SUMMARY OF CHANGES

Date: November 9, 2023

Document: NCI Protocol #8264, PhII-96: "Phase II Trial of Single Agent ABT-888 with Post-Progression Therapy of ABT-888 in Combination with Carboplatin in Patients with Stage IV *BRCA*-associated Breast Cancer."

Note: The following is a Summary of Changes between the 6.1.23 and 11.9.23 versions of protocol

#	Section	Comments
1.	Protocol Version and Face page	Changed protocol version to November 9, 2023. Dates in the footers were also changed to 11.9.23v.
2.	5.1 and 9.1.1	Added information regarding the discontinuation of ABT-888 drug program. Patient will discontinue treatment by December 31, 2024 or earlier.

NCI Protocol #: 8264

Local Protocol #: PhII-96

Title: Phase II Trial of Single Agent ABT-888 with Post-Progression Therapy of ABT-888 in Combination with Carboplatin in Patients with Stage IV *BRCA*-associated Breast Cancer

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New York Consortium
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Dana Farber Cancer Institute
Beth Israel Deaconess Medical Center
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NCI Supplied Agent: ABT-888 (**NSC 737664, IND#** [redacted])

Commercially Available Agent: Carboplatin

Protocol Version Date: Original protocol v1 dated 11/12/09
Response to Consensus Review dated 2/5/10
Response to Follow-Up Review dated 2/26/10
Amendment dated 6/24/10
Amendment dated 10/18/10
RRA – CAEPR amendment dated 1/13/11
Amendment dated 2/25/11
Amendment dated 6/23/11
Amendment dated 9/01/11
Amendment dated 10/6/11
Amendment dated 11/21/11
Amendment dated 4/24/12 – Rejected
Amendment dated 5/11/12
Amendment dated 5/29/12
Amendment dated 7/17/12
Amendment dated 8/20/12 – Action Letter - CAEPR

Amendment dated 7/23/13

Amendment dated 12/31/13

Amendment dated 4/20/16 – Action Letter CAEPR

Amendment dated 3/14/18 – CTCAE change

Amendment dated 6/14/18 – RRA (disapproved)

Amendment dated 7/9/18 – RRA (disapproved)

Amendment dated 7/19/18 – RRA (disapproved)

Amendment dated 8/6/18 – RRA

Amendment dated 1/5/21 – PI change

Amendment dated 6/1/23 – Drug availability and expiration

Amendment dated 11/9/23 – Updated drug availability

SCHEMA

Safety lead-in: Stage IV *BRCA*-associated breast cancer patients will be treated with carboplatin on day 1 of each 21 day cycle, given at an AUC of 5. The dose of carboplatin may be fixed at a lower AUC if DLTs in the safety lead-in prompt adoption of any of the reduced [-] dose schedules, except for individual dose modifications in subsequent cycles to address toxicities. ABT-888 will be given on days 1-21 of each cycle, starting at 50 mg po BID (and then at 100 mg, 150 mg, and 200 mg BID) per cohort. Between 12-27 patients will be treated during the safety lead-in, and no patients in the safety lead-in will be included in the primary analysis of the Phase II study as the Phase II portion patients start treatment with single agent ABT-888. [Note: safety lead-in was completed with 25 patients, and the MTD was established with carboplatin AUC 5, ABT-888 150 mg BID]

Phase II Study:

Stage IV *BRCA (stratified by BRCA1 or BRCA2)*-associated breast cancer patients will initiate treatment with ABT-888 at the single agent recommended dose 400mg BID, based on CTEP recommendations and toxicity experience from PHI-63 NCI #8282: A Phase I Study of Chronically-Dosed, Single Agent ABT-888 in Patients with Either BRCA 1/2-Mutated Cancer: Platinum Refractory Ovarian, Fallopian Tube, or Primary Peritoneal Cancer; or Basal Like Breast Cancer.

Following progression, patients will be off treatment for one week (see justification in statistics section), and then if they meet the eligibility requirements, the patients will initiate treatment with carboplatin AUC 5 plus ABT-888 150 mg BID (as the Maximum Tolerated Dose of the combination established during the safety lead-in noted above).

The two strata (BRCA1 and BRCA2-associated breast cancer) will accrue independently: Initially 10 patients will be accrued to a stratum. More than 1 confirmed response in the first 10 patients in a strata will result in an additional 12 patients accrued to that stratum (for a total of 22). As a result, if 2 responses are seen in the first 10 patients with both BRCA1 and BRCA2-associated breast cancer, a total of 44 patients will be accrued to the Phase II portion of this study.

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PROTOCOL SYNOPSIS AND OVERALL DESIGN

Title: Phase II Trial of ABT-888 with Post-Progression Therapy of ABT-888 in Combination with Carboplatin in Patients with Stage IV *BRCA*-associated Breast Cancer

Sponsor: National Cancer Institute

Project phase: Phase II with a combination lead-in

Objectives:

- To evaluate the efficacy of single agent ABT-888 (**NSC 737664**) in *BRCA* carriers with metastatic breast cancer based on response rate (RECIST criteria)
- To evaluate progression-free survival of patients on single-agent ABT-888.
- To further describe the safety and tolerability of ABT-888 (**NSC 737664**) as a single agent and in combination with carboplatin for *BRCA*-associated breast cancer.
- To evaluate the pharmacokinetics of ABT-888 (**NSC 737664**) alone and in combination with carboplatin.
- To assess the relationship between the level of PARP inhibition by ABT-888 and biomarkers of DNA damage in PBMC's and tumor
- To explore the relationship between biomarkers of drug effect and progression-free survival
- To evaluate the efficacy and safety of the combination of carboplatin and ABT-888 in patients who have failed single agent ABT-888.
- To conduct subset analysis on *BRCA1* vs. *BRCA2* and hormone receptor status

Study design:

This is a **Phase II trial** to establish the single agent activity with ABT-888 in BRCA1 and BRCA2 patients. Following progression, patients will receive ABT-888 plus carboplatin after a one week delay according to the dose established in a safety lead-in.

Sample size: 20-44 patients are expected to be treated on the Phase II part of the trial (10-22 per BRCA1 and BRCA2 stratum).

Investigational Product(s): ABT-888 (NSC 737664)

Carboplatin (commercially available)

Dose regimen: ABT-888 at 400 mg BID. The post-progression dosing, following a 1 week delay, will be dosed according to the safety-lead in of this study (150 mg BID plus carboplatin AUC 5).

Safety lead-in: Stage IV *BRCA*-associated breast cancer patients will be treated with carboplatin on day 1 of each 21 day cycle, given at an AUC of 5 in the first dose level. The dose of carboplatin may be fixed at a lower AUC if DLTs in the safety lead-in prompt adoption of any

of the reduced [-] dose schedules. ABT-888 will be given on days 1-21 of each cycle, starting at 50 mg po BID (and then at 100 mg, 150 mg, and 200 mg BID per cohort, if those doses do not exceed the recommended Phase II single agent dose derived from the ongoing phase I trial, NCI# 8282). Between 24-27 evaluable patients will be treated during the safety lead-in, and these patients will not be included in the primary analysis of the Phase II study. Cycle length is 21 days. Patients are evaluated every 3 cycles until progression of disease or the patient is otherwise withdrawn from the trial. [Note: safety lead-in was completed with 25 patients, and the MTD was established with carboplatin AUC 5, ABT-888 150 mg BID]

Phase II Portion: Cohorts of BRCA1 and BRCA2 carriers with measurable metastatic breast cancer will be treated with ABT-888 at 400 mg BID, to assess single agent response rate.

Documentation of single agent activity (more than 1 CR or PR per RECIST) per stratum (BRCA1 or BRCA2) in the first 10 patients on each stratum is a pre-requisite to continuing to a total of 22 patients per stratum. Following progression, patients will have a one week interval of no treatment, and if eligible proceed to receive ABT-888 150 mg BID plus carboplatin AUC 5.

Route of administration:	ABT-888 will be administered BID orally Carboplatin will be administered IV
Key eligibility criteria:	Stage IV breast cancer and confirmed *BRCA*+ status. Evaluable disease is allowed in the safety lead-in component. Measurable disease as defined by RECIST criteria is required for the phase II component.
Key procedures:	RECIST measurement of tumor progression, assessment of biomarkers, pharmacokinetics (PK) and pharmacodynamics (PD) in serum, archival and, as feasible, pre- and post-treatment tumor tissue.

1 OBJECTIVES

1.1 PRIMARY OBJECTIVES

This Phase II study will be conducted as part of the N01 contract agreement (NO1 CM 62209) that the California Cancer Consortium (CCCP) has with the National Cancer Institute. The objectives of this study are:

- To evaluate the efficacy of single agent ABT-888 (**NSC 737664**) in *BRCA* carriers with metastatic breast cancer based on response rate (RECIST criteria)

1.2 SECONDARY OBJECTIVES

- To conduct subset analysis on *BRCA1* vs. *BRCA2* and hormone receptor status

- To evaluate progression-free survival of patients on single-agent ABT-888.
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2 BACKGROUND

2.1 BRCA-RELATED CANCER

DNA Repair and Toxicity. DNA repair mechanisms protect both normal and cancer cells from DNA damage, allowing them to proliferate. Classic chemotherapy agents including platinum compounds target DNA, leading to arrest of DNA replication. Generally, at least two DNA repair systems can help cells evade lethality, but repeat exposures to specific chemotherapy agents eliminate tumors. One way that tumors evade the consequences of DNA-damaging chemotherapeutic treatment is by using complementary repair systems (**Figure 1**). *BRCA1*- or *BRCA2*-associated cancers are deficient in homologous recombination repair (HRR), but other complementary DNA repair systems allow tumor cells to replicate by alleviating blocks to DNA synthesis. Therefore, elimination of complementary repair systems that would otherwise overcome blocks to DNA replication in tumors will kill those cells [1, 2]. Tumorigenesis in a *BRCA* carrier generally follows the Knudson model for tumor suppressor genes [3], wherein an early step in breast cancer (BC) and ovarian cancer (OC) development is loss of the wild type (wt) *BRCA* allele from heterozygous normal tissue. Thus, the BRCA null phenotype is limited to the tumor cells in a *BRCA* mutation carrier. Therefore, targeting the BRCA defect in tumors can theoretically increase the therapeutic index.

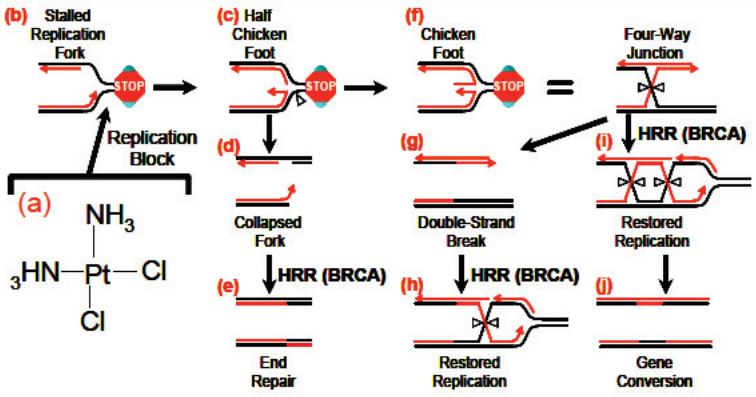

Figure 1. Stalled replication forks: consequences and solutions. (a) Some cis-platinum modification arrests DNA synthesis, (b) may reverse, (c) only one strand reversed, (d) endonuclease cleavage, (e) HRR repair, (f) reversed fork or recombination intermediate, (g) cleavage to form double strand break (DSB), (h) HRR to restore replication, (i) no DSB formed, (j) two Holliday junctions cleaved. Adapted from Ref. [1].

BRCA1 and BRCA2 (BRCA). *BRCA1* and *BRCA2* tumor suppressor genes were discovered by positional cloning after linkage was established to chromosomes 17 and 13, respectively [4-6]. BRCA1 is 1863aa long (208kDa), and has a gene composed of 24 exons covering 81kb on chromosome 17 [7]. BRCA2 is one of the largest proteins synthesized in human cells; consisting of 3418aa (384kDa) with its gene composed of 27 exons situated on chromosome 13. These proteins have multiple functions and interact with a large number of proteins.

Consequences of BRCA deficiency. Five–10% of breast and ovarian cancers are associated with mutations in the *BRCA* genes, resulting in thousands of cancer cases every year. The lifetime risk of developing breast cancer that is associated with a *BRCA* mutation is as high as 85% and the lifetime risk of ovarian cancer may be as high as 44% [8]. Cells deficient in BRCA are more sensitive to drugs that cross link DNA, such as platinum agents and mitomycin C [9]. Impaired HRR in BRCA deficient cells results in their inability to repair consequent lesions and results in increased lethality (**Figure 2**). If HRR and other complementary mechanisms are removed, cells must resort to non-homologous end-joining, which is an error prone process that can lead to cell death [10].

Base excision repair (BER) is a pathway found in all organisms. Although there are several branches to this pathway, a general mechanism for base excision repair of damage that blocks DNA synthesis is removal of the modified base by a DNA glycosylase to

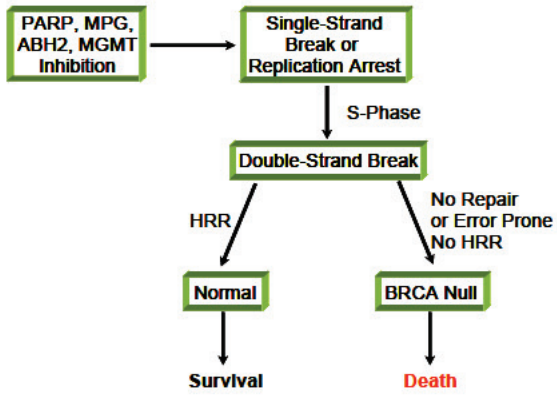

Figure 2. Goal: Replication arrest from single strand breaks can be removed by various repair mechanisms, but if HRR is also eliminated, cell death ensues from arrested replication. This cell death is specific for cancer cells that are deficient in both DNA repair pathways and could be therapeutically exploited.

generate an abasic site, incision at the abasic site by an endonuclease, insertion of a normal nucleotide by a DNA polymerase, removal of a deoxyribose phosphate, polyADP-ribosylation, and ligation. One potential therapeutic target in this pathway is the group of enzymes attaching poly(ADP-ribose), the poly(ADP-ribose) polymerases.

Poly(ADP-ribose) Polymerases (PARPs). In the last 10–15 years diverse roles for the PARP superfamily of enzymes have been identified [11]. One role for PARP is the attachment of poly(ADP-ribose) (PAR) at single-strand breaks during BER [11]. The attachment of PAR chains can serve as a signal for repair [12] and has a role in eliminating stalled replication forks [13]. PAR of proteins is a dynamic process with a short half-life (t1/2) of <1 min. The enzymes responsible for degrading these polymers are poly(ADP-ribose) glycohydrolase (PARG), which cleaves ribose-ribose bonds, and

ADP-ribosyl protein lyase, which removes the protein proximal to the ADP-ribose monomer.

PARP is an essential nuclear enzyme that plays a role in recognition of DNA damage and facilitation of DNA repair. Therefore, inhibition of PARP is expected to enhance the effects of DNA damage. Expression of PARP is higher in tumor cells as compared to normal cells. This overexpression has been linked to drug resistance and the ability of tumor cells to withstand genotoxic stress. Hence, it is anticipated that PARP inhibitors will function as sensitizers to DNA-damaging chemotherapeutic agents and radiation therapy.

2.2 ABT-888 (NSC 737664):

We are studying a potent new PARP inhibitor, ABT-888 (NSC 737664), obtained from the Cancer Therapy Evaluation Program (CTEP). Based on promising preclinical results, we propose a novel translational clinical trial of ABT-888 as a targeted therapy for *BRCA*-associated cancer.

Poly(ADP-ribosyl)ation (PAR) occurs after single or double-stranded DNA damage and represents the posttranslational modification of histones and other nuclear proteins by PARP. PAR has been implicated in many cellular processes including replication, transcription, differentiation, gene regulation, protein degradation, and spindle maintenance. PARP-1 and PARP-2 are nuclear proteins and are the only members of the PARP family with zinc-finger DNA binding domains. These domains localize PARP-1 and PARP-2 to the site of DNA damage. PARP-1 is highly conserved and has three structural domains (N-terminal DNA-binding domain; automodification domain, and the NAD+-binding domain). The catalytic domain is located at the C-terminus end of the protein. In knockout mouse models, deletion of PARP-1 is sufficient to impair DNA repair [14-16]. The residual PARP-dependent repair activity (~ 10%) is due to PARP-2. This suggests that only PARP-1 and PARP-2 need to be inhibited to impair DNA repair [17-19].

Increased PARP activity is one of the mechanisms by which tumor cells avoid apoptosis caused by DNA damaging agents. PARP activity is essential for the repair of single-stranded DNA breaks through the base excision repair (BER) pathways [18, 20]. Therefore, inhibition of PARP sensitizes tumor cells to cytotoxic agents (e.g. alkylators and topoisomerase I inhibitors) which induce DNA damage that would normally be repaired through the BER system. A significant therapeutic window appears to exist between a PARP inhibitor's ability to potentiate therapeutic benefit versus potentiation of undesirable side effects. Potent small molecule inhibitors of poly ADP-ribose polymerase entered early phase clinical trials over the last 5 years, primarily as potentiators of existing DNA damaging chemotherapies (reviewed in [21]). As expected, PARP inhibitors do not potentiate agents that do not cause DNA damage.

ABT-888 has been used with platinum agents in pre-clinical studies and with the methylating agent temozolomide in clinical studies [22-24]. However, potentiation of

platinum agents by ABT-888 is anticipated to be more efficient than potentiation of temolozomide by ABT-888, since platinum agents generate DNA modifications repaired primarily by nucleotide excision repair, whereas temozolomide forms damaged bases repaired by BER. Therefore, use of temozolomide in conjunction with ABT-888 targets principally BER, while carboplatin-ABT-888 would attack both nucleotide excision repair and BER pathways.

Exploitation of BRCA deficiencies with DNA repair inhibitors as therapeutic tools. Cells with BRCA mutant proteins are sensitive to chemotherapeutic agents [25, 26], but PARP inhibitors have an inherent advantage, the therapeutic potential to kill tumor cells that have homozygous *BRCA* mutations, while leaving heterozygous cells virtually untouched [1, 2]. This provides a large therapeutic window for PARP inhibition in patients with BRCA-associated BC. The approach has been likened to inducing "synthetic lethality", as the relatively well tolerated PARP inhibitor treatment causes endogenous DNA damage to accumulate in the HRR-deficient cell background, leading to replication arrest and apoptosis [27]. Single-agent activity in tumor cells with defective HRR (e.g., *BRCA*-associated BC) is suggested by pre-clinical data [1, 2], and preliminary results of a recent clinical trials suggested responsiveness in *BRCA*-associated breast and ovarian cancer [28-30]. As noted above, the relevant functional defect in *BRCA*-associated BC is HRR deficiency, and the mechanism of action of platinum agents is through DNA binding and associated DSBs [31]. Pre-clinical studies in a conditional mouse model for *BRCA*-associated hereditary BC indicated tumors responded well to cisplatin, and did not become resistant, although the tumors regrew after therapy stopped [32].

The results of ABT-888 testing in combination with cytotoxic agents, in several tumor models, is summarized below (**Table 1**). ABT-888 (whether administered parenterally or orally) substantially increased the efficacy of cytotoxic therapies, when measured by either treated/control tumor volumes (%T/C) or by increased time for tumors to grow to a particular size (%ILS).

Table 1. Preclinical data for ABT-888 mediated potentiation of cytotoxic agents

	Breast carcinoma (human MX-1)	**Glioblastoma multiform (rat 9L)**	**B cell lymphoma (human DOHH2)**	**Melanoma (murine B16F10)**
Carboplatin	Yes			
Cisplatin	Yes		No	
Cyclophosphamide	Yes			
Irinotecan	Yes			Yes
Temozolomide		Yes		Yes

A PARP inhibitor was recently shown to substantially potentiate cisplatin and carboplatin in a murine BRCA2 model [33, 34]. The exquisite sensitivity of these cells to the PARP inhibitor, alone or in combination with carboplatin, provides strong support for PARP inhibitors as a novel targeted therapeutic approach against BRCA-deficient cancers. A study [22] of ABT-888 alone and in combination with irinotecan in breast, ovarian, colon and lung cancer cell lines with known aberrations in DNA repair, showed significant single agent activity in the MX-1 (BRCA1-deficient) cell line (inhibitory concentration 50% [IC50] of 4 μM vs. >80 μM in several non-*BRCA* cell lines). Studies were performed at a fixed dose (210 nM) of ABT-888, a drug plasma level that can be achieved in mice and humans. ABT-888 was able to potentiate irinotecan cytotoxicity in two breast cancer cell lines (T47D [10,000-fold] and MX-1 [200-fold]), the ovarian line A2780 (20-fold) and the lung cancer cell line HOP62 (9-fold). Investigation of DNA repair abnormalities in the responsive cell lines suggested potential determinants of response: a) mutations in the BRCA1 tumor suppressor protein as found in the MX-1 cell line confer ABT-888 single agent activity; b) elevated protein levels of the nucleotide excision repair enzyme ERCC1 sensitize to the ABT-888/irinotecan combination in T47D, A2780, and HOP62 cells; and c) p53 mutations enhance tumor cell kill by the ABT-888/irinotecan combination in cell lines with high ERCC1 levels such as T47D. Taken in sum, preclinical studies suggest that BRCA1 and p53 mutational status should be assessed, as well as the measurement of ERCC1 and γH2AX levels (indicating the presence of DSBs) as response correlates in clinical trials with ABT-888. Many these questions were incorporated into the planned correlative studies associated with the proposed clinical trial (see below).

Our pre-clinical experiments with ABT-888 treatment of Brca1 or Brca2 deficient mouse embryonic stem cells (mESCs) indicated substantial single agent activity compared to wild type (wt) control cells (**Figure 3**). While the BRCA deficient cells showed the same pattern of sensitivity to both cisplatin and carboplatin, the addition of ABT-888 was synergistic in all three cell lines (data not shown), requiring significantly less of the chemotherapeutic drug to achieve the same effect.

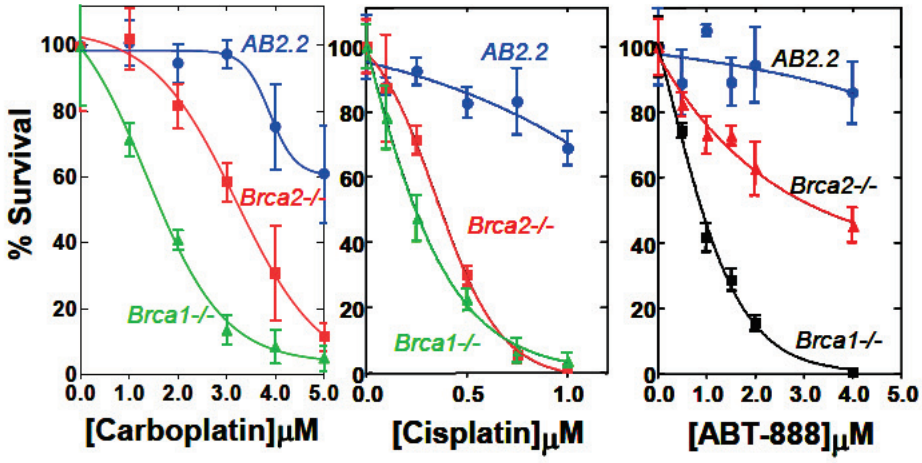

Figure 3. In vitro inhibition of Brca1 and Brca2 deficient mouse embryonic stem cells. Colony forming assay in triplicate with indicated drug concentrations. Survival (%) is depicted on the vertical axis. AB2.2 in the figure represents the *BRCA* wt control cells.

Data showing *in vivo* ABT-888 inhibition of PARP [35], and *in vitro* enzymatic inhibition comparable to the KuDOS agents (KU0058684 and KU0058948), strongly suggest that single-agent ABT-888 will act similarly to the KuDOS single agents in the BRCA null setting [2, 23, 27, 36, 37]. Although a single-agent approach with a relatively non-toxic therapy would be ideal, initial or acquired resistance is likely to necessitate combined targeted and/or conventional chemotherapies. The results of the first phase II single agent trials, presented at ASCO 2009, indicated a remarkable response rate (>30%) and clinical benefit rate (>60%) in women with *BRCA*-associated BC or OC, respectively [29, 30], further development of the agent however, is needed. A phase II trial of an intravenous PARP inhibitor iniparib, in combination with carboplatin and gemcitabine showed significantly improved response and survival in triple negative BC [38]. However, a phase III confirmatory trial of the same design failed to confirm any benefit resulting from the addition of iniparib, and subsequent laboratory analysis suggested that iniparib has no PARP-specific activity [39, 40]. Hence, there remains the unmet clinical need to investigate PARP inhibitors, alone or with concomitant cytotoxic agents, in *BRCA*-associated breast cancer.

2.3 CARBOPLATIN

Platinum agents in treatment of breast cancer. Single agent phase II trials of cisplatin and carboplatin in patients with metastatic BC were carried out in the 1980s in Europe, as well as the United States [41-43]. These trials preceded current requirements to apply RECIST criteria for response assessment. A European trial of single agent carboplatin

administered at an AUC of 7 reported a 33% response rate in previously untreated patients [442].

More recently, researchers sought to better characterize and find alternative approaches to treatment of high-grade, clinically aggressive BC that does not express steroid hormone receptors or Her2/neu amplification—"triple negative" tumors [44-46]. With the identification of impaired DNA repair mechanisms in *BRCA* carriers, and implications of a similar biology in patients with triple negative/basaloid breast cancer (a phenotype frequently seen in association with the *BRCA1* genotype), DNA-damaging agents such as the platinum compounds emerged as potential targeted therapies.

Indeed, several early reports in triple negative breast cancer suggested that cisplatin as a single agent [444], or in combination [47], may provide higher response rates, including complete responses, than what could have been expected in the general breast cancer population with such treatment. Further, CTEP has indicated that they are considering combinations with carboplatin as the only platinum agent in their long term development strategy for treatment in earlier stage breast cancer (e.g. adjuvant) settings.

Carboplatin is a commonly used platinum compound that acts by binding to DNA and interrupting cell division. It is approved by the FDA for the treatment of patients with ovarian cancer. It is also used for the treatment of non-small cell lung cancer, small cell lung cancer, head and neck cancer, endometrial cancer, metastatic seminoma and more recently in breast cancer. Carboplatin is eliminated by renal excretion. The clearance is related to the glomerular filtration rate. Therefore it is dosed based on the GFR and the target area under the concentration versus time curve (AUC). The main side effect of carboplatin is myelosuppression. Other toxicities include nausea, vomiting, renal and neurotoxicity.

Initial sensitivity and response to platinum agents may be an explanation for the observed enhanced survival in *BRCA*-associated ovarian cancer; this effect was most pronounced for advanced stage (III/IV) disease [48, 49]. However, in many cases, the cancer becomes platinum-refractory. Since HRR deficiency defines BRCA-associated defects and is correlated with the sensitivity to PARP inhibitor drugs, mechanisms reconstituting HRR could result in drug resistance. Two recent studies suggest that one mechanism of drug resistance is *in vivo* selection for *BRCA2* "reversion" mutants, wherein alteration of the abnormal allele restores the reading frame and specific functional domains, along with recovery of HRR function [50, 51]. A better understanding of the mechanism(s) of that acquired resistance has the potential to benefit many women with *BRCA*-associated cancer.

Careful study of biomarkers may reveal additional pathways to be targeted in the future, while the potentiation of drugs such as carboplatin by concomitant PARP inhibition is likely to increase efficacy of carboplatin at lower doses. In one trial of combination PARP inhibitor and temozolomide, dose reduction of the latter was necessary because of enhanced toxicity. However, the reduced-dose (25%) regimen improved tolerability over the single-agent temozolomide, while doubling the response rate and time to progression

[24]. With an ever increasing arsenal of molecularly-targeted therapies, an understanding of the specific biologic pathways operative in a given tumor (somatic) or germline context has great potential for enhanced therapeutic ratios and quality-adjusted years of life saved.

2.4 RATIONALE

BRCA proteins and other DNA repair mechanisms, including base excision repair and direct reversal of DNA damage, function in a complementary manner to remove hurdles that impede DNA cell division. Therefore, in BRCA cells, inhibition of complementary repair function should increase the sensitivity of cancer cells to killing by both endogenous mutagens and exogenous agents. The PARP inhibitor ABT-888, validated in our pre-clinical work, will be tested alone and in combination with carboplatinum this clinical trial.

Rationale for selection of starting doses: For ABT-888, the chosen starting dose is based on an ongoing phase 1 continuous dosing study (NCI#8282), in which only one of six patients at the level of 50mg BID had a DLT. Carboplatinum was able to be delivered at AUC 6 in the phase I combination study of carboplatinum, paclitaxel and ABT-888 (NCI#7967). While paclitaxel will not be used in this study, ABT-888 may behave synergistically with carboplatin and result in added toxicity, primarily myelosupression, consequently a dose modification scheme for carboplatin is included. Although we expect both arms of this regimen to be well tolerated, we have established guidelines and criteria which will be used to flag an unexpected number of patients who experience unacceptable toxicity. These rules will be applied to both arms independently, although the main motivation for such detailed monitoring is based on the combination arm.

The MTD for carboplatin dosing is established as AUC 5. The previous dose escalation schedule labelled as Table 3a has now been deleted. An expanded safety lead-in attempted to maximize the ABT-888 exposure (Table 3) while keeping the carboplatin at AUC 5. This is prompted by observation of grades 3 & 4 thrombocytopenia with an otherwise well-tolerated regimen in the initial safety lead-in experience with the first 9 patients. Given that the Phase I continuous dosing study of ABT-888 (NCI#8282) passed 400mg BID, it seems likely that ABT-888 in combination with carboplatin can be escalated safely to at least 200 mg BID in the expansion phase. [Note: safety lead-in was completed with 25 patients, and the MTD was established with carboplatin AUC 5, ABT-888 150 mg BID]

3 PATIENT SELECTION

Study Population:

The infrastructure of the multi-institutional California Cancer Consortium with Pennsylvania (CCCP) will be used to obtain access to the specific CTEP agent, and facilitate development, conduct and dissemination of the proposed targeted therapy protocol, which will be supported under a N01 phase II contract (N01CM57018). Along with the 5 affiliated CCCP institutions (City of Hope, University of California at Davis, University of Southern California, University of Pittsburgh, and Pennsylvania State University), five other N01-supported consortia are committed to participating in the clinical trial, including this latest amended version (New York Consortium [even though this consortium is no longer part of the NO1 contract mechanism, the participating institutions have agreed, and demonstrated ongoing commitment to accruing patients]; University of Chicago Consortium; Mayo Clinic Phase 2 Consortium, Princess Margaret Hospital, Toronto, Canada; MD Anderson Cancer Center, Houston; letters of collaboration are in the Appendix). All patient registrations will be handled centrally via the CCCP coordinating center.

Clinical cancer genetics resources will be used for enhanced recruitment, with strong minority representation, including our established hereditary cancer registry, community-based *Cancer Screening & Prevention Program Network* (CSPPN) and liaisons with advocates/organizations for national recruitment and dissemination. Data mining from the existing COH CSPPN cohort (described in Preliminary Results) identified approximately 65 *BRCA* carriers with locally advanced (stage III) or metastatic BC, and we accrue approximately 110 new *BRCA* carriers with BC in the CSPPN annually. CCCP partner institutions each have a set of known *BRCA* carriers with BC, and most have a formal cancer genetics unit. For example, USC has accrued 49 *BRCA* carriers with BC, and University of Pittsburgh estimates approximately 20 new *BRCA*-associated BC cases each year. Summation of estimates from the other collaborating consortia indicate approximately 90 potentially eligible women with advanced *BRCA*-associated BC will be identified annually. Overall, after selecting for advanced stage cases, we estimate that 5 of 22 potentially eligible cases across the consortia will be accrued to the study every month over the projected 18-month accrual period. Additional procedures to augment accrual include listing on COH Clinical Trials On-line, posting the studies on the FORCE web site (per Advocate Sue Friedman; letter in Appendix), and a newsletter style announcement distributed (email and USPS) to a mailing list of regional/referring physicians. The Clinical Cancer Genetics team (PI: Weitzel) will hold monthly teleconferences with the genetics units across the consortia to review progress identifying *BRCA* carriers as candidates for study, and disseminate any updated promotional materials.

Treating physicians who are approved by their respective Institutional Review Boards (IRB) will be responsible for explaining the study, answering questions and obtaining informed consent, according to regulatory guidelines and to respective IRB guidelines.

Ongoing understanding will be assessed and questions will continue to be answered by the treating physicians.

3.1 ELIGIBILITY CRITERIA

3.1.1 Patients must be female, and must have histologically confirmed breast cancer that is metastatic or locally advanced, unresectable and for which standard curative measures do not exist or are no longer effective.

3.1.2 Patients must have a known deleterious *BRCA* mutation confirmed by report from a CLIA certified laboratory (generally Myriad Genetics Laboratory). It is expected that *BRCA* testing will be covered as medically necessary care by the patient's insurance carrier.

3.1.3 Measurable disease by RECIST criteria. (Evaluable disease is allowed only for the Safety Lead-In phase).

3.1.4 Prior chemotherapy regimens for metastatic disease are completed, at least 3 weeks prior to starting therapy. Prior radiation and hormonal treatment must be completed at least 1 week prior to starting therapy.

3.1.5 Female, age ≥18 years. Because no dosing or adverse event data are currently available on the use of ABT-888 in patients <18 years of age, children are excluded from this study.

3.1.6 ECOG Performance Status 0-2 (See Appendix A).

3.1.7 Life expectancy of greater than four months.

3.1.8 Patients must have normal organ and marrow function as defined below

– absolute neutrophil count	≥1,500/mcL
– platelets	≥100,000/mcL
– total bilirubin	≤ 1.5 X institutional upper limit of normal
– AST(SGOT)/ALT(SGPT)	≤2.5 X institutional upper limit of normal *unless there is evidence of liver metastasis, in which case the AST(SGOT)/ALT(SGPT) must be ≤ 5 X institutional upper limit of normal*
– creatinine	within normal institutional limits
OR	
– creatinine clearance	≥60 mL/min/1.73 m^2 for patients with creatinine levels above institutional normal.

3.1.9 If a woman is of child-bearing potential, a negative serum or urine pregnancy test is required. (The effects of ABT-888 [NSC 737664] on the developing human fetus are unknown. For this reason and because PARP Inhibitor agents are known to be teratogenic [see Investigator Brochure], women of child-bearing potential and men must agree to use adequate contraception (hormonal or barrier method of birth control;

abstinence) prior to study entry and for the duration of study participation. Participants should agree to use contraception for at least 3 months after the completion of study therapy. Should a woman become pregnant or suspect she is pregnant while participating in this study, she should inform her treating physician immediately.)

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

3.2 EXCLUSION CRITERIA

3.2.1 Prior therapy with platinum agents (adjuvant therapy with platinum agents is allowed, if completed ≥ 12 months prior to relapse), or PARP inhibitors (prior iniparib, since it is no longer considered a PARP inhibitor, is allowed).

3.2.1 Patients may not be receiving any other investigational agents.

3.2.2 Patients with known CNS metastases requiring anticonvulsive medications, or steroids or with active symptomatology. Patients on anticonvulsant medications prescribed for reasons other than CNS metastases, not on steroids and without active symptomatology are eligible. Patients must be off anti-seizure medications and steroids for 3 months or more before enrollment.

3.2.3 Patients with active seizure or a history of seizure. Patients with CNS metastases must be stable after therapy for > 3 months and off steroid treatment prior to study enrollment.

3.2.4 History of allergic reactions attributed to compounds of similar chemical or biologic composition to ABT-888 (NSC 737664) or PARP inhibitors.

3.2.5 Patients with contraindications to platinum agents are excluded.

3.2.6 Prior or current non-breast malignancy within 5 years except non-melanoma skin cancer, or resected stage I ovarian cancer.

3.2.7 Patients with any non-malignant intercurrent illness (e.g. cardiovascular, pulmonary, or central nervous system disease) which is either poorly controlled with currently available treatment, or which is of such severity that the investigators deem it unwise to enter the patient on protocol.

3.2.8 Pregnant women are excluded from this study because ABT-888 (NSC 737664) has the potential for teratogenic or abortifacient effects. Because there is an unknown but

potential risk for adverse events in nursing infants secondary to treatment of the mother with ABT-888 (NSC 737664), breastfeeding should be discontinued.

3.2.9 Patients unable to swallow the ABT-888 tablets whole are ineligible. (The tablets cannot be crushed or broken.)

3.2.10 Patients with an active severe infection; known infection with HIV, hepatitis B virus, or hepatitis C virus. HIV-positive patients on combination antiretroviral therapy are ineligible because of the potential for pharmacokinetic interactions with ABT-888 (NSC 737664). In addition, these patients are at increased risk of lethal infections when treated with marrow-suppressive therapy. Appropriate studies will be undertaken in patients receiving combination antiretroviral therapy when indicated.

3.3 INCLUSION OF WOMEN AND MINORITIES

Women and members of all races and ethnic groups are eligible for this trial.

Plan for recruitment of underrepresented minorities: Collectively, there is a good track record and infrastructure for recruitment of underrepresented minorities into clinical trials. In addition to large Hispanic (primarily Mexican American) populations proximal to each of the CCCP institutions, the PI for this proposal conducts satellite genetic cancer risk assessment clinics as part of ongoing health services research (Komen #POP0600464) in underserved, predominantly Latina populations [52-55]. The main clinic is located at Olive View Medical Center (OVMC), the primary public health hospital in the San Fernando Valley. Dr. Nancy Feldman, Chair of Medical Oncology at OVMC, works closely with Dr. Weitzel, referring young Latinas with locally advanced and metastatic BC for genetic testing and treatment trials. Led by bilingual/biliterate genetic counselors and research coordinators and patient navigators, cancer risk counseling protocols are tailored to the respective communities. This outreach has resulted in approximately 40% accrual of Hispanics on phase I (completed)[56] and phase II (IRB#02164; accrual of female *BRCA* carriers completed) prevention trials at COH. The genetics unit at USC is establishing a genetic cancer risk assessment clinic at the main county hospital, which serves an ethnically diverse population of Hispanics and African Americans.

Please see accrual targets by ethnic and racial categories for the study (Table 2).

Table 2: Accrual Targets

Accrual Targets					
Ethnic Category	**Sex/Gender**				
	Females		**Males**		**Total**
Hispanic or Latino	15	+	0	=	15
Not Hispanic or Latino	56	+	0	=	56

Ethnic Category: Total of all subjects	71	(A1)	+	0	(B1)	=	71
Racial Category							
American Indian or Alaskan Native	0		+	0		=	0
Asian*	7		+	0		=	7
Black or African American	6		+	0		=	6
Native Hawaiian or other Pacific Islander*	0		+	0		=	0
White	58		+	0		=	58
Racial Category: Total of all subjects	71	(A2)	+	0	(B2)	=	71
		(A1 = A2)			(B1 = B2)		(C1 = C2)

***-These categories are combined.**

4 REGISTRATION PROCEDURES

4.1 GENERAL GUIDELINES

Eligible patients will be entered on study centrally at the California Cancer Consortium Data Coordinating Center at the City of Hope. All sites should call the Data Coordinating Center at (626) 256-4673 extension 65928 to verify dose level availabilities.

Following registration, patients should begin protocol treatment within 24 hours. Issues that would cause treatment delays should be discussed with the Principal Investigator. If a patient does not receive protocol therapy following registration, the patient's registration on the study may be canceled. The Data Coordinating Center should be notified of cancellations as soon as possible.

Except in very unusual circumstances, each participating institution will order DCTD-supplied agents directly from CTEP. Agents may be ordered by a participating site only after the initial IRB approval for the site has been forwarded by the Data Coordinating Center to the CTEP PIO (PIO@ctep.nci.nih.gov) except for Group studies.

4.2 REGISTRATION PROCESS

Once the signed informed consent has been obtained, all pretreatment evaluations have been performed, and patient's eligibility has been confirmed by the Data Coordinating Center a patient will be entered on study, and be considered registered.

To register a patient, the research nurse or data manager must complete the eligibility/registration form and contact the Consortium office (Data Coordinating Center for the California Cancer Consortium) at the City of Hope (626-256-4673, ext. 65928), FAX a copy of the completed eligibility checklist, required pre-study tests (pathology and baseline laboratory reports (including CT reports), BRCA genetic test result), signed Informed Consent, signed Patients' Bill of Rights and HIPAA authorization form. (FAX Number: 626-256-8654). See Appendix D ("Registration Procedures")

The research nurse or data manager at the participating site will then call the Data Coordinating Center at Tel# 626-256-4673 extension 65928 to confirm receipt of all registration documents. To complete the registration process, the Data Coordinating Center coordinator will:

- Verify the eligibility
- Register the patient on study
- Assign a patient accession number
- E-mail the patient study number and dose to the participating site
- Call the research nurse or data manager at the participating site and verbally confirm registration.

5 TREATMENT PLAN

5.1 AGENT ADMINISTRATION

Treatment will be administered on an *outpatient* basis. Reported adverse events and potential risks are described in Section 7. Appropriate dose modifications for study drug are described in Section 6. No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the patient's malignancy. Following the safety lead-in to determine the dose of ABT-888 to be used in combination with carboplatin, patients will receive single agent ABT-888 and receive the combination only after progression, if eligible, following a 1-week interval of no treatment.

Safety Lead-In of combination:

ABT-888 was started at 50 mg p.o. BID and increases in increments up to 200 mg p.o. BID (see Table 3), under the condition that the ABT-888 dose does not exceed the MTD or the recommended Phase II dose from the single agent study.

The MTD for carboplatin was established at AUC 5 (IV on Day 1 of each 21 day cycle). This was in combination with ABT-888 at 50 mg PO BID (Days 1-21 of each 3-week cycle). The dose levels (previously 'Table 3a') used are itemized here but the escalations for carboplatin have been completed due to two DLTs at AUC 6. We are now escalating only the ABT-888; the carboplatin has been set at AUC 5. Cycle length is 21 days and patients will be evaluated for response every three cycles (approximately every two months).

- Dose Level -1* Carboplatin AUC 5 (established MTD)

Starting from September 1, 2011, all new patients on the Safety Lead-In will be treated as per Table 3.

Table 3*: Dose Escalation Schedule for Expansion Phase of Safety Lead-In.

Carboplatin AUC at MTD (defined as AUC 5) IV day 1 of each 21-day cycle.

Dose Level	ABT-888
a	100 mg PO bid
b	150 mg PO bid
c	200 mg PO bid

*Previously Table 3b

No patients treated during the safety lead-in will be considered in the primary evaluation of the Phase II component.

Phase II Component:

As of the November 9, 2023 amendment, the pharmaceutical collaborator, AbbVie, has discontinued the ABT-888 development program with the NCI Cancer Therapy Evaluation Program (CTEP). Clinical supply will no longer be available after December 31, 2024.

Patients will discontinue treatment by December 31, 2024, or earlier.

Stratum 1: BRCA1-associated Breast Cancer: **ABT-888 alone, 400 mg PO BID, daily x 21 days. Initially 10 patients will be treated. If 0 or 1 responses are seen (CR or PR) this stratum will close. If there are two or more responses, an additional 12 patients will be accrued for a total of 22 patients on this stratum.**

Stratum 2: BRCA2-associated Breast Cancer: **ABT-888 alone, 400 mg PO BID, daily x 21 days. Initially 10 patients will be treated. If 0 or 1 responses are seen (CR or PR) this stratum will close. If there are two or more responses, an additional 12 patients will be accrued to a total of 22 patients on this stratum.**

Patients progressing on the Phase II component will be required to have a 1-week interval of no treatment prior to being treated with the combination (as established during the safety lead-in), and be required to meet the pre-treatment eligibility requirements (other than the prior therapy requirements). Following progression, if patients meet the eligibility requirements, the patients will initiate treatment with carboplatin AUC 5 plus ABT-888 150 mg BID (as the Maximum Tolerated Dose of the combination established during the safety lead-in).

5.2 DEFINITION OF DOSE-LIMITING TOXICITY FOR SAFETY LEAD-IN

Dose limiting toxicity (DLT) will be defined as any grade III non-hematological toxicity not reversible to grade II or less within 96 hours, or any grade IV toxicity (excluding alopecia or controllable nausea and vomiting). Additionally, patients unable to take 80% of the planned ABT-888 due to toxicity/tolerability will be considered to have had a DLT. Toxicity will be graded according to the NCI CTCAE version 5.0. To be evaluable for toxicity, a patient must receive at least one complete course of treatment (80% of the ABT-888 dose plus received planned dose of carboplatin), and be observed for at least 21 days after the start of the first course or have experienced a DLT. All patients who receive any amount of drug will be considered evaluable for toxicity. However, any

patient who does not receive at least 80% of the ABT-888 (Arm A and B) or the planned dose of carboplatin for reasons other than toxicity/tolerability, will be considered inevaluable for determination of MTD and will be replaced for the consideration of dose levels during the safety lead-in portion.

Dose reductions will be performed if a DLT is observed or if a dose reduction is deemed medically prudent. The 80% dose requirement for ABT-888 is based on the original planned dose, and not any dose modifications.

5.3 RULES FOR DOSE ESCALATION DURING SAFETY LEAD-IN

No intrapatient dose escalations are permitted (intrapatient dose escalation was only permitted for patients on dose level 1, which is complete).

Determination of MTD:

Dose escalation will proceed within each cohort according to this scheme.

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

5.4 DEFINITION OF THE MTD AND RECOMMENDED PHASE 2 DOSE

The maximum tolerated dose (MTD) is defined as the highest dose tested in which <33% of patients experienced DLT, when at least six patients were treated at that dose and are evaluable for toxicity. The MTD is one dose level below the lowest dose tested in which 33% or more of the patients experienced DLT. The MTD is based on the first cycle of therapy. The recommended Phase II dose is generally the MTD, although secondary considerations of toxicity and dose reductions on subsequent cycles and other secondary considerations may result in the recommended Phase II dose being below the MTD.

5.4.1 ABT-888

ABT-888 will be administered orally without regards to meals. Study drug can be taken up to 2 hours outside of the scheduled time, otherwise, missed doses should not be made up.

On the days when the patient is scheduled to undergo sampling of blood and/or tumor tissue for PD and correlative studies, the dose of ABT-888 will be administered under supervision (to record the time and coordinate collection of subsequent samples). However, the timing of PD and correlative studies should be based on the administration of carboplatin, not ABT-888, in the combination arm of the study.

Because there is a potential for interaction of ABT-888 with other concomitantly administered drugs, the case report form must capture the concurrent use of all other drugs, over-the-counter medications, or alternative therapies.

ABT-888 is not known to be a potent inhibitor of the major human CYPs *in vitro*, indicating a low risk for drug-drug interactions at the proposed dosing concentrations. Studies are underway to evaluate the whether ABT-888 induces the CYP enzymes.

5.4.2 Carboplatin

Carboplatin will be administered as an intravenous infusion over 30 minutes.

The carboplatin dose will be calculated using the Calvert formula using AUC of 5 as follows:

Carboplatin dose (mg) = 5 X (GFR + 25)

(Calculated total dose is in mg -not mg/m^2)

The Creatinine Clearance (to replace GFR) will be calculated for each treatment course using the formula:

For Females:

***Important: The serum creatinine level to be used in the following calculations must be greater than or equal to 0.7. If the measured serum creatinine level is less than 0.7, use 0.7 as the value in this calculation.**

$$\text{CrCl} = \frac{(140\text{-age}) \times \text{wt. in kg.} \times 0.85}{72 \times \text{serum creatinine*}}$$

Use calculated creatinine clearance for GFR in Calvert formula.

Note: Remember to re-calculate the dose for each treatment cycle. The actual body weight should be used for all calculations. **If** the actual weight is greater than 1.2 times the ideal body weight (IBW), use 1.2 times the ideal body weight as the value in this calculation.

Ideal Body Weight (Females) = 45.5 kg + 2.3 kg for each inch over 5 feet.

Note: The GFR (calculated by Cockcroft-Gault or any other means using creatinine) used in the Calvert formula to calculate AUC-based dosing should not exceed 125 mL/min under any circumstance.

By definition, this results in the following upper limits on the dose to be administered, by AUC target:

AUC target (mg•min/mL)	Maximum carboplatin dose (mg)
2	300
3	450
4	600
5	750

Questions about this calculation should be directed at the principal investigator.

5.5 CONCOMITANT MEDICATION AND SUPPORTIVE CARE GUIDELINES

In case participants develop nausea/vomiting/diarrhea or myelosuppression, supportive medications will be prescribed as per Clinical Center and ASCO guidelines. Seizures were seen in some animal toxicology studies, although at doses much higher than those anticipated for this study. Seizures in animals were successfully treated with lorazepam.

The use of prophylactic granulocyte colony stimulating factor is not allowed for the first cycle of therapy. The use of growth factors for the treatment of anemia is allowed at the discretion of the treating physician. Neupogen or Neulasta is allowed for treatment of neutropenia after cycle 1.

Patients with known metastatic disease to the bones may be allowed to take bisphosphonates as directed by the treating physician.

All supportive measures consistent with optimal patient care will be given throughout the study.

Patients should be cautioned about the concomitant use of cimetidine, trimethoprim, or other agents that interfere with creatinine secretion or the creatinine assay.

Because there is a potential for interaction of ABT-888 with other concomitantly administered drugs, the case report form must capture the concurrent use of all other drugs, over-the-counter medications, or alternative therapies.

Emesis Prophylaxis: The combination of a 5-HT3 antagonist plus dexamethasone is strongly recommended prior to carboplatin administration.

Anti-emetic choice is at the discretion of the treating investigator. A 5-HT3 antagonist (granisetron 2 mg PO/1 mg IV or ondansetron 8-24 mg IV/24 mg PO or dolasetron 100 mg either IV or PO) plus dexamethasone 20 mg PO/IV prior to each treatment is recommended.

5.6 DURATION OF THERAPY

In the absence of treatment delays due to adverse events, treatment may continue for as many cycles as are required to demonstrate that there is no apparent clinical benefit or the patient is withdrawn from the trial, or until one of the following criteria applies:

- Disease progression (on the combination),
- Intercurrent illness that prevents further administration of treatment,
- Unacceptable adverse event(s),
- Patient decides to withdraw from the study, or
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator.

5.7 DURATION OF FOLLOW-UP

Patients removed from study for unacceptable adverse events will be followed at a minimum of monthly until resolution or stabilization of the adverse event. All patients will be followed for survival at a minimum interval of every 6 months, until the patient dies or refuses further follow up.

6 DOSING DELAYS/DOSE MODIFICATIONS

Patients should meet the laboratory parameters outlined in section 3.1.8 and the performance status in section 3.1.6 before initiation of each cycle of therapy. All toxicities (except alopecia and lymphopenia, hyperglycemia, hypoalbuminemia, elevated serum alkaline phosphatase, WBC, and hemoglobin) should have resolved to grade 1 or lesser severity before initiation of the next cycle of therapy.

Qualifying laboratory tests can be obtained up to 72 hours before planned initiation of therapy from the third cycle onwards.

Dose adjustments are to be made according to the organ system showing the greatest degree of toxicity. The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for AE reporting beginning April 1, 2018. All appropriate treatment areas should have access to a copy of the CTCAE version 5.0. A copy of the CTCAE version 5.0 can be downloaded from the CTEP web site http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

The dose levels and the general approach to dose modification of ABT-888 therapy is shown in Table 4. Specific dose modification information for some AEs are provided in other sections. AEs should be treated with the appropriate maximum supportive care, and dose reductions should be clearly documented in the electronic case report form (eCRF).

Table 4: Dose modification of ABT-888 for patients on the single agent ABT-888

(As of 8/6/18, there are 3 remaining patients on study; the study is closed to accrual and all remaining patients are currently being treated with single agent ABT-888; if necessary, their doses will be reduced as indicated in this table.)

Dose Level	**ABT-888 Tablets**
Dose reduction 1	Reduce by 50 mg BID
Dose reduction 2*	Reduce by another 50 mg BID
BID = twice daily	

***No more than two dose reductions.**

At the discretion of the investigator, the study drug is held or dose modified if the observed toxicity is attributed to the drug, while the patient continues to receive another

drug not associated with the observed toxicity. The time a drug is held should not exceed 3 weeks. Once the dose of the study drug has been reduced, no dose re-escalation is permitted.

AEs requiring ABT-888 to be discontinued:

- Bone marrow findings consistent with AML/MDS
- Severe persistent anemia requiring transfusions

Patients should not be allowed to remain in the study if they are taking ABT-888 as monotherapy and one of the toxicities above occurs. If a patient is taking ABT-888 in combination with other therapies, but develops one of the toxicities listed above, the patient may be allowed to continue the other therapies if they are experiencing clinical benefit and the toxicity is not related to the other therapies, based on the opinion of the treating investigator, and after discussion with the Principal Investigator.

6.1 DOSE MODIFICATIONS FOR HEMATOLOGICAL TOXICITY

Management of neutropenia and thrombocytopenia

Neutropenia and thrombocytopenia are recognized common adverse drug reactions reported for ABT-888. Treatment should be managed according to Table 5:

Table 5: Management of neutropenia or thrombocytopenia

CTCAE Grade	Definition	ABT-888 Dose
1-2	ANC >1.0 G/L or Platelet count >50 G/L	Investigator judgment to continue treatment or allow dose interruption; dose interruptions should be for a maximum of 3 weeks; appropriate supportive treatment and causality investigation.
3-4	ANC <1.0 G/L or Platelet count <50 G/L	Dose interruption until recovered to CTCAE Grade ≤1 for a maximum of 3 weeks. Upon recovery, ABT-888 dose should be reduced by one dose level. If repeat CTCAE Grade 3-4 occurrence, further dose reduce one ABT-888 dose level.
ANC = absolute neutrophil count; CTCAE = Common Terminology Criteria for Adverse Events		

Use of hematopoietic agents

Use erythropoietin-stimulating agents per standard of care National Comprehensive Cancer Network (NCCN) and/or institutional guidelines, iron supplements, and/or transfusions as clinically indicated for management of anemia. Prescribing information for the erythropoiesis stimulating agents (including Aranesp, Epogen and Procrit) highlight that there is a potential risk of shortening the time to tumor progression or disease-free survival. Primary prophylaxis with granulocyte colony-stimulating factor (G-CSF) is not recommended. Aranesp, Epogen and Procrit may not alleviate fatigue or increase energy, and should not be used in patients with uncontrolled hypertension. The package inserts for these agents should be consulted.

If a patient develops febrile neutropenia, ABT-888 should be stopped and appropriate management including G-CSF should be given according to local hospital guidelines. Please note that G-CSF should not be used within at least 24 hours of the last dose of ABT-888 unless absolutely necessary.

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

Dose modifications for hematologic toxicity

Patients who have ABT-888 held for hematologic toxicities should have blood counts and differentials checked at least weekly until recovery; these data should be recorded in eCRF as extra laboratory examinations. If counts do not improve to CTCAE Grade 1 or better despite drug cessation for 3 weeks, patients should be referred to a hematological oncologist for further assessment. A bone marrow analysis should be considered.

For AEs that are unrelated to the study drug, study drug may be withheld for up to 3 weeks at the discretion of the treating Investigator.

Management of anemia

Anemia is a common adverse drug reaction related to ABT-888. Management of anemia is in accordance with Table 6:

Table 6: Management of anemia

CTCAE Grade	Definition	ABT-888 Dose
2	Hb <10 but ≥8 g/dL	Give appropriate supportive treatment and

CTCAE Grade	Definition	ABT-888 Dose
		investigate causality. Investigator judgement to continue ABT-888 or interrupt dose for a maximum of 3 weeks. If repeat Hb <10 but ≥8 g/dL, dose interrupt until Hb ≥10 g/dL for maximum of 3 weeks and upon recovery dose reduce by 50 mg BID from the current dose level as a first step and by another 50 mg BID as a second step.
3	Hb <8 g/dL	Give appropriate supportive treatment and investigate causality. Interrupt ABT-888 until improved to Hb ≥10 g/dL. Upon recovery dose reduce ABT-888 by 50 mg BID.
BID = twice daily; Hb = hemoglobin		

Common treatable causes of anemia (e.g., iron, vitamin B12 or folate deficiencies and hypothyroidism) should be investigated and appropriately managed. In some cases management of anemia may require blood transfusions. Any subsequently required dose interruptions related to development of anemia, or coexistent with newly developed neutropenia, and/or thrombocytopenia, reduce ABT-888 dose to no more than two dose reductions.

If Hb drops to <8 g/dL despite the dose reduction or more than one blood transfusion is required to recover Hb levels with no alternative explanation for the anemia, ABT-888 should be permanently discontinued.

Management of prolonged hematological toxicities while on study treatment

If a patient develops prolonged hematological toxicity such as:

- ≥2 week interruption/delay in velaparib due to CTCAE Grade ≥3 anemia (Hb <8 g/dL) and/or development of blood transfusion dependence
- ≥2 week interruption/delay in ABT-888 due to CTCAE Grade ≥3 neutropenia (ANC <1 x 10^9/L)

- ≥2 week interruption/delay in ABT-888 due to CTCAE Grade ≥3 thrombocytopenia and/or development of platelet transfusion dependence (Platelets <50 x 10^9/L)

Check weekly differential blood counts including reticulocytes and peripheral blood smear. If any blood parameters remain clinically abnormal after 3 weeks of dose interruption, the patient should be referred to a hematological oncologist for further investigations. Bone marrow for evaluation and cytogenetics should be considered at this stage according to standard hematological oncology practice. ABT-888 should be discontinued if blood counts do not recover to CTCAE Grade ≤1 within 3 weeks of dose interruption.

Management of ABT-888 associated toxicity

Management of MDS/AML

Patients who develop MDS/AML on treatment should discontinue ABT-888 treatment and be managed appropriately.

6.2 DOSE MODIFICATIONS FOR NON-HEMATOLOGICAL TOXICITY

6.2.1. Gastrointestinal Toxicity

Nausea and/or vomiting should be controlled with adequate antiemetic therapy. Prophylactic anti-emetic therapy can be used at the discretion of the treating physician. Patients are encouraged to take plenty of oral fluids. If symptoms persist despite maximal anti-emetic therapy, ABT-888 should be withheld until recovery to ≤ grade 1.

Diarrhea should be managed with appropriate anti-diarrheal therapy. Patients should be encouraged to take plenty of oral fluids. If symptoms do not decrease to grade 1 or less with adequate anti-diarrheal therapy, ABT-888 should be held until recovery from symptoms to ≤ grade 1. ABT-888 can be re-started at the same dose following recovery to ≤ grade 1 if worst grade of toxicity is ≤ grade 2. For worst grade ≥ 3, re-start ABT-888 with dose reduction by one dose level (see Table 4).

It is recommended that loperamide be prescribed to control diarrhea, barring any contraindication to such therapy. Loperamide should be taken at 4 mg after the first episode of diarrhea, and can be repeated at a dose of 2 mg after each subsequent episode, not to exceed 16 mgs in total dose.

If symptoms recur, the dose of ABT-888 should be re-started with a reduction by one dose level (see Table 4).

6.2.2 Hypersensitivity Reactions

Caution: Patients who had a mild to moderate hypersensitivity reaction have been successfully rechallenged, but careful attention to prophylaxis and bedside monitoring of vital signs is recommended.

6.2.2.1 Mild symptoms (e.g., mild flushing, rash, pruritus) -Complete infusion. Supervise at bedside. No treatment required.

6.2.2.2 Moderate symptoms (e.g., moderate rash, flushing, mild dyspnea, chest discomfort) -Stop infusion. Give intravenous diphenhydramine 25 mg and intravenous dexamethasone 10 mg. Resume infusion after recovery of symptoms at a low rate, 20 mg/hr. For 15 minutes, then, if no further symptoms, at full dose rate until infusion is complete. If symptoms recur, stop infusion. Record toxicity on flow sheets. Use desensitization protocol as per institutional standards for any further cycles.. However, a second moderate reaction to protocol therapy while a patient is treated on institutional desensitization protocol mandates removal from further carboplatin therapy.

6.2.2.3 Severe life threatening symptoms (e.g., hypotension requiring pressor therapy, angioedema, respiratory distress requiring bronchodilation therapy, generalized urticaria)-stop infusion. Give intravenous diphenhydramine and dexamethasone as above. Add epinephrine or bronchodialtors if indicated. If wheezing is present, that is not responsive to bronchodilators, epinephrine is recommended. Patient should be removed from further protocol therapy. Report as adverse event.

6.2.3 Other Toxicities

For any grade 3 or 4 toxicity not mentioned above, withhold both drugs until the patient recovers to grade 1 or less toxicity. The treatment should then be resumed at one lower dose level for carboplatin (see 5.4.2, permanent dose reduction) and same dose for ABT-888 (see Table 4; permanent dose reduction). For grade 2 toxicities, withhold treatment until the patient recovers, then resume treatment at a one dose-level reduction for carboplatin (permanent dose reduction) and same dose for ABT-888. For grade 1 toxicities, no dose reduction should be made. For subsequent episodes of Grade 3 or 4 non-hematological toxicities, see table below.

Non-Hem Toxicity	ABT 888	Carboplatin (if applicable)
Grade 3/4 1st episode	No change	Reduce to Current AUC minus 1**
2ndepisode	Reduce ABT-888 by one level (see Table 4)	No change
3rd episode	No change	Reduce to Current AUC minus 1**
4th episode	Reduce ABT-888 by one additional level (see Table 4)	No change
5th episode	Off study	Off study

**If reduced to AUC of 2, next episode = discontinue carboplatin, but option to continue single agent ABT-888 at current dose (at the discretion of the treating physician if patient has stable disease or better) or go off study.

6.2.4 Guidelines for treatment of patients who require dose reduction in carboplatin for cycle 2

Patients who require dose reduction in carboplatin for cycle 2 will be allowed to continue on study (with the addition of ABT-888 at the originally-intended dose level). However, the patients will be evaluable for pharmacokinetics, toxicity and efficacy analysis. If severe toxicity is noted in cycle 2 also, the patient may be removed from the study at the discretion of the treating physician.

If the dose of carboplatin is reduced for cycle 2 due to grade 4 neutropenia, in addition to dose reduction, institution of prophylactic neutrophil colony stimulating factor is recommended.

6.2.5 Guidelines for treatment of patients who require dose reduction while receiving single-agent ABT-888 in the phase II portion of the trial

Non-Hem Toxicity	ABT 888

Grade 3/4 1st episode	Reduce ABT-888 by one dose level
2ndepisode	Reduce ABT-888 by one additional dose level
3rd episode	Off study

7 ADVERSE EVENTS: CAEPR LIST AND REPORTING REQUIREMENTS

Adverse event (AE) monitoring and reporting is a routine part of every clinical trial. The following list of AEs (Section 7.1) and the characteristics of an observed AE (Section 7.2) will determine whether the event requires expedited (via CTEP-AERS) reporting **in addition to** routine reporting.

7.1 COMPREHENSIVE ADVERSE EVENTS AND POTENTIAL RISKS LIST (CAEPR)

7.1.1 CAEPRs for ABT-888 (NSC 737664)

The Comprehensive Adverse Event and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. In addition to the comprehensive list, a subset, the Specific Protocol Exceptions to Expedited Reporting (SPEER), appears in a separate column and is identified with bold and italicized text. This subset of AEs (SPEER) is a list of events that are protocol specific exceptions to expedited reporting to NCI via CTEP-AERS (except as noted below). Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements' http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf for further clarification. *Frequency is provided based on 2310 patients.* Below is the CAEPR for Veliparib (ABT-888).

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

Adverse Events with Possible Relationship to ABT-888 (Veliparib) (CTCAE 5.0 Term) [n= 2310]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
	Anemia		***Anemia (Gr 3)***
	Febrile neutropenia		***Febrile neutropenia (Gr 3)***
GASTROINTESTINAL DISORDERS			
	Abdominal pain		
	Constipation		***Constipation (Gr 2)***
	Diarrhea		***Diarrhea (Gr 3)***
Nausea			***Nausea (Gr 3)***
	Vomiting		***Vomiting (Gr 3)***
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
Fatigue			***Fatigue (Gr 3)***
INVESTIGATIONS			
	Lymphocyte count decreased		***Lymphocyte count decreased (Gr 4)***
	Neutrophil count decreased		***Neutrophil count decreased (Gr 4)***
Platelet count decreased			***Platelet count decreased (Gr 4)***
	Weight loss		***Weight loss (Gr 2)***
	White blood cell decreased		***White blood cell decreased (Gr 4)***
METABOLISM AND NUTRITION DISORDERS			

Adverse Events with Possible Relationship to ABT-888 (Veliparib) (CTCAE 5.0 Term) [n= 2310]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
	Anorexia		***Anorexia (Gr 2)***
	Dehydration		***Dehydration (Gr 3)***
	Hypophosphatemia		***Hypophosphatemia (Gr 3)***
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)			
		Leukemia secondary to oncology chemotherapy	
		Myelodysplastic syndrome	
		Treatment related secondary malignancy	
NERVOUS SYSTEM DISORDERS			
	Dizziness		
	Dysgeusia		***Dysgeusia (Gr 2)***
	Headache		***Headache (Gr 3)***
		Seizure	
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
	Rash maculo-papular		
VASCULAR DISORDERS			
		Thromboembolic event[2]	

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

[2]Thromboembolic events, including deep vein thrombosis and pulmonary embolism, have been observed at a higher frequency compared to control arm when administered in combination with temozolomide.

Adverse events reported on ABT-888 (Veliparib) trials, but for which there is insufficient evidence to suggest that there was a reasonable possibility that ABT-888 (Veliparib) caused the adverse event:

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Bone marrow hypocellular; Blood and lymphatic system disorders - Other (pancytopenia)

CARDIAC DISORDERS - Cardiac disorders - Other (Takotsubo cardiomyopathy); Heart failure; Left ventricular systolic dysfunction; Palpitations; Sinus bradycardia; Sinus tachycardia

EAR AND LABYRINTH DISORDERS - Vertigo

EYE DISORDERS - Blurred vision

GASTROINTESTINAL DISORDERS - Abdominal distension; Ascites; Colitis; Colonic obstruction; Dental caries; Dry mouth; Duodenal ulcer; Dyspepsia; Dysphagia; Enterocolitis; Esophagitis; Flatulence; Gastritis; Gastroesophageal reflux disease; Lower gastrointestinal hemorrhage; Mucositis oral; Obstruction gastric; Rectal hemorrhage; Rectal pain; Small intestinal obstruction

GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Chills; Edema limbs; Fever; Flu like symptoms; Malaise; Non-cardiac chest pain; Pain

HEPATOBILIARY DISORDERS - Hepatic failure; Hepatobiliary disorders - Other (cirrhosis)

INFECTIONS AND INFESTATIONS - Appendicitis; Catheter related infection; Infections and infestations - Other (peritonsillar abscess); Lung infection; Lymph gland infection; Mucosal infection; Sepsis; Shingles; Skin infection; Upper respiratory infection; Urinary tract infection

INJURY, POISONING AND PROCEDURAL COMPLICATIONS - Bruising; Dermatitis radiation; Radiation recall reaction (dermatologic)

INVESTIGATIONS - Alanine aminotransferase increased; Alkaline phosphatase increased; Aspartate aminotransferase increased; Blood bilirubin increased; Cardiac troponin I increased; Creatinine increased; Electrocardiogram QT corrected interval prolonged; Lipase increased

METABOLISM AND NUTRITION DISORDERS - Hyperglycemia; Hypernatremia; Hypoalbuminemia; Hypocalcemia; Hypokalemia; Hypomagnesemia; Hyponatremia

MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Arthralgia; Arthritis; Back pain; Bone pain; Generalized muscle weakness; Muscle cramp; Myalgia; Neck pain; Pain in extremity

NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS) -Tumor pain

NERVOUS SYSTEM DISORDERS - Ataxia; Cognitive disturbance; Depressed level of consciousness; Dysarthria; Extrapyramidal disorder; Intracranial hemorrhage; Lethargy; Memory impairment; Movements involuntary; Paresthesia; Peripheral motor neuropathy; Peripheral sensory neuropathy; Presyncope; Reversible posterior leukoencephalopathy syndrome; Stroke; Syncope; Tremor

PSYCHIATRIC DISORDERS - Agitation; Anxiety; Confusion; Depression; Insomnia; Psychiatric disorders - Other (emotional instability); Psychosis; Restlessness

RENAL AND URINARY DISORDERS - Dysuria; Hematuria; Proteinuria

RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Cough; Dyspnea; Epistaxis; Hypoxia; Nasal congestion; Pharyngolaryngeal pain; Pleural effusion; Pneumonitis; Respiratory failure

SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Alopecia; Dry skin; Hyperhidrosis; Nail changes; Palmar-plantar erythrodysesthesia syndrome; Pruritus; Purpura; Rash acneiform

VASCULAR DISORDERS - Flushing; Hot flashes; Hypertension; Hypotension; Vascular disorders - Other (brainstem infarction)

Note: ABT-888 (Veliparib) in combination with other agents could cause an exacerbation of any adverse event currently known to be caused by the other agent, or the combination may result in events never previously associated with either agent.

7.1.1. Adverse Event List for Carboplatin

Some of the expected adverse events from carboplatin are listed below. For further description of adverse events see Package Insert.

Hematologic:	Myelosuppresion
Gastrointestinal:	Nausea, vomiting, diarrhea, weight loss, constipation, gastrointestinal pain
Metabolic:	Electrolyte imbalances, hypomagnesemia, hypocalcemia, hyponatremia, hyperuremia
Hepatic toxicity:	Elevated alkaline phosphatase, AST, and total bilirubin
CNS:	Peripheral neuropathies (mild paresthesias, clinical ototoxicity and other sensory abnormalities are rare)
Genitourinary:	Renal tubular damage, renal insufficiency, impotence, sterility, amenorrhea, gynecomastia
Allergy:	Anaphylactoid and urticarial reactions (acute), flushing, rash, pruritis and rarely hypotension or bronchospasm
Other:	Alopecia, pain, asthenia and mucosal side effects, decreased serum electrolytes values (sodium, magnesium, calcium and potassium)

7.1.2. Other potential adverse events

Blood Draw: Drawing blood from a vein can cause minor pain and bruising at the site where the needle enters. Some people feel dizzy when blood is drawn. Rarely, infection may occur.

CT Scans: exposure to radiation from CT scans. CT scans can be associated with extremely rare allergic reactions to contrast agents.

MRI Scans: Claustrophobia is the main risk.

7.2 ADVERSE EVENT CHARACTERISTICS

- **CTCAE term (AE description) and grade:** The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for AE reporting beginning April 1, 2018. All appropriate treatment areas should have access to a copy of the CTCAE version 5.0. A copy of the CTCAE

version 5.0 can be downloaded from the CTEP web site http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

'Expectedness': AEs can be 'Unexpected' or 'Expected' (see Section 7.1 above) for expedited reporting purposes only. 'Expected' AEs (the ASAEL) are ***bold and italicized*** in the CAEPR (Section 7.1).

- **Attribution** of the AE:
  - Definite -The AE is clearly related to the study treatment.
  - Probable -The AE is likely related to the study treatment.
  - Possible -The AE may be related to the study treatment.
  - Unlikely -The AE is doubtfully related to the study treatment.
  - Unrelated -The AE is clearly NOT related to the study treatment. (In this situation, the cause of the AE should be described.)

8 EXPEDITED ADVERSE EVENT REPORTING

Expedited AE reporting for this study must use CTEP-AERS (CTEP Adverse Event Reporting System), accessed via the CTEP home page (http://ctep.cancer.gov). The reporting procedures to be followed are presented in the "CTEP, NCI Guidelines: Adverse Event Reporting Requirements" which can be downloaded from the CTEP home page (http://ctep.cancer.gov). These requirements are briefly outlined in the table below (Section 7.3.3).

In the rare occurrence when Internet connectivity is lost, a 24-hour notification is to be made to CTEP by telephone at 301-897-7497. Once Internet connectivity is restored, the 24-hour notification phoned in must be entered electronically into CTEP-AERS by the original submitter at the site.

CTEP-AERS is programmed for automatic electronic distribution of reports to the following individuals: Study Coordinator of the Lead Organization, Principal Investigator, and the local treating physician. CTEP-AERS provides a copy feature for other e-mail recipients.

Expedited Reporting Guidelines

CTEP-AERS Reporting Requirements for Adverse Events that occur within 30 Days1 of the Last Dose of the Investigational Agent on Phase 2 and 3 Trials

Phase 2 and 3 Trials									
	Grade 1	Grade 2	Grade 2	Grade 3		Grade 3		Grades 4 & 5[2]	Grades 4 & 5[2]
	Unexpected and Expected	Unexpected	Expected	Unexpected with Hospitalization	Unexpected without Hospitalization	Expected with Hospitalization	Expected without Hospitalization	Unexpected	Expected
Unrelated Unlikely	Not Required	Not Required	Not Required	10 Calendar Days	Not Required	10 Calendar Days	Not Required	10 Calendar Days	10 Calendar Days
Possible	Not	10 Calendar	Not	10 Calendar	10 Calendar	10 Calendar	Not	24-Hour;	10

Probable Definite	Required	Days	Required	Days	Days	Days	Required	5 Calendar Days	Calendar Days

[1] **Adverse events with attribution of possible, probable, or definite that occur <u>greater</u> than 30 days after the last dose of treatment with an agent under a CTEP IND require reporting as follows:**

CTEP-AERS 24-hour notification followed by complete report within 5 calendar days for:
- Grade 4 and Grade 5 unexpected events

CTEP-AERS 10 calendar day report:
- Grade 3 unexpected events with hospitalization or prolongation of hospitalization
- Grade 5 expected events

[2] Although an CTEP-AERS 24-hour notification is not required for death clearly related to progressive disease, a full report is required as outlined in the table.

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Note: All deaths on study require both routine and expedited reporting regardless of causality. Attribution to treatment or other cause must be provided.

- Expedited AE reporting timelines defined:
  - "24 hours; 5 calendar days" – The investigator must initially report the AE via CTEP-AERS within 24 hours of learning of the event followed by a complete CTEP-AERS report within 5 calendar days of the initial 24-hour report.
  - "10 calendar days" - A complete CTEP-AERS report on the AE must be submitted within 10 calendar days of the investigator learning of the event.
- Any medical event equivalent to CTCAE grade 3, 4, or 5 that precipitates hospitalization (or prolongation of existing hospitalization) must be reported regardless of attribution and designation as expected or unexpected with the exception of any events identified as protocol-specific expedited adverse event reporting exclusions.
- Any event that results in persistent or significant disabilities/incapacities, congenital anomalies, or birth defects must be reported via CTEP-AERS if the event occurs following treatment with an agent under a CTEP IND.
- Use the NCI protocol number and the protocol-specific patient ID assigned during trial registration on all reports.
- Note: A death on study requires both routine and expedited reporting, regardless of causality. Attribution to treatment or other cause must be provided.
- Death due to progressive disease should be reported as Grade 5 "Disease progression" in the system organ class (SOC) "General disorders and administration site conditions." Evidence that the death was a manifestation of underlying disease (e.g., radiological changes suggesting tumor growth or progression: clinical deterioration associated with a disease process) should be submitted.

8.1 ROUTINE ADVERSE EVENT REPORTING

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

8.2 SECONDARY AML/MDS

Investigators are required to report cases of secondary AML/MDS occurring on or following treatment on NCI-sponsored chemotherapy protocols using the NCI/CTEP Secondary AML/MDS Report Form. This form can be downloaded from the CTEP web site (http://ctep.cancer.gov). Refer to the "CTEP, NCI Guidelines: Adverse Event Reporting Requirements" (available at http://ctep.cancer.gov) for additional information about secondary AML/MDS reporting.

9 PHARMACEUTICAL INFORMATION

A list of the adverse events and potential risks associated with ABT-888 and carboplatin can be found in Section 7.1.

9.1 CTEP-SUPPLIED INVESTIGATIONAL AGENTS

9.1.1 ABT-888 (NSC 737664)

Chemical Name: 2-[(R)-2-methylpyrrolidin-2-yl]-1H-benzimidazole-4-carboxamide

Other Names: A-861695.0

Classification: Poly (ADP-ribosome) polymerase (PARP) Inhibitor

Molecular Formula: $C_{13}H_{16}N_4O$ **M.W**.: 244.29

Description: White opaque capsule

How Supplied: Abbott Laboratories supplies and DCTD distributes ABT-888. ABT-888 capsules are available in 10 mg, 20 mg, 40 mg, 50 mg and 100 mg immediate release capsules. The inactive ingredients are microcrystaline cellulose, colloidal silicon dioxide, magnesium stearate, gelatin, sodium lauryl sulfate, FD&C yellow #5, and titanium dioxide. The capsules are packaged in HDPE bottles, and each HDPE bottle contains 16 capsules or 64 capsules.

Note: ABT-888 capsules may be repackaged from the supplied HDPE bottles into amber (or other low-actinic) child resistant pharmacy dispensing bottles. Expiration will be 30 days from the repackaging date (or the original retest date, whichever is earlier) when stored at 15°C to 25°C (59°F to 77°F).

Storage: Store intact bottles between 15^0 and 25^0 C (59^0 – 77^0F), excursion permitted between 25^0 and 30^0C (77^0 – 86^0F); protect from heat and moisture.

Stability: Shelf life stability studies for ABT-888 capsules are on-going.

Route(s) of Administration: Oral. ABT-888 capsules may be administered without regard to meals.

Availability: ABT-888 is an investigational agent supplied to investigators by the Division of Cancer Treatment and Diagnosis (DCTD), NCI.

ABT-888 is provided to the NCI under a Collaborative Agreement between Abbott Laboratories and the DCTD, NCI (see Section 12.3).

As of the November 9, 2023 amendment, the pharmaceutical collaborator, AbbVie, has discontinued the ABT-888 development program with the NCI Cancer Therapy Evaluation Program (CTEP). Clinical supply will no longer be available after December 31, 2024.

Patients will discontinue treatment by December 31, 2024, or earlier.

9.1.2 CTEP IND AGENT #2 (NSC #)

N/A

9.1.3 AGENT ORDERING

NCI-supplied agents may be requested by the Principal Investigator (or their authorized designees) at each participating institution. Pharmaceutical Management Branch (PMB) policy requires that the agent be shipped directly to the institution where the patient is to be treated. PMB does not permit the transfer of investigational agents between institutions (unless prior approval from PMB is obtained). The CTEP-assigned protocol number must be used for ordering all CTEP-supplied investigational agents. The responsible investigator at each participating institution must be registered with CTEP, DCTD through an annual submission of FDA form 1572 (Statement of Investigator), Curriculum Vitae, Supplemental Investigator Data Form (IDF), and Financial Disclosure Form (FDF). If there are several participating investigators at one institution, CTEP-supplied investigational agents for the study should be ordered under the name of one lead investigator at that institution.

Agent may be requested by completing a Clinical Drug Request (NIH-986) and faxing it to the Pharmaceutical Management Branch at (301) 480-4612. For questions about drug orders, transfers, returns, or accountability call (240) 276-6575Monday through Friday between 8:30 am and 4:30 pm (ET) or email PMBAfterHours@mail.nih.gov anytime.

As of the 8/6/18 amendment, a 6-month supply may be dispensed to patients. When ordering drug with the Pharmaceutical Management Branch (PMB), the Clinical Drug Request (NIH-986) must indicate the request for a 6-month supply. A 6-month supply can only be provided if the PMB has a lot of drug with an expiration date > 6 months.

9.1.4 AGENT ACCOUNTABILITY

The Investigator, or a responsible party designated by the Investigator, must maintain a careful record of the inventory and disposition of all agents received from DCTD using the NCI Drug Accountability Record Form. See the CTEP web site for Policy and Guidelines for Accountability and Storage of Investigational Drugs (http://ctep.cancer.gov/requisition/storage.html).

9.2 OTHER INVESTIGATIONAL AGENTS

N/A

9.3 CARBOPLATIN

Availability

Carboplatin is commercially available as a sterile lyophilized powder available in single-dose vials containing 50 mg, 150 mg, or 450 mg of carboplatin. Each vial contains equal parts by weight of carboplatin and mannitol. Commercial supplies of carboplatin will be used for this study. Carboplatin is also available as an aqueous solution in 50 mg/5 mL, 150 mg/15 mL, 450 mg/45 mL and 600 mg/60 mL multidose vials

Preparation

Reconstitute lyophilized powder with Sterile Water, 0.9% Sodium Chloride, or 5% Dextrose Injection with volumes of diluents specified below. The reconstituted solution can be further diluted to a concentration as low as 0.5 mg/mL with 0.9% Normal Saline or 5% Dextrose Injection.

Vial Strength	Diluent Volume
50 mg	5 mL
150 mg	15 mL
450 mg	45 mL

Storage and Stability

When prepared as directed, the resultant carboplatin solutions, when protected from light, are stable for 8 hours at room temperature. No antibacterial preservative is contained in the formulation, and therefore, it is recommended that carboplatin solutions be discarded 8 hours after dilution.

NOTE: Aluminum reacts with carboplatin, causing precipitate formation and loss of potency. Therefore, needles or intravenous sets containing aluminum parts that may come in contact with the drug must not be used for the preparation or administration of carboplatin.

Unopened vials of carboplatin are stable for the life indicated on the package when stored at controlled room temperature (59 - 86°F) and protected from light. When prepared, carboplatin solutions are stable for 8 hours at room temperature. Carboplatin aqueous solution multidose vials maintain microbial, chemical, and physical stability for up to 14 days at 25º C following multiple needle entries.

Dosing and Administration

Carboplatin will be administered within one hour after ABT-888 as an intravenous infusion over 30 minutes. Dose calculations are specified in Section 5.1 (Treatment Administration).

10 CORRELATIVE/SPECIAL STUDIES

10.1 OPTIONAL BLOOD SAMPLES FOR FUTURE GENETIC RESEARCH STUDIES

Optional blood samples will be drawn for future genetic research studies including analysis of possible constitutional determinants of resistance and metabolism of ABT-888. Participants will be requested to provide a blood sample to be stored at ambient temperature for DNA extraction and potential pharmacogenetic analysis. Any genotyping performed will relate to the absorption, distribution, metabolism, elimination or mode of action of study drugs and any comparators, related pathways and other oncogenetic pathways.

10.2 MOLECULAR CORRELATES

We will use qualified and validated assay methods (**Table 7**) to assess the relationship between the level of PARP inhibition by ABT-888 and markers of DNA damage in surrogate tissues (PBMC's) and tumor. γH2AX and RAD51 immunohistochemical assays will be conducted using laser scanning cytometry (LSC) [59, 60]. In preliminary studies, we have shown increased γH2AX frequency in BRCA-null cells compared to the complemented cells for the PARP inhibitor ABT-888, using scanning laser cytometry (**Figure 4**) that will be used in the clinical trial.

Biomarkers for PARP inhibitors. The phospho-modified histone γH2AX serves as a marker for double strand breaks (DSBs); therefore, we will use an antibody (monoclonal mouse Ab from Upstate Biotechnology Anti-phospho-Histone H2A.X (Ser139), clone JBW301) against that protein in immunohistochemical analysis [57]. RAD51 will be loaded onto single-strand regions during HRR that co-stain with the γH2AX immunostaining, but in BRCA2 cells co-localization should be reduced due to the inability of BRCA2 to function. The number of cells with >10 spots for γH2AX should indicate the increased formation of DSBs in the presence of ABT-888 and possibly the other PARP inhibitors. We will also use immunostaining for γH2AX in hair follicles from eyebrow plucks as a biomarker of pharmacodynamic effect [64, 65].

Table 7 Assays and Biomarkers for patient samples.

Assay/Biomarker	Sample	Assay	Ref.
PARP Activity	PBMC Tumor	Immunoassay	[61, 62]
γH2AX/RAD51	PBMC Tumor	IHC/LSC	[63-65]
Reversion mutations/ HRR Assay	Tumor (top priority use)	I-SceI EGFP	[50, 66]

The recent phase 0 trial in patients with advanced malignancies demonstrated >85% reduction in PAR level in PBMCs after a single oral 25 mg dose [35].

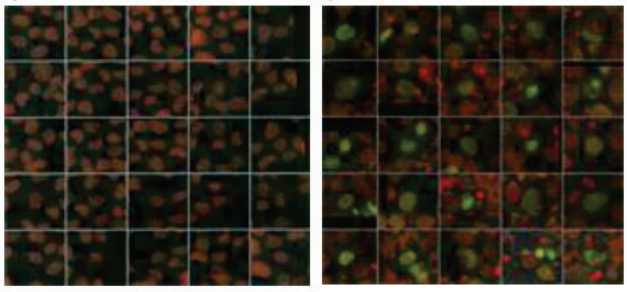

Figure 4 Laser scanning cytometry of wild type (V-79) or BRCA2-null cells (VC-8) exposed to 100 mM for 48 h of the PARP inhibitor ABT-888. Propidium iodide staining of nucleic acids (red) and γH2AX foci formation (green). Each box represents a different field of a 96-well plate.

Sample collection.

Sample Collection, Processing and Shipping of PBMCs and fresh-frozen tumor samples are detailed in the National Clinical Target Validation Laboratory (NCTVL) Standard Operating Procedures (in Appendix).

In brief, serial blood samples for PBMC analysis will be collected for all patients according to the following schedule; pre-dose, and 3 hours after ingestion of ABT-888 on Cycle 1, Day 1. In addition, PBMC samples will be obtained 1 to 3 hours after ingestion of ABT-888 on day 1 of cycle 2, and pre-dose and 3 hours post dose on Cycle X (1st cycle after progression when carboplatin is added to the treatment schedule), and 1 to 3 hours after ingestion of ABT-888 on Cycle X + 1 (the second cycle after progression). For the combination arm carboplatin should be administered within one hour after the morning dose of ABT-888 on day 1 of each cycle.

The City of Hope Analytical Pharmacology laboratory will send plasma samples for extraction and analysis of ABT-888 to the Clinical Pharmacology Analytical Facility at the University of Pittsburgh Cancer Institute.

If the patient presents with a biopsiable tumor, then the provision of tumor tissue prior to starting dosing and during treatment with study drugs will be encouraged if clinically appropriate. Optimally, biopsies for comparison will be obtained on day 1 of cycle 1, and day 1 of cycle 2, and at progression (off-study visit). Tumor biopsy will be performed pre-treatment on screening day or pre-treatment on day 1 of cycle 1, and on day 1 of cycle 2 approximately 4-8 h after start of carboplatin (or ingestion of ABT-888 in the single-

agent arm), and then again on the off-study visit. Up to 3 passes will be allowed during each biopsy procedure for obtaining tumor tissue. Samples will be immediately snap-frozen. The top priority will be to analyze for *BRCA* reading frame restoring revertant mutations at baseline and at progression. PAR/γH2AX/RAD51 assays with the tumor tissue will then be conducted. Since epinephrine can interfere with the PAR assay, the local anesthesia for the tumor biopsy will utilize lidocaine whenever possible and avoid 'lidocaine plus epinephrine'. However, if epinephrine is used, it will be clearly noted in the case report form. Patients will not be excluded from the trial if these samples are not collected.

The complete set of frozen samples will be shipped overnight on dry ice to the following address:

Analytical Pharma. Lab
City of Hope
Shapiro Bldg. (Synold/JNW) Rm. 1042
1500 E Duarte Rd.
Duarte, CA 91010
Phone (626) 359-8111, ext. 62110
Email: tsynold@coh.org

All specimens shipped must be accompanied by the Specimen Submission form found in Appendix D. Additionally, a copy of that completed form must be faxed to the Data Coordinating Center at City of Hope, (626) 256-8654 when specimens are shipped.

Expected results. We expect that the γH2AX will increase as the degree of PARP inhibition increases in PBMC and tumor, but there will be no increase in RAD51 in the tumor due to the absence of BRCA. Immunoassay for poly-ADP-ribosylated (PAR) substrates**:** Abbott Laboratories and the NCI-Frederick laboratories developed and cross-validated a quantitative immunoassay for PAR [61]. The validated assay is a sandwich enzyme chemiluminescence immunoassay employing commercially obtained antibodies to PAR, and pure PAR as a standard. Specimen handling was optimized for both PBMCs and tumor needle biopsies (18 ga), and harmonized for use with the same standards and controls. The validated assay was used to measure PAR levels in PBMCs of healthy donors, in animal models after administration of a single and multiple dosing of ABT-888, and has been used successfully in real time to measure PAR in PBMCs and tumor biopsies in a phase 0 clinical trial [61]. Kits for the CLIA-approved PAR assay will be obtained from the NCI and the research technician performing the PAR assay will be trained at the NCI.

Determine mechanisms of resistance. Cells which are BRCA null can compensate, in part, for defects in HRR DSB repair by using single-strand annealing and non-homologous end joining (NHEJ) [67]. Patients who receive PARP inhibitors could manifest drug resistance by reconstituting their BRCA function. This would lead to

restoration of normal HRR and the therapeutic footing in the original cell type (BRCA null) would be lost, as described in recent reports [50, 51]. Therefore, we will examine *BRCA* sequences from tumor cells from patients treated with ABT-888. The precise germline *BRCA* mutation will be known for all patients.

We anticipate 10-20% (n=8-16) of clinical trial participants will have accessible tumor and consent to biopsy just **prior** to treatment with study drug(s) on the trial. These samples will be used to assess HRR status and whether BRCA expression is restored indicating the presence/absence of reversion mutations prior to initiating our clinical treatments and correlative studies. A proportion of cases are likely to have reversion mutation and/or re-expression of BRCA and restored HRR due to selective pressure from chemotherapy exposure; however, platinum resistance can occur by a non-HRR mechanism so clinical resistance alone does not preclude persistent defective HRR and susceptibility to PARP inhibitors. Approximately 6-12% (n=5-10) may have accessible tumor and consent to biopsy for study **post**-clinical trial.

At the close of the protocol, the *BRCA* sequence will be re-determined in available tumor. Full length *BRCA* clones in the pcDNA3.1 expression with a promoter more active in mESCs will be constructed will be modified to introduce any sequence differences from the original *BRCA* sequences. We have the full length cDNA constructs and are constructing the vectors. Point mutations will be introduced into *BRCA* using site-directed mutagenesis, whereas larger deletions or insertions will be constructed using restriction sites. Plasmids hosting the *BRCA1* or *BRCA2* constructs will be transformed into mESCs-DR-GFP that have a GFP reporter for HRR and have either *Brca1*-/- or Brca2-/- [69] (**Figure 5**). Those cells have a *GFP* sequence with a homing endonuclease site ISce I that is unique in the *Brca* cells, which are null for one of the 2 Brca proteins. Cleavage using the Sce I and HRR reconstitutes the *GFP* coding sequence and allows production of a functional GFP. We will also monitor survival of the complemented and vector only cells to treatment using ABT-888 or ABT-888 and carboplatin. In addition, the reporter assay will be used to determine the fold-increase in GFP fluorescence, as an indicator of HRR in *Brca1*- or *Brca2*-DR-GFP cells [50]. Assays in both these types of cells will analyze both types of revertants. Analysis of BRCA1 revertants is particularly significant, since it is involved in both HRR and with single-strand annealing (SSA) repair [70]. SSA is postulated to have a role in rescue and restoration of HRR during repair processes [67, 71].

There may be other resistance mechanisms that are involved in *BRCA1* patients, as suggested by Swisher *et al* [70]. DNA repair enzymes such as XPD (Xeroderma Pigmentosum Group D) and ERCC1 (Excision repair cross-complementation group 1) are implicated in the nucleotide excision repair pathway and components of this pathway are thought to be the principal elements in platinum adduct removal. We and others have documented improved outcome after platinum-based chemotherapy associated with decreased ERCC1 expression in lung and breast cancer [72, 73]. In contrast, preclinical data with ABT-888 and irinotecan indicated responsiveness in cell lines with high ERCC1 expression [22], contrary to previous clinical data suggesting that low ERCC1 levels were associated with response to platinum agents in the lung cancer setting [73]. It is conceivable that the concomitant inhibition of PARP1 can overcome ERCC1-mediated resistance to platinum salts, a finding that may be applicable to possible uses of ABT-888 and carboplatin beyond the *BRCA* mutant setting.

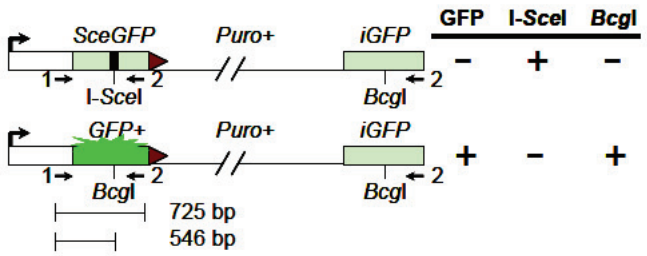

Figure 5. HRR reporter assay using a single copy reporter construct in mammalian cells. The top construct is a unique insert into genomic DNA that has an I-SceI site disrupting an EGFP sequence. Following introduction of an I-SceI coding sequence, the target site is cleaved and the sequence formed is indicative of the repair mechanism. The easiest type of repair to follow is HRR, which is indicated by GFP signal using FACS (or LSC) analysis. Observation of other modes of recombinational repair can be confirmed using restriction digest and PCR of the region indicated by primers 1 and 2. Adapted from References [64, 66]

The p53-related transcription factor p63 is an essential regulator of mammary epithelial development [25]. It is thought that the p63/p73 network controls platinum agents sensitivity in triple negative BC, and correlates with reduced BRCA1 expression. *In vivo*, the DNp63 and TAp73 isoforms were co-expressed exclusively in cells with mutant p53. Although it did not discriminate between p63 isoforms, expression detected by immunohistochemistry (IHC) will be used to follow response to treatment [74]. Together with p63, it is possible that p53 status may, in part, mediate response to therapy in *BRCA* carriers, as p53 mutations are prevalent in *BRCA*-associated BC [75], and p53 mutations enhance tumor cell kill by the ABT-888/irinotecan combination in cell lines with high ERCC1 levels [22]. We will assess p53 status (increased expression vs. non-expression) by immunohistochemistry and/or cDNA sequencing (depending on specimen type) using established methods [76, 77].

Expected results and alternate approaches: BRCA null cells, which were originally derived from germline *BRCA*-mutated cells, and which recover HRR function will potentially manifest resistance to PARP inhibitors and be a potential source of drug resistance. For example, *BRCA2* modifications that develop or are selected for in tumors during therapy may impart resistance to ABT-888 or other PARP inhibitors when the BRCA2 constructs reflecting patient mutations are transfected into VC8-DR-GFP cells.

Moreover, these transfected cells should also show increased recombination frequencies. We will correlate clinical response with tumor BRCA expression/HRR functional status and ERCC1, p63 and p53 expression via IHC and/or RT-PCR for all participants with available specimens.

We anticipate that the restoration of a BRCA open reading frame will most probably increase HRR function. For the moment, we do not know the percentage of patients who will have restored HRR function, but we expect that a functional HRR system would obviate response to the single agent DNA repair inhibitor treatment arm of the clinical trial described in this proposal. However, we expect that ABT-888 may potentiate carboplatin therapy despite functional HRR. Since it recognizes a relatively proximal (amino-) epitope, a known limitation of IHC with the Ab1 antibody against BRCA1, it is possible we will have difficulty assessing the expression status for more distal truncations or missense mutations. We are currently testing a new monoclonal antibody corresponding to C-terminal amino acids 1839-1863 of Human BRCA1, as well as alternate antibodies for detection of BRCA2 expression, for which no reports, to date, have indicated satisfactory performance in IHC on FFPE. We have lymphoblastoid cell lines for a family with a 15-bp in-frame *BRCA2* mutation, which results in a 5 amino acid loss and is considered deleterious after demonstration of allele specific LOH and tracking/linkage [78]; these should serve as useful reagents to test the systems. We will also test a known acquired intragenic deletion [50] that restores the reading frame and at least partial HRR function in tumor cells that originated from germline *BRCA2* mutant cells. If we have difficulty complementing the mouse Brca cell lines, we will use a BRCA2 deficient human cell line (e.g., CAPAN1) or VC-8 cells available in our laboratory, along with a BRCA2 complemented VC-8 as a control. In the future, we will use a method similar to that recently described using mouse ES cells to analyze unclassified mutants or reversion mutations within mammalian cells [79].

Archival Tumor Collection

If available, and with the patient's consent, archival tissue specimens should be submitted for molecular correlative studies. Archival tumor block (formalin-fixed paraffin-embedded) from initial breast diagnosis, or other specimen obtained prior to study, should be submitted, along with the corresponding path report, within four weeks of patient registration. If tissue blocks cannot be sent, 8-12 unstained slides may be submitted instead.

Fixed tissues, including paraffin-embedded tumor blocks or formalin-fixed tissues should be sent at ambient temperature. Do not send in the same box as the frozen plasma. Formalin fixed cells should be placed in a sealable bag with absorbent material and placed in an appropriate box or container for the shipping of a potentially hazardous material.

Address shipments to:

Analytical Pharma. Lab
City of Hope

Shapiro Bldg. (Synold/JNW) Rm. 1042
1500 E Duarte Rd.
Duarte, CA 91010
Phone (626) 359-8111, ext. 62110
Email: tsynold@coh.org

We anticipate access to formalin fixed paraffin embedded (FFPE) primary tumor tissue specimens for approximately 62 patients of the total 71 possible accrued to the clinical trial. Depending on the specific *BRCA* mutation, we will use IHC to assess BRCA protein expression in baseline tumors. We do not expect to identify pre-treatment reversion or resistance since one of the near obligatory steps in development of *BRCA*-associated cancer is the somatic or acquired loss of the wt allele. Subsequent genetic instability could generate reversion mutations in a small subfraction of the samples, but these subfractions are unlikely to be detectable unless subjected to selective pressure.

All specimens shipped must be accompanied by the Specimen Submission form found in Appendix D. Additionally, a copy of that completed form must be faxed to the Data Coordinating Center at City of Hope, (626) 256-8654 when specimens are shipped.

The Federal guidelines for shipment are as follows:

a. The specimen must be wrapped in an absorbable material;

b. The specimen must then be placed in an AIRTIGHT container (like a resealable bag);

c. Pack the resealable bag and specimen in a styrofoam shipping container;

d. Pack the styrofoam shipping container in a cardboard box.

e. The cardboard box must be marked as "BIOHAZARD."

11 STUDY CALENDAR

Baseline evaluations are to be conducted within 7 days prior to start of protocol therapy. Scans and x-rays must be done within 28 days prior to the start of therapy. In the event that the patient's condition is deteriorating, laboratory evaluations should be repeated within 48 hours prior to initiation of the next cycle of therapy. Tests indicated for the following weeks may be performed within ± 2 days of the indicated dates. Subsequent cycles can be adjusted +/- 48 hours.

If a patient has been on a steady dose of ABT-888 as a single agent for at least 9 months, she/he can reduce visits at the enrolling institution to every 24 weeks, provided that he/she is seen by the local/primary MD with labs (and labs/notes sent to the center), every 3 weeks.

		Cycle 1			Cycle 2			Cycle 3			Subsequent Cycles			
	Pre-Study	Wk 1	Wk 2	Wk 3	Wk 4	Wk 5	Wk 6	Wk 7	Wk 8	Wk 9	Wk 10	Wk 11	Wk 12	Off Study[e]
ABT-888		X	X	X	X	X	X	X	X	X	X	X	X	
Carboplatin*		X			X			X			X			
Informed consent	X													
Demographics	X													
Medical history	X													
Concurrent meds	X	X----------X												
Physical exam	X	X			X			X			X			X
Vital signs	X	X			X			X			X			X
Height	X													
Weight	X	X			X			X			X			X
Performance Status	X	X			X			X			X			X
CBC w/diff, plts[a]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Serum chemistry[a,b]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Urinalysis	X													
EKG (as indicated and needed)	X													

		Cycle 1			Cycle 2			Cycle 3			Subsequent Cycles			
	Pre-Study	Wk 1	Wk 2	Wk 3	Wk 4	Wk 5	Wk 6	Wk 7	Wk 8	Wk 9	Wk 10	Wk 11	Wk 12	Off Study[e]
Adverse event evaluation		X----------X												X
Tumor measurements	X	Tumor measurements are to be done at the end of cycle 3 and then repeat every 3 cycles. Documentation (radiologic) must be provided for patients removed from study for progressive disease.												X[e]
Radiologic evaluation[g]	X	1st scan will be done at the end of cycle 3 All subsequent scans will be done every 3 cycles of therapy. If the subject has a complete response/no evidence of disease or stable findings for more than a year, then annual evaluation is acceptable unless newly symptomatic.												X[e]
Urine or Serum Pregnancy Test	X[c]													
Tumor Biopsy[d]	X				X									X[e]
Pharmacodynamic blood draw[f]	X	X			X									
Archival Tumor Tissue	X													

a: If no greater than Grade 1 toxicities were seen on the most recent CBC and Serum Chemistry lab tests, after 2 cycles on a dose level, weekly CBC and Serum Chemistry will become optional (option to reduce to once per cycle).

b: Albumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, potassium, total protein, SGOT [AST], SGPT [ALT], sodium. Phosphorous at pre-study only.

c: Serum or urine pregnancy test (women of childbearing potential)

d: Optional

e: Off-study evaluation

f: Described in section 9.2. For Phase II patients, PD draws are also required on Cycle X and Cycle X+1. For Phase I patients, discontinue correlative blood draws for all cases beyond cycle 2.

g. Patients that have been on treatment for more than 2 years may have their radiologic evaluations every 4 cycles (12 weeks).

* For patients receiving carboplatin either as part of the lead-in, or in the phase II part of the trial, after progression on ABT-888 alone

12 MEASUREMENT OF EFFECT

Tumor assessments according to RECIST will be performed at baseline (within 28 days of first dose) and at the end of the first 3 cycles, and subsequently every 3 cycles according to the planned study assessments, up to and including the withdrawal visit. If the subject has a complete response/no evidence of disease or stable findings for more than a year, then annual evaluation is acceptable unless newly symptomatic.

Baseline contrast-enhanced CT of the chest, abdomen and pelvis will be performed for the assessment of measurable lesions. Where iodine contrast is contra-indicated then contrast-enhanced MRI of the abdomen and pelvis together with non-contrast enhanced CT of the chest will be preferred, rather than contrast-enhanced MRI of chest, abdomen and pelvis. Other regions will be scanned at baseline and followed-up where clinically indicated for the assessment of disease.

12.1 DEFINITIONS

Response and progression will be evaluated in this study using the new international criteria proposed by the revised Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1). Changes in only the largest diameter (unidimensional measurement) of the tumor lesions and the shortest diameter in the case of malignant lymph nodes are used in the RECIST criteria. Note: Lesions are either measurable or non-measurable using the criteria provided below. The term "evaluable" in reference to measurability will not be used because it does not provide additional meaning or accuracy.

11.1 Measurable Disease

Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as $\geq$20 mm by chest x-ray, as $\geq$10 mm with CT scan, or $\geq$10 mm with calipers by clinical exam. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

> Note: Tumor lesions that are situated in a previously irradiated area are not considered measurable, unless there is clear evidence of progression of such lesion(s) as defined by RECIST 1.1 criteria.

11.2 Non-measurable Disease

All other lesions (or sites of disease), including small lesions (longest diameter <10 mm or pathological lymph nodes with $\geq$ 10 to <15 mm short axis), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial

effusions, lymphangitis cutis/pulmonitis, inflammatory breast disease, and abdominal masses (not followed by CT or MRI), are considered as non-measurable.

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

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

11.3 Target Lesions

All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as **target lesions** and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected. A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

11.4 Non-target Lesions

All other lesions (or sites of disease) including any measurable lesions over and above the 5 target lesions should be identified as **non-target lesions** and should also be recorded at baseline. Measurements of these lesions are not required, but the presence, absence, or in rare cases unequivocal progression of each should be noted throughout follow-up.

12.2 GUIDELINES FOR EVALUATION OF MEASURABLE DISEASE

All measurements should be taken and recorded in metric notation using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the

beginning of treatment and never more than 4 weeks before the beginning of the treatment.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

Clinical lesions. Clinical lesions will only be considered measurable when they are superficial (e.g., skin nodules and palpable lymph nodes) and ≥10 mm diameter as assessed using calipers (e.g., skin nodules). In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

Chest x-ray. Lesions on chest x-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT is preferable.

Conventional CT and MRI. This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. If CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (e.g. for body scans).

Use of MRI remains a complex issue. MRI has excellent contrast, spatial, and temporal resolution; however, there are many image acquisition variables involved in MRI, which greatly impact image quality, lesion conspicuity, and measurement. Furthermore, the availability of MRI is variable globally. As with CT, if an MRI is performed, the technical specifications of the scanning sequences used should be optimized for the evaluation of the type and site of disease. Furthermore, as with CT, the modality used at follow-up should be the same as was used at baseline and the lesions should be measured/assessed on the same pulse sequence. It is beyond the scope of the RECIST guidelines to prescribe specific MRI pulse sequence parameters for all scanners, body parts, and diseases. Ideally, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans. Body scans should be performed with breath-hold scanning techniques, if possible.

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

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

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

Tumor markers. Tumor markers alone cannot be used to assess response. If markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response. Specific guidelines for both CA-125 response (in recurrent ovarian cancer) and PSA response (in recurrent prostate cancer) have been published [80][81][82]. In addition, the Gynecologic Cancer Intergroup has developed CA-125 progression criteria which are to be integrated with objective tumor assessment for use in first-line trials in ovarian cancer [83].

Cytology, Histology. These techniques can be used to differentiate between partial responses (PR) and complete responses (CR) in rare cases (e.g., residual lesions in tumor types, such as germ cell tumors, where known residual benign tumors can remain).

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

FDG-PET While FDG-PET response assessments need additional study, it is sometimes reasonable to incorporate the use of FDG-PET scanning to complement CT scanning in assessment of progression (particularly possible 'new' disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:

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

basis of the anatomic images, this is not PD.

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

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

12.3 RESPONSE CRITERIA

11.3.1. Evaluation of Target Lesions

Complete Response (CR):	Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.
Partial Response (PR):	At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters
Progressive Disease (PD):	At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progressions).
Stable Disease (SD):	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study

11.3.2. Evaluation of Non-target Lesions

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

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

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

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

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

11.3.3. Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started). The patient's best response assignment will depend on the achievement of both measurement and confirmation criteria.

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

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Overall Response when Confirmation is Required*
CR	CR	No	CR	≥3 wks. Confirmation**
CR	Non-CR/Non-PD	No	PR	≥3 wks. Confirmation**
CR	Not evaluated	No	PR	
PR	Non-CR/Non-PD/not evaluated	No	PR	
SD	Non-CR/Non-PD/not evaluated	No	SD	documented at least once ≥4 wks. from baseline**
PD	Any	Yes or No	PD	no prior SD, PR or CR
Any	PD***	Yes or No	PD	
Any	Any	Yes	PD	

* See RECIST 1.1 manuscript for further details on what is evidence of a new lesion.

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

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

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

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

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

* 'Non-CR/non-PD' is preferred over 'stable disease' for non-target disease since SD is increasingly used as an endpoint for assessment of efficacy in some trials so to assign this

category when no lesions can be measured is not advised

12.4 CONFIRMATORY MEASUREMENT/DURATION OF RESPONSE

11.4.1. Confirmation

To be assigned a status of PR or CR, changes in tumor measurements must be confirmed by repeat assessments that should be performed greater than 3 weeks after the criteria for response are first met. Confirmation of response is not required, but must be reported as "unconfirmed." In the case of SD, follow-up measurements must have met the SD criteria at least once after the start of treatment at a minimum interval of 6 weeks. (See section 11.3.3.)

11.4.2. Duration of Overall Response

The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started).

The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that recurrent disease is objectively documented.

11.4.3. Duration of Stable Disease

Stable disease is measured from the start of the treatment until the criteria for progression are met, taking as reference the smallest measurements recorded since the treatment started, including the baseline measurements.

11.4.4. Progression-Free Survival

Progression-free survival (PFS) is defined as the duration of time from start of treatment to time of progression or death, whichever occurs first.

13 DATA REPORTING / REGULATORY CONSIDERATIONS

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

13.1 DATA REPORTING

12.1.1. Method

CDUS

13.2 RESPONSIBILITY FOR SUBMISSION

Study participants are responsible for submitting CDUS data and/or data forms to the Data Coordinating Center quarterly by April 30, July 31, October 31, and January 31 to allow time for Data Coordinating Center compilation, Principal Investigator review, and timely submission to CTEP. (See Section 12.1.1.)

The Data Coordinating Center is responsible for compiling and submitting CDUS data to CTEP for all participants and for providing the data to the Principal Investigator for review.

13.3 CTEP MULTICENTER GUIDELINES

This protocol will adhere to the policies and requirements of the CTEP Multicenter Guidelines. The specific responsibilities of the Principal Investigator and the Data Coordinating Center (Study Coordinator) and the procedures for auditing are presented in Appendix B.

The Principal Investigator/Data Coordinating Center is responsible for distributing all IND Action Letters or Safety Reports received from CTEP to all participating institutions for submission to their individual IRBs for action as required.

Except in very unusual circumstances, each participating institution will order DCTD-supplied agents directly from CTEP. Agents may be ordered by a participating site only after the initial IRB approval for the site has been forwarded by the Data Coordinating Center to the CTEP PIO (PIO@ctep.nci.nih.gov).

13.4 COOPERATIVE RESEARCH AND DEVELOPMENT AGREEMENT (CRADA) / CLINICAL TRIALS AGREEMENT (CTA)

The "Agent(s)," supplied by CTEP, DCTD, NCI, used in this protocol is/are provided to the NCI under a Collaborative Agreement (CRADA, CTA) between the Pharmaceutical Company(ies) [hereinafter referred to as "Collaborator(s)"] and the NCI Division of Cancer Treatment and Diagnosis. Therefore, the following obligations/guidelines, in addition to the provisions in the "Intellectual Property Option to Collaborator" (http://ctep.cancer.gov/industryCollaborations2/default.htm), contained within the terms of award, apply to the use of Agent(s) in this study:

1. Agent(s) may not be used for any purpose outside the scope of this protocol, nor can Agent(s) be transferred or licensed to any party not participating in the clinical study. Collaborator(s) data for Agent(s) are confidential and proprietary to Collaborator(s) and shall be maintained as such by the investigators. The protocol documents for studies utilizing investigational agents contain confidential information and should not be shared or distributed without the permission of the NCI. If a copy of this protocol is requested by a patient participating on the study or patient's family member, the individual should sign a confidentiality agreement. A suitable model agreement can be downloaded from: http://ctep.cancer.gov.
2. For a clinical protocol where there is an investigational Agent used in combination with (an)other investigational Agent(s), each the subject of different collaborative agreements, the access to and use of data pertaining to such combination use (hereinafter be referred to as "Multi-Party Data") by each Collaborator shall be as follows:

a. NCI must provide all Collaborators with prior written notice regarding the existence and nature of any agreements governing their collaboration with NIH, the design of the proposed combination protocol, and the existence of any obligations that would tend to restrict NCI's participation in the proposed combination protocol.

b. Each Collaborator shall agree to permit use of the Multi-Party Data from the clinical trial by any other Collaborator solely to the extent necessary to allow said other Collaborator to develop, obtain regulatory approval, or commercialize its own investigational agent.

c. Any Collaborator having the right to use the Multi-Party Data from these trials must agree in writing prior to the commencement of the trials that it will use the Multi-Party Data solely for development, regulatory approval, and commercialization of its own investigational agent.

3. Clinical Trial Data and Results and Raw Data developed under a collaborative agreement will be made available exclusively to Collaborator(s), the NCI, and the FDA, as appropriate. All data made available will comply with HIPAA regulations.

4. When a Collaborator wishes to initiate a data request, the request should first be sent to the NCI, who will then notify the appropriate investigators (Group Chair for Cooperative Group studies, or PI for other studies) of Collaborator's wish to contact them.

5. Any data provided to Collaborator(s) for phase 3 studies must be in accordance with the guidelines and policies of the responsible Data Monitoring Committee (DMC), if there is a DMC for this clinical trial.

6. Any manuscripts reporting the results of this clinical trial must be provided to CTEP for immediate delivery to Collaborator(s) for advisory review and comment prior to submission for publication. Collaborator(s) will have 30 days from the date of receipt for review. Collaborator shall have the right to request that publication be delayed for up to an additional 30 days in order to ensure that Collaborator's confidential and proprietary data, in addition to Collaborator(s)'s intellectual property rights, are protected. Copies of abstracts must be provided to CTEP for forwarding to Collaborator(s) for courtesy review as soon as possible and preferably at least three (3) days prior to submission, but in any case, prior to presentation at the meeting or publication in the proceedings. Press releases and other media presentations must also be forwarded to CTEP prior to release. Copies of any manuscript, abstract, and/or press release/ media presentation should be sent to:

   Regulatory Affairs Branch, CTEP, DCTD, NCI
   6130 Executive Boulevard, Suite 7111
   Rockville, MD 20852
   FAX 301-402-1584
   E-mail: anshers@mail.nih.gov.

   The Regulatory Affairs Branch will then distribute them to Collaborator(s). No publication, manuscript or other form of public disclosure shall contain any of Collaborator's confidential/proprietary information.

14 STATISTICAL CONSIDERATIONS

14.1 STUDY DESIGN/ENDPOINTS

The design of this Phase II trial is also described in Section 5.0.

All patients who begin treatment as part of this trial will be accounted for in the summary of results, and the outcome status (in terms of toxicity, response, reason off study, progression, and survival) will be reported.

The toxicities observed will be summarized in terms of type (organ affected or laboratory determination such as absolute neutrophil count), severity (by CTCAE and nadir or maximum values for the laboratory measures), time of onset (i.e. course number), duration, and reversibility or outcome. Tables will be created to summarize these toxicities and side effects by course.

14.2 SAMPLE SIZE/ACCRUAL RATE

This study was initially designed as a safety lead-in of the combination of ABT-888 with carboplatin followed by a randomized Phase II study. This was changed to a safety lead-in of the combination, followed by a single agent study of ABT-888, where patients have the option of continuing to the combination following progression, after a one week off-treatment interval (personal communication, per Dr. Giranda, one week is 10 half-lives, and 3 x times the time needed to recover full PARP activity).

The safety lead-in will take between 12-27 evaluable patients.

Phase II Portion:

Stage IV *BRCA (stratified by BRCA1 or BRCA2)*-associated breast cancer patients will initiate treatment with ABT-888 at the single agent MTD (400mg BID). Following progression, patients will be off treatment for one week, and then if they meet the eligibility requirements, the patients will initiate treatment with carboplatin plus ABT-888 at the MTD of the combination established during the safety lead-in noted above.

The two strata (BRCA1 and BRCA2-associated breast cancer) will accrue independently: Simon's Optimal Two-Stage design will be employed: Initially 10 patients will be accrued to a strata. 2 or more confirmed responses in the first 10 patients in a strata will result in an additional 12 patients accrued to that stratum (for a total of 22 for that stratum). As a result, if 2 or more responses are seen in the first 10 patients with both BRCA1 and BRCA2-associated breast cancer, a total of 44 patients will be accrued to the Phase II portion of this study.

We anticipate enrollment of 6 patients per month; it should take approximately 8 months to complete accrual to this trial.

This design will allow us the opportunity to document single agent activity of ABT-888 in these two patient populations (strata), while permitting the patients to receive carboplatin/ABT-888 post-progression, which our initial Phase I data suggests has considerable activity.

For each cohort (BRCA1 and BRCA2), the primary objective will be the response rate (RR) based on RECIST criteria. Based on the response rate (11/27, 41% RR at 400mg twice daily, 6/27, 22% RR at 100mg twice daily) of the PARP inhibitor olaparib (84) in this patient population, for ABT-888 to be a candidate as a preferred PARP agent, we require ABT-888 to demonstrate clear single agent activity, with limited toxicity.

Operating Characteristics: Based on Simon's Optimal two-stage design for each cohort, 10 patients will be accrued in the first stage and if 2 or more responses are observed 12 more patients would be accrued to that strata, for a total of 22. At the end of the study, 6 responders out of the 22 patients would indicate promising activity. This design has 90% power to detect a response rate of 40%, and a type I error rate of 0.1 under the null rate of 15%.

The post-progression response and second progression-free survival data (when patients receive the combination) will also be summarized.

14.3 STRATIFICATION FACTORS

BRCA1 and 2 status patients will be treated as separate strata.

Toxicity/Safety Monitoring:

Although we expect this regimen to be well tolerated, we have established guidelines and criteria which will be used to flag an unexpected number of patients who experience unacceptable toxicity (TOX). These rules will be applied to both the single ABT-888 treatment and the combination treatment independently, although the main motivation for such detailed monitoring is based on the combination arm. Stratum will be analyzed separately.

Unacceptable toxicity (TOX) will be defined as any toxicity that results in a > 2 week delay in treatment or any toxicity resulting that the patient be taken off treatment. Patients who do not complete the first 2 cycles of treatment with the prescribed dose and do not experience a TOX will NOT be used in the decision to consider halting the trial because of toxicity and will be considered inevaluable for TOX.

Criteria for flagging an excessive number of patients with TOX are based on the sequential probability ratio test with α=0.10, β=0.10, p_o=0.05 and p_a=0.25. Every time a

patient is classified as having had a TOX, the cumulative number of patients (X) who have experienced a TOX will be compared to the number of patients (N) who are evaluable for toxicity. If the number of patients, N, is greater than N_X, the number given in the bottom row of the Table below, then accrual will not be suspended. If N is less than or equal to N_X, then accrual will be suspended for review of the data. The N_X values do not correspond to the interim analysis accrual goal, as these rules are examined when a patient experiences a TOX regardless of accrual, and we expect fewer patients evaluable for TOX than response (all treated patients).

Table: Criteria for Suspending Accrual to Evaluate Toxicity			
X: # pts who experienced a TOX	2	3	4
N_x: Suspend trial of # evaluable pts. (N) is $\leq N_x$	≤6	≤14	≤21

These rules were selected to ensure a low probability that the trial would be suspended if the true chance of unacceptable toxicity were less than 5% and a high probability that the trial would be suspended if the true chance of unacceptable toxicity were 20-25%. The Table below summarizes these probabilities. The values in the table below are based on 10,000 simulations and are accurate to ±0.01 (based on a 95% confidence interval).

Table: Probability of Suspending Accrual Because Too Many Patients Experienced a TOX							
True Chance of an Unacceptable Toxicity (TOX)		**5%**	**10%**	**15%**	**20%**	**25%**	**30%**
Probability of Suspending Accrual to Review Toxicities	N=21	0.06	0.25	0.49	0.72	0.85	0.93

Secondary Endpoint:

In the safety lead-in phase, patients will be assessed for their response rate. In the Phase II portion, progression-free survival in both the BRCA1 and BRCA2 cohorts will be evaluated, along with progression-free survival once receiving the a combination of ABT-888 and carboplatin.

14.4 ANALYSIS OF CORRELATIVE/SPECIAL STUDIES

Correlative Statistics:

In the context of this Phase II trial, the primary correlative endpoint (PAR reduction in PBMCs and response) will be evaluated. Prospective detection of *BRCA* reversion mutations that restore HRR function would be a completely novel observation in BC, and important for understanding resistance mechanisms. Other endpoints will only be statistically significant if there is a large difference. Given the sample size constraints and the multiple analyses, the other correlative studies will be exploratory and are for the purpose of generating future hypothesis-driven studies.

1. Analysis of PBMCs: It is hypothesized that PBMC PAR inhibition will predict for response. As a result patients will be pooled in a multivariate logistic regression evaluating response as a function of PAR inhibition and carboplatin (yes/no). When the sample size is 44 (pooling both strata), the logistic regression test of no effect of PAR inhibition (b=0, a = 0.05 one-sided) will have 66% power to detect a b of 0.916 (an odds ratio of 2.5), assuming the adjustment for carboplatin (yes/no) effect is adequately adjusted for in the logistic model by a simple additive term. This assumes that the proportion of responses at the mean of PAR inhibition is 0.40. This approximates the response rate, reported at ASCO 2009 [30], seen in *BRCA* carriers with advanced breast cancer who were treated with an oral PARP inhibitor. We will also evaluate the role of PAR inhibition on the response rate for each strata separately.

Patients with *BRCA* mutations may have impaired repair, and as a result, it is possible that baseline PAR levels may be elevated in these patients. Previous publications demonstrate a median PAR level of 99 pg/ml, with a standard deviation of 217 pg/ml, in non-BRCA carriers. The large variability limits the power to detect a baseline difference between non-BRCA carriers and BRCA-carriers, however, change in PAR levels will be summarized by percent of baseline. In the small amount of literature to date on non-BRCA carriers, several patients exhibited no significant PAR inhibition (e.g., <50% reduction). With 44 patients, we can estimate the percent of patients with no significant PAR inhibition with a 95% CI half-width of 15% or less.

2. Analysis of changes in correlatives: blood correlatives will be evaluated for changes due to treatment. As a result, comparing baseline to after treatment with 44 patients will result in 80% power to detect approximately a change of 43.2% of the standard deviation, using a paired t-test with a 0.050 two-sided significance level. Standard descriptive methods (scatter plots, contingency tables as well as summary statistics) will also be used to summarize the baseline levels and the changes from baseline (i.e. after treatment) and we will compare responders versus non-responders on both arms to observe if there are any unexpected patterns.

3. Analysis of baseline correlates: Tumor biopsy correlates will be available on approximately 15 patients at baseline, along with baseline blood correlates on all patients. Exploratory analysis on the role of these correlates to predict outcome (e.g., response, progression-free survival time, overall survival time), will be conducted. Kaplan-Meier plots and multivariate Cox regression will be used for exploratory analysis of the survival endpoints, and logistic regression will be used for response endpoints. This analysis will be used to determine baseline characteristics that impact clinical benefit, and allow us to search for specific markers that may predispose patients for benefit. Detection of modest interaction effects are underpowered, but

large effects can be detected. Patients who experienced an objective response will be compared to those that did not – in terms of the baseline correlates and demographics, in order to try to further understand the lack of activity.

4. A limited number of patients may have post treatment biopsies. This will allow us to explore whether action thought to be specific to ABT-888 is observed in tumor tissue, and if that action relates to baseline measurements and can help distinguish between responders and non-responders in this limited subset of patients. Prospective observation of possible *BRCA* reversion mutations that may restore HRR function and correlate with resistance to therapies is an opportunity for novel exploration. In addition, we will evaluate the difference in γH2AX between ABT-888 alone and carboplatin+ABT-888 arms in the tumor biopsies. A sample size of 15 post-treatment biopsies in each group will result in 84% power to detect a 50% increase in γH2AX positive cells or foci/cell between ABT-888 alone and carboplatin+ABT-888 arms in the tumor biopsies (a fold-change of 1.5) assuming that the coefficient of variation is 0.5 and using a two group t-test with a 0.1 one-sided significance level.

5. Statement of Exploratory Work: Analysis on correlates, effects on observed toxicities and use of response and survival endpoints will all be conducted in an exploratory fashion. Any conclusions will include a discussion of the exploratory nature of the finding, including the multiple comparison issue.

15 CCCP POLICIES FOR MONITORING CONSORTIUM TRIALS

The protocol principal investigator (PI) is responsible for monitoring the conduct and progress of this Phase I trial, including the ongoing review of accrual, data and toxicities, as well as the accumulation of reported adverse events from other trials testing the same drug(s). The participating clinicians and their designees are responsible for timely submission of adverse event reports (see Section 7.0) and case report forms. The Data Coordinating Center for the CCCP Consortium is responsible for providing the PI with access to the submitted case report form data in summary and detail in a timely fashion. Although the PI is responsible for evaluating the cumulative reported adverse events and the impact that these have on the continued conduct of the trial, it is the Data Coordinating Center of the CCCP that distributes all submitted SAE reports to the appropriate individuals, including the local protocol principal investigators, at each of the participating institutions.

The Data Coordinating Center posts a summary (accrual, toxicities, and responses) of each CCCP initiated trial on the CCCP website. In this way, each PI has access to up-to-date information on the status of his or her trial. In consultation with the collaborating statistician, the PI is responsible for review of:

(a) for Phase I trials, all dose limiting toxicities and decisions regarding dose escalation, expansion, as well as decisions to terminate escalation, and

(b) for Phase II trials, the toxicities and therapeutic endpoints referred to in the statistical plan.

The Data Coordinating Committee meets monthly to review data management and data quality issues – completeness of data submissions as well as accuracy in terms of built-in, computerized logic checks. Any issues identified and the corrective plans are presented to the Internal Committee and at the next CCCP teleconference meeting for review and approval.

15.1 OVERSIGHT

Oversight of the conduct of CCCP trials occurs at several levels:

1. The Data Coordinating Center for the CCCP flags all trials that are approaching a decision in terms of toxicity (for both Phase I and Phase II trials) or responses (for Phase II trials). Decisions are made by the PI with input from the statistician and discussion with the principal investigator of the funding mechanism (U01 Cooperative Agreement or N01 Contract, as appropriate) or his or her designee, and are communicated to the participating centers by the CCCP Data Coordinating Center. At the monthly teleconferences, the accrual of each open protocol is reviewed.

2. For CTEP sponsored Phase I trials, data are reported to the NCI-designated clinical trials monitoring service (CTMS) which will audit patients' records on each protocol – at each CCCP institution; this audit is initiated by CTEP. For all other CCCP trials, the CCCP will contract with Theradex to audit patient records at each CCCP institution.

3. An independent CCCP DSMC will review CCCP trials every 6 months. This DSMC will consist of 3 voting members (2 medical oncologists or hematologists involved in Phase I/II cancer clinical trials but not participating in CCCP studies, and a statistician) and a non-voting CCCP statistician.
   a. DSMC meetings will take place twice a year. Additional meetings will be convened if necessary.
   b. This DSMC will review each CCCP trial in terms of accrual, toxicity/safety, and adherence to trial design, audit results, and likelihood of successful completion.
   c. The DSMC will report to the CCCP leadership.

Additional Protocol Language Requirements

The following are reporting requirements and responsibilities of the Principal Investigator to the United States Army Medical Research and Materiel Command's (USAMRMC) Office of Research Protections (ORP), Human Research Protection Office (HRPO) and should be reflected in the protocol:

1. The protocol will be conducted in accordance with the protocol submitted to and approved by the USAMRMC ORP HRPO and will not be initiated until written notification of approval of the research project is issued by the USAMRMC ORP HRPO.

2. Accurate and complete study records will be maintained and made available to representatives of the U.S. Army Medical Research and Materiel Command as a part of their responsibility to protect human subjects in research. Research records will be stored in a confidential manner so as to protect the confidentiality of subject information.

3. The knowledge of any pending compliance inspection/visit by the FDA, OHRP, or other government agency concerning clinical investigation or research, the issuance of Inspection Reports, FDA Form 483, warning letters or actions taken by any Regulatory Agencies including legal or medical actions and any instances of serious or continuing noncompliance with the regulations or requirements will be reported immediately to USAMRMC ORP HRPO.

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APPENDICES

Appendix A - Performance Status Criteria

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

Appendix B - CTEP Multi-center Guidelines

If an institution wishes to collaborate with other participating institutions in performing a CTEP sponsored research protocol, then the following guidelines must be followed.

Responsibility of the Protocol Chair

- The Protocol Chair will be the single liaison with the CTEP Protocol and Information Office (PIO). The Protocol Chair is responsible for the coordination, development, submission, and approval of the protocol as well as its subsequent amendments. The protocol must not be rewritten or modified by anyone other than the Protocol Chair. There will be only one version of the protocol, and each participating institution will use that document. The Protocol Chair is responsible for assuring that all participating institutions are using the correct version of the protocol.
- The Protocol Chair is responsible for the overall conduct of the study at all participating institutions and for monitoring its progress. All reporting requirements to CTEP are the responsibility of the Protocol Chair.
- The Protocol Chair is responsible for the timely review of Adverse Events (AE) to assure safety of the patients.
- The Protocol Chair will be responsible for the review of and timely submission of data for study analysis.

Responsibilities of the Coordinating Center

- Each participating institution will have an appropriate assurance on file with the Office for Human Research Protection (OHRP), NIH. The Coordinating Center is responsible for assuring that each participating institution has an OHRP assurance and must maintain copies of IRB approvals from each participating site.
- Prior to the activation of the protocol at each participating institution, an OHRP form 310 (documentation of IRB approval) must be submitted to the CTEP PIO.
- The Coordinating Center is responsible for central patient registration. The Coordinating Center is responsible for assuring that IRB approval has been obtained at each participating site prior to the first patient registration from that site.
- The Coordinating Center is responsible for the preparation of all submitted data for review by the Protocol Chair.
- The Coordinating Center will maintain documentation of AE reports. There are two options for AE reporting: (1) participating institutions may report directly to CTEP with a copy to the

Coordinating Center, or (2) participating institutions report to the Coordinating Center who in turn report to CTEP. The Coordinating Center will submit AE reports to the Protocol Chair for timely review.

- Audits may be accomplished in one of two ways: (1) source documents and research records for selected patients are brought from participating sites to the Coordinating Center for audit, or (2) selected patient records may be audited on-site at participating sites. If the NCI chooses to have an audit at the Coordinating Center, then the Coordinating Center is responsible for having all source documents, research records, all IRB approval documents, NCI Drug Accountability Record forms, patient registration lists, response assessments scans, x-rays, etc. available for the audit.

Inclusion of Multicenter Guidelines in the Protocol

- The protocol must include the following minimum information:
  - The title page must include the name and address of each participating institution and the name, telephone number and e-mail address of the responsible investigator at each participating institution.
  - The Coordinating Center must be designated on the title page.
  - Central registration of patients is required. The procedures for registration must be stated in the protocol.
  - Data collection forms should be of a common format. Sample forms should be submitted with the protocol. The frequency and timing of data submission forms to the Coordinating Center should be stated.
  - Describe how AEs will be reported from the participating institutions, either directly to CTEP or through the Coordinating Center.
  - Describe how Safety Reports and Action Letters from CTEP will be distributed to participating institutions.

Agent Ordering

- Except in very unusual circumstances, each participating institution will order DCTD-supplied investigational agents directly from CTEP. Investigational agents may be ordered by a participating site only after the initial IRB approval for the site has been forwarded by the Coordinating Center to the CTEP PIO.

Appendix C - CCCP Registration Procedures

CCCP REGISTRATION PROCEDURES FOR PHASE II TRIALS

1. Registrations for Phase II protocols must be made through the Biostatistics office at the City of Hope between the hours of 8:30 a.m. to 4:30 p.m., Monday through Friday (except holidays).
2. Patients must be registered within 72 hours prior to initiation of protocol therapy.
3. A patient failing to meet all protocol requirements may not be registered. If you have any questions regarding eligibility, contact the City of Hope Data Coordinating Center (DCC) at (626) 256-HOPE (4673), ***extension 65928.***
4. Prestudy laboratory tests, scans and x-rays must be completed prior to registration according to study calendar/protocol.
5. Patients must sign an informed consent prior to registration.
6. Confirm that the patient meets all inclusion and exclusion eligibility criteria for a protocol.
7. Complete the Eligibility Checklist.
8. Verify that all required prestudy tests were performed.
9. Fax the completed Eligibility Checklist, signed and dated informed consent, pathology report, and relevant laboratory results to the City of Hope Consortium Coordinator for confirmation of eligibility. The FAX number is (626) 256-8654.
10. Call the City of Hope Consortium Coordinator at (626) 256-HOPE (4673), extension 65928 to confirm the FAX arrival. If the Consortium Coordinator is not in the office, have them paged at (626) 423-5365.
11. If the patient qualifies, the City of Hope Consortium Coordinator will call the registering institution to complete the registration/randomization procedure and assign the patient's study ID number.
12. Once a patient has been registered, the Data Coordinating Center will provide a "Confirmation of Registration" to the center registering the patient.

For questions regarding eligibility call City of Hope California Cancer Consortium, Data Coordinating Center

(626) 256-HOPE (4673), extension 65928

Appendix D - CCCP Specimen Submission Form

Please email the Data Coordinating Center at cccp@coh.org for the Specimen Submission Form once study is activated at your institution.

APPENDIX E - PATIENT MEDICATION DIARY

Please see following page.

APPENDIX E: PATIENT MEDICATION DIARY

CTEP-ASSIGNED PROTOCOL # 8264

Local Protocol # _____

Today's date _____ **Agent** **ABT888**

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

1. Complete one form for each cycle of treatment.
2. **ABT888** should be stored at room temperature.
3. You will take **ABT888** twice each day about 12 hours apart. If you forget to take **ABT888** and it has been more than 2 hours after your regular dosing time, skip that dose and take your regular dose at your next regular time.
4. Morning dose: take _____ mg (____capsules) **ABT888**. ********** Evening dose: take _____ mg (____capsules) **ABT888**.
5. Record the date, the number of **ABT888** capsules you swallowed in the morning and again in the evening, and when you swallowed the medicine.
6. Wash your hands after handling the capsules (patient and caregiver).
7. If you have any comments or notice any side effects, please record them in the Comments column.
8. Please bring this form and your bottles of **ABT888** when you return for each appointment.

Day	Date	Time of morning dose	Dose taken	Time of evening dose	Dose taken	Comments
			# of capsule taken		# of capsule taken	
1						
2						
3						
4						
5						
6						
7						
8						
9						
10						
11						
12						
13						
14						
15						
16						
17						
18						
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21						
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24						
25						
26						
27						
28						

Patient's signature _____

Physician's Office will complete this section:

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

Appendix F Standard Operating Procedures for Correlative Studies

Please see attached separate documents for Appendix F with SOPs and Forms.