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Protocol Title

PARP Inhibition after Preoperative Chemotherapy in Patients with Triple Negative Breast Cancer or ER/PR +, HER2 negative with known BRCA1/2 Mutations:
Hoosier Oncology Group BRE09-146

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Trial Supported by

Clovis

Investigational New Drug (IND) Application

107321

Initial Protocol Version Date: 25SEP2009
Amendment # 1: Protocol version date: 21DEC2009
Amendment #2: Protocol version date: 16NOV2010
Amendment #3: Protocol version date: 17MAR2011
Amendment #4: Protocol version date: 19MAY2011
Amendment :5: Protocol version date: 27SEP2011

PROTOCOL SIGNATURE PAGE

PARP Inhibition after Preoperative Chemotherapy in Patients with Triple Negative Breast Cancer or ER/PR +, HER2 Negative with Known BRCA1/2 Mutations: Hoosier Oncology Group BRE09-146

VERSION DATE: 27SEP2011

I confirm I have read this protocol, I understand it, and I will work according to this protocol and to the ethical principles stated in the latest version of the Declaration of Helsinki, the applicable guidelines for good clinical practices, or the applicable laws and regulations of the country of the study site for which I am responsible, whichever provides the greater protection of the individual. I will accept the monitor's overseeing of the study. I will promptly submit the protocol to applicable ethical review board(s).

Instructions to the investigator: Please **SIGN** and **DATE** this signature page. **PRINT** your name and title, the name and location of the facility in which the study will be conducted, and the expected IRB approval date. Fax the completed form to the Hoosier Oncology Group at 317.921.2053 and keep a copy for your files.

_____ _____
Signature of Investigator Date

_____
Investigator Name (print or type)

_____
Investigator Title

_____
Name of Facility

_____
Location of Facility (City and State)

_____ ❑ Not Submitting to IRB
Expected IRB Approval Date

PLEASE COMPLETE AND FAX TO THE HOG OFFICE AT 317.921.2053

HOG Protocol: BRE09-146

<table>
<tr><td>TITLE</td><td>PARP Inhibition after Preoperative Chemotherapy in Patients with Triple Negative Breast Cancer or ER/PR +, HER2 negative with known BRCA1/2 Mutations: Hoosier Oncology Group</td></tr>
<tr><td>STUDY PHASE</td><td>II</td></tr>
<tr><td>OBJECTIVES</td><td>Primary Objective:
To evaluate 2-year disease-free survival (DFS), in patients with confirmed TNBC or ER/PR + HER2-, known BRCA1/2 mutations treated with single agent cisplatin and patients treated with cisplatin in combination with rucaparibfollowing preoperative chemotherapy
Secondary Objectives:
To characterize the side effects and tolerability of cisplatin and cisplatin plus rucaparib in patients with residual disease following preoperative chemotherapy.
To evaluate 1-year DFS
To determine 5-year overall survival
To collect limited pharmacokinetic data, in patients receiving study drug to compliment ongoing PK analyses in other trials with rucaparib
To collect archived tumor specimens, and genomic DNA to explore potential correlates of PARP inhibition, recurrence and toxicity. To compare limited PK parameters between the IV and oral formulation of rucaparib</td></tr>
<tr><td>STUDY DESIGN</td><td>Safety Run-in Cohorts
Drug interaction and increased toxicity is not anticipated, however there is no clinical experience with cisplatin + rucaparib. To exclude prohibitive toxicity, 6 patients will be treated with combined therapy as outlined in Table 1.
Table 1: Treatment plan for Safety Run-in Cohorts
<table>
<tr><th>Drug</th><th>Dose</th><th>Frequency of administration</th><th>Route of administration</th><th>Number of cycles</th></tr>
<tr><td>Rucaparib (administered as the phosphate salt</td><td><u>Cohort 1:</u>
16 mg C1*
24 mg C2-4

<u>Cohort 2:</u>
24 mg C1*
30 mg C2-4</td><td>D1,2,3 every 21 days</td><td>IV ** followed in one hour by Cisplatin</td><td>4</td></tr>
<tr><td>Cisplatin</td><td>75 mg/m^2</td><td>D1 every 21 days</td><td>IV infusion per institutional guidelines</td><td>4</td></tr>
</table>
*NOTE: rucaparib dose should be increased to 24 mg for cohort 1 or 30 mg for cohort 2 during cycles 2-4 in the absence of dose limiting toxicity (as defined in Table 2) in cycle 1.

**NOTE:
16 mg dose: ~32 minute infusion time, ~117 mL infusion volume
24 mg dose: ~33 minute infusion time, ~120 mL infusion volume
30 mg dose: ~34 minute infusion time, ~124 mL infusion volume</td></tr>
</table>

Volume calculated using an assumed standard overfill of 9 mL in a 100 mL commercial bag of D5W plus the required volume of reconstituted drug product for a specific dose.

Randomization Portion of Study:
During the randomized portion of the study, patients will be randomized to either Arm A or Arm B.

Arm A (cisplatin monotherapy)
Table 3: Treatment Plan – Arm A

Drug	Dose	Frequency of administration	Route of administration	Number of cycles
Cisplatin	75 mg/m^2	D1 every 21 days	IV infusion per institutional guidelines	4

Arm B (combination therapy)

Table 4: Treatment plan - Arm B

Drug	Dose	Frequency of administration	Route of administration	Number of cycles
Rucaparib	24 mg C1* 30 mg C2-4	D1,2,3 every 21 days	IV ** followed in one hour by Cisplatin	4
Cisplatin	75 mg/m^2	D1 every 21 days	IV infusion per institutional guidelines	4

***NOTE:** Rucaparib dose should be increased to 30 mg for cycles 2-4 in the absence of dose limiting toxicity (as defined in Table 2) in cycle 1
****NOTE**: **24 mg dose**: ~ 33 minute infusion time, ~120 mL infusion volume*
30 mg dose: ~34 minute infusion time, ~124 mL infusion volume*
*Volume calculated using an assumed standard overfill of 9 mL in a 100 mL commercial bag of D5W plus the required volume of reconstituted drug product for a specific dose.

Rucaparib maintenance therapy for Safety Run-in and Arm B

Table 5: Treatment plan – IV Maintenance therapy
NOTE: All patients should proceed with oral rucaparib maintenance therapy after approval of Amendment #5 and when oral drug available.

Drug	Dose	Frequency of administration	Route of administration	Number of weeks
Rucaparib	30 mg	Weekly	IV **	24

****NOTE**:
30 mg dose: ~34 minute infusion time, ~124 mL infusion volume
Volume calculated using an assumed standard overfill of 9 mL in a 100 mL commercial bag of D5W plus the required volume of reconstituted drug product for a specific dose.

Table 6: Treatment plan – Oral maintenance therapy

Drug	Dose	Frequency of administration	Route of administration	Number of weeks
Rucaparib (administered as the camsylate salt)	100 mg total (1-60 mg tab + 1-40 mg tab)	Weekly	Oral	24

NUMBER OF PATIENTS

Total number of patients = 135

ELIGIBILITY

- Written informed consent and HIPAA authorization for release of personal health information.
  NOTE: HIPAA authorization may be included in the informed consent or obtained separately.
- Age ≥ 18 years at the time of consent.
- ECOG Performance Status 0 or 1 within 30 days prior to registration for protocol therapy.
- Women of childbearing potential and males must be willing to use an effective method of contraception from the time consent is signed until 4 weeks after treatment discontinuation.
- Women of childbearing potential must have a negative pregnancy test within 14 days prior to registration for protocol therapy.
  NOTE: Women are considered not of child bearing potential if they are surgically sterile (they have undergone a hysterectomy, bilateral tubal ligation, or bilateral oophorectomy) or they are postmenopausal.
- Women must not be breastfeeding.
- Must have histologically or cytologically confirmed triple negative (ER-/PR-/HER2-) invasive breast cancer, stage I-III at diagnosis (AJCC 6th edition) based on initial evaluation by clinical examination and/or breast imaging.
  NOTE: ER- and PR- should meet one of the following criteria:
  - Local Pathology report classifies them as negative
  - Allred Score of 2 or below
  - <5% weakly positive staining

  Patients with ER+ and/or PR+ may enroll ONLY if they are known carriers of a deleterious mutation in BRCA1 or BRCA2. Patients with HER2+ tumors may not enroll regardless of BRCA status.
- Must have completed preoperative (neoadjuvant) chemotherapy.
  NOTE: Acceptable preoperative regimens include an anthracycline or a taxane, or both. Patients may NOT have received cisplatin as part of their neoadjuvant therapy regimen. Patients who received preoperative therapy as part of a clinical trial may enroll. No adjuvant chemotherapy after surgery other than that specified in this protocol is allowed. Adjuvant bisphosphonate use is allowed.
- Must have completed definitive resection of primary tumor. The last surgery for breast

cancer must have been completed at least 14 daysprior to registration for protocol therapy.
NOTE: Negative margins for both invasive and ductal carcinoma *in situ* (DCIS) are desirable, however patients with positive margins may enroll if the treatment team believes no further surgery is possible and patient has received radiotherapy. Patients with margins positive for lobular carcinoma *in situ* (LCIS) are eligible. Either mastectomy or breast conserving surgery (including lumpectomy or partial mastectomy) is acceptable. Sentinel node biopsy is allowed but axillary dissection is strongly encouraged in patients with lymph node involvement.

- Must have significant residual invasive disease at the time of definitive surgery following preoperative chemotherapy. Significant residual disease is defined *at least one of the following:*
  - Miller-Payne response in the breast of 0-2[5]. (Please refer to Study Procedure Manual[SPM])
  - Residual Cancer Burden (RBC) classification II or III[6]
  - Residual carcinoma in one or more regional lymph nodes that would meet AJCC 6th edition criteria for N1 - N3 disease.
  - Alternatively, if Miller-Payne or RCB grading is not available, the patient will be eligible if the pathology report indicates that the area of residual invasive disease in the breast measures at least 2 cm following preoperative therapy. The presence of DCIS without invasion does not qualify as residual disease in the breast.
- Whole breast radiotherapy is required for patients who underwent breast conserving therapy, including lumpectomy or partial mastectomy. Patients receiving adjuvant radiation therapy must have completed radiotherapy at least 14 days prior to registration for protocol therapy.
  NOTE: Post-mastectomy radiotherapy is required for all patients with a primary tumor $\geq$ 5 cm or involvement of 4 or more lymph nodes. For patients with primary tumors < 5 cm or with < 4 involved lymph nodes, provision of post-mastectomy radiotherapy is at the discretion of the treating physician.
- Patients must enroll within 84 days of surgery (for those patients who do not require radiation) or within 84 days of completion of radiation when radiation is required
- No stage IV (metastatic) disease, however no specific staging studies are required in the absence of symptoms or physical exam findings that would suggest distant disease.
- No treatment with any investigational agent within 30 days prior to registration for protocol therapy.
- No history of chronic hepatitis B or C

Laboratory values must be obtained within 14 days prior to registration for protocol therapy.

- Hemoglobin (Hgb) $\geq$ 9.0 g/dL
- Platelets $\geq$ 100 K/ mm^3
- Absolute neutrophil count (ANC) $\geq$ 1.5 K/mm^3
- Calculated creatinine clearance of $\geq$ 50 cc/min using the Cockcroft-Gault formula:

  - Males: $\frac{(140 - \text{Age in years}) \times \text{Actual Body Weight in kg}}{72 \times \text{Serum Creatinine (mg/dL)}}$

- Females: Estimated creatinine clearance for males × 0.85
- Bilirubin $\leq$ upper limit of normal (except in patients with documented Gilbert's disease,

	who must have a total bilirubin ≤ 3.0 mg/dL) • Aspartate aminotransferase (AST, SGOT) ≤ 2.5 × ULN • Alanine aminotransferase (ALT, SGPT) ≤ 2.5 × ULN • Left ventricular ejection fraction within normal limits obtained within 30 days prior to registration for protocol therapy. **NOTE:** Patients with an unstable angina or myocardial infarction within 12 months of study entry are excluded. • No clinically significant infections as judged by the treating investigator. • Must consent to allow submission of archived tumor tissue sample from definitive surgery. • Must consent to collection of blood samples for PK analysis. • No clinically significant arrhythmia or baseline ECG abnormalities in the opinion of the treating investigator.
STATISTICAL CONSIDERATIONS	**Sample Size Justification** The primary endpoint for this trial is 2 year DFS. In order to detect an improvement of the fraction of patients free from disease at 2-year from 40% in the control arm to 63.2% in the rucaparib arm (corresponding to an HR=0.5), 38 events are needed to have 80% power to detect a difference in DFS using a one-side log-rank test with 0.10 level of significance (calculation done using nQuery Advisor 7.0 and assuming exponential survival). In order to observe 38 events we need to accrue about 102 patients, with an accrual time of about 13-18 months and an overall study duration around 25-30 months. In addition, 6 patients will be needed at the lower dose (cohort 1). Assuming ~20% will not be confirmed to have TNBC on central review; the total sample size will be increased to 128 to ensure 102 in the primary analysis (using cohort 2 and the randomized patients) and 6 in the safety analysis for cohort 1. **Patient Characteristics** Patient characteristics will be summarized by treatment group for demographics, baseline disease characteristics, and medical history. The two treatment groups will be compared using standard methods such as t-tests and chi-square tests. **Interim Safety Analyses** The first 12 patients (6 in cohort 1 and 6 in cohort 2) will be assigned to the PF-01367338 arm for an initial safety run-in. A safety analysis will be done after all six patients in each cohort have completed cycle 2. All toxicities will be tabulated. The study will move forward to cohort 2 if ≤ 1 of 6 in cohort 1 experience a DLT (as defined in Section 5.1). If ≥ 2 of 6 in cohort 1 experience a DLT, the study will be suspended and an amendment to explore alternate dosing schemes will be considered. Similarly, if ≤ 1 of 6 in cohort 2 experience a DLT (as defined in Section 5.1), the randomized portion will commence. If ≥ 2 of 6 in cohort 2 experience a DLT, the study will be suspended and an amendment to proceed with the randomized portion with the cohort 1 dose will be considered. Once the decision is made to move forward with the randomized portion a second safety analysis will be conducted after the first 40 patients (~20 from each group) have been randomized and completed 2 cycles of treatment. Toxicity counts and rates will be tabulated by treatment arm in a blinded fashion. The study will be terminated if the probability that the DLT rate equals 20% or less in either arm drops below .10. Accrual will continue during the interim analysis. The results of the analysis will be submitted to the CTMC for external review. **Analysis of Primary Objective** The comparison of DFS between the two groups will be made using an unstratified Kaplan-Meier analysis with a log-rank test to test for differences using the patients in safety run-in cohort 2 and the randomized portion of the study. A specific comparison of 2-year DFS will be

	made using a two-sample test based on the complementary log-log transformation as suggested in Klein, et al[32]. As supportive analysis, a stratified log-rank test will be done using the stratified randomization factors neoadjuvant anthracycline versus not and lymph node involvement at time of definitive surgery versus not. In addition, sensitivity analyses using Cox regression may be carried out to identify prognostic factors and provide adjusted estimates of the treatment group differences in DFS. **Analysis of Secondary Objectives** As support for the primary objective, overall DFS and 2-year DFS will be compared using the same techniques above using only the subjects in the randomized part of the study. One-year DFS will be tested using the test described above for 2-year DFS. Safety and tolerability variables will be tabulated separately for the two groups. Incidences of selected adverse events from the two treatment arms may be compared using Fisher's Exact tests on an exploratory basis. OS will be compared between treatment groups using the same methodology as DFS. PK levels will be described using summary statistics. In addition characteristics of tumor specimens and genomic DNA will be correlated with PARP inhibition, recurrence and toxicity. Continuous measures will be correlated with binary variables (e.g. recurrence and toxicity) using maximal chi-square tests and continuous variables (e.g. PARP inhibition) using Pearson or Spearman correlations. Binary variables such as tumor and genomic characteristics will be correlated recurrence and toxicity using chi-square or Fisher's Exact test. All of the analyses with the PK and correlative data are exploratory and are designed to complement efforts in other trials with this agent.

PARP Inhibition after Preoperative Chemotherapy in Patients with Triple Negative Breast Cancer (TNBC) or ER/PR + and HER2 negative with known BRCA1/2 Mutations: Hoosier Oncology Group BRE09-146

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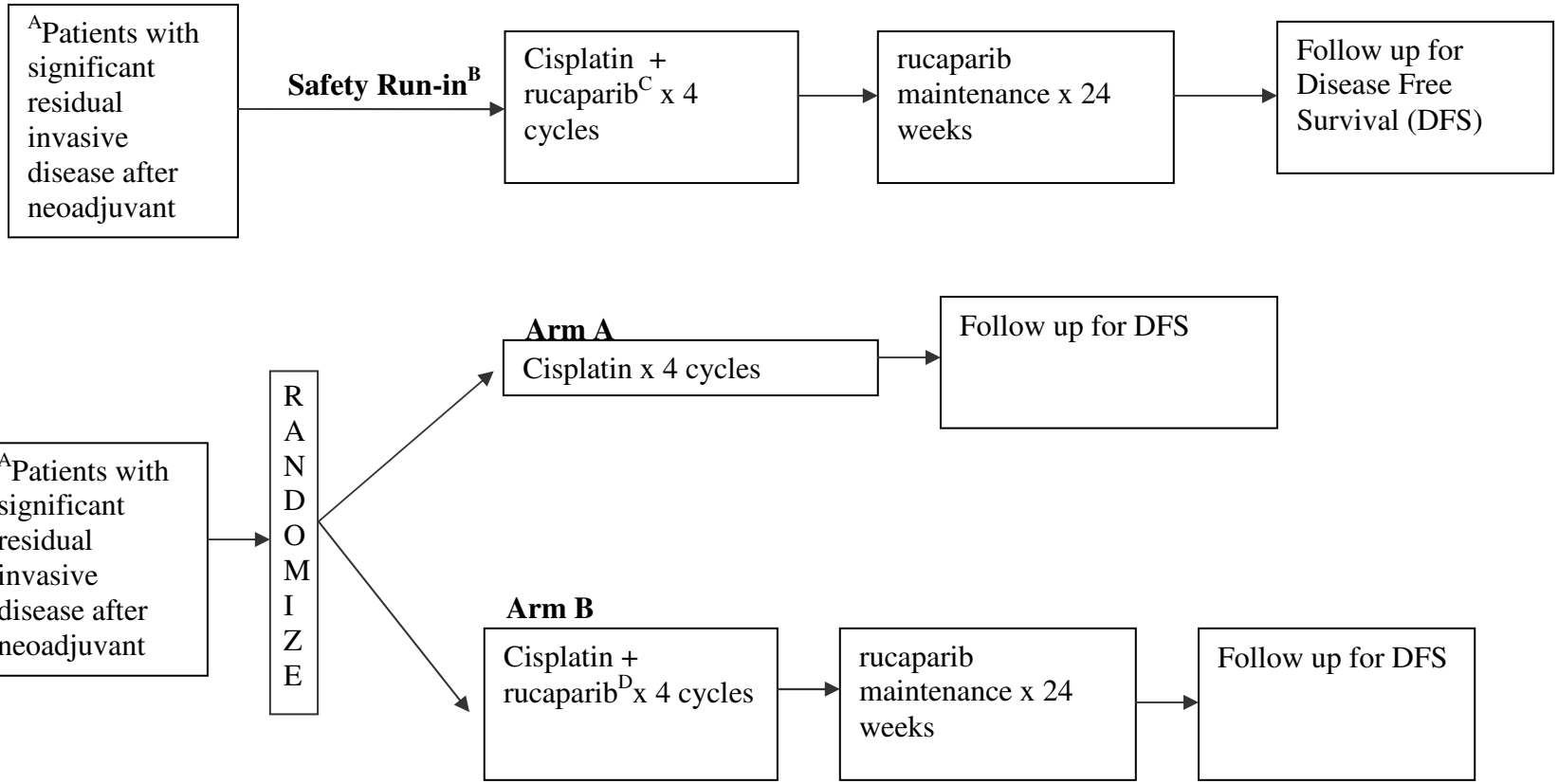
SCHEMA

PARP Inhibition after Preoperative Chemotherapy in Patients with Triple Negative Breast Cancer (TNBC) or ER/PR+, HER2 negative with Known BRCA1/2 Mutations: Hoosier Oncology Group BRE09-146



[A]Patients must have triple negative (ER-/PR-/HER2-) breast cancer or if ER/PR + must have a known mutation of BRCA1 or BRCA2. Patients with HER2+ disease are excluded regardless of BRCA mutation status.

[B] Safety Run-in will be for the first 12 patients on study only (6 in cohort 1 and 6 in cohort 2). Patients in the safety run will be included in the efficacy analysis on intent to treat basis

[C]If cycle 1 is well tolerated; the dose of rucaparib will be escalated from 16 mg to 24 mg for subsequent cycles in the cohort 1, and 24 mg to 30 mg in the cohort 2

Arm A

Cisplatin 75 mg/m^2 IV D1 every 3 weeks x 4 cycles**Safety Run-in and Arm B**

Cisplatin 75 mg/m^2 IV D1 every 3 weeks x 4 cycles rucaparib 16-30 mg IV D 1,2,3 every 3 weeks x 4 cycles

Rucaparib maintenance 30 mg IV weekly OR 100 mg orally once weekly x 24 week's total

[D] Rucaparib will be escalated from 24mg to 30mg during the treatment phase of the study.

1.0 BACKGROUND & RATIONALE

1.1 Primary (neoadjuvant) Chemotherapy for Breast Cancer

Neoadjuvant chemotherapy has a well-established role in the management of both early-stage and locally advanced breast cancer. Providing treatment prior to definitive surgery not only improves the ability to achieve breast conservation, but also allows determination of *in vivo* sensitivity to therapy and offers an ideal platform for clinical research. Although many will experience shrinkage in tumor volume with neoadjuvant therapy, at the time of surgery only about 15-25% of patients will experience a pathologic complete response (pCR) with complete lack of invasive tumor tissue in the surgical specimen. Long-term follow-up of neoadjuvant studies consistently demonstrates significantly improved survival in individuals with pCR, with comparatively inferior outcomes in those with residual disease at surgery[1-3]. The impact of residual disease is more striking in patients with triple negative (ER-/PR-/HER2-) disease compared to patients with other molecular phenotypes[4]. Unfortunately, patients with triple negative disease who have *substantial*(Miller-Payne classification[5] 1 or 2 or residual cancer burden classification II or III[6]) residual disease at the time of surgery have a dismal prognosis with only 35-40% remaining free of recurrence at 2 years.[7] In short, the presence of viable invasive tumor after appropriate neoadjuvant chemotherapy reflects inherent resistance and portends an exceedingly high risk of subsequent recurrence. No standard therapy exists in this clinical setting.

1.2 Associations between Triple Negative Breast Cancer, BRCA Mutation Status, and DNA damaging chemotherapy

Recent studies illustrate the aggressive nature of triple negative breast cancer (TNBC), a subtype of breast cancer that is clinically negative for the expression of the estrogen and progesterone receptors (ER and PR) and the Her2 protein [8-10]. The associations between basal-like breast cancer (BBC), TNBC and BRCA pathway dysfunction have apparent therapeutic implications. Although important to clarify that the terms "triple negative (TN)" and "basal-like" are not entirely synonymous, the clinico-pathologic TN (ER/PR/Her2 negative) phenotype is classified as basal-like via cDNA microarray 80-90% of the time[11-14]. In addition, TNBC expresses a high proportion of "basal-like" cytokeratins (CK) 1, 10, 13, as well as p-cadherin and Her1/epithelial growth factor receptor (EGFR)[15-19]. As a clinically-applicable test for the basal molecular classification has yet to be developed, the triple negative phenotype is a reasonable surrogate for the basal-like subtype -- a subtype of breast cancer commonly seen among *BRCA1* mutation carriers[20]. Moreover, a recent study of over 400 women reports TNBC among two-thirds of patients who carried a *BRCA1* mutation[21]. The tight association between *BRCA1* mutations, BBC and TNBC has raised the question as to whether *BRCA1* loss of function through other mechanisms participates in the pathogenesis of sporadic basal-like and TNBC – an association which could be exploited therapeutically. Pre-clinically tumors that harbor BRCA mutations are more sensitive to DNA damaging chemotherapy agents such as cisplatin. Two recent clinical trials reported high pCR rates with cisplatin monotherapy regimens in patients with known BRCA mutations (72% in Gronwald et al, ASCO 2009, #502) or cisplatin in combination with bevacizumab in those with TNBC regardless of mutation status (36% in Ryan et al, ASCO 2009 #551). This pre-clinical and emerging clinical data supports the use of cisplatin in patients with TNBC who harbor substantial residual disease after standard neoadjuvant therapy.

1.3 PARP Inhibition

PARP is an abundant, constitutively-expressed nuclear enzyme that catalyzes the transfer of ADP-ribose polymers from NAD+ to target proteins, through which it facilitates DNA repair, cellular proliferation, and signaling to other critical cell cycle proteins and oncogenes[8-22-27]. At sites of DNA damage, PARP activates intracellular signaling pathways that modulate DNA repair and cell survival through poly (ADP-ribosyl)ation of a number of nuclear proteins involved in the chromatin architecture and DNA metabolism. Immediate catalytic activation of PARP in response to DNA single- and double-strand breaks has been reported at levels up to 500-fold[26,28].

BRCA1 and *BRCA2* genes encode for proteins critical for DNA integrity and genomic stability[29-31]. BRCA1 and BRCA2 are tumor-suppressor proteins essential for cell division, DNA error control, DNA repair and apoptosis. In 2005 Bryant[32] and Farmer[33] showed that BRCA-deficient cells were extremely sensitive to PARP inhibition. Single agent PARP inhibitors led to impaired SSB repair causing double strand breaks (DSBs) in replicative cells. In BRCA wild type cells DSBs are repaired via homologous recombination (HR), but in BRCA "altered" cells HR is impaired and alternative pathways lead to complex rearrangements, loss of repair mechanisms and cell death ("synthetic lethality")[34]. Significant single agent activity was recently reported with the PARP inhibitor olaparib in patients with previously treated BRCA-deficient metastatic breast cancer. Overall responses ranged from 22% (100 mg bid) to 41% (400 mg bid) with minimal toxicity[35]

Importantly, due to molecular and pathologic similarities between TNBC and BRCA-associated breast cancers[36,37], whose homologous recombination-dependent DNA repair is impaired, pharmacological inhibition of PARP is predicted to specifically and irreversibly augment the existing instability of these tumors.

In summary, there are at least three roles of PARP inhibitors in cancer treatment: chemotherapy and radiotherapy sensitization, synthetic lethality in patients with hereditary mutations in BRCA1/2 genes (inherited defect in homologous recombination), and finally leveraging of "BRCA-like" defects tumors with spontaneous defects in DNA repair such as triple negative breast cancer.

1.4 Rucaparib

Rucaparib (also known as CO-338, formerly known as AG-14699 and/or PF-01367338) is a small molecule inhibitor of PARP being developed for cancer indications, to be used in conjunction with temozolomide, irinotecan, and other chemotherapeutic agents where PARP-related DNA repair may impede their maximum therapeutic effect. In addition, rucaparib is being investigated as a single agent in BRCA1 and BRCA2 patients with advanced/pretreated breast or ovarian neoplasia.

Results of studies with animal models suggest that rucaparib exposures that inhibit PARP will be associated with enhanced antitumor activity of temozolomide and other chemotherapeutic agents. Hence, the clinical program assessed bioactivity and safety in patients with malignancies, commonly treated with the selected chemotherapeutic agents. Based on the in vitro IC90 against the target, adjusted for protein binding, a sustained

plasma concentration of >5.9 ng/mL was projected to be needed in humans to inhibit PARP and enhance antitumor activity of chemotherapeutic agents. This target was reached at the 2 highest rucaparib doses (8 and 12 mg/m^2) in Part 1 of the Phase 1 study A4991002. Among the 3 patients who received the PID of 12 mg/m^2, concentrations of 10.6, 10.6, and 46.5 ng/mL, respectively, were observed 24 hours after rucaparib infusion on Day 1.

Non-clinical evaluation has demonstrated exquisite sensitivity of BRCA1 or BRCA2 homozygous cell lines, which is attributed to PARP inhibition alone, and provides a rationale for the clinical assessment of rucaparib as a single agent in patients with BRCA1 and BRCA2 deficient tumors.

Following administration of an IV dose of [14C]-labeled drug to intact rats, mean urine, and fecal recoveries were 33% and 61%, respectively, with a mean cumulative recovery of 95% of dose. Mean recovery of radioactivity in urine, bile, and feces from bile duct-cannulated rats was 49%, 31%, and 17%, respectively, with a mean cumulative recovery of 98%. Careful dose titration should be used in subjects with impaired renal and/or hepatic function. Following a single IV dose in rodents, dogs, or monkeys, mean systemic clearance was moderate to rapid, the apparent volume of distribution was large, and the terminal half-life was relatively short (t1/2: 2.8 hours in rats, 4.5 hours in dogs, 5.2 hours in monkeys).

Nonclinical safety studies performed to date have identified the target organs for rucaparib to be the bone marrow, lymphoid organs (eg, thymus, lymph nodes), and heart, with emesis being dose-limiting in the dog. At doses tested above the NOAEL in rats and dogs, cardiac effects (structural and functional) were observed in addition to potential QT liability detected in vitro by positive findings in the hERG - IKr assay. At the high-dose (40 mg/kg/day) in dogs, histopathologic findings in the heart were limited to endocardial hemorrhage, ECG abnormalities (persistent sinus tachycardia, atrioventricular nodal rhythm), and sudden death (2 of 12 dogs) were also noted at this rucaparib dose. The cardiac effects in the acute and multidose studies were observed at concentrations significantly higher than those predicted to inhibit PARP in humans. Peak human exposure at the projected efficacious dose of 20 mg/m^2 is estimated to be 89 ng/mL, which is 25-fold and 176-fold lower than the observed exposures associated with cardiovascular toxicity in rats and dogs, respectively.

Based on nonclinical cardiac findings, collection of ECGs was required in Phase 1 study A4991002 during the screening period; before and after rucaparib infusion on Days -7, 1, and 4 of the first cycle; before the first AG-014699 infusion of every other cycle thereafter; and at the post treatment follow-up visit. All patients completed at least 1 ECG during screening and 1 ECG after infusion. Four patients had at least 1 abnormal ECG after treatment. Two of the patients also had abnormal ECGs at screening. T inversion was observed in 1 patient in Cohort 3 before receiving cycle 3. There were no changes to suggest myocardial infarction and the ECG change was not believed by the investigator to be related to study drug. Subsequent ECGs were normal. Another patient, who was enrolled in Cohort 4, had an abnormal ECG on Day 4 of the first cycle. The patient entered the study with a normal, but flattened T-wave, which became inverted on Day 4. Follow-up ECGs were normal and the finding was not believed to be clinically

significant. Based on this experience, further ECG monitoring in subsequent trials was not recommended

Complete information on the preclinical pharmacokinetics and drug metabolism rucaparib may be found in the current Investigators' Brochure.

1.5 Rucaparib + Chemotherapy

In vitro studies in human tumor cells lines of rucaparib and similar compounds have shown that the combination of the PARP inhibitor with ionizing radiation, temozolomide, the topoisomerase I inhibitor camptothecin, and bleomycin increased the cytotoxicity of the DNA damaging agent. In the Phase 1 clinical study A4991002, 32 patients received at least 1 dose of rucaparib together with temozolomide. There were no deaths related to rucaparib. Two (6%) patients had nonfatal SAEs that were considered related to rucaparib. Many of the other events were related to the co-administered temozolomide and consistent with the known safety profile of temozolomide.

In the Phase 2 clinical study A4991005 of rucaparib and temozolomide forty-six patients were assigned to treatment and received at least 1 cycle of rucaparib (administered intravenously at a dose of 12 mg/m^2/day from Day 1 to 5 every 4 weeks) and Temozolomide (administered orally at a dose of 200 mg/m^2/day from Day 1 to 5 every 4 weeks). Eleven patients completed the study and 35 were discontinued early. All patients experienced treatment-related adverse events. The majority of CTC Grade 3 or 4 adverse events were myelotoxicities and occurred in cycle 1. The incidence of haematological toxicities appeared to be controlled by reducing the dose of temozolomide.

An ongoing phase I study is evaluating the safety, pharmacokinetic and pharmacodynamic of rucaparib administered with full combination doses of carboplatin, paclitaxel, cisplatin and pemetrexed.

1.6 Rucaparib (CO-338/AG-014699/PF-01367388) Starting Dose Rationale

In the Phase 1 clinical study A4991002 the rucaparib Recommended Phase 2 Dose (RP2D) has been determined to be 12 mg/m^2/day for 5 days every 28 day cycle with full dose of Temozolomide.

Moreover from a pharmacokinetic point of view, whether a drug should be administered on a fixed dose or Body Surface Area (BSA) normalized dose depends on whether the pharmacokinetics of the drug changes with BSA. The effect of BSA on systemic exposure of rucaparib (AUC 0-24) was evaluated for this purpose. It is observed that the AUC 0-24 normalized for actual dose and the AUC (0-24) normalized for mg/m2 dose do not correlate with BSA. Furthermore, inter-subject variability is similar for actual dose normalized AUC (0-24) (53.9%) and mg/m^2 dose normalized AUC (0-24) (54.1%). This suggests that rucaparib can be given either as a fixed dose or on a mg/m^2 based dose.

The starting dose for rucaparib in the current study will be the fixed dose of 16 mg/day, lower than the 24 mg/day that would correspond to the "per square meter" RP2D of 12 mg/m^2/day determined in study A4991002. A single dose escalation to 30 mg/day will be allowed in patients without significant toxicity in cycle 1. In addition, as the

chemotherapy regimen being studied will be administered on a 3-week basis, the rucaparib schedule has been modified accordingly. rucaparib will thus be administered from Day 1 to Day 3 every 21 days. A similar dosing strategy has been employed in the planned/ongoing phase I trial evaluating rucaparib in combination with multiple chemotherapy regimens.

Complete information for rucaparib may be found in the current Investigator's Brochure.

1.7 Rucaparib (CO-338/AG-014699/PF-01367338) Oral Formulation

The oral formulation of rucaparib contains the camsylate salt of the active agent rucaparib. All dosage strengths are express as the weight of free base rucaparib. Two strengths of oral rucaparib, 40 mg and 60 mg, are available as immediate release film coated tablets. The physical appearances of the tablets are unique in order to ensure proper identification. 40 mg rucaparib tablets are 9.5 mm round convex in shape, while 60 mg tablets are 15.4 mm x 8 mm oval in shape. In addition to active agent, tablets contain microcrystalline cellulose, sodium starch glycolate, dicalcium phosphate, and magnesium stearate. The cosmetic white film coating is Opadry II containing HPMC 2910, hypromellose 6cP, macrogol/PEG3350, triacetin, titanium dioxide, and lactose monohydrate.

In the on-going Phase I study of rucaparib in combination with chemotherapy, administration of the oral formulation is associated with average bioavailability is 30-40%, thus 100 mg is the estimated bioequivalent dose for the 30mg IV dose. Use of the oral dose during maintenance therapy will increase patient convenience and decrease the risk of infusion and/or access device related complications.

2.0 OBJECTIVES

2.1 Primary Objective:

- To evaluate 2-year disease-free survival (DFS), in patients with confirmed TNBC or ER/PR + HER2-, known BRCA1/2 mutations treated with single agent cisplatin and patients treated with cisplatin in combination with rucaparib following preoperative chemotherapy

2.2 Secondary Objectives:

- To characterize the side effects and tolerability of cisplatin and cisplatin plus rucaparib in patients with residual disease following preoperative chemotherapy.
- To evaluate 1-year DFS.
- To determine 5-year overall survival.
- To collect limited pharmacokinetic data, in patients receiving study drug to compliment ongoing PK analyses in other trials with rucaparib.
- To collect archived tumor specimens and genomic DNA to explore potential correlates of PARP inhibition, recurrence and toxicity.
- To compare limited PK parameters between the IV and oral formulation of rucaparib

3.0 ELIGIBILITY CRITERIA

3.1 Written informed consent and HIPAA authorization for release of personal health information.
NOTE: HIPAA authorization may be included in the informed consent or obtained separately.

3.2 Age $\geq$ 18 years at the time of consent.

3.3 ECOG Performance Status 0 or 1 within 30 days prior to registration for protocol therapy.

3.4 Women of childbearing potential and males must be willing to use an effective method of contraception from the time consent is signed until 4 weeks after treatment discontinuation.

3.5 Women of childbearing potential must have a negative pregnancy test within 14 days prior to registration for protocol therapy.
NOTE: Women are considered not of child bearing potential if they are surgically sterile (they have undergone a hysterectomy, bilateral tubal ligation, or bilateral oophorectomy) or they are postmenopausal.

3.6 Women must not be breastfeeding.

3.7 Must have histologically or cytologically confirmed triple negative (ER-/PR-/HER2-) invasive breast cancer, stage I-III at diagnosis (AJCC 6th edition) based on initial evaluation by clinical examination and/or breast imaging.

NOTE: ER- and PR- should meet one of the following criteria:
- Local Pathology report classifies them as negative
- Allred Score of 2 or below
- <5% weakly positive staining

Patients with ER+ and/or PR+ may enroll ONLY if they are known carriers of a deleterious mutation in BRCA1 or BRCA2. Patients with HER2+ tumors may not enroll regardless of BRCA status.

3.8 Must have completed preoperative (neoadjuvant) chemotherapy.
NOTE: Acceptable preoperative regimens include an anthracycline or a taxane, or both. Patients may NOT have received cisplatin as part of their neoadjuvant therapy regimen. Patients who received preoperative therapy as part of a clinical trial may enroll. No adjuvant chemotherapy after surgery other than that specified in this protocol is allowed. Adjuvant bisphosphonate use is allowed.

3.9 Must have completed definitive resection of primary tumor. The last surgery for breast cancer must have been completed at least 14 days prior to registration for protocol therapy.

NOTE: Negative margins for both invasive and ductal carcinoma *in situ* (DCIS) are desirable, however patients with positive margins may enroll if the treatment team believes no further surgery is possible and patient has received radiotherapy. Patients with margins positive for lobular carcinoma *in situ* (LCIS) are eligible. Either mastectomy or breast conserving surgery (including lumpectomy or partial mastectomy) is acceptable. Sentinel node biopsy is allowed but axillary dissection is strongly encouraged in patients with lymph node involvement.

3.10 Must have significant residual invasive disease at the time of definitive surgery following preoperative chemotherapy. Significant residual disease is defined *at least one of the following:*

- Miller-Payne response in the breast of 0-2[5]. (Please refer to Study Procedure Manual[SPM]).
- Residual Cancer Burden (RBC) classification II or III[6].
- Residual carcinoma in one or more regional lymph nodes that would meet AJCC 6th edition criteria for N1 - N3 disease.
- Alternatively, if Miller-Payne or RCB grading is not available, the patient will be eligible if the pathology report indicates that the area of residual invasive disease in the breast measures at least 2 cm following preoperative therapy. The presence of DCIS without invasion does not qualify as residual disease in the breast.

3.11 Whole breast radiotherapy is required for patients who underwent breast conserving therapy, including lumpectomy or partial mastectomy. Patients receiving adjuvant radiation therapy must have completed radiotherapy at least 14 days prior to registration for protocol therapy.
NOTE: Post-mastectomy radiotherapy is required for all patients with a primary tumor ≥ 5 cm or involvement of 4 or more lymph nodes. For patients with primary tumors < 5 cm or with < 4 involved lymph nodes, provision of post-mastectomy radiotherapy is at the discretion of the treating physician.

3.12 Patients must enroll within 84 days of surgery (for those patients who do not require radiation) or within 84 days of completion of radiation when radiation is required

3.13 No stage IV (metastatic) disease, however no specific staging studies are required in the absence of symptoms or physical exam findings that would suggest distant disease.

3.14 No treatment with any investigational agent within 30 days prior to registration for protocol therapy.

3.15 No history of chronic hepatitis B or C

Laboratory values must be obtained within 14 days prior to registration.

3.16 Hemoglobin (Hgb) $\geq$ 9.0 g/dL

3.17 Platelets $\geq$ 100 K/ mm^3

3.18 Absolute neutrophil count (ANC) $\geq$ 1.5 K/mm^3

3.19 Calculated creatinine clearance of $\geq$ 50 cc/min using the Cockcroft-Gault formula:

$$\text{Males: } \frac{(140 - \text{Age in years}) \times \text{Actual Body Weight in kg}}{72 \times \text{Serum Creatinine (mg/dL)}}$$

Females: Estimated creatinine clearance for males × 0.85

3.20 Bilirubin $\leq$ upper limit of normal (except in patients with documented Gilbert's disease, who must have a total bilirubin $\leq$ 3.0 mg/dL)

3.21 Aspartate aminotransferase (AST, SGOT) $\leq$ 2.5 × ULN

3.22 Alanine aminotransferase (ALT, SGPT) $\leq$ 2.5 × ULN

3.23 Left ventricular ejection fraction within normal limits obtained within 30 days prior to registration for protocol therapy**.**

3.24 Patients with an unstable angina or myocardial infarction within 12 months of study entry are excluded.

3.25 No clinically significant infections as judged by the treating investigator.

3.26 Must consent to allow submission of archived tumor tissue sample from definitive surgery.

3.27 Must consent to collection of blood samples for PK analysis.

3.28 No clinically significant arrhythmia or baseline ECG abnormalities in the opinion of the treating investigator.

4.0 PATIENT REGISTRATION

All patients must be registered through the Hoosier Oncology Group's Electronic Data Capture system.

Detailed guidelines for patient registration and electronic case report form (eCRF) completion can be found in the Study Procedures Manual (SPM).

Patients must be registered prior to starting protocol therapy and begin therapy within 5 working days of registration and randomization.

NOTE: For patients enrolled after the safety run-in period randomization will occur immediately after registering a patient. Patients will be registered through the HOG's Electronic Data Capture system.

Blinding: The study treatment is not blinded to the patient or the investigator

5.0 TREATMENT PLAN

All cisplatin doses will be based on the patient's actual weight. The actual weight at screening should be used for calculating body surface area (BSA). The BSA *may* be recalculated based on the actual weight at the start of each treatment cycle but recalculation is only *required* if a patient's weight changes by ≥ 10%.

NOTE: rucaparib dose is fixed, not based on body weight or body surface area (mg/M^2). As such, rucaparib dose is not adjusted for changes in the patient's weight.

NOTE: Prophylactic use of white blood cell growth factors (i.e. Neulasta, Neupogen, Leukine, or similar agent) is not allowed. However, white blood cell growth factors may be used in accordance with ASCO guidelines if neutropenic fever occurs.

Recombinant erythropoietin or similar compound may NOT be administered for anemia due to restrictions on their use in patients being treated with curative intent.

5.1 Pre-medication

It is strongly recommended that all patients receive adequate anti-emetics with cisplatin. **NOTE:** Pre-medication for cisplatin may be given prior to the rucaparib drug infusion. The specifics of the pre-medication regimen are at the discretion of the treating physician, provided adequate control of nausea is achieved. One potential regimen consists of 20 mg of oral dexamethasone and a high dose of oral or IV 5HT3 antagonist (such as 2 mg oral or 10 mcg/kg IV granisetron, or 32 mg oral or IV ondansetron) on the day of cisplatin administration. Followed by additional anti-emetics consisting of 4 days of oral dexamethasone (8 mg po bid for 2 days (days 2, 3) then 4 mg po bid for 2 days (days 4, 5) and scheduled metoclopramide or 5HT3 antagonist for days 2-5 for delayed emesis **NOTE:** Dexamethasone dose should be reduced by 50% when administered with aprepitant.

Hydration guidelines may be modified at the discretion of the treating physician provided adequate pre and post cisplatin hydration is achieved and renal function remains adequate. One *suggested* regimen consists of administering cisplatin in 500 cc to 1000 cc of IV fluids following adequate hydration and the establishment of adequate urinary output. It is suggested the pre-cisplatin hydration consist of NS at 500 cc/hr x 1 liter and post-cisplatin hydration consist of ½ NS + 10 meq KCl/liter + 1 gram magnesium sulfate/liter + 25 grams mannitol/liter at 500 cc/hr for at least one hour, followed by additional hydration at the discretion of the investigator.

5.2 Drug Administration

5.2.1 Safety Run-in Cohorts

Drug interaction and increased toxicity is not anticipated, however there is no clinical experience with cisplatin + rucaparib. To exclude prohibitive toxicity, up to 12 patients (6 in cohort 1 and 6 in cohort 2) will be treated with combined therapy as outlined in Table 1. If a patient goes off study before completing the DLT observation period of safety run-in for reasons other than DLT, then that patient should be replaced.

Table 1: Treatment plan for Safety Run-in Cohorts

Drug	Dose	Frequency of administration	Route of administration	Number of cycles
Rucaparib	**Cohort 1:** 16 mg C1* 24 mg C2-4 **Cohort 2:** 24 mg C1* 30 mg C2-4	D1,2,3 every 21 days	IV ** followed in one hour by Cisplatin	4
Cisplatin	75 mg/m^2	D1 every 21 days	IV infusion per institutional guidelines	4

***NOTE**: Rucaparib dose should be increased to 24 mg for cohort 1 or 30 mg for cohort 2 during cycles 2-4 in the absence of dose limiting toxicity (as defined in Table 2) in cycle 1.

****NOTE:**

- 16 mg dose: ~32 minute infusion time, ~117 mL infusion volume
- 24 mg dose: ~33 minute infusion time, ~120 mL infusion volume
- 30 mg dose: ~34 minute infusion time, ~124 mL infusion volume

Volume calculated using an assumed standard overfill of 9 mL in a 100 mL commercial bag of D5W plus the required volume of reconstituted drug product for a specific dose.

NOTE: After completing combined treatment, patients in the safety run-in cohorts will proceed with rucaparib monotherapy as described in Section 5.2.2, Table 5.

Accrual will be suspended after the initial 6 patients in cohort 1 have been enrolled. All patients in run-in cohort 1 will be observed for at least 3 weeks after administration of cycle 2 for dose limiting toxicity (DLT) as defined in table 2:

Table 2: Definition of Dose Limiting Toxicities

Toxicity Category	Criteria Defining a DLT
Hematological	Grade 4 neutropenia lasting for ≥ 7 days
	Febrile neutropenia
	Grade 3 thrombocytopenia lasting ≥7 days associated with bleeding or Grade 4 thrombocytopenia lasting ≥4 days
Non-hematological	Grade ≥3 toxicity despite the use of adequate/maximal medical interventions and/or prophylaxis as dictated by local institutional clinical practices or the judgment of the Investigator.
	Grade 2 neurotoxicity that does not recover to Grade ≤1 within 2 weeks of planned treatment
Any toxicity that results in a >14 day delay in cycle 2 Day 1 or cycle 3 Day 1 dosing will also be considered a DLT	

If ≤ 1 of 6 patients in cohort 1 experiences DLT, cohort 2 will commence. If 2 or more of 6 patients in cohort 1 experience DLT, the study will be suspended and an amendment to explore lower doses will be considered.

As with cohort 1, accrual will be suspended after the 6 patients in cohort 2 have been enrolled. All patients in run-in cohort 2 will be observed for at least 3 weeks after administration of cycle 2 for dose limiting toxicity (DLT) as defined in Table 2.

If ≤ 1 of 6 patients in cohort 2 experiences DLT, the randomized portion of the study will commence. If 2 or more of 6 patients experience DLT, the study will be suspended and an amendment to proceed with the randomized portion at the cohort 2 dose (24 mg) will be considered.

5.2.2 Randomization

During the randomized portion of the study, patients will be randomized to either Arm A or Arm B.

Stratification factors:

- Anthracycline vs. not
- Residual LN involvement vs. No Residual LN involvement

Arm A (cisplatin monotherapy)

Table 3: Treatment Plan – Arm A

Drug	Dose	Frequency of administration	Route of administration	Number of cycles
Cisplatin	75 mg/m^2	D1 every 21 days	IV infusion per institutional guidelines	4

Note: Infusions may be given ±3 days for reasons such as observed holidays, inclement weather, scheduling conflicts, etc. The reason for the schedule variation should be clearly documented in patient's chart and case report forms.

Arm B (combination therapy)

Table 4: Treatment plan - Arm B

Drug	Dose	Frequency of administration	Route of administration	Number of cycles
rucaparib	24 mg C1* 30 mg C2-4	D1,2,3 every 21 days	IV ** followed in one hour by Cisplatin	4
Cisplatin	75 mg/m^2	D1 every 21 days	IV infusion per institutional guidelines	4

***NOTE**: Rucaparib dose should be increased to 30 mg for cycles 2-4 in the absence of dose limiting toxicity (as defined in Table 2) in cycle 1

****NOTE**:

- 24 mg dose: ~33 minute infusion time, ~120 mL infusion volume
- 30 mg dose: ~34 minute infusion time, ~124 mL infusion volume

Volume calculated using an assumed standard overfill of 9 mL in a 100 mL commercial bag of D5W plus the required volume of reconstituted drug product for a specific dose.

Rucaparib maintenance therapy for Safety Run-in and Arm B

Table 5: Treatment plan – IV maintenance therapy

NOTE: All patients should proceed with oral rucaparib for maintenance therapy after approval of Amendment #5 and when oral drug available.

Drug	Dose	Frequency of administration	Route of administration	Number of weeks
Rucaparib	30mg[I]	Weekly[II]	IV *	24

***NOTE:** 30 mg dose: ~34 minute infusion time, ~124 mL infusion volume. Volume calculated using an assumed standard overfill of 9 mL in a 100 mL commercial bag of D5W plus the required volume of reconstituted drug product for a specific dose.

I: Patients receiving $\leq$ 30 mg during combined therapy should begin maintenance therapy with 30 mg weekly.

II: The first week of maintenance therapy should begin 3 weeks after Day 1 of the last cycle of combination therapy unless a delay is required to allow recovery from toxicity.

NOTE: Patients unable to initiate maintenance therapy within 6 weeks after day 1 of the last cycle of combination therapy should discontinue protocol treatment.

Table 6: Treatment plan – Oral maintenance therapy

Drug	Dose	Frequency of administration	Route of administration	Number of weeks
Rucaparib	100mg[I]	Weekly[II]	Oral	24

I: Patients receiving ≤ 30 mg IV during combined therapy should begin maintenance therapy with 100 mg orally weekly.

II: The first week of maintenance therapy should begin 3 weeks after Day 1 of the last cycle of combination therapy unless a delay is required to allow recovery from toxicity.

NOTE: Patients unable to initiate maintenance therapy within 6 weeks after day 1 of the last cycle of combination therapy should discontinue protocol treatment.

5.3 Missed doses

In general patients should be encouraged to comply with the treatment schedule. However, if IV treatment is missed for reasons other than toxicity (patient vacation, family emergency, etc.), patients able to resume treatment within 2 weeks should receive the full planned number of cycles. If a delay of more than 2 weeks is required, the missed IV treatment should be deleted (ie: not made up) and patients should proceed with the next cycle as originally scheduled.

During oral maintenance therapy, if a missed dose is discovered within 3 days of the scheduled administration time, patients should take that dose immediately. If a missed dose is not discovered until more than 3 days after the scheduled administration time, that dose should not be made up and the patient should resume treatment the following week.

5.4 Special instructions for patients initiating IV maintenance therapy *prior* to Amendment #5

Patients who initiate IV rucaparib maintenance therapy *prior* to approval of Amendment #5 should switch to oral maintenance upon local approval of Amendment #5 and when oral drug is available.

- Patients, who are at week 17 or higher of IV rucaparib when Amendment #5 is approved, should complete the study on IV rucaparib and not be switched over to oral rucaparib.

- All other patients should be switched over when Amendment # 5 is approved. However, to avoid disruption of the evaluation schedule, patients should continue

IV maintenance rucaparib until the next clinical evaluation (required every 4 weeks as per Table 12). If patients required a dose modification during IV maintenance therapy, that dose modification should carry over when patients switch to the oral formulation. See Table 7 for dose level equivalents.

- Patients switching from IV to oral maintenance should have PK samples obtained with the first and fifth week of oral maintenance therapy (see Section 7.4 and 9.3 for details)

5.5 Supportive Care

The use of supportive care including antibiotics, and blood transfusions will be permitted as clinically indicated and according to institutional guidelines.

Prophylactic use of white blood cell growth factors (i.e. Neulasta, Neupogen, Leukine, or similar agent) is not allowed. However, white blood cell growth factors may be used in accordance with ASCO guidelines if neutropenic fever occurs.

Recombinant erythropoietin or similar compound may NOT be administered for anemia due to restrictions on their use in patients being treated with curative intent.

5.6 Concomitant Medications

Concomitant aminoglycoside antibiotic use should be avoided during cisplatin therapy and until patient has fully recovered (i.e., at least 4 weeks from last dose of cisplatin).

Bisphosphonate use is allowed.

Aprepitant should be used with caution in patients receiving concomitant medicinal products, including chemotherapy agents that are primarily metabolized through CYP3A4. Inhibition of CYP3A4 by aprepitant could result in elevated plasma concentrations of these concomitant medicinal products. The effect of aprepitant on the pharmacokinetics of orally administered CYP3A4 substrates is expected to be greater than the effect of aprepitant on the pharmacokinetics of intravenously administered CYP3A4 substrates.

6.0 DOSE MODIFICATIONS

The NCI Common Terminology Criteria for Adverse Events (CTCAE) Version 3.0 will be used to grade adverse events.

Patients enrolled in this study will be evaluated clinically and with standard laboratory tests before and at regular intervals during their participation in this study as specified in section 7.0

Patients will be evaluated for adverse events (all grades), serious adverse events, and adverse events requiring study drug interruption or discontinuation at each study visit for the duration of their participation in the study.

Patients discontinued from the treatment phase of the study for any reason will be evaluated at least 30 days after the last dose of study drug.

Patients who require discontinuation of **rucaparib** due to adverse event, have a treatment interruption of > 21 days due to toxicity, or require a dose reduction below level 0, will be removed from the study.

Patients in the safety run-in, or Arm B, who require a cisplatin dose reduction below level -2, should proceed to **rucaparib** maintenance therapy.

6.1 Dose Levels

The following dose levels will be used in this protocol

Table 7: Dose Level Reductions

Dose level	Cisplatin	Rucaparib IV	Rucaparib (maintenance therapy only)
+2	------	30 mg	100 mg
+1 (safety run-in cohort 2 and Arm B starting dose)		24 mg	60 mg
0 (safety run-in cohort 1 starting dose)	75 mg/m^2	16 mg	40 mg
-1	56 mg/m^2		
-2	37 mg/m^2		

NOTE: All patients should initiate rucaparib maintenance therapy at dose level +2.

Table 8: Dose Modifications for Toxicity Cycles 1-4 – Safety Run-in Cohorts, Arms A and B

Event	Cisplatin	Rucaparib
Neutropenia (based on Day 1 CBC, no change required for interval neutropenia unless accompanied by fever)		
≥ 1.5 K/mm^3	No change	No change
< 1.5 K/mm^3	Hold until ≥ 1.5 K/mm^3, resume based on timing of recovery: ≤ 1 week – no change >1 but ≤ 3 weeks - reduce dose 1 level for subsequent cycles > 3 weeks – discontinue therapy	Hold until ≥ 1.5 K/mm^3, resume at the same dose upon recovery
Neutropenic Fever		
ANC ≤ 1000 and fever > 38.5	Interrupt until resolved (ANC >1000, fever <38.5), resume according to number of episodes: 1st - no change, growth factor use mandatory for subsequent cycles. If growth factors were already used, reduce dose one level for all subsequent cycles. 2nd - reduce dose one level 3rd - discontinue therapy	Interrupt until resolved (ANC >1000, fever <38.5), resume according to number of episodes: 1st - no change 2nd - reduce dose one level 3rd - discontinue therapy
Thrombocytopenia (based on Day 1 CBC, no change required for interval thrombocytopenia)		
≥100,000/mm^3	No change	No change
75-99,999/mm^3	Hold until ≥100,000, resume based on timing of recovery: ≤ 1 week – no change >1 but ≤ 3 weeks - reduce dose 1 level for subsequent cycles > 3 weeks – discontinue therapy	Hold until ≥ 100,000/mm^3, resume at the same dose upon recovery
<75,000	Hold until ≥100,000, Resume with 1 level dose reduction for subsequent cycles. If > 3 weeks delay is required, discontinue therapy	Hold until ≥ 100,000/mm^3, resume at same dose upon recovery
Anemia		
Symptomatic anemia	No change. Transfuse as clinically indicated. NOTE: ESAs are not allowed due to restrictions on their use in the curative setting	
Hepatic		
≥ Grade 3	Delay until recovered to ≤ Grade 2, then resume at a one dose level reduction. If unable to resume therapy within 3 weeks, discontinue therapy	Delay until able to resume cisplatin, then resume at same dose
Nausea/Vomiting		

Grade ≥ 3 in spite of maximal antiemetics	Reduce dose one level for all subsequent cycles	No change
Renal		
Creatinine ≤ 1.5 x ULN	No change	No change
> 1.5 but ≤ 2.0 x ULN	Reduce dose one level and increase hydration	No change
> 2.0 ULN	Delay until recovered to < 2.0 ULN, then resume with one dose level reduction and increased hydration	Delay until able to resume cisplatin, then resume at same dose
Neurotoxicity on Day 1		
≤ Grade 1	No change	No change
≥ Grade 2	Delay until recovered to Grade 1, then resume with one dose level reduction. If unable to resume therapy within 3 weeks, discontinue therapy	Delay until able to resume cisplatin, then resume at same dose
Hearing Loss		
Grade 2	Cisplatin is well known to cause high-frequency hearing loss. Continued use of the drug does not always result in hearing loss, although it may do so. If grade 2 or worse hearing loss is noted, the patient should be presented with a discussion of the relative risks of hearing loss versus the potential benefit of continuing cisplatin therapy, and a decision made on the continuation of cisplatin.	No change
≥ Grade 3	Discontinue Cisplatin	No change
Other *clinically significant* toxicities		
Grade 2	No change	No change
≥ Grade 3	Delay until recovered to ≤ Grade 2, then resume at a one dose level reduction. If unable to resume therapy within 3 weeks, discontinue therapy	Delay until able to resume cisplatin, then resume at same dose

Table 9: Dose Modification for Toxicity – Maintenance Therapy (Safety Run-in Cohorts and Arm B only)

Event	Rucaparib
Hematologic	
Grade 1-2	No change
Grade 3	Hold therapy. If recovery to Grade $\leq$ 2 within 14 days, resume with a one level dose reduction.
Grade 4	Discontinue therapy
Non-Hematologic	
Grade 1-2	No change
Grade 3	Hold therapy. If recovery to Grade $\leq$ 1 within 14 days, resume with a one level dose reduction.
Grade 4	Discontinue therapy

7.0 SAFETY

Safety Run-In Cohorts 1 and 2 **Maintenance Rucaparib**

	Screening		Cycle 1-2					Cycles 3-4			Weekly	Every 4 weeks	Post-treatment	Follow-up
	-30 days	-14 days	D1[1] +/-3 days	D2	D3	D8 +/-3 days	D15 +/-3 days	D1 +/-3 days	D2	D3	+/-3 days	+/-3 days	30-60 days from last treatment	+/- 1 month
REQUIRED ASSESSMENTS														
Medical history	X													
Height	X													
Physical examination	X		X					X				X	X	X[8]
BP, weight	X		X					X			X		X	X[8]
ECOG performance status	X		X					X				X	X	X[8]
Blood Chemistries[2]		X	X			X	X	X				X	X	
Calculated creatinine clearance		X	X					X						
Platelets, ANC & Hgb		X	X			X	X	X				X	X	
Breast imaging														yearly
Electrocardiogram[3]	X		X					X						
MUGA or ECHO	X													
Urine pregnancy or serum HCG[4]		X												
Adverse event and concomitant medication assessment	X		X			X	X	X				X	X	
TREATMENT														
Rucaparib			X	X	X			X	X	X	X			
Cisplatin			X					X						

Table 10 – continued on the next page

Safety Run-In Cohorts 1 and 2 **Maintenance Rucaparib**

	Screening		Cycle 1-2					Cycles 3-4				Weekly	Every 4 weeks	Post-treatment	Follow-up
	-30 days	-14 days	D1[1] +/-3 days	D2	D3	D8 +/-3 days	D15 +/-3 days	D1 +/-3 days	D2	D3		+/-3 days	+/-3 days	30-60 days from last treatment	+/- 1 month
CORRELATIVE STUDIES															
Tumor from diagnosis - Optional	X														
Tumor from definitive surgery - Mandatory	X														
Genomic DNA – Optional[5]			X												
PK – Mandatory					X[6]							X[7]			

1. Screening values obtained within 7 days of Day 1 do not need to be repeated prior to cycle 1 day 1.
2. Serum chemistries (creatinine, glucose, total protein, blood urea nitrogen [BUN], total carbon dioxide [CO_2], albumin, total bilirubin, alkaline phosphatase, and aspartate transaminase [AST] and alanine transaminase [ALT]) and electrolytes (total calcium, chloride, potassium, sodium).
3. ECG at baseline and prior to each cycle for the first 4 cycles. Additional ECG monitoring should be considered in patients who develop clinical significant electrolyte abnormalities during cisplatin therapy at the discretion of the treating physician.
4. Only in women of child bearing potential.
5. If the genomic sample collection is missed at cycle1 day 1, it can be collected at any time point during the study.
6. Mandatory PK samples are to be done pre-dose and 5 minutes (+/-5 minutes) prior to the end of study drug infusion, on cycle1 day 3 and cycle2 day3.
7. Week 1 and week 5 only.
8. Every 4 months throughout years1-2, then every 6 months for years 3-5.

Randomized Phase II – Arm A

	Screening		Cycles 1-4	Post-treatment	Follow-up
	-30 days	-14 days	D1[1] (+/-3 days)	30-60 days from last treatment	+/-1 month
REQUIRED ASSESSMENTS					
Medical history	X				
Height	X				
Physical examination	X		X	X	X[6]
BP, weight	X		X	X	X[6]
ECOG performance status	X		X	X	X[6]
Blood Chemistries[2]		X	X	X	
Calculated creatinine clearance		X	X	X	
Platelets, ANC & Hgb		X	X	X	
Breast imaging					yearly
Electrocardiogram[3]	X		X		
MUGA or Echocardiogram	X				
Urine pregnancy or serum HCG[4]		X			
Adverse event and concomitant medication assessment	X		X	X	
TREATMENT					
Cisplatin			X		
CORRELATIVE STUDIES					
Tumor from diagnosis -Optional	X				
Tumor from definitive surgery - Mandatory	X				
Genomic DNA - Optional			X[5]		

1. Screening values obtained within 7 days of Day 1 do not need to be repeated prior to cycle 1 day 1.
2. Serum chemistries (creatinine, glucose, total protein, blood urea nitrogen [BUN], total carbon dioxide [CO_2], albumin, total bilirubin, alkaline phosphatase, and aspartate transaminase [AST] and alanine transaminase [ALT]) and electrolytes (total calcium, chloride, potassium, sodium).
3. ECG will be done at baseline and prior to cycle 3. Additional ECG monitoring should be considered in patients who develop clinical significant electrolyte abnormalities during cisplatin therapy at the discretion of the treating physician.
4. Only in women of child bearing potential
5. If the genomic sample collection is missed at cycle1 day1, it can be collected at any time point during the study.
6. Every 4 months throughout years 1-2, then every 6 months for years 3-5.

Randomized Phase II - Arm B IV Maintenance Rucaparib

	Screening		Cycle 1-4				Weekly	Every 4 weeks	Post-treatment	Follow-up
	-30 days	-14 days	D1[1] +/-3 days	D 2	D 3		+/-3 days	+/-3 days	30-60 days from last treatment	+/- 1 month
REQUIRED ASSESSMENTS										
Medical history	X									
Height	X									
Physical examination	X		X					X	X	X[8]
BP, weight	X		X				X		X	X[8]
ECOG performance status	X		X					X	X	X[8]
Blood Chemistries[2]		X	X					X	X	
Calculated creatinine clearance		X	X							
Platelets, ANC & Hgb		X	X					X	X	
Breast imaging										yearly
Electrocardiogram[3]	X		X							
MUGA or Echocardiogram	X									
Urine pregnancy or serum HCG[4]		X								
Adverse event and concomitant medication assessment	X		X					X	X	
TREATMENT										
Rucaparib			X	X	X		X			
Cisplatin			X							
CORRELATIVE STUDIES										
Tumor from diagnosis - Optional	X									
Tumor from definitive surgery - Mandatory	X									
Genomic DNA – Optional[5]			X							
PK – Mandatory					X[6]		X[7]			

1. Screening values obtained within 7 days of Day 1 do not need to be repeated prior to cycle 1 day 1.
2. Serum chemistries (creatinine, glucose, total protein, blood urea nitrogen [BUN], total carbon dioxide [CO_2], albumin, total bilirubin, alkaline phosphatase, and aspartate transaminase [AST] and alanine transaminase [ALT]) and electrolytes (total calcium, chloride, potassium, sodium).
3. ECG to be done at baseline and prior to cycle 3. Additional ECG monitoring should be considered in patients who develop clinical significant electrolyte abnormalities during cisplatin therapy at the discretion of the treating physician.
4. Only in women of child bearing potential.
5. If the genomic sample collection is missed at cycle1 day1, it can be collected at any time point during the study.

6. Mandatory PK samples are to be done pre-dose and 5 minutes (+/- 5 minutes) prior to the end of study drug infusion, on cycle 1 day 3 and cycle 2 day 3.
7. Week 1 and week 5 only.
8. Every 4 months throughout years 1-2, then every 6 months for years 3-5.

Randomized Phase II - Arm B Oral Maintenance Rucaparib

	Screening		Cycle 1-4				Weekly	Every 4 weeks	Post-treatment	Follow-up
	-30 days	-14 days	D1[1] +/-3 days	D 2	D3		+/-3 days	+/-3 days	30-60 days from last treatment	+/- 1 month
REQUIRED ASSESSMENTS										
Medical history	X									
Height	X									
Physical examination	X		X					X	X	X[8]
BP, weight	X		X					X	X	X[8]
ECOG performance status	X		X					X	X	X[8]
Blood Chemistries[2]		X	X					X	X	
Calculated creatinine clearance		X	X							
Platelets, ANC & Hgb		X	X					X	X	
Breast imaging										yearly
Electrocardiogram[3]	X		X							
MUGA or Echocardiogram	X									
Urine pregnancy or serum HCG[4]		X								
Adverse event and concomitant medication assessment	X		X					X	X	
TREATMENT										
Rucaparib			X	X	X		X			
Cisplatin			X							
CORRELATIVE STUDIES										
Tumor from diagnosis - Optional	X									
Tumor from definitive surgery - Mandatory	X									
Genomic DNA – Optional[5]			X							
PK – Mandatory					X[6]		X[7]			

1. Screening values obtained within 7 days of Day 1 do not need to be repeated prior to cycle 1 day 1.
2. Serum chemistries (creatinine, glucose, total protein, blood urea nitrogen [BUN], total carbon dioxide [CO_2], albumin, total bilirubin, alkaline phosphatase, and aspartate transaminase [AST] and alanine transaminase [ALT]) and electrolytes (total calcium, chloride, potassium, sodium).
3. ECG to be done at baseline and prior to cycle 3. Additional ECG monitoring should be considered in patients who develop clinical significant electrolyte abnormalities during cisplatin therapy at the discretion of the treating physician.
4. Only in women of child bearing potential.
5. If the genomic sample collection is missed at cycle1 day1, it can be collected at any time point during the study.
6. Mandatory PK samples are to be done pre-dose and 5 minutes (+/- 5 minutes) prior to the end of study drug infusion, on cycle 1 day 3 and cycle 2 day 3.

7. Pre-dose and 2 hours post-dose during week 1 and week 5 only. PK samples should be drawn during the first and fifth week of oral maintenance therapy in patients switching from the IV formulation.
8. Every 4 months throughout years 1-2, then every 6 months for years 3-5.

7.1 BASELINE/SCREENING

7.1.1 Within 30 days prior to registration for protocol therapy:

- Complete medical history
- Physical examination including: height, weight, BP
- ECG
- MUGA or Echocardiogram
- Adverse event and concomitant medication
- ECOG performance status

7.1.2 Within 14 days of registration for protocol therapy:

- Complete metabolic profile (CMP) including: serum chemistries (creatinine, glucose, total protein, blood urea nitrogen [BUN], total carbon dioxide [CO_2], albumin, total bilirubin, alkaline phosphatase, and aspartate transaminase [AST] and alanine transaminase [ALT]) and electrolytes (total calcium, chloride, potassium, sodium
- Calculated creatinine clearance
- Platelets, ANC, Hgb
- Urine pregnancy test or serum HCG (for women of child bearing potential)

7.2 ON TREATMENT

7.2.1 Day 1 of each cycle (within 3 days prior):

Note: Cycle 1 Day 1 testing need not be repeated if completed within 7 days of starting protocol therapy.

- Physical examination including
- weight, B/P and ECOG performance
- Platelets, ANC, Hgb
- Complete metabolic profile (CMP) including: serum chemistries (creatinine, glucose, total protein, blood urea nitrogen [BUN], total carbon dioxide [CO_2], albumin, total bilirubin, alkaline phosphatase, and aspartate transaminase [AST] and alanine transaminase [ALT]) and electrolytes (total calcium, chloride, potassium, sodium
- Calculated creatinine clearance
- ECGs will be done prior to each treatment cycle in the safety-run in cohorts and prior to cycle 3 of combined therapy in randomized portion of the study. Additional ECG monitoring should be considered at the treating physician's discretion, in patients who develop clinically significant electrolyte abnormalities
- Assessment of adverse events and concomitant medications
- PK levels: For patients enrolled in the safety-run-in portion of the study and Arm B - Mandatory plasma sample to be collected prior to infusion and 5 min (+/- 5 minutes) prior to the end of infusion on Cycle 1 Day 3 and Cycle 2 Day 3
- Optional whole blood sample (genomic DNA) to be collected on all patients at cycle 1 day1.
- Correlative studies: (See SPM for collection and shipping instructions).
    - Optional - tumor tissue submission from diagnosis

- Mandatory - tumor tissue submission from definitive surgery

7.3 IV MAINTENANCE THERAPY

- During maintenance therapy patient will have weekly BP and weight along with study drug
- Every 4 weeks they need:
  - Physical examination
  - ECOG Performance status
  - Platelets, ANC, Hgb
  - Complete metabolic profile (CMP) including: serum chemistries (creatinine, glucose, total protein, blood urea nitrogen [BUN], total carbon dioxide [CO_2], albumin, total bilirubin, alkaline phosphatase, and aspartate transaminase [AST] and alanine transaminase [ALT]) and electrolytes (total calcium, chloride, potassium, sodium
  - Assessment of adverse events and concomitant medications
- PK levels: Plasma to be collected prior to infusion and 5 min (+/- 5 minutes) prior to the end of infusion during Week 1 and Week 5

7.4 ORAL MAINTENANCE THERAPY

- During maintenance therapy patient will administer the study drug weekly. Patients should be instructed to take the drug in clinic on week 1 and week 5 so PK samples can be obtained. All other doses are self-administered at home.
- Every 4 weeks they need:
  - Physical examination
  - ECOG Performance status
  - Platelets, ANC, Hgb
  - Complete metabolic profile (CMP) including: serum chemistries (creatinine, glucose, total protein, blood urea nitrogen [BUN], total carbon dioxide [CO_2], albumin, total bilirubin, alkaline phosphatase, and aspartate transaminase [AST] and alanine transaminase [ALT]) and electrolytes (total calcium, chloride, potassium, sodium
  - Assessment of adverse events and concomitant medications
- PK levels: Plasma to be collected prior to administration and 2 hours post-dose (+/- 5 minutes) during Week 1 and Week 5 only. PK samples should be drawn during the first and fifth week of oral maintenance therapy in patients switching from the IV formulation.

7.5 TREATMENT DISCONTINUATION

A patient will be discontinued from the treatment under the following circumstances:

- If there is evidence of progressive disease.
- If the attending physician thinks a change of therapy would be in the best interest of the patient.
- If the patient requests discontinuation.
- If the drug(s) exhibit(s) unacceptable adverse event. Patients will be followed until the resolution of these adverse events.
- If a patient becomes pregnant.

- Patients can stop participating at any time. However, if they decide to stop participating in the study, patients will continue to be followed for progression and survival unless the patient has also withdrawn consent for further follow-up.

7.6 POST TREATMENT EVALUATIONS: ~30 days -60 days from last treatment

- Physical examination
- weight, BP
- ECOG performance
- Platelets, ANC, Hgb
- Complete metabolic profile (CMP) including: serum chemistries (creatinine, glucose, total protein, blood urea nitrogen [BUN], total carbon dioxide [CO_2], albumin, total bilirubin, alkaline phosphatase, and aspartate transaminase [AST] and alanine transaminase [ALT]) and electrolytes (total calcium, chloride, potassium, sodium
- Assessment of adverse events and concomitant medications

7.7 FOLLOW-UP:

- Patients will be monitored by their treating physicians for the development of either local (chest wall, axillary, or supraclavicular nodes) or distal recurrent disease at least once every 4 months for the first two years, then at least every 6 months during years 3-5 after randomization.
- Suggested guidelines for surveillance of breast cancer survivors are available through the National Comprehensive Cancer Network (www.nccn.org).
- Routine blood work or radiology in the absence of symptoms suggestive of recurrent disease is not recommended.
- Remaining breast tissue (contralateral breast and ipsilateral breast in patients treated with breast conserving surgery) should be imaged annually according to standard screening guidelines.

8.0 CRITERIA FOR DISEASE EVALUATION

The primary efficacy endpoint of this trial is disease-free survival (DFS) in patients confirmed (by central testing) to have triple negative tumors or known BRCA1/2 mutation. DFS is defined as the duration of time from randomization to time of an DFS event, defined as local failure (invasive), regional failure, distant failure, contralateral breast cancer (invasive or non-invasive), any other second cancer (excluding non-melanomatous skin cancer or cervical cancer in situ), or death from any cause. The diagnosis of local or distant recurrence *should ideally be pathologically confirmed*, however if biopsy if not possible, radiology confirmation by CT, MRI, or PET scan is acceptable.

9.0 BIOLOGICAL CORRELATIVES

9.1 Central Pathology Reassessment

Analysis by an American Society of Clinical Oncology (ASCO) and College of American Pathology (CAP) expert panel suggests that approximately 20% of ER, PR, and HER2 tests performed in community laboratories are inaccurate with a fairly equal distribution of false positive and false negative results. While the ASCO/CAP guidelines seek to improve test quality and reliability, the impact of these recently published[25-28] guidelines is not yet fully known[29,30]. As such, a retrospective central reassessment of histological subtype, tumor grade, ER, PR, and HER2 will be performed by Dr. Sunil Badve for quality assurance and to confirm tumor phenotype. Tissue Microarrays (TMA) will be constructed to facilitate potential future correlative studies including genetic assessment of DNA damage repair pathways and potential gene expression profiles that might predict sensitivity to PARP inhibition.

Formalin-fixed paraffin-embedded (FFPE) tissue from biopsy at the time of initial diagnosis (optional) and from the residual disease removed at the time of definitive surgery (mandatory) should be sent within 30 days of randomization (or registration for patients enrolled to the safety run-in).

NOTE: Patients will be asked to consent to allow banking of their tumor samples for future correlative studies. Only tumor samples from consenting patients will be included in the TMAs.

Detailed instructions on sample collection, processing and shipping are outlined in the Study Procedures Manual.

9.2 Genomic DNA – Optional

It has become increasingly clear that therapeutic heterogeneity may arise from differences in the tumor (e.g. p53 expression or defects in DNA repair) and/or differences in the host (e.g. single nucleotide polymorphisms). Although a candidate gene approach is a high yield strategy for biomarker discovery, the variability seen in most disease processes is highly dependent on complex gene-gene interactions. Recently, advances in technical platforms and bioinformatics have made genome wide association studies (GWAS) feasible. This comprehensive approach has led to some important discoveries including identification of genes, SNPs, and haplotypes associated with breast cancer, lung cancer, colon cancer, prostate cancer, myocardial infarction, and type-2 diabetes. Thus, GWAS has become a powerful platform for biomarker discovery. DNA samples from patients enrolled in this trial will be an incredibly valuable resource for potential future correlative studies using these emerging genomic and pharmacogenomic technologies.

Whole blood will be collected for assessment of potential genomic determinants of response and toxicity.

NOTE: Patients will be asked to consent to allow banking of their DNA for future correlative studies. Only whole blood samples from consenting patients should be submitted.

Detailed instructions on sample collection, processing and shipping are outlined in the Study Procedures Manual.

9.3 Rucaparib Pharmacokinetics (Safety Run-in Cohorts and Arm B patients only) – Mandatory

Extensive pharmacokinetics (PK) is being conducted in several ongoing rucaparib trials and thus detailed PK sampling is not planned in this trial. However, limited PK sampling will be conducted to complement the other ongoing efforts. Plasma samples will be obtained prior to infusion and 5minutes (+/- 5 minutes) prior to the end of infusion on Day 3 of cycles 1 and 2 during combination therapy and weeks 1 and 5 of IV maintenance therapy. Plasma samples will be obtained prior to administration and 2 hours (+/- 5 minutes) post dose during week 1 and week 5 of oral maintenance therapy in all patients (including those who initiated maintenance therapy with the IV formulation). For all collections, the start and end of rucaparib infusion as well as actual time of all PK sample collections should be recorded in the source documents. PK samples will be assayed for rucaparib (CO-338/AG-014699/PF-01367388) using a validated analytical method. Detailed instructions on sample collection, processing and shipping are outlined in the Study Procedures Manual.

10.0 CTM INFORMATION & ADVERSE EVENTS MANAGEMENT

10.1 Rucaparib (CO-338/AG-014699/PF-01367388)

10.1.1 Mechanism of Action: Inhibits PARP

10.1.2 Availability: IV drug will be provide by Clovis via the Hoosier Oncology Group. rucaparib investigational drug product will be supplied as rucaparib Lyophilized Powder for Injection, 12 mg/vial (as free base), in 10 mL/20 mm, Type I amber glass vials. The composition of rucaparib drug product consists of rucaparib (phosphate salt), mannitol, water for injection (WFI), and nitrogen. The resulting drug product is an off-white to yellow cake.

Availability: Oral drug will be provide by Clovis via the Hoosier Oncology Group. rucaparib investigational drug product will be supplied as rucaparib immediate release,film coated tablets, 40 mg and 60 mg (as free base), in HDPE containers with child resistant closures. The composition of rucaparib drug product consists of rucaparib (camsylate salt), microcrystalline cellulose, sodium starch glycolate, dicalcium phosphate, and magnesium stearate. The cosmetic white film coating, Opadry II, contains HPMC 2910, hypromellose 6cP, macrogol/PEG3350, triacetin, titanium dioxide, and lactose monohydrate. 40 mg rucaparib tablets are 9.5 mm round convex in shape, while 60 mg tablets are 15.4 mm x 8 mm oval in shape.

10.1.3 Storage and Reconstitution: Vials of rucaparib Lyophilized Powder for Injection, 12 mg/vial (as free base), must be stored at room temperature (15°C to 30°C) and protected from light.

Each rucaparib drug product vial is to be reconstituted with 6 mL sterile WFI to yield a 2 mg/mL (as free base) clear yellow solution. Once 6 mL of SWFI is injected into the vial through the stopper, vigorously shake the vial for at least 30 seconds to allow complete drug dissolution in the vial. The reconstituted solution should be clear and free of particles. Segregate and store any rejected vials separately at controlled room temperature (15 to 30°C) and notify sponsor immediately. The reconstituted rucaparib drug product must be used within 24 hours and stored at controlled room temperature (15°C to 30°C). Do not refrigerate reconstituted product.

Bottles of rucaparib 40 mg and 60 mg (as free base) immediate release film coated tablets, must be stored at room temperature (15°C to 30°C)

10.1.4 **IV administration**: The reconstituted solution will be mixed in an infusion bag containing D5W. Drug should be administered as listed in table 1 of the protocol, as an intravenous infusion. Infusion equipment including infusion bags and tubing must be compatible with rucaparib. Products meeting compatibility requirements will be listed in the study documentation prior to the enrollment of the first patient.

Chemotherapy will be administered approximately one hour after the end of rucaparib administration.

Oral administration: Patients should take rucaparib fasting (at least 1 hour *before* OR at least 2 hours *after* eating)

10.1.5 Side Effects:
In general rucaparib has been well tolerated in early clinical trials; dose limiting toxicity has not been identified at doses that effectively inhibit PARP. Most adverse events were reversible and short in duration. Most hematologic toxicity was related to concurrently administered chemotherapy and was not obviously increased with combined therapy. No cardiac toxicity (changes in electrocardiogram or left ventricular ejection fraction) with repeated dosing. The main adverse event associated only with rucaparib is mild injection site reaction.

~~ADD ORAL here if needed~~

10.2 Cisplatin Other: Platinol (NSC-119875); Cis-diamminedichloroplatinum

10.2.1 **Classification:** Alkylating agent

10.2.2 **Action:**
Cisplatin forms covalent bonds with nucleophilic sites on guanine present in all DNA. As cisplatin is a bifunctional agent, it is able to bind to 2 sites in a DNA strand. This results in the formation of inter- and intra- chain cross-linkings, which interferes with cellular transcription and replication. Regulatory mechanisms detect the abnormal DNA and so

activate a chain of responses to try and correct it. This, ultimately, causes cell death (apoptosis).

10.2.3 Availability:
Cisplatin is commercially available.

10.2.4 Storage:
Cisplatin Injection is a sterile, multi-dose vial without preservatives. Store at 15° to 25°C (59° to 77°F). **Note:** Do not refrigerate. Protect unopened container from light. The cisplatin remaining in the amber vial following initial entry is stable for 28 days protected from light or for 7 days under fluorescent room light.

10.2.5 Reconstitution:
The aqueous solution should be used intravenously only and should be administered by IV. Cisplatin is a cytotoxic chemotherapeutic agent. Appropriate precautions for hazardous drug handling should be taken during handling, preparation, administration and disposal of this agent. As with other potentially toxic compounds, caution should be exercised in handling the aqueous solution. Skin reactions associated with accidental exposure to cisplatin may occur. The use of gloves is recommended. If cisplatin contacts the skin or mucosa, immediately and thoroughly wash the skin with soap and water and flush the mucosa with water.

10.2.6 Administration:
Cisplatin will be administered IV according to institutional guidelines.
Hydration for cisplatin can be administered at the discretion of the treating physician and according to institutional standards. However, the following regimen is suggested:

Table 10: Pre-dose: Hydration guidelines

	Instructions
Normal Saline	at 350 mL/hour x 1000 mL
Mannitol bolus, immediately prior to cisplatin	12.5 g IV piggyback in 25 mL D5W x1 through 1.2 micron in-line filter

Table 11: Post-dose: Hydration guidelines

	Instructions
Normal Saline	at 350 mL/hour x 1000 mL

10.2.7 Side Effects:
Nephrotoxicity: Dose related and cumulative renal insufficiency is the major dose-limiting toxicity. Renal toxicity has been noted in 28-36% of patients treated with a single dose of 50 mg/m^2. It is first noted during the second week after a dose and is manifested by elevations in BUN and creatinine, serum uric acid, and/or a decrease in creatinine clearance.
Note: Renal toxicity becomes more prolonged and severe with repeated courses of the drug. Renal function must return to normal before another dose of cisplatin can be given.

10.2.8 **Ototoxicity:** Ototoxicity has been observed in up to 31% of patients treated with a single dose of cisplatin 50 mg/m^2, and is manifested by tinnitus and/or hearing loss in the high frequency range (4,000 to 8,000 Hz). Decreased ability to hear normal conversational tones may occur occasionally. Deafness after the initial dose of cisplatin has been reported rarely. Ototoxic effects may be more severe in children receiving cisplatin. Hearing loss can be unilateral or bilateral and tends to become more frequent and severe with repeated doses. Ototoxicity may be enhanced with prior or simultaneous cranial irradiation. It is unclear whether cisplatin-induced ototoxicity is reversible. Ototoxic effects may be related to the peak plasma concentration of cisplatin. Vestibular toxicity has also been reported. Ototoxicity may become more severe in patients being treated with other drugs with nephrotoxic potential. Patients should be questioned regarding any history of hearing deficit.

10.2.9 **Hematologic:** Myelosuppression occurs in 25% to 30% of patients treated with cisplatin. The nadirs in circulating platelets and leukocytes occur between days 18 to 23 (range 7.5 to 45) with most patients recovering by day 39 (range 13 to 62). Leukopenia and thrombocytopenia are more pronounced at higher doses (>50 mg/m^2). Anemia (decrease of 2 g hemoglobin/100 mL) occurs at approximately the same frequency and with the same timing as leukopenia and thrombocytopenia. Fever and infections have also been reported in patients with neutropenia. In addition to anemia secondary to myelosuppression, a Coombs' positive hemolytic anemia has been reported. In the presence of cisplatin hemolytic anemia, a further course of treatment may be accompanied by increased hemolysis, and this risk should be weighed by the Treating Physician.

The development of acute leukemia coincident with the use of cisplatin has rarely been reported in humans. In these reports, cisplatin was generally given in combination with other leukemogenic agents.

10.2.10 **Gastrointestinal:** Marked nausea and vomiting occur in almost all patients treated with cisplatin, and are occasionally so severe that the drug must be discontinued. Nausea and vomiting usually begin within 1 to 4 hours after treatment and last for 24 hours. Various degrees of vomiting, nausea and/or anorexia may persist for up to 1 week after treatment. Delayed nausea and vomiting (begins or persists 24 hours or more after chemotherapy) has occurred in patients attaining complete emetic control on the day of cisplatin therapy. Diarrhea has also been reported.

10.2.11 **Other Toxicities:** Vascular toxicities coincident with the use of cisplatin in combination with other antineoplastic agents have been reported rarely. The events are clinically heterogeneous and may include myocardial infarction, cerebrovascular accident, thrombotic microangiopathy (HUS), or cerebral arteritis. Various mechanisms have been proposed for these vascular complications. There are also reports of Raynaud's phenomenon occurring in patients treated with the combination of bleomycin, vinblastine with or without cisplatin. It has been suggested that hypomagnesemia developing coincident with the use of cisplatin may be an added, although not essential, factor associated with this event. However, it is currently unknown if the cause of Raynaud's phenomenon in these cases is the disease, underlying vascular compromise, bleomycin, vinblastine, hypomagnesemia, or a combination of any of these factors.

10.2.12 Serum Electrolyte Disturbances: Hypomagnesemia, hypocalcemia, hyponatremia, hypokalemia, and hypophosphatemia have been reported to occur in patients treated with cisplatin and are probably related to renal tubular damage. Tetany has occasionally been reported in those patients with hypocalcemia and hypomagnesemia. Generally, administering supplemental electrolytes and discontinuing cisplatin restore normal serum electrolyte levels. Inappropriate antidiuretic hormone syndrome has also been reported.

10.2.13 Hyperuricemia: Hyperuricemia has been reported to occur at approximately the same frequency as the increases in BUN and serum creatinine. It is more pronounced after doses greater than 50 mg/m^2, and peak levels of uric acid generally occur between 3 to 5 days after the dose. Allopurinol therapy for hyperuricemia effectively reduces uric acid levels.

10.2.14 Neurotoxicity: Neurotoxicity, usually characterized by peripheral neuropathies, has been reported. The neuropathies usually occur after prolonged therapy (4 to 7 months); however, neurologic symptoms have been reported to occur after a single dose. Although symptoms and signs of cisplatin neuropathy usually develop during treatment, symptoms of neuropathy may begin 3 to 8 weeks after the last dose of cisplatin, although this is rare. Cisplatin therapy should be discontinued when the symptoms are first observed. The neuropathy, however, may progress further even after stopping treatment. Preliminary evidence suggests peripheral neuropathy may be irreversible in some patients. Lhermitte's sign, dorsal column myelopathy, and autonomic neuropathy have also been reported. Loss of taste and seizures have also been reported.

Muscle cramps, defined as localized, painful, involuntary skeletal muscle contractions of sudden onset and short duration, have been reported and were usually associated in patients receiving a relatively high cumulative dose of cisplatin and with a relatively advanced symptomatic stage of peripheral neuropathy.

10.2.15 Ocular Toxicity: Optic neuritis, papilledema, and cerebral blindness have been reported infrequently in patients receiving standard recommended doses of cisplatin. Improvement and/or total recovery usually occurs after discontinuing cisplatin. Steroids with or without mannitol have been used; however, efficacy has not been established.

10.2.16 Blurred vision and altered color perception have been reported after the use of regimens with higher doses of cisplatin or greater dose frequencies than those recommended in the package insert. The altered color perception manifests as a loss of color discrimination, particularly in the blue-yellow axis. The only finding on funduscopic exam is irregular retinal pigmentation of the macular area.

10.2.17 Anaphylactic-like Reactions: Anaphylactic- like reactions have been occasionally reported in patients previously exposed to cisplatin. The reactions consist of facial edema, wheezing, tachycardia, and hypotension within a few minutes of drug administration. Reactions may be controlled by IV epinephrine with corticosteriods and/or antihistamines as indicated. Patients receiving cisplatin should be observed carefully for possible anaphylactic- like reactions and supportive equipment and medication should be available to treat such a complication.

10.2.18 Hepatotoxicity: Transient elevations of liver enzymes, especially SGOT, as well as bilirubin, have been reported to be associated with cisplatin administration at the recommended doses.

10.2.19 Other Events: Other toxicities reported to occur infrequently are cardiac abnormalities, hiccups, elevated serum amylase, and rash. Alopecia, malaise, and asthenia have been reported as part of postmarketing surveillance.

Local soft tissue toxicity has rarely been reported following extravasation of cisplatin. Severity of the local tissue toxicity appears to be related to the concentration of the cisplatin solution. Infusion of solutions with a cisplatin concentration greater than 0.5 mg/mL may result in tissue cellulitis, fibrosis, and necrosis.

10.2.20 Pregnancy: Cisplatin can cause fetal harm when administered to a pregnant woman. Cisplatin is mutagenic in bacteria and produces chromosome aberrations in animal cells in tissue culture. In mice, cisplatin is teratogenic and embryotoxic. If this drug is used during pregnancy or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus. Patients should be advised to avoid becoming pregnant.

10.2.21 Nursing Mothers. Cisplatin has been reported to be found in human milk, patients receiving cisplatin should not breastfeed.

11.0 REPORTING ADVERSE EVENTS & SERIOUS ADVERSE EVENTS

11.1 Definitions of Adverse Events

11.1.1 Adverse Event (AE)

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

11.1.2 Serious Adverse Event (SAE)

A serious adverse event is any untoward medical occurrence resulting in one or more of the following:

- Results in death
- Is life-threatening (defined as an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe)
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly or birth defect
- Is an important medical event (defined as a medical event(s) that may not be immediately life-threatening or result in death or hospitalization but, based upon appropriate medical and scientific judgment, may jeopardize the patient or may require intervention (e.g., medical, surgical) to prevent one of the other serious outcomes listed in the definition above). Examples of such events include, but are not limited to, intensive treatment in an emergency room or at home for allergic

bronchospasm; blood dyscrasias or convulsions not resulting in hospitalization; or the development of drug dependency or drug abuse.

11.1.3 Unexpected Adverse Event

An adverse event not mentioned in the Investigator's Brochure or package insert or the specificity or severity of which is not consistent with the Investigator's Brochure or package insert.

11.2 Adverse Event (AE) Reporting

Adverse events (AEs) will be recorded from the time of consent and for at least 30 days after treatment discontinuation, regardless of whether or not the event(s) are considered related to trial medications. All AEs considered related to trial medication will be followed until resolution, return to baseline, or deemed clinically insignificant, even if this occurs post-trial.

11.3 Serious Adverse Event (SAE) Reporting

11.3.1 Study Center (Site) Requirements for Reporting SAEs

Investigators and other site personnel must report any SAEs occurring during the course of the study within one business day of discovery of the event. This includes events both related and unrelated to the investigational product.

The definition of "related" being that there is a reasonable possibility the drug caused the adverse experience.

Table 12: Relationship of adverse event to the investigational agent

Unrelated	The Adverse Event is *clearly not related* to the investigational agent(s)
Unlikely	The Adverse Event is *doubtfully related* to the investigational agent(s)
Possible	The Adverse Event *may be related* to the investigational agent(s)
Probable	The Adverse Event is *likely related* to the investigational agent(s)
Definite	The Adverse Event is *clearly related* to the investigational agent(s)

The completed SAE Report Form (see Study Procedure Manual) must be faxed to Hoosier Oncology Group within 1 business day of discovery of the event. The investigator is responsible for informing the IRB and/or the Regulatory Authority of the SAE as per local requirements.

11.3.2 Death and Immediately Life-Threatening Events

Any death and immediately life-threatening event from any cause while a patient is receiving trial treatment on this protocol or up to 30 days after the last dose of trial treatment, or any death and immediately life-threatening event occurring more than 30 days after trial treatment has ended but which is felt to be treatment related must be reported within one business day of discovery of the event. All deaths must be reported

primarily for the purposes of SAE reporting; however, deaths due unequivocally to progression are not SAEs.

Your local IRB should be notified and their reporting procedure followed. The completed SAE Reporting Form should be faxed to Hoosier Oncology Group **within one business day of discovery** of the event.

11.3.3 HOG Requirements for Reporting SAEs

The Hoosier Oncology Group will report all SAEs that occur on subjects receiving rucaparib (from the time of first dose until 30 days post discontinuation) to Clovis within one business day of receipt of the SAE Reporting Form and to regulatory authorities (FDA) per federal guidelines.

The Hoosier Oncology Group will fax a MedWatch Report to:
BioSoteria, Inc
Fax # +1-800-708-3370 or 1-510-225-3980

11.4 IND Safety Reports Unrelated to This Trial

IND safety reports not occurring on this trial but involving the study intervention (outside SAEs) received from outside sources will be reviewed by the Sponsor Investigator and will be forwarded to participating sites for submission to their Institutional Review Boards per their guidelines.

12.0 STATISTICAL CONSIDERATIONS

Table 13: Data Sets for Protocol Endpoints

Data Set/Endpoint	Criteria
Disposition	All subjects registered into the study
General safety	All subjects receiving at least one dose of any drug
Efficacy	All subjects with at least one disease evaluation

Patients will be included in the analysis for the treatment to which they were randomized.

12.1 Sample Size Justification

The primary endpoint for this trial is 2 year DFS. In order to detect an improvement of the fraction of patients free from disease at 2-year from 40% in the control arm to 63.2% in the rucaparib arm (corresponding to an HR=0.5), 38 events are needed to have 80% power to detect a difference in DFS using a one-side log-rank test with 0.10 level of significance (calculation done using nQuery Advisor 7.0 and assuming exponential survival). In order to observe 38 events we need to accrue about 102 patients, with an accrual time of about 13-18 months and an overall study duration around 25-30 months. In addition, 6 patients will be needed at the lower dose (cohort 1). Assuming ~20% will not be confirmed to have TNBC on central review; the total sample size will be increased to 135 to ensure 102 in the primary analysis (using cohort 2 and the randomized patients) and 6 in the safety analysis for cohort 1.

12.2 Patient Characteristics

Patient characteristics will be summarized by treatment group for demographics, baseline disease characteristics, and medical history. The two treatment groups will be compared using standard methods such as t-tests and chi-square tests.

12.3 Interim Safety Analyses

The first 12 patients (6 in cohort 1 and 6 in cohort 2) will be assigned to the rucaparib arm for an initial safety run-in. A safety analysis will be done after all six patients in each cohort have completed cycle 2. All toxicities will be tabulated. The study will move forward to cohort 2 if $\leq$ 1 of 6 in cohort 1 experience a DLT (as defined in Section 5.1). If $\geq$ 2 of 6 in cohort 1 experience a DLT, the study will be suspended and an amendment to explore alternate dosing schemes will be considered. Similarly, if $\leq$ 1 of 6 in cohort 2 experience a DLT (as defined in Section 5.1), the randomized portion will commence. If $\geq$ 2 of 6 in cohort 2 experience a DLT, the study will be suspended and an amendment to proceed with the randomized portion with the cohort 1 dose will be considered.

Once the decision is made to move forward with the randomized portion, a second safety analysis will be conducted after the first 40 patients (~20 from each group) have been randomized and completed 2 cycles of treatment. Toxicity counts and rates will be tabulated by treatment arm in a blinded fashion. The study will be terminated if the probability that the DLT rate equals 20% or less in either arm drops below .10. Accrual will continue during the interim analysis. The results of the analysis will be submitted to the CTMC for external review.

12.4 Analysis of Primary Objective

The comparison of DFS between the two groups will be made using an unstratified Kaplan-Meier analysis with a log-rank test to test for differences using the patients in safety run-in cohort 2 and the randomized portion of the study. A specific comparison of 2-year DFS will be made using a two-sample test based on the complementary log-log transformation as suggested in Klein, et al[32]. As supportive analysis, a stratified log-rank test will be done using the stratified randomization factors neoadjuvant anthracycline versus not and lymph node involvement at time of definitive surgery versus not. In addition, sensitivity analyses using Cox regression may be carried out to identify prognostic factors and provide adjusted estimates of the treatment group differences in DFS.

12.5 Analysis of Secondary Objectives

As support for the primary objective, overall DFS and 2-year DFS will be compared using the same techniques above using only the subjects in the randomized part of the study. One-year DFS will be tested using the test described above for 2-year DFS. Safety and tolerability variables will be tabulated separately for the two groups. Incidences of selected adverse events from the two treatment arms may be compared using Fisher's Exact tests on an exploratory basis. OS will be compared between treatment groups using the same methodology as DFS. PK levels will be described using summary statistics. In addition, characteristics of tumor specimens, and genomic DNA will be correlated with PARP inhibition, recurrence and toxicity. Continuous measures will be correlated with binary variables (e.g. recurrence and toxicity) using maximal chi-

square tests and continuous variables (e.g. PARP inhibition) using Pearson or Spearman correlations. Binary variables such as tumor and genomic characteristics will be correlated recurrence and toxicity using chi-square or Fisher's Exact test. All of the analyses with the PK and correlative data are exploratory and are designed to complement efforts in other trials with this agent.

13.0 TRIAL MANAGEMENT

13.1 Quality Controls and Quality Assurance

13.1.1 Study Monitoring/Auditing

Monitoring/Auditing visits to the trial sites will be made periodically during the trial, to ensure all aspects of the protocol are followed. Source documents will be reviewed for verification of agreement with data as submitted via the data collection system. The investigator/institution guarantee access to source documents by HOG or its designee and appropriate regulatory agencies.

The trial site may also be subject to quality assurance audit by Pfizer or its designee as well as inspection by appropriate regulatory agencies.

It is important for the investigator and their relevant personnel to be available during the monitoring/auditing visits and for sufficient time to be devoted to the process.

13.1.2 Data and Safety Monitoring Plan

HOG data safety monitoring activities include:

- Review of clinical trial conducted for progress and safety
- Review of all adverse events requiring expedited reporting as defined in the protocol
- Review of reports generated by data quality control review process
- Notification of the Sponsor Investigator of recommended action
- Notification of sites coordinated by the HOG of adverse events requiring expedited reporting and subsequent committee recommendations for study modifications

13.1.3 Data/Safety Monitoring and Reporting Guidelines

The HOG will compile data summary reports for this trial and submit these reports monthly to the Sponsor-investigator. The HOG will submit data summary reports quarterly to the Indiana University Melvin and Bren Simon Cancer Center (IUSCC) Clinical Trial Monitoring Committee (CTMC) for review.

13.2 Data Handling and Record Keeping

13.2.1 Case Report Forms

An electronic case report form (eCRF) is required and must be completed for each included patient. The completed dataset is the sole property of HOG and should not be

made available in any form to third parties, except for authorized representatives of appropriate Health/Regulatory Authorities, without written permission from HOG.

13.2.2 Record Retention

To enable evaluations and/or audits from Health Authorities/HOG, the investigator agrees to keep records, including the identity of all participating patients (sufficient information to link records; e.g., hospital records), all original signed informed consent forms, copies of all eCRF's, and detailed records of drug disposition. To comply with international regulations, the records should be retained by the investigator in compliance with regulations.

During data entry, range and missing data checks will be performed on-line. The checks to be performed will be documented in the Data Monitoring Plan for the study. A summary report (QC Report) of these checks together with any queries resulting from manual review of the eCRF's will be generated for each site and transmitted to the site and the site monitor. Corrections will be made by the study site personnel. This will be done on an ongoing basis.

13.3 Changes to the Protocol

Study procedures will not be changed without the mutual agreement of the Sponsor Investigator, Hoosier Oncology Group, and Clovis.

If it is necessary for the study protocol to be amended, the amendment or a new version of the study protocol (amended protocol) will be generated by the Hoosier Oncology Group and must be approved by each IRB, Clovis, and if applicable, also the local regulatory authority. Local requirements must be followed.

If a protocol amendment requires a change to the Written Informed Consent Form, then the IRB must be notified. Approval of the revised Written Informed Consent Form by the IRB is required before the revised form is used.

The principal investigator is responsible for the distribution of these documents to his or her IRB, and to the staff at his or her center. The distribution of these documents to the regulatory authority will be handled according to local practice.

Clovis's willingness to supply study drug is predicated upon the review of the protocol. The Hoosier Oncology Group agrees to provide written notice to Clovis of any modifications to the protocol or informed consent.

13.4 Ethics

13.4.1 Ethics Review

The final study protocol, including the final version of the Written Informed Consent Form, must be approved or given a favorable opinion in writing by an IRB. The investigator must submit written approval to the HOG office before he or she can enroll any patient into the study.

The principal investigator is responsible for informing the IRB of any amendment to the protocol in accordance with local requirements. In addition, the IRB must approve all advertising used to recruit patients for the study. The protocol must be re-approved by the IRB annually, as local regulations require.

Progress reports and notifications of serious unexpected adverse drug reactions will be provided to the IRB according to local regulations and guidelines.

The investigator is also responsible for providing the IRB with reports of any serious adverse drug reactions from any other study conducted with the investigational product. Clovis will provide this information to the Sponsor Investigator. These reports will be reviewed by the Sponsor Investigator and those considered unexpected and possibly related to protocol therapy plus all deaths within 30 days of discontinuing treatment will be forwarded to participating sites for submission to their Institutional Review Boards per their guidelines. All other events will be held and submitted to the sites for continuing review.

13.4.2 Ethical Conduct of the Study

The study will be performed in accordance with ethical principles originating from the Declaration of Helsinki, which are consistent with ICH/Good Clinical Practice, and applicable regulatory requirements.

13.5 Written Informed Consent

The investigator will ensure the patient is given full and adequate oral and written information about the nature, purpose, possible risks and benefits of the study. Patients must also be notified they are free to discontinue from the study at any time. The patient should be given the opportunity to ask questions and allowed time to consider the information provided.

The patient's signed and dated informed consent must be obtained before conducting any procedure specifically for the study. The investigator must store the original, signed Written Informed Consent Form. A copy of the signed Written Informed Consent Form must be given to the patient.

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