CHILDREN'S ONCOLOGY GROUP

The world's childhood cancer experts

G Douglas S. Hawkins, MD
Seattle Children's Research Institute
doug.hawkins@seattlechildrens.org

Group Vice Chair
Lia Gore, MD
Children's Hospital Colorado
lia.gore@cuanschutz.edu

Group Statistician
Todd Alonzo, PhD
talonzo@childrensoncologygroup.org

Executive Director of Clinical Research Operations
Mary Beth Sullivan, MPH
msullivan@childrensoncologygroup.org

Executive Director of Data Operations
Thalia Beeles, MPH
tbeeles@childrensoncologygroup.org

Executive Director of Administration and Finance
Lee Ann DeRita, MBA, CMA, CFE
lderita@childrensoncologygroup.org

Group Operations Center and **Statistics & Data Center (SDC) Headquarters**
1333 S. Mayflower Avenue
Suite 260
Monrovia, CA 91016
P 626 241 1500
F 626 445 4334

October 28, 2022

[redacted]

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

Dear [redacted]

The study committee thanks CTEP for forwarding the Amendment Request dated October 17, 2022. In response to the request, please see attached Amendment #5 to APEC1621M. The complete list of changes can be found below.

Please contact us if you have any further questions.

Sincerely,

[redacted]

CHILDREN'S ONCOLOGY GROUP

SUMMARY OF CHANGES: PROTOCOL

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

#	Section	Page(s)	Change
1.	General	All	Updated protocol version date in the footer.
2.	Cover Page	1	Updated version date and amendment number.
3.	Contact Information	2	Cancer Trials Support Unit (CTSU)information updated with email address **CTSURegHelp@coccg.org**
4.	Table of Contents	3-5	Updated for re-pagination
5.	Table of Contents	4	Updated date to **12/22/2021** for Tipifarnib
6.	Study Committee	7	Added [redacted] as Research Coordinator Removed ~~Lee Baker~~ and added [redacted] as Protocol Coordinator

Activated: 07/13/2020
Closed:

Version Date: 10/28/2022
Amendment: 5

CHILDREN'S ONCOLOGY GROUP

APEC1621M

NCI-COG PEDIATRIC MATCH (MOLECULAR ANALYSIS FOR THERAPY CHOICE)- PHASE 2 SUBPROTOCOL OF TIPIFARNIB IN PATIENTS WITH TUMORS HARBORING HRAS GENOMIC ALTERATIONS

Open to COG Member Institutions in Australia, New Zealand, Canada, and the USA

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STUDY CHAIR

[redacted]

Contact Information

For Regulatory Requirements	For patient enrollments:	For Data Submission
Regulatory documentation must be submitted to the Cancer Trials Support Unit (CTSU) via the Regulatory Submission Portal. (Sign in at www.ctsu.org, and select the Regulatory > Regulatory Submission.) Institutions with patients waiting that are unable to use the Portal should alert the CTSU Regulatory Office immediately by phone or email: at 1-866-651-CTSU (2878), or CTSURegHelp@coccg.org to receive further instruction and support. Contact the CTSU Regulatory Help Desk at 1-866-651-2878 for regulatory assistance.	Please refer to the patient enrollment section of the protocol for instructions on using the Oncology Patient Enrollment Network (OPEN). OPEN is accessed at https://www.ctsu.org/OPEN_SYSTEM/ or https://open.ctsu.org. Contact the CTSU Help Desk with any OPEN-related questions by phone or email: 1-888-823-5923, or ctsucontact@westat.com.	Data collection for this study will be done exclusively through Medidata Rave. Please see the Data Submission Schedule in the CRF packet for further instructions.

The most current version of the study protocol must be downloaded from the protocol-specific page located on the CTSU members' website (https://www.ctsu.org). Access to the CTSU members' website is managed through the Cancer Therapy and Evaluation Program - Identity and Access Management (CTEP-IAM) registration system and requires log in with a CTEP-IAM username and password. Permission to view and download this protocol and its supporting documents is restricted and is based on person and site roster assignment housed in the CTSU Regulatory Support System (RSS).

For clinical questions (ie, patient eligibility or treatment-related)
Contact the Study PI of the Lead Protocol Organization.

For non-clinical questions (ie, unrelated to patient eligibility, treatment, or clinical data submission)
Contact the CTSU Help Desk by phone or e-mail:
CTSU General Information Line – 1-888-823-5923, or ctsucontact@westat.com. All calls and correspondence will be triaged to the appropriate CTSU representative.

The CTSU Website is located at https://www.ctsu.org.

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[redacted]

[redacted]

STUDY COMMITTEE

STUDY COMMITTEE, CONT.

[redacted]

[redacted]

COG OPERATIONS STAFF

[redacted]

[redacted]

Emma Archuleta, BS

[redacted]

For Group Operations (GOC) and
Statistics & Data Center (SDC) contacts see:
http:members.childrensoncologygroup.org

AGENT NSC# AND IND#'s
NCI-Supplied Agents:
Tipifarnib
([redacted], [redacted])
IND Sponsor: DCTD, NCI

See Section 8.3.6 and Section 8.4.4 For Specimen Shipping Addresses

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

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

ABSTRACT

This subprotocol is a component of the Pediatric MATCH trial APEC1621. The APEC1621SC screening protocol details the process used to identify actionable mutations in patient tumor samples which will determine eligibility for this subprotocol. This is a phase 2 trial of tipifarnib in children with relapsed or refractory solid tumors (including lymphomas, histiocytoses and CNS) harboring specified activating mutations in the HRAS gene.

Tipifarnib will be administered with food at [redacted] mg/m^2/dose PO BID (maximum 600 mg/dose) for 7 days followed by 7 day rest period, alternating on a 28 day cycle. Eligibility for this trial includes a relapsed or refractory pediatric solid tumor that harbors an activating mutation in *HRAS* (at codons G12, G13, Q61, or A146), as determined by the Pediatric-MATCH screening protocol, APEC1621SC. The trial's primary objective is to determine the antitumor activity of tipifarnib, using objective response rate (CR +PR) as a primary endpoint. Secondary objectives include ongoing assessment of tipifarnib-associated toxicities.

EXPERIMENTAL DESIGN SCHEMA

Treatment Schedule Table	
Days 1-7	Tipifarnib orally or via NG- or G- tube twice daily
Days 8-14	Rest
Days 15-21	Tipifarnib orally or via NG- or G- tube twice daily
Days 22-28	Rest
Day 28	Evaluation

Tipifarnib will be administered with food at [redacted] mg/m^2/dose PO BID (maximum 600 mg/dose) for 7 days followed by 7 day rest period alternating on a 28 day cycle (i.e., Days 1-7 and 15-21 of a 28 day cycle). The available formulations of tipifarnib are 100 mg and 300 mg tablets. These tablets may be swallowed whole or crushed and mixed in water, orange juice, apple juice, tomato juice, protein shake, or a dietary supplement drink (such as Ensure®). Evaluations will occur every other cycle (8 weeks) for three occurrences, then every three cycles (12 weeks). It is recommended to consume the mixture within 2 hours of preparation. The mixing container should be rinsed and the rinse consumed as well.

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

1.0 GOALS AND OBJECTIVES (SCIENTIFIC AIMS)

1.1 Primary Aims

1.1.1 To determine the objective response rate (ORR; complete response + partial response) in pediatric patients treated with tipifarnib with advanced solid tumors (including CNS tumors), lymphomas or histiocytic disorders that harbor activating genetic alterations in *HRAS*.

1.2 Secondary Aims

1.2.1 To estimate the progression free survival in pediatric patients treated with tipifarnib with advanced solid tumors (including CNS tumors), lymphomas or histiocytic disorders that harbor activating genetic alterations in *HRAS*.

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

1.3 Exploratory Aims

1.3.1 To evaluate other biomarkers as predictors of response to tipifarnib and specifically, whether tumors that harbor different missense mutations or variant allele frequency will demonstrate differential response to tipifarnib treatment

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

2.0 BACKGROUND

2.1 Introduction/Rationale for Development

A large number of malignancies are driven by oncogenic RAS isoforms, including pancreatic, colorectal and lung cancer, head and neck cancer, melanoma and hematologic malignancies.[1] Despite this knowledge, clinically effective therapies targeting the RAS pathway have yet to be developed. Direct targeting of mutant RAS with small molecules has proven to be difficult and current strategies are focused on inhibition of downstream signaling pathways.[2] RAS signals through multiple effectors, including but not limited to BRAF, PI3-kinase, TIAM1, RAL-GEFs, PLCε and NORE1 and effector pathways driving tumorigenesis in each RAS-driven tumor type are often not defined.[3] Tumors also rapidly acquire resistance to targeted inhibitors, such as inhibitors of the RAF/MEK/ERK pathway. In many cases, acquired resistance to MEK inhibition in NRAS-mutated melanoma is due to MEK1 or MEK2 mutation.[4] In addition, mechanisms of intrinsic resistance to MEK inhibition in KRAS-mutant cells include rebound MEK and ERK phosphorylation[5] and activation of AKT.[6] Therefore, combinations of RAS effector pathway inhibitors, or novel

inhibitors of RAS function, may be required for clinically effective treatment.

Current clinical trials for RAS-driven adult tumors commonly include combinations of a MEK inhibitor and a PI3-kinase or AKT inhibitor. Some limitations of this approach include overlapping toxicities of the targeted agents, incomplete dual pathway inhibition and impaired apoptotic response, which ultimately leads to rapid emergence of acquired resistance to the targeted agents. Addition of targeted agents aimed at inhibiting a third RAS effector pathway or combining targeted agents with traditional cytotoxic chemotherapeutics to boost the apoptotic response may overcome these limitations.[7] Preclinical and clinical studies of these combinations in adult tumor types are currently ongoing. The advantage of a drug that inhibits RAS activation, such as tipifarnib, in this setting, is the ability to inhibit multiple effector pathways with one drug.

2.1.1 RAS as a driver of pediatric cancer:

Mutation of the RAS isoforms, and other alterations leading to aberrant ERK signaling, are also important drivers of many pediatric malignancies. For example, recent comprehensive genomic analyses of human rhabdomyosarcoma tumors indicate that the most common somatic mutation in embryonal rhabdomyosarcoma is an oncogenic change in one of the RAS isoforms.[8,9] Neuroblastomas, especially in the relapsed setting, harbor mutations in HRAS, NRAS and KRAS.[10] Pediatric melanomas arising from large or very large congenital nevi are almost exclusively driven by oncogenic mutations in NRAS.[11] Malignant ectomesenchymomas were recently discovered to harbor driver mutations in HRAS.[12] RAS is aberrantly active in neurofibromatosis type 1 (NF1)-related tumors including plexiform neurofibromas, atypical plexiform neurofibromas and malignant peripheral nerve sheath tumors (MPNST) through loss of function mutations in the RAS GTPase activating protein, NF1.[13] Some pilocytic astrocytomas are driven by an activating fusion of BRAF, KIAA1549-BRAF, while some pleomorphic xanthoastrocytomas are driven by the classical mutation in BRAF, V600E.[14] Recent next-generation sequencing studies of pediatric cancers have revealed that RAS mutations are also observed in high- and low-grade gliomas as well as Wilms tumor.[15] Pediatric hematological malignancies are also driven by aberrant activation of RAS-RAF-MEK-ERK signaling, including Langerhans cell histiocytosis (BRAF)[16], acute myeloid leukemia and acute lymphoblastic leukemia[17,18], and juvenile myelomonocytic leukemia (KRAS, NRAS, NF1, PTPN11 and CBL).[19]

In preliminary analysis of Pediatric MATCH trial data performed on 3/18/20, a total of 37 activating RAS mutations were identified in 769 patients screened, including 6 HRAS mutations in rhabdomyosarcomas. Other sequencing efforts have also identified a small number of cases of HRAS mutations in pediatric solid tumors. These include: 1) the Foundation Medicine Pediatric Portal[20] has 4 total cases of HRAS mutation (of total 1215), and of these, 3 are in embryonal RMS; 2) cBioPortal has a total of 109 cases of HRAS mutations[21] (of total 10,000 cases, frequency 1.1%), and of these, 2 were embryonal RMS and 1 was neuroblastoma; 3) the TARGET neuroblastoma data set[22] has 3 cases of HRAS CNG (out of 1089 total), but no SNV detected in this cohort; 4) the GAIN/ iCAT2 cohort has identified 2 cases of HRAS mutant RMS (out of total 250 total tumors, Janeway, personal communication); and 5) a comprehensive genomic profiling study of RMS[23] revealed HRAS mutations in 2 of 43 total RMS cases.

The three classical RAS genes encode four highly related guanine nucleotide binding proteins: HRAS, KRAS4A, KRAS4B and NRAS. RAS proteins function as guanine nucleotide-regulated binary on-off switches. In normal quiescent cells, RAS is predominantly GDP-bound and inactive. Growth factors activate RAS-selective guanine nucleotide exchange factors (RAS-GEFs; e.g., SOS1, SOS2) to promote nucleotide exchange and formation of active RAS-GTP, a reaction that requires RAS be localized to the plasma membrane. Once in the active, GTP-bound conformation,

RAS can bind to a variety of effector proteins to transmit its downstream signals, including the RAF kinases and PI3 kinase. Engagement of effector proteins also requires RAS and the effectors to be localized to the plasma membrane. RAS-selective GTPase accelerating proteins (RAS-GAPs; e.g., NF1, RASA1, RASA2, SYNGAP1) normally promote GTP hydrolysis to return RAS to its GDP-bound resting state [2,3,24]. In sporadic pediatric or adult malignancies, RAS isoforms are typically somatically mutated at three main hotspots (G12, G13 and Q61); these mutations render RAS GAP-insensitive, and thus persistently GTP-bound and active. RAS mutation at A146, in contrast, increases the fraction of GTP-bound, activated RAS by enabling RAS to spontaneously exchange GDP for GTP in the absence of a RAS-GEF [2,3,24]. Efforts to target RAS signaling in benign pediatric tumors recently have been successful clinically, leading to the breakthrough therapy designation for the MEK inhibitor, selumetinib, in patients with NF1-related plexiform neurofibromas. Clinical trials for agents targeting RAS signaling in pediatric malignancies are ongoing.

2.1.2 Tipifarnib:

Localization to the plasma membrane is required for RAS activation and function. For the RAS proteins, anchorage to the plasma membrane requires addition of a farnesyl moiety to the conserved C-terminal cysteine. This farnesylation is catalyzed by farnesyltransferase. Over 140 proteins have been identified as substrates of farnesyltransferase, including each of the RAS isoforms. Tipifarnib is a potent and selective inhibitor of farnesyltransferase. Inhibitors of farnesyltransferase have an advantage over inhibitors of RAS effectors as cancer therapeutics because they inhibit RAS membrane localization, and thus inhibit the activation of all of the RAS effector pathways, not just one pathway. Tipifarnib inhibits tumor growth by inhibiting angiogenesis, inducing apoptosis, and preventing tumor cell proliferation in multiple animal models of adult malignancies. NRAS and KRAS, like many other farnesyltransferase targets, are able to bypass the requirement for farnesylation through alternative prenylation (geranyl-geranylation), and membrane localization of these molecules is therefore unaffected in the presence of a farnesyltransferase inhibitor (FTI). HRAS, however, is unable to utilize alternative prenylation, and its membrane localization and cellular function are therefore suppressed by FTI such as tipifarnib [25]. As discussed above, mutant HRAS is a driver of both adult and pediatric solid tumors and hematological malignancies. While multiple clinical trials evaluating the efficacy of tipifarnib in adults and pediatric patients with solid tumors or hematological malignancies have been conducted, none have been conducted to date in a genomically-selected patient population.

2.2 Preclinical Studies

2.2.1 Antitumor Activity

Post-translation modification of proteins critical to cell signaling, proliferation, and differentiation is linked to lipid metabolism.[26] The best-characterized example is the family of Ras proteins, whose anchorage to the cell membrane requires most commonly a farnesyl moiety, which is a derivative of the mevalonate pathway of cholesterol synthesis.[27] Farnesylation is catalyzed by a 48 kd metallo-enzyme, farnesyltransferase. More than 140 proteins have now been identified as potential substrates for farnesyltransferase inhibitors (FTI). However, the function of many of these proteins is kept intact due to compensative prenylation through type 1 geranylgeranyl transferase.[28] Among RAS isoforms, inhibition of the farnesylation of KRAS and NRAS leads to their geranylgeranylation and unchanged membrane localization.[29] HRAS cannot be geranylgeranylated, and therefore its membrane localization and cellular function is suppressed by FTIs.[28]

Tipifarnib has been shown to be a potent and selective non-peptidomimetic inhibitor of farnesyltransferase (FTI). Using isolated human farnesyltransferase, tipifarnib competitively inhibits the farnesylation of CAAX peptide substrates, such as lamin B and KRAS, with IC50s of 0.5 nM and 8 nM, respectively. In contrast, the IC50 for inhibition of isoprenylation catalyzed by geranylgeranyltransferase type 1 by tipifarnib is greater than 50 μM, consistent with tipifarnib functioning as a specific FTI inhibitor.[30]

The proliferation of 53 human tumor cell lines in the presence of tipifarnib has been evaluated in 2D culture. Tipifarnib inhibited cell proliferation of HRAS transformed NIH3T3 cells with an IC50 of 1.7 nM but did not inhibit parental NIH3T3 cells up to a concentration of 500 nM. Consistent with a specific activity against HRAS, tipifarnib was found to potently inhibit two cell lines bearing HRAS mutations, resulting in IC50s of 1.7 nM and 5.2 nM, whereas cell lines with KRAS (n=8) and NRAS (n=2) mutations displayed a wide range sensitivity (~ 10 nM to > 500 nM).[31] Tipifarnib was also selective for activity in an HRAS mutant HNSCC cell line (IC50 of 14nM) versus an HRAS wild type HNSCC cell line (IC50 of 1000nM) using a 3D clonogenic assay format that assesses the capacity of tumor cells for anchorage-independent growth as measured by colony formation in soft agar in the presence and absence of test compounds.

Tipifarnib suppressed tumor growth in a variety of both mouse tumor xenograft models and chemical carcinogen-induced tumor models when administered orally. The mechanism of action of tipifarnib in vivo is context dependent and appears to include angiogenesis inhibition, induction of apoptosis, and direct antiproliferative effects.[32,33]

2.2.2 Animal Toxicology

In mice and rats, acute oral administration of tipifarnib was well-tolerated, with an approximate lethal dose [redacted] mg/kg in both species. In rats administered daily oral doses of tipifarnib, the no observed adverse effect levels (NOAELs) were [redacted] mg/kg/day after 1 month of dosing, [redacted] mg/kg/day after 3 months of dosing, and [redacted] mg/kg/day after 6 months of dosing. In dogs, the NOAEL was [redacted] mg/kg/day after 1 month of oral administration and [redacted] mg/kg/day after both 3 and 9 months of oral administration. The majority of effects observed in these studies were consistent with the mechanism of action of tipifarnib and related to atrophy of hematopoietic tissues/organs resulting in pronounced leukopenia or thrombocytopenia in both rats and dogs. Microscopic findings in the [redacted] were noted in both species, while in rats, the [redacted] were identified as additional target organs. [redacted] was noted in rats only, suggesting a species-specific effect. Based on the results of an in vitro study conducted in [redacted], the [redacted] potential of tipifarnib is likely related to its pharmacological activity and not a result of chemical-induced toxicity. Most findings (with the exception of findings in [redacted] and [redacted] in rats) were reversible upon cessation of dosing. The target organ profile of orally-administered tipifarnib in dogs [redacted] safety-related findings in tipifarnib-treated humans.[26]

Tipifarnib was demonstrated to be [redacted] in vitro; [redacted] in vivo only at a dose level associated with [redacted].[26]

In fertility studies conducted with tipifarnib in rats, the NOAELs for fertility and early embryonic development were both [redacted] mg/kg/day in both sexes. In embryo-fetal development studies, the maternal and developmental NOAELs were both [redacted] mg/kg/day in

rats and [redacted] mg/kg/day and [redacted] mg/kg/day, respectively, in rabbits. In a pre-/post-natal development study conducted with tipifarnib in rats, the NOAEL was [redacted] mg/kg/day.[26] Tipifarnib was found to have no [redacted] in a [redacted] assay conducted in mice. [26]

Based on data generated in in vitro and in vivo photosafety studies, tipifarnib is not considered to pose a phototoxic hazard to humans. [26]

2.3 Adult Studies

2.3.1 Phase 1 and Phase 2 Studies

A large number of clinical trials were conducted with the farnesyl transferase inhibitor tipifarnib, both in adult [34-39] and in pediatric [40-42] patients, between 1997 and 2007. Other than a few very modest responses in hematologic malignancies[43], each of these trials failed to demonstrate sufficient activity to support its advancement to later stage clinical trials[44]. No clinical trials under the earlier development plans, however, employed a patient selection strategy involving recruitment of only patients whose tumors harbored activating mutations in HRAS. [45,46]

There are a total of five planned or ongoing Phase 2 studies of tipifarnib under current Kura Oncology development (KO-TIP-001, KO-TIP-002, KO-TIP-003, KO-TIP-004 and KO-TIP-0007). These are summarized here:

2.3.1.1 Hematologic Tumors

In an ongoing Phase 2 study in peripheral T-cell lymphoma (PTCL) patients, KO-TIP-002, 50 patients have been treated with tipifarnib. In stage 1 and stage 2 of the study (n=18 evaluable patients), 3 pts achieved a partial response and 5 pts experienced stable disease (SD). Two of the patients with a partial response had angioimmunoblastic T-cell lymphoma (AITL) histology. Tumor mutational data from 16 subjects enrolled in stage 1 and 2 suggested that subjects with high levels of CXCL12 gene expression derive clinical benefit from tipifarnib. Based on these data, 2 cohorts were introduced to further evaluate the anti-tumor activity of tipifarnib subjects with tumors that express high levels of CXCL12: an AITL cohort and a cohort of wt CXCL12 3'UTR patients, whose tumors have high expression of CXCL12. In the AITL cohort, there were 3 complete responses, 2 partal responses, and 3 patients with a best response of long term stable disease among 11 evaluable patients. In the wt CXCL12 3'UTR cohort, there were 3 complete responses and 2 partial responses among 12 evaluable patients. Enrollment continues on both the AITL and wt CXCL12 3'UTR arms.[26,47]

In the ongoing Phase 2 study in MDS/MPN (including CMML) and AML patients, KO-TIP-004, 31 patients with CMML have been treated with tipifarnib. In the initial 16 pts evaluable for efficacy (9 RAS wildtype, 7 RAS mutant), the primary objective of the study was met with an overall response rate of 33% in patients with RAS wild-type CMML. All nine patients with RAS wildtype CMML had achieved stable disease or better. Analysis of gene expression in bone marrows obtained at baseline (prior to the first dose of tipifarnib) from the CMML subjects enrolled in the study indicated that a high ratio of expression of the C-X-C motif chemokine receptors CXCR4 and CXCR2 was significantly associated with

clinical benefit from tipifarnib.[26] Based on these data, the study protocol has been amended to enroll expansion cohorts designed to prospectively test the hypothesis that a high ratio of expression between CXCR4 and CXCR2 (CXCR4/2 ratio) receptors could be associated with responsiveness to tipifarnib in myeloid neoplasias. Enrollment in these expansion cohorts is ongoing.[26] In contrast, in the Kura Oncology sponsored Phase 2 study in MDS pts, KO-TIP-003, 16 pts were treated with tipifarnib. Fifteen pts achieved a best response of stable disease, with the remaining patient having a best response of progressive disease. This study has been closed to further accrual, and a biomarker for exceptional response in these patients has not been identified.[26]

2.3.1.2 Solid Tumors

In the ongoing Phase 2 study in HRAS-mutant solid tumors, KO-TIP-001, 48 patients have been treated with tipifarnib. Cohort 1 (HRAS-mutant thyroid cancer) has been closed to active accrual due to lack of efficacy. However, there have been 4 confirmed responses in 14 evaluable patients in stage 1 of Cohort 2 of the study (HRAS-mutant other solid tumors). All responses in Cohort 2 were observed in patients with HRAS mutant HNSCC. These responses were rapid and durable, with 3 responses of > 1.5 yrs in duration. Responses were observed in patients with disease resistant to chemotherapy, cetuximab and immunotherapy. Based on these data, enrollment of patients with HRAS mutant HNSCC has been extended in this cohort (stage 2) to a target of 30 patients with HRAS missense variations expressed at high variant allele frequency (VAF; at least 35% or a minimum of 20% if that patient's baseline serum albumin was least 3.5 mg/dL at the time of tumor biopsy). In stage 2 of the trial, partial responses were noted in 10 of 18 evaluable patients and the remaining 8 patients had a best response of stable disease. Partial responders had a median progression-free survival (PFS) of 8.3 months, and those with stable disease had a median PFS of 4.5 months, which compared favorably to the PFS of 3.2 months for these patients prior to enrollment on KO-TIP-001. Enrollment continues in this cohort, and additionally another cohort (HRAS mutant SCC, excluding HNSCC) was added to the protocol and is currently enrolling. [26,48]

In the ongoing pivotal study in HRAS mutant HNSCC, KO-TIP-007 (AIM-HN/SEQ-HN), no patients have yet been treated with tipifarnib and therefore no preliminary data are available for this study.[26,48]

2.3.2 Pharmacology/Pharmacokinetics/Correlative and Biological Studies

Tipifarnib, when given orally, is rapidly absorbed. The peak plasma concentration, which is dose-dependent, is achieved 3 hours after dosing. Tipifarnib is highly bound to plasma protein. The bioavailability is 29.3%, and absorption is increased by taking tipifarnib with a high fat meal. Tipifarnib is [redacted] metabolized, through mechanisms that involve both CYP450 (CYP3A4, [redacted]) as well as glucuronsyltransferase. Tipifarnib and its metabolites are predominantly [redacted], with [redacted] accounting for [redacted].[26]

2.3.3 Rationale For Dose Selection

2.3.3.1 **3 weeks on/1 week off Dosing (BID on Days 1 – 21 in 28-day treatment cycles)**

In the majority of its phase 2 program, tipifarnib was given orally at a dose of 300 mg bid for 21 days, followed by 1 week of rest, in 28 day treatment cycles (3 weeks on/1 week off schedule). Prior studies have shown that this treatment schedule results in drug exposures equivalent or above those shown to demonstrate anti-tumor activity in preclinical tumor models. In the AML studies which administered tipifarnib at doses up to 600 mg bid for 21 days in 28-day treatment cycles, the most common adverse events were myelosuppression, gastrointestinal disorders, fever, fatigue, hypokalemia, rash, renal impairment, and dyspnea. The most common drug-related grade 3 or 4 events were myelosuppression, hypokalemia, fatigue, and rash. Thrombocytopenia, renal impairment, rash, and sepsis were the most common adverse events that led to discontinuation. In the completed MDS study (INT-28) which administered tipifarnib at a dose of 300 mg bid for 21 days in 28-day treatment cycles, the most common adverse events were myelosuppression, fatigue, diarrhea, nausea, and rash. The most common drug-related grade 3 or 4 events were myelosuppression, fever, pneumonia, bacterial infection, and rash. The most common adverse events that lead to discontinuation were thrombocytopenia and rash. [26]

2.3.3.2 **Alternative Week Dosing (BID on Days 1 – 7 and Days 15 – 21 in 28-day treatment cycles)**

The effect of intermittent schedules of tipifarnib was tested in several adult phase 1 studies, including a 5-day bid dosing followed by 9-day rest (5-day schedule)[49] and two trials investigating a 7-day bid dosing followed by 7-day rest (7-day schedule).[50,51] In the 5-day schedule phase 1 trial in patients with non-hematological malignancies, doses from 25 to 1300 mg bid were explored. No MTD was identified. Dose-limiting toxicity of grade 3 neuropathy was observed in one patient and grade 2 fatigue in 4 of 6 patients treated with 1300 mg bid. Fatigue that was not dose-limiting was observed at the prior dose level (800 mg bid). Of note, myelosuppression which was the most common toxicity in the 21-day schedule, was limited with the 5-day schedule and included a grade 3 neutropenia in a patient with a prior history of myelosuppression treated with 50 mg bid and a grade 2 thrombocytopenia in a patient treated at the 1300 mg bid dose level. No objective responses were noted. [26]

In the first of the weekly schedule studies,[50] the starting dose was 300 mg bid with 300 mg dose escalations to a maximum planned dose of 1800 mg bid. Two of 6 patients with non-hematological tumors in dose level 3 (900 mg bid) developed grade 3 fatigue attributable to study drug, and 600 mg bid on alternate weeks was identified as the recommended phase 2 dose. There were no objective responses but 4 out of 21 patients, 3 of whom had NSCLC, remained on study for at least 1 year with stable disease (12, 13, 16 and 17 months). Five grade 3 events of myelosuppression (out of 21 patients) were described by the authors (doses not indicated) that were not considered dose limiting toxicities (DLTs) and hematological toxicity was described as moderate and manageable. [26]

The second weekly schedule study was conducted in patients with relapsed/refractory AML.[51] Tipifarnib was administered bid on days 1–7 and days 15–21 of 28-day cycles at doses up to 1600 mg bid. At the 400 mg bid dose level, a grade 5 hepatorenal failure occurred, potentially related to the study drug. There

were no additional DLTs reported at 600, 800 or 1000 mg bid dose levels. At the 1200 mg bid dose level, a Grade 3 creatinine elevation was seen in one patient out of 6 treated. At the 1400 mg bid dose level, one patient experienced a Grade 4 hypotension and a rising Grade 2 creatinine that were dose limiting, and a second patient had a rising Grade 2 creatinine that resulted in treatment discontinuation and was therefore considered dose limiting. At the 1600 mg dose level, Grade 3 liver function tests and a rising Grade 2 creatinine were dose limiting, and in a second patient, a rapidly rising creatinine was seen and treatment stopped. As a result, the 1200 mg bid dose was established as the MTD and 7 additional patients treated. Sixteen patients were treated at the 1000 and 1200 mg dosing levels, with 3 of them experiencing complete responses. No formal responses were seen among patients treated at the lower dose levels.[26]

The tipifarnib regimen investigated in KO-TIP-001, a phase 2 study of tipifarnib in nonhematological malignancies that carry HRAS mutations was set with a starting dose of 900 mg, orally, bid on days 1-7 and 15-21 of 28-day treatment cycles. Preliminary data from KO-TIP-001 indicate a tolerability that is broadly similar to the safety profile observed of other tipifarnib regimens in prior clinical studies which administered tipifarnib daily in a 21-day on, 7 days off treatment cycle schedule. The most common AES of tipifarnib including hematological events, gastrointestinal disturbances (nausea, vomiting and diarrhea) and fatigue have been monitorable and manageable with protocol defined assessments and management of toxicity guidance. [redacted] and several subjects have maintained their response and continued on treatment [redacted].[26]

Based on these data, the starting dose for the tipifarnib alternative week regimen was [redacted] mg, orally, bid on days 1-7 and 15-21 of 28-day treatment cycles. Stepwise [redacted] to control treatment-related, treatment-emergent toxicities are allowed and specific toxicity management is detailed in each clinical study protocol.[26]

2.4 Pediatric Studies

2.4.1 Prior Experience in Children

Tipifarnib has been well tolerated in pediatric patients, but the activity of tipifarnib in pediatric malignancies to date has been disappointing.[40-42,45,46] For example, in a phase I trial of tipifarnib in children with solid tumors or neurofibromatosis type 1 (NF1)-associated plexiform neurofibromas, the maximum tolerated dose (MTD) was determined to be 200 mg/m^2/dose given twice daily for 21 days, repeated every 28 days.[41] The observed dose limiting toxicities (DLT) in Cycle 1 were myelosuppression, rash, nausea, vomiting and diarrhea, and no cumulative toxicities were observed. Although the farnesyltransferase activity at the MTD, determined by the percent HDJ2 prenylation in peripheral blood mononuclear cells (PBMCs) was 30% of baseline, no objective responses were observed.[41] Similarly, a phase I trial of tipifarnib in children with leukemia, used a dose of 300 mg/m2/dose given twice daily for 21 days, repeated every 28 days, with observed DLTs of rash, mucositis, and nausea, vomiting and diarrhea. Importantly, neurotoxicity, which was dose limiting in adult patients, was not observed in pediatric patients treated with tipifarnib.[40] Again, although farnesyltransferase activity was inhibited in leukemic blasts, no objective responses to tipifarnib

treatment were observed in this study. Tipifarnib also failed to show clinical benefit in phase II studies in pediatric patients with diffuse intrinsic pontine glioma (DIPG), juvenile myelomonocytic leukemia (JMML) or NF1-associated plexiform neurofibromas. [42,45,46]

The lack of response to tipifarnib in pediatric malignancies may have been, in part, because these trials were conducted without genomic pre-selection of treatment subjects to include only patients with somatic *HRAS* mutations. The study in patients with JMML was the only study of tipifarnib in pediatric patients to identify somatic driver mutations in enrolled patients, but *HRAS* mutations were not among the panel of genes tested. Recently, promising activity of tipifarnib has been demonstrated in adult patients with HRAS-driven head and neck squamous cell carcinoma (HNSCC). [52] Tipifarnib may be similarly effective in pediatric patients with mutant HRAS-driven tumors.

2.4.2 Pharmacology/Pharmacokinetics/Correlative Biological Studies

As noted above, pharmacodynamic measurement of tipifarnib activity in the context of pediatric trials was measured by evaluating the percent farnesylation of HDJ2, in either peripheral blood mononuclear cells or leukemic blasts. [redacted] however, the pharmacokinetics of tipifarnib given in a one week on, one week off dosing schedule has not yet been evaluated in children.[26]

2.5 Overview of Proposed Pediatric Study

This is a phase 2 trial of tipifarnib in children with recurrent or refractory solid tumors, CNS tumors, non-Hodgkin lymphomas and histiocytic disorders harboring specific activating mutations in HRAS.

Doses of up to 300mg/m^2/dose twice daily for 21 out of 28 days have been previously tolerated in children. This is equal to a total dose of 12,600mg/m^2 per cycle. Although the MTD in adults for the 7 day on/ 7 day off schedule was not determined, the current RP2D for adults is 600mg/dose twice daily on a 7 day on/ 7 day off schedule (total dose of 16,800 mg/ cycle; equal to ~9,700mg/m^2/cycle, and therefore less than the cumulative cycle doses previously deemed safe in children). The pediatric [redacted] dose of the current adult RP2D is [redacted] /mg/m^2/dose twice daily ([redacted] mg/m^2/cycle) and therefore, also less than doses previously deemed safe in children, and therefore will serve as the recommended dose for the pediatric MATCH trial.

Tipifarnib will be administered at [redacted] mg/m^2/dose by mouth twice daily for 7 days on followed by 7 days off alternating on a 28 day cycle (i.e., days 1-7 and 15-21 of a 28 day cycle).

The primary aim of this trial will be to establish the objective response rate to tipifarnib. While there will not be multiple pre-determined mutation-based cohorts, responses will be analyzed retrospectively with respect to specific HRAS mutations and variant allele frequency.

Key secondary objectives include further evaluation of the tolerability of tipifarnib in pediatric patients. Toxicity will be assessed using CTCAE V5.0. Imaging for disease evaluation will occur every other cycle x 3, then every three cycles. Disease response will

be assessed according to RECIST v1.1 for solid tumors and 2-dimensional measurement for CNS tumors.

3.0 SCREENING AND STUDY ENROLLMENT PROCEDURES

3.1 Study Enrollment

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

3.1.1 Access requirements for OPEN:

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

Requirements for OPEN access:

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

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

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

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

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

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

Please see [redacted]

3.1.2 IRB Approval

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

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

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

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

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

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

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

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

[redacted]

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

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

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

3.1.3 Genetic Screening Procedures for Eligibility

Patient enrollment onto the APEC1621SC screening protocol is required. In Stage 2 of Pediatric MATCH (effective with Amendment #4 of APEC1621SC for patients enrolling on screening protocol) tumor genomic testing results from a CAP/CLIA-certified laboratory will be reviewed by the APEC1621SC Molecular Review Committee after APEC1621SC screening protocol enrollment to confirm the identification of an actionable Mutation of Interest (aMOI) for which a MATCH treatment subprotocol is available. Questions regarding interpretation of tumor testing results for potential APEC1621M study patients (such as whether a specific mutation would be considered actionable for the study) should be directed to the APEC1621SC and APEC1621M study chairs.

The treatment assignment to MATCH to a subprotocol (if a relevant aMOI is detected) will be communicated to the enrolling institution via the COG treatment assignment mechanism, upon which a reservation to APEC1621M 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 APEC1621M.

3.2 Informed Consent/Assent

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

3.3 Screening Procedures

Diagnostic or laboratory studies performed exclusively to determine eligibility for this trial

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

3.4 Eligibility Checklist

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

3.5 Study Enrollment

Patient may be enrolled on the study once all eligibility requirements for the study have been met. 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 in Stage 2 of Pediatric MATCH (effective with Amendment #4 of APEC1621SC for patients enrolling on screening protocol) is outlined in section 3.1.3.

Patients enrolling onto APEC1621M will have a COG ID obtained through their prior enrollment onto the APEC1621SC screening protocol or a prior COG study. Patients must be enrolled within 2 weeks (14 days) of treatment assignment. Protocol therapy must start no later than 7 calendar days after the date of enrollment. Patients enrolling onto APEC1621M will have a COG ID obtained through their prior enrollment onto the screening protocol or from a prior COG study. Patients who are started on protocol therapy prior to study enrollment will be considered ineligible.

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

3.5.1 Reassignment Request through APEC1621SC (if unable to enroll within 8 week timeframe)

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

Note: No starter supplies will be provided. Drug orders of tipifarnib should be placed with CTEP after enrollment and treatment assignment to APEC1621M with consideration for timing of processing and shipping to ensure receipt of drug supply prior to start of protocol therapy

3.6 Institutional Pathology Report

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

3.7 Dose Assignment

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

4.0 PATIENT ELIGIBILITY

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

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

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

4.1 Inclusion Criteria

4.1.1 APEC1621SC: Patient must have enrolled onto APEC1621SC and must have been given a treatment assignment to MATCH to APEC1621M based on the presence of an actionable mutation as defined in APEC1621SC. Examples of actionable mutations for APEC1621SC are listed [redacted]

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

4.1.3 BSA: Patients must have a body surface area ≥ 0.29 m^2 at enrollment.

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

Note: The following do not qualify as measurable disease:
- malignant fluid collections (e.g., ascites, pleural effusions)
- bone marrow infiltration except that detected by MIBG scan for

neuroblastoma
- lesions only detected by nuclear medicine studies (e.g., bone, gallium or PET scans) except as noted for neuroblastoma
- elevated tumor markers in plasma or CSF
- previously radiated lesions that have not demonstrated clear progression post radiation
- leptomeningeal lesions that do not meet the measurement requirements for RECIST 1.1.

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

4.1.6 Prior Therapy

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

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

i. ≥ 21 days after the last dose of cytotoxic or myelosuppressive chemotherapy (42 days if prior nitrosourea).

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

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

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

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

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

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

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

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

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

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

k. Patients must not have received prior exposure to tipifarnib.

4.1.7 Organ Function Requirements

4.1.7.1 Adequate Bone Marrow Function Defined as:

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

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

not be evaluable for hematologic toxicity.

4.1.7.2 Adequate Renal Function Defined as:

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

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

The threshold creatinine values in this Table were derived from the Schwartz formula for estimating GFR utilizing child length and stature data published by the CDC.

4.1.7.3 Adequate Liver Function Defined as:

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

4.1.7.4 Adequate Neurologic Function Defined as:

- Patients with seizure disorder may be enrolled if on anticonvulsants and well controlled.
- Nervous system disorders (CTCAEv5.0) resulting from prior therapy must be ≤ Grade 2.

4.1.8 Patients must be able to swallow intact tablets or crushed tablets mixed in water, orange juice, apple juice, tomato juice, ginger ale, applesauce, yogurt, protein shake, or a dietary supplement drink (such as Ensure®). PEG-tube or nasogastric tube administration is permitted.

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

4.2 Exclusion Criteria

4.2.1 Pregnancy or Breast-Feeding

Pregnant or breast-feeding women will not be entered on this study due to risks of fetal and teratogenic adverse events as seen in animal/human studies. Pregnancy tests must be obtained in girls who are post-menarchal. Males or females of reproductive potential may not participate unless they have agreed to use two effective contraceptive method for the duration of study treatment. Both female subjects and male subjects with female partners of child-bearing potential must agree to use a highly effective method of contraception for 2 weeks prior to protocol therapy, during, and at least 4 weeks after last dose of tipifarnib.

In addition, since tipifarnib could induce toxicity of male reproductive organs and cause impairment of fertility, sperm cryopreservation should be recommended for male subjects wishing to preserve their fertility following tipifarnib treatment.

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 Patients who are currently receiving drugs that are strong inducers or inhibitors of CYP3A4/5 or UGT are not eligible. Strong inducers or inhibitors of CYP3A4/5 or UGT should be avoided from 14 days prior to the 1st dose of tipifarnib to the end of the study. In addition, patients receiving agents that are sensitive or narrow therapeutic range substrates of CYP3A4/5 are not eligible. [redacted] Note: CYP3A4/5 inducing anti-epileptic drugs and dexamethasone for CNS tumors or metastases, on a stable dose, are allowed.

4.2.3 Patients with known hypersensitivity to tipifarnib or any components of the tablet are not eligible.

4.2.4 Patients with hypersensitivity to imidazoles, such as clotrimazole, ketoconazole, miconazole and others in this drug class are not eligible.

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

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

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

5.0 TREATMENT PROGRAM

5.1 Overview of Treatment Plan

Treatment Schedule Table	
Days 1-7	**Tipifarnib [redacted] mg/m²/dose orally or via NG- or G- tube twice daily (maximum 600 mg/dose BID)**
Days 8-14	Rest
Days 15-21	**Tipifarnib [redacted] mg/m²/dose orally or via NG- or G- tube twice daily (maximum 600 mg/dose BID)**
Days 22-28	Rest
Day 28	Evaluation

Tipifarnib will be given orally with food twice daily (approximately 12 hours apart) on Days 1-7 and Days 15-21 ([redacted]). 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 of 26 cycles).

Tablets should be swallowed whole with water. Tablets may be chewed or crushed if necessary. Crushed tablets can be mixed with water, orange juice, apple juice, apple sauce, ginger ale, yogurt, tomato juice, a protein shake or a dietary supplement drink (such as Ensure®) for oral administration. Use of a percutaneous endoscopic gastrostomy tube (G-tube) or nasogastric (NG) tube is allowed (crushed tablets may be mixed with water with NG or G-tube administration). Patients should be advised to be appropriately hydrated during the course of the study (e.g. drinking at least 8 glasses of water/day for an adolescent or young adult). Refer to [redacted]

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. If a patient vomits after the dose of tipifarnib is administered, that dose should not be repeated. Missed doses should not be taken if it is more than 4 hours past the scheduled time.

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

5.1.1 Therapy Delivery Map

See [redacted] for Cycle 1 and subsequent cycles.

5.1.2 Intra-Patient Escalation

Intrapatient dose escalation is not allowed.

5.2 Criteria for Starting Subsequent Cycles

A cycle may be repeated every 28 days if the patient has at least stable disease and has

again met laboratory parameters as defined in the eligibility section, Section 4.0 and eligible to continue agent administration per the requirements in Section 6.0

5.3 Grading of Adverse Events

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

5.4 Definition of Dose-Limiting Toxicity (DLT)

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

5.4.1 Non-hematological dose-limiting toxicity

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

- Grade 3 nausea and vomiting < 3 days duration
- Grade 3 liver enzyme elevation, including ALT/AST/GGT, that returns to Grade ≤ 1 or baseline prior to the time for the next treatment cycle. Note: For the purposes of this study the ULN for ALT is defined as 45 U/L. See [redacted]
- Grade 3 fever
- Grade 3 infection
- Grade 3 hypophosphatemia, hypokalemia, hypocalcemia or hypomagnesemia responsive to supplementation.
- Grade 3 rash

5.4.1.2 Non-hematological toxicity that causes a delay of ≥ 14 days between treatment cycles.

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

5.4.2 Hematological dose limiting toxicity

In patients evaluable for hematological toxicity (see Section 4.1.7.1), hematological dose limiting toxicity is defined as:

- Grade 4 neutropenia for > 7 days
- Platelet count < 25,000/mm^3 for > 7 days, or requiring a platelet transfusion on 2 separate days, within a 7 day period
- Myelosuppression that causes a delay of > 14 days between treatment cycles.

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

6.0 [redacted]

6.1 [redacted]

6.1.1 [redacted]

6.1.2 [redacted]

6.1.3 [redacted]

6.1.4 [redacted]

6.2 [redacted]

6.2.1 [redacted]

6.2.2 [redacted]

6.2.3 [redacted]

6.3 [redacted]

6.3.1 [redacted]

6.3.2 [redacted]

7.0 SUPPORTIVE CARE AND OTHER CONCOMITANT THERAPY

7.1 Concurrent Anticancer Therapy

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

7.2 Investigational Agents

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

7.3 Supportive Care

Appropriate antibiotics, blood products, antiemetics, fluids, electrolytes and general supportive care are to be used as necessary. See Section 7.5 for drugs that should not be used concomitantly due to potential interactions with tipifarnib. See below for recommendations on management of specific toxicities associated with tipifarnib.

7.4 Growth Factors

Growth factors that support platelet or white cell number or function can only be administered for culture proven bacteremia, invasive fungal infection, or certain hematological dose limiting toxicities. Refer to Section 6.1.2 and Section 6.1.3 for details. The Study Chair should be notified before growth factors are initiated.

7.5 Concomitant Medications

7.5.1 Patients who are currently receiving drugs that are strong inducers or inhibitors of CYP3A4/5 or UGT are not eligible. Strong inducers or inhibitors of CYP3A4/5 or UGT should be avoided from 14 days prior to the 1st dose of tipifarnib to the end of the study. See [redacted] Note: CYP3A4 inducing anti-epileptic drugs and dexamethasone for CNS tumors or metastases, on a stable dose, are allowed.

7.5.2 Patients receiving agents that are sensitive or narrow therapeutic range substrates of CYP3A4/5 are not eligible [redacted]

7.5.3 Tipifarnib is extensively bound to blood albumin and is not dependent on drug concentration. Use caution when co-administering with other highly protein-bound drugs with narrow-therapeutic ranges.

8.0 EVALUATIONS/MATERIAL AND DATA TO BE ACCESSIONED

8.1 Required Clinical, Laboratory and Disease Evaluation

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

STUDIES TO BE OBTAINED	Pre-Study	During Cycle 1	Prior to Subsequent Cycles^
History	X	Weekly	X
Physical Exam with vital signs	X	Weekly	Cycle 2 Day 1 and Cycle 2 Day 15; then prior to all subsequent cycles
Height, weight, BSA	X		X
Performance Status	X		
Pregnancy Test[1]	X		
CBC, differential, platelets	X	Weekly[2,3]	Cycle 2 Day 1 and Cycle 2 Day 15; then prior to all subsequent cycles [2,3]
Urinalysis	X		
Electrolytes including Ca^{++}, PO_4, Mg^{++}	X	Weekly	X
Creatinine, ALT, bilirubin	X	Weekly	X
Albumin	X		X
Tumor Disease Evaluation[4-A, 4-B, 4-C]	X		Every other cycle x 3 then q 3 cycles [4]
Bone Marrow Aspirate and/or biopsy[5,6]	X		
Medication Diary[7]		Weekly	X
[redacted]			[redacted]

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

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

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

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

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

4-A Neurological exam also required for CNS patients.

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

4-C Patients with neuroblastoma must have both CT/MRI and MIBG scintigraphy prior to the start of protocol therapy if the patient was enrolled with or has a history of having MIBG avid tumor. Otherwise the patient must have either FDG-PET/CT or PET/MR prior to the start of protocol therapy. For patients with neuroblastoma and measurable disease by CT or MRI, lesions should be measured and followed using the same modality (CT or MRI) in addition to MIBG or FDG-PET/CT. For patients with neuroblastoma and evaluable disease by MIBG scintigraphy, use the same modality (MIBG scintigraphy) to image and follow patients; CT/MRI are not required but may be performed as clinically indicated. Refer to Section 12.5 and Section 12.8

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

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

7. The medication diary should be collected and reviewed weekly during cycle 1 ([redacted]). The medication diary should also be reviewed after completion of each treatment cycle and uploaded into RAVE.

8. [redacted]

8.2 Radiology Studies

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

8.2.2 Technical Details of Submission:

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

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

to use that application.

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

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

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

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

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

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

8.3 [redacted]

8.3.1 [redacted]

[redacted]

8.3.2 [redacted]

8.3.3 [redacted]

8.3.4 [redacted]

[redacted]

9.0 AGENT INFORMATION

9.1 Tipifarnib (12/22/2021)

(R115777, Zarnestra®) [redacted]

9.1.1 Source and Pharmacology:

Tipifarnib is a potent and selective nonpeptidomimetic inhibitor of farnesyltranferase (FTI) both in vitro and in vivo. Its mechanism of action seems to be in the context of angiogenesis inhibition, induction of apoptosis and direct antiproliferative effects. FTIs have consistently shown high activity in HRAS mutated tumor cell lines.

9.1.1.1 Pharmacokinetics (PK)

Tipifarnib is rapidly absorbed after oral administration with Cmax observed within 2 to 4 hours after dosing. From population PK analyses, the absolute bioavailability of tipifarnib under fed conditions is 29.3% in cancer patients. Concomitant intake of a high fat meal increases the extent of absorption by an average of 26.8% compared with administration under fasting conditions. The PK profile of tipifarnib is consistent with a 3-compartment disposition model, with an initial fast distribution half-life (alpha) of about 36 minutes, followed by a dominant elimination half- life (beta) of about 2.4 hours, and a slower terminal half-life (gamma) of about 19 hours. Tipifarnib does not accumulate with multiple dosing. Linear PK are observed for tablets over the dose range of 100 mg through 600 mg. The steady-state volume of distribution following i.v. administration to cancer patients is 169 L. The binding of tipifarnib to plasma proteins is extensive, mostly to albumin and to a lesser extent alpha-1 acid glycoprotein and is not dependent on tipifarnib concentrations.

Tipifarnib is extensively metabolized following oral administration. Little or no tipifarnib is excreted unchanged in the urine. Less than 6% of the initial dose is recovered in feces as the parent compound. Approximately 14.4% of the administered dose is excreted in the urine as tipifarnib-glucuronide. The mean Cmax value in plasma was about 95% higher and the mean AUC12h value about 85% higher in subjects with mild hepatic impairment compared to subjects with normal liver function. These results are consistent with its extensive hepatic metabolism as the predominate route of tipifarnib elimination.

9.1.2 Potential Drug Interactions

Tipifarnib is a substrate for the CYP450 enzymes (mostly CYP 3A4/5) and UDP-glucuronosyltransferase (UGT). Due to the potential for drug-drug interactions, tipifarnib should not be administered with strong inhibitors or inducers of CYP3A4/5 or UGT. Additionally, CYP 2C19, 2D6, and 2E1 were observed to play a minor role in tipifarnib clearance in human liver microsomes. Population PK trials using different classes of common concomitant medications show that 1) enzyme-inducing antiepileptic drugs can significantly reduce tipifarnib plasma concentrations and 2) antifungal azoles do not alter tipifarnib clearance.

In vitro, tipifarnib inhibited the metabolism of CYP450 enzymes 2C8/9/10, 3A4/5, 2A6, and 2D6. Although the interaction is not likely based on very low unbound concentrations of tipifarnib, the potential for drug-drug interactions between tipifarnib and drugs metabolized by these enzymes cannot be excluded. Patients should not receive concomitant medication with sensitive or narrow therapeutic range substrates of these CYP isoforms while receiving tipifarnib.

Tipifarnib is extensively bound to blood albumin and is not dependent on drug concentration. Use caution when co-administering with other highly protein-bound drugs with narrow-therapeutic ranges.

Pharmacokinetic trials with tipifarnib and either omeprazole or rabeprazole showed no clinically meaningful effect on tipifarnib exposure. The impact of aluminum or magnesium-containing antacids has not been evaluated.

Patient Care Implications:
Tipifarnib is contraindicated in individuals with hypersensitivities to imidazole-containing agents (e.g. clotrimazole, ketoconazole, miconazole).

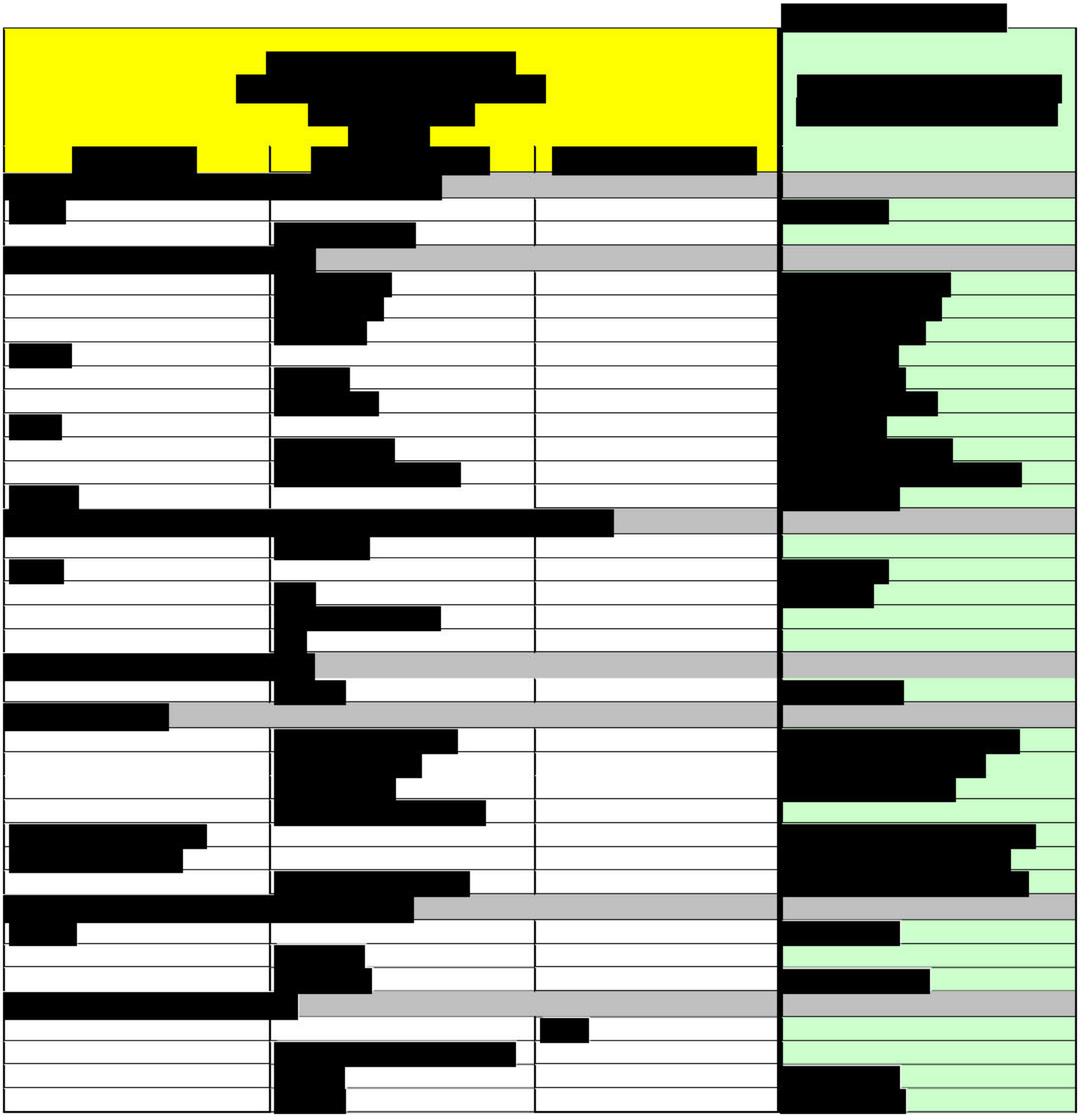
Advise women of child-bearing potential and men with female partners of child-bearing potential to use two (2) highly effective forms of contraception 2 weeks prior to starting study treatment, while receiving study treatment and for 1 (one) month after the last dose.

Since tipifarnib could induce toxicity of male reproductive organs and potentially impair fertility, sperm cryopreservation is recommended for men study participants who wish to preserve their fertility following study treatment.

9.1.3 Toxicity

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

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.



[redacted]

Note: R115777 (tipifarnib) in combination with other agents could cause an exacerbation of any adverse event currently known to be caused by the other agent, or the combination may result in events never previously associated with either agent.

9.1.4 **Formulation and Stability:**

Two strengths (100 mg and 300 mg) of film-coated, compressed tablet formulations are provided. The 100 mg tablets are circular and white with a tablet weight of 223.5 mg. The 300 mg tablets are white and capsule-shaped with a tablet weight of 669.5 mg. Tablets are supplied in HDPE bottles containing 45 tablets per bottle.

Tablet formulations have the same qualitative composition. The tablets contain tipifarnib and the following inactive ingredients: lactose monohydrate, maize starch, hypromellose, microcrystalline cellulose, crospovidone, colloidal anhydrous silica, and magnesium stearate. The film coatings contain hypromellose, titanium dioxide, lactose monohydrate, polyethylene glycol, and triacetin. The non-functional film coating is for taste masking purposes.

9.1.4.1 Storage

The tablets should be stored at 25°C (77°F); excursions permitted to 15°C to 30°C (59°F to 86°F).

If a storage temperature excursion is identified, promptly return tipifarnib to controlled room temperature (25°C/77°F) and quarantine the supplies. Provide a detailed report of the excursion (including documentation of temperature monitoring and duration of the excursion) to mailto:PMBAfterHours@mail.nih.gov for determination of suitability.

9.1.4.2 Stability

Shelf life dating is printed on the bottle label. Stability studies are ongoing. The manufacturer does not have stability data to support repackaging tablets. Dispense tablets in the original container.

9.1.5 **Guidelines for Administration**

See Section 6.0 for dose modifications and Section 5.0 Treatment section of the protocol for dosing and administration details.

Tipifarnib is administered orally twice daily with food. No dietary restrictions related to tipifarnib are required. Patients should administer their dose of tipifarnib with a meal as the presence of food has been shown to improve the absorption of tipifarnib, as well as to reduce variability in the pharmacokinetic profile.

Tablets should be swallowed whole with water. Tablets may be chewed or crushed if necessary. Use of a percutaneous endoscopic gastrostomy tube (G-tube) or nasogastric tube (NG) is allowed.

Crushed Tablets for Oral, G-Tube or NG Administration

- Tablets should be crushed with a commercial tablet crusher, transferred into a dosing cup/glass and crusher rinsed with water.
- Crushed tipifarnib tablets might have a bitter flavor profile. The crushed tablets can be mixed with the following liquids for oral administration: water, orange juice, apple juice, tomato juice, a protein shake or a dietary supplement drink (eg., Ensure®).
- Patients should be instructed to consume the mixture with a meal. Following consumption, the dosing cup or glass should be rinsed with water and each rinse completely swallowed to ensure the entire dose is consumed.
- Crushed tablets mixed with liquids intended for oral administration should be used within 2 hours of mixing. The mixing container should be rinsed and the rinse consumed as well.
- For NG or G-tube administration crushed tablets should be mixed with sterile swater.
- After completion of dosing, the NG or G-tube should be flushed with 10-20mL sterile water to ensure that the entire dose is delivered.
- Crushed tablets mixed with water intended for nasogastric or gastric tube administration should be used within 16 hours of mixing.

Unless otherwise contraindicated, subjects should be advised to be appropriately hydrated during the course of the study (e.g. drinking at least 8 glasses of water/day). Vomitted doses should not be made up. Missed doses should not be taken if it is more than 4 hours past the scheduled time. Patients should continue with the next scheduled dose.

9.1.6 Supplier:
Supplied by Kura Oncology and distributed by a Division of Cancer Treatment and Diagnosis the Pharmaceutical Management Branch (DCTD), NCI.

9.1.7 **Obtaining the Agent**

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

Note: No starter supplies will be provided. Drug orders of tipifarnib should be placed with CTEP after enrollment and treatment assignment to APEC1621M with consideration for timing of processing and shipping to

ensure receipt of drug supply prior to start of protocol therapy. If expedited shipment is required, sites should provide an express courier account through the Online Agent Order Processing (OAOP) application. Provide the patient ID number in the comment box when submitting an order request.

Submit agent requests through the PMB Online Agent Order Processing (OAOP) application. Access to OAOP requires the establishment of a CTEP Identity and Access Management (IAM) account and the maintenance of an "active" account status, "current" password, and active person registration status. For questions about drug orders, transfers, returns, or accountability call or email PMB anytime. Refer to the PMB's website for specific policies and guidelines related to agent management.

9.1.8 Agent Accountability

9.1.8.1 Agent Inventory Records

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

9.1.9 Investigator Brochure Availability

The current versions of the IBs for the agents will also be accessible to site investigators and research staff through the PMB Online Agent Order Processing (OAOP) application. Access to OAOP requires the establishment of a CTEP Identity and Access Management (IAM) account and the maintenance of an "active" account status, "current" password, and active person registration status. Questions about IB access may be directed to the PMB IB coordinator via email.

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

11.0 STATISTICAL AND ETHICAL CONSIDERATIONS

11.1 Sample Size and Study Duration

APEC1621M will require a minimum of 20 evaluable patients and a maximum of 49 patients, allowing for 15% inevaluability. Assuming an enrollment rate of 2-9 biomarker positive patients per year, the primary cohort of this subprotocol is expected to be completed within 2.7-12 years.

11.2 Dosing Considerations

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

Please see Section 5.1 for a specific discussion of the dosing of tipifarnib to be used in this study. If there is no prior pediatric phase 1 data, study investigators will review relevant data with the pharmaceutical partner to identify a drug specific dosing plan for testing in children with relapsed or refractory cancer, and trial participants will be closely monitored to ensure tolerability of the selected dose. Limited pharmacokinetic sampling may be done for patients enrolled on these arms. In general, the dosing for the Pediatric MATCH subprotocols will follow the guidelines below:

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

11.3 Study Design

The primary cohort and any biomarker negative expansion cohorts defined below will employ single stage A'Hern designs of N=20 and N=10 respectively. The agent will be deemed worthy of further study in the relevant subset of patients (i.e. biomarker positive in any histology, biomarker positive in a particular histology, etc) if the decision rule is met. Operating characteristics are shown below.

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

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

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

11.3.1 Primary Cohort:

APEC1621M will evaluate a primary cohort of 20 mutation-matched ("biomarker positive") evaluable patients of any histology for the primary study aim of determining the objective response rate (CR/PR according to the response criteria in Section 12.3) to the agent. Using an A'Hern design[53] with alpha=10%, a sample of N=20 will provide 90% power to detect an improvement in response rate from 5%, if the treatment is ineffective, to 25% if the targeted therapy is sufficiently effective to warrant further study. If there are at least 3 responses out of 20 in the primary cohort, the biomarker/therapy match will be deemed a success.

11.3.2 Histology-Specific Biomarker Positive Expansion Cohorts:

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

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.[54] 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. 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 Gender and Minority Accrual Estimates

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

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

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

12.0 EVALUATION CRITERIA

12.1 Common Terminology Criteria for Adverse Events (CTCAE)

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

12.2 Progression-Free Survival

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

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

12.3 Response Criteria for Patients with Solid Tumors

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

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

have MIBG positive lesions should be assessed for response as solid tumor patients with measurable disease.

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

12.3.1 Definitions

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

12.3.1.2 Evaluable Non-Target Disease Response:

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

12.3.2 Disease Parameters

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

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

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

12.3.2.3 Non-measurable disease: All other lesions (or sites of disease), including small lesions (longest diameter < 10 mm or pathological lymph nodes with ≥ 10 to < 15 mm short axis), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites,

pleural/pericardial effusions, lymphangitis cutis/pulmonitis, inflammatory breast disease, and abdominal masses (not followed by CT or MRI), are considered as non-measurable.

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

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

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

12.3.3 Methods for Evaluation of Measurable Disease

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

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

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

a ruler to estimate the size of the lesion, is recommended.

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

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

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

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

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

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

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

a. Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.
b. No FDG-PET at baseline and a positive FDG-PET at follow-up: If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD. If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional

follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan). If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.

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

For patients with a positive PET scan at diagnosis, PET can be used to follow response in addition to a CT scan using the International Pediatric non-Hodgkin Lymphoma Response Criteria.[55]

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 tumor markers if elevated at study enrollment (for patients with neuroblastoma).

Partial Response (PR): At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters

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

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as

reference the smallest sum diameters while on study

12.4.2 Evaluation of Non-Target Lesions

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

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

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

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

12.4.3 Overall Response Assessment

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

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

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

reported as "*symptomatic deterioration.*" Every effort should be made to document the objective progression even after discontinuation of treatment.

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

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

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

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

CT/MRI	MIBG	Bone Marrow	Overall
PD	Any	Any	PD
Any	PD	Any	PD
Any	Any	Any	PD
Any	Any	PD	PD
SD	CR/PR/SD	Non-PD	SD
PR	CR/PR	Non-PD	PR
CR/PR	PR	Non-PD	PR
CR	CR	Non-PD	PR
CR	CR	CR	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

This study will use the revised International Neuroblastoma Response Criteria for disease assessment.[56] The updated response criteria incorporate current approaches to imaging of neuroblastoma, including functional imaging. Furthermore, a standardized approach to assessment of bone marrow involvement is included. The current INRC do **not** include methods of disease assessment that are less sensitive and/or specific for neuroblastoma (^{99}Tc bone scan and catecholamine levels).

Key sites and terms

Primary site: The primary site will be identified as a measurable lesion ≥ 10 mm in diameter as assessed by cross sectional imaging (CT or MRI scan). Primary site measurements must be recorded in millimeters (or decimal fractions of centimeters). The longest diameter of the primary tumor will be recorded at baseline. Serial measurements of the primary tumor will include assessment of tumor size in the same orthogonal plane at the time of each evaluation.[57] In patients with bilateral adrenal lesions, response will be based on the sum of the longest dimensions of both adrenal lesions unless biopsy proves one to be ganglioneuroma rather than neuroblastoma/ganglioneuroblastoma. In patients with multi-focal non-adrenal disease, the largest

tumor will be considered the primary tumor. Response in additional lesions will be assessed as described below for metastatic lesions.

Tracer avidity (^{123}I-MIBG or FDG-PET) in the primary site will be recorded at baseline. The scan appropriate for serial disease assessments should be used at each disease re-evaluation timepoint (e.g. ^{123}I-MIBG avid primary lesions should be followed using ^{123}I-MIBG scans during therapy).

Malignant lymph nodes: To be considered pathologically enlarged and measurable, a metastatic lymph node must be ≥ 15 mm in short axis when assessed by CT or MRI scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis of a discreet lymph node will be measured and followed as per RECIST criteria. Patients with neuroblastoma may have conglomerate masses of non-discrete lymph nodes (i.e. multiple contiguous retroperitoneal nodes). When a short axis of a discreet node cannot be identified, a lymph node conglomerate can be measured using the longest diameter of the composite lesion. Tracer avidity of metastatic nodes will be recorded at baseline and during disease evaluations.

For the purposes of response assessment, target lesions are disease sites that are measurable (non-nodal soft tissue mass ≥ 10 mm in longest dimension or lymph node ≥ 15 mm in short axis) and tracer avid OR are biopsy positive for neuroblastoma or ganglioneuroblastoma. The sum of diameters of target lesions is defined as the sum of the short axis of discrete lymph nodes (i.e., cervical, axillary nodes) added to the sum of the longest diameters of non-lymph node soft tissue metastases.

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 are considered non-measurable.

Bone lesions: Osteomedullary disease will be assessed using ^{123}I-MIBG scans or FDG-PET scans. Technetium bone scans are no longer used as part of the revised INRC and are not included as part of disease reassessments during this trial. The extent of tracer avid disease will be evaluated using the Curie scoring system (see Curie Scoring System). SPECT may be used to confirm the presence or absence of lesions in a given segment of the body. The absolute Curie score should be reported at baseline. A relative score (Curie score at the time of disease assessment divided by baseline Curie score) should be recorded at the time of each disease evaluation.

Bone marrow disease: Bilateral bone marrow aspirates and trephine biopsies are required at disease assessment timepoints. The extent of marrow involvement in all four samples should be recorded. Use of immunohistochemical staining for evaluation of trephine biopsies is strongly encouraged. The percentage of tumor infiltration of bone marrow space assessed by histologic evaluation of trephine/biopsies or counting the number of tumor cells in aspirates by cytology or immunocytology (recommended if available) divided by the number of hematopoietic/mononuclear cells evaluated to obtain a percentage involvement (methodology described by Burchill et al.).[58] The bone marrow sample with the highest percentage of tumor infiltration is used for response assessment. If > 0% to ≤ 5% tumor infiltration is the highest percentage seen among samples obtained, the result should be recorded as minimal marrow disease.

12.5.1 Response Criteria

PRIMARY (SOFT TISSUE) TUMOR RESPONSE[1]

RESPONSE	ANATOMICAL IMAGING + MIBG (FDG-PET[2]) IMAGING
Complete Response (CR)	• < 10 mm residual soft tissue at primary site, AND • complete resolution of MIBG or FDG-PET uptake (for MIBG non-avid tumors) at primary site
Partial Response (PR)	• ≥ 30% decrease in longest diameter (LD) of primary site • MIBG or FDG-PET uptake at primary site stable, improved or resolved
Progressive Disease (PD)	• > 20% increase in longest diameter taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study), AND • a minimum absolute increase of 5 mm in longest dimension[3]
Stable Disease (SD)	Neither sufficient shrinkage for PR nor sufficient increase for PD at the primary site

[1]Not for use in assessment of metastatic sites

[2] For ^{123}I-MIBG non-avid tumors

[3] A mass that has not met PD measurement criteria but has fluctuating ^{123}I-MIBG avidity will not be considered progressive disease.

RESPONSE AT METASTATIC SOFT TISSUE AND BONE SITES

RESPONSE	ANATOMICAL IMAGING + MIBG (FDG-PET[1]) IMAGING

Complete Response (CR)	• Resolution of all sites of disease defined as:
	  • Non-primary target and non-target lesions measure < 10 mm AND
	  • Lymph nodes identified as target lesions decrease to a short axis < 15 mm, AND
	  • MIBG uptake or FDG-PET uptake (for MIBG non-avid tumors) of non-primary lesions resolves completely

Partial Response (PR)	• ≥ 30% decrease in sum of diameters[2] of non-primary target lesions compared to baseline, AND all of the following:

	• Non-target lesions may be stable or smaller in size AND • No new lesions AND • ≥ 50% reduction in MIBG absolute bone score (Relative MIBG bone score ≥ 0.1 to ≤ 0.5) or ≥ 50% reduction in number of FDG-PET avid bone lesions[3,4]
Progressive Disease (PD)	Any of the following[5]: • Any new soft tissue lesion detected by CT or MRI that is also MIBG avid or FDG-PET avid; • Any new soft tissue lesion seen on anatomic imaging that is biopsied and confirmed to be a neuroblastoma or ganglioneuroblastoma; • Any new bone site that is MIBG avid; • A new bone site that is FDG-PET avid (for MIBG non-avid tumors) AND has CT or MRI findings consistent with tumor OR has been confirmed histologically to be neuroblastoma or ganglioneuroblastoma; • > 20% increase in longest diameter taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study), AND a minimum absolute increase of 5 mm in sum of diameters of target soft tissue lesions; • Relative MIBG score ≥ 1.2[4]
Stable Disease (SD)	Neither sufficient shrinkage for PR nor sufficient increase for PD of non-primary lesions

[1] Used for MIBG non-avid tumors

[2]Sum of diameters is defined as the sum of the short axis of discrete lymph nodes (i.e., cervical, axillary nodes) added to the sum of the longest diameters of non-lymph node soft tissue metastases. Masses of conglomerate non-discrete lymph nodes will be measured using longest diameter.

[3] For patients with soft tissue metastatic disease, resolution of MIBG and/or FDG-PET uptake at the soft tissue sites is not required; all size reduction criteria must be fulfilled.

[4]Relative Curie score is the absolute score for bone lesions at time of response assessment divided by the absolute score for bone lesions at entry onto a clinical trial. MIBG-SPECT or MIBG-SPECT/CT may be used for scoring purposes but the same imaging methodology should be used for all evaluations.

[5]The post-infusion MIBG scan is not considered a diagnostic study for the purposes of response assessment. Progressive disease should NOT be designated on the basis of this scan.

BONE MARROW RESPONSE

RESPONSE	BONE MARROW STATUS[1]
Complete response (CR)	Bone marrow with no tumor infiltration upon reassessment, independent of baseline tumor involvement
Progressive disease (PD)	Any of the following: • Bone marrow without tumor infiltration that becomes > 5% tumor infiltration upon reassessment; or • Bone marrow with tumor infiltration that increases by > 2 fold and has > 20% tumor infiltration upon reassessment.
Minimal disease (MD)	Any of the following: • Bone marrow with ≤ 5% tumor infiltration and remains > 0-≤ 5% tumor infiltration upon reassessment; or • Bone marrow with no tumor infiltration that becomes ≤ 5% tumor infiltration upon reassessment; or • Bone marrow with >20% tumor infiltration that has > 0-≤ 5% tumor infiltration upon reassessment.
Stable disease (SD)	Bone marrow with tumor infiltration that remains positive with > 5% tumor infiltration upon reassessment but does not meet CR, MD or PD criteria

[1]Immunohistochemistry strongly encouraged

DETERMINATION OF OVERALL RESPONSE

RESPONSE	CRITERIA
Complete Response (CR)	All components meet criteria for CR
Partial Response (PR)	PR in at least one component and all other components are either CR, MD (Bone marrow), PR (Soft tissue or Bone) or Not involved (NI); no component with PD.
Minor Response (MR)	PR or CR in at least one component but at least one other component with SD; no component with PD.
Stable Disease (SD)	SD in one component with no better than SD or NI in any other component; no component with PD.
Progressive Disease (PD)	Any component with PD

NI = Not involved, site not involved at study entry and remains not involved; MD = Minimal Disease, for bone marrow assessment only.

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 12.8 from a sequence of overall response assessments.

Primary Tumor	Soft Tissue and Bone Metastatic Disease (MIBG or FDG-PET or PET/MR)	Bone Marrow Metastatic Disease	Overall
CR	CR	CR	CR
CR for one response component with either CR or NI for other components			CR
CR	CR	MD	PR
CR	PR	CR	PR
CR	PR	MD	PR
CR	PR	NI	PR
CR	NI	MD	PR
PR	CR	CR	PR
PR	CR	NI	PR
PR	CR	MD	PR
PR	PR	CR	PR
PR	PR	NI	PR
PR	PR	MD	PR
PR	NI	CR	PR
PR	NI	NI	PR
PR	NI	MD	PR
NI	CR	MD	PR
NI	PR	CR	PR
NI	PR	MD	PR
CR	CR	SD	MR
CR	PR	SD	MR
CR	SD	CR	MR
CR	SD	MD	MR
CR	SD	SD	MR
CR	SD	NI	MR
CR	NI	SD	MR
PR	CR	SD	MR
PR	PR	SD	MR
PR	SD	CR	MR
PR	SD	MD	MR
PR	SD	SD	MR
PR	SD	NI	MR
PR	NI	SD	MR
SD	CR	CR	MR
SD	CR	MD	MR
SD	CR	SD	MR
SD	CR	NI	MR
SD	PR	CR	MR
SD	PR	MD	MR
SD	PR	SD	MR
SD	PR	NI	MR
SD	SD	CR	MR
SD	NI	CR	MR
NI	CR	SD	MR
NI	PR	SD	MR
NI	SD	CR	MR
SD	SD	MD	SD
NI	SD	MD	SD
SD	NI	MD	SD
NI	NI	MD	SD
SD	SD	SD	SD
SD	NI	SD	SD
NI	SD	SD	SD
NI	SD	NI	SD
NI	NI	SD	SD
PD in any one component			PD
Response of Not Evaluable for any one of the 3 components that had measurable/evaluable tumor at study enrollment and no PD for any component			Not Evaluable
No response evaluation performed for any of the 3 components			Not Done

CR: Complete Response; MD: Minimal Disease; PR: Partial Response; MR: Minor Response; SD: Stable Disease; PD: Progressive disease; NI: not involved; site not involved at study entry and remains not involved

Curie Scoring Summary

Table 1a. Scoring skeletal disease

Regions 1 – 9	
Scoring	MIBG uptake
0	No MIBG uptake
1	1 focal site
2	> 1 focal site
3	≥ 50% of a region

Table 1b. Scoring soft tissue disease

Region 10 (Primary soft tissue site)	
Scoring	MIBG uptake
0	No soft tissue uptake
1	1 focal soft tissue site
2	> 1 focal soft tissue site
3	≥ 50% of a region (chest, abdomen)

Region	Site	Curie score
1	Head / Neck	
2	Cervico-Thoracic spine	
3	Ribs / Sternum / Clavicles/ Chest	
4	Lumbar / Sacral spine	
5	Abdomen/Pelvis	
6	Upper Extremity (Proximal)	
7	Upper Extremity (Distal)	
8	Lower Extremity (Proximal)	
9	Lower Extremity (Distal)	
10	Soft Tissue	
TOTAL	Total scores from Regions 1 - 10	

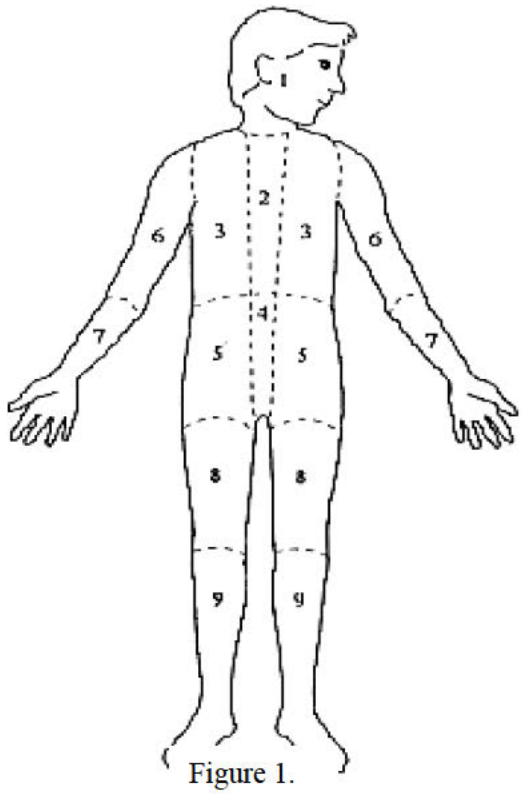


Figure 1.

12.6 Response Criteria for Patients with CNS Tumors

12.6.1 Measurable Disease

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

12.6.2 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.

12.6.3 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.

12.6.4 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.

12.6.5 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.

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

12.6.7 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.

12.7 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[55], with modification from the Lugano classification.[59]

12.7.1 Disease Parameters

12.7.1.1 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).

12.7.1.2 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).

12.7.1.3 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.

12.7.2 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

12.7.3 Evaluation of Non-measured Lesions (CT-based response, PET/CT based response not applicable)[59]

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.

12.7.4 Evaluation of organ enlargement

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

12.8 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.

12.8.1 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

12.8.2 Duration of Response

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

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

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

13.0 ADVERSE EVENT REPORTING REQUIREMENTS

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

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

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

13.1 Expedited Reporting Requirements – Serious Adverse Events (SAEs)

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

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

13.1.1 Reporting Requirements - Investigator Responsibility

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

Any medical documentation supporting an expedited report (eg, H & P, admission and/or notes, consultations, ECG results, etc.) MUST be faxed within 48-72 hours to the NCI. NOTE: English is required for supporting documentation submitted to the numbers listed below in order for the NCI to meet the regulatory reporting timelines.

Fax supporting documentation **for AEs related to investigational agents supplied under a CTEP IND** to: (301) 897-7404).

Also: Fax or email supporting documentation to COG for **all** IND studies (Fax# (310) 640-9193; email: COGAERS@childrensoncologygroup.org; Attention: COG AERS Coordinator).

- **ALWAYS include the ticket number on all faxed documents.**
- **Use the NCI protocol number and the protocol-specific patient ID provided during trial registration on all reports.**

13.1.2 CTEP-AERS Expedited Reporting Methods

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

Send supporting documentation to the NCI by fax (fax# 301-640-9193) and by email to COGCAdEERS@childrensoncologygroup.org , the APEC1621M COG Study Assigned Research Coordinator, and to COGAERS@childrensoncologygroup.org; Attention: COG AERS Coordinator. **ALWAYS include the ticket number on all faxed and emailed documents**.

13.2 Steps to Determine If an Adverse Event Is To Be Reported In an Expedited Manner

Step 1: Identify the type of adverse event using the current version of the NCI CTCAEv5.0. The descriptions and grading scales found in the current version of the CTCAEv5.0 will be used for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAEv5.0. A copy of the CTCAEv5.0 can be downloaded from the CTEP website (http://ctep.cancer.gov).

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

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

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

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

- Any medical event equivalent to CTCAEv5.0 grade 3, 4, or 5 that precipitates hospitalization (or prolongation of existing hospitalization) must be reported regardless of attribution and designation as expected or unexpected with the exception of any events identified as protocol-specific expedited adverse event reporting exclusions.
- Any event that results in persistent or significant disabilities/incapacities, congenital anomalies, or birth defects must be reported via CTEP-AERS if the event occurs following treatment with an agent under a CTEP IND.
- Use the NCI protocol number and the protocol-specific patient ID provided during trial registration on all reports.
- As referenced in the CTEP Adverse Events Reporting Requirements, an AE that resolves and then recurs during a subsequent cycle does not require CTEP-AERS reporting unless (1) the Grade increases; or (2) hospitalization is associated with the recurring AE.
- Some adverse events require notification **within 24 hours** (refer to Table A) to NCI via the web at http://ctep.cancer.gov (telephone CTEP at: **301-897-7497** within 24 hours of becoming aware of the event if the CTEP-AERS 24-Hour Notification web-based application is unavailable). Once internet connectivity is restored, a 24-hour notification phoned in must be entered electronically into CTEP-AERS by the original submitter at the site.
- When the adverse event requires expedited reporting, submit the report **within 5 or 7 calendar days** of learning of the event (refer to Table A).

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

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

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

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

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

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

Expedited AE reporting timelines are defined as:

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

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

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

- All Grade 3, 4, and Grade 5 AEs

Expedited 7 calendar day reports for:

- Grade 2 AEs resulting in hospitalization or prolongation of hospitalization

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

Effective Date: May 5, 2011

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

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

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

- 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
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	Edema Limbs
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	Pain
METABOLISM AND NUTRITION DISORDERS	Dehydration
PSYCHIATRIC DISORDERS	Insomnia
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	Cough
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	Purpura

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

13.4 Definition of Onset and Resolution of Adverse Events

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

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

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

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

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

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

13.5 Other Recipients of Adverse Event Reports

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

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

13.6 Specific Examples for Expedited Reporting

13.6.1 Reportable Categories of Death

- Death attributable to a CTCAE v5.0 term.
- Death Neonatal: A disorder characterized by "Newborn deaths occurring during the first 28 days after birth."
- Sudden Death NOS: A sudden (defined as instant or within one hour of the onset of symptoms) or an unobserved cessation of life that cannot be attributed to a CTCAE v5.0 term associated with Grade 5.
- Death NOS: A cessation of life that cannot be attributed to a CTCAE 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) should be submitted.

- Any death occurring within 30 days of the last dose, regardless of attribution to the investigational agent/intervention requires expedited reporting within 24 hours.
- Any death that occurs more than 30 days after the last dose of treatment with an investigational agent which can be attributed (possibly, probably, or definitely) to the agent and is not clearly due to progressive disease must be reported via CTEP-AERS per the timelines outlined in the table above.

13.6.2 Reporting Secondary Malignancy

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

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

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

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

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

13.6.3 Reporting Pregnancy, Pregnancy Loss, and Death Neonatal

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

13.6.4 Pregnancy

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

Pregnancy needs to be followed **until the outcome of the pregnancy is known** at

intervals deemed appropriate by her physicians. The "Pregnancy Information Form" should be used for all necessary follow ups. 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.

13.6.5 Pregnancy Loss (Fetal Death)

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

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

13.6.6 Death Neonatal

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

14.0 RECORDS, REPORTING, AND DATA AND SAFETY MONITORING PLAN

14.1 Categories of Research Records

Research records for this study can be divided into three categories

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

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

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

See separate CRF Packet, which includes submission schedule.

14.2 CDUS

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

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

14.3 **CRADA/CTA/CSA**

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

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

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

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

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

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

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

3. Clinical Trial Data and Results and Raw Data developed under a Collaborative Agreement will be made available exclusively to Collaborator(s), the NCI, and the

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

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

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

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

   Email: ncicteppubs@mail.nih.gov

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

14.4 Data and Safety Monitoring Plan

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

14.4.1 Data and Safety Monitoring Committee

This study will be monitored in accordance with the Children's Oncology Group policy for data and safety monitoring of Phase 1 and 2 studies. In brief, the role of the COG Data and Safety Monitoring Committee is to protect the interests of patients and the scientific integrity for all Phase 1 and 2 studies. The DSMC consists of a chair; a statistician external to COG; one external member; one consumer representative; the lead statistician of the developmental therapy scientific committee; and a member from the NCI. The DSMC meets at least every 6 months to review current study results, as well as data available to the DSMC from other related studies. Approximately 6 weeks before each meeting of the Phase 1 and 2 DSMC, study chairs will be responsible for working with the study

statistician to prepare study reports for review by the DSMC. The DSMC will provide recommendations to the COG Developmental Therapeutics Chair and the Group Chair for each study reviewed to change the study or to continue the study unchanged. Data and Safety Committee reports for institutional review boards can be prepared using the public data monitoring report as posted on the COG Web site.

14.4.2 Monitoring by the Study Chair and MATCH Leadership

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

REFERENCES

1. Prior IA, Lewis PD, Mattos C: A comprehensive survey of Ras mutations in cancer. Cancer Res 72:2457-67, 2012
2. Cox AD, Fesik SW, Kimmelman AC, et al: Drugging the undruggable RAS: Mission possible? Nat Rev Drug Discov 13:828-51, 2014
3. Cox AD, Der CJ: Ras history: The saga continues. Small GTPases 1:2-27, 2010
4. Villanueva J, Infante JR, Krepler C, et al: Concurrent MEK2 mutation and BRAF amplification confer resistance to BRAF and MEK inhibitors in melanoma. Cell Rep 4:1090-9, 2013
5. Lito P, Saborowski A, Yue J, et al: Disruption of CRAF-mediated MEK activation is required for effective MEK inhibition in KRAS mutant tumors. Cancer Cell 25:697-710, 2014
6. Sos ML, Fischer S, Ullrich R, et al: Identifying genotype-dependent efficacy of single and combined PI3K- and MAPK-pathway inhibition in cancer. Proc Natl Acad Sci U S A 106:18351-6, 2009
7. Zhu Z, Golay HG, Barbie DA: Targeting pathways downstream of KRAS in lung adenocarcinoma. Pharmacogenomics 15:1507-18, 2014
8. Chen X, Stewart E, Shelat AA, et al: Targeting oxidative stress in embryonal rhabdomyosarcoma. Cancer Cell 24:710-24, 2013
9. Shern JF, Chen L, Chmielecki J, et al: Comprehensive genomic analysis of rhabdomyosarcoma reveals a landscape of alterations affecting a common genetic axis in fusion-positive and fusion-negative tumors. Cancer Discov 4:216-31, 2014
10. Eleveld TF, Oldridge DA, Bernard V, et al: Relapsed neuroblastomas show frequent RAS-MAPK pathway mutations. Nat Genet 47:864-71, 2015
11. Charbel C, Fontaine RH, Malouf GG, et al: NRAS mutation is the sole recurrent somatic mutation in large congenital melanocytic nevi. J Invest Dermatol 134:1067-74, 2014
12. Huang SC, Alaggio R, Sung YS, et al: Frequent HRAS Mutations in Malignant Ectomesenchymoma: Overlapping Genetic Abnormalities With Embryonal Rhabdomyosarcoma. Am J Surg Pathol 40:876-85, 2016
13. Zhang M, Wang Y, Jones S, et al: Somatic mutations of SUZ12 in malignant peripheral nerve sheath tumors. Nat Genet 46:1170-2, 2014
14. Penman CL, Faulkner C, Lowis SP, et al: Current Understanding of BRAF Alterations in Diagnosis, Prognosis, and Therapeutic Targeting in Pediatric Low-Grade Gliomas. Front Oncol 5:54, 2015
15. Grabner A, Schramm K, Silswal N, et al: FGF23/FGFR4-mediated left ventricular hypertrophy is reversible. Scientific Reports 7:1993, 2017
16. Badalian-Very G, Vergilio JA, Degar BA, et al: Recurrent BRAF mutations in Langerhans cell histiocytosis. Blood 116:1919-23, 2010
17. Braun BS, Shannon K: Targeting Ras in myeloid leukemias. Clin Cancer Res 14:2249-52, 2008
18. Irving J, Matheson E, Minto L, et al: Ras pathway mutations are prevalent in relapsed childhood acute lymphoblastic leukemia and confer sensitivity to MEK inhibition. Blood 124:3420-30, 2014
19. Caye A, Strullu M, Guidez F, et al: Juvenile myelomonocytic leukemia displays mutations in components of the RAS pathway and the PRC2 network. Nat Genet 47:1334-40, 2015
20. Chmielecki J, Bailey M, He J, et al: Genomic Profiling of a Large Set of Diverse Pediatric Cancers Identifies Known and Novel Mutations across Tumor Spectra. Cancer Research 77:509-519, 2017
21. Zehir A, Benayed R, Shah RH, et al: Mutational landscape of metastatic cancer revealed from prospective clinical sequencing of 10,000 patients. Nature medicine 23:703-713, 2017
22. https://ocg.cancer.gov/programs/target: TARGET: Therapeutically Applicable Research To Generate Effective Treatments, 2020
23. Shern JF, Chen L, Chmielecki J, et al: Comprehensive genomic analysis of rhabdomyosarcoma reveals a landscape of alterations affecting a common genetic axis in fusion-positive and fusion-negative tumors. Cancer discovery 4:216-231, 2014
24. Cox AD, Der CJ: Ras family signaling: therapeutic targeting. Cancer Biol Ther 1:599-606, 2002

25. Cox AD, Der CJ, Philips MR: Targeting RAS Membrane Association: Back to the Future for Anti-RAS Drug Discovery? Clin Cancer Res 21:1819-27, 2015
26. [redacted]
27. Casey PJ, Solski PA, Der CJ, et al: p21ras is modified by a farnesyl isoprenoid. Proceedings of the National Academy of Sciences of the United States of America 86:8323-8327, 1989
28. Berndt N, Hamilton AD, Sebti SM: Targeting protein prenylation for cancer therapy. Nat Rev Cancer 11:775-91, 2011
29. Whyte DB, Kirschmeier P, Hockenberry TN, et al: K- and N-Ras are geranylgeranylated in cells treated with farnesyl protein transferase inhibitors. J Biol Chem 272:14459-64, 1997
30. End D, Skrzat S, Devine A: 115777: A selective farnesyl protein transferase inhibitor with antitumor activity in vitro and in vivo. . Document ID No: N124052; JRF Nonclinical Pharmacology Report (October 1996).
31. End DW, Smets G, Todd AV, et al: Characterization of the Antitumor Effects of the Selective Farnesyl Protein Transferase Inhibitor R115777 in Vivo and <em>in Vitro</em&gt. Cancer Research 61:131, 2001
32. Kelland LR, Smith V, Valenti M, et al: Preclinical antitumor activity and pharmacodynamic studies with the farnesyl protein transferase inhibitor R115777 in human breast cancer. Clin Cancer Res 7:3544-50, 2001
33. Goemans BF, Zwaan CM, Harlow A, et al: In vitro profiling of the sensitivity of pediatric leukemia cells to tipifarnib: identification of T-cell ALL and FAB M5 AML as the most sensitive subsets. Blood 106:3532-7, 2005
34. Cloughesy TF, Wen PY, Robins HI, et al: Phase II trial of tipifarnib in patients with recurrent malignant glioma either receiving or not receiving enzyme-inducing antiepileptic drugs: a North American Brain Tumor Consortium Study. J Clin Oncol 24:3651-6, 2006
35. Karp JE, Smith BD, Gojo I, et al: Phase II trial of tipifarnib as maintenance therapy in first complete remission in adults with acute myelogenous leukemia and poor-risk features. Clin Cancer Res 14:3077-82, 2008
36. Li T, Christos PJ, Sparano JA, et al: Phase II trial of the farnesyltransferase inhibitor tipifarnib plus fulvestrant in hormone receptor-positive metastatic breast cancer: New York Cancer Consortium Trial P6205. Ann Oncol 20:642-7, 2009
37. Li T, Guo M, Gradishar WJ, et al: A phase II trial of capecitabine in combination with the farnesyltransferase inhibitor tipifarnib in patients with anthracycline-treated and taxane-resistant metastatic breast cancer: an Eastern Cooperative Oncology Group Study (E1103). Breast Cancer Res Treat 134:345-52, 2012
38. Sparano JA, Moulder S, Kazi A, et al: Phase II trial of tipifarnib plus neoadjuvant doxorubicin-cyclophosphamide in patients with clinical stage IIB-IIIC breast cancer. Clin Cancer Res 15:2942-8, 2009
39. Van Cutsem E, van de Velde H, Karasek P, et al: Phase III trial of gemcitabine plus tipifarnib compared with gemcitabine plus placebo in advanced pancreatic cancer. J Clin Oncol 22:1430-8, 2004
40. Widemann BC, Arceci RJ, Jayaprakash N, et al: Phase 1 trial and pharmacokinetic study of the farnesyl transferase inhibitor tipifarnib in children and adolescents with refractory leukemias: a report from the Children's Oncology Group. Pediatr Blood Cancer 56:226-33, 2011
41. Widemann BC, Salzer WL, Arceci RJ, et al: Phase I trial and pharmacokinetic study of the farnesyltransferase inhibitor tipifarnib in children with refractory solid tumors or neurofibromatosis type I and plexiform neurofibromas. J Clin Oncol 24:507-16, 2006
42. Haas-Kogan DA, Banerjee A, Poussaint TY, et al: Phase II trial of tipifarnib and radiation in children with newly diagnosed diffuse intrinsic pontine gliomas. Neuro Oncol 13:298-306, 2011
43. Kurzrock R, Kantarjian HM, Cortes JE, et al: Farnesyltransferase inhibitor R115777 in myelodysplastic syndrome: clinical and biologic activities in the phase 1 setting. Blood 102:4527-34, 2003

44. Burnett AK, Russell NH, Culligan D, et al: The addition of the farnesyl transferase inhibitor, tipifarnib, to low dose cytarabine does not improve outcome for older patients with AML. Br J Haematol 158:519-22, 2012
45. Stieglitz E, Ward AF, Gerbing RB, et al: Phase II/III trial of a pre-transplant farnesyl transferase inhibitor in juvenile myelomonocytic leukemia: a report from the Children's Oncology Group. Pediatr Blood Cancer 62:629-36, 2015
46. Widemann BC, Dombi E, Gillespie A, et al: Phase 2 randomized, flexible crossover, double-blinded, placebo-controlled trial of the farnesyltransferase inhibitor tipifarnib in children and young adults with neurofibromatosis type 1 and progressive plexiform neurofibromas. Neuro Oncol 16:707-18, 2014
47. Thomas E. Witzig M: Tipifarnib in Relapsed or Refractory Angioimmunoblastic T-Cell Lymphoma (AITL) and CXCL12+ Peripheral T-Cell Lymphoma (PTCL): Preliminary Results from an Open-Label, Phase 2 Study [abstract]. In: American Society for Hematology 61st annual meeting in Orange County #468, 2019
48. Cox AD, Der CJ, Philips MR: Targeting RAS Membrane Association: Back to the Future for Anti-RAS Drug Discovery? Clinical Cancer Research 21:1819-1827, 2015
49. Zujewski J, Horak ID, Bol CJ, et al: Phase I and pharmacokinetic study of farnesyl protein transferase inhibitor R115777 in advanced cancer. J Clin Oncol 18:927-41, 2000
50. Lara PN, Jr., Law LY, Wright JJ, et al: Intermittent dosing of the farnesyl transferase inhibitor tipifarnib (R115777) in advanced malignant solid tumors: a phase I California Cancer Consortium Trial. Anticancer Drugs 16:317-21, 2005
51. Kirschbaum MH, Synold T, Stein AS, et al: A phase 1 trial dose-escalation study of tipifarnib on a week-on, week-off schedule in relapsed, refractory or high-risk myeloid leukemia. Leukemia 25:1543-7, 2011
52. Ho A, Chau, Nicole, Brana, Irene, Ferte, Charles, Evem, Caroline, Burrows, Francis, Kessler, Linda, Mishra, Vishnu, Magnuson, Kelly, Scholz, Catherine and Gualberto, Antonio: Preliminary Results from a Phase 2 Trial of Tipifarnib in HRAS mutant Head and Neck Squamous Cell Carcinomas. AACR Head and Neck Poster Presentation, 2018
53. A'Hern RP: Sample size tables for exact single-stage phase II designs. Stat Med 20:859-66, 2001
54. Agresti A, Coull BA: Approximate Is Better than "Exact" for Interval Estimation of Binomial Proportions. The American Statistician 52:119-126, 1998
55. Sandlund JT, Guillerman RP, Perkins SL, et al: International Pediatric Non-Hodgkin Lymphoma Response Criteria. J Clin Oncol 33:2106-11, 2015
56. Park JR, Bagatell R, Cohn SL, et al: Revisions to the International Neuroblastoma Response Criteria: A Consensus Statement From the National Cancer Institute Clinical Trials Planning Meeting. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 35:2580-2587, 2017
57. Bagatell R, McHugh K, Naranjo A, et al: Assessment of Primary Site Response in Children With High-Risk Neuroblastoma: An International Multicenter Study. J Clin Oncol 34:740-6, 2016
58. Burchill SA, Beiske K, Shimada H, et al: Recommendations for the standardization of bone marrow disease assessment and reporting in children with neuroblastoma; on behalf of the International Neuroblastoma Response Criteria Bone Marrow Working Group. Cancer, 2016
59. 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

[redacted]

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

APPENDIX II: CYP3A4 SUBSTRATES, INDUCERS, AND INHIBITORS

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

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

etoposide everolimus[5] fentanyl[4] gefitinib haloperidol ibrutinib[5] idelalisib imatinib indinavir[5] irinotecan isavuconazole[5] itraconazole ivacaftor ketoconazole lansoprazole lapatinib losartan lovastatin[5] lurasidone[5] macrolide antibiotics maraviroc[5] medroxyprogesterone methadone midazolam[5] midostaurin[5] modafinil nefazodone nilotinib olaparib ondansetron osimertinib paclitaxel palbociclib pazopanib quetiapine[5] quinidine[4] regorafenib romidepsin saquinavir[5] sildenafil[5] simvastatin[5]				

sirolimus[4,5] sonidegib sunitinib tacrolimus[4,5] tamoxifen telaprevir temsirolimus teniposide tetracycline tipranavir[5] tolvaptan[5] triazolam[5] trimethoprim vardenafil[5] vemurafenib venetoclax[5] vinca alkaloids zolpidem				

[1] Certain fruits, fruit juices and herbal supplements (star fruit, Seville oranges, pomegranate, gingko, goldenseal) may inhibit CYP 3A4 isozyme, however, the degree of that inhibition is unknown.
[2]Refer to Section 4.2.2.1 regarding use of corticosteroids.
[3]The effect of grapefruit juice (strong vs moderate CYP3A4 inhibition) varies widely among brands and is concentration-, dose-, and preparation-dependent.
[4]Narrow therapeutic range substrates
[5]Sensitive substrates (drugs that demonstrate an increase in AUC of ≥5-fold with strong inhibitors)

APPENDIX III: MEDICATION DIARY FOR TIPIFARNIB

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

Complete each day with the time and dose given for tipifarnib. If a dose is not due or is accidentally skipped leave that day blank. **Make note of other drugs and supplements taken under the Comments section below.** Take each dose with food. Tablets should be swallowed whole with a glass of water. Tablets may be chewed or crushed if necessary. If you vomit, the dose may **NOT** be repeated. If you miss or forget a dose, it can be taken up to 8 hours before the next dose is due. If tablet is broken and the powder of the tablets gets on skin, wash the exposed area with as much water as necessary. Inform your study doctor or nurse if that occurs. Add the dates to the calendar below and return the completed diary to your institution weekly after Cycle 1 and after each treatment cycle. Please refer to the example below. Refer to the instructions for Tipifarnib Preparation, Administration, and Safe Handling (Appendix XIII).

EXAMPLE			*Number of tipifarnib tablets*		*Comments*
	Date	*Time*	100 mg	300 mg	
Day 1	*1/15/20*	*8:30 AM*	2	1	*He felt nauseated an hour after taking the drug but did not vomit.*

Cycle #: _____ **Start Date:** |__/__|__/__|__/__| **End Date:** |__/__|__/__|__/__| **Dose Level:** ☐ **350 mg/m²/dose**

Week 1	Date	Time		# of _____tablets prescribed to take 100 mg: AM#_____ PM# 300 mg: AM#_____ PM# Number of tipifarnib tablets taken_____ 100 mg	300 mg	Comments (Describe any missed or extra doses, vomiting and/or bothersome effects.)
Day 1			AM			
			PM			
Day 2			AM			
			PM			
Day 3			AM			
			PM			
Day 4			AM			
			PM			
Day 5			AM			
			PM			
Day 6			AM			
			PM			
Day 7			AM			
			PM			
WEEK 2	Dates			WEEK 2 – Study drug not administered on Days 8-14		Comments (Describe any missed or extra doses, vomiting and/or bothersome effects.)

Day 8 to Day 14				Study drug not administered on Days 8-14		
Week 3	**Date**	**Time**		**Number of tablets taken**		**Comments** (Describe any missed or extra doses, vomiting and/or bothersome effects.)
				100 mg	**300 mg**	
Day 15			**AM**			
			PM			
Day 16			**AM**			
			PM			
Day 17			**AM**			
			PM			
Day 18			**AM**			
			PM			
Day 19			**AM**			
			PM			
Day 20			**AM**			
			PM			
Day 21			**AM**			
			PM			
WEEK 4	**Dates**			**WEEK 4 - Study drug not administered on Days 22-28**		**Comments** (Describe any missed or extra doses, vomiting and/or bothersome effects.)
Day 22 to Day 28				Study drug not administered on Days 22-28		

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

Signature: _____ Date: _____

(site personnel who reviewed this form)

APPENDIX IV CORRELATIVE STUDIES

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			**10-20mL**	

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

*Only for patients receiving ≥ 5 cycles of therapy only

APPENDIX V: TIPIFARNIB DOSING NOMOGRAM

Tipifarnib Dose Assignment: 350 mg/m^2 PO BID (maximum dose: 600 mg PO BID)

BSA (m2)	Tipifarnib Dosing	Total Daily Dose (mg/day)	Dose Reduction
0.29-0.35	100 mg PO BID	200 mg	Off-study
0.36-0.5	200 mg PO AM 100 mg PO PM	300 mg	100 mg PO BID
0.51-0.64	200 mg PO BID	400 mg	200 mg PO AM 100 mg PO PM
0.65-0.78	300 mg PO AM 200 mg PO PM	500 mg	200 mg PO AM 100 mg PO PM
0.79-0.93	300 mg PO BID	600 mg	200 mg PO BID
0.94-1.07	400 mg PO AM 300 mg PO PM	700 mg	300 mg PO AM 200 mg PO PM
1.08-1.21	400 mg PO BID	800 mg	300 mg PO BID
1.22-1.36	500 mg PO AM 400 mg PO PM	900 mg	300 mg PO BID
1.37-1.5	500 mg PO BID	1000 mg	400 mg PO AM 300 mg PO PM
1.51-1.64	600 mg PO AM 500 mg PO PM	1100 mg	400 mg PO BID
≥1.65	600 mg PO BID	1200 mg	500 mg PO AM 400 mg PO PM

APPENDIX VI: APEC1621M 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
Tipifarnib IND # 134661	PO or via NG- or G-tube	350 mg/m^2/dose orally twice daily (maximum 600 mg/dose BID) Refer to the dosing nomogram and dose reduction table. Appendix V	Day 1 to 7 and Days 15 to 21	See Appendix Vfor tipifarnib dosing nomogram.

Ht _____cm Wt _____kg BSA _____m^2

Date Due	Date Given	Day	**Tipifarnib** _____mg AM _____mg PM	Studies
			Enter calculated dose above as per dosing nomogram and actual dose administered below	
		1	_____mg AM _____mg PM	
		2	_____mg AM _____mg PM	
		3	_____mg AM _____mg PM	
		4	_____mg AM _____mg PM	
		5	_____mg AM _____mg PM	
		6	_____mg AM _____mg PM	
		7	_____mg AM _____mg PM	
		8	**Study drug not administered on Days 8-14**	a, b, c, d, e
		9		
		10		
		11		
		12		
		13		
		14		
		15	_____mg AM _____mg PM	a, b, c, d, e
		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	**Study drug not administered on Days 22-28**	a, b, c, d, e
		23		
		24		
		25		
		26		
		27		
		28*		a, b, c, d, e

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

Cycle 1

Required Observations in Cycle 1

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

a.	**History/Physical Exam (including VS)**
b.	**CBC/differential/platelets**- If patients have Grade 4 neutropenia then CBCs should be checked at least every other day until recovery to Grade 3 or until meeting the criteria for dose limiting toxicity. If patients develop Grade 3 or higher thrombocytopenia then CBCs should be checked every 3-4 days until recovery
c.	**Electrolytes including Ca++, PO4, Mg++**
d.	**Creatinine, ALT, bilirubin**
e.	**Medication Diary** (see Appendix III should be reviewed after completion of each treatment cycle and uploaded into RAVE. The medication diary should be collected weekly.

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

Comments
(Include any held doses, or dose modifications)

Treatment Details: Cycle 1

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

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 for up to 26 cycles. 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
Tipifarnib IND # 134661	PO or via NG-or G-tube	350 mg/m^2/dose orally twice daily (maximum 600 mg/dose BID) Refer to the dosing nomogram and dose reduction table. Appendix V	Day 1 to 7 and Days 15 to 21	See Appendix V for tipifarnib dosing nomogram.

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

Date Due	Date Given	Day	**Tipifarnib** _____mg AM _____mg PM	Studies
			Enter calculated dose above as per dosing nomogram and actual dose administered below	
		1	_____mg AM _____mg PM	a-f,i,j
		2	_____mg AM _____mg PM	
		3	_____mg AM _____mg PM	
		4	_____mg AM _____mg PM	
		5	_____mg AM _____mg PM	
		6	_____mg AM _____mg PM	
		7	_____mg AM _____mg PM	
		8	**Study drug not administered on Days 8-14**	k
		9		
		10		
		11		
		12		
		13		
		14		
		15	_____mg AM _____mg PM	a*, c*, k
		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	**Study drug not administered on Days 22-28**	k
		23		
		24		
		25		
		26		
		27		
		28*		a,-f,g*, h*, i, j*

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

Subsequent Cycles

Required Observations in All Subsequent Cycles

a.	**Physical Exam (including VS)-** Please refer to Section 8.1 for the specific timing of observation
b.	**Ht/Wt/BSA**
c.	**CBC/differential/platelets** If patients have Grade 4 neutropenia then CBCs should be checked at least every other day until recovery to Grade 3 or until meeting the criteria for dose limiting toxicity. If patients develop Grade 3 or higher thrombocytopenia then CBCs should be checked every 3-4 days until recovery
d.	**Electrolytes including Ca++, PO4, Mg++**
e.	**Creatinine, ALT, bilirubin**
f.	**Albumin**
g.	**Tumor Disease Evaluation** – Every other cycle x 3 then q 3 cycles. Tumor Disease Evaluation should be obtained on the next consecutive cycle after initial documentation of either a PR or CR. Subsequent scans may restart 2 cycles after the confirmatory scan. If the institutional investigator determines that the patient has progressed based on clinical or laboratory evidence, he/she may opt not to confirm this finding radiographically
h.	**Bone Marrow Aspirate and/or biopsy**- Every other cycle x 3 then q 3 cycles. Only required in patients suspected of having bone marrow metastasis on the basis of history, symptoms, laboratory evaluation or other clinical data. Should only be performed on patients with known bone marrow involvement at baseline. Bone marrow aspirate and/or biopsy should be performed only when complete response or partial response is identified in target disease or when progression in bone marrow is suspected.
i.	**Medication Diary-** (see Appendix III) should be reviewed after completion of each treatment cycle and uploaded into RAVE. The medication diary should be collected at the end of each cycle.
j.	[redacted]
k.	**History-** Please refer to Section 8.1 for the specific timing of observation

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

Comments
(Include any held doses, or dose modifications)

Treatment Details: Subsequent Cycles

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

APPENDIX VII: TARGET HISTOLOGIES FOR APEC1621M 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 tumor (includes RTK, MRT)
14. Rhabdomyosarcoma
15. Wilms Tumor
16. Pheochromocytoma
17. Thyroid carcinoma
18. Malignant ectomesenchymoma
19. Melanoma
20. Other Histology (based on COG/NCI-CTEP approval)

APPENDIX VIII: EXAMPLES OF ACTIONABLE MUTATIONS OF INTEREST FOR APEC1621M

INCLUSION	VARIANTS			
NON-HOTSPOT	**RULES**			
Gene Name	**Description**	**Variant Type**	**LOE**	**aMOI**
HRAS	COSM6006359	SNV	1.9	p.A146T
HRAS	rs121917759	SNV	1.9	p.A146V

HOTSPOTS				
Gene Name	Variant ID	Variant Type	aMOI	LOE
HRAS	COSM485	SNV	p.G12A	1.9
HRAS	COSM481	SNV	p.G12C	1.9
HRAS	COSM484	SNV	p.G12D	1.9
HRAS	COSM482	SNV	p.G12R	1.9
HRAS	COSM480	SNV	p.G12S	1.9
HRAS	COSM483	SNV	p.G12V	1.9
HRAS	COSM488	SNV	p.G13C	1.9
HRAS	COSM490	SNV	p.G13D	1.9
HRAS	COSM486	SNV	p.G13R	1.9
HRAS	COSM487	SNV	p.G13S	1.9
HRAS	COSM489	SNV	p.G13V	1.9
HRAS	COSM497	SNV	p.Q61E	1.9
HRAS	COSM502	SNV	p.Q61H	1.9
HRAS	COSM503	SNV	p.Q61H	1.9
HRAS	COSM496	SNV	p.Q61K	1.9
HRAS	COSM498	SNV	p.Q61L	1.9
HRAS	COSM52978	MNV	p.Q61L	1.9
HRAS	COSM500	SNV	p.Q61P	1.9
HRAS	COSM33695	MNV	p.Q61R	1.9
HRAS	COSM499	SNV	p.Q61R	1.9
HRAS	COSM501	MNV	p.Q61R	1.9

APPENDIX IX: CTEP AND CTSU REGISTRATION PROCEDURES

Requirements For APEC1621M Site Registration:

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

RCR utilizes five-person registration types.

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

RCR requires the following registration documents:

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

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

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

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

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

Cancer Trials Support Unit (CTSU) Registration Procedures

This study is supported by the NCI CTSU.

Protocol-Specific Requirements For Site Registration:

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

Submitting Regulatory Documents

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

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

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

Checking Your Site's Registration Status:

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

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

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

Data Submission / Data Reporting

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

Requirements to access Rave via iMedidata:

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

Rave role requirements:

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

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

Upon initial site registration approval for the study in Regulatory Support System (RSS), all persons with Rave roles assigned on the appropriate roster will be sent a study invitation e-mail from iMedidata. To accept the invitation, site staff must log in to the Select Login (https://login.imedidata.com/selectlogin) using their CTEP-IAM username and password and click on the *accept* link in the upper right-corner of the iMedidata page. Site staff will not be able to access the study in Rave until all required Medidata and study specific trainings are completed. Trainings will be in the form of electronic learnings (eLearnings) and can be accessed by clicking on the link in the upper right pane of the iMedidata screen. If an eLearning is required and has not yet been taken, the link to the eLearning will appear under the study name in iMedidata instead of the *Rave EDC* link; once the successful completion of the eLearning has been recorded, access to the study in Rave will be granted, and a *Rave EDC* link will display under the study name.

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

Data Quality Portal

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

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

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

Note: Some Rave protocols may not have delinquent form details or reports specified on the DQP. A protocol must have the Calendar functionality implemented in Rave by the Lead Protocol Organization for delinquent form details and reports to be available on the

DQP. Site staff should contact the LPO Data Manager for their protocol regarding questions about Rave Calendaring functionality.

APPENDIX X: 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

APPENDIX XI YOUTH INFORMATION SHEETS
INFORMATION SHEET REGARDING RESEARCH STUDY APEC1621M
(for children from 7 through 13 years of age)

We want to tell you all about this study. You and your family can decide if you want to be in it. Ask questions if you don't understand.

1. What is the name of the study? **A study of Molecular Analysis for Therapy Choice (MATCH) in children with a cancer that has come back after treatment or is difficult to treat**

2. Who is in charge of the study? The study is being done by Children's Oncology Group and is being done at other hospitals.

3. What is the study about? We are asking you to take part in a research study because other treatments did not get rid of the cancer. A research study is when doctors work together to try out new ways to help people who are sick. In this study, we are trying to learn more about how to treat the kind of cancer you have.

4. What will happen to me in the study? Children who are part of this study have been "matched" to a medicine. We think that this medicine will help you and other kids that have the same kind of cancer as you have. If you decide to be treated with this medicine, you will have some tests and check-ups done more often than if you weren't part of this study. We will follow your health after you finish the study treatment.

   Sometimes good things can happen to people when they are in a research study. These good things are called "benefits." We hope that a benefit to you of being part of this study is for your cancer to stop growing, or even shrink, but we don't know for sure if there is any benefit of being part of this study.

   Sometimes bad things can happen to people when they are in a research study. These bad things are called "risks." The risks to you from this study are that you may have more problems, or side effects, from a medicine used in this study. There may be risks that we don't know about yet.

5. Do I have to be in the study? You and your family can choose to be part of this study or not. You and your family can also decide to stop being in this study at any time once you start. There may be other treatments for your illness that your doctor can tell you about. If you have any questions or don't like what is happening, please tell your parent, the doctor or nurse.

6. We are asking your permission to collect additional tumor tissue. We want to see if there are ways to tell how the cancer will respond to treatment. These samples would be taken on tumor samples that we already have, so there would be no extra procedures. This would not change what medicines we would use to treat your tumor and would not provide any "benefits" to you. We hope that it might help us learn how to better treat other children's cancers in the future. You do not have to participate if you do not want to.

INFORMATION SHEET REGARDING RESEARCH STUDY APEC1621M
(for teens from 14 through 17 years of age)

1. What is the name of the study? **A study of Molecular Analysis for Therapy Choice (MATCH) in children with a cancer that has come back after treatment or is difficult to treat**

2. Who is in charge of the study? The study is being done by Children's Oncology Group and is being done at other hospitals.

3. What is the study about? We are asking you to take part in a research study because other treatments did not get rid of the cancer. A research study is when doctors work together to try out new ways to help people who are sick. In this study, we are trying to learn more about how to treat the kind of cancer that you have.

4. What will happen to me on the study? Your tumor has a mutation that matches tipifarnib, and so you have been assigned to tipifarnib. The doctors want to see if tipifarnib will make children with your type of cancer get better. We don't know if tipifarnib will work well to get rid of your cancer. That is why we are doing the study.

   Sometimes good things can happen to people when they are in a research study. These good things are called "benefits." We hope that a benefit to you of being part of this study is that tipifarnib may cause your cancer to stop growing or to shrink for a period of time but we don't know for sure if there is any benefit of being part of this study.

   Sometimes bad things can happen to people when they are in a research study. These bad things are called "risks." The primary risk to you from this study is that you may have side effects, from tipifarnib. Your doctor will talk to you about the risks we know about from tipifarnib. There may be other risks from tipifarnib that we don't know about yet.

5. Will I be paid to be in this study? You will not be paid for being in this study.

6. Do I have to be in the study? You and your family can choose to be part of this study or not. You and your family can also decide to stop being in this study at any time once you start. There may be other treatments for your illness that your doctor can tell you about. If you have any questions or don't like what is happening, please tell your parent, the doctor or nurse.

7. We are asking your permission to collect additional tumor tissue. We want to see if there are ways to tell how the cancer will respond to treatment. These samples would be taken on tumor samples that we already have, so there would be no extra procedures. This would not change what medicines we would use to treat your tumor and would not provide any "benefits" to you. We hope that it might help us learn how to better treat other children's cancers in the future. You do not have to participate if you do not want to.

APPENDIX XII: PATIENT DRUG INTERACTIONS HANDOUT AND WALLET CARD

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

Patient Name:	**Diagnosis:**	**Trial #:**	APEC1621M
Study Doctor:	**Study Doctor Phone #:**	**Study Drug(s):**	Tipifarnib

Please show this paper to all your healthcare providers (doctors, physician assistants, nurse practitioners, pharmacists), and tell them you are taking part in a clinical trial sponsored by the National Cancer Institute.

These are the things that your healthcare providers need to know:
Tipifarnib interacts with certain enzymes in your liver and gut.

	Explanation
CYP isoenzymes	The enzymes in question are CYP 3A4/5, 2C8/9/10, 2A6 and 2D6 and UDP-glucuronosyltransferase (UGT). Tipifarnib is broken down by CYP3A4/5 and UGT enzyme pathways. Tipifarnib levels in the body are affected by strong inducers/inhibitors of these enzymes. Tipifarnib inhibits CYP 3A4/5, 2C8/9/10, 2A6 and 2D6 and can affect sensitive substrates of these enzymes.

These are the things that you need to know:
The study drug tipifarnib, may interact with other drugs which can cause side effects. For this reason, it is very important to tell your doctors about all your medicines, including: (a) medicines you are taking before this clinical trial, (b) medicines you start or stop taking during this study, (c) medicines you buy without a prescription (over-the-counter remedy), (d) herbals or supplements (*e.g.* St. John's Wort). It is helpful to bring your medication bottles or an updated medication list with you.

Before you enroll onto the clinical trial, your study doctor will work with your regular health care providers to review any medicines and herbal supplements that are considered strong inducers/inhibitors of CYP 3A4/5 and UGT or sensitive substrates of CYP 3A4/5, 2C8/9/10, 2A6 and 2D6.

- Please be very careful! Over-the-counter drugs (including herbal supplements) may contain ingredients that could interact with your study drug. Speak to your doctors or pharmacist to determine if there could be any side effects.
    - Avoid ingesting grapefruit juice, grapefruit and Seville oranges while taking tipifarnib.
- Make sure your doctor knows to avoid certain prescription medications.
- 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.

Version *MAY/2019*

PATIENT DRUG INTERACTION WALLET CARD

NIH NATIONAL CANCER INSTI	NIH NATIONAL CANCER INSTI	NIH NATIONAL CANCER INSTI	NIH NATIONAL CANCER INSTI
EMERGENCY INFORMATION		**DRUG INTERACTIONS**	
Show this card to all of your healthcare providers. Keep it with you in case you go to the emergency room.	Tell your doctors **before** you **start** or **stop** any medicines. **Check with your doctor or pharmacist if you need to use an over-the-counter medicine or herbal supplement!**	**Carry this card with you at all times** Tipifarnib interacts with CYP450 and UGT enzymes and must be used very carefully with other medicines.	
Patient Name: **Diagnosis:** **Study Doctor:** **Study Doctor Phone #:** **NCI Trial #:** APEC1621M **Study Drug(S):** Tipifarnib	**Use caution and avoid the following drugs if possible:** • Grapefruit juice, grapefruit and Seville oranges	Your healthcare providers should be aware of any medicines that are strong inducers/inhibitors of CYP 3A4/5 and UGT or sensitive substrates of CYP 3A4/5, 2C8/9/10, 2A6 and 2D6. **Before prescribing new medicines**, your health care provider should check a **frequently-updated medical reference** for a **list of drugs to avoid** or contact your study doctor.	Version MAY/2019
For more information: 1-800-4-CANCER cancer.gov | clinicaltrials.gov	For more information: 1-800-4-CANCER cancer.gov | clinicaltrials.gov	For more information: 1-800-4-CANCER cancer.gov | clinicaltrials.gov	For more information: 1-800-4-CANCER cancer.gov | clinicaltrials.gov

Fold at dotted lines:

APPENDIX XIII: INSTRUCTIONS FOR TIPIFARNIB PREPARATION, ADMINISTRATION, AND SAFE HANDLING

Patient Name: _____ **Cycle#:** _____ **Date Range:** _____

TIPIFARNIB is an oral medicine for the treatment of cancer. This information sheet will help you prepare, administer, store, and dispose of the medicine. Please read the information before preparing and giving the medicine. If you have any questions, please contact:_____

WHAT DO I NEED?

Your TIPIFARNIB dose is twice daily: _____mg in morning and _____mg in the evening on the following dates _____ and _____.

- You should use the following number of tablets for each dose:

Time of Day	Number of TIPIFARNIB tablets/ dose	
	100 mg	300 mg
Morning		
Evening		

- Give each dose by mouth twice a day with food and plenty of water for 7 days in a row, followed by 7 days of rest (no medicine).
- Tipifarnib tablets can be chewed or crushed if needed.
- If given by mouth, you may mix crushed tablets with water, orange juice, apple juice, apple sauce, ginger ale, yogurt, tomato juice, or a protein shake. Drink ____ glasses of water or fluids during the day on days tipifarnib is given.
- If you or your child can not swallow, the tablets can be crushed, mixed with water and given through a feeding tube (NG tube or G-tube).
- You should take tipifarnib on the following days:_____

Supplies:

- Tipifarnib tablets (see the table above)
- Disposable container for crushing tablets, pad or paper towels
- Commercial tablet crusher
- Disposable gloves and mask and a pair of goggles (eye protection)
- Disposable cup and disposable spoon
- A container to collect waste (zip top plastic bag or medical waste bag or container)
- A glass of water or sterile water (for feeding tube administration). If crushing the medicine, it may also be mixed in yogurt, orange juice, apple juice, applesauce, ginger ale, tomato juice, protein shake or a tube feeds.

HOW DO I STORE THE MEDICINE AND WASTE?

Store the medication at room temperature in the original bottle away from food and out of the reach of children or pets. **Store the waste container out of the reach of children or pets**. Return the container to the clinic during your next visit.

WHAT SAFETY MEASURES SHOULD I TAKE?

If the medicine gets into eyes, hold eyelids open while flushing with water for at least 15 minutes. If you spilled the medicine on your skin, remove contaminated clothing. Wash area with soap and large amount of water. Seek medical attention if the skin becomes red, irritated, or if you are concerned. Call your doctor or nurse immediately at:_____

and/or contact the Poison Center at 1-800-222-1222.

HOW DO I PREPARE THE MEDICINE?

CAUTION: If you are pregnant, could become pregnant, or are breast-feeding, DO NOT prepare or administer this medicine.

1. Choose a quiet working space away from food, windows, fans or heat ducts.
2. Clean the working space with damp paper towels.
3. Wash your hands with soap and water; dry them well.
4. Put on disposable gloves, disposable mask, and a pair of goggles or eye protection.
5. Place a disposable pad or paper towel on the clean working space and place all supplies on the pad or paper towel.
6. Crush each tablet required for the dose using a disposable container.
7. To administer the medicine by mouth:
   - Mix crushed medicine in the cup with at least 40 mL of orange juice, yogurt, apple juice, applesauce, ginger ale, tomato juice, or protein shake.
   - Give the medicine mixture to the patient immediately or within 2 hours of mixing.
8. To administer the medicine through a feeding tube:
   - Mix crushed tablets with water.
   - Crushed tablets mixed with water for feeding tube administration should be used within 8 hours.
   - Flush the tube twice after each dose with 10-20 mL of sterile water
9. Rinse the container twice and tablet crusher with additional 1-2 teaspoons of water to get all the medicine from the sides of container and give it to the patient.

HOW DO I TAKE/GIVE THE MEDICINE?

- Take/give tipifarnib at around the same time twice a day with food. On days where you have special blood tests drawn, bring medicine.to your clinic visit and take it according to instruction given to you by your doctor or nurse
- When you are finished, place all used supplies in a plastic zip top bag or the waste container that was provided to you by your doctor, nurse, or pharmacist.
- If the dose is vomited the dose should NOT be repeated. A missed dose should be taken within 8 hours of the scheduled time. If the tablets have been crushed and the patient is unable to take a dose, or a dose is accidentally missed, place the remaining medicine from this dose in the waste container, seal, and contact your doctor or nurse for instructions.