A PHASE 2, OPEN LABEL STUDY OF MAINTENANCE RUCAPARIB IN PATIENTS WITH PLATINUM-SENSITIVE ADVANCED PANCREATIC CANCER AND A KNOWN DELETERIOUS GERMLINE OR SOMATIC BRCA1/2 OR PALB2 MUTATION

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Study Summary

Title	***A PHASE 2, OPEN LABEL STUDY OF MAINTENANCE RUCAPARIB IN PATIENTS WITH PLATINUM-SENSITIVE ADVANCED PANCREATIC CANCER AND A KNOWN DELETERIOUS GERMLINE OR SOMATIC BRCA1/2 OR PALB2 MUTATION***
Short Title	*Maintenance Rucaparib in BRCA1, BRCA2 or PALB2 mutated pancreatic cancer that has not progressed on platinum-based therapy*
IRB Number	*827054*
Protocol Number	*UPCC 05217*
Phase	*Clinical Phase II*
Methodology	*Single Arm, Open Label*
Study Duration	*4 years*
Study Center(s)	*Single Center*

Objectives	*Primary:* To evaluate the efficacy of rucaparib in patients with pancreatic carcinoma associated with a deleterious BRCA1/2 or PALB2 mutation by assessment of progression free survival rate at 6 months (PFS6) as determined by the investigator. *Secondary:* • To evaluate efficacy by assessment of objective response rate (ORR) in those with measurable disease • To assess duration of response (DOR) • To evaluate overall survival (OS) *Exploratory:* • To assess for mechanisms of resistance to PARP inhibition in patients with pancreatic cancer and a BRCA1/2 or PALB2 mutation.
Number of Subjects	*42*

Main Inclusion and Exclusion Criteria

KEY INCLUSIONS:

1. Histologically or cytologically confirmed diagnosis of pancreatic carcinoma with locally advanced or metastatic disease
2. Patients may have previously failed non-platinum containing therapy or may never have previously progressed on treatment.
3. Patients must be on treatment with platinum-based (cisplatin, oxaliplatin or carboplatin) treatment for locally advanced or metastatic pancreatic cancer and have received a minimum of 16 weeks of therapy without evidence of disease progression based on the investigator's opinion.
    a. -Discontinuation of the platinum component of the regimen for chemotherapy-related toxicity is permissible provided the patient has previously received at least 16 weeks of platinum-based therapy without evidence of disease progression ≤8 weeks after treatment with the platinum agent
    b. Patients may have received <16 weeks of platinum therapy if platinum was not able to be used for medical reasons or was medically required to be discontinued for legitimate reason in the opinion of the investigator (ie allergy, intolerable organ dysfunction).).
4. Documented deleterious BRCA1/2 or PALB2 mutation (germline or somatic) as assessed by local laboratory. Variants that are considered to be non-detrimental ("Variants of uncertain significance", "Variants of unknown significance", "Variant, favor polymorphism" or "benign polymorphism" etc) are not sufficient for study entry.
5. Measurable disease is not required for enrollment.
6. Adequate organ function
7. ECOG performance status of 0-1

KEY EXCLUSIONS:

1. Prior treatment with a PARP inhibitor
2. Patients who have demonstrated resistance to platinum agents (e.g. oxaliplatin, cisplatin) are not eligible to participate in this study
3. Clinical evidence of uncontrolled malabsorption and/or any other gastrointestinal disorder or defect that would, in the opinion of the investigator, interfere with the absorption of rucaparib
4. Received any systemic treatment for pancreatic cancer during the 14 days prior to first dose of rucaparib
5. Acute infection requiring intravenous antibiotics, antiviral or antifungal agents during the 14 days prior to first dose of rucaparib
6. Symptomatic or untreated CNS metastases.
7. Expected life expectancy of <12 weeks as determined by the investigator.

Statistical Methodology	We will enroll 42 patients in a single-arm phase II design. Progression-free survival rate at 6 months (PFS6) from the start of therapy will be the primary clinical outcome. A one sample test of the null hypothesis of a PFS6 rate equal to 44% versus the alternative hypothesis of a PFS6 rate equal to 60% will be conducted. With 42 patients enrolled over 42 months and with 6 months of additional follow-up, there is 81% power for the test assuming exponential survival and 5% 2-sided type I error rate.

Background and Study Rationale

This document is a protocol for a human research study. This study is to be conducted according to US and international standards of Good Clinical Practice (FDA Title 21 part 312 and International Conference on Harmonization guidelines), applicable government regulations and Institutional research policies and procedures.

Introduction

Pancreatic ductal adenocarcinoma (PDAC) is a highly lethal malignancy with a dismal prognosis. In metastatic disease, even our most commonly used first-line regimens (FOLFIRINOX and gemcitabine/abraxane) are associated with a median overall survival of <1 year[1, 2] and literature suggests that the progression free survival rate at 6 months (PFS6) is only 44% on standard therapy[2]. Secondly, for the patients who do remain responsive or stable on cytotoxic therapy, there does not currently exist a more manageable maintenance option. There is a great need to identify biomarkers that will predict response to specific treatments and to develop maintenance strategies for appropriately selected patients. BRCA1, BRCA2 and PALB2 mutations, whether somatic or germline, are found in patients with pancreatic cancer and may result in sensitivity to PARP inhibitors, particularly in the absence of platinum-resistance.

1.1 Background and Relevant Literature

While the majority of cases of pancreatic cancer are sporadic, an estimated 10% or more may be hereditary[3]. Familial pancreatic cancer has been associated with germline mutations in several genes, including the breast cancer susceptibility genes, BRCA1 and BRCA2[4]. Carriers of germline BRCA1 or BRCA2 mutations have a 2-4 fold[5-7] and 2-7 fold[6, 7] higher risk, respectively, of developing pancreatic cancer when compared to the general population. A germline BRCA (gBRCA) mutation, predominantly gBRCA2 and to a lesser extent gBRCA1, has been found in approximately 5-19% of pancreatic cancer patients, with a higher rate observed in patients with a family history of pancreatic cancer and/or Ashkenazi Jewish ancestry[8-12]. Germline mutations in BRCA1 and BRCA2 have also been found in patients without an extensive family history of cancer[13]. Beyond BRCA1 and BRCA2, mutations in the cancer susceptibility gene PALB2 (Partner and Localizer of BRCA2) also lead to a susceptibility to pancreatic cancer[14, 15]. The germline mutation (gPALB2) is found in <1% of pancreatic cancer patients without a family history of pancreatic cancer[14], but is as high as 3.7% in those with such a family history[16, 17]. The gene product of PALB2 acts as a linker between BRCA1 and BRCA2, helping to form the “BRCA

complex" which then binds to RAD51 and initiates the process of homologous recombination[18]. Phenotypically, these tumors appear to behave similarly to those with a BRCA mutation.

Beyond germline mutations in BRCA1, BRCA2 and PALB2, there is a subset of pancreatic cancers defined by a somatic mutation in these same genes[19]. These particular tumors may behave phenotypically much like their germline mutated counterparts, with increased sensitivity to DNA damaging agents (platinum) or PARP inhibitors.

Pancreatic cancers defined by a mutation in BRCA1 and BRCA2 have been found to respond to PARP inhibition and platinum agents, much like their ovarian and breast cancer counterparts[20]. Data suggests that these patients have a prolonged survival compared to the general pancreatic cancer population, a phenomenon that is likely to be at least partly explained by a higher sensitivity to platinum-based therapies[21]. Regarding PARP inhibition, a study of olaparib in patients with solid tumor malignancies and a gBRCA mutation demonstrated a 22% overall response rate (ORR) in the 23 patients with pancreatic cancer enrolled[22]. A more recent clinical trial using the PARP inhibitor rucaparib in patients with gBRCA mutations and pancreatic cancer demonstrated clinical activity with an ORR of 16%. This included a single complete response (CR) and 2 partial responses (PR) and four patients with stable disease (SD)[23]. Notably, in this study, patients were not selected for platinum sensitivity, which does appear to play a role in PARP inhibitor resistance based upon more recent data[24].

Currently, our treatment paradigm for patients with a known BRCA1/2 or PALB2 mutation consists of platinum-based chemotherapy, to which they typically have a durable good response. Regimens that are classically used are FOLFIRINOX and cisplatin with gemcitabine. However, there are significant drawbacks to continued chemotherapy including cumulative organ toxicities and patient fatigue. Up until this point, there has been no maintenance strategy for patients who have achieved prolonged disease control on chemotherapy.
Due to the toxicities mentioned, patients are sometimes switched to an inferior regimen (FOLFIRINOX to FOLFIRI, for example) or chemotherapy doses are spaced out in an attempt to lessen toxicity. Other patients are taken off chemotherapy completely due to toxicities, though it is known that 92% of these patients will progress or recur within 6 months without treatment[25]. Therefore, for those patients with a BRCA1/2 or PALB2 mutation who have achieved stability on a platinum-containing regimen, a lower toxicity maintenance alternative is a highly attractive therapeutic strategy.

Rucaparib is an orally available, small molecule inhibitor of poly-adenosine diphosphate (ADP) ribose polymerase (PARP) that inhibits a specific DNA-repair pathway known as base excision repair (BER). Normal cells repair single-strand breaks (SSBs) in DNA primarily through BER. While there are several variations of BER, all pathways rely on PARP enzymes, of which PARP1 is the best characterized. SSBs that are not repaired result in stalled replication forks and the development of double-strand breaks (DSBs) which are in turn primarily repaired by homologous recombination DNA repair, a complex process involving multiple proteins, including those encoded by BRCA1, BRCA2 and PALB2, as well as others. PARP inhibitors (PARPi) have been shown to effectively kill tumors with a deficit in BRCA1 or BRCA2 through a mechanism of synthetic lethality, a context in which a defect in a single DNA repair pathway, such as through a BRCA gene mutation, has no effect, but blockage of multiple DNA repair pathways through a BRCA mutation and PARPi treatment, leads to apoptosis. This concept of synthetic lethality has been demonstrated in key *in vitro* and *in vivo* studies[26, 27] as well as in several clinical trials that evaluated a single agent PARPi for treatment of locally advanced or metastatic breast and ovarian cancer associated with a BRCA mutation[28-34]. Clinical benefit has been observed in patients with a gBRCA mutation as well as those with a somatic (sBRCA) mutation[33]. Recently, olaparib has been approved by the FDA for patients with ovarian cancer and a BRCA mutation who have had at least 3 prior chemotherapy treatments. Therefore, there is both data to suggest that maintenance strategies are (1) a feasible approach and are

(2) much needed for the management of select pancreatic cancer patients who have achieved stability on chemotherapy.

Given the literature referenced, it is rational to propose using the PARP inhibitor rucaparib in patients with advanced pancreatic cancer with a BRCA1, BRCA2 or PALB2 mutation and no evidence of platinum resistance.

1.2 Name and Description of the Investigational Product

Rucaparib (CO-338) is a small molecule inhibitor of poly (adenosine diphosphate [ADP]-ribose) polymerase (PARP) being developed for the treatment of cancer associated with homologous recombination deficiency (HRD). Rucaparib has been shown to potently inhibit PARP-1, PARP-2, and PARP-3 and has demonstrated activity in a background of breast cancer gene 1 and 2 (*BRCA1* and *BRCA2*) mutations in both clinical and nonclinical studies.

Clovis Oncology, Inc. (Clovis) is developing rucaparib for oral administration in patients with relapsed cancer who have HRD based on analysis of DNA. The therapeutic rationale for PARP inhibition with rucaparib in the presence of HRD is induction of synthetic lethality.

1.3 Nonclinical Data

Refer to the Rucaparib IB for detailed nonclinical data.

Nonclinical studies have shown that rucaparib is a potent and selective inhibitor of PARP-1, PARP-2, and PARP-3. Rucaparib demonstrated robust and durable *in vitro* and *in vivo* efficacy in multiple BRCA1 or BRCA2 mutant cell lines and xenograft models. Rucaparib was also active in a BRCA wild-type model, consistent with *in vitro* data suggesting that rucaparib is active in cells with other deficits in HR through synthetic lethality. Safety pharmacology studies suggest that oral dosing of rucaparib poses a low risk for causing neurobehavioral and cardiac effects in patients.

The absorption, distribution, metabolism, excretion, and pharmacokinetic (PK) drug interaction potential of rucaparib were characterized in nonclinical studies. Rucaparib showed species-dependent oral bioavailability, moderate plasma protein binding, and large volumes of distribution in nonclinical species. As a P-glycoprotein (P-gp) and Breast Cancer Resistance Protein (BCRP) substrate, rucaparib showed minimal penetration of rucaparib-derived radioactivity through the blood-brain barrier. *In vitro* data suggested slow metabolism by cytochrome P450 (CYP) enzymes, with CYP2D6 and, to a lesser extent, CYP1A2 and CYP3A4 contributing to the metabolism of rucaparib. *In vivo* metabolite profiling in rats, dogs, and humans showed that a carboxylic acid metabolite (M324) is a common major metabolite in all three species. A Phase II N-methylated metabolite of M324 (M338) was only observed in patients. Rucaparib was mainly excreted in feces in rats and dogs. *In vitro*, rucaparib reversibly inhibited CYP1A2, CYP2C19, CYP2C9, and CYP3A, and to a less extent CYP2C8, CYP2D6, and UGT1A1. Rucaparib induced CYP1A2 and downregulated CYP2B6 and CYP3A4 in human hepatocytes at clinically relevant exposures. Rucaparib is a potent inhibitor of multidrug and toxin extrusion (MATE) 1 and MATE2-K, a moderate inhibitor of organic cation transporter 1, and also has the potential to inhibit P-gp and BCRP in the gut.

The oral toxicity of rucaparib was evaluated in a total of 12 studies, including 10 studies in rats and dogs by single and repeated oral dose administration for up to 91 days of daily treatment. In summary, toxicity involved the hematopoietic, lymphopoietic, and gastrointestinal tract systems. In general, the toxicities induced in rats and dogs reversed after a 4-week recovery period, and no additional targets were identified in animals following prolonged oral dosing. As anticipated based on the mechanism of action, rucaparib was clastogenic in an *in vitro* chromosomal aberration assay in culture human lymphocytes suggesting potential genotoxicity in humans. Although no rucaparib-related effects on sperm total count, density, motility, or morphology were identified, based on published studies, PARP inhibitors have the potential to impair spermatogenesis and reduce fertility. Overall, the results from nonclinical studies are consistent with the anticipated mechanism of action and pharmacological effects of PARP inhibition.

1.4 Clinical Data to Date

Rucaparib has been evaluated in Phase 1 and 2 clinical studies and is being evaluated in a Phase 3 clinical study. The early clinical program assessed safety and efficacy of rucaparib in patients with malignancies commonly treated with chemotherapeutic agents. Initially, an IV formulation of rucaparib was administered in combination with a variety of chemotherapies; later, the oral formulation of rucaparib was administered in combination with chemotherapy and as a monotherapy. The oral formulation as monotherapy is the focus of current development efforts.

Four studies (A4991002, A4991005, A4991014, and CO-338-023 [RUCAPANC]) with rucaparib have been completed and 4 studies (CO-338-010, CO-338-014 [ARIEL3], CO-338-017 [ARIEL2], and CO-338-044) are ongoing.

The clinical studies are described briefly below and additional information is provided in the rucaparib Investigator's Brochure (IB).

1.4.1 Completed Studies

A4991002 was a Phase 1 open-label, dose-escalation study of IV rucaparib in combination with temozolimide (TMZ) in 32 patients with advanced solid tumors or malignant melanoma. A4991005 was a Phase 2, open-label study of IV rucaparib in combination with TMZ in 46 patients with metastatic melanoma. The results from these studies are available in manuscript form.[35, 36] Clinical data indicate that rucaparib exposures were similar between extensive metabolizers and poor metabolizers of CYP2D6.

A4991014 was a Phase 1, open-label, dose-escalation study of IV and oral rucaparib administered with different chemotherapeutic agents in 85 patients (33 patients dosed orally) with advanced solid tumors. Rucaparib PK parameters following a single 30 minute IV infusion (12 to 40 mg) and oral dose (12 to 360 mg) showed dose-proportional increases in exposure and dose-independent half-life ($T_{1/2}$) of approximately 17 hours after IV or oral dosing. Oral bioavailability was 36%.

Study CO-338-010

Study CO-338-010 is a 3-part, open-label, Phase 1/2 study of oral rucaparib monotherapy administered daily in continuous 21-day cycles. Part 1 (Phase 1) evaluated PK and safety of escalating doses of rucaparib in patients with solid tumors dose (N = 56; enrollment complete) and identified 600 mg BID as the recommended starting for Phase 2 based on safety, PK, and the clinical activity profile. Part 2 (Phase 2) is evaluating the efficacy and safety of rucaparib in patients with relapsed, high-grade ovarian cancer associated with a *BRCA* mutation. Part 2A enrolled platinum-sensitive patients (i.e. disease progression occurred at least 6 months after last dose of platinum was administered) with a *gBRCA1/2* mutation who had received 2 to 4 prior treatment regimens (N = 42, enrollment complete). Part 2B enrolled patients with a *gBRCA1/2* or *sBRCA1/2* mutation who received at least 3 prior chemotherapy regimens. Part 3 enrolled patients with relapsed solid tumor and a *BRCA* mutation to characterize the PK, food-effect, and safety of a higher dose strength tablet (enrollment completed).

Dose levels of 40 to 500 mg QD and 240 to 840 mg BID rucaparib were evaluated in the 56 patients enrolled in Part 1. A dose-limiting toxicity (DLT) of National Cancer Institute (NCI) Common Toxicity Criteria for Adverse Events (CTCAE) Version 4.0 (v4.03)[37] Grade 3 nausea was observed in 1 of the 6 patients at 360 mg BID rucaparib in Cycle 1. No DLTs were observed at any other dose level in Cycle 1. However, similar to other PARP inhibitors, non-DLT myelosuppression was observed beyond Cycle 1.

Dose proportional PK were observed up to 600 mg BID. The mean T_{max} and mean $T_{1/2}$ were approximately 4 hours and 17 hours, respectively. Oral administration of 600 mg rucaparib with a high-fat meal resulted in a moderate increase of C_{max} and AUC of rucaparib compared with that under fasted conditions. The increases in rucaparib exposures were not considered clinically significant, thus rucaparib can be taken with or without food. In pooled plasma samples from 3 patients who received 600 mg rucaparib BID, rucaparib, an oxidation and deamination product (M324), and a subsequent N-methylated metabolite (M338) were tentatively identified as major circulating moieties. M324 was a major metabolite in rats and

dogs, but M338 was not observed in animals. This is to be further evaluated in a [^{14}C]rucaparib study in patients.

Efficacy data from Part 1 showed Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1 responses in patients with *gBRCA* mutant ovarian cancer, breast cancer, and pancreatic cancer. The disease control rate (complete response [CR], partial response [PR], or stable disease [SD] > 12 weeks) at doses ≥ 360 mg BID in evaluable ovarian cancer patients was 92% (11/12). Responses were durable across tumor types.

In Part 2A, the latest efficacy data indicate that rucaparib provides significant clinical benefit to patients with a *gBRCA1/2* mutation. Of the 42 patients treated, 25 patients (60%) achieved a confirmed complete or partial response according to RECIST Version 1.1 and the median duration of response (DOR) was 7.8 months (95% Confidence Interval [CI] 5.6, 10.5). (Clovis, data on file)

Treatment-related adverse events (AEs; all grades) reported in ≥15% of patients treated with 600 mg BID rucaparib include gastrointestinal and related symptoms (nausea, vomiting, dysgeusia, and abdominal pain), anemia, asthenia/fatigue, neutropenia, thrombocytopenia, and headache. Elevated alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) levels were also reported. Elevations of ALT/AST occurred early (within first 2-4 weeks of treatment), were generally mild to moderate (Grades 1-2), not accompanied by any significant changes in bilirubin levels, often transient, and resolved to within normal ranges or stabilized. As has been observed with rucaparib and other PARP inhibitors, myelosuppression may be delayed and observed after a period of continuous dosing. All treatment-related AEs were successfully managed with concomitant medication and treatment interruption and/or dose reduction, or supportive care (in the case of myelosuppression AEs).

Extensive centrally reviewed electrocardiogram (ECG) monitoring was conducted in the Phase 1 portion of Study CO-338-010 and results are available for 55 of 56 treated patients. No patient had a QTcF measurement ≥ 500 msec and only 1 patient had a QTcF measurement ≥ 480 msec.
This measurement occurred in a patient receiving 480 mg BID rucaparib and concomitant administration of citalopram, a medication with known potential to cause QT prolongation. This patient continued to receive rucaparib monotherapy at a dose of 480 mg BID with no further QTcF measurement ≥ 480 msec. Only 1 patient had a QTc increase from baseline > 60 msec. This patient had a history of QT prolongation prior to study entry and received 1 dose of rucaparib before discontinuing from the study due to eligibility violation.

Overall, rucaparib in doses up to 840 mg BID exhibited a mean change of QTcF from baseline of 11.3 msec at the maximum concentration (5565 ng/mL) observed in the study. At a dose of 600 mg BID, the mean values for change of QTcF in Cycle 1 ranged from 5.0 to 14.0 msec. Overall, the alteration of the mechanism of repolarization was minimal. There were no AEs suggestive of cardiac arrhythmia (eg, presyncope, syncope, sudden death) in any patient.

Study CO-338-017 (ARIEL2)

ARIEL2 is a 2-part, single-arm, open-label Phase 2 study in patients with relapsed, high-grade ovarian, fallopian tube, or primary peritoneal cancer. The primary purpose of this study is to define a tumor-based molecular signature of HRD in ovarian cancer that correlates with response to rucaparib and enables selection of appropriate ovarian cancer patients for treatment with rucaparib. Tumor HRD status is assessed using next generation sequencing, with an algorithm for HRD status based on the presence of a *BRCA1/2* mutation (germline or somatic) and/or degree of tumor genome-wide loss of heterozygosity (genomic LOH), a phenotypic consequence of HRD. Patients are prospectively classified into 1 of 3 subgroups: tumor BRCA mutant (tBRCA^{mut}), tumor BRCA wild-type with high genomic LOH (*BRCA^{wt}*/LOH^{high}; also referred to as BRCA-like), and tumor BRCA^{wt} with low genomic LOH (*BRCA^{wt}*/LOH^{low}; also referred to as biomarker negative).

Part 1 enrolled ovarian cancer patients with relapsed, platinum-sensitive disease who had received ≥1 prior platinum-based regimen (N = 204; enrollment complete). Enrollment of patients known to harbor a *gBRCA1/2* mutation was capped in order to maximize the ability to assess rucaparib activity in the *BRCA^{wt}*

patient population. A total of 17 patients known to harbor a germline *BRCA1/2* mutation were enrolled. Another 23 patients were identified as having a *BRCA1/2* mutation (3 germline, 20 somatic) based on analysis of their tumor.

Efficacy data indicate a RECIST ORR in *BRCA1/2*^{mut} tumor-evaluable patients of 80.0% (32/40 patients), median DOR of 11.2 months (95% CI: 7.4, 13.7), and median PFS of 12.8 months (95% CI: 9.0, 14.7). (Clovis, data on file) The objective response rate was similar in patients with a germline (85.0%; 17/20) or somatic *BRCA1/2* mutations (75.0%; 15/20). Clinical activity was also observed in patients with a BRCA-like molecular signature as assessed by genome-wide loss of heterozygosity (genomic LOH). A RECIST ORR of 28.0% (23/82 patients), median DOR of 11.0 months (95% CI: 7.6, 20.6), and median PFS of 5.7 months (95% CI: 5.3, 7.6) was observed in patients with a BRCA-like tumor (*BRCA*^{wt} with high genomic LOH) versus a RECIST ORR of 10.0% (7/70 patients), median DOR of 5.8 months (95% CI: 4.6, 8.5), and median PFS of 5.2 months (95% CI: 3.6, 5.5) in patients with a *BRCA*^{wt}/low genomic LOH tumor. (Clovis, data on file)

A BRCA-like molecular signature was observed in approximately 55% of patients with a *BRCA*^{wt} tumor, indicating there is a significant population of ovarian cancer patients beyond those who have a *BRCA1/2* mutation who may benefit from rucaparib treatment. Importantly, approximately 30% of BRCA^{wt} patients noted as having low genomic LOH in an archival tumor sample had high genomic LOH in their pre-treatment screening biopsy, indicating that a recent tumor sample is preferred to assess BRCA-like status in order to identify patients most likely to benefit from rucaparib treatment.

An exploratory objective in ARIEL2 was to assess rucaparib efficacy in tumors with an alteration in a HR gene other than BRCA1/2. The overall frequency of non-BRCA1/2 HR gene mutations was low (11%, 22/204 tumor samples) and the presence of a mutation did not always correlate with LOH, with the exception of tumors with a RAD51C or RAD51D mutation, which consistently exhibited high genomic LOH.

RECIST and/or cancer antigen-125 (CA-125) responses were observed in patients with a RAD51C (75%, 3/4), ATM (50%, 1/2), ATR (100%, 1/1), BRIP1 (50%, 1/2), NBN (100%, 2/2), and RAD51D (50%, 1/2) mutation. (Clovis, data on file)

ARIEL2 Part 2 enrolled advanced ovarian cancer patients (N=287) who received at least 3 prior chemotherapy regimens in order to refine the BRCA-like molecular signature (ie, genomic LOH) and assess its predictive utility in a more heavily pre-treated patient population. Enrollment was completed in Q3 2016.

Similar to the safety profile in Study CO-338-010 Part 2A, the most frequent (reported in ≥ 15% of patients) treatment-related AEs (all grades) included gastrointestinal-related toxicities (nausea, constipation, vomiting, and diarrhea), asthenia/fatigue, elevations in ALT/AST, anemia/decreased hemoglobin, dysgeusia, and decreased appetite.

Study CO-338-014 (ARIEL3)
ARIEL3 is a double-blind, placebo-controlled, Phase 3 study of rucaparib as switch maintenance treatment in patients with relapsed, platinum-sensitive, high-grade ovarian, fallopian tube or primary peritoneal cancer who achieve a response to platinum-based chemotherapy (N = 540 planned; target enrollment completed in Q2 2016). The primary endpoint is PFS in HRD within subgroups as determined by next generation sequencing analysis of archival tumor tissue using an optimized algorithm from Study CO-338-017 (ARIEL2). Data is anticipated to be available in 2017.

Study CO-338-023 (RUCAPANC)
Study CO-338-023 (RUCAPANC) was a single-arm, open-label Phase 2 study of rucaparib treatment in patients with previously treated locally advanced or metastatic pancreatic ductal adenocarcinoma and a known deleterious *BRCA1/2* mutation. The primary endpoint was efficacy as measured by objective response rate (ORR). Of the 19 patients enrolled and evaluable for response, 2 achieved a confirmed PR and 1 achieved a confirmed CR. A fourth patient obtained a CR which was unconfirmed by Clovis as the patient transitioned to a compassionate use protocol. These patients all received only 1 prior line of therapy. The overall safety profile was similar to that observed in ovarian cancer patients.

2 Study Objectives

2.1 Primary Objective

- To assess the efficacy of rucaparib in patients with pancreatic carcinoma associated with a deleterious BRCA1/2 or PALB2 mutation by assessment of progression-free survival rate at 6 months (PFS6).

2.2 Secondary Objectives

- To evaluate efficacy by assessment of objective response rate (ORR) by RECIST v.1.1 in those with measurable disease
- To assess duration of response (DOR)
- To evaluate overall survival (OS)
- To evaluate the safety and tolerability of rucaparib

2.3 Exploratory Objectives

- To evaluate mechanisms of resistance to PARP inhibition by gene sequence and structural rearrangements of paired tumor samples and in circulating tumor DNA.
- To evaluate changes circulating tumor DNA (ctDNA) and in circulating tumor cells (CTCs) as a molecular marker of response

3 Investigational Plan

3.1 General Design

This is an open-label study of rucaparib in patients with locally advanced or metastatic pancreatic carcinoma and a known deleterious germline or somatic BRCA1/2 or PALB2 mutation.

3.1.1 Screening Phase

All patients will undergo screening assessments within 28 days prior to the first dose of rucaparib. AEs that occur after signing of the informed consent form and before administration of the first rucaparib dose will also be collected during this period.

Screening assessments will include demographics and medical history, prior treatments for pancreatic cancer (and other malignancies if applicable), prior and current medications and procedures, 12-lead electrocardiogram (ECG), ECOG performance status, hematology, serum chemistry, serum pregnancy for women of childbearing potential, urinalysis, physical examination, vital signs, weight and height measurements, adverse events, and radiological assessment by CT or magnetic resonance imaging (MRI). An optional tumor biopsy sample will be collected from patients who provide appropriate consent.

BRCA1/2 or *PALB2* test results must be obtained for all patients prior to enrollment in order to confirm the mutation detected was classified as deleterious/pathogenic or suspected deleterious, or equivalent of either of these. *BRCA1/2* or *PALB2* mutations in blood and tumor tissue samples may be collected for confirmatory analysis.

All patients who enroll on study must have a confirmed, deleterious/pathogenic or suspected deleterious or equivalent mutation in BRCA1, BRCA2 or PALB2. Mutations may be germline or somatic in origin and must have been identified by a CLIA certified laboratory from any of the following: blood, tumor tissue or circulating tumor material.

3.1.2 Study Intervention Phase

All patients will have blood collected prior to treatment for storage. Archival tumor tissue samples, if available, will also be collected and stored. If considered safe and feasible, a tumor biopsy will be obtained prior to the first dose of rucaparib.

During the treatment phase (continuous 28 day cycles), patients will be monitored for safety and efficacy. Assessments during the treatment phase will include AEs, ECOG performance status, concomitant medications and procedures, physical examination, vital signs and weight measurements, hematology and serum chemistry, serum or urine pregnancy (per investigator discretion) for women of childbearing potential, CA 19-9 measurement, blood samples for circulating tumor material analyses and study drug administration and accountability. Patients will be assessed for disease status per RECIST v1.1 after every 2nd cycle of treatment, and then every 3rd cycle for patients who have been on the study drug for at least 2 years. Patients will continue to receive rucaparib until disease progression or other reason for treatment discontinuation.

Patients will be monitored continuously for safety. The Data and Safety Monitoring Committee (DMSC) of the University of Pennsylvania Clinical Trials Scientific Review and Monitoring Committee (CTSRMC) will evaluate safety and efficacy in compliance with a charter.

3.1.3 Treatment Discontinuation

Upon treatment discontinuation, all patients will return to the clinic for an End of Treatment (EOT) visit. Assessments at this visit will include AEs, ECOG performance status, concomitant medications and procedures, 12-lead ECG, physical examination, vital signs and weight measurements, hematology and serum chemistry, serum pregnancy for women of childbearing potential, CA 19-9 measurement, blood sample for circulating tumor material analyses, disease status assessment and study drug accountability.

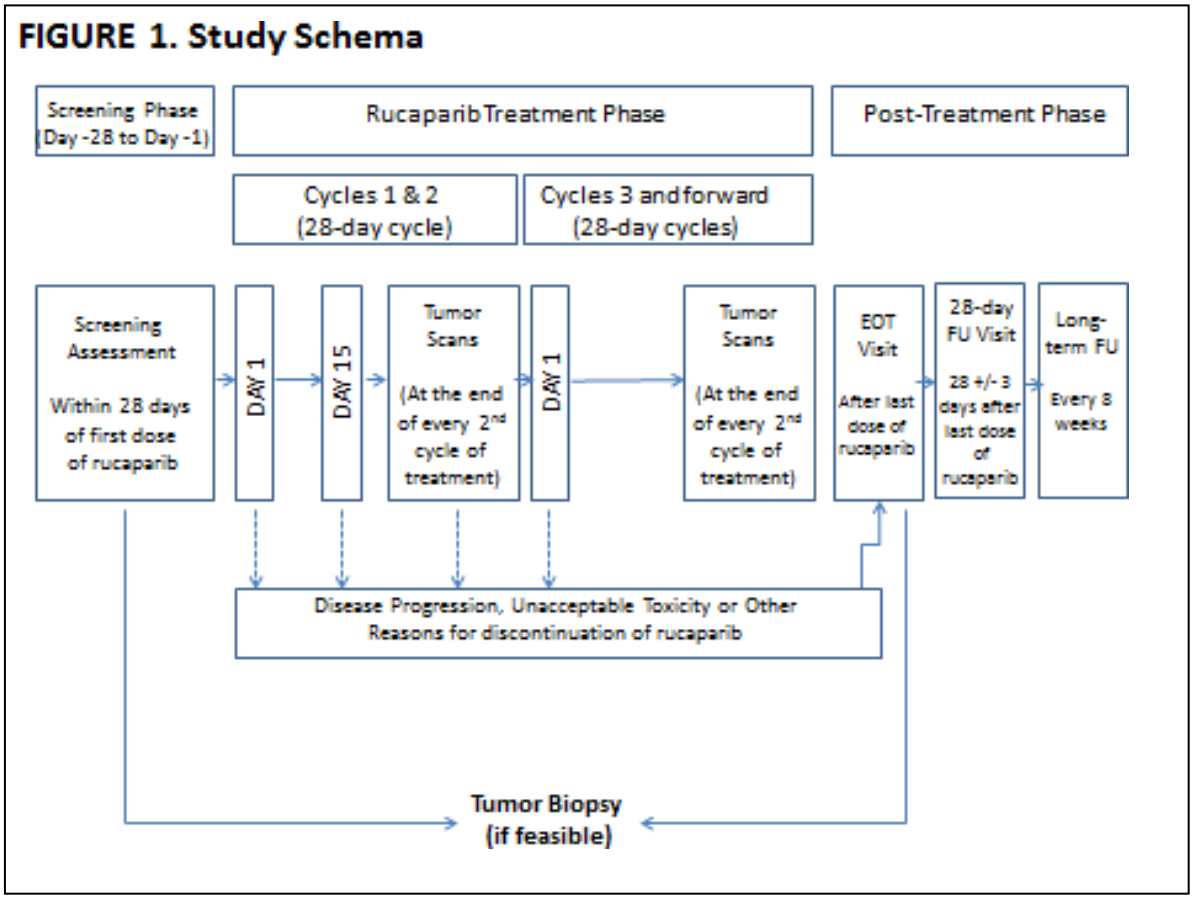
In patients who discontinue treatment due to disease progression, a tumor biopsy will be collected if considered feasible and safe.

3.1.4 Follow Up Phase

All patients will have a 28-day follow-up period for AEs following the last dose of rucaparib.
CT scans at 28-day follow-up should also be performed for patients who discontinued treatment for reason other than disease progression and did not have a radiologic assessment at the End of Treatment visit. After the 28-day follow-up visit, patients will be followed for survival every 8 weeks until death, loss to follow-up, withdrawal of consent, or study closure.

3.1.5 Study Schema

FIGURE 1. Study Schema



3.1.6 End of Study

The trial will be completed when all enrolled patients have completed 6 cycles of treatment or have experienced progressive disease (PD), whichever occurs first.

3.2 Study Endpoints

3.2.1 Primary Study Endpoints

The primary study endpoint will be the PFS rate at 6 months (PFS6) as determined from a Kaplan-Meier curve. PFS defined as the time from start of study therapy to the occurrence of disease progression according to RECIST v1.1, as assessed by the investigator, or death from any cause. Patients who are alive and progression-free will be censored on the most recent date that documents progression-free status (i.e. scan date or clinic visit date).

3.2.2 Secondary Study Endpoints

The secondary endpoints include:

- Objective response will be scored per RECIST v.1.1 in those with measurable disease.
- Objective response rate (ORR) is defined as the proportion of patients who achieve a complete or partial response, as determined by RECIST v.1.1
- Duration of response (DOR) is defined as the time from first documentation of complete or partial response by RECIST v.1.1 to date of disease progression or death due to any cause. Responders who have not progressed will be censored on the most recent date that documents progression-free status.

- Overall survival (OS) is defined as the time from start of study therapy to death due to any cause. Patients who are alive will be censored on the most recent date of patient contact.
- The incidence of adverse events (AEs), clinical laboratory abnormalities and dose modifications.

3.2.3 Exploratory Study Endpoints

The exploratory endpoints include:

- Gene sequence and structural rearrangements of tumor and circulating tumor DNA
- Circulating tumor material concentrations summarized over time
- Additional exploratory endpoints may be evaluated depending on sample availability and available technology.

4 Study Population and Duration of Participation

4.1 Inclusion Criteria

Eligible patients must meet the following inclusion criteria:

- Histologically or cytologically confirmed diagnosis of pancreatic carcinoma with locally advanced or metastatic disease
- ≥18 years of age.
- Eastern Cooperative Oncology (ECOG) performance status of 0 to 1.
- Patients may have previously failed non-platinum containing therapy or may never have previously progressed on treatment.
- Patients must be on treatment with platinum-based (cisplatin, oxaliplatin or carboplatin) treatment for locally advanced or metastatic pancreatic cancer and have received a minimum of 16 weeks of therapy without evidence of disease progression based on the investigator's opinion.
    - Discontinuation of the platinum component of the regimen for chemotherapy-related toxicity is permissible provided the patient has previously received at least 16 weeks of platinum-based therapy without evidence of disease progression ≤8 weeks after treatment with the platinum agent

Patients may have received <16 weeks of platinum therapy if platinum was not able to be used for medical reasons or was medically required to be discontinued for legitimate reason in the opinion of the investigator (ie allergy, intolerable organ dysfunction

- Documented deleterious BRCA1/2 or PALB2 mutation (germline or somatic) as assessed by CLIA certified laboratory. Variants that are considered to be non-detrimental ("Variants of uncertain significance", "Variants of unknown significance", "Variant, favor polymorphism" or "benign polymorphism" etc) are not sufficient for study entry.
- Measurable disease is not required for enrollment.
- Adequate organ function confirmed by the following laboratory values obtained ≤7 days prior to the first day of rucaparib:
    (1) Absolute neutrophil count (ANC) ≥1.0 x 10^9/L
    (2) Platelets>100 x 10^9/L
    (3) Hemoglobin≥9g/dL
    (4) Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤3 x upper limit of normal (ULN)
    (5) Total bilirubin ≤1.5 x ULN; if liver metastases or metabolic disorder such as Gilbert's syndrome, then ≤2.5 x ULN.
    (6) Serum creatinine ≤1.5 x ULN or estimated glomerular filtration rate (GFR) ≥45 mL/min using Cockcroft Gault formula.

4.2 Exclusion Criteria

Patients will be excluded from participation if any of the following criteria apply:

- Prior treatment with a PARP inhibitor
- Patients who have demonstrated resistance to platinum agents (e.g. oxaliplatin, cisplatin) are not eligible to participate in this study
- Clinical evidence of uncontrolled malabsorption and/or any other gastrointestinal disorder or defect that would, in the opinion of the investigator, interfere with the absorption of rucaparib
- Acute infection requiring intravenous antibiotics, antiviral or antifungal agents during the 14 days prior to first dose of rucaparib
- Symptomatic or untreated CNS metastases.
- Expected life expectancy of <12 weeks as determined by the investigator.
- For fertile patient (female able to become pregnant or male able to father a child), refusal to use effective contraception during the period of the trial and for 6 months after the last dose of rucaparib for female patients and 3 months for partners of male patients.
- Received any systemic treatment for pancreatic cancer ≤14 days prior to first dose of rucaparib.
- Non-study related minor surgical procedure ≤5 days, or major surgical procedure ≤21 days, prior to the first dose of rucaparib; in all cases, patients must be sufficiently recovered and stable before treatment administration.
- Active drug or alcohol use or dependence that would interfere with study compliance.
- Presence of any other condition that may increase the risk associated with study participation or may interfere with the interpretation of study results, and, in the opinion of the investigator, would make the patient inappropriate for entry into the study.

4.3 Patients or Partners of Patients with Reproductive Potential

Pregnancy is an exclusion criterion for study patients. Female study patients of childbearing potential, must not be considering getting pregnant during the study until 6 months following the last dose of rucaparib. Female partners of childbearing potential of study patients must not be considering getting pregnant during the study until 3 months following the last dose of rucaparib.

A woman is considered to be of childbearing potential unless 1 of the following applies:

- She is considered to be permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy.
- She is postmenopausal, defined as no menses for 12 months without an alternative medical cause. A high follicle-stimulating hormone (FSH) level consistently in the postmenopausal range (30 mIU/mL or higher) may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy; however, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient to confirm a postmenopausal state.

Female patients of childbearing potential must have a negative serum pregnancy test result less than 3 days prior to administration of the first dose of rucaparib. In addition, a serum pregnancy test must be performed < 3 days prior to Day 1 of every cycle from Cycle 2 and beyond. Treatment should be discontinued immediately in any woman found to have a positive pregnancy test while taking rucaparib. A serum pregnancy test will also be performed at the End-of-Treatment Visit.

Female study patients of reproductive potential must practice total abstinence or use a highly effective method of contraception (failure rate < 1% per year) during treatment and for 6 months following the last dose of rucaparib. Female partners of reproductive potential and their male partners must practice total abstinence or use a highly effective method of contraception (failure rate < 1% per year) during treatment and for 3 months following the last dose of rucaparib. The following are allowable only:

- Ongoing use of progesterone-only injectable or implantable contraceptives (e.g., Depo Provera, Implanon, Nexplanon)

- Placement of an intrauterine device or intrauterine system
- Bilateral tubal occlusion
- Male sterilization, with appropriate post-vasectomy documentation of absence of sperm in ejaculate
- True, complete (as opposed to periodic) abstinence.

Patients will be instructed to notify the investigator if pregnancy (own or female partner's) is discovered either during or within 6 months of completing treatment with rucaparib.

4.4 Total Number of Subjects and Sites

42 subjects will be enrolled at the University of Pennsylvania.

4.5 Vulnerable Populations:

Children, pregnant women, fetuses, neonates, or prisoners are not included in this research study.

5 Study Intervention (Study drug, device, biologic, vaccine, food etc.)

Oral rucaparib

5.1 Description

Rucaparib camsylate (also known as CO-338; previously known as PF-01367338-BW and AG-014447) is an oral formulation with a molecular weight of 555.67 Daltons. Rucaparib tablets for oral administration will be supplied to the study site by Clovis Pharmaceuticals Inc. A brief description of the investigational product is provided below.

Drug Name:	Rucaparib
INN:	Rucaparib
Formulation:	Tablet; film coated 200 mg – blue, round, embossed with C2 300 mg – yellow, oval, embossed with C3
How Supplied:	200 and/or 300 mg strength (based on free base) in high-density polyethylene bottles or equivalent with child-resistant caps. Patients may receive 1 or more strengths.
Storage Conditions:	Store at room temperature, with no special storage conditions. (Can remove temps all places as well)

5.2 Intervention Regimen

Patients will take 600mg rucaparib orally BID with at least 8oz (240mL) of room temperature water starting on Day 1. Rucaparib may be taken on an empty stomach or with food. Tablets should be swallowed whole without crushing or chewing. Patients should take rucaparib doses as close to 12 hours apart as possible, preferably at the same times every day. If a patient misses a dose (i.e. does not take it within 4 hours of the scheduled time), they should skip the missed dose and resume taking rucaparib with their next scheduled dose. Missed or vomited doses should not be made up.

A sufficient number of tablets will be provided to the patient to last until the next scheduled visit. Patients will be instructed to record daily doses taken or not taken in the dosing diary, and will be instructed to bring

their rucaparib tablets, all containers (empty, partially used, and/or unopened) and dosing diary to the next scheduled visit for reconciliation by the study personnel. Patients will take rucaparib BID for continuous 28-day cycles until disease progression as assessed by the investigator, or other reason for discontinuation. Treatment interruption and/or dose reductions are permitted in the event of unacceptable toxicity.

5.2.1 Starting Dose and Dose Modifications of Protocol-Specified Treatment

The starting dose in this study will be 600mg rucaparib PO (per os) BID (twice daily).

5.2.2 Dose Modification Criteria

The dose of rucaparib should be held if any of the following are observed and a dose reduction should be considered or implemented:

- Grade 3 or 4 hematologic toxicity
- Grade 3 or 4 non-hematologic toxicity (except for alopecia, nausea, vomiting, or diarrhea adequately controlled with systemic antiemetic/antidiarrheal medication administered in standard doses according to the study center routines)
- In addition, and at the discretion of the investigator, the dose of rucaparib may be held and/or reduced for Grade 2 toxicity not adequately controlled by concomitant medications and/or supportive care.

Treatment delays and modifications may be made at the discretion of the treating physician in the interest of patient safety

Treatment with rucaparib should be held until the toxicity resolves to ≤ CTCAE Grade 2. BID dosing may then be resumed at either the same dose or a lower dose, per investigator discretion. If treatment is resumed at the same dose, and the patient experiences the same toxicity, the dose should be reduced following resolution of the event to ≤ CTCAE Grade 2. If the patient continues to experience toxicity, additional dose reduction steps are permitted. If a patient continues to experience toxicity despite multiple dose reduction steps, treatment may be discontinued, upon the investigator's discretion.

Dose reduction steps are presented in Table 5.2.2.

Dose re-escalation upon resolution of toxicity to ≤ CTCAE Grade 1 is permitted, upon the investigator's discretion.

Management of Rucaparib Treatment-Emergent ALT/AST Elevations

- Grade 4 ALT/AST elevations: hold rucaparib until values have returned to Grade 2 or better, then resume rucaparib with a dose reduction. Monitor liver function tests weekly for 3 weeks after rucaparib has been restarted.
- Grade 3 ALT/AST elevations should be managed as follows:
    - Monitor liver function tests weekly until resolution to ≤ Grade 2.
    - Continuation of rucaparib with elevation of ALT/AST up to Grade 3 is permitted provided bilirubin is < ULN, alkaline phosphatase is < 3 x ULN, and there are no other signs of liver dysfunction.

If patient has Grade 3 ALT/AST and continues on rucaparib, and levels do not decline within 2 weeks or they continue to rise, treatment interruption and resolution to ≤ Grade 2 will be required before rucaparib can be resumed, either at the current dose or at a reduced dose

Table 5.2.2 Rucaparib Dose Reduction Steps

TABLE 5.2.2

Tablets	300/ 200mg
Starting Dose	600 mg BID
Dose Level -1	500 mg BID
Dose Level -2	400 mg BID
Dose Level -3*	300 mg BID
* Consult with medical monitor before reducing to this dose	

Management of anemia including: evaluation for MDS/AML and follow-up of patients who discontinue treatment with ongoing anemia.'

- If the patient develops anemia CTCAE Grade ≥ 3, rucaparib treatment should be held until the anemia resolves to CTCAE Grade ≤ 2 whereupon daily dosing may then be resumed at either the same dose or a lower dose, per investigator discretion.
- If the duration of dosing is interrupted for > 14 consecutive days due to anemia CTCAE Grade ≥ 3, treatment should be permanently discontinued, unless otherwise agreed between the investigator and the Principal Investigator
- In addition, if anemia CTCAE Grade ≥ 3 persists for > 14 consecutive days, or a dependence upon blood transfusion occurs, then weekly complete blood counts should be performed until resolution of the event.
- If, after 42 days of interruption of rucaparib, the anemia has not recovered to CTCAE Grade ≤ 1 then the patient should be referred to a hematologist and analysis of the bone marrow with cytogenetic studies are recommended according to standard hematologic practice.
- The bone marrow analysis should include a bone marrow aspirate (for cellular morphology, cytogenetic analysis, and flow cytometry) and a core biopsy (for bone marrow cellularity).

5.2.3 Criteria for Re-Treatment

A new cycle of treatment may begin if:

- ANC ≥1.0 x 10^9/L
- Platelet count ≥100 x 10^9/L
- Non-hematologic toxicities have returned to baseline or ≤CTCAE Grade 1 severity (or, at the investigator's discretion, ≤CTCAE Grade 2 severity if not considered a safety risk for the patient)
- Elevations in AST/ALT requiring a dose hold: Rucaparib may be restarted once AST/ALT return ≤CTCAE Grade 2 severity provided LFTs are measured weekly for 3 weeks following restarting rucaparib.

5.2.4 Treatment Beyond Progression

If the patient has met criteria for radiologic progression by RECIST v1.1, but the patient is still receiving benefit from rucaparib (e.g., patient has mixed radiologic response or is continuing to have symptomatic benefit without decline in performance status) according to the Investigator, then continuation of treatment will be considered. In such cases, the decision to continue will be made by the Investigator, and must be documented prior to continuing treatment with rucaparib. Patients will continue to have all protocol-required assessments specified in the Schedule of Assessments Table.

5.3 Prior and Concomitant Therapies

Patients who have received prior treatment with PARP inhibitor are not eligible to participate in this study. Patients who have demonstrated resistance to platinum agents (e.g. oxaliplatin, cisplatin) are not eligible to participate in this study.

During the study, supportive care (e.g. antiemetics; analgesics of pain control) may be used at the investigator's discretion and in accordance with institutional procedures.

All procedures performed (e.g., thoracentesis, paracentesis etc) and medications used during the study must be documented on the electronic case report form (eCRF).

5.3.1 Anticancer or Experimental Therapy

No other concomitant therapies for pancreatic cancer (including chemotherapy, radiation, hormonal treatment, antibody or other immunotherapy, gene therapy, vaccine therapy, angiogenesis inhibitors, or other experimental drugs) of any kind will be permitted while the patient is participating in the study with the exception of palliative radiation or gamma knife which may be allowed in discussion with the PI and Medical Monitor. Ongoing therapies for previously treated non-pancreatic cancer (e.g., hormonal treatment for prior breast cancer) are permitted.

5.3.2 Hematopoietic Growth Factors and Blood Products

Erythropoietin, darbepoetin alfa, and/or hematopoietic colony-stimulating factors for treatment of cytopenias should be administered according to institutional guidelines. Transfusion thresholds for blood product support will be in accordance with institutional guidelines.

5.3.3 CYP450 Isoenzyme Inhibitors, Inducers, and Substrates

Based on results of *in vitro* CYP interaction studies, caution should be used for concomitant medications with narrow therapeutic windows that are substrates of CYP2C19, CYP2C9, and/or CYP3A. Selection of an alternative concomitant medication is recommended.

Table 5.3.3 Examples of CYP Substrates with Narrow Therapeutic Range

CYP Enzyme	**Substrates with Narrow Therapeutic Range** [a]
CYP2C9	Warfarin, phenytoin
CYP2C19	S-mephenytoin
CYP3A	Alfentanil, astemizole, cisapride, cyclosporine, dihydroergotamine, ergotamine, fentanyl, pimozide, quinidine, sirolimus, tacrolimus, terfenadine

[a] The table is based on the Draft FDA Guidance on Drug Interaction Studies — Study Design, Data Analysis, Implications for Dosing, and Labeling Recommendations, 2012[38].

CYP substrates with narrow therapeutic range refers to drugs whose exposure-response relationship indicates that small increases in their exposure levels by the concomitant use of CYP inhibitors may lead to serious safety concerns (eg, Torsades de Pointes).

5.3.4 Bisphosphonates

Bisphosphonates are permitted.

5.3.5 Anticoagulants

Caution should be exercised in patients receiving oral rucaparib and concomitant warfarin as rucaparib showed a mixed inhibition of CYP2C9 *in vitro*. If appropriate, low molecular weight heparin should be considered as an alternative treatment. Patients taking warfarin should have international normalized ratio (INR) monitored regularly per standard clinical practice.

5.3.6 Other Concomitant Medications

Therapies considered necessary for the patient's well-being may be given at the discretion of the investigator. Other concomitant medications, except for analgesics, chronic treatments for concomitant medical conditions, or agents required for life-threatening medical problems, should be avoided. Herbal and complementary therapies should not be encouraged because of unknown side effects and potential drug interactions.

In vitro data showed that rucaparib is an inhibitor of P-gp and thus patients taking digoxin, a P-gp substrate, should have their digoxin levels monitored regularly via standard clinical practice. Caution should also be exercised for concomitant use of certain statin drugs (eg, rosuvastatin and fluvastatin) due to potential increase in exposure from inhibition of BCRP and CYP2C9. All concomitant medications taken by the patient should be documented appropriately on the eCRF.
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5.4 Receipt

Rucaparib will be received to our Perelman Center for Advanced Medicine Pharmacy and will be stored with no special storage conditions, ambient as per standard pharmacy practice

5.5 Storage

All tablets should be maintained in high-density polyethylene (HDPE) bottles with child-resistant caps and should be stored in the provided containers with no special storage conditions, ambient.

5.6 Preparation and Packaging

All tablets are provided in high-density polyethylene (HDPE) bottles with child-resistant caps and should be stored in the provided containers with no special storage conditions, ambient. Patients will be dispensed one or more strengths depending on their current dose of rucaparib. The number of bottles of each strength dispensed will be sufficient to supply 28 days treatment per cycle, including a small overage.

Study drug containers containing rucaparib tablets will be labeled according to national regulations for investigational products

5.7 Administration and Accountability

The investigator or designee will be responsible for distributing rucaparib to patients.

All patients will ingest rucaparib twice a day. Patients may take rucaparib on an empty stomach or with food. Each dose should be taken with at least 8 oz (240mL) of room temperature water. Tablets should be swallowed whole.

Patients should take rucaparib doses as close to 12 hours apart as possible, preferably at the same times every day. If a patient misses a dose (ie does not take it within 4 hours of the scheduled time), theyshould skip the missed dose and resume taking rucaparib with their next scheduled dose. Missed or vomited doses should not be made up.

A sufficient number of tablets will be provided to the patient to last until the next scheduled visit. Patients will be instructed to record daily doses taken or not taken in a dosing diary, and will be instructed to bring their rucaparib tablets, all containers (empty, partially used and/or unopened) and dosing diary to the next scheduled visit for reconciliation by site personnel.

5.8 Subject Compliance Monitoring

Documentation of dosing will be recorded in a study specific dosing diary. Study site personnel will review dosing information with the patient (or legally authorized representative) on scheduled clinic visit days, providing instructions regarding dose, dose frequency and the number of tablets to be taken for each dose.

Patients (or legally authorized representative) will be instructed to record dosing information for rucaparib taken at home in the dosing diary and to bring the dosing diary and all unused tablets with them to scheduled clinic visits. A compliance check and tablet count will be performed by study personnel during clinic visits. Every effort should be made to ensure patients complete the dosing diary and return their study drug containers at the end of each cycle of treatment.

5.9 Return or Destruction of Investigational Product

Upon completion or termination of the study, all unused and/or partially used investigational product will be destroyed on-site in accordance with standard policies for the destruction of investigational agents.

6 STUDY PROCEDURES

6.1 Schedule of Assessment

All procedures and assessments are to be completed within ±3 days of the scheduled time point.

Schedule of Assessments							
Procedure[α]	Screening Phase	Treatment Phase			Post-Treatment Phase		
	Day -28 to Day -1 (unless otherwise specified)	Cycles 1 & 2		Cycles 3+[x & y]			
		Day 1[b]	Day 15	Day 1	End of Treatment	28-day FU (28±3 days after last dose)	Long-term Follow-up
Informed Consent	X						
Demographics and Med/Onc History[c]	X						
Physical Exam, Height[d], Weight	X	X		X	X		
Vital Signs[f]	X	X[e]		X[e]	X		
Adverse Events	X	X	X	X	X	X	
Prior/Concomitant Medications and Procedures	X	X	X	X	X		
12-lead-ECG[g]	X				X		
Hematology[h]	X[i]	X	X	X[x]	X		
Serum Chemistry[j]	X[i]	X	X	X	X		
CA 19-9 measurement		X		X	X		
Coags if undergoing a tumor biopsy[u]	X				X		
Serum/Urine Pregnancy Test[k] (WOCBP only)	X	X		X	X		
Urinalysis[l]	X						
Disease Assessment/Tumor Scans[m]	X			X[n]	(X)[o]	(X)[p]	
	Screening Phase	Treatment Phase					
	Day -28 to Day -1 (unless otherwise specified)	Cycles 1 & 2		Cycles 3+ x & y			
		Day 1	Day 15	Day 1			
Archival Tumor Tissue (if available)		X					
Tumor Tissue Biopsy (if safe/feasible)[r]	X				X[w]		
Research sample[t]		X		X	X		

Schedule of Assessments							
Rucaparib Dispensation, Administration, Accountability		X		X	X		
Survival Status							X[s]

ALP = alkaline phosphatase, ALT = alanine transaminase, ANC = absolute neutrophil count, AST = aspartate transaminase, BUN = blood urea nitrogen, CR = complete response, CT = computed tomography, ECG = electrocardiogram, hrs = hours, MRI = magnetic resonance imaging, PET = positron emission tomography, PK = pharmacokinetics, PR = partial response, SAE = serious adverse event, WBC = white blood cell, WOCBP = women of childbearing potential

[a] = Treatment cycles are 28 days except for patients who reach C11D1 and are clinically stable as per the investigator may be extended to a 56-day cycle. Unless otherwise specified, all assessments are to be completed within ±3 days of scheduled time point. Delay of treatment schedule up to 10 days, as allowed by the protocol, is permitted at the discretion of the treating Investigator with approval of the PI (e.g. toxicity, weather, vacation). In addition, on a case by case basis the cycle length maybe extended to allow for planned vacations or emergency situations if deemed clinically stable by the PI.

[b] = Any procedures required on Day 1 of Cycle 1 may be omitted if completed ≤3 days earlier during the screening period.

[c] = Patient's medical record must include prior treatments received, dates of administration, date of progression, and radiology and/or medical report(s) to support assessment of disease progression, and, if applicable, intolerable toxicity to chemotherapy. Detailed BRCA1/2 test results are also required prior to enrollment.

[d] = Height at screening only.

[e] = Vital signs (blood pressure, pulse, and temperature) to be taken pre-dose on clinic visit days.

[f] = AEs are recorded from the time of signing informed consent through 28 days after last dose of rucaparib. Ongoing SAEs will be followed to resolution or until SAE stabilizes.

[g] = Heart rate, PR, QRS, QT, QTc and rhythm. Investigator to review results and assess as normal or abnormal (clinically significant or not clinically significant). ECGs to be repeated as clinically indicated.

[h] = Includes CBC with differential which includes: hemoglobin, hematocrit, WBC and differential (with ANC) and platelet count. Blood will be analyzed by a local laboratory.

[i] = to be performed ≤7 days prior to the first dose of rucaparib.

[j] = includes total protein, albumin, creatinine or estimated GFR using Cockcroft Gault formula, BUN, total bilirubin, ALP, ALT, AST, glucose, sodium, potassium, chloride, CO_2, calcium and phosphorous. Blood will be analyzed by a local laboratory.

[k] = Women of childbearing potential must have a negative serum pregnancy test result ≤3 days prior to the first dose of rucaparib. A serum or urine pregnancy test (investigator's discretion) must be performed ≤3 days prior to Day 1 of every cycle during the treatment phase. A serum pregnancy test must be performed at the End of Treatment visit.

[l] = includes dipstick for protein, glucose, blood, pH and ketones. If dipstick findings are abnormal based on investigator's assessment, microscopic evaluation should be performed.

[m] = Disease assessment to include clinical examination, and appropriate imaging techniques, including CT scans of the chest, abdomen and pelvis, with appropriate slice thickness per RECIST; other studies (MRI, X-ray, PET, and ultrasound) may be performed if required. The same method used to detect lesions at baseline are to be used to follow the same lesions throughout the clinical study. If a patient has known brain metastases, this disease should be evaluated at each required assessment.

[n] = Tumor scans to be performed within 7 days prior to start of every odd numbered cycle, ie prior to start of Cycle 3, Cycle 5, Cycle 7, etc. A confirmatory scan should be performed ≥4 weeks after an initial response of PR or CR is observed.

[o] = End of treatment CT scans should be performed if treatment was discontinued for reason other than radiologic disease progression.

[p] = If CT scans were not performed at End of Treatment or within 28 days prior to End of Treatment, a CT scan should be performed at the 28-day follow-up visit.

[q] = Archival tumor tissue, if available, will be collected and stored. (Note: This sample is not required to be submitted on Cycle 1, Day 1, but should be submitted as soon as possible after a patient begins treatment with rucaparib).

[r] = A screening tumor biopsy will be collected if deemed safe and feasible. A biopsy will be collected if the reason for discontinuation was radiologic disease progression.

[s] = All patients discontinued from treatment, regardless of reason, should be followed for survival every 8 weeks until death, loss to follow-up, withdrawal of consent from study, or closure of the study. Follow-up can be performed via telephone.
[t] = Up to 50cc of whole blood to be collected in 4 total tubes, likely to include EDTA and Streck tubes. Refer to laboratory manual for details. *If a patient has been on for >12 cycles, stop collecting serial ctDNA until progression or concern for progression.
[u]= Patients will have coagulation tests PT/PTT/INR in advance of the clinical trial biopsy

[w]= A biopsy will be obtained at progression if deemed safe and feasible. For patients some patients this will not be considered end of treatment as they may be permitted to remain on treatment past progression [x]= Following C11D1 of treatment, patients who are deemed to be clinically stable as per the investigator may have office visits and blood work at every odd cycle only. Subjects will be required to have monthly hematology labs (complete blood counts). A cycle will then be 56 days.
[y] = Following C24D1 of treatment, patients who are deemed to be clinically stable as per the investigator may have office visits, including imaging and clinical assessments, Q12 weeks instead of Q8 weeks. A cycle will then be 84 days. Clinical labs should still be obtained once per month.

6.2 Screening Phase

Following written informed consent, and unless otherwise specified, the following assessments will be performed during the 28 day period prior to the first dose of rucaparib. Assessments performed within this window, but prior to patient signing informed consent, are acceptable only if confirmed to have been standard of care.

Alterations to re-consenting patients:
In cases where a face-to-face scenario is not deemed practical or safe for re-consenting subjects, the study team will send the Informed Consent Form to patients in a way that is practical and convenient (e.g., email/scan or fax). In place of the face-to-face scenario, the appropriate delegated study personnel will explain the changes to the Informed Consent Form by way of a telephone call with the patient. After the re-consent discussion, the participant will be asked to sign the form and return a copy to the study team in a way that is practical and convenient (e.g., email/scan or fax). The Informed Consent Form copy will be signed by the appropriate study team personnel obtaining re-consent and filed in the designated investigator site file location. In addition to a wet ink signature, this process will be documented in the Electronic Medical Record (EMR).

Demographic information (birth date, race, gender, etc), including smoking status.

- Medical/oncology history, including date of cancer diagnosis, prior treatments and any surgical procedures
- Physical examination of body system, height and weight
- ECOG performance status (Appendix A)
- Vital signs (blood pressure, pulse, and temperature)
- Prior and concomitant medications and any surgical procedure
- 12-lead ECG
- Hematology (hemoglobin, hematocrit, WBC and differential [with ANC], and platelet count) ≤7 days prior to first dose of rucaparib.
- Serum chemistry (total protein, albumin, creatinine or estimated GFR using Cockcroft Gault formula, BUN, total bilirubin, ALP, ALT, AST, glucose, sodium, potassium, chloride, CO_2, calcium and phosphorous) ≤7 days prior to the first dose of rucaparib.
- Serum pregnancy test for women of childbearing potential (≤3 days prior to the first dose of rucaparib)
- Urinalysis performed on freshly voided clean sample (dipstick for protein, glucose, blood, pH and ketones). If dipstick findings are abnormal based on investigator judgment, then a microscopic evaluation will be performed to assess the abnormal findings.

- Tumor assessments should consist of clinical examination, appropriate imaging techniques including CT scans of the chest, abdomen and pelvis, with appropriate slice thickness per RECIST; other studies (MRI, X-ray, PET, and ultrasound) may be performed if required. The same method used to detect lesions at baseline is to be used to follow the same lesions throughout the clinical study. If a patient has known brain metastases, this disease should be evaluated at each required assessment.
- Patients will have coagulation tests PT/PTT/INR in advance of the clinical trial biopsy
- Tumor tissue biopsy if considered safe and feasible. Tumor tissue will be processed locally as formalin-fixed paraffin-embedded (FFPE) tissue. We are requesting 10-20 slides of tissue, 5-10um (preference for 20 slides, 10 um thick). Refer to the Laboratory Manual for detailed sample handing instructions.
- AE monitoring (after signing informed consent)

6.3 Treatment Phase

The following procedures should be completed before the first dose of oral rucaparib is administered, unless otherwise indicated.

6.3.1 Day 1 of Cycles 1 and 2

- Physical examination
- Weight
- ECOG performance status (Appendix A)
- Vital signs
- Concomitant medications and procedures
- Hematology
- Serum chemistry
- CA 19-9 measurement
- Serum or urine pregnancy ≤3 days prior to start of cycle (for women of childbearing potential only). (*Note: a serum pregnancy test must be performed prior to the start of Cycle 1; a urine or serum pregnancy test is permitted prior to the start of Cycle 2)*
- AE monitoring
- Research blood sample
- Submission of an FFPE archival tumor tissue sample, if available. Refer to the Laboratory Manual for detailed sample handling instructions. *(Note: this sample is not required to be submitted on Cycle 1, Day 1, but should be submitted as soon as possible after a patient begins treatment with rucaparib)*
- Study drug accountability (Cycle 2 only)

Rucaparib tablets will be dispensed to the patient in sufficient quantity to last until Day 1 of the next treatment cycle. Patients will ingest rucaparib twice daily at about the same times every day as close to 12 hours apart as possible. Rucaparib should be taken with at least 8 oz (240 mL) of room temperature water with or without food. Patients will keep all unused tablets and containers (empty, partially used, and/or unopened) for accountability at the next visit. In the event of toxicities, re-treatment or dose modification will be according to the criteria described the protocol). Patients will record dosing information in their dosing diary.

6.1.2 Day 15 of Cycles 1 and 2

Patients will be instructed to refrain from taking their first dose of oral rucaparib at home on the day of their clinic visits because certain assessments must be performed prior to dosing.

- Hematology
- Serum chemistry
- Concomitant medications and procedures
- AE monitoring
- Study drug continuation

6.1.3 Day 1 of Cycles 3 and Beyond

Patients will be instructed to refrain from taking their first dose of oral rucaparib at home on the day of their clinic visits because certain assessments must be performed prior to dosing.

The following procedures will be completed prior to oral rucaparib on Day 1 of Cycles 3 and beyond:

- Physical examination
- Weight
- ECOG performance status (Appendix A)
- Vital signs
- Concomitant medications and procedures
- Hematology
- Serum chemistry
- CA 19-9 measurement
- Research blood sample
- Serum or urine pregnancy (per investigator's discretion) <3 days prior to start of cycle (for WOCBP only)
- Disease/ tumor assessment (using the same methodology as was used at screening [eg, CT scan]) prior to the start of every odd numbered cycle (e.g. Cycle 3, 5, 7 etc.) (within 7 days before is permitted) relative to start of treatment on Day 1 of Cycle 1 through to 18 months on study, then every 16 calendar weeks (within 5 days before is permitted) relative to the start of treatment on Day 1 of Cycle 1. Timing of disease/tumor assessments is relative to Day 1 of Cycle 1 after enrollment.
- AE monitoring
- Study drug accountability.

Rucaparib tablets will be dispensed to the patient in sufficient quantity to last until Day 1 of the next treatment cycle. For patients being seen every other cycle, sufficient rucaparib for two cycles will be dispensed. Patients will ingest rucaparib twice daily at about the same times every day as close to 12 hours apart as possible. Rucaparib should be taken with at least 8 oz (240 mL) of room temperature water with or without food. Patients will keep all unused tablets and containers (empty, partially used, and/or unopened) for accountability at the next visit. In the event of toxicities, re-treatment or dose modification will be according to the criteria described the protocol). Patients will record dosing information in their dosing diary.

6.4 Day 1 of Cycles 11 and Beyond

Patients who reach C11D1 and are clinically stable as per the investigator, may elect to have blood work and office visits at odd cycles only (ie every other cycle). Imaging schedule will not change. Subjects will be required to have monthly hematology labs and can be performed locally and will be reviewed and assessed by a study Investigator. At each odd visit, patients will continue to have the evaluation as described in section 6.2.

6.5 Day 1 of Cycles 23 and Beyond

Patients who reach C23D1 and are clinically stable as per the investigator, may elect to have office visits, including imaging and clinical assessments, every 12 weeks instead of every 8 weeks. Subjects will still be required to have monthly hematology labs and can be performed locally and will be reviewed and assessed by a study investigator. Every 12 weeks, patients will continue to have the evaluation as described in section 6.4.

6.6 End of Treatment Visit

The following procedures will be performed for all patients as soon as possible after the last dose of oral rucaparib:

- Physical examination
- Weight
- ECOG performance status (Appendix A)
- Vital signs
- Concomitant medications and procedures
- Hematology
- Serum chemistry
- CA 19-9 measurement
- Research blood sample
- Tumor scans if treatment was discontinued for reason other than radiologic disease progression
- Patients will have coagulation tests PT/PTT/INR in advance of the clinical trial biopsy
- A progression biopsy (if feasible and safe) For some patients this will not be end of treatment since they may be permitted to continue treatment beyond progression.
- AE monitoring
- Study drug accountability.

6.7 28-day Follow-up Visit

The following procedures will be performed for all patients at 28 (±3) days after the last dose of oral rucaparib:

- AE monitoring (ongoing SAEs should be followed until resolution or stabilization)
- Tumor scans if not completed at end of treatment visit

6.8 Long-term Follow-Up

The following procedures will be performed for all patients every 8 weeks until death, loss to follow-up, withdrawal of consent from study or closure of study.

- Overall survival information. Follow-up can be performed via telephone.

6.9 Subject Withdrawal

Subjects may withdraw from the study at any time without impact to their care. They may also be discontinued from the study at the discretion of the Investigator for lack of adherence to intervention or study procedures or visit schedules, AEs, or due to (list protocol specific reasons that could arise here). The Investigator may also withdraw subjects who violate the study plan, or to protect the subject for reasons of safety or for administrative reasons. It will be documented whether or not each subject completes the clinical study. Subjects who withdraw early will have one final visit to collect investigational product and to follow up regarding adverse events.

6.9.1 Data Collection and Follow-up for Withdrawn Subjects

Subjects who withdraw consent to participate in the study will be seen for one final visit to collect the investigational product. During this visit they will be asked for permission to have the study team look into their survival status via publically available means.

7 Study Evaluations and Measurements

7.1 Medical Record Review

The following information will be extracted from the medical record of each subject prior to the first dose of rucaparib.

- Past medical/oncologic history including date of diagnosis, prior treatments, date of progression, and radiology and/or medical report(s) to support assessment of disease progression, and, if applicable, intolerable toxicity to chemotherapy.
- Detailed BRCA1/2 or PALB2 test results
- Detailed family history of all cancers

7.2 Physical Examination

Physical examination will include all of the major body systems. Physical examinations will be performed at screening (complete) and at most study visits (limited as appropriate).

7.3 Body Weight and Height

Height will be measured during the Screening visit only. Weight will be measured per institutional guidelines.

7.4 Vital Signs

Vital signs will include blood pressure, pulse and body temperature. Vital signs will be performed at most study visits.

7.5 ECOG Performance Status

ECOG performance status (Appendix A) will be assessed at Screening, on Day 1 of each cycle, and at the End of Treatment visit. ECOG performance status should be assessed by the same study personnel at each visit, if possible. Care will be taken to accurately score performance status, especially during screening for study eligibility purposes. Additional consideration should be given to borderline ECOG performance status to avoid enrolling patients with significant impairment.

7.6 12-Lead Electrocardiogram

For all patients, 12-lead ECGs will be performed at Screening and at the End of Treatment. During the Treatment Phase, ECGs will be performed as clinically indicated.

All 12-lead ECGs will be analyzed locally.

7.7 Clinical Laboratory Evaluations

Certified local laboratories will perform study-related clinical laboratory tests according to institutional procedures, and the results will be reviewed by the investigator. The panels of laboratory tests to be performed are shown below:

Hematology: Hemoglobin, hematocrit, WBC and differential (with ANC), and platelet count at Screening, during treatment, and at the End of Treatment visit. Screening hematology results must be reviewed by the investigator prior to the start of treatment with rucaparib. During the treatment phase, results must be evaluated by the investigator and acted upon, as appropriate, within 24 hrs of receipt.

Clinical Chemistry: Total protein, albumin, creatinine or estimated GFR using the Cockcroft Gault formula, BUN or urea, total bilirubin, alkaline phosphatase (ALP), ALT, AST, glucose, sodium, potassium, chloride, CO2, calcium, and phosphorus at Screening, during treatment, and at the End of Treatment visit. Screening clinical chemistry results must be reviewed by the Investigator prior to the start of treatment with rucaparib. During the treatment phase, results must be evaluated by the investigator and acted upon, as appropriate, within 24 hrs of receipt.

Urinalysis: Performed on freshly voided clean sample by dipstick for protein, glucose, blood, pH, and ketones per the schedule of evaluations. If dipstick findings are abnormal, then a microscopic evaluation will be performed to assess the abnormal findings. Urinalysis will be performed at screening only.

Serum/Urine Pregnancy: For women of childbearing potential only. Serum pregnancy test is to be performed ≤3 days prior to first dose of rucaparib and at the End of Treatment visit. Serum or urine pregnancy test (per investigator's discretion) is to be performed ≤3 days prior to the start of every cycle during the treatment phase.

Laboratory reports will be reviewed by the investigator or delegated physician who will then comment on out-of-range parameters and assess clinical significance. Clinically significant abnormalities and associated panel results, as well as results of any additional tests performed as follow-up to the

abnormalities, will be documented on the eCRF as an AE. Refer to Section 9.4 for guidelines on reporting of abnormal laboratory values as AEs.\

7.8 Efficacy Evaluations

7.8.1 Tumor Assessments

Tumor assessments will be performed at Screening and within 7 days prior to the start of every odd numbered cycle (i.e., prior to the start of Cycles 3, 5, 7, etc.), until C11 and then every 12 weeks, and at the End of Treatment visit. If a CT scan was not performed at the End of Treatment visit, a CT scan should be performed at the 28-day Follow-up visit. Tumor response will be interpreted using RECIST Version 1.1 (Appendix B).

Tumor assessments should consist of clinical examination and appropriate imaging techniques (CT scans of the chest, abdomen, and pelvis with appropriate slice thickness per RECIST); other studies (MRI, X-ray, PET, and ultrasound) may be performed if required. If a patient has known brain metastases, this disease should be evaluated at each required assessment. The same methods used to detect lesions at baseline are to be used to follow the same lesions throughout the clinical study. Investigators should perform scans of the anatomical sites that, in their judgment, are appropriate to assess based on each patient's tumor status.

7.8.2 Tumor Markers

CA 19-9 will be collected on Day 1 of every clinical assessment date and at the End of Treatment visit.

7.9 Genetic Testing

All enrolled patients must have documented confirmation of a deleterious or suspected deleterious (or equivalent) mutation in BRCA1, BRCA2 or PALB2 as assessed by a CLIA certified local laboratory. Mutations may be somatic or germline. Mutations may have been assessed by germline testing, tumor biopsy or sequencing of circulating material (e.g Guardant360 testing).

7.10 Correlative Science

7.10.1 Research Blood Samples

Blood draws (up to 50mL of blood; 4 tubes, likely to include Streck tube and EDTA tube) for research will be collected on Day 1 of each Cycle and at the End of Treatment. Samples will very likely be analyzed for circulating tumor DNA and circulating tumor cells. An additional sample will be banked. Details will depend on available funds, samples and technology.

7.10.2 Tumor Tissue Analysis

Paired Tumor Biopsies: Tumor tissue biopsies will be obtained during screening and at time of disease progression, as deemed safe and feasible. It will be stored at an internal facility (refer to Lab Manual) to be used for analysis at a later date. Analysis may include:

- DNA extraction and sequencing in order to identify mutations in HR pathway genes, and evaluate whether a patient has a reversion mutation or other mutation(s) that may be associated with response or resistance to rucaparib.
- Analysis of genomic structural variation to determine a signature that may correlate with response or resistance to rucaparib.
- Additional or alternate assays depending on tissue availability and available technology.

Organoids: If feasible, organoids of tumor tissue will be created at the University of Pennsylvania and analyzed for genetic concordance with the parent samples. Other analyses may be conducted depending on practical constraints.

Archival Tumor Tissue: If available, archival tumor tissue should be located during the screening process and submitted as soon as possible after a patient begins rucaparib.

Additional Tissue: If additional tissue or blood is available, it may be sent to Clovis Oncology for genetic analysis using the Foundation One platform or an alternative platform.

8 Statistical Plan

This is a single arm single stage Phase II study to evaluate progression-free survival rate at 6 months (PFS6) in 42 eligible patients. Patients who are not evaluable for efficacy, as defined within the protocol, will be replaced. Enrollment is expected to continue for 42 months and follow-up will continue for 6 additional months, prior to the final analysis of PFS. The null hypothesis is that the PFS6 rate is 44% (same as reported for standard therapies) and the alternative hypothesis is that the PFS6 rate has been increased to 60%.

8.1 Primary Endpoint

The primary study endpoint will be progression-free survival (PFS), defined as the time from start of study therapy to the occurrence of disease progression according to RECIST v1.1, as assessed by the investigator, or death from any cause. Patients who are alive and progression-free will be censored on the most recent date that documents progression-free status (ie., scan date or clinic visit date). The PFS6 will be estimated from the Kaplan-Meier curve.

8.2 Secondary Endpoints

The secondary endpoints are:

(1) Objective response will be scored per RECIST v.1.1 as assessed by radiology review.
(2) Objective response rate (ORR) is defined as the proportion of patients who achieve a complete or partial response, as determined by RECIST v1.1.
(3) Duration of response (DOR) is defined as the time from first documentation of complete or partial response by RECIST v.1.1 to date of disease progression or death due to any cause. Responders who have not progressed will be censored on the most recent date that documents progression-free status.
(4) Overall survival (OS) is defined as the time from start of study therapy to death due to any cause. Patients who are alive will be censored on the most recent date of patient contact.
(5) The incidence of adverse events (AEs), clinical laboratory abnormalities and dose modifications.

8.3 Exploratory Endpoints

The exploratory endpoints include:

(1) Gene sequence and structural rearrangements of tumor and circulating tumor DNA
(2) Circulating tumor material concentrations summarized over time
(3) Additional exploratory endpoints may be evaluated depending on sample availability and available technology.

8.4 Statistical Methods

Clinical Statistics: We plan to enroll 42 patients in a single-arm one-stage phase II design. Progression-free survival at 6 months (PFS6) will be the primary clinical outcome and it will be estimated using the Kaplan-Meier method. Based on prior research[1, 2, 21, 39] the null hypothesis is that the PFS6 rate in this population of subjects is 44%. The alternative hypothesis is that the PFS6 rate is 60%. Forty-two patients provide 81% power to detect this increase in PFS6, at a two-sided 5% significance level, assuming an exponential distribution and that enrollment will continue for 42 months with an additional 6 months of follow-up prior to the final statistical analysis. The confidence interval method will be used for the test of the primary hypothesis. A 2-sided 95% confidence interval for PFS6 will be constructed to determine whether the lower bound of this confidence interval excludes 44%, which is the historical control PFS6 rate. Secondary outcomes include overall survival (OS) and objective response rate (ORR); median OS and ORR will be estimated with 95% confidence intervals. Toxicities will be graded and tabulated and Grade 2 and Grade

3 toxicity rates will be calculated. With 42 patients, we have 88% power to detect any toxicity occurring at a rate of 5% or more.

Translational Statistics: Genomic endpoints will also be assessed. Serial testing of the presence of mutations using tissue and peripheral blood will be described using graphical plots and descriptive statistics.

8.4.1 Baseline Data

All demographic and baseline characteristics will be summarized for the safety population.

The following variables will be summarized with frequent tabulations:

- Time since diagnosis (months)
- Baseline laboratory parameters: graded based on CTCAE

Descriptive statistics may also be used to summarize these variables.

8.4.2 Efficacy Analysis

All efficacy evaluations will be conducted using the efficacy population (Section 8.5).

8.4.3 Safety Analysis

All safety evaluations will be conducted using the safety population (Section 8.5).

8.5 Subject Population(s) for Analysis

The following analysis populations are defined for the study:

Safety Population: The safety population will consist of all patients who received at least one dose of rucaparib.

Efficacy Population: The efficacy population will consist of all patients who received at least one dose of rucaparib and had a least one post-treatment assessment of response by RECIST v.1.1 (Appendix A).

9 Safety and Adverse Events

9.1 Definitions

9.1.1 Unanticipated Problems Involving Risk to Subjects or others

Any incident, experience, or outcome that meets all of the following criteria:

- Unexpected in nature, severity, or frequency (i.e. not described in study-related documents such as the IRB-approved protocol or consent form, the investigators brochure, etc)
- Related or possibly related to participation in the research (i.e. possibly related means there is a reasonable possibility that the incident experience, or outcome may have been caused by the procedures involved in the research)
- Suggests that the research places subjects or others at greater risk of harm (including physical, psychological, economic, or social harm).

9.1.2 Adverse Event

An **adverse event** (AE) is any unfavorable symptom, sign, illness or experience that occurs at any dose and develops or worsens in severity during the course of the study. Intercurrent illnesses or injuries should be regarded as adverse events. Abnormal results of diagnostic procedures are considered to be adverse events if the abnormality:

- results in study withdrawal
- is associated with a serious adverse event
- is associated with clinical signs or symptoms
- leads to additional treatment or to further diagnostic tests

is considered by the investigator to be of clinical significance

9.1.3 Adverse Events of Special Interest

AESIs (serious or non-serious) are defined as AEs of scientific and medical concern specific to the Clovis product or program, for which ongoing monitoring and rapid communication by the Principal Investigator to Clovis can be appropriate. Such an event might warrant further investigation in order to characterize and understand it. Depending on the nature of the event, rapid communication by the Principal Investigator to other parties (eg, regulators) might also be warranted.

Details on Clovis's currently agreed list of AESIs for rucaparib can be found in the current rucaparib IB. The following AESIs are to be reported to Clovis expeditiously within 24 hours of knowledge of the event, during the study through 30 days after receiving the last dose of study treatment, according to the procedures below:

- Myelodysplastic Syndrome and Acute Myeloid Leukemia
- Pneumonitis- including the following irrespective of causality assessment and severity:
    - interstitial lung disease
    - pulmonary fibrosis
    - acute interstitial pneumonitis
    - alveolitis necrotizing
    - alveolitis
    - hypersensitivity pneumonitis
    - organizing pneumonia

9.1.4 Serious Adverse Event

Adverse events are classified as serious or non-serious. A **serious adverse event** is any AE, that is:

- fatal
- life-threatening
- requires or prolongs hospital stay
- results in persistent or significant disability or incapacity
- a congenital anomaly or birth defect
- an important medical event

Important medical events are those that may not be immediately life threatening, but are clearly of major clinical significance. They may jeopardize the subject, and may require intervention to prevent one of the other serious outcomes noted above. For example, drug overdose or abuse, a seizure that did not result in in-patient hospitalization, or intensive treatment of bronchospasm in an emergency department would typically be considered serious.

All adverse events that do not meet any of the criteria for serious should be regarded as **non-serious adverse events**.

Events or Outcomes Not Qualifying as Serious Adverse Events
The following are not considered SAEs and therefore do not need to be reported as such:

- Pre-planned or elective hospitalization including social and/ or convenience situations (eg, respite care)
- Hospital visits of less than 24 hours duration (eg, patient presents to the emergency room, but is not admitted to a ward)
- Overdose of either Clovis study drug or concomitant medication unless the event meets SAE criteria (eg, hospitalization). However, the event should still be captured as a nonserious AE

- Events of progression of the patient's underlying cancer as well as events clearly related to progression of the patient's cancer (signs and symptoms of progression) should not be reported as a serious adverse event unless the outcome is fatal within the safety reporting period. If the event has a fatal outcome within the safety reporting period, then the event of Progression of Disease must be recorded as an AE and as a SAE with CTC Grade 5 (fatal outcome) indicated.

9.2 Adverse Event Reporting Period

The study period during which adverse events must be reported is normally defined as the period from the initiation of any study procedures to the end of the study treatment follow-up. For this study, the study treatment follow-up is defined as 30 days following the last administration of study treatment.

9.3 Preexisting Condition

A preexisting condition is one that is present at the start of the study. A preexisting condition should be recorded as an AE if the frequency, intensity, or the character of the condition worsens during the study period

9.4 General Physical Examination Finding

At screening, any clinically significant abnormality should be recorded as a preexisting condition. At the end of the study, any new clinically significant findings/abnormalities that meet the definition of an AE must also be recorded and documented as an AE.

9.5 Post-Study Adverse Event

All unresolved AEs should be followed by the investigator until the events are resolved, the subject is lost to follow-up, or the AE is otherwise explained. At the last scheduled visit, the investigator should instruct each subject to report any subsequent event(s) that the subject, or the subject's personal physician, believes might reasonably be related to participation in this study. The investigator should notify the Principal Investigator of any death or AE occurring at any time after a subject has discontinued or terminated study participation that may reasonably be related to this study. The Principal Investigator should also be notified if the investigator should become aware of the development of cancer or of a congenital anomaly in a subsequently conceived offspring of a subject that has participated in this study.

9.6 Abnormal Laboratory Values

An abnormal laboratory value that is not already associated with an AE is to be recorded as an AE only if any one of the following criteria is met:

- an action on the study drug is made as a result of the abnormality
- intervention for management of the abnormality is required
- at the discretion of the investigator should the abnormality be deemed clinically significant

9.7 Pregnancy or Drug Exposure

If a patient becomes pregnant during the study the investigator is to stop dosing with study drug(s) immediately.

A pregnancy is not considered to be an AE or SAE; however, any pregnancy occurring in a study patient or partner of a study patient during study participation or within 6 months of last dosing for female patients and 3 months for partners of male patients must be reported to Clovis using the Pregnancy Report Form within the

same timelines as an SAE. A pregnancy should be followed through to outcome, whenever possible. Once the outcome of the pregnancy is known, the Pregnancy Outcome Report Form should be completed and reported to Clovis. AEs, SAEs, or AESIs that occur during pregnancy will be assessed and processed according to the AE or SAE/AESI processes using the appropriate AE or SAE/AESI forms

9.8 Hospitalization, Prolonged Hospitalization or Surgery

Any AE that results in hospitalization or prolonged hospitalization should be documented and reported as an SAE unless specifically instructed otherwise in this protocol. Any condition responsible for surgery should be documented as an AE if the condition meets the criteria for an AE.

Neither the condition, hospitalization, prolonged hospitalization, nor surgery are reported as an AE in the following circumstances:

- Hospitalization or prolonged hospitalization for diagnostic or elective surgical procedures for a preexisting condition. Surgery should ***not*** be reported as an outcome of an AE if the purpose of the surgery was elective or diagnostic and the outcome was uneventful.
- Hospitalization or prolonged hospitalization required to allow efficacy measurement for the study.
- Hospitalization or prolonged hospitalization for therapy of the target disease of the study, unless it is a worsening or increase in frequency of hospital admissions as judged by the clinical investigator.

9.9 Recording of Adverse Events

At each contact with the subject, the investigator must seek information on adverse events by specific questioning and, as appropriate, by examination. Information on all adverse events should be recorded immediately in the source document, and also in the appropriate adverse event module of the case report form (CRF). All clearly related signs, symptoms, and abnormal diagnostic procedures results should recorded in the source document, though should be grouped under one diagnosis. All adverse events occurring during the study period must be recorded. The clinical course of each event should be followed until resolution, stabilization, or until it has been determined that the study treatment or participation is not the cause. Serious adverse events that are still ongoing at the end of the study period must be followed up to determine the final outcome. Any serious adverse event that occurs after the study period and is considered to be possibly related to the study treatment or study participation should be recorded and reported immediately.

9.10 Reporting of Adverse Events

Investigators must conform to the AE reporting timelines, formats and requirements of the various entities to which they are responsible, but at a minimum those events that must be reported are those that are:

- Related to study participation,
- Unexpected, and
- Serious or involve risks to subjects or others

If the AE is considered serious, Principal Investigator should report this event to Clovis and to their IRB (reference Section 9.12). An event may qualify for expedited reporting to regulatory authorities if it is a suspected unexpected serious adverse reaction (SUSAR) in line with relevant regulations (reference Section 9.13)

If the report is supplied as a narrative, the minimum necessary information to be provided at the time of the initial report includes:

- Study identifier
- Study center
- Subject number
- Investigational study product
- A description of the event

- Date of onset
- Current status
- Whether study treatment was discontinued
- The reason why the event is classified as serious
- Investigator assessment of the association between the event and study treatment.

9.11 Investigator Reporting: Notifying Drug Manufacturer

All SAEs, AESIs, and pregnancies, regardless of relationship to study drug, must be reported to the Clovis Oncology within 24 hours of knowledge of the event, during the study through 30 days after receiving the last dose of study treatment, according to the procedures below. After the 30 day specified window, only SAEs considered to be treatment related and all AESIs, regardless of treatment relationship, should be reported. It is important that the investigator provide an assessment of relationship of the SAE or AESI to study treatment at the time of the initial report.

The Clovis or the Investigator's study-specific Serious Adverse Event (SAE)/Adverse Events of Special Interest (AESI) Report Form may be used for reporting SAEs and AESIs. The contact information for reporting of SAEs and AESIs can be found on the SAE/AESI Reporting Form and Pregnancy Report Forms.

9.12 Investigator Reporting: Notifying the Penn IRB

This section describes the requirements for safety reporting by investigators who are Penn faculty, affiliated with a Penn research site, or otherwise responsible for safety reporting to the Penn IRB. The University of Pennsylvania IRB (Penn IRB) requires expedited reporting of those events related to study participation that are unforeseen and indicate that participants or others are at increased risk of harm. The Penn IRB will not acknowledge safety reports or bulk adverse event submissions that do not meet the criteria outlined below. The Penn IRB requires researchers to submit reports of the following problems within 10 working days from the time the investigator becomes aware of the event:

- Any adverse event (regardless of whether the event is serious or non-serious, on-site or off-site) that occurs any time during or after the research study, which in the opinion of the principal investigator is:

  Unexpected (An event is "unexpected" when its specificity and severity are not accurately reflected in the protocol-related documents, such as the IRB-approved research protocol, any applicable investigator brochure, and the current IRB-approved informed consent document and other relevant sources of information, such as product labeling and package inserts.)

  AND

  Related to the research procedures (An event is "related to the research procedures" if in the opinion of the principal investigator or sponsor, the event was more likely than not to be caused by the research procedures.)

Reporting Process

Unanticipated problems posing risks to subjects or others as noted above will be reported to the Penn IRB using the form: "Unanticipated Problems Posing Risks to Subjects or Others Including Reportable Adverse Events" or as a written report of the event (including a description of the event with information regarding its fulfillment of the above criteria, follow-up/resolution and need for revision to consent form and/or other study documentation).

Copies of each report and documentation of IRB notification and receipt will be kept in the Clinical Investigator's study file.

Other Reportable Events:

For clinical drug trials, the following events are also reportable to the Penn IRB:

- Any adverse experience that, even without detailed analysis, represents a serious unexpected adverse event that is rare in the absence of drug exposure (such as agranulocytosis, hepatic necrosis, Stevens-Johnson syndrome).

- Any adverse event that would cause the sponsor to modify the investigators brochure, protocol or informed consent form, or would prompt other action by the IRB to assure protection of human subjects.
- Information that indicates a change to the risks or potential benefits of the research, in terms of severity or frequency. For example:
  - An interim analysis indicates that participants have a lower rate of response to treatment than initially expected.
  - Safety monitoring indicates that a particular side effect is more severe, or more frequent than initially expected.
  - A paper is published from another study that shows that an arm of your research study is of no therapeutic value.
- Change in FDA safety labeling or withdrawal from marketing of a drug, device, or biologic used in a research protocol.
- Breach of confidentiality
- Change to the protocol taken without prior IRB review to eliminate apparent immediate hazard to a research participant.
- Incarceration of a participant when the research was not previously approved under Subpart C and the investigator believes it is in the best interest of the subject to remain on the study.
- Complaint of a participant when the complaint indicates unexpected risks or the complaint cannot be resolved by the research team.
- Protocol violation (meaning an accidental or unintentional deviation from the IRB approved protocol) that in the opinion of the investigator placed one or more participants at increased risk, or affects the rights or welfare of subjects.

Abramson Cancer Center Data Safety Monitoring Committee (DSMC):

Every effort should be made to report an event as a diagnosis, not as a list of symptoms. Symptoms that led to the diagnosis should be included in the event description, but should not be the actual event.

1. Unless covered by exclusions below, Grade 3 or higher events must be reported within 10 days of knowledge.
2. All unexpected deaths within one business day of knowledge.
3. All others deaths within 30 days of knowledge. Deaths of subjects off-study for greater than 30 days from the last study treatment/intervention are not reportable unless a longer time frame is specified in the protocol.

EXCEPTIONS to AE/SAE Reporting:

A) Grade 3 or 4 events that are judged by a study investigator to be clearly unrelated to protocol therapy.
The reason for determining that the event is unrelated must be clearly documented in the EMR.

B) Grade 3 or 4 events that are probably or definitely related to progression of disease as judged by a study investigator. The fact that this event is related to disease progression must be clearly document in the EMR.

C) Grade 3 or 4 events that are probably or definitely related to an FDA approved agent. The fact that this event is related to the FDA approved agent must be clearly documented in the EMR..

SAEs will be submitted to the DSMC through the Velos Clinical Trial Management System.

Reportable Events:

Exception

A one time, intentional action (planned prospectively) or process that departs from the IRB and CTSRMC approved study protocol, intended for one occurrence. Advance documented IRB and DSMC approval is required.

For in-house studies with a Medical Director or Safety Monitoring Committee (not DSMB), approval must be obtained from the Medical Director or Safety Monitoring Committee prior to submitting your exception request to the DSMC.
The following information must be contained in your exception request:

- When it is needed and why it is needed in that timeframe
- Has the Medical Monitor or Sponsor approved and provide the documentation of approval
- Is this an exception from eligibility, treatment, disease progression, study calendar windows, etc.
- Why the exception is needed (cite the section(s) of the protocol) along with the full clinical details of the subject. This must be determined by the sub-Investigator or PI.
- The reason why the protocol currently doesn't allow the situation for which an exception is being requested. This must be determined by the sub-Investigator or PI.
- If there are plans to amend the protocol and if not, why not.
- If additional follow-up or interventions will be required in order to protect the subject as a result of this exception.

Study Exceptions the DSMC may Reject:

Exceptions to eligibility, treatment/dosing, contraindicated treatment/therapies/interventions or safety tests for the following types of studies may be rejected by the DSMC:

1. Any investigator-initiated treatment study.
2. Any treatment study involving on-campus manufacturing of any component, regardless of sponsor.

To seek approval, you must provide the DSMC with strong and compelling scientific and clinical information to support your request. You should also include a statement explaining whether or not the protocol will be amended. If the protocol will not be amended your reasoning must be provided. If this situation is likely to happen again, the DSMC will require a protocol amendment.

Deviation

Any unintentional action or process that departs from IRB approval and is identified retrospectively. The deviation is reportable to the DSMC and the IRB within 10 days from the time the event becomes known to the study team only when: one or more participants were placed at increased risk of harm, or, the event has the potential to occur again, or the event has the potential to qualify as serious or continuing noncompliance.

If the PI determines that a deviation has **any potential** to impact participant safety (harm and/or risk), or the integrity of data produced from the participant, or some other overall impact on the study, the PI must report the deviation to the IRB and DSMC as described above. The IRB will make the final assessment of the impact. The DSMC will assess for additional safety and scientific integrity concerns.

The following information must be contained in your deviation report:

- When it happened? When the study team (any member) became aware
- The full description of the deviation including important dates, test results, actions taken towards the subject, etc. Also, why it happened and how it was identified.
- Was the Medical Monitor or Sponsor notified. If so, their response?
- The PIs assessment of the impact on risk, safety and/or outcome. If no impact, why. If impact, what and what will happen next.

- The corrective actions that have been implemented to date and the impact of those corrective action plans.
- Future corrective action plans (if applicable) and the impact of those plans.
- If there are plans to amend the protocol (if applicable to prevent future deviations) and if not, why not.

If the PI determines that the event had **no potential** to impact participant safety (harm and/or risk) or the integrity of data produced from the participant, the PI must fully document his/her rationale for each category (risk, harm, and participant data).

9.13 Discontinuations

The reason for a subject discontinuing from the study will be recorded in the case report form. A discontinuation occurs when an enrolled subject ceases participation in the study, regardless of the circumstances, prior to completion of the protocol. The reasons a patient may discontinue or be withdrawn from the study include, but are not limited to, adverse events, disease progression, patient request, Investigator decision, protocol violation, patient noncompliance, and study termination by the Sponsor. The investigator must determine the primary reason for discontinuation. Withdrawal due to adverse event should be distinguished from withdrawal due to insufficient response according to the definition of adverse event noted earlier. A discontinuation must be reported immediately to the sponsor if it is due to a serious adverse event. The final evaluation required by the protocol will be performed at the time of study discontinuation. The investigator will record the reason for study discontinuation, provide or arrange for appropriate follow-up (if required) for such subjects, and document the course of the subject's condition.

9.14 Medical Monitor

It is the responsibility of the Sponsor Investigator to oversee the safety of the study at his/her site. This safety monitoring will include careful assessment and appropriate reporting of adverse events as noted above, as well as the construction and implementation of a site data and safety-monitoring plan (see section 11 Auditing, Monitoring and Inspecting). Medical monitoring will include a regular assessment of the number and type of serious adverse events. Medical monitoring by an independent clinician, Amy Clark, MD, Department of Medicine, Division of Hematology-Oncology will include a regular assessment of the number and type of serious adverse events on a periodic basis, as well as participate in decision-making regarding dose modifications, exemption and deviation requests and an ability to stop enrollment or the study for safety concerns. All SAEs will also be reviewed by Dr. Clark.

10 Study Administration, Data Handling and Record Keeping

10.1 Confidentiality

Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Those regulations require a signed subject authorization informing the subject of the following:

- What protected health information (PHI) will be collected from subjects in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research subject to revoke their authorization for use of their PHI.

In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (i.e. that the subject is alive) at the end of their scheduled study period.

10.2 Data Collection and Management

This study will use Velos as the data management system. The study case report form (CRF) is the primary data collection instrument for the study and will be electronically created and completed in Velos. CRFs will be provided for each patient. Subjects must not be identified by name on any CRFs. Subjects will be

identified by their patient identification number (PID). All data requested on the CRF must be recorded. All missing data must be explained. If a space on the CRF is left blank because the procedure was not done or the question was not asked, write “N/D”. If the item is not applicable to the individual case, write “N/A.”*.)*

10.3 Records Retention

It is the investigator’s responsibility to retain study essential documents for at least 2 years after the last approval of a marketing application in their country and until there are no pending or contemplated marketing applications in their country or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period if required by an agreement with the drug manufacturer. In such an instance, it is the responsibility of the drug manufacturer to inform the investigator/institution as to when these documents no longer need to be retained.

11 Study Monitoring, Auditing, and Inspecting

11.1 Study Monitoring Plan

This study will be monitored in accordance with the Cancer Center’s Clinical Trials Scientific Review and Monitoring Committee (CTSRMC) Plan, approved by NCI during the Core Grant’s most recent review. This plan requires that the investigator submit a study-specific plan outlining how data will be reviewed In addition, the CTSRMC plan calls for an internal audit by the Cancer Center’s Data Safety Committee twice yearly. The investigator will allocate adequate time for such monitoring activities. The Investigator will also ensure that the monitor or other compliance or quality assurance reviewer is given access to all the above noted study-related documents and study related facilities (e.g. pharmacy, diagnostic laboratory, etc.), and has adequate space to conduct the monitoring visit.

11.2 Auditing and Inspecting

The investigator will permit study-related monitoring, audits, and inspections by the IRB, government regulatory bodies, and University compliance and quality assurance groups of all study related documents (e.g. source documents, regulatory documents, data collection instruments, study data etc.). The investigator will ensure the capability for inspections of applicable study-related facilities (e.g. pharmacy, diagnostic laboratory, etc.).
Participation as an investigator in this study implies acceptance of potential inspection by government regulatory authorities and applicable University compliance and quality assurance offices.

12 Ethical Considerations

This study is to be conducted according to US and international standards of Good Clinical Practice (FDA Title 21 part 312 and International Conference on Harmonization guidelines), applicable government regulations and Institutional research policies and procedures.

This protocol and any amendments will be submitted to a properly constituted independent Institutional Review Board (IRB), in agreement with local legal prescriptions, for formal approval of the study conduct. The decision of the IRB concerning the conduct of the study will be made in writing to the investigator and a copy of this decision will be provided to Clovis Oncology before commencement of this study.

All subjects for this study will be provided a consent form describing this study and providing sufficient information for subjects to make an informed decision about their participation in this study. This consent form will be submitted with the protocol for review and approval by the IRB and CTSRMC for the study. The formal consent of a subject, using the IRB-approved consent form, must be obtained before that subject undergoes any study procedure. The consent form must be signed by the subject and the investigator-designated research professional obtaining the consent.

13 Study Finances

13.1 Funding Source

This clinical study, including correlative work will be supported by funds provided by Clovis Oncology.

If samples are sent to Clovis Oncology for analyses, Clovis Oncology agrees to cover the cost of these tests beyond the prior agreed upon budget.

13.2 Conflict of Interest

All University of Pennsylvania Investigators will follow the University of Pennsylvania Policy on Conflicts of Interest Related to Research.

14 Publication Plan

Neither the complete nor any part of the results of the study carried out under this protocol, nor any of the information provided by the sponsor for the purposes of performing the study, will be published or passed on to any third party without the consent of the study sponsor. Any investigator involved with this study is obligated to provide the sponsor with complete test results and all data derived from the study.

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16 Appendices

16.1 Appendix A

Eastern Cooperative Oncology Group (ECOG) Performance Status Scale

ECOG Performance Status	
0	Fully active, able to carry on all predisease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature (eg light house work or office work).
2	Ambulatory and capable of all self care but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	Capable only of limited self care; confined to bed or chair more than 50% of waking hours.
4	Completely disabled. Cannot carry on any self care. Totally confined to bed or chair.
5	Dead.

16.2 Appendix B

Response Evaluation Criteria in Solid Tumors Criteria

The RECIST guidelines (Version 1.1) are described in Eisenhauer (2009)[40] and at http://www.eortc.be/Recist/Default.htm. A short summary is given below.

Measurable Disease:
Tumor lesions: measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) with the following:

• A minimum size of 10 mm by CT scan (CT scan thickness no greater than 5 mm).
• A minimum size of 10 mm caliper measurement by clinical exam (lesions that cannot be accurately measured with calipers should be recorded as nonmeasurable).
• A minimum size of 20 mm by chest X-ray.

All tumor measurements must be recorded n 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 not greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

Nonmeasurable 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), as well as truly nonmeasurable lesions, are considered nonmeasurable disease. Lesions considered truly nonmeasurable include leptomeningeal disease, ascites, pleural/pericardial effusions, inflammatory breast disease, lymphangitic involvement of skin and lung, and abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques.

Bone Lesions
Bone lesions, cystic lesion, and lesions previously treated with local therapy require particular comment. Bone scan, PET scan, or plain films are not considered adequate imaging techniques to measure bone lesions. However, these techniques can be used to confirm the presence or disappearance of bone lesions.

Lytic bone lesions or mixed lytic–blastic lesions with identifiable soft tissue components that can be evaluated by cross-sectional imaging techniques such as CT or MRI can be considered as measurable lesions if the soft tissue component meets the definition of measurability described above.

Blastic bone lesions are nonmeasurable.

Cystic Lesions
Lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor nonmeasurable) because 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 noncystic lesions are present in the same patient, these are preferred as target lesions.

Lesions with Prior Local Treatment
Tumor lesions situated in a previous irradiated area or in an area subjected to other locoregional therapy are usually not considered measurable unless there has been demonstrated progression in the lesion.

Target Lesions
All measurable lesions up to a maximum of two lesions per organ and five 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) and their suitability for accurate repeated measurements (either by imaging techniques or clinically). A sum of the longest diameter (LD) for all target lesions will be calculated and reported as the baseline sum LD. The baseline sum LD will be used as reference by which to characterize the objective tumor response.

Nontarget Lesions
RECIST criteria require unequivocal quantification of the changes in tumor size for adequate interpretation of the sum of target lesions. Consequently, when the boundaries of the primary are difficult to delineate, this tumor should not be considered a target lesion.

Guidelines for Evaluation of Measurable Disease
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 when both methods have been used to assess the antitumor effect of a treatment.

Evaluation of Target Lesions

Complete Response	Disappearance of all target lesions. Any pathological lymph nodes (whether target or nontarget) must have reduction in short axis to <10mm
Partial Response	At least a 30% decrease in the sum of the LD of target lesions, taking as reference the baseline sum LD.
Stable Disease	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as a reference the smallest sum LD since the treatment started.
Progressive Disease	At least a 20% increase in the sum of all the LD 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 5mm. The appearance of one or more new lesions is also considered progression.

Evaluation of Nontarget Lesions

Complete Response	Disappearance of all nontarget lesions and normalization of tumor marker levels.
Stable Disease/Incomplete Response	Persistence of one or more nontarget lesion(s) or/and maintenance of tumor marker level above the normal limits.

Progressive Disease	Appearance of one or more lesions and/or unequivocal progression of existing nontarget lesions.

If tumor markers are initially above the institutional ULN, they must normalize for a patient to be considered to be a complete responder.

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 PD 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.

Evaluation of Best Overall Response			
Target Lesions	**Nontarget Lesions**	**New Lesions**	**Overall Response**
CR	CR	No	CR
CR	Non-CR/Non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not evaluated	No	PR
SD	Non-PD or not evaluated	No	SD
Not Evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD
NE = not evaluable			

Patients with global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be classified as having symptomatic deterioration. Every effort should be made to document the objective progression, even after discontinuation of treatment.

In some circumstances, it may be difficult to distinguish residual disease from normal tissue. When evaluation of CR depends on this determination, it is recommended that the residual lesion be investigated (fine needle aspiration/biopsy) prior to confirming the complete response status.

Confirmatory Measurement/Duration of Response

Confirmation
CT scans are required at screening and within 7 days prior to the start of every odd numbered cycle (i.e., Cycles 3, 5, 7, etc.). If an initial CR or PR is noted, confirmatory scans must be performed >4 weeks later.

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 PD is objectively documented (taking as reference for PD 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 recurrent disease is objectively documented.

Duration of Stable Disease

SD 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.