CHILDREN'S ONCOLOGY GROUP

The world's childhood cancer experts

PPD

PPD

October 28, 2022

PPD

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

Dear PPD

The study committee thanks CTEP for forwarding the Amendment Request dated October 17, 2022. In response to the request, please see attached Amendment #6 to APEC1621D. The complete list of changes can be found below.

Please contact us if you have any further questions.

Sincerely,

PPD

SUMMARY OF CHANGES: PROTOCOL

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

#	Section	Page(s)	Change
1.	General	-	Updated protocol version date in the footer.
2.	Cover Page	1	Updated version date and amendment number.
3.	Contact Information	2	Cancer Trials Support Unit (CTSU)information updated with email address **CTSURegHelp@coccg.org**
4.	Table of Contents	3-5	Updated for re-pagination.
5.	Study Committee	7	Deleted PPD and added PPD as Protocol Coordinator

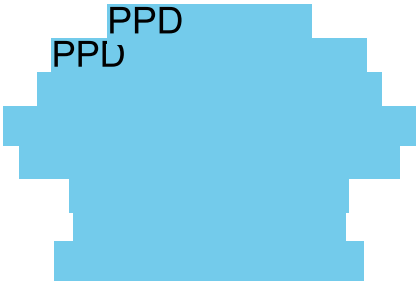
Activated: July 31, 2017
Closed:
Version Date: 10/28/2022
Amendment: 6

CHILDREN'S ONCOLOGY GROUP

APEC1621D

NCI-COG PEDIATRIC MATCH (MOLECULAR ANALYSIS FOR THERAPY CHOICE)- PHASE 2 SUBPROTOCOL OF LY3023414 IN PATIENTS WITH SOLID TUMORS

Open to COG Member Institutions in the USA



CONTACT INFORMATION		
For Regulatory Requirements	**For patient enrollments:**	**For Data Submission**
Regulatory documentation must be submitted to the Cancer Trials Support Unit (CTSU) via the Regulatory Submission Portal. (Sign in at www.ctsu.org, and select the Regulatory > Regulatory Submission.) Institutions with patients waiting that are unable to use the Portal should alert the CTSU Regulatory Office immediately by phone or email: 1-866-651-CTSU (2878), or CTSURegHelp@coccg.org to receive further instruction and support. Contact the CTSU Regulatory Help Desk at 1-866-651-CTSU (2878) for regulatory assistance.	Please refer to the patient enrollment section of the protocol for instructions on using the Oncology Patient Enrollment Network (OPEN). OPEN is accessed at https://www.ctsu.org/OPEN_SYSTEM/ or https://open.ctsu.org. Contact the CTSU Help Desk with any OPEN-related questions by phone or email: 1-888-823-5923, or ctsucontact@westat.com.	Data collection for this study will be done exclusively through Medidata Rave. Please see the Data Submission Schedule in the CRF packet for further instructions.
The most current version of the **study protocol** must be downloaded from the protocol-specific page located on the CTSU members' website (https://www.ctsu.org). Access to the CTSU members' website is managed through the Cancer Therapy and Evaluation Program - Identity and Access Management (CTEP-IAM) registration system and requires log in with a CTEP-IAM username and password. Permission to view and download this protocol and its supporting documents is restricted and is based on person and site roster assignment housed in the CTSU Regulatory Support System (RSS).		
For clinical questions (ie, patient eligibility or treatment-related) Contact the Study PI of the Lead Protocol Organization.		
For non-clinical questions (ie, unrelated to patient eligibility, treatment, or clinical data submission) Contact the CTSU Help Desk by phone or e-mail: CTSU General Information Line – 1-888-823-5923, or ctsucontact@westat.com. All calls and correspondence will be triaged to the appropriate CTSU representative.		
The CTSU Website is located at https://www.ctsu.org.		

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

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

ABSTRACT

This subprotocol is a component of the NCI-COG Pediatric MATCH trial APEC1621. The APEC1621SC screening protocol details the process used to identify actionable mutations in patient tumor samples which will determine eligibility for this subprotocol. This is a Phase 2 trial of LY3023414 in children with recurrent or refractory solid tumors, CNS tumors, and non-Hodgkin lymphomas harboring specified activating mutations of the PI3K/MTOR pathway. LY3023414 is a potent orally bioavailable small molecule inhibitor of class 1 PI3K isoforms, MTOR, and DNAPK. LY3023414 will be given twice daily continuously for 28-day cycles. Because the pediatric dose of LY3023414 has not been established, there will be a limited dose finding phase consisting of the first 12 evaluable patients enrolled on study. The primary endpoint will be objective response rate as determined by RECIST. Progression free survival (PFS) will be assessed as a secondary endpoint. In addition, toxicity will be assessed and the pharmacokinetics of LY3023414 in children will be evaluated.

EXPERIMENTAL DESIGN SCHEMA

Day 1-28	Day 28
LY3023414 (BID)	Evaluation

Patients will receive LY3023414 twice daily for 28-day cycles. Evaluations will occur at the end of every other cycle.

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 6 cycles (approximately 6 months) 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 LY3023414 with advanced solid tumors, non-Hodgkin lymphomas or CNS tumors that harbor TSC loss of function mutations, and/or other PI3K/MTOR activating mutations.

1.2 Secondary Aims

1.2.1 To estimate the progression free survival in pediatric patients treated with LY3023414 with advanced solid tumors, non-Hodgkin lymphomas or CNS tumors that harbor TSC loss of function mutations, and/or other PI3K/MTOR activating mutations.

1.2.2 To obtain information about the tolerability of LY3023414 in children with relapsed or refractory cancer.

1.2.3 To characterize the pharmacokinetics of LY3023414 in children with recurrent or refractory cancer.

1.3 Exploratory Aims

1.3.1 To increase knowledge of the genomic landscape of relapsed pediatric solid tumors and lymphomas and identify potential predictive biomarkers (other than the genomic alteration for which study treatment was assigned) using additional genomic, transcriptomic, and proteomic testing platforms.

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

1.3.3 To evaluate the frequency and mechanism of biallelic loss of function, and evaluate the expression of TSC1, TSC2, and PTEN in subjects who enroll with a loss of function mutation in one of these genes.

2.0 BACKGROUND

2.1 Introduction/Rationale for Development PI3K/MTOR pathway:

Phosphoinositide 3-kinases (PI3Ks) function downstream of receptor tyrosine kinases (RTKs) and G-protein coupled receptors (GPCRs) to stimulate a number of pro-growth and anti-apoptotic pathways within tumor cells. PI3Ks consist of a catalytic subunit (PIK3CA, PIK3CB, or PIK3CD) and a regulatory subunit (including PIK3R1). Mechanistically, PI3Ks phosphorylate phosphatidylinositol 4,5-bisphosphate (PIP2) to phosphatidyl 3,4,5-triphosphate (PIP3). Phosphatase and tensin homolog (PTEN) catalyzes the reverse reaction and thus negatively regulates this pathway. PIP3 allows the activation of protein kinase B (AKT) which in turn phosphorylates and inactivates Tuberous Sclerosis Complex 2 (TSC2). With TSC1, TSC2 normally inhibits the function of Ras homolog enriched in brain (RHEB), which stimulates mechanistic target of rapamycin (MTOR) activity. Thus, by inhibiting TSC1-TSC2, PI3K and AKT signaling stimulates MTOR activity to activate pro-growth and anti-apoptotic pathways in tumor cells.

PIK3/MTOR pathway mutations occur across a broad spectrum of pediatric cancers:
Histology specific sequencing efforts have demonstrated that activating mutations of the PI3K/MTOR pathway are present in a wide variety of pediatric solid tumors including osteosarcoma (24% of patients,) embryonal rhabdomyosarcoma (7.4% with PIK3CA mutation, rare patients with PTEN loss,) and diffuse intrinsic pontine gliomas (DIPG, 15% with PIK3CA mutation.)[1-4] While these studies can provide a suggestion of the frequency of mutations in patients eligible for the pediatric MATCH study, the precise frequency of mutations in this population as a whole is unknown. The best estimates likely come from cross-sectional studies of next generation sequencing of pediatric solid tumors and publically disclosed sequencing data released by Foundation Medicine, in which 1-10% of subjects had identified mutations in the PI3K/MTOR pathway.[5,6]

In the Foundation Medicine dataset, panel based sequencing of solid tumors from 981 pediatric patients detected the following mutations deemed to activate the PI3K/MTOR pathway:

- 42 PIK3CA mutations (including 26 brain tumors and 11 sarcomas)
- 4 PIK3R1 mutations (including 3 brain tumors and 1 sarcoma)
- 26 PTEN deletions or truncations (including 12 brain tumors, 10 sarcomas)
- 6 PTEN point mutations (including 4 brain tumors, 2 sarcomas)
- 8 TSC1 truncations or deletions (including 6 brain tumors)
- 6 TSC2 truncations or deletions (including 3 brain tumors and 2 sarcomas)
- 6 TSC2 point mutations (including 3 sarcomas and 3 extracranial embryonal tumors)
- 2 point mutations in MTOR (both in extracranial embryonal tumors)

Thus, activating PI3K/MTOR pathway alterations occurred in 10% of pediatric solid tumors, with the majority (55%) occurring in brain tumors and 31% occurring in sarcomas. However, not all of the variants reported by Foundation Medicine may be considered actionable for pediatric MATCH. As an example, the TSC2 A607T variant was observed 3 times and is reported as likely activating by the Foundation Medicine. However, a report studying the biochemical effects of TSC1 and TSC2 variants concluded that the variant was likely neutral.[7] Conversely, none of these cross-sectional sequencing studies evaluated PTEN loss by IHC, which has been selected as an variant eligible for inclusion in this arm of pediatric MATCH. Thus, we estimate that in total between 2-5% of subjects enrolled on the pediatric MATCH protocol will have one of the defined PI3K/MTOR pathway

activating lesions eligible for this arm.

PI3K/MTOR pathway mutations may confer sensitivity to PI3K/MTOR inhibitors: Multiple lines of evidence point to activating mutations of the PI3K/MTOR pathway as biomarkers of response to targeted PI3K and MTOR inhibitors.[8] In preclinical studies in breast cancer, activating mutations of PIK3CA have been shown to confer sensitivity to PI3K inhibitors, AKT inhibitors, allosteric MTOR inhibitors, TORC1/2 inhibitors, and PI3K/MTOR inhibitors.[9-16] These findings have been extended to other PIK3CA mutant tumor models including melanoma, lung, ovarian, prostate, and endometrial cancer.[17-19] In preclinical studies, the relationship between PTEN deficiency and sensitivity to PI3K pathway inhibitors has been less clear. Some studies have found that some PTEN deficient cell lines are sensitive to PI3K inhibitors,[11,13,15] but others have found that PTEN deficient cells are preferentially resistant to PI3K/MTOR inhibitors.[9,16,17] Recent studies have suggested that PTEN deficient tumors are specifically dependent on the beta rather than the alpha isoform of PI3K, and thus are sensitive to inhibitors of PIK3CB (which is inhibited by LY3023414).[20-22]

In clinical trials, evidence also suggests that PI3K pathway mutations may confer sensitivity to MTOR inhibitors. The strongest evidence links TSC mutations to sensitivity. Everolimus was studied in a randomized phase 3 trial in patients with subependymal giant cell astrocytomas (SEGA) and a clinical diagnosis of TSC, most of whom are predicted to have loss of function mutations in TSC1 or TSC2. 35% of everolimus treated patients had at least 50% reduction in SEGA volume, and 53% of everolimus treated patients had at least 50% reduction in the volume of their concurrent angiomyolipomas vs none in placebo treated patients.[23,24] Further, a retrospective study of patients with metastatic renal cell carcinoma found that mutations in MTOR, TSC1 or TSC2 were more common in patients who responded to rapalogs than those who did not respond.[25] Patients with other tumors harboring TSC mutations have experienced extraordinatory responses to MTOR inhibition: two patients with metastatic RCC and biallelic inactivation of TSC1 experienced >24 month disease control with temsirolimus, and a patient metastatic bladder cancer with TSC1 and NF2 mutations experienced a >24 month complete response to everolimus.[26,27]

There is also clinical evidence of response to MTOR inhibitors for mutations of other genes in this pathway including PIK3CA, PTEN, PIK3R1, and MTOR itself. PIK3CA mutation or PTEN loss of function mutations have correlated with response to allosteric MTOR inhibitors in several studies, although some studies have shown similar efficacy in both biomarker positive and biomarker negative patients.[10,28-32] As examples, of 258 adult patients with advanced cancers treated at a single institution on phase 1 studies that included various inhibitors of the PI3K/MTOR pathway, 35% (6 of 17) of patients with PIK3CA mutations achieved a partial response vs 6% of patients who did not have a PIK3CA mutation.[28] Similarly, of 23 patients with PIK3CA mutant breast, cervical, endometrial, and ovarian cancer treated on various phase 1 studies of PI3K/MTOR pathway inhibitors at a single institution, 30% had a partial response compared to 10% of patients with the same disease types lacking PIK3CA mutations.[33] An adult subject with an endometrial cancer harboring a PIK3R1 X448_Y452 deletion experienced a PR to LY3023414 in the phase 1 study of this agent. Several small case series have reported extraordinary responses to allosteric MTOR inhibitors in patients with activating mutations of the MTOR gene itself, including a 14-month complete remission to the combination of everolimus and pazopanib in a patient biallelic activating mutations in MTOR.[27,32,34]

RAS pathway mutations are biomarkers of resistance to PI3K/MTOR inhibitors:
Preclinical studies in a number of cancer types have demonstrated that mutations in the RAS/MAPK pathway confir resistance to PI3K/MTOR pathway inhibitors.[9,35-38] While concurrent PIK3CA mutations and RAS pathway mutations are rare in breast cancer, these mutations co-exist with high frequency in a number of other adult malignancies, including colorectal and ovarian cancer.[39] Similarly, in the Foundation Medicine pediatric dataset, 20% of pediatric patients with TSC1/2 mutations, and 28% of pediatric patients with other PI3K pathway mutaions harbor concurrent RAS pathway mutations (Figure 1).

In preclinical studies, RAS pathway mutations confer resistance to PI3K/MTOR pathway inhibitors even when there is a concurrent activating mutation of the PI3K/MTOR pathway.[36] While the number of patients treated is small, retrospective analyses of early phase clinical trials also suggest that RAS pathway mutations are biomarkers of resistance, even for patients with PI3K/MTOR pathway activating mutations. Among 18 patients with PTEN negative tumors treated on phase I/II studies of everolimus at a single institution, 6 patients were found to have concurrent BRAF or KRAS mutations, and all had progressive disease as their best response. Among the 12 patients without these muations, there was 1 partial response, 7 patients with stable disease, and 4 patients with progressive disease as the best response.[10] Therefore, we will exclude patients with mutations that activate the RAS from APEC1621D.

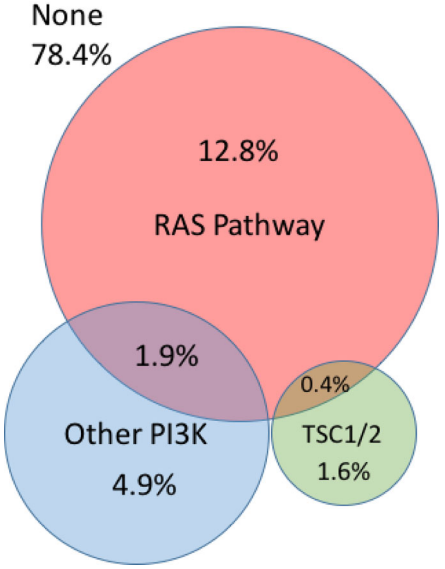


Figure 1: Percentage of pediatric tumors with TSC1/2, other PI3K pathway, and RAS pathway mutations, excluding amplification, and their overlap. From Foundation Medicine pediatric data.

PI3K/MTOR inhibitors in biomarker negative patients:
While activating mutations in the PI3K/MTOR pathway correlate with response to PI3K/MTOR inhibitors, PI3K/MTOR inhibitors have also demonstrated efficacy against tumors without identified PI3K/MTOR pathway mutations both preclinically and in clinical trials. Several inhibitors of this pathway have been studied against pediatric cancer xenografts in the pediatric preclinical testing program (PPTP). Rapamycin, an allosteric MTOR inhibitor, had intermediate or high activity against 14 of 31 evaluable solid tumor xenografts, including partial responses in a rhabdoid tumor, two rhabdomyosarcomas, and a maintained CR in an osteosarcoma.[40] A PI3K inhibitor (XL147) demonstrated significant tumor growth delay in 79% of solid tumor xenografts, and two MTOR kinase inhibitors (AZD8055 and MON1028) induced significant tumor growth delay in the majority to solid tumors xenografts studied (55.6% and 77%, respectively.)[41-43] While the correlation between mutational status and response in these models is unknown, the percentage of xenografts with tumor growth delay is much higher than the percentage predicted to have genetic alterations in this pathway.

Clinically, an analysis of 724 women with advanced hormone receptor-positive breast cancer randomly assigned to treatment with exemestane with or without everolimus demonstrated that the efficacy of everolimus was largely independent of mutations in the

PI3K/MTOR pathway, the exception of a small group of patients with MTOR mutations for whom there may have been increased efficacy.[32] In this study, everolimus was associated with a hazard ratio of 0.37 (95% CI 0.25-0.55) for disease progression in patients without identified mutations in PIK3CA, PTEN, AKT, PIK3R1, or low PTEN expression by IHC. Clinical trials in adults with colorectal cancer have also shown that patients lacking PIK3CA and PTEN mutations can respond.[29]

In pediatric patients, the allosteric MTOR inhibitor temsirolimus demonstrated improved EFS compared to bevacizumab in a COG randomized phase 2 trial in recurrent rhabdomyosarcoma in combination with vinorelbine/cyclophosphamide.[44] This population was not biomarker selected. Evaluation for activating mutations in the PI3K/MTOR pathway in these subjects has not been completed. However, activating mutations in the PI3K/MTOR pathway are rare in rhabdomyosarcoma, occurring in less than 10% of patients.[4]

Other biomarkers of PI3K/MTOR response:
There are other potential biomarkers of efficacy of MTOR inhibitors including PI3K/MTOR pathway biochemical activity as assessed by phosphorylation of target proteins. In preclinical studies, response of breast cancer cell lines has been correlated with baseline phosphorylation of both AKT and S6K.[45,46] In clinical trials, response to MTOR inhibitors has also been correlated with phosphorylation of both AKT1 and S6RP in tumor cells as measured by IHC. [47-52] As examples, elevated baseline phospho-AKT levels were predictors of progression free survival in 40 NSCLC patients treated with everolimus.[53] Similarly, among 44 patients with glioblastoma treated with temsirolimus, baseline phosphorylation of S6K was associated with response to therapy.[49] However, other studies have not found a correlation between these biomarkers and response.[52,54]

LY3023414:
LY3023414 is an orally bioavailable small molecule inhibitor of class 1 PI3K isoforms, MTOR, and DNAPK that has low nM potency, inhibiting PI3K isoforms at concentrations ranging from 6-78 nM, MTOR at 165 nM and DNAPK at 4 uM.[55] LY3023414 was selected for the PI3K/MTOR arm of the pediatric MATCH study as a broadly active inhibitor of the PI3K/MTOR pathway with an available recommended phase 2 dose in adult patients. Due to its broad activity within this pathway, LY3023414 is appropriate to study across the range of alterations in the PI3K/MTOR pathway seen in pediatric cancers.

2.2 Preclinical Studies

2.2.1 Antitumor Activity

In vitro, LY3023414 inhibits purified class I isoforms, PI3Kalpha, PI3Kbeta, PI3Kdelta, and PI3Kgamma with IC50 values of 0.006 micromolar, 0.078 micromolar, 0.038 micromolar, and 0.024 micromolar, respectively. LY3023414 inhibits MTOR and DNA-PK with IC50 values of 0.165 micromolar and 0.004 micromolar in a cell lysate assay. LY3023414 is highly selective against a panel of 101 kinase enzymes and 200 kinases in a cell lysate assay system. LY3023414 demonstrates inhibitory activity against PI3K and MTOR and antiproliferative activity in a variety of cultured cancer cells.[55]

In studies of *in vivo* activity, LY3023414 as a single agent inhibits the growth of multiple tumor models with activating mutations in the PI3K/MTOR pathway, specifically the PTEN-deficient U87MG glioblastoma and 786-O renal carcinoma

models, the PIK3CA mutant NCI-H1975 non-small cell lung cancer (NSCLC) model, and a leukemia model driven by oncogenic Myc and mutant PIK3CA E545K. LY3023414 demonstrated equivalent tumor growth inhibition at doses of 15 mg/kg dosed twice daily or 30 mg/kg dosed daily in the U87MG xenograft model. [55]

In these preclinical studies, tumor growth inhibition is associated with pharmacodynamic markers of pathway inhibition. Phosphorylation of the PIK3CA and MTOR downstream targets AKT, S6K, S6RP, and 4E-BP1 was inhibited by LY3023414 in a dose-dependent and time-dependent manner in the U87MG xenograft model. Maximum inhibition of pAKT, pS6K, and p4E-BP1 was observed 30 minutes after oral dosing, while S6RP was maximally inhibited 2 to 3 hours or 4 to 6 hours after oral dosing for pS235/236 and pS240/244 S6RP, respectively.[55]

2.2.2 Animal Toxicology

LY3023414 has been evaluated in nonclinical toxicology studies of 1 and 3 months in duration using daily oral dosing in rats and dogs.

Early deaths in the 1- and 3-month toxicology studies occurred in rats treated with daily doses ≥ 15 mg/kg and dogs treated with ≥ 9 mg/kg. The deaths in rats and dogs were preceded by premonitory clinical signs of deteriorating physical condition and moribundity. A single cause of death could not be established for the rat and dog mortalities, but indications of toxicity were present in multiple organs, including lymphoid tissue, the GI tract, and bone marrow.

Notable toxicities observed at non-lethal doses in the preclinical toxicology studies included dose related decreases in lymphocyte count and decreased or absent antibody response to keyhole limpet hemocyanin challenge in rats and dogs. Gastrointestinal toxicity was observed in both rats and dogs in a dose related manner. These included ulceration, epithelial atrophy, and villous blunting. Gastrointestinal toxicities were seen only in rats treated at doses ≥ 10 mg/kg and dogs treated at doses > 6 mg/kg. Bone marrow hypocellularity was observed in animals treated above the MTD. In rats treated with doses ≤ 15 mg/kg and dogs treated with doses ≤ 6 mg/kg, there were no or only minimal bone marrow findings. Rats were noted to develop crusted skin and sores with both 1 and 3 month treatment, which were reversible when treatment was stopped. No effects on skin were seen in dogs. Hypospermia was observed in both rats and dogs treated with LY3023414 and was reversible in the 3 month dog study.

In dogs, blood insulin and glucose concentrations increased at doses of ≥ 3 mg/kg within 30 minutes of dosing and generally peaked at 1 to 2 hours after dosing. At doses ≥ 9 mg/kg, these changes were marked. At all doses, these increases returned to normal approximately 4 hours or 8 hours after dosing. Increased QT and QTc intervals were observed on Day 25 at the 6 mg/kg and 9 mg/kg doses in dogs. At 6 mg/kg, an increase of 4 msec to 16 msec was observed postdose and was reversible. At 9 mg/kg (a dose that exceeded the MTD based on clinical observations) increased QTc intervals were observed up to 19 hours postdose, with peak increases (37 msec) observed at approximately 3 hours postdose.

Effects on glucose metabolism are an expected pharmacologic effect based on the

role that PI3K and MTOR pathways play in glucose metabolism. Consistent with what has been observed with LY3023414, other small molecule inhibitors of the PI3K/MTOR pathway cause similar changes to glucose metabolism.[56]

The genotoxic potential of LY3023414 was evaluated in a test battery that included a bacterial mutagenicity test ("Ames assay"), an in vitro chromosome aberrations assay in Chinese hamster ovary (CHO) cells, and an in vivo rat bone marrow micronucleus test. Collectively, the genetic toxicology results (negative for gene mutations in bacteria, negative for clastogenic activity in CHO cells, and positive for micronucleus induction in rat bone marrow erythrocytes) provide the weight of evidence to support the conclusion that LY3023414 has aneugenic activity. The positive micronucleus results with LY3023414 were consistently observed in rats at acute doses ≥ 30 mg/kg, while negative results were obtained at 20 mg/kg. The exposure (Cmax) associated with a 30 mg/kg dose following the first day of dosing in the 4-week repeat-dose toxicology study was 2400 ng/mL (for males). Assuming dose-proportionality of the rat exposures in the 4-week study, the Cmax value associated with an acute 20 mg/kg dose can be estimated to be 1600 ng/mL. Because dose-response curves for aneugens are well-known to have a threshold, human exposures to LY3023414 at levels below the 1600-ng/mL threshold are not expected to be accompanied by any aneugenic risks.

In an enhanced pilot embryo-fetal developmental study of LY3023414 in rats, embryo-fetal lethality was seen along with an increase in fetal and litter incidence of external, visceral, and skeletal malformations. These consisted primarily of cranial, abdominal wall, cardiovascular, vertebral, rib, and sternebrae dysmorphologies when female Sprague-Dawley rats were administered 15 mg/kg (90 mg/m^2) LY3023414 orally on gestation days 6 through 17. There were no compound-related changes in embryo-fetal survival; fetal weight; or external, visceral, or skeletal morphology at ≤ 2 mg/kg (12 mg/m^2).

In conclusion, the nonclinical toxicology findings with LY3023414 are consistent with the known toxicity profile of inhibition of the PI3K/MTOR signaling pathway. Inhibitors of the PI3K/MTOR pathway are well-characterized both clinically and nonclinically, with the predominant target organs for toxicity in nonclinical species being the GI tract, hematopoietic system, lymphoid tissues, and reproductive tissues. Additional target organs for toxicity include the kidney, skin, and the cardiovascular system. These toxicities are anticipated to be reversible. [57]

2.3 Adult Studies

2.3.1 Phase 1 Studies

The recommended phase 2 dose of LY3023414 in adult subjects with advanced cancer has been determined in a phase 1 study (NCT01655225). As of the cut-off date (08 June 2016), a total of 110 patients have received LY3023414 on this study. A total of 25 patients were enrolled in the dose-escalation portion (Part A) investigating continuous QD administration of LY3023414. Patients received LY3023414 at 7 dose levels ranging 20 mg to 450 mg daily. A dose of 325 mg once daily was determined to the maximum tolerated dose based on dose limiting toxicities (DLTs) observed in 3 of 3 patients treated at 450 mg once daily. These DLTs consisted of thrombocytopenia (Grade 4), hypotension (Grade 3), and hyperkalemia (Grade 3).

Following Part A, a second dose-escalation phase (Part A2) was initiated to investigate BID oral administration of LY3023414. Part A2 was completed with a total of 13 patients who received LY3023414 BID at dose levels ranging from 150 mg to 250 mg twice daily. A dose of 200 mg twice daily was determined to be the MTD based on DLTs observed in 3 of 4 patients treated at 250 mg twice daily. These DLTs consisted of hypophosphatemia (Grade 4), fatigue, and mucositis (Grade 3; all n = 1). At the 200 mg twice daily dose level, 1 of 6 patients experienced a DLT in the form of grade 2 nausea.

Part B of this study is ongoing enrolling patients into tumor-specific cohorts (B1 through B6) at the recommended phase 2 dose of 200 mg BID. As of the data cut-off date (08 June 2016), a total of 56 patients received 200 mg BID LY3023414 monotherapy; 9 patients received 200 mg BID LY3023414 in combination with fulvestrant; and 7 patients received 100-200 mg BID of LY3023414 with cisplatin and pemetrexed.

An additional phase 1 study of LY3023414 is now enrolling in Japanese patients with advanced malignancies with 11 of 12 planned subjects enrolled as of 8 June 2016.

2.3.2 Phase 2 Studies

No phase 2 studies of LY3023414 have been completed to date. A phase 2 double blind, placebo controlled study of enzalutamide with or without 200 mg BID of LY3023414 is currently enrolling men with castration-resistant prostate cancer (NCT02407054). As of 8 June 2016, 13 subjects have been enrolled to the open-label safety lead-in phase and enrollment to the randomized double-blind, placebo-controlled treatment part is ongoing with 6 of 132 subjects enrolled. A second phase 2 single arm study of LY3023414 with necitumumab is currently enrolled men with advanced or metastatic squamous non-small cell carcinoma of the lung (NCT02443337). 22 of 48 planned patients have been enrolled as of 8 June 2016.

2.3.3 Pharmacology/Pharmacokinetics/Correlative and Biological Studies

2.3.3.1 Pharmacology:

In vitro human microsomal data indicated possible time-dependent inhibition of CYP3A4 by LY3023414. To investigate this, one objective of the now completed Part B1 cohort in the phase 1 study of LY3023414 was to investigate whether LY3023414 impacts (decreases) the metabolic clearance of drugs that are metabolized through CYP3A4, such as midazolam. The results indicate that LY3023414 increases the exposure (AUC∞) of midazolam by a geometric mean ratio of 1.46 (90% CI 1.21-1.76). Therefore, LY3023414 is classified as a weak CYP3A4 inhibitor because it leads to less than a 2-fold increase in exposure of the enzyme substrate drug.

Extensive PK time-matched central ECGs were collected in parts A and A2 of the adult phase 1 study of LY3023414 at doses up to 450 mg. Despite changes in the QT interval in preclinical studies in dogs, LY3023414 did not lead to clinically and/or statistically significant

changes in QTcF in humans.

2.3.3.2 Pharmacokinetics:
The pharmacokinetics of LY3023414 in adults with advanced malignancies is available from subjects treated on the phase 1 study. Following oral administration, LY3023414 concentrations reach a maximum value at approximately 1 to 2 hours postdose. Cmax and AUC∞ increase approximately dose-proportionally from 20 to 325 mg; however, Cmax and AUC∞ at the dose of 450 mg show a greater than dose proportional increase.

A single 200 mg dose of LY3023414 resulted in a geometric mean Cmax value of 863 ng/mL. Cmax and $AUC_{0\text{-}12\ hr}$ at steady state on Day 15 were 884 ng/mL and 2950 ng·h/mL for the 200 mg twice daily dose.

LY3023414 has a geometric mean half-life ($t_{1/2}$) of 1.87 hours for all doses of 20 mg to 325 mg. Mean apparent clearance (CL/F) and mean apparent volume of distribution (Vz/F) were calculated to be 74.3 L/hr and 200 L, respectively, across the 20- mg to 325-mg dose range.

Based on the short terminal $t_{1/2}$, steady state is anticipated to be reached after 1 dose of LY3023414. In adult subjects, there is limited accumulation of LY3023414 with a geometric mean exposure ratio (Day 15: Day 1) of 1.28 with BID dosing. This small/moderate ratio indicates a slight decrease in LY3023414 CL/F after repeated dosing between Day 1 and Day 15 (in particular for doses ≥ 150 mg). However, once steady state is stabilized, LY3023414 CL/F, and hence exposure (AUC), is stable.

2.3.3.3 Pharmacodynamics:
Inhibition of phosphorylation of the MTOR target 4EBP1 was evaluated in 35 patients treated with LY302314 in Parts A and A2 of the phase 1 study. At doses above 150 mg daily, LY3023414 inhibits phosphorylation of 4EBP1 in PBMCs by ≥ 90%.

2.3.3.4 Response:
As of 08 June 2016, limited data are available for only a preliminary evaluation of clinical activity of LY3023414 in the ongoing adult phase 1 study. Most notably, in the dose-escalation part of this study, a woman with an endometrial cancer bearing PIK3R1 and PTEN mutations experienced a durable PR with 50% reduction in tumor volume. In the tumor-specific expansion cohorts, a partial response was observed in 5 patients (out of 74 patients enrolled).

2.4 Pediatric Studies

There have been no prior studies of LY3023414 in children.

2.5 Overview of Proposed Pediatric Study

This subprotocol is a component of the Pediatric MATCH trial. The APEC1621SC screening protocol details the assay used for the integral genomic profiling which will determine eligibility for this arm. This is a phase 2 trial of LY3023414 in children with recurrent or refractory solid tumors, CNS tumors, and non-Hodgkin lymphomas harboring

specified activating mutations of the PI3K/MTOR pathway.

Because the pediatric dose of LY3023414 has not been established, there will be a limited dose finding phase consisting of the first 12 evaluable patients enrolled on study. Patients will receive LY3023414 twice daily for 28-day cycles. The first 6 evaluable patients will be enrolled at a dose of 80 mg/m^2/dose BID, equivalent to 70% of the maximum tolerated dose (MTD) in adults. There will be a single dose escalation to 115 mg/m^2/dose BID (100% of the adult MTD) or de-escalation to 55 mg/m^2/dose BID (50% of the adult MTD) for the next six subjects. Following the first 12 evaluable patients, all subsequent patients will be enrolled at the highest dose level not exceeding the pediatric MTD. Patients enrolled in the dose escalation component will be included in the analysis of efficacy.

The primary aim of this trial will be to establish the objective response rate to LY3023414 in patients with inactivating mutations in TSC1/2 and/or other specified PI3K/MTOR activating mutations.

Key secondary objectives include evaluating the tolerability and pharmacokinetics of LY3023414 in pediatric patients as no pediatric studies of LY3023414 have been conducted to date. Toxicity will be assessed using CTCAE V5.0. Imaging for disease evaluation will occur every other cycle. Disease response will be assessed according to RECIST v1.1 criteria for solid tumors and 2-dimensional measurement for CNS tumors.

3.0 SCREENING AND STUDY ENROLLMENT PROCEDURES

3.1 Study Enrollment

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

3.1.1 Access requirements for OPEN:

Patient enrollment for this study will be facilitated using the Oncology Patient Enrollment Network (OPEN), 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: 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 X for detailed CTEP and CTSU Registration Procedures including: registration in Registration and Credential Repository (RCR),

requirements for site registration, submission of regulatory documents and how to check your site's registration status.

3.1.2 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://eapps-ctep.nci.nih.gov/iam/index.jsp >). 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://www.ctsu.org or from the OPEN tab on the CTSU members' side of the website at https://www.ctsu.org.

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 #4A 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 APEC1621D study patients (such as whether a specific mutation would be considered actionable for the study) should be directed to the APEC1621SC and APEC1621D 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 APEC1621D 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 APEC1621D.

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**

Following a MATCH treatment assignment to a protocol, patients may be enrolled on the study once all eligibility requirements for the study have been met. Before enrolling a patient on study, the Study Chair or Vice Chair should be notified. Patients who give informed consent for the protocol in order to undergo screening for eligibility are not considered enrolled and should not be enrolled until the screening is completed and they are determined to meet all eligibility criteria. Study enrollment in Stage 2 of Pediatric MATCH (effective with Amendment #4A of APEC1621SC for patients enrolling on screening protocol) is outlined in Section 3.1.3.

Patients must be enrolled within 2 weeks (14 days) of treatment assignment. The date protocol therapy is projected to start must be no later than 7 calendar days after the date of enrollment. Patients enrolling onto APEC1621D will have a COG ID obtained through their prior enrollment onto the screening protocol or from a prior COG study. Patients who are started on protocol therapy prior to study enrollment will be considered ineligible.

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

Note: No starter supplies will be provided. Drug orders of LY3023414 should be placed with CTEP after enrollment and treatment assignment to APEC1621D 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 APEC1621SC screening protocol.

3.7 **Dose Assignment**

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

4.0 PATIENT ELIGIBILITY

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

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

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

4.1 Inclusion Criteria

4.1.1 APEC1621SC: Patient must have enrolled onto APEC1621SC and must have been given a treatment assignment to MATCH to APEC1621D based on the presence of an actionable mutation as defined in APEC1621SC. Examples of actionable mutations for APEC1621D are listed in Appendix VII-A and Appendix VII-B.

Note that treatment assignment may be to primary cohort A for patients with TSC1 or TSC2 loss of function mutations or primary cohort B for patients with other PI3K/MTOR pathway mutations (see section 11.3.1).

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 accruing to Dose Level 1 must have a body surface area ≥ 0.52 m^2 at the time of study enrollment. Patients accruing to Dose Level 2 must have a body surface area ≥ 0.37 m^2 at the time of study enrollment. Patients accruing to Dose Level -1 must have a body surface area ≥ 0.75 m^2 at the time of study enrollment.

4.1.4 Disease Status:
Patients must have radiographically **measurable** disease (See section 12.0) 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.
- bone lesions without an associated soft tissue mass ⩾ 10 mm in greatest diameter. Bone lesions with an associated soft tissue mass ⩾ 10 mm in greatest diameter imaged by CT or MRI are considered measurable.

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

4.1.6 Prior Therapy

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

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

b. Anti-cancer agents not known to be myelosuppressive (e.g. not associated with reduced platelet or ANC counts): ≥ 7 days after the last dose of agent.
See https://www.cogmembers.org/Site/Disc/DevTherapeutics/Default.aspx#ToolsReferenceMaterials 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 LY3023414.

l. Patients must not have received prior exposure to an agent specifically directed at the PI3K/MTOR pathway (a PI3K inhibitor, an AKT inhibitor, an MTOR inhibitor, including rapalogs, or a combined PI3K/MTOR inhibitor).

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 Section 4.1.7.1.a (may receive transfusions provided they are not known to be refractory to red cell or platelet transfusions). These patients will not be evaluable for hematologic toxicity.

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

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

The threshold creatinine values in this Table were derived from the Schwartz formula for estimating GFR utilizing child length and stature data published by the CDC.[58]

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

4.1.7.4 Normal blood glucose for age
- Patients must have a normal blood sugar level for age. If an initial random draw (i.e. non-fasting) blood glucose value is out of range, it is acceptable to repeat this test as a fasting draw.

4.1.7.5 Lipids:
- Patients must have a serum triglyceride level ≤ 300 mg/dL and serum cholesterol level ≤ 300 mg/dL. If an initial random draw (i.e. non-fasting) is out of range, it is acceptable to repeat this test as a fasting draw.

4.1.7.6 Adequate Neurologic Function Defined as:
- Patients with seizure disorder may be enrolled if on anticonvulsants and well controlled.

- Nervous system disorders (by CTCAE V 5.0) resulting from prior therapy must be ≤ Grade 2, with the exception of decreased tendon reflex (DTR). Any grade of DTR is eligible.

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

4.1.8 Patients must be able to swallow intact tablets.

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

4.2 Exclusion Criteria

4.2.1 Pregnancy or Breast-Feeding
Pregnant or breast-feeding women will not be entered on this study due to risks of fetal and teratogenic adverse events as seen in animal 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 while receiving study treatment and for 3 months after the last dose of LY3023414.

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.

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

4.2.4 Diabetes: Patients who have insulin dependent diabetes are not eligible.

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

4.2.6 Patients with SubEpendymal Giant cell Astrocytomas (SEGAs) are not eligible because everolimus is approved by the FDA for this patient population.

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

5.0 TREATMENT PROGRAM

5.1 Overview of Treatment Plan

Day 1-28	Day 28
LY3023414 orally, twice daily	Evaluation

LY3023414 will be administered orally twice daily. For patients enrolled during the dose-confirmation part of the study, the Cycle 1 Day 1 PM dose of LY3023414 will be omitted for PK sampling.

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 a maximum of 6 cycles provided the patient meets the criteria for starting subsequent cycles (Section 5.2) and does not meet any of the criteria for removal from protocol therapy criteria (Section 10.0).

A cycle of therapy is considered to be 28 days. A cycle may be repeated for a maximum of 6 cycles.

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

LY3023414 should be taken without regards to food with a glass of water at approximately the same time each day. Patients should swallow the tablets as a whole and should not chew or crush them.

If a patient misses a dose of LY3023414, the dose should be taken as soon as possible as long as it is more than 6 hours before the next scheduled dose. If it is less than 6 hours before the next dose, then the dose should be skipped. If vomiting occurs after taking LY3023414, the patient should skip the dose and take the next dose as scheduled.

5.1.1 Determination of Recommended Phase 2 Dose (RP2D)/Tolerable Dose

Dose Level	Dose (mg/m^2)
-1	55 mg/m^2/dose BID
1*	**80 mg/m^2/dose** BID
2	115 mg/m^2/dose BID

Update (Amendment 5A): There were no cycle 1 dose limiting toxicities in the patients enrolled to either dose level 1 or dose level 2 during dose determination. Therefore, the RP2D on this study has been determined to be dose level 2 (115mg/m^2/dose BID), and all remaining subjects will enroll at this dose.

The DLT evaluation period for the purpose of dose escalation will be cycle 1 of therapy. Patients enrolled during the determination of the recommended phase 2

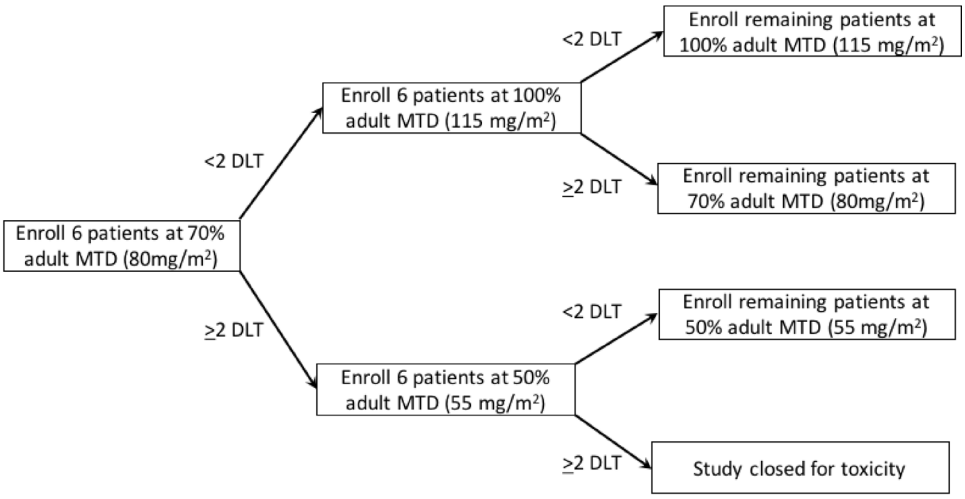
dose who are not evaluable for toxicity during cycle 1 at a given dose level will be replaced.

The starting dose will be 80 mg/m^2/dose BID (Dose Level 1), which is approximately 30% below the adult MTD. Accrual will be temporarily suspended after enrollment to the first 6 toxicity-evaluable subjects to assess for toxicity as outlined in Section 11.2.

If there are fewer than 2 DLTs in the first 6 toxicity-evaluable subjects enrolled at the starting dose, the dose will be escalated to Dose Level 2. If ≥ 2 of the first 6 toxicity-evaluable subjects enrolled at Dose Level 2 have DLTs, all subsequent subjects will be enrolled at the original starting dose. Otherwise, remaining subjects will continue to enroll at Dose Level 2.

If there are 2 or more DLTs during cycle 1 among the first 6 toxicity-evaluable subjects enrolled at Dose Level 1, the next cohort will enroll at Dose Level -1. If ≥ 2 of the first 6 toxicity-evaluable subjects enrolled at the reduced dose have DLTs, the study will be closed for toxicity. Otherwise, remaining subjects will continue to enroll at Dose Level -1.

Dose escalation schema:



5.1.2 Intra-Patient Escalation

Intra-patient dose escalation is not allowed.

5.1.3 Therapy Delivery Map

See Appendix VI for APEC1621D Therapy Delivery Map.

5.2 Criteria for Starting Subsequent Cycles

A cycle may be repeated every 28 days if the patient has at least stable disease and has again met laboratory parameters as defined in the eligibility section, Section 4.0 with the exception of hyperglycemia, hypercholesterolemia, and hypertriglyceridemia, for which the patient may proceed to the next cycle as long as there is not an ongoing dose limiting toxicity as defined in Section 5.4.1.

5.3 Grading of Adverse Events

Adverse events (toxicities) will be graded according to the current version of the NCI Common Terminology Criteria for Adverse Events (CTCAE). All appropriate treatment areas should have access to a copy of the current version of the CTCAE v5.0. A copy of the CTCAE v5.0 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 4 or greater non-hematological toxicity attributable to the investigational drug with the specific exclusion of:

- Grade 4 fever < 5 days duration.
- Hyperglycemia >500 mg/dL (>27.8 mmol/L) that returns to fasting glucose value ≤ 250 mg/dL (13.9 mmol/L) within 24 hours of initiation of appropriate supportive care as per Section 7.3.4. The severity (grade) of hyperglycemia is based upon fasting levels. If glucose >500 mg/dL (>27.8 mmol/L) is detected when routine (non-fasting) laboratory studies are performed, the test should be repeated within 24 hours in the fasting state to permit accurate grading.

Grade 4 hypercholesterolemia that returns to ≤ Grade 2 within 35 days of initiation of appropriate supportive care as per Section 7.3.6. The severity (grade) of hypercholesterolemia is based upon fasting levels. If Grade 4 hypercholesterolemia is detected when routine (non-fasting) laboratory studies are performed, the test should be repeated within 3 days in the fasting state to permit accurate grading.

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

- Nausea, vomiting, diarrhea, constipation, or anorexia of ≤ 3 days duration
- Fatigue that resolves to ≤ Grade 2 within 7 days
- Oral or pharyngeal mucositis or stomatitis ≤ 7 days duration
- Liver enzyme elevation, including ALT/AST/GGT that returns to levels that meet initial eligibility criteria or baseline within 7 days. See Appendix X 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.
- Fever < 5 days duration.
- Infection < 5 days duration.

- Hypophosphatemia, hypokalemia, hypocalcemia or hypomagnesemia responsive to supplementation.
- Hyperglycemia that returns to fasting glucose value ≤ 250 mg/dL (13.9 mmol/L) (with or without the use of insulin or oral diabetic agents) within 7 days of initiation of appropriate supportive care as per Section 7.3.4. The severity (grade) of hyperglycemia is based upon fasting levels. If glucose in the range >250 - 500 mg/dL; (>13.9 - 27.8 mmol/L) is detected when routine (non-fasting) laboratory studies are performed, the test should be repeated within 3 days in the fasting state to permit accurate grading.
- Hypertriglyceridemia that returns to Grade ≤ 2 within 14 days of initiation of appropriate supportive care as per Section 7.3.5. The severity (grade) of hypertriglyceridemia is based upon fasting levels. If Grade 3 triglycerides are detected when routine (non-fasting) laboratory studies are performed, the test should be repeated within 3 days in the fasting state to permit accurate grading.
- Hypercholesterolemia that returns to ≤ Grade 2 within 35 days of initiation of appropriate supportive care as per Section 7.3.6. The severity (grade) of hypercholesterolemia is based upon fasting levels. If Grade 3 hypercholesterolemia is detected when routine (non-fasting) laboratory studies are performed, the test should be repeated within 3 days in the fasting state to permit accurate grading.
- Papulopustular, acneiform, or maculo-papular rash that resolves to < Grade 2 or baseline within 14 days of appropriate supportive care as per Section 7.3.2. However, any investigational drug-related grade 3 rash that is considered intolerable by the patient or limits ADLs will be considered a DLT regardless of duration.

5.4.1.3 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.

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

6.0 DOSE MODIFICATIONS FOR ADVERSE EVENTS

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

6.1 Dose Modifications for Hematological Toxicity

6.1.1 If a patient experiences hematological dose-limiting toxicity as defined in Section 5.4.2, 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 meet eligibility parameters within 14 days of drug discontinuation, the patient may resume treatment at a reduced dose as outlined in the dose reduction table (Appendix IV). Doses reduced for toxicity will not be re-escalated, even if there is minimal or no toxicity with the reduced dose.

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

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

6.2 Dose Modifications for Non-Hematological Toxicity

6.2.1 If a patient experiences non-hematological dose-limiting toxicity as defined in Section 5.4.1, the treatment will be held. When the toxicity resolves such that there is no ongoing DLT of hyperglycemia, hypercholesterolemia, and hypertriglyceridemia as defined in Section 5.4.1 and other laboratory values meet eligibility parameters or baseline within 14 days of drug discontinuation, the patient may resume treatment at a reduced dose as outlined in the dose reduction table (Appendix IV). Doses reduced for toxicity will not be re-escalated, even if there is minimal or no toxicity with the reduced dose.

6.2.2 If toxicity does not resolve such that there is no ongoing DLT of hyperglycemia, hypercholesterolemia, and hypertriglyceridemia as defined in Section 5.4.1 and other laboratory values meet eligibility parameters or baseline within 14 days of drug discontinuation, the patient must be removed from protocol therapy.

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

6.2.4 If a patient experiences a Grade 2 or greater allergic reaction to LY3023414, the patient will 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 LY3023414. See below for recommendations on management of specifc toxicities associated with LY3023414.

7.3.1 Nausea and vomiting:

Nausea and vomiting has been observed frequently in adult patients treated with LY3023414. It is recommended to provide all patients a 5-HT_3-Receptor blocker (eg, ondansetron or granisetron) at the start of treatment to be used as needed or prophylactically. In the event of breakthrough nausea/vomiting, additional antiemetics may be added as needed.

7.3.2 Rash:

Rashes which can be pruritic have been observed in frequently in adult patients treated with LY3023414. For all patients, prophylactic measures should be considered including the use of sunscreen prior to any sun-exposure and application of thick emollient cream to dry areas of the body at least twice daily. For grade 1 rash, mild-moderate potency topical steroids and oral antihistamines (if pruritic) should be considered. For grade 2 rash, moderate potency topical steroids and oral antihistamines (if pruritic) are recommended. For grade 3 rash, moderate potency topical steroids should be applied at least twice daily and oral antihistamines should be used if the rash is pruritic. Patients with a grade 3 or worse rash should have a physical exam at least weekly until improvement to grade ≤ 2. As per section 5.4.1.1, any grade 3 rash that is intolerable, limiting ADLs, or that persists for > 14 days after initiation of topical steroid therapy will be considered a dose limiting toxicity. LY3023414 will be held and moderate potency topical steroids will be applied at least twice daily and a course of systemic steroid should be strongly considered with oral antihistamines given as needed for pruritis.

7.3.3 Mucositis:

Mucositis has been observed in adult patients treated with LY3023414. For grade 1 mucositis, it is recommended to use conservative measures such as non-alcoholic mouth wash or salt water (0.9%) mouth wash several times a day until resolution. For grade ≥ 2 mucositis, topical analgesic mouth treatments (i.e., local anesthetics such as benzocaine, butyl aminobenzoate, tetracaine hydrochloride, menthol, or phenol) may be used with or without topical corticosteroids, such as triamcinolone oral paste 0.1% (e.g. Kenalog in Orabase®). Agents containing hydrogen peroxide, iodine, and thyme derivatives may worsen mouth ulcers and should not be used.

Systemic antifungal agents should be avoided unless a fungal infection is diagnosed.

In particular, systemic imidazole antifungal agents (ketoconazole, fluconazole, itraconazole, etc.) should be avoided due to their strong inhibition of CYP3A4 metabolism, therefore leading to higher LY3023414 exposure. Topical antifungal agents are preferred if an infection is diagnosed.

7.3.4 **Hyperglycemia:**
Hyperglycemia has been observed in adults treated with LY3023414. **Initiation of treatment for hyperglycemia should occur under the guidance of a pediatric endocrinologist at the local institution.** Metformin or other oral anti-hyperglycemia agent may be used per local endocrinologist's recommendations. Insulin therapy should be directed by specialists in pediatric diabetes, with the goal of normal fasting blood sugars < 126 mg/dL and HgbA1C < 8%.

For fasting glucose value ≤ 160 mg/dL (8.9 mmol/L), conservative measures are recommended (dietary modification). For fasting glucose value >160 - ≤ 250 mgdL (>8.9 - ≤13.9 mmol/L), consultation with an endocrinologist and consideration of initiation of an oral anti-diabetic agent is recommended. Insulin therapy should be considered if treatment with an oral anti-diabetic is insufficient. For glucose in the range >250 - 500 mg/dL; (>13.9 - 27.8 mmol/L) or glucose >500 mg/dL (>27.8 mmol/L) persisting less than 24 hours, insulin or an oral anti-diabetic agent should be started in consultation with an endocrinologist. Patients with glucose in the range >250 - 500 mg/dL; (>13.9 - 27.8 mmol/L) or worse hyperglycemia should have fasting glucose checked at least twice weekly until resolution to less than or equal to a fasting glucose value ≤ 250 mg/dL (13.9 mmol/L). Glucose in the range >250 - 500 mg/dL; (>13.9 - 27.8 mmol/L) persisting for more than 7 days after starting an oral antidiabetic agent and glucose >500 mg/dL (>27.8 mmol/L) persisting for more than 24 hours after starting an oral antidiabetic agent are a dose limiting toxicities. LY3023414 will be held and the patient will be treated with insulin or an oral anti-diabetic agent in consultation with an endocrinologist.

7.3.5 **Hypertriglyceridemia:**
Hypertriglyceridemia has been observed in patients treated with mTOR inhibitors. **Initiation of treatment for hypertriglyceridemia should occur under the guidance of pediatric specialists with expertise in lipid disorders at the local institution.**

For grade 2 hypertriglyceridemia, consultation with a pediatric specialist with expertise in lipid disorders and consideration of initiation of an HMG-CoA reductase inhibitor is recommended. For grade 3 hypertriglyceridemia, an HMG-CoA reductase inhibitor should be started in consultation with a pediatric specialist with expertise in lipid disorders. Patients with grade 3 or worse hypertriglyceridemia should have fasting triglycerides checked at least weekly until resolution to ≤ grade 2. Grade 3 hypertriglyceridemia persisting for more than 14 days after starting an HMG-CoA reductase inhibitor and any grade 4 hypertriglyceridemia are a dose limiting toxicities. LY3023414 will be held and the patient will be treated with an HMG-CoA reductase inhibitor in consultation with a pediatric specialist with expertise in lipid disorders.

7.3.6 **Hypercholesterolemia:**
Hypercholesterolemia has been observed in patients treated with mTOR inhibitors. **Initiation of treatment for hypercholesterolemia should occur under the**

guidance of pediatric specialists with expertise in lipid disorders at the local institution.

For grade 2 hypercholesterolemia, consultation with a pediatric specialist with expertise in lipid disorders and consideration of initiation of an HMG-CoA reductase inhibitor is recommended. For grade 3 or 4 hypercholesterolemia, an HMG-CoA reductase inhibitor should be started in consultation with a pediatric specialist with expertise in lipid disorders. Patients with grade 3 or worse hypercholesterolemia should have fasting cholesterol checked at least every other week until resolution to ≤ grade 2. Grade 3 or 4 hypercholesterolemia persisting for more than 35 days after starting an HMG-CoA reductase inhibitor is a dose limiting toxicity. LY3023414 will be held and the patient will be treated with an HMG-CoA reductase inhibitor in consultation with a pediatric specialist with expertise in lipid disorders.

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 substrates, inhibitors or inducers:

In vitro data showed that LY3023414 is a substrate of CYP3A4 and CYP1A2 (to a lesser extent). Therefore, moderate to strong inducers and strong inhibitors of CYP3A4 should be substituted or avoided, if possible. (See Appendix II). However, in patients for whom there are no adequate therapeutic alternatives, CYP3A4 inducing anti-epileptic drugs and dexamethasone for CNS tumors or metastases, on a stable dose, are allowed.

LY3023414 is a weak inhibitor of CYP3A4. Monitor patients receiving drugs that are either sensitive substrates of CYP3A4 or CYP3A4 substrates with a narrow therapeutic range.

7.5.2

Strong inducers (eg., smoking) and inhibitors (eg., ciprofloxacin, enoxacin, fluvoxamine, zafirlukast) of CYP1A2 should also be avoided if possible while receiving protocol therapy.

8.0 EVALUATIONS/MATERIAL AND DATA TO BE ACCESSIONED

8.1 Required Clinical, Laboratory and Disease Evaluation

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

STUDIES TO BE OBTAINED	Pre-Study	During Cycle 1	Prior to Subsequent Cycles^
History	X	Weekly	X
Physical Exam with vital signs	X	Weekly	X
Neurologic Exam	X	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]	Weekly[3]
Urinalysis	X		
Electrolytes including Ca^{++}, PO_4, Mg^{++}	X	Weekly	X
Creatinine, ALT, bilirubin	X	Weekly	X
Glucose	X	Weekly	X
Albumin	X		X
Total cholesterol, triglycerides	X		X
Tumor Disease Evaluation[4A]	X		Every other cycle[4]
Bone Marrow Aspirate and/or biopsy[5,6]	X[5]		Every other cycle[6]
EKG	X		
Medication Diary[7]		Weekly	X
Pharmacokinetics (optional) [8]	X	X	
Circulating Tumor DNA (ctDNA-optional)[9]			Cycle 5, Day 1 and (for patients receiving ≥ 5 cycles only) at end of protocol therapy OR disease progression

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

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

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

3 If patients develop Grade 4 neutropenia then CBCs should be checked every 3 to 4 days until recovery to Grade 3

4A Neurological exam also required for CNS patients.

[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.

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

[6] Bone marrow aspirate and/or biopsy should only be performed on patients with known bone marrow involvement at baseline

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

[8] See Section 8.3 for details of PK studies.

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

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 digital format is required. Digital files must be in DICOM format. . Due to the critical time constraints for submitting data for the central review of response the following methods should be used to submit imaging data, such as sFTP, Dicommunicator, or on CD (if sent by courier). 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. Alternatively, if submission via sFTP or Dicommunicator is not feasible, the imaging may be burned to a CD and mailed to IROC RI (QARC) at the address below. Multiple studies for the same patient may be submitted on one CD; however, please submit only one patient per CD. Sites using Dicommunicator may submit imaging via that application. Contact IROC RI (QARC) with questions or for additional information.

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.

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 Pharmacology (optional)

8.3.1 Description of Studies and Assay

Pharmacokinetics (PK) will be performed to determine the PK of LY3023414 in children who consent to this optional study. Pharmacokinetic analysis will be conducted at a centralized laboratory using validated assays.

8.3.2 Sampling Schedule

Blood samples will be obtained at the following time points **for ALL patients enrolled on study who consent to optional pharmacokinetics:**

- **Day 15, Cycle 1:** Pre-dose (12 hours after the PM dose on Day 14, Cycle 1) and at 1-2 hours after the AM dose on Day 15.

Determination of the recommended phase 2 dose is complete. Blood samples will were obtained at the following time points **ONLY for patients enrolled during the determination of the recommended phase 2 dose / tolerable dose (Section 5.1.1) who consented to optional pharmacokinetics**

- **Day 1, Cycle 1:** Pre-dose, and at 30 minutes, 1, 2, 4, 6-8 hours after the AM dose on Day 1. **The PM dose of LY3023414 on Day 1, Cycle 1 will not be given for patients undergoing these PK studies.**

- **Day 2, Cycle 1:** Before the AM dose on Day 2 (24 hours after the AM dose on Day 1, Cycle 1).

8.3.3 Sample Collection and Handling Instructions

Blood samples (2 ml for each time point) will be collected in K_2-EDTA (lavender top) tubes for pharmacokinetic evaluation. Record the exact time that the sample is drawn along with the exact time that the drug is administered.

Sites are expected to use their own standard materials for PK sample collection as kits will not be provided for the PK samples for this study.

8.3.4 Sample Processing

Following collection, the sample will be immediately gently mixed by inversion 8-10 times. The sample will be stored on wet ice until centrifugation. The sample will be centrifuged at 1500 x g for 15 minutes at 4° C within 60 minutes

after the sample is drawn. The plasma will be transferred to a cryovial, ensuring no RBC contamination, and frozen as soon as possible at -80° C. If a -80° C freezer is not immediately available, the cryovial may be stored on dry ice for short term storage, but must be placed in the appropriate freezer within 24 hours of the draw-time.

8.3.5 Sample Labeling

Each sample must be labeled with the patient's study registration number, the study I.D# (APEC1621D), and the date and time the sample was drawn. Data should be recorded on the appropriate transmittal form found in RAVE, which must accompany the sample(s).

8.3.6 Sample Shipping Instructions

Samples will be shipped on dry-ice to Covance Laboratories at the address below. Samples may be batched, but should be shipped within 1 month of draw.

A notification email should be sent to Mohammad Koupaei with courier name, airway bill number, expected delivery date/time and shipment contact.

8.4 Circulating Tumor DNA Study (optional)

8.4.1 Sampling Schedule

An initial sample was previously requested at time of enrollment into the APEC1621SC screening protocol. Additional samples (optional) will be collected into Streck Cell-Free DNA BCT tubes at the following timepoints:

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

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

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

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

Established institutional guidelines should be followed for blood collection via

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

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

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

8.4.2 Sample Processing

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

8.4.3 Sample Labeling

Each tube must be labeled with the patient's study registration number, the study I.D (APEC1621D), and the date and time the sample was drawn. Data should be recorded on the appropriate transmittal form found in RAVE, which must accompany the sample(s).

8.4.4 Sample Shipping Instructions

Specimen should be shipped at room temperature to the BPC (address below). Upon arrival separation, extraction, and storage of plasma and cellular DNA will be performed. Samples should be shipped from Monday through Friday for Tuesday through Saturday delivery. If blood is collected in the Streck tube on Friday, over the weekend or on the day before a holiday, the sample can be stored at room temperature until shipped on the next business day.

Ship specimens to the following address:

Biopathology Center
Nationwide Children's Hospital
Protocol APEC1621D– Peds MATCH*
700 Children's Drive, WA1340
Columbus, OH 43205
Phone: (614) 722-2865
Fax: (614) 722-2897
Email:BPCBank@nationwidechildrens.org

*Labeling is extremely important for this project. Packages must be labeled "Peds

MATCH" in order to expedite processing at the BPC. Be sure to include the room number. Packages received without the room number may be returned to the sender

Ship samples by FedEx Priority Overnight using a FedEx shipping label obtained through the COG FedEx account. Ship blood for Saturday delivery if shipped on Friday.

9.0 AGENT INFORMATION

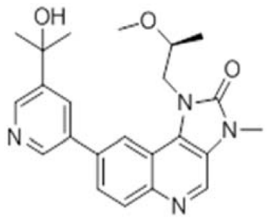
9.1 LY3023414 11/12/2021

NSC# 783668 IND#134661

9.1.1 Structure and molecular weight

LY3023414 is an orally available, potent, selective inhibitor of the class I PI3K isoforms, mTOR, and DNA-PK. LY3023414 binds the adenosine triphosphate (ATP) active site of PI3K to competitively inhibit phosphorylation of phosphatidylinositol-4,5-bisphosphate (PIP2) at low nanomolar concentrations. LY3023414 has inhibitory activity against PI3K/mTOR pathway targets in vitro and in vivo. LY3023414 has antiproliferative and cell cycle-arresting effects in cultured cancer cells and antiangiogenesis activity via inhibition of in vitro vascular cord formation.

LY3023414 is a small molecule with an empirical formula of $C_{23}H_{26}N_4O_3$ and a molecular weight of 406.48. The chemical structure is:



LY3023414

9.1.2 Supplied by: Eli Lilly and Company and distributed by the Pharmaceutical Management Branch, CTEP, DCTD, NCI.

9.1.3 Formulation

LY3023414 is supplied for clinical trial use as 50-mg and 100-mg film-coated tablets. The 50-mg tablets are green, modified, capsule-shaped tablets. The 100-mg tablets are dark yellow, modified, capsule-shaped tablets. The tablets are composed of active drug ingredient, microcrystalline cellulose, croscarmellose sodium, silicon dioxide, sodium stearyl fumarate and colorant. Tablets are available in 60-count bottles with desiccant.

9.1.4 Storage: Store intact bottles at controlled room temperature between 15° C to 30° C (59° F to 86° F) according to label.

If a storage temperature excursion is identified, promptly return LY3023414 to controlled room temperature and quarantine the supplies. Provide a detailed report of the excursion (including documentation of temperature monitoring and duration of the excursion) to PMBAfterHours@mail.nih.gov for determination of suitability.

9.1.5 Stability

Stability studies are ongoing. The manufacturer does not have stability data to support repackaging tablets. Dispense tablets in the original container.

9.1.6 Administration

See Treatment section of the protocol for dosing and administration details. LY3023414 is administered orally.

LY3023414 should be taken without regards to food with a glass of water at approximately the same time each day. Patients should swallow the tablets as a whole and should not chew, dissolve or crush them.

If a patient misses a dose of LY3023414, the dose should be taken as soon as possible as long as it is more than 6 hours before the next scheduled dose. If it is less than 6 hours before the next dose, then the dose should be skipped. If vomiting occurs after taking LY3023414, the patient should skip the dose and take the next dose as scheduled.

9.1.7 Potential Drug Interactions

LY3023414 is a weak inhibitor of CYP3A4, based on the increase in midazolam exposure observed after concomitant administration. Therefore, drugs that are either sensitive substrates of CYP3A4 or CYP3A4 substrates with a narrow therapeutic range should be administered with caution in combination with LY3023414.

In vitro data showed that the major enzymes involved in the clearance of LY3023414 were CYP3A (82%), and CYP1A2 (18%). Therefore, it is recommended to avoid moderate to strong inducers and strong inhibitors of CYP3A4. Note: In patients for whom there are no adequate therapeutic alternatives, CYP3A4 inducing anti-epileptic drugs and dexamethasone for CNS tumors or metastases, on a stable dose, are allowed. Strong inducers and inhibitors of CYP1A2 should also be avoided if possible while receiving protocol therapy.

LY3023414 is a substrate for both P-glycoprotein and BCRP; however, current information suggests these transporters appear unlikely to affect oral absorption of agent to any great extent.

9.1.8 Patient Care Considerations

Females and males of reproductive potential should be advised to avoid becoming pregnant or fathering a child during therapy with LY3023414. Both males and females of reproductive potential must agree to use medically approved contraceptive precautions during the study and for at least 3 months following the last dose of the study drug. Women choosing to breastfeed their infants should not take LY3023414.

9.1.9 LY3023414 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 165 patients.* Below is the CAEPR for LY3023414.

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, January 8, 2021[59]

Adverse Events with Possible Relationship to LY3023414 (CTCAE 5.0 Term) [n= 165]			**Specific Protocol Exceptions to Expedited Reporting (SPEER)**
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
	Anemia		***Anemia (Gr 2)***
GASTROINTESTINAL DISORDERS			
	Abdominal pain		
	Constipation		
Diarrhea			***Diarrhea (Gr 2)***
	Gastroesophageal reflux disease		
	Mucositis oral		***Mucositis oral (Gr 2)***
Nausea			***Nausea (Gr 2)***
	Oral dysesthesia		***Oral dysesthesia (Gr 2)***
Vomiting			***Vomiting (Gr 2)***
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
Fatigue			***Fatigue (Gr 2)***
	Fever		
	General disorders and administration site conditions - Other (mucosal inflammation)		
INFECTIONS AND INFESTATIONS			
		Lung infection[2]	
INVESTIGATIONS			
	Alanine aminotransferase increased		
	Aspartate aminotransferase increased		
	Creatinine increased		
		Electrocardiogram QT corrected interval prolonged	
	Platelet count decreased		

Adverse Events with Possible Relationship to LY3023414 (CTCAE 5.0 Term) [n= 165]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
	Weight loss		
METABOLISM AND NUTRITION DISORDERS			
Anorexia			***Anorexia (Gr 2)***
	Hyperglycemia		
	Hypokalemia		
	Hyponatremia		
	Hypophosphatemia		
NERVOUS SYSTEM DISORDERS			
	Dizziness		***Dizziness (Gr 2)***
	Dysgeusia		
	Headache		
	Paresthesia		
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
	Dyspnea		
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
	Dry skin		
	Pruritus		
	Rash maculo-papular		***Rash maculo-papular (Gr 2)***

[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] Lung infection may be more likely in children that have had lung radiation therapy.

Adverse events reported on LY3023414 trials, but for which there is insufficient evidence to suggest that there was a reasonable possibility that LY3023414 caused the adverse event:

CARDIAC DISORDERS - Heart failure
GASTROINTESTINAL DISORDERS - Dry mouth; Dyspepsia
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Chills; Edema limbs
INFECTIONS AND INFESTATIONS - Conjunctivitis
INVESTIGATIONS - Blood bilirubin increased; Lymphocyte count decreased; Neutrophil count decreased; White blood cell decreased
METABOLISM AND NUTRITION DISORDERS - Dehydration; Hyperkalemia; Hypertriglyceridemia; Hypomagnesemia
RENAL AND URINARY DISORDERS - Proteinuria
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Cough; Pneumonitis; Respiratory, thoracic and mediastinal disorders - Other (drug-induced lung injury)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Alopecia; Rash acneiform
VASCULAR DISORDERS - Hypotension

Note: LY3023414 in combination with other agents could cause an exacerbation of any adverse event currently known to be caused by the other agent, or the combination may result in events never previously associated with either agent.

9.1.10 Agent Ordering and Agent Accountability

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

Note: No starter supplies will be provided. Drug orders of LY3023414 should be placed with CTEP after enrollment and treatment assignment to APEC1621D 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.

9.1.11 Clinical Drug Request

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

9.1.12 Agent Inventory Records

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

9.1.13 Useful Links and Contacts

- CTEP Forms, Templates, Documents:
  http://ctep.cancer.gov/forms/
- NCI CTEP Registration:
  RCRHelpDesk@nih.gov
- PMB policies and guidelines:
  http://ctep.cancer.gov/branches/pmb/agent_management.htm
- PMB Online Agent Order Processing (OAOP) application:
  https://ctepcore.nci.nih.gov/OAOP/
- CTEP Identity and Access Management (IAM) account:
  https://ctepcore.nci.nih.gov/iam/
- PPD
- PPD

PPD

Monday through Friday between 8:30 am and 4:30 pm (ET)

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 6 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

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. Patients who are removed from protocol therapy in subsequent cycles should have the necessary observations to ensure adequate clinical care.

10.2 Follow-Up Data Submission and APEC1621SC Off Study Criteria

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

11.0 STATISTICAL AND ETHICAL CONSIDERATIONS

11.1 Sample Size and Study Duration

APEC1621D will require a minimum of 4 evaluable patients and a maximum of 144 patients (up to 98 biomarker-positive patients and up to 46 biomarker-negative 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.

As of Amendment #5A, accrual will stop once 20 evalauble patients have been accrued in the study. APEC1621D will require a maximum of 24 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 4-6 years.

11.2 Dosing Considerations

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

Please see Section 5.1.1 for a specific discussion of the dosing of LY3023414 to be used in this study. As there is no prior pediatric phase 1 data for LY3023414, study investigators have reviewed relevant data with the pharmaceutical partner to identify a drug specific dosing plan for testing in children with recurrent/refractory cancer, and trial participants will be closely monitored to ensure tolerability of the selected dose. Because the adult RP2D of LY3023414 is the adult MTD, APEC1621D will evaluate an initial cohort of patients at a dose level approximately 30% below the adult MTD of LY3023414 and then complete the study using the adult RP2D, assuming that both dose levels are tolerated. Rules for determining tolerability of these dose levels are described in Section 11.2.2. Limited pharmacokinetic sampling will be done for patients enrolled on this arm. In general, the dosing for the Pediatric MATCH subprotocols will follow the guidelines below:

11.2.2 Determination of Recommended Phase 2 Dose (RP2D)/Tolerable Dose

Because the adult RP2D of LY3023414 is the adult MTD, APEC1621D will evaluate an initial cohort of patients at a dose level approximately 30% below the adult MTD and then complete the study using the adult RP2D, assuming that both dose levels are tolerated. A modified Rolling Six design will be followed. The DLT evaluation period for the purpose of dose escalation will be cycle 1 of therapy. Note that for toxicities which require persistence for a duration of time to be considered a DLT will be included if this time window starts during cycle 1 of therapy (e.g. grade 3 hypercholesterolemia would be considered a DLT if it developed during cycle 1 of therapy and persisted for 35 days). Patients enrolled during the determination of the recommended phase 2 dose who are not evaluable for toxicity during cycle 1 at a given dose level will be replaced.

Enrollment of the initial cohort of six patients will follow the standard rules of the rolling six design to assess safety and tolerability of cycle one of protocol treatment prior to extending accrual to additional patients.

If there are fewer than 2 DLTs in the first 6 toxicity-evaluable subjects enrolled at the starting dose, the dose will be escalated to the dose equivalent to 100% of the adult MTD for subsequent subjects enrolled on the study. If ≥ 2 of the first 6 toxicity evaluable subjects enrolled at the higher dose have DLTs, all subsequent

subjects will be enrolled at the original starting dose. Otherwise, remaining subjects will continue to enroll at the dose equivalent to 100% of the adult MTD.

If there are 2 or more DLTs among the first 6 toxicity-evaluable subjects enrolled at the original starting dose, the next cohort will enroll at a reduced dose level. If ≥ 2 of the first 6 toxicity-evaluable subjects enrolled at the reduced dose have DLTs, the study will be closed for toxicity. Otherwise, remaining subjects will continue to enroll at the reduced dose.

11.3 Study Design

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

Cohort	N	Decision Rule	Alpha	Power
Primary biomarker positive	20	≥ 3 responses	10%	90%
Any biomarker negative	10	≥ 2 responses	9%	74%

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 Cohorts:

APEC1621D will evaluate two primary cohorts 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 LY3023414 (see Appendix VII):

Primary Cohort A: Patients whose tumors have TSC1 or TSC2 loss of function mutations

Primary Cohort B: Patients whose tumors have other PI3K/MTOR pathway activating mutations.

Using an A'Hern design[60] 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 either primary cohort A or B, the biomarker/therapy match will be deemed a success.

As of Amendment #5A, patients from the two primary cohorts will be combined and analyzed together in the primary analysis. The A'Hern design

with N=20 as described above will be used.

11.3.2 **Histology-Specific Biomarker Positive Expansion Cohorts:**

If ≥ 3 patients in either primary cohort A or B 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.

We will open up to 3 such expansion cohorts for biomarker positive patients for each primary cohort (i.e., if 3 histologies in cohort A and 3 histologies in cohort B have ≥ 3 responses, we will open a total of 6 expansion cohorts as described above). Note that this can only happen if the response rate in each primary cohort is at least 45% (9/20) and there cannot be more than 42 additional evaluable patients in total for these expansion cohorts.

As of Amendment #5A, there will be no histology-specific biomarker positive expansion cohort planned for this subprotocol.

11.3.3 **Biomarker Negative Expansion Cohorts:**

The following expansion cohorts may open and will preferentially enroll patients to the earliest opened cohort when possible within slot availability/cohort suspension constraints. Patients enrolled in these biomarker negative expansion cohorts will be those whose tumors do NOT have one of the defined PI3K/MTOR pathway activating alterations leading to eligibility for either primary cohort A or B and do NOT have a genomic alteration that results in assignment to any other currently enrolling arm of the pediatric MATCH study.

As of Amendment #5A, there will be no biomarker negative expansion cohort planned for this subprotocol.

11.3.3.1 **Histology-Agnostic Biomarker Negative Cohort:**

If at any time ≥ 3 patients in primary cohort A or ≥ 3 patients in primary cohort B show signs of objective response, and the responding patients in that cohort include at least 2 different histologies, then a single expansion cohort of 10 biomarker negative patients of any histology will be opened. If in the course of the study ≥ 3 responses across primary cohort A and primary cohort B are observed in the same histology, then biomarker negative cohorts will be opened as described in Section 11.3.3.2. Biomarker negative patients for whom a histology-specific cohort is opened after the patient enrolls on the histology-agnostic biomarker negative cohort on APEC1621D will be reallocated to the histology-specific cohort and not considered in the efficacy analysis for the histology-agnostic biomarker negative cohort (except in the event the criteria in section 11.3.3.3 are met). Biomarker negative patients for whom a histology specific cohort is open or has completed accrual prior to enrollment on APEC1621D will not be eligible to enroll on the histology-agnostic biomarker negative cohort.

Note that this criteria requires 3 responses in at least one of the primary cohorts of 20 patients (rather than both cohorts combined,) ensuring that the response rate is at least 15% in at least one of the primry cohorts before a histology-agnostic biomarker negative cohort would open.

If 2 or more responses are seen in the histology-agnostic biomarker negative cohort, the regimen will be declared active for biomarker negative patients. This will provide a low probability (9%) of carrying forward agents with response rates less than 5% and a moderately high probability (74%) of identifying agents with response rates ≥ 25%.

11.3.3.2 **Histology-Specific Biomarker Negative Cohorts**:

If at any time ≥ 3 patients in either primary cohort A or B with the same histology show signs of objective response, then an expansion cohort of 10 biomarker negative patients with the same histology will be opened.

Note: The criteria to open a biomarker negative histology-specific criteria applies to the combined set of subjects in primary cohorts A and B. For example, 1 response in primary cohort A and 2 responses in primary cohort B in the same histology would meet the critieria to open a histology specific biomarker negative cohort for that histology.

If 2 or more responses are seen in a histology-specific biomarker negative cohort, the regimen will be declared active for biomarker negative patients of that histology. Using this A'Hern single stage design will assure a low probability (9%) of carrying forward agents with response rates less than 5% and provide a moderately high probability (74%) of identifying agents with response rates ≥ 25%. Up to a total of 3 such biomarker negative cohorts can be opened, for a total of 30 biomarker negative patients.

Note: Biomarker negative histology-specific criteria applies to the combined set of subjects in primary cohorts A and B.

11.3.3.3 **Histology-Agnostic Biomarker Negative Stopping Rule**

If a histology-specific biomarker negative cohort has completed accrual and there are fewer than 2 responses observed, and there have not been any responses observed in the histology-agnostic biomarker-negative expansion cohort (if open), then the histology-agnostic biomarker negative cohort will not open to accrual or will close to accrual if open. In this circumstance, patients from the histology-specific biomarker negative expansion cohort will be included in the efficacy analysis for the histology-agnostic biomarker negative expansion cohort, which will by definition be considered not active with 0-1 responses out of 10-20 subjects.

Note that the histology-agnostic biomarker negative expansion cohort may accrue prior to or in parallel with biomarker negative histology-specific expansion cohorts. Enrollment to the biomarker negative histology-agnostic cohort will continue while waiting to determine if this criteria applies. This criteria will only apply after at least 9 subjects on the

histology-specific biomarker cohort have discontinued treatment such that it is not possible to have ≥ 2 responses.

11.4 Methods of Analysis

Response criteria are described in Section 12.0. 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.[61] Decision making for A'Hern design cohorts will follow rules described above.

Any responses or lack thereof in patients enrolled during the determination of the Recommended Phase 2 Dose (dose finding phase) will count toward the objective response rate in their respective cohort.

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 on any APEC1621 subprotocol will be considered evaluable for response. Any patient who receives non-protocol anti-cancer therapy during the response evaluation period will be considered a non-responder for the purposes of the statistical rule, unless they show an objective response prior to receiving the non-protocol anti-cancer therapy (in which case they will be considered a responder). Patients who demonstrate a complete or partial response confirmed by central review will be considered to have experienced a response. All other patients will be considered non-responders. Patients who are not evaluable for response evaluation may be replaced for the purposes of the statistical rule. All patients considered to have a response (CR or PR) must have imaging studies reviewed centrally at the COG. Centers will be notified by the COG about requests for scans of patients with stable disease. Preliminary assessment of activity using institutionally provided tumor measurements will be entered into CDUS quarterly. The central review by COG will be provided as the final reviewed assessment of response when such becomes available.

11.6 Evaluability for Toxicity

Any patient who experiences a DLT at any time during protocol therapy is considered evaluable for toxicity. Patients without DLT who receive at least 85% of the prescribed dose per protocol guidelines and had the appropriate toxicity monitoring studies performed during cycle 1 are also considered evaluable for 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				
	Not Hispanic or Latino		Hispanic or Latino		
	Female	Male	Female	Male	Total
American Indian/Alaska Native	0	0	0	0	0
Asian	0	0	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0	0	0
Black or African American	2	3	0	0	5
White	6	10	2	1	19
More than one race	0	0	0	0	0
Total	8	13	2	1	24

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

12.0 EVALUATION CRITERIA

12.1 Common Terminology Criteria for Adverse Events (CTCAE)

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

12.2 Progression-Free Survival

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

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

12.3 Response Criteria for Patients with Solid Tumors

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

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

Response and progression will be evaluated in this study using the revised Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1).[62] Key points are that 5 target lesions are identified and that changes in the *largest* diameter (unidimensional measurement) of the tumor lesions but the *shortest* diameter of malignant lymph nodes are used in the RECIST v 1.1 criteria.

12.3.1 Definitions

12.3.1.1 Evaluable for objective response:

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

12.3.1.2 Evaluable Non-Target Disease Response:

Eligible patients who have evaluable but not measurable disease and have received at least one dose of protocol therapy will be considered evaluable for non-target disease. The response assessment is based on

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

12.3.2 Disease Parameters

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

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

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

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

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

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

disease.

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

12.3.3 Methods for Evaluation of Measurable Disease

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

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

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

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

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

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

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

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

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

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

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

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

For patients with a positive PET scan at diagnosis, PET can be used to follow response in addition to a CT scan using the International Pediatric non-Hodgkin Lymphoma Response Criteria.[63]

12.4 Response Criteria for Patients with Solid Tumor and Measurable Disease

12.4.1 Evaluation of Target Lesions

Complete Response (CR):	Disappearance of all target and non-target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm. If immunocytology is available, no disease must be detected by that methodology. Normalization of urinary catecholamines or other tumor markers if elevated at study enrollment (for patients with neuroblastoma).
Partial Response (PR):	At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the

baseline sum diameters

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

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

12.4.2 **Evaluation of Non-Target Lesions**

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

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

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

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

12.4.3 **Overall Response Assessment**

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

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Overall Response when Confirmation is Required*

CR	CR	No	CR	≥ 28 days Confirmation
CR	Non-CR/Non-PD	No	PR	≥ 28 days Confirmation
CR	Not evaluated	No	PR	
PR	Non-CR/Non-PD/not evaluated	No	PR	
SD	Non-CR/Non-PD/not evaluated	No	SD	documented at least once ≥ 28 days from baseline
PD	Any	Yes or No	PD	no prior SD, PR or CR
Any	PD**	Yes or No	PD	
Any	Any	Yes	PD	

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

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

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

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

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

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

12.4.4 Overall Best Response Assessment

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

12.5 Response Criteria for Neuroblastoma Patients with MIBG Positive Lesions

12.5.1 MIBG Positive Lesions

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

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

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

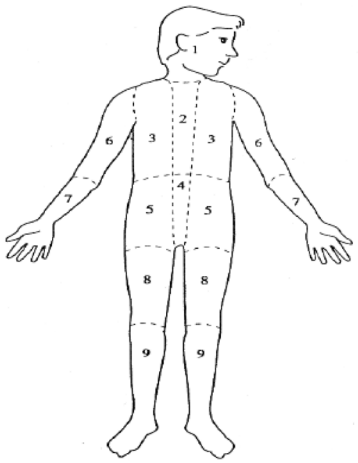
12.5.3 The response of MIBG lesions will be assessed on central review using the Curie scale14 as outlined below. Central review responses will be used to assess efficacy for study endpoint. See Section 8.2 for details on transferring images to the Imaging Research Center.

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

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

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

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



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

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

12.5.4 Overall Response Assessment

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

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

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

12.5.5 Overall Best Response Assessment

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

12.6 Response Criteria for Neuroblastoma Patients with Bone Marrow Involvement

12.6.1 Bone Marrow Involvement

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

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

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

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

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

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

12.6.2 Overall Best Response Assessment

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

12.7 Response Criteria for Patients with CNS Tumors

12.7.1 Measurable Disease

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

12.7.2 Evaluable Disease

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

12.7.3 Selection of Target and Non-Target Lesions

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

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

12.7.4 Response Criteria for Target Lesions

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

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

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

- **Stable Disease (SD):** Neither sufficient decrease in the sum of the products of the two perpendicular diameters of all target lesions to qualify for PR, nor sufficient increase in a single target lesion to qualify for PD; on a stable or decreasing dose of steroids with a stable or improving neurologic examination.

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

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

effects.

12.7.5 Response Criteria for Non-Target Lesions:

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

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

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

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

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

12.8 **Response Criteria for Patients with non-Hodgkin Lymphoma/Histiocytosis**
Response and progression will be evaluated in this study using the new international criteria proposed by the revised Response Evaluation Criteria in Pediatric non-Hodgkin Lymphoma Criteria[63], with modification from the Lugano classification.[64]

12.8.1 Disease Parameters

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

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

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

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

12.8.2 Evaluation of Measurable Disease

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

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

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

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

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

12.8.3 Evaluation of Non-measured Lesions (CT-based response, PET/CT based response not applicable)[64]

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[64]

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 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: PPD

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

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

13.1.2 CTEP-AERS Expedited Reporting Methods

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

Send supporting documentation to the NCI by fax (fax# 301-640-9193) and by email to the APEC1621D 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 of the NCI CTCAE V 5.0. The descriptions and grading scales found in the current version of the CTCAE V 5.0 will be used for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE v5.0. A copy of the CTCAE v5.0 can be downloaded from the CTEP website (http://ctep.cancer.gov).

Step 2: Grade the adverse event using the NCI CTCAE v5.0.

Step 3: Review Table A in this section to determine if:
- the adverse event is considered serious;
- there are any protocol-specific requirements for expedited reporting of specific adverse events that require special monitoring; and/or
- there are any protocol-specific exceptions to the reporting requirements.

- Any medical event equivalent to CTCAE v5.0 grade 3, 4, or 5 that precipitates hospitalization (or prolongation of existing hospitalization) must be reported regardless of attribution and designation as expected or unexpected with the exception of any events identified as protocol-specific expedited adverse event reporting exclusions.
- Any event that results in persistent or significant disabilities/incapacities, congenital anomalies, or birth defects must be reported via CTEP-AERS if the event occurs following treatment with an agent under a CTEP IND.
- Use the NCI protocol number and the protocol-specific patient ID provided during trial registration on all reports.
- As referenced in the CTEP Adverse Events Reporting Requirements, an AE that resolves and then recurs during a subsequent cycle does not require CTEP-AERS

reporting unless (1) the Grade increases; or (2) hospitalization is associated with the recurring AE.

- Some adverse events require notification **within 24 hours** (refer to Table A) to NCI via the web at http://ctep.cancer.gov (telephone CTEP at: **301-897-7497** within 24 hours of becoming aware of the event if the CTEP-AERS 24-Hour Notification web-based application is unavailable). Once internet connectivity is restored, a 24-hour notification phoned in must be entered electronically into CTEP-AERS by the original submitter at the site.
- When the adverse event requires expedited reporting, submit the report within 5 or 7 calendar days of learning of the event (refer to Table A).

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

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

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

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

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

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

Expedited AE reporting timelines are defined as:

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

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

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

- All Grade 3, 4, and Grade 5 AEs

Expedited 7 calendar day reports for:

- Grade 2 AEs resulting in hospitalization or prolongation of hospitalization

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

Effective Date: May 5, 2011

13.3 Exceptions to CTEP-AERS Expedited Reporting Requirements:

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

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

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

Category	Adverse Events
GASTROINTESTINAL DISORDERS	Constipation
GASTROINTESTINAL DISORDERS	Oral dysesthesia
INVESTIGATIONS	Alanine aminotransferase increased
INVESTIGATIONS	Creatinine increased
INVESTIGATIONS	Weight Loss
METABOLISM AND NUTRITION DISORDERS	Hyperglycemia
NERVOUS SYSTEM DISORDERS	Headache
NERVOUS SYSTEM DISORDERS	Paresthesia
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	Dyspnea
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	Dry skin
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	Pruritus

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

13.4 Definition of Onset and Resolution of Adverse Events

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

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

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

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

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

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

13.5 Other Recipients of Adverse Event Reports

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

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

13.6 Specific Examples for Expedited Reporting

13.6.1 Reportable Categories of Death

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

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

event as a patient death.

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

14.0 RECORDS, REPORTING, AND DATA AND SAFETY MONITORING PLAN

14.1 Categories of Research Records

Research records for this study can be divided into three categories

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

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

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

See separate CRF Packet, which includes submission schedule.

14.2 CDUS

This study will be monitored by the Clinical Data Update System (CDUS) version 3.0. Cumulative protocol- and patient-specific CDUS data will be submitted electronically to CTEP on a quarterly basis by FTP burst of data. Reports are due January 31, April 30, July 31 and October 31. Instructions for submitting data using the CDUS can be found on the CTEP Web site (http://ctep.cancer.gov/reporting/cdus.html).

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

14.3 CRADA/CTA/CSA

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

within the terms of award, apply to the use of the Agent(s) in this study:

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

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

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

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

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

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

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

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

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

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

14.4 Data and Safety Monitoring Plan

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

14.4.1 Data and Safety Monitoring Committee

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

14.4.2 Monitoring by the Study Chair and MATCH Leadership

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

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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] amlodapine aprepitant/fosaprepitant atorvastatin[5] avanafil[5] axitinib bortezomib bosutinib[5] brexpiprazole brigatinib budesonide[5] buspirone[5] 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	atazanavir boceprevir clarithromycin ceritinib cobicistat danoprevir/ritonavir darunavir delavirdine elivitegravir/ritonavir grapefruit[3] grapefruit juice[3] idelalisib indinavir/ritonavir itraconazole ketoconazole lopinavir/ritonavir ombitasvi +/- dasabuvir nefazodone nelfinavir paritaprevir/ritonavir 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

everolimus[5] felodipine[5] fentanyl[4] 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 olaparib ondansetron osimertinib paclitaxel palbociclib pazopanib pimozide[5] quetiapine[5] quinidine[4] regorafenib rilpivirine[5] rivaroxaban[5] romidepsin saquinavir[5] sildenafil[5] simvastatin[5] sirolimus[4,5] sonidegib sunitinib tacrolimus[4,5]				

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

[1] Certain fruits, fruit juices and herbal supplements (star fruit, Seville oranges, pomegranate, gingko, goldenseal) may inhibit CYP 3A4 isozyme, however, the degree of that inhibition is unknown.
[2]Refer to Section 7.5 regarding use of corticosteroids. Dexamethasone is considered a weak CYP3A4 inducer.
[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

APPENDIX III-A: MEDICATION DIARY FOR LY3023414

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

Complete each day with the time and dose given for LY3023414. If a dose is not due or is accidentally skipped leave that day blank. ***Make note of other drugs and supplements taken under the Comments section below***. LY3023414 tablets should not be cut, dissolved or crushed but should be swallowed whole. If the tablet is crushed and the drug gets on skin, wash the exposed area with as much water as necessary. Inform your study doctor or nurse if that occurs. LY3023414 should be taken without regard to meals, with a glass of water. You should take LY3023414, at about the same time each day. If you vomit after taking the medication, the dose should not be repeated. This should be noted in the comments section. If you forget a dose and remember it within 6 hours of the time the dose was due, you should take the dose at that time. If it is less than 6 hours before the next dose, then the forgotten dose should be skipped. Either way, the next dose should be taken at the usual time. Add the dates to the calendar below and return the completed diary to the study clinic at each visit (weekly during Cycle 1, and then after each treatment cycle).

EXAMPLE			***Number of* LY3023414 *tablets***		***Comments***
	Date	***Time***	**50 mg**	**100 mg**	
Day 1	*1/15/14*	*8:30 AM*	*2*	*1*	*He felt nauseated an hour after taking the drug but did not vomit.*

	Cycle #: _____ Start Date: | / | / | / | **End Date:** |__/__|__/__|__/__| **Dose Level: _____mg/m²/dose**					
WEEK 1	**Date**	**Time**		**# of LY3023414 tablets prescribed to take**		**Comments (Describe any missed or extra doses, vomiting and/or bothersome effects.)**
				50 mg	**100 mg**	
				AM# PM#___	**AM# PM#___**	
				# of LY3023414 tablets taken		
				50 mg	**100 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/dose					
WEEK 3	**Date**	**Time**		**# of LY3023414 tablets prescribed to take**		**Comments (Describe any missed or extra doses, vomiting and/or bothersome effects.)**
				50 mg	**100 mg**	
				AM# PM#___	**AM# PM#___**	
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 LY3023414 tablets prescribed to take**		**Comments (Describe any missed or extra doses, vomiting and/or bothersome effects.)**
				50 mg	**100 mg**	
				AM#___ PM#___	**AM#___ PM#___**	
				# of LY3023414 tablets taken		
				50 mg	**100 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/dose					
WEEK 4	**Date**	**Time**		**# of LY3023414 tablets prescribed to take**		**Comments (Describe any missed or extra doses, vomiting and/or bothersome effects.)**
				50 mg	**100 mg**	
				AM#___ PM#___	**AM#___ PM#___**	
				# of LY3023414 tablets taken		
				50 mg	**100 mg**	
Day 22			**AM**			
			PM			
Day 23			**AM**			
			PM			
Day 24			**AM**			
			PM			
Day 25			**AM**			
			PM			
Day 26			**AM**			
			PM			
Day 27			**AM**			
			PM			
Day 28			**AM**			
			PM			

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

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

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

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

Patient Name:	**Diagnosis:**	**Trial #:**
Study Doctor:	**Study Doctor Phone #:**	**Study Drug(s):** LY3023414

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

These are the things that your healthcare providers need to know:
LY3023414 interacts with certain enzymes in your liver or other tissues like the gut, certain transport proteins that help move drugs in and out of cells and the heart's electrical activity.

	Explanation
CYP isoenzymes	The enzymes in question are CYP 1A2 and 3A4. LY3023414 is broken down by CYP 1A2 and 3A4 and may be affected by other drugs that inhibit or induce these enzymes. LY3203414 weakly inhibits CYP 3A4, 2C9, 1A2 and may affect other drugs that are broken down by these enzymes.
Protein transporters	The transporter proteins in question are P-gp, BCRP, OATP1B1, OATP1B3, OCT1 and OCT2. LY3203414 is a substrate for P-gp, BCRP and OCT1 transport proteins and other drugs that are potent inhibitors or inducers of these proteins may alter how LY3203414 moves in and out of cells. LY3203414 may inhibit the ability of other drugs that require P-gp, BCRP, OATP1B1, OATP1B3, OCT1 or OCT2 to move in and out of cells. Avoid sensitive substrates of OATP1B1, OATP1B3, OCT1 or OCT2 transport proteins especially those with narrow therapeutic index.
Heart's electrical activities	The heart's electrical activity may be affected by LY3023414. The study doctor may be concerned about QTc prolongation and any other medicine that is associated with greater risk for having QTc prolongation.

These are the things that you need to know:
The study drug LY3023414, may interact with other drugs which can cause side effects. For this reason, it is very important to tell your doctors about all your medicines, including: (a) medicines you are taking before this clinical trial, (b) medicines you start or stop taking during this study, (c) medicines you buy without a prescription (over-the-counter remedy), (d) herbals or supplements (*e.g.* St. John's Wort). It is helpful to bring your medication bottles or an updated medication list with you.

Before you enroll onto the clinical trial, your study doctor will work with your regular health care providers to review any medicines and herbal supplements that are considered "strong inducers/inhibitors of CYP 1A2, 3A4, P-gp, BCRP or OCT1, are sensitive substrates of CYP 3A, 2C9 and 1A2, P-gp, BCRP, OATP1B1, OATP1B3, OCT1 or OCT2 or cause QTc prolongation."

- Please be very careful! Over-the-counter drugs (including herbal supplements) may contain ingredients that could interact with your study drug. Speak to your doctors or pharmacist to determine if there could be any side effects.
    - Avoid ingesting grapefruit, grapefruit juice and Seville oranges while taking LY3023414.

- Make sure your doctor knows to avoid certain prescription medications.
- Your regular health care provider should check a frequently updated medical reference or call your study doctor before prescribing any new medicine or discontinuing any medicine.

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(Next page: Patient Drug Interaction Wallet Card)

PATIENT DRUG INTERACTION WALLET CARD

NIH NATIONAL CANCER INSTI EMERGENCY NFORMATION	NIH NATIONAL CANCER INSTI	NIH NATIONAL CANCER INSTI DRUG INTERACTIONS	NIH NATIONAL CANCER INSTI
Show this card to all of your healthcare providers. Keep it with you in case you go to the emergency room.	Tell your doctors **before** you **start** or **stop** any medicines. **Check with your doctor or pharmacist if you need to use an over-the-counter medicine or herbal supplement!**	**Carry this card with you at all times** LY3023414 interacts with interacts with certain enzymes in your liver or other tissues like the gut, certain transport proteins that help move drugs in and out of cells and the heart's electrical activity and must be used very carefully with other medicines.	
Patient Name: **Diagnosis:** **Study Doctor:** **Study Doctor Phone #:** **NCI Trial #:** **Study Drug(S):**	**Use caution and avoid the following drugs if possible:** Grapefruit, grapefruit juice, St. John's Wort	Your healthcare providers should be aware of any medicines that are "strong inducers/inhibitors of CYP 1A2, 3A4, P-gp, BCRP or OCT1, are sensitive substrates of CYP 3A, 2C9 and 1A2, P-gp, BCRP, OATP1B1, OATP1B3, OCT1 or OCT2 or cause QTc prolongation." **Before prescribing new medicines**, your health care provider should check a **frequently-updated medical reference** for a **list of drugs to avoid** or contact your study doctor.	Version JAN/2019
For more information: 1-800-4-CANCER cancer gov | clinicaltrials gov	**For more information:** 1-800-4-CANCER cancer gov | clinicaltrials gov	**For more information:** 1-800-4-CANCER cancer gov | clinicaltrials gov	**For more information:** 1-800-4-CANCER cancer gov | clinicaltrials gov

Fold at dotted lines:

APPENDIX IV: LY3023414 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.

****Please note <u>the PM Dose on Cycle 1 Day 1</u> will be omitted for PK collection in patients participating on the dose-escalation portion of the study****

LY3043414 Dose Assignment: 55 mg/m^2/dose BID (Dose Level -1)

BSA (m^2)	Total Daily Dose (mg/day)	AM Dose (mg)	PM Dose (mg)	Dose Reduction For Toxicity (mg/day)	AM Dose (mg)	PM Dose (mg)
0.75-1.09	100	**50**	**50**	50	--	**50**
1.10-1.54	150	**50**	**100**	100	**50**	**50**
≥ 1.55	200	**100**	**100**	150	**50**	**100**

LY3043414 Dose Assignment: 80 mg/m^2/dose BID (Dose Level 1)

BSA (m^2)	Total Daily Dose (mg/day)	AM Dose (mg)	PM Dose (mg)	Dose Reduction For Toxicity (mg/day)	AM Dose (mg)	PM Dose (mg)
0.52-0.74	100	**50**	**50**	50	--	50
0.75-1.09	150	**50**	**100**	100	**50**	**50**
1.10-1.54	200	**100**	**100**	150	**50**	**100**
≥ 1.55	300	**150**	**150**	200	**100**	**100**

LY3043414 Dose Assignment: 115 mg/m^2/dose BID (Dose Level 2)

BSA (m^2)	Total Daily Dose (mg/day)	AM Dose (mg)	PM Dose (mg)	Dose Reduction For Toxicity (mg/day)	AM Dose (mg)	PM Dose (mg)
0.37-0.51	100	**50**	**50**	50	--	50
0.52-0.74	150	**50**	**100**	100	**50**	**50**
0.75-1.09	200	**100**	**100**	150	**50**	**100**
1.10-1.54	300	**150**	**150**	200	**100**	**100**
≥ 1.55	400	**200**	**200**	300	**150**	**150**

APPENDIX V: CORRELATIVE STUDIES GUIDE

Correlative Study	Section	Blood Volume		Tube Type
		Volume per Sample	Total Cycle 1	
Pharmacokinetics	8.3	2 mL	18 mL*	K_2 EDTA lavender top
Total Blood Volume in Cycle 1			**18 mL**	

* Collected from patients enrolled during the determination of the recommended phase 2 dose/ tolerable dose. All other patients will have two sample timepoints collected for a total of 4 mL during Cycle 1.

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

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

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

APPENDIX VI: APEC1621D 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
LY3023414 IND # 134661	PO	Dose Level 2: 115 mg/m^2/dose BID (Recommended Phase 2 Dose) Refer to dosing nomogram in Appendix IV.	1-28	LY3023414 should be taken without regards to food with a glass of water at approximately the same time each day. Patients should swallow the tablets as a whole and should not chew or crush them. If a patient misses a dose of LY3023414, the dose should be taken as soon as possible as long as it is more than 6 hours before the next scheduled dose. If it is less than 6 hours before the next dose, then the dose should be skipped. If vomiting occurs after taking LY3023414, the patient should skip the dose and take the next dose as scheduled

Enter Cycle #: _____ Dose Level: _____Ht _____cm Wt _____kg BSA _____m^2

Date Due	Date Given	Day	**LY3023414** mg AM mg PM	Studies
			Enter calculated dose above as per dosing nomogram and actual dose administered below	
		1	_____mg AM _____mg PM	a-l, n, o
		2	_____mg AM _____mg PM	n
		3	_____mg AM _____mg PM	f
		4	_____mg AM _____mg PM	
		5	_____mg AM _____mg PM	
		6	_____mg AM _____mg PM	
		7	_____mg AM _____mg PM	
		8	_____mg AM _____mg PM	a, b, f, h, i, m
		9	_____mg AM _____mg PM	
		10	_____mg AM _____mg PM	
		11	_____mg AM _____mg PM	
		12	_____mg AM _____mg PM	f
		13	_____mg AM _____mg PM	
		14	_____mg AM _____mg PM	
		15	_____mg AM _____mg PM	a, b, f, h, i, m, n
		16	_____mg AM _____mg PM	
		17	_____mg AM _____mg PM	
		18	_____mg AM _____mg PM	f
		19	_____mg AM _____mg PM	
		20	_____mg AM _____mg PM	
		21	_____mg AM _____mg PM	
		22	_____mg AM _____mg PM	a, b, f, h, i, m
		23	_____mg AM _____mg PM	
		24	_____mg AM _____mg PM	
		25	_____mg AM _____mg PM	f
		26	_____mg AM _____mg PM	
		27	_____mg AM _____mg PM	
		28/1	_____mg AM _____mg PM	a-c, f, h-j, m

Cycle 1

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.

a. History/Physical Exam (including VS)
b. Neurological Exam
c. Ht/Wt/BSA
d. Performance Status
e. Pregnancy Test. Women of childbearing potential require a negative pregnancy test prior to starting treatment; sexually active patients must use an acceptable method of birth control. Abstinence is an acceptable method of birth control.
f. CBC/differential/platelets- If patients have Grade 4 neutropenia then CBCs should be checked at least every other day until recovery to Grade 3 or until meeting the criteria for dose limiting toxicity.
g. Urinalysis
h. Electrolytes including Ca++, PO4, Mg++
i. Creatinine, ALT, bilirubin; Glucose
j. Albumin; Total cholesterol, triglycerides
k. Tumor Disease Evaluation
l. Bone Marrow Aspirate and/or biopsy- At baseline, only required for patients suspected of having bone marrow metastasis on the basis of history, symptoms, laboratory evaluation or other clinical data.
m. Patient Diary- (see Appendix III) should be reviewed after completion of each treatment cycle and uploaded into RAVE. The patient diary should be collected weekly.
n. Pharmacokinetics- see Section 8.3 for details of PK studies.
o. EKG

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)

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
LY3023414 IND # 134661	PO	Dose Level 2: 115 mg/m^2/dose BID (Recommended Phase 2 Dose) Refer to dosing nomogram in Appendix IV.	1-28	LY3023414 should be taken without regards to food with a glass of water at approximately the same time each day. Patients should swallow the tablets as a whole and should not chew or crush them. If a patient misses a dose of LY3023414, the dose should be taken as soon as possible as long as it is more than 6 hours before the next scheduled dose. If it is less than 6 hours before the next dose, then the dose should be skipped. If vomiting occurs after taking LY3023414, the patient should skip the dose and take the next dose as scheduled.

Enter Cycle #: _____ Dose Level: _____Ht _____cm Wt _____kg BSA _____m^2

Date Due	Date Given	Day	**LY3023414** _____mg AM _____mg PM	Studies
			Enter calculated dose above as per dosing nomogram and actual dose administered below	
		1	_____mg AM _____mg PM	a-f,
		2	_____mg AM _____mg PM	
		3	_____mg AM _____mg PM	
		4	_____mg AM _____mg PM	
		5	_____mg AM _____mg PM	
		6	_____mg AM _____mg PM	
		7	_____mg AM _____mg PM	
		8	_____mg AM _____mg PM	c
		9	_____mg AM _____mg PM	
		10	_____mg AM _____mg PM	
		11	_____mg AM _____mg PM	
		12	_____mg AM _____mg PM	
		13	_____mg AM _____mg PM	
		14	_____mg AM _____mg PM	
		15	_____mg AM _____mg PM	c
		16	_____mg AM _____mg PM	
		17	_____mg AM _____mg PM	
		18	_____mg AM _____mg PM	
		19	_____mg AM _____mg PM	
		20	_____mg AM _____mg PM	
		21	_____mg AM _____mg PM	
		22	_____mg AM _____mg PM	c
		23	_____mg AM _____mg PM	
		24	_____mg AM _____mg PM	
		25	_____mg AM _____mg PM	
		26	_____mg AM _____mg PM	
		27	_____mg AM _____mg PM	
		28/1	_____mg AM _____mg PM	a-f, i

Subsequent Cycles

Required Observations in All Subsequent Cycles

a. History/Physical Exam (including VS and neurological exam)
b. Ht/Wt/BSA
c. CBC/differential/platelets If patients develop Grade 4 neutropenia then CBCs should be checked every 3 to 4 days until recovery to Grade 3
d. Electrolytes including Ca++, PO4, Mg++
e. Creatinine, ALT, bilirubin; Glucose
f. Albumin; Total cholesterol, triglycerides
g. Tumor Disease Evaluation – Every other cycle. Tumor Disease Evaluation should be obtained on the next consecutive cycle after initial documentation of either a PR or CR. Subsequent scans may restart 2 cycles after the confirmatory scan. If the institutional investigator determines that the patient has progressed based on clinical or laboratory evidence, he/she may opt not to confirm this finding radiographically
h. Bone Marrow Aspirate and/or biopsy- Every other cycle. Should only be performed on patients with known bone marrow involvement at baseline.
i. Patient Diary- (see Appendix III) should be reviewed after completion of each treatment cycle and uploaded into RAVE. The patient diary should be collected weekly.
j. Circulating Tumor DNA (ctDNA-optional)- With consent, two samples will be collected on this protocol (Cycle 5 Day 1; and for patients receiving ≥ 5 cycles, at progression or end of protocol therapy) see Section 8.4 for details of the ctDNA studies.

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)

Subsequent Cycles

APPENDIX VII-A: EXAMPLES OF ACTIONABLE MUTATIONS OF INTEREST FOR APEC1621D COHORT A (TSC)

NON-HOTSPOT RULES			
Gene Name	Description	Variant Type	LOE
TSC1	Include	Deleterious	3
TSC2	Include	Deleterious	3
NF1	Exclude	Deleterious	
NF2	Exclude	Deleterious	

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

NRAS	COSM562	SNV	p.G12C
HRAS	COSM503	SNV	p.Q61H
HRAS	COSM502	SNV	p.Q61H
HRAS	COSM499	SNV	p.Q61R
HRAS	COSM500	SNV	p.Q61P
HRAS	COSM498	SNV	p.Q61L
HRAS	COSM33695	MNV	p.Q61R
HRAS	COSM501	MNV	p.Q61R
HRAS	COSM497	SNV	p.Q61E
HRAS	COSM496	SNV	p.Q61K
HRAS	COSM52978	MNV	p.Q61L
HRAS	COSM490	SNV	p.G13D
HRAS	COSM489	SNV	p.G13V
HRAS	COSM488	SNV	p.G13C
HRAS	COSM487	SNV	p.G13S
HRAS	COSM486	SNV	p.G13R
HRAS	COSM483	SNV	p.G12V
HRAS	COSM484	SNV	p.G12D
HRAS	COSM485	SNV	p.G12A
HRAS	COSM482	SNV	p.G12R
HRAS	COSM481	SNV	p.G12C
HRAS	COSM480	SNV	p.G12S
KRAS	COSM19900	MNV	p.A146V
KRAS	COSM19404	SNV	p. A146T
KRAS	COSM19940	MNV	p.K117N
KRAS	COSM28519	MNV	p.K117N
KRAS	COSM554	SNV	p.Q61H
KRAS	COSM555	SNV	p.Q61H
KRAS	COSM553	SNV	p.Q61L
KRAS	COSM552	SNV	p.Q61R
KRAS	COSM551	SNV	p.Q61P
KRAS	COSM1168052	MNV	p.Q61R
KRAS	COSM550	SNV	p.Q61E
KRAS	COSM549	SNV	p.Q61K
KRAS	COSM87298	MNV	p.Q61K
KRAS	COSM539	SNV	p.G15D
KRAS	COSM538	SNV	p.G15S
KRAS	COSM87280	SNV	p.G13E
KRAS	COSM30567	SNV	p.G13E
KRAS	COSM533	SNV	p.G13A

KRAS	COSM534	SNV	p.G13V
KRAS	COSM532	SNV	p.G13D
KRAS	COSM531	MNV	p.G13D
KRAS	COSM530	MNV	p.G13V
KRAS	COSM12721	MNV	p.G13V
KRAS	COSM528	SNV	p.G13S
KRAS	COSM527	SNV	p.G13C
KRAS	COSM529	SNV	p.G13R
KRAS	COSM13643	SNV	p.G12N
KRAS	COSM512	SNV	p.G12F
KRAS	COSM514	SNV	p.G12L
KRAS	COSM87281	MNV	p.G13C
KRAS	COSM520	SNV	p.G12V
KRAS	COSM521	SNV	p.G12D
KRAS	COSM522	SNV	p.G12A
KRAS	COSM14209	MNV	p.G12D
KRAS	COSM515	MNV	p.G12V
KRAS	COSM518	SNV	p.G12R
KRAS	COSM517	SNV	p.G12S
KRAS	COSM516	SNV	p.G12C
KRAS	COSM513	MNV	p.G12C
KRAS	COSM5413585	MNV	p.G12A
KRAS	COSM1716372	MNV	p.G12L
KRAS	COSM249888	MNV	p.G12R
KRAS	COSM4387522	MNV	p.G12V
KRAS	COSM4745557	MNV	p.G13R
ARAF	COSM5044705	SNV	p.S214C
ARAF	COSM1742787	SNV	p.S214A
ARAF	COSM612884	SNV	p.S214F
BRAF	COSM1132	SNV	p.K601N
BRAF	COSM6265	SNV	p.K601N
BRAF	COSM308550	MNV	p.V600D
BRAF	COSM477	MNV	p.V600D
BRAF	COSM475	MNV	p.V600E
BRAF	COSM1127	MNV	p.V600R
BRAF	COSM1583011	MNV	p.V600R
BRAF	COSM473	MNV	p.V600K
BRAF	COSM474	MNV	p.V600R
BRAF	COSM6137	SNV	p.V600G
BRAF	COSM18443	SNV	p.V600A

BRAF	COSM249889	MNV	p.V600Q
BRAF	COSM476	SNV	p.V600E
BRAF	COSM1130	SNV	p.V600M
BRAF	COSM219798	SNV	p.V600L
BRAF	COSM33808	SNV	p.V600L
BRAF	COSM1133	DEL	p.V600_K601>E
BRAF	PM_COSM30730	INS	p.T599_V600insT
BRAF	PM_COSM26625	INS	p.A598_T599insV
BRAF	COSM457	SNV	p.G469R
BRAF	COSM455	SNV	p.G469R
BRAF	COSM1112	SNV	p.G466R
BRAF	COSM478	SNV	p.K601E
BRAF	COSM472	SNV	p.T599I
BRAF	COSM21549	SNV	p.A598V
BRAF	COSM1126	MNV	p.L597S
BRAF	COSM1125	SNV	p.L597Q
BRAF	COSM471	SNV	p.L597R
BRAF	COSM470	SNV	p.L597V
BRAF	COSM469	SNV	p.G596R
BRAF	COSM53198	SNV	p.F595L
BRAF	COSM468	SNV	p.F595L
BRAF	COSM21612	SNV	p.F595L
BRAF	COSM466	SNV	p.D594V
BRAF	COSM467	SNV	p.D594G
BRAF	COSM211600	MNV	p.D594N
BRAF	COSM1583010	SNV	p.D594A
BRAF	COSM27639	SNV	p.D594N
BRAF	COSM463	SNV	p.E586K
BRAF	COSM462	SNV	p.N581S
BRAF	COSM1133046	SNV	p.Y472C
BRAF	COSM459	SNV	p.G469V
BRAF	COSM460	SNV	p.G469A
BRAF	COSM461	SNV	p.G469E
BRAF	COSM451	SNV	p.G466V
BRAF	COSM453	SNV	p.G466E
BRAF	COSM452	SNV	p.G466A
BRAF	COSM253328	SNV	p.G466R
BRAF	COSM449	SNV	p.G464E
BRAF	COSM450	SNV	p.G464V
BRAF	COSM1448615	SNV	p.G464R

BRAF	COSM1111	SNV	p.G464R
BRAF	COSM448	SNV	p.I463S
BRAF	COSM447	SNV	p.R462I
MAP2K1	PM_E1	DEL	p.F53_Q58delFLTQKQaddL
MAP2K1	PM_E2	DEL	p.Q56_V60delQKQKV
MAP2K1	COSM1235481	SNV	p.Q56P
MAP2K1	COSM4756761	SNV	p.K57T
MAP2K1	COSM1235478	SNV	p.K57N
MAP2K1	COSM5520914	SNV	p.K57N
MAP2K1	PM_COSM4166150	DEL	p.K57_G61del
MAP2K1	PM_COSM5031101	DEL	p.Q58_E62delQKVGE
MAP2K1	PM_COSM5031100	DEL	p.Q58_E62delQKVGE
MAP2K1	PM_COSM1235479	SNV	p.D67N
MAP2K1	COSM1678546	SNV	p.D67N
MAP2K1	PM_COSM404998	DEL	p.E102_I103delEI
MAP2K1	PM_COSM4166152	DEL	p.E102_I103del
MAP2K1	PM_COSM4166153	DEL	p.E102_I103del
MAP2K1	PM_COSM5730253	DEL	p.I103_K104delIK
MAP2K1	PM_COSM5702512	DEL	p.I103_K104del
MAP2K1	PM_E3	SNV	p.E120Q
MAP2K1	COSM555601	SNV	p.C121S
MAP2K1	COSM1315829	SNV	p.C121S
MAP2K1	PM_E4	SNV	p.S123T
MAP2K1	COSM1374186	SNV	p.G128D
MAP2K1	COSM232755	SNV	p.E203K
GNA11	COSM52969	SNV	p.Q209L
GNA11	COSM52970	SNV	p.Q209P
GNAQ	COSM28757	SNV	p.Q209L
GNAQ	COSM28758	SNV	p.Q209P
GNAQ	COSM28760	SNV	p.Q209R
GNAQ	COSM52975	SNV	p.R183Q

Fusions

Gene Name	Variant ID	Variant Type	aMOI
BRAF	AGAP3-BRAF.A10B11	Fusion	BRAF Gene Fusion
BRAF	AGAP3-BRAF.A9B9	Fusion	BRAF Gene Fusion
BRAF	AGK-BRAF.A2B8	Fusion	BRAF Gene Fusion
BRAF	AGTRAP-BRAF.A5B8.COSF828.1	Fusion	BRAF Gene Fusion
BRAF	AKAP9-BRAF.A21B10	Fusion	BRAF Gene Fusion

BRAF	AKAP9-BRAF.A22B9	Fusion	BRAF Gene Fusion
BRAF	AKAP9-BRAF.A28B9	Fusion	BRAF Gene Fusion
BRAF	AKAP9-BRAF.A7B11	Fusion	BRAF Gene Fusion
BRAF	AKAP9-BRAF.A8B9.COSF1013.1	Fusion	BRAF Gene Fusion
BRAF	AP3B1-BRAF.A22B9	Fusion	BRAF Gene Fusion
BRAF	ARMC10-BRAF.A4B11	Fusion	BRAF Gene Fusion
BRAF	ATG7-BRAF.A18B9	Fusion	BRAF Gene Fusion
BRAF	BAIAP2L1-BRAF.B12B9	Fusion	BRAF Gene Fusion
BRAF	BBS9-BRAF.B19B4	Fusion	BRAF Gene Fusion
BRAF	BCL2L11-BRAF.B3B10	Fusion	BRAF Gene Fusion
BRAF	BRAF-AP3B1.B8A23	Fusion	BRAF Gene Fusion
BRAF	BRAF-BRAF.B1B11	Fusion	BRAF Gene Fusion
BRAF	BRAF-BRAF.B1B9	Fusion	BRAF Gene Fusion
BRAF	BRAF-BRAF.B3B11	Fusion	BRAF Gene Fusion
BRAF	BRAF-BRAF.B3B9	Fusion	BRAF Gene Fusion
BRAF	BRAF-CIITA.B9C6	Fusion	BRAF Gene Fusion
BRAF	BRAF-MACF1.B8M15	Fusion	BRAF Gene Fusion
BRAF	BRAF-MRPS33.B1M2	Fusion	BRAF Gene Fusion
BRAF	BRAF-SLC26A4.B3S7	Fusion	BRAF Gene Fusion
BRAF	BRAF-SUGCT.B1S13	Fusion	BRAF Gene Fusion
BRAF	BTF3L4-BRAF.B3B11	Fusion	BRAF Gene Fusion
BRAF	C7orf73-BRAF.C2B9	Fusion	BRAF Gene Fusion
BRAF	CCDC6-BRAF.C1B9	Fusion	BRAF Gene Fusion
BRAF	CCDC91-BRAF.C11B9	Fusion	BRAF Gene Fusion
BRAF	CCNY-BRAF.C1B10	Fusion	BRAF Gene Fusion
BRAF	CDC27-BRAF.C16B9.1	Fusion	BRAF Gene Fusion
BRAF	CEP89-BRAF.C16B9	Fusion	BRAF Gene Fusion
BRAF	CLCN6-BRAF.C2B11.COSF1440	Fusion	BRAF Gene Fusion
BRAF	CLIP2-BRAF.C6B11	Fusion	BRAF Gene Fusion
BRAF	CUL1-BRAF.C7B9	Fusion	BRAF Gene Fusion
BRAF	CUX1-BRAF.C10B9	Fusion	BRAF Gene Fusion
BRAF	DYNC1I2-BRAF.D7B10	Fusion	BRAF Gene Fusion
BRAF	EML4-BRAF.E6B10	Fusion	BRAF Gene Fusion
BRAF	EPS15-BRAF.E22B10	Fusion	BRAF Gene Fusion
BRAF	ERC1-BRAF.E12B10	Fusion	BRAF Gene Fusion
BRAF	ERC1-BRAF.E17B8	Fusion	BRAF Gene Fusion
BRAF	FAM114A2-BRAF.F9B11	Fusion	BRAF Gene Fusion
BRAF	FAM131B-BRAF.F1B10.COSF1191	Fusion	BRAF Gene Fusion
BRAF	FAM131B-BRAF.F2B9.COSF1189.1	Fusion	BRAF Gene Fusion
BRAF	FAM131B-BRAF.F3B9.COSF1193	Fusion	BRAF Gene Fusion

BRAF	FCHSD1-BRAF.F13B9.COSF403	Fusion	BRAF Gene Fusion
BRAF	FXR1-BRAF.F13B10	Fusion	BRAF Gene Fusion
BRAF	GATM-BRAF.G2B11	Fusion	BRAF Gene Fusion
BRAF	GHR-BRAF.G1B10	Fusion	BRAF Gene Fusion
BRAF	GNAI1-BRAF.G1B10.COSF1442	Fusion	BRAF Gene Fusion
BRAF	GTF2I-BRAF.G4B10	Fusion	BRAF Gene Fusion
BRAF	HERPUD1-BRAF.H4B7	Fusion	BRAF Gene Fusion
BRAF	KCTD7-BRAF.K3B8	Fusion	BRAF Gene Fusion
BRAF	KCTD7-BRAF.K4B8	Fusion	BRAF Gene Fusion
BRAF	KDM7A-BRAF.K11B11	Fusion	BRAF Gene Fusion
BRAF	KIAA1549-BRAF.K12B11	Fusion	BRAF Gene Fusion
BRAF	KIAA1549-BRAF.K12B9.COSF1474	Fusion	BRAF Gene Fusion
BRAF	KIAA1549-BRAF.K13B9	Fusion	BRAF Gene Fusion
BRAF	KIAA1549-BRAF.K14B11.COSF1226	Fusion	BRAF Gene Fusion
BRAF	KIAA1549-BRAF.K14B9.COSF483	Fusion	BRAF Gene Fusion
BRAF	KIAA1549-BRAF.K15B10.COSF1283.1	Fusion	BRAF Gene Fusion
BRAF	KIAA1549-BRAF.K15B11.COSF485.1	Fusion	BRAF Gene Fusion
BRAF	KIAA1549-BRAF.K15B9.COSF481.1	Fusion	BRAF Gene Fusion
BRAF	KIAA1549-BRAF.K16B10	Fusion	BRAF Gene Fusion
BRAF	KIAA1549-BRAF.K17B10.COSF509	Fusion	BRAF Gene Fusion
BRAF	KIAA1549-BRAF.K18B9.COSF511	Fusion	BRAF Gene Fusion
BRAF	KIAA1549-BRAF.K9B9	Fusion	BRAF Gene Fusion
BRAF	KLHL7-BRAF.K5B9	Fusion	BRAF Gene Fusion
BRAF	LSM12-BRAF.L3B9	Fusion	BRAF Gene Fusion
BRAF	LSM14A-BRAF.L9B9	Fusion	BRAF Gene Fusion
BRAF	MACF1-BRAF.M60B9	Fusion	BRAF Gene Fusion
BRAF	MAD1L1-BRAF.M16B9	Fusion	BRAF Gene Fusion
BRAF	MAD1L1-BRAF.M17B10	Fusion	BRAF Gene Fusion
BRAF	MKRN1-BRAF.M4B11.COSF1444	Fusion	BRAF Gene Fusion
BRAF	MKRN1-BRAF.M4B9	Fusion	BRAF Gene Fusion
BRAF	MYRIP-BRAF.M16B9	Fusion	BRAF Gene Fusion
BRAF	MZT1-BRAF.M2B11	Fusion	BRAF Gene Fusion
BRAF	NUB1-BRAF.N3B9	Fusion	BRAF Gene Fusion
BRAF	NUDCD3-BRAF.N4B9	Fusion	BRAF Gene Fusion
BRAF	NUP214-BRAF.N21B10	Fusion	BRAF Gene Fusion
BRAF	PAPSS1-BRAF.P5B9.1	Fusion	BRAF Gene Fusion
BRAF	PLIN3-BRAF.P1B9	Fusion	BRAF Gene Fusion
BRAF	RAD18-BRAF.R7B10	Fusion	BRAF Gene Fusion
BRAF	RBMS3-BRAF.R11B11	Fusion	BRAF Gene Fusion
BRAF	RNF11-BRAF.R1B11	Fusion	BRAF Gene Fusion

BRAF	RNF130-BRAF.R3B9.COSF1483	Fusion	BRAF Gene Fusion
BRAF	RP2-BRAF.R3B10	Fusion	BRAF Gene Fusion
BRAF	SLC12A7-BRAF.S17B11	Fusion	BRAF Gene Fusion
BRAF	SLC45A3-BRAF.S1B8.COSF871	Fusion	BRAF Gene Fusion
BRAF	SND1-BRAF.S10B11	Fusion	BRAF Gene Fusion
BRAF	SND1-BRAF.S10B9	Fusion	BRAF Gene Fusion
BRAF	SND1-BRAF.S11B11	Fusion	BRAF Gene Fusion
BRAF	SND1-BRAF.S14B11	Fusion	BRAF Gene Fusion
BRAF	SND1-BRAF.S14B9	Fusion	BRAF Gene Fusion
BRAF	SND1-BRAF.S16B9.1	Fusion	BRAF Gene Fusion
BRAF	SND1-BRAF.S18B10	Fusion	BRAF Gene Fusion
BRAF	SND1-BRAF.S9B2	Fusion	BRAF Gene Fusion
BRAF	SND1-BRAF.S9B9	Fusion	BRAF Gene Fusion
BRAF	SOX6-BRAF.S5B9	Fusion	BRAF Gene Fusion
BRAF	SOX6-BRAF.S6B9	Fusion	BRAF Gene Fusion
BRAF	STRN3-BRAF.S3B10	Fusion	BRAF Gene Fusion
BRAF	TANK-BRAF.T4B9	Fusion	BRAF Gene Fusion
BRAF	TAX1BP1-BRAF.T8B11.1	Fusion	BRAF Gene Fusion
BRAF	TMEM178B-BRAF.T2B9	Fusion	BRAF Gene Fusion
BRAF	TMPRSS2-BRAF.T3B11	Fusion	BRAF Gene Fusion
BRAF	TRIM24-BRAF.T10B9	Fusion	BRAF Gene Fusion
BRAF	TRIM24-BRAF.T11B2	Fusion	BRAF Gene Fusion
BRAF	TRIM24-BRAF.T3B10	Fusion	BRAF Gene Fusion
BRAF	TRIM24-BRAF.T3B11	Fusion	BRAF Gene Fusion
BRAF	TRIM24-BRAF.T5B8	Fusion	BRAF Gene Fusion
BRAF	TRIM24-BRAF.T9B9.1	Fusion	BRAF Gene Fusion
BRAF	TRIM4-BRAF.T6B10	Fusion	BRAF Gene Fusion
BRAF	UBN2-BRAF.U3B11	Fusion	BRAF Gene Fusion
BRAF	ZC3HAV1-BRAF.Z3B10	Fusion	BRAF Gene Fusion
BRAF	ZC3HAV1-BRAF.Z7B11	Fusion	BRAF Gene Fusion
BRAF	ZKSCAN5-BRAF.Z2B9	Fusion	BRAF Gene Fusion
BRAF	ZSCAN30-BRAF.Z3B10	Fusion	BRAF Gene Fusion

INCLUSION	**VARIANTS**			
Hotspots				
Gene Name	Variant ID	Variant Type	aMOI	LOE
TSC1	PM_MCH12	SNV	p. Q527*	3
TSC1	PM_COSM1636659	DEL	p.E636fs*51	3

TSC1	PM_MCH11	SNV	p. Q781*	3
TSC1	PM_D22	SNV	F158S	3
TSC1	PM_D23	SNV	F216S	3
TSC1	PM_D24	SNV	G132D	3
TSC1	PM_D25	SNV	G305R	3
TSC1	PM_D26	SNV	G305W	3
TSC1	PM_D27	SNV	I76N	3
TSC1	PM_D28	SNV	K121R	3
TSC1	PM_D29	SNV	L117P	3
TSC1	PM_D30	SNV	L180P	3
TSC1	PM_D31	SNV	L191H	3
TSC1	PM_D32	SNV	L191R	3
TSC1	PM_D33	SNV	L50P	2
TSC1	COSM5013848	SNV	L61P	3
TSC1	PM_D34	SNV	L61R	3
TSC1	COSM277850	SNV	L72P	3
TSC1	PM_D35	SNV	L93R	3
TSC1	PM_D36	SNV	M224R	3
TSC1	PM_D1	DEL	p.128delV	3
TSC1	PM_D2	INDEL	p.N198F199delinsI	3
TSC1	COSM1314592	SNV	R190P	3
TSC1	PM_D37	SNV	R204P	3
TSC1	PM_D38	SNV	R246K	3
TSC1	PM_D39	SNV	R246T	3
TSC1	PM_D3	DEL	S201del	3
TSC1	PM_D40	SNV	V133F	3
TSC2	PM_COSM4440414	SNV	p. Q1178*	3
TSC2	PM_D41	SNV	A1141T	3
TSC2	PM_D42	SNV	A328P	3
TSC2	PM_D43	SNV	A607E	3
TSC2	PM_D44	SNV	A614D	3
TSC2	PM_D45	SNV	A889P	3
TSC2	PM_D46	SNV	A889V	3
TSC2	PM_D47	SNV	C244R	3
TSC2	PM_D48	SNV	C696Y	3
TSC2	PM_D49	SNV	C804R	3
TSC2	PM_D50	SNV	D1028N	3
TSC2	PM_D51	SNV	D1535A/D1512A	3
TSC2	PM_D4	DEL	E1552del/E1529del	3
TSC2	PM_D52	SNV	E337K	3

TSC2	PM_D53	SNV	E412V	3
TSC2	PM_D54	SNV	E75G	3
TSC2	PM_D55	SNV	F615S	3
TSC2	PM_D56	SNV	F897S	3
TSC2	PM_D57	SNV	G1204E	3
TSC2	PM_D58	SNV	G1567D/D1544D	3
TSC2	PM_D59	SNV	G1567V/G1544V	3
TSC2	PM_D60	SNV	G1579S/G1556S	3
TSC2	PM_D61	SNV	G1596V/G1573V	3
TSC2	PM_D62	SNV	G1642D/G1619D	3
TSC2	PM_D5	SNV	G305V	3
TSC2	PM_D63	SNV	H1620R/H1597R	3
TSC2	PM_D64	SNV	H1640Y/H1617Y	3
TSC2	PM_D65	SNV	H597Y	3
TSC2	PM_D66	SNV	L1061P	3
TSC2	PM_D67	SNV	L146R	3
TSC2	PM_D68	SNV	L1534H/L1511H	3
TSC2	PM_D69	SNV	L1548P/L1525P	3
TSC2	PM_D70	SNV	L1578P/L1555P	3
TSC2	PM_D71	SNV	L1584R/L1561R	3
TSC2	PM_D6	INDEL	L1750Afs25/L1727Afs25	3
TSC2	PM_D72	SNV	L219P	3
TSC2	PM_D73	SNV	L340P	3
TSC2	PM_D74	SNV	L410R	3
TSC2	PM_D75	SNV	L448P	3
TSC2	PM_D76	SNV	L466P	3
TSC2	PM_D77	SNV	L493P	3
TSC2	PM_D7	SNV	L612P	2
TSC2	PM_D78	SNV	L693P	3
TSC2	PM_D8	SNV	L713R	2
TSC2	PM_D79	SNV	L737P	2
TSC2	PM_D80	SNV	L792R	3
TSC2	PM_D81	SNV	L826P	3
TSC2	PM_D82	SNV	L830R	3
TSC2	PM_D83	SNV	L844R	3
TSC2	PM_D84	SNV	L850P	2
TSC2	PM_D9	SNV	L916R	3
TSC2	PM_D85	SNV	M1I - no start codon	3
TSC2	PM_D86	SNV	M788R	3
TSC2	PM_D87	SNV	N1643H/N1620H	3

TSC2	PM_D88	SNV	N1643I/N1620I	3
TSC2	PM_D89	SNV	N1643K/N1620K	3
TSC2	PM_D90	SNV	N1643S/N1620S	3
TSC2	PM_D10	INS	p.105insALL	3
TSC2	PM_D12	DEL	p.1746del6/1723del6	3
TSC2	PM_D13	DEL	p.275delN	3
TSC2	PM_D14	DEL	p.412del8	3
TSC2	PM_D16	INS	p.597insH	3
TSC2	PM_D17	INS	p.609insS	3
TSC2	PM_D18	DEL	p.820delI	3
TSC2	PM_D91	SNV	P1202H	3
TSC2	PM_D92	SNV	P1497R/P1474R	3
TSC2	PM_D93	SNV	P1497S/P1474S	3
TSC2	PM_D94	SNV	P1497T/P1474T	3
TSC2	PM_D95	SNV	P1675L/P1652L	2
TSC2	PM_D96	SNV	P1709L/P1686L	3
TSC2	PM_D97	SNV	P419S	3
TSC2	PM_D98	SNV	Q1503P/Q1480P	3
TSC2	PM_D99	SNV	Q1554H/Q1531H	3
TSC2	PM_D100	SNV	Q1686P/Q1663P	3
TSC2	PM_D101	SNV	Q373P	3
TSC2	PM_D102	SNV	R1032P	3
TSC2	PM_D103	SNV	R1200W	3
TSC2	PM_D104	SNV	R1713H/R1690H	3
TSC2	PM_D105	SNV	R1743Q/R1720Q	2
TSC2	PM_D106	SNV	R1743W/R1720W	2
TSC2	PM_D107	SNV	R261P	3
TSC2	PM_D108	SNV	R462C	3
TSC2	PM_D109	SNV	R462H	3
TSC2	PM_D19	SNV	R462P	3
TSC2	PM_D110	SNV	R57H	3
TSC2	PM_D111	SNV	R611Q	2
TSC2	PM_D112	SNV	R611W	2
TSC2	PM_D113	SNV	R622W	3
TSC2	PM_D114	SNV	R628G	3
TSC2	PM_D115	SNV	R905G	3
TSC2	PM_D116	SNV	R905Q	3
TSC2	PM_D117	SNV	R905W	2
TSC2	PM_D118	SNV	R98W	3
TSC2	PM_D119	SNV	S1036P	3

TSC2	PM_D120	SNV	S1653F/S1630F	3
TSC2	PM_D121	SNV	S1653P/S1630P	3
TSC2	PM_D20	SNV	T1068I	3
TSC2	PM_D122	SNV	T1203K	3
TSC2	PM_D123	SNV	T1623I/T1600I	3
TSC2	PM_D124	SNV	V1199G	3
TSC2	PM_D125	SNV	V1500G/V1477G	3
TSC2	PM_D126	SNV	V1646G/V1623G	3
TSC2	PM_D127	SNV	V1673D/V1650D	3
TSC2	PM_D128	SNV	V1673F/V1650F	3
TSC2	PM_D21	DEL	V241del	3
TSC2	PM_D129	SNV	V299G	3
TSC2	PM_D130	SNV	V334A	3
TSC2	PM_D131	SNV	V334G	3
TSC2	PM_D132	SNV	V560M	3
TSC2	PM_D133	SNV	V705E	3
TSC2	PM_D134	SNV	V705M	3
TSC2	PM_D135	SNV	V769E	3
TSC2	PM_D136	SNV	W1610G/W1587G	3
TSC2	PM_D137	SNV	Y1571N/Y1548N	3
TSC2	PM_D138	SNV	Y598C	3
TSC2	PM_D139	SNV	Y598H	3

APPENDIX VII-B: EXAMPLES OF ACTIONABLE MUTATIONS OF INTEREST FOR APEC1621D COHORT B (PI3K)

NON-HOTSPOT	RULES			
Gene Name	Description	Variant Type	LOE	Region:
PTEN	Include	Deleterious	3	
PIK3R1	Include	Deleterious	3	iSH2 domain aa 414-622
TSC1	Exclude	Deleterious	(Included in cohort A)	
TSC2	Exclude	Deleterious	(Included in cohort A)	
NF1	Exclude	Deleterious		
NF2	Exclude	Deleterious		
PIK3R1	Exclude	Deleterious		nSH2 domain aa 331-413

EXCLUSION	VARIANTS		
Hotspots			
Gene Name	Variant ID	Variant Type	aMOI
NRAS	COSM586	SNV	p.Q61H
NRAS	COSM585	SNV	p.Q61H
NRAS	COSM583	SNV	p.Q61L
NRAS	COSM582	SNV	p.Q61P
NRAS	COSM584	SNV	p.Q61R
NRAS	COSM30646	MNV	p.Q61L
NRAS	COSM33693	MNV	p.Q61R
NRAS	COSM580	SNV	p.Q61K
NRAS	COSM581	SNV	p.Q61E
NRAS	COSM53223	MNV	p.Q61K
NRAS	COSM12725	MNV	p.Q61L
NRAS	COSM579	MNV	p.Q61R
NRAS	COSM12730	MNV	p.Q61K
NRAS	COSM574	SNV	p.G13V
NRAS	COSM573	SNV	p.G13D
NRAS	COSM575	SNV	p.G13A
NRAS	COSM572	MNV	p.G13V
NRAS	COSM569	SNV	p.G13R
NRAS	COSM570	SNV	p.G13C
NRAS	COSM571	SNV	p.G13S
NRAS	COSM564	SNV	p.G12D

NRAS	COSM565	SNV	p.G12A
NRAS	COSM566	SNV	p.G12V
NRAS	COSM561	SNV	p.G12R
NRAS	COSM563	SNV	p.G12S
NRAS	COSM562	SNV	p.G12C
HRAS	COSM503	SNV	p.Q61H
HRAS	COSM502	SNV	p.Q61H
HRAS	COSM499	SNV	p.Q61R
HRAS	COSM500	SNV	p.Q61P
HRAS	COSM498	SNV	p.Q61L
HRAS	COSM33695	MNV	p.Q61R
HRAS	COSM501	MNV	p.Q61R
HRAS	COSM497	SNV	p.Q61E
HRAS	COSM496	SNV	p.Q61K
HRAS	COSM52978	MNV	p.Q61L
HRAS	COSM490	SNV	p.G13D
HRAS	COSM489	SNV	p.G13V
HRAS	COSM488	SNV	p.G13C
HRAS	COSM487	SNV	p.G13S
HRAS	COSM486	SNV	p.G13R
HRAS	COSM483	SNV	p.G12V
HRAS	COSM484	SNV	p.G12D
HRAS	COSM485	SNV	p.G12A
HRAS	COSM482	SNV	p.G12R
HRAS	COSM481	SNV	p.G12C
HRAS	COSM480	SNV	p.G12S
KRAS	COSM19900	MNV	p.A146V
KRAS	COSM19404	SNV	p. A146T
KRAS	COSM19940	MNV	p.K117N
KRAS	COSM28519	MNV	p.K117N
KRAS	COSM554	SNV	p.Q61H
KRAS	COSM555	SNV	p.Q61H
KRAS	COSM553	SNV	p.Q61L
KRAS	COSM552	SNV	p.Q61R
KRAS	COSM551	SNV	p.Q61P
KRAS	COSM1168052	MNV	p.Q61R
KRAS	COSM550	SNV	p.Q61E
KRAS	COSM549	SNV	p.Q61K
KRAS	COSM87298	MNV	p.Q61K
KRAS	COSM539	SNV	p.G15D

KRAS	COSM538	SNV	p.G15S
KRAS	COSM87280	SNV	p.G13E
KRAS	COSM30567	SNV	p.G13E
KRAS	COSM533	SNV	p.G13A
KRAS	COSM534	SNV	p.G13V
KRAS	COSM532	SNV	p.G13D
KRAS	COSM531	MNV	p.G13D
KRAS	COSM530	MNV	p.G13V
KRAS	COSM12721	MNV	p.G13V
KRAS	COSM528	SNV	p.G13S
KRAS	COSM527	SNV	p.G13C
KRAS	COSM529	SNV	p.G13R
KRAS	COSM13643	SNV	p.G12N
KRAS	COSM512	SNV	p.G12F
KRAS	COSM514	SNV	p.G12L
KRAS	COSM87281	MNV	p.G13C
KRAS	COSM520	SNV	p.G12V
KRAS	COSM521	SNV	p.G12D
KRAS	COSM522	SNV	p.G12A
KRAS	COSM14209	MNV	p.G12D
KRAS	COSM515	MNV	p.G12V
KRAS	COSM518	SNV	p.G12R
KRAS	COSM517	SNV	p.G12S
KRAS	COSM516	SNV	p.G12C
KRAS	COSM513	MNV	p.G12C
KRAS	COSM5413585	MNV	p.G12A
KRAS	COSM1716372	MNV	p.G12L
KRAS	COSM249888	MNV	p.G12R
KRAS	COSM4387522	MNV	p.G12V
KRAS	COSM4745557	MNV	p.G13R
ARAF	COSM5044705	SNV	p.S214C
ARAF	COSM1742787	SNV	p.S214A
ARAF	COSM612884	SNV	p.S214F
BRAF	COSM1132	SNV	p.K601N
BRAF	COSM6265	SNV	p.K601N
BRAF	COSM308550	MNV	p.V600D
BRAF	COSM477	MNV	p.V600D
BRAF	COSM475	MNV	p.V600E
BRAF	COSM1127	MNV	p.V600R
BRAF	COSM1583011	MNV	p.V600R

BRAF	COSM473	MNV	p.V600K
BRAF	COSM474	MNV	p.V600R
BRAF	COSM6137	SNV	p.V600G
BRAF	COSM18443	SNV	p.V600A
BRAF	COSM249889	MNV	p.V600Q
BRAF	COSM476	SNV	p.V600E
BRAF	COSM1130	SNV	p.V600M
BRAF	COSM219798	SNV	p.V600L
BRAF	COSM33808	SNV	p.V600L
BRAF	COSM1133	DEL	p.V600_K601>E
BRAF	PM_COSM30730	INS	p.T599_V600insT
BRAF	PM_COSM26625	INS	p.A598_T599insV
BRAF	COSM457	SNV	p.G469R
BRAF	COSM455	SNV	p.G469R
BRAF	COSM1112	SNV	p.G466R
BRAF	COSM478	SNV	p.K601E
BRAF	COSM472	SNV	p.T599I
BRAF	COSM21549	SNV	p.A598V
BRAF	COSM1126	MNV	p.L597S
BRAF	COSM1125	SNV	p.L597Q
BRAF	COSM471	SNV	p.L597R
BRAF	COSM470	SNV	p.L597V
BRAF	COSM469	SNV	p.G596R
BRAF	COSM53198	SNV	p.F595L
BRAF	COSM468	SNV	p.F595L
BRAF	COSM21612	SNV	p.F595L
BRAF	COSM466	SNV	p.D594V
BRAF	COSM467	SNV	p.D594G
BRAF	COSM211600	MNV	p.D594N
BRAF	COSM1583010	SNV	p.D594A
BRAF	COSM27639	SNV	p.D594N
BRAF	COSM463	SNV	p.E586K
BRAF	COSM462	SNV	p.N581S
BRAF	COSM1133046	SNV	p.Y472C
BRAF	COSM459	SNV	p.G469V
BRAF	COSM460	SNV	p.G469A
BRAF	COSM461	SNV	p.G469E
BRAF	COSM451	SNV	p.G466V
BRAF	COSM453	SNV	p.G466E
BRAF	COSM452	SNV	p.G466A

BRAF	COSM253328	SNV	p.G466R
BRAF	COSM449	SNV	p.G464E
BRAF	COSM450	SNV	p.G464V
BRAF	COSM1448615	SNV	p.G464R
BRAF	COSM1111	SNV	p.G464R
BRAF	COSM448	SNV	p.I463S
BRAF	COSM447	SNV	p.R462I
MAP2K1	PM_E1	DEL	p.F53_Q58delFLTQKQaddL
MAP2K1	PM_E2	DEL	p.Q56_V60delQKQKV
MAP2K1	COSM1235481	SNV	p.Q56P
MAP2K1	COSM4756761	SNV	p.K57T
MAP2K1	COSM1235478	SNV	p.K57N
MAP2K1	COSM5520914	SNV	p.K57N
MAP2K1	PM_COSM4166150	DEL	p.K57_G61del
MAP2K1	PM_COSM5031101	DEL	p.Q58_E62delQKVGE
MAP2K1	PM_COSM5031100	DEL	p.Q58_E62delQKVGE
MAP2K1	PM_COSM1235479	SNV	p.D67N
MAP2K1	COSM1678546	SNV	p.D67N
MAP2K1	PM_COSM404998	DEL	p.E102_I103delEI
MAP2K1	PM_COSM4166152	DEL	p.E102_I103del
MAP2K1	PM_COSM4166153	DEL	p.E102_I103del
MAP2K1	PM_COSM5730253	DEL	p.I103_K104delIK
MAP2K1	PM_COSM5702512	DEL	p.I103_K104del
MAP2K1	PM_E3	SNV	p.E120Q
MAP2K1	COSM555601	SNV	p.C121S
MAP2K1	COSM1315829	SNV	p.C121S
MAP2K1	PM_E4	SNV	p.S123T
MAP2K1	COSM1374186	SNV	p.G128D
MAP2K1	COSM232755	SNV	p.E203K
GNA11	COSM52969	SNV	p.Q209L
GNA11	COSM52970	SNV	p.Q209P
GNAQ	COSM28757	SNV	p.Q209L
GNAQ	COSM28758	SNV	p.Q209P
GNAQ	COSM28760	SNV	p.Q209R
GNAQ	COSM52975	SNV	p.R183Q
TSC1	PM_MCH12	SNV	p. Q527*
TSC1	PM_COSM1636659	DEL	p.E636fs*51
TSC1	PM_MCH11	SNV	p. Q781*
TSC1	PM_D22	SNV	F158S
TSC1	PM_D23	SNV	F216S

TSC1	PM_D24	SNV	G132D
TSC1	PM_D25	SNV	G305R
TSC1	PM_D26	SNV	G305W
TSC1	PM_D27	SNV	I76N
TSC1	PM_D28	SNV	K121R
TSC1	PM_D29	SNV	L117P
TSC1	PM_D30	SNV	L180P
TSC1	PM_D31	SNV	L191H
TSC1	PM_D32	SNV	L191R
TSC1	PM_D33	SNV	L50P
TSC1	COSM5013848	SNV	L61P
TSC1	PM_D34	SNV	L61R
TSC1	COSM277850	SNV	L72P
TSC1	PM_D35	SNV	L93R
TSC1	PM_D36	SNV	M224R
TSC1	PM_D1	DEL	p.128delV
TSC1	PM_D2	INDEL	p.N198F199delinsI
TSC1	COSM1314592	SNV	R190P
TSC1	PM_D37	SNV	R204P
TSC1	PM_D38	SNV	R246K
TSC1	PM_D39	SNV	R246T
TSC1	PM_D3	DEL	S201del
TSC1	PM_D40	SNV	V133F
TSC2	PM_COSM4440414	SNV	p. Q1178*
TSC2	PM_D41	SNV	A1141T
TSC2	PM_D42	SNV	A328P
TSC2	PM_D43	SNV	A607E
TSC2	PM_D44	SNV	A614D
TSC2	PM_D45	SNV	A889P
TSC2	PM_D46	SNV	A889V
TSC2	PM_D47	SNV	C244R
TSC2	PM_D48	SNV	C696Y
TSC2	PM_D49	SNV	C804R
TSC2	PM_D50	SNV	D1028N
TSC2	PM_D51	SNV	D1535A/D1512A
TSC2	PM_D4	DEL	E1552del/E1529del
TSC2	PM_D52	SNV	E337K
TSC2	PM_D53	SNV	E412V
TSC2	PM_D54	SNV	E75G
TSC2	PM_D55	SNV	F615S

TSC2	PM_D56	SNV	F897S
TSC2	PM_D57	SNV	G1204E
TSC2	PM_D58	SNV	G1567D/D1544D
TSC2	PM_D59	SNV	G1567V/G1544V
TSC2	PM_D60	SNV	G1579S/G1556S
TSC2	PM_D61	SNV	G1596V/G1573V
TSC2	PM_D62	SNV	G1642D/G1619D
TSC2	PM_D5	SNV	G305V
TSC2	PM_D63	SNV	H1620R/H1597R
TSC2	PM_D64	SNV	H1640Y/H1617Y
TSC2	PM_D65	SNV	H597Y
TSC2	PM_D66	SNV	L1061P
TSC2	PM_D67	SNV	L146R
TSC2	PM_D68	SNV	L1534H/L1511H
TSC2	PM_D69	SNV	L1548P/L1525P
TSC2	PM_D70	SNV	L1578P/L1555P
TSC2	PM_D71	SNV	L1584R/L1561R
TSC2	PM_D6	INDEL	L1750Afs25/L1727Afs25
TSC2	PM_D72	SNV	L219P
TSC2	PM_D73	SNV	L340P
TSC2	PM_D74	SNV	L410R
TSC2	PM_D75	SNV	L448P
TSC2	PM_D76	SNV	L466P
TSC2	PM_D77	SNV	L493P
TSC2	PM_D7	SNV	L612P
TSC2	PM_D78	SNV	L693P
TSC2	PM_D8	SNV	L713R
TSC2	PM_D79	SNV	L737P
TSC2	PM_D80	SNV	L792R
TSC2	PM_D81	SNV	L826P
TSC2	PM_D82	SNV	L830R
TSC2	PM_D83	SNV	L844R
TSC2	PM_D84	SNV	L850P
TSC2	PM_D9	SNV	L916R
TSC2	PM_D85	SNV	M1I - no start codon
TSC2	PM_D86	SNV	M788R
TSC2	PM_D87	SNV	N1643H/N1620H
TSC2	PM_D88	SNV	N1643I/N1620I
TSC2	PM_D89	SNV	N1643K/N1620K
TSC2	PM_D90	SNV	N1643S/N1620S

TSC2	PM_D10	INS	p.105insALL
TSC2	PM_D12	DEL	p.1746del6/1723del6
TSC2	PM_D13	DEL	p.275delN
TSC2	PM_D14	DEL	p.412del8
TSC2	PM_D16	INS	p.597insH
TSC2	PM_D17	INS	p.609insS
TSC2	PM_D18	DEL	p.820delI
TSC2	PM_D91	SNV	P1202H
TSC2	PM_D92	SNV	P1497R/P1474R
TSC2	PM_D93	SNV	P1497S/P1474S
TSC2	PM_D94	SNV	P1497T/P1474T
TSC2	PM_D95	SNV	P1675L/P1652L
TSC2	PM_D96	SNV	P1709L/P1686L
TSC2	PM_D97	SNV	P419S
TSC2	PM_D98	SNV	Q1503P/Q1480P
TSC2	PM_D99	SNV	Q1554H/Q1531H
TSC2	PM_D100	SNV	Q1686P/Q1663P
TSC2	PM_D101	SNV	Q373P
TSC2	PM_D102	SNV	R1032P
TSC2	PM_D103	SNV	R1200W
TSC2	PM_D104	SNV	R1713H/R1690H
TSC2	PM_D105	SNV	R1743Q/R1720Q
TSC2	PM_D106	SNV	R1743W/R1720W
TSC2	PM_D107	SNV	R261P
TSC2	PM_D108	SNV	R462C
TSC2	PM_D109	SNV	R462H
TSC2	PM_D19	SNV	R462P
TSC2	PM_D110	SNV	R57H
TSC2	PM_D111	SNV	R611Q
TSC2	PM_D112	SNV	R611W
TSC2	PM_D113	SNV	R622W
TSC2	PM_D114	SNV	R628G
TSC2	PM_D115	SNV	R905G
TSC2	PM_D116	SNV	R905Q
TSC2	PM_D117	SNV	R905W
TSC2	PM_D118	SNV	R98W
TSC2	PM_D119	SNV	S1036P
TSC2	PM_D120	SNV	S1653F/S1630F

TSC2	PM_D121	SNV	S1653P/S1630P
TSC2	PM_D20	SNV	T1068I
TSC2	PM_D122	SNV	T1203K
TSC2	PM_D123	SNV	T1623I/T1600I
TSC2	PM_D124	SNV	V1199G
TSC2	PM_D125	SNV	V1500G/V1477G
TSC2	PM_D126	SNV	V1646G/V1623G
TSC2	PM_D127	SNV	V1673D/V1650D
TSC2	PM_D128	SNV	V1673F/V1650F
TSC2	PM_D21	DEL	V241del
TSC2	PM_D129	SNV	V299G
TSC2	PM_D130	SNV	V334A
TSC2	PM_D131	SNV	V334G
TSC2	PM_D132	SNV	V560M
TSC2	PM_D133	SNV	V705E
TSC2	PM_D134	SNV	V705M
TSC2	PM_D135	SNV	V769E
TSC2	PM_D136	SNV	W1610G/W1587G
TSC2	PM_D137	SNV	Y1571N/Y1548N
TSC2	PM_D138	SNV	Y598C
TSC2	PM_D139	SNV	Y598H

Fusions

Gene Name	Variant ID	Variant Type	aMOI
BRAF	AGAP3-BRAF.A10B11	Fusion	BRAF Gene Fusion
BRAF	AGAP3-BRAF.A9B9	Fusion	BRAF Gene Fusion
BRAF	AGK-BRAF.A2B8	Fusion	BRAF Gene Fusion
BRAF	AGTRAP-BRAF.A5B8.COSF828.1	Fusion	BRAF Gene Fusion
BRAF	AKAP9-BRAF.A21B10	Fusion	BRAF Gene Fusion
BRAF	AKAP9-BRAF.A22B9	Fusion	BRAF Gene Fusion
BRAF	AKAP9-BRAF.A28B9	Fusion	BRAF Gene Fusion
BRAF	AKAP9-BRAF.A7B11	Fusion	BRAF Gene Fusion
BRAF	AKAP9-BRAF.A8B9.COSF1013.1	Fusion	BRAF Gene Fusion
BRAF	AP3B1-BRAF.A22B9	Fusion	BRAF Gene Fusion
BRAF	ARMC10-BRAF.A4B11	Fusion	BRAF Gene Fusion
BRAF	ATG7-BRAF.A18B9	Fusion	BRAF Gene Fusion
BRAF	BAIAP2L1-BRAF.B12B9	Fusion	BRAF Gene Fusion
BRAF	BBS9-BRAF.B19B4	Fusion	BRAF Gene Fusion
BRAF	BCL2L11-BRAF.B3B10	Fusion	BRAF Gene Fusion

BRAF	BRAF-AP3B1.B8A23	Fusion	BRAF Gene Fusion
BRAF	BRAF-BRAF.B1B11	Fusion	BRAF Gene Fusion
BRAF	BRAF-BRAF.B1B9	Fusion	BRAF Gene Fusion
BRAF	BRAF-BRAF.B3B11	Fusion	BRAF Gene Fusion
BRAF	BRAF-BRAF.B3B9	Fusion	BRAF Gene Fusion
BRAF	BRAF-CIITA.B9C6	Fusion	BRAF Gene Fusion
BRAF	BRAF-MACF1.B8M15	Fusion	BRAF Gene Fusion
BRAF	BRAF-MRPS33.B1M2	Fusion	BRAF Gene Fusion
BRAF	BRAF-SLC26A4.B3S7	Fusion	BRAF Gene Fusion
BRAF	BRAF-SUGCT.B1S13	Fusion	BRAF Gene Fusion
BRAF	BTF3L4-BRAF.B3B11	Fusion	BRAF Gene Fusion
BRAF	C7orf73-BRAF.C2B9	Fusion	BRAF Gene Fusion
BRAF	CCDC6-BRAF.C1B9	Fusion	BRAF Gene Fusion
BRAF	CCDC91-BRAF.C11B9	Fusion	BRAF Gene Fusion
BRAF	CCNY-BRAF.C1B10	Fusion	BRAF Gene Fusion
BRAF	CDC27-BRAF.C16B9.1	Fusion	BRAF Gene Fusion
BRAF	CEP89-BRAF.C16B9	Fusion	BRAF Gene Fusion
BRAF	CLCN6-BRAF.C2B11.COSF1440	Fusion	BRAF Gene Fusion
BRAF	CLIP2-BRAF.C6B11	Fusion	BRAF Gene Fusion
BRAF	CUL1-BRAF.C7B9	Fusion	BRAF Gene Fusion
BRAF	CUX1-BRAF.C10B9	Fusion	BRAF Gene Fusion
BRAF	DYNC1I2-BRAF.D7B10	Fusion	BRAF Gene Fusion
BRAF	EML4-BRAF.E6B10	Fusion	BRAF Gene Fusion
BRAF	EPS15-BRAF.E22B10	Fusion	BRAF Gene Fusion
BRAF	ERC1-BRAF.E12B10	Fusion	BRAF Gene Fusion
BRAF	ERC1-BRAF.E17B8	Fusion	BRAF Gene Fusion
BRAF	FAM114A2-BRAF.F9B11	Fusion	BRAF Gene Fusion
BRAF	FAM131B-BRAF.F1B10.COSF1191	Fusion	BRAF Gene Fusion
BRAF	FAM131B-BRAF.F2B9.COSF1189.1	Fusion	BRAF Gene Fusion
BRAF	FAM131B-BRAF.F3B9.COSF1193	Fusion	BRAF Gene Fusion
BRAF	FCHSD1-BRAF.F13B9.COSF403	Fusion	BRAF Gene Fusion
BRAF	FXR1-BRAF.F13B10	Fusion	BRAF Gene Fusion
BRAF	GATM-BRAF.G2B11	Fusion	BRAF Gene Fusion
BRAF	GHR-BRAF.G1B10	Fusion	BRAF Gene Fusion
BRAF	GNAI1-BRAF.G1B10.COSF1442	Fusion	BRAF Gene Fusion
BRAF	GTF2I-BRAF.G4B10	Fusion	BRAF Gene Fusion
BRAF	HERPUD1-BRAF.H4B7	Fusion	BRAF Gene Fusion
BRAF	KCTD7-BRAF.K3B8	Fusion	BRAF Gene Fusion
BRAF	KCTD7-BRAF.K4B8	Fusion	BRAF Gene Fusion
BRAF	KDM7A-BRAF.K11B11	Fusion	BRAF Gene Fusion

BRAF	KIAA1549-BRAF.K12B11	Fusion	BRAF Gene Fusion
BRAF	KIAA1549-BRAF.K12B9.COSF1474	Fusion	BRAF Gene Fusion
BRAF	KIAA1549-BRAF.K13B9	Fusion	BRAF Gene Fusion
BRAF	KIAA1549-BRAF.K14B11.COSF1226	Fusion	BRAF Gene Fusion
BRAF	KIAA1549-BRAF.K14B9.COSF483	Fusion	BRAF Gene Fusion
BRAF	KIAA1549-BRAF.K15B10.COSF1283.1	Fusion	BRAF Gene Fusion
BRAF	KIAA1549-BRAF.K15B11.COSF485.1	Fusion	BRAF Gene Fusion
BRAF	KIAA1549-BRAF.K15B9.COSF481.1	Fusion	BRAF Gene Fusion
BRAF	KIAA1549-BRAF.K16B10	Fusion	BRAF Gene Fusion
BRAF	KIAA1549-BRAF.K17B10.COSF509	Fusion	BRAF Gene Fusion
BRAF	KIAA1549-BRAF.K18B9.COSF511	Fusion	BRAF Gene Fusion
BRAF	KIAA1549-BRAF.K9B9	Fusion	BRAF Gene Fusion
BRAF	KLHL7-BRAF.K5B9	Fusion	BRAF Gene Fusion
BRAF	LSM12-BRAF.L3B9	Fusion	BRAF Gene Fusion
BRAF	LSM14A-BRAF.L9B9	Fusion	BRAF Gene Fusion
BRAF	MACF1-BRAF.M60B9	Fusion	BRAF Gene Fusion
BRAF	MAD1L1-BRAF.M16B9	Fusion	BRAF Gene Fusion
BRAF	MAD1L1-BRAF.M17B10	Fusion	BRAF Gene Fusion
BRAF	MKRN1-BRAF.M4B11.COSF1444	Fusion	BRAF Gene Fusion
BRAF	MKRN1-BRAF.M4B9	Fusion	BRAF Gene Fusion
BRAF	MYRIP-BRAF.M16B9	Fusion	BRAF Gene Fusion
BRAF	MZT1-BRAF.M2B11	Fusion	BRAF Gene Fusion
BRAF	NUB1-BRAF.N3B9	Fusion	BRAF Gene Fusion
BRAF	NUDCD3-BRAF.N4B9	Fusion	BRAF Gene Fusion
BRAF	NUP214-BRAF.N21B10	Fusion	BRAF Gene Fusion
BRAF	PAPSS1-BRAF.P5B9.1	Fusion	BRAF Gene Fusion
BRAF	PLIN3-BRAF.P1B9	Fusion	BRAF Gene Fusion
BRAF	RAD18-BRAF.R7B10	Fusion	BRAF Gene Fusion
BRAF	RBMS3-BRAF.R11B11	Fusion	BRAF Gene Fusion
BRAF	RNF11-BRAF.R1B11	Fusion	BRAF Gene Fusion
BRAF	RNF130-BRAF.R3B9.COSF1483	Fusion	BRAF Gene Fusion
BRAF	RP2-BRAF.R3B10	Fusion	BRAF Gene Fusion
BRAF	SLC12A7-BRAF.S17B11	Fusion	BRAF Gene Fusion
BRAF	SLC45A3-BRAF.S1B8.COSF871	Fusion	BRAF Gene Fusion
BRAF	SND1-BRAF.S10B11	Fusion	BRAF Gene Fusion
BRAF	SND1-BRAF.S10B9	Fusion	BRAF Gene Fusion
BRAF	SND1-BRAF.S11B11	Fusion	BRAF Gene Fusion
BRAF	SND1-BRAF.S14B11	Fusion	BRAF Gene Fusion
BRAF	SND1-BRAF.S14B9	Fusion	BRAF Gene Fusion
BRAF	SND1-BRAF.S16B9.1	Fusion	BRAF Gene Fusion

BRAF	SND1-BRAF.S18B10	Fusion	BRAF Gene Fusion
BRAF	SND1-BRAF.S9B2	Fusion	BRAF Gene Fusion
BRAF	SND1-BRAF.S9B9	Fusion	BRAF Gene Fusion
BRAF	SOX6-BRAF.S5B9	Fusion	BRAF Gene Fusion
BRAF	SOX6-BRAF.S6B9	Fusion	BRAF Gene Fusion
BRAF	STRN3-BRAF.S3B10	Fusion	BRAF Gene Fusion
BRAF	TANK-BRAF.T4B9	Fusion	BRAF Gene Fusion
BRAF	TAX1BP1-BRAF.T8B11.1	Fusion	BRAF Gene Fusion
BRAF	TMEM178B-BRAF.T2B9	Fusion	BRAF Gene Fusion
BRAF	TMPRSS2-BRAF.T3B11	Fusion	BRAF Gene Fusion
BRAF	TRIM24-BRAF.T10B9	Fusion	BRAF Gene Fusion
BRAF	TRIM24-BRAF.T11B2	Fusion	BRAF Gene Fusion
BRAF	TRIM24-BRAF.T3B10	Fusion	BRAF Gene Fusion
BRAF	TRIM24-BRAF.T3B11	Fusion	BRAF Gene Fusion
BRAF	TRIM24-BRAF.T5B8	Fusion	BRAF Gene Fusion
BRAF	TRIM24-BRAF.T9B9.1	Fusion	BRAF Gene Fusion
BRAF	TRIM4-BRAF.T6B10	Fusion	BRAF Gene Fusion
BRAF	UBN2-BRAF.U3B11	Fusion	BRAF Gene Fusion
BRAF	ZC3HAV1-BRAF.Z3B10	Fusion	BRAF Gene Fusion
BRAF	ZC3HAV1-BRAF.Z7B11	Fusion	BRAF Gene Fusion
BRAF	ZKSCAN5-BRAF.Z2B9	Fusion	BRAF Gene Fusion
BRAF	ZSCAN30-BRAF.Z3B10	Fusion	BRAF Gene Fusion

INCLUSION VARIANTS

Hotspots

Gene Name	Variant ID	Variant Type	aMOI	LOE
MTOR	COSM51889	SNV	p.L2220F	3
MTOR	COSM3965698	SNV	p.L2216P	3
MTOR	MCH4	SNV	p.R2217W	3
MTOR	COSM1560108	SNV	p.S2215P	3
MTOR	COSM20417	SNV	p.S2215Y	3
MTOR	COSM1686998	SNV	p.S2215F	3
MTOR	COSM462592	SNV	p.A2210P	3
MTOR	COSM414183	SNV	p.L2209V	3
MTOR	COSM527403	SNV	p.N2206S	3
MTOR	COSM893813	SNV	p.F1888L	3
MTOR	COSM462604	SNV	p.F1888L	3
MTOR	COSM3358968	SNV	p.F1888I	3

MTOR	COSM3358967	SNV	p.F1888L	3
MTOR	PM_D142	SNV	p.E1799K	3
MTOR	COSM180789	SNV	p.E1799K	3
MTOR	OM9	SNV	p.C1483W	3
MTOR	COSM462615	SNV	p.C1483Y	3
MTOR	COSM462616	SNV	p.C1483F	3
MTOR	COSM3747775	SNV	p.C1483R	3
MTOR	COSM462618	SNV	p.L1460P	3
MTOR	COSM462619	SNV	p.A1459P	3
PIK3CA	COSM746	SNV	p.R88Q	2
PIK3CA	COSM27493	SNV	p.R93W	3
PIK3CA	COSM748	SNV	p.G106V	3
PIK3CA	COSM13570	SNV	p.K111E	3
PIK3CA	COSM751	SNV	p.G118D	3
PIK3CA	COSM754	SNV	p.N345K	2
PIK3CA	COSM757	SNV	p.C420R	3
PIK3CA	COSM759	SNV	p.P539R	3
PIK3CA	COSM760	SNV	p.E542K	3
PIK3CA	COSM763	SNV	p.E545K	3
PIK3CA	COSM764	SNV	p.E545G	3
PIK3CA	COSM12458	SNV	p.E545A	3
PIK3CA	COSM765	SNV	p.E545D	2
PIK3CA	COSM766	SNV	p.Q546K	3
PIK3CA	COSM767	SNV	p.Q546P	3
PIK3CA	COSM12590	SNV	p.T1025S	3
PIK3CA	COSM12591	SNV	p.M1043V	3
PIK3CA	COSM773	SNV	p.M1043I	3
PIK3CA	COSM94984	SNV	p.M1043I	3
PIK3CA	COSM29313	SNV	p.M1043I	3
PIK3CA	COSM774	SNV	p.H1047Y	3
PIK3CA	COSM775	SNV	p.H1047R	2
PIK3CA	COSM776	SNV	p.H1047L	3
PTEN	COSM5133	SNV	p.Y16C	3
PTEN	COSM5247	SNV	p.Y27S	3
PTEN	COSM86058	SNV	p.A34D	3
PTEN	OM1539	SNV	p.N48K	3
PTEN	COSM5223	SNV	p.M35R	3
PTEN	MCH13	SNV	p.H61D	3
PTEN	COSM5042	SNV	p.H61R	3
PTEN	COSM5036	SNV	p.Y68H	3

PTEN	MCH14	SNV	p.Y68D	3
PTEN	COSM5102	SNV	p.C71Y	3
PTEN	COSM23566	SNV	p.D92H	3
PTEN	COSM5099	SNV	p.D92G	3
PTEN	COSM5264	SNV	p.D92A	3
PTEN	COSM5236	SNV	p.D92V	3
PTEN	COSM35759	SNV	p.D92E	3
PTEN	COSM125653	SNV	p.D92E	3
PTEN	COSM5043	SNV	p.H93Y	3
PTEN	COSM5283	SNV	p.H93D	3
PTEN	COSM5265	SNV	p.P96Q	3
PTEN	COSM5266	SNV	p.C105F	3
PTEN	COSM5212	SNV	p.D107Y	3
PTEN	COSM5106	SNV	p.L112P	3
PTEN	MCH15	SNV	p.L112R	3
PTEN	COSM5214	SNV	p.A121P	3
PTEN	COSM5273	SNV	p.A121E	3
PTEN	COSM5234	SNV	p.I122S	3
PTEN	COSM921088	SNV	p.H123D	3
PTEN	COSM921089	SNV	p.C124R	3
PTEN	COSM5224	SNV	p.C124S	3
PTEN	COSM5082	SNV	p.K125E	3
PTEN	COSM5041	SNV	p.A126V	3
PTEN	COSM5143	SNV	p.G127E	3
PTEN	COSM246853	SNV	p.G129R	3
PTEN	COSM28917	SNV	p.G129E	3
PTEN	COSM5276	SNV	p.G129V	3
PTEN	COSM5219	SNV	p.R130G	3
PTEN	COSM5216	SNV	p.R130L	3
PTEN	COSM5033	SNV	p.R130Q	3
PTEN	COSM5104	SNV	p.T131I	3
PTEN	COSM5044	SNV	p.V133I	3
PTEN	COSM12734	SNV	p.C136Y	3
PTEN	COSM5144	SNV	p.Y155C	3
PTEN	COSM5091	SNV	p.G165R	3
PTEN	COSM5114	SNV	p.G165E	3
PTEN	COSM249877	SNV	p.G165V	3
PTEN	MCH20	SNV	p.S170R	3
PTEN	COSM5045	SNV	p.S170N	3
PTEN	MCH22	SNV	p.S170R	3

PTEN	MCH21	SNV	p.S170R	3
PTEN	COSM5089	SNV	p.R173C	3
PTEN	COSM5039	SNV	p.R173H	3
PTEN	MCH16	SNV	p.R173P	3
PTEN	COSM5221	SNV	p.Y174N	3
PTEN	MCH17	SNV	p.L181P	3
PTEN	COSM5220	SNV	p.G251C	3
PTEN	COSM5255	SNV	p.F341V	3
PTEN	MCH18	SNV	p.V343E	3
PTEN	SM5213	SNV	p.L345Q	3
PIK3R1	PM_D147	DEL	p.KS459delN	3
PIK3R1	PM_D150	DEL	p.QY579_580H	3
PIK3R1	PM_D153	DEL	p.QYL579L	3
PIK3R1	PM_D157	DEL	p.DKRMNS560del	3
PIK3R1	PM_D158	DEL	p.NSIKPDLIQL564del	3
PIK3R1	PM_D159	SNV	p.N564D	3
PIK3R1	COSM35808	SNV	p.N564DK	3
PIK3R1	COSM35765	SNV	p.D560Y	3

IHC	RESULTS
GENE:	STATUS:
PTEN	NEGATIVE *

*Patients who have PTEN loss by IHC but a technical sequencing failure will be eligible for Cohort B of this sub-protocol.

APPENDIX VIII: TARGET HISTOLOGIES FOR APEC1621D EXPANSION COHORTS

Target tumor types considered for biomarker-positive expansion cohorts and biomarker-negative 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 IX: YOUTH INFORMATION SHEETS

INFORMATION SHEET REGARDING RESEARCH STUDY APEC1621D
(for children from 7 through 13 years of age)

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

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

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

3. What is the study about? We are asking you to take part in a research study because you have a cancer that has come back after treatment or is difficult to treat. 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? Children who are a part of this study will be given LY3023414 that could "match" your tumor. The doctors want to see if LY3023414 will help children with your type of cancer get better. We don't know if LY3023414 will work well to get rid of your cancer. That is why we are doing the study. You will have some tests and check-ups done more often than if you weren't part of this study. Some of these tests will require extra needle sticks for blood collection. 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 that LY3023414 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 risks to you from this study are that you may have problems, or side effects from LY3023414. Your doctor will talk to you about the risks we know about from LY3023414. Other things may happen to you that we don't yet know about.

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. The doctors and nurses will still take care of you. 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 blood. We want to see if there are ways to tell how the cancer will respond to treatment. You can still take part in this study even if you don't allow us to collect the extra blood samples for research.

INFORMATION SHEET REGARDING RESEARCH STUDY APEC1621D
(for teens from 14 through 17 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 you have a cancer that has come back after treatment or is difficult to treat. 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 in the study? Children and teens who are part of this study will be given LY3023414 that could "match" your tumor. The doctors want to see if LY3023414 will help children with your type of cancer get better. We don't know if LY3023414 will work well to get rid of your cancer. That is why we are doing the study. You will have some tests and check-ups done more often than if you weren't part of this study. Some of these tests will require extra needle sticks for blood collection. We will collect information about 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 that LY3023414 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 risks to you from this study are that you may have side effects from LY3023414. Your doctor will talk to you about the risks we know about from LY3023414. Other things may happen to you that we don't yet know about.

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. The doctors and nurses will still take care of you. 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, tell your parent, the doctor or nurse.

7. We are asking your permission to collect additional blood. We want to see if there are ways to tell how the cancer will respond to treatment. You can still take part in this study even if you don't allow us to collect the extra blood samples for research.

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).

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: TOXICITY-SPECIFIC GRADING

Bilirubin

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

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

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

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

Grade 1:	≤ 150
Grade 2:	151-250
Grade 3:	251-1000
Grade 4:	> 1000

GGT:

Grade 1:	> ULN- 2.5 x ULN
Grade 2:	> 2.5 x ULN- 5 x ULN
Grade 3:	> 5 x ULN-20 x ULN
Grade 4:	> 20 x ULN