To: CTEP Protocol and Information Office

From: Timothy Yap, M.D., Ph.D.

Branch: Investigational Drug Branch, CTEP, DCTD, NCI

Date: 11/14/2022

Re: Amendment #10 of Protocol #10329: "Phase I Sequential Trial of Agents Against DNA Repair (STAR)"

I. PI-initiated Changes:

#	Section	Comments
1.	Throughout and title page	**PI Response: The protocol version date was updated on the Title Page and throughout the document on the headers.** **Old Text:** February 21, 2022 **New Text:** November 14, 2022
2.	5.7	**PI Response: The name of the RPPA Core Facility was updated in the Assay Laboratory and Lab PI table found in the biomarker plan.** **Old Text**: RPPA Core Laboratory/MD Anderson **New Text**: Functional Proteomics RPPA Core Facility, MD Anderson Cancer Center (MDACC)
3.	5.7	**PI Response: The Assay Laboratory and Lab PI performing the WES, RNAseq, and ctDNA analysis were updated in the biomarker plan.** **Old Text**: NCLN Genomics Laboratory Mickey Williams mickey.williams@nih.gov **New Text**: NCLN Genomics Laboratory or MoCha, Frederick National Laboratory for Cancer Research (FNLCR) Mickey Williams mickey.williams@nih.gov

#	Section	Comments
4.	5.9.1.1	**PI Response: The instructions for specimen receipt and processing at the EET Biobank regarding RPPA analysis has been updated.** **Old Text**: Frozen tissue for RPPA will be stored in liquid nitrogen vapor phase at the EET Biobank until batch shipping to Dr. Yiling Lu at the MD Anderson RPPA Core Laboratory. **New Text**: Frozen tissue for RPPA will be stored in liquid nitrogen vapor phase at the EET Biobank until batch shipping to Dr. Yiling Lu at the Functional Proteomics RPPA Core Facility, MD Anderson Cancer Center (MDACC).
5.	5.9.1.2	**PI Response: The name of the site performing the RPPA specimen analysis was updated.** **Old Text**: This assay will be performed by Dr. Yiling Lu at the MD Anderson RPPA Core Laboratory. **New Text**: This assay will be performed by Dr. Yiling Lu at the Functional Proteomics RPPA Core Facility, MD Anderson Cancer Center (MDACC).
6.	5.9.1.3	**PI Response: Instructions regarding the shipment of specimens from the EET Biobank to the site performing the RPPA specimen analysis was added.**
7.	5.9.1.4	**PI Response: Contant information for the site performing the RPPA specimen analysis was added.**
8.	5.10.1.2	**PI Response: The site performing WES analysis was updated.** **Old Text**: WES will be conducted in the NCLN Genomics Laboratory under the leadership of Mickey Williams, Ph.D. **New Text**: WES will be conducted in the NCLN Genomics Laboratory or MoCha, Frederick National Laboratory for Cancer Research (FNLCR) under the leadership of Mickey Williams, Ph.D.
9.	5.10.1.3	**PI Response: Instructions regarding the shipment of specimens from the EET biobank to the site performing WES analysis was added.**

#	Section	Comments
10.	5.10.1.4	**PI Response: Contact information for the lab performing WES analysis was added.**
11.	5.10.3.2	**PI Response: The site performing the correlative studies for γH2AX and pRAD50 IHC and cycIF/mIHC was updated.** **Old Text**: γH2AX and pRAD50 IHC and cycIF/mIHC will be performed by Dr. Gordon Mills at Oregon Health & Science University (ATTN: Dong Zhang, Oregon Health & Science University, 2730 S. Moody Ave., KCRB Mills Lab 2001.14, Portland, OR 97201). **New Text**: γH2AX and pRAD50 IHC and cycIF/mIHC will be performed by Dr. Gordon Mills at Oregon Health & Science University.
12.	5.10.3.3	**PI Response: The shipping address to send specimens from the EET biobank to the site performing γH2AX and pRAD50 IHC and cycIF/mIHC analysis was added.**
13.	5.10.3.4	**PI Response: The contact information for the site performing γH2AX and pRAD50 IHC and cycIF/mIHC analysis was added.**
14.	5.10.4.3	**PI Response: The shipping address to send specimens from the EET biobank to the site performing scRNAseq was added.**
15.	5.10.4.4	**PI Response: The contact information for the site performing scRNAseq analysis was added.**
16.	5.10.5.2	**PI Response: The lab performing the ctDNA analysis was updated.** **Old Text**: ctDNA Analysis will be conducted in the NCLN Genomics Laboratory under the leadership of Mickey Williams, Ph.D. **New Text**: ctDNA Analysis will be conducted in the NCLN Genomics Laboratory or MoCha, Frederick National Laboratory for Cancer Research (FNLCR)under the leadership of Mickey Williams, Ph.D.
17.	5.10.5.3	**PI Response: The shipping address to send specimens from the EET biobank to the site performing ctDNA analysis was added.**
18.	5.10.5.4	**PI Response: The contact information for the lab performing the ctDNA analysis was added.**

NCI Protocol #: 10329

Local Protocol #: *TBD*

ClinicalTrials.gov Identifier: NCT04197713

TITLE: Phase I Sequential Trial of Agents Against DNA Repair (STAR)

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Dose Escalation Phase Participating Organizations

LAO-TX035 / University of Texas MD Anderson Cancer Center LAO *Restricted to:* TX035 / MD Anderson Cancer Center

Dose Expansion Phase Participating Organizations

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LAO-CA043 / City of Hope Comprehensive Cancer Center LAO
LAO-CT018 / Yale University Cancer Center LAO
LAO-MA036 / Dana-Farber - Harvard Cancer Center LAO
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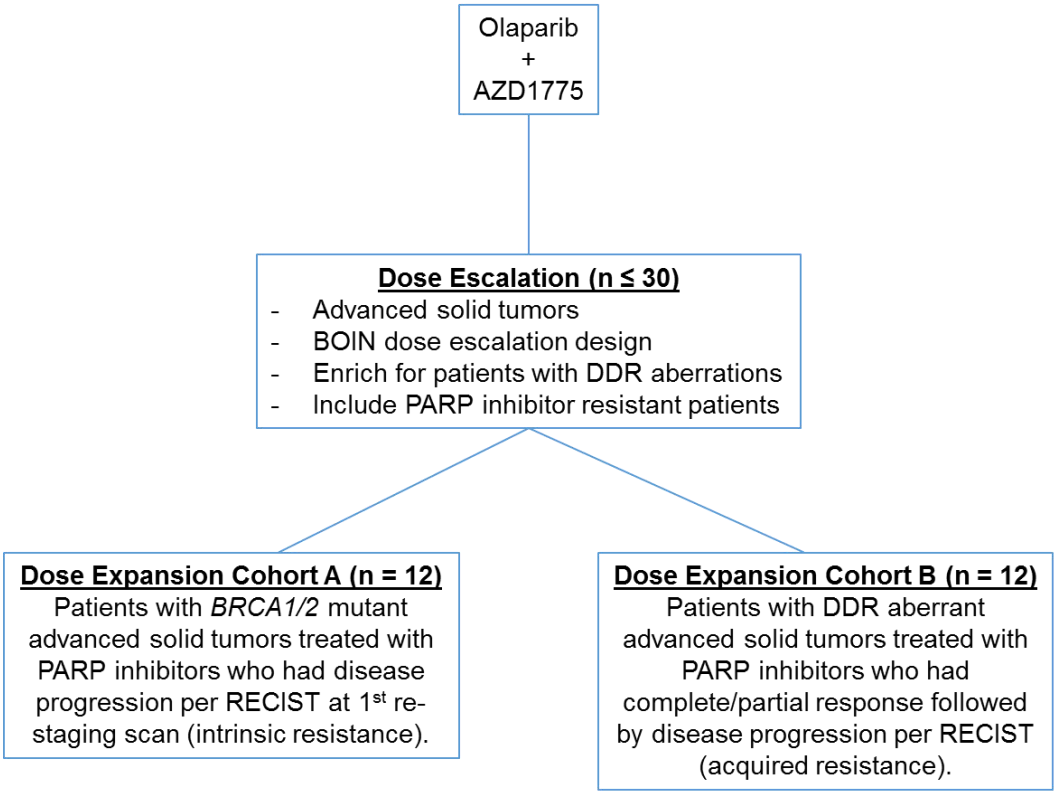
NCI-Supplied Agents: AZD1775 (adavosertib, NSC 751084) and olaparib (AZD2281, NSC 747856)

IND #: [redacted]

IND Sponsor: DTCD, NCI

Protocol Type / Version # / Version Date:	Original / May 7, 2019 Revision 1 / August 20, 2019 Revision 2 / September 26, 2019 Revision 3 / November 13, 2019 Revision 4a / January 22, 2020 Revision 5 / February 14, 2020 Amendment 1 / May 22, 2020 Amendment 4/ October 5, 2020 Amendment 5/ March 24, 2021 Amendment 6/May 10, 2021 Amendment 7/August 26, 2021 Amendment 8/September 28, 2021 Amendment 9/February 21, 2022 Amendment 10/November 14, 2022

SCHEMA



Dose Level	Treatment
MTD/RP2D expansion in 2 cohorts: • Patients with *BRCA1/2* mutant advanced solid tumors treated with PARP inhibitors who had disease progression per RECIST at 1st re-staging (intrinsic resistance). • Patients with DDR aberrant advanced solid tumors treated with PARP inhibitors who had complete/partial response followed by disease progression per RECIST (acquired resistance). One cycle = 28 days	
2	Olaparib 300 mg BID Days 1-5 and 15-19, AZD1775 300 mg QD Days 8-12 and 22-26.
1*	Olaparib 300 mg BID Days 1-5 and 15-19, AZD1775 250 mg QD Days 8-12 and 22-26.
-1**	Olaparib 200 mg BID Days 1-5 and 15-19, AZD1775 200 mg QD Days 8-12 and 22-26.
*Starting dose level **Either or both olaparib or AZD1775 may be reduced to 200mg BID or 200mg QD, respectively BID = twice a day QD = once a day	

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1. OBJECTIVES

1.1 Primary Objectives

1.1.1 To determine the safety and tolerability of olaparib in sequential treatment with AZD1775, and to establish the maximum tolerated dose/recommended phase 2 dose (MTD/RP2D) of this sequential schedule in patients with advanced solid tumors in a post-poly ADP ribose polymerase inhibitor (PARPi) population.

1.1.2 To assess the safety and toxicity profile of the sequential treatment of olaparib and AZD1775 in a post-PARPi population.

1.2 Secondary Objectives

1.2.1 To assess putative predictive biomarkers of response and resistance to the sequential treatment of olaparib and AZD1775 in a post-PARPi population.

1.2.2 To evaluate a novel experimental trial design involving sequential dosing of olaparib and AZD1775 in a post-PARPi population.

1.2.3 To observe and record anti-tumor activity. Although the clinical benefit of these agents has not yet been established, the intent of offering this treatment is to provide a possible therapeutic benefit, and thus the patient will be carefully monitored for tumor response and symptom relief in addition to safety and tolerability.

2. BACKGROUND

2.1 Study Disease

The development of combination regimens to increase the depth and duration of response and survival benefit of single agent DNA Damage Response (DDR) inhibitors is a rational anti-tumor strategy (Brown *et al.*, 2017). Such combinations may also widen the range of tumor and molecular subtypes of patients who may respond. To date, combination strategies explored in the clinic have included the concurrent administration of DDR agents, including the rational combination of the PARP inhibitor, olaparib, and WEE1 inhibitor, adavosertib (AZD1775). However, these strategies have largely been hampered by combination-related toxicities, particularly chronic toxicities, necessitating dose reductions and delays, all of which contribute to limiting potential clinical efficacy. [redacted]. This alternating strategy may also

potentially avoid the development of drug resistance through sustained pressure on a specific target (Yap *et al.*, 2013).

2.2 CTEP IND Agents

2.2.1 Olaparib (AZD2281)

In December 2014, the European Commission approved olaparib capsules as a maintenance treatment for platinum-sensitive, relapsed, high grade serious epithelial ovarian, fallopian tube, or primary peritoneal cancer in adult patients with breast cancer (*BRCA*) mutations (germline [g*BRCA*m] and/or somatic [s*BRCA*m]) who are in a CR or PR to platinum-based chemotherapy. In December 2014, the Food and Drug Administration (FDA) approved olaparib capsules as monotherapy for advanced ovarian cancer in patients with deleterious or suspected g*BRCA*m who have been treated with three or more prior lines of chemotherapy. In August 2017, the FDA approved the tablet formulation of olaparib for the maintenance treatment of adult patients with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer, who are in a CR or PR to platinum-based chemotherapy; olaparib tablets were also approved for the December 2014 indication. On January 12, 2018, the FDA granted regular approval to olaparib tablets for the treatment of patients with deleterious or suspected deleterious germline *gBRCAm*, human epidermal growth factor receptor 2 (HER2)-negative metastatic breast cancer who have been treated with chemotherapy either in the neoadjuvant, adjuvant, or metastatic setting. In December 2018, the FDA granted approval to olaparib as a 1st line maintenance therapy for adult patients deleterious or suspected deleterious germline or somatic BRCA-mutated advanced epithelial ovarian, fallopian tube or primary peritoneal cancer who are in complete or partial response to 1st-line platinum-based chemotherapy.

2.2.1.1 Mechanism of Action

Olaparib inhibits PARP, a protein that repairs single-strand breaks (SSBs) via base excision repair (BER), a backup repair system to homologous recombination (HR) repair (Farmer et al.,; Olaparib Investigator's Brochure, 2019). Olaparib potently inhibits PARP1 (IC_{50}=5 nM), PARP2 (IC_{50}=1 nM), and PARP3 (IC_{50}=4 nM) *in vitro* (Olaparib Investigator's Brochure, 2019). The inhibition of PARP and disruption of BER via olaparib treatment leads to accumulation of double-strand breaks (DSBs); in tumors with defective components of HR repair, these DSBs cannot be accurately repaired, resulting in genomic instability and induction of synthetic lethality (Olaparib Investigator's Brochure, 2019). Cultures of cells deficient in HR repair factors, notably BRCA1 and BRCA2, are particularly sensitive to treatment with olaparib (Olaparib Investigator's Brochure, 2019). Furthermore, olaparib may enhance the effects of DNA damage caused by ionizing radiation and chemotherapy.

2.2.1.2 Overview of Clinical Pharmacology

Single PO dosing of olaparib tablets was rapidly absorbed with peak plasma concentrations typically observed at 1.5 hours (Olaparib Investigator's Brochure, 2019). A population PK analysis characterized the absorption phase of olaparib as a sequential zero- and first-order absorption and showed a significant impact of olaparib tablet strength on the absorption rate

constant. Once t_{max} was reached, plasma concentrations of olaparib declined in a biphasic manner with an average $t_{1/2}$ of 14.9 hours (standard deviation [StD]: 8.2 hours). The mean apparent clearance (CL) after a single dose of olaparib tablets at 300 mg PO was approximately 7.4 L/h (StD: 3.9 L/h). Olaparib exhibited a mean volume of distribution (Vd) of 158 L (StD: 136 L), indicating distribution into the tissues. The plasma protein binding *in vitro* was moderate and showed evidence of concentration dependence (81.9% at 10 mcg/ml).

Multiple-dose PK was reasonably well predicted from single-dose data, and accumulation on multiple dosing was not extensive (Olaparib Investigator's Brochure, 2019). At a 300 mg BID dose, olaparib PK appeared to be slightly time dependent with a temporal change parameter (TCP; AUC at steady state/AUC following a single dose) of approximately 1.45 (StD: 0.6). Exposure (measured by AUC from zero to 12 hours [AUC_{0-12}]) increased approximately proportionally with olaparib tablets at 25-450 mg; C_{max} increased slightly less than proportionally for the dose range. The estimated geometric mean (Gmean) maximum steady state plasma concentration ($C_{max\ ss}$), AUC_{0-12}, and minimum plasma concentration (C_{min}) after dosing with 300 mg tablet BID were 9.13 mcg/mL, 57.9 mcg.h/mL and 1.76 mcg/mL: equivalent to unbound concentrations of 1.65 mcg/mL, 10.5 mcg.h/mL and 0.318 mcg.h/mL, respectively. The inter-individual variability was moderate to high (36% for $C_{max\ ss}$, 49% for AUC_{0-12}, and 104% for the minimum steady state plasma concentration [$C_{min\ ss}$]). After administration of a radiolabeled dose of olaparib capsules (100 mg BID) in study D0810C00010, unchanged drug accounted for approximately 70% of the circulating material in the plasma with the remainder accounted for by three other components (each approximately 10% of the material), all of which were also present in the excreta. Drug-related material was eliminated in the urine (approximately 44% of the dose) and in the feces (approximately 42% of the dose) predominantly as metabolites. Metabolism was extensive. The metabolites produced were predominantly a consequence of oxidation of the piperazine carboxycyclopropyl, the fluorophenyl, and phthalazinone ring systems. The pharmacological activity of the three circulating metabolites is not known.

Although based on limited data, there was no evidence of any marked ethnic difference in the PK of olaparib tablets between Japanese, Chinese, and Caucasian patients for the olaparib tablet formulation (Olaparib Investigator's Brochure, 2019). In a population analysis, age, body weight, and gender covariates were not found to be predictors of olaparib plasma exposure.

Data from a renal impairment study (D0816C00006) showed that olaparib tablets (300 mg BID) mean Cmax and AUC were approximately 15% and 24% higher, respectively, in patients with mild renal impairment (creatinine CL determined by Cockcroft-Gault: 51-80 mL/min; N=14), and olaparib mean Cmax and AUC were 26% and 44% higher, respectively, in patients with moderate renal impairment (creatinine CL determined by Cockcroft-Gault: 31-50 mL/min; N=14) (Olaparib Investigator's Brochure, 2019).

2.2.1.3 Overview of Safety

As of December 15, 2017, approximately 8,319 patients are estimated to have received olaparib in the clinical program including AstraZeneca-sponsored studies (4575 patients), a MAP (810 patients), investigator-sponsored studies (ISS), and collaborative group studies (2934 patients)

(Olaparib Investigator's Brochure, 2019). Since 2012/2013, most new clinical studies have utilized the tablet formulation which was designed to deliver the therapeutic dose of olaparib in fewer dose units than the capsule. Of the 4575 patients in AstraZeneca-sponsored, interventional studies, 1512 received the capsule formulation, 3038 received the tablet formulation, and 25 received both capsule and tablet. The recommended olaparib monotherapy capsule dose is 400 mg BID. The recommended olaparib monotherapy tablet dose is 300 mg BID. Olaparib monotherapy appears to be generally well tolerated across studies up to and including these doses.

Toxicities considered to be associated with administration of olaparib include hematological effects (anemia, neutropenia, lymphopenia, leukopenia, thrombocytopenia, mean corpuscular volume [MCV] elevation), decreased appetite, nausea and vomiting, diarrhea, dyspepsia, stomatitis, upper abdominal pain, dysgeusia, fatigue (including asthenia), increase in blood creatinine, headache, dizziness, hypersensitivity, rash, dermatitis, and cough (Olaparib Investigator's Brochure, 2019). Anemia was the most common CTCAE Grade ≥3 adverse reaction reported in clinical studies. Median time to first onset of anemia was approximately 4 weeks (approximately 7 weeks for CTCAE Grade ≥3 events). An exposure-response relationship between olaparib and decreases in hemoglobin has been demonstrated. In clinical studies with olaparib, the incidence of CTCAE Grade ≥2 shifts (decreases) from baseline in hemoglobin was 20%, absolute neutrophils 15%, platelets 5%, lymphocytes 30% and leukocytes 20% (all % approximate) and the incidence of CTCAE Grade ≥2 shifts (elevations) from baseline in blood creatinine was approximately 15%.

In a small number of patients, pneumonitis, myelodysplastic syndrome (MDS)/AML and new primary malignancies have been reported (Olaparib Investigator's Brochure, 2019). The incidence of MDS/AML in patients treated in clinical trials with olaparib monotherapy, including long-term survival follow-up, was <1.5%, and the majority of events had a fatal outcome. All patients had potential contributing factors for the development of MDS/AML, having received previous chemotherapy with platinum agents. SOLO2 and OlympiAD safety data provide additional supportive evidence that a causal relationship has not been established between olaparib treatment and the development of these AEs. New primary malignancies other than MDS/AML have been reported in <1% of patients. Pneumonitis has been reported in <1.0% patients treated with olaparib monotherapy in clinical studies. Reports of pneumonitis had no consistent clinical pattern and were confounded by a number of pre-disposing factors (cancer and/or metastases in lungs, underlying pulmonary disease, smoking history, and/or previous chemotherapy and radiotherapy).

Data from Phase 1 dose escalation studies of olaparib in combination with various chemotherapy agents indicated an increase in bone marrow toxicity (anemia, neutropenia, thrombocytopenia) greater than expected if the agents had been administered alone. However, tolerable regimens combining olaparib with paclitaxel, attenuated dosed liposomal doxorubicin, and attenuated dosed carboplatin/paclitaxel have been established, supporting studies in the combination setting.

2.2.2 Adavosertib (AZD1775)

2.2.2.1 Mechanism of Action

[redacted] Proper functioning of these checkpoints is essential for deoxyribonucleic acid (DNA) metabolism and the DNA damage response (Coleman and Dunphy, 1994, Parker and Piwnica-Worms, 1992). Wee1 overexpression has been demonstrated in hepatocellular carcinoma (Masaki *et al.*, 2003), luminal and HER-2 positive breast cancers (Iorns *et al.*, 2009), colon, lung carcinoma, and seminoma tumor samples (Mir *et al.*, 2010).

[redacted]

[redacted]

Inhibition of WEE1 is therefore expected to cause aberrantly high CDK2 activity in S-phase cells that will have multiple consequences for cancer cells that already have G1/S checkpoint aberrations such as p53 mutations or cyclin dependent kinase inhibitor 2A (CDKN2A) deletions (Sherr, 1996). These include de-regulated replication origin firing before sufficient dNTPs are available, resulting in a higher degree of replication stress (already greater in cancer cells). [redacted]

Since the majority (if not all) of human cancers harbor abnormalities in their p53 G1/S checkpoint control, they become more dependent on S- and G2- phase checkpoints (Sherr, 1996).

Thus, S- and G2-checkpoint abrogation caused by AZD1775 may selectively sensitize p53-deficient cells to anti-cancer agents (Wang *et al.*, 2001) while single-agent activity may be seen in cancers with sufficiently high levels of replication stress and endogenous DNA damage.

[redacted]

2.2.2.2 Preclinical Studies

Early preclinical data demonstrated enhancement of chemotherapeutic effect of AZD1775 in combination with carboplatin, cisplatin, and gemcitabine in p53-deficient colon and lung carcinoma cells (Hirai *et al.*, 2009), and with 5-FU in p53-deficient colon and pancreatic cells, but not p53 wild-type colon cancer cells (Hirai *et al.*, 2010). The same group also demonstrated objective tumor regression in xenograft models using immunodeficient nude rats subcutaneously bearing p53 mutant colon carcinoma exposed to AZD1775 in combination with gemcitabine, in xenografts bearing breast carcinomas exposed to combination with capecitabine (Hirai *et al.*, 2009), and in p53-deficient primary pancreatic cancer xenografts, in combination with gemcitabine (Rajeshkumar *et al.*, 2011). [redacted]

Clinical evaluation of AZD1775 in combination with chemotherapeutic agents has demonstrated the need for a cautious approach. The AZD1775 plus olaparib concurrent combination arm of the phase 2 VIOLETTE clinical trial in metastatic triple negative breast cancer was closed prematurely by SRC due to a low risk and low benefit result of the combination (ClinicalTrials.gov, 2019; Tutt *et al.,* 2019). To summarise, on the VIOLETTE study, the initial dose of AZD1775 in combination concurrently with olaparib was 175 mg BID. The dose was amended after the first 5 patients had been dosed and after 2 patients were reported to have experienced febrile neutropenia CTCAE Grade 3, with one additional patient experiencing a neutropenia CTCAE Grade 2. All events occurred within the first cycle of the treatment and as a result the AZD1775 starting dose was reduced from 175 to 150 mg BID in July 2018.

At the time of data cut-off (17-Mar-2019), a total of 38 subjects received treatment with concurrent AZD1775 (150 mg BID) + olaparib (200 mg continuous), Arm 3. A review of the cumulative (unblinded) safety data available for these subjects observed that the most common adverse events (AEs; any grade) which were generally consistent with the known safety profiles of concurrent AZD1775 and olaparib. The most common CTCAE grade ≥3 AEs (System Organ Class [SOC] with Preferred Terms [PTs] >10%) were mainly blood and lymphatic system disorders and gastrointestinal disorders specifically neutropenia (very common), thrombocytopenia (common), anaemia and diarrhoea (both common). There were 4 reports of febrile neutropenia (2 pre-amendment and 2 post-amendment) in this study arm. Laboratory abnormalities of elevated liver function tests and unspecified cardiac abnormalities were also reported, which were all considered to be not medically significant. There was a single AE with

an outcome of death (PT: death) which was not considered to be related to study treatment by the reporting investigator.

Overall, there have been no new/unanticipated/unexpected safety findings for the concurrent AZD1775 and olaparib combination. However, a general increase in the frequencies of grade ≥3 AEs in the blood and lymphatic system disorders SOC and GI disorders SOC (PT: diarrhea) in the concurrent AZD1775 + olaparib arm when compared to the olaparib monotherapy arm was noted. This provided the rationale for this sequential combination of adavosertib plus olaparib based on the rationale from the lab of Gordon Mills (Fang *et al.*, 2019).

[redacted] and patient-derived sarcoma samples (Kreahling *et al.*, 2012). Cyclin E expression demonstrated increased sensitivity to AZD1775 in triple negative breast cancer cell lines and patient derived xenograft mouse models (Chen *et al.*, 2018).

2.2.2.3 Non-Clinical Pharmacokinetics

[redacted]

2.2.2.4 Non-Clinical Toxicology

[redacted]

2.2.2.5 Clinical Experience

[redacted]

[redacted]

2.2.2.6 Clinical Efficacy

Of 176 evaluable patients who received AZD1775 (either single or multiple doses) as monotherapy or in combination with gemcitabine, cisplatin, or carboplatin on Study PN001, a partial response (PR) (confirmed and unconfirmed) was observed in 17 (9.7%) patients, and stable disease (SD) was observed in 94 (53.4%) patients (Leijen *et al.*, 2016a). A phase II trial of AZD1775 in combination with carboplatin in patients with refractory or resistant TP53-mutated ovarian cancer (Study PN009) has also been performed, yielding a 43% overall response rate (PR + complete response [CR]) (Leijen *et al.*, 2016b).

2.2.2.7 Safety

Based on the preliminary safety data available, [redacted]

In study PN009 (Leijen *et al.*, 2016b) and the PK sub-study to PN001 (Leijen *et al.*, 2016a) which used the pre-market formulation, (both combining 2.5-day BID dosing of AZD1775 with carboplatin) toxicities were not qualitatively different from the ones observed in the carboplatin arm of PN001. However, increased hematological toxicity was observed, which was attributed to a drug-drug interaction with aprepitant (which was administered as anti-nausea medication in these studies). Preliminary PK analyses revealed that co-administration of AZD1775 and aprepitant resulted in a ~40% increase of AZD1775 exposure.

2.2.2.8 Clinical Pharmacokinetics

[redacted]

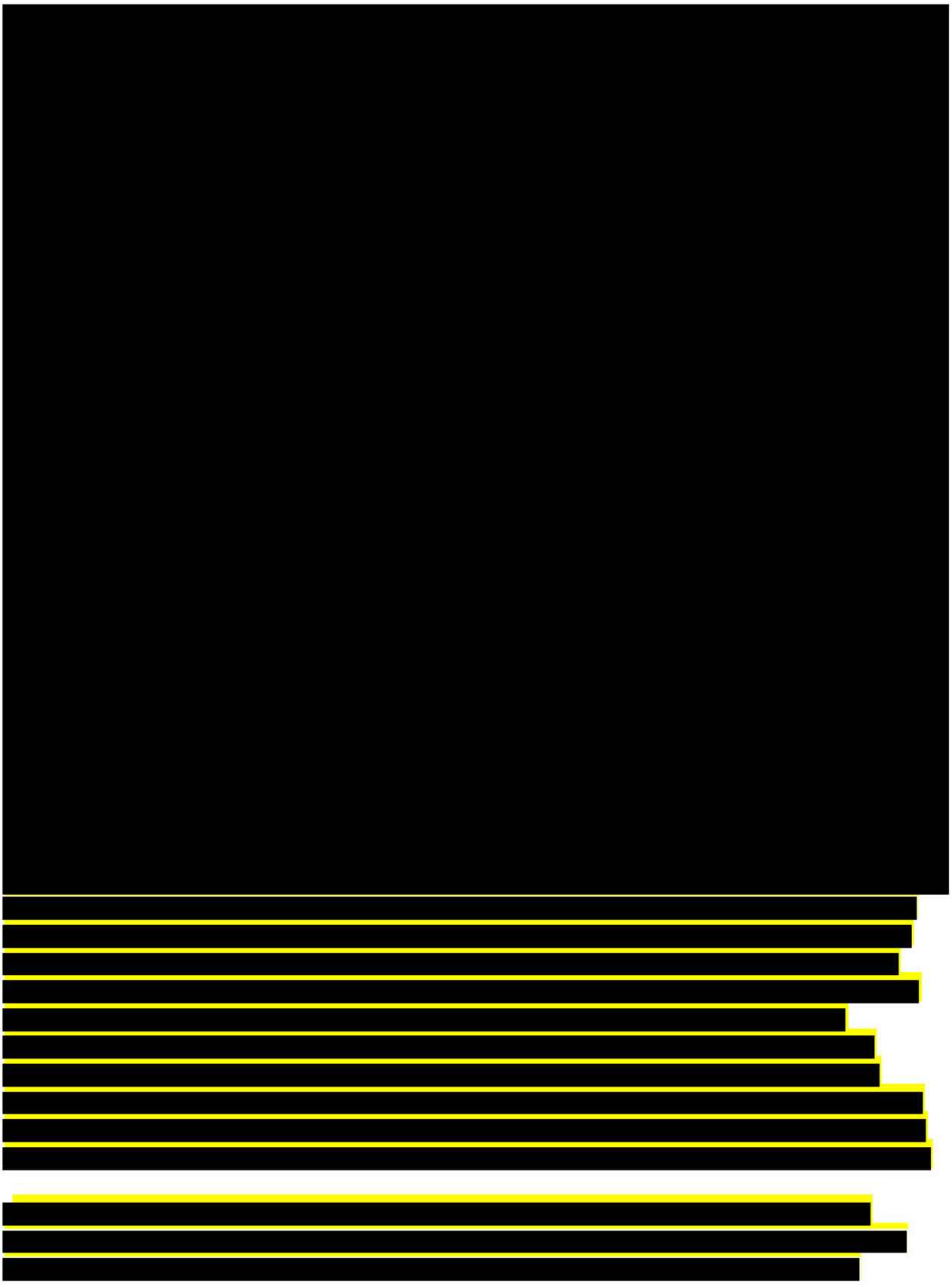
2.3 Rationale

2.3.1 Rationale for combining olaparib and AZD1775

The underlying rationale for why these combinations (such as olaparib + AZD1775) do not need to be concurrent is that PARP inhibition induces DNA damage, which is maintained after withdrawal of olaparib. AZD1775 then drives aberrant mitosis and cell death through WEE1 inhibition. This has been demonstrated by extensive *in vitro* and *in vivo* pre-clinical studies from the laboratory of Dr. Gordon Mills at MD Anderson Cancer Center (Fang *et al.*, 2019).

[redacted]

Figure 2: Schema of G2 cell cycle activation by PARP inhibitor



[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

Clinically, phase 1 trials have shown early signals of anti-tumor activity of the combination of olaparib and AZD1775. For example, in an ongoing phase 1b study of the combination of olaparib and AZD1775, evaluable responses of partial response (PR; 1 of 6 patients), stable disease (SD; 4 of 6 patients), and progressive disease (PD; 1 of 6 patients) were observed in patients with refractory solid tumors (Hamilton *et al.*, 2016). [redacted]

[redacted]

[redacted]

Toxicity associated adverse events have impacted the clinical progression of this therapeutic combination with the SRC closure of the concurrent AZD1775 (adavosertib) plus olaparib combination arm of the phase 2 VIOLETTE clinical trial in metastatic triple negative breast cancer (Tutt *et al*., 2018). This concurrent combination is also currently under evaluation in the EFFORT trial in advanced ovarian cancer patients who have failed prior PARP inhibitor monotherapy (NCT03579316).

[redacted]

The preclinical data generated by Dr. Gordon Mills and his research team, and the early phase clinical data outlined above clearly demonstrate that the combination of

PARP and WEE1 inhibitors is a viable anti-tumor strategy that warrants clinical development.

[redacted] Therefore, on the basis of the evidence presented here, ***we propose conducting a phase 1 trial to assess sequential scheduling of olaparib and AZD1775.***

[redacted]

2.4 Correlative Studies Background

[redacted]

[redacted]

[redacted]

2.4.2 Exploratory Studies

The molecular landscape of cancer is just beginning to be defined. However, we do not know enough about the genomic and molecular landscape of tumors from patients who enter early phase clinical trials. With this study, we will attempt to learn more about specific molecular features of cancers from this patient subgroup. It is particularly important to learn, as early as possible, if there are molecular features within a particular malignant histology or across malignant histologies that can inform about potential response or resistance to treatments in early phase clinical trials. Such knowledge will be used to design more efficient later stage clinical trials for more efficient and more effective drug development.

[redacted]

[redacted]

3. PATIENT SELECTION

3.1 Eligibility Criteria

3.1.1 Subjects must have histologically confirmed malignancy that is metastatic or unresectable and for which standard curative measures do not exist or are no longer effective.

3.1.2 Patients in dose expansion Cohort A (intrinsic resistance), must have:

- prior treatment with PARP inhibitors,
- disease progression per RECIST at 1st re-staging, and
- germline or somatic mutations in *BRCA1* or *BRCA2*.

Patients in dose expansion Cohort B (acquired resistance) must have:

- prior treatment with PARP inhibitors,
- complete/partial response followed by disease progression per RECIST, and
- germline or somatic mutations in any of the following DDR genes: *BRCA1, BRCA2, BRIP1, FANCA, PALB2,* or the non-DDR gene marker Cyclin E amplification. Local testing in CLIA-certified laboratory will be accepted. All alterations will be reviewed by MD Anderson's Precision Oncology Decision Support (PODS) team. No variants of uncertain significance (VUS) will be allowed as the qualifying genetic mutation. Recruitment of patients with relevant molecular aberrations in the dose escalation phase is encouraged but not mandated.

3.1.3 Subjects must have RECIST measureable disease and a tumor that is safely accessible for biopsy and must be willing to undergo biopsy.

3.1.4 Subjects must have received at least one line of systemic therapy in the advanced/metastatic setting. Subjects with diseases without known effective options, and subject who have declined standard of care therapy prior to study introduction are also eligible.

3.1.5 Any prior palliative radiation therapy must have been completed at least 14 days prior to the start of study drugs, and patients must have recovered from any acute adverse effects prior to the start of study treatment.

3.1.6 HIV-infected (HIV1/2 antibody-positive) patients may participate if they meet all the following eligibility requirements:

- They must be on an anti-retroviral regimen with evidence of at least two undetectable viral loads within the past 6 months on this same regimen; the most recent undetectable viral load must be within the past 12 weeks.
- They must have a CD4 count ≥250 cells/μL over the past 6 months on this same anti-retroviral regimen and must not have had a CD4 count <200 cells/μl over the past 2 years, unless it was deemed related to the cancer and/or chemotherapy-induced bone marrow suppression. For patients who have received chemotherapy in the past 6 months, a CD4 count <250 cells/μl during chemotherapy is permitted as long as viral loads were undetectable during this same chemotherapy.
- They must have an undetectable viral load and a CD4 count ≥250 cells/μL within 7 days of enrolment.
- They must not be currently receiving prophylactic therapy for an opportunistic infection and must not have had an opportunistic infection within the past 6 months. Monitoring for HIV-infected patients should include:
    - Viral load and CD4 count q12w.
    - If CD4 count drops to less than 200 cells/μl while on study, initiate viral load test. If viral load proves undetectable at this time, continue CD4 and viral load checks q8w. If 2 consecutive viral load tests are undetectable, revert to q12w testing for CD4 and viral load testing.
    - If an opportunistic infection occurs with a CD4 count of <200 cells/μl, hold study treatment. Initiate treatment of the infection and continue to hold study treatment; once clinically stable, CD4 count is >200 cells/μl and viral load has remained undetectable, reinitiate study treatment.

3.1.7 Patients with a past or resolved hepatitis B virus (HBV) infection (defined as the presence of hepatitis B core antibody and absence of HBsAg) are eligible. Active HBV is defined by a known positive HBV surface antigen (HBsAg) result. Patients positive for hepatitis C virus (HBC) antibody are eligible only if polymerase chain reaction (PCR) is negative for HCV RNA. Patients with known active HBV or HBC infection are ineligible.

3.1.8 Patients with **treated brain metastases** are eligible if follow-up brain imaging after central nervous system (CNS)-directed therapy shows no evidence of progression within 28 days.

3.1.9 Patients with **new or progressive brain metastases** (active brain metastases) or **leptomeningeal disease** are eligible if the treating physician determines that immediate CNS specific treatment is not required and is unlikely to be required during the first cycle of therapy.

3.1.10 Patients must have adequate organ and marrow function within 7 days of study drugs initiation, as defined by the following baseline laboratory values:

- ANC ≥1500/μL
- Hemoglobin (Hgb) ≥10g/dL with no blood transfusion in the past 28 days
- Platelets ≥100,000/μL
- Aspartate aminotransferase (AST) (Serum Glutamic Oxaloacetic Transaminase (SGOT)) / Alanine aminotransferase (ALT) (Serum Glutamic Pyruvate Transaminase (SGPT) ≤ 2.5X upper limit of normal (ULN), unless liver metastases are present in which case they must be ≤ 5x ULN
- Serum bilirubin within normal limits (WNL) or ≤1.5X ULN in patients with liver metastases, or total bilirubin ≤3X ULN with direct bilirubin WNL in patients with well-documented Gilbert's Syndrome
- Serum creatinine ≤1.5X ULN. If elevated, check creatinine clearance (CrCl) with cut off ≥ 51mL/min as calculated by the Cockcroft-Gault method or based on a 24-hour urine test (confirmation of creatinine clearance is only required when serum creatinine is >1.5X institutional ULN).
- Estimated CrCl (glomerular filtration rate [GFR]) = (140-age [years]) x (weight [kg]) x F^{a} (72 x serum creatinine mg/dL) (^{a} where F = 0.85 for females and F = 1 for males)

3.1.11 The effects of AZD1775 and olaparib on the developing human fetus are either unclear or are known to be teratogenic, women of childbearing potential and their partners, who are sexually active, must agree to the use of TWO highly effective forms of contraception in combination. This should be started from the signing of the informed consent and continue throughout the period of taking study treatment and for at least 1 month after last dose of study drug(s), or they must totally/truly abstain from any form of sexual intercourse. Male patients must use a condom during treatment and for 3 months after the last dose of study drug when having sexual intercourse with a pregnant woman or with a woman of childbearing potential. Female partners of male patients should also use a highly effective form of contraception if they are of childbearing potential. Male patients should not donate sperm throughout the period of taking study drugs and for 3 months following the last dose of study drugs.

Acceptable non-hormonal birth control methods include:

- Total/True abstinence: When the patient refrains from any form of sexual intercourse and this is in line with their usual and/or preferred lifestyle; this must continue for the total duration of the trial and for at least 1 month after the last dose of study drug for women of child bearing potential. For male patients, 3 months after last dose. [Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods, or declaration of abstinence solely for the duration of a trial) and withdrawal are not acceptable methods of contraception.]
- Vasectomised sexual partner PLUS male condom. With participant assurance that partner received post-vasectomy confirmation of azoospermia.
- Tubal occlusion PLUS male condom.
- IUD PLUS male condom. Provided coils are copper-banded.

Acceptable hormonal methods:

- Normal and low dose combined oral pills PLUS male condom.
- Cerazette (desogestrel) PLUS male condom. Cerazette is currently the only highly efficacious progesterone based pill.
- Hormonal shot or injection (e.g., Depo-Provera) PLUS male condom.
- Etonogestrel implants (e.g., Implanon, Norplant) PLUS male condom.
- Norelgestromin / EE transdermal system PLUS male condom.
- Intrauterine system [IUS] device (e.g., levonorgestrel releasing IUS -Mirena®) PLUS male condom.
- Intravaginal device (e.g., EE and etonogestrel) PLUS male condom.
- In the case of use of oral contraception, women should be stable on the same pill before taking study treatment.
- Note: oral contraceptives are allowed but should be used in conjunction with a barrier method of contraception due to unknown effect of drug-drug interaction. Women are considered post-menopausal and not of childbearing potential if they have had 12 or more months of natural (spontaneous) amenorrhea following cessation of exogenous hormonal treatment with an appropriate clinical profile (e.g. age appropriate, history of vasomotor symptoms) or have had surgical bilateral oophorectomy (with or without hysterectomy). In the case of oophorectomy alone, she will be considered not of childbearing potential only when her reproductive status has been confirmed by follow up hormone level assessment.
- Male patients will be advised to arrange for the freezing of sperm samples prior to the start of the study should they wish to father children while on study drugs or during the 3 months after stopping study drugs.

3.1.12 Male or female patient ≥18 years of age. Because no dosing or adverse event data are currently available on the use of AZD1775 in combination with olaparib in patients <18 years of age, children are excluded from this study, but will be eligible for future pediatric trials.

3.1.13 Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) score of 0-1 (Karnofsky ≥70%, see Appendix A).

3.1.14 Ability to understand and the willingness to sign a written informed consent document. Participants with impaired decision-making capacity (IDMC) who have a legally-authorized representative (LAR) and/or family member available will also be eligible. Has read and understands the informed consent form (ICF) and has given written informed consent (IC) prior to any study procedures.

3.1.15 Willingness and ability to comply with study and follow-up procedures.

3.2 Exclusion Criteria

3.2.1 History of allergic reactions attributed to compounds of similar chemical or biologic composition to AZD1775 or olaparib.

3.2.2 Use of anti-cancer treatment drug ≤28 days or 5 half-lives (whichever is shorter) prior to the first dose of study treatment. For drugs for which 5 half-lives is ≤21 days, a minimum of 10 days between termination of the prior treatment and administration of study treatment is required.

3.2.3 Use of radiotherapy (except for palliative reasons) within ≤28 days prior to study treatment.

3.2.4 No other anti-cancer therapy (chemotherapy, immunotherapy, hormonal anticancer therapy radiotherapy), biological therapy or other novel agent is to be permitted while the patient is receiving study medication. Patients with castration-resistant prostate cancer on luteinizing hormone-releasing hormone (LHRH) analogue treatment for more than 6 months are allowed entry into the study and may continue at the discretion of the investigator.

3.2.5 Concomitant use of CYP3A inducers/inhibitors:

- Concomitant use of known strong CYP3A inhibitors (e.g., itraconazole, telithromycin, clarithromycin, protease inhibitors boosted with ritonavir or cobicistat, indinavir, saquinavir, nelfinavir, boceprevir, telaprevir) or moderate CYP3A inhibitors (e.g., ciprofloxacin, erythromycin, diltiazem, fluconazole, verapamil). The required washout period prior to starting olaparib is 2 weeks.
- Concomitant use of known strong (e.g., phenobarbital, enzalutamide, phenytoin, rifampicin, rifabutin, rifapentine, carbamazepine, nevirapine and St John's Wort) or moderate CYP3A inducers (e.g., bosentan, efavirenz, modafinil). The required washout period prior to starting study treatment is 5 weeks for enzalutamide or phenobarbital and 3 weeks for other agents.

3.2.6 Major surgical procedures ≤28 days of beginning study treatment, or minor surgical procedures ≤7 days. Patients must have recovered from any of the effects of any major surgery. No waiting period required following port-a-cath placement or other central venous access placement.

3.2.7 Known malignant central nervous system (CNS) disease other than neurologically stable, treated brain metastases – defined as metastasis having no evidence of progression or hemorrhage for at least 2 weeks after treatment (including brain radiotherapy). Must be off any systemic corticosteroids for the treatment of brain metastases for at least 14 days prior to enrollment. Subjects with brain metastases

must have completed treatment, either surgery or radiation, and be stable for at least 28 days off steroid prior to screening. A brain MRI demonstrating there is no current evidence or progressive brain metastases is required in subjects with previous brain metastasis. Patients with breast tissue expanders may have brain CT for assessment.

3.2.8 Patients with either previous or current myelodysplastic syndrome (MDS)/acute myeloid leukemia (AML) or features suggestive of MDS/AML (*e.g.*, persistent anemia or other blood dyscrasias) are excluded because olaparib and AZD1775 are agents with the potential to induce MDS/AML.

3.2.9 AZD1775 should not be given to patients who have a history of Torsades de pointes (TdP) unless all risk factors that contributed to TdP have been corrected.

3.2.10 Any of the following cardiac diseases currently or within the last 6 months:
- Unstable angina pectoris
- Acute myocardial infarction
- Congestive heart failure ≥ Class 2 (as defined by New York Heart Association (NYHA))
- Conduction abnormality not controlled with pacemaker or medication
- Significant ventricular or supraventricular arrhythmias (patients with chronic rate-controlled atrial fibrillation in the absence of other cardiac abnormalities are eligible)

3.2.11 Participants with a mean resting corrected QT interval (QTc) ≥ 480msec at study entry, as calculated by the Frederica formula (QTcF) by institutional standards obtained from an electrocardiogram (ECG) or congenital long QT syndrome. (Note: if one ECG demonstrates a QTcF >480 msec, then a mean QTcF of ≤ 480 msec obtained from 3 ECGs 2-5 minutes apart is required at study entry.

3.2.12 Patients considered a poor medical risk due to a serious, uncontrolled medical disorder, non-malignant systemic disease or active, uncontrolled infection. Examples include, but are not limited to, uncontrolled ventricular arrhythmia, recent (within 3 months) myocardial infarction, uncontrolled major seizure disorder, unstable spinal cord compression, superior vena cava syndrome, extensive interstitial bilateral lung disease on High Resolution Computed Tomography (HRCT) scan or any psychiatric disorder that prohibits obtaining informed consent..

3.2.13 Patients with uncontrolled intercurrent illness.

3.2.14 Patients with psychiatric illness/social situations, or other psychological, familial, sociological, or geographical conditions that would limit compliance with study requirements.

3.2.15 Persistent grade >1 toxicity from prior cancer therapy (except alopecia).

3.2.16 Patients with previous allogeneic, bone marrow, or double umbilical cord blood transplants are not allowed.

3.2.17 Consumption of grapefruit juice while on study drugs.

3.2.18 Involvement in the planning and/or conduct of the study.

3.2.19 Patients unable to swallow orally administered medications and patients with gastrointestinal disorders likely to interfere with absorption of the study medication.

3.2.20 Pregnant or breastfeeding women are excluded from this study because AZD1775 and olaparib are agents with the potential for teratogenic or abortifacient effects. Because there is an unknown but potential risk for adverse events in nursing infants secondary to treatment of the mother with AZD1775 and olaparib, breastfeeding should be discontinued if the mother is treated with AZD1775 and olaparib.

3.2.21 Other malignancy unless curatively treated with no evidence of disease for ≥5 years exept: adequalty treated non-melanoma skin cancer, curatively treated in situ cancer of the cervix, ductal carcinoma in situ (DCIS), Stage 1, grade 1 endometrial carcinoma.

3.3 Inclusion of Women and Minorities

NIH policy requires that women and members of minority groups and their subpopulations be included in all NIH-supported biomedical and behavioral research projects involving NIH-defined clinical research unless a clear and compelling rationale and justification establishes to the satisfaction of the funding Institute & Center (IC) Director that inclusion is inappropriate with respect to the health of the subjects or the purpose of the research. Exclusion under other circumstances must be designated by the Director, NIH, upon the recommendation of an IC Director based on a compelling rationale and justification. Cost is not an acceptable reason for exclusion except when the study would duplicate data from other sources. Women of childbearing potential should not be routinely excluded from participation in clinical research. Please see http://grants.nih.gov/grants/funding/phs398/phs398.pdf.

4. REGISTRATION PROCEDURES

4.1 Investigator and Research Associate Registration with CTEP

Food and Drug Administration (FDA) regulations and National Cancer Institute (NCI) policy require all individuals contributing to NCI-sponsored trials to register and to renew their registration annually. To register, all individuals must obtain a Cancer Therapy Evaluation

Program (CTEP) Identity and Access Management (IAM) account at https://ctepcore.nci.nih.gov/iam. In addition, persons with a registration type of Investigator (IVR), Non-Physician Investigator (NPIVR), or Associate Plus (AP) must complete their annual registration using CTEP's web-based Registration and Credential Repository (RCR) at https://ctepcore.nci.nih.gov/rcr.

RCR utilizes five person registration types.

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

RCR requires the following registration documents:

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

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

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

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

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

4.2 Site Registration

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

IRB Approval

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

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

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

In addition, the Site-Protocol PI (*i.e.*, the investigator on the IRB/REB approval) must meet the following five criteria to complete processing of the IRB/REB approval record:

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

Additional Requirements

Additional requirements to obtain an approved site registration status include:

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

4.2.1 Downloading Regulatory Documents

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

- Log on to the CTSU members' website (https://www.ctsu.org) using your CTEP-IAM username and password,
- Click on *Protocols* in the upper left of your screen
    - Enter the protocol number in the search field at the top of the protocol tree, or
    - Click on the By Lead Organization folder to expand, then select LAO-TX035, and protocol number 10329,
- Click on *Documents*, select *Site Registration*, and download and complete the forms provided. (Note: For sites under the CIRB initiative, IRB data will load automatically to the CTSU.)

4.2.2 Requirements For 10329 Site Registration

- Specimen Tracking System Training Requirement:
    - All data entry users (Clinical Research Associate role) at each participating site will need to complete the Theradex-led training.
    - Theradex will provide a certificate of completion, which will need to be submitted to the CTSU through the Regulatory Submission Portal.

- The training is a one-time only requirement per individual. If an individual has previously completed the training for another ETCTN study, the training does not need to be completed again nor does the certificate of completion need to be resubmitted to the CTSU. However, new versions of the Specimen Tracking system may require new training.
- This training will need to be completed before the first patient enrollment at a given site.
- Please contact STS Support at Theradex for the training (STS.Support@theradex.com, Theradex phone: 609-799-7580)

4.2.3 Submitting Regulatory Documents

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

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

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

Delegation of Tasks Log (DTL)

Each site must complete a protocol-specific DTL using the DTL application in the Delegation Log section on the CTSU members' website. The Clinical Investigator (CI) is required to review and electronically sign the DTL prior to the site receiving an Approved site registration status and enrolling patients to the study. To maintain an approved site registration status the CI must re-sign the DTL at least annually and when a new version of the DTL is released; and activate new task assignments requiring CI sign-off. Any individual at the enrolling site on a participating roster may initiate the site DTL. Once the DTL is submitted for CI approval, only the designated DTL Administrators or the CI may update the DTL. Instructions on completing the DTL are available in the Help Topics button in the DTL application and include a Master Task List, which describes DTL task assignments, CI signature, and CTEP registration requirements.

4.2.4 Checking Site Registration Status

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

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

- Additional filters are available to sort by Protocol, Registration Status, Protocol Status, and/or IRB Type.

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

4.3 Patient Registration

4.3.1 OPEN / IWRS

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

Requirements for OPEN access:

- A valid CTEP-IAM account.
- To perform enrollments or request slot reservations: Be on an LPO roster, ETCTN Corresponding roster, or Participating Organization roster with the role of Registrar. Registrars must hold a minimum of an AP registration type.
- The registrar(s) must hold the OPEN Registrar task on the DTL for the site.
- Have an approved site registration for a protocol prior to patient enrollment.

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

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

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

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

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

Patient enrollment for this study will be facilitated using the Slot Reservation System in conjunction with the registration system in OPEN. Prior to discussing protocol entry with the patient, all site staff must use the CTSU OPEN Slot Reservation System to ensure that a slot on the protocol is available to the patient. Once a slot reservation confirmation is obtained, site staff may then proceed to enroll the patient to this study.

4.3.2 Special Instructions for Patient Enrollment

This Study will use the ETCTN Specimen Tracking System (STS).

- All biospecimens collected for this trial must be submitted using the ETCTN Specimen Tracking System (STS) unless otherwise noted.
- The system is accessed through special Rave user roles: "CRA Specimen Tracking" for data entry at the treating institutions and "Biorepository" for users receiving the specimens for processing and storage at reference labs and the Biorepository.
- Please refer to the Medidata Account Activation and Study Invitation Acceptance link on the CTSU website under the Rave/DQP tab.
- **Important: Failure to complete required fields in STS may result in a delay in sample processing.** Any case reimbursements associated with sample submissions will not be credited if samples requiring STS submission are not logged into STS.

Detailed instructions can be found in Section 5.4.

4.3.3 OPEN/IWRS Questions?

Further instructional information on OPEN is provided on the OPEN tab of the CTSU website at https://www.ctsu.org or at https://open.ctsu.org. For any additional questions contact the CTSU Help Desk at 1-888-823-5923 or ctsucontact@westat.com.

Theradex has developed a Slot Reservations and Cohort Management User Guide, which is available on the Theradex website: http://www.theradex.com/clinicalTechnologies/?National-Cancer-Institute-NCI-11. This link to the Theradex website is also on the CTSU website OPEN tab. For questions about the use of IWRS for slot reservations, contact the Theradex Helpdesk at 609-619-7862 or Theradex main number 609-799-7580; CTMSSupport@theradex.com.

4.4 General Guidelines

Following registration, patients should begin protocol treatment within 8 days. Issues that would cause treatment delays should be discussed with the Principal Investigator. If a patient does not receive protocol therapy following registration, the patient's registration on the study may be canceled. The Study Coordinator should be notified of cancellations as soon as possible.

5. BIOMARKER, CORRELATIVE, AND SPECIAL STUDIES

5.1 Summary Table for Specimen Collection

Time Point	Specimen	Send Specimens To:
Baseline[1,2]		
	• 3 tumor cores, snap frozen • 1 tumor core, FFPE • 20 mL blood in Streck cfDNAtubes	EET Biobank
Cycle 1, Day 12[1,2]		
	• 3 tumor cores, snap frozen • 1 tumor core, FFPE • 20 mL blood Streck cfDNA tubes	EET Biobank
Each Restaging[1]		
	• 20 mL blood Streck cfDNA tubes	EET Biobank
Progression[1,2]		
	• 3 tumor cores, snap frozen (optional) • 1 tumor core, FFPE (optional) • 20 mL blood Streck cfDNA tubes	EET Biobank

[1]All samples are mandatory except tissue at time of progression.
[2]For new biopsies, the Tissue Biopsy Verification Form (Appendix H), a copy of the radiology and/or operative reports from the tissue removal procedure *and* the diagnostic anatomic pathology report must be sent with the tissue to the EET Biobank.

5.2 Summary Table(s) for Interventional Radiologist for Research Biopsies

Biopsy #: 1				
Trial Time Point: Baseline				
IR Biopsy Definition: Research – No Clinical Impact				
Core Priority	**Use in the Trial**	**Biomarker Name(s)**	**Tumor Content Required**	**Post-Biopsy Processing**
1	Integrated	Proteomic Analysis	>50%	Snap Frozen
2	Exploratory	WES/RNAseq	>50%	Snap Frozen
3	Exploratory	γH2AX and pRAD50 IHC and cycIF/mIHC	>50%	FFPE

4	Exploratory	scRNAseq	>50%	Snap Frozen

Biopsy #: 2				
Trial Time Point: Cycle 1, Day 12				
IR Biopsy Definition: Research – No Clinical Impact				
Core Priority	**Use in the Trial**	**Biomarker Name(s)**	**Tumor Content Required**	**Post-Biopsy Processing**
1	Integrated	Proteomic Analysis	>50%	Snap Frozen
2	Exploratory	WES/RNAseq	>50%	Snap Frozen
3	Exploratory	γH2AX and pRAD50 IHC and cycIF/mIHC	>50%	FFPE
3	Exploratory	scRNAseq	>50%	Snap Frozen

Biopsy #: 3				
Trial Time Point: Disease Progression (optional biopsy)				
IR Biopsy Definition: Research – No Clinical Impact				
Core Priority	**Use in the Trial**	**Biomarker Name(s)**	**Tumor Content Required**	**Post-Biopsy Processing**
1	Integrated	Proteomic Analysis	>50%	Snap Frozen
2	Exploratory	WES/RNAseq	>50%	Snap Frozen
3	Exploratory	γH2AX and pRAD50 IHC and cycIF/mIHC	>50%	FFPE
3	Exploratory	scRNAseq	>50%	Snap Frozen

Note: Pre-biopsy assessments will be reported and tracked through a trial-specific CRF within the CTEP Medidata Rave system (see Appendix B).

5.3 Specimen Procurement Kits and Scheduling

5.3.1 Specimen Procurement Kits

Kits for the collection and shipment of blood in Streck cfDNA tubes to the EET Biobank can be ordered online via the Kit Management system: (https://ricapps.nationwidechildrens.org/KitManagement).

Users at the clinical sites will need to set up an account in the Kit Management system and select a specific clinical trial protocol to request a kit. Please note that protocol may include more than one type of kit. Each user may order two kit types per protocol per day (daily max = 6 kits). Kits are shipped ground, so please allow 5-7 days for receipt. A complete list of kit contents for each kit type is located on the Kit Management system website.

5.3.2 Scheduling of Specimen Collections

5.3.3 Specimen Collections at the EET Biobank

Please adhere to the following guidelines when scheduling procedures to collect samples:

- Tumor tissue specimens collected during biopsy procedures and paraffin embedded and fixed in formalin must be shipped on the same day of collection. FFPE tissue can be collected Monday through Wednesday and shipped overnight for arrival on Tuesday through Thursday at the EET Biobank at Nationwide Children's Hospital.

- **Frozen Tissue:** Tumor tissue submitted frozen can be collected on any day but must be stored frozen and shipped to the EET Biobank on Monday through Thursday. In the event that frozen specimens cannot be shipped immediately, they must be maintained in a -70°C to -80°C freezer.

- **Fresh Blood:** Fresh blood specimens may be collected and shipped Monday through Friday.

- FFPE Tumor Cores: Tumor tissue specimens collected during biopsy procedures fixed in formalin and paraffin embedded can be collected on any day but must be shipped to the EET Biobank on Monday through Thursday.

5.4 Specimen Tracking System Instructions

5.4.1 Specimen Tracking System Overview and Enrollment Instructions

For the ETCTN STS, the following information will be requested:

- Protocol Number
- Investigator Identification
  - Institution and affiliate name
  - Investigator's name
- Eligibility Verification: Patients must meet all the eligibility requirements listed in Section 3.
- Additional Requirements:
  - Patients must provide a signed and dated, written informed consent form.

Upon enrolling a patient, IWRS will communicate with OPEN, assigning two separate and unique identification numbers to the patient, a Universal patient ID (UPID) and a Treatment patient ID. The UPID is associated with the patient and used each and every time the patient engages with the portion of this or any other protocol that uses the ETCTN Specimen Tracking System. The UPID contains no information or link to the treatment protocol. IWRS will maintain an association between the UPID for ETCTN biobanking and molecular characterization and any treatment protocols the patient participates in, thereby allowing analysis of the molecular characterization results with the clinical data.

Immediately following enrollment, the institutional anatomical pathology report for the diagnosis under which the patient is being enrolled must be uploaded into Rave. The report must include the surgical pathology ID (SPID), collection date, block number, and the IWRS-assigned UPID and patient study ID for this trial. For newly acquired biopsies, the radiology and operative report(s) must also be uploaded into Rave. **Important: Remove any personally identifying information, including, but not limited to, the patient's name, date of birth, initials, medical record number, and patient contact information from the institutional pathology report prior to submission.**

Additionally, please note that the STS software creates pop-up windows when reports are generated, so you will need to enable pop-ups within your web browser while using the software.

For questions regarding the Specimen Tracking System, please contact STS Support at STS.Support@theradex.com.

The Shipping List **must** be included with all sample submissions.

5.4.2 Specimen Labeling

5.4.2.1 Blood Specimen Labels

Include the following on blood specimens (including whole blood and frozen, processed blood products – like serum and plasma):

- Patient Study ID
- Universal Patient ID (UPID)
- Specimen ID (automatically generated by Rave)
- Time point
- Specimen type (*e.g.*, blood)
- Collection date (to be added by hand)

5.4.2.2 Tissue Specimen Labels

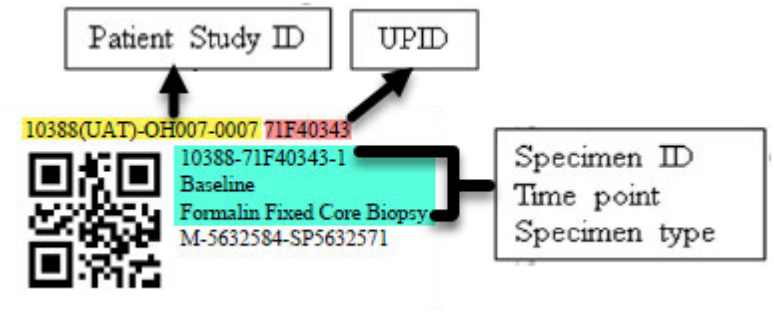
Include the following on all tissue specimens or containers:

- Patient Study ID
- Universal Patient ID (UPID)
- Specimen ID (automatically generated by Rave)
- Time point
- Specimen type (*e.g.*, formalin-fixed paraffin-embedded [FFPE] Block, Frozen Tissue)
- Tissue type (P for primary, M for metastatic or N for normal)
- Surgical pathology ID (SPID) number (if applicable)
- Block number from the corresponding pathology report (archival only)
- Collection date (to be added by hand)

5.4.2.3 Example of Specimen Label Generated by STS

STS includes a label printing facility, accessed va the Print Label CRF in the All Specimens folder. A generated PDF is emailed to the user as a result of saving that form.

The following image is an example of a tissue specimen label printed on a label that is 0.5" high and 1.28" wide.



The QR code in the above example is for the Specimen ID shown on the second line.

Labels may be printed on a special purpose label printer, one label at a time, or on a standard laser printer, multiple labels per page. Theradex recommends the use of these low temperature waterproof labels for standard laser printers:
https://www.labtag.com/shop/product/cryo-laser-labels-1-28-x-0-5-cl-23-colors-available/

The last line item on the label includes the following data points joined together:

1. Tissue only: Primary (P), Metastatic (M), Normal (N) tissue indicated at the beginning of the specimen ID; this field is blank if not relevant (*e.g.*, for blood)
2. Block ID or blank if not relevant
3. SPID (Surgical Pathology ID) or blank if none
4. An alpha-numeric code is protocol specific and is only included if the protocol requires an additional special code classification

Space is provided at the bottom of the label for the handwritten date and optional time. The last line on the example label is for the handwritten date and optional time.

5.4.3 Overview of Process at Treating Site

5.4.3.1 OPEN Registration

All registrations will be performed using the Oncology Patient Enrollment Network (OPEN) system. OPEN communicates automatically with the Interactive Web Response System (IWRS) which handles identifier assignments, any study randomization, and any prescribed slot assignments. If specimen analysis is required to determine eligibility, the protocol will be setup with multi-step registration.

Registration without eligibility specimen analysis:

1. Site enters registration data into OPEN during one or more steps.
2. IWRS receives data from OPEN, generates the Patient Study ID and the Universal Patient ID, both of which are sent back to OPEN.
3. IWRS sends all applicable registration data directly to Rave at the end of the final registration step.

Any data entry errors made during enrollment should be corrected in Rave.

5.4.3.2 Rave Specimen Tracking Process Steps

Step 0: Log into Rave via your CTEP-IAM account, then navigate to the appropriate participant.

Step 1: Complete the **Histology and Disease** form (but do not upload reports until a specimen label can be applied to them) and the Baseline forms regarding **Prior Therapies**. Enter the initial clinical specimen data:

- **Specimen Tracking Enrollment** CRF: Enter Time Point, Specimen Category, Specimen Type, Block number, Tissue type, Surgical Path ID, and number of labels needed (include extra labels to apply to reports to be uploaded). CRF generates unique Specimen ID.

Step 2: Print labels using the **Print Labels** CRF located in the All Specimens folder, then collect specimen.

- Label specimen containers and write collection date on each label.
- After collection, store labeled specimens as described in Section 5.4.2.
- Apply an extra specimen label to *each* report before scanning. Return to the **Histology and Disease** form to upload any initial Pathology, Radiology, Molecular Reports (up to 4), Surgical (or Operative) reports and Tissue Biopsy Verification form (when applicable). Return to **Specimen Tracking Enrollment** CRF to upload any molecular report (one per specimen) and/or specimen specific pathology or related report (one per specimen). Uploaded reports should have protected health information (PHI) data, like name, date of birth, mailing address, medical record number or social security number (SSN), redacted. Do not redact SPID, block number , diagnosis or relevant dates, and include the UPID and patient study ID on each document.

Step 3: Complete specimen data entry.

- **Specimen Transmittal** Form: Enter collection date and time and other required specimen details.

Step 4: When ready to ship, enter shipment information.

- **Shipping Status** CRF: Enter tracking number, your contact information, recipient, number of containers and ship date once for the first specimen in a shipment.
- **Copy Shipping** CRF: In the specimen folders for additional specimens (if any) that will be shipped with the initial specimen, please use the **Copy Shipping** form to derive common data into the additional **Shipping Status** forms. A few unique fields will still need to be entered in Shipping Status.

Step 5: Print shipping list report and prepare to ship.

- Shipping List report is available at the site level.
- Print two copies of the shipping list, one to provide in the box, the other for your own records.
- Print pathology or other required reports to include in the box. Be sure the printed copy includes the specimen label.

Step 6: Send email notification.

- For only one of the specimens in the shipment, click "Send Email Alert" checkbox on the **Shipping Status** CRF to email recipient.

Step 7: Ship the specimen(s).

Step 8: Monitor the Receiving Status form located in each specimen folder for acknowledgment of receipt and adequacy.

5.5 Specimen Collection

5.5.1 Core Needle Biopsy (CNB) and Other Small Biopsy Specimens

A maximum number of 3 cores (1 cm in length) or small biopsies (3 mm diameter) will be obtained from the procedure. The number of specimens obtained will be affected by the patient's clinical condition at the time of biopsy and determined by the specialist performing the procedure. Core biopsy should be performed using a 16-18-gauge needle, condition permitting.

- Number of Cores: Two cores (1 cm in length) or small biopsies (3 mm diameter) should be obtained for proteomic RPPA analysis and nucleic acid analysis (WES and RNAseq) at the MD Anderson RPPA Core Laboratory and the NCLN Genomics Laboratory, respectively. One core (1 cm in length) or small biopsy (3 mm diameter) should be obtained for γH2AX/pRAD50 IHC and cycIF/mIHC and one core (1 cm in length) or small biopsy (3 mm diameter) should be obtained for scRNAseq at Oregon Health & Science University (Dr. Gordon Mills). Alternating passes: First obtain 1 core for RPPA (snap freezing), followed by 1 core for WES and RNAseq (snap freezing), followed by 1 core for γH2AX/pRAD50 IHC and cycIF/mIHC (FFPE), followed by 1 core for scRNAseq (snap freezing).

5.5.1.1 Formalin-Fixed Paraffin-Embedded (FFPE)Tumor Biopsies

At each time point, one core should be fixed in formalin for 12-24 hours and then embedded in paraffin.

See Section 5.4.2 for labeling instructions.

5.5.1.2 Collection of Snap-Frozen Biopsies for WES and RNAseq

1. Tissue should be frozen as soon as possible. Optimally, freeze within 30 minutes from resection.
2. Label cryovial(s) according to instructions in Section 5.4.2.
3. Using clean forceps, place the tissue in a cryovial and freeze the tube in either vapor phase liquid nitrogen, on dry ice, or by immediate placement in a -70 to -80°C freezer. Keep frozen until shipment to the EET Biobank.

5.5.1.3 Collection of Snap-Frozen Core Needle Biopsies for RPPA

1. Label collection tubes according to instructions in section 5.4.2.
    1. Arrive at the biopsy collection site early enough to allow sufficient time to set up laboratory supplies, collect relevant clinical information, and ensure rapid transport of specimens to the laboratory for placement at -80ºC (or lower) after collection.
    2. Bring all necessary lab supplies including: disposable tweezers, a minimum of two 1.5-mL Sarstedt tubes (one for each whole biopsy core) pre-cooled on liquid nitrogen or dry ice/ethanol in an insulated bucket, and one pre-printed specimen label (see Section 5.4.1.1) to give to the research nurse for the patient record.
    Note: Pre-chill additional 1.5-mL Sarstedt tubes for specimen collection in case the interventional radiologist collects additional passes, or one of the other tubes is compromised prior to collection.
    3. The total time elapsed between biopsy collection and placement into the pre-chilled tube is of **key importance** to biomarker analysis; biopsies should be frozen within **2 min** of collection. The interventional radiologist will eject the biopsy onto a sterile slide (for optimal analyte recovery the slide should be pre-chilled). Start a stop watch (or note the time) at this point (Appendix C, Biopsy Collection) and immediately walk the slide to the sample preparation table.
    Note: The preferred method of collection, when whole biopsies are collected, is for the interventional radiologist to eject the biopsy directly into the pre-chilled tube (next step). This minimizes the time between collection and fixation of analytes.
    4. Indicate if a full or halved biopsy is prepared in the Batch Record (Appendix C, Biopsy Collection).
        a. <u>For whole biopsies</u>: Uncap an empty, prechilled 1.5-mL Sarstedt tube and using disposable tweezers, pick up the freshly collected needle biopsy with the tweezers at one end, and touch the opposite end of the biopsy to the inner surface of the prechilled 1.5-mL Sarstedt tube. This should attach the tissue to the tube, allowing it to be dropped into the tube while releasing the tissue from the tweezers without sticking. Dispose of the tweezers in the appropriate biohazardous waste container(s).
        b. <u>For halved biopsies</u>: Use 1-2 disposable tweezers and cut/shear the biopsy in half cross-wise while it is on the slide (do not pull or stretch the biopsy longitudinally). Use the tweezers to transfer the halved biopsies to sterile pre-chilled tubes as indicated above.

5. Immediately snap freeze the biopsy by placing the tube in liquid nitrogen or a dry ice/ethanol bath.
6. Calculate the total time elapsed from biopsy collection to biopsy freezing and record the total number of minutes and seconds elapsed in the Batch Record (Appendix C, Biopsy Collection).
7. If biopsy procedure details can be obtained from the interventional radiologist or research nurse, record them in the Batch Record (Appendix C, Biopsy Procedure Details). Some information may not be available until a later time from the clinical staff.
8. Transfer the frozen biopsy specimen(s) to -80ºC (or lower) for storage until shipment to the EET Biobank. Record the date and time specimens are placed at -80ºC (or lower; Appendix C, Biopsy Storage).
9. Review and finalize the Batch Record and document ANY and ALL deviations in the Batch Record (Appendix C, Notes).
10. The appropriate laboratory personnel should review the Batch Record and sign to affirm the data contained within are correct (Appendix C, Review of Batch Record).

5.5.2 Collection of Blood in cfDNA Streck Tube

1. Label two 10 mL cfDNA Streck tube according to the instructions in Section 5.4.2.
2. Collect 20 mL of blood into the pre-labeled tube and gently invert to mix. **Note:** blood must be thoroughly mixed to ensure preservation of specimen. Heparin should be avoided in pre-collection flush procedures. If therapeutic heparin dosing contamination is a possibility, then venipuncture is recommended as a first choice collection method. If a cfDNA Streck tube immediately follows a heparin tube in the draw order, then collecting an EDTA tube as a waste tube prior to collection in the Streck Cell-Free DNA BCT is recommended.
3. **After collection, blood in cfDNA Streck tubes should never be refrigerated,** as this will compromise the specimen. Blood collected in cfDNA Streck tubes is stable at room temperature.

5.6 Shipping Specimens to the EET Biobank

5.6.1 General Shipping Information

Core biopsies that are fixed in formalin and paraffin embedded and fresh blood should be shipped as one shipment at ambient temperature, whenever possible. The same box sent with Streck cfDNA tubes should be used to ship blood to the EET Biobank. Frozen cores are shipped frozen on dry ice in a container provided by the institution. FFPE tissue is shipped ambient in a container provided by the institution.

For tissue from biopsies, if the corresponding anatomical pathology report is not available at the time of shipment, then the surgical and/or radiology reports from the tissue removal procedure and the diagnostic anatomic pathology report and Tissue Biopsy Verification Form (Appendix H) must be included in the package, or the specimen will not be processed. Once completed,

upload the corresponding pathology report to the ETCTN specimen trackind system and send a copu to the EET Biobank.

5.6.2 Specimen Shipping Instructions

- FFPE tissue must be shipped on Monday through Thursday.
- Frozen specimens may be shipped on Monday through Thursday.
- Fresh blood may be shipped on Monday through Friday. Please select "Saturday Delivery" when shipping fresh blood on a Friday.

5.6.2.1 Shipping of FFPE Blocks
1. Before packaging blocks, verify that each specimen is labeled according to Section 5.4.2.2.
2. Blocks should be placed in a hard-sided container, preferably a special block holder, to protect the specimen.
3. Place the blocks in a reinforced cardboard shipping box with appropriate packaging filler to minimize the movement of specimens within the shipping box.
4. Include a copy of the forms listed above and a shipping manifest from the Specimen Tracking System with each shipment.
5. Please include a cold pack when shipping on hot days and extra insulation on cold days.
6. Ship specimens to the address listed below. FedEx Priority Overnight is strongly recommended to prevent delays in package receipt.

5.6.2.2 Shipping Blood in an Ambient Shipper

1. Before packaging specimens, verify that each specimen is labeled according to the instructions above and that the lids of all primary receptacles containing liquid are tightly sealed.
2. Prepare the SAF-T-TEMP Gel Pak for shipment. **Note:** If contents of the Pak are crunchy, place Pak in a warm water bath until gel is smooth. **Do not refrigerate, freeze, or microwave.**
3. Place the SAF-T-TEMP Pak in bottom of insulated chest. **Note:** The insulated chest must be shipped inside the provided cardboard box(es).
4. Place the blood collection tubes in zip-lock bags.
5. Next, place blood into a biohazard envelope with absorbent material. Expel as much air as possible and seal the envelope securely.
6. Place the biohazard envelope into a Tyvek envelope. Expel as much air as possible and seal securely.
7. Place packaged blood collection tube(s) and a copy of the shipping manifest from the Sample Tracking System on top of SAF-T-TEMP Pak.
8. Place the lid on the insulated chest.
9. Close the outer flaps of the shipping box and tape shut.
10. Attach a shipping label to the top of the shipping container.
11. Attach an Exempt Human Specimen sticker to the side of the box.
12. Ship specimens via overnight courier to the address below. FedEx Priority Overnight is strongly recommended to prevent delays in package receipt.

5.6.2.3 Shipping Frozen Specimens in an Insulated Shipping Container

1. Before packaging specimens, verify that each specimen is labeled according to the instructions above and that lids of all primary receptacles containing liquid are tightly sealed.
2. Place the specimens in zip-lock bags. Use a separate zip-lock bag for each specimen type and time point.
3. Place the zip-lock bags in the biohazard envelope containing absorbent material. Expel as much air as possible and seal securely.
4. Put the secondary envelope into a Tyvek envelope. Expel as much air as possible and seal securely.
5. Place frozen specimens in an insulated shipping container with dry ice. Layer the bottom of the container with dry ice until it is approximately one-third full. Place the frozen specimens on top of the dry ice. Cover the specimens with the dry ice until the compartment is almost completely full. When packaging specimens, ensure that you leave enough room to include at least 5 pounds of dry ice in the shipment.
6. Insert a copy of the required forms into a plastic bag and place in the shipping container.
7. Place the lid on top to secure specimens during shipment.
8. Close the flaps of the outer box and tape it shut with durable sealing tape. Do not completely seal the container.
9. Complete a FedEx air bill and attach to top of shipping container.
10. Complete a dry ice label.
11. Attach the dry ice label and an Exempt Human Specimen sticker to the side of the shipping container.
12. Ship specimens via overnight courier to the address below. FedEx Priority Overnight is strongly recommended to prevent delays in package receipt.

5.6.2.4 Shipping Frozen and Ambient Specimens in a Dual-Chamber Kit

The Dual-Chambered Specimen Procurement Kit is constructed to allow the shipment of frozen (on dry ice) and ambient (room temperature) specimens in the same container. **Dry ice may be placed in either compartment of the kit but should not be put in both.** The dual chambered kit is only used for shipments that contain both frozen and ambient specimens. If formalin-fixed tissue is shipped separately (not in the same shipment as frozen specimens), then it must be shipped using institutional shipping supplies.

- **Frozen specimens** may be shipped on Monday through Thursday. Ensure that sufficient dry ice is included to completely encase the specimens to maintain specimen integrity during shipment.
- **FFPE tissue** may only be shipped on Monday through Wednesday.

1. Before packaging specimens, verify that each specimen is labeled according to the instructions above and that lids of all primary receptacles containing liquid are

tightly sealed. If included in the shipment, formalin jar lids should be wrapped in parafilm.

2. Pre-fill one of the kit chambers about 1/3 with dry ice.
3. Place the specimens in zip-lock bags. Use a separate zip-lock bag for each specimen type.
4. Two biohazard envelopes are provided so that ambient and frozen specimens can be packaged separately.
   - Place the zip-lock bags containing room temperature specimens in a biohazard envelope with absorbent material. Expel as much air as possible and seal the envelope securely.
   - Place the zip-lock bags containing frozen specimens into the other biohazard envelope containing absorbent material. Expel as much air as possible and seal securely.
5. Put each secondary envelope into a Tyvek envelope. Expel as much air as possible and seal each envelope securely.
6. Quickly place the Tyvek envelope containing frozen specimens (*e.g.*, frozen tumor, serum, *etc.*) in the kit compartment that is pre-filled with dry ice. Place the Tyvek envelope on top of the dry ice. Cover the specimens with additional dry ice until the compartment is almost completely full.
7. Place the Styrofoam lid on top to secure specimens during shipment. Do not tape the inner chamber shut.
8. Place the Tyvek envelope containing ambient temperature specimens (*e.g.*, formalin-fixed tissue) in the other kit compartment at room temperature.
9. Insert a copy of the required forms into a plastic bag and place in the kit chamber with the ambient specimens.
10. Place the Styrofoam lid on top of the kit compartment to secure specimens during shipment. Do not tape the inner chamber shut.
11. Close the outer lid of the Specimen Procurement Kit and tape it shut with durable sealing tape. Do not completely seal the container.
12. Complete a FedEx air bill and attach to top of shipping container.
13. Complete a dry ice label.
14. Attach the dry ice label and an Exempt Human Specimen sticker to the side of the shipping container.
15. Ship specimens via overnight courier to the address below. FedEx Priority Overnight is strongly recommended to prevent delays in package receipt.

5.6.3 Shipping Address

Ship to the address below. Ship formalin-fixed and fresh blood specimens the same day of specimen collection. Do not ship specimens the day before a holiday.

EET Biobank
The Research Institute at Nationwide Children's Hospital
700 Children's Drive, WA1340
Columbus, Ohio 43205
PH: (614) 722-2865

FAX: (614) 722-2897
Email: BPCBank@nationwidechildrens.org

FedEx Priority Overnight service is very strongly preferred.

NOTE: The EET Biobank FedEx Account will not be provided to submitting institutions.

5.6.4 Contact Information for Assistance

For all queries, please use the contact information below:

EET Biobank
Toll-free Phone: (800) 347-2486
E-mail: BPCBank@nationwidechildrens.org

5.7 Biomarker Plan

List of Biomarker Assays in Order of Priority

Priority	Biomarker Name	Assay (CLIA: Y/N)	Use in the Trial and Purpose	Specimens Tested	Collection Time Points	Mandatory or Optional	Assay Laboratory and Lab PI
Tissue-Based Biomarkers							
N/A	*BRCA* mutations	NGS or equivalent (any local CLIA-certified assay will be accepted)	Integral To qualify for *BRCA* aberration cohort.	Archival tumor tissue	• Prior to Registration	• Optional for Dose Escalation • Mandatory for Dose Expansion	MD Anderson or Local CLIA-Certified Laboratory
N/A	*DDR* mutations	NGS or equivalent (any local CLIA-certified assay will be accepted)	Integral To qualify for *DDR* aberration cohort.	Archival tumor tissue	• Prior to Registration	• Optional for Dose Escalation • Mandatory for Dose Expansion	MD Anderson or Local CLIA-Certified Laboratory
1	Proteomic Analysis (RPPA)	Reverse Phase Protein Array (RPPA) CLIA: N	Integrated To assess treatment induced changes in G2 cell cycle proteins in order to correlate with treatment response and progression; to assess changes in the levels of G2 cell cycle proteins including: FOXM1, CDC-(Y15), Cyclin B1, pRB, pWEE1, CHK1/pCHK1, CHK2/pCHK2, ATM/pATM, CDK1.	Tumor tissue (snap frozen)	• Baseline • Cycle 1, Day 12 • Disease progression	• Mandatory • Optional at disease progression	Functional Proteomics RPPA Core Facility, MD Anderson Cancer Center (MDACC)Yiling Lu yilinglu@mdanderson.org
2	Genomic Analysis (WES)	Next Generation Sequencing CLIA: N	Exploratory To correlate SNV and CNV profiles with treatment response.	DNA from Tumor tissue (snap frozen)	• Baseline • Disease progression	• Mandatory • Optional at disease progression	NCLN Genomics Laboratory or MoCha, Frederick National Laboratory for Cancer Research (FNLCR) Mickey Williams mickey.williams@nih.gov

Priority	Biomarker Name	Assay (CLIA: Y/N)	Use in the Trial and Purpose	Specimens Tested	Collection Time Points	Mandatory or Optional	Assay Laboratory and Lab PI
3	Gene Expression Analysis (RNAseq)	Next Generation Sequencing CLIA: N	Exploratory To correlate gene expression profiles with treatment response.	RNA from Tumor tissue (snap frozen)	• Baseline • Cycle 1, Day 12 • Disease progression	• Mandatory • Optional at disease progression	NCLN Genomics Laboratory or MoCha, Frederick National Laboratory for Cancer Research (FNLCR) Mickey Williams mickey.williams@nih.gov
4	γH2AX and pRAD50 IHC and cycIF/mIHC	IHC CLIA: N	Exploratory To measure overall DNA damage and WEE1 inhibition efficacy; To assess the activity of PARP as indicated by PARylation and changes in potential adaptive resistance pathways including AKT and RAS/MAPK pathway activity; To assess the effects of olaparib on the immune system including interferon signaling and lymphocyte infiltration; To assess the effects of olaparib on replication stress, DNA damage, and decreased cell cycle blockade; To assess the effects of WEE1 inhibition on replication stress, DNA damage, and decreased cell cycle blockade; To assess the effects of the combination on apoptosis.	Tumor tissue (FFPE)	• Baseline • Cycle 1, Day 12 • Disease progression	• Mandatory • Optional at disease progression	Oregon Health & Science University Gordon Mills, MD millsg@ohsu.edu
5	scRNAseq	scRNAseq CLIA: N	Exploratory To assess the transcriptome at single-cell resolution	Tumor tissue (snap frozen)	• Baseline • Cycle 1, Day 12 • Disease progression	• Mandatory • Optional at disease progression	Oregon Health & Science University Gordon Mills, MD millsg@ohsu.edu
Blood-Based Biomarkers							

Priority	Biomarker Name	Assay (CLIA: Y/N)	Use in the Trial and Purpose	Specimens Tested	Collection Time Points	Mandatory or Optional	Assay Laboratory and Lab PI
1	Circulating Tumor DNA (ctDNA) Analysis	Next Generation Sequencing CLIA: N	Exploratory To correlate ctDNA mutation profiles with tumor sequencing; correlate baseline ctDNA mutations with treatment response; and correlate changes in ctDNA variant allele frequencies with responses; assess emergent resistant mutations at progression, including BRCA reversion.	Plasma from Blood in Streck cfDNA tubes	• Baseline • Cycle 1, Day 12 • Each Restaging • Disease progression	• Mandatory	NCLN Genomics Laboratory or MoCha, Frederick National Laboratory for Cancer Research (FNLCR) Mickey Williams mickey.williams@nih.gov
2	Genomic Analysis (WES)	Next Generation Sequencing CLIA: N	Exploratory To remove patient specific germline polymorphisms and improve the detection of somatic tumor mutations	Germline DNA from Blood in Streck cfDNA tube	• Baseline	• Mandatory	NCLN Genomics Laboratory or MoCha, Frederick National Laboratory for Cancer Research (FNLCR) Mickey Williams mickey.williams@nih.gov

5.8 Integral Correlative Studies

5.8.1 BRCA Mutations

BRCA mutation status will be evaluated prior to registration. Eligibility for the dose expansion Cohort A (with intrinsic resistance) will be based on the presence of germline or somatic mutations in *BRCA1* or *BRCA2*. All alterations will be reviewed by MD Anderson's Precision Oncology Decision Support (PODS) team. No VUS will be allowed as the qualifying genetic mutation .

5.8.1.1 Specimen Receipt and Processing

Local labs should process these samples per institutional SOPs as part of standard of care.

5.8.1.2 Site Performing Correlative Study

A local CLIA-certified laboratory or Dr. Timothy Yap at MD Anderson will analyze samples.

5.8.2 DDR Mutations

DDR mutation status will be evaluated prior to registration. Eligibility for the dose expansion Cohort B (with acquired resistance) will be based on the presence of any of the following DDR genes: *BRCA1, BRCA2, BRIP1, FANCA, PALB2,* or the non-DDR gene marker *Cyclin E amplification,* or other genes at the discretion of the principal investigator. All alterations will be reviewed by MD Anderson's Precision Oncology Decision Support (PODS) team. No VUS will be allowed as the qualifying genetic mutation.

5.8.2.1 Specimen Receipt and Processing

Local labs should process these samples per institutional SOPs as part of standard of care.

5.8.2.2 Site Performing Correlative Study

A local CLIA-certified laboratory or Dr. Timothy Yap at MD Anderson will analyze samples.

5.9 Integrated Correlative Studies

5.9.1 Proteomic Analysis via Reverse Phase Protein Array (RPPA)

RPPA-based proteomic analysis will be performed using 181 high-quality antibodies that target total (n=128), cleaved (n=1), acetylated (n=1) and phosphorylated forms (n=51) of proteins in patient samples. The function space covered by the antibodies used in the RPPA analysis encompasses major functional and signaling pathways of relevance to human cancer. Different batches of RPPA data will be merged using an algorithm, called Replicates Based Normalization

(RBN), which mitigates batch effects facilitating creation of a single protein dataset merging samples across different batches. Two-way unsupervised hierarchical clustering analysis will be used to discover the groups of biological objects sharing common characteristics, and a two-dimensional heat map to visualize protein expression patterns. To detect the discriminating biomarkers for each cluster (obtained by hierarchical clustering using the RPPA data normalized by RBN), LIMMA will be used to select biomarkers by comparing samples in each cluster with samples in all the other clusters together. In addition, pathway activity scores will be computed using a series of pathway predictors developed based on member proteins selected by literature review.

5.9.1.1 Specimen Receipt and Processing at the EET Biobank

Frozen tissue for RPPA will be stored in liquid nitrogen vapor phase at the EET Biobank until batch shipping to Dr. Yiling Lu at the Functional Proteomics RPPA Core Facility, MD Anderson Cancer Center (MDACC).

5.9.1.2 Site Performing Correlative Study

This assay will be performed by Dr. Yiling Lu at the Functional Proteomics RPPA Core Facility, MD Anderson Cancer Center (MDACC).

5.9.1.3 Shipment of Specimens from the EET Biobank to Site Performing Correlative Study

Prior to shipping specimens, set up an account with the Functional Proteomics RPPA Core Facility at MDACC at https://mdanderson.ilabsolutions.com. After an account has been set up, proceed to the RPPA Core iLab Page to submit a service request. The Functional Proteomics RPPA Core facility will review and approve all requests before the specimen is shipped to the address below:

Functional Proteomics RPPA Core Facility
Attn: Doris Siwak, PhD
6565 MD Anderson Blvd., Room Z4.2040
Houston, TX 77030

5.9.1.4 Contact information for Notification of Specimen Shipment

Yiling Lu (yilinglu@mdanderson.org)

5.10 Exploratory/Ancillary Correlative Studies

5.10.1 Genomic Analysis via Whole Exome Sequencing (WES)

5.10.1.1 Specimen Receipt and Processing at the EET Biobank

Frozen tissue specimens received from the collection site should be stored in liquid nitrogen vapor phase. DNA and RNA will be co-extracted from tumor tissue. The nucleic acids will be analyzed to determine concentration and quality. Aliquots of DNA and RNA will be shipped to the central sequencing laboratory for analysis.

At baseline, whole blood collected in Streck cfDNA tubes will be processed for plasma. DNA will be extracted from the blood following plasma removal. DNA and plasma will be stored at -80ºC until distribution for testing.

5.10.1.2 Site Performing Correlative Study

WES will be conducted in the NCLN Genomics Laboratory or MoCha, Frederick National Laboratory for Cancer Research (FNLCR) under the leadership of Mickey Williams, Ph.D.

5.10.1.3 Shipment of Specimens from the EET Biobank to Site Performing Correlative Study

Specimens will be shipped from the EET Biobank to one of the laboratories designated in Section 5.10.1.2.

5.10.1.4 Contact information for Notification of Specimen Shipment

Thomas Forbes (NCLNGenomicsReceiving@nih.gov)

5.10.2 Gene Expression Analysis via RNA Sequencing (RNAseq)

5.10.2.1 Specimen Receipt and Processing at the EET Biobank

Please see Section 5.10.1.1.

5.10.2.2 Site Performing Correlative Study
RNAseq will be conducted in the NCLN Genomics Laboratory or MoCha, Frederick National Laboratory for Cancer Research (FNLCR) under the leadership of Mickey Williams, Ph.D.

5.10.2.3 Shipment of Specimens from the EET Biobank to Site Performing Correlative Study

Specimens will be shipped from the EET Biobank to one of the laboratories designated in Section 5.10.2.2.

5.10.2.4 Contact information for Notification of Specimen Shipment

Thomas Forbes (NCLNGenomicsReceiving@nih.gov)

5.10.3 γH2AX and pRAD50 IHC and cycIF/mIHC

cycIF will assess the composition and molecular states of tumor cells and the microenvironment in which they live. Using the process of staining and registration, we will stain 48 proteins on FFPE sections using a cycIF analysis that proceeds through successive rounds of 5 color fluorescence staining (DAPI plus 4 immunofluorescence markers), imaging using Zeiss Axioscan, and hydrogen peroxide bleaching. We will assess over 150 proteins selected from 107 validated antibodies that interrogate aspects of differentiation, DNA damage repair, proliferation, architecture, immune cell composition, and aspects of the stroma and vasculature. Quantitative features are extracted by segmentation of each individual cell in the tissue, followed by measurement of its protein expression profile. Spatial information is distilled by relating neighboring cell-cell interactions, and identifying architectural patterns, such as tumor nests and islanda of resistance. This results in a high dimensional single-cell based feature space for each tissue and unsupervised clustering methods will be used to reduce the complexity and allow exploration of the molecular consequences of cell-cell interactions.

mIHC is a 36-plex IHC procedure that proceeds through repeated rounds of IHC staining, detection with AEC (3-amino-9-ethylcarbazole) chromagen, image acquisition using an Aperio scanner, removal of AEC with ethanol, and heating to strip antibodies. The panel of 17 distinct epitopes allows phenotyping of lymphoid and myeloid lineage cells and functional status of T cells.

5.10.3.1 Specimen Receipt and Processing at the EET Biobank

Upon receipt, FFPE tissue will be accessioned, barcoded, and stored at room temperature until distribution.

5.10.3.2 Site Performing Correlative Study

γH2AX and pRAD50 IHC and cycIF/mIHC will be performed by Dr. Gordon Mills at Oregon Health & Science University.

5.10.3.3 Shipment of Specimens from the EET Biobank to Site Performing Correlative Study

ATTN: Dong Zhang
Oregon Health & Science University
2730 S. Moody Ave.
KCRB Mills Lab 2001.14
Portland, OR 97201

5.10.3.4 Contact information for Notification of Specimen Shipment

Gordon Mills (millsg@ohsu.edu)

5.10.4 scRNAseq

scRNA-seq will be used to assay transcriptomes of several thousand cells from each tumor biopsy. The scRNASeq technology provides us with a unique tool to dissect the heterogeneous response in individual tumor cells to PARPinhibitor and WEE1 inhibitor treatment. Samples will be dissociated using standard single-cell nuclei extraction protocols, and scRNAseq performed using the 10x Chromium platform. Initial analysis will identify constituent cellular subtypes using unsupervised UMAP clustering algorithms. Transcriptome information will then be analyzed to identify key molecular pathways predominant in each cellular subtype and track changes in these pathways as they evolve in response to therapeutic stress at a single-cell level.

5.10.4.1 Specimen Receipt and Processing at the EET Biobank

Frozen tissue will be accessioned, barcoded, and stored in a liquid nitrogen freezer until distribution.

5.10.4.2 Site Performing Correlative Study

scRNAseq will be performed by Dr. Gordon Mills at Oregon Health & Science University.

5.10.4.3 Shipment of Specimens from the EET Biobank to Site Performing Correlative Study

ATTN: Dong Zhang
Oregon Health & Science University
2730 S. Moody Ave.
KCRB Mills Lab 2001.14
Portland, OR 97201

5.10.4.4 Contact information for Notification of Specimen Shipment

Gordon Mills (millsg@ohsu.edu)

5.10.5 Circulating Tumor DNA (ctDNA) Analysis via Next Generation Sequencing (NGS)

5.10.5.1 Specimen Receipt and Processing at the EET Biobank

Whole blood collected in Streck cfDNA tubes will be centrifuged to separate plasma. At baseline, residual blood will be processed for DNA; at other time points buffy coat will be processed and banked. Plasma and buffy coat aliquots will be stored in a -80°C freezer.

5.10.5.2 Site Performing Correlative Study

ctDNA Analysis will be conducted in the NCLN Genomics Laboratory or MoCha, Frederick National Laboratory for Cancer Research (FNLCR)under the leadership of Mickey Williams, Ph.D.

5.10.5.3 Shipment of Specimens from the EET Biobank to Site Performing Correlative Study

Specimens will be shipped from the EET Biobank to one of the laboratories designated in Section 5.10.5.2.

5.10.5.4 Contact information for Notification of Specimen Shipment

Thomas Forbes (NCLNGenomicsReceiving@nih.gov)

6. TREATMENT PLAN

6.1 Agent Administration

Treatment will be administered on an outpatient basis. Reported adverse events and potential risks are described in Section 10. Appropriate dose modifications are described in Section 7. No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the patient's malignancy.

Dose Escalation Phase						
Dose Level	**Olaparib**			**AZD1775**		
	Dose	**Frequency**	**Days**	**Dose**	**Frequency**	**Days**
2	300 mg	BID	1-5 15-19	300 mg	QD	8-12 22-26
1*	300 mg	BID	1-5 15-19	250 mg	QD	8-12 22-26
-1	200 mg	BID	1-5 15-19	200 mg	QD	8-12 22-26

*starting dose level. Alternative dosages and schedules may be pursued depending on toxicities from this trial, and PK, PD, and efficacy data generated from other trials.

**Either or both olaparib or AZD1775 may be reduced to 200mg BID or 200mg QD, respectively

All Dose Levels are conducted on a 28-day cycle.

BID = twice a day.

QD = once a day.

[redacted]

6.1.1 CTEP IND Investigational Agents

6.1.1.1 Olaparib

Patients will be administered olaparib BID, PO. Olaparib tablets should be taken at the same time each day, approximately 12 hours apart with one glass of water. The olaparib tablets should be swallowed whole and not chewed, crushed, dissolved or divided. Olaparib tablets can be

taken with or without food. Consumption of grapefruit, grapefruit juice, or Seville oranges while on olaparib therapy is prohibited.

If vomiting occurs shortly after the olaparib tablets are swallowed, the dose should only be replaced if all of the intact tablets can be seen and counted. Should any patient enrolled on the study miss a scheduled dose for whatever reason (*e.g.*, as a result of forgetting to take the tablets or vomiting), the patient will be allowed to take the scheduled dose up to a maximum of 2 hours after that scheduled dose time. If greater than 2 hours after the scheduled dose time, the missed dose is not to be taken and the patient should take their allotted dose at the next scheduled time.

6.1.1.2 AZD1775

[redacted]

[redacted]

6.2 Definition of Dose-Limiting Toxicity

6.2.1 Dose Limiting Toxicities in the Dose Escalation phase

Severity of AEs will be graded according to CTCAE v5.0. Management and dose modifications associated with the adverse events below are outlined in Section 7.

Any Grade 5 toxicities or any of the following AEs occurring during the DLT observation period (28 days) which are attributable to at least one of the investigational products will be classified as DLTs:

Non-Hematological Toxicities:

- Grade ≥ 3 Non-hematological toxicity
- Grade ≥ 3 Non-hematological toxicity felt to be related to study medications will be considered dose-limiting with the following clarifications:
    - Diarrhea Grade 3 will only be considered dose-limiting if it is refractory to treatment, and unable to be corrected to Grade 2 or less within 24 hours. Bloody or Grade 4 diarrhea will be dose-limiting.
    - Nausea and vomiting Grade 3 will only be considered dose-limiting if it is refractory to anti-emetic therapy and unable to be corrected to Grade 1 or less within 24 hours.
    - Rise in creatinine to Grade 3, not corrected to Grade 1 or less within 48 hours with IV fluids will be considered dose-limiting. All Grade 4 rises in creatinine will be dose limiting.
    - Grade ≥ 3 metabolic toxicities unable to be corrected to Grade 1 or baseline within 48 hours (hypocalcemia or hypercalcemia, hypomagnesemia or hypermagnesemia, and hyponatremia) will be considered dose limiting. For hypokalemia or hyperkalemia, grade ≥ 2 toxicities unable to be corrected to grade 1 or less within 48 hours will be considered dose limiting. Grade 4 metabolic toxicities that are symptomatic will be considered dose-limiting regardless of duration or ability to correct.
- Grade 3 fatigue of greater than 1 week duration.
- Failure to receive at least 70% of dosing due to trial drug-related toxicities, or experiencing a drug-related toxicity that meets criteria for a DLT.

Hematological Toxicities:

- Grade 4 thrombocytopenia or Grade 3 thrombocytopenia associated with bleeding.
- Grade 4 neutropenia ≥ 5 days or febrile neutropenia.
- Any degree of anemia, leukopenia in the absence of grade 4 neutropenia ≥ 4 days, or lymphopenia will not be considered dose limiting.

The following toxicities will not be considered DLTs:

- Alopecia of any grade
- Isolated laboratory changes of any grade without clinical sequelae or clinical significance

6.3 Dose Expansion Cohorts

[redacted]

[redacted]

6.4 General Concomitant Medication and Supportive Care Guidelines

Because there is a potential for interaction of olaparib or adavosertib with other concomitantly administered drugs, the case report form must capture the concurrent use of all other drugs, over-the-counter medications, vitamins, nutritional supplements, or alternative therapies at the time of enrollment and throughout the study. The CRF should capture the dates of administration (including start/end dates if known), dosage (including dosing frequency/schedule), and reason for use. The PI should be alerted if the patient is taking any agent known to affect or with the potential for drug interactions. The study team should check a frequently-updated medical reference for a list of drugs to avoid or minimize use of. Appendix E (Patient Drug Interactions Handouts and Wallet Cards) and Appendix F (Patient Clinical Trial Wallet Card) should be provided to patients if available.

[redacted]

[redacted]

[redacted]

6.4.4 Anticoagulant Therapy

Patients who are taking warfarin may participate in this trial; however, it is recommended that international normalised ratio (INR) be monitored carefully at least once per week for the first month, then monthly if the INR is stable. Non-vitamin K antagonist oral anticoagulants (NOACs), subcutaneous heparin and low molecular weight heparin may be given concomitantly with olaparib and INR monitoring is not required. If NOACs are used, it is preferable to avoid CYP3A substrates (e.g apixaban and rivaroxaban) if possible.

6.4.5 Anti-Emetics/Anti-Diarrheals

If a patient develops nausea, vomiting, and/or diarrhea, then these symptoms should be reported as AEs and appropriate treatment of the event given. Diarrhea is a common problem experienced by many patients and is a risk with olaparib. If it is not controlled quickly, it can lead to dehydration.

[redacted]

[redacted]

[redacted]

6.4.6 Administration of other Anti-Cancer Agents

Patients must not receive any other concurrent anti-cancer therapy, except the study drugs, while on study treatment. [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

6.5 Duration of Therapy

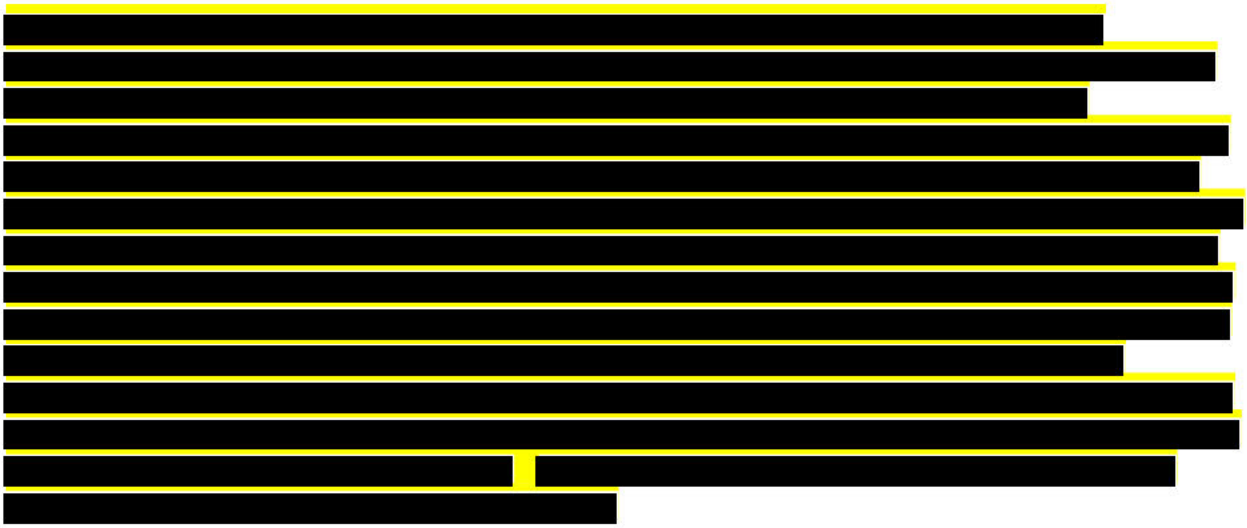
In the absence of treatment delays due to adverse event(s), treatment may continue until one of the following criteria applies:

- Disease progression
- Intercurrent illness that prevents further administration of treatment
- Unacceptable adverse event(s)
- Patient decides to withdraw from the study
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator
- Clinical progression
- Patient non-compliance
- Pregnancy
    - All women of child bearing potential should be instructed to contact the investigator immediately if they suspect they might be pregnant (*e.g.*, missed or late menstrual period) at any time during study participation.
    - The investigator must immediately notify CTEP in the event of a confirmed pregnancy in a patient participating in the study.

- Termination of the study by sponsor
- The drug manufacturer can no longer provide the study agent

The reason(s) for protocol therapy discontinuation, the reason(s) for study removal, and the corresponding dates must be documented in the Case Report Form (CRF).

6.6 Duration of Follow-Up



AEs and SAEs will be recorded from time of signature of informed consent, throughout the treatment period, up to 90 days after the administration of the last dose of study drug.

During the course of the study, all AEs and SAEs should be proactively followed up for each patient. Every effort should be made to obtain a resolution for all events, even if the events continue after discontinuation/study completion.

If a patient discontinues from treatment for reasons other than disease progression, and therefore continues to have tumor assessments, drug or procedure-related SAEs must be captured until the patient is considered to have confirmed PD and will have no further tumor assessments.

The investigator is responsible for following all SAEs until resolution, until the patient returns to baseline status, or until the condition has stabilized with the expectation that it will remain chronic, even if this extends beyond study participation.

7. DOSING DELAYS/DOSE MODIFICATIONS

7.1 Olaparib

Except where otherwise specified, the table below provides olaparib dose reduction recommendations from an assumed initial dose of 300 mg BID (the single-agent RP2D for olaparib).

Any toxicity observed during the course of the study could be managed by interruption of the dose of study treatment or dose reductions. Repeat dose interruptions are allowed as required, for a maximum of 4 weeks on each occasion. If the interruption is any longer, the study team must be informed. Study treatment can be dose reduced to 200 mg twice daily. If the reduced dose of 200 mg twice daily is not tolerable, no further dose reduction is allowed and study treatment should be discontinued.

Once dose is reduced, escalation is not permitted.

Olaparib dose reductions for study treatment

Initial Olaparib Dose	Following re-challenge post interruption: Dose reduction 1
300 mg BID	200 mg BID

7.1.1 Dose Reduction/Discontinuation for Organ Dysfunction

7.1.1.1 Hepatic Impairment

The effect of mild or moderate hepatic impairment (Child-Pugh classification A or B) on single dose PK of olaparib has been characterized and no olaparib dose adjustment in patients with mild or moderate hepatic impairment is required.

Olaparib is not recommended for use in patients with severe hepatic impairment as the PK and safety of olaparib in patients with severe hepatic impairment has not been studied.

7.1.1.2 Renal Impairment

If, subsequent to study entry and while still on study therapy, a patient's Cockcroft-Gault estimated CrCl falls below the threshold for study inclusion (≥51 mL/min), retesting should be performed promptly.

A dose reduction is recommended for patients who develop moderate renal impairment (CrCl between 31 and 50 mL/min, as estimated by Cockcroft-Gault or based on a 24-hour urine test) for any reason during the course of the study: the dose of olaparib should be reduced to 200 mg BID.

Because the CrCl determination is only an estimate of renal function, in instances where the CrCl falls to between 31 and 50 mL/min, the investigator should use his or her discretion in determining whether a dose change or discontinuation of therapy is warranted.

The effect of mild and moderate renal impairment on the single dose PK of olaparib has been evaluated in a formal renal impairment study. Olaparib has not been studied in patients with severe renal impairment (CrCl ≤30 mL/min) or end-stage renal disease; if patients develop severe impairment or end stage disease, is it recommended that olaparib be discontinued.

Olaparib dose reduction if patient develops moderate renal impairment

Initial Olaparib Dose	Moderate renal impairment (calculated creatinine clearance by Cockcroft-Gault equation or based on a 24 hour urine test between 31 and 50 mL/min): Dose reduction
300 mg BID	200 mg BID

7.1.2 Management of Hematological Toxicity

7.1.2.1 Management of Anemia

Management of Anemia

Hemoglobin (Hb)	Action to be taken
Hb <10 *but* ≥8 g/dL (CTCAE Grade 2)	**First occurrence:** Give appropriate supportive treatment and investigate causality. Investigator judgement to continue olaparib with supportive treatment (*e.g.* transfusion) *or* interrupt dose for a maximum of 2 weeks. Study treatment can be restarted if Hb has recovered to >9 g/dL. **Subsequent occurrences:** If Hb **<10** *but* **≥9 g/dL**, investigator judgement to continue olaparib with supporting treatment (*e.g.* transfusion) and dose reduction may be considered (to **200 mg twice daily**). If Hb **<9** *but* **≥8 g/dL**, dose reduction (to **200 mg twice**) until Hb ≥9 g/dL.
Hb <8 g/dL (CTCAE Grade 3)	Give appropriate supportive treatment (*e.g.* transfusion) and investigate causality. Interrupt olaparib for a maximum of 2 weeks until improved to Hb ≥9 g/dL. Upon recovery dose reduce to **200 mg twice daily** in the case of repeat Hb decrease.

Common treatable causes of anemia (*e.g.*, iron, vitamin B12, or folate deficiencies and hypothyroidism) should be investigated and appropriately managed. In some cases, management of anemia may require blood transfusions. For cases where patients develop prolonged hematological toxicity (warranting ≥2 week interruption/delay in study treatment due to CTCAE grade 3 or worse anemia and/or development of blood transfusion dependence), refer to Section 7.1.3.3 for the management of this.

7.1.2.2 Management of Neutropenia, Leukopenia and Thrombocytopenia

Management of Neutropenia, Leukopenia and Thrombocytopenia

Toxicity	Study treatment dose adjustment
CTCAE Grade 1-2	Investigator judgement to continue treatment or if dose interruption, this should be for a maximum of 4 weeks; appropriate supportive treatment and causality investigation
CTCAE Grade 3-4	Dose interruption until recovered to CTCAE grade 1 or better for a maximum of 4 weeks. If repeat CTCAE grade 3-4 occurrence, dose reduce olaparib to **200 mg twice daily**

AEs of neutropenia and leukopenia should be managed as deemed appropriate by the investigator with close follow-up and interruption of study drug if CTCAE grade 3 or worse neutropenia occurs.

Primary prophylaxis with granulocyte colony-stimulating factor (G-CSF) is not recommended; however, if a patient develops febrile neutropenia, study treatment should be stopped and appropriate management including G-CSF should be given according to local hospital guidelines. Please note that study drug should not be administered within 24 hours of G-CSF (7 days for pegylated G-CSF).

Platelet transfusions, if indicated, should be done according to local hospital guidelines.

For cases where patients develop prolonged hematological toxicity (≥2 week interruption/delay in study treatment due to CTCAE grade 3 or worse), refer to the next section.

7.1.2.3 Management of Prolonged Hematological Toxicities While on Study Treatment

If a patient develops prolonged hematological toxicity such as:

- ≥2 week interruption/delay in study treatment due to CTCAE grade 3 or worse anemia and/or development of blood transfusion dependence
- ≥2 week interruption/delay in study treatment due to CTCAE grade 3 or worse neutropenia (ANC $<1\times10^9$/L)
- ≥2 week interruption/delay in study treatment due to CTCAE grade 3 or worse thrombocytopenia and/or development of platelet transfusion dependence (platelets $<50\times10^9$/L)

Check weekly differential blood counts including reticulocytes and peripheral blood smear. Study treatment should be discontinued if blood counts do not recover to CTCAE grade 1 or better within 4 weeks of dose interruption. Refer to a hematologist.

If any blood parameters remain clinically abnormal after 4 weeks of dose interruption, the patient should be referred to hematologist for further investigations. Patients with laboratory findings consistent with AML or MDS should receive a full work up as per the local standard of care for evaluation of a suspected hematological malignancy including, but not limited to, bone marrow

aspirate/smear, flow cytometric evaluation of the marrow, and evaluation of cytogenetics. If it is not possible to conduct cytogenetic analysis or flow cytometry on the bone marrow aspirate, then attempts should be made to carry out the tests on a blood sample.

Development of a confirmed MDS, AML, or other clonal blood disorder should be reported as an SAE via CTEP-AERS and full reports must be provided by the investigator to the CTEP Medical Officer. Olaparib treatment should be discontinued if the patient's diagnosis of MDS and/or AML is confirmed.

7.1.3 Management of Non-Hematological Toxicity

Repeat dose interruptions are allowed as required, for a maximum of 4 weeks on each occasion. If the interruption is longer than 4 weeks, the CTEP Medical Monitor must be informed. Where toxicity reoccurs following re-challenge with study treatment, and where further dose interruptions are considered inadequate for management of toxicity, then the patient should be considered for dose reduction or must permanently discontinue study treatment.

Olaparib can be dose reduced to 200 mg BID. Treatment must be interrupted if any NCI-CTCAE grade 3 or 4 AE occurs which the investigator considers to be related to administration of study treatment.

7.1.3.1 Management of New or Worsening Pulmonary Symptoms

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 CTEP Medical Monitor.

7.1.3.2 Management of Nausea and Vomiting

Events of nausea and vomiting are known to be associated with olaparib treatment. These events are generally mild to moderate (CTCAE grade 1 or 2) severity, intermittent, and manageable on continued treatment. The first onset generally occurs in the first month of treatment for nausea and within the first 6 months of treatment for vomiting. For nausea, the incidence generally plateaus at around 9 months, and for vomiting at around 6 to 7 months.

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 (*i.e.*, two pieces of toast or a couple of cookies, crackers, or biscuits).

As per international guidance on anti-emetic use in cancer patients (European Society for Medical Oncology [ESMO], National Comprehensive Cancer Network [NCCN]), generally a single agent antiemetic should be considered, such as a dopamine receptor antagonist, antihistamine, or dexamethasone. Aprepitant and fosaprepitant must not be used in this study.

7.1.3.3 Interruptions for Intercurrent Non-Toxicity Related Events

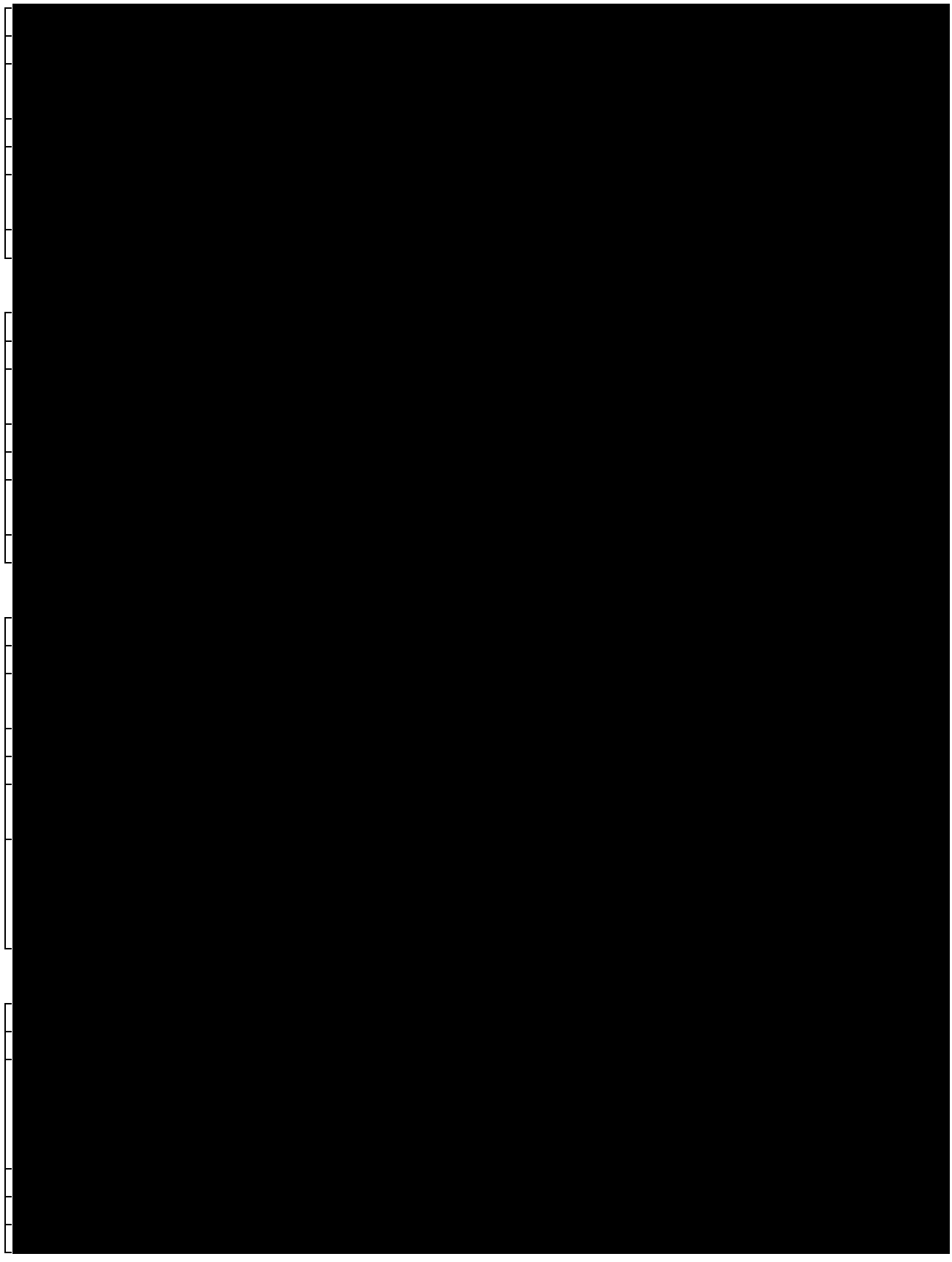
Study treatment dose interruption for conditions other than toxicity resolution should be kept as short as possible. If a patient cannot restart study treatment within 4 weeks for resolution of intercurrent conditions not related to disease progression or toxicity, the case should be discussed with the CTEP Medical Monitor.

All dose reductions and interruptions (including any missed doses), and the reasons for the reductions/interruptions are to be recorded in the electronic CRF (eCRF).

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.

Study treatment should be discontinued for a minimum of 3 days before a patient undergoes radiation treatment. Study treatment should be restarted within 4 weeks as long as any bone marrow toxicity has recovered.

Because the AEs related to olaparib may include asthenia, fatigue, and dizziness, patients should be advised to use caution while driving or using machinery if these symptoms occur.



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[redacted]

8. PHARMACEUTICAL INFORMATION FOR CTEP IND AGENTS

A list of the adverse events and potential risks associated with the investigational agents administered in this study can be found in Section 10.1.

8.1 Olaparib (NSC 747856)

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

Other Names: AZD2281; KU-0059436; CO-CE 42; Lynparza

Classification: PARP inhibitor

CAS Registry Number: 763113-22-0

Molecular Formula: $C_{24}H_{23}FN_4O_3$ **M.W.:** 434.46

Approximate Solubility: 0.1 mg/mL pH independent solubility across physiologic range

Mode of Action: Olaparib is an inhibitor of subclasses 1, 2, and 3 of polyadenosine 5′ diphosphoribose polymerase (PARP-1, PARP-2, and PARP-3). In tumors that are deficient in the homologous recombination DNA repair pathway (example, BRCA mutants), inhibition of PARP by olaparib causes accumulation of DNA double-strand breaks and genomic instability. Olaparib may also enhance the effects of DNA damage caused by ionizing radiation and chemotherapy.

Description: crystalline solid

How Supplied: AstraZeneca supplies and the CTEP, DCTD distributes olaparib as green, film-coated tablets in 100 mg and 150 mg strengths.

- 100 mg tablets are 14.5 mm x 7.25 mm oval-shaped
- 150 mg tablets 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.

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

If a storage temperature excursion is identified, promptly return olaparib (AZD2281) to 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.

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. Instruct patients not to open a bottle until they are ready to use it.

Route and Method of Administration: Oral. Take tablets without regard to meals. Olaparib tablets should be taken at the same time each day, approximately 12 hours apart with one glass of water. The tablets should be swallowed whole and not chewed, crushed, dissolved or divided. If vomiting occurs, the dose should only be replaced if all of the intact tablets can be seen and counted. Should a patient miss a scheduled dose (*e.g.*, as a result of forgetting to take the tablets or vomiting), the patient will be allowed to take the scheduled dose up to a maximum of 2 hours after that scheduled dose time. If greater than 2 hours have passed, the missed dose is skipped and the patient should take their allotted dose at the next scheduled time.

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-gp, but not for organic anion-transporting polypeptides (OATP1B1 and OATP1B3), OCT1, MRP-2 efflux transporter or 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. 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.

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 six (6) months after the last dose of olaparib. It is not known whether olaparib is found in seminal fluid, so as a precaution, male study participants must use a condom during treatment and for three (3) months after the last dose and should avoid fathering a child or donating sperm during this same time period. The study investigator should discuss the most appropriate forms of highly effective contraceptive methods for each patient.

Lactation is a protocol exclusion criterion and not advised since there is potential for serious adverse reactions in breastfed infants. Advise lactating women to not breastfeed during study treatment and for one (1) month after receiving the last dose of olaparib.

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.

There are no data on the effect of olaparib on wound healing, therefore as a precaution, olaparib treatment should be stopped at least 3 days prior to planned surgery. After surgery olaparib can be restarted when the wound has healed. No stoppage of olaparib is required for any needle biopsy procedure.

Availability: Olaparib is an investigational agent supplied to investigators by the DCTD, NCI. Olaparib is provided to the NCI under a Collaborative Agreement between the Pharmaceutical Collaborator and the DCTD, NCI (see Section 13.4).

8.2 AZD1775 (NSC 751084)

Chemical Name: 2-allyl-1-[6-(1-hydroxy-1-methyl-ethyl)-2-pyridyl]-6-[4-(4-methylpiperazin-1-yl)anilino]pyrazolo[3,4-d]pyrimidin-3-one hemihydrate

Other Names: Adavosertib; MK-1775

Classification*:* inhibitor of WEE1 kinase

CAS: 1277170-60-1

Molecular Formula: $C_{27}H_{32}N_8O_2 \cdot 0.5H_2O$ **M.W.:** 500.6

Mode of Action: AZD1775 inhibits WEE1 which phosphorylates and inhibits cyclin-dependent kinases 1 (CDK1) and 2 (CDK2), and is involved in regulation of the intra-S and G2 cell cycle checkpoints. In in vitro and in vivo preclinical models, AZD1775 selectively enhanced chemotherapy induced death of cells deficient in p53 signaling.

Description: AZD1775 is a crystalline, hemihydrate form of the drug substance.

How Supplied: AZD1775 is supplied by AstraZeneca and distributed by the Pharmaceutical Management Branch, CTEP/DCTD/NCI as capsules available in 25 mg (yellow color, size 2 gelatin capsule) and 100 mg (orange color, size 2 gelatin capsule) strengths. The dry-filled capsules consist of a roller-compacted granule of drug substance, lactose monohydrate, microcrystalline cellulose, croscarmellose sodium, and magnesium stearate. Each high density polypropylene (HDPE) bottle contains 20 capsules. The pharmaceutical collaborator does not have stability data to support repackaging AZD1775 capsules in any container other than what is provided.

Storage: Store at 2 to 30˚C (36 to 86˚F). Do not freeze. If a storage temperature excursion is identified, promptly return AZD1775 to between 2-30°C 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.

Stability: Shelf-life stability studies of AZD1775 capsules are ongoing.

Route of Administration: Oral administration. Capsules should not be opened.

Potential Drug Interactions: AZD1775 is primarily metabolized by CYP3A4 and is a weak, time-dependent inhibitor of CYP3A4. Avoid concomitant CYP3A4 moderate or strong inhibitors/inducers, and sensitive substrates with a narrow therapeutic index. AZD1775 is also a weak inhibitor of CYP2C19. Caution should be exercised with concomitant administration of sensitive substrates or substrates with a narrow therapeutic index.

In vitro transporter studies have shown that AZD1775 was an inhibitor of OATP1B1, OATP1B3, MATE1, MATE2K, P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP), and a substrate for P-gp and BCRP. The PK parameters of AZD1775 could be altered if AZD1775 is coadministered with P-gp and BCRP inhibitors/inducers, and there is potential for drug-drug interactions when coadministered with OATP1B1, OATP1B3, MATE1, MATE2K, P-gp and BCRP substrates. This finding is particularly relevant for drugs administered orally where exposure is normally limited by BCRP-mediated efflux, in particular some statins. Modelling has predicted a substantial increase in the exposure of atorvastatin when coadministered with AZD1775 and the use of atorvastatin is therefore prohibited.

Availability: AZD1775 is an investigational agent supplied to investigators by the DCTD, NCI. AZD1775 is provided to the NCI under a Collaborative Agreement between the Pharmaceutical Collaborator and the DCTD, NCI (see Section 13.4).

8.3 CTEP IND Agents – General Information

8.3.1 Agent Ordering

NCI-supplied agents may be requested by eligible participating Investigators (or their authorized designee) at each participating institution. The CTEP-assigned protocol number must be used

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

In general, sites may order initial agent supplies when a subject is being screened for enrollment onto the study.

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

8.3.2 Agent Accountability and 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.

8.3.3 Investigator Brochure Availability

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

8.3.4 Useful Links and Contacts

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

9. STATISTICAL CONSIDERATIONS

9.1 Study Design/Endpoints

In this trial olaparib (300 mg) will be combined with AZD1775 at a maximum dose of 300 mg in a sequential alternating dosing schedule. This treatment combination will assess 2 separate cohorts of patients: 1) those with BRCA1/2 mutant cancers that have been treated with PARP inhibitors who had disease progression per RECIST at 1st re-staging (intrinsic resistance) 2) those with DDR aberrant advanced solid tumors treated with PARP inhibitors who had complete/partial response followed by disease progression per RECIST (acquired resistance). Mandatory tumor biopsies and blood sampling will be undertaken at baseline and on C1D12.

Please refer to "SCHEMA" section for study design.

1. Primary Endpoints:
   - Identify the incidence and severity of dose-limiting toxicities.
   - Determine the causality of each adverse event to the sequential treatment of olaparib and AZD1775 and grade severity according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.

2. Secondary Endpoints: objective response (OR) rate (CR+PR); clinical benefit rate (OR+SD>6 months); progression free survival; overall survival

3. Correlative Endpoints:
   - Correlation of molecular alterations in the DDR pathway (BRCA1/2, DDR mutation) with objective response to the sequential alternating combination of olaparib with AZD1775.
   - Correlation of change in expression of pharmacodynamics markers downstream of DDR inhibition and change in expression of genes involved in DNA repair pathways with objective response to treatment.
   - Correlation of mutations not associated with DDR pathway with presence and absence of objective response to treatment.

Safety and toxicity data from the dose escalation phase (n ≤30) has been formally reviewed by and discussed with the study team and CTEP, and Dose Level 2 was established as the MTD and RP2D and schedule for use in the dose expansion phase. Any treatment-related deaths will be carefully discussed in specially-convened ad hoc Safety Management Committee (SMC) meeting (including the PI and NCI CTEP medical monitor) to review the trial drug related toxicities, clinical management of patient, and the SMC recommendation for the dose/schedule for the drug. The protocol has been amended to open the trial to the ETCTN network during the dose expansion phase upon establishement of the MTD. The dose expansion phase will enroll a maximum of 12 patients per cohort to verify toxicity and perform correlative studies.

To identify the MTD in the dose escalation phase, we will employ the Bayesian optimal interval (BOIN) design (Liu and Yuan, 2015; Yuan *et al.*, 2016). The BOIN design is implemented in a simple way similar to the traditional 3+3 design, but is more flexible and possesses superior operating characteristics that are comparable to those of the more complex model-based designs, such as the continual reassessment method (CRM) (Zhou, *et al.*, 2018).

The target toxicity rate for the MTD is $\phi = 0.25$ and the maximum sample size is 30. We will enroll and treat patients in cohorts of size 3. The maximum number of patients treated at a dose is set to 9. The dose elimination cut-off was chosen as 0.85 to improve the safety when initial doses are too toxic, such that when 2/3 patients have DLT on the initial dose, the trial will be stopped for safety. The trial design is illustrated in the figure below and described as follows:

1. Patients in the first cohort are treated at dose level 1.
2. To assign a dose to the next cohort of patients, conduct dose escalation/de-escalation according to the rule displayed in Table 1, which minimizes the probability of incorrect dose assignment. When using Table 1, please note the following:
    a. "Eliminate" means eliminate the current and higher doses from the trial to prevent treating any future patients at these doses because they are overly toxic.
    b. When we eliminate a dose, automatically de-escalate the dose to the next lower level. When the lowest dose is eliminated, stop the trial for safety. In this case, no dose should be selected as the MTD.
    c. If none of the actions (*i.e.*, escalation, de-escalation or elimination) is triggered, treat the new patients at the current dose.
    d. If the current dose is the lowest dose and the rule indicates dose de-escalation, treat the new patients at the lowest dose unless the number of DLTs reaches the elimination boundary, at which point terminate the trial for safety.
    e. If the current dose is the highest dose and the rule indicates dose escalation, treat the new patients at the highest dose.
3. Repeat step 2 until the maximum sample size of 30 is reached or stop the trial early when one of the following two conditions is satisfied:
    a. The number of patients who experienced DLTs at the lowest dose level reaches the stopping boundaries listed in Table 2 below. In this case, no dose should be selected as the MTD.
    b. The number of patients treated at the current dose >= 9 and the decision based on Table 1 is to stay at the current dose.

Table 1. Dose escalation/de-escalation rule for the BOIN design.

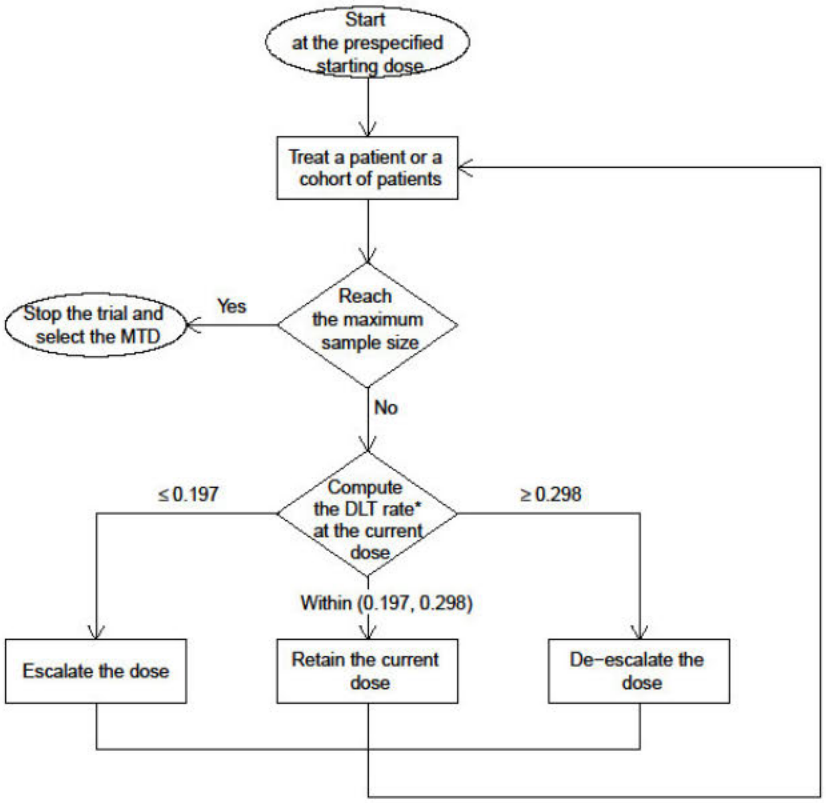
Actions	The number of patients treated **at the current dose**								
	1	2	**3**	4	5	**6**	7	8	**9**
Escalate if # of DLT <=	0	0	**0**	0	0	**1**	1	1	**1**

De-escalate if # of DLT >=	1	1	**1**	2	2	**2**	3	3	**3**
Eliminate if # of DLT >=	NA	NA	**3**	3	3	**4**	4	4	**5**

Table 2. Stopping boundaries

Actions	The number of patients treated **at the lowest dose**								
	1	2	**3**	4	5	**6**	7	8	**9**
Stop trial if # of DLT >=	NA	NA	**2**	2	3	**3**	3	4	**4**

BOIN Design Flowchart



$$* \text{ DLT rate} = \frac{\text{Total number of patients who experienced DLT at the current dose}}{\text{Total number of patients treated at the current dose}}$$

After the trial is completed, select the MTD based on isotonic regression as specified in Liu and Yuan (2015). This computation is implemented by the shiny app "BOIN" available at http://www.trialdesign.org. Specifically, select as the MTD the dose for which the isotonic estimate of the toxicity rate is closest to the target toxicity rate. If there are ties, select the higher dose level when the isotonic estimate is lower than the target toxicity rate and select the lower dose level when the isotonic estimate is greater than or equal to the target toxicity rate.

Expansion Phase: Once we determine the MTD, an additional 12 patients will be enrolled for additional experience with safety and efficacy in each of 2 cohorts. Dose Level 2 was established as the MTD and RP2D and schedule for use in the dose expansion phase. We will use the elimination boundaries in the dose escalation/de-escalation rule for the BOIN Design Table for toxicity monitoring during this phase.

Operation Characteristics: The operating characteristics of the BOIN Design for the combinations tables below shows the operating characteristics of the trial design based on 1000 simulations of the trial using shiny app "BOIN" available at http://www.trialdesign.org. The operating characteristics show that the design selects the true MTD, if any, with high probability and allocates more patients to the dose levels with the DLT rate closest to the target of 0.25. The actual average sample size for dose escalation phase is about 20 or less, depending on the scenario.

Operating characteristics of the BOIN Design

	Dose Level			Number of Patients	% Early Stopping
	-1	**1**	**2**		
Scenario 1					
True DLT Rate	**0.25**	0.42	0.59	16.26	26.8
Selection %	**51.7**	21.1	0.4		
# Pts Treated	**8.0**	7.1	1.2		
Scenario 2					
True DLT Rate	0.10	**0.25**	0.40	19.25	2.1
Selection %	20.7	**61.4**	15.8		
# Pts Treated	5.0	**10.0**	4.3		
Scenario 4					
True DLT Rate	0.05	0.12	**0.25**	19.04	0.1
Selection %	1.8	34.1	**64.0**		

# Pts Treated	1.8	8.5	**8.7**		

9.2 Analysis of Secondary Endpoints

Secondary endpoints are two-fold:

1. Correlate antitumor activity of the sequentially-administered combination of olaparib and AZD1775 with the detection of putative predictive biomarkers of response and resistance.

2. Assess if an MTD can be safely established using sequentially-administered combination olaparib and AZD1775.

To evaluate the capacity of our biomarkers to predict response, we will assess:

- ORR (Complete Response [CR] + Partial Response [PR])
- Duration of Response (DOR)
- Progression-Free Survival (PFS)
- Overall Survival (OS)

We will estimate ORR with 95% confidence intervals (CI). Inferences and estimation are based on the exact binomial test. With 12 patients, the 95% CI for an observed ORR of 25% would extend from 5% to 57%. A treatment will be declared worthy of further study if we see at least 2 patients (17%) out of 12 with ORR; the probability of doing so would be 12% if the true OR rate was 5% and would be 73% if the true ORR was 20%. We will use the Kaplan-Meier method to estimate DOR, PFS, and OS in these distributions.

For correlative studies, we will assess changes using paired t-tests or Wilcoxon signed rank tests. With 12 patients, we would have 80% power to detect an effect size (mean difference divided by standard deviation of differences) = 0.90 assuming Normal data with two-sided 5% alpha. We will assess associations between marker levels and response using receiver operating characteristic (ROC) curve analysis, graphical analysis and logistic regression analysis as appropriate. If success rate is 50%, then we would have 80% power to detect an area under the ROC curve of 0.82 as statistically different from the null value of 0.50 assuming a 20% alpha and 12 patients with data.

9.3 Sample Size/Accrual Rate

Planned accrual rate is 3-4 patients per month for the dose escalation phase of the study, and 5-10 patients per month for the dose expansion phase of the study. We plan to enroll up to 54 evaluable patients.

PLANNED ENROLLMENT REPORT

Racial Categories	Ethnic Categories	Total

	Not Hispanic or Latino		Hispanic or Latino		
	Female	**Male**	**Female**	**Male**	
American Indian/ Alaska Native	1	0	1	0	**2**
Asian	1	1	1	0	**3**
Native Hawaiian or Other Pacific Islander	0	1	0	0	**1**
Black or African American	5	5	0	0	**10**
White	17	12	0	1	**30**
More Than One Race	3	3	1	1	**8**
Total	**27**	**22**	**3**	**2**	**54**

10. ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

Adverse event (AE) monitoring and reporting is a routine part of every clinical trial. The following list of AEs (Section 10.1) and the characteristics of an observed AE (Sections 10.2 and 10.3) will determine whether the event requires expedited reporting via the CTEP Adverse Event Reporting System (CTEP-AERS) **in addition** to routine reporting.

10.1 Comprehensive Adverse Events and Potential Risks Lists (CAEPRs)

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.
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.

10.1.1 CAEPRs for CTEP IND Agent: Olaparib (AZD2281, NSC 747856)

Frequency is based on 3449 patients

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			
	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		

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%)**	
	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.

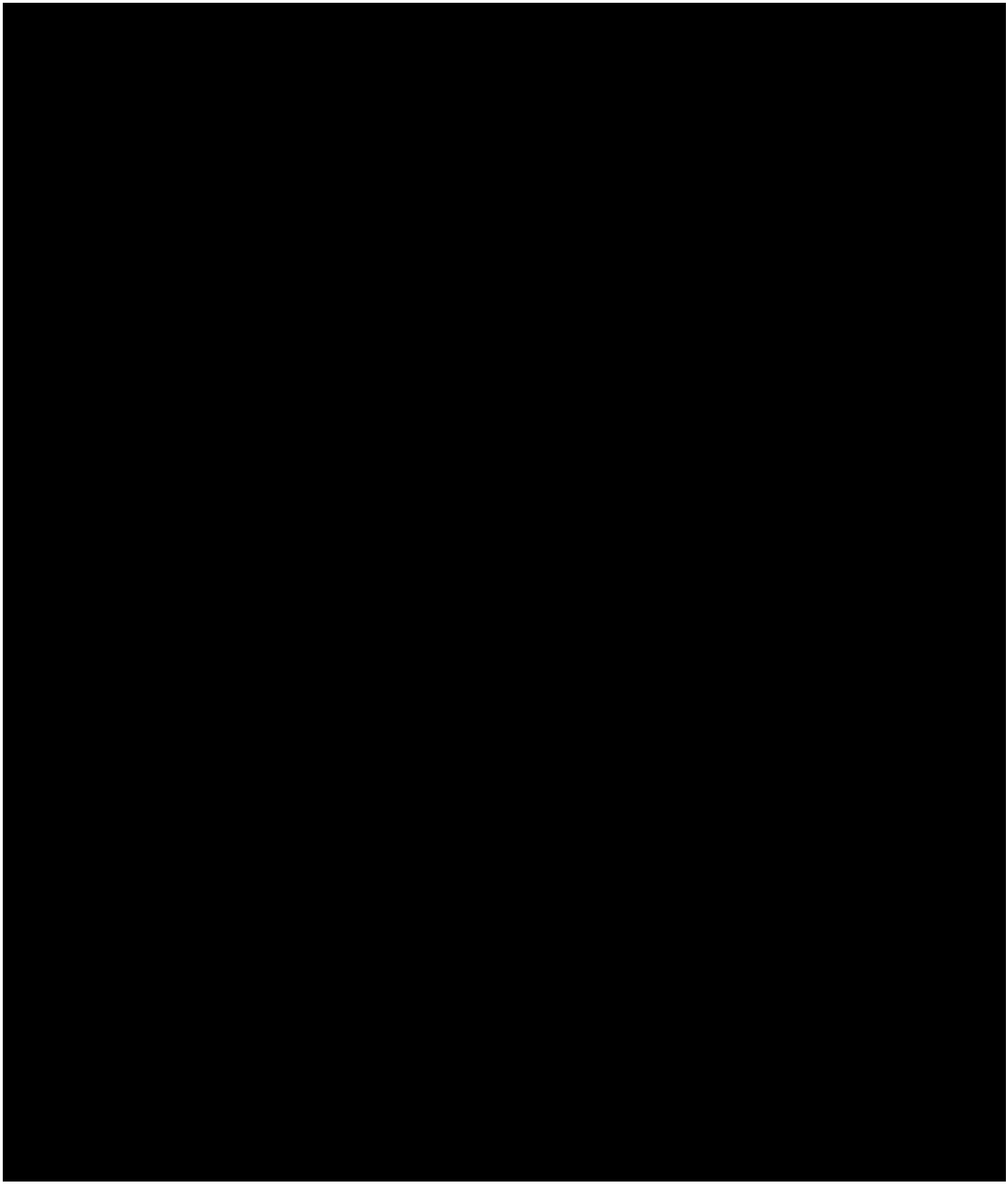
[1]This table will be updated as the toxicity profile of the agent is revised. Updates will be distributed to all Principal Investigators at the time of revision. The current version can be obtained by contacting PIO@CTEP.NCI.NIH.GOV. Your name, the name of the investigator, the protocol and the agent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



[redacted]

10.2 Adverse Event Characteristics

- **CTCAE term (AE description) and grade:** The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 5.0. A copy of the CTCAE version 5.0 can be downloaded from the CTEP website http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

- **For expedited reporting purposes only:**
  - AEs for the agent that are ***bold and italicized*** in the CAEPR (*i.e.*, those listed in the SPEER column, Section 10.1) should be reported through CTEP-AERS only if the grade is above the grade provided in the SPEER.

- **Attribution** of the AE:
  - Definite – The AE *is clearly related* to the study treatment.
  - Probable – The AE *is likely related* to the study treatment.

- Possible – The AE *may be related* to the study treatment.
- Unlikely – The AE *is doubtfully related* to the study treatment.
- Unrelated – The AE *is clearly NOT related* to the study treatment.

10.3 Expedited Adverse Event Reporting

10.3.1 Rave CTEP-AERS Integration

The Cancer Therapy Evaluation Program Adverse Event Reporting System (CTEP-AERS) integration enables evaluation of post-baseline AEs entered in Rave to determine whether they require expedited reporting, and facilitates entry in CTEP-AERS for those AEs requiring expedited reporting.

All AEs that occur after baseline are collected in Medidata Rave using the Adverse Event form, which is available for entry at each treatment or reporting period, and used to collect AEs that start during the period or persist from the previous reporting period. The Clinical Research Associate (CRA) will enter AEs that occur prior to the start of treatment on a baseline form that is not included in the Rave-CTEP-AERS integration. AEs that occur prior to enrollment must begin and end on the baseline Adverse Event form and should not be included on the standard Adverse Events form that is available at treatment unless there has been an increase in grade.

Prior to sending AEs through the rules evaluation process, site staff should verify the following on the Adverse Event form in Rave:

- The reporting period (course/cycle) is correct, and
- AEs are recorded and complete (no missing fields) and the form is query-free (fields added to the form during study build do not need to be query-free for the integration call with CTEP-AERS to be a success).

The CRA reports AEs in Rave at the time the Investigator learns of the event. If the CRA modifies an AE, it must be re-submitted for rules evaluation.

Upon completion of AE entry in Medidata Rave, the CRA submits the AE for rules evaluation by completing the Expedited Reporting Evaluation form. Both NCI and protocol-specific reporting rules evaluate the AEs submitted for expedited reporting. A report is initiated in CTEP-AERS using information entered in Medidata Rave for AEs that meet reporting requirements. The CRA completes the report by accessing CTEP-AERS via a direct link on the Medidata Rave Expedited Reporting Evaluation form.

In the rare occurrence that Internet connectivity is lost, a 24-hour notification is to be made to CTEP by telephone at 301-897-7497. Once Internet connectivity is restored, the 24-hour notification that was phoned in must be entered immediately into CTEP-AERS using the deep link from Medidata Rave.

Additional information about the CTEP-AERS integration is available on the CTSU website:

- Study specific documents: Protocols > Documents > Education and Promotion, and
- Expedited Safety Reporting Rules Evaluation user guide: Resources > CTSU Operations Information > User Guides & Help Topics.

NCI requirements for SAE reporting are available on the CTEP website:

- NCI Guidelines for Investigators: Adverse Event Reporting Requirements is available at https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf.

10.3.2 Distribution of Adverse Event Reports

CTEP-AERS is programmed for automatic electronic distribution of reports to the following individuals: Principal Investigator and Adverse Event Coordinator(s) (if applicable) of the Corresponding Organization or Lead Organization, the local treating physician, and the Reporter and Submitter. CTEP-AERS provides a copy feature for other e-mail recipients.

10.3.3 Expedited Reporting Guidelines

Use the NCI protocol number and the protocol-specific patient ID assigned during trial registration on all reports.

Note: A death on study requires <u>both</u> routine and expedited reporting, regardless of causality as long as the death occurred less than 30 days after the last administration of the investigational agent. Attribution to treatment or other cause must be provided.

Death due to progressive disease should be reported as **Grade 5 "Disease progression"** in the system organ class (SOC) "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.

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 **<u>MUST</u>** immediately report to the sponsor (NCI) **<u>ANY</u>** 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 **<u>ANY</u>** 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 to the NCI via electronic submission within the timeframes detailed in the table below.

Hospitalization	Grade 1 and Grade 2 Timeframes	Grade 3-5 Timeframes
Resulting in Hospitalization ≥ 24 hrs	10 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 submitted electronically within 24 hours of learning of the AE, followed by a complete expedited report within 5 calendar days of the initial 24-hour report.
- "10 Calendar Days" - A complete expedited report on the AE must be submitted electronically within 10 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 10 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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10.3.4 Adverse Events After the 30 Day Follow Up Period

For Pharmacovigilance purposes and characterization, any SAE of MDS/AML or new primary malignancy occurring after the 30 day follow up period should be reported to CTEP regardless of investigator's assessment of causality or knowledge of the treatment arm. Investigators will be asked during the regular follow up for overall survival if the patient has developed MDS/AML or a new primary malignancy and prompted to report any such cases.

At any time after a patient has completed the study, if an Investigator learns of any SAE including sudden death of unknown cause, and he/she considers there is a reasonable possibility that the event is causally related to the investigational product, the investigator should notify CTEP via CTEP-AERS.

If patients who are gaining clinical benefit are allowed to continue study treatment post data cut off and/or post study completion, then all SAEs must continue to be collected and reported to CTEP-AERS within the usual timeframe.

Otherwise, after study treatment completion (*i.e*. after any scheduled post treatment follow-up period has ended) there is no obligation to actively report information on new AEs or SAEs occurring in former study patients. This includes new AEs/SAEs in patients still being followed up for survival but who have completed the post treatment follow up period (30 days).

Overdose: There is currently no specific treatment in the event of overdose with olaparib and possible symptoms of overdose are not established. 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. The Maximum Tolerated Dose is 300 mg twice daily (tablet).

Adverse reactions associated with overdose should be treated symptomatically and should be managed appropriately.

10.4 Routine Adverse Event Reporting

All Adverse Events **must** be reported in routine study data submissions. **AEs reported expeditiously through CTEP-AERS must also be reported in routine study data submissions.**

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. AEs are reported in a routine manner at scheduled times during the trial using Medidata Rave. For this trial the Adverse Event CRF is used for routine AE reporting in Rave.

10.5 Pregnancy

Although not an adverse event in and of itself, pregnancy as well as its outcome must be documented via CTEP-AERS. In addition, the ***Pregnancy Information Form*** included within the NCI Guidelines for Adverse Event Reporting Requirements must be completed and submitted to CTEP. Any pregnancy occurring in a patient or patient's partner from the time of consent to 90 days after the last dose of study drug must be reported and then followed for outcome. Newborn infants should be followed until 30 days old. Please see the "NCI Guidelines for Investigators: Adverse Event Reporting Requirements for DCTD (CTEP and CIP) and DCP INDs and IDEs" (at http://ctep.cancer.gov/protocolDevelopment/adverse_effects.htm) for more details on how to report pregnancy and its outcome to CTEP.

10.6 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 expeditiously via Medidata Rave. 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.

10.7 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 AE reporting unless otherwise specified.

11. STUDY CALENDAR

Baseline evaluations are to be conducted within 1 week prior to start of protocol therapy. Scans and x-rays must be done $\leq$4 weeks prior to the start of therapy. In the event that the patient's condition is deteriorating, laboratory evaluations should be repeated within 48 hours prior to initiation of the next cycle of therapy.

11.1 Calendar (each cycle is 28 days)

	Pre-Study	Baseline	Cycle 1					Cycle 2				Cycle 3+				Disease Progression / End of Study
			Day 1	Day 8	Day 12	Day 15	Day 21	Day 1	Day 8	Day 15	Day 21	Day 1	Day 8	Day 15	Day 21	
Window	≤28 days prior to C1D1	≤7 days prior to C1D1	±2 days	±2 days	±2 days	±2 days	±2 days	±2 days	±2 days	±2 days	±2 days	±2 days	±2 days	±2 days	±2 days	
Olaparib [a]			X												X	
AZD1775 [a]			X												X	
Archival Tumor [b]	X															
Tumor Core Collection [c] (RPPA, WES, RNAseq, γH2AX and pRAD50 IHC/cycIF/mIHC, scRNAseq)		X			X[j]											X [i]
Blood Collection [d] (ctDNA)		X			X[j]							X [d]				X
Tumor Measurements and Radiologic Evaluation [e]		X									X [e]				X [e]	X
Physical Exam, Vital Signs, Performance Status, and Weight [f]	X		X			X		X		X		X				X
Laboratory Assessments [g]	X		X	X		X	X	X		X		X				X
ECG [h]	X							X				X				X
Adverse Event Evaluation			X												X	
Informed Consent, Demographics, and Medical History	X															

a – Treatments dosed as assigned.

b – A fresh tumor sample from Baseline can be used if archival tissue is not available.

c – Tumor biopsies are mandatory at Baseline and Cycle 1 Day 12.

d – Blood collections will occur at baseline, C1D12, each restaging, and disease progression.

e – Radiologic scans to occur at the start of the study, then every 2nd cycle beginning with a scan at the end of Cycle 2 (*i.e.*, every 8 weeks). Radiologic documentation must be provided for patients removed from the study for disease progression.

f – Physical exam to include vital signs, weight, and performance status.

- Vital signs, weight, and performance status to be evaluated at Baseline, every other week during Cycles 1 and (Days 1 and 15), then Day 1 of every cycle thereafter, at disease progression, and at the 30-Day Follow-Up Visit.
- Height to be recorded only at Baseline and as clinically indicated thereafter.

g – If screening laboratory assessments are performed within 3 days prior to Day 1, they do not need to be repeated at Day 1. General assessments to occur at pre-study, weekly during Cycle 1, twice during Cycle 2, Day 1 of each subsequent cycle, at disease progression, and at the 30-Day Follow-Up Visit, or as clinically indicated. The frequency of the hematology, serum chemistry and liver function test testing may need to be increased to every two weeks, depending on clinical need. These assessments are to include:

- **CBC** with differential and platelets.
- **urinalysis**: to include hemoglobin/erythrocytes/blood, protein/albumin, and glucose. To be conducted at pre-study, Cycle 1 Day 1, Cycle 2 Day 1, and as clinically indicated.
- **comprehensive chemistry panel**: including albumin, alkaline phosphatase, amylase, total bilirubin, bicarbonate, blood urea nitrogen (BUN), calcium, chloride, creatinine, glucose, LDH, lipase, phosphorus, potassium, total protein, SGOT (AST), SGPT (ALT), and sodium. Gamma glutamyl transferase to be tested at pre-study, Day 1 of each cycle, and as clinically indicated.
- **coagulation factors**: aPTT, INR; required at pre-study and as clinically indicated. Patients receiving warfarin must also be assessed weekly for aPTT and INR during the first month of the study; if the INR is stable, coagulation factor assessments may be performed on a monthly basis. Each coagulation test result will be recorded in the CRF.
- **pregnancy test** for women of childbearing potential. Pregnancy tests on blood or urine samples will be performed for women of childbearing potential within 28 days prior to the start of study treatment, on Day 1 of the study prior to commencing treatment and at each subsequent visit during study treatment and at the 30 day follow up visit. Tests will be performed by the hospital's local laboratory. If pregnancy results are positive the patient is ineligible/must be discontinued from study treatment immediately. Details of the pregnancy tests must be recorded in the patient's medical records.

h – Single 12-lead ECG to be performed at spre-study, at D1 of C2 and higher, at end of study/progression, and when clinically indicated. Triplicate ECGs will be performed for patients whose QTcF is >480 msec on the initial screening ECG.

i – Optional collection.

j – Should occur on C1D12 unless documented as unavoidable.

11.2 Laboratory Assessments

Full hematology assessments for safety (hemoglobin, red blood cells [RBC], platelets, mean cell volume [MCV], mean cell hemoglobin concentration [MCHC], mean cell hemoglobin [MCH], white blood cells [WBC], absolute differential white cell count (neutrophils, lymphocytes, monocytes, eosinophils and basophils) and absolute neutrophil count or segmented neutrophil count and band forms should be performed at pre-study, at each visit, and when clinically indicated. If absolute differentials are not available, please provide % differentials.

Serum biochemistry assessments for safety include sodium, potassium, calcium, magnesium, fasting glucose, creatinine, total bilirubin, gamma glutamyltransferase (GGT), alkaline phosphatase (ALP), aspartate transaminase (AST), alanine transaminase (ALT), urea or blood urea nitrogen (BUN), total protein, albumin, amylase, lipase, and lactic dehydrogenase (LDH). These assessments should be performed at pre-study, at every clinic visit, and when clinically indicated. Gamma glutamyltransferase (GGT) testing is to be performed at pre-study, Day 1 of each cycle, and as clinically indicated.

Coagulation (activated partial thromboplastin time [aPTT] and INR) will be performed at pre-study and if clinically indicated unless the patient is receiving warfarin. Patients taking warfarin may participate in this study; however, it is recommended that prothrombin time (INR and aPTT) be monitored carefully at least once per week for the first month, then monthly if the INR is stable. Each coagulation test result will be recorded in the CRF.

Urinalysis by dipstick should be performed at pre-study and only if clinically indicated thereafter. Microscopic analysis should be performed by the hospital's local laboratory if required.

Bone marrow or blood cytogenetic samples may be collected for patients with prolonged hematological toxicities as defined in Section 7.1.3.

Bone marrow analysis should include an aspirate for cellular morphology, cytogenetic analysis and flow cytometry, and a core biopsy for bone marrow cellularity. If it is not possible to conduct cytogenetic analysis or flow cytometry on the bone marrow aspirate, then attempts should be made to carry out the tests on a blood sample. Full reports must be provided by the investigator for documentation on the Patient Safety database. These data are not required to be entered into CRF.

These tests will be performed by the hospital's local laboratory. Additional analyses may be performed if clinically indicated.

Any clinically significant abnormal laboratory values should be repeated as clinically indicated and recorded on the eCRF.

In case a patient shows an AST **or** ALT ≥3×ULN **or** total bilirubin ≥2×ULN, please refer to Appendix G, "Actions required in cases of combined increase of Aminotransferase and Total Bilirubin – Hy's Law", for further instructions.

11.3 ECG

Single 12-lead ECG will be performed at pre-study, at Day 1 of Cycle 2 and higher, at end of study/progression, and when clinically indicated. Triplicate ECGs will be performed for patients whose QTcF is >480 msec on the initial screening ECG.

Twelve-lead ECGs will be obtained after the patient has been rested in a supine position for at least 5 minutes in each case. The investigator or designated physician will review the paper copies of each of the timed 12-lead ECGs on each of the study days when they are collected. ECGs will be recorded at 25 mm/sec. All ECGs should be assessed by the investigator as to whether they are clinically significantly abnormal/not clinically significantly abnormal. If there is a clinically significant abnormal finding, the Investigator will record it as an AE on the eCRF. The original ECG traces must be stored in the patient medical record as source data.

12. MEASUREMENT OF EFFECT

Although the clinical benefit of these drug has not yet been established, the intent of offering this treatment is to provide a possible therapeutic benefit, and thus the patient will be carefully monitored for tumor response and symptom relief in addition to safety and tolerability. Patients with measurable disease will be assessed by standard criteria.

12.1 Antitumor Effect – Solid Tumors

For the purposes of this study, patients should be re-evaluated for response every 8 weeks. In addition to a baseline scan, confirmatory scans should also be obtained at least 4 (not less than 4) weeks following initial documentation of objective response.

Response and progression will be evaluated in this study using the new international criteria proposed by the revised Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1) (Eisenhauer *et al.*, 2009). Changes in the largest diameter (unidimensional measurement) of the tumor lesions and the shortest diameter in the case of malignant lymph nodes are used in the RECIST criteria.

12.1.1 Definitions

- Evaluable for toxicity. All patients will be evaluable for toxicity from the time of their first treatment with olaparib.

- Evaluable for objective response. Only those patients who have measurable disease present at baseline, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for response. These patients will have their response classified according to the definitions stated below. (Note: Patients who exhibit objective disease progression prior to the end of Cycle 1 will also be considered evaluable.)

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

12.1.2 Disease Parameters

- 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 (≥2 cm) by chest x-ray or as ≥10 mm (≥1 cm) with CT scan, MRI, or 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. Tumor lesions that are situated in a previously irradiated area may be considered measurable if they have progressed by RECIST since being irradiated.

- Malignant lymph nodes. To be considered pathologically enlarged and measurable, a lymph node must be ≥15 mm (≥1.5 cm) in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm [0.5 cm]). At baseline and in follow-up, only the short axis will be measured and followed.

- Non-measurable disease. All other lesions (or sites of disease), including small lesions (longest diameter <10 mm [<1 cm] or pathological lymph nodes with ≥10 to <15 mm [≥1 to <1.5 cm] 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.

- 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 which 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.

- 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.

12.1.3 Methods for Evaluation of Measurable Disease

All measurements should be taken and recorded in metric notation using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.

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.

- Clinical lesions. Clinical lesions will only be considered measurable when they are superficial (*e.g.*, skin nodules and palpable lymph nodes) and ≥10 mm (≥1 cm) 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.

- 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.

- Conventional CT and MRI. CT should be diagnostic quality with IV and oral contrast, if possible. This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm (0.5 cm) or less. If CT scans have slice thickness greater than 5 mm (0.5 cm), 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).

  Use of MRI remains a complex issue. MRI has excellent contrast, spatial, and temporal resolution; however, there are many image acquisition variables involved in MRI, which greatly impact image quality, lesion conspicuity, and measurement. Furthermore, the availability of MRI is variable globally. As with CT, if an MRI is performed, the technical specifications of the scanning sequences used should be optimized for the evaluation of the type and site of disease. Furthermore, as with CT, the modality used at follow-up should be the same as was used at baseline and the lesions should be

measured/assessed on the same pulse sequence. It is beyond the scope of the RECIST guidelines to prescribe specific MRI pulse sequence parameters for all scanners, body parts, and diseases. Ideally, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans. Body scans should be performed with breath-hold scanning techniques, if possible.

- PET-CT. PET-CT is not an acceptable imaging method.

- Ultrasound. Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later date and, because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from one assessment to the next. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised. If there is concern about radiation exposure at CT, MRI may be used instead of CT in selected instances.

- Endoscopy, Laparoscopy. The utilization of these techniques for objective tumor evaluation is not advised. However, such techniques may be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in trials where recurrence following complete response (CR) or surgical resection is an endpoint.

- 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. Specific guidelines for both CA-125 response (in recurrent ovarian cancer) and PSA response (in recurrent prostate cancer) have been published [*JNCI* 96:487-488, 2004; *J Clin Oncol* 17, 3461-3467, 1999; *J Clin Oncol* 26:1148-1159, 2008]. In addition, the Gynecologic Cancer Intergroup has developed CA-125 progression criteria which are to be integrated with objective tumor assessment for use in first-line trials in ovarian cancer [*JNCI* 92:1534-1535, 2000].

- 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).

  The cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when the measurable tumor has met criteria for response or stable disease is mandatory to differentiate between response or stable disease (an effusion may be a side effect of the treatment) and progressive disease.

- 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:
  - Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.
  - 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.

- FDG-PET may be used to upgrade a response to a CR in a manner similar to a biopsy in cases where a residual radiographic abnormality is thought to represent fibrosis or scarring. The use of FDG-PET in this circumstance should be prospectively described in the protocol and supported by disease-specific medical literature for the indication. However, it must be acknowledged that both approaches may lead to false positive CR due to limitations of FDG-PET and biopsy resolution/sensitivity.

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

12.1.4 Response Criteria

12.1.4.1 Evaluation of Target Lesions

- Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm (<1 cm).

- 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 (0.5 cm). (Note: the appearance of one or more new lesions is also considered progressions).

- 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.

12.1.4.2 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 [<1 cm] 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.
    - Although a clear progression of "non-target" lesions only is exceptional, the opinion of the treating physician should prevail in such circumstances, and the progression status should be confirmed at a later time by the review panel (or Principal Investigator).

12.1.4.3 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.

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	≥4 wks. Confirmation**
CR	Non-CR/Non-PD	No	PR	≥4 wks. Confirmation**
CR	Not evaluated	No	PR	
PR	Non-PD/not evaluated	No	PR	
SD	Non-PD/not evaluated	No	SD	Documented at least once ≥4 wks. 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.
** Only for non-randomized trials with response as primary endpoint.
*** 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.

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		

12.1.5 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.

- Patients who withdraw from treatment will be regarded as censored.

12.1.6 Progression-Free Survival

PFS is defined as the duration of time from start of treatment to time of progression or death, whichever occurs first. Patients who withdraw from treatment will be regarded as censored.

12.1.7 Overall Survival

OS is defined as the duration of time from start of treatment to time of death. Patients who withdraw from treatment will be regarded as censored.

13. STUDY OVERSIGHT AND DATA REPORTING / REGULATORY REQUIREMENTS

Adverse event lists, guidelines, and instructions for AE reporting can be found in Section 10 (Adverse Events: List and Reporting Requirements).

13.1 Study Oversight

This protocol is monitored at several levels, as described in this section. The Protocol Principal Investigator is responsible for monitoring the conduct and progress of the clinical trial, including the ongoing review of accrual, patient-specific clinical and laboratory data, and routine and serious adverse events; reporting of expedited adverse events; and accumulation of reported adverse events from other trials testing the same drug(s). The Protocol Principal Investigator and statistician have access to the data at all times through the CTMS web-based reporting portal.

All decisions regarding dose escalation/expansion/de-escalation require sign-off by the Protocol Principal Investigator through the CTMS/IWRS. In addition, the Protocol Principal Investigator will have at least monthly, or more frequently, conference calls with the Study Investigators and the CTEP Medical Officer(s) to review accrual, progress, and adverse events and unanticipated problems.

All Study Investigators at participating sites who register/enroll patients on a given protocol are responsible for timely submission of data via Medidata Rave and timely reporting of adverse events for that particular study. This includes timely review of data collected on the electronic CRFs submitted via Medidata Rave.

All studies are also reviewed in accordance with the enrolling institution's data safety monitoring plan.

13.2 Data Reporting

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

Requirements to access Rave via iMedidata:

- A valid account, and
- Assigned a Rave role on the LPO or PO roster at the enrolling site of: Rave CRA, Rave Read Only, Rave CRA (LabAdmin), Rave SLA, or Rave Investigator. Rave role requirements:
    - To hold Rave CRA or Rave CRA (Lab Admin) role, site staff must hold a minimum of an Associate Plus (AP) registration type,
    - To hold Rave Investigator role, the individual must be registered as an Non-Physician Investigator (NPIVR) or Investigator (IVR), and
    - To hold Rave Read Only role, site staff must hold an Associates (A) registration type.
- Refer to https://ctep.cancer.gov/investigatorResources/default.htm for registration types and documentation required.

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

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

13.2.1 Monitoring Method: CTMS Comprehensive

This study will be monitored by the Clinical Trials Monitoring Service (CTMS). Data will be submitted to CTMS at least once every two weeks via Medidata Rave (or other modality if approved by CTEP). Information on CTMS reporting is available at http://www.theradex.com/clinicalTechnologies/?National-Cancer-Institute-NCI-11. On-site audits will be conducted three times annually (one annual site visit and two data audits). For CTMS monitored studies, after users have activated their accounts, please contact the Theradex Help Desk at (609) 619-7862 or by email at CTMSSupport@theradex.com for additional support with Rave and completion of CRFs.

13.2.2 Responsibility for Data Submission

For ETCTN trials, it is the responsibility of the PI(s) at the site to ensure that all investigators at the ETCTN Sites understand the procedures for data submission for each ETCTN protocol and that protocol specified data are submitted accurately and in a timely manner to the CTMS via the electronic data capture system, Medidata Rave.

Data are to be submitted via Medidata Rave to CTMS on a real-time basis, but no less than once every 2 weeks. The timeliness of data submissions and timeliness in resolving data queries will be tracked by CTMS. Metrics for timeliness will be followed and assessed on a quarterly basis. For the purpose of Institutional Performance Monitoring, data will be considered delinquent if it is greater than 4 weeks past due.

Data from Medidata Rave and CTEP-AERS is reviewed by the CTMS on an ongoing basis as data is received. Queries will be issued by CTMS directly within Rave. The queries will appear on the Task Summary Tab within Rave for the CRA at the ETCTN to resolve. Monthly web-based reports are posted for review by the Drug Monitors in the IDB, CTEP. Onsite audits will be conducted by the CTMS to ensure compliance with regulatory requirements, GCP, and NCI policies and procedures with the overarching goal of ensuring the integrity of data generated from NCI-sponsored clinical trials, as described in the ETCTN Program Guidelines, which may be found on the CTEP (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/adverse_events.htm) and CTSU websites.

CTMS will utilize a core set of eCRFs that are Cancer Data Standards Registry and Repository (caDSR) compliant (http://cbiit.nci.nih.gov/ncip/biomedical-informatics-resources/interoperability-and-semantics/metadata-and-models). Customized eCRFs will be included when appropriate to meet unique study requirements. The PI is encouraged to review the eCRFs, working closely with CTMS to ensure prospectively that all required items are appropriately captured in the eCRFs prior to study activation. CTMS will prepare the eCRFs with built-in edit checks to the extent possible to promote data integrity.

CDUS data submissions for ETCTN trials activated after March 1, 2014, will be carried out by the CTMS contractor, Theradex. CDUS submissions are performed by Theradex on a monthly basis. The trial's lead institution is responsible for timely submission to CTMS via Rave, as above.

Further information on data submission procedures can be found in the ETCTN Program Guidelines (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/adverse_events.htm).

13.3 Data Quality Portal

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

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

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

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

Note: Some Rave protocols may not have delinquent form details or reports specified on the DQP. A protocol must have the Calendar functionality implemented in Rave by the Lead Protocol Organization (LPO) for delinquent form details and reports to be available on the DQP. Site staff should contact the LPO Data Manager for their protocol regarding questions about Rave Calendaring functionality.

13.4 Collaborative Agreements Language

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 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 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 NCI, 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 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 Agent.

3. Clinical Trial Data and Results and Raw Data developed under a Collaborative Agreement will be made available 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 by the Group office for Cooperative Group studies or by the principal investigator for non-Cooperative Group studies 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.

13.5 Genomic Data Sharing Plan

The investigators and statistician and/or bioinformaticians for a study will have access to all data on mutations and variants stored in the Theradex Data Base and the GDC. This information will be sequestered from access throughout the study until it is analyzed for purposes of reporting and publishing of the study results. As specified in the CRADA for the agents used in the clinical study, the pharmaceutical collaborator will have at least 6 months, longer if needed for a regulatory filing, to review the data and or receive copies of the data once the study is completed and analyzed, or sooner, if specified for purposes of generating Intellectual Property. Once these timeframes have been exceeded, the data will be available through a Data Access Committee (DAC) in the GDC following NCI and Collaborator review of the proposals.

13.6 Incidental/Secondary Findings Disclosure Procedure

Given the potential clinical implications conferred by detecting a germline and/or somatic mutation in one of the proven cancer susceptibility genes, this protocol will use the following disclosure procedure, consistent with the recommendations of the American College of Medical and Genomics [ACMG] (Green *et al.*, 2013 and Kalia *et al.,* 2016):

The NCI Molecular Characterization Laboratory will review the mutations/variants once at the time of initial specimen evaluation according to the most recent version of the ACMG guidance on variants. The NCI Molecular Characterization Laboratory will not re-review all specimens received if a new version of the ACMG guidance is published after the initial review.

For each participant with a pathogenic or likely pathogenic germline and/or somatic variant detected in the WES of blood (as defined in the ACMG guidance), the NCI Molecular Characterization Laboratory will report to the Program Director or Scientific Officer the UPID and variant(s) identified. The Program Director or Scientific Officer will contact Theradex to obtain the name of the protocol, investigator treating the patient, and the Principal Investigator of the grant. The treating physician will be contacted by phone and in writing to ask the patient whether he or she is interested in learning more about the finding.

If the patient wants to know more, the physician should contact the Program Director for more information about the mutation/variant. The treating physician and a medical genetics counselor should meet with the patient to discuss the importance and meaning of the finding, but not the finding itself, and notify the patient that this research finding must be confirmed by Sanger sequencing at the patient's/patient insurer's expense in a Clinical Laboratory Improvement Amendments (CLIA)-approved laboratory. The treating physician and genetic counselor should inform the patient of the confirmed result and its meaning and significance to the patient. If desired, the patient may elect to undergo genetic counseling and confirmatory CLIA-approved clinical testing on his or her own. Neither the research laboratory nor the National Cancer Institute will be responsible for the costs incurred for any confirmatory genetic testing or counseling.

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APPENDIX A PERFORMANCE STATUS CRITERIA

ECOG Performance Status Scale		**Karnofsky Performance Scale**	
Grade	Descriptions	Percent	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease.
		90	Able to carry on normal activity; minor signs or symptoms of disease.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (*e.g.*, light housework, office work).	80	Normal activity with effort; some signs or symptoms of disease.
		70	Cares for self, unable to carry on normal activity or to do active work.
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.	60	Requires occasional assistance, but is able to care for most of his/her needs.
		50	Requires considerable assistance and frequent medical care.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	40	Disabled, requires special care and assistance.
		30	Severely disabled, hospitalization indicated. Death not imminent.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	20	Very sick, hospitalization indicated. Death not imminent.
		10	Moribund, fatal processes progressing rapidly.
5	Dead.	0	Dead.

APPENDIX B PRE-BIOPSY ASSESSMENT

A pre-biopsy lesion assessment can increase trial safety and efficiency. By agreement between all investigators, an attempt at biopsy will be made if the clinical trial team determines that a biopsy poses minimal relative risk, provides potential clinical gain to the participant, and will likely yield sufficient tissue for analysis.

Pre-biopsy assessments will be reported and tracked through a trial-specific CRF within the CTEP Medidata Rave system. Additional information can be found in the Investigational Radiology SOP available at:
https://ctep.cancer.gov/initiativesPrograms/docs/ETCTN_IR_Research_Biopsy_SOP.pdf.

Individual Patient Pre-Biopsy Assessment. IR co-investigators are encouraged to apply this pre-biopsy scoring and correlation system to assist in the determination of biopsy appropriateness.

- IR co-investigators assign a subjective score of 1-3 based on likelihood of success due to lesion characteristics.

    1. Biopsy should not be done
        A. Due to safety concerns
        B. Due to lack of suitable lesion for biopsy

    2. Uncertainty about success
        A. Due to access path to lesion
        B. Due to lesion characteristics

    3. Likely successful

- Lesion characteristics to be considered
    - Size (small) (<2 cm)
    - Location/path to lesion
    - Morphologic features (necrosis, sub-solid, sclerosis, ill-defined/infiltrative)
    - PET (+/-), avidity
    - Organ/site (sclerotic bone is low yield; fine needle aspiration to be used)

APPENDIX C FROZEN BIOPSY SPECIMEN BATCH RECORD

Batch Record

A separate Batch Record should be started for each patient sample.

Facility / Clinic Collecting Specimens: _____

NCI Protocol Number: 10329
Patient ID:_____

1. Biopsy Collection

	1st Pass	2nd Pass	3rd Pass	4th Pass
Specimen ID				
Biopsy size prepared for PD or histological analysis:	☐ Full ☐ Halved	☐ Full ☐ Halved	☐ Full ☐ Halved	☐ Full ☐ Halved
Required: Time elapsed from collection to placement in tube	min sec	min sec	min sec	min sec
Time biopsy collected (opt)	:	:	:	:
Time biopsy placed in tube (opt)	:	:	:	:

2. Biopsy Procedure Details

Specimen ID	
Time local anesthesia administered	:
Dose of local anesthetic	mg
Name of local anesthetic used (from Research Nurse)	
Time of skin incision	:
Needle Type (e.g., Temno)	
Needle diameter	gauge
Needle Length	cm
Time guide needle introduced	:
Time guide needle placement confirmed	:
Time biopsy needle introduced	:

3. Biopsy Storage

Date/time biopsy specimen(s) placed at -80°C (or lower) _____/ /_____ _____:_____ _____°C

4. Notes, including any deviations from this protocol

_____

_____

_____

5. Review of Batch Record

Laboratory Personnel: _____ (Print)

Laboratory Personnel: _____ (Sign)

Date: _____

APPENDIX D PATIENT MEDICATION DIARIES – OLAPARIB AND AZD1775

PATIENT'S MEDICATION DIARY FOR OLAPARIB (aka AZD2281)

CTEP-assigned Protocol # 10329
Local Protocol # _____

Today's date _____ **Agents**: Olaparib

Patient Name_____ *(initials acceptable)* **Patient Study ID**_____

INSTRUCTIONS TO THE PATIENT:

1. Complete one form every four weeks.
2. On the days that you take olaparib: You will take 2 tablets twice each day (supplied as 100 or 150 mg tablets), taken in the morning and taken at night at the same time each day. You should take the tablets with 8 oz. water, with or without any moderate fat or low-fat food. Do not consume grapefruit, grapefruit juice, or Seville oranges while on olaparib therapy.
3. On your "rest" days: Do not take any medications on your rest days. Shaded rows indicate the days that you will NOT take olaparib.
4. Record the date, medication, number of tablets you took, and what time you took them.
5. Swallow each tablet whole - do not chew, crush, dissolve, or divide them.
6. If you vomit shortly after you take your medications: the dose should only be replaced if all of the intact tablets can be seen and counted. Should you miss a scheduled dose for whatever reason (e.g., as a result of forgetting to take the tablets or vomiting), you can take the scheduled dose up to a maximum of 2 hours after that scheduled dose time. If greater than 2 hours after the scheduled dose time, do not take the missed dose. Take your assigned dose at the next scheduled time.
7. Notify your doctor at the first sign of poorly formed or loose stools, or an increased frequency of bowel movements. Loperamide should be kept on hand and should be taken as recommended by your doctor.
8. If you have any comments or notice any side effects, please record them in the Comments column.
9. Please return the forms to your physician when you go for your next appointment.

Day	Date	Medication	Time of a m. dose	# of tablets taken	Time of p m. dose	# of tablets taken	Comments
Example	*11/2/2019*	*Olaparib*	*7:02 am*	*2*	*7:05 pm*	*2*	*Experienced nausea 1 hr after medication.*
1							
2							
3							
4							
5							
6		*Rest*					
7		*Rest*					
8							
9							
10							
11							
12							
13		*Rest*					

14		*Rest*					
15							
16							
17							
18							
19							
20		*Rest*					
21		*Rest*					
22							
23							
24							
25							
26							
27		*Rest*					
28		*Rest*					

Patient's Signature_____

Physician's Office will complete this section:

1. Date patient started protocol treatment_____
2. Date patient was removed from study_____
3. Patient's planned total daily dose_____
4. Total number of tablets taken this month _____
5. Physician/Nurse/Data Manager's Signature _____

PATIENT'S MEDICATION DIARY FOR AZD1775

Today's date _____ **Agents**: AZD1775

Patient Name_____ *(initials acceptable)* **Patient Study ID**_____

INSTRUCTIONS TO THE PATIENT:

1. Complete one form every four weeks.
2. On the days that you take AZD1775: You will take multiple capsules once per day (supplied as either 25 or 100 mg capsules or a combination of both) in the morning or evening, at the same time each day.
3. You should take the capsules with 8 oz. water, with or without any moderate fat or low-fat food. Do not consume grapefruit, grapefruit juice, or Seville oranges while on AZD1775 therapy.
4. On your "rest" days: Do not take any medications on your rest days. Shaded rows indicate the days that you will NOT take AZD1775.
5. Record the date, medication, number of capsules you took, and what time you took them.
6. Swallow each capsule whole - do not chew, crush, dissolve, or divide them.
7. If you vomit shortly after you take your medications: the dose should only be replaced if all of the intact capsules can be seen and counted. Should you miss a scheduled dose for whatever reason (e.g., as a result of forgetting to take the tablets or vomiting), you can take the scheduled dose up to a maximum of 2 hours after that scheduled dose time. If greater than 2 hours after the scheduled dose time, do not take the missed dose. Take your assigned dose at the next scheduled time.
8. Notify your doctor at the first sign of poorly formed or loose stools, or an increased frequency of bowel movements. Loperamide should be kept on hand and should be taken as recommended by your doctor.
9. If you have any comments or notice any side effects, please record them in the Comments column.
10. Please return the forms to your physician when you go for your next appointment.

Day	Date	Medication	Time of daily dose	# of tablets taken	Comments
Example	*11/2/2019*	*AZD1775*	*7:02 am*	*3*	*Experienced nausea 1 hr after medication.*
1					
2					
3					
4					
5					
6		*Rest*			
7		*Rest*			
8					
9					
10					
11					
12					
13		*Rest*			
14		*Rest*			
15					
16					
17					

18					
19					
20		*Rest*			
21		*Rest*			
22					
23					
24					
25					
26					
27		*Rest*			
28		*Rest*			

Patient's Signature_____

Physician's Office will complete this section:

1. Date patient started protocol treatment_____
2. Date patient was removed from study_____
3. Patient's planned total daily dose_____
4. Total number of tablets taken this month _____
5. Physician/Nurse/Data Manager's Signature _____

APPENDIX E PATIENT DRUG INTERACTIONS HANDOUT AND WALLET CARD – AZD1775

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

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

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

These are the things that your healthcare providers need to know:
AZD1775 (adavosertib) interacts with certain specific enzymes in the liver or other tissues like the gut and certain transport proteins that help move drugs in and out of cells.

	Explanation
CYP isoenzymes	The enzymes in question are ***CYP 3A4 and 2C19*****.** AZD1775 (adavosertib) is metabolized by CYP3A4 and may be affected by other drugs that inhibit or induce these enzymes. AZD1775 (MK-1775) is an inhibitor of CYP 3A4 and 2C19 and may affect the metabolism of other drugs.
Protein transporters	The proteins in question are ***P-gp, MATE1, MATE2K, and BCRP*****.** AZD1775 (adavosertib) is a substrate of P-gp and BCRP and may be affected by other drugs that inhibit or induce these transporters. AZD1775 (adavosertib) is an inhibitor of P-gp, MATE1, MATE2K, and BCRP and may affect transport of other drugs in and out of cells.

These are the things that you need to know:
The study drug AZD1775 (adavosertib), may interact with other drugs which can cause side effects. For this reason, it is very important to tell your doctors about all your medicines, including: (a) medicines you are taking before this clinical trial, (b) medicines you start or stop taking during this study, (c) medicines you buy without a prescription (over-the-counter remedy), (d) herbals or supplements (e.g. St. John's Wort). It is helpful to bring your medication bottles or an updated medication list with you.

Before you enroll onto the clinical trial, your study doctor will work with your regular health care providers to review any medicines and herbal supplements that are considered "strong inducers/inhibitors or substrates of **CYP 3A4, 2C19, P-gp, MATE1, MATE2K, and BCRP."**

- Please be very careful! Over-the-counter drugs (including herbal supplements) may contain ingredients that could interact with your study drug. Speak to your doctors or pharmacist to determine if there could be any side effects.

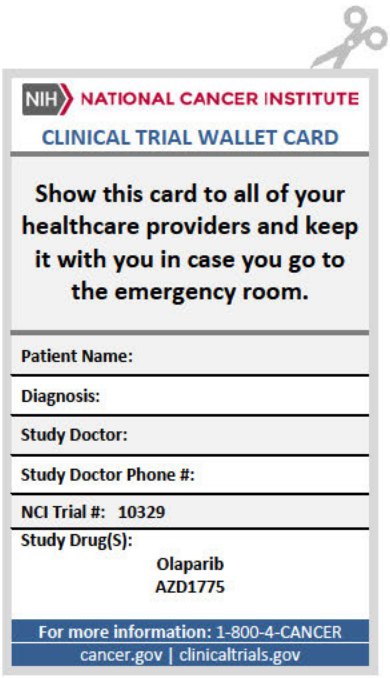
- Make sure your doctor knows to avoid certain prescription medications.
- Your regular health care provider should check a frequently updated medical reference or call your study doctor before prescribing any new medicine or discontinuing any medicine.

Version *May/2019*

PATIENT DRUG INTERACTION WALLET CARD

NIH NATIONAL CANCER INSTITUTE **EMERGENCY INFORMATION**	NIH NATIONAL CANCER INSTITUTE	NIH NATIONAL CANCER INSTITUTE **DRUG INTERACTIONS**	NIH NATIONAL CANCER INSTITUTE
Show this card to all of your healthcare providers. Keep it with you in case you go to the emergency room.	Tell your doctors **before** you start or stop any medicines. **Check with your doctor or pharmacist if you need to use an over-the-counter medicine or herbal supplement!**	**Carry this card with you at all times** AZD1775 (adavosertib) interacts with certain specific enzymes in the liver or other tissues like the gut and certain transport proteins that help move drugs in and out of cells and must be used very carefully.	
Patient Name: **Diagnosis:** **Study Doctor:** **Study Doctor Phone #:** **NCI Trial #:** 10329 **Study Drug(S):** Olaparib AZD1775	**Use caution and avoid the following drugs if possible:**	Your healthcare providers should be aware of any medicines that are strong inducers/inhibitors or substrates of **CYP 3A4, 2C19, P-gp, MATE1, MATE2K, and BCRP.** **Before prescribing new medicines**, your health care provider should check a **frequently-updated medical reference** for a **list of drugs to avoid** or contact your study doctor. Version May/2019	
For more information: 1-800-4-CANCER cancer gov | clinicaltrials gov	**For more information:** 1-800-4-CANCER cancer gov | clinicaltrials gov	**For more information:** 1-800-4-CANCER cancer gov | clinicaltrials gov	**For more information:** 1-800-4-CANCER cancer gov | clinicaltrials gov

APPENDIX F PATIENT CLINICAL TRIAL WALLET CARD – OLAPARIB AND AZD 1775



NIH NATIONAL CANCER INSTITUTE

CLINICAL TRIAL WALLET CARD

Show this card to all of your healthcare providers and keep it with you in case you go to the emergency room.

Patient Name:

Diagnosis:

Study Doctor:

Study Doctor Phone #:

NCI Trial #: 10329

Study Drug(S):
Olaparib
AZD1775

For more information: 1-800-4-CANCER
cancer.gov | clinicaltrials.gov

APPENDIX G ACTIONS REQUIRED IN CASES OF COMBINED INCREASE OF AMINOTRANSFERASE AND TOTAL BILIRUBIN – HY'S LAW

Briefly, Hy's Law cases have the following three components:

- The drug causes hepatocellular injury, generally shown by a higher incidence of 3-fold or greater elevations above the ULN of ALT or AST than the (non-hepatotoxic) control drug or placebo
- Among trial subjects showing such AT elevations, often with ATs much greater than 3xULN, one or more also show elevation of serum TBL to >2xULN, without initial findings of cholestasis (elevated serum ALP)
- No other reason can be found to explain the combination of increased AT and TBL, such as viral hepatitis A, B, or C; preexisting or acute liver disease; or another drug capable of causing the observed injury

Finding one Hy's Law case in the clinical trial database is worrisome; finding two is considered highly predictive that the drug has the potential to cause severe drug induced liver injury (DILI) when given to a larger population.

The following actions are required in cases of combined increase of aminotransferase and total bilirubin:

1. Confirmation

In general, an increase of serum AST/A:T to >3xULN should be followed by repeat testing within 48 to 72 hours of all four of the usual serum measures (ALT, AST, ALP, and TBL) to confirm the abnormalities and to determine if they are increasing or decreasing. There also should be inquiry made about symptoms. Serum AT may rise and fall quite rapidly, and waiting a week or two before obtaining confirmation of elevations may lead to a false conclusion that the initially observed abnormality was spurious. Of greater concern, delay in retesting may allow progression to severe worsening if the initial abnormality was the herald of a severe reaction to follow. The need for prompt repeat testing is especially great if AST/ALT is much greater than 3xULN and/or TBL is greater than 2xULN. For outpatient trials, or trials in which subjects are far away from the trial site, it may be difficult for the subjects to return to the trial site promptly. In this case, the subjects should be retested locally, but normal laboratory ranges should be recorded, results should be made available to trial investigators immediately, and the data should be included in the case reports. If symptoms persist or repeat testing shows AST/ALT >3xULN for subjects with normal baseline measures or 2-fold increases above baseline values for subjects with elevated values before drug exposure, it is appropriate to initiate close observation to determine whether the abnormalities are improving or worsening. If close monitoring is not possible, the drug should be discontinued.

2. Close Observation

It is critical to initiate close observation immediately upon detection and confirmation of early signals of possible DILI, and not to wait until the next scheduled visit or monitoring interval. A threshold of aminotransferase levels greater than 3xULN seems reasonable, as lesser elevations are common and nonspecific. If additional testing, beyond that specified in the trial protocol, is carried out, it is important that the subject's information be added to the case report forms and database.
Close observation includes:

Repeating liver enzyme and serum bilirubin tests two or three times weekly. Frequency of retesting can decrease to once a week or less if abnormalities stabilize or the trial drug has been discontinued and the subject is asymptomatic.
Obtaining a more detailed history of symptoms and prior or concurrent diseases.
Obtaining a history of concomitant drug use (including nonprescription medications and herbal and dietary supplement preparations), alcohol use, recreational drug use, and special diets.
Ruling out acute viral hepatitis types A, B, C, D, and E; autoimmune or alcoholic hepatitis; nonalcoholic steatohepatitis; hypoxic/ischemic hepatopathy; and biliary tract disease.
Obtaining a history of exposure to environmental chemical agents.
Obtaining additional tests to evaluate liver function, as appropriate (e.g., INR, direct bilirubin).
Considering gastroenterology or hepatology consultations.

3. Decision to Stop Drug Administration

It has been observed that de-challenge (stopping drug administration) does not always result in immediate improvement in abnormal lab values. Abnormal test values and symptoms may progress for several days or even weeks after discontinuation of the drug that caused the abnormality. For example, rising TBL usually follows serum AT increases by a few days to weeks. The primary goal of close observation is to determine as quickly as possible whether observed abnormal findings are transient and will resolve spontaneously or will progress. For most DILI, no specific antidotes are available (except N-acetylcysteine for acute acetaminophen overdose if given promptly, and, possibly, intravenous carnitine for valproic acid hepatotoxicity).

Promptly stopping the offending drug usually is the only potentially effective therapy.

Because transient fluctuations of ALT or AST are common, and progression to severe DILI or acute liver failure is uncommon, automatic discontinuation of trial drug upon finding a greater than 3xULN elevation of ALT or AST may be unnecessary. For most people, the liver appears capable of adapting to injury by foreign chemical substances, which may render a person tolerant to the drug despite continued exposure. Stopping a drug at the first hint of mild injury does not permit learning whether adaptation will occur, as it does for drugs such as tacrine, which cause liver injury but do not cause severe DILI. On the other hand, continuing drug appears unacceptably dangerous if there is marked serum aminotransferase elevation or evidence of functional impairment, as indicated by rising bilirubin or INR, which represent substantial liver injury. Although there is no published consensus on exactly when to stop a drug in the face of laboratory abnormalities and the decision will be affected by information on related drugs, the accumulating clinical experience, the clinical status of the patient, and many other factors, the following can be considered a basic guide. Discontinuation of treatment should be considered if:

ALT or AST >8xULN
ALT or AST >5xULN for more than 2 weeks
ALT or AST >3xULN and (TBL >2xULN or INR >1.5)
ALT or AST >3xULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)

It should be noted that although these guidelines have not been evaluated systematically in a prospective fashion, they represent an approach that is similar to current practice.

4. Evaluating Data for Alternative Causes

An important purpose of close observation is to gather additional clinical information to seek other possible causes of the observed liver test abnormalities, such as one of the following common causes:

Acute viral hepatitis. The usual onset of hepatocellular DILI is indistinguishable from acute viral hepatitis A or B. Hepatitis C is much less often acute in its onset and tends to be insidious, but it sometimes can resemble acute DILI. The presence of acute viral hepatitis A, B, and C should be evaluated by serological markers. Viral hepatitis D (requires concomitant hepatitis B infection) and E are relatively rare in the United States. Hepatitis E is more common in developing countries, including Southeast Asia, and should be considered in recent travelers to those countries and in patients in trials conducted in those countries. Also rare are hepatocellular liver injuries caused by Epstein-Barr virus, cytomegalovirus, herpes simplex virus, toxoplasmosis, varicella, and parvovirus, although these infections are seen more typically in immuno-suppressed individuals. Adolescent and young adult patients with possible DILI should be tested for Epstein-Barr virus. Hepatitis is common among transplant patients with cytomegalovirus disease.

Alcoholic and autoimmune hepatitis. Acute alcoholic hepatitis usually is recurrent, with a history of binging exposure to alcohol preceding episodes, and it has some characteristic features, such as associated fever, leukocytosis, right upper quadrant pain and tenderness, hepatomegaly, and AST >ALT, that may help distinguish it from other causes of liver injury. Other features of the physical examination may include the presence of stigmata of cirrhosis, such as spider nevi, palmar erythema, estrogenic changes in males, and Dupuytren's contractures. Alcoholic and autoimmune hepatitis should be assessed by history, physical examination, and laboratory testing, including serologic testing (e.g., antinuclear or other antibodies).

Hepatobiliary disorders. Biliary tract disease, such as migration of gallstones or intrahepatic lesions, more often causes cholestatic injury initially and should be investigated with gall bladder and ductal imaging studies, especially if ALP is increased. Malignant interruption of the biliary tract also should be considered.

Nonalcoholic steatohepatitis. Nonalcoholic steatohepatitis may be seen in obese, hyperlipoproteinemic, and/or diabetic patients and may be associated with fluctuating

aminotransferase levels, and hepatic and sometimes splenic enlargement. It is sometimes associated with cirrhosis and portal hypertension.

Cardiovascular causes. Cardiovascular disease, especially right heart failure and hypotension or any cause of impaired oxygenation of the liver, may cause acute centrilobular hypoxic cell necrosis (ischemic hepatitis) with rapid and sometimes spectacular increases of serum AT (e.g., AT >10,000 U/L). Cardiovascular dysfunction or impaired liver oxygenation, including hypotension or right heart failure, should be assessed by physical examination and history.

Concomitant treatments. It is critical to discover concomitant treatments, including exposure to nonprescription and dietary supplement products that might be responsible for injury. Many people take multiple drugs, perhaps less often in controlled clinical trials because of exclusion criteria, but subjects may not report taking disallowed drugs or other agents. The possible exposure to potentially toxic herbal or dietary supplement mixtures (sometimes of unknown composition), nonprescription medications such as acetaminophen, or to occupational chemical agents may not be volunteered unless subjects are specifically questioned.

5. Follow-Up to Resolution

All trial subjects showing possible DILI should be followed until all abnormalities return to normal or to the baseline state. DILI may develop or progress even after the causative drug has been stopped. Results should be recorded on the case report form and in the database. Note that longer follow-up can sometimes reveal an off-drug repetition of what had appeared to be DILI, indicating that liver injury was related to underlying liver disease.

6. Re-challenge

Whether or not to re-challenge a subject who showed mild DILI is a difficult decision. Re-exposure may initiate a sometimes explosive and more severe reaction, as was observed with halothane several decades ago. Some cases of DILI show indicators of immunological reaction such as eosinophilia, rash, fever, or other symptoms or findings, and it is possible that such cases are more prone to recur with re-exposure. Re-challenge may not be considered negative unless the subject is exposed to and tolerates the same dose and treatment duration that preceded the original reaction. A negative re-challenge does not necessarily allow a conclusion that the drug did not cause the injury. Most people can adapt to xenobiotic substances, including new drugs, and develop tolerance for them. This has been observed even for drugs that can cause severe injury, such as isoniazid. The large majority of people showing hepatocellular injury while taking isoniazid recover fully or recover while continuing to take the drug, and some, but not all, can resume or continue taking the drug without further adverse consequence. If such tolerance has developed, the use of re-challenge to verify drug causation would give a false negative result.

Generally, re-challenge of subjects with significant AT elevations (>5xULN) should not be attempted. If such subjects are re-challenged, they should be followed closely. Re-challenge can be considered if the subject has shown important benefit from the drug and other options are not available or if substantial accumulated data with the test drug do not show a potential for severe

injury. The subject should be made aware of the potential risk, and consent to the re-challenge, and the PI consulted.

APPENDIX H TISSUE BIOPSY VERIFICATION FORM

A copy of the diagnostic pathology report must be shipped with all tissue specimens sent to the EET Biobank.

If the *corresponding* pathology report is not available for the biopsy, then a copy of the radiology report or operative report from the biopsy procedure and the diagnostic pathology report must be sent to the EET Biobank. A completed copy of this appendix (i.e., Tissue Biopsy Verification) must also be submitted to the EET Biobank.

Note: If this information is not provided with the biopsy specimen, then it will not be accepted by the EET Biobank.

Please have the Clinician* responsible for signing out this patient's case complete the following:

ETCTN Universal Patient ID: _____

ETCTN Patient Study ID: _____

Date of Procedure (mm/dd/yyyy): _____

Tissue Type (circle one): Primary Metastatic

Time point (circle one): Baseline Cycle 1, Day 12 Each Restaging Progression

Site Tissue Taken From: _____

Diagnosis: _____

I agree that this tissue may be released for research purposes only and that the release of this tissue will not have any impact on the patient's care.

_____ _____
Clinician Signature Date

_____
Clinician Printed Name

*Note: For the purposes of this form, Clinician could include the Nurse Practitioner, Registered Nurse, Pathologist, Radiologist, Interventional Radiologist, Surgeon, Oncologist, Internist, or other medical professional responsible for the patient's care.