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October 28, 2022

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

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

Dear Ms. Kruhm,

The study committee thanks CTEP for forwarding the Amendment Request dated October 17, 2022. In response to the request, please see attached Amendment #3 to APEC1621K. The complete list of changes can be found below.

Please contact us if you have any further questions.

Sincerely,

Emma Archuleta, B.S., Protocol Coordinator (for)
Elizabeth Alva, M.D., MSPH, **APEC1621K** Study Chair, and
Douglas S. Hawkins, M.D., Group Chair, Children's Oncology Group

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SUMMARY OF CHANGES: PROTOCOL

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

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

Activated: 06/08/2020
Closed:

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

CHILDREN'S ONCOLOGY GROUP

APEC1621K

NCI-COG PEDIATRIC MATCH (MOLECULAR ANALYSIS FOR THERAPY CHOICE)- PHASE 2 SUBPROTOCOL OF AG-120 (IVOSIDENIB) IN PATIENTS WITH TUMORS HARBORING IDH1 MUTATIONS

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

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Contact Information

For Regulatory Requirements	For patient enrollments:	For Data Submission
Regulatory documentation must be submitted to the Cancer Trials Support Unit (CTSU) via the Regulatory Submission Portal. (Sign in at www.ctsu.org, and select the Regulatory > Regulatory Submission.) Institutions with patients waiting that are unable to use the Portal should alert the CTSU Regulatory Office immediately by phone or email: 1-866-651-CTSU (2878), or CTSURegHelp@coccg.org to receive further instruction and support. Contact the CTSU Regulatory Help Desk at 1-866-651-2878 for regulatory assistance.	Please refer to the patient enrollment section of the protocol for instructions on using the Oncology Patient Enrollment Network (OPEN). OPEN is accessed at https://www.ctsu.org/OPEN_SYSTEM/ or https://open.ctsu.org. Contact the CTSU Help Desk with any OPEN-related questions by phone or email: 1-888-823-5923, or ctsucontact@westat.com.	Data collection for this study will be done exclusively through Medidata Rave. Please see the 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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AGENT NSC# AND IND#'s

NCI-Supplied Agents:

AG-120 (ivosidenib) (NSC# 804600 , IND# [redacted])
IND Sponsor: DCTD, NCI

SEE Section 8.3.6 AND Section 8.4.4 FOR
SPECIMEN SHIPPING ADDRESSES

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

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

ABSTRACT

This subprotocol is a component of the Pediatric MATCH trial APEC1621. The APEC1621SC screening protocol details the process used to identify actionable mutations in patient tumor samples will determine eligibility for this subprotocol. This is a phase 2 trial of AG-120 (ivosidenib) in children with relapsed or refractory solid tumors (including lymphomas, histiocytoses and CNS tumors) harboring specified activating mutations of the IDH pathway. AG-120 (ivosidenib) will be given at a dose of 290 mg/m^2 by mouth once daily for 28-day cycles. The primary endpoint will be objective response rate as determined by RECIST. Progression free survival (PFS) will be assessed as a secondary endpoint.

EXPERIMENTAL DESIGN SCHEMA

Treatment Schedule Table	
Days 1-28	AG-120 (ivosidenib)
Day 28	Evaluation

Patients will receive AG-120 (ivosidenib) 290 mg/m^2 by mouth once daily for 28 days, which is equivalent to the adult RP2D of 500 mg by mouth; a cycle will be 28 days. Disease evaluations will occur 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. 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 AG-120 (ivosidenib) with advanced solid tumors (including CNS tumors), lymphomas or histiocytic disorders that harbor activating genetic alterations in the IDH1 pathway.

1.2 Secondary Aims

1.2.1 To estimate the progression free survival in pediatric patients treated with AG-120 (ivosidenib) with advanced solid tumors (including CNS tumors), lymphomas or histiocytic disorders that harbor activating genetic alterations in the IDH1 pathway.

1.2.2 To obtain information about the tolerability of AG-120 (ivosidenib) in children and adolescents with relapsed or refractory cancer.

1.2.3 To provide preliminary estimates of the pharmacokinetics and pharmacodynamics of AG-120 (ivosidenib) in children and adolescents with relapsed or refractory cancer.

1.3 Exploratory Aims

1.3.1 To evaluate other biomarkers as predictors of response to AG-120 (ivosidenib) and specifically, whether tumors that harbor different missense mutations or fusions will demonstrate differential response to AG-120 (ivosidenib) treatment.

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

2.0 BACKGROUND

2.1 Introduction/Rationale for Development

The isocitrate dehydrogenase (IDH) family is comprised of three isozymes (IDH1, IDH2 and IDH3) that play a critical role in the citric acid cycle by converting isocitrate to αKG via oxidative decarboxylation. Mutations in IDH1 can alter this pathway to increase production of the oncometabolite 2-hydroxyglutarate (2-HG). Increased 2-HG induces histone and DNA hypermethylation and blocks cellular differentiation resulting in tumorigenesis.[1,2,3,4] Mouse models expressing IDH1 mutations in hematopoietic tissue have shown that expression of IDH1 mutations lead to block in myeloid differentiation, extramedullary hematopoiesis and an mRNA signature similar to AML, helping establish the link between IDH1 mutations and leukaemogenesis.[5] The majority of cancer associated IDH mutations can been mapped to an arginine within the catalytic pocket of the enzyme, which is critical for isocitrate binding. IDH1 mutations typically occur at arginine 132 and are missense substitutions.[6]

IDH1 mutations have been identified as a therapeutic target in multiple adult cancer types, including acute myeloid leukemia (AML), central nervous system (CNS) malignancies, including both high and low grade gliomas, chondrosarcomas, and cholangiocarcinoma. In

adult AML, approximately 10-15% of patients harbor IDH mutations.[7,8,9] The incidence of IDH1 mutations in patients with WHO grade II and WHO grade III gliomas as well as secondary glioblastoma is 70-80%.[10,11] However, the incidence of IDH1 mutations in adult primary glioblastoma is less than 10%.[10,11] IDH mutations have also been found in ~50% of chondrosarcomas and ~15-20% of cholangiocarcinoma.[12, 13]

IDH1 mutations have also been identified in several pediatric malignancies. In pediatric AML, the frequency of IDH1 mutations is approximately 1-2%.[14, 15,16,17] For pediatric patients with high grade gliomas, the incidence of IDH1 mutations appears to be age dependent, with 35% of patients greater than or equal to 14 years of age being found to have IDH1 mutations compared to 0% of patients under the age of 14.[18] Additionally, IDH1 mutations have been shown to be present in 8% of pediatric patients with gliomatosis cerebri.[19]

2.2 Preclinical Studies

2.2.1 Antitumor Activity

The information provided in this protocol is from the AG-120 (ivosidenib) investigator's brochure and is summarized here.[20] The inhibitory activity of AG-120 (ivosidenib) against IDH1 and IDH2 mutant enzymes and selectivity of AG-120 (ivosidenib) against IDH1-WT and IDH2-WT were characterized in a diaphorase/resazurin coupled system. AG-120 (ivosidenib) is highly selective for IDH1 mutant isoforms with IC_{50} values (μM) ranging from 0.002-0.017. Against IDH1 (R132H), AG-120 (ivosidenib) showed noncompetitive inhibition with respect to α-KG substrate and NADPH cofactor, and no time-dependence in IC_{50} values between 1 and 16 hours of incubation. These observations are consistent with AG-120 (ivosidenib) being a rapid equilibrium inhibitor of IDH1 homodimer in the presence or absence of substrate and cofactor. Against IDH1-WT homodimer, AG-120 (ivosidenib) showed noncompetitive inhibition with respect to NADP cofactor. IC_{50} for IDH1 WT alone at 1 hour was 1.326 μM compared to 0.071 μM and 0.024 μM when incubated with NADP and 1 hour and 16 hours respectively. The increase in potency observed when incubation was carried out in the presence of cofactor is consistent with the mechanism of action. AG-120 (ivosidenib) was shown to be a low-binding inhibitor of IDH1-WT homodimer.

The potency and specificity of AG-120 (ivosidenib) against cellular IDH1 mutations were evaluated in multiple cell based systems. AG-120 (ivosidenib) is a potent inhibitor of 2-HG production in cells expressing IDH1 R132 mutations but not for cell lines expressing IDH2. The potency and specificity against cellular IDH1 and IDH2 mutations of AG-120 (ivosidenib) is shown in the table below.

Cell Line	2-HG IC_{50} (nM)	N	GI_{50} (3 μM top dose)
COR-L105 (R132C)	10 ± 4	3	> 3 μM
HCCC-9810 (R132S)	10 ± 2	4	> 3 μM
RBE (R132S)	3	1	> 3 μM
HT1080 (R132C)	8 ± 4	15	> 3 μM
U876MG pLVS IDH1 (R132C)	4 ± 1.6	4	> 3 μM
U876MG pLVS IDH1 (R132H)	20 ±11	14	> 3 μM

Neurosphere 603 (R132H)	2.4 ± 0.2	8	> 3 µM
TF1 pLVX IDH1 (R132H) clone 27	20	1	> 3 µM
U87MG pLVX IDH2 (R140Q)	No Fit	1	> 3 µM

Abbreviations: 2-HG = 2-hydroxyglutarate; GI_{50} = concentration of drug which effects half-maximal growth inhibition; IC_{50} = concentration of drug which achieves half maximal inhibition; pLVX = control cell line
Source: AG-120 (ivosidenib) investigator's brochure[20]

2.2.2 Animal Toxicology

The information provided in this protocol is from the investigator's brochure and summarized here.[20] *In vivo* GLP toxicology studies included repeat-dose GLP 28-day and 3-month Sprague-Dawley rat and cynomolgus monkey studies, and definitive embryo/fetal development studies in Sprague-Dawley rats and New Zealand White rabbits, and a GLP micronucleus study in Sprague-Dawley rats. AG-120 (ivosidenib) was well tolerated at $AUC_{0\text{-}12hr}$ exposure levels that are 0.5- to 1.1-fold (3 month rat) and 2.4-fold (3-month monkey) the human 500 mg/day $AUC_{0\text{-}10hr}$ exposure level.

Dose limiting toxicity in the rat occurred at a dosage of 2000 mg/kg/day in the 28-day study. At this dose level, the $AUC_{0\text{-}12hr}$ values were 3.5- to 3.7-fold the human $AUC_{0\text{-}10hr}$ value on Day 0 and declined to 1.2- to 1.8-fold on Day 27. The cause of early DLT (between days 2 and 6) was centrilobular hepatocellular degeneration and necrosis with additional contributing factors including tubular necrosis in the kidney as well as hypocellularity, hemorrhage, and necrosis of the femoral and/or sternal bone marrow. When DLT occurred later in the dosing period (day 19-20), it was due to mucosal atrophy of the intestines, erosions and ulcerations of the glandular stomach and/or rectum, and lymphoid depletion. The next lower dose level tested in rats (500 mg/kg/day) was tolerated over 28 days of dosing and was utilized as the top dose in the GLP 3-month toxicology study.

In the rat, the dosage level of 500 mg/kg/day (highest dosage tested) was tolerated over a 3-month dosing period and did not result in any test article-related moribundity or mortality. The Day 90 plasma $AUC_{0\text{-}12hr}$ values at this dosage level were 0.5- to 1.1-fold the C2D1 human $AUC_{0\text{-}10hr}$ valuate at 500 mg/day. Target tissues and findings at this dose level in the 3-month rat study included liver and thyroid findings consistent with hepatocellular enzyme induction and red cell parameter alterations and splenic extramedullary hematopoiesis. All significant findings at this dose level in both 28-day and 3-month studies were partially or fully reversible following a 14- and 28-day non-dosing period respectively.

In the GLP, 28-day monkey study, DLT occurred in male monkeys at the highest dose level tested, 270 mg/kg/day) at a Day 27 $AUC_{0\text{-}12hrs}$ value which is 4.2-fold the human $AUC_{0\text{-}10hr}$ value. The cause of DLT was general malaise and poor body condition, gastrointestinal clinical signs with emesis and secondary aspiration. The next lower dose level in monkeys (90 mg/kg/day) was very well tolerated. A dose of 180mg/kg/day was subsequently chose as the top dose in the GLP 3-month toxicology study.

In the 3-month dosing period, the dose level of 180 mg/kg/day was well tolerated and did not result in any test article-related morbundity or mortality. The day 90 plasma

$AUC_{0\text{-}12hr}$ value at this dose level was approximately 2.4-fold the C2D1 human $AUC_{0\text{-}10hr}$ value at 500 mg/day. Findings at this dose level included intermittent diarrhea as well as liver findings consistent with hepatocellular enzyme induction. A cardiovascular assessment was conducted toward the end of the study (week 12) and possible/probable test-article-related prolongations of QTcB intervals were noted in individual animals. All findings were partially or fully reversible following a 28-day non-dosing period.

2.3 Adult Studies

2.3.1 Phase 1 and Phase 2 Studies

Phase 1 trials with AG-120 (ivosidenib) are ongoing in patients with advanced hematologic malignancies harboring IDH1 mutations (AG120-C-001) and patients with advanced solid tumors harboring IDH1 mutations, including gliomas (AG120-C-002). Durable responses were seen in patients with relapsed/ refractory AML with IDH1 mutations treated with AG-120 (ivosidenib). [21] Similarly, patients with non-enhancing gliomas treated with AG-120 (ivosidenib) on AG120-C-002 were found to have 6% overall response rate (ORR) and 83% stable disease (SD).[22] AG-120 (ivosidenib) also showed encouraging responses in patients with chondrosarcoma treated on AG120-C-002, with a 58% progression free survival (PFS) at 3 months.[23] Similarly, patients with cholangiocarcinoma treated on AG120-C-002 experienced a 6 month PFS of 38.5% and a 12 month PFS of 20.7%.[24] AG-120 (ivosidenib) was found to be well tolerated and no maximum tolerated dose (MTD) was reached in either Phase 1 trial. Recommended phase 2 dose (RP2D) of AG-120 (ivosidenib) in adults is 500 mg PO daily for 28 day cycles.

AG120-C-001 (NCT02074839) was a phase 1, multicenter trial to assess the safety, pharmacokinetics, pharmacodynamics and clinical activity of AG–120 (ivosidenib) in advanced hematologic malignancies harboring an IDH1 mutation. This study included a dose escalation phase to determine MTD and RP2D as well as a dose expansion phase where four cohorts of patients received AG-120 (ivosidenib) at the RP2D to assess the tolerability, safety and clinical activity of AG-120 (ivosidenib). The study included patients with relapsed/refractory AML, untreated patients with AML who were not eligible for standard of care treatment and other relapsed/refractory advanced hematologic malignancies. A total of 78 patients were treated in the dose phase of the study. The dose was escalated up to a dose of 1200 mg PO daily and no MTD was reached. Pharmacokinetic and pharmacodynamics data supported the selection of 500 mg PO daily for the dose expansion portion of the trial. The most common adverse events (AEs) of any grade were fatigue (36%), nausea (33%) and diarrhea (32%). The most common grade $\geq$ 3 AEs were febrile neutropenia (21%) and anemia (18%). Dose limiting toxicities (DLTs) were observed in only 2 patients. One DLT consisted of a grade 3 QT prolongation at a dose of 800 mg daily and one consisted of a grade 3 rash at 1200 mg daily. An ORR of 38% with a complete response (CR) rate of 18% was observed with a duration of study treatment up to 24.2 months. The median duration of overall response in all patients was 10.2 months. IDH1 mutational clearance was also assessed during this study with next generation sequencing (FoundationOne Heme Panel) and it was found that treatment with AG-120 (ivosidenib) as a single agent can result in mIDH1 clearance by NGS.

AG120-C-002 (NCT02073994) was a phase 1, multicenter trial to assess the safety, pharmacokinetics, pharmacodynamics and clinical activity of AG-120 (ivosidenib) in advanced solid tumors, including glioma, that harbor an IDH1 mutation. This study also included a dose escalation and a dose expansion phase, a total of 168 patients were treated in study AG120-C-002. The four dose expansion cohorts consisted of gliomas, cholangiocarcinoma, chondrosarcoma, and other advanced solid tumors. The dose was escalated to 1200 mg PO daily on the dose escalation phase and no MTD was reached. The RP2D was determined to be 500mg PO daily. The most common adverse events seen in patients with gliomas include headache (26%), nausea (21%) and diarrhea (15%). The most common grade ≥ 3 AEs in glioma patients were headaches (5%) and hypophosphatemia (3%). An ORR of 9% was observed with 83% SD. 64% of tumors showed decrease in tumor growth rate by volumetric assessment. In the chondrosarcoma cohort, the most common AEs included diarrhea (29%), nausea (24%), decreased appetite (19%) and QT prolongation (19%). Grade ≥ 3 AEs were rare with only one patient each experiencing anemia, peripheral edema and elevated alkaline phosphatase. In the chondrosarcoma cohort, 55% of patients experienced stable disease and a 58% progression free survival was observed at 3 months. Of the evaluable patients with SD, 41% had decrease in the size of target lesions. In the cholangiocarcinoma expansion cohort, the most common AEs included fatigue (45%), nausea (37%), decreased appetite (31%) and diarrhea (29%). The most common grade ≥ 3 AEs in the cholangiocarcinoma cohort included ascites (5%), abdominal distension (3%) and anemia (3%). The 6 month progression free survival (PFS) rate in the cholangiocarcinoma cohort was 38.5% with a 12 months PFS of 20.7%. No DLTs were observed in any of the cohorts.

AG-120 (ivosidenib) is also currently being investigated in a phase 1 randomized, open-label study in patients with recurrent, non-enhancing, IDH1 mutant low grade, gliomas (NCT03343197). In this study, patients with recurrent, non-enhancing low grade gliomas in which surgical resection is indicated are randomized to receive 4 weeks of AG-120 (ivosidenib), 4 weeks of AG-881, or no treatment prior to surgical resection. All patients have the option to receive AG-120 (ivosidenib) or AG-881 post-operatively.

2.3.2 Phase 3 Studies

Currently, there are three phase three trials using AG-120 (ivosidenib) in combination with HMA and standard chemotherapy chemotherapeutic agents in previously untreated adult patients with IDH1 mutated AML (NCT02632708, NCT03173248, NCT02677922).

AG-120 (ivosidenib) has also expanded in to a phase 3 trial in patients with advanced IDH1 mutated cholangiocarcinoma (NCT02989857). In this study, patients with IDH1 mutated cholangiocarcinoma who are not eligible for curative resection, transplantation or ablative therapies and have experienced progression of disease after at least 1 but nor more than 2 prior treatments are eligible to be randomized to AG-120/ disease progression while on placebo.

2.3.3 Pharmacology/Pharmacokinetics/Correlative and Biological Studies

AG-120 (ivosidenib) demonstrated good oral bioavailability, rapid absorption, and a long half-life in subjects with IDH1 mutant AML and solid tumors.[20] This supports a

once daily dosing regimen. Following multiple does of AG-120 (ivosidenib), steady state was reached within 14 days, with approximately 2-fold accumulation in plasma exposure. Ivosidenib has a terminal half-life of 93 hours and an apparent clearance (CL/F) of 4.3 L/hour. The mean apparent volume of distribution of ivosidenib at steady-state is 234 L and median time to C_{max} is approximately 3 hours. Protein binding of ivosidenib ranges from 92 to 96% in vitro. Ivosidenib is primarily metabolized by CYP3A4 with minor contributions by N-dealkylation and hydrolytic pathways. [25]

The plasma exposure of AG-120 (ivosidenib) increased less than dose proportionally, from 200 to 1200 mg. Results from AG120-C-001 and AG120-C-002 indicated that plasma 2-HG levels were substantially reduced in subjects with an IDH1 mutation at dose ranging from 200 to 1200mg daily. 2-HG levels were reduced to levels similar to those in healthy volunteers. In addition, multiple doses of AG-120 (ivosidenib) at doses of 200 to 1200 mg daily also decreased 2-HG levels in bone marrow in patients with AML as well as in tumor biopsies in patients with cholangiocarcinoma and chondrosarcoma.

The absorption, excretion, and metabolism of AG-120 (ivosidenib) were investigated in healthy male subjects. Fecal excretion appeared to be the predominant route of elimination. AG-120 (ivosidenib) was readily absorbed and slowly eliminated from plasma with unchanged AG-120 (ivosidenib) representing the majority of circulating total radioactivity in plasma. PK studies in health volunteers also showed that there was an effect of food on AG-120 (ivosidenib) exposure, with a 2-fold increase in Cmax and a 25% increase in AUC with a high fat meal; a drug-drug interaction study evaluating the effect of itraconazole on the PK of AG-120 (ivosidenib) was also performed. Following AG-120 (ivosidenib) administration with itraconazole, AG-120 (ivosidenib) exposure (assessed by AUC_{0-t} and $AUC_{0-\infty}$) was increased approximately 2.6-fold.

AG-120 (ivosidenib) is a weak direct inhibitor of CYP2C8, CYP2C19, CYP2D6, and CYP3A4/5 with IC50 values >50 μM and shows little or no evidence of direct inhibition of CYP1A2, CYP2B6, or CYP2C9. AG-120 (ivosidenib) shows no time- or metabolism-dependent inhibition of any of the CYP enzymes evaluated, suggesting that formation of reactive metabolites is unlikely.

AG-120 (ivosidenib) is a substrate of P-gp, but not BCRP. AG-120 (ivosidenib) is an inhibitor of P-gp (48% and 99% inhibition at 5 and 100 μM, respectively) and a weak inhibitor of BCRP (17% and 48% at 5 and 100 μM, respectively). AG-120 (ivosidenib) is not a substrate of OATP1B1 or OATP1B3 transporters but appears to be a weak inhibitor of OATP1B1, and OATP1B3 with IC_{50} values of 9.56 and 22.8 μM, respectively. AG-120 (ivosidenib) does not inhibit the OAT1- and OCT2-mediated uptake of the probe substrate (IC50 > 65 μM) but inhibits OAT3 (IC50 ~0.322 μM).

2.4 Pediatric Studies

2.4.1 Prior Experience in Children

There have been no trials using mIDH inhibitors in pediatric patients.

2.5 Overview of Proposed Pediatric Study

This is a phase 2 trial of AG-120 (ivosidenib) in children with recurrent or refractory solid tumors, CNS tumors, non-Hodgkin lymphomas and histiocytic disorders harboring specific activating mutations that result in pathologic activation of the IDH pathway.

The adult RP2D of AG-120 (ivosidenib) is 500 mg PO once daily. Doses up to 1200 mg PO once daily were evaluated in the Phase 1 trials and no MTD was reached. Since the adult RP2D is 500 mg PO daily, the MTD was not reached and the starting dose as per standard Pediatric MATCH routine (described in additional detail in Section 11.2.1 of the screening protocol APEC1621SC) will be the adult RP2D adjusted for BSA, which is 290 mg/m^2/day (500 mg/1.7 m^2) up to a maximum daily dose of 500 mg PO once daily.

The primary aim of this trial will be to establish the objective response rate to AG-120 (ivosidenib).

Key secondary objectives include further evaluation of the tolerability of AG-120 (ivosidenib) in pediatric patients. Toxicity will be assessed using CTCAE V5.0. 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 for solid tumors and 2-dimensional measurement for CNS tumors.

3.0 SCREENING AND STUDY ENROLLMENT PROCEDURES

3.1 Study Enrollment

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

3.1.1 Access requirements for OPEN:

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

Requirements for OPEN access:

- A valid CTEP-IAM account;
- To perform enrollments 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 HIPAA authorization form (if applicable).

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

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

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

3.1.2 IRB Approval

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

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

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

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

In addition, the Site-Protocol Principal Investigator (PI) (i.e. the investigator on the

IRB/REB approval) must meet the following criteria in order for the processing of the IRB/REB approval record to be completed:

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

Additional Requirements
Additional requirements to obtain an approved site registration status include:

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

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

Institutions with patients waiting that are unable to use the Portal should alert the CTSU Regulatory Office immediately at 1-866-651-2878 in order to receive further instruction and support. For general (non-regulatory) questions call the CTSU General Helpdesk at: 1-888-823-5923.

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

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

3.1.3 Genetic Screening Procedures for Eligibility

Patient enrollment onto the APEC1621SC screening protocol is required. In Stage 2 of Pediatric MATCH (effective with Amendment #4 of APEC1621SC for patients enrolling on screening protocol) tumor genomic testing results from a CAP/CLIA-certified laboratory will be reviewed by the APEC1621SC Molecular Review Committee after APEC1621SC screening protocol enrollment to confirm the identification of an actionable Mutation of Interest (aMOI) for which a MATCH treatment subprotocol is available. Questions regarding interpretation of tumor testing results for potential APEC1621K study patients (such as whether a specific mutation would be considered actionable for the study)

should be directed to the APEC1621SC and APEC1621K study chairs.

The treatment assignment to MATCH to a subprotocol (if a relevant aMOI is detected) will be communicated to the enrolling institution via the COG treatment assignment mechanism, upon which a reservation to APEC1621K 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 APEC1621K.

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

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

Patients enrolling onto APEC1621K 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 enrolling onto APEC1621K will have a COG ID obtained through their prior enrollment onto the screening protocol or from a prior COG study. Patients who are started on protocol therapy prior to study enrollment will be considered ineligible.

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

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

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

Note: No starter supplies will be provided. Drug orders of AG-120 (ivosidenib) should be placed with CTEP after enrollment and treatment assignment to APEC1621K 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 APEC1621 master screening protocol.

3.7 **Dose Assignment**

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

4.0 PATIENT ELIGIBILITY

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

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

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

4.1 **Inclusion Criteria**

4.1.1 APEC1621SC: Patient must have enrolled onto APEC1621SC and must have been given a treatment assignment to MATCH to APEC1621K based on the presence of

an actionable mutation as defined in APEC1621SC. Examples of actionable mutations for APEC1621SC are listed in Appendix VIII.

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

4.1.3 BSA: Patients must have a body surface area ≥ 0.78 m^2 at enrollment.

4.1.4 Patients must be able to swallow intact tablets

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

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

4.1.6 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.

4.1.7 Prior Therapy

4.1.7.1 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.

- ≥ 21 days after the last dose of cytotoxic or myelosuppressive

chemotherapy (42 days if prior nitrosourea).

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

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

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

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

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

g. Stem cell Infusions (with or without TBI):

Allogeneic (non-autologous) bone marrow or stem cell transplant, or any stem cell infusion including DLI or boost infusion: ≥ 84 days after infusion and no evidence of GVHD.

Autologous stem cell infusion including boost infusion: ≥ 42 days.

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

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

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

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

k. Patients must not have received prior exposure to AG-120 (ivosidenib) or other IDH1 inhibitors.

4.1.8 Organ Function Requirements

4.1.8.1 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 4.1.8.1.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.

4.1.8.2 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.

4.1.8.3 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.

4.1.8.4 Adequate Cardiac Function Defined As:
- QTc interval ≤ 450 milliseconds

Note: Patients should avoid concomitant medication known or suspected to prolong QTc interval or cause Torsades De Pointes. Patients who are receiving drugs that prolong the QTc are eligible if

the drug is necessary and no alternatives are available. See Appendix X for drugs that may prolong the QTc.

4.1.8.5 Adequate Neurologic Function Defined as:
- Patients with seizure disorder may be enrolled if on anticonvulsants and well controlled.
- Nervous system disorders (CTCAEv5.0) resulting from prior therapy must be ≤ Grade 2, with the exception of decreased tendon reflex (DTR). Any grade of DTR is eligible.

4.1.9 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 due to risks because there is yet 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 non-hormonal contraceptive method for the duration of study treatment and for at least 1 month after last dose of AG-120 (ivosidenib). Since AG-120 (ivosidenib) may decrease concentrations of hormonal contraceptives, hormonal contraceptives are not considered effective contraception when co-administered with AG-120 (ivosidenib).

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 moderate to strong inhibitors of CYP3A4 are not eligible. Strong inducers or moderate to strong 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.

In addition, patients receiving sensitive or narrow therapeutic range substrates of CYP3A4 are not eligible. See Appendix II for a list of agents.

4.2.3 Patients with a history of progressive multifocal leukoencephalopathy are not eligible.

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

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

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

5.0 TREATMENT PROGRAM

5.1 Overview of Treatment Plan

Treatment Schedule Table	
Days 1-28	AG-120 (ivosidenib) 290 mg/m^2/dose orally once daily (maximum of 500 mg per day).
Day 28	Evaluation

Patients will receive AG-120 (ivosidenib) by mouth once daily, continuously for 28-day cycles (please see dosing nomogram in Appendix V). Disease evaluations will occur at the end of every other cycle x3, then every 3 cycles. A cycle may be repeated up to a total duration of therapy of 2 years (maximum of 26 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).

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. Take AG-120 (ivosidenib) tablets by mouth, without regard to meals. High fat meals should be avoided when taking AG-120 (ivosidenib). Tablets should not be crushed or chewed. Vomited dose should not be re-administered. Missed doses of AG-120 (ivosidenib) should not be administered if within 12 hours of the next scheduled dose. Otherwise, the dose will be missed. Please refer to Section 7.3 for specific supportive care guidelines.

AG-120 (ivosidenib) is supplied by Agios Pharmaceuticals and distributed by DCTD, NCI. **Do not use commercial supply.**

Since the MTD was not reached and the adult RP2D is 500 mg PO once daily, the starting dose as per standard Pediatric MATCH routine (described in additional detail in Section 11.2.1 of the screening protocol APEC1621SC) will be the adult RP2D adjusted for BSA, which is 290 mg/m^2 once daily (500 mg/1.72 m^2) up to a maximum daily dose of 500 mg PO once daily.

5.1.1 Therapy Delivery Map

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

5.1.2 Intra-Patient Escalation

Intrapatient dose escalation is not allowed.

5.2 Criteria for Starting Subsequent Cycles

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

5.3 Grading of Adverse Events

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

5.4 Definition of Dose-Limiting Toxicity (DLT)

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

5.4.1 Non-Hematological Dose-Limiting Toxicity

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

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

- Grade 3 nausea and vomiting of less < 3 days duration
- Grade 3 liver enzyme elevation, including ALT/AST/GGT that returns to levels that meet initial eligibility criteria or baseline within 7 days. See Appendix XII 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

a) 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.

b) Note: Allergic reactions that necessitate discontinuation of study drug will not be considered a dose-limiting toxicity.

5.4.2 Hematological dose limiting toxicity

5.4.2.1 Hematological dose limiting toxicity is defined as:

In patients evaluable for hematological toxicity (see Section 4.1.8.1),

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

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

6.0 DOSE MODIFICATIONS FOR ADVERSE EVENTS

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

6.1 Dose Modifications for Hematological Toxicity

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

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

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

6.2 Dose Modifications for Non-Hematological Toxicity

6.2.1 If a patient experiences non-hematological dose-limiting toxicity as defined in Section 5.4.1, the treatment will be held. When the toxicity resolves to meet eligibility parameters or baseline within 14 days of drug discontinuation, the patient may resume treatment at a reduced dose (see Appendix V for tablet formulation dosing nomogram). Doses reduced for toxicity will not be re-escalated, even if there is

minimal or no toxicity with the reduced dose.

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

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

6.3 Dose Modification for QTc Prolongation

Adverse Reactions	Recommended Action
QTc interval > 480	• Monitor and supplement electrolyte levels as clinically indicated, evaluation by a cardiologist and other necessary interventions may be considered. • Review and adjust concomitant medications with known QTc interval-prolonging effects (See Section 7.5.3 and Appendix X). • Interrupt AG-120 (ivosidenib). • Restart AG-120 (ivosidenib) at 50% dose once daily (refer to Appendix V) (rounding to the closest 50 mg) after the QTc interval returns to less than or equal to 480 msec. • Monitor ECGs at least weekly for 2 weeks following resolution of QTc prolongation. • Consider twice weekly monitoring of EKGs in patients with QTc prolongation > 500 msec.
QTc interval prolongation with signs/symptoms of life-threatening arrhythmia	Discontinue AG-120 (ivosidenib) permanently.
Please refer to Section 6.2.3 for instructions on management of a recurrence of dose-limiting toxicity who has resumed treatment at the reduced dose.	

6.4 Dose Modifications for mIDH1 differentiation Syndrome (only applicable to NHL or Histocytosis)

Adverse Reactions	Recommended Action
Differentiation syndrome [see Section 7.3].	If differentiation syndrome is suspected administer Dexamethasone 0.25 mg/kg (up to 10 mg) IV every 12 hours (or equivalent) and hemodynamic monitoring should be initiated and continued until improvement. Taper corticosteroids after resolution of symptoms. Corticosteroids should be administered for a minimum of 3 days; differentiation syndrome symptoms may recur if corticosteroid treatment are discontinued too early. If severe signs/symptoms persist for more than 48 hours after initiation of corticosteroids, interrupt AG-120 (ivosidenib) treatment until signs and symptoms are no longer severe (≤ grade 2) .
Concomitant Noninfectious leukocytosis (white blood cell [WBC] count greater than 25 x 10^9/L or an absolute increase in total WBC of greater than 15 x 10^9/L from baseline)	If concomitant noninfectious leukocytosis is present, hydroxyurea treatment or leukapheresis should be initiated as clinically indicated. Taper corticosteroids and hydroxyurea after resolution of symptoms. Corticosteroids should be administered for a minimum of 3 days; differentiation syndrome symptoms may recur if corticosteroid and/or hydroxyurea treatment are discontinued too early.

	If severe signs/symptoms persist for more than 48 hours after initiation of corticosteroids, interrupt AG-120 (ivosidenib) treatment until signs and symptoms are no longer severe (≤ grade 2).

6.5 Dose Modifications for Noninfectious leukocytosis (only applicable to NHL or Histiocytosis)

Adverse Reactions	Recommended Action
Noninfectious leukocytosis (white blood cell [WBC] count greater than 25 x 10^9/L or an absolute increase in total WBC of greater than 15 x 10^9/L from baseline)	• Initiate treatment with hydroxyurea, as per standard institutional practices, and leukapheresis if clinically indicated. • Taper hydroxyurea only after leukocytosis improves or resolves. • Interrupt AG-120 (ivosidenib) if leukocytosis is not improved with hydroxyurea, and then resume AG-120 (ivosidenib) at 290 mg/m^2 (up to 500 mg) daily when leukocytosis has resolved. • Contact the APEC1621K study chair

*Grade 1 is mild, Grade 2 is moderate, Grade 3 is severe, Grade 4 is life-threatening

6.6 Dose Modification for Guillain-Barré Syndrome

Adverse Reactions	Recommended Action
• Guillain-Barré syndrome	• Discontinue AG-120 (ivosidenib) permanently

6.7 If a new case of Progressive Multifocal Leukoencephalopathy (PML) occurs, the patient will be discontinued from treatment permanently.

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 AG-120 (ivosidenib). See below for recommendations on management of specific toxicities associated with AG-120 (ivosidenib).

AG-120 (ivosidenib) is associated with a mild emetic potential; administer antiemetics, if necessary, prior to treatment to prevent nausea and vomiting. Patients may receive hydroxyurea for management of ivosidenib-induced non-infectious leukocytosis per institutional guidelines (see Section 6.5).

IDH Differentiation Syndrome:
Patients with hematologic malignancies that are treated with AG-120 (ivosidenib) have experienced symptoms of differentiation syndrome (may be fatal if not treated). Symptoms include fever, dyspnea, hypoxia, pulmonary infiltrates, pleural or pericardial effusions, rapid weight gain or peripheral edema, hypotension, and/or hepatic, renal, or multi-organ dysfunction. If differentiation syndrome is suspected, initiate corticosteroid therapy and hemodynamic monitoring until symptom resolution. Differentiation syndrome is associated with rapid proliferation and differentiation of myeloid cells; may be life-threatening. Other symptoms of differentiation syndrome have included noninfectious leukocytosis, pulmonary edema, pneumonitis, rash, fluid overload, tumor lysis syndrome, and/or increased serum creatinine. Of patients who experienced differentiation syndrome, most recovered after corticosteroid treatment or AG-120 (ivosidenib) treatment interruption. The onset of differentiation syndrome occurred from 1 day up to 3 months after AG-120 (ivosidenib) treatment initiation; may occur with or without concomitant leukocytosis. See Section 6.4 for dose modification instructions.

Guillain-Barré syndrome:
Guillain-Barré syndrome occurred in a small (2) number of patients treated with ivosidenib. Monitor for onset of new signs or symptoms of motor and/or sensory neuropathy (eg, unilateral or bilateral weakness, sensory alterations, paresthesias, or difficulty breathing). Permanently discontinue ivosidenib if Guillain-Barré syndrome is diagnosed.

7.4 Growth Factors

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

7.5 Concomitant Medications

7.5.1 CYP3A4/5 inhibitors or inducers:

Strong inducers or moderate to strong 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. Grapefruit and grapefruit products should be avoided. Note: CYP3A4 inducing anti-epileptic drugs and dexamethasone for CNS tumors or metastases, on a stable dose, are allowed.

AG-120 (ivosidenib) is a potential inducer of human CYP3A4 and CYP2C9 isozymes. Patients receiving sensitive or narrow therapeutic range substrates of CYP3A4 (see Appendix II) are not eligibile. In addition, sensitive or narrow therapeutic range substrates of CYP2C9 (eg., celecoxib, phenytoin, warfarin) should be used with caution or avoided, if reasonable alternatives exist. International normalized ratio (INR) levels should be monitored more frequently in subjects receiving warfarin (a CYP2C9 substrate) during initiation or discontinuation of ivosidenib.

7.5.2 Transporter interactions:

- AG-120 (ivosidenib) should be used with caution with agents that are inhibitors of P-glycoprotein (P-gp).
- Use caution when co-administering AG-120 (ivosidenib) with other agents that may be substrates of OAT3.

7.5.3

Avoid combination with other drugs with potential to lead to prolongation of QTc interval, if possible (see Appendix X).

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 each 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		X[1]
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
CPK	X		
EKG	X	Twice Weekly x 2 weeks, then weekly	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		
Medication Diary[7]		Weekly	X
Pharmacokinetics and Pharmacodynamics (optional)[8,9]	X	X	X
Circulating Tumor DNA (ctDNA-optional)[10]			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. Prior to the start of each subsequent cycle a pregnancy test may be administered to women of childbearing potential, if clinically indicated.

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

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

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

[4-A] Neurological exam also required for CNS patients.

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

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

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

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

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

8. See Section 8.3 for details of PK studies.

9. Patients who are removed from therapy during Cycle 1 after receiving the dose of AG-120 (ivosidenib) on Day 28 should have their last PK sample collected on Day 28 of Cycle 1. Patients who are removed from therapy during Cycle 3 after receiving the dose of AG-120 (ivosidenib) on Day 28 should have their last PK sample collected on Day 28 of Cycle 3

10. With consent two samples will be collected on this protocol (Cycle 5 Day 1; and for patients receiving ≥ 5 cycles, at progression or end of protocol therapy) see Section 8.4 and Appendix VI for details of the ctDNA studies. Note that a ctDNA sample is scheduled to be obtained on the APEC 162SC 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 (prestudy) evaluations as well as all end of cycle tumor disease evaluations which occurred while the patient was on the subprotocol therapy study.

8.2.2 Technical Details of Submission:

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

Submission of Diagnostic Imaging data in DICOM format is required.
Submission of the digital files and reports via TRIAD is preferred. Instructions for

TRIAD set up are below.

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

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

Questions may be directed to DataSubmission@QARC.org or (401) 753-7600.

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

TRIAD Access Requirements:
Site physics staff who will submit images through TRIAD will need to be registered with the Cancer Therapy Evaluation Program (CTEP) and have a valid and active CTEP Identity and Access Management (IAM) account. Please refer to CTEP Registration Procedures of the protocol for instructions on how to request a CTEP-IAM account.
To submit images, the site TRIAD user must be on the site roster and be assigned the 'TRIAD site user' role on the CTSU roster. Users should contact the site's CTSU Administrator or Data Administrator to request assignment of the TRIAD site user role.

TRIAD Installations:

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

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

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

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

For FDG-PET imaging, the transferred imaging data should include uncorrected and attenuation-corrected PET projection data, as well as the reconstructed PET or PET/CT images used by the institution to achieve a response assessment. If low-dose CT was used for attenuation correction, the acquired CT images should also be submitted. The imaging data submitted for central review must allow the study

to be reconstructed and displayed in transaxial, sagittal and coronal formats using standard reconstruction techniques. Reconstructed MPEG clips and similar types of reconstructions will not be accepted. CT and MRI images similarly should be submitted in a format that either includes properly reconstructed multi-planar viewing formats in soft tissue and bone windows, or includes the thin-section axial acquisition data from which multi-planar reconstructions can be re-created.

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

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

8.3 Pharmacology and Pharmacodynamics Correlatives (optional)

8.3.1 Description of Studies and Assay

Pharmacokinetics (PK) and pharmacodynamics (PD) will be performed to determine the PK and PD of AG-120 (ivosidenib) in children. Pharmacokinetic sample analysis will be conducted at a bioanalytical laboratory using a validated assay. Pharmacodynamic analysis will determine 2-HG concentrations using a qualified assay.

8.3.2 Sampling Schedule

Blood samples will be obtained at the following time points:

Blood Sample No.	Time Point	Scheduled Collection Time
1	**Cycle 1, Day 1**	Pre-dose
2	**Cycle 1, Day 1**	1 hr after dose
3	**Cycle 1, Day 1**	2 hrs after dose
4	**Cycle 1, Day 1**	3 hrs after dose
5	**Cycle 1, Day 1**	4 hrs after dose
6	**Cycle 1, Day 1**	6-8 hrs after dose
7	**Cycle 1, Day 2**	Pre-dose
8	**Cycle 1, Day 15**	Pre-dose
9	**Cycle 1, Day 15**	1 hr after dose
10	**Cycle 1, Day 15**	2 hrs after dose
11	**Cycle 1, Day 15**	3 hrs after dose
12	**Cycle 1, Day 15**	4 hrs after dose
13	**Cycle 1, Day 15**	6-8 hrs after dose
Subsequent Cycles		

14	**Cycle 2, Day 1***	Pre-dose
15	**Cycle 4, Day 1***	Pre-dose

* Patients who are removed from therapy during Cycle 1 after receiving the dose of AG-120 (ivosidenib) on Day 28 should have their last PK sample collected on Day 28 of Cycle 1.

* Patients who are removed from therapy during Cycle 3 after receiving the dose of AG-120 (ivosidenib) on Day 28 should have their last PK sample collected on Day 28 of Cycle 3

8.3.3 Sample Collection and Handling Instructions

A total of 2 ml of blood will be collected for each time point; blood is collected in K_2- EDTA (lavender top) tubes. Blood samples will be used for pharmacokinetic and pharmacodynamic 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 and PD sample collection as kits will not be provided for the PK and PD correlatives 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 in an ice bath until centrifugation.

- The sample will be centrifuged at 1500 x g for 15 minutes at 2-8° C within 60 minutes after the sample is drawn.
- The plasma will then be evenly divided and transferred into two separate (2mL) cryovials, ensuring no RBC contamination, and frozen as soon as possible at (-90° C to -70° C).
- If a (-90° C to -70° C) freezer is not immediately available, the cryovial may be stored in an ice bath for short term storage, but must be placed in the appropriate freezer within 120 minutes 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# (APEC1621K), and the date and time the sample was drawn. To ensure processing of samples: PK samples must include 'AG120' on the label. PD samples must include '2HG' in the label. Data should be recorded on the appropriate transmittal form found in RAVE, which must accompany the sample(s).

8.3.6 Sample Shipping Instructions

- Ship PK and PD samples separately. Ship PK samples first, PD samples can be shipped once the receipt of the PK samples is confirmed. Confirmation of receipt of PK samples will occur via email from the analytical laboratory. Samples can be batched and shipped on a monthly basis.
- **Before Shipment** Notify PPD and the APEC1621K COG Study Assigned Research Coordinator by e-mail.
- Frozen samples must be shipped **Monday through Wednesday** via overnight

courier with an adequate amount of dry ice. Do not ship samples on Thursdays, Fridays, weekends, or holiday.

PPD
Attn: Jay Schaefgen, Sr. Group Leader Specimen Management
3230 Deming Way
Middleton, WI 53562
Phone: (608) 662-7706
Fax: (608) 662-9025
Email: Jay.Schaefgen@ppdi.com

The FedEx account number for sample shipment is 454696409

8.4 Circulating Tumor DNA Study (optional)

8.4.1 Sampling Schedule

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

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

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

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

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

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

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

a) Keep patient's arm in the downward position during the collection procedure.

b) 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.

c) Release tourniquet once blood starts to flow in the tube, or within 2 minutes of application.

d) Fill tube completely.

e) 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 (APEC1621K), and the date and time the sample was drawn. Data should be recorded on the appropriate transmittal form found in RAVE, which must accompany the sample(s).

8.4.4 Sample Shipping Instructions

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

Ship specimens to the following address:

Biopathology Center
Nationwide Children's Hospital
Protocol APEC1621K-Peds MATCH*
700 Children's Drive, WA1340*
Columbus, OH 43205
Phone: (614) 722-2865
Fax: (614) 722-2897
Email:BPCBank@nationwidechildrens.org

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

9.0 AGENT INFORMATION

9.1 AG-120 (09/22/2020)

(Ivosidenib, **Tibsovo®,** AGI-16678) NSC# 804600 IND# [redacted]

9.1.1 Source and Pharmacology:

AG-120 is a potent, selective, orally active small molecule inhibitor of mutated isocitrate dehydrogenase 1 (IDH1). Isocitrate dehydrogenase is a critical enzyme in the citric acid cycle catalyzing the oxidative decarboxylation of isocitrate to produce carbon dioxide (CO2) and alpha-ketoglutarate (α-KG). The mutant IDH enzymes are not catalytically inactive, but rather possess a novel enzyme activity, catalyzing the reduction of α-KG to the "oncometabolite" 2-hydroxyglutarate (2-HG), which has been found to be elevated in patients with several tumor types, including both solid and liquid tumors. Ivosidenib is FDA approved for treatment of adult patients with relapsed or refractory acute myeloid leukemia (AML) with a susceptible isocitrate dehydrogenase-1 (IDH1) mutation.

Pharmacokinetics/Pharmacodynamics:
Ivosidenib was rapidly absorbed with a mean peak plasma concentration of 4 hours (Tmax range: 2-24 hours). After reaching a peak, mean concentrations of ivosidenib declined in a bi-exponential manner, with a mean half-life of 71.8 to 138 hours after single dosing. Inter-subject variability was generally moderate and similar across doses and study days. CLss/F generally increased with increasing dose levels after single and multiple doses and ranged from 2.68 to 6.09 L/hr on C2D1 of dose escalation across the 100 mg BID and 300 to 1,200 mg QD dose range. Moderate accumulation was observed after multiple dosing. Mean ivosidenib plasma concentrations and exposure suggests that steady-state is achieved within 14 days of dosing. Ivosidenib exposure increased less than proportionally to dose after either single or multiple dosing. There was an effect of food on ivosidenib exposure, with an approximately 2-fold increase in Cmax and a 25% increase in AUC in the fed state. Maximal inhibition of 2-HG by ivosidenib was observed in the majority of subjects at 500 mg QD, with no additional inhibition observed at higher doses (800 mg or 1,200 mg QD). In subjects with newly diagnosed AML receiving intensive chemotherapy, plasma 2-HG reduction reached a plateau within 14 days of dosing and was maintained from Day 15 onward during induction, consolidation, and maintenance cycles.

9.1.1.1 Potential Drug Interactions:

AG-120 (ivosidenib) is primarily metabolized by CYP3A4, and to a lesser extent by CYP2B6 and CYP2C8. Avoid use of concomitant medications that are moderate or strong inhibitors or strong inducers of CYP3A4. Patients should be advised to avoid grapefruit or grapefruit juice.

AG-120 is an inducer of CYP3A4 and may also induce CYP2B6, CYP2C8, and CYP2C9. Coadministration of AG-120 with sensitive or narrow therapeutic index drugs that are extensively metabolized by CYP3A4 or CYP2C9 may result in decreased concentrations of these drugs. Patients receiving sensitive or narrow therapeutic range substrates of CYP3A4 (see Appendix II) are not eligible. In addition, sensitive or narrow therapeutic range substrates of CYP2C9 (eg., celecoxib, phenytoin, warfarin) should be used with caution or avoided, if reasonable alternatives exist. International normalized ratio (INR) levels should be monitored more frequently in subjects receiving warfarin (a CYP2C9 substrate) during initiation or discontinuation of AG-120. Animal studies have shown the potential for autoinduction of AG-120 metabolism.

AG-120 (ivosidenib) is a weak direct inhibitor CYP2C8, CYP2C19, CYP2D6, and CYP3A4/5 and showed little or no evidence of direct inhibition of CYP1A2, CYP2B6, or CYP2C9. The likelihood of direct or time-dependent inhibition of these enzymes causing drug-drug interactions is low.

Studies show AG-120 (ivosidenib) is a substrate for P-glycoprotein (P-gp), but not breast cancer resistance protein (BCRP), organic anion transporting polypeptides OATP1B1 or OATP1B3. AG-120 (ivosidenib) is an inhibitor of P-gp, OATP1B1 and OATP1B3, and organic anion transporter OAT3, but did not inhibit BCRP, OAT1 or organic cation transporter OCT2. . Although the relevance of these interactions is unknown at this time, use caution when co-administering with other agents that affect or may be affected by these transport enzymes.

Antacid, proton pump inhibitor or H2-receptor antagonist use does not significantly alter the pharmacokinetics of AG-120 (ivosidenib).

Co-administration with hormonal contraceptives may decrease the concentrations of hormonal contraceptives.

AG-120 (ivosidenib) has the potential to prolong the QTc interval. Avoid co-administration of medications that are known to prolong the QT interval and have a risk of causing Torsade de Pointes. Avoid concomitant administration with moderate to strong CYP3A4 inhibitors that may increase the risk of QTc interval prolongation from increased AG-120 (ivosidenib) exposure. Clinicians should refer to a regularly updated medical reference for a list of medications that can prolong the QT interval and have a risk of causing Torsade de Pointes.

9.1.1.2 Patient Care Implications:

AG-120 (ivosidenib) must not be administered to pregnant or nursing females. Women study participants of reproductive potential and fertile men study participants and their partners must either abstain or use effective contraception while receiving study treatment and for at least 1 month after the last dose of AG-120 (ivosidenib). Since AG-120 (ivosidenib) may decrease concentrations of hormonal contraceptives, hormonal contraceptives are not considered effective contraception when co-administered with AG-120 (ivosidenib).

9.1.2 **Toxicities**:

Comprehensive Adverse Events and Potential Risks list (CAEPR)
for
AG-120 (Ivosidenib, NSC 804600)

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 692 patients.* Below is the CAEPR for AG-120 (Ivosidenib).

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 2.2, July 9, 2020[1]

Adverse Events with Possible Relationship to AG-120 (Ivosidenib) (CTCAE 5.0 Term) [n= 692]			**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)***
	Febrile neutropenia		***Febrile neutropenia (Gr 3)***
	Leukocytosis		***Leukocytosis (Gr 3)***
GASTROINTESTINAL DISORDERS			
	Abdominal pain		***Abdominal pain (Gr 2)***
	Constipation		***Constipation (Gr 2)***
Diarrhea			***Diarrhea (Gr 2)***
	Mucositis oral		
Nausea			***Nausea (Gr 2)***
Vomiting			***Vomiting (Gr 2)***
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
	Edema limbs		***Edema limbs (Gr 2)***
Fatigue			***Fatigue (Gr 2)***
	Fever		***Fever (Gr 2)***
	Non-cardiac chest pain		
INFECTIONS AND INFESTATIONS			
	Lung infection		
INVESTIGATIONS			
Electrocardiogram QT corrected interval prolonged (Fredericia's formula)			***Electrocardiogram QT corrected interval prolonged (Fredericia's formula) (Gr 2)***
	Neutrophil count decreased		
	Platelet count decreased		
METABOLISM AND NUTRITION DISORDERS			
	Anorexia		***Anorexia (Gr 2)***
	Hyperuricemia		
	Hypokalemia		***Hypokalemia (Gr 2)***
	Hypomagnesemia		
	Hyponatremia		
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			
	Arthralgia		***Arthralgia (Gr 2)***
	Back pain		***Back pain (Gr 2)***
	Pain in extremity		
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)			
	Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other (IDH differentiation syndrome)[2]		
NERVOUS SYSTEM DISORDERS			
	Dizziness	Guillain-Barre syndrome	
	Headache		***Headache (Gr 2)***

Adverse Events with Possible Relationship to AG-120 (Ivosidenib) (CTCAE 5.0 Term) [n= 692]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
		Leukoencephalopathy	
		Reversible posterior leukoencephalopathy syndrome	
PSYCHIATRIC DISORDERS			
	Insomnia		
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
	Cough		***Cough (Gr 2)***
	Dyspnea		***Dyspnea (Gr 2)***
	Epistaxis		
	Pleural effusion		
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
	Pruritus		
	Rash maculo-papular		
VASCULAR DISORDERS			
	Hypotension		

[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]These adverse events have been observed only in hematologic malignancies and NOT in patients with solid tumors.

Adverse events reported on AG-120 (Ivosidenib) trials, but for which there is insufficient evidence to suggest that there was a reasonable possibility that AG-120 (Ivosidenib)caused the adverse event:

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Blood and lymphatic system disorders - Other (pancytopenia)
CARDIAC DISORDERS - Cardiac arrest; Cardiac disorders - Other (supraventricular extrasystoles); Chest pain - cardiac; Myocardial infarction; Pericardial tamponade; Ventricular arrhythmia; Ventricular tachycardia
GASTROINTESTINAL DISORDERS - Abdominal distension; Flatulence; Gingival pain
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Generalized edema; Localized edema; Multi-organ failure
HEPATOBILIARY DISORDERS - Hepatobiliary disorders - Other (hepatic dysfunction); Hepatobiliary disorders - Other (cholangitis); Hepatobiliary disorders - Other (jaundice cholestatic)
INFECTIONS AND INFESTATIONS - Bacteremia; Enterocolitis infectious; Pharyngitis; Sepsis; Skin infection; Upper respiratory infection
INVESTIGATIONS - Alkaline phosphatase increased; Aspartate aminotransferase increased; Blood bilirubin increased; Weight loss
METABOLISM AND NUTRITION DISORDERS - Hypercalcemia; Hyperglycemia; Hypertriglyceridemia; Hypocalcemia; Hypophosphatemia; Tumor lysis syndrome
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Generalized muscle weakness; Muscle cramp
NERVOUS SYSTEM DISORDERS - Ataxia; Dysgeusia; Intracranial hemorrhage; Nervous system disorders - Other (lumbrosacral plexopathy); Paresthesia; Peripheral sensory neuropathy; Seizure
PSYCHIATRIC DISORDERS - Anxiety; Confusion; Psychiatric disorders - Other (abnormal dreams)
RENAL AND URINARY DISORDERS - Acute kidney injury; Renal and urinary disorders - Other (renal dysfunction)

REPRODUCTIVE SYSTEM AND BREAST DISORDERS - Reproductive system and breast disorders - Other (increased erection)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Adult respiratory distress syndrome; Hypoxia; Nasal congestion; Pulmonary edema; Respiratory failure

Note: AG-120 (Ivosidenib) 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.

9.1.3 **Formulation and Stability**:

AG-120 (ivosidenib) is supplied by Agios Pharmaceuticals and distributed by the Pharmaceutical Management Branch, CTEP, DCTD, NCI as 50 mg uncoated and 250 mg film-coated tablets in 75 cc HDPE bottles with 38 mm child-resistant closures and heat-induction seals. Bottles contain 30 tablets each with a 1 gm silica gel desiccant. Tablet descriptions are as follows:

50 mg: white, round, uncoated tablets with no markings.

250 mg: blue, oval, film-coated tablets with no markings.

Tablets contain the following inactive ingredients: hypromellose acetate succinate, microcrystalline cellulose, croscarmellose sodium, sodium lauryl sulfate, colloidal silicon dioxide, and magnesium stearate. The 250 mg film-coated tablets also include the inactive ingredient Opadry® II Blue.

9.1.3.1 Storage:

Store below 30°C.

If a storage temperature excursion is identified, promptly return AG-120 (ivosidenib) 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.

9.1.3.2 Stability:

Intact bottles are undergoing on-going stability testing. Dispense medication in the original container.

9.1.4 Guidelines for Administration

See Treatment (Section 5.0) and Dose Modification (Section 6.0) sections of the protocol.

Oral tablets are to be swallowed whole; do not crush or chew. AG-120 (ivosidenib) may be administered with or without food but avoid administration with a high-fat meal. Vomited doses should not be re-administered. Missed doses should not be administered if within 12 hours of the next scheduled dose.

9.1.5 **Supplier**:

AG-120 (ivosidenib) is supplied by Agios Pharmaceuticals and distributed by a Division

of Cancer Treatment and Diagnosis the Pharmaceutical Management Branch (DCTD), NCI. **Do not use commercial supply.**

9.1.6 Obtaining the Agent

9.1.6.1 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 AG-120 (ivosidenib) should be placed with CTEP after enrollment and treatment assignment to APEC1621K with consideration for timing of processing and shipping to ensure receipt of drug supply prior to start of protocol therapy. Submit agent requests through the PMB Online Agent Order Processing (OAOP) application. Access to OAOP requires the establishment of a CTEP Identity and Access Management (IAM) account and the maintenance of an "active" account status and a "current" password and active person registration status. For questions about drug orders, transfers, returns, or accountability call or email PMB. Refer to the PMB's website for specific policies and guidelines related to agent management. If expedited shipment is required, sites should provide an express courier account through the Online Agent Order Processing (OAOP) application. Provide the patient ID number in the comment box when submitting an order request.

9.1.7 Agent Accountability

9.1.7.1 Agent Inventory Records

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

9.1.7.2 Investigator Brochure Availability

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

9.1.8 Useful Links and Contacts

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

- NCI CTEP Investigator Registration: RCRHelpDesk@nih.gov
- PMB policies and guidelines: http://ctep.cancer.gov/branches/pmb/agent_management.htm
- PMB Online Agent Order Processing (OAOP) application: https://ctepcore.nci.nih.gov/OAOP
- CTEP Identity and Access Management (IAM) account: https://ctepcore.nci.nih.gov/iam/
- 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 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). 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). Follow-up data will be required until off study criteria are met unless 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

APEC1621K will require a minimum of 10 evaluable patients and a maximum of 49 patients, allowing for 15% inevaluability. Assuming an enrollment rate of 2-6 biomarker positive patients per year, the primary cohort of this subprotocol is expected to be completed within 4-12 years.

11.2 Dosing Considerations:

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

Please see Section 5.1 for a specific discussion of the dosing of AG-120 (ivosidenib) to be used in this study. If there is no prior pediatric phase 1 data, study investigators will review relevant data with the pharmaceutical partner to identify a drug specific dosing plan for testing in children with relapsed or refractory cancer, and trial participants will be closely monitored to ensure tolerability of the selected dose. Limited pharmacokinetic sampling may be done for patients enrolled on these arms. In general, the dosing for the Pediatric MATCH subprotocols will follow the guidelines below:

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

11.3 Study Design

The primary cohort will employ a two-stage design[26] with a sample size of 20. In the first stage, 10 evaluable mutation-matched ("biomarker positive") patients of any histology will be accrued. Accrual will be suspended when a cohort of ten patients has enrolled or when the study endpoints have been met. The evaluation period for determination of opening the second stage will be 6 treatment cycles. If there is no response observed in these 10 patients, the study will be terminated. Otherwise, 10 additional patients will be accrued for a total of 20 evaluable patients. If there are at least 3 responses out of 20 in the primary cohort, the study will be deemed a success.

	Cumulative Number of Responses	Decision
Stage 1: Enter 10 evaluable patients	0	Terminate the trial early; agent ineffective
	1 or more	Inconclusive result, continue trial (proceed to Stage 2)
Stage 2: Enter 10 additional evaluable patients	2 or fewer	Conclude therapy is ineffective
	3 - 20	Conclude therapy is effective

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

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

11.3.1 Primary Cohort:

APEC1621K l will evaluate a primary cohort of 20 mutation-matched "biomarker positive") evaluable patients of any histology for the primary study aim of determining the objective response rate (CR/PR according to the response criteria in Section 12.3) to the agent. Using a two-stage design with alpha=10%, a sample of N=20 will provide 88% power to detect an improvement in response rate from 5%, if the treatment is ineffective, to 25% if the targeted therapy is sufficiently effective to warrant further study. If there are at least 3 responses out of 20 in the primary cohort, the biomarker/therapy match will be deemed a success.

11.3.2 Histology-Specific Biomarker Positive Expansion Cohorts:

If $\geq$ 3 patients in the primary cohort with the same histology show signs of objective response (CR/PR according to the response criteria in Section 12.3), a histology-specific biomarker positive expansion cohort will open after the primary cohort is completed to up to 7 evaluable patients for a total sample size of 10 evaluable biomarker positive patients with that histology. This will allow us to estimate more precisely the activity in biomarker positive patients of that histology. See Appendix VII for a list of target tumor histologies. We will open up to 3 such expansion cohorts for biomarker positive patients (i.e., if 3 histologies have $\geq$ 3 responses, we will open a total of 3 expansion cohorts as described above). Note that this can only happen if the response rate in the primary cohort is at least 45% (9/20) and there cannot be more than 21 additional evaluable patients in total for these expansion cohorts.

11.4 Methods of Analysis

Response criteria are described in Section 12. A responder is defined as a patient who achieves a best response of PR or CR on the study. Response rates will be calculated as the

percent of evaluable patients who are responders, and confidence intervals will be constructed using the Wilson score interval method.[27] Decision making for the two-stage design cohorts will follow rules described above.

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

11.5 Evaluability for Response

Any eligible patient who is enrolled and receives at least one dose of protocol therapy will be considered evaluable for response. Any patient who receives non-protocol anti-cancer therapy during the response evaluation period will be considered a non-responder for the purposes of the statistical rule, unless they show an objective response prior to receiving the non-protocol anti-cancer therapy (in which case they will be considered a responder). Patients who demonstrate a complete or partial response confirmed by central review will be considered to have experienced a response. When opening expansion cohorts, the evaluation period for determination of best response will be 6 treatment cycles. All other patients will be considered non-responders. Patients who are not evaluable for response evaluation may be replaced for the purposes of the statistical rule. All patients considered to have a response (CR or PR) must have imaging studies reviewed centrally at the COG. Centers will be notified by the COG about requests for scans of patients with stable disease. Preliminary assessment of activity using institutionally provided tumor measurements will be entered into CDUS quarterly. The central review by COG will be provided as the final reviewed assessment of response when such becomes available.

11.6 Evaluability for Toxicity

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

11.7 Progression free survival (PFS)

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

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

11.8 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	1	1	0	0	2
Native Hawaiian or Other Pacific Islander	0	0	0	0	0
Black or African American	3	5	0	0	8
White	12	20	4	2	38
More than one race	1	0	0	0	1
Total	17	26	4	2	49

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

12.0 EVALUATION CRITERIA

12.1 Common Terminology Criteria for Adverse Events (CTCAE)

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

12.2 Progression-Free Survival

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

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

12.3 Response Criteria for Patients with Solid Tumors

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

As outlined, patients will be assigned to one of the following categories for assessment of response: a) solid tumor (non-CNS) and measurable disease (Section 12.4); b) neuroblastoma with MIBG positive lesions (Section 12.5); c) CNS tumor (Section 12.7); and d) lymphoma/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

12.3.1.11 Evaluable for objective response:

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

12.3.1.2 Evaluable Non-Target Disease Response:

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

12.3.2 Disease Parameters

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

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

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

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

lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonitis, inflammatory breast disease, and abdominal masses (not followed by CT or MRI), are considered as non-measurable.

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

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

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

12.3.3 Methods for Evaluation of Measurable Disease

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

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

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

ruler to estimate the size of the lesion, is recommended.

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

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

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

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

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

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

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

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

b) No FDG-PET at baseline and a positive FDG-PET at follow-up: If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD. If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional

follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan). If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.

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

For patients with a positive PET scan at diagnosis, PET can be used to follow response in addition to a CT scan using the International Pediatric non-Hodgkin Lymphoma Response Criteria.[28]

12.4 Response Criteria for Patients with Solid Tumor and Measurable Disease

12.4.1 Evaluation of Target Lesions

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

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

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

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor

sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study

12.4.2 Evaluation of Non-Target Lesions

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

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

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

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

12.4.3 Overall Response Assessment

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

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

12.4.4 Overall Best Response Assessment

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

12.5 Response Criteria for Neuroblastoma Patients

This study will use the revised International Neuroblastoma Response Criteria for disease assessment.[30] The updated response criteria incorporate current approaches to imaging of neuroblastoma, including functional imaging. Furthermore, a standardized approach to assessment of bone marrow involvement is included. The current INRC do **not** include methods of disease assessment that are less sensitive and/or specific for neuroblastoma (^{99}Tc bone scan and catecholamine levels).

Key sites and terms
Primary site: The primary site will be identified as a measurable lesion ≥ 10 mm in diameter as assessed by cross sectional imaging (CT or MRI scan). Primary site measurements must be recorded in millimeters (or decimal fractions of centimeters). The longest diameter of the primary tumor will be recorded at baseline. Serial measurements of the primary tumor will include

assessment of tumor size in the same orthogonal plane at the time of each evaluation.[31] In patients with bilateral adrenal lesions, response will be based on the sum of the longest dimensions of both adrenal lesions unless biopsy proves one to be ganglioneuroma rather than neuroblastoma/ganglioneuroblastoma. In patients with multi-focal non-adrenal disease, the largest tumor will be considered the primary tumor. Response in additional lesions will be assessed as described below for metastatic lesions.

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

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

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

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

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

Bone marrow disease: Bilateral bone marrow aspirates and trephine biopsies are required at disease assessment timepoints. The extent of marrow involvement in all four samples should be recorded. Use of immunohistochemical staining for evaluation of trephine biopsies is strongly encouraged. The percentage of tumor infiltration of bone marrow space assessed by histologic evaluation of trephine/biopsies or counting the number of tumor cells in aspirates by cytology or immunocytology (recommended if available) divided by the number of hematopoietic/mononuclear cells evaluated to obtain a percentage involvement (methodology described by Burchill et al.).[32] The bone marrow sample with the highest percentage of tumor infiltration is used for response assessment. If > 0% to ≤ 5% tumor infiltration is the highest percentage seen among samples obtained, the result should be recorded as minimal marrow disease.

Response Criteria

PRIMARY (SOFT TISSUE) TUMOR RESPONSE[1]

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

[1]Not for use in assessment of metastatic sites

[2] For ^{123}I-MIBG non-avid tumors

[3] A mass that has not met PD measurement criteria but has fluctuating ^{123}I-MIBG avidity will not be considered progressive disease.

RESPONSE AT METASTATIC SOFT TISSUE AND BONE SITES

RESPONSE	ANATOMICAL IMAGING + MIBG (FDG-PET[1]) IMAGING

Complete Response (CR)	• Resolution of all sites of disease defined as:
	  • Non-primary target and non-target lesions measure < 10 mm AND
	  • Lymph nodes identified as target lesions decrease to a short axis < 15 mm, AND
	  • MIBG uptake or FDG-PET uptake (for MIBG non-avid tumors) of non-primary lesions resolves completely

Partial Response (PR)	• ≥ 30% decrease in sum of diameters[2] of non-primary target lesions compared to baseline, AND all of the following:

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

[1] Used for MIBG non-avid tumors

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

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

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

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

BONE MARROW RESPONSE

RESPONSE	BONE MARROW STATUS[1]
Complete response (CR)	Bone marrow with no tumor infiltration upon reassessment, independent of baseline tumor involvement
Progressive disease (PD)	Any of the following: • Bone marrow without tumor infiltration that becomes > 5% tumor infiltration upon reassessment; or • Bone marrow with tumor infiltration that increases by > 2 fold and has > 20% tumor infiltration upon reassessment.
Minimal disease (MD)	Any of the following: • Bone marrow with ≤ 5% tumor infiltration and remains > 0-≤ 5% tumor infiltration upon reassessment; or • Bone marrow with no tumor infiltration that becomes ≤ 5% tumor infiltration upon reassessment; or • Bone marrow with >20% tumor infiltration that has > 0-≤ 5% tumor infiltration upon reassessment.
Stable disease (SD)	Bone marrow with tumor infiltration that remains positive with > 5% tumor infiltration upon reassessment but does not meet CR, MD or PD criteria

[1]Immunohistochemistry strongly encouraged

DETERMINATION OF OVERALL RESPONSE

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

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

Overall Best Response Assessment

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

Primary Tumor	Soft Tissue and Bone Metastatic Disease (MIBG or FDG-PET or PET/MR)	Bone Marrow Metastatic Disease	Overall
CR	CR	CR	CR
CR for one response component with either CR or NI for other components			CR
CR	CR	MD	PR
CR	PR	CR	PR
CR	PR	MD	PR
CR	PR	NI	PR
CR	NI	MD	PR
PR	CR	CR	PR
PR	CR	NI	PR
PR	CR	MD	PR
PR	PR	CR	PR
PR	PR	NI	PR
PR	PR	MD	PR
PR	NI	CR	PR
PR	NI	NI	PR
PR	NI	MD	PR
NI	CR	MD	PR
NI	PR	CR	PR
NI	PR	MD	PR
CR	CR	SD	MR
CR	PR	SD	MR
CR	SD	CR	MR
CR	SD	MD	MR
CR	SD	SD	MR
CR	SD	NI	MR
CR	NI	SD	MR
PR	CR	SD	MR
PR	PR	SD	MR
PR	SD	CR	MR
PR	SD	MD	MR
PR	SD	SD	MR
PR	SD	NI	MR
PR	NI	SD	MR
SD	CR	CR	MR
SD	CR	MD	MR
SD	CR	SD	MR
SD	CR	NI	MR
SD	PR	CR	MR
SD	PR	MD	MR
SD	PR	SD	MR
SD	PR	NI	MR
SD	SD	CR	MR
SD	NI	CR	MR
NI	CR	SD	MR
NI	PR	SD	MR
NI	SD	CR	MR
SD	SD	MD	SD
NI	SD	MD	SD
SD	NI	MD	SD
NI	NI	MD	SD
SD	SD	SD	SD
SD	NI	SD	SD
NI	SD	SD	SD
NI	SD	NI	SD
NI	NI	SD	SD
PD in any one component			PD
Response of Not Evaluable for any one of the 3 components that had measurable/evaluable tumor at study enrollment and no PD for any component			Not Evaluable
No response evaluation performed for any of the 3 components			Not Done

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

Curie Scoring Summary

Table 1a. Scoring skeletal disease

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

Table 1b. Scoring soft tissue disease

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

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

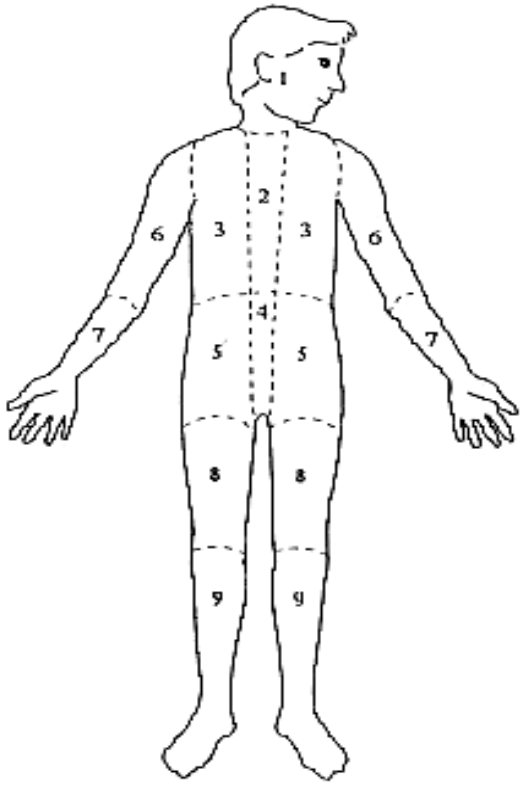

Figure 1.

12.6 Response Criteria for Patients with CNS Tumors

12.6.1 Measurable Disease

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

12.6.2 Evaluable Disease

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

12.6.3 Selection of Target and Non-Target Lesions

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

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

12.6.4 Response Criteria for Target Lesions

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

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

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

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

- **Progressive Disease (PD):** 25% or more increase in the sum of the products of the perpendicular diameters of the target lesions, taking as reference the

smallest sum of the products observed since the start of treatment, or the appearance of one or more new lesions.

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

12.6.5 Response Criteria for Non-Target Lesions:

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

12.6.6 Response criteria for tumor markers (if available):

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

12.6.7 Overall Response Assessment

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

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

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

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

Response and progression will be evaluated in this study using the new international criteria proposed by the revised Response Evaluation Criteria in Pediatric non-Hodgkin Lymphoma Criteria[28], with modification from the Lugano classification.[33]

12.7.1 Disease Parameters

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

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

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

12.7.1.4 Evaluation of Measurable Disease:

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

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

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

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

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

12.7.2 Evaluation of Non-measured Lesions (CT-based response, PET/CT based response not applicable)[33]

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.

Evaluation of organ enlargement

Complete Response (CR): Regress to normal

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

Stable Disease (SD): No increase consistent with progression

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

New or recurrent splenomegaly

12.8 Best Response

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

12.8.1 Evaluation of Best Overall Response

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

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

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

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

12.8.2 Duration of Response

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

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

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

13.0 ADVERSE EVENT REPORTING REQUIREMENTS

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

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

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

13.1 Expedited Reporting Requirements – Serious Adverse Events (SAEs)

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

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

13.1.1 Reporting Requirements - Investigator Responsibility

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

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

Fax supporting documentation **for AEs related to investigational agents supplied under a CTEP IND** to: (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 COGCAdEERS@childrensoncologygroup.org , the APEC1621K 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 v5.0. The descriptions and grading scales found in the current version of the CTCAE v5.0 will be used for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE v5.0. A copy of the CTCAE v5.0 can be downloaded from the CTEP website (http://ctep.cancer.gov).

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

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

1. the adverse event is considered serious;
2. 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 v5.0 grade 3, 4, or 5 that precipitates hospitalization (or prolongation of existing hospitalization) must be reported regardless of attribution and designation as expected or unexpected with the exception of any events identified as protocol-specific expedited adverse event reporting exclusions.
- Any event that results in persistent or significant disabilities/incapacities, congenital anomalies, or birth defects must be reported via CTEP-AERS if the event occurs following treatment with an agent under a CTEP IND.
- Use the NCI protocol number and the protocol-specific patient ID provided during trial registration on all reports.
- As referenced in the CTEP Adverse Events Reporting Requirements, an AE that resolves and then recurs during a subsequent cycle does not require CTEP-AERS reporting unless (1) the Grade increases; or (2) hospitalization is associated with the recurring AE.
- Some adverse events require notification **within 24 hours** (refer to Table A) to NCI via the web at http://ctep.cancer.gov (telephone CTEP at: **301-897-7497** within 24 hours of becoming aware of the event if the CTEP-AERS 24-Hour Notification web-based application is unavailable). Once internet connectivity is restored, a 24-hour notification phoned in must be entered electronically into CTEP-AERS by the original submitter at the site.
- When the adverse event requires expedited reporting, submit the report **within 5 or 7 calendar days** of learning of the event (refer to Table A).

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

FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)

NOTE: Investigators **MUST** immediately report to the sponsor **ANY** Serious Adverse Events, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64)

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

- Death
- A life-threatening adverse event
- An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect.
- 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:

a. "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.

b. "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:

1) All Grade 3, 4, and Grade 5 AEs

Expedited 7 calendar day reports for:

- Grade 2 AEs resulting in hospitalization or prolongation of hospitalization

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

Effective Date: May 5, 2011

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

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

Category	Adverse Events
INVESTIGATIONS	Platelet count decreased
INVESTIGATIONS	White blood cell decreased
INVESTIGATIONS	Neutrophil count decreased
INVESTIGATIONS	Lymphocyte count decreased

BLOOD/LYMPHATICS DISORDERS	Anemia

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

Category	Adverse Events
BLOOD AND LYMPHATIC SYSTEM DISORDERS	Blood and lymphatic system disorders - Other (IDH differentiation syndrome)
GASTROINTESTINAL DISORDERS	Mucositis oral
METABOLISM AND NUTRITIONAL DISORDERS	Hyperuricemia
METABOLISM AND NUTRITIONAL DISORDERS	Hypomagnesemia
METABOLISM AND NUTRITIONAL DISORDERS	Hypophosphatemia
METABOLISM AND NUTRITIONAL DISORDERS	Tumor lysis syndrome
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	Pruritus
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	Rash maculo-papular

- See also the Specific Protocol Exceptions to Expedited Reporting (SPEER) in Section 9.1.9 of the protocol.

13.4 Definition of Onset and Resolution of Adverse Events

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

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

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

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

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

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

13.5 Other Recipients of Adverse Event Reports

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

Section 14.1).

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

13.6 Specific Examples for Expedited Reporting

13.6.1 Reportable Categories of Death

- Death attributable to a CTCAE v5.0 term.
- Death Neonatal: A disorder characterized by "Newborn deaths occurring during the first 28 days after birth."
- Sudden Death NOS: A sudden (defined as instant or within one hour of the onset of symptoms) or an unobserved cessation of life that cannot be attributed to a CTCAE v5.0 term associated with Grade 5.
- Death NOS: A cessation of life that cannot be attributed to a CTCAE v5.0 term associated with Grade 5.
- Death due to progressive disease should be reported as ***Grade 5 "Disease progression"*** under the system organ class (SOC) of General disorders and administration site conditions." Evidence that the death was a manifestation of underlying disease (*e.g.*, radiological changes suggesting tumor growth or progression: clinical deterioration associated with a disease) should be submitted.
- Any death occurring within 30 days of the last dose, regardless of attribution to the investigational agent/intervention requires expedited reporting within 24 hours.
- Any death that occurs more than 30 days after the last dose of treatment with an investigational agent which can be attributed (possibly, probably, or definitely) to the agent and is not clearly due to progressive disease must be reported via CTEP-AERS per the timelines outlined in the table above.

13.6.2 Reporting Secondary Malignancy

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

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

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

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

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

13.6.3 Reporting Pregnancy, Pregnancy Loss, and Death Neonatal

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

13.6.4 Pregnancy

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

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

13.6.5 Pregnancy Loss (Fetal Death)

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

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

13.6.7 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

- Non-computerized Information: Roadmaps, Pathology Reports, Surgical Reports. These forms are uploaded into RAVE.
- 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.
- Computerized Information Electronically Submitted: All other data will be entered in RAVE with the aid of schedules and worksheets (essentially paper copies of the OPEN and RAVE screens) provided in the case report form (CRF) packet.

See separate CRF Packet, which includes submission schedule.

14.2 CDUS

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

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

14.3 CRADA/CTA/CSA

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

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

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 all-inclusive list. Because the lists of these agents are constantly changing, it is important to regularly consult frequently updated medical references.

CYP3A4 substrates	Strong Inhibitors[1]	Moderate Inhibitors	Strong Inducers	Moderate Inducers
acalabrutinib[5]	atazanavir	aprepitant	barbiturates	bosentan
alfentanil[4,5]	boceprevir	conivaptan	carbamazepine	dabrafenib
amiodarone[4]	clarithromycin	crizotinib	enzalutamide	efavirenz
aprepitant/fosaprepitant	cobicistat	diltiazem	fosphenytoin	etravirine
atorvastatin	darunavir	dronedarone	phenobarbital	modafinil
axitinib	delavirdine	erythromycin	phenytoin	nafcillin
bortezomib	grapefruit[3]	fluconazole	primidone	rifapentin
bosutinib[5]	grapefruit juice[3]	fosamprenavir	rifampin	
budesonide[5]	idelalisib	grapefruit[3]	St. John's wort	
buspirone[5]	indinavir	grapefruit juice[3]		
cabozantinib	itraconazole	imatinib		
calcium channel blockers	ketoconazole	isavuconazole		
cisapride	lopinavir/ritonavir	mifepristone		
citalopram/escitalopram	nefazodone	nilotinib		
cobimetinib[5]	nelfinavir	verapamil		
conivaptan[5]	posaconazole			
copanlisib	ritonavir			
crizotinib	saquinavir			
cyclosporine[4]	telaprevir			
dabrafenib	telithromycin			
dapsone	voriconazole			
darifenacin[5]				
darunavir[5]				
dasatinib[5]				
dexamethasone[2]				
diazepam				
dihydroergotamine				
docetaxel				
doxorubicin				
dronedarone[5]				
eletriptan[5]				
eplerenone[5]				
ergotamine[4]				
erlotinib				
estrogens				
etoposide				

everolimus[5]				
fentanyl[4]				
gefitinib				
haloperidol				
ibrutinib[5]				
idelalisib				
imatinib				
indinavir[5]				
irinotecan				
isavuconazole[5]				
itraconazole				
ivacaftor				
ketoconazole				
lansoprazole				
lapatinib				
losartan				
lovastatin[5]				
lurasidone[5]				
macrolide antibiotics				
maraviroc[5]				
medroxyprogesterone				
methadone				
midazolam[5]				
midostaurin[5]				
modafinil				
nefazodone				
nilotinib				
olaparib				
ondansetron				
osimertinib				
paclitaxel				
palbociclib				
pazopanib				
quetiapine[5]				
quinidine[4]				
regorafenib				
romidepsin				
saquinavir[5]				
sildenafil[5]				
simvastatin[5]				
sirolimus[4,5]				

sonidegib sunitinib tacrolimus[4,5] tamoxifen telaprevir temsirolimus teniposide tetracycline 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 7.3 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: MEDICATION DIARY FOR AG-120 (IVOSIDENIB)

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

Please do not write patient names on this form.

Complete each day with the time and dose given for AG-120 (ivosidenib). 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***. Take AG-120 (ivosidenib) tablets by mouth once daily, without regard to meals. Fatty and greasy meals should be avoided when taking AG-120 (ivosidenib). Tablets should not be crushed, or chewed; but should be swallowed whole. If tablets are broken and the powder of the tablets gets on skin, wash the exposed area with as much water as necessary. Inform your study doctor or nurse if that occurs. If you vomit a dose, an additional dose should not be taken. Missed doses of AG-120 (ivosidenib) should not be administered if within 12 hours of the next scheduled dose. Otherwise, the dose will be missed. Add the dates to the calendar below and return the completed diary to your institution after each treatment cycle. AG-120 (ivosidenib) needs to be kept in a room that is below 86°F (30°C). The maximum dose that can be taken per day is 500mg.

EXAMPLE			***Number of AG-120 (IVOSIDENIB) tablets***		***Comments***
	Date	***Time AM/PM***	**50 mg**	**250 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:** |__/__|__/__|__/__| **Your Dose:** _____**mg once a day**

WEEK 1	**Date**	**Time**		**Take _____x 50 mg tablets and _____x 250 mg tablets at the same time each day.**		**Comments (Describe any missed or extra doses, vomiting and/or bothersome effects.)**
				50 mg	**250 mg**	
Day 1			**AM/PM**			
Day 2			**AM/PM**			
Day 3			**AM/PM**			
Day 4			**AM/PM**			
Day 5			**AM/PM**			
Day 6			**AM/PM**			
Day 7			**AM/PM**			
WEEK 2	**Date**	**Time**		**Take _____x 50 mg tablets and _____x 250 mg tablets at the same time each day.**		**Comments (Describe any missed or extra doses, vomiting and/or bothersome effects.)**
				50 mg	**250 mg**	
Day 8			**AM/PM**			
Day 9			**AM/PM**			
Day 10			**AM/PM**			
Day 11			**AM/PM**			
Day 12			**AM/PM**			
Day 13			**AM/PM**			
Day 14			**AM/PM**			
WEEK 3	**Date**	**Time**		**Take _____x 50 mg tablets and _____x 250 mg tablets at the same time each day.**		**Comments (Describe any missed or extra doses, vomiting and/or**

				50 mg	250 mg	bothersome effects.)
Day 15			**AM/PM**			
Day 16			**AM/PM**			
Day 17			**AM/PM**			
Day 18			**AM/PM**			
Day 19			**AM/PM**			
Day 20			**AM/PM**			
Day 21			**AM/PM**			
WEEK 4	**Date**	**Time**		**Take _____ x 50 mg tablets and _____ x 250 mg tablets at the same time each day.**		**Comments (Describe any missed or extra doses, vomiting and/or bothersome effects.)**
				50 mg	**250 mg**	
Day 22			**AM/PM**			
Day 23			**AM/PM**			
Day 24			**AM/PM**			
Day 25			**AM/PM**			
Day 26			**AM/PM**			
Day 27			**AM/PM**			
Day 28			**AM/PM**			

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

Signature: _____ Date: _____

(site personnel who administered the drug)

Medication Diary for AG-120 (ivosidenib) for patients with changes in heart rhythm (QTc Toxicities)

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

Please do not write patient names on this form.

Complete each day with the time and dose given for AG-120 (ivosidenib). 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***. Take AG-120 (ivosidenib) tablets by mouth once daily, without regard to meals. Fatty and greasy meals should be avoided when taking AG-120 (ivosidenib). Tablets should not be crushed, or chewed; but should be swallowed whole. If tablets are broken and the powder of the tablets gets on skin, wash the exposed area with as much water as necessary. Inform your study doctor or nurse if that occurs. If you vomit a dose, an additional dose should not be taken. Missed doses of AG-120 (ivosidenib) should not be administered if within 12 hours of the next scheduled dose. Otherwise, the dose will be missed. Add the dates to the calendar below and return the completed diary to your institution after each treatment cycle.

EXAMPLE					
Take (3) 50 mg tablets on ☒ Monday ☐ Tuesday ☒ Wednesday ☐ Thursday ☒ Friday ☐ Saturday ☐ Sunday at the same time each day, and: Take (4) 50 mg ☐ Monday ☒ Tuesday ☐ Wednesday ☒ Thursday ☐ Friday ☒ Saturday ☒ Sunday tablets at the same time each day.					
			Number of AG-120 (IVOSIDENIB) tablets		***Comments***
	Day of Week	***Time AM/PM***	**50 mg**	**250 mg**	
Day 1 12/15/19	☐ **Mon** ☐ **Tues** ☐ **Wednesday** ☒ **Thursday** ☐ **Friday** ☐ **Saturday** ☐ **Sunday**	*8:30 AM*	# of tablets taken ___4__	# of tablets taken _____	*He felt nauseated an hour after taking the drug but did not vomit.*
Day 2 12/16/19	☐ **Mon** ☐ **Tues** ☐ **Wednesday** ☐ **Thursday** ☒ **Friday** ☐ **Saturday** ☐ **Sunday**	*8:30AM*	# of tablets taken __3___	# of tablets taken _____	
Day 3 12/17/19	☐ **Mon** ☐ **Tues** ☐ **Wednesday** ☐ **Thursday** ☐ **Friday** ☒ **Saturday** ☐ **Sunday**	*8:30AM*	# of tablets taken ___4__	# of tablets taken _____	

Cycle #: _____ Start Date: |__/__|__/__|__/__| End Date: |__/__|__/__|__/__| Your Dose: _____mg tablets on Monday, Wednesday, and Friday; and _____mg tablets on Tuesday, Thursday, Saturday, and Sunday at the same time each day.

WEEK 1 Date	Day of week	Time	Take (_____) ____ mg tablets on ☐ Monday ☐ Tuesday ☐ Wednesday ☐ Thursday ☐ Friday ☐ Saturday ☐ Sunday at the same time each day, and: Take (_____) ____ mg ☐ Monday ☐ Tuesday ☐ Wednesday ☐ Thursday ☐ Friday ☐ Saturday ☐ Sunday tablets at the same time each day.		Comments (Describe any missed or extra doses, vomiting and/or bothersome effects.)
			50 mg	250 mg	
Day 1 -----/---/---	☐ Monday ☐ Tuesday ☐Wednesday ☐ Thursday ☐ Friday ☐ Saturday ☐ Sunday	AM/PM	# of tablets taken _____	# of tablets taken _____	
Day 2 -----/---/---	☐ Monday ☐ Tuesday ☐Wednesday ☐ Thursday ☐ Friday ☐ Saturday ☐ Sunday	AM/PM	# of tablets taken _____	# of tablets taken _____	
Day 3 -----/---/---	☐ Monday ☐ Tuesday ☐Wednesday ☐ Thursday ☐ Friday ☐ Saturday ☐ Sunday	AM/PM	# of tablets taken _____	# of tablets taken _____	

Day 4 -----/---/---	☐ **Monday** ☐ **Tuesday** ☐ **Wednesday** ☐ **Thursday** ☐ **Friday** ☐ **Saturday** ☐ **Sunday**		**AM/PM**	# of tablets taken _____	# of tablets taken _____	
Day 5 -----/---/---	☐ **Monday** ☐ **Tuesday** ☐ **Wednesday** ☐ **Thursday** ☐ **Friday** ☐ **Saturday** ☐ **Sunday**		**AM/PM**	# of tablets taken _____	# of tablets taken _____	
Day 6 -----/---/---	☐ **Monday** ☐ **Tuesday** ☐ **Wednesday** ☐ **Thursday** ☐ **Friday** ☐ **Saturday** ☐ **Sunday**		**AM/PM**	# of tablets taken _____	# of tablets taken _____	
Day 7 -----/---/---	☐ **Monday** ☐ **Tuesday** ☐ **Wednesday** ☐ **Thursday** ☐ **Friday** ☐ **Saturday** ☐ **Sunday**		**AM/PM**	# of tablets taken _____	# of tablets taken _____	
WEEK 2 **Date**	**Day of week**	**Time**	**Take _____x ____ mg tablets on ☐ Monday ☐ Tuesday ☐ Wednesday ☐ Thursday ☐ Friday ☐ Saturday ☐ Sunday at the same time each day, and:** **_____ x ____ mg ☐ Monday ☐ Tuesday ☐ Wednesday ☐ Thursday ☐ Friday ☐ Saturday ☐ Sunday tablets at the same time each day.** **50 mg** | **250 mg**		**Comments** **(Describe any missed or extra doses, vomiting and/or bothersome effects.)**

Day 8 -----/---/---	☐ **Monday** ☐ **Tuesday** ☐ **Wednesday** ☐ **Thursday** ☐ **Friday** ☐ **Saturday** ☐ **Sunday**		**AM/PM**	# of tablets taken _____	# of tablets taken _____	
Day 9 -----/---/---	☐ **Monday** ☐ **Tuesday** ☐ **Wednesday** ☐ **Thursday** ☐ **Friday** ☐ **Saturday** ☐ **Sunday**		**AM/PM**	# of tablets taken _____	# of tablets taken _____	
Day 10 -----/---/---	☐ **Monday** ☐ **Tuesday** ☐ **Wednesday** ☐ **Thursday** ☐ **Friday** ☐ **Saturday** ☐ **Sunday**		**AM/PM**	# of tablets taken _____	# of tablets taken _____	
Day 11 -----/---/---	☐ **Monday** ☐ **Tuesday** ☐ **Wednesday** ☐ **Thursday** ☐ **Friday** ☐ **Saturday** ☐ **Sunday**		**AM/PM**	# of tablets taken _____	# of tablets taken _____	
Day 12 -----/---/---	☐ **Monday** ☐ **Tuesday** ☐ **Wednesday** ☐ **Thursday** ☐ **Friday** ☐ **Saturday** ☐ **Sunday**		**AM/PM**	# of tablets taken _____	# of tablets taken _____	

Day 13 -----/---/---	☐ **Monday** ☐ **Tuesday** ☐ **Wednesday** ☐ **Thursday** ☐ **Friday** ☐ **Saturday** ☐ **Sunday**		**AM/PM**	# of tablets taken _____	# of tablets taken _____	
Day 14 -----/---/---	☐ **Monday** ☐ **Tuesday** ☐ **Wednesday** ☐ **Thursday** ☐ **Friday** ☐ **Saturday** ☐ **Sunday**		**AM/PM**	# of tablets taken _____	# of tablets taken _____	
WEEK 3/ Date	**Day of week**	**Time**	**Take _____x ____ mg tablets on ☐ Monday ☐ Tuesday ☐ Wednesday ☐ Thursday ☐ Friday ☐ Saturday ☐ Sunday at the same time each day, and:** **_____ x ____ mg ☐ Monday ☐ Tuesday ☐ Wednesday ☐ Thursday ☐ Friday ☐ Saturday ☐ Sunday tablets at the same time each day.** **50 mg** / **250 mg**			**Comments** **(Describe any missed or extra doses, vomiting and/or bothersome effects.)**
Day 15 -----/---/---	☐ **Monday** ☐ **Tuesday** ☐ **Wednesday** ☐ **Thursday** ☐ **Friday** ☐ **Saturday** ☐ **Sunday**		**AM/PM**	# of tablets taken _____	# of tablets taken _____	
Day 16 -----/---/---	☐ **Monday** ☐ **Tuesday** ☐ **Wednesday** ☐ **Thursday** ☐ **Friday** ☐ **Saturday** ☐ **Sunday**		**AM/PM**	# of tablets taken _____	# of tablets taken _____	

Day 17 -----/---/---	☐ **Monday** ☐ **Tuesday** ☐ **Wednesday** ☐ **Thursday** ☐ **Friday** ☐ **Saturday** ☐ **Sunday**		**AM/PM**	# of tablets taken _____	# of tablets taken _____	
Day 18 -----/---/---	☐ **Monday** ☐ **Tuesday** ☐ **Wednesday** ☐ **Thursday** ☐ **Friday** ☐ **Saturday** ☐ **Sunday**		**AM/PM**	# of tablets taken _____	# of tablets taken _____	
Day 19 -----/---/---	☐ **Monday** ☐ **Tuesday** ☐ **Wednesday** ☐ **Thursday** ☐ **Friday** ☐ **Saturday** ☐ **Sunday**		**AM/PM**	# of tablets taken _____	# of tablets taken _____	
Day 20 -----/---/---	☐ **Monday** ☐ **Tuesday** ☐ **Wednesday** ☐ **Thursday** ☐ **Friday** ☐ **Saturday** ☐ **Sunday**		**AM/PM**	# of tablets taken _____	# of tablets taken _____	
Day 21 -----/---/---	☐ **Monday** ☐ **Tuesday** ☐ **Wednesday** ☐ **Thursday** ☐ **Friday** ☐ **Saturday** ☐ **Sunday**		**AM/PM**	# of tablets taken _____	# of tablets taken _____	

WEEK 4/ Date	Day of week	Time	Take _____x ____ mg tablets on ☐ Monday ☐ Tuesday ☐ Wednesday ☐ Thursday ☐ Friday ☐ Saturday ☐ Sunday at the same time each day, and: _____ x ____ mg ☐ Monday ☐ Tuesday ☐ Wednesday ☐ Thursday ☐ Friday ☐ Saturday ☐ Sunday tablets at the same time each day.		Comments (Describe any missed or extra doses, vomiting and/or bothersome effects.)
			50 mg	250 mg	
Day 22 -----/---/---	☐ Monday ☐ Tuesday ☐ Wednesday ☐ Thursday ☐ Friday ☐ Saturday ☐ Sunday	AM/PM	# of tablets taken _____	# of tablets taken _____	
Day 23 -----/---/---	☐ Monday ☐ Tuesday ☐ Wednesday ☐ Thursday ☐ Friday ☐ Saturday ☐ Sunday	AM/PM	# of tablets taken _____	# of tablets taken _____	
Day 24 -----/---/---	☐ Monday ☐ Tuesday ☐ Wednesday ☐ Thursday ☐ Friday ☐ Saturday ☐ Sunday	AM/PM	# of tablets taken _____	# of tablets taken _____	
Day 25 -----/---/---	☐ Monday ☐ Tuesday ☐ Wednesday ☐ Thursday ☐ Friday ☐ Saturday ☐ Sunday	AM/PM	# of tablets taken _____	# of tablets taken _____	
Day 26 -----/---/---	☐ Monday ☐ Tuesday ☐ Wednesday ☐ Thursday ☐ Friday ☐ Saturday ☐ Sunday	AM/PM	# of tablets taken _____	# of tablets taken _____	

Day 27 -----/---/---	☐ **Monday** ☐ **Tuesday** ☐ **Wednesday** ☐ **Thursday** ☐ **Friday** ☐ **Saturday** ☐ **Sunday**		**AM/PM**	# of tablets taken _____	# of tablets taken _____	
Day 28 -----/---/---	☐ **Monday** ☐ **Tuesday** ☐ **Wednesday** ☐ **Thursday** ☐ **Friday** ☐ **Saturday** ☐ **Sunday**		**AM/PM**	# of tablets taken _____	# of tablets taken _____	

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

Signature: _____ Date: _____

(Site personnel who administered the drug)

APPENDIX IV: CORRELATIVE STUDIES

Correlative Study	Section	Blood Volumes				Tube Type
		Volume per Sample	Total Cycle 1	Total Cycle 2	Total Cycle 4	
Pharmacokinetic and Pharmacodynamic	8.3	2 mL	26 mL	2 mL	2 mL	K_2 EDTA lavender top
Total Blood Volume:		**30 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

APPENDIX V: AG-120 (IVOSIDENIB) DOSING NOMOGRAM

AG-120 (ivosidenib) Dose Assignment: 290 mg/m^2/day (maximum dose of 500 mg per day)

BSA (m^2)	Total Daily Dose (mg/day)	Dose Reduction(mg/day)
0.78-0.94	250	150
0.95-1.12	300	200
1.13-1.29	350	250
1.3-1.46	400	300
1.47-1.63	450	300
≥ 1.64	500	350

Dose Reduction for QTc Toxicities (Refer to Section 6.3)

BSA (m^2)	Initial Dose (mg/day)	Dose Reduction
0.78-0.94	250	100 mg on Mon-Wed-Fri **and** 150 mg on Tue-Thur-Sat-Sun
0.95-1.12	300	150 mg daily
1.13-1.29	350	150 mg on Mon-Wed-Fri **and** 200 mg Tue-Thur-Sat-Sun
1.3-1.46	400	200 mg daily
1.47-1.63	450	200 mg on Mon-Wed-Fri **and** 250 mg on Tue-Thur-Sat-Sun
≥ 1.64	500	250 mg daily

APPENDIX VI: APEC1621K 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
AG-120 (ivosidenib) IND# 804600 **Do not use commercially available supply.**	PO	290 mg/m^2/dose orally once daily (maximum of 500 mg per day).	1-28	Refer to dosing nomogram (Appendix V)

Ht _____cm Wt _____kg BSA _____m^2

Date Due	Date Given	Day	**AG-120 (ivosidenib)** _____ mg PO once daily	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, i
		5	_____mg	
		6	_____mg	
		7	_____mg	
		8	_____mg	a, c, d, e, g, i
		9	_____mg	
		10	_____mg	
		11	_____mg	
		12	_____mg	c, i
		13	_____mg	
		14	_____mg	
		15	_____mg	a, c, d, e, g, h* ,i
		16	_____mg	
		17	_____mg	
		18	_____mg	c
		19	_____mg	
		20	_____mg	
		21	_____mg	
		22	_____mg	a, c, d, e, g, i
		23	_____mg	
		24	_____mg	
		25	_____mg	c
		26	_____mg	
		27	_____mg	
		28/1	_____mg	a, b, c, d, e, f, g, i*

Cycle 1

* Please refer to Section 8.1 and Section 8.3 for the specific timing of these observations

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** Additionally, per Section 5.1: 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.
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++, PO^4, Mg++**
e.	**Creatinine, ALT, bilirubin**
f.	**Albumin**
g.	**Medication Diary**- (see Appendix III) should be reviewed after completion of each treatment cycle and uploaded into RAVE. The medication diary should be collected weekly.
h.	**Pharmacokinetics and pharmacodynamics (optional)** please refer to Section 8.1 for the specific timing instructions. Please Note: Patients who are removed from therapy during Cycle 1 after receiving the dose of AG-120 (ivosidenib) on Day 28 should have their last PK sample collected on Day 28 of Cycle 1.
i	**EKG-** Twice weekly x 2, then weekly

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

Comments (Include any held doses, or dose modifications)

Treatment Details: Cycle 1

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

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 for up to 26 cycles. 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
AG-120 (ivosidenib) IND# 804600 **Do not use commercially available supply.**	PO	290 mg/m^2/dose orally once daily (maximum of 500 mg per day).	1-28	Refer to the dosing nomogram. Appx V

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

Date Due	Date Given	Day	**AG-120 (ivosidenib)** _____mg PO once daily	Studies
			Enter calculated dose above as per dosing nomogram and actual dose administered below	
		1	_____mg	a-f, g*, i*, l*
		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,-f, g*, h, i*, j* k* m*

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.	**Medication Diary**- (see Appendix III) should be reviewed after completion of each treatment cycle and uploaded into RAVE. The medication diary should be collected at the end of every cycle.
i.	**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.
j.	**EKG**
k.	**Bone Marrow Aspirate and/or biopsy**- Bone marrow aspirate and/or biopsy should only be performed when complete response or partial response is identified in target disease or when progression in bone marrow is suspected.
l.	**Pharmacokinetics and Pharmacodynamics (optional)** Please refer to Section 8.3 for the specific timing instructions. Please Note: Patients who are removed from therapy during Cycle 3 after receiving the dose of AG-120 (ivosidenib) on Day 28 should have their last PK sample collected on Day 28 of Cycle 3
m.	**Pregnancy Test (optional)** Prior to the start of each subsequent cycle a pregnancy test may be administered to women of childbearing potential as clinically indicated

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

Comments (Include any held doses, or dose modifications)

Treatment Details: Subsequent Cycles

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

APPENDIX VII: TARGET HISTOLOGIES FOR APEC1621K EXPANSION COHORTS

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

Tumor type
• Ependymoma • Ewing Sarcoma/Peripheral PNET • Hepatoblastoma • Glioma, high grade • Glioma, low grade • Langerhans Cell Histiocytosis • Malignant Germ Cell Tumor • Medulloblastoma • Neuroblastoma • Non-Hodgkin Lymphoma • Non-RMS Soft Tissue Sarcoma • Osteosarcoma • Rhabdoid Malignancy • Rhabdomyosarcoma • Wilms Tumor • Other Histology (based on COG/NCI-CTEP approval)

APPENDIX VIII: EXAMPLES OF ACTIONABLE MUTATIONS OF INTEREST FOR APECH1621K

INCLUSION	VARIANTS			
NON-HOTSPOT	RULES			
Gene Name	**Description**	**Variant Type**	**LOE**	**aMOI**
IDH1	COSM6942014	Indel	2	p.R132I
IDH1	COSM221574	SNV	2	p.R132P

HOTSPOTS				
Gene Name	**Variant ID**	**Variant Type**	**LOE**	**aMOI**
IDH1	COSM28748	SNV	1	p.R132S
IDH1	COSM28749	SNV	1	p.R132G
IDH1	COSM28747	SNV	1	p.R132C
IDH1	COSM28751	Indel	2	p.R132V
IDH1	COSM1169216	Indel	1	p.R132S
IDH1	COSM28746	SNV	1	p.R132H
IDH1	COSM28750	SNV	1	p.R132L
IDH1	COSM86993	Indel	1	p.R132H

APPENDIX IX: CTEP AND CTSU REGISTRATION PROCEDURES

Requirements for APEC1621K Site Registration:

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

RCR utilizes five-person registration types.

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

RCR requires the following registration documents:

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

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

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

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

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

CTSU REGISTRATION PROCEDURES

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

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

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

Protocol-Specific Requirements For Site Registration:

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

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

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

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

Checking Your Site's Registration Status

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

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

Note: The status shown only reflects institutional compliance with site registration requirements as outlined within the protocol. It does not reflect compliance with protocol requirements for

individuals participating on the protocol or the enrolling investigator's status with NCI or their affiliated networks.

Data Submission / Data Reporting

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

Requirements to access Rave via iMedidata:

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

Rave role requirements:

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

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

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

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

Data Quality Portal

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

The DQP is located on the CTSU members' website under Data Management. The Rave Home

section displays a table providing summary counts of Total Delinquencies and Total Queries. DQP Queries, DQP Delinquent Forms and the DQP Reports modules are available to access details and reports of unanswered queries, delinquent forms, and timeliness reports. Review the DQP modules on a regular basis to manage specified queries and delinquent forms.

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

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

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

APPENDIX X: MEDICATIONS ASSOCIATED WITH PROLONGED QTC

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

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

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

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

APPENDIX XI: YOUTH INFORMATION SHEETS
INFORMATION SHEET REGARDING RESEARCH STUDY APEC1621K
(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 APEC1621K
(for teens from 14 through 17 years of age)

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

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

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

4. What will happen to me on the study? Your tumor has a mutation that matches AG-120 (ivosidenib), and so you have been assigned to AG-120 (ivosidenib). The doctors want to see if AG-120 (ivosidenib) will make children with your type of cancer get better. We don't know if AG-120 (ivosidenib) will work well to get rid of your cancer there have only been a few research studies using AG-120 (ivosidenib) in children.. 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 AG-120 (ivosidenib) may cause your cancer to stop growing or to shrink for a period of time but we don't know for sure if there is any benefit of being part of this study.

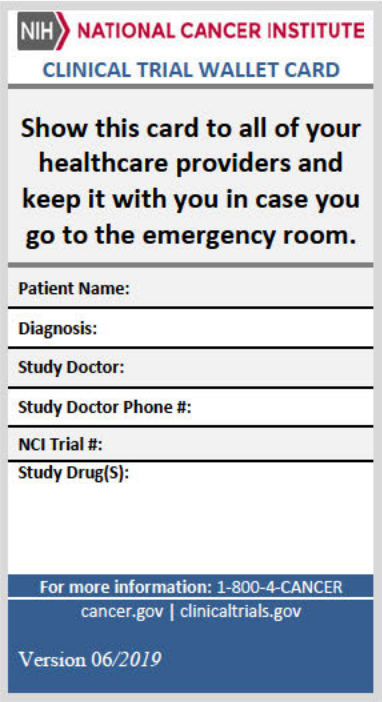
   Sometimes bad things can happen to people when they are in a research study. These bad things are called "risks." The primary risk to you from this study is that you may have side effects, from AG-120 (ivosidenib). Your doctor will talk to you about the risks we know about from AG-120 (ivosidenib). There may be other risks from AG-120 (ivosidenib) that we don't know about yet.

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

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

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 XII: PATIENT DRUG INFORMATION HANDOUT AND WALLET CARD



NIH NATIONAL CANCER INSTITUTE

CLINICAL TRIAL WALLET CARD

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

Patient Name:

Diagnosis:

Study Doctor:

Study Doctor Phone #:

NCI Trial #:

Study Drug(S):

For more information: 1-800-4-CANCER

cancer.gov | clinicaltrials.gov

Version 06/*2019*

APPENDIX XII: 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 U/L
Grade 2:	136 U/L - 225 U/L
Grade 3:	226 U/L - 900 U/L
Grade 4:	> 900 U/L

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

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

GGT:

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