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CHILDREN'S ONCOLOGY GROUP

APEC1621H

NCI-COG PEDIATRIC MATCH (MOLECULAR ANALYSIS FOR THERAPY CHOICE)- PHASE 2 SUBPROTOCOL OF OLAPARIB IN PATIENTS WITH TUMORS HARBORING DEFECTS IN DNA DAMAGE REPAIR GENES

Open to COG Member Institutions in the USA

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AGENT NSC# AND IND#'s
NCI-Supplied Agents:
Olaparib (Lynparza)
(NSC#747856 , [redacted])

IND Sponsor: DCTD, NCI

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ABSTRACT

This subprotocol is a component of the Pediatric MATCH trial APEC1621. The APEC1621SC screening protocol details the assay used for the integral genomic profiling which will determine eligibility for this subprotocol. The presence of specific defects in DNA damage repair (DDR) mechanisms may be exploited for cancer therapy, by allowing for the accumulation of double strand breaks, genomic instability and eventual cell death. Functional BRCA1 and BRCA2 proteins (and partner proteins RAD51 and PALB2) are required for efficient double-strand break repair by homologous repair (HR). Poly(ADP-ribose) polymerase (PARP) family members are essential to single-strand DNA by base excision repair (BER) and facilitate HR. Inactivating mutations in *BRCA1* or *BRCA2* and a limited number of other genomic alterations leading to impaired double-strand break repair sensitize cells to PARP inhibition by a principle known as synthetic lethality. Olaparib (Lynparza) is potent orally bioavailable small molecule inhibitor of PARP. FDA approved olaparib as monotherapy for the treatment of patients with advanced, heavily pretreated ovarian cancer who carry deleterious, or suspected deleterious, germline *BRCA1/2*-mutations. In adults, low-grade nausea, fatigue, vomiting, and anemia are the most common adverse events related to olaparib. Here we will conduct a phase 2 trial of olaparib in children with relapsed or refractory solid tumors (including non-Hodgkin lymphomas, histiocytoses and CNS involvement) harboring specified defects in DNA damage repair genes. Olaparib will be given twice daily continuously for 28-day cycles. Because the pediatric dose of olaparib 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 limited pharmacokinetics of olaparib in children will be evaluated.

EXPERIMENTAL DESIGN SCHEMA

Day 1-28	Day 28
OLAPARIB (BID)	Evaluation

Patients will receive olaparib twice daily for 28-day cycles. Evaluations will occur at the end of every other cycle x 3, then every 3 cycles.

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

1.0 GOALS AND OBJECTIVES (SCIENTIFIC AIMS)

1.1 Primary Aims

1.1.1 To determine the objective response rate (ORR; complete response + partial response) in pediatric patients treated with olaparib with advanced solid tumors (including CNS tumors), non-Hodgkin lymphomas or histiocytic disorders that harbor activating genetic alterations in the deleterious genetic alterations in the DNA damage repair (DDR) pathway,

1.2 Secondary Aims

1.2.1 To estimate the progression free survival in pediatric patients treated with olaparib with advanced solid tumors including non-Hodgkin lymphomas, CNS tumors, and histiocytosis that harbor deleterious genetic alterations in the DDR pathway.

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

1.2.3 To provide preliminary estimates of the pharmacokinetics of olaparib in children and adolescents with relapsed or refractory cancer

1.3 Exploratory Aims

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

2.0 BACKGROUND

2.1 Introduction/Rationale for Development

Under normal circumstances, loss of DNA integrity triggers cell-cycle checkpoints, cell-cycle arrest, genomic survey and activation of high fidelity DNA damage repair (DDR) mechanisms. Defects in DDR have been identified as one of the hallmarks of cancer, causing genomic instability and favoring tumor progression and metastasis. Inherited inactivating alterations of DDR genes such as *BRCA1 and BRCA2* (breast cancer susceptibility genes 1 and 2) are associated with cancer predisposition. Nevertheless, defects in DRR genes can be exploited for cancer therapy by rendering DDR mutant cells selectively vulnerable to pharmacological inhibition of a parallel pathway, a process known as "synthetic lethality," where either one condition might be tolerable, but the combination is lethal.[1] More explicitly, cancer cells which harbor defects in double- strand break repair can be specifically targeted by Poly(ADP-ribose) polymerase (PARP) inhibition, which blocks the repair of single-strand breaks, leaving cells with comparatively intact DDR mechanisms relatively unharmed. Olaparib (Lynparza) is an oral PARP inhibitor FDA-approved as monotherapy for the treatment of patients with advanced, heavily pretreated ovarian cancer who carry deleterious, or suspected deleterious, germline *BRCA1/2*-mutations leading to the accumulation of double strand breaks.

Defects in double- strand DNA damage repair and synthetic lethality with PARP inhibition:

DNA damage induced by exposure to environmental, endogenous or pharmacologic toxins

can interfere with critical cellular processes and stimulate the DNA damage response. Single-strand breaks rely on the base excision repair (BER) and nucleotide excision repair (NER) pathways whereas double-stranded breaks are dependent on the high fidelity, homologous recombination (HR) or the less accurate, nonhomologous end joining (NHEJ) mechanism.[2] PARP proteins bind to nicks and breaks in DNA, interact with histones, recruit scaffolding proteins and activate complexes of enzymes essential to single-strand repair via the BER pathway. Normal or DDR sufficient cells can tolerate PARP inhibition by using HR, the complementary double-strand break repair mechanism. Efficient double-strand break repair by HR, however requires functional BRCA1 and BRCA2 proteins [and partner proteins RAD51 and PALB2 (partner and localizer of BRCA2)].[3-5]

Germline inactivating mutations in *BRCA1* or *BRCA2* lead to the use of alternative repair pathways, such as NHEJ, resulting in imprecise repair, genomic instability, cell death, or survival with genomic alteration and cancer predisposition, mainly breast and ovarian.[6] However, the presence of a germline inactivating mutation in *BRCA1* or *BRCA2* has also been found to sensitize cancer cells to PARP inhibition[7,8] and identifies an enriched subset of patients with ovarian and breast carcinoma likely to respond to therapeutic PARP inhibition.[9-12] Likewise, deleterious alteration of *ATM* (ataxia-telangiectasia mutated), a key regulator of double-strand break repair, cell cycle checkpoint signaling and telomere homeostasis can cause ataxia telangiectasia, a disease characterized by genomic instability, premature aging, neurologic degeneration, immunodeficiency and predisposition to cancer.[13] Nevertheless, *in vitro*, pharmacologic inhibition of ATM activation or ATM deficiency induces PARP inhibitor sensitivity.[14,15] Similar vulnerabilities to PARP inhibition have been demonstrated in cell lines with deficiency or silencing of additional proteins integral to HR including: RAD51; FANCA, FANCC or FANCD2 (Fanconi anemia proteins); ATR (ataxia telangiectasia and Rad3-related) kinase; and other DNA repair factors such as MRE11A (Meiotic Recombination 11), NBS1(Nijmegen breakage syndrome 1) and RAD50.[14] These data suggest that treatment with PARP inhibitors may have broad clinical utility across tumor histologies, including pediatric cancers, which harbor inactivating mutations in *BRCA1*, *BRCA2, ATM* and other deleterious genomic alterations leading to impaired double-strand break repair.

Inactivating mutations of DDR genes as biomarkers of response to olaparib monotherapy:

Olaparib (Lynparza) is an oral PARP inhibitor capable of trapping inactivated PARP at single strand nicks, blocking BER, leading to the collapse of DNA replication forks, the accumulation of DNA double-strand breaks and dependency on HR. In 2014, Olaparib was FDA approved as monotherapy for the treatment of patients with advanced, heavily pretreated ovarian cancer who carry deleterious, or suspected deleterious, germline *BRCA1/2*-mutations (g*BRCA*m) based on single arm phase 2 study demonstrating an objective response rate (ORR) of 31%.[12,16] Clinical data from the same study, although in smaller numbers, also supported single agent activity in g*BRCA*m patients with recurrent breast, pancreatic and prostate cancer.[17] However, there has been a growing understanding that other genetic aberrations may produce a phenocopy of the HR defect produced by presumptive biallelic somatic loss of BRCA1/2, so-called tumor "BRCAness," that may also render cancers sensitive to PARP inhibition.[18] Recently, a clinical trial of patients with sporadic, metastatic, castration-resistant prostate cancers used a next generation targeted sequencing platform of DDR genes to study germline and fresh biopsy tissue and explore biomarkers of response to olaparib.[19] Of 49 evaluable patients, 16 (33%) had DNA-repair defects which were not only detected as genomic aberrations in *BRCA2* (7), and *BRCA1* (1), but also *ATM* (5), *PALB2* (2), *CHEK2* (2), *FANCA* (3), and *HDAC2* (1), all genes

previously reported to exhibit a synthetic lethal interaction with PARP inhibition *in vitro*.[14,19] Fourteen of these 16 patients (88%) responded to olaparib, including all patients with *BRCA2* inactivation and 4 of 5 patients with *ATM* loss. While tumors with *BRCA2* mutation uniformly demonstrated biallelic loss (4 with biallelic somatic loss, and 3 with germline mutations), strikingly, there were patients with monoallelic *ATM* aberrations affecting the kinase catalytic domain who also responded to therapy, suggesting either a dominant negative effect of the truncated protein or haploinsufficiency. Additionally, there was a prolonged response in a patient who harbored a combined monoallelic loss of *BRCA2* and *PALB2*.[19] Of late, a phase 2 trial in relapsed, platinum-sensitive high-grade ovarian carcinoma of a different PARP inhibitor, rucaparib (ARIEL 2) has identified RAD51C mutation or promoter hypermethylation as another potential predictive biomarker of response to PARP inhibition.[20]

Inactivating mutations of DDR genes and PARP inhibition in pediatric cancer:
The frequency of double-strand DNA repair defects in pediatric tumors is not well characterized. To date, studies in suggest that there is an 8.5- 10% risk of germline cancer predisposition in patients with childhood malignancy, the vast majority being *TP53* mutations, with only 14-27% of these in putative DDR genes, for an overall estimated frequency of 1-3%.[21,22] In addition, not all aberrations in DDR genes will result in pathway inactivation and monoallelic loss may be insufficient. For example, protein-truncating mutations, missense mutations and large segmental rearrangements within the *BRCA* genes are expected to be deleterious, however in one recent study by Parsons *et al*, there was no evidence of somatic loss of heterozygosity in the tumors of patients with germline *BRCA1* or *BRCA2* mutations.[22] Of note, germline (n=3) or somatic (n=2) *BRCA1* or *BRCA2* mutations have been identified in this study cohort (total frequency of 2-3%).[22]

Nevertheless, the principle of synthetic lethality has been demonstrated in the context of a pediatric tumor model. During the preclinical testing of the potent PARP inhibitor BMN 673, KT10, a Wilms tumor cell line showed exquisite sensitivity to PARP inhibition both *in vitro* and *in vivo* with a sustained complete responses in tumor xenografts. KT10 was subsequently demonstrated to have a frameshift mutation in PALB2 resulting in a premature stop codon and a truncated protein at the C-terminal end and loss of the BRCA2 binding site. Sequence read frequency almost exclusively favored the mutated over the wild type allele providing evidence the cell line was either homozygous or hemizygous for the *PALB2* mutation.[23]

The PARP inhibitor BMN 673 has undergone phase 1 clinical testing in an unselected pediatric population in combination with temozolomide, where the maximum tolerated dose of BMN 673 in combination with temozolomide in children was equivalent to the recommended phase 2/3 dose for BMN 673 monotherapy in adults, 1 mg daily. Dose limiting toxicities of the combination included myelosuppression with neutropenia (Grade 4 x $\geq$ 7 days), thrombocytopenia ($\geq$ 2 platelet transfusions in 7 days), Grade 4 abdominal hemorrhage, Grade 4 sepsis and prolonged Grade 3 ALT elevation.

This will be the first clinical trial of olaparib (Lynparza) in children, and the first phase 2 clinical trial of a PARP inhibitor in a pediatric population enriched for patients whose malignancies harbor deleterious alterations in DDR genes.

2.2 Preclinical Studies of Olaparib

2.2.1 Antitumor Activity

Olaparib was tested against a KU95, a mixed panel of 95 cancer cell lines derived from breast, ovarian, colorectal, head and neck, lung and pancreatic tumors. Olaparib exhibited a broad range of growth inhibitory (IC50) activity (ranging from 0.018 μM through to >10 μM), but a clear association with enhanced olaparib sensitivity (IC50 <1 μM) was observed in cell lines with known *BRCA1* or *BRCA2* mutations, *BRCA1* promoter methylation, or low expression of DDR genes/ proteins, notably ATM, ATR and MRE11.[24] *In vivo,* genetically engineered mice with spontaneous murine mammary tumors have been used to model *BRCA1* $^{-/-}$ and *BRCA2*$^{-/-}$ conditions and show prolonged survival and tumor regression, respectively, when compared to BRCA wild type controls.[25,26]

An olaparib sensitive, homozygous *BRCA*2 deleted, triple negative breast cancer patient derived xenograft has also been utilized to model the pharmacokinetics and pharmacodynamics required for efficacy. This model predicts that a large enough increase in single- stranded breaks to generate cell death in HR deficient tumors requires maintaining >90% inhibition of PAR at steady state.[24]

In an Ames bacterial mutation test, olaparib was not mutagenic, but chromosomal breakage was observed in a Chinese Hamster Ovary chromosome aberration test consistent with the mechanism of action of PARP inhibition.[24]

Pharmacology

At concentrations 6-fold the human mean free Cmax at the clinical dose of 300 mg bid (3.65 μM), olaparib showed no significant off-target activity against a diverse panel of molecular targets including enzymes, receptors, transporters and ion channels; concentrations 60-fold greater than the human mean free Cmax were required to inhibit the hERG encoded potassium channel.[24]

In vitro, olaparib is actively taken up by isolated human hepatocytes and CYP3A4 and CYP3A5 are the major isozymes responsible for its metabolism. It is a direct inhibitor of CYP3A (IC50 119 μM), a time dependent inhibitor of CYP3A (Kinact 0.0675 min-1; KI 72.2 μM) and can induce expression of messenger RNA for CYPs 1A2, 2B6 and 3A4. Olaparib can inhibit UGT1A1 (IC5096.7 μM) but had no appreciable effect against UGT2B7.[24]

Animal Toxicology

Nonclinical animal pharmacology and toxicology data for olaparib is based a variety of single and repeat dose studies. It should be noted that in repeat dosing studies, the exposures achieved were lower than those anticipated at the clinical dose of 400mg BID (capsule) or 300mg PO BID (tablet). The absolute bioavailability of olaparib following po dosing to mice, rats and dogs, was approximately 60%, 20% and 80%, respectively. *In vitro*, plasma protein binding, showed some variation between species. Unbound fraction was ~31% in mice and 29% in rat (between 0.023 and 46 μM), 38% to 48% in dog and 9% to 30% human (concentration dependent between 0.023 μM and 92.1 μM). Drug distribution was rapid in the rat, but with little or no distribution to brain, spinal cord or the lens of the eye. Whole-body autoradiography of xenograft bearing nude mice, suggested increased concentration an slower clearance of radiolabelled drug in the tumor versus the blood.[24]

In rats and dogs, receiving olaparib daily for 1 to 6 months, the principal toxicity was reversible myelosuppression, as demonstrated by anemia, neutropenia, lymphopenia and thrombocytopenia with full or partial recovery following cessation of the agent. Olaparib also induced micronuclei in bone marrow of rats, consistent with the induction of genomic instability. In rats but not dogs, daily therapy was also associated with anorexia and decreased weight gain. There were no significant effects on either dog cardiovascular and respiratory functions or rat Irwin (behavioural) tests.[24]

In reproductive toxicology studies in rats, olaparib produced no adverse effects on male or female fertility. However, pre, peri or post-conception treatment with olaparib caused reductions in early embryofetal survival and fetal weights. Treatment during pregnancy was also associated with increases incidence of visceral and skeletal abnormalities including major eye and vertebral/rib malformations at dose levels that were not toxic to the mother. These findings are felt to be consistent with the mechanism of action of olaparib.[24]

2.3 Adult Studies

As of December 15, 2016, an estimated 4475 patients patients with ovarian, breast, pancreatic, gastric and a variety of other solid tumors are estimated to have received treatment with olaparib in AstraZeneca-sponsored, interventional studies (3799 patients) and the Managed Access Program (676 patients). Of the 4475 patients, 2109 received the capsule formulation, 2341 received the tablet formulation, and 25 received both capsule and tablet. The bioavailability of the two preparations are not equivalent. **This trial will use the tablet formulation of olaparib.**

2.3.1 Phase 1 Studies

Initially, the **capsule formulation** of olaparib was studied in phase 1 adult solid tumors. The dose and schedule began at 10 mg daily for 2 of every 3 weeks, and escalated to 600 mg twice daily on a continuous basis using a modified accelerated-titration design. Reversible dose- limiting toxicities included mood alteration/fatigue (Grade 3 400 mg BID), somnolence (Grade 3 600 mg BID) and myelosuppression (Grade 4 thrombocytopenia, 600 mg BID). The maximum tolerated dose of olaparib capsule was determined to be 400 mg PO twice daily. The most commonly reported adverse events related to drug include low-grade nausea (32%), fatigue (30%), vomiting (20%), taste alteration (13%), and anorexia (12%); Anemia (5%) and thrombocytopenia (3%) were the most common grade $\geq$ 3 hematologic events. Olaparib capsule exhibited a terminal-elimination half-life of 5 to 7 hours with less than proportional increases in exposure with dose escalation, but maximized by the twice daily schedule. 400 mg BID (capsule) was associated with a maximum plasma concentration (Cmax) of 18 μM. Maximum PARP inhibition (>90%; as evidence by decreased PAR signal and the formation of γH2AX foci in hair follicles), was achieved at the lower dose of 100mg PO BID capsule, and associated with Cmin of 1μM and Cmax of 8.5 μM.[9] Clinical responses were seen only in g*BRCA*m patients with breast, ovarian or prostate tumors. No obvious increases in adverse effects have been reported in mutation carriers. All doses exceeding 100mg PO (capsule) BID have been associated with clinical response in g*BRCA*m patients. [9-12,17]

The **tablet formulation** developed by AstraZeneca for ease of administration will be used in this trial. The tablet demonstrates higher bioavailability than the capsular formulation. Based on single dose data, olaparib tablet is rapidly absorbed with peak plasma concentrations typically observed at 1.5 hours. The population PK analysis are consistent with sequential zero- and first-order absorption and show a significant impact of olaparib tablet strength on the absorption rate constant. Following Tmax, plasma concentrations of olaparib declined in a biphasic manner with an average terminal elimination half-life (t½) of 14.9 hours (standard deviation 8.2 hours). Exposure (AUC0-12) increased approximately proportionally with dose for the dose range 25 to 450 mg; while maximum plasma concentration (Cmax) increased slightly less than proportionally. The observed geometric mean steady state maximum plasma concentration (Cmax ss), area under the plasma concentration-time curve for the dosing interval (AUC0-τ) and minimum plasma concentration (Cmin ss) following multiple dosing of 300 mg PO BID tablet formulation are approximately 53%, 17% and 32% higher than those, respectively, for the capsule formulation (400 mg BID pooled population analysis). At 300 mg BID dosing, the estimated geometric mean Cmax ss, AUC0-12 and Cmin were 8.76 µg/mL, 56.45 µg.h/mL and 1.67 µg/mL, respectively (equivalent to unbound concentrations of 1.59 µg/mL, 10.22 µg.h/mL and 0.302 µg.h/mL, respectively). The inter-individual variability was moderate to high. Food slowed the rate of absorption (Tmax delayed by 2.5 hours and Cmax reduced by 20%), however there was no significant food effect on the extent of absorption (AUC), therefore olaparib tablets can be administered without regard to food.[24] **Based on an efficacy and toxicity matching trial, the MTD and recommended phase 2 dose the tablet formulation is 300mg PO twice daily**. Dose limiting toxicities were mainly hematologic.[27]

2.3.2 Phase 2 Studies

Subsequent Phase 2 studies of olaparib have confirmed the sustained antitumor activity in patients with g*BRCA*m breast cancer,[11,12,17] high-grade serous epithelial ovarian cancer [10,12,16,17,28] and other tumor types including pancreatic[17] and castration resistant prostate cancer.[17,19] The FDA approval for olaparib monotherapy in patients with heavily pretreated ovarian cancer and *gBRCA*m was based on a group of 193 patients, of which 137 had measurable disease and had received at least three prior lines of chemotherapy. The objective response rate (ORR) was 34% with median duration of response (DOR) of 7.9 month. A subset of 59 patients had retrospectively confirmed *gBRCA*m by a companion diagnostic test. This subgroup had an ORR of 41% (95% CI, 28–54), with a median DOR of 8.0 months.[29] The phase 2 safety cohort reviewed by the FDA included 223 patients from 6 studies with olaparib monotherapy. The most common adverse reactions of any grade in ≥ 20% of patients were anemia, nausea, fatigue, vomiting, diarrhea, dysgeusia, dyspepsia, headache, decreased appetite, nasopharyngitis/ pharyngitis/ upper respiratory infection, cough, arthralgia/musculoskeletal pain, myalgia, back pain, dermatitis/rash, and abdominal pain/discomfort. Despite the heavily pretreated population, the most common grade 3-4 toxicity was anemia (18%). However, myelodysplastic syndrome and/or acute myeloid leukemia occurred in 2% of the olaparib treated patients as compared with 0.8% of those treated with placebo.[29] Olaparib antitumour activity has also been observed in sporadic ovarian cancers,[12] and castration resistant prostate cancer where biallelic somatic *BRCA2* mutation, germline truncating *ATM* mutations and monoallelic *ATM* mutations affecting the kinase catalytic domain, as well as aberrations in

PALB2 and *HDAC2* emerged as tractable DDR defects associated with olaparib response. No new safety signals emerged from this trial. A dose reduction was required in 26%; anemia was the most common indication for the dose reduction.[19]

2.4 Pediatric Studies

2.4.1 Prior Experience in Children

There is no prior experience with olaparib in children.

2.5 Overview of Proposed Pediatric Study

We will conduct a phase 2 trial of olaparib in children with relapsed or refractory solid tumors (including non-Hodgkin lymphomas, histiocytoses and CNS involvement) harboring specified defects in DNA damage repair genes. The primary endpoint will be objective response rate (ORR; complete response + partial response) as determined by RECIST. Progression free survival (PFS) will be assessed as a secondary endpoint. Olaparib tablet formulation will be given twice daily continuously, without break. A cycle will be 28 days. Because the pediatric dose of olaparib has not been established, there will be a limited dose finding phase consisting of the first 12 evaluable patients enrolled on study. Toxicity will be assessed and the pharmacokinetics of olaparib will be evaluated in the dose finding cohorts. [redacted]

3.0 SCREENING AND STUDY ENROLLMENT PROCEDURES

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

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

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

3.1 Genetic Screening Procedures for Eligibility

Patient enrollment onto the APEC1621SC screening protocol is required. Tumor and blood samples will be obtained and the results of the evaluation of the tumor specimens will determine if the patient's tumor has an actionable Mutation of Interest (aMOI) for which a MATCH treatment subprotocol is available.

The treatment assignment to MATCH to a subprotocol will be communicated to the enrolling institution via the COG or MATCHBox treatment assignment mechanism at the time the results of MATCH are returned, upon which a reservation to APEC1621H 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 APEC1621H.

3.2 IRB Approval

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

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

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

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

Specific Worksheet for Local Context (SSW) to the CIRB (via IRBManager) to indicate their intention to open the study locally. The CIRB's approval of the SSW is then communicated to the CTSU Regulatory Office for compliance in the RSS. The Signatory Institution must inform the CTSU which CIRB-approved institutions aligned with the Signatory Institution are participating in the study so that the study approval can be applied to those institutions. Other site registration requirements (e.g., laboratory certifications, protocol-specific training certifications, or modality credentialing) must be submitted to the CTSU Regulatory Office or compliance communicated per protocol instructions.

3.3 Informed Consent/Assent

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

3.4 Screening Procedures

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

3.5 Eligibility Checklist

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

3.6 Study Enrollment

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

Patients must be enrolled within 8 weeks (56 days) of treatment assignment. Protocol therapy must start no later than 7 calendar days after the date of enrollment. Patients enrolling onto APEC1621H will have a COG ID obtained through their prior enrollment onto the screening protocol or from a prior COG study.

Note: No starter supplies will be provided. Drug orders of olaparib should be placed with CTEP after enrollment and treatment assignment to APEC1621H with consideration for timing of processing and shipping to ensure receipt of drug supply prior to start of protocol therapy.

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

3.8 **Dose Assignment**
The dose will be assigned via OPEN at the time of study enrollment.

4.0 PATIENT ELIGIBILITY

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

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

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

4.1 Inclusion Criteria

4.1.1 APEC1621SC: Patient must have enrolled onto APEC1621SC and must have been given a treatment assignment to MATCH to APEC1621H based on the presence of an actionable mutation as outlined in Appendix VIII.

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

4.1.3 BSA: Patients must have a body surface area ≥ 0.65 m^2 at enrollment.

4.1.4 Disease Status:
Patients must have radiographically **measurable** disease (see Section 12) at the time of study enrollment. Patients with neuroblastoma who do not have measurable disease but have MIBG+ evaluable disease are eligible. Measurable disease in patients with CNS involvement is defined as tumor that is measurable in two perpendicular diameters on MRI and visible on more than one slice.

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

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

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

4.1.6 Prior Therapy

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

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

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

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

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

e. Hematopoietic growth factors: ≥ 14 days after the last dose of a long-acting growth factor (e.g. pegfilgrastim) or 7 days for short-acting

growth factor. For growth factors that have known adverse events occurring beyond 7 days after administration, this period must be extended beyond the time during which adverse events are known to occur. The duration of this interval must be discussed with the study chair and the study-assigned Research Coordinator.

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

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

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

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

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

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

k. Patients must not have received prior exposure to olaparib, veliparib, niraparib, rucaparib, talazoparib or other PARPi.

4.1.7 Organ Function Requirements

4.1.7.1 Adequate Bone Marrow Function Defined as:

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

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

patients will not be evaluable for hematologic toxicity.

4.1.7.2 Adequate Renal Function Defined as:

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

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

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

4.1.7.3 Adequate Liver Function Defined as:

i. Patients with solid tumors:

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

4.1.7.4 Adequate Coagulation Defined as:

- Activated partial thromboplastin time (aPTT) ≤ 1.5 × ULN
- INR ≤ 1.5.

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/human studies. Pregnancy tests must be obtained in girls who are post-menarchal. Women of child-bearing potential and their partners should agree to use two (2) highly effective forms of contraception throughout study participation and for at least one (1) month after the last dose of olaparib. Male study participants should avoid fathering a child or donating sperm during the study and for three (3) months after the last dose of olaparib.

4.2.2 Concomitant Medications

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

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

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

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

4.2.2.5 CYP3A/ CYP3A4 Agents: Patients who are currently receiving drugs that are strong and moderate inducers or inhibitors of CYP3A or CYP3A4 are not eligible. Strong inducers or inhibitors of CYP3A4 should be avoided from 21 days prior to enrollment to the end of the study. See Appendix II for a list of CYP3A4 agents.

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

4.2.4 Patient who are known to be serologically positive for human immunodeficiency virus (HIV).

4.2.5 Patients with known active hepatitis (i.e. Hepatitis B or C).

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

4.2.7 Patients with symptomatic uncontrolled brain metastases. A scan to confirm the absence of brain metastases is not required. The patient can receive a stable dose of corticosteroids before and during the study as long as these were started at least 4 weeks prior to enrollment. Patients with spinal cord compression unless considered to have received definitive treatment for this and evidence of clinically stable disease for 28 days.

4.2.8 Patients with known symptomatic Fanconi Anemia (FA), Ataxia-telangiectasia (A-T) Syndrome, Bloom syndrome (BS) and Nijmegen breakage syndrome (NBS) are not eligible (Asymptomatic carriers are acceptable).

4.2.9 Major surgery must not have occurred within 2 weeks prior to enrollment and patients must have recovered from any effects of any major surgery.

4.2.10 Patients who in the opinion of the investigator may not be able to comply with the

safety monitoring requirements of the study are not eligible.

5.0 TREATMENT PROGRAM

5.1 Overview of Treatment Plan

Treatment Schedule Table	
Days 1-28	Olaparib BID
Day 28	Evaluation

Olaparib will be given orally twice daily [redacted]. A cycle of therapy is considered to be 28 days. A cycle may be repeated up to a total duration of therapy of 2 years (maximum 26 cycles). Olaparib must only be used in accordance with the dosing recommendations in this protocol. Any dose or frequency of dosing that exceeds the dosing regimen specified in this protocol should be reported as an overdose. Adverse reactions associated with overdose should be treated symptomatically and should be managed appropriately.

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

Drug doses should be adjusted based on the BSA calculated from height and weight measured within 7 days prior to the beginning of each cycle and according to the dosing nomogram in Appendix IV. Patients should swallow the tablets as a whole and should not chew or crush them. If a patient vomits within 30 minutes after the dose of olaparib is administered, and all the tablets are intact and can be accounted for, that dose may be repeated once. Otherwise, the dose will be missed.

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

[redacted]

[redacted]

[redacted]

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

5.1.2 Intra-Patient Escalation
Intrapatient dose escalation is not allowed.

5.1.3 Therapy Delivery Map
See Appendix V for APEC1621H Therapy Delivery Map

5.2 Criteria for Starting Subsequent Cycles

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

5.3 Grading of Adverse Events

Adverse events (toxicities) will be graded according to 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. The DLT evaluation period for the purpose of dose escalation will be cycle 1 of therapy.

5.4.1 Non-Hematological Dose-Limiting Toxicity

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

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

- Grade 3 hypophosphatemia, hypokalemia, hypocalcemia or hypomagnesemia responsive to supplementation

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

5.4.2 Hematological dose limiting toxicity

5.4.2.1 Hematological dose limiting toxicity is defined as:

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

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

6.0 DOSE MODIFICATIONS FOR ADVERSE EVENTS

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

6.1 Dose Modifications for Hematological Toxicity

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

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

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

6.2 Dose Modifications for Non-Hematological Toxicity

6.2.1 If a patient experiences non-hematological dose-limiting toxicity as defined in Section 5.4.1, the treatment will be held. When the toxicity resolves to meet

eligibility parameters or baseline within 14 days of drug discontinuation, the patient may resume treatment at a reduced dose as outlined in the dosing nomogram (See Appendix IV). Doses reduced for toxicity will not be re-escalated, even if there is minimal or no toxicity with the reduced dose.

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

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

6.3 Dose Modifications for Pulmonary Toxicity

If new or worsening pulmonary symptoms (e.g., dyspnea) or radiological abnormalities occur in the absence of a clear diagnosis, an interruption in study treatment dosing is recommended and further diagnostic workup (including a high resolution CT scan) should be performed to exclude pneumonitis.

Following investigation, if no evidence of abnormality is observed on CT imaging and symptoms resolve, then study treatment can be restarted, if deemed appropriate by the investigator. If significant pulmonary abnormalities are identified, these need to be discussed with the Study Physician.

6.4 Dose Modification for Surgery

Study treatment should be stopped at least 3 days prior to planned surgery. After surgery study treatment can be restarted when the wound has healed. No stoppage of study treatment is required for any needle biopsy procedure.

6.5 Dose Interruption for Conditions Other than Toxicity

Interruptions should be kept as short as possible. If a patient cannot restart study treatment within 14 days for resolution of an intercurrent condition not related to disease progression or toxicity, the patient must be removed from protocol therapy.

7.0 SUPPORTIVE CARE AND OTHER CONCOMITANT THERAPY

7.1 Concurrent Anticancer Therapy

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

7.2 Investigational Agents

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

7.3 Supportive Care

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

7.4 Growth Factors

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

7.5 Concomitant Medications

7.5.1 CYP3A4/5 inhibitors or inducers: *In vivo* data indicate that CYP3A4/5 is important for olaparib metabolism and clearance in humans. For this reason, avoid concomitant administration of strong and moderate CYP 3A4/5 inducers and inhibitors. Strong CYP3A4/5 inhibitors such as ketoconazole, itraconazole, clarithromycin, atazanavir, indinavir, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, and voriconazole are not permitted on study. Strong CYP3A4/5 inducers (such as rifampin, dexamethasone, phenytoin, carbamazepine, rifabutin, rifapentine, phenobarbital, and St John's wort), grapefruit, and grapefruit juice are not permitted on study. (See Appendix II). Note: Dexamethasone for CNS tumors or metastases, on a stable dose, is allowed.

7.5.2 Strong or moderate CYP3A inhibitors: Known strong CYP3A inhibitors (e.g., itraconazole, telithromycin, clarithromycin, boosted protease inhibitors, indinavir, saquinavir, nelfinavir, boceprevir, telaprevir) or moderate CYP3A inhibitors (ciprofloxacin, erythromycin, diltiazem, fluconazole, verapamil) should not be taken with olaparib.

If there is no suitable alternative concomitant medication then the dose of olaparib should be reduced by at least 25% and rounded down to the nearest tablet size for the period of concomitant administration.

7.5.3 Strong or moderate CYP3A inducers: Strong and moderate CYP3A inducers should not be taken with olaparib. (See Appendix II for list of agents)

7.5.4 *In vitro* data shows olaparib is a substrate for P-glycoprotein (P-gp). Administration of strong P-gp inhibitors and inducers should be avoided with concurrent olaparib.

7.5.5 Based on *in vitro* data, olaparib inhibits CYP 3A4 and UGT1A1 enzyme systems and induces CYP 1A2, 2B6, and 3A4 and potentially induces CYP 2C9, 2C19 and P-gp. Therefore, avoid concomitant administration of sensitive substrates, particularly those with narrow therapeutic ranges.

7.5.4 Olaparib is also an inhibitor of P-gp, OATP1B1, OCT1, OCT2, OAT3, multi-drug and toxin extrusion proteins (MATE1 and MATE2K) and a weak inhibitor of BRCP. *In vitro* studies suggest that olaparib may increase exposure of substrates of these transport systems, although the clinical relevance is not clear. The manufacturer recommends that statins, in particular, should be administered with caution when given concomitantly with olaparib.

7.5.6 Patients who are taking warfarin may participate in this trial; however, it is recommended that international normalized ratio (INR) be monitored carefully at least once per week for the first month, then monthly if the INR is stable. Subcutaneous heparin and low molecular weight heparin are permitted.

7.6 Nausea and Vomiting

No routine prophylactic anti-emetic treatment is required at the start of study treatment, however, patients should receive appropriate anti-emetic treatment at the first onset of nausea or vomiting and as required thereafter, in accordance with local treatment practice guidelines. Alternatively, olaparib tablets can be taken with a light meal/snack.

8.0 EVALUATIONS/MATERIAL AND DATA TO BE ACCESSIONED

8.1 Required Clinical, Laboratory and Disease Evaluation

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

STUDIES TO BE OBTAINED	Pre-Study	During Cycle 1	Prior to Subsequent Cycles^
History	X	Weekly	X
Physical Exam with vital signs	X	Weekly	X
Neurologic Exam	X		
Height, weight, BSA	X		X
Performance Status	X		
Pregnancy Test[1]	X		
CBC, differential, platelets	X	Twice Weekly (every 3 to 4 days)[2,3]	Weekly[2,3]
Urinalysis	X		
Electrolytes including Ca^{++}, PO_4, Mg^{++}	X	Weekly	X
Creatinine, ALT, bilirubin	X	Weekly	X
Albumin	X		X
aPTT/INR	X		
Tumor Disease Evaluation[4-A,4-B, 4-C]	X		Every other cycle x 3 then q 3 cycles [4]
Bone Marrow Aspirate and/or biopsy[5,6]	X[6]		
Patient Diary[7]		Weekly	X
Pharmacokinetics (Optional) [8]	X	X	
Circulating Tumor DNA (ctDNA-optional)[9]			Cycle 5, Day 1 and 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 3 or greater thrombocytopenia then CBCs should be checked every 3 to 4 days until recovery per section 6.1.

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

[4-A] Neurological exam is also required for CNS patients.

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

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

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

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

7. Patient diary (see Appendix III) should be reviewed weekly during cycle 1, 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; at progression or end of protocol therapy) see Section 8.4 for details of the ctDNA studies. Note that a ctDNA sample is scheduled to be obtained on the APEC1621SC screening protocol prior to the initiation of treatment on this subprotocol.

8.2 Radiology Studies

8.2.1 Central Radiology Review for Response:

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

8.2.2 Technical Details of Submission:

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

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

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

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

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

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

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

TRIAD Installations:

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

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

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

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

For FDG-PET imaging, the transferred imaging data should include uncorrected

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

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

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

8.3 Pharmacology (optional)

8.3.1 Description of Studies and Assay

Pharmacokinetics (PK) will be performed to determine the PK of olaparib 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:

Blood Sample No.	Time Point	Scheduled Collection Time
1	Cycle 1, Day 1	Pre-dose
Cycle 1 Day 1 AM Dose		
2	Cycle 1, Day 8	Pre-dose
Cycle 1 Day 8 AM Dose		
3	Cycle 1, Day 8	1 hr after AM dose
4	Cycle 1, Day 8	2 hrs after AM dose
5	Cycle 1, Day 8	4 hrs after AM dose
6	Cycle 1, Day 8	6-8 hrs after AM dose

* Please contact study chair or pharmacologist to adjust PK schedule if there are missed doses during days 1-7.

8.3.3 Sample Collection and Handling Instructions

Blood samples (2 ml) will be collected in 2 mL BD Vacutainer tubes containing Lithium Heparin as anti-coagulant for the analysis of olaparib. 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 studies 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. Within 30 minutes of blood collection. The sample will be centrifuged at 1500 x g for 10 minutes at 4° C. From each blood sample, transfer roughly equal volumes into a total of two 1.8ml polypropylene cryovials using a disposable polypropylene pipette.

Store plasma samples at -20°C in an upright position within 30 minutes of plasma preparation and keep frozen at this temperature until shipment.

8.3.5 Sample Labeling

Each sample must be labeled with the patient's study registration number, the study I.D# (APEC1621H), and the date and time the sample was drawn. Data should be recorded appropriate transmittal form found in RAVE.

8.3.6 Sample Shipping Instructions

Ship the aliquots frozen on dry ice. The samples must be securely packed in boxes to avoid breakage during transit, double-bagged to contain leaks, and where applicable, packed with a sufficient quantity of dry ice to ensure they remain frozen for at least 72 hours.

Sample Receiver:
Trish Hansen
Covance Laboratories
8211 SciCor Drive, Suite B
Indianapolis, IN46214
Phone: 317.715.3985
Fax: 317.616.2301
Email: Patricia.Hansen@covance.com
and IndyBioSA@Covance.com

8.4 Circulating Tumor DNA Study (optional)

8.4.1 Sampling Schedule

An initial sample was previously required at time of enrollment onto the pediatric MATCH screening protocol. Two additional samples (optional) will be collected into Streck Cell-Free DNA BCT tubes at the timepoints: (1) Cycle 5 Day 1
(2) At disease progression or end of protocol therapy

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 (APEC1621H), and the date and time the sample was drawn. Data should be recorded on the appropriate transmittal form found in RAVE.

8.4.4 Sample Shipping Instructions

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

Ship specimens to the following address:

Biopathology Center
Nationwide Children's Hospital
Protocol APEC1621H– Peds MATCH*
700 Children's Drive, WA1340
Columbus, OH 43205
Phone: (614) 722-2865
Fax: (614) 722-2897
Email:BPCBank@nationwidechildrens.org

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

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

9.0 AGENT INFORMATION

9.1 Olaparib

(Lynparza®, AZD2281, KU-0059436; CO-CE 42)
NSC# 747856 [redacted]

9.1.1 Structure and molecular weight

Chemical name: 4-[(3-{[4-(cyclopropylcarbonyl)piperazin-1-yl]carbonyl}-4-fluorophenyl)methyl]phthalazin-1(2*H*)-one

Molecular Formula: $C_{24}H_{23}FN_4O_3$ **Molecular Weight:** 434.46

9.1.2 Supplied by: Astrazeneca supplies and PMB, CTEP, DCTD, NCI distributes Olaparib.

9.1.3 Formulation

Olaparib is supplied as film-coated tablets in 25 mg, 100 mg and 150 mg strengths.

- 25 mg tablets are 6 mm round-shaped
- 100 mg tablets are 14.5 mm x 7.25 mm oval-shaped
- 150 mg are 14.5 mm x 7.25 mm oval-shaped

Tablets are packaged in induction-sealed high-density polyethylene (HDPE) bottles with child-resistant closures. Each bottle contains 32 tablets with desiccant.

Tablet core components include active drug substance, copovidone, colloidal silicon dioxide, mannitol and sodium stearyl fumarate. Film coating contains hydroxypropyl methylcellulose (hypromellose), macrogol 400 (polyethylene glycol 400), titanium dioxide, iron oxide yellow and iron oxide black.

9.1.4 Storage

Store in a secure location below 30° C (86° F).

If a storage temperature excursion is identified, promptly return olaparib 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

Shelf-life studies are ongoing. Sites are not permitted to re-package tablets. Once the bottle is opened, olaparib tablets must be used within 3 months of the opening date; unused tablets should be discarded. Use as few tablet sizes as possible. Instruct patients not to open a bottle until they are ready to use it.

9.1.6 Administration

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

Olaparib tablets should be administered orally twice a day without regard to meals. If a patient vomits within 30 minutes after the dose of olaparib is administered, and all the tablets are intact and can be accounted for, that dose may be repeated once. Otherwise, the dose will be missed.

9.1.7 Potential Drug Interactions

In vivo data indicate that CYP3A4/5 is important for olaparib metabolism and clearance in humans. For this reason, avoid concomitant administration of strong and moderate CYP 3A4/5 inducers and inhibitors. Consult the protocol document or study investigator prior to making any dose adjustments related to potential drug-drug interactions.

In vitro data shows olaparib is a substrate for P-glycoprotein (P-gp), but not for organic anion-transporting polypeptides (OATP1B1 and OATP1B3), organic cation transporter 1 (OCT1), multi-drug resistance protein 2 (MRP-2) efflux transporter or breast cancer resistance protein (BCRP). Administration of strong P-gp inhibitors and inducers should be avoided with concurrent olaparib.

Based on *in vitro* data, olaparib inhibits CYP 3A4 and UGT1A1 enzyme systems and induces CYP 1A2, 2B6, and 3A4 and potentially induces CYP 2C9, 2C19 and P-gp. Therefore, avoid concomitant administration of sensitive substrates, particularly those with narrow therapeutic ranges.

Olaparib is also an inhibitor of P-gp, OATP1B1, OCT1, OCT2, OAT3, multi-drug and toxin extrusion proteins (MATE1 and MATE2K) and a weak inhibitor of BRCP, but not an inhibitor of OATP1B3 or MRP-2. *In vitro* studies suggest that olaparib may increase exposure of substrates of these transport systems, although the clinical relevance is not clear. The manufacturer recommends that statins, in particular, should be administered with caution when given concomitantly with olaparib.

9.1.8 Patient Care Implications:

Pre-clinical data indicate that olaparib adversely affects embryofetal survival and development. Therefore, women of child-bearing potential and their partners should

agree to use two (2) highly effective forms of contraception throughout study participation and for at least one (1) month after the last dose of olaparib. Male study participants should avoid fathering a child or donating sperm during the study and for three (3) months after the last dose of olaparib. The study investigator should discuss the most appropriate forms of highly effective contraceptive methods for each patient.

Because the adverse events related to olaparib may include asthenia, fatigue and dizziness, patients should be advised to use caution while driving or using machinery.

9.1.9 Olaparib Toxicities

Comprehensive Adverse Events and Potential Risks list (CAEPR)
for
Olaparib (AZD2281, NSC 747856)

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 3449 patients*. Below is the CAEPR for Olaparib (AZD2281).

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 2.5, July 1, 2021[1]

Adverse Events with Possible Relationship to Olaparib (AZD2281) (CTCAE 5.0 Term) [n= 3449]			**Specific Protocol Exceptions to Expedited Reporting (SPEER)**
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
Anemia			***Anemia (Gr 4)***
		Febrile neutropenia	
GASTROINTESTINAL DISORDERS			
	Abdominal distension		
Abdominal pain			***Abdominal pain (Gr 3)***
	Constipation		***Constipation (Gr 2)***
Diarrhea			***Diarrhea (Gr 3)***
	Dyspepsia		***Dyspepsia (Gr 2)***
	Mucositis oral		
Nausea			***Nausea (Gr 3)***
Vomiting			***Vomiting (Gr 3)***
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			

Adverse Events with Possible Relationship to Olaparib (AZD2281) (CTCAE 5.0 Term) [n= 3449]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
	Edema limbs		
Fatigue			***Fatigue (Gr 3)***
IMMUNE SYSTEM DISORDERS			
		Allergic reaction	
INFECTIONS AND INFESTATIONS			
	Upper respiratory infection		
	Urinary tract infection		
INVESTIGATIONS			
	Creatinine increased		
	Neutrophil count decreased		***Neutrophil count decreased (Gr 4)***
		Platelet count decreased	
	White blood cell decreased		
METABOLISM AND NUTRITION DISORDERS			
Anorexia			***Anorexia (Gr 2)***
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			
	Arthralgia		
	Back pain		***Back pain (Gr 2)***
	Muscle cramp		
	Myalgia		
	Pain in extremity		
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)			
		Leukemia secondary to oncology chemotherapy	
		Myelodysplastic syndrome	
NERVOUS SYSTEM DISORDERS			
	Dizziness		***Dizziness (Gr 2)***
	Dysgeusia		***Dysgeusia (Gr 2)***
	Headache		***Headache (Gr 2)***
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
	Cough		***Cough (Gr 2)***
	Dyspnea		***Dyspnea (Gr 2)***
		Pneumonitis	
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
	Rash maculo-papular		
		Skin and subcutaneous tissue disorders - Other (angioedema)	
		Skin and subcutaneous tissue disorders - Other (erythema nodosum)	

NOTE: New Primary Malignancies other than MDS/AML

New primary malignancies have been reported in <1% of patients. There were other contributing factors/potential alternative explanations for the development of the new primary malignancy in all cases, including documented *BRCA* mutation, treatment with radiotherapy and extensive previous chemotherapy including carboplatin, taxanes, anthracyclines and other alkylating and DNA damaging agents. Most are not attributed to olaparib.

[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.

Adverse events reported on olaparib (AZD2281) trials, but for which there is insufficient evidence to suggest that there was a reasonable possibility that olaparib (AZD2281) caused the adverse event:

CARDIAC DISORDERS - Atrial fibrillation; Cardiac disorders - Other (nodal rhythm); Chest pain - cardiac; Sinus bradycardia; Sinus tachycardia
EAR AND LABYRINTH DISORDERS - Tinnitus
ENDOCRINE DISORDERS - Hypothyroidism
GASTROINTESTINAL DISORDERS - Ascites; Colitis; Colonic obstruction; Dry mouth; Dysphagia; Enterocolitis; Esophageal stenosis; Flatulence; Gastroesophageal reflux disease; Gastrointestinal disorders - Other (gastrointestinal hemorrhage); Gastrointestinal disorders - Other (intestinal obstruction); Gastrointestinal disorders - Other (intestinal perforation); Ileus; Jejunal perforation; Obstruction gastric; Pancreatitis; Periodontal disease; Rectal hemorrhage; Small intestinal obstruction; Stomach pain
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Death NOS; Fever; Malaise; Non-cardiac chest pain
IMMUNE SYSTEM DISORDERS - Immune system disorders - Other (systemic inflammatory response syndrome)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS - Dermatitis radiation; Fracture; Gastrointestinal anastomotic leak; Injury, poisoning and procedural complications - Other (vena cava injury); Wound dehiscence
INVESTIGATIONS - Alanine aminotransferase increased; Aspartate aminotransferase increased; Blood bilirubin increased; GGT increased; Hemoglobin increased; Lipase increased; Lymphocyte count decreased; Serum amylase increased; Weight loss
METABOLISM AND NUTRITION DISORDERS - Dehydration; Hyperglycemia; Hypermagnesemia; Hypocalcemia; Hypokalemia; Hypomagnesemia; Hyponatremia
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Avascular necrosis; Bone pain; Generalized muscle weakness; Muscle weakness lower limb; Muscle weakness upper limb; Neck pain; Rotator cuff injury; Soft tissue necrosis lower limb
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS) - Treatment related secondary malignancy; Tumor pain
NERVOUS SYSTEM DISORDERS - Amnesia; Ataxia; Cognitive disturbance; Concentration impairment; Encephalopathy; Intracranial hemorrhage; Peripheral sensory neuropathy; Reversible posterior leukoencephalopathy syndrome; Stroke; Syncope; Transient ischemic attacks
PSYCHIATRIC DISORDERS - Anxiety; Confusion; Delirium; Hallucinations; Insomnia
RENAL AND URINARY DISORDERS - Acute kidney injury; Renal and urinary disorders - Other (decreased glomerular filtration rate); Renal and urinary disorders - Other (hydronephrosis); Urinary tract obstruction
REPRODUCTIVE SYSTEM AND BREAST DISORDERS - Vaginal hemorrhage
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Bronchopulmonary hemorrhage; Hypoxia; Oropharyngeal pain; Pleural effusion; Respiratory failure; Respiratory, thoracic and mediastinal disorders - Other (chronic obstructive pulmonary disease)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Alopecia; Erythema multiforme; Pruritus
VASCULAR DISORDERS - Arterial thromboembolism; Flushing; Hot flashes; Hypertension; Hypotension; Peripheral ischemia; Thromboembolic event

Note: Olaparib (AZD2281) in combination with other agents could cause an exacerbation of any adverse event currently known to be caused by the other agent, or the combination may result in events never previously associated with either agent.

9.2 Agent Ordering and Agent Accountability

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

Note: No starter supplies will be provided **Drug orders of olaparib should be placed with CTEP after enrollment and treatment assignment to APEC1621H with consideration for timing of processing and shipping to ensure receipt of drug supply prior to start of protocol therapy**. If expedited shipment is required, sites should provide an express courier account through the Online Agent Order Processing (OAOP) application. Provide the patient ID number in the comment box when submitting an order request.

9.3 Clinical Drug Request and Investigator Brochure Availability

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

9.4 Agent Inventory Records

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

9.4.1 Useful Links and Contacts

- CTEP Forms, Templates, Documents: http://ctep.cancer.gov/forms/
- NCI CTEP Registration: RCRHelpDesk@nih.gov
- PMB policies and guidelines: http://ctep.cancer.gov/branches/pmb/agent_management.htm

- PMB Online Agent Order Processing (OAOP) application: https://ctepcore.nci.nih.gov/OAOP
- CTEP Identity and Access Management (IAM) account: https://ctepcore.nci.nih.gov/iam/
- CTEP IAM account help: ctepreghelp@ctep.nci.nih.gov
- PMB email: PMBAfterHours@mail.nih.gov
- PMB phone and hours of service: (240) 276-6575
  Monday through Friday between 8:30 am and 4:30 pm (ET)
- PMB IB Coordinator: IBcoordinator@mail.nih.gov
- Registration and Credential Repository (RCR): https://ctepcore.nci.nih.gov/rcr/

10.0 CRITERIA FOR REMOVAL FROM PROTOCOL THERAPY AND OFF STUDY CRITERIA

10.1 Criteria for Removal from Protocol Therapy

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

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

10.2 Follow-Up Data Submission and APEC1621SC Off Study Criteria

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

via RAVE and CTEP-AERS (if applicable). Follow-up data will be required until off study criteria are met unless consent is withdrawn or the patient dies or is lost to follow-up.

11.0 STATISTICAL AND ETHICAL CONSIDERATIONS

11.1 Sample Size and Study Duration

[redacted] Assuming an enrollment rate of 4-6 biomarker positive patients per year, this subprotocol is expected to be completed within 8-12 years.

11.2 Dosing Considerations

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

Please see Section 5.1 for a specific discussion of the dosing of olaparib to be used in this study. As there is no prior pediatric phase 1 data for olaparib, study investigators have reviewed relevant data with the pharmaceutical partner to identify a drug specific dosing plan for testing in children with relapsed/refractory cancer, and trial participants will be closely monitored to ensure tolerability of the selected dose. Limited pharmacokinetic sampling may be done for patients enrolled on these arms. [redacted]

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

[redacted] The DLT evaluation period for the purpose of dose escalation will be cycle 1 of therapy. Note that adverse events that begin during cycle 1 and specify a duration of time in order to be considered a DLT must be followed to resolution or until the definition of DLT has been met, regardless of the schedule end of cycle 1 (e.g. grade 2 thrombocytopenia would be considered a DLT if it developed during cycle 1 of therapy and caused, or would have caused, a delay of >14 days to begin cycle 2).

Enrollment of the initial cohort of up to six patients will follow the standard rules of the rolling six design [31] to assess safety and tolerability of cycle one of protocol treatment prior to extending accrual to additional patients.

The rolling six phase 1 trial design will be used for the conduct of this study. Two to six patients can be concurrently enrolled onto a dose level, dependent upon (1) the number of patients enrolled at the current dose level, (2) the number of patients who have experienced DLT at the current dose level, and (3) the number of patients entered but with tolerability data pending at the current dose level. Accrual is suspended when a cohort of six has enrolled or when the study endpoints have been met.

Dose level assignment is based on the number of participants currently enrolled in the cohort, the number of DLTs observed, and the number of participants at risk

for developing a DLT (i.e., participants enrolled but who are not yet assessable for toxicity). For example, when three participants are enrolled onto a dose cohort, if toxicity data is available for all three when the fourth participant entered and there are no DLTs, the dose is escalated and the fourth participant is enrolled to the subsequent dose level. If data is not yet available for one or more of the first three participants and no DLT has been observed, or if one DLT has been observed, the new participant is entered at the same dose level. Lastly, if two or more DLTs have been observed, the dose level is de-escalated. This process is repeated for participants five and six. In place of suspending accrual after every three participants, accrual is only suspended when a cohort of six is filled. When participants are inevaluable for toxicity, they are replaced with the next available participant if escalation or de-escalation rules have not been fulfilled at the time the next available participant is enrolled onto the study.

The following table provides the decision rules for enrolling a patient at (i) the current dose level (ii) at an escalated dose level, (iii) at a de-escalated dose level, or whether the study is suspended to accrual:

# Pts Enrolled	# Pts with DLT	# Pts without DLT	# Pts with Data Pending	*Decision*
2	0 or 1	0, 1 or 2	0, 1 or 2	Same dose level
2	2	0	0	De-escalate*
3	0	0, 1 or 2	1, 2 or 3	Same dose level
3	1	0, 1 or 2	0, 1 or 2	Same dose level
3	0	3	0	Escalate**
3	≥ 2	0 or 1	0 or 1	De-escalate*
4	0	0, 1, 2 or 3	1, 2, 3 or 4	Same dose level
4	1	0, 1, 2 or 3	0, 1, 2 or 3	Same dose level
4	0	4	0	Escalate**
4	≥ 2	0, 1 or 2	0, 1 or 2	De-escalate*
5	0	0, 1, 2, 3 or 4	1, 2, 3, 4 or 5	Same dose level
5	1	0, 1, 2, 3 or 4	0, 1, 2, 3 or 4	Same dose level
5	0	5	0	Escalate**
5	≥ 2	0, 1, 2 or 3	0, 1, 2 or 3	De-escalate*
6	0	0, 1, 2, 3, or 4	2, 3, 4, 5 or 6	Suspend
6	1	0, 1, 2, 3 or 4	0, 1, 2, 3 or 4	Suspend
6	0 or 1	5 or 6	0 or 1	Escalate**
6	≥ 2	0, 1, 2, 3 or 4	0, 1, 2, 3 or 4	De-escalate*

* If six patients already entered at next lower dose level, the MTD has been defined.
**If final dose level has been reached, the recommended dose has been reached.

If two or more of a cohort of up to six patients experience DLT at a given dose level, then dose escalation will be stopped.

In addition to determination of the RP2D, a descriptive summary of all toxicities will be reported.

11.3 Study Design

The primary cohort will employ a single stage A'Hern design of N=20. The agent will be

deemed worthy of further study in the relevant subset of patients (i.e. biomarker positive in any histology, biomarker positive in a particular histology, etc) if the decision rule is met. Operating characteristics are shown below.

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

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

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

11.3.1 **Primary Cohort**:

APEC1621H will evaluate a primary cohort of 20 mutation-matched ("biomarker positive") evaluable patients of any histology for the primary study aim of determining the objective response rate (CR/PR according to the response criteria in Section 12.3) to olaparib. Using an A'Hern design[32] with alpha=10%, a sample of N=20 will provide 90% power to detect an improvement in response rate from 5%, if the treatment is ineffective, to 25% if the targeted therapy is sufficiently effective to warrant further study. If there are at least 3 responses out of 20 in the primary cohort, the biomarker/therapy match will be deemed a success.

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

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

We will open up to 3 such expansion cohorts for biomarker positive patients (i.e., if 3 histologies have ≥ 3 responses, we will open a total of 3 expansion cohorts as described above). Note that this can only happen if the response rate in the primary cohort is at least 45% (9/20) and there cannot be more than 21 additional evaluable patients in total for these expansion cohorts.

11.4 Methods of Analysis

Response criteria are described in Section 12. A responder is defined as a patient who achieves a best response of PR or CR on the study. Response rates will be calculated as the percent of evaluable patients who are responders, and confidence intervals will be constructed using the Wilson score interval method.[33] 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 will be considered evaluable for response Patients who are not evaluable for response evaluation may be replaced for the purposes of the statistical rule. Patients who demonstrate a complete or partial response confirmed by central review will be considered to have experienced a response. When opening expansion cohorts, the evaluation period for determination of best response will be 6 treatment cycles. All other patients will be considered non-responders. Patients who are not evaluable for response evaluation may be replaced for the purposes of the statistical rule. All patients considered to have a response (CR or PR) must have imaging studies reviewed centrally at the COG. Centers will be notified by the COG about requests for scans of patients with stable disease. Preliminary assessment of activity using institutionally provided tumor measurements will be entered into CDUS quarterly. The central review by COG will be provided as the final reviewed assessment of response when such becomes available.

11.6 Evaluability for Toxicity

Any eligible patient who receives at least one dose of the study drug(s) or who experiences a dose-limiting toxicity is considered evaluable for Adverse Events. In addition, for the dose-escalation portion during Cycle 1, patients without DLT who receive at least 85% of the prescribed dose per protocol guidelines and must have the appropriate toxicity monitoring studies performed during cycle 1 to be 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	1	1	0	0	2
Native Hawaiian or Other Pacific Islander	0	0	0	0	0
Black or African American	3	5	0	0	8
White	12	20	4	2	38
More than one race	1	0	0	0	1
Total	17	26	4	2	49

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

12.0 EVALUATION CRITERIA

12.1 Common Terminology Criteria for Adverse Events v5.0 (CTCAE)

The descriptions and grading scales found in the current version of the NCI Common Terminology Criteria for Adverse Events 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. In addition to the scheduled scans, a confirmatory scan should be obtained on the next consecutive cycle following initial documentation of objective response.

As outlined, patients will be assigned to one of the following categories for assessment of

response: a) solid tumor (non-CNS) and measurable disease (Section 12.4); b) neuroblastoma with MIBG positive lesions (Section 12.5); c) CNS tumor (Section 12.7); and d) non-Hodgkin lymphoma/hystiocytosis (Section 12.8). Note: Neuroblastoma patients who do not have MIBG positive lesions should be assessed for response as solid tumor patients with measurable disease.

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

12.3.1 Definitions

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

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

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.[34]

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

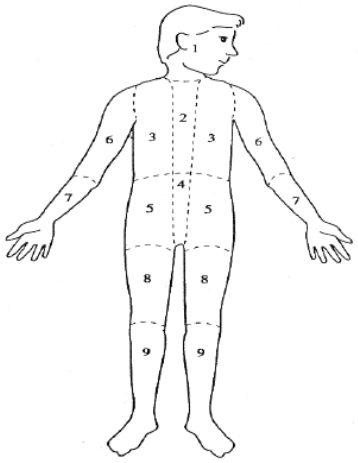
for study endpoint. See Section 8.2 for details on transferring images to the Imaging Research Center.

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

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

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

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

12.7.5 Response Criteria for Non-Target Lesions:

- **Complete Response (CR):** Disappearance of all non-target lesions.

- **Incomplete Response/Stable Disease (IR/SD):** The persistence of one or more non-target lesions.

- **Progressive Disease (PD):** The appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions.

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

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

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

PD	Any	Any	Yes or No	**PD**
Any	PD	Any	Yes or No	**PD**
Any	Any	Any	Yes	**PD**

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

12.8 Response Criteria for Patients with non-Hodgkin Lymphoma/Histiocytosis

Response and progression will be evaluated in this study using the new international criteria proposed by the revised Response Evaluation Criteria in Pediatric non-Hodgkin Lymphoma Criteria, with modification from the Lugano classification. [35 33 35 34]

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)[35]

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[35]

Complete Response (CR): Regress to normal

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

Stable Disease (SD): No increase consistent with progression

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

New or recurrent splenomegaly

12.9 **Best Response**
Two objective status determinations of disease status, obtained on two consecutive determinations, separated by at least a 3 week time period, are required to determine the patient's overall best response. Two objective status determinations of CR before progression are required for best response of CR. Two determinations of PR or better before progression, but not qualifying for a CR, are required for a best response of PR. Two determinations of stable/no response or better before progression, but not qualifying as CR or PR, are required for a best response of stable/no response; if the first objective status is unknown, only one such determination is required. Patients with an objective

status of progression on or before the second evaluations (the first evaluation is the first radiographic evaluation after treatment has been administered) will have a best response of progressive disease. Best response is unknown if the patient does not qualify for a best response of progressive disease and if all objective statuses after the first determination and before progression are unknown.

12.9.1 Evaluation of Best Overall Response

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

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

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

12.9.2 Duration of Response

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

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

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

13.0 ADVERSE EVENT REPORTING REQUIREMENTS

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

about expedited reporting.

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

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

13.1 Expedited Reporting Requirements – Serious Adverse Events (SAEs)

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

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

13.1.1 Reporting Requirements - Investigator Responsibility

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

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

13.1.2 CTEP-AERS Expedited Reporting Methods

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

Send supporting documentation to the NCI by fax (fax# 301-897-7404) and by

email to both COGCAdEERS@childrensoncologygroup.org and to the APEC1621H COG Study Assigned Research Coordinator. **ALWAYS include the ticket number on all faxed and emailed documents**.

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

Step 1: Identify the type of adverse event using the current version of the NCI CTCAE V 5.0. The descriptions and grading scales found in the current version of the CTCAE v5.0 will be used for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE v5.0. A copy of the CTCAE v5.0 can be downloaded from the CTEP website (http://ctep.cancer.gov).

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

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.

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

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

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

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

Category	Adverse Events
GASTROINTESTINAL DISORDERS	Abdominal Distension
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	Edema limbs
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	Fever
INFECTIONS AND INFESTATIONS	Infection
INVESTIGATIONS	Creatinine increased
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	Arthralgia
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	Back pain

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

- MDS/AML, new primary malignancy (other than MDS/AML) and pneumonitis must be reported via CTEP-AERS

13.4 Definition of Onset and Resolution of Adverse Events

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

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

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

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

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

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

13.5 Other Recipients of Adverse Event Reports

13.5.1 Events that do not meet the criteria for CTEP-AERS reporting (Section 13.2)

should be reported at the end of each cycle using the forms provided in the CRF packet (See Section 14.1).

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

13.6 Specific Examples for Expedited Reporting

13.6.1 Reportable Categories of Death

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

13.6.2 Reporting Secondary Malignancy

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

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)-897-7404. The potential risk of exposure of the fetus to the investigational agent should be documented in the "Description of Event" section of the CTEP-AERS report.

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

Pregnancy needs to be followed **until the outcome of the pregnancy is known** at intervals deemed appropriate by her physicians. The "Pregnancy Information Form" should be used for all necessary follow-ups. If the baby is born with a birth defect or anomaly, then a second CTEP-AERS report is required.

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

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

Death Neonatal
Neonatal death, defined in 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.

13.6.4 Reporting of Study Drug Overdose

Study drug overdose refers to the uses of the study drug outside of that specified by the protocol.

- Overdose: Accidental or intentional use of the study drug in an amount higher than the protocol defined dose.

Any study drug overdose should be reported on the Reporting Period-Dosing CRF. All AEs associated with an overdose should be entered both on the Reporting Period CRF and reported expeditiously using the CTEP-AERS.

14.0 RECORDS, REPORTING, AND DATA AND SAFETY MONITORING PLAN

14.1 Categories of Research Records

Research records for this study can be divided into three categories

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

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

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

See separate CRF Packet, which includes submission schedule.

14.2 CDUS

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

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

14.3 CRADA/CTA/CSA

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

The agent(s) supplied by CTEP, DCTD, NCI used in this protocol is/are provided to the NCI under a Collaborative Agreement (CRADA, CTA, CSA) between the Pharmaceutical Company(ies) (hereinafter referred to as "Collaborator(s)") and the NCI Division of Cancer

Treatment and Diagnosis. Therefore, the following obligations/guidelines, in addition to the provisions in the "Intellectual Property Option to Collaborator" (http://ctep.cancer.gov/industryCollaborations2/intellectual_property.htm) contained within the terms of award, apply to the use of the Agent(s) in this study:

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

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

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

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

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

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

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

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

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

   Email: ncicteppubs@mail.nih.gov

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

14.4 Data and Safety Monitoring Plan

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

14.4.1 Data and Safety Monitoring Committee

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

14.4.2 Monitoring by the Study Chair and MATCH Leadership

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

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

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

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

APPENDIX III: MEDICATION DIARY FOR OLAPARIB

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

Complete each day with the time and dose given for olaparib. You should take olaparib doses twice a day, at about the same time each day, without regard to meals with no less than 8 hours between each dose. If a dose is accidentally skipped leave that dose time blank. If you vomit within 30 minutes after taking olaparib tablets, the dose can be repeated once. This should be noted in the comments section below. ***Make note of other drugs and supplements taken under the Comments section below***. Olaparib tablets should not be broken or crushed but should be swallowed whole. Add the dates and times 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 olaparib tablets*			*Comments*
	Date	*Time*	25 mg	100 mg	150 mg	
Day 1	*1/15/19*	*8:30 AM*	1	1		*He felt nauseated an hour after taking the drug but did not vomit.*

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

End Date: |__/__|__/__|__/__| **Dose Level:** _____mg/m^2/

WEEK 1	Date	Time		# of olaparib tablets prescribed to take 25 mg AM# PM#___ 100 mg AM# PM#___ 150 mg AM# PM#___ # of olaparib tablets taken 25 mg	100 mg	150 mg	Comments (Describe any missed or extra doses, vomiting and/or bothersome effects.)
Day 1			AM				
			PM				
Day 2			AM				
			PM				
Day 3			AM				
			PM				
Day 4			AM				
			PM				
Day 5			AM				
			PM				
Day 6			AM				
			PM				
Day 7			AM				
			PM				

WEEK 2	Date	Time		# of olaparib tablets prescribed to take 25 mg AM# PM#___ 100 mg AM# PM#___ 150 mg AM# PM#___ # of olaparib tablets taken 25 mg	100 mg	150 mg	Comments (Describe any missed or extra doses, vomiting and/or bothersome effects.)
Day 8			AM				
			PM				
Day 9			AM				
			PM				
Day 10			AM				
			PM				
Day 11			AM				
			PM				
Day 12			AM				
			PM				
Day 13			AM				
			PM				
Day 14			AM				
			PM				
WEEK 3	Date	Time		# of olaparib tablets prescribed to take 25 mg AM# PM#___ 100 mg AM# PM#___ 150 mg AM# PM#___ # of olaparib tablets taken 25 mg	100 mg	150 mg	Comments (Describe any missed or extra doses, vomiting and/or bothersome effects.)
Day 15			AM				
			PM				
Day 16			AM				
			PM				
Day 17			AM				
			PM				
Day 18			AM				
			PM				
Day 19			AM				
			PM				
Day 20			AM				
			PM				
Day 21			AM				
			PM				

WEEK 4	Date	Time		# of olaparib tablets prescribed to take 25 mg AM# PM#___ 100 mg AM# PM#___ 150 mg AM# PM#___ # of olaparib tablets taken 25 mg	100 mg	150 mg	Comments (Describe any missed or extra doses, vomiting and/or bothersome effects.)
Day 22			AM				
			PM				
Day 23			AM				
			PM				
Day 24			AM				
			PM				
Day 25			AM				
			PM				
Day 26			AM				
			PM				
Day 27			AM				
			PM				
Day 28			AM				
			PM				

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

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

[redacted]

APPENDIX V: APEC1621H 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
Olaparib IND # 134661	PO	[redacted]	1-28	Drug doses should be adjusted based on the BSA calculated from height and weight measured within 7 days prior to the beginning of each cycle and according to the dosing nomogram in Appendix IV. Patients should swallow the tablets as a whole and should not chew or crush them. If a patient vomits within 30 minutes after the dose of olaparib is administered, and all the tablets are intact and can be accounted for, that dose may be repeated once. Otherwise, the dose will be missed.

Ht _____cm Wt _____kg BSA _____m^2

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

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. For information related to prestudy observations please refer to Section 8.1. Studies on Day 28/1 may be obtained within 72 hours prior to the start of the subsequent cycle.

a.	**History/Physical Exam (including VS)**
b.	**Ht/Wt/BSA**
c.	**CBC/differential/platelets**- If patients have Grade 4 neutropenia then CBCs should be checked at least every other day until recovery to Grade 3 or until meeting the criteria for dose limiting toxicity. If patients develop Grade 3 or greater thrombocytopenia then CBCs should be checked every 3 to 4 days until recovery per section 6.1.
d.	**Electrolytes** including Ca++, PO4, Mg++
e.	**Creatinine, ALT, bilirubin**
f.	**Albumin**
g.	**Patient Diary**- (see Appendix III) should be reviewed after completion of each treatment cycle and uploaded into RAVE. The patient diary should be collected weekly.
h.	**Pharmacokinetics (optional)**-see Section 8.3 for details of PK studies.

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

Comments (Include any held doses, or dose modifications)

Treatment Details: Cycle 1

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

Cycle 1

All Subsequent Cycles

Therapy Delivery Map – All Subsequent Cycles

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

_____
Patient COG ID number

_____
Accession number

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

DRUG	ROUTE	DOSAGE	DAYS	IMPORTANT NOTES
Olaparib IND # 134661	PO	[redacted]	1-28	Drug doses should be adjusted based on the BSA calculated from height and weight measured within 7 days prior to the beginning of each cycle and according to the dosing nomogram in Appendix IV. Patients should swallow the tablets as a whole and should not chew or crush them. If a patient vomits within 30 minutes after the dose of olaparib is administered, and all the tablets are intact and can be accounted for, that dose may be repeated once. Otherwise, the dose will be missed.

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

Date Due	Date Given	Day	**Olaparib** _____ mg	Studies
			Enter calculated dose above as per dosing nomogram and actual dose administered below	
		1	_____ mg AM _____ mg PM	a-f, h
		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, g* h, i*

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

* Please refer to Section 8.1 for the specific timing of these observations. Studies on Day 28/1 may be obtained within 72 hours prior to the start of the subsequent cycle.

Required Observations in All Subsequent Cycles

a.	**History/Physical Exam (including VS)**
b.	**Ht/Wt/BSA**
c.	**CBC/differential/platelets** If patients have Grade 4 neutropenia then CBCs should be checked at least every other day until recovery to Grade 3 or until meeting the criteria for dose limiting toxicity. If patients develop Grade 3 or greater thrombocytopenia then CBCs should be checked every 3 to 4 days until recovery per section 6.1.
d.	**Electrolytes including Ca++, PO4, Mg++**
e.	**Creatinine, ALT, bilirubin**
f.	**Albumin**
g.	**Tumor Disease Evaluation** – Every other cycle x 2 then q 3 cycles. Tumor Disease Evaluation should be obtained on the next consecutive cycle after initial documentation of either a PR or CR. Subsequent scans may restart 2 cycles after the confirmatory scan. If the institutional investigator determines that the patient has progressed based on clinical or laboratory evidence, he/she may opt not to confirm this finding radiographically
h.	**Patient Diary**- (see Appendix III) should be reviewed after completion of each treatment cycle and uploaded into RAVE.
i.	**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.
j.	**Bone Marrow Aspirate and/or biopsy-** Bone marrow aspirate and/or biopsy should only be performed only when complete response or partial response is identified in target disease or when progression in bone marrow is suspected.

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

Comments (Include any held doses, or dose modifications)

Treatment Details: Subsequent Cycles

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

APPENDIX VI: TARGET HISTOLOGIES FOR APEC1621H EXPANSION COHORTS

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

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

APPENDIX VII CORRELATIVE STUDIES

Correlative Study	Section	Blood Volume		Tube Type
		Volume per Sample	Total Cycle 1	
Pharmacokinetics	8.3	2 mL	12 mL	2 mL BD Vacutainer tubes containing Lithium Heparin
Total Blood Volume in Cycle 1			**12 mL**	

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

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

APPENDIX VIII: APEC1621H ACTIONABLE MUTATIONS OF INTEREST

NON-HOTSPOT	**RULES**		
Gene Name	Description	Variant Type	LOE
BRCA1	Include	Deleterious	1
BRCA2	Include	Deleterious	1
ATM	Include	Deleterious	1
RAD51C	Include	Deleterious	2
RAD51D	Include	Deleterious	2

APPENDIX IX APEC1621H PATIENT DRUG INFORMATION HANDOUT AND WALLET CARD

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

The patient _____ is enrolled on a clinical trial using the experimental study drug, **olaparib (AZD2281).** This clinical trial is sponsored by the National Cancer Institute (NCI). This form is addressed to the patient, but includes important information for others who care for this patient.

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

Olaparib interacts with certain specific enzymes in the liver and certain transport proteins that help move drugs in and out of cells.

- The enzymes in question are CYP 3A4/5, 1A2, 2B6, 2C9, 2C19 and UGT1A1. Olaparib is cleared by CYP3A4/5 and is affected by strong and moderate inhibitors and inducers of CYP3A4/5. Olaparib inhibits CYP3A4 and UGT1A1enzymes and may increase levels of other drugs that are cleared by these enzymes. Olaparib induces CYP 1A2, 2B6 and 3A4 enzymes and has the possibility of inducing CYP 2C9, 2C19 enzymes that may result in decreased levels of other drugs that are cleared by these enzymes.
- The transport proteins in question are P-glycoprotein (P-gp), organic anion-transporting polypeptides (OATP1B1 and OAT3), organic cation transporters (OCT1 and OCT2), multi-drug and toxin extrusion proteins (MATE1 and MATE2K) and breast cancer resistance protein (BCRP). Olaparib requires P-gp to move in and out of cells and concomitant administration of strong P-gp inhibitors and inducers should be avoided. Olaparib inhibits P-gp, BCRP, OATP1B1, OCT1, OCT2, OAT3, MATE1 and MATE2K transporters and has the possibility of inducing P-gp and that may affect the transport of other drugs that depend on these proteins to move in and out of cells. Use caution when taking substrates of these transporters, such as statins.

November 2015

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

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

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

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

Olaparib must be used very carefully with other medicines that need certain liver enzymes and transport proteins to be effective or to be cleared from your system. Before you enroll onto the clinical trial, your study doctor will work with your regular health care providers to review any medicines and herbal supplements that are considered "strong inducers/inhibitors of CYP3A4/5 and P-gp." Olaparib inhibits enzymes "CYP3A4, UGT1A1, P-gp, OATP1B1, OCT1, OCT2, OAT3, MATE1, MATE2K and BCRP." Olaparib possibly induces "CYP 1A2, 2B6, 3A4, 2C9, 2C19 and P-gp." These characteristics may change how other medicine works in your body.

- Please be very careful! Over-the-counter drugs (including herbal supplements) may contain ingredients that could interact with your study drug. Speak to your doctor or pharmacist to determine if there could be any side effects.
- Avoid ingesting grapefruit, grapefruit juice and Seville oranges while taking olaparib.
- You may need to be monitored more frequently if you are taking any drugs that have narrow therapeutic ranges.
- Your regular health care provider should check a frequently updated medical reference or call your study doctor before prescribing any new medicine or discontinuing any medicine. Your study doctor's name is _____ and he or she can be contacted at _____.

November 2015

STUDY DRUG INFORMATION WALLET CARD

You are enrolled on a clinical trial using the experimental drug **olaparib (AZD2281).** This clinical trial is sponsored by the NCI. Olaparib interacts with drugs that are processed by your liver, or use certain transport proteins in your body. Because of this, it is very important to:

- Tell your doctors if you stop taking regular medicines or if you start taking any new medicines.
- Tell all of your health care providers (doctors, physician assistants, nurse practitioners, pharmacists) that you are taking part in a clinical trial.
- Check with your doctor or pharmacist whenever you need to use an over-the-counter medicine or herbal supplement.
- Olaparib interacts with liver enzymes, CYP3A4/5, 1A2, 2B6, 2C9, 2C19, UGT1A1, and transport proteins, P-gp, OATP1B1, OCT1, OCT2, OAT3, MATE1, MATE2K and BCRP.

- Olaparib must be used very carefully with other medicines that interact with these enzymes and proteins.
- Before you enroll onto the clinical trial, your study doctor will work with your regular health care providers to review any medicines that are considered ""strong or moderate inducers/inhibitors of CYP3A4/5 and P-gp." Olaparib inhibits "CYP 3A4, UGT1A1 and transport proteins P-gp, OATP1B1, OCT1, OCT2, OAT3, MATE1, MATE2K and BCRP and induces CYP 1A2, 2B6, 3A4, 2C9, 2C19 and transport protein P-gp." It may change how other medicine works in your body.
- Before prescribing new medicines, your regular health care providers should go to a frequently-updated medical reference for a list of drugs to avoid, or contact your study doctor.
- Your study doctor's name is _____

  and can be contacted at _____.

APPENDIX X: YOUTH INFORMATION SHEETS
INFORMATION SHEET REGARDING RESEARCH STUDY APEC1621H
(for children from 7 through 12 years of age)

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

1. We have been talking with you about your cancer. You have had treatment for the cancer already but it did not go away or it came back after treatment.

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

3. You agreed to be part of a study to see if your cancer has any specific changes that could help us decide what medicine might "match" best to your cancer.

4. We have found a medicine called olaparib that could "match" your tumor. The doctors want to see if olaparib will help children with your type of cancer get better. We don't know if olaparib will work well to get rid of your cancer. That is why we are doing the study.

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

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

7. Your family can choose to be part of this study or not. Your family can also decide to stop being in this study at any time once you start. There may be other treatments for your cancer that your doctor can tell you about.

8. If you decide to be treated with olaparib you might have some tests and check-ups done more often that you might if you weren't part of the study.

9. As part of the study we are also trying to learn more about children's cancers and how olaparib works in them. We will draw some extra blood samples for this if your family agrees.

INFORMATION SHEET REGARDING RESEARCH STUDY APEC1621H
(for teens from 13 through 17 years of age)

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

1. We have been talking with you about your cancer. You have had treatment for the cancer already but the cancer did not go away or it came back after treatment.

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

3. The main purpose of this study is to learn how well cancers that have specific changes (mutations) respond to medicines that are aimed at those changes. This combination of a tumor with a mutation and a medicine that aims at that mutation is called a "match".

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

5. You will get olaparib by mouth twice daily for a 28-day period. This entire 28-day period is called a cycle. Olaparib should be swallowed whole, not chewed or crushed. You may continue to receive olaparib for up to about 24 months (approximately 26 cycles) as long as you do not have bad effects from it and your cancer does not get any worse. If you decide to be treated with olaparib, you will also have exams and tests done that are part of normal cancer care. Some of these may be done more often while you are being treated with olaparib. The doctors want to see if olaparib will help children or adolescents with your type of cancer get better. We don't know if olaparib is better than other medicines. That is why we are doing this study.

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

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

8. Your family can choose to be part of this study or not. Your family can also decide to stop being in this study at any time once you start. There may be other treatments for your illness that your doctor can tell you about. Make sure to ask your doctors any questions that you have.

9. As part of the study we are also trying to learn more about the mutations that occur in cancers that happen in children and teens, as well as how olaparib works. If your family agrees we will draw some extra blood samples to do these tests.

APPENDIX XI: CTEP AND CTSU REGISTRATION PROCEDURES

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

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

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

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

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

CTSU REGISTRATION PROCEDURES

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

Requirements for APEC1621H Site Registration:

- IRB approval (For sites not participating via the NCI CIRB; local IRB documentation, an IRB-signed CTSU IRB Certification Form, Protocol of Human Subjects Assurance Identification/IRB Certification/Declaration of Exemption Form, or combination is accepted)
- IROC Credentialing Status Inquiry (CSI) Form
  NOTE: For studies with a radiation and/or imaging (RTI) component, the enrolling site must be aligned to a RTI provider. To manage provider associations access the Provider Association tab on the CTSU website at https://www.ctsu.org/RSS/RTFProviderAssociation, to add or remove associated providers. Sites must be linked to at least one IROC credentialed provider to participate on trials with an RT component.

Submitting Regulatory Documents:

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

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

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

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

Checking Your Site's Registration Status:

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

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

Note: The status given only reflects compliance with IRB documentation and institutional compliance with protocol-specific requirements as outlined by the Lead Network. It does not reflect compliance with protocol requirements for individuals participating on the protocol or the enrolling investigator's status with the NCI or their affiliated networks.

Data Submission / Data Reporting

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

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

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

APPENDIX XII: TOXICITY-SPECIFIC GRADING

Bilirubin

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

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

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

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

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

GGT:

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