CHILDREN'S ONCOLOGY GROUP

The world's childhood cancer experts

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November 30, 2021

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

Dear Ms. Kruhm,

Please find attached Amendment #4 to **APEC1621I**, *NCI-COG Pediatric MATCH (Molecular Analysis for Therapy Choice)- Phase 2 subprotocol of Palbociclib in Patients with Tumors Harboring Activating Alterations in Cell Cycle Genes*.

The protocol and ICD have been amended in preparation for Stage 2 of Pediatric MATCH. Descriptions of screening and enrollment procedures have been revised to align with Amendment #4 of APEC1621SC to implement Stage 2.

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

Please contact us if you have any further questions.

Sincerely,

Lee Baker, MPH, Protocol Coordinator (for)
Rajen Mody, MD, APEC1621I Study Chair, and
Douglas S. Hawkins, MD, Group Chair, Children's Oncology Group

SUMMARY OF CHANGES

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

#	Page(s)	Section	Change
1.	Through out	Throughout	• Updated version date and amendment number. • Ensured all hyperlinks are present and functioning
2.	2	Contact Information	Included, as this is part of the most recently approved template.
3.	5-6	Study Committee	Updated COG operations staff information for the PC, RC and master statistician.
4.	7	Abstract	To be consistent with the stage 2 process amendment #4 for APEC1621SC, removed language about performing the assay for genomic profiling and replaced with the process to identify aMOI's for subprotocol placement.
5.	14	3.1	Updated language to most recently approved templated language.
6.	14-16	3.1.1 3.1.2 3.1.3	To be consistent with the stage 2 process amendment #4 for APEC1621SC, language has been revised to include the MRC review process of pathology results to review potential mutations for eligibility in subprotocol therapies.
7.	17	3.5	To be consistent with the stage 2 process amendment #4 for APEC1621SC, revised enrollment periods for treatment assignment to 2-weeks
8.	18	4.1.1	Included language to reference the process for identifying aMOIs as defined in AMD #4 for APEC1621SC.
9.	18	4.1.4	The definition of measurable disease for CNS tumors was updated to match the definition in Section 12
10.	26	8.1	~~Patient~~ Diary has been revised to **Medication** Dairy
11.	29	8.3.1	Revised language to state that ctDNA samples are requested, but not required. This is consistent with AMD #4 of APEC1621SC Stage 2.
12.	53	13.1.1	Included new templated language for expediated adverse event reporting.
13.	54	13.1.2	Updated fax number for NCI and email for COG for reporting expedited AEs.
14.	66	Appendix II	CYP3A4 appendix updated.
15.	69	Appendix III	Title of appendix has been changed from ~~Patient~~ Diary for Palbociclib to **Medication** Diary for Palbociclib
16.	81	Appendix VIII	Included "**Examples of**" and "**for APEC1621I**" in the title of this appendix.
17.	82-83	Appendix IX	Updated youth information sheets to reflect new language
18.	84-87	Appendix X	Updated appendix, in accordance with the most recently approved templated language.

SUMMARY OF CHANGES: ICD

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	Comments
19.	Throughout	• Updated version date. • Ensured all hyperlinks are included and functioning.
20.	Why am I being invited to take part in this study?	Revised language to be consistent with AMD #4 of APEC1621SC, where tumor tissue pathology results are reviewed by the Molecular Review Committee (MRC) for eligibility into the subprotocol.

Activated:06/25/2018
Closed:
Version Date: 11/30/2021
Amendment# 4

CHILDREN'S ONCOLOGY GROUP

APEC1621I

NCI-COG PEDIATRIC MATCH (MOLECULAR ANALYSIS FOR THERAPY CHOICE)- PHASE 2 SUBPROTOCOL OF PALBOCICLIB IN PATIENTS WITH TUMORS HARBORING ACTIVATING ALTERATIONS IN CELL CYCLE GENES

Open to COG Member Institutions in the USA

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

The most current version of the study protocol 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.

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AGENT NSC#
NCI-Supplied Agents:
Palbociclib
(NSC# 772256)
IND Sponsor: DCTD, NCI

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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 will determine eligibility for this subprotocol. This is a phase 2 trial of palbociclib in children with relapsed or refractory solid tumors (including non-Hodgkin lymphomas, histiocytoses and CNS) harboring specified genomic alterations in the cyclinD-cdk4/6-INK4a-Rb pathway, including CDK4 or CDK6 amplification and CCND1, CCND2, or CCND3 amplification, along with positive Rb expression by immunohistochemistry.

Palbociclib is a reversible, selective oral small molecule inhibitor of CDK 4 and 6. It arrests the cell cycle by blocking the progression from G1 to S phase by preventing the phosphorylation of the RB protein resulting in cell cycle arrest thereby inhibiting cell proliferation and cellular DNA synthesis at low nanomolar concentrations.[1] Palbociclib's activity is dependent on the expression of tumor suppressor retinoblastoma (Rb1) protein. Palbociclib was granted accelerated approval in February 2015 and received full FDA approval in March 2017 for the treatment of breast cancer. It has demonstrated promising antitumor potential as monotherapy or combined therapy in numerous clinical trials.

Palbociclib will be given orally once daily on days 1-21 with 7 days off in a 28-day cycle. The pediatric MTD and RP2D was determined to be 75 mg/m^2.

EXPERIMENTAL DESIGN SCHEMA

Treatment Schedule Table	
Days 1-21	75 mg/m^2 once daily palbociclib
Days 22-28	Rest
Day 28	Evaluation

Palbociclib will be administered on days 1-21; a cycle will be 28 days. Evaluations will occur at the end of every other cycle x 3, then every 3 cycles.

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

1.0 GOALS AND OBJECTIVES (SCIENTIFIC AIMS)

1.1 Primary Aims

1.1.1 To determine the objective response rate (ORR; complete response + partial response) in pediatric patients treated with palbociclib with advanced solid tumors (including CNS tumors), non-Hodgkin lymphomas or histiocytic disorders that harbor activating genetic alterations in cell cycle genes.

1.2 Secondary Aims

1.2.1 To estimate the progression free survival in pediatric patients treated with palbociclib with advanced solid tumors (including CNS tumors), non-Hodgkin lymphomas or histiocytic disorders that harbor activating genetic alterations in alterations in cell cycle genes.

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

1.3 Exploratory Aims

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

2.0 BACKGROUND

2.1 Introduction/Rationale for Development

CDK4 and *CDK6* (*CDK4/6*) encode cyclin-dependent serine-threonine kinases that form a complex with cyclinD to phosphorylate the pRb tumor suppressor protein, leading to release of bound E2F transcription factors and cell cycle progression from G1 to S phase. Cancer cells have many alterations that overcome the pRb-dependent restriction checkpoint, most commonly through either loss of pRb or other alterations that lead to constitutive activation of the cyclin-D-CDK4/6 complex. In fact, recent next generation sequencing studies suggest that this signaling pathway is the first or second most commonly altered in adult and pediatric tumors. [2] Examples of the three most common genetic alterations include (1) amplification or deregulated transcription of the *CCND1* gene, which encodes cyclinD1, (2) mutation, deletion or epigenetic inactivation of *CDKNA* loci that encodes $p14^{ARF}$ and $p16^{INK4A}$, an inhibitor of the kinase activity of the cyclinD-CDK4/6 complex, and (3) amplification or mutation of *CDK4* or *CDK6*. In addition >90% of pediatric malignant rhabdoid tumors (MRT) harbor deletions of *INI1/SMARCB1* gene which results in altered activity of the SNF5/SWI chromatin remodeling complex, resulting in dependence on cyclin D for MRT cell survival.[3] There are currently three selective CDK4/6 inhibitors, including palbociclib (PD0332991), ribociclib (LEE011), and abemaciclib (LY2835219). There are more than 60 adult clinical trials for these agents (one with ribociclib including pediatric subjects) and palbociclib was recently FDA-approved for use in combination with an aromatase inhibitor in women with advanced estrogen receptor positive HER-2 negative breast cancer. Of note many adult clinical trials currently use cdk4/6 inhibitors, which have generally been shown to be cytostatic, in combination with other drugs, and eligibility often includes detection of a genomic

alteration in the cyclinD-cdk4/6-INK4a-Rb axis as well as intact pRb gene and/or protein.

Table 1: Palbociclib selectively inhibits CDK 4 and 6

CDK (cyclin partner)	IC50 (uM)
CDK4 (cyclin D_1)	0.011
CDK4 (cyclin D_3)	0.009
CDK6 (cyclin D_2)	0.015
CDK2 (cyclin A)	>5
CDK1 (cyclin B)	>5
CDK5 (p25)	>5

CCND1 amplification has been reported in 30% of primary breast cancers[4], however it is also observed in other tumors. The varying frequency of CCND1 amplification from both the Penn trial[5] as well as TCGA[6] are depicted in Table 2.

Table 2: Frequencies of *CCND1* Amplification in Penn Study and TCGA

Tumor Type	Number Screened	Number with *CCDN1* Amplification from Penn Study (% positive)	Number with SD or PR/Number Enrolled (%)	Number with *CCND1* Amplification from TCGA (% positive)
Breast	143	26 (18.2 %)	7/17 (41%)	79 (16.4%)
Colon	41	1 (2.4%)	0/1 (0%)	n/a
Esophageal	20	8 (40%)	1/4 (25%)	51 (55.4%)
Gastric	20	2 (10%)	0/1 (0%)	18 (6.3%)
SCC (Head & Neck)	5	2 (40%)	0/1 (0%)	77 (27.6%)
Osteosarcoma	1	1 (100%)	NA/0	n/a
Renal Cell	1	1 (100%)	NE/1	1 (0.6%)

Frequency of biomarker in pediatric malignancies

Genomic alterations leading to activation of the cyclinD-cdk4/6-INK4a network are commonly detected in both adult and pediatric tumors. Of note, the majority of published studies discussed below identified alterations using diagnostic specimens and a variety of different platforms. Furthermore, these estimates of prevalence are likely to underestimate the frequency of alterations at recurrence. Recent data for neuroblastoma demonstrates evidence of new mutations at relapse as well as clonal evolution of low frequency alterations, including recurrence-specific deletions of the *CDKN2A* locus in 3 of 23 relapse specimens.[7,8] The majority of alterations detected in diagnostic pediatric samples to date are due to copy number changes and not missense mutations. In a cohort of 82 neuroblastoma patients analyzed by array CGH, SNP and expression arrays amplification of the 11q13 region that contains *CCND1* was detected in 15% of tumors, deletion of one or both alleles of *CDKN2A* in 7 tumors and amplification of cdk4 or cdk6 loci in 3 tumors. Other neuroblastoma tumors without detectable cdk4/6 copy number gains showed elevated mRNA.[9] In an independent group of 375 high risk neuroblastoma tumors *CDK4*(5%), *CDK6*(15%) and *CCND1*(19%) copy number gains were detected.[10] The majority of these tumors stained positive for endogenous pRb.

CDK4/6 or *CCND1*amplification was detected in 25% of supratentorial PNET and 1-5%

of medulloblastoma tumors, respectively.[11] Alterations in this pathway were more frequent in glioblastoma[12,13], with *CDK4/6* amplifications in 20 of 281 tumors and more than 50% contained homozygous deletion of *CDKN2A*.[13] Several reports in newly diagnosed Ewings sarcoma patients detect *CDKN2A* deletions in approximately 10% of cases, but copy number alterations in other members of this pathway have not been studied.[14-16] In osteosarcoma rare *CDK4* amplifications have been reported; however, the frequency of pRb alterations is higher than in other solid tumors (6% mutations, 40% deletions/structural).[17-20] *CDK4* amplification and protein expression have also been detected in small subsets of rhabdomyosarcoma.[21,22] The majority of MRT have mutations and/or deletions in *SMARCB1*[23] and less commonly in *SMARCA4*.[24] Germline mutations are detected in up to 50% of patients

Consideration of specific agents

As mentioned above these agents are cytostatic and thus, may be more effective in combination trials. Given the mechanism of action for these agents there is some concern and early pre-clinical studies to support that they might be protective or antagonistic with commonly used cytotoxic chemotherapy agents.[25] Most adult studies now combine cdk4/6 inhibition with other targeted agents that unlike common chemotherapies do not rely on effects on DNA replication/S phase. These include mTOR inhibitors in several cancers, MEK and BRAF inhibitors in melanoma, ALK inhibitors in NSLC, and HDM2 inhibitors for liposarcoma. These drugs are given orally and LEE011 has a liquid formulation in development. Although there is no published data supporting ability to cross the blood brain barrier, palbociclib efficacy has been shown for intracranial GBM xenografts[26], and there are adult Phase II studies ongoing for CNS tumors, suggesting that patients with CNS tumors and metastatic lesions could be eligible for this agent.

2.2 Preclinical Studies

2.2.1 Antitumor Activity against pediatric tumors

Palbociclib has been shown to have pre-clinical evidence of activity in CDK4/6 mutated and retinoblastoma wild-type glioblastoma multiforme (GBM), diffuse intrinsic pontine gliomas (DIPG), and neuroblastoma tumor xenograft cell lines.[10,26] Neuroblastoma is the third most common pediatric malignancy, and CCND 1, 4, and 6 have been shown to be overexpressed in most neuroblastoma cases.[27] Palbociclib reduced cell proliferation in a large subset of neuroblastoma cell lines and xenograft models (12 of 17 human neuroblastoma-derived cell lines) by inducing cytostasis at nanomolar concentrations (mean IC50 = 307 ± 68 nmol/L in sensitive lines).[28]

2.2.2 Animal Toxicology

The toxicity profile of palbociclib was studied in rats, rabbits and dogs and included single and repeat dose studies, reproductive, developmental and genotoxicity studies. Based on the nonclinical safety studies conducted with palbociclib, the primary toxicities included effects on hematolymphopoietic and male reproductive organ tissues in rats and dogs. Additional target organ findings observed in rats only included altered glucose metabolism in relationship to effects on the pancreas with secondary findings in the eye, kidney, and adipose tissue; and effects on bone and actively growing incisor teeth. Palbociclib also caused effects on cardiovascular function, fetotoxicity in embryofetal development studies, and aneugenicity in genetic toxicity assessments. Other palbociclib-related findings were in gastrointestinal tissue, appeared as vacuolation in multiple tissues, and

included effects on the liver, kidney, adrenal gland, respiratory system, and coagulation times (prolonged) that were of limited severity and/or lacked degenerative features.

2.3 Adult Studies

Palbociclib is FDA approved in combination with endocrine therapy to treat patients with hormone receptor positive, HER2 negative metastatic breast cancer.[29-31] Its side effect profile is consistent across a multitude of studies with neutropenia, the most common adverse event, occurring in approximately 50-62% of patients receiving the drug. Febrile neutropenia is extremely infrequent, occurring in 0-3% of patients.[29-32]

2.3.1 Phase 1 Studies

A Phase I clinical study was conducted to assess the pharmacokinetic profile of palbociclib at 75, 125, and 150 mg once daily dose levels for 21 days of 28-day cycle in 41 adult patients with RB-positive solid tumors (except small cell lung cancer or retinoblastoma) or non–Hodgkin lymphoma that were refractory to standard chemotherapy. Neutropenia was the only dose-limiting effect. The most common non-hematologic adverse events included fatigue, nausea, and diarrhea. [5]

A phase 1 trial in 33 adult patients with retinoblastoma protein-positive advanced solid tumors or non-Hodgkin lymphoma refractory to standard therapy received palbociclib once daily for 14 days followed by 7 days off (21-day cycle). Six patients had dose limiting toxicities due to neutropenia, four receiving 200 mg daily; two receiving 225 mg daily, therefore the maximum tolerated dose was 200 mg daily.[33]

Palbociclib was administered as 125 mg daily for three weeks, followed by one week off in a phase 1/2 clinical trial assessed the safety and tolerability in combination with letrozole 2.5 mg daily was conducted in twelve post-menopausal women with ER-positive, HER-2 negative breast cancer. The most common adverse events included neutropenia, leucopenia, and fatigue. Two patients experienced grade 4 neutropenia, one patient required a dose interruption.[34]

2.3.2 Phase 2/3 Studies

In a Phase-II study of palbociclib (PD0332991) in histologically confirmed, metastatic breast cancer positive for retinoblastoma (Rb) protein and measureable disease, palbociclib was shown to be efficacious in endocrine-resistant, HR(+), Rb-positive breast cancer.[28] Palbociclib was given at 125 mg orally on days 1 to 21 of a 28-day cycle. Thirty-seven patients were enrolled; 84% hormone-receptor (HR)(+)/Her2(-), 5% HR(+)/Her2(+), and 11% HR(-)/Her2(-), with a median of 2 prior cytotoxic regimens. Two patients had partial response (PR) and 5 had stable disease $\geqslant$ 6 months for a clinical benefit rate (CBR = PR + 6moSD) of 19% overall, 21% in HR(+), and 29% in HR(+)/Her2(-) who had progressed through $\geqslant$ 2 prior lines of hormonal therapy. Median PFS overall was 3.7 months [95% confidence interval (CI), 1.9-5.1], but significantly longer for those with HR(+) versus HR(-) disease (P = 0.03) and those who had previously progressed through endocrine therapy for advanced disease (P = 0.02). Grade 3/4 toxicities included neutropenia (51%), anemia (5%), and thrombocytopenia (22%). Twenty-four percent had treatment interruption and 51% had dose reduction, all for cytopenias. No biomarker identified a sensitive tumor population.[29]

A phase 2 clinical trial evaluated the and safety of palbociclib 125 mg daily for 3 weeks, followed by one week off in combination with letrozole 2.5 mg daily compared with letrozole 2.5 mg daily monotherapy in 83 postmenopausal women with advanced estrogen receptor positive (ER+) and HER2-negative breast cancer who had not received any systemic treatment. There were 41 progression-free survival events in the combination group compared with 59 in the letrozole monotherapy group. The median progression free survival was 20.2 months in the combination group, and 10.2 months in the letrozole monotherapy group. Forty-five patients (54%) of patients in the combination group reported grade 3-4 neutropenia, compared with one patient (1%) of the patients in the letrozole monotherapy group. This study demonstrated that the addition of palbociclib to letrozole significantly improved progression-free survival in women with advanced estrogen receptor-positive and HER2-negative breast cancer.[30]

Another phase II study in patients with CDK4-amplified liposarcoma revealed a 66% progression free survival at 12 weeks including one CR lasting more than 2 years in a patient with CDK4 amplified liposarcoma.[35] [32]

In another Phase-II study of palbociclib in adults with advanced, metastatic hetatocellular carcinoma who have failed or are intolerant of first line therapy with sorafenib, subjects were treated with 125 mg /day palbociclib (PD-0332991), days 1-21 of a 28-day cycle, until disease progression, unacceptable toxicity, withdrawal from study or death. Of the 21 pts (18 M, 3 F), all had pathologically confirmed Retinoblastoma-positive HCC and one patient experienced a 1 PR.[35]

The major dose limiting toxicity of palbociclib is neutropenia. Median time to episode of neutropenia is 15 days, with a media duration of seven days. Myelosuppression is not due to apoptosis, rather it occurs through cell-cycle arrest, and is reversible with discontinuation.[36]

The PALOMA3 study assessed the efficacy of palbociclib in a double blind, randomized control trial. 521 patients with endocrine-resistant advanced breast cancer were randomized to receive either palbociclib 125 mg/d for 3 weeks followed by 1 week off and fulvestrant 500 mg, or fulvestrant 500 mg and placebo. The progression-free survival in the combination group was 9.2 months, and 3.8 months in the placebo control group. The most common adverse effects reported with neutropenia, leucopenia, and fatigue. Palbociclib in combination with fulvestrant improved progression free survival in hormone receptor positive advanced breast cancer that had progressed on prior endocrine compared with fulvestrant monotherapy.[37]

2.3.3 Pharmacology/Pharmacokinetics/Correlative and Biological Studies

In plasma collected from patients enrolled on the Phase I trials, palbociclib concentrations were detectable 1 hour following oral administration. This indicates rapid absorption. Pharmacokinetics did not vary among the schedules or within each trial, and PK did not appear to be dose dependent over a dose-range from 25 to 225 mg flat dosing. The volume of distribution of palbociclib is 2793 L, which is high and indicates substantial tissue binding. The half-life of palbociclib is 25.9 h and supports the appropriateness of once daily dosing. Extended PK analyses are not available; however, the reproducible toxicity of the drug over long-term dosing indicates that drug accumulation is unlikely. Excretion has not been characterized in detail, however is predominantly non-renal given a measured renal

excretion of less than 2%. [5,33]

In another adult Phase 1 trial palbociclib was also absorbed slowly (mean T_{max}, 4.2 hours), the mean elimination half-life was 26.7 hours, and it demonstrated a large volume of distribution (mean 32411 L).[33]

2.4 Pediatric Studies

2.4.1 Prior Experience in Children

Pediatric tumors such as brainstem gliomas and neuroblastomas are thought to have defects in cell cycle regulation. The maximum tolerated dose of palbociclib for pediatric patients with Rb positive, recurrent, progressive or refractory central nervous system tumors is being evaluated in an ongoing phase 1 clinical trial by Pediatric Brain Tumor Consortium (PBTC). The study is evaluating CNS tumors in less heavily (stratum I) pre-treated patients (pts) and the primary objectives of the study are to determine maximum tolerated dose (MTD), pharmacokinetics (PK), dose limiting toxicities (DLT), and preliminary evidence of efficacy. Presence of specific genomic alterations was not an eligibility requirement. Palbociclib was given orally daily for 21 days in a 28 day cycle for up to 2 yrs. Cohorts of 3-6 patients were treated at 50 (n = 3), 75 (n = 7), or 95 (n = 6) mg/m^2/day. Among the sixteen eligible patients enrolled (median age 13.3 yrs; male 59%), 13 pts (76%) had either malignant glioma (n = 7) or DIPG (n = 6). Median number of courses received was 2 (range 1-9). Of 14 evaluable patients, the only DLT observed was Grade 4 neutropenia in 2/4 patients treated at 95mg/m^2/day. Other significant drug related course 1 toxicities included Grade 3 neutropenia (n = 5) and Grade 3 lymphopenia (n = 2). The MTD was therefore determined to be 75 mg/m^2/day. At 75 mg/m^2, the median C_{max} and T_{max} for Course 1 Day 1 was 94 ng/ml and 4.02 hr, respectively. The trial is currently enrolling an expansion cohort at 75 mg/m^2 and an amendment to expand eligibility to more heavily pre-treated patients is underway.[38]

There is another recent pediatric Phase I study for patients with MRT, neuroblastoma, or other tumors with alterations in cyclinD-cdk4/6-INK4a pathway using LEE011 (NCT NCT01747876) that is not yet reported. An interim abstract publication on the first 22 patients (mainly neuroblastoma and MRT) suggested there was an acceptable safety profile.[39]

2.4.2 Pharmacology/Pharmacokinetics/Correlative Biological Studies:

Pediatric pharmacokinetic studies are underway as a part of Phase-I PBTC study.

2.5 Overview of Proposed Pediatric Study

We propose a single arm phase 2 study of palbociclib monotherapy in pediatric patients with advanced solid tumors, non-Hodgkin lymphomas or CNS tumors that harbor genetic alterations in cell cycle genes, specifically CDK4, CDK6, CCND1, CCND2, or CCND3 amplification. Palbociclib will be given orally once daily on days 1-21 with 7 days off in a 28-day cycle at the previously determined RP2D of 75 mg/m^2.[38] Evaluations will occur at the end of every other cycle x 3, then every 3 cycles. Therapy will be discontinued if there is evidence of progressive disease or drug related dose-limiting toxicity that requires removal from therapy. Therapy may otherwise continue for up to 2 years provided the patient meets the criteria for starting subsequent cycles and does not meet any of the criteria for removal from protocol therapy criteria.

In the primary cohort of the study we will evaluate 20 mutation-matched ("biomarker positive") evaluable patients of any histology for the primary study aim of determining the objective response rate (CR/PR) to the agent. If ≥ 3 patients in the primary cohort with the same histology show signs of objective response (CR/PR), a histology-specific biomarker positive expansion cohort will open after the primary cohort is completed to up to 7 evaluable biomarker positive patients with that histology in order to allow us to estimate more precisely the activity in biomarker positive patients of that histology. A maximum of 3 such histology specific, biomarker positive expansion cohorts will be permitted under this study.

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 Appendix IX for detailed CTEP and CTSU Registration Procedures including: registration in Registration and Credential Repository (RCR), requirements for site registration, submission of regulatory documents and how to check your site's registration status.

3.1.2 IRB Approval

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

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

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

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

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

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

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

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

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

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 APEC1621I study patients (such as whether a specific mutation would be considered actionable for the study) should be directed to the APEC1621SC and APEC1621I study chairs.

The treatment assignment to a MATCH 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 APEC1621I 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 APEC1621I.

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

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 APEC1621I 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 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.

Note: No starter supplies will be provided. Drug orders of palbociclib should be placed with CTEP after enrollment and treatment assignment to APEC1621I 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 level 75 mg/m^2/dose PO once daily 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 APEC1621I based on the presence of an actionable mutation as defined in APEC1621SC. Examples of actionable mutations for APEC1621I are listed in Appendix VIII.

4.1.1.1 In addition to the actionable mutations listed in section 4.1.1 positive Rb expression by immunohistochemistry is required for study enrollment.

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

4.1.3 BSA: Patients must have a body surface area ≥ 0.87 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 (See Appendix I). Note: Neurologic deficits in patients with CNS tumors must have been relatively stable for at least 7 days prior to study enrollment. Patients who are unable to walk because of paralysis, but who are up in a wheelchair, will be considered ambulatory for the purpose of assessing the performance score.

4.1.6 Prior Therapy

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

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

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

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

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

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

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

chair and the study-assigned Research Coordinator.

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

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

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

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

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

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

k. Patients must not have received prior exposure to palbociclib ribociclib, abemaciclib or any other CDK4/6 inhibitors.

4.1.7 Organ Function Requirements

4.1.7.1 Adequate Bone Marrow Function Defined as:

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

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

4.1.7.2 Adequate Renal Function Defined as:
- Creatinine clearance or radioisotope GFR ≥ 70ml/min/1.73 m^2 or

- A serum creatinine based on age/gender as follows:

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

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

4.1.7.3 Adequate Liver Function Defined as:

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

4.1.8 Patients must be able to swallow intact capsules.

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

4.2 Exclusion Criteria

4.2.1 Pregnancy or Breast-Feeding

Pregnant or breast-feeding women will not be entered on this study due to risks of fetal and teratogenic adverse events as seen in animal/human studies. Pregnancy tests must be obtained in girls who are post-menarchal. Males or females of reproductive potential may not participate unless they have agreed to use an effective contraceptive method for the duration of study treatment. Females study participants of child-bearing potential and their partners, should agree to use highly effective forms of contraception for at least 3 weeks after the last dose of palbociclib. Male study participants should avoid fathering a child, donating sperm, and should agree to use highly effective forms of contraception for at least 3 months after the last dose of palbociclib

4.2.2 Concomitant Medications

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

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

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

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

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

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

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

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

5.0 TREATMENT PROGRAM

5.1 Overview of Treatment Plan

Treatment Schedule Table	
Days 1-21	Palbociclib 75 mg/m^2/dose (max dose 125 mg) PO once daily
Days 22- 28	Rest
Day 28	Evaluation

Palbociclib will be given orally with food on Days 1-21, then rest for 7 days. Please see Appendix IV for the palbociclib dosing nomogram. **Do not use commercial supply.**

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.

Patients will be treated at the established pediatric MTD/RP2D which is 75 mg/m^2 (up to 125 mg) once daily.

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 the patient vomits or misses a dose, an additional dose should not be taken. The next prescribed dose should be taken at the usual time.

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

5.1.1 Therapy Delivery Map
See Appendix V for therapy delivery map 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 the investigational drug with the specific exclusion of:

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

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

5.4.2 Hematological dose limiting toxicity

5.4.2.1 Hematological dose limiting toxicity is defined as:

a) In patients evaluable for hematological toxicity (see Section 4.1.7.1),
- Grade 4 thrombocytopenia or neutropenia, not due to malignant infiltration
- Grade 3 thrombocytopenia that persists for ≥ 7 days
- Grade 3 thrombocytopenia requiring a platelet transfusion on two separate days within a 7-day period
- Grade 3 thrombocytopenia with clinically significant bleeding
- Neutropenia or thrombocytopenia that causes a delay of > 14 days between treatment cycles (e.g. platelets <100K or ANC<1000).

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

6.0 DOSE MODIFICATIONS FOR ADVERSE EVENTS

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

6.1 Dose Modifications for Hematological Toxicity

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

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

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

6.2 Dose Modifications for Non-Hematological Toxicity

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

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

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

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 palbociclib. See below for recommendations on management of specific toxicities associated with palbociclib.

7.4 Growth Factors

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

7.5 Concomitant Medications

7.5.1 CYP3A4 inhibitors or inducers: Strong CYP3A4 inhibitors such as ketoconazole, itraconazole, clarithromycin, atazanavir, indinavir, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, voriconazole, grapefruit, and grapefruit juice are not permitted on study. Strong CYP3A4 inducers such as rifampin, phenytoin, carbamazepine, rifabutin, rifapentine, phenobarbital, and St John's wort are not permitted on study. (See Appendix II for a list of additional agents).

7.5.2 Palbociclib is a weak time-dependent inhibitor of CYP3A4 in humans. The use of sensitive CYP3A4 substrates and CYP3A4 substrates with a narrow therapeutic range should be avoided for the duration of the study, if reasonable alternatives exist (Appendix II).

8.0 EVALUATIONS/MATERIAL AND DATA TO BE ACCESSIONED

8.1 Required Clinical, Laboratory and Disease Evaluation

All clinical and laboratory studies to determine eligibility must be performed within 7 days prior to enrollment unless otherwise indicated. Laboratory values used to assess eligibility (see Section 4.0) must be no older than seven (7) days at the start of therapy. Laboratory tests need **not** be repeated if therapy starts **within** seven (7) days of obtaining labs to assess eligibility. If a post-enrollment lab value is outside the limits of eligibility, or laboratory

values are older than 7 days, then the following laboratory evaluations must be re-checked within 48 hours prior to initiating therapy: CBC with differential, bilirubin, ALT (SGPT) and serum creatinine. If the recheck is outside the limits of eligibility, the patient may not receive protocol therapy and will be considered off protocol therapy. Imaging studies, bone marrow aspirate and/or biopsy, must be obtained within 14 days prior to start of protocol therapy (repeat the tumor imaging if necessary).

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

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

1 Women of childbearing potential require a negative pregnancy test prior to starting treatment; sexually active patients must use an acceptable method of birth control. Abstinence is an acceptable method of birth control see Section 4.2 for further details.

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

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

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

4-A Neurological exam also required for CNS patients

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

4-C Patients with neuroblastoma must have both CT/MRI and MIBG scintigraphy prior to enrollment if the patient was enrolled with or has a history of having MIBG avid tumor. Otherwise, the patient must have both CT/MRI and bone scan prior to enrollment. For patients with neuroblastoma and measurable disease by CT or MRI, lesions should be measured and followed using the same modality (CT or MRI) in addition to MIBG or bone scan. For patients with neuroblastoma and evaluable disease by MIBG scintigraphy or bone scan, use the same modality (MIBG scintigraphy or bone scan) to image and follow

patients; CT/MRI are not required but may be performed as clinically indicated. Refer to Section 12.5.4 and Section 12.9.

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

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

[7]. Patient diary (see Appendix III) should be reviewed after completion of each treatment cycle and uploaded into RAVE. The patient diary should be collected and reviewed weekly during Cycle 1.

[8]. With consent two samples will be collected on this protocol (Cycle 5 Day 1; and for patients receiving ≥ 5 cycles, at progression or end of protocol therapy) see Section 8.3 details of the ctDNA studies. Note that a ctDNA sample is scheduled to be obtained on the APEC 162SC screening protocol prior to the initiation of treatment on this subprotocol

8.2 Radiology Studies

8.2.1 Central Radiology Review for Response:

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

8.2.2 Technical Details of Submission:

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

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

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

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

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

TRIAD de-identifies and validates the images as they are transferred.

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

TRIAD Installations:

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

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

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

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

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

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

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

8.3 Circulating Tumor DNA Study (optional)

8.3.1 Sampling Schedule

An initial sample was previously requested at time of enrollment onto the pediatric MATCH screening protocol. Two additional samples will be collected into Streck Cell-Free DNA BCT tubes at the timepoints:

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

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

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

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

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

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

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

8.3.2 Sample Processing

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

8.3.3 Sample Labeling

Each tube must be labeled with the patient's study registration number, the study

I.D (APEC1621I), and the date and time the sample was drawn. Data should be recorded on the appropriate transmittal form found in RAVE.

8.3.4 Sample Shipping Instructions

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

Ship specimens to the following address:

Biopathology Center
Nationwide Children's Hospital
Protocol APEC1621I– Peds MATCH*
700 Children's Drive, WA1340
Columbus, OH 43205
Phone: (614) 722-2865
Fax: (614) 722-2897
Email:BPCBank@nationwidechildrens.org

*Packages must be labeled "Peds MATCH" in order to expedite processing at the BPC.

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

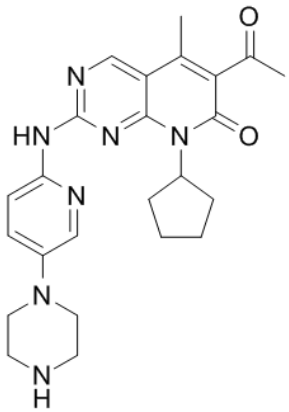
9.0 AGENT INFORMATION

9.1 **Palbociclib** (Ibrance®, PD-033299, 571190-30-2)
NSC# 772256

9.1.1 Structure and molecular weight

Chemical name: 6-acetyl-8-cyclopentyl-5-methyl-2-[(5-piperazin-1-ylpyridin-2-yl)amino]pyrido[2,3-d]pyrimidin-7-one

Molecular Formula: $C_{24}H_{29}N_7O_2$
Molecular weight: 447.54 Daltons



9.1.2 Supplied by: Palbociclib is supplied by Pfizer Inc. and distributed by a Division of Cancer Treatment and Diagnosis the Pharmaceutical Management Branch (DCTD), NCI. **Do not use commercial supply.**

9.1.3 Formulation

Palbociclib is supplied as 75 mg, 100 mg, and 125 mg hard shell gelatin capsules. Capsule excipients include microcrystalline cellulose, lactose monohydrate, sodium starch glycolate, colloidal silicon dioxide, and magnesium stearate. Gelatin capsule colorants include red iron oxide, yellow iron oxide, and titanium dioxide. White printing ink contains shellac, titanium dioxide, ammonium hydroxide, propylene glycol and simethicone.

- 75 mg capsules are opaque, hard gelatin capsules, size 2, with light orange cap and body, printed with white ink "Pfizer" on the cap, "PBC 75" on the body
- 100 mg capsules are opaque, hard gelatin capsules, size 1, with caramel cap and light orange body, printed with white ink "Pfizer" on the cap, "PBC 100" on the body on the body
- 125 mg capsules are opaque, hard gelatin capsules, size 0, with caramel cap and body, printed with white ink "Pfizer" on the cap, "PBC 125"

Each bottle contains 21 capsules.

9.1.4 Storage

Store capsules at room temperature between 20 to 25ºC (68 to 77ºF); excursions permitted between 15 to 30 ºC (59 to 86 ºF)

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

9.1.5 Stability

Refer to the package label for expiration.

9.1.6 Administration

See Treatment and Dose Modification sections of the protocol.
Palbociclib capsules should be swallowed whole and taken with food. Do not crush, chew or open capsules prior to swallowing. If the patient vomits or misses a dose, an additional dose should not be taken. The next prescribed dose should be taken at the usual time.

9.1.7 Potential Drug Interactions

In vivo data indicate that CYP3A4 is important for palbociclib metabolism and clearance in humans. For this reason, avoid concomitant administration of strong and moderate CYP 3A4 inducers and inhibitors (see Appendix II for list of agents).

In vitro data indicated that palbociclib has a low potential to inhibit the activities of drug transporters P-glycoprotein (P-gp), breast cancer resistance protein (BCRP), organic anion transporter (OAT)1, OAT3, organic cation transporter (OCT)2 and organic anion transporting polypeptide (OATP)1B1, OATP1B3 at clinically relevant concentrations. Based on in vitro data, P-gp and BCRP mediated transport are unlikely to affect the extent of oral absorption of palbociclib at therapeutic doses. [40]

Palbociclib is a weak time-dependent inhibitor of CYP3A4 in humans. The use of sensitive CYP3A4 substrates and CYP3A4 substrates with a narrow therapeutic range should be avoided for the duration of the study, if reasonable alternatives exist (Appendix II).

9.1.8 Palbociclib Toxicities

The Comprehensive Adverse Events and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. In addition to the comprehensive list, a subset, the Specific Protocol Exceptions to Expedited Reporting (SPEER), appears in a separate column and is identified with bold and italicized text. This subset of AEs (SPEER) is a list of events that are protocol specific exceptions to expedited reporting to NCI (except as noted below). Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements' http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf for further clarification. *Frequency is provided based on 1751 patients.* Below is the CAEPR for Palbociclib (PD-0332991).

NOTE: Report AEs on the SPEER **ONLY IF** they exceed the grade noted in parentheses next to the AE in the SPEER. If this CAEPR is part of a combination protocol using multiple investigational agents and has an AE listed on different SPEERs, use the lower of the grades to determine if expedited reporting is required.

Version 2.4, September 13, 2019[1]

Adverse Events with Possible Relationship to Palbociclib (PD-0332991) (CTCAE 5.0 Term) [n= 1751]			**Specific Protocol Exceptions to Expedited Reporting (SPEER)**
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
BLOOD AND LYMPHATIC SYSTEM DISORDERS			

Adverse Events with Possible Relationship to Palbociclib (PD-0332991) (CTCAE 5.0 Term) [n= 1751]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
Anemia			***Anemia (Gr 2)***
		Febrile neutropenia	
EYE DISORDERS			
	Blurred vision		
	Dry eye		
	Watering eyes		
GASTROINTESTINAL DISORDERS			
	Constipation		***Constipation (Gr 2)***
	Diarrhea		***Diarrhea (Gr 2)***
	Mucositis oral		***Mucositis oral (Gr 2)***
Nausea			***Nausea (Gr 2)***
	Vomiting		***Vomiting (Gr 2)***
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
Fatigue			***Fatigue (Gr 2)***
	Fever		
INFECTIONS AND INFESTATIONS			
Infection[2]			***Infection[2] (Gr 2)***
INVESTIGATIONS			
	Alanine aminotransferase increased		
	Aspartate aminotransferase increased		
	Lymphocyte count decreased		***Lymphocyte count decreased (Gr 2)***
Neutrophil count decreased			***Neutrophil count decreased (Gr 2)***
	Platelet count decreased		***Platelet count decreased (Gr 2)***
White blood cell decreased			***White blood cell decreased (Gr 2)***
METABOLISM AND NUTRITION DISORDERS			
	Anorexia		***Anorexia (Gr 2)***
NERVOUS SYSTEM DISORDERS			
	Dysgeusia		
	Headache[3]		
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
	Epistaxis		
		Pneumonitis	
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
	Alopecia		***Alopecia (Gr 2)***
	Dry skin		
	Skin and subcutaneous tissue disorders - Other (rash)[4]		

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

[2] Infection includes all 75 infection sites under the INFECTIONS AND INFESTATIONS SOC.

[3]Headache has been observed in trials using Palbociclib (PD-0332991) in combination with fulvestrant.

[4] Rash includes rash, rash maculo-papular, erythema, erythematous rash, erysipelas, rash pruritic, rash papular, generalized rash, exanthema, allergic dermatitis, dermatitis acneiform, and dermatitis.

[5] Peripheral neuropathy includes both peripheral motor neuropathy and peripheral sensory neuropathy under the NERVOUS SYSTEM DISORDERS SOC..

Adverse events reported on palbociclib (PD-0332991) trials, but for which there is insufficient evidence to suggest that there was a reasonable possibility that palbociclib (PD-0332991) caused the adverse event:

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Bone marrow hypocellular; Blood and lymphatic system disorders - Other (pancytopenia)
CARDIAC DISORDERS - Atrial fibrillation; Cardiac arrest; Cardiac disorders - Other (paroxysmal atrial fibrillation with rapid ventricular response); Palpitations; Pericarditis; Sinus bradycardia; Supraventricular tachycardia
EYE DISORDERS - Cataract; Eye disorders - Other (retinal hemorrhage)
GASTROINTESTINAL DISORDERS - Abdominal distension; Abdominal pain; Ascites; Colitis; Colonic perforation; Dry mouth; Dyspepsia; Dysphagia; Esophageal stenosis; Flatulence; Gastric hemorrhage; Gastrointestinal disorders - Other (gastrointestinal hemorrhage); Intra-abdominal hemorrhage; Lower gastrointestinal hemorrhage; Small intestinal obstruction; Small intestinal perforation; Upper gastrointestinal hemorrhage
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Chills; Death NOS; Edema limbs; Localized edema; Malaise; Non-cardiac chest pain; Pain; Sudden death NOS
HEPATOBILIARY DISORDERS - Hepatic failure; Hepatobiliary disorders - Other (bile duct obstruction); Hepatobiliary disorders - Other (jaundice)
IMMUNE SYSTEM DISORDERS - Allergic reaction
INJURY, POISONING AND PROCEDURAL COMPLICATIONS - Fall; Fracture
INVESTIGATIONS - Alkaline phosphatase increased; Blood bilirubin increased; CPK increased; Creatinine increased; Ejection fraction decreased; GGT increased; INR increased; Weight loss
METABOLISM AND NUTRITION DISORDERS - Dehydration; Hypercalcemia; Hyperglycemia; Hyperkalemia; Hypermagnesemia; Hyperuricemia; Hypoalbuminemia; Hypocalcemia; Hypokalemia; Hyponatremia; Hypophosphatemia; Metabolism and nutrition disorders - Other (failure to thrive)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Arthralgia; Back pain; Flank pain; Generalized muscle weakness; Muscle cramp; Musculoskeletal and connective tissue disorder - Other (osteomyelitis); Myalgia; Neck pain; Osteonecrosis; Pain in extremity
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL. CYSTS AND POLYPS) - Treatment related secondary malignancy
NERVOUS SYSTEM DISORDERS - Dizziness; Dysesthesia; Dysphasia; Intracranial hemorrhage; Nervous system disorders - Other (peripheral neuropathy)[5]; Syncope
PSYCHIATRIC DISORDERS - Confusion; Insomnia; Psychiatric disorders - Other (altered mental status)
RENAL AND URINARY DISORDERS - Acute kidney injury; Hematuria
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Cough; Dyspnea; Hypoxia; Oropharyngeal pain; Pleural effusion; Postnasal drip; Pulmonary edema; Pulmonary hypertension
SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Hyperhidrosis; Pruritus
VASCULAR DISORDERS - Hypertension; Hypotension

Note: Palbociclib (PD-0332991) in combination with other agents could cause an exacerbation of any adverse event currently known to be caused by the other agent, or the combination may result in events never previously associated with either agent.

9.2 Agent Ordering and Agent Accountability

NCI-supplied agents may be requested by eligible participating Investigators (or their authorized designee) at each participating institution. The CTEP-assigned protocol number must be used for ordering all CTEP-supplied investigational agents. The eligible participating investigators at each participating institution must be registered with CTEP, DCTD through an annual submission of FDA Form 1572 (Statement of Investigator), NCI

Biosketch, Agent Shipment Form, and Financial Disclosure Form (FDF). If there are several participating investigators at one institution, CTEP-supplied investigational agents for the study should be ordered under the name of one lead participating investigator at that institution.

Note: No starter supplies will be provided. Drug orders of palbociclib should be placed with CTEP after enrollment and treatment assignment to APEC1621I with consideration for timing of processing and shipping to ensure receipt of drug supply prior to start of protocol therapy. If expedited shipment is required, sites should provide an express courier account through the Online Agent Order Processing (OAOP) application. Provide the patient ID number in the comment box when submitting an order request.

9.3 Clinical Drug Request and Investigator Brochure Availability

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

9.4 Agent Inventory Records

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

9.4.1.1 Useful Links and Contacts

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

10.0 CRITERIA FOR REMOVAL FROM PROTOCOL THERAPY AND OFF STUDY CRITERIA

10.1 Criteria for Removal from Protocol Therapy

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

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

10.2 Follow-Up Data Submission and APEC1621SC Off Study Criteria

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

11.0 STATISTICAL AND ETHICAL CONSIDERATIONS

11.1 Sample Size and Study Duration

APEC1621I will require a minimum of 20 evaluable patients and a maximum of 49 patients, allowing for 15% inevaluability. Assuming an enrollment rate of 4-6 biomarker positive patients per year, this subprotocol is expected to be completed within 8-12 years.

11.2 Dosing Considerations

A pediatric MTD/RP2D has been established for palbociclib; therefore patients will be treated at that dose[38]. Please see section 5.1 for a specific discussion of the dosing of palbociclib to be used in this study.

11.3 Study Design

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

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

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

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

11.3.1 **Primary Cohort**:
APEC1621I 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[41] with alpha=10%, a sample of N=20 will provide 90% power to detect an improvement in response rate from 5%, if the treatment is ineffective, to 25% if the targeted therapy is sufficiently effective to warrant further study. If there are at least 3 responses out of 20 in the primary cohort, the biomarker/therapy match will be deemed a success.

11.3.2 **Histology-Specific Biomarker Positive Expansion Cohorts:**
If ≥ 3 patients in the primary cohort with the same histology show signs of objective response (CR/PR according to the response criteria in Section 12.3), a histology-specific biomarker positive expansion cohort will open after the primary cohort is completed to up to 7 evaluable patients for a total sample size of 10 evaluable biomarker positive patients with that histology. This will allow us to estimate more precisely the activity in biomarker positive patients of that histology. See Appendix VII for a list of target tumor histologies.
We will open up to 3 such expansion cohorts for biomarker positive patients (i.e., if 3 histologies have ≥ 3 responses, we will open a total of 3 expansion cohorts as described above). Note that this can only happen if the response rate in the primary cohort is at least 45% (9/20) and there cannot be more than 21 additional evaluable patients in total for these expansion cohorts.

11.4 Methods of Analysis

Response criteria are described in Section 12. A responder is defined as a patient who achieves a best response of PR or CR on the study. Response rates will be calculated as the percent of evaluable patients who are responders, and confidence intervals will be constructed using the Wilson score interval method.[42] Decision making for A'Hern design cohorts will follow rules described above.

Toxicity tables will be constructed to summarize the observed incidence by type of toxicity and grade. A patient will be counted only once for a given toxicity for the worst grade of

that toxicity reported for that patient. Toxicity information recorded will include the type, severity, time of onset, time of resolution, and the probable association with the study regimen.

11.5 Evaluability for Response

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

11.6 Evaluability for Toxicity

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

11.7 Progression free survival (PFS)

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

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

11.8 Correlative Studies

A descriptive analysis of pharmacokinetic (PK) parameters will be performed to define systemic exposure, drug clearance, and other pharmacokinetic parameters. The PK parameters will be summarized with simple summary statistics, including means, medians, ranges, and standard deviations (if numbers and distribution permit).

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

11.9 Gender and Minority Accrual Estimates

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

Racial category	Ethnicity				Total
	Not Hispanic or Latino		Hispanic or Latino		
	Female	Male	Female	Male	
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 v5.0 (CTCAE)

The descriptions and grading scales found in the current version of the NCI Common Terminology Criteria for Adverse Events v.5.0 (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/protocolDevelopment/electronic_applications/ctc.htm.).

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/hystiocytosis (Section 12.8). Note: Neuroblastoma patients who do not have MIBG positive lesions should be assessed for response as solid tumor patients with measurable disease.

Response and progression will be evaluated in this study using the revised Response

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

12.3.1 Definitions

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

12.3.1.2 Evaluable Non-Target Disease Response:

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

12.3.2 Disease Parameters

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

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

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

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

Note: Cystic lesions that meet the criteria for radiographically defined

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

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

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

12.3.3 Methods for Evaluation of Measurable Disease

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

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

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

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

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

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

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

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

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

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

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

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

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

12.4 Response Criteria for Patients with Solid Tumor and Measurable Disease

12.4.1 Evaluation of Target Lesions

Complete Response (CR): Disappearance of all target and non-target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm. If immunocytology is available, no disease must be detected by that methodology. Normalization of urinary catecholamines or other tumor markers if elevated at study enrollment (for patients with neuroblastoma).

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

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

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

12.4.2 Evaluation of Non-Target Lesions

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

short axis)

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

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

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

12.4.3 Overall Response Assessment

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

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

* See RECIST 1.1 manuscript for further details on what is evidence of a new lesion.

** In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.

Note: Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "*symptomatic deterioration.*" Every effort should be made to document the objective progression even after discontinuation of treatment.

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

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

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

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

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

12.4.4 **Overall Best Response Assessment**

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

12.5 Response Criteria for Neuroblastoma Patients with MIBG Positive Lesions

12.5.1 MIBG Positive Lesions

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

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

Complete response: Complete resolution of all MIBG positive lesions
Partial Response: Resolution of at least one MIBG positive lesion, with persistence of other MIBG positive lesions
Stable disease: No change in MIBG scan in number of positive lesions
Progressive disease: Development of new MIBG positive lesions

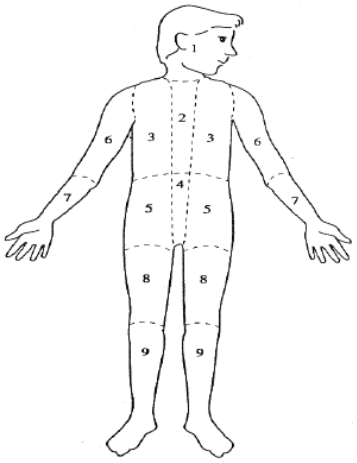
12.5.3 The response of MIBG lesions will be assessed on central review using the Curie scale14 as outlined below. Central review responses will be used to assess efficacy for study endpoint. See Section 8.2 for details on transferring images to the Imaging Research Center.

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

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

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

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



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

1. **Complete response:** all areas of uptake on MIBG scan completely resolved. If morphological evidence of tumor cells in bone marrow biopsy or aspiration is present at enrollment, no tumor cells can be detected by routine morphology on two subsequent bilateral bone marrow aspirates and biopsies done at least 21 days apart to be considered a **Complete Response**.
2. **Partial response**: Relative score ≤ 0.2 (lesions almost disappeared) to ≤ 0.5 (lesions strongly reduced).
3. **Stable disease**: Relative score > 0.5 (lesions weakly but significantly reduced) to 1.0 (lesions not reduced).
4. **Progressive disease**: New lesions on MIBG scan.

12.5.4 Overall Response Assessment

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

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

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

12.5.5 Overall Best Response Assessment

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

12.6 Response Criteria for Neuroblastoma Patients with Bone Marrow Involvement

12.6.1 Bone Marrow Involvement

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

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

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

Progressive Disease: In patients who enroll with neuroblastoma in bone marrow by morphology have progressive disease if there is a doubling in the amount of tumor in the marrow AND a minimum of 25% tumor in bone marrow by morphology. (For example, a patient entering with 5% tumor in marrow by morphology must increase to ≥ 25% tumor to have progressive disease; a patient entering with 30% tumor must increase to > 60%).

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

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

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

12.7 Response Criteria for Patients with CNS Tumors

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

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

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

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

12.7.4 Response Criteria for Target Lesions
Response criteria are assessed based on the product of the longest diameter and its longest perpendicular diameter. Development of new disease or progression in any established lesions is considered progressive disease, regardless of response in other lesions – e.g., when multiple lesions show opposite responses, the progressive disease takes precedence. Response Criteria for target lesions:

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

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

- **Stable Disease (SD):** Neither sufficient decrease in the sum of the products of the two perpendicular diameters of all target lesions to qualify for PR, nor

sufficient increase in a single target lesion to qualify for PD; on a stable or decreasing dose of steroids with a stable or improving neurologic examination.

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

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

12.7.5 Response Criteria for Non-Target Lesions:

- **Complete Response (CR):** Disappearance of all non-target lesions.
- **Incomplete Response/Stable Disease (IR/SD):** The persistence of one or more non-target lesions.
- **Progressive Disease (PD):** The appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions.

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

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

Target Lesions	**Non-target Lesions**	**Markers**	**New Lesions**	**Overall Response**
CR	CR	Normal	No	**CR**
CR	IR/SD	Normal	No	**PR**
CR	CR, IR/SD	Abnormal	No	**PR**
PR	CR, IR/SD	Any	No	**PR**
SD	CR, IR/SD	Any	No	**SD**
PD	Any	Any	Yes or No	**PD**
Any	PD	Any	Yes or No	**PD**
Any	Any	Any	Yes	**PD**

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

12.8 Response Criteria for Patients with Lymphoma/Histiocytosis

Response and progression will be evaluated in this study using the new international criteria proposed by the revised Response Evaluation Criteria in Pediatric non-Hodgkin Lymphoma Criteria[43], with modification from the Lugano classification.[44]

12.8.1 Disease Parameters

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).

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).

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

12.8.2 Evaluation of Measurable Disease

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

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

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

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

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

12.8.3 Evaluation of Non-measured Lesions (CT-based response, PET/CT based

response not applicable)[44]

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

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

Stable Disease (SD): No increase consistent with progression

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

12.8.4 Evaluation of organ enlargement[44]

Complete Response (CR): Regress to normal

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

Stable Disease (SD): No increase consistent with progression

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

New or recurrent splenomegaly

12.9 **Best Response**

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

12.9.1 **Evaluation of Best Overall Response**

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

Table 5. Sequences of overall response assessments with corresponding best

response.

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

12.9.2 **Duration of Response**

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

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

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

13.0 ADVERSE EVENT REPORTING REQUIREMENTS

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

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

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

13.1 Expedited Reporting Requirements – Serious Adverse Events (SAEs)

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

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

13.1.1 Reporting Requirements - Investigator Responsibility

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

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://ctepcore.nci.nih.gov/ctepaers/pages/task.

Send supporting documentation to the NCI by fax (fax# 301-640-9193) and by email to COGCAdEERS@childrensoncologygroup.org , the APEC1621I COG Study Assigned Research Coordinator, and 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 5.0 of the NCI CTCAE. All appropriate treatment areas should have access to a copy of the CTCAE version 5.0. A copy of the CTCAE version 5.0 can be downloaded from the CTEP web site http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

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
EYE DISORDERS	Dry Eye
EYE DISORDERS	Watering Eyes
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	Fever
NERVOUS SYSTEM DISORDERS	Dysgeusia
NERVOUS SYSTEM DISORDERS	Headache
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	Epistaxis
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	Dry Skin
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	Skin and subcutaneous tissue disorders - Other (rash)

- 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 CTCAEv5.0 term.
- Death Neonatal: *"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 CTCAEv5.0 term associated with Grade 5.
- Death NOS: A cessation of life that cannot be attributed to a CTCAEv5.0 term associated with Grade 5.
- Death due to progressive disease should be reported as ***Grade 5 "Disease progression"*** under the system organ class (SOC) of "General disorders and administration site conditions." Evidence that the death was a manifestation of underlying disease (*e.g.*, radiological changes suggesting tumor growth or progression: clinical deterioration associated with a disease process) should be submitted.
- Any death occurring within 30 days of the last dose, regardless of attribution to the investigational agent/intervention requires expedited reporting within 24 hours.
- Any death that occurs more than 30 days after the last dose of treatment with an investigational agent which can be attributed (possibly, probably, or definitely) to the agent and is not clearly due to progressive disease must be reported via CTEP-AERS per the timelines outlined in the table above.

13.6.2 Reporting Secondary Malignancy

Secondary Malignancy:
A *secondary malignancy* is a cancer caused by treatment for a previous malignancy (*e.g.*, treatment with investigational agent/intervention, radiation or

chemotherapy). A secondary malignancy is not considered a metastasis of the initial neoplasm.

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

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

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

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

13.6.3 Reporting Pregnancy, Pregnancy Loss, and Death Neonatal

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

Pregnancy

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

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

Pregnancy Loss (Fetal Death)

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

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

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

14.0 RECORDS, REPORTING, AND DATA AND SAFETY MONITORING PLAN

14.1 Categories of Research Records

Research records for this study can be divided into three categories

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

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

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

See separate CRF Packet, which includes submission schedule.

14.2 CDUS

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

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

14.3 CRADA/CTA/CSA

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

The agent(s) supplied by CTEP, DCTD, NCI used in this protocol is/are provided to the NCI under a Collaborative Agreement (CRADA, CTA, CSA) between the Pharmaceutical Company(ies) (hereinafter referred to as "Collaborator(s)") and the NCI Division of Cancer Treatment and Diagnosis. Therefore, the following obligations/guidelines, in addition to the provisions in the "Intellectual Property Option to Collaborator"

(http://ctep.cancer.gov/industryCollaborations2/intellectual_property.htm) contained within the terms of award, apply to the use of the Agent(s) in this study:

4. 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.

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

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

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

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

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

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

5. Any data provided to Collaborator(s) for Phase 3 studies must be in accordance

with the guidelines and policies of the responsible Data Monitoring Committee (DMC), if there is a DMC for this clinical trial.

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

   Email: ncicteppubs@mail.nih.gov

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

14.4 Data and Safety Monitoring Plan

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

14.4.1 Data and Safety Monitoring Committee

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

14.4.2 Monitoring by the Study Chair and MATCH Leadership

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

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APPENDIX I: PERFORMANCE STATUS SCALES/SCORES

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

APPENDIX II: CYP3A4 SUBSTRATES, INDUCERS AND INHIBITORS

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

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

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

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

[1] Certain fruits, fruit juices and herbal supplements (star fruit, Seville oranges, pomegranate, gingko, goldenseal) may inhibit CYP 3A4 isozyme, however, the degree of that inhibition is unknown.
[2]Refer to Section 4.2.2 regarding use of corticosteroids.
[3]The effect of grapefruit juice (strong vs moderate CYP3A4 inhibition) varies widely among brands and is concentration-, dose-, and preparation-dependent.
[4]Narrow therapeutic range substrates
[5]Sensitive substrates (drugs that demonstrate an increase in AUC of ⩾5-fold with strong inhibitors)

APPENDIX III: MEDICATION DIARY FOR PALBOCICLIB

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

Complete each day with the time and dose given for palbociclib. Palbociclib will be given by mouth once daily with food on days 1-21, then rest for 7 days. Take at approximately the same time each day. If a dose is accidentally skipped leave that day blank. ***Make note of other drugs and supplements taken under the Comments section below***. Palbociclib capsules should not be opened or crushed but should be swallowed whole. If capsule is broken and the powder of the capsules gets on skin, wash the exposed area with as much water as necessary. If the patient vomits or misses a dose, an additional dose should not be taken. The next prescribed dose should be taken at the usual time. Inform your study doctor or nurse if that occurs. Add the dates to the calendar below and return the completed diary to your institution after each treatment cycle.

EXAMPLE			***Number of Palbociclib capsules***			***Comments***
	Date	***Time***	**75 mg**	**100 mg**	**125 mg**	
Day 1	*1/15/14*	*8:30 AM*	1	0	0	*He felt nauseated an hour after taking the drug but did not vomit.*

Cycle #: _____ Start Date: |__/__|__/__|__/__| **End Date**: |__/__|__/__|__/__| **Dose Level: _____mg/m²**

WEEK 1	**Date**	**Time**		**# of palbociclib capsules prescribed to take**			**Comments (Describe any missed or extra doses, vomiting and/or bothersome effects.)**
				75 mg	**100 mg**	**125 mg**	
				# of palbociclib capsules taken			
				75 mg	**100 mg**	**125 mg**	
Day 1			**AM / PM**				
Day 2			**AM/ PM**				
Day 3			**AM/ PM**				
Day 4			**AM/ PM**				
Day 5			**AM/ PM**				
Day 6			**AM/ PM**				
Day 7			**AM/ PM**				

Cycle #: _____ Start Date: | _ _ | _ _ | _ _ _ _ | **End Date:** | _ _ | _ _ | _ _ _ _ | **Dose Level: _____ mg/m²**

WEEK 2	Date	Time	# of palbociclib capsules prescribed to take			Comments (Describe any missed or extra doses, vomiting and/or bothersome effects.)
			75 mg	100 mg	125 mg	
			# of palbociclib capsules taken			
			75 mg	100 mg	125 mg	
Day 8		AM / PM				
Day 9		AM/ PM				
Day 10		AM/ PM				
Day 11		AM/ PM				
Day 12		AM/ PM				
Day 13		AM/ PM				
Day 14		AM/ PM				

WEEK 3	Date	Time	# of palbociclib capsules prescribed to take			Comments (Describe any missed or extra doses, vomiting and/or bothersome effects.)
			75 mg	100 mg	125 mg	
			# of palbociclib capsules taken			
			75 mg	100 mg	125 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				

Cycle #: _____ Start Date: |__/__|__/__|__/__| **End Date**: |__/__|__/__|__/__| **Dose Level: _____mg/m²**	
WEEK 4	**Comments (Describe any missed or extra doses, vomiting and/or bothersome effects.)**
Day 22	
Day 23	
Day 24	
Day 25	
Day 26	
Day 27	
Day 28	

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

Signature: _____ Date: _____

(site personnel who administered the study drug)

APPENDIX IV: PALBOCICLIB DOSING NOMOGRAM

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

Palbociclib Dose Assignment: 75 mg/m^2/dose PO once daily (max dose 125 mg)

BSA (m2)	Palbociclib dose (mg/dose)	Dose Reduction for Toxicity (mg/dose)
0.87-1.16	75	Off Protocol Therapy
1.17-1.5	100	75
≥ 1.51	125	100

APPENDIX V: APEC1621I 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
Palbociclib **Do not use commercial supply.**	PO	Dose Level : 75 mg/m^2(max dose 125 mg) Refer to the dosing nomogram.	1-21	Drug doses should be adjusted based on the BSA calculated from height and weight measured within 7 days prior to the beginning of each cycle and according to the dosing nomogram in Appendix IV. Palbociclib will be given by mouth once daily with food on Days 1-21, then rest for 7 days. Take at approximately the same time each day. If vomiting occurs after taking the dose, the dose should NOT be repeated and the next dose should be administered at the regularly scheduled time.

Ht _____cm Wt _____kg BSA _____m^2

Date Due	Date Given	Day	**Palbociclib** _____ mg	Studies
			Enter calculated dose above as per dosing nomogram and actual dose administered below	
		1	_____ mg	
		2	_____ mg	
		3	_____ mg	
		4	_____ mg	c
		5	_____ mg	
		6	_____ mg	
		7	_____ mg	
		8	_____ mg	a, c, d, e, m
		9	_____ mg	
		10	_____ mg	
		11	_____ mg	
		12	_____ mg	c
		13	_____ mg	
		14	_____ mg	
		15	_____ mg	a, c, d, e, m
		16	_____ mg	
		17	_____ mg	
		18	_____ mg	c
		19	_____ mg	
		20	_____ mg	
		21	_____ mg	
		22	Study Drug not Administered on Days 22-28	a, c, d, e, m
		23	Study Drug not Administered on Days 22-28	
		24	Study Drug not Administered on Days 22-28	

Cycle 1

		25	Study Drug not Administered on Days 22-28	c
		26	Study Drug not Administered on Days 22-28	
		27	Study Drug not Administered on Days 22-28	
		28/1	Study Drug not Administered on Days 22-28	a, b, d, e, f , g

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

Required Observations in Cycle 1

All baseline studies must be performed prior to starting protocol therapy unless otherwise indicated below. For information related to prestudy observations, please refer to section 8.1

a. History/Physical Exam (including VS)
b. Ht/Wt/BSA
c. CBC/differential/platelets- If patients have Grade 4 neutropenia then CBCs should be checked at least every other day until recovery to Grade 3 or until meeting the criteria for dose limiting toxicity. If patients develop Grade 3 or greater thrombocytopenia then CBCs should be checked every 3 to 4 days until recovery per section 6.1.
d. Electrolytes including Ca++, PO4, Mg++
e. Creatinine, ALT, bilirubin
f. Albumin
g. Patient Diary- (see Appendix III) should be reviewed after completion of each treatment cycle and uploaded into RAVE. The patient diary should be collected and reviewed weekly.

Cycle 1

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

Comments (Include any held doses, or dose modifications)

Treatment Details: Cycle 1

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

Cycle 1

All Subsequent Cycles

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

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

DRUG	ROUTE	DOSAGE	DAYS	IMPORTANT NOTES
Palbociclib **Do not use commercial supply.**	PO	Dose Level : 75 mg/m^2(max dose 125 mg) Refer to the dosing nomogram.	1-21	Drug doses should be adjusted based on the BSA calculated from height and weight measured within 7 days prior to the beginning of each cycle and according to the dosing nomogram in Appendix IV. Palbociclib will be given by mouth once daily with food on Days 1-21, then rest for 7 days. Take at approximately the same time each day. If vomiting occurs after taking the dose, the dose should NOT be repeated and the next dose should be administered at the regularly scheduled time.

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

Date Due	Date Given	Day	**Palbociclib** _____ mg	Studies
			Enter calculated dose above as per dosing nomogram and actual dose administered below	
		1	_____ mg	a,b,d,e,f,i
		2	_____ mg	
		3	_____ mg	
		4	_____ mg	
		5	_____ mg	
		6	_____ mg	
		7	_____ mg	
		8	_____ mg	c
		9	_____ mg	
		10	_____ mg	
		11	_____ mg	
		12	_____ mg	
		13	_____ mg	
		14	_____ mg	
		15	_____ mg	c
		16	_____ mg	
		17	_____ mg	
		18	_____ mg	
		19	_____ mg	
		20	_____ mg	
		21	_____ mg	
		22	Study Drug not Administered on Days 22-28	c
		23	Study Drug not Administered on Days 22-28	

		24	Study Drug not Administered on Days 22-28	
		25	Study Drug not Administered on Days 22-28	
		26	Study Drug not Administered on Days 22-28	
		27	Study Drug not Administered on Days 22-28	
		28/1	Study Drug not Administered on Days 22-28	a,b,d,e,f, g*, h*,i, j*

See Section 6.0 for Dose Modifications for Toxicities and the COG Member website for Supportive Care Guidelines
* Please refer to section 8.1 for the specific timing of these observations

Required Observations in All Subsequent Cycles

a. History/Physical Exam (including VS)
b. Ht/Wt/BSA
c. CBC/differential/platelets- If patients have Grade 4 neutropenia then CBCs should be checked at least every other day until recovery to Grade 3 or until meeting the criteria for dose limiting toxicity. If patients develop Grade 3 or greater thrombocytopenia then CBCs should be checked every 3 to 4 days until recovery per section 6.1.
d. Electrolytes including Ca++, PO4, Mg++
e. Creatinine, ALT, bilirubin
f. Albumin
g. Tumor Disease Evaluation – Every other cycle x 3 then q 3 cycles. Tumor Disease Evaluation should be obtained on the next consecutive cycle after initial documentation of either a PR or CR. Subsequent scans may restart 2 cycles after the confirmatory scan. If the institutional investigator determines that the patient has progressed based on clinical or laboratory evidence, he/she may opt not to confirm this finding radiographically. Refer to Section 8.1 for more detailed information.
h. Bone Marrow Aspirate and/or biopsy- Only required in patients suspected of having bone marrow metastasis on the basis of history, symptoms, laboratory evaluation or other clinical data. Should only be performed on patients with known bone marrow involvement at baseline. Refer to section 8.1 for more detailed information.
i. Patient Diary- (see Appendix III) should be reviewed after completion of each treatment cycle and uploaded into RAVE. The patient diary should be collected and reviewed weekly.
j. Circulating Tumor DNA (ctDNA-optional)- With consent, two samples will be collected on this protocol (Cycle 5 Day 1; and for patients receiving ≥ 5 cycles, at progression or end of protocol therapy) see Section 8.3 for details of the ctDNA studies.

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

Comments (Include any held doses, or dose modifications)

Treatment Details: Subsequent Cycles

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

Subsequent Cycles

APPENDIX VI CORRELATIVE STUDIES

Correlative Study	Section	Blood Volume		Tube Type
		Volume per Sample	Total Cycle 5 Day 1	
Circulating tumor DNA analysis (optional)	8.3	• For patients ≥ 10 kg collect 20 mLs (10 mL per tube x 2 tubes) • For patients ≥ 5 kg but < 10 kg collect 10 mL (one tube) • For patients < 5 kg research samples will not be collected	10 -20 mL	Streck Cell-Free DNA BCT tubes
Total Blood Volume in Cycle 5 Day 1			**10-20 mL**	

Correlative Study	Section	Blood Volume		Tube Type
		Volume per Sample	Total 'Time of progression' or 'End of protocol therapy'	
Circulating tumor DNA analysis (optional)	8.3	• 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**	

APPENDIX VII: TARGET HISTOLOGIES FOR APEC1621I EXPANSION COHORTS

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

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

APPENDIX VIII: EXAMPLES OF ACTIONABLE MUTATIONS OF INTEREST FOR APEC1621I

INCLUSION CNV	**VARIANTS**	
Gene Name	Variant Type	LOE
CDK4	Amplification	2
CDK6	Amplification	2
CCND1	Amplification	2
CCND2	Amplification	2
CCND3	Amplification	2

One of the above amplifications AND

IHC	**RESULTS**
GENE:	STATUS:
RB	POSITIVE

APPENDIX IX APEC1621I YOUTH INFORMATION SHEETS
INFORMATION SHEET REGARDING RESEARCH STUDY APEC1621I
(for children from 7 through 12 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 APEC1621I
(for teens from 13 through 17 years of age)

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

1. 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 palbociclib, and so you have been assigned to palbociclib. The doctors want to see if palbociclib will make children with your type of cancer get better. We don't know if palbociclib 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 palbociclib 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 palbociclib. Your doctor will talk to you about the risks we know about from palbociclib. There may be other risks from palbociclib 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 X CTEP AND CTSU REGISTRATION PROCEDURES

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

RCR utilizes five person registration types.

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

RCR requires the following registration documents:

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

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

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

In addition, all investigators acting as the Site-Protocol PI (investigator listed on the IRB approval), consenting/treating/drug shipment investigator in OPEN, or as the CI on the DTL must be rostered at the enrolling site with a participating organization.

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

CTSU REGISTRATION PROCEDURES

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

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

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

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

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

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

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

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.

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

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

Note: Some Rave protocols may not have delinquent form details or reports specified on the DQP. A protocol must have the Calendar functionality implemented in Rave by the Lead Protocol Organization 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 XI PATIENT DRUG INFORMATION HANDOUT AND WALLET CARD

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

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

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

Palbociclib interacts with *certain specific enzyme(s) in your liver*. The enzyme in question is ***[CYP3A***, and Palbociclib is *broken down by this enzyme and may be affected by other drugs that inhibit or induce this enzyme.*

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

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

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

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

Palbociclib must be used very carefully with other medicines that use certain ***liver enzymes***. 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 or inhibitors of CYP3A."***

- 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 use of strong CYP3A inhibitors (e.g., clarithromycin, indinavir, itraconazole, ketoconazole, lopinavir/ritonavir, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, telaprevir, telithromycin, and voriconazole). Avoid grapefruit or grapefruit juice during palbociclib treatment. Avoid use of strong CYP3A inducers (e.g., phenytoin, rifampin, carbamazepine, enzalutamide, and St John's Wort).
- Your regular health care provider should check a frequently updated medical reference or call your study doctor before prescribing any new medicine or discontinuing any medicine. Your study doctor's name is _____ and he or she can be contacted at _____.

STUDY DRUG INFORMATION WALLET CARD

You are enrolled on a clinical trial using the experimental study drug **palbociclib.** This clinical trial is sponsored by the NCI. Palbociclib may interact with drugs that are processed by your liver or use certain transport proteins in your body. Because of this, it is very important to:

- Tell your doctors if you stop taking any medicines or if you start taking any new medicines.
- Tell all of your health care providers (doctors, physician assistants, nurse practitioners, or pharmacists) that you are taking part in a clinical trial.
- Check with your doctor or pharmacist whenever you need to use an over-the-counter medicine or herbal supplement.
- No grapefruit juice, Seville oranges, or grapefruit can be consumed while on palbociclib.

Palbociclib interacts with specific liver enzymes called CYP3A and must be used very carefully with other medicines that interact with these enzymes.

- 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 or inhibitors of CYP3A."***
- The use of proton pump inhibitors (PPIs) must be avoided if possible while taking palbociclib. Your study doctor will review any medicines you are taking.
- Before prescribing new medicines, your regular health care providers should go to a frequently updated medical reference for a list of drugs to avoid, or contact your study doctor.
- Your study doctor's name is _____

  and can be contacted at _____.

APPENDIX XII TOXICITY-SPECIFIC GRADING

Bilirubin

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

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

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

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

Grade 1:	≤ 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 - 5X ULN
Grade 3:	> 5 X ULN -20X ULN
Grade 4:	> 20 X ULN