Communication, J. Gastier Foster (Head of Reference Laboratory, BPC; M. Granger, COG ANBL12P1 Study PI), which is similar to the frequency of alterations in retrospective studies.

There is also evidence that, in addition to the 10% of neuroblastoma patients at diagnosis with clonal *ALK* mutations, additional tumors have subclonal mutations at variant allele frequencies (VAF) that can be detected at levels <1% and the VAF has been shown to increase in serial samples obtained from progression and/or relapse [7,8]. This discovery of subclonal ALK mutations at diagnosis may account for the recent findings from NGS studies suggesting that *ALK* mutations are more common at recurrence. [9,10] In a study of matched diagnostic and relapse neuroblastoma samples Elevid et al detected RAS/MAPK aberrations in 18/23 relapse tumors, including 9 with *ALK* point mutations. It should be noted that in NSCLC tumors with *ALK* fusions missense mutations have been identified as a mechanism of resistance to ALK TKI treatment.[11] This has not yet been reported in pediatric patients, but as increased numbers are treated upfront with crizotinib and other TKIs the development of missense mutations in resistant tumors will need to be studied. In addition to neuroblastoma and NSCLC a subset of anaplastic papillary thyroid carcinomas harbor ALK missense mutations.[12]

Based on these reports, the prevalence of *ALK* mutations in neuroblastoma at recurrence is likely to be significantly more than the 10% incidence at the time of diagnosis and with NGS platforms it is possible that in addition to neuroblastoma and thyroid cancers other malignancies may have detectable ALK missense mutations.

Fusions: ALCL and IMT: ALK rearrangements are observed in a variety of tumor types and ALK fusion proteins, which preserve the kinase domain, dimerize to constitutively activate ALK. Translocations involving ALK are detected in Anaplastic Large Cell

Lymphoma (ALCL), inflammatory myofibroblastic tumor (IMT), and non-small cell lung cancer (NSLC) and most of these tumors express high levels of the ALK protein that can be detected by immunohistochemistry. [1,13] In 83% of pediatric ALCL ALK-NPM [14] translocations are identified, and several other less common ALK fusions have also been reported including ALK fusions to ALO17, TFG, MSN, TPM3, TPM4, ATIC, MYH9, CLTC [13]. In approximately half of all IMTs ALK fusions have been identified, involving at least 13 different genes, including TPM3, TPM4, CLTC, ATIC, SEC31A, RANBP2, PPFIBP, CARS. [13,15] With NGS strategies increasingly used, ALK fusions (involving the ALK kinase domain) and mutations are being identified in other histologic tumor types including undifferentiated renal cell carcinoma[16], and leukemia. [17]

Other ALK aberrations: There are several reports describing increased ALK protein expression in subsets of rhabdomyosarcoma tumors (most commonly translocation positive subsets), in part due to gene amplification.[18] There are also reports of overexpression in melanoma, NSLC, neuroblastoma, glioblastoma, astrocytoma ovarian cancer breast cancer, Ewing's sarcoma and retinoblastoma (reviewed in [1,19]). In addition, there is evidence for the expression of alternative ALK protein isoforms in melanoma and less commonly in other tumor types including detection in neuroblastoma cell lines.[20] The novel ALK transcripts initiate from an alternative transcription initiation site in intron 19 and result in three truncated ALK proteins with molecular weights between 58-61 kd, including the intracellular tyrosine kinase domain, but lacking the extracellular domains. The expression of these truncated ALK isoforms found in melanoma results in activated signaling *in vitro* and promotes tumorigenesis *in vivo*. Isoforms that result in splicing of exon 23 and 27, resulting in loss of part of the TKD, are detected in 11% of NSLC and often co-exist with ALK-EML4 fusions. [21] The role of ALK inhibitors in most tumors with high expression of wild-type full length ALK or the truncated isoforms has not been reported. There are reports examining the sensitivity of a single neuroblastoma cell line (NB-1) with *ALK* amplification to ALK TKIs. Crizotinib and ensartinib inhibit the growth of NB-1 cells [5] (and C. Liang, X-covery, personal communication).

***ROS1 alterations in pediatric cancer*:** *ROS1* is localized on chromosome 6q21and encodes the ROS1 protein that is a member of the sevenless subfamily of tyrosine kinase insulin receptor genes.[22] Like ALK ROS1 has an extracellular ligand binding domain, transmembrane spanning region and an intracellular tyrosine kinase domain. Signaling downstream of ROS1 involves JAK/STAT, RAS/MAPK, and PI3K pathways. Fusions involving ROS1 have also been identified in subsets of ALK fusion negative IMT in pediatric and adult patients [23] and NSLC (Reviewed in [24,22]) . In all ROS1 fusions reported to date the ROS1 TK domain is retained and the breakpoint usually clusters between introns 32 and 35.[22] Fusions often lead to loss of the ROS1 transmembrane domain, which affects subcellular localization. There are more than 20 ROS1 fusion partners that have been identified including CD74, SDC4, EZR, SLC34A2.

Responses to the ALK/met/ROS1 inhibitor crizotinib have been reported in subsets of patients with ROS1 fusions. [13,23] In addition to IMT several other histologic tumor types have been reported to harbor ROS1 fusions (glioblastomas, NSCLC, ovarian, gastric and colon cancers) as well as subsets of spitz tumors and melanomas[25,26] and thus, it is possible with NGS approaches that, in addition to IMT, other pediatric tumors may have ROS1 gene rearrangements. ROS1 rearranged tumors often acquire crizotinib resistance due to acquisition of point mutations and activation of alternative secondary kinases. Second generation ROS1 inhibitors such as cerinitib, foratenib, and cabozantinib have been shown to overcome ROS1 resistance in ROS1 rearranged tumors with additional resistance /

missense mutations.[27]

There are few studies examining the incidence of ROS1 rearrangements in IMT. Antonescu identified 6/62 IMT to have ROS1 rearrangements.[28] Lovly and colleagues detected ROS1 fusions in 44% of ALK negative IMT.[23]

Pediatric ALK and ALK/ROS1 inhibitor trials:
The first pediatric ALK inhibitor Phase 1 trial (ADVL0912) was reported by Mosse et al[29] and the Phase 2 expansion is closed to accrual, but not yet reported. In the Phase 1 study of 79 patients aged 1-22 years there were 14 objective responses, which were enriched in patients with known ALK aberrations. The majority of responses in patients with ALK aberrations were reported in patients harboring ALK fusions, including 8 of 9 patients with ALCL, 3 of 7 patients with IMT, and 1 of 2 with NSCLC. One of 11 patients with neuroblastoma harboring ALK missense mutations had an objective response and two had stable disease. These data may reflect the findings in pre-clinical studies that cell lines and xenografts harboring ALK missense mutations are less sensitive than those expressing ALK fusion proteins[5] (described in more detail in Section 2.2.1).

A pediatric Phase 1 trial combining crizotinib with chemotherapy (COG ADVL1212) is ongoing. Pre-clinical studies support synergy for combination therapies in xenografts harboring various ALK missense mutations including 1174 substitutions, which are resistant to single agent crizotinib.[30] There is also an ongoing pediatric Phase 1 trial for ceritinib (LDK378) for patients with ALK missense mutations, fusions, or overexpression (NCT01742286).

Two ALK inhibitors (crizotinib and ceritinib) are FDA approved for adults. Additional trials are ongoing in adults with other ALK 1st and 2nd generation inhibitors including Phase 3 (alectinib) and Phase 1/2 (ensartinib, loratinib, AP26113, ASP3026, TSR-011).

Ensartinib
Ensartinib (X-396) is an ALK second generation TKI that has 10-fold increased potency in blocking ALK phosphorylation in comparison to crizotinib with an IC50 <0.25 nM. In vitro kinase binding assays also showed IC50 < 25 nM for other kinases including ABL T315I, EPHA2 (Ephrin A2 kinase), MET, and ROS1.[31,32] In addition, ensartinib demonstrated efficacy against multiple cells with ALK fusions and ALK missense mutations at IC50 <100nM. Cells and xenografts treated with doses of ensartinib that inhibit growth also demonstrate downregulation of downstream signaling targets including Akt and Erk (*see Section 2.2.1*). This data together with *in vitro*, *in vivo* efficacy and toxicity data summarized below support study of ensartinib in patients with crizotinib sensitive and resistant ALK and ROS1 alterations.

2.2 Preclinical Studies

2.2.1 Antitumor Activity

There are many publications demonstrating efficacy in pre-clinical models for the first generation ALK inhibitor crizotinib (*in vitro* and ,in a subset, *in vivo*) in cells with fusions of ALK and ROS1 and a subset of ALK missense mutations (reviewed in [13]). These include pre-clinical models of pediatric malignancies such as ALCL[33] and neuroblastoma.[2,5] The common neuroblastoma missense mutation at codon 1174 is resistant to crizotinib and other 1st generation ALK inhibitors[2,5] and not all patients with ALK aberrations demonstrated responses to crizotinib in the pediatric

Phase 1 trial.[29] Cells that express ALK fusions as well as crizotinib-resistant mutant proteins are sensitive to the 2nd generation ALK inhibitors loratinib[6] and ensartinib.[31,32] To date it appears that, in comparison to cells with missense mutations, in general cells harboring most ALK fusions are more sensitive to many 1st generation ALK TKIs. For neuroblastoma associated missense mutations the sensitivity to ALK TKIs varies depending on the specific mutation site, which influences its effect on ALK binding to ATP and/ or to crizotinib.[5] Recent data also suggests that among different ALK fusion variants some are more sensitive than others to crizotinib *in vitro* and in humans. [34]

In comparison to crizotinib, ensartinib is 10-fold more potent at inhibiting ALK phosphorylation and growth *in vitro*.[32] Summaries of the *in vitro* and *in vivo* studies demonstrating ensartinib efficacy are summarized in Table 1. *In vitro* studies comparing the sensitivity of cell lines with ALK fusions (H3122, H228, and STE-1) to 4 ALK TKIs (crizotinib, ceritinib, alectinib, ensartinib) demonstrate that ensartinib is the most potent at inhibiting growth[32] (and personal communication C. Lovly and C. Liang, Xcovery). Baf cells transfected to overexpress ALK missense mutant and fusion proteins also were sensitive to ensartinib. Furthermore, neuroblastoma cells harboring missense mutations (at codons 1174 and 1275) were more sensitive to ensartinib (compared to crizotinib) *in vitro*. Furthermore, mice with subcutaneous or intracranial SH-SY5Y (F1174L) tumors responded to ensartinib but not crizotinib treatment (Table 1).[32] Ensartinib was also effective in mice with ALCL xenografts (SU-DHL-1) harbouring NPM-ALK fusions *and* F1174L mutations. In addition *in vitro* ensartinib sensitivity was reported for one neuroblastoma cell line with ALK amplification (NB-1) and a glioblastoma cell line (U87) with activated MET [32]. Although cell lines with ROS1 alterations have not been tested with ensartinib two different in vitro assays demonstrate similar levels of ROS1 and ALK inhibition by ensartinib- the Ambit in vitro kinase binding assay and Invitrogen in vitro kinase catalytic assay.[32] In addition, crizotinib has activity in pre-clinical ROS1 rearranged models of NSCLC [35-37] and in patients with tumors harboring ROS1 fusions including NSCLC (reviewed in [24]) as well as at least one pediatric patient with IMT. [23]

Specific data demonstrating ensartinib activity against different ALK missense mutations and fusions *in vitro* are also shown in Tables 2 and 3. Table 2 lists ALK mutant proteins for which phosphorylation is inhibited by ensartinib. Table 3 lists the IC50 for ensartinib-mediated inhibition of wild-type, fusion and missense mutant variants of ALK and ROS1 as well as other kinases targeted by ensartinib.

Table 1: Efficacy of ensartinib against cells with varying ALK genomic alterations.

Cells	Genomic alteration	In vitro /in vivo Efficacy	Other
H3122 (NSCLC)	EML4-ALK v1*	In vitro	Superior;comparsion: crizotinib,ceritinib, alcetinib
H228 (NSCLC)	EML4-ALK v3	In vitro	"
STE-1 (NSCLC)	EML4-ALK v1	In vitro	"
"	"	In vivo	

Baf/ F1174L	F1174L	In vitro	Crizotinib resistant
Baf/ C1156Y	C1156Y	In vitro	Crizotinib resistant
Baf/ L1196M	L1196M	In vitro	Crizotinib resistant
NB-1643 (NB)	R1275Q	In vitro	Ensartinib superior to 6 other ALK inhibitors
SH-SY5Y (NB)	F1174L	In vitro	"
SH-SY5Y(NB)	F1174L	In vivo (including intracranial)	Crizotinib resistant
SU-DHL-1 (ALCL)	NPM-ALK *and* ALKF1174L	In vivo	

Table 1: Shown are cell lines harboring ALK genomic alterations for which there is activity of ensartinib.
* the variants refer to differing EML4 breakpoints. The ALK breakpoint in EML4-ALK fusions always lies close to the 5' end of exon 20; however, the fusion points within the EML4 gene are variable.

Table 2: In vitro phosphorylation inhibition of ALK mutant proteins by Ensartinib

ALKmutant proteins
Wild-type
M1166R
I1170N
I1170S
I1171N
R1275Q
Y1278S
G1286R
F1174L
F1245C
F1245V
G1128V
T1151M
L1196M

Table 2: Shown are mutant proteins for which ensartinib inhibits ALK phosphorylation. In all cases ensartinib inhibition was more potent than crizotinib (personal communication, Xcovery)

Table 3 Kinases Inhibited by Ensartinib (IC_{50}, nM)

Kinase	IC_{50} (nM)	Kinase	IC_{50} (nM)
ALK	0.16	AXL	12.3
ALK (C1156Y)	0.28	c-MER	18.8
ALK (F1174L)	0.16	c-MET	9.59
ALK (F1174L)-EML4	0.53	EPHA1	6.22
ALK (F1174L)-NPM1	0.47	EPHA2	1.14
ALK (F1174S)	0.17	EPHB1	8.59
ALK (G1202R)	3.83	FMS	13.44
ALK (G1269A)	1.14	LTK	11.00
ALK (G1269S)	1.39	NEK1	6.08
ALK (L1152R)	0.58	ROS/ROS1	1.41
ALK (L1196M)	0.32	ROS1-GOPC	0.98
ALK (R1275Q)	1.06	SLK	11.00
ALK (S1206R)	0.17	TRKA	8.00
ALK(T1151L-1152insT)	0.26	TRKA-TFG (TRK-T3)	0.46
ALK (T1151M)	0.13	TRKA-TPM3	0.62
ALK-NPM1	0.68	TRKA-TPR	1.22
ALK-TFG	0.73	TRKB	3.39
ALK-TPM3	0.21	TRKC	0.46

Table 3: Kinases most potently inhibited by ensartinib. [31] Isotope labeled biochemical assay to determine IC_{50} for ensartinib inhibition of each of the indicated kinases.

2.2.2 Animal Toxicology

Short-term (single and multiple doses) and longer term (28 day, 13 week) studies were carried out in dogs and rats and overall there were similar findings in both species, which are outlined in detail in the Investigational Brochure.[32] In the 28 day studies the severely toxic dose to 10% (STD10) of the rats was 50mg/kg/day and the highest non-severely toxic dose (HNSTD) in dogs was 15 mg/kg/day. Findings included skin lesions, emesis, decreased weight, clinical pathology changes, and microscopic changes in the skin, stomach (non-glandular in rats) or skin, marrow, spleen and thymus (dogs only).

For the 13-week studies rats were administered once daily doses of 12.5, 25 or 50 mg/kg/day via oral gavage. Main findings included scabs and thinning of the hair coat (mainly at the highest dose). Skin lesions improved during the recovery phase. The no observable adverse effect level (NOAEL) was determined to be 50 mg/kg/day and corresponded to an AUC 0-24 of 619 and 1230 ng/ml and 8010 and 16900 ng-hr/ml on day 1 and during week 13, respectively. For dogs the doses were 5,10, 20/15 mg/kg/day and also resulted in adverse skin and pelage lesions that required veterinary intervention and dose suspension for 6 days. Dose reduction to 15mg/kg/day was tolerated with less severe skin lesions and reversal of the initial severe findings. Thus, the NOAEL is 15 mg/kg/day in dogs corresponding to a peak Cmax of 575 ng/ml and AUC 0-24 of 6610 ng-hr/ml on week 13.

Single dose pharmacokinetic studies were performed in rats and dogs. For the rats (fasted) doses were 1 mg/kg IV or 10mg/kg oral gavage and samples were

collected over 8 hours. $T_{1/2}$ was approximately 1.5 hour and clearance (CL) was 1.6 L/hr/kg for the IV dosage. Following oral gavage, the masimal concentration was at 0.1 hours in the 1mg/kg IV and 0.8 hours in the 10mg/kg Po dose. $T_{1/2}$ was approximately 2.8 hours. In a separate study rats dosed at 25 mg/kg oral gavage had a Tmax a cmax of 307 ng/ml and AUC0-8 esteimated at 1453ng-hr/ml. For dogs (beagle) dosed at 1mg/kg IV $t_{1/2}$ was ~2.7 hours and Cl was 2.4 L/hr/kg. Following po administration there was rapid absorption (Tmax 1.3 hour), cmax 410ng/ml, AUC 0-24 of 4,427 ng-hr/ml with a systemic bioavailaility of 119% and $t_{1/2}$ of 7.8 hours.

Toxicokinetics was also performed for dose escalation and 10 day repeat dosing at the Phase 2 dose for 10 days in dogs and monkeys and the data is provided in the investigational brochure.[32]

Distribution and Metabolism: Tissue Distribution studies were performed in mice (including mice with SH-SY5Y neuroblastoma xenografts) and demonstrated that by 8 hours post dose administration the plasma concentrations had decreased more rapidly that the brain and tumor concentrations. This resulted in brain concentrations that were 20-23% of the plasma concentration and tumor concentrations that were 17-32-fold higher than plasma. The binding of plasma proteins was evaluated by analyzing plasma from mice, rats, dogs and humans. Binding was similar across species with values ranging from 90-97%. For metabolism studies ensartinib was incubated with liver microsomes from dogs, monkeys and humans and analyzed by mass spectrometry, which identified 20 metabolites, the majority of which were detected in all species. No excretion studies were performed in animals.

Pharmacology studies were also done and are summarized in Section 2.3.3.

2.3 Adult Studies

There have been numerous clinical trials of ALK inhibitors (Phase 1, 2, and 3) alone and in combination with other agents and the majority of the >150 current ALK/ROS1 TKI trials listed on nci.gov site as of August 2016 include an eligibility requirement for the presence of somatic genomic alteration in ALK, ROS1, or c-met. Summarized below is the experience with ensartinib.

2.3.1 Phase 1 Studies:

The dose escalation of the Phase 1/2 trial ("Xalt2" /NCT01625234) used doses ranging from 25 to 250 mg daily. The MTD was not officially reached but 2 DLTs were identified. Fluid retention (200 mg dose) and skin toxicity were observed at the highest dose level (250 mg). No additional DLTs were identified at these dose levels or in the subsequent dose expansion to date. The dose of 225 mg/day was chosen as the RP2D for the expansion cohort of patients with ALK aberrations. Thus, the RP2D was *below* the MTD. Preliminary results for the Phase 1 and part of the Phase 2 were presented at AACR, 2016[31] (and personal communication, C Liang, X-covery). The abstract reported on the first 63 patients including 35 with ALK fusions. The longest duration of treatment was 40 cycles (28 days/cycle). No study related deaths were observed. The most common adverse event related to ensartinib treatment was rash, mostly grade 1 or 2 in 52% of patients. Other commonly reported related adverse events were nausea (29%), fatigue (25%), vomiting (24%), and pruritus (21%). No other related AEs were seen at a rate of >

20%. The incidence of all grade 3/4 toxicities was 15.9% with the most common related grade 3 or higher adverse event being rash (11%). Rash improved with holding therapy and dose reduction or addition of topical steroids while maintaining dose. No additional > grade 3 toxicities were observed in more than one patient. To date no significant CNS toxicities have been identified.

Preliminary response data is available for 63 total patients. Of the total cohort of 63 patients there was 1CR, 19 PR, 12 SD and 18 PD (2 not evaluable, 11 missing data (Personal communication/ X-Alt2 Study report, L.Horn, C. Liang, X-covery). The objective response rate was 40%. At the 2016 AACR meeting preliminary response data was presented for the 35 evaluable ALK+ NSCLC patients treated at 200 to 250 mg daily for up to 30 months.[31,32] Seven of eight crizotinib naïve patients had a PR with durable responses and only two progressed after more than 2 years on study. Notably the 1 patient of 8 who did not respond had an ALK FISH that was reported as borderline and no fusion transcript could not be detected by NGS. In crizotinib-resistant patients 12 of 20 (60%) had an objective response. In crizotinib-resistant patients that did not receive a prior 2nd generation ALK TKI (ceritinib, alectinib), 16 of 19 have demonstrated reductions in their target lesion dimensions. In patients with target CNS lesions, 5 of 8 have demonstrated reductions in the measurements of the CNS lesion. These results suggest that both ALK TKI naïve and resistant patients with ALK fusion positive NSCLC tumors, including those in CNS, have responses to ensartinib.[32]

2.3.2 Phase 2 and 3 Studies:

The Phase 2 portion of the first Phase 1/2 study of ensartinib is discussed above in *section 2.3.1.* There is also a Phase 3 trial ("eX-alt3"), which opened in 2016, comparing ensartinib to crizotinib in patients with NSCLC with ALK genomic alterations (NCT02767804).

2.3.3 Pharmacology/Pharmacokinetics/Correlative and Biological Studies

Pharmacology

In vitro: The *in vitro* SelectScreen Biochemical hERG (human ether-a-gogo-related gene) using the Predictor™ hERG fluorescence polarization assay was used to predict whether ensartinib may inhibit potassium channels responsible for repolarization and affect the cardiac action potential, and potentially alter the QT interval. Ensartinib demonstrated no inhibition of polarization at concentrations between 1nM-10μM.

Cytochrome P450 *in vitro* studies with human liver microsomes were performed to determine whether ensartinib demonstrated inhibition of isozymes CYP1A2, 2C9, 2D6, and 3A4. At 10 μM ensartinib did not inhibit CYP1A2 or 2D6; however, ensartinib did inhibit 3A4 (22% inhibition) and 2C9 (43%). The Cmax at the recommended Phase 2 dose of 225 mg daily is < 1μM. Thus, this suggests there would not be significant drug-drug interactions.

***Animal Safety Pharmacology*:** Non clinical GLP studies were conducted to assess the safety pharmacology of ensartinib based testing for respiratory and central nervous system (CNS) effects in Sprague Dawley rats.[32] There were no significant effects of single oral doses of 50-150mg/kg on tidal volume or respiratory rates or neurological/behavioral assessments assessed up to 24 hours post dosing. Thus, the NOAEL was determined to be ≥ 150 mg/kg. In addition, doses of up to

30mg/kg given to dogs (male Beagle) did not result in changes in hemodynamic parameters (heart rate, diastolic and systolic and mean arterial pressures) or ECG abnormalities (including QTc interval and absence of arrhythmias on telemetry).

Pharmacokinetics

Adult PK data is available from data for 41 patients at different doses (Personal communication/ X-Alt2 Study report, L.Horn, C. Liang, X-covery). Maximal plasma concentration (C_{max}) was achieved 2-4 hours post day 1 drug dose and 1-4 hours post Day 22 drug dose and there was a monophasic decline. The mean value of trough concentrations on Day 8, 15, 22 were used as 24-hour concentrations on Day 22. For daily doses of 25-100 mg and 200-250 mg the $t_{1/2}$ was 15.4-22.1 hours and 20.1-42.4 hours, respectively. Steady state plasma concentration following daily dosing (25-250 mg) was reached by approximately 8 days with a mean accumulation ratio of 2.68-5.55 calculated based on AUC_{0-8}. Within the dose range of 50-225 mg the AUC_{0-8} increased in a linear dependent manner. With a dose increase of two-fold the AUC_{0-8} increased by 4.7x on day 1 and 4.1x on day 22. Compared with the 50 mg dose, at the 225 mg dose the AUC_{0-8} increased in a dose-dependent manner. When increased to 250 mg the increase in the AUC_{0-8} increased slightly more that the proportional dose increase.

The effect of food on absorption was initially examined at the 200 mg dose. For ensartinib administered after meals the maximum plasma concentration was achieved at 4 hours post dose (median Tmax) and was similar to the level for the fasting cohort (Personal communication/ X-Alt2 Study report, L.Horn, C. Liang, X-covery). However, there were differences in the exposure. After mealtime dosing was associated with delayed Cmax. With a single dose administered the Cmax occurred at 3 hours post dosing under fasting conditions (≥ 1 hour before mealtime or 2 hours after mealtime) and 6 hours when administered with food (within 30 minutes after a meal). For multiple-dose administration the Cmax was 3 hours and 4 hours for fasting and fed conditions, respectively. Following the administration with food exposure decreased by approximately 26% on day 1 and 20% on day 72 with a mean AUC_{0-8} of 526 hr-ng/ml on day 1 and 1340 hr-ng/ml on day 22. In contrast, under fasting conditions the AUC_{0-8} was 714 hr-ng/ml on day 1 and 1690 hr-ng/ml on day 22. The $t_{1/2}$ elimination half-life could not be obtained due to the short sampling interval (day 1, 24 hours and day 22, 8 hours). $T_{1/2}$ values were provided only for reference.[32] For the fasted cohort the $t_{1/2}$ at 200 mg was 13.6-23.6 hours on day 1 and 20.1-24.9 hours on day 22. For the fed cohort the $t_{1/2}$ at 200mg was 17.8 hours on day 1 and 20.3-21.5 hours on day 22.

Additional preliminary PK data to evaluate the effects of food has now been obtained for 23 patients on the expansion cohort at the RP2D dose of 225 mg, including 12 patients dosed at 225 mg without food and 11 at 225 mg with food. There was no significant difference on day 1 exposure but on day 22 the exposure is slightly higher in patients who took ensartinib with food. In addition, food significantly reduces gastrointestinal adverse events and thus, it will be recommended that ensartinib be taken with food on this study.

There is currently no PK data available in patients or healthy adults in which the capsule contents are opened and mixed with juice and thus, capsules will be administered intact on this study.

***CNS activity**:* There is pre-clinical activity in several intracranial murine models including intracranial SH-SY5Y (F1174L) neuroblastoma and H3122 EML4-ALK positive NSCLC cells. Based on murine models the estimated concentration of ensartinib in the brain is > 5 fold the concentration required to inhibit ALK positive tumors. [32] In addition, data from the ongoing Phase 1/2 trial of ensartinib reported objective responses in 4/8 patients with NSCLC brain metastases. Expansion cohorts for patients with CNS and leptomeningeal metastases are planned in the adult clinical trials.

Correlative Biological studies: Correlative Biological studies are ongoing on the Ensartinib Phase 1/2 study in adults with NSCLC. Preliminary results have demonstrated the feasibility of using cell free DNA (cfDNA) (or circulating tumor (ct) DNA) isolated from the plasma of patients to detect ALK fusions and missense mutations and monitor these alterations during therapy with ensartinib.[38] Similar studies are planned for patients enrolled on this trial to determine the feasibility of detecting ALK and ROS1 alterations in cfDNA at diagnosis and during therapy. In addition, in future studies this method may be used to identify the development of new mutations that confer resistance to therapy. Strek tubes will be used to collect cfDNA. Importantly, several publications demonstrate the ability to detect ALK fusions and missense mutations commonly found in pediatric tumors in the cfDNA isolated from patient plasma.[39,40]

2.4 Pediatric Studies

2.4.1 Prior Experience in Children

There is no prior experience with ensartinib in the pediatric age population. Two other ALK inhibitors are currently under study. The two COG crizotinib studies were summarized above in Section 2.1. There is an ongoing Phase 1 pediatric study of LDK378 (ceritinib); however, pre-clinical studies support the prediction that ensartinib would be more effective in a subset of ALK alterations (*eg* F1174L).

2.4.2 Pharmacology/Pharmacokinetics/Correlative Biological Studies

Pharmacology studies in animals and adults as discussed above, but none have been performed in pediatric patients.

2.5 Overview of Proposed Pediatric Study

This study will determine the efficacy of ensartinib in tumors with ALK and ROS1 activating mutations and fusions in pediatric and AYA patients. The pre-clinical data in tumors with ALK fusions and numerous neuroblastoma cell lines and xenografts with ALK missense mutations, including the crizotinib resistant F1174L mutation, suggest ensartinib may be effective in pediatric patients with these alterations, which may be de novo or potentially develop in patients who receive crizotinib upfront for newly diagnosed ALCL or neuroblastoma. Since approximately 1/3 of neuroblastoma associated ALK mutations involve codon 1174 and a subset of patients may have CNS lesions ensartinib is also predicted to have potential activity in these patients. Preliminary data from the first Phase 1/2 trial of ensartinib in adults with NSCLC support use of this agent in patients with crizotinib naive and resistant ALK genomic alterations, including those with CNS lesions. Since in comparison to ALK and ROS1 fusions, ALK missense mutations have shown differential sensitivity to 1st generation ALK inhibitors *in vitro* and *in vivo* this study will have two different strata- one for ALK or ROS1 fusions and a second strata for ALK missense mutations. Specific variants that can be detected by the MATCH NGS platform

that are eligible for this trial are summarized in Appendix VII-A and Appendix VII-B.

Toxicity will be assessed using CTCAE. Imaging for disease evaluation will occur every other cycle x 3, then every three cycles. Disease response will be assessed according to RECIST v1.1 criteria for solid tumors and 2-dimensional measurement for CNS tumors.

To assess biological correlates samples will be collected to isolate ctDNA for the detection of *ALK* and *ROS1* alterations in plasma at entry on MATCH and at different time points during ensartinib treatment. The study will also include pharmacokinetic studies of pediatric patients.

3.0 SCREENING AND STUDY ENROLLMENT PROCEDURES

3.1 Study Enrollment

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

3.1.1 Access requirements for OPEN:

Patient enrollment will be facilitated using the Oncology Patient Enrollment Network (OPEN).The Oncology Patient Enrollment Network (OPEN) is a web-based registration system available on a 24/7 basis. OPEN is integrated with CTSU regulatory and roster data and with the Lead Protocol Organization (LPOs) registration/randomization systems or Theradex Interactive Web Response System (IWRS) for retrieval of patient registration/randomization assignment. OPEN will populate the patient enrollment data in NCI's clinical data management system, Medidata Rave.

Requirements for OPEN access:

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

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

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

- Patient has met all eligibility criteria within the protocol stated timeframes; and
- All patients have signed an appropriate consent form and 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. Please print this confirmation for your records.

Access OPEN at https://open.ctsu.org or from the OPEN link on the CTSU members' website. Further instructional information is in the OPEN section of the CTSU website at

https://www.ctsu.org or https://open.ctsu.org. For any additional questions, contact the CTSU Help Desk at 1-888-823-5923 or ctsucontact@westat.com.

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

3.1.2 IRB Approval

Each investigator or group of investigators at a clinical site must obtain IRB approval for this protocol and submit IRB approval and supporting documentation to the CTSU Regulatory Office before they can be approved to enroll patients. For CTEP and Division of Cancer Prevention (DCP) studies open to the National Clinical Trials Network (NCTN) and NCI Community Oncology Research Program (NCORP) Research Bases after March 1, 2019, all U.S.-based sites must be members of the NCI Central Institutional Review Board (NCI CIRB). In addition, U.S.-based sites must accept the NCI CIRB review to activate new studies at the site after March 1, 2019. Local IRB review will continue to be accepted for studies that are not reviewed by the CIRB, or if the study was previously open at the site under the local IRB. International sites should continue to submit Research Ethics Board (REB) approval to the CTSU Regulatory Office following country-specific regulations.

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

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

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

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

- Holds an active CTEP status;
- 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, rostered on the NCI CIRB roster under the applicable CIRB Signatory Institution(s) record;
- Includes the IRB number of the IRB providing approval in the Form FDA 1572 in the RCR profile;
- Lists all sites on the IRB/REB approval as Practice Sites in the Form FDA 1572 in the RCR profile; and
- Holds 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 protocol-specific requirements (PSRs).

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

Institutions with patients waiting that are unable to use the Regulatory Submission Portal should alert the CTSU Regulatory Office immediately at 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 on the NCI CIRB initiative and accepting CIRB approval for the study are not required to submit separate IRB approval documentation to the CTSU Regulatory Office for initial, continuing or amendment review.

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

3.1.3 Genetic Screening Procedures for Eligibility

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

tumor testing results for potential APEC1621F study patients (such as whether a specific mutation would be considered actionable for the study) should be directed to the APEC1621SC and APEC1621F study chairs.

The treatment assignment to a MATCH subprotocol (if a relevant aMOI is detected) will be communicated to the enrolling institution via the COG treatment assignment mechanism, upon which a reservation to APEC1621F will be secured by COG. Reservations should be withdrawn by the institution if at any point the patient indicates they do NOT intend to consent to participation, or the site investigator indicates the patient will never be eligible for APEC1621F.

3.2 Informed Consent/Assent

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

3.3 Screening Procedures

Diagnostic or laboratory studies performed exclusively to determine eligibility for this trial must only be done after obtaining written informed consent. This can be accomplished through the study-specific protocol. Documentation of the informed consent for screening will be maintained in the patient's research chart. Studies or procedures that were performed for clinical indications (not exclusively to determine eligibility) may be used for baseline values even if the studies were done before informed consent was obtained.

3.4 Eligibility Checklist

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

3.5 Study Enrollment

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

Patients enrolling onto APEC1621F will have a COG ID obtained through their prior enrollment onto the APEC1621SC screening protocol or a prior COG study. Patients must be enrolled within 2 weeks (14 days) of treatment assignment. Protocol therapy must start no later than 7 calendar days after the date of enrollment. Patients who are started on protocol therapy prior to study enrollment will be considered ineligible.

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

Note: No starter supplies will be provided. Drug orders of ensartinib should be placed with CTEP after enrollment and treatment assignment to APEC1621F with

consideration for timing of processing and shipping to ensure receipt of drug supply prior to start of protocol therapy.

3.6 Institutional Pathology Report

The institutional pathology report from the tumor specimen submitted for sequencing will have been uploaded into RAVE immediately following enrollment on the APEC1621SC screening protocol.

3.7 Dose Assignment

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

4.0 PATIENT ELIGIBILITY

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

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

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

4.1 Inclusion Criteria

4.1.1 APEC1621SC: Patient must have enrolled onto APEC1621SC and must have been given a treatment assignment to MATCH to APEC1621F based on the presence of an actionable mutation as defined in APEC1621SC. Examples of actionable mutations for APEC1621F are listed in Appendix VII-A and Appendix VII-B.

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

4.1.3 BSA: Patients must have a body surface area ≥ 0.5 m^2 at enrollment.

4.1.4 Disease Status:
Patients must have radiographically **measurable** disease (See Section 12) at the time of study enrollment. Patients with neuroblastoma who do not have measurable disease but have MIBG+ evaluable disease are eligible. Measurable disease in

patients with CNS involvement is defined as any lesion that is at minimum 10 mm in one dimension on a standard MRI or CT.

Note: The following do not qualify as measurable disease:
- malignant fluid collections (e.g., ascites, pleural effusions)
- bone marrow infiltration except that detected by MIBG scan for neuroblastoma
- lesions only detected by nuclear medicine studies (e.g., bone, gallium or PET scans) except as noted for neuroblastoma
- elevated tumor markers in plasma or CSF
- previously radiated lesions that have not demonstrated clear progression post radiation
- leptomeningeal lesions that do not meet the measurement requirements for RECIST 1.1.

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

4.1.6 Prior Therapy

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

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

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

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

recovered to Grade ≤ 1.

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

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

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

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

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

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

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

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

k. Patients must not have received prior exposure to ensartinib. Prior treatment with other ALK inhibitors is permitted given that at least 5 half-lives or 21 days have elapsed since therapy discontinuation, whichever is greater.

4.1.7 Organ Function Requirements

4.1.7.1 Adequate Bone Marrow Function Defined as:

a. For patients with solid tumors without known bone marrow involvement:
- Peripheral absolute neutrophil count (ANC) ≥ 1000/mm^3

- Platelet count ≥ 100,000/mm^3 (transfusion independent, defined as not receiving platelet transfusions for at least 7 days prior to enrollment)

b. Patients with known bone marrow metastatic disease will be eligible for study provided they meet the blood counts in 4.1.7.1.a (may receive transfusions provided they are not known to be refractory to red cell or platelet transfusions). These patients will not be evaluable for hematologic toxicity.

4.1.7.2 Adequate Renal Function Defined as:

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

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

The threshold creatinine values in this Table were derived from the Schwartz formula for estimating GFR utilizing child length and stature data published by the CDC.

4.1.7.3 Adequate Liver Function Defined as:

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

4.1.8 Patients must be able to swallow intact capsules.

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

4.2 Exclusion Criteria

4.2.1 Pregnancy or Breast-Feeding

Pregnant or breast-feeding women will not be entered on this study because there is currently no available information regarding human fetal or teratogenic toxicities. Pregnancy tests must be obtained in girls who are post-menarchal. Males or females of reproductive potential may not participate unless they have agreed to use an effective contraceptive method for the duration of study treatment and for one week after the last dose of ensartinib.

4.2.2 Concomitant Medications

4.2.2.1 Corticosteroids: Patients receiving corticosteroids who have not been on a stable or decreasing dose of corticosteroid for at least 7 days prior to enrollment are not eligible. If used to modify **immune adverse events** related to prior therapy, ≥ 14 days must have elapsed since last dose of corticosteroid (See Section 4.1.6.1.d).

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

4.2.2.3 Anti-cancer Agents: Patients who are currently receiving other anti-cancer agents are not eligible.

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

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

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

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

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

5.0 TREATMENT PROGRAM

5.1 Overview of Treatment Plan

Treatment Schedule Table	
Days 1-28	Ensartinib 130 mg/m^2 PO daily (maximum of 225 mg/day)
Day 28	Evaluation

Ensartinib will be administered orally in capsules given once a day and can be taken without regard to food. Therapy will be discontinued if there is evidence of progressive disease or drug related dose-limiting toxicity that requires removal from therapy (Section 6.0). Therapy may otherwise continue for up to 2 years provided the patient meets the criteria for starting subsequent cycles (Section 5.2) and does not meet any of the criteria for removal from protocol therapy criteria (Section 10.0).

A cycle of therapy is considered to be 28 days. A cycle may be repeated up to a total duration of therapy of approximately 2 years (maximum 26 cycles).

Drug doses should be adjusted based on the BSA calculated from height and weight

measured within 7 days prior to the beginning of each cycle, and according to the dosing nomogram (see Appendix IV). Patients should swallow the capsules as a whole and should not chew or open them. Repeating a dose after vomiting is not recommended. The next dose should be taken as scheduled. If a patient misses a dose, the dose should be taken as soon as possible but not less than 12 hours before the next dose is due. If the next dose is due in less than 12 hours, the patient should skip the missed dose and take the next dose as scheduled.

Since the adult RP2D (225 mg PO daily) was below the MTD [32] the starting dose will be the adult RP2D adjusted for BSA, which is 130 mg/m^2/day (225 mg/1.73 m^2) up to a maximum daily dose of 225 mg.

5.1.1 Therapy Delivery Map
See Appendix V for APEC1621F Therapy Delivery Map

5.2 Criteria for Starting Subsequent Cycles

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

5.3 Grading of Adverse Events

Adverse events (toxicities) will be graded according to version 5.0 of the NCI Common Terminology Criteria for Adverse Events (CTCAE). All appropriate treatment areas should have access to a copy of version 5.0 of the CTCAE. A copy of the CTCAE v5.0 can be downloaded from the CTEP website (http://ctep.cancer.gov). Any suspected or confirmed dose-limiting toxicity should be reported immediately (within 24 hours) to the Study Chair.

5.4 Definition of Dose-Limiting Toxicity (DLT)

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

5.4.1 Non-Hematological Dose-Limiting Toxicity

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

- Grade 3 nausea and vomiting of less < 3 days duration
- Grade 3 liver enzyme elevation, including ALT/AST/GGT that returns to levels that meet initial eligibility criteria or baseline within 7 days. See Appendix X for values that represent thresholds between CTCAE grades.

  Note: For the purposes of this study the ULN for ALT is defined as 45 U/L regardless of baseline.
- Grade 3 or 4 fever < 5 days duration.
- Grade 3 infection < 5 days duration.
- Grade 3 hypophosphatemia, hypokalemia, hypocalcemia or hypomagnesemia responsive to supplementation

- Any Grade 2 non-hematological toxicity that persists for ≥ 7 days and is

considered sufficiently medically significant or sufficiently intolerable by patients that it requires treatment interruption.
- Grade 2 skin toxicity that does not resolve to < grade 1 within 14 days (see Section 6.3)
- Note: Allergic reactions that necessitate discontinuation of study drug will not be considered a dose-limiting toxicity.

5.4.2 Hematological dose limiting toxicity
Hematological dose limiting toxicity is defined as:

In patients evaluable for hematological toxicity (see Section 4.1.7.1),
- Grade 4 thrombocytopenia or neutropenia, not due to malignant infiltration.
- Grade 3 thrombocytopenia that persists for ≥ 7 days
- Grade 3 thrombocytopenia requiring a platelet transfusion on two separate days within a 7-day period
- Grade 3 thrombocytopenia with clinically significant bleeding
- Myelosuppression that causes a delay of > 14 days between treatment cycles

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

6.0 DOSE MODIFICATIONS FOR ADVERSE EVENTS

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

6.1 Dose Modifications for Hematological Toxicity

If a patient experiences hematological dose-limiting toxicity as defined in Section 5.4.2, the treatment will be held. Counts should be checked every 3-4 days for thrombocytopenia and every other day for neutropenia during this time. If the toxicity resolves to meet eligibility parameters within 14 days of drug discontinuation, the patient may resume treatment at a reduced dose as outlined in the dose reduction table (Appendix IV). Doses reduced for toxicity will not be re-escalated, even if there is minimal or no toxicity with the reduced dose.

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

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

6.2 Dose Modifications for Non-Hematological Toxicity

If a patient experiences non-hematological dose-limiting toxicity as defined in Section 5.4.1, the treatment will be held. When the toxicity resolves to meet eligibility parameters or baseline within 14 days of drug discontinuation, the patient may resume treatment at a reduced dose as outlined in the dose reduction table (Appendix IV). Doses reduced for

toxicity will not be re-escalated, even if there is minimal or no toxicity with the reduced dose.

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

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

6.3 Recommendations for Skin Toxicity:

The most common drug related adverse event is rash, which have included many different types and can begin as early as cycle 1 or 2. Descriptions include: erythematous rash, maculopapular rash, pruritic rash, acneiform dermatitis, exfoliative rash. Grade 3 rashes are often associated with pruritus and can have scaling. Based on the adult Phase 2 and 3 ensartinib trials (which used CTCAE v4) the CTCAE v5 grading of rash/skin toxicity will be based on severity of symptoms; and not percentage of BSA affected.

Based on the experience on the current adult Phase 1/2 study and the recommendations for the new adult Phase 3 study the following recommendations should be followed. For mild (Grade 1) continue treatment at same dose, follow, and if necessary, use topical treatments. Topical corticosteroids may be used if based on the rash appearance they would be considered appropriate treatment. For moderate and symptomatic (Grade 2) continue treatment at same dose and topical steroids may be used. If after one week the rash is worse or there is no improvement give a 7-day course of tapering oral steroids. If one week later (total of 14 days from start of Grade 2 skin toxicity) it has not improved to $\leq$ Grade 1, hold drug until < Grade 1. At that time, resume ensartinib at a one dose level reduction (Appendix IV). For severe (Grade 3) ensartinib should be held. Topical treatments should be used. Oral cortiocsteroids can be considered. When skin toxicity is < Grade 1, resume at one level dose reduction (Appendix IV). Note that antibiotics should not be given routinely unless the rash is acneiform/pustular.

7.0 SUPPORTIVE CARE AND OTHER CONCOMITANT THERAPY

7.1 Concurrent Anticancer Therapy

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

7.2 Investigational Agents

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

7.3 Supportive Care

Appropriate antibiotics, blood products, antiemetics, fluids, electrolytes and general supportive care are to be used as necessary. Please see COG Supportive Care guidelines at https://childrensoncologygroup.org/index.php/cog-supportive-care-guidelines. See Section 7.5 for drugs that should not be used concomitantly due to potential interactions with ensartinib. See below for recommendations on management of specific toxicities associated with ensartinib.

7.3.1 Recommendations for Skin Toxicity:

The most common drug related adverse event is rash, which have included many

different types and can begin as early as cycle 1 or 2. Descriptions include: erythematous rash, maculopapular rash, pruritic rash, acneiform dermatitis, exfoliative rash. Grade 3 rashes are often associated with pruritus and can have scaling. Based on the experience in the current adult Phase ½ and Phase 3 studies the following recommendations should be followed. For mild (Grade 1) continue treatment at same dose, follow, and if necessary, use topical treatments. Topical corticosteroids may be used if based on the rash appearance they would be considered appropriate treatment. For moderate and symptomatic (Grade 2) continue treatment at same dose and topical steroids may be used. If after one week the rash is worse or there is no improvement give a 7-day course of tapering oral steroids. If one week later (total of 14 days from start of Grade 2 skin toxicity) it has not improved to ≤ Grade 1, hold drug until < Grade 1. At that time, resume ensartinib at a one dose level reduction (Appendix IV). For severe (Grade 3) ensartinib should be held. Topical treatments should be used. Oral cortiocsteroids can be considered. When skin toxicity is < Grade 1, resume at one level dose reduction (Appendix IV). Note that antibiotics should not be given routinely unless the rash is acneiform/pustular.

7.4 Growth Factors

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

7.5 Concomitant Medications

7.5.1 Ensartinib is a weak inhibitor of CYP3A4 and CYP2C9 isozymes in vitro. Ensartinib should be used with caution in patients receiving sensitive or narrow therapeutic range substrates of CYP3A4 (Appendix II) and 2C9 (celecoxib, glimepiride, phenytoin, tolbutamide, warfarin). If reasonable alternatives exist they should be used instead.

7.5.2 Ensartinib is highly protein bound with plasma protein binding ranging from 90.2% to 97%. Use caution in patients who are receiving concomitant medications that are also highly protein-bound.

7.5.3 CYP3A4/5 inhibitors or inducers: Strong CYP3A4/5 inhibitors or inducers are prohibited 14 days prior to enrollment to the end of the study. (See Appendix II for a list of agents). Note: CYP3A4 inducing anti-epileptic drugs and dexamethasone for CNS tumors or metastases, on a stable dose, are allowed.

8.0 EVALUATIONS/MATERIAL AND DATA TO BE ACCESSIONED

8.1 Required Clinical, Laboratory and Disease Evaluation

All clinical and laboratory studies to determine eligibility must be performed within 7 days prior to enrollment unless otherwise indicated. Laboratory values used to assess eligibility (see Section 4.0) must be no older than seven (7) days at the start of therapy. Laboratory tests need **not** be repeated if therapy starts **within** seven (7) days of obtaining labs to assess eligibility. If a post-enrollment lab value is outside the limits of eligibility, or laboratory values are older than 7 days, then the following laboratory evaluations must be re-checked within 48 hours prior to initiating therapy: CBC with differential, bilirubin, ALT (SGPT) and serum creatinine. If the recheck is outside the limits of eligibility, the patient may not receive protocol therapy and will be considered off protocol therapy. Imaging studies, bone

marrow aspirate and/or biopsy, must be obtained within 14 days prior to start of protocol therapy (repeat the tumor imaging if necessary).

STUDIES TO BE OBTAINED	Pre-Study	During Cycle 1	Prior to Subsequent Cycles^
History	X	Weekly	X
Physical Exam with vital signs	X	Weekly	X
Neurologic Exam	X		
Height, weight, BSA	X		X
Performance Status	X		
Pregnancy Test[1]	X		
CBC, differential, platelets	X	Twice Weekly (every 3 to 4 days)[2,3]	Weekly[2,3]
Urinalysis	X		
Electrolytes including Ca^{++}, PO_4, Mg^{++}	X	Weekly	X
Creatinine, ALT, bilirubin	X	Weekly	X
Albumin	X		X
Tumor Disease Evaluation[4-A, 4-B,4-C]	X		Every other cycle x 3 then q 3 cycles [4]
Bone Marrow Aspirate and/or biopsy[5,6]	X[6]		
Medication Diary[7]		Weekly	X
Pharmacokinetics (Optional)[8]	X	X	
Circulating Tumor DNA (ctDNA-optional)[9]			Cycle 5, Day 1 and (for patients receiving ≥ 5 cycles only) at end of protocol therapy OR disease progression

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

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

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

3 If patients develop Grade 3 or greater thrombocytopenia then CBCs should be checked every 3 to 4 days until recovery per Section 6.1.

4 Tumor Disease Evaluation should be obtained on the next consecutive cycle after initial documentation of either a PR or CR. Subsequent scans may restart 2 cycles after the confirmatory scan. 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.

4-A Neurological exam also required for CNS patients.

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

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

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

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

7. Medication diary (see Appendix III-A) should be reviewed weekly during cycle 1 and after completion of each treatment cycle and uploaded into RAVE.
8. See Section 8.3 for details of PK studies.
9. With consent, two samples will be collected on this protocol (cycle 5 Day 1; and for patients receiving ≥ 5 cycles only: at progression or end of protocol therapy), see Section 8.4 for details of the ctDNA studies. Note that a ctDNA sample is scheduled to be obtained on the APEC1621SC screening protocol prior to the initiation of treatment on this subprotocol.

8.2 Radiology Studies

8.2.1 Central Radiology Review for Response:

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

8.2.2 Technical Details of Submission:

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

Submission of Diagnostic Imaging data in DICOM format is required.

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

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

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

Address for submission: IROC RI (QARC)
Building B, Suite 201

640 George Washington Highway
Lincoln, RI 02865-4207
Phone: (401) 753-7600
Fax: (401) 753-7601
Web: http://irocri.qarc.org

8.3 Pharmacology (optional)

8.3.1 Description of Studies and Assay

Pharmacokinetics (PK) will be performed to determine the PK of ensartinib in children who consent to this optional study. Pharmacokinetic analysis will be conducted at a centralized laboratory using validated assays.

8.3.2 Sampling Schedule

Blood samples will be obtained at the following time points:

Blood Sample No.	Time Point	Scheduled Collection Time
1	**Cycle 1, Day 1**	Pre-dose
Cycle 1 Day 1 Dose		
2	**Cycle 1, Day 1**	1 hr after dose
3	**Cycle 1, Day 1**	2 hrs after dose
4	**Cycle 1, Day 1**	4 hrs after dose
5	**Cycle 1, Day 1**	6-8 hrs after dose
6	**Cycle 1, Day 2**	Pre-dose (20-24 hours post-Day 1)
7	**Cycle 1, Day 28**	Pre-dose
Cycle 1 Day 28 Dose		
8	**Cycle 1, Day 28**	1 hr after dose
9	**Cycle 1, Day 28**	2 hrs after dose
10	**Cycle 1, Day 28**	4 hrs after dose
11	**Cycle 1, Day 28**	6-8 hrs after dose

* Please contact study chair or pharmacologist to adjust PK schedule if there are missed doses during days 1, 2, and 28 of cycle 1.

8.3.3 Sample Collection and Handling Instructions

Blood samples (2-3 ml for each time point) will be collected in K_2-EDTA (lavender top) tubes for pharmacokinetic evaluation. Record the exact time that the sample is drawn along with the exact time that the drug is administered.

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

8.3.4 Sample Processing

Following collection, the sample will be immediately gently mixed by inversion 8-10 times. The sample will be stored on wet ice until centrifugation. The sample will be centrifuged at 1500 x g for 15 minutes at 4°C within 60 minutes after the

sample is drawn. The plasma will be transferred to a cryovial, ensuring no RBC contamination, and frozen as soon as possible at (-20° C to -80° C). If a (-20° C to -80° C) freezer is not immediately available, the cryovial may be stored on dry ice for short term storage but must be placed in the appropriate freezer within 24 hours of the draw-time.

8.3.5 Sample Labeling

Each sample must be labeled with the patient's study registration number, the study I.D# (APEC1621F), and the date and time the sample was drawn. Data should be recorded on the appropriate transmittal form found in RAVE, which must accompany the sample(s).

8.3.6 Sample Shipping Instructions

Samples may be batched for monthly shipment, in freezer boxes containing at least 10 kg of DRY ICE. The samples must be securely packed in boxes to avoid breakage during transit, double-bagged to contain leaks, and where applicable, packed with a sufficient quantity of dry ice to ensure they remain frozen for at least 72 hours.

Shipments should be sent **Monday or Tuesday only** for priority overnight delivery to the following address:

Larry F. Sanchez
Q Squared Solutions
Specimen Processing 27027 Tourney Road, Suite 2E
Valencia, CA 91355
USA

Phone: 661-799-6480
Fax: 678-374-4476
Email: Larry.Sanchez@q2labsolutions.com
"A notification email should be sent to Larry F Sanchez with courier name, airway bill number, expected delivery date/time and shipment contact."

Ship samples by FedEx Priority overnight using Q Squared Solutions FedEx account number 1547-6305-8.

8.4 Circulating Tumor DNA Study (optional)

8.4.1 Sampling Schedule

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

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

Peripheral blood samples for cell-free DNA should be obtained as follows:

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

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

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

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

- Keep patient's arm in the downward position during the collection procedure.
- Hold the tube with the stopper in the uppermost position so that the tube contents do not touch the stopper or the end of the needle during sample collection.
- Release tourniquet once blood starts to flow in the tube, or within 2 minutes of application.
- Fill tube completely.
- Remove tube from adapter and immediately mix by gentle inversion 8 to 10 times. Inadequate or delayed mixing may result in inaccurate test results.

8.4.2 Sample Processing

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

8.4.3 Sample Labeling

Each tube must be labeled with the patient's study registration number, the study I.D (APEC1621F), and the date and time the sample was drawn. Data should be recorded on the appropriate transmittal form found in RAVE, which must accompany the sample(s).

8.4.4 Sample Shipping Instructions

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

Ship specimens to the following address:

Biopathology Center
Nationwide Children's Hospital
Protocol APEC1621F- Peds MATCH*
700 Children's Drive, WA1340
Columbus, OH 43205
Phone: (614) 722-2865
Fax: (614) 722-2897
Email:BPCBank@nationwidechildrens.org

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

9.0 AGENT INFORMATION

9.1 Ensartinib (05/22/2024)

(X-396 hydrochloride) NSC# 784729, IND#[redacted]

9.1.1 Source and Pharmacology:

Anaplastic lymphoma kinase (ALK) is a highly conserved receptor tyrosine kinase (RTK) first discovered as a fusion with nucleophosmin (NPM) in anaplastic large cell lymphomas (ALCL). In addition to NPM in lymphoma, other fusion partners for ALK have been described in NSCLC and in inflammatory myofibroblastic tumors. Activating mutations in wild-type ALK have also been identified in both familial and sporadic neuroblastoma. Ensartinib (X-396), a novel, potent and selective, second generation ALK inhibitor with a favorable effectiveness profile *in vitro* and *in vivo* relative to crizotinib, including anti-tumor activity against multiple ALK mutants that are resistant to crizotinib.

Pharmacokinetics:
Ensartinib exposure has been observed to increase in a greater than dose-proportional manner. The food effect is unclear at this time due to limited data and variability. The half-life is approximately 20 - 38 hours, and inter-patient variability is moderate. At the 225 mg daily dose level (RP2D) the steady state Cmax (range 311-481 ng/mL) was reached after ~ 3 hours (Tmax).

9.1.2 Potential Drug Interactions

In vitro, ensartinib did not inhibit cytochrome P450 isozymes CYP 1A2 or 2D6 but did inhibit 3A4 by 22% and 2C9 by 43% at 10 µM. While drug-drug interactions via cytochrome P450 isozymes are not expected at concentrations achieved in the clinic, sensitive or narrow therapeutic range substrates of CYP3A4 (Appendix II) and 2C9 (celecoxib, glimepiride, phenytoin, tolbutamide, warfarin) should be used with caution.

Ensartinib is primarily metabolized by CYP3A4 with a minor contribution from 2C19 in vitro. The use of strong inhibitors and inducers of CYP3A4 should be avoided (see Appendix II).

Plasma protein binding ranged from 90.2% to 97%. Use caution in patients who are receiving concomitant medications that are also highly protein-bound.

9.1.3 **Toxicity:**

The Comprehensive Adverse Events and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. In addition to the comprehensive list, a subset, the Specific Protocol Exceptions to Expedited Reporting (SPEER), appears in a separate column and is identified with bold and italicized text. This subset of AEs (SPEER) is a list of events that are protocol specific exceptions to expedited reporting to NCI (except as noted below). Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements' http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf for further clarification. *Frequency is provided based on 612 patients.* Below is the CAEPR for Ensartinib (X-396 hydrochloride).

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

Version 2.4, April 18, 2024[1]

Adverse Events with Possible Relationship to Ensartinib (X-396 hydrochloride) (CTCAE 5.0 Term) [n= 612]			**Specific Protocol Exceptions to Expedited Reporting (SPEER)**
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
Anemia			***Anemia (Gr 2)***
	Leukocytosis		***Leukocytosis (Gr 3)***
CARDIAC DISORDERS			
	Palpitations		***Palpitations (Gr 2)***
	Sinus bradycardia		
	Sinus tachycardia		
EYE DISORDERS			
	Blurred vision		
GASTROINTESTINAL DISORDERS			
	Abdominal distension		
	Abdominal pain		***Abdominal pain (Gr 2)***
Constipation			***Constipation (Gr 2)***
	Diarrhea		***Diarrhea (Gr 2)***
	Dyspepsia		
	Mucositis oral		
Nausea			***Nausea (Gr 2)***
Vomiting			***Vomiting (Gr 2)***

Adverse Events with Possible Relationship to Ensartinib (X-396 hydrochloride) (CTCAE 5.0 Term) [n= 612]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
	Edema face		***Edema face (Gr 2)***
	Edema limbs		***Edema limbs (Gr 2)***
Fatigue			***Fatigue (Gr 2)***
	Fever		***Fever (Gr 2)***
	Flu like symptoms		
	Non-cardiac chest pain		***Non-cardiac chest pain (Gr 2)***
	Pain		
INFECTIONS AND INFESTATIONS			
	Lung infection		
Upper respiratory infection			***Upper respiratory infection (Gr 2)***
	Urinary tract infection		
INVESTIGATIONS			
Alanine aminotransferase increased			***Alanine aminotransferase increased (Gr 2)***
	Alkaline phosphatase increased		***Alkaline phosphatase increased (Gr 2)***
Aspartate aminotransferase increased			***Aspartate aminotransferase increased (Gr 2)***
	Blood bilirubin increased		***Blood bilirubin increased (Gr 2)***
	Blood lactate dehydrogenase increased		
	CPK increased		
	Cholesterol high		
	Creatinine increased		***Creatinine increased (Gr 2)***
	GGT increased		***GGT increased (Gr 2)***
	Investigations - Other (blood urea increased)		
	Investigations - Other (c-reactive protein increased)		
	Investigations - Other (neutrophil count increased)		
	Investigations - Other (platelet count increased)		
	Investigations - Other (occult blood positive)		
	Lymphocyte count decreased		
	Platelet count decreased		
	Serum amylase increased		

Adverse Events with Possible Relationship to Ensartinib (X-396 hydrochloride) (CTCAE 5.0 Term) [n= 612]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
	Weight gain		
	Weight loss		
	White blood cell decreased		
METABOLISM AND NUTRITION DISORDERS			
	Anorexia		***Anorexia (Gr 2)***
	Hyperglycemia		***Hyperglycemia (Gr 2)***
	Hyperuricemia		
	Hypoalbuminemia		***Hypoalbuminemia (Gr 2)***
	Hypocalcemia		
	Hypokalemia		
	Hyponatremia		
	Hypophosphatemia		
	Metabolism and nutrition disorders - Other (hypoproteinemia)		
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			
	Arthralgia		
	Back pain		***Back pain (Gr 2)***
	Myalgia		
	Pain in extremity		
NERVOUS SYSTEM DISORDERS			
	Dizziness		***Dizziness (Gr 2)***
	Dysgeusia		
	Headache		***Headache (Gr 2)***
	Paresthesia		
PSYCHIATRIC DISORDERS			
	Insomnia		
RENAL AND URINARY DISORDERS			
	Hematuria		
	Proteinuria		
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
	Bronchopulmonary hemorrhage		
Cough			***Cough (Gr 2)***
	Dyspnea		***Dyspnea (Gr 2)***
	Pleural effusion		
	Pneumonitis		
	Productive cough		
	Respiratory, thoracic and mediastinal disorders - Other		

Adverse Events with Possible Relationship to Ensartinib (X-396 hydrochloride) (CTCAE 5.0 Term) [n= 612]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
	(tachypnea)		
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
	Alopecia		
	Dry skin		***Dry skin (Gr 2)***
	Erythroderma		
Pruritus			***Pruritus (Gr 2)***
Skin and subcutaneous tissue disorders - Other (rash)[2]			***Skin and subcutaneous tissue disorders - Other (rash)[2] (Gr 3)***

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

[2]Rash includes the terms: rash, rash erythematous, rash macular, rash maculo-papular, rash pruritic, erythema, rash follicular, dermatitis, dermatitis contact.

Adverse events reported on Ensartinib (X-396 hydrochloride) trials, but for which there is insufficient evidence to suggest that there was a reasonable possibility that Ensartinib (X-396 hydrochloride) caused the adverse event:

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Blood and lymphatic system disorders - Other (lymphadenopathy); Eosinophilia; Thrombotic thrombocytopenic purpura
CARDIAC DISORDERS - Atrial fibrillation; Atrial flutter; Atrioventricular block first degree; Cardiac disorders - Other (bundle branch block left); Cardiac disorders - Other (sinus arrythmia); Cardiac disorders - Other (supraventricular extrasystoles); Cardiac disorders - Other (ventricular extrasystoles); Chest pain - cardiac; Conduction disorder; Pericardial effusion; Pericarditis; Supraventricular tachycardia; Ventricular arrhythmia
EAR AND LABYRINTH DISORDERS - External ear pain; Tinnitus; Vertigo
ENDOCRINE DISORDERS - Testosterone deficiency
EYE DISORDERS - Dry eye; Eye disorders - Other (diplopia); Eye disorders - Other (eye pruritus); Eye disorders - Other (eye swelling); Eye disorders - Other (eyelid pruritus); Eye disorders - Other (ocular hyperemia); Eye pain; Flashing lights; Floaters; Periorbital edema; Vision decreased; Watering eyes
GASTROINTESTINAL DISORDERS - Belching; Dry mouth; Dysphagia; Esophagitis; Flatulence; Gastroesophageal reflux disease; Gastrointestinal disorders - Other (lip dry); Gastrointestinal disorders - Other (salivary hypersecretion); Oral pain; Periodontal disease; Rectal hemorrhage; Toothache
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Chills; Gait disturbance; General disorders and administration site conditions - Other (hyperthermia); General disorders and administration site conditions - Other (temperature intolerance); General disorders and administration site conditions - Other (nodule); Generalized edema; Localized edema; Malaise
HEPATOBILIARY DISORDERS - Hepatic failure; Hepatobiliary disorders - Other (liver injury); Hepatobiliary disorders - Other (hepatic function abnormal); Hepatobiliary disorders - Other (liver function

test abnormal)
IMMUNE SYSTEM DISORDERS - Autoimmune disorder
INFECTIONS AND INFESTATIONS - Bronchial infection; Conjunctivitis; Folliculitis; Fungemia; Infections and infestations - Other (coxsackie); Otitis media; Paronychia; Pharyngitis; Rash pustular; Shingles; Sinusitis; Skin infection; Viremia
INJURY, POISONING AND PROCEDURAL COMPLICATIONS - Fall; Injury, poisoning and procedural complications - Other (ligament sprain); Injury, poisoning and procedural complications - Other (nail bed bleeding); Injury, poisoning and procedural complications - Other (sunburn); Wound complication
INVESTIGATIONS - Activated partial thromboplastin time prolonged; Blood prolactin abnormal; Cardiac troponin I increased; Ejection fraction decreased; Electrocardiogram QT corrected interval prolonged; Electrocardiogram T wave abnormal; Hemoglobin increased; Investigations - Other (alpha hydroxybutyrate dehydrogenase increased); Investigations - Other (blood chloride increased); Investigations - Other (blood fibrinogen increased); Investigations - Other (blood follicle stimulating hormone increased); Investigations - Other (blood luteinizing hormone decreased); Investigations - Other (blood luteinizing hormone increased); Investigations - Other (blood testosterone decreased); Investigations - Other (blood testosterone increased); Investigations - Other (creatinine renal clearance); Investigations - Other (electrocardiogram high voltage); Investigations - Other (estradiol decreased); Investigations - Other (estradiol increased); Investigations - Other (fibrin D dimer increased); Investigations - Other (gamma-glutamyl transferase decreased); Investigations - Other (granulocyte count increased); Investigations - Other (progesterone decreased); Investigations - Other (progesterone increased); Investigations - Other (protein total decreased); Investigations - Other (monocyte count increased); Investigations - Other (neutrophil percentage increased); Investigations - Other (nitrite urine present); Investigations - Other (thrombin time prolonged); Investigations - Other (total bile acids increased); Investigations - Other (urobilinogen urine increased); Investigations - Other (white blood cells urine positive); Lipase increased; Lymphocyte count increased; Neutrophil count decreased; Urine output decreased
METABOLISM AND NUTRITION DISORDERS - Dehydration; Hyperkalemia; Hyperlipidemia; Hypermagnesemia; Hypernatremia; Hyperphosphatemia; Hypertriglyceridemia; Hypoglycemia; Hypomagnesemia; Metabolism and nutrition disorders - Other (fluid overload); Metabolism and nutrition disorders - Other (hypochloremia); Metabolism and nutrition disorders - Other (hypophagia); Metabolism and nutrition disorders - Other (hypouricemia)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Arthritis; Bone pain; Chest wall pain; Flank pain; Generalized muscle weakness; Muscle cramp; Muscle weakness lower limb; Musculoskeletal and connective tissue disorder - Other (mastication disorder); Musculoskeletal and connective tissue disorder - Other (muscle atrophy); Neck pain
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS) - Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other (neoplasm progression); Skin papilloma; Treatment related secondary malignancy
NERVOUS SYSTEM DISORDERS - Anosmia; Dysesthesia; Dysphasia; Edema cerebral; Memory impairment; Nervous system disorders - Other (osmotic demyelination syndrome); Nervous system disorders - Other (poor quality sleep); Nervous system disorders - Other (visual field defect); Peripheral motor neuropathy; Peripheral sensory neuropathy; Seizure; Somnolence; Syncope; Tremor
PSYCHIATRIC DISORDERS - Anxiety; Confusion; Depression
RENAL AND URINARY DISORDERS - Acute kidney injury; Dysuria; Glucosuria; Urinary incontinence; Urinary tract pain
REPRODUCTIVE SYSTEM AND BREAST DISORDERS - Breast pain; Reproductive system and breast disorders - Other (vulvovaginal erythema)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Epistaxis; Hoarseness; Nasal congestion; Oropharyngeal pain; Pulmonary hypertension; Respiratory, thoracic and mediastinal disorders - Other (breath sounds abnormal); Respiratory, thoracic and mediastinal disorders - Other (chronic obstructive pulmonary disease); Respiratory, thoracic and mediastinal disorders - Other (nasal dryness); Sore throat; Wheezing

SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Bullous dermatitis; Eczema; Erythema multiforme; Hyperhidrosis; Nail changes; Nail discoloration; Nail loss; Nail ridging; Palmar-plantar erythrodysesthesia syndrome; Photosensitivity; Purpura; Rash acneiform; Skin and subcutaneous tissue disorders - Other (drug eruption); Skin and subcutaneous tissue disorders - Other (drug rash with eosinophilia & systemic symptoms); Skin and subcutaneous tissue disorders - Other (lichenoid keratosis); Skin and subcutaneous tissue disorders - Other (pigmentation disorder); Skin and subcutaneous tissue disorders - Other (scab); Skin and subcutaneous tissue disorders - Other (skin discoloration); Skin and subcutaneous tissue disorders - Other (skin fissures); Skin and subcutaneous tissue disorders - Other (skin fragility); Skin and subcutaneous tissue disorders - Other (skin irritation); Skin and subcutaneous tissue disorders - Other (skin lesion); Skin and subcutaneous tissue disorders - Other (skin mass); Skin atrophy; Skin hyperpigmentation; Skin ulceration; Telangiectasia; Urticaria
VASCULAR DISORDERS - Flushing; Hypertension; Hypotension; Thromboembolic event; Vascular disorders - Other (jugular vein distension)

Note: Ensartinib (X-396 hydrochloride) in combination with other agents could cause an exacerbation of any adverse event currently known to be caused by the other agent, or the combination may result in events never previously associated with either agent.

9.1.4 **Formulation and Stability**:
Ensartinib is supplied for clinical trial use as 25-mg capsules (white opaque, size 2) and 100-mg capsules (yellow opaque body with blue opaque cap, size 0). Inactive components consist of microcrystalline cellulose and stearic acid. The capsules are packaged (30 capsules/bottle) in 30 cc (25 mg) and 60 cc (100 mg) high density polyethylene (HDPE) with a child resistant screw cap.

Note: Ensartinib 100 mg capsules contain FD+C Yellow No. 5 (tartrazine) which may cause allergic-type reactions (including bronchial asthma) in certain susceptible persons.

Storage
Store at controlled room temperature (15ºC-30ºC/59ºF-86ºF)

If a storage temperature excursion is identified, promptly return ensartinib to controlled room temperature and quarantine the supplies. Provide a detailed report of the excursion (including documentation of temperature monitoring and duration of the excursion) to PMBAfterHours@mail.nih.gov for determination of suitability.

Stability
Stability studies are ongoing. Exact quantity may be dispensed in a pharmacy vial and assigned a 30-day expiration.

9.1.5 **Guidelines for Administration**
See Treatment (Section 5.0) of the protocol for dosing and administration details, see Section 6.0 for information related to dose modifications. Ensartinib is administered orally once daily without regard to food.

9.1.6 Supplier:
Ensartinib is supplied by Xcovery Holdings, Inc. and is distributed by a Division of Cancer Treatment and Diagnosis; the Pharmaceutical Management Branch (DCTD), NCI.

9.2 Obtaining the Agent

9.2.1 Agent Ordering

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

Note: No starter supplies will be provided. **Drug orders of ensartinib should be placed with CTEP after enrollment and treatment assignment to APEC1621F with consideration for timing of processing and shipping to ensure receipt of drug supply prior to start of protocol therapy**. Agent orders can be expedited overnight Monday-Thursday when sites provide expedited courier information.

Submit agent requests through the PMB AURORA application. Access to AURORA requires the establishment of credentials necessary to access secure NCI Clinical Oncology Research Enterprise (CORE) systems, maintenance of an "active" account status, a "current" password, and active person registration status. For questions about drug orders, transfers, returns, or accountability, call or email PMB any time or use the dialog function in AUORA to communicate with PMB staff. Refer to the PMB's website for specific policies and guidelines related to agent management.

9.3 Agent Accountability

9.3.1.1 Agent Inventory Records

The investigator, or a responsible party designated by the investigator, must maintain a complete accountability of the receipt, dispensing and final disposition of all agents received from the PMB using the appropriate NCI Investigational Agent (Drug) Accountability Record (DARF) available on the CTEP forms page. Store and maintain separate NCI Investigational Agent Accountability Records for each agent, strength, formulation and ordering investigator on this protocol.

9.3.1.2 Product Quality Complaint (PQC)

A product quality complaint is defined as any suspicion of a product defect related to a potential quality issue during manufacturing, packaging, release testing, stability monitoring, dose preparation, storage or distribution of the product, or delivery system. Not all PQCs involve a study subject. Lot or batch numbers are of high significance and need to be provided where and when possible. PQC must be reported to the PMB as soon as the PQC is identified. Report PQC to PMB at PMBAfterHours@mail.nih.gov or by using the dialog function in AURORA to communicate with PMB staff.

9.3.1.3 Investigator Brochure Availability

The current versions of the IBs for the agents will also be accessible to site investigators and research staff through the PMB AURORA application. Access to AURORA requires the establishment of credentials necessary to access secure NCI Clinical Oncology Research Enterprise (CORE) systems, maintenance of an "active" account status, "current" password, and active person registration status. Questions about IB access may be directed to the PMB IB coordinator via email.

9.3.2 Useful Links and Contacts

- CTEP Forms, Templates, Documents: http://ctep.cancer.gov/forms/
- NCI CTEP Investigator Registration: RCRHelpDesk@nih.gov
- PMB policies and guidelines: http://ctep.cancer.gov/branches/pmb/agent_management.htm
- PMB centralized inventory management system (AURORA): https://ctepcore.nci.nih.gov/aurora/login
- CTEP Identity and Access Management (IAM) account: https://ctepcore.nci.nih.gov/iam/
- CTEP IAM account help: ctepreghelp@ctep.nci.nih.gov
- PMB email: PMBAfterHours@mail.nih.gov
- PMB phone and hours of service: (240) 276-6575
  Monday through Friday between 8:30 am and 4:30 pm (ET)
- PMB IB Coordinator: IBcoordinator@mail.nih.gov
- Registration and Credential Repository (RCR): https://ctepcore.nci.nih.gov/rcr/

10.0 CRITERIA FOR REMOVAL FROM PROTOCOL THERAPY AND OFF STUDY CRITERIA

10.1 Criteria for Removal from Protocol Therapy

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

Patients who are removed from protocol therapy during cycle 1 should continue to have the required observations in Section 8.1 until the originally planned end of the cycle or until all adverse events have resolved per Section 13.4.4, whichever happens

LATER. The only exception is with documentation of the patient's withdrawal of consent from the APEC1621SC screening protocol. Patients who are removed from protocol therapy in subsequent cycles should have the necessary observations to ensure adequate clinical care.

10.2 Follow-Up Data Submission and APEC1621SC Off Study Criteria

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

11.0 STATISTICAL AND ETHICAL CONSIDERATIONS

11.1 Sample Size and Study Duration

APEC1621F will require a minimum of 40 evaluable patients and a maximum of 98 patients (up to 49 biomarker-positive patients per cohort), allowing for 15% inevaluability. Assuming an enrollment rate of 4-9 biomarker positive patients per year, the primary cohorts of this subprotocol is expected to be completed within 5.3-12 years.

11.2 Dosing Considerations

11.2.1 Pediatric MATCH Subprotocol Dosing in the Absence of Pediatric Phase 1 Data

Please see Section 5.1 for a specific discussion of the dosing of ensartinib to be used in this study. As there is no prior pediatric phase 1 data for ensartinib, study investigators have reviewed relevant data with the pharmaceutical partner to identify a drug specific dosing plan for testing in children with recurrent/refractory cancer, and trial participants will be closely monitored to ensure tolerability of the selected dose. Since the adult RP2D (225 mg PO daily) was below the MTD [32] the starting dose will be the adult RP2D adjusted for BSA, which is 130 mg/m^2/day (225 mg/1.73 m^2). Limited pharmacokinetic sampling will be done for patients enrolled on this arm. The dosing for ensartinib will follow the general Pediatric MATCH subprotocol guidelines as below:

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

11.2.2 Safety Phase Component

Enrollment of the initial cohort of up to six patients will follow the rules of the modified rolling six design[42] to assess safety and tolerability of protocol treatment prior to extending accrual to additional patients. The DLT evaluation period for the safety phase will be cycle 1 of therapy. Note that adverse events that begin during cycle 1 and specify a duration of time in order to be considered a DLT must be followed to resolution or until the definition of DLT has been met, regardless of the schedule end of cycle 1; (e.g. Grade 2 thrombocytopenia would be considered a DLT if it developed during cycle 1 of therapy and caused, or would have caused, a delay of >14 days to begin cycle 2). Two to six patients can be concurrently enrolled in the study. Accrual is suspended when a cohort of six has enrolled or when the study endpoints have been met. When participants are inevaluable for toxicity, they are replaced with the next available participant. If two or more DLTs among the first up to six toxicity-evaluable subjects have been observed, we will suspend the accrual and consider dose, schedule or duration of treatment modification. The COG DSMC will be notified and CTEP consulted regarding the next steps to take with respect to the protocol. Otherwise, we'll extend the accrual to additional patients.

11.2.3 Determination of Recommended Phase 2 Dose (RP2D)/ Tolerable Dose

For agents for which the adult RP2D is below the adult MTD, the adult RP2D will be the starting dose and no escalation is planned.

11.3 Study Design

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

Cohort	N	Decision Rule	Alpha	Power
Primary biomarker positive	20	≥ 3 responses	10%	90%

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

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

11.3.1 **Primary Cohort**:

APEC1621F will evaluate two primary cohorts of 20 mutation-matched ("biomarker positive") evaluable patients of any histology for the primary study aim of determining the objective response rate (CR/PR according to the response criteria in Section 12.3) to ensartinib. See Appendix VII-A and Appendix VII-B.

Primary Cohort A: Patients whose tumors have ALK or ROS1 fusions

Primary Cohort B: Patients whose tumors have ALK missense mutations.

Using an A'Hern design[43] with alpha=10%, a sample of N=20 will provide 90% power to detect an improvement in response rate from 5%, if the treatment is ineffective, to 25% if the targeted therapy is sufficiently effective to warrant further study. If there are at least 3 responses out of 20 in the primary cohort, the biomarker/therapy match will be deemed a success.

11.3.2 **Histology-Specific Biomarker Positive Expansion Cohorts:**

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

We will open up to 3 such expansion cohorts for biomarker positive patients for each primary cohort (i.e., if 3 histologies in cohort A and 3 histologies in cohort B have ≥ 3 responses, we will open a total of 6 expansion cohorts as described above). Note that this can only happen if the response rate in the primary cohort is at least 45% (9/20) and there cannot be more than 42 additional evaluable patients in total for these expansion cohorts.

11.4 Methods of Analysis

Response criteria are described in Section 12. A responder is defined as a patient who achieves a best response of PR or CR on the study. Response rates will be calculated as the percent of evaluable patients who are responders, and confidence intervals will be constructed using the Wilson score interval method.[44] Decision making for A'Hern design cohorts will follow rules described above.

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

11.5 Evaluability for Response

Any eligible patient who is enrolled and receives at least one dose of protocol therapy will be considered evaluable for response. Any patient who receives non-protocol anti-cancer therapy during the response evaluation period will be considered a non-responder for the purposes of the statistical rule, unless they show an objective response prior to receiving the non-protocol anti-cancer therapy (in which case they will be considered a responder). Patients who demonstrate a complete or partial response confirmed by central review will be considered to have experienced a response. When opening expansion cohorts, the evaluation period for determination of best response will be 6 treatment cycles. All other patients will be considered non-responders. Patients who are not evaluable for response evaluation may be replaced for the purposes of the statistical rule. All patients considered to have a response (CR or PR) must have imaging studies reviewed centrally at the COG.

Centers will be notified by the COG about requests for scans of patients with stable disease. Preliminary assessment of activity using institutionally provided tumor measurements will be entered into CDUS quarterly. The central review by COG will be provided as the final reviewed assessment of response when such becomes available.

11.6 Evaluability for Toxicity

All eligible patients who receive at least one dose of protocol therapy will be considered in the evaluation of toxicity. In addition, for the safety phase during cycle 1, patients without DLT must receive at least 85% of the prescribed dose per protocol guidelines and must have the appropriate toxicity monitoring studies performed to be considered evaluable for toxicity for the purpose of assessing safety and tolerability of protocol treatment prior to extending accrual to additional patients.

11.7 Progression free survival (PFS)

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

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

11.8 Correlative Studies

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

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

11.9 Gender and Minority Accrual Estimates

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

Racial category	Ethnicity				
	Not Hispanic or Latino		Hispanic or Latino		
	Female	Male	Female	Male	Total
American Indian/Alaska Native	0	0	0	0	0
Asian	2	2	0	0	4
Native Hawaiian or Other Pacific Islander	0	0	0	0	0

Racial category	Ethnicity				
	Not Hispanic or Latino		Hispanic or Latino		
	Female	Male	Female	Male	Total
Black or African American	6	10	0	0	16
White	24	42	6	4	76
More than one race	2	0	0	0	2
Total	34	54	6	4	98

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

12.0 EVALUATION CRITERIA

12.1 Common Terminology Criteria for Adverse Events (CTCAE)

The descriptions and grading scales found in version 5.0 of the NCI Common Terminology Criteria for Adverse Events (CTCAE) v5 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of CTCAE version 5.0. A copy of the CTCAE v5 can be downloaded from the CTEP website (http://ctep.cancer.gov).

12.2 Progression-Free Survival

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

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

12.3 Response Criteria for Patients with Solid Tumors

See the table in Section 8.0 for the schedule of tumor evaluations. Eligible patients must have measurable disease present at baseline and have had their disease re-evaluated after at least one dose of protocol therapy. In addition to the scheduled scans, a confirmatory scan should be obtained on the next consecutive cycle following initial documentation of objective response.

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

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

12.3.1 Definitions

12.3.1.1 Evaluable for objective response:

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

12.3.1.2 Evaluable Non-Target Disease Response:

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

absence, or unequivocal progression of the lesions.

12.3.2 Disease Parameters

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

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

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

12.3.2.3 Non-measurable disease: All other lesions (or sites of disease), including small lesions (longest diameter < 10 mm or pathological lymph nodes with ≥ 10 to < 15 mm short axis), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonitis, inflammatory breast disease, and abdominal masses (not followed by CT or MRI), are considered as non-measurable.

Note: Cystic lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts. 'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.

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

any objective tumor regression in the measurable dimension of the disease.

12.3.2.5 Non-target lesions: All other lesions (or sites of disease) including any measurable lesions over and above the 5 target lesions should be identified as non-target lesions and should also be recorded at baseline. Measurements of these lesions are not required, but the presence, absence, or in rare cases unequivocal progression of each should be noted throughout follow-up.

12.3.3 Methods for Evaluation of Measurable Disease

All measurements should be taken and recorded in metric notation using a ruler or calipers.

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

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

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

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

12.3.3.4 PET-CT: At present, the low dose or attenuation correction CT portion of a combined PET-CT is not always of optimal diagnostic CT quality for use with RECIST measurements. However, if the site can document that the CT performed as part of a PET-CT is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast), then the CT portion of the PET-CT can be used for RECIST or International Pediatric non-Hodgkin Lymphoma Response Criteria measurements and can be used interchangeably with conventional CT in accurately measuring cancer lesions over time. Note, however, that the PET portion of the CT introduces additional data which may bias an investigator if it is not routinely or serially performed.

12.3.3.5 Tumor markers: Tumor markers alone cannot be used to assess response. If markers are initially above the upper normal limit, they must normalize

for a patient to be considered in complete clinical response.

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

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

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

a. Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.

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

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

For patients with a positive PET scan at diagnosis, PET can be used to follow response in addition to a CT scan using the International Pediatric non-Hodgkin Lymphoma Response Criteria.[45]

12.4 Response Criteria for Patients with Solid Tumor and Measurable Disease

12.4.1 Evaluation of Target Lesions

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

patients with neuroblastoma).

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

Progressive Disease (PD): At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progressions). Note: in presence of SD or PR in target disease but unequivocal progression in non-target or non-measurable disease, the patient has PD if there is an overall level of substantial worsening in non-target disease such that the overall tumor burden has increased sufficiently to merit discontinuation of therapy

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

12.4.2 **Evaluation of Non-Target Lesions**

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

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

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

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

12.4.3 **Overall Response Assessment**

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

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Overall Response when Confirmation is Required*
CR	CR	No	CR	≥ 28 days Confirmation
CR	Non-CR/Non-PD	No	PR	≥ 28 days Confirmation
CR	Not evaluated	No	PR	
PR	Non-CR/Non-PD/not evaluated	No	PR	
SD	Non-CR/Non-PD/not evaluated	No	SD	documented at least once ≥ 28 days from baseline
PD	Any	Yes or No	PD	no prior SD, PR or CR
Any	PD**	Yes or No	PD	
Any	Any	Yes	PD	

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

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

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

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

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

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

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

CT/MRI	MIBG	Bone Scan	Bone Marrow	Catechol	Overall
PD	Any	Any	Any	Any	PD
Any	PD	Any	Any	Any	PD
Any	Any	PD	Any	Any	PD
Any	Any	Any	PD	Any	PD
SD	CR/PR/SD	Non-PD	Non-PD	Any	SD
PR	CR/PR	Non-PD	Non-PD	Any	PR
CR/PR	PR	Non-PD	Non-PD	Any	PR
CR	CR	Non-PD	Non-PD	Elevated	PR
CR	CR	CR	CR	Normal	CR

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

12.5 Response Criteria for Neuroblastoma Patients with MIBG Positive Lesions

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

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

Complete response: Complete resolution of all MIBG positive lesions

Partial Response: Resolution of at least one MIBG positive lesion, with persistence of other MIBG positive lesions

Stable disease: No change in MIBG scan in number of positive lesions

Progressive disease: Development of new MIBG positive lesions

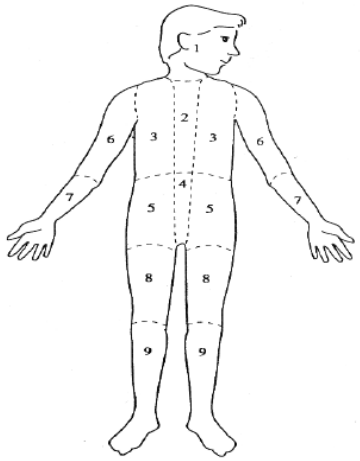
12.5.3 The response of MIBG lesions will be assessed on central review using the Curie scale14 as outlined below. Central review responses will be used to assess efficacy for study endpoint. See Section 8.2 for details on transferring images to the Imaging Research Center.

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

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

0 = no site per segment,
1 = 1 site per segment,
2 = more than one site per segment,
3 = massive involvement (>50% of the segment).

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



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

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

12.5.4 Overall Response Assessment

Table 4: Overall Response Evaluation for Neuroblastoma Patients and MIBG Positive Disease Only
If patients are enrolled without disease measurable by CT/MRI, any new or newly identified lesion by CT/MRI that occurs during therapy would be considered progressive disease.

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

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

12.6 Response Criteria for Neuroblastoma Patients with Bone Marrow Involvement

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

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

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

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

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

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

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

12.7 Response Criteria for Patients with CNS Tumors

12.7.1 Measurable Disease

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

12.7.2 Evaluable Disease

Evaluable disease is defined as at least one lesion, with no lesion that can be accurately measured in at least one dimension. Such lesions may be evaluable by nuclear medicine techniques, immunocytochemistry techniques, tumor markers, CSF cytology, or other reliable measures.

12.7.3 Selection of Target and Non-Target Lesions

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

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

12.7.4 Response Criteria for Target Lesions

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

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

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

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

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

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

12.7.5 Response Criteria for Non-Target Lesions:

- **Complete Response (CR):** Disappearance of all non-target lesions.
- **Incomplete Response/Stable Disease (IR/SD):** The persistence of one or more non-target lesions.
- **Progressive Disease (PD):** The appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions.

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

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

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

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

12.8 **Response Criteria for Patients with non-Hodgkin Lymphoma/Histiocytosis**
Response and progression will be evaluated in this study using the new international criteria proposed by the revised Response Evaluation Criteria in Pediatric non-Hodgkin Lymphoma Criteria[45], with modification from the Lugano classification.[46]

12.8.1 Disease Parameters

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

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

12.8.1.3 Target lesions: For patients staged with CT, up to six of the largest target nodes, nodal masses, or other lymphomatous lesions that are measurable in two diameters (longest diameter [LDi] and shortest diameter) should be identified from different body regions representative of the patient's overall disease burden and include mediastinal and retroperitoneal disease, if involved.

12.8.2 Evaluation of Measurable Disease

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

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

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

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

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

12.8.3 Evaluation of Non-measured Lesions (CT-based response, PET/CT based response not applicable)[46]

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

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

Stable Disease (SD): No increase consistent with progression

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

12.8.4 Evaluation of organ enlargement[46]

Complete Response (CR): Regress to normal

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

Stable Disease (SD): No increase consistent with progression

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

New or recurrent splenomegaly

12.9 Best Response

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

12.9.1 Evaluation of Best Overall Response

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

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

1st Assessment	2nd Assessment	Best Response
Progression		Progressive disease
Stable, PR, CR	Progression	Progressive disease
Stable	Stable	Stable

Stable	PR, CR	Stable
Stable	Not done	Not RECIST classifiable
PR	PR	PR
PR	CR	PR
PR, CR	Not done	Not RECIST classifiable
CR	CR	CR

12.9.2 Duration of Response

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

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

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

13.0 ADVERSE EVENT REPORTING REQUIREMENTS

Adverse event data collection and reporting which are required as part of every clinical trial, are done to ensure the safety of patients enrolled in the studies as well as those who will enroll in future studies using similar agents. Adverse events are reported in a routine manner at scheduled times during a trial. (Please follow directions for routine reporting provided in the Case Report Forms for this protocol). Additionally, certain adverse events must be reported in an expedited manner to allow for optimal monitoring of patient safety and care. The following sections provide information about expedited reporting.

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

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

13.1 Expedited Reporting Requirements – Serious Adverse Events (SAEs)

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

1) Death.
2) A life-threatening adverse drug experience.
3) An adverse event resulting in inpatient hospitalization or prolongation of existing hospitalization (for ≥ 24 hours). This does not include hospitalizations that are part of routine medical practice.
4) A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
5) A congenital anomaly/birth defect.
6) Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

13.1.1 Reporting Requirements - Investigator Responsibility

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

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

Fax supporting documentation **for AEs related to investigational agents supplied under a CTEP IND** to: (301) 897-7404).

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

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

13.1.2 CTEP-AERS Expedited Reporting Methods

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

Send supporting documentation to the NCI by fax (fax# 301-640-9193) and by email to both COGCAdEERS@childrensoncologygroup.org, the APEC1621F COG Study Assigned Research Coordinator, and COGAERS@childrensoncologygroup.org; Attention: COG AERS Coordinator. **ALWAYS include the ticket number on all faxed and emailed documents**.

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

Step 1: Identify the type of adverse event using the current version of the NCI CTCAE. V. 5.0 The descriptions and grading scales found in the current version of the CTCAE v 5.0 will be used for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE. A copy of the CTCAE can be downloaded from the CTEP website (http://ctep.cancer.gov).

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

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

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

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

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

FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)
NOTE: Investigators **MUST** immediately report to the sponsor **ANY** Serious Adverse Events, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64)
An adverse event is considered serious if it results in **ANY** of the following outcomes:

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

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

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

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

Expedited AE reporting timelines are defined as:

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

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

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

- All Grade 3, 4, and Grade 5 AEs

Expedited 7 calendar day reports for:

- Grade 2 AEs resulting in hospitalization or prolongation of hospitalization

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

Effective Date: May 5, 2011

13.3 Exceptions to CTEP-AERS Expedited Reporting Requirements:

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

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

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

Category	Adverse Events
EYE DISORDERS	Blurred Vision
GASTROINTESTINAL DISORDERS	Abdominal pain
GASTROINTESTINAL DISORDERS	Dyspepsia
GASTROINTESTINAL DISORDERS	Gasoesophageal reflux disease
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	Edema face
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	Edema limbs
INVESTIGATIONS	Alkaline phosphatase increased
INVESTIGATIONS	Creatinine Increase
INVESTIGATIONS	Weight loss
METABOLISM AND NUTRITION DISORDERS	Hypoalbuminemia
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	Arthralgia
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	Generalized muscle weakness
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	Muscle Cramp
NERVOUS SYSTEM DISORDERS	Dizziness
NERVOUS SYSTEM DISORDERS	Dysgeusia
NERVOUS SYSTEM DISORDERS	Headache
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	Cough
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	Rash acneiform
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	Skin and subcutaneous tissue disorders - Other (lichenoid keratosis)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	Skin and subcutaneous tissue disorders - (skin exfoliation)
VASCULAR DISORDERS	Flushing

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

13.4 Definition of Onset and Resolution of Adverse Events

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

If an adverse event occurs more than once in a course (cycle) of therapy only the most severe grade of the event should be reported.

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

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

The resolution date of the AE is defined as the date at which the AE returns to baseline or less than or equal to Grade 1, whichever level is higher (note that the resolution date may therefore be different from the date at which the grade of the AE decreased from its highest grade). If the AE does not return to baseline the resolution date should be recorded as "ongoing."

An adverse event that persists from one course to another should only be reported once unless the grade becomes more severe in a subsequent course. An adverse event which resolves and then recurs during a different course, must be reported each course it recurs.

13.5 Other Recipients of Adverse Event Reports

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

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

13.6 Specific Examples for Expedited Reporting

13.6.1 Reportable Categories of Death

- Death attributable to a CTCAE v5.0 term.
- Death Neonatal: A disorder characterized by "Newborn deaths occurring during the first 28 days after birth."
- Sudden Death NOS: A sudden (defined as instant or within one hour of the onset of symptoms) or an unobserved cessation of life that cannot be attributed to a CTCAE v5.0 term associated with Grade 5.
- Death NOS: A cessation of life that cannot be attributed to a CTCAE term associated with Grade 5.
- Death due to progressive disease should be reported as ***Grade 5 "Disease progression"*** under the system organ class (SOC) of General disorders and

administration site conditions." Evidence that the death was a manifestation of underlying disease (*e.g.*, radiological changes suggesting tumor growth or progression: clinical deterioration associated with a disease) should be submitted.

- Any death occurring within 30 days of the last dose, regardless of attribution to the investigational agent/intervention requires expedited reporting within 24 hours.

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

13.6.2 Reporting Secondary Malignancy

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

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

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

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

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

13.6.3 Reporting Pregnancy, Pregnancy Loss, and Death Neonatal

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

Pregnancy: Patients who become pregnant on study risk intrauterine exposure of the fetus to agents that may be teratogenic. For this reason, pregnancy needs to be reported in an expedited manner via CTEP-AERS as **Grade 3 "*Pregnancy,***

puerperium and perinatal conditions - Other (pregnancy)*"** under the ***Pregnancy, puerperium and perinatal conditions SOC.

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

Pregnancy Loss (Fetal Death)
Pregnancy loss is defined in CTCAE v5.0 as "Death in utero."

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

Death Neonatal:
Neonatal death, defined in CTCAE v5.0 as "***Newborn deaths occurring during the first 28 days after birth***" that is felt by the investigator to be at least possibly due to the investigational agent/intervention, should be reported expeditiously, as **Grade 4 "*Death Neonatal*"** under the system organ class (SOC) of "General disorders and administration site conditions." **When the death is the result of a patient pregnancy or pregnancy in partners of men on study**. Do NOT report a neonatal death resulting from a patient pregnancy or pregnancy in partners of men on study as a Grade 5 event since CTEP-AERS recognizes any Grade 5 event as a patient death.

14.0 RECORDS, REPORTING, AND DATA AND SAFETY MONITORING PLAN

14.1 Categories of Research Records

Research records for this study can be divided into three categories

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

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

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

See separate CRF Packet, which includes submission schedule.

14.2 CDUS

This study will be monitored by the Clinical Data Update System (CDUS) version 3.0. Cumulative protocol- and patient-specific CDUS data will be submitted electronically to

CTEP on a quarterly basis. Reports are due January 31, April 30, July 31 and October 31. This is not a responsibility of institutions participating in this trial.

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

14.3 **CRADA/CTA/CSA**

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

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

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

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

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

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

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

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

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

5. Any data provided to Collaborator(s) for Phase 3 studies must be in accordance with the guidelines and policies of the responsible Data Monitoring Committee (DMC), if there is a DMC for this clinical trial.

6. Any manuscripts reporting the results of this clinical trial must be provided to CTEP for immediate delivery to Collaborator(s) for advisory review and comment prior to submission for publication. Collaborator(s) will have 30 days from the date of receipt for review. Collaborator shall have the right to request that publication be delayed for up to an additional 30 days in order to ensure that Collaborator's confidential and proprietary data, in addition to Collaborator(s)'s intellectual property rights, are protected. Copies of abstracts must be provided to CTEP for forwarding to Collaborator(s) for courtesy review as soon as possible and preferably at least three (3) days prior to submission, but in any case, prior to presentation at the meeting or publication in the proceedings. Press releases and other media presentations must also be forwarded to CTEP prior to release. Copies of any manuscript, abstract and/or press release/ media presentation should be sent to:

   Email: ncicteppubs@mail.nih.gov

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

14.4 Data and Safety Monitoring Plan

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

14.4.1 Data and Safety Monitoring Committee

This study will be monitored in accordance with the Children's Oncology Group policy for data and safety monitoring of Phase 1 and 2 studies. In brief, the role of the COG Data and Safety Monitoring Committee is to protect the interests of patients and the scientific integrity for all Phase 1 and 2 studies. The DSMC consists of a chair; a statistician external to COG; one external member; one consumer representative; the lead statistician of the developmental therapy scientific committee; and a member from the NCI. The DSMC meets at least every 6 months to review current study results, as well as data available to the DSMC from other related studies. Approximately 6 weeks before each meeting of the

Phase 1 and 2 DSMC, study chairs will be responsible for working with the study statistician to prepare study reports for review by the DSMC. The DSMC will provide recommendations to the COG Developmental Therapeutics Chair and the Group Chair for each study reviewed to change the study or to continue the study unchanged. Data and Safety Committee reports for institutional review boards can be prepared using the public data monitoring report as posted on the COG Web site.

14.4.2 Monitoring by the Study Chair and MATCH Leadership

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

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APPENDIX I: PERFORMANCE STATUS SCALES/SCORES

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

APPENDIX II: CYP3A4 SUBSTRATES, INDUCERS AND INHIBITORS

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

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

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

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

[1] Certain fruits, fruit juices and herbal supplements (star fruit, Seville oranges, pomegranate, gingko, goldenseal) may inhibit CYP 3A4 isozyme, however, the degree of that inhibition is unknown.
[2]Refer to Section 7.5 regarding use of corticosteroids.
[3]The effect of grapefruit juice (strong vs moderate CYP3A4 inhibition) varies widely among brands and is concentration-, dose-, and preparation-dependent.
[4]Narrow therapeutic range substrates
[5]Sensitive substrates (drugs that demonstrate an increase in AUC of ≥ 5-fold with strong inhibitors)

APPENDIX III-A: MEDICATION DIARY FOR ENSARTINIB

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

Complete each day with the time and dose given for ensartinib. Ensartinib will be given in capsules. You should take ensartinib once a day by mouth. Ensartinib should be taken without regard to meals. Ensartinib should be stored at 59ºF-86ºF (room temperature). If a dose is not due or is accidentally skipped leave that day blank. ***Make note of other drugs and supplements taken under the Comments section below***. Ensartinib capsules should be swallowed whole. If capsule is broken and the powder of the capsules gets on skin, wash the exposed area with as much water as necessary. Inform your study doctor or nurse if that occurs. Do not repeat a dose after vomiting. The next dose should be taken as scheduled. If a dose is missed, the dose should be taken as soon as possible but not less than 12 hours before the next dose is due. If the next dose is due in less than 12 hours, you should skip the missed dose and take the next dose as scheduled. Add the dates to the calendar below and return the completed diary to the study clinic at each visit (weekly during Cycle 1, and then after each treatment cycle).

EXAMPLE			***Number of Ensartinib capsules***		***Comments***
	Date	***Time***	**25 mg**	**100 mg**	
Day 1	*12/15/19*	*8:30 AM*	2	1	*He felt nauseated an hour after taking the drug but did not vomit.*

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

WEEK 1	**Date**	**Time**	**# of ensartinib capsules prescribed to take**		**Comments (Describe any missed or extra doses, vomiting and/or bothersome effects.)**
			25 mg	**100 mg**	
			# _____	# _____	
			# of ensartinib capsules taken		
			25 mg	**100 mg**	
Day 1					
Day 2					
Day 3					
Day 4					
Day 5					
Day 6					
Day 7					
WEEK 2	**Date**	**Time**	**# of ensartinib capsules prescribed to take**		**Comments (Describe any missed or extra doses, vomiting and/or bothersome effects.)**
			25 mg	**100 mg**	
			# _____	# _____	
			# of ensartinib capsules taken		
			25 mg	**100 mg**	
Day 8					

Day 9					
Day 10					
Day 11					
Day 12					
Day 13					
Day 14					
WEEK 3	**Date**	**Time**	**# of ensartinib capsules prescribed to take** **25 mg** / **100 mg** # _____ / # _____ **# of ensartinib capsules taken** **25 mg** / **100 mg**		**Comments (Describe any missed or extra doses, vomiting and/or bothersome effects.)**
Day 15					
Day 16					
Day 17					
Day 18					
Day 19					
Day 20					
Day 21					
WEEK 4	**Date**	**Time**	**# of ensartinib capsules prescribed to take** **25 mg** / **100 mg** # _____ / # _____ **# of ensartinib capsules taken** **25 mg** / **100 mg**		**Comments (Describe any missed or extra doses, vomiting and/or bothersome effects.)**
Day 22					
Day 23					
Day 24					
Day 25					
Day 26					
Day 27					
Day 28					

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

Signature: _____ Date: _____

(Site personnel who reviewed this form)

APPENDIX III-B: PATIENT DRUG INFORMATION HANDOUT AND WALLET CARD

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

The patient _____ is enrolled on a clinical trial using the experimental study drug, **ensartinib (X-396 HCl)**. This clinical trial is sponsored by the National Cancer Institute. This form is addressed to the patient but includes important information for others who care for this patient.

These are the things that you as a healthcare provider need to know:

Ensartinib may interact with certain specific enzymes in your liver.

- The enzymes in question are **CYP 3A4 and 2C9**. Ensartinib is broken down mainly by CYP 3A4 and may be affected by other drugs that inhibit or induce this enzyme. Ensartinib inhibits CYP 3A4 and 2C9 and may affect other drugs that are broken down by these enzymes.
- Ensartinib is highly protein bound. Patients receiving other medications that are also highly protein bound may need to be monitored more frequently.

To the patient: Take this paper with you to your medical appointments and keep the attached information card in your wallet.

Ensartinib may interact with other drugs which can cause side effects. For this reason, it is very important to tell your study doctors of any medicines you are taking before you enroll onto this clinical trial. It is also very important to tell your doctors if you stop taking any regular medicines, or if you start taking a new medicine while you take part in this study. When you talk about your current medications with your doctors, include medicine you buy without a prescription (over-the-counter remedy), or any herbal supplements such as St. John's Wort. It is helpful to bring your medication bottles or an updated medication list with you.

Many health care providers can write prescriptions. You must tell all of your health care providers (doctors, physician assistants, nurse practitioners, pharmacists) you are taking part in a clinical trial.

These are the things that you and they need to know:

Ensartinib must be used very carefully with other medicines that use certain liver enzymes to be effective. Before you enroll onto the clinical trial, your study doctor will work with your regular health care providers to review any medicines and herbal supplements that are considered strong inhibitors or inducers of CYP3A4 and substrates of CYP3A4 and 2C9.

- Please be very careful! Over-the-counter drugs (including herbal supplements) may contain ingredients that could interact with your study drug. Speak to your doctors or pharmacist to determine if there could be any side effects.
- You may need to be monitored more frequently if you are receiving other medications that are also highly protein bound
- Your regular health care provider should check a frequently updated medical reference or call your study doctor before prescribing any new medicine or discontinuing any medicine. Your study doctor's name is _____ and he or she can be contacted at _____.

January 2017

STUDY DRUG INFORMATION WALLET CARD	
You are enrolled on a clinical trial using the experimental study drug **ensartinib (X-396 HCl).** This clinical trial is sponsored by the NCI. **Ensartinib** may interact with drugs that are processed by your liver. Because of this, it is very important to: ➢ Tell your doctors if you stop taking any medicines or if you start taking any new medicines. ➢ Tell all of your health care providers (doctors, physician assistants, nurse practitioners, or pharmacists) that you are taking part in a clinical trial. ➢ Check with your doctor or pharmacist whenever you need to use an over-the-counter medicine or herbal supplement. ➢ You may need to be monitored more frequently if you are receiving other medications that are also highly protein bound.	**Ensartinib interacts with specific liver enzymes called CYP3A4 and 2C9**, and must be used very carefully with other medicines that interact with these enzymes. ➢ Before you enroll onto the clinical trial, your study doctor will work with your regular health care providers to review any medicines and herbal supplements that are considered **strong inhibitors or inducers of CYP 3A4 and substrates of CYP3A4 and 2C9.** ➢ Before prescribing new medicines, your regular health care providers should go to a frequently-updated medical reference for a list of drugs to avoid, or contact your study doctor. ➢ Your study doctor's name is _____ and can be contacted at _____.

APPENDIX IV: ENSARTINIB DOSING NOMOGRAM

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

Ensartinib Dose Assignment: 130 mg/m^2 once daily (with a maximum of 225 mg per day).

BSA (m^2)	Total Daily Dose (mg/day)	Dose Reduction For Toxicity (mg/day)
0.5-0.67	75	50
0.68-0.86	100	75
0.87-1.05	125	75
1.06-1.24	150	100
1.25-1.44	175	125
1.45-1.63	200	150
≥ 1.64	225	175

APPENDIX V: APEC1621F THERAPY DELIVERY MAP

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

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

DRUG	ROUTE	DOSAGE	DAYS	IMPORTANT NOTES
Ensartinib IND # 134661	PO	130 mg/m^2/dose once daily **(maximum dose of 225 mg per day)** Refer to the dosing nomogram in Appx IV.	1-28	Ensartinib will be administered orally in capsules given once a day and can be taken without regard to food. Patients should swallow the capsules as a whole and should not chew or open them. Repeating a dose after vomiting is not recommended. The next dose should be taken as scheduled. If a patient misses a dose, the dose should be taken as soon as possible but not less than 12 hours before the next dose is due.

Ht _____cm Wt _____kg BSA _____m^2

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

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

Cycle 1

Required Observations in Cycle 1

All baseline studies must be performed prior to starting protocol therapy unless otherwise indicated below. For information related to prestudy observations please refer to Section 8.1 Studies on Day 28/1 may be obtained within 72 hours prior to the start of the subsequent cycle.

a.	**History/Physical Exam (including VS)**
b.	**Ht/Wt/BSA**
c.	**CBC/differential/platelets**- If patients have Grade 4 neutropenia then CBCs should be checked at least every other day until recovery to Grade 3 or until meeting the criteria for dose limiting toxicity. If patients develop Grade 3 or greater thrombocytopenia then CBCs should be checked every 3 to 4 days until recovery per section 6.1.
d.	**Electrolytes including Ca^{++}, PO4, Mg^{++}**
e.	**Creatinine, ALT, bilirubin**
f.	**Albumin**
g.	**Medication Diary-** (see Appendix III-A) should be reviewed after completion of each treatment cycle and uploaded into RAVE. The medication diary should be collected weekly.
h.	**Pharmacokinetics (optional)-**see Section 8.3 for details of PK studies.

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

Comments (Include any held doses, or dose modifications)

Treatment Details: Cycle 1

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

Cycle 1

All Subsequent Cycles

Therapy Delivery Map – All Subsequent Cycles

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

_____
Patient COG ID number

_____
Accession number

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

DRUG	ROUTE	DOSAGE	DAYS	IMPORTANT NOTES
Ensartinib IND # 134661	PO	130 mg/m^2/dose once daily **(maximum dose of 225 mg per day)** Refer to the dosing nomogram in Appx IV.	1-28	Ensartinib will be administered orally in capsules given once a day and can be taken without regard to food. Patients should swallow the capsules as a whole and should not chew or open them. Repeating a dose after vomiting is not recommended. The next dose should be taken as scheduled. If a patient misses a dose, the dose should be taken as soon as possible but not less than 12 hours before the next dose is due.

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

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

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

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

Subsequent Cycles

Required Observations in All Subsequent Cycles

a.	**History/Physical Exam (including VS)**
b.	**Ht/Wt/BSA**
c.	**CBC/differential/platelets** If patients have Grade 4 neutropenia then CBCs should be checked at least every other day until recovery to Grade 3 or until meeting the criteria for dose limiting toxicity. If patients develop Grade 3 or greater thrombocytopenia then CBCs should be checked every 3 to 4 days until recovery per Section 6.1.
d.	**Electrolytes including Ca^{++}, PO4, Mg^{++}**
e.	**Creatinine, ALT, bilirubin**
f.	**Albumin**
g.	**Tumor Disease Evaluation** – Every other cycle x 3 then q 3 cycles. Tumor Disease Evaluation should be obtained on the next consecutive cycle after initial documentation of either a PR or CR. Subsequent scans may restart 2 cycles after the confirmatory scan. If the institutional investigator determines that the patient has progressed based on clinical or laboratory evidence, he/she may opt not to confirm this finding radiographically.
h.	**Bone Marrow Aspirate and/or biopsy**- Only required in patients suspected of having bone marrow metastasis on the basis of history, symptoms, laboratory evaluation or other clinical data. Bone marrow aspirate and/or biopsy should be performed only when complete response or partial response is identified in target disease or when progression in bone marrow is suspected.
i.	**Medication Diary**- (see Appendix III-A) should be reviewed after completion of each treatment cycle and uploaded into RAVE. The medication diary should be collected weekly.
j.	**Circulating Tumor DNA (ctDNA-optional)**- With consent, two samples will be collected on this protocol (Cycle 5 Day 1; and for patients receiving ≥ 5 cycles, at progression or end of protocol therapy) see Section 8.4 for details of the ctDNA studies.

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

Comments
(Include any held doses, or dose modifications)

Treatment Details: Subsequent Cycles

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

APPENDIX VI: TARGET HISTOLOGIES FOR APEC1621F EXPANSION COHORTS

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

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

APPENDIX VII-A: EXAMPLES OF ACTIONABLE MUTATIONS FOR SUB-PROTOCOL APEC1621F COHORT A (ALK, ROS1 FUSIONS)

INCLUSION	VARIANTS			
Hotspots				
Gene Name	Variant ID	Variant Type	LOE	aMOI
ALK	A2M-ALK.A22A19	Fusion	1	ALK translocation
ALK	ACTG2-ALK.A2A18	Fusion	1	ALK translocation
ALK	ALK-PTPN3.A11P3	Fusion	1	ALK translocation
ALK	ATIC-ALK.A7A20.COSF444	Fusion	1	ALK translocation
ALK	ATRNL1-ALK.A19A20	Fusion	2	ALK translocation
ALK	BEND5-ALK.B3A20	Fusion	2	ALK translocation
ALK	BIRC6-ALK.B10A20	Fusion	2	ALK translocation
ALK	CAD-ALK.C35A20	Fusion	2	ALK translocation
ALK	CARS-ALK.C17A20.COSF437	Fusion	1	ALK translocation
ALK	CCDC88A-ALK.C12A20	Fusion	2	ALK translocation
ALK	CLIP1-ALK.C13A20	Fusion	1	ALK translocation
ALK	CLIP4-ALK.C12A23	Fusion	1	ALK translocation
ALK	CLTC-ALK.C31A20.COSF434	Fusion	1	ALK translocation
ALK	CLTC-ALK.C31A20.COSF470	Fusion	1	ALK translocation
ALK	CLTC-ALK.C31ins63A20	Fusion	1	ALK translocation
ALK	DCTN1-ALK.D26A20	Fusion	1	ALK translocation
ALK	DCTN1-ALK.D29A20	Fusion	2	ALK translocation
ALK	EML4-ALK.E13A20.AB462411	Fusion	1	ALK translocation
ALK	EML4-ALK.E13A20.COSF1062.2	Fusion	1	ALK translocation
ALK	EML4-ALK.E13ins90A20	Fusion	1	ALK translocation
ALK	EML4-ALK.E14A20.COSF1064.1	Fusion	1	ALK translocation
ALK	EML4-ALK.E14A20.COSF477.1	Fusion	1	ALK translocation
ALK	EML4-ALK.E14del36A20	Fusion	1	ALK translocation
ALK	EML4-ALK.E14ins124A20.1	Fusion	1	ALK translocation
ALK	EML4-ALK.E14ins2del52A20	Fusion	1	ALK translocation
ALK	EML4-ALK.E15A20.COSF413.1	Fusion	1	ALK translocation
ALK	EML4-ALK.E17A20.COSF1366.2	Fusion	1	ALK translocation
ALK	EML4-ALK.E17A20.COSF1367.2	Fusion	1	ALK translocation
ALK	EML4-ALK.E17ins30A20_V8a	Fusion	1	ALK translocation
ALK	EML4-ALK.E17ins65A20	Fusion	1	ALK translocation
ALK	EML4-ALK.E17ins68A20	Fusion	1	ALK translocation
ALK	EML4-ALK.E17int17Aint19E20	Fusion	1	ALK translocation
ALK	EML4-ALK.E18A20.COSF487.1	Fusion	1	ALK translocation
ALK	EML4-ALK.E19A20	Fusion	1	ALK translocation
ALK	EML4-ALK.E20A20.COSF409.1	Fusion	1	ALK translocation

ALK	EML4-ALK.E20A20.COSF730.1	Fusion	1	ALK translocation
ALK	EML4-ALK.E21A20	Fusion	1	ALK translocation
ALK	EML4-ALK.E2A20.COSF478.1	Fusion	1	ALK translocation
ALK	EML4-ALK.E2A20.COSF479.1	Fusion	1	ALK translocation
ALK	EML4-ALK.E3p53insA20	Fusion	1	ALK translocation
ALK	EML4-ALK.E6A17	Fusion	1	ALK translocation
ALK	EML4-ALK.E6A18	Fusion	1	ALK translocation
ALK	EML4-ALK.E6A19.COSF1296.1	Fusion	1	ALK translocation
ALK	EML4-ALK.E6aA20.AB374361	Fusion	1	ALK translocation
ALK	EML4-ALK.E6bA20.AB374362	Fusion	1	ALK translocation
ALK	EML4-ALK.E6ins18A20	Fusion	1	ALK translocation
ALK	EML4-ALK.E7A20.NGS	Fusion	1	ALK translocation
ALK	FN1-ALK.F20A19	Fusion	2	ALK translocation
ALK	FN1-ALK.F23A19.COSF1301	Fusion	2	ALK translocation
ALK	GFPT1-ALK.G18A20.1	Fusion	2	ALK translocation
ALK	GTF2IRD1-ALK.G7A20	Fusion	1	ALK translocation
ALK	GTF3C2-ALK.G1A18	Fusion	2	ALK translocation
ALK	HIP1-ALK.H21A20	Fusion	1	ALK translocation
ALK	HIP1-ALK.H28A20	Fusion	1	ALK translocation
ALK	HIP1-ALK.H30A20	Fusion	1	ALK translocation
ALK	KANK2-ALK.K4A16	Fusion	2	ALK translocation
ALK	KCNQ5-ALK.K1A10	Fusion	2	ALK translocation
ALK	KIF5B-ALK.K15A20.COSF1060.1	Fusion	1	ALK translocation
ALK	KIF5B-ALK.K15A20.COSF1381	Fusion	1	ALK translocation
ALK	KIF5B-ALK.K17A20.COSF1257	Fusion	1	ALK translocation
ALK	KIF5B-ALK.K24A19	Fusion	1	ALK translocation
ALK	KIF5B-ALK.K24A20.COSF1058	Fusion	1	ALK translocation
ALK	KLC1-ALK.K9A20.COSF1276	Fusion	1	ALK translocation
ALK	KTN1-ALK.K43A19	Fusion	2	ALK translocation
ALK	MCFD2-ALK.M1A20	Fusion	2	ALK translocation
ALK	MEMO1-ALK.M2A7	Fusion	1	ALK translocation
ALK	MSN-ALK.M11A20.COSF421	Fusion	1	ALK translocation
ALK	MSN-ALK.M11int12A20	Fusion	1	ALK translocation
ALK	MYH9-ALK.M34A20del23	Fusion	2	ALK translocation
ALK	MYH9-ALK.M9A6ins10	Fusion	1	ALK translocation
ALK	NCOA1-ALK.N21A1.NGS	Fusion	1	ALK translocation
ALK	NPM1-ALK.N4A20.COSF198	Fusion	1	ALK translocation
ALK	PPFIBP1-ALK.P12A20.COSF1461	Fusion	1	ALK translocation
ALK	PPFIBP1-ALK.P8A20ins49	Fusion	1	ALK translocation
ALK	PPM1G-ALK.P1A18	Fusion	2	ALK translocation

ALK	PPP4R3B-ALK.P9A2	Fusion	2	ALK translocation
ALK	PRKAR1A-ALK.P2A20.NGS.2	Fusion	1	ALK translocation
ALK	RANBP2-ALK.R18A20.COSF415	Fusion	1	ALK translocation
ALK	RNF213-ALK.R20A20	Fusion	2	ALK translocation
ALK	SEC31A-ALK.S21A20.COSF460	Fusion	1	ALK translocation
ALK	SEC31A-ALK.S22A20.COSF459	Fusion	1	ALK translocation
ALK	SQSTM1-ALK.S5A20.COSF1051	Fusion	1	ALK translocation
ALK	STK32B-ALK.S11A20	Fusion	2	ALK translocation
ALK	STRN-ALK.S3A20.COSF1430	Fusion	1	ALK translocation
ALK	TERT-ALK.T11A5	Fusion	2	ALK translocation
ALK	TFG-ALK.T4A20.COSF424	Fusion	1	ALK translocation
ALK	TFG-ALK.T5A20.COSF426	Fusion	1	ALK translocation
ALK	TFG-ALK.T6A20.COSF428	Fusion	1	ALK translocation
ALK	TFG-ALK.T7A19	Fusion	1	ALK translocation
ALK	TPM1-ALK.T8A20.NGS	Fusion	1	ALK translocation
ALK	TPM3-ALK.T7A20.COSF439	Fusion	1	ALK translocation
ALK	TPM4-ALK.T7A20.COSF441	Fusion	1	ALK translocation
ALK	TPR-ALK.T15A20	Fusion	1	ALK translocation
ALK	TPR-ALK.T4A20	Fusion	1	ALK translocation
ALK	TRAF1-ALK.T6A20	Fusion	1	ALK translocation
ALK	TRMT61B-ALK.T1A9	Fusion	2	ALK translocation
ALK	VCL-ALK.V16A20.COSF1057	Fusion	1	ALK translocation
ROS1	CCDC6-ROS1.C5R35.1	Fusion	2	ROS1 translocation
ROS1	CD74-ROS1.C4R33.NGS	Fusion	2	ROS1 translocation
ROS1	CD74-ROS1.C6R32.COSF1202	Fusion	2	ROS1 translocation
ROS1	CD74-ROS1.C6R34.COSF1200	Fusion	2	ROS1 translocation
ROS1	CD74-ROS1.C6R35.COSF1478	Fusion	2	ROS1 translocation
ROS1	CEP85L-ROS1.C8R36	Fusion	2	ROS1 translocation
ROS1	CLIP1-ROS1.C19R36	Fusion	2	ROS1 translocation
ROS1	ERC1-ROS1.E11R36	Fusion	2	ROS1 translocation
ROS1	EZR-ROS1.E10R34.COSF1267	Fusion	2	ROS1 translocation
ROS1	EZR-ROS1.E10R35	Fusion	2	ROS1 translocation
ROS1	GOPC-ROS1.G4R36.COSF1188	Fusion	2	ROS1 translocation
ROS1	GOPC-ROS1.G8R35.COSF1139	Fusion	2	ROS1 translocation
ROS1	HLA_A-ROS1.H7R34	Fusion	2	ROS1 translocation
ROS1	KDELR2-ROS1.K5R35	Fusion	2	ROS1 translocation
ROS1	KDELR2-ROS1.K5Rintron34	Fusion	2	ROS1 translocation
ROS1	KIAA1598-ROS1.K11R36	Fusion	2	ROS1 translocation
ROS1	LRIG3-ROS1.L16R35.COSF1269	Fusion	2	ROS1 translocation
ROS1	MSN-ROS1.M9R34	Fusion	2	ROS1 translocation

ROS1	MYO5A-ROS1.M23R35	Fusion	2	ROS1 translocation
ROS1	NCOR2-ROS1.N7R36	Fusion	2	ROS1 translocation
ROS1	NFKB2-ROS1.N13R36	Fusion	2	ROS1 translocation
ROS1	PPFIBP1-ROS1.P9R35	Fusion	2	ROS1 translocation
ROS1	PWWP2A-ROS1.P1R36	Fusion	2	ROS1 translocation
ROS1	SDC4-ROS1.S2R32.COSF1265	Fusion	2	ROS1 translocation
ROS1	SDC4-ROS1.S2R34	Fusion	2	ROS1 translocation
ROS1	SDC4-ROS1.S4R32.COSF1278	Fusion	2	ROS1 translocation
ROS1	SDC4-ROS1.S4R34.COSF1280	Fusion	2	ROS1 translocation
ROS1	SLC34A2-ROS1.S13R32.COSF1259	Fusion	2	ROS1 translocation
ROS1	SLC34A2-ROS1.S13R34.COSF1261	Fusion	2	ROS1 translocation
ROS1	SLC34A2-ROS1.S13R36	Fusion	2	ROS1 translocation
ROS1	SLC34A2-ROS1.S4R32.COSF1196	Fusion	2	ROS1 translocation
ROS1	SLC34A2-ROS1.S4R34.COSF1198	Fusion	2	ROS1 translocation
ROS1	TFG-ROS1.T4R35	Fusion	2	ROS1 translocation
ROS1	TMEM106B-ROS1.T3R35	Fusion	2	ROS1 translocation
ROS1	TPM3-ROS1.T3R36	Fusion	2	ROS1 translocation
ROS1	TPM3-ROS1.T7R35.COSF1273	Fusion	2	ROS1 translocation
ROS1	YWHAE-ROS1.Y4R36	Fusion	2	ROS1 translocation
ROS1	ZCCHC8-ROS1.Z2R36	Fusion	2	ROS1 translocation

APPENDIX VII-B: EXAMPLES OF ACTIONABLE MUTATIONS FOR SUB-PROTOCOL APEC1621F COHORT B (ALK MISSENSE)

INCLUSION	**VARIANTS**			
Hotspots				
Gene Name	Variant ID	Variant Type	LOE	aMOI
ALK	COSM98475	SVN	3	p.G1128A
ALK	COSM98478	SVN	3	p.T1151M
ALK	PM_COSM28497	SVN	2	p.M1166R
ALK	PM_COSM4989835	SVN	2	p.I1170N
ALK	PM_COSM98477	SVN	2	p.I1170S
ALK	PM_COSM98476	SVN	2	p.I1170T
ALK	COSM28498	SVN	3	p.I1171N
ALK	COSM28491	SVN	2	p.F1174I
ALK	COSM28057	SVN	2	p.F1174L
ALK	COSM28055	SVN	2	p.F1174L
ALK	COSM28061	SVN	2	p.F1174L
ALK	COSM99137	SVN	3	p.L1196M
ALK	COSM28492	SVN	2	p.F1245I
ALK	COSM28499	SVN	2	p.F1245V
ALK	COSM28500	SVN	2	p.F1245C
ALK	COSM28493	SVN	2	p.F1245L
ALK	COSM28056	SVN	2	p.R1275Q
ALK	COSM28060	SVN	2	p.R1275L
ALK	COSM28058	SVN	3	p.Y1278S

APPENDIX VIII: YOUTH INFORMATION SHEETS
INFORMATION SHEET REGARDING RESEARCH STUDY APEC1621F
(for children from 7 through 13 years of age)

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

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

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

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

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

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

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

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

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

INFORMATION SHEET REGARDING RESEARCH STUDY APEC1621F
(for teens from 14 through 17 years of age)

A study of Molecular Analysis for Therapy Choice (MATCH) in children with a cancer that has come back after treatment or is difficult to treat

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

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

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

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

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

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

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

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

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

APPENDIX IX: CTEP AND CTSU REGISTRATION PROCEDURES

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

RCR utilizes five person registration types.

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

RCR requires the following registration documents:

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

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

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

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

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

CTSU REGISTRATION PROCEDURES

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

Protocol-Specific Requirements For Site Registration:

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

Submitting Regulatory Documents:
Submit required forms and documents to the CTSU Regulatory Office using the Regulatory Submission Portal on the CTSU 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 a clinical data management system being used for data collection for this trial/study. Access to the trial in Rave is controlled through the CTEP-IAM system and role assignments.
Requirements to access Rave via iMedidata:

- A valid CTEP-IAM account; and

- Assigned a Rave role on the LPO or PO roster at the enrolling site of: Rave CRA, Rave Read Only, Rave CRA (LabAdmin), Rave SLA, or Rave Investigator.

Rave role requirements:

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

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

Upon initial site registration approval for the study in Regulatory Support System (RSS), all persons with Rave roles assigned on the appropriate roster will be sent a study invitation e-mail from iMedidata. To accept the invitation, site staff must either click on the link in the email or log in to iMedidata via the CTSU members' website under *Data Management* > *Rave Home* and click to *accept* the invitation in the *Tasks* pane located in the upper right-corner of the iMedidata screen. 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.

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

Data Quality Portal

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

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

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

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

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

Appendix X: Toxicity-Specific Grading

Bilirubin:

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

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

Grade 1:	≤ 135
Grade 2:	136- 225
Grade 3:	226- 900
Grade 4:	> 900

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

Grade 1:	≤ 150
Grade 2:	151-250
Grade 3:	251-1000
Grade 4:	> 1000

GGT:

Grade 1:	> ULN- 2.5 x ULN
Grade 2:	> 2.5 x ULN- 5 x ULN
Grade 3:	> 5 x ULN-20 x ULN
Grade 4:	> 20 x ULN

APPENDIX XI: CORRELATIVE STUDIES

Correlative Study	Section	Blood Volume		Tube Type
		Volume per Sample	Total Cycle 1	
Pharmacokinetics	8.3	2-3 mL	22-33 mL	K_2-EDTA (lavender top) tubes
Total Blood Volume in Cycle 1			**22-33 mL**	

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

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

*Only for patients receiving ≥ 5 cycles of therapy only