1.0 TITLE PAGE

A Phase I/II Study of ABT-888 in combination with 5-Fluorouracil and Oxaliplatin in Patients with Metastatic Pancreatic Cancer

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2.0 SYNOPSIS

2.1 Investigational Agents:

1) ABT-888, an inhibitor of Poly(ADP-ribose) polymerase (PARP) (Abbott)
2) 5-Fluorouracil (5FU)
3) Oxaliplatin (Eloxatin, Sanofi-Aventis)

2.2 Phase: Phase I/II, multi-institution, open label

2.3 Indications: Metastatic pancreatic cancer

2.4 Objectives:

2.4.1 Primary Objectives:

2.4.1.1 Primary Objective of Phase I Portion: To determine the Recommended Phase II Dose (RP2D) of ABT-888 combined with 5FU and oxaliplatin in patients with metastatic pancreatic cancer

2.4.1.2 Primary Objective of the Phase II Portion: To determine the objective response rate of ABT-888 combined with 5FU and oxaliplatin in patients with metastatic pancreatic cancer

2.4.2 Secondary Objectives

2.4.2.1 Secondary Clinical Objectives: To determine, in patients with metastatic pancreatic cancer treated with ABT-888 combined with 5FU and oxaliplatin:

1) Disease control rate (CR+PR+SD at 6 months)
2) Progression free survival
3) Overall survival
4) Time to disease progression
5) Duration of disease control
6) Tolerability and safety of the combination
7) Degree of Neuropathy, as measured by the FACT/GOG-NTX-4 (Version 4)

2.4.2.2 Secondary Scientific Objectives To correlate the response rate of ABT-888 plus 5FU and oxaliplatin to:

1) Tumors that have decreased expression of or mutations in BRCA-1 or -2 or related pathway genes.
2) PARP activity levels in serial tumor samples
3) Expression levels of DNA repair enzymes in tumor tissues
4) Pharmacokinetic and pharmacogenomic parameters associated with the metabolism of ABT-888
5) To isolate and propagate tumor cell lines obtained from patient samples and circulating tumor cells

2.5 Trial Design Summary:

This is a single arm, open-label Phase I/II study to evaluate the clinical activity of the combination of the novel inhibitor of Poly(ADP-ribose) polymerase (PARP), ABT-888 combined with 5FU and oxaliplatin in patients with metastatic pancreatic cancer. Patients with metastatic, unresectable pancreatic cancer, and with a known BRCA-associate genetic mutation OR family history suggestive of a breast or ovarian cancer syndrome (as defined in the inclusion criteria) who still have an adequate performance status and normal hepatic and renal function will be eligible. Patients will be stratified into two groups: Untreated or previously treated:

- Untreated patients should have received zero prior therapies for metastatic disease.
  i. They may have received prior adjuvant chemotherapy and/or radiation therapy, but not within 6 months prior to treatment.
  ii. They may have received prior *palliative* radiation therapy for unresectable disease, but without any systemic chemotherapy, even as a radiosensitizer
- Previously treated patients may have received any number of prior therapies, including prior adjuvant chemotherapy and/or radiation therapy within 6 months of treatment.

One cycle will be 14 days. Patients will receive 5FU and oxaliplatin without a 5FU bolus (oxaliplatin (85mg/m^2) and leucovorin (400mg/m^2) on day 1, followed by a continuous infusion of 5FU (2400mg/m^2) over 46 hours on days 1-3). Patients will also receive ABT-888 twice-a-day on Days 1-7 of each 14-day cycle (Figure 1).

The dose of ABT-888 will be determined by a Phase I dose escalation study. As detailed below, ABT-888 has been safely combined with traditional cytotoxic chemotherapy in previous clinical trials, though it has

not been combined with 5FU and oxaliplatin. Therefore a traditional 3+3 dose escalation approach with doses of ABT-888 ranging from 40mg to 300mg twice-a-day will be employed to determine the recommended Phase II dose of ABT-888 to be used with 5FU and oxaliplatin. Intra-patient dose escalation will not be allowed.

As of April, 2013 (updated in Version 8.0, 04-15-2013), the recommended Phase II dose has been chosen to be 200mg of ABT-888 twice a day.

Patients will be evaluated, including laboratory testing every cycle (every 14 days) and restaging studies will be performed every 4 cycles (or not more than every 12 weeks if there have been treatment delays). Patients whose tumors have not progressed at the time of restaging, as determined by RECIST 1.1 and who continue to tolerate treatment will continue on study.

The primary endpoint for Phase II will be the objective response rate (ORR), as determined by RECIST 1.1 criteria. Secondary clinical endpoints are listed above, and include the determination of the disease control rate (DCR, defined as ORR + rate of stable disease at 6 months), progression free survival (PFS), overall survival (OS), time to disease progression (TTP), duration of disease control (DDC), and tolerability and safety of the combination.

This stratified trial will follow two Simon's two-stage optimal designs(1), one for the untreated group, and one for the previously treated group. Each study (or otherwise stated, each stratum) has the same hypothesized design which will run in parallel. For the first stage, 9 patients will be accrued. If none of the 9 patients achieve a partial or complete response with ABT-888 plus 5FU and oxaliplatin, the combination will be rejected and the trial stopped. However, if at least 1 patient of the 9 (11%) achieves a partial or complete response in the first stage, then an additional 15 patients will be entered into the second stage, for a total of 24 patients in each stratum of these Phase II studies. If 3 (12%) or more patients achieve a partial or complete response, then the combination will be considered for further investigation among those patients. The sample sizes of 9 and 24 patients and the decision rules, in stages 1 and 2 respectively, are designed to differentiate a 5% ORR from a 25% ORR at a 1-sided 10% significance level and 90% power. Historically, the response rate of patients receiving single agent gemcitabine (previously considered the standard of care) is only about 8%.

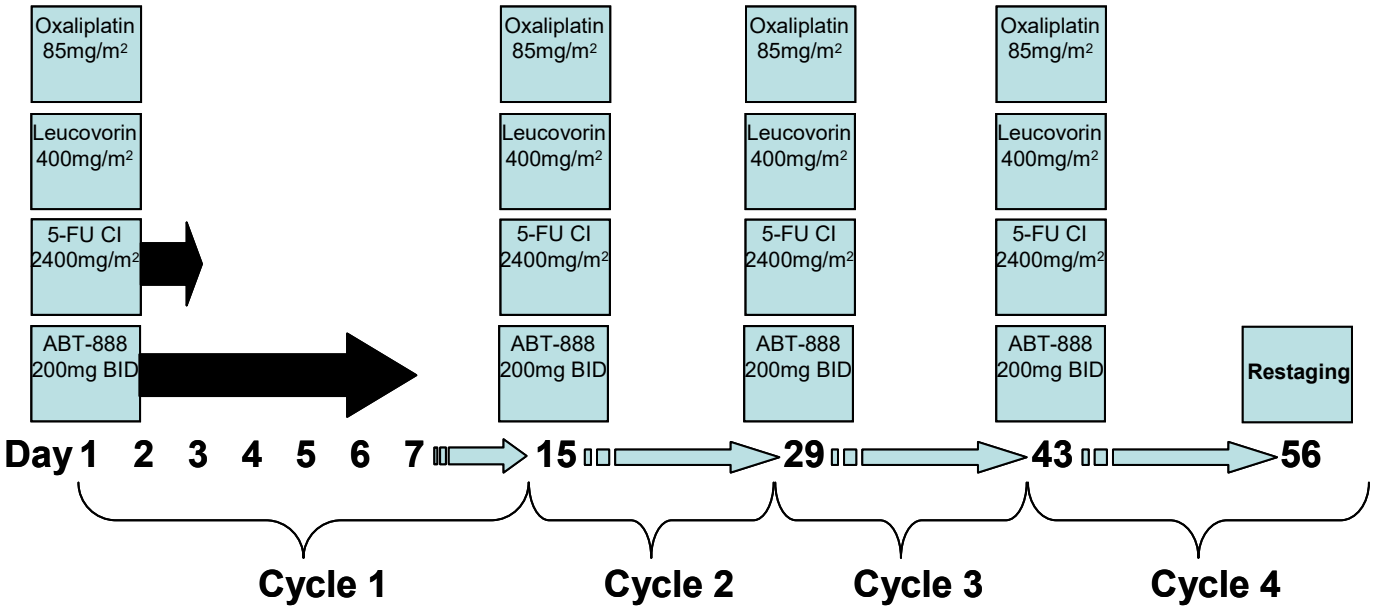

Figure 1: Treatment schema

2.6 Correlative Research

The premise that underlies the use of this combination is that 5FU and oxaliplatin (primarily oxaliplatin) will induce significant DNA damage, and that pancreatic cancer cells, in which PARP is activated, will be particularly dependent upon PARP activity to recover from the oxaliplatin-induced DNA damage. Thus, concurrent inhibition of PARP will result in overwhelming DNA damage in cancer cells, ultimately leading to increased cancer cell death. Tumors that have other abnormalities in the DNA-repair pathway may be even more susceptible to this combination. It is possible that tumors that exhibit these deficiencies will be particularly sensitive to DNA damage and PARP inhibition, which may predict for an increased ORR with therapy. Thus, we will perform a correlative analysis of BRCA-2-related gene germline mutations from patient specimens, as well as screen the expression of a panel of DNA repair genes (Table 7) in patient tumor

samples. Thus, all patients with biopsy-able tumor deposits will be required to undergo fresh tumor biopsies prior to enrollment. (Patients whose tumors are not accessible, will still be allowed to enroll in the trial). We hope this will ensure high quality tissue acquisition.

Finally, all patients will be required to undergo a biopsy upon progression to assess the underlying mechanisms of resistance to PARP inhibitor-based therapy.

2.7 Selection of Study Population

This is a multi-institutional study, enrolling patients with metastatic pancreatic cancer.

2.7.1 Key Inclusion Criteria

1) Histologically proven pancreatic adenocarcinoma with measurable disease, defined as at least 1 unidimensionally measurable lesion by standard imaging as defined by RECIST 1.1 criteria.
2) A known BRCA-associate genetic mutation OR family history suggestive of a breast or ovarian cancer syndrome (as defined in the inclusion criteria of the main protocol)
3) ECOG performance status 0-2
4) Age >= 18 years
5) Adequate hepatic, bone marrow, and renal function

2.7.2 Key Exclusion Criteria

1) Untreated CNS metastases (details below).
2) No active severe infection, or known chronic infection with HIV or hepatitis B virus
3) No cardiovascular disease problems including unstable angina, therapy for life-threatening ventricular arrhythmia, or myocardial infarction, stroke, or congestive heart failure within the last 6 months
4) No women who are pregnant or breastfeeding, and no women of childbearing potential without using dual forms of effective contraception
5) Anticipated patient survival under 3 months

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5.0 BACKGROUND AND JUSTIFICATION

5.1 Scope of the Problem

Pancreatic cancer remains a major unresolved health problem in the United States, and metastatic pancreatic cancer is a uniformly fatal disease. In the last decade, despite increases in our understanding of the molecular and genetic etiology of this disease, little progress has been made to extend survival in this patient population. In fact, the accepted standard of care, which is gemcitabine-based therapy has increased median overall survival from 2-4 months in untreated patients to only 6-7 months in treated patients(2). Moreover, until recently no treatment has definitively demonstrated a benefit to patients whose disease has progressed on gemcitabine-based therapy. However, data from the CONKO-003 trial suggests the combination of 5-fluorouracil (5FU) and oxaliplatin may be a promising regimen. This combination demonstrated a significant improvement in progression-free survival and overall survival, when compared to 5FU alone(3, 4). The median overall survival of ~11 months as measured from the start of gemcitabine therapy is among the longest seen in a Phase III trial. Furthermore, the combination of oxaliplatin and 5FU have repeatedly demonstrated intriguing overall survival rates and response rates in several first-line, and second-line Phase II trials, making 5FU and oxaliplatin a very attractive combination for further study in this disease(3, 5-7). Nevertheless, despite the optimism stirred by these results, more than 50% of patients in the CONKO-003 trial did not live past twelve months, emphasizing the fact that additional treatment options are desperately needed for patients with this disease. In this era of targeted therapy, treatment regimens that incorporate novel approaches to targeting pancreatic cancer cells, and a better determination of the molecular markers that define individual patient tumors will aid in our overall goal of individualized, targeted therapy for pancreatic cancer. Since pancreatic tumor cells survive and thrive under stressful conditions, we hypothesize that targeting an activated or disrupted response pathway such as DNA repair could more effectively kill cancer cells.

5.2 Targeted therapies against DNA repair in pancreatic cancer

One of the defining hallmarks of gastrointestinal malignancies including pancreatic cancer is chromosomal instability (CIN). The critical events that contribute to CIN, and thus pancreatic tumorigenesis, are linked to a disruption in an internal repair system that can set the stage for DNA mutations and events such as loss of heterozygosity (LOH) of tumor suppressor genes. Furthermore, the ability of pancreatic cancer cells to thrive with such genetic instability provides an opportunity to target an altered DNA repair network in pancreatic cancer cells. Logically, it has been shown that a defect in this repair pathway can render pancreatic cancer cells hypersensitive to DNA damaging agents. This approach has shown success in pre-clinical models. For instance, pancreatic cancer cells altered in the DNA repair genes, *BRCA2*, *FANCC* and *G* (labeled as "BRCA-deficient"), are all hypersensitive to intra-strand cross-linking agents and platinum-based drugs in *in vitro* and *in vivo* models(8). It has been estimated that roughly between 5-10% of sporadic pancreatic tumors, and over 15% of familial cases harbor mutations in this BRCA-pathway, including the recent discovery of *PALB2* mutations(9). Regardless of whether mutations were artificially introduced or naturally occurring in pancreatic cancer cells(8), all pre-clinical models selected platinum drugs as promising therapeutic choices to target pancreatic tumor cells deficient in this repair pathway. Additionally, Ashworth and colleagues showed that cells deficient in the homologous recombination repair pathway of double-stranded breaks (including *RAD51, RAD54, DSS1, RPA1, NBS1, ATR, ATM, CHK1, CHK2, FANCD2, FANCA,* or *FANCC*) are also hypersensitive to a promising new class of drug, PARP-inhibitors(10, 11). Specifically, it has been shown that cells that are deficient in *BRCA2* and related genes are sensitive to PARP inhibitors(10). Hence, PARP inhibitors are being investigated as a therapeutic option for various cancers disrupted in the BRCA2 pathway. Conceptually, tumors with loss of expression due to a 'second hit' of the DNA repair gene will be more sensitive to these targeted agents than normal cells, thus providing a good therapeutic window(8, 12). It also has been shown that increased or aberrant PARP expression in cancer cells is a mechanism of chemo-resistance(13). Accordingly, PARP-inhibitors have shown success in sensitizing cells to platinum based therapy(14). This suggests that PARP-inhibitors can effectively sensitize both BRCA-proficient and deficient pancreatic cancer cells to agents such as oxaliplatin. This strategy is borrowed loosely from the concept of targeting cancer cells from two points of the same pathway (i.e. synthetic lethality), which may break the *de novo* and acquired chemo-resistance inherent to most pancreatic cancer cells. Thus, this strategy may work for the majority of pancreatic cancers ("BRCA-proficient") and may be especially beneficial for a subset of patients with BRCA-deficiency in their tumor cells.

5.3 Poly(ADP-ribose) Polymerase (PARP)

Poly(ADP-ribose) polymerase (PARP) is a nuclear enzyme that plays a critical role in the repair of DNA damage(4). Inactive PARPs 1 and 2 are autoactivated upon binding to damaged DNA, and the activated PARP subsequently poly(ADP-ribosyl)ates many nuclear target proteins, including those that facilitate DNA repair of both single-stranded and double-stranded DNA breaks. Thus PARP inhibition results in less efficient DNA repair following a cytotoxic insult. DNA damaging agents, including cytotoxic chemotherapy and radiation therapy, remain a mainstay of cancer therapy, and cancer cells are often genetically unstable and/or exhibit deficiencies in DNA repair systems(15, 16). These deficiencies render cells more dependent on PARP for DNA repair and thus more sensitive to PARP inhibition(17). Additionally, higher expression of PARP in cancer cells compared to normal cells has been linked to drug resistance and the overall ability of cancer cells to sustain genotoxic stress(4). Consequently, PARP inhibitors are proposed as sensitizing agents for ionizing radiation therapy and a variety of DNA-damaging agents including platinums, alkylators, and topoisomerase inhibitions.

Recently, it was revealed that mutations disrupting the DNA-binding domain of PARP-1 can affect the overall structure of the enzyme(18). Experimentally, we utilized these functional *PARP-1* mutants (which act like PARP-inhibitors) to screen for various chemotherapeutic agents that would act synergistically with a potent PARP inhibitor (Figure 2). When the PARP-1 enzyme was expressed in a mutant form, we found an increased sensitivity to platinum-based drugs, including cisplatin, carboplatin, and oxaliplatin (Data not shown and Figure 1). Thus, we have shown that mutations in PARP-1 (i.e. dominant-negative PARP-1 mutations) can behave like PARP inhibitors and allow pancreatic cancer cells (wild-type for BRCA1/2, labeled BRCA-proficient) to become sensitized to clinically available platinum-based drugs. Interfering with the function of PARP-1 (mutations or inhibitors) may effectively sensitize cancer cells to such treatment strategies.

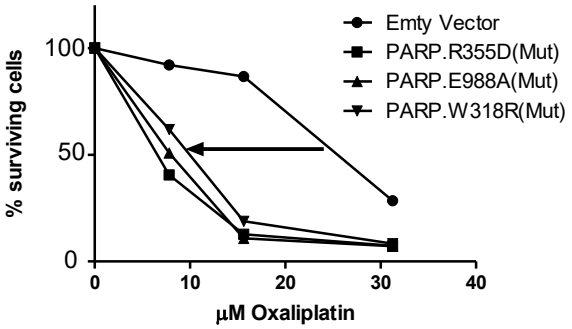

Figure 2: Exogenous expression of mutant forms of the PARP protein into BRCA-proficient pancreatic cancer cell lines (MiaPaCa2 cells) render these cells hypersensitive to oxaliplatin compared to empty vector control cells (Our unpublished results). Cells are stained with picogreen to label double-stranded DNA (viable cells) after 6 days treatment in culture. Representative experiment of three separate experiments shown.

5.4 ABT-888 Activity and Pharmacokinetic Profile

5.4.1 Mechanism of Action and Anti-Tumor Activity

ABT-888 is a potent PARP inhibitor that delays the repair of DNA damage induced by chemotherapeutics. ABT-888 increases sensitivity of tumor cells to damaging agents, *in vitro*, and demonstrated PARP inhibition in murine tumors, *in vivo* and human peripheral blood mononuclear cells, *ex vivo*. ABT-888 is a novel small molecule that is a potent PARP inhibitor (Ki of 5 nM and 3 nM for PARP-1 and PARP-2 enzymes, respectively). In cells under oxidative stress, ABT-888 inhibits the PARP induced formation of poly-(ADP-ribose) (PAR) with an EC50 of 2.4 nM. *In vitro* assays showed that ABT-888 increased sensitivity of tumor cells to DNA damaging agents including temozolomide, irinotecan, cyclophosphamide, BCNU, and cisplatin. *In vivo* pharmacology studies have demonstrated that ABT-888 has enhanced the antitumor activities of DNA damaging agents that include alkylating/methylating agents (TMZ and cyclophosphamide), topoisomerase I inhibitors (irinotecan), crosslinking agents (cisplatin and carboplatin) and radiation(13, 14). For example, in a mouse xenograft model, ABT-888 increased the effective “cure rate” of cisplatin from 33% to ~90%(14). We assessed the pre-clinical efficacy of ABT-888 in pancreatic cancer cells, the vast majority of which are known to be BRCA-proficient (>10% of sporadic pancreatic cancers). We hypothesized that, similar to the PARP-mutants, ABT-888 could effectively sensitize BRCA-proficient pancreatic cancer cell to platinum based drugs. Our data show that ABT-888 can indeed sensitize pancreatic cancer cells to cisplatin (Figure 3). Human pharmacokinetics indicate that an oral dose of 40 mg twice a day would achieve exposures greater than the AUC (0-24) of 3.0 μg•hr/mL, consistent with the preclinically maximally efficacious dose. Preclinically, significant inhibition of tumor PAR levels was observed at doses similar to those with antitumor effect, consistent with ABT-888 mediating the potentiation of DNA damaging agents through mechanistic inhibition of PARP.

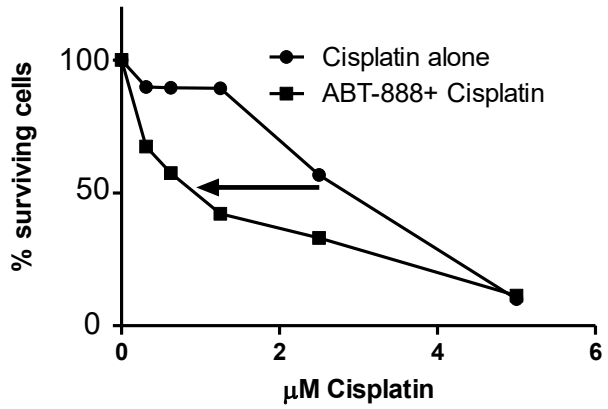

Figure 3. BRCA-wild type pancreatic cancer cells are rendered sensitive to cisplatin. Experiments performed as described in Figure 2. The arrow indicates the lower IC_{50}. Representative experiment of three separate experiments.

Furthermore, it has been demonstrated in a BRCA-2-deficient breast cancer xenograft model that ABT-888 also significantly increases the antitumor efficacy of cisplatin and carboplatin (Figure 4)(14). Given the known sensitivity of BRCA2-deficient pancreatic cancer cells to oxaliplatin, and the enhanced effects of ABT-888, as shown in figure 2, the addition of ABT-888 to platinum-based therapies (mFOLFOX-6) may optimize an already promising treatment strategy against tumors with BRCA-deficiency. Thus, the combination of ABT-888 and a platinum analog is effective in both BRCA-proficient *and* -deficient tumors(10), laying the proof-of-principle work that ABT-888 can sensitize pancreatic cancer cells (regardless of a defined genetic alteration in a DNA repair gene) to a platinum based drug (*i.e.,* oxaliplatin). Moreover, targeting two aspects of the repair pathway follows the logic of inducing synthetic lethality in cancer cells, and not allowing cancer cells the opportunity to develop *de nova* drug resistance (*i.e*., an acquired addiction to other aspects of the repair network).

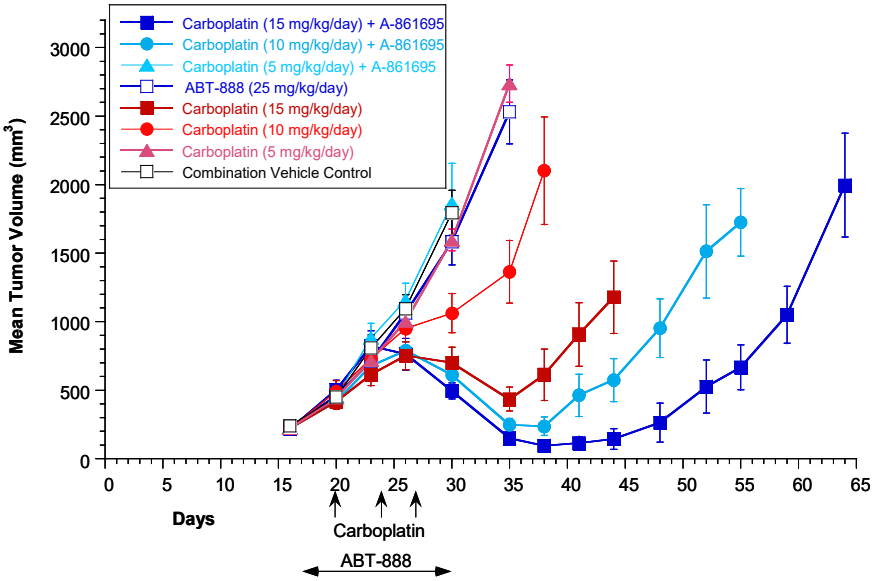

Figure 4. In a BRCA-deficient breast xenograft model ABT-888 increased the sensitivity of these tumors to cisplatin and carboplatin (as shown here)(14). A dose increase in ABT-888 enhances the therapeutic reduction of tumor volume in mice.

5.4.2 Pharmacokinetics of ABT-888

In rats and dogs, ABT-888 is primarily cleared in the urine as intact parent drug, with minor contributions from metabolism. The renal clearance and minimal metabolism observed in rats and dogs and the minimal metabolism observed in vitro in all species evaluated are consistent with the low molecular weight (244.296 g/mol) and good solubility of ABT-888. These data support the prediction that in the human, ABT-888 will be primarily cleared as intact parent in urine. ABT-888 is not a potent inhibitor of the major human cytochrome P450s (CYPs), suggesting a minimal potential for drug-drug interactions at the anticipated therapeutic concentrations.

5.4.3 Penetration of the Blood-Brain Barrier

Much of the pre-clinical work studying the effects of ABT-888 plus alkylating agents has been done with the atypical alkylating agent, Temozolomide (TMZ) – though subsequent pre-clinical studies with other alkylating agents such as the platinums have demonstrated similar safety profiles.

For example, a transplantable rat glioma cell line, 9L that produces orthotopic gliosarcoma in syngeneic Fisher 344 rats is used to assess the efficacy of a compound in an environment where drug must cross the blood-brain barrier. In this experiment, rats were randomized to treatment with vehicle, TMZ (17.5 mg/kg/day, PO QD administered Days 4 to 8), and ABT-888 (5, 18, and 50 mg/kg/day, PO BID administered Days 3 to 13) with TMZ (17.5 mg/kg, PO QD). When combined with TMZ, ABT-888 significantly potentiated its antitumor activity. Tumor growth inhibition was dose-dependent. ABT-888 at 50 mg/kg/day in combination with TMZ reduced tumor volume compared to control as assessed by contrast-enhanced magnetic resonance imaging (MRI) on Day 14 by 63%, which was 44% better than TMZ alone ($p < 0.005$). After multiple doses of ABT-888 (50 mg/kg/day), the concentration of the compound 2 hours post dosing (near Cmax) was 1.36 ± 0.16 µg/mL, 0.72 ± 0.12 µg/g, and 3.00 ± 0.16 µg/g, in plasma, brain, and tumor tissues, respectively.

5.4.4 Toxicology

In a 4-week repeat dose dog toxicity studies, the No-Observed-Adverse-Effect-Level (NOAEL) was 10 mg/kg/day (Cmax of 1.68 µg/mL and AUC0-24 of 8.01 µg•hr/mL). The dose-limiting toxicity in this study was seizure observed at 30 mg/kg/day. Seizures were also noted in a 2-week study, at dosages varying from 30 to 60 mg/kg/day. A dedicated EEG study in the conscious dog also determined that seizures were observed at a dose of 30 mg/kg BID, with no evidence of abnormal cortical activity or seizures occurring at a lower dose of 20 mg/kg BID. Plasma exposure at the 30 mg/kg BID dose corresponded to a mean plasma exposure approximately 10-fold above the predicted clinical AUC0-24 of 3 µg•hr/mL. Therefore, preclinical dog studies determined an approximate 10-fold safety margin for seizure, when exposures were compared to anticipated therapeutic AUC0-24. In repeat-dose oral rat toxicity studies, the NOAEL was 25 mg/kg/day with key findings at higher exposures including decreased body weight, decreased white blood cell and erythron parameters, and testis degeneration. ABT-888 did not induce seizures at doses as high as 400 mg/kg/day. Additionally, ABT-888 did not induce seizures in a model of orthotopically implanted rat glioblastoma with a dose of up to 50 mg/kg. In safety pharmacology studies, ABT-888 did not affect the electronically induced seizure threshold, except for a small decrease at 30 mg/kg. The secondary and safety pharmacology studies conducted with ABT-888 demonstrated minimal effects on the cardiovascular, pulmonary, and GI systems. In the anesthetized dog model, there was a trend towards delayed cardiac repolarization at plasma concentrations 21-fold higher than the predicted clinical Cmax. In humans, QTc prolongation is predicted to be less than 3 ms at a dose of 50 mg BID. ABT-888 produced no effect on heart rate or cardiac output at a concentration of 12.96 µg/mL in the dog (≈61-fold over predicted clinical exposure level) and no effect on pulmonary function at a plasma concentration of 5.82 µg/mL in the rat (≈28-fold over predicted clinical exposure level). ABT-888 was determined to unlikely be emetic or to elicit adverse GI effects at efficacious plasma concentrations.

In a separate study in rats in which ABT-888 was combined with TMZ, observed toxicities were consistent with exacerbation of known TMZ toxicity. Coadministration of TMZ at 16 mg/kg/day and ABT-888 at doses of 12.5 and 25 mg/kg/day (divided BID) resulted in increased toxicity over that observed with TMZ administration alone, affecting bone marrow (manifesting as decreased neutrophils, lymphocytes, and reticulocytes), lymphoid tissues, testes, and ovaries. Recovery of toxicologic findings was observed at the end of a 28-day recovery period (with the exception of the testes). At a higher dose of ABT-888 (75 mg/kg/day divided BID), there was watery diarrhea with histologic changes, including intestinal crypt necrosis, and dose-related hematologic toxicity. Full exposure data for ABT-888 was not obtained in this study as the majority of the plasma was utilized to evaluate the pharmacokinetic profile of TMZ. However, evaluation of selected pharmacokinetic time points was comparable to that noted in previous studies. In these previous preclinical toxicology studies, a dose of 25 mg/kg/day resulted in an exposure that exceeded anticipated clinical efficacious exposure by 1.3 to 4 fold in the male rat and 2.6 to 7 fold in the female rat. ABT-888 resulted in a reversible and non-lethal exacerbation of TMZ hematologic toxicity in the rat at doses that, in previous studies, resulted in exposures that were similar to or greater than the maximally efficacious exposure (AUC) in the melanoma murine model. However, even in the most sensitive preclinical model (dog) seizures were not seen at exposures less than or equal to 8-fold above the preclinical efficacious exposure (AUC). Therefore, hematological toxicity is expected to be the dose-limiting toxicity in the clinic occurring at doses and exposures well below those at which seizures have been observed. Subjects in the clinic will be carefully monitored for hematologic abnormalities.

5.5 5-Fluorouracil and Oxaliplatin

5.5.1 5-Fluorouracil

5-Fluorouracil is an inactive agent in its parent form, and requires intracellular activation for its anti-cancer effects. In the cell, thymidine phosphorylase converts 5FU to FUDR, which is then phosphorylated by thymidine kinase to generate the active metabolite, FdUMP which then covalently binds to and inhibits thymidilate synthase, leading to a depletion of dTTP and preventing DNA synthesis and repair. A metabolite, FUTP is also generated interfering with RNA synthesis as well. The most common mechanism of resistance to 5FU is overexpression of or mutation in the thymidilate synthase gene. 5FU is administered intravenously, and metabolism is rapid, with a half-life of only minutes, for the parent compound. Toxicities of 5FU are dependent upon the dose, but also the route and schedule of administration. IV 5FU can be given as a rapid bolus, or as a continuous infusion. Bolus administration is more associated with myelosuppression while continuous infusion is more associated with the development of hand-foot syndrome. Both schedules can lead to nausea, vomiting, diarrhea, mucositis, fatigue and rarely coronary vasospasm.

5.5.2 Oxaliplatin

Oxaliplatin is a potent, third generation platinum analog, that, similar to other alkylating agents, binds to DNA, forming intra-strand cross links and DNA adducts. These DNA abnormalities inhibit DNA replication and transcription. Oxaliplatin can be administered as a single agent, but is typically given in combination with 5FU (see FOLFOX, below). It can be safely administered in patients with hepatic or renal dysfunction. The primary side effects include neurotoxicity (cold hypersensitivity and paresthesias) which can be dose limiting and also increase with repeated cycles of administration. Additionally, oxaliplatin can cause nausea, vomiting, diarrhea, and myelosuppression, all of which tend to be relatively mild. Rarely, patients may experience laryngospasm at the time of administration, which is often ameliorated by slowing the infusion and co-administration of benadryl.

5.5.3 FOLFOX

The FOLFOX regimen is a combination of 5FU, oxaliplatin, and leucovorin. FOLFOX was initially investigated and proven to be effective in patients with metastatic colorectal cancer, and still remains a standard option for such patients. Additionally, FOLFOX has demonstrated clinical activity in a number of cancer types, including pancreatic, gastric, esophageal, biliary, small bowel, breast, and lung cancers. There have been several different iterations of the FOLFOX regimen, but the one most commonly used is modified FOLFOX-6, consisting of:

- Oxaliplatin, 85mg/m^2 IV on Day 1
- Leucovorin, 400mg/m^2 IV on Day 1
- 5FU, 400mg/m^2 IV bolus on Day 1
- 5FU, 2400mg/m^2, continuous infusion over 46 hours (by portable pump), days 1-3

Toxicities of FOLFOX are essentially those of the single agent regimens. There is no additive or synergistic increase in toxicities, except perhaps the nausea and vomiting, which is generally easily controlled with an appropriate anti-emetic regimen, and fatigue, which tends to peak on days 3-5, and can be moderate, but not severe. Myelosuppression can become significant enough as to delay therapy, which may be an issue when combined with ABT-888. Thus, for this protocol, to reduce the risk of significant myelosuppression, we will not include the 5FU bolus altogether. A similar strategy is employed routinely in clinical practice for patients with a poor performance status or significant co-morbidities.

5.6 Justification for the use of FOLFOX in Pancreatic Cancer

As described above, one standard option as first line therapy for patients with metastatic pancreatic caner is single agent gemcitabine. Gemcitabine was approved after demonstrating a significant increase in overall survival over 5FU(19). However, in the last twelve years, dozens of clinical trials have been performed, attempting to improve efficacy over single agent gemcitabine. Remarkably, no clinically meaningful improvements have been obtained with regards to overall survival when gemcitabine was combined with a number of cytotoxic nor biological therapies (reviewed in(2)), and the overall survival consistently remains in the 6-7 month range for patients receiving first line therapy. Furthermore, the response rates for gemcitabine have been dismally low, and very consistently about 8%(2). Thus, the putative “standard” backbone of gemcitabine justifiably should be questioned and reconsidered.

The combination of 5FU and oxaliplatin (typically a FOLFOX iteration) as a therapeutic option for patients with metastatic pancreatic cancer has been promising. Numerous phase II trials have demonstrated intriguing overall survival rates in the first, and even the second line setting for patients with metastatic pancreatic cancer. For example, Ducreux, *et al*, demonstrated a response rate of 10% with an overall survival rate of 9 months in previously untreated patients with metastatic pancreatic cancer treated with 5FU + oxaliplatin(5). In another first-line trial, Ghoshn, *et al*, demonstrated a response rate of 27%, with a median overall survival of 7.5 months(6). Second line trials have demonstrated response rates of 2.5 to 23% and overall survival rates (as second line therapy) of 4 to 6 months(7, 20, 21).

Recently, the most promising data came from the results of the CONKO-003 trial. Patients who had progressed on gemcitabine were randomized to 5FU + oxaliplatin vs. 5FU alone. Patients treated with a combination of 5FU and oxaliplatin had a median overall survival of ~11 months as measured from the start of gemcitabine therapy, which is the longest seen in a Phase III trial(3). Surprisingly, a Phase III comparison of FOLFOX and gemcitabine has never been attempted.

5.7 Clinical Experience with ABT-888

A Phase 0 dose-ranging pharmacokinetic and pharmacodynamic study of ABT-888 has been completed(13). In this trial, 13 subjects with various types of advanced cancer received a single dose of single-agent ABT-888 (10 mg, n = 3; 25 mg, n = 3; 50 mg, n = 7). The pharmacokinetic results from this study demonstrated that ABT-888 is orally bioavailable and primarily cleared through renal excretion, with a half-life of 4 to 5 hours. Additionally, this study provided proof of mechanism, as tumor PARP inhibition (> 90%) was demonstrated in 5 out of 6 human tumor biopsies that were obtained 3 to 6 hours after dosing with ABT-888. No serious adverse events were reported for this study.

The efficacy of ABT-888 in combination with DNA-damaging agents (including carboplatin, irinotecan, and temozolomide) is being explored in several Phase I and Phase II clinical trials. For example, a Phase I study of ABT-888 in combination with temozolomide is near completion. ABT-888 was given at escalating doses twice a day (BID), days 1-7 and Temozolomide daily at 200mg/m^2, days 1-5 of an every 28 day cycle. Correlative studies revealed significant PARP inhibition in peripheral blood mononuclear cells at doses as low as 20mg of ABT-888 BID. No dose limiting toxicities (DLTs) were reported for the first 3 dose cohorts of ABT-888 (10 mg BID, 20 mg BID and 40 mg BID). However, at 80 mg BID, 2 of 3 subjects enrolled experienced Grade 4 thrombocytopenia or neutropenia, and at 60 mg BID, 1 of 3 subjects enrolled experienced Grade 4 thrombocytopenia or neutropenia. Thus, 20 to 40 mg of ABT-888 BID have been the starting doses of ABT-888 combined with standard doses of chemotherapy for subsequent Phase II trials. However, in other trials a much higher dose of ABT-888 has been safely used. For example, our ongoing trial of ABT-888 plus FOLFIRI (5FU and irinotecan) has increased to 160mg of ABT-888 BID as of September, 2011, with further dose escalation anticipated. The optimal dose of ABT-888 with 5FU and oxaliplatin has not been identified. For this reason, a Phase I trial will first be performed to demonstrate safety with the combination of ABT-888 and 5FUand oxaliplatin, as well as to determine the Recommended Phase II dose of the combination.

ABT-888 is being used for 7 days, as was done in the Phase I trial of ABT-888 and temozolomide, and as is currently being replicated in multiple Phase II trials of ABT-888 plus other chemotherapies. The specific rationale is based on the intention that the PARP inhibitor (ABT-888) be present in the patient for significantly longer than the time that the DNA-damaging agent is impacting cancer cell DNA. This would in theory prevent cellular DNA repair, leading to overwhelming DNA damage and presumably cancer cell death.

6.0 INDICATIONS

Metastatic pancreatic cancer

7.0 STUDY OBJECTIVES

7.1 Primary Objectives:

7.1.1 Primary Objective of Phase I Portion: To determine the Recommended Phase II Dose (RP2D) of ABT-888 combined with 5FU and oxaliplatin in patients with metastatic pancreatic cancer

7.1.2 Primary Objective of the Phase II Portion: To determine the objective response rate of ABT-888 combined with 5FU and oxaliplatin in patients with metastatic pancreatic cancer

7.2 Secondary Objectives

7.2.1 Secondary Clinical Objectives To determine, in patients with metastatic pancreatic cancer treated with ABT-888 combined with 5FU and oxaliplatin:

1) Disease control rate (CR+PR+SD at 6 months)
2) Progression free survival
3) Overall survival
4) Time to disease progression
5) Duration of disease control
6) Tolerability and safety of the combination
7) Degree of Neuropathy, as measured by the FACT/GOG-NTX-4 (Version 4)

7.2.2 Secondary Scientific Objectives To associate the response rate of ABT-888 plus 5FU and oxaliplatin to:

1) Tumors that have decreased expression of or mutations in BRCA-1 or -2 or related pathway genes
2) PARP activity levels in serial tumor samples
3) Expression levels of DNA repair enzymes in tumor tissues
4) Pharmacokinetic and pharmacogenomic parameters associated with the metabolism of ABT-888
5) To isolate and propagate tumor cell lines obtained from patient samples and circulating tumor cells

8.0 TRIAL DESIGN

8.1 Treatment Plan

This is stratified single-treatment, open-label Phase I/II study to evaluate the clinical activity of the combination of the novel inhibitor of Poly(ADP-ribose) polymerase (PARP), ABT-888 with 5FU and oxaliplatin, *without the 5FU bolus* in patients with metastatic pancreatic cancer. Patients with metastatic, unresectable pancreatic cancer and a known BRCA-associate genetic mutation OR family history suggestive of a breast or ovarian cancer syndrome (as defined below) who still have an adequate performance status and normal hepatic and renal function will be eligible. As many as 24+48 patients will be enrolled. Patients will be stratified into two groups: Untreated or previously treated:

- Untreated patients should have received zero prior therapies for metastatic disease.
  i. They may have received prior adjuvant chemotherapy and/or radiation therapy, but not within 6 months prior to treatment.
  ii. They may have received prior *palliative* radiation therapy for unresectable disease, but without any systemic chemotherapy, even as a radiosensitizer
- Previously treated patients may have received any number of prior therapies, including prior adjuvant chemotherapy and/or radiation therapy within 6 months of treatment.

Cohort	ABT-888 (mg)
-1	20
1	40
2	60
3	80
4	100
5	150
6	200
7	250
8	300

The dose of ABT-888 will be determined by a Phase I dose escalation study. As detailed above, ABT-888 has been safely combined with traditional cytotoxic chemotherapy in previous clinical trials, though it has not been combined with 5FU and oxaliplatin. Therefore a traditional 3+3 dose escalation approach with doses of ABT-888 ranging from 40mg to 300mg twice-a-day will be employed to determine the RP2D of ABT-888 to be used with 5FU and oxaliplatin. Once the RP2D has been determined, all remaining patients will be enrolled in the Phase II portion of the study.

The starting dose of ABT-888 will be 40mg orally twice daily on days 1-7. Patients will be enrolled in a standard 3+3 dose escalating fashion to a maximal dose of ABT-888 of 300mg twice a day (Table 1). The *starting doses* of 5FU and oxaliplatin will not be adjusted, except that the 5FU bolus will be dropped. Patients will be enrolled in cohorts of three patients.

Table 1: Phase I Treatment Cohorts

However, given the concern over possible additive toxicity with the combination of ABT-888 and 5FU and oxaliplatin, the first patient for each dose level must have completed at least one full cycle, without any dose limiting toxicities before the last two patients in each cohort may be enrolled.

If there are no dose limiting toxicities (DLTs) in the first cohort, then three patients will be enrolled in the next cohort, as detailed in Table 1. Within any cohort, if one patient experiences a DLT, then the cohort will be expanded to 6 patients. If no additional patients experience a DLT, then three patients will be enrolled in the next cohort. If 2/6 or greater of the patients experiences a DLT, then the dose level below will be considered the MTD, and will be employed as the RP2D. The RP2D will be used for the Phase II portion of the study.

A dose de-escalation contingency has also been included (Table 1). If 2/6 or greater of the patients at Dose level 1 experiences a DLT, then patients will be enrolled at dose level -1. If 2/6 or greater of the patients at Dose level -1 experiences a DLT, then the trial will be terminated.

One cycle will be 14 days. Patients will receive 5FU and oxaliplatin without the 5FU bolus (oxaliplatin (85mg/m^2) and leucovorin (400mg/m^2) on day 1, followed by a continuous infusion of 5FU (2400mg/m^2) over 46 hours on days 1-3). Patients will also receive ABT-888 twice-a-day on Days 1-7 of each 14-day cycle (Figure 1, above). The doses of 5FU, oxaliplatin, and leucovorin will be determined using the body surface area (BSA) calculated from the height obtained at the baseline evaluation and the weight obtained prior to each cycle. Subjects will self-administer the morning dose of ABT-888, and then the evening dose of ABT-888 will be taken approximately 12 hours after the morning dose.

As of April, 2013 (updated in Version 8.0, 04-15-2013), the recommended Phase II dose has been chosen to be 200mg of ABT-888 twice a day.

Study activities are presented in Table 3, and an early study activities checklist through cycle 2 is detailed in Table 4. Screening will occur within 14 days, prior to administration of the first dose of ABT-888 on Day 1 (baseline imaging scans must be done within 28 days of Day 1). All patients with biopsy-able tumor deposits will undergo the pre-treatment tumor biopsy prior to cycle 1, Day 1. During cycles 1 and 2, subject assessments (physical examinations including neurologic assessment, vital signs, performance status, medication review, chemistry, hematology and adverse event evaluations) will be conducted on Day 1 of each cycle. Beginning at cycle 3, patients will be seen on Day 1 of every other cycle (*i.e.* C3, D1; C5, D1; C7, D1, etc). Study procedures may be performed 2 days before or after the scheduled visit date, due to unforeseen or unavoidable circumstances. The neuropathy quality of Life assessment will occur during treatment for each odd-numbered treatment. Restaging studies will be performed every 4 cycles (or not more than every 12 weeks if there have been treatment delays). . Patients who are adequately tolerating therapy, and whose restaging studies reveal no evidence of disease progression, by RECIST 1.1 criteria, will continue on study for an additional 4 cycles.

The primary endpoint of the Phase I portion is the determination of the recommended Phase II dose. The primary endpoint of the Phase II portion will be the objective response rate (ORR), as determined by RECIST 1.1 criteria. Secondary clinical endpoints are determination of the disease control rate (DCR, defined as ORR + rate of stable disease at 6 months), progression free survival (PFS), overall survival (OS), time to disease progression (TTP), duration of disease control (DDC), tolerability and safety of the combination, and degree of neuropathy, as measured by the FACT/GOG-NTX-4 (Version 4). Patients whose tumors have not progressed at the time of restaging, as determined by RECIST 1.1 criteria, and who continue to tolerate treatment will continue treatment for an additional eight weeks. When an investigator has determined that a subject should discontinue the study, a Final Visit will be conducted. Information pertaining to survival and post treatment therapy will be collected approximately every 12 weeks (Month 3, 6, 9, 12, 15 and 18) beginning after the final visit, for a period up to 24 months. Tumor biopsy procedures for the pilot subgroup are discussed in detail in section 12.

8.2 Selection of Study Population

This is a multi-institutional study for patients with metastatic pancreatic cancer. Only patients with metastatic pancreatic cancer not amenable for resection will be considered for entry. Subjects must have measurable disease, defined as at least 1 unidimensionally measurable lesion on a CT scan as defined by RECIST.

The target recruitment for this study is 24+48 patients. At the LCCC alone, approximately 150 new cases of pancreatic cancer are seen yearly, at least one-third of which have metastatic disease. Because patients with both untreated (for metastatic disease) and pretreated cancers are eligible, most patients seen in the medical oncology clinic with metastatic disease will be eligible for this trial. As of April 2013, the enrollment criteria were modified to include only patients with a known BRCA-associate genetic mutation OR family history suggestive of a breast or ovarian cancer syndrome (as defined below), which is likely to delay enrollment. However, concurrently, the trial is opening at several centers, which may compensate for the

slower accrual. Therefore, recruitment is anticipated to take 24 – 30 months, and with each patient followed for a minimum of 8 weeks, the anticipated time to complete follow-up of all patients will be 30 – 36 months.

Subjects will undergo screening procedures within 14 days prior to administration of the first dose of ABT-888 on Day 1, unless otherwise specified (though baseline imaging scans must be done within 28 days of Day 1). Adult male and female subjects who meet all the inclusion criteria and who do not meet any of the exclusion criteria will be eligible for enrollment into the study.

8.2.1 Inclusion Criteria

1) Histologically proven pancreatic adenocarcinoma with measurable disease, defined as at least 1 unidimensionally measurable lesion on imaging as defined by RECIST 1.1 criteria.
2) A known BRCA-associate genetic mutation OR family history suggesting of a breast or ovarian cancer syndrome, as defined by one or more of the following:
   - Personal or known family history of a deleterious (or indeterminate) mutation in the *BRCA1*, *BRCA2*, *PALBB2*, or one of the *FANC* genes.
   - Personal history of breast cancer and one or more of the following:
     - Diagnosed ≤ 45 years old
     - Diagnosed at any age with ≥1 1st, 2nd, or 3rd degree relative with breast cancer ≤ 50 years old and/or ≥1st, 2nd, or 3rd relative with epithelial ovarian cancer at any age
     - Two primary breast cancer with the first diagnosed at ≤ 50 years old
     - Diagnosed ≤ 60 years old with triple negative breast cancer
     - Diagnosed at any age with ≥2 1st, 2nd, or 3rd degree relatives with breast cancer at any age
     - Diagnosed at any age with ≥2 1st, 2nd, or 3rd degree relatives with pancreatic cancer or aggressive prostate cancer (Gleason score ≥7) at any age
     - 1st, 2nd, or 3rd degree male relative with breast cancer
     - Ashkenazi Jewish descent
   - Personal history of epithelial ovarian cancer
   - Personal history of male breast cancer
   - Personal history of pancreatic cancer and ≥2 1st, 2nd, or 3rd degree relatives with breast, epitherlial ovarian, pancreatic, or aggressive prostate cancer (Gleason score ≥7) at any age
3) Age >= 18 years
4) ECOG performance status 0-2 (See Table 2, Below)
5) Subjects with no brain metastases or a history of previously treated brain metastases who:
   - Have been treated by surgery or stereotactic radiosurgery (SRS) at least 4 weeks prior to enrollment
   - AND have a baseline MRI that shows no evidence of active intercranial disease
   - AND have not had treatment with steroids *for brain metastases* within 1 week of study enrollment
6) Prior therapies:
   a. For patients stratified to the untreated arm:
      i. Untreated patients should have received zero prior therapies for metastatic disease.
      ii. They may have received prior adjuvant chemotherapy and/or radiation therapy, but not within 6 months prior to treatment.
      iii. They may have received prior *palliative* radiation therapy for unresectable disease, but without any systemic chemotherapy, even as a radiosensitizer
   b. For patients in the previously treated arm:
      i. Previously treated patients may have received any number of prior therapies
      ii. Patients who received prior adjuvant chemotherapy and/or radiation therapy within 6 months of treatment will be considered previously treated
         - Patients may have received any prior therapies **EXCEPT prior therapy with a PARP inhibitor**
      iii. Timing of prior therapies:
         - At least 14 days must have passed since all prior anti-cancer therapy, including chemotherapy, biological therapy, or radiation therapy
         - However, at least 28 days must have passed since any prior antibody-based therapies (such as, but not limited to cetuximab or bevacizumab)
         - Additionally, at least 28 days must have passed since any prior investigational agent.

- All patients must have completely recovered from all transient side effects related to prior therapies
    a. However, any side effects that are expected to be more durable or even permanent (*e.g.,* neurotoxicity or ototoxicity) must have resolved to at least grade 1.

7) Adequate hepatic, bone marrow, and renal function:
    a. Bone Marrow: Absolute neutrophil count (ANC) ≥ 1,500/mm^3; Platelets ≥ 75,000/mm^3; Hemoglobin ≥ 9.5 g/dL
    b. Renal function: Serum creatinine ≤ 1.5 × upper normal limit of institution's normal range **OR** creatinine clearance ≥ 50 mL/min/1.73 m^2 for subjects with creatinine levels above institutional normal
    c. Hepatic function: AST or ALT ≤ 3 X the upper normal limit of institution's normal range; bilirubin ≤ 2.5 X the upper normal limit of institution's normal range.
        i. 5FU and oxaliplatin are known to be safe to be administered in patients with such abnormal liver function tests
        ii. ABT-888 is primarily excreted in the urine, and is not even metabolized by the liver. Thus such degree of hepatic impairment is not expected to affect the dosing of ABT-888.
8) Partial Thromboplastin Time (PTT) must be ≤ 2 X upper normal limit of institution's normal range and INR (International Normalized Ratio) < 2. Subjects on anticoagulant (such as coumadin) must have a PTT ≤ 5 X upper normal limit of institution's normal range and INR (International Normalized Ratio) < 5.
9) Subject's with significant fluid retention, including ascites or pleural effusion, may be allowed at the discretion of the PI.
10) Life expectancy > 12 weeks.
11) Women of childbearing potential must have a negative serum pregnancy test within 14 days prior to initiation of treatment and/or postmenopausal women must be amenorrheic for at least 12 months to be considered of non-childbearing potential.
12) Men and women enrolled in the protocol must agree to use adequate contraceptive measure when the female (patient, or partner of the male patient) has childbearing potential (the woman is not post-menopausal and has an intact uterus).
13) Subject is capable of understanding and complying with parameters as outlined in the protocol and able to sign and date the informed consent, approved by the Institutional Review Board (IRB), prior to the initiation of any screening or study-specific procedures.
14) Patients must have fully recovered from all effects of surgery. Patients must have had at least two weeks after minor surgery and four weeks after major surgery before starting therapy. Minor procedures requiring “Twilight” sedation such as endoscopies or mediport placement may only require a 24 hour waiting period, but this must be discussed with an investigator.

Table 2: ECOG Performance Status

8.2.2 Exclusion Criteria

1) CNS metastases which do not meet the criteria outlined in the inclusion criteria.
2) Clinically significant peripheral neuropathy at the time of randomization (defined in the NCI Common Terminology Criteria for Adverse Events Version 4.0 [CTCAE v4.0] as grade 2 or greater neurosensory or neuromotor toxicity).
3) Active severe infection, or known chronic infection with HIV, hepatitis B virus
    a. Patients with chronic Hepatitis C virus *may* be enrolled if there is no clinical/laboratory evidence of cirrhosis AND the patient's liver function tests fall within the parameters set in Section 8.2.1, Inclusion Criteria number 6c, "Hepatic Function."
4) Cardiovascular disease problems including unstable angina, therapy for life-threatening ventricular arrhythmia, or myocardial infarction, stroke, or congestive heart failure within the last 6 months
5) Life-threatening visceral disease or other severe concurrent disease
6) Women who are pregnant or breastfeeding
7) Anticipated patient survival under 3 months
8) Regarding prior malignancies:
    a. Patients with a second active malignancy being actively treated at the time of screening with palliative or curative intent with cytotoxic chemotherapy, surgery, or radiation are ineligible
    b. Patients with **Stage III or Stage IV** cancers of any type who have completed cytotoxic chemotherapy, surgery, or radiation in the adjuvant setting within 3 years of screening are ineligible.
        i. For these patients, if more than three years have passed from the completion of adjuvant therapy to screening for the current protocol, then the patient **is eligible** for enrollment.
    c. However, patients with **Stage I or Stage II** cancers of any type, and who have **completed** cytotoxic chemotherapy, surgery, or radiation in the adjuvant setting by the time they are screening for the current protocol **are eligible** for enrollment.
    d. Patients who are being treated with adjuvant hormonal therapies, such as anti-estrogens or anti androgens and meet criteria 8.b.1 or 8.c above, **are eligible** for enrollment provided they stop the hormonal therapy prior to starting the study medications.
    e. Finally, patients with cervical cancer in situ, in situ carcinoma of the bladder, or non-melanoma carcinoma of the skin that have been removed, **are eligible** for enrollment at any time.

    Questions regarding the inclusion of individual subjects should be directed to the Principle Investigator.
9) Clinically significant and uncontrolled major medical condition(s) including but not limited to:
    a. Active uncontrolled infection
    b. Symptomatic congestive heart failure
    c. Unstable angina pectoris or cardiac arrhythmia
    d. Psychiatric illness/social situation that would limit compliance with study requirements.
    e. Any medical condition, which in the opinion of the study investigator places the subject at an unacceptably high risk for toxicities.

8.2.3 Prior and Concomitant Therapy

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins and/or herbal supplements) that the subject is receiving at Screening up to the Final Visit must be recorded in source documents and the case report forms (CRFs). The reason for use, date(s) of administration (including start and end dates), and dosage information (including dose and frequency) must be recorded. Any change in concomitant therapy during the study period must be similarly recorded. Questions regarding prior or concomitant therapy should be directed to one of the investigators.

8.2.3.1 Prior Anti-cancer Therapy

For purposes of this protocol, anti-tumor treatment may be defined as, but is not limited to, anti-cancer agents (cytotoxic chemotherapy, immunotherapy, or biologic therapy), radiotherapy and investigational agents. An investigational agent is any drug or therapy not currently approved for use in humans.

8.2.3.2 Prior Surgery

Patients must have fully recovered from all effects of surgery. Patients must have had at least two weeks after minor surgery and four weeks after major surgery before starting therapy. Minor procedures requiring "Twilight" sedation such as endoscopies or mediport placement may only require a 24 hour waiting period, but this must be discussed with an investigator.

8.2.3.3 Supportive Care

Subjects should receive best supportive care and treatment of symptoms during the study as appropriate, including transfusion of blood and blood products, oxygen therapy, nutritional support, intravenous fluids, and treatment with appropriate medications (antibiotics, antiemetics, antidiarrheals, and analgesics, etc.). Medications, including steroids, which are given for supportive care, such as appetite stimulation, may be given concurrently.

8.3 Efficacy and Safety Assessments/Variables

8.3.1 Efficacy and Safety Measurements Assessed and Flow Chart

Study procedures for safety and exploratory efficacy assessments will be performed as summarized in Table 3, and a checklist of study activities through cycle 2 is detailed in Table 4.

Table 3: Study Activities

	Screening	Cycle 1 and Cycle 2, Day 1[aaa]	Day 3 of Each Cycle	Day 1 of every odd numbered cycle (Beginning cycle 3)	Day 1 of every even numbered cycle (Beginning cycle 4)	After every 4 cycles	Off Study	Final Follow-up Visit	Every 3 months
Informed consent	X								
Demographics	X								
Medical history	X								
Concurrent meds	X	X		X			X	X	
β-HCG	X[bbb]	X[bbb]							
Dispense Medications		X		X	X				
Disconnect 5-FU			X						
Physical exam	X	X		X			X	X	
Vital signs	X	X	X	X	X		X	X	
Height	X								
Weight	X	X		X	X		X	X	
Performance Status	X	X		X			X	X	
CBC w/diff	X	X		X	X		X	X	
Serum chemistry[ccc]	X	X		X	X		X	X	
PT/PTT/INR	X								
Adverse event evaluation	X	X		X			X	X	
Neuropathy QOL Assessment	X			X					
PK Sampling	*See Table 5 for Details*								
Radiologic evaluation and Tumor Measurments	X[ddd]					X[fff]	X[ggg]		
Tumor Biopsy	X						X		
Research Serum Sample	X					X	X		
Progression and Survival						X		X	X

[aaa]For the phase I portion, if any patient has been escalated from one dose cohort to another (up or down) then that particular patient will be on Day 1 of the first two cycles of the new dose level as well.

[bbb]Urine or Serum pregnancy test (women of childbearing potential) at screening and Cycle 1, Day 1 ONLY

[ccc]Albumin, alkaline phos, total bili, bicarbonate, BUN, calcium, chloride, creatinine, glucose, potassium, total protein, AST, ALT, sodium.

[ddd]Screening scans should have been within 4 weeks of starting treatment.

[eee]Optional serial samples

[fff]But not more than every 12 weeks, if there have been treatment delays

[ggg]If not done within the previous 4 weeks

Table 4: Early Study Activities Checklist

Screening/Pre-Treatment

Subject Assessment	_____
Eligibility Criteria	_____
Informed Consent	_____
Pregnancy Test (if appropriate)	_____
Radiology within 4 weeks	_____
Blood for research	_____
PT/PTT/INR	_____
Tumor biopsy	_____

Cycle 1, Day 1

Subject Assessment	_____
Pregnancy Test (if appropriate)	_____
5FU, oxaliplatin, and ABT-888 Dosing	_____
ABT-888 Pharmacogenomics	_____
ABT-888 PKs (0, .5, 1, 2, 4, and 6 hours)	_____

Cycle 1, Day 3

Vital Signs	_____
5-Fluorouracil disconnect	_____
ABT-888 PKs (0, .5, 1, 2, 4, and 6 hours)	_____

Cycle 2, Day 1

Subject Assessment	_____
5FU, oxaliplatin, and ABT-888 Dosing	_____

Cycle 2, Day 3

Vital Signs	_____
5-Fluorouracil disconnect	_____

8.3.2 Study Procedures

Screening will occur within 14 days prior to administration of the first dose of ABT-888 on Day 1. For procedures performed at Screening and repeated, the later procedure performed prior to dosing, will serve as a baseline for clinical assessment.

For patients being considered for enrollment outside of Georgetown-Lombardi, all primary source documentation should be sent to the multi-institutional coordinator and the study PI, Dr. Pishvaian for review and approval. Patients must be approved for accrual prior to starting study medications. Faxed records should be sent to 202-687-3821, with an email to the multi-institutional coordinator and Dr. Pishvaian to confirm receipt of those records.

8.3.2.1 Informed Consent

Signed informed consent will be obtained from the subject or the subject's legally acceptable representative before any study-specific procedures are undertaken. A separate informed consent will be required for the Tumor Biopsy Tissue Collection.

8.3.2.2 Physical Examination

A complete physical examination, including neurologic assessment will be performed at the Screening Visit, on C1 and C2 D1, and then on Day 1 of every odd numbered cycle and at the Final Visit. Any significant physical examination findings after the administration of the first dose of ABT-888 will be recorded as adverse events. Body weight will be recorded during every physical exam. The subject will wear lightweight clothing and no shoes during weighing. Height will be measured at the Screening Visit only; the subject will not wear shoes.

8.3.2.3 Medical History

The following information will be collected during the Screening Visit:

1) Complete medical history, including documentation of any clinically significant medical condition
2) History of tobacco and alcohol use
3) Presence and severity of any symptoms/conditions associated with metastatic pancreatic cancer
4) Detailed oncology history, including:
    a. Date of primary cancer diagnosis
    b. Pathology (histology or cytology) of primary tumor
    c. Metastasis information (including the location)
    d. Surgical history
    e. Anti-cancer and radiation treatments administered (including dates and type of modality)
5) At each visit, the subject's medical history will be reviewed and any changes from baseline will be recorded on the adverse event CRF. On C1D1 any changes observed from the screening assessments, prior to dosing, will be recorded in the subject's medical history. All medication (prescription or over-the-counter, including vitamins and/or herbal supplements) will be recorded beginning with the Screening Visit and continuing up through the date of the Final Visit.

8.3.2.4 Vital Signs

Vital sign determinations of heart rate, blood pressure and body temperature will be obtained at the Screening Visit, on C1 D1, C1 D3, and on Day 1 and 3 of subsequent cycles and at the Final Visit. If possible, blood pressure and heart rate measurements should not immediately follow scheduled blood collections.

Please note: patients do not need to return to the study institution for 5FU pump disconnect. The disconnect can be provided at their primary (local) oncologist's office OR by a qualified home nursing agency. In this case, the nurse performing the disconnect must document the time of disconnect, and the estimated volume of 5FU remaining (if any). A record of this documentation will be filed in the patient's study chart. The patient is responsible for returning the 5FU pump.

8.3.2.5 Pregnancy Test

For female subjects of childbearing potential, a serum pregnancy test will be performed at the Screening Visit within 14 days of C1D1 and a urine pregnancy test will be done at the C1D1 visit prior to the first dose of study drug. Subjects considered not of childbearing potential must be documented as being surgically sterile or post-menopausal (for at least 1 year). The test results must be reviewed and determined to be negative prior to dosing. If the urine pregnancy test is positive at C1D1, it should be confirmed by a serum pregnancy test. The

test may be repeated at the discretion of the investigator at any time during the study. Should a female study subject become pregnant or suspect she is pregnant while participating in this study, she should inform the treating Investigator immediately.

8.3.2.6 Clinical Laboratory Tests

All subjects will undergo the laboratory assessments outlined in Table 3.

1) Hematology and chemistry samples will be collected at the Screening Visit, and on Day 1 of each cycle and at the Final Visit. For Day 1 of each cycle after Cycle 2, hematology and chemistry samples may be collected up to 48 hours prior to the scheduled visit.
2) PT/INR and PTT will be collected at Screening.

Laboratory samples for this study will be assessed using the certified laboratories at investigators' institutions, or at a clinical laboratory such as Quest or LabCorp. The PI or sub-investigator will review, initial and date all laboratory results. Any laboratory value outside the reference range that is considered clinically significant by the investigator will be followed as appropriate. Clinically significant laboratory values will be recorded as adverse events if they meet the criteria as specified in Section 9.

8.3.2.7 Pharmacokinetic and Pharmacogenomic Analysis of ABT-888

Pharmacokinetic assessment of ABT-888 in patient plasma for the patients in the Phase I portion of the study will be performed and compared to historical controls, to identify any effect on ABT-888 PKs by oxaliplatin or 5-fluorouracil. Pharmacogenomic analyses of the variation of enzymes involved in the metabolism of ABT-888 will be performed for all patients in the study.

Of note, the Phase I portion of the study will be performed only at Georgetown University. Thus, there is no plan for PK samples to be shipped from institutions outside of Georgetown University.

8.3.2.7.1 Collection of Samples for Analysis

For pharmacogenomic analysis, on C1, D1, 3 mL of blood will be collected by any standard phlebotomy technique from a venous access point into one 3 mL potassium EDTA (purple cap) tube, and processed as below. For the PK analysis, approximately 3 mL of blood will be collected by any standard phlebotomy technique from a venous access point into one 3 mL potassium EDTA (purple cap) tube for ABT-888 concentrations on C1D1, C1D3, and C1D7 at the following times relative to the morning dose: 0 (predose), 0.5, 1, 2, 4 and 6 hours (See Table 5).

Table 5: Pharmacokinetic Sampling Schedule

	Hours after Dose of ABT-888
Day 1	0 (predose), 0.5, 1, 2, 4 and 6
Day 3	0 (predose), 0.5, 1, 2, 4 and 6
Day 7	0 (predose), 0.5, 1, 2, 4 and 6

8.3.2.7.2 Processing of Blood Samples for ABT-888 Pharmacokinetic and Pharmacogenomic Analyses

Samples will be collected via venipuncture (if an indwelling catheter must be used, 3 catheter volumes of blood must be collected and discarded prior to collection of the sample) into evacuated potassium EDTA-containing collection tubes. Sufficient blood (approximately 3mL each) will be collected to produce approximately 1.5 mL of plasma for each sample. Immediately after collection, the tubes will be inverted 8 to 10 times to ensure good mixing of blood and anticoagulant and placed in an ice bath. The drug lot number, protocol number, the subject number, the study period and/or study day, and the planned time of sampling relative to dosing and date and time of collection for each sample will be recorded. The complete process of centrifugation, transfer to polypropylene tubes and freezing should be accomplished within 60 minutes from blood draw. The processing of PK samples should be performed as described below:

1. Immediately invert the collection tubes 8 to 10 times.
2. Centrifuge sample at 1100 to 1300 × g for 10 minutes at 2° to 8°C to separate the plasma.
3. Transfer plasma using plastic pipettes into screw-capped polypropylene tubes labeled with the protocol number, the patient number, date and time of collection relative to dosing.
4. Store samples at –20°C or colder until shipped.
5. Samples may be batched and shipped monthly.

8.3.2.7.3 Disposition of Samples for ABT-888 Pharmacokinetic Analysis
The frozen plasma samples for ABT-888 will be packed in dry ice sufficient to last during transport for 3 days and shipped from the study site to Abbott according to instructions from Abbott. An inventory of the samples included will accompany the package. Arrangements will be made with Abbott for the shipment of samples to:
Sample Receiving
Dept. R46W, Bldg. AP13A, Room 2310
Abbott Laboratories
100 Abbott Park Road
Abbott Park, IL 60064
Phone: (847) 937-0889
Fax: (847) 938-9898

8.3.2.7.4 Measurement Methods
Plasma concentrations of ABT-888 will be determined under the supervision of the Drug Analysis Department at Abbott. Additionally, ABT-888 metabolite(s) concentrations in plasma samples may be determined.

8.3.2.8 Neuropathy Quality of Life Assessment
Patients will fill out a brief neuropathy quality of life assessment, included in Appendix 1. The assessment will be completed by the patient prior to starting therapy, and after initiating every odd numbered cycle of treatment (starting with Cycle 3).

8.4 Multi-Institution Study Coordination

8.4.1 Personnel

At each site, personnel dedicated to this protocol will be:

- A study PI
- A research coordinator
- A data manager

In addition, at Lombardi-Georgetown, there will be a dedicated "multi-institutional" research coordinator who will play the primary role in coordinating the trial between Lombardi-Georgetown and additional sites. This coordinator will be the main point of contact for Dr. Pishvaian and the other site PIs for any study related concerns, and to screen each patient being considered for enrollment (Including "remote" screening for the patients being screened at other sites). This coordinator will also be the point of contact for the data managers for data entry questions. Finally, this coordinator will play a major role in regulatory coordination of the study, specifically by: 1) Reviewing and confirming all study-related adverse events; 2) Submitting all SAE reports to the Georgetown IRB (The research coordinators at the other sites will prepare SAE reports for patients treated at their respective sites, but the "multi-institutional" coordinator will submit the final report); 3) Gathering and preparing all primary source data for review/audit by Theradex, Inc.

8.4.2. Patient Enrollment

Enrollment at the sites will be competitive. If a patient is being screened for enrollment, the local research coordinator must send an email within 24 hours containing the patient's name, to the local PI, to Dr. Pishvaian, and to the multi-institutional coordinator. If a patient is successfully screened, the local research coordinator must send all supporting documentation to the multi-institutional research coordinator (by email or fax). Patients should not start therapy until both Dr. Pishvaian and the multi-institutional coordinator have reviewed the patient's records and confirmed that the patient is indeed eligible for enrollment.

8.4.3. Data Collection and Management

Patient data will be entered into the on-line accessible database. This database is housed at Lombardi-Georgetown, but is accessible anywhere there is internet access. The data manager and research coordinator at each site will attend an on-line training session so that they may learn how to enroll data into the data base. All screening data should be entered prior to starting therapy, and all ongoing patient data should be entered within one week of each patient visit.

8.4.4 Conference Calls
A monthly conference call will be held between Lombardi-Georgetown and the other sites to review patient enrollment, toxicity, and response assessment.

8.4.5. Trial Auditing
Theradex, Inc will provide trial auditing at Lombardi-Georgetown. The multi-institutional coordinator will arrange all primary source documents for the patients to be audited. This will include collecting copies of the primary source data for any patients treated at other sites.

8.5 Removal of Subjects from Therapy or Assessment
Each subject has the right to withdraw from study treatment at any time. In addition, the investigator may discontinue a subject from the study treatment at any time for any reason if the investigator considers it necessary, including the occurrence of an adverse event or noncompliance with the protocol. Each subject will be withdrawn from the study if any of the following occur:

1) The subject experiences either clinical or radiographic progressive disease.
2) The subject requires radiotherapy or alternate antineoplastic agents during the study period.
3) The investigator believes it is in the best interest of the subject.
4) Clinically significant deterioration of the subject's medical status as determined by the investigator.
5) The subject requires alternative anti-cancer agents or non-palliative radiation therapy for primary or metastatic disease during the treatment portion of the study.
6) Subject becomes pregnant or begins breastfeeding during the treatment portion of the study.
7) The subject or subject's legally acceptable representative decides to withdraw consent for any reason.
8) Any other medical reason that the study investigator deems appropriate.

8.5.1 Discontinuation of Individual Subjects
When a subject discontinuation from the study (without reaching a protocol-defined endpoint) is planned, the investigator will notify the clinical team representative via telephone as soon as possible (provided, in each case, subject care and safety are not compromised). When a subject discontinues the study, a Final Visit will be conducted (preferably prior to the initiation of another anticancer therapy). However, these procedures should not interfere with the initiation of any new treatments or therapeutic modalities that the investigator feels are necessary to treat the subject's condition. Following discontinuation of the study drug, the subject will be treated in accordance with the investigator's best clinical judgment. At the Final Visit, the reason(s) for the discontinuation from the study will be recorded and a physical examination including neurologic assessment, body weight, vital signs measurement, laboratory analyses, performance status, tumor assessment, collection of unused study drug and an assessment of adverse events will be performed as soon as possible after discontinuation from the study. All subjects will have one Follow-Up Visit approximately 30 days after the Final Visit. This Follow-Up Visit does not need to be performed for subjects who have had a Final Visit conducted ≥ 30 days after discontinuation of ABT-888. If a subject is discontinued from the study with an ongoing adverse event or an unresolved clinically significant laboratory result, the site will attempt to provide follow up until a satisfactory clinical resolution of the laboratory result or adverse event is achieved. In the event that a positive result is obtained on a pregnancy test for a subject during the study, the administration of study drug to that subject must be discontinued immediately.

8.5.2 Discontinuation of Entire Study
The investigators may terminate this study provided that written notice is submitted at a reasonable time in advance of the intended termination. The following procedures for discontinuation will be followed:

1) If the investigators have decided to prematurely discontinue the study, the investigators will promptly notify in writing the IRB of the decision and give detailed reasons for the discontinuation.
2) The principal investigator must promptly notify the enrolled subjects of the premature discontinuation and administer appropriate treatments such as replacement of protocol therapy, if applicable, by other appropriate regimens.

9.0 SAFETY VARIABLES

The Principle Investigator or Sub-investigators will assess adverse events, laboratory data and vital signs throughout the study. Adverse events will be assessed by NCI CTCAE Version 4.0.
http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/ctcaev4.pdf

9.1 Adverse Events

The investigator will monitor each subject for clinical and laboratory evidence of adverse events on a routine basis throughout the study. The investigator will assess and record any adverse event in detail including the date of onset, event diagnosis (if known) or sign/symptom, severity, time course, duration and outcome, relationship of the adverse event to study drug, and any action(s) taken. For serious adverse events not considered "probably related" to study drug, the investigator will provide an "Other" cause of the event. For adverse events to be considered intermittent, the events must be of similar nature and severity. Adverse events, whether in response to a query, observed by site personnel, or reported spontaneously by the subject will be recorded. All adverse events will be followed to a satisfactory conclusion.

9.2 Data Safety Monitoring Board

The Georgetown Lombardi Comprehensive Cancer Center will be responsible for the data and safety monitoring of this multi-site trial. As this study is an investigator initiated study Phase I/II study utilizing a non-FDA approved drug for which the PI holds the IND it is considered a high risk study which requires real-time monitoring by the PI and study team and quarterly reviews by the LCCC Data and Safety Monitoring Committee (DSMC).

The Principal Investigator and the Co-Investigators will review the data including safety monitoring at their weekly institution based disease group meetings and on monthly teleconferences with participating sites.

All Severe Adverse Events (SAEs) are required to be reported to the IRB. Based on SAEs, the IRB retains the authority to suspend further accrual pending more detailed reporting and/or modifications to further reduce risk and maximize the safety of participating patients.

Progress on the trial and the toxicities experienced will be reviewed by the LCCC Data and Safety Monitoring Committee every 3 months from the time the first patient is enrolled on the study. Results of the DSMC meetings will be forwarded to the IRB with recommendations regarding need for study closure. .

DSMC recommendations should be based not only on results for the trial being monitored as well as on data available to the DSMC from other studies. It is the responsibility of the PI to ensure that the DSMC is kept apprised of non-confidential results from related studies that become available. It is the responsibility of the DSMC to determine the extent to which this information is relevant to its decisions related to the specific trial being monitored.

A written copy of the DSMC recommendations will be given to the trial PI and the IRB. If the DSMC recommends a study change for patient safety or efficacy reasons the trial PI must act to implement the change as expeditiously as possible. In the unlikely event that the trial PI does not concur with the DSMC recommendations, then the LCCC Associate Director of Clinical Research must be informed of the reason for the disagreement. The trial PI, DSMC Chair, and the LCCC AD for Clinical Research will be responsible for reaching a mutually acceptable decision about the study and providing details of that decision to the IRB. Confidentiality must be preserved during these discussions. However, in some cases, relevant data may be shared with other selected trial investigators and staff to seek advice to assist in reaching a mutually acceptable decision.

If a recommendation is made to change a trial for reasons other than patient safety or efficacy the DSMC will provide an adequate rationale for its decision. If the DSMC recommends that the trial be closed for any reason, the recommendation will be reviewed by the Associate Director for Clinical Research at G-LCCC. Authority to close a trial for safety reasons lies with the IRB, with the above described input from DSMC and the AD for Clinical Research.

Of note, the DSMB will also review the safety data of the patients enrolled outside of Georgetown University. The multi-institutional coordinator will be tasked with the job of collecting all primary source documentation for patients enrolled outside of Georgetown University. In addition, the data managers at each site will be entering data into the Georgetown database, so that all data will be available for the DSMB at Georgetown to review. Faxed records should be sent to 202-687-2399, with an email to the multi-institutional coordinator and Dr. Pishvaian to confirm receipt of those records.

9.3 Definitions

9.3.1 Adverse Event

An adverse event (AE) is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not the event is considered causally related to the use of the product. Such an event can result from use of the drug as stipulated in the protocol or labeling, as well as from accidental or intentional overdose, drug abuse, or drug withdrawal. Any worsening of a pre-existing condition or illness is considered an adverse event. Laboratory abnormalities and changes in vital signs are considered to be adverse events only if they result in discontinuation from the study, necessitate therapeutic medical intervention, and/or if the investigator considers them to be adverse events.

An elective surgery/procedure scheduled to occur during a study will not be considered an adverse event if the surgery/procedure is being performed for a pre-existing condition and the surgery/procedure has been pre planned prior to study entry. However, if the pre-existing condition deteriorates unexpectedly during the study (*e.g.*, surgery performed earlier than planned) then the deterioration of the condition for which the elective surgery/procedure is being done will be considered an adverse event.

9.3.2 Serious Adverse Events

If an adverse event meets any of the following criteria, it is to be reported to the DSMB as a serious adverse event (SAE) within 24 hours of the site being made aware of the serious adverse event.

1) **Death of Subject** An event that results in the death of a subject.
2) **Life-Threatening** An event that, in the opinion of the investigator, would have resulted in immediate fatality if medical intervention had not been taken. This does not include an event that would have been fatal if it had occurred in a more severe form.
3) **Hospitalization or**
4) **Prolongation of Hospitalization** An event that results in an admission to the hospital for any length of time or prolongs the subject's hospital stay. This does not include an emergency room visit or admission to an outpatient facility.
5) **Congenital Anomaly** An anomaly detected at or after birth, or any anomaly that results in fetal loss.
6) **Persistent or Significant Disability/Incapacity** An event that results in a condition that substantially interferes with the activities of daily living of a study subject. Disability is not intended to include experiences of relatively minor medical significance such as headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle).
7) **Important Medical Event Requiring Medical or Surgical Intervention to Prevent Serious Outcome** An important medical event that may not be immediately life-threatening or result in death or hospitalization, but based on medical judgment may jeopardize the subject and may require medical or surgical intervention to prevent any of the outcomes listed above (i.e., death of subject, life-threatening, hospitalization, prolongation of hospitalization, congenital anomaly, or persistent or significant disability/incapacity). Examples of such events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.
8) **Spontaneous Abortion** Miscarriage experienced by study subject.
9) **Elective Abortion** Elective abortion performed on study subject.

9.3.3 Adverse Event Severity

The study investigator will rate the severity of each adverse event according to the NCI CTCAE Version 3.0. For adverse events not captured by the NCI CTCAE Version 3.0, the following should be used:

1) **Grade 1 (Mild)** The adverse event is transient and easily tolerated by the subject.
2) **Grade 2 (Moderate)** The adverse event causes the subject discomfort and interrupts the subject's usual activities.
3) **Grade 3/4 (Severe or Life Threatening)** The adverse event causes considerable interference with the subject's usual activities and may be incapacitating or life-threatening.
4) **Grade 5 (Severe)** The adverse event resulted in death of the subject.

9.3.4 Relationship to Study Drug

The investigator will use the following definitions to assess the relationship of the adverse event to the use of study drug:

1) **Probably Related** An adverse event has a strong temporal relationship to study drug or recurs on re-challenge and an Other cause of event is unlikely or significantly less likely.
2) **Possibly Related** An adverse event has a strong temporal relationship to the study drug and an Other cause of event is equally or less likely compared to the potential relationship to study drug.
3) **Probably Not Related** An adverse event has little or no temporal relationship to the study drug and/or a more likely Other cause of event exists.
4) **Not Related** An adverse event is due to an underlying or concurrent illness or effect of another drug and is not related to the study drug (e.g., has no temporal relationship to study drug or has a much more likely Other cause of event).

If an investigator's opinion of possibly, probably not, or not related to study drug is given, an Other cause of event must be provided by the investigator for the serious adverse event.
Additionally, the investigator shall attempt to attribute any relationships to specific agents (5FU, oxaliplatin, or ABT-888) when possible.

9.3.5 Adverse Event Collection Period

All adverse events reported from the time of study drug administration until 30 days following discontinuation of study drug administration have elapsed will be collected, whether elicited or spontaneously reported by the subject. In addition, serious adverse events will be collected from the time the subject signed the study-specific informed consent.

9.3.6 Adverse Event Reporting

In the event of a serious adverse event, whether related to study drug or not, the investigator will notify the IRB within 24 hours of being made aware of the serious adverse event.

For patients enrolled outside of Georgetown University, serious adverse events will be reported, and all supporting documentation sent (faxed or emailed) to the multi-institutional coordinator and to the study PI, Dr. Pishvaian within 24 hours. Faxed records should be sent to 202-687-3821, with an email to the multi-institutional coordinator and Dr. Pishvaian to confirm receipt of those records.

In addition to compliance with all FDA reporting requirements pursuant to 21 C.F.R. § 312, the Principal Investigator shall: a. report all serious adverse events experienced by a study subject receiving an ABBVIE product within 24 hours of learning of the event regardless of the relationship of the event to the ABBVIE product. Principal Investigator shall make available to ABBVIE promptly such records as may be necessary and pertinent to investigate any such event, if specifically requested by ABBVIE; and b. copy ABBVIE on the submission to the FDA of events meeting the definition of IND safety reports at the time of submission to the Agency; and c. notify ABBVIE upon any subject receiving an ABBVIE Product whose pregnancy has resulted in a negative outcome or untoward event during the course of pregnancy or upon delivery. d. ABBVIE's contact for reporting serious adverse drug experiences, pregnancy experiences, and communication of FDA submissions of IND safety reports shall be: PPDINDPharmacovigilance@abbvie.com.

9.3.7 Pregnancy

In the event of a positive pregnancy test result, study drugs will be immediately discontinued. The investigator must report the positive pregnancy test within 1 working day of the site becoming aware of the pregnancy to the IRB. Information regarding a pregnancy occurrence in a study subject and the outcome of the pregnancy

will be collected. Pregnancy in a study subject is not considered an adverse event but does require discontinuation of the subject from the study. However, the medical outcome of an elective or a spontaneous abortion, stillbirth or congenital anomaly is considered a serious adverse event and must be reported to the IRB within 24 hours of the site becoming aware of the event. Male subjects should also notify the investigators if the subject's partner should become pregnant during the study, this should also be reported within 1 working day of site awareness.

9.3.8 Toxicity Management

For the purpose of medical management, all adverse events and laboratory abnormalities that occur during the study must be evaluated by the investigator. The table of clinical toxicity grades modified from the National Cancer Institute Common Terminology Criteria for Adverse Events, Version 4.0, available at http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/ctcaev3.pdf is to be used in the grading of adverse events and laboratory abnormalities that are reported as adverse events, each of which will be followed to satisfactory clinical resolution. A drug-related toxicity is an adverse event or laboratory value outside of the reference range that is judged by the investigator to be either "possibly related" or "probably related" to the study drug. A toxicity is deemed "clinically significant" based on the medical judgment of the investigator.

9.3.9 Protocol Deviations

The investigator should not implement any deviation from the protocol without prior review and agreement by, and in accordance with the IRB and local regulations, except when necessary to eliminate an immediate hazard to study subjects.

9.4 Treatment-Related Toxicities

9.4.1 Dose Limiting Toxicities (DLTs)

For the Phase I portion of the study, a DLT will be defined as any of the following events that are definitely, possibly or probably related to one or both agents. *Please note that these definitions apply only to patients in the Phase I portion of the study.* A DLT is defined if it has occurred in the first cycle of therapy.

9.4.1.1 Grade 4 neutropenia lasting greater than 5 days or complicated by fever or infection.

9.4.1.2 Grade 4 anemia or thrombocytopenia

9.4.1.3 Grade 3 thrombocytopenia associated with bleeding for which a transfusion is required.

9.4.1.4 Grade 3 or 4 non-hematologic toxicity not manageable with routine supportive care (e.g. over the counter anti-diarrheals for diarrhea).

- For patients with baseline elevated liver enzymes (AST, ALT, alkaline phosphatase, bilirubin) due to known intrahepatic metastases, the DLT will be defined only as a grade 4 elevation of AST, ALT, alkaline phosphatase, or bilirubin.

9.4.1.5 Any toxicity, regardless of grade, which results in withholding of therapy for greater than three weeks.

9.4.2 ABT-888 Dose Reductions in the Phase I Portion of the Study

Patients who experience a DLT may restart therapy after resolution of all adverse events back to baseline level. However, the dose of ABT-888 must be restarted at one dose level lower.

9.4.3 Dose Definitions

9.4.3.1 Maximally Tolerated Dose (MTD)

The MTD will be defined as the dose level one level below the dose level at which 2 or more patients out of 6 experiences a DLT.

9.4.3.2 Recommended Phase II Dose (RP2D)

The RP2D will be defined as the same dose level as the MTD. Alternatively, the RP2D may be lower than the MTD, based on correlative, biomarker studies, or based on concurrent study publications, at the discretion of the investigators.

9.4.3.3 Dose Reductions or Delays due to toxicities NOT defined as DLTs

9.4.3.3.1 Dose Reductions or Delays

If a subject experiences an adverse event that results in ABT-888, 5FU, and/or oxaliplatin being interrupted during a cycle, the subject will complete the planned activities of the cycle as scheduled. Study drug interruptions for events that are clearly not related to the study drug, *e.g.*, underlying cancer, planned surgical procedures or acute viral illnesses, should not necessitate a dose reduction. The timing of dose resumption should be at the discretion of the Investigator. The following are guidelines for dose reduction, delay and discontinuation of ABT-888, 5FU, and oxaliplatin, and apply only:

- *In the Phase I portion of the study, when the patient has not experienced an adverse event that would meet the definition of a DLT*
- *All patients in the Phase II portion of the study:*

1) If the treatment delay is for *toxicity*, ABT-888 should be discontinued at the same time of discontinuation of 5FU and oxaliplatin.
    a. However, several patients in the Phase II portion have done exceptionally well for prolonged periods. Thus, based on physician's discretion, the patient's may miss a dose of oxaliplatin and/or 5FU while continuing the ABT-888 as scheduled as long as the infusions are NOT being withheld during that cycle for toxicity (prior omission, for example of oxaliplatin for neuropathy is acceptable). Thus, for example, patients may be administered ABT-888 pills to be taken while on an extended vacation during a cycle, and may miss the oxaliplatin and/or 5FU infusion.
    b. Under these circumstances, patients may not miss more than one infusion every 4 cycles, and they must continue to be compliant with the ABT-888 administration.
2) For any subject who experiences Grade 3/4 toxicity which is not attributable to the underlying disease, treatment will be discontinued until the toxicity resolves to Grade 1 or lower or to baseline if Grade 2 at the time of study entry.
    a. Subjects may extend the rest period off of treatment up to 4 weeks to allow the toxicity to resolve.
    b. The dose of ABT-888 will be reduced to one dose cohort lower for subsequent cycles
        i. For patients in the Phase I portion of the study , this will be one dose cohort lower
        ii. For patients in the Phase II portion of the study, this will be one dose cohort below the RP2D
        iii. Only **<u>two</u>** dose reductions of ABT-888 are allowed. *Please note, patients who start at 40mg of ABT-888 (whether in the Phase I or Phase II portion of the study), will only be allowed **<u>one</u>** dose reduction of ABT-888, to 20mg twice daily.*
    c. The dose of 5FU and oxaliplatin will be reduced according to Table 6, below
        i. Table 6A details modifications for the Phase I portion of the trial
        ii. Table 6B details modifications for the Phase II portion of the trial, wherein the recommended Phase II dose of ABT-888 is 200mg BID
    d. Any event of seizure, regardless of grade or attribution, requires interruption of ABT-888 and reporting to the IRB regarding the decision to resume treatment.
3) If a patient has reached the lowest dose level of the study medication(s), and is benefitting clinically and/or radiographically, but continues to have toxicity(ies) that requires time to resolve, the patient may stay at the lowest dose level of therapy as long as the toxicity(ies) resolves to Grade 1 prior to each subsequent dose of therapy.
4) For any patient who remains on treatment for ≥ 1year, at the discretion of the treating physician, the patient may continue therapy with the ABT-888 alone, without the 5-fluorouracil (and without the oxaliplatin – which most likely had been previously discontinued due to neuropathy) until disease progression.

Table 6A: Dose Reductions and Delays - Phase I Only				
	Adverse Event	**First Occurrence/ First Dose Reduction**	**Second Occurrence/ Second Dose Reduction**	**Third Occurrence/Third Dose Reduction**
Hematologic Toxicity	ANC <500/mL	1. Hold all therapy and check CBC weekly until recovery to: ANC >1500/mL AND Platelets >75000/mL	1. Hold all therapy and check CBC weekly until recovery to: ANC >1500/mL AND Platelets >75000/mL	**Off Study**
	OR			
	Platelets <50000/mL	AND	AND	
	OR	2. Decrease 5-FU continuous infusion to 1800mg/m2 and decrease oxaliplatin to 65mg/m2 on Day 1 at the next cycle	2. Decrease 5-FU continuous infusion to 1200mg/m2 and decrease Oxaliplatin to 50mg/m2 on Day 1 at the next cycle	
	Any Febrile Neutropenia			
	ANC >1000/ml but <1500/mL	1. Hold all therapy and check CBC weekly until recovery to: ANC >1500/mL AND Platelets >75000/mL	1. Hold all therapy and check CBC weekly until recovery to: ANC >1500/mL AND Platelets >75000/mL	1. Hold all therapy and check CBC weekly until recovery to: ANC >1500/mL AND Platelets >75000/mL
	OR	AND	AND	AND
	Platelets >50000/ml but <75000/mL	2. Decrease oxaliplatin to 65mg/m2 on Day 1 at the next cycle	2. Decrease 5-FU continuous infusion to 1800mg/m2 and decrease oxaliplatin to 65mg/m2 on Day 1 at the next cycle	2. Decrease 5-FU continuous infusion to 1200mg/m2 and decrease Oxaliplatin to 50mg/m2 on Day 1 at the next cycle
	Any other CTC ≥ Grade 3 hematologic toxicity, (e.g. HgB <8.0g/dL)	1. Hold all therapy and check CBC weekly until recovery to: ANC >1500/mL AND Platelets >75000/mL	1. Hold all therapy and check CBC weekly until recovery to: ANC >1500/mL AND Platelets >75000/mL	1. Hold all therapy and check CBC weekly until recovery to: ANC >1500/mL AND Platelets >75000/mL
		AND	AND	AND
		2. Decrease oxaliplatin to 65mg/m2 on Day 1 at the next cycle	2. Decrease 5-FU continuous infusion to 1800mg/m2 and decrease oxaliplatin to 65mg/m2 on Day 1 at the next cycle	2. Decrease 5-FU continuous infusion to 1200mg/m2 and decrease Oxaliplatin to 50mg/m2 on Day 1 at the next cycle
Non-Hematologic Toxicity	Nausea , Vomiting, or Diarrhea CTC ≥ Grade 3, despite optimal antiemetic therapy	1. Hold all therapy until recovery to Grade 1 (or Grade 2 level, if present at baseline)	1. Hold all therapy until recovery to Grade 1 (or Grade 2 level, if present at baseline)	1. Hold all therapy until recovery to Grade 1 (or Grade 2 level, if present at baseline)
	Fatigue, constipation, anorexia, headaches CTC ≥ Grade 3	AND	AND	AND
	Stomatitis or Hand-Foot syndrome CTC ≥ Grade 3	2. Decrease 5-FU continuous infusion to 1800mg/m2 at the next cycle	2. Decrease 5-FU continuous infusion to 1800mg/m2 and decrease oxaliplatin to 65mg/m2 on Day 1 at the next cycle	2. Decrease 5-FU continuous infusion to 1200mg/m2 and decrease Oxaliplatin to 50mg/m2 on Day 1 at the next cycle
Attributable to ABT-888	Any Grade 3 or 4 toxicity which is not attributable to 5-FU, Oxaliplatin, or the underlying disease	1. Delay treatment until recovery to Grade 1 (or to baseline if above Grade 1 at baseline)	1. Delay treatment until recovery to Grade 1 (or to baseline if above Grade 1 at baseline)	**Off Study**
		AND	AND	
		2. Reduce ABT-888 Dose by 20mg BID at next cycle	2. Reduce ABT-888 Dose by an additional 20mg BID at next cycle	

Table 6B: Dose Reductions and Delays - Phase II Only				
	Adverse Event	**First Occurrence/ First Dose Reduction**	**Second Occurrence/ Second Dose Reduction**	**Third Occurrence/Third Dose Reduction**
Hematologic Toxicity	ANC <1000/mL OR Platelets <50000/mL OR Any Febrile Neutropenia	1. Hold all therapy and check CBC weekly until recovery to: ANC >=1500/mL AND Platelets >=75000/mL AND 2. Decrease 5-FU continuous infusion to 1800mg/m2 and decrease oxaliplatin to 65mg/m2 and decrease ABT-888 to 150mg BID on Day 1 at the next cycle	1. Hold all therapy and check CBC weekly until recovery to: ANC >=1500/mL AND Platelets >=75000/mL AND 2. Decrease 5-FU continuous infusion to 1200mg/m2 and decrease oxaliplatin to 50mg/m2 and decrease ABT-888 to 100mg BID on Day 1 at the next cycle	1. Hold all therapy and check CBC weekly until recovery to: ANC >=1500/mL AND Platelets >=75000/mL AND 2. Continue 5-FU continuous infusion at 1200mg/m2, oxaliplatin at 50mg/m2, and ABT-888 at 100mg BID on Day 1 at the next cycle
	ANC >=1000/ml but <1500/mL OR Platelets >=50000/ml but <75000/mL	1. Hold all therapy and check CBC weekly until recovery to: ANC >=1500/mL AND Platelets >=75000/mL 2. Decrease ABT-888 to 150mg BID on Day 1 at the next cycle	1. Hold all therapy and check CBC weekly until recovery to: ANC >=1500/mL AND Platelets >=75000/mL 2. Decrease 5-FU continuous infusion to 1800mg/m2 and decrease oxaliplatin to 65mg/m2 on Day 1 at the next cycle	1. Hold all therapy and check CBC weekly until recovery to: ANC >=1500/mL AND Platelets >=75000/mL 2. Decrease 5-FU continuous infusion to 1200mg/m2 and decrease oxaliplatin to 50mg/m2 and decrease ABT-888 to 100mg BID on Day 1 at the next cycle
	Any other CTC ≥ Grade 3 hematologic toxicity, (e.g. HgB <8.0g/dL)	1. Hold all therapy and check CBC weekly until recovery to: ANC >=1500/mL AND Platelets >=75000/mL 2. Decrease ABT-888 to 150mg BID on Day 1 at the next cycle	1. Hold all therapy and check CBC weekly until recovery to: ANC >=1500/mL AND Platelets >=75000/mL 2. Decrease 5-FU continuous infusion to 1800mg/m2 and decrease oxaliplatin to 65mg/m2 on Day 1 at the next cycle	1. Hold all therapy and check CBC weekly until recovery to: ANC >=1500/mL AND Platelets 2. Decrease 5-FU continuous infusion to 1200mg/m2 and decrease oxaliplatin to 50mg/m2 and decrease ABT-888 to 100mg BID on Day 1 at the next cycle
Non-Hematologic Toxicity	Nausea or Vomiting CTC ≥ Grade 3, despite optimal antiemetic therapy	1. Hold all therapy until recovery to Grade 1 (or Grade 2 level, if present at baseline) 2. Decrease ABT-888 to 150mg BID on Day 1 at the next cycle	1. Hold all therapy until recovery to Grade 1 (or Grade 2 level, if present at baseline) 2. Decrease ABT-888 to 100mg BID on Day 1 at the next cycle	1. Hold all therapy until recovery to Grade 1 (or Grade 2 level, if present at baseline) 2. Decrease 5-FU continuous infusion to 1800mg/m2 on Day 1 at the next cycle
	Fatigue, constipation, anorexia, headaches CTC ≥ Grade 3 Stomatitis or Hand-Foot syndrome CTC ≥ Grade 3	1. Hold all therapy until recovery to Grade 1 (or Grade 2 level, if present at baseline) AND	1. Hold all therapy until recovery to Grade 1 (or Grade 2 level, if present at baseline) AND	1. Hold all therapy until recovery to Grade 1 (or Grade 2 level, if present at baseline) AND
	Any other AE CTC ≥ Grade 3	2. Decrease 5-FU continuous infusion to 1800mg/m2 at the next cycle	2. Decrease oxaliplatin to 65mg/m2 on Day 1 at the next cycle	2. Decrease 5-FU continuous infusion to 1200mg/m2 and decrease Oxaliplatin to 50mg/m2 on Day 1 at the next cycle

9.4.3.3.2 Oxaliplatin Induced Toxicities

In addition to the general guidelines listed in Table 6, three specific toxicities of oxaliplatin should be addressed as follows:

1) Oxaliplatin-Induced Pharyngolaryngeal dysesthesias - If a subject experiences severe pharyngolaryngeal dysesthesia, the following adjustments are to be made:
    a. Stop the infusion
    b. Give 50mg of diphenhydramine intraveneously
    c. Restart the infusion, but increase the oxaliplatin infusion time to 4 hours
    d. If the severe pharyngolaryngeal dysesthesia persists despite these maneuvers, then the oxaliplatin should be discontinued altogether.

2) Oxaliplatin-Induced Pulmonary Toxicity
    a. Oxaliplatin will be held in the event of the development of grade 2 cough, grade 2 dyspnea, grade 2 hypoxia, grade 2 pneumonitis, or grade 2 pulmonary fibrosis. If any of the grade 2 toxicities listed above were present PRIOR to therapy, then oxaliplatin will be held in the event of progression from grade 2 to grade 3. The oxaliplatin will be held until a complete pulmonary evaluation has been performed (which must include imaging (at least a chest x-ray) and a clear explanation for the pulmonary toxicity is established (for example pneumonia or the development of pleural effusions). If no explanation is established, patients may undergo escalating evaluation, that may included a high resolution CT scan, V/Q scan, angiography, and lung biopsy until interstitial lung disease or pulmonary fibrosis are clearly ruled out or an alternative explanation is clearly established. Alternatively, if the escalating evaluation is not clinically warranted, or rejected by the patient, the patient may continue treatment with the combination of 5FU and ABT-888 alone (without Oxaliplatin).

3) Oxaliplatin-Induced Neuropathy
    a. Oxaliplatin will be discontinued with Grade 3 or 4 neurotoxicity
    b. Oxaliplatin may also be discontinued for prolonged, intolerable Grade 2 neuropathy
    c. If the oxaliplatin is discontinued, the other study medications may continue

9.4.4 Use of Growth Factor Support

9.4.4.1 Erythropoietin Analogs

For patients in the Phase II portion of the study, any patient with a hemoglobin ≤ 10g/dL may receive an erythropoietin analog injection as per standard institutional protocol.

9.4.4.2 Pegfilgrastim Use

For patients in the Phase II portion of the study, any patient experiencing a second occurrence of severe neutropenia, defined as grade 4 neutropenia OR any febrile neutropenia, may be treated with 6mg of pegfilgrastim subcutaneously on day 4 of each cycle.

10.0 EFFICACY ASSESMENT

10.1 Efficacy Variables

Tumor response and/or disease progression will be assessed by CT scan, MRI, CT/PET scan, X-ray, or ultrasound utilizing RECIST 1.1 criteria. The imaging modality will be at the discretion of the investigator BUT must be consistent from screening to reassessment for each patient (e.g. CT at baseline → CT at reassessment). Assessments will be performed at Screening, and every 4 cycles thereafter (or not more than every 12 weeks if there have been treatment delays), and at the Final Visit, if not performed within the last four weeks. If subjects respond to treatment and are able to have their disease resected, the patient's response will be assessed prior to the surgery.

The *clinical* efficacy endpoints will be the objective response rate (ORR), as determined by RECIST criteria. Secondary clinical endpoints are listed above, and include disease control rate (DCR, defined as response rate + rate of stable disease at 6 months), progression free survival (PFS), overall survival (OS), time to disease progression (TTP), duration of disease control (DDC), and tolerability and safety of the combination. Analyses of these endpoints are described in Section 13.

10.2 RECIST 1.1 Criteria for Tumor Response

Changes in the measurable lesions over the course of therapy will be evaluated using the RECIST 1.1 criteria.

10.2.1 Definition of Lesions

10.2.1 Measurable Disease

The presence of at least one measurable lesion. If the measurable disease is restricted to a solitary lesion, its neoplastic nature should be confirmed by cytology/histology.

10.2.2 Measurable Lesions

Lesions that can be accurately measured in at least one dimension with longest diameter ≥ 20 mm using conventional techniques or ≥ 10 mm with spiral CT scan.

10.2.3 Non-measurable Lesions

All other lesions, including small lesions (longest diameter < 20 mm with conventional techniques or < 10 mm with spiral CT scan), bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusion, inflammatory breast disease, lymphangitis cutis/pulmonis, cystic lesions and also abdominal masses that are not confirmed and followed by imaging techniques.

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 14 days 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. Clinical lesions will only be considered measurable when they are superficial (e.g., skin nodules and palpable lymph nodes). For the case of skin lesions, documentation by color photography including a ruler to estimate the size of the lesion is required.

10.2.2 Methods of Measurement

CT and MRI are the best currently available and reproducible methods to measure target lesions selected for response assessment. Conventional CT and MRI should be performed with cuts of 10 mm or less in slice thickness contiguously. Spiral CT should be performed using a 5 mm contiguous reconstruction algorithm. This

applies to tumors of the chest, abdomen and pelvis. For accurate objective response evaluation, ultrasound should not be used to measure tumor lesions. However, ultrasound is a possible alternative to clinical measurements of superficial palpable lymph nodes, subcutaneous lesions and thyroid nodules. Ultrasound might also be useful to confirm the complete disappearance of superficial lesions usually assessed by clinical examination. Cytology and histology can be used to differentiate between PR and CR in rare cases (e.g., after treatment to differentiate between residual benign lesions and residual malignant lesions in tumor types such as germ cell tumors).

10.2.3 Baseline Documentation of "Target" and "Non-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) and their suitability for accurate repeated measurements (either by imaging techniques or clinically). A sum of the longest diameter (LD) for all target lesions will be calculated and reported as the baseline sum LD. The baseline sum LD will be used as reference by which to characterize the objective tumor response. All other lesions (or sites of disease) should be identified as non-target lesions and should also be recorded at baseline. Measurements of these lesions are not required, but the presence or absence of each should be noted throughout follow-up.

10.2.4 Definitions of Tumor Response-Measurable Disease

10.2.4.1 Complete Response (CR)

The disappearance of all known disease, determined by two observations not less than 4 weeks apart. There can be no appearance of new lesions.

10.2.4.2 Partial Response (PR)

A 30% or more decrease in total tumor load of the lesions that have been measured to determine the effect of therapy by two observations not less than 4 weeks apart. There can be no appearance of new lesions or progression of any lesion.

10.2.4.3 Progressive Disease (PD)

At least a 20% increase in the sum of the LD of target lesions, taking as reference the smallest sum LD recorded since the treatment started, the appearance of one or more new lesions and/or an unequivocal progression of non-target lesions.

10.2.4.4 Stable Disease (SD)

Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum LD since the treatment started.

10.2.5 Definition of Disease Progression

Disease progression will be defined as:

1) Radiologic progression of disease by RECIST 1.1 criteria.
2) Clinical progression as determined by the investigator, which may be characterized as, but is not limited to:
    a. Increase of at least 2 points in ECOG performance status attributable to cancer progression.
    b. Requirement for palliative radiation, chemotherapy or surgery.
    c. Death from disease progression.

11.0 DOSAGES AND DISPENSATION OF DRUG

11.1 Dispensation of Study Drug

The study drugs are defined as ABT-888, 5FU, and oxaliplatin. Subjects will receive an IV infusion of leucovorin and oxaliplatin on Day 1 of each cycle, according to standard practice. Additionally, subjects will be hooked up to a pump that administers 5FU over 46 hours from Day 1 to Day 3 of each cycle. Subjects will also receive sufficient quantities of ABT-888 for 7 days of administration in each cycle. ABT-888 will be dispensed prior to dosing at each cycle (Day 1 of each cycle). Patients will receive bottles of ABT-888. Subjects will be provided with self-administration instructions and subject diaries to record the date and time they took the ABT-888. Subjects will be instructed to store ABT-888 according to specific directions described below. Subjects

should return bottles of ABT-888 (empty, partially filled or full) and their diaries to the study site prior to each cycle and at the Final Visit.

11.2 Treatments Administered

One cycle will be 14 days. Patients will receive oxaliplatin (85mg/m^2) and leucovorin (400mg/m^2) on day 1, followed by a continuous infusion of 5FU (2400mg/m^2) over 46 hours on days 1-3. Patients will also receive ABT-888 twice-a-day on Days 1-7 of each 14-day cycle. The dose of ABT-888 in the Phase I portion will be set according to the cohort level. The dose in the Phase II portion of the study will be 200mg orally twice a day. The evening dose of ABT-888 will be taken approximately 12 hours after the morning dose, both doses with or without food. Abbott will supply ABT-888 capsules.

11.2.1 Packaging and Labeling

11.2.1.1 ABT-888

ABT-888 is supplied as 20, 40, or 50mg tablets. ABT-888 will be packaged in bottles containing sufficient capsules for 8 days of therapy per cycle (which includes 1 extra day's worth of pills).

11.2.1.2 ABT-888 Liquid Formulation

For patients who cannot take oral medications and require feeding through a PEG tube (or by mouth, but liquid only), a dose equivalent liquid formulation is available that has been tested and proven to be of equivalent potency. The liquid formulation may be supplied on an as needed basis.

a. The Liquid formulation is supplied as a 10mg/ml liquid
b. Patients will be supplied with pre-filled syringes containing the proper dose (e.g. 14 syringes for 7 days of BID treatment)
c. Dose modifications will be modified by filling syringes with only the proper amount of medication to meet the dose modification
d. Patients will continue to note compliance in the patient diary, but the notations will be for the syringes used, rather than the pills taken
e. The used and unused syringes should be returned to the nurse prior to the next dosing for documentation of compliance.

11.2.1.3 Bottle Labels

Each bottle will be labeled with an open-label white single panel or booklet label that will include, but is not limited to, the following information:

1) Protocol number
2) Drug identification
3) Lot number
4) Number of capsules
5) Storage conditions
6) Dosing instructions
7) Blank spaces to write the subject's identification number, initials and date dispensed

Each bottle label must remain affixed to the bottle.

11.2.2 Storage and Disposition of Study Drug

11.2.2.1 ABT-888

ABT-888 and placebo must be stored at 15° to 25°C (59 to 77°F). Excursions are permitted up to 30°C (86°F).

All clinical supplies must be stored in a secure place until they are dispensed for subject use or are returned to Abbott. Investigational products are for investigational use only, and are to be used only within the context of this study. The clinical supplies supplied for this study must be maintained under adequate security and stored under conditions specified on the label. If pre-arranged between Abbott and the site, destruction of used and unused study drug will be performed at the site.

11.2.3 Treatment Compliance

Subjects will be instructed to return all ABT-888 bottles (empty, partially filled or full) to the study site personnel prior to each cycle and at the Final Visit. The study site personnel will document the bottles of study drug

returned and the number of capsules per bottle, according to institutional policy. If the number of capsules taken and the number of capsules returned do not add up to the number of capsules dispensed, an explanation will be provided. Unless otherwise directed by the principal investigator, a subject will be considered compliant with study drug, ABT-888, if 80% of the assigned dose is taken during a cycle.

11.2.4 Drug Accountability

The investigator or designee will verify that ABT-888 supplies are received intact and in the correct amounts. A signed and dated Proof of Receipt (POR) or similar document will support documentation of the receipt of supplies. An accurate running inventory of ABT-888 will be maintained by the site, and will include the lot number, POR number(s), the bottle numbers, and the date study drug was dispensed for each subject. Upon completion or termination of the study, all original containers (empty or containing unused study drug) will be returned to Abbott according to instructions from Abbott or, if pre-arranged between Abbott and the site, destruction of used and unused study drug will be performed at the site. Labels must remain attached to the containers. The investigator or his/her designated representative agrees not to supply study medication to any persons not enrolled in the study or not named as a sub-investigator. The site will record the lot number and dose of ABT-888 given to each subject.

11.2.5 Selection of Doses in the Study

The standard doses of 5FU and oxaliplatin are part of the modified FOLFOX-6 regimen as detailed above. These are the standard doses used in patients with colon cancer, in particular, but are also used in patients with several other cancer types. These doses will not be compromised, unless the patient experiences toxicities requiring dose reductions.

The starting dose of ABT-888 (40mg) is derived from the Phase 1 trial of ABT-888 in subjects with Non-Hematologic Malignancies (NHM) and Metastatic Melanoma (MM). ABT-888 pharmacokinetic results following the 20 and 40 mg BID doses achieved the steady-state exposures (AUC) that were effective in murine efficacy models. However, newer information available from Abbott, but as yet unpublished states that greater anti-cancer efficacy is seen with higher doses of ABT-888. Thus, the Phase I portion of this trial aims to assess the maximally tolerated dose of ABT-888. The dose of 40mg of ABT-888 is being applied in several other Phase II studies in combination with multiple other chemotherapy regimens.

12.0 CORRELATIVE RESEARCH AND TUMOR BIOPSIES

The premise that underlies the use of this combination is that 5FU and oxaliplatin (primarily oxaliplatin) will induce significant DNA damage, and that pancreatic cancer cells, in which PARP is activated, will be particularly dependent upon PARP activity to recover from the oxaliplatin-induced DNA damage. Thus, concurrent inhibition of PARP will result in overwhelming DNA damage in cancer cells, ultimately leading to increased cancer cell death. Tumors that have other abnormalities in the DNA-repair pathway may be even more susceptible to this combination. It is possible that tumors that exhibit these deficiencies will be particularly sensitive to DNA damage and PARP inhibition, which may predict for an increased ORR with therapy. Thus, we will perform a correlative analysis of BRCA2 related gene germline mutations from patient specimens, as well as screen the expression of a panel of DNA repair genes (Table 7) in patient tumor samples. All patients will undergo a fresh, pre-treatment tumor biopsy unless it is technically not feasible.

Also, all patients will be required to undergo a tumor biopsy upon disease progression to assess the mechanisms of resistance to PARP inhibitor-based therapy.

Finally, serial plasma samples for patients will be collected prior to treatment on C1 D1; C1, D7; and concurrent with each restaging study. 5 mL of blood will be collected via venipuncture (venipuncture is preferred, however if an indwelling catheter must be used, 3 catheter volumes of blood must be collected and discarded prior to collection of the sample) into evacuated tubes containing potassium EDTA. Immediately after collection, the tubes will be inverted 8 to 10 times to ensure good mixing of blood and anticoagulant and placed in an ice bath. The date and time of collection for each sample will be recorded. The complete process of centrifugation, transfer to polypropylene tubes and freezing should be accomplished within 60 minutes from blood draw. The processing of should be performed as described below:

1. Immediately invert the collection tubes 8 to 10 times.
2. Centrifuge sample at 1100 to 1300 × g for 10 minutes at 2° to 8°C to separate the plasma.

3. Transfer plasma using plastic pipettes into screw-capped polypropylene tubes labeled with the patient number, the protocol number, and the study period and/or study day.
4. Store samples at –20°C or colder in Dr. Pishvaian's lab.
Samples collected outside of Georgetown University can be batched, but ultimately must be shipped to Dr. Pishvaian on dry ice at:

Lombardi Comprehensive Cancer Center
c/o Michael Pishvaian, MD, PhD
3800 Reservoir Road, NW
Washington, DC 20007

Importantly, the correlative studies will take place at Georgetown University under the guidance of Dr. Pishvaian; and/or at Thomas Jefferson University under the guidance of Dr. Brody; and/or samples may be oursourced to a third party vendor (e.g. Tempus) for additional analysis.

- All correlative samples will have been de-identified prior to testing, as per Section 12.4 below.

Secondary Scientific Objectives: To correlate the response rate of ABT-888 plus 5FU and oxaliplatin to:

1) Tumors that have decreased expression of or mutations in BRCA-1 or -2
2) PARP activity levels in serial tumor samples
3) Expression levels of DNA repair enzymes in tumor tissues
4) Pharmacokinetic and pharmacogenomic parameters associated with the metabolism of ABT-888
5) As well as to isolate and propagate tumor cell lines obtained from patient samples and circulating tumor cells

12.1 Tumor Biopsies and Serial Tumor Biopsies

For all patients for the pre-treatment and post-treatment (progression) tumor biopsies, needle biopsies will be obtained prior to therapy (Screening or prior to dosing on C1D1). An 18-20 gauge needle will be used. At least three 1-2cM core biopsies should be obtained. All samples should be labeled with the date, protocol number, protocol assigned patient number, and biopsy number (1 – pre-treatment; 2 – post-treatment). One sample will be placed in a cryotube and snap frozen in liquid nitrogen. The sample will be stored in liquid nitrogen in the Lombardi Cancer Center. The second and third samples will be placed in formalin, and submitted to the histopathology and tissue shared resource in the Lombardi Cancer Center for tissue embedding. The tumor block will be stored in the lab of Dr. Pishvaian. Samples collected outside of Georgetown University can be batched, but ultimately must be shipped to Dr. Pishvaian on dry ice at:

Lombardi Comprehensive Cancer Center
c/o Michael Pishvaian, MD, PhD
3800 Reservoir Road, NW
Washington, DC 20007

Of note, patients who are on chronic anticoagulation will be required to hold anticoagulation prior to the biopsies being performed. Patients on warfarin must hold treatment for 5 days, but will be on low-molecular weight heparin (LMWH), 1mg/kg sub-cutaneously twice a day. The LMWH will continue until the last biopsy is complete. Patients may then resume warfarin the day after the last biopsy. Additionally, patients on LMWH will hold (*i.e.*, not receive) the dose of LMWH the morning of the procedure, but will resume the LMWH the evening of the day of the biopsy.

12.2 PARP Activity Levels

One core sample will be assayed to evaluate PARP inhibition. Tumor samples will be assayed using an enzyme-linked immunosorbent assay (ELISA) to evaluate PARP inhibition, and exploratory analysis will be performed to correlate the results with clinical outcomes.

12.3 Assessment of BRCA-1 and -2 mutations, PARP activity, and Expression of DNA repair enzymes

12.3.1 Tumor Block Submission

Formalin-fixed, paraffin embedded tissue blocks will be used for analysis. If blocks cannot be submitted, 1 H&E stained slide and 10 unstained slides of a 4 micron section mounted on positively-charged glass slides from each type of block (mucosa and tumor) are acceptable. Two separate formalin-fixed, paraffin embedded tissue blocks must be submitted: one block with **normal mucosa and one block with resection tumor**. (One block with both normal mucosa and tumor is acceptable if 2 blocks cannot be obtained).

12.3.2 Cancer Cell Isolation

Tumor specimens will be used to isolate components of the pancreatic cancer (tumor cells and stromal cells). This will be accomplished by using laser capture microdissection either on frozen or paraffin materials.

12.3.3 Familial and High Likelihood Screening

First any patients, based on family history, who qualify as having the familial form of pancreatic cancer will go through a systematic screening process (Figure 5)(22). Our strategy includes the following screen. A) Genomic DNA of patients with a history of *BRCA2* mutations in their families (based on previous work(22)) will be sent for sequencing (based on their medical insurance) to Myriad Genetics (Salt Lake City, UT). B) Patients with at least 2 or more relatives that have been diagnosed with pancreatic, ovarian, or breast cancers will be screened by a real-time PCR based assay that will test for expression levels of the clinically informative DNA repair genes in this study (BRCA1, BRCA2, FANCC, and FANCG). Recently, a novel gene, *PALB2*, was directly linked to familial pancreatic cancer and the protein is a binding partner of *BRCA2*(9). Although the significance of this finding as it relates to targeted therapy is still being explored, *PALB2* will still be included in the screening process, because in theory tumors mutated in *PALB2* will be sensitive to our targeted therapeutic strategy. The template for these assays will be isolated RNA (using the Qiagen RNAeasy kit) from laser capture microdissected (LCM) tumor cells. C) Any suggestive loss of expression of any of these genes will allow us to move to the next step of direct sequencing of the specific gene (s) (i.e., *PALB2, BRCA2, FANC and G*) whose expression in the tumor cells has been lost. Sequencing templates will be PCR amplified products from LCM gDNA samples isolated (DNAeasy, Qiagen) and amplified from LCM pancreatic cancer tumor cells (to detect alterations in both alleles). We are experienced in depicting the components of pancreatic cancer tissue(23).. Finally, 'sporadic' pancreatic cancer patients who have an objective partial or complete response (as defined by RECIST criteria) will be put through a similar screening strategy as described above. Our hypothesis is that patients with a defined molecular 'BRCA-deficiency' will be part of our responder group. Further, our serial biopsy specimens will be screened as described in this task.

12.3.3.1 Genetic Testing Patient Rights

All patients have the right to refuse genetic testing. Patients who wish to undergo genetic testing, based on family history or otherwise will be required to meet with a genetic counselor, and if they choose, will have genomic DNA testing done at Myriad Genetics.

Moreover, for this study, patient tumor samples which are used to test expression patterns of DNA repair enzymes will be deidentified (as detailed below).

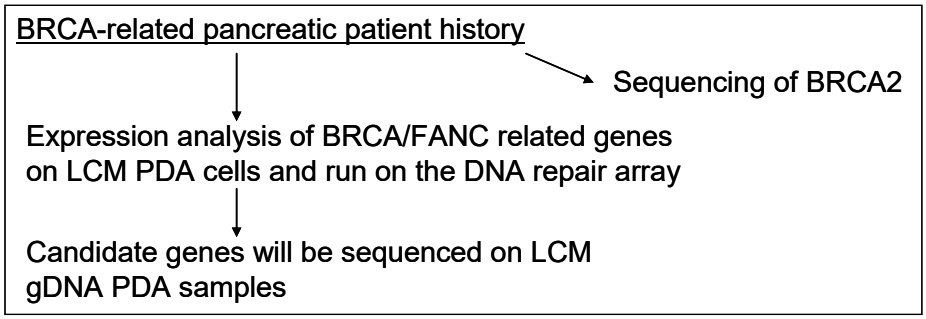

Figure 5: Step-wise screening for Patients with Possible Familial Pancreatic Cancer

12.3.4 Defining a novel response signature

RNA samples obtained as described above will be used as a resource to study a, logical focused group of DNA repair pathway genes that have been shown to be good candidate targets (see Table 7). We will use the samples processed above with Super Array technology (SA Biosciences) to screen for a putative molecular signature from their pathway specific array (DNA repair). These platforms are based on straightforward real-

time, optimized PCR technology which includes a web-based program that performs statistical, data analysis. As noted PARP-1 and related genes are all part of this condensed array platform. If other related DNA repair genes emerge in the literature, we will add them to our platform immediately.

Table 7: DNA Repair Enzymes to be Analyzed (SA Biosciences):

Enzyme Class	Specific Gene Abbreviations
Damaged DNA Binding	Brca1, Brca2, FANCC, FANCG, FANCF Ercc1, Ercc2, H2afx, Msh2, Msh3, Rad1, Rad51, RGD1563765 (Rad51c), RGD1564823 (Xrcc2), Rad51l1, Trpc2, Xpa, Xpc, Xrcc1, Rad1, Rad9, RGD1566025 (Pinx1), Smc1l1 (Smc1a), Tp53. *Base-excision Repair:* LOC680915 (Mbd4), Mpg, Mutyh, Nthl1, Ogg1, Parp1 (Adprt1), Parp2 (Adprtl2), RGD1308665 (Mare)
Base-excision Repair	LOC680915 (Mbd4), Mpg, Mutyh, Nthl1, Ogg1, Parp1 (Adprt1), Parp2 (Adprtl2), RGD1308665 (Mare).
Nucleotide-excision Repair	Dclre1a, Fancc, Nthl1, Rad23a, Slk, Xpa, Xpc
Double-strand Break Repair	Brca2, H2afx, Mre11a, Prkdc, Rad52, Xrcc6 (G22p1)
Mismatch Repair	MGC72584 (Pms1), Mlh1, Mlh3, Msh2, Msh3, Pms2, Pold3, Trex1
Other Genes Related to DNA Repair	Apex1, Atm, Atrx, Cry2, Cspd6 (Smc3), Exo1, Fen1, Gtf2h1, Gtf2h2, Lig1, LOC363333 (Chaf1a), LOC685491 (Rbbp4), LOC691105 (Fancg), Mgmt, Mif, Pold1, Pole, Polh, Poli, Polk, Pttg1, Rad17, Rad18, MGC116373 (Rad21), Rad50, Rad9, Rad9b, Rbm4, Rev1l, Smc1l1 (Smc1a), Srd5a2, Sumo1, Tdg, Tnp1, Ube2a, Ung, Wrn, Wrnip1, Xrn2, ERCC1, ALD6IP6, SSBP2

12.3.5 Construction of pancreatic cancer tissue arrays obtained from the trial

Central to the successful analysis of such a large number of tumors in a cost-effective manner, is a newly devised tissue arraying approach that is particularly well suited for arraying multiple pancreatic tumors. This arraying technology is based on serial transverse cutting and edge-to-edge-bonding of thick tissue sections to assemble a high density matrix of rectangular tumor specimens, termed cutting edge matrix assembly (CEMA)(24-26). The technology has been developed by our collaborator at Thomas Jefferson, Dr. Hallgeir Rui, and is simple, fast, and relies on standard equipment available in histotechnology laboratories. Increased sample density is achieved by a self-supporting construction that eliminates space loss due to a structural scaffold (e.g. paraffin block). CEMA uses a space saving rectangular feature design instead of circular features, and includes improved control of sample quality, and availability of thick tumor blocks is not a requirement(25, 27). Each block will be sectioned and stained with H&E for pathologic evaluation of the pancreatic cancer. A 300 μm thick section is then cut from the face of the block, and is used for construction of the CEMA arrays as described(24-26).

At the completion of the trial we will construct an array of all 50 pancreatic cancer specimens. These specimens will be represented once in each array block with a 2 mm^2 "tissue spot" (0.3mm x 6.6mm). Five replicate array blocks will be generated to achieve 5 parallel array replicates for 5-fold redundancy, ensuring representative analysis of pancreatic cancer cells in each specimen. The three key benefits of tissue arrays are 1) parallel *in situ* analyses of multiple samples without confounding inter-assay variation, 2) side-by-side quantitative image analyses on samples treated the same way, and 3) extraordinary savings in histology processing and reduced reagent cost due to low incubation volumes needed.

12.3.6 Validation of array platform: In situ biomarker profiling and quantitation using the AQUA system

The immunostaining will be performed using our validated antibodies and established conditions published(28, 29). Marker levels discovered in our DNA repair platform analysis (see task 2) in individual pancreatic cancer specimens will be determined by automated quantitative analysis (AQUA) using multiplexed and fluorescence-based immunodetection on the AQUA/ PM2000 platform(30, 31) available in Kimmel Cancer Center Histopathology Translational Research Core (TJU). Pancreatic cancer specimens will be analyzed at 5-fold redundancy for representative and accurate quantification of proposed markers. In total, there will be 4 replicate arrays that will be analyzed for all new promising markers that are identified.

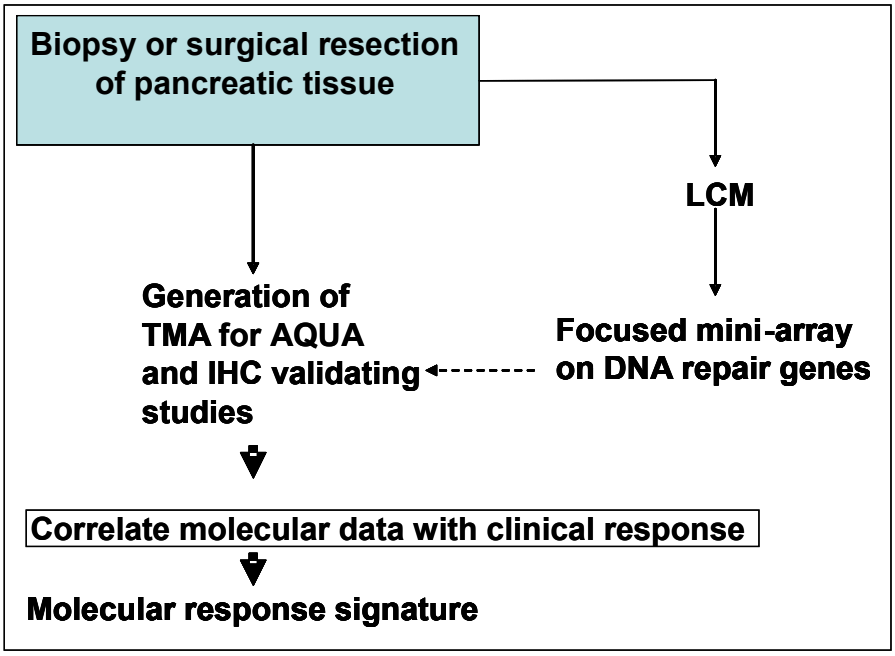

Figure 6: DNA Repair Pathway Testing Algorithm

12.3.7 Assessment of ERCC1, RRM 1, and Thymidilate Synthase

A portion of patient tumor samples will be sent to Response Genetics for laser capture microdissection of tumor samples, and assessment by quantitative RT-PCR of levels of expression of genes involved in response to chemotherapeutic agents. These include ERCC1, Thymidilate Synthase, and RRM1. These tests are performed at a Clia certified lab, and are not billed to patients or insurance.

12.4 Protection of Patient Confidentiality

All patient records, questionnaires, and tissue specimens will be de-identified using a letter and number assigned to their case at the time of enrollment on study. No record or specimen will contain information which could identify the patient. The key which connects patient identifiable information with this assigned number will be held by the Principal investigator. For computer records, the key will be protected by a double password protection system. Any paper records will be contained in a locked cabinet within a locked office to ensure patient's privacy is protected.

13.0 STATISTICAL CONSIDERATIONS

13.1 Objectives

The primary objective of the phase I portion of this study is to establish the recommended phase II dose. The primary objective of the phase II study is to determine the objective response rate (CR+PR) of ABT-888 combined with 5FU and oxaliplatin in patients with metastatic pancreatic cancer, stratified by prior therapy. Secondary clinical objectives include determining the disease control rate, progression free survival, overall survival, time to disease progression, duration of disease control, and tolerability and safety of the combination of ABT-888 and 5FU and oxaliplatin.

The secondary scientific objectives include examining the association between response to ABT-888 plus 5FU and oxaliplatin to: 1) Tumors that have decreased expression of or mutations in BRCA-1 or -2; 2) PARP activity levels in serial tumor samples; 3) The expression levels of DNA repair enzymes in tumor tissues; and 4) Pharmacokinetic and pharmacogenomic parameters associated with the metabolism of ABT-888; as well as 5) To isolate and propagate tumor cell lines obtained from patient samples and circulating tumor cells.

13.2 Study Design

The dose of ABT-888 will be determined by a brief Phase I dose escalation study. A traditional 3+3 dose escalation approach with doses of ABT-888 ranging from 40mg to 300mg will be employed to determine the recommended Phase II dose of 5FU and oxaliplatin plus ABT-888. It is possible, even likely that the Phase I portion of this study will identify the RP2D of ABT-888 as 40mg, thus as few as 9 patients may be enrolled in the Phase I portion of the study.

This trial will follow a standard 3+3 Phase I design. Patients are enrolled in groups of three. The following dose escalation rules will be used and applied to Cycle 1 of therapy:

1) Three patients are studied at the first dose level.

2) If none of these three patients experience DLT, then the dose is escalated to the next higher level in the three subsequent patients.

3) If one of three patients experiences DLT at the current dose, then up to three more patients are accrued at the same level.

a) If none of these three additional patients experience DLT, then the dose is escalated in subsequent patients.

b) If one or more of these three additional patients experiences DLT, then patient entry at that dose level is stopped, the MTD has been exceeded and dose escalation will be stopped. Up to three more patients are treated at the next lower dose (unless six patients have already been treated at that prior dose).

4) If two or more of a cohort of up to six patients experience DLT at a given dose level, then the MTD has been exceeded and dose escalation will be stopped. Up to three more patients are treated at the next lower dose (unless six patients have already been treated at that prior dose).

5) Using this dose escalation scheme, the probability of escalating to the next dose level, based on the true rate of DLT at the current dose, is given by the following table:

	True DLT rate at a Given Dose					
	10%	20%	30%	40%	50%	60%
Probability of Escalating	.91	.71	.49	.31	.17	.08

Thus, if the true underlying proportion of toxic events is 30% at the current dose, there is a 49% chance of escalating to the next dose.

The phase II portion of the trial will follow two parallel Simon's two-stage optimal designs(1) that will continue or stop independently from one another. For each stratum, in the first stage, 9 patients will be accrued. If none

of the 9 patients achieve an objective response with ABT-888 plus 5FU and oxaliplatin, the combination will be rejected and the trial stopped. However, if at least 1 patient of the 9 (11%) exhibits response in the first stage, then an additional 15 patients will be entered into the second stage, for a total of 24 patients in this phase II study. If 3 (12%) or more patients exhibit response, then the treatment will be considered for further investigation. *Because of the change in the inclusion criteria prior to initiating Phase II, patients enrolled in the Phase I portion of the study at the phase II* dose ***will not be*** included *in the efficacy assessment as part of the Simon Two Stage design.*

13.3 Sample Size Considerations

For phase I, the sample size will range from 3 to 48 (estimate =24) depending on DLTs experienced. For each stratum of the phase II portion, the sample sizes of 9 and 24 patients and the decision rules, in stages 1 and 2 respectively, are designed to differentiate a 25% ORR from a 5% ORR. The ORR associated with single agent gemcitabine (the standard of care in pancreatic cancer) is only 8% across multiple large Phase III trials. The ORR of the combination of 5FU and oxaliplatin in the first or second-line setting ranges from 2.5 to 23% in Phase II studies. Thus the lower efficacy limit of 5% is essentially that of gemcitabine, and would suggest the combination is no more effective than single agent gemcitabine, and further investigation would not be warranted. The upper efficacy limit of 25% would be the highest observed to date in a Phase II study of 5FU and oxaliplatin in pancreatic cancer, and would be highly suggestive of a significant benefit to the addition of ABT-888 to the regimen and there would be sufficient evidence to warrant further investigation of this combination. The probability of erroneously concluding that the treatment regimen merits further investigation is 10% (α=0.10) when the true ORR is less than 5%. Similarly, the probability of erroneously concluding that the treatment has an ORR of 5% (p_0) or less when the true ORR is 25% (p_1) is 10% (β); therefore the overall power of the study is 90%. The decision rule for this Simon design will accept this agent for further investigation if the sample ORR is 12% or greater at the end of stage 2.

13.4 Endpoints

13.4.1 Primary Endpoint: Objective response rate

Response classification will follow the RECIST criteria and will be defined as partial response (PR) or complete response (CR) as described in section 10. Patients who are lost to follow-up without a valid response assessment will be classified as non-responders.

13.4.2 Secondary Endpoints

13.4.2.1 Disease Control Rate

Disease control response classification will follow the RECIST criteria and will be defined as successful confirmed classification of stable disease (SD), partial response (PR), or complete response (CR) as described in section 10. Patients who are lost to follow-up without a valid response assessment will be classified as non-responders

13.4.2.2 Progression Free Survival

Progression-free survival will be defined as the time in days from study entry until progression or death. Patients who are alive and free from progression on the date of closing follow-up will be censored on that date.

13.4.2.3 Overall Survival

Overall survival will be defined as the time in days from study entry until death. Patients who are alive on the date of closing follow-up will be censored on that date. All events of death will be included, regardless of whether the event occurred while the subject was still taking study drug, or after the subject discontinued study drug. If a subject has not died, then the data will be censored according to the following rule: if the subject was lost to follow-up, then data will be censored at the last study visit, or the last contact date, or the date the subject was last known to be alive, whichever is later; if the subject was not lost to follow-up, then data will be censored at the last study visit or the last contact date, whichever is later. The date of the last study visit will be determined by selecting the last available date of the following study procedures for a subject: tumor assessment, physical examination including neurologic assessment, vital signs assessment, blood chemistry and hematology collection, and performance status.

13.4.2.4 Time to Disease Progression

Time to disease progression will be defined as the time in days from study entry until progression or death. Patients who are free from progression on the date of closing follow-up or death will be censored on that date.

13.4.2.5 Duration of Disease Control

The duration of disease control for a given subject is defined as the number of days from the date the criteria are met for CR, PR, or SD (whichever is recorded first) to the date that recurrence or PD is objectively documented. The reference for PD will be the smallest measurements recorded since the treatment started. If a subject is still responding then the subject's data will be censored at the date of the subject's last study dose or last available tumor assessment, whichever is later. For subjects who never experienced CR, PR, or SD for 6 months, the subject's data will be censored on the date initiation of therapy.

13.4.2.6 Statistical survival analyses of marker levels to determine impact on prognosis and response to treatment

The relative risk for disease progression will be estimated using the Cox proportional hazards regression model. The Cox model will be used for both univariate and multivariate analyses provided the assumption of proportional hazards is verified. The Xtiles software(31, 32) will be employed to determine cut-points for the quantitative signals for analyzed biomarkers in association with survival and response to treatment as primary outcome. This software has built-in features for dividing the cohort into training and validation subsets, with correct assessments of p values for multiple cut-points. In the multivariate analyses of biomarkers, the Cox regression models will be adjusted for tumor size (continuous variable, 1 mm units), tumor grade (well, moderately, poorly differentiated), tumor stage (T1, T2, T3), lymph node metastasis (N0, N1). Univariable models will be run, with covariates having $p < 0.2$ included in backwards stepwise multivariable models. Final covariates will be retained with $p <= 0.05$ based on two-sided tests. Limited interactions may be explored based on the final main effects model to avoid over-fitting of the models with this small sample size.

13.4.2.7 Degree of Neuropathy

This will be measured by the FACT/GOG-NTX-4 (Version 4)

The secondary scientific objectives include examining the association between the response rate of ABT-888 plus 5FU and oxaliplatin to: 1) Tumors that have decreased expression of or mutations in BRCA-1 or -2; 2) PARP activity levels in serial tumor samples; 3) The expression levels of DNA repair enzymes in tumor tissues; and 4) Pharmacokinetic and pharmacogenomic parameters associated with the metabolism of ABT-888; as well as 5) To isolate and propagate tumor cell lines obtained from patient samples and circulating tumor cells.

13.5 Analysis Plan

The primary and secondary efficacy analyses will be performed on all subjects in the study, except for the secondary efficacy analyses which are being performed in only a subgroup of patients. Subjects who have experienced an adverse event or how have received at least one cycle of the study drugs (ABT-888 and 5FU and oxaliplatin) will be included in the safety analysis.

13.5.1 Efficacy Endpoints

13.5.1.1 Primary Efficacy Endpoint: Objective Response Rate

The objective response rate will be computed for all subjects with at least one measurable lesion at baseline.

13.5.1.2 Secondary Efficacy Endpoints

13.5.1.2.1 Disease Control Rate

The proportion of patients who achieve stable disease (SD) or a partial (PR) or complete (CR) response will be reported with a 95% exact binomial confidence interval.

13.5.1.2.2 Progression Free Survival

The progression-free survival estimate curves will be calculated and presented by the methods of Kaplan and Meier (1958) and 95% confidence interval will be constructed for the estimated 12-month progression-free survival rate and for the median.

13.5.1.2.3 Overall Survival
The overall survival rate will be estimated using Kaplan-Meier methodology and 95% confidence interval will be constructed for the estimated 12-month overall survival rate and for the median.

13.5.1.2.4 Time to Disease Progression
The distribution of time-to-disease progression (TTP) will be estimated using Kaplan-Meier methodology. The median and one-year estimates will be reported.

13.5.1.2.5 Duration of Disease Control
The distribution of the duration of disease control will be estimated using Kaplan-Meier methodology.

13.5.1.2.6 Degree of Neuropathy, as measured by the FACT/GOG-NTX-4 (Version 4)
The neuropathy associated with ABT-888 + 5FU and oxaliplatin will be cross tabulated with the number of cycles of therapy.

13.5.2 ORR Comparisons
13.5.2.1 ORR in patients whose tumors evidence decreased expression of or mutations in BRCA-1 or -2
ORR will be compared in patients whose tumors demonstrate evidence of decreased expression of or mutations in BRCA-1 or -2 in both pre-and post-treatment samples.

13.5.2.2 ORR in patients as a function of the PARP activity level in pre and post-treatment tumor samples
ORR will be compared in patients whose tumors exhibit low vs. high PARP activity level (as defined in section 5) in both pre-and post-treatment samples. However, for statistical purposes, only 10 patients will be evaluated for PARP activity. Thus, this efficacy endpoint will be considered as a pilot, hypothesis-generating endpoint only.

13.5.2.3 ORR in patients as a function of the expression levels of DNA repair enzymes in tumor tissues in pre and post-treatment samples
ORR will be compared in patients whose tumors exhibit low vs. high levels of the various DNA repair enzymes listed in Table 7 in both pre-and post-treatment samples. However, for statistical purposes, only 10 patients will be evaluated. Thus, this efficacy endpoint will be considered as a pilot, hypothesis-generating endpoint only.

13.5.3 Baseline Characteristics
All baseline summary statistics and analyses will be based on characteristics prior to the initiation of study drug (or randomization for non-treated subjects). Unless otherwise stated, baseline for a given variable will be defined as the last value for that variable obtained prior to the first dose of study drug.

13.5.3.1 Demographics
Age, height, weight will be summarized with means, standard error, standard deviation and range. Frequencies and percentages will be computed for the following parameter: gender, race, number of prior anti-tumor treatments, performance status, LDH status, history of previously treated brain metastases, and time since last anti-tumor treatment.

13.5.3.2 Medical Histories
Frequencies and percentages will be computed for each medical history parameter.

13.5.4 Timing of Efficacy Analyses and Safety Evaluations
As described above, this trial will follow a Simon's two-stage optimal design(1). Thus, by definition an interim efficacy analysis will be performed after the first 9 patients. A Data Safety and Monitoring Committee will also review the safety data quarterly and ensure that the early stopping rules are carried out as planned.

The date after which the 9th patient has received at least two cycles of therapy will be defined as the primary data "cutoff" date for the efficacy analyses (as detailed in Section 8). All data available at the time of database lock will be included in the efficacy and safety analyses. When data collection is complete and reviewed for completeness and all data management quality assurance (QA) and quality control (QC) procedures are

performed, the clinical database data will be extracted for documentation and statistical analyses. Once the last enrolled subject discontinues/completes the study, the study will be considered complete and all remaining data will be collected and entered into the clinical database. Overall survival will be collected on all subjects for up to 24 months after they discontinue from the study. After all survival data have been collected and entered into the clinical database, the clinical database data will be extracted once again for documentation and a "Final Analysis" will be performed on this dataset.

13.5.4.1 Safety Assessments

The safety of ABT-888 + 5FU and oxaliplatin will be assessed by evaluating study drug exposure, adverse events, serious adverse events, oncology-related events, all deaths, as well as changes in laboratory determinations and vital sign parameters.

13.5.4.2 Duration of Study Drug

A summarization of the number of days and/or cycles subjects were exposed to study drug will be provided.

13.5.4.3 Adverse Events

Analyses of adverse events (and Serious adverse events) will include only "treatment-emergent" events, i.e., those that have an onset on or after the day of the first dose of study drug. Analyses will not include those that have an onset greater than 30 days after the last dose of study drug. Treatment emergent adverse events will be summarized by system organ class and preferred term according to the MedDRA adverse event coding dictionary. The percentage of subjects experiencing an adverse event at a given severity, NCI CTCAE toxicity grade, and relationship to study drug will be provided.

13.5.4.4 Deaths

The number of subject deaths will be summarized (1) for deaths occurring while the subject was still receiving study drug in this study, (2) for deaths occurring off treatment within 30 days after the last dose of study drug, and (3) for all deaths in this study regardless of the number of days after the last dose of study drug.

13.5.4.5 Longitudinal Analyses of Laboratory and Vital Signs Data

Changes and/or percent changes from baseline will be analyzed for each scheduled post-baseline visit and for the final visit for blood chemistry and hematology parameters, as well as urinalysis and vital sign parameters. If more than one measurement exists for a subject on a particular day, then an arithmetic average will be calculated. This average will be considered to be that subject's measurement for that day. Post-baseline measurements more than seven days after the last dose of study drug will not be included. Subjects that do not have a baseline measurement or do not have any post-baseline measurements will not be included.

14.0 ETHICAL CONSIDERATIONS

14.1 Institutional Review Board (IRB)

Good Clinical Practice (GCP) requires that the clinical protocol, any protocol amendments, the Investigator's Brochure, the informed consent and all other forms of subject information related to the study (e.g., advertisements used to recruit subjects) and any other necessary documents be reviewed by an IRB. IRB approval of the protocol, informed consent and subject information and/or advertising, as relevant, will be obtained prior to the authorization of drug shipment to a study site. Any amendments to the protocol will require IRB approval prior to implementation of any changes made to the study design. Any serious adverse events that meet the reporting criteria, as dictated by local regulations, will be reported to the IRB. During the conduct of the study, the investigator should promptly provide written reports to the IRB of any changes that affect the conduct of the study and/or increase the risk to subjects.

14.2 Ethical Conduct of the Study

The study will be conducted in accordance with the protocol, International Conference on Harmonization (ICH) guidelines, applicable regulations and guidelines governing clinical study conduct and the ethical principles that have their origin in the Declaration of Helsinki.

14.3 Subject Information and Consent

Prior to the initiation of any screening or study-specific procedures, the investigator or his/her representative will explain the nature of the study to the subject and answer all questions regarding this study. A separate informed consent is also required from subjects who provide blood for genetic testing or fresh biopsy tissue samples for analyses. Each informed consent will be reviewed, signed and dated by the subject and the person who administered the informed consent. A copy of each informed consent will be given to the subject and each original will be placed in the subject's medical record. An entry must also be made in the subject's dated source documents to confirm that informed consent was obtained prior to any study-related procedures and that the subject received a signed copy. Tissue sample collection for analysis will only be performed if the subject has voluntarily consented to participate after the nature of the testing has been explained and the subject has had the opportunity to ask questions. If the subject does not consent to the tissue sample collection, it will not impact the subject's participation in the study.

14.4 Ethical Consideration for Enrollment

Only patients with metastatic pancreatic cancer will be considered for enrollment. As described above, the standard treatment for previously untreated patients is single agent gemcitabine. Furthermore, for previously treated patients, there is not standard treatment option. Yet, the standard of gemcitabine is only associated with a minimal improvement in overall survival. Thus, consideration of another “backbone” of therapy is justified, and in fact, the combination of 5FU an oxaliplatin has demonstrated efficacy in this patient population. Furthermore, the combination of ABT-888 and 5FU and oxaliplatin has significant scientific rational and a legitimate hope to improve patient survival over what would be expected from mFOLFOX-6 alone.

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16.0 APPENDIX

Appendix 1: Neuropathy Quality of Life Assessment

FACT/GOG-NTX-4 (Version 4)

Below is a list of statements that other people with your illness have said are important**. Please circle or mark one number per line to indicate your response as it applies to the past 7 days.**

		Not at all	A little bit	Some-what	Quite a bit	Very much
NTX 1	I have numbness or tingling in my hands	0	1	2	3	4
NTX 2	I have numbness or tingling in my feet	0	1	2	3	4
NTX 3	I feel discomfort in my hands	0	1	2	3	4
NTX 4	I feel discomfort in my feet	0	1	2	3	4

Appendix 2: Patient Registration Form

Patient Registration Form ABT-888 Patient Initials: _____ Study ID: _____

Instructions: This form should be completed by the research staff before registering the patient into the trial. Completed form can be f [redacted]

☐ Georgetown University Medical Center ☐ Thomas Jefferson University ☐ Hackensack University Medical Center

1. Date Informed Consent signed: ___/___/_____
2. Start date for Treatment: ___/___/_____
3. Prior anti-cancer therapy (Date/Type):

_____
_____
_____
_____
_____

4. Please fax the following documentation:
   - ☐ Pathology Report
   - ☐ Physicians Note validating:
     - o Previous treatments
     - o BRACA-associated genetic mutation OR family history
   - ☐ CT showing RECIST criteria
   - ☐ Laboratory Results
   - ☐ Past Medical History
   - ☐ Genetic Test Summary

ON-STUDY CARD

MRN: _____

DOB: ___/___/___

Zip Code: _____

Race ☐ African American
☐ Asian
☐ Caucasian
☐ Hispanic
☐ Native American
☐ Pacific Islander
☐ Other
☐ Unknown

Gender: ☐ Male ☐ Female ☐ Unknown

Treating Physician _____
RN _____

Ethnicity: ☐ Hispanic or Latino
☐ Not Hispanic or Latino
☐ Unknown

Consent Approval Date: ___/___/___

Screen Failure ☐ Yes ☐ No

Baseline Start Date: ___/___/___

On Study Date ___/___/___

Protocol Waiver: ☐ Yes ☐ No

Reason _____

Registration Site: _____

First Scheduled Date: ___/___/___

Primary Site: _____

Appendix 3: Eligibility Checklist

Eligibility Checklist

ID: Site: ☐ Georgetown University Medical Center ☐ Oher: _____

INCLUSION CRITERIA (ALL ITEMS MUST BE CHECKED YES)

YES | NO

☐ | ☐ Histologically proven pancreatic adenocarcinoma with measurable disease, defined as at least 1 unidimensionally measurable lesion on imaging as defined by RECIST 1.1 criteria.

☐ | ☐ Known BRACA-associated genetic mutation OR family history suggesting of a breast or ovarian cancer syndrome as defined by one or more of the following:

- Personal or known family history of a deleterious (or indeterminate) mutation in the BRCA1, BRCA2, PALBB2, or one of the FANC genes.
- Personal history of epithelial ovarian cancer
- Personal history of male breast cancer
- Personal history of pancreatic cancer and ≥2 1st, 2nd, or 3rd degree relatives with breast, epitherlial ovarian, pancreatic, or aggressive prostate cancer (Gleason score ≥7) at any age
- Personal history of breast cancer and one or more of the following:
  - Diagnosed ≤ 45 years old
  - Diagnosed at any age with ≥1 1st, 2nd, or 3rd degree relative with breast cancer ≤ 50 years old and/or ≥1st, 2nd, or 3rd relative with epithelial ovarian cancer at any age
  - Two primary breast cancer with the first diagnosed at ≤ 50 years old
  - Diagnosed ≤ 60 years old with triple negative breast cancer
  - Diagnosed at any age with ≥2 1st, 2nd, or 3rd degree relatives with breast cancer at any age
  - Diagnosed at any age with ≥2 1st, 2nd, or 3rd degree relatives with pancreatic cancer or aggressive prostate cancer (Gleason score ≥7) at any age
  - 1st, 2nd, or 3rd degree male relative with breast cancer
  - Ashkenazi Jewish descent

☐ | ☐ ≥ 18 years old

☐ | ☐ ECOG performance status 0 to 2

☐ | ☐ Patient with no brain metastases or a history of previously treated brain metastases who:

- Have been treated by surgery or stereotactic radiosurgery (SRS) at least 4 weeks prior to enrollment
- **AND** have a baseline MRI that shows no evidence of active intercranial disease
- **AND** have not had treatment with steroids for brain metastases within 1 week of study enrollment

☐ | ☐ Patient has not had prior therapies- **UNTREATED ARM**-

YES | NO

☐ | ☐ Untreated patients should have received zero prior therapies for metastatic disease.

☐ | ☐ They may have received prior adjuvant chemotherapy and/or radiation therapy, but not within 6 months prior to treatment.

☐ | ☐ They may have received prior palliative radiation therapy for unresectable disease, but without any systemic chemotherapy, even as a radiosensitizer

☐ | ☐ Patients may have received any number of prior therapies (including prior adjuvant chemotherapy and/or radiation therapy within 6 months of treated) - **TREATED ARM**

YES | NO

☐ | ☐ Patients did not have any prior therapy with a PARP inhibitor

☐ | ☐ 14 days have passed since all prior anti-cancer therapy, including chemotherapy, biological therapy, or radiation therapy

☐ | ☐ 28 days must have passed since any prior antibody-based therapies (such as, but not limited to cetuximab or bevacizumab)

☐ | ☐ 28 days must have passed since any prior investigational agent.

☐ | ☐ All patients must have completely recovered from all transient side effects related to prior therapies

☐ | ☐ Any side effects that are expected to be more durable or even permanent (e.g., neurotoxicity or ototoxicity) must have resolved to at least grade 1.

LAB VALUES (ALL MUST BE CHECKED YES)

YES | NO

☐ | ☐ Absolute neutrophil count (ANC) ≥ 1,500/mm3

☐ | ☐ Platelets ≥ 75,000/mm3

☐ | ☐ Hemoglobin ≥ 9.5 g/dL

☐ | ☐ Serum creatinine ≤ 1.5 × upper normal limit of institution's normal range OR creatinine clearance ≥ 50 mL/min/1.73 m2 for subjects with creatinine levels above institutional normal

☐ | ☐ AST or ALT and alkaline phosphatase ≤ 3 X the upper normal limit of institution's normal range

☐ | ☐ Bilirubin ≤ 2.5 X the upper normal limit of institution's normal range

☐ | ☐ Partial Thromboplastin Time (PTT) must be ≤ 2 X upper normal limit of institution's normal range*

☐ | ☐ INR (International Normalized Ratio) < 2*

***Subjects on anticoagulant (such as coumadin) must have a PTT ≤ 5 X upper normal limit of institution's normal range and INR (International Normalized Ratio) < 5**

INCLUSION CRITERIA CONT. (ALL ITEMS MUST BE CHECKED YES)

YES | NO

- ☐ | ☐ Subject's with significant fluid retention, including ascites or pleural effusion, may be allowed at the discretion of the PI.
- ☐ | ☐ Life expectancy > 12 weeks.
- ☐ | ☐ Men and women enrolled in the protocol must agree to use adequate contraceptive measure when the female (patient, or partner of the male patient) has childbearing potential (the woman is not post-menopausal and has an intact uterus).
- ☐ | ☐ Subject is capable of understanding and complying with parameters as outlined in the protocol and able to sign and date the informed consent, approved by the Institutional Review Board (IRB), prior to the initiation of any screening or study-specific procedures.
- ☐ | ☐ Patients must have fully recovered from all effects of surgery. Patients must have had at least two weeks after minor surgery and four weeks after major surgery before starting therapy. Minor procedures requiring "Twilight" sedation such as endoscopies or mediport placement may only require a 24 hour waiting period, but this must be discussed with an investigator.

EXCLUSION CRITERIA (ELIGIBLE PATIENTS MUST ALL BE CHECKED NO)

YES | NO

- ☐ | ☐ CNS metastases which do not meet the criteria outlined in the inclusion criteria.
- ☐ | ☐ Clinically significant peripheral neuropathy at the time of randomization (defined in the NCI Common Terminology Criteria for Adverse Events Version 4.0 [CTCAE v4.0] as grade 2 or greater neurosensory or neuromotor toxicity).
- ☐ | ☐ Active severe infection, or known chronic infection with HIV, hepatitis B virus **Patients with chronic Hepatitis C virus may be enrolled if there is no clinical/laboratory evidence of cirrhosis AND the patient's liver function tests fall within the parameters set in Section 8.2.1, Inclusion Criteria number 6c, "Hepatic Function."**
- ☐ | ☐ Cardiovascular disease problems including unstable angina, therapy for life-threatening ventricular arrhythmia, or myocardial infarction, stroke, or congestive heart failure within the last 6 months
- ☐ | ☐ Life-threatening visceral disease or other severe concurrent disease
- ☐ | ☐ Women who are pregnant or breastfeeding (women of childbearing potential must have a negative serum pregnancy test within 14 days prior to initiation of treatment and/or postmenopausal women must be amenorrheic for at least 12 months to be considered non-childbearing potential.
- ☐ | ☐ Anticipated patient survival under 3 months
- ☐ | ☐ The subject has had another active malignancy, as per the criteria #8 in Section 8.2.1 above. Questions regarding the inclusion of individual subjects should be directed to the Principle Investigator.
- ☐ | ☐ Clinically significant and uncontrolled major medical condition(s) including but not limited to:
  - Active uncontrolled infection
  - Symptomatic congestive heart failure
  - Unstable angina pectoris or cardiac arrhythmia
  - Psychiatric illness/social situation that would limit compliance with study requirements.
  - Any medical condition, which in the opinion of the study investigator places the subject at an unacceptably high risk for toxicities

Table 8: ECOG Performance Status

I have reviewed the eligibility information for this patient and attest to its authenticity.

Clinical Research Coordinator _____ Date _____

Principal Investigator_____ Date _____

Appendix 4: Study Medication Calendar

GEORGETOWN UNIVERSITY MEDICAL CENTER

Study Medication Calendar

Instructions for the Patient: Please fill in the calendar with your medication information. The dosage of ABT-888 is taken TWICE daily. The morning dose of ABT-888 will be taken at the same time, under fasting (at least 2 hours) conditions. The evening dose of ABT-888 will be taken approximately 12 hours after the morning dose with or without food. ABT-888 and placebo must be stored at 15° to 25°C (59 to 77°F).

Pt Initials ___ ID____
Cycle #___

If you have any questions please call _____ Phone: _____

DATE	DAY 1 __/__/__	DAY 2__/__/__	DAY 3__/__/__	DAY 4__/__/__	DAY 5__/__/__	DAY 6__/__/__	DAY 7__/__/__
	___: ___ AM / PM ___: ___	___: ___ AM / PM ___: ___	___: ___ AM / PM ___: ___	___: ___ AM / PM ___: ___	___: ___ AM / PM ___: ___	___: ___ AM / PM ___: ___	___: ___ AM / PM ___: ___
Side effects or Symptoms							

Be sure to bring this calendar and the pill bottles with you for your return appointment at the end of the cycle, and return them to the Research Nurse.

Signature of Patient _____ Date _____

For Research Staff to Complete: Review pill chart and check for toxicities. Report AEs and toxicities according to the protocol.

Report Period: Start: __ /__ /____ date End: __ / __ / _____ date

Pills Dispensed _____ Pills Returned _____ Signature of Research Staff_____ Date_____