TITLE: A Phase I Study of veliparib (ABT-888) in combination with Gemcitabine and Intensity Modulated Radiation Therapy in Patients with Locally Advanced, Unresectable Pancreatic Cancer

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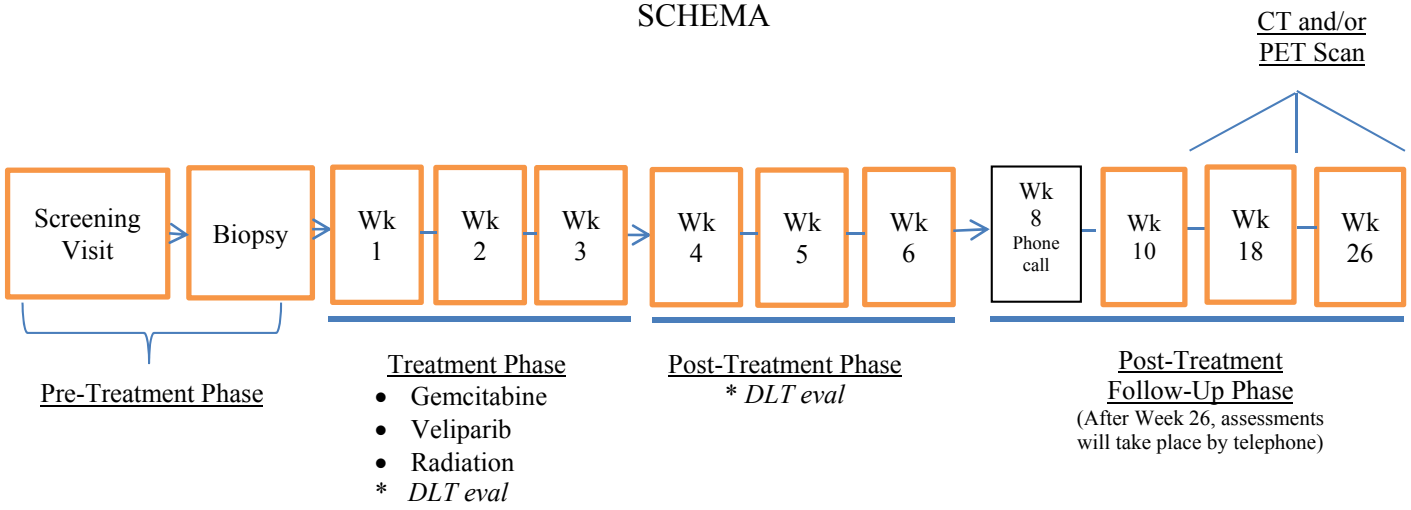
CT and/or
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1. OBJECTIVES

1.1. Primary Objectives

1. Determine the maximum tolerable dose of veliparib in combination with gemcitabine and intensity modulated radiation therapy in patients with locally advanced pancreatic cancer.

2. Determine the safety and toxicity of the combination of veliparib with gemcitabine and radiation therapy in patients with locally advanced pancreatic cancer.

1.2. Secondary Objectives

1. Measure clinical activity of veliparib, gemcitabine and radiation in patients with locally advanced pancreatic cancer by assessing response rates using RECIST 1.1 criteria

2. Evaluate pre-treatment biopsy specimen for baseline levels of various DNA repair proteins (PAR, XRCC1, BRCA1, BRCA2, etc.) and assess BRCA1/2, PTEN, PALB2, P16 mutational status.

3. Evaluate PAR levels in peripheral blood mononuclear cells from blood samples.

4. Evaluate planning technique, daily patient localization accuracy during treatment, dose distributions delivered, and other data related to the patient imaging which has been performed.

2. BACKGROUND

2.1 Veliparib

ABT-888 is an orally available, small molecule inhibitor of poly (ADP-ribose) polymerase (PARP). PARP is an essential nuclear enzyme that plays a role in recognition of DNA damage and facilitation of DNA repair. Therefore, inhibition of PARP is expected to enhance the effects of DNA damage. Expression of PARP is higher in tumor cells as compared to normal cells. This overexpression has been linked to drug resistance and the ability of tumor cells to withstand genotoxic stress. Hence, it is anticipated that PARP inhibitors will function as sensitizing agents for chemotherapy and radiation therapy that are designed to cause DNA damage.

Mechanism of Action

Poly (ADP-ribosyl)ation (PAR) occurs after single or double-stranded DNA damage and represents the posttranslational modification of histones and other nuclear proteins by PARP. Based on conserved genetic sequences, encoded for by 18 different genes, 18 nuclear proteins have been classified as members of the PARP superfamily. The superfamily is further subdivided into three branches, the PARP-1 group, the tankyrase group, and other PARP enyzmes. The PARP-1 group of NAD^+-dependent enzymes has been extensively studied, and its members PARP-1 and PARP-2 are generally considered as the primary enzymes involved in DNA repair (1).

PAR has been implicated in many cellular processes including replication, transcription, differentiation, gene regulation, protein degradation, and spindle maintenance. Enhanced PARP-1 expression and/or activity in tumor cells, as compared to normal cells, has been demonstrated in malignant lymphomas (2), hepatocellular carcinoma (3), cervical carcinoma (4), colorectal carcinoma (5), non-Hodgkin's lymphoma (6), leukemic lymphocytes (7), and colon adenomatous polyps (8). PARP-1 and PARP-2 are nuclear proteins and are the only members of the PARP family with zinc-finger DNA binding domains. These domains localize PARP-1 and PARP-2 to the site of DNA damage. PARP-1 is highly conserved and has three structural domains (N-terminal DNA-binding domain; automodification domain, and the NAD^+-binding domain). The catalytic domain is located at the C-terminus end of the protein. In knockout mouse models, deletion of PARP-1 is sufficient to impair DNA repair (9-11). The residual PARP-dependent repair activity (~ 10%) is due to PARP-2. This suggests that only PARP-1 and PARP-2 need to be inhibited to impair DNA repair (12-14).

The zinc finger domain of PARP binds to both single- and double-stranded DNA breaks, resulting in increased catalytic activity (12, 14, 15). Once activated, PARP cleaves NAD^+ and attaches multiple ADP-ribose units to the target nuclear protein. This results in a highly negative charge on the target protein and affects its function. Overactivation of PARP can be induced by DNA damage, leading to the depletion of

NAD^+ and energy stores and, thus, cellular demise by necrosis. An alternate mechanism has been identified where PARP overactivation can induce cell death through apoptosis by releasing the Apoptosis Inducing Factor (AIF) from mitochondria (16). Consequently, multiple mechanisms to prevent overactivation of PARP exist. First, auto-PAR negatively regulates PARP activity (17). In addition, the cleavage of PARP by caspases yields a peptide fragment that acts as a trans-dominant negative inhibitor for uncleaved PARP. PAR of proteins is a dynamic process with a short half-life ($t_{1/2}$) of <1 min. The enzymes responsible for degrading these polymers are poly(ADP-ribose) glycohydrolase (PARG), which cleaves ribose-ribose bonds, and ADP-ribosyl protein lyase, which removes the protein proximal to the ADP-ribose monomer.

Increased PARP activity is one of the mechanisms by which tumor cells avoid apoptosis caused by DNA damaging agents. PARP activity is essential for the repair of single-stranded DNA breaks through the base excision repair (BER) pathways (14, 18). Therefore, inhibition of PARP sensitizes tumor cells to cytotoxic agents (*e.g.* alkylators [temozolomide, cyclophosphamide, BCNU] and topoisomerase I inhibitors [irinotecan, camptothecin, topotecan]) which induce DNA damage that would normally be repaired through the BER system. A significant therapeutic window appears to exist between a PARP inhibitor's ability to potentiate therapeutic benefit *versus* potentiation of undesirable side effects. As expected, PARP inhibitors do not potentiate agents that do not cause DNA damage.

Ionizing radiation induces both double- and single-stranded DNA breaks. While part of the radiosensitization caused by PARP inhibition is through the inhibition of the single-stranded break repair pathways, it appears likely that repair of double-stranded breaks, which are thought to be more cytotoxic, is also affected. Double-stranded breaks are strong activators of PARP-1, resulting in PARP-1 mediated activation of DNA-PK and Ku80, important components of the non-homologous end-joining (NHEJ) double-stranded break repair pathway (19, 20). Also, small molecule inhibitors of PARP can directly inhibit the repair of double-stranded breaks (9, 21). Thus, it is likely that PARP activity is important for repair of both the single- and double-stranded stranded DNA breaks caused by ionizing radiation.

Nonclinical Activity

In vitro, veliparib inhibited PARP-1 and PARP-2 with K_i values of 3.6 nM and 2.9 nM, respectively. These values were observed in enzyme assays measuring the incorporation of [^{3}H]-NAD^+ into histone H1, an important physiological substrate of PARP. In assays measuring inhibition of H_2O_2-induced poly(ADP-ribosyl)ation in C-41 cervical carcinoma cells, veliparib inhibited PARP with an EC_{50} value of 2.4 nM. The extent of DNA damage in cells was indicated by γ-H2AX levels. To determine the effect of veliparib in combination with cytotoxic agents on DNA damage, the cellular content of γ-H2AX in C-41 cells was assayed by flow cytometry using an anti-γ-H2AX antibody. Addition of 1 mM of temozolomide alone resulted in increased numbers of γ-H2AX foci, a result which was further potentiated by

veliparib in a dose-dependent manner. When cell survival was measured by an AlamarBlue assay, veliparib potentiated cytotoxicity in the same concentration range as used in the γ-H2AX assay, demonstrating that veliparib potentiates cytotoxicity of temozolomide by delaying DNA repair. Veliparib achieved a maximal potentiation of approximately 15-fold. Veliparib also potentiates the DNA damage cause by irinotecan.

The combination of PARP inhibitors with different classes of chemotherapeutics was examined. Cisplatin-induced potentiation was observed in a long-term clonogenic assay, but not in the short-term cytotoxicity assay. The potentiation of cisplatin by veliparib *in vitro* is consistent with the potent enhancement of the efficacy of platinum agents (cisplatin and carboplatin) observed *in vivo*. PARP inhibition was shown to sensitize cells that are mismatch repair (MMR)-deficient to a greater extent than cells that are MMR competent (22). Alkylating agents such as temozolomide form methyl adducts in DNA and resistance is frequently encountered in the clinic with either the overexpression of O^6-alkylguanine DNA alkyltransferase (AGT) or functional defects in the MMR system. However, when PARP was inhibited, cells were sensitized to methylpurine formation, regardless of their resistance factors (23).

There are data to suggest that PARP inhibitors have activity against some BRCA-deficient cells in the absence of any DNA damaging agent (24, 25). These inhibitors did not demonstrate single agent activity in BRCA-competent cells, and restoring functional BRCA to deficient cells abrogated single agent cytotoxicity. It is possible that, in BRCA-deficient cells, PARP inhibition stops the BER pathway, and thus single-stranded breaks are carried through DNA synthesis, resulting in double-stranded breaks. The increase in double-stranded breaks cannot be repaired by homologous recombination (HR), due to the lack of BRCA1 or 2, resulting in increased cell death. However, since not all BRCA deficient cells are sensitive to the PARP inhibitors, it is unclear why single agent cytotoxicity is observed in some BRCA-deficient cells.

Consistent with PARP-1 being a radiosensitization target, PARP-1 knockout mice showed enhanced sensitivity to γ-radiation (26, 27). There is evidence to suggest that PARP inhibitors sensitize cancer cells to radiation, both *in vitro* and *in vivo* (28-30). Furthermore, a PARP inhibitor in the same class as veliparib potentiated radiation in the HCT116 colon carcinoma model. Veliparib was tested, in combination with cytotoxic agents, in several tumor models and demonstrated a similar profile of antitumor activity to that seen in the literature (See table below). Veliparib substantially increased the efficacy of cytotoxic therapies, when measured by either treated/control tumor volumes (%T/C) or by increased time for tumors to grow to a particular size (%ILS).

Table 1: Preclinical data for veliparib mediated potentiation of cytotoxic agents

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

Veliparib potentiated cytotoxic therapy when administered either parenterally or orally (PO). When administered parenterally, significant efficacy was observed at doses as low as 1 mg/kg/day, and maximal efficacy was achieved at approximately 12.5 mg/kg/day. 3.1 mg/kg/day PO (divided, twice daily) provided significant potentiation, with maximal potentiation achieved at approximately 25 mg/kg/day. No increased toxicity was observed at any of these veliparib doses, either parenteral or PO. Supratherapeutic doses of veliparib (50 mg/kg/day), administered via osmotic minipump (OMP), resulted in skin toxicity at the pump implantation site. The observation that supratherapeutic doses of PARP inhibitors may potentiate toxicity is consistent with preclinical and clinical observations. It is also consistent with the results from a two-week veliparib /cisplatin combination study. When administered as a continuous infusion, an veliparib C_{ss} (plasma concentration at steady-state) of 70 ng/mL was maximally efficacious (area under the curve [AUC]=1.7 µg•hr/mL). Comparable efficacy was seen in oral studies at a 25 mg/kg/day (divided, twice daily) dose that yielded AUCs between 1.6 and 3.0 µg•hr/mL. At this dose, the plasma concentrations were above 70 ng/mL for only 2-4 hours per dose, demonstrating that 24 hour/day coverage above 70 ng/mL was not required for efficacy.

An enzyme-linked immunosorbent assay (ELISA) that can measure PAR formation was used to demonstrate PARP inhibition in murine tumors *in vivo* and human peripheral blood mononuclear cells (PBMCs) *ex vivo* at clinically relevant doses. This ELISA was used as the primary assay for PARP biomarker analysis. The degree of PARP inhibition was assessed in B16F10 syngeneic flank tumors from mice treated *in vivo* using tumor efficacy schedules. In this study, PAR formation was measured in tumors treated with veliparib alone. Two hours after administration, veliparib inhibited PAR formation in B16F10 tumors in a dose-dependent manner. The same response was reflected in a parallel efficacy experiment, where temozolomide (50 mg/kg/day, PO, daily × 5) was administered with veliparib. In another study, PAR formation was measured in tumors treated simultaneously with temozolomide and veliparib. As in the veliparib only study, tumor PAR levels in the combination study were also inhibited. Inhibition of PARP activity was significant at 12.5, 5 and 1 mg/kg/day in both the vehicle and temozolomide treated groups. Overall, these results indicate the ability of veliparib to inhibit both baseline and cytotoxic-induced PARP activity in tumors treated *in vivo* and provide evidence of the ability of veliparib to target PARP *in vivo.*

Inhibition of PAR was similarly analyzed with *ex vivo* treatment of human PBMCs from eight healthy volunteers. The cells from one of the eight volunteers showed no detectable PARP activity, while in another patient, PARP activity was not assessable by the assay. In the remaining six individuals, not only were baseline levels of PAR detected, but more importantly, a dose-dependent inhibition of PAR was observed with *ex vivo* treatment with veliparib. Inhibition occurred at 10 nM (2.4 ng/mL), and PAR formation was almost eliminated at 300 nM (71 ng/mL).

Nonclinical Pharmacology and Toxicology

The pharmacokinetics (PK) of veliparib was evaluated in CD-1 mice, Sprague-Dawley rats, beagle dogs and cynomolgus monkeys. The non-clinical PK profile of veliparib was characterized by high plasma clearance (CL) values, ranging from a high of 4.1 L/hr•kg in the mouse to a low of 0.57 L/hr•kg in the dog. Veliparib exhibits moderate volumes of distribution (V_{ss}) in all species (V_{ss} > 2.0 L/kg), with terminal elimination $t_{1/2}$ in the 1.2-2.7 hr range. In rats and dogs, [^{3}H] veliparib was rapidly absorbed and cleared primarily in the urine as intact parent drug. A-925088 (M8), a lactam derivative and the major product of veliparib metabolism, was also cleared primarily in the urine. In both rats and dogs, parent drug was the major component in systemic circulation, followed by M8. Elimination of total radioactivity was rapid, with most (>80%) of the dose recovered within 24 hours post-dose, indicating that parent drug and the major metabolites are not likely to accumulate. Bioavailability following an oral dose was high (F>50%) in all species, with values ranging from a low of 56.1% in the monkey to a high of 92.0% in the mouse, and low animal-to-animal variability across all species.

The bioavailability from a non-formulated capsule was only slightly lower than from the solution formulation with values of 59.7% and 65.5% in fasted and non-fasted dogs, respectively. This suggests that there are no major food effects. The compound has high solubility at physiological pH and high permeability. Protein binding values in plasma (assessed *in vitro* as % bound at 5 μM) for veliparib were moderate in all species averaging 42% in dog, 41% in monkey, 43% in mouse, 49% in rat and 51% in human. The stability of veliparib was evaluated in rat, dog, monkey and human plasma and the drug was found to be very stable, with minimal degradation over the 8-hour incubation interval. *In vitro* metabolism studies indicated that several CYPs (1A1, 1A2, 2C9 and 2C19) have the potential to mediate the formation of M8. However, veliparib is not a potent inhibitor of the major human CYPs *in vitro,* indicating a low risk for drug-drug interactions at the anticipated therapeutic concentrations. Veliparib partitioned slowly into and out of the brain, in both mouse and rat, with high plasma to brain ratios (~3:1) during the first 3-6 hours after dosing. The plasma to brain ratios approached 1:1 in samples obtained 12 hours after dosing.

PK parameters in humans were estimated by a variety of methods. The oral clearance (CL/F) of veliparib was estimated as a function of the projected clearance after IV administration (CL) and the fraction of the dose systemically available after oral administration (F). Clearance predictions were based on allometric scaling.

Bioavailability was estimated by simulations with sensitivity analyses using software which took into account human gastrointestinal physiology and the drug's physicochemical characteristics. V_{ss} was estimated either from an average of values observed in animal species, a method averaging the fraction unbound in animal tissues, or by allometric scaling. Terminal phase $t_{1/2}$ values were estimated either by regression relationships between animal and human $t_{1/2}$ values (31), or from the estimates of CL and V_{ss}. The human PK profile is projected to have CL=26 L/hr, with oral bioavailability of ~ 70%. The predicted human $t_{1/2}$ of veliparib is ~4 hrs. Simulations of 50 mg twice daily dosing in humans mimic a maximally efficacious dosing regimen in mouse (12.5 mg/kg, twice daily), with concentrations above 71 ng/mL for 8 of 24 hours and an AUC_{24} of 3 µg•hr/mL at steady state.

Veliparib was tested in receptor-binding, CNS/neurobehavioral, cardiovascular, cardiac electrophysiological and gastrointestinal assays. In 74 receptor-binding assays at a concentration of 10 µM (2.4 µg/mL), veliparib displaced control-specific binding at the human H_1 (61%), the human 5-HT_{1A} (91%), and the human 5-HT_7 (84%) sites only, with IC_{50} values of 1.2-5.3 µM.

Veliparib did not display clear adverse CNS effects in the rat and mouse between 3-30 mg/kg PO. At 100 mg/kg PO, mild sedation-like effects were observed, followed in time by mild excitation. At 300 mg/kg PO, more moderate to marked CNS effects were observed, including abnormal gait and sedation. Further, at 100 mg/kg, PO, there was an increased incidence of death after electrically-induced tonic convulsions in mice. Death was also noted in a second convulsant model (audiogenic seizures in mice). In a repeated dosing mini-Irwin observational test, in which rats were dosed with veliparib at 30, 100, and 300 mg/kg intraperitoneally (IP) every day for 5 days, tonic-clonic seizures/death were observed in approximately 50% of the animals treated at the highest dose on day 1. A similar incidence of seizures was observed after dosing the remaining animals at the same dose on each of the subsequent days. In an acute follow-up study with rats dosed with veliparib 300 mg/kg IP, protection against seizures was not provided by pretreatment with either valproic acid (300 mg/kg IP, 15 min prior to veliparib) or diphenylhydantoin (75 mg/kg IP, 100 min prior to veliparib). In a 2-week toxicology study, seizures were also noted in dogs treated with veliparib at either 60 mg/kg/day, 30 mg/kg twice daily, or 30 mg/kg every day. Plasma concentrations in dogs with seizures were in excess of 5.4 µg/mL (26-fold the predicted clinical C_{max} of 0.21 µg/mL).

In the anesthetized dog, veliparib produced no physiologically relevant changes in mean arterial pressure, heart rate, dP/dt_{max}, pulmonary arterial pressure, or systemic or pulmonary vascular resistance compared to vehicle controls at mean plasma concentrations as high as 4.45 ± 0.13 µg/mL (21-fold the predicted clinical C_{max} of 0.21 µg/mL). As mean plasma concentrations increased to 12.96 ± 0.92 µg/mL (62-fold), veliparib produced a modest reduction in mean arterial pressure (–16 ± 5% below baseline) and systemic vascular resistance (–10 ± 7% below baseline).

Veliparib blocked hERG current with an IC_{50} value of 57.6 ± 1.7 µg/mL (236 ± 7 µM), a value 278-fold higher than the predicted clinical C_{max}. The M8 metabolite of veliparib (A-925088) minimally affected hERG at the highest concentration tested (81.5 µg/mL). While no effect on repolarization (*in vitro* action potential duration measures) was noted at the lowest measured concentration of veliparib (0.42 µg/mL, 2-fold higher than the predicted clinical C_{max}), veliparib prolonged the action potential duration at the intermediate and highest measured concentrations (4.8% and 18.6% prolongation at 4.22 ± 0.02 and 39.49 ± 0.70 µg/mL respectively), suggesting delayed repolarization risk between 20- and 190-times the C_{max}. There was a trend (7%) towards delayed repolarization in the anesthetized dog model (QTc intervals) at plasma concentrations 21-fold higher than the predicted clinical C_{max}; greater concentrations elicited prolongation (15 ± 3% above baseline [QTcV] at 12.96 ± 0.92 µg/mL). In humans, QTc prolongation is predicted to be less than 3 msec at the anticipated dose of 50 mg twice daily. These cardiac effects need to be monitored during clinical trials.

Gavage administration of veliparib up to 10 mg/kg was generally well tolerated in the ferret emesis model. No emesis was noted at this dose (resulting in mean plasma concentrations of 3.80 ± 0.11 µg/mL, a value 18-fold greater than the predicted C_{max}), with significant emesis noted in response to the 20 mg/kg dose (resulting in mean plasma concentrations of 6.61 ± 0.26 µg/mL, a value 31-fold greater than predicted C_{max}). Parenteral (subcutaneous) dosing of veliparib at doses and plasma concentrations similar to those used in the gavage study revealed a similar emetic dose-response relationship, suggesting a centrally-mediated emetic response. Veliparib had no significant effect on gastrointestinal transit up to 100 mg/kg (resulting in a mean plasma concentration of 1.63 ± 0.14 µg/mL, a value 7-fold greater than the predicted clinical C_{max}).

Veliparib dihydrochloride was evaluated in repeated dose toxicity studies in rats and dogs. When administered as a sole agent to rats, the compound did not result in adverse effects at C_{max} values that were greater than 19-fold the estimated therapeutic peak plasma drug concentration (highest dose tested). When rats were administered veliparib dihydrochloride in conjunction with a cytotoxic agent (cisplatin), no clinically meaningful exacerbations of cisplatin-associated toxicity were apparent at C_{max} values that were up to 8-fold greater for veliparib than the estimated therapeutic value. Exacerbation of cisplatin-associated toxicity was limited to rats that received veliparib dihydrochloride in conjunction with cisplatin at the highest dose that yielded C_{max} values 22-fold greater than the estimated therapeutic peak plasma drug concentration. In dogs, emesis, body weight losses related to anorexia, and convulsions were observed at doses of 30 mg base/kg/day with C_{max} values 26-fold greater than the estimated therapeutic peak plasma concentration. Veliparib dihydrochloride was found to be negative *in vitro* for both mutagenicity and clastogenicity.

The non-toxic dose observed in the most sensitive mammalian species (beagle dogs) was 300 mg/m^2. Emesis and QT prolongation were observed in animal models, at 31-

fold and 21-fold higher concentrations than the predicted clinical C_{max} (0.21 μg/mL), respectively. Based on different sensitivities to seizures between rodents and dogs, the plasma concentration that would be associated clinically with pro-convulsant activity will be difficult to define.

Clinical Investigations

A single-dose pharmacokinetic and pharmacodynamic endpoint study in cancer patients was initiated under an exploratory IND by the National Cancer Institute as the initial study in their phase 0 program (32). In this study, participants had baseline assessments of PAR in peripheral blood mononuclear cells (PBMCs) and at higher dose levels, in tumor from needle biopsies, assessed by a validated immunoassay. Participants received a single dose of veliparib at 10, 25, or 50 mg. PBMCs were collected over a 24 hour period at all dose levels, and tumor biopsies were obtained at the 25 mg dose level, approximately 3 to 6 hours after administration of veliparib. A total of 6 patients have been studied so far, 3 each for the 10 mg and 25 mg cohorts. No treatment related adverse events have been observed. The target plasma C_{max} of 210 nM was exceeded in 2 of 3 patients at the 10 mg dose level, and in all three patients for at least 4 hours at the 25 mg dose level. Levels of PAR were reduced 80-99% from baseline levels after administration of veliparib in both the PBMCs and tumor samples at the 25 mg dose level. Thus, there is reason to believe that target inhibition is seen at least at the 25 mg dose level, and may be occurring at doses lower than 25 mg.

Currently, several combination phase I trials are underway. Also, single agent dose escalation trial is ongoing in the BRCA deficient population. Of these, A Phase I study of veliparib in combination with metronomic cyclophosphamide in adults with refractory solid tumors and lymphomas has finished. The combination was well tolerated and 60mg QD veliparib was determined to be the MTD to be combined with 50mg QD of cyclophosphomide (Kummar S et al, Clin Cancer Res. 2012 Mar 15;18(6):1726-1734). Multiple phase II studies with the veliparib/cyclophosphamide combinationto treat breast cancer, ovarian cancer and lymphoma are ongoing. In another study, 10mg BID veliparib was determined to be the MTD in combination with topotecan 0.6 mg/m²/d (Kummar S Cancer Res. 2011 Sep 1;71(17):5626-34).

2.2 Gemcitabine and Intensity Modulated Radiation Therapy for Pancreatic Cancer

Surgical resection is considered to be the only treatment option with curative potential for patients with pancreatic cancer (2). However, the majority of these patients do not have resectable disease at presentation. More than 85% of patients have locally advanced or metastatic disease when initially diagnosed. First-line chemotherapy for locally advanced/metastatic pancreatic cancer is gemcitabine, (2',2'-Difluoro-2'-deoxycytidine), which is a fluorine substituted analog of Cytarabine. It has demonstrated anti-tumor activity in a number of murine tumor models and in human tumor xenografts. Gemcitabine has been used as either a single agent or in combination with other drugs for the primary treatment of locally advanced and metastatic pancreatic carcinomas. In the pivotal trial for which the FDA approved this

drug, patients treated with gemcitabine had a modest improvement in survival compared to patients treated with 5FU (3). The median survival was improved from 4.41 months to 5.56 months. However, nearly 25% of patients receiving gemcitabine were noted to have a clinical benefit compared to 5% of patients receiving 5FU.

In a recent meta-analysis, the addition of platinum analogs to gemcitabine demonstrated a survival benefit in patients with a good performance status. However, additional studies are necessary to determine which therapeutics are best combined with gemcitabine (4). Response rates of 11-22% have been reported in heavily pre-treated patients, and up to 42% in chemo naïve patients. Gemcitabine has been shown to decrease the intracellular deoxyribose nucleotide pools and to increase the radiosensitivity of cells in vitro. Thus, gemcitabine is not only an agent with significant systemic activity (33), but also a potent radiosensitizer (34). A recent study compared full dose gemcitabine (1000 mg/m2) to a lower dose of gemcitabine (600 mg/m^2) combined with standard fractionated radiation (50.4 Gy over 5.5 weeks). Although the study was closed prior to reaching its planned accrual, there was a significant improvement in survival with combined gemcitabine and radiation compared to gemcitabine alone (5). Objective responses were observed in 2.7% in the gemcitabine alone arm (95% CI [0.09%, 14.1%]) and 8.8% in the combined arm (95% CI [1.9%, 23.7%]). In this trial, the dose of gemcitabine was reduced to 600 mg/m^2 with radiation and patients required a 4 week break prior to resuming full dose gemcitabine. Grade IV toxicity, principally gastrointestinal and hematologic, was more common in the combined group (41.2 vs. 5.7%; $p<0.0001$). Although there was an improvement in survival, patients who received combined chemoradiation had substantially more toxicity when compared to gemcitabine alone. A formal full-dose gemcitabine with concurrent radiation dose escalation trial was conducted but, with 3D techniques, it was not possible to escalate the radiation dose beyond 36Gy (35).

IMRT can reduce the dose to Organs-At-Risk and simultaneously allow an increase in target dose in unresectable pancreatic cancer (36). To determine the maximum tolerated radiation dose deliverable with IMRT and concurrent full-dose gemcitabine a phase I/II trial (UMCC 2006-018) was initiated at the University of Michigan by Ben Josef et al. In this trial it was elected to combine radiotherapy with concurrent gemcitabine administered by a fixed dose-rate infusion schedule (FDR-G). The rationale was based on the finding that phosphorylation of gemcitabine to the monophosphate form by deoxycytidine kinase is the rate-limiting step in the accumulation of the active diphosphate and triphosphate metabolites (37). It has been demonstrated in clinical trials that accumulation of gemcitabine triphosphate in mononuclear cells during therapy is saturable, and that the optimal plasma concentration of gemcitabine that maximized the rate of formation of gemcitabine triphosphate is approximately 20 □mol/L (38). Optimal levels were achieved at an infusion rate of gemcitabine of approximating 10 mg/m^2/min. Preclinical data, using human tumor cell lines (including pancreatic carcinoma cell lines), have suggested improved cytoxicity (39, 40). The concept was then tested in phase I (41) and phase II (42) trials. In the later, patients with locally advanced and metastatic pancreatic adenocarcinoma were treated with 2,200 mg/m2 gemcitabine over 30 minutes

(standard arm) or 1,500 mg/m2 gemcitabine over 150 minutes (FDR arm) on days 1, 8, and 15 of every 4-week cycle. Ninety-two patients were enrolled; 91% of the patients had metastatic disease. The median survival for all patients was 5.0 months in the standard arm and 8.0 months in the FDR arm (P = .013). Patients in the FDR infusion arm experienced increased but acceptable hematologic toxicity. Pharmacokinetic analyses demonstrated a two-fold increase in intracellular gemcitabine triphosphate concentration in the FDR arm.

In UMCC 2006-018, patients received FDR-G (1000 mg/m^2, 100-minute infusion) on days -22 and -15 during a run in period. Protocol therapy started on day 1 and consisted of FDR-G on days 1, 8, 22, and 29, concurrently with IMRT at escalating doses. Post IMRT, 4 cycles of FDR-G were administered. The radiation doses ranged from 50Gy to 60Gy, all in 25 fractions. DLT's were observed in 6 patients; the interim posterior estimates of probability of DLT ranged from 0.17 to 0.28. The response rate was 52.4% (95% CI 29.8% to 74.3%). The median overall survival and progression-free survival were 23.1 months (95% CI 9-23.1) and 7.2 months (95% CI 5.0-8.0), respectively.

2.3 Study Disease

This study will be open to participation by patients with locally advanced, unresectable or borderline-resectable pancreatic cancer as determined by a pancreatic cancer surgeon or assessment at a GI oncology tumor board.

2.4 Rationale

Current treatment of non-metastatic, unresectable pancreatic cancer results in dismal median survival rates of 11-12 months, nearly uniform local persistence of disease and poor local control. Indeed, recent data suggests that failure to control the primary tumor results in complications that contribute to mortality in approximately 30% of patients (43). Gemcitabine has been used as a single agent, as well as in combination with other drugs, for the primary treatment of locally advanced and metastatic pancreatic carcinomas. Response rates of 11-22% have been reported in heavily pre-treated patients, and up to 42% in chemo naïve patients. Whereas its value has been substantiated in many clinical trials, its use with concurrent radiation therapy remains controversial with mixed results. A Phase I study evaluated radiation dose escalation using three-dimensional conformal techniques with full-dose gemcitabine, yet it was not possible to escalate the dose beyond 36 Gray (Gy; 2.4 Gy daily fractions) secondary to gastrointestinal toxicities (35). A follow-up multi-center Phase II study confirmed this regimen to be well-tolerated, while showing response rates of 5.1% and disease control rates of 84.6% (44). In an attempt to minimize dose-limiting toxicities to organs-at-risk and simultaneously allow an increase in target dose, Ben Josef et al. recently reported excellent outcomes (response rate of 52.4%, median overall survival 23.1 months) using dose-escalated intensity modulated radiation therapy (IMRT) with full-dose gemcitabine (Ben-Josef 2008 ASCO). Unfortunately, other contemporary trials have failed to show such promising results with the use of

concurrent radiation therapy (Chauffert 2008; Loehrer 2008 ASCO). As a result, more effective multimodal treatment strategies are required and clinical trials integrating novel therapeutic agents should be initiated.

Targeting of the poly (ADP-ribose) polymerase (PARP)-1 and 2 proteins has shown excellent anti-tumor activity when combined with other cytotoxic therapies, including gemcitabine and radiation (45-47). As a result, clinical development of PARP inhibitors follows two distinct approaches: targeting tumor cells with pre-existing defects in DSB repair, such as BRCA-deficient cells, which are genetically predisposed to die when PARP activity is lost; and combining PARP inhibition with DNA-damaging agents, such as ionizing radiation, to derive additional therapeutic benefit from DNA damage (48). A recent phase II study evaluated BSI-201, a potent PARP1 inhibitor, in combination with gemcitabine (1000 mg/m^2) and carboplatin (AUC = 2) in subjects with metastatic triple negative breast cancer. Patients randomized to receive concurrent BSI-201 had improved CBR, median PFS, and median OS, compared with chemotherapy alone. Additionally, the frequency and nature of adverse events did not differ between arms. A phase 0, single-dose pharmacokinetic and pharmacodynamic endpoint study of ABT-888 (veliparib) in cancer patients showed reduction in PAR levels (80-99%) in tumor biopsies after a single dose of 25 mg with no treatment related adverse events noted.

Recognizing the therapeutic potential of PARP1/2 inhibition in pancreatic adenocarcinoma, we have investigated the addition of veliparib to gemcitabine and focused radiotherapy in vitro and in vivo using our novel preclinical pancreatic cancer radiation research model [Tuli et al., in press]. *In vitro*, irradiation of the human pancreatic carcinoma cell line, MiaPaCa-2, led to significant upregulation of PAR protein, which was abrogated following co-treatment with veliparib, confirming PARP as a potential target in pancreatic cancer. Simultaneous upregulation of phospho-ATM levels were also noted with irradiation plus veliparib relative to either therapy alone, suggesting increased double-strand DNA damage and repair through HR. Co-treatment with 5 Gy and 1, 10 or 100 uM of veliparib led to dose enhancement factors of 1.29, 1.41 and 2.36, respectively suggesting a synergistic mechanism of cell death. Additionally, minimal cytotoxicity was noted when cells were treated with veliparib alone up to 100 uM. Radiation-induced caspase 3/7 activity was also significantly enhanced by veliparib, thereby indicating increased cell death through apoptosis. PARP activity was quantified using ELISA and confirmed expression patterns seen with Western blot. These levels also correlated with levels of tumor apoptosis suggesting accurate target inhibition, as well as the potential to use PARP activity and PAR levels as a predictive clinical biomarker. *In vivo*, treatment with a single dose of veliparib, radiotherapy or veliparib plus radiotherapy led to tumor growth inhibition of 8, 30 and 39 days ($p<.05$), respectively; survival at 30 days for these groups was 63%, 75% and 100%, while at 60 days, it was 0%, 0% and 29% ($p<.05$), respectively.

Taken together, these data support our concept of a phase I clinical trial with ABT-888 in combination with gemcitabine and radiation therapy for pancreatic cancer

patients. If the combination of ABT-888, gemcitabine and radiation is deemed safe, future studies will assess whether this potential intensification of local and systemic therapy will result in improved local and systemic control.

2.5 Correlative Studies Background

Laboratory correlative studies will be performed on biopsy specimen, which will be flash frozen and formalin fixed and paraffin embedded. PARP inhibitors have been shown to have preclinical and clinical activity in cancers that have impaired DNA repair through homologous recombination (25). Additionally, other baseline DNA repair proteins, such as ERCC1 have previously been shown to be predictive of response to DNA damaging agents such as cisplatin in lung (49). We will assess the levels of a panel of DNA repair protein to explore this hypothesis with our regimen, hypothesizing that aberations in levels of these proteins will predict sensitivity to our regimen. We plan to use standard immunohistochemistry as used by other groups in previously published clinical trials. These techniques were accepted as well-performing through the publication of previous studies in high-ranking, peer-reviewed medical journals and are commonly used at our institution. We will utilize patient blood samples obtained prior to, during and post-treatment to quantitatively assess PAR protein levels and correlate to the ABT-888 dose levels. Additionally, given the single agent cytotoxicity of PARP inhibitors seen in BRCA1/2 mutation carriers, we will assess pre-treatment tumor and peripheral blood specimen for germline/somatic BRCA1/2, PALB2 and PTEN mutations using quantitative RT-PCR, gene sequencing and immunohistochemistry through a research collaboration with Myriad Genetics. All such analyses will be done in an exploratory capacity, as this study is not powered to validate these biomarkers/findings, described in statistics section 13. Our hypothesis for future phase II/III trials is that patients with DNA repair deficient tumors will be more sensitive to combination PARP inhibition with gemcitabine and radiation therapy.

3. PATIENT SELECTION

3.1 Inclusion Criteria

3.1.1 Patients with histolopathological or cytological diagnosis of adenocarcinoma of the pancreas, as well as those with high clinical suspicion of adenocarcinoma, which is deemed locally advanced unresectable or borderline resectable as determined by a pancreatic cancer surgeon and/or following evaluation by a GI oncology tumor board.

3.1.2 Age $\geq$18 years.
Rationale: No dosing or adverse event data are currently available on the use of veliparib in combination with gemcitabine and radiation therapy in patients <18 years of age

3.1.3 Karnofsky $\geq$70% (Appendix A)

3.1.4 Life expectancy of greater than 6 months, in the opinion of the investigator.

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

Absolute Neutrophil Count (ANC)	≥1,500/mcL
Platelets	≥100,000/mcL
Total bilirubin	≤ 2X upper limit of normal (ULN) biliary stents
AST(SGOT) and ALT(SGPT)	≤2.5 X ULN
Creatinine OR creatinine clearance	≤ 1.5 times the upper limit of normal OR ≥ 45 mL/min/1.73 m^2 for patients with creatinine levels above normal.

Note: Patients with biliary stent are eligible provided that all other inclusion criteria are met.

3.1.6 Negative pregnancy test in women of childbearing potential (WOCBP) within 30 days of study drug administration.
Rationale: The effects of veliparib on the developing human fetus are unknown. Should a woman become pregnant or suspect she is pregnant while participating in this study, she should inform her treating physician immediately.

Because there is an unknown but potential risk for adverse events in nursing infants secondary to treatment of the mother with veliparib, breastfeeding should be discontinued if the mother is treated with veliparib. These potential risks may also apply to other agents used in this study.

3.1.7 Woman of child-bearing potential (WOCBP) and men must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) from the time of signing the informed consent form, for the duration of study participation, and for at least 30 days after discontinuing from study treatment.

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

3.2 Exclusion Criteria

3.2.1 Patients who have had prior anti-cancer treatment for their disease.

3.2.2 Patients who are currently receiving any other investigational agents.

3.2.3 Metastatic disease.

3.2.4 History of allergic reactions attributed to compounds of similar chemical or biologic composition to PARP inhibitors or gemcitabine.

3.2.5 Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements.

3.2.6 Patients who have demonstrated an inability to swallow oral medications.

3.2.7 Known HIV positivity
Rationale: HIV-positive patients on combination antiretroviral therapy are ineligible because of the potential for pharmacokinetic interactions with veliparib. In addition, these patients are at increased risk of lethal infections when treated with marrow-suppressive therapy. Patients felt to be at high risk for HIV infection will be tested at the discretion of the treating physician.

3.2.8 Patients who are receiving radiation treatment outside of Cedars-Sinai Medical Center

3.2.9 Patients with a history of seizures.

3.2.10 Patients with gross tumor volume exceeding 500 cc.

3.2.11 Patients with inflammatory disease of the bowel.

3.3 Inclusion of Women and Minorities

Both men and women of all races and ethnic groups and age ≥ 18 are eligible for this trial.

4. REGISTRATION PROCEDURES

4.1 General Guidelines

All subjects that sign informed consent will be assigned a subject number sequentially by their date of consent. Those subjects that do not pass the screening phase will be listed as screen failures on the master list of consented subjects. Eligible subjects, as determined by screening procedures and verified by a treating investigator, will be registered on study at Cedars Sinai Medical Center by the Study Coordinator.

Issues that would cause treatment delays after registration should be discussed with the Principal Investigator (PI). If a patient does not receive protocol therapy following registration, the patient's registration on the study may be canceled. The Study Coordinator should be notified of cancellations as soon as possible.

4.2 Registration Process

The study team will track all subjects who sign consent on a subject screening/enrollment log using a unique screening ID (S01, S02, etc.). Subjects found to be ineligible will be recorded as screen failures. Subjects found to be eligible will be registered.

A) Eligibility Verification
Prior to registration, all subjects must undergo eligibility verification by the SOCCI Clinical Research Office (CRO). The following documents will be completed and provided for review:

- Registration form (or equivalent)
- Copy of required laboratory tests
- Copy of required imaging reports
- Eligibility checklist (signed by investigator)
- Signed patient consent form and Subject's Bill of Rights
- HIPAA authorization form

B) Registration
After eligibility is verified, registration is completed as follows:

- Assign a patient study number
- Assign the patient a dose as determined through communication with Biostatistics and the principal investigator
- Enter the patient in OnCore
- Notify the investigational pharmacy and treating physicians that a subject has gone on study and anticipated treatment start date.

Oversight by the principal investigator is required throughout the entire registration process.

5.1 Agent Administration

Treatment will be administered on an outpatient basis. Reported adverse events and potential risks for veliparib, gemcitabine and radiation therapy are described in Section 9. Appropriate dose modifications for gemcitabine and radiation therapy are described in Section 6. No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the patient's malignancy.

The investigational treatment cycle is 3 weeks followed by once weekly evaluation for an additional 3 weeks. First post-treatment imaging with follow up will be performed 10 weeks after initiating therapy. Patients removed from study for unacceptable adverse events will be followed until resolution or stabilization of the adverse event. In addition, subjects will be evaluated for safety/toxicity and post-treatment imaging at weeks 18 and 26 as clinically indicated. After Week 26, telephone follow-up will occur every 3 months for 2 years, every 4 months during year 3, and annually thereafter.

Gemcitabine will be administered by intravenous infusion of 1000 mg/m^2 over 30 minutes on days 1, 8, 15 of the cycle. Intensity modulated radiation therapy (IMRT) will be given to a total dose of 36 Gy in 15 fractions (2.4 Gy per fraction, one fraction per day, 5 fractions per week, Monday through Friday) beginning on day 1. Veliparib will be administered per the dose escalation schema, below, beginning on day 1. The starting dose of veliparib is 20 mg BID based upon safety/efficacy data available from the Investigator's Brochure. Dose escalation will continue in 20 mg increments until the maximum tolerated dose (MTD) is reached. Intra-patient dose escalation will not be allowed.

In this trial, the minimum veliparib dose to be given is 20 mg BID. The first patient will be enrolled to the trial and assigned 20 mg BID. Treatment will be delivered over 3 weeks. Patients will be evaluated for DLT during the treatment period and in follow-up as outlined in the schema above[1]. Therefore, patients will be evaluable for DLT during a 6 week period (treatment cycle). The second patient may enter the trial once the first patient has cleared the DLT evaluation period and/or a DLT has occurred and it has been determined that the subject will need to be replaced. After the first patient clears the DLT evaluation window, subsequent patients may be enrolled per EWOC design after consultation with the biostatistician or his/her designee. Documentation of all enrollment decisions will be documented in the trial master file.

The trial will be terminated if three DLTs are observed from patients treated with 20 mg. The maximum number of patients to be treated simultaneously with unresolved

DLT status cannot exceed 3. In other words, if there are three patients currently under study with unresolved DLT status, a new patient cannot be treated until at least one patient finishes one cycle of therapy. After the first patient clears the 20 mg BID dose, i.e. no DLT at the end of treatment cycle, subsequent patients may be enrolled at any time after consultation with Biostatistics. It is estimated that a maximum of 30 patients will be accrued to the trial. Upon completion of the trial, the MTD will be estimated as the median of the marginal posterior distribution of the MTD. The computation of the dose to be administered to each patient and the 95% highest posterior density credible interval estimate of the MTD will be carried out by the study statisticians with the software WinBUGS [7].

In order to appropriately assess toxicity and possible dose limiting toxicities during treatment, patients will be seen in clinic by a practitioner every week with blood work drawn as per the study calendar (section 12) for a total of 6 consecutive weeks and again during week 10 follow up. Therapy may be administered provided that the patient has no evidence of progressive disease and meets criteria for treatment as defined in Section 6 "Dose Modifications."

Toxicity will be evaluated using the NCI Common Terminology Criteria for Adverse Events, Version 4.0. The frequency of toxicities per organ system will be tabulated using descriptive statistics. All patients who receive any amount of the study drug will be evaluable for toxicity.

Veliparib Dose Escalation Schedule

Dose Level	**Dose**		
	Veliparib* Dose PO BID Days 1-21 (weeks 1-3)	***Gemcitabine IV 1000 mg/m2 Days 1, 8, and 15 (weeks 1-3)†***	***Radiation Dosage Monday-Friday weeks 1-3***
Level 1	20 mg	1000 mg/m^2	36 Gy
Level 2	40 mg	1000 mg/m^2	36 Gy
Level 3	60 mg	1000 mg/m^2	36 Gy
Level 4	80 mg	1000 mg/m^2	36 Gy

**Dose escalation will continue in 20 mg increments until MTD is achieved.*
† Gemcitabines and veliparib dose reductions are outlined in section 6.2.

5.1.1 Veliparib

Veliparib is supplied by AbbVie as immediate release capsules at dosage strengths of 10, 20, 40, 50, and 100 mg. Capsules should be stored in their original container at room temperature. Patients should be instructed to swallow the tablets whole (do not chew, crush, or break the tablets). Veliparib will be dosed BID, orally, one in the morning and the other in the evening. The time interval should be ~12 hr in between the two doses. Fasting is not required for veliparib dosing.

If the subject vomits within 15 minutes of taking veliparib AND all capsules come out intact, another dose should be administered. The dose may only be repeated once. If more than 15 minutes have passed from the time of oral dosing OR the capsules have been broken or dissolved, then no additional doses should be taken.

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

Veliparib is not known to be a potent inhibitor of the major human CYPs in vitro, indicating a low risk for drug-drug interactions at the proposed dosing concentrations.

5.1.2 Radiation Therapy

The dose to the PTV will be 36 Gy in 2.4 Gy fractions in 15 fraction delivered 5 days a week. Heterogeneity of -5% to +10% is permitted provided that normal-tissue constraints are met. Ninety-five percent of the PTV should receive at least 99% of the dose. If planned using 3D-CRT, then 95% of PTV may receive at least 95% of the dose. Photon beams of 6MV or higher should be used.

5.1.2.1 Localization, Simulation and Immobilization

Treatment on this protocol requires placement of 3-5 gold radio-opaque fiducials for targeting purposes. These will be placed intratumorally or peripheral to the tumor under endoscopic ultrasound guidance. If surgical resection is aborted or a bypass procedure is conducted, fiducials may also be implanted intraoperatively. Fiducials will be used as a surrogate for targeting the tumor. IMRT will be planned based on a helical pancreatic protocol CT (3-D or 4-D) obtained in the treatment position following administration of oral (VoLumen is recommended) and intravenous contrast. If IMRT is not an option for the patient, may plan using 3D-CRT. Simulation scan slice thickness must be no greater than 2.5 mm, and the contouring can be done every other slice with interpolation if desired. Patients will be simulated (and treated) supine with arms up. Immobilization is required. A thorax board is recommended.

5.1.2.2 Treatment Planning/Target Volumes

The gross tumor volume (GTV) will be the primary tumor plus any involved (≥1.5 cm) regional lymph nodes identifiable on CT or MRI scan. The clinical target volume (CTV) will be defined as the GTV

plus 0.5 cm. The planning target volumes (PTV) will be the CTV plus 0.5 cm.

5.1.2.3 Breathing Motion Management

Two motion management methods are allowed in this trial:

- Breath-hold with the use of Active Breathing Control (ABC) or feedback-assisted voluntary breath-hold.
- Incorporation of an internal target volume (ITV) into the PTV based on tumor, diaphragmatic or abdominal wall excursion on 4D-CT.

For any breathing management method, pre-treatment image guidance to an appropriate anatomic surrogate is required on each fraction. Appropriate surrogates include the vertebral bodies adjacent to the PTV for ABC treatments. If in-room CT scanning is used, soft tissue may be selected but appropriate documentation must be provided that the pancreatic tumor itself is properly positioned.

5.1.2.4 Critical Structures

The normal structures to be contoured include: left and right kidneys, liver, stomach, duodenum, small intestine, spinal cord. If the duodenum is invaded by the tumor, the normal duodenum outside of this region should be contoured as the critical structure.

Normal-tissue dose-volume constraints are as follows:

Structure	Constraints
Kidney (L & R)	Max dose ≤20Gy; not more than 10% of the volume can be between 18 and 20Gy
Liver	Mean dose≤30 Gy
Stomach Small intestine	Max dose ≤54Gy; 2% of the volume can be between 50 and 54Gy, 25% of the volume can be between 45 and 54Gy
Spinal cord	Max dose ≤45Gy
Duodenum	Max dose ≤55Gy; not more than 30% of the volume can be between 45 and 55Gy

5.1.3 Gemcitabine

5.1.3.1 Formulation

Gemcitabine is an antineoplastic agent that is structurally related to cytarabine. It is a pyrimidine analogue that is cell-cycle specific. Gemcitabine is available commercially as a lyophilized powder in sterile vials containing 200 mg or 1 gram of gemcitabine as the

hydrochloric salt (expressed as the free base) formulated with mannitol and sodium acetate.

5.1.3.2 Mechanism of Action

Gemcitabine is cytotoxic to cells undergoing DNA synthesis (S-phase) and also blocks the progression of cells through the G1/S- phase boundary. Gemcitabine is converted intracellularly to gemcitabine-5'-triphosphate, its active form. Steady-state plasma levels of gemcitabine occur within 15 minutes after starting the infusion. The elimination half-life of gemcitabine ranges from 32 to 638 minutes, depending on the age and gender of the patient and the rate of administration of gemcitabine.

5.1.3.3 Preparation and Administration

The lyophilized product should be stored at controlled room temperature (20-25°C or 68-79° F). Once the drug has been reconstituted, it should be stored at controlled room temperature and used within 24 hours. The manufacturer recommends solutions of gemcitabine not be refrigerated as crystallization may occur. Drug vials will be reconstituted with normal saline added to the vial to make a solution ideally containing 10 mg/mL. The concentration for 200 mg and 1g vials should be no greater than 40 mg/mL. An appropriate amount of drug will be prepared with normal saline and administered as a 30-minute intravenous infusion on days 1, 8, 15 of the treatment cycle.

5.2 Definition of Dose-Limiting Toxicity (DLT)

- Grade ≥ 4 thrombocytopenia or anemia
- Grade 3 thrombocytopenia associated with bleeding
- Grade ≥ 3 febrile neutropenia
- ANC < 100 for ≥ 3 days
- ANC < 500 for ≥ 5 days
- Any non-hematologic grade ≥ 3 will be dose-limiting with the exception of Grade 3 nausea, vomiting, and diarrhea that resolves within 5 days
- Grade 4 toxicity

Management and dose modifications associated with the above adverse events are outlined in Section 6.

5.3 Maximum Tolerated Dose (MTD)

The MTD is defined to be the dose level of veliparib that when administered to a patient twice a day, orally, results in a probability equal to $\theta = 0.25$ that a dose limiting toxicity

(section 5.2) will be manifest within 6 weeks (treatment cycle). The dose escalation will follow a Bayesian method permitting precise determination of the therapeutic working-dose while directly controlling the likelihood of an overdose. The method is an extension of EWOC (Escalation With Overdose Control) see (50-54) for a review of EWOC), where we model the time to DLT using a proportional hazards model with constant baseline hazard rate. Patients are allowed to enter the trial at any time and the dose allocated to the next patient is determined based on all available data from all previously treated and current patients under observation. The defining property of EWOC is that the expected proportion of patients treated at doses above the MTD is equal to a specified value α, the *feasibility bound*. This value is selected by the clinician and reflects his/her level of concern about overdosing. Zacks et al. showed that among designs with this defining property, EWOC minimizes the average amount by which patients are under dosed. This means that EWOC approaches the MTD as rapidly as possible, while keeping the expected proportion of patients overdosed less than the value α.

The dose for the first patient in the trial will be 20 mg BID**,** previous results indicating this to be a safe dose. The dose for each subsequent patient will be determined so that, on the basis of all available data, the probability that it exceeds the MTD is equal to a pre-specified value *α*. In this trial, we start at α = 0.25 and increase α in small increments of 0.05 until α = 0.5, this value being a compromise between the therapeutic aspect of the agent and its toxic side effects. Chu et al. showed that in general, this design provides a better safety protection in limiting higher dose for patients than four versions of CRM designs with a similar convergence rate. The prior distribution of the MTD is based on the correlated priors model M*4* where the support of the MTD is (0, ∞). The *a priori* probability that the MTD exceeds 100 mg is 10%.

5.4 General Concomitant Medication and Supportive Care Guidelines

In case participants develop nausea/vomiting/diarrhea or myelosuppression, supportive medications will be prescribed as per Clinical Center and ASCO guidelines (see Section 6.4 for Supportive Care guidelines).

5.5 Criteria for Subject Withdrawal

In the absence of treatment delays due to adverse events, treatment may continue until one of the following is met:

- Disease progression
- Grade 4 toxicity
- Intercurrent illness that prevents further administration of all protocol treatment,
- Experiencing DLT(s), which in the opinion of the PI precludes resuming treatment with dose reduction due to unfavorable risk-benefit ratio
- Patient decides to withdraw from the study
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator
- Subject unable to comply with protocol

The reason for study removal and the date the patient was removed must be documented in the source and recorded on the Case Report Form. When a subject discontinues/withdraws study treatment prior to study completion, the subject will immediately enter the follow-up phase of the study unless the PI determines that no additional data are required from the subject's participation. Any data collected prior to the date of discontinuation/withdrawal will be retained.

5.5.1. Exceptions to Cessation of Therapy

Patients who have experienced substantial clinical benefit in the form of reduction in tumor burden, who develop manageable, but increased toxicity that would otherwise require cessation of therapy, will be reviewed on an individual basis and patient may be allowed to continue on therapy for the duration of the study at the discretion of the investigator. The investigator must document a note describing the benefit/risk consideration to the medical chart in these circumstances. In addition, investigator may allow a patient to remain on study if they have had significantly improved symptoms in the face of possible progressive disease, considering the lack of other therapeutic options for this patient population. In this eventuality, the patient will be reported as progressive disease at the time of that assessment when study data is reported.

5.6 Duration of Follow Up

Patients will be treated for 3 weeks and will be followed for an additional 23 weeks after the last dose of veliparib or until death. After Week 26, telephone follow-up will occur every 3 months for 2 years, every 4 months during year 3, and annually thereafter. Patients removed from study for unacceptable adverse events will be followed until resolution or stabilization of the adverse event (until grade $\leq$1 or baseline) or until death.

6. DOSING DELAYS/DOSE MODIFICATIONS

6.1 Veliparib dose delays/reductions

Any subject who experiences Grade 3 or 4 toxicity felt at least possibly attributable to veliparib, with the exception of asymptomatic grade 3 lymphopenia, will stop veliparib until the toxicity resolves to $\leq$ Grade 1 or baseline at time of study entry. After recovery, the subject will be allowed to resume veliparib at 1 dose level below the current level). Any dose reduction below dose level 1 will result in veliparib discontinuation. At the investigator's discretion, gemcitabine and radiotherapy may continue after veliparib has been discontinued.

Note: In instances when patients experience Grade 3 or 4 toxicity that is at least possibly related to veliparib but the investigator determines that the patient has experienced substantial clinical benefit which outweighs any potential risk as described in Section 5.5.1, patients will continue and/or resume veliparib at the

starting dose per the investigator's discretion. A dose reduction is not required in these instances.

6.2 Gemcitabine dose delays/reductions

Protocol treatment will be dose modified at the discretion of the treating oncologist based on criteria outlined in the dose modification table (6.2.6).

Dose modifications can occur based on clinical evaluation at any point during the course of treatment and laboratory evaluations on Days 1, 8 and 15 of the cycle.

Any grade 3 adverse event may be cause for gemcitabine to be withheld. Any grade 2 toxicity could be cause for dose modifications, at the discretion of the treating physician.

Non-hematological Grade 2 adverse event may be cause to reduce the dose of gemcitabine by one dose level and maintained throughout therapy. This will be at the discretion of the treating physician.

If ANC is < 500 or platelets < 50 K, or the patient experiences febrile neutropenia, gemcitabine will be held until recovery per dose reduction guidelines below.

Erythropoietin is allowed. Myeloid growth factors should not be used prophylactically but may be utilized to treat grade 3-4 ANC.

Gemcitabine dose reduction guidelines:

	Gemcitabine dose levels
Level 0 (Starting dose)	1000 mgm2
Level -1	750 mg/m2
Level -2	500 mg/m2
Level -3	400 mg/m2
Level -4	250 mg/m2

Absolute granulocyte Count ($x\ 10^6$/L)		Platelet count ($x\ 10^6$/L)	% of full dose
≥1000	And	≥100,000	100
500 to 999	Or	50,000 to 99,999	75
<500	Or	<50,000	Hold

6.3 Radiation dose delays/reductions

Holding of radiation will be at the discretion of the treating radiation oncologist; missed dosing will be made up at the discretion of the treating radiation oncologist.

All grade 4 discontinuations and/or toxicities will be reviewed by the principal investigator to determine if patients should remain on study with appropriate dose adjustments. Radiation will be continued unless toxicity is possibly related to radiation treatment; for example, diarrhea, intractable nausea and/or vomiting, and/or unable to maintain 30% of their body weight during treatment. If these toxicities are thought to be caused by radiation then radiation treatment will be delayed until these toxicities are grade 1 or less. Dose reduction or withholding of gemcitabine does not necessarily preclude treatment with radiation.

Toxicity	**Parameters**	**Agent**	**Modification**
Gastrointestinal*	≥ Grade 3	RT	Hold until AE has resolved to ≤ Grade 1

*nausea, vomiting, dehydration, diarrhea, fatigue, gastric or duodenal ulceration or bleeding

6.4 Supportive Care

6.4.1 Diarrhea. Patients will be instructed to begin taking loperamide at the earliest signs of (1) a loose stool, (2) occurrence of 1-2 more bowel movements than usual in one day, or (3) unusually high volume of stool. Patients will be instructed to take loperamide as follows: 4 mg at the first onset of diarrhea, then 2 mg every 2 hours around the clock until diarrhea-free for at least 12 hours. Additional antidiarrheal medications such as lomotil or tincture of opium may be used at the discretion of the treating physician.

6.4.2 Nausea/Vomiting: Patients will be provided with a prescription for prochlorperazine and/or ondansetron prn at initiation of treatment and instructed on optimizing anti-emetic therapy. If patient continues to experience nausea and vomiting despite optimal treatment additional anti-emetics would be added to patient‟s regimen. These could include but are not limited to 5-HT3 receptor antagonists, steroids, or lorazepam. Intravenous fluids will be administered as needed at the discretion of the treating physician for continued nausea and vomiting causing dehydration.

6.4.3 Rash: Patients who develop topical rash may be treated with topical emollients (such as Aquaphor) as well as topical steroids or antihistamine agents if appropriate. If rash persists despite above measures, doxycycline 100 mg po bid may be prescribed at the discretion of the treating physician.

7. ADVERSE EVENTS: DEFINITIONS AND REPORTING REQUIREMENTS

7.1 Definitions

7.1.1 **Adverse Event (AE or Adverse Experience):** Any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. Therefore, an AE can 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 considered related to the medicinal (investigational) product (attribution of unrelated, unlikely, possible, probable, or definite).

7.1.2 **Unanticipated Problems**

An unanticipated problem involving risk to subjects or others (UP) is defined as any unexpected incident, event, or problem that is related or possibly related to the research and poses greater risk of harm than was previously known to an individual or group of individuals (including research subjects, research staff, or others not directly involved in the research).

Examples of Unanticipated Problems may include:

- Adverse Events
- Subject complaints
- Medication or device errors
- Other errors in the conduct of the research
- Protocol deviations or violations
- Protocol exceptions (changes made to the research without prior approval in order to eliminate apparent immediate harm to subjects)
- Breach of confidentiality
- Billing problems that pose unanticipated financial risk to subjects

7.1.3 **Serious Adverse Event (SAE):** Any adverse event occurring at any dose that results in **ANY** of the following outcomes:

1) Death.
2) A life-threatening adverse drug experience.
3) Inpatient hospitalization or prolongation of existing hospitalization (for >24 hours).
4) A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
5) A congenital anomaly/birth defect.
6) Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition

7.1.4 Severity vs. Seriousness

Severity is not synonymous with seriousness. SAE is based on patient/event outcome or action criteria usually associated with events that pose a threat to a patient's life or functioning. **Seriousness** (not severity) serves as a guide for defining regulatory reporting obligations. SAEs need to fulfill additional reporting process (reported to corporate global drug safety group or pharmacovigilence group, regulatory authorities, IRBs). On the other hand, **Severity** of an AE is a point on a scale of intensity of the adverse event in question. See Section 7.3 below for the severity grading system.

7.1. 5 Pregnancy

Pregnancy will be recorded as an AE of special interest with immediate notification in all cases. It will be qualified as a SAE only if meeting one of the seriousness criteria. Pregnancy occurring in a female partner of a male participant in the clinical trial should also be collected.

In the event of pregnancy, Investigational Product should be discontinued and the Sponsor informed immediately.

Follow-up of pregnancy will be mandatory until its outcome has been determined.

7.2 Data Collection Procedures for Adverse Events

The principal investigator is responsible for evaluating all adverse events, obtaining supporting documents, and determining that documentation of the event is adequate. He/she is responsible for determining the seriousness, severity, and relationship of the adverse event to the investigational drug. The principal investigator may delegate these duties to sub-investigators and must assure that these sub-investigators are qualified to perform these duties under the supervision of the principal investigator. All adverse events will be documented in the subject's source and recorded on Case Report Form(s).

The term of the adverse event should reflect the diagnosis rather than its symptoms, when available. In the event of death, the cause of death should be recorded as the adverse event. The detailed description of the event will include appropriately graded severity of the adverse event and its relationship to the study drug.

"Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or SAE. However, the signs and symptoms and/or clinical sequelae resulting from lack of efficacy will be reported if they fulfill the definition of an AE or SAE.

Events that **do not** meet the definition of an AE include:

- Any clinically significant abnormal laboratory finding or other abnormal safety assessments that is associated with the underlying disease, unless judged by the investigator to be more severe than expected for the subject's condition.
- The disease/disorder being studied, or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the subject's condition
- Medical or surgical procedure (e.g., endoscopy, appendectomy); the condition that leads to the procedure is an AE
- Situations where an untoward medical occurrence did not occur (social and/or convenience admission to a hospital)
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen

7.3 Grading and Attribution

Grading (severity grading): Terminology Criteria for Adverse Events will be evaluated using the following criteria (The NCI Common Toxicity Criteria, Version 4.0 shall be used):

- **Grade 1 - Mild**: Awareness of symptom, but easily tolerated; usually transient requiring no special treatment; does not interfere with usual status or activities
- **Grade 2 – Moderate:** May be ameliorated by simple therapeutic measures; may interfere with usual activities
- **Grade 3 – Severe:** Incapacitating, inability to perform usual activities
- **Grade 4 – Life-threatening/Disabling:** Subject was at risk of death or significant disability at the time of the event
- **Grade 5 – Death** related to AE

Attribution is an assessment of the relationship between the AE/SAE and the medical intervention**.** Although all of the drugs used in this study have been used in man before, this combination of drugs has not, therefore the phase 1 study is considered a "first in human" study and therefore **all adverse events should be considered relevant to determining dose-limiting toxicities and to reporting unless the event can clearly be determined to be unrelated to the study drug.** Relationship of the adverse event to the investigational drug will be determined by the principal investigator, or qualified designee, and will be categorized as:

Relationship	Attribution	Description
Unrelated to investigational agent/intervention[1]	Unrelated	The AE is clearly ***NOT* related** to the intervention

	Unlikely	The AE is ***doubtfully related*** to the intervention
Related to investigational agent/intervention[1]	Possible	The AE ***may be related*** to the intervention
	Probable	The AE is ***likely related*** to the intervention
	Definite	The AE is ***clearly related*** to the intervention

[1]**NOTE**: AEs listed as possibly, probably, or definitely related to the investigational agent/intervention are considered to have a suspected reasonable causal relationship to the investigational agent/intervention. For routine, adverse event reporting purposes, "Attribution" defines the relationship between the adverse event and the investigational agent(s)/intervention. Additional Instructions and Guidelines that can be found at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/cdus_ig_3r4.pdf.

7.4 Reporting Guidelines

All serious adverse events (SAE) regardless of causality must be documented according to the table outlined in section 7 above. Criteria for reporting are outlined below.

Phone number for Expedited reporting –
Richard Tuli, MD: (310) 423-8077

Alternate phone number for expedited reporting –
Andrew Hendifar, MD (310) 423-2217

Serious adverse events, occurring after the informed consent is signed but prior to the initial dose of the investigational product will be collected as part of the subject's medical history/baseline symptoms but will only be reportable if they are considered by the Investigator to be causally related to required research procedures.

Non-serious adverse events (AEs) and serious adverse events (SAEs) will be collected throughout the treatment period and DLT evaluation phase (21 days after last dose of study drug) through the Week 10 evaluation. Events occurring during this period must be followed until resolution or death unless in the Investigator's opinion, the condition is unlikely to resolve due to the patient's underlying disease. After the Week 10 evaluation, any adverse event documented in the subject's medical record as being at least possibly related to study intervention will also be recorded in the Case Report Form.

SAEs must be reported to oversight agencies as described below.

7.4.1 Reporting to the FDA

The sponsor-investigator must notify the FDA of potential serious risks, from clinical

trials or any other source, as soon as possible, ***but in no case later than 15 calendar days after the sponsor determines that the information qualifies for reporting as defined below.***

Requirements for reporting:

(i) Serious and unexpected suspected adverse reaction. The sponsor-investigator must report any suspected adverse reaction that is both serious and unexpected. The sponsor must report an adverse event as a suspected adverse reaction only if there is evidence to suggest a causal relationship between the drug and the adverse event, such as:

a. A single occurrence of an event that is uncommon and known to be strongly associated with drug exposure (e.g., angioedema, hepatic injury, Stevens-Johnson Syndrome);

b. One or more occurrences of an event that is not commonly associated with drug exposure, but is otherwise uncommon in the population exposed to the drug (e.g., tendon rupture);

c. An aggregate analysis of specific events observed in a clinical trial (such as known consequences of the underlying disease or condition under investigation or other events that commonly occur in the study population independent of drug therapy) that indicates those events occur more frequently in the drug treatment group than in a concurrent or historical control group.

(ii) Increased rate of occurrence of serious suspected adverse reactions. The sponsor-investigator must report any clinically important increase in the rate of a serious suspected adverse reaction over that listed in the protocol or investigator brochure.

Unexpected fatal or life-threatening suspected adverse reaction reports. The sponsor-investigator must also notify FDA of any unexpected fatal or life-threatening suspected adverse reaction ***as soon as possible but in no case later than 7 calendar days after the sponsor's initial receipt of the information.***

Submission of safety reports. All safety reports will be submitted to the FDA on the FDA Form 3500A mandatory MedWatch form. In each safety report, the sponsor-investigator must identify all IND safety reports previously submitted to FDA concerning a similar suspected adverse reaction, and must analyze the significance of the suspected adverse reaction in light of previous, similar reports or any other relevant information. Reports should go to Center for Drug Evaluation and Research or in the Center for Biologics Evaluation and Research that has responsibility for review of the IND at:

Food and Drug Administration

Center for Drug Evaluation and Research
Central Document Room
5901-B Ammendale Road
Beltsville, MD 20705

Upon request from FDA, the sponsor must submit to FDA any additional data or information that the agency deems necessary, as soon as possible, but in no case later than ***15 calendar days after receiving the request***. Relevant follow-up information to an IND safety report must be submitted as soon as the information is available and must be identified as such, i.e., "Follow-up IND Safety Report."

If the results of a sponsor's investigation show that an adverse event not initially determined to be reportable under paragraph (c) of this section is so reportable, the sponsor must report such suspected adverse reaction in an IND safety report as soon as possible, but in no case later than 15 calendar days after the determination is made.

7.4.2 Reporting to the Institutional Review Board

The CSMC IRB requires that investigators report all adverse events that may represent an unanticipated problem involving risks to subjects or others as defined below.

All adverse events (those involving subjects who were enrolled at CSMC), that have a reasonable possibility of relationship to the study AND meet the following criteria must be reported to the IRB:

- Unanticipated (regardless of severity); OR
- Anticipated and serious

All reportable events should be ***submitted in Webridge*** to the Office of Research Compliance and Quality Improvement ***as soon as possible, but no more than 10 days from the investigator's awareness of the event***.

The report must contain at least:

- Identification of the PI, study coordinator (if applicable), contact information, study title, and IRB number.
- A detailed summary of the problem, including all relevant details and the PI's assessment of the events leading up to the problem, to assist the IRB in its evaluation.
- A description of any action taken to address or remedy the problem, including a description of the resolution, if any, or current status.
- An assessment as to whether any changes are required in the conduct of the research to resolve the problem or prevent further problems.

7.4.3 Reporting to Drug Manufacturer (AbbVie)

Principal Investigator to report all serious adverse drug experiences as defined in Section 7.4.1 (Reporting to FDA) to AbbVie within twenty-four (24) hours of learning of the event.

AbbVie's contact for reporting serious adverse drug experiences:
AbbVie Oncology Safety Management, AbbVie, Inc. Dept. R477, Bldg. AP30, 1 N. Waukegan Road, North Chicago, IL 60064,
Fax: 847-775-6706, Email: oncology.safety@abbvie.com.

In addition, the PI must notify AbbVie, at least one time per year, of all non-serious adverse events that: (a) are grade 3-4 toxicity, or (b) result in a subject's premature discontinuation of the study.

8. PHARMACEUTICAL INFORMATION

A list of the adverse events and potential risks associated with the investigational or commercial agents administered in this study can be found in Section 7.1. Veliparib will be supplied as an investigational agent, by AbbVie and at no cost to subjects.

8.1 Veliparib (ABT-888)

Chemical Name: 2-[(R)-2-methylpyrrolidin-2-yl]-1H-benzimidazole-4-carboxamide
Other Names*:* A-861695.0
Classification: Poly (ADP-ribosome) polymerase (PARP) Inhibitor
Molecular Formula: $C_{13}H_{16}N_4O$ **M.W**.: 244.29
Description: White opaque capsule
How Supplied: Veliparib is supplied by AbbVie to investigators as a 10, 20, 40 and 50 mg immediate release capsule. Each HDPE bottle contains 16 capsules.
Storage: Store intact bottles between 15° and 25°C (59° – 77°F),; protect from heat and moisture.
Stability: Shelf-life stability studies for veliparib capsules are ongoing.
Route(s) of Administration: Oral. Veliparib capsules may be administered without regard to meals.

8.2 Commercial Agent(s)

8.2.1 Gemcitabine will be commercially available

Product description: Gemcitabine is an antineoplastic agent that is structurally related to cytarabine. It is a pyrimidine analogue that is cell-cycle specific. Gemcitabine is available commercially as a lyophilized powder in sterile vials containing 200 mg or 1 gram of gemcitabine as the hydrochloric salt (expressed as the free base) formulated with mannitol and sodium acetate.

Solution preparation: The lyophilized product should be stored at controlled room temperature (20-25°C or 68-79° F). Once the drug has been reconstituted, it should be stored at controlled room temperature and used within 24 hours. The manufacturer recommends solutions of gemcitabine not be refrigerated as crystallization may occur. Drug vials will be reconstituted with normal saline added to the vial to make a solution ideally containing 10 mg/mL. The concentration for 200 mg and 1g vials should be no greater than 40 mg/mL.

Route of administration: An appropriate amount of drug will be prepared with normal saline and administered as a 30-minute intravenous infusion.

9. EXPECTED ADVERSE EVENTS

9.1 Comprehensive Adverse Events and Potential Risks for VELIPARIB

The Comprehensive Adverse Event and Potential Risks list (CAEPR) provides a single, complete list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. In addition to the comprehensive list, a subset, the Agent Specific Adverse Event List (ASAEL), appears in a separate column and is identified with ***bold*** and ***italicized*** text. This subset of AEs (the ASAEL) contains events that are considered 'expected.'

Adverse Events with Possible Relationship to Veliparib (ABT-888) (CTCAE 4.0 Term) [n= 565]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
	Anemia		*Anemia (Gr 3)*
	Febrile neutropenia		*Febrile neutropenia (Gr 3)*
GASTROINTESTINAL DISORDERS			
	Abdominal pain		
	Constipation		*Constipation (Gr 2)*
	Diarrhea		*Diarrhea (Gr 2)*
Nausea			*Nausea (Gr 2)*
	Vomiting		*Vomiting (Gr 2)*
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
Fatigue			*Fatigue (Gr 2)*
INVESTIGATIONS			
	Lymphocyte count decreased		*Lymphocyte count decreased (Gr 3)*
Neutrophil count decreased			*Neutrophil count decreased (Gr 4)*
Platelet count decreased			*Platelet count decreased (Gr 4)*
	Weight loss		*Weight loss (Gr 2)*
	White blood cell decreased		*White blood cell decreased (Gr 4)*
METABOLISM AND NUTRITION DISORDERS			
	Anorexia		*Anorexia (Gr 2)*
	Dehydration		*Dehydration (Gr 2)*
	Hypophosphatemia		*Hypophosphatemia (Gr 2)*
NERVOUS SYSTEM DISORDERS			
	Dizziness		
	Dysgeusia		*Dysgeusia (Gr 2)*
	Headache		*Headache (Gr 2)*
		Seizure	
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
	Rash maculo-papular		
VASCULAR DISORDERS			
		Thromboembolic event[4]	

Also reported on veliparib trials but with the relationship to veliparib still undetermined:

CARDIAC DISORDERS - Left ventricular systolic dysfunction
EAR AND LABYRINTH DISORDERS - Vertigo
EYE DISORDERS - Blurred vision
GASTROINTESTINAL DISORDERS - Abdominal distension; Colitis; Dry mouth; Dyspepsia; Dysphagia;
Enterocolitis; Flatulence; Gastroesophageal reflux disease; Gastrointestinal disorders - Other (mouth ulceration);
Lower gastrointestinal hemorrhage; Mucositis oral; Small intestinal obstruction
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Chills; Edema limbs; Fever; Non-cardiac
chest pain; Pain
HEPATOBILIARY DISORDERS - Hepatic failure
INFECTIONS AND INFESTATIONS - Lymph gland infection; Skin infection; Upper respiratory infection
INJURY, POISONING AND PROCEDURAL COMPLICATIONS - Bruising

INVESTIGATIONS - Alkaline phosphatase increased; Blood bilirubin increased; Creatinine increased;
Electrocardiogram QT corrected interval prolonged
METABOLISM AND NUTRITION DISORDERS - Hyperglycemia; Hypernatremia; Hypoalbuminemia;
Hypocalcemia; Hypokalemia; Hypomagnesemia; Hyponatremia
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Arthralgia; Back pain; Bone pain;
Generalized muscle weakness; Musculoskeletal and connective tissue disorder - Other (muscle spasms);
Myalgia; Pain in extremity
NERVOUS SYSTEM DISORDERS - Ataxia; Depressed level of consciousness; Lethargy; Paresthesia; Peripheral
sensory neuropathy; Syncope
PSYCHIATRIC DISORDERS - Anxiety; Confusion; Depression; Insomnia; Psychosis
RENAL AND URINARY DISORDERS - Hematuria
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Cough; Dyspnea; Epistaxis; Hypoxia;
Pharyngolaryngeal pain; Pleural effusion; Respiratory failure
SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Alopecia; Dry skin; Hyperhidrosis; Palmar-plantar
erythrodysesthesia syndrome; Pruritus; Purpura
VASCULAR DISORDERS - Hot flashes; Hypotension; Vascular disorders - Other (brainstem infarction)

Animal Data: veliparib has been administered to humans in a limited fashion as part of a phase 0 and 5 phase 1 studies and a limited number of toxicities have been seen. However, the following toxicities have been observed in animal studies:

Dogs: Increased salivation; ataxia; decreased activity; tremors; decreased reticulocytes; convulsions/seizure.

Rats and Mice: Mild hypothermia; decreased muscle tone; mild miosis (CNS effects); abnormal gait; mild sedation followed in time by mild excitation.

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

9.2 Adverse Event List(s) for Gemcitabine

The major side effects observed with gemcitabine include leukopenia, thrombocytopenia, anemia, and a collection of signs and symptoms referred to

collectively as a flu-like syndrome with fever, headache, rigors, nausea, diarrhea, itchy skin rash, myalgia, and anorexia. Other side effects have included fatigue, peripheral edema, and proteinuria. Less likely side effects include abnormal renal and liver function tests, vomiting, constipation, malaise, and anorexia. Rare side effects include Stevens-Johnson syndrome (severe skin reaction) and shortness of breath, cough, inflammation or scarring of the lung. Rare side effects have included hemolytic uremic syndrome/renal failure and liver failure have occurred following therapeutic gemcitabine therapy. Cardiac dysfunction (myocardial infarction, congestive heart failure, and atrial fibrillation) have been infrequently reported.

9.3 Adverse Event List(s) for Radiation Therapy

Toxicities commonly associated with external beam radiation to pancreatic tumors includes nausea, vomiting, anorexia and weight loss. Severe side effects such as gastrointestinal (GI) obstruction, perforation, or hemorrhage are uncommon complications, occurring in <5% of patients undergoing standard radiation therapy for pancreatic cancer. It is important to note that vomiting, GI obstruction, GI hemorrhage, anorexia and weight loss are also commonly associated with pancreatic cancer progression. Clinical and radiographic assessments will be performed in an effort to identify these effects, ascertain their etiology and provide the most appropriate palliative measures. Hepatic and renal toxicity is not anticipated given the expectation of limited incidental irradiation of these organs. Complications, if any, will be graded according to the CTCAE, National Cancer Institute, version 4.0.

10. DRUG ACCOUNTABILITY

Gemcitabine
Gemcitabine will be maintained and dispensed according to institutional guidelines.

Veliparib (ABT-888)
Upon receipt of a shipment of veliparib, the pharmacist will 1) open and inspect the shipment; 2) verify that the veliparib has been received intact, in the correct amounts, and at the correct address and; 3) sign and date the Proof of Receipt (POR) or similar documentation accompanying the shipment. All study drugs must be retained in the designated secure area under proper storage conditions.

An accurate running inventory of veliparib will be kept by the pharmacist and will include the lot number, POR numbers, the bottle/carton numbers, and the date veliparib, was dispensed for each subject. Upon completion or termination of the study, all original bottles/cartons containing unused veliparib will be returned to AbbVie according to AbbVie's instructions, or if pre-arranged between AbbVie and CSMC, destruction of used and unused veliparib, will be performed at the CSMC.

The investigator or his or her designated representative agrees not to supply veliparib, to any persons not enrolled in the study or not named as a subinvestigator listed on the FDA 1572. The

CSMC pharmacist will record the bottle number and dose of veliparib given to each subject in the source documents.

11. CORRELATIVE/SPECIAL STUDIES

Blood samples, flash frozen and archival tumor tissue will be collected for each patient. Tissue will be transported to Dr. Tuli's laboratory at Cedars Sinai Medical Center for assessment.

11.1 Laboratory Correlative Studies

11.1.1 Interrogating DNA damage pathways

11.1.1.1 Rationale

Archival tissue will be interrogated using standard Western blotting, ELISA, PCR and immunohistochemistry techniques for DNA damage repair pathway proteins, including PAR, cleaved-PARP, XRCC1, ERCC1, ATM, ATR, XPF, MLH1, MSH2, γ-H2AX , BRCA1/2, PALB2, PTEN and p53.

11.1.1.2 Collection of Specimen(s)

If consent for enrollment is obtained prior to initial diagnostic biopsy (EGD or CT-guided), this core/fine needle aspiration biopsy specimen will be utilized for laboratory correlative studies. Otherwise, biopsy specimen for correlative studies will be obtained at time of fiducial placement (5.1.2.1). Tissue will obtained from fine needle aspiration using either a 19-22 gauge or 25 gauge needle. Alternatively, tissue will be obtained via core biopsy using a 19-22 gauge needle. Approximately 2-4 passes will be made until adequate specimen is obtained.

11.1.1.3 Handling of Specimens(s)

Half of the specimen will be snap frozen in liquid nitrogen within 30 minutes of performing biopsy to minimize tissue anoxia; specimen will be frozen long-term at -80 ^{o}C in cryovials. The remaining specimen will be fixed in 4% paraformaldehyde.

11.1.1.4 Analysis of Specimen(s)

Frozen tissue specimen will be processed for DNA/protein extraction and isolation; formalin-fixed tissues will be paraffin embedded and sectioned. DNA damage repair proteins will be quantitated using Western, ELISA and immunohistochemistry.

11.1.1.5 Site(s) Performing Correlative Study

Cedars Sinai Medical Center

11.1.2 Evaluating PAR Levels in PBMCs

11.1.2.1 Collection of Specimen(s)
An extra tube of blood (EDTA preserved with anticoagulant – 5 mL) will be drawn once a week during the evaluation period along with the patient's regular labs for research purposes. PAR levels will be assessed using a standardized, commercially available ELISA from Trevigen.

11.1.2.2 Handling of Specimens(s)
Immediately after collection, blood will be centrifuged and plasma collected and aliquoted for storage at -80^{o}C.

11.1.2.3 Site(s) Performing Correlative Study
Cedars Sinai Medical Center

11.1.3 Evaluation of BRCA1/2, PTEN and PALB2

11.1.3.1 Collection of Specimen(s)
0.5 g tumor tissue will be obtained for PCR-based gene sequencing of pancreatic tumors for somatic BRCA1/2 mutational analysis and expression assessment. 3 ml whole blood or extracted DNA with a minimum volume/concentration of DNA of 200 µL @ 4 ng/µl will be obtained for germline BRCA1/2 analysis and PALB2 mutation analysis. 3 to 5 FFPE tissue specimens will be obtained for PTEN IHC analysis.

11.1.3.2 Handling of Specimens(s)
Immediately after collection, blood will be centrifuged and plasma collected and aliquoted for storage at -80oC.

11.1.3.3 Site(s) Performing Correlative Study
Cedars-Sinai Medical Center

11.1.4 Samples, and associated data, will be stored indefinitely in Dr. Tuli's laboratory unless the patient withdraws consent.

11.1.5 The PI will document any destroyed, lost, or otherwise compromised and unused samples.

12. STUDY CALENDAR

Baseline evaluations, excluding diagnostic biopsies, are to be conducted within 4 weeks prior to registration. No protocol-directed screening procedures may be performed prior to obtaining informed consent. Required assessments performed per standard of care prior to consent may be used as baseline evaluations if performed within the screening window. Scans and x-rays must be done ≤6 weeks prior to registration.

Issues that would cause treatment delays after registration should be discussed with the PI. Screening procedures may be repeated prior to treatment as deemed clinically necessary by the treating investigator.

Patients will resume standard of care therapy after week 6 assessment or at the investigator's discretion for those who have been taken off study treatment prior to completing the treatment phase.

Allowable evaluation windows: 1) Treatment phase: +/- 3 business days; 2) Follow-up phase – Weeks (Wk) 4, 5, 6, 8 and 10: +/- 7 business days; and 3) Follow-up Phase – Wks 18 and 26: +/- 14 business days; and 4) Follow-up Phase – Long term telephone follow-up-up: +/- 1 month.

		Treatment Phase			Follow-Up Phase						
Tests, procedures, and Treatment	Baseline	Wk 1	Wk 2	Wk 3	Wk 4	Wk 5	Wk 6	Wk 8[d]	Wk 10	Wks 18 & 26 On Study	Telephone Follow-up[e]
Veliparib		A	A	A							
Gemcitabine		B	B	B							
IMRT		C	C	C							
Diagnostic Biopsy†	X										
Fiducial placement	X										
Rad Onc consultation	X										
Med Onc consultation	X										
Informed Consent	X										
Demographics[f]	X										
Medical History	X										
Concurrent medications	X	X	X	X	X	X	X		X	X	
Physical Exam	X	X	X	X	X	X	X		X	X	
Vital Signs	X	X	X	X	X	X	X		X	X	
Height	X										
Weight	X	X	X	X	X	X	X		X	X	

Performance Status	X	X	X	X	X	X	X		X	X	
CBC w/diff, plts	X	X	X	X	X	X	X		X	X	
Serum chemistry[a]	X	X	X	X	X	X	X		X	X	
Adverse event evaluation	X	X	X	X	X	X	X	X	X	X[g]	X[g]
CT and/or PET scan[h]	X								X	X	
B-HCG	X[b]										
Tumor markers	X								X[c]	X[c]	
Archival tissue	X										
Research blood	X	X	X	X	X	X	X		X	X	

A: *VELIPARIB*: Dose as assigned; *administration schedule*
B: *Gemcitabine*: Dose as assigned*; administration schedule*
C: IMRT: Dose as assigned; *administration schedule.*
a: Albumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, LDH, phosphorus, potassium, total protein, SGOT [AST], SGPT [ALT], sodium.
b: Urine pregnancy test (women of childbearing potential).
c: If associated tumor marker elevated at baseline.
d: Week 8 assessment for adverse events may occur by telephone
e: After Week 26, telephone follow-up will occur every 3 months for 2 years, every 4 months during year 3, and annually thereafter.
f: Subjects will be asked to complete the Demographics Questionnaire
g: Only adverse events documented as being possibly related to study intervention will be recorded in the CRF.
h: Follow-up scans are performed at Weeks 10, 18, and/or 26 as clinically indicated.
† Archival tissue may be collected for confirmation of diagnosis. Biopsy may have been performed at any time prior to enrollment.

13. MEASUREMENT OF EFFECT

For the purposes of this study, patients should be re-evaluated for response 10, 18, and 26 weeks after initiation of therapy per outlined follow-up schedule.

13.1 Antitumor Effect – Solid Tumors

Response and progression will be evaluated in this study using the new international criteria proposed by the Response Evaluation Criteria in Solid Tumors (RECIST 1.1) [57]. Changes in only the largest diameter (unidimensional measurement) of the tumor lesions are used in the RECIST 1.1 criteria.

13.1.1 Definitions

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

Evaluable for objective response. Only those patients who have measurable

disease present at baseline, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for response. These patients will have their response classified according to the definitions stated below. (Note: Patients who exhibit objective disease progression prior to the end of cycle 1 will also be considered evaluable.)

Note: Patients who do not meet criteria as eligible for objective response will be replaced.

13.1.2 Disease Parameters

Measurable disease. Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥10 mm with spiral CT scan. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

Malignant lymph nodes. To be considered pathologically enlarged and measurable, a lymph node must be ≥15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

13.1.3 Methods for Evaluation of Measurable Disease

All measurements should be taken and recorded in metric notation using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 6 weeks before the beginning of the treatment. The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up.

Conventional CT and MRI These techniques 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. Head and neck tumors and those of extremities usually require specific protocols.

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

Endoscopy, Laparoscopy The utilization of these techniques for objective tumor evaluation has not yet been fully and widely validated. Their uses in this specific context require sophisticated equipment and a high level of expertise that may only be available in some centers. Therefore, the utilization of such techniques for objective tumor response should be restricted to validation purposes in reference centers. However, such techniques may be useful to confirm complete pathological response when biopsies are obtained.

Tumor markers Tumor markers alone cannot be used to assess response. If markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response.

Cytology, Histology These techniques can be used to differentiate between partial responses (PR) and complete responses (CR) in rare.

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

a. Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.
b. No FDG-PET at baseline and a positive FDG-PET at follow-up: If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD. If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan). If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.
c. FDG-PET may be used to upgrade a response to a CR in a manner similar to a biopsy in cases where a residual radiographic abnormality is thought to represent fibrosis or scarring. The use of FDG-PET in this circumstance should be prospectively described in the protocol and supported by disease-specific medical literature for the indication. However, it must be acknowledged that both approaches may lead to false positive CR due to limitations of FDG-PET and biopsy resolution/sensitivity.

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

13.1.4 **Response Criteria**

13.1.4.1 Evaluation of Target Lesions

Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.

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

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 or the appearance of one or more new lesions

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

13.1.4.2 Evaluation of Best Overall Response

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

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Response for this Category Also Requires:
CR	CR	No	CR	≥4 wks. confirmation
CR	Non-CR/Non-PD	No	PR	≥4 wks. confirmation
PR	Non-PD	No	PR	
SD	Non-PD	No	SD	documented at least once ≥4 wks. from baseline
PD	Any	Yes or No	PD	no prior SD, PR or CR
Any	PD*	Yes or No	PD	
Any	Any	Yes	PD	

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

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

13.1.5 **Duration of Response**

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

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

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

14. STATISTICAL CONSIDERATIONS

14.1 Study Design

This is a Phase I study of veliparib in combination with gemcitabine and radiation therapy in patients with locally advanced pancreatic cancer. The dose escalation portion of the study will be used to determine the maximum tolerable dose (MTD) of veliparib in combination with radiation and gemcitabine.

14.2 Primary Objectives

1. Determine the maximum tolerable dose of veliparib in combination with gemcitabine and intensity modulated radiation therapy in patients with locally advanced pancreatic cancer.

2. Determine the safety and toxicity of the combination of veliparib with gemcitabine and radiation therapy in patients with locally advanced pancreatic cancer.

14.3 Secondary Objectives

1. Measure clinical activity of veliparib, gemcitabine and radiation in patients with locally advanced pancreatic cancer by assessing response rates using RECIST 1.1 criteria

2. Evaluate pre-treatment biopsy specimen for baseline levels of various DNA repair proteins (ERCC1, XRCC1, BRCA1, BRCA2, PAR) and assess BRCA1/2, PALB2, P16 and PTEN mutational status.

3. Evaluate PAR levels in peripheral blood mononuclear cells from blood samples.

14.4 Analysis of Primary Endpoints

The aim of this phase I trial is to determine the MTD of veliparib administered orally to patients with locally advanced, unresectable pancreatic cancer. The MTD is defined to be the dose level of veliparib that when administered to a patient twice a day results in a probability equal to $\theta = 0.25$ that a dose limiting toxicity (section 5.2) will be manifest within six weeks.

Escalation Scheme

The dose escalation will follow a Bayesian method permitting precise determination of the therapeutic working-dose while directly controlling the likelihood of an overdose. The method is an extension of EWOC (Escalation With Overdose Control, see (50-54) for a review of EWOC), where we model the time to DLT using a proportional hazards model with constant baseline hazard rate. Patients are allowed to enter the trial at any time and the dose allocated to the next patient is determined based on all available data from all previously treated and current patients under observation, see Appendix D for a detailed description of the model and trial design. The defining property of EWOC is that the expected proportion of patients treated at doses above the MTD is equal to a specified value α, the feasibility bound. This value is selected by the clinician and reflects his/her level of concern about overdosing. Zacks et al. (54) showed that among designs with this defining property, EWOC minimizes the average amount by which patients are underdosed. This means that EWOC approaches the MTD as rapidly as possible, while keeping the expected proportion of patients overdosed less than the value α.

The dose for the first patient in the trial will be 20 mg BID**,** previous results indicating this to be a safe dose. The dose for each subsequent patient will be determined so that, on the basis of all available data, the probability that it exceeds the MTD is equal to a prespecified value α. In this trial, we start at $\alpha = 0.25$ and increase α in small increments of 0.05 until $\alpha = 0.5$, this value being a compromise between the therapeutic aspect of the agent and its toxic side effects. Chu et al. (55) showed that in general, this design provides a better safety protection in limiting higher dose for patients than four versions of CRM designs with a similar convergence rate. The prior distribution of the MTD is based on the correlated priors model M4 described in (52) where the support of the MTD is $(0, \infty)$. After consulting with the PI, we will assume that the a priori probability that the MTD exceeds 100 mg is 10%. Figure 1 shows the prior probability density of the MTD.

The first patient in the trial will be given a dose of 20 mg BID. If this patient experiences DLT any time during the treatment cycle, the second patient will be given a dose of 20 mg BID with a dose reduction of Gemcitabine to 750 mg/m2. If this second patient exhibits DLT any time during the first cycle of therapy, then the third patient will be given 20 mg BID with another dose reduction of Gemcitabine to 500 mg/m2. Gemcitabine dose reductions will continue to 400 mg/m2 and 250 mg/m2. If a patient experiences DLT at 250 mg/m2 then the trial will stop. Otherwise, the trial will proceed using EWOC algorithm using the smallest safe dose of Gemcitabine. The maximum number of patients to be treated simultaneously with unresolved DLT status cannot exceed 3. In other words, if there are three patients currently under study with unresolved

DLT status, a new patient cannot be treated until at least one patient finishes one cycle of therapy. Since the doses in this trial are discrete, at each stage of the trial, the dose recommended by the algorithm for the next patient will be rounded down to the nearest available dose in the trial. No intermediate doses will be introduced in the trial and dose skipping is not allowed.

A minimum of 20 patients and a maximum of 30 patients will be accrued to the trial. Upon completion of the trial, the MTD will be estimated as the median of the marginal posterior distribution of the MTD. The computation of the dose to be administered to each patient and the 95% highest posterior density credible interval estimate of the MTD will be carried out by Drs. Rogatko and Tighiouart with the software WinBUGS (56).

Figure 2 shows an example of a simulated trial when the true value of the MTD $\gamma = 70$ mg and the probability of DLT at the initial dose is 0.05 assuming 30 patients have been enrolled. Patients enter the trial according to a time homogeneous Poisson process with an average number of 3 patients per 6 weeks (1 cycle=6 weeks). The figure shows patients number, the time when they enter the trial, the DLT status and how long it took to exhibit DLT if they did. This shows that in the absence of DLT, the allocated dose tends to go up and the recommended dose drops whenever DLTs are encountered. For example, patient # 1 is given a dose of 20 mg and has no DLT by the end of 6 weeks. Patients 2, 3, 4 were given higher doses because there was no DLT by the time patient # 4 was enrolled. Patients 5 and 6 were still given higher doses because by the time they were enrolled in the trial, patient # 4 did not experience DLT. However, the dose for patient # 7 drops because by the time this patient is enrolled, patient # 4 had exhibited DLT.

Design Operating Characteristics

We simulated 1000 trials under 3 scenarios for the true value of the MTD γ. In each case, the probability of DLT at the initial doe is 0.05, the arrival times follow a time homogeneous Poisson process with rate 3 per cycle. Sample sizes of n=20 and n=30 patients per trial were used. Table 1 shows the summary statistics based on 1000 trials. We can see that the estimated MTD is close to the true underlying γ when $\gamma = 0.4, 0.7$ but the bia is higher when the true MTD is highand the overdose protection property of EWOC is illustrated by the observed rate of DLTs.

Table 1. Design operating characteristics Based on 1000 trial replicates.	True MTD γ		
	40	70	100
Estimated MTD (n=30)	49	71.8	83.9
Proportion of DLT (n=30)	21.1%	16.2%	12.4%
Estimated MTD (n=20)	50.1	70.4	79.6

Proportion of DLT (n=20)	21%	14.7%	11.1%

Figure 1

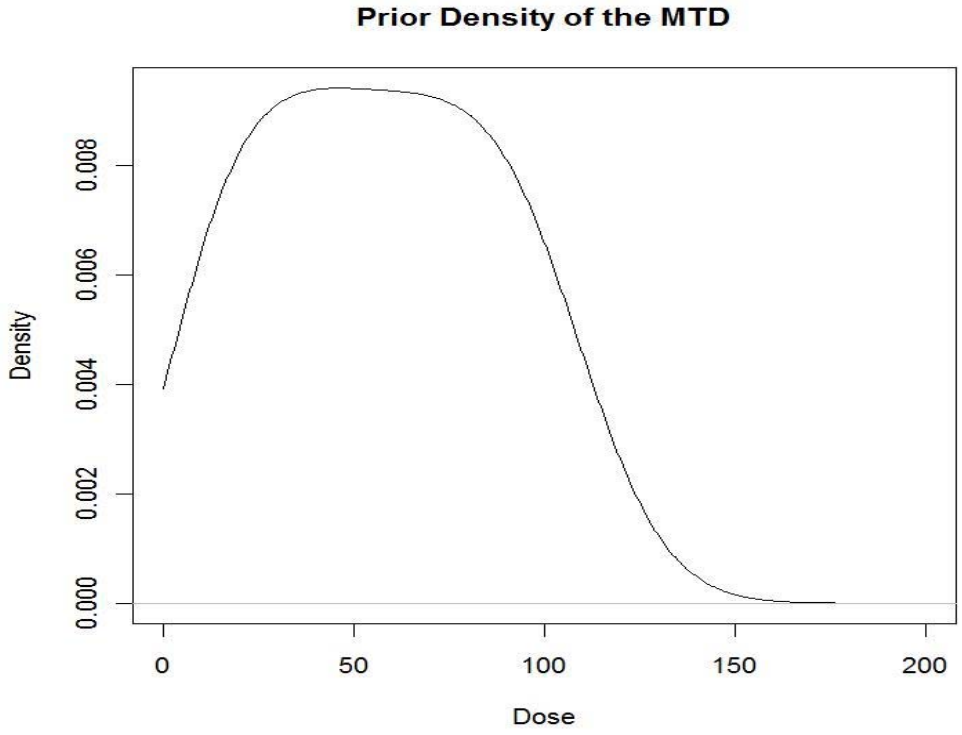
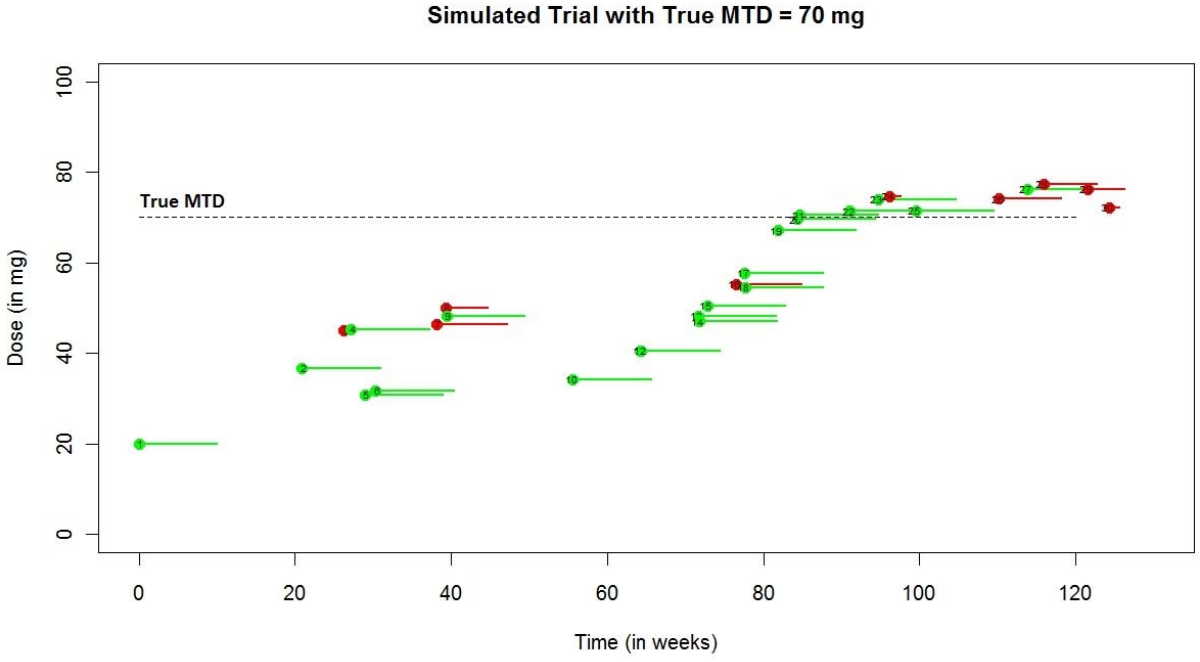


Figure 2



14.5 Analysis of Secondary Endpoints

1. Response and progression will be evaluated in this study using the new international criteria proposed by the revised Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1). Changes in the largest diameter (unidimensional measurement) of the tumor lesions and the shortest diameter in the case of malignant lymph nodes are used in the RECIST criteria. Only those patients who have measurable disease present at baseline, have received at least the entire cycle of therapy, and have had their disease re-evaluated will be considered evaluable for response. These patients will have their response classified according to the definitions stated below. For the purposes of determining response, patients will receive a baseline CT and PET scan within 4 weeks prior to initiating treatment and 10 weeks after initiating treatment. The proportion of individuals with a response (complete, partial) will be calculated with exact 95% confidence intervals. Logistic regression will be used to evaluate the impact of key covariates on response.

   Note: RECIST measurements are completed for data analysis purposes only as part of the secondary objective to assess RECIST as a potential correlate of response to therapy. It is not to be used for real-time clinical decision making. Response and progression are determined by the treating investigator/clinical team.

2. The presence of DNA repair proteins will be determined using immunohistochemical analysis of tissue obtained from initial diagnostic biopsy and categorized by the level of staining: none, mild or strong. Pre-treatment tumor and peripheral blood specimen will be assessed for germline/somatic BRCA1/2, PALB2, P16 and PTEN mutations using quantitative RT-PCR, immunohistochemistry and gene sequencing (Myriad Genetics).

3. Peripheral blood sampling of PBMCs will be performed weekly for 6 weeks from initiation of therapy and again during the weeks 10, 18, and 26 follow ups to measure PAR levels using an established ELISA (Trevigen, Gaithersburg, MD).

4. Technical data related to planning technique, daily patient localization accuracy during treatment, dose distributions delivered, and other data related to the patient imaging will be acquired before, during and after simulation, imaging, and treatment sessions, and analyzed within Eclipse, Mosaiq, Velocity, and other software packages.

14.6 Sample size/Accrual Rate:

A maximum of 30 patients will be accrued to the trial. Approximately 150 patients with resectable, locally advanced and metastatic pancreatic cancer are seen annually at the Cedars-Sinai Medical Center through close collaborative efforts between Radiation, Medical and Surgical Oncology, as well as Gastroenterology, Pathology and Radiology. We estimate that 40% of these patients have locally advanced

unresectable disease. As a result, we believe this patient volume would adequately support the feasibility of our study.

15. Study Monitoring

Safety Committee on Early Phase Studies (SCOEPS)

This protocol will utilize additional oversight by a Safety Committee for Early Phase Studies (SCOEPS). The committee is comprised of experts in the field of oncology early phase studies and biostatistics.

The SCOEPS will provide routine monitoring of safety and enrollment for all early phase investigator-initiated trials (IITs). Generally, the committee is responsible for reviewing and adjudicating all dose-limiting toxicities, dose escalations and appropriateness of the escalation, cohort expansion, subject replacements, select AEs, SAEs, and confirmation of attainment of maximal tolerated dose.

The SCOEPS findings and any concerns and recommendations will be reported in writing to the Principal Investigator. This report will be forwarded by the Principal Investigator or his/her designee to the Cedars-Sinai Medical Center IRB.

APPENDIX A

Performance Status Criteria

Karnofsky Performance Scale	
Percent	Description
100	Normal, no complaints, no evidence of disease.
90	Able to carry on normal activity; minor signs or symptoms of disease.
80	Normal activity with effort; some signs or symptoms of disease.
70	Cares for self, unable to carry on normal activity or to do active work.
60	Requires occasional assistance, but is able to care for most of his/her needs.
50	Requires considerable assistance and frequent medical care.
40	Disabled, requires special care and assistance.
30	Severely disabled, hospitalization indicated. Death not imminent.
20	Very sick, hospitalization indicated. Death not imminent.
10	Moribund, fatal processes progressing rapidly.
0	Dead.

APPENDIX B

Patient's Medication Diary

PATIENT'S MEDICATION DIARY - veliparib
Today's date _____ **Agent**: **veliparib**
Patient Name_____ (*initials acceptable)*
Patient Study ID
_____

INSTRUCTIONS TO THE PATIENT:
1. Complete one form for each cycle.
2. Take your dose of veliparib twice daily twelve hours apart. Take your dose at the same time every day. You should swallow the tablets whole. **Do not chew, crush, or break the tablets.**
3. Record the date, the number of tablets of each size you took, and when you took them.
4. If you have any comments or notice any side effects, please record them in the Comments column.
5. Please return the forms to your physician when you go for your next appointment.

Day	Date	Times medication taken		Comments/Side effects
		AM	PM	
1				
2				
3				
4				
5				
6				
7				
8				
9				
10				
11				
12				
13				
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APPENDIX C

MedWatch Form 3500A (Mandatory Reporting)

http://www.fda.gov/downloads/Safety/MedWatch/HowToReport/DownloadForms/ucm082728.pdf

Appendix D

We model the risk of DLT given dose $h(t|x)$ by assuming that patients given different doses of an agent have proportional risks of DLT. Following Cox proportional hazards model [18], we have

$$h(t \mid x) = h_0(t;\lambda)\exp(\beta \cdot (x - X_{\min})),$$

where $h_0(t; \lambda)$ is the baseline hazard function corresponding to the risk of DLT for a patient given dose $X_{\min}$ and λ is a vector of parameters associated with the parametric baseline hazard.

We assume that $\beta > 0$ so that the hazard of DLT is an increasing function of dose. After enrolling n patients in the trial, the likelihood function for the parameters is

$$L(\beta, \lambda \mid D_n) = \prod_{i=1}^{n} h(Y_i \mid x_i)^{\delta_i} \exp\left\{-\int_0^{Y_i} h(s \mid x_i)ds\right\}.$$

We reparameterize model (2.2) in terms of γ and ρ_0, the probability that a DLT manifests within the first cycle of therapy for a patient given dose $x = X_{\min}$.

Let $g(\rho_0,\gamma)$ be a prior distribution on ρ_0 and γ on $[0, \theta]$x$[X_{\min}, X_{\max}]$. Using Bayes rule, the posterior distribution of the model parameters is proportional to the product of the likelihood and prior distribution

$$\pi(\rho_0, \gamma \mid D_n) \propto L(\rho_0, \gamma \mid D_n) \times g(\rho_0, \gamma).$$

Dose levels in the trial are selected in the interval $[X_{\min}, X_{\max}]$. The adaptive design adapted to this trial proceeds as follows. The first patient receives the dose $x_1 = X_{\min}$. If this patient experiences DLT within the observation window $(0, \tau]$, the second patient will be given the same dose $x_1 = X_{\min}$ with a dose reduction of Gemcitabine to 750 mg/m2. If this second patient exhibits DLT any time during the first cycle of therapy, then the third patient will be given the same dose $x_1 = X_{\min}$ with another dose reduction of Gemcitabine to 500 mg/m2. Gemcitabine dose reductions will continue

to 400 mg/m2 and 250 mg/m2. If a patient experiences DLT at 250 mg/m2 then the trial will stop. Otherwise, the marginal posterior cdf of the MTD given that the first time a patient did not exhibit DLT by the end of the cycle of therapy is denoted by $\Pi_1(\gamma) = \Pi(\gamma \mid (\tau, x_1, 0))$. The second patient receives the dose $x_2 = \Pi_1^{-1}(\alpha)$ so that the posterior probability of exceeding the MTD is equal to the feasibility bound α. This is the overdose protection property of EWOC, where at each stage of the design, we seek a dose to allocate to the next patient while controlling the posterior probability of exposing patients to toxic dose levels. Suppose the kth patient is ready to enter the trial at time t_k. We then calculate $\Pi_{k-1}(\gamma) = \Pi(\gamma \mid (Y_i, x_i, \delta_i), i=1,\ldots,k-1)$ up to time t_k. Note that here, Y_i is either equal to τ if patient i already finished one cycle of therapy with no evidence of DLT by the time patient k is ready to enter the trial, or Y_i is the time since patient i was given dose x_i until time t_k if this patient is still at risk by this time. Otherwise, Y_i is the time to DLT for that patient. The kth patient receives the dose $x_k = \Pi_{k-1}^{-1}(\alpha)$. The trial proceeds until a pre-determined number of patients are enrolled to the trial. At the end of the trial, we estimate the MTD as the median of the posterior distribution of γ.

Design operating characteristics of the method.

We studied the performance of the proposed method called EWOC-PH by comparing its operating characteristics with 3 other designs; EWOC which assumes that the DLT outcome is binary and dose allocation is carried only after the DLT status of all previously treated patients have been resolved, EWOC-NW, which stands for EWOC no-waiting and works just like EWOC except that dose allocation is carried whenever a patient is available for treatment, and TITE-EWOC which stands for time to event EWOC proposed by Mauguen et all. (Mauguen A, Le Deley MC, Zohar S. Dose-finding approach for dose escalation with overdose control considering incomplete observations. *Statistics in Medicine* 2011; **30**: 1584-1594.). Dose levels

were selected in the interval [0, 1]. We considered nine scenarios corresponding to three values for the true MTD $\gamma = 0.3, 0.5, 0.7$ and three values for the accrual rate 1, 2, and 4 patients per unit of time equal to the length of the observation window $[0, \tau]$. The parameter ρ_0 was fixed at 0.05 and the target probability of DLT is $\theta = 0.33$. For each scenario, we simulated $M = 1000$ trials of $n = 48$ patients each. In order to have a fair comparison between the different models and assess the performance of EWOC-PH under model misspecification, we simulated the DLT responses using a baseline Weibull hazard function $h_0(t) = (k/\lambda)\left(t/\lambda\right)^{k-1}$ under the proportional hazards model using λ=1, k=0.8, 1, 1.2. Note that the case $k = 1$ corresponds to the exponential true model for EWOC-PH. We also simulated the DLT responses under a non-proportional hazards model with baseline exponential distribution

$h(t \mid x) = h_0(t)\, e^{\beta_1 x I(t \le t_1) + \beta_2 x I(t > t_1)}, \quad 0 < t_1 < \tau.$ We used $h_0(t) = 0.15$, and two different values for β_2, $\beta_2 = 0.5, 2$. The values for β_1 were selected to match the MTDs with the other models. Specifically, the following six combination were selected: (1) $\gamma = 0.3, \beta_2 = 0.5, \beta_1 = 4.81$, (2) $\gamma = 0.5, \beta_2 = 0.5, \beta_1 = 2.83$, (3) $\gamma = 0.7, \beta_2 = 0.5, \beta_1 = 1.97$, (4) $\gamma = 0.3, \beta_2 = 2, \beta_1 = 4.25$, (5) $\gamma = 0.5, \beta_2 = 2, \beta_1 = 1.97$, (6) $\gamma = 0.7, \beta_2 = 2, \beta_1 = 0.43$. The models were compared with respect to the average bias of the estimate of the MTD, $ave_{bias} = 1/M \sum_{i=1}^{M} (\hat{\gamma}_i - \gamma_{true})$, where $\hat{\gamma}_i$ is the estimate of the MTD for the i-th trial and γ_{true} is the true MTD under a particular scenario, the average proportion of patients exhibiting DLT $1/(M \cdot N) \sum_{i=1}^{M} \sum_{j=1}^{N} I(Y_{i,j} = 1)$, the average proportion of patients being overdosed,

$1/(M \cdot N) \sum_{i=1}^{M} \sum_{j=1}^{N} I(Dose_{i,j} > \gamma_{true})$, the percent of trials with estimated MTD within 5% of the dose range of the true MTD, i.e., within 0.05 of the true MTD, and the percent of trials with

DLT rate exceeding 40%. These last two summary statistics approximate the probability that a given trial will result in an estimated MTD close to the true MTD and the probability that a trial will be safe, respectively.

Figures 1—5 show the simulation results for when the DLT responses are generated using the proportional hazards model with Weibull baseline hazard and Figure 6—10 show the summary statistics using a non-proportional hazards model. Figure 1 shows that the average bias is lower when using EWOC-PH relative to EWOC, EWOC-NW, and TITE-EWOC when k = 0.8, 1 and there is little differences in this bias when $k = 1.2$ between the four different methods. Figure 6 shows the same pattern using the non-proportional hazards model except in the case where $\beta_2 = 2.0$ and the MTD is high. Figure 2 show that the average proportion of patients exhibiting DLT is less than 33% for EWOC-PH in all cases except when the MTD is low and $k = 1.2$ where this rate is close to 40%. This proportion is always less than 33% under the non-proportional hazards model, see Figure 7. Similarly, the proportion of patients being overdoses is less than 25% for all scenarios, all 4 methods, and under the two models generating the DLT responses, see Figures 3 and 8. Figures 4 and 9 show that EWOC-PH gives the highest percent of MTD recommendation under most scenarios relative to EWOC, EWOC-NW, and TITE-EWOC and all of these methods are safe in the sense of having a very small probability that a trial will result in a DLT rate exceeding 40%. We conclude that EWOC-PH is a good alternative design for late onset toxicity relative to TITE-EWOC and EWOC and EWOC-NW since it tends to recommend the MTD with a higher frequency under most of the scenarios considered here and that the trial is safe.

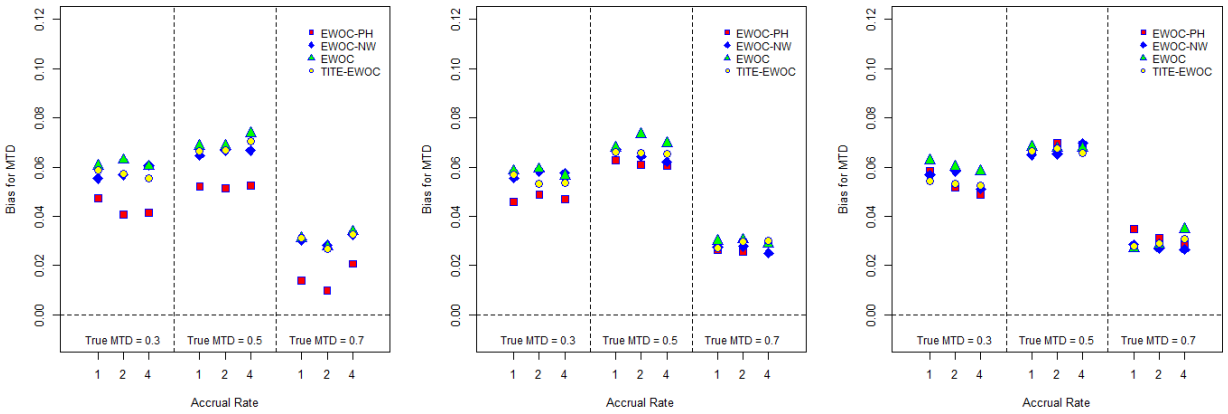

Figure 1. Average bias of the estimate of the MTD under the nine different scenarios. DLT responses are generated from a Weibull model with shape parameter $k = 0.8$ (left plot), $k = 1.0$ (middle plot), and $k = 1.2$ (right plot).

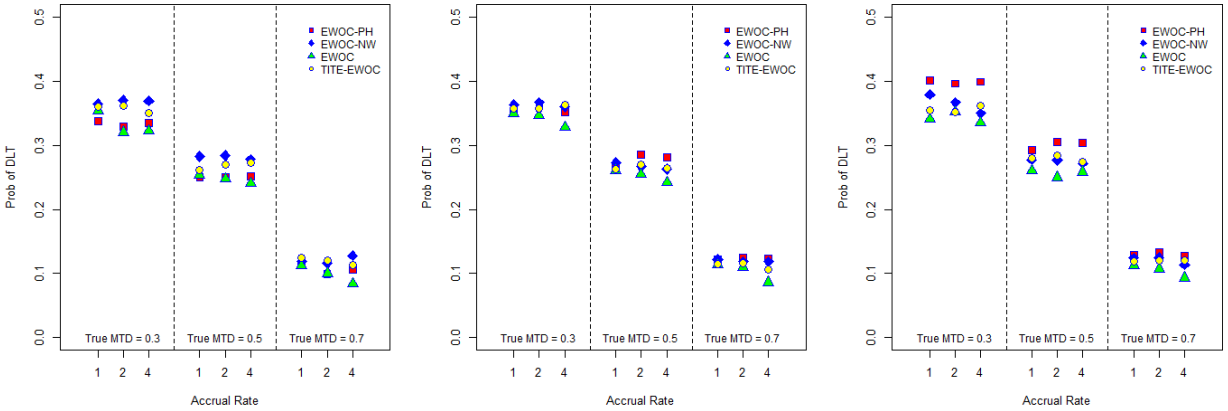

Figure 2. Average proportion of patients exhibiting DLT under the nine different scenarios. DLT responses are generated from a Weibull model with shape parameter $k = 0.8$ (left plot), $k = 1.0$ (middle plot), and $k = 1.2$ (right plot).

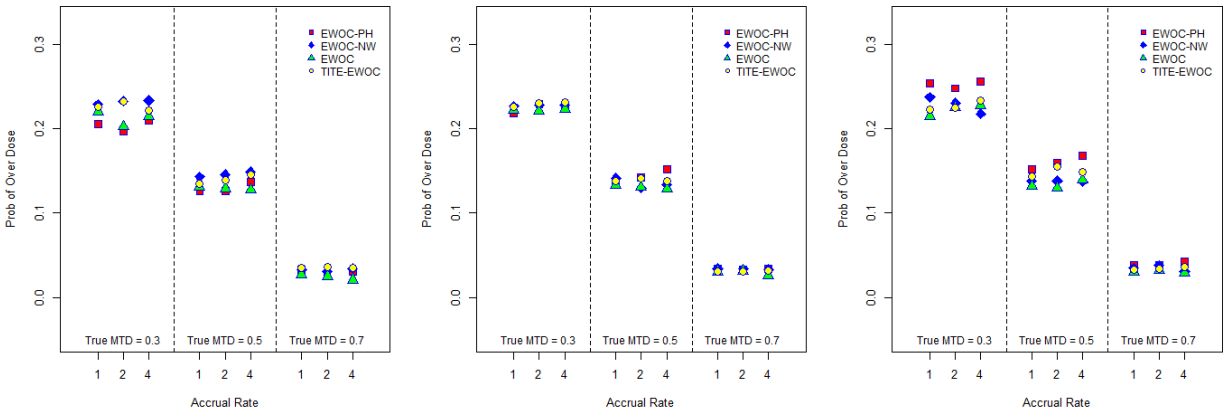

Figure 3. Average proportion of patients given doses above the true MTD. DLT responses are generated from a Weibull model with shape parameter $k = 0.8$ (left plot), $k = 1.0$ (middle plot), and $k = 1.2$ (right plot).

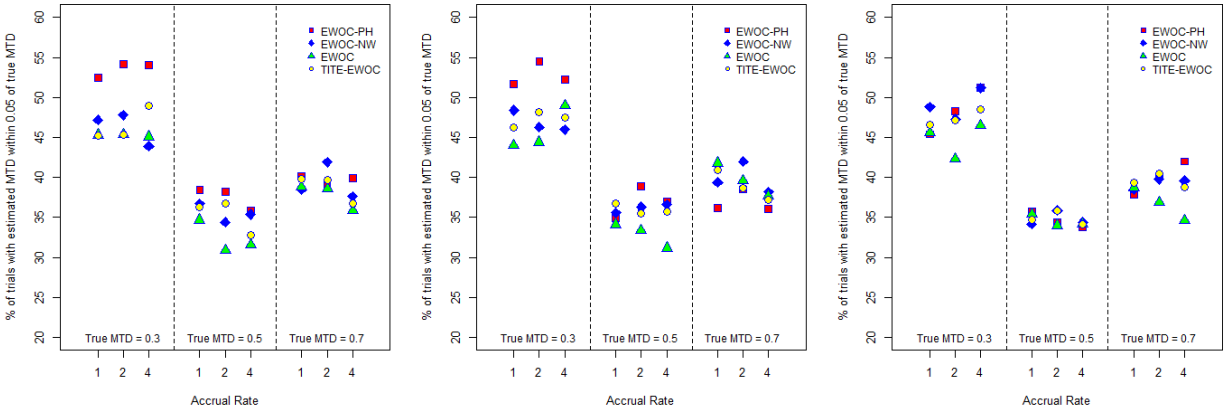

Figure 4. Percent of trials with recommended MTD within 0.05 of the true MTD. DLT responses are generated from a Weibull model with shape parameter $k = 0.8$ (left plot), $k = 1.0$ (middle plot), and $k = 1.2$ (right plot).

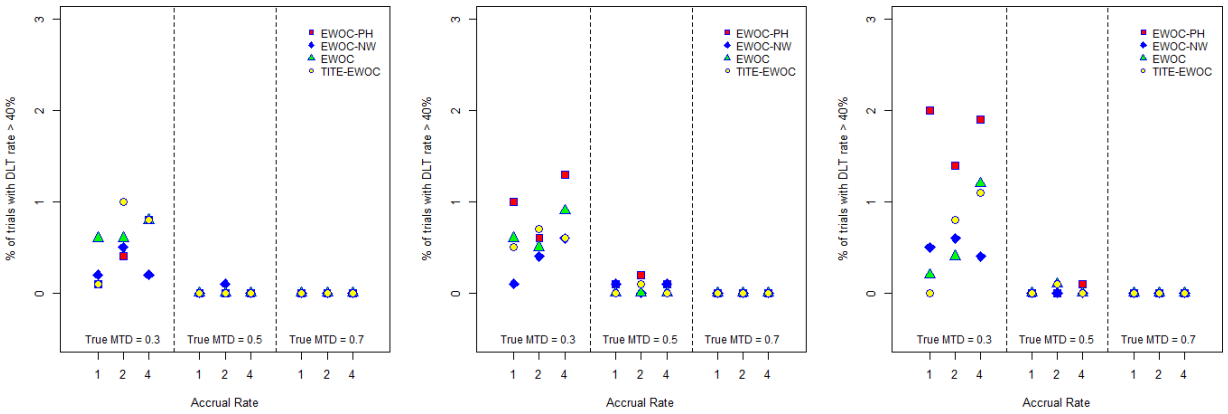

Figure 5. Percent of trials with DLT rate exceeding 40%. DLT responses are generated from a Weibull model with shape parameter $k = 0.8$ (left plot), $k = 1.0$ (middle plot), and $k = 1.2$ (right plot).

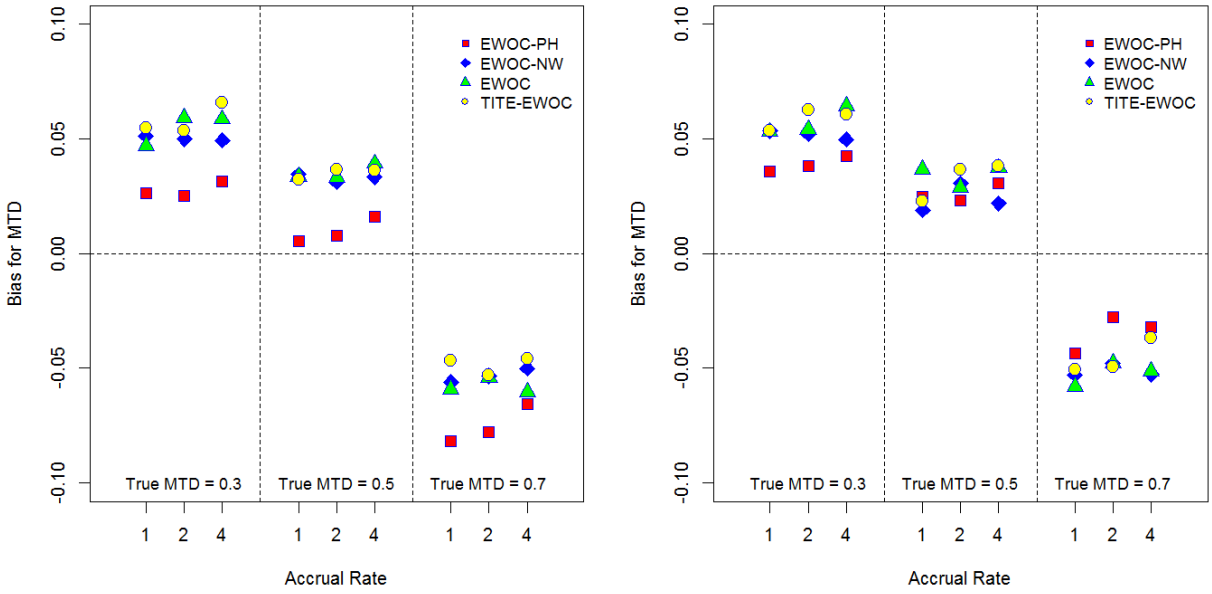

Figure 6. Average bias of the estimate of the MTD under the nine different scenarios. DLT responses are generated from a non-proportional hazards model with $\beta_2 = 0.5$ (left plot) and $\beta_2 = 2.0$ (right plot).

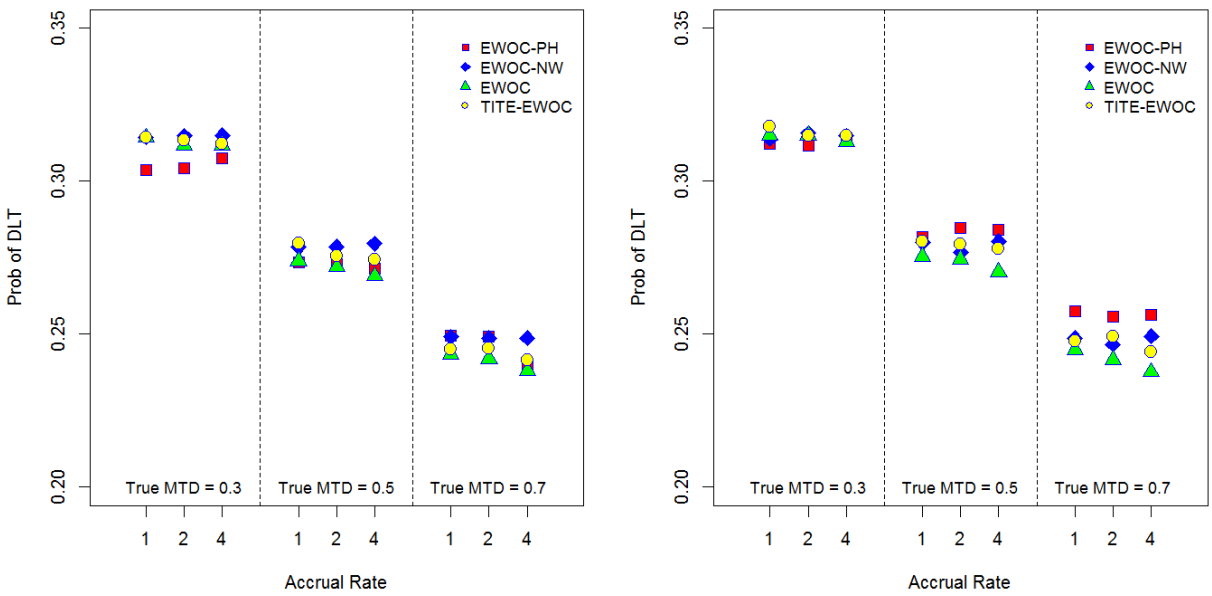

Figure 7. Average proportion of patients exhibiting DLT under the nine different scenarios. DLT responses are generated from a Weibull model with shape parameter $k = 0.8$ (left plot), $k = 1.0$ (middle plot), and $k = 1.2$ (right plot).

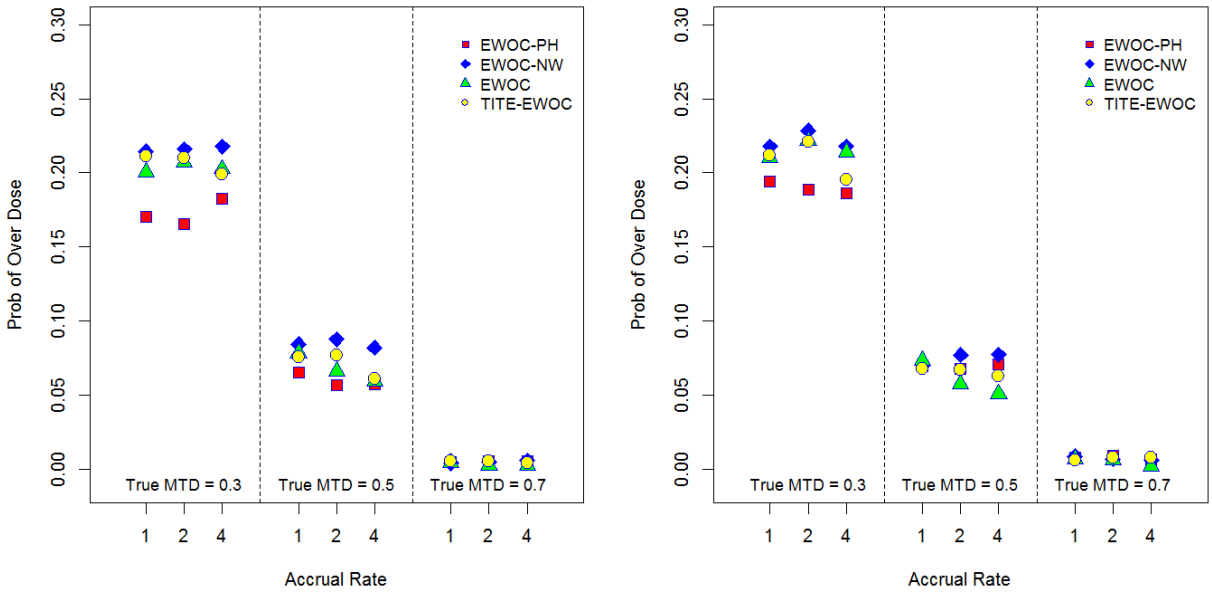

Figure 8. Average proportion of patients given doses above the true MTD. DLT responses are generated from a non-proportional hazards model with $\beta_2 = 0.5$ (left plot) and $\beta_2 = 2.0$ (right plot).

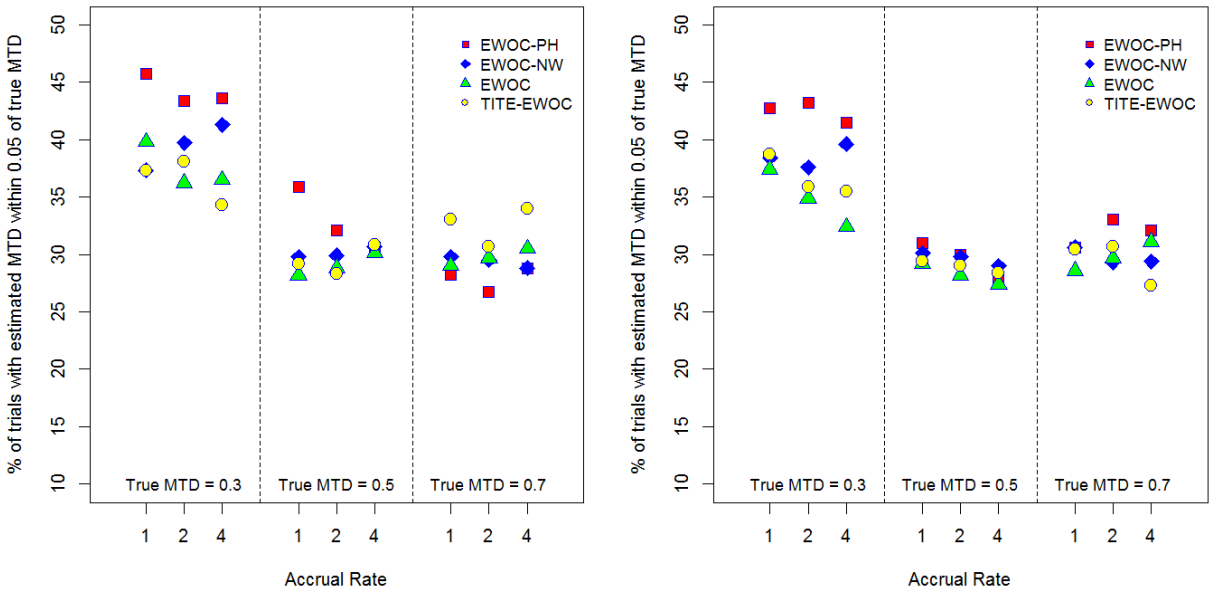

Figure 9. Percent of trials with recommended MTD within 0.05 of the true MTD. DLT responses are generated from a non-proportional hazards model with β2= 0.5 (left plot) and β2= 2.0 (right plot).

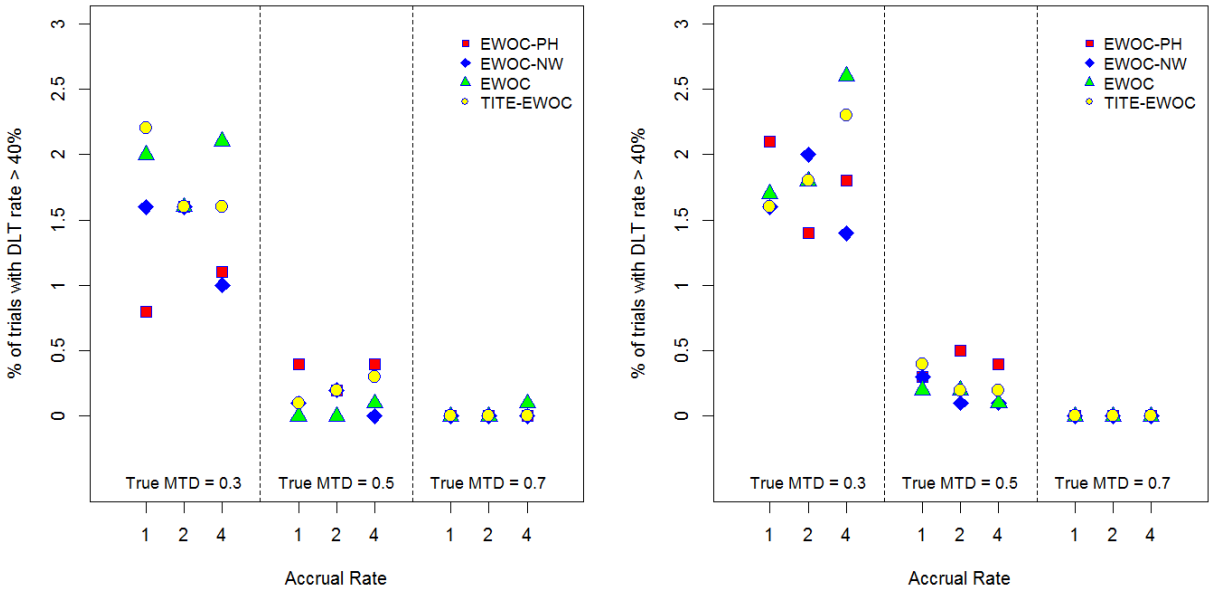

Figure 10. Percent of trials with DLT rate exceeding 40%. DLT responses are generated from a non-proportional hazards model with β2= 0.5 (left plot) and β2= 2.0 (right plot).

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