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June 15, 2021

Martha Kruhm, MS, RAC
Head, Protocol and Information Office
Operations and Informatics Branch
Cancer Therapy Evaluation Program
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National Cancer Institute
Executive Plaza North Room 730
Bethesda, MD 20892

Dear Ms. Kruhm,

Please find attached Amendment #5 to **APEC1621C**, *NCI-COG Pediatric MATCH (Molecular Analysis for Therapy Choice) - Phase 2 subprotocol of tazemetostat for patients with tumors harboring alterations in EZH2 or members of the SWI/SNF complex*

Amendment #5 provides a response to a Request for Amendment (RA) from CTEP, dated May 11, 2021. The CAEPR within the protocol and associated risk information contained within the consent document for Tazemetostat, NSC 791066 have been modified to satisfy the RA received. Additionally, minor administrative changes have been included in to the protocol. CRFs have been updated to include changes to the language of the inclusion criteria. No changes have been made to the training module Please contact us if you have any further questions.

Sincerely,

Samuel Baird, MPH, Protocol Coordinator for
Susan Chi, M.D., **APEC1621C** Study Chair, and
Donald Parsons, M.D., PhD, PI, Chair, Molecular Analysis for Therapy Choice

I. Protocol Changes:

Section	Comment
Throughout	Updated amendment number and version dates.
Table of Contents	Updated on repagination.
Study Committee	Updated PC, RC and MS statistician Information.
9.1.9	Updated CAEPR to version 2.4, March 30, 2021, per RA instructions.
Appendix II	Updated Appendix to most recent version.

Activated: July 24th, 2017
Closed: 05/07/2021
Version Date: 06/15/2021
Amendment: 5

CHILDREN'S ONCOLOGY GROUP

APEC1621C

NCI-COG PEDIATRIC MATCH (MOLECULAR ANALYSIS FOR THERAPY CHOICE)- PHASE 2 SUBPROTOCOL OF TAZEMETOSTAT IN PATIENTS WITH TUMORS HARBORING ALTERATIONS IN EZH2 OR MEMBERS OF THE SWI/SNF COMPLEX

Open to COG Member Institutions in the USA

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AGENT NSC# AND IND#'s
NCI-Supplied Agents:
Tazemetostat
(NSC# 791066)
IND Sponsor: DCTD, NCI

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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 tazemetostat in children with recurrent or refractory solid tumors (including non-Hodgkin lymphomas, histiocytoses and CNS tumors) harboring specified activating genetic alterations in EZH2 or members of the SWI/SNF complex. EPZ-6438 (tazemetostat) is a selective small molecule inhibitor of the histone methyltransferase EZH2.[1] Tazemetostat will be administered orally twice daily at the recommended phase 2 dose (RP2D) as determined by the ongoing pediatric phase 1 trial. 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

For patient(s) enrolled Pre-amendment #3B:

Day 1-28	Day 28
Tazemetostat 1200 mg/m^2/dose (Orally, twice daily)	**Evaluation**

For patient(s) enrolled post-amendment #3B:

	Day 1-28	Day 28
Patients without CNS involvement	**Tazemetostat 520mg/m^2/dose** (Orally, twice daily)	Evaluation
Patients with CNS involvement	**Tazemetostat 1200 mg/m^2/dose** (Orally, twice daily)	Evaluation

Tazemetostat will be administered orally twice daily (based on disease location per above table); a cycle will be 28 days.

Tumor 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 (maximum of 26 cycles) provided the patient meets the criteria for starting subsequent cycles (Section 5.2) and does not meet any of the criteria for removal from protocol therapy criteria (Section 10.0).

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 tazemetostat with advanced solid tumors(including CNS tumors), non-Hodgkin lymphoma or histiocytic disorders that harbor gain of function mutations in EZH2, or loss of function mutations in the SWI/SNF complex subunits SMARCB1 or SMARCA4 at a dose of 520 mg/m2/dose twice daily for patients without any CNS involvement or 1200 mg/m2/dose orally twice daily for patients with CNS involvement.

1.2 Secondary Aims

1.2.1 To estimate the progression-free survival in pediatric patients treated with tazemetostat that harbor gain of function mutations in EZH2, or loss of function mutations in the SWI/SNF complex subunits SMARCB1 or SMARCA4.

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

1.3 Exploratory Aims

1.3.1 To evaluate other biomarkers as predictors of response to tazemetostat and specifically, whether tumors that harbor different missense mutations or fusions will demonstrate differential response to tazemetostat 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

Histone methyltransferases (HMT) play a critical role in the transcriptional control. EZH2 (Enhancer of zeste homologue-2) is the catalytic subunit of the multi-protein Polycomb Repressive Complex 2 (PRC2) and PRC2 is the only human HMT that can methylate H3K27 (lysine 27 of histone H3), catalyzing the mono, di and tri-methylation of H3K27.[2] Hyper-trimethylation of H3K27 is transcriptionally repressive, resulting in the silencing of tumor suppressor genes. Aberrant trimethylation of H3K27 has been postulated to be oncogenic in a broad spectrum of human cancers including non-Hodgkins lymphoma, INI-1 deficient tumors, carcinomas, cutaneous melanoma, gliomas, medulloblastoma, and ependymoma via mutation, amplification and overexpression.

EZH2 overexpression is mainly found in solid tumors, whereas activating or inactivating mutations are identified in hematologic malignancies. EZH2 gain of function mutations were initially identified in NHL[3], specifically in follicular lymphoma (FL, 7.2%) and

diffuse large B-cell lymphoma (DLBCL, 9.7%, exclusively in germinal center B-cell [GCB] subtype). Genetic databases suggest that the incidence of EZH2 point mutations is 15-25% in FL and GCB-DLBCL. The oncogenic mutations at tyrosine 646 (Y646), A682 and A692 are those responsible for an excess of H3K27me3 repressive marks, impairing gene expression programs in lymphomas.

A natural antagonistic relationship between the SWI/SNF complex and PRC2 complex has been demonstrated with regards to stem cell-associated program. Loss of SWI/SNF complex members, such as SMARCB1, has been demonstrated to aberrantly activate those programs.[4] Consistent with the reciprocal relationship of PRC2 and SWI/SNF conditional mouse models, genetic inactivation of EZH2 has been shown to block tumor formation driven by SMARCB1 loss.

It is not possible to precisely determine the frequency of relevant genetic alterations in childhood malignancies eligible for this arm of the pediatric MATCH protocol using available databases. Detection of such genetic alterations requires advanced sequencing methods yet these methods have not been utilized on a sufficient number or broad diversity of samples from recurrent childhood solid tumors and lymphomas, as such data is limited to determine an accurate prediction of frequency.

2.2 Preclinical Studies

2.2.1 Antitumor Activity

Tazemetostat has been shown to induce apoptosis and differentiation in INI1-negative MRT cell lines.[5] In xenograft-bearing mice, treatment with tazemetostat resulted in dose-dependent regression of MRTs with correlated diminution of intra-tumoral H3K27 methylation and prevention of tumor regrowth after dosing cessation. See Section 2.3.3 for further preclinical experience including human lymphoma cell lines, *SMARCB1*-deficient malignant rhabdoid tumor (MRT) cell lines, and SMARCA2/A4 negative small cell carcinoma of the ovary, hypercalcemic type (SCCOHT) cell lines.

2.2.2 Animal Toxicology

Non-clinical repeated-dose oral toxicity studies in Sprague-Dawley (S-D) rats and cynomolgus monkeys, which may be relevant to human safety, revealed the following toxicities and target organs in the two species as follows:

- In the gastrointestinal (GI) tract: ulcer/erosion in the stomach, duodenum, jejunum, and/or ileum
- In lymphoid tissues: lymphoid depletion
- In a 13-week study in adult S-D rats, T- cell lymphoma occurred in a non - dose and non-concentration related fashion and was observed in 11 of 40 rats at 300 mg/kg/day (mid-dose) and in 1 of 40 animals at 600 mg/kg/day (high dose) dose groups. No cases of lymphoma were observed in the 100 mg/kg/day (low dose) tazemetostat dose cohort in adult rats or at any dose cohort (100-600 mg/kg/day) in cynomolgus monkeys treated for 4 or 13 weeks. In a 13-week study in juvenile S-D rats, thymic lymphoma was observed in male and female animals. However, the incidence of T-cell lymphoma did not increase continuously as systemic exposure to tazemetostat increased. At doses that resulted in steady-state AUC_{0-24} values less than 100,000 ng*h/mL, T-cell lymphoma was observed in 2/81 juvenile rats. However, T-cell lymphoma was observed in 24/63 juvenile rats at doses that resulted in AUC_{0-24} from 125,000 ng*h/mL to 290,000 ng*h/mL. The greatest tazemetostat AUC_{0-24} was

425,000 ng*h/mL and was observed in female juvenile rats that received 150/600 mg/kg/day tazemetostat. T-cell lymphoma was observed in 2/20 female juvenile rats in the tazemetostat 150/600 mg/kg/day dose group. The etiology of the rat lymphoma is currently unknown, but does not appear to be related to alterations in the Notch signaling pathway or endogenous rat leukemia virus reactivation. Please see Section 2.7 for relevance to pediatric patients.

- In bone in S-D rats only: there was trabecular bone formation in the femur and sternum in the 4- and 13-week studies
- In the serum of monkeys only: increase of chloride due to bromide derived from the tazemetostat bromide salt formulation (subsequent Phase 1 studies in humans have determined no detectable bromide levels)
- In the liver of monkeys only: hepatocyte and Kupffer cell hypertrophy in the 4-week and 13-week studies, which was accompanied by pigmentation of Kupffer cells and bile duct hyperplasia in some cases in the 13-week study
- In the kidney of monkeys only: glomerulopathy in the 13-week study

Additional animal toxicology is provided in the Investigator's Brochure (IB) for tazemetostat.

2.3 Adult Studies

2.3.1 Phase 1 Studies

Epizyme has conducted a Phase 1/2, first-in-human clinical study (E7438-G000-101, NCT01897571), a multicenter, open-label, dose-escalation study in adult patients with advanced solid tumors. The Phase 1 portion of this study completed enrollment in December 2015. Fifty-eight adult patients (21 B-cell lymphomas, 37 solid tumors) were enrolled and treated at five dose levels of 100, 200, 400, 800, and 1600 mg BID. Tazemetostat PK exhibits rapid absorption, T_{max} =1-2 hrs post-dose, as well as rapid elimination ($t_{1/2}$ ~ 3-5 hr), justifying twice daily dosing. Tazemetostat exposure was linearly dose-proportional with maximal inhibition (~40%) at observed at the 800 mg and 1600 mg dose levels. Correlation between dose exposure and target inhibition (decreased H3K27Me3 inhibition by IHC of skin) was demonstrated. One DLT of thrombocytopenia was reported at the 1600 mg dose level. The most frequently occurring adverse events (≥ 15%) were asthenia, anemia, decreased appetite, muscle spasms, nausea, vomiting, constipation, thrombocytopenia, and dyspnea. All other adverse events occurred with a frequency of < 15% of patients. In the B-cell lymphoma cohort, 3 CR and 5 PR were observed. One CR was observed in the solid tumor cohort, this subject had malignant rhabdoid tumor. To date, 8 subjects with INI1-negative tumors have been treated. Two subjects have had objective responses (1 CR and 1 PR) and one with SD (with 15% reduction in tumor). Based on the safety, PK, biological activity and responses, the RP2D was determined to be 800 mg BID.

The most common treatment-emergent AEs in all studies to date, in descending order of frequency, were asthenia, nausea, thrombocytopenia, decreased appetite, anemia, constipation, dysgeusia, vomiting, diarrhea, dry skin, dyspnea, muscle spasms, and abdominal pain.

The effect of food on the bioavailability of tazemetostat and the drug-drug interaction (DDI) potential of tazemetostat has been evaluated in adults. Administration of tazemetostat with a high-fat meal resulted in a non-clinically

relevant effect on systemic disposition and overall systemic exposure, thus tazemetostat may be taken without regard to meals. Tazemetostat is metabolized primarily by CYP3A. It is a weak inducer of CYP3A4/5 isozyme as well as an inhibitor of the CYP3A, CYPA2C family, CYP2D6 and P-glycoprotein (P-gp). A Phase 2 study is ongoing for subjects with relapsed/refractory DLBCL and FL.

2.3.2 Phase 2 Studies

Currently, Epizyme is conducting a Phase 2 clinical study (NCT02601950) for adult subjects with INI1-negative tumors or relapsed/refractory synovial sarcoma as well as a Phase 2 clinical study (NCT02860286) in adult subjects with malignant mesothelioma with BAP1 loss of function**.**

2.3.3 Pharmacology/Pharmacokinetics/Correlative and Biological Studies

EPZ-6438 (tazemetostat) is a selective small molecule inhibitor of the histone methyltransferase EZH2.[1] Tazemetostat is an inhibitor of both wild type and mutated EZH2 containing residues Y646, A682G and A692 with half maximal inhibitory concentrations (IC50) ranging from 2-38 nmol/L. The compound shows a 35-fold selectivity over the most closely related HMT, EZH1, and greater than a 4500-fold selectivity over other HMTs. It selectively inhibits H3K27 methylation in a concentration and time dependent manner leading to selective killing of cell lines, specifically, human lymphoma cell lines with mutant or wildtype EZH2, *SMARCB1*-deficient malignant rhabdoid tumor (MRT) cell lines, and SMARCA2/A4 negative SCCOHT cell lines with IC50 in the nanomolar range. Tazemetostat administered orally has demonstrated antitumor activity in vivo against several EZH2 wild type and mutant human lymphoma xenograft murine models.[6] *SMARCB1* mutant MRT xenografts treated for 21-28 days demonstrated near elimination of the tumors with no regrowth observed. The MRT tumors demonstrated strong inhibition of H3K27Me3 which correlated with anti-tumor activity.[5]

2.4 Pediatric Studies

2.4.1 Prior Experience in Children

The first pediatric phase 1 study of tazemetostat (EZH-102, NCT02601937) for children with relapsed/refractory malignant rhabdoid tumors, including CNS ATRT, and other INI-deficient tumors and synovial sarcoma enrolled its first patient in January 2016 and completed the dose escalation phase of the trial (dose expansion is ongoing). As of July 2017, the RP2D was determined to be 1200 mg/m^2/dose twice daily. On this study, a liquid formulation of tazemetostat is administered PO BID. Pharmacology, pharmacokinetics and correlative biological studies are currently being collected in the ongoing phase 1study.

2.4.2 Hydrobromide Salt Formulation

An analysis of chloride levels in subjects on study EZH-102 at the 1200 mg/m2 dose level showed elevated chloride levels (beyond the ULN) in 5/7 subjects who had been treated at this dose level. Reviewing this finding further, subjects at lower dose levels (4/6 subjects at 900 mg/m2, 4/6 subjects at 700mg/m2 and 4/6 subjects at 520 mg/m2) also demonstrated elevated chloride levels.

Hyperchloremia is considered an artifact resulting from interference of serum bromide with the serum chloride assay (tazemetostat is a bromide salt). The

hydrobromide salt of tazemetostat is the form used in clinical studies, including the EZH-102 study. Bromide may artificially increase chloride measurements, and this phenomenon was noted in non-clinical studies of tazemetostat in which artifactually elevated serum chloride was noted in repeat-dose toxicology studies of tazemetostat in rats and monkeys at doses up to 1000 mg/kg/day (equivalent surface area doses in humans = 142-333 mg/m^2). Ion exchange chromatography showed increased serum chloride in these nonclinical studies to be pseudo-hyperchloremia, representing increased bromide and decreased chloride in serum. Due to this nonclinical finding, which could indicate the potential for elevated bromide levels in clinical studies, bromide levels were measured in the Phase 1 study of tazemetostat in adults. Bromide was within normal levels (<6.2 mmol/L) for all subjects taking the oral tablet formulation in doses up to 1600 mg BID. However, mean tazemetostat AUC(0-24) in children at the 1200 mg/m^2 dose level exceeded that observed in the 1600 mg BID dose group in adults from Study E7438-G000-101. There is a potential risk of bromide toxicity related to the hydrobromide salt used in the formulation of tazemetostat. Signs of bromide toxicity consist of CNS AEs including lethargy, headache, ataxia, and coma. No subject on any study as of 20 July 2017 has been reported to have experienced AEs consistent with bromide toxicity.

Although bromide is no longer typically used as an anti-epileptic agent, it has been used in the past as a treatment for refractory epilepsy. Thus, there are few current published guidelines for therapeutic monitoring and treatment of bromide. Ryan and Baumann (1999) presented an overview of available literature which provides therapeutic bromide ranges including levels associated with bromide toxicity. As different units of measure have been used at various testing laboratories with no clear preferred unit of measure used, the authors recommend the following conversion: 1 mEq/L = 8 mg/dL = 0.96 mmol/L. The central testing laboratory (ARUP) being utilized in the EZH-102 study provides results using the mg/dL unit of measure. The authors report therapeutic ranges as being between 10-35 mEq/L (80-280 mg/dL) with toxicity occurring in some studies at approximately the 20 mEq/L range (160 mg/dL). Elevated bromide levels can cause neurologic toxicity; drowsiness is often the first symptom that may occur and has been reported at levels of 20 mEq/L (160 mg/dL), with severe neurologic symptoms occurring at 200 mg/dL or greater.

To date, no patients on EZH-102 have experienced any adverse events that are suggestive or indicative of bromide toxicity. However, assessment of bromide levels was instituted in the Phase 1 study and therefore will be incorporated into this subarm protocol.

2.5 Overview of Proposed Pediatric Study

For patients with CNS involvement, Tazemetostat will be administered orally at the MTD and recommended phase 2 dose (RP2D) of 1200 mg/m^2/dose BID. Patients without any CNS involvement will be administered Tazemetostat orally at the lower starting dose of 520mg/m^2/dose BID. For patient(s) enrolled pre-amendment #3B Tazemetostat will be administered orally at the MTD and recommended phase 2 dose (RP2D) of 1200 mg/m^2/dose BID.

The primary aim of this trial will be to establish the objective response rate to tazemetostat.

Key secondary objectives include further evaluation of the tolerability of tazemetostat 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.

2.6 **Rationale for Amendment #1 (Increase in Dose Level)**

The purpose of Amendment #1 is to increase the starting dose level from 900 mg/m^2 BID to 1200 mg/m^2 BID. The most common treatment- emergent adverse events (TEAE) were vomiting (41%), pyrexia (28%), headache (24%), and nausea (24%), while the most common grade ≥3 TEAEs were death (17%, all unrelated to study drug) and anemia (9%). One patient at the 300 mg/m^2 dose level had DLTs of dyspnea (grade 4) and hypoxia (grade 3), however, no other DLT s were noted in any other cohort. Though the "rolling 6" design of the pediatric Phase I clinical trial supported further escalation of the dose level, of special note, elevated serum chloride levels were observed in 3/6 evaluable patients at the 1200 mg/m^2 BID dose level as well as in earlier dose levels (retrospective observation). The observed hyperchloremia was considered to be factitious and related to the formulation of tazemetostat as a bromide salt. Elevated serum bromide levels were detected in 2/5 active patients without any associated clinical signs or symptoms. With these data and on the basis of pharmacodynamic activity demonstrating H2K27me3 in peripheral mononuclear cells, as of July 2017, the RP2D was determined to be 1200 mg/m^2/dose twice daily.

2.7 **Rationale for Amendment #3B T-cell Lymphoblastic Lymphoma Monitoring (changes in dose level)**

In the Epizyme-sponsored pediatric phase I trial, one child developed T-cell lymphoblastic lymphoma (T-LBL) after receiving tazemetostat for 14 months. As of 1 May 2018, this is the only case of T-cell lymphoma that has occurred out of a total of 79 children enrolled in tazemetostat clinical trials. In addition, there have been no cases of T-LBL or related T-acute lymphoblastic leukemia (T-ALL) in the 702 adult patients treated across multiple studies conducted in different types of cancer. All tazemetostat trials were temporarily halted while a risk assessment was conducted. Pediatric patients were noted to have higher tazemetostat exposures than had been seen in adults (specifically high AUC (0-24h)). In the company's assessment, the risk for T-LBL/T-ALL in tazemetostat clinical trials appears to be largely concentrated in pediatric patients based on:

1) The known epidemiology / pathophysiology of T-LBL/ALL.
2) Age-related intact and active thymus (thymic involution increases over time with reduced risk with increasing age)
3) Higher AUC (0-24h) exposures in pediatric patients

Based on these data, amendment 3B will adjust the dosing for new APEC1621C patients based on site of disease (CNS vs. non-CNS) and will allow for increased monitoring of T-LBL/ALL(see Section 5 and Section 6.2). Based on the pediatric phase I trial of lower Tazemetostat exposures in children receiving 520mg/m2, and one patient in this cohort receiving prolonged benefit, 520mg/m2 was chosen for patients not requiring higher, CNS-penetrant doses to limit exposures and potential secondary malignancies.

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 record 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.

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

3.1 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 APEC1621C 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 APEC1621C.

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
Email: CTSURegulatory@ctsu.coccg.org (for regulatory document submission only)
Fax: 215-569-0206
Mail: CTSU Regulatory Office

1818 Market Street, Suite 1100
Philadelphia, PA 19103

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.**

Should the Epizyme-sponsored Phase 1/2 protocol for patients with recurrent or refractory malignant rhabdoid tumors, including CNS ATRT and other INI-deficient tumors and synovial sarcoma (EZH-102, NCT02601937) be open, matching patients may be preferentially referred for enrollment on that study if found eligible.

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 APEC1621C 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 tazemetostat should be placed with CTEP after enrollment and treatment assignment to APEC1621C with consideration for timing of processing and shipping to ensure receipt of drug supply prior to start of protocol therapy.

3.7 Institutional Pathology Report

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

3.8 Dose Assignment

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

4.0 PATIENT ELIGIBILITY

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

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

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

4.1 Inclusion Criteria

4.1.1 APEC1621SC: Patient must have enrolled onto APEC1621SC and must have been given a treatment assignment to MATCH to APEC1621C based on the presence of an actionable mutation as outlined in Appendix VII.

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

4.1.3 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.

4.1.4 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.

4.1.5 Prior Therapy

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

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

b. Anti-cancer agents not known to be myelosuppressive (e.g. not associated with reduced platelet or ANC counts): ≥ 7 days after the last dose of agent.

See https://www.cogmembers.org/site/disc/devtherapeutics/default.aspx for commercial and Phase 1 investigational agent classifications. For agents not listed, the duration of this interval must be discussed with the study chair and the study-assigned Research Coordinator

prior to enrollment.

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

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

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

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

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

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

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

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

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

k. Patients must not have had prior exposure to tazemetostat or other inhibitor(s) of EZH2.

4.1.6 Organ Function Requirements:

4.1.6.1 Adequate Bone Marrow Function Defined as:

a. For patients with solid tumors without known bone marrow

involvement:
- Peripheral absolute neutrophil count (ANC) ≥ 1000/mm^3
- Platelet count ≥ 100,000/mm^3 (transfusion independent, defined as not receiving platelet transfusions for at least 7 days prior to enrollment)
- Hemoglobin ≥ 8.0 g/dL at baseline (may receive RBC transfusions) (See Section 4.2.6)

b. Patients with known bone marrow metastatic disease will be eligible for study provided they meet the blood counts in 4.1.6.1.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.

4.1.6.2 Adequate Renal Function Defined as:
- Creatinine clearance or radioisotope GFR ≥ 70 ml/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.

4.1.6.3 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.

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

4.1.6.5 Adequate Neurologic Function Defined as:
- Patients with seizure disorder may be enrolled if on anticonvulsants and well controlled.
- Nervous system disorders (CTCAE v5.0) resulting from prior therapy must be ≤ Grade 2, with the exception of decreased tendon reflex (DTR). Any grade of DTR is eligible.

4.1.6.6 Adequate Coagulation Defined as:
- INR ≤ 1.5

- For subjects with CNS involvement (primary tumor or metastatic disease): Subjects must not have any active bleeding, or new intratumoral hemorrhage of more than punctate size on screening MRI or known bleeding diathesis or treatment with anti-platelet or anti-thrombotic agents.

4.1.7 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. Males or females of reproductive potential may not participate unless they have agreed to use an effective contraceptive method for the duration of study treatment. Female subjects of childbearing potential should agree to remain abstinent or use adequate contraceptive methods for 30 days after the last dose of tazemetostat. Male subjects should agree to remain abstinent or use adequate contraceptive methods, and agree to refrain from donating sperm, and for 90 days after the last dose of tazemetostat.

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 strong inhibitors of CYP3A4 are not eligible. Strong inducers or inhibitors of CYP3A4 are prohibited from 14 days prior to the first dose of tazemetostat to the end of the study. See Appendix II for a list of agents. Note: Dexamethasone for CNS tumors or metastases, on a stable dose, is

allowed.

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

4.2.4 On CBC differential, patients must not have any significant morphologic abnormalities concerning for MPN/MDS or T- ALL.

4.2.5 Patients must not have thrombocytopenia, neutropenia, or anemia of Grade ≥ 3 (per CTCAE 5.0 criteria) or any prior history of myeloid malignancies, including myelodysplastic syndrome (MDS). (See Section 4.1.6.1 for hemoglobin eligibility criteria.)

4.2.6 Patients with a history of prior history of T-LBL/T-ALL.

4.2.7 Patients with any prior history of myeloid malignancies, including myelodysplastic syndrome (MDS).

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

4.2.9 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

For patient(s) enrolled pre-amendment #3B:

Day 1-28	Day 28
Tazemetostat 1200 mg/m^2/dose (Orally, twice daily)	**Evaluation**

For patient(s) enrolled post-amendment #3B:

	Day 1-28	Day 28
Patients without CNS involvement	**Tazemetostat 520mg/m^2/dose** (Orally, twice daily)	Evaluation
Patients with CNS involvement	**Tazemetostat 1200 mg/m^2/dose** (Orally, twice daily)	Evaluation

Tazemetostat will be administered as a liquid suspension at a dose of 520 mg/m^2/dose orally, twice daily (for patients without any CNS involvement); or 1200 mg/m^2/dose orally twice daily (for patients with CNS involvement) (based on disease location per above table); without regard to meals with no less than 8 hours between each dose. For patient(s) enrolled pre-amendment #3B Tazemetostat will be administered orally at the MTD and recommended phase 2 dose (RP2D) of 1200 mg/m^2/dose BID. If vomiting occurs after taking oral suspension formulation, the dose should NOT be repeated and the next dose should be administered at the regularly scheduled time. See Section 9.1.6 and Appendix

IV for additional oral suspension administration and preparation instructions. See Appendix V for treatment roadmap.

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 2 years (maximum 26 cycles).

All patients with CNS involvement enrolled after AMD#3 will be treated at the established pediatric MTD/RP2D which is 1200 mg/m^2/dose BID. All patients without any CNS involvement patients enrolled after AMD#3 will be treated at the lower starting dose of 520mg/m2/dose BID. (See Section 6.1 and Section 6.2).

Drug doses should be adjusted based on the BSA calculated from height and weight measured within 7 days prior to the beginning of each cycle, and according to the dosing nomogram. Calculated dosing volumes of tazemetostat oral suspension should be rounded to the nearest 1 mL (30 mg) for the actual deliverable dose (Appendix IV). Patients who experience dose-limiting toxicity should have their dose reduced by 25% so that patients receive 75% of the original administered dose.

5.1.1 Therapy Delivery Map

See Appendix V for APEC1621C 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 and Section 10.1.

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 v5 can be downloaded from the CTEP website (http://ctep.cancer.gov). Any suspected or confirmed dose-limiting toxicity should be reported immediately (within 24 hours) to the Study Chair.

5.4 Definition of Dose-Limiting Toxicity (DLT)

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

5.4.1 Non-Hematological Dose-Limiting Toxicity

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

- Grade 3 nausea and vomiting of less < 3 days duration

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

- Toxicity due to bromide elevation/neurological toxicity that requires a dose reduction per Section 6.3 will be considered dose-limiting
- Any Grade 2 non-hematological toxicity that persists for ≥ 7 days and is considered sufficiently medically significant or sufficiently intolerable by patients that it requires treatment interruption.
- Note: Allergic reactions that necessitate discontinuation of study drug will not be considered a dose-limiting toxicity.

5.4.2 Hematological dose limiting toxicity

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 two separate days, within a 7 day period
- Grade 3 thrombocytopenia with clinically significant bleeding
- Neutropenia or thrombocytopenia that causes a delay of > 14 days between treatment cycles" (e.g. platelets <100K or ANC<1000).

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 Modification for Patients Newly Diagnosed with T-LBL/T-ALL

- If a new case of T-LBL/T-ALL occurs in patients at the dose level > 520 mg/m^2 then the patient will be discontinued from treatment, a case assessment will be conducted to better understand the event, and enrollment will be suspended.

- If a new case of T-LBL/T-ALL occurs at ≤ 520 mg/m^2 or less than 1 year on study treatment, the patient will be discontinued from treatment and a case assessment will be conducted to better understand the event. Enrollment will be suspended and risk/benefit of the drug will be assessed to decide whether to continue the study or not.

6.2 Dose Modifications for Hematological Toxicity

6.2.1 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 (See Appendix IV). Patients who experience dose-limiting toxicity should have their dose reduced by 25% so that patients receive 75% of the original administered dose (Patients enrolled at 1200mg/m^2/dose should dose reduce to 900 mg/m^2/dose and patients enrolled at 520mg/m^2/dose should dose reduce to 390 mg/m^2/dose) 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 parameters within 14 days of drug discontinuation, the patient must be removed from protocol therapy.

6.2.3 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.

6.3 Dose Modifications for Non-Hematological Toxicity

6.3.1 If a patient experiences non-hematological dose-limiting toxicity as defined in Section 5.4.1, the treatment will be held. When the toxicity resolves to meet eligibility parameters or baseline within 14 days of drug discontinuation, the patient may resume treatment at a reduced dose (See Appendix IV). Patients who experience dose-limiting toxicity should have their dose reduced by 25% so that patients receive 75% of the original administered dose, patients enrolled at 1200mg/m^2/dose should dose reduce to 900 mg/m^2/dose and patients enrolled at 520mg/m^2/dose should dose reduce to 390mg/m^2/dose.. Doses reduced for toxicity will not be re-escalated, even if there is minimal or no toxicity with the reduced dose.

6.3.2 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.

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

6.4 Dose Modifications for Toxicities Related to Bromide

6.4.1 For toxicities determined to be related to bromide, the following table should be used for dose modifications.

Bromide Level	**Neurologic Findings[a]**	**Dose Adjustment[b,c]**
10-50 mg/dL	None	Continue
10-50 mg/dL	Grade 1	Discuss with Study Chair possibility of dose reduction
10-50 mg/dL	Grade 2	Reduce by one dose reduction of at least 25% of starting dose. • 1200mg/m^2/dose→decrease to 900 mg/m^2/dose • 520mg/m^2/dose→decrease to 390mg/m^2/dose

Bromide Level	**Neurologic Findings[a]**	**Dose Adjustment[b,c]**

10-50 mg/dL	Grade 3 and above	• Interrupt dosing and discuss with Study Chair increased frequency of bromide monitoring and potential for restarting treatment
		• Treatment may be restarted if approved by the Study Chair by one dose reduction of at least 25% of starting dose.
		  • 1200mg/m^2/dose→decrease to 900 mg/m^2/dose
		  • 520mg/m^2/dose→decrease to 390mg/m^2/dose

>50-75 mg/dL	None	Continue
>50-75 mg/dL	Grade 1	Discuss with Study Chair possibility of dose reduction

>50-75 mg/dL	Grade 2 and above	• Interrupt dosing and discuss with Study Chair increased frequency of bromide monitoring and potential for restarting treatment
		• Treatment may be restarted if approved by the Study Chair Reduce by one dose reduction of at least 25% of starting dose.
		  • 1200mg/m^2/dose→decrease to 900 mg/m^2/dose
		  • 520mg/m^2/dose→decrease to 390mg/m^2/dose

>50-75 mg/dL	Grade 3 and above	• Interrupt dosing and discuss with Study Chair increased frequency of bromide monitoring and potential for restarting treatment
		• Treatment may be restarted if approved by the Study Chair Reduce by one dose reduction of at least 25% of starting dose.
		  • 1200mg/m^2/dose→decrease to 900 mg/m^2/dose
		  • 520mg/m^2/dose→decrease to 390mg/m^2/dose

>75 mg/dL	None	• Discuss with Study Chair increased frequency of bromide monitoring and potential need for dose reduction. • Reduce by one dose reduction of at least 25% of starting dose, if deemed appropriate.
>75 mg/dL	Grade 1	• Discuss with Study Chair increased frequency of bromide monitoring and potential need for dose interruption and dose reduction by one dose reduction of at least 25% of starting dose.

>75 mg/dL	Grade 2	• Interrupt dosing and discuss with Study Chair increased frequency of bromide monitoring and potential for restarting treatment.
		• Treatment may be restarted if approved by the Study Chair
		• Reduce by one dose reduction of at least 25% of starting dose.
		  • 1200mg/m^2/dose→decrease to 900 mg/m^2/dose
		  • 520mg/m^2/dose→decrease to 390mg/m^2/dose

>75 mg/dL	Grade 3 and above	• Interrupt dosing and discuss with Study Chair increased frequency of bromide monitoring and potential for restarting treatment

Bromide Level	Neurologic Findings[a]	Dose Adjustment[b,c]
		• Treatment may be restarted if approved by the Study Chair Reduce by one dose reduction of at least 25% of starting dose. • 1200mg/m^2/dose→decrease to 900 mg/m^2/dose • 520mg/m^2/dose→decrease to 390mg/m^2/dose

a. Neurologic signs or symptoms not related to disease under study or concomitant medication
b. If the Investigator believes a dose modification or interruption is warranted but not specified in the table above, the Study Chair should be contacted to discuss the appropriate treatment plan.
c. If more than 1 dose modification is required, contact Study Chair to discuss risk: benefit ratio of continuing on study.

7.0 SUPPORTIVE CARE AND OTHER CONCOMITANT THERAPY

7.1 Concurrent Anticancer Therapy

Concurrent cancer therapy, including chemotherapy, radiation therapy, immunotherapy, or biologic therapy may NOT be administered to patients receiving study drug. If these treatments are administered the patient will be removed from protocol therapy.

7.2 Investigational Agents

No other investigational agents may be given while the patient is on study.

7.3 Supportive Care

Appropriate antibiotics, blood products, antiemetics, fluids, electrolytes and general supportive care are to be used as necessary. Please see COG Supportive Care guidelines at https://childrensoncologygroup.org/index.php/cog-supportive-care-guidelines. See Section 7.5 for drugs that should not be used concomitantly due to potential interactions with tazemetostat.

7.4 Growth Factors

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

7.5 Concomitant Medications

7.5.1 CYP3A4/5 inhibitors or inducers: Strong CYP3A4/5 inhibitors or inducers are prohibited from 14 days prior to the first dose of tazemetostat to the end of the study (See Appendix II for list of agents). Note: Dexamethasone for CNS tumors or metastases, on a stable dose, is allowed.

7.5.2 Strong inhibitors and inducers of CYP2C8, CYP2D6, and P-glycoprotein (P-gp) should be used with caution.

7.5.3 Medications that are sensitive or narrow therapeutic range substrates of CYP3A, CYP2C8, CYP2C9, CYP2C19, CYP2D6 should be avoided if possible. Other substrates of CYP2C8, 2C9, 2C19, 2D6, 3A, P-gp, OATP1B1, OATP1B3, OAT3, MATE1, and MATE2K should be used with caution.

7.5.4 Medications that are sensitive or narrow therapeutic range substrates of P-gp, BCRP, CYP3A, CYP2C8, CYP2C9, CYP2C19, CYP2D6, or have a narrow therapeutic range should be used with caution.

7.5.5 No grapefruit juice, Seville oranges, or grapefruit can be consumed while on tazemetostat.

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		X
Height, weight, BSA	X		X
Performance Status	X		
Pregnancy Test[1]	X		
CBC, differential[10], platelets	X	Weekly[2,3]	X[2,3]
Urinalysis	X		
Electrolytes including Ca^{++}, PO_4, Mg^{++}	X	Weekly	X
Creatinine, ALT, bilirubin	X	Weekly	X
Albumin	X		X
Bromide Level	X		X
INR	X		
EKG	X		Every 3 cycles
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		
Plain radiograph tibial growth plate (Bone X-Ray Tests)[9]	X		Prior to cycles 2, 5 and every 6 months
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

^ 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.

3 If patients develop Grade 3 or greater thrombocytopenia then CBCs should be checked every 3 to 4 days until recovery to Grade 3, 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 weekly during Cycle 1 and then 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, 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. 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.

10. Patients should get a manual differential if automated differential demonstrates blasts

8.2 Monitoring for Specific Toxicities

8.2.1 Growth Plate Toxicities:

Patients will have a plain AP radiograph of a single proximal tibial growth plate (bone X-ray tests) 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. MRI should be performed without contrast.
- Patients with knee MRI changes should be managed in an individualized manner. Decisions regarding continuation of tazemetostat 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 tazemetostat. 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 tazemetostat 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. The COG operations center and IROC are available to assist with any queries regarding the corresponding radiology reports which should be included when the scans are submitted

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

Digital RT Data Submission Using TRIAD (if TRIAD is available at your site):
TRIAD is the American College of Radiology's (ACR) image exchange

application. TRIAD provides sites participating in clinical trials a secure method to transmit DICOM and DICOM RT files and other digital objects, such as reports. TRIAD de-identifies and validates the images as they are transferred.

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

TRIAD Installations:

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

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

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

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

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

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

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

8.4 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. Two additional samples (optional) will be collected into Streck Cell-Free DNA BCT tubes at the timepoints:

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

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

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

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

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

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

- Keep patient's arm in the downward position during the collection procedure.
- Hold the tube with the stopper in the uppermost position so that the tube contents do not touch the stopper or the end of the needle during sample collection.
- Release tourniquet once blood starts to flow in the tube, or within 2 minutes of application.
- Fill tube completely.
- Remove tube from adapter and immediately mix by gentle inversion 8 to 10 times. Inadequate or delayed mixing may result in inaccurate test results.
- Store blood in 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 (APEC1621C), 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.

Ship specimens to the following address:

Biopathology Center
Nationwide Children's Hospital
Protocol APEC1621C- 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.

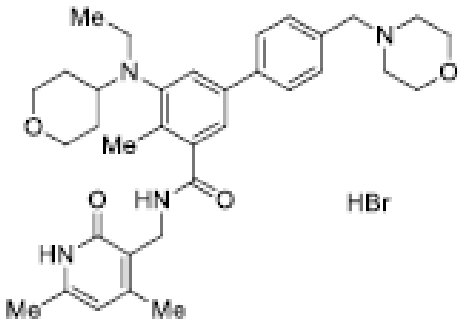
9.0 AGENT INFORMATION

9.1 Tazemetostat

(EPZ-6438, E7438) NSC# 791066

9.1.1 Structure and molecular weight

The chemical structure of tazemetostat drug substance is shown below:



Molecular Formula:
$C_{34}H_{45}BrN_4O_4$ (Hydrobromide salt)
$C_{34}H_{44}N_4O_4$ (Free base)

Molecular Weight:
653.65 (Hydrobromide salt)
572.74 (Free base)

9.1.2 Supplied by

Supplied by: Epizyme supplies and PMB, CTEP, DCTD, NCI distributes tazemetostat.

9.1.3 Formulation

Tazemetostat will be supplied as powder for oral suspension.
Powder for oral suspension is supplied in 2-gram and 7-gram high-density polyethylene bottles containing only drug substance (no excipients). Reconstitute tazemetostat powder with Ora-sweet®, which will be provided by the site, to produce tazemetostat 30 mg/mL oral suspension (based on free base content). Once reconstituted with Ora- sweet®, the suspension contains purified water, sucrose, glycerin, sorbitol, citric acid, sodium phosphate, methylparaben, potassium sorbate, and citrus-berry flavoring. Once reconstituted, the suspension is pink in color.

- **A site-supplied a press-in bottle adapter is required for use with an oral syringe for dosing purposes.**

Oral Suspension Preparation Instructions [Refer to Appendix IV for the Tazemetostat Oral Suspension Preparation Worksheet and Guidance Table]**:**

1) The oral suspension should be prepared in a biologic safety cabinet, personal protective equipment (PPE) should be worn during preparation as per institutional guidelines.

2) Determine the total number of tazemetostat powder for oral suspension bottles required to prepare 14 days of dosing (including overfill per institutional guidelines), while using a combination of bottle sizes to minimize waste.
3) Determine the amount of Ora-Sweet® required: 32.5 mL is needed per gram of tazemetostat. Each 2 gram bottle requires 65 mL Ora-Sweet® and each 7 gram bottle requires 227.5 mL Ora-Sweet®.
4) Select the appropriate size and number of empty medication bottles required. Choose bottles that are large enough so that each bottle can be filled to 40-80% of capacity to ensure adequate mixing. The medication bottles should be light protective, HDPE, PETE, or glass bottle with a child-resistant, liquid-tight closure. Note: Use of a funnel is helpful to transfer tazemetostat powder to the bottle containing Ora-Sweet
5) Add the required amount of Ora-Sweet® to each empty medication bottle.
6) Transfer the appropriate amount of tazemetostat powder for oral suspension to the corresponding medication bottle containing Ora-Sweet®.
7) Tightly seal with cap and shake the bottle vigorously for 1 minute.
8) Allow the bottle to rest for approximately 5 minutes then re-shake the bottle vigorously for an additional 1 minute.
9) Remove the bottle cap and inspect visually for any unwetted powder. If present, repeat steps 7-8 above.
10) Apply appropriate label(s) as required by law/institution.
11) The final concentration is 30 mg/mL.
12) Assign a 21-day expiration from preparation date and store the bottles at refrigerated temperature between 2-8 °C (36-46 °F) and protect from light.
13) Instruct the patient or caregiver to shake the bottle for 1 minute prior to dosing. Avoid vigorous shaking due to foaming and allow sufficient time for any bubbles to dissipate prior to measuring the dose. **If multiple bottles are dispensed, daily shaking of all bottles is required to ensure the suspension stays properly suspended.**

9.1.4 Storage

Powder for oral suspension: Do not store above 25°C (77°F). Protect from light. Once oral suspension is prepared, store refrigerated between 2-8 °C (36-46 °F) and protect from light. Brief excursion (less than 4 hours) up to 30°C is allowable for transfer from the clinic to home, but bottles must be immediately refrigerated upon arrival. A cold pack may be provided to the patient as required.

If a storage temperature excursion is identified, promptly return tazemetostat unreconstituted powder for oral suspension to below 25°C (77°F) and prepared oral suspension to 2-8°C (36-46 °F) 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. Powder for oral suspension is stable for 21 days following reconstitution under refrigerated storage conditions.

9.1.6 Administration

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

Tazemetostat will be given orally twice daily without regard to meals. The powder for suspension must be reconstituted prior to administration. Doses must be taken twice per day with no less than 8 hours between each dose. If vomiting occurs after taking oral suspension formulation, the dose should NOT be repeated and the next dose should be administered at the regularly scheduled time.

The oral suspension should be given by mouth immediately after the dose is prepared in the oral syringe. Patients should drink additional water after administration (about 4 ounces). For feeding tube dosing, administer directly into the feeding tube with the syringe. Rinsing with 10 mL of water for NG tubes and 40 mL of water for G-tubes is recommended.

9.1.7 Potential Drug Interactions

In vitro, tazemetostat is metabolized primarily by CYP3A and to a lesser extent by CYP2C8 and CYP2D6. It is a P-gp substrate but not a substrate of BCRP, OAT1B1, OAT1B3, OAT1, OAT3, OCT2, and MATE1. Therefore, treatment with strong inhibitors or strong inducers of CYP3A are prohibited from 14 days prior to the first dose of tazemetostat to the end of the study. Strong inhibitors and inducers of CYP2C8, 2D6, and P-gp should be used with caution.

In vitro, tazemetostat inhibits CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP3A, P-gp, OATP1B1, OATP1B3, OAT3, MATE1, and MATE2K. . Tazemetostat also induces CYP3A4 and is a weak inducer of CYP1A, CYP2B6, and CYP2C9. Medications that are sensitive or narrow therapeutic range substrates of CYP3A, CYP2C8, CYP2C9, CYP2C19, or CYP2D6 should be avoided if possible. Other substrates of CYP2C8, 2C9, 2C19, 2D6, 3A, P-gp, OATP1B1, OATP1B3, OAT3, MATE1, and MATE2K should be used with caution.

No grapefruit juice, Seville oranges, or grapefruit can be consumed while on tazemetostat.

9.1.8 Patient care implications:

Prolonged exposure to sunlight should be avoided during treatment with tazemetostat. Patients should wear protective clothing, sunscreen, and avoid tanning beds. Female subjects of childbearing potential should agree to remain abstinent or use adequate contraceptive methods for 30 days after the last dose of tazemetostat. Female subjects that use hormonal contraceptives should also use an additional barrier method. Male subjects should agree to remain abstinent or use adequate contraceptive methods, and agree to refrain from donating sperm for 90 days after the last dose of tazemetostat.

9.1.9 Tazemetostat Toxicities

Comprehensive Adverse Events and Potential Risks list (CAEPR)
for
Tazemetostat (NSC 791066)

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 815 patients. Below is the CAEPR for Tazemetostat.

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 2.4, March 30, 2021[1]

Adverse Events with Possible Relationship to Tazemetostat (CTCAE 5.0 Term) [n= 815]			**Specific Protocol Exceptions to Expedited Reporting (SPEER)**
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
	Anemia		
GASTROINTESTINAL DISORDERS			
	Constipation		
	Diarrhea		
	Nausea		***Nausea (Gr 2)***
	Vomiting		***Vomiting (Gr 2)***
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
	Fatigue		***Fatigue (Gr 2)***
INVESTIGATIONS			
	Neutrophil count decreased		
	Platelet count decreased		***Platelet count decreased (Gr 2)***
	Weight loss		
METABOLISM AND NUTRITION DISORDERS			
	Anorexia		
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)			
		Leukemia secondary to oncology chemotherapy	
		Myelodysplastic syndrome	
		Treatment related secondary malignancy[2]	
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
		Cough	
		Dyspnea	
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
	Alopecia		
	Dry skin		
		Photosensitivity	

[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] Treatment related secondary malignancies includes Peripheral T-cell lymphoma (PTCL), T-cell lymphoblastic lymphoma (T-LBL), and B-cell acute lymphoblastic leukemia (B-ALL). It may be worth noting that the adult patient observed with B-ALL may be due to an underlying Diffuse large B-cell lymphoma (DLBCL).

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

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Blood and lymphatic system disorders - Other (pancytopenia); Febrile neutropenia
CARDIAC DISORDERS - Chest pain - cardiac; Left ventricular systolic dysfunction
EAR AND LABYRINTH DISORDERS - Vertigo
ENDOCRINE DISORDERS - Hypothyroidism
EYE DISORDERS - Dry eye; Periorbital edema; Vision decreased; Watering eyes
GASTROINTESTINAL DISORDERS - Abdominal distension; Abdominal pain; Dry mouth; Dyspepsia; Dysphagia; Flatulence; Gastric perforation; Gastrointestinal disorders - Other (defecation urgency); Hemorrhoids; Mucositis oral; Rectal hemorrhage; Toothache
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Chills; Edema limbs; Fever; Flu like symptoms; General disorders and administration site conditions - Other (early satiety); General disorders and administration site conditions - Other (general physical health deterioration); Localized edema; Malaise; Non-cardiac chest pain
HEPATOBILIARY DISORDERS - Gallbladder obstruction; Hepatobiliary disorders - Other (hepatocellular injury)
INFECTIONS AND INFESTATIONS - Conjunctivitis; Device related infection; Esophageal infection; Infections and infestations - Other (lower respiratory tract infection); Lung infection; Pharyngitis; Sepsis; Sinusitis; Skin infection; Soft tissue infection; Upper respiratory infection; Urinary tract infection
INJURY, POISONING AND PROCEDURAL COMPLICATIONS - Wound dehiscence
INVESTIGATIONS - Alanine aminotransferase increased; Aspartate aminotransferase increased; Blood bilirubin increased; CPK increased; Electrocardiogram QT corrected interval prolonged; Investigations - Other (c-reactive protein increased); Lymphocyte count decreased; Serum amylase increased; White blood cell decreased
METABOLISM AND NUTRITION DISORDERS - Dehydration; Hyperglycemia; Hyperkalemia; Hyperlipidemia; Hypertriglyceridemia; Hypokalemia; Hyponatremia; Hypophosphatemia; Metabolism and nutrition disorders - Other (diabetic metabolic decompensation); Metabolism and nutrition disorders - Other (polydipsia)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Arthralgia; Back pain; Muscle cramp; Myalgia; Neck pain; Pain in extremity
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS) - Tumor hemorrhage; Tumor pain
NERVOUS SYSTEM DISORDERS - Dizziness; Dysesthesia; Dysgeusia; Dysphasia; Headache; Hydrocephalus; Lethargy; Memory impairment; Nervous system disorders - Other (vocal cord paralysis); Paresthesia; Peripheral motor neuropathy; Peripheral sensory neuropathy; Radiculitis; Seizure
PSYCHIATRIC DISORDERS - Anxiety; Depression; Hallucinations; Insomnia; Psychiatric disorders - Other (mood swings)
RENAL AND URINARY DISORDERS - Proteinuria; Renal and urinary disorders - Other (polyuria); Urinary frequency
REPRODUCTIVE SYSTEM AND BREAST DISORDERS - Reproductive system and breast disorders - Other (vulvovaginal rash)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Bronchopulmonary hemorrhage; Epistaxis; Hypoxia; Nasal congestion; Oropharyngeal pain; Pleural effusion; Pulmonary edema; Respiratory failure; Respiratory, thoracic and mediastinal disorders - Other (tachypnea)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Bullous dermatitis; Hair color changes; Hair texture abnormal; Hirsutism; Hyperhidrosis; Hypertrichosis; Nail ridging; Pruritus; Purpura; Rash acneiform; Rash maculo-papular; Skin and subcutaneous tissue disorders - Other (psoriasis); Skin hyperpigmentation; Urticaria
VASCULAR DISORDERS - Hot flashes; Hypertension; Superior vena cava syndrome; Thromboembolic event; Vascular disorders - Other (peripheral venous disease)

Note: Tazemetostat 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.

Note: AESI: Based on preclinical findings in toxicology studies, FDA has requested the following Adverse Events of Special Interest (AESI) to be reported in an expedited manner: 1) T-cell lymphoma; and 2) abnormal bone growth. It should be noted that abnormal bone growth has not been observed in clinical trials of tazemetostat.

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. Study agent must be ordered after enrollment and treatment assignment to APEC1621C 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 field 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, 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

APEC1621C will require a minimum of 20 evaluable patients and a maximum of 49 patients, allowing for 15% inevaluability. Assuming an enrollment rate of 4-9 biomarker positive patients per year, the primary cohort of this subprotocol is expected to be completed within 2.7-6 years.

11.2 Dosing Considerations

Please see Section 5.1 for a specific discussion of the dosing of tazemetostat to be used in this study, based on site of disease.

11.3 Study Design

The primary cohort will employ a single stage A'Hern designs of N=20. Tazemetostat 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%

Per amendment 3B, Tazemetostat will be administered at a dose of 520 mg/m^2/dose BID for patients without any CNS involvement; or 1200 mg/m^2/dose BID for patients with CNS involvement. The response will be examined in the combined primary cohort consisting of patients with or without CNS involvement. Patients who enrolled pre-amendment #3B treated with at 1200 mg/m^2/dose BID and meet evaluation criteria will also be counted in the evaluation.

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:

APEC1621C 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 tazemetostat. Using an A'Hern design[8] 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.

If at any time, there is one occurrence of secondary T-cell lymphomas in patients exposed to tazemetostat, we will suspend the accrual and consider dose, schedule

or duration of treatment modification. The COG DSMC will be notified and CTEP consulted regarding the next steps to take with respect to the protocol.

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/types.

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

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

11.5 Evaluability for Response

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

11.6 Evaluability for Toxicity

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

11.7 Progression free survival (PFS)

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

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

11.8 Correlative Studies

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

11.9 Gender and Minority Accrual Estimates

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

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

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

12.0 EVALUATION CRITERIA

12.1 Common Terminology Criteria for Adverse Events (CTCAE)

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

12.2 Progression-Free Survival

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

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

12.3 Response Criteria for Patients with Solid Tumors

See the table in Section 8.0 for the schedule of tumor evaluations. Eligible patients must have measurable disease present at baseline and have had their disease re-evaluated after 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.[10]

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-	No	SD	documented at least once ≥

	CR/Non-PD/not evaluated			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

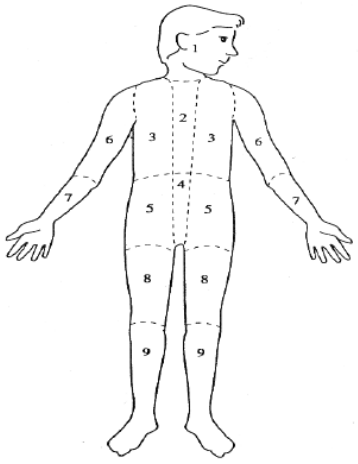
12.5.3 The response of MIBG lesions will be assessed on central review using the Curie scale14 as outlined below. Central review responses will be used to assess efficacy for study endpoint. See Section 8.2 for details on transferring images to the Imaging Research Center.

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[10], with modification from the Lugano classification.[11]

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)[11]

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[11]

Complete Response (CR): Regress to normal

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

Stable Disease (SD): No increase consistent with progression

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

New or recurrent splenomegaly

12.9 Best Response

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

12.9.1 Evaluation of Best Overall Response

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

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

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

12.9.2 Duration of Response

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

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

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

13.0 ADVERSE EVENT REPORTING REQUIREMENTS

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

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

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

13.1 Expedited Reporting Requirements – Serious Adverse Events (SAEs)

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

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

13.1.1 Reporting Requirements - Investigator Responsibility

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

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

13.1.2 CTEP-AERS Expedited Reporting Methods

Expedited AE reporting for this study must only use CTEP-AERS (Adverse Event Expedited Reporting System), accessed via the CTEP home page https://ctepcore.nci.nih.gov/ctepaers/pages/task

Send supporting documentation to the NCI by fax (fax# 301-897-7404) and by email to both COGCAdEERS@childrensoncologygroup.org and to the APEC16-21C 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. The descriptions and grading scales found in the current version of the CTCAE v5.0 will be used for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE v5.0. A copy of the CTCAE v5.0 can be downloaded from the CTEP website (http://ctep.cancer.gov).

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

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

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

- Any medical event equivalent to CTCAE v5 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	Abdominal Pain
GASTROINTESTINAL DISORDERS	Constipation
GASTROINTESTINAL DISORDERS	Diarrhea
GASTROINTESTINAL DISORDERS	Vomiting
METABOLISM AND NUTRITION DISORDERS	Anorexia
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	Muscle Cramp
NERVOUS SYSTEM DISORDERS	Dysgeusia
NERVOUS SYSTEM DISORDERS	Headache
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	Photosensitivity

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

13.4 Definition of Onset and Resolution of Adverse Events

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

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

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

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

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

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

13.5 Other Recipients of Adverse Event Reports

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

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

13.6 Specific Examples for Expedited Reporting

13.6.1 Reportable Categories of Death

- Death attributable to a CTCAE v5.0 term.
- Death Neonatal: A disorder characterized by "Newborn deaths occurring during the first 28 days after birth."
- Sudden Death NOS: A sudden (defined as instant or within one hour of the onset of symptoms) or an unobserved cessation of life that cannot be attributed to a CTCAE v5.0 term associated with Grade 5.
- Death NOS: A cessation of life that cannot be attributed to a CTCAE v5.0 term associated with Grade 5.
- Death due to progressive disease should be reported as ***Grade 5 "Disease Progression"*** under the system organ class (SOC) of "General Disorders and Administration Site Conditions." Evidence that the death was a manifestation of underlying disease (*e.g.*, radiological changes suggesting tumor growth or progression: clinical deterioration associated with a disease 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. **The occurrence of T-cell lymphoma should be reported via CTEP-AERS.**

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: https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/PregnancyReportFormUpdated.pdf, needs to be completed and faxed along with any additional medical information to (301)-897-7404. The potential risk of exposure of the fetus to the investigational agent should be documented in the "Description of Event" section of the CTEP-AERS report.

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

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

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

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

Death Neonatal
Neonatal death, defined in CTCAE v5.0 as ***Newborn deaths occurring during the***

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

14.0 RECORDS, REPORTING, AND DATA AND SAFETY MONITORING PLAN

14.1 Categories of Research Records

Research records for this study can be divided into three categories

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

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

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

See separate CRF Packet, which includes submission schedule.

14.2 CDUS

This study will be monitored by the Clinical Data Update System (CDUS) version 3.0. Cumulative protocol- and patient-specific CDUS data will be submitted quarterly to CTEP by electronic means. Reports are due January 31, April 30, July 31 and October 31. 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.

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7. 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.,
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9. Agresti A, Coull BA: Approximate Is Better than "Exact" for Interval Estimation of Binomial Proportions. The American Statistician 52:119-126, 1998
10. Sandlund JT, Guillerman RP, Perkins SL, et al: International Pediatric Non-Hodgkin Lymphoma Response Criteria. J Clin Oncol 33:2106-11, 2015
11. Cheson BD, Fisher RI, Barrington SF, et al: Recommendations for initial evaluation, staging, and response assessment of Hodgkin and non-Hodgkin lymphoma: the Lugano classification. J Clin Oncol 32:3059-68, 2014

APPENDIX I: PERFORMANCE STATUS SCALES/SCORES

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

APPENDIX II: CYP3A4 SUBSTRATES, INDUCERS AND INHIBITORS

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

CYP3A4 substrates	Strong Inhibitors[1]	Moderate Inhibitors	Strong Inducers	Moderate Inducers
abemaciclib acalabrutinib[5] alfentanil[4,5] alprazolam[5] amiodarone[4] amlodipine aprepitant/fosaprepitant atorvastatin avanafil[5] axitinib bortezomib bosutinib[5] brexpiprazole brigatinib budesonide[5] buspirone[5] cabozantinib calcium channel blockers cisapride citalopram/escitalopram cobimetinib[5] colchicine[5] conivaptan[5] copanlisib crizotinib cyclosporine[4] dabrafenib dapsone darifenacin[5] darunavir[5] dasatinib[5] dexamethasone[2] diazepam dihydroergotamine docetaxel doxorubicin dronedarone[5] ebastine[5] eletriptan[5] eliglustat[5] eplerenone[5] ergotamine[4] erlotinib estrogens etoposide everolimus[5] felodipine[5] fentanyl[4]	atazanavir boceprevir clarithromycin ceritinib cobicistat danoprevir/ritonavir darunavir delavirdine elvitegravir/ritonavir grapefruit[3] grapefruit juice[3] idelalisib indinavir/ritonavir itraconazole ketoconazole lopinavir/ritonavir nefazodone nelfinavir paritaprevir/ritonavir/ ombitasvir +/- dasabuvir posaconazole ritonavir saquinavir telaprevir telithromycin tipranavir/ritonavir tucatinib voriconazole	aprepitant conivaptan crizotinib diltiazem dronedarone duvelisib erythromycin fedratinib fluconazole fosamprenavir fosnetupitant grapefruit[3] grapefruit juice[3] imatinib isavuconazole lefamulin letermovir mifepristone netupitant nilotinib ribociclib verapamil	apalutamide barbiturates carbamazepine enzalutamide fosphenytoin lumacaftor/ ivacaftor mitotane phenobarbital phenytoin primidone rifampin St. John's wort	bosentan cenobamate dabrafenib efavirenz eslicarbazepine etravirine lorlatinib modafinil nafcillin rifabutin rifapentin

14.

gefitinib haloperidol ibrutinib[5] idelalisib imatinib indinavir[5] irinotecan isavuconazole[5] itraconazole ivacaftor ketoconazole lansoprazole lapatinib lomitapide[5] lorlatinib losartan lovastatin[5] lurasidone[5] macrolide antibiotics maraviroc[5] medroxyprogesterone methadone midazolam[5] midostaurin[5] modafinil naloxegol[5] nefazodone nilotinib nisoldipine[5] olaparib ondansetron osimertinib paclitaxel palbociclib pazopanib pimozide[5] quetiapine[5] quinidine[4] regorafenib rilpivirine[5] rivaroxaban[5] romidepsin saquinavir[5] sildenafil[5] simvastatin[5] sirolimus[4,5] sonidegib sunitinib tacrolimus[4,5] tamoxifen tadalafil[5] telaprevir temsirolimus				

teniposide tetracycline ticagrelor[5] tipranavir[5] tolvaptan[5] triazolam[5] trimethoprim vardenafil[5] vemurafenib venetoclax[5] vinca alkaloids zolpidem				

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

APPENDIX III-A: MEDICATION DIARY FOR TAZEMETOSTAT (ORAL SUSPENSION FORMULATION)

COG Patient ID:_____ Acc#_____ Institution :_____

Please do not write patient names on this form.

Instructions: Complete each day with the time and dose given for tazemetostat. Make note of other drugs and supplements taken in the Comments section below. Tazemetostat suspension should be given twice a day without regard to meals, with no less than 8 hours between each dose. Shake the bottle for one minute before you take tazemetostat, do not shake too much if there are bubbles wait for them to dissipate before measuring the dose.

Note: If multiple bottles are dispensed, daily shaking of all bottles is required to ensure the suspension stays properly suspended. Store your oral suspension in the refrigerator. If you vomit after taking tazemetostat suspension, the dose should NOT be repeated and the next dose should be taken at a regular scheduled time. This should be noted in the Comments section. Add the dates to the calendar below and return the completed diary to the study clinic at each visit (weekly during Cycle 1, and then after each treatment cycle).

EXAMPLE				***AM Dose: Take 12 mL PM Dose: Take 12 mL***	***Comments (Describe any missed or extra doses, vomiting and/or bothersome effects.)***
WEEK 1	***Date***	***Time***		***Amount of oral suspension taken (mL)***	
Day 1	*2/15/19*	*8:30*	*AM*	12	*He felt nauseated an hour after taking the drug but did not vomit.*
		8:30	*PM*	12	

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

Dose Level: _____mg/m^2/dose

WEEK 1	**Date**	**Time**		**AM Dose: Take _____mL PM Dose: Take _____mL Amount of oral solution taken (mL)**	**Comments (Describe any missed or extra doses, vomiting and/or bothersome effects.)**
Day 1			**AM**		
			PM		
Day 2			**AM**		
			PM		
Day 3			**AM**		
			PM		
Day 4			**AM**		
			PM		
Day 5			**AM**		
			PM		
Day 6			**AM**		
			PM		
Day 7			**AM**		
			PM		

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

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

Dose Level: _____mg/m^2/dose

WEEK 2	Date	Time		AM Dose: Take _____mL PM Dose: Take _____mL Amount of oral suspension taken (mL)	Comments (Describe any missed or extra doses, vomiting and/or bothersome effects.)
Day 8			AM		
			PM		
Day 9			AM		
			PM		
Day 10			AM		
			PM		
Day 11			AM		
			PM		
Day 12			AM		
			PM		
Day 13			AM		
			PM		
Day 14			AM		
			PM		

WEEK 3	Date	Time		AM Dose: Take _____mL PM Dose: Take _____mL Amount of oral suspension taken (mL)	Comments (Describe any missed or extra doses, vomiting and/or bothersome effects.)
Day 15			AM		
			PM		
Day 16			AM		
			PM		
Day 17			AM		
			PM		
Day 18			AM		
			PM		
Day 19			AM		
			PM		
Day 20			AM		
			PM		
Day 21			AM		
			PM		

WEEK 4	Date	Time		AM Dose: Take _____mL PM Dose: Take _____mL Amount of oral suspension taken (mL)	Comments (Describe any missed or extra doses, vomiting and/or bothersome effects.)
Day 22			AM		
			PM		
Day 23			AM		
			PM		
Day 24			AM		
			PM		
Day 25			AM		
			PM		
Day 26			AM		
			PM		
Day 27			AM		
			PM		
Day 28			AM		
			PM		

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

Signature: _____ Date: _____
(Site personnel who administered the study drug)

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, **tazemetostat**. This clinical trial is sponsored by the National Cancer Institute. This form is addressed to the patient but includes important information for others who care for this patient.

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

Tazemetostat interacts with certain specific enzyme(s) in your liver and certain transport proteins that help move drugs in and out of cells.

- The enzymes in question are **CYP3A, 2C8, 2D6, 2C9, and 2C19**.
- Tazemetostat is broken down by CYP3A, 2C8, and 2D6, and may be affected by other drugs that inhibit or induce these enzymes. Treatment with strong inhibitors or inducers of CYP3A are prohibited from 14 days prior to the first dose of tazemetostat to the end of the study.
- Tazemetostat inhibits CYP3A4, 2C8, 2C9, 2C19, and 2D6 and may affect other drugs that are broken down by these enzymes.
- Tazemetostat induces CYP3A4 and may affect other drugs that are broken down by this enzyme.
- The proteins in question are **P-gp, OATP1B1, OATP1B3, OAT3, MATE1, and MATE2K**.
- Tazemetostat is moved in and out of cells/organs by P-gp and may be affected by other drugs that inhibit or induce this protein.
- Tazemetostat inhibits P-gp, OATP1B1, OATP1B3, OAT3, MATE1, and MATE2K and may affect other drugs that require them to move in and out of cells.

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

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

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

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

Tazemetostat must be used very carefully with other medicines that use certain liver enzymes or transport proteins to be effective or to be cleared from your system. 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 CYP3A, 2C8, 2D6, or P-gp; or substrates of CYP3A, 2C8, 2D6, 2C9, 2C19, P-gp, OATP1B1, OATP1B3, OAT3, MATE1, or MATE2K."

- Please be very careful! Over-the-counter drugs (including herbal supplements) may contain ingredients that could interact with your study drug. Speak to your doctors or pharmacist to determine if there could be any side effects.
- No grapefruit juice, Seville oranges, or grapefruit can be consumed while on tazemetostat.
- Avoid prolonged exposure to the sun and wear protective clothing and sunscreen when out in the sun.
- Your regular health care provider should check a frequently updated medical reference or call your study doctor before prescribing any new medicine or discontinuing any medicine. Your study doctor's name is _____ and he or she can be contacted at _____.

October 2018

STUDY DRUG INFORMATION WALLET CARD

You are enrolled on a clinical trial using the experimental study drug **tazemetostat.** This clinical trial is sponsored by the NCI. Tazemetostat may interact 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 any medicines or if you start taking any new medicines.
- Tell all of your health care providers (doctors, physician assistants, nurse practitioners, or pharmacists) that you are taking part in a clinical trial.
- Check with your doctor or pharmacist whenever you need to use an over-the-counter medicine or herbal supplement.
- No grapefruit juice, Seville oranges, or grapefruit can be consumed while on tazemetostat.
- Avoid prolonged exposure to the sun and wear protective clothing and sunscreen when out in the sun.

Tazemetostat interacts with specific liver enzymes called CYP3A, 2C8, 2D6, 2C9, 2C19 and transport proteins P-gp, OATP1B1, OATP1B3, OAT3, MATE1, and MATE2K, and must be used very carefully with other medicines that interact with these enzymes or transporter.

- 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 CYP3A, 2C8, 2D6 or P-gp or substrates of CYP3A, 2C8, 2D6, 2C9, 2C19 or transporters P-gp, OATP1B1, OATP1B3, OAT3, MATE1, and MATE2K.***"
- 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: TAZEMETOSTAT DOSING PREPARATION (ORAL SUSPENSION FORMULATION)

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. Shake the bottle for one minute before you take tazemetostat; do not shake too much if there are bubbles wait for them to dissipate before measuring the dose. Note: If multiple bottles are dispensed, daily shaking of all bottles is required to ensure the suspension stays properly suspended. Store your oral suspension in the refrigerator.

Patients who experience dose-limiting toxicity should have their dose reduced by 25% so that patients receive 75% of the original administered dose. A site-supplied press-in bottle adapter is required for use with an oral syringe for dosing purposes.

Tazemetostat Oral Suspension Preparation Worksheet and Guidance Table

Protocol:	Date of preparation:
Subject ID and Initials:	Cycle #:
BSA (m^2):	• Assigned dose level: 1200mg/m^2/dose BID (Pre-AMD#3)
	• Assigned dose level: 520 mg/m^2/dose BID (For patients enrolled post-AMD#3 **Patients without CNS involvement** see Section 5.1)
	• Assigned dose level: 1200 mg/m^2/dose BID (For patients enrolled post-AMD#3 — **Patients with CNS involvement** see Section 5.1)

Steps:

1) Calculate the mg of tazemetostat required per dose: **BSA x dose level**	_____ mg per dose BID	
2) Calculate the total mg of tazemetostat required per dosing period, including any overfill per institution guidelines* **mg per dose x # of doses per day x # of days x overfill (if needed)** *An overfill will most likely be needed in order to dispense sufficient quantity to last 14 days	_____ mg per dosing period	
3) Calculate total # of grams of tazemetostat required per dosing period. **mg from step 2 divided by 1000**	_____ grams per dosing period (round up to nearest whole number)	
4) Enter # of 2 gram and 7 gram bottles required for dosing period. (refer to the suspension preparation guidance table)	2 gram bottles: _____ 7 gram bottles: _____	Total # of grams: _____
5) Calculate the total volume of Ora-Sweet® required. **Total grams of tazemetostat from step 4 x 32.5 mL/gram**	_____ mL (refer to the suspension preparation guidance table)	

6) Determine # of empty medication bottles required so that each bottle is filled between 40-80% capacity for adequate mixing. 7) Follow the oral suspension preparation instructions in the protocol.	<table><tr><th>Bottle #</th><th>Grams of tazemetostat</th><th>mL of Ora-Sweet® to add</th></tr><tr><td></td><td></td><td></td></tr><tr><td></td><td></td><td></td></tr><tr><td></td><td></td><td></td></tr><tr><td></td><td></td><td></td></tr><tr><td></td><td></td><td></td></tr></table>
8) Calculate the volume required per dose **mg per step 1 divided by 30 mg/ml**	_____ mL per dose BID

Suspension preparation guidance table:

Total tazemetostat required	**2 gm bottles**	**7 gm bottles**	**Ora-Sweet® volume* (mL)**	**Allowable medication bottle size** (mL)**
< 2 grams	1	0	65	100-150
2 to <4 grams	2	0	130	200-300
4 to <6 grams	3	0	195	250-500
6 to <7 grams	0	1	228	250-500
7 to <9 grams	1	1	293	400-700
9 to <11 grams	2	1	358	400-800
11 to <12 grams	3	1	423	600-1000
12 to <14 grams	0	2	455	600-1100
14 to <16 grams	1	2	520	600-1200
16 to <18 grams	2	2	585	700-1400
18 to <20 grams	3	2	650	750-1500
20 to <21 grams	0	3	683	850-1600
21 to <23 grams	1	3	748	1000-1800
23 to <25 grams	2	3	813	1000-2000
25 to <27 grams	3	3	878	1100-2100
27 to <28 grams	0	4	910	1200-2400
28 to <30 grams	1	4	975	1300-2500
30 to <32 grams	2	4	1040	1400-2600
32 to <34 grams	3	4	1105	1500-2800
This table is for guidance purposes only, larger volumes should be calculated using the Tazemetostat Oral Suspension Preparation Worksheet.				

*The volume of Ora-Sweet® to obtain a concentration of 30 mg tazemetostat/mL of suspension accounts for the volume of tazemetostat in the solution.

** Total volume listed may require more than one medication bottle to accommodate. Each medication bottle must be prepared separately but multiple whole bottles of tazemetostat powder for oral suspension can be combined into one medication bottle.

APPENDIX V: APEC1621C 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
Tazemetostat	PO	Please circle one: -1200 mg/m^2/dose BID **(Pre-Amendment #3B)** **-Patient without CNS involvement:** 520 mg/m^2/dose BID **-Patient with CNS involvement:**1200 mg/m^2/dose BID Refer to the dosing preparation Appendix IV.	1-28	Tazemetostat will be administered as a liquid suspension orally given twice a day without regard to meals with no less than 8 hours between each dose. If vomiting occurs after taking oral suspension formulation, the dose should NOT be repeated and the next dose should be administered at the regularly scheduled time. See Section 9.1.6 and Appendix IV for additional oral suspension administration and preparation instructions.

Ht _____cm Wt _____kg BSA _____m^2 Patient with CNS involvement: Yes/No (please circle 1)

Date Due	Date Given	Day	**Tazemetostat** _____mg AM _____mg PM	Studies
			Enter calculated dose above and actual dose administered below	
		1	_____mg AM _____mg PM	
		2	_____mg AM _____mg PM	
		3	_____mg AM _____mg PM	
		4	_____mg AM _____mg PM	
		5	_____mg AM _____mg PM	
		6	_____mg AM _____mg PM	
		7	_____mg AM _____mg PM	
		8	_____mg AM _____mg PM	a, c, d, e, h
		9	_____mg AM _____mg PM	
		10	_____mg AM _____mg PM	
		11	_____mg AM _____mg PM	
		12	_____mg AM _____mg PM	
		13	_____mg AM _____mg PM	
		14	_____mg AM _____mg PM	
		15	_____mg AM _____mg PM	a, c, d, e, h
		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	

Cycle 1

		22	_____ mg AM	_____ mg PM	a, c, d, e, h
		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, h, i, j*,k

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

Required Observations in Cycle 1

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

a.	**History/Physical Exam (including VS)**
b.	**Ht/Wt/BSA**
c.	**CBC/differential/platelets**- If patients have Grade 4 neutropenia then CBCs should be checked at least every other day until recovery to Grade 3 or until meeting the criteria for dose limiting toxicity. Automated differentials acceptable unless concern for blasts; then please obtain manual differential.
d.	**Electrolytes including Ca++, PO4, Mg++**
e.	**Creatinine, ALT, bilirubin**
f.	**Albumin**
g.	**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
h	**Medication Diary**- (see Appendix III-A and Appendix II-B) should be reviewed after completion of each treatment cycle and uploaded into RAVE. The medication diary should be collected weekly.
i.	**Bromide Level**
j.	**Plain radiograph tibial growth plate (Bone X-Ray Tests)**. Plain radiographs of at least one tibial growth plate should be obtained in all patients prior to first dose of protocol therapy. In patients with open growth plates, follow-up plain radiographs of the same growth plate(s) should be obtained according to Section 8.2.
k.	**Neurological Exam.**

Cycle 1

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
Tazemetostat	PO	Please circle one: -1200 mg/m^2/dose BID **(for patients enrolled pre-amendment #3B)** **-Patient without CNS involvement:** 520 mg/m^2/dose BID **(only for patients enrolled post-amendment #3B)** **-Patient with CNS involvement:** 1200 mg/m^2/dose BID **(only for patients enrolled post-amendment #3B)** Refer to the dosing preparation Appendix IV.	1-28	Tazemetostat will be administered as a liquid suspension orally given twice a day without regard to meals with no less than 8 hours between each dose. If vomiting occurs after taking oral suspension formulation, the dose should NOT be repeated and the next dose should be administered at the regularly scheduled time. See Section 9.1.6 and Appendix IV for additional oral suspension administration and preparation instructions.

Ht _____cm Wt _____kg BSA _____m^2 Patient with CNS involvement: y/n (please circle 1)

Date Due	Date Given	Day	**Tazemetostat** _____mg AM _____mg PM	Studies
			Enter calculated dose above and actual dose administered below	
		1	_____mg AM _____mg PM	a-g, m, n, k
		2	_____mg AM _____mg PM	
		3	_____mg AM _____mg PM	
		4	_____mg AM _____mg PM	
		5	_____mg AM _____mg PM	
		6	_____mg AM _____mg PM	
		7	_____mg AM _____mg PM	
		8	_____mg AM _____mg PM	
		9	_____mg AM _____mg PM	
		10	_____mg AM _____mg PM	
		11	_____mg AM _____mg PM	
		12	_____mg AM _____mg PM	
		13	_____mg AM _____mg PM	

Subsequent Cycles

		14	_____ mg AM	_____ mg PM	
		15	_____ mg AM	_____ mg PM	
		16	_____ mg AM	_____ mg PM	
		17	_____ mg AM	_____ mg PM	
		18	_____ mg AM	_____ mg PM	
		19	_____ mg AM	_____ mg PM	
		20	_____ mg AM	_____ mg PM	
		21	_____ mg AM	_____ mg PM	
		22	_____ mg AM	_____ mg PM	
		23	_____ mg AM	_____ mg PM	
		24	_____ mg AM	_____ mg PM	
		25	_____ mg AM	_____ mg PM	
		26	_____ mg AM	_____ mg PM	
		27	_____ mg AM	_____ mg PM	
		28/1	_____ mg AM	_____ mg PM	a-g, h*, j*, k*, l* m, n

See Section 6.0 for Dose Modifications for Toxicities and the COG Member website for Supportive Care Guidelines
* Please refer to Section 8.1 for the specific timing of these observations. Studies on Day 28/1 may be obtained within 72 hours prior to the start of the subsequent cycle.

Required Observations in All Subsequent Cycles

a.	**History/Physical Exam (including VS)**
b.	**Neurological Exam**
c.	**Ht/Wt/BSA**
d.	**CBC/differential/platelets** If patients develop Grade 4 neutropenia then CBCs should be checked every 3 to 4 days until recovery to Grade 3. Automated differentials acceptable unless concern for blasts; then please obtain manual differential.
e.	**Electrolytes including Ca++, PO4, Mg++**
f.	**Creatinine, ALT, bilirubin**
g.	**Albumin**
h.	**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.
i.	**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.
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.	**Plain radiograph tibial growth plate (Bone X-Ray Tests)**. Plain radiographs of at least one tibial growth plate should be obtained in all patients prior to first dose of protocol therapy. In patients with open growth plates, follow-up plain radiographs of the same growth plate(s) should be obtained according to Section 8.2.
l.	**EKG.**
m.	**Medication Diary**- (see Appendix III-A and Appendix-B) should be reviewed after completion of each treatment cycle and uploaded into RAVE.
n.	**Bromide Level**

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 APEC1621C EXPANSION COHORTS

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

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

APPENDIX VII: APEC1621C ACTIONABLE MUTATIONS OF INTEREST

Actionable Mutations for Sub-Protocol APEC1621C

NON-HOTSPOT RULES (To be used only if IHC testing of gene is equivocal or cannot be performed.)			
Gene Name	Description	Variant Type	LOE
SMARCB1	Include	Two Deleterious mutations	2
SMARCA4	Include	Two Deleterious mutations	2

INCLUSION VARIANTS				
Gene Name	Variant ID	Variant Type	aMOI	LOE
EZH2	COSM37032	SNV	p.Y646C	3
EZH2	COSM37028	SNV	p.Y646F	3
EZH2	COSM37030	SNV	p.Y646H	3
EZH2	COSM37031	SNV	p.Y646N	3
EZH2	COSM37029	SNV	p.Y646S	3
EZH2	COSM220386	SNV	p.A682G	3
EZH2	COSM1315851	SNV	p.A682V	3
EZH2	COSM220529	SNV	p.A692V	3

IHC	RESULTS
GENE:	STATUS:
SMARCB1	NEGATIVE
SMARCA4	NEGATIVE

APPENDIX VIII 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	10-20 mL	Streck Cell-Free DNA BCT tubes
Total Blood Volume in Cycle 5 Day 1			**10-20 mL**	

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

* Only collected from patients from whom the sample at Cycle 5 Day 1 is collected.

APPENDIX IX YOUTH INFORMATION SHEETS
INFORMATION SHEET REGARDING RESEARCH STUDY APEC1621C
(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 tazemetostat that could "match" your tumor. The doctors want to see if tazemetostat will help children with your type of cancer get better. We don't know if tazemetostat 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 tazemetostat 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 tazemetostat. 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 tazemetostat 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 tazemetostat works in them. We will draw some extra blood samples for this if your family agrees.

INFORMATION SHEET REGARDING RESEARCH STUDY APEC1621C
(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 tazemetostat, and so you have been assigned to tazemetostat. The doctors want to see if tazemetostat will make children with your type of cancer get better. We don't know if tazemetostat will work well to get rid of your cancer. That is why we are doing the study.

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

APPENDIX X 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 APEC1621C 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 XI: TOXICITY-SPECIFIC GRADING

Bilirubin

Grade 1:	> ULN- ≤ 1.5 x ULN
Grade 2:	> 1.5 x ULN - 3.0 x ULN
Grade 3:	> 3.0 x ULN -10.0 x ULN
Grade 4:	> 10.0 x ULN

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

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

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

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

GGT:

Grade 1:	> ULN- 2.5 x ULN
Grade 2:	> 2.5 x ULN - 5.0 x ULN
Grade 3:	> 5.0 x ULN -20.0 x ULN
Grade 4:	> 20.0 x ULN