SUMMARY OF CHANGES – Protocol

For Protocol Amendment # 1 to 21

NCI Protocol #: 10031
Local Protocol #: 17-715

NCI Version Date: February 10, 2020
Protocol Date: February 10, 2020

#	Section	Page	Change
1.	Header; Title Page	All; 2	Protocol version date updated from December 13, 2019 to February 10, 2020.
2.	8.1.1 Availability	62	Revision of the Protocol as Specified Below: Please add, "AT13387 clinical drug development program is completed. The current clinical supply is expiring on May 31, 2020; thus, all patients must be off treatment by May 31, 2020." Please make this change in your next amendment request. **PI Response: Statement added as outlined above**
3.	5.5	43	Revision of the Protocol as Specified Below: Please indicate if patients will be allowed to continue olaparib alone if AT13387 is discontinued after May 31, 2020. It's not clear if monotherapy is allowed. **PI Response: Added "Patients may continue olaparib alone after May 31, 2020".**
4.	10	71	Revision of the Protocol as Specified Below: • Added "j. Patients who continue on olaparib monotherapy will have concomitant meds, physical exam, vital signs, CBC w/diff, platelets, serum chemistry, and adverse event evaluation on day 1 only of each cycle following AT13387 discontinuation".
5.	ICF	All	Consent version updated from December 13, 2019 to February 10, 2020
6.	ICF	2	Revision of the ICD as Specified Below: Please indicate if patients will be allowed to continue olaparib alone if AT13387 is discontinued after May 31, 2020. It's not clear if monotherapy is allowed. **PI Response: Added "Patients who stop taking AT13387 (onalespib) may continue to take olaparib alone".**

NCI Protocol #: 10031
Local Protocol #: 17-715

ClinicalTrials.gov Identifier: TBD

TITLE: A Phase 1 Study of PARP inhibitor olaparib and HSP90 inhibitor AT13387 for treatment of advanced solid tumors with expansion in patients with recurrent epithelial ovarian, fallopian tube, peritoneal cancer or recurrent triple-negative breast cancer

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NCI-Supplied Agent(s): olaparib NSC 747856
AT13387 (onalespib) NSC 749712

IND #:

IND Sponsor: DCTD, NCI

Protocol Type / Version # / Version Date: Amendment 18 / Version 21 / February 10, 2020

PROTOCOL SYNOPSIS

A Phase 1 Study of HSP90 Inhibitor AT13387 (NSC# 749712) in Combination with PARP Inhibitor Olaparib (NSC# 747856) for Treatment of Advanced Solid Tumors with Expansion in Patients with Recurrent Epithelial Ovarian, Fallopian Tube, or Peritoneal Cancer or Recurrent Triple-Negative Breast Cancer

STUDY DRUGS:	AT13387 (NSC# 749712) and Olaparib (NSC# 747856)
PHASE:	1
INDICATION:	Advanced Solid Tumors with Expansion in Patients with Recurrent Epithelial Ovarian, Fallopian Tube, or Peritoneal Cancer or Recurrent Triple-Negative Breast Cancer
RATIONALE:	Based on the results of our preclinical work, we hypothesize that the HSP90 inhibitor AT13387 will enhance the anticancer effects of the PARP inhibitor olaparib at tolerable doses in patients with advanced solid tumors
TARGET POPULATION:	Patients eligible for this study will have a solid tumor malignancy that is unresectable or metastatic and for which standard treatment is not available.
NUMBER OF SUBJECTS:	Phase 1 dose/regimen exploration: estimated 20 patients. Phase 1b expansion cohorts: estimated 20 patients.
PRIMARY OBJETIVES:	To establish the maximum tolerated dose (MTDs) of olaparib and AT13387 administered in combination in patients with advanced solid tumors.
SECONDARY OBJECTIVES:	To identify the dose-limiting toxicity (DLT) and other toxicities associated with olaparib and AT13387 administered in combination as assessed by CTCAE v5.0. To determine the recommended phase 2 doses (RP2D) of the combination of olaparib and AT13387. To document anti-tumor activity of the combination of olaparib and AT13387 as assessed by RECIST 1.1 and progression free survival (PFS).

To determine the plasma pharmacokinetics of olaparib and AT13387.

EXPLORATORY OBJECTIVES:

STUDY DESIGN

This is a multi-center, Phase 1/1b clinical trial that will be conducted to define the MTD, RP2D and safety and tolerability of the combination of AT13887 and olaparib in patients with advanced solid tumor malignancies. The study will begin with an exploration of the dose and regimen of the combination of these 2 novel agents. As viable regimens are identified, an expansion cohort of patients with epithelial ovarian, fallopian or primary peritoneal or triple negative breast cancer (TNBC) patients will be enrolled with one of the schedules, for confirmation of safety, PK and PD. This cohort will include patients with BRCA-wildtype TNBC or patients with platinum resistant epithelial ovarian or fallopian or primary peritoneal cancers. A total of 40 patients is expected to be enrolled; approximately 20 in the exploration cohort and an additional 20 in the expansion cohort.

In mouse xenograft models, continuous daily administration of olaparib yielded greater antitumor activity than intermittent administration at the same or at higher dose levels so it is recommended that olaparib is administered continuously. Therefore, in this trial we propose that olaparib will be dosed orally continuously twice daily.

Regarding AT13387, the optimal schedule for HSP90 inhibition is unclear. However, our tolerability and efficacy studies with olaparib and AT13387 in ovarian PDX models, support twice weekly dosing of AT13387 (on Days 1 and 2 every week, i.e. 2 days on/5 days off). The twice weekly (Days 1 and 2) of AT13387 was also chosen based on previous experience by Dr Shapiro with another HSP90 inhibitor ganetespib (STA-9090)[1]. Therefore, the proposed regimen will be olaparib twice daily for 28 consecutive days and AT13387 on Days 1 and 2 every week, 3 weeks of a 4 week (28 day) cycle (Days 1, 2, 8, 9, 15, 16).

Cycle 0 is only 7 days and Cycle 1 begins 8 days after start of Cycle 0, i.e. immediately after Cycle 0 ends. During cycle 0, olaparib will be administered alone twice daily for 1 week (D1-7). Cycle 1 and beyond, olaparib will continue to be administered twice daily (days 1-28) and AT13387 will be administered for 2 consecutive days on 3 of a 4 week cycle. Given that our hypothesis is that AT13387 sensitizes to olaparib by inhibiting HR, by administering olaparib alone for cycle 0 only, we can test the hypothesis as a "proof of mechanism" for the combination of AT13387 and olaparib. Specifically, we expect that there will be induction of BRCA1 and RAD51 foci after administration of olaparib alone and reduced formation of these foci and downregulation of expression of HR pathway genes after the combination of AT13387 and olaparib.
A standard 3+3 design will be utilized. Doses of olaparib will range from 50mg–300 mg twice daily; AT13387 doses will range from 20–160 mg/m2 (20-40-80-120-160) using a ping-pong

strategy as shown in the Table below. DLT events will be based on adverse events during cycles 0 and 1, utilizing CTCAE v.5.0.

There will be no stratification factors for the phase I of this study. We anticipate that between 2-3 patients will be enrolled per month to this study. If the RP2D is at the highest dose level, we would expect a sample size of approximately 40 subjects. Therefore, recruitment for the current study will be done in approximately 12-18 months. The schedule will facilitate the assessment of olaparib PK (C_{max}, T_{max} AUC, $t_{1/2}$) and PD in the absence and presence of AT13387.

The following escalation scheme will be followed (one cycle is 28 days):

DOSE LEVEL	olaparib (tablets, oral, twice daily dosing continuous)	AT13387 (IV two consecutive days weekly)
-4	50mg BID	10mg/m2
-3	100mg BID	10mg/m2
-2*	50mg BID	20mg/m2
-1**	100mg BID	20mg/m2
0 (Starting Dose)	200mg BID	20mg/m2
1	200mg BID	40mg/m2
2***	300mg BID	40mg/m2
3***	300mg BID	80mg/m2
4	300mg BID	120mg/m2
5	300mg BID	160mg/m2

*If dose level -2 is tolerated, then escalation of AT13387 in combination with olaparib 50mg BID will be attempted i.e.

-2a	50mg BID	40mg/m2
-2b	50mg BID	80mg/m2
-2c	50mg BID	120mg/m2

-2d	50mg BID	160mg/m2

**If dose level -1 is tolerated, then escalation of AT13387 in combination with olaparib 100mg BID will be attempted i.e.

-1a	100mg BID	40mg/m2
-1b	100mg BID	80mg/m2
-1c	100mg BID	120mg/m2
-1d	100mg BID	160mg/m2

***If dose level 2 or dose level 3 is not tolerated, then escalation of AT13387 in combination with olaparib 200mg BID will be attempted i.e.

2a	200mg BID	80mg/m2
3a	200mg BID	120mg/m2
4a	200mg BID	160mg/m2

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1. OBJECTIVES

1.1 Primary Objectives

To establish the maximum tolerated dose (MTDs) of olaparib and AT13387 administered in combination in patients with advanced solid tumors.

1.2 Secondary Objectives

To identify the dose-limiting toxicity (DLT) and other toxicities associated with olaparib and AT13387 administered in combination as assessed by CTCAE v5.0.

To determine the recommended phase 2 doses (RP2D) of the combination of olaparib and AT13387.

To determine the plasma pharmacokinetics of olaparib and AT13387.

To document anti-tumor activity of the combination of olaparib and AT13387 as assessed by RECIST 1.1 and progression free survival (PFS). Although the clinical benefit of [this/these] drug(s) 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.

1.3 Exploratory Objectives

2. BACKGROUND

2.1 Study Diseases

2.1.1 Ovarian Cancer

Epithelial ovarian cancer is the most lethal of the gynecologic malignancies, with an estimated 22,000 new cases and 15,000 deaths in the United States per year[28]. Patients initially are diagnosed during exploratory laparotomy, during which time surgical staging is performed and gross disease is debulked. Over 70% of patients present with advanced disease, with spread of disease to the upper abdomen (Stage III) or more widely metastatic disease such as malignant pleural effusions or liver/splenic intraparenchymal lesions (Stage IV). Post-operative adjuvant chemotherapy is indicated for all patients with advanced disease, and options include intraperitoneal chemotherapy with cisplatin and paclitaxel or intravenous chemotherapy with carboplatin and paclitaxel. In over 70% of cases, platinum and taxane-based combination therapy results in a clinical complete remission, typically defined as having no evidence of residual tumor, based on a normal serum CA-125 level, normal exam, and normal radiographic study such as a CT scan.

Unfortunately, despite achieving initial remission, the majority of patients will develop a relapse of their cancer and eventually die of disease due to the persistence of chemoresistant and platinum-resistant cancer cells. Despite aggressive surgical and chemotherapeutic approaches, the chance of achieving long-term disease-free survival for subjects with stage III and stage IV disease is only approximately 25% and <10%, respectively[29]. Other less common Mullerian tumors such as primary peritoneal serous cancers and fallopian tube cancers have similar clinical courses and behavior. Thus, it is these 3 types of gynecologic cancers into one entity for the purpose of treatment and clinical investigation. Relapse in advanced ovarian cancer is generally incurable, and the goal of treatment changes to palliation. The treatment of recurrent ovarian cancer with conventional cytotoxic agents is limited by the development of chemoresistance as well as intolerable side effects.

2.1.2 Triple-Negative Breast Cancer

There is an estimated 180,510 new cases of breast cancer diagnosed in the United States per year, and approximately 41,910 deaths attributed to this cancer[30]. Up to 20% of breast cancers are negative for expression of all three receptors and constitute the subtype TNBC.

Chemotherapy has been the mainstay of treatment for women with TNBC, but the current standard of care is inadequate. Despite treatment with chemotherapy, TNBC is associated with poorer outcomes compared to other breast cancer subtypes. TNBC has an aggressive clinical course, marked by higher rates of visceral and central nervous system metastases and worse survival compared to hormone receptor-positive subtypes[31].

Approximately 70% of breast cancers in individuals carrying a germline BRCA1 mutation are TNBC; BRCA1-associated and sporadic TNBCs share many histopathologic features. These cancers are frequently high grade, have frequent p53 mutations, and are typically basal-like by hierarchical clustering of transcriptional profiles with these cancers sharing a pattern of genomic instability characterized by allelic loss[32-33].

Drugs such as cisplatin have demonstrated activity in TNBC. A recently published neoadjuvant cisplatin study in TNBC using 4 cycles of cisplatin at 75 mg/m2 every 21 days showed efficacy[34]. These similarities have led to speculation that BRCA1-associated and at least a subset of sporadic TNBCs may share defects in a BRCA1-associated pathway as do HGSC (high grade serous cancer), hence the reason for both cancer subtypes to be included in this protocol with observed similarities between TNBC and HGSC both clinically as well as from a genetic standpoint[35].

2.2 CTEP IND Agents

2.2.1 PARP inhibitor olaparib

Olaparib is a potent and well-tolerated oral inhibitor of polyadenosine 5'-diphosphoribose [poly-(ADP-ribose)] polymerization (PARP)-1 and PARP2. Olaparib is an active monotherapy in

tumors with defective components of homologous recombination repair (HRR), which includes those with BRCA1/2 mutations. A first-in-man phase 1 dose escalation trial of single agent olaparib in a patient cohort enriched for patients with BRCA germline mutations indicated substantial PARP inhibition in surrogate tissues and anti-tumor activity in 40% of ovarian cancer patients with germline BRCA mutations, using combined RECIST and GCIG CA-125 criteria [2-4].

Mechanism of Action

Preclinically, olaparib displays antitumor activity against a variety of tumor cell lines and this sensitivity of the cells is believed to depend upon components of a defective HRR capability (Olaparib Investigator's Brochure, 2013). As a major example of this selective activity, both BRCA1- and 2-deficient (-/-) tumors are sensitive to PARP inhibition. Early studies indicated that PARP inhibition in BRCA1/2 homozygous null cells, but not the isogenic BRCA heterozygous cells, led to cell death. BRCA1 and 2 are proteins necessary for proper function of HRR, the high fidelity repair system that addresses DNA double-strand breaks (DSBs). The backup repair system to HRR is base-excision repair (BER), which requires PARP function and primarily addresses single-strand breaks (SSBs). However, the system works both ways in that repair of SSBs in BER can lead to stalled replication forks that strain the system and cause double strand breaks, resulting in a situation that requires intact HRR and BRCA1 or BRCA2. Thus, HRR dysfunction sensitizes cells to PARP inhibition leading to further chromosomal instability, cell cycle arrest and apoptosis [2]. This sensitivity is suggested to result in a large therapeutic window for PARP inhibition in mutation carriers. Pre-clinical studies support these findings showing that other BRCA mutant, but not wild-type, human cell lines are highly sensitive to olaparib[5].

Nonclinical Pharmacology and Efficacy

Olaparib has demonstrated cellular activity in the low nM range with a cellular dose for 50% inhibition (IC50) of 2 nM in HeLa cells (Olaparib Investigator's Brochure, 2013). The effective concentration for inhibiting cellular PARP activity in cancer cells by >90% is approximately 30 nM to 100 nM olaparib in several tumor cell lines including ovarian A2780, breast MCF-7, and colorectal SW620. These concentrations lead to significant ablation of PARP activity (based on the inhibition of PAR formation), with maximal PARP-1 inhibition occurring at around 100 nM. Consistent with this, maximal potentiation of an appropriate DNA SSB-inducing chemotoxic agent (MMS) was also seen in vitro at 100 nM, which equates to 43.4 ng/mL.

An analysis of the correlation of olaparib response with several standard-of-care (SOC) chemotherapies in a panel of breast cancer cell lines has demonstrated a strong correlation with both carboplatin (0.84, p=0.0006) and camptothecin (0.8, p=0.0018) (Olaparib Investigator's Brochure, 2013). This is consistent with what is known about the types of DNA damage they induce (intra-strand and inter-strand cross-links for platinum and trapped topoisomerases-DNA adducts for camptothecins, both of which result in DNA DSB formation in replicating cells) and the DDR pathways that deal with them (primarily HRR in cells undergoing DNA replication). The same does not hold for a mechanistically unrelated chemotherapy, such as paclitaxel (-0.11) whose mechanism of action is unrelated to the induction of DNA damage.

The analysis of olaparib and platinum response was extended to additional tumor indications where platinum treatment is SOC and included ovarian, non-small cell lung cancer (NSCLC) and head and neck squamous cell carcinoma cell lines (Olaparib Investigator's Brochure, 2013). Consistent with the breast cancer cell line data, the strong correlation between platinum response and olaparib response was observed. These in vitro data have been extended further into in vivo patient-derived tumor explant (PTX) models of both breast and NSCLC and again the correlation is seen between platinum sensitivity and olaparib sensitivity.

In vitro combination studies demonstrate that olaparib is able to potentiate the cytotoxicity of DNA-damaging agents, including the monomethylating agent temozolomide (melanoma, glioblastoma, colorectal), topoisomerase-1 inhibitors such as camptothecin, irinotecan, and topotecan (ovarian, pancreatic, colorectal), and platinumbased agents such as cisplatin and carboplatin (breast) (Olaparib Investigator's Brochure, 2013). Studies with BRCA1-deficient orthotopically-transplanted in vivo mouse mammary tumor models showed that, in addition to single agent activity of olaparib, sequential treatment of mice with olaparib following a single dose of platinum agent increased the time to progression on treatment and extended OS. These data support the idea that olaparib can extend the antitumor effect of platinum agents when given as a maintenance treatment.

Following single oral doses, absorption was rapid (maximum plasma concentration [Cmax] <2 hours in mice, rats and dogs) while bioavailability was <60% in male and female mice, <20% in male and female rats and ~79% in male dogs (Olaparib Investigator's Brochure, 2013). Low oral bioavailability in rat may have been due to poor absorption or rapid first pass metabolism. Distribution of olaparib is in the gastrointestinal tract and in tissues associated with the metabolism and elimination of foreign compounds. Further investigations are still ongoing. Excretion is primarily via the feces and, to a lesser extent, the urine. Investigations in human in vitro systems indicated metabolism of olaparib was CYP mediated and that CYP3A4 and 3A5 were the dominant metabolic enzymes (Olaparib Investigator's Brochure, 2013). Similar studies indicated flavin mono-oxygenase-3 was not able to metabolize olaparib. In in-vitro direct inhibition assays, olaparib (100 μM) had only limited effect against CYP3A (up to 46% inhibition) and less effect against other CYPs tested. In time dependent inhibition assays, olaparib had only very minor effects against CYP3A and no effect against other CYPs. Clinically significant direct inhibition of intestinal CYP3A is possible but significant effects against hepatic CYP3A are less likely. The CYP induction potential of olaparib was investigated in cultures of human hepatocytes. At the highest olaparib concentration (30 mcM), minor induction of CYP2B6 activity was observed (<40% positive control) and smaller effects on CYPs 2C9 and 2C19 activities were noted. These changes were unlikely to be of clinical significance. A small decrease in CYP3A activity was noted, which may suggest time dependent inhibition, however, this was not explored further.

In studies using Madin-Darby Canine Kidney (MDCK) II cells transfected with multidrug resistance 1 (MDR1; Pgp), BCRP or MRP-2 drug efflux transporters, olaparib was shown to be a substrate of MDR1 but not BCRP or MRP-2 (Olaparib Investigator's Brochure, 2013). In the

same systems, olaparib was an inhibitor of BCRP and MRP-2 but had little or no inhibitory effect on MDR1.

In isolated human hepatocytes, olaparib was a substrate for organic anion transport proteins. In the same system, olaparib was shown to be an organic cation transporter 1 (OCT1) inhibitor (IC50 11.9 μM) (Olaparib Investigator's Brochure, 2013). In HEK-293 cells transfected with OATP1B1, olaparib functioned as an inhibitor and IC50 values of 20.3 mcM and 27.1 mcM were derived (substrate dependent). Using the criteria defined in the European Medicines Agency (EMA) guidelines on the investigations of drug interactions (EMA 2013), it is possible olaparib may precipitate an interaction via hepatic drug uptake transporters, particularly OCT1.

SimCYP population PK simulations of the separate effect of co-administration of itraconazole and rifampicin (clinically relevant CYP3A inhibitor and inducer, respectively) on olaparib PK in humans, when administered at the recommended human dose, were performed (Olaparib Investigator's Brochure, 2013). The itraconazole (200 mg twice daily [BID] x 7 days) simulation indicated olaparib (400 mg bd x 7 days) steady state Cmax and area under the concentration-time curve (AUC) would increase by 2.8 and 3.5 fold, respectively. The rifampicin simulation (600 mg x 6 days) indicated olaparib (400 mg BID x 6 days) steady state Cmax and AUC in the presence of rifampicin would be reduced to 33% and 29%, respectively, of the values in the absence of rifampicin.

Nonclinical Toxicology
Olaparib has been tested in dogs and rats (Olaparib Investigator's Brochure, 2013). There were no noted effects on the cardiovascular or respiratory parameters of an anesthesized dog or any behavioral, autonomic, or motor effects in the rat. Toxicology studies indicate that the target organ of toxicity is the bone marrow. *Ex vivo* work has confirmed that olaparib is also active against human marrow. The cytotoxic effect becomes evident at a higher concentration than required to fully ablate PARP activity. 28-day dog and rat studies demonstrate a reversible myelotoxic effect that is mild to moderate. Platelets are first affected, followed by white blood cells. In 26-week repeatdose studies in rats, doses were well-tolerated in male rats, with hematological effects and increased spleen weights observed at all dosages. In female rats, doses of 15 mg/kg/day resulted in significant reduction in body weight. Hematological effects and increased spleen weights were again observed at all dosages. The difference between sexes was considered to be due to the fact that females had greater plasma exposure levels than males. In 26-week repeat-dose studies in dogs, olaparib was well-tolerated. Hematological changes were observed, characterized by pancytopenia.

Clinical Pharmacology
Olaparib is rapidly absorbed following capsule oral dosing in cancer patients (Olaparib Investigator's Brochure, 2013). Mean volume of distribution was 40.3 L, mean plasma clearance was 4.55 L/h, and the estimated terminal half-life (t1/2) was between 5 and 12 hours. Exposure increased proportionally with dose at doses up to 100 mg but increased in a less than proportional fashion at higher doses. On multiple dosing, there was no evidence of time dependency of the PK and no marked accumulation. There was no

evidence of ethnic difference in olaparib PK between Japanese and Caucasian patients. Recovery of administered radiolabelled olaparib dose was >94% in four patients and approximately 60% in a further two with the lower recoveries apparently due to slower fecal excretion of dosed material by these two patients. Drug-related material was eliminated in the urine (35-50%) and in the feces (12-60%) with 6-20% of the dosed material recovered in the urine as unchanged drug. Plasma concentrations of olaparib were similar to those of total radioactivity up to 6 or 8 hours after dosing but the profiles diverged thereafter indicating the presence of circulating metabolites. Metabolite identification in plasma and the excreta is ongoing.
Studies of the relative single-dose bioavailability of capsule vs. tablet formulations showed that at the two lower tablet doses, the Cmax with the tablet formulation tended to be slightly higher and the AUC was similar (Olaparib Investigator's Brochure, 2013). However, at the highest tablet dose (250 mg), the exposure delivered by the tablet formulation (both Cmax and AUC) was higher than that delivered by the 400 mg capsule. The tablet and the capsule formulations cannot therefore be considered to be bioequivalent. Further details regarding PK comparisons between the capsule and tablet formulations may be found in the 2013 Olaparib Investigator's Brochure.

Clinical Efficacy
The first clinical study in man of olaparib (KU-36-92) was a dose-escalation study in patients with advanced solid tumors (Olaparib Investigator's Brochure, 2013). Preliminary data demonstrated that olaparib is generally well-tolerated at doses up to and including the MTD of 400 mg BID in patients with various solid tumors. As of October 2, 2013, approximately 2103 patients with ovarian, breast, pancreatic, melanoma, and other advanced solid tumors have received olaparib, either as monotherapy or in combination with other chemotherapy agents. AEs considered to be associated with olaparib included anemia (mild to moderate), neutropenia (mild to moderate), and thrombocytopenia (generally mild to moderate, sometimes severe), nausea and vomiting (mild to moderate), and fatigue (mild to moderate).
Olaparib has also been studied in an expansion phase in BRCA-deficient ovarian cancer at a dose of 200 mg BID. Fifty patients were treated, including 48 with BRCA-deficient germline mutations and two patients of unknown status or significance. Twenty (40%) patients achieved complete response (CR) or partial response (PR) by RECIST and/or GCIG-CA125 criteria. An additional three patients experienced stable disease (SD) for more than four cycles [4]. A multicenter phase 2 study enrolled two sequential cohorts of women with known germline BRCA2 or BRCA2 mutations and recurrent advanced ovarian cancer to receive olaparib continuously at a dose of 400 mg BID (Cohort 1) or 100 mg BID (Cohort 2) [6]. Responses were observed in 33% (11 of 33) patients enrolled in the 400mg BID cohort and 13% (3 of 24) patients enrolled in the 100 mg BID cohort. A phase 2 study of olaparib in advanced serous ovarian cancer and triple-negative breast cancer included a cohort of 46 ovarian cancer patients who were known not to carry a germline BRCA mutation, in which an overall response rate (ORR) of 23.9% was observed [7].
Additional studies of olaparib as monotherapy or in combination with a platinum reagent for treatment of metastatic BRCA-deficient ovarian cancer are ongoing. Results from a phase 2 trial investigating olaparib as maintenance therapy following platinum-based therapy for platinum-sensitive serous ovarian cancer demonstrated a significant

progression-free survival (PFS) benefit (8.4 vs. 4.8 months, P<0.001), with subgroup analyses demonstrating evidence of benefit regardless of BRCA status [8, 9]. Additional phase 1 and 2 trials in both BRCA-deficient and BRCA-competent ovarian cancer are currently ongoing. Olaparib was granted accelerated approved by the FDA in the United States as monotherapy in women with advanced ovarian cancer associated with germline BRCA mutation in the companion diagnostic test BRACAnalysis CDx and who have received at least 3 prior lines of therapy for ovarian cancer on December 19, 2014.

2.2.2 HSP90 inhibitor AT13387

Mechanism of Action: AT13387 (onalespib) is a synthetic non-ansamycin small molecule that acts as an inhibitor of heat shock protein 90 (HSP90). HSP90, which regulates the folding, stability and degradation of many oncogenic signaling proteins, is upregulated in a variety of tumor cells. HSP90 inhibitors are thought to affect multiple aberrant signaling pathways and may therefore be of clinical benefit in the treatment of a wide range of cancers.

Pharmacodynamic Properties: AT13387 (onalespib) exhibited high affinity for the ATP binding site at the N-terminal domain of HSP90, and was a potent inhibitor of the growth and survival of a variety of tumor cell lines. AT13387 (onalespib) caused degradation of multiple HSP90 client proteins, key regulators of cell proliferation and survival. In cancer xenograft models in nude or severe combined immunodeficiency (SCID) mice (tyrosine kinase inhibitor [TKI]-sensitive or -resistant non-small-cell lung cancer [NSCLC] driven by mutated epidermal growth factor receptor [EGFR] or translocated anaplastic lymphoma kinase [ALK]; vemurafenib-sensitive and -resistant B isoform of RAF kinase [BRAF] mutant melanoma), AT13387 (onalespib) inhibited tumor growth and was best tolerated weekly or twice weekly. In upfront combination with kinase inhibitors, AT13387 (onalespib) was able to delay the emergence of resistance in melanoma and NSCLC xenograft models. AT13387 (onalespib) caused prolonged knockdown of HSP90 client proteins in cells and tumors with a half-life of 38-75 hours in tumor xenografts in mice, suggesting a potential for prolonged effect after a single dose.

Pharmacokinetics (PK): After intravenous (IV) administration to mice, rats, and dogs and intraperitoneal (IP) administration to mice, AT13387 (onalespib) displayed a short plasma half-life in mice and rats (1-3 hours) and a moderate half-life in dogs (11 hours) despite high plasma clearance. Volume of distribution was greater than total body water indicating distribution of AT13387 (onalespib) into tissues. PK studies demonstrated that AT13387 (onalespib) is highly distributed into xenograft tumors and is cleared slowly from tumors. The in vitro intrinsic clearance of AT13387 (onalespib) determined in isolated intact hepatocytes was high across all the species tested (mouse, rat, dog and human; scaled values ranged from 35 mL/min/kg in human to 184 mL/min/kg in rat). Binding of AT13387 (onalespib) to plasma proteins was moderate and comparable across all species tested, ranging from 77.2% in dog plasma to 90.1% in mouse plasma. Blood:plasma distribution in mouse, rat, dog and human whole blood ranged from 0.8, indicating approximately equal distribution between the plasma and cellular fraction, to 5.0, showing that AT13387 (onalespib) favored partitioning into the red blood cells, depending on concentration and species. The potential for AT13387 (onalespib) to inhibit cytochromes P450 (CYP) 1A2, 3A4, 2D6, 2C9, and 2C19 was assessed, and results indicated a concentration

giving half-maximal inhibition (IC50) >10μM, suggesting a low potential for clinically significant drug-drug interactions mediated by these enzymes. AT13387 (onalespib) is a substrate for P-gp, a modest inhibitor of BCRP and P-gp, and strong inhibitor of MATE1 and MATE2-K. Glucuronidation, sulphation and N-oxidation appear to be routes of metabolism for AT13387 (onalespib) based on in vitro studies of cryopreserved hepatocytes as well as metabolites detected in samples in vivo. In a radiolabeled mass balance study in dogs, a mean maximum measured concentration (Cmax) of 793 ng-Eq/g occurred at the end of infusion. Area under the curve concentration-time curve from time 0 to the last data point (AUC0-t) values were 5924 hr•ng-Eq/g and 7590 hr•ng-Eq/g for male and female dogs, respectively, with half life (t1/2) values of 21.3 and 20.5 hour, respectively. The majority (~83% in the male and ~72% in the female) of [14C] AT13387 (onalespib)-derived radioactivity was excreted via feces, with less found in urine (~15% in the male and ~22% in the female).

Non clinical safety: No adverse central nervous system (CNS) effects were observed in the rat with AT13387 (onalespib) doses up to 200 mg/kg in males and 125 mg/kg in females, compared with control vehicle-treated animals. In a cardiovascular and respiratory (CV/R) safety study in Beagle dogs, a dose-related increase in heart rate was observed at 4 mg/kg and above, from 10 minutes after the start of infusion, which peaked at the end of infusion and returned to control levels by approximately 5 hours after the end of infusion. The increased heart rate observed at 15 mg/kg was associated with a concomitant decrease in blood pressure (systolic, diastolic and mean arterial). AT13387 (onalespib) had no significant effect on QT interval or QTc at any dose level tested.
The toxicity profile of AT13387 (onalespib) was evaluated in rats and dogs. Infusion-site reactions were observed in both species, including local irritation/inflammation. While clinical pathology changes suggestive of adverse effects in the bone marrow, kidney, and liver were observed for both species, histopathologic changes were only seen in dogs and included testes, gallbladder, bone marrow (sternum), kidneys, and thymus. The overall effects observed in surviving rats and dogs were transient and reversible, with the exception of the testicular lesions observed in dogs at high doses, for which the recovery period of 14 days was not sufficient.
In the definitive 1-cycle rat study, no unambiguous target organs of toxicity were identified and the no-observed-adverse-effect level (NOAEL) was estimated to be 50 mg/kg/dose given twice per week for 3 weeks (2QW×3). A dose severely toxic to 10% of rodents (STD10) could not be confidently determined in rats, although safety was established in this species. Dosing for 3 cycles in rats using the 2QW×3 regimen (for 3 of 4 weeks per cycle) resulted in systemic inflammation secondary to local irritation at the infusion site, which led to mortalities beyond the first cycle and early termination of higher dose groups. A less aggressive, once-weekly (current clinical regimen for study AT13387-05) infusion study in rats is ongoing. In dogs dosed via a peripheral vein for 1 cycle, a clear dose-effect relationship was established for AT13387 (onalespib). Histopathology in dogs revealed changes in the bone marrow, thymus, testes, gallbladder and kidney at 3, 10/7, and 12.5/10/7 mg/kg. The nominal highest non-severely toxic dose (HNSTD) was 3 mg/kg/dose given 2QW×3 over 1 or 3 cycles, and the NOAEL was 1 mg/kg/dose on the same schedule for 1 cycle and 0.5 mg/kg over 3 cycles.

Clinical Studies:

AT13387 (onalespib) is administered by IV infusion over 1 hour.

Maximum tolerated dose (MTD) and/or recommended Phase 2 dose (RP2D) for 28-day cycles:

- 2QW×3 (Days 1, 4, 8, 11, 15, 18) regimen: 120 mg/m2/dose (monotherapy)
- 2QW×3 (Days 1, 2, 8, 9, 15, 16) regimen: 160 mg/m2/dose (monotherapy) or 120 mg/m2/dose (combination with abiraterone acetate + steroid)

1QW×3 (Days 1, 8, 15) regimen: 260 mg/m2/dose (monotherapy) or 220 mg/m2/dose (combination with imatinib, crizotinib, or abiraterone acetate+ steroid)

Number of subjects treated with AT13387 (onalespib) for the purpose of safety reporting in various clinical trials include 275 subjects:

i) Six subjects died within 30 days of receiving treatment with AT13387 (onalespib) in Astex trials from causes not attributed to progression of disease. The causes of all deaths were considered to be not related to treatment.

ii) For Astex-sponsored studies, the most common serious adverse events (SAEs) by System Organ Class (SOC; subjects counted once per SOC), regardless of relationship, through the cut-off date of 30 December 2014, were categorized under Respiratory, Thoracic, and Mediastinal Disorders (23/237; 10%); Gastrointestinal Disorders (17/237; 7%); and General Disorders and Administration Site Conditions (12/237; 5%). Individual event terms reported for >3 subjects were 8/237 (3.4%) for dyspnea (6 resolved, 1 decreased in severity, and 1 not resolved); 6/237 (2.5%) for diarrhea (5 resolved and 1 not resolved); 5/237 (2.1%) each for dehydration (4 resolved and 1 resolved with sequelae) and pulmonary embolism (4 resolved and 1 not resolved); and 4/237 (1.7%) each for back pain (all resolved), muscular weakness (1 resolved, 1 decreased in severity, and 2 not resolved), and pneumonia (2 resolved and 2 fatal). For Studies AT13387-01, -02, -04, and -05, the most common individual events (occurring in ≥25.0% of subjects) were diarrhea (70.5%), fatigue (51.5%), nausea (48.9%), decreased appetite (35.4%), and vomiting (32.9%). Most AEs were reported as Grade 1 or 2. The most common related AEs (occurring in ≥25.0% of subjects) across all studies were diarrhea (65.0%), nausea (41.8%), and fatigue (40.9%). Most related AEs were reported as Grade 1 or 2. Related Grade 3 or 4 AEs reported for ≥2.0% subjects were diarrhea (10.5%), fatigue (3.8%), and anemia (3.4%).

The PK of AT13387 (onalespib) showed dose-dependent increase in AUC0-t and Cmax from 10 to 310 mg/m2/dose with relatively low inter-individual variability. Elimination half-life (t1/2 el) was dose-independent with mean cohort values ranging from 6.6 to 11.5 hours. Maximum t1/2 observed was 14 hours. There was no notable accumulation or reduction in exposures between Day 1 and Day 18 (twice weekly) or Day 1 and Day 15 (once weekly) of Cycle 1. The AT13387 (onalespib) PK profile and exposures were similar across several studies, whether as a single agent (AT13387-01) or in combination with imatinib (AT13387-02), abiraterone acetate (AT13387-04), or crizotinib (AT13387-05), at comparable dose levels, indicating no potential for interactions affecting AT13387 (onalespib) PK by these agents. Plasma increases in HSP70 were detected at all dose levels in Study AT13387-01. HSP70 induction is a pharmacodynamic marker of target engagement, but has not been demonstrated to be predictive of clinical response.

Dedicated drug-drug interaction studies have not been conducted. However, olanespib PK does not appear to be affected when coadministered with imatinib (AT13387-02), abiraterone acetate (AT13387-04), or crizotinib (AT13387-05). Olanespib did not affect the PK of crizotinib.

In terms of efficacy, in Study AT13387-01 (monotherapy), the best response to treatment was 1 partial response (PR) in a subject with GIST and stable disease persisting for ≥6 months in 4 subjects (2 with GIST, 1 with adenoid cystic carcinoma of the right parotid, 1 with metastatic uveal melanoma). In Study AT13387-02 (coadministration with imatinib) in GIST subjects, disease control at 4 months occurred in 5 (19.2%) subjects. In ongoing Study AT13387-05 (coadministration with crizotinib) in NSCLC subjects, 4 PRs have been reported during the dose-escalation part of the study (Part A).

Overall, risks and common AEs in clinical studies include:

- Gastrointestinal toxicities (diarrhea, nausea, abdominal pain, vomiting, dry mouth, constipation), which are mostly Grade 1 to 2 and manageable with medications.
- Local infusion-related irritation occurring during the infusion or systemic infusion reactions occurring during the infusion or shortly afterwards. Systemic reactions are reversible and often characterized by flushing, itching, rigors, chills, nausea, tachycardia/ bradycardia, alterations in blood pressure, and dizziness. Incidence increases at higher doses.
- Visual impairment including peripheral flashes (photopsia), blurred or double vision, floaters, color distortion and dimness, difficulties with light/dark accommodation, tunnel vision or other field defects, halos, apparent movement of stationary objects, and complex disturbances. Symptoms are generally Grade 1, intermittent, reversible, and transient, lasting a few seconds to a few minutes and occurring on 1-3 days/cycle.
- Other common toxicities include fatigue, decreased appetite, dizziness, anemia, headache, muscle spasms, insomnia, chills, dehydration, and hyperhidrosis.
- Renal AEs were reported in combination with imatinib.
- Electrocardographic (ECG) analysis of AT13387 (onalespib) as monotherapy could not exclude a small effect on cardiac repolarization (QTcF duration), <10 ms, which is not likely to be clinically relevant. Dose-related changes in heart rate and in QTc were reported in combination with imatinib.

2.3 Rationale

PARP-inhibitors as anticancer agents*:* PARP-inhibitors (PARPis) have demonstrated single agent activity in homologous recombination (HR)-deficient tumors [2-4, 6, 10, 11]. Of these drugs, olaparib has been the most widely studied thus far, associated with an objective response rate (ORR) of 28%-33% and a median duration of response of 28-41 weeks in BRCA1 or 2-mutated, recurrent epithelial ovarian cancer. PARPis have also demonstrated activity in BRCA1-mutated triple negative breast cancers [7, 12]. In addition, an association between response to olaparib and platinum sensitivity has been observed, and in BRCA1/2-mutated epithelial ovarian cancer the olaparib clinical benefit response decreases from 69.2% in platinum-sensitive disease, to 45.8% in platinum-resistant disease, to 23.1% in platinum-refractory disease [4]. Olaparib has also demonstrated objective response rate (ORR) in 24% of non-BRCA1/2-mutated ovarian cancer;

(50% among platinum sensitive but only 4% among platinum resistant non-BRCA1/2 ovarian cancers)[7]. This activity is thought to be related to the presence of defective homologous recombination (HR) in these tumors which may occur in the absence of germline BRCA1/2 mutations. For example in ovarian cancer, defective HR may result from genetic and epigenetic alterations involving members of the HR DNA-repair pathway, i.e. somatic BRCA1/2 mutations, hypermethylation of BRCA1 or RAD51C, amplification or mutation of EMSY, focal deletion or mutation of PTEN, mutation of ATM or ATR, and mutation of Fanconi anemia genes [13]. Tumors that exhibit defective HR via mechanisms that are unrelated to germline BRCA1 or BRCA2 mutations are commonly referred to as having a 'BRCAness' phenotype [14, 15]. Although several potential biomarkers of BRCAness and defective HR have been developed [16-19], there is currently no clinically available biomarker of HR-deficient cancers that accurately predicts defective HR and responsiveness to platinum and PARP inhibitors, and this is an area of high priority for ovarian and breast cancer research.

PARPis in HR proficient tumors: The promise of PARP inhibitors in the management of ovarian and breast cancers is tempered by the fact that HR-proficient cancers do not respond well to these agents, suggesting that approximately 50% of ovarian cancer patients (i.e. those without HR alterations) do not benefit from this novel class of drugs. Combination of PARPis with agents that inhibit HR may represent an effective strategy to sensitize HR proficient tumors to PARPis and thus potentially expand use of these agents beyond patients with HR deficient EOCs. Strategies designed to selectively disrupt HR in cancer cells and sensitize them to PARP inhibition, thereby extending the use of this class of agents to HR-proficient cancers, include PI3K-pathway inhibition [20, 21] and CDK inhibition [22], both of which have been translated to clinical trials.

Rationale for combination of HSP90 and PARPis: Multiple components of the HR pathway are HSP90 clients, including BRCA1, BRCA2 and RAD51, suggesting that HSP90 inhibition may similarly sensitize cancer cells to PARP inhibition. We have previously shown that exposure of HR-proficient breast cancer cell lines to HSP90 inhibitor (HSP90i) 17-AAG(17-allylamino-17-demethoxygeldanamycin) downregulated HR, ATM and Fanconi Anemia pathways [23]. In HR-proficient epithelial ovarian cancer (EOC) cells, 17-AAG suppressed HR as assessed using the RAD51 foci formation assay and this was further confirmed using the Direct Repeat-GFP reporter assay. Furthermore, 17-AAG downregulated BRCA1 and/or RAD51 protein levels, and induced significantly more γH2AX activation in combination with olaparib compared to olaparib alone[23]. Of note, sublethal concentrations of 17-AAG sensitized HR-proficient EOC lines to olaparib and carboplatin thereby provide the preclinical rationale for using a combination of PARP inhibitors/HSP90 inhibitors in HR-proficient EOC. Similar experiments have also been conducted in non small cell lung cancer (NSCLC) cells, showing that HSP90 inhibition depletes BRCA2, BRCA1 and RAD51 from HR-proficient NCI-H1299 cells and sensitizes them to PARP inhibition thus providing the proof of principle that HSP90 inhibitor mediated sensitization to PARP inhibition can occur in additional solid tumor models.

In addition, we have recently published on a novel mechanism of PARP inhibitor resistance [24]. MDA-MB-436 triple-negative breast cancer cells harboring a BRCA1 BRCT domain mutation were rendered rucaparib-resistant via exposure to graded concentrations over time. Resistance was associated with HSP90-mediated stabilization of the mutant protein, without evidence for

BRCA1 reversion mutation. Because the BRCT domain mutant protein cannot engage CtIP, there was a concomitant 53BP1 mutation in resistant clones, which lowered 53BP1 levels and permitted BRCA1-independent end resection. However, the mutant protein remains capable of binding to PALB2 and BRCA2 and is critical for efficient RAD51 loading, mediating restoration of HR and ultimate resistance. Importantly, resistance was reversed with the application of an HSP90 inhibitor, so that PARP inhibitor sensitivity was restored[24].

We have also performed additional in vitro and in vivo experiments to demonstrate the cytotoxicity of the combination of an HSP90 inhibitor with a PARP-inhibitor.
a. In vitro: We have now assessed the combination of the PARP-inhibitor talazoparib (BMN673) and the HSP90-inhibitor AT13387 in 4 HR proficient ovarian cancer cell lines (OVCAR4, OVCAR5, SKOV3 and CAOV3) using colony formation assays. In all cases, addition of sublethal concentrations of AT13387 enhanced the cytotoxicity of talazoparib (BMN673).
b. In vivo: We have performed tolerability and efficacy studies of PARP-inhibitor olaparib and the HSP90-inhibitor AT13387 in ovarian PDX models.
We initially performed tolerability studies and as shown in Figure 1, doses of olaparib up to 100mg/kg po daily x 3 weeks and AT13387 up to 45mg/kg po for 2 days (D1,D2) on / 5 days off x 3 weeks (i.e. Days 1, 2, 8, 9, 15, 16) were well tolerated without weight loss in the mice.

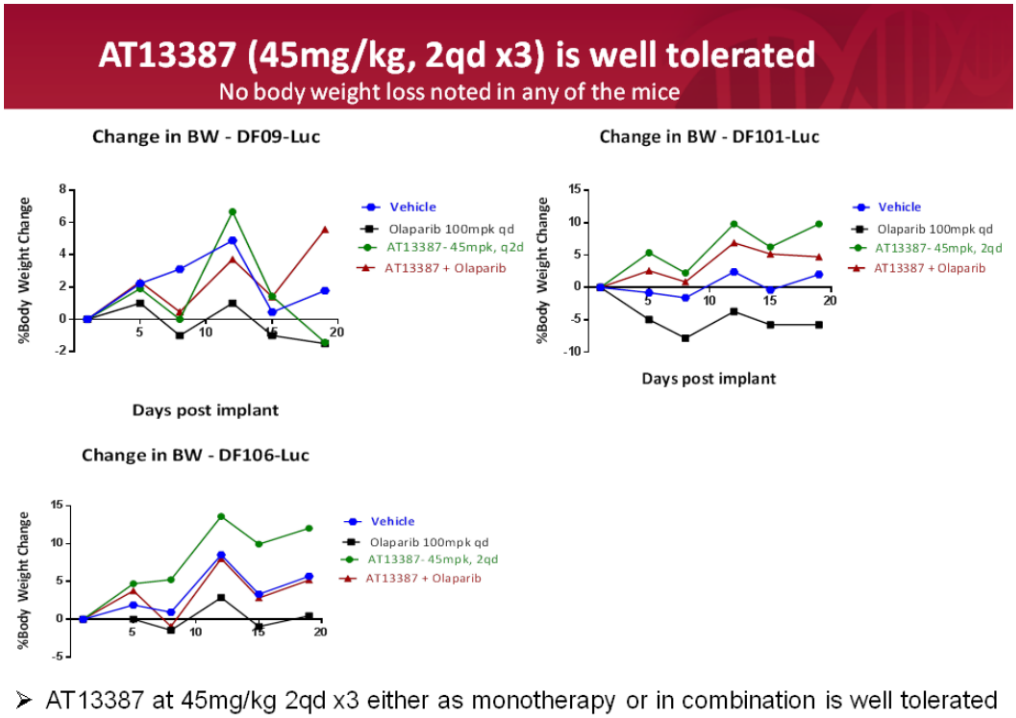

Figure 1. Tolerability of olaparib and AT13387 combination in ovarian PDX models.

Efficacy studies were subsequently performed. Olaparib was dosed at 100mg/kg po daily x 4 weeks, AT13387 was administered at 45mg/kg po for 2 days (D1,D2) on / 5 days off x 4 weeks (i.e. Days 1, 2, 8, 9, 15, 16, 22, 23). As shown in Figure 2, the combination of AT13387 and olaparib induced inhibition of tumor growth in several ovarian PDX models as opposed to

vehicle control, olaparib alone and AT13387 alone.

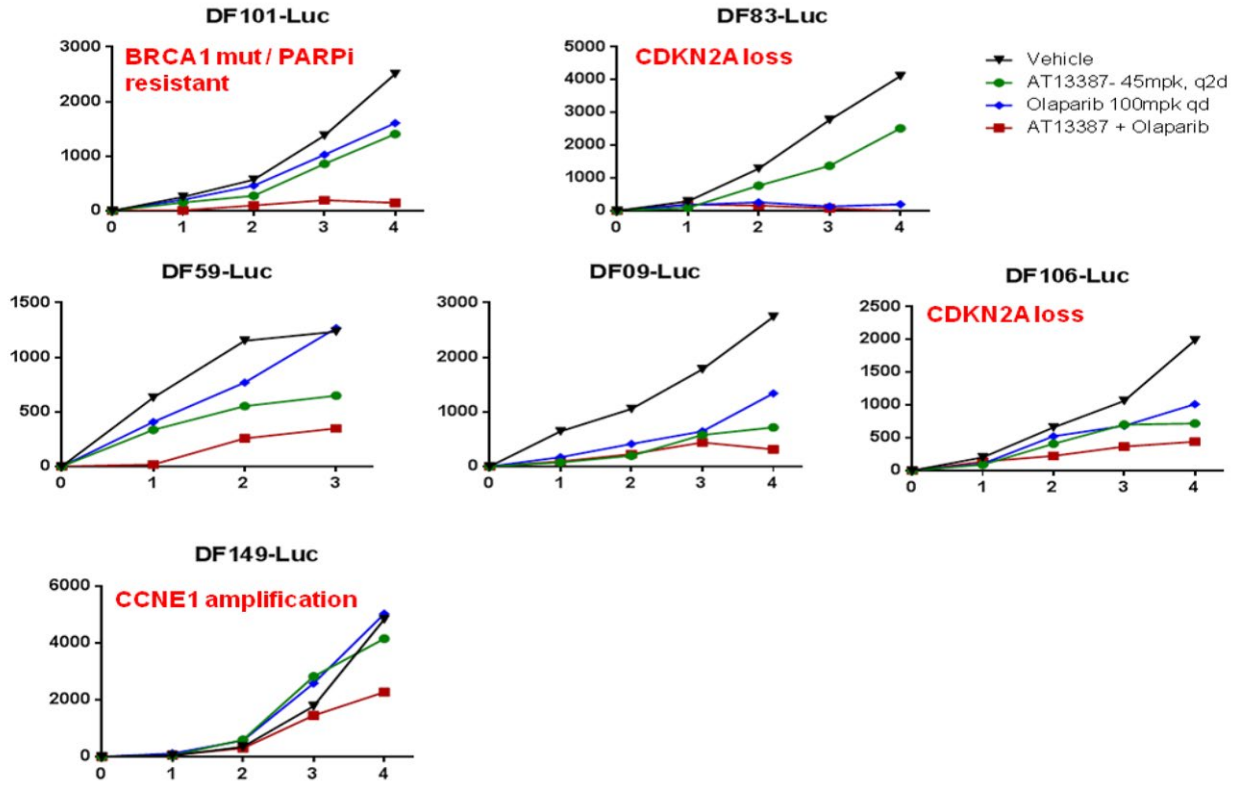

Figure 2. AT13387+olaparib vs olaparib alone vs AT13387 alone vs vehicle in ovarian PDX models.

Of note, all models except for DF83 were derived from patients with platinum resistant tumors. Strikingly, the DF101 model was derived from a patient with BRCA1-mutation and platinum and PARPi resistant disease, which has been resistant to combinations of olaparib and the PI3K inhibitors BKM120 or BYL719. Finally, we noted that 2 of the models harbored CDKN2A loss and 1 CCNE1 amplification. Amplification of CCNE1 is one of the most common focal copy number change events in serous ovarian cancer, occurring at a frequency of 20%; these tumors are enriched for platinum resistance and are associated with inferior outcome. Furthermore, in the TCGA dataset, expression of CDKN2A, which is a negative regulator of cyclins and cyclin-dependent kinases, is very low or not expressed in approximately 1/3 of ovarian cancer cases.

Based on these tolerability and efficacy studies with olaparib and AT13387 in ovarian PDX models, we will proceed with twice weekly dosing of AT13387 (on Days 1 and 2 every week, i.e. 2 days on/5 days off).

2.4 Correlative Studies Background

Clinical Pharmacology:

The pharmacokinetic study has been designed to assess the effect of olanespib on the steady state pharmacokinetics of olaparib and if the pharmacokinetics of olanespib is affected by the concurrent administration of olaparib. Pharmacokinetic sampling will be performed in all patients enrolled in the dose escalation and expansion cohorts to provide data that may be informative for dose escalation decisions and correlation analysis with clinical and pharmacodynamic data. Pharmacokinetic sampling will be performed to define the plasma concentration-time profile of olaparib over the dosing interval for the day 7 dose when given alone in cycle 0. Pharmacokinetic samples will also be collected over a 24 h interval on days 1 and 15 of cycle 1 to define the plasma profiles for olaparib and olanespib.

The sampling schedule has been devised to accommodate treatment on an outpatient basis. Patients will be instructed to take the two daily doses of olaparib at the same time every day during the pharmacokinetic study. The morning dose of olaparib should be taken at a time that will allow the patient to arrive at the clinical to obtain pharmacokinetic samples before dosing and to remain for an additional 8 hours. The second daily dose of olaparib should be taken approximately 12 hours after the morning dose. It is very important that the patient is aware that the morning dose of olaparib must not be taken before arriving at the clinic on cycle 0 day 7, cycle 1 day 1, and cycle 1 day 15. The olanespib i.v. infusion should be started at the same time that the patient takes the olaparib dose on days 1 and 15 of cycle 1. The first set of blood samples (3 mL) on cycle 0 day 7 will be obtained at the indicated times according to the PK Sample Collection Time Points table below. The second and third sets of blood samples (6 mL) on cycle 1 day 1 and cycle 1 day 15 will be obtained at the same time points as indicated by the PK Sample Collection Time Points table below, with one additional sample collected 30 min after completing the 1 h IV infusion of olanespib. Procedures for PK sample collection, processing, storage, and shipment is provided in Appendix G.

PK Sampling Schedule		
Visit	**Collection Time**	**Sample No.**
Cycle 0 Day 1	Pre-dose (0-5 min prior to first olaparib dose)	PK-00
Cycle 0 Day 7	Pre-dose (0-5 min prior to morning olaparib dose)	PK-01
Cycle 0 Day 7	0.5 h ± 5 min post-dose	PK-02
Cycle 0 Day 7	1.0 h ± 5 min post-dose	PK-03
Cycle 0 Day 7	1.5 h ± 5 min post-dose	PK-04
Cycle 0 Day 7	2.0 h ± 5 min post-dose	PK-05
Cycle 0 Day 7	3.0 h ± 5 min post-dose	PK-06
Cycle 0 Day 7	4.0 h ± 10 min post-dose	PK-07
Cycle 0 Day 7	6.0 h ± 10 min post-dose	PK-08
Cycle 0 Day 7	8.0 h ± 10 min post-dose	PK-09
Cycle 1 Day 1	Pre-dose (0-5 min prior to study medication dosing)	PK-10
Cycle 1 Day 1	0.5 h ± 5 min post-dose	PK-11
Cycle 1 Day 1	1.0 h ± 5 min post-dose	PK-12
Cycle 1 Day 1	1.5 h ± 5 min post-dose	PK-13
Cycle 1 Day 1	2.0 h ± 5 min post-dose	PK-14

Cycle 1 Day 1	3.0 h ± 5 min post-dose	PK-15
Cycle 1 Day 1	4.0 h ± 10 min post-dose	PK-16
Cycle 1 Day 1	6.0 h ± 10 min post-dose	PK-17
Cycle 1 Day 1	8.0 h ± 10 min post-dose	PK-18
Cycle 1 Day 2	Pre-dose (0-5 min prior to study medication dosing)	PK-19
Cycle 1 Day 15	Pre-dose (0-5 min prior to study medication dosing)	PK-20
Cycle 1 Day 15	0.5 h ± 5 min post-dose	PK-21
Cycle 1 Day 15	1.0 h ± 5 min post-dose	PK-22
Cycle 1 Day 15	1.5 h ± 5 min post-dose	PK-23
Cycle 1 Day 15	2.0 h ± 5 min post-dose	PK-24
Cycle 1 Day 15	3.0 h ± 5 min post-dose	PK-25
Cycle 1 Day 15	4.0 h ± 10 min post-dose	PK-26
Cycle 1 Day 15	6.0 h ± 10 min post-dose	PK-27
Cycle 1 Day 15	8.0 h ± 10 min post-dose	PK-28
Cycle 1 Day 16	Pre-dose (0-5 min prior to study medication dosing)	PK-29

Analytical methods for the determination of olaparib and olanespib by high performance liquid chromatography with tandem mass spectrometric detection have been developed and validated as recommended by the FDA Guidance for Industry: Bioanalytical Method Validation, May 2001 (http://www.fda.gov/downloads/Drugs/Guidances/ucm070107.pdf). Individual patient plasma concentration-time curves will be analyzed by noncompartmental methods using routines supplied in the WinNonlin Professional software package (Pharsight Corp., Cary, NC). Pharmacokinetic parameters and variables will be calculated according to standard equations. Mean values of pharmacokinetic parameters will be statistically compared using the two-tailed t-test of the log-transformed data.

3. PATIENT SELECTION

3.1 Eligibility Criteria

3.1.1 For the dose escalation cohort:
i) Patients must have histologically or cytologically confirmed malignancy that is metastatic or unresectable and for which standard curative or palliative measures do not exist or are no longer effective.
ii) Patients may have received any number of prior therapies.

3.1.2 For the dose expansion cohort:
i) Participants must have histologically or cytologically confirmed diagnosis of either:
a) ovarian, fallopian tube, or primary peritoneal cancer of high grade serous histology which has recurred despite standard therapy. Up to 3 prior lines in the platinum resistant setting (i.e. up to 3 lines after patients have become platinum resistant); patients may have received unlimited lines while platinum sensitive.
b) triple-negative breast cancer (TNBC) which has recurred despite standard therapy. Recurrent TNBC needs to have metastatic disease and patients with an in breast recurrence are not eligible. Up to 4 prior lines in the recurrent setting for patients with triple-negative breast cancer are allowed.
ii) Patients with ovarian, fallopian tube or primary peritoneal cancer must have platinum resistant disease defined as progression within 6 months after last platinum regimen. Platinum refractory disease is allowed.
iii) Patients with triple-negative breast cancer may not be BRCA1/2 germline mutation carriers

3.1.3 Age ≥18 years. Because no dosing or adverse event data are currently available on the use of olaparib in combination with AT13387 in patients <18 years of age, children are excluded from this study, but will be eligible for future pediatric trials.

3.1.4 There must be availability of a formalin-fixed, paraffin-embedded tumor specimen.

3.1.5 ECOG performance status 0 or 1 (Karnofsky >60%, see Appendix A).

3.1.6 Life expectancy of greater than 12 weeks.

3.1.7 Patients must have normal organ and marrow function as defined below:

– leukocytes	≥3,000/mcL
– hemoglobin	≥10 g/dL with no blood transfusion in the past 28 days
– absolute neutrophil count	≥1,500/mcL
– platelets	≥100,000/mcL
– total bilirubin	within normal institutional limits
– AST(SGOT)/ALT(SGPT)	≤ 3 × institutional upper limit of normal
– creatinine	≤ the institutional upper limit of normal OR
– creatinine clearance	≥60 mL/min/1.73 m2 for patients with creatinine levels above institutional normal.

– QTcF ≤450 ms
– Any clinically significant electrolyte imbalance, particularly hypokalemia and hypomagnesemia, should be corrected before treatment.
– Pre-Study evaluation must include an ophthalmologic exam by an opthalmologist (not optometrist) and should minimally include visual acuity testing, slit lamp examination, and fundoscopic examination. Follow up eye-exams will only be performed if subjects develop/report any visual impairment. Visual impairment may include peripheral flashes (photopsia), blurred or double vision, floaters, color distortion and dimness, difficulties with light/dark accommodation, tunnel vision or

other field defects, halos, apparent movement of stationary objects, and complex disturbances. Follow up eye-exams will minimally include visual acuity testing, slit lamp examination, and fundoscopic examination; additional testing will be based on symptoms, what is observed and ophthalmologist recommendations.

3.1.8 For the expansion cohort only: measurable disease by RECIST v1.1 with at least one measurable target lesion.

3.1.9 The effects of olaparib in combination with AT13387on the developing human fetus are unknown. For this reason and because olaparib and AT13387 are anti-neoplastic small molecule inhibitors, which are agents that are potentially teratogenic, women of child-bearing potential and men must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) prior to study entry, for the duration of study participation, and for 3 months after the last dose of study drugs. Should a woman become pregnant or suspect she is pregnant while she or her partner is participating in this study, she should inform her treating physician immediately. Men treated or enrolled on this protocol must also agree to use adequate contraception prior to the study, for the duration of study participation, and 4 months after completion of olaparib and/or AT13387 administration.

3.1.10 Patients must be able to swallow tablets and have no significant impairment in gastrointestinal absorption.

3.1.11 Ability to understand and the willingness to sign a written informed consent document.

3.2 Exclusion Criteria

3.2.1 Patients who have had chemotherapy or radiotherapy within 4 weeks (6 weeks for nitrosoureas or mitomycin C) prior to entering the study or those who have not recovered from adverse events due to agents administered more than 4 weeks earlier.

3.2.2 All acute, clinically significant treatment-related toxicity from prior therapy, except for alopecia, must have resolved to Grade ≤1.

3.2.3 Patients who are receiving any other investigational agents.

3.2.4 Patients with known active or history of brain metastases should be excluded from this clinical trial because of their poor prognosis and because they often develop progressive neurologic dysfunction that would confound the evaluation of neurologic and other adverse events.

3.2.5 History of allergic reactions attributed to compounds of similar chemical or biologic composition to olaparib and AT13387 used in study.

3.2.6 Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements.

3.2.7 Pregnant women are excluded from this study because olaparib and AT13387 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 AT13387 or olaparib, breastfeeding should be discontinued if the mother is treated with olaparib or AT13387.

3.2.8 HIV-positive patients on combination antiretroviral therapy are ineligible because of the potential for pharmacokinetic interactions with olaparib or AT13387. In addition, these patients are at increased risk of lethal infections when treated with marrow-suppressive therapy. Appropriate studies will be undertaken in patients receiving combination antiretroviral therapy when indicated.

3.2.9 Known history of QT/QTc prolongation or Torsades de Pointes (TdP). Patients who are currently receiving treatment with medication with a known risk to prolong the QT interval or inducing Torsades de Pointes and the treatment cannot either be discontinued or switched to a different medication prior to starting study drugs.

3.2.10 Participants receiving any medications or substances that are strong inhibitors or inducers of CYP3A4 or moderate inhibitors of CYP3A4 are ineligible (see Appendix C). The study team should check a frequently-updated medical reference for a list of drugs to avoid or minimize use of. As part of the enrollment/informed consent procedures, the patient will be counseled on the risk of interactions with other agents, and what to do if new medications need to be prescribed or if the patient is considering a new over-the-counter medicine or herbal product.

3.2.11 Participants with myelodysplastic syndrome/acute myeloid leukemia or with features suggestive of MDS/AML.

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.

Members of all races and ethnic groups are eligible for this trial. For the expansion cohort, only women develop ovarian cancer, but men with recurrent triple negative breast cancer will be eligible for this study. Please refer to Planned Enrollment Report table in Section 13.2.

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 (https://ctepcore.nci.nih.gov/iam). In addition, persons with a registration type of Investigator (IVR), Non-Physician Investigator (NPIVR), or Associate Plus (AP) (i.e., clinical site staff requiring write access to OPEN or RAVE or acting as a primary site contact) must complete their annual registration using CTEP's web-based Registration and Credential Repository (RCR) (https://ctepcore.nci.nih.gov/rcr). Documentation requirements per registration type are outlined in the table below.

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

An active CTEP-IAM user account and appropriate RCR registration is required to access all CTEP and

CTSU (Cancer Trials Support Unit) websites and applications. In addition, IVRs and NPIVRs must list all clinical practice sites and IRBs covering their practice sites on the FDA Form 1572 in RCR to allow the following:

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

For questions, please contact the RCR ***Help Desk*** by email at < RCRHelpDesk@nih.gov >.

Additional information can be found on the CTEP website at https://ctep.cancer.gov/investigatorResources/default.htm.

4.2 Site Registration

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

Each investigator or group of investigators at a clinical site must obtain IRB approval for this protocol and submit IRB approval and supporting documentation to the CTSU Regulatory Office before they can be approved to enroll patients. Assignment of site registration status in the CTSU Regulatory Support System (RSS) uses extensive data to make a determination of whether a site has fulfilled all regulatory criteria including but not limited to the following:

- An active Federal Wide Assurance (FWA) number
- An active roster affiliation with the Lead Network or a participating organization
- A valid IRB approval
- Compliance with all protocol specific requirements.

In addition, the site-protocol Principal Investigator (PI) must meet the following criteria:

- Active registration status
- The IRB number of the site IRB of record listed on their Form FDA 1572
- An active status on a participating roster at the registering site

Sites participating on the NCI CIRB initiative that are approved by the CIRB for this study are not required to submit IRB approval documentation to the CTSU Regulatory Office. For sites using the CIRB, IRB approval information is received from the CIRB and applied to the RSS in an automated process. Signatory Institutions must submit a Study Specific Worksheet for Local Context (SSW) to the CIRB via IRBManager to indicate their intent to open the study locally. The CIRB's approval of the SSW is then communicated to the CTSU Regulatory Office. In order for the SSW approval to be processed, the Signatory Institution must inform the CTSU which CIRB-approved institutions aligned with the Signatory Institution are participating in the study.

4.2.1 Downloading Regulatory Documents

Site registration forms may be downloaded from the 10031 protocol page located on the CTSU Web site. Permission to view and download this protocol is restricted and is based on person and site roster data housed in the CTSU RSS. To participate, Investigators and

Associates must be associated with the Corresponding or Participating protocol organization in the RSS.

- Go to https://www.ctsu.org and log in using your CTEP IAM username and password.
- Click on the Protocols tab in the upper left of your screen.
- Either enter the protocol # in the search field at the top of the protocol tree, or
- Click on the By Lead Organization folder to expand and then select LAO-MA036 and protocol 10031.
- Click on LPO Documents, select the Site Registration documents link, and download and complete the forms provided. (Note: For sites under the CIRB initiative, load to RSS as described above.)

4.2.2 Requirements For 10031 Site Registration:

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

4.2.3 Submitting Regulatory Documents

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

Regulatory Submission Portal: www.ctsu.org (members' area) → Regulatory Tab →Regulatory Submission
When applicable, original documents should be mailed to:
CTSU Regulatory Office
1818 Market Street, Suite 3000
Philadelphia, PA 19103

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

4.2.4 Checking Site Registration Status

- You can verify your site registration status on the members' section of the CTSU website. Go to https://www.ctsu.org and log in using your CTEP IAM username and password.
- Click on the Regulatory tab at the top of your screen.
- Click on the Site Registration tab.
- Enter your 5-character CTEP Institution Code and click on Go.

Note: The status given only reflects compliance with IRB documentation and institutional compliance with protocol-specific requirements as outlined by the Lead Network. It does

not reflect compliance with protocol requirements for individuals participating on the protocol or the enrolling investigator's status with the NCI or their affiliated networks.

4.3 Patient Registration

4.3.1 OPEN / IWRS

Patient enrollment will be facilitated using the Oncology Patient Enrollment Network (OPEN). OPEN is a web-based registration system available to users on a 24/7 basis. It is integrated with the CTSU Enterprise System for regulatory and roster data interchange and with the Theradex Interactive Web Response System (IWRS) for retrieval of patient registration/randomization assignment. Patient enrollment data entered by Registrars in OPEN / IWRS will automatically transfer to the NCI's clinical data management system, Medidata Rave.

For trials with slot reservation requirements, OPEN will connect to IWRS at enrollment initiation to check slot availability. Registration staff should ensure that a slot is available and secured for the patient before completing an enrollment.

Once a slot reservation request has been made, the following source documentation should be emailed to the Lead Institution Project Manager or designee for confirmation of eligibility.

- Copy of required laboratory tests:
  - CBC with differential
  - Serum chemistries (sodium, potassium, chloride, CO2, BUN, creatinine, glucose, albumin, calcium, phosphorus, ALP, AST (SGOT), ALT (SGPT), total bilirubin, total protein)
  - Coagulation (PT or INR with PTT)
- Signed informed consent form
- HIPAA authorization form (if separate from the informed consent document)
- EKG
- MUGA or ECHO
- CT scan or MRI (with documentation of measurable disease per RESIST 1.1)
- Pathology report
- Documentation that archival tissue is available
- Screening or most recent clinic visit note (including documentation of oncologic history, past medical history, concomitant medications, and vitals)
- Clinic note from eye exam

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

4.3.2 OPEN/IWRS User Requirements

OPEN/IWRS users must meet the following requirements:

- Have a valid CTEP-IAM account (*i.e.*, CTEP username and password).
- To enroll patients or request slot reservations: Be on an ETCTN Corresponding or Participating Organization roster with the role of Registrar. Registrars must hold a minimum of an AP registration type.
- To approve slot reservations or access cohort management: Be identified to Theradex as the "Client Admin" for the study.
- Have regulatory approval for the conduct of the study at their site.

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

- All eligibility criteria have been met within the protocol stated timeframes.
- If applicable, all patients have signed an appropriate consent form and HIPAA authorization form.

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: 609-619-7802 or Theradex main number 609-799-7580; CTMSSupport@theradex.com.

4.4 General Guidelines

Following registration, patients should begin protocol treatment within 7 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 TREATMENT PLAN

5.1 Agent Administration

Screening tests including tumor measurements must be done and deemed acceptable per Section 3 and completed ≤ 4 weeks prior to start of protocol therapy. Treatment will be administered on an outpatient basis. Reported adverse events and potential risks are described in Section 7. Appropriate dose modifications are described in Section 6. 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
A standard 3+3 design will be utilized, escalating if 0/3 or 1/6 participants have a DLT during Cycles 0 and 1 of therapy. Cycle 0 is only 7 days and Cycle 1 begins 8 days after start of Cycle 0, i.e. immediately after Cycle 0 ends.
If ≥ 2 DLT's are encountered on a dose level, that dose level will be considered the DLT dose, and the next dose level lower will be considered the MTD. Dose-limiting toxicity (DLT) will be based on the NCI Common Terminology Criteria for Adverse Events (CTCAE), Version 5.0 and refers to toxicities experienced during the first 1 cycle of treatment. Based on our tolerability and efficacy studies with olaparib and AT13387 in ovarian PDX models, AT13387 will be administered for 2 consecutive days every week for 3 weeks of a 4 week (28 day) cycle (Days 1, 2, 8, 9, 15, 16). The RP2D of AT13387 administered IV for 2 consecutive days every week for 3 weeks of a 4 week (28 day) cycle (Days 1, 2, 8, 9, 15, 16) is 160 mg/m2/dose.
Doses of olaparib will range from 50mg–300 mg twice daily; AT13387 doses will range from 20–160 mg/m2 (20-40-80-120-160) using a ping-pong strategy as shown in the Table below.

Number of Patients with DLT at a Given Dose Level	**Escalation Decision Rule**
0 out of 3	Enter 3 patients at the next dose level.
≥2	Dose escalation will be stopped. This dose level will be declared the maximally administered dose (highest dose administered). Three (3) additional patients will be entered at the next lowest dose level if only 3 patients were treated previously at that dose.
1 out of 3	Enter at least 3 more patients at this dose level. • If 0 of these 3 patients experience DLT, proceed to the next dose level. • If 1 or more of this group suffer DLT, then dose escalation is stopped, and this dose is declared the maximally administered dose. Three (3) additional patients will be entered at the next lowest dose level if only 3 patients were treated previously at that dose.
≤1 out of 6 at highest dose level below the maximally administered dose	This is generally the recommended phase 2 dose. At least 6 patients must be entered at the recommended phase 2 dose.

The following escalation scheme will be followed (one cycle consists of 28 days):

DOSE LEVEL	olaparib (tablets, oral, twice daily dosing continuous)	AT13387 (IV two consecutive days weekly)

-4	50mg BID	10mg/m2
-3	100mg BID	10mg/m2
-2*	50mg BID	20mg/m2
-1**	100mg BID	20mg/m2
0 (Starting Dose)	200mg BID	20mg/m2
1	200mg BID	40mg/m2
2***	300mg BID	40mg/m2
3***	300mg BID	80mg/m2
4	300mg BID	120mg/m2
5	300mg BID	160mg/m2

*If dose level -2 is tolerated, then escalation of AT13387 (40mg/m2, 80mg/m2, 120mg/m2 and 160mg/m2) in combination with olaparib 50mg BID will be attempted i.e.

-2a	50mg BID	40mg/m2
-2b	50mg BID	80mg/m2
-2c	50mg BID	120mg/m2
-2d	50mg BID	160mg/m2

**If dose level -1 is tolerated, then escalation of AT13387 (40mg/m2, 80mg/m2, 120mg/m2 and 160mg/m2) in combination with olaparib 100mg BID will be attempted i.e.

-1a	100mg BID	40mg/m2
-1b	100mg BID	80mg/m2
-1c	100mg BID	120mg/m2
-1d	100mg BID	160mg/m2

***If dose level 2 or dose level 3 is not tolerated, then escalation of AT13387 (80mg/m2, 120mg/m2 and 160mg/m2) in combination with olaparib 200mg BID will be attempted i.e.

2a	200mg BID	80mg/m2
3a	200mg BID	120mg/m2
4a	200mg BID	160mg/m2

In mouse xenograft models, continuous daily administration of olaparib yielded greater antitumor activity than intermittent administration at the same or at higher dose levels so it is recommended that olaparib is administered continuously.

The twice weekly (Days 1 and 2) of AT13387 was also chosen based on previous experience by Dr. Shapiro with another HSP90 inhibitor ganetespib (STA-9090)[1] . Therefore, the proposed regimen will be olaparib twice daily and AT13387 on Days 1 and 2 every week, cycle (Days 1, 2, 8, 9, 15, 16) of a 28 day cycle.

Agent	***Dose***	***Route***	***Schedule***	***Cycle Length***
olaparib	See dose level table above	Oral	Days 1-28 twice daily, 12 hours apart	*28 days (4 weeks)*
AT13387	See dose level table above	1-hour IV infusion	Days 1, 2, 8, 9, 15,16	

During cycle 0, olaparib will be administered alone twice daily at the same times each day,12 hours apart, for 1 week (D1-7). Cycle 1 and beyond, olaparib will continue to be administered twice daily and AT13387 will be administered for 2 consecutive days every week for 3 weeks of a 4 week cycle, i.e. on Days 1, 2, 8, 9, 15 and 16 of a 28 day cycle. On days that olaparib and AT13387 are administered on the same day, during cycle 1, AT13387 should be started at the same time that the patient takes olaparib. For all other cycles, olaparib can be administered at any time during the AT13387 infusion. Given that our hypothesis is that AT13387 sensitizes to olaparib by inhibiting HR, by administering olaparib alone for cycle 0 only (7 days), we can test this hypothesis as a "proof of mechanism" for the combination of AT13387 and olaparib. Specifically, we expect that there will be induction of BRCA1 and RAD51 foci after administration of olaparib alone and reduced formation of these foci and downregulation of expression of HR pathway genes after the combination of AT13387 and olaparib. To reiterate, olaparib will be administered alone in cycle 0 (7 days); in all subsequent cycles, olaparib will be administered daily and AT13387 will be administered QDx2 for QWx3 (Days 1, 2, 8, 9, 15, 16) of a 28 day cycle.

COMPLIANCE: The patient will be requested to maintain a medication diary of each dose of medication. A copy of the medication diary is in Appendix F. It will be returned to clinic staff at the end of each cycle.

The dose will depend on which combination and dose level the participant is on. Participants will be reassessed for tumor response every 2 cycles (8 weeks from Cycle 1 Day 1), +/- 1 week. During the DLT dosing period (Cycles 0 and 1), if dosing needs to be interrupted for toxicities, both drugs should be stopped and reinstituted simultaneously when appropriate according to Section 6. During cycles 2 and beyond, if a toxicity can be ascribed to a specific study drug, then that drug may be stopped while the non-offending drug can be maintained (see Section 6). Patients will have up to 28 days to resolve a toxicity to at least grade 1; if the toxicity does not decrease to grade 1 or less, the patient will be removed from the study. Furthermore, DLT

definition also includes toxicities that do not resolve to at least grade 1 within 28 days to allow patients to start Cycle 2. In other words, if patients are unable to start Cycle 2 because the toxicities have not resolved to at least grade 1 after 28 days, then this is also a DLT.
During the first 2 cycles of therapy, participants will be seen weekly for blood count and chemistry/liver/renal panels in addition to clinical status (which includes performance status, history/physical, medication reconciliation, vital signs). The DLT assessment period will be during the first 5 weeks of therapy (i.e., cycle 0 and 1). PK samples will be collected during cycle 1 as per section 2.3. During cycle 1, patients will be called by someone on the research team on Monday through Friday to confirm they are dosing study medications correctly. If the patient is being seen in clinic on one of these week days and confirmation of dosing was obtained during the clinic visit then a phone call is not necessary.

Intrapatient Dose Escalation
Intrapatient dose escalation in this trial will be allows given that AT13387 and olaparib have non-overlapping toxicities and that both drugs are not associated with any cumulative toxicities. Intrapatient dose escalation may occur as long as patients are tolerating their current drug dose levels, the next higher dose is deemed safe via the 3+3 design, and dose escalation is agreed upon with the treating physician and principal investigator. This dose escalation will not count towards the next cohort of 3+3 in the formal escalation of the trial. Patients must be treated on their initial dose level for at least 2 cycles before their dose can be escalated. Patients who have their dose escalated will follow the same rules for dose delays and modifications as described in section 6.0. Since DLT refers to toxicities experienced during cycle 0 and the first cycle of treatment, and intrapatient dose escalation is allowed after patients have been treated on their initial dose level for at least 2 cycles, toxicities after intrapatient dose escalation are not considered DLTs. There is no maximum number of times a patient can be dose escalated, as long as they have acceptable toxicities for 2 cycles on a specific dose level and are receiving benefit from the study drugs.

5.1.1 Pre-Treatment Criteria

Screening Visit
Participants must meet criteria at screening as outlined in Section 3.0.

Cycle 0: Day 1
Participants must continue to meet all eligibility criteria as outlined in protocol section 3.0 and the table below.

Cycle 1: Day 8, 15, and 22
Participants must meet the laboratory and performance status criteria listed in the table below. If dosing needs to be interrupted for toxicities, both drugs should be stopped and reinstituted when appropriate according to Sections 5 and 6.

Cycle 2 and Beyond: Day 1
Participants must meet the laboratory and performance status criteria listed in the table below. All toxicities experienced during the preceding cycle must have returned to grade 1 or less with the exception of specific laboratory parameters as listed in the table below. If dosing needs to be

interrupted for toxicities, the offending drug(s) should be stopped and reinstituted when appropriate according to Section 6. If one study drug is being taken the study clock does not stop, and the offending drug will be marked as held at the start of the next cycle. The study clock will not stop for drug(s) held and restarted within a cycle. If on day one both drugs are held, the next cycle will not start until one or both of the drugs are restarted.

TABLE: Pre-treatment Criteria

	Cycle 0: D1	**Cycle 1: D 8, 15 and 22**	**Cycle 2 and Beyond: Day 1***
ANC	≥1,500/mcL	≥1,000/mcL	≥1,000/mcL
Platelets	≥100,000/mcL	≥75,000/mcL	≥75,000/mcL
HgB	≥10g/dl	≥8g/dl	≥8g/dl
WBC	≥3,000/mcL	N/A	N/A
Tot Bili	WNL	≤1.5 x ULN	≤1.5 x ULN
SGPT	≤ 3 x ULN	≤ 3 x ULN	≤ 3 x ULN
SGOT	≤ 3 x ULN	≤ 3 x ULN	≤ 3 x ULN
Creatinine	≤ institutional ULN**	≤1.5 x ULN	≤1.5 x ULN
Magnesium	WNL	≤ Grade 1	≤ Grade 1
Potassium	WNL	≤ Grade 1	≤ Grade 1
ECOG	0 or 1	0 or 1	0 or 1

*For cycle 2 and beyond, hold only offending drug if pre-treatment criteria are not met
** or creatinine clearance ≥60mL/min/1.73m2 if creatinine above normal

At All Times During the Study
Participants must meet the following criteria at all times during the study to continue dosing:

- No evidence of life-threatening medical problems.
- No evidence of an impending bowel obstruction.
- Patient must be able and willing to swallow capsules.

5.1.2 **olaparib**

Administration
Olaparib at the appropriate dose level will be given orally continuously twice daily. Tablets are taken by mouth and can be taken with a light meal/snack if needed to reduce stomach irritation. The correct number of tablets comprising the appropriate dose should be taken at the same times each day with approximately 240 mL of water. The olaparib tablets should be swallowed whole and not chewed, crushed, dissolved, or divided.

A 28-day supply (+/-4 day window to allow for holidays and vacations) of Olaparib will be dispensed at the start of each cycle. Participants will be provided with a pill diary (Appendix F), instructed in its use, and asked to bring it with them to each appointment.

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 participant enrolled on the study miss a scheduled dose, the participant 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 should not be taken, and the participant should take their allotted dose at the next scheduled time.

Dosing: Please refer to section 5.1.

5.1.3 **AT13387 (Olanespib)**

Administration

In this trial, AT13387 will be administered in the following dosing schedule:
One hour IV infusion (+/- 10 minutes) on Days 1, 2, 8, 9, 15, and 16 of a 28-day cycle (twice-weekly for 3 weeks of a 4 week cycle); refer to section 5.1 for dose schedule. Dosing of AT13387 will be based on the weight obtained on days 1, 8 and 15 of each cycle, and this weight can be used for dosing on the following day, that is, days 2, 9 and 16, respectively.. AT13387 dose rounding will be done as per institutional guidelines.

Treatment with AT13387 (onalespib) may be associated with local infusion-related irritation, as well as systemic infusion reactions, which occur either during the infusion or shortly afterwards (same day).

Infuse over 1 hour (+/- 10 minutes) through a central line or a well-defined peripheral vein. If using a peripheral line, be sure to aspirate venous blood prior to starting the infusion. Check the infusion site every 15 minutes and change the site of infusion should evidence if swelling or discoloration is observed.

If patient experiences pain at the infusion site, slow the infusion rate (i.e. > 1-hour duration) and/or infuse D5W or 0.9% NS through a "Y" connector. The additional volume of D5W or 0.9% NS dilutes AT13387 concentration at the local site of the infusion and alleviates the irritation. Premedication with dexamethasone, antihistamine and 5HT3 antagonists can also be given.

5.2 Definition of Dose-Limiting Toxicity

Dose-limiting toxicity (DLT) is based on the NCI Common Terminology Criteria for Adverse Events (CTCAE), Version 5.0.

Definition of DLT: Dose limiting toxicity (DLT) refers to both non-hematologic and hematologic toxicities experienced during cycle 0 and the first cycle (i.e. first 4 weeks) of treatment.

A DLT will be defined as any of the following, numbers 1-5, occurring during Cycles 0 and 1:

1. Non-Hematologic Toxicity
Any Grade 3 or 4 event, excluding:

- Grade 3 Fatigue
- Grade 3 nausea and/or vomiting controlled with supportive measures within 24 hours
- Grade 3 constipation controlled with supportive measures within 24 hours
- Grade 3 diarrhea controlled with supportive measures within 24 hours
- Grade 3 hypophosphatemia
- Grade 3 hyponatremia
- Grade 3 hypomagnesemia
- Grade 3 rash that resolves to grade 2 or grade 1 within < 5 days

2. Hematologic Toxicity

- Grade 4 neutropenia of > 7 day's duration
- Febrile neutropenia (a disorder characterized by an ANC < 1000/mm3 and a single temperature of > 38.3 °C (101 °F) or a sustained temperature of > 38 °C (100.4 °F) for more than one hour.
- Grade 4 thrombocytopenia or bleeding associated with grade 3 thrombocytopenia.
- Requirement for repeated blood transfusion within 4-6 weeks
- All other Grade 4 hematologic toxicities

3. Any study treatment related death.

4. Any Grade 3 or grade 4 toxicity considered, in the opinion of the investigator, to be dose-limiting.

5. Inability to take 75% or more of the planned dose for olaparib and 4 out of 6 doses for AT13387 in Cycle 1 due to treatment-related AEs.
If patients cannot take 75% or more of the planned olaparib or who receive fewer than 4 doses of AT13387, for reasons other than toxicity or DLT, these patients will not be evaluable for DLT assessment and will be replaced.

If a participant experiences a DLT, a PK sample should not be drawn.

Management and dose modifications associated with the above adverse events are outlined in Section 6.

The study team will review data and the progress of the study on a monthly bases including during the expansion cohort

5.3 Dose Expansion Cohorts

Once the RP2D is reached, an additional 20 patients with either TNBC or ovarian cancer will be treated at this dose. Monitoring of all safety and toxicity data is done by the Principal Investigator and the Corresponding Organization on a real-time basis as data are entered into

Medidata Rave using the Web Reporting Module. All participating sites are expected to notify the Principal Investigator when a DLT has occurred.

5.4 General Concomitant Medication and Supportive Care Guidelines

Please see section 8 for potential drug interactions.

Patient should receive general concomitant and supportive care medications based on best medical practice. Neupogen and other bone marrow-supportive agents, including erythropoiesis stimulating agents, are not allowed during treatment. The use of any natural/herbal products or other "folk remedies" is not allowed on study. All medications must be recorded in the case report form and be reviewed by the treating physician at each visit.

Because there is a potential for interaction of olaparib and/or AT13387 with other concomitantly administered drugs, the case report form must capture the concurrent use of all other drugs, over-the-counter medications, or alternative therapies. The Principal Investigator should be alerted if the patient is taking any agent known to affect or with the potential for drug interactions.

Participants on chronic medications that can be given concomitantly with protocol drugs should be maintained on the same dose and dose schedule throughout the study period, as medically feasible. The investigator should instruct the participant to notify the study site about any new medications he/she takes after the start of the study drug. All supportive measures consistent with optimal patient care will be given throughout the study. Bisphosphonates, vitamin D and calcium supplementation, topical medications, antiemetics, anti-diarrheal medications, anticoagulants and anti-infective agents may be used at the discretion of the treating physician.

In general, the use of any concomitant medication/therapies deemed necessary for the care of the patient is permitted with the following exceptions:

- Other investigational therapies must not be used while the participant is on the study.
- Myeloid growth factors are not permitted during any cycle of therapy.
- Anticancer therapy (chemotherapy, biologic or radiation therapy, and surgery) other than the study treatments must not be given to participants while he/she is on the study. If such agents are required for a participant then the participant must be removed from this study.

The study team should check a frequently-updated medical reference for a list of drugs to avoid or minimize use of. APPENDIX B – AT13387 PATIENT DRUG INFORMATION handout and wallet card should be provided to patients.

Medications that could alter the QTc interval

Participants must also not take medications that could alter the QTc interval which are listed in Appendices C and D. Medications listed in Appendix C can be used but with caution. Please note that some anti-emetics have a known risk for Torsades de Pointes (TdP) and are prohibited.
If a participant, after study enrollment, requires the concomitant use of any QT prolonging medication with a possible or conditional risk for torsade de pointes then the investigators, at

their discretion, may co-administer such medications. Participants receiving such medications must be monitored. Refer to Appendix C for a list of QT prolonging medications to be used with caution. Please refer also to Appendix D for a list of prohibited QT prolonging medication.

5.5 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
- Participant demonstrates an inability or unwillingness to comply with the oral medication regimen and/or documentation requirements

Due to the expiration date of the terminal lot of AT13387 (Onalespib), all participants must discontinue AT13387 treatment before May 31, 2020. Patients may continue olaparib alone after May 31, 2020.

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).

5.6 Duration of Follow Up

Final Visit
The final visit will occur at the time the participant discontinues study medication. Following the Final Visit, participants will be followed for disease progression (if reason for treatment discontinuation is other than progression) and survival. Follow-up will be reported in 3 month intervals for up to two years after removal from study treatment or until death, whichever occurs first. Participants removed from study treatment for unacceptable adverse events will be followed until resolution or stabilization of the adverse event.

Follow Up
Participants will be followed for disease progression (if reason off treatment is other than progression) and survival. Follow-up will be reported in 3 month intervals for up to two years after removal from study treatment or until death, whichever occurs first. Participants removed from study treatment for unacceptable adverse events will be followed until resolution or stabilization of the adverse event.

5.7 Criteria for Removal from Study

Participants will be removed from study when any of the following criteria apply:

- Lost to follow-up
- Withdrawal of consent for data submission
- Death
- Completion of all study requirements

The reason for study removal and the date the patient was removed must be documented in the Case Report Form (CRF). Alternative care options will be discussed with the participant. In the event of unusual or life-threatening complications, participating investigators must immediately notify the Principal Investigator.

6 DOSING DELAYS/DOSE MODIFICATIONS

Dose delays and modifications will be made using the following recommendations. Toxicity assessments will be done using version 4.0 of the NCI Common Terminology Criteria for Adverse Events (CTCAE) until March 31, 2018. CTCAE version 5.0 will be used for toxicity assessments beginning April 1, 2018. The CTCAE is identified and located on the CTEP website at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm. If possible, symptoms should be managed symptomatically. In the case of toxicity, appropriate medical treatment should be used (including anti-emetics, anti-diarrheals, etc.).
All adverse events experienced by participants will be collected from the time of the first

dose of study treatment, through the study and until the final study visit. Participants continuing to experience toxicity at the off study visit may be contacted for additional assessments until the toxicity has resolved or is deemed irreversible.

6.1 Anticipated Toxicities

A list of the adverse events and potential risks associated with the agents administered in this study appears below and will determine whether dose delays and modifications will be made or whether the event requires expedited reporting in addition to routine reporting. Please refer to section 7 for specifics.

6.2 General Toxicity Management, Dose Modifications / Delays

The management of general adverse events not otherwise specified will be as per the table in section 6.2.1; for specific toxicities of diarrhea, QTc prolongation, nausea and hematological toxicities, please see section 6.3.

Investigators will make the determination of whether a toxicity is related either to olaparib or AT13387. If dose reductions are necessary, the agent that will be dose reduced will be the one that has toxicities attributed to it. If both drugs are causing drug-related toxicities, both agents will be dose reduced one dose level (i.e. immediately lower dose on dose escalation Table, Section 5.1).

6.2.1 General Dose Modifications and Management of olaparib and AT13387 toxicities

For toxicities that have their own management algorithm as listed in 6.2, please see that specific section below.

In this phase 1 study, doses of olaparib and AT13387 will be administered at the same dose level throughout a cycle if no toxicities that require a dose reduction occur.

If any individual participant develops a DLT, the study drugs should be held. If the toxicity is not resolved within 28 days, the participants will be removed from the study. Participants who experience a DLT that resolves to baseline or Grade 1 and whose therapy has been held for less than or equal to 28 days may resume therapy at the next lowest dose of drug(s), if necessary.

Observation	Action
AE resolves within 48 hours with supportive care	Maintain dose level
Any non-hematologic or hematologic AE at least possibly related to olaparib or AT13387 **that meets DLT definition**	Hold treatment (both study drugs in Cycle 1, and offending drug in cycle 2 and beyond) for up to 28 days until toxicity resolves to ≤ grade 1. Treatment will be restarted at the next lowest dose levels of drug(s) causing the toxicity (section 5.1, dose escalation table). The

	overall PI of the study should be informed of all dose modifications.
Other grade 2 or 3 non-hematologic toxicities that last ≤ 7 days, and at least possibly related to either olaparib or AT13387	Hold treatment (both study drugs in Cycle 1, and offending drug in cycle 2 and beyond) for up to 7 days until toxicity resolves to ≤ grade 1. Resume at the same dose level.
Other grade 2 or 3 non-hematologic toxicities that are persistent (lasting greater than 7 days despite maximal supportive measures) and/or intolerable and at least possibly related to either olaparib or AT13387. **and** for grade 3 or 4 events that are unlikely/unrelated to either AT13387 or olaparib	Hold treatment (both study drugs in Cycle 1, and offending drug in cycle 2 and beyond) for up to 28 days until toxicity resolves to ≤ grade 1. Treatment will be restarted at the next lowest dose levels of drug(s) causing the toxicity (section 5.1, dose escalation table). The overall PI of the study should be informed of all dose modifications.

6.3 Dose Modifications/Delays and Management for Specific Toxicities

6.3.1 **Diarrhea**

Management of Diarrhea	
Toxicity Grade	**Action**
Grade 1	Consider loperamide (4 mg at first onset, followed by 2 mg q 2–4 hours until free of diarrhea for 12 hours. The total maximum daily dose of loperamide should not exceed 8 tablets (16 mg). Maintain dose level.
Grade 2	Loperamide (4 mg at first onset, followed by 2 mg q 2–4 hours until free of diarrhea for 12 hours. The total maximum daily dose of loperamide should not exceed 8 tablets (16 mg). Omit dose until resolved to ≤ grade 1, then restart the same dose.
Grade 3 and Grade 4	Loperamide as above. Omit dose until resolved to Grade ≤ 1, then reduce AT13387 by 1 dose level.

Diarrhea has been reported within the ongoing studies of AT13387. In order to effectively manage diarrhea and mitigate the escalation in severity or duration of diarrhea, patient education as well as proper management of diarrhea is mandatory.
The following section outlines the recommended algorithm for management and treatment of AT13387-induced diarrhea.

Patient history of diarrhea
At screening, the patient's history of diarrhea should be reviewed and the patient should be appropriately informed of potential study drug-induced diarrhea and its management:

- Review previous medical history of diarrhea within the last 12 months; laxative use, colon surgery, abdominal and pelvic irradiation, nocturnal diarrhea, pain, ulcerative colitis and other diarrhea-inducing diseases/conditions;
- Stop all diarrheogenic agents at screening if possible, otherwise exclude from trial;
- Instruct patients regarding risk of developing diarrhea;
- Perform baseline clinical/laboratory studies according to the trial protocol (e.g. one could rule out carrier state of Salmonella spp., Clostridium difficile, Campylobacter spp., Giardia, Entamoeba, Cryptosporidium which can lead to opportunistic infections in immunosuppressed patients)
- Explain the frequency of diarrhea and its relationship to NCI CTCAE grading

First report of diarrhea

- Obtain history of onset and duration of diarrhea
- Description of number of stools and stool composition (e.g. watery, blood, mucus in stool)
- Assess patient for fever, abdominal pain, cramps, distension, bloating, nausea, vomiting, dizziness, weakness (i.e., rule out risk for sepsis, bowel obstruction, dehydration)
- Obtain medication profile (i.e., to identify any diarrheogenic agents) and dietary profile (i.e., to identify diarrhea-enhancing foods)

Proactively look for occurrence of diarrhea. If no problems occur, instruct the patient to call when a problem does arise.

Management of diarrhea

General recommendations:

- Stop all lactose-containing products, alcohol
- Stop laxatives, bulk fiber (e.g. Metamucil®) and stool softeners (e.g. docusate sodium, Colace®)
- Stop high-osmolar food supplements such as Ensure Plus® and Jevity Plus® (with fiber)
- Drink 8 to 10 large glasses of clear liquids per day (e.g. water, Pedialyte®, Gatorade®, broth)
- Eat frequent small meals (e.g. bananas, rice, apple sauce, toast)

It is recommended that patients are provided with loperamide tablets at the start of each cycle. Patients should be instructed on the use of loperamide at Cycle 1 in order to manage signs or symptoms of diarrhea at home. Patients should be instructed to start oral loperamide (initial administration of 4 mg, then 2 mg every 4 hrs (maximum of 16 mg/day) at the first sign of loose stool or symptoms of abdominal pain. These instructions should be provided at each cycle and the site should ensure that the patient understands the instruction. At the beginning of each cycle, each patient should be specifically questioned regarding any experience of diarrhea or diarrhea related symptoms. If symptoms were experienced, then the site should question the patient regarding the actions taken for these symptoms.

Intensive management of diarrhea must be instituted at the first sign of abdominal cramping, loose stools or overt diarrhea. Note that all concomitant therapies used for treatment of diarrhea must be recorded on the Concomitant Medications/Non-drug Therapies eCRF. Loperamide is the first-line treatment of diarrhea (any Grade) in this recommended algorithm. Persistent symptoms may require the administration of high dose loperamide followed by treatment with second-line agents such as opium tincture and octreotide acetate, based on severity and duration of diarrhea

and related signs/symptoms. Another first-line treatment for diarrhea is diphenoxylate hydrochloride/atropine sulfate. This medication may be used in place of loperamide however it is important to note that loperamide and diphenoxylate hydrochloride/atropine sulfate must not be used in conjunction with one another due to the risk of developing paralytic ileus. Upon treatment with any antidiarrheal agents, the patient's response to treatment should be observed and appropriately documented in the source document and eCRF.

Treatment of diarrhea CTCAE grade 1 or 2
Diarrhea CTCAE grade 1 or 2 will be treated with standard loperamide (initial at first administration 4 mg, then 2 mg every 4 hrs (maximum of 16 mg/day) or after each unformed stool).

12-24 hrs later:
Diarrhea resolved

- Continue instructions for dietary modification
- Gradually add solid foods to diet
- Discontinue loperamide after 12 hrs diarrhea-free interval

Diarrhea unresolved
Persisting diarrhea CTCAE grade 1 or 2 will be treated with addition of opium tincture or dihydrocodeine tartrate tablets/injections with monitoring of patients condition to rule out dehydration, sepsis, ileus) medical check and selected workup if patient does not need hospitalization (see section Diarrhea workup and additional test in the particular trial protocol). Observe patient for response to antidiarrheal treatment.
Persisting diarrhea CTCAE grade 3 or 4 may be treated with hospitalization, high dose loperamide (initial 4 mg, then 2 mg every 2 hrs) and addition of opium tincture (DTO) or dihydrocodeine tartrate tablets/injections, start of IV fluids and antibiotics as needed with monitoring of patient's condition (to rule out dehydration, sepsis, ileus) medical check and workup (perform appropriate additional testing). Observe patient for response.

After 12-24 hrs:
Diarrhea resolved

- Continue instructions for dietary modification
- Gradually add solid foods to diet
- Discontinue loperamide and/or other treatment after 12 hrs diarrhea-free interval

Diarrhea unresolved

- If diarrhea still persisting (CTCAE grades 1 and 2), after 2x 24 hrs with high dose loperamide and opiates then admit to hospital and employ measures as for CTCAE grade 3 and 4 until diarrhea resolved.
- If diarrhea still persisting and progressed to CTCAE grades 3 and 4, employ measures described below.

Treatment of diarrhea CTCAE grade 3 or 4
Severe diarrhea CTCAE grade 3 or 4 may be treated with hospitalization, high dose loperamide (initial 4 mg, then 2 mg every 2 hrs and addition of opium tincture or dihydrocodeine tartrate tablets/injections, start of IV fluids and antibiotics as needed with monitoring of patients condition (to rule out dehydration, sepsis, ileus) medical check and

workup (see section Diarrhea workup and additional test in the particular trial protocol). Observe patient for response.

After 12-24 hrs:

- If diarrhea persisting administer s.c. Sandostatin/octreotide (100-500 mcg tid)
- Continue IV fluids and antibiotics as needed
- If diarrhea CTCAE grade 3 or 4 still persists patients should receive opium tincture or dihydrocodeine tartrate injections s.c. or i.m.
- If diarrhea CTCAE grade 3 or 4 is still persisting s.c. Sandostatin/octreotide (500-1000 mcg TID) should be administered.
- To control and/or resolve diarrhea, next cycle of treatment should be delayed by 1 or 2 weeks. Treatment should be continued only when diarrhea resolved.

Diarrhea workup
Perform appropriate tests:
Spot stool analysis

- Collect stool separating it from urine (special containers, analysis immediately, exceptionally freeze samples)
- Blood
- Fecal leukocytes (Wright's staining and microscopy) or
- Clostridium difficile toxin
- Fecal cultures including Salmonella spp., Campylobacter spp., Giardia, Entamoeba, Cryptosporidium (which can lead to opportunistic infections in immunosuppressed patients), plus Shigella and pathogenic E. coli - enterotoxigenic, enterohemorrhagic etc., possibly Aeromonas, Pleisiomonas (if suspected exposure to contaminated water)

Endoscopic examinations
Endoscopic examinations may be considered only if absolutely necessary. The bowel is likely to be fragile with evidence of colitis and thus great care and caution must be exercised in undertaking these invasive procedures.

- Gastroscopy to obtain jejunal fluid - re. bacterial overgrowth for cultures and biopsy of proximal jejunum to assess extent of inflammatory jejunitis
- Sigmoidoscopy - reassessment of colitis

6.3.2 QTc prolongation

Management of QTc prolongation:
At the screening visit a 12-lead electrocardiogram (ECG), and an echocardiogram or MUGA (ECHO/MUGA) will be performed to assess eligibility. A 12 lead ECG will be done in triplicate at 2-5 minute intervals as part of screening, cycle 1, day 15, cycle 2, day 15 and day 1 of each following cycle.

Management of QTc Prolongation	
Observation	**Action**
QTcF > 500 ms	**First Occurrence:**

(> grade 3) or > 60 ms change from baseline on at least two separate ECGs	Omit AT13387. Perform a repeat ECG within one hour of the first QTc of >500ms or >60 ms from baseline: if QTcF remains >500ms or >60 ms from baseline, repeat ECG as clinically indicated, but at least once a day until QTcF returns to <480ms. Seek cardiologist input; address electrolytes, calcium and magnesium abnormalities; concomitant medication must be reviewed. Once QTcF prolongation has resolved, AT13387 may be restarted at one lower dose level. **Second Occurrence:** Permanently discontinue AT13387

6.3.3 **Nausea (olaparib and AT13387)**

Nausea	**Management/Next Dose for olaparib**	**Management/Next Dose for AT13387**
≤ Grade 1	No change in dose	No change in dose
Grade 2	Hold until ≤ Grade 1. Resume at same dose level.	Hold until ≤ Grade 1. Resume at same dose level.
Grade 3	Hold* until < Grade 2. Resume at one dose level lower, if indicated.**	Hold* until < Grade 2. Resume at one dose level lower, if indicated.**
Grade 4	Off protocol therapy	Off protocol therapy
*Patients requiring a delay of >2 weeks should go off protocol therapy. **Patients requiring > two dose reductions should go off protocol therapy.		
Recommended management: antiemetics.		

6.3.4 **Hematologic Toxicities**

Management of Hematologic Toxicities

If:
any study treatment is interrupted/delayed because of one or more of the following:
1) ≥ 2 week interruption/delay in study treatment due to CTC grade >2 neutropenia
2) ≥ 2 week interruption/delay in study treatment due to CTC grade >2 thrombocytopenia
3) ≥ 2 week interruption/delay in study treatment due to CTC grade >2 anemia and or development of blood transfusion dependence
Note: Myeloid growth factors are not permitted during any cycle of therapy.

Then:
Weekly blood counts should be performed during the study treatment interruption/delay. If the levels have still not recovered to CTC Grade ≤1 after 4 weeks of dose interruption, the participant should be referred to a hematologist for further investigations. Bone marrow analysis or blood cytogenetic analysis should be considered at this stage according to standard hematological practice.

For any participants with an episode of grade 3 anemia, the olaparib dose should be reduced to the next lowest dose of drug. If grade 3 anemia persists despite one dose reduction, the dose of olaparib can be reduced by another dose. A maximum of 2 dose reductions can be made. Participants should be transfused as per institutional policies. For participants who receive multiple blood transfusions because of anemia that is related to olaparib use, the treating investigator can dose reduce olaparib in consultation with the Principal Investigator.

Dose Modification and Management of Hematologic Adverse Events	
Absolute neutrophil count ≥ 1000/mcL (1.0 x 109/L) AND Platelets ≥ 75,000/mcL AND Hemoglobin ≥ 8g/dL	Maintain dose level
Absolute neutrophil count < 1000/mcL (1.0 x 109/L) OR Platelets < 75,000/mcL OR Hemoglobin < 8g/dL	Hold treatment for up to 28 days until absolute neutrophil count ≥ 1000/mcL, platelets ≥ 75,000/mcL, and hemoglobin ≥ 8 g/dL. Treatment will be restarted at one dose level lower for the drug(s) causing the toxicity, if the participant has experienced a DLT in cycle 1, or for participants in cycle 2 and beyond. Treatment may be restarted at the same dose level for participants still in the DLT period and have not experienced a DLT, after discussion with the PI. Patients whose counts have not recovered to absolute neutrophil count ≥ 1000/mcL, platelets ≥ 75,000/mcL, and hemoglobin ≥ 8 g/dL after 28 days should be removed from study. The overall PI of the study should be informed regarding all dose modifications.

7 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 7.1) and the characteristics of an observed AE (Section 7.2) will determine whether the event requires expedited reporting via the CTEP Adverse Event Reporting System (CTEP-AERS) **in addition** to routine reporting.

7.1 Comprehensive Adverse Events and Potential Risks List(s) (CAEPRs)

The Comprehensive Adverse Event and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. In addition to the comprehensive list, a subset of AEs, the Specific Protocol Exceptions to Expedited Reporting (SPEER), appears in a separate column and is identified with ***bold*** and ***italicized*** text. The 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/adverse_effects.htm for further clarification.

NOTE: The highest grade currently reported is noted in parentheses next to the AE in the SPEER. Report **ONLY** AEs higher than this grade expeditiously. 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.

7.1.1 CAEPRs for olaparib and AT13387

7.1.1.1 CAEPR for olaparib

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

The Comprehensive Adverse Events and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. In addition to the comprehensive list, a subset, the Specific Protocol Exceptions to Expedited Reporting (SPEER), appears in a separate column and is identified with bold and italicized text. This subset of AEs (SPEER) is a list of events that are protocol specific exceptions to expedited reporting to NCI (except as noted below). Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements' http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf for further clarification. *Frequency is provided based on 2073 patients.* Below is the CAEPR for Olaparib (AZD2281).

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

Version 2.4, April 24, 2019[1]

Adverse Events with Possible Relationship to Olaparib (AZD2281) (CTCAE 5.0 Term) [n= 2073]			**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)***
GASTROINTESTINAL DISORDERS			
	Abdominal distension		
	Abdominal pain		***Abdominal pain (Gr 2)***
	Constipation		***Constipation (Gr 2)***

Adverse Events with Possible Relationship to Olaparib (AZD2281) (CTCAE 5.0 Term) [n= 2073]			**Specific Protocol Exceptions to Expedited Reporting (SPEER)**
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
Diarrhea			***Diarrhea (Gr 2)***
	Dyspepsia		***Dyspepsia (Gr 2)***
Nausea			***Nausea (Gr 3)***
Vomiting			***Vomiting (Gr 3)***
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
	Edema limbs		
Fatigue			***Fatigue (Gr 3)***
	Fever		
INFECTIONS AND INFESTATIONS			
	Infection[2]		
INVESTIGATIONS			
	Creatinine increased		
	Lymphocyte count decreased		
	Neutrophil count decreased		
	Platelet count decreased		
	White blood cell decreased		
METABOLISM AND NUTRITION DISORDERS			
Anorexia			***Anorexia (Gr 2)***
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			
	Arthralgia		
	Back pain		
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	

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.

[2]Infection may include any of the 75 infection sites under the INFECTIONS AND INFESTATION SOC.

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 - Cardiac disorders - Other (nodal rhythm); Chest pain - cardiac; Sinus tachycardia
EAR AND LABYRINTH DISORDERS - Tinnitus
ENDOCRINE DISORDERS - Hypothyroidism
GASTROINTESTINAL DISORDERS - Ascites; Colitis; Colonic obstruction; Dry mouth; Dysphagia; Flatulence; Gastroesophageal reflux disease; Gastrointestinal disorders - Other (gastrointestinal hemorrhage); Gastrointestinal disorders - Other (intestinal obstruction); Gastrointestinal disorders - Other (intestinal perforation); Ileus; Jejunal perforation; Mucositis oral; Pancreatitis; Periodontal disease; Rectal hemorrhage; Small intestinal obstruction; Stomach pain
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Malaise; Non-cardiac chest pain
IMMUNE SYSTEM DISORDERS - Immune system disorders - Other (systemic inflammatory response syndrome)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS - 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; 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 cramp; Muscle weakness lower limb; Myalgia; Neck pain; Pain in extremity; Rotator cuff injury
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS) - Tumor pain
NERVOUS SYSTEM DISORDERS - Amnesia; Ataxia; Cognitive disturbance; Concentration impairment; Encephalopathy; Intracranial hemorrhage; Peripheral sensory neuropathy; 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; Oropharyngeal pain; Pleural effusion; Respiratory failure; Respiratory, thoracic and mediastinal disorders - Other (chronic obstructive pulmonary disease)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Alopecia; Pruritus; Rash maculo-papular
VASCULAR DISORDERS - Flushing; Hot flashes; Hypertension; Hypotension; 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.

7.1.1.2 CAEPR for AT13387

Comprehensive Adverse Events and Potential Risks list (CAEPR) for AT13387 (Onalespib, NSC 749712)

The Comprehensive Adverse Events and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. In addition to the comprehensive list, a subset, the Specific Protocol Exceptions to Expedited Reporting (SPEER), appears in a separate column and is identified with bold and italicized text. This subset of AEs (SPEER) is a list of events that are protocol specific exceptions to expedited reporting to NCI (except as noted below). Refer to the

'CTEP, NCI Guidelines: Adverse Event Reporting Requirements'
http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf for further clarification.
Frequency is provided based on 119 patients. Below is the CAEPR for AT13387 (Onalespib).

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

Version 2.1, December 28, 2018[1]

Adverse Events with Possible Relationship to AT13387 (Onalespib) (CTCAE 5.0 Term) [n= 119]			**Specific Protocol Exceptions to Expedited Reporting (SPEER)**
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
Anemia			***Anemia (Gr 2)***
EYE DISORDERS			
	Blurred vision		
	Vision decreased		***Vision decreased (Gr 2)***
GASTROINTESTINAL DISORDERS			
	Abdominal pain		***Abdominal pain (Gr 2)***
	Constipation		***Constipation (Gr 2)***
Diarrhea			***Diarrhea (Gr 2)***
	Dry mouth		***Dry mouth (Gr 2)***
	Dyspepsia		***Dyspepsia (Gr 2)***
	Flatulence		***Flatulence (Gr 2)***
	Gastrointestinal hemorrhage[2]		
	Hemorrhoids		***Hemorrhoids (Gr 2)***
Nausea			***Nausea (Gr 2)***
	Vomiting		***Vomiting (Gr 2)***
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
	Edema limbs		
Fatigue			***Fatigue (Gr 2)***
	Fever[3]		***Fever[3] (Gr 2)***
Injection site reaction[4]			***Injection site reaction[4] (Gr 2)***
	Malaise		***Malaise (Gr 2)***
INFECTIONS AND INFESTATIONS			
	Infection[5]		***Infection[5] (Gr 2)***
INJURY, POISONING AND PROCEDURAL COMPLICATIONS			
	Infusion related reaction[3]		***Infusion related reaction[3] (Gr 2)***
INVESTIGATIONS			
	Alanine aminotransferase increased		***Alanine aminotransferase increased (Gr 2)***
	Alkaline phosphatase increased		***Alkaline phosphatase increased (Gr 2)***
	Aspartate aminotransferase increased		***Aspartate aminotransferase increased (Gr 2)***
	CPK increased		***CPK increased (Gr 2)***
	Electrocardiogram QT corrected interval prolonged		
	Lymphocyte count decreased		***Lymphocyte count decreased (Gr 2)***
	Platelet count decreased		***Platelet count decreased (Gr 2)***
	Weight loss		***Weight loss (Gr 2)***
	White blood cell decreased		
METABOLISM AND NUTRITION DISORDERS			

Adverse Events with Possible Relationship to AT13387 (Onalespib) (CTCAE 5.0 Term) [n= 119]			**Specific Protocol Exceptions to Expedited Reporting (SPEER)**
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
	Anorexia		***Anorexia (Gr 2)***
	Dehydration		***Dehydration (Gr 2)***
	Hypocalcemia		***Hypocalcemia (Gr 2)***
	Hypokalemia		
	Hypomagnesemia		
	Hyponatremia		***Hyponatremia (Gr 2)***
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			
	Muscle cramp		***Muscle cramp (Gr 2)***
	Myalgia		***Myalgia (Gr 2)***
NERVOUS SYSTEM DISORDERS			
	Dizziness		***Dizziness (Gr 2)***
	Dysgeusia		
	Headache		***Headache (Gr 2)***
PSYCHIATRIC DISORDERS			
	Insomnia		***Insomnia (Gr 2)***
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
	Cough		***Cough (Gr 2)***
	Dyspnea		***Dyspnea (Gr 2)***
	Hiccups		***Hiccups (Gr 2)***
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
	Dry skin		***Dry skin (Gr 2)***
	Hyperhidrosis[3]		***Hyperhidrosis[3] (Gr 2)***
	Rash acneiform		
	Rash maculo-papular		***Rash maculo-papular (Gr 2)***
VASCULAR DISORDERS			
	Flushing		***Flushing (Gr 2)***

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

[2]Gastrointestinal hemorrhage includes Anal hemorrhage, Cecal hemorrhage, Colonic hemorrhage, Duodenal hemorrhage, Esophageal hemorrhage, Esophageal varices hemorrhage, Gastric hemorrhage, Hemorrhoidal hemorrhage, Ileal hemorrhage, Intra-abdominal hemorrhage, Jejunal hemorrhage, Lower gastrointestinal hemorrhage, Oral hemorrhage, Pancreatic hemorrhage, Rectal hemorrhage, Retroperitoneal hemorrhage, and Upper gastrointestinal hemorrhage under the GASTROINTESTINAL DISORDERS SOC.

[3]Infusion-related reactions may include, tachycardia/bradycardia, hypotension/hypertension, flushing, chills, fever, hyperhidrosis, itching, rigors, and abdominal cramps.

[4]Injection site reaction may include injection site irritation, injection site pain, injection site inflammation or redness, or erythema.

[5]Infection may include all 75 sites of infection under the INFECTIONS AND INFESTATIONS SOC.

Adverse events reported on AT13387 (Onalespib) trials, but for which there is insufficient evidence to suggest

that there was a reasonable possibility that AT13387 (Onalespib) caused the adverse event:

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Febrile neutropenia
CARDIAC DISORDERS - Cardiac disorders - Other (atrioventricular block NOS); Left ventricular systolic dysfunction; Palpitations
EYE DISORDERS - Dry eye; Eye disorders - Other (color distortion); Eye disorders - Other (diplopia); Eye disorders - Other (halos); Eye disorders - Other (loss of visual acuity during changes in ambient light levels); Eye disorders - Other (tunnel vision); Eye disorders - Other (visual color darkening); Eye disorders - Other (visual disturbances); Eye pain; Flashing lights; Floaters; Keratitis; Night blindness; Papilledema; Photophobia; Retinopathy
GASTROINTESTINAL DISORDERS - Colitis; Mucositis oral; Oral dysesthesia; Oral pain; Salivary duct inflammation
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Chills[3]; Flu like symptoms
HEPATOBILIARY DISORDERS - Hepatic hemorrhage
INVESTIGATIONS - Activated partial thromboplastin time prolonged; Blood bilirubin increased; Creatinine increased; Ejection fraction decreased; Neutrophil count decreased
METABOLISM AND NUTRITION DISORDERS - Hyperglycemia; Hypoalbuminemia; Hypophosphatemia
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Back pain; Bone pain; Generalized muscle weakness
NERVOUS SYSTEM DISORDERS - Seizure; Syncope; Tremor
PSYCHIATRIC DISORDERS - Anxiety
RENAL AND URINARY DISORDERS - Acute kidney injury; Proteinuria
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Pneumonitis
SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Palmar-plantar erythrodysesthesia syndrome; Pruritus; Skin hyperpigmentation
VASCULAR DISORDERS - Hypertension[3]

Note: AT13387 (Onalespib) 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.

7.2 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 4.0 will be utilized until March 31, 2018 for AE reporting. CTCAE version 5.0 will be utilized for AE reporting beginning April 1, 2018. All appropriate treatment areas should have access to a copy of the CTCAE version 5.0. A copy of the CTCAE version 5.0 can be downloaded from the CTEP web site http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

- **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 7.1.1) should be reported through CTEP-AERS only if the grade is above the grade provided in the SPEER.
  - Other AEs for the protocol that do not require expedited reporting are outlined in section 7.3.4.

- **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.

7.3 Expedited Adverse Event Reporting

Expedited AE reporting for this study must use CTEP-AERS (CTEP Adverse Event Reporting System), accessed via the CTEP Web site (https://eapps-ctep.nci.nih.gov/ctepaers). The reporting procedures to be followed are presented in the "NCI Guidelines for Investigators: Adverse Event Reporting Requirements for DCTD (CTEP and CIP) and DCP INDs and IDEs" which can be downloaded from the CTEP Web site (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/adverse_events.htm). These requirements are briefly outlined in the tables below (Section 7.3.2).

In the rare occurrence when 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 phoned in must be entered electronically into CTEP-AERS by the original submitter at the site.

7.3.1 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.

7.3.2 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 both routine and expedited reporting, regardless of causality. Attribution to treatment or other cause must be provided.

Death due to progressive disease should be reported as **Grade 5 "Disease progression"** under 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 **MUST** immediately report to the sponsor (NCI) **ANY** Serious Adverse Events, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64)
An adverse event is considered serious if it results in **ANY** of the following outcomes:

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

ALL SERIOUS adverse events that meet the above criteria MUST be immediately reported 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.

Effective Date: May 5, 2011

7.4 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.

7.5 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 CTEP-AERS. Three options are available to describe the event:

- Leukemia secondary to oncology chemotherapy (*e.g.*, acute myelocytic leukemia [AML])
- Myelodysplastic syndrome (MDS)
- 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.

7.6 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.

8 PHARMACEUTICAL INFORMATION

A list of the adverse events and potential risks associated with the investigational agents administered in this study can be found in Section 7.1.

8.1 CTEP IND Agent(s)

8.1.1 CTEP IND AT13387 (NSC 749712)

Chemical Name: **(**2,4-dihydroxy-5-isopropyl-phenyl)-[5-(4-methyl-piperazin-1-ylmethyl)-1,3-dihydro-isoindol-2-yl]-methanone, *L*-lactic acid salt

Other Name: AT13387AU, onalespib

Classification: Heat shock protein 90 (HSP90) inhibitor

Molecular Formula: $C_{24}H_{31}N_3O_3.C_3H_6O_3$ **M.W.:** 499.61

Mode of Action: AT13387 is a synthetic non-ansamycin small molecule that inhibits heat shock protein 90 (HSP90. HSP90 seems to affect multiple aberrant signaling pathways and therefore may be of clinical benefit in several cancer treatments.

How Supplied: AT13387 is supplied by Astex Pharmaceuticals Inc. and distributed by CTEP, NCI as a 265 mg free base equivalent (L-lactic acid salt) vial, containing white to off-white lyophilized powder. The agent is formulated in **pH 5.0 (red cap).**

Preparation: Reconstitute the 265 mg lyophilized powder with 10 mL of Sterile Water for Injection (SWFI) resulting in 25.7 mg/mL concentration (10.3 mL total volume). A sticky mass will be formed. Vigorously shake the vial. Agitate until the contents are fully dissolved (about 5 minutes). Leave the diluted vial at ambient temperature for 15-30 minutes to allow any foam to dissipate. If not used immediately, store the reconstituted vial(s) at 2^0 to 8^0 C not to exceed 8 hours.
Withdraw the calculated dose of AT13387 and further dilute it in 250 mL of D5W or 0.9% NS. The Prepared IV solution is compatible in PVC or non-PVC infusion bags.

Store the prepared IV solution refrigerated at 2^0 to 8^0 C not to exceed 8 hours if not used immediately. When removed from the refrigerator, allows the prepared IV solution to sit at room temperature between 15 to 30 minutes before administering to patients. The prepared IV solution must be used within 24 hours -i.e., from the time the drug vial is diluted to the time the IV administration is complete. Protection from light during the infusion period is not required.

Storage: Store the intact vials at 15^0 to 25ºC (59 to 77ºF). Protect from light.

If a storage temperature excursion is identified, promptly return AT13387 to 15^0 to 25ºC (59 to 77ºF) 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 surveillance of the intact vials is ongoing**.**

Route of Administration: Intravenous

Method of Administration: Infuse over 1 hour through a central line or a well-defined peripheral vein (Note: an in-line filter is NOT required). If use a peripheral line, be sure to aspirate venous blood prior to starting the infusion. Check the infusion site every 15 minutes. Change infusion site should evidence of swelling or discoloration is observed.

Potential Drug Interactions: AT13387 is a substrate of UGT with a relatively low affinity for UGT isoforms. In vitro data demonstrate that AT13387 is a weak inhibitor of UGT1A1, UGT1A3 and UGT1A9. AT13387 is also a weak inhibitor of CYP1A2, -3A4, -2D6, -2C9 and -2C19.

AT13387 appears to metabolize via the glucuronidation, sulphation and N-oxidation.

Pre-clinical studies suggest that AT13387 is a substrate of P-gp, the efflux ratios was above 2 (ranging from 3.4 to 4.6); a moderate inhibitor of BCRP (35.9% +/- 2%, p=0.0001) and P-gp (31.3% +/- 1.2%, p= 0.0009), and a strong inhibitor of MATE1 (94.6% +/- 0.2%, p=0.0001) and MATE2-K (91.2% +/- 1.2%, p= 0.0002).

Patient Care Implications: There are no genotoxicity, carcinogenicity, developmental and reproductive studies conducted with AT13387. Women of childbearing potential should not become pregnant or breastfeed and men should not father a child during the study. All subjects must use acceptable contraceptive measures during the treatment of AT13387 and 3 months after the last dose of the investigational drug.
Systemic infusion reactions (e.g., vomiting, itching skin, or swelling), slow the infusion and/or administer NS or D5W through a "Y" connector in parallel to AT13387 IV infusion. Pre-medication (e.g., dexamethasone, H-1 and H-2 antagonist) may be given before subsequent infusions and/or administer additional volume of 500 mL over 1 hour if medically appropriate.

Avoid extravasation. For local irritation, apply cold compress or topical pain medication.

Availability

AT13387 is an investigational agent supplied to investigators by the Division of Cancer Treatment and Diagnosis (DCTD), NCI. AT13387 is provided to the NCI under a Collaborative Agreement between the Pharmaceutical Collaborator and the DCTD, NCI (see Section 12.3).

AT13387 clinical drug development program is completed. The current clinical supply is expiring on May 31, 2020; thus, all patients must be off treatment by May 31, 2020.

8.1.2 CTEP IND 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

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 25 mg, 100 mg and 150 mg strengths.

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

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

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

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

Stability: Shelf-life studies are ongoing.
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.

Route and Method of Administration: Tablets are taken by mouth and can be taken with a light meal/snack if needed to reduce stomach irritation.

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

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

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

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

Patient Care Implications: Pre-clinical data indicate that olaparib adversely affects embryofetal survival and development. Therefore, women of child-bearing potential and their partners should agree to use two (2) highly effective forms of contraception throughout study participation and for at least one (1) month after the last dose of olaparib. Male study participants should avoid fathering a child or donating sperm during the study and for three (3) months after the last dose of olaparib. The study investigator should discuss the most appropriate forms of highly effective contraceptive methods for each patient.

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

8.1.3 Agent Ordering and Agent Accountability

8.1.3.1 NCI-supplied agents may be requested by the Principal Investigator (or their authorized designee) at each participating institution. Pharmaceutical Management Branch (PMB) policy requires that agent be shipped directly to the institution where the patient is to be treated. PMB does not permit the transfer of agents between institutions (unless prior approval from PMB is obtained). The CTEP-assigned protocol number must be used for ordering all CTEP-supplied investigational agents. The responsible investigator at each participating institution must be registered with CTEP, DCTD through an annual submission of FDA Form 1572 (Statement of Investigator), Curriculum Vitae, Supplemental Investigator Data Form (IDF), 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 investigator at that institution.

A starter supply is not allowed. A confirmation of patient enrollment is needed in the "Comments" field in OAOP for the initial drug shipment.

Active CTEP-registered investigators and investigator-designated shipping designees and ordering designees can 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 and a "current" password. 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.

8.1.3.2 Agent Inventory Records

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

8.1.3.3 Investigator Brochure Availability

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

8.1.3.4 Useful Links and Contacts

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

9 BIOMARKER, CORRELATIVE, AND SPECIAL STUDIES

Based on the results of our preclinical work, we hypothesize that the HSP90 inhibitor AT13387 will enhance the anticancer effects of the PARPi olaparib at tolerable doses in patients with advanced solid tumors.

During cycle 0, olaparib will be administered alone once daily for 1 week (D1-7). Then in cycle 1 and afterwards, olaparib will continue to be administered twice daily and AT13387 will be

administered for 2 consecutive days every week for 3 weeks of a 4 week cycle, i.e. on Days 1, 2, 8, 9, 15 and 16 of a 28 day cycle. Given that our hypothesis is that AT13387 sensitizes to olaparib by inhibiting HR, by administering olaparib alone for cycle 0 only, we can test this hypothesis as a "proof of mechanism" for the combination of AT13387 and olaparib. Specifically, we expect that there will be induction of BRCA1 and RAD51 foci after administration of olaparib alone and reduced formation of these foci and downregulation of expression of HR pathway genes after the combination of AT13387 and olaparib.

Three biopsies, one pretreatment, one after olaparib alone and one after one of the combinations of olaparib/AT13387 will be voluntary, but encouraged in the expansion and dose escalation cohorts.

9.1 Exploratory/Ancillary Correlative Studies

9.1.1 Collection, Shipping and Sites performing exploratory assays.

As a part of the eligibility criteria, only patients with available archival FFPE tissue (either one paraffin embedded tissue block OR 10 5-micron unstained slides from the block on regular [non-plus] slides and 1 H&E slide) will be accrued onto this study. This archival FFPE tissue specimen will be analyzed with the aforementioned assays (section 9.1).

On study biopsies collection: FFPE core biopsies (neutral buffered formalin) will be collected per institutional guidelines.

FFPE block or 10 unstained slides and on-study biopsies will be batch shipped to Dr. Panagiotis Konstantinopoulos (address below):

Jennifer Curtis
Dana-Farber Cancer Institute
450 Brookline Ave, Dana 116
Boston, MA 02215
Phone: 617-582-7183
Email: jennifer_curtis@dfci.harvard.edu

9.2 Clinical Pharmacology:

The pharmacokinetic study has been designed to assess the effect of olanespib on the steady state pharmacokinetics of olaparib and if the pharmacokinetics of olanespib is affected by the concurrent administration of olaparib. Pharmacokinetic sampling will be performed in all patients enrolled in the dose escalation and expansion cohorts to provide data that may be informative for dose escalation decisions and correlation analysis with clinical and pharmacodynamic data. Pharmacokinetic sampling will be performed to define the plasma concentration-time profile of olaparib over the dosing interval for the day 7 dose when given alone in cycle 0. Pharmacokinetic samples will also be collected over a 24 h interval on days 1

and 15 of cycle 1 to define the plasma profiles for olaparib and olanespib.

The sampling schedule has been devised to accommodate treatment on an outpatient basis. Patients will be instructed to take the two daily doses of olaparib at the same time every day during the pharmacokinetic study. The morning dose of olaparib should be taken at a time that will allow the patient to arrive at the clinical to obtain pharmacokinetic samples before dosing and to remain for an additional 8 hours. The second daily dose of olaparib should be taken approximately 12 hours after the morning dose. It is very important that the patient is aware that the morning dose of olaparib must not be taken before arriving at the clinic on cycle 0 day 7, cycle 1 day 1, and cycle 1 day 15. The olanespib i.v. infusion should be started at the same time that the patient takes the olaparib dose on days 1 and 15 of cycle 1. The first set of blood samples (3 mL) on cycle 0 day 7 will be obtained at the indicated times according to the PK Sample Collection Time Points table below. The second and third sets of blood samples (6 mL) on cycle 1 day 1 and cycle 1 day 15 will be obtained at the same time points as indicated by the PK Sample Collection Time Points table below, with one additional sample collected 30 min after completing the 1 h IV infusion of olanespib. Procedures for PK sample collection, processing, storage, and shipment is provided in Appendix G.

PK Sampling Schedule		
Visit	**Collection Time**	**Sample No.**
Cycle 0 Day 1	Pre-dose (0-5 min prior to first olaparib dose)	PK-00
Cycle 0 Day 7	Pre-dose (0-5 min prior to morning olaparib dose)	PK-01
Cycle 0 Day 7	0.5 h ± 5 min post-dose	PK-02
Cycle 0 Day 7	1.0 h ± 5 min post-dose	PK-03
Cycle 0 Day 7	1.5 h ± 5 min post-dose	PK-04
Cycle 0 Day 7	2.0 h ± 5 min post-dose	PK-05
Cycle 0 Day 7	3.0 h ± 5 min post-dose	PK-06
Cycle 0 Day 7	4.0 h ± 10 min post-dose	PK-07
Cycle 0 Day 7	6.0 h ± 10 min post-dose	PK-08
Cycle 0 Day 7	8.0 h ± 10 min post-dose	PK-09
Cycle 1 Day 1	Pre-dose (0-5 min prior to study medication dosing)	PK-10
Cycle 1 Day 1	0.5 h ± 5 min post-dose	PK-11
Cycle 1 Day 1	1.0 h ± 5 min post-dose	PK-12
Cycle 1 Day 1	1.5 h ± 5 min post-dose	PK-13
Cycle 1 Day 1	2.0 h ± 5 min post-dose	PK-14
Cycle 1 Day 1	3.0 h ± 5 min post-dose	PK-15
Cycle 1 Day 1	4.0 h ± 10 min post-dose	PK-16
Cycle 1 Day 1	6.0 h ± 10 min post-dose	PK-17
Cycle 1 Day 1	8.0 h ± 10 min post-dose	PK-18
Cycle 1 Day 2	Pre-dose (0-5 min prior to study medication dosing)	PK-19

Cycle 1 Day 15	Pre-dose (0-5 min prior to study medication dosing)	PK-20
Cycle 1 Day 15	0.5 h ± 5 min post-dose	PK-21
Cycle 1 Day 15	1.0 h ± 5 min post-dose	PK-22
Cycle 1 Day 15	1.5 h ± 5 min post-dose	PK-23
Cycle 1 Day 15	2.0 h ± 5 min post-dose	PK-24
Cycle 1 Day 15	3.0 h ± 5 min post-dose	PK-25
Cycle 1 Day 15	4.0 h ± 10 min post-dose	PK-26
Cycle 1 Day 15	6.0 h ± 10 min post-dose	PK-27
Cycle 1 Day 15	8.0 h ± 10 min post-dose	PK-28
Cycle 1 Day 16	Pre-dose (0-5 min prior to study medication dosing)	PK-29

10 STUDY CALENDAR

In pre-study/screen the baseline eye exam, physical examination, medical history, concomitant medications recorded, ECOG PS, complete blood count with differential and platelets, and clinical chemistry should be done ≤14 days prior to initiation of treatment. However, if these initial examinations are obtained within 3 days prior to the initiation of treatment they do not have to be repeated. Scans to document evaluable disease (i.e., tumor measurement) should be performed ≤ 28 days prior to initiation of treatment and should be performed as close to the start of treatment as possible.

Assessments must be performed prior to administration of any study agent.

No treatment window will be allowed for Cycle 0 and Cycle 1, however, Cycle 1 day 1 assessments can be done on day 7 of Cycle 0. A +/- 3 day window will be allowed for Cycle 2 Day 1 and subsequent treatment cycles Day 1. If Day 1 is adjusted, days 8 and 15 will be re-adjusted accordingly, A +/- 1 day window will be allowed for Day 8 and 15 of Cycle 2 and subsequent treatment cycles.

	Screen/ Baseline	**Cycle 0 (1 week)**	**Cycle 1 (4 Week Duration)**				**Cycle 2 and subsequent cycles (4 Week Duration)[j]**			**Off Treatment[h]**	**Follow-up [i]**
	Pre-Study/Screen	Day 1	Day 1	Day 8	Day 15	Day 22	Day 1 (+/- 3 days)	Day 8 (+/- 1 day)	Day 15(+/- 1 day)		
AT13387			Days 1,2	Days 8,9	Days 15,16		Day 1,2	Day 8,9	Day 15, 16		
olaparib		Days 1-7	Days 1-28				Days 1-28				
Informed consent	X										
Demographics	X										
Archival FFPE sample	X										
Medical history	X										
Concomitant Meds	X	X	X	X	X	X	X	X	X	X	
Physical exam	X	X	X	X	X	X	X		X	X	
Vital signs [a]	X	X	Days1, 2	Days 8,9	Days 15,16	X	Day 1, 2	Day 8, 9	Day 15, 16	X	
Height	X										
Performance status	X		X				X			X	
CBC w/diff, plts	X	X	X	X	X	X	X	X	X	X	
Serum Chemistry [b]	X	X	X	X	X	X	X	X	X	X	
Coagulation [c] (PT,PTT,INR)	X										
ECG (as indicated) [d]	X				X				X[d]		
Adverse event		X	X	X	X	X	X		X	X	

evaluation											
Echo/MUGA	X										
Eye Exam [e]	X	If ocular toxicity has occurred.									
B-HCG	X	X	X				X				
CT or MRI (chest, abdomen, pelvis) and Tumor Assessments (RECIST 1.1) [f]	X	CT scan and tumor assessment should be performed before cycle 3 and every 2 cycles (± 7 days) thereafter.								X	
Optional Tumor Biopsies [g]	X	X (Day 5 or 6 or 7)			X (+/- 5 days)						
PK		X	X		X						
Survival status											X

a. Vital signs will include resting heart rate, blood pressure, temperature and weight, and at the screening visit will include height. After Screening, height will not be measured. Vital signs and weight will be obtained prior to chemotherapy administration. Dosing of AT13387 will be based on the weight obtained on days 1, 8 and 15 of each cycle, and this weight can be used for dosing on the following day, that is, days 2, 9 and 16, respectively.
b. Clinical chemistry will include measurements of glucose, BUN, creatinine, sodium, magnesium, potassium, chloride, calcium, CO2, ALP, AST, ALT, total bilirubin, total protein, and albumin.
c. Coagulation studies will be performed at baseline only (PT or INR with PTT); they will be repeated beginning of every cycle if patient on coumadin.
d. ECGs will be performed in triplicate at 2-5 minute intervals. All ECGs after Cycle 2 will be performed on Day 1 of the cycle.
e. More frequent eye exams can be performed as clinically indicated. Pre-Study evaluation must include an ophthalmologic exam by an opthalmologist (not optometrist) and should minimally include visual acuity testing, slit lamp examination, and fundoscopic examination. Follow up eye-exams will only be performed if subjects develop/report any visual impairment. Visual impairment may include peripheral flashes (photopsia), blurred or double vision, floaters, color distortion and dimness, difficulties with light/dark accommodation, tunnel vision or other field defects, halos, apparent movement of stationary objects, and complex disturbances. Follow up eye-exams will minimally include visual acuity testing, slit lamp examination, and fundoscopic examination; additional testing will be based on symptoms, what is observed and ophthalmologist recommendations.
f. CT scans of the chest and abdomen and pelvis are required at baseline and every 2 cycles (± 7 days). The same method of assessment and the same technique must be used to characterize each identified and reported lesion at baseline and during subsequent imaging procedures. Patients continuing study treatment for a minimum of 1 year may have the tumor imaging assessments expanded to every 4 cycles (12 weeks [±7 days]). Patients with unacceptable toxicity should be discontinued from the study; patients with SD or response to therapy will continue treatment. Patients without evidence of undue toxicity may continue treatment with study drugs until disease progression occurs as long as they are achieving clinical benefit and desire to continue therapy. Patients with progressive disease per RECIST 1.1 will be discontinued from the study.
g. Refer to section 9.1 for details.
h. The End of Study Treatment Visit will be performed at the 30 day follow-up visit. Reassessments for toxicity, disease progression, and survival will be performed 30 days from last treatment dose.
i. Please see section 5.6 for specifics on Follow-up.
j. Patients who continue on olaparib monotherapy will have concomitant meds, physical exam, vital signs, CBC w/diff, platelets, serum chemistry, and adverse event evaluation on day 1 only of each cycle following AT13387 discontinuation.

11 MEASUREMENT OF EFFECT

Although the clinical benefit of Olaparib and AT13387 have 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. For the purposes of this study, patients should be re-evaluated every 8 or 9 weeks. In addition to a baseline scan,

confirmatory scans will also be obtained every 8 or 9 weeks following initial documentation of an objective response.

11.1 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 8 weeks (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) [*Eur J Ca* 45:228-247, 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.

11.1.1 Definitions

Evaluable for toxicity. All patients will be evaluable for toxicity from the time of their first treatment with olaparib and/or AT13387.

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.

11.1.2 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.

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.

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

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:

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

11.1.4 Response Criteria

11.1.4.1 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.

11.1.4.2 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).

11.1.4.3 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-CR/Non-PD/not evaluated	No	PR	
SD	Non-CR/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.
** A confirmation scan will be required for CR and PR responses.
*** 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

11.1.5 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.

11.1.6 Progression-Free Survival

PFS is defined as the duration of time from start of treatment to time of progression or death, whichever occurs first.

11.1.7 Response Review

For patients enrolled at DF/HCC sites, tumor metrics central imaging will serve as the reading for all radiographic imaging for this study. For patients enrolled at non-DF/HCC sites, assessment of response will be performed by the investigators in each site participating in the study.

11.2 Antitumor Effect – Hematologic Tumors

Not Applicable.

11.3 Other Response Parameters

Not Applicable.

12 STUDY OVERSIGHT AND DATA REPORTING / REGULATORY REQUIREMENTS

Adverse event lists, guidelines, and instructions for AE reporting can be found in Section 7.0 (Adverse Events: List and Reporting Requirements).

12.1 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.

For the Phase 1 portion of this study, all decisions regarding dose escalation/expansion/de-escalation require sign-off by the Protocol Principal Investigator through the CTMS/IWRS. In addition, for the Phase 1 portion, 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.

12.2 Data Reporting

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

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

Users that have not previously activated their iMedidata/Rave account at the time of initial site registration approval for the study in RSS will also receive a separate invitation from iMedidata

to activate their account. Account activation instructions are located on the CTSU website, Rave tab under the Rave resource materials (Medidata Account Activation and Study Invitation Acceptance). Additional information on iMedidata/Rave is available on the CTSU members' website under the Rave tab or by contacting the CTSU Help Desk at 1-888-823-5923 or by e-mail at ctsucontact@westat.com.

12.2.1 Method

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 on an 18-36 month basis as part of routine cancer center site visits. More frequent audits may be conducted if warranted by accrual or due to concerns regarding data quality or timely submission. For CTMS monitored studies, after users have activated their accounts, please contact the Theradex Help Desk at (609) 799-7580 or by email at CTMSSupport@theradex.com for additional support with Rave and completion of CRFs.

12.2.2 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.

An End of Study CRF is to be completed by the PI, and is to include a summary of study endpoints not otherwise captured in the database, such as (for phase 1 trials) the recommended phase 2 dose (RP2D), and a description of any dose-limiting toxicities (DLTs). 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).

12.3 CTEP Multicenter Guidelines

Not Applicable.

12.4 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.

12.5 Genomic Data Sharing Plan

Not applicable

13 STATISTICAL CONSIDERATIONS

13.1 Study Design/Endpoints

The phase I component of this study will employ a 3+3 design, escalating if 0/3 or 1/6 participants have a DLT during Cycles 0 and 1, at the discretion of the Principal Investigator.

The planned dose escalation and dose levels of olaparib and AT13387 for this study are outlined in Section 5.1. Additional dose levels or schedules may be tested based on ongoing phase I results and/or preclinical testing.

Safety:
Dose limiting toxicity (DLT) refers to toxicities experienced during cycles 0 and 1 of treatment. A DLT will be defined using the criteria in Section 5.2.
Probabilities of escalation in a 3+3 design are tabulated below for a series of assumed true toxicity rates (based on a binomial distribution):

True Toxicity Rate	**0.1**	**0.2**	**0.3**	**0.4**	**0.5**	**0.6**	**0.65**	**0.7**	**0.8**	**0.9**
Probability of Escalation	0.91	0.71	0.49	0.31	0.17	0.08	0.053	0.032	0.009	0.001

At least 6 patients will be treated at MTD, and no more than 1 patient should experience a DLT at the MTD level. Based on the exact binomial distribution, we would be unlikely to escalate the dose level (the probability is 0.053) if the true toxicity was 65% or greater.

To evaluate the properties of the 3+3 (x+y) escalation/de-escalation design, a simulation study was performed. In the simulation study, each dose-level was considered to be the 'true MTD', defined using a two-parameter logistic model for the dose-toxicity relationship of each agent. Using an intercept of 0.183 and slope of 1 on the log2-scale for each agent, the probability of a DLT at the true MTD of the combination would be the common assumption of 33.3% and odds would double with a doubling of either agent.

Dose level	**Olaparib dose**	**AT13387 dose**	**Probability or reaching**			
			True MTB	**No MTB**	**Below**	**Above ***
-4	50	10	0.459	0.408	n/a	0.133

-3	100	10	0.475	0.099	0.29	0.136
-2	50	20	0.439	0.098	0.343	0.12
-1	100	20	0.477	0	0.418	0.105
0	200	20	0.487	0	0.441	0.072
1	200	40	0.296	0	0.587	0.117
2	300	40	0.329	0	0.611	0.06
3	300	80	0.313	0	0.564	0.123
4	300	120	0.2	0	0.664	0.136
5	300	160	0.203	0	0.797	n/a
2a	200	80	0.187	0	0.538	0.275
2b	200	120	0.116	0	0.557	0.327
2c	200	160	0.11	0	0.656	0.234
-1a	100	40	0.35	0	0.536	0.114
-1b	100	80	0.199	0	0.598	0.203
-1c	100	120	0.141	0	0.634	0.225
-1d	100	160	0.169	0	0.727	0.104
-2a	50	40	0.342	0.042	0.479	0.137
-2b	50	80	0.224	0.039	0.546	0.191
-2c	50	120	0.139	0.03	0.65	0.181
-2d	50	160	0.15	0.029	0.72	0.101

* In the simulation study, dose levels are defined as being above the MTD if the probability of a DLT under the bivariable logistic model is greater than 33.3%.

13.2 Sample Size/Accrual Rate

Depending on the number of dose levels, it is anticipated that between 15 and 30 patients will be enrolled to the dose escalation portion of this study and an additional 20 patients with either TNBC or ovarian cancer will be enrolled in the dose expansion cohort. With 20 patients treated at the MTD, the probability of observing at least one serious toxicity event is 0.88 if the true toxicity rate is 10% and 0.64 if the true toxicity rate is as low as 5%. With 20 participants, the maximum width to a binomial exact 90% confidence interval is 0.456.

We anticipate that between 2-3 patients will be enrolled per month to this study. If the RP2D is at the highest dose level, we would expect a sample size of approximately 40 subjects. Therefore, recruitment for the current study will be done in approximately 12-18 months.

PLANNED ENROLLMENT REPORT

Racial Categories	**Ethnic Categories**				**Total**
	Not Hispanic or Latino		**Hispanic or Latino**		
	Female	**Male**	**Female**	**Male**	

Racial Categories	**Ethnic Categories**				**Total**
	Not Hispanic or Latino		**Hispanic or Latino**		
	Female	**Male**	**Female**	**Male**	
American Indian/ Alaska Native	0	0	0	0	**0**
Asian	2	0	0	0	**2**
Native Hawaiian or Other Pacific Islander	0	0	0	0	**0**
Black or African American	3	1	1	0	**5**
White	28	3	2	0	**33**
More Than One Race	0	0	0	0	**0**
Total	**33**	**4**	**3**	**0**	**40**

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13.3 Stratification Factors

There will be no stratification factors for this study. One expanded MTD cohort of epithelial ovarian, fallopian or primary peritoneal or triple negative breast cancer (TNBC) patients will be enrolled with one of the schedules, for confirmation of safety, PK and PD. A total of 20 patients will be enrolled in this expansion cohort.

13.4 Interim Analysis

For the dose expansion cohort, a continuous monitoring plan will be conducted following the method of Ivanova, et al[36] with Pocock-style boundaries for early stopping. Required input parameters are the proportion which represents a maximum-tolerated level of toxicity, θ, and the probability of early stopping , φ, if θ is true toxicity rate.

We specified $\theta = 0.333$ according to the MTD corresponding to the 3+3 design, and allow for a $\varphi = 0.2$ chance of early stopping. Boundaries are listed in the table below. If the number of subjects with toxicity reaches the specified limits, accrual of additional patients to this study will stop until satisfactory changes to the RP2D have been made to ensure subject safety

Number Enrolled	1-2	3	4-5	6-8	9-10	11-12	13-15	16-17	18-20

Number with an Adverse Event	-	3	4	5	6	7	8	9	10

The probabilities of stopping the trial early are presented below for a range of true adverse event rates:

True rate	**Probability of stopping early**
0.333	0.19
0.4	0.37
0.5	0.69
0.6	0.91
0.7	0.99
0.8	>0.99

13.5 Analysis of Secondary Endpoints

13.6 Reporting and Exclusions

13.6.1 Evaluation of Toxicity

All participants will be evaluable for toxicity from the time of their first treatment.

13.6.2 Evaluation of response

All participants included in the study must be assessed for response to treatment, even if there are major protocol treatment deviations or if they are ineligible. Each participant should be assigned one of the following categories:

1) complete response,
2) partial response,
3) stable disease,
4) progressive disease,
5) early death from malignant disease,
6) early death from toxicity,
7) early death because of other cause, or
9) unknown (not assessable, insufficient data).

By arbitrary convention, category 9 usually designates the "unknown" status of any type of data in a clinical database.
All of the participants who met the eligibility criteria and who receive at least one dose of study drug will be included in the main analysis of the response rate.

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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: PATIENT DRUG INFORMATION HANDOUT AND WALLET CARD

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

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

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

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

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

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

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

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

These are the things that you (the patient) and your prescribers need to know:

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

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

STUDY DRUG INFORMATION WALLET CARD

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

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

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

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

The patient _____ is enrolled on a clinical trial using the experimental study drug, **AT13387 (onalespib).** This clinical trial is sponsored by the National Cancer Institute (NCI). This form is addressed to the patient, but includes important information for others who care for this patient.

These are the things that your prescriber needs to know:

Pre-clinical data show that AT13387 (onalespib) interacts with certain specific enzymes in the liver and certain transport proteins that help move drugs in and out of cells.

The enzymes in question are UGT1A1, UGT1A3, UGT1A9 and CYP 1A2, 3A4, 2D6, 2C9, and 2C19.

- AT13387 (onalespib) is metabolized by UGT1A1 and UGT1A3 and may be affected by other drugs that inhibit or induce these enzymes.
- AT13387 (onalespib) is a "weak" inhibitor of UGT1A1, UGT1A3, UGT1A9 and CYP 1A2, 3A4, 2D6, 2C9, and 2C19 and may affect the metabolism of other drugs.
- The proteins in questions are P-gp, BCRP, MATE-1, and MATE2-K. AT13387 (onalespib) is a P-gp substrate and may be affected by other drugs that inhibit/induce P-gp. AT13387 is a "moderate inhibitor" of BCRP and P-gp, and a "strong inhibitor" of MATE1 and MATE2-K and may affect transport of other drugs in and out of cells.

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

AT13387 (onalespib) may interact with other drugs which can cause side effects. For this reason, it is very important to tell your study doctors of any medicines you are taking before you enroll onto this clinical trial. It is also very important to tell your doctors if you stop taking any regular medicines, or if you start taking a new medicine while you take part in this study. When you talk about your current medications with your doctors, include medicine you buy without a prescription (over-the-counter remedy), or herbal supplements such as St. John's Wort. It is helpful to bring your medication bottles or an updated medication list with you.
Many health care providers can write prescriptions. You must tell all of your health care providers (doctors, physician assistants, nurse practitioners, or pharmacists) you are taking part in a clinical trial.

These are the things that you (the patient) and your prescribers need to know:
AT13387 (onalespib) must be used very carefully with other medicines that need certain liver enzymes or transport proteins to be effective or to be cleared from your body. 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/moderate inhibitor/inducer or substrate of UGT1A1, UGT1A3, BCRP, P-gp, MATE1 and MATE2-K,

CYP1A2, -3A4, -2D6, -2C9, and -2C19."

- 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.
- Your regular health care provider should check a frequently updated medical reference or call your study doctor before prescribing any new medicine or discontinuing any medicine.
- Your study doctor's name is: _____ and he or she can be contacted at _____.

STUDY DRUG INFORMATION WALLET CARD

You are enrolled on a clinical trial using the experimental drug **AT13387 (onalespib).** This clinical trial is sponsored by the NCI. AT13387 interacts with drugs that are processed by your liver, or use certain transport proteins in your body. Because of this, it is very important to:

- Tell your doctors if you stop taking regular medicines or if you start taking any new medicines.
- Tell all of your health care providers (doctors, physician assistant, nurse practitioners, pharmacists) that you are taking part in a clinical trial.
- Check with your doctor or pharmacist whenever you need to use an over-the-counter medicine or herbal supplement.
- AT13387 (onalespib) interacts with drugs that are processed via UGT1A1, UGT1A3. It may also interact with transport proteins (P-gp, BCRP, MATE1, and MATE2K) and liver enzymes (CYP 1A2, -3A4, -2D6, -2C9, and -2C19); thus, it must be used very carefully with other medicines that interact with these enzymes and proteins.
- Before you enroll onto the clinical trial, your study doctor will work with your regular health care providers to review any medicines that are considered ""strong or moderate inducers/inhibitors" of these enzymes and protein transporters.
- Before prescribing new medicines, your regular health care providers should go to a frequently-updated medical reference for a list of drugs to avoid, or contact your study doctor.
- Your study doctor's name is _____ and can be contacted at _____.

APPENDIX C: KNOWN CYP3A4 INDUCERS AND INHIBITORS.

INVESTIGATORS SHOULD ALSO REFERENCE THE FOLLOWING WEBSITES FOR UPDATED INFORMATION REGARDING CYP3A4 INTERACTIONS:

CYP3A4 Inducers (prohibited)

Armodafenil[1]	Modafinil[2]	Primidone[1]
Barbiturates[2]	Nafcillin[1]	Rifabutin
Bosentan[1]	Nevirapine	Rifampin
Carbamazepine	Oxcarbazepine	Rifapentine[1]
Dexamethasone[1]	Pentobarbital[1]	St. John's wort[2]
Efavirenz	Phenobarbital	Troglitazone[3]
Fosphenytoin[1]	Phenytoin	
Glucocorticoids[2] (see note)	Pioglitazone[2]	

Note: Topical steroids are permitted. Please contact overall PI if systemic steroids are clinically indicated while on trial.

[1] Cited in Cytochrome P450 Enzymes: Substrates, Inhibitors, and Inducers. In: Lacy CF, Armstrong LL, Goldman MP, Lance LL, eds. Drug Information Handbook 20th ed. Hudson, OH; LexiComp Inc. 2011-2012: 1810-1818

[2] Cited in Flockhart DA. Drug Interactions: Cytochrome P450 Drug Interaction Table. Indiana University School of Medicine (2007). http://medicine.iupui.edu/clinpharm/ddis/table.asp. Accessed Nov 2011.

[3] Weak inhibitor per Lacy et al. May be used with caution.

Note: Drugs without a superscript are cited in both the Lacy and Flockhart references.

CYP3A4 Inhibitors

Strong Inhibitors (prohibited)	**Moderate Inhibitors (prohibited)**	**Weak Inhibitors** (use with caution, avoid if possible)
Amprenavir[1]	Amiodarone[1]	Chloramphenicol[2]
Atazanavir[1]	Aprepitant	Ciprofloxacin[2]
Clarithromycin	Cimetidine[1]	Diethyldithiocarbamate[2]
Conivaptan[1]	Clotrimazole[1]	Fluvoxamine[2]
Delavirdine[1]	Cyclosporine[1]	Gestodene[2]
Fosamprenavir[1]	Desipramine[1]	Mibefradil[2]
Fospropofol[1]	Doxycycline[1]	Mifepristone
Imatinib[1]	Efavirenz[1]	Norfluoxetine[2]
Indinavir	Erythromycin	Star fruit[2]
Isoniazid[1]	Fluconazole	Troleandomycin[2]
Itraconazole	Fosaprepitant[1]	
Ketoconazole	Grapefruit juice	
Miconazole[1]	Haloperidol[1]	
Nefazodone	Lidocaine[1]	
Nelfinavir	Metronidazole[1]	
Nicardipine[1]	Norfloxacin[1]	
Posaconazole[1]	Sertraline[1]	
Propofol[1]	Tetracycline[1]	
Quinidine[1]	Verapamil	
Ritonavir	Voriconazole[1]	
Saquinavir[2]		
Telithromycin		

[1] Cited in Cytochrome P450 Enzymes: Substrates, Inhibitors, and Inducers. In: Lacy CF, Armstrong LL, Goldman MP, Lance LL, eds. Drug Information Handbook 20th ed. Hudson, OH; LexiComp Inc. 2011-2012: 1810-1818

[2] Cited in Flockhart DA. Drug Interactions: Cytochrome P450 Drug Interaction Table. Indiana University School of Medicine (2007). http://medicine.iupui.edu/clinpharm/ddis/table.asp. Accessed Nov 2011.

Note: Drugs without a superscript are cited in both the Lacy and Flockhart references.

APPENDIX D: List of QT prolonging drugs to be used with caution

This table does not contain an exhaustive list of drugs with QT-prolongation. The drug list is frequently updated and the following website should be checked for the most current information as needed: https://www.crediblemeds.org/index.php.

List of QT prolonging drugs to be used with caution		
Drug	**QT risk**	**Comment**
Alfuzosin	possible risk for Torsades de Pointes	
Amantadine	possible risk for Torsades de Pointes	
Amitriptyline	conditional risk for Torsades de Pointes	
Azithromycin	possible risk for Torsades de Pointes	
Chloral hydrate	possible risk for Torsades de Pointes	
Citalopram	conditional risk for Torsades de Pointes	
Clomipramine	conditional risk for Torsades de Pointes	
Clozapine	possible risk for Torsades de Pointes	
Desipramine	conditional risk for Torsades de Pointes	
Diphenhydramine	conditional risk for Torsades de Pointes	
Dolasetron	possible risk for Torsades de Pointes	
Doxepin	conditional risk for Torsades de Pointes	
Dronedarone	possible risk for Torsades de Pointes	
Felbamate	possible risk for Torsades de Pointes	
Flecainide	possible risk for Torsades de Pointes	
Fluoxetine	conditional risk for Torsades de Pointes	
Foscarnet	possible risk for Torsades de Pointes	
Fosphenytoin	possible risk for Torsades de Pointes	
Galantamine	conditional risk for Torsades de Pointes	
Gatifloxacin	possible risk for Torsades de Pointes	
Gemifloxacin	possible risk for Torsades de Pointes	
Granisetron	possible risk for Torsades de Pointes	
Imipramine	conditional risk for Torsades de Pointes	
Indapamide	possible risk for Torsades de Pointes	
Isradipine	possible risk for Torsades de Pointes	
Levofloxacin	possible risk for Torsades de Pointes	
Lithium	possible risk for Torsades de Pointes	
Mexiletine	conditional risk for Torsades de Pointes	
Moexipril/HCTZ	possible risk for Torsades de Pointes	

List of QT prolonging drugs to be used with caution		
Drug	**QT risk**	**Comment**
Moxifloxacin	possible risk for Torsades de Pointes	
Nicardipine	possible risk for Torsades de Pointes	
Nortriptyline	conditional risk for Torsades de Pointes	
Octreotide	possible risk for Torsades de Pointes	
Ofloxacin	possible risk for Torsades de Pointes	
Ondansetron	possible risk for Torsades de Pointes	
Oxytocin	possible risk for Torsades de Pointes	
Paliperidone	possible risk for Torsades de Pointes	
Paroxetine	conditional risk for Torsades de Pointes	
Perflutren lipid microspheres	possible risk for Torsades de Pointes	
Protriptyline	conditional risk for Torsades de Pointes	
Ranolazine	possible risk for Torsades de Pointes	
Risperidone	possible risk for Torsades de Pointes	
Roxithromycin*	possible risk for Torsades de Pointes	*not available in the United States
Sertindole	possible risk for Torsades de Pointes	
Sertraline	conditional risk for Torsades de Pointes	
Solifenacin	conditional risk for Torsades de Pointes	
Tizanidine	possible risk for Torsades de Pointes	
Trazodone	conditional risk for Torsades de Pointes	
Trimethoprim-Sulfa	conditional risk for Torsades de Pointes	
Trimipramine	conditional risk for Torsades de Pointes	
Venlafaxine	possible risk for Torsades de Pointes	
Ziprasidone	possible risk for Torsades de Pointes	
(*) Classification according to the Qtdrugs.org Advisory Board of the Arizona CERT		

APPENDIX E: List of Prohibited QT-Prolonging Drugs

All QT-prolonging drugs listed in Appendix E are prohibited for all participants from screening through permanent discontinuation of study treatment. This Appendix lists drugs with a known risk for Torsades de Pointes (TdP) as well as sensitive CYP3A substrates (with narrow TI) with a possible or conditional risk for TdP.

This table does not contain an exhaustive list of drugs with QT-prolongation. The drug list is frequently updated and the following website should be checked for the most current information as needed: https://www.crediblemeds.org/index.php.

List of Prohibited QT-Prolonging Drugs

Drug	QT risk(*)	Comment
Amiodarone	Known risk for TdP	Females>Males,TdP risk regarded as low
Arsenic trioxide	Known risk for TdP	
Astemizole	Known risk for TdP	No Longer available in U.S.
Bepridil	Known risk for TdP	Females>Males
Chloroquine	Known risk for TdP	
Chlorpromazine	Known risk for TdP	
Cisapride	Known risk for TdP	Restricted availability; Females>Males.
Disopyramide	Known risk for TdP	Females>Males
Dofetilide	Known risk for TdP	
Domperidone	Known risk for TdP	Not available in the U.S.
Droperidol	Known risk for TdP	
Halofantrine	Known risk for TdP	Females>Males
Haloperidol	Known risk for TdP	When given intravenously or at higher-than-recommended doses, risk of sudden death, QT prolongation and torsades increases.
Ibutilide	Known risk for TdP	Females>Males
Levomethadyl	Known risk for TdP	
Mesoridazine	Known risk for TdP	
Methadone	Known risk for TdP	Females>Males
Pentamidine	Known risk for TdP	Females>Males
Pimozide	Known risk for TdP	Females>Males

List of Prohibited QT-Prolonging Drugs

Drug	QT risk(*)	Comment
Probucol	Known risk for TdP	No longer available in U.S.
Procainamide	Known risk for TdP	
Quetiapine	Possible risk for TdP	Prohibited as this drug is a sensitive 3A4 substrate
Quinidine	Known risk for TdP	Females>Males
Sotalol	Known risk for TdP	Females>Males
Sparfloxacin	Known risk for TdP	
Tacrolimus	Possible risk for TdP	Prohibited as this drug is a sensitive 3A4 sibstrate with narrow TI
Terfenadine	Known risk for TdP	No longer available in U.S.
Thioridazine	Known risk for TdP	
Vardenafil	Possible risk for TdP	Prohibited as this drug is a sensitive 3A4 substrate

(*) Classification according to the Qtdrugs.org Advisory Board of the Arizona CERT

Sensitive substrates: Drugs whose plasma AUC values have been shown to increase 5-fold or higher when co-administered with a potent inhibitor of the respective enzyme.

APPENDIX F: PATIENT'S PILL DIARY: olaparib

Today's Date _____ Cycle #_____

Patient Name_____ Patient Study ID _____
(*initials acceptable for patient's name)*

INSTRUCTIONS TO THE PATIENT:

1. You will take ___ (number) ____mg (dosage) tablet(s)twice a day 12 hours apart..
2. Complete one form for each cycle (28 days). Record the date, the number of tablets you took, and when you took them.
3. Tablets **cannot** be chewed, dissolved or crushed.
4. Tablets are taken by mouth and can be taken with a light meal/snack if needed to reduce stomach irritation.
5. If you **vomit a dose**, please record in the diary. Replace the dose ONLY if you can see **all of the intact tablets**. If you **forget** to take your dose and it is **2 hours past** your scheduled dose, then record in your diary and do NOT make up the missed dose.
6. Please bring your pill bottle (including empty bottles) and this form to your physician when you go for your next appointment.

Day	Date	# of tablets and when taken: olaparib					Day	Date	# of tablets and when taken: olaparib				
		25mg	100mg	150mg	Time AM	Time PM			25mg	100mg	150mg	Time AM	Time PM
1							15						
2							16						
3							17						
4							18						
5							19						
6							20						
7							21						
8							22						
9							23						
10							24						
11							25						
12							26						
13							27						
14							28						

Patient's Signature: _____ Date: _____

Physician's Office will complete this section:

1.Date patient started protocol treatment_____ Date patient was removed from study _____

2.Patient's planned daily dose_____ Total number of tablets taken this month _____

Physician/Nurse/Data Manager's Signature _____

_____

APPENDIX G: PHARMACOKINETIC SAMPLE COLLECTION AND HANDLING

1. Do not collect pharmacokinetic blood samples from the catheter used to infuse olanespib, including the port of a multi-lumen catheter that was not used for infusing the drug.

2. When using a peripheral catheter for sampling, use a syringe to clear the catheter of the lock solution approximately 1 min before the specified sample time and withdraw about 0.5 mL of blood into the syringe for disposal.

3. Collect samples in a 3.0 mL (cycle 0) or 6.0 mL (cycle 1) plastic purple stoppered Vacutainer tube with spray dried K2EDTA.

4. Immediately after filling the tube, gently invert the collection tube 5-times to thoroughly mix the blood with the anticoagulant and place the tube on wet ice until centrifuged.

5. Centrifuge at 1,500 x g for 10 min at 4°C within 30 min after collection.

6. Use a disposable pipette to transfer the plasma, removed without disturbing the blood cells, equally into two (2) 2.0 mL self-standing polypropylene cryogenic storage vials with external threads for Aliquot A and Aliquot B.

7. Affix a computer printed label with the following information onto the tube: CTEP Protocol No., Subject Study No., Sample No., Aliquot #. Orient the label crosswise toward the upper part of the tube being careful not to overlap the vial cap. Wrap the label with polyester protective label tape (Fisher Scientific, cat. no. 11-867B) to prevent the label from detaching from the vial when stored frozen.

8. Immediately place the cryovials in crushed dry ice until transferred to an ultralow temperature freezer (≤-70°C) for storage until shipment.

9. Ship the complete set of "Aliquot A" samples for each patient after the last sample has been collected. Ship the Aliquot B samples separately after verifying receipt of the Aliquot A samples. Do not send the Aliquot A and Aliquot B samples for the same patient in the same package.

10. Place the sample tubes for each patient in a separate zip lock plastic bag and seal the bag.

11. Put at least three inches of crushed dry ice in a seamless styrofoam container.

12. Place the plastic bag(s) containing the samples in the box, on top of the crushed dry ice, and cover with an additional three inches or more of dry ice.

13. Seal the styrofoam container within a tight-fitting cardboard shipping box.

14. Send the samples on Monday to Wednesday by overnight courier for delivery by 10:00 a.m. on the following day. **Never ship samples on a Thursday or Friday.**

15. Recipient address: Dr. Jeffrey G. Supko

Massachusetts General Hospital
55 Fruit St., GRJ 1025
Boston, MA 02114
Tel: 617-724-1970

16. Notification of the shipment and the courier tracking no. must be made by sending and e-mail to the following: (1) MGHCCPOSPL@partners.org; and (2) jsupko@partners.org. Attached a scanned copy of the Pharmacokinetic Time Record for all samples in the shipment to the email.

APPENDIX H: DIARRHEA MANAGEMENT

Diarrhea is a common problem experienced by many patients and is a risk with olaparib as well as AT13387. If it is not controlled quickly, it can lead to dehydration.

WHEN TO CALL YOUR DOCTOR TO REPORT DIARRHEA

- Fever 100.5° or higher with diarrhea.
- If you are experiencing diarrhea for the first time after starting therapy. Based on questions answered during that phone call, we will advise starting Imodium AD if it seems the symptoms are related to the treatment.
- If you still have diarrhea 24 hours after starting Imodium AD (your doctor may advise additional medications or want to evaluate you in person if there is a concern that you are becoming dehydrated).

OVER THE COUNTER MEDICATION MANAGEMENT OF DIARRHEA:

- For diarrhea that occurs more than 2 episodes a day, use **Imodium AD.** We recommend that you have Imodium AD on hand at home before starting therapy.
  - 1st episode of diarrhea: Take 2 caplets (4mg)
  - During the day: Take 1 caplet (2mg) after each episode of diarrhea
  - During the night: Take 2 caplets (4mg) at bedtime if you are still having diarrhea

DRINK PLENTY OF FLUIDS

- Drink 8 to 10 large glasses of liquids a day to replace those lost by diarrhea. Drink small quantities at a time slowly.
- **AVOID** caffeinated, very hot, or very cold fluids
  Examples of fluids:
  - **Water (**should only be part of the 8 to 10 glasses a day)
  - **Jello**
  - **Gatorade**
  - **Clear soup** or **broth**

EAT SMALL MEALS OFTEN

- A good choice of foods for diarrhea is the BRAT diet:
  - **B**- bananas
  - **R**- rice
  - **A**- apple sauce
  - **T**- toast
- When these foods are being well tolerated, then you can add other bland low fiber foods such as:
  - Chicken- white meat without the skin, steamed rice, crackers, white bread, pasta noodles without sauce, and canned or cooked fruits without skins
  - Foods high in potassium: bananas, apricots without skin, peach nectar, potatoes without skin, broccoli, halibut, mushrooms, asparagus, non-fat milk
- Foods that can make diarrhea and cramping worse:
  - Fatty, fried, greasy, or spicy foods can cause more problems and discomfort
  - High-fiber foods: bran, whole grain cereals, dried fruit, fruit skins, popcorn, nuts and vegetables
  - Foods that cause gas: Beer, beans, cabbage, carbonated drink