CHILDREN'S ONCOLOGY GROUP

The world's childhood cancer experts

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

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Operations and Informatics Branch
Cancer Therapy Evaluation Program
Division of Cancer Treatment and Diagnosis
National Cancer Institute
Executive Plaza North Room 730
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Dear [redacted],

Enclosed please find Amendment #4 to protocol **APEC1621G**, *NCI-COG Pediatric MATCH (Molecular Analysis for Therapy Choice) – Phase 2 Subprotocol of Vemurafenib in Patients with Tumors Harboring BRAF V600 Mutations*.

This is amendment is in response to the Request for Amendment from NCI PMB, dated October 6, 2020, for which the 120 mg tablets of vemurafenib are no longer available.

Administrative changes have been made; specific changes are detailed in the Summary of Changes table below. Minor administrative updates (such as the correction of typographical errors, spelling, or updates to the numbers of referenced sections) are tracked in the protocol but not specified.

Please let me know if you have any questions or need additional information.

Sincerely,

[redacted]
AeRang Kim, MD, APEC1621G Study Chair, **and**
[redacted], MD, [redacted]

SUMMARY OF CHANGES: PROTOCOL

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

#	Section	Page(s)	Change
1.	General	-	Updated protocol version date in the footer.
2.	Cover Page	1-2	Updated version date and amendment number. **Contact Information table has been added**
3.	Table of Contents		Updated for re-pagination.
4.	Study Committee	5-6	The study committee has been updated.
5.	2.4; 2.5	14-15	Reference to study NCT01748149 (personal communication) has been updated with the published article reference.
6.	3.2	17-18	The IRB Approval information has been updated to the most recent CTEP approved language.
7.	4.1.3	20	~~Due to limited drug supply of the 120 mg strength tablets,~~ Patients must have a body surface area ≥ ~~0.37~~ **0.55** m^2 at enrollment. Patients < 0.73 m^2 must follow the dosing nomogram provided in Appendix IV-A; patients ≥ 0.73 m2 at enrollment must follow the dosing nomogram provided in Appendix IV-B. ~~Patients enrolled after the drug supply of the 120mg strength has been exhausted must have a body surface area of ≥0.73 m^2 at enrollment and follow the dosing nomogram provided in Appendix IV-B.~~
8.	7.5	29-30	**Vemurafenib can increase plasma concentrations of P-gp substrates (eg., digoxin). Dose reduction of the concomitant P-gp substrate drug may be considered, if clinically indicated.** **Co-administration of vemurafenib resulted in an 18% increase in AUC of S-warfarin (CYP2C9 substrate). Exercise caution and consider additional INR monitoring when vemurafenib is used concomitantly with warfarin.**
9.	9.1	35	Agent information has been updated: **Co-administration of vemurafenib resulted in an 18% increase in AUC of S-warfarin (CYP2C9 substrate). Exercise caution and consider additional INR monitoring when vemurafenib is used concomitantly with warfarin.** **Multiple oral doses of vemurafenib (960 mg BID) increased the exposure of a single oral dose of digoxin, with an approximately 1.8 and 1.5 fold increase in digoxin AUC0-last and Cmax, respectively.** Dose reduction of the concomitant P-gp substrate drug may be considered, if clinically indicated.
10.	9.1.5	40-41	Vemurafenib is available as ~~120 mg (for a limited supply) and~~ 240 mg film-coated tablets for oral administration containing 112 tablets per bottle.

			The 240 mg strength will be supplied in the commercially available formulation, refer to the package label for expiration information. ~~Stability studies for the 120 mg tablets are ongoing.~~
11.	References		A reference has been added: **Nicolaides T, Nazemi KJ, Crawford J, et al.: Phase I study of vemurafenib in children with recurrent or progressive BRAF (V600E) mutant brain tumors: Pacific Pediatric Neuro-Oncology Consortium study (PNOC-002). Oncotarget 11:1942-1952, 2020**
12.	Appendix III-A	74-76	All references to 120 mg has been removed.
13.	Appendix IV-A	79	The dosing nomogram for smaller patients (**BSA ≥ 0.55 and < 0.73 m2**) has been updated.
14.	Appendix IV-B	80	Dosing Nomogram **Patients ≥ 0.73 m^2** Patients with a body surface area of ≥ ~~0.37~~ **0.55** and < 0.73 m^2
15.	Appendix XI	93-95	The CTEP and CTSU Registration Procedures have been updated to the most current template language.

SUMMARY OF CHANGES: INFORMED CONSENT

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

#	Section	Page(s)	Change
1.	General	All	Updated version date of consent to match the current version of the protocol.

Activated: July 24th, 2017
Closed:

Version Date: 11/10/2020
Amendment # 4

CHILDREN'S ONCOLOGY GROUP

APEC1621G

NCI-COG PEDIATRIC MATCH (MOLECULAR ANALYSIS FOR THERAPY CHOICE)- PHASE 2 SUBPROTOCOL OF VEMURAFENIB IN PATIENTS WITH TUMORS HARBORING BRAF V600 MUTATIONS

Open to COG Member Institutions in the USA

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CONTACT INFORMATION		
For Regulatory Requirements	**For patient enrollments:**	**For Data Submission**
Regulatory documentation must be submitted to the CTSU via the Regulatory Submission Portal. (Sign in at www.ctsu.org, and select the Regulatory > Regulatory Submission.) Institutions with patients waiting that are unable to use the Portal should alert the CTSU Regulatory Office immediately 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). OPEN is accessed at https://www.ctsu.org/OPEN_SYSTEM/ or https://open.ctsu.org. Contact the CTSU Help Desk with any OPEN-related questions by phone or email: 1-888-823-5923, or ctsucontact@westat.com.	Data collection for this study will be done exclusively through Medidata Rave. Please see the Data Submission Schedule in the CRF packet for further instructions.
The most current version of the **study protocol and all supporting documents** must be downloaded from the protocol-specific page located on the CTSU members' website (https://www.ctsu.org). Access to the CTSU members' website is managed through the Cancer Therapy and Evaluation Program - Identity and Access Management (CTEP-IAM) registration system and requires log in with a CTEP-IAM username and password. Permission to view and download this protocol and its supporting documents is restricted and is based on person and site roster assignment housed in the CTSU Regulatory Support System (RSS).		
For clinical questions (ie, patient eligibility or treatment-related) Contact the Study PI of the Lead Protocol Organization.		
For non-clinical questions (ie, unrelated to patient eligibility, treatment, or clinical data submission) Contact the CTSU Help Desk by phone or e-mail: CTSU General Information Line – 1-888-823-5923, or ctsucontact@westat.com. All calls and correspondence will be triaged to the appropriate CTSU representative.		
The CTSU Website is located at https://www.ctsu.org.		

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AGENT NSC# AND IND#'s

NCI-Supplied Agents:
Vemurafenib (NSC#761431 , [redacted])
IND Sponsor: DCTD, NCI

SEE Section 8.3.4 FOR SPECIMEN SHIPPING ADDRESSES

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

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

ABSTRACT

This subprotocol is a component of the NCI-COG Pediatric MATCH trial APEC1621. The APEC1621SC screening protocol details the assay used for the integral genomic profiling which will determine eligibility for this subprotocol. Here we will conduct a phase 2 trial of vemurafenib in children with relapsed or refractory solid tumors (including lymphomas, histiocytoses and CNS tumors) harboring specified activating genetic alterations of the BRAF gene. 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	Vemurafenib PO BID
Day 28	Evaluation

Vemurafenib will be administered orally twice daily continuously; a cycle will be 28 days. Evaluations will occur at the end of every other cycle x 3, then every 3 cycles.

Therapy will be discontinued if there is evidence of progressive disease or drug related dose-limiting toxicity that requires removal from therapy. 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 vemurafenib with advanced solid tumors (including CNS tumors), lymphomas or histiocytic disorders that harbor activating BRAF V600 mutations.

1.2 Secondary Aims

1.2.1 To estimate the progression free survival in pediatric patients treated with vemurafenib with advanced solid tumors (including CNS tumors), lymphomas or histiocytic disorders that harbor activating BRAF V600 mutations.

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

1.3 Exploratory Aims

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

2.0 BACKGROUND

2.1 Introduction/Rationale for Development

BRAF V600 mutations in pediatric cancer:
BRAF is a major component of RAS/RAF/MEK/ERK pathway which has a key role in cellular responses to growth signals.[1] BRAF typically signals as a dimer through activation of its downstream targets MEK and ERK. Activating mutations in the gene encoding BRAF, most commonly in valine to glutamic acid substitution at codon 600 (BRAF V600E), are present in a substantial portion of malignant melanomas and other cancers including colorectal cancer, non-small cell lung cancer, papillary thyroid cancer, diffuse gliomas, cholangiocarcinoma, hairy cell leukemia, multiple myeloma, and langerhans cell histocytosis.[1, 2] Thus targeted therapies to inhibit BRAF V600 mutant proteins have been developed as potential anticancer drugs.

Mutated BRAF proteins are being identified in an increasing number of pediatric tumors, with some histologies that overlap with those seen in adults, and others that differ between pediatric and adult patients.[3] In pediatric brain tumors, various alterations in BRAF are associated with a number of pediatric brain tumors including low grade glioma, high grade glioma, ganglioglioma, pleomorphic xanthroastrocytomas, and craniopharyngiomas.[3] The initial discovery of BRAF abnormalities in pediatric low grade glioma was of an oncogenic KIAA1549-BRAF fusion as a hallmark genetic event.[4-6] However, inhibition of BRAF V600 in these tumors lead to an *in vitro* paradoxical activation of MAPK signaling, and thus would be contraindicated in these patients.[7] However, this discovery lead to a search for other abnormalities in these tumor types, and the BRAF V600 mutation is observed in many low grade glioma subtypes including 20% of fibrillary astrocytomas, 50% of gangliogliomas, 75% of pleomorphic xanthroastrocytomas, 5% of pilocytic astrocytomas

and other brain tumor histologies where BRAF V600 inhibitors may play a role. [8-11] The V600E mutation is especially common among gliomas in the diencephalic region. [12] BRAF V600E mutation has also been identified in high grade gliomas with anecdotal reports of clinical response with BRAF V600E inhibition.[13]

Other tumor types such as histiocytic disorders including Langerhans cell histiocytosis (LCH), pediatric melanomas, papillary thyroid carcinoma and other rare tumors also have identified BRAF mutations. LCH is the most common type of histiocytosis, most commonly affects children, and clinical behavior is heterogeneous, but can have long term, irreversible adverse effects.[14] About 38-64% of LCH patients harbor the BRAF V600E mutation [15, 16, 17, 18]. BRAF V600K mutations can also be observed infrequently in this histology.[19] An infant with refractory, resistant multi-system LCH treated with vemurafenib demonstrated complete response to therapy. [20] Objective and sustained response in adults with Erdheim-Chester disease, a non-LCH histiocytosis with high prevelance of V600E mutations, has been described. [21]

Pediatric melanoma is a rare entity and heterogeneous group. The conventional melanomas in children, which typically occur in adolescence (>12 y), have very similar genomic profile to adults with majority harboring the BRAF V600 point mutations. [22] It was first reported in 2002 that over 50% of melanomas had activating mutations in BRAF, the majority of which are now known to be the V600E mutation. [2] Based on this, selective small molecule inhibitors of BRAF V600 have been developed and FDA approval obtained based on survival advantage. In contrast, the rate of BRAF V600 mutation in pediatric papillary thyroid carcinoma is significantly lower than what is seen in the adults (0-37% vs. 37-52%). [23] Other rare tumors that may also arise in the pediatric population have been described to have BRAF V600E mutations such as clear cell sarcoma and pediatric metanephric tumors. [24, 25]

Drug Name: Vemurafenib

Vemurafenib is a selective oral inhibitor of the oncogenic BRAF V600 mutated kinase and has potent anti-cancer effects in cellular and animal models.[1] The maximum tolerated dose (MTD) and recommended phase 2 dose (RP2D) was determined to be 960 mg orally twice daily in adults. [26] In a randomized open label study of V600E mutated unresectable or metastatic melanoma patients comparing vemurafenib to dacarbazine, vemurafenib demonstrated improved progression free survival (16 vs. 5.3 months), overall response rate (48% vs. 5%) and overall survival at 6 months (84% vs. 64%). [27] Vemurafenib is approved by the FDA for the treatment of patients with unresectable or metastatic melanoma with BRAF V600E mutations as detected by an FDA approved test.[28] The most commonly reported adverse effects with vemurafenib are arthralgia, alopecia, fatigue, rash, photosensitivity, nausea, diarrhea, headache, hyperkeratosis and skin papilloma, pruritus, pain, decreased appetite, and squamous cell carcinoma. [28]

Not all BRAF mutations appear to be the primary driver of tumor progression for all tumor types, and how or why some have substantial response to inhibition where others do not is not fully understood.[29] Mutated BRAF proteins are being identified in an increasing number of pediatric tumors. Vemurafenib, a highly selective inhibitor of BRAF V600 kinase, has the potential to represent a new therapy for children with tumors that harbor BRAF V600 mutations. By estimating response rate in pediatric patients with relapsed/refractory solid tumors and histiocytosis, this study will provide information on the prognostic value of genomic alterations of this pathway as a biomarker of response.

2.2 Preclinical Studies

2.2.1 Antitumor Activity

Vemurafenib displays selectivity against a broad range of kinases in biochemical assays and high degree of selectivity against BRAF V600 mutated kinases in anti-proliferative cellular assays. The information provided in protocol is from the investigator's brochure and summarized here [30]. The IC50 of vemurafenib for the BRAF V600E kinase is 8 nM and almost 5-fold less potent against the wild type BRAF (39nM). The anti-proliferative IC50 (nM) of vemurafenib against a variety of tumor cell lines ranged from 0.042 to 0.55. Since vemurafenib displays potent and selective activity against activated mutant BRAF kinase in the biochemical assay, it was of interest to assess activity in suppressing RAF-MEK-ERK pathway via suppression of the BRAF kinase activity. Vemurafenib inhibited phosphorylation of the downstream targets MEK and ERK in all the BRAF V600E, V600D, V600R, and V600K expressing melanoma cell lines tested. Vemurafenib shows selective inhibition on cellular proliferation in cells expressing BRAF V600E, V600D, V600R, V600K, but not BRAF WT.

The anti-tumor activity of vemurafenib in BRAF V600E expressing xenograft models demonstrate significant inhibition of BRAF V600E expressing tumors compared to BRAF WT expressing tumors. The effect of three doses of vemurafenib (12.5, 25, 75 mg/kg BID) on antitumor activity and survival was determined in a LOX melanoma model. Vemurafenib significantly inhibited tumor growth and tumor regression for all three doses with complete regression in 10 out of 10 mice treated with 25 mg/kg BID and 75 mg/kg BID, and 5 out of 9 mice treated with 12.5 mg/kg BID.

2.2.2 Animal Toxicology

The toxicity of vemurafenib was evaluated in single-dose and series of repeat toxicity and toxicokinetic studies in rats and in dogs. The information provided in protocol is from the investigator's brochure and summarized here.[30] Vemurafenib at doses given up to the maximum feasible dose with a given formulation was generally well tolerated with no significant drug related adverse findings in any of the single dose or repeat dose toxicology studies for up to 26 weeks in rats or 13 weeks in dog with once daily dosing.

To increase vemurafenib exposures achieved in toxicity studies, two studies were initiated in dogs using twice daily dosing: a 39-week study that was terminated prematurely due to intolerability as well as a 13-week toxicity and toxicokinetic study. In both studies, the liver was identified as the target organ of toxicity. In addition, in the prematurely terminated 39-week study, the bone marrow was also identified as a target organ. An *in vitro* bone marrow cytotoxicity study was conducted to examine whether the bone marrow necrosis observed in one moribund euthanized dog in the 39-week toxicity study was a direct cytotoxic effect. Vemurafenib did not show direct cytotoxic effects on rat, dog, or human lympho hematopoietic cells including stem cells.

No significant effects on heart rate, arterial blood pressure, body temperature or ECG parameters were observed in an ECG radiotelemetry study in dogs with a single oral administration of vemurafenib at doses up to 1000 mg/kg (estimated Cmax, 42 µM, about half of the Cmax [~90 µM] observed in patients dosed at 960

mg BID). In the repeat-dose toxicity studies in dogs for up to 13 weeks, all ECG measurements were qualitatively and quantitatively within normal limits at Cmax values up to 91 µM, which is about the Cmax (~90 µM) observed in patients dosed at 960 mg BID. No adverse effects were observed in rats in the central nervous and respiratory systems after single oral dose administration of vemurafenib up to 1000 mg/kg (estimated Cmax, 160 µM). Vemurafenib was shown to be phototoxic in an *in vitro* test, but not in an *in vivo* test at doses up to 450 mg/kg/day, the highest dose tested and the maximum feasible dose.

Vemurafenib did not show signs of genotoxicity in a standard core battery of tests and revealed no evidence of teratogenicity in rat or rabbit embryos/fetuses at doses up to the highest dose levels tested.

2.3 Adult Studies

2.3.1 Phase 1 Studies

In a multicenter phase 1 study of solid tumors with melanoma patients over represented due to strong preclinical data, the recommended phase 2 dose was determined to 960 mg orally twice daily. The most common side effects seen were grade 2 or 3 arthralgia, rash, nausea, photosensitivity, fatigue, cutaneous squamous cell carcinoma, pruritus, and palmar-plantar dysesthesia. Eight patients in the dose-escalation cohort and 10 patients in extension cohort of BRAF V600E metastatic melanoma patients had cutaneous squamous cell carcinoma. The median time to appearance was 8 weeks, the majority were resected and did not lead to discontinuation of medication. [26] The BRAF V600E mutation metastatic melanoma extension phase (n=32) demonstrated 2 confirmed and 24 partial responses in this cohort. The estimated median progression free survival in this cohort was more than 7 months.

Another phase 1 study of vemurafenib in BRAF V600E mutation positive melanoma evaluated the dose escalation across drug ranges of 240- 960 mg twice daily using the commercial formulation. Vemurafenib was well tolerated across all dose cohorts. Most patients experienced at least one adverse effect during the study, which were mild or moderate, and safety profile similar to prior trials. [31]

Pharmacokinetic data summarized in Section 2.3.3.

2.3.2 Phase 2 and 3 Studies

There is significant clinical efficacy data to support the use of vemurafenib for the treatment of patients with BRAF V600 mutation positive unresectable or metastatic melanoma. The phase 1/2 study with extension cohort is described above. In a randomized phase 3 study comparing vemurafenib to dacarbazine, vemurafenib demonstrated improved progression free survival (16 vs. 5.3 months), overall response rate (48% vs 5%) and overall survival at 6 months (84% vs 64%). [27] Vemurafenib is FDA approved for treatment of patients with unresectable or metastatic melanoma with BRAF V600E mutations as detected by FDA approved tests.

Other phase 2 studies have been performed in other adult tumor types or targeting metastatic lesions. A phase 2 trial of vemurafenib in patients with BRAF V600E

positive metastatic or unresectable papillary thyroid cancer refractory to radioactive iodine demonstrated anti-tumor activity with partial responses recorded in 10 of 26 patients.[32] A phase 2 study of vemurafenib in patients with metastatic BRAF mutated colorectal cancer, however in marked contrast to melanoma patients, did not show meaningful clinical activity.[33] Only one patient out of 21 had confirmed partial response, and median progression free survival was 2.1 months. A phase 2 trial of vemurafenib in BRAF V600 mutated melanoma with brain metastases demonstrated clinically meaningful responses without significant CNS toxicity. Evaluating the intracranial best overall response rate was 18% with 2 complete responses and 14 partial responses out of 90 patients with previously untreated brain metastases.[34]

A histology-independent phase 2 basket studies of vemurafenib in BRAF V600 mutation positive non-melanoma patients was performed. [35] A total of 122 patients with BRAF V600 mutation positive cancers were stratified into six pre-specified cohorts and all other tumor types were enrolled in seventh cohort. Patients were treated at the adult recommended dose of 960mg BID with the primary endpoint of response rate. The overall safety data were similar to prior studies with most common adverse event being rash (68%), fatigue (56%), and arthralgia (40%). Best responses were seen among patients with non-small cell lung cancer (42% response rate) and histiocytoses (43% response rate). V600 appears to be targetable in some but not all of the non-melanoma cancers with BRAF V600 mutations.

2.3.3 Pharmacology/Pharmacokinetics/Correlative and Biological Studies

Non-clinical pharmacokinetic and metabolism [30]

The major nonclinical pharmacokinetic and metabolism findings are:

- The volume of distribution was modest and clearance was low in both rats and dogs following intravenous administration.
- Vemurafenib was absorbed and widely distributed to tissues, and mainly eliminated via biliary excretion in rats as metabolites. Drug levels in the rat central nervous system were undetectable following a single oral dose of 100 mg/kg.
- Plasma protein binding is high (>99%) in vitro.
- Unchanged vemurafenib was the major component and only minor metabolites were detected in the plasma samples in rats, dogs, and human after multiple oral doses.
- Vemurafenib is not an inhibitor and/or an irreversible inactivator of CYP3A4/5 in vitro.
- In the in vitro human hepatocyte induction assay, CYP3A4 mRNA was weakly-to moderately induced, and a decrease in CYP1A2 mRNA was observed.
- Weak to moderate in-vitro inhibition of cytochrome P450 isoenzymes (< 25 μM) was noted for CYP2C9 (IC50 5.9 μM), CYP2C8 (IC50 12 μM), CYP1A2 (10 – 32.5 μM) and CYP2C19 (IC50 22.5 μM).
- In vitro results demonstrated that vemurafenib is a P-glycoprotein (P-gp) substrate and an inhibitor of P-gp (IC50 3.5-17 μM). However, P-gp efflux activity was saturated at higher concentrations (25-50 μM) of vemurafenib.

- Vemurafenib was neither a substrate nor an inhibitor for OATP1B1 and OATP1B3.

Clinical pharmacokinetic and metabolism
Vemurafenib pharmacokinetics (PK) have been evaluated in multiple clinical studies. At the 960 mg BID dose, the mean (+/-SD) area under the plasma concentration time curve over the 24 hour period (AUC 0-24h) was 1741 +/-639 µM x 1hour and mean maximum concentration at steady state was 86 +/- 32 µM.[26] Vemurafenib concentration increases with multiple doses to steady state observed after day 15. [31] Mean vemurafenib Cmax and AUC increased proportionately among doses tested from 240mg to 960mg. At steady state, the peak to trough ratio for vemurafenib exhibited a relatively flat concentration during the 12 hour dosing interval. The terminal half-life was 34.1 +/- 19.7 hours following multiple doses 960mg BID.

Following a single 960-mg oral dose of 14C-vemurafenib at steady state, the majority of the radioactivity (94%) was recovered in feces while a very small proportion (< 1 %) was recovered in urine (Study NP25158). Limited amounts of metabolites (≤ 5%) were found in plasma within 48 hours after oral dose of 14C-vemurafenib with the parent compound vemurafenib being the predominant component (≥ 95%). Over 0 to 96 hours period, each potential metabolite accounted for less than 0.25% of the total administered dose in urine and ≤ 6% of the total administered dose in feces. Limited hepatic metabolism and excretion of the parent molecule and its metabolites via bile into feces is likely the predominant elimination route for vemurafenib. Oxidation (CYP3A4), glucuronidation and glycosylation account for low level of metabolites. [30]

Food (high-fat meal) increased vemurafenib AUC0-last, AUCinf, and Cmax approximately 5.1-fold, 4.6-fold, and 2.5-fold, respectively, following a single 960-mg oral dose of vemurafenib (Study NP25396). [30]

Data from BRIM-P suggest the PK characteristics of vemurafenib in adolescent patients appear to be generally similar to what has been observed in adult patients. However, it is difficult to draw a conclusion based on the small number of patients. [30]

Clinical Pharmacodynamics [30]
Pharmacodynamic effects were explored in melanoma lesions from patients receiving 14 days of vemurafenib therapy, with the following key findings:

- BRAF-driven MAPK signaling (ERK and MEK phosphorylation) decreased, proliferation was inhibited (Ki-67 expression decreased), and cell cycle progression was blocked (Cyclin D1 level decrease, P27 level increased).
- Absolute ERK phosphorylation level changes from baseline to cycle 1 day 15 correlated weakly with decrease in tumor size.
- A trend toward reduced expression of the disease prognostic markers S100B and MIA was observed.

Acquired resistance was explored in melanoma lesion biopsies taken at the time of disease progression, with the following key findings:

- In most patients with tumor biopsies in this study, acquired resistance to vemurafenib appears to be driven by a reactivation of MAPK signaling (as observed by increased ERK phosphorylation levels), although the overall patient numbers are too small to draw conclusions.
- The reactivation of MAPK signaling appears to be coupled to an increased frequency of NRAS mutations observed in the progressive lesions. The observation that NRAS mutations are detectable at a higher frequency at progression supports the hypothesis that tumors may escape BRAF inhibition by development of BRAF/NRAS double mutant subclones. Such tumor subclones may be able to continue to grow due to a switch from BRAF-driven MAPK signaling to CRAF driven signaling in the presence of NRAS oncogenic mutations. The range of responses and times to progression in these patients does not allow for definitive conclusions, but suggests that these patients do derive benefit from vemurafenib, of a similar magnitude to patients.
- Patients with acquired resistance to vemurafenib who have NRAS/BRAF mutation positive disease may benefit from the addition of a MEK inhibitor or a CRAF inhibitor to the BRAF inhibition treatment regimen.

2.4 Pediatric Studies

There are two known studies of vemurafenib in the pediatric population. One is the BRIM-P study, a phase 1 dose escalation with efficacy tail extension study of vemurafenib in pediatric patients with stage IIIC or IV melanoma harboring BRAFV600 mutations (NCT01519323). This study evaluated two separate cohorts of children aged ≥ 12 to <17 years of age based on weight (≥ 45 kg cohort and < 45 kg cohort). For children ≥ 45kg, two dose levels were evaluated: 720 mg PO BID and 960 mg BID. Three patients enrolled on each dose cohort. No patients enrolled on the < 45kg cohort. A MTD could not be determined on this study because of the low number of patients enrolled. As of the Feb 2015 [30], all patients enrolled underwent tumor response assessments at the end of 4 weeks followed by evaluations every 8 weeks. None of the 6 patients in the study had a CR or PR and the best objective response rate was 0%. One patient had an unconfirmed PR observed at only one time point. Four patients had an overall response status of stable disease for at least 6 weeks, and the CBR was 66.7%. All patients experienced disease progression with the PFS being 76, 83, and 138 days for 3 patients in cohort 1 and 131, 157, and 294 for patients in cohort 2. This study closed prematurely in December 2015 due to recruitment challenges and low enrollment.

There is currently a safety, phase 0, and pilot efficacy study of vemurafenib for children with recurrent/refractory BRAFV600E mutant gliomas (NCT01748149). This study is currently open for accrual and results are not yet published. This is a pediatric dose escalation and pharmacokinetic study and the MTD/RP2D of vemurafenib has been determined to be 550 mg/m^2 PO BID.[36] The trial is also evaluating PK of crushed tablets.

2.4.1 Prior Experience in Children

In published case reports of children treated with vemurafenib, doses range from 240 mg- 960 mg PO BID (370 mg/m^2 to 660 mg/m^2; adult MTD conversion would roughly be 550 mg/m^2 based on an average adult BSA of 1.76 m^2) for children aged 18 months to 13 years of age [13, 37, 38]. All patients had partial response to single

agent therapy. One case report of vemurafenib in an 8 month old girl with systemic refractory LCH was treated off label with an initial dose of 120 mg twice daily. The tablets were split, crushed, and suspended in water for oral administration [20]. This patient showed complete remission after 60 days after which vemurafenib was discontinued. 90 days after discontinuation, the patient had skin recurrence and was restarted on therapy with effective clinical results for two additional months and subsequently remained in remission. Toxicities reported have been similar to that of adults including skin phototoxicity, rash, arthralgia, appearance of new nevi, itching, and elevated transaminases [13, 37, 39].

2.4.2 Pharmacology/Pharmacokinetics/Correlative Biological Studies

Pediatric Pharmacokinetics

Pharmacokinetics data is available on two patients with high grade glioma dosed at 450 mg/m^2 (patient 1) and 375 mg/m^2 PO BID (patient 2).[13] In patient 1, maximum vemurafenib concentration (Cmax) on day 1 was 18.4 µM at 3 hours and at day 7 after repeated dosing 88.6 µM at 1.5 hours. In patient 2, the Cmax on day 1 was 12.9 µM at 6 hours and steady state 47.9 µM at 6 hours. One month after increasing vemurafenib to 555 mg/m2 BID, the Cmax was 64.3 µM at 3 hours. In the infant with LCH treated with crushed vemurafenib [20] between 2 and 8 hours after ingestion, a mean concentration of 8.9 µg/mL at day 3 and 11.8 µg/mL at day 18.

Data from BRIM-P suggest the PK characteristics of vemurafenib in adolescent patients appear to be generally similar to what has been observed in adult patients. However, it is difficult to draw a conclusion based on the small number of patients. [30]

2.5 Overview of Proposed Pediatric Study

This subprotocol is a component of the Pediatric MATCH trial. This is a phase 2 trial of vemurafenib in children with relapsed or refractory solid tumors, lymphomas, or histocytic disorders that harbor activating BRAF V600 BRAF mutations.

Vemurafenib will be given at 550 mg/m^2 (adult MTD equivalent) orally BID continuously; capped at the adult MTD of 960 mg/dose; one cycle will be 28 days. This is MTD recommended from the pilot dose finding study of vemurafenib for children with relapsed or refractory BRAFV600E mutant gliomas (NCT01748149).[36]

The primary aim of this trial is to determine the objective response rate in pediatric patients with advanced solid tumors, lymphomas, CNS tumors, or histiocytic disorders that harbor BRAF V600 mutations. Key secondary objectives include estimating the progression free survival in this population and to obtain further information about the safety and tolerability of vemurafenib in patients with relapsed or refractory cancer. Imaging for disease evaluation will occur every other cycle x 3, then every three cycles. Disease response will be assessed per RECIST v1.1 criteria and 2-dimensional measurements for CNS tumors.

3.0 SCREENING AND STUDY ENROLLMENT PROCEDURES

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

Requirements for OPEN access:

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

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

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

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

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

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

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 APEC1621G 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 APEC1621G.

3.2 IRB Approval

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

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

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

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

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

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

Additional Requirements

Additional requirements to obtain an approved site registration status include:

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

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

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

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

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

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 8 weeks (56 days) of treatment assignment. Protocol therapy must start no later than 7 calendar days after the date of enrollment. Patients enrolling onto APEC1621G will have a COG ID obtained through their prior enrollment onto the screening protocol or from a prior COG study.

3.6.1 Reassignment Request through APEC1621SC (if unable to enroll within 8 week

timeframe)

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

Note: No starter supplies will be provided. Drug orders of vemurafenib should be placed with CTEP after enrollment and treatment assignment to APEC1621G 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 APEC1621SC screening protocol.

3.8 Dose Assignment

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

4.0 PATIENT ELIGIBILITY

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

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

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

4.1 Inclusion Criteria

4.1.1 APEC1621SC: Patient must have enrolled onto APEC1621SC and must have been given a treatment assignment to MATCH to APEC1621G based on the

presence of a BRAF V600 mutation (see Appendix VII).

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:

4.1.3.1 Patients must have a body surface area ≥ 0.55 m^2 at enrollment. Patients < 0.73 m^2 must follow the dosing nomogram provided in Appendix IV-A; patients ≥ 0.73 m^2 at enrollment must follow the dosing nomogram provided in Appendix IV-B.

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 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 Hematopoietic Growth Factors): ≥ 21 days after the completion of interleukins, interferon or cytokines (other than Hematopoietic Growth Factors)

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

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

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

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

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

k. Patients must not have received prior exposure to a BRAF inhibitor (e.g. vemurafenib, dabrafenib or encorafenib).

4.1.7 Organ Function Requirements

4.1.7.1 Adequate Bone Marrow Function Defined as:

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

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

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

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

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

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

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

Note: Patients should avoid concomitant medication known or suspected to prolong QTc interval or cause Torsades De Pointes. If possible, alternative agents should be considered. Patients who are receiving drugs

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

4.1.8 Patients must be able to swallow intact tablets.

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

4.2 Exclusion Criteria

4.2.1 Pregnancy or Breast-Feeding
Pregnant or breast-feeding women will not be entered on this study due to risks of fetal and teratogenic adverse events as seen in animal/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 6 months after the last dose of vemurafenib.

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 moderate to strong inducers or inhibitors of CYP3A4 are not eligible. Moderate to 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 BCRP and p-glycoprotein (p-gp): Patients who are currently receiving drugs that are inhibitors or inducers of P-gp or BCRP are not eligible.

4.2.3 Patients with known active cutaneous squamous cell carcinoma (includes

keratoacanthoma or mixed keratocanthoma subtype) are not eligible. Patients who have fully excised lesions with dermatologic confirmation of absence of disease are eligible.

4.2.4 Patients with low grade glioma patients (WHO grades I and II) are not eligible.

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

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

4.2.7 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	Vemurafenib 550 mg/m^2/dose BID (max: 960 mg PO BID)
Day 28	Evaluation

Vemurafenib will be given orally twice daily without regards to meals. Doses should be administered orally in the morning and evening. If vomiting occurs after a dose is taken, do not take an additional dose; continue with the next scheduled dose. Swallow whole with a glass of water; do not crush or chew. A missed dose can be taken up to 4 hours prior to the next dose.

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

Patients will be treated at the established pediatric MTD/RP2D which is 550 mg/m^2/dose BID (capped at the adult MTD of 960 mg/dose).

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

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).

Vemurafenib is distributed by the Pharmaceutical Management Branch, CTEP, DCTD, NCI. **Do not use commercial supply for study purposes.**

5.1.1 Therapy Delivery Map

See Appendix V for APEC1621G Therapy Delivery Map

5.2 Criteria for Starting Subsequent Cycles

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

5.3 Grading of Adverse Events

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

5.4 Definition of Dose-Limiting Toxicity (DLT)

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

5.4.1 Non-Hematological Dose-Limiting Toxicity

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

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

- Any Grade 2 non-hematological toxicity that 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 dose-limiting 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 as outlined in the dose reduction guidelines (see Appx IV-A and Appx IV-B). 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 Two dose reductions will be allowed for toxicity. If a patient experiences a hematological dose-limiting toxicity after two dose reductions, 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 as outlined in the dose reduction table (see Appx IV-A and Appx IV-B). Doses reduced for toxicity will not be re-escalated, even if there is minimal or no toxicity with the reduced dose. See specific guidelines for QTc changes, severe hypersensitivity reactions, and dermatologic reactions below.

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 Two dose reductions will be allowed for toxicity. If a patient experiences dose-limiting toxicity after two dose reductions, the patient must be removed from protocol therapy.

6.3 Management/Dose Modification for QTc Prolongation

6.3.1 Avoid combination with other drugs with potential to lead to prolongation of QTc interval, if possible (See Appendix VIII).

6.3.2 ECG monitored prior to therapy and then monthly x 3 cycles and then every 3rd cycle (Section 8.1)

6.3.3 See table below for dose modifications based on prolongation of the QTc interval:

Dose modification schedule based on prolongation of the QTc interval	Recommended dose modification
QTc increase meets values of both > 500msec and > 60 msec change from pre-treatment value	• Discontinue permanently
1st occurrence of QTc > 500 msec during treatment and change from pre-treatment value remains <60 msec	• Interrupt treatment • Monitor Electrolytes and any electrolyte abnormality should be corrected • Monitor ECG weekly until QTc decreases to ≤ 500 msec • Reinstitute therapy at reduced dose level -1 (or dose level -2 if patient has already had dose lowered) (see Appx IV-A and Appx IV-B)
2nd occurrence of QTc > 500 msec during treatment and change from pre-treatment value remains < 60msec	• Interrupt treatment • Monitor Electrolytes and any electrolyte abnormality should be corrected • Monitor ECG weekly until QTc decreases to ≤ 500 msec • Reinstitute therapy at reduced dose level -2 (or discontinue if patient already has already been lowered to dose level -2) (see Appx IV-A and Appx IV-B)
3rd occurrence of QTc > 500 msec during treatment and change from pre-treatment value remains < 60msec	• Discontinue permanently

6.4 Management for cutaneous squamous cell carcinoma

6.4.1 A complete dermatological history of prior medications and cutaneous squamous cell carcinoma (cuSCC) risk factors (i.e. radiation therapy, sun exposure, immunosuppression, prior SCC, use of tanning beds, precursor lesions, photo chemotherapy) must be collected.

6.4.2 A dermatologist will perform regular skin exams to monitor for cuSCC, BCC, actinic keratosis, keratoacanthoma, and second primary melanomas. Any suspicious lesion should be mapped and photographed, and must be definitively treated (i.e. full surgical excision) and sent for pathological examination (shaved biopsies are not recommended).

6.4.3 Dermatology examinations will occur at baseline prior to starting drug, prior to

every cycle x 3, and then every 3 cycles while on therapy treatment, and continue for 30 days after last study treatment or until death, withdrawal of consent or lost to follow up, whichever is earlier.

6.4.4 Actinic keratosis, keratoacanthoma or other skin conditions identified by the dermatologist should be treated as per local standard of care.

6.4.5 Treatment interruption or dose modification is not required for occurrence of cuSCC.

6.5 Management for other secondary malignancies potentially promoted by vemurafenib

6.5.1 A thorough documented head and neck exam including a visual inspection of the mouth and lymph node palpitation will be performed by the treating physician at baseline prior to starting drug, prior to every cycle x 3, and then every 3 cycles while on therapy, and continue for 30 days after the last study treatment or until death, withdrawal of consent or lost to follow up, whichever is earlier.

6.5.2 A chest CT should be performed at baseline and then every 6 cycles to for a maximum of 30 days post discontinuation of study drug, death, withdrawal of consent or lost to follow up, whichever is earlier.

6.5.3 Abnormal findings should be evaluated as clinically indicated.

6.6 Management/dose modifications for serious hypersensitivity reactions

6.6.1 Severe hypersensitivity reactions including anaphylaxis have been reported in associated with vemurafenib. Severe hypersensitivity reactions include generalized rash and erythema or hypotension. In patients who experience severe hypersensitivity reaction, vemurafenib should be permanently discontinued.

6.7 Management/dose modifications for dermatologic reactions

6.7.1 Severe dermatologic reactions have been reported in patients receiving vemurafenib, including rare cases of Stevens-Johnson Syndrome and toxic epidermal necrolysis in the pivotal clinical trial. Drug reaction with eosinophilia and systemic symptoms syndrome (DRESS) has been reported in association with vemurafenib. In patients who experience a severe dermatologic reaction, vemurafenib should be permanently discontinued.

6.7.2 Patients who experience Grade ≤ 3 photosensitivity/rash should be managed with supportive care. For intolerable Grade 2 or Grade ≥ 3 photosensitivity, vemurafenib should be held until resolution to Grade ≤ 1 and managed with dose modification per Section 6.2.

6.8 Management of liver injury

6.8.1 Liver injury, including severe cases of liver injury has been reported with vemurafenib. Liver enzymes (transaminases and alkaline phosphatases) and bilirubin should be measured as per Section 8.1. Laboratory abnormalities should be managed with dose modification per Section 6.2.

6.9 Management of ophthalmologic reactions

6.9.1 Serious ophthalmologic reactions including uveitis have been reported with vemurafenib. Patients should be monitored for ophthalmologic reactions and any

changes may be referred to ophthalmologist. Abnormalities should be managed with dose modification per Section 6.2.

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 vemurafenib.

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: Moderate to strong CYP3A4/5 inhibitors and inducers are not permitted on this study and should be discontinued 14 days prior to enrollment (See Appendix II for list of agents). Note: CYP3A4 inducing anti-epileptic drugs and dexamethasone for CNS tumors or metastases, on a stable dose, are allowed.

7.5.2 Vemurafenib is a substrate for both BCRP and p-glycoprotein (p-gp). The use of known BCRP and p-gp inhibitors and inducers should be avoided for the duration of the study if reasonable alternatives exist.

Vemurafenib is an also an inhibitor of BCRP, CYP1A2 (moderate), CYP2D6 (weak), P-glycoprotein and an inducer of CYP3A4 (weak). Concomitant use of vemurafenib with agents that are sensitive or narrow therapeutic range substrates of CYP1A2 and CYP3A4 is not recommended as vemurafenib may alter their concentrations. If co-administration cannot be avoided, exercise caution and consider a dose reduction of the concomitant CYP1A2 substrate drug.

Vemurafenib can increase plasma concentrations of P-gp substrates (eg., digoxin). Dose reduction of the concomitant P-gp substrate drug may be considered, if clinically indicated.

7.5.3 Co-administration of vemurafenib resulted in an 18% increase in AUC of S-warfarin (CYP2C9 substrate). Exercise caution and consider additional INR

monitoring when vemurafenib is used concomitantly with warfarin.

7.5.4 Avoid combination with other drugs with potential to lead to prolongation of QTc interval, if possible.

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
Head and neck exam[1]	X		Every cycle x 3, and then q 3 cycles
Dermatologic Exam	X		Every cycle x 3, and then q 3 cycles[2]
Height, weight, BSA	X		X
Performance Status	X		
Pregnancy Test[3]	X		
CBC, differential, platelets	X	Weekly[4,5]	X[4,5]
Urinalysis	X		
Electrolytes including Ca^{++}, PO_4, Mg^{++}	X	Weekly	X
Creatinine, ALT, bilirubin	X	Weekly	X
Albumin	X		X
EKG	X		Every cycle x 3, and then q 3 cycles
Tumor Disease Evaluation[6,6-A,6-B]	X		Every other cycle x 3 then q 3 cycles [7]
Chest CT scan[8]	X		Every 6 cycles
Bone Marrow Aspirate and/or biopsy[9, 10]	X[10]		
Medication Diary[11]		Weekly	X
Circulating Tumor DNA (ctDNA-optional)[12]			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 unless otherwise stated.

1 Document a thorough head and neck examination to monitor for non-cutaneous SCC. This should include a visual inspection of mouth and lymph node palpation.

2 See section 6.4. Dermatologic exam other than baseline can be obtained within 14 days prior to cycle.

3 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.

4 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.

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

6 Neurological exam also required for CNS patients.

6-A 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

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

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

8 CT Chest will be performed prior to treatment and then every 6 cycles to evaluate for non-cutaneous squamous cell carcinoma. CT Chest performed as part of tumor disease assessment may be used to evaluate non-cutaneous squamous cell carcinoma.

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

10 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.

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

12 With consent, two samples will be collected on this protocol (cycle 5 Day 1; and for patients receiving $\geq$ 5 cycles only: at progression or end of protocol therapy); see Section 8.3 for details of the ctDNA studies. Note that a ctDNA sample is scheduled to be obtained on the APEC1621SC screening protocol prior to the initiation of treatment on this subprotocol.

8.2 Radiology Studies

8.2.1 Central Radiology Review for Response:

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

8.2.2 Technical Details of Submission:

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

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

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

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

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

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

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

TRIAD Installations:

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

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

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

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

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

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

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

8.3 Circulating Tumor DNA Study (optional)

8.3.1 Sampling Schedule

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

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

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

Established institutional guidelines should be followed for blood collection via vascular access devices. Heparin should be avoided in pre-collection flush

procedures. If therapeutic heparin dosing contamination is a possibility, venipuncture is recommended as a first choice collection method. If a Streck Cell-Free DNA BCT tube immediately follows a heparin tube in the draw order, we recommend collecting an EDTA tube as a waste tube prior to collection in the Streck Cell-Free DNA BCT.

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

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

8.3.2 Sample Processing

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

8.3.3 Sample Labeling

Each tube must be labeled with the patient's study registration number, the study I.D (APEC1621G), and the date and time the sample was drawn. Data should be recorded on the appropriate transmittal form found in RAVE, which must accompany the sample(s).

8.3.4 Sample Shipping Instructions

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

Ship specimens to the following address:

Biopathology Center
Nationwide Children's Hospital
Protocol APEC1621G- Peds MATCH*
700 Children's Drive, WA1340
Columbus, OH 43205
Phone: (614) 722-2865
Fax: (614) 722-2897
Email: BPCBank@nationwidechildrens.org

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

Ship samples by FedEx Priority Overnight using a FedEx shipping label obtained through the COG FedEx account.

9.0 AGENT INFORMATION

9.1 Vemurafenib (10/05/20)

(Zelboraf®, RO5185426) NSC#761431 [redacted]

9.1.1 Source and Pharmacology:

Vemurafenib is a low molecular weight oral potent BRAF kinase inhibitor, which inhibits tumor growth in melanomas by inhibiting kinase activity of certain mutated forms of BRAF, including BRAF with V600E mutation, thereby blocking cellular proliferation in cells with the mutation. Vemurafenib does not have activity against cells with wild-type BRAF. BRAF V600E activating mutations are present in ~50% of melanomas as well as other cancers. In pediatric tumors, various alterations in BRAF are associated with a number of pediatric brain tumors including low grade glioma, high grade glioma, ganglioglioma, pleomorphic xanthroastrocytomas, and craniopharyngiomas. V600E mutation involves the substitution of glutamic acid for valine at amino acid 600.

Pharmacokinetics (PK):

The mean bioavailability of vemurafenib at steady state is 57.8%. High fat meals appear to significantly increase AUC, Cmax and Tmax of vemurafenib. Mean Cmax and $AUC_{0\text{-}8}$ appear to be dose proportional at vemurafenib doses between 240–960 mg BID. The 960 mg BID dose was considered as the MTD in adults. An analysis of pre-dose (trough) vemurafenib concentrations in patients who received 960 mg BID suggested that steady-state was reached by Day 15. Mean steady-state (Day 15) concentrations (Css) and $AUC_{0\text{-}8}$ for the MTD of vemurafenib (960 mg BID) were 69.6 ±11.2 µM and 469.1 ± 87.2 µM·h, respectively. For the 960 mg BID dose, the half-life is 34.1 ± 19.7 hours, with the mean C_{trough} concentrations at steady state ranging 52.0–58.49 µg/mL.

The majority of vemurafenib (94%) is recovered in feces; a very small proportion (< 1 %) was recovered in urine. Therefore, renal excretion plays a minimal role in the disposition of vemurafenib. Limited hepatic metabolism and excretion of the parent molecule and its metabolites via bile into feces is likely the predominant elimination route for vemurafenib. Oxidation (CYP3A4), glucuronidation and glycosylation account for low level of metabolites.

9.1.2 Potential Drug Interactions

Effects of Vemurafenib on Drug Metabolizing Enzymes

Results from an *in vivo* drug-drug interaction study in metastatic melanoma patients demonstrated that vemurafenib is a moderate CYP1A2 inhibitor and a CYP3A4 inducer.

Concomitant use of vemurafenib with agents with narrow therapeutic windows that are metabolized by CYP1A2 and CYP3A4 is not recommended as vemurafenib may alter their concentrations. If co-administration cannot be avoided, exercise caution and consider a dose reduction of the concomitant CYP1A2 substrate drug.

Co-administration of vemurafenib resulted in an 18% increase in AUC of S-warfarin (CYP2C9 substrate). Exercise caution and consider additional INR monitoring when vemurafenib is used concomitantly with warfarin.

Vemurafenib moderately inhibited CYP2C8 *in vitro*. The *in vivo* relevance of this finding is unknown, but a risk for a clinically relevant effect on concomitantly administered CYP2C8 substrates cannot be excluded. Concomitant administration of CYP2C8 substrates with a narrow therapeutic window should be made with caution since vemurafenib may increase their concentrations.

Drugs that inhibit or induce CYP3A4

Based on *in vitro* data, vemurafenib is a substrate of CYP3A4, and therefore, concomitant administration of moderate to strong CYP3A4 inhibitors or inducers may alter vemurafenib concentrations. Moderate or strong CYP3A4 inhibitors and inducers should be avoided from 14 days prior to enrollment to the end of the study. See Appendix II for list of agents.

Interaction of Vemurafenib with Drug Transport Systems

In vitro studies have demonstrated that vemurafenib is both a substrate and an inhibitor of the efflux transporters P-gp and BCRP. Multiple oral doses of vemurafenib (960 mg BID) increased the exposure of a single oral dose of digoxin, with an approximately 1.8 and 1.5 fold increase in digoxin $AUC_{0\text{-last}}$ and C_{max}, respectively. Dose reduction of the concomitant P-gp substrate drug may be considered, if clinically indicated.

The effects of vemurafenib on drugs that are substrates of BCRP, and the effects of P-gp or BCRP inducers and inhibitors on vemurafenib exposure are unknown. Concomitant drugs that are inhibitors or inducers of P-gp or BCRP should be avoided. In vitro studies have also demonstrated that vemurafenib is a weak inhibitor of BSEP. The in vivo relevance of this finding is unknown.

9.1.3 Patient Care Implications

Serious ophthalmologic reactions including uveitis have been reported with vemurafenib. Patients should be monitored for ophthalmologic reactions.

Due to the risk of photosensitivity, all patients should be advised to minimize sun exposure and use sun block and lip balm with broad-spectrum, UVA and UVB protection (minimum of SPF 30, re-applied every 2 to 3 hours) during vemurafenib treatment and for at least 5 to 10 days after study drug discontinuation.

Women of childbearing potential and male partners of such women should take necessary precautions to avoid pregnancy while receiving vemurafenib and for at least 6 months after discontinuation of vemurafenib. It is not known if vemurafenib is present in breast milk. Due to potential for serious adverse reactions in the breastfed infant, breastfeeding is not recommended by the manufacturer during treatment and for 2 weeks after the last dose.

9.1.4 **Toxicity:**

The Comprehensive Adverse Event and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. In addition to the comprehensive list, a subset, the Specific Protocol Exceptions to Expedited Reporting (SPEER), appears in a separate column and is identified with bold and italicized text. This subset of AEs (SPEER) is a list of events that are protocol specific exceptions to expedited reporting to NCI (except as noted below). Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements' http://ctep.cancer.gov/protocolDevelopment/electronic_applications/adverse_events.htm for further clarification. *Frequency is provided based on 5019 patients. Below is the CAEPR for Vemurafenib (Zelboraf, RO5185426).*

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, April 2, 2019[1]

Adverse Events with Possible Relationship to Vemurafenib (Zelboraf, RO5185426) (CTCAE 5.0 Term) [n= 5019]			**Specific Protocol Exceptions to Expedited Reporting (SPEER)**
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
EYE DISORDERS			
		Uveitis	
GASTROINTESTINAL DISORDERS			
	Abdominal pain		***Abdominal pain (Gr 2)***
	Constipation		***Constipation (Gr 2)***
	Diarrhea		***Diarrhea (Gr 2)***
Nausea			***Nausea (Gr 2)***
		Pancreatitis	
	Vomiting		***Vomiting (Gr 2)***
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
	Edema limbs		***Edema limbs (Gr 2)***
Fatigue			***Fatigue (Gr 2)***
	Fever		***Fever (Gr 2)***
HEPATOBILIARY DISORDERS			
		Hepatic failure	
IMMUNE SYSTEM DISORDERS			
	Allergic reaction*		
		Anaphylaxis	

Adverse Events with Possible Relationship to Vemurafenib (Zelboraf, RO5185426) (CTCAE 5.0 Term) [n= 5019]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
INFECTIONS AND INFESTATIONS			
	Folliculitis		
	Infections and infestations - Other (nasopharyngitis)		
INJURY, POISONING AND PROCEDURAL COMPLICATIONS			
		Injury, poisoning and procedural complications - Other (radiation injury)[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		
	Creatinine increased		*Creatinine increased (Gr 2)*
	Electrocardiogram QT corrected interval prolonged		*Electrocardiogram QT corrected interval prolonged (Gr 2)*
	GGT increased		*GGT increased (Gr 2)*
	Neutrophil count decreased*		*Neutrophil count decreased* (Gr 2)*
	Serum amylase increased*		*Serum amylase increased* (Gr 2)*
	Weight loss		*Weight loss (Gr 2)*
METABOLISM AND NUTRITION DISORDERS			
	Anorexia		*Anorexia (Gr 2)*
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			
Arthralgia			*Arthralgia (Gr 2)*
	Back pain		*Back pain (Gr 2)*
	Musculoskeletal and connective tissue disorder - Other (Dupuytren's contracture and plantar fibromatosis)*		
	Myalgia		*Myalgia (Gr 2)*
	Pain in extremity		*Pain in extremity (Gr 2)*
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)			
	Skin papilloma		*Skin papilloma (Gr 2)*
	Treatment related secondary malignancy - Cutaneous squamous cell carcinoma (SCC), including keratocanthoma or mixed keratocanthoma subtype		
		Treatment related secondary malignancy - including non-cutaneous squamous cell carcinoma, melanoma and others	
		Treatment related secondary malignancy - progression of RAS mutant tumors	
NERVOUS SYSTEM DISORDERS			
	Dizziness		*Dizziness (Gr 2)*
	Dysgeusia		*Dysgeusia (Gr 2)*

Adverse Events with Possible Relationship to Vemurafenib (Zelboraf, RO5185426) (CTCAE 5.0 Term) [n= 5019]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
		Facial nerve disorder	
	Headache		***Headache (Gr 2)***
	Peripheral motor neuropathy*		***Peripheral motor neuropathy* (Gr 2)***
	Peripheral sensory neuropathy*		***Peripheral sensory neuropathy* (Gr 2)***
RENAL AND URINARY DISORDERS			
	Acute kidney injury*		***Acute kidney injury* (Gr 2)***
		Renal and urinary disorders - Other (renal failure)	
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
	Cough		
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
Alopecia			***Alopecia (Gr 2)***
	Dry skin		***Dry skin (Gr 2)***
Hyperkeratosis			***Hyperkeratosis (Gr 2)***
	Palmar-plantar erythrodysesthesia syndrome		***Palmar-plantar erythrodysesthesia syndrome (Gr 2)***
Photosensitivity			***Photosensitivity (Gr 2)***
	Pruritus		***Pruritus (Gr 2)***
Rash maculo-papular			***Rash maculo-papular (Gr 2)***
		Skin and subcutaneous tissue disorders - Other (DRESS; drug reaction with eosinophilia and systemic symptoms)	
	Skin and subcutaneous tissue disorders - Other (including actinic keratosis, keratosis pilaris)		***Skin and subcutaneous tissue disorders - Other (including actinic keratosis, keratosis pilaris) (Gr 2)***
	Skin and subcutaneous tissue disorders - Other (panniculitis)*		
		Stevens-Johnson syndrome	
		Toxic epidermal necrolysis	
	Urticaria*		

* Denotes adverse events that are <3%

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

[2] Radiation injury includes recall phenomenon and radiation sensitization. Observed events include radiation dermatitis and skin necrosis; radiation pneumonitis, hepatitis, and esophagitis; and radiation proctitis and cystitis.

Adverse events reported on vemurafenib (Zelboraf, RO5185426) trials, but for which there is insufficient evidence to suggest that there was a reasonable possibility that vemurafenib (Zelboraf, RO5185426) caused the adverse event:

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Anemia
CARDIAC DISORDERS - Heart failure; Pericardial effusion; Ventricular arrhythmia
EAR AND LABYRINTH DISORDERS - Ear pain; Vertigo
EYE DISORDERS - Blurred vision; Dry eye; Eye disorders - Other (chorioretinopathy); Eye disorders - Other (ocular

hyperemia); Eye disorders - Other (retinal vein occlusion); Eye disorders - Other (visual disturbance); Eye disorders - Other (vitritis); Eye pain; Floaters; Photophobia; Scleral disorder; Watering eyes
GASTROINTESTINAL DISORDERS - Dry mouth; Dyspepsia; Dysphagia; Flatulence; Gastritis; Gastroesophageal reflux disease; Mucositis oral
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Chills; Edema face; Multi-organ failure; Non-cardiac chest pain; Pain
HEPATOBILIARY DISORDERS - Hepatobiliary disorders - Other (cholestasis)
INFECTIONS AND INFESTATIONS - Conjunctivitis
INJURY, POISONING AND PROCEDURAL COMPLICATIONS - Bruising
INVESTIGATIONS - Activated partial thromboplastin time prolonged; Cholesterol high; Lipase increased; Lymphocyte count decreased; Platelet count decreased
METABOLISM AND NUTRITION DISORDERS - Dehydration; Hypercalcemia; Hyperglycemia; Hyperkalemia; Hypertriglyceridemia; Hyperuricemia; Hypoalbuminemia; Hypocalcemia; Hypoglycemia; Hypokalemia; Hypomagnesemia; Hyponatremia; Hypophosphatemia; Metabolism and nutrition disorders - Other (blood phosphorus level increased)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Arthritis; Generalized muscle weakness; Joint range of motion decreased; Muscle cramp; Neck pain
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS) - Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other (adenomatous colon polyp)
NERVOUS SYSTEM DISORDERS - Intracranial hemorrhage; Lethargy; Seizure; Somnolence; Tremor
PSYCHIATRIC DISORDERS - Anxiety; Confusion; Depression; Insomnia; Irritability
RENAL AND URINARY DISORDERS - Hemoglobinuria; Proteinuria; Urinary frequency; Urinary incontinence
REPRODUCTIVE SYSTEM AND BREAST DISORDERS - Erectile dysfunction; Premature menopause
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Allergic rhinitis; Bronchopulmonary hemorrhage; Dyspnea; Epistaxis; Nasal congestion; Pharyngolaryngeal pain; Postnasal drip; Respiratory failure; Voice alteration
SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Erythema multiforme; Hyperhidrosis; Nail changes; Nail discoloration; Skin and subcutaneous tissue disorders - Other (acrochordon); Skin and subcutaneous tissue disorders - Other (dermal cyst); Skin and subcutaneous tissue disorders - Other (madarosis)
VASCULAR DISORDERS - Flushing; Hot flashes; Hypertension; Hypotension; Thromboembolic event; Vasculitis

Note: Vemurafenib (Zelboraf, RO5185426) in combination with other agents could cause an exacerbation of any adverse event currently known to be caused by the other agent, or the combination may result in events never previously associated with either agent.

9.1.5 Formulation and Stability:

Vemurafenib is available as 240 mg film-coated tablets for oral administration containing 112 tablets per bottle. Film-coated tablets contain the following excipients: Croscarmellose sodium; colloidal anhydrous silica; magnesium stearate; and hydroxypropylcellulose; Film Coat: Polyvinyl alcohol, titanium dioxide, polyethylene glycol 3350, talc, iron oxide red

9.1.5.1 Storage

Store at room temperature 20°C - 25°C (68°F - 77°F); excursions permitted between 15°C - 30°C (59°F - 86°F). Store in original container with the lid tightly closed.

If a storage temperature excursion is identified, promptly return vemurafenib 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.

9.1.5.2 Stability
The 240 mg strength will be supplied in the commercially available formulation, refer to the package label for expiration information.

9.1.6 **Guidelines for Administration:**
See Treatment (Section 5.0) and Dose Modification (Section 6.0) sections of the protocol.

Administer orally with or without food. Tablets should be taken whole and not crushed or chewed. **Only use supplies provided by PMB specifically for this study.**

9.1.7 **Supplier:**
Genentech and distributed by the Pharmaceutical Management Branch, CTEP, DCTD, NCI. **Do not use commercial supply for study purposes.**

9.2 Obtaining the Agent

9.2.1 Agent Ordering
NCI supplied agents may be requested by eligible participating investigator (or their authorized designee) at each participating institution. The CTEP-assigned protocol number must be used for ordering all CTEP-supplied investigational agents. The responsible investigator at each participating institution must be registered with CTEP, DCTD through an annual submission of FDA Form 1572 (Statement of Investigator), 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 vemurafenib should be placed with CTEP after enrollment and treatment assignment to APEC1621G 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.

Submit agent requests through the PMB Online Agent Order Processing (OAOP) application. Access to OAOP requires the establishment of a CTEP Identity and Access Management (IAM) account and the maintenance of an "active" account status, "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.

9.3 Agent Accountability

9.3.1 Agent Inventory Records

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

9.3.2 Investigator Brochure Availability

The current versions of the IBs for the agents will also be accessible to site investigators and research staff through the PMB 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. Questions about IB access may be directed to the PMB IB coordinator via email.

9.3.3 **Useful Links and Contacts**

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

10.0 CRITERIA FOR REMOVAL FROM PROTOCOL THERAPY AND OFF STUDY CRITERIA

10.1 Criteria for Removal from Protocol Therapy

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

i) Pregnancy
j) Patient did not receive protocol treatment after study enrollment

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

10.2 Follow-Up Data Submission and APEC1621SC Off Study Criteria

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

11.0 STATISTICAL AND ETHICAL CONSIDERATIONS

11.1 Sample Size and Study Duration

APEC1621G will require a minimum of 20 evaluable patients and a maximum of 49 patients, allowing for 15% inevaluability. Assuming an enrollment rate of 6-15 biomarker positive patients per year, the primary cohort of this subprotocol is expected to be completed within 1.6-4 years.

11.2 Dosing Considerations

Vemurafenib will be given at 550 mg/m^2/dose (adult MTD equivalent) orally BID continuously; capped at the adult MTD of 960 mg/dose; one cycle will be 28 days. This is the likely pediatric MTD/RP2D to be recommended from the pilot dose finding study of vemurafenib for children with relapsed or refractory BRAFV600E mutant gliomas (NCT01748149). The dosing nomogram is in Appendix IV-A and Appendix IV-B.

11.3 Study Design

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

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

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

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

11.3.1 **Primary Cohort**:
APEC1621G 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[40] 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 VI 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.[41] Decision making for A'Hern design cohorts will follow rules described above.

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

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

evaluation period for determination of best response will be 6 treatment cycles. All other patients will be considered non-responders. Patients who are not evaluable for response evaluation may be replaced for the purposes of the statistical rule. All patients considered to have a response (CR or PR) must have imaging studies reviewed centrally at the COG. Centers will be notified by the COG about requests for scans of patients with stable disease. Preliminary assessment of activity using institutionally provided tumor measurements will be entered into CDUS quarterly. The central review by COG will be provided as the final reviewed assessment of response when such becomes available.

11.6 Evaluability for Toxicity

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

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 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	3	2	37
More than one race	1	0	1	0	2
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) version 5.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the current CTCAE version 5.0. A copy of the CTCAE version 5.0 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. Eligible patients must have measurable disease present at baseline and have had their disease re-evaluated after at least one dose of protocol therapy. In addition to the scheduled scans, a confirmatory scan should be obtained on the next consecutive cycle following initial documentation of objective response.

As outlined, patients will be assigned to one of the following categories for assessment of response: a) solid tumor (non-CNS) and measurable disease (Section 12.4); b) neuroblastoma with MIBG positive lesions (Section 12.5); c) CNS tumor (Section 12.7); and d) 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).[42] 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 evaluable but not measurable disease and have received at least one dose of protocol therapy will be considered evaluable for non-target disease. The response assessment is based on

the presence, absence, or unequivocal progression of the lesions.

12.3.2 Disease Parameters

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

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

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

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

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

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

used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

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

12.3.3 Methods for Evaluation of Measurable Disease

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

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

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

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

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

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

12.3.3.5 Tumor markers: Tumor markers alone cannot be used to assess response.

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

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

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

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

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

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

For patients with a positive PET scan at diagnosis, PET can be used to follow response in addition to a CT scan using the International Pediatric non-Hodgkin Lymphoma Response Criteria.[43]

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

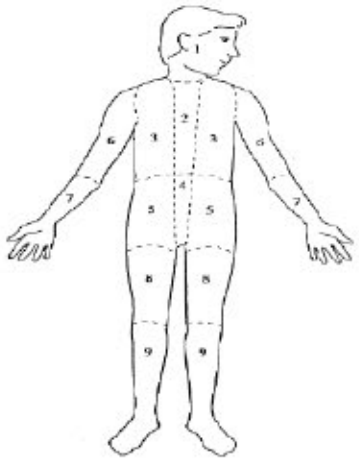
12.5.3 The response of MIBG lesions will be assessed on central review using the Curie scale14 as outlined below. Central review responses will be used to assess efficacy for study endpoint. See Section 8.2 for details on transferring images to the Imaging Research Center.

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[43], with modification from the Lugano classification.[44]

12.8.1 Disease Parameters

12.8.1.1 Measurable disease: A measurable node must have an LDi (longest diameter) greater than 1.5 cm. A measurable extranodal lesion should

have an LDi greater than 1.0 cm. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

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

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

12.8.2 Evaluation of Measurable Disease

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

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

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

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

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

12.8.3 Evaluation of Non-measured Lesions (CT-based response, PET/CT based response not applicable)[44]

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

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

Stable Disease (SD): No increase consistent with progression

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

12.8.4 Evaluation of organ enlargement[44]

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 the APEC1621G 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 CTCAE V5.0 The descriptions and grading scales found in the current version of CTCAE V5.0 will be used for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE V5.0. A copy of the CTCAE V5.0 can be downloaded from the CTEP website (http://ctep.cancer.gov).

Step 2: Grade the adverse event using the NCI CTCAE V5.0.

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

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

- Any medical event equivalent to CTCAE v5.0 grade 3, 4, or 5 that precipitates hospitalization (or prolongation of existing hospitalization) must be reported regardless

of attribution and designation as expected or unexpected with the exception of any events identified as protocol-specific expedited adverse event reporting exclusions.

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

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

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

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

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

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

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

Expedited AE reporting timelines are defined as:

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

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

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

- All Grade 3, 4, and Grade 5 AEs

Expedited 7 calendar day reports for:

- Grade 2 AEs resulting in hospitalization or prolongation of hospitalization

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

Effective Date: May 5, 2011

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

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

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

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

Category	Adverse Events
IMMUNE SYSTEM DISORDERS	Allergic Reaction
INFECTIONS AND INFESTATIONS	Infection
INVESTIGATIONS	Blood bilirubin increased
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	Musculoskeletal and connective tissue disorder - Other (Dupuytren's contracture and plantar fibromatosis)
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	Treatment related secondary malignancy - Cutaneous squamous cell carcinoma (SCC), including keratocanthoma or mixed keratocanthoma subtype
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	Cough
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	Skin and subcutaneous tissue disorders - Other (panniculitis)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	Urticaria

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

of the protocol.

13.4 Definition of Onset and Resolution of Adverse Events

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

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

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

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

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

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

13.5 Other Recipients of Adverse Event Reports

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

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

13.6 Specific Examples for Expedited Reporting

13.6.1 Reportable Categories of Death

- Death attributable to a CTCAE version 5.0 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 version 5.0 term associated with Grade 5.
- Death NOS: A cessation of life that cannot be attributed to a CTCAE version 5.0 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). Because vemurafenib is known to cause secondary malignancy and promote growth/clinical emergence of RAS-activated tumors such as melanoma, pancreatic cancer and MDS, any second malignancy should also be reported via CTEP-AERS.

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

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

Pregnancy needs to be followed **until the outcome of the pregnancy is known** at intervals deemed appropriate by her physicians. The "Pregnancy Information Form" should be used for all necessary follow-ups. If the baby is born with a birth defect or anomaly, then a second CTEP-AERS report is required.

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

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

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

14.0 RECORDS, REPORTING, AND DATA AND SAFETY MONITORING PLAN

14.1 Categories of Research Records

Research records for this study can be divided into three categories

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

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

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

See separate CRF Packet, which includes submission schedule.

14.2 **CDUS**

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

Note: This 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.

REFERENCES

1. Flaherty KT, Yasothan U,Kirkpatrick P: Vemurafenib. Nat Rev Drug Discov 10:811-2, 2011
2. Davies H, Bignell GR, Cox C, et al.: Mutations of the BRAF gene in human cancer. Nature 417:949-54, 2002
3. Kieran MW: Targeting BRAF in pediatric brain tumors. Am Soc Clin Oncol Educ Book:e436-40, 2014
4. Pfister S, Janzarik WG, Remke M, et al.: BRAF gene duplication constitutes a mechanism of MAPK pathway activation in low-grade astrocytomas. J Clin Invest 118:1739-49, 2008
5. Sievert AJ, Jackson EM, Gai X, et al.: Duplication of 7q34 in pediatric low-grade astrocytomas detected by high-density single-nucleotide polymorphism-based genotype arrays results in a novel BRAF fusion gene. Brain Pathol 19:449-58, 2009
6. Jones DT, Kocialkowski S, Liu L, et al.: Tandem duplication producing a novel oncogenic BRAF fusion gene defines the majority of pilocytic astrocytomas. Cancer Res 68:8673-7, 2008
7. Sievert AJ, Lang SS, Boucher KL, et al.: Paradoxical activation and RAF inhibitor resistance of BRAF protein kinase fusions characterizing pediatric astrocytomas. Proc Natl Acad Sci U S A 110:5957-62, 2013
8. Dahiya S, Emnett RJ, Haydon DH, et al.: BRAF-V600E mutation in pediatric and adult glioblastoma. Neuro Oncol 16:318-9, 2014
9. Dahiya S, Haydon DH, Alvarado D, et al.: BRAF(V600E) mutation is a negative prognosticator in pediatric ganglioglioma. Acta Neuropathol 125:901-10, 2013
10. Dias-Santagata D, Lam Q, Vernovsky K, et al.: BRAF V600E mutations are common in pleomorphic xanthoastrocytoma: diagnostic and therapeutic implications. PLoS One 6:e17948, 2011
11. Brastianos PK, Taylor-Weiner A, Manley PE, et al.: Exome sequencing identifies BRAF mutations in papillary craniopharyngiomas. Nat Genet 46:161-5, 2014
12. Ho CY, Mobley BC, Gordish-Dressman H, et al.: A clinicopathologic study of diencephalic pediatric low-grade gliomas with BRAF V600 mutation. Acta Neuropathol 130:575-85, 2015
13. Bautista F, Paci A, Minard-Colin V, et al.: Vemurafenib in pediatric patients with BRAFV600E mutated high-grade gliomas. Pediatr Blood Cancer 61:1101-3, 2014
14. Heritier S, Emile JF, Barkaoui MA, et al.: BRAF Mutation Correlates With High-Risk Langerhans Cell Histiocytosis and Increased Resistance to First-Line Therapy. J Clin Oncol 34:3023-30, 2016
15. Berres ML, Lim KP, Peters T, et al.: BRAF-V600E expression in precursor versus differentiated dendritic cells defines clinically distinct LCH risk groups. J Exp Med 211:669-83, 2014
16. Badalian-Very G, Vergilio JA, Degar BA, et al.: Recurrent BRAF mutations in Langerhans cell histiocytosis. Blood 116:1919-23, 2010
17. Satoh T, Smith A, Sarde A, et al.: B-RAF mutant alleles associated with Langerhans cell histiocytosis, a granulomatous pediatric disease. PLoS One 7:e33891, 2012
18. Haroche J, Charlotte F, Arnaud L, et al.: High prevalence of BRAF V600E mutations in Erdheim-Chester disease but not in other non-Langerhans cell histiocytoses. Blood 120:2700-3, 2012
19. Sahm F, Capper D, Preusser M, et al.: BRAFV600E mutant protein is expressed in cells of variable maturation in Langerhans cell histiocytosis. Blood 120:e28-34, 2012
20. Heritier S, Jehanne M, Leverger G, et al.: Vemurafenib Use in an Infant for High-Risk Langerhans Cell Histiocytosis. JAMA Oncol 1:836-8, 2015
21. Haroche J, Cohen-Aubart F, Emile JF, et al.: Reproducible and sustained efficacy of targeted therapy with vemurafenib in patients with BRAF(V600E)-mutated Erdheim-Chester disease. J Clin Oncol 33:411-8, 2015
22. Lu C, Zhang J, Nagahawatte P, et al.: The genomic landscape of childhood and adolescent melanoma. J Invest Dermatol 135:816-23, 2015
23. Gertz RJ, Nikiforov Y, Rehrauer W, et al.: Mutation in BRAF and Other Members of the MAPK Pathway in Papillary Thyroid Carcinoma in the Pediatric Population. Arch Pathol Lab Med 140:134-9, 2016

24. Protsenko SA, Semionova AI, Komarov YI, et al.: BRAF-mutated clear cell sarcoma is sensitive to vemurafenib treatment. Invest New Drugs 33:1136-43, 2015
25. Chami R, Yin M, Marrano P, et al.: BRAF mutations in pediatric metanephric tumors. Hum Pathol 46:1153-61, 2015
26. Flaherty KT, Puzanov I, Kim KB, et al.: Inhibition of mutated, activated BRAF in metastatic melanoma. N Engl J Med 363:809-19, 2010
27. Chapman PB, Hauschild A, Robert C, et al.: Improved survival with vemurafenib in melanoma with BRAF V600E mutation. N Engl J Med 364:2507-16, 2011
28. FDA: FDA labeling information Zelboraf. FDA website (online); www.accessdata.fda.gov/drugsatfda_docs/label/2016/202429s010lbl.pdf, 2016
29. Stites EC: The response of cancers to BRAF inhibition underscores the importance of cancer systems biology. Sci Signal 5:pe46, 2012
30. Roche FH-L: Zelboraf ® (Vemurafenib) RO5185426 (PLX4032) Investigator's Brochure. Version 14, December 2016
31. Grippo JF, Zhang W, Heinzmann D, et al.: A phase I, randomized, open-label study of the multiple-dose pharmacokinetics of vemurafenib in patients with BRAF V600E mutation-positive metastatic melanoma. Cancer Chemother Pharmacol 73:103-11, 2014
32. Brose MS, Cabanillas ME, Cohen EE, et al.: Vemurafenib in patients with BRAF(V600E)-positive metastatic or unresectable papillary thyroid cancer refractory to radioactive iodine: a non-randomised, multicentre, open-label, phase 2 trial. Lancet Oncol 17:1272-82, 2016
33. Kopetz S, Desai J, Chan E, et al.: Phase II Pilot Study of Vemurafenib in Patients With Metastatic BRAF-Mutated Colorectal Cancer. J Clin Oncol 33:4032-8, 2015
34. McArthur GA, Maio M, Arance A, et al.: Vemurafenib in Metastatic Melanoma Patients with Brain Metastases: An Open-Label, Single-Arm, Phase 2, Multicentre Study. Ann Oncol, 2016
35. Hyman DM, Puzanov I, Subbiah V, et al.: Vemurafenib in Multiple Nonmelanoma Cancers with BRAF V600 Mutations. N Engl J Med 373:726-36, 2015
36. Nicolaides T, Nazemi KJ, Crawford J, et al.: Phase I study of vemurafenib in children with recurrent or progressive BRAF(V600E) mutant brain tumors: Pacific Pediatric Neuro-Oncology Consortium study (PNOC-002). Oncotarget 11:1942-1952, 2020
37. Aguilera D, Janss A, Mazewski C, et al.: Successful Retreatment of a Child with a Refractory Brainstem Ganglioglioma with Vemurafenib. Pediatr Blood Cancer 63:541-3, 2016
38. del Bufalo F, Carai A, Figa-Talamanca L, et al.: Response of recurrent BRAFV600E mutated ganglioglioma to Vemurafenib as single agent. J Transl Med 12:356, 2014
39. Rush S, Foreman N,Liu A: Brainstem ganglioglioma successfully treated with vemurafenib. J Clin Oncol 31:e159-60, 2013
40. A'Hern RP: Sample size tables for exact single-stage phase II designs. Stat Med 20:859-66, 2001
41. Agresti A,Coull BA: Approximate Is Better than "Exact" for Interval Estimation of Binomial Proportions. The American Statistician 52:119-126, 1998
42. Eisenhauer EA, Therasse P, Bogaerts J, et al.: New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer 45:228-47, 2009
43. Sandlund JT, Guillerman RP, Perkins SL, et al.: International Pediatric Non-Hodgkin Lymphoma Response Criteria. J Clin Oncol 33:2106-11, 2015
44. Cheson BD, Fisher RI, Barrington SF, et al.: Recommendations for initial evaluation, staging, and response assessment of Hodgkin and non-Hodgkin lymphoma: the Lugano classification. J Clin Oncol 32:3059-68, 2014

43. Sandlund JT, Guillerman RP, Perkins SL, et al: International Pediatric Non-Hodgkin Lymphoma Response Criteria. J Clin Oncol 33:2106-11, 2015
44. Cheson BD, Fisher RI, Barrington SF, et al: Recommendations for initial evaluation, staging, and response assessment of Hodgkin and non-Hodgkin lymphoma: the Lugano classification. J Clin Oncol 32:3059-68, 2014

APPENDIX I: PERFORMANCE STATUS SCALES/SCORES

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

APPENDIX II: CYP3A4 SUBSTRATES, INDUCERS AND INHIBITORS

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

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

ketoconazole lansoprazole lapatinib losartan lovastatin[5] lurasidone[5] macrolide antibiotics maraviroc[5] medroxyprogesterone methadone midazolam[5] midostaurin[5] modafinil nefazodone nilotinib olaparib ondansetron osimertinib paclitaxel palbociclib pazopanib quetiapine[5] quinidine[4] regorafenib romidepsin saquinavir[5] sildenafil[5] simvastatin[5] sirolimus[4,5] sonidegib sunitinib tacrolimus[4,5] tamoxifen telaprevir temsirolimus teniposide tetracycline tipranavir[5] tolvaptan[5] triazolam[5] trimethoprim vardenafil[5] vemurafenib venetoclax[5] vinca alkaloids zolpidem				

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

APPENDIX III-A: MEDICATION DIARY FOR VEMURAFENIB

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

Institution: _____

Please do not write patient names on this form.

Complete each day with the time and dose given for vemurafenib. 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***. Vemurafenib tablets should be swallowed whole. Vemurafenib may be taken without regards to meals. If you vomit after taking the medication, the dose will not be repeated. A missed dose can be taken within 4 hours prior to next scheduled dose. Add the dates to the calendar below and return the completed diary to the study clinic at each visit (weekly during Cycle 1, and then after each treatment cycle).

EXAMPLE			***Number of Vemurafenib tablets***	***Comments***
	Date	***Time***	**240 mg**	
Day 1	*1/15/19*	*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/m²/dose**

WEEK 1	**Date**	**Time**		**# of vemurafenib tablets prescribed to take** **240 mg** **AM#** **PM#**___ **# of vemurafenib tablets taken** **240 mg**	**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		

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

COG Patient ID:_____ Acc#_____
Dose Level: _____mg/m^2/dose

WEEK 2	Date	Time		# of vemurafenib tablets prescribed to take 240 mg AM# PM#___ # of vemurafenib tablets taken 240 mg	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 vemurafenib tablets prescribed to take** **240 mg** **AM#** **PM#___** **# of vemurafenib tablets taken** **240 mg**	**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		

Cycle #: _____ Start Date: |__/__|__/__|__/__| **COG Patient ID:_____** **Acc#_____**
End Date: | / | / | / | **Dose Level: _____mg/m²/dose**

WEEK 4	Date	Time		# of vemurafenib tablets prescribed to take 240 mg AM# PM#___ # of vemurafenib tablets taken 240 mg	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 reviewed this form must sign and date this form below:

Signature: _____ Date: _____
(the site personnel who reviewed this form)

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

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

[Note to authors: This appendix consists of an "information sheet" to be handed to the patient at the time of enrollment. Use or modify the text as appropriate for the study agent, so that the patient is aware of the risks and can communicate with their regular prescriber(s) and pharmacist. A convenient wallet-sized information card is also included for the patient to clip out and retain at all times. If you choose to use them, please note that the information sheet and wallet card will require IRB approval before distribution to patients.]

The patient _____ is enrolled on a clinical trial using the experimental study drug, ***vemurafenib***. 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:

Vemurafenib interacts with *certain specific enzymes in your liver*, certain transport proteins that help move drugs in and out of cells**, the heart's electrical activity (QTc prolongation)***.*

- *The enzymes in question are CYP1A2, CYP3A4 and CYP2C8. Vemurafenib is broken down by these enzymes and may be affected by other drugs that inhibit or induce this enzyme.
- **The proteins in question are **P-gp and BCRP.** Vemurafenib is moved in and out of cells/organs by these transport proteins.
- ***The heart's electrical activity may be affected by vemurafenib. The study doctor may be concerned about QTc prolongation and any other medicine that is associated with greater risk for having QTc prolongation.

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

Vemurafenib 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:

Vemurafenib must be used very carefully with other medicines that use certain liver enzymes or transport proteins to be effective or to be cleared from your system or that may affect your heart's electrical activity. 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 inducers/inhibitors or substrates of CYP1A2, CYP3A4 and CYP2C8, P-gp and BCRP, or any medicine associated with greater risk for

having QTc prolongation.

- 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.
- 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 vemurafenib. This clinical trial is sponsored by the NCI. **Vemurafenib** may interact with drugs that are ***processed by your liver, or use certain transport proteins in your body or affects the electrical activity of your heart***. 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.

Vemurafenib interacts with ***specific liver enzymes called*** CYP1A2, CYP3A4 and CYP2C8, ***transport proteins*** P-gp and BCRP, ***and can impact the heart's electrical activity (QTc prolongation)***, and must be used very carefully with other medicines that interact CYP1A2, CYP3A4 and CYP2C8, P-gp and BCRP.

- 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 inducers/inhibitors or substrates of CYP1A2, CYP3A4 and CYP2C8, or transporters P-gp or BCRP; or affect the heart's electrical activity***.
- Before prescribing new medicines, your regular health care providers should go to a frequently-updated medical reference for a list of drugs to avoid, or contact your study doctor.
- Your study doctor's name is _____ and can be contacted at _____.

APPENDIX IV-A: VEMURAFENIB DOSING NOMOGRAM (PATIENTS ≥ 0.55 AND < 0.73 m^2)

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

Patients with a body surface area of ≥ 0.55 and < 0.73 m^2 at enrollment must follow the dosing nomogram below. Patients ≥ 0.73 m^2 at enrollment must follow the dosing nomogram provided in Appendix IV-B.

Vemurafenib Dose Assignment: 550 mg/m^2/dose BID

BSA (m^2)	Vemurafenib Dose (mg/dose)	Dose level -1	Dose level -2
0.55-0.72	240 mg qAM 480 mg qPM	240 mg BID	off protocol therapy

APPENDIX IV-B: VEMURAFENIB DOSING NOMOGRAM (PATIENTS ≥ 0.73 m^2)

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

Patients ≥ 0.73 m^2 at enrollment must follow the dosing nomogram below. Patients with a body surface area of ≥ 0.55 and < 0.73 m^2 at enrollment must follow the dosing nomogram provided in Appendix IV-A.

Vemurafenib Dose Assignment: 550 mg/m^2/dose BID

BSA (m^2)	Vemurafenib Dose (mg/dose)	Dose level -1	Dose level -2
0.73-1.09	480 mg BID	240 mg qAM 480 mg qPM	240 mg BID
1.1-1.53	720 mg BID	480 mg BID	240 mg qAM 480 mg qPM
≥1.54	960 mg BID	720 mg BID	480 mg BID

APPENDIX V: APEC1621G 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
Vemurafenib [redacted] **Do not use commercial supply.**	PO	Vemurafenib 550 mg/m^2/dose BID (maximum 960 mg BID) Refer to dosing nomogram in Appendix IV-A and IV-B.	1-28	Vemurafenib will be given orally twice daily without regards to meals. Doses should be administered orally in the morning and evening. If vomiting occurs after a dose is taken, do not take an additional dose; continue with the next scheduled dose. Swallow whole with a glass of water; do not crush or chew. A missed dose can be taken up to 4 hours prior to the next dose.

Enter Cycle #: _____ **Dose Level:** _____ **Ht** _____ **cm** **Wt** _____ **kg** **BSA** _____ **m^2**

Date Due	Date Given	Day	**Vemurafenib** mg AM mg PM	Studies
			Enter calculated dose above as per dosing nomogram and actual dose administered below	
		1	mg AM mg PM	
		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	a,e,f,g,i
		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	a,e,f,g,i
		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	a,e,f,g,i
		23	mg AM mg PM	
		24	mg AM mg PM	
		25	mg AM mg PM	
		26	mg AM mg PM	
		27	mg AM mg PM	
		28/1	mg AM mg PM	a,b,c,d,e,f,g,h,i,

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

Cycle 1

Cycle 1

Required Observations in Cycle 1

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

a.	**History/Physical Exam (including VS)**
b.	**Head and Neck Exam**. Document a thorough head and neck examination to monitor for non-cutaneous SCC. This should include a visual inspection of mouth and lymph node palpation.
c.	**Dermatologic Exam**. See Section 6.4
d.	**Ht/Wt/BSA**
e.	**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.
f.	**Electrolytes including Ca++, PO4, Mg++**
g.	**Creatinine, ALT, bilirubin**
h.	**Albumin**
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.

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

Comments
(Include any held doses, or dose modifications)

Treatment Details: Cycle 1

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

All Subsequent Cycles

Therapy Delivery Map – All Subsequent Cycles

This Therapy Delivery Map (TDM) relates to all subsequent cycles. Each cycle lasts 28 days. Treatment may continue in the absence of disease progression or unacceptable toxicity. 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
Vemurafenib [redacted] **Do not use commercial supply.**	PO	Vemurafenib 550 mg/m^2/dose BID (maximum 960 mg BID) Refer to dosing nomogram in Appendix IV-A and IV-B.	1-28	Vemurafenib will be given orally twice daily without regards to meals. Doses should be administered orally in the morning and evening. If vomiting occurs after a dose is taken, do not take an additional dose; continue with the next scheduled dose. Swallow whole with a glass of water; do not crush or chew. A missed dose can be taken up to 4 hours prior to the next dose.

Enter Cycle #: _____ **Dose Level:** _____ **Ht** _____ **cm Wt** _____ **kg** **BSA** _____ **m^2**

Date Due	Date Given	Day	**Vemurafenib** mg AM mg PM	Studies
			Enter calculated dose above as per dosing nomogram and actual dose administered below	
		1	_____ mg AM _____ mg PM	a,d,e,f,g,h,m
		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	
		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	
		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	
		23	_____ mg AM _____ mg PM	
		24	_____ mg AM _____ mg PM	
		25	_____ mg AM _____ mg PM	
		26	_____ mg AM _____ mg PM	
		27	_____ mg AM _____ mg PM	
		28/1	_____ mg AM _____ mg PM	
		29/1		a, b*,c*, d, e, f, g, h, i*,j*,k*,m, n*

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.	**Head and Neck Exam**. With Tumor Disease Evaluation. Document a thorough head and neck examination to monitor for non-cutaneous SCC. This should include a visual inspection of mouth and lymph node palpation.
c.	**Dermatologic Exam**. With Tumor Disease Evaluation. See Section 6.4. Dermatologic exam other than baseline can be obtained within 14 days prior to cycle.
d.	**Ht/Wt/BSA**
e.	**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.
f.	**Electrolytes including Ca++, PO4, Mg++**
g.	**Creatinine, ALT, bilirubin**
h.	**Albumin**
i.	**EKG**- Every cycle x 3, and then every 3 cycles.
j.	**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
k.	**Chest CT scan**. Every 6 cycles to evaluate for non-cutaneous squamous cell carcinoma.
l.	**Bone Marrow Aspirate and/or biopsy**-Only required in patients suspected of having bone marrow metastasis on the basis of history, symptoms, laboratory evaluation or other clinical data. Bone marrow aspirate and/or biopsy should be performed only when complete response or partial response is identified in target disease or when progression in bone marrow is suspected.
m.	**Medication Diary**- (see Appendix III) should be reviewed after completion of each treatment cycle and uploaded into RAVE.
n.	**Circulating Tumor DNA (ctDNA-optional)-** With consent two samples will be collected on this protocol (Cycle 5 Day 1; and for patients receiving ≥ 5 cycles, at progression or end of protocol therapy) see Section 8.4 for details of the ctDNA studies.

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

Comments (Include any held doses, or dose modifications)

Treatment Details: Subsequent Cycles

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

Subsequent Cycles

APPENDIX VI: TARGET HISTOLOGIES FOR APEC1621G 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. Langerhans Cell Histiocytosis 6. Malignant Germ Cell Tumor 7. Medulloblastoma 8. Neuroblastoma 9. Non-Hodgkin Lymphoma 10. Non-RMS Soft Tissue Sarcoma 11. Osteosarcoma 12. Rhabdoid Malignancy 13. Rhabdomyosarcoma 14. Wilms Tumor 15. Other Histology (based on COG/NCI-CTEP approval)

APPENDIX VII: APEC1621G ACTIONABLE MUTATIONS OF INTEREST

INCLUSION	VARIANTS			
Hotspots				
Gene Name	**Variant ID**	**Variant Type**	**LOE**	**aMOI**
BRAF	COSM1127	MNV	2	p.V600R
BRAF	COSM1583011	MNV	2	p.V600R
BRAF	COSM308550	MNV	2	p.V600D
BRAF	COSM473	MNV	1	p.V600K
BRAF	COSM474	MNV	2	p.V600R
BRAF	COSM476	SNV	1	p.V600E
BRAF	COSM477	MNV	2	p.V600D
BRAF	COSM6137	SNV	2	p.V600G
BRAF	COSM475	MNV	1	p.V600E
BRAF	COSM1130	SNV	2	p.V600M
BRAF	COSM18443	SNV	2	p.V600A
BRAF	COSM219798	SNV	2	p.V600L
BRAF	COSM33808	SNV	2	p.V600L
BRAF	COSM249889	MNV	2	p.V600Q

APPENDIX VIII: MEDICATIONS ASSOCIATED WITH PROLONGED QTC

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

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

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

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

APPENDIX IX YOUTH INFORMATION SHEET
INFORMATION SHEET REGARDING RESEARCH STUDY APEC1621G

(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 vemurafenib that could "match" your tumor. The doctors want to see if vemurafenib will help children with your type of cancer get better. We don't know if vemurafenib 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 vemurafenib 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 vemurafenib. 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 vemurafenib you might have some tests and check-ups done more often that 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 vemurafenib works in them. We will draw some extra blood samples for this if your family agrees.

INFORMATION SHEET REGARDING RESEARCH STUDY APEC1621G
(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 vemurafenib, and so you have been assigned to vemurafenib. The doctors want to see if vemurafenib will make children with your type of cancer get better. We don't know if vemurafenib will work well to get rid of your cancer. That is why we are doing the study.

5. You will get vemurafenib by mouth twice daily for a 28-day period. This entire 28-day period is called a cycle. Vemurafenib should be swallowed whole. You may continue to receive vemurafenib 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 vemurafenib, 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 vemurafenib. The doctors want to see if vemurafenib will help children or adolescents with your type of cancer get better. We don't know if vemurafenib 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 vemurafenib 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 vemurafenib. Your doctor will talk to you about the risks we know about from vemurafenib. There may be other risks from vemurafenib 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 vemurafenib works. If your family agrees we will draw some extra blood samples to do these tests.

APPENDIX X CORRELATIVE STUDIES GUIDE

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

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

*Only for patients receiving ≥ 5 cycles of therapy only

APPENDIX XI: CTEP AND CTSU REGISTRATION PROCEDURES

Requirements for APEC1621G Site Registration

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

RCR utilizes five-person registration types.

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

RCR requires the following registration documents:

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

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

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

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

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

Cancer Trials Support Unit (CTSU) Registration Procedures

This study is supported by the NCI CTSU.

Downloading Site Registration Documents:
Download the site registration forms from the protocol-specific page located on the CTSU members' website. Permission to view and download this protocol and its supporting documents is restricted 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 APEC1621G.
- Click on *Documents*, select *Site Registration*, and download and complete the forms provided. (Note: For sites under the CIRB, IRB data will load automatically to the CTSU.)

Protocol-Specific Requirements For Site Registration:

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

Submitting Regulatory Documents:

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

To access the Regulatory Submission Portal log on to the CTSU members' website → Regulatory → 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:

You can verify your site's registration status on the members' side of the CTSU website.

- Log on to the CTSU members' website;
- Click on *Regulatory* at the top of your screen;
- Click on *Site Registration;*
- Enter your 5-character CTEP Institution Code and click on Go.

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

Data Submission / Data Reporting

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

Requirements to access Rave via iMedidata:

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

Rave role requirements:

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

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

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 XII: TOXICITY-SPECIFIC GRADING

Bilirubin

Grade 1:	> ULN- ≤ 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:	> 45 U/L - ≤ 135 U/L
Grade 2:	136 U/L - 225 U/L
Grade 3:	226 U/L - 900 U/L
Grade 4:	> 900 U/L

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

Grade 1:	> 50 U/L - ≤ 150 U/L
Grade 2:	151 U/L - 250 U/L
Grade 3:	251 U/L - 1000 U/L
Grade 4:	> 1000 U/L

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