Abbreviated Title: EP0057 in Advanced Cancers
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Title: A Phase I/II Trial of EP0057, a Nanoparticle Camptothecin with Olaparib in Patients with Relapsed/Refractory Small Cell Lung, Bladder and Prostate Cancers

NCI Principal Investigator: Anish Thomas, MBBS, M.D.
Developmental Therapeutics Branch (DTB)
Center for Cancer Research (CCR)
National Cancer Institute (NCI)
10 Center Drive, Room 4-5330
Bethesda, MD 20892
Phone: 240-760-7343
E-mail: anish.thomas@nih.gov

Drug Name:	EP0057 (formerly CRLX101)	Olaparib
IND Number:	130102	130102
Sponsor:	Center for Cancer Research	Center for Cancer Research
Manufacturer:	Ellipses Pharma Limited	AstraZeneca
Supplier:	Ellipses Pharma Limited	AstraZeneca

PRÉCIS

Background:

- Small cell lung cancer (SCLC) is an aggressive cancer with a poor prognosis.
- Although highly responsive to chemotherapy initially, SCLC relapses quickly and becomes refractory to treatment within a few months.
- Urothelial Carcinoma (UC) of the Bladder is the fourth most common malignancy in men and the ninth most common in women.
- Prostate cancer is the most common cancer among men in the United States. While prostate cancer is initially responsive to androgen deprivation therapy (ADT), the median duration of sensitivity is 24-36 months. Moreover, patients develop resistance to current treatment options.
- The use of PARP inhibitors in combination with chemotherapy builds upon pre-clinical data in lung cancer and other cancers supporting the notion that PARP inhibitors potentiate the effect of DNA damaging therapies.
- Despite their highly synergistic activity in preclinical models, human studies combining PARP inhibitors and camptothecins have not translated into clinical benefit due to enhanced toxicity with the combination.
- One approach to improve ability to combine camptothecins with agents that sensitize their activity like PARP inhibitors is to use alternative formulations that minimize toxicity to the normal tissues.
- EP0057 is a nanoparticle drug conjugate composed of 20 (S)-camptothecin (a potent and highly selective topoisomerase I inhibitor) conjugated to a linear, cyclodextrin-polyethylene glycol-based polymer.
- Olaparib is a PARP inhibitor indicated as monotherapy in patients with deleterious or suspected deleterious germline BRCA mutated advanced ovarian cancer who have been treated with three or more prior lines of chemotherapy. Olaparib has an established safety profile and it is under investigation in a number of different cancers.

Objectives:

- Phase I: To determine the MTD/recommended Phase 2 dose (RP2D) of EP0057 in combination with olaparib in patients with refractory cancers.
- Phase II: To determine the antitumor activity of olaparib plus EP0057 with respect to progression free survival at 16 weeks in SCLC patients with resistant or sensitive relapse.
- Expansion Cohorts: To determine overall response rate of EP0057 plus olaparib in patients with mCRPC and urothelial carcinoma.

Eligibility:

<u>Phase I</u>

- Adult patients ≥18 years of age

- Histologically or cytologically confirmed, advanced solid tumor that is refractory to standard therapy and/or for whom no further standard therapy is available
- ECOG Performance Status of 0, 1 or 2

Phase II

- Adult patients ≥ 18 years old
- Have a pathologically (histology or cytology) confirmed diagnosis of SCLC
- Disease progression on or after at least one platinum-based standard chemotherapy regimen and/or an immune-checkpoint inhibitor for either limited or extensive stage disease.
- Have measurable disease per RECIST 1.1
- ECOG performance status of 0, 1 or 2

Phase II Expansion Cohorts

- Have a pathologically (histology or cytology) confirmed diagnosis of urothelial carcinoma or metastatic, progressive, castrate resistant prostate cancer (mCRPC)
- Disease progression on or after at least one platinum-based standard chemotherapy regimen and/or an immune-checkpoint inhibitor (except prostate cohort)
- Have measurable disease per RECIST 1.1 (except prostate cohort)
- Prior treatment with enzalutamide and/or abiraterone (prostate cancer cohort only)
- Patients must have castrate levels of testosterone (<50 ng/dl [1.74 nmol/l]) (Prostate cohort only)

Design:

- Patients meeting eligibility criteria will receive EP0057 (IV Q 2weeks) plus olaparib (PO BID days 3-13 and days 17-26 administered in 28-day cycles, until disease progression or development of intolerable side effects. The MTD of the combination will be used in Phase II.
- Patients in Phase II will receive, the RP2D at DL4R EP0057 12 mg/m2 and olaparib 250 mg BID.
- Blood, tumor and hair samples will be collected at multiple time points for PK, PD analyses. Hair sample collection is optional. Tumor biopsies are optional for SCLC and UC patients and mandatory for mCRPC patients (only baseline biopsy is mandatory).
- Toxicity will be graded according to CTCAE version 4.0.
- Tumor assessments will be made using CT scans (chest, abdomen and pelvis) at baseline and after every 2 cycles (3 cycles for mCRPC) according to RECIST version 1.1.
- After discontinuation of study treatment, follow-up for survival will be carried out every 3 months.

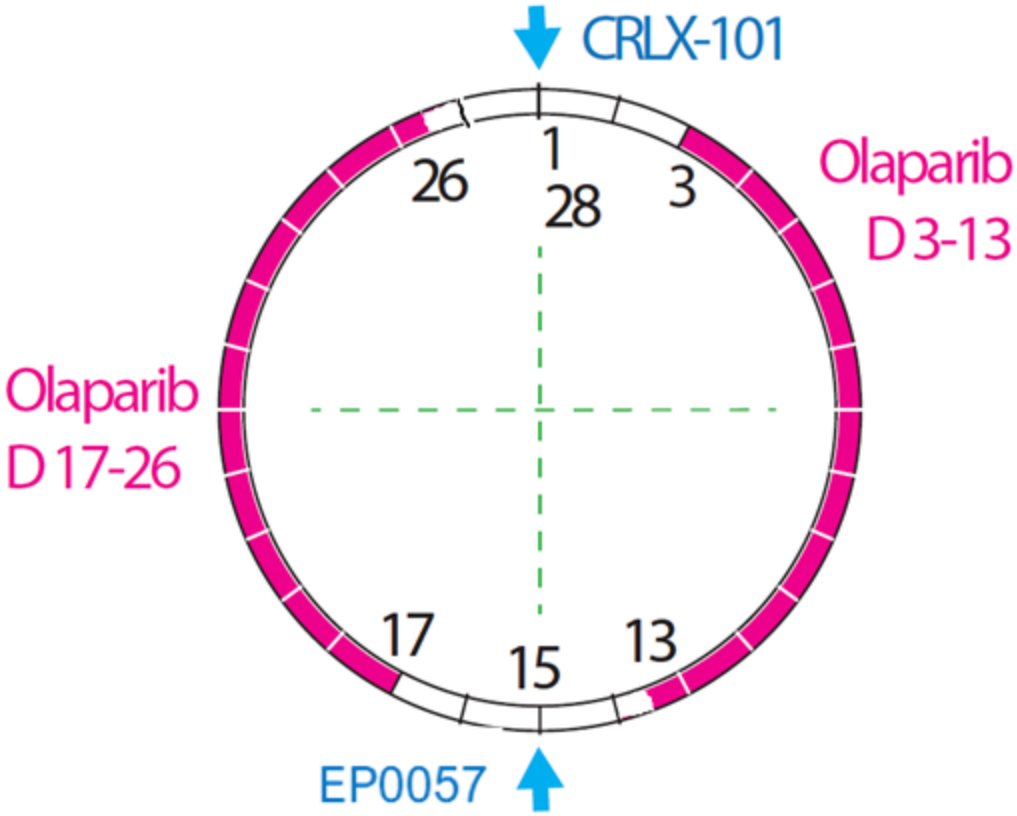
Trial schema and dose escalation

Provisional Dose levels	EP0057, mg/m2 (IV q 2 weeks D1 and D15)	Olaparib tablet, mg (PO BID Days 3-13* and 17-26*)
1	12	100
2	12	150
3	12	200
4	12	300**
$4R_{(educed)}$ (MTD/RP2D)	12	250
5 (Not explored)	15	300
5B (Not explored)	15	300

28-day cycles; biopsies pre-treatment and on day 4 (24 hours post- olaparib) and at disease progression.
* There should be a minimum 48-hour window between EP0057 and olaparib except dose level 5B which allows the interval to be abbreviated to 24 hours.

The recommended phase 2 dose (RP2D) may be lower than, or equal to, the MTD. Phase II portion of this study may start with RP2D, and/or at MTD.

** An additional dose level (4R) of 250 mg has been evaluated with DLTs in 1 of 6 patients as there were 2 or more DLTs among 6 patients treated at dose level 4.


CRLX-101
Olaparib
D 3-13
Olaparib
D 17-26
EP0057
1
3
13
15
17
26
28

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STATEMENT OF COMPLIANCE

The trial will be carried out in accordance with International Council for Harmonisation Good Clinical Practice (ICH GCP) and the following:

- United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, 21 CFR Part 312, and/or 21 CFR Part 812)

National Institutes of Health (NIH)-funded investigators and clinical trial site staff who are responsible for the conduct, management, or oversight of NIH-funded clinical trials have completed Human Subjects Protection and ICH GCP Training.

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the Institutional Review Board (IRB) for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. In addition, all changes to the consent form will be IRB-approved; an IRB determination will be made regarding whether a new consent needs to be obtained from participants who provided consent, using a previously approved consent form.

1 INTRODUCTION

1.1 STUDY OBJECTIVES

1.1.1 Primary Objectives

1.1.1.1 Phase I: To determine the MTD/recommended Phase 2 dose (RP2D) of EP0057 plus olaparib in patients with refractory cancers.

1.1.1.2 Phase II: To determine the antitumor activity of olaparib plus EP0057 with respect to progression free survival 16 weeks in SCLC patients with resistant or sensitive relapse

1.1.1.3 Phase II Expansion Cohorts: To determine overall response rate of EP0057 plus olaparib in patients with mCRPC and urothelial carcinoma

1.1.2 Secondary Objectives

Phase I and Phase II Cohorts:

1.1.2.1 To determine the duration of response (DOR), overall survival (OS), and progression-free survival (PFS) of the combination.

1.1.2.2 To further explore safety for combination.

Phase II Expansion Cohorts:

1.1.2.3 To determine safety and progression-free survival (PFS) in patients with mCRPC and urothelial carcinoma.

1.1.2.4 To determine duration of response and PSA responses in patients with mCRPC.

1.1.3 Exploratory Objectives

Phase I and Phase II Cohorts:

1.1.3.1 To explore possible correlations between clinical response and biomarkers

Phase II Expansion Cohorts:

1.1.3.2 To determine correlation between molecular markers and clinical outcomes (ORR and PFS) in urothelial carcinoma patients.

1.1.3.3 To explore pharmacodynamic changes in immune characteristics in tumor, circulating tumor cells (CTCs), and PBMCs in response to treatment of patients with mCRPC.

1.1.3.4 To evaluate the pharmacokinetic profile of EP0057 (both the total drug and released camptothecin) and olaparib in plasma.

1.1.3.5 To evaluate the pharmacodynamic (PD) activity of EP0057 in blood, surrogate tissue and tumor biopsy specimens.

1.2 BACKGROUND AND RATIONALE

1.2.1 Small Cell Lung Cancer

Small cell lung cancer (SCLC) is an aggressive cancer with a poor prognosis. Annually there are approximately 34,000 new cases in the United States alone. SCLC is characterized by rapid doubling time, high growth fraction and early and widespread metastatic involvement. Approximately two thirds of patients present with extensive-stage disease with tumor

involvement of contralateral lung, liver, adrenal glands, brain, bones and/or bone marrow. The median survival of patients with extensive-stage SCLC (ES-SCLC) ranges from 8 to 13 months. Less than 5% of patients survive two years and less than 2% of patients survive five years after diagnosis.

Standard therapy for patients with ES-SCLC consists of platinum and etoposide followed by prophylactic cranial irradiation in patients with a response (2). Although highly responsive to chemotherapy initially, SCLC relapses quickly and becomes refractory to treatment within a few months. There is only one FDA approved treatment for patients with relapsed SCLC after first-line chemotherapy: topotecan, a camptothecin which inhibits relegation of topoisomerase I-mediated single-strand DNA breaks leading to lethal double-strand DNA breaks. In patients with disease that is refractory to or relapsed after first-line chemotherapy, the median survival ranges from 2 to 6 months.

Patients with disease progression during or after their initial treatment are classified into categories based on the treatment free intervals from the initial chemotherapy. Sensitive relapse is tumor progression that occurs 90 days or more after the last day of initial chemotherapy. Resistant relapse is tumor progression that occurs within 90 days of the last day of initial chemotherapy. Refractory relapse is when tumor progresses during the initial therapy or did not respond to initial therapy. These parameters have been found to be independent predictors of probability of responding to second-line chemotherapy (3).

The standard treatment of ES-SCLC today reflects the prevailing state-of-the-art from the early 1980s. Among the many strategies that have been evaluated unsuccessfully over the last three decades are dose-dense chemotherapy regimens, addition of a third drug to standard two drug chemotherapies, alternating non-cross resistant chemotherapy regimens, maintenance therapy and more recently targeted therapies. Not unexpectedly, the outcomes for these patients have not significantly changed over this time. Clearly there is a critical need for newer therapeutic approaches for patients with SCLC.

1.2.2 Urothelial Carcinoma (UC) of the Bladder

In the United States, urothelial carcinoma (UC) of the bladder is the fourth most common malignancy in men and the ninth most common in women, with 76,960 new cases and 31,540 deaths estimated for 2016 (4). Although UC is a chemo-sensitive malignancy, there is no FDA-approved second-line therapy that have demonstrated a survival benefit in patients who have progressed after first-line platinum-based chemotherapy. Second-line trials with cytotoxic agents have generally yielded discouraging response rates with a median progression-free survival (PFS) of 2–3 months and a median overall survival (OS) of 6–9 months (5-9).

Two immune-checkpoint inhibitors have been FDA-approved as second-line therapy for patients with metastatic UC after disease progression following or during platinum-containing chemotherapy. Atezolizumab, an anti-programmed death-ligand 1 (PD-L1) humanized monoclonal antibody, showed an overall response rate (ORR) confirmed by independent review of 14.8% (95% CI: 11.1-19.3) in all treated patients (10) and nivolumab, a PD-1 humanized monoclonal antibody, that has demonstrated ORR of 19.6% (95% CI, 15.1 - 24.9). The estimated median duration of response was 10.3 months with nivolumab (11). Unfortunately, only a subset of patients with metastatic UC benefit from immune-checkpoint inhibitors highlighting the need to develop novel therapies to treat such population.

Specific genes involved in the DNA damage response (DDR) are mutated in UC increasing the genomic instability of cancer cells. Nickerson and colleagues at the National Cancer Institute, the TCGA, and other investigators have recognized that a marked number of somatic and germline mutations in genes encoding proteins involved in the DNA-repair pathway are present in UC (roughly 30% of cases) (**Table 1**) (12-14) These events may render UC particularly sensitive to inhibition of PARP in homologous recombination DNA repair, creating opportunities for synthetic lethality or synergistic cytotoxicity (potentiate the effect of other DNA damaging therapies).

Table 1. Summary of observed somatic/germline mutations frequencies in UC of the bladder

	Yap, K.L.; et al. (Whole-exome sequencing) Somatic Mutations % (n)	Nickerson, M.; et al. (Exome and Sanger sequencing of tumor-normal DNA) Somatic Mutations % (n)	Nickerson, M.; et al. (Exome and Sanger sequencing of tumor-normal DNA) Germline Mutations % (n)
TP53	40.7% (33/81)	9.2% (5/54)	-
KDM6A	17% (21/81)	22.2% (12/54)	3.7% (2/54)
BAP1	NA	15% (8/54)	1.8% (1/54)
TSC1	12.3% (10/81)	3.7% (2/54)	-
ATM	12.3% (10/81)	7.4% (4/54)	1.8% (1/54)
UNC5C	9.9% (8/81)	NA	-
BRCA2	8.6% (7/81)	1.8% (1/54)	9.2% (5/54)
ERCC2	6.2% (5/81)	NA	-
FANCD2	4.9% (4/81)	NA	-
PALB2	4.9% (4/81)	3.7% (2/54)	5.5% (3/54)
BRAC1	3.7% (3/81)	3.7% (2/54)	1.8% (1/54)

PARP inhibitors (PARPi) such as olaparib are highly effective in combination with camptothecins in tumors with and without defects in homologous recombination. (15-17) In the case of UC, studies of human xenograft in vivo models and clinical studies have confirmed activity of irinotecan (CPT) and its combinations in human urothelial tumors. In the clinical setting, gemcitabine combined CPT has demonstrated to be with manageable toxicities in cisplatin-ineligible patients with locally-advanced or metastatic UC(18). Other clinically evaluated combination with irinotecan includes mitomycin, fluorouracil, and CPT in cisplatin-pretreated and cisplatin-ineligible metastatic UC patients. This regimen demonstrated modest activity with an overall response rate of 19%(19).

EP0057 is a novel nanoparticle consisting of camptothecin (10% by weight) conjugated to a biocompatible copolymer of cyclodextrin and polyethylene glycol designed to maximize CPT efficacy without problematic hematologic toxicity. This offers a unique opportunity to revisit the use of topoisomerase-1 inhibitors for urothelial carcinoma treatment.

The observation that the administration of an agent that acts to inhibit the repair of single strand DNA damage, such as olaparib, will potentiate DNA damage and increase the potency of

topoisomerase-1 inhibitors (10, 12, 20) provided rational for EP0057 being assessed in combination with olaparib at the National Institute of Health (NCT02769962). Initial safety results are favorable at dose level 2 in this Phase I study.

Given the high proportion of DNA-repair abnormalities and sensitivity to CPT of UC, our intent is to examine the clinical activity of EP0057 in combination with olaparib in patients with UC.

1.2.2.1 Rationale for expansion cohort in patients with metastatic/advanced urothelial carcinoma

As of Amendment C we propose an expansion to our current study protocol # 16-C-0107 [NCT02769962] for 34 additional patients with metastatic or advanced UC. The expansion would enroll patients with metastatic or unresectable locally advanced UC who must have received prior treatment with at least one platinum-based chemotherapy and/or an immune-checkpoint inhibitor. To be eligible for this expansion cohort, patients must have histologically confirmed diagnosis of UC and at least one measurable site of disease (according per RECIST criteria v 1.1).

This study will provide further insight into the potential increased efficacy of EP0057 in combination with olaparib in UC patients with manageable toxicity. Primary end-point is ORR. Secondary end-points are PFS and safety. Exploratory end-point include correlation between molecular markers and clinical outcomes (ORR and PFS).

1.2.3 Castrate resistant prostate cancer (mCRPC)

Prostate cancer is the most common cancer among men in the United States with an estimated 161,360 new cases and 26,730 deaths in 2017 (21). While prostate cancer is initially responsive to androgen deprivation therapy (ADT), the median duration of sensitivity is 24-36 months,(22) and a majority of men will go on to develop castration-resistant disease. Over the last several years, the landscape of treatment in metastatic castration-resistant prostate cancer (mCRPC) has heralded new treatment options including potent hormonal agents abiraterone(23, 24) and enzalutamide(25, 26). Both abiraterone and enzalutamide have shown overall survival (OS) benefits in mCRPC, but unfortunately, men will develop resistance to these agents and to chemotherapeutic agents such as docetaxel. Furthermore, emerging data suggests that DNA repair mutations are present in 25-30% of tumors(27) and up to ~12% of patients with mCRPC may have germline mutations (28). Therefore, therapies that can exploit this target may improve clinical outcomes in advanced prostate cancer.

1.2.3.1 DNA Damage Repair

Next generation sequencing (NGS) techniques have been used to characterize recurrent mutations and genomic alterations in advanced prostate cancer (29) which include alterations in key genes important for DNA repair such as BRCA2. An international consortium of 8 medical center clinical sites conducted prospective whole-exome and trascriptome sequencing of bone or soft tissue tumor biopsies in 150 patients with mCRPC (27). Informative mutations were frequent, with clinically actionable alterations often seen in the DNA repair pathway (19%). Aberrations of BRCA2 and BRCA1 were observed with BRCA2 alterations in 19/150 (12.7%) of cases. Pathogenic germline BRCA2 mutations were found in 8 patients (5.3%) with a subsequent somatic event that resulted in biallelic loss. Events were also noted in BRCA1. Overall, 19.3% of patients harbored aberrations in DNA repair pathway involving BRCA2, BRCA1, and ATM.

Early clinical data has supported DNA repair defects as a target in mCRPC. In the phase II TOPARP-A study, fifty patients with mCPRC were treated with a single agent PARP inhibitor, olaparib(30). All patients had been treated previously with docetaxel, 49 patients (98%) had been previously treated with abiraterone or enzalutamide, and 29 patients (58%) with cabazitaxel. In 33% (16/49) of evaluable patients, NGS revealed homozygous deletions and/or deleterious mutations in DNA repair genes, with the majority in BRCA2 and ATM. Of these 16 patients, 14 (88%) had a response to olaparib, including all 7 patients with BRCA2 loss (4 with biallelic somatic loss, and 3 with germline mutations) and 4 of 5 with ATM aberrations. The specificity of the biomarker suite was 94%. In the 7 patients with BRCA2 loss, 57% (4/7) were somatic aberrations and 43% (3/7) were germline. Targeting genetic defects in DNA repair genes in mCRPC offer possibilities for treatment options in heavily pre-treated patients and larger confirmatory trials are underway.

Recent data shows DNA damage plays an important role in priming the type I interferon (INF) system, where DNA damage results in enhanced production of type I IFNs via the cystolic DNA sensor STING (stimulator of interferon genes) which can prime the innate immune system for an amplified response (31). STING is a signaling molecule which is involved in controlling the transcription of host defense genes including Type I IFNs following recognition of aberrant DNA species and also self-DNA as a result of DNA damage (32). Instigating DNA damage can lead to nuclear DNA leakage into the cytosol and trigger STING-dependent cytokine activity (32). Loss of DNA repair mechanisms, via PARP inhibition, may enable DNA to leak into the cytoplasm to activate STING leading to production of Type I IFNs which exert potent effects on the priming of anti-tumor T cells (32).

1.2.3.2 Camptothecin Derivatives Investigated in Prostate Cancer

Camptothecin (CPT) is a potent Top1 inhibitor that failed clinical development due to poor solubility and high systemic toxicity. CPT derivatives such as irinotecan and topotecan have clinical utility for the treatment of a limited subset of advanced solid tumors. Both irinotecan and topotecan demonstrated improvements in plasma solubility but decreased target affinity compared to CPT. The primary cellular target of CPT is the Top1-DNA cleavage complex. CPT stabilizes the Top1-DNA cleavage complex during DNA replication and prevents Top1-mediated DNA relegation, leading to double strand breaks. The accumulation of double-strand breaks via CPT leads to apoptosis.

Camptothecin has shown activity in several prostate cancer cell lines (e.g. PC3, DU145, LNCaP).(33-35) The administration of CPT in LNCaP cells was shown to down-regulate expression of the AR and PSA.(36) Camptothecin was shown to suppress the expression of matrix-metalloproteinase-9 (MMP-9) and VEGF through inhibition of NF-κB activity in DU145 cells.(37)
Synergistic activity between camptothecin and olaparib has been shown in DU145 prostate cancer cells. The combination's activity is independent of defects in homologous recombination (e.g. BRCA1, BRCA2, etc.) and is due to catalytic PARP inhibitory activity.(1)

1.2.3.3 Rationale for the expansion cohort in patients with mCRPC

The rationale for combination of a PARP inhibitor, olaparib, and EP0057, is based upon the potential complementary mechanisms of action of the two therapies. Synergy between camptothecin and PARP inhibitors has been established.(38) PARP1 plays a role in the repair of topoisomerase I-induced DNA damage. By inhibiting PARP, via olaparib, the potency of

topoisomerase I inhibitors may be increased and thus olaparib plus EP0057 offers a potential treatment option in patients with heavily pre-treated advanced prostate cancer.

The purpose of the expansion cohort is to test the hypothesis that the EP0057 in combination with olaparib could yield durable responses in mCRPC. Increased DNA damage should complement the activity of topoisomerase I inhibitor EP0057 in mCRPC.

1.2.4 PARP as a Therapeutic Target in Small Cell Lung Cancer

Poly-(ADP)-ribose polymerases (PARPs) are a large family comprising of proteins that are critical regulatory components in DNA damage repair, maintenance of genomic integrity and other cellular processes (39). PARP-1 and PARP-2 are activated by single-strand DNA breaks (SSB). When SSBs are formed, PARP binds at the end of broken DNA strands, activating its enzymatic activity. Activated PARP catalyzes addition of long polymers of ADP-ribose (PAR). This lengthening PAR chain (PARylation) builds up a large negatively charged structure at the SSB which recruits other DNA repair enzymes that collectively repair DNA breaks via base excision repair (BER). PARP inhibition by inhibiting BER leads to the conversion of SSB to DNA double-strand breaks (DSB). The activity of PARP inhibitors are best established in cancers with mutations in BRCA1/2 and other DNA repair genes that result in synthetic lethality in the setting of PARP inhibition (which provides a second “hit” to the DNA repair machinery). Olaparib monotherapy was recently FDA-approved for patients with advanced, BRCA-mutated ovarian cancer who have received three or more lines of chemotherapy.

Drugs that target DNA damage response (DDR), including PARP inhibitors, have shown promising activity against SCLC in pre-clinical models and in early clinical trials. Proteomic profiling of a large panel of SCLC cell lines led to the observation that PARP1, Chk1, and several other DNA repair proteins are expressed at high levels in SCLC (40). These studies also confirmed PARP1 overexpression in patient tumors at the protein level by immunohistochemistry and at the mRNA level. Based on this finding, several PARP inhibitors were tested in pre-clinical models of SCLC. Olaparib, rucaparib, and talazoparib (previously BMN-673) all demonstrated striking single agent activity in a majority of SCLC cell lines tested. Furthermore, the addition of a PARP inhibitor to standard chemotherapies (e.g., cisplatin, etoposide and/or topotecan) and radiation further potentiated their effect (41). In animal models including xenografts and patient-derived xenografts (PDXs), talazoparib has demonstrated significant anti-tumor activity as a single agent, comparable or superior to cisplatin (42).

Following these observations, several clinical trials were initiated to investigate the effects of PARP inhibition in SCLC patients. The first two studies to complete enrollment investigated the use of PARP inhibitors in relapsed SCLC. In the first study, single-agent talazoparib (BMN-673) was tested in an expansion cohort of patients with platinum-sensitive SCLC relapse (NCT01286987). Preliminary data from this trial demonstrated 2/23 patients with RECIST confirmed partial responses and 3/23 with stable disease lasting more than 24 weeks (clinical benefit rate of 25%). More than half of patients treated had some tumor volume reduction as their best response (43). In the second study, the oral alkylating drug temozolomide with or without veliparib (ABT-888) was studied in 100 patients with sensitive or refractory relapse (NCT01638546). This trial recently completed enrollment and analysis of the results are ongoing.

1.2.5 PARP Inhibitors and DNA Damaging Chemotherapy are Synergistic

The use of PARP inhibitors in combination with chemotherapy builds upon prior pre-clinical data in lung cancer and other malignancies supporting the notion that PARP inhibitors potentiate the effect of other DNA damaging therapies. Supporting this hypothesis, PARP inhibition has been reported to down regulate key components of the DNA repair machinery and enhanced the efficacy of chemotherapy in preclinical SCLC models (40). PARP inhibition sensitizes cancer cells both to cytotoxic chemotherapy, such as alkylators (temozolomide, cyclophosphamide) or camptothecins (irinotecan, topotecan) and to ionizing radiation- all of which induce DNA damage requiring BER (44). PARP inhibitors are highly effective in combination with camptothecins in tumors with and without defects in homologous recombination (1, 15, 16, 45). The Pommier laboratory has demonstrated highly synergistic activity of olaparib in combination with camptothecins (**Figure 1**) (1). They observed that the synergistic activity is due to its catalytic PARP inhibitory activity rather than due to trapping of PARP-DNA complexes.

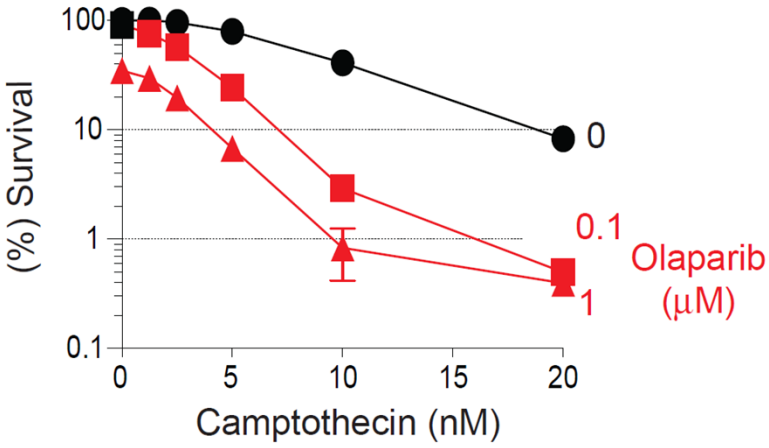


Figure 1: Synergistic activity of camptothecins and olaparib in DT40 cells with a synergistic combination index (<0.3), even when the doses of individual agents are low **(1)**.

Despite their highly synergistic activity in preclinical models, human studies combining PARP inhibitors and camptothecins have not translated into clinical benefit due to enhanced toxicity with the combination (46, 47). In combination with chemotherapy, olaparib and veliparib enhanced the myelosuppression of their chemotherapy partners. In these studies, unacceptable toxicity necessitated dose reductions to sub-therapeutic levels.

1.2.6 Safely combining PARP Inhibitors with Camptothecins

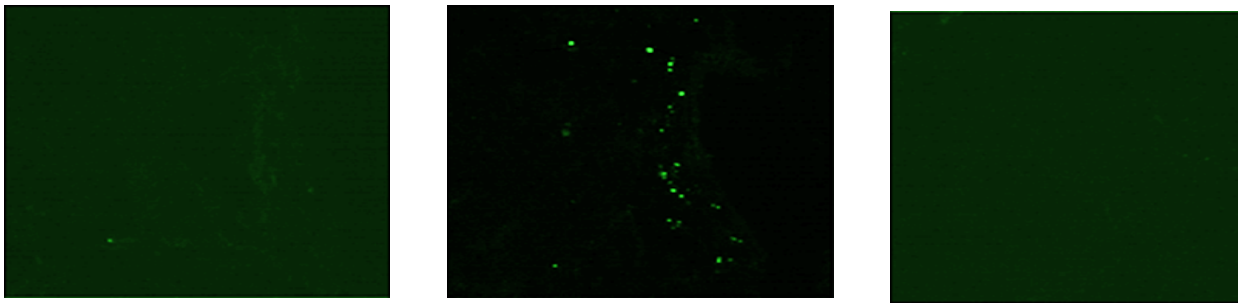
One approach to safely combine camptothecins with agents that sensitize their activity like PARP inhibitors is to use alternative formulations that could minimize toxicity to the normal tissues.

EP0057 (formerly named CRLX101 and IT-101) is a nanoparticle-drug conjugate (NDC) composed of 20(S) -camptothecin conjugated to a linear, cyclodextrin-polyethylene glycol-based polymer (Poly-CD-PEG-Camptothecin) (EP0057 Investigators Brochure) In solution, EP0057 self-assembles into nanoparticles and releases CPT over prolonged periods of time (48) (49).

Camptothecin (CPT) is a potent topoisomerase I (Top1) inhibitor that failed clinical development due to poor solubility and high systemic toxicity. CPT derivatives such as irinotecan and topotecan demonstrate clinical utility for the treatment of advanced solid tumors. The primary cellular target of CPT, the Top1–DNA cleavage complex, is stabilized, preventing Top1-mediated DNA relegation. Exposure of cancer cells to CPT leads to replication-mediated accumulation of DNA double-strand breaks and subsequent apoptosis.

EP0057 localizes to the tumor and is retained for a prolonged duration by a mechanism referred to as enhanced permeability and retention (EPR) wherein macromolecules penetrate and are trapped in tumor tissue due to the abnormally leaky vasculature of tumors. EP0057 provides sustained release of CPT from polymer in the tumor for prolonged periods while sustaining low unconjugated (released) CPT concentrations in the blood. Animal xenograft models of cancer indicate that EP0057 accumulates in solid tumors and releases CPT over a period of several days to give sustained inhibition of its target (49). Sustained release of camptothecin from polymer in the tumor and low unconjugated camptothecin concentrations in the blood could optimize the cell cycle specific antitumor activity associated with the prolonged drug exposure in tumor tissue and improve tolerability associated with low systemic exposure. Drug localization analyses have been conducted in tumor from subjects with HER-2 negative gastric cancer who enrolled in a clinical trial of EP0057. Pre- and post- treatment biopsies involving tumor tissue and healthy adjacent tissue were collected from 10 subjects, 9 of whom had evaluable biopsies. Biopsies from all subjects were analyzed for differential drug accumulation between tumor and normal tissue using immunofluorescence techniques. Post-treatment biopsies were obtained between 24 and 48 hours after a single dose of EP0057 and CPT was visualized by direct fluorescent excitation of tissues. Of the 9 patients with evaluable biopsies, 7 showed clear evidence of CPT within the post-treatment tumor while only one patient showed potential evidence of CPT in the post-treatment normal tissue. Images show bright, punctuate CPT signal specific to tumor tissue following treatment with EP0057 and rare events of CPT signal co-localized with anti-PEG signal as demonstrated in **Figure 2.**

Figure 2: Immunofluorescence Visualization in Gastric Cancer Tumor and Adjacent Normal Tissue after First Dose with EP0057 in Subjects on the Gastric Investigator-Sponsored Trial



Left: Tumor pre-treatment; **Middle:** Tumor 24 hour post-treatment; **Right**: Healthy adjacent tissue 24 hours pos
Green dots = CPT from nanoparticles

1.2.7 EP0057 Preclinical Toxicology

Dose-limiting toxicity in rat and dog were largely body weight losses. Reductions in neutrophil and platelet counts were observed in the acute dog toxicity study and reversible reductions in neutrophil and platelet counts were observed at the mid dose in the sub-acute multi-dose dog toxicity study (EP0057 Investigators Brochure). Reversible reductions in neutrophil and increases in platelet counts were observed at the high dose in the sub-acute multi-dose rat toxicity study.

1.2.8 EP0057 phase I clinical trial

Patients with advanced solid malignancies were enrolled to an open-label, single-arm, dose-escalation study, in which EP0057 was administered intravenously over 60 min among two dosing schedules, initially weekly at 6, 12, and 18 mg/m2 and later bi-weekly at 12, 15, and 18 mg/m2. The MTD was determined at 15 mg/m2 bi-weekly, and an expansion phase 2a study was completed. Sixty-two patients (31 male; median age 63 years, range 39-79) received treatment. Bi-weekly dosing was generally well tolerated with myelosuppression being the dose-limiting toxicity. Among all phase 1/2a patients receiving the MTD (n=44), most common grade 3/4 adverse events were neutropenia (Grade 3 neutropenia = 9% and no grade 4) and fatigue (Grade 3 fatigue = 9%, no grade 4). Evidence of systemic plasma exposure to both the polymer-conjugated and unconjugated CPT was observed in all treated patients. Mean elimination unconjugated CPT Tmax values ranged from 17.7 to 24.5 h, and maximum plasma concentrations and areas under the curve were generally proportional to dose for both polymer-conjugated and unconjugated CPT. Best overall response was stable disease in 28 patients (64 %) treated at the MTD and 16 (73 %) of a subset of NSCLC patients. Median progression-free survival (PFS) for patients treated at the MTD was 3.7 months and for the subset of NSCLC patients was 4.4 months.

1.2.9 Adverse Events with EP0057 (CRLX101) Monotherapy

Table 2. Treatment-emergent AEs Related to EP0057 (CRLX101) Monotherapy in Cerulean-sponsored Studies (as of 12 March 2016)

	15 mg/m² Q2W (MTD) (N=141)		**6 mg/m² QW (N=6)**		**12 mg/m² QW (N=10)**		**15 mg/m² QW (N=5)**		**18 mg/m² QW (N=3)**		**12 mg/m² Q2W (N=3)**		**18 mg/m² Q2W (N=3)**		**Total (N=171)**	
MedDRA Preferred Term[a]	**All Grades n (%)**	**Grade 3/4 n (%)**	**All Grades n (%)**	**Grade 3/4 n (%)**	**All Grades n (%)**	**Grade 3/4 n (%)**	**All Grades n (%)**	**Grade 3/4 n (%)**	**All Grades n (%)**	**Grade 3/4 n (%)**	**All Grades n (%)**	**Grade 3/4 n (%)**	**All Grades n (%)**	**Grade 3/4 n (%)**	**All Grades n (%)**	**Grade 3/4 n (%)**
At Least 1 TEAE Related to Study Drug	*88 (62.4)*	*21 (14.9)*	*5 (83.3)*	*3 (50.0)*	*10 (100.0)*	*5 (50.0)*	*5 (100.0)*	*1 (20.0)*	*3 (100.0)*	*3 (100.0)*	*2 (66.7)*	*0*	*3 (100.0)*	*2 (66.7)*	116 (67.8)	35 (20.5)
Anaemia	25 (17.7)	1 (0.7)	1 (16.7)	0	1 (10.0)	0	0	0	3 (100.0)	1 (33.3)	0	0	1 (33.3)	1 (33.3)	31 (18.1)	3 (1.8)
Fatigue	17 (12.1)	4 (2.8)	3 (50.0)	2 (33.3)	6 (60.0)	1 (10.0)	2 (40.0)	0	2 (66.7)	1 (33.3)	0	0	1 (33.3)	0	31 (18.1)	8 (4.7)
Cystitis	19 (13.5)	1 (0.7)	1 (16.7)	0	3 (30.0)	0	2 (40.0)	0	1 (33.3)	0	0	0	1 (33.3)	0	27 (15.8)	1 (0.6)
Nausea	20 (14.2)	1 (0.7)	0	0	3 (30.0)	0	2 (40.0)	0	1 (33.3)	0	1 (33.3)	0	0	0	27 (15.8)	1 (0.6)
Haematuria	11 (7.8)	1 (0.7)	2 (33.3)	0	3 (30.0)	0	0	0	2 (66.7)	1 (33.3)	0	0	0	0	18 (10.5)	2 (1.2)
Neutropenia	9 (6.4)	6 (4.3)	0	0	0	0	0	0	3 (100.0)	3 (100.0)	0	0	1 (33.3)	1 (33.3)	13 (7.6)	10 (5.8)
Diarrhoea	8 (5.7)	0	0	0	0	0	2 (40.0)	1 (20.0)	0	0	0	0	2 (66.7)	0	12 (7.0)	1 (0.6)
Vomiting	5 (3.5)	1 (0.7)	1 (16.7)	0	4 (40.0)	0	0	0	1 (33.3)	0	1 (33.3)	0	0	0	12 (7.0)	1 (0.6)
Dysuria	6 (4.3)	0	3 (50.0)	1 (16.7)	1 (10.0)	0	0	0	1 (33.3)	0	0	0	0	0	11 (6.4)	1 (0.6)
Constipation	3 (2.1)	0	1 (16.7)	0	2 (20.0)	0	3 (60.0)	0	0	0	0	0	0	0	9 (5.3)	0
Thrombocytopenia	4 (2.8)	1 (0.7)	0	0	0	0	1 (20.0)	0	2 (66.7)	2 (66.7)	0	0	2 (66.7)	2 (66.7)	9 (5.3)	5 (2.9)
Alopecia	7 (5.0)	0	0	0	0	0	0	0	0	0	0	0	1 (33.3)	0	8 (4.7)	0
Decreased appetite	3 (2.1)	0	1 (16.7)	0	2 (20.0)	0	0	0	2 (66.7)	0	0	0	0	0	8 (4.7)	0
Leukocyturia	4 (2.8)	0	2 (33.3)	0	1 (10.0)	0	0	0	1 (33.3)	0	0	0	0	0	8 (4.7)	0
Leukopenia	4 (2.8)	0	0	0	1 (10.0)	0	0	0	3 (100.0)	2 (66.7)	0	0	0	0	8 (4.7)	2 (1.2)
Neuropathy peripheral	5 (3.5)	1 (0.7)	0	0	0	0	1 (20.0)	0	0	0	0	0	0	0	6 (3.5)	1 (0.6)
Proteinuria	3 (2.1)	0	1 (16.7)	0	0	0	1 (20.0)	0	1 (33.3)	0	0	0	0	0	6 (3.5)	0
Pyrexia	4 (2.8)	0	0	0	2 (20.0)	0	0	0	0	0	0	0	0	0	6 (3.5)	0
Dyspnoea	3 (2.1)	1 (0.7)	0	0	0	0	1 (20.0)	0	0	0	0	0	1 (33.3)	1 (33.3)	5 (2.9)	2 (1.2)

MedDRA Preferred Term[a]	15 mg/m² Q2W (MTD) (N=141)		6 mg/m² QW (N=6)		12 mg/m² QW (N=10)		15 mg/m² QW (N=5)		18 mg/m² QW (N=3)		12 mg/m² Q2W (N=3)		18 mg/m² Q2W (N=3)		Total (N=171)	
	All Grades n (%)	Grade 3/4 n (%)	All Grades n (%)	Grade 3/4 n (%)	All Grades n (%)	Grade 3/4 n (%)	All Grades n (%)	Grade 3/4 n (%)	All Grades n (%)	Grade 3/4 n (%)	All Grades n (%)	Grade 3/4 n (%)	All Grades n (%)	Grade 3/4 n (%)	All Grades n (%)	Grade 3/4 n (%)
Urinary tract infection	3 (2.1)	0	1 (16.7)	0	0	0	0	0	0	0	1 (33.3)	0	0	0	5 (2.9)	0
Alanine aminotransferase increased	4 (2.8)	0	0	0	0	0	0	0	0	0	0	0	0	0	4 (2.3)	0
Dehydration	2 (1.4)	1 (0.7)	1 (16.7)	0	1 (10.0)	1 (10.0)	0	0	0	0	0	0	0	0	4 (2.3)	2 (1.2)
Haemoglobin decreased	2 (1.4)	0	0	0	0	0	0	0	0	0	1 (33.3)	0	1 (33.3)	0	4 (2.3)	0
Neutrophil count decreased	3 (2.1)	3 (2.1)	0	0	0	0	0	0	0	0	0	0	1 (33.3)	1 (33.3)	4 (2.3)	4 (2.3)
Pain in extremity	3 (2.1)	0	1 (16.7)	0	0	0	0	0	0	0	0	0	0	0	4 (2.3)	0
White blood cell count decreased	3 (2.1)	1 (0.7)	0	0	0	0	0	0	0	0	0	0	1 (33.3)	1 (33.3)	4 (2.3)	2 (1.2)
Abdominal pain	3 (2.1)	0	0	0	0	0	0	0	0	0	0	0	0	0	3 (1.8)	0
Aspartate aminotransferase increased	3 (2.1)	0	0	0	0	0	0	0	0	0	0	0	0	0	3 (1.8)	0
Asthenia	2 (1.4)	1 (0.7)	1 (16.7)	0	0	0	0	0	0	0	0	0	0	0	3 (1.8)	1 (0.6)
Blood creatinine increased	3 (2.1)	1 (0.7)	0	0	0	0	0	0	0	0	0	0	0	0	3 (1.8)	1 (0.6)
Chills	2 (1.4)	0	0	0	0	0	0	0	0	0	0	0	1 (33.3)	0	3 (1.8)	0
Dizziness	2 (1.4)	0	0	0	0	0	0	0	1 (33.3)	0	0	0	0	0	3 (1.8)	0
Micturition urgency	2 (1.4)	0	0	0	1 (10.0)	0	0	0	0	0	0	0	0	0	3 (1.8)	0
Abdominal distension	1 (0.7)	0	0	0	1 (10.0)	0	0	0	0	0	0	0	0	0	2 (1.2)	0
Bladder spasm	2 (1.4)	0	0	0	0	0	0	0	0	0	0	0	0	0	2 (1.2)	0
Blood alkaline phosphatase increased	2 (1.4)	0	0	0	0	0	0	0	0	0	0	0	0	0	2 (1.2)	0
Bone pain	2 (1.4)	0	0	0	0	0	0	0	0	0	0	0	0	0	2 (1.2)	0
Cough	2 (1.4)	0	0	0	0	0	0	0	0	0	0	0	0	0	2 (1.2)	0

MedDRA Preferred Term[a]	15 mg/m² Q2W (MTD) (N=141)		6 mg/m² QW (N=6)		12 mg/m² QW (N=10)		15 mg/m² QW (N=5)		18 mg/m² QW (N=3)		12 mg/m² Q2W (N=3)		18 mg/m² Q2W (N=3)		Total (N=171)	
	All Grades n (%)	Grade 3/4 n (%)	All Grades n (%)	Grade 3/4 n (%)	All Grades n (%)	Grade 3/4 n (%)	All Grades n (%)	Grade 3/4 n (%)	All Grades n (%)	Grade 3/4 n (%)	All Grades n (%)	Grade 3/4 n (%)	All Grades n (%)	Grade 3/4 n (%)	All Grades n (%)	Grade 3/4 n (%)
Cystitis haemorrhagic	0	0	1 (16.7)	0	1 (10.0)	1 (10.0)	0	0	0	0	0	0	0	0	2 (1.2)	1 (0.6)
Dysgeusia	1 (0.7)	0	0	0	1 (10.0)	0	0	0	0	0	0	0	0	0	2 (1.2)	0
Dyspepsia	0	0	1 (16.7)	0	1 (10.0)	0	0	0	0	0	0	0	0	0	2 (1.2)	0
Flatulence	0	0	1 (16.7)	0	0	0	1 (20.0)	0	0	0	0	0	0	0	2 (1.2)	0
Hyperglycaemia	2 (1.4)	0	0	0	0	0	0	0	0	0	0	0	0	0	2 (1.2)	0
Hypersensitivity	1 (0.7)	1 (0.7)	0	0	0	0	0	0	0	0	0	0	1 (33.3)	1 (33.3)	2 (1.2)	2 (1.2)
Hypokalaemia	1 (0.7)	0	0	0	0	0	0	0	1 (33.3)	0	0	0	0	0	2 (1.2)	0
Infusion related reaction	1 (0.7)	1 (0.7)	0	0	0	0	1 (20.0)	0	0	0	0	0	0	0	2 (1.2)	1 (0.6)
Insomnia	1 (0.7)	0	0	0	0	0	0	0	1 (33.3)	0	0	0	0	0	2 (1.2)	0
Lymphocyte count decreased	0	0	0	0	2 (20.0)	2 (20.0)	0	0	0	0	0	0	0	0	2 (1.2)	2 (1.2)
Myalgia	2 (1.4)	0	0	0	0	0	0	0	0	0	0	0	0	0	2 (1.2)	0
Nocturia	1 (0.7)	0	1 (16.7)	0	0	0	0	0	0	0	0	0	0	0	2 (1.2)	0
Oedema peripheral	0	0	1 (16.7)	0	0	0	0	0	0	0	0	0	1 (33.3)	0	2 (1.2)	0
Pollakiuria	0	0	0	0	2 (20.0)	0	0	0	0	0	0	0	0	0	2 (1.2)	0
Rash	2 (1.4)	0	0	0	0	0	0	0	0	0	0	0	0	0	2 (1.2)	0
Urinary retention	2 (1.4)	0	0	0	0	0	0	0	0	0	0	0	0	0	2 (1.2)	0
Abdominal pain upper	1 (0.7)	0	0	0	0	0	0	0	0	0	0	0	0	0	1 (0.6)	0
Acute kidney injury	0	0	0	0	0	0	1 (20.0)	0	0	0	0	0	0	0	1 (0.6)	0
Acute respiratory distress syndrome	1 (0.7)	1 (0.7)	0	0	0	0	0	0	0	0	0	0	0	0	1 (0.6)	1 (0.6)
Adrenal insufficiency	1 (0.7)	0	0	0	0	0	0	0	0	0	0	0	0	0	1 (0.6)	0
Angina pectoris	1 (0.7)	0	0	0	0	0	0	0	0	0	0	0	0	0	1 (0.6)	0
Anxiety	0	0	0	0	0	0	0	0	1 (33.3)	0	0	0	0	0	1 (0.6)	0

MedDRA Preferred Term[a]	15 mg/m² Q2W (MTD) (N=141)		6 mg/m² QW (N=6)		12 mg/m² QW (N=10)		15 mg/m² QW (N=5)		18 mg/m² QW (N=3)		12 mg/m² Q2W (N=3)		18 mg/m² Q2W (N=3)		Total (N=171)	
	All Grades n (%)	Grade 3/4 n (%)	All Grades n (%)	Grade 3/4 n (%)	All Grades n (%)	Grade 3/4 n (%)	All Grades n (%)	Grade 3/4 n (%)	All Grades n (%)	Grade 3/4 n (%)	All Grades n (%)	Grade 3/4 n (%)	All Grades n (%)	Grade 3/4 n (%)	All Grades n (%)	Grade 3/4 n (%)
Atrial flutter	1 (0.7)	0	0	0	0	0	0	0	0	0	0	0	0	0	1 (0.6)	0
Back pain	1 (0.7)	0	0	0	0	0	0	0	0	0	0	0	0	0	1 (0.6)	0
Bacteriuria	1 (0.7)	0	0	0	0	0	0	0	0	0	0	0	0	0	1 (0.6)	0
Bladder discomfort	1 (0.7)	0	0	0	0	0	0	0	0	0	0	0	0	0	1 (0.6)	0
Bladder pain	1 (0.7)	0	0	0	0	0	0	0	0	0	0	0	0	0	1 (0.6)	0
Bronchospasm	1 (0.7)	0	0	0	0	0	0	0	0	0	0	0	0	0	1 (0.6)	0
Candida infection	0	0	0	0	0	0	1 (20.0)	0	0	0	0	0	0	0	1 (0.6)	0
Cystitis noninfective	1 (0.7)	0	0	0	0	0	0	0	0	0	0	0	0	0	1 (0.6)	0
Cytokine release syndrome	1 (0.7)	1 (0.7)	0	0	0	0	0	0	0	0	0	0	0	0	1 (0.6)	1 (0.6)
Dry mouth	0	0	1 (16.7)	0	0	0	0	0	0	0	0	0	0	0	1 (0.6)	0
Dysphagia	0	0	0	0	0	0	0	0	1 (33.3)	0	0	0	0	0	1 (0.6)	0
Dysphonia	0	0	0	0	0	0	0	0	1 (33.3)	0	0	0	0	0	1 (0.6)	0
Dyspnoea exertional	1 (0.7)	0	0	0	0	0	0	0	0	0	0	0	0	0	1 (0.6)	0
Electrocardiogram qt prolonged	1 (0.7)	0	0	0	0	0	0	0	0	0	0	0	0	0	1 (0.6)	0
Epistaxis	0	0	0	0	1 (10.0)	0	0	0	0	0	0	0	0	0	1 (0.6)	0
Febrile neutropenia	0	0	0	0	1 (10.0)	1 (10.0)	0	0	0	0	0	0	0	0	1 (0.6)	1 (0.6)
Gait disturbance	1 (0.7)	0	0	0	0	0	0	0	0	0	0	0	0	0	1 (0.6)	0
Gastric haemorrhage	1 (0.7)	0	0	0	0	0	0	0	0	0	0	0	0	0	1 (0.6)	0
Gastrointestinal disorder	1 (0.7)	0	0	0	0	0	0	0	0	0	0	0	0	0	1 (0.6)	0
Gastrointestinal pain	1 (0.7)	0	0	0	0	0	0	0	0	0	0	0	0	0	1 (0.6)	0
Glucose tolerance impaired	0	0	0	0	1 (10.0)	0	0	0	0	0	0	0	0	0	1 (0.6)	0

MedDRA Preferred Term[a]	15 mg/m² Q2W (MTD) (N=141)		6 mg/m² QW (N=6)		12 mg/m² QW (N=10)		15 mg/m² QW (N=5)		18 mg/m² QW (N=3)		12 mg/m² Q2W (N=3)		18 mg/m² Q2W (N=3)		Total (N=171)	
	All Grades n (%)	Grade 3/4 n (%)	All Grades n (%)	Grade 3/4 n (%)	All Grades n (%)	Grade 3/4 n (%)	All Grades n (%)	Grade 3/4 n (%)	All Grades n (%)	Grade 3/4 n (%)	All Grades n (%)	Grade 3/4 n (%)	All Grades n (%)	Grade 3/4 n (%)	All Grades n (%)	Grade 3/4 n (%)
Headache	1 (0.7)	0	0	0	0	0	0	0	0	0	0	0	0	0	1 (0.6)	0
Herpes zoster	1 (0.7)	0	0	0	0	0	0	0	0	0	0	0	0	0	1 (0.6)	0
Hiccups	0	0	0	0	1 (10.0)	0	0	0	0	0	0	0	0	0	1 (0.6)	0
Hypercreatininaemia	1 (0.7)	0	0	0	0	0	0	0	0	0	0	0	0	0	1 (0.6)	0
Hyperkalaemia	0	0	0	0	0	0	0	0	1 (33.3)	0	0	0	0	0	1 (0.6)	0
Hypertension	1 (0.7)	0	0	0	0	0	0	0	0	0	0	0	0	0	1 (0.6)	0
Hypoglycaemia	1 (0.7)	0	0	0	0	0	0	0	0	0	0	0	0	0	1 (0.6)	0
Hypomagnesaemia	1 (0.7)	0	0	0	0	0	0	0	0	0	0	0	0	0	1 (0.6)	0
Hypotension	1 (0.7)	0	0	0	0	0	0	0	0	0	0	0	0	0	1 (0.6)	0
Hypoxia	1 (0.7)	0	0	0	0	0	0	0	0	0	0	0	0	0	1 (0.6)	0
Lip swelling	0	0	0	0	0	0	0	0	1 (33.3)	0	0	0	0	0	1 (0.6)	0
Lymphadenopathy	1 (0.7)	0	0	0	0	0	0	0	0	0	0	0	0	0	1 (0.6)	0
Lymphopenia	1 (0.7)	1 (0.7)	0	0	0	0	0	0	0	0	0	0	0	0	1 (0.6)	1 (0.6)
Mucosal inflammation	1 (0.7)	0	0	0	0	0	0	0	0	0	0	0	0	0	1 (0.6)	0
Musculoskeletal discomfort	1 (0.7)	0	0	0	0	0	0	0	0	0	0	0	0	0	1 (0.6)	0
Nitrituria	1 (0.7)	0	0	0	0	0	0	0	0	0	0	0	0	0	1 (0.6)	0
Ocular discomfort	1 (0.7)	0	0	0	0	0	0	0	0	0	0	0	0	0	1 (0.6)	0
Pancytopenia	1 (0.7)	0	0	0	0	0	0	0	0	0	0	0	0	0	1 (0.6)	0
Paraesthesia	1 (0.7)	0	0	0	0	0	0	0	0	0	0	0	0	0	1 (0.6)	0
Pelvic pain	1 (0.7)	1 (0.7)	0	0	0	0	0	0	0	0	0	0	0	0	1 (0.6)	1 (0.6)
Penile pain	0	0	0	0	1 (10.0)	1 (10.0)	0	0	0	0	0	0	0	0	1 (0.6)	1 (0.6)
Platelet count decreased	0	0	0	0	1 (10.0)	1 (10.0)	0	0	0	0	0	0	0	0	1 (0.6)	1 (0.6)

MedDRA Preferred Term[a]	15 mg/m² Q2W (MTD) (N=141)		6 mg/m² QW (N=6)		12 mg/m² QW (N=10)		15 mg/m² QW (N=5)		18 mg/m² QW (N=3)		12 mg/m² Q2W (N=3)		18 mg/m² Q2W (N=3)		Total (N=171)	
	All Grades n (%)	Grade 3/4 n (%)	All Grades n (%)	Grade 3/4 n (%)	All Grades n (%)	Grade 3/4 n (%)	All Grades n (%)	Grade 3/4 n (%)	All Grades n (%)	Grade 3/4 n (%)	All Grades n (%)	Grade 3/4 n (%)	All Grades n (%)	Grade 3/4 n (%)	All Grades n (%)	Grade 3/4 n (%)
Polydipsia	1 (0.7)	0	0	0	0	0	0	0	0	0	0	0	0	0	1 (0.6)	0
Polyuria	1 (0.7)	0	0	0	0	0	0	0	0	0	0	0	0	0	1 (0.6)	0
Pyelonephritis chronic	1 (0.7)	0	0	0	0	0	0	0	0	0	0	0	0	0	1 (0.6)	0
Rash generalised	0	0	0	0	0	0	0	0	0	0	0	0	1 (33.3)	1 (33.3)	1 (0.6)	1 (0.6)
Rash maculo-papular	0	0	0	0	0	0	1 (20.0)	0	0	0	0	0	0	0	1 (0.6)	0
Rash papular	1 (0.7)	0	0	0	0	0	0	0	0	0	0	0	0	0	1 (0.6)	0
Right ventricular dysfunction	1 (0.7)	0	0	0	0	0	0	0	0	0	0	0	0	0	1 (0.6)	0
Sinus tachycardia	0	0	1 (16.7)	0	0	0	0	0	0	0	0	0	0	0	1 (0.6)	0
Stomatitis	1 (0.7)	0	0	0	0	0	0	0	0	0	0	0	0	0	1 (0.6)	0
Tachycardia	0	0	0	0	0	0	0	0	0	0	0	0	1 (33.3)	0	1 (0.6)	0
Upper respiratory tract infection	0	0	0	0	0	0	0	0	1 (33.3)	0	0	0	0	0	1 (0.6)	0
Urethritis	1 (0.7)	0	0	0	0	0	0	0	0	0	0	0	0	0	1 (0.6)	0
Urine flow decreased	0	0	0	0	1 (10.0)	0	0	0	0	0	0	0	0	0	1 (0.6)	0
Urobilinogen urine increased	1 (0.7)	0	0	0	0	0	0	0	0	0	0	0	0	0	1 (0.6)	0
Urticaria	0	0	0	0	0	0	0	0	0	0	0	0	1 (33.3)	0	1 (0.6)	0
Ventricular extrasystoles	1 (0.7)	0	0	0	0	0	0	0	0	0	0	0	0	0	1 (0.6)	0
Vertigo	1 (0.7)	0	0	0	0	0	0	0	0	0	0	0	0	0	1 (0.6)	0
Vision blurred	0	0	0	0	0	0	0	0	1 (33.3)	0	0	0	0	0	1 (0.6)	0
Weight decreased	1 (0.7)	0	0	0	0	0	0	0	0	0	0	0	0	0	1 (0.6)	0

1.2.10 Adverse Events Associated with EP0057 (CRLX101) Combination Therapy

Table 3. Treatment-Emergent AEs Related to EP0057 (CRLX101) + bevacizumab combination therapy in Cerulean-sponsored Studies (as of 12 March 2016)

	12 mg/m² QW + bevacizumab Q2W (N=7)		**15 mg/m² QW + bevacizumab Q2W (N=4)**		**15 mg/m² Q2W + bevacizumab Q2W (N=55)**		**Total (N=66)**	
MedDRA Preferred Term[a]	**All Grades n (%)**	**Grade 3/4 n (%)**	**All Grades n (%)**	**Grade 3/4 n (%)**	**All Grades n (%)**	**Grade 3/4 n (%)**	**All Grades n (%)**	**Grade 3/4 n (%)**
At Least 1 TEAE Related to Study Drug	*3 (42.9)*	*0*	*1 (25.0)*	*0*	*47 (85.5)*	*13 (23.6)*	*51 (77.3)*	*13 (19.7)*
Fatigue	2 (28.6)	0	1 (25.0)	0	23 (41.8)	4 (7.3)	26 (39.4)	4 (6.1)
Nausea	2 (28.6)	0	0	0	16 (29.1)	0	18 (27.3)	0
Constipation	0	0	0	0	10 (18.2)	0	10 (15.2)	0
Anaemia	2 (28.6)	0	0	0	5 (9.1)	2 (3.6)	7 (10.6)	2 (3.0)
Decreased appetite	0	0	0	0	7 (12.7)	0	7 (10.6)	0
Cystitis noninfective	1 (14.3)	0	0	0	5 (9.1)	0	6 (9.1)	0
Diarrhoea	1 (14.3)	0	0	0	5 (9.1)	1 (1.8)	6 (9.1)	1 (1.5)
Headache	0	0	0	0	6 (10.9)	1 (1.8)	6 (9.1)	1 (1.5)
Cystitis	0	0	0	0	5 (9.1)	1 (1.8)	5 (7.6)	1 (1.5)
Dysuria	0	0	0	0	5 (9.1)	0	5 (7.6)	0
Haematuria	1 (14.3)	0	0	0	3 (5.5)	0	4 (6.1)	0
Vomiting	2 (28.6)	0	0	0	2 (3.6)	1 (1.8)	4 (6.1)	1 (1.5)
Weight decreased	0	0	0	0	4 (7.3)	0	4 (6.1)	0
Aspartate aminotransferase increased	0	0	0	0	3 (5.5)	0	3 (4.5)	0
Asthenia	0	0	0	0	3 (5.5)	1 (1.8)	3 (4.5)	1 (1.5)
Chills	0	0	0	0	3 (5.5)	0	3 (4.5)	0
Dizziness	0	0	0	0	3 (5.5)	0	3 (4.5)	0
Dyspepsia	0	0	0	0	3 (5.5)	0	3 (4.5)	0
Dyspnoea	0	0	0	0	3 (5.5)	0	3 (4.5)	0
Epistaxis	0	0	0	0	3 (5.5)	0	3 (4.5)	0
Hypersensitivity	0	0	0	0	3 (5.5)	0	3 (4.5)	0

MedDRA Preferred Term[a]	12 mg/m² QW + bevacizumab Q2W (N=7)		15 mg/m² QW + bevacizumab Q2W (N=4)		15 mg/m² Q2W + bevacizumab Q2W (N=55)		Total (N=66)	
	All Grades n (%)	Grade 3/4 n (%)	All Grades n (%)	Grade 3/4 n (%)	All Grades n (%)	Grade 3/4 n (%)	All Grades n (%)	Grade 3/4 n (%)
Hypokalaemia	1 (14.3)	0	0	0	2 (3.6)	0	3 (4.5)	0
Hyponatraemia	0	0	0	0	3 (5.5)	0	3 (4.5)	0
Insomnia	0	0	0	0	3 (5.5)	0	3 (4.5)	0
Onychoclasis	0	0	0	0	3 (5.5)	0	3 (4.5)	0
Stomatitis	0	0	0	0	3 (5.5)	0	3 (4.5)	0
Urinary tract infection	0	0	0	0	3 (5.5)	0	3 (4.5)	0
Abdominal pain	1 (14.3)	0	0	0	1 (1.8)	0	2 (3.0)	0
Flushing	0	0	0	0	2 (3.6)	0	2 (3.0)	0
Hiccups	0	0	0	0	2 (3.6)	0	2 (3.0)	0
Hypertension	0	0	0	0	2 (3.6)	2 (3.6)	2 (3.0)	2 (3.0)
Infusion related reaction	0	0	0	0	2 (3.6)	0	2 (3.0)	0
Mucosal inflammation	0	0	0	0	2 (3.6)	0	2 (3.0)	0
Myalgia	0	0	0	0	2 (3.6)	0	2 (3.0)	0
Neutropenia	0	0	0	0	2 (3.6)	1 (1.8)	2 (3.0)	1 (1.5)
Neutrophil count decreased	0	0	0	0	2 (3.6)	1 (1.8)	2 (3.0)	1 (1.5)
Night sweats	0	0	0	0	2 (3.6)	0	2 (3.0)	0
Oedema peripheral	0	0	0	0	2 (3.6)	0	2 (3.0)	0
Proteinuria	0	0	0	0	2 (3.6)	0	2 (3.0)	0
Acidosis	0	0	0	0	1 (1.8)	0	1 (1.5)	0
Acute kidney injury	1 (14.3)	0	0	0	0	0	1 (1.5)	0
Alanine aminotransferase increased	0	0	0	0	1 (1.8)	0	1 (1.5)	0
Arthralgia	0	0	0	0	1 (1.8)	0	1 (1.5)	0
Asymptomatic bacteriuria	0	0	0	0	1 (1.8)	0	1 (1.5)	0
Blood alkaline phosphatase increased	0	0	0	0	1 (1.8)	0	1 (1.5)	0
Blood bilirubin increased	0	0	0	0	1 (1.8)	0	1 (1.5)	0

MedDRA Preferred Term[a]	12 mg/m² QW + bevacizumab Q2W (N=7)		15 mg/m² QW + bevacizumab Q2W (N=4)		15 mg/m² Q2W + bevacizumab Q2W (N=55)		Total (N=66)	
	All Grades n (%)	Grade 3/4 n (%)	All Grades n (%)	Grade 3/4 n (%)	All Grades n (%)	Grade 3/4 n (%)	All Grades n (%)	Grade 3/4 n (%)
Blood phosphorus decreased	0	0	0	0	1 (1.8)	0	1 (1.5)	0
Blood urine present	0	0	0	0	1 (1.8)	0	1 (1.5)	0
Cheilitis	0	0	0	0	1 (1.8)	0	1 (1.5)	0
Cognitive disorder	0	0	0	0	1 (1.8)	0	1 (1.5)	0
Confusional state	0	0	0	0	1 (1.8)	0	1 (1.5)	0
Cough	1 (14.3)	0	0	0	0	0	1 (1.5)	0
Dysgeusia	1 (14.3)	0	0	0	0	0	1 (1.5)	0
Dysphonia	0	0	0	0	1 (1.8)	0	1 (1.5)	0
Gingival bleeding	0	0	0	0	1 (1.8)	0	1 (1.5)	0
Hyperkeratosis	0	0	0	0	1 (1.8)	0	1 (1.5)	0
Hypoaesthesia	0	0	0	0	1 (1.8)	0	1 (1.5)	0
Hypoalbuminaemia	0	0	0	0	1 (1.8)	0	1 (1.5)	0
Hypocalcaemia	0	0	0	0	1 (1.8)	0	1 (1.5)	0
Hypomagnesaemia	0	0	0	0	1 (1.8)	0	1 (1.5)	0
Hypophosphataemia	0	0	0	0	1 (1.8)	1 (1.8)	1 (1.5)	1 (1.5)
Influenza like illness	0	0	0	0	1 (1.8)	0	1 (1.5)	0
Leukopenia	0	0	0	0	1 (1.8)	0	1 (1.5)	0
Lung infection	0	0	0	0	1 (1.8)	1 (1.8)	1 (1.5)	1 (1.5)
Micturition urgency	0	0	0	0	1 (1.8)	0	1 (1.5)	0
Musculoskeletal discomfort	0	0	0	0	1 (1.8)	0	1 (1.5)	0
Nail infection	0	0	0	0	1 (1.8)	0	1 (1.5)	0
Oedema	0	0	0	0	1 (1.8)	0	1 (1.5)	0
Pain	0	0	0	0	1 (1.8)	0	1 (1.5)	0
Palmar-plantar erythrodysaesthesia syndrome	0	0	0	0	1 (1.8)	0	1 (1.5)	0

MedDRA Preferred Term[a]	12 mg/m² QW + bevacizumab Q2W (N=7)		15 mg/m² QW + bevacizumab Q2W (N=4)		15 mg/m² Q2W + bevacizumab Q2W (N=55)		Total (N=66)	
	All Grades n (%)	Grade 3/4 n (%)	All Grades n (%)	Grade 3/4 n (%)	All Grades n (%)	Grade 3/4 n (%)	All Grades n (%)	Grade 3/4 n (%)
Paronychia	0	0	0	0	1 (1.8)	0	1 (1.5)	0
Peripheral sensory neuropathy	1 (14.3)	0	0	0	0	0	1 (1.5)	0
Pollakiuria	0	0	0	0	1 (1.8)	0	1 (1.5)	0
Procedural headache	0	0	0	0	1 (1.8)	0	1 (1.5)	0
Pyrexia	0	0	0	0	1 (1.8)	0	1 (1.5)	0
Rash	0	0	0	0	1 (1.8)	0	1 (1.5)	0
Retching	0	0	0	0	1 (1.8)	0	1 (1.5)	0
Sinus congestion	0	0	0	0	1 (1.8)	0	1 (1.5)	0
Skin irritation	0	0	0	0	1 (1.8)	0	1 (1.5)	0
Thrombocytopenia	1 (14.3)	0	0	0	0	0	1 (1.5)	0
Tongue ulceration	0	0	0	0	1 (1.8)	0	1 (1.5)	0
Upper gastrointestinal haemorrhage	0	0	0	0	1 (1.8)	0	1 (1.5)	0
Urine analysis abnormal	0	0	0	0	1 (1.8)	0	1 (1.5)	0
Visual impairment	0	0	0	0	1 (1.8)	0	1 (1.5)	0
White blood cell count decreased	0	0	0	0	1 (1.8)	0	1 (1.5)	0
White blood cells urine positive	0	0	0	0	1 (1.8)	0	1 (1.5)	0

Table 4. Treatment-emergent AEs Related to EP0057 (CRLX101) + paclitaxel combination therapy in Cerulean-sponsored Studies (as of 12 March 2016)

	12 mg/m² Q2W + paclitaxel QW (3 out of 4 weeks) (N=3)		**15 mg/m² Q2W + paclitaxel QW (3 out of 4 weeks) (N=6)**		**Total (N=9)**	
MedDRA Preferred Term[a]	**All Grades n (%)**	**Grade 3/4 n (%)**	**All Grades n (%)**	**Grade 3/4 n (%)**	**All Grades n (%)**	**Grade 3/4 n (%)**
Subjects With at Least 1 TEAE Related to Study Drug	*3 (100.0)*	*2 (66.7)*	*6 (100.0)*	*3 (50.0)*	*9 (100.0)*	*5 (55.6)*
Fatigue	3 (100.0)	0	3 (50.0)	0	6 (66.7)	0
Neutrophil count decreased	3 (100.0)	2 (66.7)	3 (50.0)	2 (33.3)	6 (66.7)	4 (44.4)
Nausea	2 (66.7)	0	2 (33.3)	0	4 (44.4)	0
Infusion related reaction	1 (33.3)	0	2 (33.3)	0	3 (33.3)	0
Alopecia	1 (33.3)	0	1 (16.7)	0	2 (22.2)	0
Headache	0	0	2 (33.3)	0	2 (22.2)	0
Urinary tract infection	1 (33.3)	0	1 (16.7)	0	2 (22.2)	0
Vomiting	1 (33.3)	0	1 (16.7)	0	2 (22.2)	0
Alanine aminotransferase increased	0	0	1 (16.7)	0	1 (11.1)	0
Anemia	1 (33.3)	0	0	0	1 (11.1)	0
Aspartate aminotransferase increased	0	0	1 (16.7)	0	1 (11.1)	0
Constipation	1 (33.3)	0	0	0	1 (11.1)	0
Cystitis noninfective	1 (33.3)	0	0	0	1 (11.1)	0
Dizziness	0	0	1 (16.7)	0	1 (11.1)	0
Dyspnea	1 (33.3)	0	0	0	1 (11.1)	0
Hypertension	0	0	1 (16.7)	1 (16.7)	1 (11.1)	1 (11.1)
Insomnia	0	0	1 (16.7)	0	1 (11.1)	0
Peripheral sensory neuropathy	1 (33.3)	0	0	0	1 (11.1)	0
Sinusitis	0	0	1 (16.7)	0	1 (11.1)	0

1.2.11 EP0057 (CRLX101) Clinical Development Overview

As of 12 March 2016, there have been 5 clinical trials sponsored by Cerulean: CRLX-001, CRLX-002, CRLX101-208, CRLX101-209, and CRLX101-102.

- Studies CRLX-001 and CRLX-002 have been completed; studies CRLX101-208, CRLX101-209, and CRLX101-102 are ongoing.
- 246 subjects received CRLX101/EP0057 at doses ranging from 6 to 18 mg/m^2 in the 5 cerulean-sponsored trials.

There have been 7 Investigator-sponsored trials (ISTs) with EP0057 (named CRLX101 at the time), (see **Table 4** for details); as of 12 March 2016, 138 subjects received at least 1 dose of EP0057 in the ISTs at doses ranging from 12 to 15 mg/m^2.

- A total of 384 subjects across all studies have received at least 1 dose of CRLX101. When tested in the QOW schedule, the MTD/RP2D of EP0057 monotherapy was determined to be 15 mg/m^2.
- EP0057 has been generally well-tolerated, and has shown preliminary antitumor activity in subjects with solid tumors such as with gastroesophageal, lung, and ovarian cancers.

As of 12 March 2020, there have been 6 clinical trials sponsored by Cerulean Pharma (prior to 17 April 2017) and BlueLink Genetics (as of 17 April 2017). Overall, 286 subjects received at least 1 dose of EP0057 at doses ranging from 6 to 18 mg/m2 in these 6 BlueLink Genetics-sponsored studies. There have been 8 Investigator-sponsored trials with EP0057 in which 193 subjects received at least 1 dose of EP0057 at starting doses ranging from 12 to 15 mg/m2. When tested in the every-other-week schedule, the MTD/recommended phase 2 dose (RP2D) of EP0057 monotherapy was determined to be 15 mg/m2. EP0057 has been generally well-tolerated, and has shown preliminary antitumor activity in subjects with solid tumors.

Overall Safety Assessment from these trials indicated:

- Infusion-related reactions, cystitis, hematologic toxicity, and gastrointestinal disorders have been recognized as the risks associated with EP0057.
- Infusion-related hypersensitivity reactions have been well managed with the mandatory premedication and slower rate of infusion.
- Cystitis symptoms have been well managed with IV hydration before and after the EP0057 infusion. In addition, the impact of urine alkalization (oral and/or IV) on the incidence and severity of cystitis in subjects treated with EP0057 continue to be evaluated.

EP0057 is contraindicated for subjects who have a history of infusion-related hypersensitivity reactions to a topo-1 inhibitor or any EP0057 excipients. The effects of EP0057 on the developing human fetus or concentration in breast milk with respect to nursing mothers are unknown. Olaparib

Olaparib is a PARP inhibitor indicated as monotherapy in patients with deleterious or suspected deleterious germline BRCA mutated (as detected by an FDA-approved test) advanced ovarian

cancer who have been treated with three or more prior lines of chemotherapy. Olaparib has an established safety profile and it is under investigation in a number of different cancers.

Olaparib (AZD2281, KU-0059436) is a potent Polyadenosine 5'diphosphoribose [poly (ADP ribose] polymerisation (PARP) inhibitor (PARP-1, -2 and -3) that is being developed as an oral therapy, both as a monotherapy (including maintenance) and for combination with chemotherapy and other anti-cancer agents.

PARP inhibition is a novel approach to targeting tumors with deficiencies in DNA repair mechanisms. PARP enzymes are essential for repairing DNA single strand breaks (SSBs). Inhibiting PARPs leads to the persistence of SSBs, which are then converted to the more serious DNA double strand breaks (DSBs) during the process of DNA replication. During the process of cell division, DSBs can be efficiently repaired in normal cells by homologous recombination repair (HR). Tumors with HR deficiencies (HRD), such as serous ovarian cancers and SCLC cannot accurately repair the DNA damage, which may become lethal to cells as it accumulates. In such tumor types, olaparib may offer a potentially efficacious and less toxic cancer treatment compared with currently available chemotherapy regimens.

Olaparib has been shown to inhibit selected tumor cell lines in vitro and in xenograft and primary explant models as well as in genetic BRCA knock-out models, either as a stand-alone treatment or in combination with established chemotherapies. Cells deficient in homologous recombination DNA repair factors, notably BRCA1/2, are particularly sensitive to olaparib treatment.

PARP inhibitors such as olaparib may also enhance the DNA damaging effects of chemotherapy (50-52). For further information, please refer to the current version of the olaparib Investigator Brochure.

1.2.12 Preclinical Data of EP0057 (CRLX101) plus Olaparib

In vivo studies (conducted by Astra Zeneca) show that concurrent combination of EP0057 and olaparib resulted in a dose-dependent decrease in hematological parameters in preclinical rat bone marrow model (53). However, combination with delay (24h+) between EP0057 and olaparib provided sparing effect on peripheral blood cells (nadir and recovery) (**Figure 3**).

The combination of EP0057 with olaparib (starting 24 hours after EP0057) administered for 14 days had significantly more anti-tumor activity than olaparib administered for 2 days and provided greater efficacy than EP0057 alone (**Figure 4**). The combination was also significantly more efficacious than topotecan (standard-of-care for SCLC).

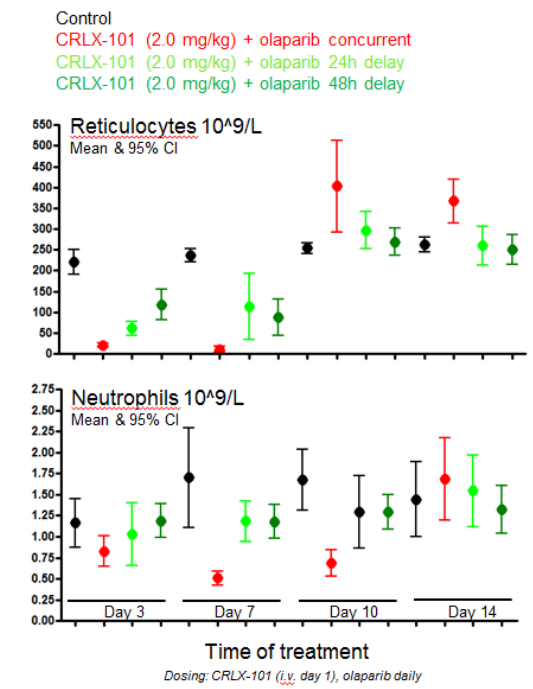


Figure 3: Hematological response to sequenced versus concurrent combination schedule in Wistar rat. Animals were treated with a single dose of EP0057 and either simultaneously or with 24h and 48h delay with daily olaparib. Peripheral blood was collected from tail vain and analysis was performed on the Siemens Advia 2120i hematology analyzer.

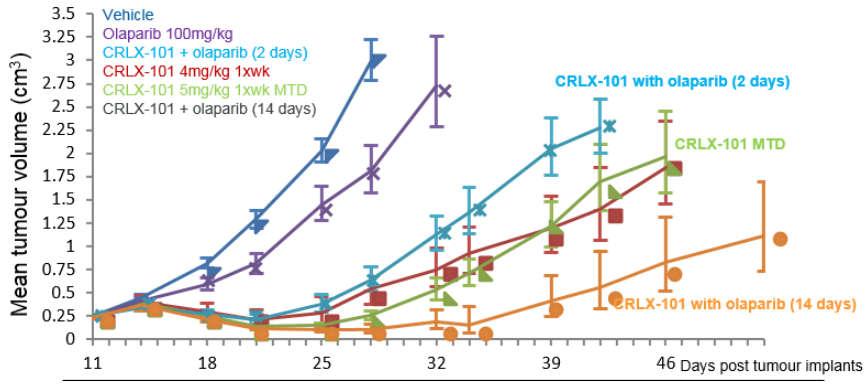


Figure 4: In vivo efficacy of EP0057 combination with various duration of olaparib dosing in SCLC xenograft model. Mice implanted with NCI-H417a tumor cells were dosed with single dose of EP0057 + olaparib for 2 days or 14 days starting 24h after the EP0057.

1.2.13 Hypothesis

Despite their highly synergistic activity in preclinical models, human studies combining PARP inhibitors and camptothecins have not translated into clinical benefit due to enhanced toxicity with the combination. EP0057 (and free camptothecin) is cleared out more slowly from tumor cells compared to plasma/bone marrow and induces sustained activation of DNA damage response in tumor. Of note, in preclinical models, most EP0057 is cleared from the bone marrow by 24 hours; in contrast, durable topoisomerase 1 inhibition in the tumor is apparent. This effect combined with low systemic exposure lends EP0057 to combinations with PARP inhibitors where both drugs can potentially be used at effective doses. Based on preclinical studies, PARP inhibitors used 48 hours after EP0057 administration will provide synergy while minimizing risk of myelosuppression.

1.2.14 Rationale

PARP inhibitors are highly synergistic in combination with camptothecins in preclinical models. However, this has not translated to clinical effectiveness, primarily due to enhanced toxicity which precludes administration of effective doses of either the PARP inhibitor or chemotherapy. Major dose limiting toxicity of this combination is myelosuppression. EP0057 is a nanoparticle drug conjugate with a camptothecin payload that provides durable inhibition of topoisomerase I (Top1) specifically in the tumor. EP0057 is cleared from the bone marrow relatively quickly. These properties allow combination of EP0057 with PARP inhibitors where both drugs can potentially be used at doses close to the MTD of each. Based on preclinical studies, PARP inhibitors used 48 hours after EP0057 and continued for 11 days will provide maximum synergy while minimizing risk of myelosuppression.

Since the safety of this combination is not established, we propose a phase I trial where escalating doses of olaparib will be combined with EP0057 administered at 80% of its MTD (12 mg/kg IV q2 weeks). The starting dose of olaparib is 100 mg bid which is a third of its single-agent maximum tolerated dose (MTD; 300 mg tablet BID).

1.2.15 Rationale for Amendment C

This is a phase I/II trial of EP0057, a nanoparticle drug conjugate plus olaparib. The goal of phase I this to determine the MTD/recommended Phase 2 dose (RP2D) of EP0057 in combination with olaparib in patients with refractory cancers. The goal of the existing phase II trial is to determine the antitumor activity of olaparib plus EP0057 with respect to progression free survival at 16 weeks separately in SCLC patients with resistant and sensitive relapse.

Between May 2016 and April 2017, 13 patients enrolled on phase 1 portion of this trial. No DLTs were observed among the first 3 patients who enrolled at dose level 1 (EP0057 12 mg/m2 IV q2weeks plus olaparib 100 mg tablet PO BID). At dose level 2 (EP0057 12 mg/m2 plus olaparib 150 mg), five patients were enrolled. Two patients in this cohort were not evaluable due to early and rapid disease progression prior to completion of DLT assessment period. At dose level 3 (EP0057 12 mg/m2 plus olaparib 200 mg), three patients enrolled with no DLTs. Two patients started on dose level 4 (EP0057 12 mg/m2 plus olaparib 300 mg), on 4/4/2017 and are currently in the DLT evaluation period.

Adverse event profile of the combination is consistent with what is expected from the AEs of both EP0057 and olaparib and consists mostly of myelosuppression. These events have not been dose-limiting and managed with dose delays/ growth factors. One patient at dose level 3 required dose delays for ANC not recovering to 1500 prior to the next cycle. Two patients treated at dose level 3 and two patients who recently enrolled at dose level 4 remain on treatment. Among 8 evaluable patients with multiple histologies, 6 patients had progressive disease, one patient with cervical cancer had stable disease with -17% reduction in target tumor lasting 6 months, and another patient with refractory small cell lung cancer has ongoing stable disease at 3 months.

1.2.16 Rationale for Amendment E

Summary of Dose Escalation and Determination of MTD/Recommended Phase II Dose

Twenty-four patients were enrolled between May 2016 and December 2017. All patients had received one or more lines of prior systemic therapy and had evidence of disease progression at enrollment.

Patients across different dose levels received the same dose of EP0057 (EP0057 12mg/m2 Q2W) and increasing doses of olaparib. There were no DLTs at DL1 (n=3; olaparib 100 mg BID), DL2 (n=5, 2 patients were not evaluable for DLT; olaparib 150 mg BID), or DL3 (n=3; olaparib 200 mg BID). One patient at DL4 (olaparib 300 mg BID) experienced a DLT- grade 4 neutropenia not recovering within 7 days. This cohort was expanded with 5 additional patients. One additional patient had a DLT at this dose level- inability to begin subsequent treatment course within 28 days of the scheduled date, due to neutropenia. Therefore, DL4 was considered too toxic and 3 patients were enrolled at DL4R with lower dose of olaparib 250 mg BID. One of the 3 patients enrolled at DL4R with lower dose of olaparib had a DLT- grade 4 neutropenia that did not resolve within 7 days. This cohort was expanded with 3 additional patients. No DLTs were observed in the additional patients, which established DL4R (EP0057 12 mg/m2 and olaparib 250 mg) as the MTD/RP2D.

1.2.17 Rationale for mCRPC cohort accrual closure (amendment version date: 07/27/2021)

Accrual to the mCRPC cohort is to cease with amendment version date 7/27/2021. Accrual to this cohort has been slow given the recent FDA approval of olaparib for prostate cancer. Additionally, underlying conditions such as history of pelvic irradiation or surgery predispose the prostate cancer cohort to cystitis and hematuria.

1.2.18 Rationale for urothelial carcinoma cohort accrual closure (amendment version date: 08/17/22)

Accrual to this cohort has been slow due to currently active protocols competing for the same patient population. There are also protocols in development which the team believes are better suited for these patients. The decision was made to close cohort accrual on this trial to prioritize current and upcoming studies.

2 ELIGIBILITY ASSESSMENT AND ENROLLMENT

2.1 ELIGIBILITY CRITERIA

2.1.1 Inclusion Criteria - Phase I

2.1.1.1 Patients must have histologically or cytologically confirmed advanced solid tumor that is resistant or refractory to standard therapy.

2.1.1.2 A minimum of 2 weeks will be required from any prior therapy, including chemotherapy, immunotherapy and/or radiation. In addition, recovery to Grade ≤ 1 from all reversible toxicities related to prior therapy is required at study entry.

2.1.1.3 Patients do not need to have measurable disease to enroll on phase I.

2.1.1.4 Age ≥18 years.

2.1.1.5 ECOG performance status ≤2 (**Appendix A**, Section 16.1).

2.1.1.6 Patients with treated brain metastases (surgery, whole or stereotactic brain radiation) are allowed provided the lesions have been stable for at least 2 weeks and the patient is off steroids or is on a stable dose of steroids. Patients with brain metastases should not require use of enzyme-inducing antiepileptic drugs (e.g., carbamazepine, phenytoin, or phenobarbital) within 14 days before first dose and during study. Use of newer

antiepileptics that do not produce enzyme induction drug-drug interactions (DDIs) is allowed.

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

– leukocytes	≥3,000/mcL
– absolute neutrophil count	≥1,500/mcL without growth factor support
– platelets	≥100,000/mcL without growth factor support
– hemoglobin	≥9 g/dL, and no blood transfusion within 4 weeks.
	OR
– hemoglobin	>10 g/dL, and no blood transfusion within 2 weeks.
– total bilirubin	≤1.5 x ULN (unless Gilbert's Disease)
– AST(SGOT)/ALT(SGPT)	≤2.5 X institutional upper limit of normal (≤ 5X ULN if liver mets)
– creatinine	≤ ULN
	OR
– creatinine clearance	≥51 mL/min (calculated using the Cockroft-Gault formula) for patients with creatinine levels above institutional normal.

2.1.1.8 Individuals who can father children and their partners must agree to use highly effective contraception (refer to section 4.2 for details) prior to study entry, for the duration of study participation and for 3 months following last dose of study drugs. Individuals who are of childbearing potential and sexually active must agree to the use of 1 highly effective form of contraception, and their partners, if they can father children, must use a condom, or they must totally/truly abstain from any form of sexual intercourse, throughout their participation in the study and for at least 6 months after last dose of study drugs. Individuals should not donate sperm throughout the period of taking olaparib and for 3 months following the last dose of olaparib. Individuals of childbearing potential (IOCBP) are defined as being physically capable of becoming pregnant unless unable have children because of surgery or other medical reasons (effective tubal ligation, ovaries or the uterus removed, or are post-menopausal). Post-menopausal is defined as:

- Amenorrheic for 1 year (12 months in a row) or more following cessation of exogenous hormonal treatments,
- LH and FSH levels in the post-menopausal range for individuals under 50,
- radiation-induced oophorectomy with last menses >1 year ago,
- chemotherapy-induced menopause with >1 year interval since last menses,
- or surgical sterilization of participant (bilateral oophorectomy or hysterectomy) and/or partner.

2.1.1.9 Negative urine pregnancy test ≤3 days prior to C1D1 (IOCBP)

2.1.1.10 Patient is willing and able to comply with the protocol for the duration of the study including undergoing treatment and scheduled visits and examinations including follow up.

2.1.2 Inclusion Criteria - Phase II SCLC

2.1.2.1 Age ≥18 years.

2.1.2.2 Patients must have histologically or cytologically confirmed diagnosis of SCLC from a CLIA-certified laboratory.

2.1.2.3 Have received and progressed during or after a platinum-based standard chemotherapy regimen and/or an immune-checkpoint inhibitor

2.1.2.4 Patients could have received any number of therapies for relapsed or progressive disease, including re-treatment with original frontline regimen. A minimum of 2 weeks will be required from any prior therapy, including chemotherapy, immunotherapy and/or radiation. In addition, recovery to Grade ≤ 1 from all reversible toxicities related to prior therapy is required at study entry. No previous irradiation to the site of measurable or evaluable disease, unless that site had subsequent evidence of progression.

2.1.2.5 Patients must have measurable disease as per Response Evaluation Criteria in Solid Tumors, version (RECIST 1.1). See Section 6.3 for the evaluation of measurable disease.

2.1.2.6 Radiographic evidence of disease progression after initial therapy should have been documented.

2.1.2.7 ECOG performance status ≤2 (see **Appendix A**, Section 16.1).

2.1.2.8 Patients with treated brain metastases (surgery, whole or stereotactic brain radiation) are allowed provided the lesions have been stable for at least 2 weeks and the patient is off steroids or is on a stable dose of steroids. Patients with brain metastases should not require use of enzyme-inducing antiepileptic drugs (e.g., carbamazepine, phenytoin, or phenobarbital) within 14 days before first dose and during study. Use of newer antiepileptics that do not produce enzyme induction drug-drug interactions (DDIs) is allowed.

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

– leukocytes	≥3,000/mcL
– absolute neutrophil count	≥1,500/mcL without growth factor support
– platelets	≥100,000/mcL without growth factor support
– hemoglobin	≥9 g/dL, and no blood transfusion within 4 weeks.
	OR
– hemoglobin	>10 g/dL, and no blood transfusion within 2 weeks.

– total bilirubin	≤1.5 x ULN (unless Gilbert's Disease)
– AST(SGOT)/ALT(SGPT)	≤2.5 X institutional upper limit of normal (≤ 5X ULN if liver mets)
– creatinine	≤ ULN
	OR
– creatinine clearance	≥51 mL/min (calculated using the Cockroft-Gault formula) for patients with creatinine levels above institutional normal.

2.1.2.10 Individuals who can father children and their partners must agree to use highly effective contraception (refer to section 4.2 for details) prior to study entry, for the duration of study participation and for 3 months following last dose of study drugs. Individuals who are of childbearing potential and sexually active must agree to the use of 1 highly effective form of contraception, and their partners, if they can father children, must use a condom, or they must totally/truly abstain from any form of sexual intercourse, throughout their participation in the study and for at least 6 months after last dose of study drugs. Individuals should not donate sperm throughout the period of taking olaparib and for 3 months following the last dose of olaparib. Individuals of childbearing potential (IOCBP) are defined as being physically capable of becoming pregnant unless unable to have children because of surgery or other medical reasons (effective tubal ligation, ovaries or the uterus removed, or are post-menopausal). Post-menopausal is defined as:

- Amenorrheic for 1 year (12 months in a row) or more following cessation of exogenous hormonal treatments,
- LH and FSH levels in the post-menopausal range for individuals under 50,
- radiation-induced oophorectomy with last menses >1 year ago,
- chemotherapy-induced menopause with >1 year interval since last menses,
- or surgical sterilization of participant (bilateral oophorectomy or hysterectomy) and/or partner.

2.1.3 Inclusion Criteria for Urothelial Carcinoma Expansion Cohort (accrual to the cohort ended with amendment version 08/17/2022)

2.1.3.1 Patients must have a histologically confirmed diagnosis of urothelial carcinoma of the bladder, urethra, ureter, or renal pelvis from a CLIA-certified laboratory, with measurable disease by RECIST (version 1.1) including lymphadenopathy and visceral metastatic disease

2.1.3.2 Adult patients ≥ 18 years of age.

2.1.3.3 Patient must have received at least one platinum based regimen of chemotherapy and/or an immune-checkpoint inhibitor if appropriate with progressive disease.

2.1.3.4 Prior antiangiogenic and radiation therapy are permitted (2-week washout from therapy is required).

2.1.3.5 Bisphosphonates and denosumab are permitted if on a stable dose for ≥4 weeks.

2.1.3.6 ECOG 0–2

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

– leukocytes	≥3,000/mcL
– absolute neutrophil count	≥1,500/mcL without growth factor support
– platelets	≥100,000/mcL without growth factor support
– hemoglobin	≥9 g/dL, and no blood transfusion within 4 weeks.
	OR
– hemoglobin	>10 g/dL, and no blood transfusion within 2 weeks.
– total bilirubin	≤1.5 x ULN (≤ 3 × ULN for subjects with Gilbert's Disease)
– AST(SGOT)/ALT(SGPT)	≤2.5 X institutional upper limit of normal (≤ 5X ULN if liver mets)
– creatinine	≤ ULN
	OR
– creatinine clearance	≥51 mL/min (calculated using the Cockroft-Gault formula) for patients with creatinine levels above institutional normal.
– PT/INR and aPTT	within 1.25 X ULN institutional limits, except where a lupus anti-coagulant has been confirmed

2.1.3.8 Individuals who can father children and their partners must agree to use highly effective contraception (refer to section 4.2 for details) prior to study entry, for the duration of study participation and for 3 months following last dose of study drugs. Individuals who are of childbearing potential and sexually active must agree to the use of 1 highly effective form of contraception, and their partners, if they can father children, must use a condom, or they must totally/truly abstain from any form of sexual intercourse, throughout their participation in the study and for at least 6 months after last dose of study drugs. Individuals should not donate sperm throughout the period of taking olaparib and for 3 months following the last dose of olaparib. Individuals of childbearing potential (IOCBP) are defined as being physically capable of becoming pregnant unless unable have children because of surgery or other medical reasons (effective tubal ligation, ovaries or the uterus removed, or are post-menopausal). Post-menopausal is defined as:

- Amenorrheic for 1 year (12 months in a row) or more following cessation of exogenous hormonal treatments,
- LH and FSH levels in the post-menopausal range for individuals under 50,
- radiation-induced oophorectomy with last menses >1 year ago,

- chemotherapy-induced menopause with >1 year interval since last menses,
- or surgical sterilization of participant (bilateral oophorectomy or hysterectomy) and/or partner.

2.1.3.9 Patients must be able to tolerate oral medications and not have gastrointestinal illnesses that would preclude absorption of olaparib.

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

2.1.3.11 Willingness to release archival tissue sample for research purposes, if available

2.1.4 Inclusion Criteria for mCRPC Expansion Cohort (accrual to the mCRPC cohort ended with amendment version 7/27/2021)

2.1.4.1 Patients must have metastatic, progressive, castrate resistant prostate cancer (mCRPC).

2.1.4.2 Documented histopathological confirmation of prostate cancer from a CLIA-certified laboratory.

2.1.4.3 All patients must have at least one lesion deemed safe to biopsy and be willing to undergo a mandatory baseline biopsy.

2.1.4.4 Patients must have received prior treatment with enzalutamide and/or abiraterone with the exception of patients who were treated with docetaxel and androgen deprivation therapy for metastatic castrate-sensitive prostate cancer and progressed on docetaxel treatment or who progress within one month of the last docetaxel dose.

2.1.4.5 Patients must have castrate levels of testosterone (<50 ng/dl [1.74 nmol/l])

2.1.4.6 Patients must have undergone bilateral surgical castration or must agree to continue on GnRH agonists/antagonists for the duration of the study.

2.1.4.7 ECOG performance status ≤ 2

2.1.4.8 Patients must have adequate bone marrow, hepatic, and renal function with:

– leukocytes	≥3,000/mcL
– absolute neutrophil count	≥1,500/mcL without growth factor support
– platelets	≥100,000/mcL without growth factor support
– hemoglobin	≥9 g/dL, and no blood transfusion within 4 weeks.
	OR
– hemoglobin	>10 g/dL, and no blood transfusion within 2 weeks.
– total bilirubin	≤1.5 x ULN (≤ 3 × ULN for subjects with Gilbert's Disease)
– AST(SGOT)/ALT(SGPT)	≤3 X institutional upper limit of normal (≤ 5X ULN if liver mets)

– creatinine	≤ ULN OR
– creatinine clearance	≥51 mL/min (calculated using the Cockroft-Gault formula) for patients with creatinine levels above institutional normal.

2.1.4.9 Men must be at least 18 years of age.

2.1.4.10 Patient must be capable of understanding and complying with protocol requirements and is willing to give informed consent.

2.1.4.11 Individuals who can father children and their partners must also agree to use adequate contraception (refer to section 4.2 for details) prior to the study and for the duration of study participation and for 3 months after last dose of study drugs. Individuals should not donate sperm throughout the period of taking olaparib and for 3 months following the last dose of olaparib

2.1.4.12 Patients who were treated for metastatic castrate-sensitive prostate cancer with docetaxel and androgen deprivation therapy who progress on docetaxel treatment or who progress within one month of the last docetaxel dose are eligible.

2.1.5 Exclusion Criteria - Phase I and II SCLC and UC Expansion Cohort (note: accrual to the UC cohort ended with amendment version 08/17/2022)

2.1.5.1 Patients who are receiving any other investigational agents.

2.1.5.2 Persistent toxicities (≥ CTCAE grade 2) with the exception of alopecia and neuropathy, caused by previous cancer therapy

2.1.5.3 Patients who have had prior treatment with olaparib or other camptothecin inhibitors (UC expansion Cohort Only).

2.1.5.4 Patients with myelodysplastic syndrome/acute myeloid leukemia or active pneumonitis; or baseline features suggestive of myelodysplastic syndrome or acute myelogenous leukemia on peripheral blood smear or bone marrow biopsy, if clinically indicated.

2.1.5.5 Hypersensitivity to study therapies and its excipients

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

2.1.5.7 History of allergic reactions attributed to compounds of similar chemical or biologic composition to EP0057 and/or olaparib or other agents used in study.

2.1.5.8 Patients receiving any medications or substances that are strong and moderate inhibitors or inducers of CYP3A are ineligible. Lists including medications and substances known or with the potential to interact with the CYP3A isoenzymes are provided in **Appendix B**, Section 16.2.

2.1.5.9 Pregnant individuals are excluded from this study because EP0057 and/or olaparib are agents with the potential for teratogenic or abortifacient effects. Because there is an unknown but potential risk for adverse events in nursing infants secondary to treatment of the mother with EP0057 and/or olaparib, breastfeeding should be discontinued if the

mother is treated with EP0057 and/or olaparib. These potential risks may also apply to other agents used in this study.

2.1.5.10 HIV-positive patients on combination antiretroviral therapy are ineligible because of the potential for pharmacokinetic interactions with EP0057 and/or olaparib. 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.

2.1.5.11 Prolongation of QT/QTc interval (QTc interval >500 msec) using the Fredericia method of QTc analysis or family history of long QT syndrome. If single reading is above these minimum ranges, then repeat test in triplicate and evaluate eligibility based on average value

2.1.5.12 Any chronic or concurrent acute liver disease.

2.1.5.13 History of stroke, transient ischemic attack (TIA), or myocardial infarction, within 6 months prior to C1D1

2.1.5.14 Uncontrolled concurrent disease or illness including but not limited to:

- symptomatic congestive heart failure, unstable angina pectoris, clinically significant cardiac arrhythmia
- unstable or untreated cardiac conditions or ejection fraction of <50% as determined by echocardiogram (ECHO) or multiple gated acquisition scan (MUGA)
- uncontrolled diabetes mellitus
- psychiatric illness that would limit compliance with study requirements, as determined by the Investigator

2.1.5.15 Other severe, acute, or chronic medical or psychiatric condition or laboratory abnormality that may increase the risk associated with study participation or study drug administration or that may interfere with the interpretation of study results and, in the judgment of the investigator, would make the patient inappropriate for the study.

2.1.6 Exclusion Criteria - mCRPC Expansion Cohort (accrual to the mCRPC cohort ended with amendment version 7/27/2021)

2.1.6.1 Patients who have had prior treatment with olaparib or other camptothecin inhibitors.

2.1.6.2 The patient has received chemotherapy, radiotherapy, biologic agents or enzalutamide within 3 weeks before the first dose of study treatment (nitrosoureas or mitomycin within 6 weeks). However, for patients receiving abiraterone, they must discontinue the medication at least 14 days before the first dose of study treatment.

2.1.6.3 The patient has received any other type of investigational agent within 28 days before the first dose of study treatment.

2.1.6.4 The patient has received radionuclide treatment within 6 weeks prior to the first dose of the study treatment

2.1.6.5 Patients with evidence of CNS metastasis or leptomeningeal disease within 1 year prior to enrollment will 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. Patients with a remote history of brain metastases may be considered if they received sterilizing therapy to the CNS (resection or radiation) and have been CNS progression-free for the 1-year period. Baseline imaging to rule out brain metastases is not required for screening, but should be performed prior to study enrollment if clinically indicated.

2.1.6.6 Patients receiving any medications or substances that are strong and moderate inhibitors or inducers of CYP3A are ineligible. Lists including medications and substances known or with the potential to interact with the CYP3A isoenzymes are provided in **Appendix B**, Section 16.2.

2.1.6.7 The patient has not recovered to baseline or CTCAE ≤ Grade 1 from toxicity due to all prior therapies, including surgery, except alopecia and other non-clinically significant AEs.

2.1.6.8 Uncontrolled concurrent disease or illness including but not limited to:

- symptomatic congestive heart failure, unstable angina pectoris, clinically significant cardiac arrhythmia
- unstable or untreated cardiac conditions or ejection fraction of <50% as determined by echocardiogram (ECHO) or multiple gated acquisition scan (MUGA)
- uncontrolled diabetes mellitus
- psychiatric illness that would limit compliance with study requirements, as determined by the Investigator

2.1.6.9 Any of the following within 6 months before the first dose of study treatment:

- unstable angina pectoris
- stroke (including TIA, or other ischemic event)
- myocardial infarction

2.1.6.10 Other clinically significant disorders such as:

- active infection requiring intravenous treatment within 7 days of starting protocol treatment
- serious non-healing wound/ulcer/bone fracture (excluding stable compression fracture) within 28 days before the first dose of study treatment

2.1.6.11 HIV-positive patients on combination antiretroviral therapy are ineligible because of the potential for pharmacokinetic interactions with the study agent.

2.1.6.12 HBV-or HCV-positive patients are ineligible

2.1.6.13 Prolongation of QT/QTc interval (QTc interval >500 msec) using the Fredericia method of QTc analysis or family history of long QT syndrome. If single reading is above these

minimum ranges, then repeat test in triplicate and evaluate eligibility based on average value

2.2 RECRUITMENT STRATEGIES

It is expected that participants for this single site study will be enrolled from across the United States though there is no exclusion for participants from foreign countries.

Recruitment strategies that can be used for this study *may* include:

1. The study will be publicized on
    a. NIH official websites; (e.g., www.clinicaltrials.gov, NCI cancer clinical trial listing (PDQ), and CCR)
    b. NIH moderated social media platforms [e.*g., Facebook, X, Instagram*]. These sites comply with government terms of service per the NIH Social Media Guidelines)
    c. Research Match https://www.researchmatch.org/about/
    d. Newsletters

The protocol may be abstracted into a plain language announcement-information to be abstracted includes-study title; purpose of the study; protocol summary; basic eligibility criteria; study site location(s); and how to contact the site for further information) and posted/distributed on the above media without IRB approval. Should we add additional descriptive information about the study to these announcements, we will seek IRB approval.

2. Television advertisements/radio advertisements
    a. Clinical Center TV (CCTV) – Clinical Center Television - CCTV | NIH Clinical Center - America's Research Hospital TVs placed all around the NIH Clinical Center will rotate through various messages including one for this study.
3. Newspaper advertisements
4. Videos
5. Publicly posted recruitment flyers and posters
6. Brochures
7. Clinical Center Office of Patient Recruitment Services (OPR) including OPR
    b. Listservs (Email list of those interested in receiving study recruitment updates.) Includes the OPR Protocols and OPR Healthy Volunteers listservs and 3 NIH listservs (NIH Post bac, NIH Clinical Fellows & NIH Study Volunteers)
8. Recruitment Letters
    c. Doctor to patient informational letter: distribution of letters to private health care physicians who will then share the letters with potential participants. This information will be made available in electronic and/or a hard copy as needed. (Note: if material is not to be shared with participants, these are not submitted to the IRB)
    d. Investigator to potential participant letters.

Prior to the distribution of any individual recruitment materials not included in item #1, such materials will be submitted for IRB review, as appropriate.

2.3 SCREENING EVALUATION

2.3.1 Screening activities performed prior to obtaining informed consent

Minimal risk activities that may be performed before the subject has signed a consent include the following:

- Email, written, in person or telephone communications with prospective participants
- Review of existing medical records to include H&P, laboratory studies, etc.
- Review of existing MRI, x-ray, or CT images, etc.
- Review of existing photographs or videos
- Review of existing pathology specimens/reports from a specimen obtained for diagnostic purposes

A waiver of consent for these activities has been requested in Section **12.4.1**.

2.3.2 Screening activities performed after a consent for screening has been signed

The following activities will be performed only after the participant has signed the study consent OR the consent for study 01-C-0129 (provided the procedure is permitted on that study) on which screening activities may also be performed. Assessments performed at outside facilities or on another NIH protocol within the timeframes below may also be used to determine eligibility once a participant has signed the consent.

Screening must be completed within 2 weeks prior to C1D1.

- History and physical exam (including height, weight, vital signs and performance status)
- Blood tests (for organ function)
    - Complete blood count (CBC/Diff)
    - Acute care panel (sodium, potassium, chloride, total CO2 (Bicarbonate), creatinine, glucose, urea nitrogen)
    - Hepatic panel (alkaline phosphatase, ALT/GPT, AST/GOT, total bilirubin, direct bilirubin)
    - Prothrombin time (PT)
    - Partial thromboplastin time (PTT)
    - Viral Markers Protocol Screen (HBsAg, anti-HCV, anti-HIV) within 3 months of C1D1.
- Collection of pathology reports from any certified laboratory for confirmation of diagnosis (may be done prior to the two week screening window).
- CT chest/abdomen/pelvis (mCRPC patients will have baseline CT scans and technetium-99 bone scan imaging within 30 days prior to initiation of therapy)
- Electrocardiogram
- Echocardiogram within 4 weeks prior to C1D1
- Urine or serum HCG for IOCBP (to be performed within 3 days prior to C1D1)
- Serum testosterone level (mCRPC patients only)

2.4 PARTICIPANT REGISTRATION AND STATUS UPDATE PROCEDURES

Registration and status updates (e.g., when a participant is taken off protocol therapy and when a participant is taken off-study) will take place per CCR SOP ADCR-2, CCR Participant Registration & Status Updates found at https://nih.sharepoint.com/sites/NCI-CCR-OCD-Communications/SitePages/OEC-Administrative---Clinical-Research-(ADCR).aspx?Mode=Edit.

2.4.1 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical trial but are not subsequently assigned to the study intervention or entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants, to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details and eligibility criteria.

2.4.2 Treatment Assignment Procedures

Cohorts

Number	Name	Description
1	Phase I	Phase I subjects
2	Phase II SCLC expansion	Phase II expansion cohort of subjects with SCLC
3	Phase II urothelial carcinoma expansion	Phase II expansion cohort of subjects with urothelial carcinoma
4	Phase II mCRPC expansion	Phase II expansion cohort of subjects with mCRPC

Arms

Number	Name	Description
1	Phase I	EP0057 + olaparib
2	Phase II	EP0057 + olaparib at MTD/RP2D

Arm Assignment

All subjects in cohort 1 will be enrolled on arm 1. All subjects in cohorts 2-4 will be enrolled on arm 2. There is no randomization.

Note: Accrual to cohort 4 (mCRPC) ended with amendment version 7/27/2021. Accrual to cohort 3 (urothelial carcinoma) ended with amendment version 8/17/2022.

2.5 BASELINE EVALUATION

Please refer to the Study Calendar (Section 3.4).

3 STUDY IMPLEMENTATION

3.1 STUDY DESIGN

This is a phase I / II open label single center trial. Patients will be enrolled to the phase I portion of the study to determine the maximum tolerated dose (MTD) or recommended phase 2 dose (RP2D). The RP2D is EP0057 12mg/m2 and olaparib 250 mg BID. In phase II, up to 27 evaluable patients with SCLC will be enrolled (Amendment H). To further evaluate clinical response rate to EP0057, up to 34 evaluable patients will be enrolled into a urothelial carcinoma cohort and 25 evaluable patients enrolled into an mCRPC expansion cohort as described in section 10.

Patients meeting the eligibility criteria will receive EP0057 (IV Q 2weeks) plus olaparib (PO BID days 3-13* and days 17-26* administered in 28-day cycles, until disease progression or development of intolerable side effects.

* There should be at least a 48-hour window between EP0057 and olaparib with the exception of dose level 5B in which the window is reduced to 24 hours.

Blood, tumor and hair samples will be collected at multiple time points for PK, PD analyses as described in Section 5.1.1. Tumor biopsies are optional for SCLC and UC patients. mCRPC must have a mandatory baseline biopsy. If an SCLC patient opts for a biopsy, it will be performed at the following time points: pre-treatment, on cycle 1 day 4 and at disease progression. Patients will be asked to consent to the optional biopsy at the time of the procedure. If patients choose not to have the biopsy, that will be documented in the medical record and noted in the research record.

Toxicity will be graded according to CTCAE version 4.0. Tumor assessments will be made using CT scans (chest, abdomen and pelvis) at baseline and after every 2 cycles according to RECIST version 1.1. Tumor assessments will be discontinued at the time of progression. Subsequently follow-up for survival will be carried out every 3 months.

Between May 2016 and November 2016, 8 patients enrolled on this trial. No DLTs were observed among the first 3 patients who enrolled at dose level 1. At dose level 2, three patients did not have DLTs. Patients 6 and 7 at dose level 2 were not evaluable due to early and rapid disease progression prior to completion of DLT assessment period. In the patients enrolled to date at 2 dose levels, we have not seen dose limiting toxicities, specifically myelosuppression.

With amendment A, we would like to dose escalate olaparib from 200 mg to 300 mg between dose levels 3 and 4. This represents a 50% increase in the dose of olaparib (compared with 25% increase proposed in the earlier schema from 200 to 250 mg). If olaparib 300 mg is not tolerated (2 or more DLTs), dose escalation will be stopped and 250 mg dose level will be explored. Additionally, with amendment A, if the highest dose level (dose level 5) is well tolerated, the interval between EP0057 and olaparib will be abbreviated at the next dose level (dose level 5B) from 48 hours to 24 hours.

With amendment E, patients are to be enrolled at RP2D (DL 4R, EP0057 at 12 mg/m^2 and olaparib at 250 mg) in Phase II part of the trial as Phase I part of the study is now completed; it was determined that olaparib at the dose level 4R, 250 mg, is well tolerated.

Provisional Dose levels	EP0057, mg/m2 (IV q 2 weeks D1 and D15)	Olaparib tablet, mg (PO BID Days 3-13* and 17-26*)
1	12	100
2	12	150
3	12	200
4	12	300**
$4R_{(educed)}$ (MTD/RP2D)	12	250
5 (Not explored)	15	300
5B (Not explored)	15	300
28-day cycles; biopsies pre-treatment and on day 4 (24 hours post- olaparib) and at disease progression; * There should be a minimum 48-hour window between EP0057 and olaparib except dose level 5B which allows the interval to be abbreviated to 24 hours. The recommended phase 2 dose (RP2D) may be lower than, or equal to, the MTD. Phase II portion of this study may start with RP2D, and/or at MTD. ** An additional dose level (4R) of 250 mg has been evaluated with DLTs in 1 of 6 patients as there were 2 or more DLTs among 6 patients treated at dose level 4.		

With amendment version 07/27/2021, accrual to the mCRPC cohort is to cease given the incidence and possibly the severity of hematuria/cystitis in participants with GU malignancies and slow cohort accrual following FDA approval of Olaparib for prostate cancer.

Accrual to the urothelial carcinoma cohort ended with amendment version 08/17/2022.

3.1.1 Dose Limiting Toxicity

During the phase 1 portion of the study subjects will be monitored for DLTs during the first cycle unless otherwise indicated. DLTs will be defined using the National Cancer Institute (NCI) CTCAE (Version 4). The following events, occurring during cycle 1 of the study combination, will be considered DLTs if deemed drug-related:

- Grade 4 neutropenia complicated by fever ≥ 38.5 °C (i.e. febrile neutropenia) and/or documented infection;
- Grade 4 neutropenia that does not resolve within 7 days*
- Grade 4 thrombocytopenia that does not resolve within 7 days* or any grade 3-4 thrombocytopenia complicated with hemorrhage;

- Grade 4 anemia that does not resolve within 7 days despite optimal therapy (withholding study drug and red blood cell transfusions);
- Inability to begin subsequent treatment course within 28 days of the scheduled date, due to study drug toxicity;
- Any grade 3-4 non-hematologic toxicity (except fatigue/asthenia < 2 weeks in duration; mucositis in subjects who have not received optimal therapy for mucositis; vomiting or diarrhea lasting less than 72 hours whether treated with an optimal anti-emetic or anti-diarrheal regimen or not; or alkaline phosphatase changes).

*Note: In the event of a Grade 4 neutropenia or thrombocytopenia, a full blood count must be performed no more than 7 days after the onset of the event to determine if a DLT has occurred. The subject will be closely monitored until resolution to Grade 3 or less.

3.1.2 Dose Escalation

Dose escalation will proceed in groups of 3–6 patients. The MTD is the dose level at which no more than 1 of up to 6 patients experience DLT during the DLT evaluation period, and the dose below that at which at least 2 (of ≤6) patients have DLT as a result of the drug. If a patient did not experience DLT and did not finish cycle 1 of treatment, he or she will not be evaluable for toxicity and will be replaced in the dose level. Patients who do not complete the DLT evaluation period and do not have a DLT will be replaced.

The theoretical maximum number of subjects required to determine the MTD in the phase 1 portion of the study is 30 subjects (6 per dose level), although it is expected that as few as 15 subjects in 4 dose levels would be required to reach an MTD.

The recommended phase 2 dose (RP2D) may be lower than, or equal to, the MTD. Phase II portion of this study may start with RP2D, and/or at MTD.

Dose escalation will follow the rules outlined in the **Table 5** below.

Table 5. Dose Escalation Guidelines

Number of Patients with DLT at a Given Dose Level	**Escalation Decision Rule**
0 out of 3	Enter up to 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). Up to 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 up to 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. UP to 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 the MTD and is generally the recommended phase 2 dose. At least 6 patients must be entered at the recommended phase 2 dose.

3.2 DRUG ADMINISTRATION

3.2.1 EP0057

EP0057 will be diluted with 5% dextrose for injection (D5W) to a total volume of 500 mL and should be infused intravenously as described in section 14.1.6 over 60-75 minutes. Nothing else should be added to the bag.

The EP0057 infusion should begin immediately after preparation and diluted EP0057 infusion solution not used within 6 hours should be destroyed following institutional practices.

3.2.1.1 Premedication Prior to EP0057 Treatment and Pre and Post Hydration

Subjects will receive up to 1,000 ml of 0.9% normal saline solution IV hydration before and after administration of EP0057 to reduce risk of cystitis adverse reaction. Hydration levels should be adjusted as needed by the Investigator based on any underlying health conditions of the subject.

Hypersensitivity reaction (HSR) have been observed in a small number of subjects treated with EP0057. Most HSR associated with EP0057 are mild and moderate, reversible upon study drug interruption. In general, subjects restarted EP0057 infusion at a slower infusion rate without recurrence. In addition to the mandatory premedication to prevent HSR, the duration of EP0057 infusion must be prolonged from 1 hour to approximately 2 hours.

Appropriate resuscitation equipment should be available in the room and a physician readily available during the period of study drug infusion.

Subjects should be pre-medicated with the following 3 drug classes 30-120 minutes* prior to start of EP0057 infusion to reduce likelihood of hypersensitivity adverse reactions:

- a corticosteroid (dexamethasone 20 mg IV) 30-120 minutes prior to start of EP0057
- an antihistamine (diphenhydramine 50 mg PO)
- an H2 antagonist (ranitidine 50 mg IV)

Premedication with antiemetics such as a 5-HT3 receptor antagonist are to be administered to reduce the potential for nausea. Suggested antiemetics include dolasetron (PO), granisetron (PO or IV) or ondansetron (PO or IV) 30-120 minutes prior to starting EP0057 infusion.

The example medications, route of administration, and dose indicated should be the medication-of-choice if clinically feasible. It is acknowledged that the premedication regimen may be altered for patient safety during the study (for example, if a patient experiences a hypersensitivity/infusion reaction related to study drug, the premedication regimen may be altered for subsequent cycle dosing based on the investigator's discretion).

* Contact study team if the time after pre-medications exceeds 120 minutes.

3.2.2 Olaparib

Olaparib tablet at the appropriate dose level will be given orally on days 3-13* and days 17-26* twice daily (*there should be at least a 48-hour window between olaparib and EP0057 except dose level 5B which allows the window to be abbreviated to 24 hours). The correct number of 25 mg, 100 mg, 150 mg or 200 mg tablets comprising the appropriate dose should be taken at the same times each day with approximately 240 mL of water. A light snack (biscuits/ toast) is advised at the time of dosing to help alleviate nausea but no specific timing needs to be observed. The olaparib tablets should be swallowed whole and not chewed, crushed, dissolved or divided.

Olaparib will be dispensed at the start of each cycle. Patients will be provided with a pill diary (**Appendix C**, Section 16.3), instructed in its use, and asked to bring it with them to each appointment.

For Phase II, it is recommended, but not required, that growth factors be given prophylactically starting cycle 1 on the phase II part of the study. Please note that G-CSF should not be used within at least 24 hours of the last dose of EP0057 administration.

If vomiting occurs shortly after the olaparib capsules are swallowed, the dose should only be replaced if all of the intact capsules can be seen and counted. Should any patient enrolled on the study miss a scheduled dose, the patient will be allowed to take the scheduled dose up to a maximum of 2 hours after that scheduled dose time. If greater than 2 hours after the scheduled dose time, the missed dose should not be taken, and the patient should take their allotted dose at the next scheduled time.

Olaparib can be taken continuously in cases where EP0057 is missed for any reason.

3.3 DOSE MODIFICATIONS

The dose levels and the general approach to dose modification of EP0057 and olaparib are shown below. AEs should be treated with the appropriate maximum intervention, and dose reductions should be clearly documented in the note.

3.3.1 General Recommendation for Dose Modification

Table 6. Olaparib Dosage Schedule

Dose Level	Olaparib dosage schedule		
	Starting dose	**First dose reduction**	**Second dose reduction**

-1	100 mg twice daily	75 mg twice daily	50 mg twice daily
1	100 mg twice daily	75 mg twice daily	50 mg twice daily
2	150 mg twice daily	100 mg twice daily	75 mg twice daily
3	200 mg twice daily	150 mg twice daily	100 mg twice daily
4 and 5	300 mg twice daily	250 mg twice daily	200 mg twice daily
4R (RP2D)	250 mg twice daily	200 mg twice daily	150 mg twice daily

Table 7. EP0057 Dosage Schedule

Dose Level	**EP0057 dosage schedule**		
	Starting dose	**First dose reduction**	**Second dose reduction**
-1	9 mg/m2 q 2weeks	6 mg/m2 q 2weeks	4 mg/m2 q 2weeks
1-4 & 4R	12 mg/m2 q 2weeks	9 mg/m2 q 2weeks	6 mg/m2 q 2weeks
5	15 mg/m2 q 2weeks	11 mg/m2 q 2weeks	7 mg/m2 q 2weeks

3.3.2 Dosing Delays/Dose Modifications and Management of Toxicities

- In the case of toxicity, appropriate medical treatment should be used (including anti-emetics, anti-diarrheals, etc.).
- Once a patient has a dose reduction for toxicity, the dose will not be increased.
- A maximum of 2 dose reductions is permitted
- If either agent is discontinued due to toxicity, the patient may continue on the other agent.
- Participants continuing to experience toxicity at the off treatment visit will be contacted for additional assessments until the toxicity has resolved or is deemed irreversible. Patients must remain on the study to have additional assessment.
- For AEs that are unrelated to the study drugs, study drug may be held for up to 21 days at the discretion of the PI.
- The associate investigator and/or PI will determine whether one or both drugs are responsible for an observed toxicity and will manage that toxicity as described below.

3.3.2.1 Hematologic toxicities

Table 8. Dose Modification and Management of Hematologic Adverse Events

Observation	Action
<u>On day 1 and 15</u> Absolute neutrophil count (ANC) ≥ 1500/mcL **AND** Platelets ≥ 75,000/mcL **AND** Hemoglobin ≥ 8 g/dL	No interruption.
<u>On day 1 and 15</u> ANC < 1500/mcL **OR** Platelets < 75,000/mcL **OR** Hemoglobin < 8 g/dL	If any weekly evaluation demonstrates grade ≥ 3 neutropenia or grade ≥ 2 thrombocytopenia, a repeat **hematology assessment will be obtained 2-4 days later.** *On first occurrence*, hold the drug(s) causing the toxicity for up to 21 days until ANC ≥ 1500/mcL, platelets ≥ 75,000/mcL, and hemoglobin ≥ 9 g/dL. The associate investigator and/or PI will determine whether one or both drugs are responsible for an observed toxicity and will initiate appropriate medical therapy and no change in dose upon re-initiation. *On second occurrence*, hold the drug(s) causing the toxicity for up to 21 days until ANC ≥ 1500/mcL, platelets ≥ 75,000/mcL, and hemoglobin ≥ 9 g/dL. Initiate appropriate medical therapy. Treatment with olaparib or EP0057 may be restarted at one dose level (DL) lower. Patients whose counts have not recovered to ANC ≥ 1500/mcL, platelets ≥ 75,000/mcL, and hemoglobin ≥ 9 g/dL after 21 days should be removed from the drug causing the toxicity.
<u>At any time during cycle</u> Grade 4 hematologic AE	*On first occurrence,* hold the drug(s) causing the toxicity for up to 21 days until ANC ≥ 1500/mcL, platelets ≥ 75,000/mcL, and hemoglobin ≥ 9 g/dL. Initiate appropriate medical therapy. Treatment with olaparib or EP0057 may be restarted at one DL lower. *On second occurrence,* discontinue the drug(s) causing the toxicity. Follow patient until

Table 8. Dose Modification and Management of Hematologic Adverse Events	
Observation	**Action**
	resolution/stabilization of toxicity. Patients whose counts have not recovered to ANC ≥ 1500/mcL, platelets ≥ 75,000/mcL, and hemoglobin ≥ 9 g/dL after 21 days should be removed from the drug causing the toxicity. See section 3.3.2.1 for exceptions.
Toxicities requiring more than 2 dose reductions	Remove patient from the drug causing the toxicity.

- Treatment may be delayed for a maximum of 21 days after holding the treatment for toxicities that develop and do not resolve as defined above (the following AE's are exempt from hold: lymphopenia, or leukopenia in the absence of grade 3 or higher neutropenia).
- Weekly blood counts will be obtained during the first cycle, and then at day 1 and 15 of subsequent cycles.
- Management of prolonged hematological toxicities while on study treatment

  If a patient develops prolonged hematological toxicity such as:
  ≥2 week interruption/delay in study treatment due to CTC grade 3 or worse anemia and/or development of blood transfusion dependence
  ≥3 week interruption/delay in study treatment due to CTC grade 3 or worse neutropenia (ANC < 1,000/mcL)
  ≥3 week interruption/delay in study treatment due to CTC grade 3 or worse thrombocytopenia (Platelets < 50,000/mcL)

  Weekly differential blood counts including reticulocytes (calculate reticulocyte index (RI), RI = reticulocyte count x hematocrit (Hct)/normal Hct; a value of 45 is usually used for normal Hct) and peripheral blood smear should be performed. If any blood parameters remain clinically abnormal after 4 weeks of dose interruption, the patient should be referred to hematologist for further investigations. Bone marrow analysis and/or blood cytogenetic analysis should be considered at this stage according to standard hematological practice.

  Development of a confirmed myelodysplastic syndrome or other clonal blood disorder should be reported as an SAE. Study treatment should be discontinued if diagnosis of myelodysplastic syndrome is confirmed.

3.3.2.2 Neutropenia

- Phase I: Growth factors to prevent neutropenia will not be administered during the DLT period in phase I but may be used thereafter to prevent/treat neutropenia. Please note that G-CSF should not be used within at least 24 hours of the last dose of EP0057 administration.

3.3.2.3 Thrombocytopenia

- Thrombocytopenia will be treated conservatively. In the absence of bleeding, or a necessary invasive procedure, platelet transfusions should be given for a platelet count ≤ 10,000/mcL.
- If invasive procedure(s) is (are) planned, or the patient develops bleeding, platelet transfusions should be administered in accordance with the standard of practice, usually maintaining a platelet count above 50,000/mcL.

3.3.2.4 Anemia

- Symptomatic anemia should be treated with red blood cell transfusion and is recommended if the hemoglobin falls below 8 g/dL or the patient is symptomatic.

3.3.3 General Recommendations for Dose Modification and Management of Non-Hematologic Adverse Events

- The management of general AEs not otherwise specified in the following sections should be as per **Table 9**.
- At the discretion of the investigator, the study drugs may be held or dose modified independently if the observed toxicity is attributed to only one of the drugs, while the patient continued to receive the drug not associated with the observed toxicity.
- Dose modifications for nausea, vomiting, and diarrhea will be made only if they are refractory to treatment. The time a given drug is held should not exceed 21 days.

Table 9. General Management of Adverse Events (Non-Hematologic)

Observation	Action
Grade 1 or 2 AEs resolves promptly (within 48 hours) with supportive care	Maintain dose level (DL)
Any ≥ grade 3 non-hematologic*	Hold study drug(s) causing the toxicity for up to 21 days until toxicity resolves to ≤ grade 1. Treatment with olaparib or EP0057 may be restarted at one DL lower, as per the dose reduction guidelines.
Grade 3 or 4 non-hematologic AE related to drugs that does not resolve to grade 1 or less within 21 days despite maximum supportive care after treating patient at the lowest reduced DL	Remove patient from the drug causing the toxicity.
Toxicities requiring more than 2 dose reductions	Remove patient from the drug causing the toxicity.

*Except fatigue/asthenia < 2 weeks in duration; mucositis in subjects who have not received optimal therapy for mucositis; vomiting or diarrhea lasting less than 72 hours whether treated with an optimal anti-emetic or anti-diarrheal regimen or not; or alkaline phosphatase changes

- Management of new or worsening pulmonary symptoms

If new or worsening pulmonary symptoms (e.g. dyspnea) or radiological abnormality occurs, an interruption in olaparib dosing is recommended and a diagnostic workup (including a high resolution CT scan) should be performed, to exclude active pneumonitis. Following investigation, if no evidence of abnormality is observed on CT imaging and symptoms resolve, then olaparib treatment can be restarted, if deemed appropriate by the investigator.

3.3.4 Management of the hypersensitivity/infusion reactions

Table 10. Management of the hypersensitivity/infusion reactions

Hypersensitivity reaction	
Grade 1 or 2	**Stop** infusion immediately, continue hydration fluids and provide medications as indicated per institutional guidelines. If symptoms resolve within 1-2 hours, at Investigator's discretion may re-start study drug administration at slower rate (i.e. 2x slower rate) and increase rate slowly to complete administration of full dose. OR **Hold** dose administration on day of event, and resume treatment at next scheduled day at same dose level. At Investigator's discretion may administer subsequent dose using a desensitization protocol as per institutional guidelines.
Grade 3 or 4	**Stop** infusion immediately and administer medical support as indicated per institutional guidelines. **Hold** dose administration on day of event. **Review** with study Principal Investigator to determine whether to discontinue from study drug treatment. Confirm that rate of administration was appropriate and premeds were given as suggested.

Administration of EP0057 should be over 2 hours (using the following infusion schedule) with additional pre-medications (dexamethasone 20mg IV, ranitidine 50mg IV, acetaminophen 650mg PO, ondansetron 16mg PO or IV and Benadryl 50mg PO).

EP0057 in 500ml 5% dextrose IV infusion

15mL/hr for 15 minutes, then increase to

30mL/hr for 15 minutes, then increase to

60mL/hr for 15 minutes, then increase to

120mL/hr for 15 minutes, then increase to

240mL/hr for 15 minutes, then increase to

480mL/hr for 15 minutes, then increase to

528mL/hr for 30 minutes to complete infusion

3.3.5 Dose Modification for Surgical Procedures or Palliative Radiation

- Olaparib should be stopped 3 days before surgery and re-started after wound has healed following recovery.
- No stoppage of olaparib is required for any biopsy procedures.
- Olaparib should be discontinued for a minimum of 3 days before a patient undergoes therapeutic palliative radiation treatment.

3.3.6 Laboratory safety assessment

Full hematology assessments for safety (hemoglobin, red blood cells [RBC], platelets, mean cell volume [MCV], mean cell hemoglobin concentration [MCHC], mean cell hemoglobin [MCH], white blood cells [WBC], absolute differential white cell count (neutrophils, lymphocytes, monocytes, eosinophils and basophils) and absolute neutrophil count or segmented neutrophil count and Band forms should be performed weekly during Cycle 1, at each subsequent visit, and when clinically indicated. If absolute differentials are not available, percentage differentials are acceptable. Coagulation [activated partial thromboplastin time (APTT) and international normalized ratio (INR)] will be performed at baseline and if clinically indicated. Patients taking warfarin may participate in this study; however, it is recommended that prothrombin time (INR and APTT) be monitored carefully at least once per week for the first month, then monthly if the INR is stable.

Biochemistry assessments for safety include an acute care panel and hepatic panel. These tests should be performed weekly during Cycle 1, at each subsequent visit, and when clinically indicated. The mCRPC cohort will have additional assessments specified in 3.4**.**

Urine or serum HCG for IOCBP (to be performed within 3 days of C1D1) is to be performed at screening only.

Bone marrow or blood cytogenetic samples may be collected for patients with prolonged hematological toxicities.

Additional analyses may be performed if clinically indicated.

Any clinically significant abnormal laboratory values should be repeated as clinically indicated.

3.4 STUDY CALENDAR

On study assessments can be performed within ±7 days of the specified time, unless otherwise indicated. Treatments may be delayed up to 7 days to accommodate scheduling.

Procedure	***Screening***	***Baseline[2]***	***Cycles = 28 days[1]***										***End of Treatment/ Disease Progression[13]***	***Post Therapy Follow-up[4]***
			Day 1	***2***	***3***	***4***	***5***	***7***	***15[28]***	***21***	***28***	***Cycle 2[22] Day 1***		
History	X											X	X	
Physical exam[3]	X	X							X				X	
PTT/PT [23]	X	X												
Viral Markers Protocol Screen[17]	X													
CBC diff [5, 20]	X	X						X[14]	X	X		X	X	
Acute Care Panel[6,20]	X	X						X[14]	X	X		X	X	
Hepatic Panel[7, 20]	X	X						X[14]	X	X		X	X	
Mineral Panel (mCRPC only) [24]			X						X					
LDH, Creatine kinase, Uric Acid, Total Protein (mCRPC only)		X										X		
Pregnancy test[8]	X	X										X		
CT scan[12]	X[15]	X											X	
CT c/a/p and bone scan (mCRPC only)	X	X										X[25]	X	
PSA (mCRPC only)		X										X[25]	X	
Clinical disease assessment		X									X		X	
ECG	X	X	X[27]						X[27]			X[27]		
Echocardiogram[21]	X													
Whole blood, plasma, hair[26] and saliva for correlative studies[9, 29]		Refer to tables in section **5**. **Table 11**– Phase 1 and Phase 2 SCLC; **Table 13** – UC expansion; **Table 14** – mCRPC expansion												

Procedure	***Screening***	***Baseline[2]***	***Cycles = 28 days[1]***									***End of Treatment/ Disease Progression[13]***	***Post Therapy Follow-up[4]***
			Day 1	***2***	***3***	***4***	***5***	***7***	***15[28]***	***21***	***28***	***Cycle 2[22] Day 1***		
PK[16, 29]			X	X	X				X[19]					
Biopsies[10]		X				X							X	
EP0057			X						X			X		
Olaparib[11]					X	X	X	X		X				
Follow-up phone call														X

[1] Number of cycles depends on disease progression and development of intolerable side effects
[2] Baseline procedures are performed within 2 weeks of initiation of study therapy with the exception of pregnancy test which must be performed within 3 days prior to the initiation of study therapy. If the procedure was performed during the appropriate timeframe at screening, it is not necessary to repeat at baseline.
[3] Symptom-directed physical examinations will be performed as clinically indicated in the investigator's judgment
[4] Follow-up for survival will be carried out every 3 months
[5] Includes Neutrophils, Lymphs, Monos, Eos, Basos, WBC, RBC, Hemoglobin, Hematocrit, RBC Indices, MCV, RDW, Platelet. Results should be available prior to administration of study drugs
[6] Includes Sodium (NA), Potassium (K), Chloride (CL), Total CO2 (Bicarbonate), Creatinine, random Glucose, Urea or blood urea nitrogen [BUN], eGFR.
[7] Includes Alkaline Phosphatase, ALT/GPT, AST/GOT, Total Bilirubin, Direct Bilirubin
[8] Only for IOCBP; may be obtained up to 3 days prior to Day 1 of each cycle.
[9] Blood, plasma, hair and saliva samples will be collected at multiple time points during cycles 1,2 and each cycle thereafter for hair collection (for specific timepoints on correlative samples collection please refer to section 5.1.1 for Phase I and Phase II cohorts, section 5.1.2 for UC expansion cohort and section 5.1.3 for mCRPC expansion cohort). C1D15 timepoint for correlative studies will only be done for Phase II SCLC cohort. Only whole blood will be drawn for that cohort at that timepoint.
[10] Optional biopsies will be obtained at baseline, during the first treatment cycle (approximately 24 hours after the first dose of olaparib) and at disease progression. In the mCRPC cohort, biopsy at baseline is mandatory.
[11] PO days 3-13 and days 17-26, as indicated in Section 3.2. There should be at least a 48-hour window between EP0057 and olaparib except dose level 5B which allows the interval to be abbreviated to 24 hours. Olaparib can be taken continuously if EP0057 is missed for any reason.
[12] Performed after every 2 cycles
[13] Approximately 4 weeks after treatment discontinuation
[14] Only done in cycle 1
[15] Only done in phase 2
[16] Phase 1 portion of the study in cycles 1 and 6 only.

[17] Within 3 months of C1D1.
[19] D15 PKs can be obtained +/- 5 days.
[20] Weekly during C1, at every visit for subsequent cycles, and whenever clinically indicated
[21] Within 4 weeks
[22] C2 and all subsequent cycles, Day 1
[23] All patients should get tested at screening. Patients taking warfarin will be monitored at least weekly for C1, then monthly if the INR is stable.
[24] Includes Albumin, Calcium, Magnesium and Phosphorus
[25] PSA is to be analyzed along with measurable lesions evaluated by CT scan of chest/abdomen/pelvis and technetium 99 bone scan every 3 cycles (every 12 weeks).
[26] Hair collection will only be done for Phase I cohorts.
[27] ECG required within 60 -180 minutes post-infusion for first two cycles of EP0057 for patients with any conduction abnormality on baseline ECG.
[28] Day 15 assessments not required for patients on olaparib only.
[29.] This protocol targets patients with aggressive tumors and, historically, minimal tissue is available (majority of patients are unresectable at diagnosis). Hence, the priority is to perform biopsies followed by treatment initiation as quickly as possible. In instances where research labs including PKs cannot be obtained due to scheduling conflicts, samples may be omitted or collected in a delayed fashion.

3.5 COST AND COMPENSATION

3.5.1 Costs

NIH does not bill health insurance companies or participants for any research or related clinical care that participants receive at the NIH Clinical Center. If some tests and procedures are performed outside the NIH Clinical Center, participants may have to pay for these costs. Medicines that are not part of the study treatment will not be provided or paid for by the NIH Clinical Center.

3.5.2 Compensation

Participants will not be compensated on this study.

3.5.3 Reimbursement

The NCI will cover the costs of some expenses associated with protocol participation. Some of these costs may be paid directly by the NIH and some may be reimbursed to the participant/guardian as appropriate. The amount and form of these payments are determined by the NCI Travel and Lodging Reimbursement Policy.

3.6 CRITERIA FOR REMOVAL FROM PROTOCOL THERAPY AND OFF STUDY CRITERIA

Prior to removal from protocol, effort must be made to have all subjects complete a safety visit approximately 30 days following the last dose of study therapy.

3.6.1 Criteria for Removal from Protocol Therapy

- Progressive disease
- Participant requests to be withdrawn from active therapy
- Unacceptable Toxicity as defined in Sections 3.1.1 and 3.3
- Toxicity related dose delay lasting longer than 21 days in which case patient will be removed from the drug causing the toxicity.
- Investigator discretion
- Requirement for any of the prohibited study drugs as described in **Appendix B**, Section 16.2 (Strong and moderate Inhibitors and Inducers of CYP3A)
- The subject becomes pregnant
- Active pneumonitis

3.6.2 Off-Study Criteria

- Participant requests to be withdrawn from study
- Investigator decision to end study
- Death
- Permanent loss of capacity to consent
- Screen failure

4 CONCOMITANT MEDICATIONS/MEASURES

- No other chemotherapy, hormonal therapy (HRT is acceptable) or other novel agent is to be permitted during the course of the study for any patient (the patient can receive a stable dose of corticosteroids during the study as long as these were started at least 4 weeks prior to treatment, as per exclusion criteria above). For the mCRPC cohort, patients may receive hormonal therapy in the form of GnRH agonists/antagonists as per eligibility criteria above and corticosteroids are permissible.
- Live virus and bacterial vaccines should not be administered whilst the patient is receiving study medication and during the 30 day follow up period. An increased risk of infection by the administration of live virus and bacterial vaccines has been observed with conventional chemotherapy drugs and the effects with olaparib are unknown.
- No concomitant use of alternative, complementary therapies or over-the-counter agents will be allowed without approval of the PI. All medications must be recorded in the case report form and be reviewed by the treating physician at each visit.
- Caution should be exercised in the concomitant use of any medication that may markedly affect renal function. Such medications may be used with caution as deemed essential for treatment, or if already in use prior to entry in the study without any effect on renal function.
- Caution should be exercised in concomitant use of any medication that may significantly affect hepatic CYP450 drug metabolizing activity by way of enzyme induction (e.g. Phenytoin) or inhibition (e.g. ketoconazole, ritonavir, erythromycin) within 2 weeks before the first dose of olaparib and throughout the study period.
- Given this data, potent inhibitors or inducers of CYP3A4 (as outlined in **Appendix B**, Section 16.2 must not be used during this study.
- CYP3A4 known potent inhibitors: wash-out period 1 week, or at least 4.5x elimination half-lives for drugs and metabolites known to inhibit CYP3A subfamily enzymes: Ketoconazole, itraconazole, ritonavir, indinavir, saquinavir, telithromycin, clarithromycin and nelfinavir
- CYP3A4 inducers (potential reduction in efficacy of olaparib) a wash-out period for 3 weeks for Phenytoin, rifampicin, rifapentin, rifabutin, carbamazepine, phenobarbital, nevirapine, modafinil and St John's Wart.
- Patients should avoid concomitant use of drugs, herbal supplements and/or ingestion of foods known to modulate CYP3A4 enzyme activity from the time they enter the screening period until 30 days after the last dose of study medication. *In vitro* data have shown that the principal enzyme responsible for the formation of the 3 main metabolites of olaparib is CYP3A4 and consequently, this restriction is required to ensure patient safety.
- Olaparib inhibits CYP3A4 *in vitro* and is predicted to be a mild CYP3A inhibitor *in vivo*. Therefore, caution should be exercised when sensitive CYP3A substrates or substrates with a narrow therapeutic margin (e.g. simvastatin, cisapride, cyclosporine, ergot alkaloids, fentanyl, pimozide, sirolimus, tacrolimus and quetiapine) are combined with olaparib.
- Substrates of UGT1A1 should also be given with caution in combination with olaparib (e.g. irinotecan, nintedanib, ezetimibe, raltegravir or buprenorphine).

- Induction of CYP1A2, 2B6 and 3A4 has been shown in vitro with CYP3A4 CYP2B6 being most likely to be induced to a clinically relevant extent. The potential for olaparib to induce CYP2C9, CYP2C19 and P-gp is unknown. It cannot be excluded that olaparib upon co administration may reduce the exposure to substrates of these metabolic enzymes and transport protein. The efficacy of hormonal contraceptives may be reduced if co administered with olaparib.
- In vitro olaparib has been shown to be an inhibitor of P-gp, OATP1B1, OCT1, OCT2, OAT3, MATE1 and MATE2K and is a weak inhibitor of BRCP. It cannot be excluded that olaparib may increase the exposure to substrates of P-gp (e.g. statins, digoxin, dabigatran, colchicine), OATP1B1 (e.g. bosentan, glibenclamide, repaglinide, statins, and valsartan), OCT1 (e.g. metformin), OCT2 (e.g. serum creatinine), OAT3, MATE1 and MATE2K. In particular, caution should be exercised if olaparib is administered in combination with any statin.

4.1 SUPPORTIVE CARE

Patient should receive general concomitant and supportive care medications based on best medical practice.

The use of any natural/herbal products or other "folk remedies" should be discouraged.

Olaparib is an investigational drug for which no data on in vivo interactions are currently available. Based on in vitro data and clinical exposure data, olaparib is considered unlikely to cause clinically significant drug interactions through inhibition or induction of cytochrome P450 enzyme activity. In vitro data have, however, also shown that the principal enzyme responsible for the formation of the 3 main metabolites of olaparib is CYP3A4 and consequently, to ensure patient safety, the following potent inhibitors of CYP3A4 must not be used during this study for any patient receiving olaparib.

While this is not an exhaustive list, it covers the known potent inhibitors, which have most often previously been reported to be associated with clinically significant drug interactions:

- ketoconazole, itraconazole, ritonavir, idinavir, saquinavir, telithromycin, clarithromycin and nelfinavir

For patients taking any of the above, the required wash-out period prior to starting olaparib is one week.

In addition, to avoid potential reductions in exposure due to drug interactions and therefore a potential reduction in efficacy, the following CYP3A4 inducers should be avoided:

- Phenytoin, rifampicin, rifapentine, rifabutin, carbamazepine, phenobarbitone, nevirapine, modafinil and St John's Wort (*Hypericum perforatum*)

For patients taking any of the above, the required wash-out periods prior to starting olaparib are:

- phenobarbitone 5 weeks, and for any of the others, 3 weeks.

4.1.1 Other Concomitant Medications

All medications (prescriptions or over-the-counter medications) continued at the start of the trial or started during the study or until 30 days from the end of the last protocol treatment and different from the study medication must be documented.

Anticoagulant Therapy: Subcutaneous heparin is permitted.

4.1.2 Palliative radiotherapy

Palliative radiotherapy may be used for the treatment of pain at the site of bony metastases that were present at baseline, provided the Investigator does not feel that these are indicative of clinical disease progression during the study period. Study treatment should be discontinued for a minimum of 3 days before the patient undergoes palliative radiation treatment. Study treatment should be restarted within 28 days from the scheduled date as long as any bone marrow toxicity has recovered.

4.1.3 Administration of other anti-cancer agents

Patients must not receive any other concurrent anti-cancer therapy, including investigational agents, while on study treatment. Patients may continue the use of bisphosphonates for bone disease and corticosteroids for the symptomatic control of brain metastases provided the dose is stable before and during the study

4.1.4 Medications that may NOT be administered

- No other chemotherapy, immunotherapy, hormonal therapy or other novel agent is to be permitted while the patient is receiving study medication. For the mCRPC cohort, patients may receive hormonal therapy in the form of GnRH agonists/antagonists as per eligibility criteria above.

4.1.5 Overdose

There is currently no specific treatment in the event of overdose with olaparib and possible symptoms of overdose are not established.

Olaparib must only be used in accordance with the dosing recommendations in this protocol. Any dose or frequency of dosing that exceeds the dosing regimen specified in this protocol should be reported as an overdose.

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

4.2 HIGHLY EFFECTIVE METHODS OF BIRTH CONTROL

The study drugs used in the study are regarded as having with medium/high fetal risk.

Individuals of childbearing potential and their partners, who are sexually active, must agree to the use of one highly effective form of contraception and their partner must use a condom [as listed below]. This should be started from the signing of the informed consent and continue throughout the period of taking study treatment and for at least 6 months after last dose of study drug(s), or they must totally/truly abstain from any form of sexual intercourse (see below).

Individuals who can father children must use a condom during treatment and for 3 months after the last dose of olaparib when having sexual intercourse with a pregnant woman or with a woman of childbearing potential. Their partners should also use a highly effective form of contraception if they are of childbearing potential (as listed below). Individuals who can father children should not donate sperm throughout the period of taking olaparib and for 3 months following the last dose of olaparib.

4.2.1 Acceptable non-hormonal birth control methods

- Total/true abstinence: When the patient refrains from any form of sexual intercourse and this is in line with their usual and/or preferred lifestyle; this must continue for the total duration of the study treatment and for at least 6 months (for individuals able to bear children) or at least 3 months (for individuals able to father children) after the last dose of study treatment. Periodic abstinence (eg, calendar ovulation, symptothermal, post-ovulation methods, or declaration of abstinence solely for the duration of a trial) and withdrawal are not acceptable methods of contraception.
- Vasectomised sexual partner PLUS condom (with participant assurance that partner received post-vasectomy confirmation of azoospermia).
- Tubal occlusion PLUS condom.
- Intrauterine device (provided coils are copper-banded) PLUS condom.

4.2.2 Acceptable hormonal methods

- Mini pill PLUS condom: Progesterone-based oral contraceptive pill using desogestrel. Cerazette (Merck Sharp & Dohme) is currently the only highly efficacious progesterone-based pill available.
- Combined pill PLUS condom: Normal and low-dose combined oral pills.
- Injection PLUS condom: Medroxyprogesterone injection (eg, Depo-Provera [Pfizer]).
- Implants PLUS condom: Etonorgestrel-releasing implants (eg, Nexplanon [Merck Sharp & Dohme]).
- Patch PLUS condom: Norelgestromin/ethinyl estradiol transdermal system (eg, Xulane).
- Intravaginal device (eg, ethinyl estradiol-/etonogestrel-releasing intravaginal devices such as NuvaRing [Merck Sharp & Dohme]) PLUS condom.
- Levonorgestrel-releasing intrauterine system (eg, Mirena [Bayer]) PLUS condom.

5 CORRELATIVE STUDIES FOR RESEARCH

5.1 BIOSPECIMEN COLLECTION

5.1.1 Phase I and Phase II Cohorts

Table 11. Correlative studies

Phase I

Sample	Assay	Time points	Type of tube/sample [a]	Amount of blood
Optional Tumor (only in patients with SCLC)	gH2AX	(1) Pre-treatment on C1D1 (2) Pre-treatment C1D4 (24hr after olaparib) (3) At disease progression	NA	NA
	SLFN11 IHC SLFN11 gene expression		NA	NA
	Exome/RNAseq/ droplet digital PCR		NA	NA
Whole blood (only in patients with SCLC)	Germline DNA	(1) Pre-treatment	Purple top EDTA	5 ml
	Circulating tumor DNA mutation analyses	(1) Pre-treatment	Lavender top tubes	Three 10-ml
	Immune subsets (Peripheral blood mononuclear cells)	(1) Pre-treatment on C1D1 (2) Pre-treatment C1D3 (pre-olaparib) (3) C1D4 (24hr after olaparib) (4) Pre-treatment C2D1	CPT citrate blue/black tubes	Two 8-ml tubes
	Circulating tumor cells enumeration RAD51 foci	(1) Pre-treatment on C1D1 (2) Pre-treatment C2D1 (3) At disease progression	Lavender top tubes	Two 10-ml

Sample	Assay	Time points	Type of tube/sample [a]	Amount of blood
	Nanostring immune panel (770 genes)	(1) Pre-treatment on C1D1 (2) Pre-treatment C2D1 (3) At disease progression	PAXgene RNA	One 2.5 ml
	Nanostring DNA damage response panel (180 genes) [3,4]	(1) Pre-treatment on C1D1 (2) Pre-treatment C2D1 (3) At disease progression	PAXgene RNA	One 2.5 ml
Whole Blood (in all phase I patients)	gH2AX	(1) Pre-treatment on C1D1 (2) Pre-treatment C1D3 (pre-olaparib) (3) C1D4 (24hr after olaparib)	green top	One 6-ml tube
Hair (optional)	gH2AX	(1) Pre-treatment on C1D1 (2) Pre-treatment on C1D3 (pre-olaparib) (3) C1D4 (24hr after olaparib) (4) End of each cycle (any time after the last dose of olaparib but prior to the next dose of EP0057)	12 follicles	12 follicles
Plasma	PK	Refer to **Table 12**	Refer to **Table 12**	

a. Please note that tubes and media may be substituted based on availability with the permission of the PI or laboratory investigator.

Phase II SCLC only

Sample	Assay	Time points	Type of tube [a]	Amount of blood	Lab/ Instruction
Tumor (Optional)	gH2AX	(1) Pre-treatment C1D1 (2) Pre-treatment C1D4 (24hr after olaparib) (3) At disease progression	NA	NA	Please call DTB Clinical Translational Unit when the samples are ready for pick-up at 240-760-6330 10/12C208 Keep all tubes at room temperature
	SLFN11 IHC SLFN11 gene expression		NA	NA	
	Exome/RNAseq/droplet digital PCR		NA	NA	
Whole Blood	Germline DNA	Pre-treatment	Lavender top EDTA	5 ml	
	Immune subsets (Peripheral blood mononuclear cells)	(1) Pre-treatment on C1D1 (2) Pre-treatment on C1D15 (3) Pre-treatment on C2D1 (4) At disease progression	CPT citrate blue/black tubes	Two 8-ml tubes	
	Circulating tumor cells enumeration	(1) Pre-treatment C1D1 (2) Pre-treatment C2D1 (3) At disease progression	CellSave tubes	One 10 ml	
	Nanostring immune panel (770 genes)	(1) Pre-treatment C1D1 (2) Pre-treatment C2D1 (3) At disease progression	PAXgene RNA	One 2.5 ml	
	Nanostring DNA Damage and Repair panel (180 genes)	(1) Pre-treatment C1D1 (2) Pre-treatment C2D1 (3) At disease progression	PAXgene RNA	One 2.5 ml	

a. Please note that tubes and media may be substituted based on availability with the permission of the PI or laboratory investigator.

5.1.1.1 γ-H2AX

Phosphorylated H2AX (γ-H2AX) plays an important role in the recruitment and/or retention of DNA repair and checkpoint proteins such as BRCA1, MRE11/RAD50/NBS1 complex, MDC1 and 53BP1. DNA damage has been shown to increase H2AX phosphorylation in cancer cells following exposure to camptothecins. If olaparib is able to increase the degree of DNA damage due to EP0057, it may be detectable by measurement of H2AX phosphorylation. We plan to study patient PBMCs, hair follicles, and tumor biopsies if obtained. Tumor tissue (optional) and hair follicles will be obtained if patients are suitable candidates and willing to allow such sampling. The ideal biomarker would confirm that there was increased DNA damage following addition of olaparib relative EP0057 alone. This analysis will be exploratory only and data will be used in planning biomarker endpoints in subsequent trials with the combination of EP0057and olaparib.

Hair follicles will be collected at multiple time points per **Table 11**. At least 24 hours prior to the start of the study, the research nurse will contact Dr. Redon in Dr. Aladjem's lab (DTB-LMP/CCR/NCI, Bldg 37/ Rm 5056) to inform him when samples will be taken (Tel: 240-760-7338 (L); 301-760-6275 (Cell); redonc@mail.nih.gov). Dr. Redon will provide tubes for collecting the plucked hairs. The tubes contain ice cold PBS labeled with the date/time of sampling, the protocol, and the unique identifier. Dr. Redon will also provide forceps for plucking. Dr. Redon should be notified of when the samples should be picked up.

Single hairs are plucked from the scalp with forceps. Plucked hairs from eyebrows will be collected only if scalp hairs cannot be provided. The aim is to acquire 12 hairs that contain a full intact follicle and sheath. All the hairs from a patient are placed in microfuge tubes containing cold PBS and stored on ice. Upon delivery in Dr. Aladjem's lab, hairs will be fixed with paraformaldehyde and analyzed under a dissection microscope to select those containing a full intact follicle and sheath. Plucked hairs will be fluorescently stained for γ-H2AX and images will be recorded by using a confocal microscope.

Blood will be collected per **Table 11**. When the patient is scheduled, the DTB Clinical Translational Unit will be contacted [by email to leesun@mail.nih.gov]. Blood from heparinized syringe will be mixed with a 1:1 ratio of room temperature PBS and layered over a 1:1 blood-PBS/Ficoll ratio in a conical centrifuge tube. The conical centrifuge tube should be centrifuged 25 minutes at room temperature at approximately 1000 rpm. The cell layer resting above the Ficoll and containing the peripheral blood mononuclear cells (PBMCs) will be aspirated and transferred to a 15 ml conical tube for washing in 15 ml PBS. PBMCs will be fixed with paraformaldehyde, spun onto a microscope slide and stain for γH2AX detection. Images from γ-H2AX-stained PBMCs will be recorded by using a confocal microscope.

5.1.1.2 SLFN11

Expression of the gene SLFN11 has been found to correlate with the activity of topoisomerase inhibitors in studies using the National Cancer Institute cell line panel (NCI60) and the Cancer Cell Line Encyclopedia (CCLE) (54, 55). SLFN11 expression predicted sensitivity to DNA damaging chemotherapy including Top1 and Top2 inhibitors, alkylating agents, platinum derivatives, DNA synthesis and PARP inhibitors (54-56). In experiments using cells with endogenously high and low SLFN11 expression and siRNA- and Crispr-mediated silencing,

SLFN11 was found to be causative in determining cell cycle arrest and cell death in response to DNA damaging agents in cancer cells (56). Data from the CCLE, the NCI60 and The Cancer Genome Atlas (TCGA) indicate a broad range of SLFN11 expression in lung cancers, raising the possibility that high SLFN11 expression might enrich for tumors that are more likely to respond to DNA damaging chemotherapy; conversely low SLFN11 expression may predict tumors that are likely resistant. Pre-treatment SLFN11 expression in tumor samples will be assessed (IHC and RNA) to assess in an exploratory manner, the potentially role of SLFN11 as a predictor of response to EP0057 plus olaparib.

5.1.1.3 Tumor biopsies and genomic DNA

Biopsies will be done only in phase II part of the study and in SCLC patients in the phase I part of the study.

Paired tumor biopsies will be obtained by minimally invasive methods such as CT guided percutaneous biopsies before and after treatment [C1D4 (24hr after olaparib)] and at disease progression per **Table 11**. The site of biopsy will be determined in discussion with interventional radiologist. If it can be safely obtained, 4 cores of tumor tissue will be collected. Two cores will be sent to pathology- one for confirmation of diagnosis and another will be used for making an FFPE block. The other 2 cores will be flash frozen at the time of biopsy. When the patient is scheduled, the DTB Clinical Translational Unit lab will be contacted [by email to Sunmin Lee leesun@mail.nih.gov]. Interventional Radiology will call the lab at 240-760-6330 when the patient arrives in IR and a lab member will be present at Interventional Radiology for the procedure. The cores will be flash frozen, 2D barcoded, and stored in liquid nitrogen.

Formalin fixed paraffin embedded tumor tissue (FFPE) from the new biopsies and or from archived FFPE tissue from prior biopsies/surgical procedures will be sent to the DTB Clinical Translational Unit as described above. Genomic DNA and RNA will be extracted from the tumor and archived for genomic analysis. Tumor tissue when obtained before start of treatment will be used for the following assessments: γ-H2AX, SLFN11, and POLQ expression; post-treatment biopsy samples will be assessed for γ-H2AX expression.

5.1.1.4 Immune Subsets

Little is known of the immunomodulatory effects of DNA damage-inducing cytotoxic therapy. Peripheral blood mononuclear cells (PBMC) will be obtained per **Table 11** and will be assessed by the DTB Clinical Translational Unit using multiparameter flow cytometry for immune subsets including but not necessarily limited to Tregs, myeloid-derived suppressor cells, effector and exhausted CD4+ and CD8+ T-cells, and CD14+ monocytes. Assessment will include functional markers, i.e. PD-1, Tim-3, CTLA-4, CD40, HLA-DR, and/or PD-L1. Members of the lab will procure the peripheral blood samples, enter the samples in a secure patient database, process the samples for viable cell storage, label each sample with a unique 2D barcode, and viably store the samples. They will prepare the samples for staining, stain and run the samples by multiparametric flow cytometry (MACSQuant, Miltenyi Biotec, Bergisch Gladbach, DE), the data will be analyzed by FlowJo v.X.0.6. Peripheral blood will be drawn into two 8-ml CPT citrate blue/black tubes for each time point. These assessments will be performed by the DTB Clinical Translational Unit.

Accumulating evidence has revealed the interplay between the host immune system and anticancer therapies.(57, 58) Several classical chemotherapeutics and molecular-targeted

therapies have been reported to stimulate tumor-specific immune responses either by inducing immunogenic cell death (ICD) or by engaging immune effector mechanisms. We propose to study the impact of combination therapy of EP0057 with olaparib on immune subsets and test for clinical relevance. These analyses offer the opportunity to obtain new insights into the immunomodulatory action of these combination therapies.

5.1.1.5 Circulating Tumor Cells and Circulating Tumor DNA

Circulating tumor cells (CTCs), which can be prevalent in SCLC, present a readily accessible 'liquid biopsy'. Peripheral blood will be collected per **Table 11** to correlate circulating tumor cell (CTC) levels at baseline or levels pre- and post-therapy with clinical response and survival. CTCs will be assessed using ferrofluidic enrichment and multiparameter flow cytometric detection. CTCs will be identified as viable, nucleated cells, that positively express one or more epithelial or tumor markers and are negative for expression of hematopoietic markers. CTCs will be enumerated and if sufficient, additional characterization performed included RAD51 foci, gene expression by droplet digital PCR, NanoString, whole transcriptome by Illumina or another platform as appropriate to the sample. Peripheral blood will be drawn into two 10-ml lavender top tubes and one 2.5 ml PAXgene RNA tube for each time point. These assessments will be performed by the DTB Clinical Translational Unit.

Circulating tumor DNA will be isolated from plasma separated from peripheral blood. Mutations identified by analysis of patient tumor samples may be included as personalized tumor markers in the circulating nucleic acid analysis. Mutations will be assessed by the appropriate technology. A multiplexed gene expression approach to profiling immune gene and DNA damage response signatures

Peripheral immune and DNA damage response transcriptional signatures will be evaluated by the DTB Clinical Translational Unit using the NanoString nCounter® platform (NanoString Technologies, Seattle, WA). We will use the nCounter 770 gene PanCancer Immune Profiling Panel and the newly released 170 gene DNA Damage & Repair panel, built in collaboration with the Developmental Therapeutics Branch. Peripheral blood will be collected in a PAXgene tube (PreAnalytix; 2.5 cc peripheral blood per tube) per the manufacturer's instructions. RNA will be isolated using the PAXgene Blood RNA Kit according to the manufacturer's instructions. The peripheral gene signatures will be evaluated at baseline and post-therapy to look for correlates of clinical response.

5.1.1.6 PK (Phase I only)

In Phase I only, blood samples for the determination of EP0057 and olaparib plasma levels will be obtained from participating patients via 6mL sodium heparin tube (BD, Franklin Lakes, NJ) per the table below. Samples will be obtained following the first dose on Cycle 1, day 1, and again on Cycle 6, day 1 in order to assess the extent of accumulation from repeated dosing at the time points specified below:

Table 12. Phase I PK Sample Collection Timeline

sample	cycle	day	time (approx.)	hr post-EP0057 start	post-olaparib
1	1	1	8:00a	0 hr (predose, may be drawn 24 hrs prior start of dosing)	-
2	1	1	8:30a	0.5 hr [+/- 5 minutes] (mid-infusion)	-
3	1	1	9:00a	1 hr [+/- 5 minutes] (end of infusion (EIO))	-
4	1	1	10:00a	2 hr [+/- 5 minutes] (1 hr post EOI)	-
5	1	1	11:00a	3 hr [+/- 5 minutes] (1 hr post EOI)	-
6	1	1	9:00p	13 hr [+/- 60 minutes] (12 hr post EOI)	-
7	1	2	9:00a	25 hr [+/- 60 minutes] (24 hr post EOI)	-
8	1	3	10:00a	50 hr [+/- 120 minutes] (49 hr post EOI)	2 hr
9	1	15	8:00a	360 hr [+/- 5 days] (359 hr post EOI)	-
10	6	1	8:00a	0 hr (predose, may be drawn 24 hrs prior start of dosing)	-
11	6	1	8:30a	0.5 hr [+/- 5 minutes] (mid-infusion)	-
12	6	1	9:00a	1 hr [+/- 5 minutes] (end of infusion (EIO))	-
13	6	1	10:00a	2 hr [+/- 5 minutes] (1 hr post EOI)	-
14	6	1	11:00a	3 hr [+/- 5 minutes] (1 hr post EOI)	-
15	6	1	9:00p	13 hr [+/- 60 minutes] (12 hr post EOI)	-
16	6	2	9:00a	25 hr [+/- 60 minutes] (24 hr post EOI)	-
17	6	3	10:00a	50 hr [+/- 120 minutes] (49 hr post EOI)	2 hr
18	6	15	8:00a	360 hr [+/- 5 days] (359 hr post EOI)	-

The PK samples will be placed immediately on wet ice and refrigerated. The date and exact time of each blood draw should be recorded on the sample tube and the PK sheet. Please e-mail the Biospecimen Processing Core (BPC) at NCIBloodcore@mail.nih.gov at least 24 hours before transporting samples (the Friday before is preferred). For sample pick up, please page 102-11964. For immediate help, call 240-760-6180 (main BPC number) or, if no answer, 240-760-6190 (main clinical pharmacology lab number).

Bioanalytical measurements of EP0057 and olaparib will be measured by individual ultra HPLC-MS/MS assays optimized for each drug by BPC. This data will be used to assess any drug-drug interactions are present between olaparib and EP0057, as well as to correlate adverse events and efficacy to each drug's exposure. Neither olaparib nor camptothecin are extensively metabolized into pharmacologically active metabolites, therefore there are no relevant pharmacogenomic considerations regarding drug metabolizing enzymes or transporters with this combination.

5.1.2 UC Expansion Cohort

Tumor biopsies and blood samples will be obtained at the time points as described below. Archival tissue and blood or saliva will be collected at baseline and will be stored under uniform conditions or, preferably, processed immediately for DNA. Tumor biopsies (nodal or visceral) will be optional for molecular analyses and will be obtained at baseline, on-treatment (timing at the discretion of PI) and at disease progression.

In the case of tumor biopsy and limited material, tissue distribution should be prioritized as follows:

1. Storage and diagnosis confirmation (Dr. Maria Merino)
2. MET analysis (Dr. Don Bottaro)
3. RNA sequencing (Dr. Michael Nickerson)
4. Genetic/Genomic Analysis (Dr. Michael Nickerson)

Table 13. UC Expansion Cohort Sample Collection Guideline

Test Description	Amount/ Type/Tube/Handling	Collection Time	Contact	Special Instructions
Fresh Tumor Biopsy at NIH CCR (voluntary)	3-4 cores	Baseline (Pre-Treatment), On-treatment, At Disease Progression	Email: Rene Costello, rene.costello@nih.gov 24 hours prior to anticipated collection Call Rene Costello at 301-443-6975 immediate pick-up of sample collection day.	3-4 cores will be flash frozen at the time of biopsy. When the patient is scheduled for biopsy will call, Dr. Bottaro/Rene Costello (tech) (301-443-6975), and BPC (pager 102-11964). The cores will be flash frozen, 2D barcoded, and stored in liquid nitrogen. The tumor tissue will be divided among three laboratories for storage and will be batched: 1.1 core: Laboratory of pathology (Maria Merino) will perform diagnosis confirmation. 2. 1-2 cores: Genitourinary Malignancies Branch. Molecular Pharmacology Section will store 1-2 core of fresh tumor per patient (for Dr. Nickerson WES/RNA seq) 3. 1 core will be stored with Dr. Don Bottaro (MET protein) Samples will be sent in batches of 10 to Dr. Nickerson lab. When the samples will be shipped, the Nickerson lab will be contacted by email to NCICGFDESLReceiving@mail.nih.gov about the timing of the shipment and the number and type of samples with typed sample IDs.

Test Description	Amount/ Type/Tube/Handling	Collection Time	Contact	Special Instructions
				Nickerson laboratory: DNA Extraction and Staging Laboratory (DESL) ATTN: Amy Hutchinson 8717 Grovemont Circle ATC, Room 149 Gaithersburg, MD 20877 Phone: 240-760-6496
Saliva	3ml Oragene saliva collection kits (DNA Genotek)	Baseline (or any time after consent is signed but preferably at baseline)	Email: BPC NCIBloodcore@mail.nih.gov 24 hours prior to collection For sample pickup, page 102-11964 - BPC lab	Store at room temperature Will be stored in BPC
Plasma and urine HGF and MET	One 4mL EDTA tube and collect at least 20 mL of urine specimen container	Baseline, Day 1 Each Cycle	E-mail BPC NCIBloodcore@mail.nih.gov at least 24 hours before transporting samples (the Friday before is preferred). For sample pickup, page 102-11964 - BPC lab	Invert EDTA tube 2-4 times, place on wet ice and store at 4°C in the refrigerator until processing for a maximum of 30-60 min. Should be centrifuged within 30 min. Mix urine sample well by inverting 5-8 times. Take 20ml of urine from the center of the container and put into a 50ml tube. sMET analysis requires 1-2ml urine HGF analysis requires 10-20ml urine. Adjust urine to pH 7.5 with 2 mol/L, ph 7.5 Trizma-HCL (Sigma, St. Louis, MO) using 50uL per 2 mL urine volume. Centrifuge the conical at 3000xg for 10 min at room temperature to remove cells and debris. Make as

Test Description	Amount/ Type/Tube/Handling	Collection Time	Contact	Special Instructions
				many 2 mL aliquots as possible. Store at -80°C until requested by Dr. Don Bottaro's lab
Comprehensive cytokine/chemokine study	One 10mL EDTA tube	Baseline C2D1 C3D1	NIH CCR: E-mail BPC NCIBloodcore@mail.nih.gov at least 24 hours before transporting samples (the Friday before is preferred). For sample pickup, page 102-11964 - Figg lab	Invert EDTA tube 2-4 times, place on wet ice and store at 4°C in the refrigerator until processing for a maximum of 30-60 min.
Immunologic Subsets	Two 8 ml BD Vacutainer Cell Preparation Tubes (CPT) citrate (blue/black tiger top closure)	C1D1 (Pre-treatment) C2D1 (Pre-treatment) Disease Progression	NIH CCR: When scheduled email Sunmin Lee (leesun@mail.nih.gov), Min-Jung Lee (leemin@mail.nih.gov) and when samples are ready call 240-760-6330	Invert several times and leave at room temperature for DTB Clinical Translational Unit member pick up within NIH
Nanostring immune panel (770 genes)	PAXgene tube 2.5 cc peripheral blood per tube	C1D1 (Pre-treatment) C2D1 (Pre-treatment)	NIH CCR: When scheduled email Sunmin Lee (leesun@mail.nih.gov), Min-Jung Lee (leemin@mail.nih.gov) and when samples are ready call 240-760-6330	Invert several times and place at room temp or refrigerate Store up to 3 days at room temperature (15–25°C); up to 5 days at 2–8°C and 8 years at –20°C or –70°C
Nanostring DNA damage response panel (180 genes)	PAXgene tube 2.5 cc peripheral blood per tube	Pretreatment on C1D1 Pretreatment on C2D1	NIH CCR: When scheduled email Sunmin Lee (leesun@mail.nih.gov), Min-Jung Lee (leemin@mail.nih.gov) and when samples are ready call 240-760-6330	Invert several times and place at room temp or refrigerate Store up to 3 days at room temperature (15–25°C); up to 5 days at 2–8°C and 8 years at – 20°C or –70°C

Test Description	Amount/ Type/Tube/Handling	Collection Time	Contact	Special Instructions
CTC (DTB Clinical Translational Unit)	CellSave tube 7.5 cc	C1D1 (Pre-treatment) C2D1 (Pre-treatment) Disease Progression	NIH CCR: When scheduled email Sunmin Lee (leesun@mail.nih.gov), Min-Jung Lee (leemin@mail.nih.gov) and when samples are ready call 240-760-6330	Invert several times and leave at room temperature for DTB Clinical Translational Unit member pick up within NIH.
CTC (Epic Science)	10mL Streck Cell-Free DNA BCT	C1D1 (Pre-treatment) C3D1 (Pre-treatment)	Have patient bring sample to clinic. Contact Katie Graap, 240-506-8634, for pick-up of specimen Send notification to: partners@epicsciences.com Ship to: Epic Science Attn: (Partner Protocol #/Epic internal ID) 9381 Judicial Dr. Suite 200 Sand Diego, CA 92121 Contact phone number is: 1-858-356-6610	Confirm blood tube is not expired. Expired tubes should not be used for blood collection. • Ensure first 5ml blood is discarded or the blood for CTC analysis is not the first tube to be collected • Draw whole blood sample into 10 mL Streck Cell-Free DNA BCT tube (*see note regarding prevention of backflow). Fill tube until blood low stops. NOTE: Epic requires a minimum of 4 mL blood per sample, but a full 10 mL tube of blood should be provided when possible.

Test Description	Amount/ Type/Tube/Handling	Collection Time	Contact	Special Instructions
Cell-free DNA	One 10mL lavender top (EDTA) Tube (minimum of blood required 3 cc)	Every 2weeks	E-mail BPC NCIBloodcore@mail.nih.gov at least 24 hours before transporting samples (the Friday before is preferred). For sample pickup, page 102-11964 - BPC lab When the samples will be shipped, the Nickerson lab will be contacted by email to NCICGFDESLReceiving@mail.nih.gov about the timing of the shipment and the number and type of samples with typed sample IDs	After the tube has been filled with blood, immediately invert the tube several times to prevent coagulation. Process within 2 hours following a double-spin protocol.

5.1.2.1 MET studies for UC expansion cohort

Prior work from our group showed that MET overexpression in cancer cells is associated with increased proteolytic release of soluble MET (sMet) protein from the cell surface into blood and urine, a potentially useful biomarker of tumor aggressiveness and progression. (59)We also found that urinary sMET levels differentiated urothelial bladder cancer (N=141) and benign bladder pathology (N=64), (P=0.0093) and non-muscle-invasive (N=110) from muscle-invasive (N=31) disease (P<0.0001) (60). In an independent cohort of patients with metastatic (N=23) and muscle-invasive (N=8) (not metastatic) urothelial cancer, we found that sMET levels in urine samples from ileal conduits and neobladders were significantly higher than in normally voided urine, regardless of stage (N=31) (P=0.0489), and in patients with visceral metastasis (N=14) (P=0.0111) (data not shown). Serum sMET levels showed a trend toward higher values in patients with metastatic versus non-metastatic disease. The process that increases MET shedding in the urine and blood of patients with UC are likely multi-factorial and not fully understood. However, there is great excitement for the potential of MET as a potential biomarker of disease status and progression. We plan to analyze plasma and urine sMET during treatment and correlate the results with baseline clinical parameters and response to therapy. We also plan to analyze cMET by real time PCR (RT-PCR).

5.1.2.2 Circulating Tumor Cells (DTB Clinical Translational Unit)

Blood will be collected per **Table 13** to correlate baseline or changes in CTCs with clinical outcome. CTCs will be investigated using ferrofluidic enrichment and multi-parameter flow cytometric analysis. CTCs will be identified by positivity for epithelial markers including but not limited to EpCAM and negative for expression of hematopoetic markers including but not limited to the panhematopoietic marker CD45.

5.1.2.3 Circulating Tumor Cells (Epic Science)

The patients on the bladder expansion cohort will also have CTC's measured using fee-for-service Epic Science's "no cell left behind" platform.

CTC Samples should be collected in the 10 mL Streck Cell-Free DNA BCT at timepoints per **Table 13** baseline and day 1 of cycle 2 and 3. These tubes are commercially available through Streck (Omaha, NE).

IMPORTANT: The first 5 mL of blood collected from the fresh venipuncture cannot be used for the collection into the Streck tubes due to possibility of contaminating epithelial cells during venipuncture. Please ensure that at least one blood tube of 5 mL or more is collected prior to collection of the CTC sample to avoid adversely affecting the test results.

Prevention of Backflow:

Since Streck Cell-Free DNA BCT tubes contain chemical additives, it is important to avoid possible backflow from the tube. To guard against backflow, observe the following precautions:

- Keep patient's arm in the downward position during the collection procedure.
- Hold the tube with the stopper uppermost.
- Release tourniquet once the blood starts to flow into the tube, or within 2 minutes of application.

- Tube contents should not touch stopper or the end of the needle during the collection procedure.

Blood Collection Instructions:

**Arrange for the same day shipment!

- Confirm blood tube is not expired. Expired tubes should not be used for blood collection.
- Draw whole blood sample into 10 mL Streck Cell-Free DNA BCT tube (*see note regarding prevention of backflow). Fill tube until blood flow stops. NOTE: Epic requires a minimum of 4 mL blood per sample, but a full 10 mL tube of blood should be provided when possible.
- Remove tube from adapter and immediately mix by gentle inversion 8 to 10 times. Tube inversion prevents clotting. Inadequate or delayed mixing may result in inaccurate test results.
- Label the tube with subject's identification and date and time of blood draw. Unlabeled blood tubes may not be processed.
- Keep sample at room temperature and ship on day of collection in shipper with ambient gel packs.

Specimen Shipment Logistics

All shipments must include requisition forms that contain Patient ID, Collection Date and time, Collection Site (including address), Time Point (if applicable), and the appropriate trial code (CTEP # 9681/ Epic Internal ID: NE-003). Clinical sites should provide email notification of sample shipment to Epic Sciences on the day of collection. The email should contain:

- Trial codes (CTEP # 9681/ Epic Internal ID: NE-003)
- Patient ID
- Collection date and time*
- Time point/Visit
- Tracking information

If possible, include a scanned copy of the completed sample requisition form. Partner will be responsible for all blood collection supplies, shipping materials, and shipping expenses.

* When collection time is not provided, Epic Sciences will assume the sample was collected at 8:00AM (local time) on the date of collection.

Send notification to: partners@epicsciences.com
Ship to: Epic Science
Attn: (CTEP # 9681/Epic internal ID: NE-003)
9381 Judicial Dr. Suite 200
Sand Diego, CA 92121
Contact phone number is: 1-858-356-6610

Holiday Outages

In observance of the following holidays, Epic Sciences sample processing locations will be closed, and samples will be processed on the next business day. Epic holidays are reviewed regularly and are subject to change. Notification of any changes to the holiday schedule will be communicated promptly via email to the project stakeholders.

Epic Sciences (USA) Holidays

New Year's Day or Business Day after New Year's Day
President's Day
Memorial Day
Business day before Independence Day
Independence Day
Labor Day
Thanksgiving Day
Day after Thanksgiving Day
Business day before Christmas or Christmas Day

5.1.2.4 Nanostring immune panel & Nanostring DNA damage response panel (UC Expansion Cohort)

Peripheral immune and DNA damage response transcriptional signatures will be evaluated by the DTB Clinical Translational Unit using the NanoString nCounter® platform (NanoString Technologies, Seattle, WA). We will use the nCounter 770 gene PanCancer Immune Profiling Panel and the newly released 170 gene DNA Damage & Repair panel, built in collaboration with the Developmental Therapeutics Branch. Peripheral blood will be collected in a PAXgene tube (PreAnalytix; 2.5 cc peripheral blood per tube) per the manufacturer's instructions. RNA will be isolated using the PAXgene Blood RNA Kit according to the manufacturer's instructions. The peripheral gene signatures will be evaluated at baseline and post-therapy to look for correlates of clinical response.

5.1.2.5 Whole exome sequencing and RNA sequencing for UC expansion cohort

Recent data indicate that subsets of bladder cancer have dysfunctions in genes related to DNA damage repair pathways. Analysis of DNA copy number and mutation status of UC by The Cancer Genome Atlas Research Network has revealed that up to 30% (germline or somatic mutations) of the cases included had BRCA pathway alterations (12). Nickerson and colleagues also found multiple germline and somatic mutations in genes encoding BRCA pathway proteins in bladder cancer, including BRCA1, BRCA2, ATM, BAP1, and PALB2. (14) Based on these data, exome sequencing will be done for bladder cancer cohort to investigate potential predictive biomarkers with particular focus on abnormalities in DNA-repair genes. Molecular finding will be correlate with response and time-to-event outcomes.

Inhibition of PARP1 could lead to an increase in SSBs, and if left unrepaired or additional DNA damaged is conferred – for example adding chemotherapy- these SSBs would lead to the formation of increased DSBs and in turn increased cell death.(61, 62) However, cells contain alternative mechanism for DNA damage repair in the absence of PARP activity. In this regard, differential expression of proteins involved in such alternative DNA repair mechanisms would further enhance the efficacy of PARP inhibitors. We propose to analyze DNA damage response transcriptional signatures in peripheral blood of our cohort of patients to correlate with response to olaparib. We hypothesize that differential expression of genes involved in DNA damage response and repair processes influence the response to olaparib. This part will be performed in collaboration with Michael Nickerson in the Genetics Branch/CCR/NCI.

5.1.2.6 Circulating Tumor Cell DNA

FM panel and targeted sequencing results will be used to identify germline and somatic cancer-gene alterations associated with tumor cells. This data will be used to design a patient-specific targeted sequencing panel to detect and monitor mutation load based on sequencing read counts in

blood before, during and after treatment using whole blood DNA and Illumina and Ion Torrent sequencing.

Peripheral blood will be collected in EDTA-containing (lavender tops) tube at designated time points (see **Table 13**). Blood samples for isolation of DNA containing circulating tumor cell DNA will be processed per guidelines in **Table 13** and stored at 4^0C at BPC (Section 5.2.2).

DNA will be shipped to Dr. Nickerson's Laboratory for analysis in batches of 5-10 samples.

5.1.2.7 Blood Serum for Cytokine Analysis by Liang Cao: UC Cohort

Blood Serum will be collected for cytokine analysis by Liang Cao (to be stored in BPC) at baseline and Day 1 of every cycle. Page 102-11964 for BPC to pick up.

i. Blood Serum: Collect 7-10 mLs blood in one (1) serum separator tube (SST) or red top tube with no preservatives.

ii. Allow the blood to clot by standing at room temperature for 30 minutes.

iii. Separate serum from cells by centrifuging at 4 degrees C for 10 minutes at 1200 x g.

iv. Pipette two (2) aliquots of serum 1.5mLs each into two 2mL cryovials.

v. Freeze immediately at -20 or lower.

vi. Maintain in -80 freezer for storage until shipment to Dr. Cao's lab.

5.1.2.8 Urine Cytology Tumor DNA (in patients with intact primary tumors only) by Mark Raffeld: UC Cohort

Urine will be collected for urine cytology tumor DNA by Mark Raffeld (to be stored in BPC). Page 102-11964 for BPC to pick up.

Urine Cytology tumor DNA Standard Operating Procedure

Objective: To identify 10 urines morphologically positive for HG transitional cell carcinoma with tumor available in surgical pathology for parallel 50 CGMP +Tert analysis

1. Urine samples with clinical information suggesting the presence of a HG transitional cell carcinoma will be divided in the cytology laboratory into two aliquots.
    a. One aliquot will be processed for routing laboratory cytomorphologic evaluation (i.e., Thin Prep)
    b. A second aliquot will be stored in the refrigerator (-4 C)
    c. The cytotechologist will make a note on the request form that a second aliquot exists/ has been saved
2. If routine cytologic evaluation confirms the presence of a HG transitional cell carcinoma
    a. The cytopathologist will check whether the Pt's tumor exists in surgical pathology
    b. If surgical pathology material exists – the cytopathologist will notify the cytotechnologist that the second aliquot should be centrifuged per laboratory routine to create a pellet and a supernatant
        i. Up to 5 ml of supernatant should be pipetted into a conical tube labelled with the case number

ii. The tube with the remaining cell pellet should also be labelled with the case number

3. Both tubes should be stored at -20 C (freezer to be determined)
4. When ten samples with corresponding surgical pathology material have been collected, these will be transferred to the Molecular Pathology Section for DNA extraction and CGMP50 +Tert analysis.

5.1.2.9 Tissue: UC Cohort

Patient must be able to provide either archival tumor samples (H&E slides and one paraffin block or 15 unstained slides) or undergo tumor biopsy. If tissue was already collected for another CCR study run by Dr. Apolo, no additional tissue is needed. Biopsies are encouraged but voluntary.

- 10 unstained slides and 1 H&E for Dr. Paul Meltzer's laboratory
- 5 unstained slides and 1 H&E for DTB Clinical Translational Unit's laboratory

Biopsies obtained by surgery or interventional radiology will be processed immediately by Don Bottaro and DTB Clinical Translational Unit's laboratory. Three cores will be collected when possible (1-2 cores for pathology and 1 core for Don Bottaro). Fresh tumor obtained at NCI CCR will also be divided among the above 3 labs and additionally Dr. Bottaro will use one core to perform the MET tumor assay. Biospecimens will be collected and processed using validated SOPs that will ensure both specimen quality and patient confidentiality. Using a computerized inventory system and a backup hardcopy process, all specimen collection and processing steps will be documented and the specific location of each specimen will be tracked.

- Please contact Dr. Bottaro to notify of biopsy date and time at 240-858-3967 (or Rene Costello at 301-443-6915) and to arrange for pick-up of sample during biopsy (1 core)
- 1-2 biopsy cores will be submitted to pathology
- Tissue blocks and slides from outside pathology departments will be stored in the NIH pathology department with attention to Dr. Maria Merino.

5.1.3 mCRPC Expansion Cohort

Correlative Studies: mCRPC cohort

Patients will undergo one mandatory pretreatment biopsy and two optional research biopsies (timepoints assessed at PI discretion) to assess the effect of response to olaparib plus EP0057.

Table 14. mCRPC Sample Collection Guidelines

Test	Amount/Type/Tube	Collection Timing	Contact	Special Instruction
Chemokine and cytokine analysis	Purple, Tube size: 10 cc, 2 tubes, Draw volume: 20 cc	Baseline, C4D1, and progression	CPC pickup at 102-11964	Immediately pack on wet ice

Test	Amount/Type/Tube	Collection Timing	Contact	Special Instruction
Immune subsets PBMC	Black/Blue, Tube size: 8 cc, 2 tubes, Draw volume: 16 cc	Baseline, C2D1, and C3D1	DTB Clinical Translational Unit at 240-760-6330	Invert blood tubes 3-4 times keep at room temperature
Circulating Tumor Cells (CTC)	Purple (LVV), Tube size: 7.5 cc Draw volume: 7.5 cc	Baseline, C2D1, and progression	DTB Clinical Translational Unit at 240-760-6330	Invert blood tubes 3-4 times keep at room temperature
Nanostring Immune Panel	PAX red, Tube size, 2.5 cc, Draw volume 2.5 cc	Baseline, C2D1, and progression	DTB Clinical Translational Unit at 240-760-6330	Invert blood tubes 3-4 times keep at room temperature or refrigerate
Nanostring DNA damage response panel	PAXgene tube, Draw volume 2.5 cc	Baseline, C2D1, and progression	DTB Clinical Translational Unit at 240-760-6330	Invert blood tubes 3-4 times keep at room temperature or refrigerate
CTC (Epic Science)	Brown/Black Streck tube, 10 cc, Draw volume 10 cc	Baseline, C4D1	Page 102-11964 for BPC to pick up	Keep at room temperature

5.1.3.1 Tumor biopsies on mCRPC expansion cohort

Biopsy will be performed at the following time: mandatory-prior to treatment on cycle 1 day 1. Optional tumor biopsies may be obtained at 2 additional time points as determined by the investigator(s) and/or the PI.

Biopsies may be not performed on the specific dates and times due to the following reasons, including but not limited to, delayed recovery of hematologic toxicities, delayed clinic schedule, or national holidays.

At least 1 core biopsy specimen will be obtained via Interventional Radiology and members of the Kelly lab will be on call to receive the biopsies: Dr. Kelly's lab representative: 240-760-7121.

5.1.3.2 Exome sequencing for mCRPC expansion cohort

Exome sequencing will be done for mCRPC cohort on tumor tissue to investigate potential predictive biomarkers in responders and non-responders in collaboration with Dr. Paul Meltzer in the Genetics Branch/CCR/NCI. Additionally, culturing of patient-derived organoids (cell lines) will be performed in collaboration with Kathleen Kelly Siebenlist in the Laboratory of Genitourinary Cancer Pathogenesis/CCR/NCI, if there is biopsy core specimen available.

5.1.3.3 Saliva sample collection for mCRPC expansion cohort

A one-time saliva sample will be collected anytime during the study as a source of normal tissue for genomics comparison. Saliva sample will be collected in one Oragene Saliva Kit at room temperature and page BPC for pick up at 102-11964. BPC will barcode the sample, remove patient identifier, and send the sample to Dr. Meltzer's lab via courier. Patients will be instructed not to eat, drink, smoke or chew gum for 30 minutes before giving their saliva sample. Sequencing of DNA will be performed by the Genetics Branch/CCR/NCI.

5.2 SAMPLE STORAGE, TRACKING AND DISPOSITION

All samples [except PK samples- which will be sent to BPC; one core of research biopsy- which will be stored in the Laboratory of Pathology; hair samples which will be collected and processed by Dr. Redon, Developmental Therapeutics Branch] will be sent to and stored in DTB Clinical Translational Unit at NCI, Bldg 10, Bethesda, MD. Place all samples at room temperature, phone the Lab at 240-760-6330 and a laboratory member will come to pick up the sample.

Samples will be ordered in CRIS and tracked through a Clinical Trial Data Management system. Should a CRIS screen not be available, the CRIS downtime procedures will be followed.

Samples will not be sent outside NIH without appropriate approvals and/or agreements, if required. Any transfer of materials to other NIH or non-NIH investigators will occur following NIH Intramural Research Program guidelines. If the subject withdraws consent the participant's data will be excluded from future distributions, but data that have already been distributed for approved research use will not be able to be retrieved.

5.2.1 DTB Clinical Translational Unit

Tracking and disposition of samples will conform to the NCI CCR Biospecimen Guidelines.

All samples will be barcoded and data entered and stored in the Labmatrix system utilized by the NIH Clinical Center. This is a secure system with access limited to defined personnel.

Labmatrix creates a unique barcode ID for every sample which cannot be traced back to subjects without Labmatrix access. The data recorded for each sample may include the subject ID, name, trial name/protocol number, date/time drawn, as well as box and freezer location. Subject demographics associated with the clinical center patient number are provided in the system. For each sample, there are notes associated with the processing method (delay in sample processing, storage conditions on the ward, etc.). Access to personally identifiable information (PII) is limited to the PI and associate investigators.

An additional layer of encryption will be added for samples undergoing genetic analysis in the DTB Clinical Translational Unit where a separate clinically annotated unique sample ID will be generated linked with the sample ID in Labmatrix. As additional clinical information is generated and linked to the unique patient ID, it is also electronically linked via Labmatrix to the sample ID. The DTB Clinical Translational Unit will proceed with sample analysis and record data under the unique sample ID.

Barcoded samples are stored in barcoded boxes in a locked freezer at either -20 or -80°C or in liquid nitrogen according to stability requirements. These freezers are located onsite, and access to stored clinical samples is restricted. Samples will be stored until requested by a researcher named on the protocol. All requests are monitored and tracked in the Labmatrix System. All

researchers are required to sign a form stating that the samples are only to be used for research purposes associated with this trial (as per the IRB approved protocol) and that any unused samples must be returned to the NCI. It is the responsibility of the NCI Principal Investigator to ensure that the samples requested are being used in a manner consistent with IRB approval.

Samples will be stored in a freezer at either -4° C or -70° C behind a door locked after working hours. Samples will be tracked by a designated member of the laboratory who is responsible for notifying the PI about requests for use of the material, for allocating the material to other members of the laboratory, for recording the disposition of the allocated material.

5.2.2 Biospecimen Processing Core (BPC)

All samples sent to the Biospecimen Processing Core (BPC) will be barcoded, with data entered and stored in Labmatrix utilized by the BPC. This is a secure program, with access to Labmatrix limited to defined BPC personnel, who are issued individual user accounts. Installation of Labmatrix is limited to specified computers. These computers all have a password restricted login screen.

Labmatrix creates a unique barcode ID for every sample and sample box, which cannot be traced back to participants without Labmatrix access. Data will be recorded for each sample, as appropriate (e.g., patient/participant ID, name, trial name/protocol number, time drawn, cycle time point, dose, material type, as well as box and freezer location). Participant demographics associated with the Clinical Center patient number are provided in the system. For each sample, there are notes associated with the processing method (delay in sample processing, storage conditions on the ward, etc.).

Sample barcodes are linked to participant demographics and limited clinical information. This information will only be provided to investigators listed on this protocol, via registered use of the Labmatrix. It is critical that the sample remains linked to participant information such as race, age, dates of diagnosis and death, and histological information about the tumor, in order to correlate genotype with these variables.

Barcoded samples are stored in barcoded boxes in locked freezers at either -20 C or -80 C according to stability requirements. These freezers are located onsite in the BPC and offsite at NCI Frederick Central Repository Services in Frederick, MD. Visitors to the laboratory are required to be accompanied by laboratory staff at all times.

Access to stored clinical samples is restricted. Samples will be stored until requested by a researcher named on the protocol. All requests are monitored and tracked in Labmatrix. All researchers are required to sign a form stating that the samples are only to be used for research purposes associated with this trial (as per the IRB approved protocol) and that any unused samples must be returned to the BPC. It is the responsibility of the NCI Principal Investigator to ensure that the samples requested are being used in a manner consistent with IRB approval.

5.2.3 Redon (Aladjem) Lab

At least 24 hours in advance, the research nurse will contact Dr. Redon in Dr. Aladjem's lab (DTB-LMP/CCR/NCI, Bldg 37/ Rm 5056) to inform him when samples will be taken (Tel: 240-760-7338 (L); 301-760-6275 (Cell); redonc@mail.nih.gov). Dr. Redon will provide tubes for collecting the plucked hairs which contain ice cold PBS, and are labeled with the date/time of sampling, the protocol, and the unique identifier. Dr. Redon should be notified of when the samples should be picked up.

All of the hairs from a patient will be placed in microfuge tubes containing cold PBS and stored on ice. Upon delivery in Dr. Aladjem's lab, hairs will be fixed with paraformaldehyde and analyzed under a dissection microscope to select those containing a full intact follicle and sheath. Plucked hairs will be fluorescently stained for γ-H2AX and images will be recorded by using a confocal microscope.

5.2.4 Paul Meltzer Lab

All samples will be stored in monitored freezers/refrigerators in the Meltzer laboratory at specified temperatures with alarm systems in place. All samples will be tracked by unique sample identifiers with bar code labeling, using the Labmatrix software and the Genologic Clarity LIMS system. Secure computer database systems (Labmatrix and Clarity LIMS) will be used to track all samples collected on this protocol. The system will contain data that includes, but is not limited to the unique sample identifiers, storage locations and conditions, biologic study results, clinical information, and corresponding records of all derivatives generated from samples/tissues collected on this protocol. The system will employ mechanisms for restricting users to viewing only the level of data appropriate for each individual user, will provide the capability to audit any data modification, and will be maintained and backed up according to established standards.

5.2.5 Laboratory of Genitourinary Cancer Pathogenesis (Kathleen Kelly Siebenlist)

All samples will be assigned a unique barcode ID and entered into the Labmatrix system. Tissue will be processed immediately after biopsy and placed into organoid culture. Organoids that fail to grow will be destroyed. Organoids that are cultured successfully will be maintained in the Kelly lab. Viably frozen stocks of organoids will be stored in liquid nitrogen in the Kelly lab and tracked by the unique ID. DNA and RNA derivatives will be added into the Labmatrix system, The system will contain data that includes, but is not limited to the unique sample identifiers, storage locations (freezer and box identifiers) and conditions, and corresponding records of all derivatives generated from samples/tissues collected on this protocol. Access to the tracking system is limited to appropriate personnel. Material will be stored in a monitored -80° C freezer, and access to material will be restricted to appropriate lab personnel.

5.2.6 Urologic Oncology Branch Molecular Therapeutics Facility (Donald Bottaro)

Each patient research sample will be assigned a unique patient identifier and relevant sample characteristics (such as timing of sample collection, treatment cycle and day identifiers) will be recorded. The location of all samples will be carefully tracked in the secure UOB database. All stored samples will be coded and no identifying patient information will be on placed on sample containers. Stored samples will be kept in freezers / refrigerators or secure containers located in the Urologic Oncology Branch research laboratories or in the laboratories of collaborators.

Samples will be stored until requested by an authorized researcher(s). All researchers are required to use the samples for research purposes associated with this trial (as per the NIH IRB approved protocol). Subjects will be given the option of consenting to future use of their research samples per the informed consent process with their option declared in the consent document. Samples from those patients who consent to this will be stored permanently. However, these samples will be used only for research studies on active NIH IRB approved protocols covered by a valid informed consent document. Samples will be destroyed at the completion of the study from those subjects who decline future use of their samples. Once primary research objectives

for the protocol are achieved, intramural researchers can request access to remaining samples provided they have an IRB approved protocol and patient consent. Any unused samples must be returned to the UOB laboratories as appropriate.

5.2.7 Laboratory of Pathology

Tissues designated for clinical diagnostics are transported to the Laboratory of Pathology (LP) where they are examined grossly and relevant portions are fixed, embedded in paraffin and sectioned and stained for diagnostic interpretation. Unutilized excess tissue that is not placed in paraffin blocks is stored in formalin for up to three months, in accordance with College of American Pathologists/Joint Commission on Accreditation of Healthcare Organizations (CAP/JCAHO) guidelines, and then discarded. Following completion of the diagnostic workup, the slides and tissue blocks are stored indefinitely in the LP's clinical archives. All specimens are catalogued and retrieved utilizing the clinical laboratory information systems, in accordance with CAP/JCAHO regulations. The use of any stored specimens for research purposes is only allowed when the appropriate IRB approval has been obtained. In some cases, this approval has been obtained via the original protocol on which the patient was enrolled.

5.2.8 Laboratory of Pathology NCI COMPASS Program

Participants may undergo genetic analysis through the NCI COMPASS program for tumor-normal exome and transcriptome. For additional information on consenting, ordering and results, refer to CCR SOP ADGC-5, Tumor/Normal Whole Exome Sequencing: Consenting, Ordering, and Obtaining Results found at https://nih.sharepoint.com/sites/NCI-CCR-OCD-Communications/SitePages/OEC-Administrative---Clinical-Research-(ADCR).aspx?Mode=Edit.

5.2.9 Future Use/IRB Reporting/Protocol Completion/Sample Destruction

Blood and tissue specimens collected in the course of this research project may be banked and used in the future to investigate new scientific questions related to this study, including gene/protein expression and germline analysis. However, this research may only be done if the risks of the new questions were covered in the consent document and the proposed research has undergone prospective IRB review and approval. If new risks are associated with the research (e.g., analysis of germ line genetic mutations.) the Principal Investigator must amend the protocol and obtain informed consent from all research subjects.

Following completion of this study, samples will remain in storage as detailed above only for those subjects that agreed to future use in the Optional Studies section of the consent form. Access to these samples will only be granted following IRB approval of an additional protocol, granting the rights to use the material. Currently, there is no plan to use these samples outside of the use described in the protocol.

All specimens obtained in the protocol are used as defined in the protocol. Any specimens that are remaining at the completion of the protocol will be stored in the conditions described below. The study will remain open so long as sample or data analysis continues. Samples from consenting subjects will be stored until they are no longer of scientific value or if a subject withdraws consent for their continued use, at which time they will be destroyed.

If the patient withdraws consent the participants data will be excluded from future distributions, but data that have already been distributed for approved research use will not be able to be retrieved.

The PI will record any loss or unanticipated destruction of samples as a deviation. Reporting will be per the requirements of section 7.2.

5.3 SAMPLES FOR GENETIC/GENOMIC ANALYSIS

5.3.1 Description of the scope of genetic/genomic analysis

One of the exploratory endpoints of this protocol is to characterize genetic alterations which predict response and changes associated with the development of chemoresistance. To this end, whole and targeted genome sequencing may be performed on banked tumor samples collected pre-treatment and/or post-progression. Since analysis of germline variants is essential to fully characterize the somatic mutations identified in genome sequencing, these assays will involve both somatic and germline DNA.

5.3.2 Certificate of Confidentiality

Refer to section 13.4.

5.3.3 Management of Results

The analyses that we perform in our laboratory are for research purposes only; they are not nearly as sensitive as the tests that are performed in a laboratory that is certified to perform genetic testing. Changes that we observe unrelated to our research may or may not be valid. Therefore, we do not plan to inform participants of the results of testing on the tissue and blood that is performed in our research lab. However, in the unlikely event that a clinically actionable gene variant is discovered, subjects will be contacted. Clinically actionable findings for the purpose of this study are defined as disorders appearing in the American College of Medical Genetics and Genomics recommendations for the return of incidental findings that is current at the time of primary analysis. Subjects will be contacted at this time with a request to provide a sample to be sent to a CLIA certified laboratory. If the research findings are verified in the CLIA certified lab, the subject will be referred to the NCI CCR Genetics Branch for the disclosure of the results.

This is the only time during the course of the study that incidental findings will be returned. No interrogations regarding clinically actionable findings will be made after the primary analysis.

For samples undergoing analysis through the NCI COMPASS, results will be reported per CCR SOP ADGC-5, Tumor/Normal Whole Exome Sequencing: Consenting, Ordering, and Obtaining Results found at https://nih.sharepoint.com/sites/NCI-CCR-OCD-Communications/SitePages/OEC-Administrative---Clinical-Research-(ADCR).aspx?Mode=Edit

6 DATA COLLECTION AND EVALUATION

6.1 DATA COLLECTION

The PI will be responsible for overseeing entry of data into a 21 CFR Part 11-compliant data capture system provided by the NCI CCR and ensuring data accuracy, consistency and timeliness. The principal investigator, associate investigators/research nurses and/or a contracted data manager will assist with the data management efforts. Primary and final analyzed data will have identifiers so that research data can be attributed to an individual human subject participant.

Document AEs from the first study intervention, Study Day 1, through 30 days after the last study drug administration. Adverse events that are serious need to be recorded through 30 days

after the last study drug administration. Beyond 30 days after the last study drug administration and through the end of study participation, only adverse events which are serious and related to the study intervention need to be recorded.

An abnormal laboratory value will be considered an AE if the laboratory abnormality is characterized by any of the following:

- Results in discontinuation from the study
- Is associated with clinical signs or symptoms
- Requires treatment or any other therapeutic intervention
- Is associated with death or another serious adverse event, including hospitalization.
- Is judged by the Investigator to be of significant clinical impact

If any abnormal laboratory result is considered clinically significant, the investigator will provide details about the action taken with respect to the test drug and about the patient's outcome.

End of study procedures: Data will be stored according to HHS, FDA regulations, and NIH Intramural Records Retention Schedule as applicable.

Loss or destruction of data: Should we become aware that a major breach in our plan to protect subject confidentiality and trial data has occurred, this will be reported expeditiously per requirements in section 7.2.1.

6.2 DATA SHARING PLANS

6.2.1 Human Data Sharing Plan

What data will be shared?

I will share human data generated in this research for future research as follows (check all that apply):

_x__ Coded and linked data in an NIH-funded or approved public repository.

_x__ Coded and linked data in BTRIS (automatic for activities in the Clinical Center)

_x__ Coded and linked or identified data with approved outside collaborators under appropriate agreements.

How and where will the data be shared?

Data will be shared through (check all that apply):

_x__ An NIH-funded or approved public repository: clinicaltrials.gov; dbGaP.

_x__ BTRIS (automatic for activities in the Clinical Center)

_x__ Approved outside collaborators under appropriate individual agreements.

_x__ Publication and/or public presentations.

When will the data be shared?

_x__ Before publication.

_x__ At the time of publication or shortly thereafter.

6.2.2 Genomic Data Sharing Plan

Unlinked genomic data will be deposited in public genomic databases such as dbGaP in compliance with the NIH Genomic Data Sharing Policy.

6.3 RESPONSE CRITERIA

For the purposes of this study, patients should be re-evaluated for response every 2 cycles (every 3 cycles for patients on mCRPC cohort as per section 6.3.5). In addition to a baseline scan, confirmatory scans should also be obtained 4 weeks (8 weeks for mCRPC) 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) (61). 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.

6.3.1 Definitions

Evaluable for toxicity: All patients will be evaluable for toxicity from the time of their first treatment with EP0057.

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.

6.3.2 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:

- By chest x-ray: ≥20 mm;
- By CT scan:
    - Scan slice thickness 5 mm or under as ≥10 mm with CT scan
    - Scan slice thickness >5 mm: double the slice thickness
- With calipers on clinical exam: ≥10 mm.

All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

Malignant lymph nodes. To be considered pathologically enlarged and measurable, a lymph node must be ≥15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). 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 or pathological lymph nodes with ≥10 to <15 mm short axis), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonitis, inflammatory breast disease, and abdominal masses (not followed by CT or MRI), are considered as non-measurable.

Note: Cystic lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.

'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.

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.

6.3.3 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 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 or less. If CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (e.g. for body scans).

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 (62-64). 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 (65).

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.

6.3.4 Response Criteria

6.3.4.1 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.

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

Progressive Disease (PD): At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progressions).

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

6.3.4.2 Evaluation of Non-Target Lesions

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

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

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

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

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).

6.3.4.3 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.

** Only for non-randomized trials with response as primary endpoint.

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

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

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

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

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

6.3.5 Response Criteria for mCRPC Cohort

Changes in PSA and measurable lesions will be analyzed for efficacy according to the Prostate Cancer Clinical Trials Working Group 2 recommendations (63). PSA alone will not be utilized as a means to take a patient off-treatment.

Patients will be assessed primarily by CT scan of the chest, abdomen and pelvis and by technetium 99 bone scan at baseline and every 12 weeks (66). 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) (67) and Prostate Cancer Clinical Trials Working Group criteria (PCWG2) (66). 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.

Metastatic Bone Lesions

Disease progression is considered if a minimum of two new lesions is observed on bone scan. New lesions seen by the end of cycle 3 or before cycle 4 (after the first staging bone scan) may represent disease that was not detected on the pre-study scan, and a confirmatory scan will be

required at the next scheduled staging bone scan. If confirmed, progression should be dated by the initial time when the lesions are first detected. If new lesions are seen after cycle 3 but no additional lesions are seen on confirmatory scans, the scans from after cycle 3 would serve as the baseline scan to evaluate for disease progression (66).

6.3.6 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.

6.3.7 Progression-Free Survival

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

6.3.8 Response Review

Tumor measurements will be performed in consultation with the Center for Cancer Research Radiology and Imaging Sciences image processing service.

6.4 TOXICITY CRITERIA

The following adverse event management guidelines are intended to ensure the safety of each patient while on the study. The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 4.0. A copy of the CTCAE version 4.0 can be downloaded from the CTEP web site (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_40).

7 NIH REPORTING REQUIREMENTS / DATA AND SAFETY MONITORING PLAN

7.1 DEFINITIONS

Please refer to definitions provided in Policy 801: Reporting Research Events found https://irbo.nih.gov/hrpp-policy-guidelines/.

7.2 OHSRP OFFICE OF COMPLIANCE AND TRAINING / IRB REPORTING

7.2.1 Expedited Reporting

Please refer to the reporting requirements in Policy 801: Reporting Research Events and Policy 802 Non-Compliance Human Subjects Research found https://irbo.nih.gov/hrpp-policy-guidelines/.

Note: Only IND Safety Reports that meet the definition of an unanticipated problem or present new information that might affect the willingness of participants to enroll or remain on the study will need to be reported per these policies.

7.2.2 IRB Requirements for PI Reporting at Continuing Review

Please refer to the reporting requirements in Policy 801: Reporting Research Events found https://irbo.nih.gov/hrpp-policy-guidelines/.

7.3 NCI Clinical Director Reporting

Problems expeditiously reviewed by the OHSRP in the NIH eIRB system will also be reported to the NCI Clinical Director/designee; therefore, a separate submission for these reports is not necessary.

In addition to those reports, all deaths that occur within 30 days after receiving a research intervention **s**hould be reported via email unless they are due to progressive disease.

To report these deaths, please send an email describing the circumstances of the death to NCICCRQA@mail.nih.gov within one business day of learning of the death.

7.4 NIH Required Data and Safety Monitoring Plan

7.4.1 Principal Investigator/Research Team

The clinical research team will meet on a regular basis when patients are being actively treated on the trial to discuss each patient. Decisions about dose level enrollment and dose escalation if applicable will be made based on the toxicity data from prior patients.

All data will be collected in a timely manner and reviewed by the principal investigator or a lead associate investigator. Events meeting requirements for expedited reporting as described in section 7.2.1 will be submitted within the appropriate timelines.

The principal investigator will review adverse event and response data on each patient to ensure safety and data accuracy. The principal investigator will personally conduct or supervise the investigation and provide appropriate delegation of responsibilities to other members of the research staff.

8 SPONSOR PROTOCOL/SAFETY REPORTING

8.1 Definitions

8.1.1 Adverse Event

Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An adverse event (AE) can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product (ICH E6 (R2)).

8.1.2 Serious Adverse Event (SAE)

An adverse event or suspected adverse reaction is considered serious if in the view of the investigator or the sponsor, it results in any of the following:

- Death (except if from progressive disease, see 8.4)
- A life-threatening adverse event (see 8.1.3)
- Inpatient hospitalization or prolongation of existing hospitalization
    - A hospitalization/admission that is pre-planned (i.e., elective or scheduled surgery arranged prior to the start of the study), a planned hospitalization for pre-existing condition, or a procedure required by the protocol, without a serious deterioration in health, is not considered a serious adverse event.
    - A hospitalization/admission that is solely driven by non-medical reasons (e.g., hospitalization for patient convenience) is not considered a serious adverse event.
    - Emergency room visits or stays in observation units that do not result in admission to the hospital would not be considered a serious adverse event. The reason for seeking medical care should be evaluated for meeting one of the other serious criteria.
- Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect.
- Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate 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.

8.1.3 Life-threatening

An adverse event or suspected adverse reaction is considered "life-threatening" if, in the view of either the investigator or sponsor, its occurrence places the patient or subject at immediate risk of death. It does not include an adverse event or suspected adverse reaction that, had it occurred in a more severe form, might have caused death. (21CFR312.32).

8.1.4 Severity

The severity of each Adverse Event will be assessed utilizing the CTCAE version 4.

8.1.5 Relationship to Study Product

All AEs will have their relationship to study product assessed using the terms: related or not related.

- Related – There is a reasonable possibility that the study product caused the adverse event. Reasonable possibility means that there is evidence to suggest a causal relationship between the study product and the adverse event.
- Not Related – There is not a reasonable possibility that the administration of the study product caused the event.

8.2 Assessment of Safety Events

AE information collected will include event description, date of onset, assessment of severity and relationship to study product and alternate etiology (if not related to study product), date of resolution of the event, seriousness and outcome. The assessment of severity and relationship to

the study product will be done only by those with the training and authority to make a diagnosis and listed on the Form FDA 1572 as the site principal investigator or sub-investigator. AEs occurring during the collection and reporting period will be documented appropriately regardless of relationship. AEs will be followed through resolution.

SAEs will be:

- Assessed for severity and relationship to study product and alternate etiology (if not related to study product) by a licensed study physician listed on the Form FDA 1572 as the site principal investigator or sub-investigator.
- Recorded on the appropriate SAE report form, the medical record and captured in the clinical database.
- Followed through resolution by a licensed study physician listed on the Form FDA 1572 as the site principal investigator or sub-investigator.

For timeframe of recording adverse events, please refer to section 6.1. All serious adverse events recorded from the time of first investigational product administration must be reported to the sponsor with the exception of any listed in section 8.4.

8.3 Reporting of Serious Adverse Events

Any AE that meets protocol-defined serious criteria or meets the definition of Adverse Event of Special Interest that require expedited reporting must be submitted immediately (within 24 hours of awareness) to OSRO Safety. Any exceptions to the expedited reporting requirements are found in section 8.4.

All SAE reporting must include the elements described in 8.2.

SAE reports will be submitted via an electronic SAE reporting system (e.g. HiLIT). In the event of system downtime or issues , SAE reports will be submitted using the CCR SAE Report form to the sponsor at: OSROSafety@mail.nih.gov. CCR SAE report form and instructions can be found at: https://nih.sharepoint.com/:u:/r/sites/NCI-CCR-OCD-Communications/SitePages/Forms-and-Instructions.aspx?csf=1&web=1&e=uWBXtI.

Following the assessment of the SAE by OSRO, other supporting documentation of the event may be requested by the OSRO Safety and should be provided as soon as possible.

8.4 Waiver of Expedited Reporting to CCR/OSRO

As death/hospitalization due to disease progression is part of the study objectives (DOR, OS and PFS), and captured as endpoints in this study, they will not be reported in expedited manner to the sponsor. However, if there is evidence suggesting a causal relationship between the study drug and the event, report the event in an expedited manner according to section 8.3.

The Sponsor might request case summaries for those events if, upon review, the Sponsor determines that an aggregate safety report is required (21CFR312.32(c)(1)(iv)).

8.5 SAFETY REPORTING CRITERIA TO THE PHARMACEUTICAL COLLABORATORS

8.5.1 Ellipses Reporting Requirements

The study team will report every SAE, regardless of suspected causality, occurring after the patient begins taking study drug and until 30 days after the patient has stopped study treatment to Ellipses within 24 hours of learning of its occurrence. The MedWatch 3500A or equivalent form will be used to report all SAEs. The study team will report any SAE experienced after this 30 day period only if there is a causal relationship to the study drug.

Recurrent episodes, complications, or progression of the initial SAE will be reported by the study team as follow-up to the original episode within 24 hours of follow-up information receipt. An SAE occurring at a different time interval or otherwise considered completely unrelated to a previously reported one will be reported separately as a new event. The investigator will assess and record the relationship of each SAE to each specific study drug (if there is more than one study drug).

SAEs will be reported to:

- Ellipses pharmacovigilance vendor, Simbec-Orion: pharmacovigilance@simbecorion.com (Or alternatively by fax to +1 609 514 1000 or Back-up SAE fax: +1 609 452 7888)
- Ellipses contacts: Rina Patel at rina@ellipses.life Other Adverse Events of Special Interest

For all subjects, the following adverse events are categorized as Adverse Events of Special Interest (AESI) for EP0057:

- infusion-related hypersensitivity reaction(s) of any Grade
- any newly developed cystitis (including grade 1) in subjects without cystitis at baseline

The study team will report any occurrence of cystitis or patient hypersensitivity/allergic reactions a patient experiences associated with EP0057 to Ellipses (via Simbec-Orion) within 24 hours of learning of its occurrence using MedWatch 3500A or equivalent form.

8.5.2 AstraZeneca Reporting Requirements

8.5.2.1 To be performed by Sponsor

The Sponsor shall report any adverse events or adverse reactions (each as defined in the protocol) that arise in relation to the study to (i) the relevant regulatory authorities in accordance with the applicable laws; and (ii) any overseeing ethics committee in accordance with its policies.

Adverse events will be collected from the time consent is given, throughout the treatment period and up to and including the 30 day follow-up period. After withdrawal from treatment, subjects will be followed-up for all existing and new AEs for 30 calendar days after the last dose of trial drug and/or until event resolution. All new AEs occurring during that period will be recorded (if SAEs, then they will be reported to the FDA and AstraZeneca). All study-related toxicities/ SAEs will be followed until resolution, unless in the Investigator's opinion, the condition is unlikely to resolve due to the patient's underlying disease.

The Sponsor will report to the Company per the following guidelines:

- The Sponsor will notify the Company of all Suspected Unexpected Serious Adverse Reactions (SUSARs) subject to expedited reporting under the Applicable Laws at the same time that the reports are sent to the FDA using a medwatch 3500A form or equivalent.
- The Sponsor will notify the company within 30 days of all other SAEs [non-expedited reports], plus any AE reports relating to topics of special interest [MDS/AML, new primary malignancy and pneumonitis] using a medwatch 3500A form or equivalent.
- The Sponsor will inform the Company of any other matter relating to safety, quality or efficacy of the Company's medicinal product or which might affect the conduct of the study or the safety of subjects as soon as possible and at least in parallel with correspondence to regulators, IECs/IRBs and investigators.
- The Sponsor will provide the Company all adverse events (AEs and SAEs) on the Final Study Report upon completion of the Study.
- The Sponsor will respond to any query from the Company relating to SAEs, as part of the Company's pharmacovigilance processes.

The sponsor will send reports described above to:

AEMailboxClinicalTrialTCS@astrazeneca.com.

Tata Consultancy Services (TCS) will be responsible for processing all SAEs onto the AZ Patient Safety Database. Reports can also be sent via FAX to 1-302-886-4114.

Overdose

If an overdose on an AstraZeneca study drug occurs in the course of the study, then the sponsor will inform appropriate AstraZeneca representatives **within one day**, i.e., immediately but no later than **the end of the next business day** of when he or she becomes aware of it.

For overdoses associated with SAE, standard reporting timelines apply. For other overdoses, reporting should be done within 30 days.

Pregnancies

If any pregnancy occurs in the course of the study, then the Sponsor will inform appropriate AstraZeneca and Ellipses representatives **within one day** i.e., immediately but no later than the **end of the next business day** of when he or she becomes aware of it.

All outcomes of pregnancy should be reported to AstraZeneca and Ellipses.

8.5.2.2 To be Performed by Study Team

The PI and Research Team will be responsible for reporting the AEs that are not specifically listed above including:

- Providing the Company with line listing of all adverse events reported in the study. These line listings will be sent when the investigator receives an e-mail from Company.
- A summary report of other AEs and SARs will also be sent at a frequency no less than once a year and in a format agreed upon at Study Start-up. Instructions on sending these additional reports will be agreed upon at Study Start-up.

8.6 REPORTING PREGNANCY

All required pregnancy reports/follow-up to OSRO will be submitted to: OSROSafety@mail.nih.gov and to the CCR PI and study coordinator.

Forms and instructions can be found here: https://nih.sharepoint.com/:u:/r/sites/NCI-CCR-OCD-Communications/SitePages/Forms-and-Instructions.aspx?csf=1&web=1&e=uWBXtI

8.6.1 Maternal exposure

If a patient becomes pregnant during the course of the study, the study treatment should be discontinued immediately, and the pregnancy reported to the Sponsor no later than 24 hours of when the Investigator becomes aware of it. The Investigator should notify the Sponsor no later than 24 hours of when the outcome of the Pregnancy become known,

Pregnancy itself is not regarded as an SAE. However, congenital abnormalities or birth defects and spontaneous miscarriages that meet serious criteria (8.1.2) should be reported as SAEs.

The outcome of all pregnancies should be followed up and documented.

8.6.2 Paternal exposure

Patients should refrain from fathering a child or donating sperm during the study and for (3 months) after the last dose of EP0057 or olaparib.

Pregnancy of the patient's partner is not considered to be an AE. The outcome of all pregnancies occurring from the date of the first dose until (3 months) after the last dose should, if possible, be followed up and documented. Pregnant partners may be offered the opportunity to participate in an institutional pregnancy registry protocol (e.g., the NIH IRP pregnancy registry study) to provide data about the outcome of the pregnancy for safety reporting purposes.

8.7 REGULATORY REPORTING FOR STUDIES CONDUCTED UNDER CCR-SPONSORED IND

Following notification from the investigator, CCR, the IND sponsor, will report any suspected adverse reaction that is both serious and unexpected. CCR will report an AE as a suspected adverse reaction only if there is evidence to suggest a causal relationship between the study product and the adverse event. CCR will notify FDA and all participating investigators (i.e., all investigators to whom the sponsor is providing drug under its INDs or under any investigator's IND) in an IND safety report of potential serious risks from clinical trials or any other source, as soon as possible, in accordance to 21 CFR Part 312.32.

All serious events will be reported to the FDA at least annually in a summary format.

8.8 SPONSOR PROTOCOL DEVIATION REPORTING

A Protocol Deviation is defined as any non-compliance with the clinical trial Protocol, Manual of Operational Procedures (MOP) and other Sponsor approved study related documents, GCP, or protocol-specific procedural requirements on the part of the participant, the Investigator, or the study site staff inclusive of site personnel performing procedures or providing services in support of the clinical trial.

It is the responsibility of the study Staff to document any protocol deviation identified by the Staff or the site Monitor in the CCR Protocol Deviation Tracking System (PDTS) online application. The entries into the PDTS online application should be timely, complete, and maintained per CCR PDTS user requirements.

In addition, any deviation to the protocol should be documented in the participant's source records and reported to the reviewing IRB per their guidelines. OSRO required protocol deviation reporting is consistent with E6(R2) GCP: Integrated Addendum to ICH E6(R1): 4.5 Compliance with Protocol; 5.18.3 (a), and 5.20 Noncompliance; and ICH E3 16.2.2 Protocol deviations.

9 CLINICAL MONITORING

Clinical site monitoring is conducted to ensure:

- that the rights of the participants are protected;
- that the study is implemented per the approved protocol, Good Clinical Practice and standard operating procedures; and,
- the quality and integrity of study data and data collection methods are maintained.

Monitoring for this study will be performed by NCI CCR Office of Sponsor and Regulatory Oversight (OSRO) and Regulatory Oversight Support (SROS) Services contractor. Clinical site monitoring activities will be based on OSRO standards, FDA Guidance E6(R2) Good Clinical Practice: Integrated Addendum to ICH E6(R1) March 2018, and applicable regulatory requirements.

Details of clinical site monitoring will be documented in a Clinical Monitoring Plan (CMP) developed by OSRO. CMPs will be protocol-specific, risk-based and tailored to address human subject protections and integrity of the study data. OSRO will determine the intensity and frequency of monitoring based on several factors, including study type, phase, risk, complexity, expected enrollment rate, and any unique attributes of the study and the site. The Sponsor will conduct a periodic review of the CMP to confirm the plan's continued appropriateness. A change to the protocol, significant or pervasive non-compliance with GCP, or the protocol may trigger CMP updates.

OSRO SROS Monitoring visits and related activities will be conducted throughout the life cycle of each protocol. The first activity is before the study starts to conduct a Site Assessment Visit (SAV) (as warranted), followed by a Site Initiation Visit (SIV), Interim Monitoring Visit(s) (IMVs), and a study Close-Out Visit (COV).

Some monitoring activities may be performed remotely, while others will occur at the study site(s). Monitoring visit reports will describe visit activities, observations, and associated action items or follow-up required for resolution of any issues, discrepancies, or deviations. Monitoring reports will be distributed to the study PI, NCI CCR QA, CCR Protocol Support Office, coordinating center (if applicable), and the Sponsor regulatory file.

The site Monitor will inform the study team of any deviations observed during monitoring visits. If unresolved, the Monitor will request that the site Staff enter the deviations in the CCR Protocol Deviation Tracking System (PDTS) for deviation reporting to the Sponsor and as applicable per institutional and IRB guidance.

10 STATISTICAL CONSIDERATIONS

- Phase I: To determine the MTD/ recommended Phase 2 dose (RP2D) of EP0057 in combination with olaparib in patients with refractory cancers

- Phase II: To determine the antitumor activity of olaparib plus EP0057 with respect to progression free survival at 16 weeks in SCLC patients with resistant or sensitive relapse
- Expansion: To determine overall response rate of EP0057 plus olaparib in patients with mCRPC and urothelial carcinoma

10.1 PHASE I AND PHASE II

For the phase I portion of the trial, a standard 3+3 design will be used, to determine the RP2D/MTD of EP0057 in combination with olaparib. The theoretical maximum number of subjects required to determine the MTD in the phase I portion of the study is 30 subjects (6 per dose level), although it is expected that as few as 15 subjects in 4 dose levels would be required to reach an MTD.

Sensitivity to first-line chemotherapy has been considered as the main driver of second-line therapy outcome in SCLC. For this reason, relapsed SCLC has been traditionally classified into sensitive and resistant disease according to the type of response to first-line therapy and to treatment-free interval (treatment-free interval longer or shorter than 60–90 days) (68). Although this definition was derived many years ago and based on a small patient series (69), first-line chemotherapy sensitivity has since been confirmed to be a prognostic factor to predict response to second line and further therapy in meta-analyses (3) and randomized studies (70, 71).

Published results suggest that the median PFS for single agent therapy with topotecan (currently the only approved second line therapy) for previously treated patients which included a combination of sensitive and resistant /refractory SCLC patients was approximately 3 months (median 3.0-4.3 months for sensitive and 1.5-2.6 months for refractory; (68, 70-73) (refer to **Table 15**).

A recent randomized study of PARP inhibitor plus chemotherapy in relapsed SCLC patients (both platinum-sensitive and resistant patients were included) found no significant difference in 4-month PFS between temozolomide/veliparib (20 of 55; 36%) and temozolomide /placebo (13 of 49; 27%; $P = .19$) (74). Median PFS was 3.8 months and 2.0 months in the temozolomide /veliparib and temozolomide /placebo arms, respectively (log-rank $P = .39$; hazard ratio, 0.84; 95% CI, 0.56 to 1.25).

Patients with both sensitive and resistant SCLC will be enrolled in the phase II study and analyzed together. The phase II trial will be conducted using an optimal two-stage design in order to rule out an unacceptably low success rate of 25% (p0=0.25) in favor of an improved success rate of 45% (p1=0.45). With alpha=0.10 (probability of accepting a poor treatment=0.10) and beta = 0.20 (probability of rejecting a good treatment=0.20), this first stage will enroll 15 evaluable patients, and if 0 to 4 of the 15 have a success (that is, 0 to 4 make it to 16 weeks without progression), then no further patients will be accrued. If 5 or more of the first 15 patients have success, then accrual would continue until a total of 27 evaluable resistant/refractory patients have been enrolled. As it may take up to 4 months to determine if a patient has experienced a success at 16 weeks, a temporary pause in the accrual may be necessary to ensure that enrollment to the second stage is warranted. If there are 5 to 9 patients with a success out of 27 patients, this would be an uninterestingly low success rate. If there were 10 or more of 27 (37%) who experienced a success, this would be sufficiently interesting to warrant further study in later trials. Under the null hypothesis (25% success rate), the probability of early termination is 68.7%.

Patients who receive at least one dose of the study drug will be evaluable for safety. Patients who complete at least one cycle of treatment and have a follow up imaging study will be evaluable for efficacy. The maximum number of patients on the phase I portion of the trial is 30 and phase II SCLC may accrue up to 27 evaluable patients. Thus, the maximum number of evaluable patients which may enroll on the phase I and II cohorts is 57. In order to allow for a small number of in-evaluable patients, the accrual ceiling will be set at 60 for these cohorts. It is anticipated that approximately 1 to 2 patients per month may enroll onto these cohorts.

Table 15. Selected randomized studies of cytotoxic agents for SCLC

No.	Patients	Treatments	Primary endpoint	Median PFS-topotecan	Median OS-topotecan	Reference
1	Sensitive SCLC	Topotecan (N=107) *vs.* CAV (N=104)	ORR	3.3 months (sensitive)	6.3 months (sensitive)	(68)
2	Refractory or sensitive SCLC; 2nd line	Topotecan (N=213) *vs.* amrubicin (N=424)	OS	4.3 months (sensitive) 2.6 months (refractory)	9.9 months (sensitive) 5.7 months (refractory)	(71)
3	Sensitive SCLC 2:1	Topotecan (N=26) *vs.* amrubicin (N=50)	ORR	3.3 months (sensitive)	7.6 months (sensitive)	(73)
4	Refractory or sensitive SCLC	Topotecan (N=30) *vs.* amrubicin (N=29)	ORR	3.0 months (sensitive) 1.5 months (refractory)	NA	(70)
5	Sensitive SCLC; 2nd line	PO (N=153) *vs.* IV (N=151) topotecan	ORR	3.7 months (sensitive)	8.7 months (sensitive)	(72)

10.2 PHASE II EXPANSION COHORTS

10.2.1 Expansion Cohort (Urothelial Carcinoma)

The primary objective of this cohort is to determine the clinical response rate to EP0057 and olaparib in patients with bladder cancer. Data from a single trial of 310 patients with metastatic bladder cancer receiving atezolizumb alone demonstrated an ORR of 15%. To establish at least slightly improved efficacy of this treatment combination compared to single agent atezolizumab, the primary objective would be to determine if using the proposed agents would rule out a 10% response rate and result in a response rate consistent with 25%. As such, this cohort of the trial

will be conducted using a Simon optimal two-stage phase II trial design (75) to rule out an unacceptably low PR+CR rate of 10% (p0=0.10) in favor of an improved response rate of 25% (p1=0.25). With alpha=0.10 (probability of accepting a poor treatment=0.15) and beta = 0.20 (probability of rejecting a good treatment=0.20), the first stage will enroll 13 evaluable patients, and if 0 to 1 of the 13 have a clinical response, then no further patients will be accrued in this cohort. If 2 or more of the first 13 patients have a response, then accrual would continue until a total of 34 evaluable patients have been treated. As it may take up to several months to determine if a patient has experienced a response, a temporary pause in the accrual may be necessary to ensure that enrollment to the second stage is warranted. If there are 2 to 5 patients with a response out of 34 patients, this would be an uninterestingly low response rate. If there were 6 or more of 34 (17.6%) who experienced a response, this would be sufficiently interesting to warrant further study in later trials. Under the null hypothesis (10% response rate), the probability of early termination is 62.1%.

It is expected that approximately 1 to 2 patients per month may enroll onto this cohort in the trial. Thus, it is expected that 2 to 3 years may be required to enroll up to 34 evaluable patients. To allow for a small number of inevaluable patients, the accrual ceiling for this cohort will be set at 36 patients. Analysis of correlative studies will be exploratory.

10.2.2 Expansion Cohort (mCRPC)

The primary objective of this exploratory cohort is to determine the clinical response rate to EP0057 and olaparib in patients with prostate cancer who are identified as having one of several possible genetic mutations.

In a published study of 16 patients with prostate cancer who have one of a set of specified mutations, 14 (87.5%) had experienced a clinical response when treated with olaparib alone. While it is unlikely that this could be improved upon, it would be of interest to explore if a similarly high response rate could be seen in patients treated at the NCI with EP0057 and olaparib.

Patients with prostate cancer will be enrolled onto this cohort and biopsied, and the patients who are found to have any of a set of defined genetic mutations (in the DNA damage repair pathways), will receive EP0057 and olaparib and be evaluated for clinical response by PSA and RECIST criteria. It is anticipated that 25-30% of patients will be found to possess one of the mutations of interest. To obtain at least 5 patients who could be evaluated for response, 25 total patients will undergo procedures necessary to determine if they possess the appropriate mutations. If the true probability of a mutation were 30%, then with 25 patients, there is a 91.0% probability of identifying 5 or more with mutations, including a 32.3% probability of identifying 9 or more patients with mutations. If the true probability of a mutation were 25%, with 25 patients, there is a 78.6% probability of identifying 5 or more with mutations, and a 14.9% probability of obtaining 9 or more with mutations. Thus, by enrolling 25 patients, there should be between 79% and 91% probability of identifying 5 or more patients with mutations, and between 15% and 32% probability of potentially identifying 9 or more with mutations.

For however many patients are identified with mutations, expected to be between 5 and 9 out of 25, these patients will receive treatment with EP0057 and olaparib, and will have their responses evaluated using PSA and RECIST criteria. The fraction with responses obtained will be reported along with 80% and 95% two-sided confidence intervals, and the results compared, at least informally, to those from the published study with similar patients treated with olaparib alone.

While the actual number of these patients to receive EP0057 and olaparib is likely to between 5 and 9, the trial will continue to enroll and evaluate up to the ceiling of 25 patients with prostate cancer, unless an early stopping rule is invoked. If among the first 5 treated patients with prostate cancer who have DNA damage repair pathway mutations, only 1 of 5 responds, then no further patients will be enrolled since the upper one-sided 90% CI bound on 1/5 = 58.4%, which would be below the lower one sided 90% CI bound on 14/16 from the published study (70.0%), and thus be inconsistent with the prior results.

The remaining patients without a mutation in their DNA damage repair pathway will also receive the combination of EP0057 and olaparib. It is expected that out of 25 evaluable patients enrolled on the trial, between 16 and 20 will not have these mutations. For these patients, it would be desirable to determine if their response rate would exceed 5% and be consistent with 25% or greater. Using that as a guideline, if there are 16 patients without the proper mutations who receive the combination treatment, 3 responses in 16 would be associated with a two-sided 80% exact confidence interval of 7.1-37.1%, and 4 responses in 16 would be associated with a two-sided 80% exact confidence interval of 11.4 to 43.9%. With 20 patients without the proper mutations, 3 responses in 20 is associated with the same confidence interval of 5.6 to 30.4%, and 4 responses in 20 would have a confidence interval of 9.0-36.1%. The values for 17 to 19 patients have similar confidence intervals. Thus, in the expected range of 16 to 20 patients without mutations, a minimum of 3 responses, but preferably 4 or more, would be the lowest numbers of responses obtained which could be considered sufficiently interesting to allow the treatment to be evaluated further in these patients. As these patients are being accrued and treated while aiming to attain the greatest number of patients with the DNA damage repair pathway mutations, there will be no early stopping rule based on poor response in this group of 16 to 20 patients.

It is expected that approximately 1 patient per month may enroll onto this cohort in the trial. Thus, it is expected that 2 years may be required in order to enroll up to 25 evaluable patients. To allow for a small number of inevaluable patients, the accrual ceiling for this cohort will be set at 27 patients.

10.3 SAMPLE SIZE DETERMINATION

With up to 30+27+34+25= 116 evaluable participants needed for the phase 1 dose escalation and expansion phases, as well as planning for a small number of inevaluable participants (10), we intend to initiate intervention in up to 126 participants. Note: To allow for screen failures (10), a total of 136 will be set for the purposes of the NIH accrual ceiling.

Overall, 1 – 2 patients per month are expected to enroll across all of the cohorts. It is expected that enrollment will be completed in 6 – 8 years.

11 COLLABORATIVE AGREEMENTS

11.1 COOPERATIVE RESEARCH AND DEVELOPMENT AGREEMENT (CRADA)

11.1.1 BlueLink (CRADA #03049)

The investigational study agent formerly named CRLX101 was being provided by the company, BlueLink under a Collaborative Agreement [Cooperative Research and Development Agreement (CRADA)].

As of March 2020, the CRADA has been amended to switch the manufacturer from BlueLink to Ellipses and drug name from CRLX101 to EP0057.

11.1.2 Astra Zeneca (CRADA #02299)

The investigational study agent, olaparib is provided by the company, Astra Zeneca under a Collaborative Agreement [Cooperative Research and Development Agreement (CRADA)].

12 HUMAN SUBJECTS PROTECTIONS

12.1 Rationale For Subject Selection

As previously described, the subjects for this study will include all subjects who meet the eligibility criteria outlined in section 2.1. No sex, racial, or ethnic groups will be excluded from participation in this trial.

The effects of EP0057 and olaparib on the developing human fetus are unknown. For this reason, participants will be required to use contraception

12.2 Participation of Children

Because no dosing adverse event data are currently available on the use of EP0057 in combination with olaparib in subjects <18 years of age, children are excluded from this study.

12.3 Evaluation of Benefits and Risks/Discomforts

12.3.1 Risks

12.3.1.1 Study drug risks

The risks associated with the specific study agents are described in sections 14.1.9 and 14.2.9. Subjects will be adequately monitored for the occurrence of any possible side effects.

12.3.1.2 Biopsy risks

The risks associated with biopsies are pain and bleeding at the biopsy site. In order to minimize pain, local anesthesia will be used. Rarely, there is a risk of infection at the sampling site. CT guidance may be used in obtaining biopsies.

12.3.1.3 Conscious sedation risks

There is a possibility that conscious sedation may be used for the procedure. The common side effects of conscious sedation include drowsiness, delayed reflexes, hypotension, headache, and nausea. These are generally mild and last no more than a few hours.

12.3.1.4 Radiation risks

Subjects will be exposed to radiation from 3 CT guided biopsies and up to 9 CTs. The amount of radiation exposure is equal to approximately up to 12.3 rem.

Note: As accrual to cohort 4 (mCRPC) ended with amendment version 7/27/2021, CT c/a/p and bone scan every 3 weeks are not included in the calculated radiation dose above.

12.3.1.5 Risks from CT scans

There is a chance of developing an allergic reaction from the contrast material, which may cause symptoms ranging from mild itching or a rash to severe difficulty breathing, shock or rarely,

death. The contrast material may also cause kidney problems. Patients may feel discomfort when the contrast material is injected.

12.3.1.6 Risks related to blood sampling

Side effects of blood draws include pain and bruising, lightheadedness, and rarely, fainting. Up to 225 mL of blood may be drawn at any given visit, with a maximum of 529 mL in an 8-week period.

12.3.1.7 Risk related to hair collection

The only risk associate with hair collection is pain.

12.3.2 Benefits

The benefits include a possible decrease in the size of the tumor and the scientific knowledge that could be acquired through this trial.

12.4 CONSENT PROCESS AND DOCUMENTATION

The informed consent document will be provided as a physical or electronic document to the participant for review prior to consenting. A designated study investigator will carefully explain the procedures and tests involved in this study, and the associated risks, discomforts and benefits. In order to minimize potential coercion, as much time as is needed to review the document will be given, including an opportunity to discuss it with friends, family members and/or other advisors, and to ask questions of any designated study investigator. A signed informed consent document will be obtained prior to entry onto the study.

The initial consent process as well as re-consent, when required, may take place in person or remotely (e.g., via telephone or other NIH approved remote platforms used in compliance with policy, including HRPP Policy 303) per discretion of the designated study investigator and with the agreement of the participant. Whether in person or remote, the privacy of the subject will be maintained. Consenting investigators (and participant, when in person) will be located in a private area (e.g., clinic consult room). When consent is conducted remotely, the participant will be informed of the private nature of the discussion and will be encouraged to relocate to a more private setting if needed.

Consent will be documented with required signatures on the physical document (which includes the printout of an electronic document sent to participant) or as described below, with a manual (non-electronic signature) on the electronic document. When required, witness signature will be obtained similarly as described for the investigator and participant.

<u>Manual (non-electronic) signature on electronic document</u>:

When a manual signature on an electronic document is used for the documentation of consent at the NIH Clinical Center, this study will use the following to obtain the required signatures:

- Adobe platform (which is not 21 CFR Part 11 compliant); or,
- iMedConsent platform (which is 21 CFR Part 11 compliant)

During the consent process, participants and investigators will view individual copies of the approved consent document on screens at their respective locations (if remote consent); the same screen may be used when in the same location, but is not required.

Both the investigator and the participant will sign the document using a finger, stylus or mouse.

Note: Refer to the CCR SOP PM-2, Obtaining and Documenting the Informed Consent Process for additional information (e.g., verification of participant identity when obtaining consent remotely) found at: https://nih.sharepoint.com/sites/NCI-CCR-OCD-Communications/SitePages/OEC-Administrative---Clinical-Research-(ADCR).aspx?Mode=Edit.

12.4.1 Request for Waiver of Consent for Screening Activities

Prior to the participant signing the consent for this study pre-screening activities listed in Section **2.3.1** may be performed.

We request a waiver of consent for these activities as they involve only minimal risk to the participants. A waiver will not adversely affect the rights and welfare of the participants given that the activities are only intended to determine suitability for screening for participation in research protocols. These activities could not practicably be carried out without the wavier as central recruiting services, utilized in the NIH Clinical Center, perform pre-screening activities for multiple studies and obtaining consent for each one is beyond their resources. The participants will be provided with additional pertinent information after participation as they will be informed whether or not they are eligible to sign a consent for additional screening.

13 REGULATORY AND OPERATIONAL CONSIDERATIONS

13.1 STUDY DISCONTINUATION AND CLOSURE

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to study participants, investigator, funding agency, the Investigational New Drug (IND) sponsor and regulatory authorities. If the study is prematurely terminated or suspended, the Principal Investigator (PI) will promptly inform study participants, the Institutional Review Board (IRB), and sponsor and will provide the reason(s) for the termination or suspension. Study participants will be contacted, as applicable, and be informed of changes to study visit schedule.

Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants
- Demonstration of efficacy that would warrant stopping
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable
- Determination that the primary endpoint has been met
- Determination of futility

Study may resume once concerns about safety, protocol compliance, and data quality are addressed, and satisfy the sponsor, IRB and as applicable, Food and Drug Administration (FDA).

13.2 QUALITY ASSURANCE AND QUALITY CONTROL

The clinical site will perform internal quality management of study conduct, data and biological specimen collection, documentation and completion. An individualized quality management plan will be developed to describe the site's quality management.

Quality control (QC) procedures will be implemented beginning with the data entry system and data QC checks that will be run on the database will be generated. Any missing data or data anomalies will be communicated to the site(s) for clarification/resolution.

Following written Standard Operating Procedures (SOPs), the monitors will verify that the clinical trial is conducted and data are generated and biological specimens are collected, documented (recorded), and reported in compliance with the protocol, International Council for Harmonisation Good Clinical Practice (ICH GCP), and applicable regulatory requirements (e.g., Good Laboratory Practices (GLP), Good Manufacturing Practices (GMP)).

The investigational site will provide direct access to all trial related sites, source data/documents, and reports for the purpose of monitoring and auditing by the sponsor, and inspection by local and regulatory authorities.

13.3 Conflict of Interest Policy

The independence of this study from any actual or perceived influence, such as by the pharmaceutical industry, is critical. Therefore, any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the design and conduct of this trial. The study leadership in conjunction with the National Institutes of Health has established policies and procedures for all study group members to disclose all conflicts of interest and will establish a mechanism for the management of all reported dualities of interest.

13.4 Confidentiality and Privacy

Participant confidentiality and privacy is strictly held in trust by the participating investigators, their staff, and the sponsor(s). This confidentiality is extended to cover testing of biological samples and genetic tests in addition to the clinical information relating to participants. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor.

All research activities will be conducted in as private a setting as possible.

The study monitor, other authorized representatives of the sponsor, representatives of the Institutional Review Board (IRB), and/or regulatory agencies may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study. The clinical study site will permit access to such records.

The study participant's contact information will be securely stored at the/each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the reviewing IRB, Institutional policies, or sponsor requirements.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be stored at the NCI CCR. This will not include the participant's contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems

used by the clinical site(s) and by NCI CCR research staff will be secured and password protected. At the end of the study, all study databases will be archived at the NIH.

To further protect the privacy of study participants, a Certificate of Confidentiality has been issued by the National Institutes of Health (NIH). This certificate protects identifiable research information from forced disclosure. It allows the investigator and others who have access to research records to refuse to disclose identifying information on research participation in any civil, criminal, administrative, legislative, or other proceeding, whether at the federal, state, or local level. By protecting researchers and institutions from being compelled to disclose information that would identify research participants, Certificates of Confidentiality help achieve the research objectives and promote participation in studies by helping assure confidentiality and privacy to participants.

14 PHARMACEUTICAL INFORMATION

14.1 EP0057 (IND#130102)

14.1.1 Description

EP0057 is a polymer drug conjugate composed of 20 (S)-camptothecin conjugated to a biocompatible polymer. The compound self assembles into soluble nanoparticles composed of several molecules when dissolved in aqueous solution. Camptothecin (CPT) is an antineoplastic that inhibits topoisomerase I resulting in cell death during the S phase of the cell cycle. EP0057 nanoparticles are believed to be taken up by tumor cells followed by release of the active pharmaceutical ingredient 20(S)-camptothecin.

14.1.2 Supplier/How Supplied

The EP0057 is provided by the company, Ellipses, the manufacturer of the drug under a Collaborative Agreement [Cooperative Research and Development Agreement (CRADA)].

EP0057 will be provided at no cost to the study patient. It is supplied as a lyophilized cakein 30 mL single-use vial containing 35 mg of CPT equivalents (approximately 350 mg of polymer drug conjugate).

14.1.3 Handling and Dispensing

EP0057 is a sterile injectable and must be handled under appropriate controls, conditions, and aseptic techniques to maintain product sterility. EP0057, a cytotoxic, should be prepared in a class II biological safety cabinet using standard precautions for the safe handling of antineoplastic agents. Latex gloves are recommended. It must be dispensed only from official study sites by authorized personnel according to local regulations, and stored in a secure area according to local regulations. It is the responsibility of the Investigator to ensure that study drug is only dispensed to eligible study patients.

14.1.4 Preparation

Vials of EP0057 should be removed from the refrigerator and warmed to room temperature for approximately one hour prior to preparation. Concentrated EP0057 solution is prepared by adding 14 mL of SWFI to each 35 mg vial. The required volume of SWFI is to be aseptically withdrawn into a sterile calibrated syringe and the syringe needle inserted through the vial septum. The SWFI should be slowly added along the inside of the vial wall and not directly onto

the lyophilized product cake to minimize foaming. The product is dissolved by gentle swirling (do not shake) until a clear homogenous solution is achieved. The majority of the product cake will dissolve quickly, however complete dissolution to a clear, homogenous solution will take longer and may require up to 30 minutes. The EP0057 concentrated solution should be inspected visually for particulate matter prior to further preparation. Visually inspect for completion of reconstitution every 2-3 minutes. Reconstitution is complete when (i) foam head has dissipated down to a thin bubble ring along inner wall of vial, (ii) solids in solution and foam head are no longer visible, and (iii) translucent polymer "vapors" are no longer visible in solution and the solution is clear and uniform in appearance. Complete reconstitution of the vial may take up to 30 minutes.

Each milliliter of concentrated solution contains 2.5 mg of camptothecin equivalents. Concentrated EP0057 solution is diluted to the recommended dose with 5% dextrose in water for injection (D5W) to a total volume of 500 mL. After determining the amount of EP0057 concentrated solution required for dosing, an equivalent volume is aseptically withdrawn from a 500 mL infusion bag or bottle of D5W with a calibrated syringe. The measured volume of concentrated EP0057 solution is then withdrawn with a calibrated syringe and injected into the prepared 500 mL D5W infusion bag or bottle. The solution is thoroughly mixed by gentle manual rotation.

14.1.5 Storage and Stability

EP0057 vials should be stored at refrigerated conditions (2° - 8°C) and should only be accessible to authorized individuals. EP0057 is stable for at least 3 years when stored at refrigerated conditions (2° - 8°C). The reconstituted solution is stable for 24 hours when stored at room temperature. Any unused product solution from the reconstituted vials should be destroyed per the site's standard operating procedures.

Formulated EP0057 (i.e., IV bag) should be used within 6 hours of reconstituting the drug product vials.

14.1.6 Dosage and Administration

See Sections 3.2 and 3.3 for the dose levels and administration of EP0057 to be evaluated in this study.

See Section 3.3.4 for management of any EP0057 infusion related/hypersensitivity reactions.

The second and subsequent dose of EP0057 may be delayed if related AEs have not resolved to grade 1 or better. If a dose of EP0057 is delayed, then the subsequent dose should be administered 2 weeks later to avoid significant carry-over of unconjugated plasma CPT from one dose to the next (see Section 3.3). However, the maximum delay for AEs to resolve is 21 days beyond which the patient will be taken off treatment.

14.1.7 Premedication and Hydration

The premedication prior to EP0057 treatment and pre and post hydration and additional prevention measurements to prevent hypersensitivity/infusion reaction have been described in Section 3.2.1.1.

14.1.8 Return and Retention of EP0057

Any used study drug vials, or partially used vials, remaining after trial is complete will be destroyed per institution drug destruction policy. Unused study drug vials may be destroyed in the same manner or returned if requested to Ellipses.

14.1.9 Toxicity

Possible toxicities from EP0057 include: neutropenia, thrombocytopenia, anemia, nausea, vomiting, diarrhea, mucositis, anorexia, and cystitis. Commonly reported toxicities in clinical trials with EP0057 are anemia, fatigue, cystitis, nausea, hematuria, neutropenia, diarrhea, vomiting, dysuria, constipation, thrombocytopenia, decreased appetite, and infusion-related reaction.

For additional details, refer to section 1.2 and investigator brochure.

14.2 OLAPARIB (AZD2281; OLAPARIB; IND#130102)

(Please refer to the Investigator's Brochure and the package insert for further details)

14.2.1 Source

The olaparib is provided by the company, Astra Zeneca under a Collaborative Agreement [Cooperative Research and Development Agreement (CRADA)].

Olaparib (AstraZeneca Pharmaceuticals LP) has been commercially Food and Drug Administration approved as monotherapy for the treatment of patients with deleterious or suspected deleterious germline BRCA mutated (gBRCAm) (as detected by an FDA-approved test) advanced ovarian cancer who have been treated with three or more prior lines of chemotherapy.

As of 20 March 2015, >3800 patients with ovarian, breast, pancreatic, gastric and a variety of other solid tumors are estimated to have received treatment with olaparib in clinical studies as either monotherapy or in combination with other chemotherapy/anti-cancer agents. Most new clinical studies are investigating the tablet formulation which delivers the therapeutic dose of olaparib in fewer dose units than the capsule.

14.2.2 Pre-clinical experience

The pre-clinical experience is fully described in the current version of the olaparib Investigator's Brochure (IB).

14.2.3 Toxicology and safety pharmacology summary

Olaparib has been tested in a standard range of safety pharmacology studies e.g. dog cardiovascular and respiratory function tests, and the rat Irwin test. There were no noticeable effects on the cardiovascular or respiratory parameters in the anaesthetized dog or any behavioral, autonomic or motor effects in the rat at the doses studied.

The toxicology studies indicate that the target organ of toxicity is the bone marrow.

Further information can be found in the current version of the olaparib Investigator's Brochure

14.2.4 Approved indications and clinical experience

Clinical experience with olaparib is fully described in the current version of the olaparib Investigator's Brochure.

AstraZeneca is planning to voluntarily withdraw olaparib for the treatment of adult patients with deleterious or suspected deleterious germline BRCA-mutated (gBRCAm) advanced ovarian cancer who have been treated with three or more prior lines of chemotherapy (Dear ESR Sponsor Letter dated 8/10/22). This is currently an approved indication in the US.

A recent subgroup analysis indicated a potential detrimental effect on overall survival (OS) for olaparib as a line of treatment compared to the chemotherapy control arm in patients who had received three or more prior lines of chemotherapy in the randomized Phase III study, SOLO3 (D0816C00010; NCT02282020). SOLO3 met its primary endpoint of ORR and the key secondary endpoint of progression-free survival (PFS). Safety data, other than OS, reported for olaparib in the SOLO3 study were consistent with that reported in other clinical trials with olaparib, and no new safety signals were identified.

14.2.5 Indications and Usage

Olaparib is a poly (ADP-ribose) polymerase (PARP) inhibitor indicated as monotherapy in patients with deleterious or suspected deleterious germline BRCA mutated (as detected by an FDA-approved test) advanced ovarian cancer who have been treated with three or more prior lines of chemotherapy.

The indication is approved under accelerated approval based on objective response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.

14.2.6 Dosage and Administration

Please refer to section 3.2.2 for administration instructions. Dose will be according to assigned dose level (see section 3.1).

14.2.7 Tablet Dosage Forms and Strengths

Olaparib is presented for oral administration as a green, film-coated tablet containing 25 mg, 100 mg, 150 mg or 200 mg of drug substance.

14.2.8 Warnings and Precautions

• Myelodysplastic syndrome/Acute Myeloid Leukemia: (MDS/AML) occurred in patients exposed to olaparib, and some cases were fatal. Monitor patients for hematological toxicity at baseline and monthly thereafter. Discontinue if MDS/AML is confirmed.

• Pneumonitis: occurred in patients exposed to olaparib, and some cases were fatal. Interrupt treatment if pneumonitis is suspected. Discontinue if active pneumonitis is confirmed.

• Embryo-Fetal toxicity: olaparib can cause fetal harm. Advise individuals of reproductive potential of the potential risk to a fetus and to avoid pregnancy.

14.2.9 Adverse Reactions

Table 16. Adverse Drug Reactions Reported in Clinical Trials

MedDRA SOC	MedDRA term	CIOMS descriptor/ overall frequency (All CTCAE grades)	Frequency of CTCAE Grade 3 and above

Neoplasms benign, malignant and unspecified (including cysts and polyps)	Myelodysplastic syndrome/acute myeloid leukaemia	Uncommon	Uncommon
Blood and lymphatic system disorders	Anaemia[a]	Very common	Very common
	Neutropenia[a]	Very common	Common
	Leukopenia[a]	Very common	Common
	Thrombocytopenia[a]	Common	Common
	Lymphopenia[a]	Common	Common
Immune system disorders	Hypersensitivity[a]	Uncommon	Rare
	Angioedema[b]	Uncommon	-
Metabolism and nutrition disorders	Decreased appetite	Very common	Uncommon
Nervous system disorders	Dizziness	Very common	Uncommon
	Headache	Very common	Uncommon
	Dysgeusia[a]	Very common	-
Respiratory, thoracic and mediastinal disorders	Cough[a]	Very common	Uncommon
	Dyspnoea[a]	Very common	Common
Gastrointestinal disorders	Vomiting	Very common	Common
	Diarrhoea	Very common	Uncommon
	Nausea	Very common	Common
	Dyspepsia	Very common	Rare
	Stomatitis[a]	Common	Uncommon
	Upper abdominal pain	Common	Rare
Skin and subcutaneous tissue disorders	Rash[a]	Common	Uncommon
	Dermatitis[a]	Uncommon	Rare
	Erythema nodosum[b]	Rare	-
General disorders	Fatigue (including asthenia)	Very common	Common
Investigations	Blood creatinine increased	Common	Rare
	Mean cell volume increased	Uncommon	-
Vascular disorders	Venous thromboembolism[a]	Common	Common

[a] Anaemia includes preferred terms (PTs) of anaemia, anaemia macrocytic, erythropenia, haematocrit decreased haemoglobin decreased, normocytic anaemia and red blood cell count decreased; Cough includes PTs of cough and productive cough; Dermatitis includes PTs of dermatitis and dermatitis allergic; Dysgeusia includes PTs of dygeusia and taste disorder; Dyspnoea includes PTs of dyspnoea and dyspnoea exertional; Hypersensitivity includes PTs of drug hypersensitivity and hypersensitivity; Leukopenia includes PTs of leukopenia and white blood cell count decreased; Lymphopenia includes PTs of lymphocyte count decreased and lymphopenia; Neutropenia includes PTs of febrile neutropenia, neutropenia, neutropenic infection, neutropenic sepsis, and neutrophil count decreased; Rash includes PTs of exfoliative rash, generalized erythema, rash, rash erythematous, rash macular, rash maculo-papular, rash papular and rash pruritic; Stomatitis includes PTs of aphthous ulcer, mouth ulceration and stomatitis;

Thrombocytopenia includes PTs of platelet count decreased, and thrombocytopenia; Venous thromboembolism includes PTs of deep vein thrombosis, embolism, pulmonary embolism, thrombosis, vena cava thrombosis and venous thrombosis.

[b] Observed in the post-marketing setting.

CIOMS = Council for International Organizations of Medical Sciences; CTCAE = Common Terminology Criteria for Adverse Events; MedDRA = Medical Dictionary for Regulatory Activities; PT = Preferred term; SOC = System organ class.

MedDRA version 24.0.

Table 17. Serious Adverse Reactions for Olaparib Considered Expected for Safety Reporting Safety Reporting Purposes

MedDRA[a] SOC	Preferred Term	Number of patients exposed (N) = 4098
		CIOMS frequency indicator
Neoplasms benign, malignant and unspecified (including cysts and polyps)	Acute myeloid leukaemia	Uncommon
	Myelodysplastic syndrome	Uncommon
Blood and lymphatic system disorders	Anaemia	Common
	Anaemia macrocytic	Rare
	Febrile neutropenia	Uncommon
	Leukopenia	Rare
	Neutropenia	Uncommon
	Thrombocytopenia	Uncommon
Gastrointestinal disorders	Diarrhoea	Rare
	Nausea	Uncommon
	Vomiting	Uncommon
General disorders	Fatigue	Rare
	Asthenia	Rare
Investigations	Blood creatinine increased	Rare
	Haematocrit decreased	Rare
	Haemoglobin decreased	Uncommon
	Lymphocyte count decreased	Rare
	Neutrophil count decreased	Uncommon
	Platelet count decreased	Uncommon
	Red blood cell count decreased	Rare
	White blood cell count decreased	Uncommon
Metabolism and nutrition disorders	Decreased appetite	Rare
Nervous system disorders	Dizziness	Rare
Respiratory, thoracic and mediastinal	Cough	Rare

disorders	Dyspnoea	Uncommon
Vascular disorders	Embolism	Uncommon
	Pulmonary embolism	Uncommon

[a] MedDRA version 24.0.

CIOMS = Council for International Organizations of Medical Sciences; DCO = Data cut-off;

MedDRA = Medical Dictionary for Regulatory Activities; PT = Preferred term; SAE = Serious adverse event.

For additional information, refer to investigator brochure.

14.2.10 Drug Interactions

• CYP3A Inhibitors: Avoid concomitant use of strong and moderate CYP3A inhibitors. If the inhibitor cannot be avoided, reduce the dose.

• CYP3A Inducers: Avoid concomitant use of strong and moderate CYP3A inducers. If a moderate CYP3A inducer cannot be avoided, be aware of a potential for decreased efficacy.

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16 APPENDICES

16.1 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.

16.2 APPENDIX B : LIST OF DRUGS THAT MAY HAVE POTENTIAL CYP3A4 INTERACTIONS

16.2.1 CYP3A4 Substrates

Albuterol
Alfentanil
Alprazolam
Amiodarone
Amlodipine
Amprenavir
Aprepitant
Aripiprazole
Atazanavir
Atorvastatin
Benzphetamine
Bisoprolol
BortezomibBosentan
Bromazepam
Bromocriptine
Budesonide
Buprenorphine
Buspirone
Busulfan
Carbamazepine
Cerivastatin
Chlordiazepoxide
Chloroquine
Chlorpheniramine
Cilostazol
Cisapride
Citalopram
Clarithromycin
Clobazam
Clonazepam
Clorazepate
Cocaine
Colchicine
Conivaptan
Cyclophosphamide
Cyclosporine
Dantrolene
Dapsone
Dasatinib
Delavirdine
Diazepam
Dihydroergotamine
Diltiazem
Disopyramide
Docetaxel
Doxepin
Doxorubicin
Doxycycline
Efavirenz
Eletriptan
Enalapril
Eplerenone
Ergoloid mesylates
Ergonovine
Ergotamine
Erythromycin
Escitalopram
Estradiol
Estrogens, conj., synthetic
Estrogens, conj., equine
Estrogens, conj., esterified
Estrone
Estropipate
Ethinyl estradiol
Ethosuximide
Etoposide
Exemestane
Felbamate
Felodipine
Fentanyl
Flurazepam
Flutamide
Fluticasone
Fosamprenavir
Gefitinib
Haloperidol
Ifosfamide
Imatinib
Indinavir
Irinotecan
Isosorbide
Isosorbide dinitrate
Isosorbide mononitrate
Isradipine
Itraconazole
Ketamine
Ketoconazole
Lansoprazole
Letrozole
Levonorgestrel
Lidocaine
Losartan
Lovastatin
Medroxyprogesterone
Mefloquine
Mestranol
Methadone
Methylergonovine
Methysergide
Miconazole
Midazolam
Miglustat
Mirtazapine
Modafinil
Montelukast
Moricizine
Nateglinide
Nefazodone
Nelfinavir
Nevirapine
Nicardipine
Nifedipine
Nimodipine
Nisoldipine
Norethindrone
Norgestrel
Ondansetron
Paclitaxel
Pergolide
Phencyclidine
Pimozide
Pipotiazine
Primaquine
Progesterone
Quetiapine
Quinidine
Rabeprazole
Ranolazine
Repaglinide
Rifabutin
Ritonavir
Salmeterol
Saquinavir
Sibutramine
Sildenafil
Simvastatin
Sirolimus
Spiramycin
Sufentanil
Sunitinib
Tacrolimus
Tamoxifen
Tamsulosin
Telithromycin
Teniposide
Tetracycline
Theophylline
Tiagabine
Ticlopidine
Tipranavir
Tolterodine
Toremifene
Trazodone
Triazolam
Trimethoprim
Trimipramine
Troleandomycin
Vardenafil
Venlafaxine
Verapamil
Vinblastine
Vincristine
Vinorelbine
Zolpidem
Zonisamide
Zopiclone

16.2.2 CYP3A4 Inhibitors

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In Vivo Inhibitors of CYP3A Probes

Inhibitor	Therapeutic Class	Inhibitor dosing (oral)	Object[1] (oral, unless otherwise specified)	AUC_{ratio}	PMID or NDA #	Published
Potent CYP3A Inhibitors (yielding substrate AUCr > 5)						
VIEKIRA PAK[2]	Antivirals	See note[2]	tacrolimus[2]	**55.76**	25708713	2015 May
indinavir /RIT	Protease Inhibitors	800/100 mg BID (1 day)	alfentanil	**36.5**	19225389	2009 Mar
tipranavir/RIT	Protease Inhibitors	500/200 mg BID (2 days)	midazolam	**26.91**	20147896	2010 Jun
ritonavir	Protease Inhibitors	3 doses of 100 mg over 24 h	midazolam	**26.41**	20002087	2009 Dec
cobicistat (GS-9350)	None	200 mg QD (14 days)	midazolam	**19.03**	20043009	2010 Mar
indinavir	Protease Inhibitors	800 mg TID (7 days)	vardenafil	**16.25**	NDA # 021400	2003 Aug
ketoconazole	Antifungals	400 mg QD (4 days)	midazolam	**15.9**	8181191	1994 May
troleandomycin	Antibiotics	500 mg single dose	midazolam	**14.8**	15536460	2004 Dec
telaprevir	Antivirals	750 mg TID (16 days)	midazolam	**13.5**	22162542	2012 Oct
danoprevir / RIT	Antivirals	200/100 mg QD (14 days)	midazolam	**13.42**	23872824	2013 Nov
elvitegravir / RIT	Treatments of AIDS	150/100 mg QD (10 days)	midazolam	**12.8**	NDA # 203100	2012
saquinavir / RIT	Protease Inhibitors	1000/100 mg BID (14 days)	midazolam	**12.48**	19792991	2009 Oct
lopinavir / RIT	Protease Inhibitors	400/100 mg BID (2 days)	alfentanil	**11.47**	24067429	2013 Dec
itraconazole	Antifungals	200 mg QD (4 days)	midazolam	**10.8**	8181191	1994 May
voriconazole	Antifungals	200 mg BID (9 days)	midazolam	**9.63**	21937987	2011 Nov
mibefradil	Calcium Channel Blockers	100 mg single dose	midazolam	**8.86**	14517191	2003 Oct

Inhibitor	**Therapeutic Class**	**Inhibitor dosing** (oral)	**Object**[1] (oral, unless otherwise specified)	**AUC_{ratio}**	**PMID or NDA #**	**Published**
LCL161	Cancer Treatments	600 mg single dose	midazolam	**8.8**	23585187	2013 Jun
clarithromycin	Antibiotics	500 mg BID (7 days)	midazolam	**8.39**	16432272	2006 Feb
posaconazole	Antifungals	400 mg BID (7 days)	midazolam	**6.23**	19302901	2009 Feb
telithromycin	Antibiotics	800 mg QD (6 days)	midazolam	**6.2**	NDA# 021144	2004
grapefruit juice DS[3]	Food Products	240 mL TID (2 days) and 90 min, 60min, 30 min prior to midazolam	midazolam	**5.95**	12953340	2003 Aug
conivaptan	Diuretics	40 mg BID (5 days)	midazolam	**5.76**	NDA # 021697	2005
nefazodone	Antidepressants	100-200 mg BID (12 days)	midazolam	**5.44**	14551182	2003 Nov
nelfinavir	Protease Inhibitors	1250 mg BID (14 days)	midazolam	**5.29**	21406602	2011 Jun
saquinavir	Protease Inhibitors	1200 mg TID (5 days)	midazolam	**5.18**	10430107	1999 Jul
idelalisib	Kinase Inhibitors	150 mg BID (8 days)	midazolam	**5.15**	NDA # 206545	2014
boceprevir	Antivirals	800 mg TID (6 days)	midazolam	**5.05**	NDA # 202258	2011
Moderate CYP3A Inhibitors (AUCr ≥ 2 and < 5)						
erythromycin	Antibiotics	1000 mg single dose	midazolam	**4.99**	25139487	2014 Dec
fluconazole	Antifungals	400 mg single dose	midazolam	**4.93**	16172184	2005 Oct
atazanavir / RIT	Protease Inhibitors	300/100 mg BID	maraviroc	**4.9**	18333863	2008 Apr
darunavir	Protease Inhibitors	1200 mg BID (14 days)	saquinavir	**4.9**	NDA # 021976	2006
diltiazem	Calcium Channel Blockers	60 mg TID (2 days)	midazolam	**4.06**	21209240	2011 Nov
darunavir / RIT	Protease Inhibitors	400/100 mg BID (8 days)	sildenafil	**4.0**	NDA # 021976	2006
dronedarone	Antiarrhythmics	400 mg BID (14 days)	simvastatin	**3.66**	NDA # 022425	2009
crizotinib	Kinase Inhibitors	250 mg BID (28 days)	midazolam	**3.65**	NDA # 202570	2011
atazanavir	Protease Inhibitors	400 mg QD (7 days)	maraviroc	**3.57**	18333863	2008 Apr
aprepitant	Antiemetics	80-125 mg QD (5 days)	midazolam	**3.29**	12891225	2003 Aug
casopitant	Antiemetics	120 mg QD (14 days)	midazolam	**3.13**	20840445	2010 Oct
amprenavir	Protease Inhibitors	1200 mg BID (10 days)	rifabutin	**2.93**	11158747	2001 Feb

Inhibitor	**Therapeutic Class**	**Inhibitor dosing** (oral)	**Object**[1] (oral, unless otherwise specified)	**AUC_{ratio}**	**PMID or NDA #**	**Published**
faldaprevir	Antivirals	240 mg BID (14 days)	midazolam IV	**2.92**	25449227	2015 Apr
imatinib	Antineoplastic Agents	400 mg QD (7 days)	simvastatin	**2.92**	14612892	2003 Nov
verapamil	Calcium Channel Blockers	80 mg TID (2 days)	midazolam	**2.92**	8198928	1994 Mar
netupitant	Antiemetics	300 mg single dose	midazolam	**2.44**	23729226	2013 Oct
nilotinib	Kinase Inhibitors	400 mg BID (12 days)	midazolam	**2.4**	25418605	2015 Apr
grapefruit juice	Food Products	240 mL QD (4 days)	midazolam	**2.39**	10546919	1999 Oct
tofisopam	Benzodiazepines	100 mg TID (9 days)	midazolam	**2.36**	17989974	2008 Jan
cyclosporine	Immunosuppressants	Not provided (1-5 years)	midazolam	**2.21**	21753749	2011 Sep
ACT-178882	Renin Inhibitors	300 mg QD (14 days)	midazolam	**2.19**	22849770	2013 Dec
ciprofloxacin[4]	Antibiotics	500 mg single dose	sildenafil	**2.12**	16372380	2005 Dec
schisandra	Herbal Medications	3 capsules (= 11.25 mg	midazolam	**2.05**	19552749	2009 May
isavuconazole	Antifungals	clinical dose (detail not provided)	midazolam	**2.03**	NDA # 207500	2015
cimetidine	H-2 Receptor Antagonists	200-400 mg QID (1.5 days)	midazolam	**2.02**	6152615	1984 Sep
FK1706	Central Nervous System	60 mg QD (14 days)	midazolam	**2.01**	19889885	2010 Feb
Weak CYP3A Inhibitors (AUCr ≥ 1.25 and < 2)						
tabimorelin	Hormone Replacement	2.86-3.21 mg QD (7 days)	midazolam	**1.93**	12610745	2003 Feb
ranolazine	Cardiovascular Drugs	1000 mg BID (7 days)	simvastatin	**1.89**	NDA # 021526	2006
amlodipine	Calcium Channel Blockers	10 mg QD (9 days)	simvastatin	**1.8**	23965645	2014 Apr
lomitapide	Other Antilipemics	60 mg QD (7 days)	simvastatin	**1.77**	24734312	2014 Mar
fosaprepitant (IV)	Antiemetics	150 mg single 30-min infusion	midazolam	**1.76**	21209230	2011 Dec
Seville orange juice	Food Products	240 mL single dose	felodipine	**1.76**	11180034	2001 Jan
amiodarone	Antiarrhythmics	400 mg QD (4 days)	simvastatin	**1.76**	17301736	2007 May
chlorzoxazone	Muscle Relaxants	250 mg single dose (part of a 6-drug	midazolam	**1.68**	11736864	2001 Nov
M100240	Antihypertensive Agents	50 mg single dose	midazolam	**1.66**	15051745	2004 Apr
fluvoxamine	Antidepressants	50-00 mg BID (12 days)	midazolam	**1.66**	14551182	2003 Nov

Inhibitor	Therapeutic Class	Inhibitor dosing (oral)	Object[1] (oral, unless otherwise specified)	AUC_{ratio}	PMID or NDA #	Published
ranitidine	H-2 Receptor Antagonists	150 mg BID (1.5 days)	midazolam	**1.66**	6135440	1983 Jun
fostamatinib[5]	Anti-inflammatory Drugs	100 mg BID (7 days)	simvastatin	**1.64**	26748647	2016 Mar
goldenseal	Herbal Medications	1,323 mg (= 24.1 mg isoquinoline	midazolam	**1.63**	17495878	2008 Jan
clotrimazole	Antifungals	10 mg TID (5 days)	midazolam	**1.61**	20233179	2010 Feb
tacrolimus	Immunosuppressants	Not provided (1-5 years)	midazolam	**1.61**	21753749	2011 Sep
palbociclib	Kinase Inhibitors	125 mg QD (8 days)	midazolam	**1.58**	NDA # 207103	2015
cilostazol	Antiplatelets	100 mg BID (7 days)	lovastatin	**1.56**	10702889	1999
ticagrelor	Antiplatelets	180 mg bid (7 days)	simvastatin	**1.56**	NDA # 022433	2011
peppermint oil	Food Products	600 mg (= 300 uL peppermint oil)	felodipine	**1.55**	12235445	2002 Sep
ivacaftor	Cystic fibrosis treatments	150 mg BID (6 days)	midazolam	**1.54**	NDA # 203188	2012
GSK2248761	Transcriptase Inhibitors	100 mg QD (12 days)	midazolam	**1.54**	22288567	2012 Aug
Guan Mai Ning	Herbal Medications	3 tablets TID (7 days)	simvastatin	**1.51**	25801058	2015 Sep
AZD2327	Depression Treatments	15 mg QD (7 days)	midazolam	**1.49**	26081137	2015 Nov
resveratrol	Food Products	500 mg QD (10 days)	carbamazepin	**1.48**	25624269	2015 May
roxithromycin	Antibiotics	300 mg QD (6 days)	midazolam	**1.47**	7995324	1994
suvorexant	Hypnotics - Sedatives	80 mg QD (14 days)	midazolam	**1.47**	NDA # 204569	2014
propiverine	Anticholinergics	15 mg BID (7 days)	midazolam	**1.46**	16183781	2005 Dec
isoniazid	Antibiotics	90 mg BID (4 days)	triazolam	**1.46**	6140941	1983 Dec
berberine	Herbal Medications	300 mg TID (14 days)	midazolam	**1.45**	21870106	2012 Feb
oral contraceptives	Oral contraceptives	OC with low doses of estrogen (< 35	triazolam	**1.44**	6149030	1984 Nov
delavirdine	NNRTIs	400 mg TID (9 days)	indinavir	**1.44**	9665503	1998 Jul
daclatasvir	Antivirals	60 mg QD (7 days)	simeprevir	**1.44**	NDA # 205123	2013
simeprevir	Protease Inhibitors	150 mg QD (11 days)	midazolam	**1.43**	NDA # 205123	2013
atorvastatin	HMG CoA Reductase	10-40 mg/day (chronic treatment)	midazolam IV	**1.41**	12911366	2003 Sep
tolvaptan	Vasopressin Antagonists	60 mg single dose	lovastatin	**1.41**	NDA # 022275	2009

Inhibitor	Therapeutic Class	Inhibitor dosing (oral)	Object[1] (oral, unless otherwise specified)	AUC_{ratio}	PMID or NDA #	Published
almorexant	Hypnotics - Sedatives	200 mg QD (9 days)	midazolam	**1.37**	22990330	2013 Mar
GSK1292263	Other Antilipemics	300 mg BID (9 days)	simvastatin	**1.36**	23256625	2013 Jun
evacetrapid	CETP inhibitors	300 mg QD (15 days)	midazolam	**1.35**	26264702	2015 Dec
linagliptin	Dipeptidyl Peptidase	10 mg QD (6 days)	simvastatin	**1.34**	20497745	2010 Jun
lacidipine	Calcium Channel Blockers	4 mg QD (8 days)	simvastatin	**1.33**	11259986	2001 Feb
cranberry juice	Food Products	240 mL double strength juice, 1 glass	midazolam	**1.33**	19114462	2009 Mar
pazopanib	Kinase Inhibitors	800 mg QD (17 days)	midazolam	**1.32**	20881954	2010 Nov
everolimus	Immunosuppressants	10 mg QD (5 days)	midazolam	**1.31**	23426978	2013 Apr
blueberry juice	Food Products	two doses of 300 mL, separated by 16 hours	buspirone	**1.31**	22943633	2013 Apr
AMD070	Fusion Inhibitors	200 mg BID (8 days)	midazolam	**1.29**	18362694	2008 Apr
alprazolam	Benzodiazepines	1 mg TID (7 days)	buspirone	**1.29**	8300893	1993 Nov
Tong Xin Luo	Herbal Medications	4 capsules TID (7 days)	simvastatin	**1.29**	25801058	2015 Sep
bicalutamide	Antiandrogens	150 mg QD (>3 months)		**1.27**	15509184	2004
sitaxentan	Endothelin Receptor	100 mg QD (7 days)		**1.27**	20078609	2010 Jan
azithromycin	Antibiotics	500 mg QD (3 days)		**1.27**	8720318	1996 Feb
ginkgo	Herbal Medications	120 mg TID (28 days)		**1.25**	17050793	2006 Nov
teriflunomide	Other Immunomodulators	14-70 mg QD (14 days)		**1.25**	NDA # 202992	2012

[1] To allow better comparability, DDI studies with the probe substrate midazolam were selected first.
When no study with midazolam was available, the AUCratio of another probe or sensitive substrate is presented.

[2] VIEKIRA PAK = 150/100 mg paritaprevir/ritonavir + 25 mg ombitasvir + 800 mg dasabuvir for 28 days. Tacrolimus is also a substrate of

[3] 240 mL GFJ double-strength administered TID for 3 days

[4] Of note, co-administration of ciprofloxacin (750 mg BID for 7 days) did not affect plasma concentrations of ivacaftor, which is also a

[5] Fostamatinib also inhibits BCRP, and BCRP inhibition likely participates to the increase in exposure of simvastatin

Inhibitor	Therapeutic Class	Inhibitor dosing (oral)	Object[1] (oral, unless otherwise specified)	AUC_{ratio}	PMID or NDA #	Published

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16.2.3 CYP3A4 Inducers

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In Vivo CYP3A Inducers

Inducers	Therapeutic class	Object (oral, unless otherwise specified)	% ↓ AUC	% ↑ oral CL	Precipitant Dose (oral)	PMID or NDA #	Published
Potent Inducers (AUC decreased by ≥ 80% or CL increased by more than 5 fold (400%))							
rifampin	Antibiotics	budesonide	**99.7**	**36904.5**	600 mg QD (7 days)	15726657	2005 Mar
mitotane	Other	midazolam	**94.5**	Not Provided	maximum of 3.5 g TID	21220434	2011 Apr
avasimibe	Other Antilipemics	midazolam	**93.5**	Not Provided	750 mg/day (7 days)	12766253	2003 Sep
phenytoin	Anticonvulsants	nisoldipine	**89.5**	Not Provided	200-450 mg/day (chronic treatment)	8917062	1996 Nov
carbamazepine	Anticonvulsants	quetiapine	**86.6**	**643.1**	200 mg TID (26 days)	16390352	2006 Jan
enzalutamide	Antiandrogens	midazolam	**85.9**	Not Provided	160 mg QD (85±3 days)	NDA # 203415	2012
St John's Wort xtract	Herbal Medications	midazolam	**80.0**	Not Provided	300 mg TID (14 days)	16341856	2006 Jan
rifabutin	Antibiotics	delavirdine	Not Provided	**458.0**	300 mg QD (14 days)	9224961	1997 Jun

Inducers	**Therapeutic class**	**Object** (oral, unless otherwise specified)	**% ↓ AUC**	**% ↑ oral CL**	**Precipitant Dose** (oral)	**PMID or NDA #**	**Published**
phenobarbital	Anticonvulsants	verapamil	**76.6**	**400.9**	100 mg QD (21 days)	3392664	1988 Jul
Moderate Inducers (AUC decreased by 50-80% or CL increased by 2-5 fold (100-400%))							
ritonavir and St. Johns wort	None	midazolam	**77.2**	Not Provided	ritonavir: 300 mg BID and SJW: 300 mg T ID (14 days)	19924124	2010 Feb
semagacestat	Alzheimer's Treatments	midazolam	**76.4**	**324.6**	140 mg QD (10 days)	22789530	2012 Oct
efavirenz	NNRTIs	alfentanil	**76**	**369.4**	600 mg QD (20 days)	22398970	2012 Apr
tipranavir and ritonavir	Protease Inhibitors	saquinavir	**75.6**	Not Provided	tipranavir: 500 mg and ritonavir: 200 mg BID (14	18176328	2008 Apr
bosentan	Endothelin	sildenafil	**69.0**	**239.8**	62.5-125 mg BID (8 weeks)	15963102	2005 Jul
genistein	Food Products	midazolam	**13.7**	**136.9**	1000 mg QD (14 days)	21943317	2012 Feb
thioridazine	Antipsychotics	quetiapine	**68.7**	**104.5**	100-300 mg QD (15 days)	22569350	2012 Jun
nafcillin	Antibiotics	nifedipine	**62.6**	**145.1**	500 mg 4 times daily (5 days)	12814453	2003 Jun
talviraline	NNRTIs	indinavir	**61.7**	**181.2**	500 mg TID (14 days)	10516944	1999 Oct
lopinavir	Protease Inhibitors	amprenavir	**59.7**	Not Provided	400 mg BID (4 weeks)	15060509	2004 Apr
modafinil	Psychostimulants	triazolam	**57.6**	**35.7**	200-400 mg QD (28 days)	11823757	2002 Jan
etravirine	NNRTIs	sildenafil	**56.7**	Not Provided	800 mg BID (13.5 days)	NDA# 022187	2008
lersivirine	NNRTIs	midazolam	**51.4**	**105.5**	1000 mg BID (14 days)	22527351	2012 Nov
Weak Inducers (AUC decreased by 20-50% or CL increased by 20-100% (less than 2 fold))							
eslicarbazepine	Anticonvulsants	simvastatin	**49.4**	**98.4**	800 mg QD (14 days)	23726291	2013 Sep
telaprevir	Antivirals	darunavir	**48.4**	Not Provided	1125 mg BID (4 days)	NDA# 201917	2011
garlic	Food Products	saquinavir	**44.7**	Not Provided	caplet of GarliPure BID (20 days)	11740713	2002 Jan

Inducers	**Therapeutic class**	**Object** (oral, unless otherwise specified)	**% ↓ AUC**	**% ↑ oral CL**	**Precipitant Dose** (oral)	**PMID or NDA #**	**Published**
bexarotene	Other Antineoplastics	atorvastatin	**45.3**	Not Provided	400 mg/m2 QD (at least two 4-week cycles)	22057855	2012 Feb
amprenavir	Protease Inhibitors	lopinavir	**43.0**	Not Provided	700 mg BID (2-4 weeks)	15668539	2005 Jan
raltegravir	HIV-Integrase	darunavir	**42.0**	Not Provided	400 mg BID	21958880	2012 Feb
lesinurad	Antigout and Uricosuric Agents	amlodipine	**41.9**	**72.5**	400 mg QD (24 days)	NDA # 207988	2015
vemurafenib	Kinase Inhibitors	midazolam	**39.4**	Not Provided	960 mg BID (15 days)	NDA # 202429	2011
troglitazone	Thiazolidinediones	simvastatin	**37.7**	Not Provided	400 mg QD (24 days)	11361054	2001 May
sorafenib	Kinase Inhibitors	sirolimus	**36.9**	Not Provided	200 mg BID (11 days)	21045832	2010 Nov
rufinamide	Anticonvulsants	triazolam	**36.7**	**53.4**	400 mg BID (11.5 days)	NDA # 021911	2008
sirukumab* **	Immunomodulators Biologics	midazolam	**35.7**	Not Provided	300 mg single dose subcutaneously	26054042	2015 Dec
pleconaril	Antivirals	midazolam	**34.6**	**52.8**	400 mg TID (6 days)	16467135	2006 May
ginseng	Herbal Medications	midazolam	**34.2**	**50.7**	500 mg BID (28 days)	21646440	2012 Jun
boceprevir	Antivirals	darunavir	**34.2**	**41.0**	800 mg every 8 hrs (6 days)	23155151	2013 Mar
sulfinpyrazone	Antigout and Uricosuric Agents	cyclosporine	**33.9**	(change in C_{avg})	200 mg/day	11124491	2000 Dec
ginkgo	Herbal Medications	midazolam	**33.7**	**52.6**	120 mg BID (28 days)	18205997	2008 Feb
vinblastine	Vinca Alkaloids	midazolam IV	**33.2**	**48.8**	not provided (4 cycles)	20959500	2010 Nov
nevirapine	NNRTIs	indinavir	**32.5**	Not Provided	200 mg QD (14 days), then BID (19 days)	10191212	1999 May
armodafinil (R-modafinil)	Psychostimulants	midazolam	**32.2**	**54.7**	100-250 mg/day (31 days)	18076219	2008
ticagrelor	Anticoagulants and	midazolam	**31.7**	**46.5**	400 mg QD (6 days)	23870610	2013 Jul
LCL161	Cancer Treatments	midazolam	**29.8**	**34.0**	600 mg single dose	23585187	2013 Jun

Inducers	**Therapeutic class**	**Object** (oral, unless otherwise specified)	**% ↓ AUC**	**% ↑ oral CL**	**Precipitant Dose** (oral)	**PMID or NDA #**	**Published**
vicriviroc and ritonavir	Treatments of AIDS	ethinyl estradiol	**29.4**	Not Provided	30 mg vicriviroc and 100 mg ritonavir QD (10 days)	22015327	2011 Oct
ritonavir	Protease Inhibitors	ethinyl	**29.2**	Not Provided	100 mg QD (10 days)	22015327	2011 Oct
prednisone	Corticosteroids	tacrolimus	**29.0**	Not Provided	1.5 mg/kg/day	15787787	2005 Apr
oxcarbazepine	Anticonvulsants	felodipine	**28.1**	Not Provided	450 mg BID (7 days)	8451779	1993 Feb
danshen	Herbal Medications	midazolam	**27.9**	**32.8**	4 g TID (14 days)	20565457	2010 Jun
clobazam	Benzodiazepines	midazolam	**27.7**	Not Provided	40 mg QD (15 days)	22422635	2012 Apr
echinacea	Herbal Medications	midazolam	**27.3**	**37.5**	500 mg TID (28 days)	20653355	2010 Aug
ticlopidine	Anticoagulants and	alfentanil	**27.0**	**50.0**	250 mg BID (4 days)	23361846	2013 Mar
brivaracetam	Anticonvulsants	ethinyl	**26.8**	**37.3**	200 mg BID (21 days)	24386664	2013 Dec
Stribild*	Treatments of AIDS	ethinyl estradiol	**26.2**	**31.3**	150 mg ELV + 150 mg COB + 200 mg EMT+ 300 mg	NDA # 203100	2012
pioglitazone	Thiazolidinediones	midazolam	**26.0**	Not Provided	45 mg QD 7 days	Actos® Product	2004 Aug
VIEKIRA PAK**	Antivirals	darunavir	**25.7**	Not Provided	See note**	NDA # 206619	2014
dexamethasone	Corticosteroids	aprepitant	**25.0**	Not Provided	8 mg/day (5 days)	NDA # 021549	2003
terbinafine	Antifungals	midazolam	**24.5**	Not Provided	250 mg QD (4 days)	8527290	1995 Sep
quercetin	Food Products	midazolam	**23.6**	Not Provided	500 mg QD (13 days)	21680781	2012 Jun
glycyrrhizin	Herbal Medications	midazolam	**23.0**	Not Provided	150 mg BID (15 days)	20393696	2010 Aug
aprepitant	Neurokinin-1	midazolam IV	**22.1**	**28.5**	125/80 mg QD (3 days)	14973304	2004 Mar
pretomanib (PA-824)	Antibiotics	midazolam	**22.1**	**20.7**	400 mg QD (14 days)	23689718	2013 Aug
oritavancin	Antibiotics	midazolam	**18.7**	**23.9**	1200 mg IV single infusion	NDA # 206334	2014
AZD 7325	Anxiolytics	midazolam	**18.7**	**22.6**	10 mg QD (12 days)	22122233	2012 Jul
methylprednisolone	Corticosteroids	cyclosporine	**15.8**	**35.0**	16 mg/day (12 days) then 8 mg/day (6 months)	12164891	2002 Sep
topiramate	Anticonvulsants	ethinyl	**12.0**	**20.2**	50 mg/day (21 days)	12681003	2003 Apr

Inducers	**Therapeutic class**	**Object** (oral, unless otherwise specified)	**% ↓ AUC**	**% ↑ oral CLPrecipitant Dose** (oral)	**PMID or NDA # Published**

1- Ritonavir has dual effects of simultaneous CYP3A inhibition and induction, and the net pharmacokinetic outcome during chronic
2- All the substrates presented in the table are sensitive CYP3A substrates (see definition in FDA guidance) except verapamil, cyclosporine, ethinyl estradiol, and delavirdine.

* **Stribild** is a combination of elvitegravir, cobicistat, emtricitabine and tenofovir DF

** VIEKIRA PAK = paritaprevir/ritonavir/ombitasvir 150/100/25 mg QD + dasabuvir 250 mg BID for 14 days

*** Sirukumab is not a CYP inducer per se. It reverses the IL-6 mediated suppression of CYP3A activity in patients with active rheumatoid

16.3 APPENDIX C : PATIENT'S PILL DIARY: OLAPARIB

Today's date _____
Patient Name_____ Patient Study ID _____
Cycle #_____ **Days 1-14**
(*initials acceptable for patient's name)*

INSTRUCTIONS TO THE PATIENT:

1. Complete one form for each cycle (28 days).
2. You will take each dose twice a day **12 hours apart** on days 3 – 13* and days 17 -26*. Each dose is ___150mg tablets and ___ 100mg tablets. You must take the tablets with a large glass of water. A light snack (biscuits/ toast) is also recommended to help reduce nausea.
3. Record the date, the number of tablets you took, and when you took them. (*You will be given additional instructions about the timing of the doses on Days 13 and 26 each cycle.)
4. If you have any comments or notice any side effects, please record them in the Comments column.
5. Please bring your pill bottle and this form to your physician when you go for your next appointment.

DAY	**DATE**	**# TABLETS AND WHEN TAKEN: OLAPARIB** **AM PM** **12 HOURS APART**	**COMMENTS (side effects or missed doses)**
1		**Do not take olaparib**	
2		**Do not take olaparib**	
3		_____AM _____PM	
4		_____AM _____PM	
5		_____AM _____PM	
6		_____AM _____PM	

7		_____AM _____PM	
8		_____AM _____PM	
9		_____AM _____PM	
10		_____AM _____PM	
11		_____AM _____PM	
12		_____AM _____PM	
13		_____AM	
14		**Do not take olaparib**	

Patient's Signature: _____ Date: _____

The Study Team 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 pills taken Days 1-14 _____

Physician/Nurse Signature _____

Appendix C: Patient's Pill Diary: Olaparib

Today's date _____

Patient Name_____ Patient Study ID _____

Cycle #_____ **Days 15-28**

(*initials acceptable for patient's name)*

INSTRUCTIONS TO THE PATIENT:

1. Complete one form for each cycle (28 days).
2. You will take ___ tablets twice a day **12 hours apart** on days 3 – 13* and days 17 -26*. Each dose is ___150mg tablets and ___ 100mg tablets. You must take the tablets with a large glass of water. A light snack (biscuits/ toast) is also recommended to help reduce nausea. (*You will be given additional instructions about the timing of the doses on Days 13 and 26 each cycle.)
3. Record the date, the number of tablets you took, and when you took them.
4. If you have any comments or notice any side effects, please record them in the Comments column.
5. Please bring your pill bottle and this form to your physician when you go for your next appointment.

DAY	**DATE**	**# TABLETS AND WHEN TAKEN: OLAPARIB** **AM PM** **12 HOURS APART**	**COMMENTS (side effects or missed doses)**
15		**Do not take olaparib**	
16		**Do not take olaparib**	
17		_____AM _____PM	
18		_____AM _____PM	
19		_____AM _____PM	
20		_____AM _____PM	

21		_____AM _____PM	
22		_____AM _____PM	
23		_____AM _____PM	
24		_____AM _____PM	
25		_____AM _____PM	
26		_____AM	
27		**Do not take olaparib**	
28		**Do not take olaparib**	

Patient's Signature: _____ Date: _____

The Study Team 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 pills taken Days 15-28 _____

3. Total number of pills taken this cycle (Days 1-28)_____

Physician/Nurse Signature _____