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

August 19, 2019

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

Dear Ms. Kruhm,

Attached for review is Amendment #3 to **APEC1621E**, NCI-*COG Pediatric MATCH (Molecular Analysis for Therapy Choice) - Phase 2 Subprotocol of selumetinib (AZD6244 hydrogen sulfate) in patients with tumors harboring activating MAPK pathway mutations*. This amendment is being submitted in response to an RRA from Dr. Doyle (doylela@mail.nih.gov). In this amendment, the revised CAEPR for Selumetinib (AZD6244 hydrogen sulfate) (Version 2.8, June 13, 2019) has been inserted in the protocol, and the associated risk information in the informed consent document has been revised.

SUMMARY OF CHANGES

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

I. Changes made to the protocol by Principal Investigator:

#	Section	Comments

1.	9.1.8	The CAEPR has been updated in response to a rapid request for amendment:
		• The SPEER grades have been updated.
		• Added New Risk:
		  • Rare but Serious: Eye disorders - Other (central serous retinopathy); Eye disorders - Other (retinal pigment epithelial detachment); Eye disorders - Other (retinal vein occlusion); Folliculitis; Nail infection; Papulopustular rash; Skin infection
		• Increase in Risk Attribution:
		  • Changed to Rare but Serious from Also Reported on Selumetinib Trials But With Insufficient Evidence for Attribution: Ejection fraction decreased; Musculoskeletal and connective tissue disorder - Other (neck extensor muscle weakness)
		• Provided Further Clarification:
		  • Footnote#4 is now deleted.

II. Changes to the Informed Consent by Principal Investigator:

#	Section	Comments

1.	ICD	The Risk Profile has been updated.
		• Added New Risk:
		  • Rare: Vision changes; Blood clot which may cause blurred vision or blindness
		• Increase in Risk Attribution:
		  • Changed to Rare from Also Reported on Selumetinib Trials But With Insufficient Evidence for Attribution (i.e., added to the Risk Profile): Change in heart function; Muscle weakness
		• Provided Further Clarification:
		  • Blurred vision (under Rare) is now reported as part of Blurred vision or blindness (under Rare).

Sincerely,

Rita Tawdros, Senior Protocol Coordinator, for
Carl Allen, MD PhD, **APEC1621E** Study Chair
Peter Adamson, M.D., Chair, Children's Oncology Group

Activated: July 24th, 2017
Closed:

Version Date: 08/19/2019
Amendment# 3

CHILDREN'S ONCOLOGY GROUP

APEC1621E

NCI-COG PEDIATRIC MATCH (MOLECULAR ANALYSIS FOR THERAPY CHOICE)- PHASE 2 SUBPROTOCOL OF SELUMETINIB (AZD6244 HYDROGEN SULFATE) IN PATIENTS WITH TUMORS HARBORING ACTIVATING MAPK PATHWAY MUTATIONS

Open to COG Member Institutions in the USA

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AGENT NSC# AND IND#'s
NCI-Supplied Agents:
Selumetinib (AZD6244 hydrogen sulfate)
(NSC#748727)
IND Sponsor: DCTD, NCI

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

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

ABSTRACT

This subprotocol is a component of the NCI-COG Pediatric MATCH trial APEC1621. The APEC1621SC screening protocol details the assay used for the integral genomic profiling which will determine eligibility for this subprotocol. Here we will conduct a phase 2 trial of selumetinib (AZD6244 hydrogen sulfate) in children with recurrent or refractory solid tumors (including non-Hodgkin lymphomas, histiocytoses and CNS tumors) harboring specified activating genetic alterations of the MAPK signaling pathway. Selumetinib (AZD6244 hydrogen sulfate) is a potent orally bioavailable small molecule inhibitor against ERK activation by activated MEK proteins. Selumetinib (AZD6244 hydrogen sulfate) will be given twice daily continuously for 28-day cycles. The primary endpoint will be objective response rate as determined by RECIST. Progression free survival (PFS) will be assessed as a secondary endpoint.

EXPERIMENTAL DESIGN SCHEMA

Day 1-28	Day 28
Selumetinib (AZD6244 hydrogen sulfate) (BID)	Evaluation

Patients will receive selumetinib (AZD6244 hydrogen sulfate) twice daily for 28-day cycles. Evaluations will occur at the end of every other cycle x 3, then every 3 cycles.

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

1.0 GOALS AND OBJECTIVES (SCIENTIFIC AIMS)

1.1 Primary Aims

1.1.1 To determine the objective response rate (ORR; complete response + partial response) in pediatric patients treated with selumetinib (AZD6244 hydrogen sulfate) with advanced solid tumors (including CNS tumors), non-Hodgkin lymphomas or histiocytic disorders that harbor activating genetic alterations in the MAPK pathway.

1.2 Secondary Aims

1.2.1 To estimate the progression free survival in pediatric patients treated with selumetinib (AZD6244 hydrogen sulfate) with advanced solid tumors (including CNS tumors), non-Hodgkin lymphomas or histiocytic disorders that harbor MAPK activation mutations.

1.2.2 To obtain additional information about the tolerability of selumetinib (AZD6244 hydrogen sulfate) in children with relapsed or refractory cancer.

1.3 Exploratory Aims

1.3.1 To evaluate other biomarkers as predictors of response to selumetinib (AZD6244 hydrogen sulfate) and specifically, whether tumors that harbor different mutations or fusions will demonstrate differential response to selumetinib (AZD6244 hydrogen sulfate) treatment.

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

2.0 BACKGROUND

2.1 Introduction/Rationale for Development

The RAS–RAF–MEK1/2–ERK1/2 pathway, also known as the classical MAPK pathway, is responsible for controlling multiple key physiological processes.[1] The MAPK pathway is one of the most frequently dysregulated signaling cascades in human cancer and the aberrant activation of this pathway commonly occurs through gain-of-function mutations in genes encoding RAS and RAF family members as well as by loss of NF1. Despite the low frequency of mutations in the MEK1/2 genes themselves[2,3], MEK1 and MEK2 have emerged as an ideal targets for therapeutic development due to their narrow substrate specificities, distinctive structure and their place at the bottleneck in the MAPK signaling pathway. Among the malignances seen in pediatric and young adult population with known MAPK pathway aberrations include: hematological and lymphoid malignancies (activating N/K RAS mutations, 20%[4]), rhabdomyosarcoma (activating BRAF, NRAS and PTPN11 mutations 20%[5]), low grade glioma (activating mutation or fusion in BRAF 70-100%), as well as in glioblastoma multiforme (loss of NF-1, 15%), neuroblastoma (activating mutations in NRAS, PTPN11, 2.9-3.6%[6]) malignant peripheral nerve sheath tumors (NF1 loss 40-88%)[7] and melanoma (activating mutation in BRAF, 86%).[8]

MEK inhibitors have shown clinical responses in patients with BRAF mutated melanoma refractory to BRAF inhibitors leading to FDA approval of trametinib for refractory

melanoma both as a single agent[9] as well as in combination with BRAF inhibitor dabrafenib.[10] Similarly, they have also shown clinical responses (20% with PR) in melanoma with NRAS mutated melanomas.[11] In patients with KRAS mutant lung cancers MEK inhibitors combined with gemcitabine[12] improves response rate and event-free survival. There is pre-clinical evidence for activity of MEK inhibitors in *NF1* deficient neurofibromas and melanomas and a phase 1 trial of selumetinib (AZD6244 hydrogen sulfate) (AZD6244) demonstrated clinical responses in 17/24 (17%) pediatric patients with neurofibromatosis-1 (NF-1) with large plexiform neurofibroma.[13-16] In uveal melanoma, which is characterized by mutations in GNAQ and GNA11, G-binding protein alpha subunits that signal via the MAPK pathway, selumetinib (AZD6244 hydrogen sulfate) results in a higher response rate and prolonged progression free survival when compared with chemotherapy.[17] In summary, there is currently clinical evidence supporting diverse alterations in multiple MAPK genes as biomarkers for response, for example: activating RAS gene mutations (NRAS/KRAS/HRAS), activating BRAF mutations (V600E and others) and fusions, GNAQ and GNA11 activating mutations, inactivating mutations in PTPN11 and loss of NF1 through inactivating mutations or insertion/deletion. [14]

2.2 Preclinical Studies

2.2.1 Antitumor Activity

There are several pre-clinical studies demonstrating efficacy of MEK inhibitors in pediatric tumors with known RAS-ERK pathway aberrations. MEK/ERK inhibitor UO126 has shown to inhibit growth of rhabdomyosarcoma both as a single agent *in vivo and in vitro*[18] as well as in combination with dual PI3K/mTOR inhibitor PI103. [19] In addition, *in vitro and in vivo* synergy has also been seen between inhibitors of TORC1/2 (AZD8055), and MEK (AZD6244) in embryonal rhabdomyosarcoma.[20] Pre-clinical data also support potential activity for MEK inhibitors against neuroblastoma with MAPK gene mutations.[21] Lastly, NF-1 deficiency has shown to be predictive of sensitivity to MEK inhibitors *in vitro* in glioblastoma multiforme.[22] In preclinical studies, some *MAP2K1* mutations are sensitive to MEK inhibition.[23,24] In view of the high frequency of aberrations seen in target biomarkers of MEK inhibitors within the pediatric oncology population, as well as the promising clinical activity in melanoma as well as in plexiform neurofibroma, TAP committee members were enthusiastic for including MEK inhibitors as a part of the Pediatric MATCH trial.

2.2.2 Animal Toxicology

Mice and monkeys treated with selumetinib (AZD6244 hydrogen sulfate) were reported to develop diarrhea, dehydration and electrolyte imbalance in some animals. Tissue mineralization was reported in mice that was not reversible with discontinuation of drug. At the highest dose levels, skin lesions and/or scabs were observed in some mice as well as decreased cellularity of femoral bone marrow. Embryofetal development and survival in mice was impacted at levels that do not induce maternal toxicity (Selumetinib Investigators Brochure).

2.3 Adult Studies

2.3.1 Phase 1 Studies

As of October 2015, selumetinib (AZD6244 hydrogen sulfate) has been used in approximately 2880 subjects, including two trials with pediatric subjects 8799 [NCT01362803; Phase 1] and PBTC-029 [NCT01089101; Phase 1/2]. The

recommended Phase 2 dose for monotherapy has been established as 75 mg bid based on Phase 1 and PK data [D1532C00005; D1532C00066]. Early Phase 1 studies reported the best overall response of stable disease in 18-40% of patients.[25-28]

The most frequent AEs reported in Phase 1 studies with selumetinib (AZD6244 hydrogen sulfate) dose 100 mg bid included rash (74%), diarrhea (58%), nausea (55%), fatigue (55%), and peripheral edema. Grade 3 rash was reported in 14%, and 5.3% experienced Grade 3 fatigue. [D1532C0005].

2.3.2 Phase 2 Studies

Phase 2 studies treating patients with malignant melanoma, pancreatic cancer, colorectal cancer, non-small-cell lung cancer, advanced hepatocellular carcinoma, metastatic biliary tract cancer, refractory papillary thyroid cancer, acute myeloid leukemia, multiple myeloma, and ovarian/peritoneal carcinoma, report that 11-80% of subjects experienced stable disease with selumetinib (AZD6244 hydrogen sulfate) .[29-43] The most common AEs reported in Phase 2 monotherapy studies included dermatitis (94%), diarrhea (54%), nausea (49%), peripheral edema (31%), vomiting (24%), and fatigue (21%) [DC1532C00003/8/11/12].

2.3.3 Pharmacology/Pharmacokinetics/Correlative and Biological Studies

The PK of selumetinib (AZD6244 hydrogen sulfate) in the above studies was approximately dose proportional across the dose ranges studied for the Hyd-Sulfate formulation (25-100 mg). Drug exposure was reduced by CYP3A4 induction with rifampicin, and increased by the CYP3A4 inhibitor itraconazole and the CYP2C19 inhibitor fluconazole. Minimal effects on drug exposure were observed in subjects with end stage renal disease compared to healthy volunteers, and dialysis had minimal effect on removal of systemic selumetinib (AZD6244 hydrogen sulfate). While there was no change in exposure in subjects with mild hepatic impairment, subjects with moderate or severe hepatic impairment showed higher selumetinib (AZD6244 hydrogen sulfate) AUC compared to healthy volunteers receiving the same dose. Food was observed to decrease the rate of selumetinib (AZD6244 hydrogen sulfate) absorption, but with relatively small reduction in total exposure. Therefore, pending further study, it is recommended to take the drug on an empty stomach (1 hour before or 2 hours after food).

2.4 Pediatric Studies

2.4.1 Prior Experience in Children

Two pediatric studies including children with NF1-associated plexiform neurofibromas and low-grade gliomas report partial responses in 21% and 55% of patients, respectively.[44,45] Early studies suggest that the adult RP2D (75 mg twice daily) equivalent may be toxic in children. In a phase 1 study, Banerjee and colleagues report treating children with recurrent/refractory low-grade gliomas with 33 and 43 mg/m^2/dose twice daily (patient numbers not noted in the abstract), and both levels were deemed intolerable due to DLTs of headache, rash and mucositis. De-escalation to 25 mg/m^2/dose twice daily (n=24) improved tolerability and resulted in plasma levels sufficient to inhibit ERK activation. The authors conclude that 25 mg/m^2/dose twice daily is optimal for pediatric studies. Gross and colleagues describe a plan for a phase 2 study, for children with NF1 and inoperable neurofibromas to receive 25 mg/m^2 twice daily.[46] In a phase 1

study, Widemann reported DLT in the first three cycles in 1/6 children and young adults with NF1 and inoperable neurofibromas treated with 25 mg/m^2 twice daily (approximately 50% of the adult recommended phase 2 dose), which was reversible grade 3 rash. By comparison 4/6 children receiving 30 mg/m^2 twice daily dosing experienced DLTs. Throughout all treatment cycles, 3/6 patients in the 25 mg/m^2 group and 4/6 in the 30 mg/m^2 group experienced DLTs including creatine kinase elevation, gastrointestinal toxic effects, acneiform or maculopapular rash, and decreased left ventricular ejection fraction, all of which were reversible. The authors conclude that 25 mg/m^2/dose twice daily is optimal for pediatric studies. [16]

2.4.2 Pharmacology/Pharmacokinetics/Correlative Biological Studies

Selumetinib (AZD6244 hydrogen sulfate) PK in children appear to be similar to adults.[16,26] Selumetinib (AZD6244 hydrogen sulfate) was absorbed rapidly and the increase in drug exposures with increasing dose were less than dose-proportional. The selumetinib (AZD6244 hydrogen sulfate) half-life in children was approximately 6 hours at the 25 mg/m^2 dose.[16]

2.5 Overview of Proposed Pediatric Study

This is a phase 2 trial of selumetinib (AZD6244 hydrogen sulfate) in children with recurrent or refractory solid tumors, CNS tumors, non-Hodgkin lymphomas and histiocytic disorders harboring specific activating mutations that result in pathologic activation of the MAPK pathway.

Patients will receive selumetinib (AZD6244 hydrogen sulfate) for 28-day cycles at the MTD and recommended Phase 2 dose (RP2D) of 25 mg/m^2/dose BID.

The primary aim of this trial will be to establish the objective response rate to selumetinib (AZD6244 hydrogen sulfate). While there will not be multiple pre-determined mutation-based cohorts, responses will be analyzed retrospectively with respect to specific MAPK pathway activating mutations.

Key secondary objectives include further evaluation of the tolerability of selumetinib (AZD6244 hydrogen sulfate) in pediatric patients. Toxicity will be assessed using CTCAE V5.0. Imaging for disease evaluation will occur every other cycle x 3, then every three cycles. Disease response will be assessed according to RECIST v1.1 for solid tumors and 2-dimensional measurement for CNS tumors.

3.0 SCREENING AND STUDY ENROLLMENT PROCEDURES

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

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

All site staff will use OPEN to enroll patients to this study. It is integrated with the CTSU Enterprise System for regulatory and roster data and, upon enrollment, initializes the patient position in the Rave database. OPEN can be accessed at https://open.ctsu.org or from the OPEN tab on the CTSU members' side of the website at https://www.ctsu.org. To assign an IVR or NPIVR as the treating, crediting, consenting, drug shipment (IVR only), or investigator receiving a transfer in OPEN, the IVR or NPIVR must list on their Form FDA 1572 in RCR the IRB number used on the site's IRB approval. If a DTL is required for the study, the IVR or NPIVR must also be assigned the appropriate OPEN-related tasks on the DTL.

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 a MATCH 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 APEC1621E 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 APEC1621E.

3.2 IRB Approval

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

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

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

Sites participating on the NCI CIRB initiative and accepting CIRB approval for the study

are not required to submit separate IRB approval documentation to the CTSU Regulatory Office for initial, continuing, or amendment review. However, sites must submit a Study Specific Worksheet for Local Context (SSW) to the CIRB (via IRBManager) to indicate their intention to open the study locally. The CIRB's approval of the SSW is then communicated to the CTSU Regulatory Office for compliance in the RSS. The Signatory Institution must inform the CTSU which CIRB-approved institutions aligned with the Signatory Institution are participating in the study so that the study approval can be applied to those institutions. Other site registration requirements (e.g., laboratory certifications, protocol-specific training certifications, or modality credentialing) must be submitted to the CTSU Regulatory Office or compliance communicated per protocol instructions.

3.3 Informed Consent/Assent

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

3.4 Screening Procedures

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

3.5 Eligibility Checklist

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

3.6 Study Enrollment

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

Patients must be enrolled within 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 APEC1621E will have a COG ID obtained through their prior enrollment onto the screening protocol or from a prior COG study.

Note: No starter supplies will be provided. Drug orders of selumetinib (AZD6244 hydrogen sulfate) should be placed with CTEP after enrollment and treatment assignment to APEC1621E 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 level will be assigned via OPEN at the time of study enrollment.

4.0 PATIENT ELIGIBILITY

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

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

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

4.1 Inclusion Criteria

4.1.1 APEC1621SC: Patient must have enrolled onto APEC1621SC and must have been given a treatment assignment to MATCH to APEC1621E based on the presence of an actionable mutation as outlined in Appendix VII.

Note: Patients with BRAF V600 aMOIs will be preferentially assigned to APEC1621G (vemurafenib) if that study is open and they are otherwise eligible for it.

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

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

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

Measurable disease in patients with CNS involvement is defined as 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://members.childrensoncologygroup.org/Disc/devtherapeutics/default.asp 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://members.childrensoncologygroup.org/Disc/devtherapeutics/default.asp 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 selumetinib (AZD6244 hydrogen sulfate).

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:
- Shortening fraction of ≥ 27% by echocardiogram, or Ejection fraction of ≥ 50% by gated radionuclide study.

4.1.7.5 Adequate Blood Pressure Control Defined as:
A blood pressure (BP) ≤ the 95th percentile for age, height, and gender (Appendix IX) measured as described in Section 6.7. Please note that 3 serial blood pressures should be obtained and averaged to determine baseline BP. Patients with hypertension controlled on antihypertensive medications will be allowed if otherwise eligible.

4.1.7.6 Adequate Metabolic Function Defined as:
- Serum triglyceride level ≤ 300 mg/dL
- Serum total cholesterol level ≤ 300 mg/dL

4.1.8 Patients must be able to swallow intact capsules whole.

4.1.9 Informed Consent: All patients and/or their parents or legally authorized

representatives must sign a written informed consent. Assent, when appropriate, will be obtained according to institutional guidelines.

4.2 Exclusion Criteria

4.2.1 Pregnancy or Breast-Feeding
Pregnant or breast-feeding women will not be entered on this study because there is currently no available information regarding human fetal or teratogenic toxicities. Pregnancy tests must be obtained in girls who are post-menarchal. Females of reproductive potential may not participate unless they have agreed to use an effective contraceptive method for the duration of study treatment. Males with sexual partners who are pregnant or who could become pregnant (ie, women of child-bearing potential) should use effective methods of contraception for 12 weeks after completing the study to avoid pregnancy and/or potential adverse effects on the developing embryo.

4.2.2 Concomitant Medications

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

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

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

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

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

4.2.2.6 CYP2C19 Agents: Patients who are currently receiving drugs that are strong CYP2C19 inducers (eg, rifampin, ritonavir) or inhibitors (eg., fluoxetine, fluvoxamine, ticlopidine) are not eligible.

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

4.2.4 Patients with known significant ophthalmologic conditions (uncontrolled glaucoma, history of retinal vein occlusion or retinal detachment, excluding

patients with longstanding findings secondary to existing conditions) are not eligible.

4.2.5 Patients with Low Grade Glioma 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	**Selumetinib (AZD6244 hydrogen sulfate)** 25 mg/m^2/dose orally twice daily (maximum 75 mg per dose)
Day 28	Evaluation

Selumetinib (AZD6244 hydrogen sulfate) capsules will be administered orally in capsules given twice a day at a dose of 25 mg/m^2 BID with a maximum dose of 75 mg per dose. Therapy will be discontinued if there is evidence of progressive disease or drug related dose-limiting toxicity that requires removal from therapy (Section 6.0). Therapy may otherwise continue for up to 2 years provided the patient meets the criteria for starting subsequent cycles (Section 5.2) and does not meet any of the criteria for removal from protocol therapy criteria (Section 10.0).

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

Patients will be treated at the established pediatric MTD/RP2D which is 25 mg/m^2/dose BID.

Drug doses should be adjusted based on the BSA calculated from height and weight measured within 7 days prior to the beginning of each cycle, and according to the dosing nomogram (see Appendix IV). Patients should swallow the capsules as a whole and should not chew or crush them. Selumetinib (AZD6244 hydrogen sulfate) should be taken on an empty stomach at least 2 hours after food and patients should not eat or drink (except water) for at least one hour after taking selumetinib. If a patient vomits within 30 minutes after the dose of selumetinib (AZD6244 hydrogen sulfate), is administered, that dose may be repeated once. Otherwise, the dose will be missed.

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

5.1.1 Therapy Delivery Map

See Appendix V for APEC1621E Therapy Delivery Map.

5.2 **Criteria for Starting Subsequent Cycles**

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

5.3 **Grading of Adverse Events**

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

5.4 **Definition of Dose-Limiting Toxicity (DLT)**

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

5.4.1 Non-Hematological Dose-Limiting Toxicity

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

- Grade 3 nausea and vomiting of < 3 days duration
- Grade 3 diarrhea ≤ 3 days duration
- Grade 3 liver enzyme elevation, including ALT/AST/GGT that returns to levels that meet initial eligibility criteria or baseline within 7 days. See Section 6.3. See Appendix XIII 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 papulopustular, acneiform, or maculo-papular rash that resolves to ≤ Grade 1 or baseline within 14 days of initiation of topical steroid as described in Section 7.3.1. However, any investigational drug-related Grade 3 rash that is considered intolerable by the patient or limits ADLs will be considered a DLT regardless of duration.
- Grade 3 asymptomatic elevation of CPK

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

5.4.1.2 Dose-limiting hypertension

- Any Grade 4 hypertension
- A blood pressure > 25 mmHg above the 95th percentile for age, height, and gender (Appendix IX) confirmed by repeated

measurement is dose limiting.
- In patients who begin antihypertensive therapy a blood pressure > 10 mmHg but ≤ 25 mmHg above the 95th percentile for age, height, and gender (Appendix IX) for > 14 days is dose limiting.

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

In patients evaluable for hematological toxicity (see Section 4.1.7.1),
- Grade 4 thrombocytopenia or neutropenia, not due to malignant infiltration.
- Grade 3 thrombocytopenia that persists for ≥ 7 days
- Grade 3 thrombocytopenia requiring a platelet transfusion on 2 separate days
- 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).

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

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

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

6.2 Dose Modifications for Non-Hematological Toxicity

6.2.1 If a patient experiences non-hematological dose-limiting toxicity as defined in

Section 5.4.1, the treatment will be held. When the toxicity resolves to meet eligibility parameters or baseline within 14 days of drug discontinuation, the patient may resume treatment at a reduced dose as outlined in the dose reduction table (Appendix IV). Doses reduced for toxicity will not be re-escalated, even if there is minimal or no toxicity with the reduced dose.

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

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

6.3 Dose Modifications for Hepatic Adverse Events

6.3.1 If a patient experiences Grade ≥ 3 ALT, treatment will be held. If toxicity resolves to meet eligibility criteria within 7 days, the drug may be resumed at the same dose. Grade ≥ 3 ALT that persists ≥ 7 days will be considered dose-limiting and require dose modification per Section 6.2.

6.4 Dose Modifications for Dermatology/Skin Disorders

Grade	Action
Grade 1 or 2	• Maintain dose
Intolerable Grade 2; Grade 3	• Hold AZD6244 selumetinib (AZD6244 hydrogen sulfate) until resolution to ≤ tolerable Grade 2 and dose reduce as per Section 6.2. See also Section 7.3.1

6.5 Dose Modifications for Visual Disturbances

Grade	Action
Grade 1	• Maintain Dose
Grade 2	• Hold selumetinib (AZD6244 hydrogen sulfate) until eye exam is completed; If the Ophthalmology exam is normal and the toxicity resolves to < Grade 1 within 1 week or an alternate cause for the vision problem is identified – restart selumetinib (AZD6244 hydrogen sulfate) at the same dose level. Otherwise Grade 2 visual disturbance that persists for ≥ 1 week hours will be considered a DLT and require a dose reduction as per Section 6.2.
Grade 3 or 4	• Hold AZD6244 selumetinib (AZD6244 hydrogen sulfate) until Eye exam is completed; If alternate etiology for vision change is identified, contact study chair to discuss restarting of selumetinib (AZD6244 hydrogen sulfate). Otherwise ≥ Grade 3 visual disturbance will be considered a DLT and require a dose reduction as per Section 6.2.

6.6 Dose Modifications for Elevation of CPK

Grade	Action
Grade 1 or 2 or Grade 3 asymptomatic	• Maintain dose; continue monitoring as per protocol, or more frequently if clinically indicated.
Grade 3 symptomatic or Grade 4	• Hold AZD6244 selumetinib (AZD6244 hydrogen sulfate) until resolution to ≤ Grade 1 and dose reduce as per Section 6.2.

6.7 Dose Modifications for Hypertension

- **Baseline blood pressure** (BP) is defined as the blood pressure obtained at the examination used for study enrollment. This baseline BP should be obtained as follows: 1) Obtain 3 serial blood pressures from the same extremity with the patient in the same position at rest with an appropriately sized cuff. Measures must be obtained at least 5 minutes apart. Avoid using the lower extremity if possible. 2) Average the systolic blood pressure from the 2nd and 3rd measurements. 3) Average the diastolic blood pressure from the 2nd and 3rd measurements. 4) The baseline BP is the average of the systolic over the average of the diastolic measurements.

- **Elevation** in either the systolic or diastolic blood pressure should be considered when following the algorithm below.

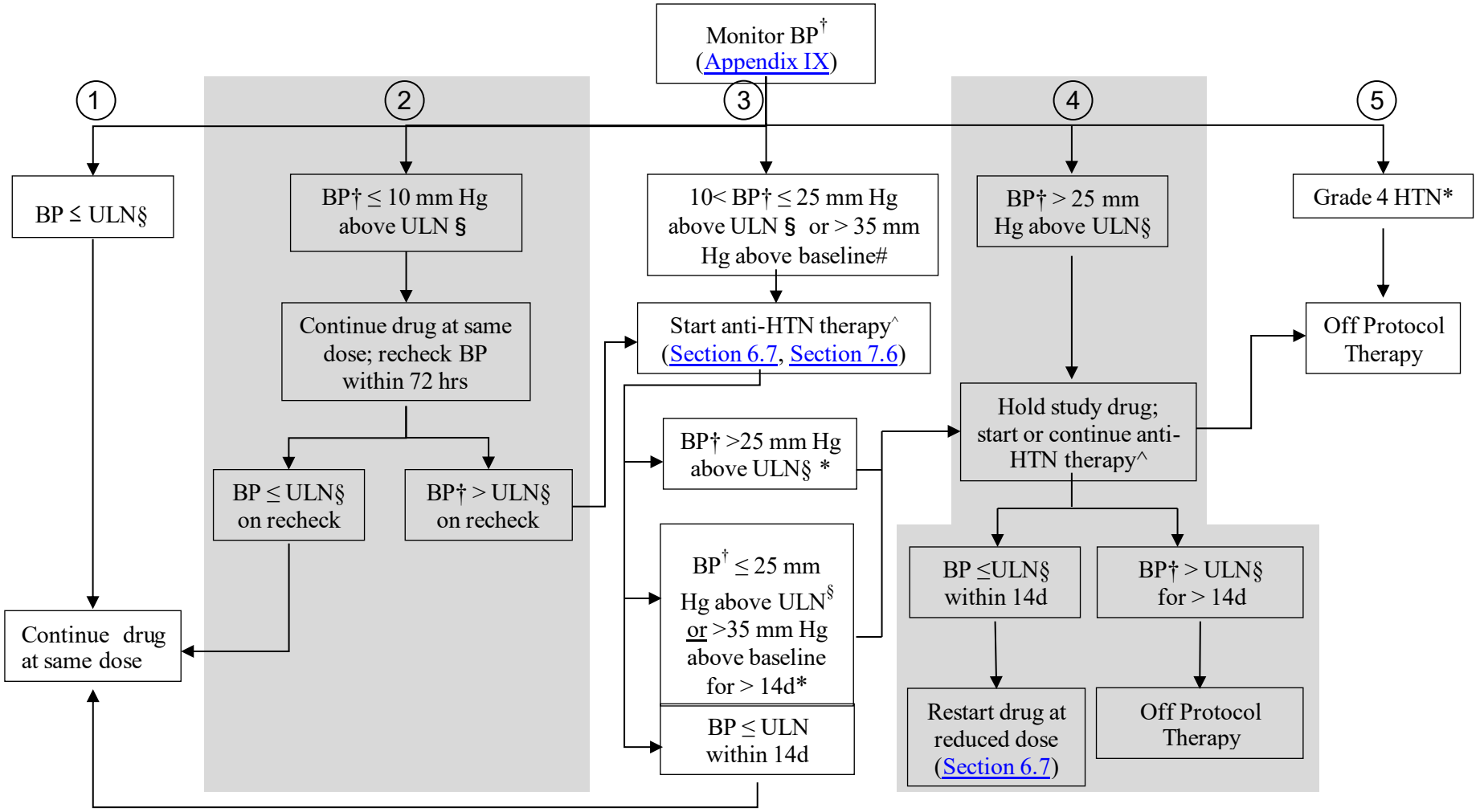
- **The upper limit of normal (ULN)** is defined as a BP equal to the 95th percentile for age, height, and gender. See Appendix IX.

- The NCI CTCAE version 5.0 will be utilized to determine the grade of hypertension for reporting purposes.

- Elevated BP measurements should be repeated on the same day to confirm the elevation. If confirmed, patients with elevated BP should have BP measurements performed at least twice weekly until BP is ≤ ULN.

- The algorithm below will be used to manage selumetinib-related hypertension.

- Hypertension should be managed with appropriate anti-hypertensive agent(s) as clinically indicated. It is strongly recommended that nephrology or cardiology be consulted in the evaluation and management of hypertension.



Elevations in BP are based on systolic or diastolic pressures.

† Elevated blood pressure (BP) measurements should be repeated on the same day to confirm the elevation. Patients with elevated BP at any time should have BP measurements performed at least twice weekly until BP is within the ULN.

§ ULN (Upper Limit of Normal) is a BP equal to the 95th percentile from age, height, and gender-appropriate normal values (Appendix IX)

* If BP > 25 mm Hg above ULN for age (verified) or Grade 4 HTN at any time, hold drug. Study drug should also be held for BP ≤ 25 mm Hg above the ULN age for > 14 days or 35 mmHg above baseline for > 14 days. Antihypertensive agents can be used to control hypertension as

clinically indicated after study drug is held.

^ Anti-hypertensive therapy should be prescribed as clinically indicated, including the use of multiple anti-hypertensive agents.

Baseline BP is defined in Section 4.1.7.5.

Arm 1 of algorithm:

- If blood pressure (BP) ≤ 95% for age, height, and gender, continue selumetinib at the same dose.

Arm 2 of algorithm:

- If BP ≤ 10 mm Hg above the ULN for age, height, and gender, continue selumetinib at the same dose and recheck the BP within 72 hours.
  - If the BP is ≤ ULN on recheck, continue selumetinib at the same dose.
  - If the BP remains above the ULN on recheck, then start antihypertensive therapy (Section 7.6) and follow Arm 3 of the algorithm from the point that anti-hypertensive therapy is started.

Arm 3 of algorithm:

- If BP is 11 to 25 mm Hg above the 95% for age, height, and gender on ≥ 2 of 3 measurements or > 35 mmHg above baseline on ≥ 2 of 3 measurements, start anti-hypertensive therapy (see Section 7.6), continue selumetinib at the same dose, and monitor BP at least twice weekly.
  - If the BP returns to ≤ ULN within 14 days, continue selumetinib at the same dose and continue anti-hypertensive therapy.
    - If the BP remains elevated ≤ 25 mm Hg above the 95% or > 35 mm Hg above baseline for more than 14 days after the institution of anti-hypertensive therapy, **hold** selumetinib, monitor BP at least every 3 days, and follow Arm 4 of the algorithm from the point that selumetinib is held. If selumetinib is stopped, antihypertensives should be continued until BP is < ULN. If selumetinib is resumed, anihypertensives should continue for the duration of selumetinib therapy unless clinically indicated to discontinue.
      - If the BP returns to ≤ ULN within 14 days, restart selumetinib at a reduced dose (Section 6.2).
      - If the BP remains > ULN for more than 14 days, patient is Off Protocol Therapy.
  - If the BP increases to > 25 mm Hg above the ULN despite anti-hypertensive therapy, **hold** selumetinib, but continue the anti-hypertensive agent(s). Monitor the BP as clinically indicated and follow Arm 4 of the algorithm from the point that selumetinib is held.
    - If the BP is ≤ ULN within 14 days, selumetinib may be restarted at a reduced dose (Section 6.2).
    - If the BP is > ULN for > 14 days, the patient is Off Protocol Therapy (Section 10.1).

Arm 4 of algorithm:

- If BP is > 25 mm Hg above the 95% for age, height, and gender **hold** selumetinib, monitor BP and administer anti-hypertensive therapy as clinically indicated.
  - If the BP returns to ≤ ULN within 14 days, selumetinib may be restarted at a reduced dose (Section 6.2).
  - If the BP is > ULN for >14 days, the patient is Off Protocol Therapy (Section 10.1).

Arm 5 of algorithm:

- If the participant develops Grade 4 hypertension, **discontinue** selumetinib, monitor BP and administer anti-hypertensive therapy as clinically indicated. The patient is Off Protocol Therapy (Section 10.1).

6.8 Dose Modification for Elevated Fasting Cholesterol

The following guidelines should be used for patients who develop elevated fasting cholesterol.

Grade	Action
Grade 2	• Continue selumetinib; consider treatment with an HMG-CoA reductase inhibitor depending upon recommendations of institutional hyperlipidemia consultants.
Grade 3	• An HMG-CoA reductase inhibitor should be started, and dosages adjusted based upon recommendations of institutional hyperlipidemia consultants. • It is expected that optimal effects of the lipid lowering medication will be observed 2-4 weeks after its initiation. Treatment with selumetinib is to be restarted at the same dose level when recovery of hypercholesterolemia to ≤ Grade 2 is observed.
Grade 4	• Hold selumetinib. • An HMG-CoA reductase inhibitor should be started, and dosages should be adjusted based upon recommendations from institutional hyperlipidemia consultants.

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. See Section 7.5 for drugs that should not be used concomitantly due to potential interactions with selumetinib (AZD6244 hydrogen sulfate). See below for recommendations on management of specific toxicities associated with selumetinib (AZD6244 hydrogen sulfate).

7.3.1 Recommendations for Skin Toxicity:

The most common drug related adverse event is rash, which have included many different types and can begin as early as cycle 1 or 2. Descriptions include: erythematous rash, maculopapular rash, pruritic rash, acneiform dermatitis, exfoliative rash. Grade 3 rashes are often associated with pruritus and can have scaling. Based on the experience on the current adult Phase 1/2 study the following recommendations should be followed. For Grade 3 rash selumetinib (AZD6244 hydrogen sulfate) should be held until resolution to Grade 1 or better and then treatment can be resumed at a reduced dose as outlined in the dose reduction table

(Appendix IV). For eczematous rashes, moisturizers or low-dose topical corticosteroids may be used if based on the rash appearance they would be considered appropriate treatment. For pustular rash, topical clindamycin gel or lotion may be applied twice daily. For more severe cases, oral teracyclines may be useful in older children. Ketoconazole shampoo may be used for scalp rash. If oral corticosteroids are required for severe rash, selumetinib (AZD6244 hydrogen sulfate) should be held until improvement to < Grade 1 at a reduced dose as outlined in the dose reduction table (Appendix IV).

7.3.2 Recommendations for Paronychiae:
Patients who develop paronychiae may be treated with flurandrenolide tape, topical steroid cream, topical antibiotics or systemic antibiotics as clinically indicated.

7.3.3 Recommendations for Diarrhea:
Patients who experience diarrhea may be treated symptomatically with oral hydration and anti-diarrheal medications according to institutional standards. Example loperamide dosing is outlined in Appendix VIII.

7.3.4 Recommendations for Visual Disturbance:
Patients who experience visual disturbance should undergo complete ophthalmologic examination including visual acuity, visual fields (if feasible) and fundoscopic exam.

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 Selumetinib (AZD6244 hydrogen sulfate) is metabolized by CYP 1A2, 2C8, 2C9, 2C19, 3A4/5 to form active N-desmethyl selumetinib (AZD6244 hydrogen sulfate) metabolite; In addition, UGT 1A1 and 1A3 form glucuronide conjugates. Use caution in patients who are taking strong inducers or inhibitors of these CYP or UGT enzymes.

7.5.2 CYP3A4/5 inhibitors or inducers: Strong CYP3A4/5 inhibitors and inducers are not permitted on this study (See Appendix II for list of agents). Note: CYP3A4 inducing anti-epileptic drugs and dexamethasone for CNS tumors or metastases, on a stable dose, are allowed.

7.5.3 The use of drugs that are strong CYP2C19 inducers (eg., rifampin, ritonavir) or inhibitors (eg., fluoxetine, fluvoxamine, ticlopidine) should be avoided during the study.

7.5.4 High vitamin E doses may potentiate warfarin's anticoagulant activity. Monitor PT/INR more frequently in patients receiving both warfarin and selumetinib (AZD6244 hydrogen sulfate) capsules. Avoid concomitant intake of supplemental vitamin E.

7.5.5 Selumetinib (AZD6244 hydrogen sulfate) is also a substrate of BCRP (breast

cancer resistance protein) and P-glycoprotein (P-gp) transporters. Use caution in patients who are taking strong inducers or inhibitors of either transport protein.

7.6 Concurrent Anti-Hypertensive Therapy

The algorithm in Section 6.7 will be used to manage selumetinib- related hypertension. Should initiation of anti-hypertensive therapy be required, single agent therapy (commonly including the calcium channel blockers amlodipine or nifedipine, which are permissible without discussion with the study chair) should be started and the blood pressure should be monitored at least twice weekly until BP is within the 95th percentile for age, height, and gender per Section 6.7.

8.0 EVALUATIONS/MATERIAL AND DATA TO BE ACCESSIONED

8.1 Required Clinical, Laboratory and Disease Evaluation

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

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

Creatine Kinase (CPK)	X		X
Blood Pressure[9]	X	Weekly	Prior to each cycle and every other week
Ophthalmologic exam	X		Prior to cycle 3, then Prior to every other cycle
Plain radiograph tibial growth plate (Bone X-Ray Tests)[10]	X		Prior to cycles 2, 5 and every 6 months
Total Cholesterol, Triglycerides[11]	X	X	X

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

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

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

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

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

4-A Neurological exam also required for CNS patients.

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

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

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

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

7 Patient diary (see Appendix III) should be reviewed after completion of each treatment cycle and uploaded into RAVE.

8 With consent, two samples will be collected on this protocol (cycle 5 Day 1; and for patients receiving ≥ 5 cycles only: at progression or end of protocol therapy), see Section 8.4 for details of the ctDNA studies. Note that a ctDNA sample is scheduled to be obtained on the APEC1621SC screening protocol prior to the initiation of treatment on this subprotocol.

9 Blood pressure will be measured with an appropriate sized cuff at rest. Blood pressure measurement will be repeated within the same day if the blood pressure (BP) is elevated (> the 95th percentile for age, height, and gender). Please note that 3 serial blood pressures should be obtained and averaged to determine baseline BP (See Section 6.7). If both BP measurements are >95th percentile for age, height, and gender, follow the guidelines in Section 6.7. Patients with elevated BP at any time should have BP measurements performed at least twice weekly until BP is within the 95th percentile for age, height, and gender (See Appendix IX).

10 Plain radiographs of at least one tibial growth plate should be obtained in all patients prior to first dose

of protocol therapy. In patients with open growth plates, follow-up plain radiographs of the same growth plate(s) should be obtained according to Section 8.2.1.

[11] If Grade 3 or 4 hypercholesterolemia or Grade 3 or 4 hypertriglyceridemia is detected when routine (non-fasting) laboratory studies are performed, the tests should be repeated within 3 days in the fasting state to permit accurate grading.

8.2 Monitoring for Specific Toxicities

8.2.1 Growth Plate Toxicity

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

a. If patients are found to have a closed tibial growth plate, no further radiographs will be required.
b. If patients are found to have an open tibial growth plate, then repeat plain AP radiographs of the same tibial growth plate will be obtained prior to cycles 2, 5 and every 6 months.
   - Patients with evidence of growth plate thickening or other changes should have a knee MRI performed to further assess the degree of physeal pathology and undergo more frequent x-ray follow up at least every 3 cycles or as clinically indicated. MRI should be performed without contrast.
   - Patients with knee MRI changes should be managed in an individualized manner. Decisions regarding continuation of selumetinib should be made after discussion with the Study Chair or Study Vice-Chair and MATCH Leadership, taking into account the presence of any symptoms referable to the knee as well as the patient's response to selumetinib. Consultation with an orthopedic surgeon may also be indicated. Plans for follow-up imaging will also be made on an individualized basis, taking into account the presence of symptoms at the knee or other joints as well as the decision to continue selumetinib or not.

8.3 Radiology Studies

8.3.1 Bone Age/Knee MRI

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

8.3.2 Central Radiology Review for Response:

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

8.3.3 Technical Details of Submission:

To ensure an adequate interpretation of FDG-PET and CT with contrast scans, scans transferred between the treating institutions and the Imaging and Radiation Oncology Core Group IROC RI (QARC) must be submitted in Digital Imaging and Communications in Medicine (DICOM) format. BMP files, JPG files, or hard copies (films) are unacceptable for adequate interpretation of PET and CT with contrast scans. Imaging studies must be submitted electronically as outlined in the

following paragraph. The images will be made available to study radiologists and nuclear medicine physicians for central review.

Submission of Diagnostic Imaging data in DICOM format is required. 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.

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

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

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

TRIAD Installations:

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

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

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

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

For FDG-PET imaging, the transferred imaging data should include uncorrected and attenuation-corrected PET projection data, as well as the reconstructed PET or

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

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

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

8.4 Circulating Tumor DNA Study (optional)

8.4.1 Sampling Schedule

An initial sample was previously required at time of enrollment onto the APEC1621SC screening protocol. Additional samples 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)

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

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

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

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

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

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

8.4.2 Sample Processing

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

8.4.3 Sample Labeling

Each tube must be labeled with the patient's study registration number, the study I.D (APEC1621E), and the date and time the sample was drawn. Data should be recorded on the appropriate transmittal form found in RAVE, which must accompany the sample(s).

8.4.4 Sample Shipping Instructions

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

Ship specimens to the following address:

Biopathology Center
Nationwide Children's Hospital
Protocol APEC1621E- Peds MATCH
700 Children's Drive, WA1340*
Columbus, OH 43205
Phone: (614) 722-2865
Fax: (614) 722-2897
Email:BPCBank@nationwidechildrens.org

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

9.0 AGENT INFORMATION

9.1 Selumetinib
(AZD6244 hydrogen sulfate) NSC#748727 IND#

9.1.1 Structure and molecular weight
Chemical Name or Amino Acid Sequence: 5-[(4-bromo-2-chlorophenyl)amino]-4-fluoro-6-[(2-hydroxyethoxy)carbamoyl]-1-methyl-1H-benzimidazol-3-ium hydrogen sulfate

Molecular Formula: $C_{17}H_{15}BrClFN_4O_3 \bullet H_2SO_4$

Molecular Weight: 555.76

9.1.2 Supplied by: Astrazeneca supplies and CTEP, DCTD, NCI distributes selumetinib (AZD6244 hydrogen sulfate).

9.1.3 Formulation
Selumetinib (AZD6244 hydrogen sulfate) is supplied for clinical trial use as size 4 hydroxypropylmethylcellulose (HPMC) capsules available in 10 mg (plain white) and 25 mg (blue) strengths, expressed as free base. Capsules are packaged in white, high density polyethylene (HDPE) containers with induction-seals and child-resistant closures. Each bottle contains 60 capsules with desiccant.

Selumetinib (AZD6244 hydrogen sulfate) capsules contain a dispersion of drug in D-α-tocopheryl polyethylene glycol 1000 succinate (TPGS; a water soluble form of vitamin E). Each 10 mg capsule contains 32.4 mg TPGS and each 25 mg capsule contains 35.9 mg TPGS.

9.1.4 Storage
Store the selumetinib (AZD6244 hydrogen sulfate) capsules at controlled room temperature (20°C- 25°C). Bottles can be refrigerated between 2°C- 8°C if necessary.

If a storage temperature excursion is identified (either above 25°C or below 2°C), promptly return selumetinib (AZD6244 hydrogen sulfate) to controlled room temperature and quarantine the supplies. Provide a detailed report of the excursion (including documentation of temperature monitoring and duration of the excursion) to PMBAfterHours@mail.nih.gov for determination of suitability.

9.1.5 Stability: Stability studies are ongoing.

9.1.6 Administration
Oral. Do not eat or drink (except water only) for 2 hours prior to dosing and 1 hour after dosing selumetinib (AZD6244 hydrogen sulfate) capsules.

9.1.7 Potential Drug Interactions
High vitamin E doses may potentiate warfarin's anticoagulant activity. Monitor PT/INR more frequently in patients receiving both warfarin and selumetinib (AZD6244 hydrogen sulfate) capsules.

Avoid concomitant intake of supplemental vitamin E.

Selumetinib (AZD6244 hydrogen sulfate) is primarily metabolized by CYP 1A2 to form the active N-desmethyl metabolite; in addition, UGT 1A1 and1A3 form glucuronide conjugates. CYP 2C8, 2C9, 2C19, 3A4/5 can also metabolize the parent agent to form N-desmethyl selumetinib; however, as observed during in vitro studies using a pan-CYP inhibitor, other available pathways contribute to selumetinib (AZD6244 hydrogen sulfate) and N-desmethyl selumetinib metabolism. Use caution in patients who are taking strong inducers or inhibitors of these CYP or UGT enzymes.

Selumetinib (AZD6244 hydrogen sulfate) is also a substrate of BCRP (breast cancer resistance protein) and P-gp transporters. Use caution in patients who are taking strong inducers or inhibitors of either transport protein.

Selumetinib (AZD6244 hydrogen sulfate) does not inhibit CYP 1A2, 2C8, 2C19and 3A4 or UGT isoforms 1A1 and 2B7. It is a weak inducer of CYP enzymes 3A, 1A and 2C9 and a weak inhibitor of CYP 2C9, 2B6 and 2D6. In vitro studies demonstrate selumetinib (AZD6244 hydrogen sulfate) is an inhibitor of BCRP, OATP1B1, OATP1B3, OCT2, OAT1 and OAT3 transporters. It does not inhibit OCT1, MATE1, MATE2K or P-glycoprotein (MDR1). The N-desmethyl metabolite is a weak inhibitor of CYP 3A4 and 1A2. In vitro data suggest that selumetinib (AZD6244 hydrogen sulfate) is unlikely to cause clinically relevant drug-drug interactions by these mechanisms.

Patient Care Implications: Study participants should be counseled to avoid excessive sun exposure and use adequate sun protection measures if sun exposure is anticipated during the study.

9.1.8 Selumetinib (AZD6244) Toxicities

Comprehensive Adverse Events and Potential Risks list (CAEPR) for Selumetinib (AZD6244 hydrogen sulfate [NSC 748727]), AZD6244 (NSC 741078)

The Comprehensive Adverse Events and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. In addition to the comprehensive list, a subset, the Specific Protocol Exceptions to Expedited Reporting (SPEER), appears in a separate column and is identified with bold and italicized text. This subset of AEs (SPEER) is a list of events that are protocol specific exceptions to expedited reporting to NCI (except as noted below). Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements' http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf for further clarification. *Frequency is provided based on 986 patients.* Below is the CAEPR for Selumetinib (AZD6244 hydrogen sulfate).

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 2,8, June 13, 2019[1]

Adverse Events with Possible Relationship to Selumetinib (AZD6244 hydrogen sulfate), AZD6244 (CTCAE 5.0 Term) [n= 986]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
	Anemia		***Anemia (Gr 3)***
		Febrile neutropenia[2]	
CARDIAC DISORDERS			
		Left ventricular systolic dysfunction	***Left ventricular systolic dysfunction (Gr 2)***
EYE DISORDERS			
		Blurred vision	
		Eye disorders - Other (central serous retinopathy)	
		Eye disorders - Other (retinal pigment epithelial detachment)	
		Eye disorders - Other (retinal vein occlusion)	
	Periorbital edema		
GASTROINTESTINAL DISORDERS			
	Abdominal pain		***Abdominal pain (Gr 3)***
	Constipation		***Constipation (Gr 2)***
Diarrhea[3]			***Diarrhea[3] (Gr 3)***
	Dry mouth		
	Mucositis oral		***Mucositis oral (Gr 3)***
Nausea			***Nausea (Gr 3)***
	Vomiting		***Vomiting (Gr 3)***
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
	Edema face		***Edema face (Gr 2)***
Edema limbs			***Edema limbs (Gr 3)***
Fatigue			***Fatigue (Gr 3)***
	Fever		***Fever (Gr 2)***
	Pain		
INFECTIONS AND INFESTATIONS			
		Folliculitis	
		Nail infection	
		Papulopustular rash	
	Paronychia		
		Skin infection	
INVESTIGATIONS			
	Alanine aminotransferase increased		***Alanine aminotransferase increased (Gr 3)***
	Aspartate aminotransferase increased		***Aspartate aminotransferase increased (Gr 3)***
	CPK increased		***CPK increased (Gr 3)***
		Ejection fraction decreased	
	Neutrophil count decreased		
	Platelet count decreased		

Adverse Events with Possible Relationship to Selumetinib (AZD6244 hydrogen sulfate), AZD6244 (CTCAE 5.0 Term) [n= 986]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
	White blood cell decreased		
METABOLISM AND NUTRITION DISORDERS			
	Anorexia		***Anorexia (Gr 2)***
		Hyperphosphatemia	
		Hypoalbuminemia	
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			
		Growth suppression	
		Musculoskeletal and connective tissue disorder - Other (neck extensor muscle weakness)	
NERVOUS SYSTEM DISORDERS			
	Dizziness		
	Headache		***Headache (Gr 2)***
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
	Cough		***Cough (Gr 2)***
	Dyspnea		***Dyspnea (Gr 3)***
		Pneumonitis	
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
	Alopecia		
	Dry skin		***Dry skin (Gr 2)***
	Pruritus		
Rash acneiform			***Rash acneiform (Gr 3)***
Rash maculo-papular			***Rash maculo-papular (Gr 3)***
VASCULAR DISORDERS			
	Hypertension		

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. Febrile neutropenia/neutropenic infection has been observed primarily in trials combining Selumetinib (AZD6244) and docetaxel.
3. SBE-CD (Captisol®, vehicle) in the mix and drink formulation is known to cause soft stools and/or diarrhea in rats and dogs; however, it is possible that some of these findings might be related to exacerbation of the vehicle effect by Selumetinib (AZD6244)

Adverse events reported on Selumetinib (AZD6244) trials, but for which there is insufficient evidence to suggest that there was a reasonable possibility that Selumetinib (AZD6244) caused the adverse event:

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Blood and lymphatic system disorders - Other (hemorrhagic anemia)
CARDIAC DISORDERS - Atrial fibrillation; Atrioventricular block complete; Atrioventricular block first degree; Cardiac disorders - Other (Takotsubo cardiomyopathy syndrome); Cardiac disorders - Other (valvular heart disease); Chest pain - cardiac; Heart failure; Myocardial infarction; Palpitations; Pericardial effusion; Right ventricular dysfunction; Sinus bradycardia; Sinus tachycardia
EYE DISORDERS - Dry eye; Eye disorders - Other (bilateral macular edema); Eye disorders - Other (black haze in line of vision); Eye disorders - Other (chalazion); Eye disorders - Eye disorders - Other (diplopia); Eye disorders - Other (retinal bleeding); Eye disorders - Other (spotty vision; itchy vision); Flashing lights; Floaters; Glaucoma; Optic

nerve disorder; Papilledema; Photophobia; Retinal detachment; Retinopathy; Uveitis; Vision decreased
GASTROINTESTINAL DISORDERS - Abdominal distension; Ascites; Bloating; Cheilitis; Colitis; Duodenal ulcer; Dyspepsia; Dysphagia; Enterocolitis; Esophagitis; Flatulence; Gastric hemorrhage; Gastritis; Gastroesophageal reflux disease; Gastrointestinal disorders - Other (pneumatosis coli); Gingival pain; Ileal stenosis; Oral hemorrhage; Rectal hemorrhage; Stomach pain; Upper gastrointestinal hemorrhage
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Chills; Death NOS; Disease progression; Facial pain; Flu like symptoms; Generalized edema; Localized edema; Malaise; Non-cardiac chest pain
HEPATOBILIARY DISORDERS - Hepatic failure; Hepatobiliary disorders - Other (liver dysfunction/ failure [clinical])
INFECTIONS AND INFESTATIONS - Biliary infection; Bone infection; Bronchial infection; Conjunctivitis; Kidney infection; Laryngitis; Lung infection; Mucosal infection; Penile infection; Periorbital infection; Sepsis; Upper respiratory infection; Urinary tract infection; Wound infection
INVESTIGATIONS - Alkaline phosphatase increased; Blood bilirubin increased; Cardiac troponin I increased; Creatinine increased; Electrocardiogram QT corrected interval prolonged; Electrocardiogram T wave abnormal; Hemoglobin increased; INR increased; Investigations - Other (ECG signs of myocardial ischemia); Lipase increased; Lymphocyte count decreased; Lymphocyte count increased; Serum amylase increased; Weight gain; Weight loss
METABOLISM AND NUTRITION DISORDERS - Dehydration; Hyperglycemia; Hyperkalemia; Hypermagnesemia; Hypernatremia; Hypertriglyceridemia; Hyperuricemia; Hypocalcemia; Hypoglycemia; Hypokalemia; Hypomagnesemia; Hyponatremia; Hypophosphatemia; Metabolism and nutrition disorders - Other (electrolyte abnormalities);
Metabolism and nutrition disorders - Other (elevated calcium phosphorus product); Metabolism and nutrition disorders - Other (sensation of warmth)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Arthralgia; Arthritis; Back pain; Bone pain; Chest wall pain; Generalized muscle weakness; Joint effusion; Joint range of motion decreased; Muscle weakness lower limb; Muscle weakness upper limb; Musculoskeletal and connective tissue disorder - Other (bilateral stiffness hands and feet [intermittent]); Musculoskeletal and connective tissue disorder - Other (neck myopathy); Myalgia; Myositis; Neck pain; Pain in extremity; Rhabdomyolysis
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS) - Treatment related secondary malignancy; Tumor pain
NERVOUS SYSTEM DISORDERS - Amnesia; Cognitive disturbance; Concentration impairment; Depressed level of consciousness; Dysarthria; Dysgeusia; Dysphasia; Intracranial hemorrhage; Ischemia cerebrovascular; Lethargy; Leukoencephalopathy; Memory impairment; Oculomotor nerve disorder; Paresthesia; Peripheral motor neuropathy; Peripheral sensory neuropathy; Reversible posterior leukoencephalopathy syndrome; Seizure; Spinal cord compression; Syncope
PSYCHIATRIC DISORDERS - Anxiety; Confusion; Delusions; Depression; Insomnia
RENAL AND URINARY DISORDERS - Acute kidney injury; Hematuria; Nephrotic syndrome
REPRODUCTIVE SYSTEM AND BREAST DISORDERS - Vaginal inflammation
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Adult respiratory distress syndrome; Bronchopulmonary hemorrhage; Epistaxis; Hoarseness; Hypoxia; Nasal congestion; Pharyngolaryngeal pain; Pleural effusion; Pulmonary edema; Sore throat; Voice alteration; Wheezing
SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Erythema multiforme; Erythroderma; Nail loss; Pain of skin; Palmar-plantar erythrodysesthesia syndrome; Photosensitivity; Scalp pain; Skin and subcutaneous tissue disorders - Other (skin fissures); Skin ulceration; Stevens-Johnson syndrome; Urticaria
VASCULAR DISORDERS - Flushing; Hypotension; Lymphedema; Thromboembolic event

Note: Selumetinib (AZD6244 hydrogen sulfate) in combination with other agents could cause an exacerbation of any adverse event currently known to be caused by the other agent, or the combination may result in events never previously associated with either agent.

9.2 Agent Ordering and Agent Accountability

NCI-supplied agents may be requested by eligible participating Investigators (or their authorized designee) at each participating institution. The CTEP-assigned protocol number must be used for ordering all CTEP-supplied investigational agents. The eligible participating investigators at each participating institution must be registered with CTEP,

DCTD through an annual submission of FDA Form 1572 (Statement of Investigator), NCI Biosketch, Agent Shipment Form, and Financial Disclosure Form (FDF). If there are several participating investigators at one institution, CTEP-supplied investigational agents for the study should be ordered under the name of one lead participating investigator at that institution.

Note: No starter supplies will be provided. Drug orders of selumetinib (AZD6244 hydrogen sulfate) should be placed with CTEP after enrollment and treatment assignment to APEC1621E with consideration for timing of processing and shipping to ensure receipt of drug supply prior to start of protocol therapy. If expedited shipment is required, sites should provide an express courier account through the Online Agent Order Processing (OAOP) application. Provide the patient ID number in the comment box when submitting an order request.

9.3 Clinical Drug Request and Investigator Brochure Availability

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

9.4 Agent Inventory Records

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

9.4.1 Useful Links and Contacts

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

10.0 CRITERIA FOR REMOVAL FROM PROTOCOL THERAPY AND OFF STUDY CRITERIA

10.1 Criteria for Removal from Protocol Therapy

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

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

10.2 Follow-Up Data Submission and APEC1621SC Off Study Criteria

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

11.0 STATISTICAL AND ETHICAL CONSIDERATIONS

11.1 Sample Size and Study Duration

APEC1621E will require a minimum of 20 evaluable patients and a maximum of 49 patients, allowing for 15% inevaluability. Assuming an enrollment rate of 4-6 biomarker positive patients per year, this subprotocol is expected to be completed within 8-12 years.

11.2 Dosing Considerations

A pediatric MTD/RP2D dose has been established for selumetinib (AZD6244 hydrogen sulfate)[16]; therefore patients will be treated at that dose. Please see Section 5.1 for a specific discussion of the dosing of selumetinib (AZD6244 hydrogen sulfate) to be used in this

study.

11.3 **Study Design**

The primary cohort will employ a single stage A'Hern designs 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**:

APEC1621E 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 selumetinib (AZD6244 hydrogen sulfate). Using an A'Hern design[47] 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.[48] 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 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	4	2	38
More than one race	1	0	0	0	1
Total	17	26	4	2	49

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

12.0 EVALUATION CRITERIA

12.1 Common Terminology Criteria for Adverse Events (CTCAE)

The descriptions and grading scales found in version 5.0 of the NCI Common Terminology Criteria for Adverse Events (CTCAE) will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of CTCAE version 5.0. A copy of the CTCAE v5.0 can be downloaded from the CTEP website (http://ctep.cancer.gov).

12.2 Progression-Free Survival

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

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

12.3 Response Criteria for Patients with Solid Tumors

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

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

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

12.3.1 Definitions

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

12.3.1.2 Evaluable Non-Target Disease Response: Eligible patients who have lesions present at baseline that are evaluable but do not meet the definitions of measurable disease and have received at least one dose of protocol therapy will be considered evaluable for non-target disease. 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.[49]

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

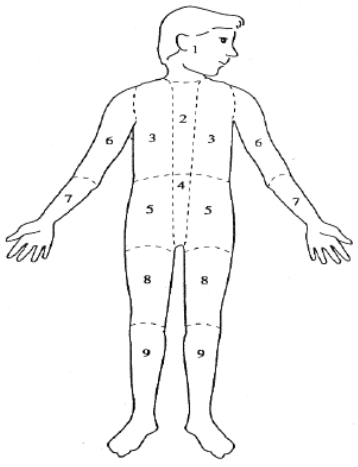
12.5.3 The response of MIBG lesions will be assessed on central review using the Curie scale14 as outlined below. Central review responses will be used to assess efficacy for study endpoint. See Section 8.2 for details on transferring images to the Imaging Research Center.

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, with modification from the Lugano classification.[50]

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)[50]

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[50]

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# 301-230-0159) and by email to the APEC1621E 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. A copy of the CTCAE v5 can be downloaded from the CTEP website (http://ctep.cancer.gov).

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

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

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

- Any medical event equivalent to CTCAE grade 3, 4, or 5 that precipitates hospitalization (or prolongation of existing hospitalization) must be reported regardless of attribution and designation as expected or unexpected with the exception of any events identified as protocol-specific expedited adverse event reporting exclusions.
- Any event that results in persistent or significant disabilities/incapacities, congenital anomalies, or birth defects must be reported via CTEP-AERS if the event occurs following treatment with an agent under a CTEP IND.
- Use the NCI protocol number and the protocol-specific patient ID provided during trial registration on all reports.

- As referenced in the CTEP Adverse Events Reporting Requirements, an AE that resolves and then recurs during a subsequent cycle does not require CTEP-AERS reporting unless (1) the Grade increases; or (2) hospitalization is associated with the recurring AE.
- Some adverse events require notification **within 24 hours** (refer to Table A) to NCI via the web at http://ctep.cancer.gov (telephone CTEP at: **301-897-7497** within 24 hours of becoming aware of the event if the CTEP-AERS 24-Hour Notification web-based application is unavailable). Once internet connectivity is restored, a 24-hour notification phoned in must be entered electronically into CTEP-AERS by the original submitter at the site.
- When the adverse event requires expedited reporting, submit the report **within 5 or 7 calendar days** of learning of the event (refer to Table A).

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

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

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

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

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

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

Expedited AE reporting timelines are defined as:

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

[1]Serious adverse events that occur more than 30 days after the last administration of investigational agent/intervention and have an attribution of possible, probable, or definite require reporting as follows:
Expedited 24-hour notification followed by complete report within 5 calendar days for:

- All Grade 3, 4, and Grade 5 AEs

Expedited 7 calendar day reports for:

- Grade 2 AEs resulting in hospitalization or prolongation of hospitalization

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

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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
GASTROINTESTINAL DISORDERS	Dry Mouth
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	Pain
NERVOUS SYSTEM DISORDERS	Dizziness
PSYCHIATRIC DISORDERS	Insomnia
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	Pruritus

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

13.6.2 Reporting Secondary Malignancy

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

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

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

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

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

13.6.3 Reporting Pregnancy, Pregnancy Loss, and Death Neonatal

When submitting CTEP-AERS reports for "Pregnancy", "Pregnancy loss", or "Neonatal loss", the Pregnancy Information Form, available at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/PregnancyReportForm.pdf, needs to be completed and faxed along with any additional medical information to (301) 230-0159. The potential risk of exposure of the fetus to the investigational agent should be documented in the "Description of Event" section of the CTEP-AERS report.

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

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

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

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

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

14.0 RECORDS, REPORTING, AND DATA AND SAFETY MONITORING PLAN

14.1 Categories of Research Records

Research records for this study can be divided into three categories

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

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

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

See separate CRF Packet, which includes submission schedule.

14.2 CDUS

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

Note: 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. Zhao Y, Adjei AA: The clinical development of MEK inhibitors. Nat. Rev. Clin. Oncol 11:385-400, 2014
2. Marks JL, Gong Y, Chitale D, et al: Novel MEK1 mutation identified by mutational analysis of epidermal growth factor receptor signaling pathway genes in lung adenocarcinoma. Cancer Res 68:5524-5528, 2008
3. Murugan AK, Dong J, Xie J, et al: MEK1 mutations, but not ERK2 mutations, occur in melanomas and colon carcinomas, but none in thyroid carcinomas. Cell Cycle 8:2122-2124, 2009
4. Pui CH, Carroll WL, Meshinchi S, et al: Biology, risk stratification, and therapy of pediatric acute leukemias: an update. J Clin Oncol 29:551-65, 2011
5. Shukla N, Ameur N, Yilmaz I, et al: Oncogene mutation profiling of pediatric solid tumors reveals significant subsets of embryonal rhabdomyosarcoma and neuroblastoma with mutated genes in growth signaling pathways. Clin. Cancer Res 18:748-757, 2012
6. Bentires-Alj M, Paez JG, David FS, et al: Activating mutations of the noonan syndrome-associated SHP2/PTPN11 gene in human solid tumors and adult acute myelogenous leukemia. Cancer Res 64:8816-20, 2004
7. Puissant A, Frumm SM, Alexe G, et al: Targeting MYCN in neuroblastoma by BET bromodomain inhibition. Cancer Discov 3:308-323, 2013
8. Lu C, Zhang J, Nagahawatte P, et al: The genomic landscape of childhood and adolescent melanoma. J. Invest Dermatol 135:816-823, 2015
9. Flaherty KT, Robert C, Hersey P, et al: Improved survival with MEK inhibition in BRAF-mutated melanoma. N. Engl. J. Med 367:107-114, 2012
10. Long GV, Stroyakovskiy D, Gogas H, et al: Combined BRAF and MEK inhibition versus BRAF inhibition alone in melanoma. N. Engl. J. Med 371:1877-1888, 2014
11. Ascierto PA, Schadendorf D, Berking C, et al: MEK162 for patients with advanced melanoma harbouring NRAS or Val600 BRAF mutations: a non-randomised, open-label phase 2 study. Lancet Oncol 14:249-256, 2013
12. Janne PA, Shaw AT, Pereira JR, et al: Selumetinib plus docetaxel for KRAS-mutant advanced non-small-cell lung cancer: a randomised, multicentre, placebo-controlled, phase 2 study. Lancet Oncol 14:38-47, 2013
13. Jessen WJ, Miller SJ, Jousma E, et al: MEK inhibition exhibits efficacy in human and mouse neurofibromatosis tumors. J. Clin. Invest 123:340-347, 2013
14. Nissan MH, Pratilas CA, Jones AM, et al: Loss of NF1 in cutaneous melanoma is associated with RAS activation and MEK dependence. Cancer Res 74:2340-2350, 2014
15. Spunt SL, Million L, Anderson JR, et al: Risk-based treatment for nonrhabdomyosarcoma soft tissue sarcomas (NRSTS) in patients under 30 years of age: Children's Oncology Group study ARST0332. J. Clin. Oncol 32, 2014
16. Dombi E, Baldwin A, Marcus LJ, et al: Activity of Selumetinib in Neurofibromatosis Type 1-Related Plexiform Neurofibromas. N Engl J Med 375:2550-2560, 2016
17. Carvajal RD, Sosman JA, Quevedo JF, et al: Effect of selumetinib vs chemotherapy on progression-free survival in uveal melanoma: a randomized clinical trial. JAMA 311:2397-2405, 2014
18. Marampon F, Bossi G, Ciccarelli C, et al: MEK/ERK inhibitor U0126 affects in vitro and in vivo growth of embryonal rhabdomyosarcoma. Mol. Cancer Ther 8:543-551, 2009
19. Guenther MK, Graab U, Fulda S: Synthetic lethal interaction between PI3K/Akt/mTOR and Ras/MEK/ERK pathway inhibition in rhabdomyosarcoma. Cancer Lett 337:200-209, 2013
20. Renshaw J, Taylor KR, Bishop R, et al: Dual blockade of the PI3K/AKT/mTOR (AZD8055) and RAS/MEK/ERK (AZD6244) pathways synergistically inhibits rhabdomyosarcoma cell growth in vitro and in vivo. Clin. Cancer Res 19:5940-5951, 2013
21. Eleveld TF, Oldridge DA, Bernard V, et al: Relapsed neuroblastomas show frequent RAS-MAPK pathway mutations. Nat Genet 47:864-71, 2015
22. See WL, Tan IL, Mukherjee J, et al: Sensitivity of glioblastomas to clinically available MEK

inhibitors is defined by neurofibromin 1 deficiency. Cancer Res 72:3350-3359, 2012
23. Chakraborty R, Hampton OA, Shen X, et al: Mutually exclusive recurrent somatic mutations in MAP2K1 and BRAF support a central role for ERK activation in LCH pathogenesis. Blood 124:3007-15, 2014
24. Goetz EM, Ghandi M, Treacy DJ, et al: ERK mutations confer resistance to mitogen-activated protein kinase pathway inhibitors. Cancer Res 74:7079-7089, 2014
25. Adjei AA, Cohen RB, Franklin W, et al: Phase I pharmacokinetic and pharmacodynamic study of the oral, small-molecule mitogen-activated protein kinase kinase 1/2 inhibitor AZD6244 (ARRY-142886) in patients with advanced cancers. J Clin Oncol 26:2139-46, 2008
26. Banerji U, Camidge DR, Verheul HM, et al: The first-in-human study of the hydrogen sulfate (Hyd-sulfate) capsule of the MEK1/2 inhibitor AZD6244 (ARRY-142886): a phase I open-label multicenter trial in patients with advanced cancer. Clin Cancer Res 16:1613-23, 2010
27. Boers-Sonderen MJ, Desar IM, Blokx W, et al: A prolonged complete response in a patient with BRAF-mutated melanoma stage IV treated with the MEK1/2 inhibitor selumetinib (AZD6244). Anticancer Drugs 23:761-4, 2012
28. Leijen S, Middleton MR, Tresca P, et al: Phase I dose-escalation study of the safety, pharmacokinetics, and pharmacodynamics of the MEK inhibitor RO4987655 (CH4987655) in patients with advanced solid tumors. Clin Cancer Res 18:4794-805, 2012
29. Kirkwood JM, Bastholt L, Robert C, et al: Phase II, open-label, randomized trial of the MEK1/2 inhibitor selumetinib as monotherapy versus temozolomide in patients with advanced melanoma. Clin Cancer Res 18:555-67, 2012
30. Bennouna J, Lang I, Valladares-Ayerbes M, et al: A Phase II, open-label, randomised study to assess the efficacy and safety of the MEK1/2 inhibitor AZD6244 (ARRY-142886) versus capecitabine monotherapy in patients with colorectal cancer who have failed one or two prior chemotherapeutic regimens. Invest New Drugs 29:1021-8, 2011
31. Bodoky G, Timcheva C, Spigel DR, et al: A phase II open-label randomized study to assess the efficacy and safety of selumetinib (AZD6244 [ARRY-142886]) versus capecitabine in patients with advanced or metastatic pancreatic cancer who have failed first-line gemcitabine therapy. Invest New Drugs 30:1216-23, 2012
32. Hainsworth JD, Cebotaru CL, Kanarev V, et al: A phase II, open-label, randomized study to assess the efficacy and safety of AZD6244 (ARRY-142886) versus pemetrexed in patients with non-small cell lung cancer who have failed one or two prior chemotherapeutic regimens. J Thorac Oncol 5:1630-6, 2010
33. O'Neil BH, Goff LW, Kauh JS, et al: Phase II study of the mitogen-activated protein kinase 1/2 inhibitor selumetinib in patients with advanced hepatocellular carcinoma. J Clin Oncol 29:2350-6, 2011
34. Bekaii-Saab T, Phelps MA, Li X, et al: Multi-institutional phase II study of selumetinib in patients with metastatic biliary cancers. J Clin Oncol 29:2357-63, 2011
35. Prado CM, Bekaii-Saab T, Doyle LA, et al: Skeletal muscle anabolism is a side effect of therapy with the MEK inhibitor: selumetinib in patients with cholangiocarcinoma. Br J Cancer 106:1583-6, 2012
36. Hayes DN, Lucas AS, Tanvetyanon T, et al: Phase II efficacy and pharmacogenomic study of Selumetinib (AZD6244; ARRY-142886) in iodine-131 refractory papillary thyroid carcinoma with or without follicular elements. Clin Cancer Res 18:2056-65, 2012
37. Jain N, Curran E, Iyengar NM, et al: Phase II study of the oral MEK inhibitor selumetinib in advanced acute myelogenous leukemia: a University of Chicago phase II consortium trial. Clin Cancer Res 20:490-8, 2014
38. Farley J, Brady WE, Vathipadiekal V, et al: Selumetinib in women with recurrent low-grade serous carcinoma of the ovary or peritoneum: an open-label, single-arm, phase 2 study. Lancet Oncol 14:134-40, 2013
39. Holkova B, Zingone A, Kmieciak M, et al: A Phase II Trial of AZD6244 (Selumetinib, ARRY-

142886), an Oral MEK1/2 Inhibitor, in Relapsed/Refractory Multiple Myeloma. Clin Cancer Res 22:1067-75, 2016
40. Coleman RL, Sill MW, Thaker PH, et al: A phase II evaluation of selumetinib (AZD6244, ARRY-142886), a selective MEK-1/2 inhibitor in the treatment of recurrent or persistent endometrial cancer: an NRG Oncology/Gynecologic Oncology Group study. Gynecol Oncol 138:30-5, 2015
41. Carvajal RD, Sosman JA, Quevedo JF, et al: Effect of selumetinib vs chemotherapy on progression-free survival in uveal melanoma: a randomized clinical trial. JAMA 311:2397-405, 2014
42. Catalanotti F, Solit DB, Pulitzer MP, et al: Phase II trial of MEK inhibitor selumetinib (AZD6244, ARRY-142886) in patients with BRAFV600E/K-mutated melanoma. Clin Cancer Res 19:2257-64, 2013
43. Lopez-Chavez A, Thomas A, Rajan A, et al: Molecular profiling and targeted therapy for advanced thoracic malignancies: a biomarker-derived, multiarm, multihistology phase II basket trial. J Clin Oncol 33:1000-7, 2015
44. Banerjee Aea: A phase 1 study of AZD6244 in children with recurrent or refractory low-grade gliomas: A Pediatric Brain Tumor Consortium report. . J Clin Oncol 32, 5s, (suppl; abstr 10065), 2014
45. Widemann BCea: Phase I study of the MEK1/2 inhibitor selumetinib (AZD6244) hydrogen sulfate in children and young adults with neurofibromatosis type 1 (NF1) and inoperable plexiform neurofibromas (PNs). J Clin Oncol 32, 5s (suppl; abstr 10018) 2014
46. Gross AMea: Phase II Study of the MEK 1/2 inhibitor selumetinib (AZD6244, ARRY-142886) in children with neurofibromatosis type 1 (NF1) and inoperable plexiform neurofibromas (PN). J Clin Oncol 34, (suppl; abstr TPS10586), 2016
47. A'Hern RP: Sample size tables for exact single-stage phase II designs. Stat Med 20:859-66, 2001
48. Agresti A, Coull BA: Approximate Is Better than "Exact" for Interval Estimation of Binomial Proportions. The American Statistician 52:119-126, 1998
49. Sandlund JT, Guillerman RP, Perkins SL, et al: International Pediatric Non-Hodgkin Lymphoma Response Criteria. J Clin Oncol 33:2106-11, 2015
50. Cheson BD, Fisher RI, Barrington SF, et al: Recommendations for initial evaluation, staging, and response assessment of Hodgkin and non-Hodgkin lymphoma: the Lugano classification. J Clin Oncol 32:3059-68, 2014

APPENDIX I: PERFORMANCE STATUS SCALES/SCORES

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

APPENDIX II: CYP3A4 SUBSTRATES, INDUCERS AND INHIBITORS

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

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

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

[1] Certain fruits, fruit juices and herbal supplements (star fruit, Seville oranges, pomegranate, gingko, goldenseal) may inhibit CYP3A4 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: PATIENT DIARY FOR SELUMETINIB

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

Complete each day with the time and dose given for selumetinib (AZD6244 hydrogen sulfate). 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***. Selumetinib (AZD6244 hydrogen sulfate) capsules should not be opened or crushed but should be swallowed whole. If capsule is broken and the powder of the capsules gets on skin, wash the exposed area with as much water as necessary. Inform your study doctor or nurse if that occurs. Selumetinib (AZD6244 hydrogen sulfate) should be taken on an empty stomach at least 2 hours after food, do not eat or drink (except water) for at least one hour after taking selumetinib. If vomiting occurs within 30 minutes after the dose of selumetinib (AZD6244 hydrogen sulfate) is administered, that dose may be repeated once. Otherwise, the dose will be missed. Add the dates to the calendar below and return the completed diary to the study clinic at each visit.

EXAMPLE			*Number of selumetinib (AZD6244 hydrogen sulfate) capsules*		*Comments*
	Date	*Time*	10 mg	25 mg	
Day 1	*1/15/14*	*8:30 AM*	2	1	*He felt nauseated an hour after taking the drug but did not vomit.*

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

WEEK 1	Date	Time		# of Selumetinib (AZD6244 hydrogen sulfate) capsules prescribed to take: 10 mg AM#___ PM#___	# of Selumetinib (AZD6244 hydrogen sulfate) capsules prescribed to take: 25 mg AM#___ PM#___	Comments (Describe any missed or extra doses, vomiting and/or bothersome effects.)
				# of Selumetinib (AZD6244 hydrogen sulfate) capsules taken: 10 mg	# of Selumetinib (AZD6244 hydrogen sulfate) capsules taken: 25 mg	
Day 1			AM			
			PM			
Day 2			AM			
			PM			
Day 3			AM			
			PM			
Day 4			AM			
			PM			
Day 5			AM			
			PM			
Day 6			AM			
			PM			
Day 7			AM			
			PM			

WEEK 2	Date	Time	# of Selumetinib (AZD6244 hydrogen sulfate) capsules prescribed to take: 10 mg AM#___ PM#___	# of Selumetinib (AZD6244 hydrogen sulfate) capsules prescribed to take: 25 mg AM#___ PM#___	Comments (Describe any missed or extra doses, vomiting and/or bothersome effects.)

				# of Selumetinib (AZD6244 hydrogen sulfate) capsules taken		
				10 mg	25 mg	
Day 8			AM			
			PM			
Day 9			AM			
			PM			
Day 10			AM			
			PM			
Day 11			AM			
			PM			
Day 12			AM			
			PM			
Day 13			AM			
			PM			
Day 14			AM			
			PM			
WEEK 3	Date	Time		# of Selumetinib (AZD6244 hydrogen sulfate) capsules prescribed to take 10 mg: AM#___ PM#___ 25 mg: AM#___ PM#___		Comments (Describe any missed or extra doses, vomiting and/or bothersome effects.)
				# of Selumetinib (AZD6244 hydrogen sulfate) capsules taken		
				10 mg	25 mg	
Day 15			AM			
			PM			
Day 16			AM			
			PM			
Day 17			AM			
			PM			
Day 18			AM			
			PM			
Day 19			AM			
			PM			
Day 20			AM			
			PM			
Day 21			AM			
			PM			
WEEK 4	Date	Time		# of Selumetinib (AZD6244 hydrogen sulfate) capsules prescribed to take 10 mg: AM#___ PM#___ 25 mg: AM#___ PM#___		Comments (Describe any missed or extra doses, vomiting and/or bothersome effects.)

				# of Selumetinib (AZD6244 hydrogen sulfate) capsules taken		
				10 mg	25 mg	
Day 22			**AM**			
			PM			
Day 23			**AM**			
			PM			
Day 24			**AM**			
			PM			
Day 25			**AM**			
			PM			
Day 26			**AM**			
			PM			
Day 27			**AM**			
			PM			
Day 28			**AM**			
			PM			

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

Signature: _____ Date: _____
(site personnel who collected samples)

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

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

The patient _____ is enrolled on a clinical trial using the experimental study drug, **selumetinib (AZD6244 hydrogen sulfate)**. This clinical trial is sponsored by the National Cancer Institute (NCI). 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 prescriber need to know:

Selumetinib (AZD6244 hydrogen sulfate) interacts with certain specific enzymes in the liver and certain transport proteins that help move drugs in and out of cells.

- The enzymes in question are CYP 1A2, 2C8, 2C9, 2C19, 3A4/5 and UGT 1A1 and 1A3. Selumetinib (AZD6244 hydrogen sulfate) is metabolized by these enzymes and may be affected by other drugs that inhibit or induce these enzymes.
- The proteins in question are P-gp and BCRP. Selumetinib (AZD6244 hydrogen sulfate) is a substrate of BCRP and P-gp transporters and may be affected by other drugs that inhibit or induce these transporters.

March 2016

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

Selumetinib (AZD6244 hydrogen sulfate) interacts with many drugs which can cause side effects. Because of this, it is very important to tell your study doctors about all of your medicines before you enroll on this clinical trial. It is also very important to tell them 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 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 prescribers can write prescriptions. You must also tell 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:

Selumetinib (AZD6244 hydrogen sulfate) must be used very carefully with other medicines that need certain liver enzymes and transport proteins to be effective or to be cleared from your system. 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 of CYP 1A2, 2C8, 2C9, 2C19, 3A/5, UGT 1A1 and 1A3, P-gp and BCRP."

- Please be very careful! Over-the-counter drugs (including herbal supplements) may contain ingredients that could interact with your study drug. Speak to your doctor or pharmacist to determine if there could be any side effects.
- Avoid taking extra vitamin E found in vitamins or supplements.
- 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
_____.

March 2016

STUDY DRUG INFORMATION WALLET CARD

You are enrolled on a clinical trial using the experimental drug **selumetinib (AZD6244 hydrogen sulfate).** This clinical trial is sponsored by the NCI. AZD6244 hydrogen sulfate (selumetinib) interacts with drugs that are processed by your liver, or use certain transport proteins in your body. Because of this, it is very important to:

- Tell your doctors if you stop taking regular medicines or if you start taking any new medicines.
- Tell all of your health care providers (doctors, physician assistant, nurse practitioners, 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.
- Selumetinib (AZD6244 hydrogen sulfate) interacts with CYP 1A2, 2C8, 2C9, 2C19, 3A4/5, UGT 1A1 and 1A3, P-gp, and BCRP, and must be used very carefully with other medicines that interact with these enzymes and proteins.
- Before you enroll onto the clinical trial, your study doctor will work with your regular health care providers to review any medicines that are considered "strong inducers/inhibitors of CYP 1A2, 2C8, 2C9, 2C19, 3A4/5, UGT 1A1 and 1A3, P-gp and BCRP."
- You should avoid taking extra vitamin E found in vitamins or supplements.
- 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: SELUMETINIB (AZD6244 HYDROGEN SULFATE) DOSING NOMOGRAM

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

Patients must have a body surface area of ≥ 0.5 m^2 at enrollment.

Selumetinib (AZD6244 hydrogen sulfate) Dose Assignment: 25 mg/m^2/dose BID

BSA (m^2)	Selumetinib (AZD6244 hydrogen sulfate) AM Dose (mg)	Selumetinib (AZD6244 hydrogen sulfate) PM Dose (mg)	Selumetinib (AZD6244 hydrogen sulfate) Dose Reduction for Toxicity AM Dose (mg)	Selumetinib (AZD6244 hydrogen sulfate) Dose Reduction for Toxicity PM Dose (mg)
0.5-0.67	10	20	10	10
0.68-0.89	20	20	10	20
0.9-1.09	25	25	10	25
1.1-1.29	30	30	20	20
1.3-1.49	35	35	25	25
1.5-1.69	40	40	30	30
1.7-1.89	45	45	30	30
1.9-2.1	50	50	35	35
2.11-2.3	55	55	40	40

APPENDIX V: APEC1621E 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
Selumetinib	PO	25 mg/m^2/dose BID (maximum 75 mg per dose) Refer to dosing nomogram in Appendix IV.	1-28	Patients should swallow the capsules as a whole and should not chew or crush them. Selumetinib (AZD6244 hydrogen sulfate) should be taken on an empty stomach at least 2 hours after food and not eat or drink (except water) for at least one hour after taking selumetinib. If a patient vomits within 30 minutes after the dose of selumetinib (AZD6244 hydrogen sulfate), is administered, that dose may be repeated once. Otherwise, the dose will be missed.

Ht _____cm Wt _____kg BSA _____m^2

Cycle 1

Date Due	Date Given	Day	**Selumetinib** _____ mg	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	f
		5	_____ mg AM _____ mg PM	
		6	_____ mg AM _____ mg PM	
		7	_____ mg AM _____ mg PM	
		8	_____ mg AM _____ mg PM	a, f, h, i, m, p
		9	_____ mg AM _____ mg PM	
		10	_____ mg AM _____ mg PM	
		11	_____ mg AM _____ mg PM	f
		12	_____ mg AM _____ mg PM	
		13	_____ mg AM _____ mg PM	
		14	_____ mg AM _____ mg PM	
		15	_____ mg AM _____ mg PM	a, f, h, i, m, p, s
		16	_____ mg AM _____ mg PM	
		17	_____ mg AM _____ mg PM	
		18	_____ mg AM _____ mg PM	f
		19	_____ mg AM _____ mg PM	
		20	_____ mg AM _____ mg PM	
		21	_____ mg AM _____ mg PM	
		22	_____ mg AM _____ mg PM	a, f, h, i, m, p
		23	_____ mg AM _____ mg PM	
		24	_____ mg AM _____ mg PM	
		25	_____ mg AM _____ mg PM	f
		26	_____ mg AM _____ mg PM	
		27	_____ mg AM _____ mg PM	
		28/1	_____ mg AM _____ mg PM	a, c, f, h, i, j, m, o, p, s

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

Cycle 1

For information related to prestudy observations please refer to Section 8.1

Required Observations in Cycle 1

All baseline studies must be performed prior to starting protocol therapy unless otherwise indicated below.

a. History/Physical Exam (including VS)
b. Neurological Exam
c. Ht/Wt/BSA
d. Performance Status
e. Pregnancy Test. 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.
f. 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.
g. Urinalysis
h. Electrolytes including Ca++, PO4, Mg++
i. Creatinine, ALT, bilirubin
j. Albumin
k. Tumor Disease Evaluation
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. Should only be performed on patients with known bone marrow involvement at baseline. Bone marrow aspirate and/or biopsy should be performed only when complete response or partial response is identified in target disease or when progression in bone marrow is suspected.
m. Patient Diary- (see Appendix III) should be reviewed weekly during cycle 1, after completion of each treatment cycle; and uploaded into RAVE. The patient diary should be collected weekly.
n. ECHO or gated radionuclide study
o. Creatine Kinase (CPK)
p. Blood Pressure. Blood pressure will be measured with an appropriate sized cuff at rest. Blood pressure measurement will be repeated within the same day if the blood pressure (BP) is elevated (> the 95th percentile for age, height, and gender). Please note that 3 serial blood pressures should be obtained and averaged to determine baseline BP (See Section 6.7). If both BP measurements are >95th percentile for age, height, and gender, follow the guidelines in Section 6.7. Patients with elevated BP at any time should have BP measurements performed at least twice weekly until BP is within the 95th percentile for age, height, and gender (See Appendix IX).
q. Ophthalmologic exam.
r. Plain radiograph tibial growth plate. Plain radiographs of at least one tibial growth plate should be obtained in all patients prior to first dose of protocol therapy. In patients with open growth plates, follow-up plain radiographs of the same growth plate(s) should be obtained according to Section 8.2.1.
s. Total Cholesterol, Triglycerides-If Grade 3 or 4 hypercholesterolemia or Grade 3 or 4 hypertriglyceridemia is detected when routine (non-fasting) laboratory studies are performed, the tests should be repeated within 3 days in the fasting state to permit accurate grading

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

Comments (Include any held doses, or dose modifications)

Treatment Details: Cycle 1

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

Cycle 1

All Subsequent Cycles

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

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

DRUG	ROUTE	DOSAGE	DAYS	IMPORTANT NOTES
Selumetinib	PO	25 mg/m²/dose BID (maximum 75 mg per dose) Refer to dosing nomogram in Appendix IV.	1-28	Patients should swallow the capsules as a whole and should not chew or crush them. Selumetinib (AZD6244 hydrogen sulfate) should be taken on an empty stomach at least 2 hours after food and not eat or drink (except water) for at least one hour after taking selumetinib. If a patient vomits within 30 minutes after the dose of selumetinib (AZD6244 hydrogen sulfate), is administered, that dose may be repeated once. Otherwise, the dose will be missed.

Enter Cycle #: _____ Ht _____cm Wt _____kg BSA _____m²

Date Due	Date Given	Day	**Selumetinib** _____ mg	Studies
			Enter calculated dose above as per dosing nomogram and actual dose administered below	
		1	_____mg AM _____mg PM	a,b,c,d,e,f,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	c
		9	_____mg AM _____mg PM	
		10	_____mg AM _____mg PM	
		11	_____mg AM _____mg PM	
		12	_____mg AM _____mg PM	
		13	_____mg AM _____mg PM	
		14	_____mg AM _____mg PM	
		15	_____mg AM _____mg PM	c, m,
		16	_____mg AM _____mg PM	
		17	_____mg AM _____mg PM	
		18	_____mg AM _____mg PM	
		19	_____mg AM _____mg PM	
		20	_____mg AM _____mg PM	
		21	_____mg AM _____mg PM	
		22	_____mg AM _____mg PM	c,
		23	_____mg AM _____mg PM	
		24	_____mg AM _____mg PM	
		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,j*,k* l,m*,n*,o* p

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

Subsequent Cycles

* Please refer to section 8.1 for the specific timing of these observations

Required Observations in All Subsequent Cycles

a. History/Physical Exam (including VS)
b. Ht/Wt/BSA
c. CBC/differential/platelets If patients develop Grade 3 or greater thrombocytopenia then CBCs should be checked every 3 to 4 days until recovery per Section 6.1
d. Electrolytes including Ca++, PO4, Mg++
e. Creatinine, ALT, bilirubin
f. Albumin
g. Tumor Disease Evaluation – Every other cycle x 3 then q 3 cycles. Tumor Disease Evaluation should be obtained on the next consecutive cycle after initial documentation of either a PR or CR. Subsequent scans may restart 2 cycles after the confirmatory scan. If the institutional investigator determines that the patient has progressed based on clinical or laboratory evidence, he/she may opt not to confirm this finding radiographically
h. Bone Marrow Aspirate and/or biopsy- Only required in patients suspected of having bone marrow metastasis on the basis of history, symptoms, laboratory evaluation or other clinical data. Should only be performed on patients with known bone marrow involvement at baseline. Bone marrow aspirate and/or biopsy should be performed only when complete response or partial response is identified in target disease or when progression in bone marrow is suspected.
i. Patient Diary- (see Appendix III) should be reviewed after completion of each treatment cycle and uploaded into RAVE. The patient diary should be collected weekly.
j. Circulating Tumor DNA (ctDNA-optional)- With consent two samples will be collected on this protocol (Cycle 5 Day 1; and for patients receiving ≥ 5 cycles, at progression or end of protocol therapy) see Section 8.4 for details of the ctDNA studies.
k. ECHO or gated radionuclide study. Every 3 months.
l. Creatine Kinase (CPK)
m. Blood Pressure. Blood pressure will be measured with an appropriate sized cuff at rest. Blood pressure measurement will be repeated within the same day if the blood pressure (BP) is elevated (> the 95th percentile for age, height, and gender). Please note that 3 serial blood pressures should be obtained and averaged to determine baseline BP (See Section 6.7). If both BP measurements are >95th percentile for age, height, and gender, follow the guidelines in Section 6.7. Patients with elevated BP at any time should have BP measurements performed at least twice weekly until BP is within the 95th percentile for age, height, and gender (See Appendix IX).
n. Ophthalmologic exam. Prior to every other cycle
o. Plain radiograph tibial growth plate. Plain radiographs of at least one tibial growth plate should be obtained in all patients prior to first dose of protocol therapy. In patients with open growth plates, follow-up plain radiographs of the same growth plate(s) should be obtained according to Section 8.2.1.
p. Total Cholesterol, Triglycerides-If Grade 3 or 4 hypercholesterolemia or Grade 3 or 4 hypertriglyceridemia is detected when routine (non-fasting) laboratory studies are performed, the tests should be repeated within 3 days in the fasting state to permit accurate grading

Subsequent Cycles

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

Comments (Include any held doses, or dose modifications)

Treatment Details: Subsequent Cycles

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

Subsequent Cycles

APPENDIX VI: TARGET HISTOLOGIES FOR APEC1621E 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: APEC1621E ACTIONABLE MUTATIONS OF INTEREST

NON-HOTSPOT RULES			
Gene Name	Description	Variant Type	LOE
NF1	Include	Deleterious	3

INCLUSION VARIANTS Hotspots				
Gene Name	Variant ID	Variant Type	aMOI	LOE
NRAS	COSM586	SNV	p.Q61H	2
NRAS	COSM585	SNV	p.Q61H	2
NRAS	COSM583	SNV	p.Q61L	2
NRAS	COSM582	SNV	p.Q61P	2
NRAS	COSM584	SNV	p.Q61R	2
NRAS	COSM30646	MNV	p.Q61L	2
NRAS	COSM33693	MNV	p.Q61R	2
NRAS	COSM580	SNV	p.Q61K	2
NRAS	COSM581	SNV	p.Q61E	2
NRAS	COSM53223	MNV	p.Q61K	2
NRAS	COSM12725	MNV	p.Q61L	2
NRAS	COSM579	MNV	p.Q61R	2
NRAS	COSM12730	MNV	p.Q61K	2
NRAS	COSM574	SNV	p.G13V	2
NRAS	COSM573	SNV	p.G13D	2
NRAS	COSM575	SNV	p.G13A	2
NRAS	COSM572	MNV	p.G13V	2
NRAS	COSM569	SNV	p.G13R	2
NRAS	COSM570	SNV	p.G13C	2
NRAS	COSM571	SNV	p.G13S	2
NRAS	COSM564	SNV	p.G12D	2
NRAS	COSM565	SNV	p.G12A	2
NRAS	COSM566	SNV	p.G12V	2
NRAS	COSM561	SNV	p.G12R	2
NRAS	COSM563	SNV	p.G12S	2
NRAS	COSM562	SNV	p.G12C	2
HRAS	COSM503	SNV	p.Q61H	2
HRAS	COSM502	SNV	p.Q61H	2
HRAS	COSM499	SNV	p.Q61R	2
HRAS	COSM500	SNV	p.Q61P	2
HRAS	COSM498	SNV	p.Q61L	2
HRAS	COSM33695	MNV	p.Q61R	2

HRAS	COSM501	MNV	p.Q61R	2
HRAS	COSM497	SNV	p.Q61E	2
HRAS	COSM496	SNV	p.Q61K	2
HRAS	COSM52978	MNV	p.Q61L	2
HRAS	COSM490	SNV	p.G13D	2
HRAS	COSM489	SNV	p.G13V	2
HRAS	COSM488	SNV	p.G13C	2
HRAS	COSM487	SNV	p.G13S	2
HRAS	COSM486	SNV	p.G13R	2
HRAS	COSM483	SNV	p.G12V	2
HRAS	COSM484	SNV	p.G12D	2
HRAS	COSM485	SNV	p.G12A	2
HRAS	COSM482	SNV	p.G12R	2
HRAS	COSM481	SNV	p.G12C	2
HRAS	COSM480	SNV	p.G12S	2
KRAS	COSM19900	SNV	p.A146V	2
KRAS	COSM19404	SNV	p. A146T	2
KRAS	COSM19940	SNV	p.K117N	2
KRAS	COSM28519	SNV	p.K117N	2
KRAS	COSM554	SNV	p.Q61H	2
KRAS	COSM555	SNV	p.Q61H	2
KRAS	COSM553	SNV	p.Q61L	2
KRAS	COSM552	SNV	p.Q61R	2
KRAS	COSM551	SNV	p.Q61P	2
KRAS	COSM1168052	MNV	p.Q61R	2
KRAS	COSM550	SNV	p.Q61E	2
KRAS	COSM549	SNV	p.Q61K	2
KRAS	COSM87298	MNV	p.Q61K	2
KRAS	COSM539	SNV	p.G15D	2
KRAS	COSM538	SNV	p.G15S	2
KRAS	COSM87280	SNV	p.G13E	2
KRAS	COSM30567	SNV	p.G13E	2
KRAS	COSM533	SNV	p.G13A	2
KRAS	COSM534	SNV	p.G13V	2
KRAS	COSM532	SNV	p.G13D	2
KRAS	COSM531	MNV	p.G13D	2
KRAS	COSM530	MNV	p.G13V	2
KRAS	COSM12721	MNV	p.G13V	2
KRAS	COSM528	SNV	p.G13S	2
KRAS	COSM527	SNV	p.G13C	2
KRAS	COSM529	SNV	p.G13R	2
KRAS	COSM13643	SNV	p.G12N	2
KRAS	COSM512	SNV	p.G12F	2

KRAS	COSM514	SNV	p.G12L	2
KRAS	COSM87281	MNV	p.G13C	2
KRAS	COSM520	SNV	p.G12V	2
KRAS	COSM521	SNV	p.G12D	2
KRAS	COSM522	SNV	p.G12A	2
KRAS	COSM14209	MNV	p.G12D	2
KRAS	COSM515	MNV	p.G12V	2
KRAS	COSM518	SNV	p.G12R	2
KRAS	COSM517	SNV	p.G12S	2
KRAS	COSM516	SNV	p.G12C	3
KRAS	COSM513	MNV	p.G12C	2
KRAS	PM_COSM5413585	MNV	p.G12A	2
KRAS	PM_COSM1716372	MNV	p.G12L	2
KRAS	PM_COSM249888	MNV	p.G12R	2
KRAS	PM_COSM4387522	MNV	p.G12V	2
KRAS	PM_COSM4745557	MNV	p.G13R	2
ARAF	COSM5044705	SNV	p.S214C	3
ARAF	COSM1742787	SNV	p.S214A	3
ARAF	COSM612884	SNV	p.S214F	3
BRAF	COSM308550	MNV	p.V600D	2.1
BRAF	COSM477	MNV	p.V600D	2.1
BRAF	COSM475	MNV	p.V600E	1.1
BRAF	COSM1127	MNV	p.V600R	2.1
BRAF	COSM1583011	MNV	p.V600R	2.1
BRAF	COSM473	MNV	p.V600K	1.1
BRAF	COSM474	MNV	p.V600R	2.1
BRAF	COSM6137	SNV	p.V600G	2.1
BRAF	COSM18443	SNV	p.V600A	2.1
BRAF	COSM249889	MNV	p.V600Q	2.1
BRAF	COSM476	SNV	p.V600E	1.1
BRAF	COSM1130	SNV	p.V600M	2.1
BRAF	COSM219798	SNV	p.V600L	2.1
BRAF	COSM33808	SNV	p.V600L	2.1
BRAF	COSM1132	SNV	p.K601N	3
BRAF	COSM6265	SNV	p.K601N	3
BRAF	COSM1133	DEL	p.V600_K601>E	3
BRAF	PM_COSM30730	INS	p.T599_V600insT	3
BRAF	PM_COSM26625	INS	p.A598_T599insV	3
BRAF	COSM457	SNV	p.G469R	3
BRAF	COSM455	SNV	p.G469R	3
BRAF	COSM1112	SNV	p.G466R	3
BRAF	COSM478	SNV	p.K601E	3
BRAF	COSM472	SNV	p.T599I	3

BRAF	COSM21549	SNV	p.A598V	3
BRAF	COSM1126	MNV	p.L597S	3
BRAF	COSM1125	SNV	p.L597Q	3
BRAF	COSM471	SNV	p.L597R	3
BRAF	COSM470	SNV	p.L597V	3
BRAF	COSM469	SNV	p.G596R	3
BRAF	COSM53198	SNV	p.F595L	3
BRAF	COSM468	SNV	p.F595L	3
BRAF	COSM21612	SNV	p.F595L	3
BRAF	COSM466	SNV	p.D594V	3
BRAF	COSM467	SNV	p.D594G	3
BRAF	COSM211600	MNV	p.D594N	3
BRAF	COSM1583010	SNV	p.D594A	3
BRAF	COSM27639	SNV	p.D594N	3
BRAF	COSM463	SNV	p.E586K	3
BRAF	COSM462	SNV	p.N581S	3
BRAF	COSM1133046	SNV	p.Y472C	3
BRAF	COSM459	SNV	p.G469V	3
BRAF	COSM460	SNV	p.G469A	3
BRAF	COSM461	SNV	p.G469E	3
BRAF	COSM451	SNV	p.G466V	3
BRAF	COSM453	SNV	p.G466E	3
BRAF	COSM452	SNV	p.G466A	3
BRAF	COSM253328	SNV	p.G466R	3
BRAF	COSM449	SNV	p.G464E	3
BRAF	COSM450	SNV	p.G464V	3
BRAF	COSM1448615	SNV	p.G464R	3
BRAF	COSM1111	SNV	p.G464R	3
BRAF	COSM448	SNV	p.I463S	3
BRAF	COSM447	SNV	p.R462I	3
MAP2K1	PM_E1	MNV	p.F53_Q58delFLTQKQaddL	3
MAP2K1	PM_E2	DEL	p.Q56_V60delQKQKV	2
MAP2K1	COSM1235481	SNV	p.Q56P	2
MAP2K1	COSM4756761	SNV	p.K57T	3
MAP2K1	COSM1235478	SNV	p.K57N	2
MAP2K1	COSM5520914	SNV	p.K57N	2
MAP2K1	PM_COSM4166150	DEL	p.K57_G61del	3
MAP2K1	PM_COSM5031101	DEL	p.Q58_E62delQKVGE	3
MAP2K1	PM_COSM5031100	DEL	p.Q58_E62delQKVGE	3
MAP2K1	PM_COSM1235479	SNV	p.D67N	3
MAP2K1	COSM1678546	SNV	p.D67N	3
MAP2K1	PM_COSM404998	DEL	p.E102_I103delEI	3
MAP2K1	PM_COSM4166152	DEL	p.E102_I103del	3

MAP2K1	PM_COSM4166153	DEL	p.E102_I103del	3
MAP2K1	PM_COSM5730253	DEL	p.I103_K104delIK	3
MAP2K1	PM_COSM5702512	DEL	p.I103_K104del	3
MAP2K1	PM_E3	SNV	p.E120Q	3
MAP2K1	PM_COSM555601	SNV	p.C121S	3
MAP2K1	COSM1315829	SNV	p.C121S	3
MAP2K1	PM_E4	SNV	p.S123T	3
MAP2K1	COSM1374186	SNV	p.G128D	3
MAP2K1	COSM232755	SNV	p.E203K	3
GNA11	COSM52969	SNV	p.Q209L	2
GNA11	COSM52970	SNV	p.Q209P	2
GNAQ	COSM28757	SNV	p.Q209L	2
GNAQ	COSM28758	SNV	p.Q209P	2
GNAQ	COSM28760	SNV	p.Q209R	2
GNAQ	COSM52975	SNV	p.R183Q	3
FUSIONS:				
BRAF	AGAP3-BRAF.A10B11	Fusion	AGAP3-BRAF.A10B11	2
BRAF	AGAP3-BRAF.A9B9	Fusion	AGAP3-BRAF.A9B9	2
BRAF	AGK-BRAF.A2B8	Fusion	AGK-BRAF.A2B8	2
BRAF	AGTRAP-BRAF.A5B8.COSF828.1	Fusion	AGTRAP-BRAF.A5B8.COSF828.1	2
BRAF	AKAP9-BRAF.A21B10	Fusion	AKAP9-BRAF.A21B10	2
BRAF	AKAP9-BRAF.A22B9	Fusion	AKAP9-BRAF.A22B9	2
BRAF	AKAP9-BRAF.A28B9	Fusion	AKAP9-BRAF.A28B9	2
BRAF	AKAP9-BRAF.A7B11	Fusion	AKAP9-BRAF.A7B11	2
BRAF	AKAP9-BRAF.A8B9.COSF1013.1	Fusion	AKAP9-BRAF.A8B9.COSF1013.1	2
BRAF	AP3B1-BRAF.A22B9	Fusion	AP3B1-BRAF.A22B9	2
BRAF	ARMC10-BRAF.A4B11	Fusion	ARMC10-BRAF.A4B11	2
BRAF	ATG7-BRAF.A18B9	Fusion	ATG7-BRAF.A18B9	2
BRAF	BAIAP2L1-BRAF.B12B9	Fusion	BAIAP2L1-BRAF.B12B9	2
BRAF	BBS9-BRAF.B19B4	Fusion	BBS9-BRAF.B19B4	2
BRAF	BCL2L11-BRAF.B3B10	Fusion	BCL2L11-BRAF.B3B10	2
BRAF	BRAF-AP3B1.B8A23	Fusion	BRAF-AP3B1.B8A23	2
BRAF	BRAF-BRAF.B1B11	Fusion	BRAF-BRAF.B1B11	2
BRAF	BRAF-BRAF.B1B9	Fusion	BRAF-BRAF.B1B9	2
BRAF	BRAF-BRAF.B3B11	Fusion	BRAF-BRAF.B3B11	2
BRAF	BRAF-BRAF.B3B9	Fusion	BRAF-BRAF.B3B9	2
BRAF	BRAF-CIITA.B9C6	Fusion	BRAF-CIITA.B9C6	2
BRAF	BRAF-MACF1.B8M15	Fusion	BRAF-MACF1.B8M15	2
BRAF	BRAF-MRPS33.B1M2	Fusion	BRAF-MRPS33.B1M2	2
BRAF	BRAF-SLC26A4.B3S7	Fusion	BRAF-SLC26A4.B3S7	2
BRAF	BRAF-SUGCT.B1S13	Fusion	BRAF-SUGCT.B1S13	2
BRAF	BTF3L4-BRAF.B3B11	Fusion	BTF3L4-BRAF.B3B11	2

BRAF	C7orf73-BRAF.C2B9	Fusion	C7orf73-BRAF.C2B9	2
BRAF	CCDC6-BRAF.C1B9	Fusion	CCDC6-BRAF.C1B9	2
BRAF	CCDC91-BRAF.C11B9	Fusion	CCDC91-BRAF.C11B9	2
BRAF	CCNY-BRAF.C1B10	Fusion	CCNY-BRAF.C1B10	2
BRAF	CDC27-BRAF.C16B9.1	Fusion	CDC27-BRAF.C16B9.1	2
BRAF	CEP89-BRAF.C16B9	Fusion	CEP89-BRAF.C16B9	2
BRAF	CLCN6-BRAF.C2B11.COSF1440	Fusion	CLCN6-BRAF.C2B11.COSF1440	2
BRAF	CLIP2-BRAF.C6B11	Fusion	CLIP2-BRAF.C6B11	2
BRAF	CUL1-BRAF.C7B9	Fusion	CUL1-BRAF.C7B9	2
BRAF	CUX1-BRAF.C10B9	Fusion	CUX1-BRAF.C10B9	2
BRAF	DYNC1I2-BRAF.D7B10	Fusion	DYNC1I2-BRAF.D7B10	2
BRAF	EML4-BRAF.E6B10	Fusion	EML4-BRAF.E6B10	2
BRAF	EPS15-BRAF.E22B10	Fusion	EPS15-BRAF.E22B10	2
BRAF	ERC1-BRAF.E12B10	Fusion	ERC1-BRAF.E12B10	2
BRAF	ERC1-BRAF.E17B8	Fusion	ERC1-BRAF.E17B8	2
BRAF	FAM114A2-BRAF.F9B11	Fusion	FAM114A2-BRAF.F9B11	2
BRAF	FAM131B-BRAF.F1B10.COSF1191	Fusion	FAM131B-BRAF.F1B10.COSF1191	2
BRAF	FAM131B-BRAF.F2B9.COSF1189.1	Fusion	FAM131B-BRAF.F2B9.COSF1189.1	2
BRAF	FAM131B-BRAF.F3B9.COSF1193	Fusion	FAM131B-BRAF.F3B9.COSF1193	2
BRAF	FCHSD1-BRAF.F13B9.COSF403	Fusion	FCHSD1-BRAF.F13B9.COSF403	2
BRAF	FXR1-BRAF.F13B10	Fusion	FXR1-BRAF.F13B10	2
BRAF	GATM-BRAF.G2B11	Fusion	GATM-BRAF.G2B11	2
BRAF	GHR-BRAF.G1B10	Fusion	GHR-BRAF.G1B10	2
BRAF	GNAI1-BRAF.G1B10.COSF1442	Fusion	GNAI1-BRAF.G1B10.COSF1442	2
BRAF	GTF2I-BRAF.G4B10	Fusion	GTF2I-BRAF.G4B10	2
BRAF	HERPUD1-BRAF.H4B7	Fusion	HERPUD1-BRAF.H4B7	2
BRAF	KCTD7-BRAF.K3B8	Fusion	KCTD7-BRAF.K3B8	2
BRAF	KCTD7-BRAF.K4B8	Fusion	KCTD7-BRAF.K4B8	2
BRAF	KDM7A-BRAF.K11B11	Fusion	KDM7A-BRAF.K11B11	2
BRAF	KIAA1549-BRAF.K12B11	Fusion	KIAA1549-BRAF.K12B11	2
BRAF	KIAA1549-BRAF.K12B9.COSF1474	Fusion	KIAA1549-BRAF.K12B9.COSF1474	2
BRAF	KIAA1549-BRAF.K13B9	Fusion	KIAA1549-BRAF.K13B9	2
BRAF	KIAA1549-BRAF.K14B11.COSF1226	Fusion	KIAA1549-BRAF.K14B11.COSF1226	2
BRAF	KIAA1549-BRAF.K14B9.COSF483	Fusion	KIAA1549-BRAF.K14B9.COSF483	2
BRAF	KIAA1549-BRAF.K15B10.COSF1283.1	Fusion	KIAA1549-BRAF.K15B10.COSF1283.1	2
BRAF	KIAA1549-BRAF.K15B11.COSF485.1	Fusion	KIAA1549-BRAF.K15B11.COSF485.1	2
BRAF	KIAA1549-BRAF.K15B9.COSF481.1	Fusion	KIAA1549-BRAF.K15B9.COSF481.1	2
BRAF	KIAA1549-BRAF.K16B10	Fusion	KIAA1549-BRAF.K16B10	2
BRAF	KIAA1549-BRAF.K17B10.COSF509	Fusion	KIAA1549-BRAF.K17B10.COSF509	2
BRAF	KIAA1549-BRAF.K18B9.COSF511	Fusion	KIAA1549-BRAF.K18B9.COSF511	2
BRAF	KIAA1549-BRAF.K9B9	Fusion	KIAA1549-BRAF.K9B9	2
BRAF	KLHL7-BRAF.K5B9	Fusion	KLHL7-BRAF.K5B9	2

BRAF	LSM12-BRAF.L3B9	Fusion	LSM12-BRAF.L3B9	2
BRAF	LSM14A-BRAF.L9B9	Fusion	LSM14A-BRAF.L9B9	2
BRAF	MACF1-BRAF.M60B9	Fusion	MACF1-BRAF.M60B9	2
BRAF	MAD1L1-BRAF.M16B9	Fusion	MAD1L1-BRAF.M16B9	2
BRAF	MAD1L1-BRAF.M17B10	Fusion	MAD1L1-BRAF.M17B10	2
BRAF	MKRN1-BRAF.M4B11.COSF1444	Fusion	MKRN1-BRAF.M4B11.COSF1444	2
BRAF	MKRN1-BRAF.M4B9	Fusion	MKRN1-BRAF.M4B9	2
BRAF	MYRIP-BRAF.M16B9	Fusion	MYRIP-BRAF.M16B9	2
BRAF	MZT1-BRAF.M2B11	Fusion	MZT1-BRAF.M2B11	2
BRAF	NUB1-BRAF.N3B9	Fusion	NUB1-BRAF.N3B9	2
BRAF	NUDCD3-BRAF.N4B9	Fusion	NUDCD3-BRAF.N4B9	2
BRAF	NUP214-BRAF.N21B10	Fusion	NUP214-BRAF.N21B10	2
BRAF	PAPSS1-BRAF.P5B9.1	Fusion	PAPSS1-BRAF.P5B9.1	2
BRAF	PLIN3-BRAF.P1B9	Fusion	PLIN3-BRAF.P1B9	2
BRAF	RAD18-BRAF.R7B10	Fusion	RAD18-BRAF.R7B10	2
BRAF	RBMS3-BRAF.R11B11	Fusion	RBMS3-BRAF.R11B11	2
BRAF	RNF11-BRAF.R1B11	Fusion	RNF11-BRAF.R1B11	2
BRAF	RNF130-BRAF.R3B9.COSF1483	Fusion	RNF130-BRAF.R3B9.COSF1483	2
BRAF	RP2-BRAF.R3B10	Fusion	RP2-BRAF.R3B10	2
BRAF	SLC12A7-BRAF.S17B11	Fusion	SLC12A7-BRAF.S17B11	2
BRAF	SLC45A3-BRAF.S1B8.COSF871	Fusion	SLC45A3-BRAF.S1B8.COSF871	2
BRAF	SND1-BRAF.S10B11	Fusion	SND1-BRAF.S10B11	2
BRAF	SND1-BRAF.S10B9	Fusion	SND1-BRAF.S10B9	2
BRAF	SND1-BRAF.S11B11	Fusion	SND1-BRAF.S11B11	2
BRAF	SND1-BRAF.S14B11	Fusion	SND1-BRAF.S14B11	2
BRAF	SND1-BRAF.S14B9	Fusion	SND1-BRAF.S14B9	2
BRAF	SND1-BRAF.S16B9.1	Fusion	SND1-BRAF.S16B9.1	2
BRAF	SND1-BRAF.S18B10	Fusion	SND1-BRAF.S18B10	2
BRAF	SND1-BRAF.S9B2	Fusion	SND1-BRAF.S9B2	2
BRAF	SND1-BRAF.S9B9	Fusion	SND1-BRAF.S9B9	2
BRAF	SOX6-BRAF.S5B9	Fusion	SOX6-BRAF.S5B9	2
BRAF	SOX6-BRAF.S6B9	Fusion	SOX6-BRAF.S6B9	2
BRAF	STRN3-BRAF.S3B10	Fusion	STRN3-BRAF.S3B10	2
BRAF	TANK-BRAF.T4B9	Fusion	TANK-BRAF.T4B9	2
BRAF	TAX1BP1-BRAF.T8B11.1	Fusion	TAX1BP1-BRAF.T8B11.1	2
BRAF	TMEM178B-BRAF.T2B9	Fusion	TMEM178B-BRAF.T2B9	2
BRAF	TMPRSS2-BRAF.T3B11	Fusion	TMPRSS2-BRAF.T3B11	2
BRAF	TRIM24-BRAF.T10B9	Fusion	TRIM24-BRAF.T10B9	2
BRAF	TRIM24-BRAF.T11B2	Fusion	TRIM24-BRAF.T11B2	2
BRAF	TRIM24-BRAF.T3B10	Fusion	TRIM24-BRAF.T3B10	2
BRAF	TRIM24-BRAF.T3B11	Fusion	TRIM24-BRAF.T3B11	2
BRAF	TRIM24-BRAF.T5B8	Fusion	TRIM24-BRAF.T5B8	2
BRAF	TRIM24-BRAF.T9B9.1	Fusion	TRIM24-BRAF.T9B9.1	2

BRAF	TRIM4-BRAF.T6B10	Fusion	TRIM4-BRAF.T6B10	2
BRAF	UBN2-BRAF.U3B11	Fusion	UBN2-BRAF.U3B11	2
BRAF	ZC3HAV1-BRAF.Z3B10	Fusion	ZC3HAV1-BRAF.Z3B10	2
BRAF	ZC3HAV1-BRAF.Z7B11	Fusion	ZC3HAV1-BRAF.Z7B11	2
BRAF	ZKSCAN5-BRAF.Z2B9	Fusion	ZKSCAN5-BRAF.Z2B9	2
BRAF	ZSCAN30-BRAF.Z3B10	Fusion	ZSCAN30-BRAF.Z3B10	2

APPENDIX VIII: PATIENT INSTRUCTIONS FOR TREATING DIARRHEA

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

APPENDIX IX: BLOOD PRESSURE LEVELS FOR CHILDREN BY AGE AND HEIGHT PERCENTILE

Blood pressure (BP) levels for BOYS

		Systolic Blood Pressure, mm Hg							Diastolic Blood Pressure, mm Hg						
Age	BP	Percentile of Height							Percentile of Height						
(years)	Percentile	5th	10th	25th	50th	75th	90th	95th	5th	10th	25th	50th	75th	90th	95th
1	95th	98	99	101	103	104	106	106	54	54	55	56	57	58	58
2	95th	101	102	104	106	108	109	110	59	59	60	61	62	63	63
3	95th	104	105	107	109	110	112	113	63	63	64	65	66	67	67
4	95th	106	107	109	111	112	114	115	66	67	68	69	70	71	71
5	95th	108	109	110	112	114	115	116	69	70	71	72	73	74	74
6	95th	109	110	112	114	115	117	117	72	72	73	74	75	76	76
7	95th	110	111	113	115	117	118	119	74	74	75	76	77	78	78
8	95th	111	112	114	116	118	119	120	75	76	77	78	79	79	80
9	95th	113	114	116	118	119	121	121	76	77	78	79	80	81	81
10	95th	115	116	117	119	121	122	123	77	78	79	80	81	81	82
11	95th	117	118	119	121	123	124	125	78	78	79	80	81	82	82
12	95th	119	120	122	123	125	127	127	78	79	80	81	82	82	83
13	95th	121	122	124	126	128	129	130	79	79	80	81	82	83	83
14	95th	124	125	127	128	130	132	132	80	80	81	82	83	84	84
15	95th	126	127	129	131	133	134	135	81	81	82	83	84	85	85
16	95th	129	130	132	134	135	137	137	82	83	83	84	85	86	87
≥17	95th	131	132	134	136	138	139	140	84	85	86	87	87	88	89

Instructions for using this BP Chart:

1. Measure the patient's blood pressure using an appropriate size cuff.
2. Select appropriate chart for a female or male patient.
3. Using the "age" row and "height" column determine if the BP is within the ULN.
4. See Section 5.4.1.2 for definition of dose limiting hypertension, Section 6.7 for management and grading of hypertension, and Section 7.6 for medical treatment of selumetinib- related hypertension.

This table was taken from "The Fourth Report on the Diagnosis, Evaluation, and Treatment of High Blood Pressure in Children and Adolescents" PEDIATRICS Vol. 114 No. 2 August 2004, pp. 555-576.

Blood pressure (BP) levels for GIRLS

		Systolic Blood Pressure, mm Hg							Diastolic Blood Pressure, mm Hg						
Age	BP	Percentile of Height							Percentile of Height						
(years)	Percentile	5th	10th	25th	50th	75th	90th	95th	5th	10th	25th	50th	75th	90th	95th
1	95th	100	101	102	104	105	106	107	56	57	57	58	59	59	60
2	95th	102	103	104	105	107	108	109	61	62	62	63	64	65	65
3	95th	104	104	105	107	108	109	110	65	66	66	67	68	68	69
4	95th	105	106	107	108	110	111	112	68	68	69	70	71	71	72
5	95th	107	107	108	110	111	112	113	70	71	71	72	73	73	74
6	95th	108	109	110	111	113	114	115	72	72	73	74	74	75	76
7	95th	110	111	112	113	115	116	116	73	74	74	75	76	76	77
8	95th	112	112	114	115	116	118	118	75	75	75	76	77	78	78
9	95th	114	114	115	117	118	119	120	76	76	76	77	78	79	79
10	95th	116	116	117	119	120	121	122	77	77	77	78	79	80	80
11	95th	118	118	119	121	122	123	124	78	78	78	79	80	81	81
12	95th	119	120	121	123	124	125	126	79	79	79	80	81	82	82
13	95th	121	122	123	124	126	127	128	80	80	80	81	82	83	83
14	95th	123	123	125	126	127	129	129	81	81	81	82	83	84	84
15	95th	124	125	126	127	129	130	131	82	82	82	83	84	85	85
16	95th	125	126	127	128	130	131	132	82	82	83	84	85	85	86
≥17	95th	125	126	127	129	130	131	132	82	83	83	84	85	85	86

Instructions for using this BP Chart:

1. Measure the patient's blood pressure using an appropriate size cuff.
2. Select appropriate chart for a female or male patient.
3. Using the "age" row and "height" column determine if the BP is within the ULN.
4. See Section 5.4.1.2 for definition of dose limiting hypertension, Section 6.7 for management and grading of hypertension, and Section 7.6 for medical treatment of selumetinib related hypertension.

This table was taken from "The Fourth Report on the Diagnosis, Evaluation, and Treatment of High Blood Pressure in Children and Adolescents" PEDIATRICS Vol. 114 No. 2 August 2004, pp. 555-576.

APPENDIX X: YOUTH INFORMATION SHEETS
INFORMATION SHEET REGARDING RESEARCH STUDY APEC1621E
(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 selumetinib that could "match" your tumor. The doctors want to see if selumetinib will help children with your type of cancer get better. We don't know if selumetinib 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 selumetinib 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 selumetinib. 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 selumetinib 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 selumetinib works in them. We will draw some extra blood samples for this if your family agrees.

INFORMATION SHEET REGARDING RESEARCH STUDY APEC1621E
(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 selumetinib, and so you have been assigned to selumetinib. The doctors want to see if selumetinib will make children with your type of cancer get better. We don't know if selumetinib will work well to get rid of your cancer. That is why we are doing the study.

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

APPENDIX XI 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 mL**	

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

APPENDIX XII: CTEP AND CTSU REGISTRATION PROCEDURES

Food and Drug Administration (FDA) regulations and National Cancer Institute (NCI) policy require all investigators participating in any NCI-sponsored clinical trial 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 (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 TRIAD or acting as a primary site contact) must complete their annual registration using CTEP's web-based Registration and Credential Repository (RCR) (https://ctepcore.nci.nih.gov/rcr). Documentation requirements per registration type are outlined in the table below.

Documentation Required	IVR	NPIVR	AP	A
FDA Form 1572	✔	✔		
Financial Disclosure Form	✔	✔	✔	
NCI Biosketch (education, training, employment, license, and certification)	✔	✔	✔	
HSP/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 CTSU (Cancer Trials Support Unit) websites and applications. In addition, IVRs and NPIVRs must list all clinical practice sites and IRBs covering their practice sites on the FDA Form 1572 in RCR to allow the following:

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

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

CTSU REGISTRATION PROCEDURES

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

Requirements For APEC1621E 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)
- IROC Credentialing Status Inquiry (CSI) Form
  NOTE: For studies with a radiation and/or imaging (RTI) component, the enrolling site must be aligned to a RTI provider. To manage provider associations access the Provider Association tab on the CTSU website at https://www.ctsu.org/RSS/RTFProviderAssociation, to add or remove associated providers. Sites must be linked to at least one IROC credentialed provider to participate on trials with an RT component.

Submitting Regulatory Documents:

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

Regulatory Submission Portal: www.ctsu.org (members' area) → Regulatory Tab →Regulatory Submission

When applicable, original documents should be mailed to:
CTSU Regulatory Office
1818 Market Street, Suite 3000
Philadelphia, PA 19103

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.

Checking Your Site's Registration Status:

You can verify your site registration status on the members' section of the CTSU website. (Note: Sites will not receive formal notification of regulatory approval from the CTSU Regulatory Office.)

- Go to https://www.ctsu.org and log in to the members' area using your CTEP-IAM username and password
- Click on the Regulatory tab at the top of your screen
- Click on the Site Registration tab
- Enter your 5-character CTEP Institution Code and click on Go

Note: The status given only reflects compliance with IRB documentation and institutional compliance with protocol-specific requirements as outlined by the Lead Network. 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

Data collection for this study will be done exclusively through the Medidata Rave clinical data management system. Access to the trial in Rave is granted through the iMedidata application to all persons with the appropriate roles assigned in Regulatory Support System (RSS). To access Rave via iMedidata, the site user must have an active CTEP-IAM account (check at https://ctepcore.nci.nih.gov/iam) and the appropriate Rave role (Rave CRA, Read-Only, CRA (Lab Admin, SLA or Site Investigator) on either the LPO or participating organization roster at the enrolling site. To the hold Rave CRA role or CRA Lab Admin role, the user must hold a minimum of an AP registration type. To hold the Rave Site Investigator role, the individual must be registered as an NPIVR or IVR. Associates can hold read-only roles in Rave. If the study has a DTL, individuals requiring write access to Rave must also be assigned the appropriate Rave tasks on the DTL.

Upon initial site registration approval for the study in RSS, all persons with Rave roles assigned on the appropriate roster will be sent a study invitation e-mail from iMedidata. To accept the invitation, site users must log into the Select Login (https://login.imedidata.com/selectlogin) using their CTEP-IAM user name and password, and click on the "accept" link in the upper right-corner of the iMedidata page. Please note, site users will not be able to access the study in Rave until all required Medidata and study specific trainings are completed. Trainings will be in the form of electronic learnings (eLearnings), and can be accessed by clicking on the link in the upper right pane of the iMedidata screen.

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

APPENDIX XIII: 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 SGPT 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 SGOT 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