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The world's childhood cancer experts

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A National Cancer Institute-supported member group of the National Clinical Trials Network

December 9, 2020

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

Dear Ms. Kruhm,

APEC1621J, *NCI-COG Pediatric MATCH (Molecular Analysis for Therapy Choice) - Phase 2 Subprotocol of BVD-523FB (ulixertinib) in Patients with Tumors Harboring Activating MAPK Pathway Mutations*. A dose modification table for diarrhea has been added along with an additional appendix for the treatment of diarrhea. In addition, there have been various administrative changes added to this amendment. These changes are outlined in a point-by-point summary below. No changes have been made to the informed consent document.

Please contact us if you have further questions.

Sincerely,

Samuel Baird, MPH, Protocol Coordinator for
Kieuhoa T. Vo, MD MAS, **APEC1621J** Study Chair
Douglas Hawkins, M.D., Chair, Children's Oncology Group

SUMMARY OF CHANGES

The following specific revisions have been made to the protocol and informed consent document. Additions are in **boldfaced font** and deletions in ~~strikethrough font~~.

I. Protocol Changes made by the Principal Investigator:

#	Section	Page(s)	Comments
1.	throughout	-	The amendment # and version date have been updated.
2.	Contact Information	2	Included updated, templated language for contact information from NCTN protocol template, based on recommendation received from CTEP 3/25/2020.
3.	Table of Contents	3-5	Updated for repagination
4.	Study Committee	6	• Replaced ~~Dr. Peter C. Adamson~~ with **Dr. Douglas Hawkins** • Updated Dr. Fox's info
5.	COG Operations Staff	7	• Removed ~~222 East Huntington Dr. Suite 100~~ from all COG staff info. • Removed ~~Nita Tawdros~~ as scientific writer and replaced with **Samuel Baird**. • Removed ~~Jonathan Bennett~~ as RC and replaced with **Bumjin Lee**.
6.	6.4	27-29	Section **6.4 Dose Modifications for GI Toxicities (Nausea, Vomiting, Dehydration)** was added.
7.	8.4.5	36	Deleted, ~~Each sample must be labeled with the patient's study registration number, the study I.D# (APEC1621J), and the date and time the sample was drawn. Data should be recorded on the Pharmacokinetic Study Form, which must accompany the sample(s).~~" And replaced with… "**Each tube must be labeled with the patient's study registration number, the study I.D (APEC1621J), and the date and time the sample was drawn. Data should be recorded on the appropriate transmittal form found in RAVE**.
8.	8.4.6	36	Updated PK sample shipment contact info for Covance.
9.	9.1.3	38	Added, "**size 0**" to clarify capsule size for participating sites.
10.	Appendix IX	94-99	**Added updated templated language** from newest NCTN protocol template.
11.	Appendix XIII	105	**Added Appendix for the treatment of diarrhea.**

Activated:10/01/2018
Closed:

Version Date: 12/09/2020
Amendment# 3

CHILDREN'S ONCOLOGY GROUP

APEC1621J

NCI-COG PEDIATRIC MATCH (MOLECULAR ANALYSIS FOR THERAPY CHOICE)- PHASE 2 SUBPROTOCOL OF BVD-523FB (ULIXERTINIB) IN PATIENTS WITH TUMORS HARBORING ACTIVATING MAPK PATHWAY MUTATIONS

Open to COG Member Institutions in the USA

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CONTACT INFORMATION		
To submit site registration documents:	**For patient enrollments:**	**Submit study data**
Regulatory documentation must be submitted to the CTSU via the Regulatory Submission Portal. Regulatory Submission Portal: (Sign in at www.ctsu.org, and select the Regulatory Submission sub-tab under the Regulatory tab.) Institutions with patients waiting that are unable to use the Portal should alert the CTSU Regulatory Office immediately at 1-866-651-2878 to receive further instruction and support. Contact the CTSU Regulatory Help Desk at 1-866-651-2878 for regulatory assistance.	Please refer to the patient enrollment section of the protocol for instructions on using the Oncology Patient Enrollment Network (OPEN) which can be accessed at https://www.ctsu.org/OPEN_SYSTEM/ or https://open.ctsu.org. Contact the CTSU Help Desk with any OPEN-related questions at 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 Web page of the CTSU Member Web site located at 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 user log on with 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 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 Agent :
BVD-523FB (ulixertinib)
(NSC#799018)
IND Sponsor: DCTD, NCI

SEE SECTION 8.4.6 AND 8.5.6 FOR SPECIMEN SHIPPING ADDRESSES

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

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ABSTRACT

This subprotocol is a component of the Pediatric MATCH trial APEC1621. The APEC1621SC screening protocol details the assay used for the integral genomic profiling which will determine eligibility for this subprotocol. This is a phase 2 trial of BVD-523FB (ulixertinib) in children with relapsed or refractory solid tumors (including Non-Hodgkin lymphomas, histiocytoses and CNS tumors) harboring specified activating mutations of the MAPK pathway. BVD-523FB (ulixertinib) is a novel, reversible, ATP-competitive ERK1/2 inhibitor with high potency and ERK1/2 selectivity. BVD-523FB (ulixertinib) will be given at the dose determined by the dose escalation table (or at the established MTD/RP2D once dose escalation phase has been completed) twice daily continuously for 28-day cycles. The primary endpoint will be objective response rate as determined by RECIST. Progression free survival (PFS) will be assessed as a secondary endpoint.

EXPERIMENTAL DESIGN SCHEMA

Treatment Schedule Table	
Days 1-28	BVD-523FB (ulixertinib)
Day 28	Evaluation

Patients will receive BVD-523FB (ulixertinib) at a dose determined by the dose escalation table (Section 5.1.1) (or at the established MTD/RP2D once dose escalation phase has been completed) will be administered twice daily per nomogram by mouth on an empty stomach. One treatment cycle is 28 days. Evaluations will occur every other cycle x 3, then every 3 cycles.

Therapy will be discontinued if there is evidence of progressive disease or drug related dose-limiting toxicity that requires removal from therapy (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 BVD-523FB (ulixertinib) with advanced solid tumors (including CNS tumors), Non-Hodgkin lymphomas or histiocytic disorders that harbor activating genetic alterations in the MAPK pathway.

1.2 Secondary Aims

1.2.1 To estimate the progression free survival in pediatric patients treated with BVD-523FB (ulixertinib) with advanced solid tumors (including CNS tumors), Non-Hodgkin lymphomas or histiocytic disorders that harbor activating genetic alterations in the MAPK pathway.

1.2.2 To obtain information about the tolerability of BVD-523FB (ulixertinib) in children and adolescents with relapsed or refractory cancer.

1.2.3 To provide preliminary estimates of the pharmacokinetics of BVD-523FB (ulixertinib) in children and adolescents with relapsed or refractory cancer.

1.3 Exploratory Aims

1.3.1 To evaluate other biomarkers as predictors of response to BVD-523FB (ulixertinib) and specifically, whether tumors that harbor different mutations or fusions will demonstrate differential response to BVD-523FB (ulixertinib) treatment.

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

2.0 BACKGROUND

2.1 Introduction/Rationale for Development

A critical hallmark of cancer is the activation of cell-growth signaling cascades independent of appropriate growth stimuli. A canonical example of a cell growth control circuit is the mitogen-activated protein kinase, or MAPK, pathway. The RAS–RAF–MEK–ERK pathway, also known as the classical MAPK pathway, is responsible for controlling multiple key physiological processes, making it an attractive therapeutic target in cancer.[1] Here, surface receptors activated by growth ligands signal via downstream effectors in a linear relay system: RAS family GTPases activate RAF family protein kinases, which in turn trigger a phosphorylation cascade involving MEK and ERK family kinases. ERK kinases activate an array of direct effectors that ultimately translate growth signaling into essential cellular functions including cell division and cell survival.

Aberrant activation of the MAPK pathway is frequently observed in cancer. Often, components of the MAPK pathway undergo direct genetic mutation, causing constitutive activation of the signaling cascade in the absence of appropriate ligands. This commonly

occurs through gain-of-function mutations in genes encoding RAS and RAF family members as well as by loss of NF1. Among the malignances seen in pediatric and young adult population with known MAPK pathway aberrations include: hematological and lymphoid malignancies (activating N/K RAS mutations, 20%), rhabdomyosarcoma (activating BRAF, NRAS and PTPN11 mutations 20%), low grade glioma (activating mutation or fusion in BRAF 70-100%), as well as in glioblastoma multiforme (loss of NF-1, 15%), neuroblastoma (activating mutations in NRAS, PTPN11, 2.9-3.6%) malignant peripheral nerve sheath tumors (NF1 loss 40-88%) and melanoma (activating mutation in BRAF, 86%).[2-6]

There are several pre-clinical studies demonstrating the efficacy of inhibitors of MAPK pathway aberrations in pediatric tumors. For example, MEK/ERK inhibitor UO126 has shown to inhibit growth of rhabdomyosarcoma both as a single agent *in vivo* and *in vitro* as well as in combination with dual PI3K/mTOR inhibitor PI103.[7,8] In addition, *in vitro* and *in vivo* synergy has also been seen between inhibitors of TORC1/2 (AZD8055), and MEK (AZD6244) in embryonal rhabdomyosarcoma.[9] Pre-clinical data also support potential activity for MEK inhibitors against neuroblastoma with MAPK gene mutations.[6] Lastly, NF-1 deficiency has shown to be predictive of sensitivity to MEK inhibitors *in vitro* in glioblastoma multiforme.[10] In preclinical studies, some *MAP2K1* mutations are sensitive to MEK inhibition.[11,12]

There is clinical evidence supporting diverse alterations in multiple MAPK genes as biomarkers for response to RAF and MEK inhibitors. These examples include: activating RAS gene mutations (NRAS/KRAS/HRAS); activating BRAF mutations (V600E and others) and fusions; GNAQ and GNA11 activating mutations; inactivating mutations in PTPN11 and loss of NF1 through inactivating mutations or insertion/deletion.[13]

The US Food and Drug Administration (FDA) has approved two selective BRAF inhibitors, vemurafenib and dabrafenib, as monotherapies for patients with $BRAF^{V600}$-mutant metastatic melanoma. Though response rates can be as high as 50%, duration of response is often measured in months, not years. MEK inhibitors have shown clinical responses in patients with BRAF mutated melanoma refractory to BRAF inhibitors leading to FDA approval of trametinib for refractory melanoma both as a single agent as well as in combination with BRAF inhibitor dabrafenib.[14,15] In addition, first-line use of trametinib administered in combination with dabrafenib offers an even greater improvement in overall survival compared with vemurafenib monotherapy, without increased overall toxicity, highlighting the potential usefulness of simultaneously targeting multiple stages of the MAPK signaling pathway.[16]

Similarly, MEK inhibitors have also shown clinical responses (20% with PR) in melanoma with NRAS mutated melanomas.[17] In patients with KRAS mutant lung cancers MEK inhibitors combined with gemcitabine improves response rate and event-free survival.[18] There is pre-clinical evidence for activity of MEK inhibitors in *NF1* deficient neurofibromas and melanomas and a phase 1 trial of selumetinib (AZD6244) demonstrated clinical responses in 17/24 (17%) pediatric patients with neurofibromatosis-1 (NF-1) with large plexiform neurofibroma.[13,19,20] In uveal melanoma, which is characterized by mutations in GNAQ and GNA11, G-binding protein alpha subunits that signal via the MAPK pathway, selumetinib (AZD6244) results in a higher response rate and prolonged progression free survival when compared with chemotherapy.[21]

BVD-523FB (ulixertinib) represents a new targeted inhibitor of the MAPK pathway,

specifically targeting ERK1 and ERK2 protein kinases. Although BRAF- and/or MEK-targeted therapy has demonstrated significant clinical benefit, we know from the adult experience that the majority of patients develop resistance and disease progression after approximately 12 months.[22] Since reactivation of ERK signaling is a common driver of resistance in this setting, the clinical development of small-molecule ERK inhibitors is of considerable interest. Moreover, ERK signaling represents a key downstream effector of RAS mutations in many cancer types, suggesting that ERK inhibitors might eventually have multiple indications in oncology.

2.2 Preclinical Studies

2.2.1 Antitumor Activity

BVD-523FB (ulixertinib) is a novel, reversible, ATP-competitive ERK1/2 inhibitor with high potency and ERK1/2 selectivity. BVD-523FB (ulixertinib) potently inhibits growth and survival in cultured cancer cell lines; melanoma, colorectal and pancreatic lines harboring *BRAF* or *RAS* mutations are among those most susceptible to the drug.[23] In *in vivo* xenograft studies, BVD-523 showed dose-dependent growth inhibition and tumor regression. BVD-523 yielded synergistic anti-proliferative effects in a BRAFV600E mutant melanoma cell line xenograft model when used in combination with BRAF inhibition. Antitumor activity was also demonstrated in *in vitro* and *in vivo* models of acquired resistance to single-agent and combination BRAF/MEK targeted therapy.[23] Based on these promising results, these studies demonstrate BVD-523FB (ulixertinib) holds promise as a treatment for ERK-dependent cancers, including those whose tumors have acquired resistance to other treatments targeting upstream nodes of the MAPK pathway.

2.2.2 Animal Toxicology

When BVD-523 was characterized using *in vitro* screens against 66 receptors and ion channels no toxicologically significant interactions were identified. Additionally, BVD-523 was negative in bacterial mutation and *in vivo* micronucleus screening assays, so BVD-523 is not considered to have a significant genetic toxicology risk.[24]

While BVD-523 modestly inhibits the hERG current (IC_{50} 3.4 μM), no significant effects were seen in action potentials recorded from dog Purkinje fibers exposed to up to 10 μg/mL, and no significant cardiovascular findings were observed upon acute oral dosing of the compound at dose levels up to 50 mg/kg in dogs (C_{max} = 17.3 μM). Thus BVD-523 is considered to have a low potential to cause QT prolongation in patients, but the study will monitor for signs of cardiovascular effects of BVD-523 in humans.[24]

No significant cytochrome P450 (CYP) inhibition has been observed with the compound. *In vitro* studies suggest that the compound is metabolized primarily via oxidation by multiple CYPs, including 3A4, 2D6, and 1A2. Furthermore, no significant CYP induction was observed after up to 14 days drug treatment in rats, nor during *in vitro* studies with human hepatocytes. These data suggest a limited potential for drug-drug interactions.[24]

BVD-523 HCl salt is orally available in multiple species (absolute bioavailability %F = 23% in dog to 100% in monkey) when formulated as a simple suspension in 1% carboxymethylcellulose (CMC) and has a half-life of 2−4 hours across all species.[24]

BVD-523 was administered to male and female Sprague-Dawley rats in several toxicology studies: a GLP study for up to 28 days at dose levels up to 50 mg/kg/day twice daily; for up to 14 days at dose levels up to 100 mg/kg twice daily; and for up to 5 days at dose levels up to 150 mg/kg/dose once daily. The incidence and severity of mineralization seen in these studies was dose-dependent and effects were observed in 1 or more tissues at toxic doses. In animals in which mineralization occurred after treatment with BVD-523, significantly increased serum phosphorus and modestly decreased serum calcium were seen; these effects were not observed in animals in which there was no mineralization. Therefore, the risk of tissue mineralization can be assessed by serum phosphorus and calcium monitoring. A clinical monitoring strategy similar to this was previously employed for related drugs that target the MAPK pathway because those compounds likewise elicited mineralization in rodents.[24]

When BVD-523 was administered to male and female Sprague-Dawley rats for up to 28 days at a dose level of 25 or 50 mg/kg twice daily, it was poorly tolerated. Although most clinical signs and clinical pathology findings reversed following 4 weeks of recovery, skin lesions and histopathology findings persisted in many tissues at both dose levels after the recovery phase. Based on these findings, 25 and 50 mg/kg twice daily dose levels were considered severely toxic. Administration of 12.5 mg/kg twice daily for 28 days was generally well-tolerated by rats of both sexes; however, this dose level was associated with test article-related findings that included: swelling in the neck; decreased forelimb strength; multiple clinical pathology findings; enlarged lymph nodes, spleen, and mammary gland. Based on these findings, the severely toxic dose in 10% of the animals (STD10) for BVD-523 when administered for up to 28 days in Sprague-Dawley rats is 12.5 mg/kg given twice daily (25 mg/kg/day). On Day 28 of the dosing phase, this dose level corresponded with a C_{max} of 28700 and 15323 ng/mL and AUC_{0-12} of 264868 and 124341 hr.ng/mL for males and females, respectively.[24]

BVD-523 was administered to male and female beagle dogs for up to 28 days at dose levels of 15, 5, or 2 mg/kg twice daily. Initial analysis of the toxicity profile observed shows that BVD-523 was well tolerated in dogs. The rat was designated the most sensitive species and rat data were used to calculate the starting dose in humans.[24]

BVD-523 has a measured UV absorbance at 320 nm, which means that it can absorb both UV-A and UV-B. BVD-523 may therefore act as a photosensitizing agent in humans.[24]

Based on the data accumulated to date, BVD-523 possesses a toxicology profile which presents no impediment to its development as an anti-cancer agent.

2.3 Adult Studies

2.3.1 Phase 1 Studies

The final results of the first in human, phase 1 study of BVD-523FB (ulixertinib), NCT01781429) were recently presented at the American Society of Clinical Oncology (ASCO) annual conference, with a more detailed follow up publication.[25,26] A total of 135 patients were enrolled in the dose escalation and dose expansion phases of the study. Twenty-seven patients were enrolled in the dose escalation phase (10-900 mg BID). The maximum tolerated dose (MTD) and recommended phase 2 dose (RP2D) was determined to be 600 mg twice daily given continuously. Dose-limiting toxicities (DLT) included rash, diarrhea, elevated AST, and elevated creatinine. Drug exposure was dose proportional up to the RP2D, which provided near-complete inhibition of ERK activity in whole blood. In expansion cohort (108 patients), there were no drug related deaths; however, 65% of patients in cohort expansion had dose interruptions for adverse events regardless of attribution, with a median dose intensity of 89% at the RP2D. The most common adverse events were rash (76%), diarrhea (48%), fatigue (42%), and nausea (42%). In addition to 3 patients with partial responses during escalation (12%), an additional 11 of 81 (14%) evaluable patients at expansion had a partial response: 1 *BRAF* V600E mutant melanoma patient refractory to prior BRAF/MEK inhibitor treatment, 3 *NRAS* mutant melanoma patients, 2 patients with *BRAF* V600E mutant lung cancers including response in brain metastases, 1 patient with *BRAF* L597Q mutant lung cancer, 1 with *BRAF* V600E mutant glioblastoma multiforme, 1 with *BRAF* G469A head & neck cancer, 1 with *BRAF* G469A small bowel cancer, and 1 with *BRAF* L485W gallbladder cancer. The duration of response ranged from 2 to 24+ months.

Based on these data it was concluded that BVD-523FB (ulixertinib) at 600 mg twice a day has an acceptable safety profile and has produced durable responses in patients with *NRAS* mutant melanoma, *BRAF* V600 and non-V600 mutant solid tumors including melanoma, glioblastoma multiforme, gallbladder, head and neck cancers, and lung cancers with clear CNS activity. BVD-523FB (ulixertinib) also resulted in durable responses in patients who progressed on prior BRAF +/- MEK inhibitor treatment or who were treatment naïve. A cohort-expansion phase (Part 2 of Study BVD-523-01) to assess response in particular tumor types and/or cancers harboring specific activating mutations in the MAPK pathway is ongoing.

Phase 1 studies of BVD-523FB (ulixertinib) in combination with chemotherapy are ongoing: BVD-523FB (ulixertinib) combined with palbociclib patients in advanced pancreatic and other solid tumors (NCT03454035); and BVD-523FB (ulixertinib) with nab-paclitaxel and gemcitabine in patients with metastatic pancreatic cancer (NCT02608229).

2.3.2 Phase 2 Studies

No phase 2 studies of BVD-523FB (ulixertinib) have been completed to date. A phase 2 trial of BVD-523FB (ulixertinib) will be studied in uveal melanoma (NCT03417739).

While the preclinical toxicology studies of BVD-523 have not revealed any exposure-dependent ophthalmological toxicities, based on clinical studies of MEK1/2 inhibitors which highlighted ocular toxicities that may reflect mechanistically attributable risks observable in a proportion of patients, clinical studies of BVD-523 have included close monitoring for ocular toxicities. In the ongoing clinical trials to date, the following treatment-emergent adverse events (TEAEs) have been rarely reported: visual impairment (5 patients), vision blurred (3 patients), vitreous floaters (2 patients), and, in single patients, abnormal sensation in eye, chorioretinopathy, vision blurred, halo vision, retinal detachment, retinopathy. While it is not definitively understood whether ocular toxicities reflect primary pharmacology associated with global inhibition of the MAPK pathway, specific management and exclusion criteria will be defined in this study protocol as the toxicities could potentially severely and irreversibly impact patient well-being.

2.3.3 Pharmacology/Pharmacokinetics/Correlative and Biological Studies

Absorption:
Orally administered BVD-523 at doses ranging from 10 to 900 mg BID was generally slowly absorbed in patients with advanced malignancies, with individual t_{max} values of 2 to 8 hours at dose levels of 10 to 150 mg BID, and median t_{max} values of 3 to 4 hours at dose levels of 300 to 900 mg BID. After reaching C_{max}, plasma BVD-523 concentrations remained somewhat sustained for approximately 2-4 hours.[24,25]

Exposure (C_{max} and AUC0-12) to BVD-523, as well as selected metabolites, generally increased in a dose-related fashion from dose levels of 10 to 600 mg BVD-523 BID. At Day 1, a further increase in exposure was seen at 750 mg BVD-523 BID, but exposure was similar between 750 and 900 mg BID. At Day 15, no further increase in exposure was observed as the dose increased from the 600 to 900 mg BVD-523 BID, though this may in part be due to a limited number of patients treated at these higher dose levels. [24,25]

At Day 15, minimal accumulation of BVD-523 and metabolites were observed at the 10, 20, and 300 mg dose levels, whereas accumulation compared to Day 1 ranged from approximately 1.3 to 4.0-fold for the other dose levels. Pre-dose concentrations on Day 22 were generally similar to those on Day 15, indicating that steady state had been attained by Day 15.[24]

The combined AUC values of the three BVD-523 metabolites measured represented a maximum of 42% of that of BVD-523, indicating that the plasma exposure to drug-derived material was mainly to the parent drug. Moderate between-subject variability was seen in plasma exposure to the metabolites.[24]

Metabolism:
The majority of identified drug derived material in plasma was due to parent drug, with the plasma concentrations of metabolites relatively low at all dose levels. Metabolite-to-parent AUC_{0-12} ratios for three selected metabolites ranged from 0.0313 to 0.292. For individual subjects, the sum of the AUC_{0-12} values for the three metabolites represented 9.57 to 41.6% of the AUC_{0-12} values for BVD-523.[24]

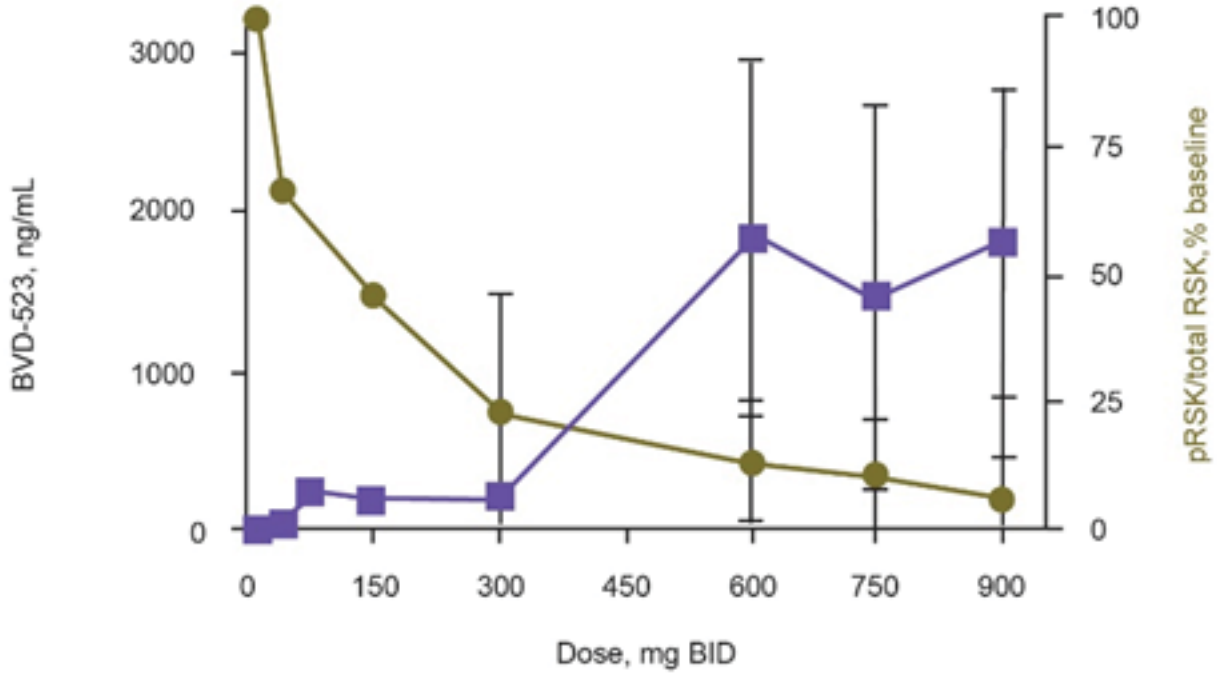
Elimination:
After reaching C_{max}, plasma concentrations of BVD-523 declined slowly. Since plasma drug concentrations were measured only up to 12 hours after the morning dose, it was not possible to calculate an effective or terminal phase. Based on limited data, the estimated $T_{1/2}$ values ranged from 3.60 to 5.91 hours on Days 1 and 15. However, these values should be interpreted with caution, because the true elimination phase at the higher doses may not have been captured.[24]

The urinary excretion of unchanged BVD-523 was negligible (<0.2% of the dose) at all dose levels within 12 hours post-dose, and was not dose-related within the very low percentage range observed.[24]

Renal clearance of BVD-523 appeared to be dose-independent. Individual renal clearance values ranged from 0.128 to 0.0895 L/hr (where n=1 per dose level) and mean values ranged from 0.0149 to 0.0300 L/hr (where n≥3).[24]

Clinical Pharmacology:
In preliminary studies, measurements of phorbol ester-dependent RSK phosphorylation of whole blood samples collected from patients dosed orally with BVD-523 have demonstrated dose- and concentration-dependent bioactivity of BVD-523 (Figure 1). These ERK inhibitory effects are manifest following a single dose of BVD-523 and after repeated dosing, showing biological activity consistent with the mechanism of action of BVD-523.[24 25]

Figure 1: Patient Blood Samples Show Dose- and Concentration-Dependent Activity of BVD-523



Detailed analysis of the effects of BVD-523FB (ulixertinib) on 24 patients in dose escalation and 81 patients from cohort expansion has been published. [27]. Twelve hours of ECG data were collected through the use of continuous Holter monitors

on days 1 and 15 for these patients, along with 12-lead ECGs in triplicate at PK timepoints for a subset of patients. Exposure-response modeling (ERM) provided a robust linear model between QTc and BVD-523FB (ulixertinib) C_{max}, showing positive but not statistically significant correlation of 0.53 ms per μg/mL. At expected exposures, upper 90% confidence intervals would predict a change to the QTc of < 10 ms. No changes on PR or QRS intervals was seen. In summary, the risk of QT/QTc prolongation with BVD-523FB (ulixertinib) is low.[24]

2.4 Pediatric Studies

2.4.1 Prior Experience in Children

There have been no prior studies of BVD-523FB (ulixertinib) in children.

2.4.2 Pharmacology/Pharmacokinetics/Correlative Biological Studies

There have been no pediatric Pharmacology/Pharmacokinetics/Correlative Biological Studies of BVD-523FB (ulixertinib).

2.5 Overview of Proposed Pediatric Study

This is a phase 2 trial of BVD-523FB (ulixertinib) in children with recurrent or refractory solid tumors, CNS tumors, non-Hodgkin lymphomas and histiocytic disorders harboring specific activating mutations that result in pathologic activation of the MAPK pathway.

Because the pediatric dose of BVD-523FB (ulixertinib) has not been established, there will be a limited dose finding phase consisting of the first 12 evaluable patients enrolled on study. BVD-523FB (ulixertinib) will be administered for 28-day cycles twice daily per nomogram by mouth on an empty stomach. The first 6 evaluable patients will be enrolled at a dose of 260 mg/m^2/dose BID (450 mg BID Max Dose), equivalent to 75% of the maximum tolerated dose (MTD) in adults. There will be a single dose escalation to 350 mg/m^2/dose BID (100% of the adult MTD [600 mg BID Max Dose]) or de-escalation to 175 mg/m^2/dose BID (50% of the adult MTD [300 mg BID Max Dose]) for the next six subjects. Following the first 12 evaluable patients, all subsequent patients will be enrolled at the highest dose level not exceeding the pediatric MTD. Patients enrolled in the dose escalation component will be included in the analysis of efficacy.

The primary aim of this trial will be to establish the objective response rate to BVD-523FB (ulixertinib). While there will not be multiple pre-determined mutation-based cohorts, responses will be analyzed retrospectively with respect to specific MAPK pathway activating mutations.

Key secondary objectives include further evaluation of the tolerability of BVD-523FB (ulixertinib) in pediatric patients. Toxicity will be assessed using CTCAE V5.0. Imaging for disease evaluation will occur every other cycle x 3, then every three cycles. Disease response will be assessed according to RECIST v1.1 for solid tumors and 2-dimensional measurement for CNS tumors.

3.0 SCREENING AND STUDY ENROLLMENT PROCEDURES

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.

Access requirements for OPEN:
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://open.ctsu.org . Registrars must hold a minimum of an AP registration type.

All site staff will use OPEN to enroll patients to this study. It is integrated with the CTSU Enterprise System for regulatory and roster data and, upon enrollment, initializes the patient position in the Rave database. 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. To assign an IVR or NPIVR as the treating, crediting, consenting, drug shipment (IVR only), or investigator receiving a transfer in OPEN, the IVR or NPIVR must list on their Form FDA 1572 in RCR the IRB number used on the site's IRB approval. Please see Appendix IX for detailed CTEP and CTSU Registration Procedures including: registration in Registration and Credential Repository (RCR), requirements for site registration, submission of regulatory documents and how to check your site's registration status.

3.1 Genetic Screening Procedures for Eligibility

Patient enrollment onto the APEC1621SC screening protocol is required. Tumor and blood samples will be obtained and the results of the evaluation of the tumor specimens will determine if the patient's tumor has an actionable Mutation of Interest (aMOI) for which a MATCH treatment subprotocol is available.

The treatment assignment to MATCH to a subprotocol (if a relevant aMOI is detected) will be communicated to the enrolling institution via the COG or MATCHBox treatment assignment mechanism at the time the results of MATCH are returned, upon which a reservation to APEC1621J 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 APEC1621J.

3.2 IRB Approval

In order to participate in Pediatric MATCH, an institution must participate in the NCI Pediatric CIRB. NCI Pediatric CIRB approval of this study must be obtained by a site prior to enrolling patients

Submitting Regulatory Documents: Submit required forms and documents to the CTSU Regulatory Office, where they will be entered and tracked in the CTSU RSS.

Online: http://www.ctsu.org (members' section) → Regulatory Submission Portal
Regulatory Help Desk: 866-651-2878

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. However, sites must submit a Study Specific Worksheet for Local Context (SSW) to the CIRB (via IRBManager) to indicate their intention to open the study locally. The CIRB's approval of the SSW is then communicated to the CTSU Regulatory Office for compliance in the RSS. The Signatory Institution must inform the CTSU which CIRB-approved institutions aligned with the Signatory Institution are participating in the study so that the study approval can be applied to those institutions. Other site registration requirements (e.g., laboratory certifications, protocol-specific training certifications, or modality credentialing) must be submitted to the CTSU Regulatory Office or compliance communicated per protocol instructions.

3.3 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.

3.4 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.

3.5 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.

3.6 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 12 weeks (84 days) of treatment assignment. Protocol therapy must start no later than 7 calendar days after the date of enrollment. Patients enrolling onto APEC1621J will have a COG ID obtained through their prior enrollment onto the screening protocol or from a prior COG study.

Note: No starter supplies will be provided. Drug orders of BVD-523FB (ulixertinib) should be placed with CTEP after enrollment and treatment assignment to

APEC1621J with consideration for timing of processing and shipping to ensure receipt of drug supply prior to start of protocol therapy

3.7 **Institutional Pathology Report**
The institutional pathology report from the tumor specimen submitted for sequencing will have been uploaded into RAVE immediately following enrollment on the APEC1621 master screening protocol.

3.8 **Dose Assignment**
The dose level will be assigned via OPEN at the time of study enrollment.

4.0 PATIENT ELIGIBILITY

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

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

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

4.1 Inclusion Criteria

4.1.1 APEC1621SC: Patient must have enrolled onto APEC1621SC and must have been given a treatment assignment to MATCH to APEC1621J based on the presence of an actionable mutation as outlined 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 ≥ 0.54 m^2 at the time of study 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 tumor that is measurable in two perpendicular diameters on MRI and visible on more than one slice.

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 BVD-523FB (ulixertinib) or other ERK inhibitors.

4.1.7 Organ Function Requirements

4.1.7.1 Adequate Bone Marrow Function Defined as:

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

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

4.1.7.1.a (may receive transfusions provided they are not known to be refractory to red cell or platelet transfusions). These patients will not be evaluable for hematologic toxicity.

4.1.7.2 Adequate Renal Function Defined as:

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

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

The threshold creatinine values in this Table were derived from the Schwartz formula for estimating GFR (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:

- Shortening fraction of ≥ 27% by echocardiogram, or
- Ejection fraction of ≥ 50% by gated radionuclide study.
- QTc interval ≤ 480 milliseconds

4.1.8 Patients must be able to swallow intact capsules.

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

4.2 Exclusion Criteria

4.2.1 Pregnancy or Breast-Feeding

Pregnant or breast-feeding women will not be entered on this study due to risks of fetal and teratogenic adverse events as seen in animal/human studies. Pregnancy tests must be obtained in girls who are post-menarchal. Males or females of reproductive potential may not participate unless they have agreed to use an effective contraceptive method for the duration of study treatment and for 3 months after last dose of BVD-523FB (ulixertinib).

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

4.2.2.6 CYP2D6 and CYP1A2: Patients who are currently receiving drugs that are strong inducers or inhibitors of CYP1A2 and CYP2D6 are not eligible. Strong inhibitors of CYP1A2 (eg., ciprofloxacin, enoxacin, fluvoxamine, zafirlukast) should be avoided from 14 days prior to enrollment to the end of the study. Strong inhibitors of CYP2D6 (e.g., bupropion, paroxetine, fluoxetine, quinidine, terbinafine) should also be avoided from 14 days prior to enrollment to the end of the study.

4.2.2.7 Patients with known significant ophthalmologic conditions (uncontrolled glaucoma, history of retinal vein occlusion or retinal detachment, excluding patients with longstanding findings secondary to existing conditions) are not eligible.

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

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

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

5.0 TREATMENT PROGRAM

5.1 Overview of Treatment Plan

Treatment Schedule Table	
Days 1-28	BVD-523FB (ulixertinib) orally twice daily
Day 28	Evaluation

Patients will receive BVD-523FB (ulixertinib) twice daily, continuously for 28-day cycles (please see dosing nomogram in Appendix V). Evaluations will occur at the end of every other cycle x 3, then every 3 cycles. A cycle may be repeated up to a total duration of therapy of 2 years (maximum 26 cycles).

Drug doses should be adjusted based on the BSA calculated from height and weight measured within 7 days prior to the beginning of each cycle. Take by mouth on an empty stomach either 1 hour before a meal or 2 hours after a meal. Capsules should not be opened, crushed or chewed. If a patient misses or vomits a dose of BVD-523FB (ulixertinib), an additional dose should not be taken. Patients should resume dosing at the next scheduled time.

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).

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

Dose Level	BVD-523FB (ulixertinib)Dose (mg/m^2)
-1	175 mg/m^2/dose PO BID* (300 mg BID Max Dose)
1*	**260 mg/m^2/dose PO BID* (450 mg BID Max Dose)**
2	350 mg/m$^{2/}$/dose PO BID* (600 mg BID Max Dose)

*Refer to the dosing nomogram in Appendix V for more information.

The starting BVD-523FB (ulixertinib) dose will be 260 mg/m^2/dose (Dose Level 1), which is approximately 25% below the adult MTD. Accrual will be temporarily suspended after enrollment to the first 6 toxicity-evaluable subjects to assess for toxicity as outlined in Section 11.

If there are fewer than 2 DLTs in the first 6 toxicity-evaluable subjects enrolled at the starting dose, the dose will be escalated to Dose Level 2. If ≥ 2 of the first 6 toxicity-evaluable subjects enrolled at Dose Level 2 have DLTs, all subsequent subjects will be enrolled at the original starting dose. Otherwise, remaining subjects will continue to enroll at Dose Level 2.

If there are 2 or more DLTs during cycle 1 among the first 6 toxicity-evaluable subjects enrolled at Dose Level 1, the next cohort will enroll at Dose Level -1. If ≥ 2 of the first 6 toxicity-evaluable subjects enrolled at the reduced dose have

DLTs, the study will be closed for toxicity. Otherwise, remaining subjects will continue to enroll at Dose Level -1.

5.1.2 Therapy Delivery Map
See Appendix VI for therapy delivery map for Cycle 1 and subsequent cycles.

5.1.3 Intra-Patient Escalation
Intrapatient dose escalation is not allowed.

5.2 Criteria for Starting Subsequent Cycles

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

5.3 Grading of Adverse Events

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

5.4 Definition of Dose-Limiting Toxicity (DLT)

DLT will be defined as any of the following events that are possibly, probably or definitely attributable to protocol therapy. Dose limiting hematological and non-hematological toxicities are defined differently. The DLT evaluation period for the purpose of dose escalation will be Cycle 1 of therapy.

5.4.1 Non-Hematological Dose-Limiting Toxicity

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

- Grade 3 nausea and vomiting of less < 3 days duration
- Grade 3 liver enzyme elevation, including ALT/AST/GGT that returns to levels that meet initial eligibility criteria or baseline within 7 days. See Appendix XI for values that represent thresholds between CTCAE grades.
  Note: For the purposes of this study the ULN for ALT is defined as 45 U/L regardless of baseline.
- Grade 3 or 4 fever < 5 days duration.
- Grade 3 infection < 5 days duration.
- Grade 3 hypophosphatemia, hypokalemia, hypocalcemia or hypomagnesemia responsive to supplementation.

- Any Grade 2 visual disturbance that persists for ≥ 1 week.
- Any Grade 2 non-hematological toxicity that persists for ≥ 7 days and is considered sufficiently medically significant or sufficiently intolerable by patients that it requires treatment interruption.
- Note: Allergic reactions that necessitate discontinuation of study drug will not be considered a dose-limiting toxicity.

5.4.2 Hematological dose limiting toxicity

5.4.2.1 Hematological dose limiting toxicity is defined as:

a) In patients evaluable for hematological toxicity (see Section 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 or ANC <1000).

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

6.0 DOSE MODIFICATIONS FOR ADVERSE EVENTS

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

6.1 Dose Modifications for Hematological Toxicity

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

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

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

6.2 Dose Modifications for Non-Hematological Toxicity

6.2.1 If a patient experiences non-hematological dose-limiting toxicity as defined in Section 5.4.1, the treatment will be held. When the toxicity resolves to meet eligibility parameters or baseline within 14 days of drug discontinuation, the patient may resume treatment at a reduced dose (see Appendix V for capsule formulation dosing nomogram). Doses reduced for toxicity will not be re-escalated, even if there is minimal or no toxicity with the reduced dose.

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

6.2.3 If 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 Visual Disturbances

Grade	Action
Grade 1	• Maintain Dose
Grade 2	• Hold BVD-523FB (ulixertinib) until eye exam is completed; If the ophthalmology exam is normal and the toxicity resolves to < Grade 1 within 1 week or an alternate cause for the vision problem is identified – restart BVD-523FB (ulixertinib) at the same dose level. Otherwise Grade 2 visual disturbance that persists for ≥ 1 week will be considered a DLT and require a dose reduction as per Section 6.2.
Grade 3 or 4	• Hold BVD-523FB (ulixertinib) until eye exam is completed; if alternate etiology for vision change is identified, contact Study Chair to discuss restarting of BVD-523FB (ulixertinib). Otherwise ≥ Grade 3 visual disturbance will be considered a DLT and require a dose reduction as per Section 6.2.

6.4 Dose Modifications for GI Toxicities (Nausea, Vomiting, Dehydration)

Heightened attention should be paid to hydration during treatment for all patients on study.

Management and Dose Modification Guidelines for Diarrhea

Diarrhea	Adverse Event Management	Action and Dose Modification
Grade 1	• Loperamide: Please see weight-based dosing of loperamide in Appendix XIII. Please use loperamide at first onset of diarrhea. • If diarrhea >24 hours: Continue loperamide and add second line anti-diarrhea drug if needed. • Oral hydration • IV hydration if indicated	• Continue BVD-523FB (ulixertinib). • Start loperamide and continue anti-diarrhea medications until diarrhea resolves to Grade ≤1.
Grade 2		• Hold BVD-523FB (ulixertinib). • Start loperamide and continue anti-diarrhea medications until diarrhea resolves to Grade ≤1. • If Grade 2 diarrhea resolves in < 7 days, may resume BVD-523FB (ulixertinib) once diarrhea resolves to Grade ≤1. • If Grade 2 diarrhea persists for ≥ 7 days, this will be considered a DLT. Hold BVD-523FB (ulixertinib) until diarrhea resolves to baseline and restart with one dose level reduction per Section 6.2.
Grade 3		• Hold BVD-523FB (ulixertinib). • Start loperamide and continue anti-diarrhea medications until

Management and Dose Modification Guidelines for Diarrhea

Diarrhea	Adverse Event Management	Action and Dose Modification
		diarrhea resolves to baseline. • This will be considered a DLT and restart with one dose level reduction per Section 6.2 once diarrhea resolves to baseline.
Grade 4		Complicated diarrhea: • Discontinue BVD-523FB (ulixertinib)
If treatment is delayed by > 14 days or a DLT recurs after dose reduction, permanently discontinue BVD-523FB (ulixertinib).		

Management and Dose Modification Guidelines for Nausea

Nausea	Adverse Event Management	Dose modifications
Grade 1	5-HT3 antagonist and additional anti-emetics as needed IV hydration as needed Drugs that are strong inhibitors or inducers of CYP1A2, CYP2D6, and CYP3A4 must be avoided (see Sections 4.2.2.5 and 4.2.2.6; Appendix II).	• Medical management. • Continue BVD-523FB (ulixertinib).
Grade 2		• Medical management • Continue BVD-523FB (ulixertinib). • If Grade 2 nausea persists for ≥ 7 days and is considered sufficiently medically significant or sufficiently intolerable by patients that it requires treatment interruption per Section 5.4.1.1 will be considered a DLT. Hold BVD-523FB (ulixertinib) until nausea resolves to baseline and restart with one dose level reduction per Section 6.2.
Grade 3		• Medical management. • Hold BVD-523FB (ulixertinib). • If Grade 3 nausea persists for > 3 days, this will be considered a DLT. Hold BVD-523FB (ulixertinib) until nausea resolves to baseline and restart with one dose level reduction per Section 6.2.
If treatment is delayed by > 14 days or a DLT recurs after dose reduction, permanently discontinue BVD-523FB (ulixertinib).		

Management and Dose Modification Guidelines for Vomiting

Vomiting	Adverse Event Management	Dose modification
Grade 1	5-HT3 antagonist and additional anti-emetics as needed	• Medical management. • Continue BVD-523FB (ulixertinib).

Grade 2	IV hydration as needed Drugs that are strong inhibitors or inducers of CYP1A2, CYP2D6, and CYP3A4 must be avoided (see Sections 4.2.2.5 and 4.2.2.6; Appendix II).	• Medical management • Hold BVD-523FB (ulixertinib). • If Grade 2 vomiting resolves in < 7 days, may resume BVD-523FB (ulixertinib) once vomiting resolves to Grade ≤1. • If Grade 2 vomiting persists for ≥ 7 days, this will be considered a DLT. Hold BVD-523FB (ulixertinib) until vomiting resolves to baseline and restart with one dose level reduction per Section 6.2.
Grade 3		• Medical management. • Hold BVD-523FB (ulixertinib). • If Grade 3 vomiting persists for > 3 days, this will be considered a DLT. Hold BVD-523FB (ulixertinib) until vomiting resolves to baseline and restart with one dose level reduction per Section 6.2.
Grade 4		Off protocol therapy
If treatment is delayed by > 14 days or a DLT recurs after dose reduction, permanently discontinue BVD-523FB (ulixertinib).		

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 BVD-523FB (ulixertinib). See below for recommendations on management of specific toxicities associated with BVD-523FB (ulixertinib).

7.3.1 Recommendations for Visual Disturbance:

Patients who experience visual disturbance should undergo complete ophthalmologic examination including visual acuity, visual fields (if feasible) and fundoscopic exam. Optical coherence tomography (OCT) is particularly helpful in identifying retinal pathology that can be seen with MAPK inhibitors, and so is strongly encouraged as an adjunct to the above assessment.

7.3.2 Advise patients to minimize sun exposure, use broad-spectrum sunscreens, and wear sunglasses. Patients should be informed that relevant sun exposure may occur even through glass, such as while driving.

7.4 Growth Factors

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

7.5 Concomitant Medications

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

7.5.2 CYPA1A2 and CYP2D6:
Patients must not be receiving drugs that are strong inducers or inhibitors of CYP1A2 and CYP2D6. Strong inhibitors of CYP1A2 (eg., ciprofloxacin, enoxacin, fluvoxamine, zafirlukast) should be avoided from 14 days prior to enrollment to the end of the study. Strong inhibitors of CY2D6 (eg., bupropion, paroxetine, fluoxetine, quinidine, terbinafine) should also be avoided from 14 days prior to enrollment to the end of the study.

7.5.3 BVD-523FB (ulixertinib) is a P-glycoprotein (P-gp) transporter substrate, and is highly protein bound (99-100% protein binding). Use caution in patients who are also receiving strong P-gp inhibitors (eg., amiodarone, carvedilol, clarithromycin, dronedarone, itraconazole, lapatinib, lopinavir and ritonavir, propafenone, quinidine, ranolazine, ritonavir, saquinavir and ritonavir, telaprevir, tipranavir and ritonavir, verapamil) or highly protein-bound drugs with narrow therapeutic ranges.

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
ECHO or gated radionuclide study	X		Every 3 cycles
EKG	X	End of Cycle 1	
Ophthalmologic Exam[10]	X		
Tumor Disease Evaluation[4-A, 4-B, 4-C]	X		Every other Cycle x 3 then q 3 Cycles [4]
Plain radiograph tibial growth plate (bone x-ray tests)[11]	X		Prior to Cycles 2 and 5, then every 6 months
Bone Marrow Aspirate and/or biopsy[5,6]	X[6]		
Medication Diary[7]		Weekly	X
Pharmacokinetics (optional)[8]		X	
Circulating Tumor DNA (ctDNA-optional)[9]			Cycle 5, Day 1 and (for patients receiving ≥ 5 cycles only) at end of Protocol Therapy OR disease progression

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

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

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

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

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

4-A Neurological exam also required for CNS patients

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

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

clinically indicated. Refer to Section 12.5.4 and Section 12.9

5 Bone marrow aspirate and/or biopsy only required in patients suspected of having bone marrow metastasis on the basis of history, symptoms, laboratory evaluation or other clinical data. Should only be performed on patients with known bone marrow involvement at baseline.

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

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

8. See Section 8.4 for details of PK studies.

9. With consent two samples will be collected on this protocol (Cycle 5 Day 1; and for patients receiving ≥ 5 cycles, at progression or end of protocol therapy) see Section 8.5 and Appendix IV for details of the ctDNA studies. Note that a ctDNA sample is scheduled to be obtained on the APEC162SC screening protocol prior to the initiation of treatment on this subprotocol

10. Ophthalmological examinations will be performed by an ophthalmologist at screening and if clinically indicated during treatment.

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.

- 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 BVD-523FB (ulixertinib) 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 BVD-523FB (ulixertinib). 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 BVD-523FB (ulixertinib) or not.

8.3 Radiology Studies

8.3.1 Central Radiology Review for Response:

Patients who respond (CR, PR) to therapy or have long term stable disease (SD) (≥ 6 cycles) on protocol therapy will be centrally reviewed. The Operations center will notify the site when a patient has met the criteria for review. The tumor disease evaluations to be

submitted for review include baseline (prestudy) evaluations as well as all end of cycle tumor disease evaluations which occurred while the patient was on the subprotocol therapy study

8.3.2 Technical Details of Submission:

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

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

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

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

Digital RT Data Submission Using TRIAD (if TRIAD is available at your site):

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

TRIAD Access Requirements:

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

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

TRIAD Installations:

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

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

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

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

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

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

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

8.4 Pharmacology (optional)

8.4.1 Description of Studies and Assay

Pharmacokinetics (PK) will be performed to determine the PK of BVD-523FB (ulixertinib) in children. Pharmacokinetic analysis will be conducted at a centralized laboratory using validated assays.

8.4.2 Sampling Schedule

Blood samples will be obtained at the following time points:

Blood Sample No.	Time Point	Scheduled Collection Time
1	**Cycle 1, Day 1**	Pre-dose

Cycle 1 Day 1 AM Dose **The PM dose of BVD-523FB (ulixertinib) on Day 1, Cycle 1 will not be given for patients undergoing these PK studies.**		
2	**Cycle 1, Day 1**	1 hr after AM dose
3	**Cycle 1, Day 1**	2 hrs after AM dose
4	**Cycle 1, Day 1**	4 hrs after AM dose
5	**Cycle 1, Day 1**	6-8 hrs after AM dose
6	**Cycle 1, Day 2**	Pre-dose
7	**Cycle 1, Day 15**	Pre-dose
Cycle 1 Day 15 AM Dose		
8	**Cycle 1, Day 15**	1 hr after AM dose
9	**Cycle 1, Day 15**	2 hrs after AM dose
10	**Cycle 1, Day 15**	4 hrs after AM dose
11	**Cycle 1, Day 15**	6-8 hrs after AM dose
12	**Cycle 1, Day 22**	Pre-dose

* Please contact study chair or pharmacologist to adjust PK schedule if there are missed doses during Days 1-21.

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.

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

8.4.4 Sample Processing and Storage

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 resultant plasma should be withdrawn in two aliquots:
    - 0.5 mL in Aliquot 1 (label as “PK Primary”) and the remainder in Aliquot 2 (label as “PK Back-up”) into two clearly labeled 2mL polypropylene screw cap cryovials.
- Secure the cryovial caps and within 60-120 min after collection, place the samples into storage at (-20°C to -70°C) until shipment.
- Backup samples (Aliquot 2) will be held at the study site at (-20°C to -70°C), until the end of the study or as requested by the sponsor.

8.4.5 Sample Labeling

Please label Aliquot 1 as "PK Primary" and Aliquot 2 as "PK Back-up".Each tube must be labeled with the patient's study registration number, the study I.D (APEC1621J), and the date and time the sample was drawn. Data should be recorded on the appropriate transmittal form found in RAVE.

8.4.6 Sample Shipping Instructions

Ship the aliquots overnight frozen on dry ice. The samples must be securely packed in boxes to avoid breakage during transit, double-bagged to contain leaks,

Attn: Anita Wyeth, Covance Laboratories Inc.
3301 Kinsman Blvd
Attn: Andrea Varese, Sample Management—Bioanalytical (Rm 1S 160)
Madison WI 53704
Email: anita.wyeth@covance.com

Biomed Valley Discoveries FedEx account number is #438681043

8.5 Circulating Tumor DNA Study (optional)

8.5.1 Sampling Schedule

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

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

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

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

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

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

For patients who do not have indwelling catheters, blood should be collected via

venipuncture. To guard against backflow, observe the following precautions:

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

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 (APEC1621J), 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 APEC1621J-Peds MATCH*
700 Children's Drive, WA1340*
Columbus, OH 43205
Phone: (614) 722-2865
Fax: (614) 722-2897
Email: BPCBank@nationwidechildrens.org

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

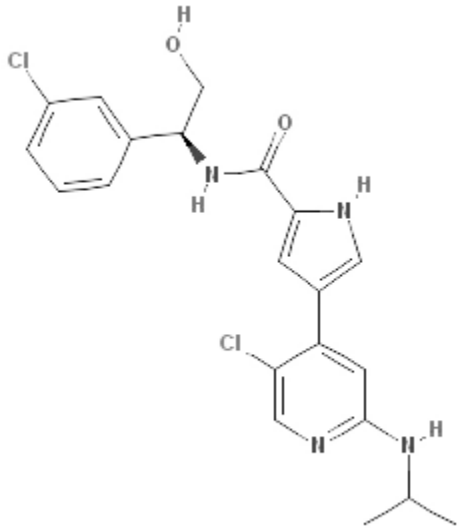
9.0 AGENT INFORMATION

9.1 **BVD-523FB (ulixertinib)**
NSC# 799018 IND# 134661

9.1.1 Structure and molecular weight

Chemical Name: *(S)*-4-(5-chloro-2-(isopropylamino)pyridin-4-yl)-*N*-(1-(3-chlorophenyl)-2-hydroxyethyl)-1*H*-pyrrole-2-carboxamide hydrochloride

Molecular Formula: $C_{21}H_{22}C_{l2}N_4O_2 \cdot HCl$
Molecular Weight: 469.79 g/mol for HCl salt



9.1.2 Supplied by:
BVD-523FB (ulixertinib) is supplied by BioMed Valley and distributed by a Division of Cancer Treatment and Diagnosis the Pharmaceutical Management Branch (DCTD), NCI.

9.1.3 Formulation
BVD-523FB (ulixertinib) is supplied as mono-chloride salt in hard gelatin capsule. Each yellow size 0 capsule contains 150 mg of drug substance (FB or free base equivalent) and is packaged in a 30-count white HDPE bottle with induction seal and child-resistant polypropylene cap.

9.1.4 Storage
Store at 15°C to 25°C (59°F to 77°F).

If a storage temperature excursion is identified, promptly return BVD-523FB (ulixertinib) to controlled room temperature and quarantine the supplies. Provide a detailed report of the excursion (including documentation of temperature monitoring and duration of the excursion) to PMBAfterHours@mail.nih.gov for determination of suitability.

9.1.5 Stability
Shelf life studies are ongoing. Dispense BVD-523FB (ulixertinib) in the original

manufacturer's container. Do not repackage capsules.

9.1.6 Administration

See treatment (Section 5.0) and Dose Modification (Section 6.0) sections of the protocol. Take by mouth on an empty stomach either 1 hour before a meal or 2 hours after a meal. Capsules should not be opened, crushed or chewed. If a patient misses or vomits a dose, an additional dose should not be taken. Patients should resume dosing at the next scheduled time.

9.1.7 Potential Drug Interactions

In vitro studies suggest that BVD-523FB (ulixertinib) is metabolized primarily by CYP450-mediated oxidation, involving CYP isozymes 3A4, 2D6 and 1A2. Concomitant use of strong inducers or inhibitors of CYP 1A2, 2D6 or 3A4 is prohibited during the study.

In vitro and *ex vivo* results indicate that BVD-523FB (ulixertinib) has minimal potential to inhibit CYP 1A2, 2C9, 2C19, 2D6, 2E1, and 3A4 isozymes. The potential for BVD-523FB (ulixertinib) to affect CYP450 as an inducer is considered low even though some increases in CYP450 activity were observed in human hepatocyte and animal liver microsome systems.

BVD-523FB (ulixertinib) is a highly cell permeable, putative P-glycoprotein (P-gp) transporter substrate, and is highly protein bound in multiple species, including humans at 99-100% protein binding. Use caution in patients who are also receiving strong P-gp inhibitors or highly protein-bound drugs with narrow therapeutic ranges.

9.1.8 Patient Care Implications:

Advise patients to minimize sun exposure, use broad-spectrum sunscreens, and wear sunglasses. Patients should be informed that relevant sun exposure may occur even through glass, such as while driving.

Advise study participants to use contraception while receiving study treatment and for 3 months after the last dose of BVD-523FB (ulixertinib).

Inhalation of powder or contact with skin and mucous membranes, especially those of the eyes, must be avoided. Should accidental exposure of the eye or skin occur, copious irrigation with water should be instituted immediately.

9.1.9 BVD-523FB (ulixertinib) Toxicities

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/docs/aeguidelines.pdf for

further clarification. *Frequency is provided based on 208 patients.* Below is the CAEPR for BVD-523FB (ulixertinib).

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 2.1, October 31, 2018[1]

Adverse Events with Possible Relationship to BVD-523FB (ulixertinib) (CTCAE 5.0 Term) [n= 208]			**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)***
		Thrombotic thrombocytopenic purpura	
CARDIAC DISORDERS			
		Heart failure	
ENDOCRINE DISORDERS			
	Hypothyroidism		***Hypothyroidism (Gr 2)***
EYE DISORDERS			
	Blurred vision		***Blurred vision (Gr 2)***
	Eye disorders – Other[2] (eye symptoms)		***Eye disorders – Other[2] (eye symptoms) (Gr 2)***
		Eye disorders - Other (retinal vein occlusion)	
	Photophobia		***Photophobia (Gr 2)***
		Retinal detachment	
	Vision decreased		***Vision decreased (Gr 2)***
GASTROINTESTINAL DISORDERS			
	Abdominal pain		***Abdominal pain (Gr 2)***
	Bloating		***Bloating (Gr 2)***
	Constipation		***Constipation (Gr 2)***
Diarrhea			***Diarrhea (Gr 2)***
	Dry mouth		***Dry mouth (Gr 2)***
	Dyspepsia		***Dyspepsia (Gr 2)***
	Gastritis		***Gastritis (Gr 2)***
	Gastroesophageal reflux disease		***Gastroesophageal reflux disease (Gr 2)***
		Gastrointestinal disorders - Other (gastrointestinal hemorrhage)[3]	
	Mucositis oral		***Mucositis oral (Gr 2)***
Nausea			***Nausea (Gr 2)***
	Vomiting		***Vomiting (Gr 2)***
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
	Chills		***Chills (Gr 2)***

Adverse Events with Possible Relationship to BVD-523FB (ulixertinib) (CTCAE 5.0 Term) [n= 208]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
		Edema face	
	Edema limbs		***Edema limbs (Gr 2)***
Fatigue			***Fatigue (Gr 2)***
	Fever		***Fever (Gr 2)***
	Non-cardiac chest pain		***Non-cardiac chest pain (Gr 2)***
	Pain		***Pain (Gr 2)***
INFECTIONS AND INFESTATIONS			
	Infection[4]		***Infection[4] (Gr 2)***
INVESTIGATIONS			
	Alanine aminotransferase increased		***Alanine aminotransferase increased (Gr 2)***
	Alkaline phosphatase increased		***Alkaline phosphatase increased (Gr 2)***
	Aspartate aminotransferase increased		***Aspartate aminotransferase increased (Gr 2)***
	Blood bilirubin increased		***Blood bilirubin increased (Gr 2)***
	Creatinine increased		***Creatinine increased (Gr 2)***
		Electrocardiogram QT corrected interval prolonged	
	Lymphocyte count decreased		***Lymphocyte count decreased (Gr 2)***
	Neutrophil count decreased		***Neutrophil count decreased (Gr 2)***
METABOLISM AND NUTRITION DISORDERS			
	Anorexia		***Anorexia (Gr 2)***
	Dehydration		***Dehydration (Gr 2)***
	Hyperglycemia		***Hyperglycemia (Gr 2)***
	Hyperphosphatemia		***Hyperphosphatemia (Gr 2)***
	Hypoalbuminemia		***Hypoalbuminemia (Gr 2)***
	Hypocalcemia		***Hypocalcemia (Gr 2)***
	Hypokalemia		***Hypokalemia (Gr 2)***
	Hypomagnesemia		***Hypomagnesemia (Gr 2)***
	Hyponatremia		***Hyponatremia (Gr 2)***
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			
	Arthralgia		***Arthralgia (Gr 2)***
	Generalized muscle weakness		***Generalized muscle weakness (Gr 2)***
	Musculoskeletal and connective tissue disorder – Other (muscle twitch)		***Musculoskeletal and connective tissue disorders – Other (muscle twitch) (Gr 2)***
	Myalgia		***Myalgia (Gr 2)***
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)			
		Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other (squamous cell carcinoma, keratoacanthoma-type, mid forehead)	
NERVOUS SYSTEM DISORDERS			
	Dizziness		***Dizziness (Gr 2)***
	Dysgeusia		***Dysgeusia (Gr 2)***

Adverse Events with Possible Relationship to BVD-523FB (ulixertinib) (CTCAE 5.0 Term) [n= 208]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
	Paresthesia		***Paresthesia (Gr 2)***
PSYCHIATRIC DISORDERS			
	Anxiety		***Anxiety (Gr 2)***
	Delirium		***Delirium (Gr 2)***
RENAL AND URINARY DISORDERS			
	Acute kidney injury		***Acute kidney injury (Gr 2)***
	Hematuria		***Hematuria (Gr 2)***
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
	Cough		***Cough (Gr 2)***
	Dyspnea		***Dyspnea (Gr 2)***
	Sore throat		***Sore throat (Gr 2)***
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
	Alopecia		***Alopecia (Gr 2)***
	Dry skin		***Dry skin (Gr 2)***
		Erythema multiforme	
		Erythroderma	
	Nail changes		***Nail changes (Gr 1)***
		Palmar-plantar erythrodysesthesia syndrome	
	Photosensitivity		***Photosensitivity (Gr 2)***
	Pruritus		***Pruritus (Gr 2)***
Rash acneiform			***Rash acneiform (Gr 2)***
Rash maculo-papular			***Rash maculo-papular (Gr 2)***
	Skin and subcutaneous tissue disorders - Other (skin fissures)		***Skin and subcutaneous tissue disorders - Other (skin fissures) (Gr 2)***
	Urticaria		***Urticaria (Gr 2)***
VASCULAR DISORDERS			
	Hot flashes		***Hot flashes (Gr 2)***
	Hypotension		***Hypotension (Gr 2)***

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

[2] Eye symptoms may include floaters, night blindness, and watering eyes, and halo vision.

[3] Gastrointestinal hemorrhage may include gastric hemorrhage, colonic hemorrhage, rectal hemorrhage, or other gastrointestinal tract hemorrhage.

[4] Infection may include infections around the rectum, eyes, mucosa, and other sites.

Adverse events reported on BVD-523FB (ulixertinib) trials, but for which there is insufficient evidence to suggest that there was a reasonable possibility that BVD-523FB (ulixertinib) caused the adverse event:

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Febrile neutropenia; Leukocytosis
CARDIAC DISORDERS - Atrial fibrillation; Myocardial infarction; Pericardial effusion; Sinus bradycardia; Sinus tachycardia

GASTROINTESTINAL DISORDERS - Anal pain; Colonic ulcer; Flatulence; Gastrointestinal disorders - Other (diverticulum); Hemorrhoids; Small intestinal obstruction; Stomach pain
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Gait disturbance
INVESTIGATIONS - Blood lactate dehydrogenase increased; Platelet count decreased; Weight loss; White blood cell decreased
METABOLISM AND NUTRITION DISORDERS - Hyperkalemia; Hypoglycemia
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Arthritis; Back pain; Flank pain; Muscle cramp; Musculoskeletal and connective tissue disorder - Other (musculoskeletal stiffness)
NERVOUS SYSTEM DISORDERS - Headache; Ischemia cerebrovascular; Nervous system disorders - Other (neuropathy peripheral); Seizure
PSYCHIATRIC DISORDERS - Insomnia
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Bronchopulmonary hemorrhage; Oropharyngeal pain; Pleural effusion; Pneumothorax; Stridor
SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Hirsutism; Pain of skin; Scalp pain; Skin and subcutaneous tissue disorders - Other (skin lesion)
VASCULAR DISORDERS - Flushing; Hematoma; Thromboembolic event

Note: BVD-523 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.

9.2 Agent Ordering and Agent Accountability

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

Note: No starter supplies will be provided. Drug orders of BVD-523FB (ulixertinib) should be placed with CTEP after enrollment and treatment assignment to APEC1621J with consideration for timing of processing and shipping to ensure receipt of drug supply prior to start of protocol therapy. If expedited shipment is required, sites should provide an express courier account through the Online Agent Order Processing (OAOP) application. Provide the patient ID number in the comment box when submitting an order request.

9.3 Clinical Drug Request and Investigator Brochure Availability

Submit agent requests through the PMB Online Agent Order Processing (OAOP) application. The current versions of the IBs for the agents will also be accessible to site investigators and research staff through the PMB Online Agent Order Processing (OAOP) application. Access to OAOP requires the establishment of a CTEP Identity and Access Management (IAM) account and the maintenance of an "active" account status, "current" password, and active person registration status. For questions about drug orders, transfers, returns, or accountability call or email PMB anytime. Refer to the PMB's website for specific policies and guidelines related to agent management. Questions about IB access may be directed to the PMB IB coordinator via email.

9.4 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.

9.4.1 Useful Links and Contacts

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

10.0 CRITERIA FOR REMOVAL FROM PROTOCOL THERAPY AND OFF STUDY CRITERIA

10.1 Criteria for Removal from Protocol Therapy

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

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

10.2 Follow-Up Data Submission and APEC1621SC Off Study Criteria

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

11.0 STATISTICAL AND ETHICAL CONSIDERATIONS

11.1 Sample Size and Study Duration

APEC1621J will require a minimum of 4 evaluable patients and a maximum of 49 patients, allowing for 15% inevaluability. Assuming an enrollment rate of 10-30 biomarker positive patients per year, the primary cohort of this subprotocol is expected to be completed within 0.8-2.4 years.

11.2 Dosing Considerations

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

Please see Section 5.1 for a specific discussion of the dosing of BVD-523FB (ulixertinib) to be used in this study. As there is no prior pediatric Phase 1 data, study investigators have reviewed relevant data with the pharmaceutical partner to identify a drug specific dosing plan for testing in children with relapsed or refractory cancer, and trial participants will be closely monitored to ensure tolerability of the selected dose. Limited pharmacokinetic sampling may be done for patients enrolled on these arms.

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

Because the adult RP2D of the agent is the adult MTD, the pediatric subprotocol will evaluate an initial cohort of patients at a dose level approximately 30% below the adult MTD and then complete the study using the adult RP2D, assuming that both dose levels are tolerated.. The DLT evaluation period for the purpose of dose escalation will be Cycle 1 of therapy. Note that adverse events that begin during Cycle 1 and specify a duration of time in order to be considered a DLT must be followed to resolution or until the definition of DLT has been met, regardless of the schedule end of Cycle 1 (e.g. grade 2 thrombocytopenia would be considered a DLT if it developed during Cycle 1 of therapy and caused, or would have caused, a delay of >14 days to begin Cycle 2). Patients enrolled during the determination of the recommended Phase 2 dose who are not evaluable for toxicity during Cycle 1 at a given dose level will be replaced.

The rolling six phase 1 trial design[28] will be used for the conduct of this study. Two to six patients can be concurrently enrolled onto a dose level, dependent upon (1) the number of patients enrolled at the current dose level, (2) the number of patients who have experienced DLT at the current dose level, and (3) the number of patients entered but with tolerability data pending at the current dose level. Accrual is suspended when a cohort of six has enrolled or when the study endpoints have been met.

Dose level assignment is based on the number of participants currently enrolled in the cohort, the number of DLTs observed, and the number of participants at risk for developing a DLT (i.e., participants enrolled but who are not yet assessable for toxicity). For example, when three participants are enrolled onto a dose cohort, if toxicity data is available for all three when the fourth participant entered and there are no DLTs, the dose is escalated and the fourth participant is enrolled to the subsequent dose level. If data is not yet available for one or more of the first three participants and no DLT has been observed, or if one DLT has been observed, the new participant is entered at the same dose level. Lastly, if two or more DLTs have been observed, the dose level is de-escalated. This process is repeated for participants five and six. In place of suspending accrual after every three participants, accrual is only suspended when a cohort of six is filled. When participants are inevaluable for toxicity, they are replaced with the next available participant if escalation or de-escalation rules have not been fulfilled at the time the next available participant is enrolled onto the study.

The following table provides the decision rules for enrolling a patient at (i) the current dose level (ii) at an escalated dose level, (iii) at a de-escalated dose level, or whether the study is suspended to accrual:

# Pts Enrolled	**# Pts with DLT**	**# Pts without DLT**	**# Pts with Data Pending**	***Decision***
2	0 or 1	0, 1 or 2	0, 1 or 2	Same dose level
2	2	0	0	De-escalate*
3	0	0, 1 or 2	1, 2 or 3	Same dose level
3	1	0, 1 or 2	0, 1 or 2	Same dose level
3	0	3	0	Escalate**
3	≥ 2	0 or 1	0 or 1	De-escalate*
4	0	0, 1, 2 or 3	1, 2, 3 or 4	Same dose level
4	1	0, 1, 2 or 3	0, 1, 2 or 3	Same dose level
4	0	4	0	Escalate**
4	≥ 2	0, 1 or 2	0, 1 or 2	De-escalate*
5	0	0, 1, 2, 3 or 4	1, 2, 3, 4 or 5	Same dose level
5	1	0, 1, 2, 3 or 4	0, 1, 2, 3 or 4	Same dose level
5	0	5	0	Escalate**
5	≥ 2	0, 1, 2 or 3	0, 1, 2 or 3	De-escalate*
6	0	0, 1, 2, 3, or 4	2, 3, 4, 5 or 6	Suspend
6	1	0, 1, 2, 3 or 4	0, 1, 2, 3 or 4	Suspend
6	0 or 1	5 or 6	0 or 1	Escalate**
6	≥ 2	0, 1, 2, 3 or 4	0, 1, 2, 3 or 4	De-escalate*

* If six patients already entered at next lower dose level, the MTD has been defined.
** If final dose level has been reached, the recommended dose has been reached.

If two or more of a cohort of up to six patients experience DLT at a given dose level, then dose escalation will be stopped.

In addition to determination of the RP2D, a descriptive summary of all toxicities will be reported.

11.3 Study Design

The primary cohort defined below will employ single stage A'Hern designs of N=20 and N=10 respectively. 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:

APEC1621J 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[29] 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.[30] Decision making for A'Hern design cohorts will follow rules described above.

Any responses or lack thereof in patients enrolled during the determination of the Recommended Phase 2 Dose (dose finding phase) will count toward the objective response rate in their respective cohort.

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

11.5 Evaluability for Response

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

11.6 Evaluability for Toxicity

All eligible patients who receive at least one dose of protocol therapy will be considered in the evaluation of toxicity. In addition, for the dose-escalation portion during Cycle 1, patients without DLT must receive at least 85% of the prescribed dose per protocol guidelines and must have the appropriate toxicity monitoring studies performed to be considered evaluable for toxicity for the purpose of determining dose escalation and defining the recommended phase 2 dose. Patients under Section 4.1.7 are not evaluable for DLT if they do not experience a non-hematologic DLT.

11.7 Progression free survival (PFS)

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

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

11.8 Correlative Studies

A descriptive analysis of pharmacokinetic (PK) parameters will be performed to define systemic exposure, drug clearance, and other pharmacokinetic parameters. The PK

parameters will be summarized with simple summary statistics, including means, medians, ranges, and standard deviations (if numbers and distribution permit).

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

11.9 Gender and Minority Accrual Estimates

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

Racial category	Ethnicity				
	Not Hispanic or Latino		Hispanic or Latino		
	Female	Male	Female	Male	Total
American Indian/Alaska Native	0	0	0	0	0
Asian	1	1	0	0	2
Native Hawaiian or Other Pacific Islander	0	0	0	0	0
Black or African American	3	5	0	0	8
White	12	20	4	2	38
More than one race	1	0	0	0	1
Total	17	26	4	2	49

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

12.0 EVALUATION CRITERIA

12.1 Common Terminology Criteria for Adverse Events (CTCAE)

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

12.2 Progression-Free Survival

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

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

12.3 Response Criteria for Patients with Solid Tumors

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

following initial documentation of objective response.

As outlined, patients will be assigned to one of the following categories for assessment of response: a) solid tumor (non-CNS) and measurable disease (Section 12.4); b) neuroblastoma with MIBG positive lesions (Section 12.5); c) CNS tumor (Section 12.7); and d) 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 at least one dose of protocol therapy will be considered evaluable for response. Evaluable patients who demonstrate a complete or partial response confirmed by central review before receiving non-protocol anti-cancer therapy will be considered a responder. All other evaluable patients will be considered non-responders

12.3.1.2 Evaluable Non-Target Disease Response:

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

12.3.2 Disease Parameters

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

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

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

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

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

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

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

12.3.3 Methods for Evaluation of Measurable Disease

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

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

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

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

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

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

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

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

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

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

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

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

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

For patients with a positive PET scan at diagnosis, PET can be used to follow response in addition to a CT scan using the International Pediatric non-Hodgkin Lymphoma Response Criteria.[31]

Response Criteria for Patients with Solid Tumor and Measurable Disease

12.4 Response Criteria for Patients with Solid Tumor and Measurable Disease

12.4.1 Evaluation of Target Lesions

Complete Response (CR):	Disappearance of all target and non-target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm. If immunocytology is available, no disease must be detected by that methodology. Normalization of urinary catecholamines or other tumor markers if elevated at study enrollment (for patients with neuroblastoma).
Partial Response (PR):	At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters
Progressive Disease (PD):	At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progressions). Note: in presence of SD or PR in target disease but unequivocal progression in non-target or non-measurable disease, the patient has PD if there is an overall level of substantial worsening in non-target disease such that the overall tumor burden

has increased sufficiently to merit discontinuation of therapy

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

12.4.2 Evaluation of Non-Target Lesions

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

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

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

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

12.4.3 Overall Response Assessment

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

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

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

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

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

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

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

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

12.4.4 Overall Best Response Assessment

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

12.5 Response Criteria for Neuroblastoma Patients with MIBG Positive Lesions

12.5.1 MIBG Positive Lesions

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

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

Complete response: Complete resolution of all MIBG positive lesions
Partial Response: Resolution of at least one MIBG positive lesion, with

persistence of other MIBG positive lesions
Stable disease: No change in MIBG scan in number of positive lesions
Progressive disease: Development of new MIBG positive lesions

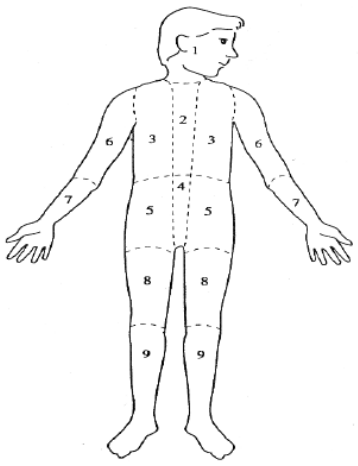
12.5.3 The response of MIBG lesions will be assessed on central review using the Curie scale14 as outlined below. Central review responses will be used to assess efficacy for study endpoint. See Section 8.2 for details on transferring images to the Imaging Research Center.

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

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

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

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



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

1. **Complete response:** all areas of uptake on MIBG scan completely resolved. If morphological evidence of tumor cells in bone marrow biopsy or aspiration is present at enrollment, no tumor cells can be detected by routine morphology on two subsequent bilateral bone marrow aspirates and biopsies done at least 21 days apart to be considered a **Complete Response**.
2. **Partial response**: Relative score ≤ 0.2 (lesions almost disappeared) to ≤ 0.5 (lesions strongly reduced).
3. **Stable disease**: Relative score > 0.5 (lesions weakly but significantly reduced)

to 1.0 (lesions not reduced).

4. **Progressive disease**: New lesions on MIBG scan.

12.5.4 Overall Response Assessment

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

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

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

12.5.5 Overall Best Response Assessment

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

12.6 Response Criteria for Neuroblastoma Patients with Bone Marrow Involvement

12.6.1 Bone Marrow Involvement

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

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

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

Progressive Disease: In patients who enroll with neuroblastoma in bone marrow by morphology have progressive disease if there is a doubling in the amount of tumor in the marrow AND a minimum of 25% tumor in bone marrow by

morphology. (For example, a patient entering with 5% tumor in marrow by morphology must increase to ≥ 25% tumor to have progressive disease; a patient entering with 30% tumor must increase to > 60%).

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

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

12.6.2 Overall Best Response Assessment

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

12.7 Response Criteria for Patients with CNS Tumors

12.7.1 Measurable Disease

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

12.7.2 Evaluable Disease

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

12.7.3 Selection of Target and Non-Target Lesions

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

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

12.7.4 Response Criteria for Target Lesions

Response criteria are assessed based on the product of the longest diameter and its longest perpendicular diameter. Development of new disease or progression in any

established lesions is considered progressive disease, regardless of response in other lesions – e.g., when multiple lesions show opposite responses, the progressive disease takes precedence. Response Criteria for target lesions:

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

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

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

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

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

12.7.5 Response Criteria for Non-Target Lesions:

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

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

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

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

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

Target Lesions	**Non-target Lesions**	**Markers**	**New Lesions**	**Overall**

				Response
CR	CR	Normal	No	**CR**
CR	IR/SD	Normal	No	**PR**
CR	CR, IR/SD	Abnormal	No	**PR**
PR	CR, IR/SD	Any	No	**PR**
SD	CR, IR/SD	Any	No	**SD**
PD	Any	Any	Yes or No	**PD**
Any	PD	Any	Yes or No	**PD**
Any	Any	Any	Yes	**PD**

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

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

Response and progression will be evaluated in this study using the new international criteria proposed by the revised Response Evaluation Criteria in Pediatric non-Hodgkin Lymphoma Criteria[31], with modification from the Lugano classification.[32]

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

Evaluation of Non-measured Lesions (CT-based response, PET/CT based response not applicable)[32]

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.

12.8.3 Evaluation of organ enlargement[32]

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.

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

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 APEC1621J 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 of the NCI CTCAEv5.0. The descriptions and grading scales found in the current version of the CTCAEv5.0 will be used for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAEv5.0. A copy of the CTCAEv5.0 can be downloaded from the CTEP website (http://ctep.cancer.gov).

Step 2: Grade the adverse event using the NCI CTCAEv5.0.

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 CTCAEv5.0 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 or Exceptions to CTEP-AERS Expedited Reporting Requirements:

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

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

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

13.4 Definition of Onset and Resolution of Adverse Events

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

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

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

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

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

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

13.5 Other Recipients of Adverse Event Reports

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

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

13.6 Specific Examples for Expedited Reporting

13.6.1 Reportable Categories of Death

- Death attributable to a CTCAEv5.0 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 "Neonatal loss", the Pregnancy Information Form, available at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/PregnancyReportForm.pdf, needs to be completed and faxed along with any additional medical information to (301) 897-7404. The potential risk of exposure of the fetus to the investigational agent should be documented in the "Description of Event" section of the CTEP-AERS report.

Pregnancy

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

Pregnancy Loss (Fetal Death)

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

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

Death Neonatal

Neonatal death, defined in CTCAEv5.0 as *"**Newborn deaths occurring during the first 28 days after birth***" that is felt by the investigator to be at least possibly due to the investigational agent/intervention, should be reported expeditiously, as **Grade 4 "*Death Neonatal*"** under the system organ class (SOC) of "General disorders and administration site conditions." **When the death is the result of a patient pregnancy or pregnancy in partners of men on study**. Do NOT report a neonatal death resulting from a patient pregnancy or pregnancy in partners of men on study as a Grade 5 event since CTEP-AERS recognizes any Grade 5 event as a patient death.

14.0 RECORDS, REPORTING, AND DATA AND SAFETY MONITORING PLAN

14.1 Categories of Research Records

Research records for this study can be divided into three categories

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

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

3. Computerized Information Electronically Submitted: All other data will be

entered in RAVE with the aid of schedules and worksheets (essentially paper copies of the OPEN and RAVE screens) provided in the case report form (CRF) packet.

See separate CRF Packet, which includes submission schedule.

14.2 **CDUS**

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

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

14.3 **CRADA/CTA/CSA**

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

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

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

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

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

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

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

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

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

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

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

Email: ncicteppubs@mail.nih.gov

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

14.4 Data and Safety Monitoring Plan

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

14.4.1 Data and Safety Monitoring Committee

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

14.4.2 Monitoring by the Study Chair and MATCH Leadership

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

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APPENDIX I: PERFORMANCE STATUS SCALES/SCORES

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

APPENDIX II: CYP3A4 SUBSTRATES, INDUCERS, AND INHIBITORS

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

CYP3A4 substrates	Strong Inhibitors1	Moderate Inhibitors	Strong Inducers	Moderate Inducers
acalabrutinib5	atazanavir	aprepitant	barbiturates	bosentan
alfentanil4,5	boceprevir	conivaptan	carbamazepine	dabrafenib
amiodarone4	clarithromycin	crizotinib	enzalutamide	efavirenz
aprepitant/fosaprepitant	cobicistat	diltiazem	fosphenytoin	etravirine
atorvastatin	darunavir	dronedarone	phenobarbital	modafinil
axitinib	delavirdine	erythromycin	phenytoin	nafcillin
bortezomib	grapefruit3	fluconazole	primidone	rifapentin
bosutinib5	grapefruit juice3	fosamprenavir	rifampin	
budesonide5	idelalisib	grapefruit3	St. John's wort	
buspirone5	indinavir	grapefruit juice3		
cabozantinib	itraconazole	imatinib		
calcium channel blockers	ketoconazole	isavuconazole		
cisapride	lopinavir/ritonavir	mifepristone		
citalopram/escitalopram	nefazodone	nilotinib		
cobimetinib5	nelfinavir	verapamil		
conivaptan5	posaconazole			
copanlisib	ritonavir			
crizotinib	saquinavir			
cyclosporine4	telaprevir			
dabrafenib	telithromycin			
dapsone	voriconazole			
darifenacin5				
darunavir5				
dasatinib5				
dexamethasone2				
diazepam				
dihydroergotamine				
docetaxel				
doxorubicin				
dronedarone5				
eletriptan5				
eplerenone5				
ergotamine4				
erlotinib				
estrogens				
etoposide				
everolimus5				
fentanyl4				
gefitinib				
haloperidol				
ibrutinib5				
idelalisib				
imatinib				
indinavir5				
irinotecan				
isavuconazole5				
itraconazole				
ivacaftor				
ketoconazole				

lansoprazole lapatinib losartan lovastatin5 lurasidone5 macrolide antibiotics maraviroc5 medroxyprogesterone methadone midazolam5 midostaurin5 modafinil nefazodone nilotinib olaparib ondansetron osimertinib paclitaxel palbociclib pazopanib quetiapine5 quinidine4 regorafenib romidepsin saquinavir5 sildenafil5 simvastatin5 sirolimus4,5 sonidegib sunitinib tacrolimus4,5 tamoxifen telaprevir temsirolimus teniposide tetracycline tipranavir5 tolvaptan5 triazolam5 trimethoprim vardenafil5 vemurafenib venetoclax5 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: MEDICATION DIARY FOR BVD-523FB (ULIXERTINIB)

COG Patient ID:_____ Acc#_____ Institution :_____

Please do not write patient names on this form.

Complete each day with the time and dose given for BVD-523FB (ulixertinib). If a dose is not due or is accidentally skipped leave that day blank. ***Make note of other drugs and supplements taken under the Comments section below***. BVD-523FB (ulixertinib) capsules should not be opened, chewed, or crushed but should be swallowed whole. If capsule is broken and the powder of the capsules gets on skin, wash the exposed area with as much water as necessary. Inform your study doctor or nurse if that occurs. BVD-523FB (ulixertinib) should be taken by mouth on an empty stomach either 1 hour before a meal or 2 hours after a meal. If you miss or vomit a dose, an additional dose should not be taken. Resume dosing at the next scheduled time. Add the dates to the calendar below and return the completed diary to the study clinic after each treatment cycle (weekly during cycle 1, and then after each treatment cycle).

*Please Note: If you are taking part in the optional pharmacokinetic studies. For Day 1 of cycle 1, only take the AM dose, do not take the PM dose.

EXAMPLE			***Number of BVD-523FB (ulixertinib) capsules***	***Comments***
	Date	***Time***	**150 mg**	
Day 1	*1/15/14*	*8:30 AM*	1	*He felt nauseated an hour after taking the drug but did not vomit.*

Cycle #: _____ Start Date: |__/__|__/__|__/__|
End Date: |__/__|__/__|__/__|

Dose Level: _____mg/m^2/dose

WEEK 1	**Date**	**Time**		**# of BVD-523FB (ulixertinib) 150 mg capsules prescribed to take** **AM#___ PM#___** **# of BVD-523FB (ulixertinib) 150 mg capsules taken**	**Comments (Describe any missed or extra doses, vomiting and/or bothersome effects.)**
Day 1*			**AM**		
			PM*		
Day 2			**AM**		
			PM		
Day 3			**AM**		
			PM		
Day 4			**AM**		
			PM		
Day 5			**AM**		
			PM		
Day 6			**AM**		
			PM		
Day 7			**AM**		
			PM		

WEEK 2	Date	Time		# of BVD-523FB (ulixertinib) 150 mg capsules prescribed to take AM#___ PM#___ / # of BVD-523FB (ulixertinib) 150 mg capsules taken	Comments (Describe any missed or extra doses, vomiting and/or bothersome effects.)
Day 8			AM		
			PM		
Day 9			AM		
			PM		
Day 10			AM		
			PM		
Day 11			AM		
			PM		
Day 12			AM		
			PM		
Day 13			AM		
			PM		
Day 14			AM		
			PM		
WEEK 3	**Date**	**Time**		**# of BVD-523FB (ulixertinib) 150 mg capsules prescribed to take AM#___ PM#___ / # of BVD-523FB (ulixertinib) 150mg capsules taken**	**Comments (Describe any missed or extra doses, vomiting and/or bothersome effects.)**
Day 15			AM		
			PM		
Day 16			AM		
			PM		
Day 17			AM		
			PM		
Day 18			AM		
			PM		
Day 19			AM		
			PM		
Day 20			AM		
			PM		
Day 21			AM		
			PM		

WEEK 4	Date	Time		# of BVD-523FB (ulixertinib) 150 mg capsules prescribed to take AM#___ PM#___ # of BVD-523FB (ulixertinib) 150mg capsules taken	Comments (Describe any missed or extra doses, vomiting and/or bothersome effects.)
Day 22			AM		
			PM		
Day 23			AM		
			PM		
Day 24			AM		
			PM		
Day 25			AM		
			PM		
Day 26			AM		
			PM		
Day 27			AM		
			PM		
Day 28			AM		
			PM		

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

Signature: _____ Date: _____

(site personnel who administered the drug)

;

APPENDIX IV CORRELATIVE STUDIES

Correlative Study	Section.	Blood Volume		Tube Type
		Volume per Sample	Total Cycle 1	
Pharmacokinetics	8.4	2 mL	24 mL	K_2 EDTA lavender top
Total Blood Volume in Cycle 1			**24 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 V: BVD-523FB (ULIXERTINIB) DOSING NOMOGRAM

BVD-523FB (ulixertinib) Dose Assignment: 175 mg/m^2/dose PO BID (Dose Level -1)

BSA (m^2)	BVD-523FB (ulixertinib) dosing	Total Daily dose (mg/day)	Total Daily pill count	Dose Reduction for Toxicity
0.54-0.72	Off-Study	Off-Study	Off-study	Off-study
0.73-1.07	150 mg PO BID	300	2	Off-Study
1.08-1.58	300 mg PO AM, 150 mg PO PM	450	3	150 mg PO BID
≥1.59	300 mg PO BID	600	4	300 mg PO AM, 150 mg PO PM

BVD-523FB (ulixertinib) Dose Assignment: 260 mg/m^2/dose PO BID (Dose Level 1)

BSA (m^2)	BVD-523FB (ulixertinib) dosing	Total Daily dose (mg/day)	Total Daily pill count	Dose Reduction for Toxicity
0.54-0.72	150 mg PO BID	300	2	off study
0.73-1.07	300 mg PO AM, 150 mg PO PM	450	3	150 mg PO BID
1.08-1.29	300 mg PO BID	600	4	300 mg PO AM, 150 mg PO PM
1.3-1.58	450 mg PO AM, 300 mg PO PM	750	5	300 mg PO AM, 150 mg PO PM
≥1.59	450 mg PO BID	900	6	300 mg PO BID

BVD-523FB (ulixertinib) Dose Assignment: 350 mg/m^2/dose PO BID (Dose Level 2)

BSA (m^2)	BVD-523FB (ulixertinib) dosing	Total Daily dose (mg/day)	Total Daily pill count	Dose Reduction for Toxicity
0.54-0.72	300 mg PO AM, 150 mg PO PM	450	3	150 mg PO BID
0.73-1.07	300 mg PO BID	600	4	300 mg PO AM, 150 mg PO PM
1.08-1.29	450 mg PO BID	900	6	300 mg PO BID
1.3-1.58	600 mg PO AM, 450 mg PO PM	1050	7	450 mg PO AM, 300 mg PO PM
≥1.59	600 mg PO BID	1200	8	450 mg PO BID

APPENDIX VI: APEC1621J 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
BVD-523FB (ulixertinib) IND # 134661	PO	**Dose Level -1**: 175 mg/m^2/dose BID (max 300 mg BID) **Dose Level 1**: 260 mg/m^2/dose BID (max 450 mg BID) **Dose Level 2**: 350 mg/m^2/dose BID (max 600 mg BID)	1-28	Refer to dosing nomogram (Appendix V) Take by mouth on an empty stomach either 1 hour before a meal or 2 hours after a meal. Capsules should not be opened, crushed or chewed. If a patient misses or vomits a dose, an additional dose should not be taken. Patients should resume dosing at the next scheduled time. If capsule is broken and the powder of the capsules gets on skin, wash the exposed area with as much water as necessary.

Ht _____cm Wt _____kg BSA _____m^2

Date Due	Date Given	Day	**BVD-523FB (ulixertinib)** _____mg AM _____mg PM	Studies
			Enter calculated dose above as per dosing nomogram and actual dose administered below	
		1	_____mg AM _____mg PM	g*
		2	_____mg AM _____mg PM	g
		3	_____mg AM _____mg PM	c
		4	_____mg AM _____mg PM	
		5	_____mg AM _____mg PM	
		6	_____mg AM _____mg PM	
		7	_____mg AM _____mg PM	
		8	_____mg AM _____mg PM	a, c, d, e, f
		9	_____mg AM _____mg PM	
		10	_____mg AM _____mg PM	
		11	_____mg AM _____mg PM	
		12	_____mg AM _____mg PM	c
		13	_____mg AM _____mg PM	
		14	_____mg AM _____mg PM	
		15	_____mg AM _____mg PM	a, c, d, e, f, g
		16	_____mg AM _____mg PM	
		17	_____mg AM _____mg PM	
		18	_____mg AM _____mg PM	c
		19	_____mg AM _____mg PM	
		20	_____mg AM _____mg PM	
		21	_____mg AM _____mg PM	
		22	_____mg AM _____mg PM	a, c, d, e, f, g
		23	_____mg AM _____mg PM	
		24	_____mg AM _____mg PM	
		25	_____mg AM _____mg PM	c

Cycle 1

		26	_____mg AM	_____mg PM	
		27	_____mg AM	_____mg PM	
		28/1	_____mg AM	_____mg PM	a, b, c, d, e, f, h, i, j
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).					

See Section 6.0 for Dose Modifications for Toxicities and the COG Member website for Supportive Care Guidelines.
* The PM dose of BVD-523FB (ulixertinib) on Day 1, Cycle 1 will not be given for patients undergoing these PK studies.

Required Observations in Cycle 1

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

a.	History/Physical Exam (including VS).
b.	Ht/Wt/BSA
c.	CBC/differential/platelets- If patients have Grade 4 neutropenia then CBCs should be checked at least every other day until recovery to Grade 3 or until meeting the criteria for dose limiting toxicity. If patients develop Grade 3 or greater thrombocytopenia then CBCs should be checked every 3 to 4 days until recovery per Section 6.1.
d.	Electrolytes including Ca++, PO4, Mg++
e.	Creatinine, ALT, bilirubin
f.	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.
g.	Pharmacokinetics- see Section 8.4 for details of PK studies.
h.	EKG For information related to prestudy observations please refer to section 8.1
i.	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.
j.	Albumin

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)

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
BVD-523FB (ulixertinib) IND # 134661	PO	**Dose Level -1**: 175 mg/m^2/dose BID (max 300 mg BID) **Dose Level 1**: 260 mg/m^2/dose BID (max 450 mg BID) **Dose Level 2**: 350 mg/m^2/dose BID (max 600 mg BID)	1-28	Refer to dosing nomogram (Appendix V) Take by mouth on an empty stomach either 1 hour before a meal or 2 hours after a meal. Capsules should not be opened, crushed or chewed. If a patient misses or vomits a dose, an additional dose should not be taken. Patients should resume dosing at the next scheduled time. If capsule is broken and the powder of the capsules gets on skin, wash the exposed area with as much water as necessary.

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

Date Due	Date Given	Day	**BVD-523FB (ulixertinib)** _____mg AM _____mg PM	Studies
			Enter calculated dose above as per dosing nomogram and actual dose administered below	
		1	_____mg AM _____mg PM	a-f, j
		2	_____mg AM _____mg PM	
		3	_____mg AM _____mg PM	
		4	_____mg AM _____mg PM	
		5	_____mg AM _____mg PM	
		6	_____mg AM _____mg PM	
		7	_____mg AM _____mg PM	
		8	_____mg AM _____mg PM	c
		9	_____mg AM _____mg PM	
		10	_____mg AM _____mg PM	
		11	_____mg AM _____mg PM	
		12	_____mg AM _____mg PM	
		13	_____mg AM _____mg PM	
		14	_____mg AM _____mg PM	
		15	_____mg AM _____mg PM	c
		16	_____mg AM _____mg PM	
		17	_____mg AM _____mg PM	
		18	_____mg AM _____mg PM	
		19	_____mg AM _____mg PM	
		20	_____mg AM _____mg PM	
		21	_____mg AM _____mg PM	
		22	_____mg AM _____mg PM	c
		23	_____mg AM _____mg PM	
		24	_____mg AM _____mg PM	

Subsequent Cycles

		25	_____mg AM	_____mg PM	
		26	_____mg AM	_____mg PM	
		27	_____mg AM	_____mg PM	
		28/1	_____mg AM	_____mg PM	a-f, g*,i. j*, k* l*, m*
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).					

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

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

Required Observations in All Subsequent Cycles

a.	History/Physical Exam (including VS)
b.	Ht/Wt/BSA
c.	CBC/differential/platelets- If patients have Grade 4 neutropenia then CBCs should be checked at least every other day until recovery to Grade 3 or until meeting the criteria for dose limiting toxicity. If patients develop Grade 3 or greater thrombocytopenia then CBCs should be checked every 3 to 4 days until recovery per section 6.1.
d.	Electrolytes including Ca++, PO4, Mg++
e.	Creatinine, ALT, bilirubin
f.	Albumin
g.	Tumor Disease Evaluation – Every other cycle x 3 then q 3 cycles. Tumor Disease Evaluation should be obtained on the next consecutive cycle after initial documentation of either a PR or CR. Subsequent scans may restart 2 cycles after the confirmatory scan. If the institutional investigator determines that the patient has progressed based on clinical or laboratory evidence, he/she may opt not to confirm this finding radiographically
h.	Bone Marrow Aspirate and/or biopsy- Only required in patients suspected of having bone marrow metastasis on the basis of history, symptoms, laboratory evaluation or other clinical data. Should only be performed on patients with known bone marrow involvement at baseline. Bone marrow aspirate and/or biopsy should be performed only when complete response or partial response is identified in target disease or when progression in bone marrow is suspected.
i.	Medication Diary- (see Appendix III) should be reviewed after completion of each treatment cycle and uploaded into RAVE. The medication diary should be collected weekly.
j.	Circulating Tumor DNA (ctDNA-optional)- With consent, two samples will be collected on this protocol (Cycle 5 Day 1; and for patients receiving ≥ 5 cycles, at progression or end of protocol therapy) see Section 8.5 for details of the ctDNA studies.
k.	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.
l.	Ophthalmological examinations will be performed by an ophthalmologist at prestudy and if clinically indicated during treatment.
m.	ECHO or gated radionuclide study- Every 3 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)

APPENDIX VII: TARGET HISTOLOGIES FOR APEC1621J EXPANSION COHORTS

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

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

APPENDIX VIII: APEC1621J ACTIONABLE MUTATIONS OF INTEREST

NON-HOTSPOT	**RULES**			
Gene Name	Description	Variant Type	Region	LOE
NF1	Include	Deleterious		3.2
MAPK1	Include	missense	aa 321-321	2
BRAF	Include	missense	aa 485-485	2
INCLUSION	**VARIANTS**			
Hotspots				
Gene Name	Variant ID	Variant Type	aMOI	LOE
NRAS	COSM586	SNV	p.Q61H	3.2
NRAS	COSM585	SNV	p.Q61H	3.2
NRAS	COSM583	SNV	p.Q61L	3.2
NRAS	COSM582	SNV	p.Q61P	3.2
NRAS	COSM584	SNV	p.Q61R	2.2
NRAS	COSM30646	MNV	p.Q61L	3.2
NRAS	COSM33693	MNV	p.Q61R	2.2
NRAS	COSM580	SNV	p.Q61K	2.2
NRAS	COSM581	SNV	p.Q61E	3.2
NRAS	COSM53223	MNV	p.Q61K	2.2
NRAS	COSM12725	MNV	p.Q61L	3.2
NRAS	COSM579	MNV	p.Q61R	2.2
NRAS	COSM12730	MNV	p.Q61K	2.2
NRAS	COSM574	SNV	p.G13V	2.2
NRAS	COSM573	SNV	p.G13D	3.2
NRAS	COSM575	SNV	p.G13A	3.2
NRAS	COSM572	MNV	p.G13V	2.2
NRAS	COSM569	SNV	p.G13R	3.2
NRAS	COSM570	SNV	p.G13C	3.2
NRAS	COSM571	SNV	p.G13S	3.2
NRAS	COSM564	SNV	p.G12D	3.2
NRAS	COSM565	SNV	p.G12A	3.2
NRAS	COSM566	SNV	p.G12V	3.2
NRAS	COSM561	SNV	p.G12R	3.2
NRAS	COSM563	SNV	p.G12S	3.2
NRAS	COSM562	SNV	p.G12C	3.2
HRAS	COSM503	SNV	p.Q61H	3.2
HRAS	COSM502	SNV	p.Q61H	3.2
HRAS	COSM499	SNV	p.Q61R	3.2
HRAS	COSM500	SNV	p.Q61P	3.2
HRAS	COSM498	SNV	p.Q61L	3.2
HRAS	COSM33695	MNV	p.Q61R	3.2
HRAS	COSM501	MNV	p.Q61R	3.2
HRAS	COSM497	SNV	p.Q61E	3.2
HRAS	COSM496	SNV	p.Q61K	3.2
HRAS	COSM52978	MNV	p.Q61L	3.2
HRAS	COSM490	SNV	p.G13D	3.2
HRAS	COSM489	SNV	p.G13V	3.2

HRAS	COSM488	SNV	p.G13C	3.2
HRAS	COSM487	SNV	p.G13S	3.2
HRAS	COSM486	SNV	p.G13R	3.2
HRAS	COSM483	SNV	p.G12V	3.2
HRAS	COSM484	SNV	p.G12D	3.2
HRAS	COSM485	SNV	p.G12A	3.2
HRAS	COSM482	SNV	p.G12R	3.2
HRAS	COSM481	SNV	p.G12C	3.2
HRAS	COSM480	SNV	p.G12S	3.2
KRAS	COSM19900	SNV	p.A146V	3.2
KRAS	COSM19404	SNV	p. A146T	3.2
KRAS	COSM19940	SNV	p.K117N	3.2
KRAS	COSM28519	SNV	p.K117N	3.2
KRAS	COSM554	SNV	p.Q61H	3.2
KRAS	COSM555	SNV	p.Q61H	3.2
KRAS	COSM553	SNV	p.Q61L	3.2
KRAS	COSM552	SNV	p.Q61R	3.2
KRAS	COSM551	SNV	p.Q61P	3.2
KRAS	COSM1168052	MNV	p.Q61R	3.2
KRAS	COSM550	SNV	p.Q61E	3.2
KRAS	COSM549	SNV	p.Q61K	3.2
KRAS	COSM87298	MNV	p.Q61K	3.2
KRAS	COSM539	SNV	p.G15D	3.2
KRAS	COSM538	SNV	p.G15S	3.2
KRAS	COSM87280	MNV	p.G13E	3.2
KRAS	COSM30567	MNV	p.G13E	3.2
KRAS	COSM533	SNV	p.G13A	3.2
KRAS	COSM534	SNV	p.G13V	3.2
KRAS	COSM532	SNV	p.G13D	3.2
KRAS	COSM531	MNV	p.G13D	3.2
KRAS	COSM530	MNV	p.G13V	3.2
KRAS	COSM12721	MNV	p.G13V	3.2
KRAS	COSM528	SNV	p.G13S	3.2
KRAS	COSM527	SNV	p.G13C	3.2
KRAS	COSM529	SNV	p.G13R	3.2
KRAS	COSM13643	MNV	p.G12N	3.2
KRAS	COSM512	MNV	p.G12F	3.2
KRAS	COSM514	MNV	p.G12L	3.2
KRAS	COSM87281	MNV	p.G13C	3.2
KRAS	COSM520	SNV	p.G12V	3.2
KRAS	COSM521	SNV	p.G12D	3.2
KRAS	COSM522	SNV	p.G12A	3.2
KRAS	COSM14209	MNV	p.G12D	3.2
KRAS	COSM515	MNV	p.G12V	3.2
KRAS	COSM518	SNV	p.G12R	3.2
KRAS	COSM517	SNV	p.G12S	3.2
KRAS	COSM516	SNV	p.G12C	3.2
KRAS	COSM513	MNV	p.G12C	3.2

KRAS	PM_COSM5413585	MNV	p.G12A	3.2
KRAS	PM_COSM1716372	MNV	p.G12L	3.2
KRAS	PM_COSM249888	MNV	p.G12R	3.2
KRAS	PM_COSM4387522	MNV	p.G12V	3.2
KRAS	PM_COSM4745557	MNV	p.G13R	3.2
ARAF	COSM5044705	SNV	p.S214C	3.2
ARAF	COSM1742787	SNV	p.S214A	3.2
ARAF	COSM612884	SNV	p.S214F	3.2
BRAF	COSM308550	MNV	p.V600D	3.2
BRAF	COSM477	MNV	p.V600D	3.2
BRAF	COSM475	MNV	p.V600E	2.2
BRAF	COSM1127	MNV	p.V600R	3.2
BRAF	COSM1583011	MNV	p.V600R	3.2
BRAF	COSM473	MNV	p.V600K	3.2
BRAF	COSM474	MNV	p.V600R	3.2
BRAF	COSM6137	SNV	p.V600G	3.2
BRAF	COSM18443	SNV	p.V600A	3.2
BRAF	COSM249889	MNV	p.V600Q	3.2
BRAF	COSM476	SNV	p.V600E	2.2
BRAF	COSM1130	SNV	p.V600M	3.2
BRAF	COSM219798	SNV	p.V600L	3.2
BRAF	COSM33808	SNV	p.V600L	3.2
BRAF	COSM1132	SNV	p.K601N	3.2
BRAF	COSM6265	SNV	p.K601N	3.2
BRAF	COSM1133	DEL	p.V600_K601>E	3.2
BRAF	PM_COSM30730	INS	p.T599_V600insT	3.2
BRAF	PM_COSM26625	INS	p.A598_T599insV	3.2
BRAF	COSM457	SNV	p.G469R	3.2
BRAF	COSM455	SNV	p.G469R	3.2
BRAF	COSM1112	SNV	p.G466R	3.2
BRAF	COSM478	SNV	p.K601E	3.2
BRAF	COSM472	SNV	p.T599I	3.2
BRAF	COSM21549	SNV	p.A598V	3.2
BRAF	COSM1126	MNV	p.L597S	3.2
BRAF	COSM1125	SNV	p.L597Q	2.2
BRAF	COSM471	SNV	p.L597R	3.2
BRAF	COSM470	SNV	p.L597V	3.2
BRAF	COSM469	SNV	p.G596R	3.2
BRAF	COSM53198	SNV	p.F595L	3.2
BRAF	COSM468	SNV	p.F595L	3.2
BRAF	COSM21612	SNV	p.F595L	3.2
BRAF	COSM466	SNV	p.D594V	3.2
BRAF	COSM467	SNV	p.D594G	3.2
BRAF	COSM211600	MNV	p.D594N	3.2
BRAF	COSM1583010	SNV	p.D594A	3.2
BRAF	COSM27639	SNV	p.D594N	3.2
BRAF	COSM463	SNV	p.E586K	3.2
BRAF	COSM462	SNV	p.N581S	3.2

BRAF	COSM1133046	SNV	p.Y472C	3.2
BRAF	COSM459	SNV	p.G469V	3.2
BRAF	COSM460	SNV	p.G469A	2.2
BRAF	COSM461	SNV	p.G469E	3.2
BRAF	COSM451	SNV	p.G466V	3.2
BRAF	COSM453	SNV	p.G466E	3.2
BRAF	COSM452	SNV	p.G466A	3.2
BRAF	COSM253328	SNV	p.G466R	3.2
BRAF	COSM449	SNV	p.G464E	3.2
BRAF	COSM450	SNV	p.G464V	3.2
BRAF	COSM1448615	SNV	p.G464R	3.2
BRAF	COSM1111	SNV	p.G464R	3.2
BRAF	COSM448	SNV	p.I463S	3.2
BRAF	COSM447	SNV	p.R462I	3.2
MAP2K1	PM_E1	DEL	p.F53_Q58delFLTQKQaddL	3.2
MAP2K1	PM_E2	DEL	p.Q56_V60delQKQKV	3.2
MAP2K1	COSM1235481	SNV	p.Q56P	3.2
MAP2K1	COSM4756761	SNV	p.K57T	3.2
MAP2K1	COSM1235478	SNV	p.K57N	3.2
MAP2K1	COSM5520914	SNV	p.K57N	3.2
MAP2K1	PM_COSM4166150	DEL	p.K57_G61del	3.2
MAP2K1	PM_COSM5031101	DEL	p.Q58_E62delQKVGE	3.2
MAP2K1	PM_COSM5031100	DEL	p.Q58_E62delQKVGE	3.2
MAP2K1	PM_COSM1235479	SNV	p.D67N	3.2
MAP2K1	COSM1678546	SNV	p.D67N	3.2
MAP2K1	PM_COSM404998	DEL	p.E102_I103delEI	3.2
MAP2K1	PM_COSM4166152	DEL	p.E102_I103del	3.2
MAP2K1	PM_COSM4166153	DEL	p.E102_I103del	3.2
MAP2K1	PM_COSM5730253	DEL	p.I103_K104delIK	3.2
MAP2K1	PM_COSM5702512	DEL	p.I103_K104del	3.2
MAP2K1	PM_E3	SNV	p.E120Q	3.2
MAP2K1	PM_COSM555601	SNV	p.C121S	3.2
MAP2K1	COSM1315829	SNV	p.C121S	3.2
MAP2K1	PM_E4	SNV	p.S123T	3.2
MAP2K1	COSM1374186	SNV	p.G128D	3.2
MAP2K1	COSM232755	SNV	p.E203K	3.2
GNA11	COSM52969	SNV	p.Q209L	3.2
GNA11	COSM52970	SNV	p.Q209P	3.2
GNAQ	COSM28757	SNV	p.Q209L	3.2
GNAQ	COSM28758	SNV	p.Q209P	3.2
GNAQ	COSM28760	SNV	p.Q209R	3.2
GNAQ	COSM52975	SNV	p.R183Q	3.2
MAPK1	COSM461148	SNV	p.E322K	2
MAPK1	COSM1616272	SNV	p.E322V	3
FUSIONS:				
BRAF	AGAP3-BRAF.A10B11	Fusion	AGAP3-BRAF.A10B11	3.2
BRAF	AGAP3-BRAF.A9B9	Fusion	AGAP3-BRAF.A9B9	3.2

BRAF	AGK-BRAF.A2B8	Fusion	AGK-BRAF.A2B8	3.2
BRAF	AGTRAP-BRAF.A5B8.COSF828.1	Fusion	AGTRAP-BRAF.A5B8.COSF828.1	3.2
BRAF	AKAP9-BRAF.A21B10	Fusion	AKAP9-BRAF.A21B10	3.2
BRAF	AKAP9-BRAF.A22B9	Fusion	AKAP9-BRAF.A22B9	3.2
BRAF	AKAP9-BRAF.A28B9	Fusion	AKAP9-BRAF.A28B9	3.2
BRAF	AKAP9-BRAF.A7B11	Fusion	AKAP9-BRAF.A7B11	3.2
BRAF	AKAP9-BRAF.A8B9.COSF1013.1	Fusion	AKAP9-BRAF.A8B9.COSF1013.1	3.2
BRAF	AP3B1-BRAF.A22B9	Fusion	AP3B1-BRAF.A22B9	3.2
BRAF	ARMC10-BRAF.A4B11	Fusion	ARMC10-BRAF.A4B11	3.2
BRAF	ATG7-BRAF.A18B9	Fusion	ATG7-BRAF.A18B9	3.2
BRAF	BAIAP2L1-BRAF.B12B9	Fusion	BAIAP2L1-BRAF.B12B9	3.2
BRAF	BBS9-BRAF.B19B4	Fusion	BBS9-BRAF.B19B4	3.2
BRAF	BCL2L11-BRAF.B3B10	Fusion	BCL2L11-BRAF.B3B10	3.2
BRAF	BRAF-AP3B1.B8A23	Fusion	BRAF-AP3B1.B8A23	3.2
BRAF	BRAF-BRAF.B1B11	Fusion	BRAF-BRAF.B1B11	3.2
BRAF	BRAF-BRAF.B1B9	Fusion	BRAF-BRAF.B1B9	3.2
BRAF	BRAF-BRAF.B3B11	Fusion	BRAF-BRAF.B3B11	3.2
BRAF	BRAF-BRAF.B3B9	Fusion	BRAF-BRAF.B3B9	3.2
BRAF	BRAF-CIITA.B9C6	Fusion	BRAF-CIITA.B9C6	3.2
BRAF	BRAF-MACF1.B8M15	Fusion	BRAF-MACF1.B8M15	3.2
BRAF	BRAF-MRPS33.B1M2	Fusion	BRAF-MRPS33.B1M2	3.2
BRAF	BRAF-SLC26A4.B3S7	Fusion	BRAF-SLC26A4.B3S7	3.2
BRAF	BRAF-SUGCT.B1S13	Fusion	BRAF-SUGCT.B1S13	3.2
BRAF	BTF3L4-BRAF.B3B11	Fusion	BTF3L4-BRAF.B3B11	3.2
BRAF	C7orf73-BRAF.C2B9	Fusion	C7orf73-BRAF.C2B9	3.2
BRAF	CCDC6-BRAF.C1B9	Fusion	CCDC6-BRAF.C1B9	3.2
BRAF	CCDC91-BRAF.C11B9	Fusion	CCDC91-BRAF.C11B9	3.2
BRAF	CCNY-BRAF.C1B10	Fusion	CCNY-BRAF.C1B10	3.2
BRAF	CDC27-BRAF.C16B9.1	Fusion	CDC27-BRAF.C16B9.1	3.2
BRAF	CEP89-BRAF.C16B9	Fusion	CEP89-BRAF.C16B9	3.2
BRAF	CLCN6-BRAF.C2B11.COSF1440	Fusion	CLCN6-BRAF.C2B11.COSF1440	3.2
BRAF	CLIP2-BRAF.C6B11	Fusion	CLIP2-BRAF.C6B11	3.2
BRAF	CUL1-BRAF.C7B9	Fusion	CUL1-BRAF.C7B9	3.2
BRAF	CUX1-BRAF.C10B9	Fusion	CUX1-BRAF.C10B9	3.2
BRAF	DYNC1I2-BRAF.D7B10	Fusion	DYNC1I2-BRAF.D7B10	3.2
BRAF	EML4-BRAF.E6B10	Fusion	EML4-BRAF.E6B10	3.2
BRAF	EPS15-BRAF.E22B10	Fusion	EPS15-BRAF.E22B10	3.2
BRAF	ERC1-BRAF.E12B10	Fusion	ERC1-BRAF.E12B10	3.2
BRAF	ERC1-BRAF.E17B8	Fusion	ERC1-BRAF.E17B8	3.2
BRAF	FAM114A2-BRAF.F9B11	Fusion	FAM114A2-BRAF.F9B11	3.2
BRAF	FAM131B-BRAF.F1B10.COSF1191	Fusion	FAM131B-BRAF.F1B10.COSF1191	3.2
BRAF	FAM131B-BRAF.F2B9.COSF1189.1	Fusion	FAM131B-BRAF.F2B9.COSF1189.1	3.2
BRAF	FAM131B-BRAF.F3B9.COSF1193	Fusion	FAM131B-BRAF.F3B9.COSF1193	3.2
BRAF	FCHSD1-BRAF.F13B9.COSF403	Fusion	FCHSD1-BRAF.F13B9.COSF403	3.2
BRAF	FXR1-BRAF.F13B10	Fusion	FXR1-BRAF.F13B10	3.2
BRAF	GATM-BRAF.G2B11	Fusion	GATM-BRAF.G2B11	3.2
BRAF	GHR-BRAF.G1B10	Fusion	GHR-BRAF.G1B10	3.2
BRAF	GNAI1-BRAF.G1B10.COSF1442	Fusion	GNAI1-BRAF.G1B10.COSF1442	3.2

BRAF	GTF2I-BRAF.G4B10	Fusion	GTF2I-BRAF.G4B10	3.2
BRAF	HERPUD1-BRAF.H4B7	Fusion	HERPUD1-BRAF.H4B7	3.2
BRAF	KCTD7-BRAF.K3B8	Fusion	KCTD7-BRAF.K3B8	3.2
BRAF	KCTD7-BRAF.K4B8	Fusion	KCTD7-BRAF.K4B8	3.2
BRAF	KDM7A-BRAF.K11B11	Fusion	KDM7A-BRAF.K11B11	3.2
BRAF	KIAA1549-BRAF.K12B11	Fusion	KIAA1549-BRAF.K12B11	3.2
BRAF	KIAA1549-BRAF.K12B9.COSF1474	Fusion	KIAA1549-BRAF.K12B9.COSF1474	3.2
BRAF	KIAA1549-BRAF.K13B9	Fusion	KIAA1549-BRAF.K13B9	3.2
BRAF	KIAA1549-BRAF.K14B11.COSF1226	Fusion	KIAA1549-BRAF.K14B11.COSF1226	3.2
BRAF	KIAA1549-BRAF.K14B9.COSF483	Fusion	KIAA1549-BRAF.K14B9.COSF483	3.2
BRAF	KIAA1549-BRAF.K15B10.COSF1283.1	Fusion	KIAA1549-BRAF.K15B10.COSF1283.1	3.2
BRAF	KIAA1549-BRAF.K15B11.COSF485.1	Fusion	KIAA1549-BRAF.K15B11.COSF485.1	3.2
BRAF	KIAA1549-BRAF.K15B9.COSF481.1	Fusion	KIAA1549-BRAF.K15B9.COSF481.1	3.2
BRAF	KIAA1549-BRAF.K16B10	Fusion	KIAA1549-BRAF.K16B10	3.2
BRAF	KIAA1549-BRAF.K17B10.COSF509	Fusion	KIAA1549-BRAF.K17B10.COSF509	3.2
BRAF	KIAA1549-BRAF.K18B9.COSF511	Fusion	KIAA1549-BRAF.K18B9.COSF511	3.2
BRAF	KIAA1549-BRAF.K9B9	Fusion	KIAA1549-BRAF.K9B9	3.2
BRAF	KLHL7-BRAF.K5B9	Fusion	KLHL7-BRAF.K5B9	3.2
BRAF	LSM12-BRAF.L3B9	Fusion	LSM12-BRAF.L3B9	3.2
BRAF	LSM14A-BRAF.L9B9	Fusion	LSM14A-BRAF.L9B9	3.2
BRAF	MACF1-BRAF.M60B9	Fusion	MACF1-BRAF.M60B9	3.2
BRAF	MAD1L1-BRAF.M16B9	Fusion	MAD1L1-BRAF.M16B9	3.2
BRAF	MAD1L1-BRAF.M17B10	Fusion	MAD1L1-BRAF.M17B10	3.2
BRAF	MKRN1-BRAF.M4B11.COSF1444	Fusion	MKRN1-BRAF.M4B11.COSF1444	3.2
BRAF	MKRN1-BRAF.M4B9	Fusion	MKRN1-BRAF.M4B9	3.2
BRAF	MYRIP-BRAF.M16B9	Fusion	MYRIP-BRAF.M16B9	3.2
BRAF	MZT1-BRAF.M2B11	Fusion	MZT1-BRAF.M2B11	3.2
BRAF	NUB1-BRAF.N3B9	Fusion	NUB1-BRAF.N3B9	3.2
BRAF	NUDCD3-BRAF.N4B9	Fusion	NUDCD3-BRAF.N4B9	3.2
BRAF	NUP214-BRAF.N21B10	Fusion	NUP214-BRAF.N21B10	3.2
BRAF	PAPSS1-BRAF.P5B9.1	Fusion	PAPSS1-BRAF.P5B9.1	3.2
BRAF	PLIN3-BRAF.P1B9	Fusion	PLIN3-BRAF.P1B9	3.2
BRAF	RAD18-BRAF.R7B10	Fusion	RAD18-BRAF.R7B10	3.2
BRAF	RBMS3-BRAF.R11B11	Fusion	RBMS3-BRAF.R11B11	3.2
BRAF	RNF11-BRAF.R1B11	Fusion	RNF11-BRAF.R1B11	3.2
BRAF	RNF130-BRAF.R3B9.COSF1483	Fusion	RNF130-BRAF.R3B9.COSF1483	3.2
BRAF	RP2-BRAF.R3B10	Fusion	RP2-BRAF.R3B10	3.2
BRAF	SLC12A7-BRAF.S17B11	Fusion	SLC12A7-BRAF.S17B11	3.2
BRAF	SLC45A3-BRAF.S1B8.COSF871	Fusion	SLC45A3-BRAF.S1B8.COSF871	3.2
BRAF	SND1-BRAF.S10B11	Fusion	SND1-BRAF.S10B11	3.2
BRAF	SND1-BRAF.S10B9	Fusion	SND1-BRAF.S10B9	3.2
BRAF	SND1-BRAF.S11B11	Fusion	SND1-BRAF.S11B11	3.2
BRAF	SND1-BRAF.S14B11	Fusion	SND1-BRAF.S14B11	3.2
BRAF	SND1-BRAF.S14B9	Fusion	SND1-BRAF.S14B9	3.2
BRAF	SND1-BRAF.S16B9.1	Fusion	SND1-BRAF.S16B9.1	3.2
BRAF	SND1-BRAF.S18B10	Fusion	SND1-BRAF.S18B10	3.2
BRAF	SND1-BRAF.S9B2	Fusion	SND1-BRAF.S9B2	3.2
BRAF	SND1-BRAF.S9B9	Fusion	SND1-BRAF.S9B9	3.2

BRAF	SOX6-BRAF.S5B9	Fusion	SOX6-BRAF.S5B9	3.2
BRAF	SOX6-BRAF.S6B9	Fusion	SOX6-BRAF.S6B9	3.2
BRAF	STRN3-BRAF.S3B10	Fusion	STRN3-BRAF.S3B10	3.2
BRAF	TANK-BRAF.T4B9	Fusion	TANK-BRAF.T4B9	3.2
BRAF	TAX1BP1-BRAF.T8B11.1	Fusion	TAX1BP1-BRAF.T8B11.1	3.2
BRAF	TMEM178B-BRAF.T2B9	Fusion	TMEM178B-BRAF.T2B9	3.2
BRAF	TMPRSS2-BRAF.T3B11	Fusion	TMPRSS2-BRAF.T3B11	3.2
BRAF	TRIM24-BRAF.T10B9	Fusion	TRIM24-BRAF.T10B9	3.2
BRAF	TRIM24-BRAF.T11B2	Fusion	TRIM24-BRAF.T11B2	3.2
BRAF	TRIM24-BRAF.T3B10	Fusion	TRIM24-BRAF.T3B10	3.2
BRAF	TRIM24-BRAF.T3B11	Fusion	TRIM24-BRAF.T3B11	3.2
BRAF	TRIM24-BRAF.T5B8	Fusion	TRIM24-BRAF.T5B8	3.2
BRAF	TRIM24-BRAF.T9B9.1	Fusion	TRIM24-BRAF.T9B9.1	3.2
BRAF	TRIM4-BRAF.T6B10	Fusion	TRIM4-BRAF.T6B10	3.2
BRAF	UBN2-BRAF.U3B11	Fusion	UBN2-BRAF.U3B11	3.2
BRAF	ZC3HAV1-BRAF.Z3B10	Fusion	ZC3HAV1-BRAF.Z3B10	3.2
BRAF	ZC3HAV1-BRAF.Z7B11	Fusion	ZC3HAV1-BRAF.Z7B11	3.2
BRAF	ZKSCAN5-BRAF.Z2B9	Fusion	ZKSCAN5-BRAF.Z2B9	3.2
BRAF	ZSCAN30-BRAF.Z3B10	Fusion	ZSCAN30-BRAF.Z3B10	3.2

APPENDIX IX: 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).

IRB Approval

U.S. sites participating in the PEP-CTN network are required to use the NCI CIRB as of March 1, 2019. Local IRB review will continue to be accepted for studies that are not reviewed by the CIRB, or if the study was previously open at the site under the local IRB. International sites should continue to submit Research Ethics Board (REB) approval to the CTSU Regulatory Office following country-specific regulations.

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

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

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

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

- Holds an Active CTEP status;
- Rostered at the site on the IRB/REB approval and on at least one participating roster;
- If using NCI CIRB, rostered on the NCI CIRB Signatory record;
- Includes the IRB number of the IRB providing approval in the Form FDA 1572 in the Registration and Credential Repository (RCR) profile; and
- Holds the appropriate CTEP registration type for the protocol.

Additional Requirements

Additional requirements to obtain an approved site registration status include:

- An active Federal Wide Assurance (FWA) number;

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

Downloading Site Registration Documents

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

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

Submitting Regulatory Documents

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

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

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

Checking Your Site's Registration Status

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

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

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

Requirements ForAPEC1621J 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, and/or Protocol Human Subjects Assurance Identification/IRB Certification/Declaration of Exemption Form.

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.

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Rave CTEP-AERS Integration

The Rave Cancer Therapy Evaluation Program Adverse Event Reporting System (CTEP-AERS) integration enables evaluation of post-baseline Adverse Events (AE) entered in Rave to determine whether they require expedited reporting, and facilitates entry in CTEP-AERS for those AEs requiring expedited reporting.

All AEs that occur after baseline are collected in Rave using the Adverse Event form, which is available for entry at each treatment or reporting period, and used to collect AEs that start during the period or persist from the previous reporting period. The Clinical Research Associate (CRA) will enter AEs that occur prior to the start of treatment on a baseline form that is not included in the Rave-CTEP-AERS integration. Baseline AEs must begin and end on the baseline Adverse Events form and should not be included on the Adverse Events form that is available at treatment unless there has been an increase in grade.

Prior to sending AEs through the rules evaluation process, site staff should verify the following on the Adverse Event form in Rave:

- The reporting period (course/cycle) is correct; and
- AEs are recorded and complete (no missing fields) and the form is query free.

The CRA reports AEs in Rave at the time the Investigator learns of the event. If the CRA modifies an AE, it must be re-submitted for rules evaluation.

Upon completion of AE entry in Rave, the Rave CRA submits the AE for rules evaluation by completing the Expedited Reporting Evaluation form in Rave. Both NCI and protocol-specific reporting rules evaluate the AEs submitted for expedited reporting. A report is initiated in CTEP-AERS using information entered in Rave for AEs that meet reporting requirements. The CRA completes the report by accessing CTEP-AERS via a direct link on the Rave Expedited Reporting Evaluation form.

In the rare occurrence, that Internet connectivity is lost; a 24-hour notification is to be made to CTEP by telephone at 301-897-7497. Once internet connectivity is restored, the 24-hour notification that was phoned in must be entered electronically into CTEP-AERS using the

direct link from Medidata Rave..

Additional information about the CTEP-AERS integration is available on the CTSU website:

- Study specific documents: Protocols > Documents> Education and Promotion; and
- Expedited Safety Reporting Rules Evaluation user guide: Resources > CTSU Operations Information> User Guides & Help Topics.

NCI requirements for SAE reporting are available on the CTEP website:

- NCI Guidelines for Investigators: Adverse Event Reporting Requirements is available at https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf.

Data Quality Portal

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

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

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

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

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

Central Monitoring

Central Monitoring (CM) Review is required for this protocol. CM allows Lead Protocol Organizations (LPOs) to remotely compare data entered in Rave to source documentation to ensure that sites are adhering to the protocol and central monitoring plan as well as accurately transcribing

data from patients' charts (i.e., source data verification).

Sites can upload source documents required for CM Review as documented in the central monitoring plan using the Source Document Portal (SDP). This application is available on the CTSU members' website under Auditing & Monitoring and may also be accessed using a direct link within Rave on the CM Alert form. Site staff with the CRA or Investigator roles in Rave can view and upload source documents. Prior to saving source documents on the SDP, each site is responsible for removing or redacting any Personally Identifiable Information (PII) (note that functionality to do this redaction exists within the SDP itself). Designated LPO staff will review each document after it has been loaded on the SDP to ensure the appropriate documents have been uploaded and to ensure PII is redacted.

Additional information on the SDP is available on the CTSU members' website under Auditing & Monitoring > Source Document Portal in the Help Topics button or by contacting the CTSU Help Desk (1-888-823-5923 or ctsucontact@westat.com).

APPENDIX X: PATIENT DRUG INFORMATION HANDOUT AND WALLET CARD

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

The patient _____ is enrolled on a clinical trial using the experimental study drug, BVD-523FB (ulixertinib)**.** This clinical trial is sponsored by the National Cancer Institute. This form is addressed to the patient, but includes important information for others who care for this patient.

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

BVD-523FB (ulixertinib) interacts with certain enzymes in your liver and a transport protein that helps move drugs in and out of cells.

- The enzymes in question are CYP 3A4, 2D6 and 1A2, which are responsible for breaking down BVD-523FB (ulixertinib) in the body. BVD-523FB (ulixertinib) may be affected by strong inhibitors or inducers of these enzymes.

- The protein in question is P-glycoprotein (P-gp) which moves BVD-523FB (ulixertinib) in and out of cells/organs in the body. BVD-523FB (ulixertinib) may be affected by strong inhibitors of P-gp.

- BVD-523FB (ulixertinib) is highly protein-bound and may interfere with binding of other drugs that are also highly protein-bound. Use caution with these drugs that have narrow therapeutic ranges.

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

BVD-523FB (ulixertinib) may interact with other drugs which can cause side effects. For this reason, it is very important to tell your study doctors of any medicines you are taking before you enroll onto this clinical trial. It is also very important to tell your doctors if you stop taking any regular medicines, or if you start taking a new medicine while you take part in this study. When you talk about your current medications with your doctors, include medicine you buy without a prescription (over-the-counter remedy), or any herbal supplements such as St. John's Wort. It is helpful to bring your medication bottles or an updated medication list with you.

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

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

BVD-523FB (ulixertinib) must be used very carefully with other medicines that are strong inhibitors of CYP 3A4, 2D6 or 1A2, strong inducers of CYP3A4 or strong inhibitors of the P-gp transport protein that is responsible for moving BVD-523FB (ulixertinib) in and out of cells in your body. Also, BVD-523FB (ulixertinib) is highly protein-bound and might affect how well other highly protein-bound drugs work in your body. Before you enroll onto the clinical trial, your study doctor will work with your regular health care providers to review any medicines and herbal supplements that are considered "strong inhibitors of CYP 3A4, 2D6, 1A2 or P-glycoprotein or strong inducers of CYP 3A4."

- Please be very careful! Over-the-counter drugs (including herbal supplements) may contain ingredients that could interact with your study drug. Speak to your doctors or pharmacist to determine if there could be any side effects.
- Avoid ingesting grapefruit, grapefruit juice or Seville oranges while taking BVD-523FB (ulixertinib).
- Avoid prolonged exposure to the sun and wear protective clothing and sunscreen when out in the sun.
- Your regular health care provider should check a frequently updated medical reference or call your study doctor before prescribing any new medicine or discontinuing any medicine.

Your study doctor's name is _____ and he or she can be contacted at _____.

STUDY DRUG INFORMATION WALLET CARD

You are enrolled on a clinical trial using the experimental study drug BVD-523FB (ulixertinib). This clinical trial is sponsored by the NCI. BVD-523FB (ulixertinib) may interact with drugs that affect certain liver enzymes, the P-gp transport protein in your body or affect the protein-binding of other drugs in your body. Because of this, it is very important to:

- Tell your doctors if you stop taking any medicines or if you start taking any new medicines.
- Tell all of your health care providers (doctors, physician assistants, nurse practitioners, or pharmacists) that you are taking part in a clinical trial.
- Check with your doctor or pharmacist whenever you need to use an over-the-counter medicine or herbal supplement.
- Avoid ingesting grapefruit, grapefruit juice or Seville oranges while taking BVD-523FB (ulixertinib).
- Avoid prolonged exposure to the sun and wear protective clothing and sunscreen when out in the sun

BVD-523FB (ulixertinib) interacts with CYP 3A4, 2D6, 1A2 and P-gp transport protein and is highly-protein bound and must be used very carefully with other medicines that interact with these CYP enzymes, P-gp or are highly protein-bound.

- Before you enroll onto the clinical trial, your study doctor will work with your regular health care providers to review any medicines and herbal supplements that are considered "strong inhibitors of CYP 3A4, 2D6, 1A2, strong inducers of CYP3A4, strong inhibitors of P-gp transporter or are highly-protein bound."
- Before prescribing new medicines, your regular health care providers should go to a frequently-updated medical reference for a list of drugs to avoid, or contact your study doctor.
- Your study doctor's name is _____

  and can be contacted at _____.

APPENDIX XI: TOXICITY-SPECIFIC GRADING

Bilirubin

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

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

Grade 1:	≤ 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

APPENDIX XII: YOUTH INFORMATION SHEETS
INFORMATION SHEET REGARDING RESEARCH STUDY APEC1621J
(for children from 7 through 12 years of age)

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

1. We have been talking with you about your cancer. You have had treatment for the cancer already but it did not go away or it came back after treatment.

2. 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.

3. You agreed to be part of a study to see if your cancer has any specific changes that could help us decide what medicine might "match" best to your cancer.

4. We have found a medicine called BVD-523FB (ulixertinib) that could "match" your tumor. The doctors want to see if BVD-523FB (ulixertinib) will help children with your type of cancer get better. We don't know if BVD-523FB (ulixertinib) will work well to get rid of your cancer. That is why we are doing the study.

5. Sometimes good things can happen to people when they are in a research study. These good things are called "benefits." We hope that a benefit to you of being part of this study is that BVD-523FB (ulixertinib) 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.

6. Sometimes bad things can happen to people when they are in a research study. These bad things are called "risks." The risks to you from this study are that you may have problems, or side effects from BVD-523FB (ulixertinib). There may be risks that we don't know about.

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

8. If you decide to be treated with BVD-523FB (ulixertinib) you might have some tests and check-ups done more often than you might if you weren't part of the study.

9. As part of the study we are also trying to learn more about children's cancers and how BVD-523FB (ulixertinib) works in them. We will draw some extra blood samples for this if your family agrees.

INFORMATION SHEET REGARDING RESEARCH STUDY APEC1621J
(for teens from 13 through 17 years of age)

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

1. We have been talking with you about your cancer. You have had treatment for the cancer already but the cancer did not go away or it came back after treatment.

2. 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.

3. The main purpose of this study is to learn how well cancers that have specific changes (mutations) respond to medicines that are aimed at those changes. This combination of a tumor with a mutation and a medicine that aims at that mutation is called a "match".

4. Your tumor has a mutation that matches BVD-523FB (ulixertinib), and so you have been assigned to BVD-523FB (ulixertinib). The doctors want to see if BVD-523FB (ulixertinib) will make children with your type of cancer get better. We don't know if BVD-523FB (ulixertinib) will work well to get rid of your cancer. That is why we are doing the study.

5. You will get BVD-523FB (ulixertinib) by mouth twice daily for a 28-day period. This entire 28-day period is called a cycle. BVD-523FB (ulixertinib) should be swallowed whole, not chewed or opened. You may continue to receive BVD-523FB (ulixertinib) for up to about 24 months (approximately 26 cycles) as long as you do not have bad effects from it and your cancer does not get any worse. If you decide to be treated with BVD-523FB (ulixertinib), you will also have exams and tests done that are part of normal cancer care. Some of these may be done more often while you are being treated with BVD-523FB (ulixertinib). The doctors want to see if BVD-523FB (ulixertinib) will help children or adolescents with your type of cancer get better. We don't know if BVD-523FB (ulixertinib) is better than other medicines. That is why we are doing this study.

6. 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 BVD-523FB (ulixertinib) 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.

7. 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 BVD-523FB (ulixertinib). Your doctor will talk to you about the risks we know about from BVD-523FB (ulixertinib). There may be other risks from BVD-523FB (ulixertinib) that we don't know about yet.

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

9. As part of the study we are also trying to learn more about the mutations that occur in cancers that happen in children and teens, as well as how BVD-523FB (ulixertinib) works. If your family agrees we will draw some extra blood samples to do these tests.

APPENDIX XIII: PATIENT INSTRUCTIONS FOR TREATING DIARRHEA

Guidelines for the Treatment of Diarrhea

Institutional practice may be used in place of these guidelines.

You should purchase or will be given a prescription for loperamide to have available to begin treatment at the first episode of poorly formed or loose stools or the earliest onset of bowel movements more frequent than normally expected for the patient. Patients will also be instructed to contact their physician if any diarrhea occurs. Patients will be given **loperamide** based on body weight.

LOPERAMIDE DOSING RECOMMENDATIONS (NOTE: maximum dose of loperamide for adults is 16 mg/day) *ALL patients: discontinue loperamide when the patient is no longer experiencing significant diarrhea.*	
Weight (kg)	**ACTION**
<13 kg	Take 0.5 mg (2.5 mL [one-half teaspoonful] of the 1 mg/5 mL oral solution) after the first loose bowel movement, followed by 0.5 mg (2.5 mL [one-half teaspoonful] of the 1 mg/5 mL oral solution) every 3 hours. During the night, the patient may take 0.5 mg (2.5 mL [one-half teaspoonful] of the 1 mg/5 mL oral solution) every 4 hours. Do not exceed 4 mg (20 mL or 4 teaspoonfuls) per day.
≥ 13 kg to < 20 kg	Take 1 mg (5 mL [1 teaspoonful] of the 1 mg/5 mL oral solution or one-half tablet) after the first loose bowel movement, followed by 1 mg (5 mL [one teaspoonful] of the 1 mg/5 mL oral solution or one-half tablet) every 3 hours. During the night, the patient may take 1 mg (5 mL [one teaspoonful] of the 1 mg/5 mL oral solution or one-half tablet) every 4 hours. Do not exceed 6 mg (30 mL or 6 teaspoonfuls) per day.
≥ 20 kg to < 30 kg	Take 2 mg (10 mL [2 teaspoonfuls] of the 1 mg/5 mL oral solution or 1 tablet) after the first loose bowel movement, followed by 1 mg (5 mL [one teaspoonful] of the 1 mg/5 mL oral solution or one-half tablet) every 3 hours. During the night, the patient may take 2 mg (10 mL [2 teaspoonfuls] of the 1 mg/5 mL oral solution or 1 tablet) every 4 hours. Do not exceed 8 mg (40 mL or 8 teaspoonfuls) per day.
≥ 30 kg to < 43 kg	Take 2 mg (10 mL [2 teaspoonfuls] of the 1 mg/5 mL oral solution or 1 tablet) after the first loose bowel movement, followed by 1 mg (5 mL [one teaspoonful] of the 1 mg/5 mL oral solution or one-half tablet) every 2 hours. During the night, the patient may take 2 mg (10 mL [2 teaspoonfuls] of the 1 mg/5 mL oral solution or 1 tablet) every 4 hours. Do not exceed 12 mg (60 mL or 12 teaspoonfuls) per day.
Over 43 kg	Take 4 mg (20 mL [4 teaspoonfuls] of the 1 mg/5 mL oral solution or 2 capsules or tablets) after the first loose bowel movement, followed by 2 mg (10 mL [2 teaspoonfuls] of the 1 mg/5 mL oral solution or 1 capsule or tablet) every 2 hours. During the night, the patient may take 4 mg (20 mL [4 teaspoonfuls] of the 1 mg/5 mL oral solution or 2 capsules or tablets) every 4 hours. Do not exceed 16 mg (80 mL or 16 teaspoonfuls) per day.