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The world's childhood cancer experts

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October 28, 2022

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

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

Dear Ms. Kruhm,

The study committee thanks CTEP for forwarding the Amendment Request dated October 17, 2022. In response to the request, please see attached Amendment #4 to APEC1621B. The complete list of changes can be found below.

Please contact us if you have any further questions.

Sincerely,

Lee Baker, MPH, Protocol Coordinator (for)
Alice Lee, M.D., **APEC1621B** Study Chair, and
Douglas S. Hawkins, M.D., Group Chair, Children's Oncology Group

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I. Changes made to the protocol by the Principal Investigator:

#	Section	Comments
1.	General	The version date has been updated throughout the protocol.

II. Changes made to the informed consent document by the Principal Investigator:

#	Section	Comments
2.	General	The version date has been updated throughout the informed consent document.
3.	Why is this study being done?	The following phrase has been added: • **Please know that your eligibility for this trial may have been determined in part on the basis of a laboratory-developed test that has not been reviewed or approved by the FDA.**
4.	Specimens for additional optional research tests	The descriptions of the correlative studies have been updated to match their associated title.

Activated: 10/5/17 Version Date: 10/28/2022

Closed: Amendment # 4

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APEC1621B

NCI-COG PEDIATRIC MATCH (MOLECULAR ANALYSIS FOR THERAPY CHOICE)- PHASE 2 SUBPROTOCOL OF ERDAFITINIB IN PATIENTS WITH TUMORS HARBORING FGFR1/2/3/4 ALTERATIONS

Open to COG Member Institutions in the USA

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Contact Information

For Regulatory Requirements	For Patient Enrollments	For Data Submission
Regulatory documentation must be submitted to the Cancer Trials Support Unit (CTSU) via the Regulatory Submission Portal. (Sign in at https://www.ctsu.org, and select the Regulatory > Regulatory Submission.) Institutions with patients waiting that are unable to use the Portal should alert the CTSU Regulatory Office immediately by phone or email: 1-866-651-CTSU (2878), or CTSURegHelp@coccg.org to receive further instruction and support. Contact the CTSU Regulatory Help Desk at 1-866-651-CTSU (2878) for regulatory assistance.	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:
Erdafitinib
(NSC# 781558 , [redacted])
IND Sponsor: DCTD, NCI

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

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 NCI-COG Pediatric MATCH trial APEC1621. The APEC1621SC screening protocol details the process used to identify actionable mutations in patient tumor samples which will determine eligibility for this subprotocol. This is a phase 2 trial of erdafitinib in children and adolescents with recurrent or refractory solid tumors (including non-Hodgkin lymphomas, histiocytoses and CNS tumors) harboring specified activating mutations of the *FGFR1/2/3/4* pathway.

Erdafitinib is an orally bioavailable, highly potent inhibitor of FGFR-1, 2, 3 and 4 with nanomolar affinity. Erdafitinib has demonstrated a broad spectrum of antitumor activity in cell line, xenograft and patient-derived explant models harboring abnormalities in the FGFR signaling pathway such as FGFR gene amplification, activating mutation and translocation. In addition, early clinical trials with erdafitinib have resulted in an objective response rate of 42% in advanced urothelial cancer, in which FGFR mutations are highly prevalent, and an unconfirmed partial response in a patient whose tumor carried an *FGFR2:OFD1* translocation, suggesting its broad utility against cancers with FGFR mutation, amplification and translocation.

EXPERIMENTAL DESIGN SCHEMA

Treatment Schedule Table	
Days 1-28	4.7 mg/m^2 erdafitinib once daily, with maximum of 8 mg per day
Day 28	Evaluation

Erdafitinib will be administered orally once a day on a continuous basis; a cycle will be 28 days. Evaluations will occur at the end every other cycle x 3, then every 3 cycles.

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

1.0 GOALS AND OBJECTIVES (SCIENTIFIC AIMS)

1.1 Primary Aims

1.1.1 To determine the objective response rate (ORR; complete response + partial response) in pediatric patients treated with erdafitinib) with advanced solid tumors (including CNS tumors), non-Hodgkin lymphomas or histiocytic disorders that harbor genetic alterations in the *FGFR1/2/3/4* pathway.

1.2 Secondary Aims

1.2.1 To estimate the progression free survival in pediatric patients treated with erdafitinib with advanced solid tumors (including CNS tumors), non-Hodgkin lymphomas or histiocytic disorders that harbor genetic alterations in the FGFR1/2/3/4.

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

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

1.3 Exploratory Aims

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

2.0 BACKGROUND

2.1 Introduction/Rationale for Development

The fibroblast growth factor receptor (FGFR) family of receptor tyrosine kinases regulates several aspects of growth and development and when inappropriately activated, results in abnormal development and disease. Four different FGFRs have been identified (FGFR1, FGFR2, FGFR3, FGFR4) and bind to an array of fibroblast growth factors (FGFs), inducing their dimerization then auto- and cross-phosphorylation. This, in turn, leads to subsequent downstream phosphorylation events, which activate a number of molecules and signaling pathways such as the mitogen-activated protein kinase pathway and the phosphoinositide 3-kinase pathway, which contribute to FGFR-mediated cell proliferation, survival and migration.[1]

Deregulated, constitutive FGFR signaling secondary to amplifications, translocations, and point mutations in *FGFR* genes has been shown to mediate oncogenic downstream signaling[1] and these genetic lesions represent biomarkers that may predict response to FGFR inhibitors.[2-4] For example, in pediatric malignancies, translocations involving *FGFR1* or *FGFR3* are present in 2.9% of glioblastomas[5, 6]; activating mutations of *FGFR1* are seen in 3% of rhabdomyosarcoma[7]; activating mutations of *FGFR4* are seen in 8% of rhabdomyosarcoma[7] and infrequently in other pediatric types.

Given these recurrent genetic alterations in FGFR genes and the key role of FGFR signaling in the pathogenesis of multiple pediatric tumor types, targeting FGFRs represents

an attractive anti-cancer strategy.
Erdafitinib is a potent, oral pan-FGFR tyrosine kinase inhibitor with IC50 values in the low nanomolar range for all members of the FGFR family (FGFR1-4). When evaluated against a panel of 387 kinases (KinomeScan) using a competition binding assay which shows thermodynamic interaction affinities independent of the adenosine triphosphate (ATP) concentration, erdafitinib showed high selectivity with binding affinity (Kd) of less than 10 nM to only 10 of the 387 kinases tested and Kd values as low as 1 nM for all 4 members of the FGFR family [ref JNJ Study Number: EDMS-ERI-37672174].

Erdafitinib has demonstrated potent inhibition of cell proliferation with IC50 values ranging from <1 to <1000 nM in FGFR pathway-activated cancer cell lines including squamous non-small cell lung cancer (NSCLC), gastric, breast, hepatocellular cancer (HCC), endometrial, bladder, multiple myeloma, and acute myeloid leukemia. Non-FGFR driven cell lines require significantly higher drug concentration for inhibition of cell proliferation to be observed, supporting on-target efficacy of erdafitinib.

Target inhibition and pathway modulation have been demonstrated in cellular models at the active cellular concentrations. Brief exposure (1 hour) to erdafitinib has been demonstrated to result in long term (>8 hours) target inhibition and erdafitinib inhibits the growth of pre-established subcutaneously (s.c.) and orthotopically injected xenograft tumors in both immunodeficient mice and rats. Tumor regression was observed in the human SNU-16 (over-expressing the FGFR2 receptor) gastric xenograft implanted s.c. after oral administration at 20 and 50 mg/kg daily doses of erdafitinib in the rat model. Similar findings were observed when using the SNU-16 tumors in the mouse model and mouse xenografts using tumor cells from patients with gastric, breast, hepatocellular, and NSCLC cancers.[8, 9]

2.2 Effect of erdafitinib in human subjects

Overview
As of June 3, 2016, eight clinical trials studying erdafitinib in humans have been opened (ongoing and completed) with a total of 305 subjects treated with erdafitinib. Pharmacokinetic data are based on Studies EDI1001, EDI1002, EDI1003, and EDI1004 below, while efficacy data are based on Studies EDI1001 and BLC2001 and in part, GAC1001[10].

Summary of clinical studies
Study EDI1001: Study EDI1001 is a Phase 1, first-in-human, open label, multicenter, 4-part, dose escalation study to explore the safety, pharmacokinetics, and pharmacodynamics of erdafitinib administered orally to subjects ≥ 18 years of age with advanced or refractory solid malignancies or lymphoma who are not candidates for approved or available therapies.

Part 1 of Study EDI1001 was the Dose Escalation Phase, guided by pharmacokinetics and safety. Two recommended Phase 2 doses (9 mg once daily and 10 mg intermittent [7 days on, 7 days off]) were selected based upon results from Part 1 of this study.

Part 2 of Study EDI1001 was the Target Inhibition Confirmation Cohort, to confirm the safety and pharmacodynamic activity of erdafitinib at doses of 6 mg once daily and 9 mg once daily.

Part 3 of Study EDI1001 explored potential clinical activity at the first recommended Phase 2 dose of 6 mg once daily in tumor subtypes likely driven by FGFR pathway activation. Up to 30 subjects for each tumor subtype (squamous non-small cell lung cancer [NSCLC], small cell lung cancer, breast cancer, and other solid tumor subtypes with FGFR pathway activation and KRAS wild-type) were treated.

Part 4 of Study EDI1001, which as of the writing of this protocol is ongoing, explores potential clinical activity at the second recommended Phase 2 dose of 10 mg intermittent (7 days on, 7 days off; with option to up-titrate to 12 mg based on phosphate level) in tumor subtypes likely driven by FGFR pathway activation, with the intention to treat up to 30 subjects with NSCLC (squamous and non-squamous), along with up to 120 subjects with other solid tumor subtypes based on evolving information regarding FGFR molecular aberrations.

As of June 3, 2016, Parts 1, 2, and 3 were completed and part 4 was on-going with a total of 185 subjects having received treatment with erdafitinib in 8 dose schedules ranging from 0.5 mg daily to 12 mg daily. The subject population is 57% women and 43% men, predominantly white (91%), with a median age of 60.0 years (range 21 to 84). One hundred thirty-eight subjects (74.6%) have discontinued treatment due to disease progression. Twenty subjects (10.8%) are continuing treatment; all of these subjects are in Part 4 (10 mg intermittent dose regimen).

The median extent of drug exposure as of the data cut-off for the total population was 7.0 weeks (range: 0 to 102 weeks). There does not appear to be any dose-related trends in mean or median drug exposure, suggestive of tolerability to the drug.

Study EDI1002
Study EDI1002 was a PK study conducted in 8 healthy volunteers to evaluate the relative bioavailability of an oral solution to an oral tablet. The pharmacokinetic results indicated that the erdafitinib oral tablets and oral solution exhibit comparable bioavailability.

Study EDI1003
Study EDI1003 was a PK study conducted in 12 healthy volunteers to evaluate the relative bioavailability of an oral capsule to an oral tablet. The pharmacokinetic results indicated that the erdafitinib oral tablets and oral capsules exhibit comparable bioavailability.

Study EDI1004
Study EDI1004 was a PK study conducted in 12 healthy volunteers to evaluate the relative bioavailability of 2 prototype tablet formulations with larger particle sizes (77 microns and 122 microns) and clinical tablet formulation (particle size of 19 microns). The pharmacokinetic results indicated that the 2 prototype tablet formulations and the reference clinical tablet formulation were bioequivalent in both AUC and Cmax.

Study EDI1005
Study EDI1005 is a PK study conducted in 8 healthy men to evaluate the absorption, metabolism, and excretion of erdafitinib after administration of a single oral dose of 12 mg of unlabeled erdafitinib admixed with 14C-labeled erdafitinib (14C JNJ42756493). This study was ongoing at the time of writing of this protocol.

Study BLC2001
Study BLC2001 was a Phase 2 study to evaluate the objective response rate following

treatment with 1 of 2 dose regimens (Regimen 1: 10 mg dose, 7 days on/7 days off [with option to up-titrate to 12 mg 7 days on/7 days off] in 28 day cycles; Regimen 2: 6 mg dose, once daily [with option to up-titrate to 8 mg 7 days on/7 days off] in 28 day cycles) in subjects with metastatic or surgically unresectable urothelial cancers that harbor specific FGFR genomic alterations. These 2 dose regimens were initially selected to test whether high exposure levels with intermittent dosing could maximize antitumor effects while minimizing drug-related toxicities as compared with moderate exposures sustained over a longer period. The 6 mg daily was the lowest sustained dose that was predicted to generate continuously efficacious drug concentrations for the majority of patients, and the 10 mg dose was the lowest intermittent dose given for a 1 week on/1 week off schedule that generates drug exposures continuously in the efficacious range for most patients.

As recommended by the Data Review Committee (DRC) following their review of Interim Analysis 1 (IA1) data for Study BLC2001, an analysis was conducted of safety and efficacy data in urothelial cancer of the 2 dosing schedules. No new safety signals were identified. Also, it was observed that, for subjects attaining a phosphate level of at least 5.5 mg/dL, the objective response rate (ORR) was higher (57%, 4/7 subjects) as compared to those who did not attain this same level (21%, 3/14 subjects). From Study EDI1001, it was known that 6 mg once daily continuous was a well-tolerated schedule without significant unplanned treatment interruptions, while 9 mg once daily continuous in non-selected patients frequently led to treatment interruptions or dose reductions. Based on observed data and PK/PD modeling, it seemed possible to increase the highest continuous dose to 9 mg once daily in subjects who did not attain the target phosphate level of 5.5 mg/dL or higher. Furthermore, approximately half of the subjects starting at 6 mg once daily were up-titrated to 8 mg once daily, and most tolerated this higher dose without the need for interruptions for hyperphosphatemia or other drug-related, mainly skin and nail, toxicity. Modeling was performed to assess different scenarios for dosing. ***Based on this modeling, the starting dose of the study was increased to 8 mg once daily, with a provision for up-titration to 9 mg once daily for subjects whose serum phosphate levels on Day 14 did not reach a target of at least 5.5 mg/dL, in the absence of drug-related toxicity.*** It was determined that 8 mg daily continuous dosing was the recommended Phase 2 dose, as the study drug was found to be tolerable in the range of doses studied (10% of patients discontinued treatment due to adverse events) and that the mean relative dose intensity was over 90% for both dosing regimens.

Of the 99 patients in the 8 mg/day group, the confirmed response rate was 40% (95% CI, 31 to 50). The response rate among the 74 patients with FGFR mutations in the 8 mg/day group was 49%; an additional 26 patients with FGFR mutations had stable disease for a median of 3.7 months (range, 0 to 13.6). Responses were not affected by the presence of a specific mutation. Among the 25 patients with FGFR fusions, the response rate was 16%. In terms of safety and toxicity, all 99 patients in the 8 mg/day group reported an adverse event due to any cause during treatment. Of all adverse events, 67% were considered grade 3 or 4 with 46% of the patients having a $\geq$ grade 3 adverse event considered related to treatment. The most commonly reported $\geq$ grade 3 adverse events were hyponatremia (11%), stomatitis (10%), and asthenia (7%). Serious adverse events were reported in 39 patients. Disease progression was the most common reason for treatment discontinuation, occurring in 62 patients. Thirteen patients discontinued treatment because of adverse events, including detachment of the retinal pigment epithelium, hand–foot syndrome, dry mouth, and skin or nail events. A dose reduction due to toxicity was required in 55 patients with the most common reasons being stomatitis (16 patients) and hyperphosphatemia (9 patients)[11].

Study GAC1001
This study was an open-label, multicenter, 2-part, Phase 1 dose escalation study followed by dose expansion to evaluate the safety, PK, and pharmacodynamics of erdafitinib in Japanese and Asian patients. Nineteen (19) subjects were treated at 5 different dose levels. The study was terminated, not pertaining to any safety observations, but because of the lack of an appropriate assay to detect molecular eligible patients in this population. The subject population was 58% men and 42% women, with a median age of 65.0 (range 32 to 79). The median drug exposure was 6.4 weeks (range 1-18 weeks). All 19 subjects discontinued treatment, 16 subjects due to disease progression, 2 subjects due to withdrawal of consent, and 1 subject due to an investigator decision.

The best response to treatment was stable disease, for 1 subjects in the 4 mg group continuous dosing cohort. Fifteen of the 18 response-evaluable subjects (83.3%) experienced progressive disease; 2 subjects were not evaluable. All subjects (100%) experienced a treatment-emergent adverse event (TEAE) and 18 subjects (94.7%) experienced a drug-related TEAE. No Grade 3 or Grade 4 TEAEs were reported. No deaths or serious AEs were reported. The most frequently reported AEs were hyperphosphatemia (73.7%), nausea (36.8%), dysguesia (26.3%), stomatitis (26.3%), and dry mouth (21.1%). A single subject, in the 12 mg intermittent dosing cohort, discontinued study treatment due to detachment of retinal pigment epithelium, which was considered a dose limiting toxicity [DLT]).

Study HCC1001
This study was an open-label, multicenter, 2-part, Phase 1/2a study to evaluate the safety, PK, PD, and clinical responses of erdafitinib administered orally to Asian subjects ⩾18 years of age and with advanced HCC. Eleven subjects have been treated in this study, 3 subjects in the 8.0 mg group, and 8 subjects in the 10.0 mg group. The subject population was all male (91%) with 1 female (9%), with a median age of 49 years (range 31-67). Median duration of exposure is 5.9 weeks (range 2-33 weeks). Six subjects (54.5%) have discontinued treatment; 5 subjects due to progressive disease and 1 subject due to death.

The best response to treatment was partial response (PR), for 1 subject in the 10 mg group. Five of the 7 response-evaluable subjects (71.4%) experienced progressive disease; 1 subject was not evaluable. All subjects (100%) experienced a TEAE and 9 subjects (81.8%) experienced a drug-related TEAE. The most frequently reported AEs were hyperphosphatemia (72.7%), anemia (36.4%), ALT increased (27.3%) and AST increased (27.3%). Grade 3 or 4 AEs were reported for 4 subjects, and were hyponatremia, abdominal pain, bacterial infection, hypovolemic shock, nosocomial infection, fatigue, ALT increased, AST increased, bilirubin increased, urine output decreased, and hyperbilirubinemia. Four subjects experienced serious AEs, these were abdominal pain, gastrointestinal hemorrhage, esophageal varices hemorrhage, pyrexia, bacteremia, hemoptysis, and hypovolemic shock. Esophageal varices hemorrhage led to treatment discontinuation and death of 1 subject. None of the Grade 3 or 4 AEs, serious AEs, or AEs resulting in death or treatment discontinuation was considered by the investigator to be related to study drug.

2.2.1 Pharmacology/Pharmacokinetics/Correlative and Biological Studies
Preliminary pharmacokinetic characteristics of erdafitinib have been studied after single and repeat administration in healthy volunteers and in patients with cancer from Studies EDI1001, EDI1002, EDI1003, and EDI1004.

Single dose PK
Erdafitinib exhibits a linear increase of Cmax and AUC24 with dose (ranged from 0.5 mg to 12 mg following a single dose). Median tmax ranged from 2-3 hrs following oral administration of capsules, respectively. Mean total plasma terminal phase half-life of erdafitinib is long and is between 44 to 56 hrs.

Total plasma pharmacokinetics of erdafitinib was lower in healthy volunteers when compared with those in patients with cancers. However, α 1-AGP level in healthy volunteers is also lower when compared with patients with cancers, resulting in similar unbound plasma exposure of erdafitinib in both healthy volunteers and patients with cancers.

Multiple dose PK
Erdafitinib exhibits a linear increase of Cmax and AUC with dose (ranged from 0.5 mg to 12 mg following multiple daily dosing) and time-independent PK. Median tmax ranged from 2 to 4 hrs following multiple daily dosing using the capsule formulation. Erdafitinib has low total plasma oral clearance (mean CL/F ranged from 0.3 to 0.5 L/h) following oral administration of capsules.

Long plasma terminal phase half-life of erdafitinib resulted in approximately 3-fold accumulation in Cmax and AUC following multiple daily dosing. In patients with cancers, average free fractions of erdafitinib in human plasma were small (~0.36%).

Bioavailability
Erdafitinib oral tablets and oral solution exhibit comparable bioavailability in humans.

Distribution
Plasma protein binding
The plasma protein binding of erdafitinib was studied by equilibrium dialysis in human. Erdafitinib was highly bound to plasma proteins. Binding of 3H-erdafitinib to human purified α 1-acid glycoprotein (α 1-AGP) and human serum albumin (HSA) was shown to be dependent on the protein concentration. Depending on the level of α 1-AGP in individuals, total plasma concentration of erdafitinib may vary between individuals. In patients and healthy volunteers, average free fractions of erdafitinib in human plasma were 0.36 and 0.50%, respectively.

Transporters
Based on Caco-2 data, erdafitinib showed an intermediate to high permeability. Studies using LLC-PK1 cells stably expressing ABCB1 (P-glycoprotein) showed that erdafitinib is a P-glycoprotein (P-gp) substrate with an efflux ratio of about 5.

Volume of distribution
Volume of distribution of total plasma erdafitinib in healthy subjects is small (31 L), suggesting erdafitinib tends to stay in the blood binding to plasma protein (Study EDI1003).

Metabolism
The metabolism of 3H-erdafitinib in human liver microsomes was limited leading to relatively low metabolite levels. CYP3A4 and CYP2C9 are the dominant

CYP450 enzymes involved in the metabolism of 3H-erdafitinb in human liver microsomes and human hepatocytes based on inhibition of the formation of metabolites by diagnostic inhibitors. Other minor cytochromes involved in the microsomal metabolism of erdafitinib were CYP2C8 and CYP2D6 (based on inhibition data in human liver microsomes and heterologous expression systems).

Inter- and intra-subject variability in PK

The between- and within-subject variability in the PK of erdafitinib was studied in both healthy volunteers and patients with cancer. In Study EDI1003, the between-subject variability for plasma clearance and central volume of distribution in healthy volunteers were 32% and 38%, respectively. Intra-subject variability of PK of total plasma erdafitinib in studies EDI1002 and EDI1003 was 11% or lower in healthy volunteers. Similarly, the between-subject variability of Cmax and AUC in patients with cancer ranged from 30% to 50% in Study EDI1001.

Effect of Intrinsic Factors (Special Population)

There is no specific study conducted to investigate the influence of intrinsic factors on the PK of erdafitinib. Based on limited and preliminary data from EDI1001 in cancer patients, population PK analysis suggested that no major influence by age, gender, race, BW, Height, BSI, BMI, renal function (creatinine clearance), and LFT (AST, total bilirubin) on the PK of erdafitinib. The influence of intrinsic factors on the PK of erdafitinib will be further investigated in future studies.

PK-PD relationship

QT or QTc Interval

Pre-clinical studies have shown erdafitinib is an intrinsic hERG blocker with a proarrhythmic liability and QT prolongation associated with erdafitinib was seen across several species in nonclinical studies. However, intravenous administration of erdafitinib to female anesthetized guinea-pigs yielded no adverse effects up to a total plasma exposure of 771 ng/mL and a CV threshold of unbound fraction ~ 81 ng/ml. At the highest clinical dose tested in Study EDI1001 (i.e., 12 mg once per day), mean unbound Cmax on Day 8 was 7.26 ng/mL, approximately 1/11th times (or 9%) of the CV threshold. Review of subjects for any AEs of QT prolongation concluded that the risk of QT prolongation due to treatment with erdafitinib in human subjects is low.

Serum Phosphate

There is an expected exposure-related increase in serum phosphate observed based on inhibition of renal FGF-23 mediated signaling by erdafitinib. This relationship was quantified using a non-linear mixed effects PK-PD approach. Using a 3-compartment PK model, factoring in the effect of erdafitinib fraction unbound and AAG, the phosphate change from baseline was linearly related to erdafitinib unbound plasma concentration via an effect compartment. Simulations based on this model were performed to support the dose recommendation and modification recommended in the BLC2001 study.

Efficacy

In Study EDI1001, 153 subjects were evaluable for response. The best response was partial response, confirmed for 17 subjects and not confirmed for 2 subjects. The overall response rate, including unconfirmed responses, was 12.4%. Responses were observed at doses of 9 mg once daily and higher. Among subjects

with bladder cancer, the response rate was 35.7% (10/28 subjects. Furthermore, among subjects with bladder cancer that was FGFR mutation positive, the response rate was 40.0% (10/25 subjects). The best response in subjects with lung cancer was stable disease (5/17 subjects, 29.4%). Three subjects with breast cancer have responded with a best response of partial response (3/25 subjects, overall response rate of 12.0%).

In Study BLC2001, 30 subjects were evaluable for response. Accounting for responses that were not confirmed (due to lost to follow-up or still awaiting confirmation), a best response of partial response was observed for 6 subjects in the 6 mg group and 6 subjects in 10 mg group. The overall response rate was 42.9% in the 6 mg group and 37.5% in the 10 mg dosing group.

2.3 Pediatric Studies

2.3.1 Prior Experience in Children

None.

2.4 Overview of Proposed Pediatric Study

This Phase 2 study will assess the clinical effects of erdafitinib administered orally, once daily, in 28-day cycles to pediatric and adolescent patients.

Since the adult RP2D (8 mg PO once daily) is below the MTD (at least 12 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 4.7 mg/m^2/day (8 mg/1.7 m^2) up to a maximum daily dose of 8 mg PO once daily.

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

3.0 SCREENING AND STUDY ENROLLMENT PROCEDURES

3.1 Study Enrollment

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

3.1.1 Access requirements for OPEN:

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

Requirements for OPEN access:

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

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

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

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

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

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

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

3.1.2 IRB Approval

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

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

establishing site preferences can be addressed to the CTSU Regulatory Office by email or calling 1-888-651-CTSU (2878).

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

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

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

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

Additional Requirements

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

- An active Federal Wide Assurance (FWA) number;
- An active roster affiliation with the Lead Protocol Organization (LPO) or a Participating Organization (PO);
- An active roster affiliation with the NCI CIRB roster under at least one CIRB Signatory Institution (US sites only); and
- Compliance with all protocol-specific requirements (PSRs).

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

Institutions with patients waiting that are unable to use the 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 APEC1621B study patients (such as whether a specific mutation would be considered actionable for the study) should be directed to the APEC1621SC and APEC1621B study chairs.

The treatment assignment to a MATCH to a subprotocol (if a relevant aMOI is detected) will be communicated to the enrolling institution via the COG treatment assignment mechanism at the time the results of MATCH are returned, upon which a reservation to APEC1621B 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 APEC1621B.

3.2 Informed Consent/Assent

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

3.3 Screening Procedures

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

3.4 Eligibility Checklist

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

3.5 Study Enrollment

Following a MATCH treatment assignment to a protocol, patients may be enrolled on the study once all eligibility requirements for the study have been met. Before enrolling a patient on study, the Study Chair or Vice Chair should be notified. Patients who give informed consent for the protocol in order to undergo screening for eligibility are not considered enrolled and should not be enrolled until the screening is completed and they are determined to meet all eligibility criteria. Study enrollment is accomplished by going to the CTSU OPEN (Oncology Patient Enrollment Network) https://open.ctsu.org/open/. For questions, please contact the COG Study Research Coordinator, or the CTSU OPEN helpdesk at https://www.ctsu.org/CTSUContact.aspx. Patients must be enrolled before treatment begins. **Patients must not receive any protocol therapy prior to enrollment.**

Patients must be enrolled within 2 weeks (14 days) of treatment assignment. The date protocol therapy is projected to start must be no later than 7 calendar days after the date of enrollment. Patients enrolling onto APEC1621B will have a COG ID obtained through their prior enrollment onto the screening protocol or from a prior COG study. Protocol therapy must start no later than 7 calendar days after the date of enrollment. Patients who are started on protocol therapy prior to study enrollment will be considered ineligible.

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

Note: No starter supplies will be provided. Drug orders of erdafitinib should be placed with CTEP after enrollment and treatment assignment to APEC1621B with consideration for timing of processing and shipping to ensure receipt of drug supply prior to start of protocol therapy.

3.6 Institutional Pathology Report

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

3.7 Dose Assignment

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

4.0 PATIENT ELIGIBILITY

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

Clarification in timing when counting days: As an example, please note that if the patient's last day of prior therapy is September 1st, and the protocol requires waiting at least 7 days for that type of

prior therapy, then that patient cannot be enrolled until September 8th.

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

4.1 Inclusion Criteria

4.1.1 APEC1621SC: Patient must have enrolled onto APEC1621SC and must have been given a treatment assignment to MATCH to APEC1621B based on the presence of an actionable mutation as defined in APEC1621SC. Examples of actionable mutations for APEC1621B 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 ≥ 0.53 m^2 at enrollment.

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

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

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

4.1.6 Prior Therapy

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

criteria, the patient is considered to have recovered adequately.

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

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

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

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

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

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

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

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

i. XRT/External Beam Irradiation including Protons: ≥ 14 days after

local XRT; ≥ 150 days after TBI, craniospinal XRT or if radiation to ≥ 50% of the pelvis; ≥ 42 days if other substantial BM radiation.

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

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 erdafitinib or another FGFR inhibitor such as (but not limited to) AZD4547, BGJ398, BAY1163877, LY2874455.

4.1.7 Organ Function Requirements

4.1.7.1 Adequate Bone Marrow Function Defined as:

a. For patients with solid tumors without known bone marrow involvement:
- Peripheral absolute neutrophil count (ANC) ≥ 1000/mm^3
- Platelet count ≥ 100,000/mm^3 (transfusion independent, defined as not receiving platelet transfusions for at least 7 days prior to enrollment)
- Hemoglobin ≥ 8.0 g/dL at baseline (may receive RBC transfusions)

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

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

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

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

4.1.7.3 Adequate Liver Function Defined as:
- Bilirubin (sum of conjugated + unconjugated) ≤ 1.5 x upper limit

of normal (ULN) for age
- SGPT (ALT) ≤ 135 U/L. (For the purpose of this study, the ULN for SGPT is 45 U/L.)
- Serum albumin ≥ 2 g/dL

4.1.7.4 Adequate Cardiac Function Defined as:
- QTc interval ≤ 480 milliseconds

4.1.7.5 Adequate Pulmonary Function Defined as:
- Pulse oximetry > 94% on room air if there is clinical indication for determination (e.g. dyspnea at rest).

4.1.8 Patients must be able to swallow intact tablets.

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 of fetal and teratogenic adverse events as seen in animal studies. Pregnancy tests must be obtained in girls who are post-menarchal. Males or females of reproductive potential may not participate unless they have agreed to use an effective contraceptive method, while receiving study treatment and for 3 months after the last dose of erdafitinib. Male subjects (with a partner of child-bearing potential) must use a condom with spermicide when sexually active and must not donate sperm from the first dose of study drug until 3 months after the last dose of study drug.

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 inhibitors of CYP3A4 are not eligible. See Appendix

II for a list of agents. Note: CYP3A4 inducing anti-epileptic drugs and dexamethasone for CNS tumors or metastases, on a stable dose, are allowed.

4.2.2.6 CYP2C9 Agents: Patients who are currently receiving drugs that are strong inducers or moderate inhibitors of CYP2C9 are not eligible. See Section 7.5.2.

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

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

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

4.2.6 A history of cardiovascular diseases: Unstable angina, myocardial infarction, or known congestive heart failure Class II-IV within the preceding 12 months; cerebrovascular accident or transient ischemic attack within the preceding 3 months, pulmonary embolism within the preceding 2 months.

4.2.7 A history of any of the following: sustained ventricular tachycardia, ventricular fibrillation, Torsades de Pointes, cardiac arrest, Mobitz II second degree heart block or third degree heart block; known presence of dilated, hypertrophic, or restrictive cardiomyopathy.

4.2.8 Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements.

4.2.9 Patients with significant ophthalmologic conditions (uncontrolled glaucoma, central serous retinopathy, history of retinal vein occlusion or retinal detachment, excluding patients with longstanding findings secondary to existing conditions) are not eligible, to be confirmed with baseline ophthalmologic exam. All patients must have a baseline ophthalmologic exam, including fundoscopy to confirm no significant ophthalmologic conditions are present.

5.0 TREATMENT PROGRAM

5.1 Overview of Treatment Plan

Treatment Schedule Table	
Days 1-28	4.7 mg/m^2 erdafitinib once daily, with maximum of 8 mg per day
Day 28	Evaluation

Erdafitinib tablets will be given orally once daily. A cycle of therapy is considered to be 28 days. A cycle may be repeated up to a total duration of therapy of 2 years (maximum 26 cycles). **On Day 1 of Cycle 2, the dose of erdafitinib should be held until a pre-dose plasma sample can be obtained. In order to obtain the 24-hour time point, the dose on Day 2, Cycle 2 should also be held until plasma sample is obtained.**

Erdafitinib is provided by NCI. Do not use commercial supply.

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

Drug doses should be adjusted based on the BSA calculated from height and weight measured within 7 days prior to the beginning of each cycle, and according to the dosing nomogram (see Appendix IV). If vomiting occurs within 30 minutes of erdafitinib administration, then the dose can be repeated once. If a dose is missed, it can be taken up to 6 hours after the scheduled time. If it has been more than 6 hours since the missed dose, then that dose should be skipped. The next dose should be taken at the usual time

Please refer to Section 7.3 for specific supportive care guidelines.

Since the adult RP2D (8 mg PO once daily) is below the MTD (at least 12 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 4.7 mg/m^2/day (8 mg/1.7 m^2) up to a maximum daily dose of 8 mg PO once daily.

5.1.1 Therapy Delivery Map
See Appendix V 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 CTCAE V5.0. A copy of the CTCAE V5.0 can be downloaded from the CTEP website (http://ctep.cancer.gov). Any suspected or confirmed dose-limiting toxicity should be reported immediately (within 24 hours) to the Study Chair.

5.4 Definition of Dose-Limiting Toxicity (DLT)

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

5.4.1 Non-Hematological Dose-Limiting Toxicity

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

- Grade 3 nausea and vomiting of < 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 Section 6.3, and Appendix XI for values that represent thresholds between CTCAE grades.
Note: For the purposes of this study the ULN for ALT is defined as 45 U/L regardless of baseline.

- Grade 3 or 4 fever < 5 days duration.
- Grade 3 infection < 5 days duration.
- Grade 3 hypophosphatemia, hypokalemia, hypocalcemia or hypomagnesemia responsive to supplementation

5.4.1.2 Any Grade 1 visual disturbance that persists for ≥ 4 weeks

5.4.1.3 Any Grade 2 non-hematological toxicity that persists for ≥ 7 days and is considered sufficiently medically significant or sufficiently intolerable by patients that it requires treatment interruption.

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

5.4.1.4 Hyperphosphatemia will be reported as a DLT if a dose modification is required (as described in Section 6.4 for serum phosphate of 7.0 or greater)

5.4.2 Hematological dose limiting toxicity

5.4.2.1 Hematological dose limiting toxicity is defined as:

a) In patients evaluable for hematological toxicity (see Section 4.1.7.1),
- Grade 4 thrombocytopenia or neutropenia, not due to malignant infiltration.
- Grade 3 thrombocytopenia that persists for ≥ 7 days
- Grade 3 thrombocytopenia requiring a platelet transfusion on two separate days within a 7-day period
- Grade 3 thrombocytopenia with clinically significant bleeding
- Neutropenia or thrombocytopenia that causes a delay of > 14 days between treatment cycles (e.g. platelets < 100K/mm^3 or ANC < 1000/mm^3).

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, the treatment will be held. Counts should be checked every 3-4 days for thrombocytopenia and every other day for neutropenia during this time. If the toxicity resolves to meet eligibility parameters within 14 days of drug discontinuation, the patient may resume treatment at a reduced dose as outlined in the dosing nomogram table in Appendix IV. 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. If the toxicity resolves to meet eligibility parameters or baseline within 14 days of drug discontinuation, the patient may resume treatment at a reduced dose as outlined in the dosing nomogram table in Appendix IV. 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 a non-hematologic dose-limiting toxicity as defined in Section 5.4.1 does not resolve to meet eligibility or baseline parameters within 14 days of drug discontinuation, the patient must be removed from protocol therapy. Any Grade 1 visual disturbance that persists for ≥ 4 weeks and does not resolve to meet eligibility or baseline parameters within ≥ 4 weeks of drug discontinuation must be removed from protocol therapy.

6.2.3 If non- hematologic 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 Modifications for Hepatic Adverse Events

6.3.1 If a patient experiences Grade 3 ALT/AST/GGT, treatment will be held. If toxicity resolves to meet eligibility criteria within 7 days, the drug may be resumed at the same dose. Grade 3 ALT/AST/GGT that persists ≥ 7 days will be considered dose-limiting and require dose modification per Section 6.2. See Appendix XI for values that represent thresholds between CTCAE grades.

6.3.2 If a patient experiences Grade 4 ALT/AST/GGT, the patient must be removed from protocol therapy. See Appendix XI for values that represent thresholds between CTCAE grades.

6.4 Guidelines for the Management of Elevated Phosphate Levels

Guidelines for the clinical management of elevated serum phosphate levels are presented below.

Guidelines for Management of Serum Phosphate Elevation

Serum Phosphate Level	Study Drug Management	Medical Management
All subjects in the study	Continue erdafitinib treatment.	Restriction of phosphate intake to 600 – 800 mg/day.

5.6-6.9 mg/dL (1.8-2.3 mmol/L)	Continue erdafitinib treatment.	Restriction of phosphate intake to 600 – 800 mg/day. May consider sevelamer: Children 1-2 years: sevelamer 100-140 mg/kg/day divided TID titrated to desired phosphate level Children ≥ 2 years: sevelamer initial dose: 400 or 800 mg TID with food; titrate to desired phosphate level at monthly intervals in 1200 mg/day increments (ie, 400 mg at each meal) up to a maximum of 1,600 mg PO TID with food
7.0-9.0 mg/dL (2.3-2.9 mmol/L)	Withhold[a] erdafitinib treatment until serum phosphate level returns to <5.5 mg/dL (or baseline). Then re-start treatment at the same dose. A dose reduction may be implemented for persistent[b] hyperphosphatemia (≥7 mg/dL) lasting > 1 week if clinically necessary	Restriction of phosphate intake to 600 – 800 mg/day. Children 1-2 years: sevelamer 100-140 mg/kg/day divided TID until phosphate level is <5.5 mg/dL. Children ≥ 2 years: sevelamer initial dose: 400 or 800 mg TID with food; titrate at monthly intervals in 1200 mg/day increments (ie, 400 mg at each meal) up to a maximum of 1,600 mg PO TID with food until phosphate level is <5.5 mg/dL.
>9.0 mg/dL (>2.9 mmol/L)	Withhold[a] erdafitinib treatment until serum phosphate level returns to <5.5 mg/dL (or baseline). Re-start treatment at the reduced dose outlined in Appendix IV.	Restriction of phosphate intake to 600 – 800 mg/day. Sevelamer: Children 1-2 years: 100-140 mg/kg/day divided TID Children ≥ 2 years: initial dose: 400 or 800 mg TID with food; titrate at monthly intervals in 1200 mg/day increments (ie, 400 mg at each meal) up to a maximum of 1,600 mg PO TID with food AND Acetazolamide 5-7.5 mg/kg/dose (up to 250 mg/dose) BID or TID only until serum phosphate level returns to <5.5 mg/dL.
>10.0 mg/dL (>3.2 mmol/L) and/or significant alteration in baseline renal function and/or Grade 3 hypercalcemia	Erdafitinib should be discontinued permanently. (In situations where the subject is having clinical benefit and the study chair agrees that re-starting drug is in the best interest of the subject, the drug may be re-introduced at the reduced dose level outlined in Appendix IV if appropriate[c]. Follow other recommendations described above.)	Medical management as clinically appropriate.

Note: These are general guidelines that are based on emerging data and consensus experience of participating investigators and/or the experts in the field. The treating physicians must use clinical judgment and local standard of care to decide the best way to manage phosphate elevation. If sevelamer hydrochloride is not available, the use of other phosphate binders (non-calcium containing) based on the local standard is recommended. These guidelines will be updated based on emerging data. Additional information on phosphorous in foods by class of food can also be found at www.permanente net/homepage/kaiser/pdf/42025.pdf. Additional information for phosphate management and diet can be found the National Kidney Foundation website (http://www kidney.org/atoz/content/phosphorus.cfm)
a. Drug interruptions for hyperphosphatemia suggested to be 7 days duration

b. Persistent hyperphosphatemia is considered to be more than 1 sequential phosphate value of >=7 mg/dL

6.5 Guidelines for the Management of Dry Skin and Skin Toxicity

Guidelines for the management of dry skin are provided below.

General prophylaxis:

- Avoid unnecessary exposure to sunlight and excessive use of soap.
- Avoid bathing in excess; use tepid rather than hot water.
- Use moisturizers regularly; apply thick, alcohol-free and oil-in-water based emollient cream on exposed and dry areas of the body.
- Avoid perfumed products, bubble bath, perfumed soaps, and take breaks from shaving.
- Use broad spectrum sunscreen with a skin protection factor (SPF) ≥15.
- Wear cotton clothes next to skin rather than wool, synthetic fibers, or rough clothing.
- Use occlusive alcohol-free emollient creams (jar or tub) for treatment of mild/moderate xerosis.
- For scaly areas, use exfoliants (ammonium lactate 12% or lactic acid cream 12%).

Guidelines for Management of Dry Skin

Grade and Definition	Study Drug Management	Medical Management
Grade 1: Dry skin covering less than 10% body surface area (BSA) and no associated erythema or pruritus	Continue study drug at current dose.	Use fragrance free moisturizing cream or ointment BID over entire body. Use ammonium lactate 12% cream or salicylic acid 6% cream BID over dry/scaly/hyperkeratotic areas such as palms and soles.
Grade 2: Dry skin covering 10 to 30% BSA and associated with erythema or pruritis with limited instrumental activities of daily living (IADL)	Continue study drug at current dose.	Use fragrance free moisturizing cream or ointment BID over entire body. Use ammonium lactate 12% cream or salicylic acid 6% cream BID over dry/scaly/hyperkeratotic areas such as palms and soles. Use zinc oxide 13-40% at night for areas with fissures.
Grade 3: Dry skin covering >30% BSA and associated with pruritis; limiting self-care activities of daily living (ADL)	Hold study drug (for up to 14 days), with weekly reassessments of clinical condition. When resolves to ≤ Grade 1 or baseline, restart at 1 dose level below in consultation with the Study Chair.	Use topical steroid ointment or cream* BID and zinc oxide 13-40% at night for areas with fissures.
Grade 4: Dry skin with life-threatening consequences, urgent intervention indicated	Discontinue study drug.	Evaluation and therapy as clinically indicated
*Topical Steroid Ointments: Clobetasol 0.05%, Betamethasone 0.05%, Fluocinonide 0.05%		

6.6 Dose Modifications for Dermatology/Skin Disorders

Grade	Action
Grade 1 or 2	• Maintain dose
Intolerable Grade 2; Grade 3	• Hold erdafitinib until resolution to ≤ tolerable Grade 2 and dose reduce as per Section 6.2.

6.7 Guidelines for Management of Nail Toxicity (Onycholysis, Onychodystrophy, and Paronychia)

General Prophylaxis:

- Good hygienic practices, keep fingers and toes clean.
- Keep nails trimmed
- Use gloves for housecleaning and gardening to minimize damage and prevent infection
- Nail polish and imitation fingernails should not be worn until the nails have grown out and returned to normal
- Wearing comfortable shoes (wide sized shoes with room for the toes)
- Trimming nails but avoiding aggressive manicuring

Guidelines for Management of Nail Discoloration/Loss/Ridging (Onycholysis/Onychodystrophy)

Grade and Definition	Study Drug Management	Medical Management
Grade 1: Asymptomatic; clinical or diagnostic observations only, intervention not indicated	Continue study drug at current dose,	Over the counter nail strengthener OR poly-urea urethane nail lacquer (Nuvail) OR diethylene glycol monoethylether nail lacquer daily (Genadur)
Grade 2: Symptomatic separation of the nail bed from the nail plate or nail loss, limiting instrumental ADLs	Continue study drug at current dose. Consider holding study drug if no improvement in 1 to 2 weeks. When resolves to ≤ Grade 1 or baseline, restart at same or at a reduced dose (Appendix IV) in consultation with the Study Chair.	For signs of infection (periungal edema/erythema/ tenderness and/or discharge), obtain bacterial cultures, and then start the following: • treatment with oral antibiotic for 2 weeks (cefadroxil 15 mg/kg/dose (up to 500 mg/dose) every 12 hours, ciprofloxacin 15 mg/kg/dose (up to 500 mg/dose) every 12 hours, or sulfamethoxazole/trimethoprim (TMP) 6 to 12 mg TMP/kg/day in divided doses every 12 hours; maximum single dose: 160 mg TMP/dose) AND • topical antifungal lacquer daily for 6+ weeks (ciclopirox olamine 8% OR efinaconazole 10% OR amorolfine 5% weekly OR bifonazole/urea ointment daily)
Grade 3: Severe nail tip pain, symptomatic separation of the nail bed from the nail plate or nail loss, significantly limiting IADLs	Hold study drug (for up to 14 days), with weekly reassessments of clinical condition. When resolves to eligibility or baseline parameters, restart at a reduced dose (Appendix IV) below in consultation with the Study Chair.	Silver nitrate application weekly AND topical antibiotics AND vinegar soaks.[a] For signs of infection (periungal edema/erythema/ tenderness and/or discharge), obtain bacterial cultures, and then start the following: treatment with oral antibiotic for 2 weeks (cefadroxil 15 mg/kg/dose (up to 500 mg/dose) every 12 hours, ciprofloxacin 15 mg/kg/dose (up to 500 mg/dose) every 12 hours, or sulfamethoxazole/trimethoprim (TMP) 6 to 12 mg TMP/kg/day in divided doses every 12 hours;

		maximum single dose: 160 mg TMP/dose). For cases of severe/refractory infection consider intravenous antibiotics. Consider dermatological and/or surgical evaluation.
Grade 4: life-threatening consequences, urgent intervention indicated	Discontinue study drug	Evaluation and therapy as clinically indicated

[a] Vinegar soaks consist of soaking fingers or toes in a solution of white vinegar in water 1:1 for 15 minutes every day. Examples of topical antibiotic ointments: Mupirocin 2%, gentamycin, bacitracin zinc/polymixin B

Guidelines for Management of Paronychia

Grade and Definition	Study Drug Management	Medical Management
Grade 1: Nail fold edema or erythema; disruption of the cuticle	Continue study drug at current dose.	Topical antibiotics AND vinegar soaks[a]
Grade 2: Nail fold edema or erythema with pain; associated with discharge or nail plate separation; limiting instrumental ADL	Continue study drug at current dose. Consider study drug holding if no improvement in 1 to 2 weeks. When resolves to ≤Grade 1 or baseline, restart at same or 1 dose level below in consultation with the Study Chair.	Topical antibiotics AND vinegar soaks[a] AND topical antifungal lacquer daily for 6+ weeks (ciclopirox olamine 8% OR efinaconazole 10% OR amorolfine 5% weekly OR bifonazole/urea ointment daily). For signs of infection (periungal edema/erythema/tenderness and/or discharge), obtain bacterial cultures, and then start the following: treatment with oral antibiotic for 2 weeks (cefadroxil 15 mg/kg/dose (up to 500 mg/dose) every 12 hours, ciprofloxacin 15 mg/kg/dose (up to 500 mg/dose) every 12 hours, or sulfamethoxazole/trimethoprim (TMP) 6 to 12 mg TMP/kg/day in divided doses every 12 hours; maximum single dose: 160 mg TMP/dose).
Grade 3: Limiting self-care ADLs, surgical intervention, or intravenous antibiotics indicated	Hold study drug (for up to 14 days), with weekly reassessments of clinical condition. When resolves to eligibility or baseline parameters, restart at a reduced dose (Appendix IV) in consultation with the Study Chair.	Vinegar soaks[a] AND consider nail avulsion For signs of infection (periungal edema/erythema/tenderness and/or discharge), obtain bacterial cultures, and then start the following: treatment with oral antibiotic for 2 weeks (cefadroxil 15 mg/kg/dose (up to 500 mg/dose) every 12 hours, ciprofloxacin 15 mg/kg/dose (up to 500 mg/dose) every 12 hours, or sulfamethoxazole/trimethoprim (TMP) 6 to 12 mg TMP/kg/day in divided doses every 12 hours; maximum single dose: 160 mg TMP/dose)). For cases of severe/refractory infection consider intravenous antibiotics. Consider dermatological and/or surgical evaluation.
Grade 4: life-threatening consequences, urgent intervention indicated	Discontinue study drug.	Evaluation and therapy as clinically indicated

[a] Vinegar soaks consist of soaking fingers or toes in a solution of white vinegar in water 1:1 for 15 minutes every day. Examples of topical antibiotic ointments: Mupirocin 2%, gentamycin, bacitracin zinc/polymixin B

Dose Modifications for Visual Disturbances

Grade	Immediate Action	Subsequent Action
Grade 1	Hold erdafitinib until an ophthalmologic exam can be completed (if possible, within 7 days).	• If the diagnosis is keratitis or retinal abnormality such as central serous retinopathy (CSR)/retinal pigment epithelial detachments (RPED) withhold erdafitinib until signs and symptoms have resolved. For retinal pathology perform OCT as appropriate and consider referral to a retinal specialist for further evaluation. • Follow specific treatment as per the ophthalmologist's recommendation. • If the toxicity resolves to < Grade 1 within 4 weeks according to ophthalmologic exam, resume erdafitinib therapy at the reduced dose (Appendix IV) level after consultation with the study chair per Section 6.2. Refer to Appendix IV for dose reduction information. • Monitor for recurrence every 1-2 weeks for a month and as clinically appropriate thereafter. • If there is no evidence of eye toxicity, resume erdafitinib therapy at the same dose level.
Grade 2	Hold erdafitinib until ophthalmologic exam is completed (if possible, within 7 days).	• If the diagnosis is keratitis or retinal abnormality such as CSR/RPED, hold erdafitinib until signs and symptoms have resolved, stabilized. For retinal pathology perform OCT as appropriate and consider referral to a retinal specialist for further evaluation. • Monitor for recurrence every 1-2 weeks for a month and as clinically appropriate thereafter. • Follow specific treatment as per the ophthalmologist's recommendation. • If there is no evidence of eye toxicity, resume erdafitinib therapy at the same dose level. • If the Ophthalmology exam is normal and the toxicity resolves to < Grade 1 within 4 weeks or according to ophthalmologic exam, resume erdafitinib therapy at the reduced dose level (Appendix IV) after consultation with the study chair per Section 6.2.

Grade 3	Immediately stop erdafitinib and promptly refer subject to an ophthalmologist for evaluation with an ophthalmologic exam	• Hold erdafitinib until eye exam is completed. If vision change is determined to be unrelated to erdafitinib, contact the study chair to discuss restarting of erdafitinib. Otherwise ≥ Grade 3 visual disturbance will be considered a DLT and require a dose reduction as per Section 6.2 if resolves within 4 weeks. • Follow specific treatment as per the ophthalmologist's recommendation. • Monitor for recurrence every 1-2 weeks for a month and as clinically appropriate thereafter. • If recurs, consider permanent discontinuation.
Grade 4	Permanently discontinue erdafitinib and promptly refer subject to an ophthalmologist for evaluation with an ophthalmologic exam	• Refer to Section 13.0 for reporting guidelines; monitor resolution of eye finding until complete resolution, stabilization, or other off-study criteria are met (see Section 10.1)

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 erdafitinib. See below for recommendations on management of specific toxicities associated with erdafitinib.

7.3.1 Nausea and vomiting:

Nausea and vomiting has been observed frequently in adult patients treated with erdafitinib. It is recommended to provide all patients a 5-HT_3-Receptor blocker (e.g., ondansetron or granisetron) at the start of treatment to be used as needed or prophylactically. In the event of breakthrough nausea/vomiting, additional antiemetics may be added as needed.

7.3.2 Mucositis:

For grade 1 mucositis, it is recommended to use conservative measures such as non-alcoholic mouth wash or salt water (0.9%) mouth wash several times a day until resolution. For grade ≥ 2 mucositis, topical analgesic mouth treatments (i.e., local

anesthetics such as benzocaine, butyl aminobenzoate, tetracaine hydrochloride, menthol, or phenol) may be used with or without topical corticosteroids, such as triamcinolone oral paste 0.1% (e.g. Kenalog in Orabase®). Agents containing hydrogen peroxide, iodine, and thyme derivatives may worsen mouth ulcers and should not be used.

Systemic antifungal agents should be avoided unless a fungal infection is diagnosed. In particular, systemic imidazole antifungal agents (ketoconazole, fluconazole, itraconazole, voriconazole, etc.) should be avoided due to their strong inhibition of CYP3A4 metabolism, therefore leading to higher erdafitinib exposure. Topical antifungal agents are preferred if an infection 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 inhibitors or inducers: Strong CYP3A4 inhibitors or inducers are not permitted on study (See Appendix II for list of agents). Note: CYP3A4 inducing anti-epileptic drugs and dexamethasone for CNS tumors or metastases, on a stable dose, are allowed. No grapefruit juice, Seville oranges, or grapefruit can be consumed while on erdafitinib.

7.5.2 CYP2C9 inhibitors or inducers: Moderate CYP2C9 inhibitors or strong CYP2C9 inducers are not permitted on the study.

7.5.3 CYP3A4 substrates: Until further data become available, concomitant use of erdafitinib with CYP3A4 substrates with narrow therapeutic indices should be avoided.

7.5.4 Co-administration of erdafitinib with other serum phosphate altering agents may affect serum phosphate concentrations. Avoid co-administration of serum phosphate altering agents if reasonable alternatives exist.

7.5.4 Concomitant administration of erdafitinib with P-glycoprotein (P-gp) substrates may increase their systemic exposure if administered concurrently.

7.5.5 P-glycoprotein: Concomitant administration of erdafitinib with P-glycoprotein (P-gp) substrates may increase their systemic exposure if administered concurrently. Oral narrow therapeutic index P-gp substrates such as digoxin should be taken at least 6 hours before or after erdafitinib to minimize the potential for interactions

7.5.6 OCT2: Erdafitinib was shown to be an OCT2 inhibitor in vitro. Until further data are available, consider alternative agents that are not OCT2 substrates. Metformin is an example of an OCT2 substrate.

7.6 Pharmacogenomic considerations

The exposure of erdafitinib is predicted to increase by 50% in subjects with the CYP2C9 *3/*3 genotype. Therefore, monitor for increased adverse reactions in subjects who are known or suspected to have CYP2C9*3/*3 genotype. Dose changes are guided by serum phosphate levels in all subjects irrespective of genotype.

8.0 EVALUATIONS/MATERIAL AND DATA TO BE ACCESSIONED

8.1 Required Clinical, Laboratory and Disease Evaluation

All clinical and laboratory studies to determine eligibility must be performed within 7 days prior to enrollment unless otherwise indicated. Laboratory values used to assess eligibility (see Section 4.0) must be no older than seven (7) days at the start of therapy. Laboratory tests need **not** be repeated if therapy starts **within** seven (7) days of obtaining labs to assess eligibility. If a post-enrollment lab value is outside the limits of eligibility, or laboratory values are older than 7 days, then the following laboratory evaluations must be re-checked within 48 hours prior to initiating therapy: CBC with differential, bilirubin, ALT (SGPT) and serum creatinine. If the recheck is outside the limits of eligibility, the patient may not receive protocol therapy and will be considered off protocol therapy. Imaging studies, bone marrow aspirate and/or biopsy, must be obtained within 14 days prior to start of protocol therapy (repeat the tumor imaging if necessary).

STUDIES TO BE OBTAINED	Pre-Study	During Cycle 1	Prior to Subsequent Cycles^
History	X	Weekly	X
Physical Exam with vital signs	X	Weekly	X
Neurologic Exam	X		
Height, weight, BSA	X		X
Performance Status	X		
Pregnancy Test[1]	X		
CBC, differential, platelets	X	Twice Weekly (every 3 to 4 days)[2,3]	Weekly[2,3]
Urinalysis	X		
Electrolytes including Ca^{++}, PO_4, Mg^{++}	X	Weekly	X
Creatinine, ALT, bilirubin	X	Weekly	X
Albumin	X		X
Tumor Disease Evaluation [4-A, 4-B,	X		Every other cycle x 3 then q 3 cycles [4]
Bone Marrow Aspirate and/or biopsy[5,6]	X[6]		
EKG	X		
Ophthalmologic exam[10]	X	X	Every cycle during the first 4 cycles of treatment, then every 3 cycles afterward[10]
Plain radiograph tibial growth plate (Bone X-Ray Tests)[11]	X		Prior to cycles 2, 5 and every 6 months
Medication Diary[7]		Weekly	X
Pharmacokinetics (optional)[8]			
Circulating Tumor DNA (ctDNA-optional)[9]			Cycle 5, Day 1 and (for patients receiving ≥ 5 cycles

			only) at end of Protocol Therapy OR disease progression

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

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

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

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

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

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

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

5 Bone marrow aspirate and/or biopsy only required in patients 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 8.4 for details of PK and plasma protein studies.

9 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 8.5 for details of the ctDNA studies. Note that a ctDNA sample is scheduled to be obtained on the APEC1621SC screening protocol prior to the initiation of treatment on this subprotocol.

10 Patients are required to have a baseline ophthalmological exam including fundoscopy, prior to the first dose of study medication, patients with significant ophthalmologic exams should refer to Section 4.2.9. Additionally, an ophthalmological exam should be performed every cycle for the first 4 cycles of treatment, then every 3 cycles afterward.

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

8.2 Monitoring for Specific Toxicities

8.2.1 Growth Plate Toxicity

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

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

b. If patients are found to have an open tibial growth plate, then repeat plain AP

radiographs of the same tibial growth plate will be obtained prior to cycles 2, 5 and every 6 months thereafter.

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

8.3 Radiology Studies

8.3.1 Bone Age/Knee MRI

All tibial radiographs and knee MRIs (if obtained) should be submitted for review.

8.3.2 Central Radiology Review for Response:

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

8.3.3 Technical Details of Submission:

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

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

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

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

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

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

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

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

8.4 Pharmacology and Plasma Protein Binding (Optional)

8.4.1 Description of Studies and Assay

Pharmacokinetics (PK) will be performed to determine the PK of JNJ-42756493 (erdafitinib) in children. Pharmacokinetic analysis will be conducted at a centralized laboratory using validated assays.

Erdafitinib is avidly bound to plasma proteins (fraction of unbound approx. 0.36%), preferentially to alpha-1 acid glycoproteins (AGP). Therefore, in addition to the PK samples on Day 1 of Cycle 2, an additional sample will be collected for the assessment of the binding of erdafitinib to plasma proteins pre-dose and 2 h after the erdafitinib dose. In the same samples the concentration of alpha-1 acid glycoprotein will be determined.

8.4.2 Sampling Schedule

Blood samples will be obtained at the following time points:

Blood Sample No.	Pharmacokinetics Time Point	Scheduled Collection Time
1	**Cycle 2, Day 1^**	Pre-dose
2	**Cycle 2, Day 1**	1-hour post-dose
3	**Cycle 2, Day 1^**	2-hour post-dose
4	**Cycle 2, Day 1**	4-hour post-dose
5	**Cycle 2, Day 1**	6–8-hour post-dose
6	**Cycle 2, Day 2**	24-hour post-dose

^ An additional 4 mL blood sample will be collected for plasma-protein binding at these time points.

Plasma samples for erdafitinib will be collected on Day 1 of Cycle 2. **On Day 1 of Cycle 2, the dose of erdafitinib should be held until a pre-dose plasma sample can be obtained. In order to obtain the 24-hour time point, the dose on Day 2, Cycle 2 should also be held until plasma sample is obtained.**

8.4.3 Sample Collection and Handling Instructions

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

For the purpose of plasma protein binding draw a separate 4 mL venous blood sample pre-dose and then at 2 h after erdafitinib dose and transfer to K_2-EDTA (lavender top) tubes.

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

8.4.4 Sample Processing

8.4.4.1 Pharmacokinetics

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

8.4.4.2 Plasma Protein Binding

Invert the tube gently several times to avoid clotting. Within 60 minutes of collection, centrifuge the tube for 10-15 minutes at 650 to 1450 X G. Transfer the plasma supernatant and divide equally into 1 uniquely labeled amber polypropylene screwtop cryotube and freeze immediately on dry ice until sample can be transferred to a -20°C (or below) freezer for storage until shipment. The time between blood collection and freezing the plasma

will not exceed 2 hours.

Please Note: If an amber polypropylene screwtop cryotube is not available to protect the samples from light, a clear polypropylene screwtop cryotube may be wrapped in black tape. Ensure that the sample identification is not covered by the tape. Clear polypropylene screwtop cryotube must be wrapped before transfer of the plasma to the tube to minimize the time of exposure to light.

8.4.5 Sample Labeling

Each sample must be labeled with the patient's study registration number, the study I.D# (APEC1621B), and the date and time the sample was drawn. Data should be recorded on the Pharmacokinetic Study Form, which must accompany the sample(s).

8.4.6 Institutional Sample Shipping Information

Institutional Sample Shipping Instructions:

Samples should be batched per patient and shipped frozen on dry ice monthly. Frozen samples must be shipped Monday through Wednesday via overnight courier. Do not ship samples on Thursdays, Fridays, weekends, or holidays.

Notify Diana Lozano via email at dl2595@cumc.columbia.edu and the study assigned research coordinator when samples are shipped and **include the tracking number.**

Attn: Diana Lozano
161 Fort Washington Ave-Room 706
Columbia University-Pediatric Oncology
New York, NY 10032
Phone: (212) 3056-2486
Email: dl2595@cumc.columbia.edu

8.4.7 Sample Analysis

Samples will be analyzed at the locations below, **for sample shipment information please see Section 8.4.6**

Plasma PK Sample Analysis Shipping:
Naomi Teekamp PhD
Alex J. AttemaProject Manager- PRA Health Sciences
Bioanalytical Laboratory NL / Quality Control Laboratory – Early Development Services
Amerikaweg 18
9407 TK Assen
The Netherlands
Telephone: +31 59 230 3474+31 (0) 592.303.421
E-mail: teekampnaomi@prahs.com AttemaAlex@prahs.com

Protein binding Sample Analysis Shipping:
Jo-Anne Jensen
Sample Management, Department of Bioanalysis
Janssen Research & Development,

Building 017 Room 035a Division of Janssen Pharmaceutica N.V.

Turnhoutseweg 30
B-2340 Beerse
Tel: +32 14 60 3335
Fax: +32 14 60 5110
Email: bioansup@its.jnj.com

8.5 Circulating Tumor DNA Study (Optional)

8.5.1 Sampling Schedule

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

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

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

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

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

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

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

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

- Remove tube from adapter and immediately mix by gentle inversion 8 to 10 times. Inadequate or delayed mixing may result in inaccurate test results.
- Store blood in a Streck tube at **room temperature** until shipment.

8.5.2 Sample Processing

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

8.5.3 Sample Labeling

Each tube must be labeled with the patient's study registration number, the study I.D (APEC1621B), 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).

8.5.4 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 APEC1621B-Peds MATCH*
700 Children's Drive, WA1340
Columbus, OH 43205
Phone: (614) 722-2865
Fax: (614) 722-2897
Email: BPCBank@nationwidechildrens.org

* Packages must be labeled "Peds MATCH" in order to expedite processing at the BPC. Be sure to include the room number. Ship samples by FedEx Priority Overnight using a FedEx shipping label obtained through the COG FedEx account

9.0 AGENT INFORMATION

9.1 Erdafitinib (01-30-2022)
(Balversa®, NSC# 781558, IND# 134661

9.1.1 **Source and Pharmacology:**

Erdafitinib is a highly selective and potent oral pan-fibroblast growth factor receptor (FGFR) tyrosine kinase inhibitor with high affinity and low nanomolar inhibitory activity for all FGFR family members, FGFR 1, 2, 3 and 4. The FGFR

are tyrosine kinases that are present in many types of endothelial and tumor cells and are shown to play an important role in tumor cell growth, survival, and migration as well as in maintaining tumor angiogenesis. Over-expression of FGFRs, or inappropriate activation through point mutation, chromosomal translocation, or aberrant splicing, has been implicated in many forms of human malignancies. Erdafitinib is FDA approved for the treatment of adult patients with locally advanced or metastatic urothelial carcinoma that has susceptible FGFR3 or FGFR2 genetic alterations.

Pharmacokinetics

Absorption of erdafitinib was estimated to be near complete. Following single and multiple once-daily administration, erdafitinib exposure (C_{max} and AUC) increased in a dose-proportional manner across the dose range of 0.5 to 12 mg. Multiple dose erdafitinib PK was time independent and steady state was achieved after 2 weeks of daily administration. With a once daily dose regimen, mean (coefficient of variation [CV%]) steady state accumulation ratio for AUC from time 0 to 24 hours after daily dosing (AUCτ) was 4.07 (32.0%), corresponding to a mean effective half-life ($t_{1/2}$) of 58.9 hours. Erdafitinib can be administered with or without food due to lack of effect of concomitant food intake. Estimated clearance of erdafitinib consisted of metabolism (67%), of which primarily by CYP2C9 (39%) and CYP3A4 (20%), renal clearance (13%), and intestinal secretion (21%). Excretion of erdafitinib was primarily in feces (68.7%), in the form of unchanged drug (14.1% to 20.8% of total dose) and M6 (approximately 24%). Erdafitinib was excreted to a lesser extent in urine (18.7%), with unchanged drug being the major entity (13.3%). Unchanged erdafitinib was the major drug-related moiety in plasma; there were no circulating metabolites.

Potential Drug Interactions

Erdafitinib is a weak time-dependent inhibitor and weak inducer of CYP3A4. Until further data become available, concomitant use of erdafitinib with CYP3A4 substrates with narrow therapeutic indices should be avoided.

Co-administration with a moderate CYP2C9 or strong CYP3A4 inhibitor increased erdafitinib exposure and may lead to increased drug-related toxicity. The use of moderate inhibitors of CYP2C9 and strong inhibitors of CYP3A4 are not permitted for the duration of the study.

The impact of strong CYP2C9 or CYP3A4 inducers (such as rifampin) on erdafitinib was not clinically studied. The concomitant use of strong CYP2C9 and CYP3A4 inducers with erdafitinib should be avoided as co-administration may significantly decrease erdafitinib exposure. Caution should be exercised for concomitant administration of erdafitinib and moderate CYP2C9 or CYP3A4 inducers as this may result in decreased erdafitinib exposure.

Co-administration of erdafitinib with other serum phosphate altering agents may affect serum phosphate concentrations. Avoid co-administration of serum phosphate altering agents if reasonable alternatives exist.

Concomitant administration of erdafitinib with P-glycoprotein (P-gp) substrates may increase their systemic exposure if administered concurrently. Oral narrow therapeutic index P-gp substrates such as digoxin should be taken at least 6 hours

before or after erdafitinib to minimize the potential for interactions.

Erdafitinib was shown to be an OCT2 inhibitor in vitro. PK simulations with metformin, an OCT2 substrate, predicted a lack of clinically relevant interaction with erdafitinib. However, until further data are available, consider alternative therapies that are not OCT2 substrates.

No clinically significant QT prolongation or cardiovascular effects have been noted to date. Clinical trials revealed no effects of erdafitinib on cardiac repolarization or other electrocardiographic parameters.

Acid lowering agents (e.g., antacids, H2-antagonists, or proton pump inhibitors) are not expected to affect the bioavailability of erdafitinib. Erdafitinib may be co-administered with an acid lowering agent.

Pharmacogenomics:
The exposure of erdafitinib is predicted to increase by 50% in subjects with the CYP2C9 *3/*3 genotype, estimated to be 0.4% to 3% of the population among various ethnic groups. Therefore, monitor for increased adverse reactions in subjects who are known or suspected to have CYP2C9*3/*3 genotype. Dose changes are guided by serum phosphate levels in all subjects irrespective of genotype; therefore, the implications of higher exposures of erdafitinib including safety may be addressed.

Patient Care Implications

Patients should have a baseline ophthalmological exam including fundoscopy, prior to the first dose of study medication. Additional ophthalmological exams should be performed every cycle for the first four cycles of treatment and then every 3 cycles afterward, manage as in accordance with the "Dose Modifications" table in Section 6.8.

Female subjects (of child-bearing potential and sexually active) must use medically acceptable methods of birth control prior to study entry and for the duration of the study, and for at least 3 months after the last dose of study drug. Male subjects (with a partner of child-bearing potential) must use a condom with spermicide when sexually active and must not donate sperm from the first dose of study drug until 3 months after the last dose of study drug. Medically acceptable methods of contraception that may be used by the subject and/or his/her partner include hormonal prescription oral contraceptives, contraceptive injections, contraceptive patch, intrauterine device, true sexual abstinence, and surgical sterilization (e.g., confirmed successful vasectomy or tubal ligation). True sexual abstinence is an acceptable method of contraception and is defined as refraining from heterosexual intercourse during the entire period of the study, including up to 3 months after the last dose of study drug is given.

All subjects should be closely monitored with special attention to cardiovascular function and evidence of disturbance of phosphate homeostasis and bone pathology and ocular symptoms until sufficient clinical experience is obtained.

9.1.2 Toxicity

The Comprehensive Adverse Event 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/adverse_events.htm for further clarification. *Frequency is provided based on 417 patients. Below is the CAEPR for Erdafitinib.*

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, January 04, 2019[1]

Adverse Events with Possible Relationship to Erdafitinib (CTCAE 5.0 Term) [n= 417]			**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)***
EYE DISORDERS			
	Dry eye		***Dry eye (Gr 2)***
	Keratitis		
Eye disorders – Other (central serous retinopathy)[12]			
	Eye disorders – Other (eye disorders)[13]		
GASTROINTESTINAL DISORDERS			
	Abdominal pain		***Abdominal pain (Gr 2)***
	Constipation		***Constipation (Gr 2)***
	Diarrhea		***Diarrhea (Gr 2)***
Dry mouth			***Dry mouth (Gr 2)***
Mucositis oral			***Mucositis oral (Gr 2)***
	Nausea		***Nausea (Gr 2)***
	Vomiting		***Vomiting (Gr 2)***
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
	Fatigue		***Fatigue (Gr 2)***
	Fever		***Fever (Gr 2)***
INFECTIONS AND INFESTATIONS			
	Conjunctivitis		
	Paronychia		***Paronychia (Gr 2)***
INVESTIGATIONS			

Adverse Events with Possible Relationship to Erdafitinib (CTCAE 5.0 Term) [n= 417]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
	Alanine aminotransferase increased		***Alanine aminotransferase increased (Gr 2)***
	Aspartate aminotransferase increased		***Aspartate aminotransferase increased (Gr 2)***
	Weight loss		***Weight loss (Gr 2)***
METABOLISM AND NUTRITION DISORDERS			
Anorexia			***Anorexia (Gr 2)***
Hyperphosphatemia			***Hyperphosphatemia (Gr 2)***
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			
	Arthralgia		***Arthralgia (Gr 2)***
	Back pain		***Back pain (Gr 2)***
NERVOUS SYSTEM DISORDERS			
	Dysgeusia		***Dysgeusia (Gr 2)***
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
	Cough		***Cough (Gr 2)***
	Dyspnea		***Dyspnea (Gr 2)***
	Epistaxis		***Epistaxis (Gr 2)***
	Respiratory, thoracic and mediastinal disorders - Other (nasal dryness)		
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
	Alopecia		***Alopecia (Gr 2)***
Dry skin			***Dry skin (Gr 2)***
	Palmar-plantar erythrodysesthesia syndrome		***Palmar-plantar erythrodysesthesia syndrome (Gr 2)***
	Pruritus		
Skin and subcutaneous tissue disorders - Other (nail disorder)[14]			***Skin and subcutaneous tissue disorders - Other (nail disorder)[14] (Gr 2)***
	Skin and subcutaneous tissue disorders - Other (skin fissures)		

[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]Central serous retinopathy includes: chorioretinopathy, retinal detachment, retinal oedema, detachment of retinal pigment epithelium, detachment of macular retinal pigment epithelium, retinopathy and vitreous detachment.

[3]Eye disorders includes, but is not limited to eye disorder with redness and irritation of the eye, maybe associated with increased tearing of the eyes, itchy eyes, and inflamed eyes.

[4]Nail disorder includes, but is not limited to, onycholysis, onychalgia, onychoclasis, nail dystrophy, nail loss, nail bed bleeding, nail bed inflammation, nail discomfort, nail discoloration, and nail ridging.

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Blood and lymphatic system disorders - Other (lymphadenopathy)
CARDIAC DISORDERS - Sinus tachycardia

EYE DISORDERS - Blurred vision; Eye disorders - Other (blepharitis); Eye disorders - Other (blindness unilateral); Eye disorders - Other (corneal erosion); Eye disorders - Other (corneal infiltrates); Eye disorders - Other (eyelid edema); Eye disorders - Other (foreign body sensation in eyes); Eye disorders - Other (lagophthalmos); Eye disorders - Other (macular degeneration); Eye disorders - Other (metamorphopsia); Eye disorders - Other (ocular hyperemia); Eye disorders - Other (xanthopsia); Eye pain; Night blindness; Papilledema; Photophobia; Vision decreased
GASTROINTESTINAL DISORDERS - Abdominal distension; Ascites; Colitis; Dysphagia; Gastrointestinal disorders - Other (intestinal obstruction); Salivary duct inflammation
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Edema limbs; General disorders and administration site conditions - Other (general physical health deterioration); Non-cardiac chest pain; Pain
INFECTIONS AND INFESTATIONS - Herpes simplex reactivation; Infections and infestations - Other (clostridum difficile colitis); Infections and infestations - Other (lower respiratory tract infection); Infections and infestations - Other (oral herpes); Sepsis; Urinary tract infection
INVESTIGATIONS - Alkaline phosphatase increased; Creatinine increased; GGT increased
METABOLISM AND NUTRITION DISORDERS - Dehydration; Hypercalcemia; Hypoalbuminemia; Hypocalcemia; Hyponatremia; Hypophosphatemia
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS) - Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other (metastases to spine)
NERVOUS SYSTEM DISORDERS - Lethargy; Somnolence
PSYCHIATRIC DISORDERS - Insomnia
RENAL AND URINARY DISORDERS - Acute kidney injury
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Hypoxia; Pleural effusion; Respiratory, thoracic and mediastinal disorders - Other (respiratory distress)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Bullous dermatitis; Eczema; Hyperkeratosis; Rash maculo-papular; Skin and subcutaneous tissue disorders - Other (cutaneous calcification); Skin and subcutaneous tissue disorders - Other (skin exfoliation); Skin and subcutaneous tissue disorders - Other (skin lesion); Skin and subcutaneous tissue disorders - Other (skin toxicity); Skin atrophy; Skin hyperpigmentation; Skin ulceration
VASCULAR DISORDERS - Hypotension; Thromboembolic event

Note: Erdafitinib 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

Erdafitinib is a yellow powder. Tablet excipients include mannitol, microcrystalline cellulose, meglumine, croscarmellose sodium and magnesium stearate. Tablets are coated with Opadry AMB II. The agent is available as 3 mg (yellow), 4 mg (orange), and 5 mg (brown) film coated tablets.

The approximate dimensions of the round tablets are in the table below:

Strength	Diameter (mm)	Thickness (width) (mm)
3 mg	7.7 $\pm$ 0.2	3.7 $\pm$ 0.4
4 mg	8.2 $\pm$ 0.2	4.2 $\pm$ 0.4
5 mg	8.7 $\pm$ 0.2	4.6 $\pm$ 0.4

Erdafitinib tablets are provided in 30 count bottles made of high density polyethylene (HDPE), with an induction seal and child resistant cap. Tablets must be dispensed in the original container.

Storage
Store intact bottles at controlled room temperature 15°C to 30°C (59°F to 86°F). Tablets must be dispensed in the original container.

If a storage temperature excursion is identified, promptly return erdafitinib to 15°C to 30°C and quarantine the supplies. Provide a detailed report of the excursion (including documentation of temperature monitoring and duration of the excursion) to PMBAfterHours@mail.nih.gov for determination of suitability.

Stability
Shelf-life dating is printed on the bottle label.

9.1.4 Guidelines for Administration

See Treatment (Section 5.0) and Dose Modification (Section 6.0) sections of the protocol. Administer erdafitinib orally once a day with or without food, at approximately the same time each day. Tablets must be swallowed whole, with approximate 8 ounces of water. Do not crush or chew. If vomiting occurs within 30 minutes of erdafitinib administration, then the dose can be repeated once. If a dose is missed, it can be taken up to 6 hours after the scheduled time. If it has been more than 6 hours since the missed dose, then that dose should be skipped. The next dose should be taken at the usual time.

9.1.5 Supplier

Erdafitinib is supplied by Johnson & Johnson and distributed by the Division of Cancer Treatment and Diagnosis (DCTD), NCI. **Do not use commercial supply.**

9.1.6 Obtaining the Agent

NCI supplied agent may be requested by the eligible participating investigator (or their authorized designee) at each participating institution. The CTEP assigned protocol number must be used for ordering all CTEP supplied investigational agents. The responsible investigator at each participating institution must be registered with CTEP, DCTD through an annual submission of FDA form 1572 (Statement of Investigator), NIH 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 erdafitinib (JNJ-42756493) should be placed with CTEP after enrollment and treatment assignment to APEC1621B 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 any time. 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**

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.

9.1.8 **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.

9.1.9 Useful Links and Contacts

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

10.0 CRITERIA FOR REMOVAL FROM PROTOCOL THERAPY AND OFF STUDY CRITERIA

10.1 Criteria for Removal from Protocol Therapy

a) Clinical (including physical examination or serum tumor markers) or radiographic evidence of progressive disease (See Section 12).
b) Adverse Events requiring removal from protocol therapy (See Section 6).
c) Refusal of protocol therapy by patient/parent/guardian
d) Non-compliance that in the opinion of the investigator does not allow for ongoing participation.
e) Completion of 26 cycles of therapy.
f) Physician determines it is not in the patient's best interest.

g) Repeated eligibility laboratory studies (CBC with differential, bilirubin, ALT (SGPT) or serum creatinine) are outside the parameters required for eligibility prior to the start of protocol therapy (See Section 8.1).
h) Study is terminated by Sponsor.
i) Pregnancy
j) Patient did not receive protocol treatment after study enrollment

Patients who are removed from protocol therapy during cycle 1 should continue to have the required observations in Section 8.1 until the originally planned end of the cycle or until all adverse events have resolved per Section 13.4.4, whichever happens LATER. The only exception is with documentation of the patient's withdrawal of consent from the APEC1621SC screening protocol. Patients who are removed from protocol therapy in subsequent cycles should have the necessary observations to ensure adequate clinical care.

10.2 Follow-Up Data Submission and APEC1621SC Off Study Criteria

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

11.0 STATISTICAL AND ETHICAL CONSIDERATIONS

11.1 Sample Size and Study Duration

APEC1621B will require a minimum of 20 evaluable patients and a maximum of 49 patients, allowing for 15% inevaluability. Assuming an enrollment rate of 4-9 biomarker positive patients per year, the primary cohort of this subprotocol is expected to be completed within 2.7-6 years.

11.2 Dosing Considerations

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 erdafitinib to be used in this study. As there is no prior pediatric phase 1 data for erdafitinib, study investigators have reviewed relevant data with the pharmaceutical partner to identify a drug specific dosing plan for testing in children with recurrent/refractory cancer, and trial participants will be closely monitored to ensure tolerability of the selected dose. Limited pharmacokinetic sampling may be done for patients enrolled on this arm. Since the adult RP2D (8 mg PO once daily) is below the MTD (at least 12 mg PO once daily) the starting dose will be the adult RP2D adjusted for BSA, which is 4.7 mg/m^2/day (8 mg/1.7 m^2) up to a maximum daily dose of 8 mg PO once daily. The dosing for erdafitinib will follow the general Pediatric MATCH subprotocol guidelines as below:

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

11.3 Study Design

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

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

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

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

11.3.1 Primary Cohort:

APEC1621B will evaluate a primary cohort of 20 mutation-matched ("biomarker positive") evaluable patients of any histology for the primary study aim of determining the objective response rate (CR/PR according to the response criteria in Section 12.3) to the agent. Using an A'Hern design[15] with alpha=10%, a sample of N=20 will provide 90% power to detect an improvement in response rate from 5%, if the treatment is ineffective, to 25% if the targeted therapy is sufficiently effective to warrant further study. If there are at least 3 responses out of 20 in the primary cohort, the biomarker/therapy match will be deemed a success.

11.3.2 Histology-Specific Biomarker Positive Expansion Cohorts:

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

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

11.4 Methods of Analysis

Response criteria are described in Section 12. A responder is defined as a patient who achieves a best response of PR or CR on the study. Response rates will be calculated as the percent of evaluable patients who are responders, and confidence intervals will be constructed using the Wilson score interval method.[16] Decision making for A'Hern design cohorts will follow rules described above.

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

11.5 Evaluability for Response

Any eligible patient who is enrolled and receives at least one dose of protocol therapy will be considered evaluable for response. Any patient who receives non-protocol anti-cancer therapy during the response evaluation period will be considered a non-responder for the purposes of the statistical rule, unless they show an objective response prior to receiving the non-protocol anti-cancer therapy (in which case they will be considered a responder). Patients who demonstrate a complete or partial response confirmed by central review will be considered to have experienced a response. When opening expansion cohorts, the evaluation period for determination of best response will be the first 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 v5.0 (CTCAE)

The descriptions and grading scales found in the current version of the NCI Common Terminology Criteria for Adverse Events v5.0 (CTCAE) will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the current CTCAE v5.0. A copy of the CTCAE v5.0 can be downloaded from the CTEP website (http://ctep.cancer.gov).

12.2 Progression-Free Survival

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

Development of new disease or progression in any established lesions is considered progressive disease, regardless of response in other lesions – e.g., when multiple lesions

show opposite responses, the progressive disease takes precedence.

12.3 Response Criteria for Patients with Solid Tumors

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

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

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

12.3.1 Definitions

12.3.1.1 Evaluable for objective response:
Eligible patients who receive exhibit objective disease progression and who have received 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 evaluable but not measurable disease and have received at least one dose of protocol therapy, have lesions present at baseline that are evaluable but do not meet the definitions of measurable disease, 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.[17]

12.4 Response Criteria for Patients with Solid Tumor and Measurable Disease

12.4.1 Evaluation of Target Lesions

Complete Response (CR):	Disappearance of all target and non-target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm. If immunocytology is available, no disease must be detected by that methodology. Normalization of urinary catecholamines or other tumor markers if elevated at study enrollment (for patients with neuroblastoma).
Partial Response (PR):	At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters
Progressive Disease (PD):	At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline

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

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

12.4.2 Evaluation of Non-Target Lesions

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

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

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

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

12.4.3 Overall Response Assessment

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

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

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

* See RECIST 1.1 manuscript for further details on what is evidence of a new lesion.
** In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.
Note: Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "*symptomatic deterioration.*" Every effort should be made to document the objective progression even after discontinuation of treatment.

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

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

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

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

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

12.4.4 Overall Best Response Assessment

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

12.5 Response Criteria for Neuroblastoma Patients with MIBG Positive Lesions

12.5.1 MIBG Positive Lesions

Patients who have a positive MIBG scan at the start of therapy will be evaluable for MIBG response. The use of ^{123}I for MIBG imaging is recommended for all

scans. If the patient has only one MIBG positive lesion and that lesion was radiated, a biopsy must be done at least 28 days after radiation was completed and must show viable neuroblastoma.

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

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

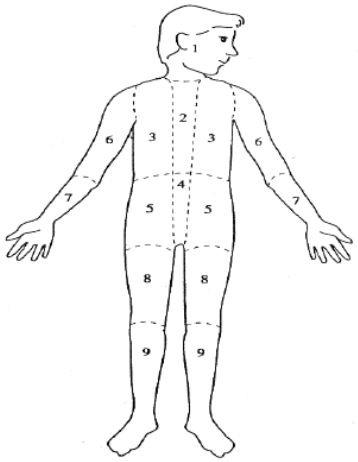
12.5.3 The response of MIBG lesions will be assessed on central review using the Curie scale14 as outlined below. Central review responses will be used to assess efficacy for study endpoint. See Section 8.2 for details on transferring images to the Imaging Research Center.

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

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

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

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



The **relative score** is calculated by dividing the absolute score at each time point

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

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

12.5.4 Overall Response Assessment

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

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

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

12.5.5 Overall Best Response Assessment

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

12.6 Response Criteria for Neuroblastoma Patients with Bone Marrow Involvement

12.6.1 Bone Marrow Involvement

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

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

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

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

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

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

12.6.2 Overall Best Response Assessment

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

12.7 Response Criteria for Patients with CNS Tumors

12.7.1 Measurable Disease

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

12.7.2 Evaluable Disease

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

12.7.3 Selection of Target and Non-Target Lesions

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

(e.g., 8 mm lesion for a 4 mm slice).

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

12.7.4 Response Criteria for Target Lesions

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

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

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

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

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

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

12.7.5 Response Criteria for Non-Target Lesions:

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

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

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

12.7.6 Response criteria for tumor markers (if available):

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

12.7.7 Overall Response Assessment

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

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

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

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

Response and progression will be evaluated in this study using the new international criteria proposed by the revised Response Evaluation Criteria in Pediatric non-Hodgkin Lymphoma Criteria[18], with modification from the Lugano classification.[19]

12.8.1 Disease Parameters

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

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

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

12.8.2 Evaluation of Measurable Disease

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

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

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

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

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

12.8.3 Evaluation of Non-measured Lesions (CT-based response, PET/CT based response not applicable)[19]

Complete Response (CR):	Absent non-measured lesions.
Partial response (PR):	Absent/normal, regressed, lesions, but no increase.
Stable Disease (SD):	No increase consistent with progression
Progressive Disease (PD):	New or clear progression of preexisting non-measured lesions.

12.8.4 Evaluation of organ enlargement[19]

Complete Response (CR):	Regress to normal
Partial response (PR):	Spleen must have regressed by >50% in length beyond normal
Stable Disease (SD):	No increase consistent with progression
Progressive Disease (PD):	In the setting of splenomegaly, the splenic length must increase by 50% of the extent of its prior

increase beyond baseline. If no prior splenomegaly, must increase by at least 2 cm from baseline.

New or recurrent splenomegaly

12.9 **Best Response**

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

12.9.1 **Evaluation of Best Overall Response**

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

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

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

12.9.2 **Duration of Response**

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

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

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

13.0 ADVERSE EVENT REPORTING REQUIREMENTS

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

Reporting requirements may include the following considerations: 1) whether the patient has received an investigational 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# 301-897-7404) and by email to both COGCAdEERS@childrensoncologygroup.org and to the APEC16-21B COG Study Assigned Research 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 5.0 of the NCI CTCAE. The descriptions and grading scales found in the current version 5.0 of the CTCAE will be used for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE v5.0. A copy of the CTCAE v5.0 can be downloaded from the CTEP website (http://ctep.cancer.gov).

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

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

- The adverse event is considered serious;
- There are any protocol-specific requirements for expedited reporting of

specific adverse events that require special monitoring; and/or

- There are any protocol-specific exceptions to the reporting requirements.

- Any medical event equivalent to CTCAE 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:

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

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

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

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

Expedited AE reporting timelines are defined as:

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

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

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

- All Grade 3, 4, and Grade 5 AEs

Expedited 7 calendar day reports for:

- Grade 2 AEs resulting in hospitalization or prolongation of hospitalization

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

Effective Date: May 5, 2011

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

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

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

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

Category	Adverse Events
EYE DISORDERS	Watering Eyes
METABOLISM AND NUTRITION DISORDERS	Hyponatremia
PSYCHIATRIC DISORDERS	Insomnia

- See also the Specific Protocol Exceptions to Non-Hematological DLTs in Section 5.4.1 and Expedited Reporting (SPEER) in Section 9.1.9 of the protocol.

13.3.1 Adverse Events of Special Interest

The following **Adverse Events of Special Interest**, whether or not resulting in hospitalization, should be reported via CTEP-AERS.

- Central Serous Retinopathy: including PTs of retinal detachment, chorioretinopathy, detachment of retinal pigment epithelium, retinopathy, vitreous detachment, retinal edema, detachment of macular retinal pigment epithelium.

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

13.7 Special Reporting Situations

In accordance with the protocol the following special situations, which are safety events of interest for a J&J medicinal product that require expediting reporting and/or safety evaluation with or without an SAE include:

- Drug exposure during pregnancy (maternal)
- Suspected abuse/misuse of erdafitinib product

The following Special Situations should be reported if associated with an SAE or as defined within the protocol

- Overdose of erdafitinib product
- Exposure to erdafitinib product from breastfeeding
- Inadvertent or accidental exposure to erdafitinib product
- Any failure of expected pharmacological action (i.e., lack of effect) of erdafitinib
- Critical Treatment Deviations as defined in CTMB Audit Guidelines:
    - Any finding identified before or during an audit that is suspected to be fraudulent activity
    - Incorrect agent/treatment/intervention used
- Suspected transmission of any infectious agent via administration of a medicinal product

These safety events may not meet the definition of an adverse event; however, from a COLLABORATOR perspective, they are treated in the same manner as adverse events. Special Situations should be recorded on the appropriate CRF.

13.8 Product Quality Compliant (PQC)

A product quality compliant is defined as any suspicion of a product defect related to a potential quality issue during manufacturing, packaging, release testing, stability monitoring, dose preparation, storage or distribution of the product, or delivery system. Not all PQCs involve a subject. Lot and batch numbers are of high significance and need to be provided upon request.

Examples of PQC include but are not limited to:

- Function Problem: e.g. altered delivery rate in a controlled release product
- Physical Defect: e.g. abnormal odor, broken or crushed tablets/capsules

- Potential Dosing Device Malfunction: e.g. autoinjector button not working, needle detaching from syringe
- Suspected Contamination
- Suspected Counterfeit

14.0 RECORDS, REPORTING, AND DATA AND SAFETY MONITORING PLAN

14.1 Categories of Research Records

Research records for this study can be divided into three categories

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

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

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

See separate CRF Packet, which includes submission schedule.

14.2 CDUS

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

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

14.3 CRADA/CTA/CSA

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

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

1. Agent(s) may not be used for any purpose outside the scope of this protocol, nor

can Agent(s) be transferred or licensed to any party not participating in the clinical study. Collaborator(s) data for Agent(s) are confidential and proprietary to Collaborator(s) and shall be maintained as such by the investigators. The protocol documents for studies utilizing investigational Agents contain confidential information and should not be shared or distributed without the permission of the NCI. If a copy of this protocol is requested by a patient or patient's family member participating on the study, the individual should sign a confidentiality agreement. A suitable model agreement can be downloaded from: http://ctep.cancer.gov.

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

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

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

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

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

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

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

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

   Email: ncicteppubs@mail.nih.gov

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

14.4 Data and Safety Monitoring Plan

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

14.4.1 Data and Safety Monitoring Committee

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

14.4.2 Monitoring by the Study Chair and MATCH Leadership

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

REFERENCES

1. Porta R, Borea R, Coelho A, et al.: FGFR a promising druggable target in cancer: Molecular biology and new drugs. Crit Rev Oncol Hematol 113:256-267, 2017
2. Bange J, Prechtl D, Cheburkin Y, et al.: Cancer progression and tumor cell motility are associated with the FGFR4 Arg(388) allele. Cancer Res 62:840-7, 2002
3. Liang G, Chen G, Wei X, et al.: Small molecule inhibition of fibroblast growth factor receptors in cancer. Cytokine Growth Factor Rev 24:467-75, 2013
4. Weiss J, Sos ML, Seidel D, et al.: Frequent and focal FGFR1 amplification associates with therapeutically tractable FGFR1 dependency in squamous cell lung cancer. Sci Transl Med 2:62ra93, 2010
5. Jones DT, Hutter B, Jager N, et al.: Recurrent somatic alterations of FGFR1 and NTRK2 in pilocytic astrocytoma. Nat Genet 45:927-32, 2013
6. Singh D, Chan JM, Zoppoli P, et al.: Transforming fusions of FGFR and TACC genes in human glioblastoma. Science 337:1231-5, 2012
7. Missiaglia E, Selfe J, Hamdi M, et al.: Genomic imbalances in rhabdomyosarcoma cell lines affect expression of genes frequently altered in primary tumors: an approach to identify candidate genes involved in tumor development. Genes Chromosomes Cancer 48:455-67, 2009
8. Karkera JD, Martinez Cardona G, Bell K, et al.: Oncogenic Characterization and Pharmacologic Sensitivity of Activating Fibroblast Growth Factor Receptor (FGFR) Genetic Alterations to the Selective FGFR Inhibitor Erdafitinib. Mol Cancer Ther, 2017
9. Perera TP, Jovcheva E, Mevellec L, et al.: Discovery and pharmacological characterization of JNJ-42756493 (erdafitinib), a functionally selective small molecule FGFR family inhibitor. Mol Cancer Ther, 2017
10. Nishina T, Takahashi S, Iwasawa R, et al.: Safety, pharmacokinetic, and pharmacodynamics of erdafitinib, a pan-fibroblast growth factor receptor (FGFR) tyrosine kinase inhibitor, in patients with advanced or refractory solid tumors. Invest New Drugs, 2017
11. Loriot Y, Necchi A, Park SH, et al.: Erdafitinib in Locally Advanced or Metastatic Urothelial Carcinoma. New England Journal of Medicine 381:338-348, 2019
12. Central serous retinopathy includes: chorioretinopathy, retinal detachment, retinal oedema, detachment of retinal pigment epithelium, detachment of macular retinal pigment epithelium, retinopathy and vitreous detachment.,
13. Eye disorders includes, but is not limited to eye disorder with redness and irritation of the eye, maybe associated with increased tearing of the eyes, itchy eyes, and inflamed eyes.,
14. Nail disorder includes, but is not limited to, onycholysis, onychalgia, onychoclasis, nail dystrophy, nail loss, nail bed bleeding, nail bed inflammation, nail discomfort, nail discoloration, and nail ridging.,
15. A'Hern RP: Sample size tables for exact single-stage phase II designs. Stat Med 20:859-66, 2001
16. Agresti A,Coull BA: Approximate Is Better than "Exact" for Interval Estimation of Binomial Proportions. The American Statistician 52:119-126, 1998
17. Sandlund JT, Guillerman RP, Perkins SL, et al.: International Pediatric Non-Hodgkin Lymphoma Response Criteria. Journal of Clinical Oncology 33:2106-2111, 2015
18. Sandlund JT, Guillerman RP, Perkins SL, et al.: International Pediatric Non-Hodgkin Lymphoma Response Criteria. J Clin Oncol 33:2106-11, 2015
19. Cheson BD, Fisher RI, Barrington SF, et al.: Recommendations for initial evaluation, staging, and response assessment of Hodgkin and non-Hodgkin lymphoma: the Lugano classification. J Clin Oncol 32:3059-68, 2014

APPENDIX I: PERFORMANCE STATUS SCALES/SCORES

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

APPENDIX II: CYP3A4 SUBSTRATES, INDUCERS AND INHIBITORS

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

CYP3A4 substrates	Strong Inhibitors[1]	Moderate Inhibitors	Strong Inducers	Moderate Inducers
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 4.2.2 regarding use of corticosteroids.
[3]The effect of grapefruit juice (strong vs moderate CYP3A4 inhibition) varies widely among brands and is concentration-, dose-, and preparation-dependent.
[4]Narrow therapeutic range substrates
[5]Sensitive substrates (drugs that demonstrate an increase in AUC of ≥ 5-fold with strong inhibitors)

APPENDIX III-A: MEDICATION DIARY FOR ERDAFITINIB

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

Institution: _____

Please do not write patient names on this form.

Complete each day with the time and dose given for erdafitinib. If a dose is not due or is accidentally skipped leave that time slot blank. ***Make note of other drugs and supplements taken under the Comments section below***. Erdafitinib tablets should be taken by mouth once a day with or without food, at approximately the same time daily. Tablets must be swallowed whole, with approximate 8 ounces of water. Do not crush or chew. Inform your study doctor or nurse if that occurs. If vomiting occurs within 30 minutes of erdafitinib administration, then the dose can be repeated once. This should be noted in the comments section. If a dose is missed, it can be taken up to 6 hours after the scheduled time. If it has been more than 6 hours since the missed dose, then that dose should be skipped. The next dose should be taken at the usual time. Add the dates to the calendar below and return the completed diary and the empty bottle or any leftover tablets to the study clinic at each visit.

EXAMPLE			***Number of erdafitinib tablets***			***Comments***
	Date	***Time***	**3 mg**	**4 mg**	**5 mg**	
Day 1	*2/15/20*	*8:30 AM*	2	0		*He felt nauseated an hour after taking the drug but did not vomit.*

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

WEEK 1	**Date**	**Time**		**# of erdafitinib tablets prescribed to take**			**Comments (Describe any missed or extra doses, vomiting and/or bothersome effects.)**
				3 mg	**4 mg**	**5 mg**	
				# of erdafitinib tablets taken			
				3 mg	**4 mg**	**5 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**				

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

WEEK 2	Date	Time		# of erdafitinib tablets prescribed to take			Comments (Describe any missed or extra doses, vomiting and/or bothersome effects.)
				3 mg	4 mg	5 mg	
				# of erdafitinib tablets taken			
				3 mg	4 mg	5 mg	
Day 8			AM / PM				
Day 9			AM/ PM				
Day 10			AM/ PM				
Day 11			AM/ PM				
Day 12			AM/ PM				
Day 13			AM/ PM				
Day 14			AM/ PM				

WEEK 3	Date	Time		# of erdafitinib tablets prescribed to take			Comments (Describe any missed or extra doses, vomiting and/or bothersome effects.)
				3 mg	4 mg	5 mg	
				# of erdafitinib tablets taken			
				3 mg	4 mg	5 mg	
Day 15			AM / PM				
Day 16			AM/ PM				
Day 17			AM/ PM				
Day 18			AM/ PM				
Day 19			AM/ PM				
Day 20			AM/ PM				
Day 21			AM/ PM				

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

WEEK 4	Date	Time	# of erdafitinib tablets prescribed to take			Comments (Describe any missed or extra doses, vomiting and/or bothersome effects.)
			3 mg	4 mg	5 mg	

				# of erdafitinib tablets taken			
				3 mg	4 mg	5 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 reviewed this form must sign and date this form below:

Signature: _____ Date: _____

(site personnel who reviewed this form)

APPENDIX III-B: PATIENT WALLET CARD

NIH NATIONAL CANCER INSTITUTE

CLINCIAL 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 #:	APEC1621B
Study Drug(S):	Erdafitinib

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

APPENDIX IV: ERDAFITINIB DOSING NOMOGRAM

Erdafitinib Dose Assignment: 4.7 mg/m^2/dose once daily (Maximum dose of 8 mg per day)

BSA (m^2)	Erdafitinib Dose (mg/dose) once daily	Dose Reduction For Toxicity (mg/dose) once daily
0.53-0.74	3	Off Protocol Therapy
0.75-0.96	4	3
0.97-1.17	5	3
1.18-1.38	6	4
1.39-1.59	7	5
≥ 1.6	8	6

APPENDIX V: APEC1621B 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
Erdafitinib IND # 134661 **Do not use commercial supply.**	PO once daily	Dose Level: 4.7 mg/m^2 Maximum dose of 8 mg per day. Refer to the dosing nomogram Appendix IV.	1-28	Drug doses should be adjusted based on the BSA calculated from height and weight measured within 7 days prior to the beginning of each cycle and according to the dosing nomogram in Appendix IV. Erdafitinib tablets should be taken by mouth once a day with or without food, at approximately the same time each day. Tablets must be swallowed whole, with approximate 8 ounces of water. Do not crush or chew. If vomiting occurs within 30 minutes of erdafitinib administration, then the dose can be repeated once. If a dose is missed, it can be taken up to 6 hours after the scheduled time. If it has been more than 6 hours since the missed dose, then that dose should be skipped. The next dose should be taken at the usual time

Ht _____cm Wt _____kg BSA _____m^2

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

Cycle 1

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

Required Observations in Cycle 1

***All baseline studies must be performed prior to starting protocol therapy unless otherwise indicated below. For information related to pre-study observations please refer to Section 8.1. Studies on Day 1 may be obtained within 72 hours prior to the start of the subsequent cycle. * Please refer to Section 8.1 for the specific timing of these observations.**

a.	**History/Physical Exam (including VS)**
b.	**Ht/Wt/BSA**
c.	. **CBC/differential/platelets**- If patients have Grade 4 neutropenia then CBCs should be checked at least every other day until recovery to Grade 3 or until meeting the criteria for dose limiting toxicity. If patients develop Grade 3 or greater thrombocytopenia then CBCs should be checked every 3 to 4 days until recovery per Section 6.1.
d.	**Electrolytes including Ca++, PO4, Mg++**
e.	**Creatinine, ALT, bilirubin**
f.	**Albumin**
g.	**Medication Diary-** (see Appendix III) should be reviewed after completion of each treatment cycle and uploaded into RAVE. The medication diary should be collected weekly.
h.	Plain radiograph tibial growth plate (bone x-ray tests) - Plain radiographs of at least one tibial growth plate should be obtained in all patients prior to first dose of protocol therapy and prior to cycle 2.

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

Comments
(Include any held doses, or dose modifications)

Treatment Details: Cycle 1

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

Cycle 1

All Subsequent Cycles

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

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

DRUG	ROUTE	DOSAGE	DAYS	IMPORTANT NOTES
Erdafitinib IND # 134661 **Do not use commercial supply.**	PO once daily	Dose Level: 4.7 mg/m^2 Maximum dose of 8 mg per day Refer to the dosing nomogram Appendix IV.	1-28	Drug doses should be adjusted based on the BSA calculated from height and weight measured within 7 days prior to the beginning of each cycle and according to the dosing nomogram in Appendix IV. Erdafitinib tablets should be taken by mouth once a day with or without food, at approximately the same time each day. Tablets must be swallowed whole, with approximate 8 ounces of water. Do not crush or chew. If vomiting occurs within 30 minutes of erdafitinib administration, then the dose can be repeated once. If a dose is missed, it can be taken up to 6 hours after the scheduled time. If it has been more than 6 hours since the missed dose, then that dose should be skipped. The next dose should be taken at the usual time

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

Date Due	Date Given	Day	**Erdafitinib** mg	Studies
			Enter calculated dose above as per dosing nomogram and actual dose administered below	
		1	mg	a,b,c,d,e,f,i,k*
		2	mg	k*
		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*	_____mg	a-f, g*, i, j*, l*, m*

Subsequent Cycles

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 1 may be obtained within 72 hours prior to the start of the subsequent cycle.**

Required Observations in All Subsequent Cycles

a.	**History/Physical Exam (including VS)**
b.	**Ht/Wt/BSA**
c.	**CBC/differential/platelets** If patients have Grade 4 neutropenia then CBCs should be checked at least every other day until recovery to Grade 3 or until meeting the criteria for dose limiting toxicity. If patients develop Grade 3 or greater thrombocytopenia then CBCs should be checked every 3 to 4 days until recovery per Section 6.1.
d.	**Electrolytes including Ca++, PO4, Mg++**
e.	**Creatinine, ALT, bilirubin**
f.	**Albumin**
g.	**Tumor Disease Evaluation** – Every other cycle x 3 then q 3 cycles. Tumor Disease Evaluation should be obtained on the next consecutive cycle after initial documentation of either a PR or CR. Subsequent scans may restart 2 cycles after the confirmatory scan. If the institutional investigator determines that the patient has progressed based on clinical or laboratory evidence, he/she may opt not to confirm this finding radiographically
h.	**Bone Marrow Aspirate and/or biopsy-** 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.
i.	**Medication Diary**- (see Appendix III) should be reviewed after completion of each treatment cycle and uploaded into RAVE.
j.	**Circulating Tumor DNA (ctDNA-optional)** - With consent, two samples will be collected on this protocol (Cycle 5 Day 1; and for patients receiving ≥ 5 cycles, at progression or end of protocol therapy) see Section 8.5 for details of the ctDNA studies.
k.	**Pharmacokinetics** - see Section 8.4 for details of PK/plasma protein studies in Cycle 2.
l.	**Ophthalmology exam -** Patients should have a baseline ophthalmological exam including fundoscopy, prior to the first dose of study medication, patients with significant ophthalmologic exams should refer to Section 4.2.9. Additionally, an ophthalmological exam should be performed every cycle for the first four cycles of treatment and then every 3 cycles afterward.
m.	**Plain radiograph tibial growth plate (bone x-ray tests)** - Plain radiographs of at least one tibial growth plate should be obtained in all patients prior to first dose of protocol therapy. In patients with open growth plates, follow-up plain radiographs of the same growth plate(s) should be obtained prior to Cycles 2 and 5, then every 6 cycles

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

Comments
(Include any held doses, or dose modifications)

Treatment Details: Subsequent Cycles

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

APPENDIX VI: CORRELATIVE STUDIES

Correlative Study	Section	Blood Volume		Tube Type
		Volume per Sample	Total Cycle 1	
Pharmacokinetics	8.4	2 mL	12 mL	K_2 EDTA lavender top
Protein Plasma-Binding	8.4	4 mL	8 mL	K_2 EDTA lavender top
Total Blood Volume in Cycle 1			**20 mL**	

Correlative Study	Section	Blood Volume		Tube Type
		Volume per Sample	Total Cycle 5 Day 1	
Circulating tumor DNA (optional)	8.5	• 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)	8.5	• 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 VII: TARGET HISTOLOGIES FOR APEC1621B EXPANSION COHORTS

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

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

APPENDIX VIII: EXAMPLES OF ACTIONABLE MUTATIONS FOR SUBPROTOCOL FOR APEC1621B

INCLUSION Hotspots	**VARIANTS**			
Gene Name	Variant ID	Variant Type	aMOI	LOE
FGFR1	COSM4771556	SNV	p.K656M	3
FGFR1	COSM35673	SNV	p.K656E	3
FGFR1	COSM19176	SNV	p.N546K	3
FGFR1	COSM302229	SNV	p.N546K	3
FGFR1	COSM48380	SNV	p.T141R	3
FGFR1	PM_COSM1456955	SNV	p.T141A	3
FGFR2	COSM49173	SNV	p.K659N	3
FGFR2	COSM683054	SNV	p.K659N	3
FGFR2	COSM49175	SNV	p.K659M	3
FGFR2	PM_B7	SNV	p.K659N	3
FGFR2	COSM36909	SNV	p.K659E	3
FGFR2	COSM29836	SNV	p.A648T	3
FGFR2	COSM36912	SNV	p.N549K	3
FGFR2	COSM36902	SNV	p.N549K	3
FGFR2	PM_COSM3665555	SNV	p.N549S	3
FGFR2	COSM250083	SNV	p.N549H	3
FGFR2	PM_COSM4604460	SNV	p.N549D	3
FGFR2	COSM36913	SNV	p.I547V	3
FGFR2	COSM250081	MNV	p.V395D	3
FGFR2	COSM915493	SNV	p.C382Y	3
FGFR2	COSM36906	SNV	p.C382R	3
FGFR2	COSM36904	SNV	p.Y375C	3
FGFR2	COSM29824	SNV	p.G305R	3
FGFR2	COSM49170	SNV	p.P253R	3
FGFR2	COSM537801	SNV	p.P253L	3
FGFR2	PM_COSM4994845	SNV	p.S252L	3
FGFR2	COSM36903	SNV	p.S252W	3
FGFR3	PM_COSM27138	INS	p.R248_S249insC	3
FGFR3	COSM714	SNV	p.R248C	2
FGFR3	PM_COSM732	INS	p.R248_S249insL	3
FGFR3	COSM29431	SNV	p.S249T	3
FGFR3	COSM715	SNV	p.S249C	2
FGFR3	PM_COSM722	SNV	p.A369A	3
FGFR3	COSM716	SNV	p.G370C	3
FGFR3	COSM17461	SNV	p.S371C	3
FGFR3	PM_B6	indel	p.Y373C	2
FGFR3	COSM718	SNV	p.Y373C	3

FGFR3	COSM24842	SNV	p.G380R	3
FGFR3	COSM51545	SNV	p.G380E	3
FGFR3	OM3151	SNV	p.A393T	3
FGFR3	COSM721	SNV	p.A391E	3
FGFR3	COSM296687	SNV	p.R399C	3
FGFR3	COSM29438	SNV	p.D641N	3
FGFR3	COSM719	SNV	p.K650E	3
FGFR3	COSM726	SNV	p.K650Q	3
FGFR3	COSM720	SNV	p.K650M	3
FGFR3	COSM731	SNV	p.K650T	3
FGFR3	COSM3993567	SNV	p.K652N	3
FGFR3	COSM24802	SNV	p.G697C	3
FGFR3	COSM732992	SNV	p.K715M	3
FGFR4	PM_B1	SNV	p.N535D	3
FGFR4	BT122	SNV	p.N535K	3
FGFR4	BT120	SNV	p.N535K	3
FGFR4	PM_B4	SNV	p.A554D	3
FGFR4	PM_B5	SNV	p.G649D	3

Fusions

Gene Name	Variant ID	Variant Type	aMOI	LOE
FGFR1	FGFR1-ADAM32.F17A14	Fusion	FGFR1 Gene Fusion	2
FGFR1	BCR-FGFR1.B4F10	Fusion	FGFR1 Gene Fusion	2
FGFR1	CNTRL-FGFR1.C40F10	Fusion	FGFR1 Gene Fusion	2
FGFR1	CUX1-FGFR1.C11F10	Fusion	FGFR1 Gene Fusion	2
FGFR1	FGFR1OP-FGFR1.F5F10	Fusion	FGFR1 Gene Fusion	2
FGFR1	FGFR1OP-FGFR1.F6F10	Fusion	FGFR1 Gene Fusion	2
FGFR1	FGFR1OP-FGFR1.F7F10	Fusion	FGFR1 Gene Fusion	2
FGFR1	LRRFIP1-FGFR1.L8F10	Fusion	FGFR1 Gene Fusion	2
FGFR1	MYO18A-FGFR1.M33F10	Fusion	FGFR1 Gene Fusion	2
FGFR1	TRIM24-FGFR1.T11F10	Fusion	FGFR1 Gene Fusion	2
FGFR1	BAG4-FGFR1.B2F6	Fusion	FGFR1 Gene Fusion	2
FGFR1	BAG4-FGFR1.B1F8	Fusion	FGFR1 Gene Fusion	2
FGFR1	ZMYM2-FGFR1.Z17F10	Fusion	FGFR1 Gene Fusion	2
FGFR1	TPR-FGFR1.T22F10	Fusion	FGFR1 Gene Fusion	2
FGFR1	FGFR1OP2-FGFR1.F4F10	Fusion	FGFR1 Gene Fusion	2
FGFR1	WHSC1L1-FGFR1.W14F5	Fusion	FGFR1 Gene Fusion	2
FGFR1	FN1-FGFR1.F22F3	Fusion	FGFR1 Gene Fusion	2
FGFR1	FN1-FGFR1.F23F3	Fusion	FGFR1 Gene Fusion	2
FGFR1	FN1-FGFR1.F23F4	Fusion	FGFR1 Gene Fusion	2
FGFR1	FN1-FGFR1.F28F5	Fusion	FGFR1 Gene Fusion	2

FGFR1	FN1-FGFR1.F22F4	Fusion	FGFR1 Gene Fusion	2
FGFR1	SQSTM1-FGFR1.S6F10	Fusion	FGFR1 Gene Fusion	2
FGFR1	ERVK3_1-FGFR1.E3F10	Fusion	FGFR1 Gene Fusion	2
FGFR1	FGFR1-NTM.F1N2	Fusion	FGFR1 Gene Fusion	2
FGFR1	FGFR1-PLAG1.F1P2.COSF1108	Fusion	FGFR1 Gene Fusion	2
FGFR1	FGFR1-PLAG1.F1P3.COSF1110	Fusion	FGFR1 Gene Fusion	2
FGFR1	FGFR1-TACC1.F17T7.COSF1362	Fusion	FGFR1 Gene Fusion	2
FGFR1	FGFR1-TACC1.F18T7	Fusion	FGFR1 Gene Fusion	2
FGFR1	FGFR1-ZNF703.F14Z2.COSF720	Fusion	FGFR1 Gene Fusion	2
FGFR1	WHSC1L1-FGFR1.W1F2	Fusion	FGFR1 Gene Fusion	2
FGFR1	ERLIN2-FGFR1.E8F2	Fusion	FGFR1 Gene Fusion	2
FGFR1	FGFR1-PLAG1.F2P2.COSF1111	Fusion	FGFR1 Gene Fusion	2
FGFR1	FGFR1-PLAG1.F2P3.COSF1113	Fusion	FGFR1 Gene Fusion	2
FGFR1	CPSF6-FGFR1.C8int8F10	Fusion	FGFR1 Gene Fusion	2
FGFR1	RANBP2-FGFR1.R20F10int9	Fusion	FGFR1 Gene Fusion	2
FGFR2	FGFR2-AHCYL1.F17A2	Fusion	FGFR2 Gene Fusion	2
FGFR2	FGFR2-BICC1.F17B2	Fusion	FGFR2 Gene Fusion	2
FGFR2	FGFR2-BICC1.F17B3.1	Fusion	FGFR2 Gene Fusion	2
FGFR2	FGFR2-BICC1.F17B18	Fusion	FGFR2 Gene Fusion	2
FGFR2	FGFR2-CASP7.F17C2	Fusion	FGFR2 Gene Fusion	2
FGFR2	FGFR2-CCAR2.F17C4	Fusion	FGFR2 Gene Fusion	2
FGFR2	FGFR2-CCDC6.F17C1	Fusion	FGFR2 Gene Fusion	2
FGFR2	FGFR2-CIT.F17C23	Fusion	FGFR2 Gene Fusion	2
FGFR2	FGFR2-COL14A1.F17C34	Fusion	FGFR2 Gene Fusion	2
FGFR2	FGFR2-CREB5.F17C8	Fusion	FGFR2 Gene Fusion	2
FGFR2	FGFR2-FAM76A.F17F2	Fusion	FGFR2 Gene Fusion	2
FGFR2	SLC45A3-FGFR2.S1F1	Fusion	FGFR2 Gene Fusion	2
FGFR2	SLC45A3-FGFR2.S1F2	Fusion	FGFR2 Gene Fusion	2
FGFR2	PARK2-FGFR2.P9F11	Fusion	FGFR2 Gene Fusion	2
FGFR2	CD44-FGFR2.C1F3	Fusion	FGFR2 Gene Fusion	2
FGFR2	CTNNB1-FGFR2.C1F10	Fusion	FGFR2 Gene Fusion	2
FGFR2	PDHX-FGFR2.P1F7	Fusion	FGFR2 Gene Fusion	2
FGFR2	SNX19-FGFR2.S7F7	Fusion	FGFR2 Gene Fusion	2
FGFR2	FGFR2-KCTD1.F17K2	Fusion	FGFR2 Gene Fusion	2
FGFR2	FGFR2-MGEA5.F17M12	Fusion	FGFR2 Gene Fusion	2
FGFR2	FGFR2-NOL4.F17N7	Fusion	FGFR2 Gene Fusion	2
FGFR2	FGFR2-OFD1.F17O3	Fusion	FGFR2 Gene Fusion	2
FGFR2	FGFR2-PPHLN1.F17P3	Fusion	FGFR2 Gene Fusion	2
FGFR2	FGFR2-SHTN1.F17S7	Fusion	FGFR2 Gene Fusion	2
FGFR2	FGFR2-TACC3.F17T11	Fusion	FGFR2 Gene Fusion	2

FGFR2	FGFR2-TXLNA.F17T6	Fusion	FGFR2 Gene Fusion	2
FGFR2	FGFR2-USP10.F17del11U5	Fusion	FGFR2 Gene Fusion	2
FGFR2	FGFR2-CCDC6.F17C2	Fusion	FGFR2 Gene Fusion	2
FGFR2	FGFR2-AFF3.F17A8.1	Fusion	FGFR2 Gene Fusion	2
FGFR2	SNX19-FGFR2.S8F7	Fusion	FGFR2 Gene Fusion	2
FGFR3	ETV6-FGFR3.E5F9	Fusion	FGFR3 Gene Fusion	2
FGFR3	FGFR3-TACC3.F17T10.COSF1434	Fusion	FGFR3 Gene Fusion	2
FGFR3	FGFR3-BAIAP2L1.F17B2.COSF1346	Fusion	FGFR3 Gene Fusion	2
FGFR3	FGFR3-TACC3.F17T8.COSF1353	Fusion	FGFR3 Gene Fusion	2
FGFR3	FGFR3-TACC3.F17T11.COSF1348	Fusion	FGFR3 Gene Fusion	2
FGFR3	FGFR3-TACC3.F15T11	Fusion	FGFR3 Gene Fusion	2
FGFR3	FGFR3-TACC3.F16T10.COSF1359	Fusion	FGFR3 Gene Fusion	2
FGFR3	FGFR3-TACC3.F16T11.COSF1348	Fusion	FGFR3 Gene Fusion	2
FGFR3	FGFR3-TACC3.F17T13.NGS	Fusion	FGFR3 Gene Fusion	2
FGFR3	FGFR3-TACC3.F17T5	Fusion	FGFR3 Gene Fusion	2
FGFR3	FGFR3-TACC3.F17T6	Fusion	FGFR3 Gene Fusion	2
FGFR3	FGFR3-TACC3.F17T9	Fusion	FGFR3 Gene Fusion	2
FGFR3	FGFR3-TACC3.F18T7.NGS	Fusion	FGFR3 Gene Fusion	2
FGFR3	FGFR3-AES.F17A2	Fusion	FGFR3 Gene Fusion	2
FGFR3	FGFR3-ELAVL3.F17E2	Fusion	FGFR3 Gene Fusion	2
FGFR3	FGFR3-TACC3.F14T11	Fusion	FGFR3 Gene Fusion	2
FGFR3	FGFR3-TACC3.F18T4and5	Fusion	FGFR3 Gene Fusion	2
FGFR3	FGFR3-TACC3.F18T10.1	Fusion	FGFR3 Gene Fusion	2
FGFR3	FGFR3-TACC3.F18T10	Fusion	FGFR3 Gene Fusion	2
FGFR3	FGFR3-TACC3.F18T11	Fusion	FGFR3 Gene Fusion	2
FGFR3	FGFR3-TACC3.TruncatedF17T4	Fusion	FGFR3 Gene Fusion	2
FGFR3	FGFR3-TACC3.F17T7	Fusion	FGFR3 Gene Fusion	2
FGFR3	FGFR3-TACC3.F17T10	Fusion	FGFR3 Gene Fusion	2
FGFR3	FGFR3-TACC3.F17T11.1	Fusion	FGFR3 Gene Fusion	2
FGFR3	FGFR3-TACC3.F17T11.2	Fusion	FGFR3 Gene Fusion	2
FGFR3	FGFR3-TACC3.F17T14	Fusion	FGFR3 Gene Fusion	2
FGFR3	FGFR3-TACC3.F18T11del5	Fusion	FGFR3 Gene Fusion	2
FGFR3	FGFR3-TACC3.F18T1	Fusion	FGFR3 Gene Fusion	2
FGFR3	FGFR3-TACC3.F17ins1T10	Fusion	FGFR3 Gene Fusion	2
FGFR3	FGFR3-JAKMIP1.F17J4	Fusion	FGFR3 Gene Fusion	2
FGFR3	FGFR3-TACC3.F17T14.1	Fusion	FGFR3 Gene Fusion	2
FGFR3	FGFR3-FBXO28.F17F4	Fusion	FGFR3 Gene Fusion	2
FGFR3	FGFR3-TACC3.F17intron17T4.1	Fusion	FGFR3 Gene Fusion	2
FGFR3	FGFR3-TACC3.F17Intron17T9	Fusion	FGFR3 Gene Fusion	2
FGFR3	FGFR3-TACC3.F17T4	Fusion	FGFR3 Gene Fusion	2

APPENDIX IX: YOUTH INFORMATION SHEETS

INFORMATION SHEET REGARDING RESEARCH STUDY APEC1621B (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 blood. If you agree, we will draw two additional blood samples from you. 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 APEC1621B
(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 erdafitinib, and so you have been assigned to erdafitinib. The doctors want to see if erdafitinib will make children with your type of cancer get better. We don't know if erdafitinib will work well to get rid of your cancer. That is why we are doing the study.

   Sometimes good things can happen to people when they are in a research study. These good things are called "benefits." We hope that a benefit to you of being part of this study is that tipifarnib 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 tipifarnib. Your doctor will talk to you about the risks we know about from tipifarnib. There may be other risks from tipifarnib 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 blood. If you agree, we will draw two additional blood samples from you. 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 X CTEP AND CTSU REGISTRATION PROCEDURES

INVESTIGATOR AND RESEARCH ASSOCIATE REGISTRATION WITH CTEP

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

RCR utilizes five person registration types.

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

RCR requires the following registration documents:

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

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

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

In addition, all investigators acting as the Site-Protocol PI (investigator listed on the IRB approval),

consenting/treating/drug shipment investigator in OPEN, or as the CI on the DTL must be rostered at the enrolling site with a participating organization.

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

CTSU REGISTRATION PROCEDURES

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

Protocol-Specific Requirements For Site Registration:

- IRB approval (For sites not participating via the NCI CIRB; local IRB documentation, an IRB-signed CTSU IRB Certification Form, Protocol of Human Subjects Assurance Identification/IRB Certification/Declaration of Exemption Form, or combination is accepted)
- This is a study with a radiation and/or imaging (RTI) component and the enrolling site must be aligned to an RTI provider. To manage provider associations or to add or remove associated providers, access the Provider Association page from the Regulatory section on the CTSU members' website at https://www.ctsu.org/RSS/RTFProviderAssociation. Sites must be linked to at least one Imaging and Radiation Oncology Core (IROC) provider to participate on trials with an RTI component. Enrolling sites are responsible for ensuring that the appropriate agreements and IRB approvals are in place with their RTI provider. An individual with a primary role on a treating site roster can update the provider associations, though all individuals at a site may view provider associations. To find who holds primary roles at your site, view the Person Roster Browser under the RUMS section on the CTSU website.

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

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

Institutions with patients waiting that are unable to use the Regulatory Submission Portal should alert the CTSU Regulatory Office immediately by phone or email: 1-866-651-CTSU (2878), or CTSURegHelp@coccg.org in order to receive further instruction and support.

Checking Your Site's Registration Status

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

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

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

Data Submission / Data Reporting

Medidata Rave is 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 email from iMedidata. To accept the invitation, site staff must either click on the link in the email or log in to iMedidata via the CTSU members' website under *Data Management* > *Rave Home* and click *accept* the invitation in the *Tasks* pane located in the upper right-corner of the iMedidata screen. Site staff will not be able to access the study in Rave until all required Medidata and study specific trainings are completed. Trainings will be in the form of electronic learnings (eLearnings) and can be accessed by clicking on the eLearning link in the *Tasks* pane located in the upper right corner of the iMedidata screen. If an eLearning is required for a study and has not yet been taken, the link to the eLearning will appear under the study name in the *Studies* pane located in the center of the iMedidata screen; once the successful completion of the eLearning has been recorded, access to the study in Rave will be granted, and a *Rave EDC* link will replace the eLearning link under the study name.

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

Data Quality Portal

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

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

and timeliness reports. Review the DQP modules on a regular basis to manage specified queries and delinquent forms.

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

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

APPENDIX XI 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